**Project Title:**

Children's Automated Respiration Monitor (ChARM) for child pneumonia diagnosis by Community Health Workers in Mali: Innovating ChARM's role in supervision, training and diagnosis, a cluster randomized control trial

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**Study Location:** Koulikoro and Banamba districts, Koulikoro region, Mali

**Proposed project dates:** **December 2017 – December 2018**

**Project Summary**

| | |
|---|---|
| Title | Children's Automated Respiration Monitor (ChARM) for child pneumonia diagnosis by Community Health Workers in Mali: Innovating ChARM's role in supervision, training and diagnosis, a cluster randomized control trial |
| Short Title | Children's Automated Respiration Monitor (ChARM) for child pneumonia diagnosis by Community Health Workers in Mali |
| Clinicaltrials.gov | NCT03457519 |
| Design | Cluster Randomized Pragmatic Parallel Trial |
| Study Duration | Intervention Group A - Community Health Workers (CHWs) (Basic training in CHW curriculum, ChARM training and 8-month application of the ChARM device, self-monitoring, direct observation and review of CHW routine monthly reports and drug supply sheets): 8 months, March-December 2018.<br><br>Intervention Group B - Community Health Workers (Basic training in CHW curriculum, ChARM training and 4-month application of the ChARM device, self-monitoring, direct observation and review of CHW routine monthly reports and drug supply sheets): 8 months,– March- December 2018.<br><br>Control Group C - Community Health Workers (Basic training in CHW curriculum, direct observation and CHW routine monthly reports and drug supply sheets): 8 months, – March- December 2018.<br><br>CHW and Field Monitor In-depth interviews – December 2018<br><br>Data analysis and report writing – December -January 2018 |
| Study site | Koulikoro and Banamba districts in Koulikoro Region, Mali |
| Primary Objective | The primary objective of this study is to estimate the impact of a self-monitoring tool (ChARM), used as a teaching/monitoring device, on the CHWs respiratory rate counting accuracy when assessing children under the age of 5 years with suspected pneumonia symptoms. |
| Study Intervention | Basic training on ChARM device and application of the device on children under five with suspected pneumonia symptoms. |
| Primary Outcome | Acute Respiratory Illness (ARI) Case fatality rate |
| Secondary Outcomes | Respiratory rate counting accuracy<br>Proportion of pneumonia cases detected and treated by CHWs<br>Proportion of suspected severe pneumonia cases referred by CHWs to the CSCom<br>Proportion of suspected pneumonia cases in the community who sought care from a CHW<br>Accuracy in drug management and procurement requests |
| # of CHWs | Intervention Group A: approximately 49 (1/3 of the CHWs, randomly selected)<br>Intervention Group B: approximately 49 (1/3 of the CHWs, randomly selected)<br>Control Group C: approximately 50 (1/3 of the CHWs, randomly selected) |
| Main Inclusion Criteria | • Be currently providing iCCM services on a full-time basis to the populations they are serving.<br>• Have completed the Malian Ministry of Health basic community health care worker training provided as part of the 2016-2020 Strengthening Maternal, Newborn and Child Health project. |

| | |
|---|---|
| | • Are using a device (a respiratory timer) as part of their basic MoH training package, or have a cell phone to use to count the respiratory rates of children under five with suspected symptoms of pneumonia.<br>• Be willing to participate in a trial to study the impact of using ChARM as a self-monitoring tool to improve the capacity to detect pneumonia. |
| Main Exclusion Criteria | • CHWs in conflict ridden geographical areas within the district or not, providing consistent services on a full-time basis to the populations they are serving.<br>• CHWs not willing to participate in the trial.<br>• CHWs who do not have a device (watch, respiratory timer or cell phone) to support measurement of respiratory rates and who are not routinely counting respiratory rate to diagnose suspected pneumonia.<br>• CHWs who did not complete the MoH basic training for CHWs provided through the 2016-2020 Strengthening Maternal, Newborn and Child Health program. |
| Main Study Procedures | • In-service trainings of community health care workers on :<br>o Using the ChARM device to assess the respiratory rate in children under the age of 5 years with suspected pneumonia.<br>o Using the ChARM device to self-monitor competency in counting respiratory rates in children under the age 5 years with suspected pneumonia.<br>• In-depth interviews (IDI) to assess the effectiveness of ChARM as a self-monitoring tool and its potential to scale up. |

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## Acronyms

| | |
|---|---|
| ARI | Acute Respiratory Illness |
| ChARM | Children's Automated Respiration Monitor |
| CHW | Community Health Worker |
| CRC | Canadian Red Cross |
| CSCom | Centre de santé communautaire (*Community Health Centre*, in English) |
| CSRef | Centre de santé de référence |
| DSMB | Data and safety monitoring board |
| DTC | Directeur Technique du Centre (*Technical Director of Health Centre*, in English) |
| FMPOS | Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie de Mali (*Faculty of Medicine, Pharmacy, Odonotology and Stomatology of Mali*, in English) |
| HH | Household |
| iCCM | Integrated Community Case Management |
| IDI | In-depth interviews |
| IPE | International Program Evaluation |
| ITT | Intention to treat |
| MNCH | Maternal, Newborn and Child Health |
| MoH | Ministry of Health |
| MRC | Mali Red Cross |
| ODK | Open Data Kit |
| PEC | Prise en charge (*Case management*, in English) |
| PI | Principal Investigator |
| RCT | Randomized Control Trial |
| REB | Research Ethics Board |
| RRT | Respiratory Rate Timer |
| SickKids | The Hospital for Sick Children (Toronto, Canada) |
| TCPS 2 | Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans, 2nd edition |
| UNICEF | United Nations Children's Fund WHO World Health Organization |

## 1. Title

Children's Automated Respiration Monitor (ChARM) for child pneumonia diagnosis by Community Health Workers in Mali: Innovating ChARM's role in supervision, training and diagnosis, a cluster randomized control trial

## 2. Trial Registration

NCT03457519

## 3. Protocol Version

Version 2 – March 05, 2018

## 4. Funding

Grand Challenges Canada grant to the Canadian Red Cross
Program officer: Lindsay Angelow (Lindsay.Angelow@redcross.ca)

## 5. Roles and Responsibilities

Names, affiliations, and roles of protocol contributors

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Role of study sponsors

*Study Sponsors (Canadian Red Cross and The Hospital for Sick Children)*:

- Overall responsibility for study design
- Collection, management, analysis, and interpretation of data
- Writing of the report; and the decision to submit the report for publication, including having joint ultimate authority over any of these activities
- Pre-intervention implementation of CHWs trainings in the MoH basic curriculum in program area

## 1. Background and Rationale

Globally, pneumonia accounts for 16% of all deaths of children under 5 years old[i]. In sub-Saharan African (SSA) countries it causes approximately 750 000 child deaths per year in. In Mali, about 900,000 pneumonia episodes occur in children under 5 years of age annually, leading to almost 8,000 deaths.[ii] Pneumonia accounts for 2% of under-five deaths in Mali, but only 38% of children under five presenting with symptoms of pneumonia are taken to an appropriate health provider. In line with the World Health Organization (WHO) guidelines, increasingly, the first point of contact with the health care system for people seeking care for pneumonia symptoms is through community health care workers (CHWs)[iii]. Aware that access to accurate diagnosis, treatment and appropriate referral determines a child's survival the Mali Ministry of Health (MoH) introduced Integrated Community Case Management (iCCM) in 2007, authorizing community health workers (CHWs) to diagnose and treat pneumonia, malaria, diarrhoea and malnutrition in children under five.[iv] Research has suggested that community case management of pneumonia, if properly implemented, could reduce under-five deaths from pneumonia by 70%[v].

In 2012, WHO and UNICEF published a joint statement that supported iCCM *as "an essential strategy that can both foster equity and contribute to sustained reduction in child mortality*" and identified fast breathing as the key presenting symptom for diagnosing and treating pneumonia using the iCCM strategy[vi]. WHO has set the threshold for respiratory rate (respiratory rate per minute) in infants less than 2 months at a respiratory rate of 60 per minute, for children 2 to 12 months at a respiratory rate of 50 per minute and for children 1 to 5 years at a respiratory rate of 40 per minute[vii] and includes these guidelines in its Integrated Management of Childhood Illness (IMCI) handbook widely used as the technical guidelines at the community level of care[viii]. Studies demonstrate that there is evidence to show that, when well-trained, CHWs can adequately manage pneumonia cases at the community level[ix]. However, when training is deficient CHWs' skills in measuring respiratory rates and accurately classifying pneumonia remain a challenge[x] [xi] [xii].

In Mali, as part of their basic training, CHWs are trained to detect suspected pneumonia cases using video, practice sessions and their basic training manual. Algorithms used for diagnosis developed in the 1980s include assessing danger signs in children with a cough, counting respiratory rates, and observing chest in drawing to classify respiratory illness[xiii]. These algorithms correspond with WHO's definition of presenting symptoms for pneumonia: cough and/or difficult breathing, with or without fever, the presence of either fast breathing or lower chest wall in- drawing where the child's chest moves in or retracts during inhalation.[xiv] Because counting respiratory rate by observing the chest, by using a stethoscope or putting one's hand on an abdomen has been shown to have conflictive results[xv], both WHO and UNICEF recommend respiratory rate timers (RRTs) as a CHW diagnostic tool for pneumonia at the community level. There are several studies that have demonstrated that these tools can be used successfully by CHWs trained to use them[xvi]. However, study results cautioned that for CHWs to be able to easily and accurately classify pneumonia cases additional practice in counting respiratory rates and simple job aides would be necessary[xvii] [xviii].

Pneumonia is the number one cause of under-five deaths in Mali and case fatality rates can exceed 20%, but in 2013, of the 231,548 reported pneumonia cases only 20% were treated by CHWs. The quality of community health workers' diagnostic skills can influence how communities accept and use these workers. Poor competency in CHWs to correctly count respiratory rate, a key indicator for pneumonia detection, puts CHWs and their patients at risk of frequently misdiagnosing pneumonia and over prescription of antibiotics. The need for strong CHW competency to correctly count respiratory rate for a quick and accurate detection of pneumonia is evident.

The challenge for many countries implementing iCCM is a lack of funding to provide consistent supervision, refresher courses and feedbacks, putting at risk the populations CHWs are placed to serve. In 2014, only 63% of routine supervisory visits to assess CHW skills in Mali were reported to be completed[xix]. Supportive supervision has been a continuous reported gap in ICCM and studies have demonstrated the correlation between strong supervision and improved CHW performance[xx] [xxi]. Research shows that the access to mHealth tools, for CHWs working in remote areas and having access to consistent training and supervision, can help improve the effectiveness of the services they provide[xxii].

Royal Philips' 2015 pledge to Every Woman, Every Child includes improved pneumonia diagnosis and treatment in low resource countries. To this end, Phillips invented the Children's Automated Respiratory Monitor (ChARM), a low cost device for low skilled health workers. Clinical tests have concluded that ChARM is *an acceptable alternate diagnostic tool for identifying fast breathing among <5 children, which may have potential for use at point-of-care by low-skilled community health workers in low resource countries* [xxiii] The proposed study will test whether or not the Children's Automated Respiratory Monitor (ChARM) can be successfully used as a tool to help CHWs self-monitor and improve their competency to count respiratory rate accurately, diagnose pneumonia cases correctly and determine whether to treat or refer a child under 5. By applying the ChARM device on the child, and at the same time counting the child's respiratory rate themselves, the CHWs can carry out an accurate real time assessment of their breath counting skills. This randomized cluster trial will evaluate ChARM's potential as a teaching/monitoring tool to support CHWs skill improvement in the diagnosis and treatment of children under 5 with symptoms of suspected pneumonia.

## 2. Objective

The primary objective of this study is to estimate the impact of a self-monitoring tool (ChARM), used as a teaching/monitoring device, on the CHWs respiratory rate counting accuracy when assessing children under the age of 5 years with suspected pneumonia symptoms.

The study is embedded in a 2016-2020 Maternal, Newborn and Child Health (MNCH) program in Mali funded by Global Affairs Canada; in partnership with the Malian and Canadian Red Cross Societies, the Mali Ministry of Health and the SickKids Centre for Global Child Health. The embedded nature of the study reduces project costs.

## 3. Trial Methodology and Sample Size

Methodology:

The study is designed as a community based, cluster randomized, pragmatic, intervention trial. It will be conducted within the existing 2016-2020 project structure. Specifically, the intervention will evaluate the potential of the ChARM device to improve CHWs competency in counting respiratory rate and diagnose pneumonia more accurately in children under 5 years presenting with symptoms in remote areas.

Sample Size:

Within the 2016-2020 Strengthening Maternal, Newborn and Child Health program 441 CHWs have been trained using the Ministry of Health curriculum to diagnose pneumonia in children under 5 by monitoring the respiratory rate visually using a timer. Counting respiratory rates visually using a timer is part of the MoH protocol for CHWs providing care to all children under 5 years of age seeking consultations presenting with symptoms of a cough and/or cold.

The study will be implemented in two (Banamba and Koulikoro) of the six districts the MNCH project is targeting. Of the 441 community health workers involved, 148 will participate in the study, 75 in Banamba and 73 in Koulikoro. This represents 34% of the 411 CHWs in the 2016-2020 program implementation area. **In each of the two** districts, 1/3 CHWs will be randomly assigned to intervention group A (monitoring the respiratory rate visually using a timer and the ChARM device for 8 months), 1/3 will be randomly assigned to intervention group B (monitoring the respiratory rate using both visual counting with a timer and the ChARM device for 4 months, followed by monitoring

the respiratory rate visually using a timer only for the next 4 months) and 1/3 of the CHWs will be assigned to group C (monitoring the respiratory rate visually using a timer only). This group will not be trained in ChARM nor use the device during the study).The CHWs will be randomly assigned to the following groups prior to the intervention.

Intervention and control groups are:

- Intervention Group A: CHWs trained in ChARM and using ChARM as a self-monitoring tool for 8 months while counting respiratory rate of children under 5 visually using a timer.
- Intervention Group B: CHWs trained in ChARM and using ChARM as a self-monitoring tool for 4 months while counting respiratory rate of children under 5 visually using a time; then discontinue using ChARM and continue to monitor the respiratory rate visually using a timer only for the remaining 4 months.
- Control Group C: CHWs who did not receive the ChARM training and will be monitoring the respiratory rate of children under 5 visually using a timer only, as per the MoH traditional training.

Throughout the study 3 independent Field Monitors will follow each group's participants in both Banamba and Koulikoro (i.e. one Field Monitor will follow 1/2 CHWs in Group A in Banamba and 1/2 CHWs in Group A Koulikoro; the Field Monitors responsible for Groups B and C will also follow one study group each, in both areas). The Field Monitors will be responsible for both testing the accuracy of the CHWs' ability to count respiratory rate and for collecting data during the study from the CHW reports and drug records. The Field Monitors will receive the same training as the CHWs in the Intervention Groups A and B, and additional training on data collection and observation protocol. The Field Monitor will test the CHWs' capacity to count respiratory rate during three intervals:

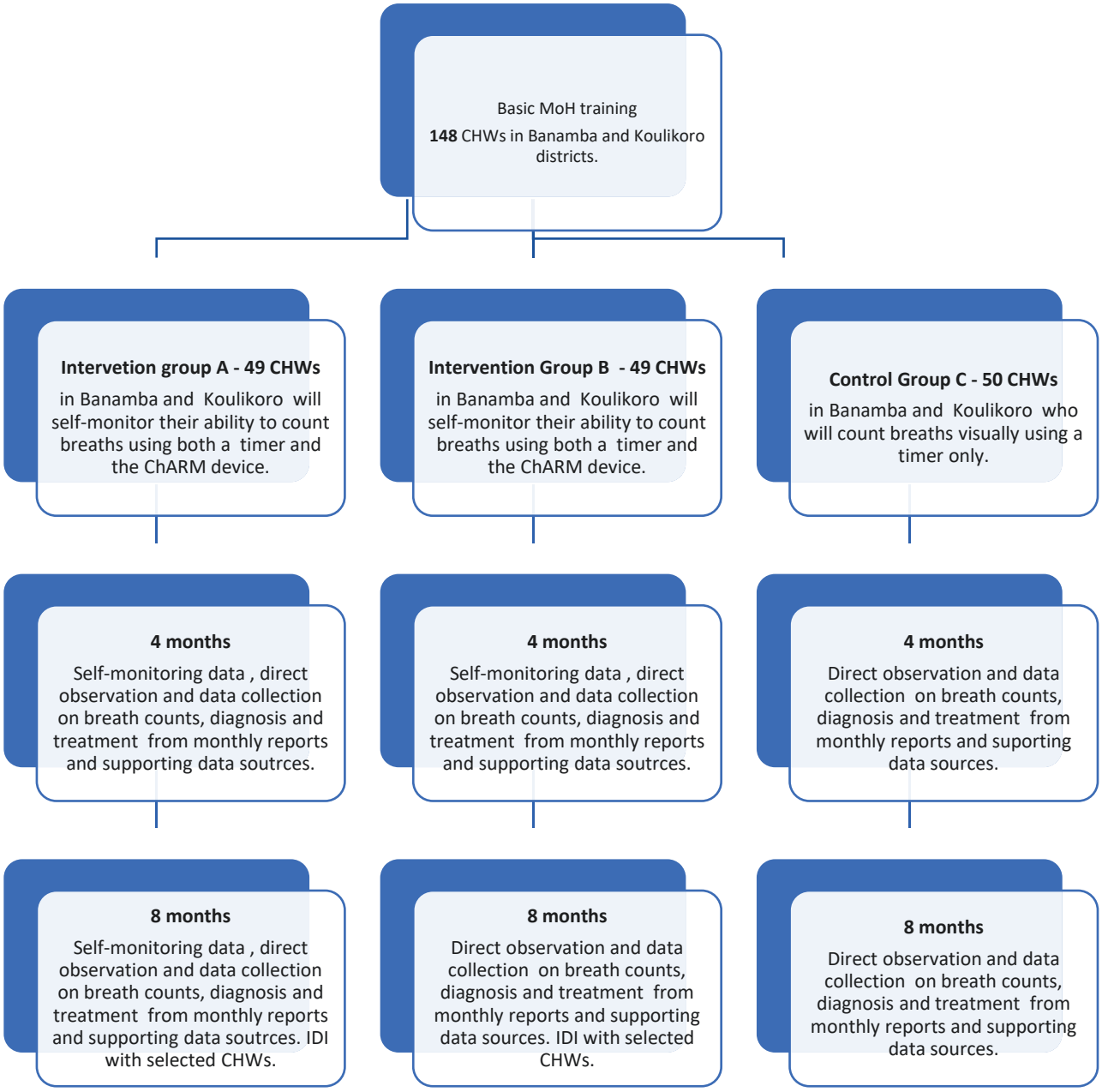
- Before the ChARM training
- 4 months after initiating the use of the ChARM device
- 8 months after initiating the use of the ChARM device (which corresponds to 4 months after the ChARM device will be discontinued for group B).

At each of the three measures, the Field Monitor will test CHWs on their visual respiratory rate counting capacity using a timer against the ChARM automated readings and review supporting data sources. To maintain the study observation periods comparable, and save on the additional logistics costs, the intervention will be rolled out in Koulikoro 1 month after it has been rolled out in Banamba. Therefore, for the 2$^{nd}$ and 3$^{rd}$ direct observation the Field Monitors will begin first in Banamba and then one month later in Koulikoro. This will allow time for the Field Monitors to carry out the site visits required for each district for each of the measurements (approximately 24 visits per Field Monitor per district). As a result, the 2$^{nd}$ and 3$^{rd}$ measure for Groups A and B and C in Banamba will be at 4 months and 8 months, and the same groups in Koulikoro will be measured one month later, but still at 4 and 8 months.

The qualitative evaluation will be undertaken only in the Intervention Groups A and B using In-depth Interviews (IDIs) with CHWs, Field Monitors and the Technical Director of the Health centre responsible for the CHWs. In total 25 IDIs will be carried out. The Study Coordinator will be responsible for supporting the research and qualitative researcher who will be carrying out the IDIs. In total, anticipated number of IDIs are:

- Field Monitors - 3 IDIs, one interview with each one
- Technical Director of Health Centre (Directeur Technique du Centre/CSCom) (DTCs) – 10 IDIs (5 in Banamba and 5 in Koulikoro)
- Community Health Workers – 12 IDIs

**Figure I: RCT Flow Chart**



## 4. Randomization

An epidemiologist not directly involved in the research project will perform randomization of clusters. Due to the nature of the intervention, blinding is not possible, however to ensure reduced measurement bias, data on the effect of the intervention will be collected by independent data collectors; not involved in the intervention delivery. The unit of randomization will be the community health worker.

## 5. Study Setting

The trial will take place in the iCCM sites in 2 districts (Banamba and Koulikoro) in the Koulikoro region in Mali. These sites were selected because of their proximity to each other, similarity in the number of CHWs working in each district and because both districts are part of the larger 2016-2020 CRC program to improve care seeking practices and utilization of CHWs in the diagnosis and treatment of pneumonia, malaria and diarrhoea. Political stability and availability of population and health facility data from the CRC program baseline survey in 2016 were also taken into account.

**Koulikoro Region** is the second-most-western region of Mali. It covers an area of 90,120 $km^2$ with an estimated population of 2,418,305 and a density of 26.83 people per square Km of land area as of 2009. Field operations for the study will be managed and coordinated by a Research Coordinator in Mali hired as part of the Canadian Red Cross locally supported staff.

Cluster Definition

A cluster is defined as the population to which a CHW is providing health services in areas more than 5 kilometers from a Centre de Santé Communautaire (CSCom). One community health worker is assigned to 1500 people (approximately 250 households dispersed across up to 3 villages).

**Figure II: Study Districts Profile**

| *Districts | *Total Population | *No. of HH | *Urban | *Rural | *Women 15-49 years | **Total CSComs | ***Total CHWs | **Total No. of children under five in 2016 who are covered by CHW sites | ***MRC Volunteers (Villages) |
|---|---|---|---|---|---|---|---|---|---|
| Banamba | 191,005 | 28,278 | - | 191,005 | 37,850 | 18 | 75 | 18,301 | 339 (107) |
| Koulikoro | 210,611 | 33,068 | 41,602 | 169,009 | 44,390 | 20 | 73 | 13,957 | 258 (101) |

*4th General Housing and Population Census of Mali (RGPH), November 2011
** Ministry of Health, Mali
*** Mali Red Cross (MRC)

## 6. Study Duration

**Phase I: (4 months)**

The first phase of the study (the baseline testing, training and rollout of the intervention) will take place in March-June 2018. (For logistic purposes, the study will roll out in both districts at a one month interval). All 148 CHWs from the two districts will have their breath counting capacity assessed against the ChARM automated reading. Monthly reports, consultation/referral forms, and the drug supply forms for all participating CHWs will be reviewed and the data will be abstracted for study purposes, and the number of pneumonia cases treated and/or referred will be documented.

CHWs randomized to intervention Groups A and B will be trained to use the ChARM device and in data collection requirements (filling out the self-monitoring sheet and getting consent from caregivers of children under 5). For the 4 months of Phase 1, CHWs in Intervention Groups A and B will count the respiratory rate of all children under five presenting with symptoms of cough or cold, using the timer and visual counting simultaneously with the ChARM device. Group C will count the respiratory rate using visual counting with the timer only.

**Phase II: (4 months)**

The second phase of the study will take place from July-November 2018. In the first month of this phase Field Monitor will retest CHWs for the 2nd time in all groups on their breath counting capacity against the ChARM automated reading and record results. The Field Monitor will also review the CHW monthly reports, consultation/referral forms, the drug supply forms, as well as the self-monitoring forms filled in by the CHWs. (Please see Annex 1 for a copy of all forms).

During Phase II, Group A will continue to count the respiratory rate of all children under five presenting with symptoms of cough and/or cold, simultaneously using the timer and visual counting and the ChARM device. However, once Group B is tested, the CHWs in that group will stop using ChARM and will start to count respiratory rate using only the visual counting measured by the timer. Group C will continue to count respiratory rate using only visual counting measured by the timer.

An interim analysis of the data from Phase II will be undertaken by an independent researcher (to be chosen by the DSMB) once testing has been completed in the three groups.

**Phase III: (4 months)**

This phase has three main activities. The first is the 3rd testing by Field Monitors of CHWs in all groups of their breath counting capacity against the ChARM automated reading and the recording of results. The Field Monitors will also review the CHW monthly reports, consultation/referral forms, the drug supply forms, as well as the self-monitoring forms filled in by the CHWs.

Once retested, CHWs in Group A will stop using ChARM and will start to count respiratory rate only using the visual counting measured by the timer. CHWs in Groups B and C will continue to count respiratory rate; only using visual counting measured by the timer.

The second activity will be qualitative research in the form of in-depth interviews. In each district, in-depth interviews with participants from Group A and B CHWs working at 5, 10 and 15 kilometres from their associated CSComs will be held to better understand their perception of working with ChARM and its value as a self-monitoring tool and their perspective on whether it is something they would recommend the MoH add to its CHW curriculum.

In addition, in-depth interviews with the three Field Monitors and a sample of the Technical Director of Health Centre (Directeur Technique du Centre/CSCom) (DTCs) from the CSComs associated with the CHWs will be conducted. The IDIs will focus on their perceptions on the effectiveness of ChARM as a tool to improve CHWs accuracy in diagnosing pneumonia and referring complicated cases to the CSCom, and whether the ChARM tool has potential to be scaled up and made part of the MoH curriculum is also something that will be examined.

The third activity will be the analysis of quantitative and qualitative data from Phase III by Sickkids in preparation for developing the final study report.

The timeline of the study can be seen in Figure IV: Timeline of the Trial.

## 1. 7. Participant Eligibility Criteria and Enrolment

All CHWs within the project area of Koulikoro and Banamba will be eligible for enrollment in this study.

**Inclusion Criteria:**

1. Be currently providing iCCM services on a full time basis to the populations they are serving.
2. Have completed the Malian Ministry of Health basic community health care worker training provided as part of the 2016-2020 Strengthening Maternal, Newborn and Child Health program.
3. Are using a device (a respiratory timer as part of their basic MoH training package) to count the respiratory rates of children under five with suspected symptoms of pneumonia.
4. Be willing to participate in a trial to study the impact of using ChARM as a self-monitoring tool to improve their capacity to detect pneumonia.

**Exclusion Criteria:**

1. CHWs in conflict ridden geographical areas within the region or not providing consistent services on a full time basis to the populations they are serving.
2. CHWs not willing to participate in a trial to assess the impact of using ChARM as a self-monitoring tool to improve their capacity to detect pneumonia.
3. CHWs who do not have a device (a respiratory timer) to measure respiratory rate and who are not routinely counting respiratory rate to diagnose suspected pneumonia.
4. CHWs who did not complete the MoH basic training for CHWs provided through the 2016-2020 Strengthening Maternal, Newborn and Child Health program.

**Enrollment**

1. Approval from the Ministry of Health Mali and the Regional Directorate of Health, Koulikoro will be obtained to enroll CHWs providing iCCM services in the districts of Koulikoro and Banamba in the study.
2. Subsequently the local study coordinator will visit the MoH district level staff and share the letters of approval from the MoH and regional directorate with the facilities responsible for the CHWs working in the Banamba and Koulikoro districts to formalize the enrollment.
3. All consenting women and men seeking care from the CHW for a child under 5 presenting with symptoms of pneumonia (i.e. cough and/or cold) will be invited to provide consent and enroll in the study.

## 8. Intervention Groups

The intervention is a training in ChARM device offered to CHWs providing iCCM services to children under-five in the districts of Banamba and Koulikoro.

Once all CHWs in the two districts have been randomized into the three groups and had their breath counting skill tested using ChARM as a global measure, the CHWs randomized to Groups A and B will receive a 1-day training on the ChARM device. During the training, CHWs in intervention groups will learn how to use the ChARM device as a self-monitoring tool by comparing the respiratory rate they count visually when using the timer against ChARM's automated read-out during assessment of all children under-5 years presenting with symptoms of pneumonia (cough and/or cold). CHWs will be instructed to record the two measurements on the self-monitoring sheet and to continue to record the child`s respiratory rates, treatment and referrals on the MoH forms they routinely fill out.

All CHWs in Groups A and B will use the both ChARM and visual breath counting using the timer for the first 4 months of the study. In the case of a discrepancy where there is enough variation that the CHW visual counts using a timer and the ChARM reading would put the child in different categories (i.e. rapid or non-rapid respiration) then the CHW will be instructed to use the ChARM reading for filling the section on the MoH form for Individual Case Management of a Sick Child (Fiche Individuelle de Prise en Charge de l'Enfant Malade – PEC) form. (Annex 1).

In the fifth month the Field Monitor will retest CHWs in Groups A and B, using the ChARM device as a global measure. The Field Monitor will also review the CHW monthly reports, PEC consultation/referral forms, drug supply forms, and the self-monitoring forms filled in by the CHWs.

For months 5 – 8, CHWs randomized to Group A will continue to use ChARM as a self-monitoring tool, continue to count respiratory rate visually using a timer and to compare and record the two measurements. Group B CHWs will discontinue using ChARM and only count respiratory rate visually using a timer. Both groups will continue to record the child`s respiratory rates, treatment and referrals on the MoH forms they routinely fill out.

## 9. Control Group

All CHWS in the three groups received training on the basic CHW curriculum given by the Ministry of Health as off August 2017. In the training, they all received respiratory timers and were trained to count respiratory rate using those timers through classroom instruction, videos, and hands on practice in a health facility setting.

The control group (Group C) composed of 1/3 of the CHWs in Banamba and 1/3 of the CHWs in Koulikoro will have completed the basic MoH training, but will not receive the additional ChARM training or receive the device. Throughout the study Group C will count respiratory rate visually using a timer only and record the child`s respiratory rates, treatment and referrals on the MoH forms they routinely fill out when assessing and treating a child presenting with symptoms of pneumonia. The Field Monitor for Group C in both districts will measure their breath counting competency, using the ChARM device as a global measure following the same testing intervals as the intervention groups A and B.

## 10. Study Trainers

The Intervention trainer for demonstrating how to count respiratory rates will be selected according to the following criteria:

a. A pediatrician from the Ministry of Health
b. Preferably a resident of the intervention district (Koulikoro and Banamba)

The ChARM trainer will be selected according to the following criteria:

a. A medical professional practicing in Mali who has been trained in using the ChARM device either by a representative of the manufacturer personally or through the instructional material developed by the manufacturer (Annex 2)

The Field Monitors for the three groups will be selected according to the following criteria:

a. A practicing health professional in Mali who has participated in the training given by the pediatrician to count respiratory rate visually using a timer.
b. A practicing health professional who will have participated in the training on how to use ChARM given by the ChARM trainer.
c. Is in agreement to be available over a 10-month period in order to carry out 3 observations, of CHWs, record results and gather supporting data from routine forms filled out by the CHWs.

The Qualitative Researcher will be selected based on the following criteria:

1. a. A Malian national fluent in French and the local language of Bambara.
2. b. Previous experience in conducting in-depth interviews (IDI) with people working at the community level.

## 11. Data Collection

**Logistics**

16.1. Field Monitors

The Field Monitors (described above) will be responsible to collect data at three different time periods, before the intervention, 4 months after the intervention begins and 8 months after the intervention begins. There will be one Field Monitor each for Groups A, B and C who will cover those groups in both districts. They will be practicing health

professionals and have participated in the 1-day ChARM training in which they will receive in-depth understanding of the required data collection forms and the ChARM device. Field Monitors will conduct 3 site visits to test the CHWs respiratory rate counting ability using a timer against the ChARM automated reading and record both readings. They will review and document the number of cases assessed for pneumonia, treated and/or referred by CHWs during the three testing periods.

**Data Collection**

**i)** Quantitative Data Collection:

Written informed consent will be taken from participating Community Health Workers in the Intervention and Control Groups, and from parents and caregivers of all children under five who will have their respiratory rates counted using the ChARM device. It will be made clear that eligible participants are under no obligation to participate in this study. In addition, the time burden associated with being involved in this study will be clearly outlined during the consent process.

Data from the CHW self-monitoring sheets filled out by Intervention Groups A and B will be reviewed and documented by the Field Monitor. The Field Monitor will also measure all CHWs respiratory rate counting capacity using ChARM as a global standard and collect routine CHW data three times during the study. This routine data is found in both the CHW monthly reports and the consultation/referral forms. Data from drug supply forms filled out by CHWs will also be collected to identify any variations that may occur due to more accurate pneumonia diagnosis by CHWs as a result of using ChARM and to triangulate this data with the consultation forms and other sections of the monthly report.

ii) Qualitative Data Collection:

Qualitative data collection will only take place in the intervention Groups A and B. Written, informed consent will be taken from CHWs, Field Monitors and MoH Technical Director of Health Centre (Directeur Technique du Centre/CSCom) participating in in-depth interviews. (Consent Forms - Annex 3, Questions for In-depth interviews - Annex 4).

**Outcomes:**

Primary outcome:

Acute Respiratory Illness (ARI) Case fatality rate

Secondary outcomes:

Respiratory rate assessment accuracy
Proportion of pneumonia cases detected and treated by CHWs
Proportion of suspected severe pneumonia cases referred by CHWs to the CSCom
Proportion of suspected cases of pneumonia in the community who sought care from a CHW
Accuracy in drug management and procurement requests

**Sample size:**

48 clusters with average size of 50 suspected ARI cases per cluster per arm (over 8 months) are sufficient to detect a 30% reduction in the ARI case-fatality rate (from 20% at baseline), with 80% power and 5% significance. Differences in all secondary outcomes are powered above 80% within this sample size.

**iCCM Curriculum Training: Intervention & Control sites**

Participants: CHWs in Koulikoro and Banamba districts (n=148)

Time frame: Completed as part of CRC program implementation in Mali (December 2016 – August 2017)

Responsibility: CRC/MoH Mali Trainers

Training Material: Ministry of Health iCCM curriculum for CHWs –18-day curriculum including classroom instruction and hands on training.

**Intervention Training: Intervention sites**

Participants: CHWs in Koulikoro (n≅49) and Banamba (n≅49) districts.

Time Frame: After iCCM curriculum training; 9 months–1month for training CHWs in ChARM and 8 months for monitoring.

Responsibility: External Trainers and Study coordinator

A. CHWs trained in ChARM and the self-monitoring data collection format.
B. Submission of regular MoH monthly reports, consultation referral forms, drug supply forms.
C. In-depth interviews for CHWs, Field Monitor and the Technical Director of Health Centres (Directeur Technique du Centre/CSCom) on their perception of ChARM tool and recommendations for future use as a teaching tool and/or scale up by the MoH.

**Control Sites**

CHWs in Koulikoro and Banamba districts (n=49)

Time frame: 8 months–including initial measurement of respiratory rate counts using a timer against ChARM`s automated reading and subsequently repeating the measurement twice during the study.

A. Pneumonia diagnosis as per usual practice of visually counting respiratory rate using a respiratory timer.
B. Submission of regular monthly reports, consultation/referral reports and drug supply reports for review by Field Monitors.

## 12. Data Processing and analysis

Data (described in section 16) will be collected on paper by the Field Monitors. Data will be entered in the ChARM database by the field monitors and study coordinator, after the data is entered it will be checked for consistency and/or missing responses. Inconsistencies and/or omissions will be flagged and communicated to interviewers for clarification.

The data entry forms, databases and interface will be developed using ODK. The data entry forms will employ range and consistency checks and logical skips to improve interview efficiency and minimize data entry errors. Special arrangements will be made to enforce referential integrity of the database so that all data tables are related to each other.

The trial data will be analyzed as "Intention to treat" (ITT).

After successful completion of data transfer agreements between the Academic Partner in Mali and SickKids, de-identified data will be transferred to SickKids using the SickKids-based secure online file transfer protocol managed by the Research Information Technology team at SickKids. Once the data have arrived at SickKids, it will be secured behind the SickKids firewall, which is backed up by the hospital system (SickKids server/cloud). Data will be encrypted and will only be made available to Dr. Diego Bassani and his SickKids' research personnel who have successfully completed the TCPSII Course on Research Ethics training and have been added to the REB application for this study. For quantitative data analysis STATA version 13 and for qualitative data analysis Nvivo will be used.

## 13. Field Supervision and Quality Control

An in-country project team composed of a part-time Study coordinator and three Field Monitor, with support from the project team, will coordinate project activities. The Study coordinator will assist with the training of Community Health Workers in the intervention and control clusters along with three Field Monitors and the CRC/MRC program staff. The project team will also be responsible for all the logistics and monitoring support of project activities and the Study coordinator will be responsible for the overall oversight.

The Field Monitors will be responsible for ensuring quality control in data collection as well as maintain close liaison with the Community Health Workers and the field project staff to have access to project data if necessary. They will also ensure timely and accurate paper data transfer from field to the Study coordinator who will also have overall responsibility for the on-ground management and supervision of the trial.

## 14. Data Safety Monitoring

A data and safety monitoring board (DSMB) will be convened with three individuals, Dr. Shaun Morris, at the Hospital for Sick Children, Dr. Poma Hachimi, Mali, Dr. Traore Bintou Sangare, Mali, with expertise in the clinical area of the trial and Nadia Akseer, a Biostatistician at the Hospital for Sick Children. The DSMB will have the mandate of making an independent, fully informed assessment of the progress of the trial. It will make recommendations to the trial PI as to whether to continue, amend or terminate the trial. The DSMB will be provided de-identified data at 2$^{nd}$ and 6$^{th}$ month of data collection. The identity of study groups will be masked unless the DSMB determines that the identities of the groups are necessary for their decision making. The DSMB may also make recommendations / escalate issues to the REB at SickKids (primary organization) and Comité d'éthique de la Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie de Mali (FMPOS).

Function / Responsibilities of the DSMB:

- Assess and monitor the trial from an ethical perspective
- Assess the quality and completeness of interim data
- Review recruitment and participant retention data
- Review protocol and deviations from the Standard Operating Procedures
- Review any individual events considered significant
- Make recommendations regarding trial continuation, amendments or termination
- Assess the need for stopping the trial prematurely based on strong evidence of unintended harm or external evidence for all or any of the following.

a) Failure to adhere to the research protocol and non-compliance with goals for recruitment and retention.
b) Any factors that might affect the study outcome or compromise the confidentiality of the trial data (such as protocol violations, unmasking, etc.); and,
c) Factors external to the study such as scientific or therapeutic developments that may impact participant safety or the ethics of the study.

## 15. Ethical Approval, Consent Process, Confidentiality, and Safety

Ethical Approval

The study proposal will be submitted for ethical approval to Comité d'éthique de la Faculté de Médecine, de Pharmacie et d'Odonto-Stomatologie de Mali (FMPOS), and the Research Ethics Board at The Hospital for Sick Children, Toronto, Canada. Subsequent to this approval, consent and agreement to participate will be obtained from the regional and district health departments of Koulikoro and Banamba in Koulikoro, Mali.

Participant Consent

Written informed consent will be obtained from mothers and/or fathers of children under five at the time of their consultation with the CHW. If the mother is not able to give consent, her husband or other adult family member present will be invited to give consent to participate in the study. The CHW will explain risks and benefits to potential enrollees and participants will be informed that they have the right to withdraw from the study at any time and that there are no penalties from doing this and this will not in any way affect their ability to receive any health care services.

Ethical issues, Benefits and Safety

Caregivers of children will be free to consent to participate or not in the study. Community Health Workers will explain that children with rapid respiratory rates will be treated on site if no complicating factors are observed, but that if there are complicating factors, children will be referred and/or treated at the next level of care. Anonymity of caregivers, their children and the community health workers and data will be ensured.

The ChARM training will be conducted in such a way that the community health workers do not feel vulnerable or persecuted in any way.

Overall, improved quality of neonatal and child care in diagnosing and treating Pneumonia are the anticipated benefits of this study which outweigh the risks in this study. Health care providers and families can refuse or are free to withdraw at any time from participating in the study and no penalties will arise from this refusal.

Confidentiality

Information obtained during this study will only be transferred in an anonymized form. The national and international regulatory agencies and sponsoring agencies may request access to the medical or other confidential records of participating subjects, but the identity of subjects will remain confidential. The final study report with aggregate anonymized data will be shared with the Minister of Health-Mali, without identifying the individual CHWs. All study records will be kept confidential in keeping with the stipulated requirements by the ethics boards of the Hospital for Sick Children and Ethics Committee of the Faculty of Medicine, Pharmacy, Odontology and Somatology of Mali (FMPOS).

Figure III: Timeline of the Trial

| **Month of Study - Number** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Month of Study - Name** | | J | F | M | A | M | J | J | A | S | O | N | **D** |
| **Cluster Randomization** | **X** | | | | | | | | | | | | |
| **MOU – Koulikoro Regional Health Directorate** | **X** | | | | | | | | | | | | |
| **Orientation of CSCom District Technical Coordinator** | **X** | | | | | | | | | | | | |
| **In-Country Study Team identification** | **X** | | | | | | | | | | | | |
| **Training of Study Team** | | **X** | | | | | | | | | | | |
| **1ST data collection of all CHWs** | | | **X** | | | | | | | | | | |
| **Training of CHWs in Intervention Groups A and B in ChARM** | | | **X** | | | | | | | | | | |
| **Groups A and B initiate use of ChARM** | | | **X** | | | | | | | | | | |
| **2nd data collection of all CHWs in Banamba** | | | | | | | **X** | | | | | | |
| **2nd data collection of all CHWs in Koulikoro** | | | | | | | | **X** | | | | | |
| **Interim data analysis** | | | | | | | | **X** | | | | | |
| **3rd data collection of all CHWs in Banamba** | | | | | | | | | | | **X** | | |
| **3rd data collection of all CHWs in Koulikoro** | | | | | | | | | | | | **X** | |
| **Individual in-depth interviews in Banamba** | | | | | | | | | | | | **X** | |
| **Individual in – depth interviews in Koulikoro** | | | | | | | | | | | | | **X** |
| **In-depth interviews with Field Monitors and MoH DTCs** | | | | | | | | | | **X** | | | |
| **Quarterly reporting** | | | **X** | | | **X** | | | **X** | | | **X** | |
| **Final data analysis** | | | | | | | | | | | | **X** | **X** |
| **Preparation of Final report** | | | | | | | | | | | | **X** | **X** |

Annexes: **(Attached)**

| Annex # | Document Name | Document |
|---|---|---|
| Annex 1: CHWs Tools | *Outil de projet:*<br>• Fiche d'auto surveillance pour les Agents de Santé Communautaire du protocole ChARM | Fiche de Auto Surveillance_ASC_2 |
| | *Ministère de Santé:*<br>• Rapport Mensuel d'Activités du Site ASC | RMA ASC_25- 06-2016_amenage.pdf |
| | • Fiche Individuelle de Prise en Charge de L'Enfant Malade | Version w ord fiche PEC 25 juin 2016 (Enr |
| | • Fiche de Reference et Contre-Reference | Fiche de reference et contre reference A |
| | • Cahier/Directives de l'agent de Sante Communautaire (ASC) p. 6 | Cahier du participant pour la formation ASC |
| **Annex 2 : ChARM Training Material** | • Spécifications techniques du ChARM | Philips ChARM Spec Sheet HR Letter FR 2 |
| | • ChARM Quick Reference Guide (Anglais seulement) | FINAL_ChARM_Quic k Reference Guide 45 |
| | • A propos du 'moniteur respiratoire pour enfant' (instructions) | ChARM_Instructions For Use 4598 010 77 |
| **Annex 3 : Consent Forms** | • Formulaire de consentement éclairé pour: Les agents de santé communautaire | Formulaire de consentement ASC.d |

| | | |
|---|---|---|
| | • Formulaire de consentement éclairé pour: Parents des enfants malades qui sont vus en consultation par les agents de santé communautaire | Formulaire de consentement ASC.d |
| | • Formulaire de consentement éclairé pour: Directeur Technique du Centre | Formulaire de consentement DTC.d |
| **Annex 4: Questions for the In-depth interviews** | • Questions pour les Entrevues en Profondeur avec les Agents de Santé Communautaires | Les Questions pour les EeP_ASC_Recher |
| | • Questions pour les Entrevues en Profondeur avec les Directeur Technique du Centre/CSCom | Les Questions pour les EeP avec les DTC |
| | • Questions pour les Entrevues en Profondeur avec les Moniteur de terrain | Les Questions pour les EeP avec les Mon |

**REFERENCES :**


[i] World Health Organization. (2016). *Pneumonia.* Retrieved September 29, 2017 from http://www.who.int/mediacentre/factsheets/fs331/en/

[ii] Rudan, I., O'Brien, K.L., Nair, H., Liu, L., Theodoratou, E., Qazi, S., Lukšić, I., Fischer Walker C.L., Black, R.E., Campbell, H. (2013). Epidemiology and etiology of childhood pneumonia in 2010: estimates of incidence, severe morbidity, mortality, underlying risk factors and causative pathogens for 192 countries. J Glob Health, 3

[iii] World Health Organization. (2016). *Pneumonia.* Retrieved September 29, 2017 from http://www.who.int/mediacentre/factsheets/fs331/en/

[iv] UNICEF and World Health Organization. (2015). A decade of tracking progress for maternal, newborn and child survival the 2015 report. Retrieved from http://countdown2030.org/documents/2015Report/Mali_2015.pdf

[v] UNICEF and World Health Organization. (2012). WHO/UNICEF Joint Statement: Integrated Community Case Management (iCCM). Retrieved from http://www.who.int/maternal_child_adolescent/documents/statement_child_services_access_whounicef.pdf

[vi] Theodoratou, E., Al-Jilaihawi , S., Woodward, F., Ferguson, J., Jhass, A., Balliet, M., Kolcic, I., Sadruddin, S., Duke, T., Rudan, I., Campbell, H. (2010). The effect of case management on childhood pneumonia mortality in developing countries. Int J Epidemiol; 39 (suppl 1): 155–71

[vii] C J Morley. Respiratory rate and Pneumonia in Infancy. Archives of Diseases in Childhood. The Journal of the British Paediatric Association. 1991;68: (81) 81-84.

[viii] World Health Organization. (2005). Handbook: Integrated management of childhood illness (IMCI). Retrieved from http://apps.who.int/iris/bitstream/10665/42939/1/9241546441.pdf

[ix] Kallander K., Tomson G., Nsabagasani X., Sabiiti J.N., Pariyo G., Peterson S. (2006). Can community health workers and caretakers recognise pneumonia in children? Experiences from western Uganda. Trans R Soc Trop Med Hyg.

[x] Gilroy K.E., Callaghan-Koru J.A., Cardemil C.V., Nsona H., Amouzou A., Mtimuni A., Daelmans B., Mgalula L., Bryce J. (2012) Quality of sick child care delivered by health surveillance assistants in Malawi: Health policy plan. 28:573–585.

[xi] Druetz, T., Siekmans, K., Goossens, S., Ridde, V., & Haddad, S. (2015). The community case management of pneumonia in Africa: a review of the evidence. Health Policy and Planning, 30(2), 253–266.

[xii] Wanduru, P., Tetui, M., Tuhebwe, D., Ediau, M., Okuga, M., Nalwadda, C., Ekirapa-Kiracho, E., Waiswa, P. & Rutebemberwa, E. The performance of community health workers in the management of multiple childhood infectious diseases in Lira, northern Uganda – a mixed methods cross-sectional study. Global Health Action Vol. 9 , Iss. 1,2016

[xiii] Marsh,D., Gilroy, K.E., Van de Weerdt, R., Wansi, E., Qazi, S. (2008). Community case management of pneumonia: at a tipping point? Retrieved on September 29, 2017 from http://www.who.int/bulletin/volumes/86/5/07-048462/en/

[xiv] World Health Organization. (2016). *Pneumonia.* Retrieved September 29, 2017 from http://www.who.int/mediacentre/factsheets/fs331/en/

[xv] C J Morley. Respiratory rate and Pneumonia in Infancy. Archives of Diseases in Childhood. The Journal of the British Paediatric Association. 1991;68: (81) 81-84.

[xvi] Mukanga, D., Tiono, A.B., Anyorigiya, T., Källander, K., Konaté, A.T., Oduro, A.R., Tibenderana, J.K., Amenga-Etego, L., Sirima, S.B., Cousens, S., Barnish, G., & Pagnoni, F. The American Journal of Tropical Medicine and Hygiene, Volume 87, Issue 5_Suppl, Nov 2012, p. 21 - 29

[xvii] D. Mukanga, R. Babirye, S. Peterson, G. W. Pariyo, G. Ojiambo, J. K. Tibenderana, P. Nsubuga, K. Kallander. Can lay community health workers be trained to use diagnostics to distinguish and treat malaria and pneumonia in children? Lessons from rural Uganda. Tropical Medicine and International Health. Volume 16, Issue 10, October 2011, pages 1234–1242.

[xviii] Paintain, L.S., Willey, B., Kedenge, S., Sharkey, A., Kim, J., Buj, V., Webster, J., Schellenberg, D., & Ngongo, N. (2014). Community health workers and stand-alone or integrated case management of malaria: A systematic literature review. Am J Trop Med Hyg. Sep 3; 91(3): 461–470.

[xix]Plan Stratégique National des Soins Essential dans la Communauté. (2014) Direction Nationale de la Santé.

[xx] Wanduru, P., Tetui, M., Tuhebwe, D., Ediau, M., Okuga, M., Nalwadda, C., Ekirapa-Kiracho, E., Waiswa, P. & Rutebemberwa, E. The performance of community health workers in the management of multiple childhood infectious diseases in Lira, northern Uganda – a mixed methods cross-sectional study. Global Health Action Vol. 9 , Iss. 1, 2016.

[xxi] Theodoratou, E., Al-Jilaihawi , S., Woodward, F., Ferguson, J., Jhass, A., Balliet, M., Kolcic, I., Sadruddin, S., Duke, T., Rudan, I., Campbell, H. (2010). The effect of case management on childhood pneumonia mortality in developing countries. Int J Epidemiol; 39 (suppl 1): 155–71

[xxii] Braun, R., Catalani, C., Wimbush, J., Israelski, D. (2013) Community Health Workers and Mobile Technology: A Systematic Review of the Literature. PLoS ONE 8(6): e65772.

[xxiii] Shah, R., Dadlani, P., Mwangi, I., Swedbergl, E., Afeworki, A., Kibria, G., Bunning, N., Gigi, E., Amukoye, E. (2016). *ChARM (Children's Automated Respiratory Monitor) - an innovative easy to use pneumonia screening tool for low resource settings*. American Journal of Tropical Medicine and Hygiene. Control/Tracking Number: 16-LB-4001-ASTMH.