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Pulse oximeter with integrated management of childhood illness improves diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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ABSTRACT

Objective: To assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at primary health care units in Southern Ethiopia.

Design: Parallel cluster randomized trial.

Setting: Government health centres

Participants: Twenty-four health centres that treat at least one pneumonia case per day in Southern Ethiopia. Children between 2 months and 59 months-of-age who present at health facilities with cough or difficulty breathing were included in the study.

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Intervention arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm and pulse oximeter.

Control arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm only.

Primary and secondary outcome measures: The primary outcome was the proportion children diagnosed with severe pneumonia. Secondary outcomes included referred cases of severe pneumonia and treatment failure on day 14 after enrolment.

Result: Twenty-four health centres were randomized into intervention (928 children) and control arms (876 children). The proportion of children with severe pneumonia was 15.9% in the intervention arm and 3.9% in the control arm. After adjusting for differences in baseline variables, children in the intervention arm were more likely to be diagnosed as severe pneumonia cases as compared to those in the control arm (AOR= 5.4, 95% CI 2.0–14.3).

Conclusion: The combined use of Integrated Management of Childhood Illness (IMCI) and pulse oximetry in health centres improves diagnostic precision of severe childhood pneumonia.

Trial registration: PACTR201807164196402 (14/06/2018).

Keywords: Community child health, Public health, Respiratory infection.

Strengths and limitations of this study

- ➢ Randomly allocation of health centres to intervention and control arms

- ➢ Participating health centres were typical of such institutions in rural communities in Ethiopia.

- ➢ Robust training on how use the Integrated Management of Childhood Illness algorithm, and how to measure oxygen saturation.

- ➢ Due to the nature of the intervention, inability to mask the health workers and the study participants of the intervention.

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➤ Unequal number of children seeking health care between the two comparison arms.

INTRODUCTION

Pneumonia killed approximately 920,000 children less than five years-of-age in 2015.[1] The mortality rate is especially high in Ethiopia, and 59 deaths per 1,000 live births occurred in 2017 in children less than five years-of-age.[2] Ethiopia ranks sixth among countries with the highest number of deaths from pneumonia.[1]

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) improves the quality of child care for common illnesses,[3, 4] but there is poor diagnostic precision for childhood pneumonia based on clinical features.[5] The ability of health care providers to count breaths and classify respiratory rate in children using the IMCI guidelines is a challenge.[6]

Clinical signs of pneumonia, such as tachypnoea, inability to drink or breastfeed, and head-nodding, used in the IMCI guidelines, are not able to identify hypoxic children with severe pneumonia as precisely as pulse oximetry.[7] Consequently, many children with severe pneumonia are dying because hypoxemia is not adequately recognized and/or oxygen therapy is unavailable.[1]

This study is an extension of a study in which we first assessed the health system support of IMCI, where we found that the basic supplies for effective management of pneumonia were inadequate. Indeed, in a large proportion of the surveyed health facilities, essential drugs, vaccines, job aids, and equipment were lacking. We also determined that many health facilities had an insufficient number of IMCI-trained health workers, and were deficient in requisite supportive supervision. In addition, health workers' knowledge of managing severe pneumonia was low.[8]

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For the abovementioned reasons, an urgent need exists for interventions that assist health workers to improve the diagnosis of severe childhood pneumonia. This study aimed to compare the effects of the combined use of pulse oximetry and IMCI guidelines, with IMCI guidelines alone, on the management of severe childhood pneumonia at rural health centres in Southern Ethiopia.

METHODS

This study adheres to the CONSORT checklist guidelines for cluster randomized trial available as supplementary files (CONSORT checklist). The full protocol of this trail was published at protocols.io (DOI: http://dx.doi.org/10.17504/protocols.io.88mhzu6).

Trial design

The present study constitutes a parallel-cluster randomized controlled trial conducted at 24 health centres. An equal number of health centres were allocated into intervention and control arms, i.e., the combined use of IMCI and pulse oximetry (intervention arm), and the IMCI guidelines only (control arm). No changes were made to the design of the study after its commencement.

Study setting and participants

The study was conducted in the Gedeo Zone of Southern Ethiopia. The zone's population is more than one million people, of which approximately 170,000 are children younger than five years-of-age.[9] There are 146 health posts (operational unit for health extension workers), 38 health centres, and one hospital. At these institutions, pneumonia is among the top-10 causes of outpatient treatment, and health professionals utilize the WHO IMCI guidelines to manage pneumonia.[10]

The study comprises 24 health centres in the rural Gedeo Zone, each of which treats at least one case of pneumonia per day. Children who were aged 2 months to 59 months with cough

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or had difficulty breathing for less than 14 days were included and followed for treatment outcome. While Children aged 2 months to 59 months with cough or difficulty breathing for more than 14 days, or whose diagnoses were for other conditions, such as pulmonary tuberculosis, were excluded. In both arms, the assessment for inclusion and exclusion of children were identical. Pulse oximetry was not used to screen patients for inclusion in the study.

Trial interventions

Health workers from the intervention arm used the WHO IMCI guidelines,[10] and a paediatric fingertip pulse oximeter (ADC® Adimals 2150) to diagnose pneumonia. Oxygen saturation was measured twice, 5 min apart. The measurement was taken when the child was calm, and recorded when the pulse oximetry accurately reflected consistent, high-amplitude plethysmographic waveforms associated with stable oxygen saturation for 1 min. Health workers from the control arm used the same WHO IMCI guidelines, but without measuring oxygen saturation.

Training was given for health workers on IMCI guidelines and how to use pulse oximetry. An IMCI-trained paediatrician offered the training, which was supported by a video-based exercise and practical session that was developed by the WHO and adopted by the Ethiopian Federal Ministry of Health.[11] Prior to implementing the trial, a pilot study was conducted to estimate the intra and inter observer reliability of the pulse oximetry. Detail about training, data collection and pilot results were given in trial protocol (http://dx.doi.org/10.17504/protocols.io.88mhzu6).

Study outcomes

The primary study outcome was severe pneumonia diagnosed using the IMCI guidelines in both arms.[10] The primary study outcome for the intervention arm was severe pneumonia, if

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a child with cough or difficulty breathing had at least one of the following general danger

signs: inability to drink or breastfeed, vomiting everything, convulsion, or lethargy.

Moreover, one of the following symptoms of pneumonia: fast breathing (respiratory rate $\geq$ 50

breaths/min in children aged 2 to 11 months-old and respiratory rate $\geq$ 40 breaths/min in

children aged 12 months to 5 years-old), lower chest wall in-drawing, and/or average oxygen

saturation recorded as a percentage, with a cut-off of 90%.[12]

The primary study outcome for the control arm was severe pneumonia. Except oxygen

saturation, the same diagnosis criteria used for intervention arm was also used to diagnose

pneumonia in control arm.

The secondary study outcomes were: Treatment failure on day 14 after enrolment,[13] and

severe pneumonia cases referred to the hospital. We considered treatment failure at day 14 if

any of the following signs were present: 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 $\geq$ 37.5 degrees Celsius),

persistence of tachypnoea (respiratory rate $\geq$ 50 breaths/min in children aged 2 to 11 months

and $\geq$ 40 breaths/min in children aged 12 months to 5 years), chest wall in-drawings,

presence of persistent cough, recurrence of fever, or death.

Follow-up visits

Children in both the intervention and control arms were scheduled for follow-up visits on day

2, day 5, and day 14 after enrolment. For children who missed a scheduled follow-up visit,

health workers contacted the families at home on the following day. A child who could not be

located was considered as lost to follow-up. In such cases, we contacted the participants'

family and neighbours by phone to collect information about deaths, relocation, or

hospitalizations.

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Study size

The sample size was calculated based on a difference in effect size of 10%, power of 90%, 95% significance level, intraclass correlation coefficient of 0.025, and a minimum of 25 children with cough per cluster. Based on previous research, we expected health workers using the IMCI-alone strategy to identify 4% of children with severe pneumonia.[14] With this assumption, we allocated 12 health centres to the intervention and 12 health centres to the control arm.

Randomization

Randomization was done after we obtained consent from the district and health facilities head. The randomization units were health centres. From 38 health centres in the study area, 31 health centres with at least one pneumonia case treated per day were included in the sampling frame. Accordingly, 24 of 31 health centres were randomly selected using the simple random sampling method. Of those 24, 12 were randomly selected for the intervention group and 12 for the control group. This random selection was performed at the University of Bergen using a list generated by SPSS software. The study itself was conducted in Ethiopia. Due to the nature of the intervention, it was impossible to blind the data collectors and the study participants.

Analyses

We used STATA version 15 (Stata Corp. LLC, College Station, TX, U.S.A.) for data analysis. An independent sample t-test for normally distributed continuous variables, Mann-Whitney U-test for skewed continuous variables, and chi-squared test for categorical variables were utilized to compare baseline data in the two arms. Mixed effect logistic regression with random intercept to account for clustering by health centres was used to estimate the effect of the intervention on primary and secondary outcomes. The effect

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estimate for primary outcome was expressed in OR with 95% CI. To control for potential

confounding factors, some of the unbalanced baseline variables, such as child's vaccination,

parents' wealth, and educational status were considered during the analysis (Table 3).

Individual level variables such as child's age, stunting, and sex constituted other potential

confounders, and were also adjusted for the regression analysis. Intraclass correlation

coefficient for the primary outcome was estimated from the random effect model output.

Patient and Public involvement

There is no tradition in Ethiopia to invite patient organisations to take part in the planning,

design and follow up of trials. In this study, and before the implementation of the

intervention, meetings were held with representatives from the Gedeo Zone Health

Department, woreda administrators, district health offices, and head of health facilities. The

meeting was about the burden of childhood pneumonia in the study area and at national level,

and the purpose of the study. After having the authorities consent to carry out the study,

written permission was obtained from Zone and district health offices. All patients were

informed about the purpose of the study, and caregivers were told that involvement is

voluntary and that they could withdraw at any time regardless of reason. Caregivers were

briefed about the oximetry procedure and routine pneumonia diagnosis. The caregivers were

informed that the instrument would not harm the child. They were also assured that refusal to

participate in the study would not affect their medical care in health centres. The findings of

this study will be communicated to each of the health institutions and through the institutions

to the patients.

RESULTS

Twenty-four health centres were randomly and equally assigned into intervention and control

arms. Children were recruited and followed from September 2018 to April 2019. All of the

24 health centres were included for the primary outcome analysis (see Figure 1 for details on

participants' flow and recruitment).

Baseline data

The baseline characteristics of the study group were comparable, except for Pneumococcal

and Haemophilus influenzae type b vaccines, and educational and wealth status of parents

(Table 1).

Table 1. Baseline comparison between groups at individual and cluster level.

Variables	Intervention	Control	P-value
Cluster level			
Number of clusters	12	12	
Number children age less than five years of age in the catchment area	63,285	50,629	
Total number of children attending health centres	2600	1755	
Total number of eligible children	928	876	
Number of eligible children per cluster	77	73	0.668
Sex of health workers			0.653
Male	8	9	
Female	4	3	
Age of health workers in year: Mean (SD)	29 (4.5)	26 (2.8)	0.171
Total service duration in months: Median (IQR)	37 (30 to 81)	45 (25 to 68)	0.932[a]
Service in child care in months: Median (IQR)	25 (23 to 45)	21 (8 to 56)	0.713[a]
Previous training in IMCI			1.000
Yes	7	8	
No	5	4	
Profession of health workers			0.632
Health officer	2	4	
BSc nursing	1	1	
Diploma nursing	9	7	

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Number of eligible children per cluster	77	73	0.668
Individual level			
Sex of child			0.354
Boys	479/914 (52%)	475/870 (55%)	
Girls	435/914 (48%)	395/870 (45%)	
Duration of cough or difficulty breathing in days: Mean (SD)	3.8 (2.3)	3.8 (1.9)	0.627
Age of child in months: Median (IQR)	12 (7 to 28)	12 (7 to 25)	0.277[a]
Weight-for-age-z score: Median (IQR)	-1.0 (-2.0, 0.1)	-1.1 (-2.2,0.1)	0.781[a]
Weight-for-height-z score: Median (IQR)	-0.1 (-1.4,1.4)	-0.1 (-1.7,1.8)	0.885[a]
Height-for-age-z score: Median (IQR)	-1.7 (-3.4, -0.0)	-1.8 (-3.5, -0.1)	0.607[a]
Pneumococcal and Haemophilus influenzae type b vaccines			0.044
Fully vaccinated	668/928 (72.0%)	667/876 (76.1%)	
Partially vaccinated	260/928 (28.0%)	209/876 (23.9%)	
Age of caregivers in years: Mean (SD)	26.6 (6.2)	27.1 (4.7)	0.055
Educational status of caregivers			<0.001
No education	386/927 (41.6%)	437/875 (49.9%)	
Primary	432/927 (46.6%)	371/875 (42.4%)	
Secondary and above	109/927 (11.8%)	67/875 (7.7%)	
Wealth tertiles			<0.001
Poor	217/830 (26.1%)	322/789 (40.8%)	
Medium	313/830 (37.7%)	208/789 (26.4%)	
Rich	300/830 (36.1%)	259/789 (32.8%)	

[a] Mann-Whitney U-test

Hypoxemia

A total of 1804 children were enrolled in the study, of which 928 children were enrolled into the intervention and 876 into the control arm. Of the 928 children in the intervention arm, 135/928 (14.5%) had oxygen saturation of less than 90%. A total of 148 severe pneumonia cases were diagnosed in the intervention arm and, of these, 70 cases (47.3%) were diagnosed

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only using pulse oximetry, 65 (43.9%) were diagnosed both using IMCI and pulse oximetry, and 13 (8.8%) were diagnosed using the IMCI strategy alone. The overall mean oxygen saturation was 92.4% (SD = 5.3). The mean oxygen saturation among children diagnosed with severe pneumonia was 79.0%, (SD = 9.4), while among pneumonia cases the mean was 93.2% (SD = 2.7), and for children with common cold the mean was 95.0% (SD=2.2).

In addition, we estimated the sensitivity and specificity of the two clinical signs used in WHO IMCI guidelines to diagnose pneumonia (fast breathing and chest in-drawing). Fast breathing had the highest sensitivity (94), but specificity was low (25) as compared to chest in-drawing (81) (Table 2). Furthermore, using a combination of both symptoms did not improve their predictive ability.

Table 2. Sensitivity and specificity of clinical signs.

Clinical signs	Pulse oximeter			Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Hypoxemia	No hypoxemia	Total				
Chest in-drawing				59	81	35	92
Yes	79	147	226				
No	56	626	682				
Total	135	773	908				
Fast breathing				94	25	18	96
Yes	127	587	714				
No	8	194	202				
Total	135	781	916				
Chest in-drawing and fast breathing				57	82	35	92
Yes	78	145	223				
No	57	641	698				
Total	135	786	921				

Outcomes and estimation

The cluster adjusted proportion of diagnosed severe pneumonia was 148/928 (15.9%, 95% CI 4.7– 27.2) for the intervention arm and 34/876 (3.9%, 95% CI 1.2 – 6.6) for the control arm. The odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was (COR= 4.7, 95% CI 1.9 –11.8) as compared to the control arm. The effect of the

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intervention remained the same after adjusting for each of the baseline variables (Table 3). In

addition, children who were boys, aged 2 months to 11 months, height for age z-scores less

than -2, and not fully vaccinated for Pneumococcal and Haemophilus influenzae type b were

more likely to be diagnosed with severe pneumonia than their counterparts (Table 3). From

the random effect model, the intraclass correlation coefficient for severe pneumonia (ICC)

was 0.04322.

Table 3. Odds ratio from the multilevel logistic regression model comparing the proportion
of diagnosed severe pneumonia between the arms.

Variables		Bivariate analysis						Multivariate analysis		
		Yes	No	Total	COR*	(95% CI)	P-value	AOR**	(95% CI)	p-value
Intervention	Yes	148	780	928	4.7	(1.9 –11.8)	0.001	5.4	(2.0–14.3)	0.001
	No	34	842	876	1			1		
Sex of child	Boy	113	841	954	1.9	(1.1–3.1)	0.014	1.5	(1.1–2.3)	0.033
	Girl	69	761	830	1			1		
Age of child (months)	2 - 11	93	680	773	1.7	(1.2 –2.4)	0.005	1.7	(1.1–2.6)	0.011
	12 - 59	89	942	1031	1			1		
Height-for-age z-score (<-2)	Yes	87	676	763	1.5	(1.0 –2.3)	0.031	1.5	(1.0–2.3)	0.055
	No	73	841	914	1			1		
Pneumococcal and Haemophilus influenzae type b vaccines	Partially vaccinated	67	402	469	2.0	(1.3 –3.0)	0.001	1.7	(1.1–2.7)	0.043
	Fully vaccinated	115	1220	1335	1			1		
Educational status of parents	No education	96	727	823	1.7	(0.9 –3.3)	0.110	1.1	(0.5–2.3)	0.797
	Primary	72	731	803	1.4	(0.7–2.6)	0.356	1.3	(0.6–2.6)	0.487
	Secondary	14	162	176	1			1		
Wealth tertiles	Poor	52	487	539	1.7	(0.8–3.3)	0.147	1.1	(0.7–1.9)	0.617
	Medium	47	474	521	1.3	(0.8–2.3)	0.328	0.9	(0.6–1.5)	0.761
	Rich	58	501	559	1			1		

* Crude odds ratio

** Adjusted odds ratio

After examining the clustering effect, the proportion of children with severe pneumonia

referred to the hospital was 116/148 (78.4%, 95% CI 67.6 – 89.2) in the intervention arm and

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15/34 (44.1, 95% CI 6.9 – 81.3) in the control arm, with P=0.496. Among these, 62/116

(53.4%) in the intervention arm, and 11/15 (73.3%) in the control arm, reached the hospital

and received the standard treatment.

Table 4 shows the total treatment failure, and treatment failure by specific causes, between

the arms. The proportion of treatment failure at day 14 was 132/928 (14.2%, 95% CI 6.0 –

22.4) in the intervention arm and similar (93/876; 10.6%, 95% CI 5.2 – 16.1) in the control

arm (P = 0.622). There were two deaths in each of the intervention and control arms. Nine

children from the intervention and three children from the control arms had persistent cough

at day 14.

T7kkable 4. Treatment failures by specific causes at day 14.

Outcome	Treatment failure at day 14	
	Intervention	**Control**
Total	132/928 (14.2%)	93/876 (10.6%)
General danger signs	17/815 (2.1%)	31/823 (3.8%)
Chest in-drawing	2/815 (0.2%)	3/823 (0.4%)
Persistence of tachypnoea	33/815 (4.0%)	18/823 (2.2%)
Persistence of fever	9/815 (1.1%)	5/823 (0.6%)
Persistent cough	9/815 (1.1%)	3/823 (0.4%)
Lost to follow-up	68/928 (7.3%)	49/876 (5.6%)

Sensitivity analysis

If we use an oxygen saturation cut off < 92% to define hypoxemia, the proportion of children

with hypoxemia would be 298/921 (32.4%, 95% CI 16.2 – 48.5). Moreover, the cluster

adjusted proportion of severe pneumonia would be 304/928 (32.8%, 95% CI 18.2– 47.3) in

the intervention arm, and (COR: 13.3, 95% CI 5.0 – 35.3) as compared to control arm.

DISCUSSION

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Introducing pulse oximetry into the WHO IMCI guidelines significantly improved the

diagnosis of severe childhood pneumonia in health centres. As expected, more children with

hypoxemia were detected in the intervention group.

One of the main strengths of this study is that it was based on randomly selected health

centres, which are typical of rural communities in Ethiopia. Moreover, we measured oxygen

saturation after checking the reliability of pulse oximetry in the study area. The intra- and

inter-rater reliability estimates ranged from good to excellent.[15] In this trial, except for

educational and wealth status of parents and vaccination status of children, the baseline

characteristics of the study arms were balanced. To control for bias due to possible

confounding factors, we used estimates adjusted for those potential confounders.

The present study also possesses certain limitations that are worth noting. The number of

children who attended the facilities were larger in the intervention arm than in the control

group. This might be due to the following two reasons: First, the base population in the

intervention arm was large (63,285) as compared to the control base population (50,629).

Accordingly, proportionally more children 2600/63,285 (4.1%) from the intervention arm

attended the study facilities than the control arm 1755/50,629 (3.5%). Second, during the

study period, approximately one million people were displaced due to inter-communal

violence in the study area.[16] From six refugee camps for the displaced people, four camps

were found in the intervention areas.[17] This might have drawn more children to seek

medical care in the intervention centres.

Our trial also did not confirm the diagnosis of severe pneumonia using radiological

examination. Hypoxemia can also occur in diseases other than childhood pneumonia,

including sepsis, meningitis, and severe malaria.[18] Our trial could include children with

acute bronchitis or acute bronchiolitis and lobar pneumonia. We used the WHO IMCI

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guidelines, which labelled these diseases clinically as pneumonia, and our findings should be interpreted within this context.

The IMCI guidelines are based on clinical symptoms, and do not involve any objective diagnostic test to identify children with severe pneumonia.[19] Health workers often misclassify pneumonia from severe pneumonia cases because of difficulty with interpretation of danger signs.[20] In our trial, we attempted to show how pulse oximetry assisted health workers in identifying severe pneumonia cases through detecting hypoxemia. The combined use of pulse oximetry with the WHO IMCI algorithm achieves better performance than the IMCI algorithm alone in identifying children with hypoxemia requiring oxygen therapy.[7, 21]

Chest in-drawings and fast breathing are keys to enable health workers to identify and provide treatment for childhood pneumonia.[22] However, IMCI-based respiratory rate and chest in-drawing increase the misclassification of pneumonia cases.[23] In subgroup analysis for the intervention arm of 135 children with hypoxemia, 56 of them did not have chest in-drawing. This means that, without pulse oximetry, 56/135 (42%) children would have been missed and inappropriately treated. Pulse oximetry identified 67% of children without chest in-drawing or danger signs.[24]

Children aged 2 months to 11 months, and partially immunized children, were more likely to be diagnosed with severe pneumonia (approximately two-fold as compared to those fully immunised). Our findings are consistent with other results, in which partial immunization constitutes a risk factor for childhood pneumonia.[25] A finding from another study also demonstrated that older children were less likely to develop childhood pneumonia.[26] Interestingly, there was no difference in severe pneumonia cases referred to a hospital between the arms. However, the total number of severe pneumonia cases referred to a hospital in the study area increased as compared to the number of cases referred to a hospital

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in the study area prior to the implementation of the intervention. In our previous survey of 66 severe pneumonia cases, only 18 (27%) were referred to a hospital.[8] In other observational research, the utilization of pulse oximetry improved the decision-making of health workers in referring children with severe pneumonia.[21, 24]

There was also no difference in treatment failure between the trial arms. A significant number of children from intervention arm didn't arrive at a hospital. This implies that only providing pulse oximetry may be insufficient to improve treatment outcome, as both pulse oximetry and adequate management, including oxygen therapy, are critical.[27] However, our study suggests that providing adequate pneumonia treatment at peripheral hospitals and health centres needs to be considered. Such strategies that decentralise treatment have, for example, been shown to reduce maternal mortality.[28]

Implications

Our results could be beneficially applied to health centres with mid-level health workers, where the management of childhood pneumonia is based on WHO IMCI guidelines. Therefore, the application of this study to health centres in rural Ethiopia could assist to significantly reduce childhood mortality from hypoxemia due to severe pneumonia.

CONCLUSION

The addition of pulse oximetry to the WHO IMCI algorithm significantly improves the diagnosis of severe pneumonia cases in health centres, and could help to substantially reduce childhood mortality from hypoxemia. Specific interventions that improve compliance with referrals and decentralize treatment to health centres for the management of severe childhood pneumonia are urgently needed.

What is already known on this subject

- Hypoxemia is a severe manifestation of severe pneumonia. The Integrated Management of Childhood Illness (IMCI) algorithm based clinical signs is poor in detecting hypoxemia in severe child hood pneumonia. Moreover, the sensitivity and specificity of this algorithm is inadequate in identifying severe pneumonia.

What this study adds

- Our results suggest that combining the existing Integrated Management of Childhood Illness (IMCI) strategy with pulse oximetry could improve the diagnosis of severe childhood pneumonia.
- Further research in decentralizing the management of severe childhood pneumonia at health centres is needed.

Contributorship

SH conceptualized the idea, designed the study, wrote the protocol, coordinated the data collection, analysed and interpreted the data, and drafted this manuscript. BL conceptualized the idea, guided the study design, wrote the protocol, analysed and interpreted the data, took part in the proposal writing and writing of this manuscript. EL provided methodological

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advice, supported the analysis and revised the draft paper. KAJ provided methodological

advice and revised the draft paper. YG took part in the training of staff at the health centres,

monitored data collection and revised the draft paper. All authors read and approved the

submitted version of the manuscript.

Competing interests: None declared

Patient consent for publication: Not required

Ethics approval

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). Children

were included in the study after giving written informed consent by parents.

Data availability statement: The data for this trial will be published if the paper is accepted.

We usually post such data sets at https://osf.io

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                                      │───────▶│ 14 health centres excluded   │
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Allocated for intervention (n = 12 clusters) Received allocated intervention (n = 12 clusters) Eligible children (n = 928) Mean cluster size: 77 (range: 20-125)	Allocated for intervention (n = 12 clusters) Received allocated intervention (n = 12 clusters) Eligible children (n = 876) Mean cluster size: 73 (range: 39-100)

Excluded children (n = 1672) Age less than two months (n = 3) No cough (n = 1667) Cough for more than 14 days (n = 0) Age less than two months and no cough (n = 2)	Excluded children (n = 879) Age less than two months (n = 38) No cough (n = 817) Cough for more than 14 days (n= 18) Age less than two months and no cough (n = 6)

Lost to follow-up (n = 68) Left study area (n = 57) Went to private clinic (n = 7) Died (n = 2)	Lost to follow-up (n = 49) Left study area (n =38) Went to private clinic (n = 3) Died (n = 2)

12 clusters with 928 individuals included for analysing primary outcome	12 clusters with 876 individuals included for analysing primary outcome

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	1,2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	3
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	3,4
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	4,5
	4b	Settings and locations where the data were collected		4,5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	5,6

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	7
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	7

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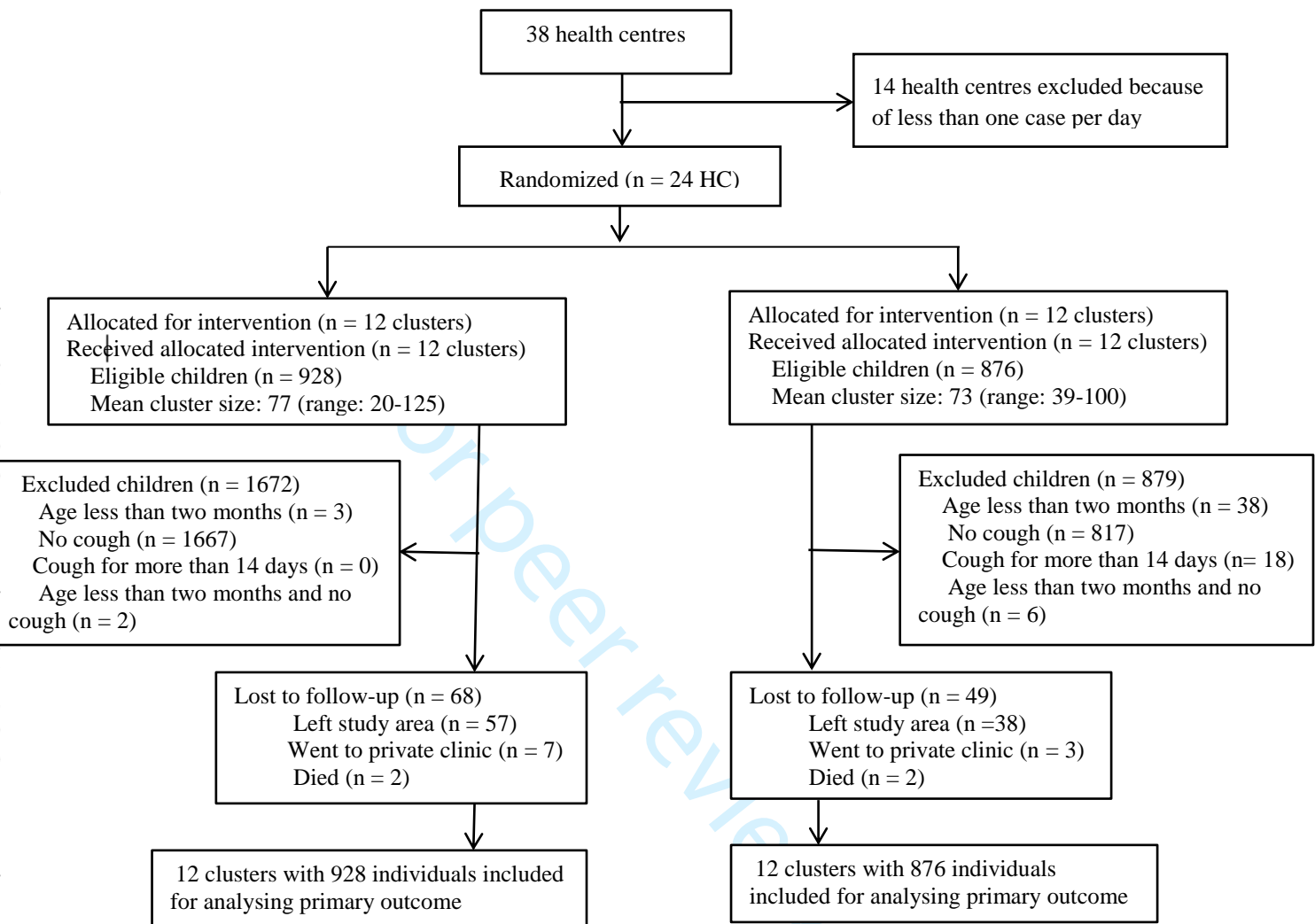41
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			enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7,8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	7,8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	8,9 and figure supplemented as separate file
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	8, and figure supplemented as separate file
Recruitment	14a	Dates defining the periods of recruitment and follow-up		8
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical	Baseline characteristics for the individual and cluster levels as	8,and table 1 on

		characteristics for each group	applicable for each group	page 9,10
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	10, 11
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		12 (Table 3)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		14
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		14,15,16
Other information				
Registration	23	Registration number and		2

		name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	4,5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

* Note: page numbers optional depending on journal requirements

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Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	Identification of study as cluster randomised
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	Eligibility criteria for clusters
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	Whether objective or hypothesis pertains to the cluster level, the individual participant level or both
Outcome	Clearly defined primary outcome for this report	Whether the primary outcome pertains to the cluster level, the individual participant level or both
Randomization	How participants were allocated to interventions	How clusters were allocated to interventions
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	Number of clusters randomized to each group
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	Number of clusters analysed in each group
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	Results at the cluster or individual participant level as applicable for each primary outcome
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

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[1] Relevant to Conference Abstracts

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BMJ Open

Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Public health
Keywords:	Community child health < PAEDIATRICS, PUBLIC HEALTH, Respiratory infections < THORACIC MEDICINE

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Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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Word count: 3445

Number of figures and tables: 5

ABSTRACT

Objective: To assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

Design: Parallel cluster randomized trial.

Setting: Government health centres

Participants: Twenty-four health centres that treat at least one pneumonia case per day in Southern Ethiopia. Children between 2 months and 59 months-of-age who present at health facilities with cough or difficulty breathing were recruited in the study from September, 2018 to April, 2019.

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Intervention arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm and pulse oximeter.

Control arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm only.

Primary and secondary outcome measures: The primary outcome was the proportion of children diagnosed with severe pneumonia. Secondary outcomes included referred cases of severe pneumonia and treatment failure on day 14 after enrolment.

Result: Twenty-four health centres were randomized into intervention (928 children) and control arms (876 children). The proportion of children with severe pneumonia was 15.9% (148 of 928 children) in the intervention arm and 3.9% (34 of 876 children) in the control arm. After adjusting for differences in baseline variables, children in the intervention arm were more likely to be diagnosed as severe pneumonia cases as compared to those in the control arm adjusted odds ratio 5.4 (95% CI 2.0–14.3).

Conclusion: The combined use of Integrated Management of Childhood Illness (IMCI) and pulse oximetry in health centres increased the number of diagnosed severe childhood pneumonia.

Trial registration: PACTR201807164196402 (14/06/2018).

Keywords: Community child health, Public health, Respiratory infection.

Strengths and limitations of this study

➢ Randomly allocation of health centres to intervention and control arms

➢ Participating health centres were typical of such institutions in rural communities in Ethiopia.

➢ Robust training on how use the Integrated Management of Childhood Illness algorithm, and how to measure oxygen saturation.

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> ➢ Due to the nature of the intervention, inability to mask the health workers and the
>   study participants of the intervention.
> ➢ Unequal number of children seeking health care between the two comparison arms.

INTRODUCTION

Pneumonia killed approximately 920,000 children less than five years-of-age in 2015.[1] The

mortality rate is especially high in Ethiopia, and 59 deaths per 1,000 live births occurred in

2017 in children less than five years-of-age.[2] Ethiopia ranks sixth among countries with the

highest number of deaths from pneumonia in children less than five years-of-age.[1]

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI)

improves the quality of child care for common illnesses,[3, 4] but there is poor diagnostic

precision for childhood pneumonia based on clinical features.[5] The ability of health care

providers to count breaths and classify respiratory rate in children using the IMCI algorithm

is a challenge.[6]

Clinical signs of pneumonia, such as tachypnoea, inability to drink or breastfeed, and head-

nodding, used in the IMCI algorithm, are not able to identify hypoxic children with severe

pneumonia as precisely as pulse oximetry.[7] Consequently, many children with severe

pneumonia are dying because hypoxemia is not adequately recognized and/or oxygen therapy

is unavailable.[1]

This study is an extension of a study in which we first assessed the health system support of

IMCI, where we found that the basic supplies for effective management of pneumonia were

inadequate. Indeed, in a large proportion of the surveyed health facilities, essential drugs,

vaccines, job aids, and equipment were lacking. None of the health centres and health posts

had pulse oximeter. We also determined that many health facilities had an insufficient

number of IMCI-trained health workers, and were deficient in requisite supportive

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supervision. In addition, health workers' knowledge of managing severe pneumonia was low.[8]

For the abovementioned reasons, an urgent need exists for interventions that assist health workers to improve the diagnosis of severe childhood pneumonia. The objective of the study was to assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

METHODS

This study adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement extension for cluster randomized trials,[9] available as supplementary files (CONSORT checklist). The full protocol of this trial was published at protocols.io (DOI: http://dx.doi.org/10.17504/protocols.io.88mhzu6).

Trial design

The study constitutes a parallel-cluster randomized controlled trial conducted at 24 health centres. An equal number of health centres were allocated into intervention and control arms, i.e., the combined use of IMCI algorithm,[10]and pulse oximetry (intervention arm), and the IMCI algorithm only (control arm). No changes were made to the design of the study after its commencement.

Study setting and participants

The study was conducted in the Gedeo Zone of Southern Ethiopia. The zone's population is more than one million people, of which approximately 170,000 are children younger than five years-of-age.[11] There are 146 health posts (operational unit for health extension workers), 38 health centres, and one hospital. At these institutions, pneumonia is among the top-10 causes of outpatient treatment, and currently health professionals in study settings

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utilize the WHO IMCI algorithm to manage pneumonia and other common childhood

illnesses.[10]

The study comprises 24 health centres in the rural Gedeo Zone, each of which treats at least

one case of pneumonia per day. Children who were aged 2 months to 59 months with cough

or had difficulty breathing for less than 14 days were included and followed for treatment

outcome. Children aged 2 months to 59 months with cough or difficulty breathing for more

than 14 days, or whose diagnoses were for other conditions, such as pulmonary tuberculosis,

were excluded. In both arms, the assessment for inclusion and exclusion of children were

identical. Pulse oximetry was not used to screen patients for inclusion in the study. Since

there was no pulse oximeter in the study settings, no pulse oximeters were removed from

their usual clinical practice for the purpose of the study. The recruitment of children started

on September, 2018 and lasted until April, 2019.

Trial interventions

Health workers from the intervention arm used the WHO IMCI algorithm,[10] and a

paediatric fingertip pulse oximeter (ADC® Adimals 2150) to diagnose pneumonia. Oxygen

saturation was measured twice, 5 min apart. The measurement was taken when the child was

calm, and recorded when the pulse oximetry accurately reflected consistent, high-amplitude

plethysmographic waveforms associated with stable oxygen saturation for 1 min. Health

workers from the control arm used the same WHO IMCI algorithm, but without measuring

oxygen saturation.

Training was given for health workers on IMCI algorithm and how to use pulse oximetry.

An IMCI-trained paediatrician offered the training, which was supported by a video-based

exercise and practical session that was developed by the WHO and adopted by the Ethiopian

Federal Ministry of Health.[12] Prior to implementing the trial, a pilot study was conducted

to estimate the intra and inter observer reliability of the pulse oximetry. Detail about training,

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data collection and pilot results were given in trial protocol

(http://dx.doi.org/10.17504/protocols.io.88mhzu6).

Study outcomes

The primary study outcome was severe pneumonia diagnosed using the IMCI algorithm in

both arms.[10] The IMCI criteria used to diagnose severe pneumonia or very severe disease

is presented in table 1. In addition to the IMCI criteria, average oxygen saturation less than

90%,[13] was used in the intervention arm.

Table 1 WHO IMCI criteria used to diagnose severe pneumonia or very severe disease.

Variable name	WHO IMCI criteria
Severe pneumonia cases detected for the intervention group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed, vomiting everything, convulsion, or lethargic) or stridor in calm child In addition one of the following symptoms of pneumonia: • Fast breathing (respiratory rate $\geq$ 50 breaths/min in children aged 2 up to 11 months and respiratory rate $\geq$ 40 breaths/min in children aged 12 months up to 5 years) • Lower chest wall in-drawing AND/OR • Oxygen saturation < 90% as measured by pulse oximetry.
Severe pneumonia cases detected for the control group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed, vomiting everything, convulsion, or lethargic) or stridor in calm child. In addition one of the following symptoms of pneumonia: • Fast breathing (respiratory rate $\geq$ 50 breaths/min in children aged 2 up to 11 months and respiratory rate $\geq$ 40 breaths/min in children aged 12 months up to 5 years)

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	• Lower chest wall in-drawing

The secondary study outcomes were: Treatment failure on day 14 after enrolment,[14] and severe pneumonia cases referred to the hospital. We considered treatment failure at day 14 if any of the following signs were present: 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 $\geq$ 37.5 degrees Celsius), persistence of tachypnoea (respiratory rate $\geq$ 50 breaths/min in children aged 2 to 11 months and $\geq$ 40 breaths/min in children aged 12 months to 5 years), chest wall in-drawings, presence of persistent cough, recurrence of fever, withdrawal from the trial or death. We originally planned to have treatment failure at 2nd, day and cumulative treatment failure at 5th and 14th days. But later, and looking at the natural history of pneumonia, we modified the treatment outcome to be assessed at day 14. In Ethiopia, children with pneumonia will be managed at home and severe pneumonia is expected to be treated at a hospital. If the child had cough or difficulty breathing after 14 days of treatment, children would have been assessed for other diseases, for example tuberculosis. That is also one reason we modified the treatment failure at days 14. Therefore we only analyse treatment failure at day 14.

Follow-up visits

Children in both the intervention and control arms were followed for a total of 14 days. Visits were scheduled on day 2, day 5, and day 14 after enrolment. For children who missed a scheduled follow-up visit, health workers contacted the families at home on the following day. A child who could not be located was considered as lost to follow-up. In such cases, we contacted the participants' family and neighbours by phone to collect information about deaths, relocation, or hospitalizations.

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Study size

The sample size was calculated based on a difference in effect size of 10%, power of 90%, 95% significance level, intraclass correlation coefficient of 0.025, and a minimum of 25 children with cough per cluster. Based on previous research, we expected health workers using the IMCI-alone algorithm to identify 4% of children with severe pneumonia.[15] With this assumption, we allocated 12 health centres to the intervention and 12 health centres to the control arm. We recruited children for 8 months (from September, 2018 to April 2019).

Randomization

Randomization was done after we obtained consent from the district and health facilities head. The randomization units were health centres. From 38 health centres in the study area, 31 health centres with at least one pneumonia case treated per day were included in the sampling frame. Accordingly, 24 of 31 health centres were randomly selected using the simple random sampling method. Of those 24, 12 were randomly selected for the intervention group and 12 for the control group. This random selection was performed at the University of Bergen using a list generated by SPSS software. The study itself was conducted in Ethiopia. Due to the nature of the intervention, it was impossible to blind the data collectors and the study participants. Those doing the analysis were not blinded to the intervention allocation.

Analyses

We used Stata version 15 (Stata Corp. LLC, College Station, TX, U.S.A.) for data analysis. An independent sample t-test for normally distributed continuous variables, Mann-Whitney U-test for skewed continuous variables, and chi-squared test for categorical variables were utilized to compare baseline data in the two arms.

Mixed effect logistic regression with random intercept to account for clustering by health centres was used to estimate the effect of the intervention on primary and secondary

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outcomes. The effect estimate for primary outcome was expressed in OR with 95% CI, and P-value less than 0.05 was considered as statistically significant. To control for potential confounding factors, some of the unbalanced baseline variables, such as child's vaccination, parents' wealth, and educational status were considered during the analysis. Individual level variables such as child's age, stunting, and sex constituted other potential confounders, and were also adjusted for the regression analysis. Intraclass correlation coefficient for the primary outcome was estimated from the random effect model output.

Where values for baseline variables were missing, they were treated as missing and the missed values for few variables were less than 5 percent. Analyses were by intention-to-treat (ITT) principle. Those who died or withdraw from the trial were classified as treatment failure and included in the ITT analysis.

Patient and Public involvement

There is no tradition in Ethiopia to invite patient organisations to take part in the planning, design and follow up of trials. In this study, and before the implementation of the intervention, meetings were held with representatives from the Gedeo Zone Health Department, district health offices, and head of health facilities. The meeting was about the burden of childhood pneumonia in the study area and at national level, and the purpose of the study. After having the authorities consent to carry out the study, written permission was obtained from Zone and district health offices. All patients were informed about the purpose of the study, and caregivers were told that involvement is voluntary and that they could withdraw at any time regardless of reason. Caregivers were briefed about the oximetry procedure and routine pneumonia diagnosis. The caregivers were informed that the instrument would not harm the child. They were also assured that refusal to participate in the

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study would not affect their medical care in health centres. The findings of this study will be

communicated to each of the health institutions and through the institutions to the patients.

RESULTS

Twenty-four health centres were randomly and equally assigned into intervention and control

arms. Nine hundred twenty eight children in the intervention arm and 876 children in the

control arm were recruited and diagnosed for severe pneumonia and followed from

September 2018 to April 2019. All of the 24 health centres and all recruited children were

included for the primary and secondary outcome analysis on the basis of the original

assignment (figure 1 for details on participants' flow and recruitment).

Baseline characteristics

The baseline characteristics of the study group were comparable, except for Pneumococcal

and Haemophilus influenzae type b vaccines, and educational and wealth status of parents

(table 2).

Table2 Baseline comparison between groups at individual and cluster level.

Variables	Intervention	Control
Cluster level		
Number of clusters	12	12
Number of children age less than five years of age in the catchment area	63,285	50,629
Total number of children attending health centres	2600	1755
Total number of eligible children	928	876
Number of eligible children per cluster	77	73
Sex of health workers		
Male	8	9
Female	4	3
Age of health workers in year: Mean (SD)	29 (4.5)	26 (2.8)

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Total service duration in months: Median (IQR)	37 (30 to 81)	45 (25 to 68)
Service in child care in months: Median (IQR)	25 (23 to 45)	21 (8 to 56)
Previous training in IMCI		
Yes	7	8
No	5	4
Profession of health workers		
Health officer	2	4
BSc nursing	1	1
Diploma nursing	9	7
Number of eligible children per cluster	77	73
Individual level		
Sex of child		
Boys	479/914 (52%)	475/870 (55%)
Girls	435/914 (48%)	395/870 (45%)
Duration of cough or difficulty breathing in days: Mean (SD)	3.8 (2.3)	3.8 (1.9)
Age of child in months: Median (IQR)	12 (7 to 28)	12 (7 to 25)
Weight-for-age-z score: Median (IQR)	-1.0 (-2.0, 0.1)	-1.1 (-2.2, 0.1)
Weight-for-height-z score: Median (IQR)	-0.1 (-1.4, 1.4)	-0.1 (-1.7, 1.8)
Height-for-age-z score: Median (IQR)	-1.7 (-3.4, -0.0)	-1.8 (-3.5, -0.1)
Pneumococcal and Haemophilus influenzae type b vaccines		
Fully vaccinated	668/928 (72.0%)	667/876 (76.1%)
Partially vaccinated	260/928 (28.0%)	209/876 (23.9%)
Age of caregivers in years: Mean (SD)	26.6 (6.2)	27.1 (4.7)
Educational status of caregivers		
No education	386/927 (41.6%)	437/875 (49.9%)
Primary	432/927 (46.6%)	371/875 (42.4%)
Secondary and above	109/927 (11.8%)	67/875 (7.7%)
Wealth tertiles		
Poor	217/830 (26.1%)	322/789 (40.8%)

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Medium	313/830 (37.7%)	208/789 (26.4%)
Rich	300/830 (36.1%)	259/789 (32.8%)

Hypoxemia

A total of 1804 children were enrolled in the study, of which 928 children were enrolled into

the intervention and 876 into the control arm. Of the 928 children in the intervention arm,

135/928 (14.5%) had oxygen saturation of less than 90%. A total of 148 severe pneumonia

cases were diagnosed in the intervention arm and, of these, 70 cases (47.3%) diagnosed with

pneumonia using IMCI algorithm had oxygen saturation < 90%, and were therefore

categorized as severe pneumonia, 65 (43.9%) were diagnosed both using IMCI and pulse

oximetry, and 13 (8.8%) were diagnosed using the IMCI algorithm alone. The overall median

oxygen saturation was 94% (IQR = 91% to 96%). The median oxygen saturation among

children diagnosed with severe pneumonia was 82%, (IQR = 72% to 86%), while among

pneumonia cases the median was 94%% (IQR = 91% to 95%), and for children with common

cold the median was 96%% (IQR=93% to 96%).

In addition, we estimated the sensitivity and specificity of the two clinical signs used in WHO

IMCI algorithm to diagnose pneumonia (fast breathing and chest in-drawing). Fast breathing

had the highest sensitivity (94), but specificity was low (25) as compared to chest in-drawing

(81). Furthermore, using a combination of both symptoms did not improve their predictive

ability (see supplementary file, table 1).

Primary outcome

The cluster adjusted proportion of diagnosed severe pneumonia was 148/928 (15.9%, 95% CI

4.7– 27.2) for the intervention arm and 34/876 (3.9%, 95% CI 1.2 – 6.6) for the control arm,

and P < 0.001. The crude odds ratio of being diagnosed with severe pneumonia for children

in the intervention arm was 4.7 (95% CI 1.9 –11.8; P < 0.001) as compared to the control

arm. The effect of the intervention remained the same after adjusting for each of the baseline

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variables (Table 3). In addition, children who were boys, aged 2 months to 11 months, height

for age z-scores less than -2, and not fully vaccinated for Pneumococcal and Haemophilus

influenzae type b were more likely to be diagnosed with severe pneumonia than their

counterparts (table 3). From the random effect model, the intraclass correlation coefficient

(ICC) for severe pneumonia was 0.043.

Table 1 Odds ratio from the multilevel logistic regression model comparing the proportion of diagnosed severe pneumonia between the arms.

Variables		Bivariate analysis					P-value	Multivariable analysis		
		Yes	No	Total	COR*	(95% CI)		AOR**	(95% CI)	p-value
Intervention	Yes	148	780	928	4.7	(1.9 –11.8)	0.001	5.4	(2.0–14.3)	0.001
	No	34	842	876	1			1		
Sex of child	Boy	113	841	954	1.9	(1.1–3.1)	0.014	1.5	(1.1–2.3)	0.033
	Girl	69	761	830	1			1		
Age of child (months)	2 - 11	93	680	773	1.7	(1.2 –2.4)	0.005	1.7	(1.1–2.6)	0.011
	12 - 59	89	942	1031	1			1		
Height-for-age z-score (<-2)	Yes	87	676	763	1.5	(1.0 –2.3)	0.031	1.5	(1.0–2.3)	0.055
	No	73	841	914	1			1		
Pneumococcal and Haemophilus influenzae type b vaccines	Partially vaccinated	67	402	469	2.0	(1.3 –3.0)	0.001	1.7	(1.1–2.7)	0.043
	Fully vaccinated	115	1220	1335	1			1		
Educational status of parents	No education	96	727	823	1.7	(0.9 –3.3)	0.110	1.1	(0.5–2.3)	0.797
	Primary	72	731	803	1.4	(0.7–2.6)	0.356	1.3	(0.6–2.6)	0.487
	Secondary	14	162	176	1			1		
Wealth tertiles	Poor	52	487	539	1.7	(0.8–3.3)	0.147	1.1	(0.7–1.9)	0.617
	Medium	47	474	521	1.3	(0.8–2.3)	0.328	0.9	(0.6–1.5)	0.761
	Rich	58	501	559	1			1		

* Crude odds ratio

** Adjusted odds ratio

Secondary outcomes

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After examining the clustering effect, the proportion of children with severe pneumonia

referred to the hospital was 116/148 (78.4%, 95% CI 67.6 – 89.2) in the intervention arm and

15/34 (44.1%, 95% CI 6.9 – 81.3) in the control arm, with P =0.496. Among these, 62/116

(53.4%) in the intervention arm, and 11/15 (73.3%) in the control arm, reached the hospital

and received the standard treatment.

Table 4 shows the total treatment failure, and treatment failure by specific causes, between

the arms. The proportion of treatment failure at day 14 was 132/928 (14.2%, 95% CI 6.0 –

22.4) in the intervention arm and 93/876 (10.6%, 95% CI 5.2 – 16.1) in the control arm (P =

0.622). There were two deaths in each of the intervention and control arms. Nine children

from the intervention and three children from the control arms had persistent cough at day 14.

The crude odds ratio of treatment failure for children with oxygen saturation < 90% was 3.3

(95% CI; 1.87 – 5.80) as compared to children with oxygen saturation greater or equal to

90%.

Table 2 Treatment failures by specific causes at day 14.

| Outcome | Treatment failure at day 14 | |
	Intervention	Control
Total	132/928 (14.2%)	93/876 (10.6%)
General danger signs	17/815 (2.1%)	31/823 (3.8%)
Chest in-drawing	2/815 (0.2%)	3/823 (0.4%)
Persistence of tachypnoea	33/815 (4.0%)	18/823 (2.2%)
Persistence of fever	9/815 (1.1%)	5/823 (0.6%)
Persistent cough	9/815 (1.1%)	3/823 (0.4%)
Lost to follow-up	68/928 (7.3%)	49/876 (5.6%)
Death	2/928 (0.22%)	2/876 (0.23%)

Sensitivity analysis

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If we use an oxygen saturation cut off < 92% to define hypoxemia, the proportion of children

with hypoxemia would be 298/921 (32.4%, 95% CI 16.2 – 48.5). Moreover, the cluster

adjusted proportion of severe pneumonia would be 304/928 (32.8%, 95% CI 18.2– 47.3) in

the intervention arm, and crude odds ratio 13.3 (95% CI 5.0 – 35.3) as compared to control

arm.

One of the health centres in intervention arm is found at high altitude (2993 metres above sea

level) and we did a sensitivity analysis adjusting oxygen saturation level at < 87% [13]. The

proportion of children with severe pneumonia in intervention arm was 124/928 (13.4%; 95%

CI 8.0 – 21.4), and 34/876 (3.9%, 95% CI 1.2 – 6.6) in the control arm. The crude odds ratio

of being diagnosed with severe pneumonia for children in the intervention arm was 4.2 (95%

CI 1.8 –9.5) as compared to the control arm.

DISCUSSION

Introducing pulse oximetry into the WHO IMCI algorithm significantly increased the

diagnosis of severe childhood pneumonia in health centres.

One of the main strengths of this study is that it was based on randomly selected health

centres, which are typical of rural communities in Ethiopia. Moreover, we measured oxygen

saturation after checking the reliability of pulse oximetry in the study area. The intra- and

inter-rater reliability estimates ranged from good to excellent.[16] In this trial, except for

educational and wealth status of parents and vaccination status of children, the baseline

characteristics of the study arms were balanced. To control for bias due to possible

confounding factors, we used estimates adjusted for those potential confounders.

The study also possesses certain limitations that are worth noting. The number of children

who attended the facilities were larger in the intervention arm than in the control group. This

might be due to the following two reasons: First, the base population in the intervention arm

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was large (63,285) as compared to the control base population (50,629). Accordingly,

proportionally more children 2600/63,285 (4.1%) from the intervention arm attended the

study facilities than the control arm 1755/50,629 (3.5%). Second, during the study period,

approximately one million people were displaced due to inter-communal violence in the

study area.[17] From six refugee camps for the displaced people, four camps were found in

the intervention areas.[18] This might have drawn more children to seek medical care in the

intervention centres.

Second, the trial also did not confirm the diagnosis of severe pneumonia using radiological

examination. Hypoxemia can also occur in diseases other than childhood pneumonia,

including sepsis, meningitis, and severe malaria.[19] Our trial could include children with

acute bronchitis or acute bronchiolitis and lobar pneumonia. We used the WHO IMCI

algorithm, which labelled these diseases clinically as pneumonia, and our findings should be

interpreted within this context.

Third, Adimals 2150 Pediatric Fingertip' pulse oximeter accurately measures oxygen

saturation of arterial hemoglobin. It is easy to use and apply with the simple press of the

button. However,the device may gave inaccurately low oxygen saturation due to low

perfusion,[20] that might not reflect the true oxygen saturation of a child. Therefore, there

may be over diagnosis of severe pneumonia in the intervention arm, as 47% of cases

diagnosed with pneumonia using IMCI algorithm had oxygen saturation < 90%, and

categorized as severe pneumonia in our trial. Previous researches have used to record oxygen

saturation when the reading was stable for 1 minutes,[21] and 3 minutes.[22] We have

recorded oxygen saturation when the reading was stable for 1 minute. However, it is difficult

to get stable oxygen saturation reading in severely ill child in 1 minutes.[23] The fourth

limitation the study was that there were missing values for few of the baseline variables.

However, the missing values were less than 5% and there was no significant difference

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between the two trial groups. Another limitation was that we used oxygen saturation level < 90%, which is high for children living at high altitude. This may increase the false positive cases of severe pneumonia. However, our sensitivity analysis shows that the result remains statistically significant after adjusting oxygen saturation level of < 87% for children living at high altitude [13].

The IMCI algorithms are based on clinical symptoms, and do not involve any objective diagnostic test to identify children with severe pneumonia.[24] Health workers often misclassify pneumonia from severe pneumonia cases because of difficulty with interpretation of danger signs.[25] In our trial, we attempted to show how pulse oximetry assisted health workers in identifying severe pneumonia cases through detecting hypoxemia. The combined use of pulse oximetry with the WHO IMCI algorithm achieves better performance than the IMCI algorithm alone in identifying children with hypoxemia requiring oxygen therapy.[7, 26]

Chest in-drawings and fast breathing are keys to enable health workers to identify and provide treatment for childhood pneumonia.[27] However, IMCI-based respiratory rate and chest in-drawing increase the misclassification of pneumonia cases.[28] In subgroup analysis for the intervention arm of 135 children with hypoxemia, 56 of them did not have chest in-drawing. This means that, without pulse oximetry, 56/135 (42%) children would have been missed and inappropriately treated. Pulse oximetry identified 67% of children without chest in-drawing or danger signs.[29]

Children aged 2 months to 11 months, and partially immunized children, were more likely to be diagnosed with severe pneumonia (approximately two-fold as compared to those fully immunised). Our findings are consistent with other results, in which partial immunization constitutes a risk factor for childhood pneumonia.[30] A finding from another study also demonstrated that older children were less likely to develop childhood pneumonia.[31]

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There was no difference in severe pneumonia cases referred to a hospital between the arms. However, the total number of severe pneumonia cases referred to a hospital in the study area increased as compared to the number of cases referred to a hospital in the study area prior to the implementation of the intervention. In our previous survey of 66 severe pneumonia cases, only 18 (27%) were referred to a hospital.[8] In other observational research, the utilization of pulse oximetry improved the decision-making of health workers in referring children with severe pneumonia.[26, 29]

There was also no difference in treatment failure between the trial arms. A significant number of children from intervention arm did not go to hospital. Limited access to transport was the main reason for low compliance with referral in the study settings.[8] This implies that only providing pulse oximetry may be insufficient to improve treatment outcome, as both pulse oximetry and adequate management, including oxygen therapy, are critical.[32] However, our study suggests that providing adequate pneumonia treatment at peripheral hospitals and health centres needs to be considered and should be future research area. Such strategies that decentralise treatment have, for example, been shown to reduce maternal mortality.[33]

Implications

Our results could be beneficially applied to health centres with mid-level health workers, where the management of childhood pneumonia is based on WHO IMCI algorithm. Therefore, the application of pulse oximeter to supplement the existing WHO IMCI algorithm to health centres in rural Ethiopia could assist health workers to find more cases of severe pneumonia

CONCLUSION

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The addition of pulse oximetry to the WHO IMCI algorithm significantly increased the number of diagnosed severe pneumonia cases in health centres, and could help to substantially reduce childhood mortality from hypoxemia. Specific interventions that improve compliance with referrals and decentralize treatment to health centres for the management of severe childhood pneumonia are urgently needed.

Contributorship

SH conceptualized the idea, designed the study, wrote the protocol, coordinated the data collection, analysed and interpreted the data, and drafted this manuscript. BL conceptualized the idea, guided the study design, wrote the protocol, analysed and interpreted the data, took part in the proposal writing and writing of this manuscript. EL provided methodological advice, supported the analysis and revised the draft paper. KAJ provided methodological advice and revised the draft paper. YG took part in the training of staff at the health centres, monitored data collection and revised the draft paper. All authors read and approved the submitted version of the manuscript.

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data collection, analysis, interpretation, writing of the manuscript, or decision to submit the

paper for publication.

Competing interests: None declared

Patient consent for publication: Not required

Ethics approval

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). Children

were included in the study after giving written informed consent by parents.

Data availability statement: The data for this trial will be published if the paper is accepted.

We usually post such data sets at https://osf.io

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38 health centres

14 health centres excluded because of less than one case per day

Randomized (n = 24 HC)

Allocated to combined use of pulse oximetry and IMCI algorithm (n = 12 clusters, 928 children)
Received allocated intervention (n = 12 clusters, 928 children): Mean cluster size 77 (range: 20 – 125)

Allocated to IMCI algorithm only (n = 12 clusters, 876 children)
Received allocated intervention (n = 12 clusters, 876 children: Mean cluster size: 73 (range: 39 - 100)

Excluded children (n = 1672)
  Age less than two months (n = 3)
  No cough (n = 1667)
  Cough for more than 14 days (n = 0)
  Age less than two months and no cough (n = 2)

Excluded children (n = 879)
  Age less than two months (n = 38)
  No cough (n = 817)
  Cough for more than 14 days (n= 18)
  Age less than two months and no cough (n = 6)

Lost to follow-up (n = 68)
  Left study area (n = 57)
  Went to private clinic (n = 7)
  Died (n = 2)

Lost to follow-up (n = 49)
  Left study area (n =38)
  Went to private clinic (n = 3)
  Died (n = 2)

Analysed (12 clusters, 928 children) included for primary and secondary analysis

Analysed (12 clusters, 876 children) included for primary and secondary analysis

Supplementary Table 1: Sensitivity and specificity of clinical signs.

Clinical signs	Pulse oximeter			Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Hypoxemia	No hypoxemia	Total				
Chest in-drawing				59	81	35	92
Yes	79	147	226				
No	56	626	682				
Total	135	773	908				
Fast breathing				94	25	18	96
Yes	127	587	714				
No	8	194	202				
Total	135	781	916				
Chest in-drawing and fast breathing				57	82	35	92
Yes	78	145	223				
No	57	641	698				
Total	135	786	921				

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	1 and 2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	3 and 4
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	3 and 4
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	4 and 5
	4b	Settings and locations where the data were collected		4 and 5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	5 and 6
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	6 and 7

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		**7**
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or *k*), and an indication of its uncertainty	8
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		8
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	8
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	8
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	8

			enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	8
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		8
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	8 and 9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		9
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	10 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up		10
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical	Baseline characteristics for the individual and cluster levels as	10 and 11

		characteristics for each group	applicable for each group	(Table1)
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	10
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	12 and 13
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		13 (Table 3)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		12, 13, 15
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		2, 3 and 15,16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	18
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		15, 16, and 17
Other information				
Registration	23	Registration number and		2

		name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	4
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	19 and 20

* Note: page numbers optional depending on journal requirements

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

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[1] Relevant to Conference Abstracts

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Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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ABSTRACT

Objective: To assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

Design: Parallel cluster randomized trial.

Setting: Government health centres

Participants: Twenty-four health centres that treat at least one pneumonia case per day in Southern Ethiopia. Children between 2 months and 59 months-of-age who present at health facilities with cough or difficulty breathing were recruited in the study from September, 2018 to April, 2019.

Intervention arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm and pulse oximeter.

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Control arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm only.

Primary and secondary outcome measures: The primary outcome was the proportion of children diagnosed with severe pneumonia. Secondary outcomes included referred cases of severe pneumonia and treatment failure on day 14 after enrolment.

Result: Twenty-four health centres were randomized into intervention (928 children) and control arms (876 children). The proportion of children with severe pneumonia was 15.9% (148 of 928 children) in the intervention arm and 3.9% (34 of 876 children) in the control arm. After adjusting for differences in baseline variables children in the intervention arm were more likely to be diagnosed as severe pneumonia cases as compared to those in the control arm (adjusted odds ratio [OR]:5.4, 95% confidence interval [CI]: 2.0 – 14.3, p=0.001)

Conclusion: The combined use of Integrated Management of Childhood Illness (IMCI) and pulse oximetry in health centres increased the number of diagnosed severe childhood pneumonia.

Trial registration: PACTR201807164196402 (14/06/2018).

Keywords: Community child health, Public health, Respiratory infection.

Strengths and limitations of this study

- ➢ Randomly allocation of health centres to intervention and control arms
- ➢ Participating health centres were typical of such institutions in rural communities in Ethiopia.
- ➢ Robust training on how use the Integrated Management of Childhood Illness algorithm, and how to measure oxygen saturation.
- ➢ Due to the nature of the intervention, inability to mask the health workers and the study participants of the intervention.
- ➢ Unequal number of children seeking health care between the two comparison arms.

INTRODUCTION

Pneumonia killed approximately 920,000 children less than five years-of-age in 2015.[1] The mortality rate is especially high in Ethiopia, and 59 deaths per 1,000 live births occurred in

2017 in children less than five years-of-age.[2] Ethiopia ranks sixth among countries with the highest number of deaths from pneumonia in children less than five years-of-age.[1]

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) improves the quality of child care for common illnesses,[3, 4] but there is poor diagnostic precision for childhood pneumonia based on clinical features.[5] The ability of health care providers to count breaths and classify respiratory rate in children using the IMCI algorithm is a challenge.[6]

Clinical signs of pneumonia, such as tachypnoea, inability to drink or breastfeed, and head-nodding, used in the IMCI algorithm, are not able to identify hypoxic children with severe pneumonia as precisely as pulse oximetry.[7] Consequently, many children with severe pneumonia are dying because hypoxemia is not adequately recognized and/or oxygen therapy is unavailable.[1]

This study is an extension of a study in which we first assessed the health system support of IMCI, where we found that the basic supplies for effective management of pneumonia were inadequate. Indeed, in a large proportion of the surveyed health facilities, essential drugs, vaccines, job aids, and equipment were lacking. None of the health centres and health posts had a pulse oximeter. We also determined that many health facilities had an insufficient number of IMCI-trained health workers, and were deficient in requisite supportive supervision. In addition, health workers' knowledge of managing severe pneumonia was low.[8]

For the abovementioned reasons, an urgent need exists for interventions that assist health workers to improve the diagnosis of severe childhood pneumonia. The objective of the study was to assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

METHODS

This study adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement extension for cluster randomized trials,[9] available as supplementary files (CONSORT checklist). The full protocol of this trial was published at protocols.io (DOI: http://dx.doi.org/10.17504/protocols.io.88mhzu6).

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Trial design

The study constitutes a parallel-cluster randomized controlled trial conducted at 24 health centres. An equal number of health centres were allocated into intervention and control arms, i.e., the combined use of IMCI algorithm,[10]and pulse oximetry (intervention arm), and the IMCI algorithm only (control arm). No changes were made to the design of the study after its commencement.

Study setting and participants

The study was conducted in the Gedeo Zone of Southern Ethiopia. The zone's population is more than one million people, of which approximately 170,000 are children younger than five years-of-age.[11] There are 146 health posts (operational unit for health extension workers), 38 health centres, and one hospital. At these institutions, pneumonia is among the top-10 causes of outpatient treatment, and currently health professionals in study settings utilize the WHO IMCI algorithm to manage pneumonia and other common childhood illnesses.[10]

The study comprises 24 health centres in the rural Gedeo Zone, each of which treats at least one case of pneumonia per day. Children who were aged 2 months to 59 months with cough or had difficulty breathing for less than 14 days were included and followed for treatment outcome. Children aged 2 months to 59 months with cough or difficulty breathing for more than 14 days, or whose diagnoses were for other conditions, such as pulmonary tuberculosis, were excluded. In both arms, the assessment for inclusion and exclusion of children were identical. Pulse oximetry was not used to screen patients for inclusion in the study. Since there was no pulse oximeter in the study settings, no pulse oximeters were removed from their usual clinical practice for the purpose of the study. The recruitment of children started on September, 2018 and lasted until April, 2019.

Trial interventions

Health workers from the intervention arm used the WHO IMCI algorithm,[10] and a paediatric fingertip pulse oximeter (ADC® Adimals 2150) to diagnose pneumonia. Oxygen saturation was measured twice, 5 min apart. The measurement was taken when the child was calm, and recorded when the pulse oximetry accurately reflected consistent, high-amplitude plethysmographic waveforms associated with stable oxygen saturation for 1 min. Hypoxemia (oxygen saturation less than 90%) diagnosis was based on the average of the two measures.

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Health workers from the control arm used the same WHO IMCI algorithm, but without measuring oxygen saturation.

Training was given for health workers on IMCI algorithm and how to use pulse oximetry. An IMCI-trained paediatrician offered the training, which was supported by a video-based exercise and practical session that was developed by the WHO and adopted by the Ethiopian Federal Ministry of Health.[12] Prior to implementing the trial, a pilot study was conducted to estimate the intra and inter observer reliability of the pulse oximetry. Detail about training, data collection and pilot results were given in trial protocol.

Study outcomes

The primary study outcome was severe pneumonia diagnosed using the IMCI algorithm in both arms.[10] The IMCI criteria used to diagnose severe pneumonia or very severe disease is presented in table 1. In addition to the IMCI criteria, average oxygen saturation less than 90%,[13] was used in the intervention arm.

Table 1 WHO IMCI criteria used to diagnose severe pneumonia or very severe disease.

Variable name	WHO IMCI criteria
Severe pneumonia cases detected for the intervention group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed, vomiting everything, convulsion, or lethargic) or stridor in calm child In addition one of the following symptoms of pneumonia: • Fast breathing (respiratory rate $\geq$ 50 breaths/min in children aged 2 up to 11 months and respiratory rate $\geq$ 40 breaths/min in children aged 12 months up to 5 years) • Lower chest wall in-drawing AND/OR • Oxygen saturation < 90% as measured by pulse oximetry.
Severe pneumonia cases detected for the control group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed,

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	vomiting everything, convulsion, or lethargic) or stridor in calm child.
	In addition one of the following symptoms of pneumonia:
	• Fast breathing (respiratory rate ≥ 50 breaths/min in children aged 2 up to 11 months and respiratory rate ≥ 40 breaths/min in children aged 12 months up to 5 years)
	• Lower chest wall in-drawing

The secondary study outcomes were: Treatment failure on day 14 after enrolment,[14] and severe pneumonia cases referred to the hospital. We considered treatment failure at day 14 if any of the following signs were present: 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/min in children aged 2 to 11 months and ≥ 40 breaths/min in children aged 12 months to 5 years), chest wall in-drawings, presence of persistent cough, recurrence of fever, withdrawal from the trial or death. Treatment failure on days 2, 5 and 14 was initially planned in this study. But for the following reasons only treatment failure on day 14 was included in the final analysis: in Ethiopia, children with pneumonia will be managed at home and severe pneumonia is expected to be treated at a hospital. If the child had cough or difficulty breathing after 14 days of treatment, children would have been assessed for other diseases, for example tuberculosis.

Follow-up visits

Children in both the intervention and control arms were followed for a total of 14 days. Visits were scheduled on day 2, day 5, and day 14 after enrolment. For children who missed a scheduled follow-up visit, health workers contacted the families at home on the following day. A child who could not be located was considered as lost to follow-up. In such cases, we contacted the participants' family and neighbours by phone to collect information about deaths, relocation, or hospitalizations.

Study size

The sample size was calculated based on a difference in effect size of 10%, power of 90%, 95% significance level, intraclass correlation coefficient of 0.025, and a minimum of 25

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children with cough per cluster. Based on previous research, we expected health workers using the IMCI-alone algorithm to identify 4% of children with severe pneumonia.[15] With this assumption, the estimated number of clusters was 11 in each arm. Drop-out of the entire clusters is uncommon, however, according to a recommendation by Rutterford et al,[16] we incorporated 1 extra cluster per treatment group. Therefore, the total size of the cluster was 12 per treatment group.

Randomization

Randomization was done after we obtained consent from the district and health facilities head. The randomization units were health centres. From 38 health centres in the study area, 31 health centres with at least one pneumonia case treated per day were included in the sampling frame. Accordingly, 24 of 31 health centres were randomly selected using the simple random sampling method. Of those 24, 12 were randomly selected for the intervention group and 12 for the control group. This random selection was performed at the University of Bergen using a list generated by SPSS software. Due to the nature of the intervention, it was impossible to blind the data collectors and the study participants. Those doing the analysis were not blinded to the intervention allocation.

Analyses

We used Stata version 15 (Stata Corp. LLC, College Station, TX, U.S.A.) for data analysis. An independent sample t-test for normally distributed continuous variables, Mann-Whitney U-test for skewed continuous variables, and chi-squared test for categorical variables were utilized to compare baseline data in the two arms.

Mixed effect logistic regression with random intercept to account for clustering by health centres was used to estimate the effect of the intervention on primary and secondary outcomes. The effect estimate for primary outcome was expressed in odds ratio (OR) with 95% confidence interval (CI), and P-value less than 0.05 was considered as statistically significant. To control for potential confounding factors, some of the unbalanced baseline variables, such as child's vaccination, parents' wealth, and educational status were considered during the analysis. Individual level variables such as child's age, stunting, and sex constituted other potential confounders, and were also adjusted for the regression analysis. Intraclass correlation coefficient for the primary outcome was estimated from the random effect model output.

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Where values for baseline variables were missing, they were treated as missing and the missed values for few variables were less than 5 percent. Analyses were by intention-to-treat (ITT) principle. Those who died or withdraw from the trial were classified as treatment failure and included in the ITT analysis.

Patient and Public involvement

There is no tradition in Ethiopia to invite patient organisations to take part in the planning, design and follow up of trials. In this study, and before the implementation of the intervention, meetings were held with representatives from the Gedeo Zone Health Department, district health offices, and head of health facilities. The meeting was about the burden of childhood pneumonia in the study area and at national level, and the purpose of the study. After having the authorities consent to carry out the study, written permission was obtained from Zone and district health offices. All patients were informed about the purpose of the study, and caregivers were told that involvement is voluntary and that they could withdraw at any time regardless of reason. Caregivers were briefed about the oximetry procedure and routine pneumonia diagnosis. The caregivers were informed that the instrument would not harm the child. They were also assured that refusal to participate in the study would not affect their medical care in health centres. The findings of this study will be communicated to each of the health institutions and through the institutions to the patients.

RESULTS

Twenty-four health centres were randomly and equally assigned into intervention and control arms. Nine hundred twenty eight children in the intervention arm and 876 children in the control arm were recruited and diagnosed for severe pneumonia and followed from September 2018 to April 2019. All of the 24 health centres and all recruited children were included for the primary and secondary outcome analysis on the basis of the original assignment (figure 1 for details on participants' flow and recruitment).

Baseline characteristics

The baseline characteristics of the study group were comparable, except for Pneumococcal and Haemophilus influenzae type b vaccines, and educational and wealth status of parents (table 2).

Table2 Baseline comparison between groups at individual and cluster level.

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Variables	Intervention	Control
Cluster level		
Number of clusters	12	12
Number of children age less than five years of age in the catchment area	63,285	50,629
Total number of children attending health centres	2600	1755
Total number of eligible children	928	876
Number of eligible children per cluster	77	73
Sex of health workers		
Male	8	9
Female	4	3
Age of health workers in year: Mean (SD)	29 (4.5)	26 (2.8)
Total service duration in months: Median (IQR)	37 (30 to 81)	45 (25 to 68)
Service in child care in months: Median (IQR)	25 (23 to 45)	21 (8 to 56)
Previous training in IMCI		
Yes	7	8
No	5	4
Profession of health workers		
Health officer	2	4
BSc nursing	1	1
Diploma nursing	9	7
Number of eligible children per cluster	77	73
Individual level		
Sex of child		
Boys	479/914 (52%)	475/870 (55%)
Girls	435/914 (48%)	395/870 (45%)
Duration of cough or difficulty breathing in days: Mean (SD)	3.8 (2.3)	3.8 (1.9)
Age of child in months: Median (IQR)	12 (7 to 28)	12 (7 to 25)
Weight-for-age-z score: Median (IQR)	-1.0 (-2.0, 0.1)	-1.1 (-2.2,0.1)
Weight-for-height-z score: Median (IQR)	-0.1 (-1.4,1.4)	-0.1 (-1.7,1.8)

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Height-for-age-z score: Median (IQR)	-1.7 (-3.4, -0.0)	-1.8 (-3.5, -0.1)
Pneumococcal and Haemophilus influenzae type b vaccines		
Fully vaccinated	668/928 (72.0%)	667/876 (76.1%)
Partially vaccinated	260/928 (28.0%)	209/876 (23.9%)
Age of caregivers in years: Mean (SD)	26.6 (6.2)	27.1 (4.7)
Educational status of caregivers		
No education	386/927 (41.6%)	437/875 (49.9%)
Primary	432/927 (46.6%)	371/875 (42.4%)
Secondary and above	109/927 (11.8%)	67/875 (7.7%)
Wealth tertiles		
Poor	217/830 (26.1%)	322/789 (40.8%)
Medium	313/830 (37.7%)	208/789 (26.4%)
Rich	300/830 (36.1%)	259/789 (32.8%)

Hypoxemia

A total of 1804 children were enrolled in the study, of which 928 children were enrolled into the intervention and 876 into the control arm. Of the 928 children in the intervention arm, 135/928 (14.5%) had oxygen saturation of less than 90%. A total of 148 severe pneumonia cases were diagnosed in the intervention arm and, of these, 65 cases (43.9%) met the IMCI algorithm and had oxygen saturation < 90%, 70 (47.3%) did not meet the IMCI algorithm, but had oxygen saturation < 90%, and 13 (8.8%) met the IMCI algorithm, but had oxygen saturation > 90%. The overall median oxygen saturation was 94% (IQR = 91% to 96%). The median oxygen saturation among children diagnosed with severe pneumonia was 82%, (IQR = 72% to 86%), while among non-severe pneumonia cases the median was 94% (IQR = 92% to 96%).

In addition, we estimated the sensitivity and specificity of the two clinical signs used in WHO IMCI algorithm to diagnose pneumonia (fast breathing and chest in-drawing). Fast breathing had the highest sensitivity (94%), but specificity was low (25%) as compared to chest in-drawing (81%). Furthermore, using a combination of both symptoms did not improve their predictive ability (see supplementary file, table 1).

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Primary outcome

The cluster adjusted proportion of diagnosed severe pneumonia was 148/928 (15.9%, 95% CI 4.7– 27.2) for the intervention arm and 34/876 (3.9%, 95% CI 1.2 – 6.6) for the control arm, and P < 0.001. The crude odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 4.7 (95% CI 1.9 –11.8; P < 0.001) as compared to the control arm. The effect of the intervention remained the same after adjusting for each of the baseline variables (Table 3). In addition, children who were boys, aged 2 months to 11 months, height for age z-scores less than -2, and not fully vaccinated for Pneumococcal and Haemophilus influenzae type b were more likely to be diagnosed with severe pneumonia than their counterparts (table 3).

We carried out effect modification analysis to see whether the effect of pulse oximeter in identifying severe pneumonia was modified by the type of health profession (Bachelor degree versus diploma degree nurses). The impact of pulse oximeter is not modified by the health professionals' medical background knowledge for diagnosing severe childhood pneumonia (P- value = 0.828). Therefore, we have removed the interaction term and present the model without interaction and present the effect of pulse oximetry adjusted for the baseline confounders.

Table 3   Odds ratio from the multilevel logistic regression model comparing the proportion of diagnosed severe pneumonia between the arms.

Variables		Total	Diagnosed severe pneumonia	Bivariate analysis	Multivariable analysis	
			n (%)	COR* (95% CI)	AOR** (95% CI)	P value
Intervention†	Yes	928	148 (15.9)	4.7 (1.9 –11.8)	5.4 (2.0–14.3)	0.001
	No	876	34 (3.9)	1	1	
Sex of child	Boy	954	113 (11.8)	1.9 (1.1–3.1)	1.5 (1.1–2.3)	0.033
	Girl	830	69 (8.3)	1	1	
Age of child (months)	2–11	773	93 (12.0)	1.7 (1.2 –2.4)	1.7 (1.1–2.6)	0.011
	12–59	1031	89 (8.6)	1	1	
Height-for-age z-score (<-2)	Yes	763	87 (11.4)	1.5 (1.0 –2.3)	1.5 (1.0–2.3)	0.055
	No	914	73 (8.0)	1	1	
Pneumococcal and Haemophilus influenzae type b vaccines	Partially vaccinated	469	67 (14.3)	2 (1.3 –3.0)	1.7 (1.1–2.7)	0.043
	Fully vaccinated	1335	115 (8.6)	1	1	
Educational status of parents	No education	823	96 (11.7)	1.7 (0.9 –3.3)	1.1 (0.5–2.3)	0.797
	Primary	803	72 (9.0)	1.4 (0.7–2.6)	1.3 (0.6–2.6)	0.487

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	Secondary	176	14 (8.0)	1	1	
Wealth tertiles	Poor	539	52 (9.6)	1.7 (0.8–3.3)	1.1 (0.7–1.9)	0.617
	Medium	521	47 (9.0)	1.3 (0.8–2.3)	0.9 (0.6–1.5)	0.761
	Rich	559	58 (10.4)	1	1	

[*]Crude odds ratio

[**]Adjusted odds ratio

[†]The intraclass correlation coefficient (ICC) for severe pneumonia was 0.043.

Secondary outcomes

After examining the clustering effect, the proportion of children with severe pneumonia referred to the hospital was 116/148 (78.4%, 95% CI 67.6 – 89.2) in the intervention arm and 15/34 (44.1%, 95% CI 6.9 – 81.3) in the control arm, with P =0.496. Among these, 62/116 (53.4%) in the intervention arm, and 11/15 (73.3%) in the control arm, reached the hospital and received the standard treatment.

Table 4 shows the total treatment failure, and treatment failure by specific causes, between the arms. The proportion of treatment failure at day 14 was 132/928 (14.2%, 95% CI 6.0 – 22.4) in the intervention arm and 93/876 (10.6%, 95% CI 5.2 – 16.1) in the control arm (P = 0.622). There were two deaths in each of the intervention and control arms. Nine children from the intervention and three children from the control arms had persistent cough at day 14. The crude odds ratio of treatment failure for children with oxygen saturation < 90% was 3.3 (95% CI; 1.87 – 5.80) as compared to children with oxygen saturation greater or equal to 90%.

Table 4 Treatment failures by specific causes at day 14.

	Treatment failure at day 14			
Outcome	Intervention	Control	Difference % (95% CI)	P value
Total	132/928 (14.2%)	93/876 (10.6%)	-3.6% (-17 to 10.7)	0.622
General danger signs	17/815 (2.1%)	31/823 (3.8%)	1.7% (-5.2 to 8.6)	0.635
Chest in-drawing	2/815 (0.2%)	3/823 (0.4%)	0.2% (-0.4 to 0.7)	0.662
Persistence of tachypnoea	33/815 (4.0%)	18/823 (2.2%)	-1.9% (-12.2 to 8.5)	0.722
Persistence of fever	9/815 (1.1%)	5/823 (0.6%)	-0.5% (-3.4 to 2.4)	0.737
Persistent cough	9/815 (1.1%)	3/823 (0.4%)	-0.7% (-5.1 to 3.6)	0.736

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| Lost to follow-up | 68/928 (7.3%) | 49/876 (5.6%) | -2.1% (-17.0 to 12.9) | 0.785 |
| Death | 2/928 (0.22%) | 2/876 (0.23%) | 0.0% (-0.4 to 0.4) | 0.954 |

Sensitivity analysis

If we use an oxygen saturation cut off < 92% to define hypoxemia, the proportion of children with hypoxemia would be 298/921 (32.4%, 95% CI 16.2 – 48.5). Moreover, the cluster adjusted proportion of severe pneumonia would be 304/928 (32.8%, 95% CI 18.2– 47.3) in the intervention arm, and crude odds ratio 13.3 (95% CI 5.0 – 35.3) as compared to control arm.

One of the health centres in intervention arm is found at high altitude (2993 metres above sea level) and we did a sensitivity analysis adjusting oxygen saturation level at < 87% [13]. The proportion of children with severe pneumonia in intervention arm was 124/928 (13.4%; 95% CI 8.0 – 21.4), and 34/876 (3.9%, 95% CI 1.2 – 6.6) in the control arm. The crude odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 4.2 (95% CI 1.8 –9.5) as compared to the control arm.

As it was the first time that mid-level health workers in this rural part of Ethiopia used pulse oximeters, this could result non-valid pulse oximeter readings. Assuming that 85% of the readings would be valid, we randomly select 85% of cases with pulse oximeter measurements and did sensitivity analysis. The proportion of children with severe pneumonia in intervention arm was 126 of 789 children (15.9%; 95% CI 10.0 – 21.9), and 34/876 (3.9%, 95% CI 0.8 – 6.9) in the control arm. The adjusted odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 5.3 (95% CI 1.9 –14.4; P = 0.001) as compared to the control arm.

DISCUSSION

Introducing pulse oximetry into the WHO IMCI algorithm significantly increased the diagnosis of severe childhood pneumonia in health centres.

The IMCI algorithms are based on clinical symptoms, and do not involve any objective diagnostic test to identify children with severe pneumonia.[17] Health workers often misclassify pneumonia from severe pneumonia cases because of difficulty with interpretation of danger signs.[18] In our trial, we attempted to show how pulse oximetry assisted health

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workers in identifying severe pneumonia cases through detecting hypoxemia. The combined use of pulse oximetry with the WHO IMCI algorithm achieves better performance than the IMCI algorithm alone in identifying children with hypoxemia requiring oxygen therapy.[7, 19]

Chest in-drawings and fast breathing are keys to enable health workers to identify and provide treatment for childhood pneumonia.[20] However, IMCI-based respiratory rate and chest in-drawing increase the misclassification of pneumonia cases.[21] In subgroup analysis for the intervention arm of 135 children with hypoxemia, 56 of them did not have chest in-drawing. This means that, without pulse oximetry, 56/135 (42%) children would have been missed and inappropriately treated. Pulse oximetry identified 67% of children without chest in-drawing or danger signs.[22]

Children aged 2 months to 11 months, and partially immunized children, were more likely to be diagnosed with severe pneumonia (approximately two-fold as compared to those fully immunised). Our findings are consistent with other results, in which partial immunization constitutes a risk factor for childhood pneumonia.[23] A finding from another study also demonstrated that older children were less likely to develop childhood pneumonia.[24]

There was no difference in severe pneumonia cases referred to a hospital between the arms. However, the total number of severe pneumonia cases referred to a hospital in the study area increased as compared to the number of cases referred to a hospital in the study area prior to the implementation of the intervention. In our previous survey of 66 severe pneumonia cases, only 18 (27%) were referred to a hospital.[8] In other observational research, the utilization of pulse oximetry improved the decision-making of health workers in referring children with severe pneumonia.[19, 22]

There was also no difference in treatment failure between the trial arms. A large number of children from the intervention arm did not go to hospital. Limited access to transport was the main reason for low compliance with referral in the study settings.[8] This implies that only providing pulse oximetry may be insufficient to improve treatment outcome, as both pulse oximetry and adequate management, including oxygen therapy, are critical.[25] However, our study suggests that providing adequate pneumonia treatment at peripheral hospitals and health centres needs to be considered and should be future research area. Such strategies that decentralise treatment have, for example, been shown to reduce maternal mortality.[26]

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One of the main strengths of this study is that it was based on randomly selected health centres, which are typical of rural communities in Ethiopia. Moreover, we measured oxygen saturation after checking the reliability of pulse oximetry in the study area. The intra- and inter-rater reliability estimates ranged from good to excellent.[27] In this trial, except for educational and wealth status of parents and vaccination status of children, the baseline characteristics of the study arms were balanced. To control for bias due to possible confounding factors, we used estimates adjusted for those potential confounders.

The study also possesses certain limitations that are worth noting. The number of children who attended the facilities was larger in the intervention arm than in the control group. This might be due to the following two reasons: (1) the base population in the intervention arm was large (63,285) as compared to the control base population (50,629). Accordingly, proportionally more children 2600/63,285 (4.1%) from the intervention arm attended the study facilities than the control arm 1755/50,629 (3.5%), (2) during the study period, approximately one million people were displaced due to inter-communal violence in the study area.[28] From six refugee camps for the displaced people, four camps were found in the intervention areas.[29] This might have drawn more children to seek medical care in the intervention centres.

Second, the trial also did not confirm the diagnosis of severe pneumonia using radiological examination. Hypoxemia can also occur in diseases other than childhood pneumonia, including sepsis, meningitis, and severe malaria.[30] Our trial could include children with acute bronchitis or acute bronchiolitis and lobar pneumonia. We used the WHO IMCI algorithm, which labelled these diseases clinically as pneumonia, and our findings should be interpreted within this context.

Third, Adimals 2150 Pediatric Fingertip' pulse oximeter accurately measures oxygen saturation of arterial hemoglobin. It is easy to use and apply with the simple press of the button. We tried to record the oxygen saturation when the reading was stable for one minute. Even if the oxygen saturation readings may not reflect the true oxygen saturation level of all children, some of the oxygen saturation readings could be a result of measurement errors. There can be three possible explanations for this. First, the pulse oximeter gives inaccurate readings. The inaccuracies can be observed in motion artefacts, poor perfusion, skin pigmentation, and irregular rhythms.[31] Second, given the requirement of stable oxygen reading for 60 seconds, may force health workers to accept the false reading as there was no

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option in case of pulse oximeter data failure to get stable reading. Finally, it was the first time that mid-level health workers used pulse oximeter and in some cases, we might not have measured valid pulse oximeter readings. However, the sensitivity analysis based on 85% of anticipated valid pulse oximetry readings showed that our conclusion is similar. The fourth limitation of the study was that there were missing values for few of the baseline variables. However, the missing values were less than 5% and there was no significant difference between the two trial groups. Another limitation was that we used oxygen saturation level < 90%, which is high for children living at high altitude. This may increase the false positive cases of severe pneumonia. However, our sensitivity analysis shows that the result remains statistically significant after adjusting oxygen saturation level of < 87% for children living at high altitude.[13] Finally, the confidence interval for the effect estimate of the primary outcome in the intervention arm is wide. It is well known that estimates accounting for clustering can result in wide confidence interval. Therefore we recommend future research to be conducted using a larger sample size.

Implications

Our results could be beneficially applied to health centres with mid-level health workers, where the management of childhood pneumonia is based on WHO IMCI algorithm. Therefore, the application of pulse oximeter to supplement the existing WHO IMCI algorithm to health centres in rural Ethiopia could assist health workers to find more cases of severe pneumonia

CONCLUSION

The addition of pulse oximetry to the WHO IMCI algorithm significantly increased the number of diagnosed severe pneumonia cases in health centres, and could help to substantially reduce childhood mortality from hypoxemia. Specific interventions that improve compliance with referrals and decentralize treatment to health centres for the management of severe childhood pneumonia are urgently needed.

Acknowledgements

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Contributorship

SHT conceptualized the idea, designed the study, wrote the protocol, coordinated the data collection, analysed and interpreted the data, and drafted this manuscript. BL conceptualized the idea, guided the study design, wrote the protocol, analysed and interpreted the data, took part in the proposal writing and writing of this manuscript. EL provided methodological advice, supported the analysis and revised the draft paper. KAJ provided methodological advice and revised the draft paper. YG took part in the training of staff at the health centres, monitored data collection and revised the draft paper. All authors read and approved the submitted version of the manuscript.

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Patient consent for publication: Not required

Ethics approval

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). Children were included in the study after giving written informed consent by parents.

Data availability statement: The data for this trial will be published if the paper is accepted. We usually post such data sets at https://osf.io
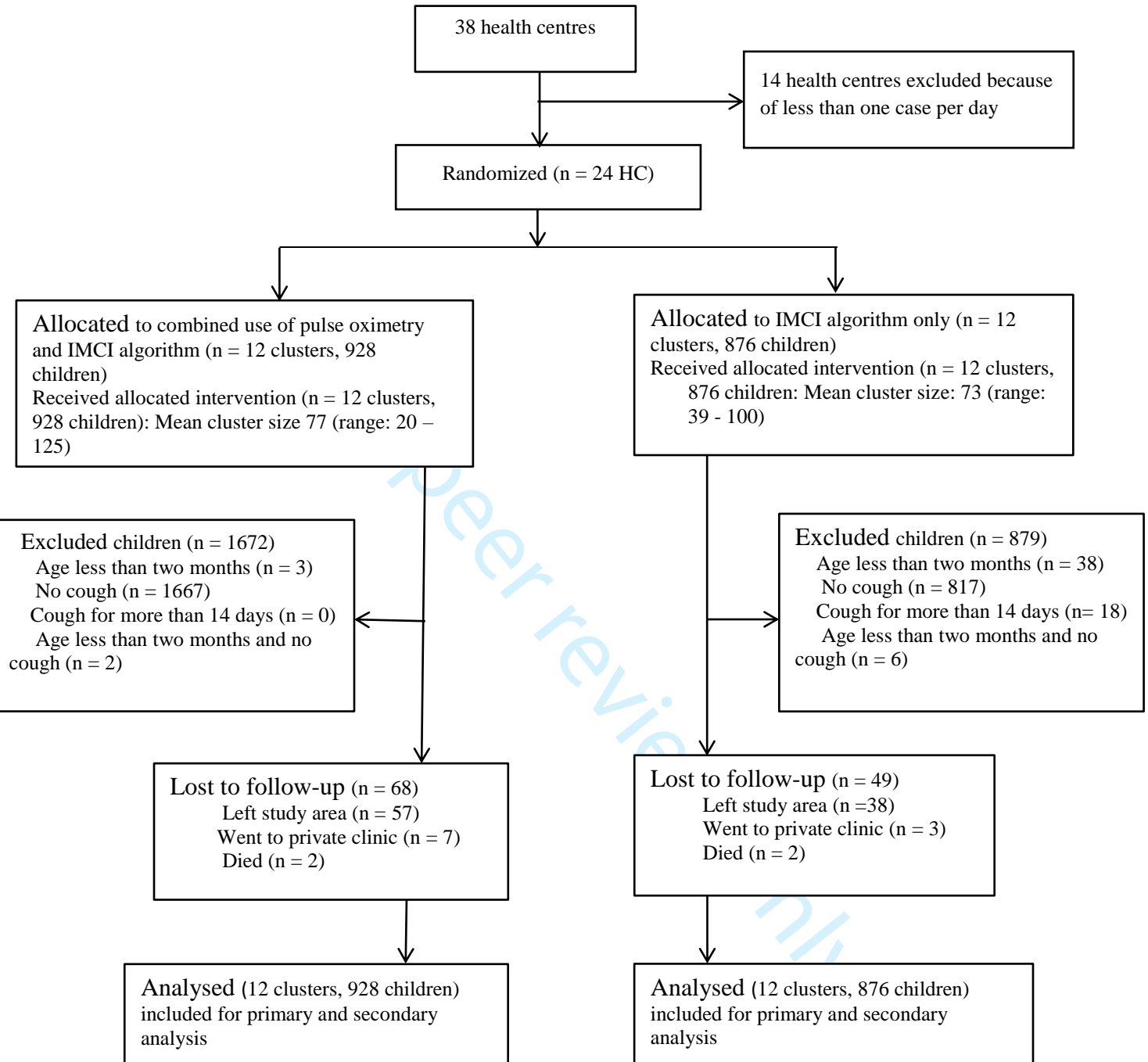
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Figure Legends

Figure1 Trial profile.

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4   38 health centres
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6   14 health centres excluded because
7   of less than one case per day
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10   Randomized (n = 24 HC)
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16   Allocated to combined use of pulse oximetry   Allocated to IMCI algorithm only (n = 12
17   and IMCI algorithm (n = 12 clusters, 928   clusters, 876 children)
     children)   Received allocated intervention (n = 12 clusters,
18   Received allocated intervention (n = 12 clusters,   876 children: Mean cluster size: 73 (range:
19   928 children): Mean cluster size 77 (range: 20 –   39 - 100)
20   125)
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24   Excluded children (n = 1672)   Excluded children (n = 879)
25   Age less than two months (n = 3)   Age less than two months (n = 38)
26   No cough (n = 1667)   No cough (n = 817)
27   Cough for more than 14 days (n = 0)   Cough for more than 14 days (n= 18)
28   Age less than two months and no   Age less than two months and no
29   cough (n = 2)   cough (n = 6)
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34   Lost to follow-up (n = 68)   Lost to follow-up (n = 49)
35   Left study area (n = 57)   Left study area (n =38)
36   Went to private clinic (n = 7)   Went to private clinic (n = 3)
37   Died (n = 2)   Died (n = 2)
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42   Analysed (12 clusters, 928 children)   Analysed (12 clusters, 876 children)
43   included for primary and secondary   included for primary and secondary
44   analysis   analysis
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Supplementary Table 1: Sensitivity and specificity of clinical signs.

Clinical signs	Pulse oximeter			Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Hypoxemia	No hypoxemia	Total				
Chest in-drawing				59%	81%	35%	92%
Yes	79	147	226				
No	56	626	682				
Total	135	773	908				
Fast breathing				94%	25%	18%	96%
Yes	127	587	714				
No	8	194	202				
Total	135	781	916				
Chest in-drawing and fast breathing				57%	82%	35%	92%
Yes	78	145	223				
No	57	641	698				
Total	135	786	921				

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	1 and 2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	2 and 3
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	3
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	4
	4b	Settings and locations where the data were collected		4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	4 and 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	5 and 6

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		6
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty	6 and 7
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	7

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			enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	7 and 8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		7
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	8 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up		8
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical	Baseline characteristics for the individual and cluster levels as	8 and (Table1)

		characteristics for each group	applicable for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	11 and 12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		11 (Table 3)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		10 and 13
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		15 and 16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		13, 14 and 15
Other information				
Registration	23	Registration number and		2

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		name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

* Note: page numbers optional depending on journal requirements

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

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[1] Relevant to Conference Abstracts

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[2] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

[3] Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.

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Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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Pulse oximeter with integrated management of childhood illness for diagnosis of severe childhood pneumonia at rural health institutions in Southern Ethiopia: Results from a cluster-randomized controlled trial

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ABSTRACT

Objective: To assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

Design: Parallel cluster randomized trial.

Setting: Government primary health centres

Participants: Twenty-four health centres that treat at least one pneumonia case per day in Southern Ethiopia. Children between 2 months and 59 months-of-age who present at health facilities with cough or difficulty breathing were recruited in the study from September, 2018 to April, 2019.

Intervention arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm and pulse oximeter.

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Control arm: Use of the Integrated Management of Childhood Illness (IMCI) algorithm only.

Primary and secondary outcome measures: The primary outcome was the proportion of children diagnosed with severe pneumonia. Secondary outcomes included referred cases of severe pneumonia and treatment failure on day 14 after enrolment.

Result: Twenty-four health centres were randomized into intervention (928 children) and control arms (876 children). The proportion of children with severe pneumonia was 15.9% (148 of 928 children) in the intervention arm and 3.9% (34 of 876 children) in the control arm. After adjusting for differences in baseline variables children in the intervention arm were more likely to be diagnosed as severe pneumonia cases as compared to those in the control arm (adjusted odds ratio [OR]:5.4, 95% confidence interval [CI]: 2.0 – 14.3, p=0.001)

Conclusion: The combined use of Integrated Management of Childhood Illness (IMCI) and pulse oximetry in health centres increased the number of diagnosed severe childhood pneumonia.

Trial registration: PACTR201807164196402 (14/06/2018).

Keywords: Community child health, Public health, Respiratory infection.

Strengths and limitations of this study

> ➤ Random allocation of health centres to intervention and control arms
> ➤ Participating health centres were typical of such institutions in rural communities in Ethiopia.
> ➤ Robust training on how use the Integrated Management of Childhood Illness algorithm, and how to measure oxygen saturation.
> ➤ Due to the nature of the intervention, inability to mask the health workers and the study participants of the intervention.
> ➤ Unequal number of children seeking health care between the two comparison arms.

INTRODUCTION

Pneumonia killed approximately 920,000 children less than five years-of-age in 2015.[1] The mortality rate is especially high in Ethiopia, and 59 deaths per 1,000 live births occurred in

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2017 in children less than five years-of-age.[2] Ethiopia ranks sixth among countries with the highest number of deaths from pneumonia in children less than five years-of-age.[1]

The World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) improves the quality of child care for common illnesses,[3, 4] but there is poor diagnostic precision for childhood pneumonia based on clinical features.[5] The ability of health care providers to count breaths and classify respiratory rate in children using the IMCI algorithm is a challenge.[6]

Clinical signs of pneumonia, such as tachypnoea, inability to drink or breastfeed, and head-nodding, used in the IMCI algorithm, are not able to identify hypoxic children with severe pneumonia as precisely as pulse oximetry.[7] Consequently, many children with severe pneumonia are dying because hypoxemia is not adequately recognized and/or oxygen therapy is unavailable.[1]

This study is an extension of a study in which we first assessed the health system support of IMCI, where we found that the basic supplies for effective management of pneumonia were inadequate. Indeed, in a large proportion of the surveyed health facilities, essential drugs, vaccines, job aids, and equipment were lacking. None of the health centres and health posts had a pulse oximeter. We also determined that many health facilities had an insufficient number of IMCI-trained health workers, and were deficient in requisite supportive supervision. In addition, health workers' knowledge of managing severe pneumonia was low.[8]

For the abovementioned reasons, an urgent need exists for interventions that assist health workers to improve the diagnosis of severe childhood pneumonia. The objective of the study was to assess whether pulse oximetry improves health workers' performance in diagnosing severe childhood pneumonia at health centres in Southern Ethiopia.

METHODS

This study adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement extension for cluster randomized trials,[9] available as supplementary files (CONSORT checklist). The full protocol of this trial was published at protocols.io (DOI: http://dx.doi.org/10.17504/protocols.io.88mhzu6).

Trial design

The study constitutes a parallel-cluster randomized controlled trial conducted at 24 health centres. An equal number of health centres were allocated into intervention and control arms, i.e., the combined use of IMCI algorithm,[10]and pulse oximetry (intervention arm), and the IMCI algorithm only (control arm). No changes were made to the design of the study after its commencement.

Study setting and participants

The study was conducted in the Gedeo Zone of Southern Ethiopia. The zone's population is more than one million people, of which approximately 170,000 are children younger than five years-of-age.[11] There are 146 health posts (operational unit for health extension workers), 38 primary health centres, and one teaching and referral hospital. At these institutions, pneumonia is among the top-10 causes of outpatient treatment, and currently health professionals in study settings utilize the WHO IMCI algorithm to manage pneumonia and other common childhood illnesses.[10]

The study comprises 24 primary health centres in the rural Gedeo Zone, each of which treats at least one case of pneumonia per day. Children who were aged 2 months to 59 months with cough or had difficulty breathing for less than 14 days were included and followed for treatment outcome. Children aged 2 months to 59 months with cough or difficulty breathing for more than 14 days, or whose diagnoses were for other conditions, such as pulmonary tuberculosis, were excluded. In both arms, the assessment for inclusion and exclusion of children were identical. Pulse oximetry was not used to screen patients for inclusion in the study. Since there was no pulse oximeter in the study settings, no pulse oximeters were removed from their usual clinical practice for the purpose of the study. The recruitment of children started on September, 2018 and lasted until April, 2019.

Trial interventions

Health workers from the intervention arm used the WHO IMCI algorithm,[10] and a paediatric fingertip pulse oximeter (ADC® Adimals 2150) to diagnose pneumonia. Oxygen saturation was measured twice, 5 min apart. The measurement was taken when the child was calm, and recorded when the pulse oximetry accurately reflected consistent, high-amplitude plethysmographic waveforms associated with stable oxygen saturation for 1 min. Hypoxemia (oxygen saturation less than 90%) diagnosis was based on the average of the two measures.

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Health workers from the control arm used the same WHO IMCI algorithm, but without measuring oxygen saturation.

Training was given for health workers on IMCI algorithm and how to use pulse oximetry. An IMCI-trained paediatrician offered the training, which was supported by a video-based exercise and practical session that was developed by the WHO and adopted by the Ethiopian Federal Ministry of Health.[12] Prior to implementing the trial, a pilot study was conducted to estimate the intra and inter observer reliability of the pulse oximetry. Detail about training, data collection and pilot results were given in trial protocol.

Study outcomes

The primary study outcome was severe pneumonia diagnosed using the IMCI algorithm in both arms.[10] The IMCI criteria used to diagnose severe pneumonia or very severe disease is presented in table 1. In addition to the IMCI criteria, average oxygen saturation less than 90%,[13] was used in the intervention arm.

Table 1 WHO IMCI criteria used to diagnose severe pneumonia or very severe disease.

Variable name	WHO IMCI criteria
Severe pneumonia cases detected for the intervention group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed, vomiting everything, convulsion, or lethargic) or stridor in calm child In addition one of the following symptoms of pneumonia: • Fast breathing (respiratory rate ≥ 50 breaths/min in children aged 2 up to 11 months and respiratory rate ≥ 40 breaths/min in children aged 12 months up to 5 years) • Lower chest wall in-drawing AND/OR • Oxygen saturation < 90% as measured by pulse oximetry.
Severe pneumonia cases detected for the control group	A child with cough or difficult breathing plus at least one of the following signs: • Any general danger signs (unable to drink or breastfeed,

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	vomiting everything, convulsion, or lethargic) or stridor in calm child. In addition one of the following symptoms of pneumonia: • Fast breathing (respiratory rate ≥ 50 breaths/min in children aged 2 up to 11 months and respiratory rate ≥ 40 breaths/min in children aged 12 months up to 5 years) • Lower chest wall in-drawing

The secondary study outcomes were: Treatment failure on day 14 after enrolment,[14] and severe pneumonia cases referred to the hospital. We considered treatment failure at day 14 if any of the following signs were present: 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/min in children aged 2 to 11 months and ≥ 40 breaths/min in children aged 12 months to 5 years), chest wall in-drawings, presence of persistent cough, recurrence of fever, withdrawal from the trial or death. Treatment failure on days 2, 5 and 14 was initially planned in this study. But for the following reasons only treatment failure on day 14 was included in the final analysis: in Ethiopia, children with pneumonia will be managed at home and severe pneumonia is expected to be treated at a hospital. If the child had cough or difficulty breathing after 14 days of treatment, children would have been assessed for other diseases, for example tuberculosis.

Follow-up visits

Children in both the intervention and control arms were followed for a total of 14 days. Visits were scheduled on day 2, day 5, and day 14 after enrolment. For children who missed a scheduled follow-up visit, health workers contacted the families at home on the following day. A child who could not be located was considered as lost to follow-up. In such cases, we contacted the participants' family and neighbours by phone to collect information about deaths, relocation, or hospitalizations.

Study size

The sample size was calculated based on a difference in effect size of 10%, power of 90%, 95% significance level, intraclass correlation coefficient of 0.025, and a minimum of 25

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children with cough per cluster. Based on previous research, we expected health workers using the IMCI-alone algorithm to identify 4% of children with severe pneumonia.[15] With this assumption, the estimated number of clusters was 11 in each arm. Drop-out of the entire clusters is uncommon, however, according to a recommendation by Rutterford et al,[16] we incorporated 1 extra cluster per treatment group. Therefore, the total size of the cluster was 12 per treatment group.

Randomization

Randomization was done after we obtained consent from the district and health facilities head. The randomization units were health centres. From 38 health centres in the study area, 31 health centres with at least one pneumonia case treated per day were included in the sampling frame. Accordingly, 24 of 31 health centres were randomly selected using the simple random sampling method. Of those 24, 12 were randomly selected for the intervention group and 12 for the control group. This random selection was performed at the University of Bergen using a list generated by SPSS software. Due to the nature of the intervention, it was impossible to blind the data collectors and the study participants. Those doing the analysis were not blinded to the intervention allocation.

Analyses

We used Stata version 15 (Stata Corp. LLC, College Station, TX, U.S.A.) for data analysis. An independent sample t-test for normally distributed continuous variables, Mann-Whitney U-test for skewed continuous variables, and chi-squared test for categorical variables were utilized to compare baseline data in the two arms.

Mixed effect logistic regression with random intercept to account for clustering by health centres was used to estimate the effect of the intervention on primary and secondary outcomes. The effect estimate for primary outcome was expressed in odds ratio (OR) with 95% confidence interval (CI), and P-value less than 0.05 was considered as statistically significant. To control for potential confounding factors, some of the unbalanced baseline variables, such as child's vaccination, parents' wealth, and educational status were considered during the analysis. Individual level variables such as child's age, stunting, and sex constituted other potential confounders, and were also adjusted for the regression analysis. Intraclass correlation coefficient for the primary outcome was estimated from the random effect model output.

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Where values for baseline variables were missing, they were treated as missing and the missed values for few variables were less than 5 percent. Analyses were by intention-to-treat (ITT) principle. Those who died or withdraw from the trial were classified as treatment failure and included in the ITT analysis.

Patient and Public involvement

There is no tradition in Ethiopia to invite patient organisations to take part in the planning, design and follow up of trials. In this study, and before the implementation of the intervention, meetings were held with representatives from the Gedeo Zone Health Department, district health offices, and head of health facilities. The meeting was about the burden of childhood pneumonia in the study area and at national level, and the purpose of the study. After having the authorities consent to carry out the study, written permission was obtained from Zone and district health offices. All patients were informed about the purpose of the study, and caregivers were told that involvement is voluntary and that they could withdraw at any time regardless of reason. Caregivers were briefed about the oximetry procedure and routine pneumonia diagnosis. The caregivers were informed that the instrument would not harm the child. They were also assured that refusal to participate in the study would not affect their medical care in health centres. The findings of this study will be communicated to each of the health institutions and through the institutions to the patients.

RESULTS

Twenty-four health centres were randomly and equally assigned into intervention and control arms. Nine hundred twenty eight children in the intervention arm and 876 children in the control arm were recruited and diagnosed for severe pneumonia and followed from September 2018 to April 2019. All of the 24 health centres and all recruited children were included for the primary and secondary outcome analysis on the basis of the original assignment (figure 1 for details on participants' flow and recruitment).

Baseline characteristics

The baseline characteristics of the study group were comparable, except for Pneumococcal and Haemophilus influenzae type b vaccines, and educational and wealth status of parents (table 2).

Table2 Baseline comparison between groups at individual and cluster level.

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Variables	Intervention	Control
Cluster level		
Number of clusters	12	12
Number of children age less than five years of age in the catchment area	63,285	50,629
Total number of children attending health centres	2600	1755
Total number of eligible children	928	876
Number of eligible children per cluster	77	73
Sex of health workers		
Male	8	9
Female	4	3
Age of health workers in year: Mean (SD)	29 (4.5)	26 (2.8)
Total service duration in months: Median (IQR)	37 (30 to 81)	45 (25 to 68)
Service in child care in months: Median (IQR)	25 (23 to 45)	21 (8 to 56)
Previous training in IMCI		
Yes	7	8
No	5	4
Profession of health workers		
Health officer	2	4
BSc nursing	1	1
Diploma nursing	9	7
Number of eligible children per cluster	77	73
Individual level		
Sex of child		
Boys	479/914 (52%)	475/870 (55%)
Girls	435/914 (48%)	395/870 (45%)
Duration of cough or difficulty breathing in days: Mean (SD)	3.8 (2.3)	3.8 (1.9)
Age of child in months: Median (IQR)	12 (7 to 28)	12 (7 to 25)
Weight-for-age-z score: Median (IQR)	-1.0 (-2.0, 0.1)	-1.1 (-2.2,0.1)
Weight-for-height-z score: Median (IQR)	-0.1 (-1.4,1.4)	-0.1 (-1.7,1.8)

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Height-for-age-z score: Median (IQR)	-1.7 (-3.4, -0.0)	-1.8 (-3.5, -0.1)
Pneumococcal and Haemophilus influenzae type b vaccines		
Fully vaccinated	668/928 (72.0%)	667/876 (76.1%)
Partially vaccinated	260/928 (28.0%)	209/876 (23.9%)
Age of caregivers in years: Mean (SD)	26.6 (6.2)	27.1 (4.7)
Educational status of caregivers		
No education	386/927 (41.6%)	437/875 (49.9%)
Primary	432/927 (46.6%)	371/875 (42.4%)
Secondary and above	109/927 (11.8%)	67/875 (7.7%)
Wealth tertiles		
Poor	217/830 (26.1%)	322/789 (40.8%)
Medium	313/830 (37.7%)	208/789 (26.4%)
Rich	300/830 (36.1%)	259/789 (32.8%)

Hypoxemia

A total of 1804 children were enrolled in the study, of which 928 children were enrolled into the intervention and 876 into the control arm. Of the 928 children in the intervention arm, 135/928 (14.5%) had oxygen saturation of less than 90%. A total of 148 severe pneumonia cases were diagnosed in the intervention arm and, of these, 65 cases (43.9%) met the IMCI algorithm and had oxygen saturation < 90%, 70 (47.3%) did not meet the IMCI algorithm, but had oxygen saturation < 90%, and 13 (8.8%) met the IMCI algorithm, but had oxygen saturation > 90%. The overall median oxygen saturation was 94% (IQR = 91% to 96%). The median oxygen saturation among children diagnosed with severe pneumonia was 82%, (IQR = 72% to 86%), while among non-severe pneumonia cases the median was 94% (IQR = 92% to 96%).

In addition, we estimated the sensitivity and specificity of the two clinical signs used in WHO IMCI algorithm to diagnose pneumonia (fast breathing and chest in-drawing). Fast breathing had the highest sensitivity (94%), but specificity was low (25%) as compared to chest in-drawing (81%). Furthermore, using a combination of both symptoms did not improve their predictive ability (see supplementary file, table 1).

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Primary outcome

The cluster adjusted proportion of diagnosed severe pneumonia was 148/928 (15.9%, 95% CI 4.7– 27.2) for the intervention arm and 34/876 (3.9%, 95% CI 1.2 – 6.6) for the control arm, and P < 0.001. The crude odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 4.7 (95% CI 1.9 –11.8; P < 0.001) as compared to the control arm. The effect of the intervention remained the same after adjusting for each of the baseline variables (Table 3). In addition, children who were boys, aged 2 months to 11 months, height for age z-scores less than -2, and not fully vaccinated for Pneumococcal and Haemophilus influenzae type b were more likely to be diagnosed with severe pneumonia than their counterparts (table 3).

We carried out effect modification analysis to see whether the effect of pulse oximeter in identifying severe pneumonia was modified by the type of health profession (Bachelor degree versus diploma degree nurses). The impact of pulse oximeter is not modified by the health professionals' medical background knowledge for diagnosing severe childhood pneumonia (P- value = 0.828). Therefore, we have removed the interaction term and present the model without interaction and present the effect of pulse oximetry adjusted for the baseline confounders.

Table 3 Odds ratio from the multilevel logistic regression model comparing the proportion of diagnosed severe pneumonia between the arms.

Variables		Total	Diagnosed severe pneumonia	Bivariate analysis	Multivariable analysis	
			n (%)	COR* (95% CI)	AOR** (95% CI)	P value
Intervention†	Yes	928	148 (15.9)	4.7 (1.9 –11.8)	5.4 (2.0–14.3)	0.001
	No	876	34 (3.9)	1	1	
Sex of child	Boy	954	113 (11.8)	1.9 (1.1–3.1)	1.5 (1.1–2.3)	0.033
	Girl	830	69 (8.3)	1	1	
Age of child (months)	2–11	773	93 (12.0)	1.7 (1.2 –2.4)	1.7 (1.1–2.6)	0.011
	12–59	1031	89 (8.6)	1	1	
Height-for-age z-score (<-2)	Yes	763	87 (11.4)	1.5 (1.0 –2.3)	1.5 (1.0–2.3)	0.055
	No	914	73 (8.0)	1	1	
Pneumococcal and Haemophilus influenzae type b vaccines	Partially vaccinated	469	67 (14.3)	2 (1.3 –3.0)	1.7 (1.1–2.7)	0.043
	Fully vaccinated	1335	115 (8.6)	1	1	
Educational status of parents	No education	823	96 (11.7)	1.7 (0.9 –3.3)	1.1 (0.5–2.3)	0.797
	Primary	803	72 (9.0)	1.4 (0.7–2.6)	1.3 (0.6–2.6)	0.487

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	Secondary	176	14 (8.0)	1	1	
Wealth tertiles	Poor	539	52 (9.6)	1.7 (0.8–3.3)	1.1 (0.7–1.9)	0.617
	Medium	521	47 (9.0)	1.3 (0.8–2.3)	0.9 (0.6–1.5)	0.761
	Rich	559	58 (10.4)	1	1	

*Crude odds ratio

**Adjusted odds ratio

†The intraclass correlation coefficient (ICC) for severe pneumonia was 0.043.

Secondary outcomes

After examining the clustering effect, the proportion of children with severe pneumonia referred to the hospital was 116/148 (78.4%, 95% CI 67.6 – 89.2) in the intervention arm and 15/34 (44.1%, 95% CI 6.9 – 81.3) in the control arm, with P =0.496. Among these, 62/116 (53.4%) in the intervention arm, and 11/15 (73.3%) in the control arm, reached the hospital and received the standard treatment.

Table 4 shows the total treatment failure, and treatment failure by specific causes, between the arms. The proportion of treatment failure at day 14 was 132/928 (14.2%, 95% CI 6.0 – 22.4) in the intervention arm and 93/876 (10.6%, 95% CI 5.2 – 16.1) in the control arm (P = 0.622). There were two deaths in each of the intervention and control arms. Nine children from the intervention and three children from the control arms had persistent cough at day 14. The crude odds ratio of treatment failure for children with oxygen saturation < 90% was 3.3 (95% CI; 1.87 – 5.80) as compared to children with oxygen saturation greater or equal to 90%.

Table 4 Treatment failures by specific causes at day 14.

Outcome	Treatment failure at day 14			
	Intervention	Control	Difference % (95% CI)	P value
Total	132/928 (14.2%)	93/876 (10.6%)	-3.6% (-17 to 10.7)	0.622
General danger signs	17/815 (2.1%)	31/823 (3.8%)	1.7% (-5.2 to 8.6)	0.635
Chest in-drawing	2/815 (0.2%)	3/823 (0.4%)	0.2% (-0.4 to 0.7)	0.662
Persistence of tachypnoea	33/815 (4.0%)	18/823 (2.2%)	-1.9% (-12.2 to 8.5)	0.722
Persistence of fever	9/815 (1.1%)	5/823 (0.6%)	-0.5% (-3.4 to 2.4)	0.737
Persistent cough	9/815 (1.1%)	3/823 (0.4%)	-0.7% (-5.1 to 3.6)	0.736

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Lost to follow-up	68/928 (7.3%)	49/876 (5.6%)	-2.1% (-17.0 to 12.9)	0.785
Death	2/928 (0.22%)	2/876 (0.23%)	0.0% (-0.4 to 0.4)	0.954

Sensitivity analysis

The cut-off point we used in the trial proposal to define hypoxemia was an issue raised by the Regional Committees for Medical Research Ethics, South East Norway that approved our study. The committee commented that the cut-off point of oxygen saturation under 90% to define hypoxemia is too low as it would contradict the Norwegian guidelines. Therefore, Oxygen saturation cut-off point < 92% was used for the sensitivity analysis. If we use an oxygen saturation cut off < 92% to define hypoxemia, the proportion of children with hypoxemia would be 298/921 (32.4%, 95% CI 16.2 – 48.5). Moreover, the cluster adjusted proportion of severe pneumonia would be 304/928 (32.8%, 95% CI 18.2– 47.3) in the intervention arm, and crude odds ratio 13.3 (95% CI 5.0 – 35.3) as compared to control arm.

One of the health centres in intervention arm is found at high altitude (2993 metres above sea level) and we did a sensitivity analysis adjusting oxygen saturation level at < 87% [13]. The proportion of children with severe pneumonia in intervention arm was 124/928 (13.4%; 95% CI 8.0 – 21.4), and 34/876 (3.9%, 95% CI 1.2 – 6.6) in the control arm. The crude odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 4.2 (95% CI 1.8 –9.5) as compared to the control arm.

As it was the first time that mid-level health workers in this rural part of Ethiopia used pulse oximeters, this could result non-valid pulse oximeter readings. Assuming that 85% of the readings would be valid, we randomly select 85% of cases with pulse oximeter measurements and did sensitivity analysis. The proportion of children with severe pneumonia in intervention arm was 126 of 789 children (15.9%; 95% CI 10.0 – 21.9), and 34/876 (3.9%, 95% CI 0.8 – 6.9) in the control arm. The adjusted odds ratio of being diagnosed with severe pneumonia for children in the intervention arm was 5.3 (95% CI 1.9 –14.4; P = 0.001) as compared to the control arm.

DISCUSSION

Introducing pulse oximetry into the WHO IMCI algorithm significantly increased the diagnosis of severe childhood pneumonia in health centres.

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The IMCI algorithms are based on clinical symptoms, and do not involve any objective diagnostic test to identify children with severe pneumonia.[17] Health workers often misclassify pneumonia from severe pneumonia cases because of difficulty with interpretation of danger signs.[18] In our trial, we attempted to show how pulse oximetry assisted health workers in identifying severe pneumonia cases through detecting hypoxemia. The combined use of pulse oximetry with the WHO IMCI algorithm achieves better performance than the IMCI algorithm alone in identifying children with hypoxemia requiring oxygen therapy.[7, 19]

Chest in-drawings and fast breathing are keys to enable health workers to identify and provide treatment for childhood pneumonia.[20] However, IMCI-based respiratory rate and chest in-drawing increase the misclassification of pneumonia cases.[21] In subgroup analysis for the intervention arm of 135 children with hypoxemia, 56 of them did not have chest in-drawing. This means that, without pulse oximetry, 56/135 (42%) children would have been missed and inappropriately treated. Pulse oximetry identified 67% of children without chest in-drawing or danger signs.[22]

Children aged 2 months to 11 months, and partially immunized children, were more likely to be diagnosed with severe pneumonia (approximately two-fold as compared to those fully immunised). Our findings are consistent with other results, in which partial immunization constitutes a risk factor for childhood pneumonia.[23] A finding from another study also demonstrated that older children were less likely to develop childhood pneumonia.[24]

There was no difference in severe pneumonia cases referred to a hospital between the arms. However, the total number of severe pneumonia cases referred to a hospital in the study area increased as compared to the number of cases referred to a hospital in the study area prior to the implementation of the intervention. In our previous survey of 66 severe pneumonia cases, only 18 (27%) were referred to a hospital.[8] In other observational research, the utilization of pulse oximetry improved the decision-making of health workers in referring children with severe pneumonia.[19, 22]

There was also no difference in treatment failure between the trial arms. A large number of children from the intervention arm did not go to hospital. Limited access to transport was the main reason for low compliance with referral in the study settings.[8] This implies that only providing pulse oximetry may be insufficient to improve treatment outcome, as both pulse

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oximetry and adequate management, including oxygen therapy, are critical.[25] However, our study suggests that providing adequate pneumonia treatment at peripheral hospitals and health centres needs to be considered and should be future research area. Such strategies that decentralise treatment have, for example, been shown to reduce maternal mortality.[26]

One of the main strengths of this study is that it was based on randomly selected health centres, which are typical of rural communities in Ethiopia. Moreover, we measured oxygen saturation after checking the reliability of pulse oximetry in the study area. The intra- and inter-rater reliability estimates ranged from good to excellent.[27] In this trial, except for educational and wealth status of parents and vaccination status of children, the baseline characteristics of the study arms were balanced. To control for bias due to possible confounding factors, we used estimates adjusted for those potential confounders.

The study also possesses certain limitations that are worth noting. First, the number of children who attended the facilities was larger in the intervention arm than in the control group. This might be due to the following two reasons: (1) the base population in the intervention arm was large (63,285) as compared to the control base population (50,629). Accordingly, proportionally more children 2600/63,285 (4.1%) from the intervention arm attended the study facilities than the control arm 1755/50,629 (3.5%), (2) during the study period, approximately one million people were displaced due to inter-communal violence in the study area.[28] From six refugee camps for the displaced people, four camps were found in the intervention areas.[29] This might have drawn more children to seek medical care in the intervention centres.

Second, the trial also did not confirm the diagnosis of severe pneumonia using radiological examination. Hypoxemia can also occur in diseases other than childhood pneumonia, including sepsis, meningitis, and severe malaria.[30] Our trial could include children with acute bronchitis or acute bronchiolitis and lobar pneumonia. We used the WHO IMCI algorithm, which labelled these diseases clinically as pneumonia, and our findings should be interpreted within this context.

Third, it is well documented that obtaining accurate saturations readings in sick children is challenging and that our documented pulse oximetry readings may not always be accurate for three main reasons (1) the pulse oximeter may have given an inaccurate reading, for example when there was   motion artefacts, poor perfusion, or irregular rhythms.[31] (2) the

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requirement to record an oxygen saturation that had been stable for 60 seconds may have forced health workers to document a reading, even when this was not always possible. (3) it was the first time that health workers at these institutions used pulse oximeter, therefore, health workers may document an inaccurate pulse oximeter reading. However, the sensitivity analysis based on 85% of anticipated valid pulse oximetry readings showed that our conclusion is similar.

The fourth limitation of the study was that there were missing values for few of the baseline variables. However, the missing values were less than 5% and there was no significant difference between the two trial groups. Another limitation was that we used oxygen saturation level < 90%, which is high for children living at high altitude. This may increase the false positive cases of severe pneumonia. However, our sensitivity analysis shows that the result remains statistically significant after adjusting oxygen saturation level of < 87% for children living at high altitude.[13]

Fifthly, the confidence interval for the effect estimate of the primary outcome in the intervention arm is wide. It is well known that estimates accounting for clustering can result in wide confidence interval. Therefore we recommend future research to be conducted using a larger sample size.

Implications

Our results could be beneficially applied to health centres with mid-level health workers, where the management of childhood pneumonia is based on WHO IMCI algorithm. Therefore, the application of pulse oximeter to supplement the existing WHO IMCI algorithm to health centres in rural Ethiopia could assist health workers to find more cases of severe pneumonia

CONCLUSION

The addition of pulse oximetry to the WHO IMCI algorithm significantly increased the number of diagnosed severe pneumonia cases in health centres, and could help to substantially reduce childhood mortality from hypoxemia. Specific interventions that improve compliance with referrals and decentralize treatment to health centres for the management of severe childhood pneumonia are urgently needed.

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Acknowledgements

Contributorship

SHT conceptualized the idea, designed the study, wrote the protocol, coordinated the data collection, analysed and interpreted the data, and drafted this manuscript. BL conceptualized the idea, guided the study design, wrote the protocol, analysed and interpreted the data, took part in the proposal writing and writing of this manuscript. EL provided methodological advice, supported the analysis and revised the draft paper. KAJ provided methodological advice and revised the draft paper. YG took part in the training of staff at the health centres, monitored data collection and revised the draft paper. All authors read and approved the submitted version of the manuscript.

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Competing interests: None declared

Patient consent for publication: Not required

Ethics approval

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). Children were included in the study after giving written informed consent by parents.

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Data availability statement: The data for this trial will be published if the paper is accepted. We usually post such data sets at https://osf.io
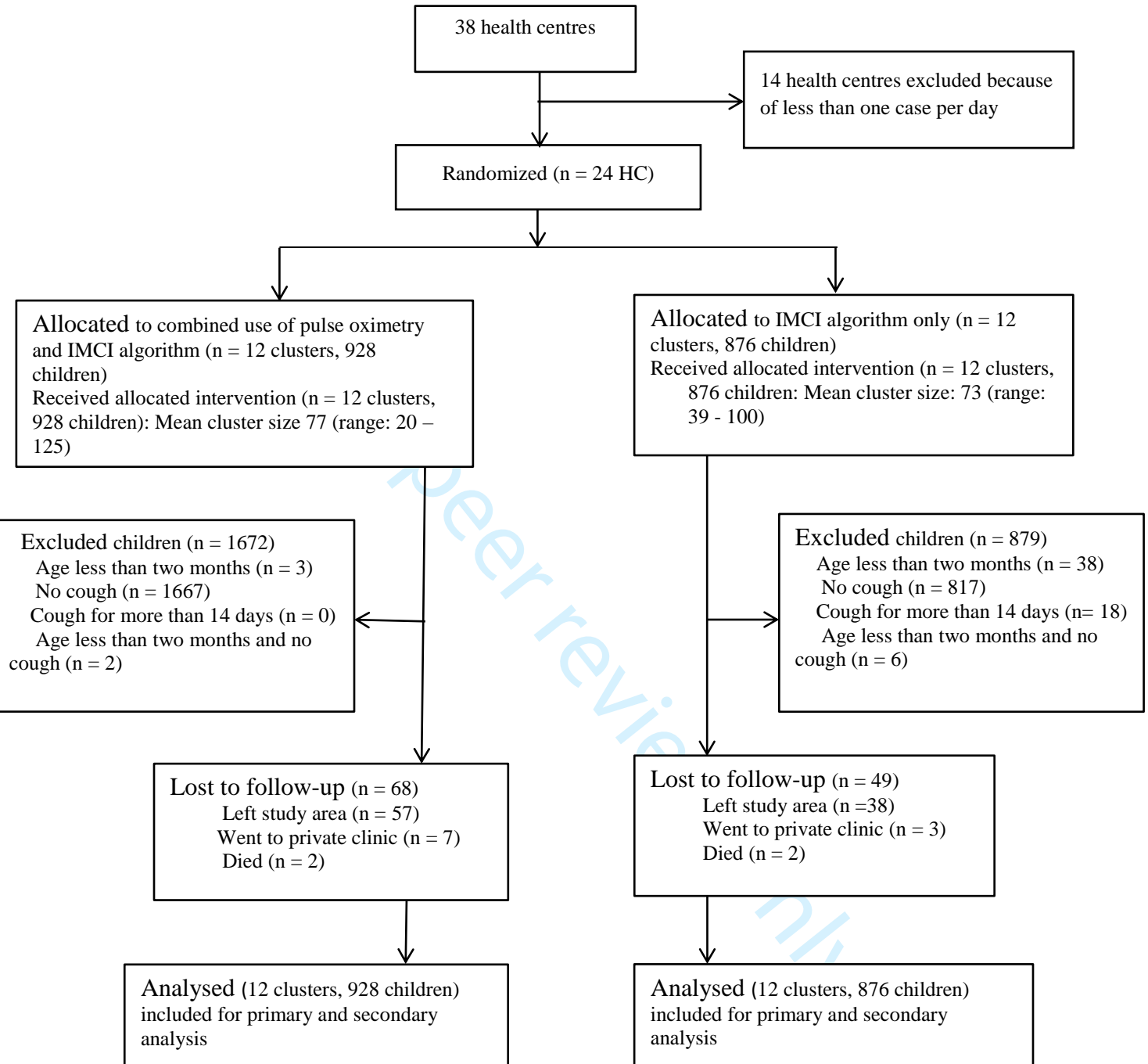
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Figure Legends

Figure1 Trial profile.

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38 health centres

14 health centres excluded because of less than one case per day

Randomized (n = 24 HC)

Allocated to combined use of pulse oximetry and IMCI algorithm (n = 12 clusters, 928 children)
Received allocated intervention (n = 12 clusters, 928 children): Mean cluster size 77 (range: 20 – 125)

Allocated to IMCI algorithm only (n = 12 clusters, 876 children)
Received allocated intervention (n = 12 clusters, 876 children: Mean cluster size: 73 (range: 39 - 100)

Excluded children (n = 1672)
  Age less than two months (n = 3)
  No cough (n = 1667)
  Cough for more than 14 days (n = 0)
  Age less than two months and no cough (n = 2)

Excluded children (n = 879)
  Age less than two months (n = 38)
  No cough (n = 817)
  Cough for more than 14 days (n= 18)
  Age less than two months and no cough (n = 6)

Lost to follow-up (n = 68)
  Left study area (n = 57)
  Went to private clinic (n = 7)
  Died (n = 2)

Lost to follow-up (n = 49)
  Left study area (n =38)
  Went to private clinic (n = 3)
  Died (n = 2)

Analysed (12 clusters, 928 children) included for primary and secondary analysis

Analysed (12 clusters, 876 children) included for primary and secondary analysis

Supplementary Table 1: Sensitivity and specificity of clinical signs.

Clinical signs	Pulse oximeter			Sensitivity	Specificity	Positive predictive value	Negative predictive value
	Hypoxemia	No hypoxemia	Total				
Chest in-drawing				59%	81%	35%	92%
Yes	79	147	226				
No	56	626	682				
Total	135	773	908				
Fast breathing				94%	25%	18%	96%
Yes	127	587	714				
No	8	194	202				
Total	135	781	916				
Chest in-drawing and fast breathing				57%	82%	35%	92%
Yes	78	145	223				
No	57	641	698				
Total	135	786	921				

Table 1: CONSORT 2010 checklist of information to include when reporting a cluster randomised trial

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)[1,2]	See table 2	1 and 2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	2 and 3
	2b	Specific objectives or hypotheses	Whether objectives pertain to the the cluster level, the individual participant level or both	3
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	4
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	4
	4b	Settings and locations where the data were collected		4
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	4 and 5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	5 and 6

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		6
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty	6 and 7
	7b	When applicable, explanation of any interim analyses and stopping guidelines		
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	7
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	7

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			enumeration, random sampling)	
	10c		From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how		7
	11b	If relevant, description of the similarity of interventions		
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account	7 and 8
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses		7
Results				
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome	8 and figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up		8
	14b	Why the trial ended or was stopped		
Baseline data	15	A table showing baseline demographic and clinical	Baseline characteristics for the individual and cluster levels as	8 and (Table1)

		characteristics for each group	applicable for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	8
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	11 and 12
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		11 (Table 3)
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		10 and 13
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms[3])		
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		15 and 16
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	16
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		13, 14 and 15
Other information				
Registration	23	Registration number and		2

		name of trial registry	
Protocol	24	Where the full trial protocol can be accessed, if available	3
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	17

* Note: page numbers optional depending on journal requirements

Table 2: Extension of CONSORT for abstracts[1,2] to reports of cluster randomised trials

Item	Standard Checklist item	Extension for cluster trials
Title	Identification of study as randomised	**Identification of study as cluster randomised**
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)	
Methods		
Participants	Eligibility criteria for participants and the settings where the data were collected	**Eligibility criteria for clusters**
Interventions	Interventions intended for each group	
Objective	Specific objective or hypothesis	**Whether objective or hypothesis pertains to the cluster level, the individual participant level or both**
Outcome	Clearly defined primary outcome for this report	**Whether the primary outcome pertains to the cluster level, the individual participant level or both**
Randomization	How participants were allocated to interventions	**How clusters were allocated to interventions**
Blinding (masking)	Whether or not participants, care givers, and those assessing the outcomes were blinded to group assignment	
Results		
Numbers randomized	Number of participants randomized to each group	**Number of clusters randomized to each group**
Recruitment	Trial status[1]	
Numbers analysed	Number of participants analysed in each group	**Number of clusters analysed in each group**
Outcome	For the primary outcome, a result for each group and the estimated effect size and its precision	**Results at the cluster or individual participant level as applicable for each primary outcome**
Harms	Important adverse events or side effects	
Conclusions	General interpretation of the results	
Trial registration	Registration number and name of trial register	
Funding	Source of funding	

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[1] Relevant to Conference Abstracts

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REFERENCES

[1] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG, et al. CONSORT for reporting randomised trials in journal and conference abstracts. *Lancet* 2008, 371:281-283

[2] Hopewell S, Clarke M, Moher D, Wager E, Middleton P, Altman DG at al (2008) CONSORT for reporting randomized controlled trials in journal and conference abstracts: explanation and elaboration. *PLoS Med* 5(1): e20

[3] Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, Moher D. Better reporting of harms in randomized trials: an extension of the CONSORT statement. *Ann Intern Med* 2004; 141(10):781-788.