ORIGINAL ARTICLE

Randomized Trial of Amoxicillin for Pneumonia in Pakistan

Fyezah Jehan, M.B., B.S., Imran Nisar, M.B., B.S., Salima Kerai, M.Sc., Benazir Balouch, M.B., B.S., M.B.A., Nick Brown, M.Sc., Najeeb Rahman, B.Sc., Arjumand Rizvi, M.Sc., Yasir Shafiq, M.Sc., and Anita K.M. Zaidi, M.B., B.S.

ABSTRACT

BACKGROUND

The World Health Organization (WHO) recommends oral amoxicillin for patients who have pneumonia with tachypnea, yet trial data indicate that not using amoxicillin to treat this condition may be noninferior to using amoxicillin.

METHODS

We conducted a double-blind, randomized, placebo-controlled noninferiority trial involving children at primary health care centers in low-income communities in Karachi, Pakistan. Children who were 2 to 59 months of age and who met WHO criteria for nonsevere pneumonia with tachypnea were randomly assigned to a 3-day course of a suspension of amoxicillin (the active control) of 50 mg per milliliter or matched volume of placebo (the test regimen), according to WHO weight bands (500 mg every 12 hours for a weight of 4 to <10 kg, 1000 mg every 12 hours for a weight of 10 to <14 kg, or 1500 mg every 12 hours for a weight of 14 to <20 kg). The primary outcome was treatment failure during the 3-day course of amoxicillin or placebo. The prespecified noninferiority margin was 1.75 percentage points.

RESULTS

From November 9, 2014, through November 30, 2017, a total of 4002 children underwent randomization (1999 in the placebo group and 2003 in the amoxicillin group). In the per-protocol analysis, the incidence of treatment failure was 4.9% among placebo recipients (95 of 1927 children) and 2.6% among amoxicillin recipients (51 of 1929 children) (between-group difference, 2.3 percentage points; 95% confidence interval [CI], 0.9 to 3.7). Results were similar in the intention-to-treat analysis. The presence of fever and wheeze predicted treatment failure. The number needed to treat to prevent one treatment failure was 44 (95% CI, 31 to 80). One patient (<0.1%) in each group died. Relapse occurred in 40 children (2.2%) in the placebo group and in 58 children (3.1%) in the amoxicillin group.

CONCLUSIONS

Among children younger than 5 years of age with nonsevere pneumonia, the frequency of treatment failure was higher in the placebo group than in the amoxicillin group, a difference that did not meet the noninferiority margin for placebo. (Funded by the Joint Global Health Trials Scheme [of the Department for International Development, Medical Research Council, and Wellcome] and others; RETAPP ClinicalTrials.gov number, NCT02372461.)

From Aga Khan University, Karachi, Pakistan (F.J., I.N., S.K., B.B., N.B., N.R., A.R., Y.S., A.K.M.Z.); Uppsala University, Uppsala, Sweden (N.B.); and the Bill and Melinda Gates Foundation, Seattle (A.K.M.Z.). Address reprint requests to Dr. Jehan at the Department of Pediatrics and Child Health, Aga Khan University, Stadium Rd., P.O. Box 3500, Karachi 74800, Pakistan, or at fyezah.jehan@aku.edu.

N Engl J Med 2020;383:24-34.
DOI: 10.1056/NEJMoa1911998

In 2015, acute lower respiratory tract infections caused 7.4 deaths per 1000 live births (95% confidence interval [CI], 6.7 to 8.8) worldwide.[1] These infections disproportionately affected children in impoverished areas.[2-4] The epidemiologic characteristics of pneumonia are changing rapidly as a result of vaccination against major pathogens such as *Haemophilus influenzae* type B and *Streptococcus pneumoniae*[4,5]; viral pathogens now cause the majority of acute lower respiratory tract infections.[6,7] Nevertheless, antibiotics continue to be used for the treatment of acute lower respiratory tract infections, resulting in antimicrobial resistance[8,9] and, possibly, alteration of gut microbiota[10,11] and immunity.[12,13]

In primary care settings in low-income communities, the diagnosis of pneumonia is generally clinical and guided by the Integrated Management of Childhood Illnesses (IMCI) approach of the World Health Organization (WHO).[14] WHO guidelines classify acute lower respiratory tract infections according to the absence of pneumonia, the presence of mild pneumonia (with tachypnea or retraction of the chest wall), or severe pneumonia with danger signs (stridor when the patient is calm, hypoxia [oxygen saturation as measured by pulse oximeter, <90% while the patient is breathing ambient air], inability to feed, persistent vomiting, convulsions, and reduced level of consciousness). For children who live in areas with a low prevalence of human immunodeficiency virus (HIV) infection and who have mild pneumonia and tachypnea, the WHO recommends a 3-day course of amoxicillin.[14,15] With the rationale that pneumonia has a bacterial cause in a substantial proportion of children, the current guidelines that are based on the presence of tachypnea emphasize sensitivity over specificity. However, as suggested by trial data, the use of vaccines against pneumonia with common bacterial causes (*Haemophilus influenzae* type B and pneumococcus) may have further reduced the specificity of the guidelines for the clinical identification of bacterial pneumonia.[16-18]

We conducted RETAPP (Randomized Trial of Amoxicillin Versus Placebo for [Fast Breathing] Pneumonia), a double-blind, randomized, controlled noninferiority trial comparing placebo with amoxicillin for the management of pneumonia with tachypnea. Our trial involved children who were 2 to 59 months of age and resided in low-income communities in Karachi, Pakistan.

METHODS

TRIAL OVERSIGHT

This trial was conducted at four primary health care centers in an area without HIV infection and with a low incidence of malaria. Oversight was provided by a technical steering committee and a data and safety monitoring board. The protocol is available with the full text of this article at NEJM.org. Ethics approval was provided by the ethics review committee of Aga Khan University. All the parents or legal guardians provided written informed consent before randomization. The trial was performed in accordance with the principles of the Declaration of Helsinki.

The trial was designed by the first two authors and the last author. The third and fourth authors oversaw data collection, and the seventh author performed the analysis. The first and second authors wrote the first draft of the manuscript with considerable input from all the authors. The first and seventh authors had full access to the data, and the first author made the final decision to submit the manuscript for publication. The funders and providers of the amoxicillin (purchased from GlaxoSmithKline Pakistan) and placebo (provided free of charge by Wilshire Laboratories) that were used in the trial had no role in the design, implementation, or interpretation of the trial. All the authors reviewed and approved the final draft of the manuscript and vouch for the completeness and accuracy of the data and analyses and for the fidelity of the trial to the protocol.

PATIENTS

Children who were 2 to 59 months of age were triaged by staff members at each primary health center according to whether they had cough or difficulty breathing. The diagnosis of pneumonia with tachypnea, defined according to the WHO classification as a respiratory rate of at least 50 breaths per minute in children 2 to 11 months of age or at least 40 breaths per minute in children 12 to 59 months of age, was based on agreement between a trained health worker and a physician. The presence of wheeze was

assessed with the use of auscultation. All children with wheeze received up to three doses of an inhaled bronchodilator according to WHO-IMCI guidelines. After each administration of a bronchodilator, the respiratory rate was rechecked and the level of tachypnea was noted.

Only children with persistent tachypnea were considered for enrollment, irrespective of whether they had wheeze. Children were excluded if they had retraction of the chest wall or any danger sign (as defined above), had received antibiotics within the previous 48 hours, had been hospitalized within the past 2 weeks, or had pedal edema, known tuberculosis, asthma, or other severe illness for which antibiotic therapy was warranted. Children were also excluded if they lived outside the catchment area, were enrolled in another trial, or had enrolled in the trial within the past 6 months (which was considered to be an adequate washout period).

TRIAL PROCEDURES

Children were randomly assigned in a 1:1 ratio to receive either amoxicillin as a syrup (the active control) daily for 3 days according to WHO-IMCI weight bands (500 mg every 12 hours for children who weighed 4 to <10 kg, 1000 mg every 12 hours for children who weighed 10 to <14 kg, and 1500 mg every 12 hours for children who weighed 14 to <20 kg) or a matched volume of placebo (the test regimen) in an equivalent dose in milliliters. Lists were generated by the clinical trials unit of Aga Khan University with block randomization[4,6,8,10] stratified according to age category (2 to 11 months or 12 to 59 months). A pharmacist in the clinical trials unit pasted treatment assignment codes on white, sealed bottles and reconstituted syrups that were stored at 4 to 8°C during the trial. A randomization identification number that was assigned by a physician who was unaware of the assignment codes was pasted on case files. Drug dispensing was independently performed in a segregated area. Physicians who assessed outcomes were also unaware of the trial-group assignments, as were participating parents and staff.

Data on baseline sociodemographic characteristics, birth and breast-feeding history, household air quality, immunization status, and clinical history were collected. All doses were administered, recorded, and observed by trial staff at a primary health care center or at the patients' home. Treatment failure was assessed on days 0, 1, 2, and 3 of randomization. Relapse was assessed up to day 14 through visits scheduled at days 5 and 14. Visits at day 8 and 12 were added on the recommendation of the data and safety monitoring board after a death occurred during the trial. If a visit was missed, trial staff conducted home visits. In all the children, vital status was checked on day 21. Any deterioration that was detected during the visit (including an oxygen saturation of ≤92%) or noticed by a family member was reported on a 24-hour telephone hotline with facilitated referral to tertiary care.

OUTCOMES

The primary outcome was treatment failure during the 3-day course of the trial regimen. Treatment failure was considered to have occurred if the patient died or had WHO-defined danger signs or retraction of the lower chest wall, if the patient was hospitalized, or if the patient's trial regimen was changed by the trial physician owing to new-onset infection or a serious adverse event. The null hypothesis was inferiority of placebo to amoxicillin; the alternative was noninferiority. A key secondary outcome was relapse (between days 4 and 14) defined according to similar criteria. Adherence for the purposes of the per-protocol analysis was defined as the receipt of at least 5 doses by day 3, including the first 4 doses, or receipt of the assigned amoxicillin or placebo until treatment failure and receipt of no other antibiotic. Adverse events were defined as nonsevere (mild diarrhea, rash, or mouth ulcer) and severe (diarrhea for which intravenous hydration was warranted, anaphylaxis, organ failure, life-threatening injury, or death).

STATISTICAL ANALYSIS

The initial sample size was based on a trial by Hazir et al.[18] and specified an incidence of treatment failure of 5% with amoxicillin and a noninferiority margin of 2.5 percentage points. The sample size was later revised to specify a more conservative noninferiority margin of 1.75 percentage points with a presumed treatment failure of 3.50% with amoxicillin (based on an interim analysis involving 1000 patients). An increase of 1.75 percentage points in the incidence of treatment failure with placebo over amoxicillin was considered to be clinically meaningful. Considering nonadherence and loss to follow-up of

5%, we estimated that 3978 children would have to complete treatment for the trial to have 90% power at a one-sided alpha level of 0.05.

Data were double entered in a structured query language (SQL)–based relational database with an audit trail (Microsoft SQL Server 2008, release 2). Interim analyses for safety were performed with the use of the O'Brien–Fleming approach by an independent statistician who was supervised by the data and safety monitoring board. A between-group difference in adverse events (including death) that was statistically meaningful, clinically meaningful, or both was assessed in a blinded manner, at an alpha level of 0.01 for stopping the trial.

A statistical analysis plan was created and approved by the data and safety monitoring board in December 2017; no changes were made before locking the database and unblinding. The intention-to-treat analysis included all the children who had undergone randomization and received at least one dose of the assigned amoxicillin or placebo. The per-protocol population, which included all the children who had received five of six doses (with four doses in the first 2 days), was used for the primary analysis. We estimated unadjusted proportions and the between-group difference in the risk of treatment failure, with 95% confidence intervals. It was planned that noninferiority would be shown if the upper boundary of the 95% confidence interval for the between-group difference was less than 1.75 percentage points. As part of a post hoc analysis, we looked at the lower boundary of the 95% confidence interval for evidence of superiority of amoxicillin. We also estimated the percentage of children with nonserious and serious adverse events and the between-group difference in these measures. The results of a stratified analysis that was performed according to age categories and the presence or absence of fever and wheeze, as prespecified, were presented with point estimates and 95% confidence intervals.

In additional exploratory analyses, we identified predictors of treatment failure using backward elimination logistic regression. At the outset, univariate analysis was conducted to identify the effect of each predictor on outcome. Variables that were significant at a P value of 0.2 or less at a univariable level were considered for adjustment in a multivariable model. Because of different cutoff values for the respiratory rate according to age, the respiratory rate was expressed in thirds (lowest third, up to 44.5 breaths per minute; middle third, from 44.6 to 51.0 breaths per minute; and highest third, >51.0 breaths per minute). We also assessed the effect of repeated randomization on treatment failure using mixed-effects logistic regression to account for potential nonindependence between observations from re-enrolled children.

Secondary outcomes (including relapse) were compared with the use of raw incidence data, since we had no prespecified information on which to base inferiority margins. In addition, we calculated the number of children who would need to be treated to prevent one treatment failure. All analyses were performed with the use of Stata software, version 14 (StataCorp).

RESULTS

PATIENT CHARACTERISTICS

From November 9, 2014, through November 30, 2017, a total of 4002 children were randomly assigned to receive placebo (1999 children) or amoxicillin (2003 children). Of these children, 1927 in the placebo group (96.4%) and 1929 in the amoxicillin group (96.3%) were eligible to be included in the per-protocol analysis (Fig. 1).

The trial groups were balanced with respect to important variables such as individual and household demographic characteristics as well as respiratory rate, oxygen saturation, and other clinical characteristics (Table 1; and Table S1 in the Supplementary Appendix, available at NEJM .org). Of the children who were eligible for the per-protocol analysis, 2030 of 3856 (52.6%) were male and 1776 of 3856 (46.1%) were between 2 and 11 months of age.

A total of 694 of 3815 children (18.2%) (335 of 1901 in the placebo group and 359 of 1914 in the amoxicillin group) had moderate-to-severe wasting. A total of 2079 of 3856 children (53.9%) had received a third dose of pentavalent and pneumococcal conjugate vaccines (1023 of 1927 children in the placebo group and 1056 of 1929 children in the amoxicillin group).

PRIMARY OUTCOME

Treatment failure occurred in 95 children in the placebo group (4.9%) and in 51 children in the amoxicillin group (2.6%) (between-group difference, 2.3 percentage points; 95% CI, 0.9 to 3.7,

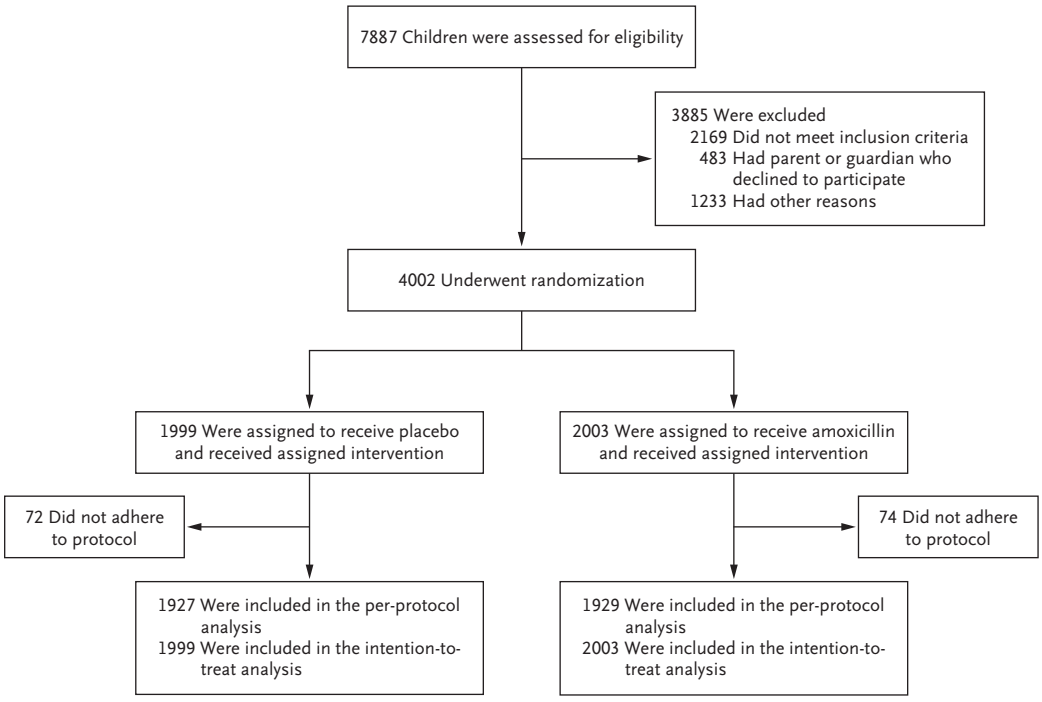

Figure 1. Screening, Randomization, and Analysis.

favoring amoxicillin), including one death in each group. This difference was above the noninferiority margin of 1.75 percentage points (Table 2), which indicates that we did not find that placebo was noninferior to amoxicillin. The 95% confidence interval suggested that amoxicillin was superior to placebo. The results were similar when the analysis was repeated in the intention-to-treat population (between-group difference, 2.3 percentage points; 95% CI, 0.9 to 3.6, favoring amoxicillin).

PREDICTORS OF TREATMENT FAILURE

Univariable analyses showed that the major factors affecting treatment failure were reported symptoms of diarrhea and fever, anemia detected on physical examination, temperature of at least 37.5°C, a respiratory rate of at least 45 breaths per minute, and poor indoor air quality (Fig. 2A and Table S2).

In an exploratory adjusted model (Fig. 2B and Table S3), amoxicillin was associated with a lower risk of treatment failure than placebo (odds ratio, 0.52; 95% CI, 0.37 to 0.74). Other independent predictors of treatment failure included respiratory rate (middle third vs. lowest third: odds ratio, 1.61; 95% CI, 1.03 to 2.52; highest third vs. lowest third: odds ratio, 2.03; 95% CI, 1.31 to 3.12), wheeze (odds ratio, 1.89; 95% CI, 1.14 to 3.14), fever (odds ratio, 1.75; 95% CI, 1.21 to 2.55), history of fever (odds ratio, 1.60; 95% CI, 1.04 to 2.46), history of diarrhea (odds ratio, 1.63; 95% CI, 1.00 to 2.71), and poor indoor air quality (odds ratio, 1.46; 95% CI, 1.04 to 2.06) (Fig. 2B).

To assess the effect of re-enrollment, child-level variability in results showed an intracluster correlation coefficient of 0 (variance=0.001), suggesting that episodes could be treated independently even when the same child was enrolled more than once (which occurred in 256 children). The analysis results are presented in Table S4.

KEY SECONDARY OUTCOME

At day 14, relapse had occurred in 40 children (2.2%) in the placebo group and in 58 children (3.1%) in the amoxicillin group (mean difference, 0.9 percentage points; 95% CI, –2.1 to 0.3) (Table 2). At day 3, adverse events had occurred

in 63 children in the placebo group (3.3%) and in 43 children in the amoxicillin group (2.2%) (mean difference, 1.0 percentage point; 95% CI, −0.2 to 2.2).

Results were consistent across subgroups defined according to age, the presence or absence of fever, and the presence or absence of wheeze (Table 3). In the placebo group, the incidence of treatment failure was higher among children with fever (difference, 4.1 percentage points; 95% CI, 1.5 to 6.7) and among those with wheeze (difference, 7.0 percentage points; 95% CI, 1.4 to 12.7) (Table 3). In order to prevent one treatment failure, the number of children with pneumonia and tachypnea who would need to be treated was 44 (95% CI, 31 to 80).

DISCUSSION

This trial, which involved children younger than 5 years of age with nonsevere pneumonia with tachypnea and which was conducted in low-income communities without HIV infection and with a low incidence of malaria, did not show that placebo was noninferior to amoxicillin in preventing treatment failure between days 0 and 3. The incidence of treatment failure was lower among patients who received amoxicillin, and the 95% confidence interval for the difference did not include 0. There were more relapses in the amoxicillin group between days 4 and 14, although the between-group differences for those results were not significant.

In our trial, almost one in five children had moderate-to-severe wasting, and only 62% of the children had received a third dose of pentavalent and pneumococcal vaccines. The results did not differ when the analysis was stratified according to age.

Data are lacking on withholding antibiotics for pneumonia with tachypnea in children from low-income and low-to-middle-income communities, and conclusions from reports are inconsistent. In a trial conducted by Hazir et al. in an outpatient setting in Pakistan, the incidence of treatment failure at day 3 (7.2% in the placebo group and 8.3% in the amoxicillin group, indicating equivalence) was higher but similar to that in our trial, but their population included far more children with wheeze than ours (50% vs. 7%).[18] In contrast, in a trial conducted by Awasthi et al. involving children who did not have a response to bronchodilators and who had normal chest radiographic findings in an ambulatory care setting in India, the incidence of treatment failure was substantially higher among children who received placebo than among those who received amoxicillin (24.0% vs. 19.9%; difference, 4.2 percentage points, 95% CI, 0.2 to 8.1).[19] In the trial by Awasthi et al., the persistence of wheeze was used as a criterion for treatment failure; this limits the generalizability of the findings. Our trial included far fewer children with wheeze than that conducted by Awasthi and colleagues. Also, none of the children with tachypnea in our trial had had a response to bronchodilator therapy; this lack of response indicates that the children in our trial were likely to have had pneumonia with an infectious cause.

In a trial in Malawi conducted by Ginsburg et al., the comparison of amoxicillin with placebo was similar to that in our current trial. The trial by Ginsburg et al. was stopped early because the incidence of treatment failure was higher in the placebo group than in the amoxicillin group (7% vs. 4%); however, the trial included fever as an additional criterion of treatment failure and was conducted in hospital outpatient departments.[20]

Our results, which were based on the current WHO categorization of pneumonia, suggest that existing recommendations are valid. However, there are a number of important considerations, including the number needed to treat, cost-effectiveness, and high-risk subgroups.

In our trial, the number of children with pneumonia and tachypnea who would have needed to be treated to prevent one treatment failure was 44 — a relatively high number. This number is high enough to suggest that antibiotics may not be warranted for a large number of children, yet there are subgroups with a clinical phenotype severe enough to warrant antibiotic therapy. Identifying these subgroups for targeted treatment can limit unnecessary antibiotic use.

Treatment costs are related to raw expenditures on antibiotics. As Zhang et al. found in a systematic review of costs associated with severe pneumonia, these expenditures are considerable at both the individual and societal levels.[21] Furthermore, the global implications of antibiotic resistance are important. Resistance to beta-lactam antibiotics is at epidemic levels in parts

Table 1. Baseline Characteristics of the Children.*

Characteristic	Placebo Group (N=1999)	Amoxicillin Group (N=2003)
Demographic characteristics		
Male sex — no. (%)	1079 (53.9)	1024 (51.1)
Age — mo		
Mean	16.5±13.9	16.4±14.0
Median (IQR)	13 (5–25)	13 (5–24)
Reported symptoms — no. (%)		
Diarrhea	154 (7.7)	161 (8.0)
Fever	1169 (58.5)	1200 (59.9)
Cough	1986 (99.3)	1988 (99.3)
Tachypnea	1300 (65.0)	1288 (64.3)
Retraction of chest wall	29 (1.4)	22 (1.1)
Upper respiratory tract infection	767 (38.4)	745 (37.2)
Vomiting	29 (1.4)	42 (2.1)
Measles within past 3 mo	11 (0.6)	17 (0.8)
Up-to-date immunization — no. (%)†		
Immunization overall	953 (47.7)	1009 (50.4)
Pneumococcal conjugate vaccine and pentavalent vaccine	1218 (60.9)	1243 (62.1)
Findings on physical examination — no./total no. (%)		
Anemia	200/1999 (10.0)	206/2003 (10.3)
Anthropometric measures — no./total no. (%)		
Mid–upper-arm circumference <11.5 cm ‡	43/1420 (3.0)	45/1430 (3.1)
Stunting§	917/1985 (46.2)	903/1989 (45.4)
Wasting¶	349/1973 (17.7)	371/1988 (18.7)
Underweight‖	823/1993 (41.3)	838/2001 (41.9)
Temperature ≥37.5°C	652/1999 (32.6)	653/2003 (32.6)
Respiratory rate — breaths/min		
Age 12–59 mo		
Mean	46.1±5.1	46.3±5.3
Median (IQR)	44.5 (42.5–48.0)	45.0 (42.5–48.5)
Age 2–11 mo		
Mean	55.6±4.8	55.2±4.7
Median (IQR)	54.5 (52.0–57.5)	54.0 (52.0–57.0)
Oxygen saturation — no. (%)		
90–92%	251 (12.6)	257 (12.8)
93–95%	552 (27.6)	525 (26.2)
>95%	1196 (59.8)	1221 (61.0)
Wheeze — no. (%)	150 (7.5)	134 (6.7)
Household indoor air quality — no. (%)**		
Good	1047 (52.4)	1092 (54.5)
Moderate	354 (17.7)	332 (16.6)

Table 1. (Continued.)

Characteristic	Placebo Group (N=1999)	Amoxicillin Group (N=2003)
Poor	598 (29.9)	579 (28.9)

* Plus–minus values are means ±SD.
† Children received age-appropriate vaccine doses according to the standard immunization schedule.
‡ The mid–upper-arm circumference was not applicable to children younger than 6 months of age.
§ Stunting was defined as a height-for-age z score lower than –2 SD.
¶ Wasting was defined as a weight-for-height z score lower than –2 SD.
‖ Underweight was defined as a weight-for-age z score lower than –2 SD.
** Principal component analysis was used to create an indoor air–quality index from six air-quality variables, including proper ventilation in the house, smoking inside the house, the source of fuel (wood, charcoal, or animal dung), the area of the house where cooking takes place, the type of stove, and the presence of children near the cooking area. Three categories were created from the principal component analysis score to group the sampled population. A binary variable that combined the lower two thirds indicated poor air quality.

Table 2. Outcomes by Day 3 and by Day 14 in the Per-Protocol and Intention-to-Treat Analyses.*

Outcome	Placebo Group (N=1999)	Amoxicillin Group (N=2003)	Difference (95% CI)
	no./total no. (%)		*percentage points*
Day 3			
Treatment failure			
Per-protocol analysis	95/1927 (4.9)	51/1929 (2.6)	2.3 (0.9 to 3.7)
Intention-to-treat analysis	96/1999 (4.8)	51/2003 (2.5)	2.3 (0.9 to 3.6)
Adverse events			
Per-protocol analysis	63/1927 (3.3)	43/1929 (2.2)	1.0 (–0.1 to 2.2)
Intention-to-treat analysis	66/1999 (3.3)	46/2003 (2.3)	1.0 (–0.2 to 2.2)
Day 4–14†			
Relapse			
Per-protocol analysis	40/1833 (2.2)	58/1878 (3.1)	–0.9 (–2.1 to 0.3)
Intention-to-treat analysis	41/1904 (2.2)	58/1952 (3.0)	–0.8 (–2.0 to 0.3)
Adverse events			
Per-protocol analysis	39/1833 (2.1)	59/1878 (3.1)	–1.0 (–2.2 to 0.2)
Intention-to-treat analysis	40/1904 (2.1)	59/1952 (3.0)	–0.9 (–2.1 to 0.2)

* Some values may differ from the expected value because of rounding. CI denotes confidence interval.
† Outcomes during the period from day 4 through day 14 were calculated from data on children with treatment success at days 0 through 3.

of Asia,[8,9] and stewardship of antibiotic prescription is the only sure means of preventing further extension of resistance to cephalosporin and carbapenem. With the changing epidemiologic characteristics of pneumonia owing to the success of pneumococcal and *Haemophilus influenzae* type B vaccination programs,[4] the equation is complex. In addition, the hypothesis that most children in our trial had viral infections is supported by the observation that treatment failure was not associated with wasting, stunting, or vaccination status.

Another issue relates to risk stratification. Although our trial was not powered for subgroup analyses, our findings raise several questions about targeted treatment. Estimates of the difference in treatment failure were higher in favor of amoxicillin in children with fever and wheeze. Reported temperature, documented fever, and wheeze at presentation have also been

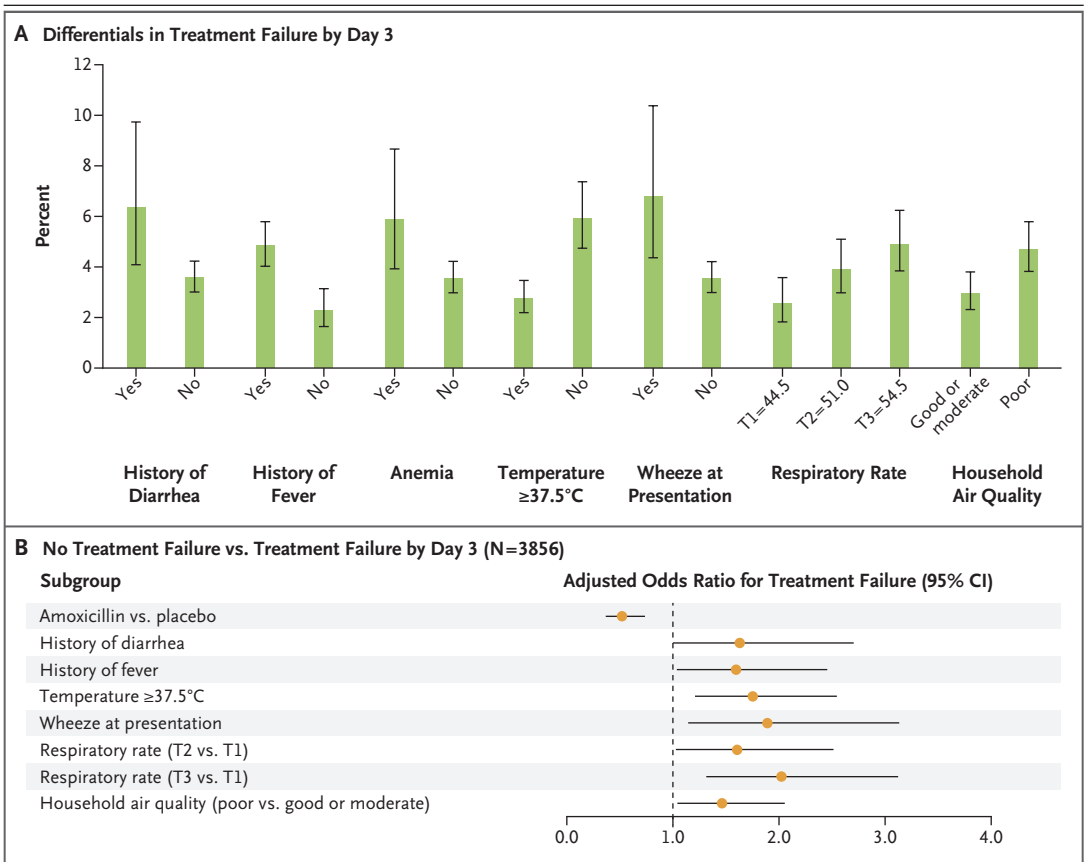

Figure 2. Subgroup Analysis of Treatment Failure.

Because of different cutoff values for the respiratory rate according to age, the respiratory rate was categorized in three groups (lowest third [T1], up to 44.5 breaths per minute; middle third [T2], from 44.6 to 51.0 breaths per minute; and highest third [T3], >51.0 breaths per minute). The I bars indicate 95% confidence intervals.

identified to be of prognostic importance in children with acute cough and respiratory infections in developed countries.[22]

Exploratory analyses suggest that changing the criteria for nonsevere pneumonia, with screening according to predictor variables, might be more cost-effective than using the current criteria for classification of pneumonia in primary care settings. It is unclear whether new methods such as measurement of oxygen saturation at presentation or point-of-care biomarker testing would enhance management.[23,24]

The strengths of our trial include a high level of adherence, directly observed treatment, a low level of attrition, assiduous reporting and investigation of adverse events, and per-protocol analyses that are necessary for the internal validity of noninferiority trials. Our trial also had important limitations, including narrow generalizability because of the strict trial exclusion criteria and short follow-up beyond what is usual in Pakistan for this population. The area in which the patients resided has substantial health care utilization for respiratory infections[25]; thus, the results may not be generalizable to areas where presentation is delayed, often until signs and symptoms worsen. The lack of imaging results was a limitation, but this was a deliberate part of the "real life" design of the trial. Amoxicillin was prescribed with the use of standard weight bands recommended by the WHO; thus, some children received lower doses and some children received higher doses of amoxicillin than the dose of 90 mg per kilogram of body weight per day recommended by the WHO. However, none of the children received a dose of

Table 3. Stratified Subgroup Analysis of Outcomes in the Per-Protocol Analysis.

Outcome	Overall	Placebo Group (N = 1999)	Amoxicillin Group (N = 2003)	Difference (95% CI)
	no.	*no./total no. (%)*		*percentage points*
Children with treatment failure at 0–3 days				
Age				
2 to <12 mo	1776	46/881 (5.2)	24/895 (2.7)	2.5 (0.7 to 4.4)
12 to 59 mo	2080	49/1046 (4.7)	27/1034 (2.6)	2.1 (0.5 to 3.7)
Temperature ≥37.5°C				
Present	1249	50/629 (7.9)	24/620 (3.9)	4.1 (1.5 to 6.7)
Absent	2607	45/1298 (3.5)	27/1309 (2.1)	1.4 (0.2 to 2.7)
Wheeze				
Present	280	15/149 (10.1)	4/131 (3.1)	7.0 (1.4 to 12.7)
Absent	3576	80/1778 (4.5)	47/1798 (2.6)	1.9 (0.7 to 3.1)
Adverse events at 0–3 days				
Age				
2 to <12 mo	1776	30/881 (3.4)	24/895 (2.7)	0.7 (–0.9 to 2.3)
12 to 59 mo	2080	33/1046 (3.2)	19/1034 (1.8)	1.3 (0 to 2.7)
Temperature ≥37.5°C				
Present	1249	32/629 (5.1)	20/620 (3.2)	1.9 (–0.4 to 4.1)
Absent	2607	31/1298 (2.4)	23/1309 (1.8)	0.6 (–0.5 to 1.7)
Wheeze				
Present	280	4/149 (2.7)	0/131	2.7 (0.1 to 5.3)
Absent	3576	59/1778 (3.3)	43/1798 (2.4)	0.9 (–0.2 to 2.0)
Children with relapse at 4–14 days				
Age				
2 to <12 mo	1707	21/836 (2.5)	34/871 (3.9)	–1.4 (–3.1 to 0.3)
12 to 59 mo	2004	19/997 (1.9)	24/1007 (2.4)	–0.5 (–1.8 to 0.8)
Temperature ≥37.5°C				
Present	1175	13/579 (2.2)	21/596 (3.5)	–1.3 (–3.2 to 0.6)
Absent	2536	27/1254 (2.2)	37/1282 (2.9)	–0.7 (–2.0 to 0.5)
Wheeze				
Present	261	6/134 (4.5)	6/127 (4.7)	–0.2 (–5.3 to 4.8)
Absent	3450	34/1699 (2.0)	52/1751 (3.0)	–1.0 (–2.0 to 0.1)
Children with adverse events at 4–14 days				
Age				
2 to <12 mo	1707	17/836 (2.0)	30/871 (3.4)	–1.4 (–3.0 to 0.1)
12 to 59 mo	2004	22/997 (2.2)	29/1007 (2.9)	–0.7 (–2.1 to 0.7)
Temperature ≥37.5°C				
Present	1175	12/579 (2.1)	14/596 (2.3)	–0.3 (–2.0 to 1.4)
Absent	2536	27/1254 (2.2)	45/1282 (3.5)	–1.4 (–2.6 to –0.1)
Wheeze				
Present	261	0/134	2/127 (1.6)	–1.6 (–3.7 to 0.6)
Absent	3450	39/1699 (2.3)	57/1751 (3.3)	–1.0 (–2.1 to 0.1)

less than 50 mg per kilogram per day, the lower limit of high-dose amoxicillin.

In conclusion, among Pakistani children younger than 5 years of age with pneumonia with tachypnea as defined by the WHO, the frequency of treatment failure was higher in the placebo group than in the amoxicillin group, a difference that did not meet the noninferiority margin for placebo.

Supported by a grant (MR/L004283/1) from the Joint Global Health Trials Scheme of the Department for International Development, Medical Research Council, and Wellcome, a grant (OPP1158281) from the Bill and Melinda Gates Foundation, and a grant (D43TW007585) for training support from the Fogarty International Center of the National Institutes of Health.

No potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

REFERENCES

1. McAllister DA, Liu L, Shi T, et al. Global, regional, and national estimates of pneumonia morbidity and mortality in children younger than 5 years between 2000 and 2015: a systematic analysis. Lancet Glob Health 2019;7(1):e47-e57.

2. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 2015;385:430-40.

3. Nair H, Simões EA, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet 2013;381:1380-90.

4. Leung DT, Chisti MJ, Pavia AT. Prevention and control of childhood pneumonia and diarrhea. Pediatr Clin North Am 2016;63:67-79.

5. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type B disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. Lancet Glob Health 2018;6(7):e744-e757.

6. Levine OS, O'Brien KL, Deloria-Knoll M, et al. The Pneumonia Etiology Research for Child Health project: a 21st century childhood pneumonia etiology study. Clin Infect Dis 2012;54:Suppl 2:S93-S101.

7. Picot VS, Bénet T, Messaoudi M, et al. Multicenter case-control study protocol of pneumonia etiology in children: Global Approach to Biological Research, Infectious diseases and Epidemics in Low-income countries (GABRIEL network). BMC Infect Dis 2014;14:635.

8. Downie L, Armiento R, Subhi R, Kelly J, Clifford V, Duke T. Community-acquired neonatal and infant sepsis in developing countries: efficacy of WHO's currently recommended antibiotics — systematic review and meta-analysis. Arch Dis Child 2013;98:146-54.

9. Isaacs D, Andresen D. Combating antibiotic resistance: the war on error. Arch Dis Child 2013;98:90-1.

10. Dethlefsen L, Huse S, Sogin ML, Relman DA. The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol 2008;6(11):e280.

11. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term impacts of antibiotic exposure on the human intestinal microbiota. Microbiology 2010;156:3216-23.

12. Johnson CL, Versalovic J. The human microbiome and its potential importance to pediatrics. Pediatrics 2012;129:950-60.

13. Murgas Torrazza R, Neu J. The developing intestinal microbiome and its relationship to health and disease in the neonate. J Perinatol 2011;31:Suppl 1:S29-S34.

14. Revised WHO classification and treatment of childhood pneumonia at health facilities. Geneva: World Health Organization, 2014.

15. Grant GB, Campbell H, Dowell SF, et al. Recommendations for treatment of childhood non-severe pneumonia. Lancet Infect Dis 2009;9:185-96.

16. Mulholland EK, Simoes EA, Costales MO, McGrath EJ, Manalac EM, Gove S. Standardized diagnosis of pneumonia in developing countries. Pediatr Infect Dis J 1992;11:77-81.

17. Hazir T, Nisar YB, Qazi SA, et al. Chest radiography in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. BMJ 2006;333:629.

18. Hazir T, Nisar YB, Abbasi S, et al. Comparison of oral amoxicillin with placebo for the treatment of World Health Organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. Clin Infect Dis 2011;52:293-300.

19. Awasthi S, Agarwal G, Kabra SK, et al. Does 3-day course of oral amoxycillin benefit children of non-severe pneumonia with wheeze: a multicentric randomised controlled trial. PLoS One 2008;3(4):e1991.

20. Ginsburg AS, Mvalo T, Nkwopara E, et al. Placebo vs amoxicillin for nonsevere fast-breathing pneumonia in Malawian children aged 2 to 59 months: a double-blind, randomized clinical noninferiority trial. JAMA Pediatr 2019;173:21-8.

21. Zhang S, Sammon PM, King I, et al. Cost of management of severe pneumonia in young children: systematic analysis. J Glob Health 2016;6:010408.

22. Hay AD, Redmond NM, Turnbull S, et al. Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. Lancet Respir Med 2016;4:902-10.

23. Enoch AJ, English M, Shepperd S. Does pulse oximeter use impact health outcomes? A systematic review. Arch Dis Child 2016;101:694-700.

24. Escadafal C, Kwasiborski A, Magro L, et al. Point-of-care molecular diagnostics for epidemic-prone viruses. Int J Infect Dis 2016;53:Suppl:26. abstract.

25. Kerai S, Nisar I, Muhammad I, et al. A community-based survey on health-care utilization for pneumonia in children in peri-urban slums of Karachi, Pakistan. Am J Trop Med Hyg 2019;101:1034-41.