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Safety and Efficacy of Simplified Antibiotic Regimens for Outpatient Treatment of Serious Infection in Neonates and Young Infants 0–59 Days of Age in Bangladesh

Design of a Randomized Controlled Trial

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Background: Because access to care is limited in settings with high mortality, exclusive reliance on the current recommendation of 7–10 days of parenteral antibiotic treatment is a barrier to provision of adequate treatment of newborn infections.

Methods: We are conducting a trial to determine if simplified antibiotic regimens with fewer injections are as efficacious as the standard course of parenteral antibiotics for empiric treatment of young infants with clinical signs suggestive of severe infection in 4 urban hospitals and in a rural surveillance site in Bangladesh. The reference regimen of intramuscular procaine-benzyl penicillin and gentamicin given once daily for 7 days is being compared with (1) intramuscular gentamicin once daily and oral amoxicillin twice daily for 7 days and (2) intramuscular penicillin and gentamicin once daily for 2 days followed by oral amoxicillin twice daily for additional 5 days. All regimens are provided in the infant's home. The primary outcome is treatment failure (death or lack of clinical improvement) within 7 days of enrolment. The sample size is 750 evaluable infants enrolled per treatment group, and results will be reported at the end of 2013.

Discussion: The trial builds upon previous studies of community case management of clinical severe infections in young infants conducted by our research team in Bangladesh. The approach although effective was not

widely accepted in part because of feasibility concerns about the large number of injections. The proposed research that includes fewer doses of parenteral antibiotics if shown efficacious will address this concern.

Key Words: safety, efficacy, simplified antibiotic regimens, young infants, clinical severe infection

(*Pediatr Infect Dis J* 2013;32:S12–S18)

An estimated 3.0 million annual neonatal deaths occur globally; 99% of these deaths occur in developing countries.^{1–4} In many settings, neonatal and infant mortality now make up the vast majority of under-5 child deaths. For example, in Bangladesh, 57% of under-5 deaths occur within the first 28 days after birth and another 23% take place in the postneonatal period.⁵ Approximately 10–20% of newborns develop life-threatening infections⁶ and one-third to one-half of all neonatal deaths are due to infection,^{1,7–9} including sepsis, pneumonia, tetanus, meningitis and diarrhea. Timely and appropriate treatment can avert most of these deaths.^{6,10}

The World Health Organization (WHO) recommends that all cases of clinical severe infection in neonates and young infants (0–59 days old) be treated in hospitals with a 7- to 10-day course of injectable antibiotics—penicillin or ampicillin and gentamicin. In low-resource settings, however, reliance on a strategy of hospitalization of young infants with clinical severe infections has a number of inherent disadvantages. Parents/caregivers often consider care-seeking outside the home to be unacceptable in the early postpartum period, or they may not be able to travel to a health facility; upon reaching the facility, infants may receive inadequate treatment because of barriers due to cost, under-staffing or lack of available beds and supplies.^{11–15} Hospitalization increases the risk of exposure to multidrug-resistant nosocomial pathogens that are increasingly difficult to treat^{16,17} and raises the cost of health care.¹⁸

Strategies for community-based management of severe infections in young infants have been developed and evaluated in several research settings.^{8,19,20} A cluster-randomized controlled trial of a package of maternal and neonatal interventions, which included assessment and management of newborns by village-based community health workers, was conducted by our group in Sylhet district, Bangladesh. Neonates with signs of severe infection were referred to a qualified provider or treated in the home with intramuscular procaine penicillin and gentamicin (Treatment regimen included a total of 10 days of gentamicin and procaine penicillin. Dosage of gentamicin was adjusted based on neonate's weight as follows: 10 mg every other day if <2.0 kg, 10 mg/day if 2.0–2.5 kg and 13.5 mg/day if >2.5 kg. Dosage for penicillin was

Accepted for publication June 5, 2013.

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The trial registration number was ClinicalTrials.gov NCT00844337.

The views and opinions expressed in this article are those of the author(s) and not necessarily the views and opinions of the United States Agency for International Development.

This research was funded by the United States Agency for International Development, through a cooperative agreement (GHS-A-00-09-00004-00) with the Johns Hopkins Bloomberg School of Public Health and by the Saving Newborn Lives program of Save the Children Federation, Inc, through a grant from the Bill and Melinda Gates Foundation. The authors have no other funding or conflicts of interest to disclose.

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ISSN: 0891-3668/13/3209-0S12

DOI: 10.1097/INF.0b013e31829ff790

80,000 units if <2.0 kg and 160,000 units if ≥ 2.0 kg.) if the caretaker declined referral but consented to home treatment. The rate of referral compliance was 34% among those diagnosed as being in the severe disease category, and another 43% accepted home treatment; the case fatality rate for neonates treated by community health workers was statistically not different from that of neonates treated by doctors and other medically qualified providers and was 78% lower than for those who received no treatment or were treated by untrained providers (adjusted hazard ratio 0.22, 95% confidence interval [CI]: 0.07–0.71).²¹ In a trial providing home-based treatment with a regimen of oral co-trimoxazole and intramuscular gentamicin, Bang et al²² reported a 60% reduction in neonatal infection case fatality. One barrier to scaling up findings from these trials is that major challenges are associated with providing parenteral antibiotic therapy in the community. It is resource intensive to train community-based health workers to provide injections and to ensure supply of antibiotics and safe administration of parenteral antibiotics daily for 7 to 10 days.

Evidence suggests that oral antibiotic therapy also reduces mortality in neonates and young infants with suspected infections.¹⁰ A meta-analysis of trials of community-based case management of pneumonia found a 27% reduction in neonatal mortality and a 20% reduction in infant mortality.²³ Five of the 7 studies included in the meta-analysis used oral antibiotic regimens. In an open-label trial in Pakistan, 3- to 59-month-old children ($n = 2037$) with severe pneumonia were randomly allocated to either (1) hospitalization and parenteral ampicillin (100 mg/kg per day in 4 doses) for 48 hours, followed by 3 days of oral amoxicillin (80–90 mg/kg per day in 2 doses), or (2) home-based treatment for 5 days with oral amoxicillin (80–90 mg/kg per day in 2 doses).²⁴ At 7 days after the start of treatment, no difference in treatment failure rates was observed between the hospitalized group (8.6%) and the ambulatory group (7.5%; risk difference 1.1%; 95% CI: –1.3 to 3.5). High failure rates, however, were associated with age 3–5 months, very fast breathing (>70 breaths per minute for children <12 months old) and low weight for age, suggesting that providing oral antibiotics alone may be inadequate for young infants with clinical severe infection. Alternatives for these infants include restricting the number of injectable antibiotics either by combining an initial short course of parenteral antibiotics with a switch to oral antibiotics or a combination of injectable and oral antibiotics.¹⁰

In 2007, a global consultation convened by the Saving Newborn Lives Initiative of Save the Children, the United States Agency for International Development and the WHO concluded that there was insufficient evidence on infection management in young infants in community-based settings to make policy recommendations for global programs. The consultation highlighted the need for research to test combinations of low cost existing oral and intramuscular antibiotic regimens that might feasibly be implemented in first-level facilities and the community, and that would be acceptable in settings characterized by weak health systems.

METHODS

Study Design

We are conducting a trial in Bangladesh to determine if 2 home-based antibiotic regimens are as efficacious as the standard regimen of intramuscular procaine-benzyl penicillin and gentamicin given once daily each for 7 days for the empiric treatment of young infants (age 0–59 days) with clinical signs suggestive of severe infection (clinical severe infection). The 2 alternative regimens are (1) intramuscular gentamicin once daily and oral amoxicillin twice daily for 7 days and (2) intramuscular penicillin and gentamicin once daily for 2 days followed by oral amoxicillin twice

daily for 5 days. The primary hypothesis is that the proportion of infants who fail treatment will be 10% in the reference group and each of the alternative treatment groups. The null hypothesis is that any one of the alternative therapies is inferior and will yield a treatment failure proportion that is at least 5% points higher than that of the standard therapy group. The null hypothesis will be rejected if the upper bound of a 95% CI around the absolute difference (alternative minus standard) is less than 5.0%. The trial's secondary objectives are (1) to identify baseline clinical predictors of treatment failure in severe infections in young infants and (2) to determine the proportion of infants with relapse, defined as young infants who were considered cured by day 7 but developed any of the signs of clinical severe infection by day 14.

Setting, Enrollment and Randomization

The study recruits young infants from the outpatient departments of Dhaka Shishu (children) Hospital, Shishu Sasthya Hospital in Dhaka, Institute of Child and Mother Health Hospital in Dhaka, Chittagong Ma O Shishu Hospital in Chittagong and a rural surveillance sites in Sylhet, Bangladesh. All 4 hospitals are in the urban areas of 2 major cities of Bangladesh, receive young infants with very similar complaints and use similar approaches to clinical management of severe infections in young infants. In the rural site, all pregnant women in the study area are identified by female community health workers (CHW) through established pregnancy surveillance and are offered a standard package of antenatal counseling. Families and birth attendants notify the CHW as promptly as possible after a birth has occurred. After birth, CHWs aim to visit all newborns in the home within 6 hours of birth and not later than 24 hours. This early postnatal visit is important to capture early-onset infections. The general health status of the infant is assessed by the CHW using criteria from the WHO Young Infant Study Group.²⁵ The CHW returns on days 2, 6, 13, 20, 27, 34, 41, 48 and 59 after birth to inquire about any illness of the infant in the intervening period and to reassess the status of the infant. CHWs refer infants meeting the criteria for clinical severe infection to 1 of 2 designated hospitals for further evaluation and care.

Recruitment and participation procedures are summarized in Figure 1. Research assistants who work for the study screen young infants presenting to the outpatient departments of the participating hospitals to determine if age and place of residence meet initial eligibility criteria. Potentially eligible infants are then screened by the study physician for signs of clinical severe infection according to the inclusion and exclusion criteria described below. Infants with ≥ 1 inclusion criteria and no exclusion criteria are considered clinically eligible; however, study physicians first recommend hospitalization before enrolment in the trial. If no hospital bed is available, the infant is referred to another hospital. If the infant's family refuses hospitalization or referral, the study physician presents the option for home treatment through study participation.

To be eligible for inclusion, infants must be 0–59 days of age, residents of a predefined geographical area based on accessibility for follow-up visits, have at least 1 sign in the 5-sign algorithm for severe infection and none of the 12 signs of critically severe infection or disease and caregivers must refuse hospitalization or referral to another hospital as well as indicate that they plan to remain in the study area for at least 2 weeks. The study aims to exclude infants with signs of either very mild or very severe infections. Thus, clinical inclusion criteria are based on a 5-sign algorithm that is a modified version of the WHO Young Infant Clinical Signs Study Group's algorithm²⁵; a comparison of the 2 algorithms is presented in Table 1. Signs in this study's algorithm include: (1) severe lower chest wall indrawing, (2) axillary temperature $\geq 100.4^\circ\text{F}$ ($\geq 38.0^\circ\text{C}$) confirmed by second

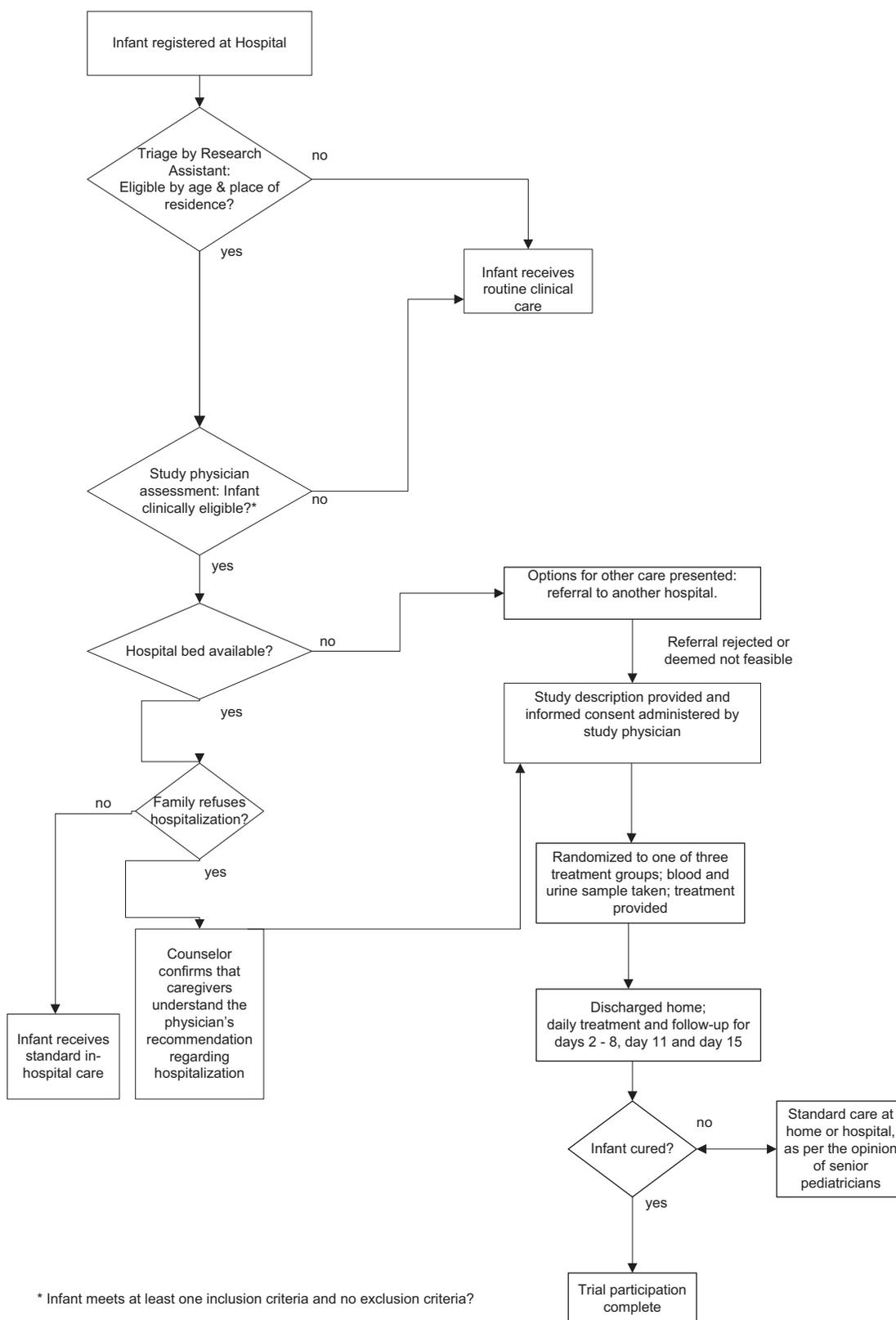


FIGURE 1. Trial profile.

TABLE 1. Comparison of WHO Young Infant Study Algorithm and the Trial Algorithm Used to Identify Infants With Clinical Severe Infection

WHO Young Infant Study-II Algorithm	Algorithm in Use in This Trial
History of convulsion	—
Respiratory rate ≥60/min	—
Severe chest indrawing present	Severe chest indrawing present
Fever: axillary temperature >99.5°F (>37.5°C)	Fever: axillary temperature ≥100.4°F (≥38.0°C)
Hypothermia: axillary temperature <95.9°F (<35.5°C)	Hypothermia: axillary temperature ≤95.9°F (≤35.5°C)
Lethargic or less than normal movement	Lethargy (movement only with stimulation)
History of feeding problems	Feeding difficulty (confirmed by poor suck on examination)

— indicates not included in the algorithm used in this trial.

reading, (3) axillary temperature ≤95.9°F (≤35.5°C) confirmed by second reading, (4) lethargy (defined operationally as movement only upon stimulation by the examining physician) and (5) history of feeding problems, confirmed by poor suck on examination. The criterion of respiratory rate ≥60 breaths per minute is excluded because data from previous studies in Bangladesh suggests that this sign alone is not predictive of severe illness.²¹ Infants with signs of very severe infection or disease are excluded because home-based treatment is felt to be potentially unsafe for this group. Very severe infection or disease is defined as the presence of any of the following signs: (1) unconsciousness, (2) history of or presence of convulsions present at assessment, (3) inability to feed, (4) apnea, (5) inability to cry, (6) cyanosis, (7) bulging fontanel, (8) major congenital malformations, (9) major bleeding, (10) surgical conditions needing hospital referral, (11) persistent vomiting after 3 attempts to feed the baby within half an hour or (12) physician’s suspicion of meningitis. Infants are also excluded from the study if they weigh <1500 g, have been hospitalized for illness in the last 2 weeks or were previously included in the study. Legal guardians of infants meeting the study’s eligibility requirements are offered participation in the study through a written informed consent process. There are quality assurance teams in all study sites to monitor activities monthly with respect to quality and consistency of study procedures.

Infants are randomized to 1 of the 3 home treatment regimens using site- and age-specific (<7 days or 7–59 days) computer-generated randomization sequences with varying random block sizes of 3, 6 and 12. The allocation sequence for each site and age groups is placed in serially numbered, sealed and opaque envelopes and delivered to each site. After consent and enrollment, the study physician selects the next envelope, and the treatment corresponding to the allocation code printed within the envelope is assigned to the infant.

Drug Dosages and Treatment Provision

Dosages (presented in Table 2) were selected to optimize efficacy, safety and feasibility. Extended-interval (24-hourly) gentamicin regimens using doses of 4–5 mg/kg/day have been shown to be effective^{26,27} and remain within the range commonly used in the United States.²⁸ For procaine penicillin, daily intramuscular doses of 25–50 mg/kg are recommended for neonatal infections,²⁸ and we have set a target range of 40–50 mg/kg per 24-hour dose. Amoxicillin is structurally almost identical to ampicillin, an antibiotic commonly used intravenously to treat invasive neonatal infections; however, amoxicillin is more commonly used in the oral form because of its high oral bioavailability. Although typically used at doses of 40–90 mg/kg/day (divided into 2 doses per day in the newborn period), oral amoxicillin doses of 200–300 mg/kg/day have been shown to be safe in newborns treated for group B streptococcal sepsis.²⁹ For this study, a target dose ranging from 90 to 115 mg/kg/day divided into 2 doses per day was chosen as this is similar to the dose of intravenous ampicillin recommended for the treatment of neonatal infections that ranges from 75–200 mg/kg/day,²⁸ yet cautiously remains close to a standard “high-dose” amoxicillin regimen (90 mg/kg/day).

All enrolled infants are given the first doses of the assigned antibiotics and discharged home after counseling about home management. Study physicians provide intramuscular injections at home and assess infants daily for the next 7 days to assess for treatment failure; clinical assessments are conducted on day 11 and day 15 to determine if a relapse has occurred. Caregivers are taught to give the oral antibiotics. If an infant vomits within 20 minutes of oral dosing, the caregiver is instructed to readminister a complete dose; this is a safe approach, even if both of the doses were to be fully absorbed, because the total maximum daily dose of amoxicillin would be <200 mg/kg/day. If the infant vomits within

TABLE 2. Antibiotic Dosage by Weight

Infant Weight Range (kg)	Gentamicin Concentration: 40 mg/mL		Procaine Penicillin Concentration: 200,000 IU/mL		Amoxicillin Concentration: 100 mg/mL	
	Volume (mL)	Daily Dose (mg)	Volume (mL)	Daily Dose (IU)	Volume (mL)	Daily Dose (mg)
1.500–1.749	0.18	7.20	0.35	70,000	1.6	160
1.750–1.999	0.20	8.00	0.40	80,000	1.9	190
2.000–2.499	0.25	10.00	0.50	100,000	2.3	230
2.500–2.999	0.30	12.00	0.60	120,000	2.8	280
3.000–3.499	0.35	14.00	0.70	140,000	3.3	330
3.500–3.999	0.40	16.00	0.85	170,000	3.8	380
4.000–4.499	0.45	18.00	0.95	190,000	4.3	430
4.500–4.999	0.50	20.00	1.00	200,000	4.8	480
5.000–5.499	0.55	22.00	1.10	220,000	5.3	530
5.500–5.999	0.60	24.00	1.20	240,000	5.8	580
6.000–6.499	0.65	26.00	1.35	270,000	6.3	630

20 minutes of the second oral dose, the caregiver is instructed to seek medical attention. It is not feasible to blind study participants or study physicians to treatment group allocation.

Definition of Treatment Failure

The trial's primary outcome is treatment failure in the 7 days after enrolment defined as 1 or more of the following 9 criteria:

1. Any time before the day 8 assessment: Death.
2. On or before the day 8 assessment: Clinical deterioration based on the presence of at least 1 of the following 8 danger signs documented by the study physician based on physical examination findings: unconscious, convulsions (may also be diagnosed based on convincing history), unable to feed, apnea, cyanosis, bulging fontanelle, major bleeding, persistent vomiting (defined as vomiting after 3 attempts to feed the baby within half an hour as assessed by study physician).
3. On or before the day 8 assessment: Decision by a study physician to change the antibiotic regimen or add another antibiotic for either of the following reasons:
 - a. New-onset infectious comorbidity (ie, severe omphalitis, bone or joint infection, or severe skin or soft tissue infection), or
 - b. Serious nonfatal antibiotic-associated adverse event (ie, severe diarrhea associated with dehydration, Stevens–Johnson syndrome, anaphylaxis or acute renal failure).
4. On or before the day 8 assessment: Hospitalization for any reason.
5. On or after day 3: Occurrence of new signs of clinical severe infection (any of the 5 signs). A “new” sign is one that was not present at the time of enrolment. Signs are defined in the same manner as for initial eligibility.
6. On day 4, for infants with multiple signs at enrollment: Presence of at least 2 of the signs that were present on enrolment;
7. On day 4, for infants with a single sign on enrolment: Presence of the same sign that was present on enrolment.
8. On or after day 5: Recurrence of at least 1 of the following signs: temperature $\geq 38^{\circ}\text{C}$ or $\leq 35.5^{\circ}\text{C}$, severe chest indrawing, lethargy or poor suck on any follow-up visit. Recurrence implies the presence of the sign on enrolment and documented resolution of the sign on at least 1 follow-up visit with subsequent reappearance of the same sign on at least 1 follow-up visit on or after day 5.
9. On day 8: Persistence of any of the 5 signs of severe infection that was present on enrolment.

All surviving infants meeting clinical treatment failure criteria by study physicians on routine follow-ups are designated as provisional treatment failures and transported to the hospital accompanied by study personnel. At the hospital, the infant undergoes a repeat examination without history-taking by a second study physician. To the extent possible, the second physician assessor is blinded to the treatment allocation and prior history of the infant. If the second assessment supports the ascertainment of treatment failure, the case is considered a confirmed treatment failure. If the second medical assessment disagrees with first assessment, the decision is referred to a supervising senior physician, whose decision is the final determination. Infants designated as treatment failures are referred for further hospital care according to standard hospital practices. Results of blood cultures may be used to guide specific therapy for treatment failures.

A random ~5% subsample of nontreatment failure visits are assessed in the home or facility by a second study physician for quality control purposes. To the extent that it is feasible, efforts are being made to blind the second physician assessor to the first physician's assessment (ie, he/she is not informed as to whether

an infant has been brought to the hospital because of provisional treatment failure or because of random selection). The assessment of the second physician does not routinely affect study procedures or outcome ascertainment. However, if danger sign(s) are deemed to be present by the second physician, the infant is brought to the hospital for management and adjudication of treatment failure by a third physician.

Data Analysis and Sample Size

We hypothesize that each of the alternative therapies will not be inferior to standard therapy and that the treatment failure proportions among infants receiving both the standard therapy (A) and alternative therapies (B and C) will be 10%. The alternative therapies will be considered not inferior to the standard therapy if the upper bound of the CI for the difference in treatment failure proportions (alternative therapy minus standard therapy) is less than 5%. For each comparison (B vs. A; C vs. A), the point estimate of the failure rate difference between the 2 treatment arms will be calculated together with a 2-sided 95% CI. In order to take into account any between-group differences in any potentially confounding variables, the difference will also be expressed as a ratio of the rate in alternative therapies to failure rate in standard therapy and model using binomial regression models with a log link.

The samples size for this 3-armed study was estimated by the method of Blackwelder³⁰ and the formula

$$N = \frac{(Z_{1-\alpha/2} + Z_{1-\beta}) [p_1(1-p_1) + p_2(1-p_2)]}{(p_1 - p_2 - \Delta^2)}, \text{ where } p_1 \text{ and } p_2 \text{ are}$$

the true treatment failure rates in the standard and alternative regimens, respectively, and Δ is the margin used to define similarity. Table 3 shows the expected power of different effective sample sizes to demonstrate the similarity of 2 treatments (with a similarity margin of +5%). It is assumed that the true failure rate in the standard treatment arm will be 10% and that the true failure rate in the experimental arm will either be identical or only slightly worse (11%). Enrolment of 750 evaluable children in each of 3 arms (2250 total) will yield 90% power to demonstrate similarity to within +5%, if the true failure rates are identical. If the difference between the true failure rates between the standard and alternative therapy is 1%, the power to demonstrate similarity to within +5% will be 71%. Some children may have missed visits, incomplete treatment compliance or may be withdrawn from the study before the completion of treatment, which will reduce the number of children who are eligible for inclusion in the primary per-protocol analysis. Infants who receive 100% of the doses of scheduled antibiotics on all 7 days or by the time of treatment failure if treatment failure occurs, and are not known to have received any other antibiotic by study or nonstudy physician, are considered “fully adherent” to study treatment. An infant who is not fully adherent is considered “partially adherent” if he/she received 100% of scheduled antibiotics on days 1–3 or by the time of treatment failure; received at least 50% of the scheduled doses of each antibiotic during days 4–7, or by the time of treatment failure; is not known to have received any nonstudy injectable antibiotic before day 8 assessment; and is not known to have received any nonstudy oral antibiotic on days 1–3. Infants who do not fulfill the criteria of either fully or partially adherent are considered nonadherent. Infants who receive scheduled follow-up on all 7 days or up-to the time of treatment failure if treatment failure occur are considered to have complete clinical follow-up. An infant is considered to have partial clinical follow-up if he/she has 1 or more days of follow-up missing, but follow-up was completed on assessment days 2–4 and on at least 1 of days 5–8, and vital status on day 8 was known. Infants who do not fulfill

TABLE 3. Power of Different Effective Sample Sizes to Demonstrate the Similarity of 2 Treatments (With a Similarity Margin of +5%) Under Different Assumptions About True Similarity of the 2 Treatments (Identical or Difference of 1% in True Failure Rates)

True Failure Rate in Group A (%)	True Failure Rate in Groups B or C (%)	Number of Per-protocol Children per Arm	Allowed Similarity Margin (%)	Probability That Study Will Demonstrate Similarity of the 2 Treatments Within the Allowable Margin (%)
10	10	550	+5	79
10	10	600	+5	82
10	10	650	+5	85
10	10	700	+5	88
10	10	750	+5	90
10	10	800	+5	92
10	10	850	+5	93
10	10	1500	+5	99
10	11	550	+5	58
10	11	600	+5	62
10	11	650	+5	65
10	11	700	+5	68
10	11	750	+5	71
10	11	800	+5	74
10	11	850	+5	77
10	11	1500	+5	95

the criteria of complete or partial clinical follow-up are considered to have incomplete clinical follow-up. The primary analysis will be a modified per-protocol analysis that includes infants with either complete or partial follow-up and who are either fully or partially adherent. Infants with either incomplete clinical follow-up or who are nonadherent are considered lost to follow-up and will be excluded from the primary analysis. Based on previous experience in similar settings, we have allowed for up to 15% loss to follow-up, and therefore will aim to enroll 866 children to each arm or 2598 total.

Approvals

This study was reviewed and approved by the Johns Hopkins Bloomberg School of Public Health's Institutional Review Board, the Bangladesh Institute of Child Health's Ethical Review Committee and the WHO's Research Ethics Review Committee.

DISCUSSION

Results from the Bangladesh simplified antibiotic regimens trial are expected to be made available in late 2013. The trial will determine whether the 2 antibiotic treatment regimens that include fewer doses of parenteral antibiotics are as efficacious as standard parenteral antibiotic treatment in young infants with signs of severe infection. Clinical equipoise exists because the relative efficacies of various antibiotic regimens for clinical severe infection in infants less than 2 months old are unknown in the outpatient setting. The findings are expected to inform decisions related to the scale-up of community-based care of young infant infections.

In this home-based trial in a highly vulnerable population, an obligation to protect the safety of participants exists alongside the duty to generate evidence that can guide practical policy decisions in the resource-poor context. A central ethical issue is that all arms of the trial involve the implementation of antibiotic therapy in the outpatient setting, a method of treatment delivery that is not standard of care for clinical severe infection in young infants but has been successfully implemented in resource-poor settings. This trial is designed not to challenge the appropriateness of hospitalization as a universal standard of care, but to develop an evidence base relevant to infants for whom hospitalization is not feasible or refused by parents/caregivers.

Hospitalization refusal is common in Bangladesh and many other similar settings. A pilot study for this trial found that caregivers refuse hospitalization because of perceived financial burdens and concern about potential disruptions to family life, such as provision of care for older children at home while a mother remains in hospital with her young infant. Bed shortages are also common at the participating hospitals. When no bed is available, the standard procedure is to recommend that the family take the baby to another hospital, but families rarely pursue this alternative because pediatric bed availability at other public hospitals is limited, travel costs may be prohibitive or other factors.

Therefore, in designing this trial, the study investigators, the trial steering committee and protocol reviewers were faced with a situation in which sick infants may go without care when hospitalization would be ideal, and thus conducting the trial would represent an expansion of clinical services for the community. However, we did not want the implementation of the trial to further discourage families from accepting hospitalization when that would be the preferred treatment option from a medical perspective. For this reason, families are not offered study participation unless: (1) caregivers refuse to accept hospitalization, or (2) no bed is available at the study hospital and referral to another hospital is refused or deemed impracticable. We have instituted procedures designed to diminish the potential for unduly influencing caregivers to accept home-based treatment when a hospital bed is available. Hospital staff have been instructed to avoid any discussion of the study with parents of prospective participants until after a spontaneous refusal of admission after diagnosis and suggested treatment plan occurs, or it is determined that no beds are available. The study physician is required to document that attempts were made to convince the caregivers to consent to hospital admission. Referring or treating physicians are not rewarded, financially or otherwise, on the basis of the number of prospective participants referred, nor are study physicians coinvestigators, in which case they could have academic interests at stake. Before families enroll in the study, they meet separately with trained study personnel called counselors whose role is to discuss their decision to refuse hospitalization at the study hospital. The counselor's primary role is to ensure that the caregivers understand that the study physician has recommended that the infant be admitted to hospital based on current standard care of clinical severe infection and to confirm that the family has refused hospital admission despite counseling.

ACKNOWLEDGMENTS

We thank the study participants who gave their time generously and the study doctors, field and data management staff who worked tirelessly.

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