# ALMANACH:
# a new electronic algorithm to promote evidence-based medicine and rational use of drugs in primary care for Tanzanian children aged 2 to 59 months.
# From development to pilot implementation

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## Summary

The worldwide rapid spread of antimicrobials resistance is a serious public health threat. In low-income countries, the expensive second- or third-line drug regimens required to treat resistant pathogens are often unavailable and/or unaffordable for patients. The correlation between the level of use of antimicrobials and resistance is well known. Rational use of antimicrobials is therefore essential to control resistance. In countries where infectious diseases are the leading cause of childhood mortality, the scarcity of diagnostic tools associated with the fear of life-threatening infections lead to an important overuse of antimicrobials. Primary care clinicians in low-income countries have limited training. In the 1990's, the World Health Organization and UNICEF developed the Integrated Management of Childhood Illness (IMCI) algorithm. IMCI is a simple clinical algorithm aimed at improving the primary care management of the five leading causes of death in children younger than 5 years: pneumonia, malaria, diarrhoea, measles, and malnutrition. Implemented in more than 75 countries, IMCI has had a limited impact on clinicians' performance and overuse of antimicrobials. Insufficient compliance to recommendations, insufficient specificity of diagnostic classifications, and lack of guidance for the management of fever once malaria has been ruled-out, are the main limitations that explain the uneven impact of IMCI on the quality of healthcare and rational prescription of antimicrobials for children. To address this public health concern we undertook a project called PeDiAtrick, aimed at developing and testing an innovative approach for a safe and rational use of antimicrobials in the management of childhood illness, by primary care health workers, in low income countries. The project had 4 main components:

(1) *Developing a new evidence-based clinical algorithm for the management of children aged 2 months up to 5 years in low income countries primary care facilities*, addressing the main treatable causes of acute illness, and assisting clinicians for decision-making to prescribe or withhold antibiotics in children.

(2) *Developing an electronic version of the new clinical algorithm,* as an android application running on mobile devices.

(3) *Assessing the safety of the new clinical algorithm* as compared to the current practices in Tanzanian health facilities in terms of health outcome and impact on antimicrobial prescription.

(4) *Assessing the impact of the implementation of the new electronic algorithm on clinicians' performance* in term of completeness of integrated assessment, appropriateness of disease classifications, and appropriateness of treatment prescriptions.

The overall aim of the PeDiAtrick project was to improve children health outcomes and rational prescriptions of antimicrobials in primary care, through the use of evidence-based clinical decision support system, in order to decrease childhood mortality and contain resistance spread.

As a first step, we undertook structured literature reviews to better understand the epidemiology of acute illnesses in low-income primary health care facilities, and to identify the best accurate diagnostic procedures for the main treatable infectious diseases. We confirmed that for the majority of childhood acute illnesses no accurate point-of-care tests are available. Apart from two exceptions (malaria and urinary tract infections) diagnoses are only based on clinical features in low resource primary care. We designed a new clinical ALgorithm for the MANAgement of CHildhood illnesses (ALMANACH) for children aged 2-59 months in primary care facilities, based on the evidence identified and on expert opinions. ALMANACH provides diagnostic procedures to rule out malaria, urinary tract infection, and typhoid fever and thus address most of the concerns of clinicians regarding the identification of bacterial infections in children younger than 5 years. ALMANACH also introduced a new classification entitled 'Likely viral infection' reached when bacterial infections are ruled out. This new diagnosis reminds clinicians that children often suffer from self-limited viral conditions that do not warrant any specific treatment beside symptomatic treatment. This should help clinicians to decrease their unnecessary prescription of antimicrobials. ALMANACH was formalised both as a paper booklet and as an electronic clinical decision support system in an android application.

Once ALMANACH was finalised, and before proposing it for formal implementation, we assessed the safety of its recommendations in terms of health outcomes. For that purpose we conducted a non-inferiority trial to assess children health outcome and antimicrobials prescriptions when managed by clinicians following strictly ALMANACH or following their routine practice primary care facilities, in Dar es Salaam, Tanzania. In these controlled conditions, ALMANACH was associated with significantly better health outcomes and an 80% reduction of antibiotic prescriptions,

as compared to routine practice. These results demonstrated the safety of ALMANACH in primary care, in Tanzanian, and the important positive impact on rational use of antimicrobials, in controlled conditions.

In order to assess whether the use of the electronic ALMANACH improves clinicians performance and rational use of medicines in programmatic conditions, we undertook a comparative study of consultation process. For this purpose, 9 health facilities in Dar es Salaam were randomised into 3 arms; 3 facilities were allocated to use the paper ALMANACH, 3 to use the electronic ALMANACH , and 3 to continue with current practice in a control arm. Four months after training, an observation survey of clinical consultation showed that the electronic ALMANACH improved the thoroughness of the clinical assessment by clinicians and reduced their prescriptions of antibiotic by 60%. These results have confirmed the positive impact of ALMANACH on rational use of antimicrobials in programmatic conditions, and demonstrated that mobile technology can facilitate the delivery of clinical algorithms to the endpoint users.

Additionally, the electronic ALMANACH is a data-collection tool. By integrating health information into the decision support system, it has potential to improve the monitoring of paediatric primary care activities, and the individual supportive supervision provided to the users.

ALMANACH has shown promising results within the core of the present thesis. Many mobile health solutions have been developed for low income countries; some have been tested in small scale pilot; and very few have been scaled up largely. The interest shown by two of the most important international humanitarian organisations will now give a chance to ALMANACH to be scaled-up and reach the initial main objective to improve health care delivered to children in low and middle income countries.

## Zusammenfassung

Die globale und schnelle Verbreitung antimikrobieller Resistenzen stellt eine ernstzunehmende Bedrohung für die öffentliche Gesundheit dar. Teuren Zweit- und Drittlinientherapien, die für die Behandlung resistenter Erreger benötigt werden, sind in Entwicklungsländern oftmals nicht erhältlich und/oder für Patienten und Patientinnen unbezahlbar. Antibiotikaresistenz korreliert stark mit dem Einsatz von Antibiotika korreliert. Deshalb ist es wichtig, Antibiotika zielgerecht anzuwenden. In Ländern mit geringem Einkommen sind übertragbare Krankheiten häufig die führende Todesursache bei Kindern—die Angst vor solch lebensbedrohlichen Infektionen, verbunden mit einem Mangel an Mitteln zur Diagnosestellung, führt zu blindem, weitgestreuten Verschreiben von Antibiotika. Hinzu kommt, dass die Ausbildung von Ärzten und Ärztinnen der medizinischen Grundversorgung in Ländern mit geringem Einkommen mangelhaft ist.

Demzufolge, entwickelten die Weltgesundheitsorganisation und das Kinderhilfswerk der Vereinten Nationen (UNICEF) n den 1990er Jahren UNICEF das „Integrierten Management von Kinderkrankheiten“ (IMCI), einen einfachen klinischen Algorithmus, der die Verbesserung der medizinischen Grundversorgung der fünf führenden Todesursachen von Kindern unter fünf Jahren zum Ziel hat: Lungenentzündung, Malaria, Durchfall, Masern und Mangelernährung. Obwohl IMCI mittlerweile in mehr als 75 Ländern eingesetzt wird, blieb die Auswirkung auf den übermässigen und fälschlichen Einsatz von Antibiotika, sowie die Qualität der Gesundheitsversorgng allgemein, gering. Dieser mangelnde Effekt wird einerseits mangelnde Einhaltung der IMCI Richtlinien und fehlende Genauigkeit bei diagnostischen Klassifizierungen seitens des Gesundheitspersonals, und andererseits lückenhafte Anleitungen zum zur Behandlung von Fiebererkrankungen, die nicht durch Malaria verursacht werden (zum Beispiel virale und bakterielle Infektionen). Um diese Problematik der öffentlichen Gesundheit anzusprechen, führten wir das PeDiAtrick Projekt durch, das zum

Ziel hatte, Gesundheitspersonal in Entwicklungsländern einen innovativen Zugang zum sicheren und rationalen Umgang mit Antibiotikain der Behandlung von Kinderkrankheiten zu schaffen. Das Projekt bestand aus vier Hauptkomponenten:

(1) *Entwicklung eines neuen, evidenzbasierten, klinischen Algorithmus zum Management von Kindern im Alter von zwei Monaten bis fünf Jahren in Einrichtungen der medizinischen Grundversorgung in Ländern mit geringem Einkommen,* der die Hauptursachen für behandelbare, akute Erkrankungen anspricht, und ÄrztInnen bei der Entscheidung zum Verschreiben oder Zurückhaltung von Antibiotika an Kindern hilft.

(2) *Entwicklung einer elektronischen Version dieses neuen klinischen Algorithmus,* in Form einer Android-App auf Mobilgeräten.

(3) *Beurteilung der Sicherheit dieses Algorithmus* im Vergleich zur gegenwärtigen Praxis in Gesundheitseinrichtungen in Tansania hinsichtlich1) gesundheitlicher Folgen 2)des Einflusses auf die Verschreibung von Antibiotika.(4) *Beurteilung des Einflusses der Anwendung des Algorithmus auf das Verhalten von Gesundheitspersonal* bezüglich der Vollständigkeit der integrierten Einschätzung, Angemessenheit der Krankheitseinteilungen und Angemessenheit der verschriebenen Behandlungen.

Das Gesamtziel des PeDiAtrick Projekts war die Verbesserung der Gesundheit von Kindern sowie die sinnvolle Verschreibung von Antibiotika in der medizinischen Grundversorgung:  durch den Gebrauch eines evidenzbasierten klinischen Unterstützungssystems zur Entscheidungsfindung, sollte die Kindersterblichkeit gesenkt werden und die Ausbreitung von Resistenzen eingedämmt werden.

Als erster Schritt unternahmen wir eine strukturierte wissenschaftliche Literaturrecherche, um die Epidemiologie von akuten Krankheiten in medizinischen Grundversorgungseinrichtungen mit mangelndem Einkommen besser zu verstehen, und, um die besten Verfahrensweisen zu einer genauen Diagnose der behandelbaren, üblichen Infektionskrankheiten zu bestimmen. Wir bestätigten, dass für den Grossteil akuter Kinderkrankheiten keine genauen Tests zur Diagnose vor Ort (Point-of-care-Tests) vorhanden sind. Von zwei Ausnahmen (Malaria und Harnwegsinfektionen) abgesehen, beruhen dort Krankheitsdiagnosen allein auf klinischen Merkmalen. Als nächsten Schritt, entwickelten wir einen neuen klinischen ALgorithmus zum MANAgement von Kinderkrankheiten (ALMANACH) für Kinder im Alter von 2 bis 59 Monaten in medizinischen Grundversorgungseinrichtungen, der auf publizierter Evidenz sowie Expertenmeinung aufbaut.

ALMANACH bietet Verfahrensweisen um Malaria, Harnwegsinfektionen und Typhus auszuschliessen, und spricht somit die meisten Bedenken von ÄrztInnen bezüglich der Identifizierung von bakteriellen Infektionen in Kindern unter fünf Jahren an. ALMANACH führt ebenfalls eine neue Klassifizierung unter dem Namen „Likely viral infection“ ein, welche eintrifft, sobald bakterielle Infektionen ausgeschlossen sind. Diese neue Diagnose erinnert Gesundheitspersonal daran, dass Kinder oftmals an selbstlimitierenden, viralen Erkrankungen leiden, welche zu keiner spezifischen Behandlunge, abgesehen der Symptombehandlung, berechtigen. Dies sollte Gesundheitspersonal dabei helfen, unnötige Antibiotikaverschreibungen zu reduzieren. ALMANACH wurde als Papierbroschüre sowie als elektronisches Unterstützungssystem zur klinischen Entscheidungsfindung als Android-App entwickelt.

Nach der Fertigstellung von ALMANACH und vor der offiziellen Implementierung, beurteilten wir die Sicherheit der Empfehlungen des Algorithmus. Zu diesem Zweck führten wir eine Nicht-Unterlegenheitsstudie in medizinischen Grundversorgungseinrichtungen in Tansania durch. Diese verglich dieden Gesundheitszustandsowie die Menge verschriebener Antibiotika zwischen PatientInnen, die gemäss ALMANACH oder gewöhnlicher Praxis versorgt wurden. Im Vergleich mit der gängigen Praxis wurde ALMANACH, unter diesen kontrollierten Bedingungen, mit signifikant besserer Gesundheitlage und einer Reduktion der Antibiotikaverschreibungen um 80% in Verbindung gebracht. Diese Resultate bewiesen, unter kontrollierten Bedingungen, die Sicherheit von ALMANACH in medizinischen Grundversorgungsinstituten in Tansania sowie den positiven Einfluss von ALMANACH auf angemessenem Antibiotikagebrauch.

Des Weiteren, um zu beurteilen, ob die Nutzung vom elektronischen ALMANACH das Verhalten von Gesundheitspersonal, wie auch die sinnvolle Verschreibung von Antibiotika verbessert, führten wir eine vergleichende Studie zum Ablauf der Konsultation durch. Hierfür wurden 9 Gesundheitseinrichtungen in Dar es Salaam zufällig in 3 Gruppen eingeteilt; 3 Einrichtungen wurden dazu angehalten, die Papierversion von ALMANACH zu benutzen, 3 sollten das elektronischen ALMANACH-App anwenden und 3 sollten ihre übliche Praxis in einer kontrollierten Gruppe weiterführen. Vier Monate nach der Einweisung zeigte eine Beobachtungsstudie der klinischen Konsultationen, dass der elektronische

ALMANACH die Gründlichkeit der klinischen Beurteilungen des Gesundheitspersonals verbesserte und deren Antibiotikaverschreibungen um 60% reduzierte. Diese Resultate bestätigten den Erfolg versprechenden Einfluss von ALMANACH auf die sinnvolle Antibiotikaverschreibungen und zeigten, dass mobile Technologie die Anwendung klinischer Algorithmen für NutzerInnen erleichtern kann.

Der elektronische ALMANACH ist zudem ein Datenerfassungsgerät: indem Gesundheitsinformationen in das Unterstützungssystem zur Entscheidungsfindung integriert werden, hat es zum einen Potential zur Verbesserung der Überwachung von medizinischen Grundversorgungsabläufen bei Kindern, als auch zur, durch die Überwachung geschaffene, individuelle Unterstützung des Nutzers.

Im Kern dieser gegenwärtigen Arbeit zeigte ALMANACH vielversprechende Resultate. Für Länder mit geringem Einkommen wurden viele Gesundheitslösungen, die auf mobilen Technologien basieren, entwickelt. Manche davon wurden in kleinformatigen Pilotstudien getestet, und sehr wenige wurden in einem grossen Massstab durchgeführt. Das Interesse, welches von zwei der wichtigsten internationalen humanitären Organisationen gezeigt wird, gibt ALMANACH die Chance sich durchzusetzen und sein ursprüngliches Hauptziel, nämlich die Verbesserung der Gesundheitsversorgung von Kindern in Ländern mit geringem und mittlerem Einkommen, zu erreichen.

## Résumé

La propagation rapide de la résistance aux antimicrobiens est une menace pour la santé publique mondiale. Dans les pays à faibles ressources, les médicaments antimicrobiens de secondes ou troisièmes lignes, nécessaires pour traiter les pathogènes résistants, sont souvent indisponibles ou inaccessibles pour les patients. La corrélation entre le niveau d'utilisation des antimicrobiens et le développement de résistance est bien connue. L'utilisation rationnelle des antimicrobiens est donc essentielle pour le contrôle des résistances. Dans les pays où les maladies infectieuses sont la première cause de mortalité infantile, le manque de moyens diagnostiques associé à la peur des infections mènent à une surutilisation des antimicrobiens. Les cliniciens de premier recours dans les pays à faible ressources reçoivent peu de formation. Dans les années 1990, l'Organisation Mondiale de la Santé et l'UNICEF ont développé la Prise en Charge Intégrée de Maladies de l'Enfant (PCIME). La PCIME est un algorithme clinique simple qui visait à améliorer la prise en charge initiale des cinq maladies causant le plus grand nombre de décès chez les moins de 5 ans : la pneumonie, le paludisme, la diarrhée, la rougeole, et la malnutrition. Mise en œuvre dans plus de 75 pays, la PCIME a eu un impact limité sur les performances des cliniciens et la surutilisation des antimicrobiens. Le manque de compliance des cliniciens aux recommandations, le manque de spécificité des classifications diagnostiques, et le manque d'orientation claire pour la prise en charge des fièvres lorsque le paludisme est exclu, sont les principales explications de l'impact inégal de la PCIME sur la qualité des soins et la prescription rationnelle des antimicrobiens pour les enfants. Pour adresser ce problème de santé publique, nous avons entrepris le projet PeDiAtrick, afin de développer et tester une approche innovante pour améliorer l'utilisation des antimicrobiens et les issues thérapeutiques pour les maladies de l'enfant. Le projet avait 4 composantes principales :

*(1) Développement d'un nouvel algorithme clinique fondé sur les données probantes pour la prise en charge, en soins de santé primaires, des enfants âgés de 2 mois à 5 ans, dans les pays à faibles ressources*, adressant les principales causes traitables de maladies aigues, et apportant aux cliniciens une aide à la décision pour la prescription des antimicrobiens.

(2) *Développement d'une version électronique du nouvel algorithme clinique,* sous la forme d'une application android pour appareils de téléphonie mobile.

(3) *Evaluation de la sécurité du nouvel algorithme en termes d'issues thérapeutique* par rapport aux pratiques en vigueur dans les centres de santé Tanzaniens, et aux prescriptions d'antimicrobiens.

(4) *Evaluation de l'impact du nouvel algorithme électronique sur les performances des cliniciens,* en particulier sur l'exhaustivité de l'examen clinique, la pertinence des classifications de maladies, et la pertinence des prescriptions médicamenteuses.

L'objectif général du projet PeDiAtrick était ainsi de diminuer la mortalité infantile et de contenir la propagation des résistances aux antimicrobiens.

Dans un premier temps, nous avons conduit des revues structurées de la littérature afin de mieux comprendre l'épidémiologie de maladies aiguës dans les structures de santé primaires des pays à faible ressources, et d'identifier les méthodes diagnostiques les plus fiables pour les principales maladies infectieuses curables. Nous avons confirmé que pour la majorité des maladies aiguës de l'enfant, aucun test précis réalisable au chevet des patients n'est disponible. A deux exceptions près (paludisme et infections urinaires) les diagnostics se font uniquement sur les signes et symptômes cliniques, dans les centres de soins primaires à faible ressources. Nous avons conçu un nouvel algorithme clinique pour le traitement des maladies de l'enfant âgé de 2 à 59 mois (ALMANACH) dans les établissements de soins primaires, sur la base des données probantes identifiées complété par des avis d'experts. ALMANACH propose des procédures diagnostiques pour identifier ou exclure le paludisme, les infections urinaires et la fièvre typhoïde, et ainsi répondre aux préoccupations principales des cliniciens concernant les infections bactériennes chez les enfants de moins de 5 ans. ALMANACH a également introduit une nouvelle classification intitulée «infection virale probable », classification atteinte lorsque les infections bactériennes sont exclues. Ce nouveau diagnostic rappelle aux cliniciens que les enfants souffrent souvent de maladies virales bénignes qui ne nécessitent aucun traitement spécifique, en dehors d'un traitement symptomatique. Cela devrait aider les cliniciens à diminuer leurs prescriptions inutiles d'antibiotiques. ALMANACH a été conçu sous forme de livret papier, et sous forme d'une application android en un véritable système électronique d'aide à la décision clinique.

Après avoir finalisé ALMANACH, et avant de le déployer, nous avons évalué la sécurité de ses recommandations pour la santé des enfants. À cette fin, nous avons mené une étude de non-infériorité pour évaluer les résultats thérapeutiques et les prescriptions d'antimicrobiens pour les enfants pris en charge par des cliniciens suivants strictement ALMANACH, ou suivants leur pratique de routine, dans des structures de santé de soins primaires, à Dar es Salaam, en Tanzanie. Dans ces conditions contrôlées, ALMANACH a été associé à des résultats thérapeutiques significativement supérieurs, et à une réduction des prescriptions d'antibiotiques de 80%, par rapport à la pratique courante. Ces résultats ont démontré, que ALMANACH, en conditions contrôlées dans les soins primaires en Tanzanie, assurait la sécurité des patients, et avait un impact positif important sur l'utilisation rationnel des antimicrobiens.

Afin d'évaluer si l'utilisation de la version électronique d'ALMANACH dans des conditions programmatiques améliorerait les performances des cliniciens, et l'utilisation rationnelle des médicaments, nous avons conduit une étude comparative des processus de consultation. A cet effet, 9 structures de santé de Dar es Salaam ont été randomisées en 3 bras; 3 structures de santé ont été désignées pour utiliser ALMANACH sous format papier, 3 pour utiliser la version électronique, et 3 pour continuer leur pratique de routine, dans un bras contrôle. Quatre mois après une formation initiale, une étude d'observation des consultations a montré que la version électronique d'ALMANACH améliorait l'exhaustivité de l'évaluation clinique et réduisait les prescriptions d'antibiotiques de 60%. Ces résultats ont confirmé l'impact positif de ALMANACH sur l'usage rationnel des antimicrobiens dans des conditions programmatiques, et a démontré que la technologie mobile peut faciliter la mise à disposition d'algorithmes cliniques pour les utilisateurs finaux.

De plus, la version électronique d'ALMANACH est un outil de collecte de données. Intégrant la collecte d'informations médicales au système d'aide à la décision clinique, ALMANACH a un fort potentiel d'amélioration du suivi des activités de soins primaires pédiatriques, et de la supervision individuelle des utilisateurs. ALMANACH a montré des résultats prometteurs dans le cadre de cette thèse. De nombreuses solutions technologiques de santé mobile ont été développées pour les pays à faible ressources, certaines ont été testées à petite échelle dans des expériences pilotes, très peu ont été déployées à grande échelle. L'intérêt manifesté

par deux des plus importantes organisations humanitaires internationales va maintenant donner une chance à ALMANACH d’être mis en place à plus grande échelle et atteindre son objectif initial d'améliorer les soins de santé pour les enfants des pays à faibles ressources.

## Muhtasari

Kuongezeka kwa haraka kwa usugu wa vijidudu dhidi ya dawa duniani limekuwa tishio kubwa kwa afya ya jamii. Katika nchi zenye kipato duni dawa za gharama kubwa za daraja pili au la tatu ambayo hutumika kutibu vijidudu sugu vya magonjwa mara nyingi hazipatikani, au hazinunuliki kutokana na kuwa na gharama kubwa. Uhusiano juu ya kiwango cha utumiaji wa dawa na usugu wake unajulikana vyema. Umakini katika utumiaji wa dawa hizo ni muhimu ili kuzuia usugu. Katika nchi ambazo magonjwa ya kuambukiza ndiyo yanayoongoza kwa vifo vya watoto, upungufu wa vifaa tiba vya kupima na kugundua aina ya magonjwa pamoja na hofu ya maambukizi yanayohatarisha maisha, ni sababu kubwa inayopelekea utumiaji usio na mipaka wa dawa. Wataalamu wa afya ya msingi katika nchi zenye kipato cha chini wana uelewa mdogo, au mafunzo hafifu. Katika miaka ya 1990, shirika la afya duniani (WHO) na UNICEF walitengeneza mpango wa pamoja wa kushughulikia magonjwa ya watoto kikamilifu, programu rahisi ambayo ililenga kuboresha utoaji huduma kwa afya ya msingi juu ya magonjwa matano makubwa ambayo huchangia sana vifo vya watoto chini ya umri wa miaka 5; yaani Nimonia, malaria, kuhara, surua, na utapiamlo. Pamoja na mpango huu kutekelezwa katika nchi zaidi ya 75, bado mpango huu haujaweza kuboresha utendaji wa wahudumu wa afya ya msingi hasa kwenye matumizi yasiyo ya lazima ya dawa. Upungufu wa watendaji wa afya kwenye kuutumia mpango huo, upungufu wa kutokuwepo mwongozo hasa wa utambuzi wa magonjwa na kutokuwepo mwongozo wa ushughulikiaji wa homa hasa pale mtoto anapokuwa hana malaria, vimetajwa kuwa ndiyo sababu kubwa za kutokuwepo na mlinganyo wa matokeo chanya ya matumizi ya mpango wa IMCI juu ya ubora wa huduma za afya na hivyo kutopunguza matumizi ya dawa kwa watoto. Ili kulishughulikia tatizo hili la afya ya jamii, tulianzisha mradi ulioitwa PeDiAtrick, uliolenga kuandaa na kujaribisha njia za kitaalamu za jinsi kutatua tatizo la matumizi yasiyo ya lazima ya dawa katika kushughulikia magonjwa ya watoto kwa wahudumu wa afya ya msingi kwenye nchi zenye kipato cha chini. Mradi huu ulikuwa na maeneo manne makubwa.

(1) *Kuandaa mpango mpya na thabiti wa hatua kwa hatua kwa ajili ya kuhudumia magonjwa ya watoto kati ya miezi miwili hadi miaka 5 katika nchi zenye kipato cha chini kwenye vituo vya afya ya msingi,* kwa kushughulikia magonjwa

makuu yanayotibika, na kuwasaidia wahudumu wa afya kufanya maamuzi sahihi juu ya kutoa dawa au kutotoa dawa kwa watoto.

(2) *Kuandaa mpango wa kielektroniki kutokana na ule mpango mpya wa hatua kwa hatua utakaotumika katika* simu za mikononi zenye mfumo wa android

(3) *Kutathmini usalama wa mpango huu mpya* ukilinganisha na utaratibu uliozoeleka hapa Tanzania katika vituo vya afya kwa kuangalia matokeo ya kiafya na matokeo ya utoaji wa madawa.

(4) *Kupima matokeo utendaji ya mpango wa kielektroniki kwa watendaji wa afya* kwa maana ya kukamilisha vipimo, usahihi wa utambuzi wa ugonjwa na usahihi wa matibabu yaliyopendekezwa.

Lengo kuu la mradi wa PeDiAtrick ni kuboresha matokeo ya matibabu ya watoto na kupunguza matumizi yasiyo ya lazima ya dawa katika vituo vya afya ya msingi kwa kufuata maamuzi sahihi yatokanayo na majibu au matokeo yanayotolewa na matumizi ya simu za mkononi ili kupunguza vifo vya watoto na kusambaa kwa usugu wa vijidudu dhidi ya magonjwa.

Kama hatua ya kwanza, tulisoma machapisho mbalimbali ili kuelewa usaambaji wa magonjwa hatari kwenye vituo vya afya ya msingi katika nchi zenye kipato kidogo, na ili kujua namna au njia bora na ya uhakika ya kutambua magonjwa makuu ambukizi yanayotibika. Tulithibitisha kwamba kwa magonjwa makuu ya watoto hapakuwa na njia sahihi kabisa ya vipimo na utambuzi wake. Isipokuwa kwa malaria na maambukizi ya njia ya mkojo, utambuzi ulitegemea tu mazoea ya muonekano wa mgonjwa kutokana na kutokuwepo kwa vifaa tiba vya vipimo na utambuzi katika vituo vya afya ya msingi. Kwa hiyo tuliandaa mpango mpya wa kushughulikia magonjwa ya watoto yaani ALgorithim for MANAgement of Child illnesses (ALMANACH) kwa watoto wenye umri kati miezi 2 hadi 59 kwa vituo vya afya ya msingi ulioandaliwa juu ya misingi thabiti na maoni ya wataalamu. ALMANACH inatoa njia ya utambuzi wa kuwepo au kutokuwepo kwa magonjwa ya malaria, maambukizi ya njia ya mkojo, na homa ya matumbo, na hivyo kuwasaidia watendaji wengi wa afya kuondoa dhana ya maambukizi ya bakteria kwa watoto walio chini ya umri wa miaka mitano. ALMANACH pia inatoa njia nyingine mpya inayoitwa “uwezekano wa maambukizi ya virusi” ambapo hufikiwa baada ya kuonyesha kuwa hakuna uwezekano wa maambukizi ya bakteria. Mpango huu mpya unasaidia kuwakumbusha watendaji wa afya kuwa mara nyingi watoto husumbuliwa na magonjwa ya virusi yanayopona

yenyewe ambayo hayahitaji matibabu yoyote maalumu isipokuwa tu kutibu dalili zinazojitokeza. Hii inapaswa kuwasaidia watendaji wa afya kupunguza matumizi yasiyo ya lazima ya dawa. ALMANACH ilitengenezwa kama kijitabu na nyingine ikawekwa kwenye programu ya simu zenye mfumo wa android.

Baada ya kukamilisha uandaaji wa ALMANACH na kabla ya kuipendekeza itumiwe kama mpango kamili wa matibabu, tulipima usalama wa mapendekezo yake kwa kuangalia matokeo ya kiafya. Kwa kusudi hilo tulifanya majaribio yakiulinganifu ili kupima matokeo ya kiafya ya watoto na matumizi ya dawa za antibiotiki wakati wakitumia ALMANACH hii au wakifuata utaratibu wa kawaida hapa Tanzania katika vituo vya afya ya msingi. Katika njia hizi mbili za matibabu, ALMANACH ilionyesha matokeo mazuri zaidi na kupunguza asilimia 80% ya matumizi ya dawa za antibiotiki ukilinganisha na utaratibu uliozoeleka wa kutoa matibabu kwa watoto. Matokeo haya yanadhihirisha usalama wa matumizi ya ALMANACH katika afya ya msingi Tanzania na matokeo chanya muhimu ya kupunguza matumizi ya dawa hizo kwa kutumia mpango unaosimamiwa.

Ili kupima kama matumizi ya ALMANACH ya kielektroniki inaboresha utendaji wa wahudumu wa afya na kupunguza matumizi yasiyo ya lazima ya dawa za kuua vijidudu katika hali ya kawaida, tulifanya utafiti wa ulinganifu wakati wagonjwa wakionwa na daktari. Kwa lengo hili, vituo 9 vya afya hapa Dar es Salam vilichaguliwa na kuwekwa katika makundi matatu kitaalamu. Kundi la kwanza ni la vituo vitatu ambavyo vilitumia kijitabu cha ALMANACH, vituo vingine vitatu vilitumia ALMANACH ya kielektroniki kwenye simu, na vituo vingine vitatu viliendelea kufuata utaratibu wa kawaida uliozoeleka wa kutibu watoto. Miezi minne baada ya mafunzo, utafiti ulifanyika na ulionyesha kuwa ALMANACH ya kielektroniki iliboresha sana utambuzi wa magonjwa kwa madaktari na kupunguza matumizi ya dawa za antibiotiki kwa asilimia 60%. Matokeo haya yanathibitisha matokeo chanya ya matumizi ya ALMANACH katika kupunguza matumizi ya madawa ya kuua vijidudu katika programu za kutibu watoto, na pia yanaonyesha kuwa teknolojia ya simu za mkononi inaweza kusaidia kutoa huduma za tiba kwa mtumiaji wa mwisho katika vituo vya afya.

Kwa nyongeza, matumizi ya ALMANACH ya kielektroniki yanasaidia kama kifaa cha kukusanya taarifa. Kwa kuingiza taarifa za kiafya katika mfumo huu wa kumsaidia daktari kufanya maamuzi, ALMANACH ina nafasi kubwa ya kuboresha ufuatiliaji wa afya ya msingi katika matibabu ya watoto na msaada wa usimamizi unaotolewa kwa watumiaji.

ALMANACH imeonyesha matokeo mazuri katika msingi wa tasnifu hii ya sasa. Fumbuzi nyingi za kitabibu zinazotumia teknolojia ya simu za mkononi zimetengenezwa kwa ajili ya nchi zenye kipato cha chini; baadhi zimejaribiwa katika tafiti ndogo ndogo za awali na chache sana zimetumiwa katika tafiti kubwa. Nia iliyoonyeshwa na mashirika mawili makubwa muhimu ya kimataifa ya misaada ya kibinadamu itaipa nafasi ALMANACH kutumiwa kwa kiasi kikubwa na kufikia lengo la msingi la kuboresha utoaji wa afya kwa watoto katika nchi zenye kipato cha chini na cha kati.

## Acronyms and abbreviations

| | |
|---|---|
| ALMANACH | Algorithm for the management of childhood illness |
| ARI | Acute Respiratory Infection |
| CDSR | Cochrane Database for Systematic Reviews |
| CHERG | Child Health Epidemiology Reference Group |
| CI | Confidence Interval |
| CXR | Chest X ray |
| DALY | Disability Adjusted Life Year |
| HF | Primary care Health Facility |
| HIV | Human Immodeficiency Virus |
| HSROC | Hierarchical Summary Receiver Operation Characteristics |
| HW | Health Worker |
| IHME | Institute for Health Metrics and Evaluation |
| IMCI | Integrated Management of Childhood Illness |
| LR | Likelihood Ratio |
| MCE | Multi Country Evaluation |
| mRDT | Malaria Rapid Diagnostic Test |
| PACTR | Pan African Clinical Trial Registry |
| PATH | Program for Appropriate Technology in Health |
| POCT | Point-of-care test |
| RR | Risk Ratio |
| SSA | Sub-Saharan Africa |
| QUADAS | Quality Assessment of Diagnostic Accuracy Studies |
| U5 | Children Under the age of 5 years |
| UNICEF | United Nations Children Funds |
| URTI | Upper Respiratory tract Infection |
| UTI | Urinary Tract Infection |
| WHO | World Health Organization |

# 1 Introduction

In 2006, a project aimed at reducing the unnecessary use of antimalarial medicines introduced accurate and easy-to-use point of care tests for malaria diagnosis, the malaria rapid diagnostic tests (mRDT). In the Tanzanian health facilities where they were introduced, mRDT led to a dramatic decrease of the proportion of children under 5 years of age (U5) prescribed antimalarials, from 75% before to 15% after mRDT introduction. But the decrease in antimalarials' prescriptions led to increased antibiotic prescriptions, that rose from 57% to 81% of the U5 attending with a complain of fever (D'Acremont et al., 2011).

## 1.1 Antimicrobial use and resistance

Over-prescription of antimicrobials is a worrying phenomenon observed worldwide (Gwimile et al., 2012) that facilitates and fasten the spread of resistant pathogens. In low income countries, and especially in Sub Saharan Africa, data to capture the extent of the problem of resistance are limited. Only few countries in Africa have an appropriate surveillance system for drug resistance (WHO, 2014), and an external audit reported weaknesses in antibiotic susceptibility testing in public health laboratories in many African countries (Frean et al., 2012). However, the available data shows that antibiotic resistance is growing in African countries as in the rest of the world. A recent review and meta-analysis of community-acquired bacteremia in neonates and infants in low income countries reported that more than 35% of the bacteria identified showed either resistance or reduced susceptibility to the first and second lines antibiotics recommended by WHO for sepsis management. i.e. combination of penicillin and gentamicin and third-generation cephalosporins. Two recent surveys conducted in Tanzanian tertiary hospitals reported high level of resistance in the bacteria isolated in bloodstream infections. In Mwanza, in children U5, isolates that were in majority enterobacteria (*Escherichia coli* 33.3% and *Klebsiella pneumoniae* 28.6%) were highly resistant to ampicillin (95%), co-trimoxazole (90%), tetracycline (90%), gentamicin (80%), augmentin (80%), chloramphenicol (65%), ceftriaxone (35%), and ciprofloxacin (30%) (Christopher et al., 2013). And in a retrospective analysis of blood cultures performed from 2005 to 2009 in the Muhimbili national hospital, pathogens isolated in bloodstream infections, mainly Gram-positive bacteria (coagulase-negative staphylococci 67.4% and

*Staphylococcus aureus* 13.2%), showed high resistance to penicillin G (70.6%), tetracycline (63.8%), cefotaxime (62.5%) and ampicillin (62.3%), and moderate to high resistance against chloramphenicol (45.2%), erythromycin (35.0%), ciprofloxacin (29.3%), co-trimoxazole (25.0%) and gentamicin (23.5%) (Moyo et al., 2010). Carbapenemase genes were also recently detected in about 10% of multi-drugs resistant Gram-negative bacteria isolated from patients in Mwanza (Mushi et al., 2014). Still in Mwanza, in patients presenting with bloody diarrhoea, all Shigella strains had high resistance to ampicillin, tetracycline, trimethoprim-sulphamethoxazole and chloramphenicol, the recommended drugs for management of dysentery in Tanzania (Temu et al., 2007). If the majority of data initially came from tertiary hospital, there is now also evidence of the presence of antimicrobial-resistant pathogens in the community. In Tanzania, 105 out of 300 (35%) healthy children U5 attending a child health clinic in Dar es Salaam were found to carry *Streptococcus pneumoniae* in their nasopharynx. The majority of the isolates (78/115; 68%) were penicillin-non-susceptible pneumococci and multidrug resistance was detected in 19 isolates (17%) (Moyo et al., 2012). In Madagascar, extended-spectrum ß-lactamase-producing Enterobacteria (ESBL-PE) were isolated from the stools of 49 out of 484 (10%) non-hospitalised patients screened (Herindrainy et al., 2011). And in 1999 in Ifakara, rural Tanzania, the majority of diarrheagenic E. coli isolates from children U5 with acute diarrhoea were resistant to co-trimoxazole (87%), ampicillin (85%) and tetracycline (80%); 42% of the isolates were also resistant to chloramphenicol and 2 out of the 130 isolates were resistant to nalidixic acid (Vila et al., 1999). These data show a worrying level of resistance of circulating pathogens to the available first and second line regimen of antibiotics in Tanzania, but also already the presence of pathogen resistant to antibiotics that are not commonly prescribed in these contexts.

Antimicrobial resistance is associated with increased mortality and prolonged hospital stays (Blomberg et al., 2007; Cosgrove, 2006; de Kraker et al., 2011). Treating resistant pathogens requires more expensive second- or third-line drug regimen that are often unavailable and/or unaffordable for patients in low and middle income countries (Laxminarayan and Heymann, 2012). The continuous emergence of pathogens with new resistance profiles and the lack of new antimicrobial classes in the pipelines of pharmaceutics industry may soon threaten the modern medicine wonders, such as surgery, organ transplantation, preterm infants' treatment, that are not possible without effective antibiotics (Laxminarayan et al., 2013). Infectious

diseases mortality declined over the 20th century; this achievement may soon be jeopardised if no actions are taken to tackle resistance to antimicrobials. If new antibiotics could help tackle this public health threat, there are few options under development and preserving the ones available today, by better targeting the patients in need of them and so decreasing the unnecessary prescriptions, is urgently needed. Indeed, level of resistance is associated with the level of antibiotic use, at the population level (Goossens et al., 2005; Stewardson et al., 2011; Vernaz et al., 2011) and at individual level (Costelloe et al., 2010; Stewardson et al., 2011). And a growing body of evidence shows that the decrease of antibiotic use, or better selection of antibiotic classes leads to decreased level of resistance in hospitals and in communities (Butler et al., 2007; Dagan et al., 2008; Guillemot et al., 2005; Kardas-Sloma et al., 2013; Molstad et al., 2008; Smith, 1999).Improving diagnosis capacity is a necessary step towards decreasing the overuse of antimicrobials, and mRDTs may definitely improve the rational use of antimalarials. But the rise of antibiotic prescription observed in D'Acremont's (2011) and other mRDT implementation projects (Baiden et al., 2012; Msellem et al., 2009) have brought concerns, and questions regarding the relevance of their implementation (Baiden et al., 2011). If mRDT implementation resulted in shifting the burden of unnecessary antimalarial to unnecessary antibiotics, this would of course be a failure. Instead of precluding the implementation of an accurate diagnostic tool, this should call for providing to clinicians better guidance for the management of the non-malaria fevers, from diagnosis to treatment. In settings were mRDT are to be implemented, clinicians were trained for decades to treat malaria presumptively in all children with history of fever. Malaria was therefore often the only cause of fever considered, and clinicians' knowledge, skills and tools for the management of non-malaria fever, a new concept brought to them by the negative mRDT, are likely to be scarce in these settings. Improving clinicians' access to appropriate non-malaria fever diagnoses and treatment procedures, while introducing mRDT, is therefore mandatory. While aiming at decreasing the unnecessary use of antimicrobials, the procedures should of course ensure appropriate identification and prompt treatment of all treatable potentially life-threatening infectious diseases that are till today the leading causes of death in children under 5 years of age (Liu et al., 2014).

## 1.2 Available guidelines for the management of childhood illness

For primary care facilities in low income countries, a standard of care for the management of paediatric acute illnesses, including fever, was developed in the 1990's by the World Health Organization (WHO) and the United Nations Children Funds (UNICEF): the Integrated Management of Childhood Illness (IMCI) guidelines (Gove, 1997). Developed to tackle childhood morbidity and mortality in low income countries, the clinical guidelines propose an integrated syndromic algorithm, relying on simple clinical signs and symptoms to improve case management and access to treatment for the 5 leading causes of child death: malaria, pneumonia, diarrhoea, measles, and malnutrition. The clinical algorithm is part of the larger IMCI strategy that aims at decreasing child mortality by improving i) the diseases case management by health workers (HWs), ii) the overall health systems, and iii) the family and community health practices. In Tanzania, where D'Acremont et al. (2011) assessed the impact of mRDT on antimicrobials prescriptions, IMCI was the national standard of care recommended for the management of children under 5 years of age, in primary care. When using IMCI algorithm, clinicians are recommended to prescribe (or administer) antimalarials to children with fever or history of fever and antibiotics to children with classification of severe or very severe diseases, lower respiratory tract infection, dysentery, or acute ear infection. The introduction of mRDT changed the IMCI antimalarial prescription recommendation from presumptive to test-based treatment. However, clinicians if they had followed IMCI recommendations for the management of acute illnesses in children should not have prescribed antibiotics to 80% of children as observed by D'Acremont et al. (2011), but rather only to the children classified as having severe or very severe diseases, lower respiratory tract infection, dysentery, or acute ear infection, as proposed by IMCI algorithm . Different elements may explain the observed high antibiotic use in this context.

## 1.3 Limitations of the existing guidelines

### 1.3.1 Insufficient uptake

The United Republic of Tanzania participated in the early development of IMCI, piloting the IMCI case management training in 1996 and starting the national roll out in 1998. In Tanzanian districts participating in the IMCI - Multi Country Evaluation (MCE)(Bryce et al., 2004), IMCI appeared to improve the quality of care (J.

Armstrong Schellenberg et al., 2004), to lower U5 mortality rates, and to be cost effective (J. R. Armstrong Schellenberg et al., 2004). If Ethiopia also observed an impact on child mortality (Rakha et al., 2013), the other countries participating in the IMCI-MCE failed to demonstrate that IMCI reduces child mortality (Amaral et al., 2005; Arifeen et al., 2009; Huicho et al., 2005b). Important constraints towards large-scale IMCI implementation exist (Ahmed et al., 2010; Prosper et al., 2009) and may explain that the expected impact was not observed in these countries. At primary care level, some surveys have shown that IMCI can improve clinicians performance, in term of thoroughness of children's health problems' assessment (Amaral et al., 2004; J. Armstrong Schellenberg et al., 2004; Chopra et al., 2005), appropriateness of disease classifications (Amaral et al., 2004; J. Armstrong Schellenberg et al., 2004), and appropriateness of treatment prescribed (Chopra et al., 2005; Gouws et al., 2004; Naimoli et al., 2006; Zhang et al., 2007). However the low training coverage (Ahmed et al., 2010; Mushi et al., 2010) and clinicians' low use of IMCI and low compliance to recommended procedures often impaired IMCI's impact on HWs' performance and rational use of medicines (Arifeen et al., 2005; Horwood et al., 2009a; Rowe et al., 2012; Senn et al., 2014). A recent mixed-method study has explored the reasons of clinicians' low compliance to IMCI guidelines (Lange et al., 2014). The main reasons identified by the authors were a lack of motivation to adhere to IMCI guidelines, partly due to a weak belief in the importance of following the guidelines, and a physical and/or cognitive "overload", resulting in lack of capacity to concentrate fully on each and every case. These represent important barriers towards guidelines implementation that should be considered and addressed when proposing new procedures for the management of fever in low resource settings.

### 1.3.2 Insufficient diagnostic accuracy

Another limitation within IMCI guidelines towards rational use of antimicrobial is the lack of specificity of some features used for diagnoses classifications. Designed to decrease U5 mortality and to be easy-to-use by lay clinicians, the clinical algorithm relies on clinical case definitions with high sensitivities. A high sensitivity is indeed necessary to detect children at risk and prevent death by prompt treatment for serious infectious diseases. But if the classification definitions have low specificities, they will result in important overuse of antimicrobial. Recent works have suggested that the definition used to diagnose pneumonia lacks specificity and that many of the children prescribed antibiotics may actually not benefit from them (Hazir et al., 2011;

Senn et al., 2014). WHO clinical case-definition of pneumonia (cough or difficult breathing associated with fast-breathing and/or chest indrawing) was derived from diagnostic test accuracy studies that initially targeted low respiratory tract infection (Shann et al., 1984). In usual medical language, the term ‘pneumonia’ refers to bacterial parenchymal lung infections, while ‘lower respiratory tract infection’ refers to all lung infections being either caused by viruses (such as bronchitis or bronchiolitis) or bacteria. In the WHO acute respiratory infections (WHO-ARI) program, the term pneumonia was kept although the clinical case definition encompassed other lower respiratory tract infections and this may lead to confusion for clinicians (Brewster, 2015). Furthermore, in countries lacking efficient civil registration systems, mortality data are collected through verbal autopsy. The verbal autopsy questionnaire cannot differentiate bacterial pneumonia from other lower respiratory tract infections. Therefore when pneumonia is designated as the leading cause of childhood mortality in low-income countries, it doesn’t mean bacterial pneumonia. In the 1980’s bacterial pneumonia were maybe the dominant causes of lower respiratory tract infections. However, recent work has found viruses to be the main causes of WHO-defined pneumonia (Berkley et al., 2010; D’Acremont et al., 2014; Rudan et al., 2008), which is in line with surveys showing that the majority of chest radiographs taken in children with WHO-defined pneumonia are normal (D’Acremont et al., 2014; Hazir et al., 2006). Therefore, this ambiguity in the use of the term ‘pneumonia’ is likely to lead to inappropriate use of antimicrobial by clinicians. Identifying predictors of bacterial pneumonia instead of predictors of lower respiratory infections used in the current WHO-ARI chart would help refining the algorithm to better target children in need of antibiotics among the many children attending primary care facilities with acute respiratory infections.

The burden of the targeted diseases in term of prevalence, etiology, and case fatality rate and the availability of diagnostic test also modulate the relevance of diagnoses’ classifications. Until 2014, IMCI recommended a presumptive treatment for malaria in all children with fever or history of fever, where malaria risk was high. If this strategy may be meaningful when the majority of fever cases are due to malaria, the decrease in malaria transmission observed in the recent decade (Ceesay et al., 2010; D’Acremont et al., 2010a; O’Meara et al., 2008), together with the rapid spread of antimalarial resistance and the cost of the present first-line regimen (artemisin-based combination therapy – ACTs), made this strategy obsolete, dangerous, and costly.

But until accurate and affordable mRDT were developed and deployed, the lack of good clinical predictors made this strategy the only possible one to tackle malaria-related child mortality. Since 2010 WHO recommends a test-based malaria treatment (WHO, 2010), and this strategy was endorsed by the WHO IMCI in the 2014 chart booklet (WHO and UNICEF, 2014). Regular and prompt updates of clinical algorithms when new epidemiological knowledge or technologies are available are mandatory, although difficult, to ensure appropriate management of the children with acute infections.

### 1.3.3 Recommendation gap: non-malaria fever

Before the introduction of a malaria test in IMCI, the fever chart was only considering malaria and measles. Although children with other associated symptoms (cough, diarrhoea or ear problem) were also assessed for other causes of fever within the dedicated symptoms charts, only malaria and measles were directly assessed in the fever chart. With the introduction of the malaria test in the fever chart (WHO and UNICEF, 2014), the following recommendation was formulated for children with history of fever or elevated temperature tested negative for malaria: “Give appropriate antibiotic treatment for an identified bacterial cause of fever”. A footnote suggest the HWs to look for the following clinical features in these patients: local tenderness; oral sores; refusal to use a limb; hot tender swelling; red tender skin or boils; lower abdominal pain or pain on passing urine in older children. Without further specifications, this may not represent a useful guidance for clinicians to achieve a rational management of the non-malaria fever in children. While reminding clinicians about the possible serious bacterial diseases, which is important to ensure the children suffering from these conditions receive life-saving treatment, these notes do not provide support to rule out bacterial diseases. Therefore, this recommendation formulation is likely to lead to important prescription of antimicrobials, clinicians fearing to miss a potentially life-threatening disease.

Understanding the reasons for antibiotics prescription and the actual treatable causes of non-malaria fever is necessary to assess whether better clinical algorithm could and should be proposed.

## 1.4 Clinicians' behaviour with regards to antibiotic prescriptions

Over-prescription of antibiotics in ambulatory children is a well-documented phenomenon in low-income (Gwimile et al., 2012; Means et al., 2014; Risk et al., 2013) and high-income countries (Nyquist et al., 1998). Recent trends of antibiotics prescription in low-income countries are not reassuring, and in Sub Saharan Africa the percentage of children younger than 5 years treated with antibiotics for an URTI almost doubled over 25 years to reach over 70% in 2004-2006 (WHO Medicines, 2009). Interventions aimed at decreasing the overuse of antimicrobials in ambulatory care have shown varying impact (Arnold and Straus, 2005; Ranji et al., 2008; Vodicka et al., 2013). Multifaceted interventions and interventions addressing the prescribing behaviour and barriers to change in the particular setting are more likely to have a positive impact on prescriptions.(Arnold and Straus, 2005)

Understanding the prescribing behaviour and barriers to change in Sub Saharan African primary care facilities is therefore of high interest. In Sub-Saharan African countries, the average consultation time in ambulatory care is 5 minutes (WHO Medicines, 2009). In surveys looking at the consultations' process, clinicians often performed only a small proportion of the assessment tasks recommended by the IMCI algorithm (Bjornstad et al., 2014; Horwood et al., 2009a; Maestad et al., 2010; Rowe et al., 2012; Zurovac and Rowe, 2006). When their level of knowledge is evaluated, it is often much higher than what they actually apply. Excessive workload is a reason often mentioned by health workers to explain this know-do gap and their low compliance to recommendations. However a recent survey in Tanzania found no association between the caseload and the efforts made in the diagnostic process (Maestad et al., 2010). The lack of trust in the recommended tasks being an important reason for not performing them (Lange et al., 2014), important efforts must be made to both ensure requested tasks are useful for the patient, and that they are perceived as useful by the clinicians. Improving guidelines to be more specific on antibiotic needs will likely be insufficient if clinicians' compliance to the recommendations is not improved.

To better understand the use of antimicrobial drugs by clinicians, it is also important to look at the social psychology knowledge on behavioural change. The classical, rational, or 'top-down' model of behavioural change that rely on changing people thinking (knowledge, attitudes, beliefs and goals) to encourage behavioural change,

has shown important limits. Illustrated by the know-do gap, changing people conscious thoughts and motivation aren't enough to achieve effective behavioural change (Webb and Sheeran, 2006). Behaviour seems more influenced by the environmental and situational factors than by individual's knowledge. (Kollmuss and Agyeman, 2002; Thaler, 2008) And a new, contextual, or bottom-up model suggests behavioural change come from an automatic, associative, rapid and unconscious cognitive process. (Evans, 2008) In Tanzania, clinicians are trained to prescribe oral antibiotics for children with pneumonia, but in many health care facilities they use injectable drugs to treat these patients. The influence of their peers' behaviour and the local informal guidelines has higher influence than their knowledge on their behaviour. New approaches are needed for interventions aimed at changing clinicians' prescriptions behaviour to reach their goal.

## 1.5 Potential benefit of mobile technology to improve clinicians' performance

The recent development of mobile technology and the rapid spread of mobile phones in low and middle income countries offer a new range of opportunities for innovative approaches to improve the quality of care. And in recent years, an increasing number of software applications to support clinical decision, patients' management, or health information management have been developed. They are referred to as mobile health (mHealth) solutions. There is already an important body of literature describing the potential of electronic clinical decision support systems to improve the quality of care in primary care settings; both in high (Bryan and Boren, 2008) and in low income countries (Källander et al., 2013; Mitchell et al., 2013, 2008; Praveen et al., 2014). Although barriers to mHealth solutions were often identified, such as lack of access to computers, need for training, and fear of increased workload (Machingura et al., 2014), the interest and willingness of health workers to use mobile technology in their personal and professional activities was present in high (Franko and Tirrell, 2012) and low income countries (Machingura et al., 2014).

Electronic clinical algorithms may therefore be of great potential to improve health workers compliance to guidelines. They also may allow delivering more complex algorithm to lay health workers in low resource countries.

# 2 Goal and objectives

## 2.1 Goal

The Goal of the present project was to improve the quality of the management of children aged 2 to 59 months attending low resource primary care health facilities (HFs) with acute illnesses, by providing health workers with evidence-based clinical decision support system in order to improve both the children health outcomes and the rational prescriptions of antimicrobials in primary care to decrease childhood mortality and contain resistance spread in the community.

## 2.2 Objectives

### 2.2.1 Objective 1

To develop a new evidence-based clinical algorithm for the management of children aged 2 to 59 months in low income countries primary care facilities, addressing the main treatable causes of acute illness, and assisting clinicians for decision-making to withhold antibiotics in children who would not benefit from it.

### 2.2.2 Objective 2

To assess the safety of the new clinical algorithm as compared to the current practices in Tanzanian health facilities in term of health outcome, and its impact on antimicrobial prescription.

### 2.2.3 Objective 3

To develop an electronic version of the clinical algorithm and assess its feasibility and impact on HWs performance in term of completeness of integrated assessment, appropriateness of disease classifications, and appropriateness of treatment prescribed.

# 3 Methods' overview

## 3.1 Study design

### 3.1.1 Development of a new clinical algorithm

*Review of the available evidence*

Structured reviews of the literature have been conducted to document

i) the clinical presentation of children aged 2-59 months attending HF in low income countries

ii) the main threatening and treatable diseases responsible for acute illness in these patients

iii) the most accurate and easy to use diagnostic procedures in HF in low income countries

*Systematic review and meta-analysis of clinical predictors of radiological pneumonia*

For pneumonia diagnosis, a systematic review of the literature and meta-analysis was conducted to evaluate the accuracy of the WHO clinical pneumonia case definition, and to look for more accurate clinical predictors. (Chapter 5)

Search strategy: Electronic databases were searched to identify articles assessing clinical predictors of radiological pneumonia in children.

Study selection: The studies selected were diagnostic accuracy studies, targeting bacterial pneumonia, in children <5 years, in ambulatory or hospital care, and assessing the accuracy of clinical features as index test as compared to chest radiography as reference standard.

Quality assessment: Quality assessment was based on the 2011 Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria.

Analyses: For each index test, sensitivity and specificity were calculated. Meta-analyses with the Bivariate model and hierarchical SROC plots were done for index tests assessed in four or more studies.

*Design of a new algorithm*

Together with the findings of these literature reviews, the results from a comprehensive study of the etiologies of fever in outpatient children, conducted in Tanzania (D'Acremont et al., 2014) were used to improve evidence on the main causes of fever and to look for clinical predictors of bacterial diseases. Building on the evidence identified through these reviews and study we developed of a new clinical algorithm that is presented in Chapter 6.

### 3.1.2 Assessment of the safety of the algorithm

A validation of this new algorithm was performed by conducting a prospective non-inferiority trial in Tanzanian health facilities, that compared the health outcome of children aged 2-59 months managed by clinicians following their routine practice to the one of children managed following strictly the new algorithm recommendation, as well as the rate of antibiotic prescription.

*Procedures*

Children coming for a first visit for an acute medical ailment were managed in the intervention arm by a study clinician following strictly the new algorithm recommendations and in the control arm by the usual HF clinician. The details of the clinical presentation, diagnoses reached and treatment prescribed were collected, in the intervention arm by the study clinician, and in the control arm by an observer on standardised case report forms. Children were followed up at home on day 7 for health outcome.

*Primary Outcomes*

Proportion of children cured at day 7 and proportion of children who received antibiotics on day 0.

The detailed methods and results of this study are presented in Chapter 7.

### 3.1.3 Feasibility of implementing the new electronic algorithm

*Intervention*

The new algorithm was introduced in 6 health facilities in Dar es Salaam; 3 facilities received the new paper algorithm and 3 others received the new electronic algorithm.

Implementation involved training of the health workers, introduction of the mobile devices when applicable, and regular supervision. A comparative study to assess the HW's performance after the pilot implementation of the new electronic algorithm in routine conditions was conducted in the involved health facilities.

*Procedures of the comparative study to assess HWs' performance*

Nine HFs in Dar es Salaam were randomised into three arms; three HFs were allocated to use the new paper algorithm, three to use the new electronic algorithm, and three to continue with their current practice (control). Four months after training, an observational survey of clinical consultations was conducted. Children coming to the health facility with an acute medical ailment for a first visit for whom a caretaker had given a written informed consent were enrolled in the survey. An observer recorded the details of the consultation process on standardised case report forms. All children were then reassessed by an expert who followed strictly the new algorithm recommendation to establish the reference for classification and treatment.

*Primary outcomes*

HWs' performance was compared between the 3 arms, using index of child's assessment, appropriateness of diagnosis classification and treatment as outcome variables.

The detailed methods and results of this survey are presented in Chapter 8

# 4 Study sites and setting

## 4.1 Study sites

The field work of the present project took place in two sites in the United Republic of Tanzania: the urban area of Dar es Salaam and a rural district in Morogoro region, Kilombero district. (Figure 1)

Located in East Africa, Tanzania is a low income country with a Gross National Income (GNI) per capita of 630$ (World Bank, 2015). More than 70% of the 45 million inhabitants live in rural areas. In 2012, the life expectancy at birth was 61 years (World Bank, 2015).

The Tanzanian health system structure follows the 6-level administrative structure, which divides the country in zones, regions, districts, divisions, wards and villages. A referral or tertiary hospitals is available per zone, secondary hospitals are found at regional level, district hospitals at district level, health centers at division level, dispensaries at ward levels, and village health posts are found in the villages. Health care services are delivered mainly by clinical officers with three years of clinical training through a network of 6321 health facilities, 85% of them being dispensaries (HRH, 2013). Children U5 represent 15% of the total population (PHC, 2012), and the U5 mortality was 81 per 1000 live births in 2010 (TDHS, 2010). The following child survival interventions are provided free of charge through both public and private health facilities countrywide: IMCI, vitamin A, deworming, prevention of mother-to-child transmission of HIV, insecticide-treated nets, and focused antenatal care, together with routine immunisation services. The Tanzanian routine immunisations include vaccines for measles, diphteria, pertussis, tetanus, polio (DTP) and tuberculosis (BCG). In 2002, hepatitis B vaccine was added to this list and in 2009, *Haemophilus influenza* B. In 2013 after the present project ended, pneumococcal conjugate and rotavirus vaccines were also introduced in the routine vaccination. In 2010 routine immunisation coverage was estimated to be 95.4% for BCG, 87.8% for DTP-HepB3 and 84.5% for measles.

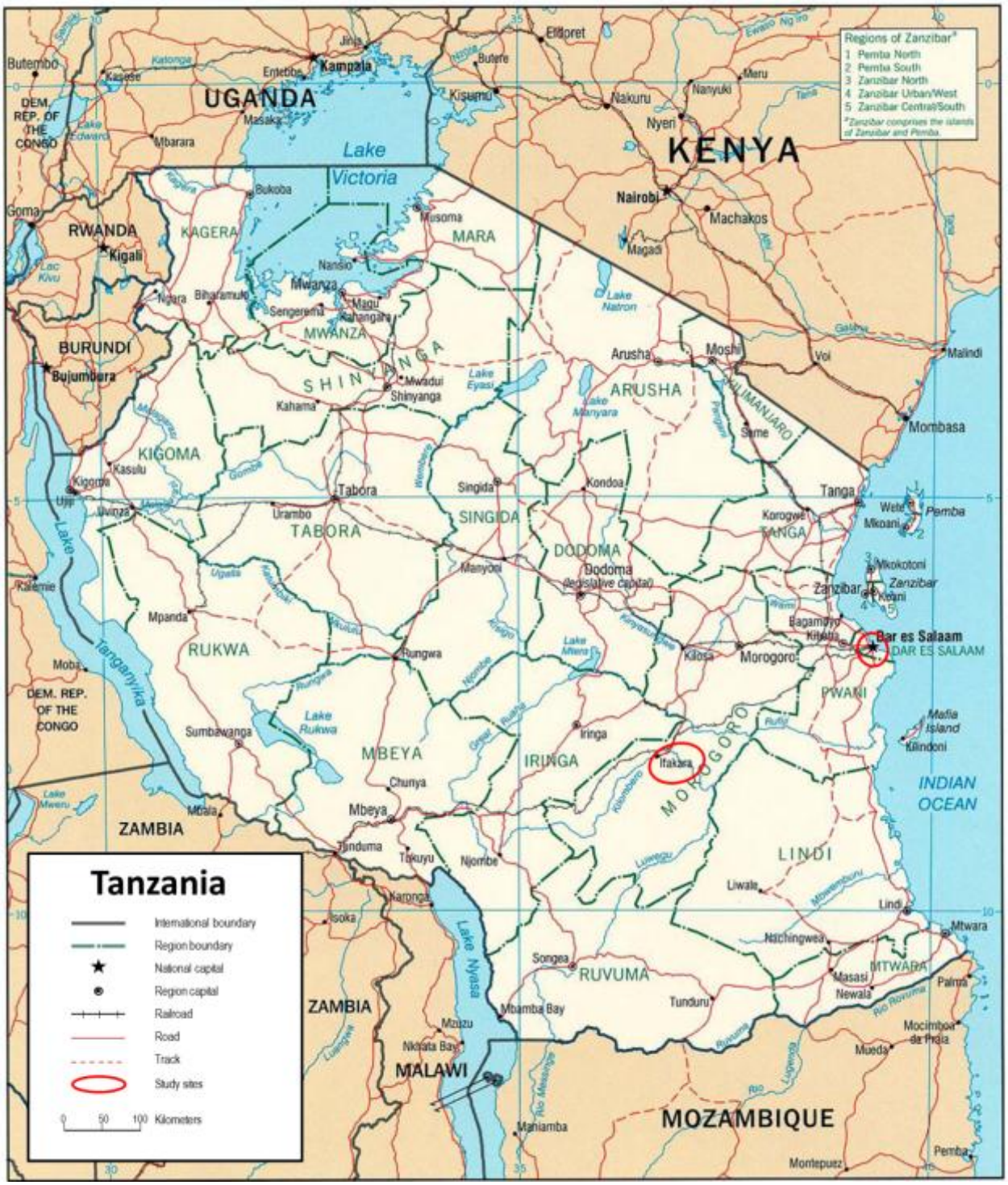


**Figure 1. Study sites**

The field work of the present thesis took place in Dar es Salaam, the economic capital, and in Kilombero, a rural district in Morogoro region. (Adapted from: http://www.lib.utexas.edu/maps/africa/tanzania_pol_2003.jpg).

In 2010/2011 the estimated prevalence of malaria in children aged 6 to 59 months was 9% according to mRDT and 4% to microscopy, with important variations between regions. mRDT were introduced and rolled out from 2010 by the National Malaria Control Program, and test-based management of malaria was endorsed in 2013 in the Tanzanian Standard Treatment Guidelines (TSTG, 2013). Tanzania was one of the first countries involved in the development of IMCI, piloting the case management training in 1996, and taking part to the IMCI-Multi Country Evaluation program. The IMCI national roll-out started in 1998, and in 2005 83% of the districts had conducted at least one training course. However national level training coverage was only 14% (Prosper et al., 2009).In 2010 17% of the household had access to electricity; 69% of households in Dar es Salaam, 33% in other urban areas an only 4% in rural area. Nevertheless, the country counted 26 million mobile phone subscribers (PHC, 2012).

*Dar es Salaam*

Dar es Salaam is the economic capital of the country, located on the East coast. Rapidly growing, with an annual growth rate of 5.6%, the city counted 4.4 inhabitants in 2012 (PHC, 2012). The administrative structure divides Dar es Salaam in three districts or municipalities, Kinondoni, Ilala, and Temeke, from North to South. Each district is further divided in wards and subwards. Within the City Council is located the City Medical Office of Health, and 3 District Medical Offices are in charge of the management of the health facilities (one district hospital, health centers and dispensaries) that are located in their district.

*Kilombero district*

Kilombero district is a one of the rural districts in Morogoro region, in southeast Tanzania. The district is located in a flood plain between the Undzungwa Mountains and the Kilombero River, and counted about 400 000 inhabitants in 2012(PHC, 2012). Ifakara is the administrative capital.

In Dar es Salaam malaria prevalence was estimated to be 3.6% with mRDT, and 0.3% with microscopy; in Morogoro region 13% and 7% respectively (THMIS, 2011).

## 4.2 Study setting

The study on the safety of the new algorithm recommendations took place in two pairs of primary health care facilities: Buguruni Health Center (intervention) and Vingunguti Dispensary (control) in Ilala district, Dar es Salaam; and Signal Dispensary (intervention) and Mang'ula (control) in Kilombero districts, both located North-East from Ifakara. The study of the implementation of the new algorithm took place in 9 primary health care facilities in Dar es Salaam. These 9 health facilities were purposively selected because they were the only primary health care facilities using malaria rapid diagnostic tests at the beginning of the project. Malaria tests were introduced in these facilities by a research project ahead of their national roll out, and were maintained by the City Medical Office of Health in collaboration with the National Malaria Control Program. For the purpose of the survey, these 9 health facilities were randomly allocated to receive i) no intervention (control), ii) the paper algorithm intervention, or iii) the electronic intervention. In Kinondoni district, Sinza, Kawe, and Tandale were respectively allocated to be part of the control, paper and electronic arm; in Ilala district, Vingunguti, Tabata A, and Buguruni were enrolled in the respective 3 arms; and in Temeke district, Mbagala Kizuiani, Kigamboni, and Mbagala rangi tatu were enrolled in the respective 3 arms.

# 5 Clinical features for diagnosing pneumonia in children younger than 5 years: a systematic review and meta-analysis

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## 5.1 Summary

**Background**: Pneumonia is the biggest cause of deaths in children younger than 5 years in developing countries, but early diagnosis and intervention can effectively reduce mortality. We aimed to assess the diagnostic value of clinical signs and symptoms to identify radiological pneumonia in children younger than 5 years and to review the accuracy of WHO criteria for diagnosis of clinical pneumonia.

**Method:** We searched Medline (PubMed), Embase (Ovid), the Cochrane Database of Systematic Reviews, and reference lists of relevant studies, without date restrictions, to identify articles assessing clinical predictors of radiological pneumonia in children. Selection was based on: design (diagnostic accuracy studies), target disease (pneumonia), participants (children <5 years), setting (ambulatory or hospital care), index test (clinical features), and reference standard (chest radiography). Quality assessment was based on the 2011 Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria. For each index test, we calculated sensitivity and specificity and, when the tests were assessed in four or more studies, calculated pooled estimates with use of bivariate model and hierarchical summary receiver operation characteristics plots for meta-analysis.

**Results**: We included 18 articles in our analysis. WHO-approved signs age-related fast breathing (six studies; pooled sensitivity 0·62, 95% CI 0·26–0·89; specificity 0·59, 0·29–0·84) and lower chest wall indrawing (four studies; 0·48, 0·16–0·82; 0·72, 0·47–0·89) showed poor diagnostic performance in the meta-analysis. Features with the highest pooled positive likelihood ratios were respiratory rate higher than 50 breaths per min (1·90, 1·45–2·48), grunting (1·78, 1·10–2·88), chest indrawing (1·76, 0·86–3·58), and nasal flaring (1·75, 1·20–2·56). Features with the lowest pooled negative likelihood ratio were cough (0·30, 0·09–0·96), history of fever (0·53 ; 0·41–0·69), and respiratory rate higher than 40 breaths per min (0·43, 0·23–0·83).

**Interpretation:** No one clinical feature was sufficient to diagnose pneumonia definitively. Combination of clinical features in a decision tree might improve diagnostic performance, but the addition of new point-of-care tests for diagnosis of bacterial pneumonia would help to attain an acceptable level of accuracy.

**Funding:** Swiss National Science Foundation

## 5.2 Introduction

In developing countries, pneumonia is the largest cause of deaths in children younger than 5 years.(Liu et al., 2012) Early identification and treatment of patients with pneumonia cases is fundamental to reduce mortality. Identification of which pneumonia cases need antibiotic treatment among the large number of children presenting with respiratory symptoms is a challenge because cough is reported in two thirds of children attending outpatient facilities in low-income countries.(Van Hemelrijck et al., 2009) Chest radiograph, the current gold standard for pneumonia diagnosis(Cherian et al., 2005), is not available in resource-poor settings where the burden of disease is the highest. Even when available, chest radiograph cannot be done for all coughing children because of the very high frequency of this complaint and the potential long-term effects of exposure to x-rays. Therefore, clinical predictors are used to identify children who should receive an antibiotic drug or undergo assessment by chest radiograph. Since the late 1980s, pneumonia diagnosis in developing countries has relied on the presence of cough, fast breathing, and chest indrawing, as recommended by WHO (WHO-ARI, 1991; WHO and UNICEF, 2014). This recommendation was based on studies published in the late 1980s and validated by other studies in the 1990s. Since then, no major innovation has been made in pneumonia diagnosis and no accurate point-of-care test is available to identify children who would benefit from antibiotics. With the rapid spread of antibiotic resistance worldwide, there is rising concern about over-prescription of antibiotics resulting from insufficient specificity of the WHO criteria used to classify acute respiratory infections.(Hazir et al., 2011; Scott et al., 2012) Here, we assess the diagnostic value of clinical signs and symptoms in identification of children younger than 5 years old (excluding infants <2 months) with radiological pneumonia. This evaluation might help to generate more accurate clinical scores from which to make decisions about the necessity of further investigation by chest radiograph or antibiotic treatment for children presenting with respiratory symptoms in low-resource ambulatory care facilities.

## 5.3 Methods

### 5.3.1 Search strategy

We did a systematic literature search in Medline (PubMed), Embase (Ovid), and the Cochrane Database of Systematic Reviews (CDSR), without date or language restrictions. We did our first search on Sept 30, 2013, with an update on Nov 6, 2014. In Medline, we used the following search terms: “pneumonia”[MeSH terms] in combination with: "predictive value of tests"[MeSH terms] OR "sensitivity and specificity"[MeSH terms] OR "reproducibility of results"[MeSH terms] OR “diagnostic test” OR “diagnostic tests” OR "physical examination"[MeSH terms] OR "medical history taking"[MeSH terms], and the following age filters: “infant 1-23 months” and “preschool child 2-5 years”. In Embase, we used ‘diagnostic accuracy'/exp OR 'predictor variable'/exp OR 'breathing rate'/exp in combination with “pneumonia” OR “lower respiratory tract infection” OR “respiratory tract infection”, and with “child”. We did an additional manual search of the reference lists from eligible articles and identified reviews to complete our search. Two reviewers (CR-A and VD’A) independently did the search using a two-step process: first, assessing the title and abstract, and second, assessing the full text, using the seven selection criteria listed in the panel. Any disagreement was resolved through discussion and consensus.
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### 5.3.2 Quality assessment

We assessed the quality of selected studies and potential risk of bias with the 2011 revised version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2),(Whiting et al., 2011), adapted to the review question, as recommended by the Cochrane Collaboration. For this Article, all clinical index tests were considered to be appropriate, irrespective of the way they had been assessed by the clinician, except for respiratory rates, which we required to be measured by observation in 1 min in a calm child, as recommended by WHO. Therefore, the index test domain of the QUADAS-2 was separated into two sections: one for the respiratory rate (defining fast breathing) and one for the other index tests. For the reference standard, the best existing one for bacterial pneumonia is end-point pneumonia on chest radiograph (WHO criteria).(Cherian et al., 2005; Lynch et al.,

2010). For this review, we selected all studies using chest radiograph as reference standard, irrespective of criteria used for interpretation. When the interpretation criteria differed from WHO criteria, we reported in the methodological quality assessment that there were great concerns about the applicability of the results to the research question. The quality assessment was done independently by two authors (CR-A and VD'A). Any disagreement was resolved through discussion and consensus.

**Panel: Criteria for studies selection**

*Design* We selected studies that assessed diagnostic accuracy, clinical predictors or derived prediction rules. Narrative reviews, letters, editorials, comments, and case series of fewer than 20 patients were excluded. Systematic reviews and meta-analyses were considered for their reference lists.

*Target disease* Studies that assessed pneumonia.

*Participants* Studies needed to include children aged between 2 months and 5 years. We excluded studies including only adults or only children younger than 6 months or older than 6 years. Studies were excluded of patients at higher risk of pneumonia because of pre-existing immune suppression (due to HIV infection, neutropenia, and malnutrition), comorbidities (cystic fibrosis, ventilated, and burned), or because of restrictive inclusion criteria (including only patients with wheeze).

*Setting* We selected studies including either ambulatory patients or patients admitted into hospitals. Studies in intensive care units were excluded. Studies done in developed and developing countries were both considered. Index test We selected studies that assessed clinical features (symptoms and physical signs).

*Reference standard* We selected studies in which the reference standard for pneumonia diagnosis was based on a chest radiograph, whatever the interpretation criteria.

*Data reporting* Studies were selected if reconstruction of the two-by-two table was possible. Studies that included children older than 5 years of age were selected only if age stratified analyses were available (so that children aged above 5 years could be excluded). When the data for this age group were not available, authors were contacted and studies included when data provided. When more than one article was published on the same patients' population, we selected only the most recent article with appropriate analyses to the review question.

### 5.3.3 Data extraction

Data were extracted by one author (CR-A). A second author (VD'A) cross-checked all extracted data compiled in a table (Microsoft Excel version 2010) comparing them to the original data available from the selected full texts (or in the subset of data sent by authors when applicable) to ensure that each data was accurate. Identified errors were discussed and corrected. We recorded characteristics of the study (design, year of publication, study country, and health-care setting), study population (size, age range, inclusion and exclusion criteria, and proportion of patients with pneumonia), reference standard (chest radiograph procedure, masking, number of readers, and interpretation criteria), and index tests (definition, procedures, and link with inclusion criteria) on predefined forms. Index tests were categorised as related to demographic and environmental factors, symptoms, or signs. When it was not possible to establish whether the index test was obtained through caretaker interview (symptom) or through clinical examination (sign), the index test was not included in the review and meta-analysis. Combinations of signs were not considered in this review. Signs or symptoms assessed at different thresholds were considered as different index tests, with a separate analysis for each threshold.

### 5.3.4 Statistical analyses

For each individual index test identified in the chosen studies, we constructed a two-by-two table with use of the data available in the publication or data provided by contacted authors. For each index test, we calculated sensitivity and specificity with corresponding 95% CIs. When an index test was assessed in four or more different studies, we calculated pooled estimates of sensitivity and specificity with a hierarchical random effects bivariate logistic regression model (bivariate model). Because of expected large differences between studies, heterogeneity in test accuracy between studies was presumed; therefore we needed a random effects meta-analysis method that provided an estimate of the average accuracy of the test and described the variability in this effect, rather than a fixed effect approach that estimated an underlying common effect. The metaanalysis method also needed to account for the correlation between sensitivity and specificity because their relationship as the threshold varies within and across studies. Therefore the bivariate model was chosen and computed using the metandi programme in Stata version 12,

(Harbord and Whiting, 2009) as recommended by the Cochrane Collaboration for meta-analysis of diagnostic accuracy studies(Macaskill et al., 2010). A minimum of four studies is required for metandi analyses; we decided not to do meta-analyses for index tests assessed in less than four studies because it would have little value. We computed summary point estimates of sensitivity and specificity, as well as the 95% confidence region around the summary operating point and the 95% prediction region. The prediction region shows the extent of statistical heterogeneity between studies by depicting a region within which, assuming the model is correct, there is 95% confidence that the true sensitivity and specificity of a future study will lie. (Macaskill et al., 2010). We pooled only index tests with a common and clear definition and a common threshold. Index tests that were necessary inclusion criteria for the study (eg, cough in eight studies) were not considered. For fast breathing that was assessed at different thresholds in the selected studies, a hierarchical summary receiver operation charac teristics (HSROC) curve was computed using the Rutter and Gatsonis HSROC model, as recommended by the Cochrane Collaboration for analysis of index tests assessed at different thresholds.(Macaskill et al., 2010)

### 5.3.5 Additional analyses on studies available in the 1990s

We identified articles that provided the evidence for the WHO definition of clinical pneumonia in the 1990s. Most of these articles could not be included in our review because of inappropriate reference standards according to our selection criteria. To better understand the evidence that was available when the WHO definition was established, we did a separate review and meta-analysis on the articles from 1990s, with pooled estimates of sensitivity and specificity calculated with the bivariate model for chest indrawing and age-related fast breathing.

### 5.3.6 Role of the funding source

The funders of the study played no role in study design, data collection, data analysis, data interpretation, report writing, or in the decision to submit the paper for publication. All authors had full access to all the data in the study. The corresponding author had final responsibility for the decision to submit for publication.

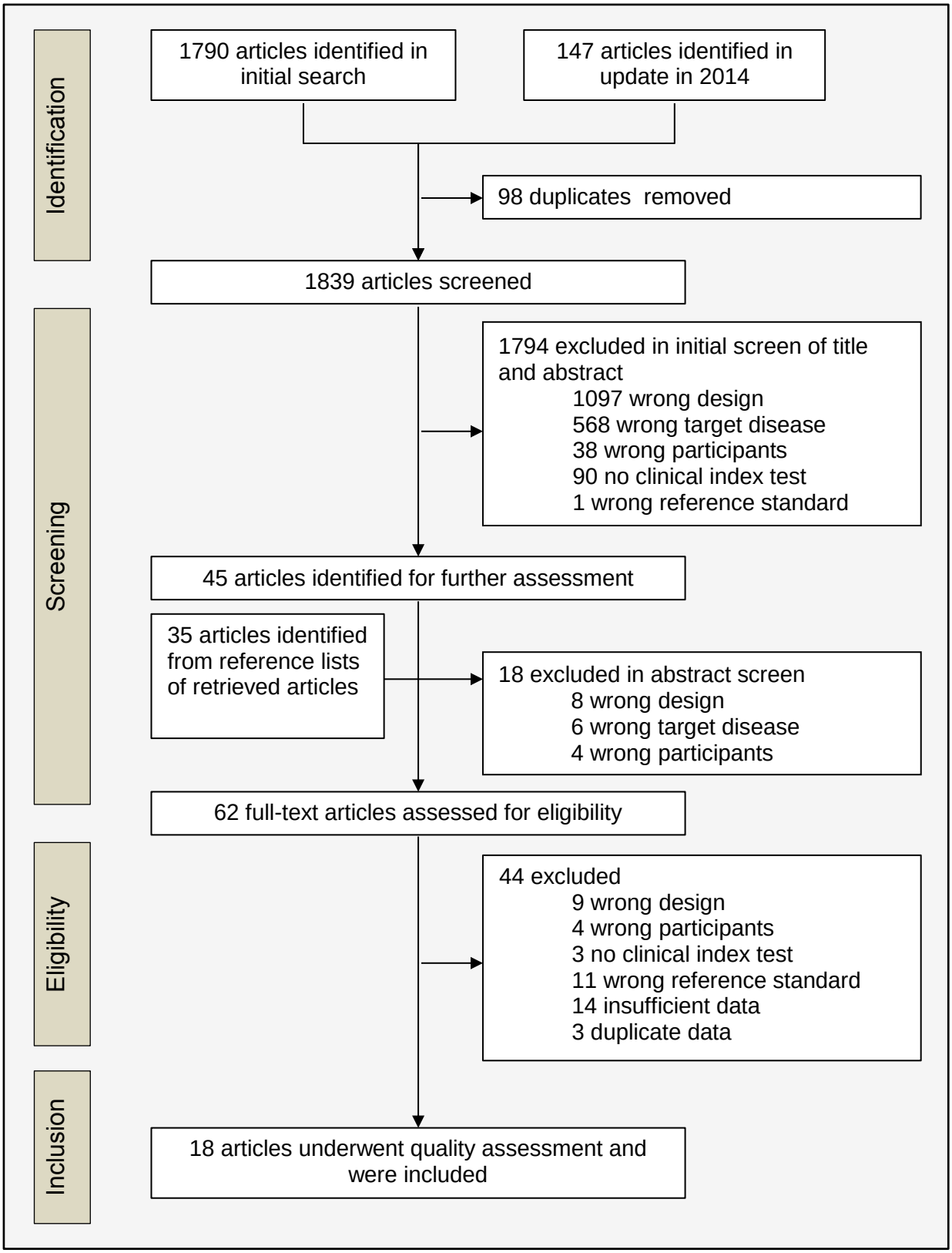


**Figure 2. Flow diagram of the study selection process**
Only the first reason for exclusion (as ordered in the panel) is reported.

## 5.4 Results

Our search identified 1839 papers. Through the study selection process (figure 2), 18 articles were included in the review and underwent quality assessment using QUADAS-2. One of the included articles reported on two separate surveys conducted in different health facilities in the same country but using the same procedures; (Lucero et al., 1990) data were extracted separately and counted as two distinct studies. Table 1 shows characteristics of the 19 studies. 16 studies were done in low-income and middle-income countries—ie, Asia (n=7), Africa (n=5), Latin America (n=3), and the Middle East (n=1), and three took place in the USA. Seven studies were done in outpatient departments, seven in emergency departments or related structures, four in inpatient departments, and one study recruited patients at community level. Except for one case-control study (Palafox et al., 2000), all studies included consecutive patients with acute respiratory infection. In these studies, the inclusion criterion was cough alone (five), clinical suspicion of pneumonia as per specified criteria (seven), and suspicion of pneumonia without specified criteria (six; table 1). The proportion of radiological pneumonia in the studied populations varied across studies from 7% to 69% (median 30%; IQR 15 to 63%). Table 2 shows quality assessment of included studies (potential bias and applicability concerns).

From the 19 included studies, we found 57 different clinical features assessed for their accuracy in diagnosis of radiological pneumonia: five related to demographic and environmental factors, 32 to symptoms, and 20 to signs. Age, duration of illness, duration of cough, heart rate, respiratory rate, and temperature were assessed using different thresholds. Seven different definitions of chest indrawing were used. 78 index tests were assessed in the 19 studies. The number of index tests assessed per study ranged from one to 25 (median eight, IQR four to 12). The Annex 1 contains coupled forest plots for each study and the estimated sensitivity and specificity with 95% CI for each of the 78 index tests. Of the 78 clinical index tests, 18 were assessed in four different studies or more.

The most frequently assessed index tests were: fast breathing (12 studies, with four different definitions), chest indrawing (10 studies, with seven different definitions), nasal flaring (eight studies), elevated temperature (seven studies, with seven different definitions), crepitations (seven studies), history of fever (six studies), and wheezing (six studies). For each index test considered in four studies or more, the

HSROC plot of point estimates of sensitivity and specificity with 95% confidence and 95% prediction regions, computed using the bivariate method, are shown in figure 3A (symptoms) and 3B (signs).

Table 3 shows pooled estimates of each diagnostic performance measure (sensitivity, specificity, and positive and negative likelihood ratio) for these index tests. Although most of the index tests showed poor diagnostic performance with a high degree of heterogeneity, some respiratory danger signs had specificities higher than 0·80, such as cyanosis (two studies, 0·98 [95% CI 0·93–1·00] and 0·94 [0·89–0·96]), stridor (two studies, 0·92 [0·86–0·96] and 1·00 [0·94–1·00]), and grunting (five studies 0·87 [0·65–0·96]). Classic auscultation signs, such as crepitations, showed poor accuracy (table 3). Among other auscultation signs, bronchial breathing had high specificity in two studies 0·97 [0·93–0·99] and 0·97 [0·95–0·98]). Two symptoms had high sensitivity with little heterogeneity: history of fever (pooled sensitivity of six studies 0·94, 0·88–0·97) and cough (five studies 0·96, 0·91–0·98). Two features that are the backbone of the WHO definition for clinical pneumonia (WHO-ARI, 1991) (age-related fast breathing and lower chest wall indrawing) had a very high degree of heterogeneity in sensitivities and specificities (table 3). Fast breathing was assessed at different respiratory rate thresholds within and between studies. Figure 4 shows the HSROC curve of fast breathing at different thresholds. It suggests that none of the fixed thresholds is better than another and that having an age-related threshold does not improve the accuracy of the diagnostic test.

**Table 1. Characteristics of included studies.**

| Study Reference | Setting | Age range | N | Pneumonia prevalence | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|
| Wafula 1984 | Kenya; Paediatric observation ward | <5 years | 377 | 67% | Admission to the observation ward with features of ARI. | Patients with no CXR traceable excluded from analyses |
| Campbell 1989 | The Gambia, community | 0-4years | 216 | 12% | Cough and one of: respiratory rate>50, indrawing, wheeze, stridor. | Not reported |
| Wafula 1989 | Kenya; outpatient department | 5 to 59 months | 150 | 60% | His of cough <2weeks | Already on medication, heart failure, congenital heart disease, moderate to severe dehydration, metabolic disorders, and chest deformities. |
| Lucero 1990 Research institute | Philippines; outpatient department | <5 years | 199 | 69% | Cough <3weeks' duration | Not reported |
| Lucero 1990 Health Center | Philippines; outpatient department | <5 years | 199 | 29% | Cough <1 week duration | Not reported |
| Harari | Papua New Guinea; outpatient department | 8 weeks to 6 years | 185 | 30% | Cough (n= 95). Cough & respiratory rate ≥40 (n=90) | Wheeze, stridor, measles, pertussis |
| Lozano 1994 | Colombia; emergency department | <3 years | 200 | 65% | Cough ≤7 days, and living at high altitude, and CXR part of emergency department evaluation; | Cardio, pulmonary, or neurological congenital defects; born before term; chronic diseases (asthma, cancer, metabolic disorders, immuno-suppression). |
| Dai 1995 | China; outpatient department | 2 to 59 months | 541 | 63% | Cough | Antibiotics received in last 4 weeks |
| Palafox 2000 | Mexico; Clinical unit | 3 days to 5 years | 110 | 32% | *Cases*: Pneumonia clinical diagnosis by a paediatrician. *Matched controls*: next child with ARI (cough or rhinorrhea, and infectious signs) without pneumonia. | Symptoms > 2weeks, chronic diseases, genetic abnormalities, neurological diseases, bronchial asthma, septicemia. |
| Rothrock 2001 | USA; emergency department | <5 years | 329 | 20% | CXR ordered as part as emergency department evaluation | Urgent portable CXR; trauma, foreign body ingestion, or submersion injury. |

**Table 1 (continued)**

| Reference standard | | | Index tests |
|---|---|---|---|
| **Reader(s)** | **Blind** | **Positve criteria** | |
| 2 independent: radiologist Attending and senior | Not reported | Lobar pneumonia or bronchopneumia | *Symptoms*: Cough; *Signs*: stridor, nasal flaring, chest indrawing, cyanosis, t°>38°C, respiratory rate >50 |
| One paediatric radiologist | Yes | Lobar consolidation | *Symptoms:* Vomiting, refusing to feed, rapid breathing; *Signs:* Chest indrawing, nasal flaring, respiratory rate >50; >60, heart rate>160, axillary t°>37.5°C >38.5°C, crepitation, bronchial breathing or reduced air entry, rhonchi, grunting. |
| One paediatric radiologist | Not reported | Lobar pneumonia or bronchopneumonia | *Symptoms*: fever, rapid breathing, poor feeding, *Signs*: respiratory rate >40; >60, heart rate>140, nasal flaring, cyanosis, chest indrawing, stridor, ronchi, crepitations, rectal t°>37.5°C |
| Not reported | Not reported | Not reported | *Signs:* respiratory rate >40, respiratory rate >50 |
| Not reported | Not reported | Not reported | *Signs:* respiratory rate >40, respiratory rate >50 |
| One paediatric radiologist | Yes | Radiographic evidence of pneumonia | Age <24 months; *Symptoms:* fever, cough>2 days, breath-less, poor feeding, poor sleeping; *Signs*: Axillary t°>38°C, chest indrawing, nasal flaring, crepitations, cyanosis, respiratory rate >40/50; >50 |
| One radiologist | Yes | Any kind of infiltrate (alveolar or interstitial) | *Symptoms*: fever, rapid breathing, difficult breathing, chest retractions, grunting, loss of appetite, food refusal (liquid, solid, breastfeeding), difficult to wake up, abdominal distension, cold to the touch, seizures; *Signs*: retractions, grunting, nasal flaring, respiratory rate, abnormal respiratory sounds (wheezes, crepitation, rhonchi, decreased breath sounds), abdominal distension, seizures. |
| 3 radiologists, independently, majority opinion prevailed. | Yes | Criteria ns. 4 cat: Pneumonia, Bronchitis, Any abnormality, Normal | *Signs*: age-related fast breathing, rales, nasal flaring, chest indrawing (lower chest wall), cyanosis of the tongue. |
| One single radiologist | Yes | Presence of micro or macro-nodular infiltrations or condensations in the lung | *Signs:* age-related fast breathing, chest indrawing, alveolar rales. |
| One attending senior board-certified radiologists at time of emergency | Unclear | 'Pneumonia' or ‘infiltrate’ on radiologist's report. Excl 'Isolated atelectasis', 'pleural effusion', or ‘elevated | *Chief complaint:* cough, fever difficulty breathing, altered mental status; *Symptoms*: respiratory distress; *Signs*: respiratory distress, rales, diminished breath sounds, age-related fast breathing |

**Table 1. Characteristics of included studies (continued)**

| Study Reference | Setting | Age range | N | Pneumonia prevalence | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|
| Shamo'on 2004 | Jordan; inpatient department | <6 years | 147 | 61% | Admitted with clinical pneumonia (cough with age-related fast breathing, indrawing, or wheezing) | Immune deficiency, known asthma, foreign body aspiration, chemical pneumonitis, failure to thrive or malnutrition and severe URTI. |
| Mahabee-Gittens 2005 | USA; emergency department | 2 to 59 months | 510 | 8.6% | Cough and at least one of: labored, rapid or noisy breathing; chest or abdominal pain; or fever. | Currently taking antibiotics, smoke inhalation, foreign body aspiration, chest trauma, asthma, bronchiolitis, cystic fibrosis, sickle cell disease, chronic cardiopulmonary disease |
| Hazir 2006 | Pakistan; outpatient department | 2 to 59 months | 1782 | 14% | WHO clinical non-severe pneumonia (cough and/or difficult breathing, and fast breathing (50/40), without lower chest wall indrawing, and without any danger signs) with readable CXR available | Underlying chronic illness, history of 3 or more episodes of wheeze or acute bronchial asthma, antibiotic use during previous 48h. |
| Enwere 2007 | Gambia; outpatient department | 40 days to 30 months | 3941 | 17% | History of cough or breathing difficulty and either i) suspicion of severe pneumonia ( study's first 18 months), or ii) raised respiratory rate and/or indrawing (study's last 27 months) | Serious chronic illness, previous DPT vaccination, received pneumococcal vaccination (intervention arm), absence of a readable CXR. |
| Puumalainen 2008 | Philippines; inpatient department | 6 weeks to 23 months | 1195 | 15% | WHO clinical pneumonia (non-severe, severe and very severe) | Not reported |
| Muangchana 2009( | Thailand; inpatient department | <5 years | 1396 | 7% | Admitted to hospital with suspected pneumonia diagnosed by a physician | Absence of parents/guardian consent |
| Sigaúque 2009 | Mozambique; inpatient department | 0 to 23 months | 634 | 43% | Admitted to hospital with cough or difficult breathing and age-related fast breathing and chest indrawing (WHO clinical definition for severe pneumonia). | Evidence of asthma, congenital heart disease, neonatal asphyxia, and chronic respiratory disorders. |

**Table 1. (continued)**

| Reference standard | | | Index tests |
|---|---|---|---|
| **Reader(s)** | **Blind** | **Positivity criteria** | |
| One radiologist | Yes | Lobar pneumonia or bronchopneumonia. | *Symptoms*: Cough, poor feeding, *Signs*: chest indrawing, grunting, diminished air entry, crepitation, wheezes, age-related fast breathing; *Not defined*: fever. |
| 2 paediatric radiologists independently | Not reported | No predefined criteria. Suggestive of pneumonia: confluent opacification without volume loss, peripheral rather than central opacification, pleural effusion | Age >12 months, breast-fed, daycare or preschool, sibling, smokers at home, *Symptoms:* illness duration >48h; *Signs*: respiratory rate, grunting, nasal flaring, retractions, decreased breath sounds, crackles, wheezing, oxymetry. |
| 2 paediatric radiologists independently. In case of disagreement CXR read by a third radiologist. | Yes | Radiological evidence of pneumonia by at least 2/3 radiologist using predefined WHO criteria. | Age >12 months; *Symptoms*: Fever, cough, difficult breathing, poor feeding, vomiting, diarrhoea, past history of wheeze, illness duration >3 days; *Signs*: wheeze |
| A paediatrician and a paediatric radiologist independently. | Yes | WHO endpoint pneumonia, other infiltrates / abnormalities. | *Symptoms*: Fever, cough, chest pain, difficult breathing, fast breathing, poor feeding, vomiting, diarrhoea, convulsion; *Signs*: Appear sick, chest indrawing, crepitation, rhonchi, bronchial breathing, hospital admission. |
| 2 radiologists independently | Yes | WHO criteria for 'Primary endpoint consolidation'. | WHO clinical pneumonia definitions, only |
| One radiologist | Yes | WHO criteria: either i) primary endpoint pneumonia, or ii) pleural infiltration. | Age ≤12 months, age ≤3 years; *Symptoms*: Illness duration >2 days, >4 days; *Signs*: t°>38°C, t°>39°C. |
| 2 primary readers and one external WHO radiologist | Not reported | Evidence of consolidation or pleural effusion: confirmed pneumonia. Non-endpoint pneumonia: interstitial or normal CXR.. | Age ≤12 months, *Symptoms:* duration of fever, duration of cough; *Signs:* nasal flaring, crepitations, wheezing or rhonchi, vomiting, prostration, hypoxemia, °≥37.5°C, t°>39°C. |

**Table 1. Characteristics of included studies (continued)**

| Reference | Setting | Age range | N | Pneumonia prevalence | Inclusion criteria | Exclusion criteria |
|---|---|---|---|---|---|---|
| Bilkis 2010 | Uruguay and Argentina; emergency department | 1 to 4 years* | 178* | 69% | Fever or his of fever during the past 48 hours, and clinically suspected pneumonia | Chronic resp disease, congenital cardiopathy, esophagogastric reflux, tumoral disease, cerebral palsy, immunodeficiency, asthmatic crisis requiring treatment, pneumonia in the last 2 months, use of antibiotics in the last 15 days. CXR already taken and interpreted. |
| Wingerter 2012 | USA; emergency department | ≤5 years | 2008 | 16% | CXR performed for clinical supsicion of pneumonia | Preexisting medical conditions with increased risk for pneumonia: sickle-cell disease, complex congenital heart disease, immuno-deficiency, chronic lung disease other than asthma (ie, cystic fibrosis or broncho-pulmonary dysplasia) or a severe neurologic disorder. |

All studies were cross-sectional, except Palafox and colleagues,(Palafox 2000) which was a case-control study. ARI=acute respiratory infection. CXR=chest X-ray. URTI= upper respiratory tract infection. DPT= Diphtheria, pertussis, and tetanus.
*Subgroup of participants aged below 5 years, provided by contacted author.

**Table 1. (continued)**

| Reference standard | | | Index tests |
|---|---|---|---|
| **Reader(s)** | **Blind** | **Positivity criteria** | |
| 2 paediatric radiologists, together (diagnoses correlated with diagnosis of the evaluating paediatricians.) | Yes | Pulmonary consolidation or asymmetric infiltrate | *Symptoms:* Fatigue, loss of appetite, loss of sleep, cough, chest pain, abdominal pain, vomiting; *Signs:* t°>39°C, grunting, intercostal retraction, nasal flaring, wheezing, rales, decreased breath sounds. |
| One of the attending radiologists at the time of emergency department evaluation | Not reported | Definite pneumonia if "consolidation", "infiltrate", "pneumonia" on CXR report. Conservative definition of pneumonia also included "atelectasis versus infiltrate", "atelectasis versus pneumonia", or "likely atelectasis but cannot exclude pneumonia". | *Symptoms:* his of fever, *Signs:* t°≥38°C, wheezing, WHO classification for pneumonia |

**Table 2. Quality assessment according to the QUADAS-2 tool: potential bias and applicability concerns of included studies**

| RISK OF BIAS | | | | | APPLICABILITY CONCERNS | | | |
|---|---|---|---|---|---|---|---|---|
| **Patient selection** | **Index test: All but respiratory rate** | **Index test: respiratory rate** | **Reference Standard** | **Flow and timing** | **Patient selection** | **Index test: All but respiratory rate** | **Index test: respiratory rate** | **Reference standard** |
| Unclear | Unclear | Unclear | Low | High | Low | Unclear | Unclear | High |
| Unclear | Low | Unclear | Low | High | High | Low | Unclear | Low |
| Unclear | Low | Low | Unclear | Unclear | Low | Low | Low | High |
| Unclear | NA | Low | Unclear | Unclear | Low | NA | Unclear | Unclear |
| Unclear | Low | Low | Unclear | Unclear | Low | Low | Unclear | Unclear |
| Unclear | Low | High | Low | High | Unclear | Low | Low | High |
| Low | Low | Low | Low | Unclear | Low | Low | Low | Unclear |
| High | Low | Low | Low | Unclear | High | Low | Low | High |
| Unclear | Low | Unclear | High | High | Unclear | Low | Unclear | High |
| High | Low | NA | Low | Low | High | Low | NA | High |
| High | Low | High | High | High | High | Low | High | Unclear |
| High | Low | NA | Low | High | High | Low | NA | Low |
| High | Low | NA | Low | High | High | Low | NA | Low |
| High | Low | NA | Low | High | High | Low | NA | Low |
| Unclear | Low | NA | Low | Low | Unclear | Low | NA | Low |
| High | Low | NA | Low | High | High | Low | NA | Low |
| Unclear | Low | High | High | High | Unclear | Low | Unclear | High |
| Unclear | Low | Unclear | High | Low | Unclear | Low | Unclear | High |

NA Not applicable.

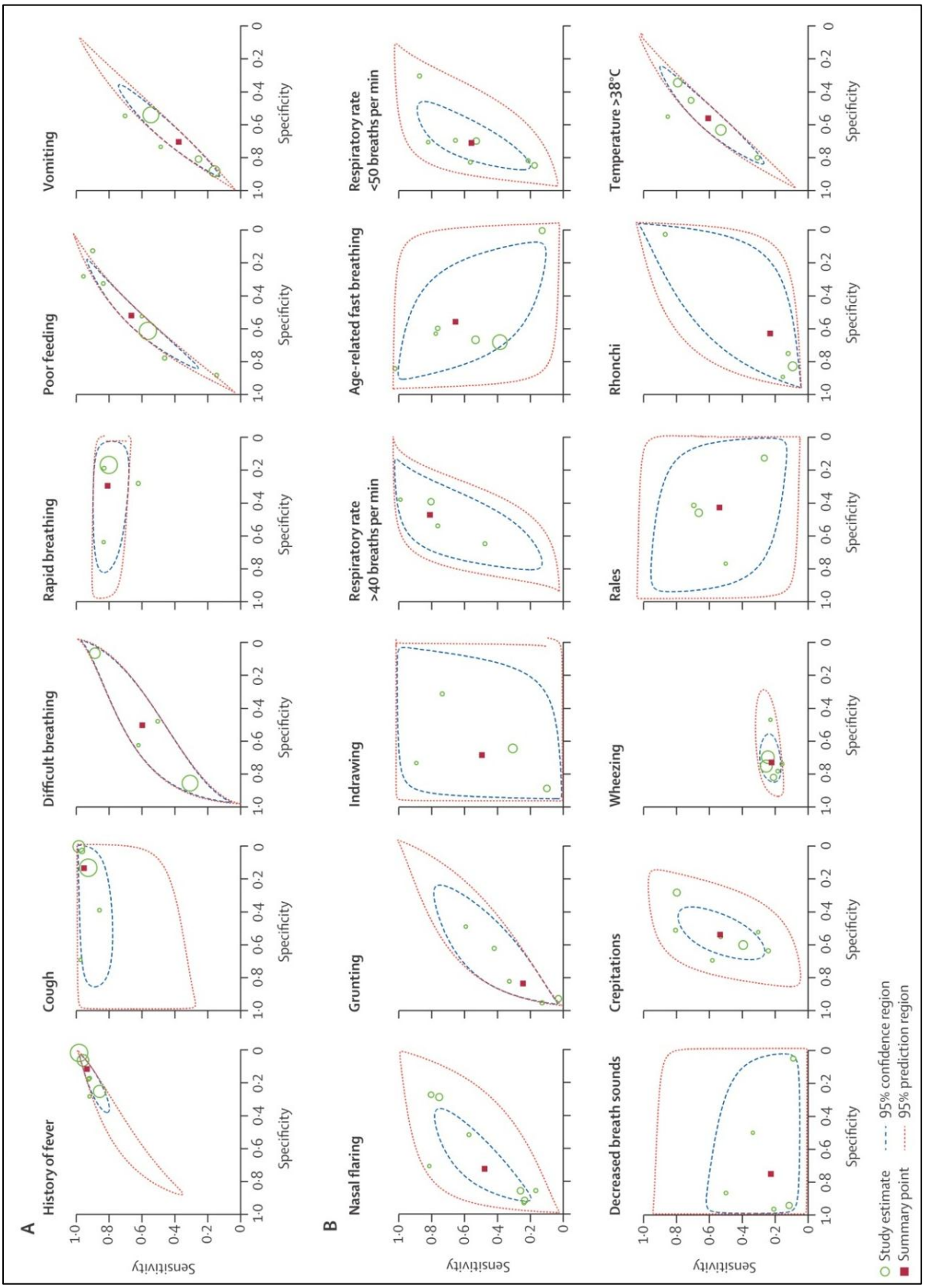


**Figure 3. Hierarchical summary receiver operating characteristic (HSROC) plots for sensitivity versus specificity for 6 symptoms (A) and 12 signs (B)**

Each circle represents a study, with the size being proportional to the study size. The square represents the summary operating point of test performance and the zone outlines surrounding it represent the 95% confidence and 95% prediction regions of this summary estimate respectively.

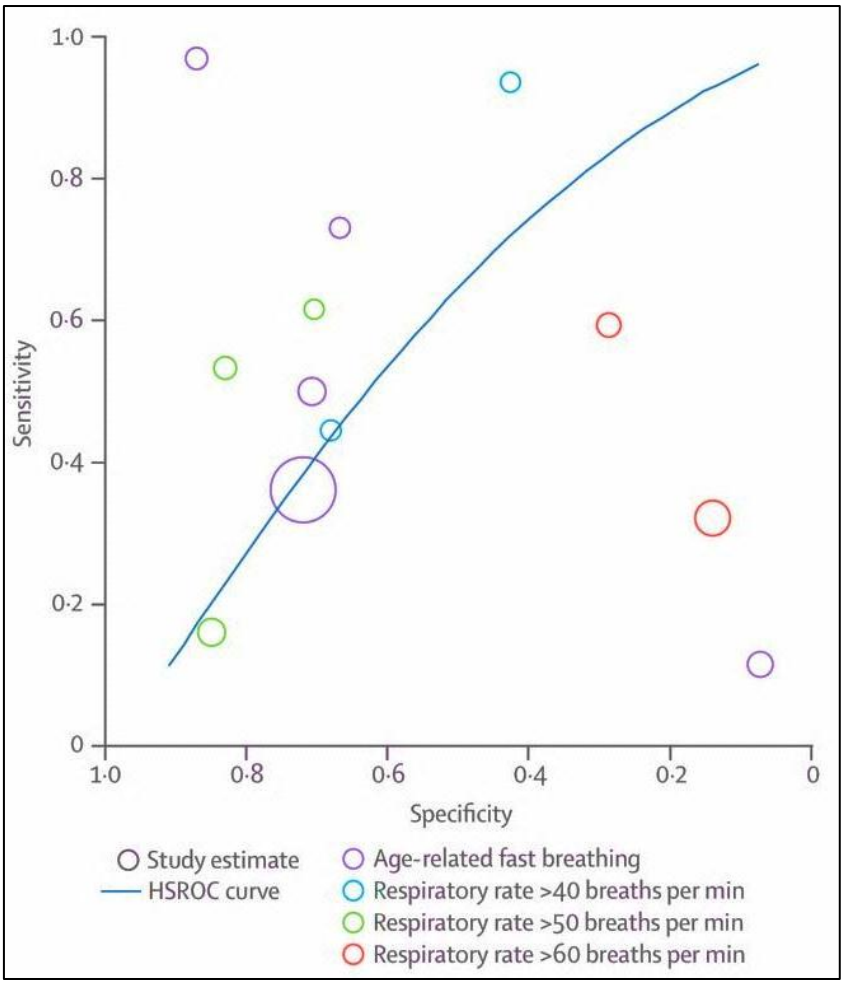


**Figure 4. Hierarchical summary receiver operating characteristics (HSROC) curve of sensitivity versus specificity of fast breathing assessed at different respiratory rate thresholds in 12 different studies.**

In the meta-analysis, when looking at the likelihood ratios (measures that are more meaningful for clinical decisions), the symptoms and signs with the highest pooled estimates of positive likelihood ratio were respiratory rate higher than 50 breaths per min, grunting, lower chest indrawing, and nasal flaring (table 3). The features with the lowest pooled estimates of negative likelihood ratio were cough (although very heterogeneous), respiratory rate higher than 40 breaths per min, and history of fever (table 3). Table 4 shows the performance of age-related fast breathing and chest indrawing in the studies that generated the evidence leading to the adoption of WHO clinical diagnosis of pneumonia in the 1990s.(Simoes, 1994) Sensitivity estimates for age-related fast breathing ranged from 0·73 to 0·82 and specificities from 0·54 to 0·89 in five studies (table 4). For chest indrawing, sensitivity estimates ranged from 0·06 to 0·77 and specificity estimates from 0·39 to 1·00 (table 4).

**Table 3. Pooled estimates of diagnostic performance measures of each index test assessed in 4 studies or more**

| | Number of studies | Total population | Sensitivity (95%CI) | Specificity (95%CI) | LR+ (95%CI) | LR- (95%CI) | 1/LR- (95%CI) |
|---|---|---|---|---|---|---|---|
| ***Symptoms*** | | | | | | | |
| history of fever | 6 | 8260 | 0.94 (0.88-0.97) | 0.12 (0.06-0.23) | 1.06 (1.00-1.12) | 0.53 (0.41-0.69) | 1.89 (1.46-2.45) |
| cough | 5 | 6421 | 0.96 (0.91-0.98) | 0.14 (0.03-0.46) | 1.12 (0.90-1.39) | 0.30 (0.09-0.96) | 3.37 (1.04-10.89) |
| difficult breathing | 4 | 6070 | 0.60 (0.35-0.81) | 0.52 (0.19-0.84) | 1.26 (0.84-1.91) | 0.76 (0.64-0.90) | 1.32 (1.11-1.56) |
| rapid breathing | 4 | 4474 | 0.79 (0.75-0.82) | 0.31 (0.17-0.49) | 1.14 (0.88-1.46) | 0.69 (0.39-1.25) | 1.44 (0.80-2.60) |
| poor feeding | 7 | 4984 | 0.64 (0.39-0.83) | 0.52 (0.3-0.73) | 1.34 (1.17-1.54) | 0.69 (0.55-0.86) | 1.46 (1.16-1.83) |
| vomiting | 5 | 6723 | 0.36 (0.22-0.52) | 0.7 (0.55-0.82) | 1.17 (1.06-1.29) | 0.93 (0.86-0.99) | 1.08 (1.01-1.16) |
| ***Signs*** | | | | | | | |
| nasal flaring | 8 | 2813 | 0.47 (0.28-0.66) | 0.73 (0.52-0.87) | 1.75 (1.20-2.56) | 0.73 (0.59-0.89) | 1.38 (1.12-1.69) |
| grunting | 5 | 1251 | 0.24 (0.10-0.47) | 0.87 (0.65-0.96) | 1.78 (1.10-2.88) | 0.88 (0.78-0.99) | 1.13 (1.01-1.28) |
| T>38°C[†] | 5 | 4631 | 0.56 (0.39-0.71) | 0.55 (0.40-0.70) | 1.25 (1.14-1.37) | 0.80 (0.70-0.91) | 1.26 (1.10-1.43) |
| respiratory rate >40/min | 4 | 1058 | 0.78 (0.54-0.91) | 0.51 (0.38-0.63) | 1.58 (1.37-1.84) | 0.43 (0.23-0.83) | 2.30 (1.20-4.41) |
| respiratory rate >50/min | 7 | 1834 | 0.53 (0.30-0.74) | 0.72 (0.58-0.83) | 1.90 (1.45-2.48) | 0.65 (0.45-0.95) | 1.53 (1.05-2.24) |
| age related fast breathing[§]* | 6 | 3320 | 0.62 (0.26-0.89) | 0.59 (0.29-0.84) | 1.55 (0.44-5.42) | 0.63 (0.16-2.55) | 1.59 (0.39-6.42) |
| crepitations | 7 | 2510 | 0.53 (0.37-0.69) | 0.58 (0.48-0.67) | 1.26 (0.99-1.60) | 0.81 (0.61-1.08) | 1.23 (0.93-1.63) |
| rales | 4 | 1158 | 0.49 (0.32-0.67) | 0.45 (0.22-0.70) | 0.90 (0.42-1.90) | 1.13 (0.48-2.62) | 0.89 (0.38-2.06) |
| rhonchi | 4 | 1543 | 0.19 (0.04-0.57) | 0.67 (0.24-0.93) | 0.57 (0.36-0.91) | 1.21 (0.88-1.67) | 0.83 (0.60-1.14) |
| decreased breath sounds | 5 | 1364 | 0.22 (0.12-0.38) | 0.76 (0.29-0.96) | 0.93 (0.15-5.67) | 1.02 (0.58-1.80) | 0.98 (0.55-1.72) |
| wheezing | 6 | 4825 | 0.22 (0.18-0.25) | 0.75 (0.66-0.82) | 0.86 (0.63-1.17) | 1.05 (0.95-1.16) | 0.95 (0.86-1.06) |
| lower chest indrawing* | 4 | 1870 | 0.48 (0.16-0.82) | 0.72 (0.47-0.89) | 1.76 (0.86-3.58) | 0.71 (0.38-1.35) | 1.40 (0.74-2.65) |

95%CI: 95% confidence interval; LR+: positive likelihood ratio; LR-: negative likelihood ratio. [†]T>38°C: rectal temperature>38°C or axillary temperature>37.5°C. [§]respiratory rate >60/min in children aged <2months, >50/min in children 2 to 11 months, and >40/min in children aged 12 to 59 months. *WHO criteria for pneumonia

**Table 4. Performance of age-related fast breathing and chest indrawing in studies used by WHO to decide on criteria for clinical pneumonia**

| Study reference | Age range | Reference standard | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|
| ***Age related fast breathing***[§] | | | | | | | | |
| Shann 1984 | <5 years | crepitations | 52 | 15 | 36 | 97 | 0.78 (0.66-0.87) | 0.73 (0.65-0.80) |
| Cherian 1988 | <5 years | crepitations or CXR | 204 | 46 | 47 | 385 | 0.82 (0.76-0.86) | 0.89 (0.86-0.92) |
| Harari 1991 | 8 weeks-6 years | CXR | 41 | 15 | 47 | 82 | 0.73 (0.60-0.84) | 0.64 (0.55-0.72) |
| Mulholland 1992 Philippine | 2-59 months | paediatrician | 81 | 21 | 95 | 111 | 0.79 (0.70-0.87) | 0.54 (0.47-0.61) |
| Mulholland 1992 Swaziland | 2-59 months | paediatrician | 20 | 6 | 64 | 201 | 0.77 (0.56-0.91) | 0.76 (0.70-0.81) |
| ***Lower chest wall indrawing*** | | | | | | | | |
| Shann 1984 | <5 years | crepitations | 4 | 63 | 0 | 133 | 0.06 (0.02-0.15) | 1.00 (0.97-1.00) |
| Cherian 1988 | <5 years | crepitations or CXR | 193 | 57 | 11 | 421 | 0.77 (0.71-0.82) | 0.97 (0.95-0.99) |
| Campbell 1989 | 0-4 years | CXR | 15 | 10 | 117 | 113 | 0.60 (0.39-0.79) | 0.39 (0.32-0.46) |
| Harari 1991 | 8 weeks-6 years | CXR | 18 | 38 | 16 | 113 | 0.32 (0.20-0.46) | 0.88 (0.81-0.93) |

[§]respiratory rate >60/min in children aged <2months, >50/min in children 2 to 11 months, and >40/min in children aged 12 to 59 months CXR: chest x-ray. TP:. FN:. FP:. TN:. CI: confidence interval

## 5.5 Discussion

To our knowledge, our Article is the first systematic review with meta-analysis of clinical predictors of pneumonia in children. The comprehensive search, unimpeded by date, country, or language restrictions, allowed the consideration of large amounts of data, compared with previous reviews. (Ayieko and English, 2007; Pio, 2003; Scott et al., 2012; Simoes, 1994) We considered only data from children aged younger than 5 years, allowing better targeting of the population of interest. Methodological quality was assessed in duplicate and based on a-priori defined rules using the latest version of the QUADAS, which reduced subjectivity in the selection of studies and index tests and allowed precise evaluation of the risk of bias in several domains. Another, strength of our article is that the method used for analysis accounted for heterogeneity in results and for correlation between sensitivity and specificity. From the 18 selected articles, a large set of clinical indices were assessed, showing both the large panel of clinical signs and symptoms that can be considered in children and the poor consensus for the clinical sign with the highest accuracy for diagnosis of pneumonia. Fast breathing and chest indrawing were the most frequently assessed clinical signs. These two signs are the cornerstone of acute respiratory infection classification in the WHO pneumonia case management strategy, with antibiotic prescription being recommended for children with cough and fast breathing or lower chest wall indrawing (classified as non-severe pneumonia).(WHO and UNICEF, 2014) Age-related fast breathing was adopted in the 1990s with sensitivity estimates ranging from 0·73 to 0·82, although heterogeneous specificities were reported (from 0·54 to 0·89; table 4). In our Article, age-related fast breathing assessed in six different studies had poorer estimates of diagnostic performance than in previous studies, with highly heterogeneous sensitivities and specificities. This difference in the diagnostic accuracy of age-related fast breathing is possibly due to the difference in reference standard: in our Article, chest radiograph was used as a reference standard, whereas in most of the early studies (table 4), the reference standard was based on the subjective assessment of a physician (this is also why these studies were not selected for analysis here). Thus, these early studies probably included lower respiratory tract infections other than pneumonia, such as bronchiolitis. At the time that these studies were done, giving antibiotics to all children with lower respiratory tract infections and withholding them only for upper respiratory tract infections was perceived to be the best option. Since pneumonia was a major cause

of mortality in resource-poor settings and no simple test was available for diagnosis of bacterial pneumonia, WHO decided to use highly sensitive clinical criteria. The benefits of presumed lives saved through antibiotic treatment were estimated to outweigh the risks of unnecessary treatment due to poor specificity of the diagnostic criteria used. By contrast, in our Article, we aimed to assess the clinical predictors for radiological pneumonia, considered an acceptable surrogate for bacterial infection, to identify children that really need antibiotic treatment. As a result, the pooled estimates of likelihood ratios for age-related fast breathing are worse in our findings (positive likelihood ratio 1·55; negative likelihood ratio 0·63; table 3) than in the 1990s' surveys (pooled estimates from the data reported in table 4: positive likelihood ratio 2·92; negative likelihood ratio 0·29) , and therefore fast breathing might not be useful clinically, at least on its own, to identify children in need of antibiotics. This was also suggested in a recent study in Pakistan, in which investigators reported that the clinical outcome of children with WHO nonsevere pneumonia (and no chest indrawing) did not differ when treated with antibiotics or placebo.(Hazir et al., 2011) Because of the rapid spread of antibiotic resistance worldwide, the overuse of antibiotics when prescription is based on cough and fast breathing is a matter of concern and should now be addressed in policy recommendations. In our Article, chest indrawing, as in the studies done in the 1990s, also produced heterogeneous estimates of sensitivities, specificities, and likelihood ratios. Chest indrawing is probably an early indicator of respiratory distress that can be due to different disorders, such as pneumonia, but also bronchiolitis. Even if chest indrawing is insufficient for diagnosing radiological pneumonia, then it might still be useful to identify children that are at risk of hypoxaemia and would benefit from oxygen therapy rather than provision of antibiotics..

Our Article has some limitations. First, to assess clinical predictors for the diagnosis of pneumonia in ambulatory care, a study should ideally include all patients presenting to the health facility without pre-selection criteria. In all our included studies only a subgroup of patients at higher risk of pneumonia were chosen based on a constellation of symptoms and signs, and diffcult-to-diagnose cases were potentially excluded. This inclusion might have biased the diagnostic performance measures. Second, the interobserver agree ment among clinicians on symptoms and signs, such as auscultation findings, can be very low. This concern about reproducibility is common to all diagnostic studies that assess clinical features.

Finally, there was hetero geneity between our chosen studies in terms of inclusion criteria, setting, and chest radiograph interpretation criteria. To do a meta-analysis in this context, we used the bivariate and the Rutter and Gatsonis HSROC models, which account for the heterogeneity inherent in diagnostic accuracy studies. (Macaskill et al., 2010) The small number of identified studies did not allow investigation of how the tests accuracies varied between studies with their methodological characteristics. The findings of this Article suggest that no one clinical feature is sufficient on its own for diagnosis of radiological pneumonia. Indeed, none of the assessed clinical features reached the level commonly accepted for clinical significance (positive likelihood ratio >5 to include the diagnosis or negative likelihood ratio <0·2 to exclude it). The highest pooled positive likelihood ratio observed was 1·9 (respiratory rate >50 breaths per min) and, besides cough, the lowest pooled negative likelihood ratio was 0·43 (respiratory rate >40 breaths per min). The relatively good pooled negative likelihood ratio (0·30) for cough was probably overestimated because cough was part of the inclusion criteria in all selected studies that assessed it as an index test. Respiratory rate, which is the cornerstone of the present WHO criteria to classify pneumonia, is thus of poor diagnostic value, even if it was the best individual clinical predictor in our Article. However, according to our results, a threshold of 50 breaths per min for all age groups would be more appropriate than would the present recommendation of 50 breaths per min in infants (<12 months) and 40 breaths per min in children older than 1 year. History of fever was the second best predictor in terms of negative likelihood ratio, and adding it to the present WHO criteria could help to increase specificity. Combination of the clinical features with the best likelihood ratios in a decision tree might indeed improve the overall diagnostic performance of symptoms and signs. Individual data from selected articles would however have been necessary to appropriately assess combination of clinical features. This was out of the scope of our Article, but it would be relevant to embark on such meta-analyses prospectively, provided the heterogeneity in methodological quality of the included studies is mitigated. The development of innovative point-of-care tests for diagnosis of bacterial pneumonia is crucial to assist clinicians in decision making. The assessment of the diagnostic value of combinations of clinical features and point-of-care tests to measure host biomarkers or specific pathogens needs appropriately designed prospective studies to propose new evidence-based diagnostic procedures. Because no gold standard

test exists for bacterial pneumonia, investigation is important of the clinical outcome of children with acute respiratory infection when treated (or not) with antibiotics (Hazir et al., 2011) to accurately identify patients truly in need of antibiotics. Potentially severe forms of acute respiratory infections also include viral pneumonia and bronchiolitis. Therefore improvements in access to oxygen therapy, rather than provision of antibiotics, will often be the life-saving treatment.

## 5.6 Contributors

CR-A, FA, and VD'A conceived the study. CR-A and VD'A did the literature search and analyses. BG and VD'A oversaw the study and provided important scientific input. All authors contributed to the interpretation of the data and the drafting of the Article. All authors revised the Article critically and approved the version to be published.

## 5.7 Declaration of interests

We declare no competing interests.

## 5.8 Acknowledgement

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# 6 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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## 6.1 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 (CDRS) 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 <2years 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.

## 6.2 Introduction

The rapid spread of resistant pathogens worldwide calls for urgent action to improve the rational use of antimicrobials. In low and middle income countries, where infectious diseases childhood mortality is high(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; WHO Medicines, 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; Msellem et al., 2009; Thiam et al., 2011) without negative impact on health outcome. (Baiden et al., 2012; D'Acremont et al., 2010b; Msellem et al., 2009; Mtove et al., 2011; Senn et al., 2012) Unfortunately it has often been accompanied with an increased antibiotics prescription(Baiden et al., 2011; D'Acremont et al., 2011; Msellem 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 recognised 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.

## 6.3 Methods

### 6.3.1 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)(CHERG, n.d.) 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 was also conducted to understand the clinical presentation (accurate clinical predictors) and diseases' distribution in children U5 attending HFs 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$^{st}$ 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 5. 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 HF, 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 5: Structured literature reviews: search strategy**

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

### 6.3.2 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).

### 6.3.3 Algorithm construction

With the IMCI algorithm for children 2-59 months of age as departure point, the evidence retrieved from the structured literature reviews 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 (MoSHW, 2007) since the algorithm was intended to be used in Tanzania and had to comply with local policies. Once the new algorithm was finalised, both a paper booklet and 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).

## 6.4 Results

Flow diagrams of studies selection for the structured literature reviews are available in Figure 5.

All modifications made to the IMCI content based on new findings are presented in Table 6. 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.

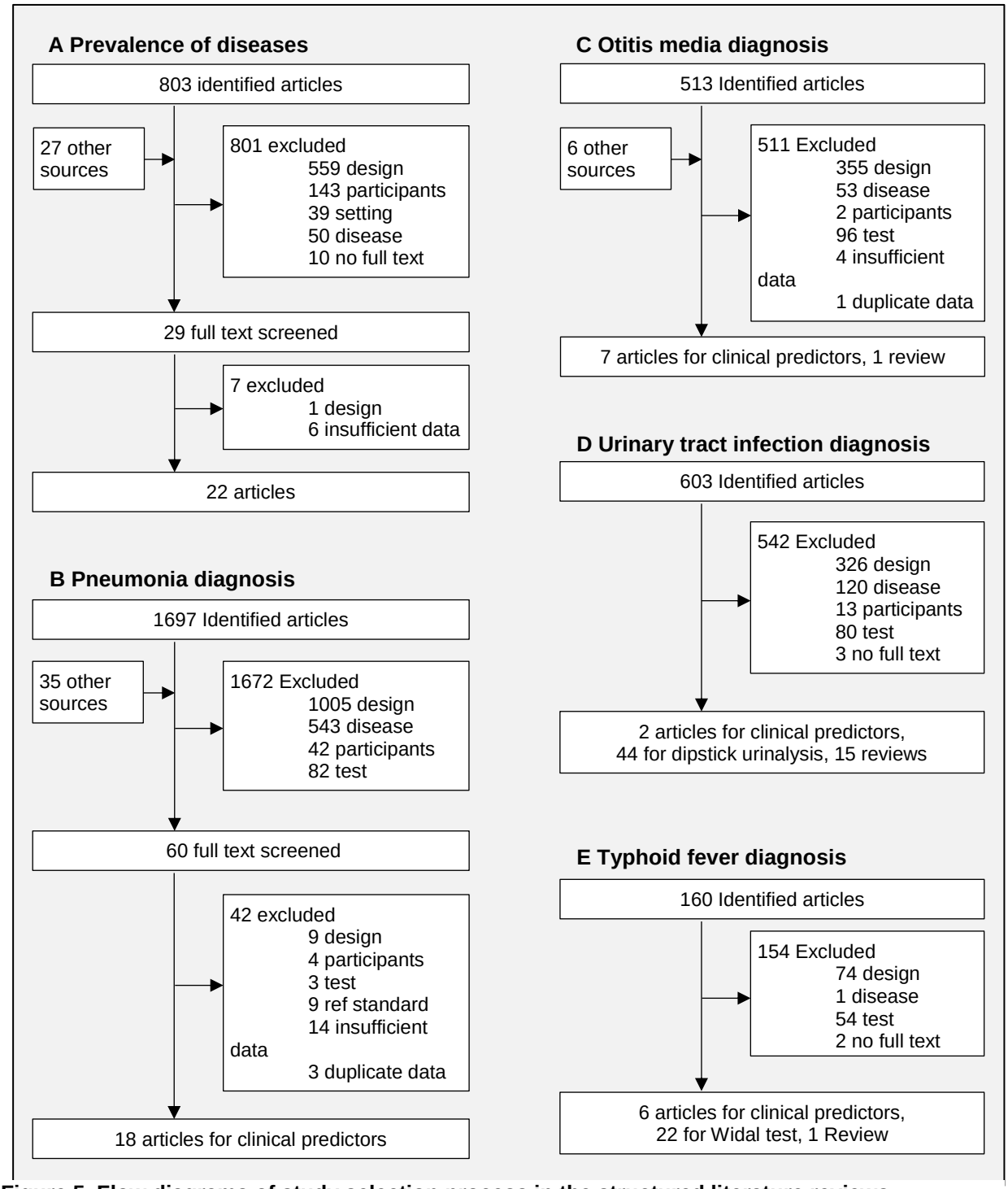


**Figure 5. Flow diagrams of study selection process in the structured literature reviews**

### 6.4.1 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 diarrhoea 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%(IHME, n.d.)). In infants aged 1 to 11 months, pertussis (2.8% of deaths in 1-11months 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.).

The structured literature review 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 diarrhoea 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; Weber et al., 1997) of children. Diseases of potential bacterial origin reported in the studies retrieved by the structured literature review 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.

### 6.4.1 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(Kalter et al., 1997; Paxton et al., 1996). 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).

**Table 6: Major changes in ALMANACH as compared to IMCI algorithm based on evidence**

| Location | Topic | IMCI | ALMANACH | Rationale |
|---|---|---|---|---|
| **Management of very severe diseases section** | **Very severe diseases** | "A child with any general danger signs needs URGENT attention; **complete the assessment** and pre-referral treatment immediately so that referral is not delayed" | 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**" | 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 antibiotic and antimalarial treatment (Dellinger et al., 2008; Gaieski et al., 2010) and to refer to hospital, where further etiological investigations will allow adapting the treatment. |
| | **List of general danger signs** | "Lethargic; Convulsing; Unable to drink/breastfeed; Vomits everything; History of convulsion" | "Convulsing; Lethargic; Unable to drink/breastfeed; Vomits everything; History of convulsion; Jaundice; Cyanosis; Stiff neck; Severe pallor; Severe wasting" | Stiff neck, severe pallor, and severe wasting (assessed later o in IMCI) are part of the ALMANACH initial assessment, in order to facilitate and fasten the detection and management o very severe diseases.<br>Jaundice and cyanosis that are strong predictors for serious bacterial diseases and severe respiratory conditions (D'Acremont et al., 2014), have been added to the general danger signs. |
| | **Pre-referral treatment** | Available in the "TREAT THE CHILD" section in the middle of the booklet | Available in the "Management of very severe diseases" section in the first pages of the booklet | To facilitate and fasten the management of severe patients, the first section "Management of very severe diseases" has al assessment, classification and treatment charts together. |
| **Management of children with no general danger signs** | **Fever**[8] | Fever[8] is one of the 4 "Main symptoms". | Fever is a crossing point in ALMANACH: different recommendations are made for children (non-severe) with or without fever[§]. | 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. |
| | **Fever** | Classifications considered in the Fever chart are: "Very severe disease", "Malaria" and "Measles".<br>*Additional classification in low malaria risk contexts: "Fever, malaria unlikely"* | Classifications considered in the Fever algorithm: "Malaria", Acute respiratory infections, including "Pneumonia"; Diarrhoea related classifications; Ear related classification; Measles; Skin infections; "UTI", "Typhoid fever", "Likely viral infection" | 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 having excluded potentially life threatening conditions |
| **Febrile chart** | **Malaria** | Presumptive diagnosis of malaria for all children with fever in high malaria risk contexts | 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. |

**(Table 6 continued on next page)**

**Table 6. Major changes in ALMANACH as compared to IMCI algorithm based on evidence (continued)**

| | | | | |
|---|---|---|---|---|
| **Febrile Cough chart** | **Pneumonia** | Pneumonia diagnosis rely on increased respiratory rate above age specific threshold: 50 breath/min if aged 2-11 months; 40/min if aged 12-59 months | Pneumonia is considered in children aged 2-59 months, if they report the presence of fever and have a respiratory rate above 50 breaths/min | 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) |
| **Ear problem chart** | **Acute ear infection** | Oral antibiotics are recommended for "Acute ear infection" defined as either "ear pain" or "ear pus/ discharge for less than 14 days" | Oral antibiotics are only recommended for children with fever and "ear pus/ discharge for less than 14 days" | 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. Antbiotics ar most useful for children with otitis media and ear discharge(Sanders et al., 2010). |
| **Skin problem chart** | **Skin and soft tissue infections** | Some guidance provided in an annex and not integrated with the complaints of the main algorithm | Referral to hospital is recommended for febrile skin lesions with a size >4 cm or associated with red streaks or tender nodes, and for multiple abscesses.<br>Local treatment and home management is recommended for impetigo and minor abscesses | Severe soft tissue infections require in hospital treatment and injectable antibiotics.<br>Limited skin infections can be safely managed by topical treatment. |
| **Febrile chart for "Fever with no identified cause" after symptom charts assessment** | **Urinary tract infection** | Not considered in IMCI | 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. | UTI is most frequent in children under 2 years of age. Above 2 years of age, the specificity of dysuria symptoms is low.<br>The accuracy and performance of dipstick for UTI diagnosis have been demonstrated.<br>Dipsticks for pregnancy follow-up were already broadly available in HFs in Tanzania; dipsticks for urinalyses were available in Health Centers. |
| | **Typhoid fever** | Not considered in IMCI | In non-severe febrile children > 2 years, 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. | Typhoid fever and other invasive enteric infections are life threatening conditions. In low resource care facilities, HWs fea 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. |

HW: health worker, IMCI: Integrated Management of Childhood Illness, HF: primary health care facility, U5: children under 5 years of age, UTI: urinary tract infection. [§]Fever is defined by either history of fever or axillary temperature above 37.5°C or child feels hot.

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 recognised 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 realising 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.

### 6.4.2 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, 2010). The safety of a mRDT-based malaria case management in U5 has been demonstrated(Baiden et al., 2012; D'Acremont et al., 2010b; Faucher

et al., 2010; Mtove et al., 2011; Mubi et al., 2011; Senn et al., 2012; Ukwaja et al., 2010). 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).

### 6.4.3 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.

### 6.4.4 Otitis Media

In the structured literature review 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(52). 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.

### 6.4.5 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 structured literature review. No additional article since the most recent review published in 2007 was found(Shaikh N 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 N 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 diarrhoea (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 CAHD, 2005). 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 N 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 CAHD, 2005). With the implementation of the WHO focused antenatal care guidelines, urine dipstick for proteinuria detection have been implemented and are thus available in HFs in many African countries. Based on the good diagnostic performance of urine dipstick, and it's feasibility in low resource setting, the new algorithm proposes to perform urine dipstick for the diagnostic of UTI in the patients at higher risk of UTI, i.e. children below 2 years of age having fever with no cause identified during the assessment (but regardless of the malaria test result, 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.

### 6.4.6 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.

### 6.4.7 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, diarrhoea, 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.

### 6.4.8 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 6 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 diarrhoea 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 categorisation allowed limiting antibiotic treatment in children without fever or history of fever.

ALMANACH was first designed as a paper booklet (Annex 2), 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 7). 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.

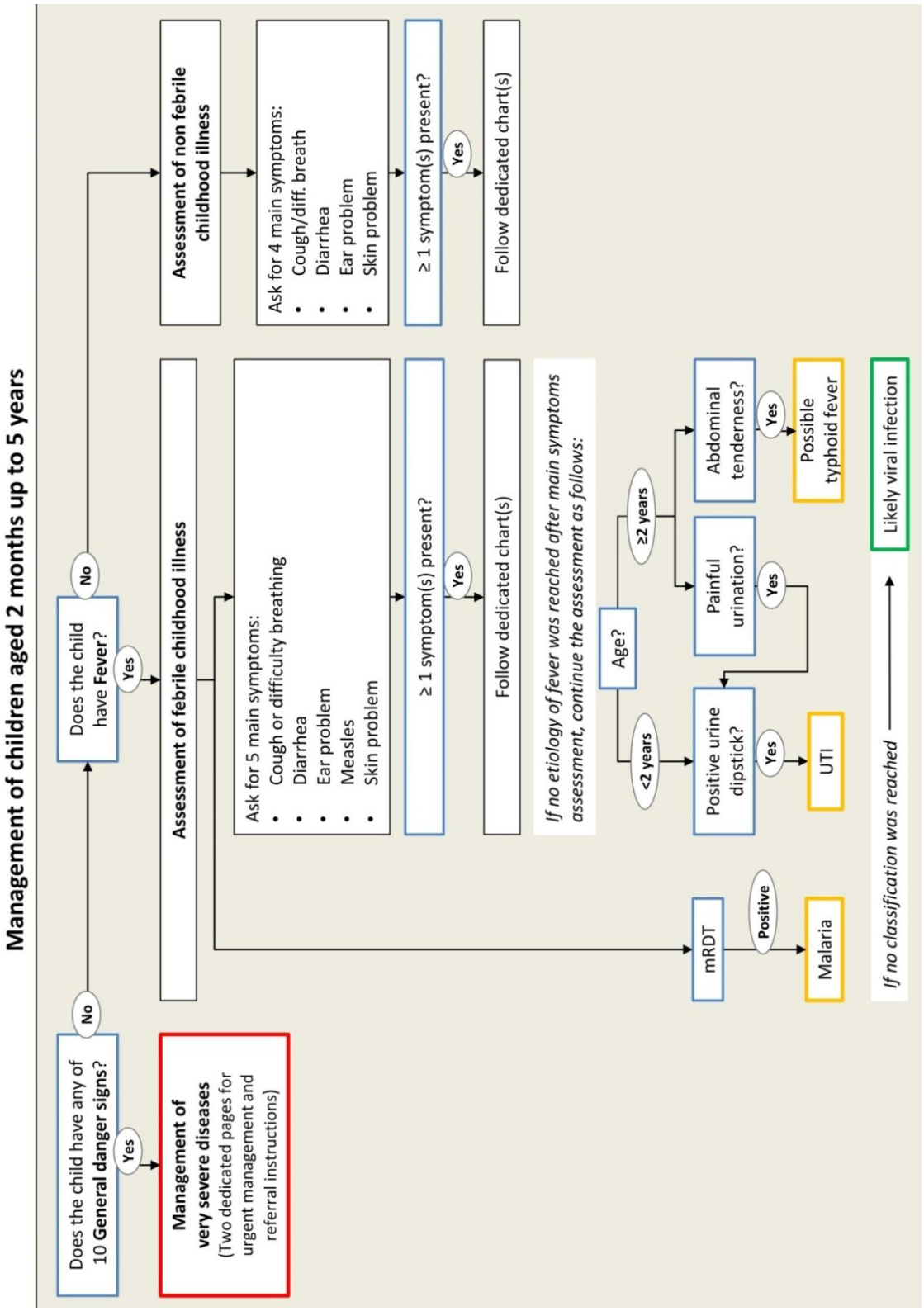


**Figure 6. Overview of ALMANACH's structure**

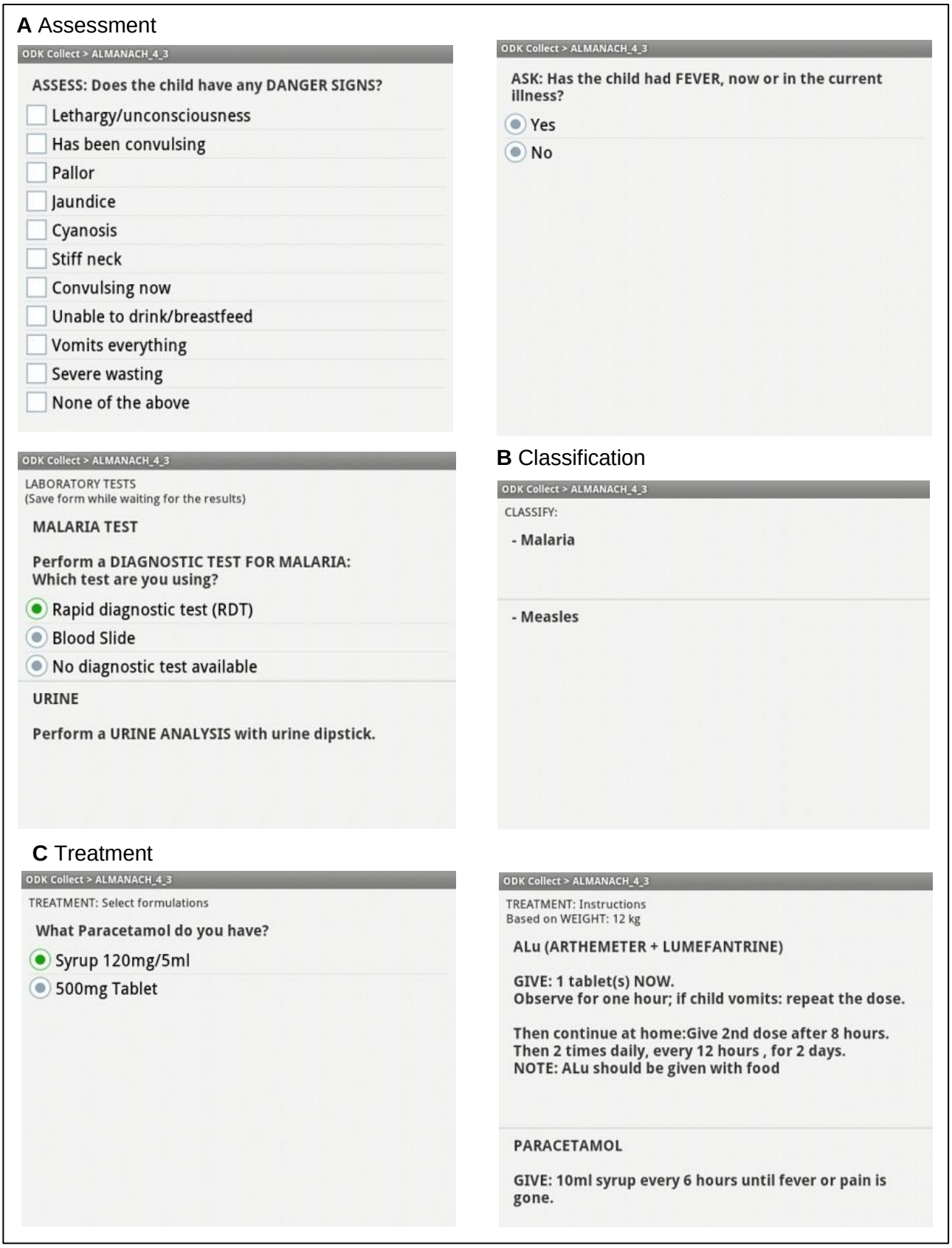


**Figure 7. Samples of ALMANACH in electronic format**

## 6.5 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 HFs, 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 paediatric 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. 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 HF, 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.

**Acknowledgement**

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# 7 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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## 7.1 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 hospitalisation 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.

## 7.2 Introduction

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(J. R. Armstrong Schellenberg et al., 2004). 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; Dominic A and Kurowski C, 2005; Munga and Mæstad, 2009), poor motivation and lack of supervision (Huicho et al., 2005a; Maestad et al., 2010). All this leads to low compliance to the IMCI guidelines (Camara et al., 2008; Kelley et al., 2001; Simoes et al., 1997) 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 (Hamer et al., 2012; Mukanga 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 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 (WHO and UNICEF, 2014), 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 (Batwala et al., 2011; D'Acremont 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.

## 7.3 Materials and Methods

### 7.3.1 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.

### 7.3.2 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 respiratory rate 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.

### 7.3.3 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).

### 7.3.4 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 7.

**Table 7: Key differences between IMCI and ALMANACH, section for the management of acute conditions in children aged 2 months to 5 years**

| | IMCI algorithm | New algorithm (ALMANACH) |
|---|---|---|
| **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<br><br>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<br>Six additional danger signs assessed later: stridor; chest indrawing; ; sunken eyes; skin pinch goes back very slowly; 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<br>+ age-related fast breathing[a] | Fever + cough<br>+ unique fast breathing[b] |
| **Urinary Tract Infection** | Not considered | Febrile child<2 years with no source identified at this point[c], and with a positive (leucocytes or nitrites) urine dipstick. |
| **Typhoid fever** | Not considered | Febrile child ≥2 years with no source identified at this point[c], and with abdominal tenderness |
| **Likely viral infection** | Not existing | Febrile child with no classification at the end of the algorithm |

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

### 7.3.5 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.

### 7.3.6 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.

### 7.3.7 Data collection, management and analysis

In the intervention arm, a standardised 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). 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.

## 7.4 Results

### 7.4.1 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 (Figure 8). 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 8. The diagnoses distribution in the ALMANACH and standard practice arms are featured in Figure 9a and 9b 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.

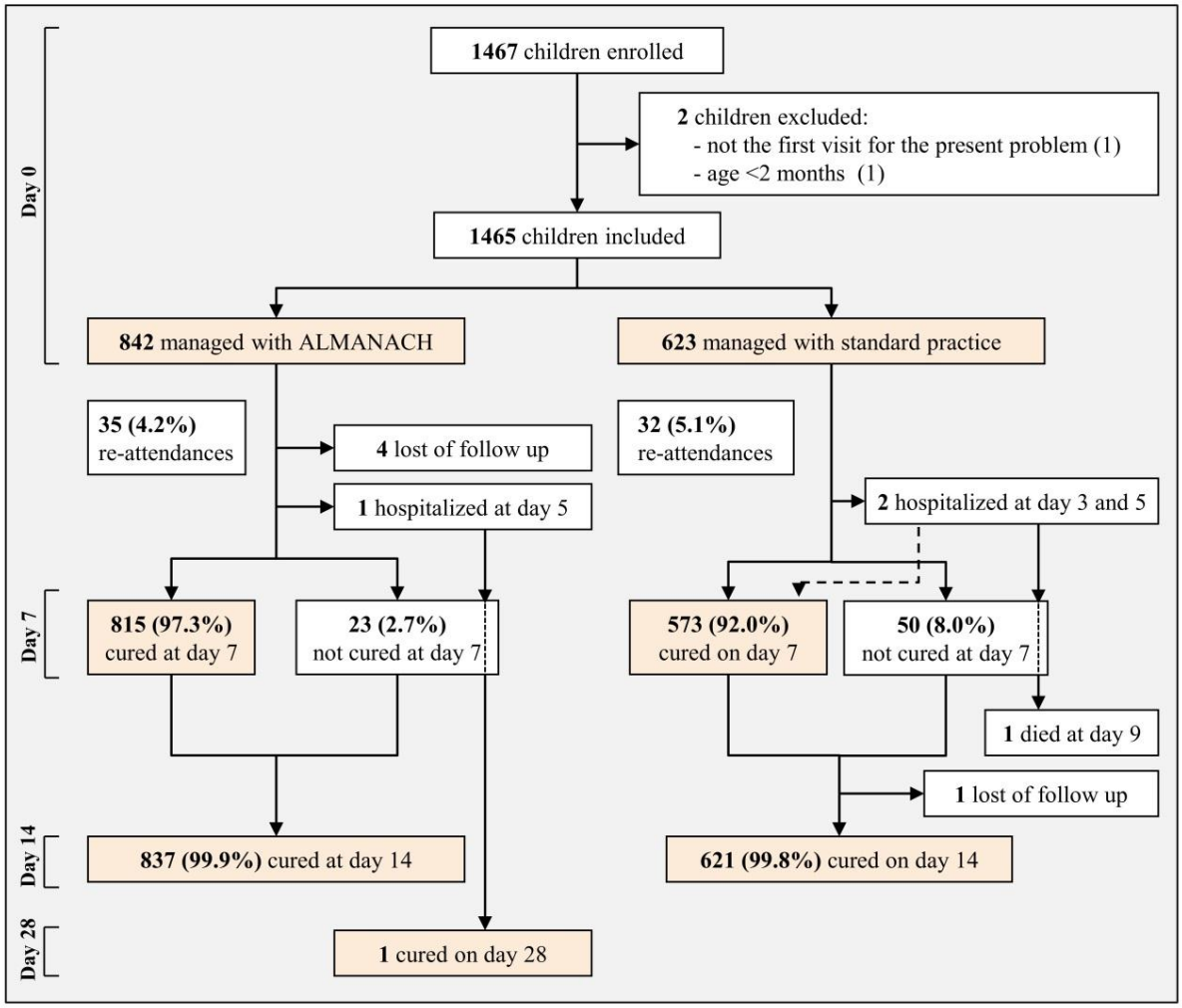


**Figure 8. Safety study profile**

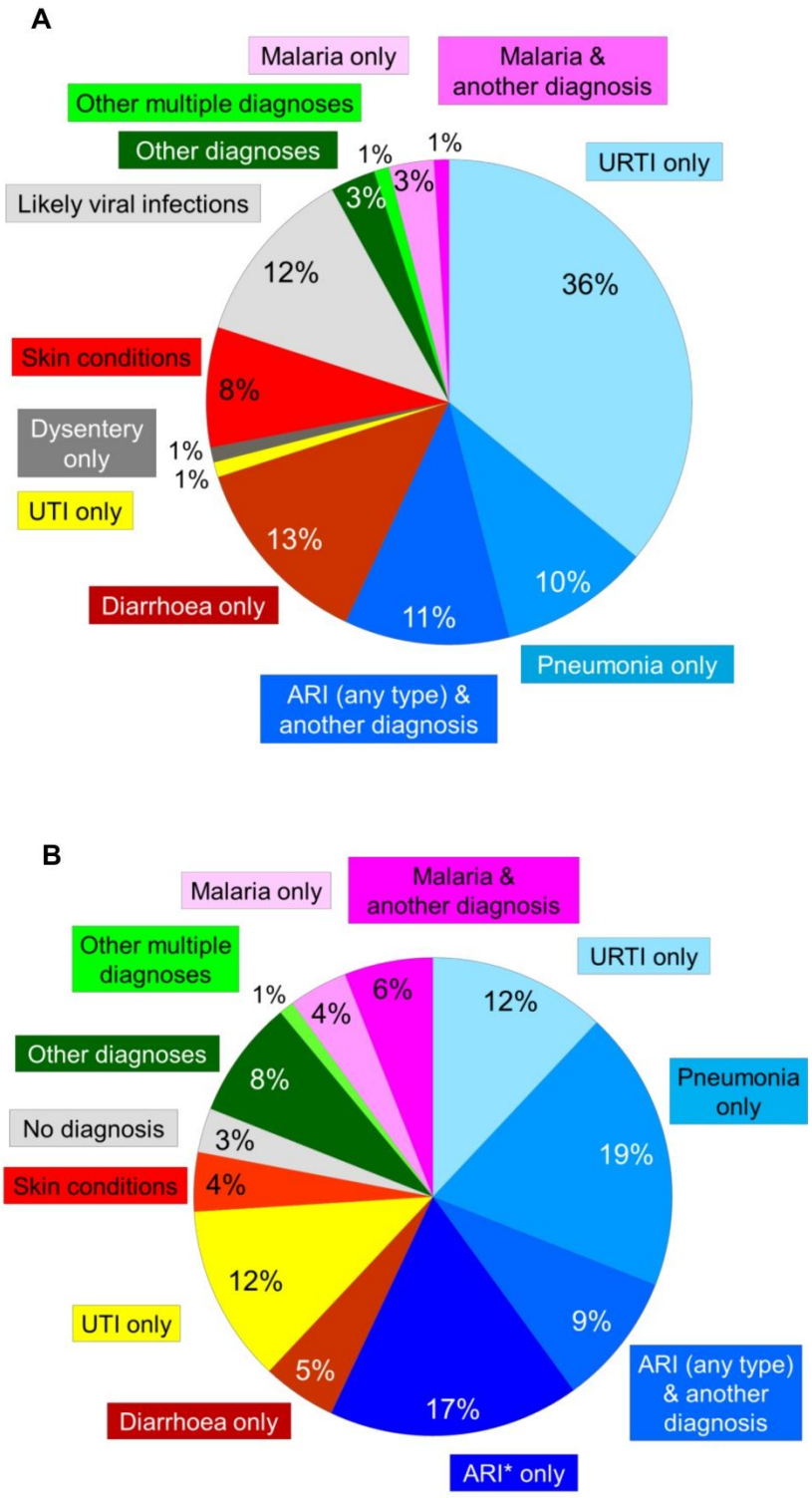


**Figure 9. Distribution of diagnoses at inclusion in the ALMANACH (A) and standard practice (B) arms**

* Diagnosis given by clinicians when they do not classify further the respiratory infection.

**Table 8: Baseline characteristics of the patients in intervention (ALMANACH) and control (standard practice) arms (n=1465)**

| | ALMANACH | | Standard practice | |
|---|---|---|---|---|
| | n/N | % | n/N | % |
| **Gender** | | | | |
| Females | 407/842 | 48·3 | 300/623 | 48·2 |
| **Age (in months)** | | | | |
| 2-12 | 426/842 | 50·6 | 241/623 | 38·7 |
| 13-24 | 216/842 | 25·7 | 174/623 | 27·9 |
| 25-36 | 106/842 | 12·6 | 89/623 | 14·3 |
| 37-48 | 64/842 | 7·6 | 81/623 | 13·0 |
| 49-59 | 30/842 | 3·6 | 38/623 | 6·1 |
| **Main symptoms** | | | | |
| Fever | 571/842 | 67·8 | 511/623 | 82·0 |
| Cough | 498/842 | 59.1 | 355/623 | 57·0 |
| Diarrhoea | 184/842 | 21·9 | 76/623 | 12·2 |
| Vomiting | 57/842 | 6·8 | 78/623 | 12·5 |
| Ear problem | 14/842 | 1·7 | 13/623 | 1·5 |
| **Fast breathing** | | | | |
| ≥50 breaths per minute | 100/351 | 28·5 | 42/310 | 13·6 |
| **Danger signs** | 1/842 | 0·1 | 5/623 | 0·8 |
| Lethargic | 1/842 | 0·1 | 0/623 | 0 |
| Vomiting everything | 0/842 | 0 | 1/623 | 0·2 |
| Unable to drink/breastfeed | 0/842 | 0 | 2/623 | 0·3 |
| History of convulsion | 0/842 | 0 | 2/623 | 0·3 |
| **Hospitalisation at inclusion** | | | | |
| Admission on day 0* | 3/842 | 0·4 | 21/623 | 3·4 |

*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).

### 7.4.2 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 9). 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 8). 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 10). 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 8).

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 diarrhoea (3/33=9·0%) in the standard practice arm.

**Table 9: Clinical outcome and antimicrobials prescribed in children managed by ALMANACH and standard practice**

| Outcome measure | ALMANACH | | | Standard practice | | | p value |
|---|---|---|---|---|---|---|---|
| | n/N | % | 95%CI | n/N | % | 95%CI | |
| **Clinical outcome** | | | | | | | |
| Cured on day 7 | 815/838 | 97·3 | 96·1-98·4 | 573/623 | 92·0 | 89·8-94·1 | <0·001 |
| Cured on Day 14 | 837/838 | 99·9 | 96·6-100·1 | 621/622 | 99·8 | 99·5-100·2 | 0·8 |
| **Antibiotics prescribed** | | | | | | | |
| On day 0 | 130/842 | 15·4 | 12·9-17·9 | 525/623 | 84·3 | 81·4-87·1 | <0·001 |
| Between day 0 and 7 | 19/838 | 2·3* | 1·3-3·3 | 20/623 | 3·2 | 1·8-4·6 | 0·3 |
| On day 7 | 11/838 | 1·3 | 0·7-2·3 | 0/623 | 0 | 0 | 0·003 |
| Total (at any day) | 160/838 | 19·0 | 16·3-21·6 | 545/623 | 87·5 | 84·9-90·1 | <0·001 |
| **Antimalarials prescribed** | | | | | | | |
| On day 0 | 33/842 | 3·9 | 2·6-5·2 | 41/623 | 6·6 | 4·6-8·5 | 0·02 |
| Between day 0 and 7 | 1/838 | 0·1 | -0·1-0·4 | 7/623 | 1·1 | 0·3-2·0 | 0·01 |
| On day 7 | 0/838 | 0 | 0 | 2/623 | 0·3 | -0·1-0·8 | 0·2 |
| Total (at any day) | 34/838 | 4·1 | 2·7-5·4 | 50/623 | 8·0 | 5·9-10·2 | 0·001 |

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

**Table 10: Characteristics of the 23 patients who were not cured at day 7 in the ALMANACH arm.**

| N° | Age (months) | Diagnosis at day 0 | rr at D0 | Antibiotic on D0 | Diagnosis at day 7 | Antibiotic on D7 | Hospitalised | Cured at D 14 |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | Severe pneumonia | NA | Yes | Pneumonia | Yes | No | Yes |
| 2 | 6 | Pneumonia | 52 | Yes | Pneumonia | Yes | No | Yes |
| 3 | 6 | Pneumonia | 55 | Yes | Pneumonia | Yes | No | Yes |
| 4 | 7 | Pneumonia | NA | Yes | URTI and dysentery | Yes | No | Yes |
| 5 | 12 | Pneumonia | 53 | Yes | URTI and diarrhoea | No | No | Yes |
| 6 | 13 | Pneumonia | 66 | Yes | URTI | No | No | Yes |
| 7 | 7 | Pneumonia and impetigo | NA | Yes | Infected heat rashes | No | No | Yes |
| 8 | 23 | URTI | NA | No | Diarrhoea | No | No | Yes |
| 9 | 18 | URTI | NA | No | URTI | No | No | Yes |
| 10 | 9 | URTI | NA | No | Diarrhoea | No | No | Yes |
| 11 | 15 | URTI and impetigo | 32 | No | URTI and soft tissue infection | Yes | No | Yes |
| 12 | 10 | URTI and impetigo | 44 | No | Impetigo | No | No | Yes |
| 13 | 7 | URTI, diarrhoea and impetigo | 36 | No | Pneumonia and diarrhoea | Yes | No | Yes |
| 14 | 10 | URTI and scabies | NA | No | Pneumonia | Yes | No | Yes |
| 15 | 12 | Impetigo | | No | Soft tissue infection | Yes | No | Yes |
| 16 | 16 | Impetigo | | No | Soft tissue infection | Yes | No | Yes |
| 17 | 10 | Infected skin rashes | | No | Skin abscess | Yes | No | Yes |
| 18 | 3 | Scabies | | No | URTI | No | No | Yes |
| 19 | 16 | Fungal infection | | No | Fungal infection | No | No | Yes |
| 20 | 12 | Likely viral infection | NA | No | URTI | No | No | Yes |
| 21 | 20 | Likely viral infection | NA | No | URTI | No | No | Yes |
| 22* | 11 | Likely viral infection | NA | No | Cellulitis | Yes | Yes | No |
| 23 | 38 | Acute ear infection | | No | Acute ear discharge | Yes | No | Yes |

Urr= respiratory rate, URTI=Upper respiratory tract infection, NA=not available * This patient is the same as patient n°8 in table 11. He was secondarily admitted for cellulitis on day 5, received antibiotics on admission, was discharged after 10 days and was cured on day 28

### *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 hospitalised for 10 days, received antibiotics and had recovered when visited on day 28. Of the 623 children managed by standard practice, two children were hospitalised 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 8).

### *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 diarrhoea, 2 UTI, 1 cellulitis and one tonsillitis (Table 11). All were cured at day 7, except the one who was hospitalised with cellulitis. Among 8 children who developed pneumonia secondarily, 6 were <12 months and had a respiratory rate at inclusion between 36 and 48/min, and 2 were ≥12 months and one had a respiratory rate of 42 (not measured for the other child due to absence of cough). On the other hand, 30 children ≥12 months with a respiratory rate between 40 and 50/min at inclusion did not develop pneumonia, and were cured at D7 without antibiotic.

**Table 11. Characteristics of the 19 patients who received antibiotics during re-attendance in the ALMANACH arm**

| N° | Age (months) | Diagnosis at day 0 | rr at D0 | Antibiotic prescribed on D0 | Clinician who prescribed antibiotics* | Diagnosis at re-attendance visit | Cured at D7 |
|---|---|---|---|---|---|---|---|
| 1 | 10 | Pneumonia | 53 | Yes | Study | Pneumonia | Yes |
| 2 | 8 | Pneumonia | NA | Yes | Routine | Pneumonia | Yes |
| 3 | 10 | Pneumonia | 52 | Yes | Study | UTI | Yes |
| 4 | 8 | Pneumonia and measles | 52 | Yes | Routine | Diarrhoea | Yes |
| 5 | 18 | Likely viral infection | NA | No | Study | Pneumonia | Yes |
| 6 | 21 | Likely viral infection | NA | No | Study | Tonsillitis | Yes |
| 7 | 56 | Likely viral infection | NA | No | Study | UTI | Yes |
| 8[&] | 11 | Likely viral infection | NA | No | Study | Cellulitis | No |
| 9 | 10 | Likely viral infection | NA | No | Routine | Diarrhoea | Yes |
| 10 | 37 | Likely viral infection | NA | No | Routine | Diarrhoea | Yes |
| 11 | 6 | URTI | 46 | No | Study | Pneumonia | Yes |
| 12 | 4 | URTI | NA | No | Study | Pneumonia | Yes |
| 13 | 5 | URTI | NA | No | Routine | Pneumonia | Yes |
| 14 | 11 | URTI | 40 | No | Routine | Pneumonia | Yes |
| 15 | 13 | URTI | 42 | No | Routine | Pneumonia | Yes |
| 16 | 8 | URTI and diarrhoea | 48 | No | Study | Pneumonia | Yes |
| 17 | 5 | UTI | | Yes | Study | Pneumonia | Yes |
| 18 | 9 | Diarrhoea | | No | Routine | Diarrhoea | Yes |
| 19 | 36 | Impetigo | | No | Routine | Diarrhoea | Yes |

rr: respiratory rate *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 10.

### 7.4.3 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 9). 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%).

## 7.5 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 respiratory rate 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 behaviour 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 (Moyo et al., 2011; Temu et al., 2007). 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 e-ALMANACH in programmatic conditions.

*Clinical failure and/or secondary antibiotic prescription according to diagnosis 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 diarrhoea. 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.

### 7.5.1 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).

## 7.6 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 generalisable 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.

## 7.7 Acknowledgements

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# 8 Performance of health workers using an electronic algorithm for the management of childhood illness (ALMANACH) in Tanzania - A pilot implementation study

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## 8.1 Abstract

In low resource settings, rational antimicrobial prescription for childhood illnesses is a challenge.

To assess whether smartphones running  guidelines, as compared to paper support, improves consultation process and rational use of medicines for children, a pilot cluster-randomized controlled study was conducted in Tanzania.  Nine primary health care facilities (HFs) were randomized into 3 arms (i. paper algorithm, ii. electronic algorithm on a smartphone, iii. control). All health workers attending children aged 2 to 59 months for acute illness in intervention HFs were trained on a new clinical ALgorithm for MANAgement of CHildhood illness (ALMANACH) either on paper or electronic support Four months after training consultations were observed. An expert consultation was the reference for classification and treatment.  Main outcomes were proportion of children checked for danger signs, and antibiotics prescription rate.

A total of 504 consultations (166, 171, and 167 in control, paper, and phone arms) were observed. The use of smartphones versus paper was associated with a significant increase in children checked for danger signs (41% vs 74%, p=0.04). Antibiotic prescriptions rate dropped from 70% in the control to 26%, and 25% in paper and electronic arms. The HWs-expert agreement on pneumonia classification remained low (expert's pneumonia identified by HWs in 26%, 30%, and 39% of patients respectively).

Mobile technology in low-income countries is implementable and has a potential to improve HWs' performance. Additional point–of-care diagnostic tests are needed to ensure appropriate management. Improving rational use of antimicrobial is a challenge that ALMANACH can help to take up.

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## 8.2 Introduction

In the context of the global rapid spread of resistance to antimicrobials, there is an urgent need to reduce the overuse of these life-saving medicines worldwide. In low income countries, where childhood mortality due to infectious diseases is high(Liu et al., 2012), rational use of antimicrobials in children is a challenge for health workers (HWs) lacking accurate tools and skills to make appropriate diagnoses(Risk et al., 2013). Providing HWs with guidelines allowing them to identify patients in need or not of antibiotics and antimalarials may help them to rationalise their antimicrobials prescription. For these guidelines to reach their goal, high HWs' compliance is necessary. The current reference standard for the management of children in primary care setting in low income countries is the Integrated Management of Childhood Illness (IMCI). Two main limitations made IMCI guidelines suboptimal to tackle antimicrobials over-prescription where implemented. First, the IMCI algorithm, designed in the 1990's to tackle the high childhood mortality(Gove, 1997), had to rely on poorly specific diseases classification that leads to over-prescription of both antibiotics and antimalarials. Antimalarials over-prescription that resulted from the presumptive treatment recommended for all febrile children in endemic areas, has recently been addressed by IMCI that now recommends test-based malaria treatment(WHO and UNICEF, 2014) (D'Acremont et al., 2008). However, regarding bacterial diseases, both the low specificity of the criteria used to classify pneumonia (Hazir et al., 2011; Rambaud-Althaus et al., 2015; Senn et al., 2014) and the lack of clear recommendations for the management of non-malaria febrile illnesses prompt clinicians to prescribe antibiotics to be 'on the safe side'(Baiden et al., 2011; Bruxvoort et al., 2013; D'Acremont et al., 2008). The second limitation lies in the low compliance of HWs to IMCI recommendations(Lange et al., 2014; Senn et al., 2014). To address these limitations, a new algorithm for the management of sick children aged 2 to 59 months (ALMANACH) was developed, both on paper and electronic support.(Rambaud-Althaus et al., 2015) Derived from IMCI, ALMANACH integrates evidence-based diagnostic procedures targeting the main infectious diseases including the use of a rapid diagnostic test for malaria diagnosis (mRDT), a urine dipstick for the classification of urinary tract infection (UTI) and abdominal tenderness for the classification of typhoid fever. For children with fever or history of fever, a new disease classification, namely 'likely viral infection', is proposed at the end of the

child's assessment when no cause of fever has been identified, and bacterial disease and malaria have been ruled out, which encourages HWs to withhold unnecessary antibiotic prescription. The electronic version of ALMANACH was developed using a set of open-source software from Open Data Kit("Open Data Kit," n.d.) and OpenMRS("OpenMRS," n.d.), to be run on android mobile devices (smartphones and tablets) (Rambaud-Althaus et al., 2015). The impact of ALMANACH's use in term of children's health outcome and antibiotic prescriptions has been demonstrated in controlled conditions in Tanzanian primary care health facilities (HFs). The use of the new algorithm achieved a better cure rate at day 7 and a dramatically lower rate of antibiotic prescription than routine practice (15% with ALMANACH vs 84% in the control; $p<0.001$). (Shao et al., 2015) Used in controlled conditions, ALMANACH was thus able to improve the rational use of antibiotics in a safely manner.
In this paper we present the results of a comparative study to assess the impact of the e-ALMANACH on HWs' performance and antimicrobials prescription when used in programmatic conditions. Performance, in term of completeness of assessment, appropriateness of diseases classification and treatment prescription, was assessed for HWs trained on and provided with paper or electronic ALMANACH, and compared to that for HWs without specific training or tool.

## 8.3 Material and Methods

### 8.3.1 Study setting

The study took place between April and December 2011 in Dar es Salaam, the economic capital of the United Republic of Tanzania, with 4'360'000 inhabitants in 2012(PHC, 2012). Dar es Salaam has 3 municipalities with a public health system organized in 4 levels (reference hospitals, district hospitals, health centres and dispensaries). Tanzania adopted the IMCI protocols as national policy in 1998(Mushi et al., 2010). In 2011, Tanzania was in the process of mRDT implementation at national scale, but the administrative region of Dar es Salaam was not yet covered. For this study we conveniently selected 9 public HFs (3 health centres and 6 dispensaries) that had been using mRDT routinely since a previous research project (IMALDIA 2006-2009)(D'Acremont et al., 2008). The 3 selected HFs per municipality were randomly allocated to: i) e-ALMANACH (electronic arm), ii) paper ALMANACH (paper arm), and iii) standard practice (control arm), by a block stratified

randomisation(Piantadosi and Cedars-Sinai Medical Center, n.d.). In each arm a total of 3 HFs were thus enrolled (Table 12).

**Table 12. Characteristics of the 9 public health facilities involved in the survey and detailed list of health workers trained and supervised**

| Health facility | Arm | District | Type | Total number of health workers | Number of health workers in OPD | Number of health workers trained | Number of health workers supervised |
|---|---|---|---|---|---|---|---|
| 1 | Control | Kinondoni | HC | 17 | 6 | - | - |
| 2 | Control | Ilala | D | 8 | 7 | - | - |
| 3 | Control | Temeke | D | 10 | 6 | - | - |
| 4 | Paper | Kinondoni | D | 5 | 4 | 4 | 4 |
| 5 | Paper | Ilala | D | 9 | 6 | 6 | 5° |
| 6 | Paper | Temeke | HC | 12 | 8 | 8 | 8 |
| 7 | Electronic | Kinondoni | D | 17 | 11 | 11 | 9° |
| 8 | Electronic | Ilala | HC | 13 | 8 | 7* | 6° |
| 9 | Electronic | Temeke | D | 16 | 12 | 12 | 11° |

*Clinicians in OPD not trained: HF8: 1 transferred out
°Clinicians trained not supervised: HF5: 1 transferred out; HF7: 1 maternity leave and 1 long leave; HF8: 1 long leave; HF9: 1 transferred out.

### 8.3.2 Intervention: ALMANACH pilot implementation

In April and May 2011, a total of 48 HWs (18 in the paper, 30 in the electronic arm) involved in children's management in the 6 enrolled intervention HFs received a 2-day training. The training was conducted by the study team (CRA, AS, SJ, NS, SP), with the support of external experts (acknowledged), in both English and Kiswahili (both Tanzanian official languages). Clinicians from both intervention arms were trained together, through lectures and practical exercises on the problem of antibiotic resistance and on the ALMANACH's content and rationale. In the afternoon of the second day, HWs were trained separately on the use of ALMANACH with clinical case studies on either the booklet or the smartphone application, according to their HF's arm. In both arms clinicians received a paper version of ALMANACH[12], written in Kiswahili. The electronic version contains all and only the information available in the booklet, both in English and Kiswahili.

After the training, 3 to 5 smartphones (according to the number of working places) were brought in the electronic arm HFs. During the following 3 months, one day of face-to-face supervision was delivered in the 6 intervention HFs to 43 HWs (17

paper, 26 electronic) by one of the study supervisors (CRA, AS, SJ, NS, SP) while the clinician was attending real patients. After all HWs had been trained and supervised, monthly supervision visits were carried out in the 6 HFs. Throughout the study period, the study team made sure that antimalarials and mRDTs were always available both in intervention and control HFs.

### 8.3.3 Study design and subjects

A cross sectional comparative survey was conducted in September and October 2011 in the 9 involved HFs to assess HWs' performance four months after the initial training and face-to-face supervision. All consecutive children aged 2 to 59 months presenting during the working hours of the study team were recruited if they fulfilled the following inclusion criteria: 1) first consultation for an acute medical problem; 2) absence of severe illness requiring immediate life-saving procedures; 3) main complaint(s) not related to injury or trauma; 5) written informed consent by the caretaker. Because they valued the intervention and the access to an expert consultation, none of the caretaker of eligible children refused to participate. The sample size estimation was based on an expected 90% proportion of children assessed for danger signs in the electronic arm. This indicator was selected for the calculation as it is a key element for patients' safety. With individual patient randomization, 72 patients per arm would have been required to detect a 20% point one-sided difference with 80% power and 5% significance for this indicator. In this cluster-randomized pilot study, the number of health facilities and children we could enroll were limited. We decided to enroll 50 children from 3 health facilities in each arm, allowing the detection of a minimum difference from 19 to 30% point in the indicator, with an assumed intracluster correlation between 0.01 and 0.05, with 80% power and 5% significance. The targeted sample size was 150 children per arm.

### 8.3.4 Procedures

After oral consent was given by the HW and written consent by the child's caretaker, the consultation was observed by an external study-trained clinical officer (hereafter referred to as the observer) who recorded details of the HW's assessment of the child, including symptoms and signs found, laboratory investigation(s) performed; classification(s) reached; advice to caretakers; and treatment(s) prescribed, without intervening. Following the HW's consultation, each enrolled child underwent a second

full clinical assessment by an experienced clinician following strictly the e-ALMANACH (expert). During the study, the classification, treatment, and advice of the expert were the basis for the final treatment of the child. The study protocol and related documents were approved by the Ethikkommission beider Basel in Switzerland, and by the Institutional Review Board of the Ifakara Health Institute and the National Institute for Medical Research Review Board in Tanzania.

### 8.3.5 Data collection, management and analyses

For each enrolled child, the observer completed a standardised paper case report form (CRF) where he/she recorded HW and child's demographics, tasks performed by the HW, and findings. The CRFs were adapted from the health facility survey checklist questionnaire developed by WHO(WHO, 2001). Data from the expert consultation were collected through the smartphone-run e-ALMANACH. All paper collected data were double entered in EpiInfo (version 3.5.3). Data cleaning, management, and analyses were conducted using Stata software version 10 (College Station, Texas, USA). A set of indicators was derived from the Health Facility Surveys tool in IMCI multi-country evaluation(WHO, 2001) to assess HWs' performance outcomes in term of i) completeness of assessment, ii) accuracy of disease classification, and iii) appropriateness of antimicrobial prescription, as compared to the expert assessment. The list of indicators and their definition is presented in Table 13. The unit of analysis was the patient. Proportions were compared by calculating odds ratios using a multilevel mixed-effects logistic regression model to account for health facility clustering. Adjusted risk ratios (aRR) were calculated from the fitted values for each cell of the 2 by 2 tables, for each intervention arm (paper and electronic) as compared to the control arm, and then compared to paper arm. The 95% confidence intervals of the aRR of each intervention arm were compared to explore the added value of the electronic intervention over the paper one. Venn diagrams were computed using Venn Diagram Plotter software ("Venn Diagram Plotter | Pan-Omics Research," n.d.) to illustrate the accuracy of the HWs' bacterial and viral classifications as compared to the expert's classifications.

**Table 13. List and definition of health workers' performance outcomes indicators**

| Performance indicator | Definition |
|---|---|
| ***Completeness of assessment*** | |
| *Assessment tasks requested for all children* | |
| Danger signs | Proportion of children asked for all of the 3 following danger signs: 'difficulty to drink', 'vomits everything', and 'history of convulsion' |
| Main symptoms | Proportion of children asked for all of the 3 following main symptoms: 'fever', 'cough', and 'diarrhoea' |
| Palmar pallor | Proportion of children checked for palmar pallor |
| Index of integrated assessment | Proportion of the 11 assessment tasks required for each child actually performed (3 danger signs, 3 main symptoms, other problem, weight, temperature, RCH card, palmar pallor; total=11 tasks) |
| *Assessment tasks requested for a subset of children* | |
| Respiratory rate | Proportion of children with fever and cough who had their respiratory rate counted |
| Malaria test | Proportion of febrile children who had a malaria rapid test ordered for |
| ***Classifications appropriateness*** | |
| Children appropriately classified | Proportion of children with all classifications of HWs matching the expert classifications |
| Bacterial classifications identified | Proportion of children with at least one expert classification potentially due to a bacteria (pneumonia, dysentery, ear infection) identified by the health worker |
| Viral infection identified | Proportion of children with expert classifications likely due to a virus (cough or cold, likely viral) identified by the health worker |
| ***Treatment appropriateness*** | |
| Children appropriately managed | Proportion of children who were prescribed antimalarial, antibiotics, ORS, and zinc when needed and no antibiotic nor antimalarial when not needed. |
| Children in need of antibiotic for whom it was prescribed | Proportion of children in need of an antibiotic as per expert classifications for whom at least one antibiotic was prescribed by the health worker |
| Children not in need of antibiotic for whom it was not prescribed | Proportion of children not in need of an antibiotic as per expert classification for whom no antibiotic was prescribed by the health worker |
| Children in need of antimalarial for whom it was prescribed | Proportion of children in need of an antimalarial as per expert classification for whom an antimalarial was prescribed by the health worker |
| Children not in need of antimalarial for whom it was not prescribed | Proportion of children not in need of an antimalarial as per expert classification for whom no antimalarial was prescribed by the health worker |

## 8.4 Results

### 8.4.1 Characteristics of the study population

From 2nd September to 23rd November 2011, 504 children with a median age of 15 months (inter quartile range [IQR]: 8-29) were enrolled (166 in the control, 171 in the paper, and 167 in the electronic arms). Fever was reported in 71% (95%CI: 67-75%) and cough in 66% (62-70%) of the 504 children. The most frequent classification given by the expert was 'Cough or cold' reached in 55% (51-60%) of the children, followed by 'acute diarrhoea without dehydration' in 19% (16-23%) and 'pneumonia', 10% (8-13%). According to the expert, 63 (13%) out of these 504 children had a condition requiring antibiotics, and 7 (1%) antimalarials. The detailed characteristics of the 504 enrolled children as per expert assessment are presented in Table 14.

**Table 14. Demographic characteristics, symptoms and disease classification as per expert's evaluation of the 504 enrolled children**

| | **Electronic (N=167)** | **Paper (N=171)** | **Control (N=166)** | **Overall (N=504)** |
|---|---|---|---|---|
| | Proportion (3 HFs Range[§]) | Proportion (3 HFs Range[§]) | Proportion (3 HFs Range[§]) | Proportion |
| ***Demographics*** | | | | |
| Children aged 2-11 months | 43% (41-47) | 36% (28-40) | 32% (25-41) | 37% |
| Girls | 48% (38-57) | 46% (43-52) | 51% (44-55) | 48% |
| ***Symptoms*** | | | | |
| Fever* | 75% (69-80) | 64% (59-67) | 73% (72-75) | 71% |
| Cough | 69% (65-72) | 64% (57-74) | 65% (63-69) | 66% |
| Fever* and cough | 55% (51-57) | 44% (39-51) | 46% (42-49) | 49% |
| Diarrhoea | 23% (22-24) | 17% (12-24) | 20% (17-24) | 20% |
| Skin lesion | 7% (2-13) | 12% (7-21) | 5% (2-7) | 8% |
| Ear problem | 0% | 4% (3-4) | 2% (0-4) | 2% |
| ***Disease classification (expert)*** | | | | |
| Severe disease | 1% (0-2)[$] | 2% (0-4)° | 0% | 1% |
| Malaria | 1% (0-2) | 1% (0-4) | 2% (0-5) | 1% |
| Pneumonia | 14% (12-15) | 6% (4-7) | 11% (4-20) | 10% |
| Cough or cold | 55% (51-57) | 57% (54-63) | 53% (47-59) | 55% |
| Acute diarrhoea | 22% (20-24) | 17% (12-24) | 19% (17-24) | 19% |
| Dysentery | 1% (0-2) | 0% | 1% (0-4) | 1% |
| UTI | 1% (0-2) | 1% (0-2) | 1% (0-2) | 1% |
| Likely viral | 11% (7-15) | 10% (4-18) | 16% (11-21) | 12% |

HF: Health facility. UTI: urinary tract infection. *history of fever as mentioned by the caretaker
[§]Range of proportions in the 3 health facilities. °3 severe classifications: 1 severe malnutrition, 1 severe anaemia, 1 'vomits everything'; [$]severe anaemia.

### 8.4.2 Completeness of integrated assessment

In the control arm, some of the assessment tasks that should be systematically performed in every child were rarely performed by the clinicians. Dangers signs were checked in only 3% of the children (range: 2-4% among 3HFs) and palmar pallor in 14% (6-20%). In this arm, only 21% of the children (18-24%) had an index of integrated assessment ≥50% (meaning that only one child out of five had at least half of the systematic assessment tasks performed) and 11% (9-14%) an index above 75% (Table 15). In the paper arm, danger signs were checked in 41% of the children (range 16-71% among 3 HFs; adjusted risk ratio as compared to control arm (aRR) [95%CI]: 14.4 [3.4-69.7]) and palmar pallor in 30% (11-50%; 2.1 [0.8-5.7]). In this arm, 58% of the children (33-85%; 2.9 [1.4-6.3]) had an index of integrated assessment ≥50%, and 16% (7-27%; 1.5 [0.7-3.1]) an index above 75%. In the electronic arm, danger signs were checked in 74% of the children (63-94%; 30.9 [9.2-120.2]) and pallor in 69% (56-80%; 5.2 [3.1-9.1]). In this arm, the proportion of children with an index ≥50% was 87% (80-98%; 4.2 [3.1-5.6]) and with one ≥75%, 43% (40-46%; 4.0 [2.5-6.4]) (Table 15). Main symptoms were checked in two thirds of the children in the control (77%, range 64-91%) and paper arm (75%, range 68-82%; aRR 1.0 [0.8-1.2]), and in almost all children in the electronic arm (99%, range 98-100%; aRR 1.3 [1.2-1.3]).

Assessment tasks to be performed in a subset of children (such as malaria test, or respiratory rate count) were not included in the index of integrated assessment. Respiratory rate was counted in only 4% (0-7%) of eligible children in the control arm, and in 53% (25-70%; 12.8 [3.6-53.5]) and 41% (32-56%; 9.4 [3.1-30.9]) in the paper and electronic arms respectively. The proportion of febrile children tested for malaria was not significantly different in the 3 arms (84%, range 75-88% in the control; 92%, range 88-95%, aRR 1.1 [1.0-1.2] in the paper; and 72%, range 56-88%, aRR 0.9 [0.7-1.0] in the electronic arms) (Table 15).

**Table 15. Indicators of completeness of assessment and appropriateness of classifications and treatments**

| Indicators | Arm | N total | Indicator % (3 HFs Range) | Risk ratio accounting for clustering aRR (95%CI) | | | |
|---|---|---|---|---|---|---|---|
| | | | | Versus control | p value | Versus paper | p value |
| ***Assessment*** | | | | | | | |
| Danger Signs | Control | 165 | 3% (2- 4) | - | - | - | - |
| | Paper | 168 | 41% (16-71) | 14.4 (3.4-69.7) | <0.001 | - | - |
| | Electronic | 152 | 74% (63-94) | 30. 9 (9.2-120.2) | <0.001 | 2.0 (1.0-3.5) | 0.04 |
| Main symptoms | Control | 163 | 77% (64-91) | - | - | - | - |
| | Paper | 168 | 75% (68-82) | 1.0 (0.8-1.2) | 0.68 | - | - |
| | Electronic | 158 | 99% (98-100) | 1.3 (1.2-1.3) | 0.001 | 1.3 (1.2-1.3) | <0.001 |
| Palmar pallor | Control | 166 | 14% (6-20) | - | - | - | - |
| | Paper | 171 | 30% (11-50) | 2.1 (0.8-5.7) | 0.12 | - | - |
| | Electronic | 167 | 69% (56-80) | 5.2 (3.1-9.1) | <0.001 | 2.5 (1.5-4.3) | 0.001 |
| Prop with an index of integrated assessment ≥50% | Control | 166 | 21% (18-24) | - | - | - | - |
| | Paper | 171 | 58% (33-85) | 2.9 (1.4-6.3) | 0.004 | - | - |
| | Electronic | 167 | 87% (80-98) | 4.2 (3.1-5.6) | <0.001 | 1.6 (1.1-2.0) | 0.027 |
| Prop with an index of integrated assessment ≥75% | Control | 166 | 11% (9-14) | - | - | - | - |
| | Paper | 171 | 16% (7-27) | 1.5 (0.7-3.1) | 0.273 | - | - |
| | Electronic | 167 | 43% (40-46) | 4.0 (2.5-6.4) | <0.001 | 2.7 (1.7-4.1) | <0.001 |
| Respiratory rate measured | Control | 69 | 4% (0-7) | - | - | - | - |
| | Paper | 73 | 53% (25-70) | 12.8 (3.6-53.5) | <0.001 | - | - |
| | Electronic | 79 | 41% (32-56) | 9.4 (3.1-30.9) | <0.001 | 0.8 (0.5-1.3) | 0.34 |
| Malaria test ordered | Control | 123 | 84% (75-88) | - | - | - | - |
| | Paper | 112 | 92% (88-95) | 1.1 (1.0-1.2) | 0.06 | - | - |
| | Electronic | 116 | 72% (56-88) | 0.9 (0.7-1.1) | 0.16 | 0.8 (0.7-0.9) | 0.07 |
| ***Classifications*** | | | | | | | |
| Children appropriately classified | Control | 166 | 34% (22-56) | - | - | - | - |
| | Paper | 171 | 39% (35-42) | 1.1 (0.7-1.9) | 0.60 | - | - |
| | Electronic | 167 | 53% (47-59) | 1.6 (1.0-2.5) | 0.045 | 1.6 (1.0-2.5) | 0.07 |
| Bacterial classifications identified | Control | 22 | 27% (0-38) | - | - | - | - |
| | Paper | 11 | 36% (20-100) | 1.3 (0.4-3.6) | 0.59 | - | - |
| | Electronic | 26 | 46% (0-70) | 1.8 (0.5-8.4) | 0.41 | 1.0 (0.3-8.7) | 0.949 |
| Viral classifications identified | Control | 114 | 36% (17-74) | - | - | - | - |
| | Paper | 115 | 33% (10-43) | 0.9 (0.3-2.8) | 0.81 | - | - |
| | Electronic | 110 | 70% (59-77) | 2.1 (1.0-4.0) | 0.04 | 2.2 (1.4-3.5) | 0.001 |
| ***Treatment*** | | | | | | | |
| Children appropriately managed | Control | 166 | 37% (29-44) | - | - | - | - |
| | Paper | 171 | 62% (55-74) | 1.7 (1.3-2.2) | <0.001 | - | - |
| | Electronic | 167 | 63% (52-72) | 1.7 (1.3-2.2) | <0.001 | 1.0 (0.8-1.3) | 0.91 |
| Children prescribed antibiotic by HW | Control | 166 | 70% (60-85) | | | - | - |
| | Paper | 171 | 26% (14-37) | 0.4 (0.2-0.6) | <0.001 | - | - |
| | Electronic | 167 | 25% (17-33) | 0.3 (0.2-0.5) | <0.001 | 1.1 (0.6-1.6) | 0.825 |
| Children in need of AB for whom it was prescribed | Control | 22 | 100% (100-100) | - | - | - | - |
| | Paper | 14 | 36% (20-67) | 0.4 (0.3-0.7) | 0.002 | - | - |
| | Electronic | 27 | 48% (0-80) | 0.5 (0.4-1.0) | 0.04 | 1.2 (0.4-6.7) | 0.823 |
| Children not in need of AB for whom it was not prescribed | Control | 144 | 34% (18-47) | - | - | - | - |
| | Paper | 157 | 75% (63-87) | 2.3 (1.5-3.4) | <0.001 | - | - |
| | Electronic | 140 | 80% (72-90) | 2.4 (1.7-3.3) | <0.001 | 1.1 (0.9-1.0) | 0.474 |
| Children in need of AM for whom it was prescribed | Control | 3 | 100% (100) | - | - | - | - |
| | Paper | 2 | 50% (50) | NA* | - | - | - |
| | Electronic | 2 | 50% (0-100) | NA* | - | NA* | |
| Children not in need of AM for whom it was not prescribed | Control | 163 | 93% (87-98) | - | | | - |
| | Paper | 169 | 100% (100-100) | 1.1 (1.0-4.0) | 0.03 | | - |
| | Electronic | 165 | 96% (89-100) | 1.1 (0.9-1.1) | 0.37 | 1.0 (1.0-1.0) | 0.466 |

*NA: Not applicable, due to a too small patients' effective

AB antibiotic. AM antimalarial. HW health worker. *NA: Not applicable, due to a too small patients' effective

### 8.4.3 Appropriateness of disease classification

The proportion of children with all HWs' disease classifications matching the expert's ones was low in both control (33%, [range in the 3 HFs 22-56%]) and paper arms (39%, [35-42%]; aRR 1.1 [0.7-1.9]) and slightly higher in the electronic one (53% [47-57%]); 1.6 [1.0-2.5]). This was due to a higher proportion of viral conditions identified by HWs in the electronic arm (70%) than in the control arm (36%; aRR 2.1 [1.0-4.0]). The proportions of bacterial conditions identified by HWs was however not significantly different between the three arms and highly heterogeneous between the HFs (27%,range 0-38% in control; 36%, range 20-100% in paper; and 46%, range 0-70% in electronic arm)(Table 15). Figure 10 presents Venn diagrams illustrating the agreement between HWs and expert in term of viral and bacterial classifications, and the proportion of children prescribed antibiotics by HWs.

### 8.4.4 Appropriateness of treatment

The proportion of children appropriately managed (antimalarials, antibiotics, zinc and rehydration prescribed when needed only) was similar in the two intervention arms and significantly higher than that in the control arm (37%, range 29-44% in control; 62%, range 55-74%, aRR 1.7 [1.3-2.2] in paper; and 63%, range 52-72%, aRR 1.7 [1.3-2.2] in the electronic arm). The proportion of children prescribed antibiotics was much lower in the interventions than in the control arm (70%, range 60-85 % in the control; 26%, range 14-37%, aRR 0.4[0.2-0.6] in the paper; and 25%, range 17-33%, aRR 0.3[0.2-0.5] in the electronic arm). Thereby, the proportion of children not in need of antibiotics and for whom it was not prescribed was higher in the paper (75% (aRR 2.3 [1.5-3.4]) and the electronic HFs (80% (aRR 2.4 [1.7-3.3]) than in the control HFs (34%). However, the proportion of children in need of antibiotics and for whom it was not prescribed was also higher in the intervention arms: only 5 of the 14 children in need of antibiotic were prescribed it by the attending HW in the paper arm, and only 13 of the 27 children in the electronic arm. In the control arm, where 70% of all children were prescribed an antibiotic, all the 22 children in need of an antibiotic were prescribed one by the HW; however more than half of the antibiotic prescriptions in the control arm were inappropriate (Table 15). Among the 7 malaria cases, 5 were appropriately treated and 2 were not prescribed any antimalarial by the HW (1 in the paper and 1 in the electronic arm). Some children received an unnecessary antimalarial treatment (11 in the control and 6 in the electronic arm).

### 8.4.5 Identification of serious conditions by health workers

Table 16 presents for each HF the list of serious conditions, i.e. either severe diseases or infections requiring antimalarial (malaria) or antibiotic treatment (pneumonia, dysentery, UTI), identified in the three arms compared to that identified by the expert. Overall only 30 (43%) out of 70 conditions were appropriately identified by the HWs. Pneumonia, that was the most frequent serious condition identified by the expert, was also the condition most often missed by the HWs in all three arms: only about one third of pneumonia was identified by the HWs (5/19, 3/10, and 9/23 in control, paper and electronic arms respectively). These proportions varied a lot among the different HFs involved. The other conditions requiring antibiotics or antimalarials, though rare, were more often recognised by the HWs. When looking at the 35 expert pneumonia that were missed by HWs (14, 7, and 14 in the control, paper and electronic arms respectively), cough was not identified in 2 children in the control arm and therefore pneumonia was not considered (2/14,0/7, 0/14) and the others were classified as 'Cough or cold', either without respiratory rate measured (9/14, 1/7, and 9/14), or with a respiratory rate below the threshold (2/14, 5/7, 5/14). For the latter children, the median respiratory rate measured by HWs was 45/min (range 38-49) for eight children <1 year and 43/min (38-49) for children ≥1 year, while it was 53/min (52-57) and 54/min (51-58) respectively when the child was assessed by the expert around half an hour later. One child in the paper arm had a respiratory rate above the threshold that was misinterpreted, and one child in the control arm had a cough attributed by the HW to worm infestation.

### 8.4.6 Direct comparison of paper and electronic arms' results

The indicators of the completeness of assessment were significantly higher in the electronic arm compared to paper, with aRR electronic vs paper (aRR-e/p) above 2 for proportion of children checked for danger signs (aRR-e/p: 2.0 [p=0.04]), checked for palmar pallor (aRR-e/p: 2.5 [p=0.001]), and with an index test of integrated assessment >75%. (Table 15) However, for respiratory rate measure (aRR- e/p: 0.8 [p=0.34]), and malaria test (aRR- e/p: 0.8 [p=0.07]), the proportion of children assessed in the electronic arm was lower than in the paper, although not significantly. Except for viral classifications that were more often correctly identified in electronic arm (aRR-e/p: 2.2 [p=0.001]), there was no difference in the identification of bacterial

infections, and overall classifications. With regards to treatment, similar outcomes were observed in the 2 interventions arms.

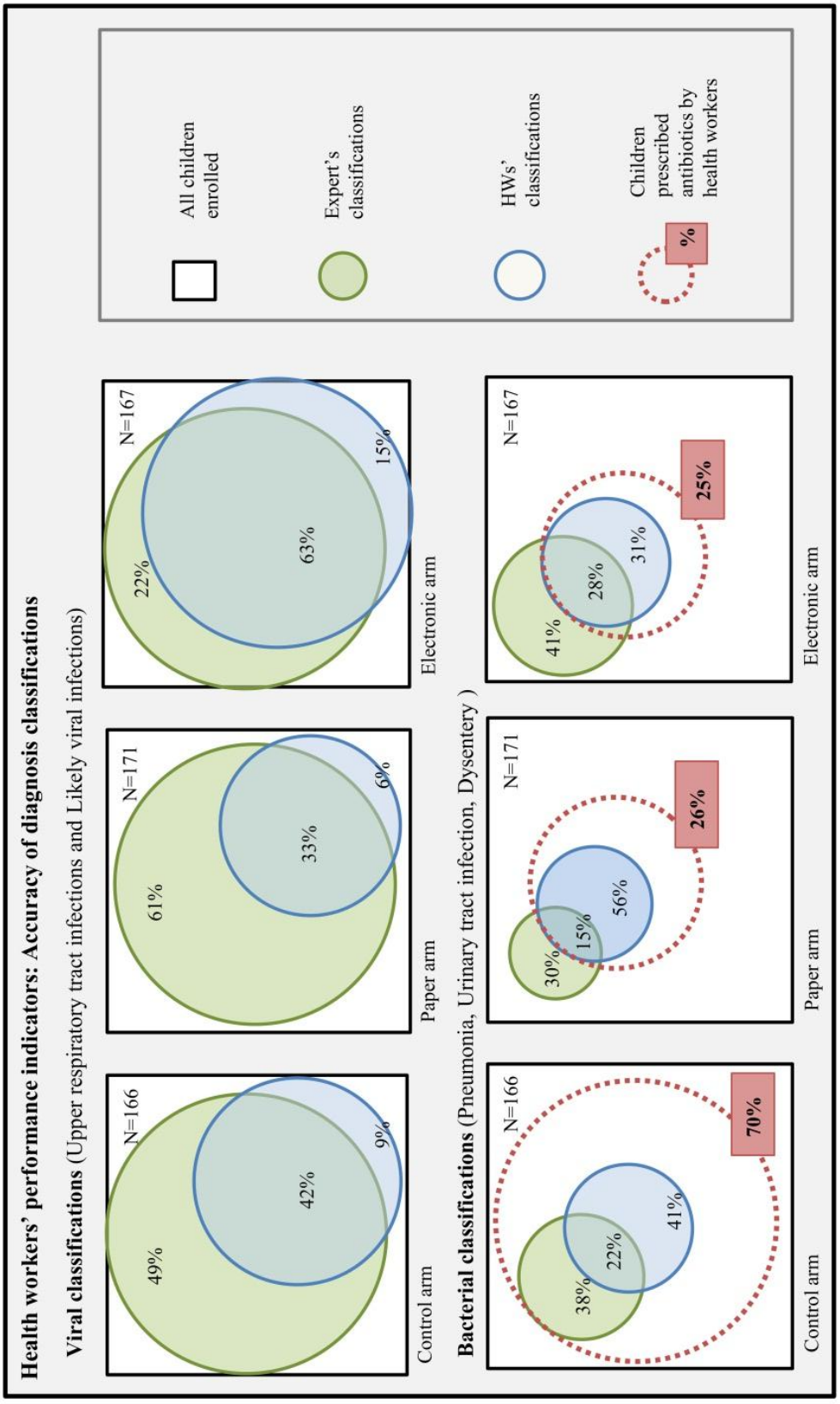


**Figure 10. Venn diagram illustrating the level of agreement (in %) between the expert and the HWs' bacterial and viral classifications, as well as the total proportion (in %) of children prescribed an antibiotic in each study arm**

**Table 16. Detailed list of serious[§] conditions identified by health workers among conditions validated by the expert**

| | Control arm | | | Paper arm | | | Electronic arm | | | Total |
|---|---|---|---|---|---|---|---|---|---|---|
| | HF1 | HF2 | HF3 | HF1 | HF2 | HF3 | HF1 | HF2 | HF3 | |
| Severe diseases | - | - | - | 2/2* (100%) | 1/1° (100%) | - | - | - | 0/1° (0%) | 3/4 (75%) |
| Malaria | 3/3 (100%) | - | - | - | 2/2 (100%) | - | - | 1/1 (100%) | 0/1 (0%) | 6/7 (86%) |
| Pneumonia | 2/6 (33%) | 0/2 (0%) | 3/11 (27%) | 2/2 (100%) | 1/4 (25%) | 0/4 (0%) | 0/8 (0%) | 5/8 (63%) | 4/7 (57%) | 17/52 (33%) |
| Dysentery | 1/2 (50%) | - | - | - | - | - | - | 1/1 (100%) | 1/1 (100%) | 3/4 (75%) |
| UTI | - | 0/1 (0%) | - | - | - | 1/1 (100%) | - | 1/1 (100%) | - | 2/3 (67%) |
| Total / HF | 6/11 | 0/3 | 3/11 | 4/4 | 4/7 | 1/5 | 0/8 | 8/11 | 5/10 | |
| Total / Arm | | 9/25 (36%) | | | 9/16 (56%) | | | 13/29 (45%) | | 31/70 (0.44) |

[§]Serious conditions: either severe diseases or non-severe bacterial infections or malaria. HF: health facility; UTI: urinary tract infection; *1 severe malnutrition and 1 very severe disease (vomits everything); °severe anemia

## 8.5 Discussion

Our findings show that the implementation of ALMANACH on either paper or electronic support has the potential to tackle some of the difficulties of HWs when managing childhood illnesses. In the control arm, HWs' compliance to integrated assessment tasks was low, and antibiotics were prescribed to more than 2/3 of the children, even when the classification did not require antibiotics according to IMCI. The use of ALMANACH (in both paper and electronic arms) was associated with a significantly higher proportion of children having an index of integrated assessment ≥50%, being checked for danger signs, having their respiratory rate measured when necessary, and being appropriately managed. A significantly lower prescription of unnecessary antibiotics as compared to the control was equally observed in paper and electronic arms. Observed in both intervention arms, these results were likely due to the recent training received by clinicians on ALMANACH's content. The use of the e-ALMANACH was further associated with a significantly higher proportion of children checked for danger signs, main symptoms and palmar pallor, children having an index of integrated assessment ≥75% and having an appropriate classification than in the control. The proportion of children identified both by the expert and the HW as viral infection was significantly higher in the electronic arm than in the control and paper arms. Although improved in intervention arms, the respiratory rate remained infrequently measured in children with cough. And the proportion of febrile children tested for malaria was lower in the electronic than in the control and paper arms.

In this pilot study, the small number of HFs involved and the limited number of consultations observed did not allow to observe significant differences in the impact of the electronic versus paper intervention as compared to the control arm (the 95%CI of the aRR always overlapped, Table 15), however the results show that the use of hand-held technology can improve the training's impact on simple easy-to-perform tasks, such as asking for danger signs and main symptoms, or looking at a child's palm. However, in this survey, the use of mobile device was insufficient in itself to convince HWs to perform more time-consuming tasks systematically, such as measuring respiratory rate over a full minute, or sending a child to the laboratory for a malaria test.

The most frequently missed serious condition was pneumonia. In previous studies assessing HWs' performance after IMCI training, pneumonia identification was always a challenge, with only 41% of pneumonia correctly identified in South Africa (Horwood et al., 2009a), and only 40 to 50% of pneumonia prescribed the recommended treatment in Benin (Rowe et al., 2012). This may be explained by problems in pneumonia definition that were not addressed by our intervention. In IMCI and ALMANACH, the pneumonia classification relies on respiratory rate. Respiratory rate fluctuates over time, and HWs have low motivation to measure it. Indeed, in our study, most of missed pneumonia had either no respiratory rate measured, or a rate below the expert one, the difference being either due to the variability over time or to the low inter-rater reproducibility of the measurement. Respiratory rate that need to be counted over a full minute is perceived as time consuming by HWs both in low and high income countries (Thompson et al., 2008). Moreover, the low performance of fast breathing to predict bacterial pneumonia render this sign in fact not very useful (Rambaud-Althaus et al., 2015) and efforts are ongoing to find better clinical ways to diagnose pneumonia. Both issues call for novel diagnostic assays or devices to identify this serious condition.

For malaria, the availability of mRDT, improves HWs' diagnoses. In this survey, all malaria cases were identified by the HWs, except one (Table 16). This missed malaria case, occurred in a 21 months old boy, who had no fever nor history of fever, but for whom the expert identified a non-severe anemia, based on palmar pallor, and therefore ordered a mRDT. The HW in this case did not assess the child's palm, and missed both anemia and malaria. The very few cases of anemia and malaria in our survey do not allow assessing the impact of our intervention on this critical issue. However the trends in the proportion of children assessed for palmar pallor (14%, 30%, and 69% in control, paper, and electronic facilities,Table 16) suggests ALMANACH could help improving anemia detection.

The use of ALMANACH resulted in an important decrease in the unnecessary antibiotic prescription. However, because of the inability of HWs to properly classify pneumonia, some of the children in need of antibiotics according to the WHO clinical pneumonia definition were not prescribed such treatment, even in the intervention HFs. In the present study, all these children actually received antibiotics from the expert, but this could be a matter of concern if real bacterial pneumonia would remain

untreated by HWs in programmatic conditions. One study on the health outcome of untreated non-severe pneumonia in children in a low-income country showed no difference in clinical outcome with the treated control group (Hazir et al., 2011), which suggest that, in young children, a high number of clinical pneumonia episodes are of viral origin, as it is the case in Northern countries. Therefore the low specificity of the present criteria used to diagnose pneumonia, even when using a higher threshold for respiratory rate (Rambaud-Althaus et al., 2015), together with the fact that most children can be followed up to look at the clinical course, must balance the concern of missing a true bacterial pneumonia case. It has often been argued that follow-up visits are difficult to organise in low resources setting due to transport and cost constraints. That was one of the reasons for encouraging presumptive treatment for malaria and having a low clinical threshold to give antibiotics for pneumonia. There is now more and more awareness that this strategy leads to over-prescription of antimicrobials and the development of resistance. While using the e-ALMANACH, the HWs were more likely to appropriately deliver messages on when to bring back the child in case his conditions would not improve or even worsen (data not shown). Follow-up is an important part of outpatient management of non-severe children and if this strategy is not promoted, there is little hope to tackle the antibiotic overuse and the spread of drug resistance.

***Strengths and limitations***

To our knowledge, this study was the first implementation in programmatic conditions of an electronic algorithm for the management of childhood illness. A previously published study also reported improved HW's performance when using an electronic IMCI compared to the paper IMCI (Mitchell et al., 2013) and a positive users' experience (Mitchell et al., 2012), but these results were observed within a short study period of 3 to 6 days, HWs using the electronic tool only over these few survey days.

The present project has demonstrated the feasibility of using innovative technology in resource limited settings, and its high potential to improve the quality of health care delivered to children. The use of this technology also allowed data collection and activity monitoring that are essential assets to monitor and improve quality of health care.

The small number of health facilities involved, their disparities in size, and the relatively small number of consultations observed limits the power of the analyses, but the results still show the potential of such a tool that deserves further assessment.

In the present survey, a high proportion of children were prescribed an antibiotic in the control health facilities. This is in line with observation made 4 years earlier in the same health facilities, after the introduction of mRDT(D'Acremont et al., 2008). In Dar Es Salaam, where the prevalence of malaria is rather low, antimalarial drugs, formerly prescribed presumptively for fever, were indeed replaced by presumptive antibiotics. In a setting where malaria prevalence would be higher, we can expect the level of antibiotic prescriptions to be lower, but in the absence of appropriate patient assessment, not more appropriate.

The choice of routine practice as a control and the deliberate short training (2 days) in the intervention HFs were decided to be as close as possible to programmatic conditions. Although IMCI is the standard of care for children in Tanzania since the 1990's, the HWs involved in the control arm had no recent IMCI refresher training. This control group does not allow comparing ALMANACH versus IMCI algorithms, but rather the difference in HWs performance when using a new tool on paper or on electronic support, as compare to the previous practice.

***Potential to scale up***

This pilot intervention comprised a short training followed by one day of HW face-to-face supervision, and monthly HF supervision visits. This short duration mitigates the resources needed for the initial training and may facilitate scale up. It raises the need for resources in the immediate aftermath that may be a bottleneck to scale up. However, close follow-up and regular supportive supervision are acknowledged as a key for sustainable improvement of the quality of care.

## 8.6 Conclusion

The use of mobile technology to support health care delivery in low-income countries is feasible and has a huge potential for improvement of quality of care and monitoring. As long as no automated devices are available to replace the key signs required for clinical diagnosis or selection of patients for testing, training of health workers on the basic clinical skills is still essential. As any other clinical support system, it also requires continuous supportive supervision to encourage HWs using it appropriately. Improving the rational use of antimicrobial is a challenge that ALMANACH can help to take up. It has to be acknowledged and accepted that, because no diagnostic tool is fully sensitive, the reduction in antibiotic prescriptions will always be accompanied by a small risk of withholding them in a child that would have benefited from them. Proposing the best available accurate diagnostic procedures to HWs, and enforcing good compliance as well as the delivery of appropriate counseling to caretakers on when to bring the child back, are needed to reach a rational use of antibiotics and slow down the development of resistance.

## 8.7 Competing interests

The authors declare that they have no competing interests.

## 8.8 Author contributions

BG was the PI of the project. CRA, VDA, BG, and MM designed the study. CRA, AS, and SP led the project in the field. NS led the data collection team. JS acted as an ALMANACH expert, reassessing all enrolled patients to establish reference classification and treatment. JKM acted as facilitator to conduct the study in the field. CRA analysed the data and wrote the manuscript. BG and VDA contributed to the manuscript. All authors commented on the paper and approved the final manuscript.

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# 9 Discussion

The main purpose of the present PhD thesis was to develop and test an innovative approach for a safe and rational use of antimicrobials in the management of childhood illness by health workers in primary level of care in low and middle income countries.

Incentives for health workers to prescribe antimicrobial medicines are many and varied, such as fear of serious bacterial infections and malaria, limited diagnostic capacity, easy access to antimicrobials, limited side effects, perceived patient's expectations, and lack of knowledge on viral diseases. Medical training often focuses on serious bacterial infections that drive the high childhood mortality. Clinician awareness on the prevalence of self-limiting viral diseases in children is low. The positive health outcomes of the children with viral diseases, unnecessarily treated with antimicrobials, are attributed by clinicians to the antimicrobial, and not to the natural history of a self-limiting viral disease. The practical knowledge clinicians build on their experience – 'I prescribe an antibiotic and the child get cured' whatever diagnosis was reached during the assessment – is thus encouraging the over-prescription of antimicrobials. Therefore, there is an urgent need for robust interventions to decrease antimicrobials inappropriate prescriptions.In the core of the present project, we designed ALMANACH, a new standardised clinical algorithm for the assessment and treatment of children aged 2-59 months at resource-limited primary care level (Chapter 6); we assessed the safety of ALMANACH as compared to routine practice, in term of children clinical outcome, when applied strictly (Chapter 7); and we assessed the impact of its pilot implementation either as an electronic algorithm or as a paper booklet on antimicrobial prescriptions in primary care facilities (Chapter 8). In controlled conditions, ALMANACH improved the children clinical outcome with an 80% reduction of antibiotic prescriptions. During the pilot implementation, ALMANACH improved the thoroughness of children assessment by HWs and reduced the antibiotic prescriptions by 60%. With regards to the primary objective of reducing antibiotic prescription this was a very successful intervention.

These highly promising results were obtained in a pilot project, using a new clinical algorithm to deliver evidence-based recommendations for the management of

children, algorithm that was provided to clinicians either on a paper or electronic support.

In this section we will discuss questions that have arisen throughout the project on clinical algorithms and electronic decision support systems. We will also discuss the challenges that can be faced while trying to maintain these good results over time and within scale up pilot interventions.

## 9.1 Design of clinical algorithms

### 9.1.1 Clinical algorithm: Bringing evidence-based guidelines into clinical practice

Clinical pathways and clinical algorithms are a way to implement evidence-based guidelines in the daily care practices. They have the potential to improve the quality of care and decrease the over-prescription of antibiotics both in low- (Gouws et al., 2004) and high-income countries (Jenkins et al., 2013). Many hospitals in high-income countries have implemented clinical pathways to improve quality of care (Rotter et al., 2010). IMCI algorithm, with its syndromic approach, is also a clinical pathway, integrating into a single algorithm management charts developed separately for pneumonia, diarrhoea, malaria, and measles. Evidence-based guidelines have been developed to reduce subjectivity in clinical decision making (Sackett et al., 1996). Historically, medical books and guidelines proposed diseases descriptions listing the classical signs and symptoms a patient with the disease should present, the expected clinical course, laboratory and imaging findings. The weight or predictive values of all clinical, laboratory, and imaging features taken individually were not stated. The clinicians, after having learned all the diseases characteristics, had to develop, while seeing patients, their clinical common sense in order to establish a diagnostic and therapeutic plan. Acknowledging that this individual empiric approach led to a highly subjective way of making decision for individual patients, evidence-based medicine was developed, with the aim to apply scientific method in medical decision-making.

### 9.1.2 Challenges towards evidence-based diagnoses

Evidence-based medicine is a revolution underway, but the lack of evidence available for some area of clinical decisions hinders its development and applications. With regards to treatment recommendations, methodology to generate evidence and critically appraise it has been well defined and described, as for its implementation into evidence-based guidelines (Guyatt et al., 2011). The results of evidence reviews and the level of evidence grading are easy to apprehend for clinicians when dealing with interventions' outcomes.

With regard to diagnosis, the methods to generate (Bossuyt et al., 2003), critically appraise (Whiting et al., 2003), and use evidence of diagnostic test accuracy studies are more recent and more difficult to apprehend and translate into clinically sound recommendations (Singh et al., 2012).

The lack of quality of published diagnostic accuracy studies (Korevaar et al., 2014) and of their statistical methods of meta-analyses (Willis and Quigley, 2011) is hampering the objective appraisal of the performance of studied diagnostic tests. The main focus of diagnostic research being on complex tests performed in secondary care specialties, insufficient evidence are generated for the performance of clinical tests in primary care settings, where the majority of patients are seen in practice (Willis and Quigley, 2011).

Often the lack of appropriate reference (gold) standard (Lynch et al., 2010), especially in primary care setting hampers the production of diagnostic test accuracy studies. Methods have been developed to overcome this barrier of an imperfect or missing reference standard. They are not straightforward for clinicians. Some of these methods attempt to fix the imperfections of the reference standard. When fixing the standard's imperfection is not possible, moving away from the classical ''gold standard'' diagnostic accuracy paradigm is warranted. Validation is a way to leave this paradigm and its indicators, such as sensitivity and specificity, and to look at whether a test result is useful for the patient management rather than if the test is identifying the target condition (Reitsma et al., 2009).

The case of pneumonia is an interesting example of the challenge that a clinical diagnosis can represent. No appropriate reference standard exist for pneumonia diagnosis (Lynch et al., 2010). Confusion in the definition of the targeted condition,

i.e. pneumonia versus lower respiratory tract infection, occurred in the first studies looking for their clinical predictors (Brewster, 2015). And when the accuracies of potential clinical predictors were estimated, and fast breathing identified as a good predictor, international experts disagreed on the choice of an appropriate respiratory rate threshold to define clinical pneumonia. The experts had different interpretations of the estimated indicators of diagnostic test accuracy. They had different perceptions of the level of sensitivity and specificity required for the test to be implemented, and different perceptions on the applicability in the remote settings of the different threshold options (single versus age-related threshold) (Shann, 1992). The objective of the clinical case definition was to identify with simple and reliable clinical features the children who should receive and would benefit antibiotics. Pneumonia was acknowledged to be a condition that warranted antibiotics. The diagnostic test accuracy studies in this field were hampered by the lack of appropriate reference standard for pneumonia. When reviewing the available evidence on clinical predictors for pneumonia (Chapter 5), we only selected studies relying on an objective reference standard that is accepted to be the best available reference for bacterial pneumonia: chest X-ray. Although the reference standard was similar in the reviewed studies, the remaining heterogeneity in study design, especially patients' selection process, brought heterogeneous results and the meta-analyses estimated a low performance of clinical predictors. If improvements in the reference standard for pneumonia diagnosis, improvements in the design of new prospective diagnostic test accuracy studies, or development of new point-of-care diagnostic tests could help improve our knowledge and evidence on pneumonia and its meaningful predictors, all this will require a lot of resources and time. A large multi-centric study on the etiologies of pneumonia in children has been recently completed and there are high expectations for the results to help better understanding the pneumonia epidemiology, presentation, and possible diagnostic procedures in low income countries (Scott et al., 2012). Meta-analyses on individual patients' data to identify clinical predictors could also bring better insight. But if we consider the initial objective of the clinical case definition, i.e. identifying children in need of antibiotics, the test validation method is an interesting way of addressing the research question in the absence of pneumonia reference standard (Reitsma et al., 2009). The study design proposed by Hazir *et al* (2011) was an interesting clinical test validation. Instead of verifying test results with a reference standard, Hazir *et al* directly

assessed whether the children identified by the WHO clinical definition of non-severe pneumonia would benefit of antibiotics in terms of health outcome. Although the study primary outcome, treatment failure at day 3, can be discussed, the results of the 14 days follow up showed that children's health outcome did not differ when receiving amoxicillin or placebo. Analyses of a passive morbidity surveillance system within a malaria prevention trial in Papua New Guinea also observed the same rate of re-attendance in children classified as having non-severe pneumonia when they had been prescribed antibiotics (according to IMCI guidelines) or not (lack of compliance to IMCI guidelines).(Senn et al., 2014) None of these studies proposed better alternative diagnostic approaches but they provided valuable evidence on the lack of accuracy of fast-breathing to identify patients in need of antibiotics. Extending this approach in clinical diagnostic research may help generating valuable evidence and clinically sounds recommendations that are needed to encourage broader adoption of diagnostic procedures.

### 9.1.3 ALMANACH development and validation

While designing ALMANACH we faced all these challenges. For malaria, accurate POCT have been developed, a large body of evidence supports their accuracy (Abba et al., 2011) and validity in children U5 (D'Acremont et al., 2010b; Odaga et al., 2014), and therefore these tests have been deployed in malaria endemic countries. But malaria is the exception rather than the rule, and for most of the other conditions addressed in ALMANACH, as for pneumonia, no POCT exist and we had to rely on clinical definitions that had either low performance or were lacking underlying evidence.

Majority of published research articles and guidelines focus on in-patients with severe conditions. The health outcome of patients with severe conditions is highly depending on their early management. Therefore bringing expertise in severe cases prompt management has been the priority of medical research. From medical training to clinical pathways, material given to clinicians mainly focus on serious, potentially life-threatening diseases. This is highly meaningful, as recognising early severe cases is the only way to deliver on time life-saving treatments for these patients. Tackling childhood mortality requires delivering appropriate and prompt case management for the infectious diseases that are the leading causes of deaths. However, not all ambulatory patients have serious infections, and if hospital experts are asked to

prepare recommendations for ambulatory care they might over-emphasise the weight of serious conditions in ambulatory patients, experts being biased by their in-hospital experience.

Clinicians with limited experiences who may lack confidence in their clinical assessment skills will often fear to miss a serious disease. This is an important trigger of unnecessary antibiotic prescription, clinicians preferring to give the drug to be 'on the safe side', when they lack confidence in their capacity to rule-out serious infections. In low-resource settings, the perception that patients follow up is impossible is also encouraging clinicians to prescribe antibiotics largely to patients with no features of bacterial infection, in order to i) prevent bacterial infections, or ii) treat a 'prodromal phase' of a bacterial disease. There is now clear evidence that prescribing antibiotics for upper respiratory tract infections have limited benefit on the patients outcome, and that they do not prevent the occurrence of bacterial suppurative complications (Ahovuo-Saloranta et al., 2014; Kenealy and Arroll, 2013; Rosenfeld and Kay, 2003; Venekamp et al., 2013). The majority of the patients with upper respiratory infections have a positive outcome without antibiotics, and this is why recent guidelines in high income countries now recommend a 'watchful waiting' strategy for antibiotic use in respiratory infections (Spurling et al., 2013). But even with this knowledge and recommendations available in high income countries, the antibiotic prescriptions remain high. In low-income countries, this knowledge is unavailable (data on natural history and antibiotic impact in suppurative complications are lacking) and the fear suppurative complications that are more frequent there than in wealthy countries, encourage the antibiotic use.

Within this project, we acknowledged that generating evidence to evaluate the diagnostic accuracy of all diseases diagnostic procedures would require resources that were not available in the project. And the lack of appropriate reference standards will hamper the production of diagnostic test accuracy studies in coming years. Therefore, we decided to design a pragmatic algorithm, based on the available evidence, common sense and few experts' opinions, and to perform a clinical test validation method to assess the appropriateness of ALMANACH recommendations (Chapter 7). The aim was to test the hypothesis that withholding antimicrobials for children with no danger signs and no clinical features of bacterial infections would be safe for the children in term of health outcome. Doing this validation survey without

diagnoses confirmation allows us to operate in the same conditions than in the targeted field of intervention. This survey provided valuable information regarding the relevance and safety of ALMANACH recommendations, and showed that the majority of antibiotics prescribed in the Tanzanian primary care facilities was not beneficial to the children. In ambulatory care, where available data is scarce, and access to confirmed diagnoses low, extending these validation methods and identifying evidence-based predictors of the benefit of antibiotics may help design better clinical algorithm for a rational use of medicines.

Documenting the health outcome of children managed with ALMANACH in other African settings would help validating these recommendations. However, we believe that strategies to decrease the high unnecessary antibiotics use are urgently needed, and that building evidence should not delay clinicians to have access to guidelines that are likely to improve their performance in childhood illnesses management. Adapting the recommendations to the epidemiological context where it is to be implemented and monitoring the impact of its introduction should help refine the algorithm in an iterative process. It is also important to remember that to improve rational use of drugs and children's safety, improved monitoring and follow-up of patients are required. Improving patients monitoring by clinicians and by family members, together with increased access to primary and secondary care, is likely to have a higher impact on health outcome than the current broad antibiotic use. Structural barriers towards patients' follow-up and timely referral must therefore be addressed in resource-limited settings.

The main objective of the present thesis project being to improve the rational use of antimicrobials, the research focused on identifying appropriate diagnostic procedures for clinicians to better target their prescription for children in need of antimicrobials. In the core of the present project, therapeutic options were not reassessed but taken from other WHO or Tanzanian accepted guidelines.

## 9.2 Health workers compliance to guidelines

The main reasons identified for HWs' lack of compliance to IMCI recommendations were first, a lack of motivation due to a weak belief in the importance of following the recommendations, and secondly a perception that IMCI consultations require

additional time not compatible with their overload (Horwood et al., 2009b; Lange et al., 2014).

### 9.2.1 Work overload

With regards to the HWs' perceived overload as a barrier to compliance, it is interesting to notice that if the thoroughness of assessment was improved in the interventions HFs, the time-consuming tasks, such as respiratory rate count, remained insufficiently performed where ALMANACH had been implemented (Chapter 8). This suggests that the paper and e- ALMANACH shared the same time-related barrier to compliance with IMCI, due to the HWs high workload. We may conclude that in order to reach good quality of care more HWs are needed in Tanzanian HFs. If this is a truism, and if improving HWs density in low income countries is necessary to improve services delivery, the taken for granted assumption that the high caseload reduces the level of effort per patient in the diagnostic process was not confirmed in a recent study that assessed Tanzanian HWs' performances in primary care. This survey revealed that HWs had ample amounts of idle time but performed only 22% of the assessment tasks required by guidelines on average, and that the performance was not related to the caseload (Maestad et al., 2010). The perceived overload may however be due to extra duty cognitive overload not addressed in this survey (Lange et al., 2014).

The time constraint and high workload in low-income countries' HFs, also calls for better diagnostic tools. HWs are reluctant to measure respiratory rate. They do not trust it is an important task to perform and prefer to prescribe antibiotics to all children with fever and cough. Together with sensitisation on the need for rational use of antimicrobials, automated methods for respiratory rate measure may help increasing the uptake of this assessment task, but if this task has limited value to identify patients in need of antimicrobials, alternative tools are necessary.

Reassessing the relevance of the tasks HWs are required to perform for all children may also be necessary, to ensure only useful tasks are requested from HWs, especially when moving to an electronic support that can make all tasks mandatory.

### 9.2.2 Clinicians' trust in guidelines

With regards to the weak belief in the IMCI recommendations, the lack of guidance for the management of fever cases with negative malaria test are likely to further weaken the motivation of HWs to use IMCI algorithm after mRDT implementation. Indeed one of the main reasons for antibiotic prescription is the fear of potentially serious bacterial diseases. In the absence of guidance on how to identify or rule out these feared bacterial diseases, it is easier for clinicians to prescribed antibiotics to all children with fever, to be on the safe side. During our pilot experience, an important decrease in unnecessary antibiotics prescription was observed in both intervention arms, and the overall antibiotics prescriptions dropped from 70% of the children in the control to 26% in the paper and 25% in the electronic arm. Three elements in ALMANACH structure and implementation may explain these results. First, within the ALMANACH algorithm, bacterial diseases feared by HWs, such as typhoid fever and UTI, were addressed, allowing clinicians to rule out these conditions with simple clinical or lab tests. Secondly, ALMANACH clinical pathway proposed a new classification entitled 'Likely viral infection' reached after the assessment had ruled out the serious bacterial diseases and malaria, and pointing to the clinicians the possibility of self-limiting viral diseases. This notion is absent from the Tanzanian and many treatment guidelines. Having added this classification in ALMANACH offers the clinician the support of the guidelines when deciding to withhold an antibiotic for a patient and relying on the guidelines may offer them protection against critics if a child worsens after the first encounter. Thirdly, during the HWs training, the data of the ALMANACH validation survey, and especially the good clinical outcomes of children managed without antimicrobials were shared with the HWs. These data allowed reinforcing the message that non-severe febrile illnesses in children were often self-limiting viral infections in their own working context. All these three features of ALMANACH may have contributed to an improved confidence of HWs in the clinical algorithm, and a following improved motivation to comply with the recommendations.

However it is important to notice that the fear of negative outcomes may often be stronger than available evidence and guidelines. And the minority of children that may develop secondary bacterial infections or complications will always have more weight in the clinicians' perceptions of their patients than the majority of children with positive health outcomes. The first will always be more visible for the clinicians than

the latter and they will have more influence on their practices, a single child negative outcome being likely perceived by the clinicians as a failure. That is why we need evidence-based medicine and science grounded decision-making process, but overcoming the barriers of individual experience and fostering the use of available evidence is a huge challenge. The high level of antibiotic prescription for upper respiratory infections still occurring in high-income countries despite the available body of evidence showing their low benefit illustrates this issue. For clinicians to accept that a secondary infection is not a failure of the initial assessment, but rather part of the clinical care process, is difficult. Accepting to withhold an antimicrobial, and to give the patient a chance to improve without it, requires a lot of courage in settings where clinicians are taught since decades that infectious diseases kill their patients. Teaching clinicians that a single negative outcome does not make the full guidelines inappropriate, and that good clinical care requires more than a single time-point assessment but rather monitoring and follow-up of the children, is therefore essential. Ensuring that danger signs are recognised by clinicians and that referral to good-quality secondary care for severe cases and appropriate follow up for non-severe cases is feasible is necessary to allow clinicians complying with ALMANACH recommendations.

### 9.2.3 Behavioural change

If designing appropriate clinical algorithms and offering good training and supportive supervision to clinicians is essential, it is also important to consider the new insights from social psychology science on behavioural change. It is now well known that behavioural change require more than only improving knowledge and attitudes (Webb and Sheeran, 2006). From tobacco to global warming, the information on the potential risks of unhealthy behaviour (at individual or collective level) is not sufficient to directly foster behavioural change (Kollmuss and Agyeman, 2002; Peterson et al., 2000). Information on the potential development of resistance may be in itself insufficient to operate changes in antibiotic prescription behaviour. This illustrates the limits of the classical rational (or top-down) behavioural change model. Recent psycho-neuroscience works have shown that the context in which people find themselves influence their decisions and behaviour through unconscious cognitive processes (Thaler, 2008). This is the basis for the contextual (or bottom-up) model. This theoretical model suggests that contextual signals have a direct impact on behaviour by influencing automatic processes without requiring any change in

knowledge or beliefs. This model brought new approaches to foster behavioural change. One of the new approaches is the normative effect approach. It aims at fostering behavioural change by indicating the desired behaviour is what other people do in a given situation. Normative messages have shown to induce behavioural change, although their influence was underestimated by the intervention participants (Nolan et al., 2008). Another interesting approach called priming relies on exposing people to environmental signals that make people behaving differently. Studies have shown that exposing people to library pictures made them talk slowly (Aarts and Dijksterhuis, 2003), and that exposing them to citrus scents in a restaurant made them keep their table cleaner (Holland et al., 2005).

Within the current project we did not explore these new approaches. Exploring their usefulness with regards to prescription behavioural change would be of great interest.

## 9.3 New technologies to support clinical decision making

### 9.3.1 Specificities of an algorithm meant to be an electronic clinical decision support system

In order to formalise an electronic clinical decision support system the clinical algorithm must be written with specific characteristics. Most of clinical guidelines and paper based pathways leave a lot of room for interpretation on which tasks to be performed, and within which sequence. On an electronic support, the navigation through the recommendations will be driven by the software. When using an algorithm on paper support, things that can be deducted from the general appearance of the child will not be assessed by the clinician. In an electronic algorithm, all the programmed steps will have to be assessed one after the other and documented in the application. These characteristics of the electronic algorithms are one of its strength, as it will encourage systematic and thorough assessment. However, the program steps need to be carefully organised to ensure consultation process is coherent and not delayed. Repetitions that may occur in paper algorithm need to be avoided in the electronic version. This is required when the tool is meant to be used in every consultation, in settings where the workload is high or perceived as high by clinicians. Electronic algorithms provide much stronger guidance than

paper algorithms. While transposing the paper algorithm, programing its logic into the application raised many clinical questions that were left unanswered in the paper algorithm, although ALMANACH paper algorithm was designed with the initial aim to provide strong guidance. Therefore close collaboration between clinicians responsible for the content and software developers designing the application is requested to ensure final electronic algorithm relevance. Intensive validation of all possible pathways was also required to ensure the application delivered the expected recommendations within the project. To perform this validation of the electronic decision support system we had no formal approved methodology to use. Although the US Food and Drug Administration (FDA) has developed guidance on medical mobile applications, no regulation was proposed yet by this institution for clinical decision support systems (Karnik, 2014). Therefore registration of an electronic algorithm as a medical device is not possible today neither in the USA nor elsewhere. However, going through a comprehensive systematic validation and certification procedure, and identifying appropriate ways to report the potential occurrence of risks, would facilitate new partners acceptability of the tool and thus facilitate scaling-up the intervention.

### 9.3.2 Acceptability, uptake and sustainability of an electronic algorithm in low-income countries

HWs received very positively the introduction of new mobile technology in their daily life. The majority of HWs learned very quickly how to use the smartphones and the ALMANACH android application, even the ones who had no previous computer literacy, and no previous experience with smartphones. Some clinicians with decreased visual acuity benefited from the option to increase the texts font size. The connectivity required to send the data collected by the app to the central server daily was ensured by a low cost pre-paid 3G data package that was available in Dar es Salaam during the study period. In the interventions HFs, both in Dar es Salaam and in Kilombero valley, the network coverage was good, and sending the data was never an issue of network. Availability of credit to send the data has been an issue in one HF in Dar es Salaam, where clinicians had used the smartphone to access other internet services, and the data package was fully used before the end of month. Restricting internet access to the job aid apps, or providing unlimited internet access should overcome this issue.

With regard to material security, maintenance, and access to power charge, no major barriers were encountered within our pilot implementation. In each intervention HF, the team in charge managed to identify a safe place where to store and charge the material when not in used, and established an appropriate procedure for the HWs to access the smartphone. Thus, during this pilot project, no smartphones disappeared and none were broken. With regards to power issues, during the pilot implementation, Dar es Salaam underwent frequent full-day power blackouts. During these periods of power shortage, the HFs management team together with the HWs adapted the smartphones management schedule, and ensured tablets were charged overnight, when the power supply was more regular. No additional sources of power were therefore needed.

Although the introduction of connected mobile technology was well received, the phone uptake was limited over time. The first barrier reported by the users was their high workload. The additional time required to conduct a consultation with the e-ALMANACH was felt incompatible with their workload. As discussed earlier, this barrier was also identified as a reason for the low compliance of HWs to the IMCI algorithm. An important attention was taken while designing the electronic algorithm to avoid unnecessary delay in the consultation process, but while driving the HWs through each step of the assessment it may result in an increased time spent with children, as would happen if the HWs followed strictly the paper guidelines step by step. Repeating the same tasks in all children may seems fastidious to clinicians, but these repetitions are necessary to ensure each child is appropriately assessed. And tasks repetition is a good learning process. Therefore the additional time, providing only useful tasks are requested, should be perceived as a positive outcome if it results in better care for children. In the present project, the use of ALMANACH led to improved health outcome (Chapter 7). Policy makers have thus a responsibility to ensure the available human resources in HFs allow appropriate patients management.

### 9.3.3 Potential for data collection, activity supervision, monitoring, and evaluation

An additional promising feature of e-ALMANACH that was not fully explored within this present thesis project is the data collection and management. Indeed, while guiding the clinicians through the child’s assessment and treatment

recommendations, the application collected anonymous data on the child's clinical presentation, his/her diagnostic classifications and the treatment prescribed by the HWs. The data were sent daily to a central server, and throughout the pilot implementation monthly reports on activity, diagnoses distribution, and prescriptions were manually computed. These reports were distributed to the districts and health facilities management teams. Within the framework of the present thesis, insufficient follow-up and guidance on the use of these data were provided to the management teams. These reports and data were not integrated into the existing health information system. We foresee that appropriate integration and use of these data could strongly strengthen the individual HW and HF-based supportive supervision. Indeed the use of the electronic algorithm allows providing clinicians with their individual activity reports with details on the diagnoses they reached in the patients they assessed and on their level of antibiotics prescriptions. Comparison with their peers' practices could also be provided to clinicians, and all these data could help the supervisor to prepare tailored supportive supervision to clinicians taken individually. These data, allowing activity monitoring and diseases surveillance, could inform policy-making and planning within the health system. All these benefits the tool can bring to the health system should be utilised and capitalised on, as they should encourage the use of the algorithm and the HWs' compliance to guidelines recommendations.

## 9.4 Scale up challenges

Many mobile Health solutions have been tested in small scale pilot projects, but failed to scale up even when the pilot showed promising results (Lemaire, 2011). ALMANACH has shown promising results within the core of the present thesis. In order not to stay stuck in the pilot phase as so many other mHealth projects, challenges of scale-up will have to be addressed.

### 9.4.1 Hardware and software

For electronic algorithms to be sustainable the chosen hardware and software should be easy to deploy and to interconnect with other existing electronic tools used in the health system. In the absence of broadly validated or accepted standards of interoperability, chosing software is difficult. Within this project we decided to use

open-source softwares (Open Data Kit and Open MRS) to formalise our algorithm. We chose open-source software to avoid licensing fees, hoping to facilitate future uptake and use in low-income countries. These two softwares initially meant for data collection (Open Data Kit) and electronic patients file (OpenMRS) had been use to formalise clinical algorithms by other research teams. However they were not ready to support the complex logic a clinical algorithm necessitates. We did manage to program our clinical algorithm within this software, but it ended up being so complex that any maintenance and modification tasks required a lot of investment, and the support of informatics specialist.  Flexiblity is an essential characteristic for an electronic algorithm towards sustainability and scalability. Indeed, a clinical algorithm should be easily modified to adapt to a new implementation setting, or to new National treatment guidelines. Ane the modification should not hamper the overall stability of the algorithm. Our initial software solution lacked this flexibility.

If the maintenance and update of the algorithm necessitate highly specialised human resources, open-source software will not be free of charge for the long-term users, and this may represent a challenge for low income countries where qualified computer scientists are lacking.

Although several electronic clinical algorithms have been developed, there is no broadly recognised standard software that meets the requirements for algorithms' broad use. Within the present project, the only software we identified that was specifically meant for the formalisation of complex clinical algorithm into mobile health applications was Mangologic. (Things Prime, 2015) Mangologic was developed by a private software developer; it may represents an interesting alternative to the currently available open-source software that seemed not ready to handle the complexity clinical algorithm . Whatever software solution is adopted, ensuring long-term funding for the software update and maintenance is absolutely needed to scale up.

With regards to hardware, we used both smartphones and tablets, under android operating system. Smartphones have the advantages of reduced cost, and may be easy to carry in a pocket. Tablets have a larger screen and improve the user experience while navigating through the algorithm. Both hardwares are usable and the choice should be made according to each particular context and to the funds available.

### 9.4.2 Connectivity and electricity

For our electronic algorithm, sustainable access to electricity and mobile network is a key issue.

Planning for solar panel or long-life extra battery when electricity is scarce, or using innovative connectivity means for areas where the mobile network coverage is poor may be necessary, and should always be adapted and planned according to the context.

Peer-to-peer wireless communications are under development. Partnership with industry or academic partners to develop such connectivity solutions should be considered. Where mobile network are available partnership with mobile network operators could help ensuring connectivity for the data transfer.

### 9.4.3 End-users and community

While planning to introduce the tool in a new context particular cautious should be taken to explore the community needs and perceptions of mobile health solution and to prepare appropriate information and sensitisation activities.

Adapting the tool to the end-user is also necessary, by translating the algorithm into the local languages or adapting the consultation process to be compatible with the local work organisation. End-users should be engaged in processes to refine the tool.

### 9.4.4 Monitoring and evaluation

Monitoring and evaluation activities should be planned. The data collected through the algorithm allows real time monitoring of the use of the algorithm, from the number of consultations to the diagnoses reached and treatment prescribed. Formalising the use of these data by the clinician, by the health facility and by all supervision chain in the health system will allow easy monitoring.

Additionally the evaluation of the impact of the intervention on clinicians performance, through observational surveys of the consultation process, should be planned on a regular basis.

### 9.4.5 Integration into the health system

Last but not least, close collaboration with the Ministry of Health for the integration of the intervention into the existing health system and policies is needed for a successful scale up.

For ALMANACH to be sustainably scaled up, the embedded recommendations should be endorsed by the Ministry, and the intervention integrated into the strategy to improve child care.

The interoperability with existing mobile health solutions and the integration of the data generated by ALMANACH into the National Health Information System should be ensured.

# 10 Conclusion and recommendations

## 10.1 Conclusion

Clinical algorithms have the potential to improve the quality of health care by providing to clinicians standard procedures designed by experts. ALMANACH has shown very positive impact on health outcome and rational use of medicines for children aged 2 months up to 5 years. The electronic ALMANACH, by integrating health information into the decision support system, has a huge potential to improve the monitoring of paediatric primary care activities and the individual supportive supervision provided to the users.

Many mobile Health solutions have been tested in small scale pilot in low income countries, but very few have been successfully scaled up. ALMANACH has shown promising results within the core of the present thesis. The interest shown by two of the most important international humanitarian organisations will now give a chance to ALMANACH to be scaled-up and reach the initial main objective to improve health care delivered to children in low and middle income countries.

## 10.2 Recommendations

### 10.2.1 Diagnoses procedures

- In the absence of evidence-based diagnostic procedures, building algorithms on experts opinion is acceptable in order to deliver expertise in diagnostic procedures to endpoint prescribers, and therefore improve the current low quality of childhood illness management.
- Meanwhile efforts must be made to identify and integrate newly available evidence that could help refine the recommendations and that will be obtained from research in the following areas:
    - Epidemiology and mapping of acute illnesses in ambulatory settings: More standardised research to document and confirm etiologies of acute illnesses in outpatient children in multiple sites would help refining the algorithm by informing the pre-test probabilities of the different diseases in the context of intervention. Data on the resistance profile of

the pathogens encountered in these studies would help adapting the first line regimen of antimicrobials.

- Point-of-care diagnostic tests: There are currently global efforts to develop new accurate and validated point-of-care tests, either for pathogen identifications or for biomarkers predicting serious bacterial infections. When validated, the newly tests should be considered for use in a new algorithm. Their added value and usefulness in the management of ambulatory children could be assessed in prospective studies comparing well defined clinical outcome endpoints and use of drugs when using an algorithm that integrate or not the new validated test.

- Benefit of antibiotics: Actual benefit of antibiotics in children presenting without danger signs at initial assessment needs to be evaluated. This could be done through prospective documentation of children health outcomes when treated or not treated with antibiotics. Well-defined and standardised primary endpoint to measure health outcomes should be used. Mortality or hospitalisations are too rare events in outpatients to be used as primary endpoint. Patients-reported or observed outcome on the resolution of the symptoms could be used, as well as time to resolution. The sample size should allow identifying a difference of 5% or more in the primary endpoints. ALMANACH recommendations endorsement, monitoring and evaluation.

For ALMANACH to be implemented and scaled up in new settings the following elements are needed:

- The content and recommendations should be endorsed by local health authorities on the basis of a clear report of the underlying evidence and rationale. Further validation of the recommendations could be performed in the new contexts by reproducing the non-inferiority trial that assessed the impact of ALMANACH on children health outcome.

- Appropriate monitoring will also be required to allow identification and analyses of adverse events or negative outcome in children managed using the tool.

- Further development in the electronic algorithm into a full electronic patient file would allow prospective documentation in programmatic conditions of the rates of re-attendance and complications. If such a data collection tool could be maintained and scaled up, the information would allow evaluating the impact on health outcome of different versions of the algorithm.

### 10.2.2 Electronic algorithm characteristics

The technology selected to formalise the electronic algorithm should allow to:

- Design user friendly applications.
- Easily visualise and validate the logic programmed into the application as compared to the recommended clinical pathways.
- Easily update the content or logic when new tools or evidence are available
- Program options to adapt the tools to its context of intervention, especially adapting the pathways to address an outbreak, or to consider the use of a diagnostic tool available in a particular setting.
- Easily send the data regularly to the server when connectivity is available.
- Safely store the data into the smartphones/tablets when offline.
- Integrate the data generated into the existing Health Information System

For further development the technology should also support an electronic patient file. The patient file should be accessed by the clinicians whenever the child presents to the health facility. It should propose follow up recommendations for acute illness episodes but also for the follow up of the child's development and growth as well as of all preventive interventions proposed in the health facility, including immunisation.

### 10.2.3 Challenges towards ALMANACH scale up

Success in scaling up the implementations of ALMANACH will require:

- Involving key actors in the preparation and evaluation of the implementation to ensure successes and failures would be appropriately documented and reported.
- Adapting the recommendations to the implementation settings and ensuring they are relevant with regards to HWs, diagnostic tools, referral structures available and to the known epidemiology.
- Ensuring the project meet the country, region, district health priorities.
- Ensuring the tool is integrated into the existing health system, from the endpoint prescribers workplace, the training and supervision systems, and up to the health information system, where data and interoperability standards must be put in place in order to ensure information collected can be used in the quality of care monitoring and evaluation.

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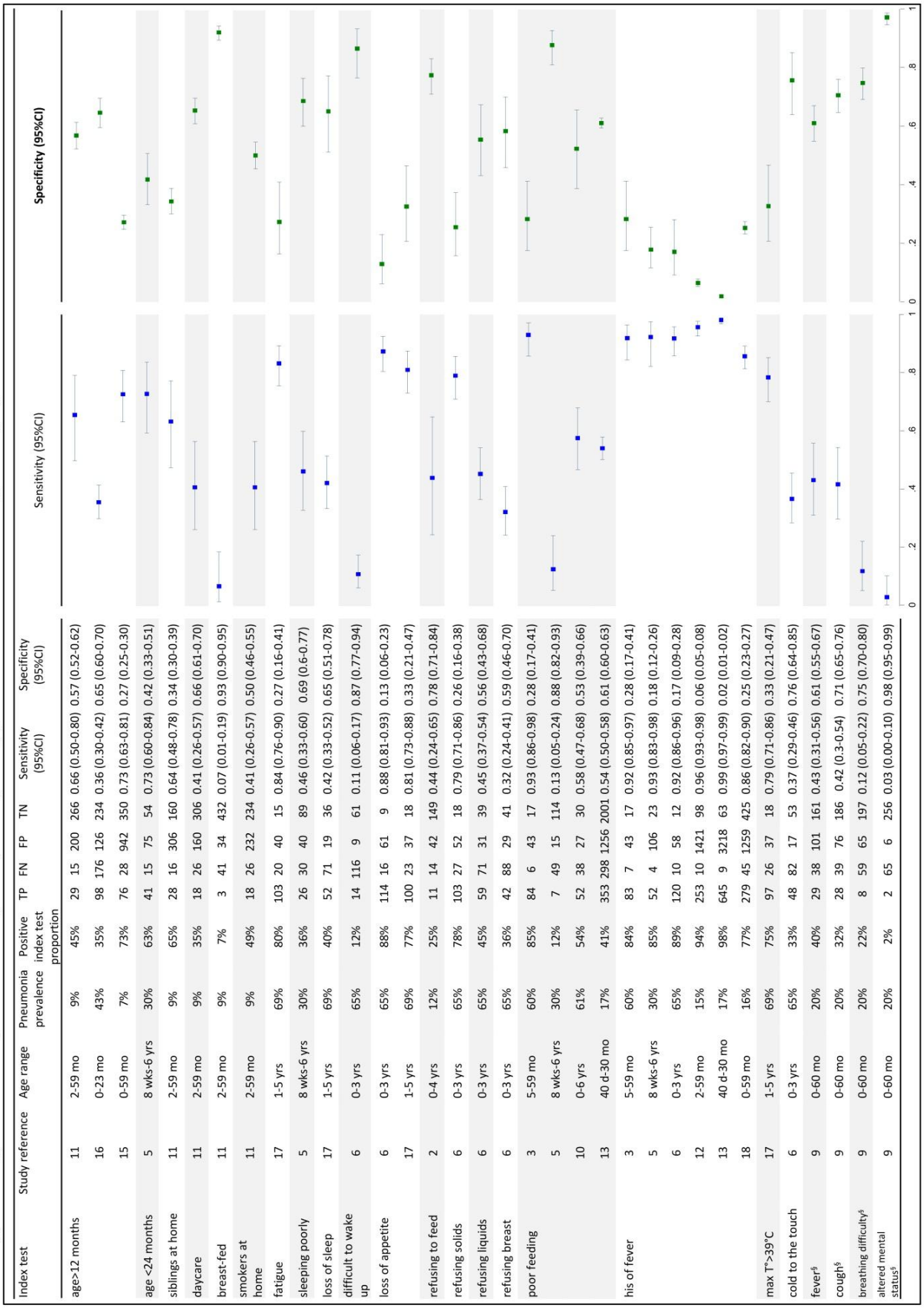
# 12 Annexes

## Annex 1: Meta-analysis of clinical features for pneumonia diagnosis: Supplementary material

**Webappendix Figure e1. Forest plot of sensitivity and specificity for age, environmental features and general symptoms**

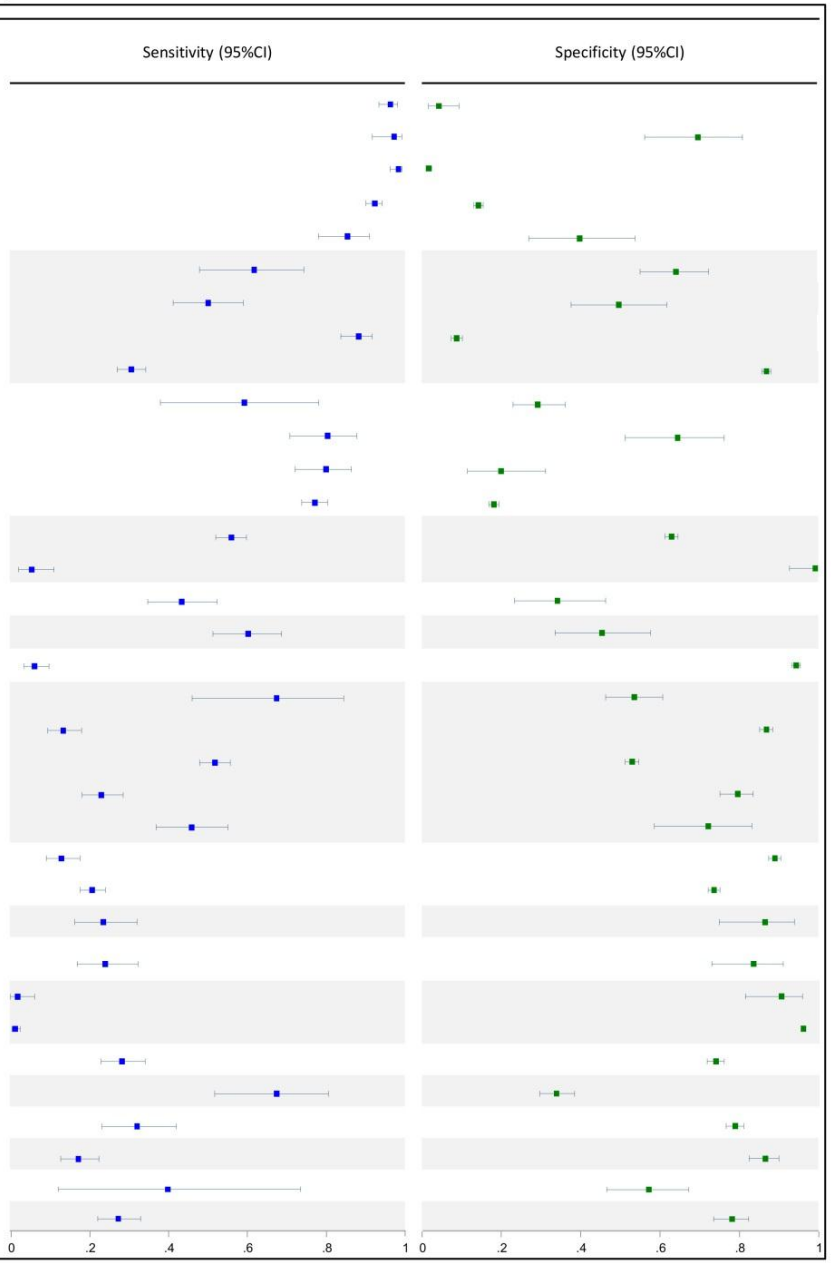



| Index test | Study reference | Age range | Pneumonia prevalence | Positive index test proportion | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| age>12 months | 11 | 2-59 mo | 9% | 45% | 29 | 15 | 200 | 266 | 0.66 (0.50-0.80) | 0.57 (0.52-0.62) |
| | 16 | 0-23 mo | 43% | 35% | 98 | 176 | 126 | 234 | 0.36 (0.30-0.42) | 0.65 (0.60-0.70) |
| | 15 | 0-59 mo | 7% | 73% | 76 | 28 | 942 | 350 | 0.73 (0.63-0.81) | 0.27 (0.25-0.30) |
| age <24 months | 5 | 8 wks-6 yrs | 30% | 63% | 41 | 15 | 75 | 54 | 0.73 (0.60-0.84) | 0.42 (0.33-0.51) |
| siblings at home | 11 | 2-59 mo | 9% | 65% | 28 | 16 | 306 | 160 | 0.64 (0.48-0.78) | 0.34 (0.30-0.39) |
| daycare | 11 | 2-59 mo | 9% | 35% | 18 | 26 | 160 | 306 | 0.41 (0.26-0.57) | 0.66 (0.61-0.70) |
| breast-fed | 11 | 2-59 mo | 9% | 7% | 3 | 41 | 34 | 432 | 0.07 (0.01-0.19) | 0.93 (0.90-0.95) |
| smokers at home | 11 | 2-59 mo | 9% | 49% | 18 | 26 | 232 | 234 | 0.41 (0.26-0.57) | 0.50 (0.46-0.55) |
| fatigue | 17 | 1-5 yrs | 69% | 80% | 103 | 20 | 40 | 15 | 0.84 (0.76-0.90) | 0.27 (0.16-0.41) |
| sleeping poorly | 5 | 8 wks-6 yrs | 30% | 36% | 26 | 30 | 40 | 89 | 0.46 (0.33-0.60) | 0.69 (0.6-0.77) |
| loss of sleep | 17 | 1-5 yrs | 69% | 40% | 52 | 71 | 19 | 36 | 0.42 (0.33-0.52) | 0.65 (0.51-0.78) |
| difficult to wake up | 6 | 0-3 yrs | 65% | 12% | 14 | 116 | 9 | 61 | 0.11 (0.06-0.17) | 0.87 (0.77-0.94) |
| loss of appetite | 6 | 0-3 yrs | 65% | 88% | 114 | 16 | 61 | 9 | 0.88 (0.81-0.93) | 0.13 (0.06-0.23) |
| | 17 | 1-5 yrs | 69% | 77% | 100 | 23 | 37 | 18 | 0.81 (0.73-0.88) | 0.33 (0.21-0.47) |
| refusing to feed | 2 | 0-4 yrs | 12% | 25% | 11 | 14 | 42 | 149 | 0.44 (0.24-0.65) | 0.78 (0.71-0.84) |
| refusing solids | 6 | 0-3 yrs | 65% | 78% | 103 | 27 | 52 | 18 | 0.79 (0.71-0.86) | 0.26 (0.16-0.38) |
| refusing liquids | 6 | 0-3 yrs | 65% | 45% | 59 | 71 | 31 | 39 | 0.45 (0.37-0.54) | 0.56 (0.43-0.68) |
| refusing breast | 6 | 0-3 yrs | 65% | 36% | 42 | 88 | 29 | 41 | 0.32 (0.24-0.41) | 0.59 (0.46-0.70) |
| poor feeding | 3 | 5-59 mo | 60% | 85% | 84 | 6 | 43 | 17 | 0.93 (0.86-0.98) | 0.28 (0.17-0.41) |
| | 5 | 8 wks-6 yrs | 30% | 12% | 7 | 49 | 15 | 114 | 0.13 (0.05-0.24) | 0.88 (0.82-0.93) |
| | 10 | 0-6 yrs | 61% | 54% | 52 | 38 | 27 | 30 | 0.58 (0.47-0.68) | 0.53 (0.39-0.66) |
| | 13 | 40 d-30 mo | 17% | 41% | 353 | 298 | 1256 | 2001 | 0.54 (0.50-0.58) | 0.61 (0.60-0.63) |
| his of fever | 3 | 5-59 mo | 60% | 84% | 83 | 7 | 43 | 17 | 0.92 (0.85-0.97) | 0.28 (0.17-0.41) |
| | 5 | 8 wks-6 yrs | 30% | 85% | 52 | 4 | 106 | 23 | 0.93 (0.83-0.98) | 0.18 (0.12-0.26) |
| | 6 | 0-3 yrs | 65% | 89% | 120 | 10 | 58 | 12 | 0.92 (0.86-0.96) | 0.17 (0.09-0.28) |
| | 12 | 2-59 mo | 15% | 94% | 253 | 10 | 1421 | 98 | 0.96 (0.93-0.98) | 0.06 (0.05-0.08) |
| | 13 | 40 d-30 mo | 17% | 98% | 645 | 9 | 3218 | 63 | 0.99 (0.97-0.99) | 0.02 (0.01-0.02) |
| | 18 | 0-59 mo | 16% | 77% | 279 | 45 | 1259 | 425 | 0.86 (0.82-0.90) | 0.25 (0.23-0.27) |
| max T°>39°C | 17 | 1-5 yrs | 69% | 75% | 97 | 26 | 37 | 18 | 0.79 (0.71-0.86) | 0.33 (0.21-0.47) |
| cold to the touch | 6 | 0-3 yrs | 65% | 33% | 48 | 82 | 17 | 53 | 0.37 (0.29-0.46) | 0.76 (0.64-0.85) |
| fever[§] | 9 | 0-60 mo | 20% | 40% | 29 | 38 | 101 | 161 | 0.43 (0.31-0.56) | 0.61 (0.55-0.67) |
| cough[§] | 9 | 0-60 mo | 20% | 32% | 28 | 39 | 76 | 186 | 0.42 (0.3-0.54) | 0.71 (0.65-0.76) |
| breathing difficulty[§] | 9 | 0-60 mo | 20% | 22% | 8 | 59 | 65 | 197 | 0.12 (0.05-0.22) | 0.75 (0.70-0.80) |
| altered mental status[§] | 9 | 0-60 mo | 20% | 2% | 2 | 65 | 6 | 256 | 0.03 (0.00-0.10) | 0.98 (0.95-0.99) |

TP: true positive. FN: false negative. FP: false positive. TN: true negative. max T°>39°C: maximum reported temperature >39°C. [§]As chief complaint.

**Webappendix Figure e2. Forest plot of sensitivity and specificity for miscellaneous symptoms**

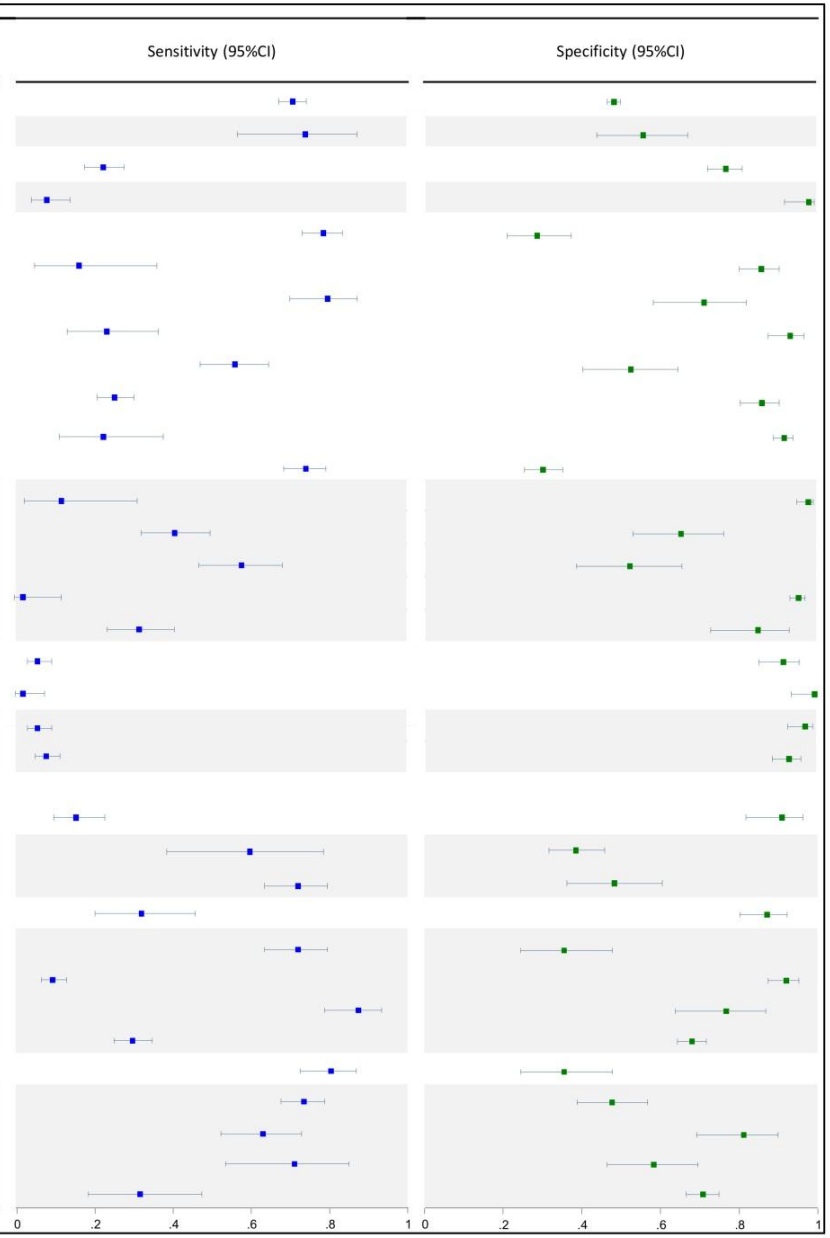
| Index test | Study reference | Age range | Pneumonia prevalence | Positive index test proportion | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| cough | 1 | 0-59 mo | 67% | 97% | 244 | 8 | 120 | 5 | 0.97 (0.94-0.99) | 0.04 (0.01-0.09) |
| | 10 | 0-6 yrs | 61% | 71% | 88 | 2 | 17 | 40 | 0.98 (0.92-1.00) | 0.70 (0.57-0.82) |
| | 12 | 2-59 mo | 15% | 99% | 260 | 3 | 1498 | 21 | 0.99 (0.97-1.00) | 0.01 (0.01-0.02) |
| | 13 | 40 d-30 mo | 17% | 87% | 609 | 45 | 2817 | 466 | 0.93 (0.91-0.95) | 0.14 (0.13-0.15) |
| | 17 | 1-5 yrs | 69% | 78% | 106 | 17 | 33 | 22 | 0.86 (0.79-0.92) | 0.40 (0.27-0.54) |
| breathing difficulty | 5 | 8 wks-6 yrs | 30% | 44% | 35 | 21 | 44 | 80 | 0.63 (0.49-0.75) | 0.65 (0.55-0.73) |
| | 6 | 0-3 yrs | 65% | 51% | 66 | 64 | 35 | 35 | 0.51 (0.42-0.60) | 0.50 (0.38-0.62) |
| | 12 | 2-59 mo | 15% | 91% | 234 | 29 | 1388 | 131 | 0.89 (0.85-0.92) | 0.09 (0.07-0.10) |
| | 13 | 40 d-30 mo | 17% | 16% | 203 | 448 | 404 | 2853 | 0.31 (0.28-0.35) | 0.88 (0.86-0.89) |
| rapid breathing | 2 | 0-4 yrs | 12% | 69% | 15 | 10 | 135 | 56 | 0.60 (0.39-0.79) | 0.29 (0.23-0.36) |
| | 3 | 5-59 mo | 60% | 63% | 73 | 17 | 21 | 39 | 0.81 (0.71-0.89) | 0.65 (0.52-0.77) |
| | 6 | 0-3 yrs | 65% | 81% | 105 | 25 | 56 | 14 | 0.81 (0.73-0.87) | 0.20 (0.11-0.31) |
| | 13 | 40 d-30 mo | 17% | 81% | 508 | 144 | 2666 | 590 | 0.78 (0.75-0.81) | 0.18 (0.17-0.19) |
| chest pain | 13 | 40 d-30 mo | 17% | 40% | 366 | 282 | 1188 | 2058 | 0.56 (0.53-0.60) | 0.63 (0.62-0.65) |
| | 17 | 1-5 yrs | 69% | 4% | 7 | 116 | 0 | 55 | 0.06 (0.02-0.11) | 1.00 (0.94-1.00) |
| chest retractions | 6 | 0-3 yrs | 65% | 52% | 57 | 73 | 46 | 24 | 0.44 (0.35-0.53) | 0.34 (0.23-0.47) |
| grunting | 6 | 0-3 yrs | 65% | 59% | 79 | 51 | 38 | 32 | 0.61 (0.52-0.69) | 0.46 (0.34-0.58) |
| past wheeze | 12 | 2-59 mo | 15% | 5% | 17 | 246 | 73 | 1446 | 0.06 (0.04-0.10) | 0.95 (0.94-0.96) |
| vomiting | 2 | 0-4 yrs | 12% | 49% | 17 | 8 | 88 | 103 | 0.68 (0.46-0.85) | 0.54 (0.47-0.61) |
| | 12 | 2-59 mo | 15% | 13% | 36 | 227 | 188 | 1331 | 0.14 (0.10-0.18) | 0.88 (0.86-0.89) |
| | 13 | 40 d-30 mo | 17% | 48% | 341 | 311 | 1523 | 1740 | 0.52 (0.48-0.56) | 0.53 (0.52-0.55) |
| | 16 | 0-23 mo | 43% | 21% | 64 | 209 | 71 | 288 | 0.23 (0.19-0.29) | 0.80 (0.76-0.84) |
| | 17 | 1-5 yrs | 69% | 40% | 57 | 66 | 15 | 40 | 0.46 (0.37-0.56) | 0.73 (0.59-0.84) |
| diarrhea | 12 | 2-59 mo | 15% | 11% | 34 | 229 | 156 | 1363 | 0.13 (0.09-0.18) | 0.90 (0.88-0.91) |
| | 13 | 40 d-30 mo | 17% | 25% | 135 | 516 | 840 | 2416 | 0.21 (0.18-0.24) | 0.74 (0.73-0.76) |
| abdominal pain | 17 | 1-5 yrs | 69% | 20% | 29 | 94 | 7 | 48 | 0.24 (0.16-0.32) | 0.87 (0.76-0.95) |
| abdominal distension | 6 | 0-3 yrs | 65% | 22% | 32 | 98 | 11 | 59 | 0.25 (0.17-0.33) | 0.84 (0.74-0.92) |
| convulsion | 6 | 0-3 yrs | 65% | 5% | 3 | 127 | 6 | 64 | 0.02 (0.00-0.07) | 0.91 (0.82-0.97) |
| | 13 | 40 d-30 mo | 17% | 3% | 11 | 640 | 97 | 3162 | 0.02 (0.01-0.03) | 0.97 (0.96-0.98) |
| illness >3days | 12 | 2-59 mo | 15% | 26% | 76 | 187 | 384 | 1135 | 0.29 (0.23-0.35) | 0.75 (0.72-0.77) |
| illness >48h | 11 | 2-59 mo | 9% | 66% | 30 | 14 | 307 | 159 | 0.68 (0.52-0.81) | 0.34 (0.30-0.39) |
| illness >4days | 15 | 0-59 mo | 7% | 21% | 34 | 70 | 263 | 1029 | 0.33 (0.24-0.43) | 0.80 (0.77-0.82) |
| fever >3 days | 16 | 0-23 mo | 43% | 15% | 46 | 213 | 41 | 282 | 0.18 (0.13-0.23) | 0.87 (0.83-0.91) |
| cough >2 days | 5 | 8 wks-6 yrs | 30% | 42% | 4 | 6 | 39 | 53 | 0.40 (0.12-0.74) | 0.58 (0.47-0.68) |
| cough >3 days | 16 | 0-23 mo | 43% | 24% | 75 | 199 | 72 | 269 | 0.27 (0.22-0.33) | 0.79 (0.74-0.83) |




TP: true positive. FN: false negative. FP: false positive. TN: true negative.

**Webappendix Figure e3. Forest plot of sensitivity and specificity for miscellaneous signs**

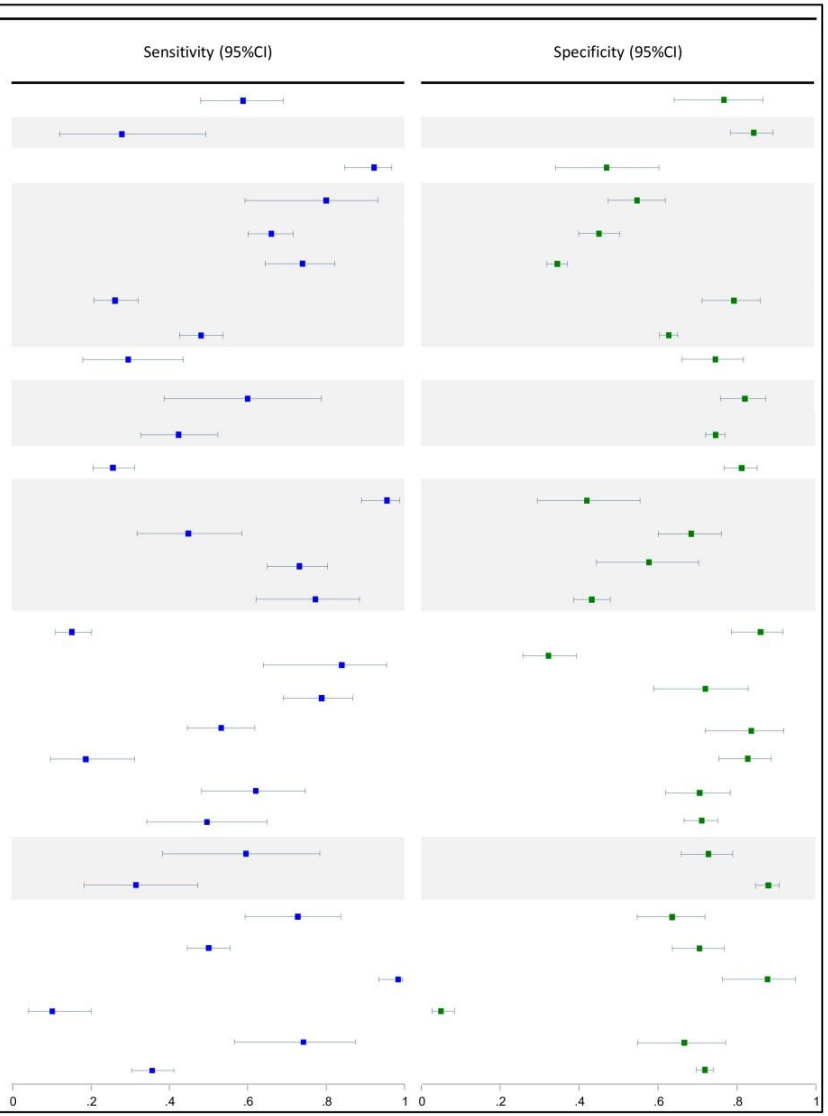
| Index test | Study reference | Age range | Pneumonia prevalence | Positive index test proportion | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| appear sick | 13 | 40 d-30 mo | 17% | 55% | 464 | 189 | 1679 | 1580 | 0.71 (0.67-0.75) | 0.48 (0.47-0.50) |
| clinical judgment | 8 | 3 d-5 yrs | 32% | 54% | 26 | 9 | 33 | 42 | 0.74 (0.57-0.88) | 0.56 (0.44-0.67) |
| prostration | 16 | 0-23 mo | 43% | 23% | 61 | 213 | 82 | 278 | 0.22 (0.17-0.28) | 0.77 (0.73-0.81) |
| seizures | 6 | 0-3 yrs | 65% | 6% | 10 | 120 | 1 | 69 | 0.08 (0.04-0.14) | 0.99 (0.92-1.00) |
| nasal flaring | 1 | 0-59 mo | 67% | 76% | 199 | 53 | 89 | 36 | 0.79 (0.73-0.84) | 0.29 (0.21-0.38) |
| | 2 | 0-4 yrs | 12% | 14% | 4 | 21 | 26 | 165 | 0.16 (0.05-0.36) | 0.86 (0.81-0.91) |
| | 3 | 5-59 mo | 60% | 59% | 72 | 18 | 17 | 43 | 0.80 (0.70-0.88) | 0.72 (0.59-0.83) |
| | 5 | 8 wks-6 yrs | 30% | 11% | 13 | 43 | 8 | 121 | 0.23 (0.13-0.36) | 0.94 (0.88-0.97) |
| | 6 | 0-3 yrs | 65% | 53% | 73 | 57 | 33 | 37 | 0.56 (0.47-0.65) | 0.53 (0.41-0.65) |
| | 7 | 2-59 mo | 63% | 21% | 86 | 255 | 27 | 173 | 0.25 (0.21-0.30) | 0.87 (0.81-0.91) |
| | 11 | 2-59 mo | 9% | 9% | 10 | 34 | 36 | 430 | 0.23 (0.11-0.38) | 0.92 (0.89-0.95) |
| | 16 | 0-23 mo | 43% | 72% | 203 | 71 | 251 | 109 | 0.74 (0.68-0.79) | 0.30 (0.26-0.35) |
| grunting | 2 | 0-4 yrs | 12% | 3% | 3 | 22 | 3 | 188 | 0.12 (0.03-0.31) | 0.98 (0.95-1.00) |
| | 6 | 0-3 yrs | 65% | 39% | 53 | 77 | 24 | 46 | 0.41 (0.32-0.50) | 0.66 (0.53-0.77) |
| | 10 | 0-6 yrs | 61% | 54% | 52 | 38 | 27 | 30 | 0.58 (0.47-0.68) | 0.53 (0.39-0.66) |
| | 11 | 2-59 mo | 9% | 4% | 1 | 43 | 19 | 447 | 0.02 (0.00-0.12) | 0.96 (0.94-0.98) |
| | 17 | 1-5 yrs | 69% | 26% | 39 | 84 | 8 | 47 | 0.32 (0.24-0.41) | 0.85 (0.73-0.94) |
| stridor | 1 | 0-59 mo | 67% | 7% | 15 | 237 | 10 | 115 | 0.06 (0.03-0.10) | 0.92 (0.86-0.96) |
| | 3 | 5-59 mo | 60% | 1% | 2 | 88 | 0 | 60 | 0.02 (0.00-0.08) | 1.00 (0.94-1.00) |
| cyanosis | 1 | 0-59 mo | 67% | 5% | 15 | 237 | 3 | 122 | 0.06 (0.03-0.10) | 0.98 (0.93-1.00) |
| | 7 | 2-59 mo | 63% | 8% | 30 | 311 | 13 | 187 | 0.09 (0.06-0.12) | 0.94 (0.89-0.96) |
| ***Chest indrawing*** | | | | | | | | | | |
| supraclavicular | 6 | 0-3 yrs | 65% | 13% | 20 | 110 | 6 | 64 | 0.15 (0.10-0.23) | 0.91 (0.82-0.97) |
| intercostal | 2 | 0-4 yrs | 12% | 61% | 15 | 10 | 117 | 74 | 0.60 (0.39-0.79) | 0.39 (0.32-0.46) |
| | 6 | 0-3 yrs | 65% | 65% | 94 | 36 | 36 | 34 | 0.72 (0.64-0.80) | 0.49 (0.36-0.61) |
| inter/subcostal | 5 | 8 wks-6 yrs | 30% | 18% | 18 | 38 | 16 | 113 | 0.32 (0.20-0.46) | 0.88 (0.81-0.93) |
| subcostal | 6 | 0-3 yrs | 65% | 70% | 94 | 36 | 45 | 25 | 0.72 (0.64-0.80) | 0.36 (0.25-0.48) |
| lower chest | 7 | 2-59 mo | 63% | 9% | 32 | 309 | 15 | 185 | 0.09 (0.07-0.13) | 0.93 (0.88-0.96) |
| | 10 | 0-6 yrs | 61% | 63% | 79 | 11 | 13 | 44 | 0.88 (0.79-0.94) | 0.77 (0.64-0.87) |
| | 13 | 40 d-30 mo | 35% | 31% | 104 | 244 | 200 | 434 | 0.30 (0.25-0.35) | 0.68 (0.65-0.72) |
| any retractions | 6 | 0-3 yrs | 65% | 75% | 105 | 25 | 45 | 25 | 0.81 (0.73-0.87) | 0.36 (0.25-0.48) |
| unspecified | 1 | 0-59 mo | 67% | 67% | 186 | 66 | 65 | 60 | 0.74 (0.68-0.79) | 0.48 (0.39-0.57) |
| | 3 | 5-59 mo | 60% | 45% | 57 | 33 | 11 | 49 | 0.63 (0.53-0.73) | 0.82 (0.70-0.90) |
| | 8 | 3 d-5 yrs | 32% | 51% | 25 | 10 | 31 | 44 | 0.71 (0.54-0.85) | 0.59 (0.47-0.70) |
| | 11 | 2-59 mo | 9% | 29% | 14 | 30 | 134 | 332 | 0.32 (0.19-0.48) | 0.71 (0.67-0.75) |




TP: true positive. FN: false negative. FP: false positive. TN: true negative.

**Webappendix Figure e4. Forest plot of sensitivity and specificity for vital signs**

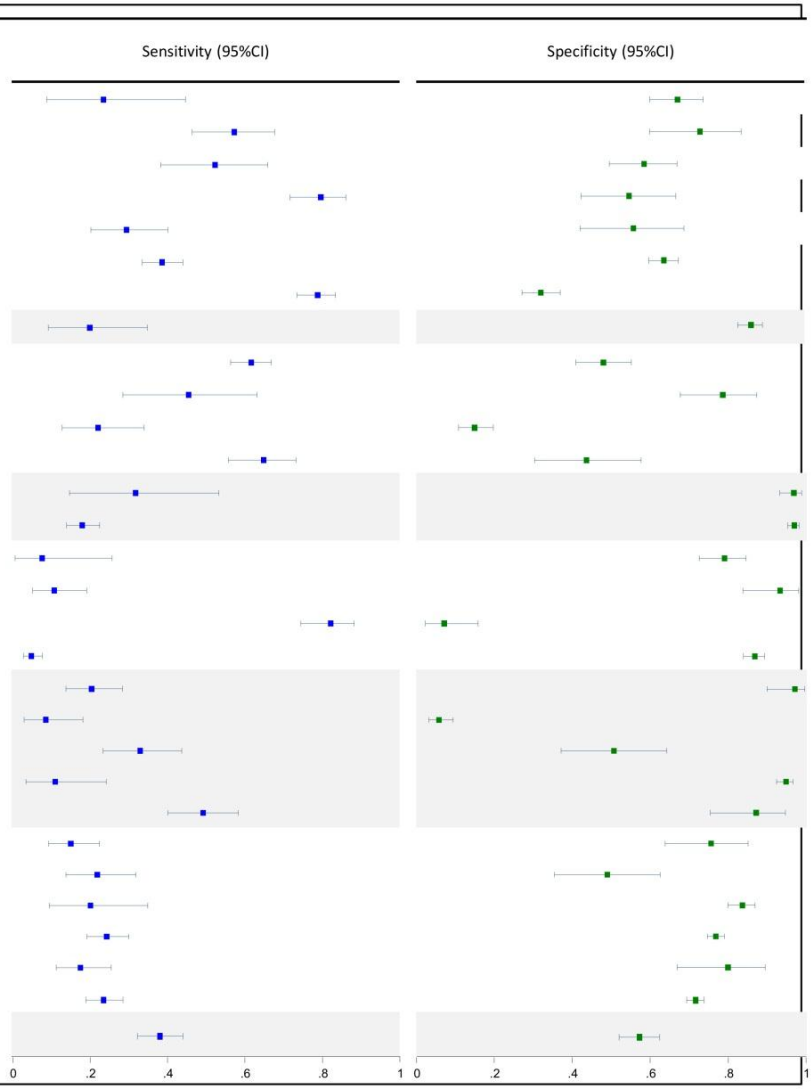
| Index test | Study reference | Age range | Pneumonia prevalence | Positive index test proportion | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| hr>140/min | 3 | 5-59 mo | 60% | 45% | 53 | 37 | 14 | 46 | 0.59 (0.48-0.69) | 0.77 (0.64-0.87) |
| hr>160/min | 2 | 0-4 yrs | 12% | 17% | 7 | 18 | 30 | 161 | 0.28 (0.12-0.49) | 0.84 (0.78-0.89) |
| T>37.5°C rectal | 3 | 5-59 mo | 60% | 77% | 83 | 7 | 32 | 28 | 0.92 (0.85-0.97) | 0.47 (0.34-0.60) |
| T>37.5°C axil | 2 | 0-4 yrs | 12% | 50% | 20 | 5 | 87 | 104 | 0.80 (0.59-0.93) | 0.54 (0.47-0.62) |
| | 16 | 0-23 mo | 43% | 60% | 181 | 93 | 199 | 161 | 0.66 (0.60-0.72) | 0.45 (0.40-0.50) |
| T>38°C rectal | 15 | 0-59 mo | 7% | 67% | 77 | 27 | 852 | 440 | 0.74 (0.65-0.82) | 0.34 (0.31-0.37) |
| T>38°C ns | 1 | 0-59 mo | 67% | 24% | 66 | 186 | 26 | 99 | 0.26 (0.21-0.32) | 0.79 (0.71-0.86) |
| | 18 | 0-59 mo | 16% | 39% | 156 | 168 | 631 | 1053 | 0.48 (0.43-0.54) | 0.63 (0.60-0.65) |
| T>38°C axil | 5 | 8 wks-6 yrs | 30% | 27% | 16 | 38 | 33 | 96 | 0.30 (0.18-0.44) | 0.74 (0.66-0.82) |
| T>38.5°C axil | 2 | 0-4 yrs | 12% | 23% | 15 | 10 | 35 | 156 | 0.60 (0.39-0.79) | 0.82 (0.75-0.87) |
| T>39°C rectal | 15 | 0-59 mo | 7% | 27% | 44 | 60 | 333 | 959 | 0.42 (0.33-0.52) | 0.74 (0.72-0.77) |
| T>39°C axil | 16 | 0-23 mo | 43% | 22% | 70 | 204 | 69 | 291 | 0.26 (0.20-0.31) | 0.81 (0.76-0.85) |
| rr>40/min | 3 | 5-59 mo | 60% | 81% | 86 | 4 | 35 | 25 | 0.96 (0.89-0.99) | 0.42 (0.29-0.55) |
| | 4_HC | 0-59 mo | 29% | 36% | 26 | 32 | 45 | 96 | 0.45 (0.32-0.58) | 0.68 (0.60-0.76) |
| | 4_RI | 0-59 mo | 69% | 64% | 101 | 37 | 26 | 35 | 0.73 (0.65-0.80) | 0.57 (0.44-0.70) |
| | 11 | 2-59 mo | 9% | 59% | 34 | 10 | 266 | 200 | 0.77 (0.62-0.89) | 0.43 (0.38-0.48) |
| rr>50/min | 1 | 0-59 mo | 67% | 15% | 38 | 214 | 18 | 107 | 0.15 (0.11-0.2) | 0.86 (0.78-0.91) |
| | 2 | 0-4 yrs | 12% | 70% | 21 | 4 | 130 | 61 | 0.84 (0.64-0.95) | 0.32 (0.25-0.39) |
| | 3 | 5-59 mo | 60% | 59% | 71 | 19 | 17 | 43 | 0.79 (0.69-0.87) | 0.72 (0.59-0.83) |
| | 4_RI | 0-59 mo | 69% | 42% | 74 | 64 | 10 | 51 | 0.54 (0.45-0.62) | 0.84 (0.72-0.92) |
| | 4_HC | 0-59 mo | 29% | 18% | 11 | 47 | 24 | 115 | 0.19 (0.1-0.31) | 0.83 (0.75-0.89) |
| | 5 | 8 wks-6 yrs | 30% | 39% | 35 | 21 | 38 | 91 | 0.63 (0.49-0.75) | 0.71 (0.62-0.78) |
| | 11 | 2-59 mo | 9% | 31% | 22 | 22 | 135 | 331 | 0.50 (0.35-0.65) | 0.71 (0.67-0.75) |
| rr>60/min | 2 | 0-4 yrs | 12% | 31% | 15 | 10 | 52 | 139 | 0.60 (0.39-0.79) | 0.73 (0.66-0.79) |
| | 11 | 2-59 mo | 9% | 14% | 14 | 30 | 56 | 410 | 0.32 (0.19-0.48) | 0.88 (0.85-0.91) |
| age related fast breathing | 5 | 8 wks-6 yrs | 30% | 48% | 41 | 15 | 47 | 82 | 0.73 (0.6-0.84) | 0.64 (0.55-0.72) |
| | 7 | 2-59 mo | 63% | 43% | 172 | 169 | 59 | 141 | 0.50 (0.45-0.56) | 0.70 (0.64-0.77) |
| | 10 | 0-6 yrs | 61% | 65% | 89 | 1 | 7 | 50 | 0.99 (0.94-1.00) | 0.88 (0.76-0.95) |
| | 9 | 0-60 mo | 20% | 78% | 7 | 60 | 249 | 13 | 0.10 (0.04-0.20) | 0.05 (0.03-0.08) |
| | 8 | 3 d-5 yrs | 32% | 46% | 26 | 9 | 25 | 50 | 0.74 (0.57-0.88) | 0.67 (0.55-0.77) |
| | 18 | 0-59 mo | 16% | 29% | 116 | 208 | 474 | 1210 | 0.36 (0.31-0.41) | 0.72 (0.70-0.74) |




TP: true positive. FN: false negative. FP: false positive. TN: true negative. hr: heart rate. T: temperature. axil: axillary. ns: not specified. rr: respiratory rate. Age related fast breathing: rr>60/min for children <2 months of age, rr>50 for children aged 2-11 months, and rr>40 for children aged 12-59 months.

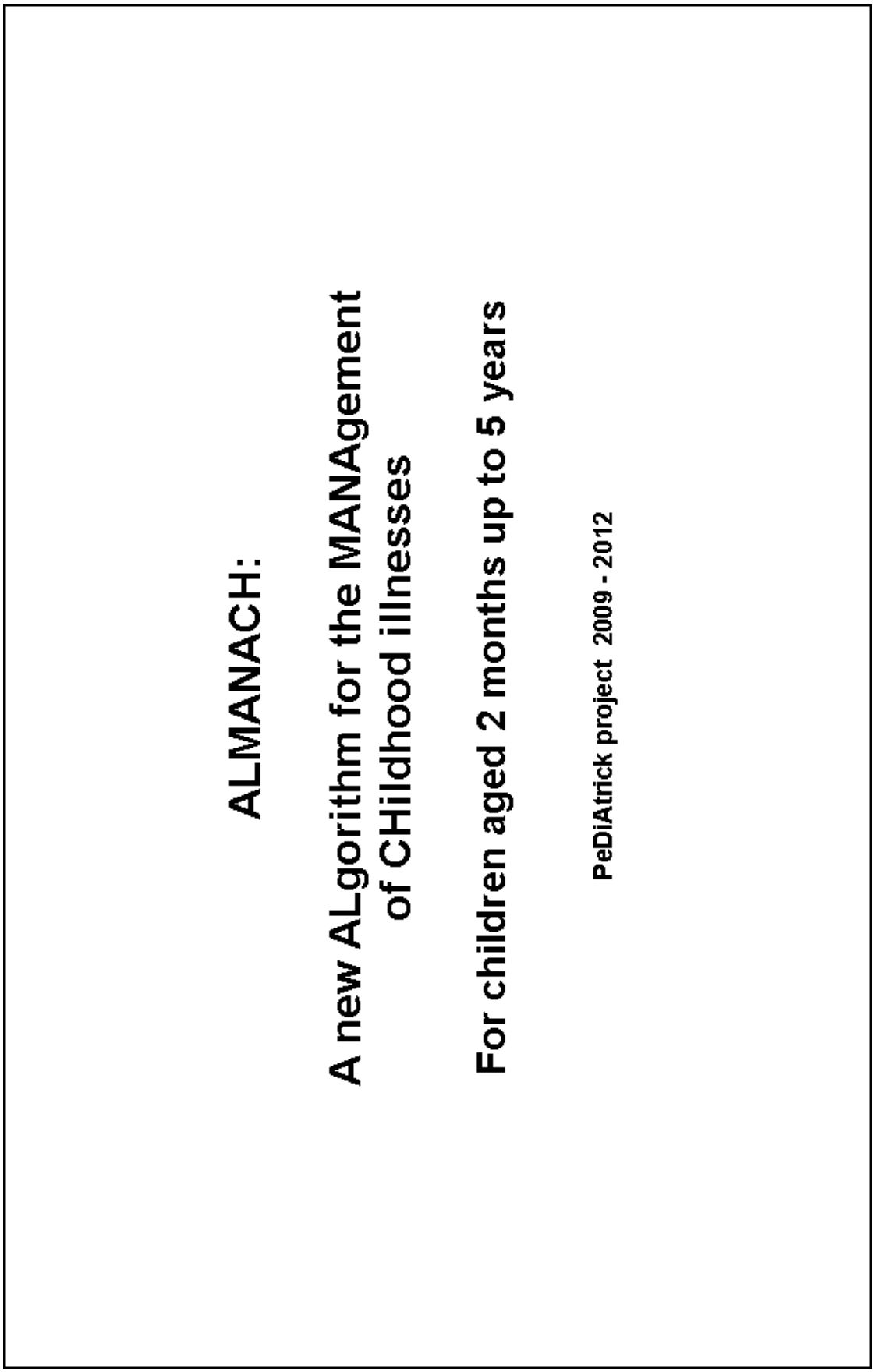
**Webappendix Figure e5. Forest plot of sensitivity and specificity for auscultation's signs**

| Index test | Study reference | Age range | Pneumonia prevalence | Positive index test proportion | TP | FN | FP | TN | Sensitivity (95%CI) | Specificity (95%CI) |
|---|---|---|---|---|---|---|---|---|---|---|
| crepitations | 2 | 0-4 yrs | 12% | 31% | 6 | 19 | 62 | 129 | 0.24 (0.09-0.45) | 0.68 (0.60-0.74) |
| | 3 | 5-59 mo | 60% | 45% | 52 | 38 | 16 | 44 | 0.58 (0.47-0.68) | 0.73 (0.60-0.84) |
| | 5 | 8 wks-6 yrs | 30% | 45% | 29 | 26 | 53 | 76 | 0.53 (0.39-0.66) | 0.59 (0.50-0.67) |
| | 6 | 0-3 yrs | 65% | 68% | 104 | 26 | 31 | 38 | 0.80 (0.72-0.86) | 0.55 (0.43-0.67) |
| | 10 | 0-6 yrs | 61% | 35% | 27 | 63 | 25 | 32 | 0.30 (0.21-0.41) | 0.56 (0.42-0.69) |
| | 13 | 40 d-30 mo | 35% | 37% | 136 | 211 | 228 | 405 | 0.39 (0.34-0.45) | 0.64 (0.60-0.68) |
| | 16 | 0-23 mo | 43% | 73% | 217 | 57 | 244 | 116 | 0.79 (0.74-0.84) | 0.32 (0.27-0.37) |
| crackles | 11 | 2-59 mo | 9% | 14% | 9 | 35 | 63 | 403 | 0.20 (0.10-0.35) | 0.86 (0.83-0.89) |
| rales | 7 | 2-59 mo | 63% | 58% | 211 | 130 | 104 | 96 | 0.62 (0.56-0.67) | 0.48 (0.41-0.55) |
| | 8 | 3 d-5 yrs | 32% | 29% | 16 | 19 | 16 | 59 | 0.46 (0.29-0.63) | 0.79 (0.68-0.87) |
| | 9 | 0-60 mo | 20% | 72% | 15 | 52 | 223 | 39 | 0.22 (0.13-0.34) | 0.15 (0.11-0.20) |
| | 17 | 1-5 yrs | 69% | 62% | 80 | 43 | 31 | 24 | 0.65 (0.56-0.73) | 0.44 (0.30-0.58) |
| bronchial breathing | 2 | 0-4 yrs | 12% | 6% | 8 | 17 | 6 | 185 | 0.32 (0.15-0.54) | 0.97 (0.93-0.99) |
| | 13 | 40 d-30 mo | 35% | 8% | 63 | 282 | 19 | 611 | 0.18 (0.14-0.23) | 0.97 (0.95-0.98) |
| rhonchi | 2 | 0-4 yrs | 12% | 19% | 2 | 23 | 40 | 151 | 0.08 (0.01-0.26) | 0.79 (0.73-0.85) |
| | 3 | 5-59 mo | 60% | 9% | 10 | 80 | 4 | 56 | 0.11 (0.05-0.19) | 0.93 (0.84-0.98) |
| | 6 | 0-3 yrs | 65% | 86% | 107 | 23 | 65 | 5 | 0.82 (0.75-0.88) | 0.07 (0.02-0.16) |
| | 13 | 40 d-30 mo | 35% | 10% | 18 | 328 | 83 | 548 | 0.05 (0.03-0.08) | 0.87 (0.84-0.89) |
| decreased breath sounds | 6 | 0-3 yrs | 65% | 15% | 27 | 103 | 2 | 68 | 0.21 (0.14-0.29) | 0.97 (0.90-1.00) |
| | 9 | 0-60 mo | 20% | 77% | 6 | 61 | 246 | 16 | 0.09 (0.03-0.18) | 0.06 (0.04-0.10) |
| | 10 | 0-6 yrs | 61% | 39% | 30 | 60 | 28 | 29 | 0.33 (0.24-0.44) | 0.51 (0.37-0.64) |
| | 11 | 2-59 mo | 9% | 6% | 5 | 39 | 24 | 442 | 0.11 (0.04-0.25) | 0.95 (0.92-0.97) |
| | 17 | 1-5 yrs | 69% | 38% | 61 | 62 | 7 | 48 | 0.50 (0.40-0.59) | 0.87 (0.76-0.95) |
| wheezing | 6 | 0-3 yrs | 65% | 19% | 20 | 110 | 17 | 53 | 0.15 (0.10-0.23) | 0.76 (0.64-0.85) |
| | 10 | 0-6 yrs | 61% | 33% | 20 | 70 | 29 | 28 | 0.22 (0.14-0.32) | 0.49 (0.36-0.63) |
| | 11 | 2-59 mo | 9% | 17% | 9 | 35 | 76 | 390 | 0.20 (0.10-0.35) | 0.84 (0.80-0.87) |
| | 12 | 2-59 mo | 15% | 23% | 65 | 198 | 350 | 1169 | 0.25 (0.20-0.30) | 0.77 (0.75-0.79) |
| | 17 | 1-5 yrs | 69% | 19% | 22 | 101 | 11 | 44 | 0.18 (0.12-0.26) | 0.80 (0.67-0.90) |
| | 18 | 0-59 mo | 16% | 28% | 77 | 247 | 479 | 1205 | 0.24 (0.19-0.29) | 0.72 (0.69-0.74) |
| wheezing or ronchi | 16 | 0-23 mo | 43% | 41% | 105 | 169 | 154 | 206 | 0.38 (0.33-0.44) | 0.57 (0.52-0.62) |




TP: true positive. FN: false negative. FP: false positive. TN: true negative.

**Annex 2: ALMANACH: The paper algorithm**



HOW TO USE **ALMANACH**



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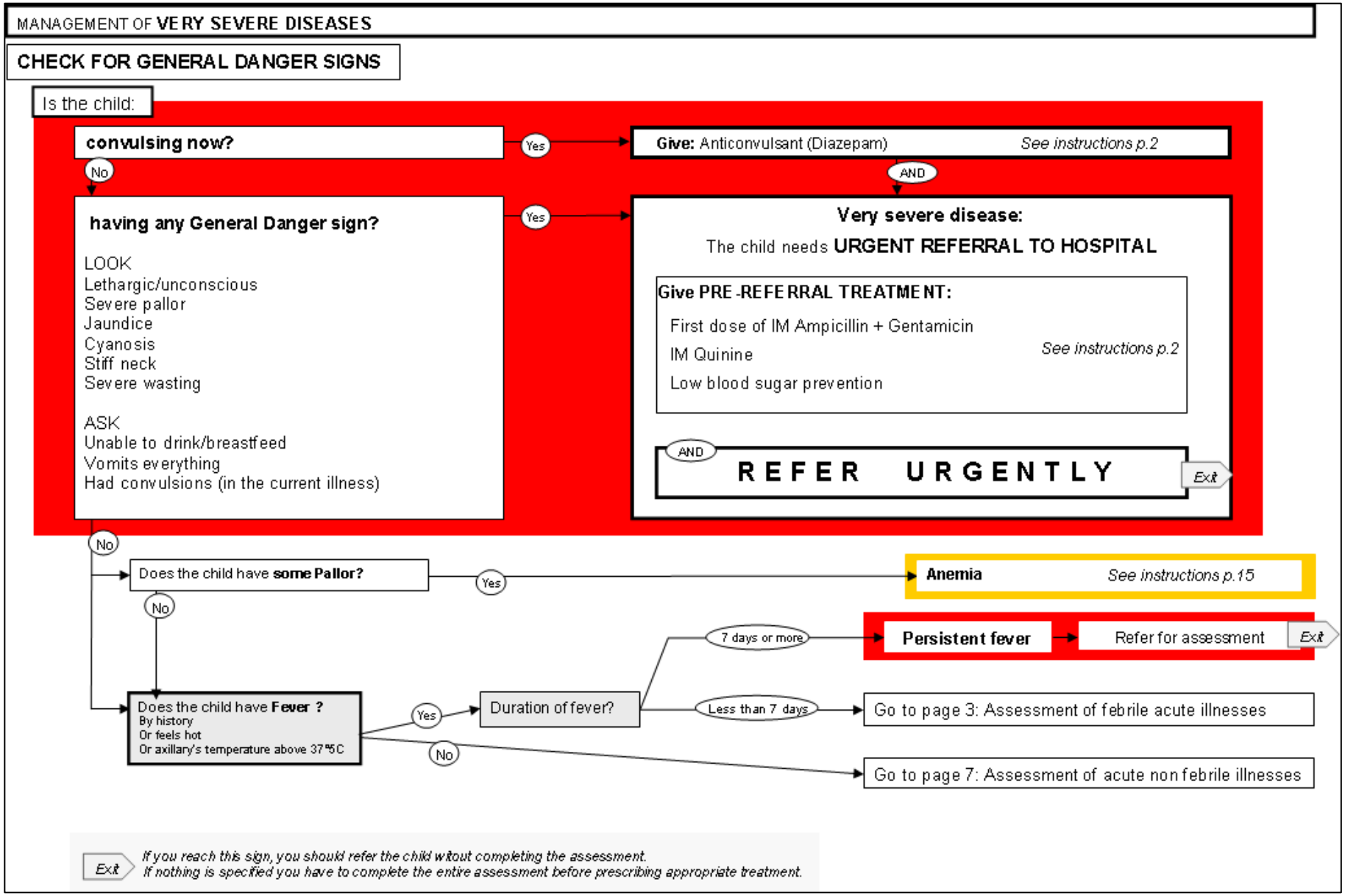

MANAGEMENT OF VERY SEVERE DISEASES
CHECK FOR GENERAL DANGER SIGNS
Is the child:
convulsing now?
Yes
Give: Anticonvulsant (Diazepam)
See instructions p.2
No
AND
having any General Danger sign?
LOOK
Lethargic/unconscious
Severe pallor
Jaundice
Cyanosis
Stiff neck
Severe wasting
ASK
Unable to drink/breastfeed
Vomits everything
Had convulsions (in the current illness)
Yes
Very severe disease:
The child needs URGENT REFERRAL TO HOSPITAL
Give PRE-REFERRAL TREATMENT:
First dose of IM Ampicillin + Gentamicin
IM Quinine
See instructions p.2
Low blood sugar prevention
AND
REFER URGENTLY
Exit
No
Does the child have some Pallor?
Yes
Anemia
See instructions p.15
No
Does the child have Fever ?
By history
Or feels hot
Or axillary's temperature above 37°5C
Yes
Duration of fever?
7 days or more
Persistent fever
Refer for assessment
Exit
Less than 7 days
Go to page 3: Assessment of febrile acute illnesses
No
Go to page 7: Assessment of acute non febrile illnesses
Exit
If you reach this sign, you should refer the child wtout completing the assessment.
If nothing is specified you have to complete the entire assessment before prescribing appropriate treatment.

**ANTIBIOTIC: AMPICILLINE** (50 mg/kg) **+ GENTAMICIN** (7.5 mg/kg)

**Ampicilline** for Very severe diseases and Severe pneumonia

***Preparation*** Check the vial: AMPICILLINE 500mg/0.4ml. Dilute the 500 mg vial in 2.1ml of sterile water. You have now 2.5ml of a solution with 200mg/ml.

Where there is a **strong suspicion of meningitis,** the **dose of ampicillin** can be **increased 4 times.**
IF REFERRAL IS NOT POSSIBLE OR DELAYED, repeat the ampicillin injection every 6 hours.

**Gentamicin** for Very severe diseases and Severe pneumonia

***Preparation*** Check the vial: GENTAMICIN 40mg/ml, 2ml. You have 80mg of Gentamicin in a 2ml solution. IF REFERRAL IS NOT POSSIBLE OR DELAYED, repeat the gentamicin injection once daily.

| AMPICILLIN 500 mg vial | |
|---|---|
| 4 - <6 kg (from 2 to <4 months) | 1 ml |
| 6 - <10 kg (4 to <12 months) | 2 ml |
| 10 - <14 kg (12mths to <3 years) | 3 ml |
| 14 - 19 kg (3 years to <5 years) | 5 ml |

| GENTAMICIN 80mg in 2ml | |
|---|---|
| 4 - <6 kg (2 to <4 months) | 0.5-1.0 ml |
| 6 - <10 kg (4 to <12 months) | 1.1-1.8 ml |
| 10 - <14 kg (12 months to <3 years) | 1.9-2.7 ml |
| 14 - 19 kg (3 years to <5 years) | 2.8-3.5 ml |

**QUININE** (10mg/kg)

***Preparation*** Check the ampoule: do you have: - QUININE 150mg/ml (300mg in 2 ml)
or - QUININE 300mg/ml (600mg in 2 ml)

IF REFERRAL IS NOT POSSIBLE OR DELAYED, The child should remain lying down for one hour. Repeat the quinine injection 8 hourly, until the child is able to take oral antimalarial, but not more than one week.

** quinine salt*

| INTRAMUSCULAR QUININE | 150mg*/ml | 300mg*/ml |
|---|---|---|
| 4 - <6 kg (2 to <4 months) | 0.4 ml | 0.2 ml |
| 6 - <10 kg (4 to <12 months) | 0.6 ml | 0.3 ml |
| 10 - <12 kg (12 mths to <2 years) | 0.8 ml | 0.4 ml |
| 12 - <14 kg (2 years to <3 years) | 1.0 ml | 0.5 ml |
| 14 - 19 kg (3 years to <5 years) | 1.2 ml | 0.6 ml |

**PREVENT LOW BLOOD SUGAR**

If the child is able to breastfeed: Ask the mother to breastfeed the child.
If the child is not able to breastfeed but is able to swallow: Give expressed breast milk or a breast-milk substitute.
If neither of these is available, give sugar water*. Give 30 - 50 ml of milk or sugar water* before departure.
If the child is not able to swallow: Give 50 ml of milk or sugar water* by nasogastric tube.

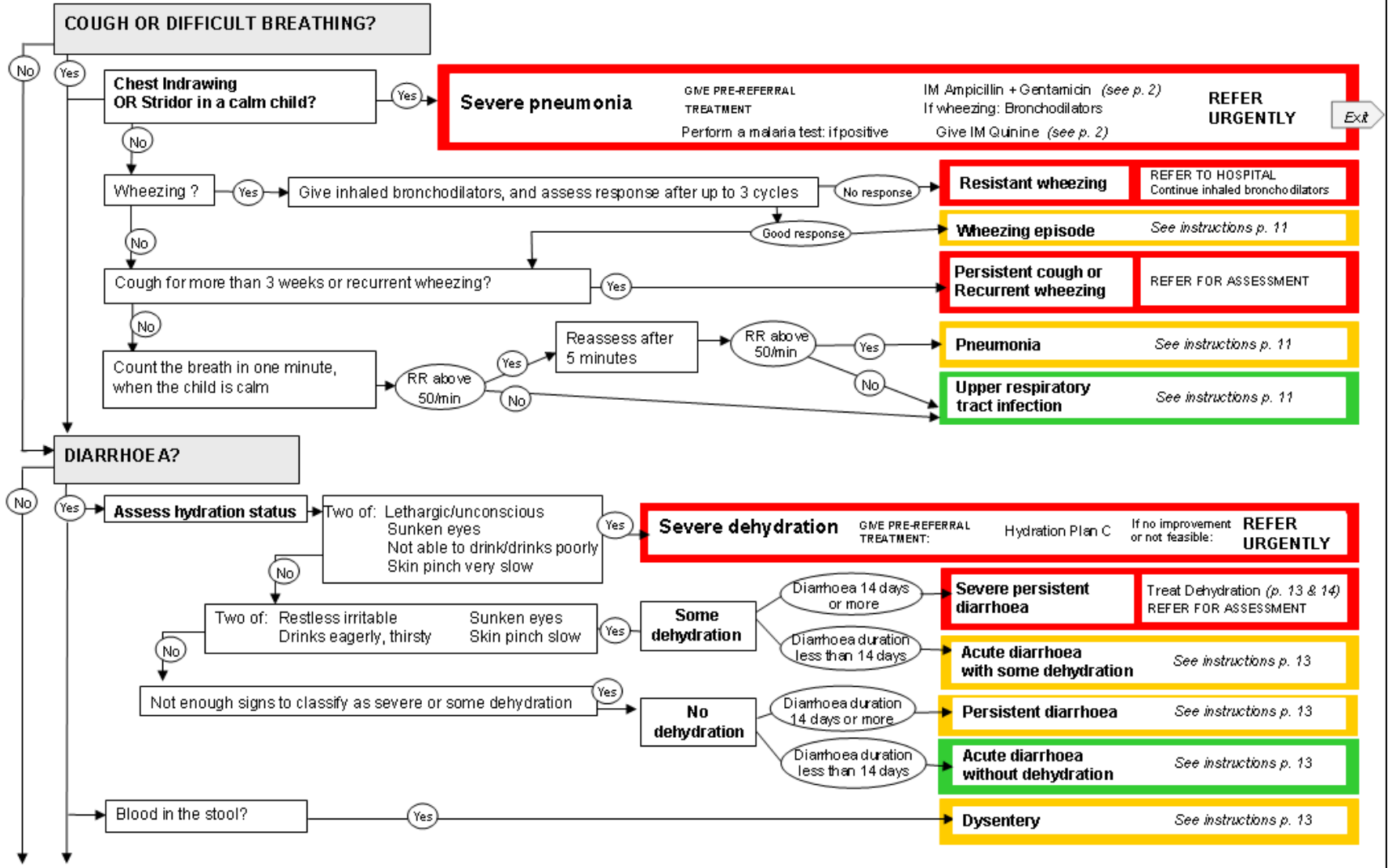
** To make sugar water: Dissolve 4 level teaspoons of sugar (20 grams) in a 200-ml cup of clean water.*

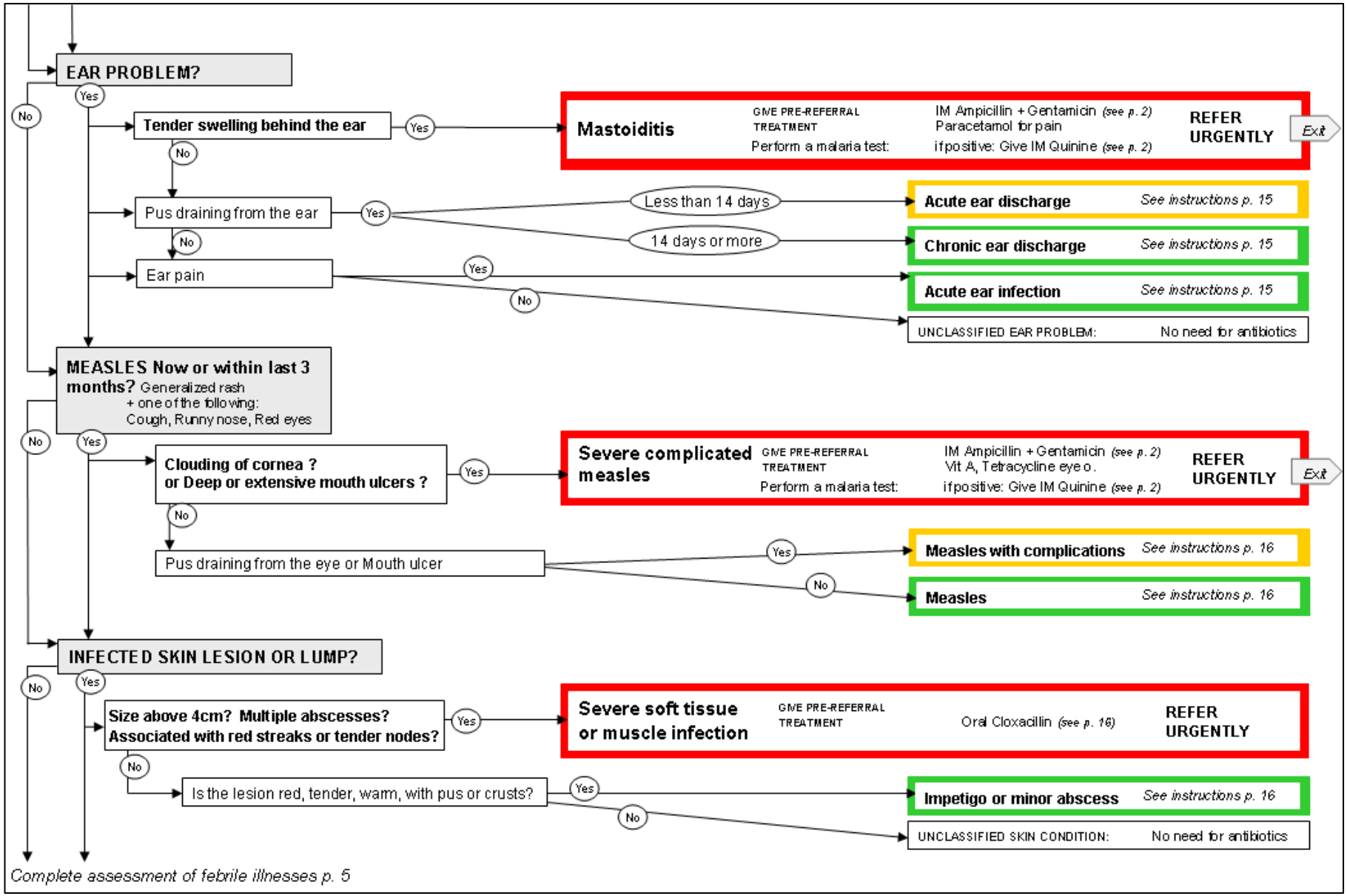
**ANTICONVULSANT: DIAZEPAM** (0.5 mg/kg)

***Instructions*** Turn the child to his/her side and clear the airway. Avoid putting things in the mouth.
Give diazepam solution per rectum using a small syringe without a needle (like a tuberculin syringe) or using a catheter.
Check for low blood sugar, then treat or prevent.
Give oxygen and REFER.
If convulsions have not stopped after 10 minutes repeat diazepam dose once.

| DIAZEPAM | 10mg/2mls |
|---|---|
| <5 kg (<6 months) | 0.5 ml |
| 5 - <10 kg (6 to <12 months) | 1 ml |
| 10 - <14 kg (12 months to <3 years) | 1.5 ml |
| 14 - 19 kg (3 years to <5 years) | 2 ml |

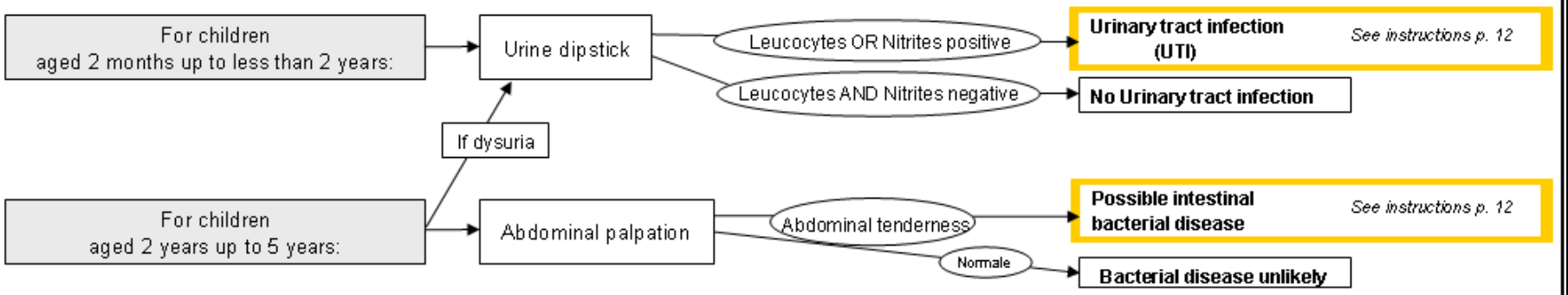
# ASSESSMENT OF FEBRILE CHILDHOOD ILLNESSES



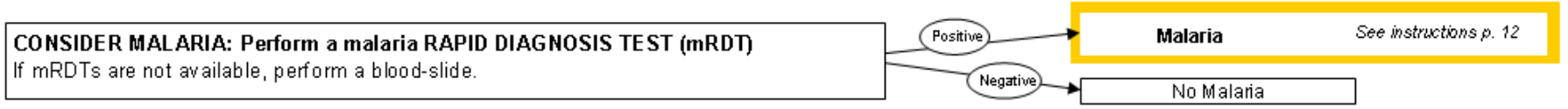

EAR PROBLEM?
Yes
No
Tender swelling behind the ear
Yes
No
Mastoiditis
GIVE PRE-REFERRAL TREATMENT
IM Ampicillin + Gentamicin (see p. 2)
Paracetamol for pain
Perform a malaria test:
if positive: Give IM Quinine (see p. 2)
REFER URGENTLY
Exit
Pus draining from the ear
Yes
No
Less than 14 days
14 days or more
Acute ear discharge
See instructions p. 15
Chronic ear discharge
See instructions p. 15
Ear pain
Yes
No
Acute ear infection
See instructions p. 15
UNCLASSIFIED EAR PROBLEM:
No need for antibiotics
MEASLES Now or within last 3 months? Generalized rash + one of the following: Cough, Runny nose, Red eyes
No
Yes
Clouding of cornea ? or Deep or extensive mouth ulcers ?
Yes
No
Severe complicated measles
GIVE PRE-REFERRAL TREATMENT
IM Ampicillin + Gentamicin (see p. 2)
Vit A, Tetracycline eye o.
Perform a malaria test:
if positive: Give IM Quinine (see p. 2)
REFER URGENTLY
Exit
Pus draining from the eye or Mouth ulcer
Yes
No
Measles with complications
See instructions p. 16
Measles
See instructions p. 16
INFECTED SKIN LESION OR LUMP?
No
Yes
Size above 4cm? Multiple abscesses? Associated with red streaks or tender nodes?
Yes
No
Severe soft tissue or muscle infection
GIVE PRE-REFERRAL TREATMENT
Oral Cloxacillin (see p. 16)
REFER URGENTLY
Is the lesion red, tender, warm, with pus or crusts?
Yes
No
Impetigo or minor abscess
See instructions p. 16
UNCLASSIFIED SKIN CONDITION:
No need for antibiotics
Complete assessment of febrile illnesses p. 5

## ASSESSMENT OF FEBRILE CHILDHOOD ILLNESSES

After this assessment **if the child has fever with no identified cause, perform the following:**



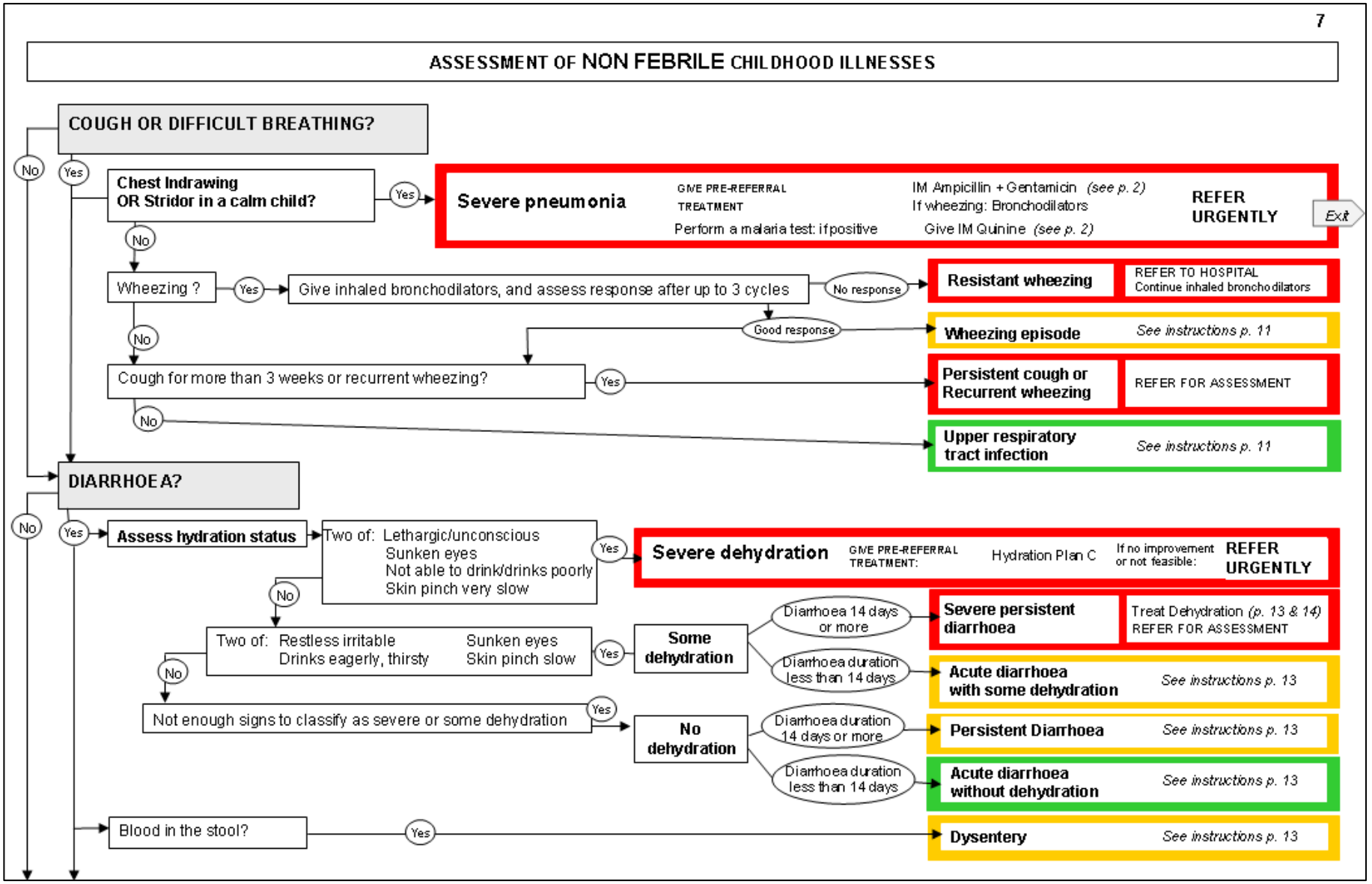

**FOR ALL CHILDREN WITH FEVER OR HISTORY OF FEVER: CONSIDER MALARIA**

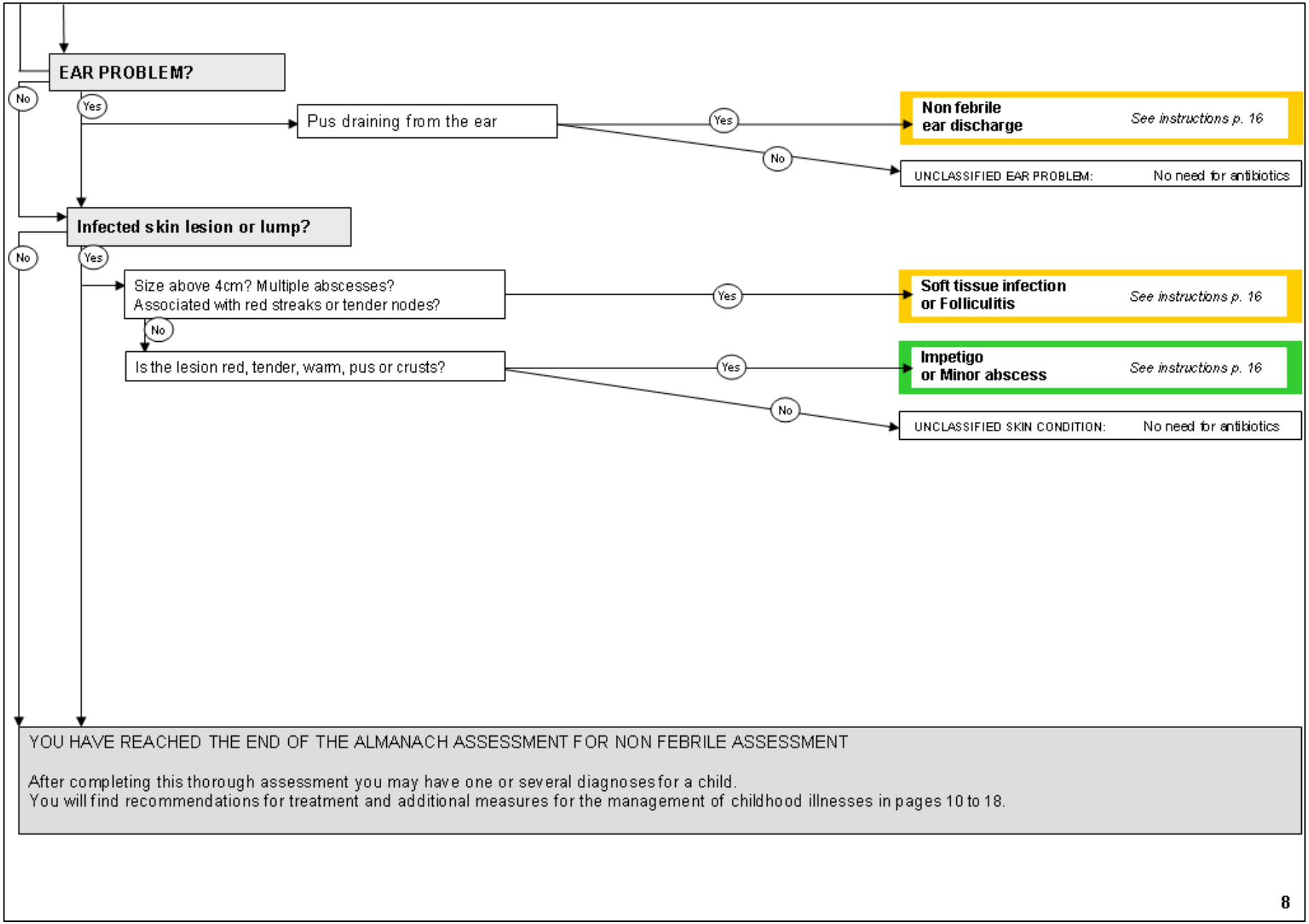



**If you answered NO to all the questions**, the child has fever with no obvious cause, no danger sign, and the malaria test is negative.
The child is likely to have a **Viral infection**. S/he does NOT need neither antibiotic nor antimalarial.
Prescribe symptomatic treatment for fever *(see page 12)*.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

YOU HAVE REACHED THE END OF THE ALMANACH ASSESSMENT FOR FEBRILE ILLNESSES

After completing this thorough assessment you may have one or several diagnoses for a child.
You will find the recommendations for treatment and additional measures for the management of childhood illnesses in pages 10 to 18.


ASSESSMENT OF NON FEBRILE CHILDHOOD ILLNESSES
COUGH OR DIFFICULT BREATHING?
No
Yes
Chest Indrawing
OR Stridor in a calm child?
Yes
Severe pneumonia
GIVE PRE-REFERRAL TREATMENT
IM Ampicillin + Gentamicin (see p. 2)
If wheezing: Bronchodilators
Perform a malaria test: if positive
Give IM Quinine (see p. 2)
REFER URGENTLY
Exit
No
Wheezing ?
Yes
Give inhaled bronchodilators, and assess response after up to 3 cycles
No response
Resistant wheezing
REFER TO HOSPITAL
Continue inhaled bronchodilators
Good response
Wheezing episode
See instructions p. 11
No
Cough for more than 3 weeks or recurrent wheezing?
Yes
Persistent cough or Recurrent wheezing
REFER FOR ASSESSMENT
No
Upper respiratory tract infection
See instructions p. 11
DIARRHOEA?
No
Yes
Assess hydration status
Two of: Lethargic/unconscious
Sunken eyes
Not able to drink/drinks poorly
Skin pinch very slow
Yes
Severe dehydration
GIVE PRE-REFERRAL TREATMENT:
Hydration Plan C
If no improvement or not feasible:
REFER URGENTLY
No
Two of: Restless irritable
Sunken eyes
Drinks eagerly, thirsty
Skin pinch slow
Yes
Some dehydration
Diarrhoea 14 days or more
Severe persistent diarrhoea
Treat Dehydration (p. 13 & 14)
REFER FOR ASSESSMENT
Diarrhoea duration less than 14 days
Acute diarrhoea with some dehydration
See instructions p. 13
No
Not enough signs to classify as severe or some dehydration
Yes
No dehydration
Diarrhoea duration 14 days or more
Persistent Diarrhoea
See instructions p. 13
Diarrhoea duration less than 14 days
Acute diarrhoea without dehydration
See instructions p. 13
Blood in the stool?
Yes
Dysentery
See instructions p. 13


EAR PROBLEM?
No
Yes
Pus draining from the ear
Yes
No
Non febrile ear discharge
See instructions p. 16
UNCLASSIFIED EAR PROBLEM:
No need for antibiotics
Infected skin lesion or lump?
No
Yes
Size above 4cm? Multiple abscesses?
Associated with red streaks or tender nodes?
Yes
Soft tissue infection or Folliculitis
See instructions p. 16
No
Is the lesion red, tender, warm, pus or crusts?
Yes
Impetigo or Minor abscess
See instructions p. 16
No
UNCLASSIFIED SKIN CONDITION:
No need for antibiotics
YOU HAVE REACHED THE END OF THE ALMANACH ASSESSMENT FOR NON FEBRILE ASSESSMENT
After completing this thorough assessment you may have one or several diagnoses for a child.
You will find recommendations for treatment and additional measures for the management of childhood illnesses in pages 10 to 18.
8

# MANAGEMENT AND TREATMENT CHART

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GENERAL RECOMMENDATIONS

Always tell the caretakers the reason for giving the drug, and teach them how to give it at home if needed.
Demonstrate how to prepare a dose, watch them preparing the first dose, explain carefully how to give the drug and to complete the treatment even if the child gets better. Check the caretakers' understanding before they leave.

REASSURING THE CARETAKER when the RDT is negative

Reassure the caretaker that:

- the child does NOT have malaria
- the diagnostic test (RDT) is very accurate
- antimalarials will NOT help the child and you do not want to unnecessarily expose the child to side effects that may accompany these medications

MANAGEMENT AND TREATMENT CHART FOR **COUGH** RELATED DIAGNOSES

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

**Resistant wheezing** — Continue inhaled bronchodilators, using a spacer, on the way to hospital *(see below)* — REFER URGENTLY

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

**Pneumonia** — Give Amoxicillin 25mg/kg, 2 times daily, for 5 days
Discuss HIV infection

Advise caretaker to:
Come back immediately if the child is not able to drink or breastfeed, or becomes sicker
Come back after 2 days if fever or difficult breathing persist

| **Amoxicillin** 25mg/kg | CAPSULES 250 mg | SYRUP 125 mg/5 ml |
|---|---|---|
| 4 - <6 kg (2 months to <4 months) | | 5 ml |
| 6 - <14 kg (4 months to <3 years) | 1 | 10 ml |
| 14 - 19 kg (3 years to <5 years) | 2 | 15 ml |

**Wheezing episode** — Treat the wheezing in the clinic following the symptomatic treatment instructions below. If the child has a good response to the treatment, and doesn't need referral, continue the treatment at home:
*At home:* continue treatment with inhaled salbutamol, 3 to 4 times a day, for 5 days.
*If inhaler not available:* Use oral salbutamol (2 months up to 12 months: 1mg, 3 times daily; 2 months up to 4 years: 2mg, 3 to 4 times daily)

Advise caretaker to:
Come back immediately if the child is not able to drink/breastfeed, becomes sicker, or develops fever
Come back if the wheezing/difficult breathing persists after treatment

**Upper respiratory tract infection (URTI)** — Explain the mother that the URTI is a viral disease that is self limiting

Advise caretaker to:
Relieve cough and soothe the throat with breast milk for an infant breastfed, or with tea with lemon or tea with honey for an older child
Come back immediately if the child is not able to drink or breastfeed, becomes sicker, develops fever, or develops fast/difficult breathing or wheeze
Come back after 5 days if the symptoms persist

**ADDITIONAL SYMPTOMATIC TREATMENTS**

**Wheezing:** *In the clinic:* Give inhaled bronchodilators: Salbutamol, using a spacer *(See page 17)*: From salbutamol metered dose inhaler (100 µg/puff) give 2 puffs.
Reassess the child after 15 minutes. Repeat up to 3 times every 15 minutes before classifying pneumonia.

**Cough and/or sore throat:** To relieve cough and soothe the throat recommend the caretaker to use the safe remedies below:
For an infant who is exclusively breastfed: breast milk For other children: breast milk, tea with honey, tea with lemon.

MANAGEMENT AND TREATMENT CHART FOR **FEVER** RELATED DIAGNOSES

**Persistent fever** — Refer to hospital for further assessment

**Malaria** — Give ALu:
- Give first dose in the clinic and observe the child for one hour. If the child vomits within an hour repeat the dose.
- Tell the mother to give second dose after 8 hours and then 2 times daily for further 2 days as shown in the table.
- ALu should be given with food.

Give one dose of paracetamol in the clinic for high fever (38.5 and above).

Advise caretaker to:
- Come back immediately if the child is not able to drink or breastfeed, or becomes sicker
- Come back after 2 days if fever persists
- Always use insecticide treated mosquito net

| **ALu** (artemether + lumefantrine) | Tablet *(artemether 20mg + lumefantrine 120mg)* | | | | | |
|---|---|---|---|---|---|---|
| | 0h | 8h | 24h | 36h | 48h | 60h |
| 5* <15 kg (2 months to <3 years) | 1 | 1 | 1 | 1 | 1 | 1 |
| 15 - <25 kg (3 years to <5 years) | 2 | 2 | 2 | 2 | 2 | 2 |

**Children weighing less than 5 kg should be treated with Quinine Give Quinine tabs 300mg: 1/4, 3 times daily, for 7 days.*

**Urinary tract infection** (UTI) — Give Ciprofloxacin 15mg/kg, 2 times a day, for 5 days

Advise caretaker to:
- Increase fluids
- Come back immediately if the child is not able to drink/breastfeed, or becomes sicker
- Come back after 2 days if fever persists

**Possible intestinal bacterial disease** — Give Ciprofloxacin 15mg/kg, 2 times a day, for 5 days

Advise caretaker to:
- Increase fluids
- Come back immediately if the child is not able to drink/breastfeed, or becomes sicker
- Come back after 2 days if fever persists

| **Ciprofloxacin** 15mg/kg | Tablet 250 mg | Tablet 500mg |
|---|---|---|
| <6 kg (less than 6 months) | 1/4 | |
| 6- <14 kg (6 months to <3 years) | 1/2 | 1/4 |
| 14-19 kg (3 years to <5 years) | 1 | 1/2 |

SYMPTOMATIC MANAGEMENT AND TREATMENT FOR **FEVER**

**For all children with FEVER:** — Give first dose of paracetamol in the clinic if high fever (38.5°C and above)

Explain caretaker to:
- Expose the child (decrease or remove the clothes)
- Increase the fluids intake
- Give paracetamol, 15mg/kg, every 6 hours until high fever or pain is gone

| **Paracetamol** 15mg/kg | Syrup 120mg/5ml | Tablet 500mg |
|---|---|---|
| <4kgs | 2ml | - |
| 4-<10 kg (2 months to <1 year) | 5ml | 1/4 |
| 10-19 kg (1 year to <5 years) | - | 1/2 |

MANAGEMENT AND TREATMENT CHART FOR **DIARRHOEA** RELATED DIAGNOSES

| | | |
|---|---|---|
| **Severe dehydration** | Give Hydration plan C *(see page 14)* | REFER URGENTLY to hospital if Plan C is not available in your health facility or if the child does not improve after 3 hours of treatment |
| **Severe persistent diarrhoea** | Give hydration plan B *(see page 14)* | and refer to hospital for further assessment |

| | | |
|---|---|---|
| **Acute diarrhoea with some dehydration** | Give hydration plan B *(see page 14)* | Give zinc* |
| Advise caretaker to: | Continue feeding and give zinc*<br>Come back immediately if the child is not able to drink/breastfeed, becomes sicker, develops fever, or blood in stool<br>Come back after 5 days if diarrhoea persists | |

| | |
|---|---|
| **Persistent Diarrhoea** | Give zinc* , Vitamin A treatment *(see page 16),* and multivitamin<br>Discuss HIV infection |
| Advise caretaker on feeding: | Continue breastfeeding, and give more frequent, longer breastfeeds, day and night<br>If the child takes other milk: Replace with increased breastfeeding OR Replace with fermented milk products, such as yoghurt<br>OR Replace half the milk with nutrient—rich semisolid food |
| Advise caretaker to come back: | Immediately if the child is not able to drink/breastfeed, becomes sicker, develops fever, or blood in stool<br>After 5 days if diarrhoea persists |

| | | |
|---|---|---|
| **Dysentery** | Give Ciprofloxacin 15mg/kg, 2 times a day, for 3 days<br>Give hydration according to dehydration status and continue feeding | |
| Advise caretaker to come back: | Immediately if the child is not able to drink/breastfeed, becomes sicker, or develops fever<br>After 2 days if the diarrhoea persists | |

| **Ciprofloxacin** 15mg/kg | Tablet 250 mg | Tablet 500mg |
|---|---|---|
| <6 kg (less than 6 months) | 1/4 | |
| 6- <14 kg (6 months to <3 years) | 1/2 | 1/4 |
| 14-19 kg (3 years to <5 years) | 1 | 1/2 |

| | | |
|---|---|---|
| **Acute diarrhoea without dehydration** | Give hydration plan A *(see page 14)* | Give zinc* |
| Advise caretaker to: | Continue feeding and give zinc*<br>Come back immediately if the child is not able to drink/breastfeed, becomes sicker, develops fever, or blood in stool<br>Come back after 5 days if diarrhoea persists | |

| | |
|---|---|
| ***Give Zinc for 14 days to all children with diarrhoea:** | From 2 months up to 6 months: 1/2 tablet daily<br>6 months or more: 1 tablet daily |
| Show caretaker how to give zinc supplements: | Infants: dissolve tablet in a small amount of expressed breast milk, ORS or clean water in a cup.<br>Older children: tablets can be chewed or dissolved in a small amount of water. |

**HYDRATION PLAN A** Give extra fluids (as much as the chid will take): Give more frequent, longer breastfeeds, and give ORS or clean water in addition to breast milk. If the child is not exclusively breastfed, also give food-based fluids (such as soup, rice water, and yoghurt drinks).

Give ORS at home especially when the child has been treated with Plan B or Plan C during this visit OR when the child cannot return to a clinic if the diarrhoea gets worse.

Teach the caretaker how to mix and give ORS: Give 2 packets of ORS. Show how much fluid to give in addition to the usual fluid intake.
Tell her/him to give after each loose stool: 50 to 100ml for a child below 2 years of age, and 100 to 200ml for a child older than 2 years.
Give frequent sips from a cup. If the child vomits, wait 10 minutes. Then continue but more slowly. Continue giving extra fluid until the diarrhoea stops.

**HYDRATION PLAN B** Give ORS at the clinic over a 4 hours period.

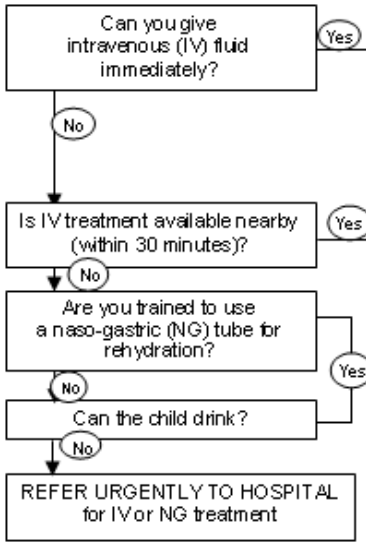
Determine recommended amount of ORS to give over a 4 hours period using the table aside. If the child wants more ORS than shown, give more.

| WEIGHT | < 6 kg | 6 - <10 kg | 10 - <12 kg | 12 - 19 kg |
|---|---|---|---|---|
| AGE | <4 months | 4 months to <12 months | 12 months to <2 years | 2 years to <5 years |
| ORS in ml | 200 - 450 | 450 - 800 | 800 - 960 | 960 - 1600 |

*Use the child's age only when you do not know the weight.*

Show caretaker how to give ORS solution**:** Give frequent small sips from a cup. If the child vomits, wait 10 minutes. Then continue, but more slowly.
Continue breastfeeding whenever the child wants.
After 4 hours: Reassess the child and classify the child for dehydration. Select the appropriate plan to continue treatment. Begin feeding the child in clinic.
Before the caretaker leaves the clinic give her/him all explanation on how to continue the treatment at home *(see plan A)*.

**HYDRATION PLAN C: TREAT SEVERE DEHYDRATION QUICKLY:** Follow the arrows. If answer is 'YES' go across. If 'NO' go down.




**Start IV fluid immediately.** If the child can drink, give ORS by mouth while the drip is set up. Give 100 ml/kg Ringer's Lactate Solution (or, if not available, normal saline), divided as in table aside.

| AGE | First give 30 ml/kg in: | Then give 70 ml/kg in: |
|---|---|---|
| Infants (under 12 months) | 1 hour* | 5 hours |
| Children (12 months up to 5 years) | 30 minutes* | 2 1/2 hours |

*Repeat once if radial pulse is still very weak or not detectable. **Reassess the child every 1-2 hours.** If hydration status is not improving, give the IV drip more rapidly. Also give ORS (about 5 ml/kg/hour) as soon as the child can drink: usually after 3-4 hours (infants) or 1-2 hours (children).
**Reassess an infant after 6 hours and a child after 3 hours.** Classify dehydration. Then choose the appropriate plan (A, B, or C) to continue treatment.

**Refer URGENTLY to hospital for IV treatment.**
If the child can drink, provide the mother with ORS solution and show her how to give frequent sips during the trip or give ORS by naso-gastric tube.

**Start rehydration by tube (or mouth) with ORS solution:** give 20 ml/kg/hour for 6 hours (total of 120 ml/kg).

**Reassess the child every 1-2 hours while waiting for transfer:** If there is repeated vomiting or increasing abdominal distension, give the fluid more slowly. If hydration status is not improving after 3 hours, send the child for IV therapy.

**After 6 hours, reassess the child.** Classify dehydration. Then choose the appropriate plan (A, B or C) to continue treatment.

**NOTE:**
If the child is not referred to hospital, observe at least 6 hours after rehydration to be sure mother can maintain hydration giving the child ORS solution by mouth.

## MANAGEMENT AND TREATMENT CHART FOR **EAR** RELATED DIAGNOSES

**Mastoiditis**

Give IM Ampicillin and Gentamicin *(see page 2 for instructions)*
Give paracetamol for pain *(see p10)*

REFER URGENTLY

**Acute febrile ear discharge**

Give Amoxicillin 25mg/kg, 2 times daily, for 5 days
Dry the ear by wicking*
Discuss HIV infection

Advise caretaker to come back: immediately if the child is not able to drink or breastfeed, or becomes sicker
after 5 days if ear discharge persists

| **Amoxicillin** 25mg/kg | CAPSULES 250 mg | SYRUP 125 mg/5 ml |
|---|---|---|
| 4 - <6 kg (2 months to <4 months) | | 5 ml |
| 6 - <14 kg (4 months to <3 years) | 1 | 10 ml |
| 14 - 19 kg (3 years to <5 years) | 2 | 15 ml |

**Chronic ear discharge OR Non febrile ear discharge**

Dry the ear by wicking* and instil quinolones eardrops just after wicking, 3 times daily, for 2 weeks.
*(Quinolones eardrops may contain ciprofloxacin, norfloxacin or ofloxacin)*
Discuss HIV infection

Advise caretaker to come back: immediately if the child is not able to drink or breastfeed, becomes sicker, or develops fever
after 5 days if ear discharge persists

**Acute ear infection**

Give paracetamol for pain *(see page 10)*

Advise caretaker to come back: immediately if the child is not able to drink or breastfeed, or becomes sicker
after 3 days if pain or fever persist

***Dry wicking to clear the ear of children with ear discharge**

Dry the ear at least 3 times daily:
Wash hands.
Roll a clean absorbent cloth or soft, strong tissue paper into a wick.
Place the wick in the child's ear. Remove the wick when wet.
Replace the wick with a clean one and repeat this steps until the ear is dry.

## MANAGEMENT AND TREATMENT CHART FOR **ANAEMIA**

**Anaemia**

Give Iron*, 1 dose daily, for a total of 2 months
Give Mebendazole 500mg single dose, if the child is one year or older and has not had a dose in the previous 6 months.

Check Malaria: Perform a Rapid diagnostic test (RDT) and treat if positive *(see page 11)*

Advise caretaker to come back: immediately if the child is not able to drink, becomes sicker, or develops fast breathing or fever
after 14 days for re-assessment

| **IRON** | Ferrous sulfate 200 mg + 250 µg Folate (60 mg elemental iron) | Ferrous fumarate 100 mg per 5 ml (20 mg elemental iron per ml) |
|---|---|---|
| 4 - <6 kg (2 to <4 months) | | 1.00 ml (< 1/4 tsp.) |
| 6 - <10 kg (4 to <12 months) | | 1.25 ml (1/4 tsp.) |
| 10 - <14 kg (1 to <3 years) | 1/2 tablet | 2.00 ml (<1/2 tsp.) |
| 14 - 19 kg (3 to <5 years) | 1/2 tablet | 2.5 ml (1/2 tsp.) |

## MANAGEMENT AND TREATMENT CHART FOR **MEASLES** RELATED DIAGNOSES

**Severe complicated measles**

Give IM Ampicillin and Gentamicin *(see page 2 for instructions)*
Give Vitamin A and Tetracycline eye ointment *(see below)*

REFER URGENTLY

**Measles with eye or mouth complication**

Give vitamin A treatment *(See below)* to children from 6 months up 5 years, except if the child has had a dose in the past month.
Give paracetamol for pain relief.

**Treat eye infection with tetracyclin eye ointment** in both eyes, 4 times daily*: Clean both eyes: Wash hands, use clean cloth and water to gently wipe the pus.
Then apply tetracyclin eye ointment: Squirt a small amount of ointment on the inside of the lower lid. Wash hands again. Treat until there is no pus discharge. Do not put anything else in the eyes.

**Treat for mouth ulcers with Gentian Violet** (GV) twice daily*: Wash hands. Wash the child's mouth with clean soft cloth wrapped around the finger and wet with salt water.
Paint the mouth with half-strength gentian violet (0.25% dilution). Wash hands again. Continue using gentian violet for 48 hours after the ulcers have been cured.

Advise caretaker to come back:
Immediately if the child is not able to drink/breastfeed, becomes sicker, develops fever
After 2 days if symptoms persist

**Measles**

Give Vitamin A treatment: Give a dose of Vitamin A to children from 6 months up to 5 years, except if the child has had a dose in the past month.

| **AGE** | 6 to <12 months | One year and older |
|---|---|---|
| **Vitamin A** dose | 100 000 IU | 200 000 IU |



## MANAGEMENT AND TREATMENT CHART FOR **SKIN** RELATED DIAGNOSES

**Severe soft tissue or muscles infection**

Give first dose of oral Cloxacillin *(see below)*

REFER TO HOSPITAL

**Soft tissue infection or folliculitis**

Give Cloxacillin, 25mg/kg, 4 times a day, for 5 days
Clean sores with antiseptic. Drain pus if fluctuance.

Advise caretaker to come back:
After 1 day if symptoms persist
Immediately if the child is not able to drink, or becomes sicker.

| **Cloxacillin** 25mg/kg | Syrup 125mg/5ml | Capsule 250 mg |
|---|---|---|
| 4 - <6 kg (2 to <4 months) | 5ml | |
| 6 - <14 kg (4 mths to <3 yrs) | 10ml | 1 |
| 14 - 19 kg (3 to <5 years) | 15ml | 2 |

**Impetigo or minor abscess**

Clean sores with antiseptic. Drain pus if fluctuance.

Advise caretaker to come back:
Immediately if the child is not able to drink/breastfeed, becomes sicker, develops fever
After 2 days if symptoms persist

* For local treatments: Explain to the caretaker what the treatment is and how it should be given. Tell her/him how often to do the treatment at home. If needed, give caretaker the tube of tetracycline ointment or a small bottle of gentian violet.

**USE OF A SPACER**

A spacer is a way of delivering the bronchodilator drugs effectively into the lungs. NO CHILD UNDER 5 YEARS OF AGE SHOULD RECEIVE AN INHALER WITHOUT A SPACER. A spacer works as well as a nebuliser if correctly used.

**Spacers can be made in the following way:**

Use a 500ml drink bottle or similar. Cut a hole in the bottle base in the same shape as the mouthpiece of the inhaler, with a sharp knife. Cut the bottle between the upper quarter and the lower 3/4 and disregard the upper quarter of the bottle.

Cut a small V in the border of the large open part of the bottle to fit to the child's nose and be used as a mask. Flame the edge of the cut bottle with a candle or a lighter to soften it. In a small baby, a mask can be made by making a similar hole in a plastic (not polystyrene) cup. Alternatively commercial spacers can be used if available.

**To use an inhaler with a spacer*:**

Remove the inhaler cap. Shake the inhaler well. Insert mouthpiece of the inhaler through the hole in the bottle or plastic cup. The child should put the opening of the bottle into his mouth and breath in and out through the mouth. A carer then presses down the inhaler and sprays into the bottle while the child continues to breath normally. Wait for three to four breaths and repeat. For younger children place the cup over the child's mouth and use as a spacer in the same way.

** If a spacer is being used for the first time, it should be primed by 4-5 extra puffs from the inhaler.*