MAJOR ARTICLE

Population-Based Incidence and Etiology of Community-Acquired Neonatal Bacteremia in Mirzapur, Bangladesh: An Observational Study

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Background. To devise treatment strategies for neonatal infections, the population-level incidence and antibiotic susceptibility of pathogens must be defined.

Methods. Surveillance for suspected neonatal sepsis was conducted in Mirzapur, Bangladesh, from February 2004 through November 2006. Community health workers assessed neonates on postnatal days 0, 2, 5, and 8 and referred sick neonates to a hospital, where blood was collected for culture from neonates with suspected sepsis. We estimated the incidence and pattern of community-acquired neonatal bacteremia and determined the antibiotic susceptibility profile of pathogens.

Results. The incidence rate of community-acquired neonatal bacteremia was 3.0 per 1000 person–neonatal periods. Among the 30 pathogens identified, the most common was *Staphylococcus aureus* ($n = 10$); half of all isolates were gram positive. Nine were resistant to ampicillin and gentamicin or to ceftiaxone, and 13 were resistant to cotrimoxazole.

Conclusion. *S. aureus* was the most common pathogen to cause community-acquired neonatal bacteremia. Nearly 40% of infections were identified on days 0–3, emphasizing the need to address maternal and environmental sources of infection. The combination of parenteral procaine benzyl penicillin and an aminoglycoside is recommended for the first-line treatment of serious community-acquired neonatal infections in rural Bangladesh, which has a moderate level of neonatal mortality. Additional population-based data are needed to further guide national and global strategies.

Trial registration. ClinicalTrials.gov identifier: NCT00198627.

Four million neonates die each year globally, 99% of them in developing countries [1]. Neonatal infectious diseases—including sepsis, pneumonia, and meningitis—account for 26% of all neonatal deaths globally and ~50% in high-mortality populations [1–3]. It is essential to understand the levels, etiology, and antimicrobial sensitivity patterns of organisms that cause neonatal infections in developing countries in order to develop effective treatment strategies and to reduce neonatal mortality [3]. However, no population-based data on the etiology of serious neonatal infections in developing countries exist. The World Health Organi-

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zation (WHO) Young Infants Clinical Signs Study Group conducted a multicenter prospective study of bacterial etiology among infants <90 days of age who were brought to health facilities by their parents or caregivers, thus underestimating the incidence and including nosocomial infections [4, 5]. Recent studies of sepsis etiology among Filipino neonates [6] and Kenyan children <5 years old [7] included only community-acquired sepsis but were also limited by self-referral selection bias due to lack of surveillance [7]. A population-based study in Bangladesh investigated the incidence and etiology of bacterial infections among children <5 years old and estimated an incidence rate of 17.4 cases per 1000 person-years among neonates. However, the study was limited because of a low level of care seeking among parents or families for sick neonates, limited household surveillance on a monthly basis, and limited focus on acute lower respiratory tract infection (ALRI) only [8].

We conducted population-based surveillance in rural Bangladesh to estimate the population-based incidence and etiology of clinically significant community-acquired neonatal bacteremia and to understand the antibiotic resistance patterns of isolated pathogens, in order to inform empirical regimens for antibiotic treatment.

METHODS

Study population and design. This study was nested within a cluster randomized and controlled intervention trial of a preventive and curative maternal-neonatal health care package conducted in Mirzapur, Bangladesh, from January 2004 through December 2006. The neonatal mortality rate was 24 deaths per 1000 live births in 2002. The area was served by Kumudini Hospital, a private, nonprofit, centrally located referral-level hospital with 750 beds [9]. The study population of ~292,000 was divided into 12 rural unions (excluding the central urban union), which were randomly allocated to the control or intervention arm.

Community-level surveillance of neonatal illness. In the intervention arm of the trial, 36 community health workers (CHWs), each covering ~4000 people, identified pregnancies in their population through routine household surveillance conducted every other month and obtained informed verbal consent for participation in the study. Pregnant women were subsequently visited at home twice during pregnancy to promote birth and newborn care preparedness, including distribution of clean delivery kits and promotion of clean delivery and clean cord care practices [10]. CHWs attended the delivery whenever possible or visited the mother and neonate on the day of delivery or as close as possible to the time of delivery. Additional routine household visits were scheduled on postnatal days 2, 5, and 8. At each postnatal visit, CHWs assessed newborns, identified the presence of illness, and made referrals to Kumudini Hospital according to a clinical algorithm, which has been presented in detail elsewhere [11]. Illnesses requiring referral included very severe disease (VSD), possible VSD (PVSD), perinatal asphyxia, jaundice on the first day of life, possible gonococcal eye infection, and diarrhea with blood or severe dehydration. Classification of neonates with VSD by CHWs was validated, relative to assessment by physicians [11]. For referred neonates, CHWs facilitated transportation, and all care at the hospital was free. After the first 28 days of life, CHWs revisited all live-born neonates and recorded survival status.

Hospital-level surveillance of neonatal infections. Newborn care capacity among physicians and nurses at Kumudini Hospital was strengthened through regular refresher training and case review sessions. A microbiology laboratory was established at Kumudini Hospital with technical assistance from the Departments of Microbiology of Dhaka Shishu Hospital, Bangladesh, and Oxford University. Blood cultures were recommended by physicians for all neonates from the intervention arm who visited Kumudini Hospital during the study period with (1) clinical suspicion of possible serious infection or (2) antibiotic treatment recommendation by the physician. Information on use of antibiotics before the hospital visit was collected through a questionnaire administered on presentation to the hospital, and serum and/or urine antimicrobial substance testing was done using methods that have been described elsewhere [12].

Blood cultures were performed by the lysis direct plating method, as described elsewhere [13]. Attempts were made to draw 2–2.5 mL of blood; however, even smaller volumes were processed, given the high magnitude of bacteremia during the neonatal period [14]. Blood was inoculated onto chocolate, blood, and MacConkey agar plates prepared with strict quality controls, as described elsewhere [13].

Isolates were provisionally identified at Kumudini Hospital using standard procedures [15] and guidelines [16]. Primary culture reports of growth or no growth were provided to the clinical care team within 18–24 h. If multiple bacterial species or *Candida* species were identified, the case was discussed with clinical investigator(s), and blood cultures were repeated to verify the growth as true or the result of contamination. Coagulase-negative *Staphylococcus*, *Diptheroids*, and *Bacillus* species were always considered to be contaminants. The antibiogram of all isolated pathogens was determined using disc diffusion methods. Results were categorized as sensitive, intermediate, and resistant on the basis of standard methods, using rigorous quality controls [13,17].

For further quality assurance, plates with any growth of bacteria were transported daily at ambient temperature from Kumudini Hospital to Dhaka Shishu Hospital, and isolate identification and antibiotic susceptibility test results were verified there on the basis of standard guidelines [16, 17], including

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identification of gram-negative isolates with the Analytical Profile Index system (bioMérieux) and serotyping of pneumococcal strains as described elsewhere [18, 19]. We regularly monitored compliance with standard zones of inhibition and minimum inhibitory concentrations [18]. Randomly selected isolates identified at Dhaka Shishu Hospital were also sent to the Department of Microbiology of John Radcliffe Hospital at Oxford University for external quality assurance.

Community-hospital linkage of surveillance records. A study identification number was included on all hospital records for neonates from the intervention arm who visited Kumudini Hospital from February 2004 through December 2006. We assumed that an admission that occurred within 2 days after an outpatient visit was a consequence of the same illness episode and considered each of these outpatient-inpatient record pairs as 1 hospital record. We linked hospital and CHW records of the 10,006 neonates born from February 2004 through November 2006 using the study number as an index variable; 98% of all hospital records were successfully linked.

Figure 1 shows the profile of the record linkage status of 1981 hospital records (813 admissions and 1168 outpatient visits without admission) and 28,063 CHW records (25,367 assessment records for 7310 neonates and survival records for 2696 neonates). Of the 1981 hospital records, 236 were for 207 neonates who were never assessed by CHWs, and 227 were for hospital visits that occurred before an initial CHW assessment; each of the remaining 1518 hospital records was linked to the most recent CHW assessment if there was >1 assessment for the index hospital record. The mean interval between a CHW assessment and a hospital visit among the 1518 linked CHW-hospital records was 4.0 days (standard deviation, 5.4 days; range, 0–26 days). We further categorized hospital visits following a CHW assessment into visits occurring either within ($n = 805$) or after ($n = 713$) 2 days of the assessment, to examine differential culture outcomes by referral and care-seeking status. Among 919 assessments with a referral recommendation, neonates visited Kumudini Hospital within 2 days following the recommendation in 495 assessments (53.9%).

Case definition of community-acquired neonatal bacteremia. Neonatal bacteremia was defined as a positive result for noncontaminated culture of blood ($n = 519$) collected between 0 and 27 days of life. We excluded 4 repeated cultures of blood collected within 4 days of a previous culture. To restrict our analysis to community-acquired infections, we further excluded 15 cultures of blood collected on day 4 or later of hospital admission, because these were considered to represent nosocomial infection. Thus, 500 cultures were retained [20]. No blood was collected within 4 days of discharge after hos-

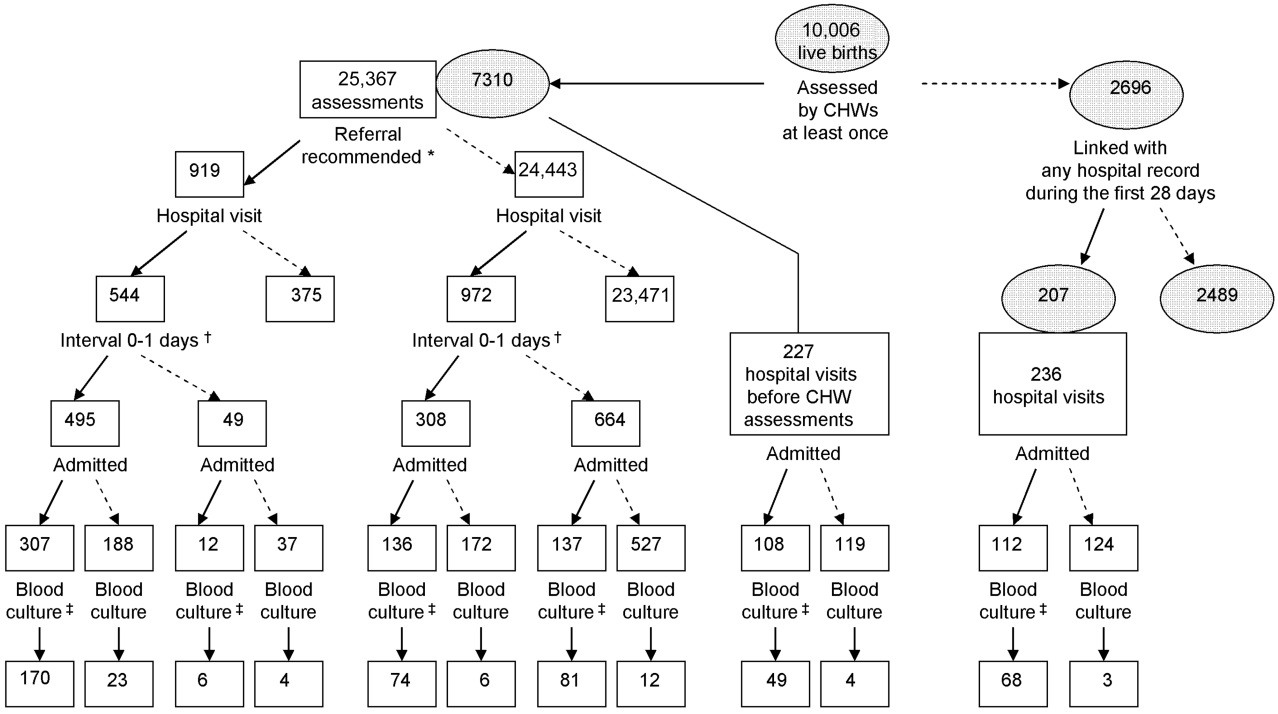

Figure 1. Surveillance profile of community-acquired neonatal sepsis, including 500 blood cultures and 1981 hospital visits for 10,006 neonates born from February 2004 through November 2006 in Mirzapur, Bangladesh. Solid arrows indicate yes, dashed arrows indicate no, shaded ovals indicate neonates, and boxes indicate community health worker (CHW) assessments, hospital visits, or cultures. The referral recommendation (*) was missing in 5 CHW assessments; 2 hospital visits without blood culture were followed after 2 of the 5 assessments. The interval (†) indicates the time between the CHW assessment and the hospital visit. Blood cultures performed on hospitalization days 0–3 only are indicated by a double dagger (‡).

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pital delivery or discharge after a prior admission, which also could represent nosocomial infection.

Analysis. We calculated the person-time exposed to the neonatal period (ie, day 0–27 of life). We estimated population-level incidence rates of hospital visits, admissions, and bacteremia. The hospital visit and admission rates were further estimated by sex and CHW assessment status (ie, neonates assessed by a CHW at least once vs neonates never assessed by a CHW), to examine potential selection bias in care seeking. Among hospitalizations, the culture rate (percentage of admissions for which a culture was performed) and the positivity rate (percentage of cultures performed that had a positive result) were calculated by provisional diagnoses at admission indicating suspected serious infection. We calculated 95% confidence intervals (CIs) for all rates, assuming Poisson distributions for the number of admissions and positive culture results and a binomial distribution for conducting cultures. Finally, among cases of bacteremia we conducted descriptive analyses to explore background and clinical characteristics and antibiotic resistance patterns. A P value of .05 or lower was considered statistically significant. Differences with $P < .05$ were considered statistically significant. Stata statistical software (version 9.0; Stata Corporation) was used.

The present study was approved by the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health; the Ethical Review Committee and the Research Review Committee at International Centre for Diarrhoeal Disease Research, Bangladesh; the Ethical Review Committee at Dhaka Shishu Hospital; and the Ethical Review Committee at Oxford University.

RESULTS

Hospital Visit and Blood Cultures

A total of 10,006 neonates (75.7% of whom were home born) contributed to 9809 person–neonatal periods (PNPs); of the neonates, 239 died (table 1). Hospital visit and admission rates were 202.0 and 82.9 per 1000 PNPs, respectively. Both hospital visit and admission rates were significantly higher among neonates who were ever assessed by CHWs, compared with those who were never assessed. Among the ever-assessed neonates, both hospital visit and admission rates were significantly higher for males than for females, whereas there were no significant sex differentials among neonates who were never assessed.

A total of 500 blood cultures were performed within the first 4 days of hospital admission ($n = 448$) or at outpatient visits ($n = 52$) (culture rate, 25.3% [500/1981]). The culture rate was significantly higher for admissions (55.1% [95% CI, 51.6%–58.6%]) than for outpatient visits (4.5% [95% CI, 3.3%–5.8%]). Culture rates for admissions are presented by provisional clinical diagnosis in table 2.

Neonatal Bacteremia

Incidence. Culture results were positive for 29 blood samples (positivity rate, 5.8%), all of which were obtained on the day of hospital visit and 11 of which were obtained at day 0–3 of age. The incidence rate for neonatal bacteremia was 3.0 cases per 1000 PNPs (95% CI, 2.0–4.2 cases per 1000 PNPs) (2.9 cases per 1000 live births [95% CI, 1.9–4.2 cases per 1000 live births]). Sixteen cultures were contaminated (contamination rate, 3.2%).

Eighteen cultures with positive results were for neonates who visited the hospital within 0–1 day after CHW assessment; 15 (83.3%) of these 18 neonates were classified as having VSD and 17 (94.4%) were classified as having VSD or PVSD by a CHW at home (table 3). There were 27 cultures with positive results for admitted neonates; the most common clinical diagnosis assigned by physicians at admission was sepsis (40.7% [11/27]).

Prior use of antibiotics. Maternal report of antibiotic use before culture was collected for 474 cases, and 16.2% reported prior use of antibiotics (table 4). Serum antimicrobial substance testing was done for 417 cultures, and 6.0% were positive for prior antibiotic use. Among cases with both maternal report and a serum antibiotic substance test, maternal report had a sensitivity of 30.4% (7/23), a specificity of 82.8% (309/373), a positive predictive value of 9.9% (7/71), and a negative predictive value of 95.1% (309/325), compared with the serum test (table 4). A urine substance test, additionally conducted in 350 of the 417 cases with the serum test, had a sensitivity of 5% and a positive predictive value of 100%, compared with the serum test (table 5). The positivity rate was 6.4% (95% CI, 4.1%–9.4%) among 392 negative antimicrobial substance cases, compared with 0% among 25 positive antimicrobial substance cases.

Pathogens. Among the 29 cultures with positive results, 2 pathogens were isolated from 1 culture; thus, 30 pathogens were isolated in total (table 6). One-third of the organisms were *Staphylococcus aureus*, which was isolated throughout the neonatal period. No patient with *S. aureus* infection died. Additional characteristics of neonates with *S. aureus* infection are presented in table 7; all 9 neonates who were assessed by a CHW at home 0–1 day before the hospital visit had VSD and/or PVSD, 1 had severe skin infection as well as pus discharge from the umbilical cord, and 1 had signs of localized skin infection without signs of VSD. Overall, half of isolates were gram positive. Various organisms comprised the gram-negative pathogens. Case fatality rates were 13.3% (2/15) and 26.7% (4/15) among neonates with gram-positive and gram-negative infections, respectively.

Antimicrobial resistance. One of 10 *S. aureus* isolates was resistant to oxacillin (ie, methicillin-resistant *S. aureus*) (table 8). Of the gram-negative isolates, approximately half were re-

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Table 1. Person–Neonatal Periods (PNPs), Hospital Visits, and Hospital Admissions, by Community Health Worker (CHW) Assessment Status and Sex, among 10,006 Neonates Born from February 2004 through November 2006 in Mirzapur, Bangladesh

Parameter	Live births	PNPs	Hospital visits		Hospital admissions	
			No.	Rate (95% CI), no. per 1000 PNPs	No.	Rate (95% CI), no. per 1000 PNPs
All	10,006	9809	1981	202.0 (193.2–211.0)	813	82.9 (77.3–88.8)
CHW assessment status						
Never assessed						
All	2696	2565	236	92.0 (80.6–104.5)	112	43.7 (36.0–52.5)
Female	1106	1057	82	77.6 (61.7–96.3)[a]	40	37.9 (27.0–51.5)
Male	1278	1201	137	114.1 (95.8–134.9)[b]	66	55.0 (42.5–69.9)
Missing	312	308	17	55.2 (32.2–88.5)	6	19.5 (7.2–42.4)
Ever assessed						
All	7310	7244	1745	240.9 (229.7–252.5)	701	96.8 (89.7–104.2)
Female	3570	3545	746	210.4 (195.6–226.1)	278	78.4 (69.5–88.2)
Male	3738	3697	997	269.7 (253.2–286.9)	423	114.4 (103.8–125.9)
Missing[c]	2	2	2	…	0	…

NOTE. The unit of analysis was a neonate. CI, confidence interval.

[a] 90% CI, 64.1–93.2.

[b] 90% CI, 98.6–131.5.

[c] The hospital visit rate and admission rate were not calculated because of small sample sizes.

sistant to gentamicin (53.3% [8/15]) and ceftriaxone (46.7% [7/15]), and 20.0% (3/15) were resistant to ciprofloxacin. Seventy percent (21/30) of isolates were sensitive either to the combination of ampicillin and gentamicin (ie, sensitive to at least 1 of the agents) or to ceftiaxone (table 8); 81.5% (22/27) of isolates were sensitive to cotimoxazole and/or gentamicin. For oral antibiotics, 76.7% (23/30) of isolates tested were resistant to ampicillin (amoxicillin), 60.0% (15/25) were resistant to cephalexin, 48.1% (13/27) were resistant to cotrimoxazole, and 16.7% (5/30) were resistant to ciprofloxacin.

Approximately 73% (22/30) of the isolates were from neonates who were treated with an initial empirical antibiotic regimen that would be expected to provide adequate coverage (data not shown). Three (1 infected with *Enterobacter cloacae* and 2 infected with *Acinetobacter* species) of the 6 neonates who died did not receive a regimen effective for treatment of a multiple-drug-resistant pathogen.

DISCUSSION

We estimated a population-based, community-acquired, culture-confirmed serious neonatal infection incidence rate of 3.0 cases per 1000 PNPs (2.9 cases per 1000 live births) in Mirzapur, Bangladesh, a rate that is roughly comparable with early-onset neonatal sepsis incidence reported in the United States [21, 22] and neonatal sepsis incidence reported in Israel [23]. To our knowledge, this is the first study to exam the burden of community-acquired neonatal infections at the population level in the setting of a developing country. The community-level surveillance system was linked with an accessible and acceptable hospital in the community [9] that has high-quality clinical and laboratory capabilities. We implemented an intensive routine-home-visitation program during the first 9 days of life, when the majority of neonatal mortality occurs. Well-trained and supervised CHWs were validated previously with high sensitivity and specificity in identifying and classifying neonatal illness using a clinical algorithm [11]. For the referred neonates, referral compliance was facilitated to the extent possible by mitigating major barriers to care seeking (eg, facilitating free transport and hospital care) [24]. Finally, a unique linking system between the community and the hospital enabled us to verify care seeking and clinical outcomes for all live-born neonates.

However, the incidence rate was still likely underestimated. First, of the 919 assessments with a referral recommendation, only 53.9% were complied with in a timely manner, which is similar to or higher than compliance rates reported in other studies for referrals made at first-level facilities for children 5 years old or younger [24–27]. Information on compliance with CHW referral for neonatal illness during household surveillance is scarce and is often complicated in other studies by the option of receiving treatment at home [2, 28, 29]. Compliance with

Table 2. Number of Admissions, Blood Cultures, and Positive Culture Results, by Selected Provisional Diagnoses at Hospital Admission

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Table 3. Clinical Characteristics at Community Health Worker (CHW) Assessment 0–1 Days before Hospital Visit and at Admission, by Blood Culture Result

Parameter	Positive		Negative	
	No.	Rate (95% CI), %	No.	Rate (95% CI), %
Clinical characteristics at CHW assessment 0–1 days before the hospital visit (n = 273)[a]		(n = 18)		(n = 248)
VSD or PVSD	17	94.4 (72.7–99.9)	191	77.0 (71.3–82.1)
VSD	15	83.3 (58.6–96.4)	156	62.9 (56.6–68.9)
Clinical characteristics identified by physicians at admission (n = 448)[b]		(n = 27)		(n = 405)
VSD[c] or PVSD[d] calculated according to algorithm	19	70.4 (49.8–86.2)	300	74.1 (69.5–78.3)
VSD[c] calculated according to algorithm	17	63.0 (42.4–80.6)	242	59.8 (54.8–64.6)
Provisional diagnosis at admission[e]				
Sepsis	11	40.7 (22.4–61.2)	128	31.6 (27.1–36.4)
Pneumonia	0	0.0 (0.0–12.8)	30	7.4 (5.1–10.4)
Seizure	0	0.0 (0.0–12.8)	7	1.7 (0.7–3.5)
Feeding difficulty	3	11.1 (2.4–29.2)	39	9.6 (6.9–12.9)
Local infection, skin	1	3.7 (0.1–19.0)	13	3.2 (1.7–5.4)
Local infection, umbilicus	2	7.4 (1–24)	52	12.8 (10–16)
Birth asphyxia	4	14.8 (4.2–33.7)	55	13.6 (10.4–17.3)
Prematurity	4	14.8 (4.2–33.7)	27	6.7 (4.4–9.6)

NOTE. PVSD, possible very severe disease; VSD, very severe disease.

[a] Intervals between CHW assessment and culture were 0 (n = 191), 1 (n = 73), 2 (n = 7), and 3 (n = 2) days. Results for 7 contaminated cultures are not presented.

[b] Results for 16 contaminated cultures are not presented. VSD/PVSD classification was not included in admission records, and the classification was computed on the basis of individual signs and symptoms assessed by physicians at admission.

[c] At admission, 2 of 11 VSD signs (unconsciousness and weak, abnormal, or absent cry) were not assessed. Thus, the VSD classification was based on the other 9 signs only: (1) convulsion, (2) respiratory rate ⩾70 breaths per minute, (3) severe chest indrawing, (4) axillary temperature >101.0°F (38.3°C), (5) axillary temperature <95.5°F (35.3°C), (6) many or severe skin pustules or blisters or a single large area of pus or redness with swelling of skin, (7) umbilical redness extending to the abdominal skin, (8) lethargic or less than normal movement, and (9) not able to feed or not able to suck at all on the basis of the breast-feeding assessment.

[d] At admission, 1 of 6 PVSD signs (vomiting everything) was not assessed. Thus, the PVSD classification was based on the other 5 signs and symptoms only: (1) history of convulsion reported by the mother, (2) bulging fontanelle, (3) axillary temperature of 100.0°F–101.0°F (37.8°C–38.3°C), (4) axillary temperature of 95.5°F–97.5°F (35.3°C–36.4°C), and (5) jaundiced palms and soles that manifested 24 h or more after birth.

[e] Assigned by physicians at admission. Multiple diagnoses were possible.

referral in the present study was significantly lower among neonates 0–6 days old than among those 7–27 days old [30]. Second, 62% of the 239 neonates who died were never assessed by a CHW, and 59% and 87% of them died within the first 2 and 7 days, respectively. Although the early deaths were likely the result of birth asphyxia and/or prematurity, 38.0% of our culture-positive neonates had cultures performed between postnatal days 0 and 3, indicating that a substantial proportion of serious neonatal infections were acquired early or vertically or were associated with the birthing process. Third, routine home visits were scheduled only during the first 9 days of life. However, hospital visits beyond 9 days of life accounted for 63% of all visits, and 27% of those visits followed a CHW assessment within 2 days before the visit, suggesting that families were vigilant to signs of infection and sought care in response to information and motivation provided by the CHWs. Finally, the surveillance was conducted only in the intervention arm of the trial, in which clean delivery and essential newborn care (including cord care) were improved (Darmstadt GL, Baqui AH, Choi Y, et al, unpublished data). The impact that underestimation of the incidence rate has on etiology is not clear; however, we speculate that young neonates (ie, 0–6 days old) and vertically transmitted pathogens may have been underrepresented. In addition, fertility in our population was lower than initially anticipated [31], resulting in a surveillance population smaller than projected [21–23]. Furthermore, because a lower incidence of culture-proven neonatal sepsis than we initially expected, our etiology and antimicrobial sensitivity results are based on only 30 pathogens, potentially limiting generalizability.

Table 4. Antibiotic Use before Blood Cultures, on the Basis of Maternal Report and Antibiotic Substance Test

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Table 5. Comparison between Serum and Urine Antibiotic Substance Test

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The most prevalent pathogen was *S. aureus*. The clinical characteristics of the infected neonates suggest that the *S. aureus* isolates were associated with acute illness and were not contaminants. Two infants had overt signs of skin or cord infection, suggesting that entry into the bloodstream may have occurred primarily through colonized sites on the cord or skin or in the respiratory tract [20, 32, 33]. *S. aureus* was also the most prevalent among neonates in the population-based Matlab ALRI study (5/8) [8] and in the facility-based 4-country WHO Young Infants Clinical Signs Study (19/84) [4]. However, the etiology in our study population is markedly different from bacterial profiles of nosocomial neonatal infections in Bangladesh [34] and of nonnosocomial infections among young infants <60 days old in rural Philippines [6], where gram-negative pathogens such as *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Enterobacter* species predominate. Group B streptococci were uncommonly isolated, similar to hospital-based studies from Bangladesh [20] and other locations in developing countries [35, 36]. These findings emphasize the need for data from ongoing, regional, population-based surveillance to guide treatment strategies.

The antimicrobial sensitivity results indicate that the combination of a procaine benzyl penicillin (eg, procaine penicillin) and extended-interval dosing of an aminoglycoside (eg, once daily gentamicin) remains the first-line regimen of choice [28, 37–39]. Antimicrobial susceptibility rates for this regimen were similar to either ceftriaxone alone or a combination of oral cotrimoxazole and injectable gentamicin, and antibiotic synergy might further increase the clinical response rate for the penicillin-aminoglycoside regimen above that predicted on the basis of laboratory susceptibility testing of 1 antibiotic at a time [38–40]. Use of ceftriaxone is more prone to select for further resistance in the population and, thus, would not be favored over a penicillin-gentamicin combination. Although the cotrimoxazole-gentamicin regimen has the advantage of ease of administration, because only 1 injectable agent is needed each day [39], recent data from a community-based study of treatment of neonatal sepsis in Karachi, Pakistan, showed a significantly higher treatment failure rate with cotrimoxazole plus gentamicin compared with procaine penicillin–gentamicin or cetraixone (A. Zaidi, personal communication).

Approximately half of isolates tested were resistant to cotrimoxazole [8]. Resistance to cotrimoxazole has been increasing in Bangladesh because of its long-term and widespread use [13, 41, 42], which raises concerns about current recommendations for this drug as first-line treatment for ALRI. Thus, since clinical algorithms validated for use in Integrated Management of

Table 6. Patterns of Isolated Pathogens and Background Characteristics

		Age at culture				Sex		Place of birth		Gestational age[a]		Mortality status	
Pathogen	No.	0–3 days	4–6 days	7–13 days	14–27 days	Female	Male	Home	Hospital	⩾37 weeks	<37 weeks	Alive	Dead
Gram positive													
Staphylococcus aureus	10	2	2	4	2	3	7	8	2	7	2	10	0
Streptococcus pneumoniae[b]	3	2	0	0	1	3	0	3	0	2	1	3	0
Streptococcus species	1	1	0	0	0	0	1	0	1	0	1	0	1
Group B streptococci	1	1	0	0	0	1	0	1	0	0	0	0	1
Gram negative													
Pseudomonas alcaligenes	1	1	0	0	0	0	1	0	1	1	0	1	0
Pseudomonas cepacia	2	0	0	2	0	1	1	2	0	1	1	2	0
Pseudomonas species	2	1	0	0	1	1	1	2	0	1	1	1	1
Acinetobacter lwoffii	1	1	0	0	0	1	0	1	0	1	0	0	1
Acinetobacter baumann	2	0	1	0	1	1	1	2	0	1	1	1	1
Klebsiella oxytoca	1	0	0	1	0	0	1	1	0	1	0	1	0
Klebsiella pneumoniae	2	0	0	0	2	1	1	2	0	2	0	2	0
Enterobacter cloacae	2	1	0	0	1	1	1	2	0	1	1	1	1
Escherichia coli[b]	1	1	0	0	0	1	0	1	0	0	1	1	0
Flavobacterium meningosepticum	1	1	0	0	0	1	0	1	0	0	1	1	0
Total	30	12	3	7	8	15	15	26	4	18	10	24	6

[a] Two of the 30 pathogens (*E. coli* and *S. pneumoniae*) from noncontaminated cultures were isolated from 1 blood culture.
[b] Gestational age was determined on the basis of maternal report of the first day of the last menstrual period. Information is missing in 2 cases (1 *S. aureus* and 1 group B streptococci).

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Table 7. Background Characteristics, Clinical Presentation, and Antibiotic Treatment among 10 Neonates with *Staphylococcus aureus* Infection

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Childhood Illness (IMCI) programs do not distinguish neonates with ALRI from those with sepsis and treat them the same [5, 11], use of oral cotrimoxazole alone to treat neonates with suspected serious infection is likely to lead to an unacceptably high rate of treatment failures; moreover, treatment success rates for neonates with pneumonia might be diminished today, compared with estimates from pneumonia case-management trials conducted in the 1980s and 1990s [43].

Although use of oral antibiotic therapy has been contemplated for the treatment of serious neonatal infections in low-resource settings that have poor access to facility-based health care, perhaps after the establishment of clinical stability by means of parenteral therapy [35, 44], our data suggest that any empirical regimen composed of an oral antibiotic only—such as a penicillin (eg, ampicillin/amoxicillin) or a first-generation cephalosporin (eg, cephradine)—would be anticipated to have a high treatment-failure rate. Only ciprofloxacin, which recent data suggest has an acceptable safety profile in neonates [45], would be expected to provide adequate empirical coverage when given orally; however, consideration must also be given to the propensity for emergence of resistant organisms with its use and the potential for erratic absorption [46, 47].

Blood culture was the criterion standard for the determination of bacteremia in our study. However, blood culture is limited by low sensitivity (partially the result of insufficient specimen volume often obtained from neonates) and may lead to underestimation of the incidence rate. Repeated cultures, which are recommend to overcome this problem [48], were not feasible in our study, nor are they feasible in most low-resource settings. Furthermore, on the basis of either maternal report or the serum antimicrobial substance test, ~14% of neonates with cultures received antibiotics before specimen sampling, potentially further impairing sensitivity. Overall, the positivity rate of 5.8% (95% CI, 3.9%–8.2%) was comparable to those in studies of community-acquired neonatal infection in Bohol, the Philippines (4.4% [95% CI, 3.1%–6.2%]), and in Matlab, Bangladesh (13.8% [6.0%–27.2%]) [6, 8]. These low positivity rates may reflect a lack of specificity in clinical criteria, suggesting the need to further refine IMCI algorithms [5], in addition to the limitations of conventional blood cultures. Viral infections are another possible reason for the low positivity rate among neonates with signs of infection, and a subsequent study will examine levels and patterns of viral infections in our study population. More-advanced molecular detection methods [49] may also uncover additional cases of bacteremia. The development of a sensitive and specific diagnostic test for identifying serious neonatal infections is urgently needed for rapid identification and treatment of cases. Population-based surveillance data from other rural populations of Bangladesh—as well as from rural populations of other regions—is now needed to

Table 8. Antimicrobial Resistance Profile of 30 Pathogens Isolated during Population-Level Surveillance of Community-Acquired Neonatal Sepsis in Mirzapur, Bangladesh

	Ampicillin		Gentamicin		Cotrimoxazole		Cephalexin		Ceftriaxone		Ciprofloxacin		Ceftazidime		Imipenim		Oxacillin		Cloxacillin	
Pathogen	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R	N	R
Gram positive																				
Staphylococcus aureus	10	10	10	1	8	4	8	2	10	1	10	2	6	2	10	1	10	1	9	2
Streptococcus pneumoniae[a]	3	0	3	2	3	1	0	0	3	0	3	0	0	0	0	0	3	0	0	0
Streptococcus species	1	0	1	0	1	1	1	0	1	1	1	0	1	1	1	0	1	1	1	1
Group B streptococci	1	0	1	1	1	1	1	0	1	0	1	0	1	0	1	0	0	0	1	0
Gram negative																				
Pseudomonas alcaligenes	1	0	1	0	1	0	1	1	1	0	1	0	1	0	1	0	0	0	0	0
Pseudomonas cepacia	2	2	2	1	2	1	2	2	2	0	2	0	2	0	2	0	0	0	0	0
Pseudomonas species	2	2	2	0	2	2	2	2	2	0	2	0	2	0	2	0	0	0	0	0
Acinetobacter lwoffii	1	1	1	1	1	0	1	1	1	1	1	0	1	0	1	0	0	0	0	0
Acinetobacter baumann	2	2	2	2	2	1	2	2	2	1	2	0	2	1	2	0	0	0	0	0
Klebsiella oxytoca	1	1	1	0	1	1	1	0	1	0	1	0	1	0	1	0	0	0	0	0
Klebsiella pneumoniae	2	2	2	1	1	0	2	2	2	2	2	1	2	2	2	0	0	0	0	0
Enterobacter cloacae	2	2	2	2	2	1	2	2	2	2	2	1	2	1	2	0	0	0	0	0
Escherichia coli[a]	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	0	0	0	0
Flavobacterium meningosepticum	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0	0	0	0
Total	30	23	30	12	27	13	25	15	30	9	30	5	23	8	27	2	11	4	11	3

NOTE. N, no. of isolates tested for susceptibility; R, no. of isolates resistant to the antibiotic among those tested for susceptibility.

[a] Two of the 30 pathogens (*E. coli* and *S. pneumoniae*) from noncontaminated cultures were isolated from 1 blood culture.

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further guide both national and global recommendations for the empirical treatment of serious community-acquired neonatal infections.

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