

inform public health policy for the management of fast breathing, there is a need to evaluate whether young infants with fast breathing alone can be safely and effectively treated in the community with oral antibiotics alone, particularly in previously unstudied African settings.

In 2009, WHO requested proposals from African sites interested in conducting a randomized, open-label equivalence trial to address this issue. After an external review process, 5 sites in Africa were selected to participate in this study using a common protocol. The sites include 1 site each in the Democratic Republic of Congo (DRC) and Kenya, and 3 sites in Nigeria (Ibadan, Ile-Ife and Zaria). This article describes the protocol for this trial.

OBJECTIVES

The overall goal of the study was to inform policy on the use of oral amoxicillin for young infants with fast breathing. Our underlying hypothesis is that young infants with “fast breathing” alone can be safely and effectively managed with an oral antibiotic.

- Primary objective: To evaluate the use of oral amoxicillin compared with intramuscular procaine penicillin and gentamicin for the provision of safe and effective treatment at first-level facilities and in the community for 0- to 59-day-old young infants with fast breathing alone, whose families do not accept or cannot access referral level care.
- Secondary objectives: To assess family acceptance of and compliance with an oral antibiotic treatment regimen compared with intramuscular antibiotic injections and to document and compare the health worker time costs and other logistical requirements of the 2 treatment regimens.

METHODS

Study Settings

This study is being carried out at 5 sites, 1 each in DRC and Kenya and 3 sites in Nigeria; Ibadan, Ile-Ife and Zaria. Of note, another study is being performed concomitantly in the same study sites for young infants with clinical severe infection (one or more of the following 5 signs: poor feeding, movement only when stimulated, severe chest indrawing, axillary temperature $>38.0^{\circ}\text{C}$ or $<35.5^{\circ}\text{C}$), who are treated with different experimental antibiotic regimens, although the reference treatment arm is the same for both studies. As some components of the methods are common for both studies, we have reported the commonalities such as the description of study sites and details of data management only in the clinical severe infection methods paper, also published in this supplement.¹⁵

Study Design

The study approach is outlined in Figure 1. This is an individually randomized, open-label equivalence trial. All 5 study sites will contribute to the overall sample size. Sites in the DRC, Kenya and Nigeria are following the same study design, with similar inclusion criteria, the same intervention, comparison and outcomes, as well as quality control and coordination mechanisms.

Participants

Identification of Newborns

Births are identified by community health workers (CHWs), community health extension workers (CHEWs) and traditional birth attendants and are reported within 24 hours of delivery. CHWs and traditional birth attendants cannot give injections; in contrast, CHEWs (only present in Nigeria) receive 2 years of professional training and thus can give injections. In the DRC, birth information is also transmitted by health center nurses directly to the study enrollment/treatment

nurse or the study community coordinator. CHWs/CHEWs transmit information to the community coordinator/supervisor/cluster coordinator as soon as possible. The CHWs/CHEWs record details of the household and the place where the birth occurred; they also perform a postnatal home visit on the day of birth (day 1) and on days 3, 7, 14, 21, 28, 35, 42, 49 and 60 to check the newborn's condition. CHWs/CHEWs provide families with contact details and counsel parents on the need to report any concerns they have about their newborn. The CHWs/CHEWs alert an enrollment nurse if there are any young infants with fast breathing or other symptoms and signs suggestive of PSBI whose parents refuse referral. In DRC and Kenya, the CHW accompanies the family to the health center if the family agrees, whereas in Nigeria the study enrollment/treatment nurse is called to infant's home.

Screening and Enrollment

Screening and enrollment are conducted by enrollment/treatment nurses. In DRC and Kenya, this takes place at the health center/dispensary. In the Nigerian sites, it takes place at the child's home. All young infants with suspected PSBI are referred by the enrollment nurse. Infants with PSBI whose parents/caretakers refuse referral for treatment are evaluated for inclusion/exclusion criteria and if found eligible, the study is explained to the parents. The mother/caregiver is counseled on the implications of refusing referral. If the parents agree to participate in the study, consent is obtained from the mother/father. If he/she is illiterate, she/he will affix a thumbprint on the form in the presence of a literate witness who signs the same form.

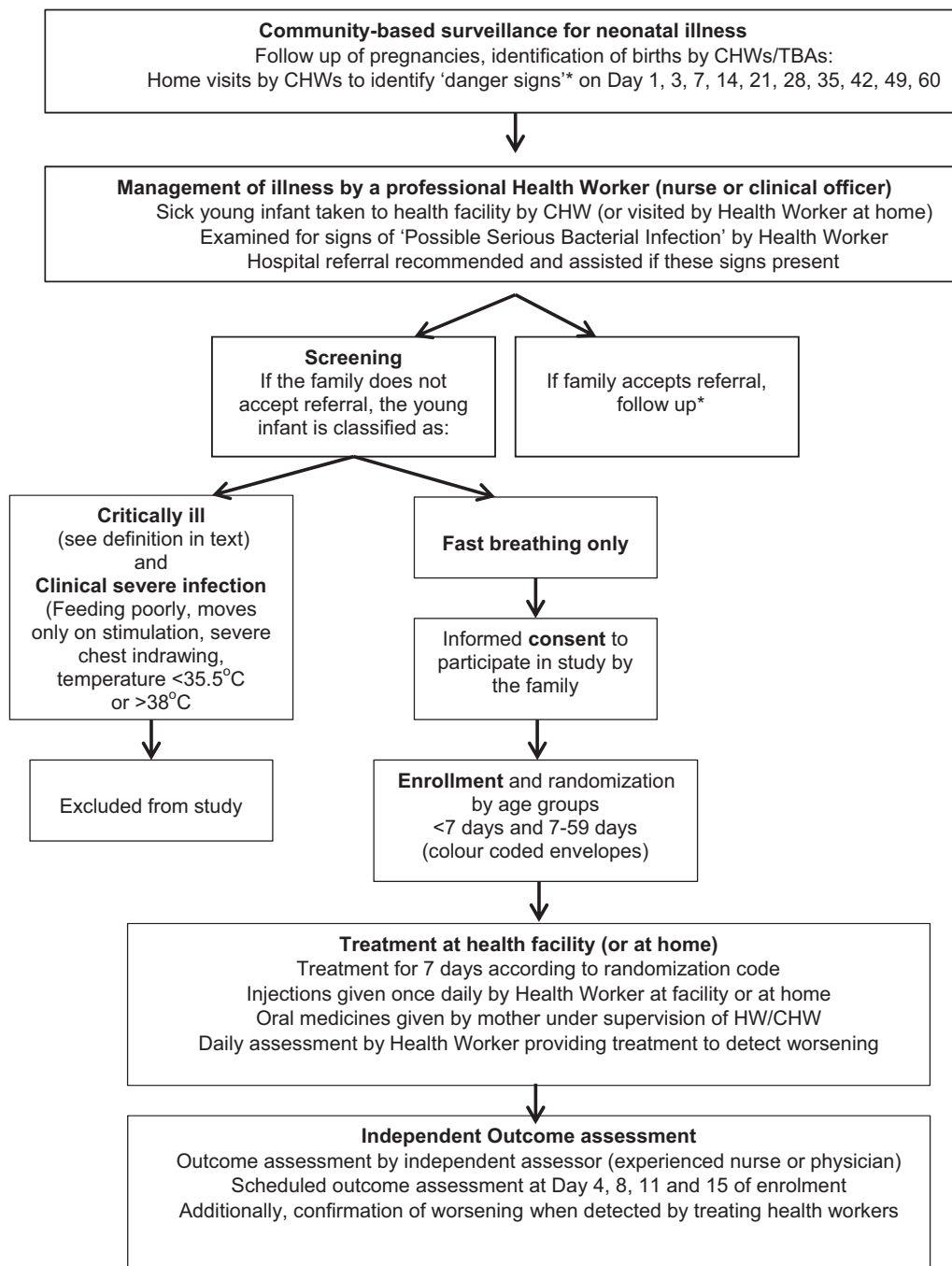
Young infants are included in the study if they fulfill the following criteria:

- Age 0–59 days of age.
- Fast breathing, defined as respiratory rate of >60 breaths per minute.
- Do not have any of the following exclusion criteria:
 - Signs of severe infection (defined as poor feeding on observation, movement only when stimulated, severe chest indrawing and axillary temperature $\geq 38.0^{\circ}\text{C}$ or $<35.5^{\circ}\text{C}$);
 - Critically ill (characterized by the presence of any of the following signs: unconsciousness, convulsions, unable to feed at all, apnea, unable to cry, cyanosis, dehydration, bulging fontanel, major congenital malformations inhibiting oral antibiotic intake, active bleeding requiring transfusion, surgical conditions needing hospital referral and persistent vomiting defined as vomiting following 3 attempts to feed the baby within one-half hour);
 - Very low weight (<1500 g at the time of presentation);
 - Hospitalized for illness in the last 2 weeks or previously enrolled in the study.
- Parents do not accept or cannot access referral level care.
- Parents give consent to participate in the study.

At the time of enrollment, infants are stratified into 2 age groups: 0–6 days and 7–59 days. They are individually randomized to treatment regimens within each site and age stratum. The reference treatment is injectable gentamicin once daily and injectable procaine penicillin once daily for 7 days (treatment regimen A). The intervention arm consists of oral amoxicillin twice daily for 7 days (dosages described below).

Randomization schemes with a block size of 8 were computer-generated off-site at WHO using STATA version 10.0 (STATA Corp., College Station, TX) by a person not involved with the study. For allocation concealment, treatment codes are printed on small pieces of card folded once and sealed in an opaque envelope (2 sets of color-coded envelopes are used, one for each age group).

Treatments are given at a health facility or at home. Injections are given once daily by a health worker at a facility or at



*Only if families provide consent for this follow-up visit to document outcome

FIGURE 1. Overall study approach.

home, whereas oral medicines are given at home by the mother under the supervision of CHWs. A daily assessment by a health worker (treatment nurses in DRC and Kenya and CHEW in Nigeria) is conducted to identify possible treatment failures.

Allocation of Treatment Arm

In the Kenyan and Nigerian sites, the randomization list is held centrally and the treatment allocation is provided to the enrollment nurse, according to the child's age category, by phone and is

confirmed by SMS. In the DRC where mobile phone communication is generally unavailable across the study catchment area, each facility where enrollment occurs is given a block of 8 envelopes for each age group, and used blocks are regularly replaced so that a sufficient number of envelopes are always available at the facility. When the first young infant is enrolled at a facility in a stratum, the first envelope of the block for that stratum and age category at the facility is opened and the infant is treated according to the treatment code inside. When the next infant is enrolled, the next envelope of

the appropriate stratum and age category block is opened. A record of all randomizations is kept by the study supervisors or study community coordinators.

Provision of Treatment

In the DRC and Kenya, all injectable treatment is provided at the health facility, by the enrollment/treatment nurse who also provides the first dose of oral therapy. Mothers observe the first dose being given and are instructed on provision of oral amoxicillin at home. In Nigeria, the first dose of injectable and of oral treatment is provided at home by the enrollment/treatment nurse after randomization. The rest of the injectable treatments are provided by CHEWs. Oral treatments are given to the mother of the enrolled infant and are administered in the home, under direct observation of the CHW/CHEW.

Outcome Assessment of Enrolled Patients

An independent outcome assessment nurse visits enrolled infants on days 4, 8, 11 and 15 after the day of enrollment to assess outcome. All assessments are conducted at the young infant's home.

Choice of Antibiotic Regimens

A combination of penicillin and gentamicin injections is currently the WHO recommended treatment for PSBI in young infants. Thus, single daily injections of procaine penicillin and gentamicin were chosen as the reference treatment. A detailed rationale for the selection of antibiotics and study outcomes is described in another article in this supplement.¹⁶

Oral amoxicillin has been shown to be superior to oral trimethoprim-sulfamethoxazole for the treatment of pneumonia^{17,18} and has been shown to be effective in treating severe pneumonia in children 2–59 months of age.^{19–22} The most frequent pathogens associated with pneumonia are generally similar in neonates and young children and are frequently susceptible to amoxicillin.^{17,23} Oral amoxicillin was therefore chosen as the experimental treatment for this study.

The antibiotic dosages for young infants enrolled in the study are injection procaine penicillin in a dose of 50,000 units/kg once-daily IM; injection gentamicin in the range 4.0–7.5 mg/kg/d once-daily dose IM (depending on age of the young infant) and oral amoxicillin in suspension form in a dose of 100 mg/kg/d (<2 kg are given 75 mg/kg/d), divided in 2 equal doses. Both treatment regimens are being used for 7 days.

Study Outcomes

Primary Outcome

The primary outcome for the study is treatment failure by the day 8 postenrollment visit. Treatment failure is defined as any one of the following:

- Death;
- Clinical deterioration, defined as the emergence of any sign of severe infection or critical illness at any time after enrollment (as defined in exclusion criteria), or hospitalization any time after enrollment;
- Persistence of fast breathing on day 4 or recurrence after day 4 up to day 8;
- Development of a serious adverse event (other than death) that is related to the study antibiotics, eg, organ failure, anaphylactic reaction, severe diarrhea, disseminated and severe rash;

Secondary Outcomes

- Death occurring 9–15 days after enrollment;
- Relapse, defined as fast breathing that disappears on day 8 of enrollment and reemerges between days 9 and 15, or development of any sign of severe infection or critical illness signs between days 9 and 15 after enrollment;
- Adherence to the study therapy between days 1 and 8.

Sample Size

In the absence of population-based incidence data, the incidence of fast breathing was conservatively estimated to be about 3.5% in Africa. The figure is based on a large multicenter study, where 5–18% of all sick young infants brought for care had fast breathing.⁸ Community-based studies in India and Bangladesh reported that 4.6–8.1% of babies had fast breathing at some point during the neonatal period.^{4,24}

The sample size calculations assumed that the statistical analysis will be based on a comparison between the failure rate observed with the reference treatment regimen of injection penicillin and gentamicin for 7 days (assumed treatment failure rate of 8%) and the experimental regimen of oral amoxicillin for 7 days. A point estimate of the failure rate difference (experimental—reference treatment) between the 2 treatment regimens will be calculated together with a 2-sided 95% confidence interval. The alternative treatment will be judged to be “of similar effectiveness” to the reference treatment if the upper bound of the 95% confidence interval lies below the allowed “similarity margin” of +4%. A power of 90% to demonstrate the similarity of 2 treatments over the 7-day period following randomization was required, assuming that the true failure rates with the reference treatment and the experimental treatment regimens will be identical (assumed to be 8%).

Using the above assumptions, the required sample size was determined to be 1150 infants for each treatment group, which is likely to yield 970 “analyzable” infants per treatment arm.

Data Collection, Management and Analysis

Data are collected either at home or in the health facility on paper-based standard case report forms; forms are completed by CHWs/CHEWs, enrollment and treatment nurses, and independent outcome assessors. All completed case report forms are checked by study supervisors before the data entry. Data are entered into a Structured Query Language database specifically developed for the study. Double data entry is carried out by data entry clerks at each site; logical checks are performed by the data manager in consultation with the study supervisor and if necessary by the principal investigator. The cleaned database is sent monthly to the central data coordination center at the London School of Hygiene and Tropical Medicine (LSHTM), which developed the data management system. Quality checks are carried out both at the site and at LSHTM. LSHTM assists in quality control through database monitoring and preparing necessary reports for the Data Safety Monitoring Board (DSMB) and the trial Technical Advisory Group (TAG); they also liaise with the WHO study coordination team. Further details are described in the accompanying article on severe infections, as the trials were conducted concurrently.¹⁵

Analysis Plan

The primary analysis will be a combined analysis across all the sites. Simple comparisons of means and proportions by treatment group will be used to check whether the randomization scheme resulted in baseline comparability of the treatment groups. The primary analyses will be for equivalence between the reference treatment and the experimental (intervention) arm. It will consist of the comparison of proportions of infants with treatment failure in each treatment arm.

The primary analysis will be conducted on a per-protocol basis; an intention-to-treat analysis will also be conducted. For an enrolled infant to be included in the per-protocol analysis, she/he should have received: (1) all antibiotic doses due to be received for the first 3 days of treatment or by the time of treatment failure; and (2) at least 50% of all scheduled doses of each antibiotic on days 4–7 or by the time of treatment failure. Furthermore, for inclusion in the per-protocol analysis, follow-up must be completed on assessment days 2–4 and on at least 1 of days 5–8, and vital status on day 8 must be known.

Analyses will be performed with data from all sites, adjusted for any baseline covariates that were unbalanced at baseline and with addition of dummy variables for site and age group. The primary and secondary outcomes, the proportion of young infants who received treatment for the entire duration and costs of such treatment will be compared across the 2 study arms. The difference in the risk of treatment failure together with 95% confidence intervals will be calculated. Secondary analyses will be performed to investigate the effect on adverse events including death and other serious outcomes such as diarrhea with severe dehydration, disseminated and severe rash, anaphylactic reaction, stopped passing urine for >12 hours, cellulitis or abscess at injection site. Univariate and multivariate regression analyses will be undertaken to identify predictors of treatment failure for young infants with fast breathing.

Ethical Issues

Study Approvals

The trial protocol and all associated data collection instruments and consent forms were submitted for ethical review to the local institutional review boards at each site as well as to the WHO Ethical Review Committee and to LSHTM. The trial was registered as ACTRN12610000286044 with Australian New Zealand Clinical Trials Registry. The trial follows the Council for International Organizations of Medical Sciences (CIOMS) and Good Clinical Practice guidelines.

Informed Consent

The study was explained to members of the community at all sites before study enrollment; this was achieved through meetings with community leaders and community groups. Informed written consent is obtained for the home visits for pregnancy and birth, enrollment and treatment, as well as for the follow-up visit of the nonenrolled infants. Safety of young infants enrolled in this trial was ensured by close monitoring and follow-up. Health workers were trained to facilitate referral through counseling using integrated management of childhood illness guidance for assisting referral. Only babies whose families refused referral and were willing to document this by witnessed signature/thumbprint were enrolled.

Monitoring of Potential Adverse Events

The families are asked to contact the CHW/CHEW if any adverse events occur (as defined in the study protocol). In the case of an adverse event, CHWs contact the supervising CHW and CHEWs call the outcome assessment nurse, who then confirms and documents the adverse event and conveys the information to the community coordinator/supervisor. All serious adverse events (including death, unable to pass urine for >12 hours, anaphylactic reaction, severe dehydration due to diarrhea, disseminated or severe rash) are reported to WHO within 48 hours of occurrence. This information is also provided on a regular basis to DSMB, institutional review boards and the WHO Ethical Review Committee.

Rescue Therapy

Should the condition of the infant worsen and he/she requires further medical care, the infant may be given rescue therapy as determined by the study protocol. This includes intramuscular ceftriaxone for 7 days if the families still refuse referral to a higher level of care.

Data Safety Monitoring Board

The DSMB is responsible for monitoring and assessing the safety of the trial and consists of an epidemiologist, a statistician and a clinician scientist/researcher from each of the 3 countries. The DSMB convenes at least once a year in a face-to-face meeting, which consists of both an open and a closed session. Two interim

analyses will be conducted, first when one-third of participants and second when two-thirds of the participants have been enrolled and treated. The interim analysis is conducted on a blinded basis.

The DSMB recommended that the trial be stopped or modified if an interim analysis of the safety endpoints of neonatal deaths and/or serious adverse events demonstrated a difference between treatment and control of at least 2 standard errors ($P = 0.01$) for effectiveness or futility. Furthermore, termination or modification may be recommended for any other perceived safety concern based on clinical judgment, including but not limited to a higher than anticipated rate for any component of the primary endpoint or unexpected serious adverse events. For this purpose, the serious adverse event forms are sent to the DSMB on the quarterly basis.

Quality Assurance

Training

Training courses were held for master trainers from all sites; these master trainers then trained local study personnel. Training covered the following courses: WHO/UNICEF Home Care for Newborns, WHO/UNICEF Young Infant integrated management of childhood illness (for study nurses) and a study-specific procedures course. All CHWs/CHEWs and enrollment, treatment and outcome assessment nurses employed by the study were trained at their respective sites by the master trainers. All supervisors and site coordinators were also trained in all courses. Further details of training are given in the accompanying methods paper on severe infection.¹⁵

Standardization, Quality Assurance of Training and Quality Control

Before starting study enrollment, standardization exercises are conducted on clinical and other study procedures for the appropriate cadres of workers, including CHW/CHEWs, enrollment and treatment nurses, independent outcome assessors, supervisors and study coordinators. Standardization exercises are repeated every 6 months over the course of the study. Data-based monitoring is also carried out with the help of the DMC in London and the WHO coordination team in Geneva. Further details on quality assurance are given in the accompanying articles.^{15,25}

Supervision

Supervisors make accompanied and unaccompanied visits regularly to oversee field activities. Investigators made random visits to check quality.

Site Monitoring

All sites prepare and submit monthly progress reports, which are reviewed by the WHO coordination team on a monthly basis. Regular conference calls are held to review progress. WHO monitors conduct site visits twice a year to review progress in the field. Further details on site monitoring are given in the accompanying methods paper.¹⁵

Coordination Mechanisms

The WHO Department of Maternal, Newborn, Child and Adolescent Health is coordinating this study. Technical advice is provided by a TAG, which includes all principal investigators, the WHO coordination team and external experts. The TAG convenes at least once a year in a face-to-face meeting. LSHTM assists in quality control through database monitoring and preparation of reports for the DSMB, the TAG and the WHO study coordination team.

Timelines

The enrollment of the study participants started in April 2011 at all study sites and is likely to be complete by May 2013.

DISCUSSION

The current WHO algorithm for identification of PSBI in young infants includes a range of signs from milder signs such as fast breathing to very serious signs like convulsions and no movement on stimulation. WHO recommends that sick infants with any of these signs be referred for hospitalization and treated with up to 50 injections with a penicillin (benzyl penicillin or ampicillin) plus gentamicin for at least 10 days. This is not always feasible for a variety of reasons, including families' lack of access to appropriate health facilities and the cost of such treatment. Young infants with fast breathing are at lower risk of serious adverse events compared with sick young infants with other more serious signs.^{10,11} Evidence also suggests that fast breathing in young infants can be treated with oral antibiotics in the community.¹³ Moreover, the safety, feasibility and cost of managing severe neonatal infections in community settings to address high neonatal mortality have been identified as a high research priority.²⁶ If this study demonstrates that young infants with fast breathing can be treated safely and effectively with oral amoxicillin at home, it would greatly benefit both the families and health system and would facilitate increased coverage of treatment.

Blinding of therapy was not possible in this trial because of the differences in delivery of the 2 experimental regimens. Although the assessment of treatment failure is to some degree subjective, based on the presence or absence of clinical signs, an independent outcome assessor who is blinded to the treatment regimen assesses the study outcomes.

The ongoing trial described in this article is a multicenter, multicountry study involving 5 sites. The primary health care system is operational in all study areas, but referral systems are weak or unavailable in most of the study areas. This study is the largest community-based study evaluating a simplified antibiotic regimen for fast breathing in neonates and young infants in Africa and will provide important information to help formulate local and global policies to better manage PSBI in young infants.

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