

Oral amoxicillin versus injectable penicillin for severe pneumonia in children aged 3 to 59 months: a randomised multicentre equivalency study

Emmanuel Addo-Yobo, Noel Chisaka, Mumtaz Hassan, Patricia Hibberd, Juan M Lozano, Prakash Jeena, William B MacLeod, Irene Mauler, Archana Patel, Shamim Qazi, Donald M Thea, Ngoc Tuong Vy Nguyen for the Amoxicillin Penicillin Pneumonia International Study (APPIS) group*

Lancet 2004; 364: 1441–48

See Comment

*Contributors listed at end of report. See details of contributorship at

www.thelancet.com

Correspondence to Dr Shamim Qazi, Department of Child and Adolescent Health and Development, WHO Geneva 27 (M1211, Switzerland) (qazim@who.int)

Summary

Background Injectable penicillin is the recommended treatment for WHO-defined severe pneumonia (lower chest indrawing). If oral amoxicillin proves equally effective, it could reduce referral, admission, and treatment costs. We aimed to determine whether oral amoxicillin and parenteral penicillin were equivalent in the treatment of severe pneumonia in children aged 3–59 months.

Methods This multicentre, randomised, open-label equivalency study was undertaken at tertiary-care centres in eight developing countries in Africa, Asia, and South America. Children aged 3–59 months with severe pneumonia were admitted for 48 h and, if symptoms improved, were discharged with a 5-day course of oral amoxicillin. 1702 children were randomly allocated to receive either oral amoxicillin (n=857) or parenteral penicillin (n=845) for 48 h. Follow-up assessments were done at 5 and 14 days after enrolment. Primary outcome was treatment failure (persistence of lower chest indrawing or new danger signs) at 48 h. Analyses were by intention-to-treat and per protocol.

Findings Treatment failure was 19% in each group (161 patients, penicillin; 167 amoxicillin; risk difference –0.4%; 95% CI –4.2 to 3.3) at 48 h. Infancy (age 3–11 months; odds ratio 2.72, 95% CI 1.95 to 3.79), very fast breathing (1.94, 1.42 to 2.65), and hypoxia (1.95, 1.34 to 2.82) at baseline predicted treatment failure by multivariate analysis.

Interpretation Injectable penicillin and oral amoxicillin are equivalent for severe pneumonia treatment in controlled settings. Potential benefits of oral treatment include decreases in (1) risk of needle-borne infections; (2) need for referral or admission; (3) administration costs; and (4) costs to the family.

Introduction

Acute respiratory infection is one of the leading causes of morbidity and mortality in children under 5 years of age in developing countries, and is responsible for an estimated 1.9 million deaths in this age group every year.^{1,2} Bacterial infection has a far greater role as a cause of pneumonia in children in developing countries than it does in developed countries. One explanation for the higher mortality associated with acute respiratory infection in developing countries is the high prevalence of a bacterial cause. Researchers using lung aspiration have isolated *Streptococcus pneumoniae* and *Haemophilus influenzae* (as well as others), in up to 74% of patients with pneumonia in developing countries.³

Standard guidelines developed by WHO⁴ recommend that children with no lower chest wall indrawing who have fast breathing (≥ 50 breaths per min in infants aged 2–11 months and ≥ 40 breaths per min in those aged 12–59 months)—ie, with non-severe pneumonia—be treated at home with oral antibiotics, and those with lower chest wall indrawing (ie, severe pneumonia), be admitted and given parenteral antibiotics (benzylpenicillin or ampicillin). Application of these guidelines in developing countries has resulted in decreased mortality from acute respiratory infection.⁵ However, admission required for administration of

injectable treatment has several drawbacks. First, routine use of injectable antibiotics, either intravenously or intramuscularly, is associated with an increase in the risk of clinically significant morbidity, such as complications of abscess formation at the injection site and transmission of HIV, hepatitis, or other pathogens associated with use of contaminated needles. Second, injection needles and administration equipment are in short supply or periodically unavailable in some settings, preventing delivery of recommended treatment. Third, admission can substantially raise the cost of health care. Fourth, children who have to be referred for admission and injectable treatment might not be brought or be able to travel to hospital.

A recent trial in Pakistan showed that oral amoxicillin was effective in 82% of bacteraemic children with a clinical diagnosis of severe pneumonia.⁶ If oral amoxicillin proved as effective as injectable penicillin in the treatment of severe pneumonia, substantial improvements in access to appropriate care, nosocomial complications, iatrogenic infections, and costs could be achieved with its widespread use. Our aim was to do a multicentre equivalency study comparing oral amoxicillin with injectable penicillin in the treatment of WHO-defined severe pneumonia in children.

Methods

Patients

We undertook a randomised, non-blinded equivalency trial of oral amoxicillin and injectable penicillin in children aged 3–59 months with WHO-defined severe pneumonia,⁵ in the paediatric departments of tertiary-care facilities at nine international sites: Colombia, Ghana, India, Mexico, Pakistan, South Africa (two sites), Vietnam, and Zambia. Children presenting as emergencies with a history of coughing or difficulty breathing and lower chest indrawing were assessed for enrolment into the study. We attempted to keep enrolment of children with reversible airways disease to a minimum because lower chest indrawing can occur with severe wheezing. Wheezing is commonly associated with respiratory syncytial virus (RSV) infection (especially in infants), which would not be expected to respond to either treatment. This effect would bias the results towards finding equivalence.

The primary endpoint was treatment failure at 48 h in children aged 3–59 months with WHO-defined severe pneumonia who were given oral amoxicillin or injectable penicillin. Secondary endpoint was relapse at days 5 and 14. Treatment failure for primary and secondary outcomes was a priori (panel).

We excluded children with a history of asthma or those with audible wheeze whose lower chest indrawing was resolved after two courses of inhaled salbutamol. We ruled out children with non-severe pneumonia showing danger signs of very severe disease (as defined by WHO; inability to drink, abnormal sleepiness, central cyanosis, convulsions, and severe malnutrition), who were then referred for immediate admission and standard hospital care. Also excluded were children with a recent history of very severe infectious or non-infectious disease, chronic or congenital illness, known asthma, clinically evident HIV infection, persistent vomiting, known penicillin allergy, or more than 48 h of antibiotic treatment for the present illness. We obtained written informed consent from parents or legal guardians of children before enrolment. Ethical approval was obtained from every local institution and both sponsoring organisations. The study was monitored by an independent data safety monitoring board.

Procedures

Clinical assessment, sampling, randomisation, and provision of study medication took place within 1 h of enrolment. Baseline assessment consisted of physical examination and administration of a standardised questionnaire. Nasopharyngeal samples were obtained before the first dose of antibiotic with a calcium alginate swab, which was inoculated onto Amies transport media (Difco Laboratories, Surrey, UK) and cultured immediately for *S pneumoniae* and *H influenzae* with standard microbiology techniques.⁶ We obtained nasal aspirates of 2.5 mL saline to test for RSV at baseline. Oxygen saturation was measured by pulse oximetry in a

Panel: Definitions of study endpoints

Primary outcome (treatment failure up to or at first 48 h)

Any of the following:

- Appearance of danger signs*
- Low oxygen saturation†
- Persistence of lower chest indrawing at 48 h
- Life-threatening or serious adverse drug reaction
- Received another antibiotic
- Newly diagnosed comorbid condition
- Parents or guardian withdrew consent
- Child left against medical advice
- Death

Secondary outcome (treatment failure at 5 or 14-day follow-up visits)

Any of the following:

- Appearance of danger signs*
- Low oxygen saturation‡
- Recurrence of lower chest indrawing at follow-up visit
- Life-threatening or serious adverse drug reaction
- Received another antibiotic
- Newly diagnosed comorbid condition
- Parents or guardian withdrew consent
- Child left against medical advice
- Death
- Previously defined as treatment failure (at 48 h or 5 days)
- Signs of non-severe pneumonia on follow-up at day 14

*Inability to drink, abnormal sleepiness, central cyanosis, convulsions. †(<80% in room air at sea level, or <75% in room air in Columbia and Mexico). ‡ (<90% in room air at sea level, or <88% in room air in Columbia and Mexico).

non-crying child on room air (Nellcor N-20E, N-25 sensor, Pleasanton, CA, USA). We did not require chest radiographs for enrolment, but we obtained them if clinically warranted. At two centres (Zambia and Durban, South Africa), parents separately gave consent to be tested for HIV, and blood samples were obtained for testing at the end of the study. Results of HIV testing and outcomes of this assessment are presented elsewhere (unpublished data). At these two sites, all parents or guardians were offered real-time HIV testing if clinically warranted.

Randomisation codes were sealed in opaque envelopes in accordance with the allocation sequence, stratified by site, and prepared in advance by WHO for random assignment to either oral amoxicillin syrup (45 mg/kg per day in three doses) or parenteral penicillin G (200 000 IU/kg per day in four doses). After completion of baseline examination, the next envelope in sequence was opened to determine treatment assignment. We standardised assessment of respiratory rate, lower chest indrawing, and danger signs in all study participants with pilot-phase training sessions using WHO-standard acute respiratory infection case-management modules and demonstration video.

All patients were admitted for at least 48 h. We obtained vital, clinical, and danger signs, and oxygen

saturation data every 6 h. General supportive care that included salbutamol and antipyretics were provided, when indicated. The site principal investigator reviewed study outcomes (ie, treatment failure) within the first 48 h before classification. Patients whose clinical status improved to non-severe pneumonia (ie, absence of lower chest indrawing with fast breathing) or better were discharged at 48 h with a course of oral amoxicillin for another 5 days and asked to return for reassessments at days 5 and 14. Children who were classified as treatment failure were treated with a local alternative standard therapy.

Two formal interim analyses were undertaken during the trial. At the second interim analysis, we noted an early (non-significant) trend towards increased early deaths at sites with high HIV prevalence (Durban, South Africa, and Zambia) compared with the other sites. Since these deaths might have been due to clinically unrecognised HIV-infected children, the data safety and monitoring board recommended expansion of the exclusion criteria to omit all children under 1 year of age with oral thrush, with hepatosplenomegaly, or who had a parent known to be infected with HIV. These changes were implemented after accrual of 286 (55%) of these patients enrolled at these two sites.

We undertook a planned subgroup analysis of data from two sites with high HIV prevalence (Durban, South Africa, and Ndola, Zambia). The goal for this subgroup analysis was to determine whether children with asymptomatic or mild (stage A) HIV⁺ infection and community-acquired severe pneumonia (treated with WHO-standard acute respiratory infection case management guidelines) failed treatment more often than HIV-uninfected children with severe pneumonia.

Neither primary prophylaxis of *Pneumocystis jirovecii* pneumonia for children born to HIV-infected women or inclusion of co-trimoxazole in the initial empiric treatment of community-acquired pneumonia was the standard of care at either site at the time of this study (1998–2000).

We tested for RSV antigen in nasal washings obtained at baseline and froze these samples at -20°C in batches using the Abbott Testpack RSV (Abbott Diagnostics, Baar, Switzerland). Study samples from the Ndola and Durban sites were tested for HIV by standard ELISA (confirmed with western blotting) in children older than 15 months and HIV-1 DNA PCR in those younger than 15 months. We used standard microbiological techniques¹ to isolate and identify *S pneumoniae* and *H influenzae*. Minimum inhibitory concentration (MIC) of amoxicillin and penicillin for both *H influenzae* and *S pneumoniae* were measured by E test according to the manufacturer's instructions (AB Biodisk, Solna, Sweden).

Statistical analysis

Sample size was estimated by use of historical outcome data of severe pneumonia obtained from every site. With

these data and previously published results,¹¹ we anticipated that about 10% of patients would fail to improve or deteriorate (ie, treatment failure) within 48 h after initiating treatment with parenteral penicillin. Equivalency was defined a priori as a 5% or less difference in the proportion of clinical failures between treatment groups within 48 h of initiation of therapy. With respect to admission needed for the study, we assumed a loss to follow-up rate at 48 h of 1% and estimated the proportions of failures in the parenteral penicillin and oral amoxicillin groups to be 11% and 16%, respectively. If a one-sided α level of 0.05 was assumed, 861 children per group were required for 90% power to detect a 5% difference in failure rates between the two treatment groups. This estimate included three interim analyses and one final analysis, with an O'Brien-Fleming stopping rule (EaSt, Cytel Software Corporation, 2000, version 1.0).¹² The final target sample size was thus 1722 children, which provided 90% power to detect a similar difference in secondary outcomes: clinical failure at days 5 and 14.

Equivalency between the two treatments was shown with the two one-sided tests procedure.¹³ We calculated the risk difference and 95% CIs of the primary and secondary outcomes. The difference was regarded as equivalent if the 95% CIs were within -5% to 5% . We also examined the effect of the intention-to-treat analysis with a per-protocol analysis, to determine whether any risk of bias towards the null hypothesis existed in this equivalence trial.

Predictors of treatment failure at 48 h were assessed with a random-effects logistic regression model (SAS package, version 8.0). Study site was included in the model as a random effect and the treatment as a fixed effect. Baseline variables studied in the model as fixed effects included: sex; age between 3 and 11 months; breastfeeding at onset of present illness (not applicable for children older than 24 months); up-to-date immunisation status; pre-enrolment antibiotic use within 48 h; presence of malnutrition (weight-for-age Z scores <-2); fever ($>38^{\circ}\text{C}$) or hypothermia; tachypnoea; hypoxia (see footnote, panel); and presence of more than one resistant nasopharyngeal isolate.

Role of the funding source

S A Qazi (of WHO), D Thea, and B MacLeod had full access to all data within the study and contributed to the decision to submit for publication. S A Qazi and D Thea also contributed to development of the protocol.

Results

Participant accrual took place between May, 1999, and May, 2002. The Cape Town and Zambia centres ended recruitment in September, 1999, and July, 2000, respectively, both because of poor accrual from changes in the referral patterns. We randomly assigned 1702 participants to penicillin and amoxicillin (figure).

27 children aged between 2 and 3 months were mistakenly allocated but this protocol deviation was distributed evenly between both treatment groups, and these babies were included in the analysis according to assignment.

All randomly assigned participants were included in the intention-to-treat analysis for the primary outcome. Children were lost to follow-up because of voluntary withdrawal or absconding by 48 h. Random assignment was successful with nearly equal numbers of individuals in each treatment group. Table 1 shows baseline characteristics. Table 2 shows the number of children enrolled at every study site.

Rate of treatment failure at 48 h (19%) was judged equivalent across the two treatment groups (table 3). The most common cause for treatment failure was persistence of lower chest indrawing. In nearly half these children (124 of 262; risk ratio 2.0, 95% CI 1.7 to 2.3), lower chest indrawing was accompanied by wheezing, which in some individuals probably contributed to lower chest indrawing in the presence of resolving pneumonia. Only 34 of these children with wheeze had RSV isolated at baseline. If we excluded from analysis the 124 patients who had persistent wheezing and lower chest indrawing at 48 h, treatment

	Penicillin (n=845)	Amoxicillin (n=857)
Male	520/845 (62%)	537/857 (63%)
Infants (3-11 months old)	513/825 (62%)	532/844 (63%)
Children (12-59 months old)	312/825 (38%)	312/844 (37%)
Breastfeeding†	532/717 (74%)	561/725 (77%)
Up-to-date immunisation status	719/811 (89%)	739/824 (90%)
Report of antibiotics in past 48 h	82/828 (10%)	75/846 (9%)
Weight-for-age Z score	-0.7 (-2.0 to 0.3)	-0.7 (-1.0 to 0.3)
Weight-for-age Z score (<-2)	133/841 (16%)	124/845 (15%)
Temperature (°C)	37.4 (37 to 38)	37.5 (37 to 38)
Respiratory rate per min		
3-11 months	61 (55 to 68)	61 (56 to 68)
12-59 months	59 (50 to 64)	57 (48 to 63)
Oxygen saturation	94 (91 to 96)	94 (92 to 97)
RSV positive‡	183/759 (24%)	191/769 (25%)
S pneumoniae isolated from nasopharynx‡	217/743 (29%)	201/743 (27%)
H influenzae isolated from nasopharynx‡	145/739 (20%)	146/743 (20%)

Values are median (IQR) unless otherwise indicated. †Denominators for breastfeeding are the number of children under 24 months of age. ‡Denominators for RSV, S pneumoniae, and H influenzae isolated are the number of children with nasopharyngeal aspirates taken.

Table 1: Baseline comparison between treatment groups

failures in the amoxicillin and penicillin groups were 95 of 785 and 109 of 793, respectively (risk difference 1.6%, -1.7 to 4.9%).

Newly diagnosed comorbid conditions and death occurred slightly more frequently in the penicillin than in the amoxicillin group. The per-protocol analysis was in agreement with the intention-to-treat analysis (table 3). Cumulative treatment failures at 5 and 14 days (secondary endpoints) increased at each follow-up assessment point, but distribution of treatment failure remained largely the same as that seen at 48 h. Rate of treatment failure at 5 days (22%) between the two treatment groups was equivalent, although the rate of treatment failure at 14 days was not equivalent, with one of the bounds of the CI just outside the lower 5% boundary. The per-protocol analysis agreed with the result at 5 days, but showed equivalence at 14 days.

During the study, a total of 12 (0.7%) children died within 14 days of enrolment. Nine had received penicillin and three oral amoxicillin. Of these deaths, nine were associated with treatment failure (table 3). We

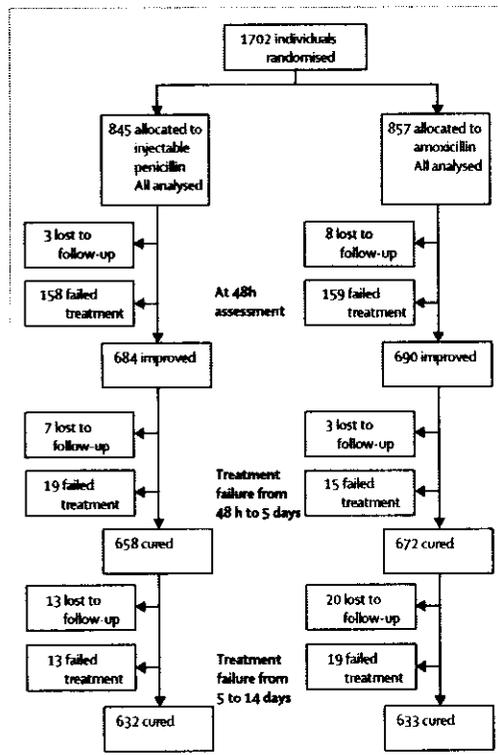


Figure: Trial profile

Site	Number of children enrolled (%)
Bogota, Columbia	105 (6.2%)
Cape Town, South Africa*	32 (1.9%)
Durban, South Africa	425 (25.0%)
Ho Chi Minh City, Vietnam	217 (12.8%)
Islamabad, Pakistan	296 (17.4%)
Kumasi, Ghana	179 (10.5%)
Mexico City, Mexico	150 (8.8%)
Nagpur, India	200 (11.8%)
Ndola, Zambia	98 (5.8%)
Total	1702 (100%)

*Cape Town ended recruitment in September, 1999, because of poor accrual as a result of changes in referral patterns

Table 2: Enrolment by study site

Outcome	Treatment failure at 48 h			Cumulative treatment failure at 5 days			Cumulative treatment failure at 14 days		
	Penicillin (n=845)	Amoxicillin (n=857)	Difference % (95% CI)	Penicillin (n=845)	Amoxicillin (n=857)	Difference % (95% CI)	Penicillin (n=845)	Amoxicillin (n=857)	Difference % (95% CI)
Total	161 (19%)	167 (19%)	-0.4% (-4.2 to 3.3)	187 (22%)	185 (22%)	0.5% (-1.4 to 4.5)	221 (26%)	231 (27%)	-0.8% (-5.0 to 3.4)
Lower chest indrawing persisting	131 (16%)	139 (16%)	-0.7% (-4.2 to 2.8)	143 (17%)	147 (17%)	0.2% (-3.8 to 3.7)	147 (17%)	158 (18%)	-1% (-4.7 to 2.4)
Very severe disease (danger signs)	11 (1%)	7 (1%)	0.5% (-0.5 to 1.5)	11 (1%)	7 (1%)	0.5% (-0.5 to 1.5)	11 (1%)	8 (1%)	0.4% (-0.6 to 1.4)
Hypoxaemia	19 (2%)	17 (1%)	0.8% (-0.4 to 2.1)	25 (3%)	15 (2%)	1.2% (-0.2 to 2.6)	26 (3%)	16 (2%)	1.2% (-0.3 to 2.7)
Serious adverse drug reaction	5 (1%)	0	0.6% (0.1 to 1.1)	6 (1%)	0	0.7% (0.1 to 1.3)	6 (1%)	0	0.7% (0.1 to 1.3)
Received another antibiotic	13 (2%)	10 (1%)	0.4% (-0.7 to 1.5)	18 (2%)	17 (1%)	0.7% (-0.5 to 2.0)	22 (3%)	18 (2%)	1.5% (-0.9 to 3.9)
Newly diagnosed condition	16 (2%)	6 (1%)	1.2% (0.1 to 2.3)	17 (2%)	10 (1%)	0.8% (-0.3 to 2.0)	21 (3%)	17 (2%)	0.5% (-0.9 to 1.9)
Voluntary withdrawal and loss to follow-up	3	8 (1%)	-0.6% (-1.3 to 0.2)	10 (1%)	11 (1%)	-0.1% (-1.1 to 0.9)	23 (3%)	33 (4%)	-0.9% (-1.6 to -0.2)
Non-severe pneumonia*	n/a	n/a	n/a	n/a	n/a	n/a	8 (1%)	7 (1%)	0.1% (-0.8 to 1.0)
Death and other criteria†	7 (1%)	0	0.8% (0.2 to 1.4)	7 (1%)	0	0.8% (0.2 to 1.4)	7 (1%)	2	0.6% (-0.1 to 1.3)
Per-protocol analysis‡	153 (18%)	154 (18%)	0.2% (-3.6 to 3.9)	172 (21%)	169 (20%)	0.9% (-3.0 to 4.8)	194 (24%)	199 (24%)	-0.3% (-4.4 to 3.9)

n/a-not applicable. *Day 14 only. †Three (of 12) deaths not reported here because patients qualified for treatment failure by other criteria. ‡Per-protocol analysis included patients who did not follow the protocol—ie, children younger than 3 months or older than 59 months, those of an unknown age, those who took less than 80% of their antibiotics, and those who were lost to follow-up.

Table 3: Cumulative treatment failures by specific causes at 48 h, 5 days, and 14 days

saw a slight but non-significant association between injectable penicillin and treatment failure with death at 48 h and 5 days. Two of the seven deaths within 48 h occurred in HIV-infected children. All deaths were in children aged 15 months or younger.

Of the clinical and laboratory factors present at baseline that were investigated, only infancy (age 3–11 months), very fast breathing (≥ 70 breaths per min in infants and ≥ 60 breaths per min in children), and hypoxaemia were predictive of treatment failure at 48 h on multivariable logistic regression analysis (table 4). Treatment failure rates were not significantly increased at the Zambia and Durban sites with HIV prevalence (data not shown).

Children with audible wheeze on initial assessment were excluded if lower chest indrawing persisted after up to two courses of salbutamol. Nevertheless, wheezing was noted in at least one of the first four clinical assessments (done every 6 h) within 24 h of enrolment in 826 children (49%). However, failure rates between these two groups were equivalent and fell within our a-priori definition of equivalence (19.25% vs 18.74%; risk difference 0.51%, 95% CI -3.2 to 4.3). Of 870 children without wheeze in the first 24 h of enrolment, the risk difference was 0.52% (-4.7 to 5.6). Notably, the CIs were only slightly greater than our a-priori 5% definition of equivalence. We see this as an indication of the robustness of the findings, since the sample size was halved.

With respect to HIV infection and treatment failure, 523 children with severe pneumonia were enrolled at two sites (425 in Durban, 98 in Ndola) and HIV testing was undertaken on 464 (89%) of these. Of the remaining 59, 43 (8%) refused HIV testing and 16 (3%) samples were lost. Baseline characteristics of children not tested for HIV did not differ from those tested. Our analysis was restricted to the 464 patients with known HIV infection status. Of these, 262 were randomly allocated to the penicillin and 261 to the amoxicillin group. 106 (23%) children were infected with HIV; 82 (22.4% site

prevalence) at the Durban site and 24 (24.5%) at the Ndola site. HIV-infected children aged 3–11 months with higher respiratory rates were twice as likely as uninfected children to present with low oxygen saturation at baseline.

Overall, 57 (12%) of the 464 HIV-tested patients failed treatment at 48 h and 110 (24%) by 14 days. 48-h failure rates between HIV-infected and uninfected children by treatment assignment were not different (33 [14%] penicillin vs 24 [10%] amoxicillin); however, this analysis was not properly powered to address this issue. Treatment failure at 48 h occurred with greater frequency in HIV-infected (20 [19%] vs 37 [10%], relative risk 1.83, 95% CI 1.11–3.01) than in uninfected children, and was increased in children aged 3–11 months (16 [36%] vs 29 [17%], 2.08, 1.25–3.49); HIV-infected children aged 12–59 months were also more likely to fail treatment, though the effect was reduced (4 [7%] vs 8 [4%], 1.54, 0.48–4.94).

RSV was detected at baseline in about a quarter of nasopharyngeal washings obtained (table 4). Isolation

	Bivariate analysis		Odds ratio (95% CI)	Multivariate analysis* Adjusted odds ratio* (95% CI)
	Yes (failures/total)	No (failures/total)		
Male	213/267	115/445	1.16 (0.9–1.49)	-
Age 3–11 months	250/1045	67/624	1.41 (1.05–1.89)	2.72 (1.95–3.79)
Bunntending†	230/1102	69/331	1.05 (0.78–1.42)	-
Up-to-date immunisation status	255/1453	53/177	1.5 (0.75–2.71)	-
Antibiotics in past 48 h	46/157	279/1517	1.84 (1.27–2.66)	-
Weight for age Z score (-2)	47/252	278/1437	1.53 (0.66–3.31)	-
Hypothermia or high fever‡	13/79	313/1619	0.95 (0.51–1.76)	-
Very fast breathing§	105/457	212/1212	1.43 (1.08–1.84)	1.94 (1.42–2.63)
Hypoxaemia	97/325	230/1369	2.11 (1.6–2.78)	1.95 (1.34–2.83)
RSV positive	73/175	209/1153	1.06 (0.81–1.47)	-
Amoxicillin	167/857	161/845	1.83 (0.81–1.31)	1.03 (0.79–1.35)

*Adjusted odds ratio by logistic regression analysis. †Only for children aged ≥ 12 months. ‡Diaphoretic temperature $\geq 35^\circ\text{C}$, high fever, temperature $\geq 39^\circ\text{C}$. §Respiratory rate for children younger than 12 months not very fast (<20 breaths per minute) and very fast (≥ 70 breaths per min). For children aged 12 months or older respiratory rate was recorded not very fast (<60 breaths per min) and very fast (≥ 60 breaths per min).

Table 4: Bivariate and multivariate analysis of baseline risk factors predictive of treatment failure at 48 h

5

Organism susceptibility	Penicillin (n=845) Number of isolates/tested	Amoxicillin (n=857) Number of isolates/tested
<i>S pneumoniae</i> *	217/743 (29%)	201/743 (27%)
Penicillin		
Non-susceptible	142/211 (67%)	132/200 (66%)
Susceptible	69/211 (33%)	68/200 (34%)
Co-trimoxazole		
Non-susceptible	154/188 (82%)	139/175 (79%)
Susceptible	34/188 (18%)	36/175 (21%)
Chloramphenicol		
Non-susceptible	35/213 (16%)	29/199 (15%)
Susceptible	178/213 (84%)	170/199 (85%)
<i>H influenzae</i> †	145/739 (20%)	146/743 (20%)
Ampicillin		
Non-susceptible	38/140 (27%)	42/139 (30%)
Susceptible	102/140 (73%)	97/139 (70%)
Co-trimoxazole		
Non-susceptible	78/123 (63%)	76/116 (66%)
Susceptible	45/123 (37%)	40/116 (34%)
Chloramphenicol		
Non-susceptible	23/144 (16%)	29/144 (20%)
Susceptible	121/144 (84%)	115/144 (80%)

*Susceptible MIC values for *S pneumoniae*: penicillin ≤ 0.0625 , co-trimoxazole MIC ≤ 0.5 , and chloramphenicol MIC ≤ 4 . †Susceptible MIC values for *H influenzae*: ampicillin ≤ 1 , co-trimoxazole MIC ≤ 0.5 , and chloramphenicol MIC ≤ 2 .

Table 5: Isolation and resistance frequency of nasopharyngeal organisms

was not associated with treatment failure (table 4). We saw a fairly wide range in the RSV detection rates across sites, from 12.5% in Zambia to 46% in Vietnam. Nasopharyngeal swabs for *S pneumoniae* and *H influenzae* were positive in 418 (28%) of 1486 and 291 (20%) of 1482 children, respectively. Intermediate-grade to high-grade resistance of *S pneumoniae* to penicillin and co-trimoxazole (142 [67%] and 154 [82%] isolates, respectively) was present but chloramphenicol remained more or less active against both organisms (table 5).

Serious adverse events were reported in 30 children, eight in the amoxicillin group and 22 in the penicillin group. Only 13 of these individuals were thought to be either possibly or probably associated with the study drugs, and treatment was discontinued or changed in 12 of the 13 cases—all improved subsequently. None of the deaths was judged to be associated with a study drug reaction. In summary, the serious adverse events were: death (12 children), rash (five), diarrhoea (five), allergy to penicillin (two), anaemia and malaria (one), severe malaria (three; which also includes one death), and unspecified events (two).

Discussion

We have shown that oral amoxicillin and injectable penicillin are equally effective at 48 h and beyond. The 48-h treatment failure rate was similar to that of 18% Straus and colleagues reported with oral amoxicillin for the treatment of severe pneumonia.⁸ Although several baseline characteristics were predictive of treatment failure at 48 h, only infancy (age 3–11 months), severe tachypnoea, and hypoxaemia were predictive in the multivariable model, which is in accordance with the

findings of others.^{8,15,16} Infant age has also been associated with high fatality rates.^{17,19} We believe that these factors are important risk indicators of treatment failure (including death) and should be considered on an individual basis when assessing a child for admission.

The high failure rate for severe pneumonia can be partly explained by the stringent clinical criteria that we used to establish treatment failure at this endpoint. The low fatality rate lends support to this observation. Over 80% of treatment failures at 48 h were due only to persistence of lower chest indrawing; most patients improved clinically at the time and pneumonia went on to resolve soon thereafter. Despite our efforts to exclude enrolment of patients with asthma and recurrent wheezing, wheezing was a prominent component of the 48-h treatment failures. Such children might not be expected to improve on antibiotic treatment.

We identified RSV in nasopharyngeal samples from a quarter of children with severe pneumonia, which is similar to previously reported data from developing countries.^{20–24} A high detection rate was consistent with the median age of patients in our study (8 months) since RSV characteristically affects young children. Additionally, exclusion of children with reversible airways disease might have increased the proportion of those with RSV infection, which is known to be associated with bronchiolitis and small airways obstruction.

With respect to the slight difference in deaths between the treatment groups and overall in children treated with penicillin, four of the deaths in the penicillin group (data not shown) were in HIV-infected children who were more likely to be infected with organisms resistant to penicillin (eg, gram-negative organisms or *Pneumocystis jirovecii*).^{25,26} This fact, along with the increased failure rate in HIV-infected children, suggests that empiric treatment of severe pneumonia with oral amoxicillin or parenteral penicillin alone is insufficient in areas of high HIV prevalence. Diagnostic capabilities in most developing countries are few for both HIV infection and *P jirovecii* pneumonia, and children with respiratory infection are usually managed on the basis of clinical algorithms; management is done with a small number of antimicrobials and without confirmation of HIV status. We have shown that the empiric treatment of severe pneumonia using the WHO clinical treatment algorithm resulted in a substantially increased failure rate in HIV-positive children, despite our attempts to exclude children with a history or evidence of moderate or severely symptomatic HIV disease. Treatment regimens that include both a wider spectrum of antibacterial and specific pneumocystis activity will be needed.

Although our final enrolment of participants was less than the calculated target, it still provided 90% power. A potential strength of this study was that very few adverse events were related to the study drugs, which necessitated a change in treatment, especially with amoxicillin.

Further, we included several sites that were representative of diverse circumstances in the developing world, to increase the generalisability of our results.

This study had several potential limitations. First, site investigators were not masked to the treatment allocation when the primary outcome of failure was recorded. Although a blinded study would have avoided such potential bias, we felt that placebo injections were not ethical to give to children. We believe that the bias that might have been introduced by being unblinded was counteracted by the strict clinical criteria used, and the requirement that the site investigator and one other clinical staff agree on all treatment failures. Second, the power to detect equivalence might have been reduced because a proportion of enrolled children had lower chest indrawing from a non-bacterial cause (eg, asthma or RSV). However, the finding that equivalence was nearly achieved when only children without wheezing in the first 24 h were analysed suggests that a non-bacterial cause was not a substantial factor and that our findings are robust. Additionally, mixed viral and bacterial infections are common in children from both developing and developed countries,^{27,28} and WHO recommends that, "Children without a previous history of wheeze who develop a lower respiratory infection with wheeze and tachypnoea may have a bacterial or a mixed viral-bacterial infection and should be treated with antibiotics for suspected bacterial pneumonia".²⁹ Third, we used clinical signs alone to diagnose severe pneumonia, without radiographic or microbiological confirmation of the diagnosis. Although lower chest indrawing is strongly correlated with bacterial and radiological pneumonia,^{30,31} adequate radiography and microbiology are generally not available in many developing countries.

A fourth potential limitation is the heterogeneity of study sites; two were at high altitude and might have increased the clinical failure rate as determined by oxygen saturation, and another two were in areas of high-HIV prevalence where the spectrum of presenting pulmonary infections was different to that in low-prevalence areas. Although we had hoped to restrict enrolment to mildly infected or non-immunocompromised children from high HIV-prevalence sites, the high initial death rate suggested that presenting clinical criteria were not an adequate indicator of such infection. The expanded exclusion criteria mandated by the independent data safety monitoring board were seemingly sufficient, since only one additional death was recorded from these sites after these changes were put in place. Fifth, we did not test for antibiotic activity in the urine of participants, which might have resulted in some children being enrolled who had received antibiotics before admission. Last, amoxicillin was given in hospital for 48 h under a controlled environment and adherence to oral amoxicillin treatment cannot be assumed to be as adequate when given at home, especially in poor communities.

Active-control equivalency trials might be difficult to interpret because of built-in design flaws that could make non-inferiority (or equivalence) difficult to firmly establish,³² as has been described for acute otitis media.³³ Because acute otitis media often resolves spontaneously, clinical trials with long-term endpoints have been criticised for including too many potentially spontaneous cures, thus reducing the number of possible cases truly responding to treatment effect. In our study, we allowed for this possibility by (1) excluding children who responded to a trial of bronchodilators and might have had lower chest indrawing due solely to airways disease, and (2) choosing 48 h for the primary outcome, during which spontaneous cures were less likely to take place.

Our findings have several important beneficial implications if applied as public-health policy; oral amoxicillin will reduce (1) the risk of needle-associated complications such as needle-borne infections; (2) the need for referral or admission; (3) treatment administration costs; and (4) transport, food, and lost income costs for the family. The role of oral amoxicillin in treatment of severe pneumonia in a public-health setting at the community or household level needs to be established. Additionally, targeted research is needed to improve the specificity of clinical treatment failure criteria. These two recommendations have been identified as priority research areas by WHO.³⁴ Finally, and importantly, a nested analysis of these data from the two sites with high HIV prevalence shows that these recommendations should not be applied in such areas, and the best treatment regimens in these settings need to be ascertained.

Contributors

S A Qazi and D Thea were involved in the study design, analysis and interpretation of data, writing of the report, and the decision to submit the paper for publication. O Fontaine was involved in the study design. W MacLeod was involved in the data coordination, analysis and interpretation of data, and writing of the report. M Fox was involved in the analysis and interpretation of data and writing of the report. J Simon was involved in the development of the study design. P Halberd was hired as a consultant by the ARCH Project to help with the study design, analysis and interpretation of data, and writing of the report.

List of contributors (in alphabetical order)

E Addo-Yobo, Y Adu-Sarkodie, P Arthur (deceased), B Baffoe-Bonnie, I Cardenas, N Chasaka, H M Coovadia, O Fontaine, E Goldard, C Granados, N Hader, M Hassan, P Halberd, C T Ho, G Hussay, P Jeena, Q T Le, T N B Le, J Lozano, W Macleod, S V Martinez, J Maulen-Radovan, G McGillivray, M Muzinaq (deceased), N T V Nguyen, A Patel, H N D Phan, S Qazi, J G Rutz, H Shiran, J Simon, N Sheele, T Sulwa, S S Tambhrawale, D Thea, S Thula, A T Tran, J Tshuma, K Yeboah-Annan.

Conflict of interest statement

S A Qazi and O Fontaine are medical officers in the Department of Child and Adolescent Health and Development, WHO. D Thea is a professor of the ARCH Project at the Boston University. W MacLeod, M Fox, and J Simon work for the ARCH Project at the Boston University. The proposal development workshop was held in Durban, South Africa, and the data analysis and manuscript writing workshop was held in NH, USA. Participants in the contributor list for these two activities were supported jointly by WHO and the ARCH Project. Other authors and contributors have declared no conflict of interest.

Acknowledgments

The Department of Child and Adolescent Health and Development, WHO, Geneva, and the Applied Research Child Health (ARCH) project, Boston University, Boston, under USAID cooperative agreement HRN-A-00-96-90010-00 provided funding for the study. The results of this study were presented in part at the 33rd World Conference on Lung Health of the International Union Against Tuberculosis and Lung Disease (IUATLD), Montreal, Canada, Oct 6–10, 2002; at the 19th INCLIN Global Meeting, Kunming, China, Feb 19–23, 2003; and at the second International Conference on Improving Use of Medicines (ICIUM), Chiang Mai, Thailand, March 30–April 2, 2004.

References

- Mulholland K. Magnitude of the problem of childhood pneumonia. *Lancet* 1999; 354: 590–92.
- Mathers CD, Murray CJL, Lopez AD, Stein C. The global burden of disease 2000 project: objectives, methods, data sources, and preliminary results. Evidence and information for policy (EIP). Geneva: World Health Organization, 2001.
- Williams BG, Gouws E, Boschi-Pinto C, Bryce J, Dye C. Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect Dis* 2002; 2: 25–32.
- Shann F. Etiology of severe pneumonia in children in developing countries. *Pediatr Infect Dis J* 1986; 5: 247–52.
- World Health Organization. WHO Programme for the Control of Acute Respiratory Infections. Acute respiratory infections in children: case management in small hospitals in developing countries. Geneva: World Health Organization, 1990. Report number 5.
- Qazi SA, Rehman GN, Khan MA. Reduction in acute respiratory infection hospital mortality with standard ari case management. Islamabad, Pakistan: Federal ARI Cell, National ARI Control Programme, the Children' Hospital, Institute of Medical Sciences, 1995.
- Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis* 2003; 3: 547–56.
- Straus WL, Qazi SA, Kundi Z, Nomani NK, Schwartz B. Antimicrobial resistance and clinical effectiveness of co-trimoxazole versus amoxicillin for pneumonia among children in Pakistan: randomised controlled trial. *Lancet* 1998; 352: 270–74.
- Forrest KV, Jorgensen JH, Murray PR. Manual of clinical microbiology, 8th edn. Washington, DC: American Society for Microbiology, 2003.
- Centers for Disease Control and Prevention. 1994 revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR Morb Mortal Wkly Rep* 1994; 43 (RR-12): 1–19.
- Qazi SA, Rehman GN, Khan MA. Standard management of acute respiratory infections in a children's hospital in Pakistan: impact on antibiotic use and case fatality. *Bull World Health Organ* 1996; 74: 501–07.
- O'Brien PC. Procedures for comparing samples with multiple endpoints. *Biometrics* 1984; 40: 1079–87.
- O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. *Biometrics* 1979; 35: 549–56.
- Chow SC, Shao J. A note on statistical methods for assessing therapeutic equivalence. *Control Clin Trials* 2002; 23: 515–20.
- MASCOT 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.
- Catchup study group. Clinical efficacy of co-trimoxazole versus amoxicillin twice daily for treatment of pneumonia: a randomised controlled clinical trial in Pakistan. *Arch Dis Child* 2002; 86: 113–18.
- Shann F, Barker J, Poore P. Clinical signs that predict death in children with severe pneumonia. *Pediatr Infect Dis J* 1989; 8: 852–55.
- Tupasi TE, Velmonte MA, Sanvictores ME, et al. Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. *J Infect Dis* 1988; 157: 615–23.
- Sehgal V, Sethi GR, Sachdev HP, Satyanarayana L. Predictors of mortality in subjects hospitalized with acute lower respiratory tract infections. *Indian Pediatr* 1997; 34: 213–19.
- Hussey GD, Apolles P, Arendse Z, et al. Respiratory syncytial virus infection in children hospitalised with acute lower respiratory tract infection. *S Afr Med J* 2000; 90: 509–12.
- Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *Pediatr Infect Dis J* 2003; 22: S21–S32.
- Weber MW, Mulholland EK, Greenwood BM. Respiratory syncytial virus infection in tropical and developing countries. *Trop Med Int Health* 1998; 3: 268–80.
- Chan FW, Chew FT, Tan TN, Chua KB, Hooi PS. Seasonal variation in respiratory syncytial virus chest infection in the tropics. *Pediatr Pulmonol* 2002; 34: 47–51.
- Delport SD, Brisley T. Aetiology and outcome of severe community-acquired pneumonia in children admitted to a paediatric intensive care unit. *S Afr Med J* 2002; 92: 907–11.
- Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: a descriptive necropsy study. *Lancet* 2002; 360: 985–90.
- Zar HJ. *Pneumocystis carinii* pneumonia (PCP) in HIV-infected African children. *SADJ* 2001; 56: 617–19.
- Ghafoor A, Nomani NK, Ishaq Z, et al. Diagnoses of acute lower respiratory tract infections in children in Rawalpindi and Islamabad, Pakistan. *Rev Infect Dis* 1990; 12: suppl-14.
- Juven T, Mertsola J, Waris M, et al. Etiology of community-acquired pneumonia in 254 hospitalized children. *Pediatr Infect Dis J* 2000; 19: 293–98.
- Forgie JM, Campbell H, Lloyd-Evans N, et al. Etiology of acute lower respiratory tract infections in children in a rural community in The Gambia. *Pediatr Infect Dis J* 1992; 11: 466–73.
- Tupasi TE, Lucero MG, Magdangal DM, et al. Etiology of acute lower respiratory tract infection in children from Alabang, Metro Manila. *Rev Infect Dis* 1990; 12 (suppl 8): S929–S939.
- Korppi M, Leinonen M, Koskela M, Makela PH, Launiala K. Bacterial coinfection in children hospitalized with respiratory syncytial virus infections. *Pediatr Infect Dis J* 1989; 8: 687–92.
- Hietala J, Uhari M, Tuokko H, Leinonen M. Mixed bacterial and viral infections are common in children. *Pediatr Infect Dis J* 1989; 8: 683–86.
- World Health Organization. Bronchodilators and other medications for the treatment of wheeze-associated illnesses in young children. Programme for the Control of Acute Respiratory Infections. http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO_AR1_93_29.htm (accessed March 25, 2004).
- Pepin J, Demers AM, Mberyo-Yaah F, et al. Acute lower respiratory infections among children hospitalized in Bangui, Central African Republic: toward a new case-management algorithm. *Trans R Soc Trop Med Hyg* 2001; 95: 410–17.
- Nascimento-Carvalho CM, Rocha H, Benguigui Y. Association of crackles and/or wheezing with tachypnea or chest indrawing in children with pneumonia. *Indian Pediatr* 2002; 39: 205–07.
- Usha N, Katariya S, Walia BN. Simple clinical signs of lower respiratory infection. *Trop Doct* 1990; 20: 158–60.
- Marchant CD. Acute otitis media, antibiotics, children and clinical trial design. *Pediatr Infect Dis J* 2002; 21: 891–93.
- Dagan R, McCracken GH Jr. Flaws in design and conduct of clinical trials in acute otitis media. *Pediatr Infect Dis J* 2002; 21: 894–902.
- Marchant CD, Carlin SA, Johnson CE, Shurin PA. Measuring the comparative efficacy of antibacterial agents for acute otitis media: the "Pollyanna phenomenon". *J Pediatr* 1992; 120: 72–77.
- World Health Organization. Report of consultative meeting to review evidence and research priorities in the management of acute respiratory infections (ARI). Geneva: WHO, 2003. WHO/FCH/CAH/04.2.

Institutional affiliations and qualifications (alphabetical order)	
Department of Pediatrics, School of Medicine, Universidad Javeriana, Bogota, Columbia	Prof Juan Lozano, MD, MSc Dr Claudia Granados, MD Prof Luis Cardenas, MD Prof Juan G Ruiz, MD, MSc
Department of Child Health, School of Medical Sciences, Komfo Anokye Teaching Hospital, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana	Dr Emmanuel Addo-Yobo, MD, MSc Dr Kojo Yeboah-Antwi, MB ChB, MPH Dr Yaw Adu-Sarkodie, MB ChB, MSc Dr Paul Arthur (deceased), MB ChB, MSc Prof Ben Baffoe-Bonnie, FWACP
Clinical Epidemiology Unit and Department of Paediatrics, Indira Gandhi Medical Institute, Nagpur, India	Dr Archana Patel, MD, MSc Dr Tankhiwale, MD
Instituto Nacional de Pediatria, Division de Investigacion, Mexico City, Mexico	Dr Irene Maulen-Radovan, MD Dr Sandra V Martinez, MD
Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan	Prof Mumtaz Hassan, FRCPC, FRCP Dr Haider Shirazi, MCPS, DCH, FCPS Dr Nadeem Haider, MBBS, DCH Dr Mohammad Mushfaq (deceased), MBBS, DCH
Red Cross Children's Hospital, Cape Town, South Africa	Prof Gregory Hussey, MD Dr George McGillivray, MD
Department of Paediatrics, University of Natal, Durban, South Africa	Prof Prakash Jeena, FCP (Paeds), FCP (Pulm) Prof Hossain M. Coovadia, MD Dr Stanley Thula, MD
Applied Research in Child Health (ARCH) Project, Center for International Health, Boston University, Boston, MA USA	Mr Matthew Fox, MPH Dr William MacLeod, DSc Dr Jonathan Simon, DSc Prof Donald Thea, MD, MSc
Clinical Research Institute, New England Medical Center Tufts University, Boston, MA, USA	Prof Patricia Hibberd, MD, PhD Dr Nguyen Ngoc Tuong Vy, MD Dr Tran Anh Tuan, MD
Children's Hospital number 1, Ho Chi Minh City, Vietnam	Dr Le Thi Ngoc Bich Dr Phan Huu Nguyet Diem Dr Ho Chi Thanh Dr Le Quoc Thinh
Department of Child and Adolescent Health and Development, World Health Organization, Geneva, Switzerland	Dr Olivier Fontaine, MD
Department of Clinical Sciences, Tropical Disease Research Centre (TDRC), Ndola, Zambia and Arthur Davidson Children's Hospital, Ndola, Zambia	Dr Shamim Qazi, MBBS, DCH, MSc, MD Paediatrics Dr Noel Chisaka, MD, MSc (TDRC)* Dr Thomas Sukwa, MD, PhD (TDRC)* Dr Nombulelo Skeile, MD (TDRC) Dr Jean Tshiula, MD (ADCH)
* Currently at WHO African Regional Office (AFRO), Harare, Zimbabwe.	