

Does 3-Day Course of Oral Amoxicillin Benefit Children of Non-Severe Pneumonia with Wheeze: A Multicentric Randomised Controlled Trial

Shally Awasthi^{1*}, Girdhar Agarwal², Sushil K. Kabra³, Sunit Singhi⁴, Madhuri Kulkarni⁵, Vaishali More⁵, Abhimanyu Niswade⁶, Raj Mohan Pillai⁷, Ravi Luke⁸, Neeraj M. Srivastava¹, Saradha Suresh⁸, Valsan P. Verghese⁹, P. Raghupathy⁹, R. Lodha³, Stephen D. Walter¹⁰

1 King George's Medical University, Lucknow, India, **2** Lucknow University, Lucknow, India, **3** All India Institute of Medical Science, New Delhi, India, **4** Post Graduate Institute of Medical Sciences, Chandigarh, India, **5** Lok Manya Tilak Medical College, Mumbai, India, **6** Government Medical College, Nagpur, India, **7** Government Medical College, Trivandrum, India, **8** Madras Medical College, Chennai, India, **9** Christian Medical College, Vellore, India, **10** McMaster University, Hamilton, Canada

Abstract

Background: WHO-defined pneumonias, treated with antibiotics, are responsible for a significant proportion of childhood morbidity and mortality in the developing countries. Since substantial proportion pneumonias have a viral etiology, where children are more likely to present with wheeze, there is a concern that currently antibiotics are being over-prescribed for it. Hence the current trial was conducted with the objective to show the therapeutic equivalence of two treatments (placebo and amoxicillin) for children presenting with non-severe pneumonia with wheeze, who have persistent fast breathing after nebulisation with salbutamol, and have normal chest radiograph.

Methodology: This multi-centric, randomised placebo controlled double blind clinical trial intended to investigate equivalent efficacy of placebo and amoxicillin and was conducted in ambulatory care settings in eight government hospitals in India. Participants were children aged 2–59 months of age, who received either oral amoxicillin (31–54 mg/Kg/day, in three divided doses for three days) or placebo, and standard bronchodilator therapy. Primary outcome was clinical failure on or before day- 4.

Principal Findings: We randomized 836 cases in placebo and 835 in amoxicillin group. Clinical failures occurred in 201 (24.0%) on placebo and 166 (19.9%) on amoxicillin (risk difference 4.2% in favour of antibiotic, 95% CI: 0.2 to 8.1). Adherence for both placebo and amoxicillin was >96% and 98.9% subjects were followed up on day- 4. Clinical failure was associated with (i) placebo treatment (adjusted OR = 1.28, 95% CI: 1.01 to 1.62), (ii) excess respiratory rate of >10 breaths per minute (adjusted OR = 1.51, 95% CI: 1.19, 1.92), (iii) vomiting at enrolment (adjusted OR = 1.49, 95% CI: 1.13, 1.96), (iv) history of use of broncho-dilators (adjusted OR = 1.71, 95% CI: 1.30, 2.24) and (v) non-adherence (adjusted OR = 8.06, 95% CI: 4.36, 14.92).

Conclusions: Treating children with non-severe pneumonia and wheeze with a placebo is not equivalent to treatment with oral amoxicillin.

Trial Registration: ClinicalTrials.gov NCT00407394

Citation: Awasthi S, Agarwal G, Kabra SK, Singhi S, Kulkarni M, et al. (2008) Does 3-Day Course of Oral Amoxicillin Benefit Children of Non-Severe Pneumonia with Wheeze: A Multicentric Randomised Controlled Trial. PLoS ONE 3(4): e1991. doi:10.1371/journal.pone.0001991

Editor: Tammy Clifford, Canadian Agency for Drugs and Technologies in Health, Canada

Received: July 20, 2007; **Accepted:** February 29, 2008; **Published:** April 23, 2008

Copyright: © 2008 Awasthi et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Funding: US AID through INCLen and IndiaClen

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: sawasthi@sancharnet.in

Introduction

Acute lower respiratory infections (ALRI) are a leading cause of morbidity and mortality in children under five years of age in developing countries and are responsible for an estimated 2.6 million deaths annually [1–3]. Wheezing and reactive airways disease is associated with or contributory to a significant proportion of childhood acute respiratory infections (ARI) [4–6]. The current Integrated Management of Childhood Illness (IMCI) algorithm prescribes that children with wheeze and fast breathing

presenting to first level health facilities be given antibiotics if they continue to have fast breathing after two doses of bronchodilators [7]. However, an unknown proportion of children managed thus will have viral related wheezing illness like bronchiolitis and asthma rather than pneumonia, where antibiotics may not alter the course of disease. Using IMCI algorithms are likely to result in unnecessary administration of antibiotics as well as inadequate treatment of wheeze [8].

Since our study hypothesis was that when given with an oral bronchodilator, 3-days treatment with either oral amoxicillin or

oral placebo would be as effective, in terms of clinical cure on day-4, we designed a double blind equivalence trial. [9]. The goal of this trial was to assess whether children of non-severe pneumonia with wheeze can be effectively managed without antibiotics and to identify which sub-group of cases do require antibiotics.

Methods

This was a multi-centric, double blind placebo-controlled randomised trial conducted in outpatient departments of 8 referral hospitals in India. Individual institutional ethics committees' as well as the IndiaClen Institutional Review Board approved the study. It was designed for equivalence of two modes of therapy with a predefined range of equivalence as an interval from -5% to $+5\%$. The trial was registered with the Clinical Trials registry (NCT00407394). The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Two-stage screening was done (verbal followed by standardised screening) for inclusion and exclusion criteria. Children aged 2–59 months were verbally screened for complaints of cough, rapid respiration, or difficulties in breathing. Excluded were those with signs of WHO defined severe pneumonia or very severe disease [7], other conditions requiring antibiotics therapy, clinically recognized congenital heart disease, chronic systemic disorders, hospitalisation in past 2 weeks, use of antibiotics in previous 2 days, measles within the last month, history of penicillin allergy and prior enrolment in the study. Those who were verbal screening positive and had no exclusion criteria were examined for study entry criteria, which were audible or auscultatory wheeze and WHO defined fast breathing, that is respiratory rate of ≥ 50 per minute (for age 2–11 months) or ≥ 40 per minute (for age 12–59 months) [10]. Those who fulfilled the study entry criteria were given a maximum of three doses of salbutamol (400 microgm/dose) by either a nebuliser or metered dose inhaler and their respiratory rate was reassessed. If fast breathing persisted above WHO defined age specific cut-offs, a chest radiograph was taken for diagnosing radiological pneumonia, defined as presence of fluids, parenchymal infiltrates or consolidation [10]. Those with radiological pneumonia were treated according to the standard hospital treatment guidelines. The rest were invited to participate in the study. Those who accepted the invitation were requested to provide informed written parental consent in local language. Local languages used were site specific and were Hindi for Lucknow, Delhi and Chandigarh sites, Marathi for Nagpur and Mumbai sites, Tamil for Chennai and Vellore site and Malayali for Trivandrum site. Children of parents consenting for participation were randomised to receive amoxicillin or placebo and continued with oral salbutamol. Coordinating centre ensured standardised training and quality assurance.

Follow up

All the participants were followed up on day-4 and between days 11–14 days. Home visits were done within 24 hours for those who failed to report on the appointed days. Children who failed on therapy, developed adverse reactions or withdrew consent were treated according to standard hospital guidelines.

Intervention

Participants received either amoxicillin, 31–54 mg/Kg/day, in three divided doses, or placebo, which looked and tasted similar to amoxicillin, in three divided doses orally. In addition all participants also received oral salbutamol, 2.5 ml or 5 ml thrice a day for ages 2–11 months and 12–59 months, respectively (each 5 ml = 2 mg

salbutamol). Patients with fever also received paracetamol (10–15 mg/kg/dose) in addition to the study intervention.

Objectives

The primary objective was to compare the proportions of eligible cases that achieve clinical cure on day-4 on three-days of treatment with either oral amoxicillin or placebo. Our secondary objective was to compare the proportions that clinically relapsed within the next 11–14 days, as well as identify the determinants, if any, of clinical failure. Secondary laboratory outcome was the proportions positive for respiratory syncycial virus (RSV) in nasopharyngeal aspirate at enrolment.

Outcome measures

Main outcome measure was clinical cure on day-4, defined as those who were not assessed to have clinical failure. Clinical failure was defined as either (i) development of WHO-defined severe pneumonia or very severe disease (with or without wheeze) before or on day-4 assessment, or (ii) oxygen saturation on pulse oximetry $< 90\%$ before or on day-4 assessment or (iii) axillary temperature > 101 degrees F on day-4 assessment, or (iv) persistence of WHO-defined non-severe pneumonia on day-4 assessment, or (v) presence of wheeze on day-4 assessment. Loss to follow up on day-4 or withdrawal from the study at any time after recruitment was also considered as therapy failure in the intention-to-treatment (ITT) analysis. Clinical relapse was defined as cases, which were clinically cured on day-4 assessment, but at days-11-14 follow-up showed signs of WHO-defined pneumonia.

Sample size

This was calculated for therapeutic equivalence of two treatments (placebo and amoxicillin). It was assumed that the overall failure rate would be 17% if the treatments were equivalent [5]. We used $\delta = 0.05$ to be the range of equivalence for the difference in failure rates. To detect this difference using Type I error probability (alpha) of 0.05 and power of 0.9, the required size of each treatment group was 970.

Randomisation

A professional not associated with clinical care (GGA) generated the randomization scheme at Lucknow. Randomised block sizes of two to four were used to avoid any uneven distribution of patients between two interventions. Unlabelled medicines were placed in serially numbered opaque envelopes by the pharmacy. Doses were provided for a maximum weight of 20 Kg. Extra doses were kept for administration to a child who vomited within 30 minutes of dosing. Health care workers, patients as well as research staff and investigators were blinded.

Adherence

Adherence was assessed by pill count on day-4 follow-up. Non-adherence was defined as intake of less than 7 doses.

Laboratory procedures

A chest radiograph was taken prior to randomisation. Nasopharyngeal aspirate was tested at enrolment for RSV using Directogen^R kit (manufactured by Becton Dickinson and Company, Sparks MD 21152, USA).

Statistical Analysis

Primary analyses were done on ITT basis. Per protocol analysis was also done on subjects with complete follow-up and adherence to treatment. We have used the two one-sided tests (TOST)

procedure as well as the confidence interval approach for assessing therapeutic equivalence of two treatments [11]. Baseline and other characteristics were compared between the two regimens. Association of clinical failure with different characteristics of patients was assessed. Chi-squared test was used for testing two-sided hypotheses, whereas Z-test was used to test one-sided hypotheses. A p value of <0.05 was considered to be statistically significant. Crude odds ratios and 95% confidence intervals were computed. The covariates, which were found to be significant or nearly significant ($p \leq 0.10$) in univariate analysis, were included to construct a multivariate model for assessing determinants of treatment failure by forward stepwise logistic regression. In the later model, we also investigated the possibility of variables acting as effect modifier for the risk factors. Final model included covariates that were statistically significant. The primary outcome measure was also assessed for each site and the overall odds ratio after stratifying for site was obtained. Mantel-Haenszel statistic for

testing independence of clinical failure with interventions, adjusting for site was used. Breslow-Day statistic for testing three-factor interaction of clinical failure, interventions and site was used. Data were analyzed using statistical software "Statistical Package for Social Sciences" (SPSS) 11.0 version.

Results

Population

We nebulised 3487 children of non-severe pneumonia with wheeze and in 46% ($n = 1604$), the respiratory rate returned to below age-specific cut-off (Figure 1). From among the remaining, we recruited 1671 patients from February 2004 to July 2006 (Figure 1), 836 in the placebo and 835 in the amoxicillin group. Loss to follow-up was 1% ($n = 8$) and 1.2% ($n = 12$) in the placebo and amoxicillin groups by day-4, respectively and 3.6% ($n = 30$) and 4.6% ($n = 38$), respectively by days-11-14.

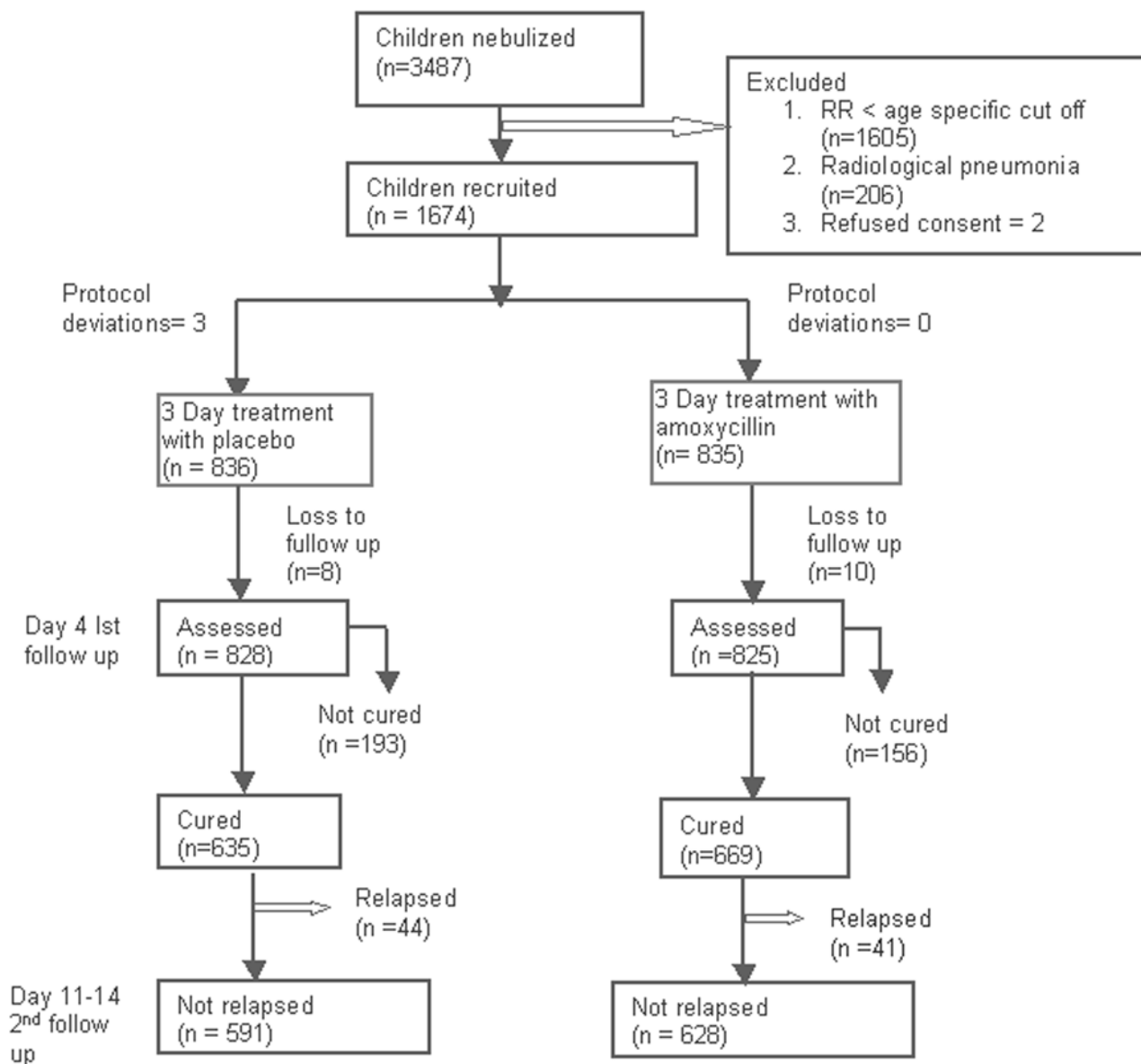


Figure 1. CONSORT Statement for the trial.

doi:10.1371/journal.pone.0001991.g001

Baseline characteristics

There were no substantial differences in the baseline characteristics of the treatment groups (Table 1).

Adherence to therapy

Adherence, defined as intake of 7 or more doses, for placebo was 96.1% (791/823) and amoxicillin was 97.8% (801/819) with the difference of -1.7% (95% CI: -3.3 to -0.03). In the placebo and amoxicillin groups 88.1% (675/766) and 90.1% (686/761)

took 7 or more doses of oral bronchodilators (difference -2.0%; 95% CI: -5.1 to 1.1).

Primary and secondary Clinical Outcomes

On ITT analysis, the clinical failure rates were 24.0% (201/836) and 19.9% (166/835) in the placebo and amoxicillin groups, respectively, and the rate difference was 4.2% (95% CI: 0.2 to 8.2) (Table 2). Comparing clinical failures in the two groups on per protocol analysis gave very similar results. Here the confidence interval for the risk difference ($p_A - p_B$) between the two treatments covers at least some points which lie outside the equivalence range ($-\delta, +\delta$). Note that δ , the magnitude of difference of clinical importance is taken to be 5.0% here. Now we used TOST approach and tested one-sided hypothesis that the placebo is non-inferior to amoxicillin, i.e. $H_0: p_A - p_B \geq \delta$ (in-equivalence) vs $H_1: p_A - p_B < \delta$ (equivalence). The corresponding test-statistic is $z = -0.41$ ($p = 0.34$) (Table 2). We conclude, therefore, that the hypothesis of “in-equivalence” cannot be disproved. The numbers needed to treat (NNT) to avoid one clinical failure (or get one additional cure) using amoxicillin is 24.

Among clinical failures on day- 4, 82.9% (160/193) in the placebo group and 83.9% (131/156) in the amoxicillin group had wheeze with or without any sign of hypoxia (oxygen saturation on pulse-oximetry $< 90\%$), severe pneumonia, very severe disease or axillary temperature $> 101^\circ\text{F}$. Only those with associated wheeze at the time of failure were at increased risk of having respiratory rate above age specific cut-off in the placebo group (OR = 6.0, 95% CI: 2.6–13.7; p value < 0.001) as well as in the amoxicillin group (OR = 4.4, 95% CI: 1.7–11.2; p value = 0.001).

There was also no difference by group in the proportion of clinical relapses, among those diagnosed as cure on day- 4 (Table 2).

Secondary laboratory Outcome

RSV antigen was positive in 5.6% (88/1558) at enrolment (Table 1).

Risk factors associated with clinical failure

Significant univariate association of clinical failure were found with current history of fever and use of liquid petroleum gas for cooking at home (Table 3), but these were not significant in the multiple regressions. Variables which had significant association in both univariate and the multiple logistic regression model with clinical failure were current history of vomiting, past history of use of bronchodilator, excess respiratory rate of > 10 breaths per minute above age specific cut-off and non-adherence (Table 4); the adjusted odds ratio for clinical failure with the use of placebo was 1.28 (95% CI: 1.01 to 1.62; p value = 0.04).

Adverse reactions

These had similar frequencies in both arms. There were no deaths and 30 hospitalisations (15 in each group). There were 11 cases of nausea and mild vomiting, 2 cases of diarrhoea with some dehydration, 9 cases of diarrhoea with no dehydration, 1 rash without itch, and 1 case of tremors.

Discussion

This was a randomised, double blind placebo controlled trial to assess whether children of non-severe pneumonia with wheeze can be effectively managed without antibiotics. We have found that clinical failure was associated with placebo treatment (adjusted OR = 1.28, 95% CI: 1.01 to 1.62). Other variables associated with clinical failure on multivariable analysis were history of vomiting,

Table 1. Comparison of Baseline characteristics of patients' pneumonia by treatment type.

CONTINUOUS VARIABLES	Placebo	Amoxicillin
	(n = 836)	(n = 835)
	Mean, SD	Mean, SD
Age (months)	19.5, 14.3	20.0, 14.6
Weight (Kg)	9.1, 2.5	9.2, 2.7
Height (Cm)	76.4, 12.1	76.6, 12.4
Duration of illness (days)	3.9, 1.8	3.8, 1.8
Temperature ($^\circ\text{Fahrenheit}$)	98.9, 0.9	98.9, 0.9
Respiratory Rate (breaths/minute)	52.6, 7.3	52.5, 7.5
Heart Rate (per minute)	115.8, 16.5	115.5, 16.4
CATEGORICAL VARIABLES	Placebo	Amoxicillin
	(n, %)	n, %
Female	301, 35.9	300, 35.9
Age 2–11months	334, 39.8	322, 38.6
Weight for height < -3 SD	33, 3.9	33, 4.0
History of Current Illness		
Duration of illness ≥ 3 days	651, 77.6	637, 76.3
Fever	468, 55.8	470, 56.3
Vomiting	183, 21.8	164, 19.6
Diarrhoea	8, 1.0	5, 0.6
History of Allergic disorders in subject		
Asthma	109, 13.0	107, 12.8
Allergic rhinitis	55, 6.6	54, 6.5
Eczema	6, 0.7	4, 0.5
Urticarial rash	7, 0.8	4, 0.5
Use of Bronchodilator	184, 21.9	183, 21.9
History of exposure Pollutants		
Smoker in family	245, 29.2	271, 32.5
Biomass fuel use for cooking	349, 41.6	348, 41.7
LPG use for cooking	531, 63.3	520, 62.3
Examination		
Respiratory Rate > 10 breaths per minute above cut-off	333, 39.7	340, 40.7
Wheeze (On Auscultation)	704, 83.9	720, 86.2
Wheeze (Audible)	135, 16.1	115, 13.8
RSV positive ¹	48/778, 6.2	40/780, 5.1

¹For these variables, the results are presented in fractions, as the denominators are different.

Abbreviations:

SD: Standard deviation, RSV: Respiratory syncytial virus, LPG: Liquid Petroleum Gas

doi:10.1371/journal.pone.0001991.t001

Table 2. Comparison of outcome measures in the two treatment groups.

PRIMARY OUTCOME: FAILURE RATE	Placebo	Amoxicillin	Difference,	p value
	m/n, %	m/n, %	95% C.I.	
Intention to Treat Analysis	201/836, 24.1	166/835, 19.9	4.2 (0.2, 8.2)	0.34
Per Protocol Analysis	172/791, 21.7	140/801, 17.5	4.3 (0.3, 8.1)	0.36
SECONDARY OUTCOME: RELAPSE RATE				
Among those cured on day- 4	44/635, 6.9	41/669, 6.1	0.8 (-1.9, 3.5)	p = 0.6

Abbreviations:

m/n: numerator/denominator

CI: Confidence Interval

doi:10.1371/journal.pone.0001991.t002

Table 3. Association of clinical failure with different characteristics of patients (univariate Intention to Treat Analysis).

Variables	Clinical failure	Clinical Cure	Adjusted ² odds ratio, 95% C.I.	p-value
	(N = 367) number, %	(N = 1304) number, %		
Female	127, 34.6	473, 36.3	0.9(0.7,1.2)	0.6
Age 2–11months	157, 42.8	497, 38.1	1.2(1.0,1.5)	0.11
Malnutrition*	9, 2.5	57, 4.4	0.6(0.3,1.1)	0.10
History of Current Illness				
Duration of illness >=3days	293, 79.8	992, 76.1	1.2(0.9,1.7)	0.14
Fever	230, 62.7	707, 54.2	1.4(1.1,1.8)	0.004
Vomiting	102, 27.8	244, 18.7	1.7(1.3,2.2)	<0.001
Cough	366, 99.7	1297, 99.5	2.0(0.2,16.1)	0.5
Diarrhea	3, 0.8	10, 0.8	1.0(0.3,3.8)	0.96
Difficult breathing	0	2, 0.2		0.5
History of Allergic disorders				
Asthma	45, 12.3	171, 13.	0.9(0.7, 1.3)	0.7
Allergic rhinitis	18, 4.9	91, 7.0	0.7(0.4, 1.2)	0.2
Eczema	2, 0.5	8, 0.6	0.9(0.2, 4.1)	0.9
Urticarial rash	0	11, 0.8		0.08
Use of Bronchodilator	107, 29.2	259, 19.9	1.7(1.3, 2.2)	<0.001
History of exposure Pollutants				
Smoker in family	127, 34.6	388, 29.8	1.3(1.0, 1.6)	0.06
Biomass fuel use for cooking	162, 44.1	534, 41.0	1.1(0.9, 1.4)	0.3
LPG use for cooking	211, 57.5	837, 64.2	0.8(0.6, 1.0)	0.02
Examination				
Respiratory Rate >10 units of cut-off	172, 46.9	500, 38.3	1.4(1.1, 1.8)	0.003
Wheeze (On Auscultation)	320, 87.2	1101, 84.4	1.3(0.9, 1.8)	0.2
RSV positive ¹	16/349, 4.6	72/1206, 6.0	0.7(0.4, 1.3)	0.3
Non-Adherence¹	34/346, 9.8	16/1296, 1.2	8.5(4.6,15.6)	<0.001

*Weight-for-height < -3SD

¹For these variables, the results are expressed in fractions as their denominators are different.²Adjusted for intervention effect.

Abbreviations:

LPG: Liquid Petroleum Gas

RSV: Respiratory Syncytial Virus

CI: Confidence Interval

doi:10.1371/journal.pone.0001991.t003

Table 4. Multivariable logistic regression model for the factors associated with Clinical failure on Intention to Treat Analysis.

Variables	Crude Odds Ratio (95% C.I.)	Adjusted odds ratio (95% CI)	p value of adjusted odds' ratio
Intervention with Placebo	1.3 (1.03, 1.66)	1.28 (1.01, 1.62)	0.04
History of Current Illness			
Vomiting	1.7 (1.3,2.2)	1.50 (1.14, 1.98)	0.004
History of Allergic disorders			
Use of Bronchodilator	1.7(1.3, 2.2)	1.72 (1.31, 2.26)	<0.001
Clinical Examination			
Respiratory Rate>10 breaths per minute above cut-off	1.4 (1.1, 1.8)	1.51 (1.18, 1.92)	0.001
Non-adherence	9.0 (4.9, 16.4)	8.24 (4.46, 15.20)	<0.001

Abbreviation:

CI: Confidence Interval

doi:10.1371/journal.pone.0001991.t004

past history of use of bronchodilators, respiratory rate >10 breaths per minute above age specific cut off and non-adherence (Table 4). Therefore, there is no need for modification of the current WHO guidelines for the treatment of pneumonia [10].

This study was designed as an equivalence trial [9,11] to get as close to the truth as possible with unbiased results. Our pre-specified value of 5% defined the smallest difference (excess) in clinical failure rates with the use of placebo that would be of clinical interest. In the ITT as well as per protocol analysis, the estimated difference in clinical failure was <5% but the confidence interval covered points that lie outside the equivalence range (upper confidence limit is greater than + δ). So the differences of potential clinical importance remain a real possibility and equivalence cannot be safely concluded on the basis of “confidence interval” approach. We used the other commonly used statistical approach of TOST to avoid any ambiguity in assessing the therapeutic equivalence. The TOST approach suggests that the hypothesis of in-equivalence cannot be disproved, which would then favour the use of antibiotics. The study was originally planned to have a power of 90%, but with the estimated overall failure rate of 22% and average sample of size of 835.5, the power of current study is 79.5%. It is recommended that a further study should be planned with a greater power using the estimates of failure rate of the current study.

Clinical failure as defined in this study was a composite measure. Since presence of hypoxia, severe pneumonia and very severe disease were responsible for similar proportions of clinical failures in both the treatment groups, and since >80% of clinically failed had wheeze along with respiratory rate above the age specific cut-off, failure was possibly due to inadequate bronchodilator therapy. However, theoretically clinical failure due to inadequate antimicrobial therapy cannot also be ruled out. We used amoxicillin that is effective against most strains of *Haemophilus influenzae* and *Streptococcus pneumoniae*, which are major causes of bacterial pneumonia [12]. Since clinical failures for reasons other than fast breathings were similar in the placebo as well as antibiotic groups, it is unlikely that these subjects would have benefited with antibiotics. On the contrary, they possibly require intensive bronchodilator therapy as recommended in the guidelines for management of cases of asthma without hypoxia [13].

Previous trials of antibiotics for treatment of non-severe pneumonia have documented respiratory rate >10 breath per minute above age specific cut off as a predictor of clinical failure [5,6], as reported in the current study. A study from Pakistan reported temperature >100°F at baseline in wheezers with

pneumonia as predictive of subsequent deterioration [14] as seen by us in univariate analysis. We have not found this relationship in multivariate analysis. Therefore, fever at baseline cannot be taken as an absolute criterion for giving antibiotics. In our study 4.9% of children with clinical failure had fever above 101°F, which could be either due to bacterial or viral etiology. Those with bacterial etiology of fever could be benefited with antibiotic therapy.

Wheezing is commonly associated with viral infections, particularly due to RSV [15]. However, the sample size of RSV positive cases in this study was too small to provide a precise estimate of the association in this particular sub-group. The proportion of RSV positivity was similar to a previous study conducted in same sites, and was low [5]. Lack of association between clinical failure and RSV could be due to the small number of RSV positive patients in the current study.

In our study past history of asthma and/or use of bronchodilators was not an exclusion criteria. This was done because in young children there are multiple causes of wheezing and asthma is just one of them. Thus, we have increased the generalizability of our results. We have found that, controlling for the use of antibiotic in logistic regression model, children with past history of use of bronchodilators are at increased risk of clinical failure, which is most likely due to inadequate bronchodilator therapy. In this sub-group of children further study is needed to define the benefit of concomitant antibiotic therapy when they get fast breathing, in the range of WHO-defined non-severe pneumonia.

We have found that among cases of non-severe pneumonia and wheeze, the respiratory came back below age specific cut-offs in 46% (1605/3487) children and thus there was no need to prescribe antibiotic. Similar findings have been reported from Pakistan [15]. The IMCI guideline also recommends use of bronchodilators among wheezers before deciding to treat them as cases of pneumonia with antibiotics. Implementation of IMCI guidelines in ambulatory care settings in India as well as other developing countries with result in a substantial reduction in prescription of antibiotics for non-severe pneumonia.

From this study we have found that treating 24 cases of non-severe pneumonia with wheeze with 3-days of oral amoxicillin along with bronchodilators will avert 1 clinical failure. With these NNT, in the developed countries treating non-severe pneumonia with wheeze without antibiotics may be considered since vaccination against *Haemophilus influenzae* and *Streptococcus pneumoniae*, are a part of their Expanded Program of Immunization (EPI). However, these vaccines are not a part of the EPI program in most developed countries, hence we have to continue to treat such

children with antibiotics as well as bronchodilators to avert clinical failures as a result of bacterial pneumonia. For a 12.5 Kg child, oral amoxicillin will cost just 0.3 USD [16] and thus in 7.2 USD one failure can be averted. Given the incidence rate of 536 non-severe acute lower respiratory infections/1000 child years from India [17] of which about 13% will have also wheeze [5] this translates into an annual cost of USD 315,0000 on oral amoxicillin in India with about 1 billion population of which 15% are below 5 years of age. This cost cannot be averted for now as we found that treatment with placebo is not equivalent to that of 3-days of oral amoxicillin in such cases.

The strength of the study was that it was a multi-centric, double blind, placebo controlled trial, with good adherence and minimal follow-up in spite of ambulatory study design. Since we were using placebo to treat children of non-severe pneumonia, where antibiotics have been recommended by the WHO [10], we had to exclude those with radiological pneumonia from the trial to avoid exposing them to risky placebo treatment arm. While this has maximized the principle of avoiding harm to the patients from ethical as well as good clinical practises point of view, it has also reduced the generalizability of our findings. Since we have concluded that treatment with placebo and amoxicillin is not equivalent we have actually benefited children with radiological pneumonia by treating them with standard guidelines that does include antibiotics. Baseline and outcome variables were homogeneous across the sites. Since there was misinterpretation of radiological pneumonia, there were 3 cases of protocol deviations. We also did not investigate for microbial profile, as this is not done in routine community practise.

To conclude, treating children with non-severe pneumonia and wheeze with a placebo is not equivalent to treatment with oral amoxicillin since even though the estimated difference in clinical

failure was <5% but the confidence interval covers points, which lie outside the equivalence range (upper confidence limit is greater than +5%). Perhaps more aggressive bronchodilator therapy will also benefit such patients, especially those with history of prior use of bronchodilators. Patients with respiratory rate >10 breaths per minute above cut-off should be studied further for the benefits of antibiotic therapy.

Supporting Information

Checklist S1 CONSORT Checklist

Found at: doi:10.1371/journal.pone.0001991.s001 (0.04 MB DOC)

Protocol S1 Trial Protocol

Found at: doi:10.1371/journal.pone.0001991.s002 (0.58 MB DOC)

Acknowledgments

Data monitoring safety committee:

Stephen D Walter, McMaster University; Indu Wakhlu, King George's Medical University, Lucknow; NC Saxena, Indian Council Of Medical Research, India and J N Pande, All India Institute of Medical Sciences, New Delhi.

Author Contributions

Conceived and designed the experiments: SA VV GA SK SSinghi MK RP SSuresh PR. Performed the experiments: SA VV SK SSinghi MK VM AN RP RL NS SSuresh PR RL. Analyzed the data: SA GA SW. Contributed reagents/materials/analysis tools: SK SSinghi MK VM AN RL RL. Wrote the paper: SA GA SK SSinghi MK VM AN RP NS SW.

References

- Murray CLZ, Lopez AD (1997) Mortality by cause for eight regions of the World Global burden of disease study. *Lancet* 349: 1269–1276.
- Mulholland K (1999) Magnitude of the problem of childhood pneumonia. *Lancet* 54: 590–592.
- Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C (2002) Estimates of world wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2: 25–32.
- Kusel MM, De Klerk NH, Holt PG, Keadze T, Johnston SL (2006) Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: A birth cohort study. *Pediatr Infect Dis J* 25: 680–686.
- ISCAP Group Study, Awasthi S (2004) Three-day versus five-day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomised controlled trial. *BMJ* 328: 791.
- Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) pneumonia study group, Qazi S (2002) Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: A multicentre double-blind trial. *Lancet* 360: 835–841.
- World Health Organization (2000) Handbook of IMCI (Integrated Management of Childhood Illnesses). Available: http://202.54.104.236/intranet/cip/immunizationmanager/pdf/CAH_00_12_Ti_Contents.pdf. Accessed 2008 March 6.
- Sachdev HPS, Mahajan SC, Garg A (2001) Improving Antibiotic and bronchodilator prescription in children presenting with difficult breathing: experience from an Urban Hospital in India. *Indian Pediatr* 38: 827–838.
- Christensen E (2007) Methodology of superiority vs. equivalence trials and non-inferiority trials. *J Hepatol* 46: 947–954.
- World Health Organization (1995) The management of acute respiratory infections in children. Practical guidelines for outpatient care. Geneva: World Health Organization. pp 14–24.
- Chow S, Shao J (2002) A note on statistical methods for assessing therapeutic equivalence. *Controlled Clinical Trials* 23: 515–520.
- Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B (1998) Antimicrobial resistance and clinical effectiveness of cotrimoxazole versus amoxicillin for pneumonia among children in Pakistan: A Randomised Controlled Trial. *Lancet* 352: 270–274.
- Kallstrom TJ (2004) Evidence based asthma management. *Respir Care* 49: 783–792.
- Hazir T, Qazi S, Nisar YB, Ansari S, Maqbool S, et al. (2004) Assessment and management of children aged 1–59 months presenting with wheeze, fast breathing, and/or lower chest indrawing; results of a multi centre descriptive study in Pakistan. *Arch Dis Child* 89: 1049–1054.
- Lazzaro T, Hogg G, Barnett P (2007) Respiratory Syncytial Virus infection and recurrent wheeze/asthma in children under five years: an epidemiological survey. *J Paediatr Child Health* 43: 29–33.
- Simoes EAF, Cherian T, Chow J, Shahid-Salles SA, Laxminarayan R, et al. (2006) "Acute Respiratory Infections in Children." Disease Control Priorities in Developing Countries (2nd Edition). New York: Oxford University Press. pp 483–498.
- Broor S, Parveen S, Bharaj P, Prasad VS, Srinivasulu KN, et al. (2007) A prospective three-year cohort study of the epidemiology and virology of acute respiratory infections of children in rural India. *PLoS ONE* 2(6): e491 doi:10.1371/journal.pone.0000491. Accessed 2008 March 6.