# Community case management of severe pneumonia with oral amoxicillin in children aged 2–59 months in Haripur district, Pakistan: a cluster randomised trial

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## Summary

**Background** First dose oral co-trimoxazole and referral are recommended for WHO-defined severe pneumonia. Difficulties with referral compliance are reported in many low-resource settings, resulting in low access to appropriate treatment. The objective in this study was to assess whether community case management by lady health workers (LHWs) with oral amoxicillin in children with severe pneumonia was equivalent to current standard of care.

**Methods** In Haripur district, Pakistan, 28 clusters were randomly assigned with stratification in a 1:1 ratio to intervention and control clusters by use of a computer-generated randomisation sequence. Children were included in the study if they were aged 2–59 months with WHO-defined severe pneumonia and living in the study area. In the intervention clusters, community-based LHWs provided mothers with oral amoxicillin (80–90 mg/kg per day or 375 mg twice a day for infants aged 2–11 months and 625 mg twice a day for those aged 12–59 months) with specific guidance on its use. In control clusters, LHWs gave the first dose of oral co-trimoxazole (age 2–11 months, sulfamethoxazole 200 mg plus trimethoprim 40 mg; age 12 months to 5 years, sulfamethoxazole 300 mg plus trimethoprim 60 mg) and referred the children to a health facility for standard of care. Participants, carers, and assessors were not masked to treatment assignment. The primary outcome was treatment failure by day 6. Analysis was per protocol with adjustment for clustering within groups by use of generalised estimating equations. This study is registered, number ISRCTN10618300.

**Findings** We assigned 1995 children to treatment in 14 intervention clusters and 1477 in 14 control clusters, and we analysed 1857 and 1354 children, respectively. Cluster-adjusted treatment failure rates by day 6 were significantly reduced in the intervention clusters (165 [9%] *vs* 241 [18%], risk difference –8·9%, 95% CI –12·4 to –5·4). Further adjustment for baseline covariates made little difference (–7·3%, –10·1 to –4·5). Two deaths were reported in the control clusters and one in the intervention cluster. Most of the risk reduction was in the occurrence of fever and lower chest indrawing on day 3 (–6·7%, –10·0 to –3·3). Adverse events were diarrhoea (n=4) and skin rash (n=1) in the intervention clusters and diarrhoea (n=3) in the control clusters.

**Interpretation** Community case management could result in a standardised treatment for children with severe pneumonia, reduce delay in treatment initiation, and reduce the costs for families and health-care systems.

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## Introduction

Pneumonia is one of the world's leading causes of morbidity and mortality in children, causing roughly 1·6 million deaths per year.[1] More than 150 million cases of pneumonia arise every year, including 61 million cases in southeast Asia, leading to 11–20 million hospital admissions.[2] Cases of pneumonia that are not properly identified, referred late, or inadequately treated lead to unnecessary deaths and account for one of the largest barriers, in addition to neonatal deaths, to attainment of the Millennium Development Goal (MDG) 4 by 2015.[1]

WHO's guidelines[3] for case management of pneumonia recommend that children with lower chest indrawing (severe pneumonia) and danger signs (very severe pneumonia) should be referred to hospital for treatment with parenteral antibiotics. However transportation, cost,[4] distance from hospital, and lack of adequate child care are huge limitations to effective and appropriate treatment.[5,6] Safely delivered community-based treatment could substantially increase the number of children receiving effective care. 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] In a meta-analysis of observational studies, effective community case management was estimated to reduce the pneumonia mortality rate in children by 70%.[8] However, community case management of severe pneumonia by community health workers has yet to be shown to be safe and efficacious compared with the current standard of care in a rigorously designed randomised trial.

Although pneumonia is a leading cause of deaths in children in Pakistan,[2] only 50% of children with pneumonia are given antibiotics.[9] Pakistan has a highly

structured national network of more than 90 000 community-based lady health workers (LHWs) who provide preventive and basic curative services to mothers and children (aged <5 years). The guidance for these LHWs is to manage simple pneumonia with oral co-trimoxazole (trimethoprim plus sulfamethoxazole) for 5 days and refer cases of severe pneumonia to the nearest health facility for appropriate care, although this rule is not always adhered to.[10–12] Similar difficulties with referral compliance have been reported in a study in Bangladesh.[6] These data draw attention to the need to assess the management of severe pneumonia as part of community case management, thus making management easily accessible to communities.

We undertook a cluster randomised trial to assess whether clinical treatment failure in children with WHO-defined severe pneumonia who were identified and treated in the community by LHWs trained to manage severe pneumonia in the community with oral amoxicillin was equivalent to that in children given standard of care (identification and referral of cases of severe pneumonia to the nearest health facility for further care).

## Methods

### Study design and participants

Haripur district is located in the northern region of Pakistan and is made up of 327 villages grouped into 44 union councils (a union council [cluster] is the smallest administrative unit). 88% of the district's 692 000 people live in rural areas.[13] The public sector has one district headquarter hospital, five rural health centres, 41 basic health units, and 14 other health centres. The private sector has seven general hospitals, three maternity homes, and several private clinics. Union councils (population sizes 15 000–25 000 individuals) have at least one basic health unit or rural health centre.

LHWs provide preventive, promotive care to newborn babies, children, and mothers, family planning services, and basic curative services for children.[14–19] They are linked to each basic health unit or rural health centre and are clinically supervised by a lady health visitor and administratively supervised by a lady health supervisor. LHWs visit their specific health facility every month for supervision, supplies, and inservice training. An LHW works from a health house in her own home and attends to roughly 1000 individuals (150–200 families). She actively visits five to eight households per day and all households every month, and is available for sick visits whenever needed. LHWs were trained to screen every child presenting to them with cough and difficulty breathing for enrolment.

Children within a cluster were eligible for the study if they were aged 2–59 months, living in the study area, and had severe pneumonia, defined as lower chest indrawing irrespective of the respiratory rate and a history of cough or difficulty breathing. Children were excluded if they had very severe disease, had diarrhoea with severe dehydration, were severely malnourished, had participated in a study in the past 2 weeks, their carer refused to participate in the study, or were already on antibiotics. Exclusion criteria for the clusters were the absence of LHWs; inaccessibility of the union council because of hilly tracks or no roads; and urban area.

The Technical Committee on Innovations of the National LHW programme and WHO Ethical Review Committee approved the study. Boston University's Institutional Review Board approved the analysis of de-identified data (by WBM, DMT, MPF). The safety of the patients in the study was overseen by a data safety monitoring board consisting of four paediatricians and a statistician. Children's legal guardians provided written informed consent.

### Randomisation and masking

We assigned Haripur union councils in a cluster randomised controlled trial, with stratified randomisation.[20] A WHO expert did the stratified randomisation and allocation of clusters to the intervention and control using STATA (version 10.0). Strata were defined according to child population, and mortality and literacy rates. Participants, carers, and assessors were not masked to treatment assignment.

### Treatment

Eligible children were enrolled by LHWs and managed according to their cluster treatment assignment. In the intervention clusters, LHWs provided oral amoxicillin (80–90 mg/kg per day or 375 mg twice a day to infants aged 2–11 months and 625 mg twice a day for those aged 12–59 months) to the mother with specific guidance about its use. In the control clusters, LHWs provided one dose of oral co-trimoxazole (age 2–11 months, sulfamethoxazole 200 mg plus trimethoprim 40 mg; age 12 months to 5 years, sulfamethoxazole 300 mg plus trimethoprim 60 mg) and referred the children to a health facility (standard of care). Details of LHW study-specific training are provided in the webappendix pp 1–3.[14–16]

See Online for webappendix

Children were seen by the LHW either in the patient's home or at the LHW health house on days 2, 3, 6, and 14 for assessment and recording of clinical outcomes on standardised forms, irrespective of whether the child complied with the LHW's recommendations. In most cases data were gathered at the child's home. Data collection assistants, graduates or individuals with masters degrees in social sciences and trained in pneumonia case management, clinical practice in hospital settings, and study procedures, independently and physically verified each case of severe pneumonia within 48 h of enrolment. Additionally, data collection assistants visited study LHWs in both intervention and control clusters to confirm the LHWs' findings during each follow-up. All treatment failures were verified on the same day by an independent assessor (study physician) not involved in the treatment of the child but not masked to cluster assignment. Study

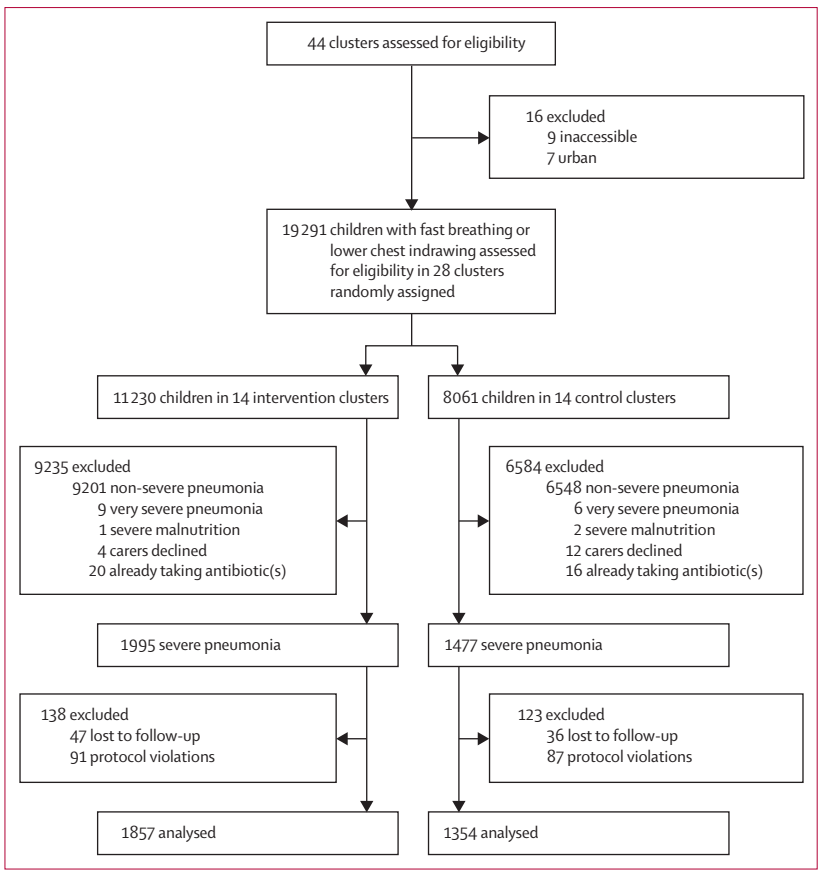


*Figure:* **Trial profile**

physicians and study coordinators made regular monthly visits and district, provincial, and federal point persons from the LHW programme made quarterly visits. To ensure quality, the data were double entered under supervision of a data manager.

### Statistical analysis

The primary outcome was development of clinical treatment failure by day 6. Treatment failure in a child was defined as the appearance of a danger sign (unable to drink or breastfeed, convulsions, vomiting after ingestion of food or drink, and abnormally sleepy or difficult to wake), temperature at least 100°F and lower chest indrawing on day 3, fever or lower chest indrawing alone on day 6, and change of antibiotic (through self-referral or by carers). The secondary outcome was clinical relapse on days 7–14, defined as reappearance on days 7–14 after a child was cured at day 6 of a fever (temperature ≥100°F), lower chest indrawing, appearance of any danger sign, or fast breathing (respiratory rate ≥50 breaths per minute).

Our sample size was calculated on the assumption that 15% of children aged 2–59 months would fail standard treatment by day 6.[17] It was chosen so as to have sufficient power to determine equivalency, defined as 95% CI for a crude risk difference in overall treatment failure within ±5% by use of a per-protocol analysis (which is appropriate for an equivalency trial). 16 of 44 clusters were excluded. With 14 clusters per group, an $\alpha=0\cdot05$, power 90%, and a coefficient of variation $0\cdot2$, we needed 99 cases of severe pneumonia per cluster, for a total of 2772 cases.

Baseline differences between treatment groups were calculated as frequencies for categorical variables and medians with IQRs for continuous variables. We calculated crude and adjusted risk differences for treatment failure between the intervention and control groups with 95% CIs. To adjust for clustering, we used two approaches. First, mean differences in the cluster-specific failure rates were compared between groups. Second, risk differences were calculated by regressing individual-level treatment outcomes as a linear function of the randomisation group and adjusted for clustering by use of a generalised estimating equation with an exchangeable correlation matrix. Last, the analysis was adjusted for individual baseline risk factors for treatment failures that were not balanced at study enrolment (age, sex, respiratory rate, and temperature). One interim analysis done midway through the study was reviewed by the data safety monitoring board who recommended continuing the trial.

### Role of the funding source

United States Agency for International Development (USAID) and National Institutes of Health had no role in the design, conduct, or analysis of this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

## Results

28 clusters were randomly assigned to intervention (n=14) and control (n=14), and analysed (figure). 511 of 750 LHWs were enlisted for the study, with intervention and control clusters having similar mean numbers of LHWs (19 [range 9–30] *vs* 17 [8–24], respectively) and populations (18 146 [12 216–24 066] *vs* 18 395 [9930–28 000], respectively).

From April 8, 2008, to Dec 31, 2009, LHWs assessed 11 230 cases of fast breathing and lower chest indrawing in children younger than 5 years in the intervention clusters and 8061 in the control clusters for the presence of severe pneumonia (figure). Most children were excluded because they did not have severe pneumonia. Since randomisation was not done at the individual level, more children were enrolled in the intervention group than in the control group, and the median number enrolled per cluster was higher in the intervention group (100 [range 65–305] *vs* 75 [30–243]). In both groups, 2% of children were lost to follow-up, and 5% were excluded as protocol violations in the intervention clusters and 6% in the control clusters. Most of the protocol violations either did not have lower chest indrawing (44 in intervention clusters and 51 in control clusters) or were previously

enrolled in the study (31 and 18, respectively). The final analysis consisted of 1857 children in the intervention clusters and 1354 in the control clusters.

Treatment groups were similar with respect to demographic characteristics and most indicators of baseline disease severity (table 1). Although differences were noted in baseline fever, median temperatures were similar. Children in intervention clusters were less likely to have very fast breathing on day 1 assessment (table 1). We noted a strong concordance between the LHW and an independent assessor for baseline diagnosis of severe pneumonia (504 [94%] of 538).

By day 6, fewer children in the intervention clusters had treatment failure—including reduced fever and lower chest indrawing on day 3, fever alone on day 6, and lower chest indrawing alone on day 6—than did those in the control clusters (table 2). Although this study was designed as an equivalency trial, we noted a significant reduction in treatment failure, our primary outcome analysis, in the intervention group compared with the control group in crude analyses that were adjusted for clustering only (table 2). Cluster-specific treatment failure was from 3% to 17% in the intervention clusters and from 10% to 26% in the control clusters (webappendix p 6). Use of a cluster-averaged approach showed similar results (mean cluster-specific treatment failure was 9·0% [SD 4·0] in the intervention clusters and 17·0% [5·6] in control clusters; risk difference –8·0%, 95% CI –11·8 to –4·2). After adjustment for major failure risk factors (age, sex, and very fast breathing), the risk difference decreased only slightly but was still significant (–7·3%, –10·1 to –4·5). Most of the reduction in overall risk of treatment failure in the intervention group was through reductions in fever and lower chest indrawing on day 3, fever on day 6, and lower chest indrawing on day 6 (table 2).

In a model that included treatment group as a predictor, we noted that age, sex, and very fast breathing were all independent risk factors for treatment failure in all children (data not shown). Infants aged 2–5 months were more likely to have treatment failure than were those aged 12–59 months (196 [21%] of 928 *vs* 99 [7%] of 1486, risk difference adjusted for clustering, age, treatment group, sex, and very fast breathing and fever, 14·2%, 95% CI 10·8 to 17·7) and 6–11 months (111 [14%] of 797, 6·9%, 4·6 to 9·2). Although very fast breathing (64 [13%] of 476 very fast breathing infants *vs* 340 [13%] of 2713 not very fast breathing infants, 3·8% [0·3 to 7·6]) and male sex (263 [14%] of 1918 boys *vs* 143 [11%] of 1298 girls, 1·9% [0 to 3·5]) were also associated with increased treatment failures, these associations were weaker.

Three deaths occurred, one of which was in the intervention group. Two deaths occurred before day 6 (table 2), and one between days 6 and 14. All three deaths were recorded by doctors at the district headquarter hospital when two children were referred by LHWs and one was taken to the hospital by parents. 54 (2%) of 2677 children who were well on day 6 relapsed between days 6 and 14, with similar proportions in each group (table 3). Very few danger signs were noted after day 6 (data not shown).

| | Intervention clusters (community-based treatment) | Control clusters (referral) |
|---|---|---|
| Boys | 1108/1857 (60%) | 810/1354 (60%) |
| Age (months) | | |
| Median (IQR) | 10·3 (5·0–24·0) | 10·0 (5·0–22·5) |
| <6 | 526/1857 (28%) | 402/1354 (30%) |
| 6–11 | 469/1857 (25%) | 328/1354 (24%) |
| 12–59 | 862/1857 (46%) | 624/1354 (46%) |
| History of current illness | | |
| Cough | 1830/1854 (99%) | 1339/1349 (99%) |
| Difficulty breathing | 1817/1853 (98%) | 1316/1346 (98%) |
| Fast breathing | 1780/1854 (96%) | 1317/1349 (98%) |
| Fever | 1565/1835 (85%) | 1259/1347 (93%) |
| Assessment on day 1 | | |
| Respiratory rate (breaths per min; median, IQR) | 56 (53–60) | 58 (54–61) |
| Fast breathing* | 1516/1850 (82%) | 1063/1339 (79%) |
| Very fast breathing† | 235/1850 (13%) | 241/1339 (18%) |
| Temperature (°F; median, IQR) | 100 (98–101) | 101 (100–102) |
| Enrolment per cluster (median, IQR) | 100 (72·0–158·0) | 74·5 (48·0–127·0) |

Data are n/N (%), unless otherwise indicated. Denominators do not always add up to the total number in the group because of missing data. *Respiratory rate at least 50 breaths per min in children aged 2–11 months and at least 40 breaths per min in children aged 12–59 months. †Respiratory rate at least 70 breaths per min for children aged 2–11 months and at least 60 breaths per min for children aged 12–59 months.

***Table 1:*** **Baseline characteristics of children with severe pneumonia in the intervention and control clusters**

| | Intervention clusters (community-based treatment) | Control clusters (referral) | Risk difference (95% CI)* |
|---|---|---|---|
| Treatment failure by day 6 | 165/1857 (9%) | 241/1354 (18%) | –8·91% (–12·38 to –5·44) |
| Reasons for treatment failure† | | | |
| Inability to drink by day 6 | 3/1857 (<1%) | 3/1354 (<%) | –0·06% (–0·36 to 0·24) |
| Convulsions by day 6 | 2/1857 (<1%) | 1/1354 (<1%) | 0·03% (–0·16 to 0·22) |
| Vomits after ingestion of food and drink by day 6 | 6/1857 (<1%) | 4/1354 (<1%) | 0·03% (–0·34 to 0·39) |
| Abnormally sleepy by day 6 | 5/1857 (<1%) | 1/1354 (<1%) | 0·20% (–0·03 to 0·42) |
| Fever and lower chest indrawing on day 3‡ | 28/1264 (2%) | 95/1071 (9%) | –6·67% (–10·00 to –3·31) |
| Fever on day 6§ | 15/1857 (<1%) | 47/1354 (3%) | –2·66% (–4·37 to –0·96) |
| Lower chest indrawing on day 6§ | 90/1857 (5%) | 106/1354 (8%) | –2·98% (–7·31 to –1·34) |
| Death by day 6¶ | 1/1857 (<1%) | 1/1354 (<1%) | –0·02% (–0·20 to 0·16) |
| Change of antibiotic‖ | 30/1857 (2%) | 29/1354 (2%) | –0·53% (–1·50 to –0·44) |

Data are n/N (%), unless otherwise indicated. *Adjusted for clustering by use of generalised estimating equations. †Number of total failures is not equal to the total number of the individual reasons for failure because treatment could fail for more than one reason. ‡Both fever and lower chest indrawing were requirements for treatment failure on day 3; the denominators are smaller because not all children were assessed on day 3. §On day 6 either fever or lower chest indrawing alone was considered to be treatment failure. ¶One additional death occurred in the control cluster between days 6 and 14. ‖Self-referral or medication (antibiotic) by carers.

***Table 2:*** **Cluster-adjusted cumulative treatment failure by day 6 (primary outcome) in children with severe pneumonia in the intervention and control clusters**

| | Intervention clusters (community-based treatment, n=1607) | Control clusters (referral, n=1070) | Risk difference (95% CI) |
|---|---|---|---|
| Total relapse | 32 (2%) | 22 (2%) | –0·07% (–1·16 to 1·03) |
| Inability to drink | 2 (<1%) | 0 | .. |
| Convulsions | 1 (<1%) | 0 | .. |
| Vomits anything ingested | 1 (<1%) | 0 | .. |
| Abnormally sleepy | 1 (<1%) | 0 | .. |
| Fever | 5 (<3%) | 0 | .. |
| Lower chest indrawing | 12 (<1%) | 14 (1%) | –0·56% (–1·36 to 0·24) |
| Respiratory rate of more than 50 breaths per min | 14 (<1%) | 9 (<1%) | 0·03% (–0·68 to 0·74) |
| Change of antibiotic | 18 (1%) | 10 (<1%) | 0·19% (–0·59 to 0·96) |

Data are number (%), unless otherwise indicated.

***Table 3:*** **Reasons for relapse between days 6 and 14 in children with severe pneumonia in the intervention and control clusters**

| | Children given antibiotics in control clusters (n=1354) | Treatment failure* |
|---|---|---|
| Only one dose of co-trimoxazole | 122 (9%) | 21 (17%) |
| Oral co-trimoxazole continued after first dose | 110 (8%) | 19 (17%) |
| Oral co-trimoxazole plus other oral antibiotics (amoxicillin, co-amoxiclav [amoxicillin plus clavulanic acid], cefradine, cefalexin, cefadroxil, cefaclor, cefixime, azithromycin, erythromycin, metronidazole, and nalidixic acid)† | 1056 (78%) | 184 (17%) |
| Injectable antibiotics (ceftriaxone, cefpodoxime, and cefotaxime)‡ | 19 (1%) | 5 (26%) |
| Injectable plus oral antibiotics§ | 47 (3%) | 12 (26%) |

Data are number (%). *Denominator is the number from the previous column . †Although all 1056 control cases were given other antibiotics after receiving the first dose of co-trimoxazole, 270 children also continued co-trimoxazole. ‡Six children also continued co-trimoxazole. §16 children also continued co-trimoxazole.

***Table 4:*** **Antibiotics given to children with severe pneumonia in the control clusters and treatment outcomes**

Compliance was assessed by use of the carer's report and checking the remaining fluid in the bottle of antibiotic; data were available for nearly 70% of children at each visit (data not shown). In the intervention group, compliance, defined as having taken the correct, age-specific amount of drug and not missing any dose, was more than 93% at all timepoints.

1242 (92%) of 1354 children in the control group who were referred after an initial dose of co-trimoxazole complied with referral and 112 (8%) did not, but only 15 (1%) of those referred were admitted to hospital. 1122 (83%) of 1354 were given other antibiotics with the first dose of co-trimoxazole (table 4). 60 (54%) of the non-compliers to referral continued co-trimoxazole at home, given by LHW, and 22 (37%) completed 5 days of treatment. 635 (51%) of 1242 cases who complied with referral went to public sector facilities, 107 (9%) to district headquarter hospitals, and 528 (43%) to basic health units or rural health centres. Treatment failure was similar—ie, 18 (17%) of 107 and 91 (17%) of 528, respectively. 79 (15%) of 524 children who were taken to private providers had treatment failure.

Reported adverse events were diarrhoea (n=4) and skin rash (n=1) in the intervention clusters and diarrhoea (n=3) in the control clusters

## Discussion

Our results show that community case management of WHO-defined severe pneumonia in children aged 2–59 months by LHWs resulted in lower treatment failure than did the current standard of care practice of one dose of oral co-trimoxazole and referral to the nearest health facility for further treatment. Although this study was designed and powered to detect equivalence, our findings show that the study intervention was better than the current practice.

In control clusters, the treatment of cases of severe pneumonia after referral was not standardised, resulting in some children being given up to three antibiotics. At the end of this study, the results of a household survey[18] confirmed care seeking by families for the same episode of acute respiratory infection from formal private providers (72·5%), public sector health facilities (39·5%), and non-formal private providers (7·4%). We postulate that various socioeconomic factors, perceptions about the illness and health providers, and confidence in health-care facilities[10–12,19,21] affected care seeking, and compliance with referral advice contributed to higher treatment failures in control clusters. Moreover, failure to comply with WHO's standard case management guidelines in control clusters by health-care providers resulted in the use of many different antibiotics for the treatment of severe pneumonia similar to that reported previously.[22,23]

Community case-management was also safe. Very few adverse events occurred in the study, of which only five in the treatment group and three in the control group required change of treatment. Two deaths occurred in the control group. The only death in the intervention group 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 from severe pneumonia would be expected.[2,24]

Our findings are consistent with those of previous studies in which oral amoxicillin and facilities-based parenteral treatment for severe pneumonia were compared (panel). With a restrictive definition of treatment failure (persistence of lower chest indrawing at 48 h), equivalence was reported with a higher rate of treatment failure (19%) in the two groups treated in hospital in the APPIS study.[17] The results of the NO-SHOTS study,[7] with a similar definition of treatment failure as in this study, showed equivalence in inhospital parenteral treatment and home-based amoxicillin, and a failure rate in the ambulatory group of 7·5%, similar to that reported here (9%). An observational study of outpatient treatment with oral amoxicillin was undertaken

in four sites (Bangladesh, Egypt, Ghana, and Vietnam) with failure criteria similar to the NO-SHOTS study, and the reported overall treatment failure was 9·2%.[28] This value is similar to that in our study and lends support to the notion that home-based treatment of severe pneumonia can be applied to different settings. Unlike in our study, children who were already at a health-care facility were enrolled in these studies, but outcomes were not assessed from the time the child became sick and care was sought from the health facility.[7,17,24] This difference suggests that the beneficial effect seen here might be a result of early assessment and treatment according to standard community case-management by LHWs known to the families because care seeking from LHWs for pneumonia increased from 0·45% at baseline to 52% at the end of the project.[18] The 2% of children relapsing after day 6 in our study is similar to the 2·7% reported in the NO-SHOTS study.[7]

A concern about community health workers implementing case management is whether they would be able to recognise severe pneumonia and clinical deterioration that necessitates referral. We noted high concordance in diagnosis of severe pneumonia between the LHW and an independent assessor (94%). The low treatment failure 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 might be hypoxaemic and would not receive oxygen. Ideally these LHWs should be equipped with low-cost pulse oximeters to identify hypoxaemia and should refer children to facilities where oxygen is available, which is currently not feasible. LHWs recognised very severe disease by identifying clinical danger signs, which correlate well with hypoxaemia, and referred those children to an appropriate health facility.

Community case management of severe pneumonia by LHWs using oral amoxicillin was well accepted by carers and enthusiastically adopted by the LHWs. The results of the study greatly increased the respect of LHWs in the communities they served. Parents expressed more confidence in their abilities to recognise and treat childhood severe pneumonia at home, evident from the improvement in care seeking for pneumonia by mothers from LHW from less than 1% of cases of suspected pneumonia at baseline to 52% in our end-line household survey.[18] Updating the knowledge and communication skills of community health workers in developing countries is invaluable to improve their credibility as health educators.[29]

This study has several strengths including a cluster randomised design, large sample size, low loss to follow-up rates, confirmation of treatment failure cases, assessment of adherence, integration of the treatment into existing health services, and inclusion of two pneumonia seasons. The limitations include enrolment of more cases in the intervention clusters than in the control clusters, probably attributable to knowledge that treatment services for severe pneumonia were available in the community in intervention clusters. Another limitation was that no laboratory investigations were undertaken. This study was undertaken in a setting of low HIV prevalence, therefore these findings are not relevant for HIV-infected patients, for whom WHO's standard treatment guidelines should be followed.

Although our study was undertaken in a research setting, it was integrated into the existing community health-delivery programme and the programme managers were closely involved throughout implementation, thus increasing the generalisability of our findings. For community case management of pneumonia to be successful and sustainable community health workers will need to be adequately compensated and supervised as indicated by other investigators.[30]

Implementation of this policy at a national level would require a substantial commitment by policy makers to include the various components of this project. After retraining, the largest expense, provision of oral amoxicillin, has already been incorporated into a list of drugs for the national LHW programme.

Over the past 15 years in Pakistan, improvements in mortality rates for neonates, infants, and children

***Panel:* Research in context**

**Systematic review**

Before we undertook this study, we searched Medline and PubMed for studies in which the association of community case management of severe pneumonia and referral outcomes was assessed in children aged 2–59 months. Our search terms were "pneumonia", "severe pneumonia", "children, "childhood", "CCM", "community case management", "amoxicillin", and "referrals". We restricted the search to English language publications; there were no date restrictions. We also searched reference lists of reports identified by this strategy and reviewed some relevant reports. We systematically reviewed the evidence. Two systematic reviews were identified,[25,26] which reviewed evidence of antibiotic use and case management of pneumonia in children. Most studies were undertaken in either inpatient or outpatient departments of hospitals or health facilities in which WHO-defined severe pneumonia was treated with injectable or oral antibiotics with regular follow-up. The results of these studies[17,27] showed that oral antibiotics were effective in the treatment of WHO-defined severe pneumonia when managed by health-care professionals working at health facilities. In a study from Bangladesh,[6] severe pneumonia identified at a first-level health facility was referred to a hospital for appropriate treatment. Compliance with referral advice and care seeking from an appropriate health facility was low even when free service at a well equipped hospital was available. There were no data to suggest that community case management of severe pneumonia with oral antibiotics by trained community health workers was effective compared with referral to a health facility for appropriate management.

**Interpretation**

Evidence indicated that community health workers can treat non-severe pneumonia effectively and safely in the community. The results of our study have shown that well trained and supervised community health workers can also manage WHO-defined severe pneumonia. Community case management could result in standardised treatment for severe pneumonia, reduce delay in treatment initiation, and reduce costs for families and health systems.

younger than 5 years have faltered. The current reduction in child mortality of 1·8% per year is far below the 9·0% per year that will be needed between 2007 and 2015 to achieve the MDG 4.[31] Implementation of community case management of pneumonia,[8,26,32] particularly in rural areas where mortality rates in children younger than 5 years is 22% higher than in urban areas,[9] could contribute towards the achievement of MDG 4.

This is the first randomised trial of community case management of severe pneumonia by community health workers. The results of this study have shown 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 a high burden of pneumonia have difficulties with referral systems.[6,10,11] Delay in care seeking can result in a high mortality rate.[33] In such situations, management of severe pneumonia as part of community case management would be beneficial. Furthermore, it provided increased convenience for the family—ie, treatment closer to home and familiar workers.

Community case management is already recommended in the WHO and UNICEF joint statement[32] and Global Action Plan for Pneumonia Technical Consensus Statement.[34] The results of our study provide strong evidence for the consideration of the inclusion of treatment for severe pneumonia in community case management. Based on previous results of reduced mortality rates with community case management,[8,26] we postulate that it will contribute further to a reduction in the number of pneumonia deaths and accelerate the process of achieving MDG 4.

#### Contributors

AB participated in the protocol development, literature review, implementation and supervision of the study, data analysis, and report writing. SS participated in the literature review, implementation of the study, interpretation of data, data analysis, and report writing. AtK participated in study implementation, data analysis, and report writing. IuHK participated in study implementation, data management and analysis, and report writing. AmK participated in the protocol development, and implementation, supervision, and monitoring the study. IAL participated in the protocol development, and implementation and supervision of the study, and writing the report. WBM and MPF participated in the data analysis. DMT participated in the interpretation of data and report writing. SAQ participated in the design, monitoring, and interpretation of the data, and report writing.

#### Conflicts of interest

All authors declare that they have no conflicts of interest.

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