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Cluster Randomized Trial of Community Case Management of Severe Pneumonia with Oral Amoxicillin in Children 2-59 Months of Age in Haripur District, Pakistan

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Abstract

Background—First dose oral cotrimoxazole and referral is the recommended treatment for WHO-defined severe pneumonia. Difficulties with referral compliance are reported from many low resource settings resulting in low access to appropriate treatment.

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Conflicts of interest statement

All other authors declare that they have no conflict of interest.

Responsibility for the manuscript

I had full access to all the data in the study and bear final responsibility for the decision to submit for publication.

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Methods—In a cluster-randomized equivalence trial in Haripur District, Pakistan 28 clusters were randomized equally to intervention and control clusters. In 14 intervention clusters children 2-59 months of age with severe pneumonia were treated with oral amoxicillin by community-based Lady Health Workers (LHW). In 14 control clusters LHWs gave first dose of oral cotrimoxazole and referred to a health facility for appropriate treatment, which was standard of care. The objective was to determine whether community case-management (CCM) of severe pneumonia by LHW using oral amoxicillin was equivalent to current standard of care. Primary outcome was treatment failure on day 6 of treatment. Participants, care givers, and assessors were not blinded to study therapy. Per-protocol analysis was conducted adjusting for clustering within arms using generalized estimating equations.

Findings—1995 children were randomized to intervention and 1477 to control clusters. We analysed 1857 children randomized to intervention and 1354 randomized to control clusters. They were similar in sex, age, and clinical characteristics. Treatment failure was 8.9% (165/1857) in intervention and 17.8% (241/1354) in control clusters. Cluster adjusted failure rates, the primary outcome, were significantly reduced in intervention clusters (risk difference (RD) -8.9%; 95% CI: -12.4% to -5.4%) by day 6. Further adjusting for baseline covariates made little difference (RD: -7.3%, CI: -10.1% to -4.5%). Three deaths occurred, only one in the intervention arm. Two deaths were before day 6, while one occurred between day 6 and 14. Most reduction in risk was in fever and lower chest indrawing on day 3 (RD -6.38%; 95% CI: -8.3% to -4.5%). Age, gender and very fast breathing were predictive of treatment failure.

Interpretation—CCM of severe pneumonia by LHWs resulted in reduced treatment failure versus current standard of care. CCM could result in standardized therapy for severe pneumonia, reduce delay in treatment initiation and costs for families and health systems.

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INTRODUCTION

Pneumonia is one of the world's leading causes of morbidity and mortality in children causing approximately 1.6 million child deaths per year.¹ Over 150 million cases of pneumonia occur yearly, including 61 million cases in South-East Asia, leading to 11-20 million hospital admissions.² Pneumonia cases which are not properly identified, referred late or inadequately treated lead to unnecessary deaths and account for the one of the largest barrier along with neonatal deaths to attaining the Millennium Development Goal (MDG) number 4 by 2015¹.

WHO guidelines for case management of pneumonia³ recommend children with lower chest in-drawing (LCI) (severe pneumonia) and danger signs (very severe pneumonia) be referred to hospital for treatment with parenteral antibiotics. However transportation, cost⁴, facility distance and lack of adequate child care are significant limitations to effective and appropriate treatment.^{5,6} Safely delivered community-based treatment could substantially increase the number of children receiving effective care. Recent evidence indicates that treatment with oral antibiotics for WHO-defined severe pneumonia at home is both efficacious and safe compared with facility-based treatment with parenteral antibiotics.⁷ A recent meta-analysis of observational studies estimated that effectively employed pneumonia community case management (CCM) could reduce pneumonia mortality in children by 70%.⁸ However, CCM of severe pneumonia by community health workers (CHW) has yet to be demonstrated safe and efficacious compared with the current standard of care in a rigorously designed randomized trial.

While pneumonia is a leading cause of childhood death in Pakistan,² only 50% of children with pneumonia receive antibiotics.⁹ Pakistan has a highly structured national network of 90,000 community based Lady Health Workers (LHW) who provide preventive and basic

curative services to mothers and children under five years old. These LHWs manage simple pneumonia with oral cotrimoxazole for 5 days and refer severe pneumonia to the nearest health facility for appropriate care, although this is not always followed.¹⁰⁻¹² Similar difficulties with referral compliance have been reported from Bangladesh.⁶ These data highlight the need for evaluating management for severe pneumonia as part of CCM thus making it easily accessible to communities.

To assess whether LHWs could identify and treat severe pneumonia in the community within an existing health delivery system, we compared LHWs trained to manage severe pneumonia in the community with oral amoxicillin to LHWs who identified and referred cases of severe pneumonia to the nearest health facility for further care.

METHODS

Study Site

Haripur District is located in the northern region of Pakistan and is comprised of 327 villages grouped in 44 union councils (smallest administrative unit). Eighty-eight percent of the District's 692,000 people live in rural areas.¹³ In the public sector there is one District Headquarter Hospital (DHQ), five Rural Health Centers (RHC), 41 Basic Health Units (BHU) and 14 other health centers. In the private sector, there are seven general hospitals, three maternity homes and numerous private clinics.

Study Design and Randomization

We sought to determine if clinical treatment failure rates among children 2-59 months with WHO-defined severe pneumonia receiving community treatment by LHWs with oral amoxicillin was equivalent to that of children receiving standard of care.

To assess this, we conducted a cluster randomized controlled trial, using stratified randomization.¹⁴ Strata were defined by child population, child mortality and literacy. We randomized 28 of the 44 Haripur union councils. Union councils range in population from 15,000 to 25,000 and contain at least one BHU or RHC.

LHWs work from a health house established in her own home and covers approximately 1000 individuals across 150-200 families. She actively visits five households daily and covers all households monthly, and is available for sick visits whenever needed. LHWs provide preventive, promotive care to newborns, children and mothers, family planning services and basic curative services for children. 15-20 LHWs are linked to each BHU/RHC and are clinically supervised by a Lady Health Visitor and administratively supervised by a Lady Health Supervisor. LHWs visit their specific health facility monthly for supervision, supplies and in-service training.

For this study, LHWs were trained to screen every child presenting to her with cough and difficulty breathing for enrollment. Children aged 2-59 months with severe pneumonia meeting enrollment criteria (Box 1) were enrolled by LHWs and managed according to cluster treatment assignment: intervention clusters - LHWs provided oral amoxicillin (80-90 mg/kg/day or 7.5 ml twice daily for infants 2-11 months, 12.5 ml for 12-59 months of age) to the mother with specific guidance on its use; control clusters - LHWs provided one dose of oral cotrimoxazole and referred to a health facility (standard of care). Details of LHW study-specific training is in the web appendix.^{15, 16,17}

Data Collection and Follow-Up

The primary outcome was development of clinical treatment failure up to day 6. Clinical relapse between day 6 and 14 as a pre-specified secondary outcome (Box 1). Children were seen by the LHW either in the subject's home or at the LHW health house on days 2, 3, 6 and 14 for assessment and recording of clinical outcomes on standardized forms, irrespective of whether the subject complied with the LHW recommendations. Data collection assistants (DCA), graduates or masters in social sciences and trained in pneumonia case management, clinical practice in hospital settings and study procedures, independently physically verified each case of severe pneumonia within 48 hours of enrollment. In addition, DCAs visited study LHWs in both arms to confirm her findings during each follow-up. All treatment failures were verified on the same day by an independent assessor (study physician) not involved with the treatment of child but not blinded to cluster assignment. Regular monthly visits were carried out by study physicians and study coordinators as well as quarterly visits by district, provincial and federal point persons from the LHW program. To ensure quality, the data was double entered under supervision of a data manager.

Data Analysis and Sample Size

We calculated our sample size assuming 15% of children 2-59 months would fail standard therapy by day 6.¹⁸ Our sample size was chosen to have sufficient power to determine equivalency, defined as 95% confidence limits for a crude risk difference (RD) in overall treatment failure within $\pm 5\%$ using a per-protocol analysis (as appropriate for an equivalency trial). With 14 clusters per arm, alpha of 0.05, power of 90% and a coefficient of variation of 0.2, we required 99 cases of severe pneumonia per cluster, for a total of 2,772 cases of severe pneumonia.

Baseline differences between treatment arms were calculated as frequencies for categorical variables and medians and interquartile ranges (IQR) for continuous variables. We calculated crude and adjusted risk differences of treatment failure between the intervention and control groups with 95% confidence intervals. To adjust for clustering, we used two approaches. First, mean differences in the cluster specific failure rates were compared between arms. Second, risk differences were calculated by regressing individual level treatment outcomes as a linear function of randomization arm and adjusted for clustering using a generalized estimating equation (GEE) with an exchangeable correlation matrix. Finally, the analysis was adjusted using individual baseline risk factors for treatment failure that were imbalanced at study enrollment (age, sex, respiratory rate, and temperature). One interim analysis done mid-way through the study was reviewed by the DSMB who recommended continuing the trial.

Ethical Clearance and Consent

The Technical Committee on Innovations (TCI) of the National LHW program and WHO Ethical Review Committee (ERC) gave clearance for the study. The Boston University IRB gave approval for analysis of de-identified data (by BM, DT, MF). Children's legal guardians gave written informed consent. The safety of study patients was overseen by a data safety monitoring board (DSMB) comprised of 4 pediatricians and a statistician.

RESULTS

Sixteen union councils were excluded due to being urban or inaccessible and 28 clusters were randomized (14 interventions, 14 control)(Figure 1a and 1b). A total of 511 of 750 possible LHWs were enlisted into the study (range per cluster 8 to 30), with intervention and

control clusters containing similar numbers of LHWs (mean 19 vs. 17 respectively) and population served (Figure 1a).

From April 2008 to December 2009, LHWs assessed 11230 cases of fast breathing and LCI in children under 5 years in intervention clusters and 8061 cases in control clusters for the presence of severe pneumonia (Figure 1b). Most were excluded because they did not have severe pneumonia. Since randomization did not occur at the individual level, more children were enrolled in the intervention group (N=1,995) than in the control group (N=1,477) and the median enrollment per cluster was higher in the intervention group (100 vs. 75). In both groups, 2% of children were lost to follow-up and 5% were excluded as protocol violations (most of whom either did not have LCI (N=95) or were previously enrolled in the study (N=49)) leaving 1857 intervention and 1354 control children in the final analysis.

Treatment arms were similar with respect to demographic characteristics and most indicators of baseline disease severity (Table 1). Slight differences existed in baseline fever history (85.3% intervention vs. 93.5% control) but median temperature was similar. Children in intervention clusters were less likely to have very fast breathing at the day 1 assessment (12.7% vs. 18.0%). We found strong concordance between the LHW and an independent assessor for baseline diagnosis of severe pneumonia (93.7%).

Clinical Outcomes

By day 6, intervention children had less treatment failure (8.9% vs. 17.8%) (Table 2): fever and LCI on day 3 (2.2% vs. 8.9%), fever alone on day 6 (0.8% vs. 3.5%), and LCI alone on day 6 (4.8% vs. 7.8%).

While designed as an equivalency trial, we found a statistically significant reduction in treatment failure in the intervention group compared to the control group in crude analyses adjusted only for clustering (risk difference -8.9%; 95% CI: -12.4% to -5.4%) (Table 2), our primary outcome analysis. Cluster specific failure rates ranged from 2.8%-14.8% in intervention clusters and from 10%-26% in the control clusters. Using a cluster averaged approach showed similar results (mean cluster specific failure rate was 9.0% in intervention clusters and 17.0% in control clusters, RD -8.0%; 95% CI: -11.8% to -4.2%). After adjusting for major failure risk factors (age, gender, and very fast breathing), the risk difference decreased only slightly but retained significance (RD: -7.3%, CI: -10.1% to -4.5%). The majority of the reduction in overall risk of failure in the intervention group was through reductions in fever and LCI on day 3 (RD -6.4%; 95% CI: -8.3% to -4.5%), fever on day 6 (-2.7%; 95% CI: -3.7% to -1.6%) and LCI on day 6 (RD: -2.8%; 95% CI: -4.5% to -1.0%).

In a model that included treatment group as a predictor, we found that age, gender, and very fast breathing were all independent risk factors for treatment failure for all children. In adjusted analyses, infants 2-5 months were more likely to experience treatment failure than children 12-59 months (RD 14.2%; 95% CI: 10.8% to 17.7%) and 6-11 months (RD 6.9%; CI: 4.6% to 9.2%). While very fast breathing and male gender were also associated with increased treatment failures, these associations were weaker: RD 3.8% (95% CI: 0.3% to 7.6%) for very fast breathing and RD 1.9% (95% CI: 0.0% to 3.5%).

Three deaths occurred, only one in the intervention arm. Two deaths were before day 6 (Table 2) while one occurred between day 6 and 14. All three were treated by doctors at the DHQ when two children were referred by LHWs and one was taken by parents. Among the 2,677 children well on day 6, 54 relapsed between day 6 and 14, with similar rates (2%) in each group (Table 3). There were very few danger signs observed after day 6.

Compliance was assessed by caretaker report and by checking the remaining fluid in the bottle and data were available on nearly 70% of children at each visit. In the intervention arm, compliance, defined as having taking the correct, age-specific amount of medication and not missing any dose, was over 93% at all time points.

Treatment in control arm

Of children in the control arm that were referred after an initial dose of cotrimoxazole (n=1354), 1242 (91.7%) complied with referral, but only 15 (1.1%) were admitted to hospital. Of those referred, 1122 (82.9%) received other antibiotics along with the first dose of cotrimoxazole (Table 4). Among 112 (8.3%) non-compliers to referral, 60 (4.4%) continued with cotrimoxazole at home given by LHW, of which 22 (1.6 %) completed five days treatment.

Of the 1242 cases accepting referrals, 635 went to public sector facilities, 107 to DHQ, and 528 to BHUs/RHCs. Treatment failure was similar, 16.8% (18/107) and 16.9% (91/528), respectively. 524 went to private providers with treatment failure of 15.1% (79/524).

DISCUSSION

Our results show that CCM of WHO-defined severe pneumonia in children aged 2-59 months by LHWs resulted in less treatment failure than the current standard of care practice of one dose of oral cotrimoxazole and referral to the nearest health facility for further treatment. Although this study was designed and powered to detect equivalence, our findings demonstrate that the study intervention was clearly superior to current practice.

In control clusters the treatment of severe pneumonia cases after referral was non-standardised, resulting in some children getting up to three antibiotics. At the end of this study a household survey¹⁹ confirmed care seeking by families from multiple sources for the same episode of acute respiratory infection i.e., formal private providers (72.5%), public sector health facilities (39.5%) and non-formal private providers (7.4%). We hypothesize that various socio-economic factors, perceptions about the illness and health providers and confidence in health care facilities^{10-12, 20, 21} affected care seeking and compliance with referral advice contributed to higher treatment failures in control clusters. Moreover, failure to comply with WHO standard case management guidelines in control clusters and by health care providers resulted in the use of many different antibiotics to treat severe pneumonia similar to as reported before.^{22, 23}

CCM was also found to be safe. Very few adverse events occurred in the study, of which only 0.23% (8/3472) required change of therapy, evenly split between intervention and control arms (0.25% 5/1995 vs. 0.20% 3/1447). Only two deaths occurred in the control arm (0.15%). The only death in the intervention arm was on the day after enrolment and the child was taken to the hospital by parents without informing the LHW. Without community intervention a higher number of deaths would be expected for severe pneumonia.^{2, 24}

Our findings are consistent with previous studies comparing oral amoxicillin and facilities-based parenteral therapy for treatment of severe pneumonia (panel 1). Using a more restrictive definition of treatment failure (persistence of LCI at 48 hours), the APPIS study reported equivalence with a higher rate of treatment failure (19%) in the two hospitalized arms¹⁸. The NO-SHOTS study⁷, using a similar definition of treatment failure as in this study, found equivalence between in-hospital parenteral therapy and home-based amoxicillin therapy, and a failure rate in the ambulatory arm of 7.5%, similar to that reported here (8.9%). A recent observational study of outpatient treatment with oral amoxicillin was conducted in four sites (Bangladesh, Egypt, Ghana and Vietnam) using

failure criteria similar to the NO-SHOTS study and found an overall failure rate of 9.2%.²⁵ This is similar to our study and supports the notion that home-based therapy of severe pneumonia can be applied to a wide variety of settings. Unlike the current study, these studies enrolled children who already reached a health care facility, but did not assess outcomes in children from the time of becoming sick and seeking care from the health facility.^{7,18,24} This suggests that the beneficial effect seen here may be a result of early assessment and treatment according to standard CCM from LHWs known to the families as care seeking from LHWs for pneumonia increased from 0.45% at baseline to 52% at project end¹⁹. Reassuringly, the 2% relapse after day 6 found in the current study is similar to the 2.7% reported relapse rate found in the NO-SHOTS study.⁷

A concern about implementing case management by CHWs is their ability to recognize severe pneumonia and clinical deterioration necessitating referral. We found high concordance in diagnosis of severe pneumonia between the LHW and an independent assessor (93.7%, data not shown). The low treatment failure rates and very low death rate indicate that clinically meaningful deterioration was identified and referred appropriately by the LHWs. Another concern is that some of the children with severe pneumonia may be hypoxemic and would not receive oxygen. Ideally these LHWs should be equipped with low cost pulse oximeters to identify hypoxemia and refer to facilities where oxygen is available, which is currently not feasible. LHWs recognized 'very severe disease' by identifying clinical danger signs, which correlate well with hypoxemia, and referred those children to an appropriate health facility.

CCM of severe pneumonia by LHWs using oral amoxicillin was well accepted by care-takers and enthusiastically adopted by the LHW. The study greatly enhanced the respect of LHW among served communities. Parents expressed more confidence in their abilities to recognize and treat childhood severe pneumonia at home. This was evident by the improvement in care seeking for pneumonia by mothers from LHW from 0.45% of cases of suspected pneumonia at the baseline to 52% noted in our end line household survey.¹⁹ Updating the knowledge and communication skills of CHW's in developing countries is valuable in enhancing their credibility as health educators.²⁶

This study has several strengths including a cluster-randomized design, large sample size, low loss to follow-up rates, confirmation of treatment failure cases, assessment of adherence, integration of the treatment into existent health services and inclusion of two pneumonia seasons. The limitations include greater enrollment of cases in the intervention clusters compared to control, likely due to knowledge that severe pneumonia treatment services were available in the community in intervention clusters. Second, no laboratory investigations were conducted. Finally, this study was conducted in a setting of low HIV prevalence, therefore these findings are not relevant for HIV infected patients, for which WHO standard treatment guidelines should be followed.

Although our study was conducted in a research setting it was integrated into the existing community health delivery program and the program managers were closely involved throughout implementation, thus increasing the generalizability of our findings. For CCM of pneumonia to be successful and sustainable it will be important for CHWs to be adequately compensated and supervised as others have pointed out.²⁷

Implementing this policy at a national level would require a significant commitment by policymakers to include the various components of this project. After retraining, the largest expense, provision of oral amoxicillin, has already been incorporated by the National LHW program.

Over the last 15 years in Pakistan improvements in neonatal, infant and under-five mortality have faltered. The current annual decrease in child mortality of 1.8% is far below the 9.0% that will be needed between 2007 and 2015 to meet MDG 4.²⁸ Implementation of CCM of pneumonia^{8, 29, 31}, particularly in rural areas where under-five mortality is 22% percent higher than in urban areas⁹, could contribute towards achieving MDG 4.

This is the first randomized trial of CCM of severe pneumonia by CHWs. This study has clearly demonstrated the benefits of this approach. The high acceptance rate by the community and potential cost savings for both families (direct and indirect) and health system are important additional considerations. Other developing countries with high burden of pneumonia face problems with referral systems.^{6, 10, 11} Delay in care seeking can result in high mortality.³⁰ In such situations, management of severe pneumonia as part of CCM would prove beneficial. Furthermore, it provided greater convenience for the family i.e., closer to home treatment and familiar workers.

Our study provides strong evidence for considering inclusion of treatment of severe pneumonia in CCM, included in the WHO/UNICEF joint statement³¹ and Global Action Plan for Pneumonia Technical Consensus Statement.³² If these plans can be adopted widely, there could be markedly increased coverage for pneumonia interventions at community level. Based on previous demonstrations of reduced mortality with CCM^{8, 29}, we hypothesize that it will contribute to reduction in pneumonia deaths and accelerate the process of achieving MDG 4.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1**Definitions of Pneumonia, Inclusion/exclusion and Treatment Failure Criteria in a Cluster Randomized Control Trial of Community Treatment of Severe Pneumonia in Children aged 2-59 months in Haripur, Pakistan****Definitions**

- **Pneumonia:** Child 2-59 months old having cough and/or difficult breathing with respiratory rate of 50 breaths per minute or more.
- **Severe pneumonia:** Lower chest in-drawing regardless of respiratory rate in children with history of cough and/or difficult breathing
- **Very severe disease:** Presence of any of danger sign (unable to drink/breast feed, convulsions, vomits every thing, abnormally sleepy/difficult to wake) in a child with history of cough and/or difficult breathing

Inclusion Criteria

- Child aged 2 to 59 months presented to LHWs with severe pneumonia
- Residing in the study area (i.e. intervention or control clusters)

Exclusion Criteria

- Very severe disease
- Diarrhea with severe dehydration
- Severely malnourished
- Children who were part of the study in the past two weeks
- Care-taker refusal to participate in the study
- Children who are already on antibiotic treatment

Treatment Failure**Day 3**

- Appearance of a danger sign (unable to drink/breast feed, convulsions, vomits every thing, abnormally sleepy/difficult to wake)
- Temperature 100 °F and lower chest in-drawing
- Change of antibiotic*

Day 6

- Appearance of a danger sign (unable to drink/breast feed, convulsions, vomits every thing, abnormally sleepy/difficult to wake)
- Temperature 100 °F
- Lower chest in-drawing
- Change of antibiotic*

Relapse

After child was cured at day 6, reappearance through day 7-14 of any one of the following:

- Temperature 100 °F

- Lower chest in-drawing
- * Self-referral and or medication (antibiotic) by care takers

Panel 1: Research in Context**Systematic review**

Before this study, we searched Medline and PubMed for studies comparing community case management of severe pneumonia among children 2-59 months and referral outcomes in these children. Our search terms were “pneumonia”, “severe pneumonia”, “children”, “childhood”, “CCM”, “community case management”, “amoxicillin” and “referrals”. We limited the search to publications in English, but not by date. We also searched reference lists of articles identified by this strategy and this was updated during the write-up of our study. Most studies were conducted at either inpatient or outpatient departments of hospitals or health facilities in which WHO defined severe pneumonia was treated with injectable and/or oral antibiotics with regular follow-up. These studies showed effectiveness of oral antibiotics for treatment of WHO defined severe pneumonia when managed by health care professionals working at health facilities. One study from Bangladesh reported referral of severe pneumonia identified at first level health facility to a hospital for appropriate treatment. Compliance to referral advice and care seeking from appropriate health facility was low even when free service at a well-equipped hospital was available. No data were identified that documented effectiveness of community case management (CCM) of severe pneumonia with oral antibiotics by trained community health workers (CHWs) versus referral to a health facility for appropriate management.

Findings

Our study was an equivalency trial powered to compare CCM of WHO defined severe pneumonia by trained CHWs versus the standard of care, which was referral for appropriate treatment at a health facility. Our results show conclusively that CCM of severe pneumonia with oral antibiotics resulted in lower treatment failures than current standard of care, where care seeking from appropriate health providers and referral compliance is relatively low. CCM could result in standardized therapy for severe pneumonia, reduce delay in treatment initiation and costs for families and health systems.

Figure 1.
Study Profile in a Cluster Randomized Trial of Community Treatment of Severe Pneumonia
in Children aged 2-59 months in Haripur, Pakistan

Table 1

Baseline Characteristics of Subjects in a Cluster Randomized Control Trial of Community-based Treatment of Severe Pneumonia in Children aged 2-59 months in Haripur, Pakistan

Parameter	Intervention	Control
Male (%)	59.7% (1108/1857)	59.8% (810/1354)
Age of Subject		
Median Age in Months (IQR) *	10.3 (5.0 to 24.0)	10.0 (5.00 to 22.46)
Infant under 6 months	28.3% (526/1857)	29.7% (402/1354)
Infant 6-11 months	25.3% (469/1857)	24.2% (328/1354)
Child 12-59 months	46.4% (862/1857)	46.1% (624/1354)
History of Current Illness		
Cough	98.7% (1830/1854)	99.3% (1339/1349)
Difficult breathing	98.1% (1817/1853)	97.8% (1316/1346)
Fast Breathing	96.0% (1780/1854)	97.6% (1317/1349)
Fever	85.3% (1565/1835)	93.5% (1259/1347)
Day 1 Examination/assessment		
Median respiratory rate (IQR) *	56 (53 to 60)	58 (54 to 61)
Fast Breathing †	81.9% (1516/1850)	79.4% (1063/1339)
Very Fast Breathing ‡	12.7% (235/1850)	18.0% (241/1339)
Median Temperature (°F) (IQR) *	100 (98 to 101)	101 (100 to 102)
Median Enrollment per Cluster (IQR) *	100 (72.0 to 158.0)	74.5 (48.0 to 127.0)

* IQR = interquartile range

† Respiratory rate 50 for children 2-11 months, respiratory rate 40 for children 12-59 months

‡ Respiratory rate 70 for children 2-11 months, respiratory rate 60 for children 12-59 months

Table 2

Cluster adjusted Cumulative Treatment Failure by Day 6 (Primary Outcome) in a Cluster Randomized Control Trial of Community-based Treatment of Severe Pneumonia in Children aged 2-59 months in Haripur, Pakistan *

	Intervention (Community based treatment arm)	Control (Referral arm)	RD (95% CI)*
Primary outcome/treatment failure	165/1857 (8.9%)	241/1354 (17.8%)	-8.91% (-12.4% to -5.4%) [‡]
Reasons for failure [†]			
Inability to drink	3/1857 (0.2%)	3/1354 (0.2%)	0.06% (-0.36% to 0.24%)
Convulsions	2/1857 (0.1%)	1/1354 (0.1%)	0.03% (-0.16% to 0.22%)
Vomits everything	6/1857 (0.3%)	4/1354 (0.3%)	0.03% (-0.34% to 0.39%)
Abnormally sleepy	5/1857 (0.3%)	1/1354 (0.1%)	0.20% (-0.03% to 0.42%)
Fever and LCI [§] by day 3 ^{//}	28/1264 (2.2%)	95/1070 (8.9%)	-6.67% (-10.0% to -3.3%)
Fever on day 6 ^{**}	15/1857 (0.8%)	47/1354 (3.5%)	-2.66% (-4.4% to -1.0%)
LCI [§] on day 6 ^{//}	90/1857 (4.8%)	106/1354 (7.8%)	-2.98% (-7.3% to -1.3%)
Death [¶]	1/1857 (0.1%)	1/1354 (0.1%)	-0.02% (-0.20% to 0.16%)
Change of antibiotics ^{**}	30/1857 (1.6%)	29/1354 (2.1%)	-0.53% (-1.5% to -0.44%)

* CI = confidence interval, RD = Risk difference

[†] Total failures is not equal to the sum of the individual failure reasons as subjects could fail for more than one reason.

[‡] Adjusted for clustering using generalized estimating equations.

[§] LCI = Lower chest indrawing.

^{//} Both fever and lower chest indrawing were required for treatment failure up to day 3. On day 6 either fever or lower chest indrawing alone was considered treatment failure. The denominator is smaller for fever and LCI as not all children were assessed on day 3.

[¶] One additional death occurred in the control cluster between day 6 and 14.

^{**} Self-referral and or medication (antibiotic) by care takers

Table 3

Rates of Relapse between Day 6-14 in a Cluster Randomized Control Trial of Community-based Treatment of Severe Pneumonia in Children aged 2-59 months in Haripur, Pakistan

Reason for relapse	Intervention (Community based treatment arm) (N=1607)	Control (Referral arm) (N=1070)	Risk Difference (95% CI*)
Total relapse	32 (2.0%)	22 (2.1%)	-0.07% (-1.2% to 1.0%)
Inability to drink	2 (0.1%)	0 (0.0%)	Undefined
Convulsions	1 (0.1%)	0 (0.0%)	Undefined
Vomits everything	1 (0.1%)	0 (0.0%)	Undefined
Abnormally sleepy	1 (0.1%)	0 (0.0%)	Undefined
Fever	5 (0.3%)	0 (0.0%)	Undefined
Lower Chest Indrawing	12 (0.7%)	14 (1.3%)	-0.56% (-1.4% to 0.24%)
Respiratory Rate > 50	14 (0.9%)	9 (0.8%)	0.03% (-0.68% to 0.74%)
Change of antibiotic	18 (1.1%)	10 (0.9%)	0.19% (-0.59% to 0.96%)

*
CI = confidence interval

Table 4

Treatment of severe pneumonia children in the control arm cluster and subsequent treatment outcomes in a Cluster Randomized Control Trial of Community-based Treatment of Severe Pneumonia in Children aged 2-59 months in Haripur, Pakistan (n=1354)

Antibiotic Use	Number (% of all control arm)	Treatment Failure n (% of row)	Generic Name of Antibiotics
Only first dose of Cotrimoxazole	122 (9.0%)	21 (1.2%)	
Oral cotrimoxazole continued after first dose	110 (8.1%)	19 (17.3)	
Oral cotrimoxazole plus other oral antibiotics *	1056 (78.0%)	184 (17.4%)	Amoxicillin, co-amoxiclav, cephradine, cephalixin, cefadroxil, cefaclor, cefixime, azithromycin, erythromycin, cotrimoxazole, metronidazole, nalidixic acid
Injectable antibiotics †	19 (1.4%)	5 (26.3%)	Ceftriaxone, cefpodoxime, cefotaxime
Injectable + oral antibiotics ‡	47 (3.5%)	12 (25.5%)	Combination of above

* 270 also continued with cotrimoxazole

† 6 also continued with cotrimoxazole

‡ 16 also continued with cotrimoxazole