Serious bacterial infections in newborn infants in developing countries

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Purpose of review

The overwhelming majority of the world's annual 4 million neonatal deaths occur in developing countries. This review therefore briefly addresses the burden, aetiology, prevention and management of serious neonatal bacterial infections in low-income settings.

Recent findings

Bacterial infection is the biggest cause of neonatal admissions to hospitals, and probably the biggest cause of morbidity in the community, but its burden is unclear. The commonest serious infections involve bacteraemia, meningitis and respiratory infection, and case fatality rates may be as high as 45%. Key pathogens are *Escherichia coli*, *Klebsiella* species, *Staphylococcus aureus* and *Streptococcus pyogenes*. The incidence of neonatal infections with group B streptococcus is highly variable, as is the spectrum of antimicrobial resistance.

Summary

Current areas of research include the rectification of micronutrient deficiencies, neonatal skin care, appropriate breastfeeding recommendations, cleansing of the birth canal, and simplified methods of diagnosis of infection. Operational activities include the control of neonatal tetanus, the diagnosis and treatment of sexually transmitted infections, integrated strategies for improving pregnancy, childbirth and neonatal survival, community-based management of acute respiratory infections, and community-based management of neonatal sepsis.

Keywords

developing countries, essential newborn child care, neonatal infection, neonatal mortality

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Abbreviation

WHO World Health Organization

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Introduction

The Millennium Development Goals include a reduction in child mortality by two-thirds between 1990 and 2015 [1]. The number of children under 5 years of age that die each year is 10.8 million, making up 32% of global deaths [2]. Neonatal deaths account for about half of these [3,4••] and two-thirds of infant deaths [5], proportions which rise as post-neonatal mortality falls [4••,6]. Of the estimated 3.9 million annual neonatal deaths [3,4••], 98% occur in developing countries [7].

This overview addresses the burden, aetiology, prevention and management of serious neonatal bacterial infections in low-income countries. Malaria, tuberculosis, HIV/AIDS and other viral or sexually transmitted infections are not its focus. The rural, home-born neonate remains relatively invisible to either research or health services and – despite the figures above – the burden of neonatal mortality in low-income countries is barely quantified [8•]. Although a range of strategies for prevention and management have been proposed, the gaps between the conceptual bases of these strategies and their implementation are wide.

Neonatal mortality caused by bacterial infection

Most births in developing countries take place at home, as do most neonatal deaths. The major causes of death are likely to be infections, preterm birth and birth asphyxia [7]. The incidence of neonatal bacterial illness is unclear [9,10]. In major reviews by Stoll [11,12], hospital data suggested that infection was a cause of 4–56% of neonatal deaths, and community data a figure of 8–84% [11]. These figures yielded an estimate of 1.5–2 million infection-related neonatal deaths per annum [11,12]. World Health Organization (WHO) estimates suggest that sepsis, pneumonia, tetanus and diarrhoea cause 32% of neonatal deaths [3].

The variability of these estimates underlines five issues. (1) The invisibility of the neonatal period makes pick-up rates variable. (2) There are difficulties in diagnosing neonatal infection and in disaggregating it from other potential causes of death, and the clinical tools available for diagnosis in poorer settings are limited. (3) The site of research is important: hospital-based studies have often been conducted in tertiary units, may include higher proportions of preterm infants, generally recruit urban participants of higher socioeconomic status, often

include more male infants, and tend to miss early neonatal illness and mortality. (4) All research in low-income countries faces the problems of workload, opportunity and consumable costs, and variations in the quality of laboratory procedures. (5) These issues aside, there is likely to be a wide range of incidences and case fatality rates across geographic, socioeconomic and demographic spectra [13].

Morbidity and clinical presentations of bacterial infection

Attempts to measure morbidity are confused by the selective nature of studies, particularly the recruitment of sick infants at health facilities [14]. In a hospital-based study from Karachi, Pakistan, infection was the biggest cause of hospitalization of newborn infants [13], and at a district hospital in Kenya, where 95% of admissions were outborn, serious infections were the most common cause of admission for infants under 2 months of age [15•]. In their review of sepsis neonatorum of 1981, Siegel and McCracken [16] suggested that the primary site of invasion was most often the bloodstream, with spread to the meninges in 25–30% of cases. Other clinical entities included acute respiratory infection, diarrhoea, and omphalitis, itself associated with neonatal tetanus. In clinical series, congenital and neonatal pneumonias are often grouped with sepsis and meningitis because of the overlap in symptom constellations. The Kenyan study [15•] looked at 432 early neonatal and 260 late neonatal admissions. Sepsis accounted for 30% of early neonatal admissions, tetanus for 6%, and meningitis for 1%. In the late neonatal period, sepsis accounted for 60% of admissions, tetanus for 7%, and meningitis for 4% [15•]. Stoll's reviews [11,12] put the global incidence of neonatal sepsis at 5–6 per 1000 live births and that of meningitis at 0.7–1 (2.4–16 in South and South-East Asia, 6–21 in sub-Saharan Africa, and 1.8–12 in the Middle East and North Africa) [11]. Estimates of case fatality rates for neonatal infections range from 13% to 45% [11,12]. There is some evidence that infants delivered to poorer families at home have higher case fatality rates, but this may also reflect later consultation [17].

Community-based studies are rare and vary in their classification of neonatal sepsis. In a prospective study of 329 births in rural Guatemala [18], infection was the largest cause of morbidity and mortality. Mortality from infectious illness was more common in the early neonatal period and in preterm and low-birth-weight infants, although the majority of illnesses occurred in term infants of normal birth weight. In Maharashtra, India, Bang and colleagues [19] employed village-based female health workers to describe the burden of morbidities by using a clinical algorithm. At the time, 95% of births took place at home, the infant mortality ratio in the area was 73 per 1000 live births, and the prevalence of low birth weight was high (42%); 763 neonates were observed and 17% developed clinical features suggestive of sepsis. Although it is possible that the clinical ascription of sepsis was over-inclusive, the case fatality rate in infants in this category was 18.5%, even when the subjects were treated with oral antibiotics. The investigators noted that no neonate was seen at a primary health centre, and that if all who merited a visit had been seen, the primary health-care system would have been overloaded.

Bacterial aetiology

Reviewing 18 hospital-based studies in 1989, a WHO expert group concluded that the aetiology of community-acquired pneumonia – and, by implication, sepsis – in young infants in developing countries was unknown [20]. Subsequently, the WHO Young Infants Study Group attempted to describe pathogenic organisms in young infants as close to community settings as possible. Four country sites were involved: a hospital in Addis Ababa, Ethiopia [21], a research institute in Alabang, the Philippines [22], a base hospital in the eastern highlands of Papua New Guinea [23], and two sites in the Gambia (a first-level facility and a referral hospital) [24]. Infants were enrolled on presentation at under 3 months of age, using a formalized sequence of assessment and investigations; 8418 infants were triaged, 4552 enrolled, and 2398 investigated [25,26].

In the neonatal period, the commonest blood-culture isolates were *Staphylococcus aureus* (23%), *Streptococcus pyogenes* (20%), and *Escherichia coli* (18%). Cerebrospinal fluid isolates were period-specific. Early neonatal meningitis was predominantly caused by Gram-negative micro-organisms, and late neonatal meningitis was caused by roughly equal numbers of Gram-negative micro-organisms and *Streptococcus pneumoniae*, particularly of serotype 2. This trend was supported by the tendency for post-neonatal meningitis to be dominated by *Strep. pneumoniae*, which accounted for 43% of proven bacterial meningitis. There were differences between sites: *Staph. aureus* was commoner in the Gambia (possibly the result of a high prevalence of scabies), *E. coli* in Ethiopia [21], *Salmonella* in the Philippines [22], and *Strep. pyogenes* in Papua New Guinea [23]. At the same site, nasopharyngeal aspirates were positive for *Chlamydia trachomatis* in 33% of severe pneumonias – an issue that requires further study [27]. Despite the investigators' efforts, the sampling frame was hospital-based, so the recruitment pool would have omitted infants who did not present to a facility. This is true of almost all previous and subsequent studies, of which there have been many, and of which a brief summary follows.

There appears to be regional variation in the split between Gram-positive and Gram-negative pathogens.

The split has been about even in studies from sub-Saharan Africa, but Gram-negative micro-organisms have been more common in Asian studies [11,25,26]. In all series, the most common Gram-negative pathogens have been *Klebsiella* species and *E. coli* [15•,17,28–37]. It is quite likely that *E. coli*, a more common isolate in outborn neonates and in vaginal swabs from women in rural areas [38], reflects community patterns of colonization and infection. *Klebsiella* species have often been isolated in hospital series and are often implicated in nursery outbreaks [39,40]. Other important pathogens have been found to be *Pseudomonas* and *Enterobacter* species. The most common Gram-positive isolate has been found to be *Staph. aureus* [17,28,31,33,34,36,37,41,42]. Studies from the Caribbean yield similar isolates, but show the effect of nosocomial outbreaks of *Pseudomonas* infection [43] and a rising incidence of neonatal sepsis associated with group B streptococcus [44,45].

It is difficult to generalize about the importance of group B streptococcal infection. Until recently, the limited role of group B streptococcus in neonatal sepsis in developing countries was a point of discussion [11,25,26]. It accounted for less than 1% of infections in Asian studies and about 8% in African studies, which is surprising in view of the possibility that maternal colonization levels appeared similar to those in high-income countries [11]. In a 10-year retrospective series from a tertiary care perinatal centre in Vellore, India, the incidence of symptomatic early neonatal group B streptococcal bacteraemia was as low as 0.17 per 1000 live births [46]. The problem may be increasing, however [15•,42]. It is not clear whether group B streptococcal sepsis runs, to some extent, in parallel with the epidemiological transition, or whether there is a connection with clustering in hospital births [47–49]. Regular monitoring of pathogens in institutional centres is necessary in order to pick up evolving patterns of infection. Identification of rising rates of group B streptococcal infection allows screening and response protocols to be put in place, in the absence of which case fatality rates can be as high as 60% [50].

Bacterial susceptibility

Ampicillin and gentamicin are currently recommended as first-line antimicrobials [26,42,51], ampicillin replacing the previous recommendation of penicillin [52]. An antistaphylococcal agent such as cloxacillin may be added when scabies or pustular skin lesions are present, and a third-generation cephalosporin should be considered for suspected meningitis. The emergence of resistant pathogens is a problem for both institutions and communities. Rahman and colleagues [36] ably summarize the situation in many areas: lack of control of antibiotic use, little legislation on prescription, over-the-counter sale of antibiotics, poor sanitary conditions, a lack of basic facilities that would help hand-washing, and a lack of surveillance for standards of health-care facilities. Although it is not clear how much institutional spectra of resistance are applicable to the community, institutional infection control presents its own problems [53]. Degrees of resistance vary: some centres report low levels [28,54], while others report rapid increases in multidrug-resistant neonatal infections [30,31,34,36,37,55]. In unusual but worrying situations, first-line therapy comprises vancomycin and amikacin or a carbapenem [34].

Reducing the burden of neonatal bacterial infection

The importance of neonatal survival in developing countries has been addressed over the last decade by a number of reviews, working groups and alliances [3,8•,11,56–62,63•,64]. The following list summarizes recommendations for the reduction of neonatal morbidity and morbidity from bacterial infection. These recommendations arise from the above-mentioned sources [3,8•,11,56–62,63•,64], as well as from the WHO initiatives for Essential Newborn Care [65], the Mother–Baby Package [66] and the Integrated Management of Pregnancy and Childbirth [67].

Broad context changes

Improved socioeconomic conditions.
Gender equity and education for women.
Hygiene and sanitation.
Political commitment to improving neonatal survival.

Improvements in general health and health care

Improved access to, and quality of, health services.
Strengthened referral systems.
Integration of health service and community activities, with the emphasis on community-based aspects of care.
Empowerment of mothers.

Improvements in mother and child health care

National strategy to reduce neonatal mortality.
Surveillance of vital events and neonatal outcomes.
Reduced prevalence of low birth weight.
Integration of neonatal survival into existing safe-motherhood and child-survival programmes.
Availability, quality and uptake of antenatal care.
Skilled attendance at delivery.
Clean delivery.
Knowledge of maternal and neonatal danger signs in health workers and families.
Recognition, management and referral of maternal and neonatal problems.
Early exclusive breast-feeding.

Operational activities

Focused antenatal care, i.e. a limited number of visits with specific effective activities.
Antenatal micronutrient supplementation (the evidence for effects on neonatal infection are currently limited).

- Immunization: tetanus toxoid administration before and during antenatal care. Pneumococcal and *Haemophilus influenzae* type B vaccines are under assessment.
- Facility-based and community-based training of birth attendants.
- Diagnosis and treatment of sexually transmitted and urinary tract infections.
- Planning for clean, safe delivery ('birth preparedness').
- Action to address infective complications: partography, limited vaginal examinations, antibiotic prophylaxis for prolonged labour.
- Clean delivery: skilled attendance, hand-washing, use of clean delivery kit, clean cord cutting and clamping, clean cord care.
- Neonatal care: essential training on newborn infant care for health workers, support for breast-feeding, 'rooming in' at facilities, identification of preterm and low-birth-weight infants, kangaroo mother care for low-birth-weight infants, prophylaxis against ophthalmia neonatorum, early immunization, postpartum maternal care linked with newborn care, vitamin A for mothers and infants.
- Home-based diagnosis and treatment of neonatal infections.

It is important to ensure that recommendations are evidence-based. However, the history of the primary health-care movement alerts us to an understandable tendency to dwell on biomedical and technical aspects of the agenda at the expense of the organizational, social and political changes that it demands [68]. There is a wide gap between the requirements and our knowledge of how to meet those needs at operational level. This is particularly true of community-based activities.

An exception is the control of neonatal tetanus: despite setbacks that resulted in shifting of the target date to 2005 [69], there has been steady progress towards the elimination of the infection [70]. Incidence fell by about 75% over the decade to 2000, at which point about 200 000 cases were reported [71]. Activities are currently focused on 57 countries. The key strategies are promotion of clean deliveries (which has implications for other bacterial infections), surveillance and immunization. Routine tetanus toxoid immunization is augmented by supplemental activities, a high-risk approach involving immunization of all women of child-bearing age (in specific areas) with three doses of tetanus toxoid.

Diagnosis and treatment of sexually transmitted infections is becoming a priority, especially with respect to the HIV pandemic. Syphilis infection is particularly relevant to neonatal health, being responsible for stillbirths, low birth weight, preterm delivery and congenital infection [72]. Its prevalence ranges from 1% to 8% [73] among pregnant women attending for antenatal care, but estimates are more reliable in settings with higher antenatal care uptake. In a survey of 22 countries in sub-Saharan Africa, where antenatal care attendance is around 72%, only 38% of attendees were screened and treated for syphilis. This leaves over 1 million women untreated despite the existence of cost-effective tests and treatment [74].

What models do we have for achieving some of the far-reaching and ambitious changes recommended in the above list? The success of the WHO strategy of identification and case management of acute respiratory infection in the community is now clear. However, field activities exclude infants below the age of 2 months who should be referred for management in hospital [75,76]. A meta-analysis of nine community-based trials of case management of pneumonia in preschool children in developing countries (all but one in Asia, the other in Africa) yielded a summary estimate for reduction in all-cause neonatal mortality of 27% (95% confidence interval, 18–35%). The reduction in neonatal pneumonia mortality was 42% (22–57%). Of particular interest was the finding that case management was successful in the neonatal period, and that it allowed for a range of activities that did not necessarily require the use of injectable antibiotics [77•].

The Integrated Management of Childhood Illness strategy of the WHO covers three areas: improving the skills of health personnel in the prevention and treatment of childhood illness; improving health systems to deliver quality care; and improving family and community practices in relation to child health [78]. The activities of the Integrated Management of Childhood Illness have so far excluded the infant under 2 months of age, but neonatal guidelines are currently being drawn up and adapted. Some of the studies mentioned in this review have been explicitly oriented towards this [15•,25,79•], and the ideal would be to dovetail the Integrated Management of Childhood Illness work with the Integrated Management of Pregnancy and Childbirth practice guide [67]. The emphasis of the activities of the Integrated Management of Childhood Illness so far has been on the tools and training of health personnel [80]. This may lead to improvements in quality that themselves encourage greater uptake of services, but there is a danger that health-system and community requirements will achieve less attention [81–83].

A trial of a community-based model designed to improve neonatal outcomes in rural Maharashtra, India, has had a strong influence on current opinion [84]. The non-randomized trial involved 39 intervention and 47 control villages. In the first year of activities, female village

health workers collected data and managed minor illnesses and pneumonia in neonates. In the second year, they undertook case management of neonatal illnesses, including the identification and treatment of presumptive sepsis with intramuscular gentamicin and oral cotrimoxazole. In the third year, health education for mothers and grandmothers was added to the package. Sepsis was suggested by a combination of any two of eight possible symptoms or signs, and hospital treatment was advised, home-based management being a second option. The study described a reduction in neonatal sepsis mortality from 27.5 to 6.6 per 1000 live births. There are some difficulties in interpretation and extrapolation: (1) the non-random nature of the sample and its reliance on two clusters; (2) the inclusiveness of the clinical diagnostic criteria; (3) the stepwise introduction of a number of interventions; and (4) the reliance on a cadre parallel to government staff. Nevertheless, it seems that locally trained workers can undertake case management of neonatal sepsis and administer parenteral antibiotics safely, and efforts are underway to systematize once-daily regimens and safe injection technology. The possibility of home-based care for neonatal illness has been raised, and the next steps are modification of the model, replication and expansion.

Other areas of current research

A number of other issues relevant to neonatal bacterial infection have seen research activity over the last few years.

Reducing micronutrient deficiencies

A link between micronutrient deficiencies – either single or multiple – and neonatal infection is plausible [85]. Although a number of studies are under way, we do not presently have evidence that improvements in micronutrient status, with the exception of vitamin A, would lead to reductions in infection-specific morbidity or mortality [86]. Vitamin A supplementation for children aged over 6 months could reduce childhood mortality by about one-quarter [87], at least part of this being mediated by a reduction in infectious morbidity. However, supplementation for infants in the later neonatal period has not been shown to reduce morbidity [88] or mortality [89]. It is possible that earlier intervention would be beneficial: an Indonesian trial [90] in which most infants received supplements on the first day of life showed a 64% reduction in infant mortality, and an Indian trial [91•] showed a promising mortality reduction in the first 3 months of life when vitamin A supplements were given in the first 48 h. Unfortunately, we do not have evidence that supplementation for mothers during pregnancy reduces neonatal mortality [92]. A double-blind, randomized, controlled trial of multivitamin supplements for pregnant HIV-infected women in Tanzania showed a reduction in low-birth-weight prevalence and an increase in laboratory measures of maternal immunocompetence [93], but the effects on bacterial infection are unclear.

Neonatal skin care

A recent review explores the possibility that topical application of natural vegetable oils might boost the skin's barrier properties. If this were the case, traditional oil massage might be a means of reducing neonatal infection, especially in preterm and small infants [94]. Sunflower seed oil accelerated the recovery of mouse epidermal barrier function and electron micrographic ultrastructure, whereas mustard oil – commonly applied in developing countries – was prone to a lack of purity, and caused deterioration in barrier function.

The benefits of breast-feeding

A pooled analysis of data from three developing country studies (Brazil, Pakistan, and the Philippines) looked at the protective effect of breast-feeding against mortality from infectious disease. The pooled odds ratio for infectious mortality associated with not breast-feeding in the first month of life was 5.8 (95% confidence interval, 3.4–9.8). Unfortunately, deaths in the first week were excluded from the analysis [95]. Breast-feeding recommendations in countries with high HIV prevalence are a subject of debate and current research. An example is the study from Kenya in which HIV-infected mothers were randomized to either exclusively breast-feed or formula feed. On one hand, the breast-feeding group showed a higher rate of mother-to-child HIV transmission; on the other, by the time the infants were 2 years old the groups had comparable all-cause mortality [96,97].

Cleansing of the birth canal

A study from Malawi [98] showed a significant reduction in early neonatal infections, admissions and mortality when chlorhexidine was used to clean the birth canal at delivery. This simple, affordable intervention warrants further study.

Prediction of neonatal bacterial infection

A score-based or algorithmic system for identifying presumptive neonatal bacterial infection would be useful given the difficulty of diagnosis [99–101]. In a hospital-based sample from Delhi, India, a respiratory rate of over 60 breaths/min was 88.3% sensitive and 6.3% specific for neonatal pneumonia; chest retractions were 93.2% sensitive and 36.1% specific [35]. The WHO Young Infants Study used regression and receiver–operator modelling to generate a list of 14 historical factors and signs that were independently predictive of severe disease [79•]. The presence of any factor had a sensitivity for severe disease of 87% and a specificity of 54%. A model involving nine factors had slightly lower

sensitivity but greater specificity, but further reductions in complexity were associated with losses of sensitivity. This is a large number of considerations on which to base a simple model for use by rural health cadres. It remains to be tested in settings where more first-week infants are seen and where infants are unselected so that the model has to deal with populations in which the likelihood of serious illness is lower.

Conclusion

Despite the scarcity of research information on bacterial infections in newborn infants in low-income countries, intervention to reduce their burden is a priority. Research should focus on scalable activities at community level, linked with health-system strengthening. This would also provide opportunities for surveillance initiatives and the testing of technical package components.

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