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

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Background: Newborns and young infants suffer high rates of infections in South Asia and sub-Saharan Africa. Timely access to appropriate antibiotic therapy is essential for reducing mortality. In an effort to develop community case management guidelines for young infants, 0–59 days old, with clinically diagnosed severe infections, or with fast breathing, 4 trials of simplified antibiotic therapy delivered in primary care clinics (Pakistan, Democratic Republic of Congo, Kenya and Nigeria) or at home (Bangladesh and Nigeria) are being conducted.

Methods: This article describes the scientific rationale for these trials, which share major elements of trial design. All the trials are in settings of high neonatal mortality, where hospitalization is not feasible or frequently refused. All use procaine penicillin and gentamicin intramuscular injections for 7 days as reference therapy and compare this to various experimental arms utilizing comparatively simpler combination regimens with fewer injections and oral amoxicillin.

Conclusion: The results of these trials will inform World Health Organization policy regarding community case management of young infants with clinical severe infections or with fast breathing.

Key Words: newborn, young infant, sepsis, pneumonia, meningitis, clinically severe infections, fast breathing, community management, community case management, antibiotic, gentamicin, amoxicillin, procaine penicillin, South Asia, sub-Saharan Africa

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is also described. Although the individual study designs are adapted
to site and country needs and are detailed in the site-specific meth-
ods articles,6,11 here we focus on the overarching scientific approach to
case definitions, selection of trial sites, participant inclusion/exclusion
criteria, choice of antibiotics and regimens and outcomes. The com-
mon design elements were made possible by extensive collaboration
between the study sponsors6,8 and investigators and will enhance the
interpretation and application of the studies’ results, in part by enabling
future pooled analyses for outcomes of subgroups of interest (eg, treat-
mament failure in newborns with early-onset infections, newborns with
multiple clinical signs of illness vs. single signs, etc.).

STUDY AGE GROUP

Newborns have increased vulnerability to infection-related
morbidity and mortality because of their immature immune systems
and underdeveloped skin barrier.13 However, a decision to include
infants beyond the newborn period, that is, in the second month of
life, was made for 2 reasons. First, the newborn immune response
matures on a gradient with age15 with increased susceptibility to
infection persisting into the second month of life, and second, the
current World Health Organization (WHO)/United Nations Inter-
national Children’s Emergency Fund Integrated Management of
Childhood Illness addresses children aged 0–59 days as a separate
group (“young infants”) from children 2–59 months old.15 There-
fore, any new case management strategy for use in developing coun-
tries needs to be applicable to infants who are 0–59 days old.

DIAGNOSTIC ALGORITHM TO STANDARDIZE
DEFINITION OF CLINICALLY DIAGNOSED SEVERE
INFECTIONS IN NEWBORNS AND YOUNG
INFANTS ACROSS THE TRIAL SITES

Infections in the newborn and young infant present with
nonspecific signs and symptoms and can be difficult to diagnose
even by experienced health professionals.13 A high index of sus-
picion and prompt initiation of antibiotic therapy are required to
save lives because of the often rapidly fulminating course of invasive
bacterial infections in young infants. This practice is followed in
industrialized countries where clinically ill-appearing newborns
and young infants are treated with parenteral antibiotics on the
basis of a diagnosis of “presumed sepsis,” although blood cultures
eventually are found to yield no growth in the vast majority.16–18

In an effort to promote the early detection and appropri-
ate referral of sick young infants by frontline health workers in
resource-limited settings, WHO, United States Agency for Inter-
national Development and the Saving Newborn Lives Initiative of
Save the Children (funded by the Bill and Melinda Gates Foundation)
sponsored a multicountry study to evaluate several clinical
signs for their utility in making referral decisions compared with the
judgment of an experienced clinician.19 Participating coun-
tries included Bangladesh, Bolivia, Ghana, India, Pakistan and
South Africa. The Young Infant Clinical Signs Study resulted in
the development of a simple clinical algorithm based on 7 signs
and symptoms for predicting severe illness in the young infant
with high sensitivity and moderate specificity for use in first-level
health facilities.19 The 7 clinical signs and symptoms are history of
difficulty feeding, history of convulsions, movement only when
stimulated, respiratory rate of 60 breaths per minute or more, severe
chest indrawing, temperature of 37.5°C or more or less than 35.5°C.
The presence of any one triggers a decision to refer the infant. The
availability of the validated Young Infant Clinical Signs of Severe
Illness algorithm presented an evidence-based starting point for the
development of a clinical definition of severe infection in the young
infant for use in the proposed trials. However, certain limitations of
this algorithm influence specificity for the diagnosis of infection,
considerations that are important in equivalence trial settings where
a nonspecific definition of infection could dilute out important dif-
fferences in therapeutic options among a smaller group of infants
who truly had severe bacterial infections included within a larger
group of mildly ill infants who would recover without antibiotic
therapy. In order to increase specificity of diagnosis of clinically
diagnosed severe infection, the following modifications have been
made: the fast respiratory rate sign has been dropped from our case
definition as accumulating evidence indicates that it substantively
reduces specificity of the case definition (see discussion below),
the upper temperature cutoff (for fever) has been increased to 38°C
(instead of 37.5°C) and history of difficulty feeding requires confir-
mation by observation of infant feeding (African sites) or determin-
ation of poor suck through digital examination if feeding cannot
be observed (Asian sites). Presence of convulsions is considered to
indicate critical illness, and infants with convulsions are excluded.
Table 1 presents the case definition used for diagnosis of clinical
severe infections in these trials.

Fast breathing (respiratory rate >60 per minutes) is frequently
present as an isolated sign in young infants who do not otherwise appear
ill.19 Fast breathing did not predict mortality in young infants in studies
from Bangladesh and India.20,21 However, fast breathing even as a single
sign is part of the WHO Integrated Management of Childhood Illness
clinical algorithm and indicates very severe disease and need for hospi-
tal referral and parenteral antibiotics.21 This has created a management
dilemma, whether to treat young infants with fast breathing alone as
a mild illness or as a severe illness. In some settings from South Asia,
neonates and young infants with fast breathing have been successfully
treated by oral antibiotics.24–25 There are no studies from Africa, and
none have compared oral antibiotics with injectable therapy for man-
agement of infants with fast breathing as the only sign of illness. Thus,
there is a need to inform policy by providing evidence whether young
infants with fast breathing alone can be treated with oral antibiotics.
Such a study is being undertaken in the multicenter African sites.

### TABLE 1. Comparison of WHO Integrated
Management of Neonatal Child Illness Algorithm and
Case Definition of Clinically Diagnosed Infection Used in
the Young Infant Simplified Antibiotic Therapy Trials

| WHO Integrated Management of Neonatal Child Illness Algorithm | Diagnostic Algorithm Used in Simplified Antibiotic Therapy Trials | Case Definition of Clinically Severe Infections (CSIs) |
|---------------------------------------------------------------|-------------------------------------------------------------|---------------------------------------------------|
| History of convulsions or convulsions                          | Severe chest indrawing                                      | Movement only with stimulation                     |
| Respiratory rate >60/min                                       | Axillary temperature ≥38.0°C                                 | Movement only with stimulation                     |
| Severe chest indrawing                                         | ≥100.4°F (≥38.0°C)                                           | Movement only with stimulation                     |
| Axillary temperature ≥37.5°C                                  | <85°F (<35.5°C)                                              | Feeding difficulty, confirmed by feeding observation or documentation of poor suck on examination if mother unavailable (Asian sites) |
| Movement only when stimulated or no movement at all           | <85°F (<35.5°C)                                              | Stopped feeding well/feeding problems confirmed by observation of infant feeding (African sites) |
| Not feeding well                                               |                                                            |                                                   |

_—_ indicates convulsions and fast respiratory rate are not included in the case defini-
tion of severe infection used in these trials.
CHOICE OF ANTIBIOTICS, REGIMENS, DOSAGE, DURATION AND DELIVERY STRATEGIES

Ideally, the selection of an appropriate antimicrobial agent is based on its ability to kill bacteria that are responsible for the infection in the majority of cases, based on efficacy and safety data, and pharmacokinetic information from relevant pediatric age groups. For the simplified antibiotic therapy trials, additional considerations include ease of delivery in community settings and cost—both factors with significant implications for future scale-up. The experimental arms, therefore, comprise combinations of injectable and oral antibiotics or switch therapy from injectable to oral antibiotics (Tables 2 and 3).

Penicillin and gentamicin are used globally for treating sepsis and presumed sepsis in the neonatal age group and the second month of life.29,30 Extended-interval (24-hourly) gentamicin regimens using doses ranging from 4 to 5 mg/kg/day have been shown to be as effective as traditional dosing regimens for treating neonatal sepsis.29,31 The combination of penicillin/amoxicillin and gentamicin targets common neonatal pathogens such as *Escherichia coli*, other enteric gram-negative rods, streptococci and pneumococci.

Benzyl penicillin and ampicillin need to be given 4 times a day, which is impractical in the outpatient setting. Based on recommendations from the 2007 London consultation on community-based strategies for management of severe infections in young infants born in high mortality settings,20 the pharmacologic profile of antibiotics32,33 and experience of their use,3–5 we decided to use a combination of procaine penicillin and gentamicin delivered by intramuscular (IM) injection as the reference arm to treat clinically diagnosed severe infection because both can be given in once daily dosing and together can successfully treat vast majority of bacterial infections in young infants.

For the simplified experimental regimens, amoxicillin was selected as the oral agent. Oral antibiotics have successfully been used in community-based management of neonatal pneumonia, resulting in significant reduction in pneumonia and overall neonatal mortality.3,4 There is extensive experience with use of oral amoxicillin in newborns and young infants, and safety of this drug is well-established in this age group.27,34 In full-term neonates, the amoxicillin in newborns and young infants, and safety of this drug is well-established in this age group.27,34 In full-term neonates, the recommended intravenous dose of amoxicillin for neonates in the first 4 days of life is 100 mg/kg divided every 12 hours, whereas the recommended intravenous dose of amoxicillin for neonates in the first week of life is 100 mg/kg divided every 12 hours, whereas in the African and South Asian trials, amoxicillin is given in doses ranging from 80 to 100 mg/kg/day based on 1 of 6 weight bands in which the infant falls.

The duration of antibiotic therapy is based on achievement of cure for an infection. The WHO recommendation of 10 or more days of antibiotic therapy for young infants with possible serious bacterial infection in young infants when families refused referral advice for their sick young infants. Documented refusal of care is rarely practiced in developing countries with high neonatal mortality rates. For ethical reasons, in the design of these trials, the duration of antibiotic therapy is based on achievement of cure for an infection. The WHO recommendation of 10 or more days of antibiotic therapy is not based on strong evidence. Studies in Bangladesh and India have used 10 days of antibiotic therapy,41 whereas in Pakistan, 7 days of amoxicillin and gentamicin once daily was found to be effective in the management of possible serious bacterial infection in young infants when families refused referral care. Very severe pneumonia in older children has been treated with 7 days of injectable antibiotics with good results,41 whereas severe pneumonia has been treated with 5 days of oral antibiotics.42 Switch therapy of injectable to oral antibiotics has been demonstrated to be efficacious for treatment of serious infections in neonates43 and in older children.42 For young infants with clinical severe infection included in this study, IM amoxicillin will be used in a dose of 50,000 units/kg once daily IM and IM gentamicin in a 4–7.5 mg/kg/day once daily dose IM (depending on weight band of the young infant). Duration of all regimens in this study will be 7 days. The trials are designed to be open-label because of the difficulty in ethically justifying use of placebo injections in the population under study and because acceptability of simplified regimens with lower number of injections is an important secondary outcome for the trials.

### TABLE 2. Antibiotics Regimens Evaluated in Trials of Simplified Antibiotic Therapy for Management of Newborns and Young Infants With Clinically Diagnosed Severe Infections (CSIs) or Fast Breathing

| Reference arm | Experimental arms | Clinically severe infections | Fast breathing only |
|---------------|------------------|----------------------------|--------------------|
| A – Daily injection procaine penicillin and gentamicin for 7 days. | B – Oral amoxicillin twice daily and once daily injection gentamicin for 7 days. | C – Daily injection gentamicin and procaine penicillin for 2 days, followed by twice daily oral amoxicillin for additional 6 days. | E – Oral amoxicillin twice daily for 7 days. |
| Experimental arms | D – Daily injection gentamicin and twice daily oral amoxicillin for 2 days, followed by oral amoxicillin for additional 5 days (African sites only). | | |
| Fast breathing only | | | |

### TABLE 3. Number of Intramuscular (IM) Injections in Each Therapeutic Arm

| Arm A | Arm B | Arm C | Arm D | Arm E |
|-------|-------|-------|-------|-------|
| 14    | 7     | 4     | 2     | 0     |

Arm A: IM procaine penicillin and IM gentamicin for 7 days; Arm B: oral amoxicillin and IM gentamicin for 7 days; Arm C: IM procaine penicillin and IM gentamicin for 2 days followed by oral amoxicillin; Arm D: oral amoxicillin and IM gentamicin for 2 days followed by oral amoxicillin; Arm E: oral amoxicillin alone in infants with only fast breathing.
hospitalization. Other site characteristics are reported in the site-specific articles in this supplement. The African trial sites in Democratic Republic of Congo, Kenya and Nigeria were chosen to be broadly representative of central, eastern and western sub-Saharan African countries with neonatal mortality rates exceeding 40 per 1000 live births and remote locations making access to hospital facilities difficult for many families. Despite the effect on study generalizability, we are excluding young infants with clinical signs of critical illness (unconscious, convulsions, apnea, unable to feed, unable to cry, cyanosed, bulging fontanelle, persistent vomiting), infants with weight less than 1500 g and infants with surgical comorbidities because we cannot ethically justify random allocation of such infants to therapeutic options with oral antibiotics.

**SELECTION OF PRIMARY STUDY OUTCOME**

Treatment failure on or before 7 days of therapy has been chosen as the primary study outcome in these trials and defined as a composite of death, clinical deterioration, serious adverse event, hospitalization or persistence of clinical signs beyond specified days. Death, although a hard outcome, has not by itself been selected as a primary outcome because we expect the number of deaths to be low (around 2%) based on prior experience as rescue therapy is going to be provided and it will be unethical to withhold such therapy. Therefore, using the comparatively rare outcome of death will inflate the sample size to unfeasible levels. Because of the subjective nature of clinical signs of deterioration, their definitions and determination have been standardized across sites and are described further in the site-specific articles.

**CONCLUSION**

This article describes the scientific rationale for the study designs of 3 trials of simplified antibiotic therapy for the management of clinically diagnosed severe infections and a trial of management of fast breathing in newborns and young infants currently being conducted in Bangladesh, Pakistan, Democratic Republic of Congo, Kenya and Nigeria. Although designed as independent studies, extensive collaboration between study sponsors and among study investigators has resulted in harmonization of study protocols wherever possible, which will allow subsequent pooled analyses by providing sufficient power to address important policy questions regarding outcomes in subgroups such as newborns with early-onset sepsis, and infants with multiple clinical signs (indicating more severe illness) versus single signs. These trials will inform the development of policies and guidelines regarding community case management of newborns and young infants with clinically diagnosed severe infections as well as for infants with fast breathing alone.

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