Improving pneumonia diagnoses using pulse oximetry at rural health institutions in South Ethiopia: Protocol for a cluster-randomized controlled trial

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SUBJECT AREAS
General Medicine

KEYWORDS
Integrated Management of Childhood Illness (IMCI), cluster-randomized controlled trial, pulse oximetry, childhood pneumonia, primary health care units, Ethiopia
Abstract

**Background:** Hypoxemia is common in children with pneumonia. The World Health Organization and United Nations Children’s Fund developed the Integrated Management of Childhood Illness strategy for diagnosing pneumonia. But the strategy has limitations to accurately detect hypoxemia in children with severe pneumonia. This study will assess whether pulse oximetry improves health workers’ performance in diagnosing severe childhood pneumonia and whether the pulse oximeter is a cost-effective tool to improve diagnoses of severe pneumonia at primary health care units in South Ethiopia.

**Methods:** A cluster-randomized controlled trial will be conducted at 24 primary health care units in South Ethiopia from September 2018 to February 2019. The trial has two arms: the first arm will examine the combined use of the Integrated Management of Childhood Illness (IMCI) strategy with pulse oximetry, and the second arm will examine the use of the IMCI strategy alone. The study population will include children between 2 months and 59 month of age who present with cough or difficult breathing. The primary outcome of this trial is severe childhood pneumonia, as diagnosed via the IMCI guideline and pulse oximetry. Secondary outcomes will be referred cases of severe pneumonia, treatment failure on day 2, and cumulative treatment failure on days 5 and 14 after enrolment. A cost effectiveness study will be conducted simultaneously.

**Discussion:** This study will determine if using a pulse oximeter at health facilities in rural South Ethiopia improves diagnostic accuracy for paediatric severe pneumonia. Our secondary aim will be to evaluate if the benefit of pulse oximetry justifies its cost.

**Trial registration:** PACTR201807164196402 (14/06/2018). URL: https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=3466

**Keywords:** Integrated Management of Childhood Illness (IMCI), cluster-randomized controlled trial, pulse oximetry, childhood pneumonia, primary health care units, Ethiopia

**Background**

Pneumonia is a leading cause of death worldwide among children younger than five years [1]. Among countries with the highest burden of childhood deaths from pneumonia, Ethiopia ranks sixth, with 15
deaths per 1,000 annual live births [2]. Hypoxemia in children with severe pneumonia is common [3, 4], and hypoxemia is associated with increased risk of death [5]. To reduce child mortality in developing countries, the World Health Organization (WHO) and United Nations Children’s Fund (UNICEF) developed a strategy known as Integrated Management of Childhood Illness (IMCI) in the mid-1990s [6]. The IMCI strategy aims to reduce death, illness, and disability among young children by improving three main areas: case management skills, overall health systems, and family and community health practices.

Yet, health workers using the IMCI accurately diagnosed only 53.0% of severe pneumonia cases and only 32.0% of pneumonia cases. [7]. When using the IMCI guidelines alone, the proportion of children who receive the recommended treatment is low [8]. Moreover, studies from South Africa and Uganda show that health workers’ performance is poor when classifying children with severe pneumonia using the IMCI [9, 10].

Studies show that none of the clinical signs of pneumonia, such as respiratory rate, retractions, grunting, cyanosis, head nodding, and nasal flaring, has sufficient sensitivity and specificity to detect hypoxemia in children with pneumonia [11-13]. Thus, pulse oximetry is a valuable and objective instrument that can improve diagnostic accuracy of severe pneumonia by measuring hypoxemia [14]. It has a sensitivity of 83% and specificity of 73% in children younger than 5 years [15]. Pulse oximetry also is an important tool to monitor treatment progress in children with severe pneumonia [16], as it can improve management of the disease [17]. It also can improve the performance of health workers in referral decision-making for children with severe pneumonia [18]. This protocol was developed according to the SPIRIT checklist (see Additional file 1).

Our study aims to improve case management of childhood pneumonia at primary health care units. The study will try to answer the following research question: Does introducing pulse oximetry into daily clinical practice at primary health care units improve the accuracy of diagnosing childhood pneumonia?

**Methods**

**Trial objectives**
The primary objective of this study will be to assess whether the combined use of the IMCI strategy and pulse oximetry improves diagnostic accuracy for severe pneumonia among children aged 2 months to 59 months, compared to using the IMCI strategy alone. The secondary objectives of the study will be to determine whether the combined use of IMCI and pulse oximetry increases the proportion of severe pneumonia cases referred to hospital; to assess treatment failure (up to 2 days, 5 days, and 14 days) after using IMCI and pulse oximetry versus using IMCI alone; and to compare the incremental cost effectiveness of using IMCI and pulse oximetry with that of using IMCI alone.

**Trial design**

A parallel-cluster, randomized, controlled trial will be conducted from September 2018 to February 2019 (see table 1 for a timeline). Clusters will include health centres, which will be randomly and equally allocated into one of two arms: the combined use of IMCI and pulse oximetry (intervention arm) and the IMCI only (control arm).

**Study setting**

The study will be conducted in the Gedeo zone (Figure 1) in South Ethiopia, which is about 360 kilometres from the capital, Addis Ababa. The zone’s population is 1.1 million people. Of these, about 170,000 are children younger than five years [19]. The Gedeo zone has 38 health centres, 146 health posts (operational unit for health extension workers), and one hospital. At these institutions, pneumonia is among the 10 top causes of outpatient treatment. Health care providers treated 13,083 pneumonia cases in 2015 and 2016. Health professionals use the IMCI to manage pneumonia, and severe cases are usually referred to a nearby hospital.

**Participants**

The study will comprise 24 health centres in the study area that treat at least one case of pneumonia per day. Children aged 2 months to 59 months with symptoms of pneumonia will be included in the study from September to January, 2019 (Table 1). Patients with a long history of cough and whose differential diagnoses are for other conditions, such as pulmonary tuberculosis, will be excluded.

**Trial interventions**

The IMCI strategy [20] will be used to manage pneumonia in the intervention and control groups. In the intervention group, a paediatric fingertip pulse oximeter (ADC® Adimals 2150) will be used to
measure each child’s oxygen saturation. Oxygen saturation will be measured twice, 5 minutes apart, and hypoxemia diagnoses will be based on the average of the two measures. Oxygen saturation shall be measured when the child is calm and recorded when the pulse oximetry accurately reflects consistent, high-amplitude plethysmographic waveforms associated with stable oxygen saturation for 1 minute.

**Study outcomes**
The primary study outcome will be severe pneumonia cases, as assessed by the IMCI guidelines [20]. All children with coughs will be classified as severe pneumonia, pneumonia, or common cold. Oxygen saturation will be recorded as a percentage, with a cut-off of 90% [21]. The secondary study outcomes will be pneumonia cases referred to hospital, treatment failure on day 2 after enrolment, cumulative treatment failure at 5 days and 14 days [22] after enrolment, and economic evaluation. Table 2 lists the treatment failure definitions. Economic evaluation will include the direct and indirect costs of intervention from societal perspectives, including the number of severe pneumonia cases detected.

**Study size**
The sample size of 24 health care units for the primary outcome was estimated using methods for a cluster-randomized trial [23]. Based on previous research, we expect health workers using the IMCI strategy to identify 4% of children with severe pneumonia [24]. We assume a power of 90%, 95% significance, coefficient of variation of 0.25, and a minimum of 25 children with pneumonia per cluster. To detect an increase from 4% to 14% in severe pneumonia proportion, we will need a minimum of 10 clusters in each group. Although drop-out of the entire clusters is uncommon, we followed Rutterford et al. [25] and add two clusters per group for a total of 12 clusters.

**Randomization**
The randomization units will be the health centres. From 38 health centres in the study area, 24 health centres with at least one pneumonia case treated per day will be included. Of those 24, 12 will be randomly selected for the intervention group and 12 for the control group. This random selection will be performed at the University of Bergen using a list generated by SPSS software. The study itself will be conducted in Ethiopia. Due to the nature of the intervention, it is impossible to blind the data
collectors and the study participants.

Data collection
A structured questionnaire will be used to collect data on general characteristics of health workers, socio-demographic and socio-economic characteristics of caregivers, clinical and non-clinical characteristics of the child, resource and cost data, and follow-up data on treatment outcomes. Data will be gathered by trained health workers at the health facilities. Health workers in both trial arms will be provided with IMCI guidelines [20] for use in assessing each child with cough or difficulty breathing.

Health workers in the intervention and control groups will receive training about cough and difficulty breathing based on the IMCI guidelines [26]. The training will be supplemented with videos, written documents, and exercises that were developed by the WHO and adapted by the Ethiopian Federal Ministry of Health. After the training, each health worker will be given a case exercise to classify a child’s cough. The results of this exercise will be validated against the paediatric classification. They also will participate in video-based exercises to learn how to identify chest wall in-drawings and lethargy or unconsciousness and how to count respiratory rates. Again, performance will be validated against the findings from the video. Health workers in the intervention arm will receive an additional day of training on how to use the pulse oximetry apparatus. This training will be supplemented with lectures and practical sessions. Members of the research team will supervise each site regularly.

Economic evaluation and data collection
The sample size that was calculated for the proportion of severe pneumonia cases will be used for estimating the cost effectiveness of the intervention. Costs of health care resources will be assessed from a societal perspective [27]. The sources of cost data will be drug and supply prices and interviews of study participants. The costs will be classified as programme or patient costs. Direct costs will be the patients’ out-of-pocket costs for accessing care, and indirect cost will be the time spent by caregivers to get health care.

Programme costs will include all resources used in making the intervention available in health centres. These costs include capital (e.g., building space), recurrent (e.g., medical devices like pulse
oximeters and batteries. Patient costs will include costs of accessing health intervention used by children and their caregivers. These costs will be estimated using a structured questionnaire for children diagnosed with severe pneumonia and their caregivers. In addition to travel time, expenses will include out-of-pocket money for medications, hospital stays, consultation, food, accommodations, and transportation. The time cost will be valued in terms of lost wages based on unskilled wage rates [27].

Follow-up
Children in both the intervention and control arms will be scheduled for follow-up visits on day 2, day 5, and day 14 after enrolment. For children who miss a scheduled follow-up visit, health workers will contact the families at home on the next day. Those who cannot be located will be considered lost to follow-up, in which case we will phone participants, family, and neighbours to collect information about deaths, relocation, or hospitalizations.

Children who have pneumonia will be treated immediately. Those with severe pneumonia or oxygen saturation < 90% will be referred urgently to a nearby hospital. Children will be referred to hospital for further investigation and management if they still have a cough at the day-14 follow-up visit.

Reliability of pulse oximetry
Prior to the start of our trial, we conducted a pilot study on 60 children aged 2 months to 59 months. The paediatrician in the pilot study trained a nurse supervisor, who then trained two nurses as “rater 1” and “rater 2.” Oxygen saturation was then measured twice, 5 minutes apart, by the supervisor, rater 1, and rater 2. Using a Bland-Altman plot, agreement between the supervisor and rater 1 showed a mean difference of -0.2 (95% CI, -3.5 to 3.1) and between the supervisor and rater 2 a mean difference of 0.1 (95% CI, -4.2 to 4.5). The Intraclass correlation coefficient (ICC) estimate of intra-rater agreement compared to the supervisor was 0.98 (95% CI, 0.97-0.99), and the estimates were 0.96 (95% CI, 0.94-0.98) for rater 1 and 0.91 (95% CI, 0.85-0.95) for rater 2. These estimates are regarded as “good” to “excellent” reliability [28].

Data management
A structured, paper-based questionnaire will be used for data collection. Data will be double-entered by two trained data clerks using the Epi Data software version 3.1 (The EpiData Association, Odense...
Range and consistency will be used for data verification. Data cleansing will be done, and any inconsistencies will be corrected against the original questionnaire.

Data analysis
Data will be analysed using SPSS-20 (IBM Corp., Armonk, NY, USA). A t test for continuous variables and chi-squared test for categorical variables will be used to compare baseline data in the two groups. We will calculate summary values for the primary and secondary outcomes for each health centres. An independent sample t test will compare the mean proportion of severe pneumonia cases, the referred cases, and the treatment failures, using health centres as the unit of analysis between the two arms. The primary and secondary outcome variables will be expressed the as mean differences (95% CI) between groups. The intracluster correlation coefficient will be calculated using one-way analysis of variance [29, 30].

We shall use identified severe pneumonia as a measure of effectiveness. The cost effectiveness will be expressed as the incremental cost effectiveness ratio, computed for the number of severe pneumonia cases identified as a result of the intervention. All primary and secondary outcomes analyses will be based on the intention-to-treat analysis.

Data monitoring
The Data Safety and Monitoring Board will not be needed, because management of childhood pneumonia using the IMCI is a routine clinical activity at health centres in Ethiopia. We do not expect any adverse effects from using pulse oximetry; therefore, we will not apply any stopping rule related to its use for this trial.

Discussion
This trial will measure whether using the IMCI strategy in combination with pulse oximetry increases the detection rate of severe childhood pneumonia, compared to using IMCI alone. We chose pulse oximetry as a complementary tool for several reasons. The IMCI guideline is based on clinical symptoms and does not involve any objective diagnostic test to identify children with severe pneumonia [31]. The symptoms outlined in the IMCI guidelines are not specific to pneumonia [32]. Moreover, they are inaccurate for diagnosing childhood pneumonia [3] or identifying children with hypoxemia [33]. Some symptoms like chest indrawings are difficult for midlevel health professional to
Because the caregivers and health care providers in this study will not be masked, a bias could occur in measuring the effect sizes of the combined effect of pulse oximetry and IMCI, compared to IMCI alone. However, the outcomes are objectively measurable, making observational biases from participants unlikely. We do not expect health workers to depend on the pulse oximetry measurements in assessing study outcomes, because children in each health centre will receive similar interventions. Moreover, to minimize information bias, the same method of assessment will be used to ascertain treatment outcomes for both groups. This study has the potential to improve diagnoses of severe pneumonia in rural communities in Ethiopia. The introduction of pulse oximetry can help health workers to detect hypoxemia in children with pneumonia and should reduce unnecessary referrals, improve management of severe pneumonia, and reduce mortality from severe pneumonia among children younger than 5 years. The findings of this study thus can be used to improve diagnostic accuracy in severe childhood pneumonia.

Abbreviations
ICC: Intraclass correlation coefficient
IMCI: Integrated Management of Childhood Illness
SPSS: Statistical Package for Social Sciences
WHO: World Health Organization
UNICEF: United Nations Children’s Fund

Declarations
Trial status
Upon submission of this manuscript, ethical approval has been obtained. We have completed the pilot study. Patient recruitment started on 10 September 2018 and will be completed in January 2019.

Ethics approval and consent to participate
The study was approved by the institutional review board of the College of Medicine and Health Sciences at Hawassa University (ref: IRB/009//2017) and the Regional Committees for Medical Research Ethics, South East Norway (ref: 2017/2473/REK sør-øst). The protocol was registered online on 14/06/2018 in the Pan African Clinical Trial Registry database under the identification number PACTR201807164196402.
Before the implementation of the intervention, meetings will be held with representatives from the Gedeo Zone Health Department, district health offices, and head of health facilities. Written permission will be obtained from Zone and district health offices. Informed verbal consent will be obtained beforehand from study caregivers. Information will be provided about the purpose of the study, and caregivers will be informed that involvement is voluntary and that they can withdraw at any time regardless of reason. Caregivers will be briefed about the oximetry procedure and routine pneumonia diagnosis. The caregivers will be informed that the instrument will not harm the child. Caregivers will be assured that refusal to participate in the study will not affect their medical care in health centres.

All information from the study participants will be held in confidence, and appropriate measures will be taken to ensure the confidentiality of the information during and after data collection. Access to information will be limited to data collectors, health workers, supervisors, data clerks, and the research team. The data will be used only for research purposes without violating confidentiality.

Consent for publication
Not applicable for this section

Availability of data and material
Data sharing is not applicable to this article, as no datasets will be generated or analysed during the submission of this manuscript.

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
SH conceptualized the idea, designed the study, wrote the protocol, and drafted this manuscript. BL
conceptualized the idea, guided the study design, the proposal writing, and helped to draft this manuscript. EL, KAJ, and YG provided constructive comments. All authors read and approved the submitted version of the manuscript.

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Tables
Table 1. Study timeline
| Enrolment | Allocation | Post-allocation |
|-----------|------------|-----------------|
| Aug 2018  | Aug 2018   | Sep 2018        |
|           |            | Oct 2018        |
|           |            | Nov 2018        |
|           |            | Dec 2018        |
|           |            | Jan 2019        |

**Enrolment**
- Selection of clusters
- Informed consent
- Allocation of clusters

**Interventions**
- Integrated Management of Childhood Illness (IMCI) strategy and pulse oximetry
- Integrated Management of Childhood Illness (IMCI) strategy alone

**Baseline variables**
- General characteristics of health workers
- Socio-demographic and socio-economic position of caregivers
- Clinical and non-clinical characteristics of child

**Outcome variables**
- Severe pneumonia
- Referral cases
- Treatment failures on days 2, 5, and 14
- Hypoxemia (< 90%) as measured by pulse oximetry

**Cost evaluation data**

Table 2. Definitions of study outcomes
| Study outcomes                                | Definition (any of the following)                                                                 |
|----------------------------------------------|--------------------------------------------------------------------------------------------------|
| Treatment failure on day 2                   | Development or persistence of general danger signs (e.g., inability to drink or breastfeed, vomits everything, convulsions, lethargy or unconsciousness)  
Persistence of fever (axillary temperature ≥ 37.5 degrees Celsius)  
Persistence of tachypnoea (respiratory rate ≥ 50 breaths/minute in children aged 1 months to 11 months and ≥ 40 breaths/minute in children aged 12 months)  
Chest wall in-drawings  
Withdrawal from the trial  
Death                                                                 |
| Cumulative treatment failure on days 5 and 14 | Any of the above symptoms plus  
Persistence of cough  
Recurrence of fever                                                                 |

Table 3. World Health Organization trial registration data set

| Data category                                      | Information                                                                                     |
|---------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Primary registry and trial identifying number     | Pan African Clinical Trial Registry.org PACTR20180716419                                          |
| Date of registration in primary registry          | 14/06/2018                                                                                      |
| Secondary identifying numbers                     | No                                                                                              |
| Source(s) of monetary or material support         | Norwegian Programme for Capacity Development in Higher Development (NORHED) in Norway           |
| Primary sponsor(s)                                | Centre for international health at University of Bergen (NORHED) in Norway                     |
| Contact for public queries                        | Solomon Hailemariam, Dilla, Ethiopia                                                           |
| Contact for scientific queries                    | Bernt Lindtjorn, Bergen, Norway                                                                |
| Public title                                      | Pulse oximetry and integrated management of childhood illness in primary health care units of rural Ethiopia: a randomized controlled trial |
| Scientific title                                  | Pulse oximetry and integrated management of childhood illness in primary health care units of rural Ethiopia: a randomized controlled trial |
| Countries of recruitment                          | Ethiopia                                                                                        |
| Health condition(s) or problem(s) studied         | Pneumonia                                                                                       |
| Intervention(s)                                   | Experimental group: Combined use of the WHO Integrated illness algorithm with pulse oximetry  
Control group: Integrated management of childhood illness: |
| Key inclusion and exclusion criteria              | Inclusion criteria: Patients aged 2 month to 59 months pre suggestive of pneumonia will be included in the study. Pat cough wherein differential diagnosis is tuberculosis, will be suspected of having tuberculosis will be referred to the ne |

Figures
Figure 1
Study area map

Supplementary Files
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Additional file 1.doc