Rational use of medicines: safety, challenges and potentials of electronic mobile devices for implementing a new algorithm for management of childhood illness (ALMANACH) in low and middle income countries
Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät auf Antrag von Prof. Dr. Blaise Genton, Prof. Dr. Marcel Tanner und Dr. Wilson Were

Basel, den 24. March 2015

Prof. Dr. Jörg Schibler

Daken
Dedication

To my beloved parents: Flexson Shao and Elimaria Shao, my wife Lightness Mrema, and our children Glory, Gladness and Giovanni.
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<th>Description</th>
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<tbody>
<tr>
<td>AB</td>
<td>Antibiotic</td>
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<tr>
<td>AB/AM</td>
<td>Antibiotic/Antimalaria</td>
</tr>
<tr>
<td>ALMANACH</td>
<td>Algorithm for management of childhood illness</td>
</tr>
<tr>
<td>ALU</td>
<td>Artemether/Lumefantrine</td>
</tr>
<tr>
<td>AM</td>
<td>Antimalaria</td>
</tr>
<tr>
<td>ARI</td>
<td>Acute respiratory infections</td>
</tr>
<tr>
<td>CDC</td>
<td>Center for Disease Control</td>
</tr>
<tr>
<td>CDSR</td>
<td>Cochrane Database for Systematic Reviews</td>
</tr>
<tr>
<td>CHERG</td>
<td>Child Health Epidemiology Reference Group</td>
</tr>
<tr>
<td>CHMT</td>
<td>Council Health Management Team</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>D0</td>
<td>Day zero</td>
</tr>
<tr>
<td>D7</td>
<td>Day seven</td>
</tr>
<tr>
<td>DALY</td>
<td>Disability-adjusted life years</td>
</tr>
<tr>
<td>DEC</td>
<td>Diarrhoeagenic <em>Escherichia coli</em></td>
</tr>
<tr>
<td>e-IMCI</td>
<td>Electronic Integrated management for childhood illness</td>
</tr>
<tr>
<td>EKBB</td>
<td>Ethikkommission beider Basel</td>
</tr>
<tr>
<td>FGD</td>
<td>Focus group discussion</td>
</tr>
<tr>
<td>HF</td>
<td>Health facility</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health Management Information System</td>
</tr>
<tr>
<td>HW</td>
<td>Health worker</td>
</tr>
<tr>
<td>IDI</td>
<td>In-depth interview</td>
</tr>
<tr>
<td>IHI</td>
<td>Ifakara Health Institute</td>
</tr>
<tr>
<td>IHME</td>
<td>Institute for Health Metrics and Evaluation</td>
</tr>
<tr>
<td>IMCI</td>
<td>Integrated management for childhood illness</td>
</tr>
<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>LR</td>
<td>Likelihood ration</td>
</tr>
<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
</tr>
<tr>
<td>MoHSW</td>
<td>Ministry of Health and Social Welfare</td>
</tr>
<tr>
<td>mRDT</td>
<td>Malaria rapid diagnostic test</td>
</tr>
<tr>
<td>MTUHA</td>
<td>Mfumo wa Taarifa za Huduma za Afya</td>
</tr>
<tr>
<td>NIMR</td>
<td>National Institute for Medical Research</td>
</tr>
<tr>
<td>OPD</td>
<td>Out-patient department</td>
</tr>
<tr>
<td>PDA</td>
<td>Personal Digital Assistant</td>
</tr>
<tr>
<td>PHCF</td>
<td>Primary health care facility</td>
</tr>
<tr>
<td>POCT</td>
<td>Point-of-care test</td>
</tr>
<tr>
<td>RR</td>
<td>Respiratory rate</td>
</tr>
<tr>
<td>SLR</td>
<td>Systematic Literature Review</td>
</tr>
<tr>
<td>SNF</td>
<td>Swiss National Science Foundation</td>
</tr>
<tr>
<td>SSA</td>
<td>Sub Saharan Africa</td>
</tr>
<tr>
<td>U5</td>
<td>Under five years of age</td>
</tr>
<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
</tr>
<tr>
<td>URTI</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>UTI</td>
<td>Urinary tract infection</td>
</tr>
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<td>WHO</td>
<td>World Health Organization</td>
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Summary
Nearly 7 million children die each year before the age of 5 despite the availability of effective low-cost interventions. Integrated Management of Childhood Illness (IMCI) guidelines have proven, when used correctly, to improve quality of care and reduce under-5 mortality. However, the actual impact of IMCI worldwide has been less than anticipated due to limited uptake of the intervention, and poor compliance to algorithms by clinicians. A recent study in Tanzania showed poor compliance to the IMCI protocols, resulting to low quality of care. Indeed 78% of the patients attending outpatient clinics with fever who tested negative for malaria were prescribed antibiotics although this was appropriate in less than 20% of the case. Such procedures lead to poor health outcomes, huge wastage of medicines and rapid spread of bacterial resistance. The rapidly changing patterns of disease, the rapid spread of resistance to antimicrobial drugs, the poor compliance to clinical guidelines using paper-based algorithms, and the increasing availability of new technologies that can improve both diagnoses accuracy and compliance to evidence-based clinical algorithms were the basis of this PhD thesis.

The objectives of the thesis were:

- To develop a new algorithm on paper and on electronic support for the management of childhood illness (based on a literature review, results of a fever study conducted in Tanzania and discussions with IMCI experts and which aims to improve clinical outcome and rational use of antimalarial and antibiotics.

- To assess whether the new ALgorithm for MANAgement of CHildhood illness (ALMANACH), which was derived from IMCI and based on the new evidence about disease patterns and drug resistance algorithms, is as safe as routine practice (IMCI) and lead to a more appropriate use of antibiotics

- To describe the distribution of acutely ill children in the various pathways of the new algorithm for the management of childhood illness in order to find out potential branches (symptoms and signs) that could be modified or dropped to facilitate its use, and hence uptake, but keeping it suitable to the epidemiology and burden of paediatric illnesses in outpatients departments of primary health care settings.

- To assess potential barriers and facilitators for the uptake of the new algorithm on electronic support in pragmatic conditions in order to recommend ways for its sustainable use and optimal compliance by clinicians in primary health care settings.
Methods

These four objectives were addressed in three different studies with the following designs and methodologies:

(i) A structured literature review in Medline, Embase and the Cochrane Database for Systematic Reviews (CDSR) searching for available evidence on (a) disease prevalence in paediatric outpatients, (b) accuracy of clinical predictors and (c) performance of point of care tests on targeted diseases (Clotilde Rambaud-Althaus et al, submitted).

(ii) A controlled non-inferiority trial to compare the clinical outcome and antibiotic prescriptions of children managed according to ALMANACH or to standard practice (IMCI). Consecutive children aged 2-59 months with acute illness were managed using ALMANACH (2 intervention facilities), or standard practice (2 control facilities) in Dar es Salaam and Morogoro in Tanzania (urban and rural settings). Children enrolled in the intervention arm were managed by two study clinicians (one for each setting) who were trained to strictly comply with the ALMANACH algorithm. Primary outcomes were proportion of children cured at day 7 and who received antibiotics on day 0.

(iii) A descriptive analysis of the data collected in the intervention arm of the study described under ii). Outcomes were i) proportions of children presenting with danger signs, with main symptoms and signs, ii) proportions of children who were prescribed antimicrobials and iii) clinical outcomes.

(iv) A qualitative study using in-depth interviews and focus group discussions among 40 primary health care workers from 6 public primary health facilities in the three municipalities of Dar es Salaam, Tanzania where the electronic clinical algorithm ALMANACH was used. Health workers’ perceptions related to factors facilitating or constraining the uptake of the electronic device were identified.

Results


The new algorithm (ALMANACH) differs from IMCI 2008 version in the following aspects:

(a) 10 general danger signs are assessed; (b) the non-severe children are classified into febrile and non-febrile patients, the latter not being recommended to receive antibiotics; (c) pneumonia is based on a respiratory rate threshold of ≥ 50 breaths per minute that is assessed twice for children aged 12-59 months; (d) all febrile patients are tested with malaria rapid diagnostic test;
when no identified source of fever at the end of assessment, then (e) urine dipstick is performed in febrile children <2 years to identify urinary tract infection (UTI), f) abdominal tenderness is performed in febrile children >2 years to 'classify possible typhoid'; (g) classification of likely viral infection is made in cases where nothing specific is found.

**ii) Clinical outcome and antibiotic prescriptions using ALMANACH**

130/842 (15·4%) in ALMANACH and 241/623 (38·7%) in control arm were diagnosed with an infection in need for antibiotics, while 3·8% and 9·6% had malaria. 815/838 (97·3%;96·1-98·4%) were cured at day 7 using ALMANACH versus 573/623 (92·0%;89·8-94·1%) using standard practice (p<0·001). Of 23 children not cured at day 7 using ALMANACH, 44% had skin problems, 30% pneumonia, 26% upper respiratory infection and 13% likely viral infection at day 0. At day 0, antibiotics were prescribed to 15·4% (12·9-17·9%) using ALMANACH versus 84·3% (81·4-87·1%) using standard practice (p<0·001) corresponding to a reduction of 82%. 2·3% (1·3-3·3%) and 3·2% (1·8-4·6%) respectively received an antibiotic secondarily. Secondary hospitalization occurred for one child using ALMANACH; one child died at day 4 in the standard practice arm.

**iii) Description of the distribution of acutely ill children in the various branches of the new algorithm for the management of childhood illness (ALMANACH)**

842 consecutive patients were assessed. 0.1% (1/842) of children had general danger signs. 67.8% (571/842) entered the fever, 59.1% the cough, 21.9% the diarrhoea and 14.5% the skin problems branches. 0.3% (1/351) of patients with fever and cough had lower chest indrawing. 71.5% (251/351) of them had a final classification of upper respiratory tract infection and 28.5% (100/351) of pneumonia. 5.6% (32/570) patients, for whom a malaria rapid diagnostic test was performed, had malaria. 7.1% (6/85) patients for whom a urine dipstick was performed had a positive result. None of the 39 patients, in whom abdominal tenderness (considered as predictive for typhoid fever) was searched for, presented this sign. On day 0, 1.9% (5/271) of non-febrile patients received antibiotics compared to 21.9% (125/571) of febrile patients. Day 7 cure rate in febrile and non-febrile patients was 97.2% and 97.4% respectively.
iv) Potential barriers and facilitators for the uptake of the new algorithm on electronic support (mobile devices) in pragmatic conditions

In general, the ALMANACH was assessed positively. The majority of the respondents felt comfortable to use the devices during consultations and stated that patient’s trust was not affected. Most health workers said that the ALMANACH simplified their work, reduced antibiotic prescription and gave correct classification and treatment for common causes of childhood illnesses.

Few reported technical challenges using the mobile devices and complained about having had difficulties typing. Majority of the respondents stated that the devices increased the consultation duration compared to routine practice. In addition, health system barriers such as lack of staff, lack of medicine and lack of financial motivation were identified as key reasons for the low uptake of the devices.

Conclusion

The new algorithm has the potential to improve clinical outcome of pediatric patients presenting at primary care facilities and drastically reduce antibiotic prescription. This was achieved through more accurate diagnoses and hence better identification of children in need of antibiotic treatment or not. A detailed count of patients with defined symptoms, signs, laboratory test results, and clinical outcome when managed by ALMANACH allowed to precisely assessing the value of each of the proposed branches of the algorithm in a primary care setting. This helped to decide on the relevance of keeping, modifying or dropping each of the algorithm components. A vast majority of children had mild illnesses and most of them did not require antibiotics to be cured. ALMANACH building on mobile technology allowed easy access, rapid update of the decision chart and has a potential to improve quality and timely use of clinical data collected at the point of care for planning at all levels of health care. Further studies are recommended to assess feasibility of phased scale up of an improved ALMANACH on mobile devices in order to improve rational use of antimicrobials and the quality of health care for children in developing countries.
Zusammenfassung

Die Ziele dieser Dissertation waren folgende:

- Beurteilung des neuen Algorithmus zum Management von Kinderkrankheiten (ALMANACH) hinsichtlich seiner Sicherheit im Vergleich zum Standardverfahren (IMCI) und der angemessenen Verschreibung von Antibiotika. ALMANACH basiert auf den IMCI Richtlinien und auf den neuen wissenschaftlichen Nachweisen bezüglich Krankheitsbildern und Medikamentenresistenzalgorithmen.

- Beurteilung von möglichen hemmenden und unterstützenden Faktoren bezüglich der Umsetzung des neuen Algorithmus' in elektronischer Form unter Realbedingungen um damit Wege für dessen nachhaltigen Nutzen und optimaler Umsetzung durch die Ärzte in Primärversorgungseinrichtungen aufzuzeigen.

Methoden:

Die zuvor genannten vier Ziele wurden im Rahmen von drei verschiedenen Studien mit folgendem Design und Methodologie verfolgt:


(iii) Eine beschreibende Analyse der Daten, die im Interventionszweig der unter ii) beschriebenen Studie gesammelt wurden. Ergebnisse waren folgende: i) Anteil der
Kindern mit Warnzeichen, mit Hauptsymptomen und Anzeichen, ii) Anteil der Kinder, denen Antibiotika verschrieben wurde und iii) klinische Ergebnisse.

(iv) Eine qualitative Studie basierend auf ausführlichen Interviews und Fokusgruppen-Diskussionen mit 40 Personen angestellt in 6 Primärversorgungseinrichtungen in den drei Stadtbezirken in Dar es Salaam, Tansania, wo der elektronische, klinische Algorithmus ALMANACH benutzt wurde. Es wurden hemmende und unterstützende Faktoren identifiziert, die die Akzeptanz des elektronischen Gerätes der im Gesundheitswesen tätigen Personen beeinflussten.

Resultate


a) Es werden 10 allgemeine Warnzeichen bewertet
b) Die minderschwer kranken Kinder werden in Patienten mit und ohne Fieber eingeteilt, wobei für letztere keine Antibiotika-Behandlung empfohlen wird
c) Lungenentzündung für Kinder zwischen 12-59 Monaten wird diagnostiziert basierend auf einer Atmungsfrequenz von >= 50 Atemzügen pro Minute, die zweimal gemessen wird
d) Falls während der Untersuchung kein anderer Grund des Fiebers identifiziert wurde, dann wurden ein Malariaquicktest durchgeführt
e) Danach wird in Kindern unter 2 Jahren mit Fieber eine Harnuntersuchung gemacht um eine Harnwegsinfektion (UTI) zu diagnostizieren
f) Kinder über 2 Jahre mit Fieber werden auf eine schmerzhafte Bauchdeckenspannung untersucht, um sie auf eine mögliche Typhuserkrankung zu testen
g) Wenn nichts Spezifisches gefunden wird, werden sie der Gruppe der viralen Infektionen zugeteilt

ii) Klinische Ergebnisse und Verschreibung von Antibiotika nach ALMANACH

130 von 842 Kinder (15,4%) in der ALMANACH Gruppe und 241 von 623 Kinder (38,7%) in der Kontrollgruppe wurden mit einer Infektion diagnostiziert, die eine Antibiotikabehandlung benötigte, während 3,8% und 9,6% Malaria hatten. Gegenüber
dem Standardverfahren, bei dem 573 von 623 Kindern (92,0%; 89,8-94,1%) nach 7 Tagen geheilt waren (p<0,001), war dies bei der Anwendung von ALMANACH bei 815 von 838 Kinder (97,3%; 96,1-98,4%) der Fall. Von 23 Kindern, die nicht nach 7 Tagen geheilt waren und bei denen ALMANACH angewendet wurde, hatten am Tag 0 44% Hautprobleme, 30% Lungenentzündung, 26% eine Infektion der oberen Atemwege und 13% eine virale Infektion. Wenn ALMANACH angewendet wurde, bekamen am Tag 0 15,4% (12,9-17,9%) der Kinder Antibiotika verschrieben und 84,3% (81,4-87,1%) wenn das Standardverfahren angewendet wurde (p<0,001). Dies entsprach einer Abnahme der Antibiotikaverschreibung von 82%. 2,3% (1,3-3,3%) und 3,2% (1,8-4,6%) bekamen sekundär ein Antibiotikum verschrieben. Spätere Aufnahme ins Krankenhaus erfolgte bei einem Kind im ALMANACH-Zweig, beim Standardverfahren verstarb ein Kind am Tag 4.

iii) Beschreibung der Aufteilung von akut kranken Kindern in die verschiedenen Zweige des neuen Algorithmus' zum Management von Kinderkrankheiten

Es wurden 842 Patienten untersucht. 0,1% (1/842) der Kinder hatten allgemeine Warnzeichen. 67,8% (571/842) wurden der Fieber-, 59,1% der Husten-, 21,9% der Durchfall- und 14,5% der Hautproblem-Gruppe zugeteilt. 0,3% (1/351) der Patienten mit Fieber und Husten hatten eine Brustwandeinziehung. Bei 71,5% (251/351) dieser Patienten wurde eine Infektion der oberen Atemweg diagnostiziert und bei 28,5% (100/351) eine Lungenentzündung. 5,6% (32/570) der Patienten, bei denen ein Malaria Schnelltest gemacht wurde, hatten Malaria. Bei 7,1% (6/85) der Patienten zeigte der Urintest ein positives Resultat. Keiner der Patienten, der auf eine schmerzhafte Bauchdeckenspannung (dies wurde als Symptom für Typhusfieber angesehen) untersucht wurde, wies dieses Anzeichen auf. Am Tag 0 erhielten 1,9% (5/271) der Patienten ohne Fieber Antibiotika, während für 21,9% (125/571) der Patienten mit Fieber eine Antibiotikabehandlung verschrieben wurde. Die Heilungsrate am Tag 7 in Patienten mit und ohne Fieber war 97,2% respektive 97,4%.

iv) Mögliche hemmende und unterstützende Faktoren bezüglich der Umsetzung des neuen Algorithmus' mit elektronischer Unterstützung (Mobilgeräte) unter Realbedingungen

ALMANACH wurde im Allgemeinen gut aufgenommen. Die Mehrheit der Befragten fühlte sich beim Benutzen von ALMANACH während den Konsultationen wohl und
gaben an, dass das Vertrauen der Patienten dadurch nicht beeinträchtigt sei. Die Mehrheit des Gesundheitspersonals gab an, dass ALMANACH deren Arbeit erleichterte, die Antibiotikaverschreibungen reduzierte und zu korrekten Klassifizierungen und Behandlungen für gängige Ursachen von Kinderkrankheiten führte.


Schlussfolgerung

xviii
Muhstasari
Karibu watoto milioni saba hufa kila mwaka kabla ya kufikisha umri wa miaka mitano pamoja na kuwepo kwa msimbo cha gharama nafuu. Mwongozo wa matibabu ya magonjwa ya watoto (IMCI) umethibishiwa kwamba ukimfunga kwa usahihii unaongeza ubora wa huduma na unapunguza vifo vya watoto waliyotumia kwa chini ya umri wa miaka mitano. Hata hivyo matokeo halisi ya IMCI duniani kote yamekuwa chini ya maturajio kwa sababu ya utumiaji mdogo na ufuatili la hafiifu wa watoto kwa waimu wa afya. Utafiti uliofanyika Tanzania hivi karibuni uwezekana kuwa ufuatili la hafiifu wa mwongozo wa IMCI hupelekea huduma la hafiifu za afya. Hakika asilimia 78% ya wagonjwa wa nje wanaohudhuria kliniki wakiwa na homa wanaapatikana na kipimo hasi cha malaria, walipewa dawa za vimelea vya bacteria, ingawa waliostahili kwa usahihii ni chini ya 20% ya wagonjwa hao. Taratibu kama hizo hupelekea matokeo dhaifu ya kiafya, upotevu mkubwa wa dawa na usaambaaji wa kasi wa usaha wa vimelea vya bakteria dhidi ya dawa. Mabadiliko ya kasi ya mwelekeo wa magonjwa, usaambaaji wa kasi wa usaha wa vimelea vya bakteria dhidi ya dawa, ufuatili hafiifu wa mwelekeo ya IMCI ya matibabu iliyochapishwa na wonevumbi na kipimo vya bakteria dhidi ya dawa. Mabadiliko ya asi ya mwelekeo wa magonjwa, usaambaaji wa kasi wa usaha wa vimelea vya bakteria dhidi ya dawa, ufuatili hafiifu wa mwelekeo ya IMCI ya matibabu iliyochapishwa na wonevumbi na kipimo vya bakteria dhidi ya dawa. Mabadiliko ya asi ya mwelekeo wa magonjwa, usaambaaji wa kasi wa usaha wa vimelea vya bakteria dhidi ya dawa, ufuatili hafiifu wa mwelekeo ya IMCI ya matibabu iliyochapishwa na wonevumbi na kipimo vya bakteria dhidi ya dawa.

Njia:
Malengo manne ya utafiti huu yalianzeshwa kwenye afya zinapatikana na mazingira halisi ili kutoa mapendekezo sanaki afya zinatupa na utambuzi sahihi za magonjwa ya watoto wa kielektroniki wa kiafya wao. Usahihii ya mpando ili kuthibitiwa kuwa ufuatili la hafiifu la afya zinapatikana na mazingira halisi ili kutoa mapendekezo sanaki afya zinatupa na utambuzi sahihi za magonjwa ya watoto wa kielektroniki wa kiafya wa afya.
ugunduzi vya papo hapo vya magonjwa yaliyodhaniwa. (Clotilde Rambaud-Althaus t al).

ii. Majaribio yalifanyika kulinganisha matokeo ya kiafa ya na madawa waliyopewa watoto kwa kutumia mwongozo wa ALMANACH au kwa kutumia utendaji uliopo wa IMCI. Watoto wenyewe umri kati ya mizizi 2 hadi 59 wenye mgonjwa ya muda mfupi walihusishwa kwa kutumia ALMANACH (utaifiti kwenye vituo viwili), au utendaji wa kawaida (vituo viwili kwa uangalizi) Dar es Salaam, na Morogoro nchini Tanzania (mazingira ya mjini na kijijini). Watoto waloandikishwa kwenye vituo vya utafiti waliohudumiwa na watumishi wa afya waiofundishwa kufuatilia kwa karibu mwongozo wa ALMANACH. Matokeo ya msingi yalikuwa ni uwiano wa watoto walioponywa siku ya saba na waliopewa dhidi ya vimelea vya bakteria siku ya mwanza (0).

iii. Uchambuzi wa maelezo ya taarifa zilizokusanywa katika vituo vya utafiti kama ilivyoelezwa (ii) hapo juu, matokeo yalikuwa

iv. Pia utafiti wa mahojiano ya kina na majadiliano katika makundi yaishirikisha wafanyakazi 40 kutoka vituo 6 vya awali vya kufanya afya vya umispaa tatu za mkoa wa Dar es Salaam, Tanzania ambapo mfumo wa kielektroniiki wa matibabu (ALMANACH) ulitumika. Mtazamo wa wahudumu wa afya kusiana na vitu vinavyorahisisha au kukwaza utumiaji wa mfumo wa kielektroniki wa ALMANACH vilibainishwa.

Matokeo

Uandaajii wa mfumo mpya wa matibabu ili watoto ili kuboresha matumizi sahihi ya dawa dhidi ya vimelea vya vijidudu (ALMANACH) bila kuathiri matokeo ya kiafa (Clotilde Rambaud-Althaus et al)

Mwongozo mpya (ALMANACH) unatofautiana na ule wa IMCI toleo la 2008 katika nyanja zifuatazo:

a) Dalili 10 hatarishi zinatathminiwa (b) watoto wasiokuwa na dalili hatarishi wawekwana katika kundi la wenyewe homa au wasio na homa. Kundi la pilinashauriwa kutopewa dawa dhidi ya vimelea vya bakteria. (c)Homa ya mapafu inafikiwa iwapo kiwango cha upumuaji ni pumzi 50 au zaidi kwa hatari kwa kiwango ni, kiwango kiochi kinatathminiwa mara mbili kwa watoto wenyewe umri wa miezi 12 hadi 59 (d) Kila mwenye homa anapima kwa kiptimo cha haraka cha malaria. Iwapo hamna chanzo cha homa mwishoni mwa tathmini hiyo, (e) kiptimo cha haraka cha mkojo kinatathminiwa kwa wenyewe homa wali chini ya miaka 2 ili kuona kama wana maambukizi kwenye njia ya mkojo (UTI), (f) tumbo linapapawasa kutambua maumivu kwa watoto wenyewe miaka miwili au ili zaidi kuweza kutambua homa ya matumbo na g) Ainisho la uwezekano wa maambukizi ya virusi linakifiwa endapo hakuna kitu mahususi kilichogundulika.
ii) Matokeo ya kitabibu na matumizi ya dawa dhidi ya vimelea vya bakteria kwa kutumia ALMANACH

130/842 (15.4%) kwa ALMANACH na 241/623 (38.7%) kwenye uaugalizi waligundulika kuwa na maambukizi na wakahitaji dawa dhidi ya vimelea vya bakteria, wakati 3.8% na 9.6% walikuwa na malaria. 815/838 (97.3%; 96.1-98.4%) walikuwa wamepona siku ya 7 kwa kutumia ALMANACH dhidi ya 573/623 (92.0%; 89.8-94.1%) kwa kutumia mwongozo wa kawaida (p<0.001). Mniononi mwa watoto 23 ambao hawakupona siku ya saba kwa kutumia ALMANACH, 44% walikuwa na matatizo ya ngozi, 30% homa ya mapafu, 26% maambukizo ya njia ya juu ya hewa na 13% wanahisiwa kuwa na maambukizi ya virusi siku ya mwanzo. Katika siku yake mwanzo, dawa dhidi ya vimelea vya bakteria ziliitolewa kwa 15.4% (12.9-17.9%) kwa kutumia ALMANACH dhidi ya 84.3% (81.4-87.1%) kwa kutumia mwongozo wa kawaida (p<0.001) ikishabihiana na punguzo la asilimia 82%. 2.3% (1.3-3.3%) and 3.2% (1.8-4.6%) walipewa dawa dhidi ya vimelea vya bakteria baada ya kuongwa tena. Mto mmoja alilazwa kwa mfumo wa ALMANACH na mmoja alifariki siku ya nne kwao kwa kawaida.

iii) Maelezo ya mgawanyiko wa watoto waliokuwa wana umwa katika matawi mbali ya mwongozo wa magonjwa wa watoto (ALMANACH)

Wagonjwa 842 walitathminiwa, 0.1% (1/842) ya watoto walikuwa na alama hatarishi. 67% (571/842) walikuwa na homa, 59.1% kikohozi, 21.9% kuhara na 14.5% matatizo ya ngozi. 0.3% ((1/351) ya wagonjwa wenye homa na kikohozi walikuwa na tatito la kuingia ndani kwa sehemu ya chini ya kifua. 71.5% (251/351) mniononi mwa wagenjwa 39 ambao maumivu ya tumbo yalitathminiwa (ilichukuliwa kama ishara ya h ofa ya matumbo) alikuwa na dalili hiyo. Katika siku yake mwanzo, 1.9% (5/271) ya wagonjwa wenye homa na wasio na homa walipatisha dawa dhidi ya vimelea vya bakteria na 21.9% (125/571) ya wasio na homa. Kwenye siku ya 7, kwango cha uponaji kwa wagonjwa wenye homa na wasio na homa kilikuwa 97.2% na 97.4% kwa mfumo wa mwanza.

iv) Vikwazo na viwezeshaji kwa ajili ya matumizi yake wa muongozo mpya wa Kieletroniki kwenye kazi za utabibu

Kwa ujumla, ALMANACH ilipata tathmini chanya. Wengi wa wahudumu waliyojibu walijisikia vizuri kutumia vifaa hivyo wa kuhudumia wagonjwa, walisema imani ya wagonjwa haikuathe ria. Wafanyakazi wengi wa afya walisema kuwa ALMANACH iliheshi kazi yao, ilipunguza matumizi ya dawa dhidi ya vimelea vya bakteria na iliwapa majibu na matibabu sahihi kwa visababishi vya kawaida vya magonjwa ya watoto.

Wachache waliieza matatizo ya kiufundi wakati wa kutumia vifaa hivyo na kulalamikia shida ya kuandika kwenge vifaa hivyo. Wengi wa waliyojibu waliieza kuwa vifaa hivyo
vihitaji muda mwingi kumuona mgongo wa ikilinganishwa na utaratibu wa kawaida. Zaidi, vizuizi vya mfumo wa huduma ya afya kama upungufu wa wahudumu, kukosekana kwa madawa na kukosa uhamashio wa kifedha vilibainishwa kama sababu za msingi kwa matumizi madogo ya hizi simu/vifaa.

Hitimisho:

Mfumo huu mpya una nafasi kubwa ya kuboresha matokeo ya kikliniki ya watoto wagonjwa wanaohudhuria vituo vya awali vya afya na kupunguza kwa kasi utoaji wa dawa dhidi ya vimelea vya bakteria. Hii ilifikiwa kutokana na ugu nduaji sahihi na hivyo utambuaji bora wa watoto wanaohitaji au wasiohitaji dawa dhidi ya vimelea vya bakteria. Tathmini ya kina ya wagonjwa wenye dalili zilizomhsusi, alama, na majibu ya vipimo vya maabara na matokeo ya kikliniki anapotibiwa na muongozo wa ALMANCH uliruhusu kutathmini thamani ya kila tawi linalopendekezwa la muongozo kwene bawe vya afya vya awali. Hii ilisaidia kuamua umuhimu wa kubakiza, kubadili au kupunguza kila sehemu ya muongozo. Watoto wengi walikuwa na magonjwa yasio makali na wengi wao hawakuhitaji dawa dhidi ya vimelea vya bakteria ili kupona. ALMANCH imetengenzwa kwene misingi ya kitekolojia inayoruhusu upatikanaji rahisi, utumiaji wa haraka wa chati ya maamuzi na ina uwezoya kuboresha ubora na utumiaji wa wakati wa taarifa ya za kikliniki zinazkubelemwa wakati wa kutoa huduma katika ngazi zote za huduma za afya. Tafiti zaidi zinashauriwa kutathmini upembuzi wa kupanu matumizi kwa awamu ya ALMANCH iliyoobeshwa kwene vifaa vya kielektroni ili kuboresha matumizi sahihi ya dawa dhidi ya vimelea vya vijidudu na ubora wa huduma za afya kwa watoto kwene nchi zinazoelewa.
PART 1: BACKGROUND

Chapter 1: Introduction

1.0 Low compliance of clinicians to evidence-based recommendations for the management of childhood illness

About 7 million children under 5 years of age die each year despite the availability of effective low-cost interventions (Chopra et al., 2013). One reason for the continuing high rates of death in children below five 5 years of age is the poor quality of medical care that many children receive due to shortage of health personnel and the limited training that is often available in child health. In response to this toll, the World Health Organization (WHO) has developed the Integrated Management of Childhood Illness (IMCI) treatment algorithms which consist of an evidence based approach to the assessment, classification and treatment of the most common causes of childhood mortality. The impact of the effective use of IMCI has been documented in a series of multi-country evaluations done by the WHO (Bryce et al., 2004, Bryce et al., 2005) that conclude that IMCI has the potential to improve quality of care, reduce the cost of treatment, and reduce under-5 mortality when used correctly. This impact has also been shown in Tanzania (Armstrong Schellenberg et al., 2004a, Bryce et al., 2005).

However, there is a growing body of evidence that the actual impact of IMCI worldwide has been less than anticipated due to limited uptake of the intervention, especially among the world’s most poor (Victora et al., 2006). There are several reasons for this including the following:

- The cost and time for IMCI training (11-16 days of initial training is required) has limited their uptake worldwide. Further, the revision of algorithms as disease patterns and drug resistance change is limited since retraining and reprinting of all materials is required, which is expensive and difficult to organize. This means that outdated algorithms are often used well beyond the need for change; this is particularly detrimental when there are new evidence available requiring a change in one or more recommendations.

- The current practice of IMCI algorithms requires health workers to follow flow diagrams, understand and use accessory information on each page, and accurately flip through up to 8-10 pages of the chart booklet in front of the patient. In actual practice, most health workers decide not to use the chart booklets because it takes time and due to the embarrassment of using a chart booklet in front of patients.

As a result, in Tanzania and elsewhere health worker’s compliance to IMCI algorithms is uneven and often quite low, both in rural and urban setting (Walter et al., 2009, Horwood et al.,
2009, Armstrong Schellenberg et al., 2004a). A study in Papua New Guinea, where some of the earliest algorithms were developed, found that despite a correct diagnosis of malaria, and the existence of paper-based algorithms, only 11% of community health workers used the correct treatment (Beracochea et al., 1995). In Tanzania, health workers’ compliance to IMCI was found to be poor in terms of consultation time, use of job aids, space use and adherence to referral (Prosper et al., 2009).

1.1 Changes in disease patterns and drug resistance

During the past 20 years since the first IMCI protocols were developed, patterns of disease and drug resistance has changed dramatically but the IMCI protocols have not kept pace with these changes.

As an example, malaria among febrile children in Dar es Salaam has gone down dramatically since the 90’s due to improvements in sanitation and housing and the wider use of insecticide treated bed nets. This fall of malaria transmission has been observed in many countries in Africa (D’Acremont et al., 2010a, Ceesay et al., 2010, O’Meara et al., 2008). Further, the medicine of choice for treatment has gone from chloroquine and quinine which were inexpensive and relatively safe to artemether/lumefantrine (ALU) and artesunate which are more expensive. Despite the evidence that only 10% of children with fever in Dar es Salaam have malaria, all these children are still often treated for malaria at great expense and with the risk of not being treated for other potentially fatal diseases (Kahama-Maro et al., 2011). Moving from presumptive to confirmed malaria diagnosis in order to improve the rational use of medicines and slow down the emergence of antimalarial resistance, is highly needed and called for revision of IMCI (D’Acremont et al., 2009). Since 2010, WHO recommends, a parasitological diagnosis to all patients with malaria suspicion before treatment is started, including children below 5 years of age (WHO, 2010a).

For bacterial infections, there are similar changes. The global problem of antibiotic resistance is particularly pressing in developing countries, where the infectious disease burden is high and cost constraints prevent the widespread application of newer, more expensive agents (Okeke et al., 2005b). In Tanzania, recent evidences show that common microorganisms are multi-resistant to drugs recommended as first line treatment. For example, in 2007, all Shigella strains isolated from diarrhoea patients showed high level of resistance to ampicillin, tetracycline, co-trimoxazole and chloramphenicol; moreover, 5% and 2% were also resistant to amoxycilline-clavulanate and azithromycin respectively (Temu et al., 2007). Resistance of bacteria causing
Acute respiratory infections (ARI) has not been extensively studied. In a carriage study published in 2003, *S. pneumoniae* showed a level of resistance to co-trimoxazole of 47% and to penicillin of 21% (Batt et al., 2003). One half of community-acquired *Salmonella* were resistant to ampicillin and co-trimoxazole, the currently prescribed treatment in Tanzania. 90.6% of Diarrhoeagenic *Escherichia coli* (DEC) and 93.3% of Shigella are resistant to Cotrimoxazole (Moyo et al., 2011). Although the correlation between reduced antibiotic susceptibility *in vitro* and clinical response is not always straightforward, recent data from Tanzania show that bacterial resistance has indeed clinical implications since children infected with resistant microorganisms were more likely to die (Blomberg et al., 2007).

One reason for this increase in antibiotic resistance is the wide inappropriate use of antibiotics in clinical practice (Hart and Kariuki, 1998). Surveys on antibiotic use in developing countries show antibiotics are prescribed in 35 to 60% of clinical encounters although appropriate in less than 20% (Trostle, 1996). In Tanzania a recent study recorded that 78% of patients with fever attending the outpatient clinic and testing negative for malaria were given antibiotics, and this mainly in relation to ARI (D’Acremont et al., 2011). Although we know that the inappropriate use of antibiotics by health workers has led to dangerous widespread of drug resistance, the different approaches used to reverse this trend have been largely ineffective. In a systematic review of the effectiveness of all possible intervention to promote rational use of antibiotics (WHO and DMP., 2001), educational/training interventions successfully improved targeted antibiotic prescribing outcomes by only 20% and even these changes were not necessarily sustainable over time. A holistic strategy is needed to contain antibiotic resistance, and improvement of clinician compliance to evidence-based guidelines is one proposed component (Okeke et al., 2005a).

1.2 Availability of new technologies for accurate diagnosis and treatment

Two recent technologies have shown significant promise in improving both diagnosis and treatment for children with fever. One of the technologies is the introduction of Rapid Diagnostic Tests for Malaria (mRDTs) which demonstrate the ability to accurate diagnose malaria, both non immune (Marx et al., 2005) and semi-immune populations (Ochola et al., 2006), as well as in urban and rural Tanzania (Kahama-Maro et al., 2011). In two systematic reviews mRDTs performed as well (Marx et al., 2005), or even better than microscopy (Ochola et al., 2006, Kahama-Maro et al., 2011).
A second technology is the development and use of hand held electronic decision support that makes it easier and faster for health workers to accurately follow electronic IMCI (e-IMCI) algorithms in a clinical setting (DeRenzi et al., 2008). Guiding health workers step-by-step through the assessment, classification (diagnosis) and treatment of sick children in rural clinics in Tanzania using mobile device has showed that e-IMCI has the potential to improve compliance to procedures, and thus the quality of care (DeRenzi et al., 2008). Training time for e-IMCI was 20 minutes, after which clinicians were easily able to follow even complex algorithms. The clinicians unanimously preferred e-IMCI to following the paper chart booklet, citing it as faster and easier to use. This same technology is being tested for other diagnostic areas such as the screening of patients living with HIV/AIDS on treatment with antiretroviral therapy for infections or side effects of treatment (Mitchell et al., 2009).

In addition to these two technologies, other diagnostic tests and decision support algorithms are being developed. Rapid diagnostic tests for many causes of both childhood and adult illness may be available in a near future (see for example Bill and Melinda Gates Foundation Grand Challenges [http://www.gcgh.org/Pages/BrowseByTechnology.aspx#Diagnostics]). Incorporating these new technologies into electronic decision support algorithms will be much easier than into paper charts.
Chapter 2: Rationale
Poor compliance to paper-based algorithms by health care workers has led to about 7 million children dying before reaching the age of five years because of poor quality of health care (poor diagnosis and poor treatment) they receive. In addition, poor compliance to paper-based algorithms has led to huge wastage of medicines (unnecessary costs to caretakers and health systems) and rapid spread of resistance of microorganisms to antibiotics and antimalarials.

High costs due to long duration for training health workers on paper-based IMCI algorithms has contributed to poor compliance because health care systems lack enough resources to train required number of health care workers. This problem has been reported to affect poor countries. Whenever updates on changes in disease patterns and new recommendations on treatment are reported, changes in paper-based algorithms such as IMCI need to be updated, then printed and training conducted to all health care workers. Due to high costs, this exercise is not often done in many countries leading to health care workers using out of date paper-based algorithms. However, the use of electronic devices in pilot studies has shown to improve compliance of health care workers for paper-based algorithms. Following such results, different questions needed to be responded to before much more wide implementations of clinical algorithms using electronic devices for the management of childhood illness in primary health care settings. It is the objective of this thesis to provide responses to some of the questions raised.

The first question is more about finding out the best process to integrate the available evidence on child health and use it to design new clinical algorithm on paper and electronic support for the management of childhood illness. Such an understanding will provide potential information for guiding clinical guideline developers; program designers and policy makers to shift from developing paper-based algorithms to electronic decision supports based algorithms. The description on how this new tool was developed, its contents and the evidence behind it is provided in chapter five.

The second question is whether the use of new algorithm designed for management of childhood illness aged 2 months to 5 years with the objective of improving rational use of medicines (antibiotics and antimalarials) will be as safe as what routine practice, i.e. a vast proportion of children being treated with antimalarials and/or antibiotics. It was important to respond to this question because there is huge wastage of drugs especially antibiotics in relation to the decline in malaria. In addition, despite of the use of rapid diagnostic tests for malaria, most of febrile children testing negative for malaria were still given antibiotics. The
consequences of such practices are poor health outcomes and increase of resistance to microorganisms. The safety of the new algorithm is reported in chapter six where the clinical outcomes and antibiotics prescriptions of children managed using the new algorithm were compared to a similar control population of children managed following the current practice.

Since ALMANACH was derived from paper-based IMCI algorithms but improved to address rational use of medicines based on literature review, results of fever study conducted in Tanzania and discussions with IMCI experts, it was important to analyze the distribution of acutely ill children to various pathways of the new algorithm in order to determine the clinical relevance and usefulness of each recommended branch/pathway of the new algorithm. Such findings from data resulting from strict compliance by health care workers can provide useful information for recommendations on how to further improve the new algorithm for management of childhood illness for sustainable uptake and compliance by health care providers. The findings of such analysis are reported in chapter seven following a careful review of safety study data.

The fourth question is whether the new algorithm built on electronic device will be taken up smoothly by clinicians or will it face uptake challenges as any other new intervention when implemented in real life conditions. The use of electronic devices in pilot studies has shown to improve compliance of health care worker for paper-based algorithms (DeRenzi et al., 2008). However, it is not known whether the use electronic devices over time and in pragmatic conditions in primary health care facilities will improve compliance of health care workers to algorithms sustainably. For example, use of these new tools might fail to improve compliance and ultimately the quality of health care of children either because the health care workers do not like them, or because these algorithms are too complex to follow or too long to follow. The responses to such questions can guide health care programme design, guideline developers and policy makers to prepare and plan well in advance on how to mitigate potential uptake challenges of interventions which have shown success in controlled conditions. The facilitating as well as constraining factors for the uptake of the new algorithms for the management of childhood illness (ALMANACH) are discussed in chapter eight using a qualitative approach to understand the perspectives of primary health care workers when using the new algorithm on mobile devices during clinical consultations.
PART II: OBJECTIVES AND METHODOLOGY

Chapter 3: Goals and objectives

The present PhD thesis is part of the PeDiAtrick project, lead together with Dr Clotilde Rambaud-Althaus, Swiss PhD student, and will address some of the project's specific objectives describes below:

3.0 Goal
To improve the quality of health care for children in developing countries by making standardized diagnostic and treatments easily accessible to providers using electronic decision support systems, with a special emphasis on the rational use of antibiotics and antimalarials.

3.1 Specific objectives
3.1.1 To develop a new algorithm on paper and electronic support for the management of childhood based on literature review, results of fever study conducted in Tanzania and discussions with IMCI experts that aims to improve clinical outcome and rational use of antimalarial and antibiotics.

3.1.2 To assess whether the new algorithm for the management of childhood illnesses is equivalent in terms of health outcomes (safety) as routine practice and to assess the rate of antibiotic and antimalarial prescription.

3.1.3 To describe the distribution of acute ill children in to various pathways of the new algorithm for the management of childhood illness in order to improve in the future the overall algorithm relevance.

3.1.4 To identify potential barriers and facilitators for the uptake of the new algorithm on electronic support in programmatic conditions
Chapter 4: Methods

4.1 Study area and setting
The data used in this thesis were collected within the PeDiAtrick project which aimed at improving the quality of healthcare for Tanzanian children by assessing the use of electronic decision support to promote evidence-based medicine and rational use of drugs. The project was implemented in Dar es Salaam, the largest city in Tanzania, and in a rural area in Morogoro region, in south-eastern Tanzania. Detailed description of study area and setting is covered in chapter six, seven and eight of the thesis.

4.2 Thesis structure
The PeDiAtrick project was conducted sequentially in 3 phases and the structure of this thesis is based on those phases as described subsequently. In the first phase, a paper as well as an electronic version of a new algorithm for management of childhood illness (ALMANACH) was developed. The description on how this new tool was developed, its contents and the evidence behind is provided in chapter five. The second phase of the project comprised the safety assessment of the ALMANACH, as well as the evaluation of the relevance and usefulness of the various pathways (branches of new algorithm) through the analysis of data collected during the safety study. The description of safety assessment of the ALMANACH is covered in chapter six while the relevance and usefulness of each branch of the new algorithm is covered in chapter seven.

The third phase of the project had two components. The first component assessed the compliance of clinicians in routine conditions to the new algorithm for the assessment and treatment of children 2 months-5 years of age. This study component was conducted in randomly selected health facilities in urban Dar es Salaam and had 3 arms: i) one arm with training and use of new decision chart using paper support, ii) one arm with training and use of new decision chart using electronic support, iii) one control arm with IMCI or routine practice. This compliance component is part of Dr. Clotilde Rambaud-Althaus PhD thesis and will not be covered in this thesis. The second component assessed qualitatively the barriers as well as the facilitating factors related to the uptake of the electronic decision support with the new algorithm among the clinicians working in the intervention health facilities in Dar es Salaam. It is described in chapter eight of this thesis.
4.3 Study design and population

4.3.1 Development of ALMANACH, an evidence-based electronic algorithm to manage childhood illness
With an objective to design evidence based new algorithm for the management of childhood illness, a structured review of literature in Medline, Embase and Cochrane Database for Systematic review was conducted. This review looked for the available evidence on (i) disease prevalence in paediatric population, (ii) accuracy of clinical predictors and (iii) performance of point of care tests for the targeted diseases. The retrieved evidence was combined with results of fever study (aetiology of fever) conducted in Tanzanian children to design the ALMANACH.

4.3.2 Safety assessment of the new algorithm for management of childhood illness (ALMANACH)
We conducted a controlled non-inferiority trial to compare the clinical outcome of children managed according to ALMANACH or to standard practice. Consecutive children aged 2 to 59 months were included if they fulfilled the inclusion criteria: 1) first consultation for the current illness; 2) absence of severe illness requiring immediate life-saving procedures; 3) main complaint(s) not related to injury or trauma; 4) living in the catchment area of the HF and; 5) written informed consent by the caretaker. The primary outcome measures were: i) proportion of children cured at day 7, and ii) proportion of children who received antibiotics on day 0. Secondary outcome measures were i) proportion of children admitted secondarily or who died, ii) proportion of children who received antibiotics during the whole study period.

4.3.3 Assessment of the relevance and usefulness of various pathways of the new algorithm for the management of childhood illness
An investigation of the detailed pathway followed by the clinician to assess and manage the children included in the intervention arm (ALMANACH algorithm) was performed. An assessment of the relevance of each branch was then conducted. Detailed procedures are covered in chapter seven of the thesis.

Main outcome measures
Outcomes were i) proportions of children presenting with danger signs, with main symptoms and signs, ii) proportions of children who were prescribed antimicrobials, iii) clinical outcomes.
4.3.4 Assessment of the factors constraining and facilitating the uptake of the new algorithm for management of childhood illness (ALMANACH)

*Intervention*

Health workers (HWs) from 6 selected health facilities (HFs) in Dar es Salaam received ALMANACH training by the field investigators on the rational use of antibiotics and antimalarials using smartphones and tablets, and face-to-face supervision by the field investigators with several real patients onsite. In addition, user manuals on how to operate the smartphones and tablets were developed and given to each health facility for reference with training and face-to-face supervision.

During the use of smartphones and tablets in the field over the course of three months, a decrease in the number of cases sent to the server was observed (Figure 11 in chapter eight). The qualitative study which was carried out in Dar es Salaam between February and March 2012 (smartphones) and between September and October 2012 (tablets) was thus designed to investigate the determinants of uptake of these electronic devices to support clinical practice.

*Methods of evaluation*

We collected data using in-depth interviews and focus group discussion from clinicians who were involved in the project. The in-depth interviews were conducted by the author using a semi-structured and pilot tested interview guide in the local language, Kiswahili from 24 HWs (12 of the smartphone and 12 of the tablet arm).

In addition, at least 2 HWs from each of the 6 health facilities, who did not participate in the in-depth interviews, were invited to participate in focus group discussions.

*Main outcome measures*

Data analysis was based on content analysis (Mayring, 2000). ATLAS.ti version 6.0 software was used to code interview transcripts for identification of common themes. Emerging themes were debated by a multidisciplinary team involved in the study. Data from both arms (smartphones and tablets) were compared to gain insights into similarities as well as differences of barriers and facilitating factors related to the uptake of the new algorithm.

*4.4 Ethical consideration*

Written informed consent was obtained from the caretakers of every study participant after the caretaker was explained the purpose of the study, the risks and the benefits of the study.
For the qualitative assessment, each clinician who participated in the in-depth interview signed a written informed consent form after explaining the purpose, the risks and the benefits of the study.

The study was approved by the National Institute for Medical Research (NIMR) Review Board in Tanzania (NIMR/HQ/R.8a/Vol.IX/823). Approval was also provided by the institutional review boards of the University of Basel (EKBB) and the Ifakara Health Institute (IHI). All study participants provided written informed consent.
PART III: DEVELOPMENT OF THE NEW ALGORITHM AND ASSESSMENT OF THE SAFETY OF NEW ALGORITHM FOR MANAGEMENT OF CHILDHOOD ILLNESS (ALMANACH)

Chapter 5: Managing the sick child in the era of declining malaria transmission: development of ALMANACH, an electronic algorithm for appropriate use of antimicrobials

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Abstract

Objective:
To review the available knowledge on epidemiology and diagnoses of acute infections in children aged 2 to 59 months in primary care setting and develop an electronic algorithm for the Integrated Management of Childhood Illness to reach optimal clinical outcome and rational use of medicines.

Methods:
A structured literature review in Medline, Embase and the Cochrane Database of Systematic Review (CPRS) looked for available estimations of diseases prevalence in outpatients aged 2-59 months, and for available evidence on i) accuracy of clinical predictors, and ii) performance of point-of-care tests for targeted diseases. A new algorithm for the management of childhood illness (ALMANACH) was designed based on evidence retrieved and results of a study on etiologies of fever in Tanzanian children outpatients.

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

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

The rapid spread of resistant pathogens worldwide calls for urgent action to improve the rational use of antimicrobials. In low and middle income countries, where infectious diseases childhood mortality is high (Liu et al., 2012), substandard drugs, auto-medication and health workers (HWs)’ over-prescription of antimicrobials are driving the rapid spread of antimicrobial resistance (Mayor, 2010, World Health Organization, 2009). Recent experience in malaria case management has shown that using appropriate diagnostic tools (malaria rapid diagnostic tests – mRDT) has the potential to improve rational use of antimalarial (D’Acremont et al., 2011, Mselleme et al., 2009, Thiam et al., 2011) without negative impact on health outcome (Baiden et al., 2011, d’Acremont et al., 2010b, Mselleme et al., 2009, Mtov et al., 2011, Senn et al., 2012). Unfortunately it has often been accompanied with an increased antibiotics prescription (Baiden et al., 2011b, D’Acremont et al., 2011, Mselleme et al., 2009), reflecting the challenge faced by HWs in front of a negative malaria test result, where diagnostic tools and skills to rule out bacterial diseases are scarce.

To support HWs’ decision making in the management of a sick child in low resource settings, WHO and UNICEF have developed the Integrated Management of Childhood Illness (IMCI) clinical algorithm in the mid 90’s (Gove, 1997). The IMCI guidelines rely on the classification of patients based on clinical signs that can be recognized by trained HWs even if their educational background is limited (Gove, 1997); no laboratory test was included in the IMCI version of 2008: presumptive malaria treatment was recommended for all febrile children (in high malaria risks area). Other causes of fever were not considered (except if the child presented also a complaint leading to another branch of the algorithm). With the advent of new evidence on etiologies and management of childhood illness and reliable point-of-care tests (POCTs), there is a need to rethink the IMCI guidelines and to propose a new algorithm for the management of acute medical illness for children aged 2 to 59 months living in low resource settings. This new algorithm should integrate reliable POCTs and, when the latter are not available, clinical predictors for acute illnesses, so that guidance based on best available evidence is provided to clinicians to decide on withholding antimalarials and antibiotics when not beneficial to the child. When no tool or strong evidence is available to propose appropriate procedures, expert opinion should be sought.

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

**Materials and Methods**

**Structured literature reviews**

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

Medline (PubMed), Embase (Ovid), and the Cochrane Database of Systematic Reviews (CDSR) were explored from inception to December 31\textsuperscript{st} 2010, looking for articles assessing i) the prevalence of diseases and clinical features in U5 attending outpatient facilities in developing countries, and ii) the accuracy of diagnostic procedures for each of the targeted diseases. The detailed search strategy is described in Table 1.

Papers involving U5 managed for acute medical conditions in ambulatory settings were selected. Studies involving only infants below 3 months of age or only adults were excluded. For prevalence of syndromes and diseases at PHCF, studies describing the clinical presentation and/or diagnoses presented by U5 attending outpatients facilities in developing countries were selected. For diagnostic procedures of targeted diseases, studies assessing accuracy of either clinical predictors or POCT were chosen. Systematic reviews addressing the questions of interest were also considered. An additional hand searching of reference lists of selected papers completed these searches. In order to better explore the accuracy of the clinical diagnosis for pneumonia, a systematic review of the literature and meta-analyses of studies assessing the diagnostic accuracy of clinical predictors was conducted, reported elsewhere (Rambaud Althaus et al, submitted).
Table 1: Structured literature reviews: search strategy

<table>
<thead>
<tr>
<th>Pubmed</th>
<th>Embase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. &quot;primary health care&quot; OR &quot;outpatients&quot; OR</td>
<td></td>
</tr>
<tr>
<td>2. &quot;family practice&quot; OR &quot;emergency service&quot; OR</td>
<td></td>
</tr>
<tr>
<td>&quot;ambulatory care&quot;</td>
<td></td>
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<tr>
<td>2. &quot;fever/etiology&quot;[MeSH Terms] OR &quot;fever/diagnosis&quot;[MeSH Terms] OR</td>
<td></td>
</tr>
<tr>
<td>&quot;fever/epidemiology&quot;[MeSH Terms]</td>
<td></td>
</tr>
<tr>
<td>3. &quot;developing countries&quot;</td>
<td></td>
</tr>
<tr>
<td>4. prevalence OR epidemiology OR incidence</td>
<td></td>
</tr>
<tr>
<td>5. 'predictive value of tests'[MeSH Terms] OR</td>
<td>'diagnostic accuracy'/exp OR</td>
</tr>
<tr>
<td>&quot;sensitivity and specificity&quot;[MeSH Terms] OR</td>
<td>'predictor variable'/exp OR</td>
</tr>
<tr>
<td>&quot;reproducibility of results&quot;[MeSH Terms] OR diagnostic test OR</td>
<td></td>
</tr>
<tr>
<td>diagnostic tests OR</td>
<td></td>
</tr>
<tr>
<td>&quot;physical examination&quot;[MeSH Terms] OR &quot;medical history taking&quot;[MeSH</td>
<td></td>
</tr>
<tr>
<td>Terms]</td>
<td></td>
</tr>
<tr>
<td>6. &quot;pneumonia&quot;[MeSH Terms]</td>
<td>'pneumonia'/exp OR 'lower respiratory tract infection'/exp OR</td>
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<tr>
<td></td>
<td>'respiratory tract infection'/exp</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>7. &quot;typhoid fever&quot; [MeSH Terms]</td>
<td>'typhoid fever'/exp</td>
</tr>
<tr>
<td>8. &quot;urinary tract infections&quot;[MeSH Terms]</td>
<td>'urinary tract infection'/exp</td>
</tr>
<tr>
<td>9. &quot;otitis media&quot;[MeSH Terms]</td>
<td>'otitis media'/exp</td>
</tr>
<tr>
<td>10. &quot;shigella&quot;[MeSH Terms] OR &quot;dysentery&quot;[MeSH Terms]</td>
<td>'shigellosis'/exp</td>
</tr>
<tr>
<td>11. Filters: Infant: 1-23 months; Preschool Child: 2-5 years</td>
<td>'child'/exp</td>
</tr>
<tr>
<td>Diagnostics 6 AND 5 AND 11</td>
<td>7 AND 5 AND 11</td>
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<td>7 AND 5 AND 11</td>
<td>8 AND 5 AND 11</td>
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<td>10 AND 5 AND 11</td>
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<td>10 AND 5 AND 11</td>
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</table>

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

In a recently published study on etiologies of fever conducted in outpatient clinics in Tanzania (Tanzanian fever study), clinical assessments and laboratory tests were performed in 1005 febrile children aged 2 months to 10 years (95% were U5) to establish the most probable causes of fever (D'Acremont et al., 2014). The distribution of diagnoses, overall and stratified by age, was taken into account to select the targeted disease included in the final algorithm. The clinical predictors for the targeted diseases identified in the Tanzanian fever study were also used to build the new algorithm (De Santis et al, in preparation).
Algorithm construction
With the IMCI algorithm for children 2-59 months of age as departure point, the evidence retrieved from the SLRs and from the Tanzanian fever study was used to propose modifications and new recommendations when relevant, and to design a new decision tree. Diseases were included in the algorithm if they were treatable, and responsible for i) high child mortality and morbidity, ii) high attendance rate at outpatient facilities, and, iii) high antimicrobial prescription rate. Clinical features that could easily be assessed by HWs of varying background and POCT easy to deploy in low resource ambulatory settings were integrated in the classification procedures, when its use improved the classification accuracy. The treatment options proposed in ALMANACH were in line with the 2008 WHO IMCI (WHO, 2008) and the Tanzanian National Standard Treatment guidelines (Ministry of Health and Social Welfare, 2007) since the algorithm was intended to be used in Tanzania and had to comply with local policies. Once the new algorithm was finalized, both a paper booklet and an electronic software running on android smartphones and tablets were developed. For the paper booklet, the IMCI structure in 3 steps was kept - “Assess, Classify, and Treat” - , as well as the color-coded triage system: red for conditions that require urgent referral, orange for conditions requiring specific treatment, and green for condition needing simple counseling and symptomatic home management (Gove, 1997).

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

Selection of syndromes or diseases to be addressed by the algorithm
Estimations of burden of diseases by CHERG (Liu et al., 2012) and IHME (IHME, n.d., Lozano et al., 2012) reported that low respiratory tract infections/pneumonia, malaria, and diarrhea were the leading causes of child mortality in 2010, globally and in Sub Saharan Africa (SSA). These 3 infectious diseases were estimated to be responsible for more than 40% of U5 deaths in SSA. They were also the leading causes of morbidity, responsible for 41% of the total 2010 DALYs in SSA (IHME, n.d.) Other frequent causes of child mortality were HIV/AIDS (3.5 to 4% of U5 deaths in SSA (IHME, n.d., Liu et al., 2012), meningitis (3 to
4% (IHME, n.d., Liu et al., 2012), measles (1%) (IHME, n.d., Liu et al., 2012), and tuberculosis (0.8%). In infants aged 1 to 11 months, pertussis (2.8% of deaths in 1-11 months infant in SSA) and syphilis (2.3%) were also frequent causes of death (IHME, n.d.). In children aged 1 to 4 years, typhoid fever was estimated to be responsible for 0.6% of both DALYs and deaths, and bacterial skin diseases for 0.7% of DALYs, and 0.2% of deaths (IHME, n.d.).
### Table 2: Major changes in ALMANACH as compared to IMCI algorithm based on evidence and experts' opinion

<table>
<thead>
<tr>
<th>Location</th>
<th>Topic</th>
<th>IMCI</th>
<th>ALMANACH</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management of very severe diseases section</td>
<td>Very severe diseases</td>
<td>“A child with any general danger signs needs URGENT attention; complete the assessment and pre-referral treatment immediately so that referral is not delayed”</td>
<td>If the child has any general danger sign, HWs are not asked to complete the assessment of all symptoms, but rather to “Give pre-referral treatment and REFER URGENTLY”</td>
<td>To complete the assessment would delay pre-referral treatment, and impair prognosis. In presence of general danger sign, the priority is to give rapidly presumptive AB/AM treatment (Dellinger et al., 2008, Gaieski et al., 2010) and to refer to hospital, where further etiological investigations will allow adapting the treatment.</td>
</tr>
<tr>
<td>List of general danger signs</td>
<td>“Lethargic; Convulsing; Unable to drink/breastfeed; Vomits everything; History of convulsion”</td>
<td>“Convulsing; Lethargic; Unable to drink/breastfeed; Vomits everything; History of convulsion; Jaundice; Cyanosis; Stiff neck; Severe pallor; Severe wasting”</td>
<td>“Convulsing; Lethargic; Unable to drink/breastfeed; Vomits everything; History of convulsion; Jaundice; Cyanosis; Stiff neck; Severe pallor; Severe wasting”</td>
<td>Stiff neck, severe pallor, and severe wasting (assessed later on in IMCI) are part of the ALMANACH initial assessment, in order to facilitate and fasten the detection and management of very severe diseases. Jaundice and cyanosis that are strong predictors for serious bacterial diseases and severe respiratory conditions (DAcremont et al., 2014), have been added to the general danger signs.</td>
</tr>
<tr>
<td>Pre-referral treatment</td>
<td>Available in the “TREAT THE CHILD” section in the middle of the booklet</td>
<td>Available in the “Management of very severe diseases” section in the first pages of the booklet</td>
<td>To facilitate and fasten the management of severe patients, the first section “Management of very severe diseases” has all assessment, classification and treatment charts together.</td>
<td></td>
</tr>
<tr>
<td>Management of children with no general danger signs</td>
<td>Fever§ is one of the 4 “Main symptoms”.</td>
<td>Fever is a crossing point in ALMANACH: different recommendations are made for children (non-severe) with or without fever§.</td>
<td>In children having no underlying chronic condition, and no danger signs, only few bacterial infections should be considered. Apart from dysentery and soft tissue infection, antibiotics are not recommended in the treatment of non-severe non-febrile conditions in ALMANACH.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Classifications considered in the Fever chart are: “Very severe disease”, “Malaria” and “Measles”. Additional classification in Fever</td>
<td>Classifications considered in the Fever algorithm: “Malaria”, Acute respiratory infections, including “Pneumonia”; Diarrhea related</td>
<td>Classifications considered in the Fever algorithm: “Malaria”, Acute respiratory infections, including “Pneumonia”; Diarrhea related</td>
<td>Designing a specific chart for patients with fever allows considering more fever related classifications than in IMCI, thus to address relevant non-malaria fever. This design allow also to consider “ Likely Viral infections” after</td>
</tr>
<tr>
<td>Condition</td>
<td>Diagnosis</td>
<td>Management</td>
<td>Notes</td>
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<td>-------------------</td>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------</td>
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<tr>
<td><strong>Febrile chart</strong></td>
<td><strong>Malaria</strong></td>
<td>Presumptive diagnosis of malaria for all children with fever in high malaria risk contexts</td>
<td>Test-based malaria diagnosis is recommended, using mRDTs in all children with fever. Antimalarials only recommended in test positive patients. The accuracy, the performance and the safety (d'Acremont et al., 2010b) of a diagnostic strategy based on mRDTs have been evaluated and demonstrated in U5.</td>
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<tr>
<td><strong>Pneumonia</strong></td>
<td>Pneumonia diagnosis rely on increased respiratory rate (RR) above age specific threshold: 50 breath/min if aged 2-11 months; 40/min if aged 12-59 months</td>
<td>Pneumonia is considered in children aged 2-59 months, if they report the presence of fever and have a RR equal to or above 50 breaths/min</td>
<td>The need of antibiotics in children aged 2-59 months with non-severe pneumonia as defined in IMCI is questioned (Hazir et al., 2011). In children aged 12-59 months the gain in sensitivity doesn’t balance the loss of specificity for the diagnosis of pneumonia when using the threshold 40 instead of 50 breath/min. (see results section)</td>
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<tr>
<td><strong>Acute ear infection</strong></td>
<td>Oral antibiotics are recommended for “Acute ear infection” defined as either “ear pain” or “ear pus/discharge for less than 14 days”</td>
<td>Oral antibiotics are only recommended for children with fever and “ear pus/discharge for less than 14 days”</td>
<td>The need for antibiotics for otitis media is questioned (Sanders et al., 2010). Ear pain is a weak predictor of otitis media (Ingvarsson, 1982, Niemela et al., 1994, Uhari et al., 1995) especially in children below 2 years of age. AB are most useful for children with otitis media and ear discharge (Sanders et al., 2010).</td>
<td></td>
</tr>
<tr>
<td><strong>Skin and soft tissue infections</strong></td>
<td>Some guidance provided in an annex and not integrated with the complaints of the main algorithm</td>
<td>Referral to hospital is recommended for febrile skin lesions with a size &gt;4 cm or associated with red streaks or tender nodes, and for multiple abscesses. Local treatment and home management is recommended for impetigo and minor abscesses</td>
<td>Severe soft tissue infections require in hospital treatment and injectable antibiotics. Limited skin infections can be safely managed by topical treatment.</td>
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<tr>
<td><strong>Febrile chart for “Fever with no identified cause” after symptom charts assessment</strong></td>
<td><strong>Urinary tract infection</strong></td>
<td><strong>Considered in non-severe febrile children, under 2 years of age, with no primary focus identified; and in children, above 2 years of age, with dysuria. Urinalysis using a dipstick is recommended for the diagnostic.</strong></td>
<td><strong>UTI is most frequent in children under 2 years of age. Above 2 years of age, the specificity of dysuria symptoms is low. The accuracy and performance of dipstick for UTI diagnosis have been demonstrated. Dipsticks for pregnancy follow-up were already broadly available in PHCFs in Tanzania; dipsticks for urinalyses were available in Health Centers.</strong></td>
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<tr>
<td><strong>Typhoid fever</strong></td>
<td><strong>Not considered in IMCI</strong></td>
<td><strong>In non-severe febrile children above 2 years of age, with no primary focus identified, abdominal palpation is recommended. In presence of tenderness, a presumptive treatment for typhoid fever and invasive intestinal bacterial infections is recommended.</strong></td>
<td><strong>Typhoid fever and other invasive enteric infections are life threatening conditions. In low resource care facilities, HWs fear to miss these diagnoses and tend to overprescribe antibiotics to children with no identified causes of fever. In the Tanzanian fever study, abdominal tenderness was associated with invasive bacterial infections and typhoid (D’Acremont et al., 2014), in children above 2 years of age.</strong></td>
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</tr>
</tbody>
</table>

AB: antibiotics, AM: antimalarials, HW: health worker, IMCI: Integrated Management of Childhood Illness, PHCF: primary health care facility, U5: children under 5 years of age, UTI: urinary tract infection. $^\text{Fever is defined by either history of fever or axillary temperature above 37.5°C or child feels hot.}$
The SLR identified 22 articles assessing either symptoms or diagnoses distributions, or both, in children attending outpatient facilities in developing countries. In all selected papers assessing symptoms, fever (by history or measured, hereafter referred as fever), cough and diarrhea were the most frequent symptoms reported, respectively by 65 to 93% (Barat et al., 1999, Kolstad et al., 1997, Perkins et al., 1997, Rowe et al., 2007, Van Hemelrijck et al., 2009, Weber et al., 1997), 44 to 82% (Kolstad et al., 1997, Perkins et al., 1997, Rowe et al., 2007, Van Hemelrijck et al., 2009, Weber et al., 1997), and 22% to 45% (Kolstad et al., 1997, Perkins et al., 1997, Rowe et al., 2007) of children. Diseases of potential bacterial origin reported in the studies retrieved by the SLR were: pneumonia (reported in 5 to 30% of children (Animut et al., 2009, Chanda et al., 2009, D'Acremont et al., 2014, Factor et al., 2001, Khallaf et al., 1996, Kolstad et al., 1997, Njama-Meya et al., 2007, Perkins et al., 1997, Salaria and Singhi, 2003, Simoes et al., 1997, Van Hemelrijck et al., 2009, Weber et al., 1997), typhoid fever (3 to 13% (Animut et al., 2009, D'Acremont et al., 2014, Van Hemelrijck et al., 2009), dysentery (3 to 12% (Factor et al., 2001, Kolstad et al., 1997, Simoes et al., 1997), otitis media (2 to 12% (d'Acremont et al., 2010b, Factor et al., 2001, Khallaf et al., 1996, Kolstad et al., 1997, Njama-Meya et al., 2007, Perkins et al., 1997, Simoes et al., 1997, Weber et al., 1997), UTI (1 to 7% (D'Acremont et al., 2014, Downs, 1999, Factor et al., 2001, Njama-Meya et al., 2007, Shaikh et al., 2008, Van Hemelrijck et al., 2009); and meningitis (0 to 3% (Factor et al., 2001, Kolstad et al., 1997, Salaria and Singhi, 2003). Tonsillitis was reported in 1% of 1005 children in the Tanzanian fever study; all had a negative streptococcal diagnostic test (D'Acremont et al., 2014). Another study reported tonsillitis or pharyngitis in 10% of the children, but no streptococcal test was performed (Njama-Meya et al., 2007).

Among the bacterial infections frequently reported, only typhoid fever, UTI and tonsillitis were not yet addressed in IMCI. The fear of these 3 infections is often a reason to prescribe antibiotics in low resource setting. With regards to tonsillitis, early recognition and treatment of streptococcal tonsillitis is of high importance to prevent rheumatic fever and its complications, but prevalence of group A β-hemolytic streptococcus is much lower in U5 than in older children(Shaikh et al., 2010), and close to zero in children under 2 years of age (Woods et al., 1999). Moreover, acute rheumatic fever and rheumatic heart disease are rare in U5 (Carapetis et al., 2000, Tibazarwa et al., 2008). Therefore addressing streptococcal tonsillitis in the management of U5 was considered not to be necessary. UTI and typhoid fever were thus selected to be addressed in the new algorithm, together with the other diseases already addressed in IMCI.
Identification of severe illnesses
In the IMCI algorithm, urgent referral to hospital is recommended in the presence of any of 5 general danger signs (difficulty in drinking, repeated vomiting, had convulsion, lethargy or unconsciousness, convulsing) or in presence of any of the 8 symptom-related danger signs (danger sign related to fever: stiff neck; related to cough: stridor or chest indrawing; related to measles features: clouding of cornea or extensive mouth ulcers; related to malnutrition: severe wasting or oedema of both feet; related to pallor: severe palmar pallor). The usefulness of these IMCI referral criteria were evaluated in two studies (Paxton et al., 1996, Kalter et al., 1997). These studies estimated the accuracy of the presence of any of the danger signs to predict hospital referral. Estimates of sensitivity and specificity were 46% and 79% respectively in the Kenyan study (Paxton et al., 1996) and 86% and 64% respectively in the study conducted in Bangladesh (Kalter et al., 1997). In the Kenyan study, accuracy of these criteria to predict death in admitted U5 patients was also assessed (sensitivity 89%, specificity 44%) (Paxton et al., 1996). A systematic review for children in developed countries (Van den Bruel et al., 2010) has also identified reduced consciousness, convulsions, cyanosis, rapid breathing, and slow capillary refill as the strongest predictors of severe illness. Meningeal irritation was also a strong predictor of serious bacterial infection in 3 reported studies [likelihood ratio (LR) ranging from 2.57 to 275] (Van den Bruel et al., 2010). While reviewing the underlying evidence used to build the recommendations for referral in IMCI, only very few studies were identified. As for IMCI, one of the main aims of the present algorithm is to allow early identification and referral of children with severe conditions and serious bacterial infections; therefore, to ensure good sensitivity, all the IMCI referral criteria were kept although underlying evidence was scarce, and 2 signs predicting serious infections were added to the IMCI general danger signs, i.e. cyanosis that is broadly recognized as a sign of severe hypoxemia (Van den Bruel et al., 2010) and jaundice that was shown to be predictive of bacterial disease in the Tanzanian fever study (D’Acremont et al., 2014) and can also be associated with severe malaria (WHO, 2000). In order to improve and fasten the identification of severe patients, all general danger signs, were grouped together with stiff neck, severe wasting, and severe pallor at the beginning of the assessment chart, instead of having some of them included in the branches for each syndrome. Danger signs related to specific symptoms were kept within the symptoms related charts, such as chest indrawing with cough, or tender swelling behind the ear with ear problem. Children with general danger signs are classified as having ‘Very severe disease’. These children with general danger signs are at risk of severe sepsis. In ALMANACH, acknowledging that early antimicrobials can improve the outcome of these children prognosis (Dellinger et al., 2008, Gaieski et al., 2010),
and realizing that the full assessment would not modify this recommendation, a separate management chart was developed for patients with danger signs, allowing prompt presumptive treatments, and skipping assessment tasks that would only delay the rapid management and referral these children require.

**Malaria diagnosis**
Decline in the proportion of fevers due to malaria (D’Acremont et al., 2010a) together with the availability of easy-to-use, reliable POCTs—i.e. mRDTs—have driven the WHO recommendations to shift in 2010 from presumptive to test-based malaria case management (WHO, 2010a). The safety of a mRDT-based malaria case management in U5 has been demonstrated (d’Acremont et al., 2010b, Baiden et al., 2012, Faucher et al., 2010, Mtwe et al., 2011, Mubi et al., 2011, Senn et al., 2012). Several African countries have now changed their malaria diagnosis policy and adopted the use of mRDTs in their national programs. Following the new WHO malaria treatment guidelines, the use of mRDTs was integrated in present algorithm. mRDTs were also recently added officially to the WHO/UNICEF generic IMCI algorithm (WHO and UNICEF, 2014).

**Pneumonia diagnosis**
In a recent meta-analysis of clinical predictors for radiological pneumonia (Rambaud Althaus et al, submitted), the clinical features with the higher pooled LR were respiratory rate ≥50 breaths/min (LR 1.90; 95%CI 1.45-2.48), grunting (1.78; 1.10-2.88), lower chest indrawing (1.76; 0.86-3.58), and nasal flaring (1.75; 1.20-2.56). The best features to rule out the diagnosis (having the lowest pooled LR) were: no history of fever (0.53; 0.41-0.69), and respiratory rate ≥40 breaths/min (0.43; 0.23-0.83). Cough had also a low but heterogeneous LR (0.30; 0.09-0.96). The IMCI criterion for pneumonia classification, i.e. age-related fast breathing (≥50/min from 2 to 11 months, and ≥40/min from 12 to 59 months) showed low diagnostic performance in the meta-analysis, both to rule in the disease (presence of fast breathing had a pooled LR of 1.55 (0.44-5.42) and to rule it out (absence of fast breathing had a pooled LR- of 0.63 (0.16-2.55). In the Tanzanian fever study, the best predictors to rule in radiological pneumonia among all febrile children were difficult breathing (LR 7.9, 2.8-22.1), chest indrawing (7.1; 2.9-17.6), nasal flaring (7.0; 2.5-19.4), respiratory rate ≥50/min (6.1; 3.5-10.4) and abnormal chest auscultation (5.5; 3.7-8.1). No feature was good at ruling out the diagnosis. In the present algorithm, in the absence of a reliable point-of-care diagnostic test, we decided to combine the best available clinical predictors (history of fever, cough, difficult breathing and fast breathing),
except nasal flaring and grunting, and abnormal chest auscultation because most IMCI trained clinicians are not familiar with these features. Chest indrawing was kept but to decide on referral to hospital rather than to diagnose pneumonia, because of the relatively high proportion of these children that harbor hypoxemia (Subhi et al., 2009). Regarding fast breathing, because using an age-related threshold did not improve the diagnostic test accuracy in the meta-analysis (Rambaud Althaus et al, submitted), a single threshold of ≥50/min for all age groups was chosen; 50/min rather than 40/min was chosen to ensure a reasonable specificity, knowing that most of pneumonias in young children are due to viruses (Feikin et al., 2013). The recommendation in the present algorithm is thus to prescribe antibiotics for pneumonia to children with [history of fever or elevated temperature] AND [cough or difficult breathing] AND respiratory rate ≥50/min, regardless of the malaria test result.

**Otitis Media**

In the SLR 7 articles and a systematic review that addressed the question of the accuracy of symptoms and signs for the diagnosis of otitis media were retrieved (Coker et al., 2010). In these studies, some otoscopic signs were strongly associated with otitis media diagnosis (Coker et al., 2010), but in low resource settings otoscopy is not available in ambulatory care. Other symptoms, such as earache, ear rubbing, and fever, although reported as associated with otitis media in 4 old studies (LR 3.03 to 7.3 (Heikkinen and Ruuskanen, 1995, Niemela et al., 1994, Uhari et al., 1995), were not associated with this diagnosis when reported by parents of children aged 6 to 36 months attending primary care offices in a more recent study (Sanders et al., 2010). Otitis media is often a self-limiting condition in young children. The 2010 Coker (Coker et al., 2010) and Sanders’ Cochrane (Sanders et al., 2010) reviews, looking at available evidence of the benefit of antibiotic treatment for otitis media, report that there is little benefit (compared to placebo) and no evidence that antibiotics reduce complications or recurrence (Coker et al., 2010, Sanders et al., 2010). An individual patient data meta-analysis from 6 randomised trial reported that antibiotics were more beneficial in children aged less than 2 years with bilateral otitis media, and in those with both otitis media and otorrhoea. In children with otorrhoea, 60% of controls and 25% of those on antibiotics still had pain, fever or both at 3-7 days, with a rate difference of -36% (95%CI -53% to -19%) and a number needed to treat of 3, whereas in children without otorrhoea the rate difference and NNT were respectively -14% (-23% to -5%) and 8 (Rovers et al., 2006).
Otitis media being often a self-limiting condition in young children, in the absence of accurate non-otoscopic clinical predictors the new algorithm propose to limit antibiotic prescription to children presenting with ear discharge.

**Urinary tract infection**

Two articles and 12 reviews assessing the accuracy of clinical predictors for the diagnosis of UTI in children were retrieved from the SLR. No additional article since the most recent review published in 2007 was found (Shaikh et al., 2007). The following predictors were identified: temperature >40°C (2 studies, LR 3.3; 1.3-8.3 (Hoberman et al., 1993) and LR 3.2; 0.7-15.6 (Krober et al., 1985), jaundice (LR 2.1; 0.3-17.4) (Musa-Aisien et al., 2003), and suprapubic tenderness (LR 4.4; 1.6-12.4) (Shaw et al., 1998). The absence of another source of fever on examination increased the probability of UTI (3 studies, summary LR 2.8; 1.9-4.3) (Shaikh et al., 2007). Among children ≥2 years, abdominal pain (LR: 6.3; 2.5-16.0) (Musa-Aisien et al., 2003), dysuria (LR 2.4; 1.8-3.1) (Heale, 1973) and new-onset of urinary incontinence (LR 4.6; 2.8-7.6) (Heale, 1973) also increased the probability of UTI.

In the Tanzanian fever study, the following predictors to rule in UTI were found: pollakiuria (LR 3.5; 1.4-8.8), temperature >40°C (3.1; 1.4-7.1), fever for more than 3 days (2.1; 1.2-3.6) and age<2 years (1.4, 1.22-1.57); the best predictors to exclude UTI were: age≥3 years (LR 0.22; 0.07-0.66), headache (0.27; 0.04-1.89) and diarrhea (0.33; 0.08-1.32) (De Santis et al, in preparation). Based on these predictors, several national and international guidelines recommend to consider this condition in febrile children below 2 years of age, with no obvious cause of fever (Downs, 1999, WHO, 2005b). No symptom or sign, nor combination of them is predictive enough in this age group to appropriately identify children with UTI. The gold standard (urine culture) is generally not available in low resources ambulatory setting. Urinalysis with urine dipsticks detecting leucocyte esterase and nitrite has been evaluated in many settings: 4 systematic reviews with meta-analyses estimated sensitivities for leucocyte esterase and/or nitrites to be 81% (Whiting et al., 2005), 88% (Gorelick and Shaw, 1999, Williams et al., 2010), and 93% (Downs, 1999) and specificities 72% (Downs, 1999), 79% (Williams et al., 2010), 93% (Gorelick and Shaw, 1999) and 97% (Whiting et al., 2005). A dipstick urinalysis negative for both nitrites and leukocyte esterase had a LR of 0.2 (95% CI, 0.16-0.26) (Shaikh et al., 2007). With either leucocyte esterase or nitrite positive the LR was 6.1 (95% CI, 4.3-8.6), increasing to 28 (95% CI, 17-46) when both leucocyte esterase and nitrite were positive (Whiting et al., 2005). In 2005, the WHO department of Child and Adolescent Health and Development recommended the use of urinalysis by urine dipstick for the diagnosis of UTI in children wherever dipstick were
feasible (WHO, 2005b). With the implementation of the WHO focused antenatal care guidelines, urine dipstick for proteinuria detection have been implemented and are thus available in PHCFs in many African countries. Based on the good diagnostic performance of urine dipstick, and its feasibility in low resource setting, the new algorithm proposes to perform urine dipstick for the diagnostic of UTI in the patients at higher risk of UTI, i.e. children below 2 years of age having fever with no cause identified during the assessment (but regardless of the malaria test result, due to the possibility that the parasites might only correspond to an incidental infection and not the actual cause of the acute illness). For children from 2 to 5 years of age, only those complaining of dysuria are proposed a dipstick urinalysis. Antibiotic treatment for UTI is recommended when either leucocyte esterase or nitrite, or both are positive.

**Typhoid fever**

Regarding the diagnosis of enteric fever, 6 articles assessing clinical predictors of enteric fever were retrieved (Davis et al., 1999, Hosoglu et al., 2006, Khan et al., 1998, Kuvandik et al., 2009, Neopane et al., 2006, Vollaard et al., 2005). Only 2 were conducted in outpatients: one included patients above 15 years of age (Hosoglu et al., 2006) and the other patients above 4 years of age (Vollaard et al., 2005). None of the studies thus included our target population of U5 outpatients. In the Tanzanian fever study (D’Acremont et al., 2014), the following predictors to rule in typhoid where identified: liver pain (LR 9.8; 2.7-35.5), abdominal tenderness (7.0; 3.3-15.2), jaundice (6.2; 3.1-12.4) and age >2 years (2.0; 1.6-2.4). To rule out typhoid, only ‘not during rainy season’ was predictive (LR 0.50; 0.27-0.92) (De Santis et al, in preparation). Jaundice being already included as danger sign and liver pain being difficult to assess in a child, the new algorithm recommends looking for abdominal tenderness in children ≥2 years of age having fever with no cause identified during the child’s assessment (regardless of the malaria test result). When present, antibiotic treatment for typhoid fever is indicated.

**Likely viral infection**

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

**Design of the algorithm**

Based on the modifications and adjunctions to IMCI that were retained, a new algorithm for the management of childhood illnesses (ALMANACH) was designed. Efforts were made to keep the ALMANACH structure simple and graphically easy to follow by HWs. Therefore the IMCI 3 steps assessment and color codes were kept. However, in order to increase the number of conditions addressed, ALMANACH has been divided into 3 charts. The first chart provides recommendations for assessment of general danger signs and management of severe patients, the second chart provides recommendations for patients with fever, and the last one for patients without fever (see Figure 2 for an overview of ALMANACH’s structure).

This 3-charts structure allows i) fastening the assessment and management of severe children, for whom all recommendations are available in the very first part of the algorithm and ii) a more comprehensive and specific assessment of children, with pneumonia, malaria, UTI and typhoid fever being considered only in febrile children. In the IMCI algorithm, fever is one of the main symptoms. The IMCI fever box only considers malaria and measles for a child with acute fever (≤7 days) without danger signs. Within ALMANACH, the aim was to address non-malaria fever causes. Although parts of the algorithms, such as the diarrhea chart, are the same in both the ‘febrile’ and ‘non-febrile’ algorithms, replacing the fever box by a full algorithm for children with fever or history of fever was necessary to propose meaningful considerations of fever causes in sequential pathways, allowing considering some conditions in a subset of patients only. In addition, this categorization allowed limiting antibiotic treatment in children without fever or history of fever.
Figure 2. An overview of the ALMANACH’s structure

ALMANACH was first designed as a paper booklet (Figure 3), it was then developed as an android application for smartphones, coding the different steps of the algorithm into a Java-Rosa X form run by OpenDataKit and OpenMRS software (Open Data Kit, n.d., OpenMRS, n.d.). The electronic ALMANACH (e-ALMANACH) guides HWs through the child’s assessment up to the classification and treatment recommendations (Figure 4). Treatment dosages are computed according to the body weight or age when weight is not available. Moreover e-ALMANACH collects in real time information on child demographic characteristics, disease classification and treatment prescribed. This information is stored by the mobile device, can be sent to a server and feed health information systems.
Discussion
The aim of ALMANACH is to provide guidance to health workers on antimicrobial prescription, in order to treat only children aged 2 to 59 months who will potentially benefit from them. Apart from malaria, IMCI was not directly addressing causes of fever, leaving HWs with their fear of life-threatening conditions once malaria was ruled out by mRDT. On the other hand, viral infections that represent the vast majority of the causes of fever in U5 children (D’Acremont et al., 2014) are never explicitly mentioned or proposed as diagnosis in IMCI, giving a wrong impression to health workers that bacterial infections are frequent and that children should often be prescribed antibiotics. Using the best available and feasible diagnostic procedures for the main causes of acute illness in children attending PHCFs, the present new algorithm should address most of the concerns of HWs regarding bacterial infections and remind them that children often suffer from self-limited viral conditions that do not warrant any specific treatment beside antipyretics. By providing tools to rule out malaria, UTI, and typhoid fever and by proposing a new ‘Likely viral infection’ classification, the use of ALMANACH has thus the potential to improve the health outcome of febrile children and at the same time decrease unnecessary antimalarial and antibiotic prescriptions. The content of ALMANACH was based on literature reviews and expert opinions. The level of evidence provided by the literature was generally low and no formal process was followed to reach a broad expert consensus. Within the current project, only the POCTs currently available in low resource settings were considered, constraining the new algorithm to rely mostly on the best available simple clinical predictors. To further improve the quality of the management of pediatric illnesses and the rational use of medicines, accurate and affordable POCTs for bacterial or even viral infections are highly needed.

While broadening the spectrum of diseases to be addressed, the algorithm became more complex than IMCI. This might be an issue for the targeted audience, i.e. HWs of different background working in low resource ambulatory settings. In order to facilitate understanding and usability of the decision chart, the 3 steps IMCI structure (Assess, Classify and Treat) and the color coded triage, already known by IMCI trained HWs, were kept. Electronic algorithms, by guiding HWs step by step through the algorithm, allow to using a more complex structure with lower risk of misuse. The electronic version of ALMANACH running on smartphones and tablets was designed to address these needs.

Although ALMANACH broadened the spectrum of diseases addressed in the algorithm, some aspects of childhood illness were left uncovered. Indeed ALMANACH does not provide recommendations for the management of chronic or non-infectious conditions.
A. Assessment: Cough in febrile children

B. Assessment: Fever

C. Management: recommendations for cough related classifications

Figure 3. Samples of ALMANACH in the paper booklet form
Figure 4. Samples of ALMANACH in the electronic form
Within the current project, only identifiable and treatable acute infections were targeted because the objective was to improve the use of antimicrobials in order to tackle both the risk of resistance development due to their overuse and the high childhood mortality related to infectious diseases.

Because the algorithm was meant for remote PHCF, full algorithms for the management of severe conditions, for HIV-infected and/or malnourished children were not developed; only recommendations on how to identify children suffering from these conditions and advice to refer them to the second level of care were provided. We foresee that developing and integrating additional algorithms for the management of these conditions, but also for other patients, either at primary or secondary level of health care systems, would allow further improvement of the quality of health services, but also better acceptability of the tool by HWs. However this was out of the scope of the present project. The paper and electronic ALMANACH have the potential to improve the management of the sick child. This has been demonstrated in a recently completed feasibility study, which showed the ALMANACH algorithm to improve health outcome of children managed with this tool and to drastically reduce antibiotic prescription (Shao et al, companion paper submitted). These results were obtained in two settings, urban and rural, albeit with a limited number of patients enrolled. They do not represent a definite validation of ALMANACH, but show great promise and should invite researchers to further explore the potentials of this new approach for a rational management of children aged 2-59 months. Further improvement could be brought by integrating other POCT detecting key pathogens once they become available, or even better, by integrating host biomarkers able to predict children in need of antibiotics or at risk of dying.

**Conclusion**

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

**Acknowledgement**

We would like to thank Wilson Were, MD and Mario Gehri, MD for useful discussions and comments on the content and design of the clinical algorithm, and Fabrice Althaus for his participation to the literature reviews and input on methodology.
Chapter 6: New algorithm for managing childhood illness using mobile technology (ALMANACH): a controlled non-inferiority study on clinical outcome and antibiotic use in Tanzania

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Abstract
Introduction
The decline of malaria and scale-up of rapid diagnostic tests calls for a revision of IMCI. A new algorithm (ALMANACH) running on mobile technology was developed based on the latest evidence. The objective was to ensure that ALMANACH was safe, while keeping a low rate of antibiotic prescription.

Methods
Consecutive children aged 2-59 months with acute illness were managed using ALMANACH (2 intervention facilities), or standard practice (2 control facilities) in Tanzania. Primary outcomes were proportion of children cured at day 7 and who received antibiotics on day 0.

Results
130/842 (15.4%) in ALMANACH and 241/623 (38.7%) in control arm were diagnosed with an infection in need for antibiotic, while 3.8% and 9.6% had malaria. 815/838 (97.3%; 96.1-98.4%) were cured at D7 using ALMANACH versus 573/623 (92.0%; 89.8-94.1%) using standard practice (p<0.001). Of 23 children not cured at D7 using ALMANACH, 44% had skin problems, 30% pneumonia, 26% upper respiratory infection and 13% likely viral infection at D0. Secondary hospitalization occurred for one child using ALMANACH and one who eventually died using standard practice. At D0, antibiotics were prescribed to 15.4% (12.9-17.9%) using ALMANACH versus 84.3% (81.4-87.1%) using standard practice (p<0.001). 2.3% (1.3-3.3) versus 3.2% (1.8-4.6%) received an antibiotic secondarily.

Conclusion
Management of children using ALMANACH improve clinical outcome and reduce antibiotic prescription by 80%. This was achieved through more accurate diagnoses and hence better identification of children in need of antibiotic treatment or not. The building on mobile technology allows easy access and rapid update of the decision chart.
Background
About 7 million children under 5 years of age die each year despite the availability of effective low-cost interventions (Chopra et al., 2013). The Integrated Management of Childhood Illness (IMCI) strategy developed by the World Health Organization (WHO), UNICEF and other partners in mid 1990s (Gove, 1997) could potentially prevent two-thirds of these deaths (Claeson et al., 2003). To date, IMCI is still a good tool and studies that assessed its impact showed borderline reduction of childhood mortality (Armstrong Schellenberg et al., 2004b). When health workers were trained to use IMCI, their performance in case management improved (Gouws et al., 2004, Nguyen et al., 2013), although cautious interpretation is needed due to heterogeneities in methodologies of assessment (Nguyen et al., 2013). Worldwide, the impact of IMCI has been less than expected due to health system challenges, such as shortage of health workers (Bryan et al., 2006, Munga and Maestad, 2009, Dominic A and Kurowski C, 2005), poor motivation and lack of supervision (Maestad et al., 2010, Huicho et al., 2005). All this leads to low compliance to the IMCI guidelines (Kelley et al., 2001, Simoes et al., 1997, Camara et al., 2008) and probably poorer health outcomes than it could be.

IMCI is facing additional challenges. First, a precise evaluation of the clinical outcome of children when managed with the IMCI algorithm is lacking, which leaves a doubt about its real benefit. Some studies evaluated the clinical outcome of children with specific diseases or conditions, such as severe pneumonia at peripheral health facilities (Chowdhury et al., 2008, Hazir et al., 2008, Soofi et al., 2012) or malaria and pneumonia at community level (Mukanga et al., 2012, Hamer et al., 2012). These studies also demonstrated that effectively trained and supervised community health workers using malaria rapid diagnostic tests (mRDTs) with (Mukanga et al., 2012), or without (Hamer et al., 2012) respiratory rate (RR) timers could adequately classify and treat children less than 5 years with malaria and/or pneumonia at community level. The overuse of antimalarials was limited, but varying degrees of antibiotics over-prescription were observed (Mukanga et al., 2012). Secondly, patterns of disease and drug resistance have evolved dramatically in the last 20 years. The prevalence of malaria has considerably declined in the last decade across different settings (D’Acremont et al., 2010a). While mRDT has just been incorporated in the new IMCI version (MoHSW. et al., 2013), many national IMCI guidelines still recommend to treat presumptively all febrile children with antimalarials. Third, since the advent of mRDT, the proportion of patients receiving antibiotics has increased (D’Acremont et al., 2011, Batwala et al., 2011, Msellem et al., 2009), probably because clinicians have not enough guidance on how to proceed when mRDTs results are
negative. The new IMCI guidelines do not include precise guidance on typhoid fever, urinary tract infections (UTI) or other causes of unspecific fever. Even if these conditions might have limited impact on mortality, they are feared by primary health care clinicians who often prescribe antibiotics to prevent potential complications.

Based on the IMCI algorithm, a review of the literature, and the results of an etiology of fever study conducted in Tanzania (D’Acremont et al., 2014), a novel ALgorithm for the MANAgement of CHildhood illness (ALMANACH) was developed (Rambaud Althaus et al, submitted). This algorithm was primarily aimed at decreasing unnecessary prescription of antibiotics in children, while ensuring same or even better clinical outcome compared to routine practice (non inferiority trial). The objective of the present study was to measure the impact of its use on clinical outcome and antibiotic prescription in children attending primary care facilities in rural and urban settings of Tanzania.

Materials and Methods

Study sites and subjects
The study was conducted as part of a larger project which aimed at improving the quality of care and rational use of medicines for children in Tanzania (PeDiAtrick project, registration number PACTR201011000262218 at www.pactr.org). For the present study, two pairs (one from urban Dar es Salaam and one from the rural Morogoro region) of two nearby primary care health facilities (HF), similar in terms of natural environment, malaria prevalence, socio-economic status of the catchment population, and type of services available, were conveniently selected. Then, in Dar es Salaam, Ilala municipality (city center), Buguruni was randomly selected as intervention and Vingunguti as control HF; in Morogoro region, Kilombero district, Signal was selected as intervention and Mangula as control. We chose to conduct the study in different health facilities rather than to use a parallel design or recruit consecutively patients in the same health facility because the latter increased the risk of including patients with different disease frequency between the intervention (ALMANACH) and routine practice arms due to seasonal variation. There was also the risk of biased results due to contamination between arms because clinicians would have gained a better understanding of disease classification or change their behaviour in terms of antimicrobial prescription because of the ALMANACH training and use. Consecutive children aged 2 to 59 months were enrolled by trained study nurse if they fulfilled the inclusion criteria: 1) first consultation for the current illness; 2) absence of severe illness
requiring immediate life-saving procedures; 3) main complaint(s) not related to injury or trauma; 4) living in the catchment area of the HF and; 5) written informed consent by the caretaker.

**Study design and procedures**
A controlled non-inferiority trial was conducted to compare the clinical outcome of children managed according to ALMANACH or to standard practice. Children enrolled in the intervention arm were managed by two study clinicians (one for each setting) who were trained to strictly comply with the ALMANACH algorithm, which was available on paper at the start of the study and used in the first 100 patients, and then built in an electronic support (smartphone running Open MRS) and used for the remaining 742 patients. Both versions were identical. In the control arm, children were attended by the usual HF clinicians, of which about 80% had been trained for IMCI (Adam et al., 2005). In general, this training had taken place several years before, and compliance to guidelines was known to be rather poor, with most patients receiving antibiotics, especially when tested negative for malaria (D’Acremont et al., 2011). mRDT and commonly prescribed medicines were made available throughout the study period in both arms. During the one-month pilot phase, study clinicians in the ALMANACH arm received face-to-face supervision with several real patients to check their ability to identify all relevant signs, including RR measurement. In the control arm, no algorithm, training or supervision was performed. Observing study clinician obtained oral consent from the routine clinician and observed the consultation to record key information such as symptoms, signs, laboratory investigation(s) performed, diagnosis(es), advice to caretakers and treatment(s) prescribed. He was instructed not to interfere with the consultation to avoid introducing additional bias to the observer effect.

**Ethics Statement**
All procedures followed the Good Clinical Practice guidelines. The study protocol and related documents were approved by Ethikkommission beider Basel in Switzerland, by the Institutional Review Board of the Ifakara Health Institute and by the National Institute for Medical Research Review Board in Tanzania (NIMR/HQ/R.8a/Vol.IX/823).

**Content of the ALMANACH algorithm**
The development and content of ALMANACH is described in another paper (Rambaud-Althaus et al, submitted). In brief, this new algorithm was based on IMCI, but differed on some key features presented in Table 3.

**Management of children during spontaneous re-attendance**
In the intervention arm, caretakers were informed to bring the child back to the study HF if he/she was not able to drink or breastfeed, became sicker, developed fever, fast or difficult
breathing, or blood in stool. During working hours, sick children were reassessed by the study clinician, and managed again according to ALMANACH. Out of working hours, children were managed by routine clinicians who were asked to record demographic data, laboratory results, diagnoses, treatments and need for referral in order to hand them back to the study clinician the day after. In the control arm, children were advised on when to come back and managed during re-attendance at the discretion of the routine clinician, who were asked to record the same information on the re-attendances and to hand them back to the study team. In both arms, information regarding visits to other health facilities than the study facilities, and on additional treatment received, was recorded during the follow-up visit at day 7.

Follow-up of children at day 7 and 14
Caretakers in both arms were asked to bring back their child on day 7 to assess if he/she was cured or not. Children were declared cured if the caretaker reported the child to be well. All children reported as not cured were attended by the clinician and managed again according to ALMANACH in the intervention arm and to usual practice in the control one. When the child had not recovered at day 7, caretakers were asked to return on day 14 for a new assessment. caretakers whose children did not turn up at day 7 were reminded by phone about the visit and, if not reached, visited at home.

Data collection, management and analysis
In the intervention arm, a standardized case report form (CRF) was completed during the paper phase of the study. Data collection included demographics, all relevant symptoms and signs, laboratory investigation(s), diagnosis(es), advice and treatment(s) received. During the electronic phase (smartphone), a shorter version of the CRF was used not to repeat data that were automatically sent to the server when running through the decision chart. In the control arm, the observing study clinician filled another CRF that included all relevant information mentioned above. The CRFs were adapted from the health facility survey checklist questionnaire developed by WHO (WHO, 2003).
Beside data sent directly from the smartphone to the server, all information was double-entered in Epi-info software version 3·5·3 (CDC Atlanta, USA). Data management and analysis were done using STATA software version 10·1 (College Station, Texas, USA).
### Table 3: Key differences the IMCI and the new Algorithm for the MANAgement of Childhood illness (ALMANACH) (section dedicated to the management of acute conditions in children aged 2 months to 5 years)

<table>
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<tr>
<th></th>
<th>IMCI algorithm</th>
<th>New algorithm (ALMANACH)</th>
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| **Danger signs** | 5 danger signs managed at the start: unable to drink or breastfeed; lethargic or unconscious; vomits everything; convulsing now or has had convulsions  
Six additional danger signs assessed later: stridor; chest indrawing; sunken eyes; skin pinch goes back very slowly; stiff neck; tender swelling behind ear | 10 danger signs managed at the start: unable to drink or breastfeed; lethargic or unconscious; jaundice; vomits everything; convulsing now or has had convulsions; cyanosis; severe pallor; stiff neck and severe wasting  
Six additional danger signs assessed later: stridor; chest indrawing; sunken eyes; skin pinch goes back very slowly; stiff neck; tender swelling behind ear; infected skin lesion or lump larger than 4 cm or with red streaks or with tender nodes or multiple abscesses |
| **Fever**        | 1 out of 4 Main symptoms                                                           | A dividing point between a febrile branch and a non-febrile branch                     |
| **Pneumonia**    | Cough + fast breathing<sup>a</sup>                                                | Fever + cough + very fast breathing<sup>b</sup>                                        |
| **Urinary Tract Infection** | Not considered                 | Febrile child<2 years with no source identified at this point<sup>c</sup>, and with a positive (leucocytes or nitrites) urine dipstick. |
| **Typhoid fever** | Not considered                                                                       | Febrile child ≥2 years with no source identified at this point<sup>c</sup>, and with abdominal tenderness |
| **Likely viral infection** | Not existing                                                                      | Febrile child with no classification at the end of the algorithm                       |

**Legend:**

- <sup>a</sup> 50 breaths/min for children aged 2 to 12 months, 40 breaths/min for children aged 12 months to 5 years.
- <sup>b</sup> 50 breaths/min for all children (aged 2 months to 5 years).
- <sup>c</sup> No cough or difficult breathing, no diarrhea, no ear problem, no measles, no infected skin lesion or lump.

The primary outcome measures were: i) proportion of children cured at day 7, and ii) proportion of children who received antibiotics on day 0. Secondary outcome measures were i) proportion of children admitted secondarily or who died, ii) proportion of children who received antibiotics.
during the whole study period. The above proportions were compared between the intervention and control group using Chi-square test and, when appropriate, Fisher exact test.

To calculate the sample size, we assumed that 95% of children managed with standard practice would be cured on day 7 (d’Acremont et al., 2010b). To show non-inferiority of the intervention arm with a 3% margin, 80% power and 0.05 level of significance, and using a ratio of 3:2 in order to have more patients in the intervention arm, we calculated that 816 patients in the intervention and 544 in the control arm were needed. Taking into account a 3% rate of loss to follow-up, the target sample size was thus 840 and 560 patients in the intervention and control arms respectively.

Results

Status at inclusion

Between December 2010 and June 2011, 1467 children (median age 14 months) were enrolled, 844 (523 in the urban and 321 in the rural setting) in the ALMANACH and 623 (353 in the urban and 270 in the rural setting) in the standard practice arm. Two children were then excluded, one because he was not visiting the health facility for the first time for the current problem, and one who was <2 months of age. Baseline characteristics of patients included are presented in Table 4.

The diagnoses distribution in the ALMANACH and standard practice arms are featured in Figure 5 respectively. Acute respiratory infections (ARI), either alone or in combination with another condition besides malaria, accounted for 57% and 58% of the diagnoses in intervention and control arms. However, the classification within respiratory infections was quite different between arms: 10.3% (95%CI 8.3-12.4%) were classified as having pneumonia in the ALMANACH arm while 18.5% (15.4-21.5%) as having pneumonia and 17.0% (14.1-20.2%) as having ARI (a diagnosis given by routine clinicians when they did not classify further the respiratory infection but for which they tended to prescribe antibiotics) in the standard practice arm. Only 1.0% (0.1-1.2%) in the ALMANACH versus 12.0% (9.3-14.4%) in the standard practice arm were classified as having UTI. 3.8% (2.5-5.1%) were diagnosed with malaria alone or in combination with another diagnosis in the ALMANACH versus 9.6% (7.3-12.0%) in the standard practice arm, despite full availability of mRDT in all HFs.
Table 4. Baseline characteristics of the patients in the intervention (ALMANACH) and control (standard practice) arms

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ALMANACH</th>
<th>Standard practice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N   %</td>
<td>n/N   %</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>407/842 48·3</td>
<td>300/623 48·2</td>
</tr>
<tr>
<td>Age (in months)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2-12</td>
<td>426/842 50·6</td>
<td>241/623 38·7</td>
</tr>
<tr>
<td>13-24</td>
<td>216/842 25·7</td>
<td>174/623 27·9</td>
</tr>
<tr>
<td>25-36</td>
<td>106/842 12·6</td>
<td>89/623 14·3</td>
</tr>
<tr>
<td>37-48</td>
<td>64/842 7·6</td>
<td>81/623 13·0</td>
</tr>
<tr>
<td>49-59</td>
<td>30/842 3·6</td>
<td>38/623 6·1</td>
</tr>
<tr>
<td>Main symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>571/842 67·8</td>
<td>511/623 82·0</td>
</tr>
<tr>
<td>Cough</td>
<td>498/842 59·1</td>
<td>355/623 57·0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>184/842 21·9</td>
<td>76/623 12·2</td>
</tr>
<tr>
<td>Vomitting</td>
<td>57/842 6·8</td>
<td>78/623 12·5</td>
</tr>
<tr>
<td>Ear problem</td>
<td>14/842 1·7</td>
<td>13/623 2·0</td>
</tr>
<tr>
<td>Fast breathing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50 breaths per minute</td>
<td>100/351 28·5</td>
<td>42/310 13·6</td>
</tr>
<tr>
<td>Danger signs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lethargic</td>
<td>1/842 0·1</td>
<td>5/623 0·8</td>
</tr>
<tr>
<td>Vomiting everything</td>
<td>0/842 0</td>
<td>1/623 0</td>
</tr>
<tr>
<td>Unable to drink/breastfeed</td>
<td>0/842 0</td>
<td>2/623 0</td>
</tr>
<tr>
<td>History of convulsion</td>
<td>0/842 0</td>
<td>2/623 0</td>
</tr>
<tr>
<td>Hospitalization at inclusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Admission on day 0*</td>
<td>3/842 0·4</td>
<td>21/623 3·4</td>
</tr>
</tbody>
</table>

*The control health facility of the rural area (Mang’ula Health Center) had a higher number of admissions on day zero because of the possibility to admit patients on site (unlike the intervention rural health facility (Signal Dispensary).

Clinical outcome

Cure rate at day 7 and 14

0·5% (4/842) of children in the ALMANACH and 0·2% (1/623) in the standard practice arm were lost of follow-up. 97·3% children managed with ALMANACH were cured on day 7 versus 92·0% by standard practice (p<0·001) (Table 5). In the ALMANACH arm, of the 23 children not cured at day 7, 11 received an antibiotic on day 7; 22 were cured on day 14 and one on day 28 (Figure 6). 10 of these 23 (44%) children had been diagnosed at inclusion with skin problems,
either alone or in combination with another diagnosis, 7 (30%) with pneumonia, 7 (30%) with URTI, 3 (13%) with likely viral infection outside URTI, and one patient with acute ear infection (Table 6). In the control arm, of the 50 children not cured on day 7, 48 children were cured on day 14, one child died and one was lost of follow-up (Figure 6).

Among diagnoses found in at least 10 children at inclusion, pneumonia (7/101=7.0%), skin conditions alone (5/84=6.0%) and multiple conditions not requiring antibiotics (4/81=4.9%) were the conditions leading to the highest proportions of clinical failure at day 7 in the ALMANACH arm, and ARI (13/119=11.0%), skin conditions (3/28=11.0%) and diarrhea (3/33=9.0%) in the standard practice arm.

Figure 5. Distribution of diagnoses at the inclusion in the ALMANACH (A) and the standard practice (B) arms.

*Diagnosis given by clinicians when they do not classify further the respiratory infections
Table 5. Clinical outcome and antimicrobials prescribed in children managed by ALMANACH and standard practice

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>ALMANACH</th>
<th></th>
<th>Standard practice</th>
<th></th>
<th>p-value</th>
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<tr>
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<td>n/N</td>
<td>%</td>
<td>95%CI</td>
<td>n/N</td>
<td>95%CI</td>
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<td><strong>Clinical outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cured on day 7</td>
<td>815/838</td>
<td>97·3</td>
<td>96·1-98·4</td>
<td>573/623</td>
<td>92·0</td>
</tr>
<tr>
<td>Cured on Day 14</td>
<td>837/838</td>
<td>99·9</td>
<td>96·6-100·1</td>
<td>621/622</td>
<td>99·8</td>
</tr>
<tr>
<td><strong>Antimicrobials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prescribed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>On day 0</td>
<td>130/842</td>
<td>15·4</td>
<td>12·9-17·9</td>
<td>525/623</td>
<td>84·3</td>
</tr>
<tr>
<td>Between day 0 and 7</td>
<td>19/838</td>
<td>2·3*</td>
<td>1·3-3·3</td>
<td>20/623</td>
<td>3·2</td>
</tr>
<tr>
<td>On day 7</td>
<td>11/838</td>
<td>1·3</td>
<td>0·7-2·3</td>
<td>0/623</td>
<td>0</td>
</tr>
<tr>
<td>Total (at any day)</td>
<td>160/838</td>
<td>19·0</td>
<td>16·3-21·6</td>
<td>545/623</td>
<td>87·5</td>
</tr>
</tbody>
</table>

* 10 patients received antibiotics from study clinicians during working hours and 9 from routine clinicians out of working hours

**Complications**

Of the 838 children managed with ALMANACH, one child with likely viral infection on day 0 was brought by the caretaker on day 5 to a referral hospital where he was diagnosed with cellulitis. He was hospitalized for 10 days, received antibiotics and had recovered when visited on day 28. Of the 623 children managed by standard practice, two children were hospitalized secondarily. One had diarrhoea on day 0 and received cotrimoxazole, oral rehydration salt and zinc tablets. At day 3 he was brought to the same HF and diagnosed with severe dehydration. He was admitted for one day, received ringer lactate intravenously and was discharged the next day. At day 7 he had recovered. The other child was diagnosed with pneumonia on day 0, received benzyl penicillin and amoxicillin, and was sent home. He was brought 5 days later to another HF where he was admitted for the same diagnosis and died 4 days later (see Figure 6).
Table 6. Characteristics of the 23 patients who were not cured at day 7 in the ALMANACH arm

URTI=Upper respiratory tract infection, RR=respiratory rate, NA=not available

<table>
<thead>
<tr>
<th>N°</th>
<th>Age (month)</th>
<th>Diagnosis at day 0</th>
<th>RR at day 0</th>
<th>Antibiotic prescribed on day 0</th>
<th>Diagnosis at day 7</th>
<th>Antibiotic prescribed on day 7</th>
<th>Hospitalized</th>
<th>Cured at day 14</th>
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<td>1</td>
<td>2</td>
<td>Severe pneumonia</td>
<td>NA</td>
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<td>Pneumonia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>Pneumonia</td>
<td>52</td>
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<td>Pneumonia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>Pneumonia</td>
<td>55</td>
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<td>Pneumonia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>Pneumonia</td>
<td>NA</td>
<td>Yes</td>
<td>URTI and dysentery</td>
<td>Yes</td>
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<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>12</td>
<td>Pneumonia</td>
<td>53</td>
<td>Yes</td>
<td>URTI and diarrhoea</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>13</td>
<td>Pneumonia</td>
<td>66</td>
<td>Yes</td>
<td>URTI</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>Pneumonia and impetigo</td>
<td>NA</td>
<td>Yes</td>
<td>Infected heat rashes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>23</td>
<td>URTI</td>
<td>NA</td>
<td>No</td>
<td>Diarrhoea</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>URTI</td>
<td>NA</td>
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<td>URTI</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
<td>URTI</td>
<td>NA</td>
<td>No</td>
<td>Diarrhoea</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>URTI and impetigo</td>
<td>32</td>
<td>No</td>
<td>URTI and soft tissue infection</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>12</td>
<td>10</td>
<td>URTI and impetigo</td>
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<td>36</td>
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<td>No</td>
<td>Yes</td>
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<td>14</td>
<td>10</td>
<td>URTI and scabies</td>
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<td>Pneumonia</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
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<tr>
<td>15</td>
<td>12</td>
<td>Impetigo</td>
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<td>No</td>
<td>Soft tissue infection</td>
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<td>Yes</td>
</tr>
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<td>16</td>
<td>16</td>
<td>Impetigo</td>
<td>No</td>
<td>No</td>
<td>Soft tissue infection</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
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<td>17</td>
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<td>Infected skin rashes</td>
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<td>No</td>
<td>Skin abscess</td>
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<td>Yes</td>
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<td>3</td>
<td>Scabies</td>
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<td>No</td>
<td>URTI</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
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<td>Fungal infection</td>
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</tr>
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<td>URTI</td>
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<td>No</td>
<td>URTI</td>
<td>No</td>
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<td>Yes</td>
</tr>
<tr>
<td>22*</td>
<td>11</td>
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<td>No</td>
<td>Cellulitis</td>
<td>Yes</td>
<td>Yes</td>
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<td>23</td>
<td>38</td>
<td>Acute ear infection</td>
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<td>No</td>
<td>Acute ear discharge</td>
<td>Yes</td>
<td>No</td>
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</tbody>
</table>

* This patient is the same as patient n°8 in Table 7. He was secondarily admitted for cellulitis on day 5, received antibiotics on admission, was discharged after 10 days and was cured on day 28.
Spontaneous attendance before day 7

4.2% of children (35/838) in the ALMANACH and 5.1% (32/623) in the standard practice arm re-attended spontaneously between day 0 and 7 (p=0.4). In the intervention arm, 19 (2.3%) patients were secondarily prescribed an antibiotic, 10 because of pneumonia, 5 diarrhea, 2 UTI, 1 cellulitis and one tonsillitis (Table 7). All were cured at day 7, except the one who was hospitalized with cellulitis. Among 8 children who developed pneumonia secondarily, 6 were <12 months and had a RR at inclusion between 36 and 48/min, and 2 were ≥12 months and one had a RR of 42 (not measured for the other child due to absence of cough). On the other hand, 30 children ≥12 months with a RR between 40 and 50/min at inclusion did not develop pneumonia, and were cured at D7 without antibiotic.
Table 7. Characteristics of the 19 patients who received antibiotics during re-attendance in the ALMANACH arm

<table>
<thead>
<tr>
<th>No</th>
<th>Age (month)</th>
<th>Diagnosis at day 0</th>
<th>Respiratory rate at day 0</th>
<th>Antibiotic prescribed on day 0</th>
<th>Clinician who prescribed antibiotics*</th>
<th>Diagnosis at re-attendance visit</th>
<th>Cured at day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Pneumonia</td>
<td>53</td>
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<td>Study</td>
<td>Pneumonia</td>
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</tr>
<tr>
<td>2</td>
<td>8</td>
<td>Pneumonia</td>
<td>NA</td>
<td>Yes</td>
<td>Routine</td>
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<td>Yes</td>
</tr>
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<td>10</td>
<td>Pneumonia</td>
<td>52</td>
<td>Yes</td>
<td>Study</td>
<td>UTI</td>
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<tr>
<td>4</td>
<td>8</td>
<td>Pneumonia and measles</td>
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<td>Yes</td>
<td>Routine</td>
<td>Diarrhoea</td>
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<td>Study</td>
<td>Tonsillitis</td>
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<td>8*</td>
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<td>37</td>
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<td>No</td>
<td>Routine</td>
<td>Diarrhoea</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Out of working hours, the patient was evaluated and managed by a routine clinician of the HF rather than the study clinician. *This patient is the same as patient n°22 in Table 6

**Treatment prescribed**

15.4% (130/842) of children managed with ALMANACH received antibiotics on day 0 compared to 84.3% (525/623) by standard practice (p<0.001). In the ALMANACH arm, only 19 (2.3%) and 11 (1.3%) children out of 842 received antibiotics secondarily, during spontaneous attendance and visit at day 7 respectively. The cumulative proportion of children prescribed antibiotics over the whole follow-up period (on day 0, between day 0 and day 7 and on day 7) was 19.0% in the intervention versus 87.5% in the control arm (p<0.001) (Table 5). In the
ALMANACH arm, the diagnoses at inclusion present in at least 10 patients for which antibiotics were most frequently prescribed secondarily were pneumonia (8/101=7.9%), likely viral infection (6/96=6.3%) and skin problem (4/84=4.8%).

Discussion
When strictly applied, the new ALMANACH algorithm resulted in better clinical outcome than standard practice, and in 80% reduction of antibiotics prescribed to children with acute illness. These improvements are probably due to a better identification of children with likely viral infection, and hence not needing antibiotics, while still identifying those with bacterial infections, or at least those who were likely to benefit from antibiotics.

The rate of clinical failure with ALMANACH was expected to be equivalent to that of the control arm, because the standard practice in Tanzania is to prescribe antibiotics to most of the febrile patients, especially when mRDT are available (D’Acremont et al., 2011). One could have even expected more failures with ALMANACH since the algorithm withholds antibiotics (compared to IMCI) in frequent clinical situations such as cough and RR between 40 and 50/min in children ≥12 months, or for children without a classification at the end of the algorithm (likely viral infection). On the contrary, we observed a better cure rate with ALMANACH, probably because clinicians were able to better identify and treat children with possible bacterial infection. Moreover, the better outcome at day 7 was neither at the price of a higher rate of spontaneous re-attendance, nor of secondary prescription of antibiotics. These rates were indeed almost identical in both arms. These findings suggest that significant bacterial infections were not missed when using ALMANACH, which is the big fear of clinicians and their main reason to give antibiotics. They often wrongly believe that antibiotics prevent secondary bacterial infections. Their behavior is also due to clinical guidelines that are often ambiguous, including the latest 2014 version of IMCI that recommends to ‘Give appropriate antibiotic treatment for an identified bacterial cause of fever’ to febrile children that are negative for malaria (WHO and UNICEF, 2014). Such a recommendation has a high risk to increase over-prescription of antibiotics. Policy makers sometimes argue that children will not be brought back if their condition worsens, because of long distance from home to health facilities, lack of transport and of cash money etc. The good clinical outcome observed in the intervention arm suggests that caretakers did come back when their child was worse, maybe because of clear messages given by clinicians. The present study thus demonstrates that giving antibiotics to all children at first place to prevent re-
attendances or complications is not worth; it does not improve clinical outcome, provided the few children who need antibiotics are accurately identified.

Giving unnecessary antibiotics does have deleterious consequences, namely the rapid spread of bacterial resistance, unnecessary adverse drug reactions, and unnecessary cost. In Tanzania, high levels of antibiotic resistance have already been reported (Temu et al., 2007, Moyo et al., 2011). Also, children infected with resistant microorganisms are more likely to die (Blomberg et al., 2007). Unfortunately the different approaches to reduce antibiotic prescription have been largely ineffective. In a systematic review, educational/training interventions successfully improved targeted antibiotic prescribing outcomes by only 20%, and these changes were not sustainable over time (WHO and DMP., 2001). Holistic strategies are needed to contain antibiotic resistance, including the use of electronic decision support to improve clinician’s compliance to guidelines. Such a strategy using electronic algorithms for the management of childhood illness in a rural dispensary in Tanzania showed promises (DeRenzi et al., 2008). The next step is thus to further evaluate this electronic ALMANACH in programmatic conditions.

Clinical failure and/or secondary antibiotic prescription according to diagnosis type in ALMANACH arm

Among children managed using ALMANACH, the diagnosis that led to the highest rate of clinical failure was pneumonia (7%), which also led to the highest rate of secondary antibiotic prescription (8%). In contrast, URTI was rarely associated with clinical failures (1 %) or secondary antibiotic prescription (2%). Because the vast majority of ARI are located in the upper tract and of viral origin, these children do not require antibiotics and cure by themselves. In young children, even most of lower respiratory tract infections, including pneumonias, are due to viruses and will thus not improve with the provision of antibiotics. This also explains why a significant number of these patients were not cured at day 7.

The second diagnosis that led to the highest rate of clinical failure (6%) and secondary antibiotic prescription (5%) was skin conditions. Skin problems are not included in the main algorithm of IMCI algorithm. Half of the skin problems were mild infections such as impetigo that had worsened enough to require antibiotics at day 7. The other half corresponded to skin problems that took longer than 7 days to cure such as fungal infection or stable impetigo, but that did not require secondary antibiotics.
A ‘likely viral infection’ was the third diagnosis that led to a relatively high rate (6%) of secondary antibiotic prescription, but to a rather low rate (3%) of clinical failure at day 7. Antibiotics were given during follow-up because of the emergence of various conditions such as pneumonia, tonsillitis, UTI, cellulitis and diarrhea. This diversity shows that it is not possible to predict at day 0 if, and what these children may develop in the following days. The only safe and rational solution is thus to evaluate them again when they do not improve. The aim of an efficient clinical algorithm is indeed not to have zero follow-up visits, but rather to have no child dying because of a delay once antibiotic are required. The message to bring the child back in case of persisting or worsening condition, or emergence of a new health problem seems to have been followed appropriately, as only one child has been secondarily admitted. When used wisely, it prevents a lot of unnecessary prescription of antibiotics during first clinical encounter.

**Limitations of the study**

One can argue that the appropriate control arm would have been a perfectly complied to IMCI algorithm. However, no study on the clinical outcome of children strictly managed according to IMCI has been performed in the past, so such results could not be used as gold standard. Also a perfectly implemented IMCI does not exist, which shows its limitation in terms of feasibility. We opted thus for the use of IMCI in real life conditions (routine practice) for the control arm to assess more precisely the public health benefit of the ALMANACH.

The new algorithm was implemented in controlled conditions, which is a necessary step before implementation in routine conditions. Its real impact, which should directly depend on the level of uptake and compliance by clinicians, needs to be precisely evaluated. We already performed this step in a study investigating health worker’s performance when using ALMANACH in pragmatic conditions (reported in Rambaud-Althaus et al, submitted).

No formal assessment of health worker satisfaction when using electronic devices was made in the present study. Previous findings from a pilot study conducted in Tanzania assessing the use of electronic IMCI showed that clinicians were enthusiastic to use it. However, this was not enough justification to believe that the clinicians would indeed follow the “standard practice ALMANACH” better than standard/routine practice. We also performed subsequently a qualitative study to assess health workers’ perception on barriers and facilitators for uptake of the ALMANACH algorithm in pragmatic conditions over time (reported in Shao et al, submitted).
Conclusion

The new ALMANACH algorithm for the management of childhood illness, primarily aimed at the rational use of antimicrobials, improved clinical outcome and led to a drastic reduction of unnecessary antibiotic prescription when compared to standard practice. This achievement was related to more precise diagnoses and better identification of children with infections that required and did not require antibiotics. These results, obtained in both urban and rural places, are probably generalizable for most locations in Sub-Saharan Africa, and even wider, since the distribution of diagnoses in small children does not vary so much across regions and over-prescription of antibiotics is a widespread problem in low resource settings (WHO, 2013). The building on mobile technology allowed easy access for clinicians and rapid update of the decision chart when new recommendations are put in place. Further studies are underway to assess the appropriateness and feasibility of using this electronic algorithm in routine practice.

Acknowledgements

The study was part of PeDiAtrick project which aimed to improve the quality of health care and rational use of medicines for children in Tanzania. This study would not have been possible without the great collaboration of all district medical officers, caretakers and patients who participated in this study.
PART IV: DIAGNOSTIC POTENTIALS OF THE NEW ALGORITHM FOR MANAGEMENT OF CHILDHOOD ILLNESS (ALMANACH)

Chapter 7: Clinical presentation and outcome of children managed by the different branches of a new electronic algorithm for the management of childhood illness (ALMANACH)

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3 This is a working paper to be submitted after being reviewed by co-authors
Abstract

Background

Clinical algorithms are rarely assessed in detail in terms of distribution of children in the various branches, antimicrobials prescription and clinical outcome. This information is essential to be able to evaluate their usefulness when applied to the target audience and patient population, and hence for their optimization. A new ALgorithm for the MANAgement of CHildhood illness (ALMANACH) built on an electronic support was developed and implemented in primary care facilities. This study aimed at examining for each branch of the algorithm: i) the distribution of patients according to their symptoms and signs, ii) the number of rapid tests performed, iii) the number of antimicrobial treatment prescribed and iii) the clinical outcome at day 7.

Methods

Data collected between December 2010 and June 2011 from acutely ill children aged 2-59 months attending primary care facilities in urban and rural Tanzania were analysed. All children were prospectively included, managed by clinicians strictly following the ALMANACH algorithm, and followed-up at day 7 (or in-between if necessary) to assess if cured or not.

Results

842 consecutive patients were assessed. 0.1% (1/842) of children had general danger signs. 67.8% (571/842) entered the fever, 59.1% the cough, 21.9% the diarrhoea and 14.5% the skin problems branches. 0.3% (1/351) of patients with fever and cough had lower chest indrawing. 71.5% (251/351) of them had a final classification of upper respiratory tract infection and 28.5% (100/351) of pneumonia. 5.6% (32/570) patients, for whom a malaria rapid diagnostic test was performed, had malaria. 7.1% (6/85) patients for whom a urine dipstick was performed had a positive result. None of the 32 patients, in whom abdominal tenderness (considered as predictive for typhoid fever) was searched for, presented this sign. On day 0, 1.9% (5/271) of non-febrile patients received antibiotics compared to 21.9% (125/571) of febrile patients. Day 7 cure rate in febrile and non-febrile patients was 97.2% and 97.4% respectively.

Conclusions

A vast majority of children had mild illnesses and most of them did not require antibiotics to be cured. A detailed count of patients with defined symptoms, signs, laboratory test results, and clinical outcome of patients managed by ALMANACH allowed to precisely assessing the value of each of the proposed branches of the algorithm in a primary care setting, and hence to decide on the relevance of keeping, modifying or deleting each of the algorithm component.
Keywords Clinical decision support, IMCI, algorithm, guidelines, primary care, Tanzania, electronic decision support, mobile technology
Background
In the mid 1990's WHO and UNICEF developed decision charts for the Integrated Management of Childhood Illness (IMCI) to address causes of childhood mortality (Gove, 1997). When used correctly, the IMCI algorithm has shown to reduce childhood mortality (Armstrong Schellenberg et al., 2004b), improve the quality of care and reduce cost of treatment (Bryce et al., 2004, Gouws et al., 2004, Armstrong Schellenberg et al., 2004a, Bryce et al., 2005). However, expected health impact due to IMCI has been less than anticipated because of low compliance of health workers (Simoes et al., 1997, Kelley et al., 2001, Camara et al., 2008, Walter et al., 2009). Expensive training costs for paper based IMCI algorithms (WHO, 2003) and the perception by the health care workers that IMCI chart booklet takes too long during consultation (DeRenzi et al., 2008) have contributed to the low compliance to these guidelines.

Efforts to improve compliance to IMCI algorithms includes programming paper IMCI chart booklet into an electronic algorithm (DeRenzi et al., 2008). A pilot study assessing the electronic IMCI (e-IMCI) showed potential for improving compliance of health care workers during clinical encounters (DeRenzi et al., 2008). Health workers were enthusiastic to use e-IMCI (DeRenzi et al., 2008) and reported positive perceptions towards the use of electronic algorithms (Mitchell et al., 2012a). They commented that they simplify their work in terms of clinical examination, diagnosis and treatment choices (Shao AF et al, submitted). A new algorithm for the management of childhood illness (ALMANACH) aimed at a rational use of antimicrobials while ensuring good health outcome has been developed (Rambiaud-Althaus et al, submitted) and evaluated under controlled conditions. The study showed better cure rates together with a drastic reduction of antibiotic prescription compared to routine practice (Shao AF et al, submitted). However, implementation of this new algorithm faced uptake challenges mainly because of the existing health system constraints (few health care workers, lack of motivation among the health care worker etc) and incompressible consultation time (Shao AF et al, submitted). In order to correctly manage a sick child, clinicians need to spend enough time with each patient in order to go through all the branches of the decision chart (Horwood et al., 2009). It is thus essential to avoid asking the unnecessary questions or checking the irrelevant clinical signs for a particular medical situation to gain time. Algorithms should thus only include the specific questions and signs that allow identifying quickly and reliably the few patients who need life-saving interventions and referral, while sending back home those who have a mild disease with, or most of the time without antibiotics or antimalarials. In order to know which elements or branches of the new ALMANACH algorithm were useful or not, we explored in detail the distribution of patients managed through various parts of the algorithm. To our knowledge, this
type of evaluation has never been undertaken in an integrated way for the IMCI algorithm. The aim of the present study was to find out the final diagnostic classification(s), the need for antimicrobial prescription and the clinical outcomes of febrile and non-febrile children managed using each branch of the ALMANACH algorithm. The expected output was to end up with an algorithm that is as simple as possible while keeping its ability to identify patients at risk of bad outcome, who need specific attention or care.

Material and Methods

ALMANACH algorithm

The ALgorithm for the MANAgement of CHildhood illness (ALMANACH) is derived from the IMCI algorithm but includes new classifications as well as specific signs or rapid diagnostic tests to guide antimicrobial prescription. The development and exact content of the ALMANACH algorithm have been described elsewhere (Rambaud-Althaus et al, submitted). The main differences between IMCI and ALMANACH are summarized in columns 2 and 3 of Table 8.

Study area and population

The study population consisted of acutely ill children aged 2-59 months attending primary health care facilities in urban Dar es Salaam (Buguruni) and rural Morogoro (Signal) between December 2010 and June 2011. Patients were the same as those involved in the PeDiAtrick clinical study whose methods have been described elsewhere (Shao AF et al, submitted). Vaccination against Hib and pneumococcus were introduced in 2009 and 2010 in Tanzania respectively.

Study procedures

Two trained study clinicians applied the ALMANACH algorithm to all presenting children. Briefly, 10 general danger signs were assessed, namely convulsions, lethargy/unconscious, history of convulsions, severe pallor, severe wasting, jaundice, cyanosis, stiff neck, child being unable to drink/breastfeed and vomiting everything. Then, the main complaint was recorded and clinicians asked for the other key symptoms, namely fever, cough or difficult breathing, diarrhoea, ear problem, measles and skin problem. Each symptom or sign leads the clinician to a specific pathway in the algorithm to reach one or more diagnostic classification(s) and the corresponding appropriate treatment(s) (Rambaud-Althaus et al, submitted). The new algorithm was first used as a paper form and then on an electronic support (smart-phone).
Data management and analysis

Paper phase data were double entered in Epi Info software version 3.5.3 (Center for Disease Control and Prevention, Atlanta, GA, USA). Smartphone's data were recorded directly by the server. Number and proportions of patients with symptoms and signs, their diagnostic classification, antibiotic prescription and clinical outcome at day 7 (and at day 14 if not cured at day 7) were calculated. Re-attendances, secondary antimicrobial prescriptions, secondary hospitalisations and deaths were also analysed. Data management and analysis were done using STATA software version 10.1 (StataCorp, College Station, Texas, USA).

Ethical clearance

All procedures followed the Good Clinical Practice guidelines. The study protocol and related documents were approved by Ethikkommission beider Basel in Switzerland, by the Institutional Review Board of Ifakara Health Institute and by the National Institute for Medical Research Review Board in Tanzania.

Role of the funding body

The sponsor of the study (Swiss National Science Foundation) had no role in study design, data collection, data analysis, interpretation or writing of the report.

Results

A total of 842 consecutive patients aged 2-59 months (median age 14 months) were enrolled. 407 (48.3%) were females. 522 (62.0%) were enrolled in the urban setting and the others in the rural setting. One (0.1%) patient had one or more general danger signs. The distribution of patients with one or more main complaints in the febrile and non-febrile branches of the algorithm is provided in Figure 7. 600/841 (72.3%) had one of the key symptoms while 110/841 (13.1%) had two. 570/841 (67.8%) had a history of fever, of which 124 (21.8%) had no other complaint. There was no difference in the proportion of clinical failure at day 7 between febrile (16/570=2.8%) and non-febrile (7/271=2.6%) patients (p=0.85).

The distribution of patients with the key symptoms in the febrile and non-febrile branches, the respective proportion of those who received antibiotics on day 0 or secondarily, and their clinical outcome on day 7 are provided in Figure 8. Out of 841 patients, 498 (59.2%) had cough, of which 351 (70.5%) had also fever. No patient with cough had difficulty in breathing, stridor, wheezing or prolonged cough for 3 or more weeks. No patient who was found to have fast breathing during the first count of the respiratory rate was found not to have it during the second count 5 to 10 minutes later. 184/841 (21.9%) had diarrhoea, of which 127 (69.0%) had also
fever. No patient had diarrhoea for 14 days or more. No patient was lethargic/unconscious, not able to drink or drinking poorly, with skin going back very slowly or slowly, or restless/irritable. 14/841 (1.7%) had ear problems, of which 12 (85.7%) had also fever. 9 of the latter had also pus discharge. No patients had tender swelling behind the ear. 11/841 (1.3%) had measles, all of them being febrile. None of them had clouding of the cornea, deep or extensive mouth ulcers, or pus draining from eyes or mouth ulcers. 122/841 (14.5%) had skin problems, of which 44 (36.1%) had also fever. The highest number of children, who received antibiotics at day 0 were among those with fever and cough (116), followed by those with fever and diarrhea (15) and fever and ear problem (9). For children prescribed antibiotics secondarily, it was among children with fever and cough (14), fever without any other symptom (7) and fever with skin problem (4). The highest number of children not cured at day 7 was among those with fever and cough (11), with fever and skin problem (5) and with skin problem without fever (5).

The distribution of patients with the diagnostic classifications, the proportion who received antibiotics on day 0 or secondarily, as well as their clinical outcome on day 7 are provided in Table 9. 588 out of 841 (69.9%) patients had a single diagnostic classification, 247 (29.4%) had two classifications and 6 (0.7%) had three classifications. Fever was positively associated with having a single diagnostic classification (OR = 5.4; 95% CI = 3.9-7.5; p<0.001). Of 570 febrile patients, 32 (5.6%) had malaria. One (0.1%) patient had both malaria and pneumonia, while 10 (1.2%) had malaria combined with URTI, diarrhoea or skin infection. Of 498 patients with cough, 398 (79.9%) had URTI, the remaining 100 (20.1%) having pneumonia. 6 out of 570 (1.1%) febrile children had urinary tract infection (UTI).

Out of 841 patients without general danger signs, 129 (15.3%), of which 124 were febrile, received antibiotics on day 0 for various classifications. These included 100 (80.6%) pneumonia, 9 (7.3%) acute ear discharge, 7 (5.6%) dysentery, 6 (4.8%) UTI, 1 (0.8%) soft tissue infection and 1 (0.8%) tonsillitis. Among the 5 non-febrile patients who received antibiotics on day 0, 3 had dysentery and 2 soft tissue infections.
Table 8. Key differences between IMCI and the new ALgorithm for the MANAgement of CHildhood illness (ALMANACH), proposed changes after assessment and their justification.

<table>
<thead>
<tr>
<th>General danger signs</th>
<th>IMCI algorithm</th>
<th>New algorithm (ALMANACH)</th>
<th>Proposed changes in the ALMANACH</th>
<th>Justifications for proposed changes in the ALMANACH</th>
</tr>
</thead>
<tbody>
<tr>
<td>General danger signs</td>
<td>5 general danger signs managed at the beginning of the algorithm and 6 additional danger signs assessed later</td>
<td>10 general danger signs managed at the beginning of the algorithm and 6 additional danger signs assessed later.</td>
<td>Lower chest indrawing&lt;sup&gt;a&lt;/sup&gt; to be shifted to non danger signs for pneumonia</td>
<td>In compliance with recent WHO IMCI generic guidelines</td>
</tr>
<tr>
<td>Jaundice and Cyanosis</td>
<td>Jaundice and Cyanosis not considered as general danger signs</td>
<td>Jaundice and Cyanosis added to ALMANACH as general danger signs</td>
<td>Jaundice and Cyanosis to be dropped</td>
<td>No patient detected with any of these 2 conditions</td>
</tr>
<tr>
<td>Danger signs</td>
<td>Infected skin lesion or lump larger than 4 cm or with red streaks or with tender nodes or multiple abscesses not considered as danger signs for skin problems</td>
<td>Infected skin lesion or lump larger than 4 cm or with red streaks or with tender nodes or multiple abscesses considered as danger signs during assessment of skin problems</td>
<td>Changes remain in ALMANACH</td>
<td>The ALMANACH propositions help to clearly identify children with skin infection who will benefit from antibiotics</td>
</tr>
<tr>
<td>Fever</td>
<td>Fever is 1 out of 4 key symptoms assessed</td>
<td>Fever is used as a dividing point between a febrile branch and a non- febrile branch in ALMANACH</td>
<td>Change remain in ALMANACH</td>
<td>The non-febrile children have a very low risk not to be cured at day 7, although antibiotics have not been prescribed</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Cough + fast breathing&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Fever + cough + very fast breathing&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Change remains in ALMANACH</td>
<td>Children aged ≥ 12 months with RR between 40 and 50 were cured on day 7 without antibiotics (Shao AF et, submitted)</td>
</tr>
<tr>
<td>Cough or difficult breathing</td>
<td>Cough or difficult breathing</td>
<td>Difficult breathing can be dropped</td>
<td>No patient with difficult breathing detected. Difficult breathing is probably detected through fast breathing</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Action</td>
<td>Action</td>
<td>Action</td>
<td></td>
</tr>
<tr>
<td>---------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Counting respiratory rate</strong></td>
<td>Counting respiratory rate twice (after 5 minutes if first count ≥ 50/min</td>
<td>Second count to be dropped and emphasis put on counting when the child is calm</td>
<td>No patient found to have lower respiratory rate during the second count</td>
<td></td>
</tr>
<tr>
<td><strong>Urinary Tract Infection</strong></td>
<td>Not considered</td>
<td>Perform a urine dipstick for a child &lt;2 years with no source of fever identified(^a) or for a child ≥2 years with dysuria and no source identified(^d)</td>
<td>None of the febrile child ≥2 years with dysuria had a positive urine dipstick test result</td>
<td></td>
</tr>
<tr>
<td><strong>Typhoid fever</strong></td>
<td>Not considered</td>
<td>Antibiotic prescription for child ≥2 years with no source of fever identified(^d), and with abdominal tenderness</td>
<td>Abdominal tenderness can be dropped and replaced with a reliable typhoid rapid test when available</td>
<td></td>
</tr>
<tr>
<td><strong>Likely viral infection</strong></td>
<td>Not existing</td>
<td>Febrile child with no classification at the end of the algorithm</td>
<td>Change remains in ALMANACH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>This classification allowed to drastically reduce antibiotics prescription without affecting the cure rate</td>
<td></td>
</tr>
</tbody>
</table>

**Legend:**

\(^a\) As noted in the new WHO/UNICEF generic IMCI for 2014 (WHO and UNICEF, 2014).

\(^b\) 50 breaths/min for children aged 2 to 12 months, 40 breaths/min for children aged 12 months to 5 years.

\(^c\) 50 breaths/min for all children (aged 2 months to 5 years).

\(^d\) No cough or difficult breathing, no diarrhea, no ear problem, no measles, no infected skin lesion or lump.
842 children aged 2-59 months with acute illness

841 (99.9%) without general danger signs
1 (0.1%) with lethargy and severe pallor

570 (67.8%) with history of fever, 305 (53.5%) had temperature ≥ 37.5°C.

271 (32.2%) had no history of fever or temperature

124 (21.8%) received antibiotics on day 0
16 (2.8%) received antibiotics secondarily
551 (97.2%) were cured on day 7

5 (1.9%) received antibiotics on day 0
3 (1.1%) received antibiotics secondarily
263 (97.4%) were cured on day 7

Figure 7. Distribution of patients with general danger signs and the key symptoms in the febrile and non-febrile branches of the new ALMANANACH
Figure 8. Proportion of patients with key symptoms in the febrile and non-febrile algorithms; proportion treated by antibiotics on day 0 or secondarily, and proportion not cured on day 7.
Table 9. Distribution of patients with main complaints alone or combined, their diagnostic classification, antibiotic prescription rates at day 0 and secondarily and clinical outcome in the febrile and non-febrile algorithms

<table>
<thead>
<tr>
<th>Main symptom(s)</th>
<th>Classification(s)/diagnosis(es)</th>
<th>Total number of children N=841 (% among the total)</th>
<th>Febrile children N=570 (% of 570)</th>
<th>Children prescribed antibiotics on day 0. n (% among febrile classification)</th>
<th>Children prescribed antibiotics secondarily n (% among febrile)</th>
<th>Children not cured on day 7 n (% among febrile)</th>
<th>Non-febrile children N=271 (% of 271)</th>
<th>Children prescribed antibiotics on day 0. n (% among non-febrile)</th>
<th>Children prescribed antibiotics secondarily n (% among non-febrile)</th>
<th>Children not cured on day 7 n (% among non-febrile)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough only</td>
<td>URTI</td>
<td>301 (35.8)</td>
<td>169 (29.6)</td>
<td>0</td>
<td>3 (1.8)</td>
<td>1 (0.6)*</td>
<td>132 (48.7)</td>
<td>0</td>
<td>2 (1.5)</td>
<td>2 (1.5)*</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>85 (10.1)</td>
<td>85 (14.9)</td>
<td>85 (100)</td>
<td>3 (3.5)</td>
<td>5 (5.9)*</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Severe pneumonia</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (100)</td>
<td>0</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>URTI and malaria</td>
<td>7 (0.8)</td>
<td>7 (1.2)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia and Malaria</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>1 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough and diarrhoea</td>
<td>URTI and diarrhea</td>
<td>50 (5.9)</td>
<td>43 (7.5)</td>
<td>0</td>
<td>1 (2.3)</td>
<td>0*</td>
<td>7 (2.6)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>URTI and dysentery</td>
<td>3 (0.4)</td>
<td>3 (0.5)</td>
<td>3 (100)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pneumonia and diarrhoea</td>
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<td>2 (0.4)</td>
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</tr>
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<td>URTI and acute ear discharge</td>
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<td>URTI and measles</td>
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<td>0</td>
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<tr>
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<td>Dysentery and measles</td>
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<td>1 (0.2)</td>
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<tr>
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<td>Diarrhoea and impetigo</td>
<td>1 (0.1)</td>
<td>1 (0.2)</td>
<td>0</td>
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<td>1 (100)</td>
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<tr>
<td>Ear problems</td>
<td>Acute ear infection</td>
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<td>Acute ear discharge and impetigo</td>
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<td>3 (100)</td>
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<td>Measles</td>
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<td>3 (0.5)</td>
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<td>46 (17)</td>
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<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
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<td>Cough, diarrhoea and skin problems</td>
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<td>Likely viral infection</td>
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<tr>
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<td>0</td>
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<td>0</td>
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<td>1 (0.4)</td>
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<td>Gaseous distension</td>
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<td>0</td>
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<td>1 (0.4)</td>
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<tr>
<td>Total</td>
<td>841 (100)</td>
<td>570 (67.8)</td>
<td>124 (21.8)</td>
<td>16 (2.8)</td>
<td>16 (2.8)</td>
<td>271 (32.2)</td>
<td>5 (1.8)</td>
<td>3 (1.1)</td>
<td>7 (2.6)</td>
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</tr>
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</table>

* 4 patients (2 Pneumonia and 2 URTI) were lost to follow up.
On day 0, 1.9% of 270 non-febrile patients received antibiotics compared to 21.8% of 570 febrile patients. Day 7 cure rate for febrile patients who did not receive antibiotics on day 0 was slightly higher (97.9%; 96.7-99.3%) than that for those who received antibiotics (94.3%; 90.2-98.4%) (p=0.03). All non-febrile patients who received antibiotics on day 0 were cured on day 7 while 97.4% of those who did not were cured (p=0.87).

Figure 9 provides the pathway and test results for the 103 febrile patients without any other key symptom or sign and malaria negative. 6 (58%) of them had UTI, none had possible typhoid and 95 (92.2%) had likely viral infection.

**Discussion**

We have provided detailed description of complaints, clinical features and, when applied, complementary investigations of acutely ill children aged <5 years at primary health care facilities, with their disease classifications, treatment and clinical outcomes following strict compliance by clinicians to a new algorithm for the management of childhood illness (ALMANACH). This descriptive analysis shows that certain branches or sub-branches included few or no patients at all. We discuss below possible explanations for those observations and rationale for keeping or removing these branches from the ALMANACH and potential alternative solutions to improve the management of childhood illness in rural and urban settings in developing countries.

**General danger signs assessment**

Among 842 patients assessed for the 10 general danger signs, only 1 (0.1%) had severe pallor and lethargy (Figure 7). Previous studies have shown varying proportion of patients with general danger signs, from 5% to 28% (D'Acremont et al., 2014, Simoes et al., 1997, Rowe et al., 2007, Factor et al., 2001). This variation is likely due to the different level of care at which patients have been recruited, i.e. at primary care health facilities, as in our study, versus emergency departments of referral hospitals. Danger signs may become rarer because of the changing epidemiology of diseases in the context of a number of interventions which have contributed to reduction in childhood mortality (WHO. and UNICEF., 2012). Also, increased awareness of caretakers to bring their child as soon as possible after symptom onset has resulted in less delay and hence less severe cases presenting to health facilities. It is also possible that this low rate of children with danger signs is due to limited skills of health workers to detect them, or difficulty to identify these somehow subjective signs.
In the ALMANACH algorithm, 2 danger signs (cyanosis and jaundice) have been added to those of IMCI but were never identified in our study.

Figure 9. Clinical and rapid test result (urine dip stick) in febrile children without other key symptoms and with a negative malaria test

Cyanosis was included because there was no danger sign in IMCI that could detect severe respiratory distress beside chest indrawing (not considered anymore as a danger sign in the 2014 IMCI version (WHO and UNICEF, 2014)); it is however only found in very advanced stages of respiratory distress and thus very rare (Duke et al., 2001). Maybe using very fast breathing, as proposed by WHO for children older than 5 years and adults, could be an option, but it has been shown to be poorly predictive of hypoxemia (Duke et al., 2001). The lack of good clinical predictor for hypoxemia suggests that there is a need to have a better tool to identify these children. One possibility would be to use pulse oximeters (Duke et al., 2001, Duke et al., 2008, Duke et al., 2009, Weber and Mulholland, 1998), which can identify children with hypoxemia either due to severe pneumonia or other causes, as a triage tool at primary care level to identify children who would benefit from referral to a level of care were oxygen is
available. Regarding jaundice, the reason why no child was identified with this sign might be the difficulty for health workers to identify it. ‘Vomiting everything’ seems to be an entity not well understood by caretakers probably due to the wording. Vomiting everything is a confusing term to caretakers because it has more than one meaning. It can mean a child vomits anything given orally or it can mean when the child takes food, s/he vomits it all and nothing is left in the stomach. Vomiting is a symptom which worries most caretakers such that when they bring a child who has vomited once or twice to the health facility and they asked if the child is “vomiting everything”, the answer is yes, irrespective of what the question wanted to capture. In this context, clinicians are argued to assess for frequency of vomiting and the quantity vomited to be able to conclude whether the child vomits everything instead of asking caretakers the direct question: “does the child vomit everything”? (WHO and UNICEF, 2014). In summary, an ideal solution for danger signs would be to develop objective, simple and affordable point-of-care tests, for example based on blood host biomarkers, which could be used at primary health care level to assist clinicians in identifying the few patients with severe disease, or who may become severe, and thus need immediate treatment and referral.

**Fever**

Fever was used as a dividing point between the febrile and the non-febrile branch of ALMANACH. In the non-febrile branch, none of the recommendations (except for the children with blood in stool or with significant infected skin lesions) was leading to the prescription of antibiotics because non-febrile children are probably at very low risk of suffering from serious bacterial infections. Therefore, only 2% of non-febrile compared to 22% of febrile patients received antibiotics on day 0. The finding that cure rates on day 7 for patients who received antibiotics was slightly higher could suggest that these children benefited from this treatment. It might however also reflect that patients with serious infections took a bit more time than the others to be cured and were thus well targeted to receive antibiotics. The only way to know which hypothesis is true would be to undertake a randomized control trial, similar to that for non-severe pneumonia in Pakistan (Hazir et al., 2011), but including all non-malaria fevers.

**Respiratory diseases**

Of 841 patients, 498 (59.2%) had cough either as single complaint or in combination with other symptoms, both in febrile and non-febrile branches. This is within the range of previous studies that report proportion from 22% to 72% (Perkins et al., 1997, Gouws et al., 2004, Rowe et al., 2007, Mukanga et al., 2012, Yeboah-Antwi et al., 2010, Horwood et al., 2011). The differences
observed are probably due to several factors, such as local epidemiology and environment, or type of patient population and level of the health system. Only 1 (0.2%) patient with cough had lower chest indrawing. This is much lower compared to the 2% found in a recent study conducted in Tanzania among children with a temperature >38°C (D’Acremont et al., 2014). In the latter, patients were however recruited at outpatient department of hospitals, where diseases are generally more severe than at primary care level; indeed 8% of patients were admitted, while in the present study it was the case for only 0.4%. Recent studies report that patients with severe but not very severe pneumonia (i.e. those with cough and lower chest indrawing but no other danger signs) can be safely managed at home (Hazir et al., 2008, Addo-Yobo et al., 2011). Therefore, WHO/UNICEF now consider lower chest indrawing as a sign for pneumonia next to fast breathing (WHO and UNICEF, 2014). Having only one patient with lower chest indrawing, suggests that either this sign is rare nowadays at primary care level in Tanzania (for example because parents attend early in the course of disease to test for malaria), or that health workers have difficulty to identify it. The other problem is that chest indrawing can be more or less severe and ‘severe chest indrawing’ is still used by WHO as a criteria to classify ‘severe pneumonia’ at hospital level (WHO, 2013). To put a severity threshold to chest indrawing to decide on referral seems however difficult and an objective measurement, such as oxygen saturation or other host markers, might replace in the future such criteria.

Stridor has been kept in the 2014 version of IMCI as a sign of epiglottitis or foreign body in patients with cough (WHO and UNICEF, 2014). None of the patients in our study had this sign, maybe because of the introduction of Hib vaccination in Tanzania two years before the start of the study. No patient had neither other specific respiratory signs, such as wheezing or duration of cough for >3 weeks. In other studies, proportion of children reported to present at least one episode of wheezing ranges from 28-49% (Moraes et al., 2014, Medeiros et al., 2011, Dela Bianca et al., 2010, Ferreira and Wandalsen, 2014). All these studies showing a high incidence were conducted in Brazil and involved infants. IMCI recommends that children with wheezing beside fast breathing and/or lower chest indrawing are given up to three cycles of a bronchodilator before being classified as having pneumonia or not (WHO, 2005a), to avoid that children with asthma are wrongly classified and treated with antibiotics unnecessarily. In ALMANACH we were proposing, rather than giving antibiotics, to refer these children for assessment and treatment of potential respiratory distress and for evaluation of asthma as a chronic condition. None of the children included had wheezing and we could thus not evaluate the appropriateness of this strategy.
A critical step in the assessment of cough is counting the respiratory rate to differentiate clinical pneumonia from URTI. ALMANACH does not recommend counting respiratory rate in patients with cough but without history of fever (representing a third of patients with cough in this study). Out of 147, 3 (2%) of them developed fever and clinical pneumonia, were treated with antibiotics secondarily and did not develop complications. This low rate suggests that it is fine not to consider and treat pneumonia in non-febrile children and to rather tell parents to come back in case fever appears. This strategy allows to save time and decrease unnecessary antibiotic prescription during the first encounter with clinicians. Also, counting respiratory rates twice at 5 minutes interval did not help in differentiating pneumonia from URTI and this recommendation should be removed from ALMANACH. Maybe waiting more time could be useful to give a chance to the child to calm down and/or to lower his/her body temperature, so that the respiratory rate can decrease. This would be feasible in non-crowded health facilities or if automated respiratory rate devices would exist. The latter would vastly improve the assessment of this sign that is critical to appropriately target children in need for antibiotics (or in the future, for deciding to perform a bacterial pneumonia diagnostic test if available).

**Urinary tract infection and typhoid fever**

Only 8.5% of patients tested by urine dipstick were positive for leucocytes or nitrites (Figure 9). This is a third of what was found in another study conducted in the same setting, which showed that 22% of patients with a temperature \( \geq 38^\circ C \) (and not just history of fever) had a positive dipstick (D'Acremont et al., 2014). Since there was no evidence that UTI is a major cause of mortality in children <5 years, WHO did not initially include this disease in IMCI. Then a WHO supplement for country adaptation proposed to use microscopy or urine dipstick in children less than 2 years with unexplained fever, should countries find it important and feasible (WHO, 2005b). In ALMANACH, we proposed a urine dipstick to all children <2 years with fever without an identified source (but regardless of the malaria test result) and to those aged \( \geq 2 \) years with dysuria. Only 4 children older than 2 years had dysuria (and all had a negative dipstick) which suggests that having this criterion does not add much to the age criteria. Abdominal tenderness was shown to be predictive of typhoid fever in children >2 years in a study on etiologies of fever (D'Acremont 2014, De Santis 2014 in preparation). This sign was thus included in ALMANACH for children >2 years with fever without an identified source to avoid having clinicians systematically prescribing antibiotics in this group due to the fear of a bacterial infection, in particular typhoid fever. In fact, in the present study, none of the patients had abdominal tenderness, either because this sign was rare or too difficult to assess for.
clinicians. It was thus not useful and should probably be dropped. Eventually, in highly typhoid endemic areas, a specific rapid diagnostic test could be added for this group of children >2 years without any identified source of fever. In low endemic areas, the limited sensitivity of the present rapid tests make them less useful but they could be considered as part of a surveillance system in sentinel primary care facilities to pick up epidemics early on.

Limitations
The findings of this study need to be interpreted with caution because the algorithm was tested in only one urban and one rural setting in Tanzania. As this algorithm was designed to integrate the management of several childhood illnesses, the number of patients per branch or per clinical or diagnostic element was quite low. Firm conclusions in terms of inclusion or exclusions of clinical or laboratory conditions in a decision chart based on this study alone can thus not be drawn.

Conclusions
A detailed description of symptoms, signs, laboratory test results, and clinical outcome of patients managed by the ALMANACH algorithm allowed to assessing the value of most of the proposed branches of the algorithm, and hence to decide on their relevance. An improved AMANACH taking into the present findings will be soon tested in the same patient population. A dynamic process is needed that allows incorporation of new predictors and point of care tests in the algorithm, using electronic decision support systems that ease rapid changes that can be quickly implemented and evaluated in the field. New algorithms should be tested similarly to what was done in the present study to increase evidence and provide thus the best possible care for children and the highest satisfaction of health care professionals.

Authors’ contributions
AFS, CRA, BG, and VDA designed the study. NS supported the organization for data collection. AFS and CRA collected and analysed the data. AFS drafted the manuscript. BG and VDA participated in data analysis and writing of the manuscript.

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Tropical and Public Health Institute (SwissTPH), D-Tree International, and Ifakara Health Institute (IHI) involved in the study.
PART V: FACTORS AFFECTING THE IMPLEMENTATION OF THE NEW ALGORITHM FOR MANAGEMENT OF CHILDHOOD ILLNESS (ALMANACH)

Chapter 8: Can smartphones and tablets improve the management of childhood illness in Tanzania? A qualitative study from a primary health care worker’s perspective

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Abstract

Background

The impact of the Integrated Management of Childhood Illness (IMCI) strategy has been less than anticipated because of poor uptake. Electronic algorithms have the potential to improve quality of health care in children. However, feasibility studies about the use of electronic protocols on mobile devices over time are limited. This study investigated constraining as well as facilitating factors that influence the uptake of a new electronic Algorithm for Management of Childhood Illness (ALMANACH) among primary health workers in Dar es Salaam, Tanzania.

Methods

A qualitative approach was applied using in-depth interviews and focus group discussions with altogether 40 primary health care workers from 6 public primary health facilities in the three municipalities of Dar es Salaam, Tanzania. Health worker’s perceptions related to factors facilitating or constraining the uptake of the electronic ALMANACH were identified.

Results

In general, the ALMANACH was assessed positively. The majority of the respondents felt comfortable to use the devices and stated that patient’s trust was not affected. Most health workers said that the ALMANACH simplified their work, reduced antibiotic prescription and gave correct classification and treatment for common causes of childhood illnesses.

Few HWs reported technical challenges using the devices and complained about having had difficulties in typing. Majority of the respondents stated that the devices increased the consultation duration compared to routine practice. In addition, health system barriers such as lack of staff, lack of medicine and lack of financial motivation were identified as key reasons for the low uptake of the devices.

Conclusions

The ALMANACH built on electronic devices was perceived to be a powerful and useful tool. However, health system challenges influenced the uptake of the devices in the selected health facilities.

Keywords

Smartphones, tablets, electronic clinical decision support, IMCI, primary care, barriers, electronic prescribing
Background
In the mid-1990s, the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF) and other partners developed a strategy called ‘Integrated Management of Childhood Illnesses’ (IMCI) to improve the assessment, classification and treatment of the common causes of childhood mortality (Gove, 1997). It was also aimed at improving health worker’s skills as well as family and community practices (Lambrechts et al., 1999). When used correctly, these guidelines were shown to improve quality of care and reduce the cost of treatment (Bryce et al., 2005, Armstrong Schellenberg et al., 2004a), and to reduce mortality in Tanzania (Armstrong Schellenberg et al., 2004b).

However, the expected impact of IMCI worldwide has been less than anticipated due to limited uptake of the strategy (Victora et al., 2006). The latter has been due to various challenges facing IMCI implementation at various levels as discussed in a study by Ahmed et al. (Ahmed et al., 2010). For example, health workers (HWs) who are supposed to implement IMCI need about 11-16 days of training. The cost and time for this training has limited the uptake of IMCI worldwide (Ahmed et al., 2010). In Tanzania, health workers’ compliance to IMCI algorithms is uneven and often quite low, both in rural and urban settings (Armstrong Schellenberg et al., 2004a, Walter et al., 2009).

To address and overcome these challenges, new technologies are increasingly used, not only to facilitate training on IMCI (WHO and Development., 2007) but also to improve compliance to evidence based guidelines (DeRenzi et al., 2008, Mitchell et al., 2009, Mitchell et al., 2012b, Mitchell et al., 2012a). In a pilot study, where HWs used personal digital assistance (PDAs) with an electronic version of IMCI (e-IMCI) in a rural dispensary in Mtwara, Southern Tanzania, DeRenzi et al. found that e-IMCI is as fast as routine practice (following IMCI from memory) and it increased compliance to the IMCI guidelines (DeRenzi et al., 2008). In another study by Mitchell et al. in Pwani region in Tanzania, HWs stated that it is much easier and faster to use electronic IMCI (e-IMCI) than paper-based IMCI for consultations (Mitchell et al., 2012a).

However, still little is known about facilitating factors and barriers and their influence on the long term uptake of electronic devices in the context of IMCI in developing countries. Using in-depth interviews and focus group discussions with primary health care workers, the present study aimed at providing insights into factors influencing the sustainable uptake of two different mobile technologies, tablets and smartphones, used as electronic decision support to implement a new algorithm aimed for rational use of antibiotics and antimalarials for the management of children in 6 health facilities (HF) in Dar es Salaam, Tanzania.
Materials and Methods

The PeDiAtrick project

The study was conducted within the PeDiAtrick project which aimed at improving the quality of healthcare for Tanzanian children by assessing the use of electronic decision support to promote evidence-based medicine and rational use of drugs. The project was implemented in Dar es Salaam, the largest city in Tanzania, and in Ifakara, a town in south-eastern Tanzania. In a first step, a paper as well as an electronic version of a new algorithm for management of childhood illness (ALMANACH) were developed (Rambaud-Althaus et al, submitted) and assessed in a safety study (Shao AF et al, submitted).

After the safety study had shown that the clinical outcome of patients was better using ALMANACH than with routine care, HWs from 3 selected HFs in Dar es Salaam received two days ALMANACH training by the field investigators (including first author) on the rational use of antibiotics and antimalarials using smartphones. Following the training each HW involved in taking care for children at the participating health facilities received face-to-face supervision by the field investigators (including first author) with several real patients onsite. In addition, user manuals on how to operate the smartphones were developed and given to each health facility for reference with training and face-to-face supervision. During the implementation of the smartphone study, the uptake and compliance to the algorithm by HWs was assessed (Rambaud-Althaus et al, submitted).

The results from the smartphone arm were used to inform the design and introduction of tablets as electronic decision support for the management of similar group of sick children but in three other health facilities which were previously controls for the uptake and compliance study (Rambaud-Althaus et al, submitted). Figure 10 provides a summary of the intervention activities for the smartphones and tablets. Clinical data for each child managed by HWs using either smartphones or tablets were sent to a web-based server.

During the use of smartphones and tablets in the field over the course of three months, a decrease in the number of clinical data for children managed by HWs in both arms sent to the web based server was observed (Figure 11).
The present study was thus designed to investigate the determinants of uptake and perception of health workers of these electronic devices to support clinical practice.
Study design and setting

The qualitative study presented here was carried out in the urban intervention sites in Dar es Salaam city in Tanzania between February and March 2012 (smartphones) and between September and October 2012 (tablets). Dar es Salaam was selected because it is a setting with moderate malaria endemicity (Wang et al., 2006) but high use of antibiotics (D’Acremont et al., 2011). The use of the new algorithm reduced unnecessary use of drugs both in low, moderate and high malaria endemic settings without exposing children to harm (Shao AF et al, submitted). Six health facilities (HF) were chosen from the three municipalities of Dar es Salaam, namely Ilala, Temeke and Kinondoni (Figure 12).
Figure 12. Map of Dar es Salaam (including two selected health facilities in each district)

In each municipality, 2 public owned HF under the Ministry of Health and Social Welfare (MoHSW) which were involved in the uptake and compliance study (Rambaud-Althaus et al, submitted) were selected. Their characteristics are illustrated in Participant selection and data collection.

Study participants were sampled among all clinicians who formed part of the project. In total 24 HWs (12 of the smartphone and 12 of the tablet arm) were purposely selected (Suri, 2011, Adam and Kamuzora, 2008) using the following selection criteria: (1) 4 HWs per HF to represent each HF; (2) equal representation of 4 different uptake levels (for each of the four levels a


Table 10.

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Table 10. Characteristics of the health facilities

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Buguruni</th>
<th>Vingungutí</th>
<th>Mbagala</th>
<th>Kizuiani</th>
<th>Sinza**</th>
<th>Tandale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum No of HWs</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Number of smartphones</td>
<td>4</td>
<td>N/A</td>
<td>5</td>
<td>N/A</td>
<td>N/A</td>
<td>3</td>
</tr>
<tr>
<td>Number of tablets</td>
<td>N/A</td>
<td>2</td>
<td>N/A</td>
<td>3</td>
<td>3</td>
<td>N/A</td>
</tr>
<tr>
<td>Maximum No of HWs in the morning shift at OPD</td>
<td>4</td>
<td>2-3</td>
<td>4-5</td>
<td>4</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Daily attendance of patients*</td>
<td>200-250</td>
<td>120-150</td>
<td>400</td>
<td>150-200</td>
<td>500</td>
<td>300-500</td>
</tr>
<tr>
<td>Daily attendance of children &lt;5 years*</td>
<td>50-60</td>
<td>40-50</td>
<td>70-100</td>
<td>60</td>
<td>160</td>
<td>100-150</td>
</tr>
</tbody>
</table>

Legend:
OPD=Out Patient Department, N/A=Not Applicable
*=Numbers were provided by health facility in-charges in 2010
**= Was upgraded to a hospital in 2013

median of the total number of patients recorded by the HWs for the first three months of implementation either by smartphones or by tablets was calculated): very low uptake (median number of cases: 2), low uptake (median 12), high uptake (median 35) and very high uptake (median 81).

The in-depth interviews were conducted by the first author, using a semi-structured and pilot tested interview guide in the local language, Kiswahili. The interviews were then transcribed in Kiswahili and translated into English by the first author. They took on average 44 minutes each (range 29-69 minutes). Only 1 HW from the smartphone arm refused to be tape-recorded but agreed to be interviewed. During this interview, detailed notes were taken.
In addition, at least 2 HWs from each of the 6 health facilities, who did not participate in the in-depth interviews, were invited to participate in focus group discussions. Three focus group discussions (FGD) were conducted, two from smartphone arm and one from tablet arm. Each FGD from the smartphone arm had 5 participants while the one from the tablet arm had 6 participants. Notes from the discussion were recorded by the first author and typed after completion of the discussion. All focus group discussions took about an hour.

Data analysis
All in-depth interviews were recorded, transcribed, and translated from Swahili to English. Detailed notes taken during focus group discussions were translated into English. Data analysis was based on content analysis (Mayring, 2000). ATLAS.ti version 6.0 software was used to code interview transcripts for identification of common themes. Emerging themes were debated by a multidisciplinary team involved in the study. Data from both arms were compared to gain insights into similarities as well as differences of barriers and facilitating factors between smartphones and tablets related to the uptake of the new algorithm.

Ethical consideration
The study was approved by the National Institute for Medical Research (NIMR) Review Board in Tanzania (NIMR/HQ/R.8a/Vol.IX/823). Approval was also provided by the institutional review boards of the University of Basel (EKBB) and the Ifakara Health Institute (IHI). All study participants provided written informed consent.

Results
Socio-demographic characteristics of the study participants
A total of 40 clinicians participated in the study, (24 in the in-depth interviews and 16 in the focus group discussions). For the in-depth interviews 24 clinicians were selected: 12 in the smartphone and 12 in the tablet arm. Of the 12 clinicians in the smartphone arm, 7 were females, 7 were aged below 40 years (range 24-55 years), 1 had smartphone experience and 1 had computer experience. Of the 12 clinicians in the tablet arm, 8 were females, 8 were aged below 40 years (range 27-58 years), none had smartphone experience while 4 had computer experience. For the focus group discussion, of 16 clinicians, 10 in the smartphone and 6 in the tablet arm. Of the 10 clinicians in the smartphones, 7 were females, 5 were aged below 40 years (range 27-53 years), none had smartphone experience while 2 had computer experience. Of the 6 clinicians in the tablet arm, 3 were females, 4 were aged below 40 years (range 30-48 years), none had smartphone experience while 1 had computer experience.
Health care worker perceptions related to the application of smartphones and tablets

This section explores factors influencing the uptake of the two different devices, smartphone and tablet. Three themes emerged from in-depth interviews and focus group discussion data analysis. Because of similarities in themes between in-depth interviews and focus group discussions, results from both groups are presented together. The first theme describes HWs perceptions related to the application of the ALMANACH compared to routine practice. The second theme focuses around the technical usability of the device by HWs. The third theme looks at health system factors that were identified by HWs as key barriers to the long-term uptake of the ALMANACH. Figure 13 illustrates different presentations of these themes depending on the uptake level of respondents. Perceptions presented below were independent of the socio-demographic characteristics of the participants.

Perceptions related to the application of smartphones and tablets

**Feeling comfortable**

Almost all HWs (12 smartphone/11 tablet) felt comfortable to use the electronic devices in front of the caretakers during consultation.

“Of course I feel comfortable, not only because the tablet is a modern equipment, I know, I will not forget any symptoms related to disease. But sometimes […] you cannot remember everything, but by using ALMANACH you can tell this [child] has high respiration rate”. (IDI, male, tablet, very high uptake)

**Rational judgement**

The majority of the study participants (9 smartphone/11 tablet) perceived that their rational judgment was not compromised by using the ALMANACH during consultations.

“…the treatment provided by the tablet is short and clear, but there is also an opportunity to add other things […], it helps you to think more about the treatment”. (IDI, female, tablet, low uptake)

**Patient’s trust**

Majority of the HWs, (8 smartphone/9 tablet) stated that patient’s trust was not affected by the use of electronic devices during consultations.

“Because as I have told you that from my experience, most of them want to be treated by using the ALMANACH, they believe that something that is electronically is much better, I think that is the belief of our patients.” (IDI, male, tablet, very high uptake)
Simplifying work
The majority of the respondents (9 smartphone/11 tablet) said that smartphones and tablets simplified their work.

“... for example [...] if the patient is coughing, for each cough we gave antibiotics but through the phone you know this is pneumonia or this is normal chest cough so there is no need of using antibiotics. But another thing is that, it simplifies work because you are instructed to give medicine according to the weight of the child, so you don’t need to do the calculation of a dose.” (IDI, male, smartphone, very low uptake)

Reduction of antibiotic prescription
Health workers pointed out that the ALMANACH assisted them to reduce antibiotic and antimalarial prescription as the device walked them step-by-step through the consultation starting from diagnosis to treatment including calculation of proper dosage of required drugs. Thus the majority of the study participants (10 smartphone/11 tablet) stated that both devices reduced antibiotic prescription compared to routine practice.

“Yes, before I was prescribing antibiotics as antibiotics, I was just prescribing antibiotics, but truly now you don’t believe, now I know many diseases are febrile diseases, they don’t need antibiotics”. (IDI, female, smartphone, very high uptake)

“... if you are using ALMANACH the antibiotic consumption is reduced, if you don’t use ALMANACH the consumption of antibiotics is high”. (IDI, female, tablet, very low uptake)

Correct classifications
The majority of study participants (9 smartphone/10 tablet) were quoted saying that both devices give correct classifications.

“... so what was making me happy is that I used to get good diagnosis and good treatment” (IDI, female, smartphone, high uptake)

“Because if you are following the phone, it guides you directly, so if you make a good follow-up, you will get accurate diagnosis”. (IDI, male, smartphone, low uptake)

Correct treatment
More than half of the respondents (8 smartphone/7 tablet) highlighted that the ALMANACH enabled correct treatment.

“There are many advantages; first, the phone is a reference point in the sense that if you have forgotten what the patient is suffering from, or treatment or medication, by following
the instructions in the phone you will know the diagnosis and medicine to that diagnosis. So the phone helps a lot." (IDI, male, smartphone, very low uptake)

Figure 13. Health worker's perceptions stratified per ALMANACH uptake level
Usability of devices

**Typing**

In general, technical usability of the smartphone as well as tablet was considered to be easy. Few users (2 smartphone and 2 tablet) who all belong to low and very low uptake levels had difficulties typing, irrespective of their socio-demographic factors as well as computer/smartphone literacy.

“This [typing] was difficult. This was a challenge for me. I was not familiar with the typing, it takes time to type.... I sometimes have to press and press, several times, it is difficult to use.” (IDI, female, smartphone, very low uptake).

**Length of ALMANACH**

While the majority of health workers found both devices user-friendly, the vast majority (11 smartphones/10 tablet) were concerned about the length of the ALMANACH as it led to increased consultation duration. Few of the study participants (2 smartphones /4 tablet), apart from health system barriers, the high number of questions in the ALMANACH for the low uptake of the two devices. The average time for consultation duration using tablets was 8.7 minutes (range 2-38 minutes). The consultation duration for smartphones is not available because the smartphones arm involved a video component which was dropped in the subsequent evaluation of the tablets.

“The biggest problem here is that we have few workers and a lot of patients, and if you see that you find it hard to ask a patient all those questions”. (IDI, female, smartphone, high uptake)

**Health system barriers**

**Few health workers and many patients**

Health system factors were identified as key barriers of the electronic ALMANACH uptake. More than half of the respondents (8 smartphone/6 tablet) expressed difficulties using the devices in an understaffed setting. Vice versa, the presence of many patients was regarded by the majority of HWs (8 smartphone/8 tablet) as a factor that prevented primary health care workers to use the two devices continuously. Thus the application of the devices was associated with over hours due to longer consultation periods. In addition, study participants were concerned about patients getting unhappy because of longer waiting times.
“I feel free [to use the device] but the problem is the crowd of patients that we are supposed to attend, in our health facility we do not have enough staff, the use of phone is a barrier. The patients want to be treated and go back home early, so if they stay longer in the health facility, it becomes a problem”. (IDI, Male, smartphone, very low uptake)

“... Now it is a challenge to us as I am alone, so sometimes I cannot use phone”. (IDI, Female, smartphone, very high uptake)

“...if we had enough health workers, some for children and some for adults, then it could have helped a lot”. (FGD, female, smartphone)

**Few laboratory staff**

Due to the use of the ALMANACH, more patients were sent to the laboratory compared to routine practice. Lack of laboratory personnel resulted in longer waiting hours for patients. In addition, clinicians had to wait for the patients whom they sent to the laboratory resulting in over hours. Few of the interviewed health workers (3 smartphone/3 tablet) stated that their concern about making patients wait negatively affected their uptake of the devices.

“You find that our laboratory has many patients, so the patient stays in the queue for long time, waiting for the results”. (IDI, female, tablet, very low uptake)

**Lack of staff motivation**

Lack of financial incentive was mentioned in almost all interviews. Majority of the participants (10 smartphone/10 tablet) expected financial compensation for using the devices at their respective health facilities. Participation in interventions or studies is often linked to financial benefits, and regarded as extra work that should be paid. They based their expectations on various reasons as narrated by a female health worker below:

“They [the health workers] know there is no financial benefit, and they have conditioned themselves that phones waste time, knowing also that they do not get any income out of the phone use, that is the only reason when you come with this . . . not only the phone, when you come with books [IMCI chart booklets], and one is working with children since morning, you find that they don’t even read them, they do not have any interest. They take the phones the same way they deal with books. The only difference is that this is a phone and that is a book, which you need to open”. (IDI, female, smartphone, high uptake)
**Increased paper work**

Health workers in Tanzania are required to keep records about cases in the Tanzanian Health Management Information System (HMIS) also known in Kiswahili as Mfumo wa Taarifa za Huduma za Afya (MTUHA) (DeRenzi et al., 2008). During consultation, health personnel are supposed to keep assessment records in patients’ notebooks including date of consultation, diagnoses and treatment. However due to lack of training and time the uptake of these registers is poor (Nyamtema, 2010). More than half of the health workers (7 smartphones/7 tablets) attributed increased paper work as an extra work because besides having to use the electronic devices, the registers had to be filled too.

“...yeah, it adds more work to us, because we have to enter the data in the phone, and then write the same data in the file, or patient’s card/notebook. In that way you do two things at the same time”. (IDI, male, smartphone, very low uptake)

**Lack of drugs**

The application of the smartphone and tablet raised expectations among patients related to treatment that often could not be fulfilled. Few of the respondents (4 smartphone/2 tablet) expressed their frustration about lack of medicines in the health facility. After having walked their patients through the ALMANACH, treatment services were often regarded to be discouraging.

“There is nothing which discourages you more as when you are using that tablet, and the caretaker has waited for such a long time, at the end you tell her, “go and buy the medicine outside or go to the medicine’s window” and there is no medicine, even the caretaker becomes discouraged, you have enrolled her in your tablet, and you have concentrated, at the end of the day, when she goes to the pharmacy she fails to get [the medicine]”. (IDI, female, tablet, very low uptake)

“When caretakers see the phones, they also expect that drugs are available”. (FGD HW, male, smartphone)

**Discussion**

To our best knowledge, this is the first qualitative study which investigated facilitating factors and barriers for routine use of electronic decision supports, namely smartphones and tablets, in developing countries.

Regardless of the type of device, results highlighted that the electronic ALMANACH was perceived to have various advantages over routine practice. Interestingly, the opinion on the two
different tools, smartphone and tablet, was quite similar. Respondents talked mainly about the content of the ALMANACH itself, as well as context, and less on device related factors that influenced the uptake. Thus it is argued that the small technical differences between both tools did not impact on the uptake. Moxey et al. in a systematic review report that computerized clinical decision support systems with minimal threats to professional autonomy have a better chance of being accepted by users (Moxey et al., 2010). The ALMANACH offered health workers the freedom to select and type additional information (DeRenzi et al., 2008).

The majority of the health workers both in high and low uptake levels felt comfortable to use smartphones and tablets in front of the caretakers for consultations. In addition, they stated that their judgement was not restricted and that caretakers’ trust was not affected. In a study using PDAs in the context of IMCI conducted in Tanzania, health workers were more skeptical about electronic decision support (Mitchell et al., 2012a). The different findings can be explained by the study design. The long-term follow up over several months including training and face-to-face supervision conducted in the present project contributed probably to the positive acceptance and evaluation of the devices. It is argued that long-term involvement is necessary to allow health workers to feel comfortable using mobile technology.

The majority of health workers concluded that the ALMANACH simplified their work, reduced the use of antibiotics, and assisted them to reach the correct diagnosis and treatment. Mitchell et al. also found that the use of PDAs lead to more accurate classifications compared to routine practice (Mitchell et al., 2013).

Considering this positive assessment, the rather low uptake of the ALMANACH over time is surprising and needs to be looked at more carefully. Hereby two reported interlinked barriers require further discussion: 1) the reported length of the ALMANACH as well as 2) health system barriers.

**Length of ALMANACH**

To address the perceived excessive duration of consultation when using ALMANACH to manage patients, we are currently assessing the utility of each diagnostic pathway (branch) in the decision tree so that unnecessary questions can be discarded without jeopardizing safety and efficacy (Shao AF et al, in preparation). However, the length of the ALMANACH can only be shortened to a certain extent. In 2005, Tanzanian clinicians trained in paper IMCI took on average 8.2 minutes per child for a consultation (Adam et al., 2005). In this study clinicians used on average 8.7 minutes (2-38 minutes) per child for consultation with tablets. Findings from
another study (Mitchell et al., 2012a) conducted in a rural setting in Pwani Region in Tanzania, which highlighted that it is faster to use electronic protocols than IMCI chart booklet, could not be confirmed. Instead results from urban Dar es Salaam showed that electronic clinical decision support systems lead to more laboratory tests done compared to routine practice (Moxey et al., 2010) resulting in longer consultation duration and more laboratory work. However, it must be considered that consultation time varies depending on the setting. In rural areas it is often longer than in urban ones. Earlier studies showed that the shorter the consultation duration, the higher the risk that children are not properly assessed (Baiden et al., 2011a, Horwood et al., 2009). This can lead to poor clinical outcomes especially when danger signs are not properly identified. Case management and health outcomes cannot be improved if clinicians are not prepared to allocate sufficient time for consultations following IMCI guidelines (Horwood et al., 2009). The willingness to follow medical standards is a pre-requisite for the sustainable application not only of electronic tools such as ALMANACH but also decision charts in general, whatever the support.

**Health system barriers**

Although the majority of the respondents assessed the devices very positively and highlighted their strengths, they also reported health system related barriers in almost all interviews. The Tanzanian health system is characterized by shortage of health care providers, which affects also intervention aimed at improving health care delivery (Bryan et al., 2006, Munga and Maestad, 2009, Dominic A and Kurowski C, 2005). Understaffing and high number of patients prevented many clinicians from making long-term use of the electronic devices as they were concerned that these new tools lead to excessive delays for patients and over hours of health workers. This may be the reality in some places, but it may also be due to health workers’ perception and beliefs. An assessment of health workers performance during outpatient consultations in Dodoma (urban) and Morogoro region (rural) reported that clinicians have ample time and are not overworked (Maestad et al., 2010). On the other hand, the same researchers mention that there could be a relationship between low performance of clinicians and high workload (Maestad et al., 2010).

Health care workers complained about recording clinical records for patients in both the mobile tools and the clinical registry books (MTUHA) required by the Tanzanian HMIS. This was perceived as double work. However, this duplication was related to the nature of this pilot implementation where routine data collected through the electronic devices directly to the server
were not considered suitable for the continuous monitoring of diagnoses and treatment, because they could not be linked to the usual HMIS. This concern would ultimately no more be relevant, once all clinical data can be collected directly in an integrated electronic monitoring system.

Lack of financial incentive was an additional barrier mentioned by the interviewees. Health workers perceived the use of the electronic tools as extra work, and expected therefore extra payment. No incentives were given during field implementation because the smartphone or tablet were designed and used as an aid to appropriately assess a sick child, and not as a research tool to satisfy scientific curiosity. The same procedure was applied when Rapid Diagnostic Tests for malaria were pilot-implemented in Dar es Salaam, and the intervention went smoothly and was then scaled up in a national strategy (D’Acremont et al., 2011). This is of course a risk since previous studies reported poor performance of health personnel when there was no monetary or non-monetary incentives (Paul F, 2009, Leshabari et al., 2008, Hor et al., 2010, Maestad et al., 2010). It is common practice to pay incentives when extra work is asked to the clinician and no benefit to either staff or patients is expected. In the present study, the use of smartphones and tablets was aimed at improving clinical outcome and reducing unnecessary antibiotic prescriptions. As a result, mechanisms for clinicians to get informal payments such as by running “private” drug shops (selling medicines within the consultation room) (Maestad and Mwisongo, 2011) were not possible. Therefore it is possible that the absence of incentives for what could be considered as extra work because of the research environment, and the potential reduction of informal payments because of smartphone or tablet use, could have contributed to their poor uptake.

Previous studies reported that interventions which interrupt or slowdown patients’ flow can lead to uptake challenges (Fossum et al., 2011, Sedlmayr et al., 2013). This was confirmed by the participants who complained about a slowdown caused by the use of the ALMANACH. Patients assessed using the electronic devices were more likely to be sent to the laboratory for testing.

The way respondents presented health system barriers was in most of the cases the same regardless of the uptake levels. Belonging to a low uptake level was therefore not linked to a negative assessment of the device. The very same health personnel with low uptake level that praised the ALMANACH, highlighted the impact of health system barriers and held them responsible for the low uptake. In a nutshell, health system barriers countervailed the positive evaluation and continued use of the ALMANACH.
Sufficient health workforce, good access to medical products and technologies, effective service delivery systems are crucial for achieving good quality of care (WHO, 2010b). Results of this study highlight that sufficient staff, adequate payment system, enabling working environments including supportive supervision, and access to affordable medicine are important factors that influenced the uptake of the ALMANACH. However, increasing, staffing, training and supervision might not be sufficient (Maestad et al., 2010, Leonard et al., 2005). Additional factors such as the individuals’ motivations or how much energy the individual staffs decide to invest in improving the quality of health care, are necessary for enhancing the quality of health care. These factors are influenced by other determinants such as individual’s ethical and medical standards (Maestad et al., 2010).

**Study limitations**
The study focused on primary health care workers in the largest city of Tanzania, Dar es Salaam. While the results might be applicable to other urban settings, they cannot be generalized to rural settings that are often characterized by less patients and different health care infrastructure.

The role of the first author which included project implementation as well as data collection might have influenced the responses of the study participants. In order to deal with that, all study participants were encouraged to be as open as possible prior to the interview. In addition, participants were assured that the interviews aimed at assessing the ALMANACH and factors affecting its implementation following the low uptake observed. The interviews showed that respondents felt at ease sharing their experiences with the first author as they had over the years developed trust and mutual respect.

Although the caretaker’s perspectives were not considered in the study, high proportion of health personnel spoke about the positive reactions of caretakers and concluded that their trust was not affected.

It is argued that future studies should not only focus on technical aspects of mobile technology. Context related aspects needs to be addressed as well in order to foster a setting that allows for sustainable uptake and use of mobile devices.

**Conclusions**
The present study contributed to the increasing body of mobile health literature from the perspective of primary care health workers. Findings show that smartphones as well as tablets using ALMANACH have the potential to improve the management of childhood illness. The
majority of the health workers had no technical problems using the two electronic devices (smartphones and tablets) with the ALMANACH. Both were perceived as powerful tools which simplify work, give correct classification and reduce unnecessary use of antibiotics. However, health system barriers influence the long-term uptake. To ensure sustainable uptake of mHealth interventions such as ALMANACH, contextual barriers identified in this study should be addressed. Further studies are needed in order to better understand whether uptake is feasible for health workers given health system barriers and additional contextual factors. The ALMANACH presented in this paper will be improved and further tested in similar patients population in resource poor settings. Hereby barriers highlighted by health workers will be addressed.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

AFS, CRA, BG, VDA and CP designed the study. NS and JKM assisted preparing the data collection. AFS collected data and drafted the manuscript. AFS, CRA, BG, VDA and CP participated in data analysis and contributed to the manuscript. All authors have read and approved the final manuscript.

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PART VI: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

Chapter 9: Discussion

This chapter builds on the previous discussion of the study main findings regarding the ALMANACH design, its safety and content assessment and HWs’s perception on its use on mobile devices in supporting them to follow evidence based guidelines. These findings include drastic reduction of unnecessary use of antibiotics which resulted from deliberate inclusion of broad categories of general danger signs and clinical strategies to differential viral illnesses from bacterial illnesses. In addition, training and supervision improved HWs’ compliance, trust and positive attitude toward ALMANACH use on mobile devices. It also provides recommendations and highlights further research areas potential for sustainable scaling up of similar interventions in similar settings.

9.0 The content and the safety of the new algorithm for the management of childhood illness ALMANACH lead to improved quality of care

The new algorithm for management of childhood illness has the potential to cover broad spectrum of childhood illnesses which need pre-referral treatment and urgent referral early during assessment of a sick child. This is because more danger signs are assessed early in the algorithm as compared to the current version of IMCI. In practice, this would have implied that more patients should be referred to the next level compared to the standard practice. However, when ALMANACH was applied in controlled conditions, fewer patients were referred to the next level of health care. A pilot study comparing ALMANACH on mobile devices and ALMANACH on paper version versus standard practice found that HWs could identify more patients with serious conditions when using the electronic ALMANACH compared to the paper one. This implies that the HWs could follow electronic ALMANACH better than paper one during consultations. However, the paper ALMANACH was not better than the standard practice (Clotilde Rambaud-Althaus et al, submitted).

Our findings also suggest that the new algorithm for management of childhood illness (ALMANACH) has the potential to reduce antibiotic prescription in the management of acutely ill children aged 2 to 59 months attending primary health care facilities. The likely reasons are: (1) the unique cut off point of respiratory rate for the diagnosis of clinical pneumonia, (2) the separation of febrile and non-febrile patients, the latter receiving none or very minimal antibiotics, (3) inclusion of a urine dipstick test for urinary tract infections in all febrile children less than 2 years of age or above 2 years but with dysuria and only those with positive urine
dipstick should receiving antibiotics. In addition, the two new diagnoses proposed in ALMANACH to guide HWs on when to give antibiotics: (1) ‘possible typhoid’ for febrile children with abdominal tenderness and (2) ‘likely viral infection’ for acute ill children with negative results (no cause of fever identified) (Clotilde Rambaud-Althaus et al, submitted). All these strategies were recommended in ALMANACH in order to guide HWs on how and when to prescribe antibiotics rationally. In IMCI, no such strategies were proposed to guide HWs on what to do in case of negative malaria test. The lack of such recommendations in IMCI algorithm leaves for HWs a room to prescribe antibiotics to febrile children with negative malaria test. In summary, withholding antibiotics to acutely ill children when using ALMANACH did no harm. This observation suggests that the majority of children attending primary health care facilities have illnesses of viral origin rather than bacterial ones. It implies that health workers in these settings need to be reminded from time to time through on job trainings that once a specific cause of illness is not found, caretakers should be counseled to go home without treatment and return the child if symptoms persist. Such messages are important to combat the problem of antibiotic resistance, which is growing over time.

In our study, we found that cure rates on day 7 was better in the ALMANACH arm as compared to the control arm (chapter six). The rates of complications in ALMANACH were similar in both arms. Our study provides initial evidence of good clinical outcomes when using a newly designed algorithm for the management childhood illness. This is an important step that has never been conducted with the current IMCI algorithm. We recommend such studies to assess new algorithm in controlled conditions to be systematically conducted. Rather than focusing on one disease only, it is important to assess these clinical algorithms holistically.

In order for HWs to reach a proper diagnosis or classification, HWs need to follow a defined clinical process for which they need supportive tools that guide them through which symptoms to ask for, what signs to check for and what investigations to perform for the most common complaints children present at primary health care settings. Without such tools, children will continue to receive low quality health care, as it has often been the case with an IMCI poorly complied to, or even not followed at all.

There are many reasons for which HWs have not been able to use paper-based IMCI guidelines and these have been summarized in previous studies (Ahmed et al., 2010). One of the potential solutions to enable healthworkers to follow evidence-based clinical guidelines is to incorporate
these clinical guidelines into an electronic tools (DeRenzi et al., 2008). Below we discuss the benefits of using electronic mobile devices to implement evidence based clinical guidelines.

9.1 The benefits of using electronic mobile devices to implement evidence clinical guidelines

Using ALMANACH on mobile devices results in better care than on paper-based guidelines

First patients can be assessed and managed more appropriately when using mobile devices rather than when using paper-based clinical guidelines because the mobile devices guide HWs from step to step in such a way that HWs cannot skip assessment or treatment (DeRenzi et al., 2008). When HW’s performance was assessed using the same algorithm on paper or electronically, we found that HWs could identify more patients with serious conditions when using the electronic ALMANACH than with the paper one. This shows that the electronic ALMANACH was more powerful than the paper one. Moreover, the paper ALMANACH was not better than standard practice (Clotilde Rambaud-Althaus et al, submitted). The reason is that paper-based ALMANACH was probably too complex to follow and thus did not add much to standard practice (chapter 5). These findings highlight further the potential of electronic mobile devices in supporting HWs in primary health care setting in following complex algorithms.

The use of ALMANACH on mobile devices is associated with fewer stigmas than using paper-based IMCI chart booklets

The findings suggest that these tools are acceptable and can be trusted (chapter 8). In addition, health workers were comfortable to use these tools in front of caretakers unlike the use of chart booklets. This implies that the stigma associated with the use of paper-based clinical guidelines such as IMCI has been alleviated by the use of electronic mobile devices. Therefore, implementing clinical guidelines with the support of mobile devices might have a higher uptake than paper-based clinical guidelines like IMCI.

The use of ALMANACH on mobile devices is associated with improved compliance and more rational use of antimicrobials than paper-based IMCI chart booklets

Our findings suggest that the use of electronic tools to implement evidence-based clinical guidelines does simplify consultation work because it guides HWs through the consultation process from history taking (which questions to ask), physical examination (signs to check for), guided laboratory work (which tests to do) and incorporates all these to end up with disease classification(s), type of medicine to prescribe, dose and schedule to prescribe, and advice to
caretaker on when to return to the health facility. Unlike paper-based guidelines like IMCI that request flipping back and forth in looking for assessment and treatment recommendations, electronic tools with clinical decision support like ALMANACH have simplified all these procedures. Previous studies on the use of electronic devices to implement clinical guidelines have shown that electronic devices improves compliance to clinical guidelines (DeRenzi et al., 2008). A pilot study assessing the use of ALMANACH by HWs in pragmatic conditions reported improved compliance to electronic ALMANACN than to paper-based ALMANACH (Clotilde Rambaud-Althaus, submitted) because paper-based ALMANACH is more complex to follow. In practice, these findings suggest that HWs using electronic tools are less likely to prescribe antimicrobials compared to those not using these tools because of improved compliance. The fight against unnecessary use of antibiotics is thus much easier if HWs are provided with electronic tools such as mobile devices with clinical algorithms.

*Updating electronic ALMANACH is easier and less costly than paper-based ALMANACH*

The use of mobile electronic decision supports has the potential to prevent clinicians from using outdated paper guidelines. The process of developing a fully electronic version of ALMANACH was iterative. Based on the experience we gained during this process, we learned that it was easier to incorporate new information and recommendations in the electronic version of the ALMANACH and load the application on the mobile phones (smartphones) and tablets than updating the paper-based ALMANACH which needed us to print all the paper versions. In addition, there were costs associated with distributing all the printed paper versions of the ALMANACH to the HWs. The costs related to printing and distributing all the paper-based clinical algorithms could be used for other purposes in the health care system like buying medicines or improving incentives for health care workers. In this way, the HWs can be retained in the health care system for longer duration than it is now. We did not yet collect cost-effectiveness data comparing the use of ALMANACH on mobile devices to standard practice, but intend to do so.

*Training health care workers to use ALMANACH on mobile devices costs few days*

One of the challenges to implement paper-based clinical guidelines such as IMCI is the huge costs associated with training of HWs. It requires up to 11 days on site to train HWs on IMCI case management. HWs in our study were able to follow ALMANACH on mobile devices after two days of training and one day of face to face supervision in their health facilities with real patients. These findings suggest that training HWs to use ALMANACH on mobile devices can
be reduced from 11 days used for paper-based IMCI case management to three days. In practice, these findings suggest that the huge costs associated with paper-based IMCI training can be saved for training HWs to use ALMANACH on mobile devices. One of the barriers associated with the use of electronic devices such as mobile phones or computers to support HWs in providing clinical care is the fear that these tools cost a lot (Jarvis, 2009). However, our findings suggest a different hypothesis. Further studies assessing the cost-effectiveness of ALMANACH on mobile devices as compared to the standard practice are recommended.

*Using ALMANACH on mobile devices has the potential to improve collection of accurate real time data*

Our own field experience shows that when the health facilities are busy and health workers are few, HWs give priority in taking care of patients rather than conducting consultations and keep records of the respective patients in the health management information system (HMIS) registers (known as MTUHA registers). Consultation data are thus filled in these HMIS registers at a later time in the day, which often leads to collection of inaccurate data. As these are used for projections at the health facility, district and national level, there is risk of poor planning. When consultations are conducted using ALMANACH on mobile devices, HWs are collecting clinical data directly. However, data resulting from the use of ALMANACH on mobile devices need further processing for it to be user-friendly. Also, there is a need of further collaboration between software developers and researchers so that this data can be generated, processed and returned to the health facility at least on a monthly basis for timely use. This should be a good incentive for HWs to use the tool as they will not be asked to process the data manually as it is the case now. The time saved from the data generated from the system could be used for other activities by the HWs.

*Using ALMANACH on mobile devices has the potential to improve routine supervision*

The other potential advantage of using ALMANACH on mobile devices is the possibility to generate data which can be used directly for routine supervision. The collected data from health facility can be easily linked to individual HW’s performance and in that way HW’s performance can be monitored by the Council Health Management Team (CHMT) remotely from the data sent to the server. Efficiency can thus be improved and costs associated with routine supervision can be reduced significantly. This further suggests that conducting a phased scale-up of the ALMANACH use on mobile devices is a viable option.
9.2 Factors influencing implementation of ALMANACH on mobile devices: challenges and solutions

Several factors could negatively influence the sustainable uptake and compliance to the ALMANACH on mobile devices over time. These factors include mobile device related factors, the content of the ALMANACH on the mobile related factors and the health system related factors as detailed in chapter 8 of this thesis. The brief discussion gives insight on how to design innovative strategies in order to improve the sustainable uptake and compliance to ALMANACH on mobile devices.

The ALMANACH content related factors

Our findings suggest that the increased number of items to check in the ALMANACH might have contributed to an increased consultation time and low uptake of ALMANACH on the mobile devices. The first thought solution was to review the current ALMANACH and propose some branches or pathways to modify or drop in order to improve ALMANACH uptake and compliance. This has been detailed in chapter 7 of this thesis and the proposed improved ALMANACH will soon be tested in the same population.

The second potential solution is to design a specific branch or pathway in the ALMANACH which can be used by nurses to fill in registration, triage and demographic data and to link this data with the improved ALMANACH used for consultation by the HWs. The same strategy can be applied for laboratory section where the ordered lab tests are filled in by the lab personnel and link this data to the HWs consultation process. This proposed task delegation is hypothesized to save time and reduce paper work, and hence operational costs of the health facilities. In addition, linking ALMANACH data to the overall HMIS data collected at health facilities will reduce paper work, and duplicate work as it was the case during the study. These strategies can also contribute to improve the data for planning at health facility, district and national level.

The health system related factors

Health system related factors such as lack of health workers, lack of enough motivation among health workers, presence of duplicate work (entering HMIS data in MTUHA books and on mobile devices) and shortage of medication and supplies have been discussed in chapter 8. Potential strategies to respond to shortage of health workers in addition to task delegation discussed above could be task shifting and introducing appointment. In Tanzania, the official
prescribers include Medical officers (with at least five years of medical school training plus one year of internship), assistant medical officers, clinical officers and assistant clinical officers. Nurses of all levels are not official prescribers in Tanzania. However, anecdotal evidence shows that in most of the rural health facilities, nurses are the ones who attend patients when the official prescribers are not available. This level of HWs could be trained on how to use ALMANACH and achieve rational use of antimicrobials in children less than five years. We recommend to conduct a pilot study during a phased scale-up to compare health outcomes of children managed by nurses with ALMANACH with other official prescribers in primary health care settings.

Currently patients come to health facilities without appointments (walk-in patients). In most cases, we observed that patients’ peak hours are between 0900hrs and 1300hrs, after which most of the health facilities have few patients. Introducing appointments in this case could distribute these patients to all HWs who will be working according to a specific schedule. Further studies to investigate and document how patients are distributed on hourly basis and reasons for such distribution will be useful in making informed decision to introduce appointment for patients to the primary health care facilities or not.

Because the use of ALMANACH gives the opportunity to monitor individual HWs’ performance, a system could be introduced to reward those who are performing better than others. Paying incentives through a system of pay per performance could motivate HWs to improve uptake and compliance to the ALMANACH. Regarding stockouts of medication and medical supplies, systems such as short messages could be put in place to send out information to central medical store for refill. Such systems have been shown to decrease the stockout of antimalarials (Barrington et al., 2010) and can be expanded to include other items frequently out of stock in primary health care facilities.

**The mobile device related factors**

The mobile device related factors which can influence implementation of ALMANACH includes things like the costs of the devices, their management to prevent high rates of turnover, and data bundle. No device was lost during the implementation of the project because all mobiles devices were kept and locked in a safe place at the health facilities either in the in-charge or dispensing room. An ALMANACH coordinator was chosen among the HWs using the devices to take care of them including charging them. The credits for sending data to the web-based server were the responsibility of the study coordinators. These tasks were possible due to the nature of
this project but not without challenges. For example, when the health facility coordinator arrived late or devices not charged or power cuts frequent, the uptake was compromised. For a larger phased implementation, we recommend the devices to be taken care by the individual health workers similar to the way they are supposed to take care of IMCI chart booklets soon after the training. Such a strategy could give them more time to practice with the devices and gain experience to use them, as currently most of the HWs had no experience to use smartphones or tablets. Regarding credits for sending data, this can be managed centrally through the use of selected mobile company network. Additional challenge related to the internet bundle for sending data by the HWs could also be taken care of by the software and system administrators proposed earlier.

In terms of costs, the price of electronic devices will go down so a phased scale-up of ALMANACH should not be too much of an issue. Because the devices will be taken care of by the HWs, they will feel ownership for the tools and the likelihood of loss is expected to be minimal. However, this hypothesis will require further confirmation during phased scale-up. How and where to store the data and which types of devices to use can be discussed with the information technology personnel taking in to consideration the existing market prices at the time of phased scale-up of ALMANACH on mobile devices.

9.3 Study limitations
Unlike IMCI chart booklet which covers the management of all children less than five years of age, the current ALMANACH covers management of children aged 2 months to 5 years. The current ALMANACH needs further modification to include patient’s follow-up data and full security of patients’ data. Further studies are recommended to find out how to design and incorporate algorithm to covers children less than 2 months of age. Such a development will enable all children less than 5 years of age to be addressed in one ALMANACH.

Study coordinators were responsible to update all mobile devices in the six health facilities involved in the project. This task was possible because all health facilities were reachable and were located in urban setting. There is a need to design a feature which will enable HWs to update on their own the devices to incorporate the new recommendations once they are out.

The current ALMANACH is compatible with mobile devices with android operating system. For sustainability of the intervention, there is a need to design an ALMANACH which will be compatible with different operating systems on mobile devices. Having software running on different platforms might contribute to a huge reduction of cost.
9.4 Conclusion
The drastic reduction of unnecessary use of antimicrobials (antibiotics and antimalarials) and improved clinical outcomes in the era of declining malaria as a result of HWs using the new (ALMANACH) suggests that it is time to make effective use of available technologies such as mobile devices (smartphones and tablets) and rapid diagnostic tests to improve the quality of health care for children in developing countries. While guiding HWs to deliver high quality care, the effective use of these tools have the potential to prevent HWs using out of date clinical algorithms (because it is easy to incorporate any new recommendations on real time basis) and improve the quality of clinical data collected at point of care, which is needed at health facility, district and the national level for accurate planning for the effective health care system.

9.5 Recommendations
Irrational use of antimicrobials (antibiotics and antimalarials) is a global challenge requiring effective use of available technologies and different partners to join effort in fighting against it. Both local and international collaborations are highly needed to address the irrational use of antimicrobials which is one of the major causes of emerging drug resistance we see spreading all over the world. While addressing that challenge, the world at larger will not only improves the quality of health care provided to children but also other population groups (adults and elderly). We therefore recommend practical applications and further research for responding to this challenge as outlined below:

Practical application areas

1. It is time to develop policy which will encourage paper-based clinical guidelines to be incorporated in to electronic formats for easy updating and distribution to HWs at various levels of health care.

2. We recommend that efficacy of clinical algorithm for managing different illnesses to be assessed holistically instead of assessing individual disease entities because assessment of individual disease entities might give false impression of efficacy and safety of the entire algorithm.

3. Development of clinical guidelines should be an iterative process that involves all stakeholders (for example health care providers who will use them)
Further research

1. We recommend a phased scale-up evaluation of the improved ALMANACH following the proposed modifications to the current ALMANACH to find out how safe are the new recommendations, how much consultation time is saved, its uptake over time and cost-effectiveness when compared to routine practice.

2. Find out how the improved ALMANACH can be integrated in to HMIS in order to collect accurate and timely data for planning and policy change at all levels of health care.

3. Find out how the improved ALMANACH can be used to improve routine supervision
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