

Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial

Ana-Luisa Vilas-Boas¹, Maria-Socorro H. Fontoura¹, Gabriel Xavier-Souza¹, César A. Araújo-Neto², Sandra C. Andrade³, Rosa V. Brim², Lucia Noblat⁴, Aldina Barral⁵, Maria-Regina A. Cardoso⁶ and Cristiana M. Nascimento-Carvalho* on behalf of the PNEUMOPAC-Efficacy Study Group^{1†}

¹Department of Paediatrics, Federal University of Bahia School of Medicine, Salvador, Brazil; ²Department of Image Diagnosis, Federal University of Bahia School of Medicine, Salvador, Brazil; ³Image Diagnosis Unit, Federal University of Bahia Hospital, Salvador, Brazil; ⁴Pharmacy Unit, Federal University of Bahia Hospital, Salvador, Brazil; ⁵Pathology Department, Federal University of Bahia School of Medicine and Centro de Pesquisa Gonçalo Moniz, Fundação Oswaldo Cruz, Salvador, Brazil; ⁶Department of Epidemiology, University of São Paulo School of Public Health, São Paulo, Brazil

*Corresponding author. Tel: +55-71-99848648; Fax: +55-71-33320725; E-mail: nascimentocarvalho@hotmail.com

†Members are listed in the Acknowledgements section.

Received 30 November 2013; returned 3 February 2014; revised 6 February 2014; accepted 22 February 2014

Objectives: Oral amoxicillin (50 mg/kg/day) thrice daily is the first-line therapy for non-severe childhood pneumonia. Compliance could be enhanced if two daily doses are employed. We assessed the equivalence of oral amoxicillin (50 mg/kg/day) thrice or twice daily in those patients.

Patients and methods: This randomized (1:1), controlled, triple-blinded investigation conducted at one centre in Brazil included children aged 2–59 months with non-severe pneumonia diagnosed by trained paediatricians based on respiratory complaints and radiographic pulmonary infiltrate/consolidation. Participants were randomly assigned to receive one bottle (Amoxicillin 1) at 6 am, 2 pm and 10 pm and the other bottle (Amoxicillin 2) at 8 am and 8 pm: one bottle contained amoxicillin and the other placebo and vice versa. Only the pharmacist knew patients' allocation. Follow-up assessments were done at 2, 5 and 14 days after enrolment. Chest radiographs were read by three independent radiologists. Primary outcome was treatment failure (development of danger signs, persistence of fever, tachypnoea, development of serious adverse reactions, death and withdrawal from the trial) at 48 h. ClinicalTrials.gov: identifier NCT01200706.

Results: Four hundred and twelve and 408 participants received amoxicillin thrice or twice daily, respectively. Treatment failure was detected in 94 (22.8%) and 94 (23.0%) patients in intention-to-treat analysis (risk difference 0.2%; 95% CI: –5.5%–6.0%) and in 80 (20.1%) and 85 (21.3%) patients in per-protocol analysis (risk difference 1.2%; 95% CI: –4.4%–6.8%). Pneumonia was radiologically confirmed by concordant reading in 277 (33.8%) cases, among whom treatment failure was registered in 25/133 (18.8%) and 27/144 (18.8%) participants from the thrice and twice daily doses subgroups, respectively (risk difference –0.05%; 95% CI: –9.3%–9.2%).

Conclusions: Oral amoxicillin (50 mg/kg/day) twice daily is as efficacious as thrice daily.

Keywords: acute respiratory infections, antibacterials, antimicrobial therapy, lower respiratory tract infection

Introduction

Pneumonia is one of the leading infectious diseases in childhood; in 2010, in children <5 years old, there were 120 million episodes globally, of which 88% were non-severe.¹ Different international guidelines recommend amoxicillin as first-line therapy for those non-severe cases,² which is based on the assumption that

Streptococcus pneumoniae is the most common bacterial pathogen.³ The US guidelines recommend amoxicillin at 90 mg/kg/day in two doses or 45 mg/kg/day in three doses in regions where the upper MIC for *S. pneumoniae* is ≤ 2.0 mg/L.⁴

In 2013, the WHO launched a recommendation for the management of childhood illnesses in which outpatients with

pneumonia in low HIV prevalence regions should receive amoxicillin at 40 mg/kg per dose twice a day.⁵ As per the initial paediatric registration trials for amoxicillin in the early 1970s, the standard dosage therapy (15 mg/kg/dose thrice daily) appeared to be uniformly successful and so it was approved.⁶ However, higher compliance is expected if the drug is administered twice a day.⁷

To date, no clinical trial has assessed the equivalence of oral amoxicillin given thrice or twice daily at 50 mg/kg/day to children with non-severe pneumonia and we aimed to achieve this goal.

Patients and methods

Study design and patient selection

We conducted a randomized, controlled, triple-blinded equivalence trial of amoxicillin (50 mg/kg/day) given orally thrice or twice daily to children aged 2–59 months with non-severe pneumonia, in the emergency room of the university hospital in Salvador, Brazil. Participants were randomized (1:1) into two groups. Potentially eligible cases were identified by paediatricians based on the report of respiratory complaints and the detection of lower respiratory findings plus presence of pulmonary infiltrate/consolidation on the chest radiograph (CXR) (frontal and lateral views) taken on admission. At this moment, the CXR was read by the paediatricians. The exclusion criteria are presented in Table 1.

Before enrolment, a written informed consent was obtained from the parents/legal guardians when those caregivers agreed to stay in the hospital with the child in the observation ward for the purpose of this study. This study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. It was approved by the Ethics Committee of the Federal University of Bahia (approval reference number 24/2006) and registered with ClinicalTrials.gov (identifier NCT01200706).

Procedures

On recruitment, a thorough examination was performed; data on demographics, clinical history and physical examination were recorded in a standardized questionnaire. The pharmacy unit of the hospital was informed about the recruitment and independent pharmacists dispensed two bottles named Amoxicillin 1 and Amoxicillin 2 (Figure S1, available as

Table 1. Exclusion criteria of study

Lower-chest indrawing
Danger signs ^a
Chronic debilitating diseases ^b
Severe malnutrition ^c
Other concurrent infection
HIV-infected mother
Hospitalization during the previous 7 days
Amoxicillin or similar antibiotic use during the last 48 h
Amoxicillin allergy
History of aspiration

^aInability to drink, seizure, somnolence, central cyanosis, grunting in a calm child and nasal flaring.

^bAnatomic abnormalities of the respiratory tract, cancer, chronic pulmonary illness besides asthma, immunological defects, progressing neurological disorders, psychomotor retardation, heart disease with clinical repercussion, haemoglobinopathy and liver or kidney disease.

^cNutritional evaluation was performed using the software 'Anthro' (WHO); malnutrition and severe malnutrition were defined as Z-scores for weight-for-age under -2.00 and under -3.00 , respectively.⁸

Supplementary data at JAC Online): one bottle contained amoxicillin and the other placebo and vice versa, according to the randomization sequence.

The CXR was sent to two independent paediatric radiologists who were blinded to clinical information. Radiographic findings were registered on a pre-defined form in accordance with standardized interpretation.⁹ Radiologically confirmed pneumonia was identified if there was agreement on the presence of pulmonary infiltrate/consolidation in two independent assessments.

Participants were followed up twice daily by trained medical students, who also observed the drug administration, supervised by a senior paediatrician from the research team. Data on complaints and findings were recorded on a standardized form. Each child was discharged from hospital when there was no more fever and respiratory discomfort and bottles of Amoxicillin 1 and Amoxicillin 2 were supplied to complete 10 days of treatment, according to the national guidelines.¹⁰ On the fifth day of treatment, the senior paediatrician called the caregiver to enquire for symptoms and interventions. A final follow-up examination was performed 2–4 weeks after enrolment, when a second CXR (frontal and lateral views) was taken. All data were registered on pre-defined forms. No change to the original protocol occurred after the trial commenced.

Definitions

Outcomes were defined *a priori* (Table 2). The primary outcome was treatment failure up to 48 h. Secondary outcomes were cumulative treatment failure at up to 5 and 14 days.

Table 2. Definitions of study endpoints

Study endpoint	Definition
Primary outcome (treatment failure up to 48 h of treatment)	any of the following: <ul style="list-style-type: none"> • development of danger signs^a • persistence of fever^b • persistence of tachypnoea^c • development of serious adverse reactions • withdrawal from the trial • death
Secondary outcome (cumulative treatment failure up to 5 and 14 days after enrolment)	any of the following: <ul style="list-style-type: none"> • development of danger signs^a • persistence of fever^b • persistence of tachypnoea^c • persistence of cough • development of serious adverse reactions • recurrence of fever • withdrawal from the trial • death • previously defined as treatment failure (at 48 h or 5 days)

^aDanger signs are inability to drink, chest indrawing, cyanosis, grunting, nasal flaring, seizure and somnolence.

^bFever: axillary temperature $>37.5^{\circ}\text{C}$.¹¹

^cTachypnoea: respiratory rate ≥ 50 breaths/min in children aged 2–11 months and respiratory rate ≥ 40 breaths/min in children aged ≥ 12 months.⁵

The upper record of axillary temperature and respiratory rate on each day was considered in the analysis.

Sample size calculation

The sample size was estimated by the general formula for trials assessing equivalence.¹² The results of a previous study of 15 mg/kg oral amoxicillin every 8 h for the treatment of non-severe childhood pneumonia showed a 20% clinical failure rate.¹³ Equivalence was defined *a priori* as $\leq 9\%$ difference in the proportion of clinical failures between treatment groups at 2 days after enrolment. With a sample size of 410 participants in each arm, a two-group large sample approximation test of proportions with a one-sided 2.5% significance level has 90% power to reject the null hypothesis that there is a difference between the groups. The formal stopping rule prescribed that interim analysis should be performed if the intervention was discontinued in $>30\%$ of patients to investigate whether the new treatment was worse than the standard one.

Randomization and masking

Patients were randomly assigned to either amoxicillin thrice or twice daily, following a blocked design with a block size of four. The randomization sequence was created by a statistician who had no clinical involvement in the trial at the University of São Paulo School of Public Health using Stata 10 (StataCorp, 2007, College Station, TX, USA). Randomization codes were sealed in opaque envelopes in accordance with the allocation sequence and were provided to the pharmacist, who was aware of study group assignments at the time of dispensing the pair of bottles. Randomization code numbers were assigned to study participants in chronological order by the pharmacist. The sealed envelopes were kept stored in a strict area at the pharmacy unit during the collection and analysis of data. The next envelope in sequence was opened after enrolment and immediately before dispensing the drugs. The randomization sequence was only known by the researchers when the database was complete with the primary and secondary outcomes recorded for each patient. Participants and their respective families, healthcare providers, data collectors and outcome adjudicators were blinded to the intervention allocation. It was not necessary to unblind any participant or member of the research team during the trial.

Data entry and statistical analysis

Data were entered in the software EPI-INFO version 6.04 and analysed in Stata (version 11.0). The primary analysis was intention to treat and involved all patients who were randomly assigned. Participants excluded after randomization because they were found not to meet eligibility criteria (protocol violators), those who had the intervention stopped and those who were lost to follow-up (Figure S2, available as Supplementary data at JAC Online) were excluded from the secondary per-protocol analyses and were assumed to have treatment failure in the intention-to-treat analysis. We calculated the risk difference and two-sided 95% CI of the primary and secondary outcomes. The same approach was used in the subgroup of patients with concordant radiologically confirmed pneumonia. We also compared data between treatment success and failure groups at 48 h using Pearson's χ^2 analysis for categorical variables and the Mann-Whitney *U*-test for continuous variables. Bivariate analysis included estimates of the OR and 95% CI. As a secondary goal, we constructed a multivariate model to look for determinants of treatment failure by forward stepwise logistic regression controlled by randomization, in all patients included in the per-protocol analysis. All significant variables from bivariate analysis were included in the model. Statistical significance was considered at the 5% level.

See Supplementary patients and methods (available as Supplementary data at JAC Online).

Results

From November 2006 to April 2011, 820 patients were enrolled and allocated into two groups: 412 were assigned to receive amoxicillin thrice daily and 408 twice daily, out of which 9

(2.2%) and 7 (1.7%) did not receive the allocated intervention, respectively (Figure S2). The baseline characteristics of the two groups are shown in Table 3.

The median (IQR) length of hospital stay was 2 (1–2) days in both groups ($P=0.6$). At up to 48 h of treatment, the rate of treatment failure was judged equivalent across the two treatment arms in the intention-to-treat (23%) and the per-protocol (21%) analyses (Table 4); likewise, among the participants with concordant radiologically confirmed pneumonia (19%) (Table 4).

Cumulative treatment failure rates for up to 5 and 14 days of treatment are compared in Table 5. Up to the 14 days follow-up visit, none died or presented inability to drink, grunting, nasal flaring or cyanosis. Concordant CXR reading was found in 97% of CXRs, out of which pneumonia (7%), normal CXR (89%) and other radiological diagnoses (4%) were diagnosed without difference in the compared groups (data not shown).

At the outpatient visit, adverse reactions were reported by 23 (6.1%) among 376 participants receiving amoxicillin thrice daily and by 28 (7.6%) among 369 receiving amoxicillin twice daily ($P=0.5$). Diarrhoea ($n=20$), urticaria ($n=1$), nausea ($n=1$) and abdominal pain ($n=1$) were reported in the former group and diarrhoea ($n=27$) and urticaria ($n=1$) in the latter group. Two adverse reactions were serious enough to discontinue intervention (one diarrhoea and one urticaria). Overall, adverse reaction rates reported at any time were 27 (6.8%) among 400 participants receiving amoxicillin thrice daily and 30 (7.5%) among 400 participants receiving amoxicillin twice daily ($P=0.7$). Serious adverse effects that led to interruption of the intervention occurred in five patients from the thrice daily doses group and in three patients from the twice daily doses group (1.3% versus 0.8%; $P=0.7$). The intervention was substituted in 20 (5%) patients in the thrice daily doses group and in 14 (3.5%) in the twice daily doses group ($P=0.4$) (Table S1, available as Supplementary data at JAC Online).

In logistic regression analysis of the baseline characteristics, wheezing, fever and tachypnoea were directly associated with failure and disease length ≥ 5 days and crackles were inversely associated with failure (Table 6).

See Supplementary results (available as Supplementary data at JAC Online).

Discussion

We have demonstrated that amoxicillin given orally at 50 mg/kg/day is equally efficacious thrice or twice daily at 48 h and beyond. The 48 h failure frequency was close to that reported (21%) when children with non-severe pneumonia received 15 mg/kg thrice daily.¹³ Tachypnoea, fever and wheezing were independent predictors of failure and these findings are similar to what has been reported.^{14–16} Notably, the frequency of intervention substitution (5% and 3.5%) was much lower than the frequency of failure as it had been defined *a priori* in the protocol and no statistical significance was found by comparing trial arms.

Antibacterial therapy in pneumonia aims to eradicate the infecting organism.¹⁷ Amoxicillin effect is time dependent and bacterial eradication is achieved when the unbound serum concentration exceeds the MIC of the causative pathogen for 40%–50% of the dosing interval.¹⁸ Based on the current breakpoints established to determine pneumococcal susceptibility to

Table 3. Baseline comparison between treatment groups

Baseline characteristics	Amoxicillin thrice daily (n=403)	Amoxicillin twice daily (n=401)
Male, n (%)	207 (51)	214 (53)
Age (months), median (IQR)	26 (14–40)	24 (14–40)
Age <1 year, n (%)	80 (20)	84 (21)
History of current illness reported by caregiver, n (%)		
disease length \geq 5 days	247 (61)	250 (62)
cough	394 (98)	388 (97)
difficulty breathing	263 (65)	237 (59)
fever	363 (90)	378 (94)
vomiting	173 (43)	188 (47)
wheezing	137 (34)	111 (28)
History of previous morbidity reported by caregiver, n (%)		
antibiotic use in the last 3 months	126 (33)	121 (32)
difficulty breathing in the last year	219 (56)	223 (56)
any previous hospitalization	175 (43)	171 (43)
any previous pneumonia	124 (31)	114 (29)
any previous hospitalization due to pneumonia	90 (22)	80 (20)
Findings by the paediatrician on enrolment, n (%)		
fever	131 (33)	136 (34)
tachypnoea	175 (43)	183 (46)
chest retraction	17 (4)	13 (3)
reduced pulmonary expansion	35 (9)	33 (8)
rhonchi	266 (66)	255 (64)
wheezing	125 (31)	113 (28)
crackles	178 (44)	177 (44)
malnutrition	19 (5)	9 (2)

Table 4. Treatment failure by specific causes at 48 h

Outcome	Amoxicillin thrice daily	Amoxicillin twice daily	Difference % (95% CI)
Intention to treat	94/412 (23%)	94/408 (23%)	0.2% (–5.5%–6.0%)
Per-protocol analysis	80/398 (20%)	85/399 (21%)	1.2% (–4.4%–6.8%)
Tachypnoea ^a	73/399 (18%)	80/399 (20%)	1.8% (–3.7%–7.2%)
Fever ^a	19/399 (5%)	16/399 (4%)	–0.8% (–3.6%–2.1%)
Chest indrawing ^a	3/399 (0.8%)	5/399 (1.3%)	0.5% (–0.9%–1.9%)
Withdrawal from the trial	3/403 (0.7%)	1/401 (0.2%)	–0.5% (–1.5%–0.5%)
Serious adverse drug reaction	2/400 (0.5%)	1/400 (0.3%)	–0.3% (–1.1%–0.6%)
For concordant radiologically confirmed pneumonia cases			
intention to treat	25/133 (19%)	27/144 (19%)	–0.05% (–9.3%–9.2%)
per protocol ^b	25/133 (19%)	26/143 (18%)	–0.6% (–9.8%–8.6%)

^aOne patient who had the intervention interrupted at 48 h of use because of severe urticaria was included in this analysis because the intervention had been given for 48 h.

^bOne patient with concordant radiologically confirmed pneumonia was withdrawn from the trial.

antimicrobials¹⁹ and data from invasive pneumococcal strains recovered from pneumonia cases between 2000 and 2005 in Latin America, the pneumococcal susceptibility to penicillin is 95.1%.²⁰ That is, this trial was conducted in a region with low prevalence of pneumococcal resistance to penicillin and this may explain why equivalence was found.

The identified predictors of failure (tachypnoea, fever and wheezing) are not novel.^{14–16} This finding suggests that they should alert paediatricians to follow up those patients with closer attention. Of note, the rate of intervention substitution (5% and 3.5%) was much lower than the failure rate defined *a priori*. Therefore, most of the patients who were classified as failure

Table 5. Cumulative treatment failure at 5 days of treatment and 14 days of follow-up

Outcome	Cumulative failure at 5 days			Cumulative failure at 14 days		
	amoxicillin thrice daily	amoxicillin twice daily	difference % (95% CI)	amoxicillin thrice daily	amoxicillin twice daily	difference % (95% CI)
Intention to treat	107/412 (26%)	113/408 (28%)	1.7% (−4.3%–7.8%)	174/412 (42%)	160/408 (39%)	−3.0% (−9.7%–3.7%)
Per protocol	85/390 (22%)	88/383 (23%)	1.2% (−4.7%–7.1%)	138/376 (37%)	121/369 (33%)	−3.9% (−10.7%–2.9%)
For concordant radiologically confirmed pneumonia cases						
intention to treat	29/133 (22%)	33/144 (23%)	1.1% (−8.7%–10.9%)	53/133 (40%)	48/144 (33%)	−6.5% (−17.9%–4.8%)
per protocol ^a	27/131 (21%)	26/137 (19%)	−1.6% (−11.2%–7.9%)	46/126 (37%)	38/134 (28%)	−8.1% (−19.5%–3.2%)

^aOne patient with concordant radiologically confirmed pneumonia was withdrawn from the trial and eight were lost to follow-up at 5 days.

Table 6. Bivariate and multivariate analysis of baseline risk factors predictive of treatment failure at 48 h

Outcome	Bivariate analysis			Multivariate analysis, adjusted OR (95% CI)
	failure (n=165)	success (n=632)	OR (95% CI)	
Age (months), median (IQR)	24 (16–38)	26 (13–41)	0.99 (0.99–1.00)	—
Disease length ≥5 days, n (%)	85 (52)	409 (65)	0.58 (0.41–0.82)	0.68 (0.47–0.98)
Report of wheezing, n (%)	65 (39)	182 (29)	1.60 (1.12–2.29)	1.49 (1.01–2.20)
On physical examination, n (%)				
fever	75 (46)	189 (30)	1.95 (1.38–2.77)	1.80 (1.24–2.61)
tachypnoea	105 (64)	249 (39)	2.69 (1.89–3.84)	2.67 (1.84–3.88)
chest retraction	11 (7)	19 (3)	2.30 (1.07–4.94)	—
wheezing	63 (38)	171 (27)	1.67 (1.16–2.39)	1.56 (1.05–2.32)
crackles	56 (34)	297 (47)	0.58 (0.41–0.83)	0.45 (0.30–0.66)
Randomization (twice daily) ^a , n (%)	85 (51)	314 (50)	1.08 (0.76–1.52)	—

^aRandomization was not associated with failure in bivariate analysis but it was included in the logistic regression.

continued to receive the intervention. This can be explained by the fact that the majority of cases judged to fail had persistence of signs present at enrolment. Indeed, only a few cases developed signs of severity or a severe adverse event (Table S1), when the intervention was substituted. The conservative definition for treatment failure was employed so that our data could be compared with previous studies. However, it has been shown that the alternative definition for therapy failure, which considers only cases who deteriorate, classifies a significantly lower number of cases as failure.²¹ Moreover, such definition has worked reasonably well, without causing any higher risk to children with non-severe pneumonia.²¹ Our findings support the use of these alternative criteria. Our findings on adverse reactions are in accordance with previous studies when <10% of patients reported any such complaint,²² severe events were rare,¹³ discontinuation was not necessary in the great majority of patients and diarrhoea was the most frequent reaction.¹³

In conclusion, amoxicillin may be given as a 25 mg/kg/dose twice a day to children with non-severe pneumonia because it is not only efficacious but also safe. Higher amounts of amoxicillin are unnecessary and money may be saved. Patients with fever, tachypnoea and wheezing should be followed up closely as they have a greater chance of failure.

Acknowledgements

Data from this manuscript were partially presented as a poster at the Thirty-first European Society for Paediatric Infectious Diseases Annual Meeting, Milan, Italy, 2013 (Abstract A-534-0004-00485) and have been previously published in a results database (<http://www.clinicaltrials.gov/ct2/show/NCT01200706?term=NCT01200706&rank=1>).

We are in debt to the paediatricians and nurses of the Professor Hosannah de Oliveira Paediatric Centre, Federal University of Bahia, Salvador, Brazil, for their cooperation in recruiting the patients.

Members of the PNEUMOPAC-Efficacy Study Group Phase I (in alphabetical order)

Adriana R. Matutino¹, Bruna B. Barreto¹, Carolina C. Silva¹, Daniel A. Braga¹, Felipe Oliveira², Giorgio V. Nogueira¹, Ícaro S. Oliveira¹, Igor Lorgetto², Itana N. Costa², Jamile Araripe², Júlia R. Vieira², Lais B. Neiva¹, Milena C. Santana¹, Monalisa Nobre-Bastos¹, Pablo M. Santos³, Sérgio F. Câmara¹, Solange Carneiro³, Uri R. Sirmos¹ and Vital F. Araújo¹ (¹Department of Paediatrics, Federal University of Bahia School of Medicine, Salvador, Bahia, Brazil; ²Bahiana School of Medicine, Bahiana Foundation for Science Development, Salvador, Bahia, Brazil; and ³Pharmacy Unit, Federal University of Bahia Hospital, Salvador, Bahia, Brazil).

Members of the PNEUMOPAC-Efficacy Study Group Phase II (in alphabetical order)

Carolina C. Silva¹, Caroline Vilas-Boas², Denise Gantois¹, Fausto Azevedo², José-Raimundo Maia Jr², Larissa Pirajá², Priscila S. Jesus², Taiane Fonseca² and Ticiana Vilar² (¹Bahiana School of Medicine, Bahiana Foundation for Science Development, Salvador, Bahia, Brazil; and ²Department of Paediatrics, Federal University of Bahia School of Medicine, Salvador, Bahia, Brazil).

Funding

This work was supported by a grant from the Bahia State Agency for Research Funding (FAPESB) (Grant No. APR N°. 0127/2006). A. B., M.-R. A. C. and C. M. N.-C. are investigators from the Brazilian Council for Scientific and Technological Development (CNPq).

Transparency declarations

None to declare.

Author contributions

C. M. N.-C., M.-R. A. C. and A. B. contributed to the study design, analysis and interpretation of data. A.-L. V.-B. and M.-S. H. F. were study coordinators and oversaw the study implementation and supervision and wrote the first draft of the paper. C. M. N.-C., M.-R. A. C. and A. B. wrote the final version of the paper. G. X.-S., C. A. A.-N., S. C. A., R. V. B. and L. N. implemented the study and took part in the discussion of the analysis and the writing of the paper. All members of the PNEUMOPAC-Efficacy Study Group took part in the recruitment and follow-up procedures as well as in the discussion of the implementation and findings. C. M. N.-C. is the principal investigator for the study and the overall guarantor.

Supplementary data

Figure S1, Figure S2, Supplementary patients and methods, Table S1 and Supplementary results are available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

References

- Walker CL, Rudan I, Liu L *et al.* Global burden of childhood pneumonia and diarrhea. *Lancet* 2013; **381**: 1405–16.
- Nascimento-Carvalho CM, Madhi SA, O'Brien KL. Review of guidelines for evidence-based management for childhood community-acquired pneumonia in under-5 years from developed and developing countries. *Pediatr Infect Dis J* 2013; **32**: 1281–2.
- Rudan I, Boschi-Pinto C, Biloglav Z *et al.* Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008; **86**: 408–16.
- Bradley JS, Byington CL, Shah SS *et al.* The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by Pediatric Infectious Diseases Society and Infectious Diseases Society of America. *Clin Infect Dis* 2011; **53**: 25–76.
- WHO. *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Childhood Illnesses*, 2nd edn. Geneva: WHO, 2013. http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/index.html (7 June 2013, date last accessed).
- Price JD, Harding JW. Amoxycillin in the treatment of respiratory tract infection in children. *Br J Clin Pract* 1975; **29**: 203–6.
- Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *J Antimicrob Chemother* 2002; **49**: 897–903.
- WHO. *Training Course on Child Growth Assessment*. Geneva: WHO, 2008. http://whqlibdoc.who.int/publications/2008/9789241595070_A_eng.pdf (13 July 2009, date last accessed).
- Cherian T, Mulholland EK, Carlin JB *et al.* Standardized interpretation of paediatric chest radiographs for the diagnosis of pneumonia in epidemiological studies. *Bull World Health Organ* 2005; **83**: 353–9.
- Nascimento-Carvalho CM, Souza-Marques HH. Recommendation of the Brazilian Society of Pediatrics for antibiotic therapy in children and adolescents with community-acquired pneumonia. *Pan Am J Public Health* 2004; **15**: 380–7.
- El-Radhi AS, Barry W. Thermometry in paediatric practice. *Arch Dis Child* 2006; **91**: 351–6.
- Friedman LM, Furberg CD, DeMets DL. *Fundamentals of Clinical Trials*. St Louis: Mosby, 1996.
- Pakistan Multicentre Amoxycillin Short Course Therapy (MASCOT) pneumonia study group. Clinical efficacy of 3 days versus 5 days of oral amoxicillin for treatment of childhood pneumonia: a multicentre double-blind trial. *Lancet* 2002; **360**: 835–41.
- Addo-Yobo E, Chisaka N, Hassan M *et al.* Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomized multicentre equivalency study. *Lancet* 2004; **364**: 1141–8.
- Hazir T, Qazi SA, Nisar YB *et al.* Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2–59 months: a multi-centre, double blind, randomized controlled trial in Pakistan. *Arch Dis Child* 2007; **92**: 291–7.
- Hazir T, Nisar YB, Abbasi S *et al.* Comparison of oral amoxicillin with placebo for the treatment of World Health Organization-defined nonsevere pneumonia in children aged 2–59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clin Infect Dis* 2011; **52**: 293–300.
- Dagan R, Klugman KP, Craig WA *et al.* Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. *J Antimicrob Chemother* 2001; **47**: 129–40.
- Andes D, Anon J, Jacobs MR *et al.* Application of pharmacokinetics and pharmacodynamics to antimicrobial therapy of respiratory tract infections. *Clin Lab Med* 2004; **24**: 477–502.
- Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: Twenty-fourth Informational Supplement M100-S24*. CLSI, Wayne, PA, USA, 2014.
- Castañeda E, Agudelo CI, Regueira M *et al.* Laboratory-based surveillance of *Streptococcus pneumoniae* invasive disease in children in 10 Latin American countries: a SIREVA II project, 2000–2005. *Pediatr Infect Dis J* 2009; **28**: e265–70.
- Hazir T, Qazi SA, Nisar YB *et al.* Can WHO therapy failure criteria for non-severe pneumonia be improved in children aged 2–59 months? *Int J Tuberc Lung Dis* 2006; **10**: 924–31.
- Awasthi A, Agarwal G, Kabra SK *et al.* Does 3-day course of oral amoxycillin benefit children of non-severe pneumonia with wheeze: a multicentric randomized controlled trial. *PLoS ONE* 2008; **3**: e1991.