Management of Newborn Infections in Primary Care Settings

A Review of the Evidence and Implications for Policy?

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Background: Long-term, sustainable programs to address high incidence and death rates from neonatal infections are required for improving child survival. There is an urgent need to define the role of community-based management for neonates with serious bacterial infections—-both at home and at first-level facilities.

Methods: We reviewed available evidence for community-based antibiotic management strategies for serious neonatal infections.

Results: Nine distinct studies contributing data for community-based management of neonatal pneumonia and sepsis were identified. In a pooled analysis of 5 controlled trials of community-based management of neonatal pneumonia (4 using cotrimoxazole, 1 ampicillin, or penicillin), all-cause neonatal mortality showed 27% [95% confidence interval (CI): 18%–35%] reduction and pneumonia-specific mortality, 42% (95% CI: 22%–57%). Substantial reductions in neonatal mortality have been demonstrated in a nonrandomized controlled study in rural India (62% reduction, $P < 0.001$) and in a cluster randomized trial in rural Bangladesh (34% reduction, 95% CI: 7%–53%). Reduced case fatalities (0%–3%) with community-based management of neonatal sepsis were observed in 2 small uncontrolled studies from India and Guatemala and a recent randomized trial from Pakistan.

Conclusions: Although methodological limitations preclude estimating the precise contribution of antibiotics toward neonatal mortality reduction in community settings in low income countries, available data suggest substantial benefit of case management approaches using antibiotics for neonatal sepsis in such settings.

Key Words: neonatal, sepsis, pneumonia, case management, community

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Of the 4 million neonatal deaths in developing countries, a large proportion occur in domiciliary settings due to poor health service coverage, shortage of health care providers, and limited or lack of access to referral services and facilities.[1,2] In addition, there is evidence to suggest that domiciliary care and care seeking practices may differ according to sociocultural norms[3] and may also be influenced by gender issues.[4] Appropriate strategies are needed for prevention of infections, as well as interventions for the domiciliary care and referral of newborn infants who develop bacterial infections. In several resource poor situations where prompt referral to a facility is not possible, health workers may have no alternative but to provide domiciliary care for the treatment of serious neonatal bacterial infections.[3,5–7]

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Figure 1 indicates a conceptual model for the prevention and treatment of neonatal bacterial infections, given various risk factors. The model includes a range of preventive strategies that may act in synergy with therapeutic strategies to improve neonatal survival and can be incorporated together into packages of maternal and newborn care for potential scale up in primary care settings.[8,9] Therapeutic strategies encompass both domiciliary care as well as care provided through first level community clinics and health outposts, frequently staffed by paramedical and nursing staff. The latter cadres may either work at these outposts or through outreach services delivering a mix of preventive and therapeutic interventions for maternal and newborn care.[10]

An in-depth evaluation of the evidence-base for preventive strategies is beyond the scope of this review, which focuses primarily on antibiotic management strategies for neonatal infections in developing country primary care settings. Recent studies of home treatment of sick newborns in rural India[5] and Bangladesh[7] have demonstrated significant reductions in neonatal mortality and have proven the feasibility of such approaches. This review examines the evidence base of home-based and first-level facility-based studies of treatment of neonatal bacterial infections. There are several context-specific assumptions on which community-based management of neonatal infections is being advocated (Table 1). Other issues such as criteria for selection of appropriate oral and/or parenteral antibiotics for use among neonates in appropriate settings, as well as pharmacological properties are explored in other articles of this series.[11,12]

METHODOLOGY

We searched PubMed (last search in February 2008) for relevant studies conducted in countries classified as middle and low income economies using standardized search criteria for studies of community-based treatment of serious neonatal infections[13] We reviewed all available observational reports, randomized controlled trials, systematic reviews, and meta-analyses, which included neonates and principally involved the management of serious neonatal infections in primary care (home or first-level facility) settings. Studies evaluating multiple interventions, which included community-based antibiotic case management for neonatal infections, were also reviewed. The available evidence was analyzed for neonatal mortality rates and case fatality with various regimens, antibiotic choice and duration, comparison data where available, delivery strategies, as well as methodological issues and other limitations. We excluded interventions that had principally been implemented in secondary or higher level facilities with little possibility of introduction in primary care settings.

RESULTS

Characteristics of Included Studies

Eleven distinct studies contributed data for neonates in this review[6,7,14–22] plus an unpublished study (Zaidi et al, unpublished data 2007). These studies encompassed community-based management of pneumonia (2 studies, data in 4 published reports[14,20–22])

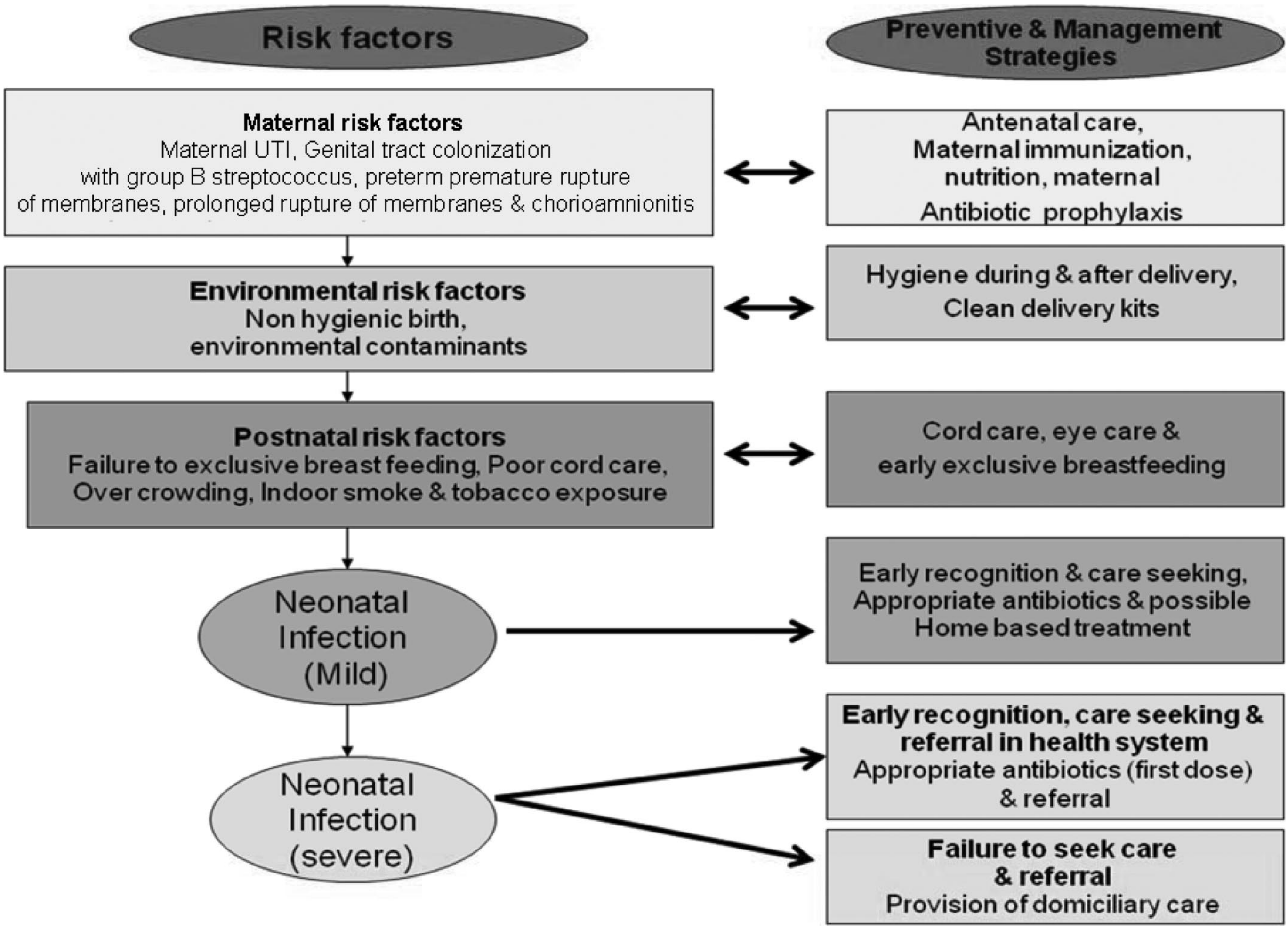

FIGURE 1. Conceptual framework of risk factors for serious neonatal infections and intervention strategies.

and sepsis (4 studies, data in 6 published reports[5–7,15,16]). Although studies of case management of pneumonia, which did not report disaggregated data for neonates were not included[17–19,23–30]; we included a meta-analysis[31] of 5 trials of community-based management of pneumonia,[14,17–20] which did obtain disaggregated data for neonates from 3 of the aforementioned excluded studies.[14,17,19] Two studies contributing to the meta-analysis, which provided disaggregated data for neonates in their original report, have been discussed in greater depth in this review.[14,20]

Tables 2 and 3 describe characteristics of studies included, namely study location, design, number of neonates included, antibiotic regimens used, additional preventive or therapeutic interventions employed, delivery strategy, and outcomes such as neonatal mortality rate and infection-specific mortality rate in treated compared with untreated neonates, or baseline or comparison mortality rates, where available, for studies of primary diagnosis of neonatal pneumonia (Table 2) and neonatal sepsis (Table 3). All community-based studies reviewed (Tables 2 and 3) used clinical criteria for sepsis and/or pneumonia; none undertook laboratory investigations and hence did not contribute any bacterial etiology or antimicrobial susceptibility data.

Evidence for Community Management of Newborn Pneumonia

As highlighted in Table 2, the major body of evidence for the benefit of community-based case management of neonatal pneumonia is synthesized in the meta-analysis[31] of 5 trials included conducted in India, Pakistan, Nepal, Tanzania, and Bangladesh[14,17–20] which compared case management of neonatal pneumonia in community settings with a control group. Only 1 study, conducted in Tanzania, was reported as a randomized trial. Various antibiotics were used—most commonly oral cotrimoxazole.[14,18–20] A variety of other interventions of varying intensity accompanied antibiotic case management in all intervention areas, including household visits, family mobilization, and immunization.[31] All trials showed reduction in all-cause and cause-specific mortality in neonates, although this was statistically significant in only 2 trials, from India and Bangladesh.[14,17] The pooled analysis showed a significant reduction in pneumonia-specific neonatal mortality of 42% [95% confidence interval (CI): 22%–57%; 4 trials],[14,17,19,20] as well as a significant reduction in the overall neonatal mortality rate (NMR) of 27% (95% CI: 18%–35%; 5 trials).[14,17–20]

Pneumonia Case Management Trials Reporting Disaggregated Data for Neonates

A trial[20] in a remote mountainous area of Nepal (which is included in the pneumonia case management meta-analysis),[31] presented disaggregated data for neonates. It evaluated a community health worker-administered program of active case detection of childhood pneumonia (respiratory rate of ≥50/min or chest in-

TABLE 1. Factors Determining Approaches to Community Management of Neonatal Sepsis

Overarching Considerations	Health System Preparedness	Availability of Community Health Care Providers	Family and Household Factors	Information Determining Antibiotic Choice and Route of Therapy
Development of an overall strategic plan for managing serious neonatal infections	Outreach services capable of supporting community health workers	Community health workers available for household visits and case detection	Care seeking practices for newborns and gender related behaviors	Local microbiology and antimicrobial resistance patterns
Epidemiological data suggestive of high burden of neonatal sepsis in domiciliary settings	Linkages with various tiers of the health services for referral and effective care	Community health workers trained to detect serious neonatal infections	Access to health services and emergency transport	Availability of common antibiotics effective for above pathogens
Patterns of care seeking and access suggestive of the need for community based care	Health information systems capable of supporting community care strategies	Community health workers trained in recognition of serious infections in newborns and young infants	Willingness to sustain regular access and supervised treatment in community clinics/ health centers	Availability of antibiotics for daily delivery, preferably once daily dosages in suitable form (eg, Uniject)
		Community health workers authorized to treat with oral or injectable antibiotics	Acceptance of home care	

drawing) and home-based treatment with 5 days of oral cotrimoxazole. There were no facilities for referral and children who failed therapy were given oral chloramphenicol. Mothers were educated on signs of pneumonia and care seeking. Among neonates with early-onset pneumonia, there was a reduction in risk of death by 20% by the third year of intervention, although this was not statistically significant (0.80; 95% CI: 0.59–1.10).[20] In further analysis, a statistically significant reduction, however, of 26% (0.74; 95% CI: 0.58–0.94) was found among infants aged 7 days to 5 months.

In the quasi-experimental pneumonia case management trial conducted by Bang et al[14,21,22] in rural Gadchiroli—an underdeveloped rural district in Maharashtra, India—births and childhood deaths from 1988 to 1991 were prospectively recorded in 58 intervention and 44 adjacent control villages. Interventions included intensive training of paramedics, village health workers (VHWs), and traditional birth attendants (TBAs) in the examination of sick neonates and children, and recognition and treatment of pneumonia (presence of cough and a respiratory rate >50/min) with cotrimoxazole syrup and advice on continued breast-feeding. Referral was advised for very sick neonates, but if this was refused by families, they were managed at home with cotrimoxazole. In the combined analysis of 4620 neonates reported in 1994,[22] pneumonia-specific mortality was significantly reduced by 11.7/1000 live births or 44.3% in the intervention area compared with the control area ($P < 0.001$). The overall mortality rate decreased by 15.9/1000 live births, or 20.2% ($P < 0.01$). Among 90 infants (1.95%) treated for pneumonia, the observed case fatality was 13.3%; it was 24% in the 0 to 7 day old infants treated, and 33% in those with referral indications.

Evidence for Community-Based Management of Neonatal Sepsis

Table 3 describes 4 published studies on community-based management of sepsis, including a nonrandomized quasi-experimental controlled trial,[6] 2 prospective observational studies,[15,16] and 1 cluster randomized trial.[7]

Evidence From Observational Studies

Bartlett et al[15] conducted a year-long, prospective, observational study on infant pneumonia and/or sepsis in a rural community in Guatemala. Three hundred twenty-nine infants surviving birth and the first day of life were followed for the first 3 months of life, biweekly home visits in the first month, and biweekly thereafter. Mothers were educated in detection of newborn illnesses. Thirty-four infants (10%) developed potentially life-threatening infectious diseases (92% of all serious medical problems encountered) and were treated in the community with various regimens (Table 3). The overall case fatality was 14%, and none of the babies managed wholly in the community died. An estimated NMR of 6/1000 live births was calculated using local population-based data, compared with a historical NMR of 39/1000 live births recorded for Guatemala, translating to an 85% reduction ($P < 0.001$) in NMR.

Bhandari et al[16] observed 2007 infants aged 0 to 2 months at 2 first-level facilities (clinics) in urban slums in New Delhi over 12 consecutive months (Table 3). Infants were evaluated by trained pediatricians and hospital admission was recommended for 14% due to severe illness, among which 76% refused and were managed at home or as outpatients. A total of 124 patients with infectious illnesses were treated with oral cephalexin and intramuscular amikacin. The overall case fatality observed was 3.3%.

Evidence From Experimental Studies

In their landmark study,[5,6,24] Bang et al evaluated a home-based package for neonatal care in rural Gadchiroli, India—an area with low female literacy and an extremely high baseline NMR of almost 100/1000 live births. Following baseline data collection (1993–1995), a comprehensive program for neonatal care was introduced in a stepwise manner in intervention villages (Table 3).

The first year of intervention (1995–1996) included visiting pregnant women in their homes, multiple postnatal visits for mother and neonate, training of TBAs in clean delivery, and training of female VHWs (1 per village) in the management of pneumonia (using cotrimoxazole) and other minor illnesses. In the following year, the VHWs were provided with basic resuscitation equipment and a neonatal care package (Table 3) and trained in recognition and home management of sepsis (collectively including sepsis, severe pneumonia, and/or meningitis). Referral was advised for babies with clinical sepsis (based on the presence on any 2 of 6 signs and in the event of refusal, VHWs administered home-based treatment using oral cotrimoxazole twice daily, and intramuscular gentamicin twice daily for 7 days in full-term babies and 10 days in preterm babies, with support for temperature maintenance and encouragement of breast-feeding, along with follow-up twice daily for 7 to 10 days. The package was continued relatively unchanged from 1998 to 2003[5,6,24] with the exception of removal of diarrhea and fast breath-

TABLE 2. Characteristics of Studies of Community-Based Management of Newborn Pneumonia

Author	Study Period	Country	Principal Diagnosis	Age Range	Study Population/No. in Study (Newborns and Young Infants 0–59 Days) (Intervention and Control)	No. Infants Treated	Regimen Used and Duration	Case Fatality Rate (%)	Cause Specific Mortality Rate/1000			Overall Mortality Rate/1000		
									Intervention Group	Control Group	% Reduction	Intervention Group	Control Group	% Reduction
Study design: non-randomized control study														
Bang et al* 1990[14]	7/1988–90	Rural India	Pneumonia	0–28 d	1533 and 1049	NR[†]	Cotrimoxazole 2.5 mL PO for 7 d		20.2	39.1	48.3	67.8	97.2	30.2
Bang et al* 1993[21]	7/1988–12/90	Rural India	Pneumonia	0–29 d	3100 and 2098	65	Cotrimoxazole 2.5 mL BD PO for 7 d	15%[‡]	17.4	29.1	40.2	63.6	83.9	24.1
				30–59 d	2904 and 1923	56		0%	1	4.7	78.7	3.8	8.3	54.2
Bang et al* 1994[22]	7/1988–6/91	Rural India	Pneumonia	0–29 d	4620 and 3226	90	Cotrimoxazole 2.5 mL BD PO for 7 d	13.3%	14.7	26.4	44.3	62.8	78.7	20.2
									Risk ratio (95% confidence interval) for Cause Specific Mortality			Risk ratio (95% confidence interval) for Overall Mortality		
									Intervention vs. Control	% (95% CI) Change		Intervention vs. Control	% (95% CI) Change	
Study design: Meta-analysis of concurrent controlled studies, including study above														
Sazawal and Black 2003[31]	1988–91	India[14]	Pneumonia	<1 mo	1533 and 1049	NR	§	NR	0.52 (0.33–0.82)	−48 (−18 to −67)		0.70 (0.54–0.91)	−30 (−9 to −46)	
	1986–89	Nepal[20]			681 and 679		Cotrimoxazole 4 mg/kg BD for 5 d Chloramphenicol if no improvement[¶]		0.92 (0.45–1.91)	−8 (−55 to +91)		0.87 (0.64–1.16)	−13 (−36 to +16)	
	1988–89	Bangladesh[17]			3815 and 4479		Injectable penicillin/ ampicilin PO[‖]		0.57 (0.36–0.92)	−43 (−8 to −64)		0.71 (0.61–0.83)	−29 (−17 to −39)	
	1985–87	Pakistan[18]			1212 and 303		Cotrimoxazole PO		Not available	Not available		0.72 (0.34–1.54)	−28 (−66 to +54)	
	1983–85	Tanzania[19]			1638 and 1652		Cotrimoxazole PO		0.44 (0.18–1.07)	−56 (−82 to +7)		0.70 (0.47–1.07)	−30 (−53 to +7)	
		Pooled analysis of above			8879 and 8162				0.58 (0.43–0.78)	−42 (−22 to −57)		0.73 (0.65–0.82)	−27 (−18 to −35)	

*Overlap of data amongst these studies.
†Overall number of children treated <5 years old is 612. Disaggregated data for neonates is not given.
‡Case fatality rate: 24% in 0 to 7 days; 33% in those with referral conditions.
§Details for study from India as above.
¶Given to 1.2% of treated cases.
‖In one-half of intervention area, cases of moderate pneumonia were managed by community health workers using procaine penicillin (5 daily injections of penicillin in doses of 400,000 to 800,000 IU (age-dependant dosage) at home; in other half of intervention area moderate cases treated with ampicillin syrup at sub-center clinics.
**Different results from the same study.
NR indicates not reported.

TABLE 3. Characteristics of Studies of Community-Based Management of Neonatal Sepsis

Author	Study Design	Study Period	Country	Principal Diagnosis	Age Range	Study Population/No. in Study (Intervention and Control)
Bartlett et al 1991[15]	Prospective study with historical control	1988–89	Guatemala	Pneumonia/sepsis	0–90 d	329
Bang et al 1999[6]	Non-randomized control study	1993–95 1995–96 1996–97 1997–98	Rural India	Sepsis[†]	0–27 d	1999 and 2271 763 685 913
Bhandari et al 1996[16]	Observational	?	Delhi, India	Pneumonia/sepsis	0–60 d	2007
Baqui et al 2008[7]	Cluster randomized trial	2003–2006	Sylhet, Bangladesh	Very severe disease, possible very severe disease with more than one sign, or possible very severe disease with one sign	Married women of reproductive age (15–49 yr) and newborns	24 clusters (20,000 in each cluster) randomly assigned in equal numbers to one of 2 intervention arms [home-care (36,059), and community-care arm (40,159)] or to the comparison arm (37,598)

*Neonatal mortality rate reported as 3.9/100 amongst 919 infants surviving day 1 of life. Baseline NMR calculated form a previous study and review of civil records.
†Term neonatal sepsis was used collectively for septicaemia, meningitis, or severe pneumonia, diagnosed clinically.
‡Figure estimated from 6.5% of neonates who were treated of a total of 1598 neonates receiving home-based care in years 2 and 3.
§Neonatal care package included resuscitation equipment, baby clothes and blanket, thermometer, weighing scale, spirit, gentian violet, tetracycline eye ointment, bleach, cotton, soap, brush for cleaning nails, sleeping bag, phota album with reference pictures, disposable insulin syringes, cotrimoxazole syrup, and gentamicin vials.
¶Education addressed care and nutrition during pregnancy, initiating early and exclusive breast feeding, prevention of infection, temperature maintenance, importance of weight gain, recognizing danger signs and symptoms in neonates, and seeking immediate help from a health worker.
‖Age-specific mortality rate/ 1000 in specific age groups are as follows.
For year 2 (1996–1997): 0–6 d: 31.1 and 33.0 in intervention and control area, respectively.
For year 3 (1997–1998): 0–6 d: 22.5 and 49.6 in intervention and control area, respectively.
For year 2 (1996–1997): 6–27 d: 5.0 and 17.0 in intervention and control area, respectively.
For year 3 (1997–1998): 6–27 d: 3.1 and 9.9 in intervention and control area, respectively.
**Data extracted for sepsis, meningitis, pneumonia, and fever patients.

ing alone from the clinical algorithm for case detection. Health outcomes were compared in 39 intervention and 47 control villages with no interventions. The results for each phase are presented in Table 3.

In the intervention area, neonatal mortality declined in year 1 by 21% compared with the control group, and 17% compared with the intervention area baseline rate, with the addition of household visits and home-based pneumonia case management. Following the introduction of the neonatal care package and intramuscular gentamicin for management of sepsis in year 2, the overall mortality declined by 28% compared with that observed in the control area, and by 29% compared with baseline. In year 3, subsequent to implementation of maternal health education, mortality rates declined further in the intervention group by 57.2% compared with the baseline control rates, and by 29% compared with the previous year in the intervention area. The overall decline in mortality from 62 to 25.5/1000 live births represented a 62% ($P < 0.001$) reduction relative to baseline control rates; sepsis-specific mortality was reduced by 76% ($P < 0.005$) from 27.5 to 6.6/1000 live births in the intervention area compared with the control.

The case fatality for suspected neonatal sepsis declined from 16.6% (year 1), before the introduction of the comprehensive care program, to 2.8% (years 2 and 3). Case fatality for neonates with sepsis among all cases treated by VHWs (during 1996–2003) was 6.9%, compared with 22% among untreated cases (probable cases of neonatal sepsis identified posthoc from verbal autopsies where the diagnosis was missed by VHWs, and those whose families refused treatment), a probable 68.6% reduction.[6] The case fatality decreased in very low birth weight infants (<1500 g) from 69% in year 1, to 25% in year 3. Although a number of factors and interventions were operative during the entire intervention period (1996–2003), this concerted experience indicated that VHWs correctly diagnosed 492 cases of suspected neonatal sepsis (89%) and treated 470 neonates with antibiotics (8.9% of all neonates). Of 552 cases considered as sepsis by a computer algorithm, VHWs correctly treated 448 (81.2%) and gave unnecessary treatment to 22/470 (4.7%) of treated neonates. The case fatality was 6.9% in treated cases versus 22% in untreated or 16.6% in the preintervention period ($P < 0.001$). Altogether, home-based treatment resulted in a 67.2% reduction in case fatality among preterm neonates and a 72% reduction among low birth weight neonates, suggesting that this approach was feasible and effective.

In a recent cluster randomized trial from Sylhet in rural Bangladesh,[7] 24 clusters (with a population of about 20,000 each) were randomly assigned in equal numbers to 1 of 2 intervention arms (home care or community care) or to a comparison arm. Because of the study design, masking was not feasible. All married women of reproductive age (15–49 years) were eligible to partici-

TABLE 3. (*Continued*)

No. Infants Treated	Regimen Used	Duration (d)	Case Fatality Rate (%)	Overall Mortality Rate/1000		% Reduction
				Intervention Group	Control Group	
34	Sepsis: ampicillin + gentamicin Pneumonia and fever: ampicillinPneumonia, no fever: erythromycin	NR	14%, 0% in home treated	6	39*	84.6
?	Baseline yr	Full term:		62.0	57.7	−8.8
	Year 1 household visits and Pneumonia management	7 d preterm: 10 d	16.6%	51	65	21.5
104‡	Year 2 neonatal care package§ gentamicin IM + Cotrimoxazole		2.8%	36.1	50‖	27.8
	Year 3 education¶ + above			25.5	59.6	57.2
? 124**	Cephalexin PO + Amikacin IM	NR	3.3%			
-	Three arms: In the home-care arm, female community health workers promoted birth and newborn-care preparedness, made postnatal home visits to assess newborns on the first, third, and seventh days of birth, and referred or treated sick neonates with Procaine penicillin and gentamicin given to newborns of families unable to visit health facility**.** In the community-care arm, only birth and newborn-care preparedness and careseeking were promoted through group sessions held by female and male community mobilizers	Once a day for 10 d	-	29.2 (Home-care arm) and 45.2 (Community-care arm)	43.5 in the comparison/control arm	34% in the home-care arm versus comparison/control arm in last 6 mo and 30% lower during the last year of the intervention. No mortality reduction noted in the community-care arm

pate. In the home-care arm, a nongovernmental organization partner, Shimantik, recruited 1 female community health worker (CHW) for every 4 villages (one per 4000 population) who identified pregnant women through routine surveillance during visits to each household once every 2 months, and made 2 antenatal home visits to promote birth and newborn-care preparedness. They made postnatal home visits to assess newborns on the first, third, and seventh days of birth, and classified sick neonates into 3 categories—very severe disease, possible very severe disease with more than one sign, or possible very severe disease with one sign. When CHWs diagnosed very severe disease or possible very severe, they referred neonates to subdistrict hospitals after giving an injectable dose each of procaine benzylpenicillin and gentamicin. If families were unable to go to a health facility but consented to home treatment, the CHWs continued treatment with procaine penicillin and gentamicin once daily for a total of 10 days. Neonates with possible very severe disease with 1 sign were not given antibiotics by the CHWs and were referred to subdistrict hospitals. When the family was not able to go to the hospital, community health workers made a follow-up visit to these neonates within the next 24 hours to monitor the infant for signs of illness and reinforce referral. In the home-care arm, female community mobilizers were recruited, each of whom took 8 months to visit her entire catchment area. In the community-care arm, each female community mobilizer was responsible for a population of 18,000, which was divided so that each geographical area of about 225 people was visited once every 4 months; male community mobilizers visited each area once every 10 months. Additionally, in the community-care arm, female volunteers called community resource people (usually TBAs from the same community) were recruited to identify pregnant women, encourage them to attend community meetings held by the community mobilizers, receive routine antenatal care, and seek care for signs of serious illness in mothers or newborns. Families in the comparison arm received the usual health services provided by the government, nongovernment organizations, and private providers.

In the last 6 months of the 30-month intervention, NMRs were 29.2 per 1000, 45.2 per 1000, and 43.5 per 1000 in the home-care, community-care, and comparison arms, respectively. Neonatal mortality was reduced in the home-care arm by 34% (adjusted relative risk 0.66; 95% CI: 0.47–0.93) during the last 6 months versus the comparison arm. No mortality reduction was noted in the community-care arm (0.95; 95% CI: 0.69–1.31).

Additional data available from a recent study of community management of suspected neonatal sepsis in Pakistan (Zaidi et al 2007, unpublished data) suggesting that CHWs can recognize serious neonatal infections and refer for treatment with injectable antibiotics in a primary care community health center. Among 434 newborn infants with suspected sepsis, an overall 86% success rate was seen for treatment with 1 of 3 regimens (daily injectable penicillin and gentamicin or daily injectable ceftriaxone or daily oral cotrimoxazole and injectable gentamicin). The latter regimen was found to be inferior to the penicillin and gentamicin combination and to the ceftriaxone regimen.

DISCUSSION

It is recognized that a range of preventive strategies can reduce the burden of neonatal infections in community settings and must be implemented at scale.[3,5,9,10,32,33] While preventive strategies can be implemented in all cases and in at-risk populations, the key factor in treating neonatal infections successfully in community settings is the appropriate rapid diagnosis and triage to therapy. In contrast to infections in older infants and children, the onset of illness and course of progression is much more rapid in newborns, thus both clinical diagnosis as well as empirical therapy are the mainstay for management of neonatal sepsis.[34] Figure 1 indicates a conceptual framework for considering preventive and therapeutic strategies for reducing the burden of neonatal infections in developing countries.

As our evidence review indicates, there is limited evidence for community-based management of serious neonatal infections. However, available data do suggest that case management approaches using antibiotics may play a substantial role in reducing mortality if integrated into home or community-based perinatal care packages.[3,10,35]

Several limitations must be recognized in evaluating these data. Three of the studies catering to newborn pneumonia.[14,21,22] used the WHO guidelines (1989) or their 1991 revised version[36] for pneumonia diagnosis and management. According to these WHO criteria, children with rapid breathing but no chest in-drawing (pneumonia) receive antibiotics as outpatients. Children who have chest in-drawing, with or without rapid breathing (severe pneumonia), are referred for hospitalization and treated with parenteral penicillin or ampicillin every 6 hours for at least 3 days, followed by oral ampicillin or amoxillin or intramuscular procain penicillin for at least 5 days. In the event of lack of recovery within 48 hours of initiation of therapy with penicillin, or deterioration, a change of antibiotic to chloramphenicol was recommended. Although these measures for the treatment of pneumonia have been modified in recent years, their application to the treatment of pneumonia in newborn infants has not been systematically evaluated.[37,38] Most of the studies reviewed by Sazawal and Black[31] are almost 2 decades old and some used a mix of measures such as active case detection, community mobilization, maternal health education and establishment of systems for referral by trained CHWs, and the criteria for triaging illness on the basis of disease severity may have changed over time. Notwithstanding the above, given the suggestion that a substantial part of neonatal sepsis may represent pneumonia,[39] it is imperative that clinical algorithms for the recognition and management of neonatal sepsis and pneumonia are evaluated afresh for their validity and outcomes.

Evidence from trials of pneumonia case management among neonates, although limited by nonrandomized open comparisons, is nevertheless consistent in showing benefit of antibiotic case management approaches, largely using cotrimoxazole. Although the contribution of cointerventions, such as education and immunization, in addition to impact of methodological limitations, could not be quantified in the pooled analysis,[31] they were estimated not to have major effects on the results of the meta-analysis. Indeed, the magnitude of reduction in neonatal mortality is comparable to the proportion of neonatal illness estimated to be due to infections,[11] suggesting that substantial impact was achieved through case management. Notwithstanding the limitations and the relatively old data cited above, it is logical to assume that case management of pneumonia in community settings by health workers is feasible and may indeed lead to significant benefits.

Interpretations of the findings from the reported reduction in neonatal mortality from rural India[22] are also limited by lack of a true control group and estimates of the impact of antibiotic management of sepsis derived from before-after comparisons of an observation phase (1995–1996) with an intervention phase (1996–2003) may be overestimated. In addition, estimates of impact of individual components obtained by "artificially disaggregating" an interdependent package of interventions, as the authors acknowledge, may exaggerate the benefit of each component.[22] Recent studies on community case management of sick newborns do suggest that treatment is possible with antibiotics forming one part of a package of home care.

The large reductions in sepsis and pneumonia-specific mortality rates, as well as the very low case fatality rates demonstrated in community settings, suggest that home-based antibiotic management could be an attractive alternative to current recommendations of hospital admission and treatment with injectable antibiotics for resource poor countries with poorly functioning health care systems. There may however, be several impediments to widespread implementation of community-based programs for serious neonatal infections in resource poor countries. First, the cost and logistic considerations of such programs may be substantial, particularly those depending upon frequent household visits for case detection, management, supervision, and follow-up. For an estimated 83% of 26 million live births per year in India which occur at home,[31] the cost of implementing home-based neonatal care in India alone is an estimated $1.14 billion per year (assuming $5.30 per neonate as documented in Gadchiroli with injectable antibiotics).[14] Other recent studies from South Asia may provide a more accurate estimate of the cost effectiveness of interventions and preliminary data from studies done in Sylhet and Hala, Pakistan, do indicate that the costs of community-based intervention packages are substantially lower (Darmstadt et al, Bhutta et al; personal communication 2008).

Second, it must be emphasized that the available evidence on case management, particularly for neonatal pneumonia, largely predates the emergence of drug resistance among causative pathogens. Given recent trends in increasing antimicrobial resistance among common respiratory pathogens, it is imperative that antibiotic choices (especially the efficacy of oral cotrimoxazole) be validated in community settings.[40] It is likely that oral amoxicillin, especially when given as a short course,[41] may represent a better choice for the ambulatory management of nonsevere pneumonia in community settings. The need to monitor resistance to antibiotics among pathogens causing neonatal infections is 1 major concern in community-based antibiotic management strategies. Widespread antimicrobial resistance may preclude the ability to design simple, inexpensive, and effective antibiotic regimens in many countries. Neonatal pathogens also vary by region and temporally,[42] which means that each country undertaking to develop and implement a case management program will need to periodically investigate the spectrum and antimicrobial resistance patterns of locally important pathogens in community-settings. This is particularly important in determining optimal antibiotic choices for empirical treatment of pneumonia.[43] Recent data from a variety of settings do indicate that it may be possible to institute appropriate therapy guidelines at scale with reduction in rates of emergence of antibiotic resistant organisms.[40]

There are additional concerns such as the need for standardized diagnostic criteria, which are suitable for use by trained community health workers to detect sepsis within communities. Compared with computer-based diagnosis, community workers were able to correctly detect 89% of suspected neonatal sepsis, using criteria developed by Bang et al.[5] The Young Infant Study group[44] has recently developed an algorithm for predicting severe illness in neonates presenting to first-level facilities with reported sensitivities of 85% and 74%, and specificities of 75% and 79%, in 0–6 and 7–59 day age groups respectively or more sensitive but less specific than criteria used by Bang et al.[45] In a community-based study in Bangladesh, CHWs were shown to have high validity compared with physicians (73% sensitivity, 98% specificity) when using an algorithm similar to the Young Infant Study algorithm during routine household surveillance, for identification of sick neonates needing referral to hospital.[46] The clinical algorithm had good sensitivity and high specificity for identification of neonates needing referral (81% sensitivity, 96% specificity) and lower sensitivity for neonatal mortality (55% sensitivity, 93% specificity).[47] It must be underscored however, that our current clinical methods for case detection of possible neonatal sepsis may be picking up a range of clinical illnesses other than bacterial infections, including viral infections. This is probable given the 70%–80% survival rates of newborn infants with suspected sepsis who did not receive antibiotics (Zaidi et al, personal communication 2008) and the impact on neonatal and young infant febrile illnesses observed in a recent study of maternal influenza vaccination in Bangladesh.[48]Further validation studies of home-based algorithms are clearly needed in a variety of settings.

Even though studies have attempted syndromic evaluation of serious newborn infections,[49] they do not concur on choice of antibiotic therapy. The selection of appropriate antibiotic regimens is impeded primarily due to insufficient data regarding etiological agents of serious neonatal infections in community settings in developing countries.[39] Further issues in the selection of appropriate regimens, elaborated elsewhere[11,12] include monitoring of potential adverse effects such as toxicity due to inappropriate dosing or altered gastrointestinal colonization, as well as use of unnecessary injections by community health workers which could exacerbate hepatitis B and C transmission, suitability of such regimens for various health workers, and acceptability in communities. With high levels of motivation and support, home-based care was found acceptable to communities in rural India—adjudged by high acceptance rate (91%) and no documented complications of injections such as infection or injury.[5] Others have successfully demonstrated the benefit of community motivation and health worker training on improved referral rates and care seeking with the public and private sectors within a district health system,[50] suggesting that perhaps a combination of home-based and facility-based strategies may be necessary in evolving health systems.

Although no direct comparisons exist of groups or communities receiving neonatal care packages with antibiotics versus neonatal care packages without antibiotics, studies have indicated that other simple interventions such as maternal education and training of birth attendants could also lead to declines in neonatal mortality rates in areas with very high burden of neonatal morbidity and mortality, and may—in contrast to antibiotic programs—be more sustainable in the long term.[10] In an uncontrolled study in India, domiciliary management of high-risk neonates (such as preterm and low birth weight or those with feeding problems) by VHWs, led to a 25% decline in neonatal mortality in the absence of management of sepsis.[51] It could also be deduced from the Gadchiroli trials that the impact of maternal education—which led to a 29% decline in neonatal mortality over the previous year—was comparable to the effect of adding intramuscular gentamicin and the neonatal care package.[14] However, some of the further decline, which cannot be quantified, may have been due to maturation of the ongoing intervention. Other interventions which have been evaluated in more methodologically rigorous cluster randomized controlled trials, have shown considerable decreases in NMR of 30% (95% CI: 6%–47%) and 29% (95% CI: 17%–38%) respectively, with a maternal and newborn care program in Nepal that did not include antibiotics but instead used a participatory approach involving women's groups,[32] training of TBAs, and use of clean delivery kits in rural Pakistan.[52] Recent data from a community behavior change management strategy from Uttar Pradesh, India also indicate that major reductions in neonatal mortality are possible (51% reduction in NMR, 95% CI: 37%–62%) with promotion of behavior change targeted at multiple stakeholders, including the mother, family, and community providers of newborn care, and not including antibiotic use.[32]

In conclusion, available evidence suggests that antibiotics have a clear role in reducing neonatal mortality in low income areas and can be effectively administered in homes via trained health workers. However, issues surrounding sustainability and acceptability on the part of families, health care workers, and policy makers, as well as selection and implementation of packages of care integrated across the continuum of care—with appropriate preventive as well as therapeutic interventions for scaling up—are areas needing further development. In a recent evaluation of the evidence for integrated interventions for maternal, newborn and child survival in primary care settings,[10] a clear case has been made for introducing packages of care for promotive, preventive, and therapeutic strategies in community settings and first-level facilities. These include the utilization of all available opportunities for treating sick newborn infants with infections, including home care where alternatives are not available.

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