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CAN IMPROVED PAEDIATRIC PNEUMONIA DIAGNOSTIC AIDS SUPPORT FRONTLINE HEALTH WORKERS IN LOW RESOURCE SETTINGS?

LARGE SCALE EVALUATION OF FOUR RESPIRATORY RATE TIMERS AND FIVE PULSE OXIMETERS IN CAMBODIA, ETHIOPIA, SOUTH SUDAN AND UGANDA

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Can improved paediatric pneumonia diagnostic aids support frontline health workers in low resource settings?

Large scale evaluation of four respiratory rate timers and five pulse oximeters in Cambodia, Ethiopia, South Sudan and Uganda

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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“You can see them labouring to breathe,

Just imagine you are fighting to take in air.

It’s really painful for you the doctor,

And worse still for the parents, who are looking at their child.

You know you could prevent this, that’s what hurts.

Sometimes, you reach a point where you can’t do anything.

You just watch as the patient breathes away…”

- Dr Violet Okaba Kayom, Mulago National Referral Hospital, Uganda

ABSTRACT

Background: Pneumonia is the leading cause of infectious death in children under-five in sub-Saharan Africa and Southeast Asia. Currently, the diagnostic criterion for pneumonia is based on increased respiratory rate (RR) in children with cough and/or difficulty breathing. Low oxygen saturation, usually measured using pulse oximeters, is an indication of severe pneumonia. Health workers report finding it difficult to accurately count the number of breaths and current RR counting aids are often difficult to use or unavailable. Improved RR counting aids and lower-cost pulse oximeters are now available but their suitability in these settings and for these populations are untested.

Objective: The studies sought to identify and evaluate the most accurate, acceptable and user-friendly respiratory rate counting devices and pulse oximeters for diagnosis of pneumonia symptoms and severity in children by frontline health workers in low-resource settings.

Methods: Three sub-studies (I-III) were conducted among health workers, children under five and their caregivers, and national stakeholders. Sub-study I uses an explanatory qualitative approach with pile sorting and focus group discussions with frontline health workers and national stakeholders to explore their perspectives regarding the potential usability and scalability of seven pneumonia diagnostic aids. In sub-study II (a & b) four RR counters and five pulse oximeters were evaluated for performance by a cross-sectional sample of frontline health workers in hospital settings against reference standards in Cambodia, Ethiopia, South Sudan and Uganda. In sub-study III the same nine devices were evaluated using mixed methods for usability and acceptability in routine practice, over three months, in the four countries.

Findings: Frontline health workers and national stakeholders' universally valued device simplicity, affordability and sustainability. They prioritised different device characteristics according to their specific focus of work, with health workers focusing more on device acceptability and national stakeholders' being less accepting of new technologies (Sub-study I). In sub-study IIa most CHWs managed to achieve a RR count with the four devices. The agreement with the reference standard was low for all; the mean difference of RR measurements or breaths per minute (bpm) from the reference standard for the four devices ranged from 0.5 bpm (95% CI -2.2 to 1.2) for the respirometer to 5.5 bpm (95% CI 3.2 to 7.8) for Rrate. Performance was consistently lower for young infants (0 to <2 months) than for older children (2 to ≤59 months). Agreement of RR classification into fast and normal breathing was moderate across all four devices, with Cohen's Kappa statistics ranging from 0.41 (SE 0.04) to

0.49 (SE 0.05). In Sub-study IIb, although all five pulse oximeters tested in the field had performed well on a simulator (±2% SpO2 from the simulator), their performance was more varied when used on real children by frontline health workers. The handheld pulse oximeters had greater overall agreement with the reference standard, ranging from -0.6% SpO2 (95% CI -0.9, 0.4) to -3.0% SpO2 (95% CI -3.4, -2.6) than the finger-tip pulse oximeters, which ranged from -3.9% SpO2 (95% CI -4.4, -3.4) to -7.9% SpO2 (95% CI -8.6,-7.2). This was particularly pronounced in the younger children, where handheld devices had -0.7 SpO2 (95% CI -1.4, -0.1) to -5.9 SpO2 (95% CI -6.9, -4.9) agreement, compared to fingertip devices, which had -8.0 SpO2 (95% CI -9.4, -6.6) to -13.3 SpO2 (95% CI -15.1, -11.5) agreement. First level health facility workers had better agreement in classification of hypoxaemia with the reference standard (κ=0.32; SE 0.05 to κ=0.86; SE 0.07) for all five devices, when compared to CHWs (κ=0.15; SE 0.02 to κ=0.59; SE 0.03). In Sub-study III health workers reported being better supported by assisted RR counters, which provided more support than their standard practice ARI timer in counting and classifying RR in sick children under 5 in these settings.

Conclusions: Frontline health workers were able to use the nine test devices to measure RR and oxygen saturation in children under 5, but with variable performance, and found it more difficult to get a successful measurement in younger children. Frontline health workers were better supported by assisted RR counters, such as Rrate and respirometer, compared to their standard practice diagnostic aid, MK2 ARI timer. Handheld pulse oximeters with multiple probes performed better than fingertip pulse oximeters, especially in younger children. The views of different stakeholder groups should be considered when looking to take these types of pneumonia diagnostic aids to scale. A consensus view on a robust research method and reference standard to evaluate future pneumonia diagnostic aids needs to be reached. While laboratory testing of new diagnostic aids can be valuable it should not replace field testing with frontline health workers in routine practice. Automated, easy to use, robust and affordable pneumonia diagnostics aids need to be developed and launched at scale to better support frontline health workers to address the high pneumonia burden in resource poor settings.

Key words: pneumonia, CHWs, diagnostic aids, innovation, pulse oximeters

LIST OF SCIENTIFIC PAPERS

I. Spence H, **Baker K**, Wharton-Smith Al, Mucunguzi A, Matata L, Habte T, Nanyumba D, Sebsibe A, Thany T and Källander K. *Childhood pneumonia diagnostics: community health workers' and national stakeholders' differing perspectives of new and existing aids.* Global Health Action, 2017, 10, 1-11

II. **Baker K**, Alfvén T, Mucunguzi A, Wharton-Smith A, Dantzer E, Habte T, Matata L, Nanyumba D, Okwir M, Posada M, Sebsibe A, Nicholson J, Marasciulo M, Izadnegahdar R, Petzold M, Källander K. *Performance of four respiratory rate counters to support community health workers to detect the symptoms of pneumonia in children in low resource settings: A prospective, multi-centre, hospital-based, single-blinded, comparative trial.* eClinical Medicine. 2019;12:20-30.

III. **Baker K**, Petzold M, Mucunguzi A, Wharton-Smith A, Dantzer E, Habte T, Matata L, Nanyumba D, Okwir M, Posada M, Sebsibe A, Nicholson J, Marasciulo M, Izadnegahdar R, Alfvén T, Källander K. *Performance of five pulse oximeters to detect the symptoms of severe illness in children under five by frontline health workers in low resource settings – results from a prospective, multicentre, single-blinded, trial in Cambodia, Ethiopia, South Sudan and Uganda.* (Manuscript)

IV. **Baker K**, Källander K, Petzold M, Mucunguzi A, Wharton-Smith A, Dantzer E, Habte T, Matata L, Nanyumba D, Okwir M, Posada M, Sebsibe A, Nicholson J, Marasciulo M, Izadnegahdar R, Mohiuddin A, Soremekun S, Alfvén T, Mölsted Alvesson H. *Acceptability, usability and utilisation of pneumonia diagnostic aids, as perceived by caregivers & frontline health workers, in supporting the detection of pneumonia symptoms in Sub-Saharan Africa and Southeast Asia.* (Submitted)

LIST OF SUPPLEMENTARY SCIENTIFIC PAPERS

I. **Baker K**, Mucunguzi A, Wharton-Smith A, Dantzer E, Habte T, Matata L, Nanyumba D, Okwir M, Posada M, Sebsibe A, Nicholson J, Marasciulo M, Petzold M, Källander K. *Performance, acceptability and usability of respiratory rate timers and pulse oximeters when used by frontline health workers to detect symptoms of pneumonia in sub-Saharan Africa and Southeast Asia: study protocol for a two-phase multisite mixed methods trial.* JMIR Protocols, 2019, Mar 7;8(3):e13755. doi: 10.2196/13755.

CONTENTS

LIST OF ABBREVIATIONS

ARIDA	Acute Respiratory Infection Diagnostic Aid
ARI	Acute Respiratory Infection
BHI	Boma Health Initiative
BPM	Breaths Per Minute
CDD	Community Drug Distributor
CHW	Community Health Worker
FLHFW	First-level Health Facility Worker
HEWs	Health Extension Workers
HEP	Health Extension Programme
MoH	Ministry of Health
HEW	Health Extension Worker
iCCM	Integrated community case management
IMCI	Integrated management of childhood illnesses
PHC	Primary Health Care
RR	Respiratory Rate
SNNPR	Southern Nations, Nationalities, and Peoples' Region
SpO2	Oxygen Saturation
UNICEF	United Nations Children's Fund
VHT	Village Health Team
WHO	World Health Organisation

1 BACKGROUND

1.1 PNEUMONIA EPIDEMIOLOGY, AETIOLOGY, PREVENTION AND CONTROL

Pneumonia is the leading cause of post-neonatal death in children under-five years, accounting for an annual 944,000 deaths globally; 15% of all under-five mortality worldwide (see Fig.1). Sixty percent of these deaths occur in ten countries in South Asia and sub-Saharan Africa (2), most facing significant challenges in the provision of effective health care, diagnosis and treatment. Pneumonia deaths in children result mostly from late presentation to appropriate care providers, inappropriate treatment or unrecognised symptoms (3). Most cases of pneumonia could be prevented by better nutrition, environmental improvements and new vaccines (4). Even when caregivers may recognise rapid breathing in a coughing child, this may not always prompt them to seek care, resulting in delays and potential development of severe disease (3, 5, 6).

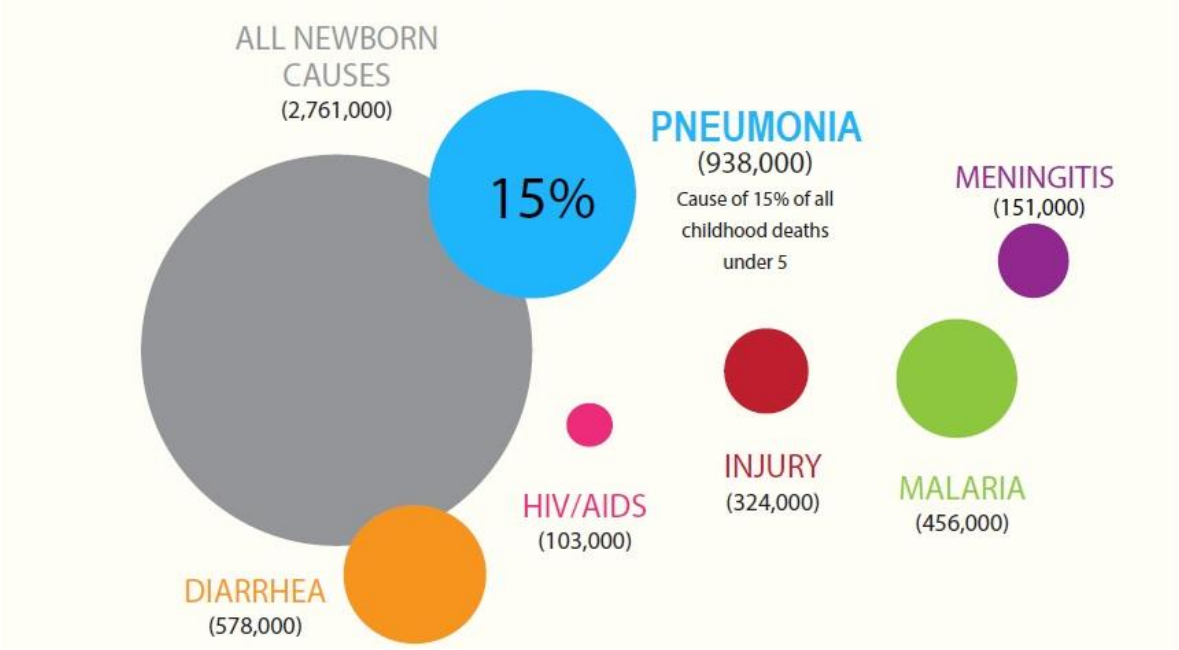


Figure 1 Causes of childhood deaths (Source: WHO Global Health Observatory, 2016)

The term pneumonia is usually used in the broader sense to refer to severe acute infections of the lungs by viral, bacterial, and other pathogens (4). Historically, Streptococcus pneumonia (pneumococcus) and Haemophilus influenza (usually type B or Hib) are the leading bacterial causes of pneumonia (7), and respiratory syncytial virus the leading viral

cause (4). Previous studies of the aetiology of childhood pneumonia in low income countries provided similar findings (8). However, the most recent evidence suggests that this is no longer the case, most probably due to the introduction of pneumococcal conjugate vaccine (PCV) and Hib vaccine, and highlights that it is now respiratory syncytial virus (RSV) that is the main cause of severe pneumonia (9).

Pneumonia symptoms include sudden onset of cough, fever, fast and difficult breathing, vomiting, convulsions and chest in-drawing (4). Pneumonia is characterised by inflammation of the alveoli and terminal airspaces in response to invasion by an infectious agent introduced into the lungs. Pneumonia is responsible for stuffing the alveoli with fibrous sticky liquid hindering the exchange of oxygen and carbon dioxide in the blood, resulting in depleted oxygen levels, increased levels of CO2 and faster breathing in the affected individual. World Health Organisation (WHO) defines non-severe pneumonia as any child with cough or difficult breathing who has fast breathing and no general danger signs, no chest in-drawing and no stridor when calm (10).

Effective vaccines against *H. influenza b* (Hib) are now widely available and continue to be rolled out in resource-poor settings, thereby reducing the total number of bacteria cases being seen. As there are more than 90 serotypes of pneumococcal bacteria, and the pneumococcal conjugate vaccine (PCV13) protects against only 13 of them, continued progress to further reduce pneumonia mortality is restricted by the absence of vaccines against the remaining required serotypes (11). Other protective and preventive measures, such as breastfeeding, measles vaccination and reducing indoor air pollution are equally important and recent studies have highlighted the need to adjust treatment algorithms to emphasise supportive care (9). Amoxicillin, an inexpensive antibiotic which can be administered at home, can effectively treat the majority of pneumonia in children in countries with high infant mortality of bacterial origin, mostly caused by Streptococcus pneumoniae or Haemophilus influenza (12). However, the efficient supply of drugs to frontline health workers has often be reported as a major issue in the effective case management of pneumonia in these settings (13).

1.2 CASE MANAGEMENT OF PNEUMONIA

The WHO Acute Respiratory Infection (ARI) Technical Advisory Group in March 1982 defined that case management of pneumonia remained the central strategy to reduce significantly, at least in the short term, the ARI-associated mortality in young children in low income countries. The group recommended a simple protocol for discrimination of pneumonia in places where X-Ray technology was not available. The protocol was developed on the basis of field investigations by Shann et al at the WHO Collaborating Centre in Papua New Guinea (14). The protocol included three objective clinical signs that were discriminatory and easy to observe: Cough plus fast breathing (non-severe pneumonia) and chest in-drawing (severe pneumonia) (14). Kumar et al successfully tested the protocol in a rural community in India (15), and the protocol was adopted globally.

Today, children with respiratory infections requiring antibiotic treatment at home or referral care are still recognised using clinical signs (rapid respiration, nasal flaring, central cyanosis and lower chest in-drawing) that can be learned and used by health workers with limited clinical training and no capacity for laboratory investigation or radiology (16). For the foreseeable future, WHO have stated that the presumptive case management of childhood pneumonia will remain an important strategy in reducing under 5 mortality. The Global Action Plan for Prevention and Control of Pneumonia (17) outlines some key interventions: case management at all levels (including community), vaccination, prevention and management of HIV infection, improvement of nutrition and reduction of low birth weight, and control of indoor air pollution. Community-level interventions have an important contribution to make through improving accessibility, uptake and appropriate use of services. Evidence has shown that correct pneumonia case management alone of infants and preschool children by community health workers (CHWs) resulted in a 36% reduction in pneumonia mortality (12). However, the necessity of targeting not only pneumonia but also other important causes of childhood illnesses (especially malaria and diarrhoea) in an integrated way has also been recognised (12, 18). Additionally, within the community it has been shown that increasing the number of illnesses CHWs treat increases demand for their services (19).

Integrated community case management (iCCM) is an approach recommended by WHO, United Nations Children's Fund (UNICEF) and partners where CHWs are trained to identify and treat symptoms of pneumonia, malaria, and diarrhoea in children under-five years, as

well as to detect and refer malnutrition and severely ill children to the nearest health facility (20). Evidence from African countries shows that CHWs, if properly trained and equipped, can potentially reduce child deaths from malaria, pneumonia and diarrhoea by up to 60 percent through the delivery of iCCM (21-23).

Children with severe pneumonia often have chest in-drawing, a symptom which some health care workers are not able to adequately recognise and subsequently treat or refer for necessary antibiotic treatment and oxygen therapy (24). Low blood oxygen saturation, or hypoxaemia, is a symptom of severe pneumonia that has been identified as a predictor for morbidity and mortality in children with respiratory illness (25). However, hypoxaemia is poorly identified based on clinical findings alone (26), and the inability of health care workers to promptly detect and refer these children, whose lives are in danger, leads to the death of many children. Pulse oximeters are an established technology in resource rich settings, which uses differential light absorbance technology to measure SpO2 and derives pulse rate (PR), and perfusion index (Pi) from the photo plethysmography waveform created when a light probe is attached to a finger or toe (27). While pulse oximetry is a reliable and non-invasive method for identifying children with hypoxaemia, pulse oximeters are rarely available outside of higher-level facilities in resource-constrained countries (28).

1.3 THE CHALLENGE WITH PNEUMONIA DIAGNOSIS

Pneumonia diagnosis by health workers includes counting the number of breaths for 60 seconds in children with history of cough and/or difficulty breathing to assess whether the respiratory rate (RR) is higher than the normal parameters for a child of that age, as defined by WHO (29). In the late 1980's, the WHO and UNICEF issued a call for the development of a one-minute acute respiratory infection (ARI) timer to assist health workers and CHWs in measuring the length of time to count the RR in children, as they felt that a timer was essential to count the frequency of the child's respiratory movements to determine whether a child with cough has fast breathing. The specification was for one-minute timer, which produced an audible alarm after 30 and 60 seconds and was non-corrodible, waterproof, last for a minimum of 5,000 uses, was suitable for storage and use at extreme temperatures and high levels of humidity by health workers with different levels of training. In 1989, UNICEF distributed these specifications to manufacturers in different parts of the world who might be interested in developing such a timer, at a cost affordable to low income countries. Field tests of three potential devices took place in 1990 with the collaboration of the Johns Hopkins University in The Gambia; the Survival for Women and Children Foundation (SWACH) in

Chandigarh, India and the John Snow International/Intercept, Boston, in Nepal. In addition, assessments were made by consultants in Bolivia and Egypt (30). In all the studies, the village health workers and auxiliary nurses found it much easier to learn to use the timing devices to count the respiratory rate than to use a watch with digital display or a second hand. The British Standards Institute at Hemel Hempstead, Hertfordshire carried out independent laboratory tests according to a protocol prepared in collaboration with Ashdown Consultants, Hartfield, in the United Kingdom, regarding reliability in adverse climatic conditions and physical robustness. These tests identified problems in the functional adequacy and performance of the three prototype devices. The manufacturers received recommendations to introduce improvements in their models (30). In 1991, two new prototype timers were submitted for laboratory testing but neither model met the exact standard requirements. Detailed technical reports were returned to the manufacturers. Several months later one of these models, coming from China, was successfully tested (31). The designer of this model was assisted to increase its capacity to produce a large amount of timers. UNICEF negotiated the mass production and the price. A first lot of 25,000 pieces was produced at the end of 1992 and 40,000 more were ordered for 1993 (32). Even with the deployment of the ARI timer counting RR continued to prove challenging to trained health workers and misclassification of the observed RR remained high (5, 33-36), partly due to difficulty in not losing count and also distracting device characteristics such as a ticking sound every second (37).

1.4 DIAGNOSTIC DEVICES TO AID DETECTING SYMPTOMS OF PNEUMONIA

In medical settings, respiratory rate counters and pulse oximeters are not referred to as "diagnostic" tools for pneumonia, because heightened respiratory rates and low oxygen saturation levels can occur in many diseases. However, an elevated respiratory rate in children with cough and/or difficulty breathing has been shown to be predictive of pneumonia and is used in the iCCM/IMCI context by frontline health workers to identify suspected pneumonia. If pulse oximetry is incorporated into future community level pneumonia guidelines, hypoxia will likely be a diagnostic indicator of severe illness and requiring referral to a health facility where oxygen is available. For these contextual reasons the devices in this thesis are referred to as pneumonia diagnostic aids.

Since the launch of the ARI timer, different types of diagnostic aids have been developed to support low literate frontline health workers, consisting of both CHWs and first level health facility workers, to assess and classify symptoms of pneumonia. The first studies published

in peer reviewed journals on tools to aid counting for pneumonia diagnosis are from 1991 in Gadchiroli, India, where trained traditional birth attendants (TBA) who used a simple device - a breath counter abacus - more often classified children correctly compared to those using visual judgment of tachypnoea (38, 39). The researchers noted several constraints in using the abacus, including the inaccuracy of the built-in sandglass and the fact that TBAs reported difficulties focusing both on the breathing as well as on the timer. However, they still concluded that the device is simple, inexpensive and effective. Often, new pneumonia diagnostic aids have been tested in smaller, under-powered evaluations, and as each study uses different methodologies and measures, results are often hard to compare, as recently highlighted (40).

Identification and evaluation of new diagnostic aids for improved classification of pneumonia ranked fifth of 20 pneumonia research priorities which were identified by a panel of global experts in 2014, and second most important and impactful (41). The wider use of improved pneumonia diagnostic aids in low-resource settings are expected to contribute to more accurate detection and classification of pneumonia (42) and more rational use of antibiotics (43). More recently, and partly in response to the scale-up of large iCCM projects in sub-Saharan Africa and Southeast Asia, new pneumonia diagnostic aids have been developed by industry, academia and other partners to improve the accuracy and effectiveness of detecting symptoms of pneumonia in resource-poor contexts (44). Similarly, wider use of pulse oximeters that are appropriate for low-resource settings are expected to contribute to higher referral rates of children with severe pneumonia (45). This should lead to improved treatment and better health outcomes of children under 5 globally (46). Currently, the routine use of pulse oximetry in children under 5 in these settings is limited (47), despite a recent study demonstrating the successful implementation and use of a pulse oximeter in Malawi (48, 49).

1.5 THE CHALLENGES IN EVALUATING NEW PNEUMONIA DIAGNOSTIC DEVICES

One important step toward introduction of new RR counting devices is to understand their accuracy. There is no established gold standard reference (i.e. the best single test, or a combination of tests, that is considered the current preferred method of diagnosing a particular disease (50)) for evaluating RR counters (51). Reference standards that have been used by others include using a trained and standardised medical professional who counts RR with the ARI timer or use auscultation to count the RR simultaneously (5), electronic monitoring using capnography (52) or review of recorded videos of the child being assessed

(53, 54). However, all these methods have limitations. While the option of using trained people doing a physical assessment, either by counting chest wall movements or by auscultation of breath sounds with a stethoscope, is currently the most common method for RR measurement in general practice, studies have shown manual methods to be unreliable (40). Even trained health workers sometimes struggle to conduct respiratory rate counting by observation of abdominal and chest wall movement, and counts obtained by auscultation have shown to be on average 14 breaths per minute higher than those obtained by observations (53).

Using videotaped children whose breathing rates have been established by expert panels to which exploratory devices are compared against, could be one way of increasing the robustness of the measurement (54-56). This methods was used as reference standard in a previous study by Gan et al (57) and while it was found to be a rapid and robust way to compare the accuracy of different manual RR counting aids, it may not be a suitable method for testing of more advanced tools, such as automated devices (e.g. accelerometers, acoustic sensors, lung ultrasound) and combined RR and pulse oximeter devices which need to be tested on real children. Another suggested methodology to increase the accuracy of RR count, established by Simoes et al (58), is to let observers count breaths for 30 plus 30 seconds, instead of for a full minute. Pneumograms and other electronic monitoring devices have been used as reference standards with varying success (58, 59) but similar to stethoscopes, they appear to pick up small breaths that are not appreciated when observing for chest or abdominal movement (53). However, new promising electronic monitoring devices have recently become available on the market, such as the non-invasive Masimo's Radical-7 pulse oximeter device (60) connected to the Phasein ISA CO2 capnography (61) to obtain oxygen saturation level (% SpO2) and RR, respectively.

Further difficulty is caused by the lack of standardisation around the use of metrics for evaluating the performance of pneumonia diagnostic aids. Recent evaluations have highlighted the difficulty in reviewing and comparing previous RR accuracy evaluations, as the wide variation in statistical methods of comparison hinders direct comparison of device performance across the different studies and methods (40).

1.6 COUNTRY SELECTION FOR THESE STUDIES

Four countries were selected to conduct data collection in the different sub-studies, based on their pneumonia prevalence, activity community health worker programme and differing demographics and abilities of community health workers in each country (see Table 1).

1.6.1 Cambodia

Cambodia, a country in the western pacific region, has an under-five population of 1,713,221 children with a 37.9 under-five mortality rate (62). About 47% of children die before they turn 28 days old. Pneumonia is the leading cause of death in children between 1 and 59 months of age (28%), followed by other conditions (18%). Between 2005 and 2010, the country saw a slight increase of suspected pneumonia children taken to health facilities, however only an estimated of 40% of pneumonia suspected children received antibiotics (63). Mortality rates are also much higher in rural than urban areas, and rates vary by province. This large disparity among rural household reflects the poor access to effective care for rural children.

The national policy, approved by the MOH in late 2011, provided a general framework for health workers introducing ORS and zinc guidelines and distribution plan. A five-year strategy was piloted to supplement the national policy to integrate diarrhoea and pneumonia at the health facility level. The updated clinical guidelines, adapted from the UNICEF/WHO Integrated Management of Childhood Illness (IMCI) guidelines, incorporated proven yet underused interventions for the prevention and clinical management of both diarrheal disease and childhood pneumonia (62).

In Cambodia, village malaria workers (VMWs) were first introduced in June 2001 as part of an insecticide treated bed net (ITN) trial conducted by the national malaria centre of Cambodia (CNM) in Ratanakiri Province. Between 2004 and 2005, the VMW scheme was rolled-out to cover 300 villages (64). Then, in 2006 Pharmaciens Sans Frontières (PSF) in collaboration with CNM, the Ministry of Health's (MoH) department for Communicable Disease Control-IMCI and the WHO implemented a pilot project in 52 remote villages in Stung Treng Province to assess the feasibility of adding case management of acute respiratory tract infections (ARIs) and diarrhoea in under-fives to the scope of work of VMWs. VMWs were trained to treat simple coughs, colds and diarrhoea as well as uncomplicated cases of pneumonia and to refer severe cases to the nearest health facility. Three different approaches were tested by randomly selecting VMWs to manage: malaria and ARIs; malaria and diarrhoea; or, malaria, ARIs and diarrhoea. Although a detailed comparison of feasibility and

efficiency within the three intervention groups was never fully assessed, findings indicated that it was feasible for these 'expanded VMWs' (eVMWs) to treat all three illnesses given proper training (64).

VMWs regularly reported to the local health facility staff who supervised and supplied commodities for the work. Malaria has rapidly declined in all areas but pneumonia and diarrhoea remained major causes of U5 mortality. The MoH was willing to expand the coverage of these eVMWs and included diagnosis and treatment of pneumonia using the UNICEF ARI respiratory timers and pre-packaged antibiotics, and included ORS and zinc for diarrhoea (64). So far 800 eVMWs from 400 malaria at-risk villages have received a two-day training in classifying and treating children with pneumonia, and how to refer children with symptoms of severe disease. These eVMWs were distributed in 10 provinces across the country, most predominantly in Ratanakiri (270), Stung Treng (104) and Kratie (100) provinces. A study conducted in 2014 in Cambodia showed that despite their utility, oxygen and pulse oximetry may be underused in Cambodia (65).

1.6.2 Ethiopia

Ethiopia, the second most populous country in Africa, has an under-five population of 14,250,000 children with an under-five mortality rate of 64.4/100,000. The country's 2011 Demographic Health Survey indicated only 27% of under-five suspected pneumonia children were taken to a health facility/provider. An estimated 8% of pneumonia suspected children received antibiotics in 2011, a very slight increase from 2005 (66). Ethiopia developed the national implementation plan for community case management (CCM) of common childhood illnesses in 2010. The overall goal of this implementation plan was to ensure the greatest possible reduction of mortality in children less than five years of age in order to achieve the MDG 4 by 2015. Looking into the health service utilization and health problem of the country, the Ethiopian government introduced "Accelerated Expansion of Primary Health Care Coverage" and the Health Extension Programme (HEP). This health policy focused mainly on providing quality promotive, preventive and selected curative health care services in an accessible and equitable manner to reach all segments of the population, with special attention to mothers and children. The policy had a particular emphasis on establishing an effective and responsive health delivery system for those who live in rural areas. At the community level, in addition to Health Extension Workers (HEWs), there were also groups of Voluntary Community Health Workers (VCHW) created, and who worked in collaboration with HEWs to extend contact with families and the community.

The HEP was a defined package of basic and essential promotive, preventive and selected high impact curative health services targeting households. Based on the concept and principles of Primary Health Care (PHC), it was designed to improve the health status of families, with their full participation, using local technologies and the community's skill and wisdom. HEP was similar to PHC in concept and principle, except HEP focused on the community level and was implemented by HEWs. The Federal Ministry of Health and regional health bureaus were involved in formulating policy and guidelines for the HEP as well as provision of financial and technical support. HEWs must be women aged at least 18 years with at least a 10th grade education. HEWs were selected from the communities in which they reside in order to ensure acceptance by community members. Following selection, the HEW completed a one-year course of training which includes coursework as well as field work to gain practical experience. Components of the HEP included disease prevention and control, family health, hygiene and environmental sanitation, health education and communication (67). More recently, with the support of UNICEF, HEWs were trained on iCCM and equipped to properly assess, classify and manage pneumonia, malaria, diarrhoea and severe acute malnutrition. As of May 2017, 37,000 HEWs had been trained in iCCM. HEWs did not use any special devices to diagnose pneumonia. Instead, the government had provided watches to HEWs that clearly display seconds for counting of breathing rate. HEWs are able to treat fast breathing with amoxicillin (68).

Currently, in all the rural kebeles of most regions including the Southern Nations, Nationalities and People's Regional State (SNNPRS), more than 85% are at full scale of implementation of the HEP. Nationally, more than 3,500 health workers and districts HEW focal persons have been trained and engaged in supervisory activities. According to the 2016 Ethiopia Health Indicator Report, the total number of HEWs who were active in SNNPR was 12,353 (69).

In 2019, a retrospective cross-sectional study conducted in 14 hospitals in Ethiopia showed low utilization of pulse oximetry (10%) in hospitalized children under five with pneumonia (70). The finding likely reflects the low availability of pulse oximeters and low awareness of healthcare workers to routinely use pulse oximeters during triaging and diagnosing of patients. In Ethiopia, patients under five with a primary diagnosis of pneumonia are rarely screened for hypoxemia with a pulse oximeter, and hypoxemia may be severely under diagnosed (70). In addition to functioning pulse oximeters, children with hypoxaemia need

to be referred to hospitals for oxygen therapy; however, access to oxygen is inconsistent across most referral facilities in Ethiopia (71).

1.6.3 South Sudan

South Sudan, one of the world's newest countries, has an under-five population of 1,785,000 children with neo-natal deaths at 43% (72). A larger proportion of children die in the 1-59 months' age bracket (60%) and a slightly higher proportion of those children between 1-4 years of life. 28% of post neonatal children are affected with pneumonia and 18% die of other conditions. The 2018 South Sudan Countdown Report showed 48% of under-five suspected pneumonia children were taken to a health facility/provider and only 33% received antibiotics (72). In order to combat the high child mortality rates iCCM has been implemented in South Sudan since 2005. By 2019, the iCCM programme was implemented in 60 of the 79 counties with support from international NGOs. iCCM in South Sudan is built into the Community-Based Child Survival programme, which is part of the MOH's 2009 Community Child Survival implementation guidelines "Community Based Management of Malaria, Pneumonia & Diarrhoea". This guideline clearly indicated the elements of the community health package for malaria, diarrhoea and pneumonia, the treatment regimen and content of training for community drug distributors (CDDs). The majority of CDDs were illiterate and female, were considered volunteers as they only receive in-kind incentives for participating in the programme, were nominated by their communities, and served between 20 to 40 households. Each CDD maintained a box of supplies which includes a month's supply of drugs, assessment and diagnostic tools (ARI timer and counting beads), job-aids, patient registers, and basic supplies such as scissors and pens (73). CDD supervisors were paid staff recruited from the catchment areas they are assigned to supervise and oversee 15 to 20 CDDs, and move throughout the county primarily on foot, also restocking the CDDS with drugs and supplies (73). In March 2017, the Republic of South Sudan launched the Boma Health Initiative (BHI), a nationwide strategy to improve access to essential health services. It was designed to standardise the package of community health services, strengthen linkages between communities and primary health facilities, and improve community ownership and governance of health services.

There is little data on the availability of pulse oximetry and oxygen supplies in South Sudan, but in our work in country for this thesis we did not see functioning devices in any of the health facilities we attended.

1.6.4 Uganda

Uganda is an East African country with a population of approximately 37.85 million based on the 2014 census (74). Uganda has an under-five population of 7,115,000 children with an under-five mortality rate of 66 deaths per 1,000 live births (75). Pneumonia, again, is the leading cause of these deaths (21%) with malaria being the second leading cause (19%), while 31% of neonatal deaths are caused by premature births. The most recent health survey data indicated 79% of under-five suspected pneumonia children were taken to a health facility and 47% received antibiotics. A clear increase occurred in health seeking practices amongst children with suspected pneumonia from 2000 to 2011 (75).

The Ugandan health system is composed of public, private and not for profit providers as well as traditional medicine providers, with overall 5,229 health facilities (76). In Uganda MoH has implemented the Village Health Team (VHT) concept since 2006, and in 2010 the iCCM strategy was added to the VHT responsibilities (77). In the VHT concept, every village in Uganda (which is the lowest administrative unit) is supposed to have five community health volunteers. These five volunteers are selected by the village itself, following pre-set criteria, are trained in a five day basic package following which they are supposed to mobilize their community members for health action across a wide of health prevention and promotion interventions including malaria prevention, water and sanitation and family health. Two of the five VHT members are further selected against other criteria and trained in a six day iCCM package, and subsequently equipped with a box with selected primary medicines (Color coded Coartem, rectal artesunate, colour-coded Amoxicillin, zinc and ORS) and a register to manage children with signs of uncomplicated malaria, pneumonia and diarrhoea and refer children with signs of severe illness. VHT do follow up visits on the third day to ensure that children are improving and complying with the prescription. For new-borns, the VHTs do home visits on day one, three and seven to identify danger signs and refer as indicated. The standard UNICEF ARI timer is used to guide counting of respiratory rate in children with cough. By 2015 Uganda had deployed more than 30,000 VHTs in approximate one-third of the country (about 30 districts) (78).

Availability of pulse oximetry and access to oxygen is low in Uganda, with a survey of hospital facilities in Uganda has previously shown that 65–76% of operating theatres in Uganda do not have pulse oximeters (79).

Table 1 Country profiles for each research sites in relation to pneumonia diagnosis and treatment statistics at community level

	Cambodia	Ethiopia	South Sudan	Uganda
Pneumonia deaths (% of total under 5 deaths [17])	17%	17%	21%	16%
Pneumonia incidence in under 5s (number of episodes/child/year) [18]	0.25	0.28	0.32*	0.27
Proportion of children <5 with suspected pneumonia received antibiotics [19]	39%	7%	33%	47%
Name for CHWs	Extended village malaria worker (eVMW)	Health extension worker (HEW)	Community drug distributor (CDD)	Village health team member (VHT)
Length of initial training	5 days (2 days malaria training + 3 days sick child case management)	1 year	6 days	11 days (5 days basic training + 6 days sick child case management)
Literacy level	Low	High	Extremely low	Low-median
Current pneumonia diagnosis tool	ARI timer	Wrist watch /ARI timer	ARI timer + beads	ARI timer
Catchment population per CHW	130-150 households	400-500 households	250-300 households	250-500 households
Average case load per month	8	12	9	12

* Data is for Sudan

2 RATIONALE FOR THESE STUDIES

This thesis originated with the idea that while there had been work done to show that the iCCM intervention was effective and feasible in low resource settings (35, 80), and specifically evaluations done on the pneumonia elements of the iCCM algorithm (81), no large scale studies focused on pneumonia diagnostics aids have been conducted in these settings and populations. Additionally, while the issues with the current standard practice diagnostic aid, the ARI timer, are well documented in the literature (40, 82, 83), there is a need to broaden the focus, and investigate the usability of other types and classes of potential diagnostic aids, notably pulse oximeters. While there have been some recent studies done on the use of pulse oximeters in these settings (84-87), none have comprehensively looked at the performance and utility of pulse oximetry in these settings.

From a health systems perspective it is not clear from the current literature where best new diagnostic aids should be situated or implemented for maximum effectiveness. While some work has been done, for example, on the cost effectiveness of introducing pulse oximetry at scale (45), no data existing on its relative utility or performance at the different levels of health systems in these settings.

From a methodological perspective, as potential new technologies are introduced it is important to have a robust and established method to evaluate their performance, in a consistent and generalizable way. There is an ongoing discussion in the literature on the need for this (40, 51). This thesis should add to this discussion and provide learnings on how best to develop a reference standard and conduct these types of evaluations in the future.

Effective interventions have often failed due to poor acceptability and a lack of awareness of stakeholder opinions (88). In documenting the factors that CHWs and national stakeholders feel influence the introduction of these types of technology at scale we hope to better support their future introduction.

3 CONCEPTUAL FRAMEWORK

Multiple frameworks exist for the introduction of new technologies or innovations. For this thesis we developed a framework (see Fig. 2) adapted from the WHO Health technology assessment of medical devices (89) and Mytton et al's introducing new technology safely (90). The WHO first developed a model to reflect the types of research questions that must be answered for the coherent introduction of technologies, especially medical devices, into health systems. These start with the need for the technology to be safe for its intended use, followed by being accurate and finally acceptable and usable to its intended users. Further to this, our framework reflects the special considerations that need to be addressed when introducing new technology in low-resource settings.

Stage 1: The first stage in the introduction of a new technology is typically where formative research is used to understand the current situation and evaluate possible technologies for further testing. Sub-study I used a human centred design (HSD) approach that engaged end-users and national stakeholders in helping us to understand their perceptions of the important attributes in potential pneumonia diagnostic aids (91). Also in this stage we conducted formative research with CHWs and national stakeholders to support the device selection process, where we used a ranking and scoring process to select the nine devices for field testing from a possible 188 devices (92). The safety of the new technologies also needs to be tested at this stage. In this regard we conducted laboratory testing of the technologies that had not be tested in these environments before, i.e. the pulse oximeters.

Stage 2: Once suitable potential technologies have been selected for further testing, the next stage is then to look at their performance in these settings. In sub-study IIa and IIb we looked at performance of the devices in measuring RR and SpO2 in comparison to reference standards.

Stage 3: Subsequently, the suitability for the setting was investigated when in sub-study III the nice devices were tested for utility, usability and acceptability in routine practice over three months. In looking at acceptability we used the theoretical framework of acceptability developed by Sekhon et al (93), which defined acceptability as " a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experiential cognitive and emotional responses to the intervention". The authors further define seven component constructs of acceptability as: affective attitude, burden, ethicality, intervention coherence, opportunity costs, perceived effectiveness and self-efficacy.

Stages of introducing a new technology

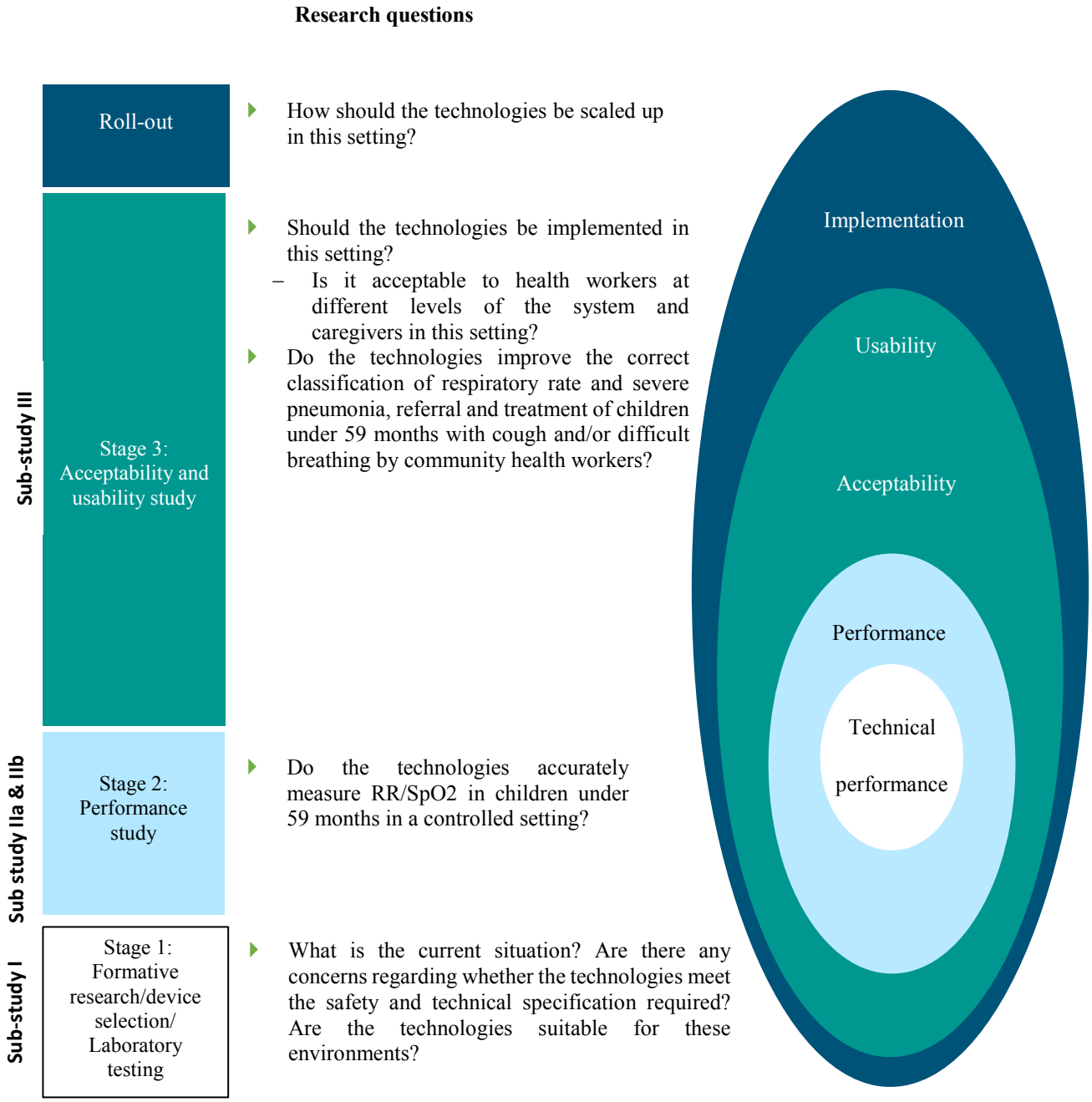


Figure 2 Stages of introducing a new technology - adapted from 'Health technology assessment of medical devices' [15] and 'Introducing new technology safely' [16].

4 AIMS AND OBJECTIVES

General aim

To identify and evaluate the most accurate, acceptable and user-friendly respiratory rate timers and pulse oximeters for diagnosis of pneumonia symptoms in children by frontline health workers in low-resource settings.

Specific objectives

Objective 1: To explore the perspectives of CHWs and national stakeholders regarding the potential usability and scalability of potential pneumonia diagnostic aids to aid community assessment of pneumonia signs (Sub-study I – Paper 1).

Objective 2: To measure the performance of four RR counters to diagnose fast breathing as a sign of pneumonia when used by frontline health workers in Sub-Saharan Africa and Southeast Asia. (Sub-study IIa – Paper 2)

Objective 3: To measure the performance of five pulse oximeter devices to measure oxygen saturation as a sign of severe pneumonia, when used by frontline health workers in Sub-Saharan Africa and Southeast Asia. (Sub-study IIb – Paper 3)

Objective 4: To explore the usability and acceptability of RR counters and pulse oximeter devices as perceived by caregivers and frontline health workers in Sub-Saharan Africa and Southeast Asia. (Sub-study III – Paper 4)

5 METHODS

5.1 STUDY AREA AND POPULATION

This was a series of multi-country studies implemented in Cambodia, Ethiopia, South Sudan and Uganda. All four countries have a high proportion of under-five deaths caused by pneumonia (16-20%) and all are implementing ministry of health defined iCCM and IMCI programmes. However, characteristics of the health worker programmes differed by country, such as length of training, literacy level and current pneumonia diagnostic devices used (see table 1).

For sub-study I, formative research, focus group discussions were held in each of the countries. The study sites selected for conducting sub-study IIa & IIb were all district hospitals selected after analysis was conducted on patient flow to understand if the individual research sites could support the sample size required by the study for enrolment (see Table 2). For sub-study III a sample of frontline health workers who took part in the previous sub-studies were selected, and all lived within 20 kilometres of the hospitals used in sub-study IIa & IIb.

Table 2 Demographic characteristics of the study sites in Cambodia, Ethiopia, South Sudan and Uganda

Description	Cambodia Ratanakiri province	Ethiopia Dale & Shebedino Districts SNNPR	South Sudan Aweil district Northern Bahr el Ghazal State	Uganda Mpigi district
Population	184,000	529,041	128,295	250,548
Under 5 population n (%)	37,720 (21)	82,582 (16)	25,000 (19)	51,363 (21)
No of CHWs	270	161	1683	650
No of health centres	23	19	20	39
No of hospitals	2	2	1	1

The specific study sites (see Fig. 3) were Mpigi Health centre IV, approximately 45 miles from Kampala in Uganda; Yergalem District Hospital in Southern Nations and Nationalities and People's Region (SNNPR) in Ethiopia; Borkeo Hospital in Ratanakiri province in Cambodia; and Aweil General Hospital in Northern Bahr el Ghazal state in South Sudan. For sub-study III, frontline health workers were selected based on having participated in sub-study 2 or 3, and were within 20 kilometres from the same health facility used in that sub-study, in order to have access to functioning oxygen equipment and case management of severe illness capabilities.

In Cambodia, the study site was in Rathanakiri province, which is approximately 540 kilometres from the capital Phnom Penh. In Rathanakiri there are 270 CHWs trained in iCCM and each has had 6 days training. They have a low level of literacy and numeracy and typically treat patients in their home.

In Ethiopia, the study site selected was in Dale and Shebedino districts in SNNPR, which are districts of approximately 529,000 people and is approximately 330 kilometres south of the capital Addis Ababa. Yergalem is the capital city of Dale district and the site of the referral hospital we conducted Sub-study IIa and IIb at. There are 19 health centres and 191 HEWs in Yergalem and Sub-study I and III were conducted amongst representative samples of these HEWs.

In South Sudan, the study site selected was in Aweil Centre and West counties in Northern Barh El Ghazal state. This state is in the north of the country, 880 kilometres from the capital Juba. There were 1,683 CDDs trained in the Home Management of Malaria programme, with 955 trained for six days on the full iCCM package. In Aweil the majority of CDDs had extremely low literacy and numeracy, hence within the programme two devices for facilitating the counting of respiratory rate in children with cough were used, the ARI timer and counting beads. The beads were color-coded and in different sizes to distinguish the three age groups.

In Uganda the studies were situated in Mpigi District, located in Central Uganda along the Kampala-Masaka highway, approximately 40 kilometres from Kampala. The district was largely rural but had implemented the VHT strategy longer than all the other districts. The district had a total population of approximately 210,000 with 40,000 children U5. It consisted of 2 counties (Mawokota North and Mawokota South), 9 sub-counties and 332 villages. Mpigi has one referral hospital (HC4), 18 sub-county health centres (HC3), 412 first level health facilities (HC2) and 650 VHTs (HC1) who are all trained in iCCM and actively supported by

Malaria Consortium. Between February 2011 and March 2013 VHTs in Mpigi had detected and treated more than 48,000 cases with fast breathing. VHTs used the ARI timer to support them to count RR in Mpigi.

Map 1 Uganda

Map 2 Ethiopia

Map 3 South Sudan

Map 4 Cambodia

Figure 3 Maps of the study areas highlighting 1) Uganda and Mpigi district, 2) Ethiopia and the Southern Nations and Nationalities and People's Region (SNNPR), 3) South Sudan and the Northern Barh El Ghazal state and 4) Ratanakiri province in Cambodia

5.2 SUMMARY OF RESEARCH METHODS

The different sub-studies in this thesis use a variety of methods as detailed below (see Table 4).

Qualitative research methods

Sub-study I and III used qualitative methods to comprehensively explore participant attitudes and perspectives towards various diagnostic devices. Specifically, in sub-study I, a series of pile sorting exercises and focus group discussions were held in each of the four countries with community health workers and national stakeholders to explore their perspectives on the potential usability and scalability of the proposed diagnostic aids. In Sub-study III semi-structured exit interviews were used to gain the user perspectives on the acceptability of the nine diagnostic aids they had bene using in routine practice.

Pile sorting exercise

Pile sorting is a qualitative method used mainly in social science and health research. It aims to capture participants' opinions or experiences by having them sort cards of words or pictures or items themselves into piles that classify a range of their opinions or categories of interest (94). Conducting a focus group discussion immediately following a pile sorting activity is designed to capture and explore participants' decision-making rationale for their choice and improve the quality and depth of data captured.

Focus Group Discussions

Focus group discussions (FGDs) are widely used in social science and applied research, as a data collection method, to establish opinion trends in selected populations. A FGD consists of seven to ten people, selected based on their common characteristics, relevant to the research question being investigated (95).

Semi-structured exit interviews

Semi-structured, conversational interviews are often used in qualitative research. They may be in-depth or key informant interviews. These are often selected if the topics being discussed are more sensitive or there are concerns that group dynamics may repress or hinder open and frank discussion and limit the quality and scope of the data being collected (95).

Quantitative research methods

Sub-studies II and III used quantitative methods to document the performance and usability of both the four RR counters and the five pulse oximeters in hospital and community settings.

Cross sectional surveys

Cross-sectional surveys are descriptive study designs in which a sample of a reference population, in this case children under five years of age, are examined at a given time point or over a short period of time. These types of studies can provide a snap-shot of the study outcome, together with any associated characteristics. These types of studies are used to estimate the prevalence of an outcome and generate hypotheses for future research studies. However, due to the potential for timing bias, they cannot be used to make causal inferences (96).

Direct observation

Participant observation is often used as a complimentary tool with interviewing. It involves systematically watching and recording behaviour and other characteristics of the user using checklists or other data collection tools. Observation may be passive or active depending on the degree of involvement (95). This can mean participants may change their behaviour as they know they are being watched, this is called the Hawthorne effect (97).

Medical record review

Record reviews use pre-recorded patient data to answer a research question. The records must be able to produce data that are both valid and reproducible. Record reviews are limited by the scope of available and accessible routine data. Ethical considerations in relation to patient confidentiality can sometimes arise, as can data qualitative and validity issues (98).

Table 3 Overview of sub-studies and associated research design, sample size and methods

Sub-study	Design and sample	Setting	Analysis and outcome
I: Childhood pneumonia diagnostics: Community health workers and national stakeholders' differing perspectives of new and existing aids	Qualitative pile sorting exercise and focus group discussions with health workers and national stakeholders (n=16 groups)	Four FGDs were held in Cambodia, Ethiopia, South Sudan and Uganda.	Aggregated pile-sorting data and thematic content analysis was used to identify thematic patterns between countries and groups on their perceptions and needs in relation to diagnostic devices.
IIa: Performance of four respiratory rate counters to support community health workers to detect the symptoms of pneumonia in children in low resource settings: A prospective, multi-centre, hospital-based, single-blinded, comparative trial	Quantitative, observational, hospital-based, cross sectional study n=454 children under 5 years old & 79 community health workers	District hospitals in: 1) Ratankiri, Cambodia 2) Yergalam, Ethiopia 3) Aweil, South Sudan 4) Mpigi, Uganda	Agreement between test devices and reference standard as shown by: • Mean difference • Proportion agreement • Bland Altman plots RR classification agreement shown by: • Kappa statistic and • Positive and negative percent agreement.
IIb: Performance of five pulse oximeters to detect the symptoms of severe illness in children under five by frontline health workers in low resource settings – results from a prospective, multicentre, single-blinded, trial in Cambodia, Ethiopia, South Sudan and Uganda	Quantitative, observational, hospital-based, cross sectional study n=454 children under 5 years old)	District hospitals in: 1) Ratankiri, Cambodia 2) Yergalam, Ethiopia 3) Aweil, South Sudan 4) Mpigi, Uganda	Agreement between test devices and reference standard as shown by mean difference in % SpO2 and classification agreement of hypoxaemia shown by Kappa statistic and positive and negative percent agreement.

III: Acceptability, usability and utilisation of pneumonia diagnostic aids, as perceived by caregivers and frontline health workers, in supporting the detection of pneumonia symptoms in Sub-Saharan Africa and Southeast Asia	Mixed methods, observational, community-based, cross sectional study Direct observation and patient record review n=1291 children under 5 years old and 100 frontline health workers Exit interviews n=40 frontline health workers	Community and health facility settings in: 1) Ratankiri, Cambodia 2) Yergalam, Ethiopia 3) Aweil, South Sudan 4) Mpigi, Uganda	Usability measured through procedures adherence scores Thematic content analysis was used to identify thematic patterns between groups on their perceptions of the acceptability of the devices

5.3 STUDY DESIGNS

5.3.1 Sub-study I

Sub-study I used a qualitative study design with an explanatory approach used a combination of pile sorting activities and focus group discussions (FGDs) to explore the factors that influences the usability and scalability of various types of pneumonia diagnostics devices to frontline health workers and national stakeholders in the four countries. The sample size of qualitative studies is not predetermined but data are collected from participants until no new further information is being captured (99).

The study protocol and data collection tools were developed by the doctoral student in consultation with the principal investigator and the four country research teams at a protocol design workshop held in Kampala, Uganda in autumn 2014. Purposive sampling was used to select participants in each of the four countries for the eight FGDs held with a total of 31 representatives of national and regional ministries, relevant staff from multilateral organizations and NGOs working at regional and national levels. A further nine FGDs, three per country as Uganda was unable to participate due to time constraints, were held with 63 CHWs who were selected from lists of active CHWs with active experience of pneumonia case management in each country. The numbers of FGDs were chosen to achieve maximum thematic saturation amongst both groups of participants, balanced with available time and resources. Before data collection was conducted the discussion guides were translated into the local languages, pre-tested and modified as required. Data collection happened between December 2014 and January 2015 in local language. Seven device types were demonstrated to participants, who were also provided a written explanation of each device functionality and purchase cost. The devices were:

1. The ARI timer (and additional counting beads in South Sudan);
2. A fingertip pulse oximeter;
3. A hand held pulse oximeter;
4. A smartphone application which tracks the breaths counted when the screen is tapped on;
5. A simple feature phone application which tracks the breaths counted when a button is pressed;
6. A pulse oximeter probe attaching to a smartphone;
7. A joint device combining the RR counting application and a pulse oximeter probe using the same smartphone (only shown to some groups in Ethiopia, South Sudan and Uganda)

Individual participants placed cards with various device names into different piles according to their perceived usability, and again for their perceived scalability. The piles were predetermined by the researchers (Table 4). The facilitator recorded the overall pile sorting results (i.e. how many times a device was placed in each pile) into a pro forma results table. Participants were asked throughout the FGDs to explain their choices and give a rationale for their placement of the various devices in the different piles. Each session was digitally recorded with the informed consent of all participants.

Table 4 Definitions of pile sorting categories

Usability	
Pile 1	Able to use the device in the community setting
Pile 2	Able to use the device with reservations in the community setting
Pile 3	Possibly unable to use the device in the community setting
Pile 4	Unable to use the device in the community setting
Scalability	
Pile 1	Feasible to scale up
Pile 2	Feasible with reservations to scale up
Pile 3	Possibly unfeasible to scale up
Pile 4	Unfeasible to scale up

5.3.2 Sub-study II

Sub-study II, was the performance evaluation element of this thesis, and was a multi-centred, single-blinded, comparison of the performance of RR counters and pulse oximeters to detect the signs and severity of pneumonia in the hands of frontline health workers using two reference standards, a continuous monitor and an expert clinician.

The sample size calculation was based on the primary outcome, i.e. the precision of the mean difference between the device and the reference respiratory count, assuming normal distribution. A standard deviation of SD=7 for the difference was obtained in a previous study evaluating the performance of respiratory rate counters [24] and in requiring a maximal total length of the 95% confidence interval of 4 units, which the same range as the WHO accepted maximal absolute breathing rate deviance (e.g. ±2 breaths/min), the minimum sample size was 47 children per strata for independent observations. The two age strata in the study were i) 0 to 60 days and ii) 2 to 59 months, and three devices pairs per country gave a total sample size of

282 children. The sample size was then increased by fifty percent to n=423 and rounded off to 430 children per country to accommodate for potential clustering at health worker level (100).

Figure 4 Data collection for sub-study II in Mpigi Health Centre IV, Uganda

In each country a research team consisting of a research nurse, a research officer, three research assistants and an expert clinician conducted the various enrolment procedures and assessments. All of the CHWs/FLHFWs underwent two days of training on a set of devices, refresher training on how to examine a child/young infant, and used a set of two or three investigational devices each time, to obtain measurements for RR. On consenting to the studying and entering the research room the child was positioned comfortably on the mother's lap and continuous monitor reference attached on the child. Once the child was calmed an assessment was then performed by the CHWs/FLHFW. Two measurements of RR/SpO2 were recorded on a data form, along with the corresponding continuous monitor reference measurements. The expert clinicians then entered the research room and took two measurements using a stopwatch for RR or the same pulse oximeter for SpO2. In the RR cases, the maximum time lag between the measurement of the expert clinician and the CHW/FLHFW was set to not exceed 5 minutes. As an additional comparison, simultaneous Masimo capnography RR measurements were recorded also for the expert clinician. The CHW/FLHFW was asked to classify the child into fast or normal breathing using WHO age-specific cut-offs for RR and hypoxemic or not-

hypoxemia using the pulse oximeters, and their classification was recorded along with the time points for all measurements. During the evaluation, research assistants equipped with a structured checklist observed the CHWs/FLHFWs using the different devices and documented their skills and challenges experienced during the evaluation. In each country data was double entered in EpiData (www.epidata.dk). The cleaned country data sets were then merged and re-structured by the study statistician into a full study data set. The study protocol has been published (101) and the study is registered with the Australia New Zealand Trials Registry (ANZCTR) (Ref: ACTRN12615000348550). A video documenting the study methods can be seen here.[1]

5.3.3 Sub-study III

Sub-study III was focused on the usability and acceptability evaluation element of this thesis. It was a mixed methods, multi-centred, observational study using both qualitative and quantitative data to document the usability and acceptability of devices to detect symptoms of pneumonia in the hands of CHWs and FLHFWs in routine practice. The study incorporating structured observations and checklists, and qualitative exit interviews with a sample of health workers in the four countries. A purposive sample of 100 HWs (5:1 ratio of CHWs to FLHFWs as in the previous performance evaluation element of the trial) were selected from the four countries and represented 33.3% of all health workers recruited for the previous performance evaluation phase of the study. This sampling was representative of gender, age and experience levels while ensuring frontline health workers selected were in close proximity to health centres for oxygen support for severe or referral cases. Health workers were trained for two days to use a RR counter and a pulse oximeter as part of their routine iCCM/IMCI activities. Each health worker had to pass a competency-based assessment before participating in the evaluation.

[1] Here is a link to the protocol video: https://tinyurl.com/y2gt69qy

Figure 5 Sub-study III data collection in Ratanakiri, Cambodia

The study team of two research assistants scheduled visits with each health worker three times (once a month) during the evaluation, each time targeting five assessments of each CHW/FLHFW. All children aged between 0-60 days who presented to CHWs/FLHFWs were included in the study regardless of their symptom status. Children between 2-59 months were only included if they presented with cough or difficulty breathing. Children who had caregivers younger than 18 years were excluded. The health worker took the medical history of the child as per iCCM/IMCI guidelines, and if cough and/or difficulty breathing was present the health worker used the RR device to count the number of breaths in one minute; a procedure that was repeated twice with the highest reading used for RR classification. The observed RR was used by the health worker to decide whether or not to provide treatment for fast breathing pneumonia using the national treatment guidelines. If fast breathing was detected the health worker assessed for hypoxemia using the pulse oximeter by taking two SpO2 readings, using the lowest reading for classification of hypoxemia. All children with signs and symptoms of severe pneumonia and with SpO2 <90% were referred. Paper-based data collection tools were developed to collect data on screening, usability and adverse events. Structured perception checklists were developed for health workers and caregivers. Semi-structured interview guides were developed for the exit interviews with health workers. All completed forms were returned

to the Malaria Consortium office for double data entry using EpiData version 3.1 (EpiData Association, Odense, Denmark) and filed. The qualitative data collection consisted of in-depth interviews with health workers at the end of data collection to capture their views on usability and acceptability. Each data form had a Unique Identification Code (UIC) in order to link data from different forms in the database.

5.4 DATA ANALYSIS

In this section, the data analysis methods applied to the different sub-studies in this thesis are described in terms of their overall principles, strengths and weaknesses. Some of the specific limitations relating to the analysis performed in the different sub-studies are further discussed in section 6.2.

5.4.1 Pile sorting

In Sub-study I pile sorting was used to capture participants' opinions or experiences by having them sort devices into piles that classify a range of opinions or categories of interest around usability and scalability (94). Results from the pile sorting exercises were collated in Microsoft Excel (2011). Comparative analysis was done to show the differences in views by respondent group and country.

5.4.2 Direct content analysis

In sub-studies I and III the audio recording from all FGDs and semi-structured exit interviews were transcribed intro English by the research teams in each country. All transcripts were imported into the qualitative software, NVivo (Version 10 QSR International Pty Ltd; USA 2015) for sorting and coding. Inductive and deductive approaches were used to assign codes to the relevant text. These codes and sub-categories were then categorised and a thematic content analysis was performed (99). The differences and similarities in thematic content between countries and between CHWs and national stakeholders was explored through the use of Comparative interpretation (102).

5.4.3 Descriptive statistics

In sub-studies II and III descriptive analysis to identify basic frequencies were carried out and were reported for each country. Characteristics were described first for health workers and then for children.

5.4.4 Procedure Adherence Score

In sub-study III device usability was reflected by a procedures adherence score, developed for both RR counters and pulse oximeters using device user checklist data. This checklist included tasks such as ensuring if the child was calm, if the health worker used their device correctly along with other recommended tasks to successfully diagnose a child with pneumonia. Six questions were summed to create the RR procedure adherence score (with a maximum score of 6. Eleven questions were summed to create the pulse oximeter procedure adherence score for the handheld and mobile devices. Similar points and coding was followed as above. For these devices, there were 3 questions related to selecting and attaching correct cables to devices. Therefore, the maximum score for the fingertip pulse oximeters was 8, as these devices do not have multiple probes. Mean procedure adherence scores and standard deviations are presented.

Three models, one each for RR counters, fingertip pulse oximeters and handheld pulse oximeters, were developed to identify if a basic relationship existed between procedure adherence and device types. Crude association assessed by linear regression for each model, with each device compared to the same base device; MK2 ARI timer for RR and Contec for fingertip pulse oximeters and Lifebox for handheld pulse oximeters. The MK2 ARI timer was used for RR comparisons because it is the closest representation to current standard practice. Similarly, Lifebox was seen as the closest device to standard practice. P-values along with the 95% confident intervals (CI) were presented.

5.4.5 Bland Altman Plots

In sub-study IIa, to visualise the agreement between a test device and a reference standard Bland-Altman plots were produced (103). Data can be analysed both as unit differences plot and as percentage differences plot (104). The analysis of Bland Altman plots provides a simple way to evaluate any bias existing between the mean differences, and also to estimate an agreement interval, within which fall 95% of the differences of the test device, compared to the reference (105). The plots define these intervals of agreements, but they do not say whether those limits are acceptable or not (106). Therefore acceptable limits should be defined a priori, based on clinical necessity, biological considerations or other study aims and objectives (106).

5.4.6 Agreement statistics

In previous performance evaluations of pneumonia diagnostics different measurement statistics have been proposed to best reflect the performance of the different devices in comparison to the reference standard used (54, 107). In sub-study II(a&b) we followed the

recommendations of the US Food and Drug Administration (108), which state that when evaluating a new diagnostic aid in comparison to a non-reference standard, unbiased estimates of sensitivity and specificity cannot directly be calculated. Therefore, they recommend that the terms sensitivity and specificity are not appropriate in describing the comparative results. They further suggest that the same numerical calculations are made, but the estimates are called positive percent agreement (PPA) and negative percent agreement (NPA), rather than sensitivity and specificity. They suggest this better reflects that the estimates are not of accuracy but of agreement of the new test with the non-reference standard. In addition the recommend that quantities such as positive predictive value, negative predictive value, and the positive and negative likelihood ratios cannot be computed since the subjects' condition (as determined by a validated reference standard) is unknown.

5.4.7 Cohen's Kappa statistic (κ)

Cohen's Kappa statistic (κ) was developed and most often used to measure interrater agreement, while also accounting for chance (109), and because of this we included this statistic in our analysis in sub-study II (a&b). In interpreting Kappa (κ) values Altman recommends intervals of agreement as follows: <0.20 as poor, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as good, and 0.81-1 very good (105).

5.5 ETHICAL CONSIDERATIONS

Studies in this thesis originated from a grant funded by Bill & Melinda Gates Foundation entitled "Use of improved tools for measuring respiratory rate and oxygen saturation among community health workers: Sub-Saharan Africa and South-East Asia". The project was implemented by Malaria Consortium, with Dr Karin Källander as principal investigator.

The studies was approved by ethical review boards in each study country at national or regional level - in Ethiopia from the Southern Nations Nationalities Peoples' Region Health Bureau Health Research Review Committee (Ref: 6-19/10342); in Uganda, from the Uganda National Council for Science and Technology (UNCST) (ref. HS 1585); in South Sudan from the Research and Ethics Committee at the Government of South Sudan, Ministry of Health (Dated 23/05/2014); and in Cambodia from the National Ethics Committee for Health Research (Ref: 0146 NECHR), Ministry of Health, and by the Regional Ethics Committee in Stockholm, Sweden (Ref. 2017/4:10).

Written informed consent was obtained from all research participants who provided primary data in all elements of data collection, both quantitative and qualitative. National, regional and local stakeholders in each of the four countries were engaged and updated on all aspects of the study before data collection commenced.

While all protocols and study sites had made provision for adverse events, as all test devices were non-invasive, this was deemed a very low-risk trial. On the recommendation of the scientific advisory committee, trials insurance was put in place for the duration of data collection in each of the four research sites. No adverse events were reported during or after data collection.

5.6 DEVICE SELECTION

To select the test devices several activities were conducted prior to the field trials. In the initial landscape review 188 possible diagnostic aids were identified (110). These devices were further evaluated by a technical expert to review their technical specifications in relation to the specific research settings (111). Thirdly, all potential devices were scored and ranked using 20 device attributes, including measures of usability, utility, scalability and user acceptance. Full details of the attributes can be found in Appendix 1. In contrast to the respiratory rate counters identified, the eight selected pulse oximeters had not previously been field tested in these settings, and therefore, before conducting the field trials they were first tested in a laboratory for accuracy and environmental robustness. Based on the laboratory test results a final nine devices were taken forward to the performance evaluation phase (Fig. 6), i.e. four respiratory rate devices (manual and assisted counters) and five pulse oximeters (fingertip and handheld devices) (112).

Mark Two Acute Respiratory Infection timer (Model: MK2 ARI): This manual counting device has a push button to start the timer, a flashing light to show it is counting and a beep sound at the end of 60 seconds. Battery operated, with a stated a lifespan of 2 years. The health worker uses this device to count 60 seconds while manually counting the RR of the child through observation of the child's chest area. In a previous study in Zambia frontline health workers were shown to have 46% with the reference standard, a medical professional counting RR manually for 60 seconds (81). The cost of this device is approx. $5. The cost of this device is approx. $5. Dimensions: 10mm X 20mm X 5mm. Weight: 20g	
Beads with ARI timer: The beads are used in conjunction with the ARI timer to support the health worker to count RR by moving a bead along each time they see a chest movement. Health workers have three sets of beads, one for each RR cut-off age group, each containing 40, 50 or 60 beads of one colour (blue in the picture) and five beads of another colour (red in the picture) respectively. If the health worker finishes counting on a red coloured bead in the picture they should classify the child as having fast breathing pneumonia.	

In one study in IRC the use of beads increased the correct classification from 13% to 63% (36). The approx. cost for these two devices are $10.	
Rrate smart phone application: a smart phone tapping application that provides a RR count within a defined number of consistent breaths, which can be set from three to six, and a defined consistency threshold from 10 to 14%. The user taps the smart phone screen for each breath viewed. Once the application has provided a RR the user has to verify the consistency by watching and agreeing with the RR of an animated child on the screen, before confirming that the RR is correct. In a previous study, where trained clinicians used RRate to count RR using videos, RRate was shown to reliably measure respiratory rate on average within 9.9 seconds and improved the efficient of counting RR (107). The approx. cost of these types of phones is $80. The app is free to download.	
Respirometer feature phone application: is a feature phone application that provides a RR reading after 10, 20 breath cycles and 60 seconds as well as categorisation of the RR (fast or normal) based on the age of the child. The user counts each breath by pressing a number button on the phone keypad. In our study the 60 second reading was used for all analysis as it was previously shown to be the best performing when the device was previously tested (54). The approx. cost of these types of phones is $20. The app is free to download.	
Contec fingertip pulse oximeter (Model: CMS50QB): measures oxygen saturation and pulse rate through attaching the device to the patient's finger or toe. This device is supplied with two rechargeable batteries which can be used up to 300 times between charging. This device is recommended for use with paediatric patients due to its smaller size. This device is CE approved as a class IIb medical device. Dimensions: 46mm X 40mm X 29mm. Weight: 35g. The device costs approx. $40. When asked, frontline health workers in	

the four study settings, had very low knowledge of these types of pulse oximeters and there performance had not been tested previously in these settings (37).	
Devon fingertip pulse oximeter (Model: PC600): measures oxygen saturation and pulse rate through attaching the device to the patient's finger or toe. Supplied with a rechargeable battery and sized for use with paediatric patients, this device has programmable audible alarms. This device is CE approved as a class IIb medical device. Dimensions: 55mm X 40mm X 30mm. Weight: 80g. The device costs approx. $80.	
Lifebox handheld pulse oximeter (Model: AH-M1): a portable hand-held device measuring oxygen saturation and pulse rate with visual and audible alarms. It is both battery and mains powered and is supplied with a rechargeable lithium battery. It is supplied with re-usable adult, neo-natal and paediatric probes. This device is CE approved as a class IIb medical device. Dimensions: 58.5mm X 123mm X 28mm. Weight: 200g (without batteries) The device costs approx. $250. The device had previously been tested for use by frontline health workers in studies in Melawi (48, 113).	
Utech handheld pulse oximeter (Model: UT100): a portable, handheld device, measuring oxygen saturation and pulse rate with visual and audible alarms, and can be used on adults, paediatric and neonatal patients. Operated with four AA batteries but it can use re-chargeable batteries they need to be purchased additionally. It is supplied with an adult reusable probe as standard, but paediatric and neonatal reusable probes are available. This device is CE approved as a class IIb medical device. Dimensions: 75mm X 135mm X 28mm. Weight: 258g (with batteries). The device costs approximately $100.	

Masimo mobile phone pulse oximeter (Model: iSpO2 Rx): a multi-probe handheld pulse oximeter operating on an Android phone and is also available for iPhone. The device features low profusion and motion software supporting SpO2 assessments of adult, paediatric and neonatal patients with single and multi-use paediatric and neonatal probes. This device is CE approved as a class IIb medical device. The device is charged through the mobile phone and does not require an independent power source. Dimensions: 25mm X 10mm X 5mm. Weight: 30g (without phone). The device costs approx. $250. In a previous study in Antwerp of 201 screened infants, with Radical-7 as the reference device, the researchers calculated a mean bias of -0.08% ± standard deviation of 1.76%, with limits of agreement of -3.52% and 3.36% (114).	

Figure 6 Potential new RR counters and pulse oximeters tested in this thesis

6 RESULTS

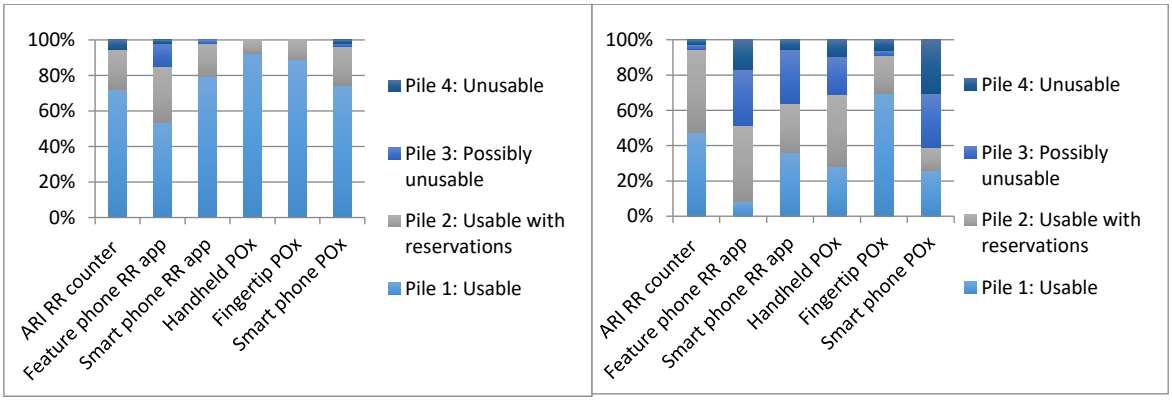
Although this thesis is based on three separate sub-studies, the results have been synthesised and are presented here under three broad themes of: 1) perceptions of frontline health workers and national stakeholders on pneumonia diagnostic aids; 2) performance of RR counters and pulse oximeters when used by frontline health workers and 3) usability, acceptability and utility of RR counters and pulse oximeters.

6.1 PERCEPTIONS OF DIAGNOSTIC AIDS

Qualitative data from sub-study I shows a range of different views on the various pneumonia diagnostics aids presented to the different participant groups.

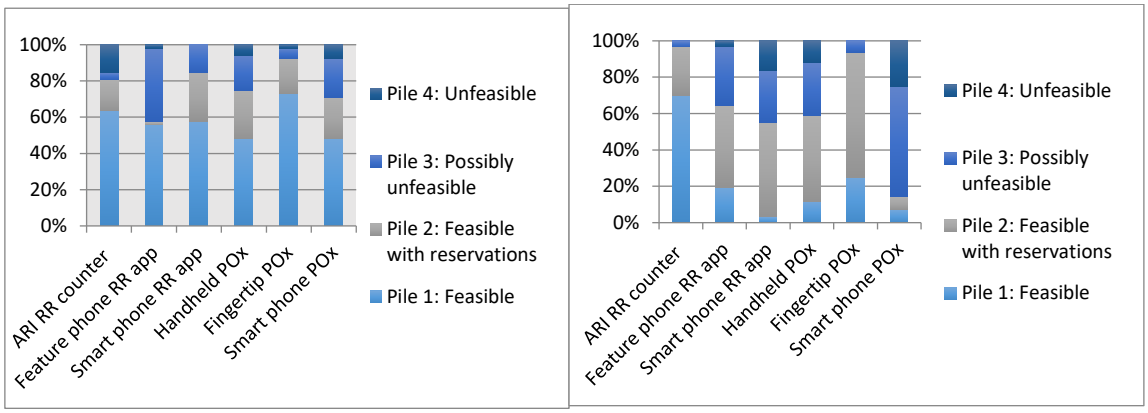
6.1.1 Pile sorting activity

The results of the pile sorting activity are detailed in Figures 5 and 6. Overall, a much higher percentage of CHWs placed devices in pile 1 (able to use or scale up) compared to national stakeholders. Both groups rated the fingertip pulse oximeter and ARI timer highly in regards of usability. National stakeholders were extremely positive about the potential to scale the ARI timer compared to other devices (70% placed it in pile 1 and none in pile 4). CHWs had more varied perceptions of this device's scalability (63% and 15% placed it in groups 1 and 4 respectively). National stakeholders rated the scalability and usability of the smartphone pulse oximeter poorly (86% placed it in pile 3 or 4 for scalability and 61% did so for usability). The fingertip pulse oximeter's usability and scalability was highly rated by both national stakeholders and CHWs.



Usability: CHWs **Usability: National stakeholders**

Figure 7 Graphs depicting the pile sorting allocations of CHWs and national stakeholders (joint device not included due to low participant numbers)



Scalability: CHWs **Scalability: National stakeholders**

Figure 8 Graphs depicting the pile sorting allocations of CHWs and national stakeholders (joint device not included due to low participant numbers)

6.1.2 Themes arising from FGDs

CHWs and national stakeholders in all countries deemed the price of pneumonia diagnostic aids to be a significant factor in determining future scale up (Table 5). Participants in both groups felt the lack of access to electricity was the greatest barrier for scale for aids requiring frequent recharging and stated a preference for battery powered diagnostic aids. Participants in both groups stated simplicity was essential to tool usability and scalability. Many national stakeholders and CHWs preferred familiar technology, such as the existing ARI timer or simple mobile phones. Participants in both groups highlighted the need for accurate aids to assist in classification of children with pneumonia. Devices producing automated results, such as pulse oximeters, the RR counting mobile phone applications and the joint device, were most appreciated by both stakeholders and CHWs.

Table 5 Overview of quotes from national stakeholders and health workers views on the usability and scalability of seven potential pneumonia diagnostic aids

Key themes and brief description	CHWs views and indicative quote	National stakeholders' views and indicative quote
Cost of diagnostic aids	• Higher cost devices would not get funded • Concerned they may be required to buy their own device • Concerned they would have to replace broken devices • Worried about the personal responsibility for repaying the cost if devices were stolen, lost or damaged.	• Questioned who would be responsible for supplying the aids to large numbers of CHWs in each country. • Preference for less expensive devices, such as the ARI timer and the fingertip pulse oximeter • Resource allocation dilemmas – where to focus spend • Thief could be an issue and CHWs could be targetted *"In our country there are about 30,000 HEWs and about 16,000 health posts. You are not supposed to buy for all of these. It is quite difficult. We have to think of this issue."* Ethiopian national stakeholder *"What are the causes that our volunteers do not understand the symptoms of pneumonia, both for the newborn and those aged under five? In order to enable the community to know the symptoms, we need to spend money. So, if we have only $100, should we spend the money on the training of how to identify the danger signs or should we spend it on a smartphone?"* Cambodian national stakeholder
Electricity, batteries and charging	• Participants in both groups frequently mentioned the lack of access to electricity in large areas of all four countries. • Potential difficulties if aids were highly reliant on electricity for charging *"As to me, the health post has no electric power access and it is about two to three hours walking distance to get electric power. In our case, the electric power access is in one of the schools found in our kebele. It has a distance of two to three hours.*	• Frequent or daily charging of devices was seen as a barrier to usability and scalability.

	Therefore, it is difficult to send the phone with students for charging at regular basis." Ethiopian CHW • Solar panels were seen as a potential solution *"If we have a small solar panel to charge the battery, it will be much better and much more convenient. We can charge the battery anywhere we want, and we can use the instrument for a long time."* Cambodian CHW	
Simplicity	• The ARI timer's inability to produce automated results reduced its perceived usability for some in Cambodia and Ethiopia and other CHWs described it being confusing to use. • Literacy level needs to be considered when developing devices • Ethiopia and Cambodia CHWs liked the disease classification system of the feature phone application, which minimised the need to interpret results using separate guidelines. • Other simplifying attributes included clear display of results in a large format for older CHWs with poor eyesight, and instructions and steps written in the local language. *"Because [it] is not simple to operate such a phone by someone who is illiterate and also it have a lot of instructions to follow*." South Sudanese CHW	• Devices producing automated results, such as pulse oximeters, the RR counting mobile phone applications and the joint device, were most appreciated by both national stakeholders and CHWs. *"The fingertip pulse oximeter is easy to use because you simply insert a finger and it displays the readings."* Ugandan national stakeholder *"For the simple phone, we can see the members in VHSGs (Village Health Support Groups) or VMWs (Village Malaria Workers) are mostly old people. Most of the members in VHSGs only know how to receive a phone call or can only make a call to a certain number. It is difficult for us to train them to use the phone."* Cambodian national stakeholder
Accuracy	• CHWs emphasised the need for accuracy when discussing problems with the ARI timer, which they often described as being inaccurate. • Participants reflected on the inherent inaccuracy of CHWs needing to count children's breaths with distractions such as children crying, moving or other people talking, leading to the need to repeat counting multiple times. This was most commonly mentioned by CHWs referring to previous experiences using the ARI timer.	• National stakeholders expressed concerns about the accuracy of tools that required CHWs to count breaths for less than one minute and then produced an automated RR. *"The other drawback of the application* (feature phone application) *is it doesn't count full one minute, it gives estimated number of breaths just after tenth or twentieth breath. This implies that it is not appropriate for irregular breathing pattern."* Ethiopian national stakeholder

	• Both CHWs and national stakeholders liked the smartphone RR counting application which allows users to validate their count findings by listening to the calculated RR and comparing it with the child's actual RR. They felt this increased its accuracy and usability.	
Durability and sustainability	• Both groups of participants raised sustainability concerns, both directly and indirectly, during the FGDs • Environmental hazards that CHWs specifically mentioned included: water exposure; being damaged whilst carried in bags; being dropped; or being broken by children during the assessment.	• National stakeholders preferred aids to be low maintenance. *"If they can use the instruments for only one year, then the instruments are not usable anymore, we do not support them with more instruments. Therefore, is what we give them sustainable?"* Cambodian national stakeholder
Acceptability	• Both groups preferred familiar technology, such as the existing ARI timer or simple mobile phones. • Generally, CHWs placed greater emphasis on the need for future aids to be acceptable to children and parents than national stakeholders. • They reported children would not like noisy devices (such as the ticking ARI timer) or those that involved attaching unfamiliar objects to their bodies (in the case of pulse oximeter probes). • CHWs preferred tools that were: small and portable; "modern" but simple to use; able to perform multiple functions; and able to provide automated results. They expressed a preference for devices producing fast results. *"When I use it to count breathing, the children do not know that I count breathing and they may think that I am using a mobile phone. The children do not know so they are not frightened."* Cambodian CHW	• There was resistance to the use of new technological aids, especially smartphones, by national stakeholders across the four countries *"I am afraid that it is too modern and complicated so that it will be difficult to use. Our volunteers get used to using simple Nokia [feature] phone because it is useful for them and it is also very convenient to use."* Cambodian national stakeholder

6.2 PERFORMANCE RESULTS

While most CHWs managed to achieve a RR count with the four different devices, the agreement was low for all, with a large range of mean differences of RR measurements from the reference standard for the four devices, from 0.5 (95% CI -2.2, 1.2) for the respirometer to 5.5 (95% CI 3.2, 7.8) for Rrate. Performance was consistently lower for young infants (0 to <2 months) than for older children (2 to ≤59 months). Agreement of RR classification into fast and normal breathing was moderate across all four devices, with Cohen's Kappa statistics ranging from 0.41 (SE 0.04) to 0.49 (SE 0.05) (Sub-study IIa).

Although all five pulse oximeters tested in field had performed well on a simulator (±2% from the simulator), their performance was more varied when used on real children by frontline health workers. The handheld pulse oximeters had greater overall agreement with the reference standard (-0.6% SpO2; 95% CI -0.9, -0.4 to -3.0% SpO2; 95% CI -3.4, -2.6) than the finger-tip pulse oximeters (-3.9% SpO2; 95% CI -4.4, -3.4 to -7.9% SpO2; 95% CI -8.6, -7.2). This was particularly pronounced in the younger children, where handheld had -0.7 (95% CI -1.4, -0.1 to -5.9 (95% CI -6.9, -4.9) agreement, compared to fingertips, which had -8.0 (95% CI -9.4, -6.6 to -13.3 95% CI -15.1, -11.5) agreement. While all devices under estimated SpO2 readings compared to the reference standard, the finger-tip devices were particularly more likely to under estimate SpO2 and subsequently over diagnose hypoxemia in the children assessed. First level health facility workers had better agreement with the reference standard (κ=0.32; SE 0.05 to κ=0.86; SE 0.07) for all five devices, when compared to CHWs (κ=0.15; SE 0.02 to κ=0.59; SE 0.03) (Sub-study IIb).

In Sub-study IIa, the differences in RR counts between CHWs using the four RR counters and the reference standard, plotted against the average RR of the two measures, is illustrated in the Bland Altman plots (Figure 7-10). These show large variation in readings for all four RR counters, but especially in the younger children. The ARI with beads plot (Figure 7) shows a mean difference of -1.9 bpm, and limits of agreement (LOA) from -19.0 bpm to 15.1 bpm, and most variation seen in the older age group. The MK2 ARI plot (Figure 8) showed a mean difference of -0.6 bpm, and LOAs from -25.4 to 23.9 bpm. The plot also shows that for the older children with lower breath rates MK2 ARI over-counted RR, whereas for older children with higher breath rates MK2 ARI under-counted RR. In the Rrate plot (Figure 9), the mean difference was 5.5 bpm with wide LOAs ranging from -24.2 to 35.2 bpm, with more variation in the younger children with higher breath rates. The Respirometer (Figure 10) had a mean difference of -0.5 bpm and the LOAs were wider than the other device, ranging from -28.6 to

27.5 bpm. Also this device had more variation in the higher breathing rates, with the younger children being over-counted and the older children under-counted.

In sub-study IIa, agreement of the RR classification into normal or fast breathing for CHWs and the reference standard measurements varied widely between the four RR counters, especially for the young infants. The MK2 ARI had the highest κ statistic, both overall (0·49; SE 0·05) and for each of the two age groups, 0·26 (SE 0·08) and 0·62 (SE 0·07) respectively (Table 6).

In sub-study IIb, using the standard WHO cut-offs ($\leq$ 90%) to classify the oxygen saturation into hypoxaemia or non-hypoxaemia, there was more variability in the agreement between the reference standard and the test devices in the younger children than the older children as highlighted by the Kappa statistic (κ) data (Table 6). The Contec fingertip pulse oximeter had poor agreement across both age groups with the reference standard (κ=0.01; SE 0.01 – κ=0.25; SE 0.03). The Devon finger-tip pulse oximeter had fair agreement overall (κ=0.38; SE 0.03). The Lifebox handheld pulse oximeter had poor agreement (κ=0.31; SE0.05) in the younger children and had moderate agreement (κ=0.51; SE0.03) in the older children. The Utech handheld pulse oximeter had poor agreement (κ=0.2; SE 0.05) in the younger children and moderate agreement (κ=0.57; SE 0.03) in the older children. The Masimo phone pulse oximeter had the best agreement of all five pulse oximeters (κ=0.67; SE 0.03) with moderate agreement (κ=0.5; SE 0.06) for the younger children and good agreement (κ=0.71, SE 0.03) for the older children.

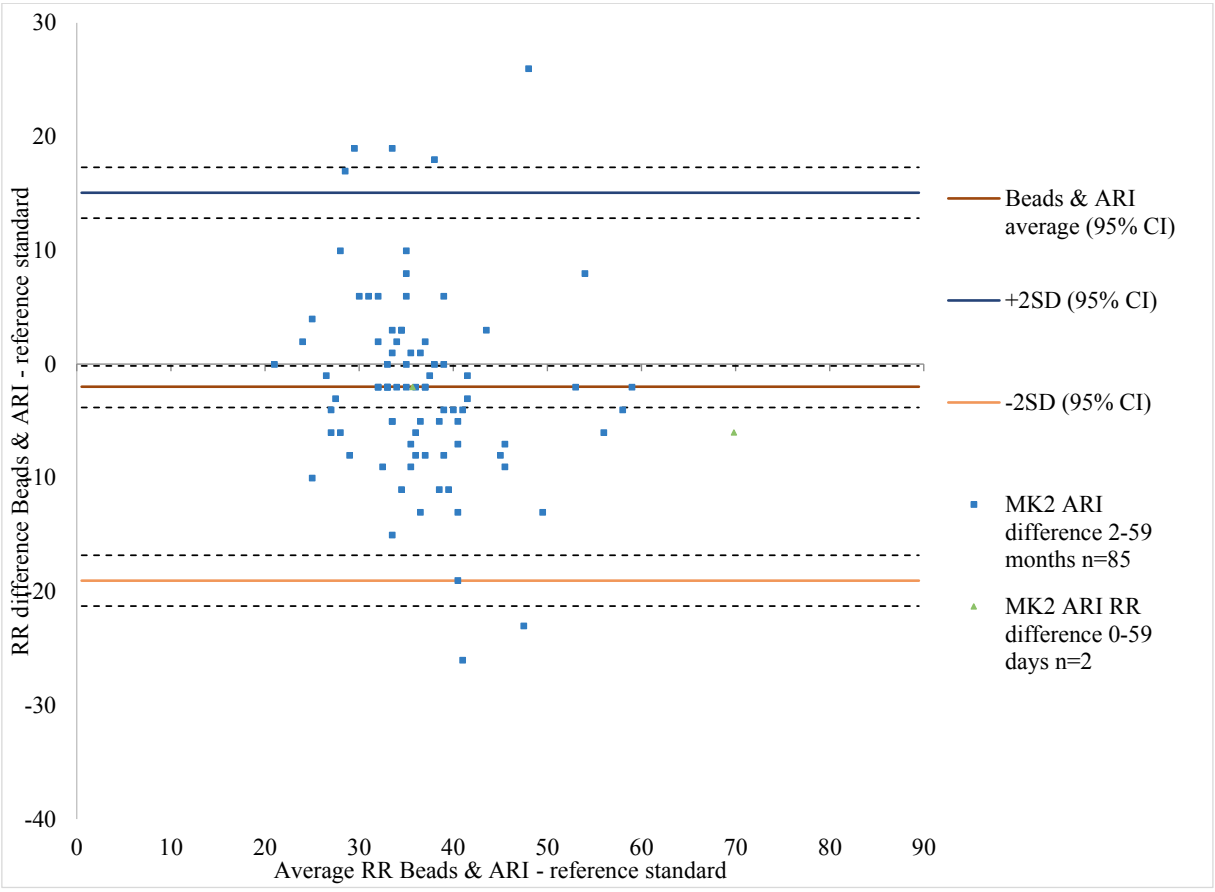


Figure 9 Bland Altman plot for ARI timer with beads n=87

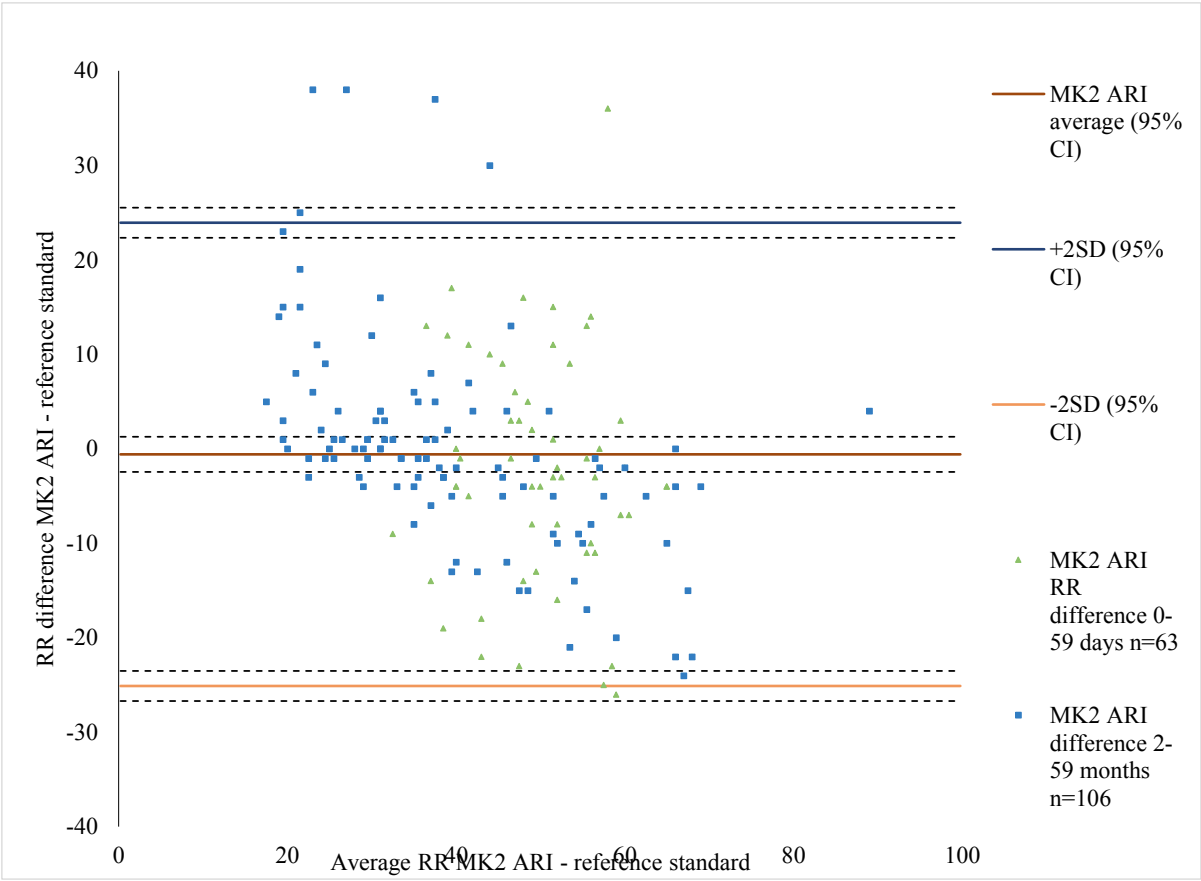


Figure 10 Bland Altman plot for the MK2 ARI timer, n=169

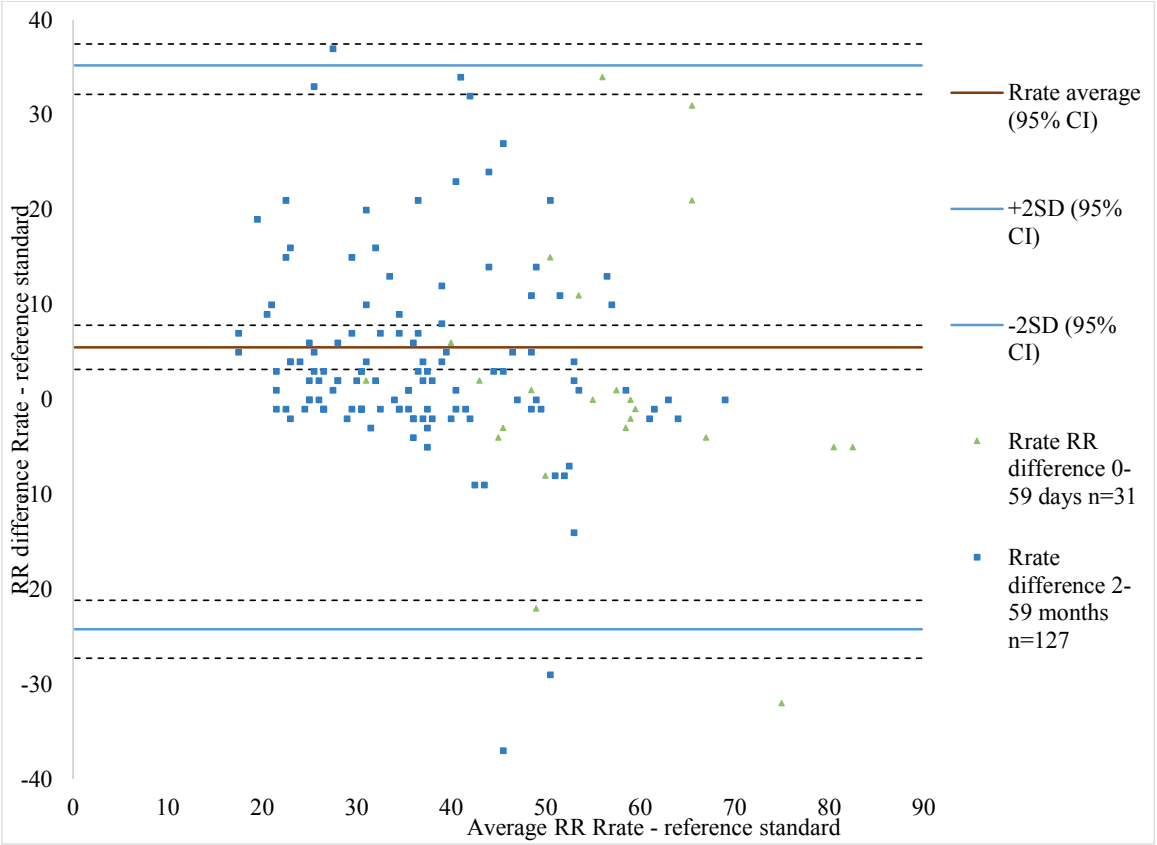


Figure 11 Bland Altman plot for the RRate, n=158

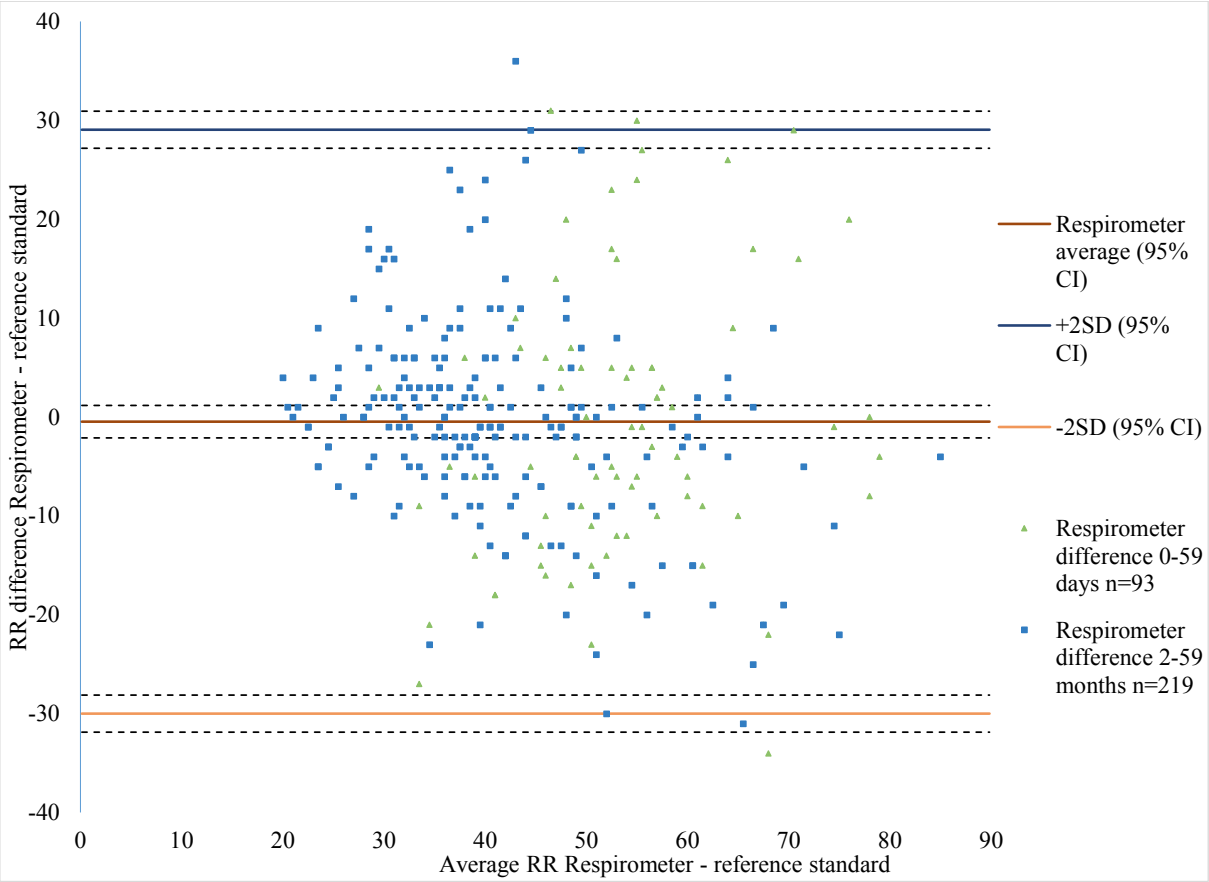


Figure 12 Bland Altman plot for the Respirometer, n=312

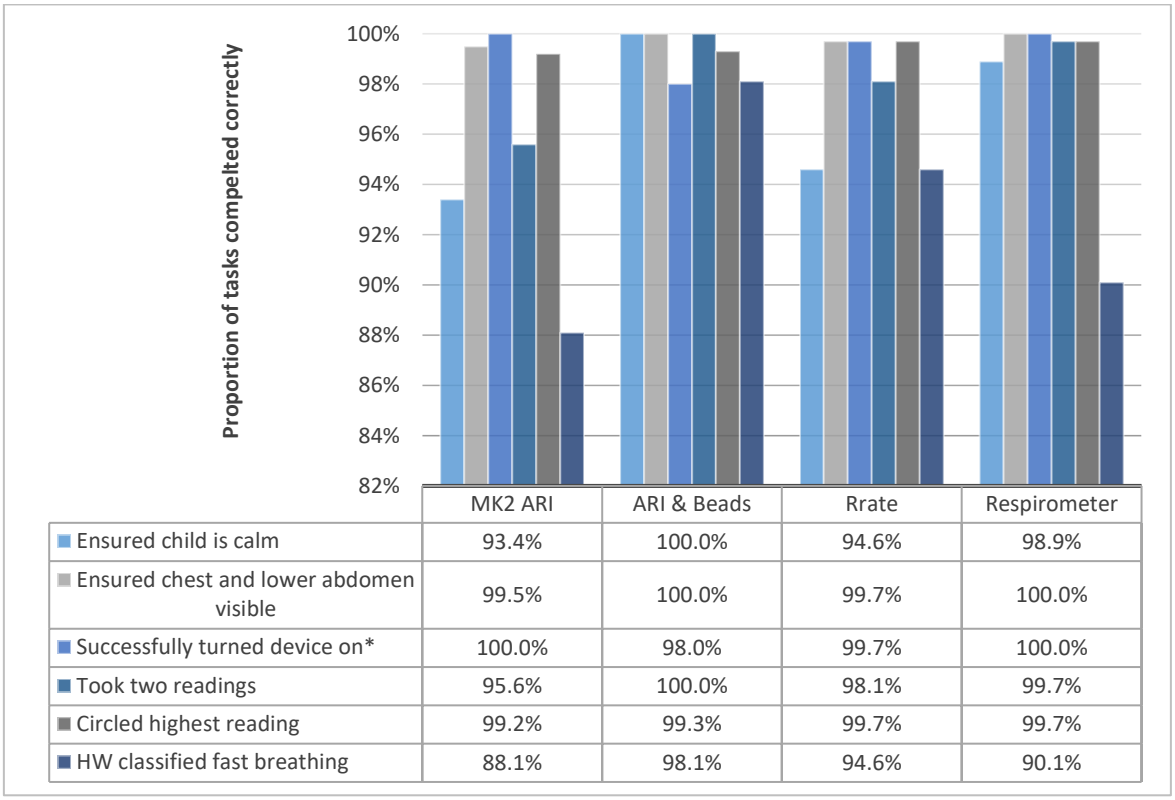
Table 6 Performance of RR timers and pulse oximeters when compared to a reference standard

Agreement measurement	Beads and ARI (n=172)	MK2 ARI (n=322)	RRate (n=304)	Respirometer (n=626)	Contec (n=1120)	Devon (n=1124)	Lifebox (n=1186)	Utech (n=1186)	Masimo (n=1186)
±2 bpm or SpO2%	35	32	34	26	31	47	56	58	68
%	60/172	104/322	102/304	165/626	303/1120	454/1124	609/1186	596/1186	784/1186
n/N									
Mean difference or 'bias'	-1.9	-0.6	5.5	-0.5	-7.9	-3.9	-2.7	-3.0	-0.6
(95% CI)	(-3.8, -0.2)	(3.8, -0.2)	(3.2, 7.8)	(-2.1, 1.2)	(-8.6, -7.2)	(-4.4, -3.4)	(-3.0, -2.3)	(-3.4, -2.6)	(-0.9, -0.4)
Kappa value	0.41	0.49	0.44	0.41	0.19	0.38	0.48	0.46	0.67
(Standard error)	(0.07)	(0.05)	(0.06)	(0.04)	(0.02)	(0.03)	(0.03)	(0.03)	(0.03)
Positive percent agreement	44	53	71	58	89	83	87	88	84
(95%CI)	(29.5-58.8)	(41.9-63.5)	(59.1-80.3)	(51.3, 64.9)	(80.0-94.8)	(72.4-90.1)	(77.6-92.8)	(79.4, 94.2)	(74.5, 90.0)
Negative percent agreement	93	92	78	82	64	84	88	87	96
(95% CI)	(86.7, 96.6)	(87.6, 95.0)	(72.4, 83.5)	(78.3, 85.9)	(60.3-66.6)	(81.0, 85.9)	(85.7, 89.9)	(84.3, 88.8)	(94.1, 96.6)

6.3 USABILITY AND ACCEPTABILITY

6.3.1 Usability

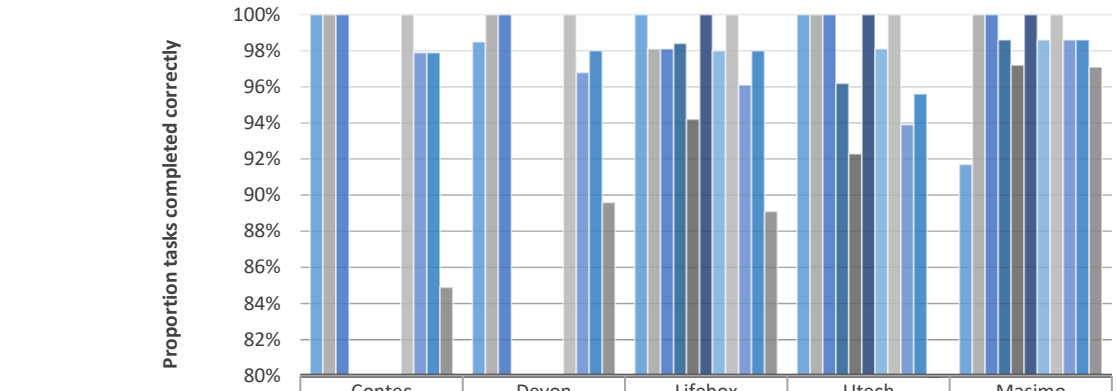
In sub-study III, 87.6% of health workers who used the RR counters (Fig.11) and 70.7% of health workers using pulse oximeters achieved full procedure adherence scores (Fig. 12). Across all four RR counters, health workers were successful in ensuring the child was in the correct position with a visible chest and lower abdomen, turning on devices, and identify and circle the highest reading for records. Data also showed a lower proportion for users correctly diagnosed a child with fast breathing using the manual device the MK2 ARI (88.1%) compared to those using the assisted devices, 90.1% for respirometer, 94.6% for Rrate and 98.1% for ARI and respiratory beads users. In using the pulse oximeters, two devices had a lower correct proportion when classifying low oxygen levels for both Contec (84.9%) and Utech (77.2%).



	MK2 ARI	ARI & Beads	Rrate	Respirometer
Ensured child is calm	93.4%	100.0%	94.6%	98.9%
Ensured chest and lower abdomen visible	99.5%	100.0%	99.7%	100.0%
Successfully turned device on*	100.0%	98.0%	99.7%	100.0%
Took two readings	95.6%	100.0%	98.1%	99.7%
Circled highest reading	99.2%	99.3%	99.7%	99.7%
HW classified fast breathing	88.1%	98.1%	94.6%	90.1%

*For beads and ARI this means selected the correct set of beads

Figure 13 Proportion of tasks performed correctly for respiratory rate counters



	Contec	Devon	Lifebox	Utech	Masimo
Ensured child is calm	100.0%	98.5%	100.0%	100.0%	91.7%
Ensured upper and lower limb are exposed	100.0%	100.0%	98.1%	100.0%	100.0%
Successfully turned device on	100.0%	100.0%	98.1%	100.0%	100.0%
Selected correct probe*			98.4%	96.2%	98.6%
Checked probe sensor*			94.2%	92.3%	97.2%
Connected probe sensor*			100.0%	100.0%	100.0%
Attached light and sensor*			98.0%	98.1%	98.6%
Identified correct reading	100.0%	100.0%	100.0%	100.0%	100.0%
Took two readings	97.9%	96.8%	96.1%	93.9%	98.6%
Circled lowest reading	97.9%	98.0%	98.0%	95.6%	98.6%
HW classified low oxygen level	84.9%	89.6%	89.1%	77.2%	97.1%

*Only applies to handheld pulse oximeters

Figure 14 Proportion of tasks performed correctly for pulse oximeters

The highest mean adherence score recorded for a RR counter was for the ARI and beads (mean=5.95, SD=0.29), followed by the Respirometer (mean=5.87, SD=0.38), with strong evidence of a small but significant different between individual device scores (p<0.001). Overall, the assisted RR counters had higher mean adherence scores than the manual MK2 ARI timer.

Table 7 Procedure mean adherence scores, standard deviations, change in mean scores, 95% confidence intervals and p values for RR counters (n=1,291)

		N	Mean score (μ)	Standard deviation (σ)	Change in mean score	95% CI	p-value
Device name	MK2 ARI Timer	395	5.68	0.85	0		
	Beads and Timer	150	5.95	0.29	0.28	(0.17, 0.41)	**<0.001**
	Rrate	372	5.82	0.61	0.14	(0.05, 0.22)	
	Respirometer	374	5.84	0.38	0.19	(0.10, 0.28)	
Cadre	CHW	1044	5.85	0.35	0		**<0.001**
	FLFHW	247	5.62	0.52	-0.22	(-0.31, -0.14)	
Country	Ethiopia	374	5.69	0.46	0		
	South Sudan	375	5.97	0.37	0.29	(0.20, 0.37)	**<0.001**
	Cambodia	167	5.52	0.52	-0.16	(-0.26, -0.06)	
	Uganda	375	5.89	0.47	0.20	(0.11, 0.28)	
Device type	Non Automated	396	5.68	0.26	0		**<0.001**
	Assisted	895	5.86	0.34	0.18	(0.11, 0.25)	
	2-12 months	401	5.71	0.54	-0.08	(-0.23, 0.07)	
	12-59 months	818	5.86	0.64	0.07	(-0.07, 0.22)	

Table 8 Procedure mean adherence scores, standard deviations, change in mean score and 95% confidence intervals and p values for pulse oximeters

		Fingertip pulse oximeter mean procedure adherence scores (N=120)					Handheld pulse oximeter procedure adherence score (N=184)				
		N	**Mean**	**Change in mean score**	**95% CI**	**p-value**	**N**	**Mean**	**Change in mean score**	**95% CI**	**p-value**
Device Name	Contec Finger	53	6.4	0							
	Devon Finger	67	6.61	0.21	(-0.48, 0.91)	0.55					
	Lifebox Handheld						55	10.10	0		
	Utech Handheld						57	9.61	-0.49	(-1.28, 0.29)	0.09
	Masimo Handheld						72	10.44	0.33	(-0.42, 1.08)	
Cadre	CHW	105	6.51	0			148	9.97	0		
	FLFHW	15	6.67	-0.3	(-1.35, 0.74)	0.56	36	10.52	0.54	(-0.23, 1.33)	0.17
	Female	65	6.75	0.63	(-0.04, 1.32)		94	10.38	0.61	(-0.01, 1.22)	

6.3.2 Acceptability

In sub-study III data from the 40 key informant interviews with frontline health workers showed that they found the new RR devices more accurate, easier to use and faster than their current standard practice in supporting them to make a diagnosis (Table 9). They further reported finding the pulse oximeters easy to use, but did find them more difficult to use on younger children. They also reported that the new devices gave them more confidence in their role diagnosing pneumonia in children under five. Health workers asked that these types of new devices be introduced at scale to support them in their work.

Table 9 Overview of research themes in relation to health worker and national stakeholder views on the scalability and usability of seven pneumonia diagnostic aids

Key themes	Key findings	Indicative respondent quote
Perceived effectiveness	• New diagnostic aids was an improvement in relation to their current standard practice, the ARI timer • Preferred the assisted devices (ARI with beads, Respirometer and Rrate) over the manual MK2 ARI • New diagnostics aids more accurate, easier to use and faster in supporting them to make a diagnosis, even of the pulse oximeters, which they had not used before. • Some found it difficult to use the pulse oximeters on younger children	*"The device I trained helped me in diagnosis of pneumonia very well, because the previous ARI timer has sound that disturbs children but the current one is no sound and child disturbance." [HEW in Ethiopia]* *"UTECH is the easiest device to use as it does require connection of the sensor and it gives instant results when inserted onto the finger of the child unlike respiratory beads that takes long time to get the diagnosis at the end". [CDD in South Sudan]*
Intervention coherence	• Health workers mainly felt they understood how to use the RR devices after their training. • They felt that their understanding of the pulse oximeter devices improved over time and with practice.	*"I preferred both pneumonia diagnostic devices (RR smart phone and Massimo smart phone) because R.R smart phone counts and shows the respiratory rate and Masimo smart phone shows oxygen concentration of the blood".* [HEW in Ethiopia]
Self-efficacy	• New dignostic aids gave them more confidence in their role • Increased confidence in their role encouraged increased care seeking behaviours	*"I enjoyed treating the children thanks to the fame Malaria Consortium brought me. It has provided me with all that I need. Pneumonia cases are very many here in the community and Malaria Consortium has stood up to fight against the encroaching disease".* [CDD in South Sudan]

Burden	• New disgnostic aids to be more user friendly than the devices they previously used • New diagnostic aids helped them more in their jobs and allowed them to see more sick children	*"The device (MK2 ARI) I trained helped me in diagnosis of pneumonia very well, because the previous ARI timer has sound that disturbs children but the current one is no sound and child disturbance".* [CDD in South Sudan]
Scalable	• New diagnostic aids should be introduced at scale to support their work diagnosing pneumonia • Some did mention that the pulse oximeters needed a higher level of skill and particularly people who have a higher level of literacy and numeracy.	*"Yes, it is better to introduce (MK2 ARI) to all. Currently it is few of us who took training and are working on this".* [HEW in Ethiopia]

7 DISCUSSION

7.1 MAIN FINDINGS

This thesis aims to identify and evaluate the most accurate, acceptable and user-friendly respiratory rate timers and pulse oximeters for diagnosis of pneumonia symptoms in children by frontline health workers in low-resource settings. Frontline health workers were able to use the nine test devices to measure RR and oxygen saturation in children under 5, but will variable performance, and found it more difficult to get a successful measurement in younger children. Frontline health workers were better supported by assisted RR counters, such as Rrate and respirometer, compared to their standard practice diagnostic aid, MK2 ARI timer. Handheld pulse oximeters with multiple probes performed better than finger-tip pulse oximeters, especially in younger children. The views of different stakeholder groups should be considered when looking to take these types of pneumonia diagnostic aids to scale. Our findings from both sub-study I and III show that both frontline health workers and national stakeholders want simple and uncomplicated, affordable diagnostic aids, this must be considered as part of the development process undertaken by device manufacturers.

7.2 PNEUMONIA: A MAJOR CHILD KILLER WITHOUT AN AGREED DEFINITION

While there is still no globally agreed clinical definition for pneumonia (115) or any test to show if the infection is bacterial or viral, RR continues to be the primary method for diagnosing pneumonia in children with cough and/or difficulty breathing in low resource settings, with sensitivity ranging from 76-81% and specificity from 60-89% (116-119). Studies have also shown relatively high sensitivity (75—81%) and specificity (81—83%) of CHWs classification of fast breathing in children using the ARI timer (5, 33, 81). However, the usefulness of including other clinical signs, such as fever and work of breathing, in the clinical management algorithms for childhood pneumonia is ongoing, driven by changes in the epidemiological context of infections (11, 120), technical advances for prevention and treatment (121), and further evidence becoming available on biomarkers (122), but as of yet none have been proved conclusive to replace RR (120, 123). Work is also being undertaken to harmonise and redesign the existing WHO guidelines (124), but there is no suggestion of the removal of respiratory rate from the IMCI or iCCM algorithms. Use of pulse oximetry screening for detection of severe pneumonia, and host biomarker point of care tests (POCTs) like C-reactive protein (CRP) and procalcitonin (PCT) for detection of bacterial pneumonia, are being investigated (123, 125, 126). While a study in Tanzania recently showed that the use of POCTs in a modified electronic case management algorithm resulted in a 49% lower relative risk of clinical

failure compared to routine care while reducing antibiotic use, the use of POCTs in primary care is only recommended for higher risk children, to avoid over referral. For example, the positive predictive value of the CRP test to diagnose radiological pneumonia in children with fever and cough drops from 54% to 32% when fast breathing is removed from the algorithm(120, 127). Hence, respiratory rate counting will continue to play an important role, along with assessing for danger and referral signs, even when POCTs become available in routine care, and the development of improved diagnostics aids for facilitating improved RR counting should continue to be a priority until further evidence is presented. However, as highlighted elsewhere (128), this should not stop continued investigations on other predictive signs and symptoms of pneumonia, such as work of breath, and other combinations of signs and symptoms and point of care markers (123, 129).

There is also a need for further clarity in the definition of symptoms currently used to presumptively diagnoses pneumonia. While RR has been included in diagnostic algorithms since the 1980s (14), little work has been done to accurately define what a breath is, and develop a standardised protocol for training how to consistently count RR. Given the variability we saw in the RR measurements in all four devices in sub-study IIa, with ±2 bpm agreement with the reference standard ranging from 26 to 35% of measurements, this work would really support future development of improved RR counters.

7.3 THE LACK OF APPROPRIATE DIAGNOSTICS FOR FRONTLINE HEALTH WORKERS

While the need for improved diagnostic aids was clear from sub-study I, where both CHWs and national stakeholders were receptive to appropriate and supportive new RR counters and pulse oximeters, our studies have shown there is a need for further development in pneumonia diagnostic aids which will adequately support frontline health workers to better manage pneumonia in children under 5. Both health worker and national stakeholder respondents highlighted that cost. Complexity and level of maintenance required were key factors when introducing new RR counting aids. This is similar to the views expressed by health workers in other studies in Cambodia and Malawi when asked about the introduction of similar technologies such as pulse oximetry (84, 130). It has been suggested that the inclusion of pulse oximetry in the management of pneumonia in resource poor settings can improve health outcomes. In 2014 the WHO amended their guidelines on facility based management of pneumonia to include the use of pulse oximetry when pulse oximeters are available (29), but in many high burden pneumonia countries, such as Ethiopia and Nigeria, the introduction of pulse oximetry also at community level has been advocated for (71, 131).

7.3.1 Issues with current diagnostic aids

Sub-study II shows that while CHWs using either of the four different RR counters were able to obtain a RR measurement from children in the majority of cases, the agreement of their measurements with the reference standard was low for all of the four devices tested. As in previous studies in Zambia and Uganda, where expert clinicians were used as the reference standard to assess agreement with CHW measurements (33, 81), our study also shows a lot of variability between the CHWs and our automated reference standard RR count. Our data shows that it was especially difficult for CHWs to obtain an accurate count (±2 breaths) in young infants, in which only 8% to 20% of the assessments were in agreement with the reference standard, regardless of the RR counter used. The agreement between the tested devices and the reference standard was significantly higher for older children, ranging from 30 to 40% in the 2 to ≤59 month olds, which is also reflected in a previous study in Zambia where decreased RR variability was seen in older children. There was no significant difference in performance between the four devices tested and, unexpectedly, the three improved manual devices tested in our study (beads with ARI timer, RRate and the Respirometer) all showed lower agreement than studies of completely manual counters, where 46% of observations were ±2 breaths from the reference in Zambia, and 64% in Uganda (33, 132). This further affirms our findings that counting RR manually, with breaths being difficult to see and count being hard to maintain without interruptions that require the count to be repeated, is a difficult procedure to do accurately and more is required of a device than simply supporting the health workers to keep count of the number of breaths a patient takes over 60 seconds. In sub-study III the mean adherence scores for the RR counters reaffirmed the difficulties health workers have with manual counting devices as the mean scores for the manual MK2 ARI was significantly lower than the assisted devices.

Similarly, in sub-study IIb device performance in all five pulse oximeters in relation to agreement with a reference standard varied largely and did not reflect the minimal differences seen when devices were tested in a controlled laboratory environment. This showed the importance of testing devices in the field and not relying on performance results from simulators or laboratory testing alone, which is often the only evidence presented for CE mark accreditation. The Masimo mobile phone pulse oximeter had the best overall performance across all measures and in both age strata of the children the device was tested on. This may be due to the motion signal processing techniques incorporated in Masimo pulse oximeters which attempts to reduce motion artefact (133), which may be particularly important when using these devices on moving children.

Furthermore, sub-study IIb showed that handheld pulse oximeters with multiple probes had higher agreement with the reference standard than the fingertip pulse oximeters and show similar levels of performance as previous studies on similar handheld pulse oximeters with multiple probes (85). This reflects the fact that these devices allowed more precise

measurements, most likely a result of their paediatric and neonatal probes. While this has been highlighted in the literature in relation to safer surgery (134, 135), it is also vital to consider when using devices on children under two months. As can be seen in our data both figure tip devices had very poor performance in this age group, which could likely be due to poor probe fit. This has also been highlighted in recent studies in Malawi and Bangladesh, where health workers recommended that devices have multiple sizes of probes for different ages (48, 85). Finger-tip devices consistently recorded lower readings compared to the reference standard in both user groups and age strata. This would mean that these devices would underreport on SpO2 measurements if used as a screening device for severe pneumonia on children and could lead to over diagnosis of cases of severe pneumonia in the children screened and over referral of "hypoxaemia" to higher level health facilities. With regards to classification into hypoxaemia or non-hypoxaemia, there were no significant differences in PPA, with the confidence intervals overlapping for all devices. However, there were large differences in NPA, with Masimo well outperforming all the other devices, and Contec performing worse than all other devices, again reflecting the issue with the figure-tip devices under reporting SpO2. These results reflect the results of another study of similar types of fingertip pulse oximeters, which saw inaccurate readings and large errors, and suggests these devices should not be used as diagnostic tools in these settings (136).

The data in sub-study II showed the first level health facility workers performed better using the pulse oximeters than community health workers. While in a previous qualitative study both types of health workers had not had previous exposure to pulse oximetry (84), other recent studies conducted in hospital settings in Nigeria showed that pulse oximetry was a new practice for all health workers (87). Key to the scale up of pulse oximetry in these settings is to further understand the drivers for adoption as the Nigeria study showed that while enhanced knowledge and skills are necessary, they are not sufficient on their own to drive usage of these devices.

Data from sub-study III did show that for the RR devices, health workers were better able to classify fast breathing when using assisted devices, rather than their standard practice (MK2 ARI timer). The usability data for the pulse oximeters was more mixed, but in general it reflected that health workers could more easily classify hypoxemia when using handheld pulse oximeters. There has been an increased focus on pneumonia diagnostic aids since the inception of this thesis, including the UNICEF Acute Respiratory Infection Diagnostic Aid (ARIDA) and Scaling Pneumonia Response Innovations (SPRINT) projects (137, 138), and the recent UNITAID fever diagnostics grant (139). Diagnostic aids incorporated in mobile phones continue to be an emerging technology and should continue to be evaluated for use

in resource-poor settings, especially given the current focus on developing multimodal and mHealth decision support platforms such as Medsinc and Feebris (140, 141). As previously advocated for (142), it is vital that robust health care technology assessments are conducted for these new technologies going forward, in order to ensure adoption and use in routine care.

7.4 THE BARRIERS TO ACCURATELY COUNTING RR IN CHILDREN UNDER FIVE

While health workers in sub-study IIa and III showed they could get a respiratory rate count using the four different RR counters most of the time, it proved challenging to accurately count the RR of children under 5 (143). Similarly, when comparing the classification of fast breathing by all four RR counters to the reference standard in Sub-study IIa we saw moderate Kappa values (κ=0.41 to 0.49). This reflects similar results in previous studies in Uganda (κ=0.665) (5), Zambia (κ=0.58) (81) and Malawi (κ=0.35) (144). Manually counting RR has well documented issues with accuracy and reliability, such as movement of the child distorting the count, mistaking movement as breaths, distraction of the health workers and the inherent variability of RR over time (116, 145, 146). Ideally, all of these challenges need to be addressed in developing an improved RR counter which could better support health workers to achieve an accurate RR count in these settings. Similarly, the definition of an accurate RR count needs to be considered and a consensus view reached. Historically, the accepted accuracy threshold recommended for training was ±2 bpm, and this continues to be suggested (147). However, given the results we have seen in sub-study II, we would suggest that this threshold needs to be reconsidered.

7.5 THE LACK OF AGREED STANDARDS FOR EVALUATION DIAGNOSTIC AIDS

In designing this thesis project we looked at the available literature for similar studies previously conducted. The literature search showed there is no consensus view on the most appropriate methods, gold standard or reference standard or metrics to use for these types of performance evaluations of respiratory rate or pulse oximetry devices. As highlighted in other papers, a consensus view on these would help to improve the generalisability of future evaluations of pneumonia diagnostic aids (40).

7.6 REFERENCE METHODS

The issues with reference standards for RR performance evaluations has been recently discussed in the literature recently (51, 148). The challenges of the variability of human

references, plus the ability of new devices to be potentially more sensitive than human counters, have both been highlighted. In sub-study IIa&b we used two different reference standards, a continuous monitor and an expert clinician, both providing reference RR measurements. This decision was based on the outcome of a technical consultation on pneumonia diagnostics evaluations that was held in Geneva in May 2014 (149). The recommendation was based on the fact that there is no gold standard for RR and therefore it would be more robust to use two, imperfect reference standards. We did see large amounts of variability in our reference standards, and while these data is not presented in this thesis, we are finalising a publication on these data (150), documenting the learnings from two recent RR performance studies we conducted, and presenting some potential solutions and learnings for future RR performance studies.

7.7 STANDARD METRICS FOR PNEUMONIA DIAGNOSTIC PERFORMANCE EVALUATIONS

While there is consensus of the need to rigorously evaluate the performance of diagnostic aids before being introduced at scale (40), there is little consensus on the most appropriate metrics to use when evaluating the performance of pneumonia diagnostic aids. In a recent systematic review, where 18 performance studies of pneumonia diagnostic aids were evaluated a wide variation in the statistical methods for comparing performance was found (40). When looking at appropriate statistical measure for RR agreement studies it is important to note that mean difference (bias) is often lower than root mean difference (RMSD) because it does not account for the positive and negative variation in RR measurements. However RMSD should not be used in these agreement studies as it does not account for both random and non-random error (51). Therefore we would recommend using the Bland Altman method, as we did in our performance evaluation of the RR counters (151), as it reflects both.

7.8 THE CHALLENGE IN CONDUCTING MULTI-COUNTRY LARGE SCALE EVALUATIONS

In designing this study, four individual countries were elected, based on their varied health systems and the different demographics of the frontline health workers in each. However, in sub-study II and III there was no significant difference in performance, usability or acceptability across the four countries where these sub-studies were conducted. To maintain consistency across the four research countries a strong focus on standardisation on each sub-study, was key in achieving quality data and output. Standardisation was largely achieved through multi-country protocol design workshops, where all country teams came together to co-create the protocols and standard operating procedures that were used in each of the sub-studies (152). The implications of not having a consensus view on evaluation methods,

reference standards or standard metrics, is that it will be very difficult to provide the evidence around clinical efficacy and cost-effectiveness that is needed for governments and donors to be able to take the decision to introduce these new devices at scale.

7.9 IMPLICATIONS FOR SCALING PNEUMONIA DIAGNOSTIC AIDS

Despite pneumonia being a leading cause of death and disability in the world and the leading infectious disease killer, responsible for an estimated 2.6 million deaths in 2017 (153), the continued lack of action on pneumonia will prevent many countries from achieving the new sustainable development health goals by 2030 (154). Despite the high burden of pneumonia in children under five, international development assistance for pneumonia has never pushed beyond 2% of all research investments in health (Fig. 13) (155).

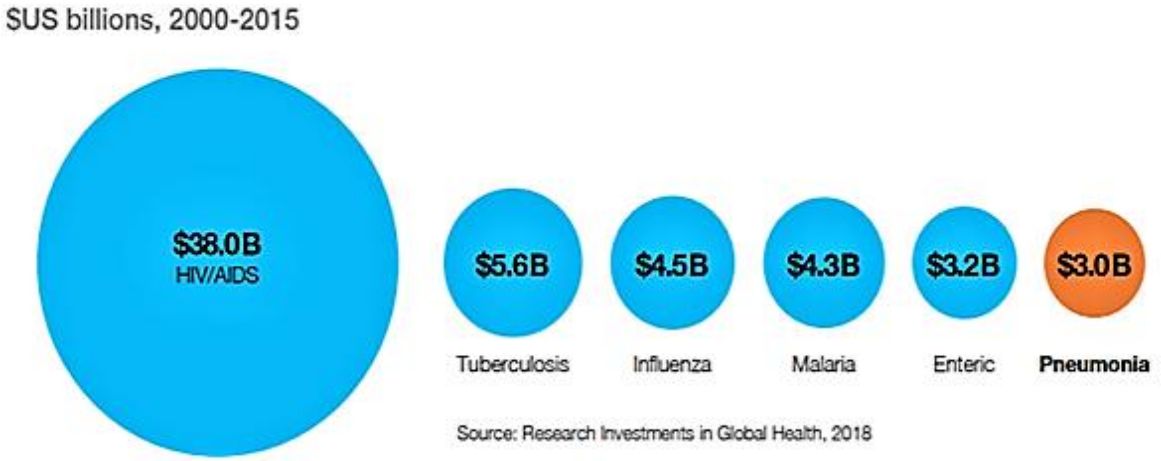


Figure 15 Cumulative research investments in global health from 2000 until 2015 (Source: Research Investments in Global Health, 2018)

While data in sub-study I and III show national stakeholder and frontline health worker felt need for rapid scaling of improved pneumonia diagnostic aids, there is still a lack of clarity from the global community on where the development focus should be. The role of a global movement to focus advocacy, research and development activities will be key going forward to provide forums to build consensus views on research and development priorities for pneumonia diagnostic aids. Every Breath Counts (EBC) is one such group, which was formed in 2018 as the first public-private partnership to support national governments to end preventable child pneumonia deaths by 2030, recognizes the need for innovation to improve pneumonia case management in children under five in primary health care settings.

7.10 CONCLUSIONS

Of the four RR devices tested in sub-study IIa and III, none performed well in the hands of frontline health workers. While frontline health workers were more supported by assisted RR counters rather than the manual counter, which is often standard practice (the MK2 ARI timer), none performed well enough to be considered replacement diagnostic aids. Therefore, as the MK2 ARI is the most affordable option, and as most CHWs are more familiar with its use, it could replace the original ARI timer. Respiratory rate counting will continue to play an important role, along with assessing for danger and referral signs, even when POCTs become available in routine care, and the development of improved diagnostics aids for facilitating improved RR counting should continue to be a priority until further evidence is presented. Stakeholder engagement throughout the development process is critical, in order to ensure new diagnostic aids fully meet the needs of end users, caregiver and the broader health system they support.

Of the five pulse oximeters tested in sub-study IIb and III, all performed consistently when tested on simulators in the laboratory. However, performance was much more varied when tested by frontline health workers in the field. Handheld pulse oximeters with multiple probes perform better when used by frontline health workers to measure oxygen saturation in children under five years of age. This should be considered when making procurement decisions for these settings. First level health facility workers had better agreement with the reference standard when using the five pulse oximeters in children under five. Again this needs to be considered when looking to introduce pulse oximetry in these types of health systems. While frontline health workers and national stakeholders requested that new technologies be developed and introduced, they were clear that any new technology should be easy to use, robust and affordable to take to scale.

8 IMPLICATIONS FOR FUTURE POLICY, PRACTICE AND RESEARCH

- To maximise the effectiveness of case management of pneumonia, it is recommended that automated, easy to use, robust and affordable RR diagnostic aids for assessing symptoms of pneumonia for use in remote, resource poor settings are developed and tested.
- Handheld pulse oximeters with multiple probes, suitable for children of all ages, need to be considered when planning scale up of this technology in resource poor settings.
- Future studies should consider a robust, tailored approach which allows direct comparison between the performance measurement of the test device and the reference standard.
- A full health technology assessment methodology should be followed, and while laboratory testing is seen as valuable it should not replace field testing with frontline health workers in routine practice.
- There is a need to validate the reference standards available to establish the performance of new devices. The reference standard and test device measurements should be taken simultaneously and use the same measurement methodology.
- Agreement measures should reflect the true performance of the test device, including both under and over estimation of the measurements compared to the reference standard. Alternative study designs looking at clinical outcomes could also be considered in the absence of a robust RR reference standard.
- The different views of all key stakeholders need to be considered when mapping research and development priorities for pneumonia diagnostic aids, and public-private partnerships are a good way of creating opportunities to document a consensus view of these.
- Future data is required on the utility of introducing pulse oximetry at the community level.

9 METHODOLOGICAL CONSIDERATIONS

Overall study design

A strength of this thesis is the use of both quantitative and qualitative methods in a mixed methods hybrid design. Hybrid designs are those that blend design components of effectiveness and implementation research (156). The benefit of these types of designs include shortening the timelines for data collection by conducting the research concurrently and more useful and complete information for decision makers. Qualitative methods in sub-study I and III provided insight into frontline health worker views on device acceptability and suitability to scale as well as national stakeholder views on their usability and scalability. Quantitative methods in sub-study II a&b documented the performance of the nine test diagnostic aids, compared to reference standards. In using both quantitative and qualitative methods, the thesis was better able to explain the performance of the different diagnostic aids, and link this to the more qualitative usability and acceptability data.

Focus group discussions and interviews

Sub-study I used focus group discussions to collect data from both frontline health workers and national stakeholders. FGDs are useful to capture trends in opinion about the topic of interest. One limitation can be participant inhibition, where the group setting can hinder the active participation of individuals and affect data quality and depth (99). We ensured we minimised the possibility of this by have separate FGDs for each study population group, thereby creating a supportive, peer-led environment to encourage better participation and engagement.

The challenges with pneumonia diagnostic aid performance evaluations

There are a number of specific challenges in conducting performance evaluations where different classes of devices are included, such as in Sub-study II a & b, which included both RR counters and pulse oximeters. The first being selecting the most appropriate reference standard. In sub-study II a&b we selected an automated RR reference standard (Masimo Root patient monitoring and connectivity platform with ISA CO2 capnography and Radical 7 pulse oximeter). This reference was selected due to its portability and suitability for these settings, and has been validated in paediatric and neonatal populations (157, 158) but not necessarily in LMIC settings. The device used nasal cannulas to capture CO2 from patients and therefore this method could have challenges in young children, as they might be less receptive to the nasal cannulas. As one of the test pulse oximeters was also from Masimo the reference standard could be calibrated the same way as this test device, resulting in positive bias to the results.

Another challenge with a multi-device trial is timing, i.e. how to time data collection correctly and align with the development timelines of new diagnostic aids to ensure including the most relevant and innovative devices in data collection. For sub-study II a&b we had over 180 devices in our initial long list and landscape analysis (110). However, more than 50% of relevant devices were not available when we conducted our data collection, and therefore could not be included in the evaluation. Finally, maintaining consistency across the four research sites was challenging in all three sub-studies. Each country had very different settings and therefore each sub-study had to be designed and implemented to account for this. For each sub-study a protocol design workshop was held were all four countries came together and ensured that the protocol was co-created, with the specific requirements of each research site and study populations accounted for. Similarly, all study materials, training guides and job aids were co-created by all teams, translated into local languages and pre-tested before data collection in all three sub-studies. In sub-study II and III all health workers were trained and standardised in the same way and had to participate and pass a competency assessment before participating in data collection.

Generalisability and transferability of the results

A limitation of sub-study II a&b was that severely sick children were excluded for safety when designing the study, which resulted in a more limited spectrum of RR measurements and oxygen saturation levels in the study sample (i.e. less children with high RR measures and low SpO2 levels). To account for this, we conducted laboratory testing of the pulse oximeters before the hospital evaluation to test the accuracy of the pulse oximeters at a range of different oxygen saturation levels, using simulators.

For sub-study II a&b busy hospitals were selected in each of our four research sites in order to ensure that we achieved the required sample of 1,720 children. This is not the routine work environment for the majority of the community-based health workers or health works that we included in the study. However, the patient load in the CHWs' home setting would be too low to allow for recruitment of the required sample size. To mitigate for this bias, we also conducted field work also in the routine work setting of the health workers to allow data to be collected on the usability, utility and acceptability of these devices in the routine care setting of health workers in the four research locations, and this will be presented elsewhere.

10 ACKNOWLEDGEMENTS

This has been an amazing journey and I can't believe I got here alive, having enjoyed it so much, but perhaps with a little more grey hair….

It absolutely would not have been possible without the support, participation and care of so many people and I hope I am not missing anyone out in the following list:

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My supervisor – Associate Professor Karin Källander, who has continued to inspire me since we met in Uganda, in what now seems like a lifetime ago, at the inception of these studies. Thank you for your constant insistency on quality and scientific rigour, often when I may have just wanted to get it done!

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To my friends around the world – without whose support and opportunities for distraction I could not have done this – thanks to all and here's to many more!

11 APPENDIX 1 DEVICE ATTRIBUTES

No.	Attribute	Description
1	Usability - ease of use	Easy for CHWs to use the device i.e. can apply it appropriately e.g. switch on the device, select the correct settings, complete the assessment to get a result
2	High level of decision support	Allows the community health worker to detect the symptoms of pneumonia without the need for decision making from them
3	Automation of diagnosis	Automatically provides the CHW with a diagnosis of pneumonia symptoms
4	High accuracy of measured/calculated result	The device consistently provides an accurate measure of the result tested for – either RR or PO
5	No or little literacy and numeracy required	The device only requires a very low level of literacy and/or numeracy to be operated by the CHW
6	No or little training required	The CHW only requires minimal amounts of training to be able to use the device effectively to detect the symptoms of pneumonia
7	No or little familiarity with technology required	The CHW does not need any prior familiarity with technology to operate the device effectively to detect the symptoms of pneumonia
8	Long operational life in the field – e.g. more than two years	The device (not probes) will have an operational life while being used by CHWs of more than 2 years
9	Does not require charging (solar, battery, grid)	The device does not require charging to be used by CHWs to detect the symptoms of pneumonia
10	Does not require replaceable parts	The device does not require replaceable parts such as non-rechargeable batteries and/or consumables throughout its functional life in the field
11	Requires little or no maintenance	The device does not require any maintenance throughout its operational life when used by CHWs to effectively detect the symptoms of pneumonia
12	High durability/mechanical robustness	The device will not break during normal use by the CHW in the detection of the symptoms of pneumonia
13	High CHW confidence in measurements	The readings provided by the device support the CHW in relation to detecting the symptoms of pneumonia
14	High caregiver acceptability of diagnosis	The readings provided by the device help and support the caregiver/parent in accepting the diagnosis offered by the CHW
15	High patient comfort	The device does not cause hurt or discomfort to the patient while being used by the CHW in the detection of the symptoms of pneumonia
16	High portability	The device is easy to carry by the CHW during normal working
17	Easy to maintain hygiene	The device is hygienic and easy to maintain in this regard – i.e. doesn't require specialist cleaning procedures or products
18	Low price (less than $50)	The annualized device cost is less than $50 (Device = total package of device plus consumables such as batteries/probes and chargers)
19	High level of safety	The device provides a high level of safety when it is being used for the detection of the symptoms of pneumonia

20.	Multi-functional (includes a minimum of RR and Pulse oximeter)	The device incorporates several applications for the detection and classification of the symptoms of pneumonia

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