Burden of Neonatal Infections in Developing Countries

A Review of Evidence From Community-Based Studies

Durrane Thaver, MBBS, MSc, and Anita K. M. Zaidi, MBBS, SM

Introduction: Infections are a major contributor to newborn deaths in developing countries. Majority of these deaths occur at home without coming to medical attention. The Millennium Development Goal for child survival cannot be achieved without substantial reductions in infection-specific neonatal mortality. We describe the burden of neonatal infections in developing countries and discuss the need for community-based management approaches to improve survival from neonatal infections in these countries.

Methods: We reviewed community-based studies published since 1990 from developing countries to estimate the rates of neonatal and young infant infections and infection-specific neonatal mortality.

Results: Thirty-two studies reviewed suggest that infections may be responsible for 8% to 80% of all neonatal deaths and as many as 42% of deaths in the first week of life. Eleven reports provided data on incidence of infections in neonates and infants up to 60 days of life. Rates of neonatal sepsis were as high as 170/1000 live births (clinically diagnosed) and 5.5/1000 live births (blood culture-confirmed).

Conclusions: Considerable heterogeneity exists among included studies, and more accurate data and standardized methodologies are required. However, data indicate that a significant proportion of neonatal deaths in developing countries are due to infections. Current recommendations of hospitalization and parenteral therapy for managing neonatal infections are inadequately followed in developing countries. Approaches for detecting and managing serious infections within the community, at home or first-level health facilities, may be more effective options in settings where delays and reluctance to seek care, health system inefficiencies, socioeconomic and cultural, as well as logistic constraints exist.

Key Words: neonatal infections, incidence, mortality, community, developing country

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Almost 99% of the estimated 4 million annual neonatal deaths occur in developing countries.[1,2] Although postneonatal mortality rates have declined substantially, in large part due to successful child survival interventions, deaths in the neonatal period have been largely unaddressed as a global health concern and account for 40% of all deaths in children under 5.[2,3] Despite the current increased efforts, much more needs to be accomplished to reduce neonatal mortality rates from levels as high as 40 to 60 per 1000 live births, and to achieve the Millennium Development Goal for child survival.[2,3]

Although the precise cause of neonatal deaths in developing countries is difficult to ascertain, estimates suggest that infections, including sepsis, pneumonia, tetanus, and diarrhea, are the most common causes.[1,2] Numerous factors contribute to such high incidence of infections and consequent mortality. These include immediate causes such as lack of antenatal care, unsupervised or poorly supervised home deliveries, unhygienic and unsafe delivery practices and cord care, prematurity, low birth weight, lack of exclusive breast-feeding, and delays in recognition of danger signs in both mother and baby.[2,4–9] Underlying factors such as health system inefficiencies, infra-structural, logistic, or economic constraints[2,4–9] also contribute to high rates of infection and infection-associated mortality. In addition, wide inequities exist in health service provision, such that the lowest coverage rates of known effective maternal and child interventions exist within the poorest income groups.[10]

In this article, we review community-based studies to describe the burden of disease from neonatal infections and infection-associated neonatal mortality in developing countries. We also review in later manuscripts, the etiology, antimicrobial resistance, management options, as well as research priorities for serious bacterial infections among neonatal and young infants in developing country community settings.

METHODS

Studies reporting rates of infections in young infants (up to 60 days of age) in community settings were identified through a search of PubMed (date of last search May 7, 2007) unrestricted by year, using combinations of the words infant*, neonat*, newborn* with communit*, "community acquired" and incidence, rate, "1000 live births" and infection*, sepsis, septic*, bacter*, cross-linked with names of all middle and low income countries, as defined by the World Bank[11] [adding an asterisk in the search term allows the search to also locate variations or expansions of the word—eg, neonate, neonatal, neonates]. Related links to a key review on neonatal infections in developing countries were also screened.[4] To identify studies reporting infection- specific neonatal mortality rates in communities, the search was restricted to 1990 onwards, with additional words such as death*, mortality, "neonatal mortality rate." The search was supplemented by screening articles in the author's collection, studies identified in other searches conducted for this review series, and relevant references from an earlier review.[6]

Community-based studies, defined as home-based surveillance, population surveys, or those conducted in first-level health facilities, where information on live births in the study population was available, were included. Studies not reporting live births or an (estimated) denominator, or adequate information for its derivation, were excluded. Studies reporting the impact of specific maternal and child interventions on mortality were also excluded, unless data were available for comparison arms. Data were extracted for all infections including sepsis, meningitis, pneumonia, tetanus, gastroenteritis, or related symptoms and/or categories. Some approximations were necessary when data were incomplete or when substantial proportions were missing, eg, applying proportion of infection-related deaths reported for a specific time period to mortality rates reported for an aggregated time-period. Confidence intervals (binomial exact) for all-cause and infection-specific rates were obtained using STATA version 9.2, using live births and number of deaths.

From the Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan.
Supported by Saving Newborn Lives (program funded by Bill and Melinda Gates Foundation), Save the Children, USA, and World Health Organization.
Address for correspondence: Anita K. M. Zaidi, MBBS, SM, Department of Pediatrics and Child Health, Aga Khan University, Karachi, Pakistan. E-mail: anita.zaidi@aku.edu.

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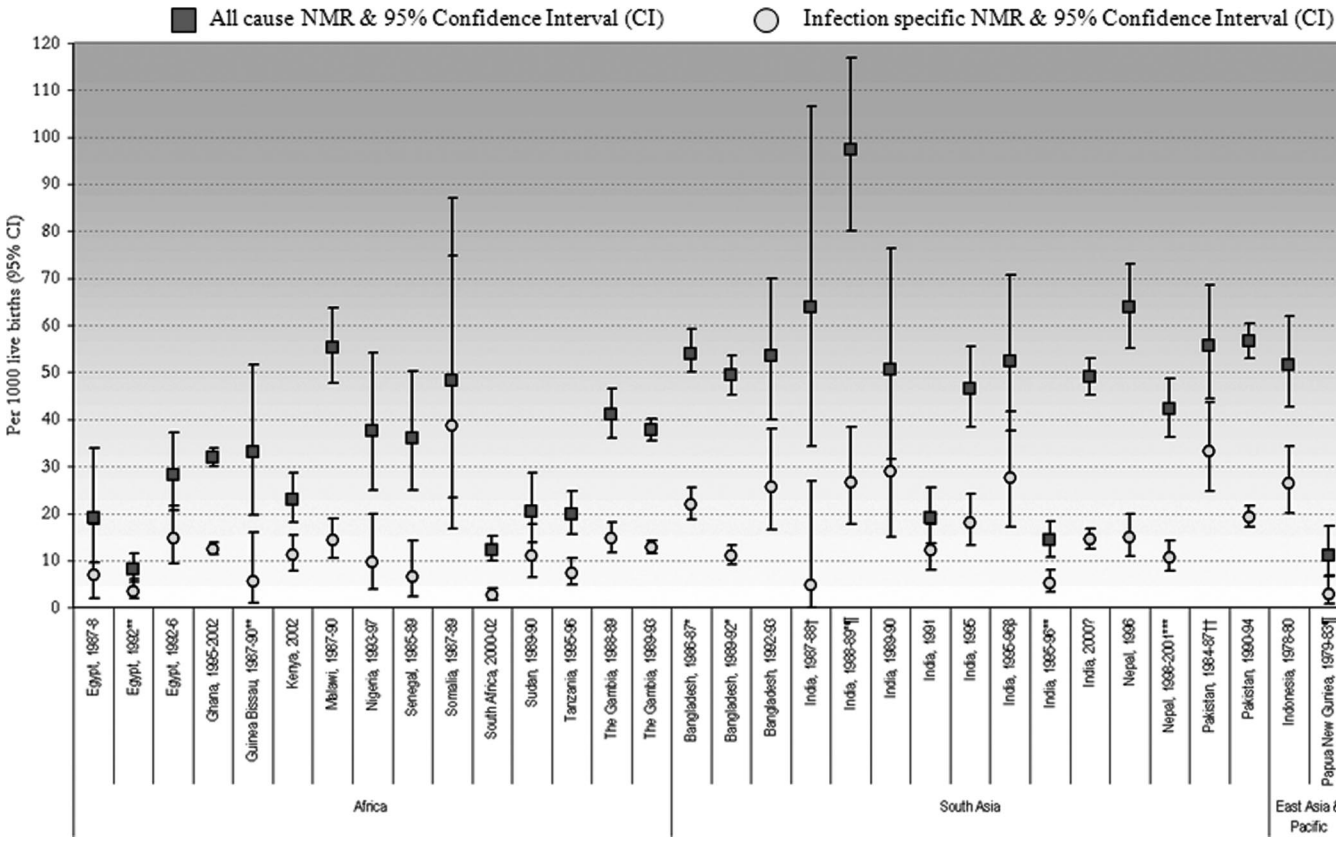

FIGURE 1. Infection specific and all cause neonatal mortality rates in community based studies from developing countries. NMR indicates neonatal mortality rate; ¶ = pneumonia only. Other causes were not available or could not be disaggregated; * = data extracted from comparison or control community; ** = urban, urban slums or semi-urban area. Rural area did not report any neonatal deaths in study from Egypt, and was excluded; †† = includes village, urban slum, peri-ruban slum and upper middle class population; ? = year of study not reported, is an approximate; † = routine antenatal care was given to pregnant women followed; *** = may be over-estimated, since data not available for some neonates who were assigned multiple causes of death by physicians; β = "observation phase" (minimal interventions) of studied conducted in rural Gadchiroli, India.

RESULTS

Infections as a Major Cause of Neonatal Morbidity and Mortality

We reviewed 32[12–43] community-based studies published since 1990. Individual studies, conducted retrospectively or prospectively, included as few as 200 and as many as over 33,000 live births. The all-cause mortality ranged from 8.1 per 1000 live births (95% CI, 5.5–11.6) in urban and semi-urban areas of Egypt to as high as 97.2 (95% CI, 80–116.8) in rural Indian villages. Infection-specific mortality rates ranged from 2.7 (95% CI, 1.6–4.2) reported from South Africa to 38.6 (95% CI, 16.8–74.7) per 1000 live births in Somalia.[12–43] Overall, these reports suggest that between 8% and 80% (median, 36.5%; interquartile range, 26%-49%) of all neonatal deaths in different regions of the developing world are due to infectious causes (Fig. 1)–representing a substantial burden of avoidable neonatal deaths. In the first week of life, during which three-fourths of all neonatal deaths are estimated to occur,[2] the studies reviewed[12,17,20,35,37,39,41,42,44–46] suggest that as many as 42% of neonatal deaths can be attributed to infections (Fig. 2).

Incidence of Serious Neonatal and Young Infant Infections

There were very few community-based studies from developing countries, which measured the incidence of sepsis in newborns and young infants, and most had biases in selection of study population (Table 1), which may have under-estimated true incidence rates. In addition to variable study quality, the lack of laboratory-based confirmation of neonatal sepsis as well as varied clinical criteria and methodology used to diagnose neonatal sepsis limits comparability across the 11 reports identified[17,44,47–58] (Table 1).

Clinically diagnosed neonatal sepsis ranged from 49 per 1000 live births in babies older than 24 hours of life in rural Guatemala,[47] to as high as 170 per 1000 live births detected by village health workers in rural India.[51,56] A first-level facility in Kenya estimated a minimal rate of blood culture confirmed sepsis of 5.5 per 1000 live births among neonates presenting to this facility.[57] In the absence of active household surveillance, however, the true incidence is expected to be significantly higher.

The incidence of neonatal meningitis among studies reviewed ranged from 0.8 in the first week of life to 6.1 per 1000 live births.[17,44,47,52] The only study based on regionally representative surveillance data reports 4.2 cases of bacterial meningitis per 1000 child-years in infants below 2 months of age.[52] Estimated incidence of severe pneumonia was 142 episodes per 1000 child-years of observation among infants seen at first-level rural health centers in Lombok, Indonesia.[53] A study from Egypt[58] reported high rates of acute respiratory infections (201 per 1000 live births) based on

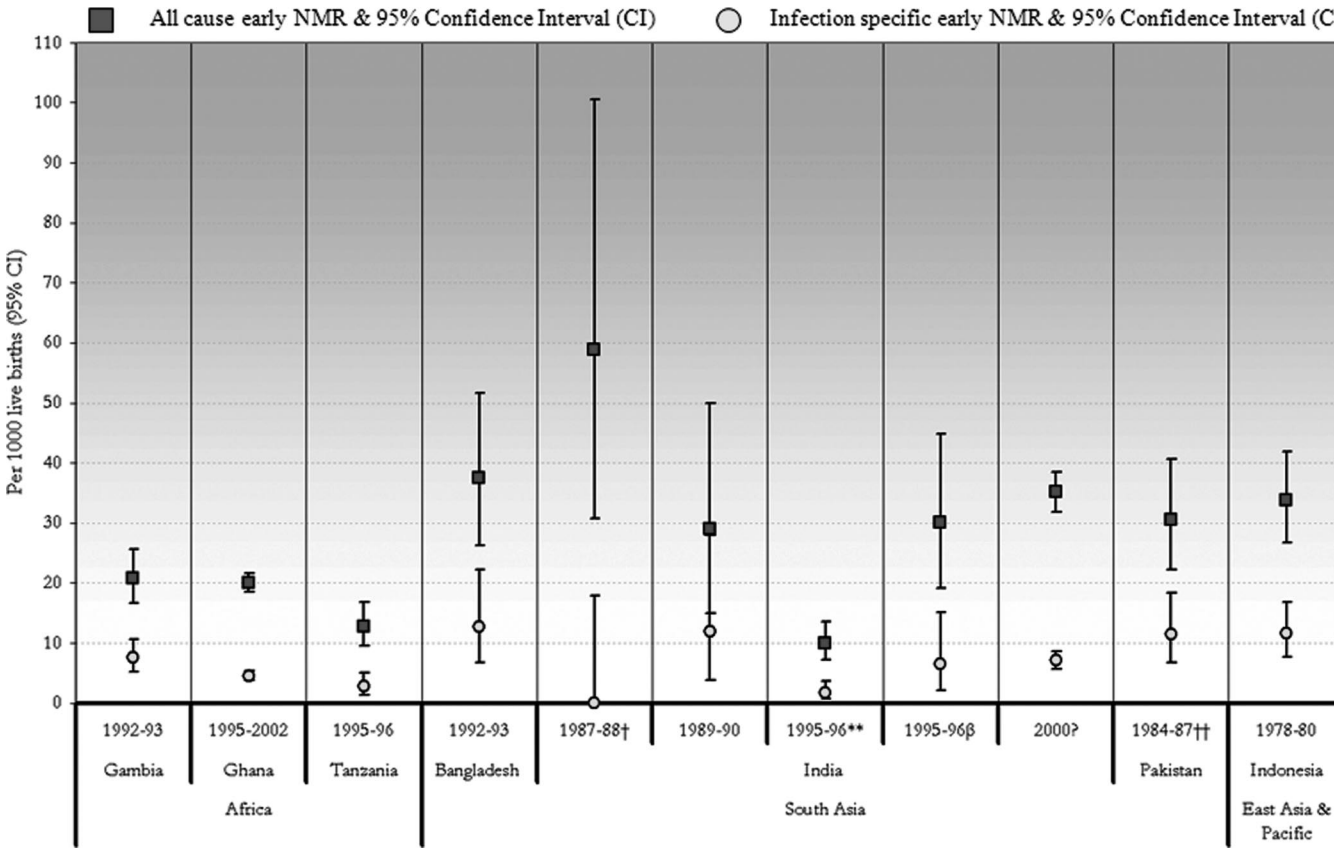

FIGURE 2. Infection specific and all cause early neonatal mortality rates in community based studies from developing countries. NMR indicates neonatal mortality rate; ¶ = pneumonia only. Other causes were not available or could not be disaggregated; * = data extracted from comparison or control community; ** = urban, urban slums or semi-urban area. Rural area did not report any neonatal deaths in study from Egypt, and was excluded; †† = includes village, urban slum, peri-ruban slum and upper middle class population; ? = year of study not reported, is an approximate; † = routine antenatal care was given to pregnant women followed; *** = may be over-estimated, since data not available for some neonates who were assigned multiple causes of death by physicians; β = "observation phase" (minimal interventions) of studied conducted in rural Gadchiroli, India.

maternal recall of infant morbidity at 1-month follow-up. Rates of diarrhea ranged from 30 to 156 per 1000 newborns among studies of heterogeneous quality[17,50,51,56,58] (Table 1).

DISCUSSION

Limitations of Available Evidence on Causes of Death

The studies reviewed and data presented are limited by substantial inter- and intracountry variation, methodological heterogeneity in population selection and completeness of follow-up, as well as possible misclassifications and/or biases in cause of death ascertainment. The main reason for such inaccuracies includes lack of vital registration or surveillance systems in developing countries, where the majority of babies are born, and succumb to infections, within their homes–seldom, if ever, coming to medical attention.[2,59] Other reasons compounding uncertainty include lack of standardization as well as inherent limitations of verbal autopsy tools, comorbid, and often multiple causes of neonatal death.[40,42,46,59–62] Sparse data from regions of the world, such as Sub-Saharan Africa, where the highest burden of childhood illness lies, also limits the generalizability of these data.[61]

Accurate information on causes of death is crucial to designing intervention programs and monitoring progress and sustainability of interventions as well as providing data for intracountry and regional comparisons.[1,62]

In addition to data on cause specific mortality, more information on incidence of neonatal infections is required to obtain accurate estimates. Very few studies have addressed this issue in developing countries, where deriving accurate incidence rates would require household surveillance capturing all births that occur at home. The information available is further limited by the lack of sensitive and specific tools to diagnose neonatal sepsis. On the one hand, using clinical signs to diagnose neonatal sepsis based on features such as rapid breathing or lethargy may be overly nonspecific, resulting in misclassifying respiratory distress syndrome, and birth asphyxia, as sepsis. On the other hand, blood cultures are often negative in neonates in whom there is strong clinical and circumstantial evidence of sepsis. This is most likely the explanation for the wide range of incidence rates reported from developing countries, ranging from 170 per 1000 live births observed by Bang et al in rural India, based on active household surveillance of newborns by village health workers, using a clinical algorithm detecting clinical signs of serious illness,[51,55] and a blood culture confirmed rate of neonatal sepsis of 5.5 per 1000 live births reported by Berkeley et al from rural Kenya.[57] However, it is important to note that there are no

TABLE 1. Incidence of Infections in Young Infants in Community Settings

Study	Year and Location	Setting and Sample Selection (A, B, C, D, E)	Data Collection	Incidence
Jalil et al[44] and Zaman et al[48]	1984-1997 4 communities (urban slum, per-urban slum, village, upper middle class) in Lahore, Pakistan	(B) Pregnant women were identified from baseline survey (excluding upper middle class community) (Pregnant women from upper middle class identified via obstetricians) [(C) if with upper middle class]	Newborns observed during 1st week of life (excluding 240 births from upper middle class families)	Clinical sepsis: 21 per 1000 live births (26/1236 newborns) Meningitis: 0.81 per 1000 live births (1/1236 newborns) Respiratory infection: 5.7 per 1000 live births (7/1236 newborns) Diarrhea: 4.9 per 1000 live births (6/1236 newborns)
			Monthly incidence among all examinations from birth to 2 mo follow-up (all 4 communities)	Sepsis: 0.4% Meningitis: 0.1% Infectious diseases: 0.5% Lower respiratory tract infection: 1.9% Diarrhea: 13.8% among 3130 examinations
Bhardwaj and Hasan[17]	1987-1988 4 villages, Uttar Pradesh, India	(C) Pregnant women were identified by home visits within specified distance of unspecified location in 4 randomly selected villages	Follow-up of pregnant women until 6 wk post-partum. Routine antenatal care was provided	Pneumonia: 24.5 per 1000 live births (5/204) Meningitis: 4.9 per 1000 live births (1/204) Diarrhea: 132 per 1000 live births (27/204)
Bartlett et al[47]	1988-1989 Rural community, Guatemala	(C) Pregnant women and newborns were identified from all potential sources (community midwives, families, government health post, field workers, municipal birth registers)	Follow up of infants surviving birth and 1st day of life	Clinical sepsis: 48.6 per 1000 live births (16/329) (12 probable, 2 each sepsis with omphalitis and meningitis) Sepsis with meningitis: 6.1 per 1000 live births (2/329)
Etuk et al[49]	1996-1997 Calabar, Nigeria	(E) Deliveries were identified from hospital booking and delivery registers	Follow up of women booked for antenatal care at hospital, but who delivered outside health facilities	Neonatal infection/tetanus: 65.5 per 1000 live births (22/336) among babies born outside health facilities
Bang et al[51] and Bang et al[56]	1995-1996 39 villages in Gadchiroli, India	(B) Pregnant women identified by village health workers	Live births followed during observational phase of study	Clinical sepsis (sepsis, meningitis, severe pneumonia): 170 per 1000 live births (130/763 live births) Pneumonia: 10.5 per 1000 live births (8/763) Diarrhea: 55 per 1000 live births (42/763)
Berkley et al[57]	1998-2002 Rural district referral hospital, Kenya	(D) Rural referral facility.	Minimal incidence among admitted neonates	Neonatal bacteremia: 5.46 per 1000 live births (denominator used was estimated live births in catchment population)
Weiss et al[52]	1997-1998 Population based surveillance, Campinas Health Department, Brazil	(B) Mandatory requirement of reporting of all cases of meningitis	Cases reported from inpatients, outpatients, emergency rooms, death certificates, autopsies and telephone calls	Bacterial meningitis: 4.2 cases per 1000 child-years in infants up to 2 mo of age
Sutanto et al[53]	1998-1999 50 villages, Lombok Island, Indonesia	(D) First level facilities in villages. Information on births during study period was obtained from village clinic records	All children from study villages who were seen at Village Health Center, admitted for pneumonia or who died during study period were included	Severe pneumonia in < 2 mo: 142 per 1000 child-years (211/1490 child-years) Hospitalized pneumonia: 112 per 1000 child-years (167/1490 child-years)
Vaheetra et al[50]	1995-1998 Rural Malawi	(D) Enrolled antenatal care attendees at free health center in rural area	Mean monthly episodes of illness on monthly visits among 703 infants	Acute respiratory infection: 90 per 1000 live births Diarrhea: 30 per 1000 live births
Mansour et al[58]	1995-1997 Districts in Egypt	(C) Health facilities, traditional birth attendants and families were used to identify deliveries in 6 districts (Sample of pregnant women followed up in 2 selected districts)	History of morbidities in low birth weight and normal birth weight infants at 1 mo follow up	Acute respiratory infection: 201 per 1000 live births (360/1792) Diarrhea and vomiting: 156 per 1000 live births (279/1792)

(*Continued*)

TABLE 1. (*Continued*)

Study	Year and Location	Setting and Sample Selection (A, B, C, D, E)	Data Collection	Incidence
English et al[54,55]	1999-2001 Kilifi district rural referral hospital, Kenya	(D) Rural referral facility-born cohort	Unsolicited outpatient consultations and treatment episodes among infants under 60 d of age who were born at the hospital	Acute respiratory infection: 81 per 1000 live births (38% of 467 outpatients among 2189 live births)
			During follow-up of hospital-born births	Rate of admissions, or deaths attributed to severe infections: 1/1000 infant days within first 27 d of life

Sample selection classified as: A = national or nationally representative; B = representative of a local region, but not national or nationally representative; C = representative of a local region, but with selection bias; D = rural racility-based; E = urban facility-based (with data for outside facility births).

published data on population-based rates of blood-culture confirmed neonatal sepsis from countries where the majority of births take place at home. The study by Berkeley et al from Kenya did not undertake active household surveillance for sick newborns, and the data reported are from newborns presenting to a hospital facility within the catchment area, and therefore may be significant underestimates.[57]

Despite the glaring limitations in the quality and quantity of data discussed above, studies consistently implicate infections as a major cause of neonatal morbidity and mortality in the developing world. Evidence-based strategies for prevention and management of newborn infections in low-income countries are thus urgently needed.

Rationale for Community-Based Approaches for Management of Newborn Infection in Developing Countries

Current WHO recommendations for treating serious bacterial infections in infants under 2 months of age include hospitalization and 10 days of parenteral therapy.[63–66] However, these recommendations are inadequately followed in developing countries with high burden of neonatal deaths–due to logistic and resource constraints–and socio-cultural factors such as confinement after birth, unwillingness of families to seek care outside the home, and frequent rejection or refusal of allopathic or facility-based care.[35,47,51,67–69] Moreover, because of delays in care seeking, inadequate or poor quality care, unhygienic handling and feeding, contaminated hospital equipment, and multiresistant hospital-acquired pathogens, case fatality rates for sepsis among hospitalized babies treated with recommended therapy are as high as 30% to 50%.[4,6,70] These findings suggest that alternate approaches for prevention, early detection, and management of neonatal infections, such as those implemented within the community or home, may have a greater impact in reducing neonatal mortality in the near-term.

Community or home-based approaches are being increasingly evaluated to deliver preventive and curative services, frequently through local community health workers.[71] Substantial reductions in neonatal mortality have resulted from community-level case management of neonatal pneumonia,[13,72] and of neonatal sepsis, delivered together with home-based care in rural India.[73] To extend this successful program to a larger population, India's recently developed neonatal Integrated Management of Childhood Illness program also incorporates a component for home-based care of the neonate in the first week of life.[74] A recent large randomized controlled trial in rural Bangladesh has also demonstrated significant reduction in neonatal mortality rates with a package of home-based care including antibiotic therapy for sick newborns where referral failed.[75]

Such approaches, by utilizing a local cadre of community workers, may ensure higher and more equitable coverage, may improve care seeking, be more cost-effective, have greater acceptability in the community, and may also ensure better adherence to case management guidelines and protocols.[71] Prompt detection and treatment of neonatal illness at the community level may also prevent adverse sequelae of serious infections.[76]

There is continued need for development and validation of simplified diagnostic algorithms, in addition to development of evidence-based treatment guidelines, to enable minimally trained health care workers to effectively manage neonatal sepsis during home-visits, or at first level facilities.[77] In addition to research addressing numerous health system challenges and constraints for implementation and sustainability, an exploration of etiological agents, drug resistance patterns, and antibiotic regimens is required before community-based case management strategies utilizing antibiotics can be employed on national scales in developing countries with high burden of neonatal mortality.

These issues are discussed further in related articles in this supplement, which aims to (1) describe the pathogens causing serious bacterial infections among neonatal and young infants in developing country community settings; (2) antimicrobial resistance patterns of major etiological agents causing these infections; (3) treatment options for management of these infections in community settings, including a pharmacological appraisal of potential antimicrobials; and (4) identify research gaps and future directions.

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