Research

Randomized controlled trial of standard versus double dose cotrimoxazole for childhood pneumonia in Pakistan

Zeba A. Rasmussen,[1] Abdul Bari,[2] Shamim Qazi,[3] Gul Rehman,[3] Iqbal Azam,[1] SherBaz Khan,[4] Farida Aziz,[5] Sadia Rafi,[6] Mehr Taj Roghani,[7] Imran Iqbal,[8] Abdul Ghaffar Nagi,[9] Waqar Hussain,[10] Nahida Bano,[1] late J.C. van Latum,[4] & Mushtaq Khan[3] for the Pakistan COMET (Cotrimoxazole Multicentre Efficacy Trial) Study Group

Objective Increasing concern over bacterial resistance to cotrimoxazole, which is recommended by WHO as a first-line drug for treating non-severe pneumonia, led to the suggestion that this might not be optimal therapy. However, changing to alternative antimicrobial agents, such as amoxicillin, is costly. We compared the clinical efficacy of twice-daily cotrimoxazole in standard versus double dosage for treating non-severe pneumonia in children.

Methods A randomized controlled multicentre trial was implemented in seven hospital outpatient departments and two community health programmes. A total of 1143 children aged 2–59 months with non-severe pneumonia were randomly allocated to receive 4 mg trimethoprim plus 20 mg sulfamethoxazole/kg of body weight or 8 mg trimethoprim plus 40 mg sulfamethoxazole/kg of body weight orally twice-daily for 5 days Treatment failure occurred when a child required a change of therapy, died or was lost to follow-up. Children required a change of therapy if their condition worsened (they developed chest indrawing or danger signs) or if at 48 hours after enrolment, their clinical condition was the same (defined as having a respiratory rate that was 5 breaths/minute higher or lower than at the time of enrolment).

Findings The results of 1134 children were analysed: 578 were assigned to the standard dose of cotrimoxazole and 556 to the double dose. Treatment failed in 112 children (19.4%) in the standard group and 118 (21.2%) in the double-dose group (relative risk 1.10; 95% confidence interval = 0.87–1.37). Using multivariate analysis we found that treatment was more likely to fail in children who were not given the medicine correctly ($P = 0.001$), in those younger than 12 months ($P = 0.004$), those who had used antibiotics previously ($P = 0.002$), those whose respiratory rate was $\geqslant$ 20 breaths/minute above the age-specific cut-off point ($P = 0.006$), and those from urban areas ($P = 0.042$).

Conclusion Both standard and double strength cotrimoxazole were equally effective in treating non-severe pneumonia. Close follow-up of patients is essential to prevent worsening of disease. Definitions of clinical failure need to be more specific. Surveillance in both rural and urban areas is essential in the development of treatment policies that are based on clinical outcomes.

Keywords Trimethoprim-sulfamethoxazole combination/administration and dosage/therapeutic use; Pneumonia, Bacterial/drug therapy; Treatment failure; Child; Randomized controlled trials; Multicenter studies; Pakistan (*source: MeSH, NLM*).

Mots clés Triméthoprime-sulfaméthoxazole, Association/administration et posologie/usage thérapeutique; Pneumonie bactérienne/chimiothérapie; Echec thérapeutique; Enfant; Essai clinique randomisé; Etude multicentrique; Pakistan (*source: MeSH, INSERM*).

Palabras clave Combinación trimetoprim-sulfametoxazol/administración y dosificación/uso terapéutico; Neumonía bacteriana/quimioterapia; Insuficiencia del tratamiento; Niño; Ensayos controlados aleatorios; Estudios multicéntricos; Pakistán (*fuente: DeCS, BIREME*).

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Voir page 17 le résumé en français. En la página 18 figura un resumen en español. يمكن الاطلاع على الملخص بالعربية في صفحة 18.

[1] Aga Khan University Departments of Community Health Sciences and Medicine, Aga Khan University, House 32B Street 25, Sector F-8-2 Islamabad, Pakistan. Correspondence should be sent to Dr Rasmussen (email zeba@comsats.net.pk).
[2] Federal ARI Cell, National ARI Programme, Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.
[3] Children's Hospital, Pakistan Institute of Medical Sciences, Islamabad, Pakistan.
[4] Aga Khan Health Services, Gilgit, Pakistan.
[5] Ayub Medical College Hospital, Department of Paediatrics, Abbottabad, Pakistan.
[6] Civil Hospital Department of Paediatrics, Karachi, Pakistan.
[7] Hayat Shaheed Teaching Hospital, Department of Paediatrics, Peshawar, Pakistan.
[8] Nishtar Hospital, Department of Paediatrics, Multan, Pakistan.
[9] Sandeman Provincial Hospital, Department of Paediatrics, Quetta, Pakistan.
[10] Shaikh Zayed Hospital, Department of Paediatrics, Lahore, Pakistan.

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Introduction

WHO estimates that 1.9 million deaths occur every year from lower respiratory infections, primarily pneumonia, mostly in developing countries (*1*). Because *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common causes of childhood bacterial pneumonia in developing countries, WHO, using standardized case management guidelines, recommends using oral cotrimoxazole or amoxicillin to treat non-severe pneumonia at first-level health facilities (*2*, *3*).

Pneumonia is a leading cause of death among children in Pakistan. In 1989, the Government of Pakistan adopted WHO's recommendation to use oral cotrimoxazole as first-line outpatient treatment for non-severe pneumonia because of its cost, twice-daily dosage schedule, efficacy and wide availability (*4*). While high rates of resistance in nasopharyngeal and blood isolates were documented from 1986 to 1994 (*5*–*8*), studies in the early 1990s showed that cotrimoxazole was effective in treating more than 90% of children who had community-acquired pneumonia (*9*, *10*). A 1991–92 hospital-based study found no difference in clinical efficacy between twice-daily cotrimoxazole and thrice-daily amoxicillin for treating non-severe pneumonia (failure rates of 13% and 12%, respectively) (*11*).

Changing from cotrimoxazole to amoxicillin would cost an estimated US$ 25 million yearly in Pakistan, a significant proportion of the national health budget (*12*). Due to the faster elimination of one component of cotrimoxazole (trimethoprim) in young children, higher doses are needed to achieve plasma concentrations comparable to those observed in adults, leading to the suggestion that the daily dose of trimethoprim should be increased by 100% for younger children (*13*). We evaluated the clinical effectiveness of cotrimoxazole in standard versus double doses to treat children with non-severe pneumonia.

Methods

Patients

We conducted a randomized controlled double-blind multicentre trial in seven urban and two rural sites, one with dispersed health centres (Table 1). Children were seen in hospital outpatient or community clinics. Free and informed consent was obtained from children's parents; procedures followed for obtaining consent were in accordance with the ethical standards of the Declaration of Helsinki (*14*). The National ARI Control Programme in Pakistan approved the study.

Children aged 2–59 months presenting with cough and difficult or fast breathing (tachypnoea) were assessed using the standard WHO acute respiratory infection (ARI) algorithm, which has been shown to have a sensitivity and specificity of 80% for the diagnosis of pneumonia (*2*, *3*). Children were classified as having non-severe pneumonia if their respiratory rate was ⩾ 50 breaths per minute and they were aged 2–11 months and if their respiratory rate was ⩾ 40 breaths per minute if they were aged 12–59 months. Children were classified as having severe pneumonia if they had lower chest wall indrawing (with or without tachypnoea); they were classified as having very severe disease if one or more danger signs were present (convulsions, drowsiness, inability to drink, stridor in a calm child, and clinically severe malnutrition).

The respiratory rate used for assessment was the average of two readings taken for 1 minute each when the child was quiet, feeding or asleep. Children who were wheezing received nebulized or inhaled salbutamol and were reassessed for tachypnoea after 30 minutes. Febrile children received paracetamol.

Children with non-severe pneumonia constituted our study population. Excluded were children with severe pneumonia, very severe disease, stridor, acute nonpulmonary or underlying chronic illness (including asthma, which was defined as a history of wheezing ⩾ 3 times if wheezing was present at the current evaluation), history of cotrimoxazole allergy, administration of WHO-recommended antimicrobials in appropriate doses during the previous 48 hours, or if the parents declined to participate. Children with severe malnutrition were excluded because WHO recommends they be referred to secondary care facilities for inpatient therapy (*2*). To ensure follow-up, at home if needed, only children living within the municipal limits of urban sites and walking distance (< 5 km) of the clinic in rural sites were enrolled.

A senior clinician supervised the study at every site. In urban sites, study physicians collected data. In rural sites, "lady health visitors" (a recognized category of paramedical workers in Pakistan) collected data under the supervision of a study physician. Study personnel were trained in standard ARI case management and study methodology at the coordinating centre, the Children's Hospital in Islamabad; at rural sites, study personnel trained the lady health visitors assigned to peripheral health centres. The study coordinator visited every site.

A randomization scheme for 200 patients was generated for each site using a computer program that allocated patients to uneven blocks of two, four and six patients. To cater for children of different weights, two bottles of medicine were prepared for each code. Each site received an equal number of each strength of cotrimoxazole packaged in identical bottles with the same appearance and taste: standard strength (200 mg sulfamethoxazole plus 40 mg trimethoprim per 5 ml suspension) and double strength (400 mg sulfamethoxazole plus 80 mg trimethoprim per 5 ml suspension). The randomization list with unique identification numbers was kept by the company preparing the cotrimoxazole and a health professional who randomly allocated the drugs but who was not involved in study implementation. Drug assignment was concealed from parents and study personnel. The code was broken after primary analysis of the data.

Data were not collected on all children eligible for enrolment, however, efforts were made to recruit as many children as possible. Children meeting entry criteria were enrolled by study personnel and randomly allocated, after informed witnessed verbal consent was obtained, to receive a uniquely coded set of two bottles containing the same strength of cotrimoxazole to be given twice daily for five days: 4 mg trimethoprim plus 20 mg sulfamethoxazole per kg of body weight (standard dose) or 8 mg (double dose) trimethoprim plus 40 mg sulfamethoxazole per kg of body weight.

All mothers received standard ARI home management instructions (feed the child, increase the intake of fluids, soothe the throat and relieve cough with safe local remedies, such as honey water or green tea) that emphasized they should watch for worsening symptoms (chest indrawing or other danger signs) and that they should bring the child in at any time if they had concerns. The proper dose and frequency and duration of administration of the drug were carefully explained. Compliance was evaluated at each follow-up visit. Children were considered to have been receiving the correct dose if the mother reported giving the prescribed dose; bottles were checked to estimate if 80% of the required dose had been given.

Table 1. **Characteristics of 1134 children with non-severe pneumonia enrolled in study of standard dose versus double dose treatment with cotrimoxazole, by treatment group**

Characteristics	Treatment group	
	Standard dose (*n* = 578)	Double dose (*n* = 556)
Site of enrolment[a]		
Abbottabad	16 (2.8)[b]	13 (2.3)
Gilgit (Oshikandass village, rural)	76 (13.1)	74 (13.3)
Gilgit (rural, dispersed centres in periphery)	56 (9.7)	49 (8.8)
Islamabad	88 (15.2)	84 (15.1)
Karachi	74 (12.8)	69 (12.4)
Lahore	28 (4.8)	39 (7.0)
Multan	100 (17.3)	99 (17.8)
Peshawar	99 (17.1)	100 (18.0)
Quetta	41 (7.1)	29 (5.2)
Urban	446 (77.2)	433 (77.9)
Age[c]	11 (5–21)	11 (5-21)
2–11 months	297 (51.4)	280 (50.4)
12–59 months	281 (48.6)	276 (49.6)
Male	369 (63.8)	330 (59.4)
History at baseline		
No. of days ill prior to presentation[c]	3 (2–5)	3 (2–5)
Fever	511 (88.4)	491 (88.3)
Cough	552 (95.5)	531 (95.5)
Difficulty breathing	313 (54.2)	319 (57.4)
Tight chest binding	8 (1.4)	8 (1.4)
Documented antibiotic use in past 7 days[d]	20 (3.5)	28 (5.0)
Wheezing ⩾ 3 times at any time in the past	23 (4.0)	22 (4.0)
Vomiting	152 (26.3)	148 (26.6)
Diarrhoea	97 (16.8)	104 (18.7)
Current breastfeeding[e]		
Age 2–11 months	257 (44.5)	238 (42.8)
Age 12–23 months	105 (18.2)	93 (16.7)
Examination at baseline		
Respiratory rate[c]		
2–11 months	58.0 (54.5–62.0)	59.0 (55.5–63.0)
12–59 months	50.0 (46.0–55.5)	50.0 (45.0–54.0)
High respiratory rate[f]	54 (9.3)	63 (11.3)
Wheezing	149 (25.8)	144 (25.9)
2–11 months	103 (34.7)	79 (28.2)
12–59 months	46 (16.4)	65 (23.6)
Malnourished[g]	88 (15.3)[h]	87 (15.7)[i]
Weight-for-age score[c]	-0.82 (-1.64 – -0.11)	-0.90 (-1.67 – 0.03)
During the study		
Was not given medicine correctly	33 (5.7)	31 (5.6)
Wheezing at any time after enrolment	159 (27.5)	157 (28.2)

[a] As defined by the local government urban areas have > 5000 inhabitants, educational and health facilities, infrastructure, a post office and are areas where most of the population works in nonagricultural sectors. Rural areas are those that have ⩽ 5000 inhabitants and where the majority of the population works in agriculture.
[b] Values in parentheses are percentages unless otherwise indicated.
[c] Values are medians (interquartile range).
[d] Assessed by either the presence of a prescription, presence of a medicine bottle or parent or caretaker knowing the name of the antibiotic.
[e] 18 children ⩾ 2 years old in the group receiving the standard dose and 20 in the group receiving the double dose were being breastfed.
[f] A high respiratory rate was one in which the child had ⩾ 20 breaths/minute above the age-adjusted WHO threshold for tachypnoea, that is ⩾ 70 for children aged 2–11 months and ⩾ 60 for those aged 12–59 months.
[g] Weight-for-age scores > 2 standard deviations below normal (*15*).
[h] *n* = 575.
[i] *n* = 553.

After enrolment (day 0), children were reassessed on day 2 and day 5, and if they had not been receiving the correct dose or if therapy was changed (see below) they were also seen on day 7; examination was generally done by the same person. Children not presenting for scheduled follow-up visits were assessed at home the next day, or if they were unable to be traced they were considered lost to follow-up. At follow-up visits, clinical assessment was based on the mother's opinion of the child's condition and the health worker's assessment. Children were considered to have improved if they had a slower respiratory rate (either within the normal range for their age, or > 5 breaths/minute lower than at the time of the previous evaluation); they were considered to be the same if there was persistent tachypnoea (their respiratory rate was 5 breaths/minute higher or lower than at the time of previous evaluation) without chest indrawing or danger signs. A child's condition was considered to have worsened if he or she had developed severe pneumonia or very severe disease. Patients whose condition worsened were referred for inpatient parenteral treatment with benzylpenicillin, ampicillin or chloramphenicol. If parenteral therapy could not be given, oral chloramphenicol (25 mg/kg every 6 hours) was prescribed.

Children whose condition had improved on day 2 continued cotrimoxazole until day 5, or if they had not been given the medicine as prescribed they continued until day 7. If a child had been given the drug correctly and his or her condition was considered to be the same on day 2 or day 5, therapy was changed to oral amoxicillin (15 mg/kg every 8 hours). Children who had not been given their medicine correctly and whose condition was the same on day 2 continued with cotrimoxazole for 2 more days and were then reassessed; if their condition remained the same, the drug was changed to amoxicillin. Children whose treatment was changed to amoxicillin were re-evaluated every 48–72 hours after changing medication until cured. Children who did not improve after 48 hours on amoxicillin were referred for parenteral therapy.

Clinical cure was defined as improvement with return of respiratory rate to the age-specific normal range. The primary outcomes were defined as treatment success (resolution on cotrimoxazole) and treatment failure (change of therapy, death or loss to follow-up).

Statistical analysis

The sample size was calculated to show a 5% difference in treatment outcomes between children receiving standard dose and those receiving double dose cotrimoxazole. Our hypothesis was that the failure rate would be lower with the double dose of cotrimoxazole (5%) than with the standard dose (10%) (*9*, *10*). With $\alpha = 0.05$ and a power of 80%, a sample size of 474 children in each group was needed.

Data were recorded on autocopy data forms, one of which was kept on-site and one of which was sent to the coordinating centre. Double data entry was performed at two sites (Children's Hospital, Islamabad, and Aga Khan Health Service, Gilgit) and validated using Epi Info software version 6, (Centers for Disease Control and Prevention, Atlanta, GA, USA). The range and internal consistency of the data were checked. Analysis was carried out using Epi Info and the SPSS software package version 10 (SPSS Inc., Chicago, IL, USA).

Baseline characteristics of the two treatment groups were compared. Outcomes for the groups were compared using an estimation of relative risk with 95% confidence intervals (CIs). Data were compared for the treatment success and treatment failure groups. Univariate analysis of categorical variables included estimates of relative risks and 95% CIs and the Student's *t*-test for continuous variables; for the *t*-test, only *P*-values are reported.

Multivariate logistic regression analysis was carried out to identify the determinants of treatment failure. In all analyses the treatment group indicator was retained to reflect the original design of the study. To ensure our results were relevant to the management of pneumonia at the programme level, we categorized some continuous variables, such as age, duration of illness and respiratory rate, for logistic regression analysis. Malnutrition was defined as weight-for-age scores that were >2 standard deviations below normal (*15*).

Findings

Between October 1995 and July 1996, 1143 children were enrolled in the study. The analysis of the primary outcome involved 1134/1143 patients, excluding 8 who were incorrectly enrolled and 1 who did not received the allocated intervention. After excluding these 9 cases of protocol violation, 578 children received the standard dose and 556 received the double dose of cotrimoxazole (Fig. 1). Thus these children received the intended treatment and their results were analysed for the primary outcome measure.

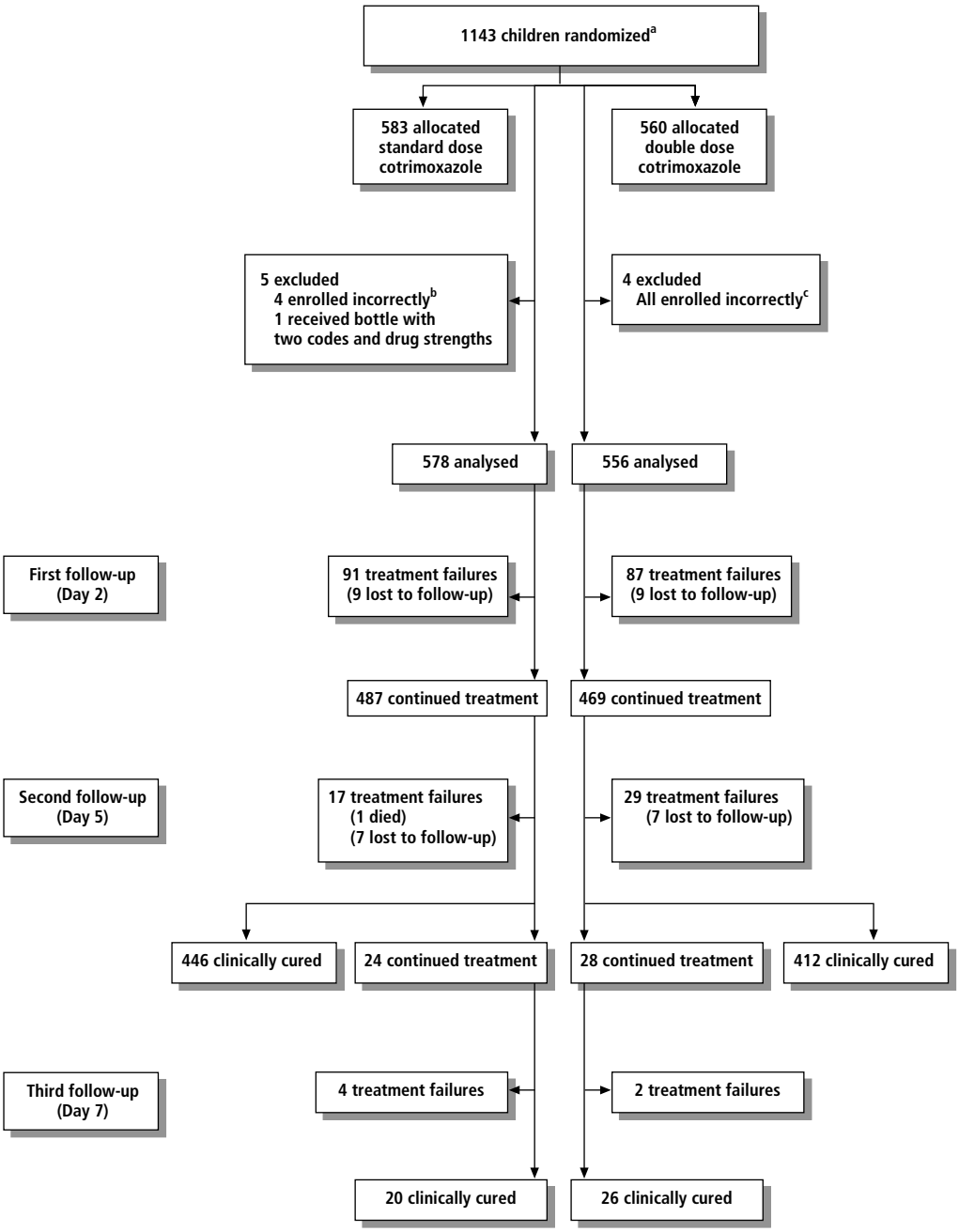
The median age of the children was 11 months (interquartile range = 5–21 months); 577 children (50.9%) were younger than 12 months old. Baseline and intrastudy characteristics are presented in Table 1. At enrolment, wheeze was more frequent in children aged < 12 months of age (182/577; 31.5%) than in older children (111/557; 19.9%) (relative risk (RR) 1.58; 95% CI = 1.29–1.94).

Treatment failure occurred in 230 children (20.3%) (Fig. 1). Clinical success was similar in the standard dose and double dose groups: 466 children in standard dose group (80.6%) and 438 in the double dose group (78.8%) (RR = 1.10; 95% CI = 0.87–1.37). A total of 32 children (2.8%) were lost to follow-up. In the standard dose group, drug treatment was withdrawn in 5 children because of rash (0.7%); it was withdrawn from 1 child (0.2%) in the double dose group. The difference was not significant (RR = 3.85; 95% CI = 0.43–34.32). No serious side-effects occurred.

Of the 198 children requiring a change of therapy (Fig. 2), 161 (81.3%) were cured on amoxicillin, 1 (0.5%) was cured with chloramphenicol, 24 (12.1%) on parenteral antibiotics, 1 died (3-month-old hospitalized male with very severe disease), and the final outcome of 11 children (5.5%) was unknown. Of these 11, 7 were referred to hospital; 3 had had their drug changed to amoxicillin; and 1 had cotrimoxazole stopped due to rash. Three had improved at the time of their last follow-up.

On day 2, 910/1134 children (80.2%) were classified as improved; 133 (11.7%) were the same; and 68 (6.0%) were worse. Altogether 23 children (2.0%) were not seen (18 lost to follow-up, 5 cured on cotrimoxazole). There was no significant difference between the two treatment groups among the children at the first follow-up visit. Of 68 whose condition deteriorated, 41 developed severe pneumonia and 27 developed very severe disease (Fig. 2). Of the 910 children who improved, 33 subsequently required a change of therapy. Of the 133 who remained the same, the drug treatment was changed according to protocol in 87 but not changed according to protocol in 46; 35 of these 46 children (76.0%) recovered on cotrimoxazole.

Fig. 1. **Flowchart showing how patients proceeded through the study**



Clinically cured	**466 (80.6%)**	**438 (78.8%)**
Treatment failures	**112 (19.4%)**	**118 (21.2%)**
Change in therapy[d]	**96 (16.6%)**	**102 (18.3%)**
Lost to follow-up	**16 (2.8%)**	**16 (2.9%)**

[a] Uniform information on all eligible patients is not available.

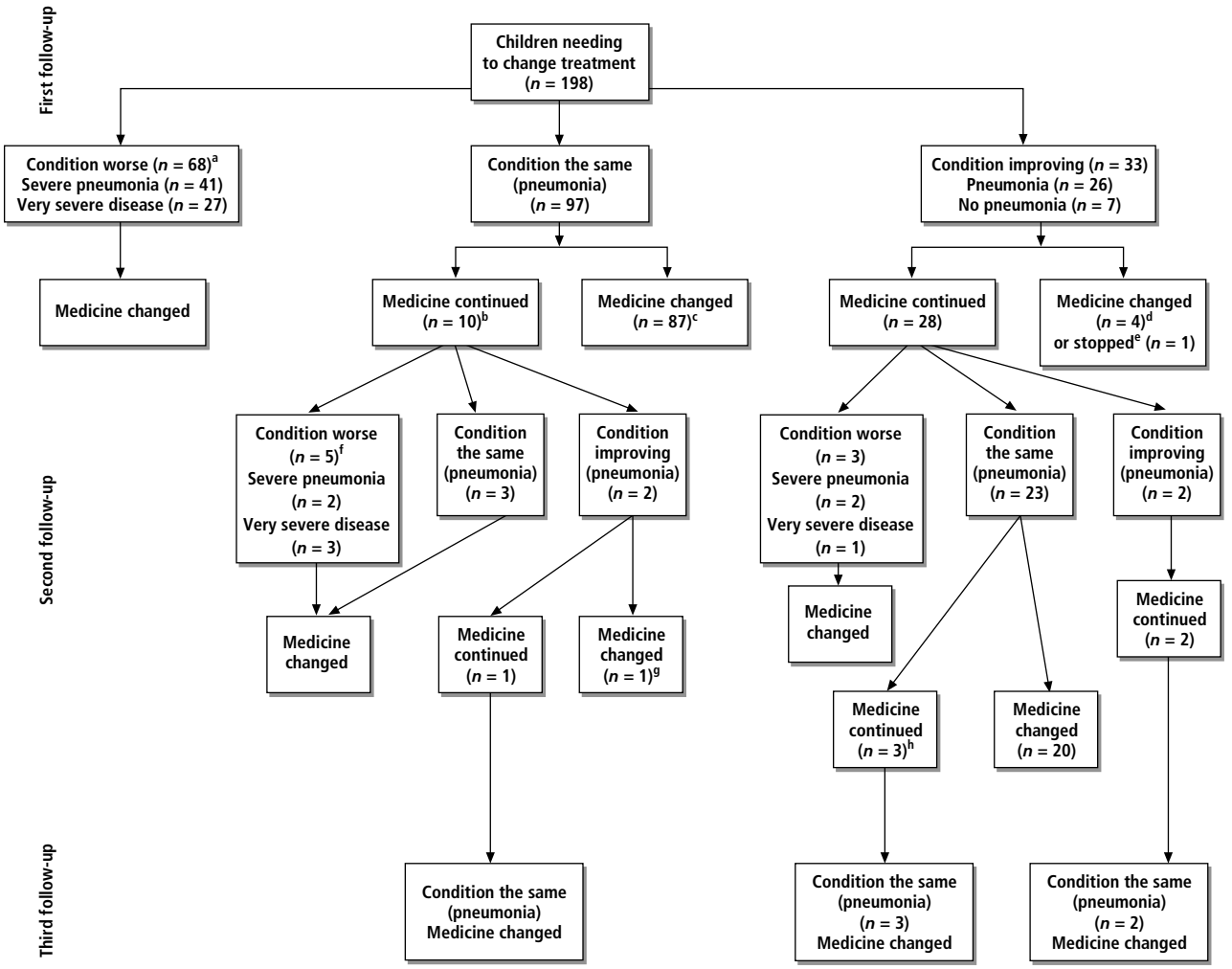
[b] 3 children did not have pneumonia and 1 with age unspecified; all cured after 5 days of cotrimoxazole treatment.

[c] 2 children without pneumonia, 1 with severe pneumonia, 1 with severe malnutrition; first 3 cured after 5 days of cotrimoxazole treatment. Treatment failed for last child who required parenteral therapy for cure.

[d] Includes 1 death.

WHO 04.144

Fig. 2. **Treatment details for the 198/1134 children treated with single dose or double dose cotrimoxazole who needed a change in treatment for non-severe pneumonia**



[a] Includes 1 death.

[b] 1 not given medicine correctly; protocol for changing medicine not followed in 9 children.

[c] Includes 1 child who developed rash.

[d] 3 children developed rash, 1 still had fast breathing. Drug changed on clinical grounds.

[e] Child developed rash.

[f] 1 child became worse before scheduled second follow-up and medicine was changed.

[g] Child still appeared sick and had high respiratory rate.

[h] 1 not given medicine correctly; protocol for changing medicine not followed in 2 children.

WHO 04.145

Fifty-seven children whose condition should have been classified as being the same at their first follow-up visit were considered to have improved and therapy was not changed; 53 of these children (93.0%) recovered on cotrimoxazole. Of the 103 children (46 + 57) who should have had their therapy changed but did not, 85% recovered on cotrimoxazole. Half of these 103 children had a decrease in their respiratory rate of 3–5 breaths/minute.

A total of 1070/1134 (94.3%) children received the correct dose of medicine for the correct length of time. There were 2337 follow-up visits, of which 16% were at home; medicine bottles were checked at 92% of visits.

When the treatment groups were combined, univariate analysis showed that children were at a greater risk of treatment failure if at enrolment they were < 12 months of age, had had a longer duration of illness, had used antibiotics in the previous 7 days, had a high respiratory rate (≥ 20 breaths/minute above the age-specific cut-off point), had a history of tight chest-binding (the practice of wrapping a child's chest tightly with cloth, which in some areas of the country is thought to be therapeutic), and lived in urban centres (Table 2, available only on the web version at http://www.who.int/bulletin). Also at higher risk of treatment failure were children who were not given the medicine correctly or who had wheezing at any time after enrolment.

Logistic regression modelling was used to adjust for possible confounding and interaction effects (Table 3). In the best multivariate model the following variables were significantly

Table 3. **Multivariate analysis of predictors of therapy failure among 1134 children treated for non-severe pneumonia with either standard dose or double dose cotrimoxazole**

Variable	Adjusted relative risk[a]	*P*-value
Age < 12 months	1.42 (1.11–1.79)	0.005
Antibiotic use in past 7 days	1.96 (1.29–2.74)	0.003
High respiratory rate at baseline[b]	1.58 (1.14–2.10)	0.007
Living in urban area at baseline	1.39 (1.00–1.87)	0.047
Child not given medicine correctly	2.00 (1.37–2.70)	0.001
Strength of cotrimoxazole	1.07 (0.84-1.34)	0.588
Wheezing any time after enrollment	1.24 (0.96-1.58)	0.094

[a] Values in parentheses are 95% confidence intervals.
[b] A high respiratory rate was one in which the child had ⩾ 20 breaths/minute above the age-adjusted WHO threshold for tachypnoea, that is ⩾ 70 for children aged 2–11 months and ⩾ 60 for those aged 12–59 months.

associated with treatment failure although strength of cotrimoxazole was not: age < 12 months, high respiratory rate at enrolment, previous antibiotic use, urban status and treatment not given correctly.

The failure rate was 14.9% (38/255) in the two rural areas compared with 21.8% (192/879) in the urban areas (RR = 0.68; 95% CI = 0.50–0.94) when both treatment groups were combined. The lowest failure rate (10/105, 9.5%) was in a rural programme that had many dispersed health centres. Children from urban centres were more likely to be younger and better nourished, present later in the course of their illness, have a history of antibiotic use as well as have a cough, difficulty breathing, vomiting, and wheeze at any time after enrolment (Table 4, available only on the web version at http://www.who.int/bulletin). They were less likely to have a history of asthma and more likely to have been given their medicine correctly.

Discussion

Clinical efficacy of cotrimoxazole

The results show that there was no significant difference between the clinical efficacy of the standard dose of cotrimoxazole and the double dose when given twice daily to treat children with non-severe pneumonia. As in two other studies (*16*, *17*), the clinical failure rate was comparatively high; however, in this study follow-up was good (and it was also very good in the other two studies cited), and almost all children with non-severe pneumonia for whom treatment failed were cured when given amoxicillin. Few children required parenteral therapy.

The failure rate of cotrimoxazole in this study is higher than the 9% reported in community-based studies (*9*, *10*) and the 13% reported in a hospital-based study (*11*) from the early 1990s, but it is similar to the failure rate from a later study (*16*). These differences could be due to temporal changes or to differences in the definition of failure. It is critical to have a standardized definition of clinical failure to detect trends over time. If failure rates are increasing then other antimicrobial regimens for treating non-severe pneumonia need to be explored. Repeating this study in other countries that have had similar failure rates with cotrimoxazole would be useful in confirming the generalizability of our results.

As in previous studies (*11*, *16*, *17*), we found that treatment failure was significantly associated with younger age, high initial respiratory rate and not being given the treatment correctly. We identified new risk factors of previous antibiotic use and living in an urban area. Children with these risk factors thus require special attention and counselling.

The high treatment failure rate could have been caused by: increasing resistance of *S. pneumoniae* and *H. influenzae* to cotrimoxazole, viral etiology, a high incidence of underlying hyperactive airway disease, and/or our use of sensitive criteria to assess therapy failure. We have previously discussed the first three factors (*15*). In this study, children who had already used antibiotics were twice as likely to be failed by treatment, suggesting that their infection could be due to resistant bacteria.

Definition of therapy failure

The definition of therapy failure was sensitive: children whose condition was considered to be the same on day 2 had a change in therapy and were classified as having had treatment failure. To be classified as improved on day 2, children had to have a decrease in their respiratory rate of > 5 breaths/minute. WHO guidelines for improvement are "slower breathing, less fever, eating better" (*2*, *3*); these are nonspecific and could be clarified further. If we had defined improvement as a decrease in respiratory rate of > 3 or 4 breaths/minute, it is possible that the failure rate would be lower. Notably, of the 103 children who according to the respiratory criteria on day 2 should have had their drug changed but did not, 85% recovered. They may have been "slow responders" to therapy or had viral infections or hyperactive airway disease. If a similar proportion of the 87 children whose condition was classified as being the same on day 2 and who had a change in therapy had also recovered without therapy change, then our failure rate would have been only 13.8%. Further work is required to improve the specificity of criteria for clinical failure, perhaps by more closely monitoring children whose condition is the same on day 2 for up to 5–7 days in order to determine indicators of subsequent worsening.

We found WHO ARI case management guidelines useful. Re-evaluation at day 2 was appropriate since 68/76 (89.4%) of those who became worse were detected on day 2. In total, 80% of children requiring a change of therapy responded well to oral amoxicillin. Counselling and follow-up after 2 days resulted in a minimal loss to follow-up.

Urban areas versus rural areas

Living in an urban area was a risk factor for failure. The low failure rate among rural children, as found in other community studies (*9*, *10*, *18*), emphasizes the need to conduct periodic surveillance of clinical effectiveness in rural areas especially since the majority of Pakistan's population (*19*), and that in many other developing countries, lives in rural areas. Most policies on managing childhood illnesses are based on data from urban settings often because the inclusion of rural areas is logistically difficult. If rural areas are consistently found to have lower rates of failure, a flexible treatment policy that specifies distinct first-line therapies for rural and urban areas may be necessary.

Limitations and strengths

The study would have been more generalizable if all children had been treated according to the protocol; however, this did not materially affect our conclusions. The study design would

have been improved by including a control group treated with amoxicillin but for reasons of cost (amoxicillin treatment would have cost four times more than cotrimoxazole treatment) and sample size (we would have needed to recruit about 600 more children), we could not do this. The study would have been more complicated if amoxicillin was given three times daily, and adding a third (placebo) dose to the cotrimoxazole group may have resulted in decreased compliance in the cotrimoxazole groups. However, in two subsequent studies (*16*, *17*), clinical response to amoxicillin has been similar to that found with cotrimoxazole. These studies were done in similar sites in Pakistan at the same time of year with comparable populations. We would expect the etiological agents for community-acquired pneumonia (bacterial being primarily *S. pneumoniae* and *H. influenzae*) to have been the same in all three studies, as has been determined in other studies in Pakistan (*7*, *11*, *20*) and in other developing countries (*3*).

Other limitations of our study include the lack of microbiological data, chest radiographs, detailed clinical examination and a longer follow-up period. Given the high incidence of pneumonia in the community in low-resource settings, it is impractical and expensive to obtain chest radiographs and do pulse oximetry, blood cultures or lung punctures in all children with suspected pneumonia. Even if, as part of the study, standard investigations were obtained for all patients, it would not have been possible to generalize the results to other low-resource settings, where pneumonia is not diagnosed using these methods. The intention of this study was to use the WHO ARI guidelines, which do not recommend such investigations for diagnosing pneumonia in the field.

The strengths of our study include the good follow-up rates, high rates of compliance with treatment, low mortality, inclusion of paramedical workers and of urban and rural sites in different geographical areas of the country. Our finding that with intermittent supervision paramedical workers in rural areas could successfully evaluate patients suggests that such workers can be used to assess the clinical effectiveness of pneumonia therapy, as has successfully been done elsewhere (*18*).

Conclusion

Children's outcomes were not improved by doubling the dose of cotrimoxazole to treat non-severe childhood pneumonia. Because another study has identified similar failure rates with a shorter course of a more expensive drug (3–5 days of amoxicillin) (*17*), we recommend testing the effectiveness of 3 days of treatment with cotrimoxazole in children with non-severe pneumonia. Periodic surveillance of the clinical effectiveness of cotrimoxazole in both urban and rural areas is important in guiding decisions on optimal first-line therapy for non-severe pneumonia. Further work is required to increase the specificity of the definition of clinical failure. We recommend that further research should be done using an observational study of children with non-severe pneumonia whose condition appears to be the same at day 2 to determine whether they actually require a change in therapy. Finally, close follow-up of all children is key to decreasing morbidity and mortality from pneumonia. ■

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Conflicts of interest: none declared.

Résumé

Essai contrôlé randomisé comparant l'efficacité d'une dose standard et d'une double dose de cotrimoxazole dans le traitement des pneumopathies infantiles au Pakistan

Objectif Les préoccupations grandissantes suscitées par la résistance bactérienne au cotrimoxazole, recommandé comme traitement de première intention par l'OMS pour faire face aux pneumopathies sans signe de gravité, ont conduit à penser qu'il ne s'agissait peut être pas du traitement optimal. Néanmoins, le passage à d'autres agents antimicrobiens, tels que l'amoxicilline, sera coûteux. Les auteurs ont comparé l'efficacité clinique de l'administration bijournalière d'une dose standard et d'une double dose de cotrimoxazole dans le traitement des pneumopathies sans signe de gravité chez l'enfant.

Méthodes On a mis en œuvre un essai multicentrique contrôlé et randomisé dans sept consultations hospitalières externes et dans deux programmes de santé communautaire. On a attribué au hasard à 1143 enfants au total, âgés de 2 à 59 mois et atteints de pneumopathie sans signe de gravité, un traitement comprenant soit 4 mg de triméthoprime plus 20 mg de sulfaméthoxazole par kilogramme de poids corporel, soit 8 mg de triméthoprime plus 40 mg de sulfaméthoxazole par kilogramme de poids corporel, par voie orale, deux fois par jour, pendant 5 jours. Il y avait échec thérapeutique lorsqu'un enfant nécessitait une modification du traitement, mourrait ou était perdu de vue. Une modification du traitement s'imposait chez les enfants dont l'état clinique se détériorait (apparition d'un tirage sous-costal ou de signes d'alerte) ou restait identique 48 h après le recrutement (c'est-à-dire que la différence entre les rythmes respiratoires mesurés lors du recrutement et 48 h après ne dépassait pas 5 respirations/minute).

Résultats On a analysé les résultats obtenus avec les 1134 enfants, dont 578 avaient reçu une dose standard de cotrimoxazole et 556 une double dose. On a relevé un échec thérapeutique chez 112 enfants (19,4 %) du groupe soumis au traitement standard et chez 118 enfants (21,2 %) du groupe recevant une double dose (risque relatif 1,10, intervalle de confiance à 95 % : 0,87 - 1,37). Une analyse multivariée a permis d'établir que le traitement avait une plus forte probabilité d'échouer chez les enfants auxquels on n'avait pas administré correctement le médicament ($p = 0,001$), chez les enfants de moins de 12 mois ($p = 0,004$), chez ceux ayant reçu auparavant des antibiotiques ($p = 0,002$), chez ceux dont le rythme respiratoire était supérieur ou égal à 20 respirations/minute et au point de coupure spécifique à l'âge ($p = 0,006$) et chez ceux provenant de zones urbaines ($p = 0,042$).

Conclusion On a constaté une efficacité équivalente du cotrimoxazole sous forme de dose standard et de double dose dans le traitement des pneumopathies sans signe de gravité. Un suivi étroit des patients est essentiel pour prévenir toute aggravation de la maladie. L'échec clinique doit être défini de manière plus spécifique. La surveillance tant dans les zones rurales qu'urbaines est indispensable au développement de stratégies thérapeutiques reposant sur les résultats cliniques.

Resumen

Ensayo controlado aleatorizado de comparación de la dosis estándar y la dosis doble de cotrimoxazol contra la neumonía infantil en el Pakistán

Objetivo La creciente preocupación en torno a la resistencia bacteriana al cotrimoxazol, producto recomendado por la OMS como medicamento de primera línea para tratar la neumonía no grave, ha llevado a pensar que ese tratamiento quizá no es el más adecuado. Sin embargo, sustituirlo por otros agentes antimicrobianos, como la amoxicilina, resulta costoso. Decidimos comparar la eficacia clínica de la dosis estándar y la dosis doble de cotrimoxazol administrado dos veces al día como tratamiento de la neumonía no grave en los niños.

Métodos Se llevó a cabo un ensayo multicéntrico controlado aleatorizado en siete departamentos ambulatorios de hospital y dos programas de salud comunitaria. Un total de 1143 niños de 2 a 59 meses con neumonía no grave fueron asignados al azar para recibir ya fuera 4 mg de trimetoprima más 20 mg de sulfametoxazol/kg de peso corporal o bien 8 mg de trimetoprima más 40 mg de sulfametoxazol/kg de peso corporal por vía oral dos veces al día durante 5 días. Se consideraron casos de fracaso terapéutico aquellos en los que el niño necesitaba un cambio de tratamiento, fallecía o se perdía en el seguimiento. Se decidía cambiar de tratamiento cuando la enfermedad se agravaba (aparecían tiraje torácico o signos de peligro) o permanecía estacionaria (se consideraba que así era cuando la frecuencia respiratoria no se desviaba más de 5 respiraciones/minuto de la que tenía el niño al entrar a participar en el estudio).

Resultados Se analizaron los resultados conseguidos en 1134 niños: a 578 se les asignó la dosis ordinaria de cotrimoxazol, y a 556 la dosis doble. El tratamiento fracasó en 112 niños (19,4%) en el grupo tratado de la forma habitual, y en 118 (21,2%) en el grupo sometido a la dosis doble (riesgo relativo: 1,10; intervalo de confianza del 95% = 0,87–1,37). El análisis multifactorial reveló que el tratamiento tenía más probabilidades de fracasar entre los niños a los que no se les administraba correctamente el medicamento ($P = 0,001$), los menores de 12 meses ($P = 0,004$), los que habían usado antibióticos anteriormente ($P = 0,002$), los que presentaban una frecuencia respiratoria ⩾ 20 respiraciones/minuto por encima del umbral específico para la edad ($P = 0,006$) y los residentes en zonas urbanas ($P = 0,042$).

Conclusión El tratamiento estándar y la dosis doble de cotrimoxazol fueron igual de eficaces en los casos de neumonía no grave. El seguimiento estrecho de los pacientes es esencial para prevenir el empeoramiento de la enfermedad. Es preciso disponer de unas definiciones de fracaso clínico más específicas. La vigilancia, tanto en las zonas rurales como en las urbanas, es esencial para poder formular políticas de tratamiento basadas en los resultados clínicos.

ملخص

تجربة معشاة ومضبوطة بالشواهد للموازنة بين الجرعة المعيارية والجرعة المضاعفة من الكوتريموكسازول لمعالجة الالتهاب الرئوي لدى الأطفال في باكستان

الغرض: أدى القلق المتزايد تجاه المقاومة التي تبديها الجراثيم للكوتريموكسازول، الذي توصي به منظمة الصحة العالمية كدواء الخط الأول لمعالجة الالتهاب الرئوي غير الوخيم، إلى الاقتراح بأن الكوتريموكسازول لم يعد الدواء الأمثل. غير أن التحول إلى دواء آخر مثل الأموكسيسلين باهظ التكلفة. وقد قمنا في هذه الدراسة بالموازنة بين الكفاءة السريرية للكوتريموكسازول بجرعته المعيارية المعطاة مرتين يومياً وبين جرعته المضاعفة المعطاة أيضاً مرتين يومياً لمعالجة الالتهاب الرئوي غير الوخيم لدى الأطفال.

الطريقة: أجريت تجربة معشاة مضبوطة بالشواهد على المرضى في العيادات الخارجية في سبعة مستشفيات ومركزين للخدمات الصحية. وقد شملت الدراسة 1143 مريضاً من الأطفال الذين تتراوح أعمارهم بين شهرين و59 شهرا لإصابتهم بالتهاب رئوي غير وخيم، وقُسِّم الأطفال بشكل عشوائي بحيث تلقى بعضهم 4 مللي غرام من تريميثوبريم لكل كيلو غرام من وزنهم مع 40 مللي غرام من سلفاميثوكسازول لكل كيلو غرام من وزنهم أو 8 مللي غرام من تريميثوبريم لكل كيلو غرام من وزنهم مع 40 مللي غرام لكل كيلو غرام من وزنهم من السلفاميثوكسازول عن طريق الفم مرتين يومياً لمدة خمسة أيام. وتُعتبر المعالجة فاشلة إذا تطلبت التغيير، أو مات الطفل أو أفلت من المتابعة. ويتطلب الطفل تغيير المعالجة إذا ساءت حالته (فظهر لديه السحب الداخلي في الصدر أو علامات الخطر)، أو إذا لم تتغير حالته بعد 48 ساعة من إدخاله المستشفى) ويعرف ذلك إذا بقيت سرعة التنفس لديه أكثر أو أقل بمقدار 5 مرات مما كانت عليه وقت بدء المعالجة).

الموجودات: تم تحليل نتائج دراسة 1134 طفلاً: تلقى 578 منهم معالجة بجرعة معيارية من الكوتريموكسازول، في حين تلقى 556 منهم جرعة مضاعفة. وقد فشلت المعالجة في 112 طفلاً ممن تلقوا الجرعة المعيارية (يشكلون 19.4% منهم) وفي 118 طفلاً ممن تلقوا المعالجة بجرعة مضاعفة (يشكلون 21.2% منهم) وهذا ما يتناسب مع خطر نسبي قدره 1.15 عند فاصلة ثقة 95% إذ تراوح بين 0.87 – 1.37). ولدى استخدام التحليل المتعدد المتغيرات وجدنا أن المعالجة ستفشل أكثر لدى الأطفال الذين لم يتلقوا الدواء الصحيح (عامل الدقة = 0.001)، والأطفال الذين يقل عمرهم عن 12 شهراً (عامل الدقة 0.004)، والأطفال الذين سبق أن تلقوا مضادات حيوية (عامل الدقة 0.002)، والأطفال الذين كانت سرعة تنفسهم في الدقيقة تزيد بمعدل 20 مرة أو أكثر على نقطة الفصل الخاصة بالعمر (عامل الدقة 0.006)، والأطفال القادمين من مناطق ريفية (عامل الدقة = 0.042).

الاستنتاج: تتساوى فعالية كل من الجرعة المعيارية والجرعة المضاعفة في معالجة الالتهاب الرئوي غير الوخيم. ومن الضروري المتابعة الوثيقة لاتقاء تدهور حالة الطفل. وتمس الحاجة لوضع تعاريف أكثر دقة للفشل السريري، كما أن الترصد في المناطق الحضرية والريفية أساسي لوضع سياسات المعالجة التي تستند على نتائج سريرية.

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Table 2. **Univariate analysis of relation between treatment failure and significant variables at baseline among 1134 children treated for non-severe pneumonia with either standard dose or double dose cotrimoxazole**

Variable	Total no. of children	Treatment success (*n* = 904)	Treatment failure (*n* = 230)	Relative risk[a]	*P*-value
Strength of cotrimoxazole					
Double dose	556	438	118	1.10 (0.87–1.37)	0.461
Standard dose	578	446	112		
Median age in months[b]	1134	12 (6–22)	8 (4–18)		0.001
Mean age in months[c]	1134	15.7 (12.7)	13.7 (13.2)		0.032
Age categories					
2–11 months	577	437	140	1.50 (1.19 –1.86)	0.001
12–59 months	557	467	90		
History at baseline					
Median no. of days ill prior to presentation[b]	1134	3 (2–5)	3 (2–5)		0.083
Mean duration of illness[c]	1134	3.6 (2.8)	4.2 (3.7)		0.022
< 3 days	456	379	77		
⩾ 3 days	678	525	153	1.33 (1.05–1.68)	0.020
Urban area	879	687	192	1.47 (1.08–1.95)	0.017
Cough	1083	867	216	0.73 (0.43–1.16)	0.211
Difficulty breathing	632	499	133	1.09 (0.86–1.36)	0.504
Fever	1002	797	205	1.09 (0.74–1.53)	0.731
Vomiting	300	243	57	0.92 (0.69–1.19)	0.558
Diarrhoea	201	157	44	1.10 (0.81–1.45)	0.562
Wheezing ⩾ 3 times at any time in the past	45	33	12	1.33 (0.78–2.08)	0.262
Currently being breastfed	731	584	147	0.98 (0.76–1.23)	0.877
Tight chest binding	16	9	7	2.19 (1.12–3.41)	0.028
Any treatment in past 7 days[d]	282	226	56	0.98 (0.74–1.26)	0.865
Documented antibiotic use in past 7 days	48	28	20	2.16 (1.47–2.92)	0.001
Examination at baseline					
Wheezing	293	224	69	1.23 (0.96–1.56)	0.110
High respiratory rate[e]	117	83	34	1.51 (1.09 –2.00)	0.015
Malnourished[f]	175	149	26	0.69 (0.47 –1.00)	0.052
Median weight-for-age score[b]	1128	–0.90 (–1.67 to –0.05)	–0.80 (–1.55 to 0.00)		0.301
During the study					
Wheezing at any time after enrolment	316	237	79	1.35 (1.06–1.69)	0.017
Was not given medicine correctly	64	42	22	1.77 (1.21–2.43)	0.006

[a] Values in parentheses are 95% confidence intervals.
[b] Values in parentheses are interquartile ranges.
[c] Values in parentheses are standard deviations.
[d] Defined as treatment with antibiotics or other medicines.
[e] A high respiratory rate was one in which the child had ⩾ 20 breaths/minute above the age-adjusted WHO threshold for tachypnoea, that is ⩾ 70 for children aged 2–11 months and ⩾ 60 for those aged 12–59 months.
[f] Weight-for-age scores > 2 standard deviations below normal (*15*).

Table 4. **Characteristics of 1134 children treated for non-severe pneumonia, by study area**

Variable	Study area[a]		Relative risk[b]	*P*-value
	Urban (*n* = 879)	Rural (*n* = 255)		
Treatment failure	192 (21.8)	38 (14.9)	1.45 (1.06–1.99)	0.017
Median age in months[c]	10 (5–18)	17 (7–26)		<0.001
Male	551 (63.0)	148 (58.0)	1.16 (0.93–1.44)	0.188
History at baseline				
Median no. of days ill prior to presentation[c]	3 (2–5)	2 (1–3)		<0.001
Fever	768 (87.4)	234 (91.8)	0.68 (0.45–1.02)	0.059
Cough	847 (96.4)	236 (92.5)	1.71 (1.18–2.48)	0.015
Difficulty breathing	515 (58.6)	117 (45.9)	1.48 (1.20–1.84)	<0.001
Tight chest binding	14 (1.6)	2 (0.8)	1.81 (0.49–6.65)	0.546
Antibiotic use in past 7 days	43 (4.9)	5 (2.0)	2.21 (0.96–5.10)	0.050
Wheezing ⩾ 3 times at any time in the past	23 (2.6)	22 (8.6)	0.44 (0.32–0.60)	<0.001
Vomiting	250 (28.4)	50 (19.6)	1.48 (1.12–1.95)	0.005
Diarrhoea	166 (18.9)	35 (13.7)	1.35 (0.98–1.87)	0.062
Currently being breastfed	561 (63.8)	170 (66.7)	0.91 (0.72–1.14)	0.415
Any treatment in past 7 days[d]	220 (25.0)	62 (24.3)	1.03 (0.80–1.33)	0.869
Examination at baseline				
High respiratory rate[e]	86 (9.8)	31 (12.2)	0.83 (0.60–1.15)	0.293
Wheezing	246 (28.0)	47 (18.4)	1.54 (1.16–2.06)	0.002
Malnutrition[f]	119 (13.6)	56 (22.0)	0.65 (0.51–0.84)	0.002
During the study				
Wheezing at any time during the study	263 (29.9)	53 (20.8)	1.47 (1.12–1.94)	0.004
Was not given medicine correctly	43 (4.9)	21 (8.2)	0.67 (0.46–0.96)	0.046

[a] Values are numbers (percentages) unless otherwise indicated.
[b] Values in parentheses in this column are 95% confidence intervals.
[c] Values in parentheses are interquartile ranges.
[d] Defined as treatment with antibiotics or other medicines.
[e] A high respiratory rate was one in which the child had ⩾ 20 breaths/minute above the age-adjusted WHO threshold for tachypnoea, that is ⩾ 70 for children aged 2–11 months and ⩾ 60 for those aged 12–59 months.
[f] Weight-for-age scores > 2 standard deviations below normal (*15*).