IndiaCLEN Multicentre Trial of Home versus Hospital Oral Amoxicillin for Management of Severe Pneumonia in Children
(ISPOT STUDY)

FINAL REPORT
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Submitted by:
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CONTENTS

1. ACRONYMS 1

2. ACKNOWLEDGEMENTS 2

3. EXECUTIVE SUMMARY 3

4. BACKGROUND 7

5. STUDY DESCRIPTION 9
5.1. RESEARCH HYPOTHESIS 9
5.2. RESEARCH OBJECTIVES 9
5.2.1. PRIMARY OBJECTIVE 9
5.2.2. SECONDARY OBJECTIVES 10
5.3. EXPECTED BENEFITS OF HOME-BASED TREATMENT 10

6. STUDY DESIGN 12
6.1. INCLUSION CRITERIA 13
6.2. EXCLUSION CRITERIA 13
6.3. DEFINITION OF TREATMENT FAILURE 15

7. DATA COLLECTION 16
7.1. ENROLLMENT OF SUBJECTS 16
7.1.1. ETHICAL REVIEW 16
7.1.2. CONSENT 16
7.1.3. RECRUITMENT OF SUBJECTS 16
7.1.4. SCREENING 16
7.2. BASELINE ASSESSMENT 16
7.3. MICROBIOLOGICAL ASSESSMENT OF SAMPLES 17
7.4. RANDOMIZATION 17
7.5. STUDY NUMBERS 18

8. INTERVENTION 19
8.1. MANAGEMENT OF HOME-RANDOMIZED CHILDREN 19
8.2. MANAGEMENT OF HOSPITAL-RANDOMIZED CHILDREN 21
8.3. UNSCHEDULED FOLLOW-UP 22
8.4. DISCONTINUED PATIENTS 23
8.5. DECISIONS ON TREATMENT FAILURE AND CHANGE OF THERAPY FOR HOME AND 48 HOURS HOSPITALIZED PATIENTS 23
8.6. REPORTING OF SERIOUS ADVERSE EVENTS, TREATMENT FAILURES AND DEATHS 23
8.7. COMPLIANCE WITH AND DEVIATIONS FROM THE STUDY PROTOCOL 23
8.8. TRAVEL REIMBURSEMENT TO PATIENT 24
8.9. COST DATA COLLECTION 24
8.10. QUALITY ASSURANCES 24
8.10.1. STANDARD OPERATING PROCEDURES 24

8.10.2. TRAINING OF RESEARCH STAFF 24
8.10.3. SITE MONITORING VISITS 24
8.11. ADVERSE EFFECTS 24
8.12. DATA SAFETY MONITORING BOARD 25

9. DATA ANALYSIS AND SAMPLE SIZE 26
9.1. CRITERIA USED TO ESTIMATE SAMPLE SIZE 26
9.2. SAMPLE SIZE ESTIMATE (NO ADJUSTMENTS FOR LOSS TO FOLLOW-UP AND INTERIM ANALYSES) 26
9.3. EFFECT OF LOSS TO FOLLOW-UP AND NON-COMPLIANCE AT 48 HOURS OF OBSERVATION 27

10. STATISTICAL ANALYSES 28
10.1. MISSING DATA 28
10.2. FINAL ANALYSIS 28
10.3. COST ANALYSES 28

11. MAINTENANCE OF STUDY MATERIALS 30
11.1. MANAGEMENT OF STUDY MATERIALS AT CLINICAL SITES 30
11.2. CASE HISTORY RECORDS 30
11.3. PROTOCOL AND RELATED DOCUMENTATION 30
11.4. RECORD RETENTION 31

12. RESULTS/FINDINGS 32
12.1. OVERALL PER PROTOCOL ANALYSIS AND INTENTION TO TREAT ANALYSIS 35
12.2. PRIMARY OUTCOME: TREATMENT FAILURE WITHIN THE FIRST 7 DAYS 27
12.3. SECONDARY OUTCOME: TREATMENT FAILURE BETWEEN DAY 8 AND DAY 14 38
12.4. COST OUTCOMES 39

13. DISCUSSION 42
13.1. STUDY STRENGTHS AND CHALLENGES 44

14. RECOMMENDATIONS 47

15. REFERENCES: 49

16. APPENDIX 50

A. CONTRIBUTORSHIP OF ISPOT STUDY GROUP 50
B. KAPLAN-MEIER SURVIVAL ESTIMATES OF TREATMENT SUCCESS AT ANY TIME POINT (BY HOUR) USING PER PROTOCOL AND INTENTION TO TREAT ANALYSIS FOR UP TO 14 DAYS. ... 52
C. CUMULATIVE TREATMENT FAILURE AT LESS THAN 72 HOURS, LESS THAN 5 DAYS, AND EQUAL TO OR LESS THAN 14 DAYS BY TREATMENT GROUP 54
D. UNADJUSTED AND ADJUSTED ANALYSIS FOR PREDICTORS OF TREATMENT FAILURE AT < 7 DAYS (PER-PROTOCOL AND INTENTION TO TREAT ANALYSIS). 54

E. UNADJUSTED AND ADJUSTED ANALYSIS FOR PREDICTORS OF TREATMENT FAILURE AT > 7 DAYS TO < 14 DAYS (INTENT TO TREAT ANALYSIS AND PER PROTOCOL ANALYSIS THE SAME). 56
F. UNADJUSTED AND ADJUSTED ANALYSIS PREDICTORS OF TREATMENT FAILURE < 72 HOURS, < 5 DAYS AND <= 14 DAYS (PER-PROTOCOL ANALYSIS). 57

ANNEX (FORMS IN SEPARATE DOCUMENT)

FIGURES AND TABLES

Figure 1: Map of ISPOT Study Sites 12

Figure 2: ISPOT Patient Enrollment Flow Chart 14

Figure 3: Study profile of patients of all sites randomized to home and first 48 hours hospital management of WHO-defined severe pneumonia 36

Figure 4: 20000 Bootstrap re-samples –cost-effectiveness plane 41

Table 1: Enrollment by Study Site 32

Table 2: Study Screening and Reasons for Exclusion 32

Table 3: Baseline Characteristics in Home and Hospitalized Children 34

Table 4: Isolation of organisms from nasopharyngeal swabs and aspirates at enrolment 35

Table 5: Overall Treatment Failure (Home + Hospital) on Oral Amoxicillin at Different Time Points by Intention to Treat and Per Protocol Analysis (N = 1118) 35

Table 6: Cox Regression Analysis for Treatment Failure Using the Per Protocol and Intention to Treat Analysis up to 14 days 37

Table 7: Cumulative Treatment Failure by Group within the First 7 Days 38

Table 8: Treatment Failure Rates between Day 8 and day 14 by Different Causes in the Two Groups 39

Table 9: Treatment costs in different cost categories in the home and hospital group. 40

Table 10: Predictors of total mean costs for treating WHO defined severe pneumonia 40

1. Acronyms

ALRI	Acute Lower Respiratory Infection
ARI	Acute Respiratory Infection
APPIS	Amoxicillin Penicillin Pneumonia International Study
ASHA	Accredited Social Health Activist
Co-I	Co-investigator
CRF	Case Report Form
GAPP	Global Action Plan for Prevention and Control of Pneumonia
GCP	Good Clinical Practice
IRB	Institutional Review Board
IMNCI	Integrated Management of Neonatal and Childhood Illness
IndiaCLEN	Indian Clinical Epidemiological Network
ISPOT	IndiaCLEN Severe Pneumonia Oral Therapy
LAMA	Left Against Medical Advice
LCI	Lower Chest Indrawing
MCH-STAR	Maternal and Child Health Sustainable Technical Assistance and Research
NO-SHOTS	New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia Study
PI	Principal Investigator
RCH	Reproductive and Child Health
RH	Relative Hazards
RR	Respiratory Rate
RSV	Respiratory Syncytial Virus
SOP	Standard Operating Procedures
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VW	Voluntary Withdrawal
WHO	World Health Organization

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USAID through its MCH-STAR initiative monitored this trial so that the planned work led to its intended results, using the Good Clinical Practices guidelines. MCH-STAR is also providing a platform for dissemination of the results to all stakeholders including the government and thereby is helping the process of influencing the policy makers. The data collection was done by the IndiaCLEN study sites, and, data management and analysis at the coordinating site at Nagpur with administrative support from IndiaCLEN. The preparation of this final report was responsibility of the principal investigator Dr. Archana Patel with inputs from the study team and approval from MCH-STAR and USAID.

The technical team was lead by the Principal Investigator (PI), Dr. Archana Patel, Professor and Head, Pediatrics, Indira Gandhi Government Medical college, Nagpur, India and the Co-Investigators (Co-Is), Dr. Leena Dhande, Associate Professor, Department of Pediatrics, and, Dr. Gopal Agarwal, Associate Professor, Department of Microbiology in the same institute. They also oversaw data collection at the Nagpur site, training and coordination of data collection at the other sites, data management, analysis and report writing. The interim and final report has been prepared by the PI, Dr. Archana Patel.

We are very grateful for the hard work of the investigators and co-investigators of different sites that worked diligently to collect accurate patient data. Chandigarh site was led by site PI Dr. Meenu Singh, Co-I Dr. Sadbhavana Pandit, Microbiologist Dr. Pallab Ray and Study Coordinator Mr. Amit Agarwal. The Chennai Site was led by site PI Dr. Luke Ravi Chelliah, Co-I Dr. Ravichandran, Microbiologist Dr. Mohammed Meeran and Study Coordinator Dr. Sardha Suresh. The Pune site was led by Dr. Sandhya Khadse and Co-I Dr. Chhaya Valvi. The Sevagram site was led by site PI Dr. Akash Bang, Co-Is Dr. Manish Jain, Dr. K Y Vilhekar and Dr. DK Mendiratta and Microbiologist Vijayshree Khairkar. The Aligarh Site was led by site PI Dr. M. Ashraf Malik, Co-Is Dr. Uzma Firdaus and Meher Rizvi. (Appendix A). We also acknowledge the valuable inputs and contribution by Ms. Sarah Hurlburt, Program Manager, Center for Global Health and Development, Boston University for helping writing the interim report.

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3. Executive Summary

Pneumonia is the single largest killer of children under the age of five worldwide. The disease takes the lives of over 2 million children under the age of five every year— nearly one fourth (400,000) of these deaths occur in India alone [1].About half of pneumonia cases in India are caused by bacteria and could be treated with antibiotics. However, only 13% of children under the age of five with suspected pneumonia receive antibiotics [2]. World Health Organization (WHO) guidelines for the treatment of severe pneumonia in children recommend referring patients to a health facility for injectable antibiotic treatment [3]. However, for many parents, seeking treatment for their children at a health care facility is often logistically and financially problematic. In addition, children with severe pneumonia are vulnerable to contracting nosocomial infections as a result of weak immunity and crowded hospital wards.

Previous studies have shown that injectable penicillin and oral amoxicillin are equivalent in the treatment of selected children aged 3-59 months with severe pneumonia treated at the hospital [4], and that home treatment with high-dose oral amoxicillin is equivalent to hospital based treatment with parenteral ampicillin in selected children aged 3-59 months with WHO defined severe pneumonia [5]. This study aimed to demonstrate that 7-day home treatment with oral amoxicillin is equivalent in clinical outcomes to 48 hours of oral amoxicillin in the hospital, followed by home treatment. This trial has been registered with the Indian Council of Medical Research (REFCTRI/2010/000629) and with ClinicalTrials.gov (NCT01386840).

Study investigators believed that if oral amoxicillin administered at home was found to be equally efficacious as that administered for the first 48 hours at the hospital, it would have important implications for the health system and for families. Benefits of home-based treatment could include: improved coverage at the community level (particularly where referral is not possible), reduced costs of treatment for the community, reduced wages-lost for families, decreased risk of cross infection and needle-associated complications in hospital, and reduced need for referral and demand on the scant inpatient services.

This study was an open-label (both the researchers and the participants knew the treatment administered) multicentric prospective two-arm randomized clinical trial conducted at 6 hospitals in 6 cities in India to determine the differences in failure of treatment with a 7-day course of oral amoxicillin administered for first 48 hours in the hospital followed by 5 days at home in comparison to amoxicillin being administered orally at home for all 7 days, in children 3 to 59 months old who have WHO defined severe pneumonia (fast breathing and lower chest indrawing). Both groups were followed up for 14 days to measure treatment failure up to 7 days (primary outcome) and between 8-14 days (secondary outcome). Other secondary outcomes were to identify clinical and microbiological predictors at baseline that predict “failure of oral treatment”, from enrollment till day 14th and the costs of home and hospital management of severe pneumonia with oral amoxicillin. Children aged 3-59 months with Lower Chest Indrawing (LCI) that was non-responsive to nebulization, cough/difficulty in breathing of less than 2 weeks duration and who did not have any of the exclusion criteria were enrolled. Children in the home group received their first dose of amoxicillin in the hospital, and all subsequent doses were given in the home by the caregiver. Home patients were followed up at 24 hours, and at day 3, 5, 8 and 14 to monitor clinical outcomes and adherence to treatment, and to ensure patient safety. Hospitalized children received the first 48 hours of treatment from clinical study staff in the hospital, and were then discharged and all

subsequent doses were given in the home by the caregiver. Hospitalised children were followed up at days 3, 5, 8 and 14.

Data from this study was analyzed using two models—*intention to treat* and *per protocol*. The *intention to treat* model analyzed all children enrolled in the study, including those who left against medical advice (LAMA), were lost to follow up, or voluntarily withdrew from the study as proposed. The *per protocol* analysis, which measures differences in clinical outcomes, included all children enrolled, except those who were not followed for the full 14 days for the above reasons to assess difference between the two treatment groups in patients who were observed for the entire duration of treatment.

To determine comparability of the two trial arms and the success of the randomization procedure, baseline characteristics of trial subjects according to assigned treatment were analyzed. Baseline characteristics of the two treatment groups were compared using chi-square tests for categorical variables and ANOVA for continuous variables. Analysis was conducted using both intention to treat and per protocol analysis to assess the univariate risk difference, and, for univariate and multivariate odds ratios for predicting treatment failure. The risk differences and the odds ratios for cumulative treatment failure have been reported for different time periods such as < 72 hours, < 5 days, < 7days (primary outcome) and for < 14 days. The analysis was also conducted for the secondary outcome of treatment failures between day 8 and day 14. The Kaplan-Meier curves for the cumulative probability of treatment success were also plotted and the overall difference in their rates of treatment failure was examined using the log-rank test. Cox proportional hazards models were also used to estimate the relative hazards (RH) of treatment failure up to 14 days in the two groups and to explore associations between the baseline covariates and outcome. Statistical analysis was conducted using STATA 10 data analysis software.

The investigators tested patients for respiratory syncytial virus (RSV) antigen in nasal washings using ELISA method and standard microbiological techniques [6-8] to isolate *S.pneumoniae* and *H.influenzae* from baseline nasopharyngeal swabs and estimated the minimum inhibitory concentration (MIC) of amoxicillin and penicillin for both *H. influenzae* and *S. pneumoniae* isolates.

The health care costs of a random 20% of patients enrolled in the trial were estimated. The costs incurred, starting from before they were randomized and continuing until they were declared well were measured using the micro-costing technique. The direct medical (variable costs), direct non-medical and indirect costs of the two treatment arms were measured. The mean differences in costs and the predictors of total cost were analyzed. The incremental cost-effectiveness of the two treatment strategies was also assessed.

Patients were enrolled between October 8, 2008 and March 15, 2011. There were 1118 children enrolled and randomized; 554 were assigned to home treatment, and 564 were assigned to hospital treatment, across the 6 sites in India. The two groups were balanced in distribution of baseline characteristics, except that the home group was more likely than the hospital group to have children in the age group of 12-59 months (57.2 % vs. 50.9%), the mean respiratory rate for infants and children was higher in the hospital group than the home group (infants mean respiratory rate: 48.9 ± 8.7 and 47.3 ± 8.9 respectively; children's mean respiratory rate: 43.9 ± 9.8 and 43 ± 9.1 respectively), and the hospital group was more likely to have infiltrates in their chest x-ray than the home group (67.6% and 60.8% respectively).

The baseline microbiological tests showed that *S. pneumonia* and *H. influenzae* were isolated from the nasopharyngeal swabs in 19% and 10% of samples respectively, and, RSV was isolated in 25% of the nasopharyngeal aspirates. There were no significant differences in rates of isolation between the two groups. The overall failure rate of severe pneumonia when treated with oral amoxicillin was 11.5% (per protocol analysis). The intention to treat analysis showed that overall the hospital group was significantly more likely than the home group to fail treatment at any time point (due largely to LAMA), during the 14 days of follow up, however the per protocol analysis shows no difference between the groups. Baseline characteristics that increased the risk of treatment failure at any time after enrollment were infancy (age group 3-11 months), receiving antibiotics within 48 hours prior to enrollment and the use of high polluting fuel.

The primary outcome of treatment failure at 7 days showed that there were no significant differences in the rates of treatment failure resulting from clinical deterioration within the first 7 days. In the unadjusted analysis, the risk of treatment failure due to clinical deterioration in the home group and hospital group was 5.4% and 7.4% respectively and statistically non significant (difference -2.0%, 95% CI -4.9 to 0.8; p=0.08). The overall failure rate (including LAMA, voluntary withdrawal and loss to follow-up) was 8.7% in the home group and 16.3% in the hospital group, which was outside of the equivalency margin (difference -7.6%, 95% CI -11.5 to -3.8).

Treatment failure at 72 hours differed by treatment groups. Children in the hospital group were significantly more likely to fail treatment both by intention to treat and per protocol analysis. This difference was largely due higher rates of clinical deterioration in the hospital group, which was perhaps due to more frequent identification of danger signs by the skilled clinical research staff and subsequent change of antibiotics during hospital monitoring, and to LAMA. Two children died within the first 7 days, 1 child (0.2%) in the home group, and 1 child (0.2%) in the hospital group. Both deaths in the study population occurred within the first 72 hours. Neither of the deaths was considered to be related to the study treatment with oral amoxicillin. There was no difference in the rates of death between the home group and the hospital group at 7 or 14 days (difference -0.0%, 95% CI -0.5 to 0.5).

The secondary outcome of treatment failure between 8 and 14 days showed that there was no significant difference between the two groups in failure rates from any cause between 8 and 14 days. In the unadjusted analysis, there were 12 (2.2%) treatment failures in the home group and 10 (1.8%) treatment failures in the hospital group. The risk difference between the two groups was within the equivalency margin (difference 0.4%, 95% CI -1.2 to 2.0). Auscultatory wheeze and the use of high polluting fuel tended to increase the risk of failure in the adjusted multivariate model, but failed to reach levels of statistical significance.

Finally, the cost analysis showed that the average total costs of oral treatment of WHO defined severe pneumonia with oral amoxicillin across four sites in India was Rs. 427 for the home group as compared to the Rs. 702 for first 48 hours of hospital treatment followed by treatment at home, for the same effect of 5% failure rate at the end of 7 days after treatment in the random sample of enrolled patients.

Given our findings, we recommend that the WHO guidelines for treatment of severe pneumonia in children be modified to recommend home based treatment for selected children with severe

pneumonia. In India, oral therapy for pneumonia in children has great outreach potential, as auxiliary nurse midwives and community health workers, i.e. Accredited Social Health Activists (ASHAs), of the National Rural Health Mission could be trained to recognize the symptoms and signs of severe pneumonia in under- five children and initiate early therapy. This ameliorates the need for hospital referral, decreasing the chances of cross infection and needle-associated complications in hospital, reduces cost of treatment and wage loss to the family. For its optimal efficacy, training of the health personnel delivering this treatment and of the mothers to recognize clinical deterioration if their child does not respond is critical. In order to ensure safe and effective therapy for pneumonia at home, parents have to be counseled regarding symptoms and signs of clinical deterioration so that they bring the child immediately to hospital if the child fails to improve on oral therapy at home. Treating selected children with severe pneumonia in the home has the potential to substantially reduce pneumonia morbidity and mortality in under-five children who currently fail to receive timely care due to hospital referral.

4. Background

Pneumonia is the single largest killer of children under the age of five worldwide. The disease takes the lives of over 2 million children under the age of five every year— nearly one fourth (400,000) of these deaths occur in India alone [1]. About half of pneumonia cases in India are caused by bacteria and could be treated with antibiotics. However, only 13% of Indian children under the age of five with suspected pneumonia receive antibiotics [2].

WHO classification of acute respiratory tract infection in children presenting with cough, difficult breathing, or both are as follows [9]:

> *Pneumonia* — respiratory rate per minute >50 breaths (2–11 months of age) or >40 breaths (12–59 months of age); no lower chest indrawing
>
> *Severe pneumonia* — Symptoms of pneumonia, and lower chest indrawing with or without rapid breathing
>
> *Very severe disease* — Symptoms of severe pneumonia, and unable to drink, convulsions, central cyanosis, abnormally sleepy or difficult to wake, stridor in calm child, or clinically severe malnutrition

As of 2008, the WHO guidelines for treatment of non-severe pneumonia advised health workers to provide oral antibiotics for 3 days at the home [3]. For severe pneumonia or very severe disease, the WHO recommends that providers administer the first dose of the appropriate antibiotic and give an urgent referral for hospitalization for parenteral (injectable) antibiotics and other supportive therapy [3]. Inability to access a referral facility deprives these children from getting appropriate care. For many parents, seeking treatment for their children at a health care facility is often logistically and financially problematic. In India, though 69% of children under the age of five with suspected pneumonia are reported to be taken to an appropriate health provider [2], transport to a distant facility can entail serious delays in effective treatment. Many children with severe pneumonia who are currently referred for admission to a hospital either die before they reach there or are too sick to be saved [10]. In addition, children with severe pneumonia are vulnerable to infections as a result of weak immunity and could be at increased risk in crowded hospital wards.

Two important studies have been done to address barriers to treatment of severe pneumonia. The first study was intended to determine whether oral antibiotics are equivalent to injectable antibiotics when both are given in the hospital. Since home treatment with injectable antibiotics is not feasible, it was important to determine if oral antibiotics could be substituted. This was an open-label (the treatment was not blinded to participants or researchers) equivalency study called APPIS (Amoxicillin Penicillin Pneumonia International Study), which was a large multicentre randomized controlled trial comparing injectable penicillin versus oral amoxicillin given for 7 days to children in the hospital [4]. It was conducted at tertiary care centres in 8 countries. Injectable penicillin and oral amoxicillin were found to be equivalent in the treatment of selected [1] children ages 3-59 months with severe pneumonia treated at the hospital. In the APPIS study, 3% of all children less than 12 months of age, and, 6% of all children more than 12 months of age progressed to very severe disease on oral amoxicillin. The researchers concluded that changing policy to support administering oral amoxicillin for severe pneumonia would reduce 1) the risk of needle-borne infections, 2) the

[1] Children with severe pneumonia who did not have other complicating factors or other danger signs as defined by the study exclusion criteria that could indicate very severe disease.

need for referral or admission, 3) treatment costs, and 4) transport, food and lost income for the family [4].

The second study was called "NO-SHOTS" (New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia Study) and was a randomized, open-label equivalency trial done at seven study sites in Pakistan [5]. NO-SHOTS compared initial hospitalization and parenteral ampicillin for 48 hours followed by 3 days of oral amoxicillin at home, to 5 days of home-based treatment with oral amoxicillin. NO-SHOTS showed that home treatment with high-dose oral amoxicillin is equivalent to hospital based treatment with parenteral ampicillin in selected [2] children aged 3-59 months with WHO defined severe pneumonia [5]. The findings from APPIS and NOSHOTS were presented at the Global Action Plan for Prevention and Control of Pneumonia (GAPP) consultation meeting in March 2008 at WHO in Geneva, with a recommendation to revise the WHO guidelines to support home-based treatment with oral amoxicillin in selected patients with severe pneumonia.

[2] Children with severe pneumonia who did not have other complicating factors or other danger signs as defined by the study exclusion criteria that could indicate very severe disease.

5. Study Description

The IndiaCLEN Multicentre Trial of Home versus Hospital Oral Amoxicillin for Management of Severe Pneumonia in Children (ISPOT) study was designed to determine the safety and efficacy of oral amoxicillin in treating WHO defined severe pneumonia (cough with LCI with or without fast breathing) at home versus treating it in the hospital for the first 48 hours followed by home care, and to identify the predictors of disease progression or deterioration of clinical condition of children on oral therapy. Knowledge of these risk factors will help to identify those patients who are less likely to respond to oral antibiotics and refer them early to the hospital for parenteral therapy to prevent compromising the safety of patients being treated with oral antibiotics at home. It was intended to support the development of guidelines for indication of home-based antibiotics for treatment of severe pneumonia, and parenteral therapy and hospitalization only in selected patients.

If this study's results are in line with the findings from previous studies, and home-based oral amoxicillin is found to be equivalent to hospital-administered oral amoxicillin with 48 hours of observation preceding discharge, then the this study would strengthen the evidence for modifying treatment guidelines to recommend oral amoxicillin given at home for treatment of severe pneumonia. Once guidelines are framed for the national program for management of pneumonia, they could be followed by the public health delivery systems in India, after appropriate training. Results of this study should be presented to policy makers at the Indian government and other stakeholders such as the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) with the recommendation that they develop/revise guidelines for community management of pneumonia in children under five in India and in other developing countries.

5.1 Research Hypothesis

The research hypothesis being tested in this study was that, in the selected study population (children who have severe pneumonia, but without co-morbid infections or other danger signs), there would be no difference in clinical outcomes among children aged 3-59 months with WHO defined severe pneumonia who were treated for 7 days at home with oral amoxicillin in comparison to those who received oral amoxicillin for first the 48 hours in the hospital followed by 5 days of treatment at home.

The investigators hypothesized that the children who were treated with oral amoxicillin at home would experience a failure rate of no more than 5% higher than those treated for first 48 hours in hospital. We estimated a failure rate in the home management group of 15% [with a 95% confidence interval (CI) of ±5%) and that the failure rate among the hospitalized children would be no more than 10 % (with a 95% CI of ±5). We also hypothesized that the overall failure rate of treatment with oral amoxicillin (both groups together) would be no more than 12% by day 7, and 15% by day 14 (95% CI of ±5%). In the trial, failure rate during days 8-14 in the hospitalized group was expected to be 12% and no greater than 17% (95% CI of ±5%) in those sent home after enrollment.

5.2 Research Objectives

5.2.1 Primary objective

The primary objective of this trial was to assess the rates of treatment failure (as defined in section 6.3) within the first 7 days of a 7-day course of oral amoxicillin when administered at home, in

comparison to a 7-day course of oral amoxicillin administered for the first 48 hours in the hospital followed by 5 days of home-administration.

The primary objective was to be measured using the following end-point:

- Treatment failure by day 7 defined by any of the following- Clinical deterioration of disease any time after enrolment[3], change of antibiotic[4], hospitalization[5], serious adverse event considered related to amoxicillin, left against medical advice (LAMA) or voluntary withdrawal of consent from study by day 7, or loss to follow up on day 8.

5.2.2 Secondary Objectives

The secondary objectives of this trial were to determine the following among children receiving oral amoxicillin for severe pneumonia:

- Determine the proportion of children who experience treatment failure between day 8 and 14
- Identify clinical predictors (at baseline and during the treatment course) of "failure of oral treatment" from enrollment up to day 14
- Determine the costs of home and hospital management of severe pneumonia with oral amoxicillin (the results on cost will be presented as a separate report)

The secondary objectives were measured using the following end-points:

- Treatment failure between day 8 and day 14 defined by any of the following- Restart of antibiotics i.e. "failure of treatment", between day 8 and day 14 due to reappearance of any danger signs, lower chest indrawing or fast breathing which is non-responsive to three trials of nebulization with bronchodilator; left against medical advice (LAMA) or voluntary withdrawal of consent from day 8 to day 14, loss to follow up from day 8 to day 14.

5.3 Expected benefits of home-based treatment

Study investigators hypothesized that if oral amoxicillin administered at home was found to be equally efficacious as that administered for the first 48 hours at the hospital; it would have important implications for the health system and for families. Benefits of home-based treatment could include: improved coverage at the community level (particularly where referral is not possible), reduced costs of treatment for the community, reduced wages-lost for families, decreased risk of cross infection and needle-associated complications in hospital, and reduced need for referral and demand on the scant inpatient services.

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[3] Any sign of very severe disease such as persistent vomiting (vomiting repeated 3 times within an hour due to any reason), central cyanosis, grunt, stridor, abnormally sleepy or difficult to wake, inability to drink, convulsions, or death.

[4] due to persistent vomiting (vomiting of amoxycillin within 20 minutes of administration; 3 such attempts), or, developing a co-morbid condition, or, persisting fever > 98.6°F with lower chest indrawing even after 3rd day, or, fever alone at day 5, or, lower chest indrawing alone (non responsive to three doses of nebulization with bronchodilator) at day 5 (as reported by the mother), or, persistence of fast breathing after day 7 which is non responsive to three doses of nebulization with bronchodilator.

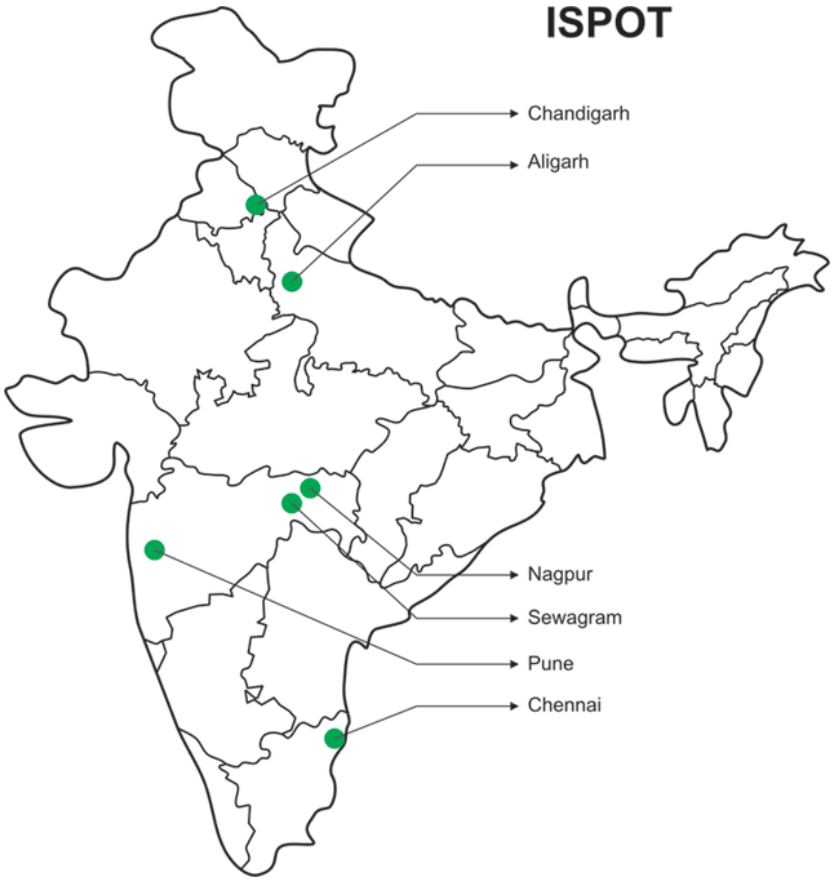
[5] Any time in home managed patients or clinical decision to extend the hospitalization longer than 48 hours in hospitalized children or re-hospitalization in those discharged after 48 hours from hospital.

Regarding acceptance of home-based treatment, it was observed in both APPIS and NO-SHOTS that parents accept home-based treatment for severe pneumonia, and in fact many preferred it as it saves transportation costs and cost of treatment. Parental acceptance of home-based treatment was also expected in the current study. Rural populations who have difficulty with transportation to referral units are most likely to benefit from this change in treatment.

6. Study Design

This study was an open-label multicentre prospective two-arm randomized clinical trial to determine the differences in treatment failure between a 7-day course of oral amoxicillin administered at home, to a course of oral amoxicillin administered for first 48 hours in the hospital followed by home treatment, among children 3 to 59 months old who have severe pneumonia. It was conducted at 6 hospitals in 6 cities in India: Chandigarh, Chennai, Nagpur, Pune, Aligarh, and Sevagram.

Figure 1: Map of ISPOT Study Sites



Children aged 3-59 months with Lower Chest Indrawing (LCI) which was non-responsive to nebulization, cough/difficulty in breathing of less than 2 weeks duration and who did not have any of the exclusion criteria described below fulfilled the case definition for enrollment, if the parents gave consent for their participation.

If a child met the inclusion criteria and had none of the exclusion criteria (pending response to the trial nebulization and radiology) then the child was administered the first dose of amoxicillin. Subsequently the child was nebulized and, if the LCI persisted, sent for radiology. If the child responded to nebulization the child was excluded and not sent for radiology. The WHO manual for standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children was followed in reading the x-rays.

6.1 Inclusion Criteria

The inclusion criteria were as follows:

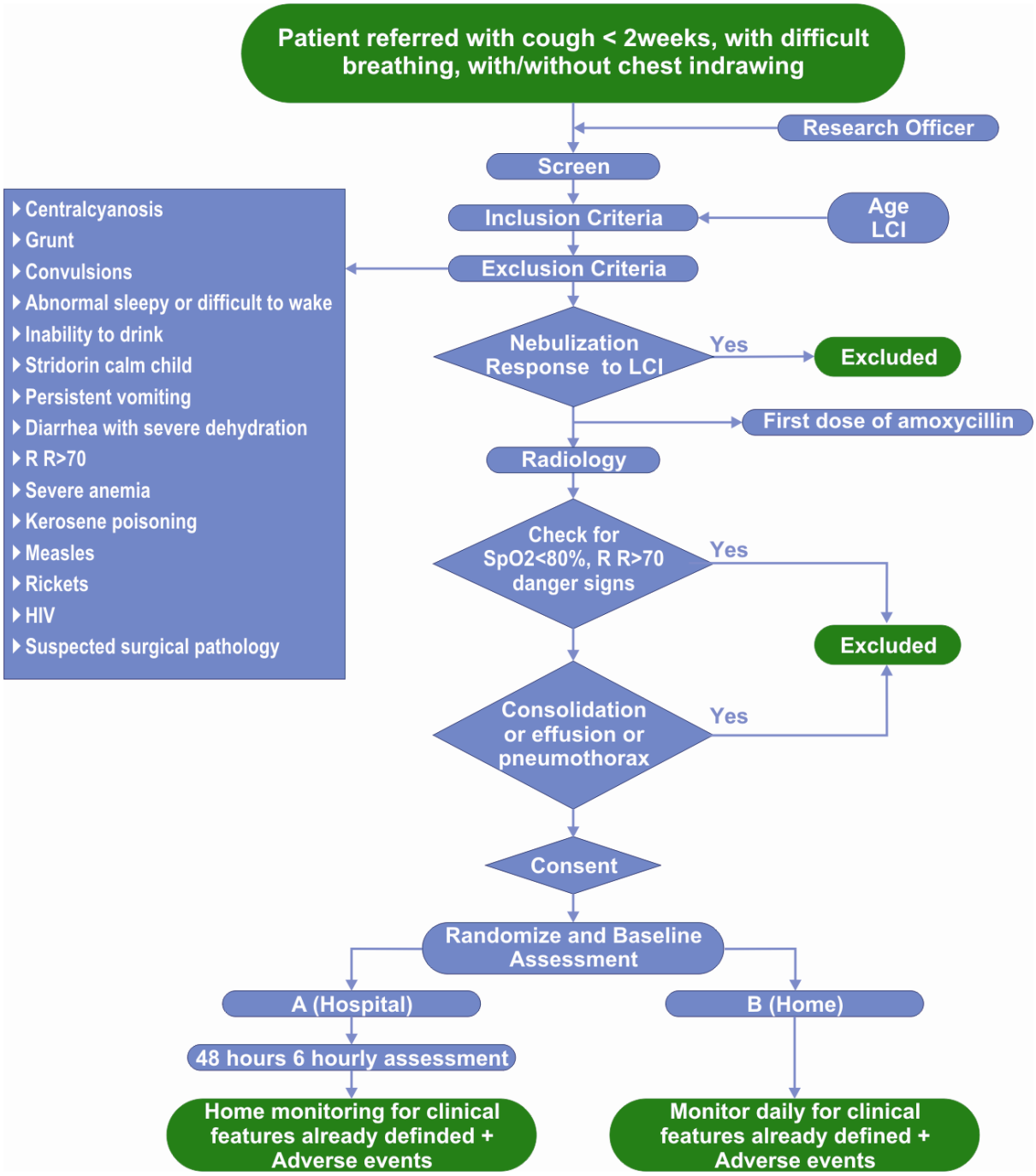
1. Children aged 3 to 59 months with pneumonia and lower chest wall indrawing
2. Ability to take antibiotics orally
3. Absence of radiological consolidation or effusion
4. Informed consent by a legal guardian

6.2 Exclusion criteria

Children with any of the following conditions were excluded:

1. Known or clinically recognizable chronic conditions
2. History of > 2 weeks of cough /difficulty in breathing
3. Past history of more than 3 wheezing episodes or physician diagnosed asthma
4. LCI that responds to trial of nebulization
5. Respiratory rate (RR) >70 breaths per minute in calm child
6. Known HIV positive child or HIV status of mother known to be positive and status of child not known/defined.
7. Hospitalization for > 48hrs in the last two weeks
8. Measles in the last month
9. Clinically severe malnutrition (weight for length < -3 SD or kwashiorkor) (refer to WHO growth chart)
10. Rickets
11. Central cyanosis
12. Kerosene poisoning within last 48 hours
13. Oxygen saturation (pulse oximetry) <88% on room air
14. Abnormally sleepy or difficult to wake
15. Inability to drink
16. Stridor in calm child
17. Convulsions during this illness
18. Known any antibiotic therapy for 48hrs or more immediately prior to admission
19. Other diseases requiring antibiotic therapy, e.g. Meningitis, tuberculosis, dysentery, etc.
20. Persistent vomiting (>3 episodes of vomiting within 1 hr)
21. Grunting
22. Known prior anaphylactic reaction to penicillin or amoxycillin
23. Severe dehydration according to WHO guidelines
24. Severe pallor
25. Suspected surgical pathology
26. Living out of the follow-up area of the study (30 kms)
27. Subject previously included in the same trial or already included in another ongoing trial anywhere
28. Presence of radiological consolidation/effusion/pneumothorax

Figure 2: ISPOT Patient Enrollment Flow Chart



6.3 Definition of Treatment Failure

Treatment failure was defined as any of the following:

1. Clinical deterioration of the child any time after enrollment: developing any sign of very severe disease such as persistent vomiting (vomiting repeated thrice within an hour due to any reason), central cyanosis, grunt, stridor, abnormally sleepy or difficult to wake, inability to drink, convulsions, or death
2. Change of antibiotic due to: persistent vomiting (vomiting of amoxycillin within 20 minutes of administration; 3 such attempts), developing a co-morbid condition, persisting fever > 98.6°F with LCI even after 3rd day, fever alone at or after day 5, LCI alone (non-responsive to three doses of nebulization with bronchodilator) at or after day 5 (as reported by the mother), persistence of fast breathing after day 7 which is non-responsive to three doses of nebulization with bronchodilator
3. Hospitalization at any time of home-managed patients or clinical decision to extend the hospitalization longer than 48 hours in hospitalized children
4. Re-hospitalization in those discharged after 48 hours from hospital. It could be related to pneumonia, or to therapy with amoxicillin [relatedness determined by the Data & Safety Monitoring Board (DSMB)]
5. Children who need to restart antibiotics i.e. “failure of treatment”, between day 8 and day 14 due to reappearance of any danger signs, LCI or fast breathing which is non-responsive to three trials of nebulization with bronchodilator.
6. Serious adverse event considered possibly or probably related to amoxicillin.
7. Left against medical advice (LAMA) or voluntary withdrawal of consent from study from enrollment up until day 14.
8. Loss to follow-up before day 14.

7. Data Collection

7.1 Enrollment of Subjects

7.1.1. Ethical review

The investigators at each study site submitted the protocol for review to their local Ethical Review Committee, or Institutional Review Board (IRB). The human investigation review board of the 6 large government hospitals participating in the trial in Nagpur, Chennai, Chandigarh, Sevagram, Pune and Aligarh all approved the trial. Approval was also obtained from IndiaCLEN. WHO and Boston University also approved the study. This trial has been registered with the Indian Council of Medical Research (REFCTRI/2010/000629) and with ClinicalTrials.gov (NCT01386840).

7.1.2. Consent

The parents or legal guardians of the children eligible to enter the study were fully informed about the study in his or her own first language (Hindi, Punjabi, Tamil or Marathi). The consent form provided adequate information for the subject to decide whether or not to participate. The study physician obtained the freely given consent of the parents or legal guardian (by signature, or if the parent or guardian was illiterate, by fingerprint, duly witnessed by somebody in addition to the person requesting consent) for the child to participate in the study. Each parent/guardian who signed consent for a minor subject received a copy of the signed consent. The copies of consent forms signed by each subject are being retained in the confidential file of the Principal Investigator for at least 5 years after completion of the research or such longer period as may be specified by program requirements. The content of the explanation provided to the parents or legal guardians of the children is described in the consent form (Annex A).

7.1.3. Recruitment of Subjects

Children aged 3-59 months who presented to the outpatient departments of participating centers with a history of cough or difficult breathing and were found to have LCI, according to the criteria mentioned above, were referred to a member of the investigation team. These individuals were screened to determine their eligibility for the trial.

7.1.4. Screening

Children referred to the investigators were screened using the Screening Form (within the Case Report Form, Annex B) to evaluate whether they fulfilled each of the inclusion criteria and had none of the exclusion criteria. Children who were excluded from the study were treated according to standard procedures at each site. Children included in the trial were randomized to either receive oral amoxicillin in hospital for 48 hours or sent home after administering the first dose in the hospital. A parent or guardian of a child who fulfilled the eligibility criteria was asked to provide consent for their child to participate in the study for oral amoxicillin therapy.

7.2 Baseline Assessment

The baseline assessment was performed as quickly as possible after complete screening, provision of informed consent and randomization. Complete screening included presence of all inclusion criteria and absence of all exclusion criteria (See sections 0 and 0). The indicators below were collected in the baseline form.

Identification: Name, address, date and time of enrolment, gender, hospital record, parents' names, detailed description of location of residence and other contact information, details of date of birth and/or age in months. If the exact date of birth was unknown the investigator requested the month of birth and assigned the 15th of that month as the birth date. All this information was recorded in the Identification form and was not included in the database.
History of present illness: With particular emphasis on breastfeeding, use of antibiotics, use of bronchodilators and immunization status.
Physical examination: Included weight, length for < 24 months and height for > 24 months, axillary temperature, respiratory rate, LCI, state of the child during counting of respiratory rate, presence of auscultatory wheezing, crackles (unilateral or bilateral), intercostals indrawing, suprasternal indrawing, bronchial breathing, diminished or absent breath sounds.
Assessment of LCI: Health workers in the community were trained in how to assess LCI. Some of the elements of this training are described below: • An initial training followed by practice on 20-30 patients evaluated independently by the study physician and the PI was conducted at each site • A video developed by WHO demonstrating fast breathing and LCI in normal children was sent to each site to serve as reference. • Study monitors evaluated the study physicians' ability to assess LCI • Once every month, the PI evaluated the diagnosis of LCI by study physician and reinforced training.
Radiological Assessment: All sites used the same definition for consolidation. Digital radiographs of consolidation and effusion were emailed to all the sites for standardization. Infiltrates were not considered as cause for exclusion from the trial.

7.3 Microbiological Assessment of Samples

Soon after enrolment nasopharyngeal swabs were collected and standard microbiological techniques [6-8] were used to isolate *S. pneumoniae* and *H. influenzae* from the swabs. Minimum inhibitory concentration (MIC) of amoxicillin and penicillin for both *S. pneumoniae* and *H. influenzae* were measured by E test according to the manufacturer's instructions (AB Biodisk, Solna, Sweden). The nasopharyngeal aspirates were obtained soon after nasopharyngeal swabbing and tested for RSV antigen using ELISA method (Abbott Testpack for RSV from Abbott Diagnostics, Baar, Switzerland).

7.4 Randomization

Subjects were randomly allocated to treatment groups as soon as the baseline examination was completed and the parent or legal caretaker had given his or her informed consent.

Random numbers were computer generated, by using variable length permuted blocks of 8 – 12 – 16 for the first 188 patients and 4 – 6 – 8 for the next 90 patients in some sites; at the coordinating site using STATA program. A separate list was generated for each site.

After the randomization code was prepared, individual patient assignments corresponding to the master randomization list were placed in a series of sealed envelopes. After each patient was selected for study, the next envelope in order of trial number (i.e., in numerical sequence) was

opened to determine the treatment assignment. Thus, the research officer or investigator did not know the order of randomization and was unable to predict what the next assignment would be.

Before opening the envelope, the physician in charge signed and dated the envelope. After the envelope was opened, the card with the patient's treatment assignment and the signed envelope were attached to the study file.

7.5 Study numbers

Each patient enrolled in the study was given a study number composed of a site number from 1 to 7, and a randomization number from 001 to 999.

The randomization list and sealed envelopes were prepared at the Coordinating site.

8. Intervention

Oral amoxicillin was provided to all children as syrups. A total of 50mg/kg/day was given to the children for 7 days. Doses were given twice daily (every 12 hours), with each dose containing 25mg/kg. Patients who vomited within half an hour of oral treatment received a repeat dose of amoxicillin, by the parent if treated at home, or by the hospital staff if treated in the hospital. This was attempted three times. If the patient failed three attempts they were excluded from the study. Dose adjustments were not permitted.

For those randomized to home management, the first dose was administered by the parent/caretaker under supervision in the health facility. All doses thereafter were administered by the parent/caretaker at home. For those randomized to hospital care for first 48 hours, the first dose was administered by the caregiver under supervision of the nurse. The hospital study staff administered subsequent doses within the first 48 hours. Doses were administered by the parent/caretaker after the child was sent home.

Below is the schedule of where each group was receiving their doses, and where they were being assessed at the follow-up visits.

Schedule of Follow up for Home and Hospital Groups – ISPOT Study

Home Group			**48 Hr Hospital Group**	
Dose given at	**Follow up at**		**Dose given at**	**Follow up at**
Hospital	Discharged	**First Dose**	Hospital	Hospital
Home	Home	**24 Hours**	Hospital	Hospital
Home	N/A	**48 Hours**	Hospital	Hospital
			Discharged	
Home	Home	**Day 3**	Home	Home
Home	Hospital	**Day 5**	Home	Hospital
Home	N/A	**Day 7**	Home	N/A
N/A	Home	**Day 8**	N/A	Home
N/A	Hospital	**Day 14**	N/A	Hospital
N/A – Not Applicable				

8.1 Management of Home-Randomized Children

The parent/caregiver of patients who were sent home after the first dose of hospitalization were counseled to continue with the oral treatment prescribed for a period of 7 days. They were advised to return to the healthcare facility at their scheduled times and any time during the study period if the child's condition worsened (unscheduled visit). The symptoms and signs of clinical deterioration were discussed with the mother / caregiver and given as "patient follow-up card" (Annex C), identifying the child as a study patient, and listing the telephone numbers where study staff can be contacted. At the time of discharge the mother / caregiver was also given a "counseling checklist" (Annex D).

Patients assigned to home treatment were clinically assessed at home or at a health facility by study staff at the following times:

Follow up Schedule for Home Group

Day of data collection	Site of assessment
At enrolment (Day 0)	Health facility
Day 1 (after 24 hours)	Home
Day 3 (after 72 hours)	Home
Day 5	Health facility
Day 8	Home
Day 14	Health facility

These home visits were to ensure safety of the patients in the trial and to assess drug compliance by calculating the amount of drug remaining in the bottle.

If the patient did not return to the health facility on day 14, they were visited at home in the next 48 hours. If the patient was well on day 16, the patient was deemed cured and no further follow-up occurred. If patient was unwell on day 16, as determined by the study physician, the patient was managed as per standard hospital practice.

The study staff assessed the following at each of the above-scheduled follow-up visits:

Indicators Measured at Follow up Visits

Indicator	Measure of Indicator
Temperature	Axillary
Respiratory rate	Counted over 60 seconds – child not crying, using a timer
LCI	Training as described previously
Pulse rate	Palpation over 60 seconds
Staff monitoring for clinical deterioration	Inability to drink, grunt, nasal flaring with intercostal indrawing, stridor, abnormally sleepy, persistent vomiting, cyanosis, convulsions
Other signs which staff feels are relevant e.g. co-morbid conditions	
Assessment of adherence	The adherence to treatment was indirectly monitored in each visit using a calibrated scale to measure how much drug was consumed from the bottle
Adverse event	Its duration, seriousness, intensity and relationship to the administration of the study medication

Caregivers were instructed to apply the following supportive care while the child was being treated at home:

- *Bronchodilators* – Children were given oral bronchodilators (salbutamol syrup 0.15mg/kg/dose) or salbutamol by spacer with metered dose inhaler if clinically suspected to have a wheeze on any clinical assessment.
- *Fever:* Patients with axillary temperature (actual reading) equal or greater than 38°C, as measured by a thermometer received oral paracetamol in the dose of 10-15 mg/kg/dose as needed, with a minimum period of 6 hours between doses. Mothers were instructed to administer paracetamol if they suspected fever in their child. In areas where *P. falciparum*

malaria is common, the physician decided to test for malaria and treat appropriately.

- *Feeding* – Nursing mothers were encouraged to continue breastfeeding. Children were supposed to receive their normal diet during the illness.
- *Hydration* – While we did not expect dehydration to be a significant problem in the study children, if present it was managed according to standard WHO rehydration protocol.
- *Nasal secretions* - Patients with significant nasal secretions had the nose cleared by gentle suction and nose drops (saline) if necessary, according to the standard practice. Caregivers were shown how to instill these drops.
- *Anti-histamines and cough syrups* were not used in any children as they have no beneficial effect, make children drowsy and interfere with the accuracy of the other assessments.
- *Other medications* (such as anticonvulsants for children with a history of a seizure disorder) were allowed and recorded on the Case Report Forms (Annex B). Some patients were given antimalarials as per the discretion of the treating physician.

In any child in whom there was concern of "failure of treatment" (as defined in Study Objectives Section 0) the health workers were instructed to refer the child to the health facility for evaluation by the study physician. The study physician would assess the child and determine if the child met criteria for treatment failure. Children classified as treatment failures received antibiotic therapy as directed by their physician. The physician obtained additional chest radiographs, blood counts, blood cultures and other laboratory tests to aid patient management according to clinical judgment and the usual practices of the participating site.

A child was discontinued from the study if there was treatment failure or parent or guardian withdrew consent, which was documented on the appropriate form. Children who experienced serious adverse events also discontinued the study therapy. Antibiotics other than penicillin related drugs were given to these patients, as well as bronchodilators, paracetamol, and other therapy as appropriate.

Parents who refused to have their child continue to participate in the trial at any time were advised about general care of the child and how to recognize increasing severity of illness. These children were treated according to their clinical condition at the time of withdrawal.

8.2 Management of Hospital-Randomized Children

Children randomized to hospital care were treated in the hospital with oral amoxicillin for 48 hours and monitored by the health personnel for clinical deterioration before being discharged. Standard monitoring was done every 6 hours and included the same assessment described above under Home Management. All hospitalized children who were wheezing were given bronchodilators until such time as the wheezing resolved (see below), unless the physician caring for the child felt that such therapy was not beneficial.

Management for Wheezing in Hospital Group

Salbutamol	Nebulizer	0.5ml solution. in 2ml water/saline, 4-6 hourly
	Meter dose inhaler	100-200mg with spacer 4-6 hourly

Study patients who were wheezing at the time of discharge were given oral salbutamol syrup 0.15mg/kg/dose, for home use. Feeding, fever, and hydration were managed as indicated above in the home management section.

When the hospitalized patients were discharged after 48 hours, the parent/caregiver of patient was counseled to continue with the oral treatment prescribed for a period of 7 days (5 additional days after discharge). Patients assigned to hospital treatment and then discharged were clinically assessed at home by study staff at the following times:

Follow up Schedule for Hospital Group

Day of data collection	Site of assessment
Day 3 (after 72 hours)	Home
Day 5	Health facility
Day 8	Home
Day 14	Health facility

If the patient did not return to the health facility on day 14, he was visited at home within the next 48 hours. If the patient was well on day 16, the patient was deemed cured and no further follow-up occurred. If patient was unwell on day 16, as determined by the study physician, the patient was managed as per standard hospital practice.

In any child in whom there was concern of "failure of treatment" (as defined in Section 0) the health workers was instructed to refer the child to the health facility for evaluation by the study physician. The study physician would assess the child and determine if the child met criteria for treatment failure. Children classified as treatment failures received antibiotic therapy as directed by their physician. The physician obtained additional chest radiographs, blood counts, blood cultures and other laboratory tests to aid patient management according to clinical judgment and the usual practices of the participating site.

A child was discontinued from the study if there was treatment failure or parent or guardian withdrew consent, which was documented on the appropriate form. Children who experienced serious adverse events also discontinued the study therapy. Antibiotics other than penicillin related drugs were given to these patients, as well as bronchodilators, paracetamol, and other therapy as appropriate.

Parents who refused to have their child continue to participate in the trial at any time were advised about general care of the child and how to recognize increasing severity of illness. These children were treated according to their clinical condition by the time of withdrawal.

8.3 Unscheduled follow-up

Patients, who were brought back to hospital by their caregiver at times other than the designated follow-up visits, were clinically assessed by the study physicians and decision was made regarding their study outcomes and further management. This information was recorded on the relevant follow-up CRF or treatment failure form (Annex B).

8.4 Discontinued patients

Study physicians followed children who were discontinued from the study and ensured that they had appropriate treatment and follow-up arrangements. Children who were discontinued from the study because of withdrawal by the parent/guardian, or removal from hospital against medical advice, were not followed by the study physicians. If there was concern about the well-being of a study patient who was removed from hospital against medical advice, the relevant social services at the site were informed.

8.5 Decisions on treatment failure and change of therapy for home and 48 hours hospitalized patients

Any time the study physician suspected a treatment failure, he or she contacted the Principal Investigator or a senior pediatrician to confirm the treatment failure. At this time antibiotic therapy was changed and other appropriate therapy was started. All cases of treatment failure were followed up until considered well. The physician obtained chest radiographs, blood counts, blood cultures and other laboratory tests to aid patient management according to clinical judgment and the usual practices of the participating site.

8.6 Reporting of Serious Adverse Events, Treatment Failures and Deaths

Amoxicillin is in widespread use and is not investigational in any study site. However, since oral amoxicillin is not yet recommended for initial treatment of children who have severe pneumonia, the appropriate Case Report Forms describing the occurrence of a serious adverse event, treatment failure or death were faxed to the coordinating center within 72 hours of the investigator knowing about the event. Adverse events, treatment failure and death were reported to allow appropriate interpretation of this critical information. If the outcome of the adverse event was unknown when the PI first notified the coordinating center, a follow-up form was faxed to the coordinating center within 10 days of knowing about the event. The PI sent a copy of the adverse event data to their local IRB as soon as possible. The coordinating center summarized the Adverse Event and Death information and sent a report to the IRB at the IndiaCLEN.

8.7 Compliance with and deviations from the study protocol

Prior to initiation of the study, the Site PI agreed with and signed the protocol and confirmed in writing that he or she had read, understood and would work according to the protocol and Good Clinical Practice. The Site PI was responsible for making sure that the protocol was strictly followed and did not make any changes to the study unless necessary to eliminate an apparent immediate hazard or damage to a trial subject.

Any deviations from the study protocol (including but not limited to inappropriate enrollment of a study subject, administration of the wrong study treatment, missed doses of study treatment, missed observation points, incorrect administration of concomitant medications, etc.) were reported to the coordinating center and each site's IRB. The report included a plan to rectify any problems at the site that may have caused the protocol deviation.

8.8 Travel reimbursement to patient

The mother/caregiver was given a travel reimbursement of Rs 150 on the day 5 and day 14 hospital visit.

8.9 Cost Data Collection

The health care costs of patients in the trial starting from before they were randomized and continuing till they are declared well were measured using the micro-costing technique. The variable costs i.e. direct medical, direct non-medical and indirect costs of the two treatment arms were measured. The protocol driven costs were excluded from calculation of these costs. The mean differences in costs and the predictors of total cost were analyzed. The incremental cost-effectiveness of the two treatment strategies was also assessed.

8.10 Quality Assurances

8.10.1 Standard Operating Procedures

In order to ensure high quality screening, recruitment, data collection, specimen collection, radiology and laboratory work and data analysis, there were five separate Standard Operating Procedures (SOP) manuals developed.

1) Standard Operating Procedures(SOPs) for the Protocol
2) Clinical Instructions Manual
3) Microbiology Manual
4) Radiology forms and standard methods (WHO) to read the films (including digitalization and transmission to the coordinating site)
5) Data Management Procedures.

8.10.2 Training of Research Staff

Research staff (research officers, preferably with diploma in clinical research) was trained using the Integrated Management of Neonatal and Childhood Illness (IMNCI) videos for clinical signs, and on patients. A pre- and post-training exam was given on the SOPs prior to data collection. The study supervisors supervised data collection for 15 days before research staff collected data independently. Every month, training was reinforced, and written assessments were given frequently.

8.10.3 Site Monitoring Visits

Site visits were done for all sites and also in the new research sites that were integrated into the study. Two additional site visits were conducted at each of the new site for training assessment, adherence to SOP and good clinical practice (GCP), quality checks in data, and for effective study coordination. Technical Staff from MCH-STAR also conducted site monitoring visits to all the study sites.

8.11 Adverse Effects

Drug information about Amoxycillin (Annex E) was provided to all the investigators for ready reference. Adverse effects were classified as described in the adverse events form in Annex B. Secondary end-points were evaluated using chi-square tests. Logistic regression was used to estimate logit differences, taking other covariates into account.

8.12 Data Safety Monitoring Board

The study was overseen by an independent data safety monitoring board (DSMB) composed of two clinicians with developing country experience, one international expert, and one statistician not involved with the design or conduct of the study. Before initiation of the data collection, the members of the DSMB were provided with the protocol and were informed about the study in great detail. The members of the DSMB then decided on the variables that they needed to monitor regularly, and with what frequency.

The DSMB conducted the first interim analysis on a total of 670 patients (321 and 330 in hospital and home group respectively) in April 2010. The analysis was done to review safety of the interventions. Loss to follow up was low; 21 participants were lost to follow-up (for any reason) in the first week and an additional 7 during the second week of the study. Total lost to follow-up was 4.2%. Lost to follow-up was much higher in the hospital group (19 to 1 in the first week). The risk difference of the per protocol failure rate was 0.026 95% CI (-0.009, 0.061). The p-value of the relationship between treatment failure and randomization arm was 0.15, far exceeding the O'Brien- Fleming stopping rule critical value of 0.0023 required for stopping the study early due to superiority of one arm over the other. Since this was an open labeled trial the DSMB recommended reviewing the enrolment and randomization procedures with study staff to ensure that randomization procedures were faithfully being followed and there was uniformity in assessing clinical signs of treatment failure at each site.

9. Data Analysis and Sample Size

9.1 Criteria used to Estimate Sample Size

Sample size was calculated with the assumption that 10% of the children in 48 hours hospitalized group were estimated to fail treatment (as defined in section 0) at the end of the 7-day course of amoxicillin. The assumption of estimated 10% treatment failures was based on the results of APPIS. Although APPIS reported a 22% treatment failure with oral amoxicillin on study day 5, the failure rate in this study was anticipated to be lower, as the definition of failure of treatment no longer included isolated persistence of LCI at 48 hours, which is often observed in wheezy children. In APPIS, it constituted 6% of children. Another 6% were lost to follow up which was also considered treatment failure. In this study we followed the children at home which were expected to reduce loss to follow up. Thirdly, children most likely to fail in APPIS were those with very fast breathing i.e. RR > 70. We excluded these children. Therefore we anticipated the failure of treatment in this study to be lower than in APPIS.

It was expected that 15% or fewer of children in the home oral amoxicillin group would fail treatment as defined in section 6.3. The null hypothesis was that the proportion of children who would fail treatment in the home oral amoxicillin group would not be greater than the proportion of those who fail in the first 48 hours in the hospital group. Based on a consensus of the principal investigators at the proposal development workshop, if a difference of 5% or less was observed in treatment failure (defined as in section 6.3) between the two groups, the two treatments will be considered equivalent. This equivalence was considered clinically equivalent.

Based on a consensus of the principal investigators, the null hypothesis would be rejected based on a one-sided test (because the study focuses only on whether oral amoxicillin is not equivalent), with a p=0.05 level of significance. No adjustments were made for multiple comparisons because there was only one primary hypothesis. A study power of 90% was selected to be 90% confident that equivalence within the 5% range could have been detected. A 1:1 allocation was considered ethically appropriate by the investigators and is maximally efficient for the sample size calculation. Investigators considered that no more than 1% of patients are likely to leave against medical advice during the first 48 hours of hospitalization. Interim analysis was considered to be critically important to ensure that children treated in the home oral amoxicillin group did not have worse outcomes than those treated for 48 hours in hospital.

9.2 Sample Size Estimate (no adjustments for Loss to Follow-up and Interim Analyses)

Sample size estimates were based on standard formulae for detecting equivalence. The required number of patients in each group is given by the following formula:

$$n = 2p\,(1-p)\,(Z_a + Z_b)^2/d^2$$

Where n is the sample size in each group, p is the proportion of children who fail in both groups (assuming that failure is equivalent) and d is the maximum difference between groups that is considered equivalent. Using the assumptions listed in section 5.2 without adjustment for loss to follow-up during the first 7 days the required number of children to be enrolled in this clinical trial was 617 per group, 1,234 in the entire study.

9.3 Effect of Loss to Follow-up and Non-compliance at 48 hours of Observation

We anticipated that no more than 1% of children would leave at the end of 7 days (loss to follow up). Children who leave cannot be classified as improved, not improved or treatment failures. The traditional adjustment for estimated loss to follow-up is to increase the sample size by dividing it by the proportion for which follow-up data are available. However, this approach assumes that the probability of being lost is unrelated to the probability of treatment failure. An alternative conservative approach for this study assumed that children who were lost to follow-up were treatment failures and the proportion of failures in the two groups increased accordingly. Specifically, assuming a 1% loss to follow-up and that all losses were treatment failures, the adjusted estimated failure in the 48 hours hospitalized group increased to 11% and to 16% in the sent home oral-amoxicillin after first day group. Using the above assumptions, with adjustment for loss to follow-up as defined, but no adjustment for interim analyses or non-compliance, the required number of children to be enrolled in this clinical trial increased from 617 per group and 1,234 in the entire study to 671 per group, and 1,342 in the entire study. Children in the two groups were analyzed in the groups to which they are randomized, even if they are non-compliant with therapy.

In September, 2009, based on the previous year's statistics of all the hospitals participating in this multicentre study, an estimate of the number of patients to be recruited per site and per year was made. With the rate of recruitment at that time, the desired case recruitment was predicted to not be achieved, therefore, two more sites, Sewagram and Aligarh were included in the trial as per recommendation of MCH-STAR after approval of their IRB. Pune site had poor recruitment rates and was experiencing problems in case-recruitment due to government guidelines for admitting children with suspected H1N1 Flu, therefore, the steering committee and IndiaCLEN decided to discontinue the Pune site.

10. Statistical Analyses

10.1 Missing Data

Although every effort was made to identify and retrieve complete data, both by the clinical site and at the coordinating center, some outcomes were missing. A conservative approach was taken for missing data except for missing outcomes at end of the 7-day course. All missing values were assigned the average value (site-specific imputation) irrespective of treatment group. The number of degrees of freedom is the number of non-missing observations. This penalizes the analysis by adding a random component to the data.

10.2 Final Analysis

Data from cases recruited between October 6, 2008 and March 31st, 2011 were included in the final analysis presented in this report. At regular intervals, corresponding to enrollment of approximately 400 patients, aggregate analysis was conducted. Interim aggregate analyses focused on differences between sites in the following areas: patient recruitment, patient characteristics, and completeness of data.

To determine comparability of the two trial arms and the success of the randomization procedure, baseline characteristics of trial subjects according to assigned treatment were conducted. Baseline characteristics of the two treatment groups were compared using chi-square tests for categorical variables and ANOVA for continuous variables. We conducted the analysis using both intention to treat (analyzed as randomized) and per protocol analysis (includes all clinical causes of treatment failure, but excludes treatment failure due to lost to follow up, LAMA, and voluntary withdrawal from the study). The risk differences and the odds ratios for cumulative treatment failure was analyzed for different time periods such as < 72 hours, < 5 days, < 7days (primary outcome) and for < 14 days. Univariate and multivariate odds ratios for predicting treatment failure at the different time periods, where the models include the treatment groups and baseline explanatory covariates such as age, feeding status, immunization, antibiotics prior to 48 hours, weight for age Z scores, body temperature, respiratory rates, oxygen saturation, auscultatory wheeze, crackles, radiological infiltrates, number of rooms in the house and type of fuel used for cooking was conducted. Similar analysis was conducted for secondary outcome of treatment failures between day 8 and 14 day. Cox proportional hazards models were used to estimate the relative hazards (RH) of treatment failure in the two groups up to 14 days and to explore associations between the same baseline covariates and outcome. We used forward step wise method and identified explanatory candidate variables ($p \leq 0.1$) for inclusion in adjusted models as plausible predictors of treatment failure. The Kaplan-Meier curves for the cumulative probability of treatment success were also plotted for the two groups and the overall difference in their rates of treatment success was examined using the log-rank test. Statistical analysis was conducted using STATA 10 data analysis software.

10.3 Cost Analyses

The costs were analysed from the provider (government) and patient's prospective (Annex- F). The mean costs of the inpatient stay and procedures, and of the outpatient visits and the procedures, their standard deviations, median and range were calculated. Group differences in mean cost of the treatment strategies were assessed using Student's t-test. Univariate analysis was conducted for the predictors of cost variation, such as data on patient demographic characteristics, clinical history,

length of stay and other utilization of resources for treatment of this episode of pneumonia before entry of patients into the trial.

Multivariable regression analysis (OLS, with or without log transformation) was also used to predict total costs across the cost categories using pre-randomization variables, the alternate treatment strategies and other covariates that relate to resource consumption. Regression analysis allows for differences in outcome attributable to the alternate strategies to be assessed while taking into account the economic impact of other characteristics of the patients. Differences were considered statistically significant if they have a two-tailed p value less than 0.05 and tending towards significance if they have a two tailed p value less than 0.1.

The hypothesis, that home treatment is more cost-effective than hospital treatment, was also tested by comparing the cost-effectiveness ratios. The incremental cost-effectiveness of the two arms was also calculated. For the incremental cost-effectiveness, the numerator was the difference in the predicted total costs and the denominator was the difference in effects. The effectiveness measures were the number of patients cured (1-treatment failure) or the number of cases of treatment failure avoided. Thus, the two treatments were compared by multivariable regression analysis (as given above) and by comparing the cost-effectiveness ratios of the two treatment strategies.

11. Maintenance of Study Materials

The principal investigator at each site was responsible for completion of all appropriate Case Report Forms up to the time that the child was discontinued from the study. Study data was collected on Case Report Forms, which were sent to the coordinating center on a monthly basis for archiving. At least once a month, the site PI or his/her designate contacted the coordinating center either by fax or electronically to report on the number of new children enrolled in the study and the status of all enrolled study children. Study specific forms (paper and electronic versions) were provided to each site.

Each month, the site PI or his/her designate were responsible for visually editing the Case Report Forms for each child who has completed or withdrawn from the study. All missing data was identified and every attempt made to complete missing data. The site PI or designate was responsible for sending by courier or surface mail (if deemed reliable and sufficiently rapid) completed Case Report Forms to the coordinating center every month.

11.1 Management of study materials at clinical sites

Each site was responsible for setting up an information system to keep track all patients screened and enrolled and a filing system to keep all study related records - case history records, study protocol or related documentation and drug distribution records. The PI at each site was responsible for the completeness and accuracy of all the study materials.

11.2 Case history records

These include the study Case Report Forms (CRF) that contained information documenting the child's eligibility to participate in the study, the signed consent form, and information from tests and examinations. Wherever possible copies of supporting documentation for the information contained in the CRF was kept with each patient's case history record. This supporting documentation included records of physical examinations, progress notes, laboratory reports, X-rays, consultations, correspondence, information and data on the subject's condition, during and after the clinical investigation, diagnoses made, concomitant therapy, etc. All information in the case history records was attributable to a specific individual. Since the CRF did not contain the patient's name, there was a unique link between the ID number on the CRF and the patient's name. Each child's case history record was evaluated to verify validity and completeness of the data on the CRF when a study monitor visited the study site.

All corrections to CRFs were made without obscuring the original entry. The revised entry was inserted and the person making the correction signed and dated the correction. Only authorized study personnel completed or corrected Case Report Forms.

11.3 Protocol and Related Documentation

All study related documents including the study protocol, manuals of operations, all correspondence sent to or received from the study monitor, materials used for obtaining informed consent, protocol modifications and records of the Institutional Review Board approval and all communications with the IRB were maintained in complete form at each site. These documents were evaluated to ensure that study documentation was complete and current when a study monitor visited the study site.

11.4 Record Retention

Retention of accurate and complete records is essential to establish the validity and completeness of the study. All records will be retained for 5 years after the data set is frozen.

12. Results/Findings

There were 6634 children screened for WHO defined severe pneumonia of which 1118 children (16.9% of those screened) enrolled in this study between October 6, 2008 and March 15, 2011. The majority of subjects were recruited at the Chandigarh, Chennai, and Nagpur sites. Enrollment of subjects by site was as follows:

Table 2: Enrollment by Study Site

Site	No. of children enrolled (%)
Chandigarh	377 (33.7%)
Chennai	328 (29.3%)
Nagpur	316 (28.3%)
Sevagram	50 (4.5%)
Aligarh	37 (3.3%)
Pune	10 (0.9%)
Total	1118 (100%)

Table 2 shows the number of children screened and the reasons for exclusion. Of all the reasons for exclusion of the child for the trial, the caretaker refusing consent for participation was the most common (44.5%), followed by LCI that disappears with nebulization (8.1%), antibiotic therapy 48 hours or more prior to screening (4.7%) and presence of danger signs (4%).

Table 2: Study Screening and Reasons for Exclusion

	Total[#]	
	n	%[*]
Screened	6,634	
Enrolled (%)	1,118	16.9
Inclusion criteria not satisfied		
Not satisfying Age 3-59 months	462	5.1
Had no lower chest indrawing on examination	1489	16.3
Caretaker is not willing to sign informed consent form	4060	44.5
Exclusion criteria, number (%)		
Known or clinically recognizable chronic conditions	224	2.5
History of >2 weeks of cough / difficulty in breathing	195	2.1
Past history of more than 3 wheezing episodes or physician diagnosed asthma	267	2.9
LCI that responds to trial of nebulization	743	8.1
Known HIV positive child. HIV status of mother known to be positive & of child not known/defined	16	0.2
Hospitalization for>48 hours in the last two weeks	127	1.4
Measles in the last month	64	0.7
Clinically severe malnutrition (weight for length < -3 SD or kwashiorkar)	163	1.8
Rickets	21	0.2
Kerosene poisoning within last 48 hrs.	17	0.2
Antibiotic therapy for 48hrs or more immediately prior to admission	431	4.7

Other diseases requiring antibiotic therapy, e.g. Meningitis, tuberculosis, dysentery, etc.	28	0.3
Known prior anaphylactic reaction to penicillin or amoxycillin	8	0.1
Severe dehydration according to WHO guidelines	12	0.1
Severe pallor	19	0.2
Suspected surgical pathology	12	0.1
Living out of the follow-up area of the study (30 kms)	308	3.4
Subject previously included in the same trial or already included in another ongoing trials anywhere.	44	0.5
Presence of danger sign $ before radiology evaluation	358	3.9
Presence of danger sign after radiology evaluation	9	0.1
Presence of radiological consolidation/ effusion / pneumothorax	45	0.5
Total reasons for exclusion&	**9122**	

* Proportion for the presence of exclusion criteria. The denominator is total reasons for exclusions.

& A child could have more than one reason for exclusions.

$ Danger signs are presence of any one clinical condition - abnormally sleepy or difficult to wake, persistent vomiting, inability to drink, grunting, stridor, central cyanosis, convulsions, RR>70 breaths per minute, Sp02 < 88% on room air.

Table 3 shows the baseline characteristics of the study participants by treatment group. Of the 1118 children enrolled and randomized, 554 were assigned to home treatment, and 564 were assigned to hospital treatment, across the 6 sites. The two groups were balanced in distribution of baseline characteristics, except that children in the hospital group were more likely than the home group to have children in the age group of 3-11 months (49.1 % vs. 42.8%), the mean respiratory rate for infants and children was higher in the hospital group than the home group (infants mean respiratory rate: 48.9 ± 8.7 and 47.3 ± 8.9 respectively; children's mean respiratory rate: 43.9 ± 9.8 and 43.0 ± 9.1 respectively), and the hospital group was more likely to have infiltrates in their chest x-ray than the home group (67.6% and 60.8% respectively).

Table 3: Baseline Characteristics in Home and Hospitalized Children

Baseline characteristic	Home (N=554)		Hospital (N=564)	
	n	%	n	%
Sex (Female)	207	37.4	204	36.2
Infants (3-11 months old)	237	42.8	277	49.1
Children (12-23 months old)	164	29.6	138	24.5
Children (24-59 months old)	153	27.6	149	26.4
Breast feeding indicators(3-59months)				
Exclusive breast feeding	361	65.2	373	66.1
Bottle feeding	231	41.7	209	37.1
Timely complementary feeding	431	77.8	443	78.6
Immunization status up-to-date	516	93.1	510	90.4
Report of antibiotics in < 48hrs prior to enrollment	56	10.1	59	10.5
Weight-for-age Z score (mean ± sd)	554	-1.5 ± 1.3	564	-1.6 ± 1.3
Weight-for-age Z score (<-2)	197	35.6	205	36.4
Length/ height (cm)(mean ± sd)	548	75.9 ± 11.7	560	74.7 ± 12.1
Temperature (˚F)(mean ± sd)	554	99.5 ± 1.5	564	99.6 ± 1.5
Respiratory rate per min (mean ± sd)				
Infants	237	47.3 ± 8.9	277	48.9 ± 8.7
Children	317	43.0 ± 9.1	287	43.9 ± 9.8
Auscultatory wheeze				
Infants	140/237	59.1	176/277	63.5
Children	155/317	48.9	121/287	42.2
Crackles				
Infants	174/237	73.4	211/277	76.2
Children	243/317	76.7	228/287	79.4
Pulse oximetry (mean ± sd)				
Infants	236	96.1 ± 2.9	277	95.9 ± 3.2
Children	317	95.9 ± 3.0	286	95.8 ± 3.1
Any Infiltrates in chest x-ray	322/530	60.8	365/540	67.6
No. of rooms in house (mean ± sd)	554	2.4 ± 1.4	564	2.3 ± 1.4
Fuel used for cooking*				
Low polluting fuel	220/553	39.8	249/556	44.8
High polluting fuel	333/553	60.2	307/556	55.2
Any smoker who smokes in the house	121	21.8	129	22.9

Table 4 reports the isolation of organisms in the nasopharngeal swabs and their sensitivity to various antibiotics. The isolation of *S. pneumoniae* and *H. influenzae* was 18.8% and 10.1% respectively and similar in both groups. Respiratory syncytial virus (RSV) was isolated in 23% of the aspirates, with similar rates in both groups.

Table 4: Isolation of organisms from nasopharyngeal swabs and aspirates at enrolment

Organism	Home (N=554)		Hospital (N=564)	
	n	Mean ± SD	n	Mean ± SD
Bacterial growth on NP swab n (%)				
S. pneumoniae	103	19.1	101	18.5
H. influenzae	60	11.2	48	8.8
RSV Positive n (%)	127	22.9	147	26.1

12.1 Overall Per Protocol Analysis and Intention to Treat Analysis

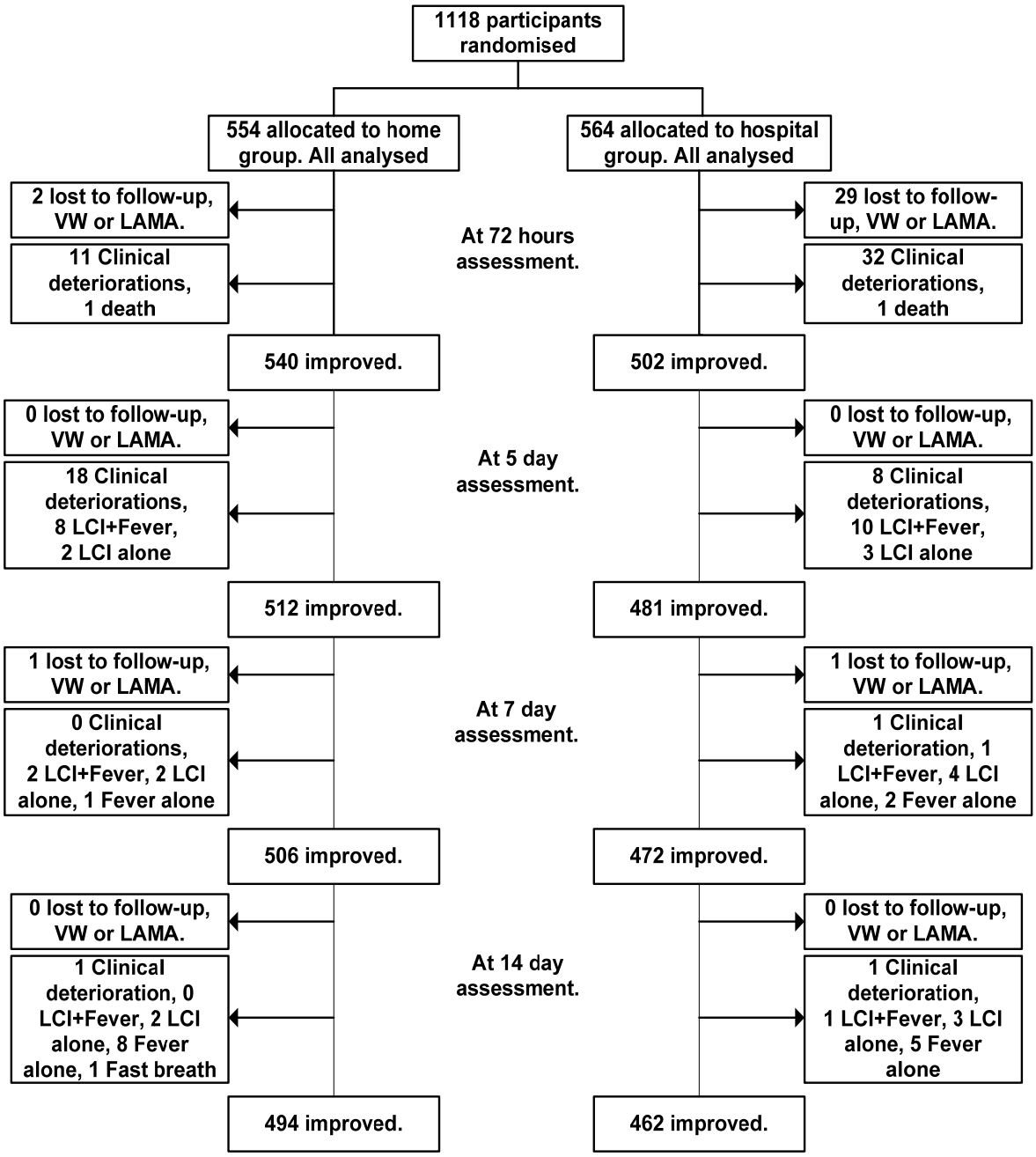
The intention to treat analysis includes all children enrolled in the study as proposed, including those who were lost to follow up, cases of LAMA, and voluntary withdrawal from the study. The per protocol analysis includes all clinical causes of treatment failure, but excludes treatment failure due to lost to follow up, LAMA, and voluntary withdrawal(VW) from the study. The overall failure rates for each time period, per the intention to treat and per protocol analysis are presented in Table 5. The overall failure rates at 7 and 14 days were lower than was projected by the study investigators (12% and 15% respectively) applying the per protocol model, and approximately as expected applying the intention to treat model. The unadjusted treatment failure rates in the hospital and home group at different time points in the study is shown in Figure 3 and Appendix C.

Table 5: Overall Treatment Failure (Home + Hospital) on Oral Amoxicillin at Different Time Points by Intention to Treat and Per Protocol Analysis (N = 1118)

Time frame	Intention to treat		Per protocol	
	n	%	N	%
< 72 hrs*	76	6.8	45	4.0
< 5 day*	125	11.2	94	8.4
≤ 7 day*	140	12.5	107	9.6
≤ 14 day*	162	14.5	129	11.5
> 7 day to ≤14 day	22	2.0	22	2.0

* Cumulative treatment failure

Figure 3: Study profile of patients of all sites randomized to home and first 48 hours hospital management of WHO-defined severe pneumonia



Kaplan Meier curves for differences between treatment successes in the home and hospital group with log rank tests for both the intention to treat analysis shows that the hospital group was significantly more likely than home children to fail treatment at any time point. While the per protocol analysis tended to show a similar trend (RR 1.34), it was statistically non-significant (p=0.10) (0 B). The Cox Regression model for both per protocol and intention to treat analysis showed that infants (3-11 months), and patients who had antibiotics within 48 hours of enrolment had a higher likelihood of failing treatment at any point from enrolment to 14 days. Additionally, the Cox Regression model applying the intention to treat analysis also showed that being in the hospital

group and coming from a home using high polluting fuels were significantly associated with treatment failure at any time. In the intention to treat model, children in the hospital group were more likely to fail treatment at any time than children in the home group (with LAMA accounting for the majority of these failures) (P=0.00, Table 6).

Table 6: Cox Regression Analysis for Treatment Failure Using the Per Protocol and Intention to Treat Analysis up to 14 days

Characteristic	Per-protocol analysis				Intention to treat analysis			
	Hazard ratio	95 % CI		p-value	Hazard ratio	95 % CI		p-value
Treatment group								
Home	1.00	-	-	-	1.00	-	-	-
Hospital	1.32	0.93	1.88	0.12	1.61	1.16	2.24	0.00
Age group								
Infants (3-11 months old)	1.00	-	-	-	1.00	-	-	-
Children (12-59 months old)	0.65	0.45	0.93	0.02	0.69	0.49	0.96	0.03
Exclusive breast feeding								
No	1.00	-	-	-	1.00	-	-	-
Yes	1.52	0.98	2.36	0.06	1.46	0.99	2.16	0.06
Antibiotics prior to enrollment								
No	1.00	-	-	-	1.00	-	-	-
Yes	1.79	1.06	3.02	0.03	1.72	1.07	2.76	0.02
Fuel used for cooking								
Low polluting fuel	1.00	-	-	-	1.00	-	-	-
High polluting fuel	1.43	0.98	2.10	0.06	1.51	1.06	2.15	0.02
Study Site								
Chandigarh	1.00	-	-	-	1.00	-	-	-
Chennai	0.18	0.09	0.33	0.00	0.41	0.26	0.64	0.00
Nagpur	0.58	0.38	0.91	0.02	0.63	0.42	0.96	0.03
Pune	2.33	0.84	6.48	0.11	2.78	1.11	6.97	0.03

12.2 Primary Outcome: Treatment Failure within the First 7 days

There were no significant differences in the rates of treatment failure resulting from clinical deterioration (per protocol) (presence of any one of these conditions - persistent vomiting, central cyanosis, grunt, stridor, abnormally sleepy or difficult to wake, inability to drink, or convulsions) within the first 7 days between the home group and the hospital group. In the unadjusted analysis, there were 30 (5.4%) treatment failures due to clinical deterioration in the home group and 42 (7.4%) treatment failures due to clinical deterioration in the hospital group. The risk difference between the two groups was within the equivalency margin (difference -2.0%, 95% CI -4.9 to 0.8; Table 7). Similarly the two groups were equivalent in treatment failures within 7 days due to voluntary withdrawal, loss to follow up, death, LCI plus fever, LCI alone, fever alone, and fast breathing.

There was however a significant difference between the overall unadjusted treatment failures rates by intention to treat analysis between the home and hospital group within the first 7 days. The home group experienced 48 (8.7%) treatment failures and the hospital group experienced 92 (16.3%) treatment failures, which was outside of the equivalency margin (difference -7.6%, 95% CI -11.5 to -3.8; table 7). Within the first 72 hours, treatment failures due to LAMA contributed a large proportion of the overall treatment failures in the hospital group, which was the only group that could experience LAMA (defined as leaving the hospital against medical advice within the first 48 hours). In the hospital group, LAMA within first 72 hrs contributed 29 out of 62 treatment failures (00 C). While not considered a primary objective, there was a significant difference in unadjusted rates of clinical deterioration in the home group (2.2%) and the hospital group (5.9%) at 72 hours (difference -3.7%, 95% CI -6.0 to -1.4;0 0 C)

Two children died within the first 7 days - 1 child in the home group, and 1 child in the hospital group. Both deaths in the study population occurred within the first 72 hours. There were no other serious adverse events. Neither of the deaths were considered to be related to the study treatment with oral amoxicillin.

Table 7: Cumulative Treatment Failure by Group Within the First 7 Days

Primary Outcome	Cumulative treatment failure on < 7 day							
	Home group		Hospital group		Difference %	Difference % 95 % CI		P value
	N=554	%	N=564	%				
Total	48	8.7	92	16.3	-7.6	-11.5	-3.8	0.00
Clinical deterioration	30	5.4	42	7.4	-2.0	-4.9	0.8	0.08
Voluntary withdrawal	5	0.9	1	0.2	0.7	-0.1	1.6	0.95
Lost to follow up	3	0.5	1	0.2	0.4	-0.3	1.1	0.85
LAMA	0	0.0	29	5.1	-5.1	-7.0	-3.3	0.00
Death	1	0.2	1	0.2	0.0	-0.5	0.5	0.50
LCI+ Fever (>98.6 F)	23	4.2	16	2.8	1.3	-0.8	3.5	0.88
LCI alone	15	2.7	21	3.7	-1.0	-3.1	1.1	0.17
Fever alone (>98.6 F)	8	1.4	11	2.0	-0.5	-2.0	1.0	0.26
Fast breathing	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Adjusted multivariate analysis using the per protocol model indicated that the baseline characteristics predictive of treatment failure within the first 7 days were being 3-11 months of age, exclusive breast feeding, the use of antibiotics less than 48 hours before enrollment and the absence of auscultatory wheeze (0Appendix D). There was site variation and Chandigarh had higher failure rates as compared to Chennai (Appendix C). The intention to treat analysis showed that being in the hospital group was predictive of treatment failure in the first 7 days (0 Appendix D).

12.3 Secondary Outcome: Treatment Failure between Day 8 and Day 14

There was no significant difference between the two groups in failure rates from any cause between 8 and 14 days. In the unadjusted analysis (Table 8) there were 12 (2.2%) treatment failures in the home group and 10 (1.8%) treatment failures in the hospital group. The risk difference between the two groups was within the equivalency margin (difference 0.4%, 95% CI -1.2 to 2.0; Table 8). In the home group there were 8 treatment failures due to fever alone, 2 treatment failures due to LCI alone and 2 treatment failures due to fast breathing (children could have multiple causes of treatment failures, which is why there are more than 12 reported). In the hospital group there were 6 treatment failures due to fever alone, 3 treatment failures due to LCI alone, and 1 treatment failure due to LCI plus fever.

Table 8: Treatment Failure Rates Between Day 8 and day 14 by Different Causes in the Two Groups

Primary Outcome	Treatment failure at > 7 to ≤ 14days							
	Home group		Hospital group		Difference %	Difference % 95% CI		P value
	N=554	%	N=564	%				
Total	12	2.2	10	1.8	0.4	-1.2	2.0	0.68
Clinical deterioration	1	0.2	1	0.2	0.0	-0.5	0.5	0.51
Voluntary withdrawal	0	0.0	0	0.0	-	-	-	-
Lost to follow-up	0	0.0	0	0.0	-	-	-	-
LAMA	0	0.0	0	0.0	-	-	-	-
Death	0	0.0	0	0.0	-	-	-	-
LCI + Fever (>98.6 F)	0	0.0	1	0.2	-0.2	-0.5	0.2	0.16
LCI alone	2	0.4	3	0.5	-0.2	-1.0	0.6	0.33
Fever alone (>98.6 F)	8	1.4	6	1.0	0.4	-0.9	1.7	0.72
Fast breathing	2	0.4	0	0.0	0.4	-0.1	0.9	0.92

Adjusted intention to treat (there were no loss to follow up, voluntary withdrawal during this period) analysis of baseline characteristics predicting treatment failure between 8 and 14 days showed that presence of wheeze and the use of high polluting fuel tended to increase risk of failure but was not statistically significant (OE).

Appendix F shows unadjusted and adjusted per protocol analysis for treatment failure rates at 72 hours, day 5 and day 14. Children in the hospital group, and those exclusively breast fed had significantly higher treatment failure rates at 72 hours. Children in the age group of 3-11 months were more likely to fail treatment by days 5 and 14. Additionally children who received antibiotics within 48 hours before enrollment also were at a higher risk of failing by day 14.

12.4 Cost Outcomes

Table 9 shows the different categories of variable costs incurred in the hospital and home group. The average cost of treating a child at a government hospital in India with subsidized rates was Rs. 567.00 when patients were hospitalized for only two days. As expected the total cost of treating at hospital for the first 48 hours was significantly more than being treated at home. There were no significant differences between the two groups in costs of outpatient visits, but significantly higher costs were observed in the hospital group for the costs of hospitalization and for non-medical costs, which includes expenditure of the caregiver on travel or meal costs when taking care of the child. Table 10 shows that it cost Rs.240 more if the patient were in the hospital group. Patient characteristics associated with higher costs of treatment were age 3-11 months, higher temperature, lower pulse oximetry readings, and presence of auscultatory wheeze.

Table 9: Treatment costs in different cost categories in the home and hospital group.

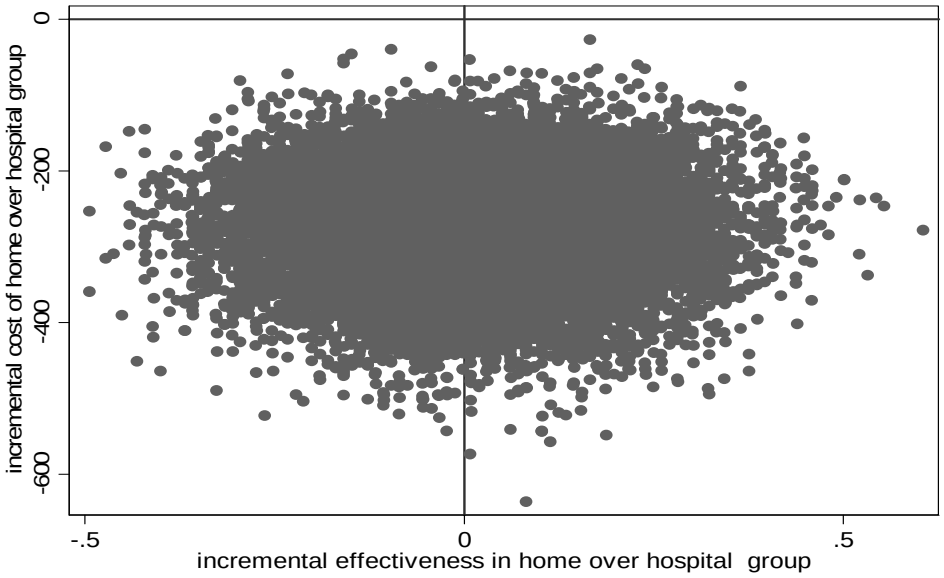
Type of costs	Home		Hospital		P-value
	n	(mean ± SD)	n	(mean ± SD)	
Cost of outpatient visits					
Direct Medical Cost	94	142.4 ± 152.9	97	128.8 ± 145.6	0.53
Direct Non Medical cost	94	74.4 ± 80.9	97	94.9 ± 144.4	0.23
Indirect Cost	86	46.2 ± 111.5	84	39.9 ± 120.1	0.72
Hospital Cost					
Direct Medical Cost	76	125.2 ± 46.3	95	166.2 ± 76.1	0.00
Direct Non Medical cost	76	44.7 ± 41.3	95	191.7 ± 179.9	0.00
Indirect Cost	76	37.7 ± 79.8	95	95.3 ± 186.6	0.01
Total Direct Medical Cost	94	243.6 ± 174.7	97	291.5 ± 196.4	0.08
Total Direct Non Medical cost	94	110.6 ± 89.9	97	282.7 ± 294.2	0.00
Total Indirect Cost	94	72.8 ± 146.9	97	127.8 ± 286.9	0.10
Total Cost	94	426.9 ± 274.0	97	702.1 ± 595.4	0.00

Table 10: Predictors of total mean costs for treating WHO defined severe pneumonia

Variable	β (95% CI)	P-value
Treatment group (Hospital)	239.8 (102.6, 377.0)	0.00
Age group (12-59 months old)	-195.7 (-341.6, -49.9)	0.01
Antibiotics prior to enrollment	-22.7 (-297.5, 252.1)	0.87
Weight for age Z-score	-36.4 (-94.0, 21.2)	0.21
Temperature	28.1 (3.9, 52.2)	0.02
Respiratory rate per min	1.9 (-6.1, 10.0)	0.64
Pulse oximetry	-26.9 (-50.4, -3.4)	0.03
Auscultatory wheeze	204.8 (59.5, 350.1)	0.01
Any infiltrates in chest X-ray	106.8 (-37.7, 251.3)	0.15

The boot strap cost estimates of Rs.702 (95% CI 701, 703) for the hospital group and Rs. 427 (95% CI 427, 428) for the home group was consistent with that determined by the above regression and significantly higher for the hospital group (p<0.001). Figure 4 shows the plotting of the boot strap estimates on the cost effectiveness plane. It indicates that it is cheaper to be treated at home (all points are below zero in the Y co-ordinate of costs) with identical effects (all points are equally distributed on either side of zero in the X co-ordinate).

Figure 4: 20000 Bootstrap re-samples –cost-effectiveness plane



13. Discussion

The study results suggest that in selected children (children without any of the study exclusion criteria) aged 3-59 months with WHO defined severe pneumonia, home based treatment of severe pneumonia with oral amoxicillin is equivalent to 48 hours of hospital administered oral amoxicillin followed by home based treatment. We therefore suggest that WHO recommendations for treatment of severe pneumonia in children be modified from their current guidelines of referring all children of severe pneumonia to the health facility for administration of parenteral antibiotics, and to recommend home based treatment for clinically stable children with WHO defined severe pneumonia.

The most common reason for exclusion in this study was refusal to consent to participate in the trial by the caregiver. The probable reason for this refusal could be the inconvenience to the family. This is endorsed by the fact a large number of children left against medical advice from the hospitalized group. Presence of co-morbidities and danger signs was an uncommon reason for exclusion. This is perhaps because children with such conditions are hospitalized without any delay and so may not be screened by the research staff. Most likely children who were clinically stable, with fast breathing and LCI were screened for trial eligibility. This implies that in absence of danger signs, children with severe pneumonia may not need hospitalization even from the perspective of the care-giver.

Although there were marginally more number of infants in age group of 3-11 months (49% vs. 43%) and higher mean respiratory rates at baseline (49 per min vs. 47 per min) in the hospital group, the randomization was successful in balancing most baseline characteristics between the two treatment groups across all sites. However despite efficient randomization, imbalances were present that were controlled for in analysis. Multivariate analysis showed that other factors which were not balanced across the two groups such as respiratory rate or presence of infiltrates were not predictive of treatment failure. Respiratory rate is also correlated with age and failed to reach level of significance in the multivariate model. Treatment failure rates between the two groups were equivalent at 7 days and between 8 and 14 days applying the per protocol analysis (which excluded treatment failures due to LAMA, loss to follow up, and voluntary withdrawal). In the intention to treat analysis, hospitalized children were significantly more likely to fail treatment at 7 days, due largely to treatment failures from LAMA in the first 48 hours of hospitalization. The high rate of LAMA in the hospital group (5.1%) demonstrates that hospitalization is a barrier to children receiving a full course of treatment and perhaps the caregivers prefer to have their children treated at home.

Clinical deterioration as a cause of treatment failure in the first 72 hours was also significantly more likely in the hospital group, after adjustment for baseline covariates in per protocol analysis. The randomization was effective and the allocation was concealed so it is unlikely that sicker children would be allocated to hospital by the research staff. However it is possible that those children who remain in the hospital were more closely monitored by the skilled research staff for presence of any one of the signs of clinical deterioration such as persistent vomiting, central cyanosis, grunt, stridor, abnormally sleepy or difficult to wake, inability to drink, or convulsions. Hospitalized children are also more likely to experience a change in antibiotic due to clinical deterioration, yet there was no difference in mortality between the two groups. There was one death in each group and neither of the deaths were related to severe pneumonia. Although not a primary outcome, the rate of treatment failure by day 3 was higher in the hospital group than in the home group. This difference was mainly due to LAMA, but there were also significantly more treatment failures due to clinical

deterioration in the hospital group than in the home group. The lack of difference in clinical deterioration by day 7 meant that there were more treatment failures in the home group than in the hospital group between day 3 and 7. The majority of treatment failures between day 3 and day 7 were due to LCI plus fever in the home group and LCI alone in the hospital group and not due to clinical deterioration by appearance of danger signs

The baseline characteristics predictive of treatment failure at day 7 were infancy (3-11 months), exclusive breastfeeding, those who had received antibiotic within 48 hours prior to enrollment and those without auscultatory wheeze. The infants were more likely to be breast fed and also fail treatment. We believe that the exclusive breastfeeding variable was subject to recall bias, as the caregivers of all children up to 59 months were asked about breastfeeding in the first 6 months. This likely resulted in over reporting of exclusive breastfeeding, which would reduce the validity of the association between exclusive breastfeeding and the outcome of treatment failure. Children who received antibiotics less than 48 hours prior to enrollment could have been sicker children and perhaps also more likely to fail treatment with oral amoxicillin. Children with no auscultatory wheeze were also more likely to fail as they could have been children with bacteremia resistant to amoxicillin and experience persistence of fever or clinical deterioration. This implies that young infants without wheeze but with clinical deterioration need injectable antibiotics as they may not respond to oral amoxicillin. The two groups had similar rates of isolation of *S. pneumoniae, H. influnzae* and RSV, which were not predictive of treatment failure. These rates of isolation are similar to those observed in the multicountry APPIS study (which included data from an Indian site) [4].

Adjusted intention to treat analysis of baseline characteristics predicting treatment failure between 8 and 14 days (there were no loss to follow up, voluntary withdrawal during this period) showed presence of wheeze and the use of high polluting fuel tended to increase risk of failure but was not statistically significant. Kerosene, coal, wood, and dung were all considered to be high-polluting fuels for this analysis. Previous studies have found that solid fuel use increases the risk of acute lower respiratory infection mortality and morbidity from community acquired pneumonia [11, 12].

WHO recommends urgent referral of children with WHO defined severe pneumonia for hospitalization for parenteral (injectable) antibiotics and other supportive therapy [3]. Results of APPIS (Amoxicillin Penicillin Pneumonia International Study) [4] that evaluated the efficacy of oral amoxicillin for treatment of severe pneumonia in children served as the basis for "NO-SHOTS" (New Outpatient Short-Course Home Oral Therapy for Severe Pneumonia) study which compared initial hospitalization and parenteral ampicillin for 48 hours followed by 3 days of oral amoxicillin at home, to 5 days of home-based treatment with oral amoxicillin [5]. NO-SHOTS showed that home treatment with high-dose oral amoxicillin is equivalent to hospital based treatment with parenteral ampicillin in selected[6] children aged 3-59 months with WHO defined severe pneumonia [5]. A recently published multisite observational study in 4 countries (MASS – Multicentric Amoxicillin Severe pneumonia Study) evaluated treatment failure rates in children treated with high dose oral amoxicillin administered for duration of 5 days [13]. The failure rate in APPIS was 22% cumulative on the 5th day in each group. The failure rates were 8.6% and 7.5% respectively in hospitalized injectable group and home group in the NOSHOTs study and, 9.2% in the MASS study. The risk

[6] Children with severe pneumonia who did not have other complicating factors or other danger signs as defined by the study exclusion criteria that could indicate very severe disease.

difference of failure in injectable versus oral amoxicillin in the APPIS study and NOSHOTS study was non-significant. In ISPOT study the per protocol treatment failure on oral amoxicillin was 9.6% , and, the efficacy of oral amoxicillin administered in hospital for first 48 hours was similar to that administered at home. This indicates that children with WHO defined severe pneumonia managed at home will have similar rates of improvement as compared to those managed in the hospital with either injectable or oral amoxicillin. Additionally this study evaluated the cost of treatment. The cost of treatment in the hospital was significantly more than the cost of treatment with oral amoxicillin at home. This was despite the fact that cost of hospitalization was perhaps an underestimate of true costs as only variable costs were measured, and, because the costs of treatment and hospitalization are subsidized at Indian government hospitals. These results thus suggest that it will be cost efficient to manage children with WHO defined severe pneumonia at home with oral amoxicillin.

13.1 Study Strengths and Challenges

This is only trial that has evaluated the efficacy of oral amoxicillin administered at the hospital for first 48 hours as compared to home administered oral amoxicillin to complete a course of 7 day treatment of WHO defined severe pneumonia in children. The protocol of this study was developed by global and national experts in acute respiratory infections from a programmatic perspective and to develop evidence for improving community case-management of pneumonias in under five children of low resource settings. The protocol was further reviewed by global experts and funded to be conducted at 6 recognized tertiary referral care centers with strong research experience following clearance from their ethics committees. The trial was coordinated by a PI who had previous research experience in case-management of severe pneumonia in children. Rigorous training and retraining of the research physicians using standard operating procedures was used to minimize the biases that may arise due to lack of uniformity in assessing clinical signs between treatment groups and across sites. Strong quality monitoring processes were also established. The case report forms were piloted and a data management system was set up. Standardized microbiological procedures were adopted to assess the presence of common etiological agents in nasopharyngeal passages and aspirates. There was a risk that threats to validity of the study could also arise not only from lack of uniformity in assessing the clinical variables but also deviations from the protocol across study groups and sites. We carefully monitored for these variations within and across sites, and no deviations were recorded. Any child who took another antibiotic for a co-morbid condition or in whom the antibiotic was changed was considered as a treatment failure by definition.

This was a multisite study over three years that captured the impact of seasonal variations on pneumonia epidemiology. Because these sites are referral centers, they receive children who are perhaps sicker than those that attend community health centers. Oral amoxicillin was found to be effective in treating WHO defined severe pneumonia at these sites, thus it could be effective for case management at the community level.

One of the challenges was an outbreak of H1N1 flu, due to which enrollment at the Pune site was stopped. This was due to a government policy that required administration of oseltamivir to all children with fast breathing, which violated the protocol leading to cessation of enrolment of patients at this site. Another challenge was that it was an open labeled study. In the circumstances, the strength was that the randomization was in variable lengths of permuted blocks for each site. This limits the ability to predict the treatment group that will be allocated to a study participant. Adequate concealment(investigators or the research physicians were masked to the sequence of the

allocation of the patient to hospital and home group) also maintained the efficiency of random allocation to avoid selection of sicker children to the hospital group. This concealment was achieved by sealing the allocation to the treatment groups in opaque envelops which had to be signed on opening the seal and then attached to the Case Report Forms. Patients were also carefully scrutinized for ineligibility after enrollment. Consequently, there was balancing of most baseline characteristics across the treatment group and residual imbalances were dealt with by multivariate analysis. Children with asthma, bronchiolitis and viral pneumonia can also manifest with clinical signs of WHO defined severe pneumonia of cough with LCI. However sincere efforts were made to exclude children with previous records of wheezing, having received bronchodilators or LCI that disappeared with nebulization with bronchodilators. Attempt was also made to understand possible etiology at baseline by using standardized microbiological techniques to isolate common organisms from nasopharyngeal swabs and aspirates.

The results showed that most baseline characteristics were similar in the treatment groups indicating successful randomization and allocation. However the hospital group did have a higher proportion of children in the age group of 3-11 months, higher respiratory rates and higher rates of infiltrates in chest radiology. In multivariate analysis respiratory rate and chest radiology were not predictive of treatment failure. Although younger age was predictive of treatment failure, the treatment groups showed equivalency in achieving similar rates of treatment failure, after adjusting for age.

Although treatment failure is a composite outcome due to presence of any one of treatment failure criteria, the frequency of presence of different criteria has been described. This provides an assessment of true clinical deterioration. As proposed, enrolled patients who refused to remain hospitalized (leaving against medical advice or LAMA) or withdraw from the study were considered as treatment failures for conservative estimates of treatment success on oral amoxicillin when the clinical outcome is unknown or patient may not have completed the prescribed course of antibiotic. However, it overestimated the rates of treatment failure in the hospitalized group not due to true clinical deterioration. Lack of information on those who leave the trial could threaten the external validity of the results. We thus have described the causes for treatment failure by treatment groups at < 7 days and between day 8 – day 14 in Table 7 (p. 38) and Table 8 (p. 39) respectively. More careful monitoring of the patients by physicians in the hospital may also have enabled early detection of clinical deterioration in the hospital group as compared to home group, and could have potentially increased the failure rate in the hospital group. However, clinical deterioration at < 7 days was not significantly different between the groups indicating that it did not cause a potential bias in this study. The rates of loss to follow-up and voluntary withdrawal were similar in both groups at < 7 days. These concerns reflect on-the-ground realities in management of clinically diagnosed severe pneumonia.

Using the intention to treat analysis, the power of the study for the current analysis for the primary study objective of treatment failures at day 7 was 97% with a loss to follow up rate of < 1%. However, this does not include any adjustments for the interim analysis or non-compliance. This was despite not achieving the proposed sample size which was expected to be a threat to the validity of the results. The first interim analysis was performed in April 2010 by the DSMB to ensure safety of the patients. This sample size is lower than the sample size needed to detect a 5% difference with power of 90% and 1% loss to follow up when the assumed failure rate in the hospitalized group is estimated at 11% and that in the home group is estimated at 16%. This power

was achieved with the current sample size because LAMA contributed to high failure rates in the hospitalized group thus increased the detectable difference to > 5% between the two groups.

The screening data shows that consenting for the trial was a challenge and was the most common reason for exclusion (44%). Receiving antibiotics and presence of danger signs children were the third (4.7%) and fourth common reasons for exclusion (4%). There is a concern that exclusion of children with additional risk factors such as measles, severe malnutrition, and those with radiological consolidation limits the external validity of the results. However, these were uncommon reasons as most seriously ill children with presence of danger signs would be immediately admitted to hospital and would not undergo the screening process. Similarly site heterogeneity also may limit this generalizability. Excluding patients with consolidation could also exclude those with bacterial pneumonia, while those children with fever, wheeze and infiltrates are more likely to be of non-bacterial causes or viral pneumonias. We excluded children with previous history of wheeze to minimize including children with allergic bronchitis. However, in developing countries, mixed viral and bacterial infections are not uncommon, and hence need to be treated with antibiotics.

Lastly, multiplicity of end points or a composite of end points of treatment failure that includes many conditions such as clinical deterioration, hospitalization, development of co-morbid conditions, changing antibiotics etc. do provide statistical efficiency but at the risk of difficulties with interpretation. Similarly, including treatment failures due to leaving against medical advice, lost to follow up or voluntary withdrawal can overestimate treatment failures and may not indicate true clinical deterioration, again causing difficulties with interpretation. Therefore, we analyzed treatment failure on intention to treat as well as per protocol basis.

Finally an important strength of the study is the information it provides on cost of treatment and the differences in cost in the hospitalized and home group. This will help greatly to guide policy for the case management of severe pneumonia in the developing countries.

14. Recommendations

For severe pneumonia or very severe disease, the WHO recommends that provider's administer the first dose of the appropriate antibiotic and give an urgent referral for hospitalization for parenteral (injectable) antibiotics and other supportive therapy [10].Considering the financial and logistics problems faced by many parents for urgent referral for hospitalization, the ISPOT study investigators hypothesized that if oral amoxicillin administered at home was found to be equally efficacious as that administered for the first 48 hours at the hospital it would have important implications for the for families and the health system.. Benefits of home-based treatment could include: improved coverage at the community level (particularly where referral is not possible), reduced costs of treatment for the community, reduced wages-lost for families, decreased risk of cross infection and needle-associated complications in hospital, and reduced need for referral and demand on the scant inpatient services.

One of the limitations of home treatment could be the acceptance of home-based treatment. It was observed in both APPIS and NO-SHOTS that parents accept home-based treatment for severe pneumonia, and in fact many preferred it as it saves transportation costs and cost of treatment. Parental acceptance of home-based treatment was also similar in this study. On the other hand hospitalization was a barrier to enroll patients due to refusal to consent by the caregiver and LAMA was the commonest cause for treatment failure in the hospitalized group. Therefore contrary to conventional thinking, urban parents prefer to treat the child at home. Rural populations who have difficulty with transportation to referral units are also most likely to prefer home treatment.

This study's results are also in line with the findings from previous studies (APPIS and NOSHOTS) and home-based oral amoxicillin has been found to be equivalent to hospital-administered oral amoxicillin and 48 hours of observation preceding discharge. Additionally, the cost of treating at home is significantly less. This study thus strengthens the evidence for modifying treatment guidelines to recommend oral amoxicillin given at home for treatment of severe pneumonia. Once these guidelines are framed for the national program for management of pneumonia, they could be followed by the public health delivery systems in India which has potentials for greater outreach. The auxiliary nurse midwives and the Accredited Social Health Activist (ASHA) workers of the National Rural Health Mission could be trained to recognize the symptoms and signs of severe pneumonia (as a part of the integrated management of childhood and neonatal illness) in under five children and initiate early therapy. This ameliorates the need for hospital referral for children who have the ability to take oral medications, do not have presence of danger signs and do not have co-morbid conditions or risk factors such as measles or malnutrition. For its optimal efficacy, training of the health personnel delivering this treatment and of the mothers to recognize clinical deterioration if their child does not respond is needed. In order to ensure safe and effective therapy for pneumonia at home, parents and ASHA workers have to be counseled regarding symptoms and signs of clinical deterioration so that they bring the child immediately to hospital if the child fails to improve on oral therapy at home. Thus, treating selected children with severe pneumonia in the home is not only cost saving but also has the potential to substantially reduce pneumonia morbidity and mortality in under five children who fail to receive timely care due to hospital referral.

However, more research needs to be done to identify the feasibility of, and the barriers experienced in, such training of the health care providers towards correct identification of the patient group who

is likely to benefit with oral therapy, identification of the signs of deterioration while on oral therapy, and identification of the patients who need to be referred in the beginning itself.

Another important risk factor for treatment failure which emerged from this study was the use of high polluting fuel in the homes of children with severe pneumonia. This endorses the need for clean cooking stoves in low resource settings where pneumonia is common in children.

These results can be now presented to policy makers at the Indian government and other stakeholders such as the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) with the recommendation that they develop/revise guidelines for community management of pneumonia in children under five in India and in other developing countries.

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16. Appendix

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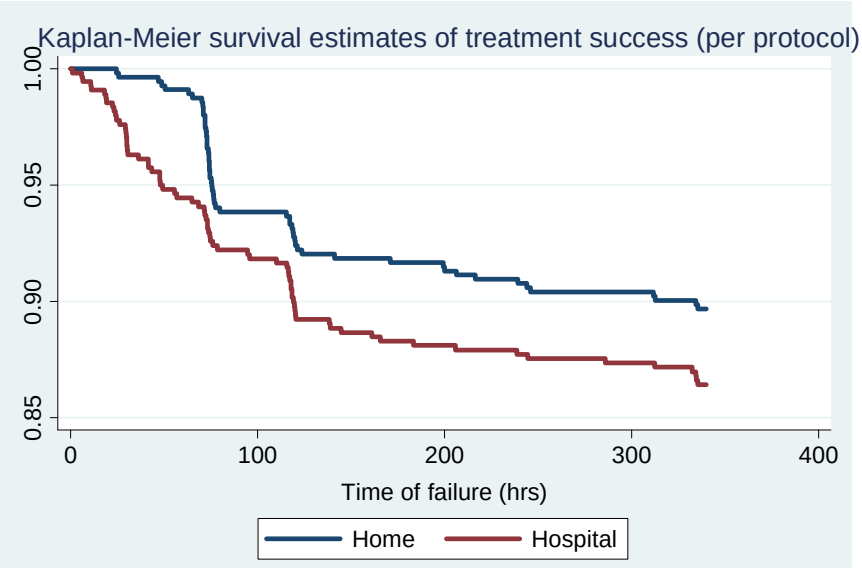
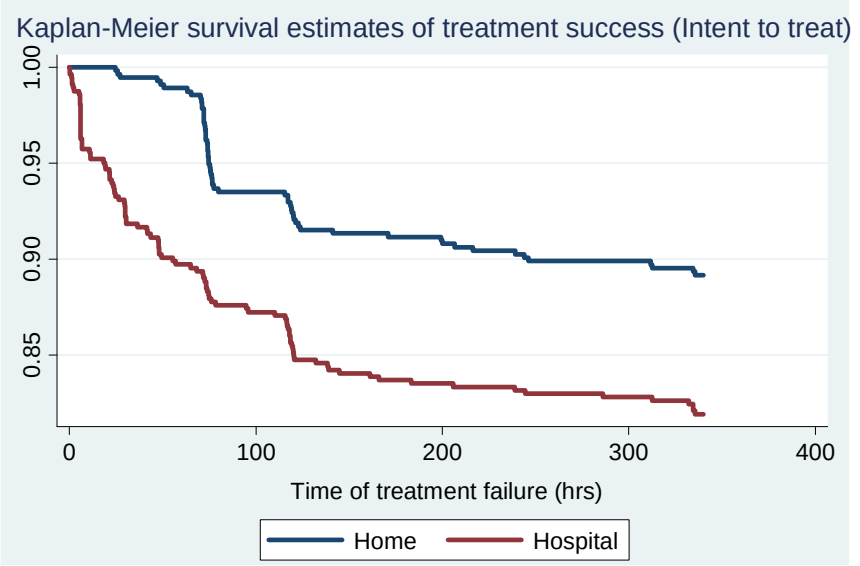
B. Kaplan-Meier Survival Estimates of Treatment Success at Any Time Point (by hour) Using per Protocol and Intention to Treat Analysis for up to 14 days.

Characteristic	Per-protocol analysis				Intention to treat analysis			
	Hazard ratio	95 % CI		p-value	Hazard ratio	95 % CI		p-value
Treatment group								
Home	1.00				1.00			
Hospital	1.34	0.95	1.90	0.10	1.79	1.30	2.46	0.00





C. Cumulative Treatment Failure at Less than 72 hours, Less than 5 days, and Equal to or Less than 14 Days by Treatment Group

Primary Outcome	Treatment failure at < 72 hrs								Cumulative treatment failure on < 5 day								Cumulative treatment failure on ≤ 14 days							
	Home group		Hospital group		Difference %	Difference % 95 % CI		P value	Home group		Hospital group		Difference %	Difference % 95 % CI		P value	Home group		Hospital group		Difference %	Difference % 95 % CI		P value
	N= 554	%	N= 564	%					N= 554	%	N= 564	%					N= 554	%	N= 564	%				
Total	14	2.5	62	11.0	-8.5	-11.4	-5.6	0.00	42	7.6	83	14.7	-7.1	-10.8	-3.5	0.00	60	10.8	102	18.1	-7.3	-11.4	-3.2	0.00
Clinical deterioration	12	2.2	33	5.9	-3.7	-6.0	-1.4	0.00	30	5.4	41	7.3	-1.9	-4.7	1.0	0.10	31	5.6	43	7.6	-2.0	-4.9	0.9	0.09
Voluntary withdrawal	2	0.4	1	0.2	0.2	-0.4	0.8	0.72	5	0.9	1	0.2	0.7	-0.1	1.6	0.95	5	0.9	1	0.2	0.7	-0.1	1.6	0.95
Lost to follow-up	2	0.4	0	0.0	0.4	-0.1	0.9	0.92	2	0.4	0	0.0	0.4	-0.1	0.9	0.92	3	0.5	1	0.2	0.4	-0.3	1.1	0.85
LAMA	0	0.0	29	5.1	-5.1	-7.0	-3.3	0.00	0	0.0	29	5.1	-5.1	-7.0	-3.3	0.00	0	0.0	29	5.1	-5.1	-7.0	-3.3	0.00
Death	1	0.2	1	0.2	0.0	-0.5	0.5	0.51	1	0.2	1	0.2	0.0	-0.5	0.5	0.50	1	0.2	1	0.2	0.0	-0.5	0.5	0.50
LCI + Fever (>98.6 F)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	21	3.8	15	2.7	1.1	-0.9	3.2	0.86	23	4.2	17	3.0	1.1	-1.0	3.3	0.85
LCI alone	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	17	3.1	24	4.3	-1.2	-3.4	1.0	0.15
Fever alone (>98.6 F)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	16	2.9	17	3.0	-0.1	-2.1	1.9	0.45
Fast breathing	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	2	0.4	0	0.0	0.4	-0.1	0.9	0.92

D. Unadjusted and adjusted analysis for predictors of treatment failure at < 7 days (per-protocol and intention to treat analysis).

Characteristic	Cumulative Treatment failure at ≤ 7 days (Per-protocol analysis)								Cumulative Treatment failure at ≤ 7 days (Intention to treat analysis)							
	Unadjusted				Adjusted				Unadjusted				Adjusted			
	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value
Treatment group																
Home	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Hospital	1.42	0.95	2.13	0.09	1.43	0.94	2.17	0.09	2.05	1.42	2.98	0.00	1.84	1.25	2.71	0.00
Age group																
Infants (3-11 months old)	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Children (12-59 months old)	0.71	0.48	1.06	0.09	0.58	0.38	0.89	0.01	0.68	0.48	0.97	0.04	0.68	0.47	1.00	0.05
Exclusive breast feeding																
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	2.30	1.40	3.77	0.00	2.04	1.20	3.46	0.01	1.79	1.19	2.71	0.01	1.99	1.27	3.11	0.00
Antibiotics prior to enrollment																
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	1.46	0.82	2.62	0.20	1.86	1.00	3.45	0.05	1.67	1.00	2.78	0.05	1.84	1.06	3.20	0.03
Weight for age Z-score	1.10	0.94	1.28	0.25					1.05	0.91	1.20	0.50				
Temperature	1.11	0.97	1.27	0.13					1.06	0.94	1.20	0.32				
Respiratory rate per min	0.98	0.96	1.00	0.05					0.99	0.97	1.01	0.47				
Pulse oximetry	1.09	1.01	1.17	0.03					1.03	0.97	1.09	0.37				
Auscultatory wheeze																
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-				
Yes	0.50	0.34	0.76	0.00	0.62	0.40	0.97	0.04	0.69	0.48	0.98	0.04				
Any infiltrates in chest X-ray																
No	1.00	-	-	-					1.00	-	-	-				
Yes	1.74	1.10	2.74	0.02					1.22	0.83	1.79	0.31				
No. of rooms in house	1.09	0.95	1.24	0.22					0.96	0.84	1.10	0.60				
Fuel used for cooking																
Low polluting fuel	1.00	-	-	-					1.00	-	-	-				
High polluting fuel	0.99	0.66	1.47	0.95					1.12	0.77	1.62	0.54				

Characteristic	Cumulative Treatment failure at ≤ 7 days (Per-protocol analysis)								Cumulative Treatment failure at ≤ 7 days (Intention to treat analysis)							
	Unadjusted				Adjusted				Unadjusted				Adjusted			
	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value
Site																
Chandigarh	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Chennai	0.18	0.09	0.35	0.00	0.24	0.12	0.48	0.00	0.62	0.39	0.97	0.04	0.53	0.33	0.86	0.01
Nagpur	0.59	0.37	0.94	0.03					0.69	0.44	1.07	0.10				
Pune	2.41	0.60	9.58	0.21					3.67	1.00	13.40	0.05	3.82	0.98	14.84	0.05
Aligarh	0.50	0.15	1.67	0.26					0.67	0.23	1.95	0.46				
Sevagram	0.62	0.24	1.64	0.34					0.75	0.31	1.84	0.53				

Notes: Independent variables adjusted for are : Treatment group, age group, exclusive breastfeeding, antibiotics prior to enrollment, weight for age Z-score, temperature, respiratory rate per min., pulse oximetry, auscultatory wheeze, any infiltrates in chest X-ray, no. of rooms in house, fuel used for cooking, study site.

E. Unadjusted and adjusted analysis for predictors of treatment failure at > 7 days to < 14 days (Intent to treat analysis and per protocol analysis the same).

Characteristic	Cumulative Treatment failure at > 7 to ≤ 14 days							
	Unadjusted				Adjusted			
	OR	95 % CI		p-value	OR	95 % CI		p-value
Treatment group								
Home	1.00	-	-	-	1.00	-	-	-
Hospital	0.82	0.35	1.90	0.64	0.89	0.37	2.15	0.79
Age group								
Infants (3-11 months old)	1.00	-	-	-				
Children (12-59 months old)	0.70	0.30	1.64	0.42				
Exclusive breast feeding								
No	1.00	-	-	-				
Yes	0.74	0.31	1.75	0.50				
Antibiotics prior to enrollment								
No	1.00	-	-	-				
Yes	0.87	0.20	3.76	0.85				
Weight for age Z-score	1.09	0.79	1.51	0.60				
Temperature	0.86	0.64	1.15	0.31				
Respiratory rate per min	0.99	0.95	1.03	0.64				
Pulse oximetry	1.14	0.96	1.35	0.13				
Auscultatory wheeze								
No	1.00	-	-	-	1.00	-	-	-
Yes	2.38	0.93	6.14	0.07	2.71	0.95	7.69	0.06
Any infiltrates in chest X-ray								
No	1.00	-	-	-				
Yes	1.20	0.48	2.97	0.70				
No. of rooms in house	1.20	0.94	1.54	0.15				
Fuel used for cooking								
Low polluting fuel	1.00	-	-	-	1.00	-	-	-
High polluting fuel	4.75	1.40	16.16	0.01	3.37	0.94	12.14	0.06
Study Site								
Chandigarh	1.00	-	-	-	1.00	-	-	-
Chennai	0.23	0.03	1.96	0.18	0.12	0.02	0.94	0.04
Nagpur	2.18	0.72	6.58	0.17				
Pune	8.27	0.87	78.16	0.07	15.57	1.48	163.85	0.02
Aligarh								
Sevagram	10.15	2.97	34.61	0.00	5.46	1.96	15.20	0.00

F. Unadjusted and adjusted analysis predictors of treatment failure < 72 hours, < 5 days and <= 14 days (Per-protocol analysis).

Characteristic	Treatment failure at < 72 hrs								Cumulative Treatment failure at < 5 days								Cumulative Treatment failure at ≤ 14 days							
	Unadjusted				Adjusted				Unadjusted				Adjusted				Unadjusted				Adjusted			
	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value	OR	95 % CI		p-value
Treatment group																								
Home	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Hospital	2.90	1.48	5.66	0.00	3.04	1.54	6.00	0.00	1.39	0.91	2.12	0.13	1.44	0.93	2.24	0.10	1.30	0.90	1.87	0.17	1.33	0.90	1.95	0.15
Age group																								
Infants (3-11 months old)	1.00	-	-	-					1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Children (12-59 months old)	1.01	0.56	1.83	0.96					0.82	0.54	1.25	0.35	0.59	0.37	0.94	0.03	0.70	0.48	1.01	0.06	0.58	0.39	0.86	0.01
Exclusive breast feeding																								
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Yes	2.99	1.32	6.75	0.01	2.31	0.98	5.40	0.05	2.19	1.31	3.69	0.00	1.73	0.98	3.05	0.06	1.84	1.20	2.82	0.01	1.53	0.95	2.45	0.08
Antibiotics prior to enrollment																								
No	1.00	-	-	-					1.00	-	-	-					1.00	-	-	-	1.00	-	-	-
Yes	1.60	0.70	3.66	0.27					1.43	0.77	2.65	0.26					1.36	0.78	2.36	0.27	1.85	1.03	3.34	0.04
Weight for age Z-score	1.04	0.82	1.30	0.76					1.12	0.95	1.31	0.18					1.10	0.95	1.27	0.19				
Temperature	1.14	0.93	1.39	0.20					1.18	1.02	1.36	0.03					1.06	0.94	1.20	0.34				
Respiratory rate per min	0.96	0.93	0.99	0.01	0.97	0.93	1.00	0.06	0.97	0.95	1.00	0.02	0.98	0.95	1.00	0.07	0.98	0.96	1.00	0.04				
Pulse oximetry	1.13	1.00	1.26	0.05					1.10	1.02	1.20	0.01					1.10	1.03	1.18	0.01	0.93	0.85	1.01	0.08
Auscultatory wheeze																								
No	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-					1.00	-	-	-				
Yes	0.37	0.20	0.70	0.00	0.56	0.28	1.12	0.10	0.44	0.28	0.68	0.00					0.65	0.45	0.95	0.02				
Any infiltrates in chest X-ray																								
No	1.00	-	-	-					1.00	-	-	-					1.00	-	-	-				
Yes	1.82	0.91	3.62	0.09					1.92	1.17	3.15	0.01					1.65	1.09	2.49	0.02				
No. of rooms in house	1.07	0.87	1.30	0.52					1.09	0.94	1.25	0.25					1.12	0.99	1.26	0.08				
Fuel used for cooking																								
Low polluting fuel	1.00	-	-	-					1.00	-	-	-					1.00	-	-	-	1.00	-	-	-
High polluting fuel	0.79	0.44	1.43	0.44					0.92	0.60	1.40	0.69					1.24	0.85	1.81	0.26	1.50	0.99	2.29	0.06
Site																								
Chandigarh	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-	1.00	-	-	-
Chennai	0.19	0.07	0.51	0.00	0.42	0.16	1.11	0.08	0.17	0.08	0.34	0.00	0.20	0.10	0.41	0.00	0.18	0.09	0.34	0.00	0.10	0.04	0.22	0.00
Nagpur	0.41	0.19	0.85	0.02					0.44	0.26	0.74	0.00	0.44	0.25	0.77	0.00	0.72	0.46	1.10	0.13	0.49	0.30	0.80	0.00
Pune	1.38	0.17	11.33	0.76					0.65	0.08	5.24	0.69					3.39	0.93	12.36	0.07				
Aligarh	0.35	0.05	2.62	0.30					0.52	0.15	1.74	0.29					0.45	0.13	1.51	0.19				
Sevagram	0.25	0.03	1.91	0.18					0.65	0.25	1.71	0.38					1.43	0.70	2.95	0.33				

Notes: Independent variables adjusted for are : Treatment group, age group, exclusive breastfeeding, antibiotics prior to enrollment, weight for age Z-score, temperature, respiratory rate per min., pulse oximetry, auscultatory wheeze, any infiltrates in chest X-ray, no. of rooms in house, fuel used for cooking, study site .

Inclusion criteria in adjusted model: P-value<=0.10

Per protocol - By excluding LAMA , Loss to follow up and Voluntary withdrawal