Community management of neonatal infections

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The substantial reduction of mortality in children younger than 5 years during the past decade is one of the most notable recent achievements in global health. The total number of deaths among children in this age group decreased from 9·88 million in 2000 to 6·28 million in 2013.[1] However, the reduction in neonatal mortality during the same period has been less impressive. Neonatal mortality decreased at an annual rate of 2·9% compared with 4·9% in children aged 1–59 months.[1] This comparatively small decrease has contributed to the global failure to achieve Millennium Development Goal 4.

Severe bacterial infection (ie, sepsis, pneumonia, and meningitis) in neonates is an important cause of child morbidity and mortality. Estimates suggest that, in 2012, 6·9 million such cases occurred and 557 000 neonates died as a result.[1,2] Furthermore, the risk of impairment in survivors is high.[3] Presentation is typically with non-specific symptoms and signs that suggest severe disease, and clinical distinction between sepsis, pneumonia, and meningitis is very difficult. In resource-poor settings, many cases never reach a health facility. Thus, treatment of young infants with suspected severe bacterial infection in developing countries has been based on clinical signs. Clinical approaches to identify and manage these young infants, such as WHO's Integrated Management of Childhood Illnesses (IMCI), have deemed these children to have possible severe bacterial infection, and traditionally targeted the first point of contact with the health system—ie, first-level trained health workers.[4]

Challenges exist in the diagnosis of young infants with severe bacterial infections. Bacteriological tests have poor sensitivity and most studies of causation are from tertiary care settings, which are not truly representative of cases in the general population. Thus, data for common bacterial pathogens and their antimicrobial resistance patterns are scarce at the community level.[5] A 2013 systematic review[6] of 13 studies from developing countries identified *Staphylococcus aureus*, *Klebsiella* spp, and *Escherichia coli* in 55% (39–70%) of bacteraemic specimens, and reported that only 57% of isolates were susceptible to recommended antibiotics.

The two African Neonatal Sepsis Trial (AFRINEST) studies[7,8] in *The Lancet*, from diverse settings in east, central, and west Africa, are important and underscore challenges associated with management of children with possible severe bacterial infection in resource-scarce settings. Existing WHO guidelines[9] recommend hospital admission and procaine benzylpenicillin (or ampicillin) and gentamicin as first-line antibiotics. However, access to hospitals is often restricted, and parents can be unwilling to accept hospital treatment and adhere to treatment regimens that include injectable antibiotics.[10] The results of previous studies in rural India,[10] Bangladesh,[11] and Nepal[12] have shown that community-based case management of neonatal infection by trained health workers can substantially decrease neonatal mortality.

Effective community-based treatment of possible severe bacterial infection with injectable antibiotics might not be feasible in settings that are remote, have inadequate numbers of community health workers, or where health workers are not licensed to provide treatment with injectable antibiotics.[13] Therefore, community-based studies that help to identify effective simplified treatment regimens, which can help improve coverage and adherence, are laudable and could have important programmatic implications. The new studies investigate two subgroups within possible severe bacterial infection—infants with mild disease (fast breathing alone);[7] and infants with severe but non-critical disease (ie, poor feeding, lethargy, temperature ≥38°C, and severe chest wall indrawing, with or without fast breathing).[8] The primary outcome in both community-based studies was treatment failure by day 8 after enrolment.

In one of the AFRINEST studies, Antoinette Tshefu and colleagues[7] compared oral amoxicillin twice per day with intramuscular gentamicin and procaine benzylpenicillin once per day in 2333 young infants aged 0–59 days. This study was an open-label equivalence trial with individual randomisation, and the authors conclude that young infants with fast breathing alone can be effectively treated in outpatient settings when referral to a hospital or hospital admission is not possible. 234 (22%) infants in the injectable gentamicin and procaine benzylpenicillin group failed treatment compared with 221 (19%) in the oral amoxicillin group (risk difference −2·6%, 95% CI −6·0 to 0·8).

Very few deaths occurred in either group (four [<1%] infants died in the intramuscular gentamicin and procaine benzylpenicillin group, and two [<1%] in the

oral amoxicillin group), and very few infants developed so-called danger signs of critical illness or severe infection (about 2% in both groups). This finding is not entirely unexpected, because many of these young infants presenting with fast breathing alone might have had transient tachypnoea or viral respiratory infections.[14] This very low fatality rate supports the study conclusion that this group of young infants do not necessarily need hospital admission, and can be managed with oral antibiotics at home or in clinics with close monitoring by a community health worker.[7] This type of treatment could improve care-seeking by parents and decrease overcrowding at hospitals. However, as the authors note, to monitor carefully the implementation of this policy in diverse settings and define the level of child follow-up that is needed would be prudent.

In the other AFRINEST study, Tshefu and colleagues[8] compared the recommended (reference) treatment regimen (group A—injectable procaine benzylpenicillin–gentamicin for 7 days) with three simplified treatment regimens (group B, injectable gentamicin and oral amoxicillin treatment for 7 days; group C, injectable procaine benzylpenicillin–gentamicin for 2 days then oral amoxicillin for 5 days; and group D, injectable gentamicin for 2 days and oral amoxicillin for 7 days) in 3564 children with possible severe bacterial infection—ie, infants with no signs of critical illness, such as convulsions, unconsciousness, and inability to feed—when referral to a hospital or hospital admission was not possible. Rates of treatment failure by day 8 were similar in all four intervention groups (67 [8%] infants in group A, 51 [6%] infants in group B, 65 [8%] infants in group C, and 46 [5%] infants in group D). The regimens that included injectable antibiotics and oral amoxicillin had the highest adherence (868 infants in group C [97%] and 863 [97%] infants in group D received all treatment doses, compared with 827 [93%] infants in group A). The authors conclude that the alternative treatment regimens are equally efficacious in the subset of young infants with moderate possible severe bacterial infection who cannot be admitted to hospital, compared with the recommended treatment.

When data from two similar ongoing community-based clinical trials (SAT trials), each with about 2500 young infants, in Bangladesh[15] and Pakistan[16] become available, the pooled results will be interesting. A combined SAT and AFRINEST dataset for roughly 7100 young infants should improve the generalisability of the findings and support analysis stratified by age (0–6 days and 7–59 days), which was not possible in the AFRINEST studies.[7,8] Previous analysis has shown that the sensitivity and specificity of clinical signs of possible severe bacterial infection are substantially different by age group, and whether the casemix included a high proportion of young infants with mild disease.[17,18]

The AFRINEST authors are to be congratulated for successfully running complex trials to a high standard (with high follow-up) in challenging settings. The studies[7,8] represent a major achievement, and such coordinated multicentre trials in low-income country settings are important to support the development of evidence-based guidelines. However, interpretation of these results is complex. WHO Young Infant Studies in several low-income countries have reported moderately high sensitivities and specificities for sets of 14,[19] nine,[17] and seven,[18] clinical signs for the identification of serious disease in young infants.[18] Tshefu and colleagues[8] include five of these signs (table) and exclude a history of convulsions—the most crucial danger sign in young infants. The case fatality rate in all participants in this community-based study was 1% (53 of 3564 infants),[8] contrasting with the high case fatality rate (14%) reported in hospital-based studies from sub-Saharan Africa.[2] Thus, infants with a mild illness spectrum (with a low probability of bacterial infection) seem to have been studied. Furthermore, since relatively few infants died, the study included several alternative endpoints for identification of treatment failure.[8] Some of these endpoints (eg, no improvement in clinical condition) have not been shown to be valid measures of treatment failure or predictors of mortality, and might be subject to observer bias in these non-blinded studies.

	YIS-1 (abridged list)[17]	YIS-2[19]	AFRINEST studies[7,8]
Feeding ability	Reduced	Reduced	Poor feeding on observation
Spontaneous movement	None	None	Only when stimulated
High temperature	>38°C	>37·5°C	≥38°C
Low temperature	..	<35·5°C	<35·5°C
Chest wall indrawing	Lower chest	Lower chest	Only severe lower chest wall
Respiratory rate	>60 breaths per min	>60 breaths per min	>60 breaths per min
History of convulsion	Yes	Yes	..
Other	Cyanosis, grunting, digital capillary refill	..	..

YIS=Young Infant Studies. AFRINEST=African Neonatal Sepsis Trial.

Table: **Comparison of clinical signs predictive of possible serious bacterial infection in neonates**

The AFRINEST studies[7,8] represent serious attempts to address important but difficult clinical questions, with careful attention to study design and quality. These data will add substantially to the information that can be used to support development of evidence-based policy. Nevertheless, to draw correct policy conclusions from trials that use non-specific clinical signs to define cases, and report proxy treatment failure measures because of low mortality in study populations is challenging.[20] To address these concerns, further developments will be needed: improved biomarkers that can identify young infants with bacterial infection at community or first facility level so that infants with an increased probability of bacterial infection can be recruited; improved measures of treatment failure that are shown to be valid predictors of mortality or poor outcome; and further increased sample sizes. Continuing investment in these areas is necessary if the validity and policy relevance of data from future trials are to be improved. These technical developments should be united with lessons learned about study design from major trials, so that future trials with improved methods will be able to generate data which more directly address the key clinical questions, and hence are more readily translated into policy. The challenge for policy makers today is to move forward based on a critical review of the best available data, including those from large trials such as AFRINEST.

An increasing proportion of child mortality is in the first few months of life. Large-scale trials to identify interventions that are effective for reduction of mortality from serious bacterial infections and other major causes of disease in young infants will continue to be of high priority. These trials will need a similar carefully coordinated, high-quality, multicentre approach supported by substantial donor commitment of funds, as shown by the AFRINEST studies.[7,8]

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