

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



AFRICan NEonatal Sepsis Trial Group, (incl. Cousens, S;) (2013)
Simplified regimens for management of neonates and young infants
with severe infection when hospital admission is not possible: study
protocol for a randomized, open-label equivalence trial. The Pedi-
atric infectious disease journal, 32 Suppl 1. S26-32. ISSN 0891-3668
DOI: 10.1097/INF.0b013e31829ff7d1

Downloaded from: <http://researchonline.lshtm.ac.uk/1878098/>

DOI: [10.1097/INF.0b013e31829ff7d1](https://doi.org/10.1097/INF.0b013e31829ff7d1)

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: <http://creativecommons.org/licenses/by-nc-nd/2.5/>

Simplified Regimens for Management of Neonates and Young Infants With Severe Infection When Hospital Admission Is Not Possible

Study Protocol for a Randomized, Open-label Equivalence Trial

AFRINEST (AFRican NEonatal Sepsis Trial) Group

Background: In resource-limited settings, most young infants with signs of severe infection do not receive the recommended inpatient treatment with intravenous broad spectrum antibiotics for 10 days or more because such treatment is not accessible, acceptable or affordable to families. This trial was initiated in the Democratic Republic of Congo, Kenya and Nigeria to assess the safety and efficacy of simplified treatment regimens for the young infants with signs of severe infection who cannot receive hospital care.

Methods: This is a randomized, open-label equivalence trial in which 3600 young infants with signs of clinical severe infection will be enrolled. The primary outcome is treatment failure in 7 days after enrollment, which includes death or worsening of the clinical condition on any day, or no improvement in the clinical condition by day 4 of treatment. Secondary outcomes include compliance with study therapy, adverse effects due to the study drugs and relapse or death during the week after completion of treatment.

Discussion: The results of this study, along with ongoing studies in Pakistan and Bangladesh, will inform the development of global policy for treatment of severe neonatal infections in resource-limited settings.

Key Words: neonates, young infants, antibiotic treatment, sepsis, severe infection

(*Pediatr Infect Dis J* 2013;32:S26–S32)

Accepted for publication June 5, 2013.

AFRINEST GROUP: Antoinette Tshetu, MD, MPH, PhD,* Adrien Lokangaka, MB BS,* Cyril Engmann, MD, FAAP,†‡ Fabian Esamai, MB ChB, MMed, MPH, PhD,§ Peter Gisore, MB ChB,§ Adejumo Idowu Ayede, MB BS, MSc, FMCpaed,¶ Adegoke Gbadegesin Falade, MB BS, FMCpaed, MD, FRCP (Edin),¶ Eburnoluwa A. Adejuyigbe, MB ChB, FMCpaed,|| Chineme Henry Anyabolu, MB BS, FWACP,|| Robinson D. Wammanda, MB BS, FWACP Paed,** William N. Ogala, MB BS, FMCpaed, FWACP Paed,** Lu Gram, MSc, Mphil,†† Simon Cousens, MA, DipMathStat,†† Rajiv Bahl, MB BS, MD Paediatrics, PhD,‡‡ Nigel Rollins, MB BS, PhD,‡‡ Sachio Yoshida, MPH,‡‡, and Shamim Ahmad Qazi, MB BS, DCH, MSc, MD Paediatrics,‡‡.

From the *Department of Community Health, Kinshasa School of Public Health, Kinshasa, Democratic Republic of Congo; †Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, North Carolina; ‡Bill and Melinda Gates Foundation, Seattle, Washington; §Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya; ¶Department of Pediatrics, College of Medicine, University of Ibadan, Ibadan, Nigeria; ||Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife, Nigeria; **Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria, Nigeria; ††Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; and ‡‡Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, Geneva, Switzerland.

The trial registration number was Australian New Zealand Clinical Trials Registry ACTRN12610000286044.

The views and opinions expressed in this article are those of the authors and not necessarily the views and opinions of the World Health Organization.

S.A.Q., R.B., N.R. and S.Y. are staff members of the World Health Organization (WHO). L.G. and S.C. contributed in data management, and S.A.Q., R.B., N.R. and S.Y. helped in study coordination. The study proposal was developed by all the authors of the article. Site authors, along with the study group from each site, implemented the study. WHO staff provided technical support, monitoring and coordination for the trials. The article was prepared jointly by all authors during a workshop and has the final approval of all authors.

This work was supported by World Health Organization through a grant from Bill and Melinda Gates Foundation. The authors have no other funding or conflicts of interest to disclose.

Address for correspondence: Shamim Ahmad Qazi, MB BS, DCH, MSc, MD Paediatrics, Department of Maternal, Newborn, Child and Adolescent Health, World Health Organization, 20 Avenue Appia, Geneva 27, 1211 Switzerland. E-mail: qazis@who.int.

Copyright © 2013 by World Health Organization and Bill and Melinda Gates Foundation (WHO and BMGF). This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives 3.0 License, where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially.

ISSN: 0891-3668/13/3209-0S26

DOI: 10.1097/INF.0b013e31829ff7d1

Neonatal infections are responsible for 700,000–800,000 neonatal deaths that occur globally every year.¹ Over 95% of all neonatal and infant deaths due to infections occur in developing countries, where rates of home delivery are high and unhygienic conditions during and after birth are common. Appropriate treatment of neonatal infections could prevent the majority of infection-specific deaths, making it one of most important child survival interventions.²

Currently, it is recommended that young infants (from birth up to 2 months of age) with signs of severe infection be referred for inpatient care and treated with intravenous broad spectrum antibiotics such as a combination of ampicillin and gentamicin for 7–10 days.³ The efficacy of the recommended treatment in reducing the risk of death of young infants with severe infections is well accepted. However, most such infants in developing countries do not currently receive inpatient care,^{4–7} largely because treatment is not readily accessible or because hospitalization is not acceptable or feasible for families.

A technical advisory group organized by Save the Children/Saving Newborn Lives, United States Agency for International Development and World Health Organization (WHO) in London in 2007 recommended large, well-designed studies to evaluate simplified antibiotic regimens for treatment of neonatal sepsis outside hospital settings.⁸ Such regimens could include an optimal combination of oral and intramuscular antibiotics or injectable to oral “switch” regimens that would be feasible in weak health systems. As a result, 2 randomized trials, using a common protocol, were initiated in Pakistan and Bangladesh. A similar trial in Africa was required to support the development of global policy.

In 2009, WHO sent out a call for African sites interested in conducting a randomized, open-label equivalence trial similar to the ones initiated in Asia. Five sites in Africa were selected after an external review process, one site each in Democratic Republic of Congo (DRC) and Kenya and 3 sites in Nigeria (Ibadan, Ile-Ife and Zaria) to take part in this trial using a common protocol. This article describes the design of the Africa trial.

OBJECTIVES

The goal of the study is to inform global policy on the use of simplified antibiotic treatment regimens for young infants with signs of clinical severe infection who cannot receive hospital care.

- Primary objective: To evaluate simpler antibiotic regimens for provision of safe and effective treatment of 0- to 59-day-old young infants with signs of clinical severe infection whose families do not accept or cannot access referral-level care, compared with a combination of injectable penicillin and gentamicin injections for 7 days.
- Secondary objectives: To assess family acceptance of different treatment options and compliance with them, and to document health worker requirements in terms of time and costs for each treatment regimen.

METHODS

Study Design

This is an individually randomized, open-label, multicenter equivalence trial. The 5 sites in DRC, Kenya and Nigeria are following the same protocol, quality control and coordination mechanisms to contribute to an overall sample size.

Study Settings

Democratic Republic of Congo

The infant mortality and neonatal mortality rates in DRC are 97 per 1000 and 31 per 1000 live births, respectively.⁹ The study is being conducted in rural areas of 4 health zones in North and South Ubangi districts, in the province of Equateur, DRC. The population of the study area is about 300,000. In the first year of the study, a total of about 12,000 births were identified in the study population. The operational primary healthcare functions in the study area are embedded within Health Zones; each Health Zone consists of between 100,000 to 250,000 inhabitants and has 1 general referral hospital. Health Zones are typically divided into 8–24 Health Areas, each with 1 Health Centre that covers a population of 5000 to 10,000 inhabitants; 30 Health areas are included in the study. Health centers are the primary site of care, where skilled health providers and the community intersect, and curative and health promotion activities are conducted. Each health center is staffed by 1 trained nurse, who oversees the activities of community health workers (CHWs) (literate village volunteer workers), who primarily engage in preventive and promotional activities.

Kenya

The infant mortality and neonatal mortality rates in Kenya are 52 per 1000 and 31 per 1000 live births, respectively.¹⁰ The study is being conducted in the counties of Busia, Bungoma and Kakamega (in the districts of Busia, Butula, Bungoma West, Bungoma South, Bungoma East, Teso South, Teso North and Mumias) in Western Kenya. The population of the study area is about 350,000. In the first year of the study, a total of about 13,000 births were identified in the study population. Thirty-four clusters were selected for the study; each cluster has 1 dispensary or health facility manned by 2 health workers. These health units do not normally have inpatient services for all cadres of patients and are the level-2 health facilities as per the Ministry of Health classification.

Nigeria

The infant mortality and neonatal mortality rates in Nigeria are 75 per 1000 and 47 per 1000 live births, respectively.¹¹ In Nigeria, the study used a cadre of health workers called community health extension workers (CHEWs). CHEWs receive 2 years of

training in government-supported training institutes in basic issues on maternal and child health, child nutrition, treatment of infections, immunization and environmental health, oral and mental health. They are also trained and allowed to provide injectable therapy.

Ile-Ife. The study is being conducted in the Ife Central and East Local Government Areas (Ile-Ife community), a semi-urban community in Osun State, in Southwestern Nigeria. The estimated population of study area is about 350,000. In the first year of the study, about 11,000 births were identified. The rate of refusal of hospital admission is very high, about 50%, usually for religious and cultural reasons. Deliveries by skilled birth attendants are very low, although booking at health facilities for antenatal care is high.

Ibadan. The study is being conducted in Ido and Lagelu peri-urban Local Government Areas of Oyo State in the south western part of Nigeria. The population is mainly rural with some suburban areas, and the study population under surveillance is about 200,000. In the first year of the study, about 8000 births were identified. Financial constraints are a barrier to referral to health services. Most women attend antenatal clinics while pregnant either in government hospitals or mission homes usually owned by traditional birth attendants; less than 50% deliver in these government health facilities.

Zaria. The third study site in Nigeria is Zaria Local Government Area, located in the northern part of Kaduna State in the North West geopolitical zone of Nigeria. It is made up of more than 100 urban, peri-urban and rural settlements populated by predominantly Hausa/Fulani Muslims. The study population of approximately 150,000 is located in 8 wards in the old, traditional part of Zaria Town. In the first year of the study, about 6000 births were identified. Although more than half the women attend antenatal clinics during pregnancy, less than 10% deliver in health facilities or under the supervision of trained attendants. Although home delivery is the norm, less than half of these home births are supervised by a traditional birth attendant.

Study Participants

A summary of site description and implementation strategy is given in Table 1 and the overall study approach in Figure 1.

Identification of Pregnancies and Births, Surveillance for Illness

A pregnancy surveillance system has been established in all 5 study sites, with the aim of identifying newborns as soon as possible after birth. CHWs in DRC and Kenya, and CHEWs in Nigeria, visit all identified births on days 1, 3, 7, 14, 21, 28, 35, 42, 49 and 60 after birth. At each home visit, they assess the newborn for signs of illness and counsel the families on recognition of these signs (stopped feeding well according to the mother, reported convulsions, fast breathing, severe chest indrawing, temperature of $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$, movement only on stimulation, yellow soles or pus from umbilicus, eye or skin). Young infants with any of these signs are advised to go to a health center or hospital. Those who refuse referral or are unable to go to a facility are assessed by a study health worker.

Screening and Enrollment

Screening and enrollment are conducted by enrollment nurses. In DRC and Kenya, this takes place at the health center or dispensary. In Nigerian sites, it takes place at the child's home. Young infants, 0–59 days of age, are eligible for inclusion in this study if:

- they have signs of clinical severe infection: not feeding well on observation, movement only when stimulated, severe chest indrawing and axillary temperature $\geq 38.0^{\circ}\text{C}$ or $< 35.5^{\circ}\text{C}$;

TABLE 1. Summary of Site Description and Implementation Strategy

	Democratic Republic of Congo	Kenya	Nigeria-1 Ibadan	Nigeria-2 Ile-Ife	Nigeria-3 Zaria
Population	300,000	350,000	200,000	350,000	150,000
Identification of pregnancies and births	CHW/TBA	CHW/TBA	TBA/CHEWs	TBA/CHEWs	TBA/CHEWs
Home visits for newborn care	CHW	CHW	CHEW	CHEW	CHEW
Screening and study enrollment	Enrollment nurse	Enrollment nurse or clinical officer	Screening by CHEW Enrollment by enrollment nurse	Screening by CHEW Enrollment by enrollment nurse	Screening by CHEW Enrollment by enrollment nurse
Treatment Injection and provision (and 1 oral dose daily assess- Second oral dose to detect dose worsening)	Auxiliary nurse	Health centre nurse	CHEW	CHEW	CHEW
Outcome assessment blinded to treatment allocation (on days 4, 8, 11 and 15 of enrollment and for confirmation of worsening)	Observed by CHW	Observed by CHW	Observed by CHEW	Observed by CHEW	Observed by CHEW
Supervision	Outcome assessment nurse	Outcome assessment nurse	Outcome assessment nurse	Outcome assessment nurse	Outcome assessment nurse
	Community coordinator	Community coordinator	Study supervisor	Study supervisor	Study supervisor

TBA indicates traditional birth attendant.

- they have no exclusion criteria: very low weight (<1500 g at the time of presentation), hospitalization for illness in the last 2 weeks or previous inclusion in the study, any sign of critical illness (unconscious, 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 after 3 attempts to feed the baby within 30 minutes]);
- their parents do not accept hospital referral; and
- their parents give consent to participate in the study.

Randomization

The enrolled infants are classified into 2 age groups, 0–6 days and 7–59 days, and randomly assigned to 1 of the treatment regimens. The unit of randomization is the individual infant with randomization stratified by age group and study site. An age-stratified randomization scheme with block size of 8 was computer-generated off-site at WHO using STATA version 10.0 (STATA Corp LP, College Station, TX) by a person not involved with the study. For allocation concealment, treatment codes are printed on small pieces of cardboard pieces which are then folded once and sealed in sequentially numbered opaque envelopes (2 color-coded envelopes, one each for 0–6 days and 7–59 days age groups).

In the Kenyan and Nigerian sites, randomization is done centrally by a designated person who keeps the randomization envelopes. The enrollment nurse calls this person at the time of enrollment of a new infant, who opens the next envelope according to the age category and conveys the treatment allocation. This process takes place by phone and is confirmed by short message service. In DRC where mobile phone communication is not reliable, 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.

Intervention and Comparison Groups

- Treatment regimen A (reference treatment): injectable gentamicin once daily and injectable procaine penicillin once daily for 7 days (14 injections in total);
- Treatment regimen B: injectable gentamicin once daily and oral amoxicillin twice daily for 7 days (7 injections in total);

- Treatment regimen C: injectable gentamicin once daily and injectable procaine penicillin once daily for 2 days, thereafter oral amoxicillin for 5 days (4 injections in total);
- Treatment regimen D: injectable gentamicin once daily and oral amoxicillin twice daily for 2 days, thereafter oral amoxicillin twice daily for 5 days (2 injections in total).

All treatments are given at a health facility or at home. The injections are given once daily by a health worker at a facility or at home, whereas oral medicines are given by the mother under the supervision of CHWs at home. Daily assessments are conducted by health workers to identify any worsening of the child's condition. Home visits to assess the outcome of the treatment are conducted by independent outcome assessment nurses at days 4, 8, 11 and 15 after enrollment to detect treatment failure or relapse.

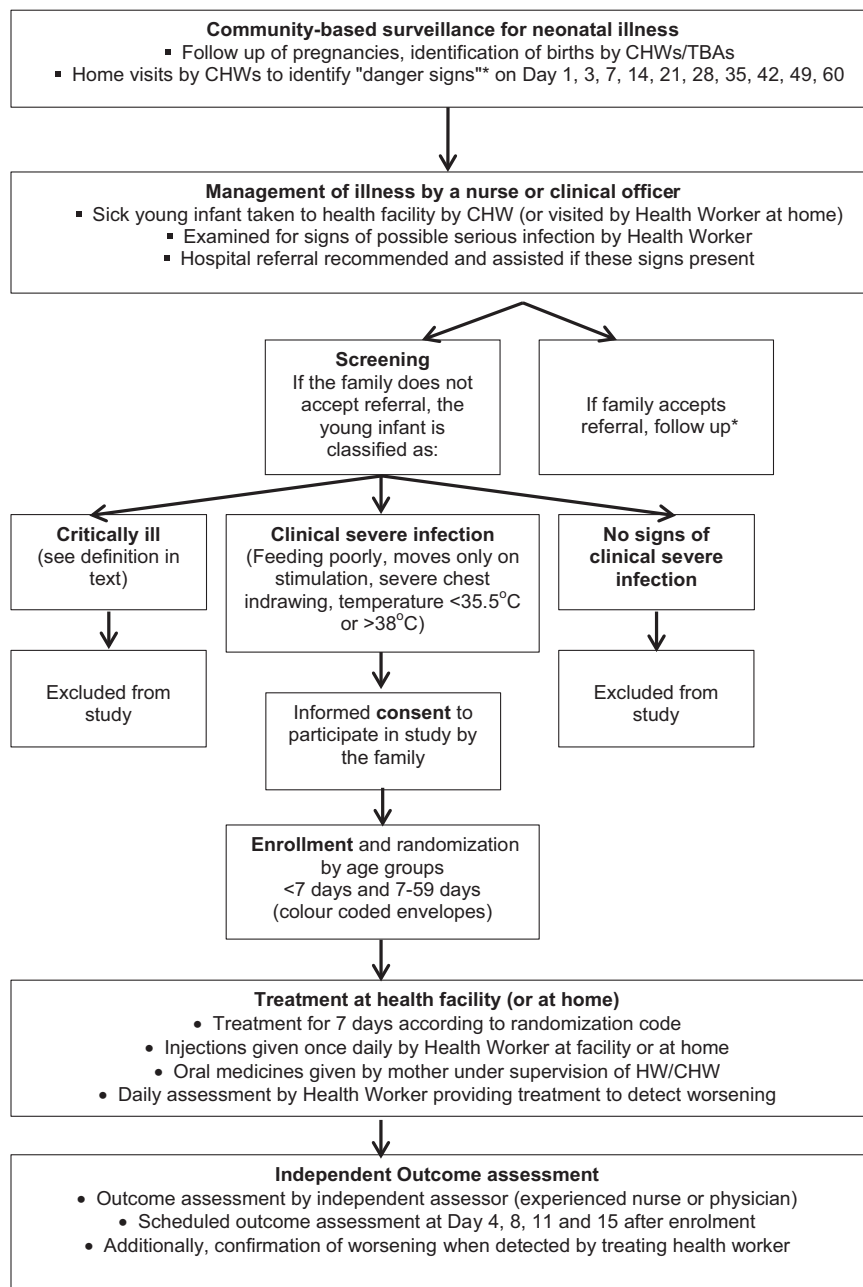
The rationale for selection, dosages and durations of antibiotics is given in detail elsewhere in this supplement.¹² The combination of penicillin and gentamicin is used globally for treating presumed sepsis in the both neonatal period group and the second month of life.^{3,13–16} The combination of penicillin/amoxicillin and gentamicin targets common neonatal pathogens such as *Escherichia coli*, other enteric gram-negative rods and streptococci. 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/day once daily IM (depending on age of the young infant) and oral amoxicillin in suspension in a dose of 100 mg/kg/day (less than 2 kg are given 75 mg/kg/day), divided in 2 equal doses. All treatment regimens are being used for 7 days.

Provision of Treatment

In DRC and Kenya, all injectable treatment is provided at a health facility by the treatment nurse, who also provides the first daily dose of oral therapy. Mothers observe the first dose being given and are instructed to provide the second daily dose of oral amoxicillin at home in the same manner. In Nigeria, the first treatment (injectable or oral) after randomization is provided by the treatment nurse at the child's home. Treatment on subsequent days is provided by CHEWs.

Study Outcomes

An independent outcome assessment nurse visits enrolled infants on days 4, 8, 11 and 15 after the day of the enrollment to



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

FIGURE 1. Overall study approach.

assess outcome. All outcome assessments are conducted at the young infant’s home.

Primary Outcome

The primary outcome is treatment failure before or at the day 8 visit. Treatment failure is defined by any one of the following:

- Death.
- Clinical deterioration (hospitalization, emergence of any sign of critical illness at any time or a new sign of clinical severe

infection after the day 2 visit or reemergence of a sign of clinical severe infection on day 4 after initial disappearance).

- No improvement in clinical condition by day 4 (if there was a single sign of clinical severe infection at enrollment, persistence of the sign; if there were multiple signs at enrollment, persistence of >1 sign).
- Not cured by day 8 (persistence of any sign of clinical severe infection on day 8 of enrollment).
- Development of a serious adverse event (SAE) other than death that is thought to be related to the study antibiotics, for example,

organ failure, anaphylactic reaction, severe diarrhea, disseminated and severe rash.

Secondary Outcomes

- Death between days 9–15 after enrollment.
- Relapse (after disappearance of all signs of clinical severe infection by day 8, emergence of any sign of critical illness or clinical severe infection between days 9–15 after enrollment).
- Adherence to the allocated treatment between days 1–8.

Sample Size

In the absence of population-based incidence data, the incidence of possible severe bacterial infection among neonates and young infants was conservatively assumed to be about 5% in Africa. This estimate was based on earlier studies conducted in Bangladesh and India where about 10–15% of all newborns had an illness with at least 1 sign of possible severe bacterial illness during follow-up,^{7,17,18} and 2 studies with more specific diagnostic criteria reported a lower incidence of possible severe bacterial infection of 7–10%.^{17,18}

The sample size calculations were performed based on comparing the failure rates observed with treatment regimen A (reference treatment regimen: injection penicillin and gentamicin for 7 days) with the failure rates expected with the 3 experimental treatment regimens. For each comparison, the point estimate of the failure rate difference (experimental–reference treatment) between the 2 treatment regimens and its 2-sided 95% confidence interval will be calculated. The alternative treatment will be judged to be “of similar effectiveness” to the reference treatment A (assumed treatment failure rate 10%) if the upper bound of the 95% confidence interval of the difference lies below the allowed “similarity margin” of +5%. The required sample size for 90% power to demonstrate the similarity of 2 treatments assuming that the true failure rates with the reference treatment and the experimental treatment regimens will be identical (assumed to be 10%) works out to be 760 “analyzable” infants per arm who would be included in the prespecified per-protocol analysis. Assuming that approximately 15% of randomized infants will be excluded from the per-protocol analysis for failure to adhere treatment, the required sample size is 900 infants for each treatment regimen (a total of approximately 3600 infants).

Data Collection

Data collection is done by CHWs/CHEWs during home visits and includes data on all births as well as deaths within the first 2 months of life. The CHWs/CHEWs also screen young infants for illness. Data are collected on the paper-based standard case report forms that have been extensively field tested and revised after pilot testing. Enrollment nurses complete a screening form after examination for every sick young infant who was referred or brought to them by CHW/CHEW. They complete a baseline information form at enrollment for every enrolled infant. Daily treatment and assessment records are maintained by the treating health worker. The outcome assessment nurses complete an assessment form at days 4, 8, 11 and 15 days after randomization and when an infant is sent to them for assessment by the treating health worker because of suspected worsening of clinical condition. Names or other identifiers of the infant and his/her family are not included on the study forms. All completed forms are checked by study supervisors for completeness before they are entered into the computer.

Data Management

Individual sites are responsible for their own day-to-day data management activities. Each individual site has its own data management team, including a data manager and team of data entry clerks. At each site, the data entry clerks enter data from paper forms into the data management system, which stores the data in a data base. The data management system consists of a front-end and a back-end. The front-end, prepared in C++, is the user interface that the data manager and the data entry clerks use to interact with the database, whereas the back-end in Structured Query Language stores the database itself. All data are double-entered and discrepancies verified to remove data entry errors. The data manager then proceeds to run range and consistency checks built into the data management system. After resolving all range and consistency errors in consultation with the data collection staff, the data manager checks for inconsistencies in information across different case report forms using inbuilt checks and resolves them in consultation with the field coordinators and if necessary with the principal investigators of the study.

The cleaned data are sent every month to the central data coordination center at London School of Hygiene and Tropical Medicine in London. Additional data quality checks are carried out, and feedback is provided to the study sites on a monthly basis.

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 has in fact resulted in baseline comparability of treatment groups. The primary analyses will be for equivalence between the reference treatment and the 3 experimental arms; it will consist of the comparison of proportions of infants with treatment failure in each treatment arm.

Analysis will be conducted on a per-protocol basis and on an intention-to-treat basis. Although the former is more conservative to establish equivalence of treatment regimens and will be the primary analysis for this study, the latter will take into account the possibility of differences in adherence to treatment across treatment arms despite the best efforts of the research team. In order for an enrolled infant to be included in the per-protocol analysis, he/she 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 to 7 or by the time of treatment failure. Furthermore, for inclusion in the per-protocol analysis, treatment outcome should have been assessed among days 2–4, days 5–8 and vital status on day 8 known.

Each experimental regimen will be compared with the reference regimen and the difference in the risk of treatment failure together with 95% confidence intervals will be calculated. Analyses will be performed with data from all sites combining the 2 age subgroups, adjusted for any baseline covariates which were unbalanced at baseline and with the addition of dummy variables for site and age group.

Subgroup analysis of primary and secondary outcomes will be performed by age subgroups (0–6 days and 7–59 days at the time of enrollment). Univariate and multivariate regression analyses will be undertaken to identify clinical predictors of treatment failure and death despite antibiotic treatment.

Ethical Issues

Study Approvals

The trial protocol and all associated data collection instruments and consent forms were approved by the local Institutional

Review Boards, the WHO Ethical Review Committee and the Institutional Review Board of the London School of Hygiene and Tropical Medicine. The trial was registered as ACTRN12610000286044 with Australian New Zealand Clinical Trials Registry. The trial follows Council for International Organizations of Medical Sciences and Good Clinical Practice guidelines.

Informed Consent

Communities in all sites were introduced to the study before initiation of enrollment. This was achieved through meetings with community leaders and with community groups. Informed written consent is obtained for the home visits for pregnancy and birth, enrollment, treatment as well as for follow-up visits of nonenrolled infants. Health workers were trained to facilitate referral through counseling using integrated management of childhood illness guidance for assisting referral. Only babies whose families refuse referral and are willing to document this by witnessed signature/thumbprint are enrolled.

Monitoring of Potential Adverse Events

The families are asked to contact the CHW/CHEW if any adverse events occur. In the case of a SAE, CHWs contact their supervising CHW and CHEWs contacts their outcome assessment nurse. The assessment nurse documents the adverse event and conveys this to the Community Coordinator/Supervisor. SAEs such as death, hospitalization, unable to pass urine for 12 hours, anaphylactic reaction, severe dehydration due to diarrhea, injection abscess or disseminated or severe rash are reported to WHO within 48 hours of their occurrence. This information is also provided on a regular basis to the Data Safety Monitoring Board (DSMB) and ethics committees.

Rescue Therapy

At any time during the study follow-up, young infants identified as treatment failures according to the study protocol are referred to a hospital. If the parents refuse to take the infant to the hospital, the infant is offered rescue therapy (intramuscular ceftriaxone for 7 days).

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 1 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: when one third of participants and when two thirds of participants have been enrolled and treated.

The DSMB determined that the trial will be stopped or modified if an interim analysis shows that the proportion of neonatal deaths between treatment and control groups differ by at least 2 standard errors with a *P* value of 0.01. 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 SAEs. For this purpose, the SAE forms are sent to the DSMB on a quarterly basis.

Quality Assurance

Training of Health Workers

Training of health workers for the study was a 2-step process. Training sessions for “master trainers” from all sites were held using the WHO/UNICEF Home Care for Newborns course, the WHO/UNICEF Young Infant integrated management of childhood illness course (for study nurses) and a study-specific procedures course. These site-specific master trainers were experienced

physicians and nurses; they subsequently trained all CHWs/CHEWs and nurses employed by the study. All supervisors and site coordinators were also trained in all courses.

Standardization

Extensive standardization exercises were conducted for each cadre of study health workers. For CHW/CHEW standardization sessions, we identified 5–10 eligible young infants in a community or a nearby health facility and asked each CHW/CHEW to assess these infants while being observed by a trained facilitator. Assessments included weighing the child, assessing danger signs (ability to feed, convulsions, elevated respiratory rate, chest indrawing, high or low temperature, lethargy and yellow soles). The facilitator compared his/her findings with those of each health worker to identify errors. After the exercise, the trainees were given feedback; those needing further standardization were given targeted refresher training.

The same standardization process was used for all staff, including enrollment nurses, treatment nurses, outcome assessment nurses, health center nurses, supervisors and coordinators. These healthcare workers were all trained to identify signs of critical illness. Standardization exercises were conducted at the start of the study and subsequently every 3–6 months for all health workers to ensure that all of them assessed clinical signs in a similar way.

Supervision

Supervised, accompanied visits and independent, unaccompanied visits are carried out regularly by the supervisors. Principal investigators and coinvestigators also make random visits to study sites to check quality.

Site Monitoring

Monthly progress reports are prepared by all sites, sent to the WHO coordinating center for the study and reviewed critically on a monthly basis. Regular conference calls are held to discuss the progress of the trial. Data-based monitoring, as well as verification of SAE forms, is carried out by the data coordination center in collaboration with the WHO study coordination team.

WHO technical staff conducts at least 2 monitoring visits to each site every year. A detailed structured review of study implementation is conducted at each visit. The key areas that are monitored included the recruitment rate, clinical practices such as identification of danger signs and critical signs, detection of treatment failure as well as data management and overall study procedures. All study documentation is checked. A proportion of completed case report forms, all treatment failures and all adverse events are reviewed. Recommendations arising from the site visit are discussed with the Principal Investigators at the sites and followed up for action. Monitoring visits are also conducted by external monitors who are not associated with the study.

Project Coordination

The project is being coordinated by the WHO Department of Maternal, Newborn, Child and Adolescent Health. Technical advice is provided by a Technical Advisory Group, which includes all principal investigators, the WHO coordination team and external experts, and convenes at least once a year in a face-to-face meeting. London School of Hygiene and Tropical Medicine assists in quality control through database monitoring, prepares necessary reports for the DSMB, Trial Advisory Group and liaises with WHO study coordination team.

Timeline

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

DISCUSSION

Evaluation of simpler treatment regimens for severe neonatal infection has been identified as an important global research priority to prevent neonatal mortality.²⁰ The current WHO recommendation for treatment of severe neonatal infection in neonates and young infants is hospitalization and treatment with injectable penicillin (benzyl penicillin or ampicillin) plus gentamicin for at least 10 days, requiring 50 injections.³ In practice, these guidelines are rarely implemented in many low resource settings, due to inadequate referral systems or parental refusal of referral.

The simplest safe and effective antibiotic regimen for treating possible severe bacterial infection in young infants is unknown. Although 7 days of treatment with once daily procaine penicillin and gentamicin injections appears to be safe and effective, this still involves 14 injections, which may also be difficult in some settings.⁷ If a simpler treatment option—that is, one that is shorter in duration and requires fewer injections—was shown to be safe and effective, it would make treatment more accessible, acceptable and less expensive for families. Furthermore, such simpler treatments could be provided at first-level health facilities, at outpatient facilities and possibly even at home by trained health workers and would contribute substantially to increasing coverage of antibiotic therapy.

The ongoing trial described in this article is a multicenter study involving 5 sites in 3 countries in Africa. It is the largest community-based study evaluating simplified antibiotic regimens for clinical severe infection in neonates and young infants. The study is an individually randomized trial, which is the most rigorous design for comparing treatment regimens. Blinding of therapy was not possible because of the differences in delivery of the regimens. Although there is an element of subjectivity involved in the assessment of treatment failure based on the presence or absence of clinical signs, an independent outcome assessor who is blinded to the treatment regimen assesses the study outcome.

This study in 3 African countries, combined with 2 similar ongoing studies in Bangladesh and Pakistan, will provide evidence on the simplified antibiotic regimen for treatment of sepsis in outpatient settings where referral is not possible. This evidence will be generalizable to Africa and South Asia and will allow development of global policy to manage severe bacterial infections in young infants.

ACKNOWLEDGMENTS

The other members of the study group mentioned below have contributed to the study, and we therefore acknowledge their substantial inputs. DRC: Serge Ngaima, Justin Ga'do, Daniel Ishoso, Kalonji Michel and John Otomba. Kenya: David Muyodi, Millsort Robins, Judith Sitti, Robin Achoki, Evelyn Etemesi, Lydia Chebet, Enock Nyambane, Sylvia Nyabera, Moses Sitati, Edwi Kirwa, Peter Nandikove, Priscah Mosol and Francisca Lagat. Ibadan, Nigeria: Akintunde Sowunmi, Elijah Afolabi Bamgboye, Ayotunde Olajide, Seye Idris, Mrs. Olumide Ovigwe, Nathanael Afolabi, Joseph Aderibigbe, Bukola Adeniji, Ronke Egunjobi and Olaide Olakehinde. Ile-Ife, Nigeria: Prof. Adetanwa Odebiyi, Dr. Olapeju Esimai, Olufolake Akano, Christiana Olufunke Olagoke, Tosin Ogunsola, Aminat Subair, Jumoke Awoyemi and Olusanjo Oyedokun. Zaria, Nigeria: Clara L. Ejembi.

REFERENCES

- Liu L, Johnson HL, Cousens S, et al.; Child Health Epidemiology Reference Group of WHO and UNICEF. Global, regional, and national causes of child mortality: an updated systematic analysis for 2010 with time trends since 2000. *Lancet*. 2012;379:2151–2161.
- Darmstadt GL, Bhutta ZA, Cousens S, et al.; Lancet Neonatal Survival Steering Team. Evidence-based, cost-effective interventions: how many newborn babies can we save? *Lancet*. 2005;365:977–988.
- World Health Organization. *Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses With Limited Resources*. 2nd edition. Geneva: World Health Organization; 2013.
- Bhandari N, Bahl R, Bhatnagar V, et al. Treating sick young infants in urban slum setting [letter]. *Lancet*. 1996;347:1774–1775.
- Baqui AH, El-Arifene S, Darmstadt GL, et al.; Projahnmo Study Group. Effect of community-based newborn-care intervention package implemented through two service-delivery strategies in Sylhet district, Bangladesh: a cluster-randomised controlled trial. *Lancet*. 2008;371:1936–1944.
- Darmstadt GL, Baqui AH, Choi Y, et al.; Bangladesh Projahnmo-2 (Mirzapur) Study Group. Validation of community health workers' assessment of neonatal illness in rural Bangladesh. *Bull World Health Organ*. 2009;87:12–19.
- Zaidi AK, Tikmani SS, Warraich HJ, et al. Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens. *Pediatr Infect Dis J*. 2012;31:667–672.
- Save the Children/Saving Newborn Lives, USAID, WHO. Expert Consultation on Community-Based Approaches for Neonatal Sepsis Management, September 26–28, 2007, London, UK. Meeting Report. Save the Children/Saving Newborn Lives 2008. Available at: http://www.harppnet.org/doc/london_sepsis_mtg09-07.pdf. Accessed July 11, 2013
- Ministère du Plan D.R. Congo, Ministère de la Santé D.R. Congo, Macro International Inc. USA. *Enquête démographique et de santé République Démocratique du Congo 2007 (EDS, 2007)*. Calverton, Maryland; Kinsasha, D.R. Congo; 2008.
- Kenya National Bureau of Statistics (KNBS) and Macro International Inc. *Kenya National Demographic and Health Survey 2008–09*. Calverton, Maryland; Nairobi, Kenya; 2010.
- National Population Commission (NPC) [Nigeria] and Macro International Inc. *Nigeria Demographic and Health Survey 2008*. Calverton, Maryland; Abuja, Nigeria; 2009.
- Bang AT, Bang RA, Baitule SB, et al. Effect of home-based neonatal care and management of sepsis on neonatal mortality: field trial in rural India. *Lancet*. 1999;354:1955–1961.
- Fanos V, Dall'Agnola A. Antibiotics in neonatal infections: a review. *Drugs*. 1999;58:405–427.
- Saez-Llorens X, Mc Cracken GH. Clinical pharmacology of antibacterial agents. In: Remington JS, Klein JO, eds. *Infectious Disease of the Fetus, Newborn and Infants*. Philadelphia, PA: Saunders; 2001:1419–1466.
- Darmstadt GL, Hossain MM, Jana AK, et al. Determination of extended-interval gentamicin dosing for neonatal patients in developing countries. *Pediatr Infect Dis J*. 2007;26:501–507.
- Darmstadt GL, Batra M, Zaidi AK. Parenteral antibiotics for the treatment of serious neonatal bacterial infections in developing country settings. *Pediatr Infect Dis J*. 2009;28(suppl 1):S37–S42.
- Zaidi AKM, Baqui AH, Qazi SA, et al. Scientific rationale for study design of community-based simplified antibiotic therapy trials in newborns and young infants with clinically diagnosed severe infections or fast breathing in South Asia and sub-Saharan Africa. *Pediatr Infect Dis J*. 2013.
- Baqui AH, Arifeen SE, Williams EK, et al. Effectiveness of home-based management of newborn infections by community health workers in rural Bangladesh. *Pediatr Infect Dis J*. 2009;28:304–310.
- Bang AT, Bang RA, Stoll BJ, et al. Is home-based diagnosis and treatment of neonatal sepsis feasible and effective? Seven years of intervention in the Gadchiroli field trial (1996 to 2003). *J Perinatol*. 2005;25(suppl 1):S62–S71.
- Bahl R, Martines J, Ali N, et al. Research priorities to reduce global mortality from newborn infections by 2015. *Pediatr Infect Dis J*. 2009;28(suppl 1):S43–S48.