
EXPLORE SIMPLIFIED ANTIMICROBIAL REGIMENS FOR THE TREATMENT OF NEONATAL SEPSIS

Geneva, 30th September – 1st October 2002

MEETING REPORT



**Department of Child and Adolescent Health and Development
World Health Organization**



Background and objectives of the meeting

It is estimated that approximately 4 million deaths occur annually in developing countries in the neonatal period, attributable mostly to infection, birth asphyxia, and consequences of premature birth and low birth weight. Most sick newborns present with signs and symptoms related to more than one condition. A large number (up to 20% of all live births) develop an infection (sepsis, pneumonia, meningitis etc.) during the neonatal period. The identification and treatment of newborns with infection is unsatisfactory in such settings. Some estimates put half of newborn deaths in the community as being due to bacterial infections.

The Department of Child and Adolescent Health and Development (CAH) recently commissioned a review of published and unpublished data on the management of neonatal sepsis in developing countries. The objective of the review was to scientifically and systematically evaluate existing therapeutic strategies for the management of serious bacterial infections (pneumonia, sepsis, and meningitis) among newborn infants in developing countries. The outcomes evaluated were success rates of therapy, ease of use of regimen, cost-effectiveness and methodological or other potential problems. Researchers at Aga Khan University, Karachi conducted the review with assistance from the Johns Hopkins University, Baltimore. At the same time researchers at Johns Hopkins University also completed a meta-analysis of available data on effectiveness of oral and parenteral therapy for treatment of neonatal pneumonia in the community in developing countries.

Objectives

- Review the results of the commissioned literature review and meta-analysis on strategies for management of neonatal bacterial infections in developing countries; and
- Identify effective therapeutic regimens that are more practical for implementation at community or first level facility for the management of neonatal sepsis in developing countries.

Expected outcomes

- Identify potentially effective therapeutic regimens for treatment of neonatal sepsis.
- Plan for testing clinical efficacy and effectiveness of the above mentioned regimens.

The agenda of the meeting and the list of participants are provided in Annexes I and II.

Dr Mathuram Santosham was nominated as the chairperson of the meeting.

In the opening discussion, the following remarks were made:

- Upcoming studies on community-based newborn health interventions in different countries provide a timely opportunity to test the effectiveness of candidate antimicrobial regimens for newborn sepsis;
- Accuracy of dose of antibiotics administered to neonates in community-based research/programme should be assured and monitored;
- Cost effectiveness of antimicrobial therapy with different regimens in the community should be evaluated; and
- Ethical issues in treating neonates in the community/home settings should be carefully examined.

This meeting probably will not be able to cover the special problems of neonates born to HIV positive mothers.

Review of etiology and management of serious bacterial neonatal infections in developing countries

WHO/HQ and Saving Newborn Lives/Save the Children (US) had commissioned a review of etiology and management of serious bacterial infections in developing countries. The review was undertaken by a team from the Aga Khan University comprising of Drs Anita Zaidi, Syed Asad Ali, and Zulfiqar Bhutta, with contributions from Dr Gary Darmstadt (Johns Hopkins University) Dr Zaidi presented the summary of the methodology and the findings.

Methodology

An extensive literature search on studies reporting etiology of neonatal and post-neonatal infections and studies reporting management in community-settings in developing countries was conducted via the PubMed and other database and bibliographies of key references. Countries in the low to middle income group as defined by the World Bank, as well as those in the Middle East, were considered “developing”. Neonatal and post-neonatal sepsis was defined as septicemia, pneumonia, or meningitis in the 0-30 day and 31-90 day periods, respectively.

Studies reporting exclusively or predominantly nosocomial (hospital-acquired) infections were excluded from the analysis (e.g. studies from neonatal intensive care units with sepsis developing in pre-term or low-birth-weight babies beyond 7 days of life). The remaining data were categorized as either non-nosocomial (where the authors excluded hospital-acquired infections) or “undifferentiated” where infections were predominantly early-onset (within 7 days of life) and/or authors discussed maternal risk factors for neonatal infection and did not report nosocomial infections as being a problem in their nursery. Studies reporting community-based management of infants or children were reviewed for inclusion of neonates and presentation of disaggregated neonatal or post-neonatal data.

Conclusions on etiological agents

No community-based studies of etiology of neonatal sepsis were identified and limited data were available from first-level health facilities and home-delivered babies. Because of the selection criteria used and the attempts to exclude hospital-acquired neonatal infections, data reported in this study predominantly reflects early-onset sepsis. However, most hospital-based studies do not distinguish between maternally acquired, community-acquired, or hospital-acquired infections. Moreover, these distinctions may not hold much value in situations where clean delivery and baby handling practices are lacking and both home and hospital environments are contaminated.

All the data available (studies reporting very-early-onset sepsis, those that have excluded hospital-acquired infections, that are from rural hospitals, and on causes of sepsis in home-delivered infants) indicate that gram-negative rods, especially *Klebsiella* organisms are the most important cause of neonatal sepsis, followed by *Staphylococcus*, and *Escherichia* (Figure 1 and Figure 2).

Figure 1 Neonatal pathogens in different settings

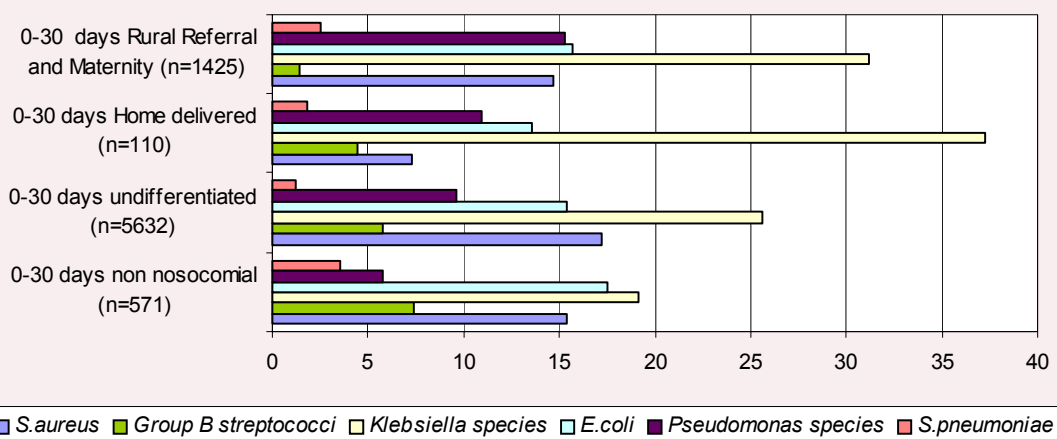
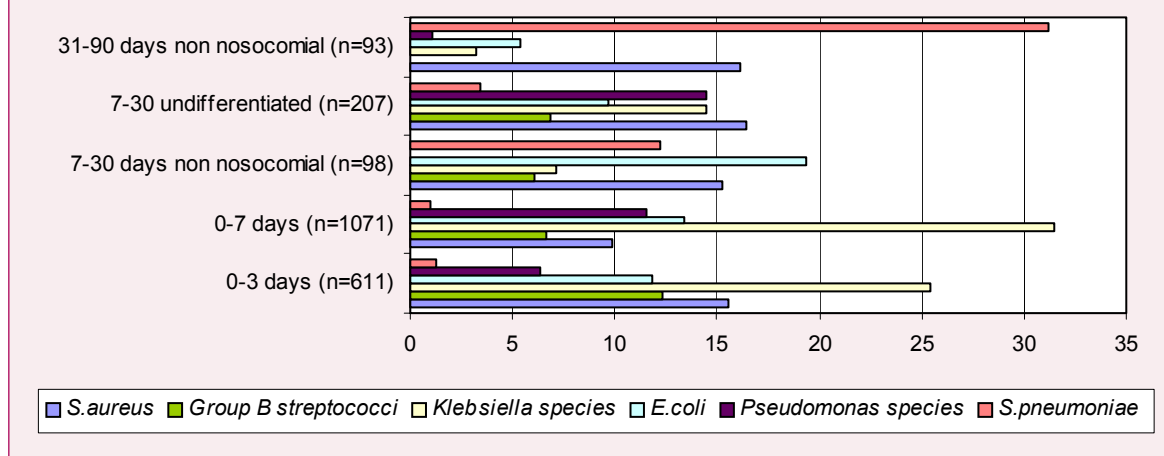


Figure 2 Changing spectrum of pathogens in early-onset neonatal sepsis, late-onset neonatal sepsis and sepsis in young infants



No conclusions can be drawn about causes of late-onset (community-acquired) neonatal sepsis from hospital-based studies because these invariably include many hospital-acquired infections. Limited data from the WHO Young Infant Study¹ indicate that *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pyogenes*, and *Salmonella* species are important pathogens beyond the first week of life in Africa and Papua New Guinea. This study, however, included only those neonates who reached the hospital and may not represent the true bacteriological spectrum in the community. No data on causes of late-onset neonatal sepsis in babies presenting from the community are available from South Asia, which is home to a major burden of neonatal mortality. Notably, the pathogens in the WHO supported Young Infant Study were mainly gram-positive, whereas hospital data indicate gram-negative organisms to be predominant. This is most likely due to the fact that hospital-based data included in this study mainly represented early-onset sepsis, whereas 85% of babies with sepsis in the Young Infant Study were older than 7 days. In the few babies who developed early-onset sepsis, gram-negative rods accounted for 56% of all invasive disease.

There are significant regional differences in pathogens of importance in neonatal sepsis, especially in the proportion of infections caused by Group B streptococci (GBS), *S. aureus*, and *Acinetobacter/Pseudomonas*. GBS is an important pathogen in some African countries (but absent in others), Middle-eastern countries, and the Caribbean Islands, but is less important in South Asia. However, intra-country differences also occur and isolated studies in India and Pakistan have reported GBS to be an important cause of early-onset sepsis. *S. aureus* is the most common pathogen in African countries and a peculiar trend of *Acinetobacter/Pseudomonas* infections was noted in Asia Pacific, even in early-onset sepsis and in the Young Infant Study.

Antimicrobial resistance patterns of neonatal pathogens

There is insufficient information on antimicrobial resistance patterns in community settings on the three most common pathogens (*E. coli*, *Klebsiella species*, and *S. aureus*) causing early-onset neonatal sepsis. Available data indicate that India and Pakistan may have significant antimicrobial resistance among *E. coli*, *Klebsiella species*, and *S. aureus* which, if confirmed by future studies, will make devising inexpensive but effective empiric regimens for treatment of neonatal sepsis difficult. Resistance among these three pathogens appears to be less common in Africa, but data are insufficient. There are important regional differences in susceptibility patterns of *Haemophilus influenzae* and pneumococci in Africa, with some countries (South Africa, Malawi) reporting high resistance rates to penicillin, chloramphenicol and cotrimoxazole; other African countries have intermediate (Kenya, Senegal), or low resistance rates (Gambia, Central African Republic, Ghana). There is a substantial resistance among respiratory pathogens to cotrimoxazole in South Asia.

¹ The WHO young infant study group. Bacterial etiology of serious infections in young infants in developing countries. PIDJ;1999:S17-22

Conclusions of the review

■ ETIOLOGY DATA

- No data from community settings
- Hospital data included in this review predominantly reflect early-onset sepsis since late-onset sepsis reported from hospital settings include significant proportions of hospital-acquired sepsis and were excluded from the review.
- Gram-negative rods, especially *Klebsiella* species are major pathogens in early-onset sepsis (hospital data), in home-born neonates, in rural hospitals, and in non-nosocomial data from hospitals.
- Limited data on late-onset sepsis; cannot use hospital data to assess spectrum
- No data on late-onset or post-neonatal community-acquired sepsis from South Asia.
- Data from Young Infant Study show *S. aureus*, *S. pyogenes*, *E. coli*, pneumococci, and *Salmonella* species to be important pathogens but insufficient numbers of 0-7 day old neonates were studied.
- *S. aureus* is important in all periods of young infancy, and in all regions except Asia-Pacific.
- Pneumococci proportion increases with age.
- GBS importance varies with country and even within country

■ ANTIMICROBIAL RESISTANCE

- Serious lack of data from community settings
- Alarming resistance in hospital-based studies in gram-negative rods and *S. aureus*
- GBS and *S. pyogenes* have predictable susceptibility to penicillin, and are “tolerant” to cotrimoxazole

Following points were made during the discussion:

- The definition of young infant should be reviewed. WHO uses infant of up to 59 days as the young infant, but it is not a universally accepted definition.
- It was clarified that omphalitis was included in sepsis in the review because many babies had positive blood cultures.
- It was suggested that a review of PUBMED and EXTRAMED alone was not enough for a comprehensive search of the subject area. Other databases including WHO databases should be included in future revisions and expansion.
- It was a matter of concern that no data was available from China.
- Low maternal group B streptococcus colonization rates in South Asia may be due to genetic factors or menstrual hygiene practices.
- In order to complete the picture of etiology of early onset sepsis, it is crucial to review the data on maternal genital colonization
- Etiology of neonatal sepsis may be birth weight specific; data from hospitals would have disproportionate representation of organisms causing sepsis among the very low birth weight infants.
- No study has attempted to characterize strains of *Klebsiella* species grown from neonates.
- The alarmingly high incidence of antimicrobial resistance among common pathogens of neonatal sepsis (*Klebsiella* species, *E. coli*, *S. aureus*, *Enterobacter* species) in hospitals in South Asia is a cause of extreme concern. Urgent steps are required to mobilize concerted action to control this menace.

Meta-analysis of community-based trials of case-management of pneumonia

Drs Robert Black and Sunil Sazawal have conducted meta-analysis of community-based trials of case management of pneumonia. Dr Black presented the summary of this meta-analysis with a focus on community management of neonatal pneumonia. Seven concurrent controlled trials conducted in India (two), Bangladesh, Pakistan, Nepal, Philippines and Tanzania were included. Five studies employed cotrimoxazole as treatment of pneumonia, one used penicillin injections, and another a combination of penicillin injections with ampicillin injections/oral. Mortality surveillance was organized with the assistance of community informants/enumerators. Verbal autopsy was employed for ascertaining the causes of death. The case management of pneumonia led to a 30% reduction (OR 0.7, 95% CI 0.59 – 0.84) in overall neonatal mortality and a 44% reduction (OR 0.56, 95% CI 0.37 – 0.83) in pneumonia-specific neonatal mortality. Overall, there was a 26% lower child mortality (OR 0.74, 95% CI 0.64 – 0.86) and a 33% lower pneumonia-specific child mortality (OR 0.67, 95% CI 0.54 – 0.83).

In the discussion, the group noted that antimicrobial treatment of neonates with pneumonia with a single oral antibiotic brings down neonatal mortality substantially. There could be a phased introduction of antibiotic treatment of infections in the community, viz. introduce oral antibiotic protocol first and then add an injectable antibiotic. It was suggested that it is quite conceivable to develop antimicrobial molecules specifically suited to the needs of neonates.

Antibiotic pharmacology in neonates

Dr Gary Darmstadt presented a review on the antibiotic pharmacology in neonates. Owing to several physiological peculiarities, the pharmacokinetics of antibiotics of neonates is different from those in older children. Pre-term neonates have additional limitations due to organ system immaturity. In particular, gastro-intestinal absorption of oral antibiotics is reduced and varies considerably among neonates.

Selection of empiric antibiotic therapy is dependent upon target organisms and their antibiotic susceptibility, spectrum of antibiotic activity, association with emergence of resistance, drug distribution, therapeutic index, cost of therapy and ease of use.

Penicillin covers streptococci, pneumococci, *Listeria monocytogenes*, meningococci and *Treponoma pallidum*. Penicillin G needs 6 to 12 hourly intravenous administration and is therefore not suited for community-based treatment protocols. Procaine penicillin requires single daily intramuscular injection and is well tolerated, but has low CSF penetration. Procaine penicillin will be evaluated as once daily intramuscular therapy for serious neonatal infections in the community in Bangladesh.

Ampicillin is preferred to penicillin for the treatment of neonatal sepsis as it is also active against some gram-negative pathogens, especially *E. coli*, one of the three most frequent causes of neonatal sepsis in developing countries. It acts synergistically with aminoglycosides, has good CSF penetration and can be administered parenterally as well as orally. In view of its safety and efficacy, most experts recommend it as a first line empiric therapy for serious neonatal infections in combination with an aminoglycoside. Amoxicillin is similar to ampicillin in its spectrum. Twice daily oral dosing is theoretically adequate in neonates. Addition of clavulanate broadens the spectrum against many beta-lactamase producing strains. However, absorption varies and in very low birth weight neonates, amoxicillin-clavulanate increases the risk of necrotizing enterocolitis.

Penicillinase resistant penicillins (methicillin, flucloxacillin and nafcillin) are empiric drugs of choice for suspected staphylococcal infections. These antibiotics are safe and well tolerated in neonates. However, their spectrum of activity is restricted to gram-positive organisms.

Aminoglycosides form the sheet anchor of antibiotic therapy of serious neonatal infections because of the broad spectrum activity against gram negative bacteria as well as staphylococci. Amikacin is active against many nosocomial gram negative organisms. Tobramycin has especially low minimum inhibitory concentrations (MIC) against pseudomonas. Therapeutic plasma aminoglycoside concentration is achieved equally well by intravenous as by intramuscular routes of administration.

There is enough data to show that once daily dosing of gentamicin is effective and safe for treating neonates. Once daily dosing leads to a higher and quicker peak serum level resulting in prolonged efficacy and greater initial bacterial killing. There is a lower risk of ototoxicity and nephrotoxicity with single daily dosing regimens because of the longer phase of subtoxic drug levels. Once daily gentamicin therapy appears to be a suitable regimen for treating neonates with sepsis. A recently developed single dose injecting system (Uniject) for gentamicin is undergoing clinical evaluation.

Cephalosporins are not recommended for routine use as first-line agents for the treatment of neonatal sepsis. A third generation cephalosporin, often in combination with an aminoglycoside, is commonly used as the second line treatment of newborn sepsis. Ceftriaxone has excellent CSF penetration, and requires only single daily dosing. Cefuroxime, a second generation cephalosporin, can be given orally (twice daily) or parenterally (thrice daily). Its broad spectrum activity is akin to that of amoxicillin-clavulanate, but less than that of the third generation cephalosporins. CSF penetration of cefuroxime is poor (12-25%), but increases with inflammation. Its use is not approved under 3 months of age in the USA due to insufficient safety and efficacy data.

Trimethoprim-sulphamethoxazole (cotrimoxazole) is active against most enterobacteriaceae species, pneumococcus, *S. aureus* and *S. pyogenes*. It displaces bilirubin from albumin and thus potentially increases

the risk of kernicterus. It is well absorbed orally and achieves good CSF concentrations. Cotrimoxazole has been successfully used in community-based studies in the treatment of pneumonia and sepsis in neonates. It is, however, not approved for use less than 2 months of age in the USA due to insufficient safety data. Widespread resistance among common neonatal pathogens is also a concern although sufficient data from community settings are lacking.

The first line empiric antibiotic therapy of neonatal sepsis recommended by Dr Darmstadt in facilities and community settings based on pharmacological considerations is given below (See box).

Empiric therapy of serious neonatal infections

■ FIRST LINE THERAPY IN FACILITY SETTINGS

- Early and late onset sepsis : ampicillin plus gentamicin
- Early-onset meningitis : ampicillin plus gentamicin
- Late-onset meningitis : ampicillin, gentamicin (or amikacin), and/or cefotaxime
- Suspected staphylococcal sepsis, focal skin, bone, joint infections (including omphalitis) : methicillin/nafcillin plus gentamicin
- For sepsis of suspected gastrointestinal origin : ampicillin, gentamicin/amikacin, plus clindamycin (or piperacillin)
- Nosocomial infection in setting with multi drug resistant *S. aureus*(MRSA) (also if penicillin-resistant pneumococci, or enterococci are suspected): vancomycin plus gentamicin (and/or ceftazidime, if high prevalence of pseudomonas)

■ REGIMENS FOR COMMUNITY-BASED TREATMENT

Parenteral or oral-parenteral combination therapy

- Procaine penicillin once daily (OD) intramuscular (IM) plus gentamicin OD IM (delivery of gentamicin using Uniject)
- Amoxicillin twice daily (BID) orally (PO) plus gentamicin OD IM
- Cotrimoxazole BID PO plus gentamicin OD IM
- Ceftriaxone IM (as first dose prior to arrival at hospital)

Oral therapy

- Amoxicillin BID
- Cotrimoxazole BID
- Cefuroxime (or Cefprozil) BID

Following points emerged in the discussion:

- There is a well known potential risk of ototoxicity with aminoglycosides but, if used properly, the incidence, even among pre-term neonates, appears low.
- There should be, as far as possible, a linkage/concordance between antimicrobial therapy at community and facility levels.
- Ciprofloxacin was not considered as an appropriate antibiotic for treating severe neonatal infections because of inadequate data on safety, efficacy and resistance predilection among neonates.
- Oral chloramphenicol does not achieve consistent drug levels in neonates and young infants, hence, not recommended.
- In practice, often, there is a dichotomy between *in vitro* antimicrobial sensitivity and clinical response to a given antibiotic.

Prophylactic use of antibiotics for asymptomatic neonates born to mothers with risk factors for infection

Dr Ornella Lincetto, in her presentation, addressed the question - how to manage asymptomatic newborns when the mother has risk factors for infection or has a confirmed infection. Maternal fever, pre-labour rupture of membranes of > 18 hours, premature onset of labour, chorioamnionitis, urinary tract infections and group B streptococcus (GBS) colonization are the key maternal risk factors. Attack rates of sepsis among newborns with maternal GBS colonization, premature onset of labour, prolonged rupture of membranes

(or chorioamnionitis) and maternal post-partum bacteremia are 1–2%, 15%, 11% and 10%, respectively. Maternal carriage rates of GBS in developing countries of Middle East/North Africa, Asia/Pacific, Sub-Saharan Africa, India/Pakistan and Americas are 22%, 19%, 19%, 12% and 14%, respectively. Different protocols recommend giving intrapartum chemoprophylaxis to all GBS carriers or to only those with additional obstetric risk factors. Emergence of antibiotic resistance is a real danger of intrapartum chemoprophylaxis. If the mother receives chemoprophylaxis and the neonate has signs of infection, he should be investigated for sepsis and treated.

Asymptomatic neonates of treated mothers should be observed for 48 hours. Sepsis workup should be carried out if risk factors mentioned above are present and the mother has received only one dose of antibiotic before delivery. There is no consensus on the approach to be taken when the mother is not treated and the baby is asymptomatic. Most western guidelines recommend giving routine antibiotics to the neonate for 72 hours during which infection may be excluded by use of laboratory analysis and blood culture. Guidelines from developed countries recommend giving penicillin G to women with intrapartum fever $>38^{\circ}\text{C}$, prolonged rupture of membranes > 10 hours, pre-term labour or fetal heart rate > 160 per minute when the maternal GBS (group B streptococcus) carrier status is unknown. In these countries the prevalence of GBS in pregnant women is around 10-14% and it is considered an important risk factor of sepsis.

The WHO Department of Reproductive Health and Research (RHR) is currently engaged, in collaboration with the Neonatal Cochrane Group in conducting a systematic review on the subject of treatment of asymptomatic newborns when the mother has risk factors for infection, , and this analysis is expected to be ready by mid-2003.

Home-based management of pneumonia/sepsis in neonates

Dr Abhay Bang summarized studies on treating acute respiratory infections and sepsis among neonates done at Gadchiroli (India) during 1988-2002. The Society for Education, Action and Research in Community Health (SEARCH) project consists of about 40 intervention and control villages each.

During 1988-95, acute respiratory infection (ARI) case management using cotrimoxazole was implemented. The neonatal mortality (per 1000 live births) at the end of the trial in intervention and control areas was 84 and 64, respectively (a difference of 24%), while ARI specific mortality rates were 29 and 17 per 1000 live births (a difference of 40%).

During 1995-96, SEARCH performed an observational study on a birth cohort to describe newborn morbidity and mortality. Of 763 neonates, 138 (18%) developed sepsis/pneumonia, of whom 24 (17.4%) died. The study yielded valuable information on causes of neonatal deaths, and a profile of neonatal morbidity and newborn care practices.

Since 1996, a package of newborn care interventions was introduced in the intervention area. This included resuscitation and care at birth, warmth, breastfeeding, prevention of infections and diagnosis and active treatment of neonatal sepsis with cotrimoxazole and gentamicin. Community-chosen village-level workers delivered these interventions to homes, including administration of oral cotrimoxazole and intramuscular gentamicin. The baseline neonatal mortality (1995-96) was 52.4 per 1000 live births. This declined to 24.1 in 1997-98 and 16.5 in 2001-02. Cause specific mortality due to neonatal sepsis dropped from 28.8 per 1000 live births at baseline to 6.6 in 1997-98 and 4.1 in 2001-02.

The initial treatment protocol at SEARCH included twice daily injections of gentamicin (1997-98). This was changed to a single daily injection of the total dose in 1998-2001. An increase in case fatality rate (CFR) from 3.1% to 8.2% was noted in the two periods. The investigators attributed this increase to the reduced frequency of gentamicin administration. Since February 2001, the twice daily schedule has been restored and the CFR dropped to 5.6% thereafter, Dr Bang believed that the once daily gentamicin schedule was possibly less than optimal.

Dr Bang also shared data showing that improved neonatal survival was not associated with excess replacement mortality in the post-neonatal period.

In summary, the SEARCH studies showed a reduction by 40 points in the infant mortality rate (per 1000 live births) from a baseline of 120 with ARI case management intervention alone. A further reduction of 40

points was achieved with the addition of a home-based newborn care package including treatment of sepsis. Recently, SEARCH introduced a simple newborn care facility at the field hospital. The IMR in the SEARCH intervention areas has now dropped to just about 30 per 1000 live births.

Following points were made during the discussion:

- The increase in CFR after single dose of gentamicin was introduced also reduced the visits by health workers from twice daily to once daily. This, rather than the change in the gentamicin dose regimen, may be responsible for the decline in CFR.
- Sustainability of domiciliary care of neonates in the 'normal' health system needs to be ascertained in operational studies.
- Vitamin K injection was given to all neonates at birth in the SEARCH study because that was the general recommendation in neonatal nurseries.
- Maternal health indicators were not measured in the SEARCH project at the baseline. There is, however, a trend towards reduced incidence of maternal morbidities. Mothers received health education and supplements in prenatal and post-partum periods.
- Risk of cotrimoxazole predisposing to bilirubin toxicity, especially in pre-term neonates, needs to be borne in mind while employing this drug.
- The birth rates in the control and intervention areas of the SEARCH project have been comparable in 1988 (about 33 per 1000) and in 2002 (about 18 per 1000). Thus, IMR decline in the intervention area does not appear to be associated with concomitant excess gains in fertility indicators.
- Drs. Bhutta and Zaidi shared information about their experience in the Gilgit area of Pakistan where a substantial reduction in neonatal mortality occurred as a result of safe motherhood interventions, including skilled birth attendance but without introducing treatment of neonatal sepsis.

Designing management strategies for neonatal infection in community settings

Dr Zulfiqar Bhutta presented a paper on the above theme, representing a consensus opinion by Drs Anita Zaidi, Gary Darmstadt and himself.

There was very little data on the subject from representative settings in developing countries. No community-based studies included microbiological information. No comparative trials of different antimicrobial regimens or of oral vs. injectable therapy have been reported. Dr Bhutta provided a summary of all the studies on community management of neonatal infections. Studies by Dr Bang at SEARCH have already been summarized above.

In a study by Dr. A. Bartlett in rural Guatemala, 329 infants 0-90 days were followed at home and at the local health centre. Of those, 34 developed infection. Antibiotic therapy included ampicillin plus gentamicin for sepsis, ampicillin for pneumonia with fever, and erythromycin for pneumonia without fever. Treatment was started in the community and infants were referred. If referral was refused, treatment was continued at home.

In this uncontrolled study, CFR of sepsis was 14%. In another observational study, Dr Bhandari and co-workers identified 126 young infants with severe illness in a study in Delhi slums. As many as 95 of them refused referral. They were then managed with oral cephalexin and intramuscular amikacin at homes. A case fatality rate of 2.3% was reported.

It was emphasized that the main focus of the interventions should be infants 0-6 day old because they have the highest burden of sepsis. Dr Bhutta suggested facility-based comparative trials of different antimicrobial regimens for treating neonatal sepsis (See box).

Suggested antibiotic combinations for comparative trials in community settings

- 0-7 DAYS OR 8-29 DAYS (SEVERE DISEASE)
 - Procaine penicillin IM plus gentamicin IM OD
versus
Cotrimoxazole PO plus gentamicin IM OD
 - Cloxacillin PO plus gentamicin IM OD
versus
Ceftriaxone IM plus gentamicin IM OD
- 8-29 DAYS (NON-SEVERE-DISEASE)
 - Oral cotrimoxazole OR oral cefuroxime/cefprozil
versus
Oral cotrimoxazole OR oral cefuroxime/cefprozil
plus gentamicin IM OD

In facility-based comparative efficacy trials, outcome measures should include not only CFR, but also morbidity / acuity scores and the need to alter therapy. Effectiveness trials, on the other hand, should measure all-cause and infection-specific mortality rates.

Using costs from international suppliers of generic medicines, the cost of a 10-day course in a 3 kg infant was estimated as follows: cefuroxime US \$ 11, procaine penicillin US \$ 1.5, gentamicin US \$ 0.6, cloxacillin US \$ 10 and ciprofloxacin US \$ 3.

Dr Bhutta made the following suggestions for studies on community-based management of neonatal sepsis:

- Refine and field test algorithms for predicting severe illness in community settings.
- Describe pathogens and susceptibility patterns from multiple geographic locations in community settings and among all four age groups (0-3 days, 4-6 days, 7-27 days, 28-59 days).
- Agree on a minimum template of clinical data (gestation, birth weight, age of onset, maternal information), microbiological / laboratory investigations in suspected sepsis/serious infection.

Recommendations

■ Antimicrobial regimens for studies evaluating community-based management of sick newborn infants.

- At the current state of our understanding, the antimicrobial regimens that may be considered acceptable for treating newborn sepsis in the community settings (See box). These regimens may, therefore, be included in intervention trials evaluating community-based management of sick neonates.

Antibiotic regimens for community-based trials

■ INJECTABLE PLUS ORAL

- Injection gentamicin intramuscular once daily plus oral cotrimoxazole¹ twice daily
- Injection gentamicin intramuscular once daily plus oral amoxicillin twice daily

■ INJECTABLE ONLY

- Injection gentamicin intramuscularly once daily plus injection procaine penicillin intramuscular once daily

■ ORAL ONLY²

- Oral amoxicillin – clavulanate combination twice daily
- Oral ampicillin thrice daily plus oral cloxacillin thrice daily
- Oral cloxacillin thrice daily plus oral cefixime once or twice daily
- Oral cefprozil twice daily

¹ In areas with high prevalence of glucose-6-phosphate dehydrogenase (G-6-PD) deficiency, cotrimoxazole should be avoided.

² Oral treatment should only be considered in case the regimens with injectable antibiotics are not feasible.

- Oral chloramphenicol, cefuroxime and ciprofloxacin were not recommended because of erratic absorption, significant side effects and uncertain safety, respectively.
- Ceftriaxone was also not recommended as it is inappropriate to use a wide-spectrum third generation cephalosporin as the first line treatment in the community. It is more suited for resistant organisms.

■ Study design issues in evaluating treatment of neonatal sepsis in the community

The study design would depend upon the primary research question (Table 1).

Table 1 Study design issues

RESEARCH QUESTION	POSSIBLE STUDY DESIGNS	COMMENT
What is the impact of a package of essential newborn care (ENC) that <i>incorporates</i> active treatment for sepsis with antibiotics on neonatal outcome(s)?	<ul style="list-style-type: none"> ● Single phase study ENC <u>plus</u> sepsis treatment versus Control group ● Two-phase study Phase I ENC versus Control group Phase II ENC <u>plus</u> Sepsis treatment versus Control group 	Phased introduction of interventions appears more practical
What is the impact of active treatment of sepsis with antibiotics on neonatal outcome(s)?	<ul style="list-style-type: none"> ● Option 1: Two groups ENC versus ENC <u>plus</u> sepsis treatment ● Option 2: Three groups ENC versus ENC <u>plus</u> sepsis treatment versus Control group ● Option 3: Four groups Sepsis treatment versus ENC <u>plus</u> sepsis treatment versus ENC versus Control group 	The study option 3 though ideal, would be very large and non-inclusion of ENC in the first arm may be ethically unacceptable

[NB: Essential newborn care (ENC) here means a package of preventive and promotive interventions that may include: care at birth, simple resuscitation, warmth, exclusive breastfeeding, prevention of infection, supervised care of low birth weight infants etc. This package would be assumed to be the current standard of care]

■ Exploring simplified antimicrobial regimens for treating newborn sepsis

- The standard antimicrobial therapy of neonatal sepsis consists of a combination of two or more antibiotics administered parenterally for 10 to 14 days (or longer as in meningitis). Parenteral antibiotics are not easy to administer in small hospitals because of poor nursing care. Families find it difficult to stay in hospital for more than a few days. There is, therefore, a need to explore effective and safe antimicrobial regimens for neonatal sepsis that are simple to administer and do not require long hospitalization. It was recommended that clinical trials be undertaken *in hospital settings* to compare standard antibiotic protocols with the following and other simplified antimicrobial treatment protocols:
 - Regimens of shorter duration (say 5 days);
 - Regimens in which after an initial parenteral therapy (of say 2-3 days), one or more injectable antibiotics are replaced by oral preparation(s) for the rest of the duration; and
 - Regimens consisting of oral plus injectable or oral only antibiotics for the full duration of treatment.

■ Improving understanding of pathogens causing newborn sepsis and their antimicrobial susceptibility

- Knowledge of etiological agents causing neonatal sepsis in the community in different regions, and their antimicrobial susceptibility, is an essential pre-requisite before formulating treatment strategies.
- Studies on the microbiological spectrum of neonatal sepsis in regions with a high burden of newborn mortality should be undertaken as a priority. These studies should ascertain sensitivity of organisms to a range of antibiotics that could be potential candidates for treating neonates with sepsis in the community presently or in the future.
- Studies are also recommended in different regions to elucidate the organisms colonizing the maternal genital tract because of their link with early onset neonatal sepsis.

■ Diagnosing neonatal sepsis in the community

- Studies are urgently required to develop simple clinical criteria to diagnose neonatal sepsis in the community. Algorithms based on symptoms/signs could be used by health workers to identify neonates for referral or for home treatment of sepsis.

■ Improving rational treatment of neonates with sepsis

- Studies are recommended to document practices of caregivers in treating neonatal sepsis and to document the clinical outcomes of septic neonates in small hospitals.
- Clinical practice guidelines emphasizing rational antimicrobial therapy and, equally importantly, effective supportive care, need to be developed and disseminated widely.

■ Tackling the problem of antimicrobial resistance among organisms causing newborn sepsis

- In view of the alarming incidence of antimicrobial resistance among the hospital strains causing newborn sepsis in developing countries, especially in South Asia, it was recommended to:
 - examine this issue more thoroughly from the available data;
 - elucidate the determinants and mechanisms of antimicrobial resistance of organisms causing neonatal sepsis;
 - study approaches to overcome this serious problem in different regions.
 - enhance awareness about this problem among neonatologists, pediatricians, nurses, policy makers, etc. in the concerned regions;
 - develop surveillance mechanisms to track antimicrobial resistance among agents causing newborn sepsis in the community and in hospitals, and
 - promote research on prevention and control of nosocomial neonatal infections.

■ Other recommendations

- Initiatives are recommended for developing antimicrobial agents specifically suited to the treatment of infection among neonates in developing countries. An ideal agent would be effective against a wide range of causative organisms, would be safe in term as well pre-term babies, and could be administered orally / intramuscularly in a single daily dose. It may also be possible to devise effective long acting antibiotic preparations that could be administered once every two days.
- Studies are recommended to evaluate accuracy, effectiveness, safety and acceptability of simplified systems of parenteral antibiotic delivery in neonates.

Agenda

Annex 1

Meeting to explore simplified antimicrobial regimens for the treatment of neonatal sepsis

30 September - 1 October 2002, Geneva, Switzerland

MONDAY, SEPTEMBER 30, 2002

- 2.00-2.15 Welcome and Introductions
2.15-2.30 Objectives of the meeting; Overview of the agenda

Strategies for management of neonatal bacterial infections in developing countries

- 2.30-3.15 Methodology of the review and analysis A. Zaidi
Microbiology data (Aetiology and sensitivity patterns, nosocomial versus non-nosocomial and community-based information) A. Zaidi
3.15-3.30 Coffee/Tea break
3.30-4.15 Meta-Analysis B. Black
4.15-4.30 Antibiotic pharmacology in neonates G. Darmstadt
4.30-5.30 Discussion

TUESDAY, OCTOBER 1, 2002

Identify potentially effective therapeutic regimens for treatment of neonatal sepsis

- 9.00-9.30 Therapeutic information from community settings and developing countries Z. Bhutta
9.30-10.00 Domiciliary management of neonatal sepsis: SEARCH experience A. Bang
10.00-10.15 Review on prophylactic use of antibiotics for asymptomatic newborns born to mothers with perinatal infections O. Lincetto
10.15-10.45 Discussion
10.45-11.00 Coffee/Tea break
11.00-11.45 Identification of simplified potential antibiotic regimens for treatment of neonatal sepsis and discussion
11.45-12.30 Way forward with management of neonatal sepsis in the community
12.30-2.00 Lunch break
2.00-3.00 Identify research needs and ways to address them
3.00-4.00 Summary, conclusions and recommendations

List of participants

Annex 2

Participants

Dr Emmanuel Addo-Yobo	Komfo Anokye Teaching Hospital, Ghana
Prof. Jacob Aranda	Children's Hospital of Michigan, United States of America
Dr Abhay Bang	SEARCH, Gartcharoli, India
Prof. Zulfiqar Ahmad Bhutta	Aga Khan University, Karachi, Pakistan
Prof. Robert Black	Johns Hopkins University, Baltimore, United States of America
Dr Gary Darmstadt	Johns Hopkins University, Baltimore, United States of America and Save New-born Lives (SNL) Washington
Dr Kalle Hoppu	University of Helsinki, Helsinki, Finland
Dr Vinod Paul	Save Newborn Lives, India (On secondment from All India Institute of Medical Sciences, Delhi)
Prof. Mathuram Santosham	Johns Hopkins University, Baltimore, United States of America
Dr Anita Zaidi	Aga Khan University, Karachi, Pakistan

WHO Secretariat

Dr Ornella Lincetto	RHR
Dr Jose Martines	CAH
Dr Shamim Qazi	CAH
Dr Martin Weber	CAH