

Challenges in the Design of Antibiotic Equivalency Studies: The Multicenter Equivalency Study of Oral Amoxicillin versus Injectable Penicillin in Children Aged 3–59 Months with Severe Pneumonia

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The World Health Organization (WHO) recommends that children with severe pneumonia (characterized by cough or difficult breathing, as well as lower chest wall indrawing) be hospitalized and treated with parenteral penicillin. Oral amoxicillin, if equally effective for treating severe pneumonia, would address challenges associated with providing parenteral therapy, including risk of transmission of bloodborne pathogens from contaminated needles, exposure to nosocomial pathogens during hospitalization, inadequate access to health care facilities, and cost. The recently completed multicenter international trial of oral amoxicillin versus parenteral penicillin for treatment of severe pneumonia demonstrated the equivalency of these agents in children with severe pneumonia. This article focuses on the challenges of designing an equivalence study and the threats to the validity of the trial results, particularly the implications of the bias toward finding equivalence when subjects are unlikely to respond to either study therapy. These considerations have implications for use of the Amoxicillin Penicillin Pneumonia International Study (APPIS) results in clinical practice and for potential modification of WHO treatment guidelines.

In developing countries, acute respiratory infection (i.e., pneumonia, severe pneumonia, and very severe pneumonia) remains a major cause of morbidity and mortality in children <5 years of age [1, 2]. The World Health Organization's (WHO's) standard case management guidelines define severe pneumonia as cough or difficult breathing, as well as lower chest wall indrawing [3]. Because

Streptococcus pneumoniae and *Haemophilus influenzae* are still the predominant causes of severe pneumonia in this age group, the WHO's standard case management guidelines for children with severe pneumonia is directed at treatment of these pathogens [4]. Children receive benzyl-penicillin (50,000 units/kg im or iv q6h) for at least 3 days as an inpatient [5], and, while improving, they complete a 5-day course with oral amoxicillin (15 mg/kg t.i.d.).

The challenges of providing the initial 3 days of parenteral therapy to children with severe pneumonia are well recognized [6]. Parenteral therapy is costly to administer, requires access to facility-based health care for hospitalization, and is associated with risks of exposure to nosocomial pathogens and transmission of

HIV and hepatitis B and C viruses through the use of contaminated needles [7–10]. In a recently published trial from Pakistan, in which children with pneumonia or severe pneumonia were randomized to receive oral amoxicillin or trimethoprim-sulfamethoxazole [11], amoxicillin was effective in treating 82% of those with severe pneumonia, which raises the possibility that oral amoxicillin may be effective initial treatment for severe pneumonia. The prospective, multicenter, randomized, controlled clinical trial—the oral amoxicillin versus parenteral penicillin for treatment of severe pneumonia international study (APPIS)—was designed to evaluate whether these 2 treatments were equivalent. The primary hypothesis was that treatment failures would be equivalent for children who received oral amoxicillin or

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injectable penicillin for 48 h, and the secondary hypothesis was that the 2 treatments would remain clinically equivalent through 5 and 14 days of follow-up.

CHALLENGES IN THE DESIGN OF THE TRIAL

The challenges and complexities in designing international studies in children are well recognized. To address the anticipated challenges, the study's steering committee, comprised of members from 9 international sites, the WHO, and the Center for International Health at Boston University (Boston), considered the following study design issues during a 7-day protocol development workshop.

Appropriate Study Design: Equivalence or Superiority

Members of the steering committee unanimously agreed that results from a randomized clinical trial would be needed to support any recommendation to modify WHO standard case management guidelines for treatment of children with severe pneumonia. Central to this discussion was whether the study should be designed to assess the equivalence of both or the superiority of 1 of the study drugs. We selected an equivalence design because of its utility in settings in which the standard therapy (in this case, injectable penicillin) has been shown to be beneficial but the new treatment (in this case, oral amoxicillin) is easier to use, has fewer side effects, or is less costly. However, true equivalence can never be established—it is necessary to select, a priori, how large a difference would still be considered equivalent (i.e., the equivalence margin) [12, 13]. This margin was determined by members of the steering committee [14] on the basis of an anticipated treatment failure rate of 11% among children treated with benzyl penicillin [6]. Deliberations included comparing the risks of selecting an equivalence margin that is too large (to avoid a meaningless result) with those of se-

lecting an equivalence margin that is too small (a conservative strategy that would waste resources) and discussion of the principle that the equivalence margin should be smaller than a difference that would be acceptable for determining superiority of one treatment over another. By means of a consensus process, a difference in failure rates of $\leq 5\%$ between treatment groups within 48 h after initiating therapy was chosen as the equivalence margin for the trial. We could not use a "superiority" design to assess equivalence, because failure to demonstrate superiority does not establish equivalence and because our study question was not whether penicillin or amoxicillin was superior in the treatment of severe pneumonia.

Threats to the Validity of the Trial Results and Approach to These Threats

Impact of patient selection. Standardized eligibility criteria were established to ensure that children enrolled in the study met WHO criteria for severe pneumonia. We considered 2 such criteria that were not part of the WHO definition because of the equivalence design: prior history of antibiotic use and unlikeliness to respond to amoxicillin or penicillin in children.

With regard to the first eligibility criterion, in developing countries, children with pneumonia frequently receive outpatient antimicrobial therapy before seeking care at a health care facility [15]. Exclusion of children who had taken any antibiotic before enrollment would limit the generalizability of the study results, whereas inclusion of children who had taken antibiotics would tend to bias the results toward equivalence, because the study antibiotics might have less influence on study outcome. WHO standard case management guidelines recommend reassessment at 48 h and advancement to second-line antibiotics if there is evidence of treatment failure [16]. The steering committee decided that first-line anti-

otics would be inappropriate for children who had already taken antibiotics for >48 h and continued to have signs of severe pneumonia. As a compromise, we elected to enroll children who had taken antibiotics for <48 h and to evaluate the potential impact of antibiotics received before study enrollment on study outcomes and conclusions.

With regard to the second eligibility criterion, specific risks of or lack of response to empirical treatment with amoxicillin or penicillin were recognized for 4 groups of children—those with bacterial pneumonia due to pathogens resistant to penicillin or amoxicillin (community acquired or nosocomially acquired), those with *Pneumocystis jiroveci* pneumonia [17, 18] as a result of HIV infection, those with viral pneumonia (primarily due to respiratory syncytial virus [RSV]), and those with hyperreactive airway disease. Because children who had been hospitalized within 2 weeks before screening were at risk of having nosocomial pneumonia caused by pathogens not likely to be treatable by either regimen, they were excluded from the study. We recognized that it was possible for children to have community-acquired *S. taphylococcus aureus* pneumonia and even methicillin-resistant *S. aureus* pneumonia. However, at enrollment, it was not possible to obtain an etiologic diagnosis or to treat according to the potential antimicrobial resistance pattern of respiratory pathogens, because of the lack of rapid diagnostic tests for most pulmonary pathogens and the difficulties of obtaining lung aspirates from children [19, 20].

Although nasopharyngeal isolates do not necessarily predict the etiologic agent of severe pneumonia, we elected to assess the potential effect of antimicrobial resistance of nasopharyngeal isolates of *S. pneumoniae* and *H. influenzae* on study outcome [21–23]. To minimize the number of children with *P. jiroveci* pneumonia, we excluded children who had HIV

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infection with a clinical category of B or C [24]. In the 2 study sites with a high prevalence of HIV infection (Durban, South Africa, and Ndola, Zambia), HIV infection was assessed using a combination of HIV antibody testing (for children ≥ 15 months of age) and PCR for detection of viral antigen (for children < 15 months of age). Finally, because real-time RSV testing was not practical at most sites, we evaluated the impact of RSV on the study results by bulk testing for the presence of RSV antigen in nasal washings collected and frozen during the baseline assessment.

The steering committee anticipated that hyperreactive airway disease could be confused with severe pneumonia. To minimize enrollment of children with bronchospasm and without severe pneumonia, we excluded children with a history of bronchial asthma or at least 3 prior episodes of wheezing. Children without this history and with a potentially reversible episode of bronchospasm were challenged with up to 3 doses of inhaled salbutamol, and they were considered to be eligible only if other criteria persisted after bronchodilator therapy. Our final eligibility criteria (table 1) reflected a compromise between unrestricted enrollment and the inclusion of children who would be less likely to respond to either treatment, because this latter group would compromise the equivalence design.

Impact of using a composite study outcome. Treatment failure ≤ 48 h after initiation of therapy—a composite outcome reflecting clinical deterioration—was the primary end point of the study. This outcome was defined as occurrence of any of the following signs and symptoms: danger signs (inability to drink, abnormal sleepiness, central cyanosis, or convulsions), low oxygen saturation ($< 80\%$ in room air at sea level or $< 75\%$ in Bogota, Colombia, and Mexico City, Mexico), persistence of lower chest indrawing, life-threatening or serious adverse drug reaction, newly di-

Table 1. Criteria for study eligibility.

Inclusion criteria
Age of 3–59 months
Cough or difficult breathing, as well as lower chest wall indrawing
Exclusion criteria
Nonsevere pneumonia
Very severe pneumonia (danger signs: inability to drink, abnormal sleepiness, central cyanosis, and convulsions)
Hospitalization during previous 2 weeks
History of bronchial asthma or ≥ 2 prior episodes of wheezing
Severe malnutrition (either weight for age z score less than or equal to -3 SD or presence of kwashiorkor)
Measles during previous month
Known or clinically recognizable chronic conditions (anomalous congenital cardiac or respiratory findings, chronic lung disease, bronchopulmonary dysplasia, neurological impairment affecting respiratory function, renal diseases, and malignant or hematological diseases)
Diseases affecting lower chest wall indrawing (rickets, severe pallor, and severe dehydration)
Low oxygen saturation ($< 75\%$ in room air at high-altitude sites [Bogota, Columbia, and Mexico City, Mexico] and $< 80\%$ in room air at other sites)
Prior anaphylactic reaction to penicillin or amoxicillin
Antibiotic therapy for ≥ 48 h before admission to the hospital
Inability to tolerate oral medications (≥ 3 episodes of vomiting per hour)
Living outside of the hospital's catchment area
Category B or C HIV infection

agnosed comorbid condition, receipt of another antibiotic, and death. If consent was withdrawn or if the child withdrew from the study against medical advice, outcome was also considered to be treatment failure because it was not known and could not be assumed to be favorable. The conceptual framework was that the appearance of danger signs, low oxygen saturation, discontinuation of study drug by the treating physician, occurrence of new comorbid conditions or complications, and death represented failure to respond to antimicrobial therapy or progressive or persistent disease due to the presence or development of an empyema or lung abscess. The timing of the primary outcome was based on the current WHO recommendation that the initial response to treatment be assessed after 48 h of antimicrobial therapy [3, 6]; this time frame is frequently used to assess initial response in patients with community-acquired pneumonia. Secondary outcomes included treatment failure on the fifth day of antibiotic therapy (the

current WHO-recommended duration of antibiotic treatment) and, for determining whether relapse had occurred, treatment failure 14 days after enrollment in the study (i.e., 9 days after completion of the course of antibiotics).

Use of a composite end point is challenging in any clinical trial [25, 26], but it is particularly challenging in equivalence studies. Composite end points reflect real clinical situations and are appropriate when there is no obvious choice of primary outcome [27]. In the APPIS, the goal was to evaluate whether oral amoxicillin and injectable penicillin were equivalent in treating severe pneumonia and preventing a range of severe outcomes in addition to death. The risks of using a composite outcome include bias toward equivalence, which could be characterized by considering a higher number of deaths and lower number of severe outcomes in one treatment arm to be equivalent to a lower number of deaths but a higher number of severe outcomes in the other treatment arm.

Unfortunately, it is often impractical to power a study to detect equivalence for all components of a composite end point. For this reason and to prevent misleading conclusions, it is particularly important that results of all components of the primary end point are included in the published version of the article. The overall strategy for the APPIS was to obtain and report unbiased assessments of each component of the composite end point.

Impact of lack of blinding on assessment of outcome. Although blinding to treatment assignment is an ideal way of minimizing bias in assessment of outcomes, administration of placebo injections to children <5 years of age was considered to be unethical. Similar conclusions have been made by investigators in other randomized clinical trials based in the United States and elsewhere [28–32]. To reduce the risk of biased assessment of subjective outcomes, we defined each outcome to minimize subjectivity and conducted intensive staff training in use of study outcomes both on-site and via video recordings. To assess adherence to study and outcome definitions, independent monitors (D.M.T., S.Q., and O.F.) audited study procedures during site visits. In addition, we expected that the most subjective outcome—switching to another antibiotic—would occur more frequently among children receiving oral therapy, leading to a bias away from equivalence. However, we recognize that our inability to blind treatment assignment was a limitation of the study.

Impact of losses to follow-up or absence of outcome information. Participants who withdrew from the trial or left against medical advice tend to dilute any difference between the groups, which biases the results toward equivalence. To address the effect that absence of information has on outcomes for children who were lost to follow-up, we set the goal that no more than 1% of the study population could have a missing primary end point at 48 h because of losses to follow-up. We planned, a priori, to con-

duct both an intent-to-treat analysis (that included all patients) and a per-protocol analysis (that excluded those who were lost to follow-up or were <3 months of age) to evaluate the impact on losses to follow-up on study conclusions. To enable us to conduct an intent-to-treat analysis, we assigned an outcome of treatment failure to children who withdrew from the trial or who left against medical advice, recognizing that overall treatment failure in the trial would represent a worst-case scenario.

Monitoring the Safety of an Equivalence Trial

The APPIS was monitored by an independent data safety monitoring board (DSMB) that was charged with evaluating subject safety throughout the trial. Because the trial outcome was treatment failure, the DSMB focused on whether there was interim evidence that treatment failure was occurring more frequently in 1 treatment arm, rather than on whether the treatments were equivalent. Because sample size calculations for equivalence studies are different from sample size calculation for detecting differences between treatment groups, we calculated sample size requirements from both perspectives, selecting the larger sample size for the study. This approach enabled the overall result to address equivalence and to provide the interim analyses of study safety with adequate power to detect statistically important differences between treatment groups. The final sample size for the study was 1722 children (861 per group). We planned to evaluate whether the 2 treatments were equivalent using the two 1-sided tests procedure and to calculate the risk differences and 95% CIs of the primary and secondary outcomes [33]. If the 95% CI limits are within the range of –5% to 5%, the treatments are considered to be equivalent. We also planned to evaluate predictors of treatment failure at 48 h using a mixed-effects model (SAS Institute), with study site as a random effect and treatment as a fixed

effect, and to assess whether baseline characteristics and results were consistent across study sites. A priori baseline covariates to be included in the model as fixed effects were sex, age of <12 months, breast-feeding at onset of present illness, immunization status (current or not), use of antibiotics before admission to the hospital, presence of malnutrition (weight for age z score, less than –2), fever (temperature, >38°C), tachypnea, and oxygen saturation.

CHALLENGES AND SOLUTIONS TO PROBLEMS DURING STUDY CONDUCT

Mortality. The DSMB conducted its first interim analysis after 8 deaths had occurred at 2 study sites in which there was a high prevalence of HIV infection (Zambia and Durban). Seven of the 8 children who died were <12 months of age and were likely to have had *P. jiroveci* pneumonia. Even though the results did not approach statistical significance for a difference between treatment groups, the DSMB recommended that the exclusion criteria for the study be revised to exclude children <1 year of age who were likely to be infected with HIV. Children <1 year of age with hepatosplenomegaly, oral thrush, or known family member(s) with HIV infection were excluded. Only 1 additional death occurred at the Zambia or Durban sites between May 2000 and the completion of the trial.

DSMB assessment of study power during the study. The target sample size of 1722 subjects was based on anticipated treatment failure rate during or after 48 h of study treatment of 10% in both groups, as described above. After 1034 children (60%) were enrolled in the study, the proportion of treatment failures was 18.6% in the amoxicillin group and 19.9% in the penicillin group. The DSMB raised the concern that the equivalence margin for the study would likely be >5% at study completion, unless the sample size was increased, but did not recommend changing the sample size. Staff at the data co-

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ordinating center recalculated sample size requirements without changing any assumptions except the proportion of treatment failures, which was now assumed to be 19.25% in both groups. To retain the 5% equivalence margin (16.75%–21.75%), a total of 2269 patients would need to be recruited to complete the trial, but the current sample size was adequate to evaluate equivalence within a margin of 5.8% (16.35%–22.15%). The alternative was to accept less power to show equivalency. At the original sample size, the power to retain the 5% equivalence margin (16.75%–21.75%) was reduced to 81.2%. After discussion between the sponsors and the DSMB about the risk/benefit ratio of increasing the size of the study sample, the study continued without change to the sample size, with the recognition that the study would evaluate equivalence within the 5.8% margin. The proportion of patients in both groups whose condition did not improve or deteriorated continued to be monitored throughout the study by the DSMB.

STUDY OUTCOME AND CONCLUSION

Injectable penicillin and oral amoxicillin were equivalent in this trial (19% of patients in each study group experienced treatment failure after 48 h of therapy) [34]. The components of the composite outcome were almost identical in the 2 study groups. However, despite the results and the careful attention to threats to the validity of the results, we recognize that our study was limited by inherent biases toward finding equivalence if subjects are unlikely to respond to study therapy (e.g., because they had nonbacterial pneumonia) and by our inability to conduct a blinded study.

STUDY GROUP MEMBERS

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Yobo, and Kojo Yeboah-Antwi (Ministry of Health; Kintampo, Ghana); Mumtaz Hassan (Children's Hospital; Islamabad, Pakistan); Prakash Jeena and Hoosan M. Coovadia (University of Natal; Durban, South Africa); Juan M Lozano (Javeriana University; Bogota, Colombia); Irene Maulen (National Institute of Pediatrics; Mexico City, Mexico); George McGillivray (University of Cape Town; Cape Town, South Africa); Archana Patel (Indira Gandhi Medical College; Nagpur, India); Tom Sukwa and Noel Chisaka (Tropical Disease Research Centre; Ndola, Zambia); Nguyen ngoc Tuong Vy (Children's Hospital No. 1; Ho Chi Minh City, Vietnam); Donald M. Thea, William B. MacLeod and Matthew Fox (Boston University; Boston); Patricia L Hibberd (Tufts–New England Medical Center; Boston); and Shamim Qazi and Olivier Fontaine (World Health Organization; Geneva, Switzerland).

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Conflict of interest. All authors: No conflict.

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