

# Ongoing Trials of Simplified Antibiotic Regimens for the Treatment of Serious Infections in Young Infants in South Asia and Sub-Saharan Africa

## Implications for Policy

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**Background:** The current World Health Organization (WHO) recommendation for treatment of severe infection in young infants is hospitalization and parenteral antibiotic therapy. Hospital care is generally not available outside large cities in low- and middle-income countries and even when available is not acceptable or affordable for many families. Previous research in Bangladesh and India demonstrated that treatment outside hospitals may be possible.

**Research:** A set of research studies with common protocols testing simplified antibiotic regimens that can be provided at the lowest-level health-care facility or at home are nearing completion. The studies are large individually ran-

domized controlled trials that are set up in the context of a program, which provides home visits by community health workers to detect serious illness in young infants with assessment and treatment at an outpatient health facility near home. This article summarizes the policy implications of the research studies.

**Policy Implications:** The studies are expected to result in information that would inform WHO guidelines on simple, safe and effective regimens for the treatment of clinical severe infection and pneumonia in newborns and young infants in settings where referral is not possible. The studies will also inform the inputs and process required to establish outpatient treatment of newborn and young infant infections at health facilities near the home. We expect that the information from research and the resulting WHO guidelines will form the basis of policy dialogue by a large number of stakeholders at the country level to implement outpatient treatment of neonatal infections and thereby reduce neonatal and infant mortality resulting from infection.

**Key Words:** policy, research, antibiotic treatment, young infants, neonates, infections

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Neonatal infection currently accounts for 12% of all under-5 deaths worldwide and is the second leading cause of under-5 deaths.<sup>1</sup> Some of the major challenges in addressing these 700,000–800,000 deaths include lack of recognition of illness by parents, a variety of barriers to care seeking and limited access to treatment services.<sup>2,3</sup>

Research has established newborn home visits—those that combine promotion of optimal care practices for the prevention of illness and early recognition of illness and care seeking—as key pillars for improving newborn survival.<sup>4–8</sup> Home visits have allowed health interventions to reach sick newborns in an unprecedented manner at the time of greatest vulnerability. The revised Integrated Management of Childhood Illness provides a reliable system of assessment that identifies young infants who require antibiotic treatment.<sup>9</sup> The development of simplified treatment regimens would help ensure that all infants with suspected infection have access to appropriate care; this could lead to dramatic improvements in neonatal and infant survival.

The World Health Organization (WHO) currently recommends hospitalization and parenteral antibiotic therapy for the treatment of severe infection in young infants.<sup>10</sup> Hospital care is generally not available outside large cities in low- and middle-income countries and even when available is often not acceptable or affordable for families.<sup>3,4,11</sup> Furthermore, the quality of hospital newborn care is often suboptimal.<sup>6,12</sup> This poses a major ethical challenge in

low- and middle-income countries, where many young infants with infections receive no treatment because only a very small proportion of these infants are hospitalized for care, and treatment outside hospitals is not considered the standard of care.

One strategy for improving access to treatment is to remove financial barriers to hospitalization of sick babies and to increase the availability and quality of referral care in hospitals. An example of this is the establishment of district-level sick newborn care units in India and the conditional cash transfer scheme used to improve access to these facilities.<sup>13–15</sup> However, a more in-depth analysis shows that these efforts may not be sufficient. Community-based studies show that about 10% of newborns have signs of possible serious bacterial infection (PSBI) at any point during the neonatal period, meaning that about 2500 newborns will need hospital care for suspected serious infections in a district with about 25,000 births per year. A sick newborn care unit is capable of caring for a maximum of 25 babies at a time and can take care of 1250 sick newborns in 1 year, assuming the average duration of admission to be 1 week. Therefore, the burden of possible serious neonatal infections is likely to be 2 times higher than the capacity of Sick Newborn Care Units. Furthermore, other newborns will still require referral care, including those with preterm birth, severe jaundice, birth asphyxia and congenital disorders. Outpatient or home-based strategies for the management of serious infections in newborns, including moderate-to-late preterm and low birthweight babies, are required to meet access needs.

The possibility of treating severe infections in neonates and young infants outside hospitals was first demonstrated by Bang et al,<sup>4</sup> who documented that home-based newborn care by village-level workers, including treatment of severe infections, with a combination of an oral and an intramuscular antibiotic resulted in substantial reduction in neonatal mortality in a remote area in India. However, the antibiotic regimen used by Bang et al<sup>4</sup> was shown to be inferior to a combination of intramuscular procaine penicillin and gentamicin in Pakistan.<sup>3</sup> Building upon Bang's work, Baqui et al<sup>5</sup> in Bangladesh documented that community health workers (CHWs) could diagnose and treat presumptive sepsis with intramuscular procaine penicillin and gentamicin. In Nepal, an alternative delivery strategy was successfully tested in which community volunteers identified neonates with severe infection but professionally trained health workers provided antibiotic treatment.<sup>16</sup> At the peripheral health facility, health workers were trained to administer antibiotic injections. To date, only a limited number of countries have adopted these approaches, limiting the potential contribution toward Millennium Development Goal 4 (reduction in child mortality by two-thirds).

Severity of illness varies among infants with infections, and treatment must be tailored to the level of severity. Infants identified as having PSBI based on Integrated Management of Childhood Illness clinical signs include those who are critically ill (eg, unconscious, convulsing, no movement at all), those with clinical severe infection (eg, not feeding well, reduced movement, chest indrawing, fever or hypothermia) and those with relatively mild illness (eg, fast breathing as a single sign). Injectable antibiotic treatment regimens for <7 days have not been evaluated for infants with clinical severe infection. Oral antibiotics alone have been used for the treatment of pneumonia in neonates, with reduction of pneumonia-specific mortality.<sup>17</sup> However, oral treatment of pneumonia or other severe infections has not been compared with treatment with parenteral antibiotics.

### THE SAT AND AFRINEST TRIALS

In this supplement, research teams describe a series of clinical trials testing simplified antibiotic regimens that can be provided at the lowest health-care facility or at home.<sup>18–21</sup> These studies—together known as the SAT and AFRINEST trials—are being conducted in a range of representative urban, peri-urban and rural sites

in Bangladesh, Pakistan, the DRC, Kenya and Nigeria and are nearing completion. The studies are large individually randomized controlled trials comparing treatment regimens in neonates and young infants (0–59 days) with signs of possible serious infections whose parents either do not accept referral-level care or are unable to transfer the infant. The trials are set up in the context of a program, which provides home visits by CHWs to detect serious illness in newborns and young infants, and the availability of assessment and treatment at an outpatient health facility near home.

This research is not a mere tinkering to improve the existing regimes. Simplified but effective antibiotic regimens that can be delivered safely outside the hospital setting have the potential to improve outcome and reduce mortality to an extent that is not currently possible through referral to hospitals alone.

### POLICY-RELEVANT FINDINGS EXPECTED FROM THE TRIALS

It is anticipated that the trials' findings will help answer a number of key policy-related questions about treating severe neonatal infections.

#### What are the Simplest Low Cost-effective Antibiotic Regimens That Can be Provided for the Treatment of Clinical Severe Infections as Alternatives to the 7–10 Days Parenteral Antibiotic Therapy With 2 Intramuscular Injections?

The primary objective of 3 trials (SAT-Bangladesh, SAT-Pakistan and AFRINEST-severe infections) was to examine whether young infants with clinical signs suggestive of severe infection can be treated with a combination of oral amoxicillin plus gentamicin or whether injections could be stopped after the first 2 days and the infant switched to oral amoxicillin alone, reducing the number of injections to be given and making treatment much simpler to administer. The studies will also evaluate whether compliance will be improved with simpler antibiotic regimens compared with the reference regimen of procaine penicillin and gentamicin injections daily for 7 days.

#### Should the Recommended Treatment for Newborns and Young Infants Who Present With Fast Breathing as the Only Clinical Sign be Changed From Intramuscular Antibiotics to Oral Amoxicillin?

The primary objective of 1 multicenter trial (AFRINEST-fast breathing) was to examine whether young infants with fast breathing as the only clinical sign can be successfully treated with oral amoxicillin compared with intramuscular procaine penicillin and gentamicin treatment. If oral amoxicillin is found to be as effective as intramuscular antibiotic injections, it would avoid using any antibiotic injections for this relatively large subgroup among those with PSBI. This would make it possible to treat many more of these babies at home.

#### What Is the Population-based Burden of Clinical Severe Infections in Asian and African Settings?

Pregnancy and birth identification and surveillance for signs of infection by CHWs are being conducted in DRC, Kenya, Nigeria and Pakistan, and one of the study sites in Bangladesh. Data from this surveillance will provide population-based incidence of PSBI, and its classification into critical illness, severe infection and fast breathing. This will provide insights into specific subgroups that may be successfully treated as outpatients, thus reducing the need for hospitalization of all young infants with PSBI.

## What Is the Mortality Rate Among Different Subgroups of Infants With PSBI Treated in Hospitals or on an Outpatient Basis?

In the ongoing studies, young infants with signs of PSBI are classified as having “critical illness,” “clinical severe infection” or “fast breathing.” All of them are referred to a hospital, and those whose parents do not accept referral are offered outpatient antibiotic treatment. Outcome is tracked for all these infants 2 weeks after the diagnosis, if consent for follow-up is obtained.

## What Is the Effect of Community-based Newborn Care Including Treatment of Severe Infections on Neonatal Mortality?

Information on mortality impact of a community-based newborn care program including treatment of severe neonatal infections is available from studies in South Asia.<sup>4,5</sup> The current studies in DRC, Kenya and Nigeria will provide information on this important issue from Africa. Baseline and endline surveys will provide neonatal mortality rate before and after implementation of the community-based intervention. This will provide evidence of impact of the program of CHW home visits to promote optimal practices for pregnant women and newborns, combined with referral for young infants with signs of infection and outpatient treatment when referral is not possible. In addition, in Kenya and Nigeria, similar baseline and endline surveys in control areas will provide evidence of impact, using a nonrandomized intervention design.

## What Is the Feasibility of Making Treatment of Severe Infections Available Close to Home and the Requirements (Including Costs) to Make It Happen?

The studies would provide cross-country evidence on how the model of CHW home visits to identify signs of possible sepsis combined with outpatient treatment at the nearest health facility is feasible and can increase coverage of treatment in diverse settings in Asia and Africa. Furthermore, the financial, human and logistic resources that would be required to implement such programs will be documented. This includes level of workers who can be used to identify sick young infants and to provide antibiotic treatment to those with signs of infection.

## Aside From Evidence of Efficacy, What Are Anticipated Concerns of Policy Makers and Health Professionals About These New Regimens and Delivery Strategies?

One of the concerns regarding the implementation of a program of antibiotic use for clinical severe infection in young infants outside the hospital setting is the perception of risk of increased antimicrobial resistance. We will draw upon existing data and reports from research teams to address this issue and recommend sentinel surveillance to measure antimicrobial resistance when outpatient treatment programs are implemented.

There are other challenges to adoption of the regimens that the research teams encountered in planning for the trials. Anecdotal evidence of practices of private providers suggests that they often use more expensive and third-/fourth-generation antibiotics, rather than the simple antibiotics that are being tested in the current studies. Furthermore, availability of antibiotic formulations of amoxicillin, procaine penicillin and gentamicin suitable for use in young infants remains a problem. We look to the ongoing United Nations Commission on Life-Saving Commodities work to help address some of these challenges.<sup>22</sup>

## What Are the Steps for Translation of the Research Results to Programmatic Action?

After the results of these studies are published, they will be pulled together with all existing evidence into systematic reviews addressing specific priority issues. This evidence will be graded for quality and be subsequently submitted to a WHO advisory group to consider whether this new evidence merits updating global guidelines. We believe that the data from the current trials will contribute to the following guidelines:

### Clinical

- Simplest regimens for the treatment of clinical severe infection that is safe and effective, in settings where referral is not possible.
- Optimal treatment of fast breathing in newborns and young infants.

### Programmatic

- Role of CHWs and home visits for identifying signs of serious infection.
- Mechanisms that create and strengthen links between communities and health facilities, particularly the role of CHWs.
- Reduced need for hospitalization, with outpatient treatment at health facilities near the home by first-level health workers.
- Health system requirements (policy, program planning, human resources, capacity strengthening, logistics and supply of commodities, supervision and monitoring) to make outpatient treatment of most young infants with PSBI a reality.

Finally, we recognize that the completion of the studies in Africa and Asia and the guidelines development by WHO is only the beginning of a process of a series of policy dialogues by a large number of stakeholders at country level to implement a program of outpatient treatment of neonatal infections. This discussion will include not only governments but also nongovernmental organizations and participants from the private sector, including professional bodies, formal and nonformal health-care providers and civil society consumer groups.

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