patients can present with advanced neck disease not amenable for salvage, impacting OS.

This trial provides level IB evidence and has the potential to change practice globally and impact the survival of patients with oral cancer. The policy of END seems to be appropriate in the management of the neck in a subset of patients with cancers of the tongue, floor of mouth and buccal area, which constitute 75% of oral cancers. A 'wait and watch' policy can be reserved for selected patients with low-risk clinicopathological characteristics and sub-sites such as the palate, alveolus and lip, which have a low propensity for lymphatic spread.

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Community-based management of neonatal infections: New field trials

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S. (Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, NC, USA; Department of Child Health and Paediatrics, School of Medicine, Moi University, Eldoret, Kenya; Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics and Department of Community Medicine, 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.) Oral amoxicillin compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with fast breathing when referral is not possible: A randomised, open-label, equivalence trial. *Lancet* 2015;**385:**1758–66.

African Neonatal Sepsis Trial (AFRINEST) group, Tshefu A, Lokangaka A, Ngaima S, Engmann C, Esamai F, Gisore P, Ayede AI, Falade AG, Adejuyigbe EA, Anyabolu CH, Wammanda RD, Ejembi CL, Ogala WN, Gram L, Cousens S. (Department of Community Health, Kinshasa School of Public Health, Kinshasa, DR Congo; Departments of Pediatrics and Maternal Child Health, Schools of Medicine and Public Health, University of North Carolina, Chapel Hill, NC, USA; Department of Child Health and Paediatrics, School of Medicine; Moi University, Eldoret, Kenya; Department of Paediatrics, College of Medicine, University of Ibadan, and University College Hospital, Ibadan, Nigeria; Department of Paediatrics and Child Health, Obafemi Awolowo University, Ile-Ife; Department of Paediatrics, Ahmadu Bello University Teaching Hospital, Ahmadu Bello University, Zaria; Department of Community Medicine, 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.) Simplified antibiotic regimens compared with injectable procaine benzylpenicillin plus gentamicin for treatment of neonates and young infants with clinical signs of possible serious bacterial infection when referral is not possible: A randomised, open-label, equivalence trial. *Lancet* 2015;**385:**1767–76.

SUMMARY

These two field trials compared the efficacy of different antibiotic regimens to treat possible severe bacterial infection (PSBI) among neonates and young infants (0–59 days) in the community. They also tested the feasibility and safety of screening for and management of these infections by trained community health workers (CHWs) and nurses. These multisite, open-label, equivalence trials were conducted at five field sites in three countries—Democratic Republic of Congo, Kenya and Nigeria from April 2011 to June 2013. Trained CHWs recorded pregnancies and births in the area and, by home visiting, followed up 85 592 babies to identify those with signs of illness. After referring to hospital those with the signs of serious illness, the remaining 'ill' babies and several self-referrals were seen by the study nurses who either excluded those with no illness or referred to hospital the critically ill. Of the remaining, those with only fast breathing were eligible for inclusion in the first trial and those who had one or more signs of PSBI were eligible for the second trial.

After a further round of exclusion, referral or refusal, finally 2333 babies with only fast breathing were randomly assigned to receive either injectable procaine penicillin and gentamicin once a day or oral amoxicillin twice a day each for 7 days. Another 3564 babies with

PSBI were enrolled and randomized into four groups to receive one of the four antibiotic regimens—injectable procaine benzyl-penicillin and gentamicin (7 days), injectable gentamicin and oral amoxicillin (7 days), injectable procaine benzyl-penicillin and gentamicin (2 days) followed by oral amoxicillin for 5 days, or injectable gentamicin (2 days) and oral amoxicillin (7 days). Injections were given by trained community nurses or health extension workers.

In the babies with fast breathing alone, the primary outcome, treatment failure (most often the persistence of the signs) was 22% in the procaine penicillin–gentamicin group compared to 19% in the oral amoxicillin group; the difference was within the 95% CI. Case fatality was 0.4% in each of these two groups. The primary outcome (treatment failure) occurred in the babies with PSBI in 8%, 6%, 8% and 5%, respectively in the four treatment groups—all within the similarity margin. Case fatality till the 15th day after randomization was 1%, 1%, 2% and 1%, respectively; without significant difference. Only one baby developed an injection abscess.

The authors concluded that in neonates and young infants with PSBI, without critical illness and who cannot be hospitalized, all the four antibiotic regimens tested, and in those with only fast breathing, the two regimens tested, were equally effective and such babies can be treated on an outpatient basis.

COMMENT

Globally, each year an estimated 6.9 million neonates develop severe bacterial infections (sepsis, pneumonia and meningitis together) and about 557 000 die.[1,2] The WHO recommends that since the diagnosis and management of such babies is difficult, all neonates and young infants with clinical signs suggestive of PSBI be referred to hospital.[3] However, in real life, because hospitals with facilities for neonatal care are few, the majority of such neonates in the community do not receive the benefits of life-saving antibiotics. The most vulnerable and needy remain the most deprived.

SEARCH (Society for Education, Action and Research in Community Health) from Gadchiroli, India, published a field trial of home-based neonatal care (HBNC) including the management of neonatal sepsis by trained CHWs using antibiotics (injection gentamicin and oral co-trimoxazole) and reported its feasibility, safety and effectiveness.[4,5] In the absence of laboratory facilities for confirming diagnosis in villages, simple clinical criteria were developed to diagnose sepsis in neonates. Simultaneous presence of at least two clinical signs was recommended as the diagnostic criteria in the field because the use of one sign alone would mean a large number of false-positives and over-treatment.[6]

Subsequent field trials in Bangladesh, Pakistan, Nepal and unpublished intervention studies in India (Ankur. *Replication of home-based neonatal care in Maharashtra,* 2006 unpublished document, SEARCH, Gadchiroli, India) have all corroborated the original Gadchiroli study.[7–10] HBNC has now become a part of the National Health Mission (NHM) in India, and nearly 850 000 accredited social health activists (ASHAs) are being trained to provide HBNC including early detection and referral of suspected sepsis and, if referral is not possible, management with an oral antibiotic.[11,12] Due to apprehensions about the feasibility and safety, frontline workers such as ASHAs and auxilliary nurse midwives (ANMs) are not authorised to administer injectable antibiotics to neonates in spite of the evidence in its favour. The next operational questions are: Is such use feasible and safe? Which antibiotic regimen should be used?

The two AFRINEST field trials successfully show that a team of CHW and nurse can deliver antibiotic treatment, including an injectable, safely and with high coverage in the community. Thus, they demonstrate that community-based or outpatient management of neonatal infections is feasible in programme conditions. The trialists deserve congratulations.

However, the conclusion that the various antibiotic regimens tested were equally effective is suspect. Probably they all were equally unnecessary. The babies treated were a selectively low-risk group, mostly false-positive cases, because of three factors:

1. Sixty-seven per cent of neonates were enrolled in the trials after the period of major risk of neonatal mortality (0–6 days) was over. Neonates <1500 g were excluded.
2. Of the 11 153 ill babies, 3038 (27%) were either referred/ hospitalized or removed as critically ill.
3. Of the 3564 babies treated for PSBI, 3111 (87%) had only one clinical sign. The use of only one clinical sign to diagnose PSBI results in inclusion of a large proportion of false-positives.

We have earlier recommended the presence of at least two clinical signs to minimize false-positivity,[6] which the NHM has incorporated.

In the other trial, 2333 babies treated had only fast breathing. The incidence of only fast breathing without other signs of bacterial infection in community-based data on neonates in Gadchiroli during 1995–2014 was 138 of 14 767, i.e. 0.93% (unpublished data). When treated with oral co-trimoxazole, the case fatality in these 138 neonates was zero, similar to the very low (0.2%) case fatality reported when treated with oral amoxicillin or injection procaine penicillin and gentamicin by the AFRINEST group. We suspect that fast breathing alone in neonates is an innocuous sign that may not need any antibiotic.

How many of the 5897 babies treated in the two AFRINEST trials really needed antibiotics? We can use the pre-intervention observational data from Gadchiroli[6,13] for this estimation. Of the total 763 neonates observed in the community during 1995–96 in Gadchiroli, by using the AFRINEST methods of diagnosis, 329 (43%) would be identified as having bacterial infection, but only 19 would be true positive. The methods of the two AFRINEST studies would have together identified 44% of neonates in the community for treatment with antibiotics when strictly only 3% (22/763) of the neonates in the community needed it.[6] No wonder all antibiotic regimens compared in the AFRINEST trials showed equal and very low case fatality. If one were to treat common cold in neonates with placebo, similar outcomes are most likely.

In the absence of an untreated control group—not possible due to ethical reasons—the AFRINEST trials proved the feasibility and safety of healthcare delivery but not the efficacy of the antibiotic regimens tested. In view of the growing global concern about antibiotic overuse and resistance,[14] it is desirable to use more rigorous clinical criteria to selectively treat those at a high risk of death. The main message for India is that the management of suspected neonatal infections with oral and injectable antibiotics can be entrusted to a team of ASHA and ANM. That potentially can prevent nearly 25% of total neonatal deaths in the community. However, which antibiotic regimen should be used remains an unanswered question.

Conflict of interest. None

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