Simple Clinical Criteria to Identify Sepsis or Pneumonia in Neonates in the Community Needing Treatment or Referral

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Background: Sepsis, meningitis and pneumonia annually kill 1.1 million neonates in developing countries; most deaths occur at home.
Objectives: To develop simple clinical criteria, enabling health workers in communities to identify neonates with potentially fatal sepsis; and to identify the danger signs alerting mothers to seek care.
Methods: In a field trial in 39 villages in Gadchiroli, India, trained health workers visited all neonates at home 8 times during the first 28 days of life, recording signs and outcome without interventions during 1995–1996 and with home-based management of sick neonates during 1996–1999. An independent neonatologist assigned the cause of death. We use the term "sepsis" to include sepsis, meningitis and pneumonia. We evaluated 31 signs as predictors of 43 sepsis deaths among 3567 neonates. We also evaluated mothers' observations as the danger signs to seek care.
Results: Simultaneous presence of any 2 of 7 signs (reduced or stopped sucking; weak or no cry; limbs becoming limp; vomiting or abdominal distension; baby cold to touch; severe chest indrawing; umbilical infection) predicted sepsis death with sensitivity 100%, specificity 92%, positive predictive value 27.2% and negative predictive value 100% in the nonintervention period. The criteria identified 10.6% of the neonates in the community as suspected sepsis, at a mean of 5.4 days before death. The criteria remained valid in the postintervention period. Any 1 of the 5 maternally observed danger signs (reduced sucking, drowsy or unconscious, baby cold to touch, fast breathing and chest indrawing) gave 100% sensitivity and identified 23.9% neonates for seeking care.
Conclusion: These criteria identify neonates in the community who are at risk for dying of infection with excellent sensitivity, specificity and negative predictive value but a moderate positive predictive value. They can be used by health workers to select sick neonates for treatment or referral. One potentially fatal case would be treated per 4 presumptive cases treated.

Key Words: neonatal sepsis, neonatal infection, diagnostic criteria, community

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Of the 4 million neonatal deaths each year, nearly 98% occur in developing countries.[1] Neonatal sepsis, which we define as septicemia, meningitis, pneumonia causes an estimated 1.1 million deaths per year.[2] Most neonates never reach the hospital; moreover pediatricians or facilities for bacterial culture are not available at most peripheral health facilities in developing countries. Simple methods to identify neonatal sepsis in the community for antibiotic treatment or referral are needed.

Simple clinical criteria developed earlier for diagnosing pneumonia in children younger than 5 years[3,4] are used in the Global Program on Acute Respiratory Infections.[5] Management of sick neonates was excluded from this strategy and from the Integrated Management of Childhood Illnesses (IMCI) strategy of the World Health Organization (WHO) and UNICEF,[6] because adequate evidence about methods to identify and treat sick neonates in the community was lacking. The clinical algorithms to diagnose the "sick child" in the IMCI strategy have been recently evaluated in studies in Gambia, Kenya and Bangladesh.[7–9] Two of these studies excluded all neonates, one excluded the early neonatal period and none developed the criteria for diagnosis of sepsis.

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A WHO-sponsored multicenter study on serious bacterial infections in infants 0–90 days of age[10] found that clinical criteria have a valid predictive relationship but that the clinical instrument developed is too cumbersome for use. Authors of the same study have recently reanalyzed the data and reported that 14 clinical variables showed significant association with severe disease or death in infants <2 months of age. However, the specificity was poor, resulting in many unnecessary referrals. The authors concluded, " Further studies are required to validate and refine the prediction of severe disease, especially in the first week of life, but there appear to be limits on the accuracy of prediction that is achievable."[11]

Earlier studies[3,4,7–11] were all clinic- or hospital-based, with consequent overrepresentation of sick children. Evaluation of screening criteria on such selected populations leads to overestimation of sensitivity and specificity, because of the verification bias,[10] making the extrapolation of clinic- or hospital-based criteria to community setting questionable. However, evaluation studies involving invasive procedures such as blood culture or lumber puncture cannot be conducted on community-based populations that include asymptomatic neonates for ethical reasons and because of parental refusal.[10]

We reported a field trial of home-based neonatal care and management of sepsis in rural Gadchiroli, India, in which the neonatal mortality rate (NMR) in the intervention area was reduced by 62%.[12] That field trial generated data based on prospective observation of neonates in rural homes.

The objectives of this study were to develop simple clinical criteria, enabling health workers in communities to identify neonates likely to die of sepsis, and to identify the danger signs alerting mothers to seek care. We did this by evaluating the various signs as predictors of death due to sepsis in neonates in community.

METHODS

Subjects and Data Collection. The field trial was conducted in rural Gadchiroli by the Society for Education, Action and Research in Community Health. The area and methods of data collection have been reported earlier.[12,13] All neonates born in 39 villages were eligible for inclusion. From April 1995 to March 1996, trained female village health workers (VHW) visited the neonates at home on 8 fixed days after birth (days 1, 2, 3, 5, 7, 15, 21 and 28). Additional visits were made when the neonate was sick and the VHW was informed. She inquired about specific signs of illness in mother and baby, made physical examinations and recorded the information.[13] She was not trained at this stage to provide treatment to most sick neonates, but she advised referral, which was almost never complied with by the parents. However, as a part of the ongoing service program, the VHW did treat suspected pneumonia (respiratory rate ≥60 or severe chest indrawing) with oral trimethoprim-sulfamethoxazole.[14] A physician visited each neonate, usually twice during the 28 days, to verify the VHW's findings. To evaluate the reliability of the VHWs' findings, the physician blindly recorded parallel information on 119 consecutive neonates, and the records were later compared.

All neonatal deaths were recorded by the VHWs and verified by the supervisor. The case records of the dead neonates were sent to a neonatologist (V.K.P.) at the All India Institute of Medical Sciences, New Delhi, who, blind to the field diagnosis, assigned the most probable cause of death (primary and associated) using WHO guidelines[15] and clinical judgment.

After this initial year (1995–1996) of observing, the VHWs were trained to educate mothers about neonatal care, diagnose various neonatal sicknesses and manage them at home, including management of suspected sepsis with 2 antibiotics.[12] Recording of the signs in mothers and neonates, the management of sick neonates and recording neonatal deaths and assigning the cause of death continued. In this analysis we have included information up to October 1999.

Choice of the Diagnostic Standard. Without facilities for laboratory or radiologic investigations to establish systemic infection in this community setting, the choice of a diagnostic standard for sepsis was a major challenge. Because earlier investigators had found it impossible to investigate all neonates in the study population, including the large number of asymptomatic ones, to identify neonates with sepsis, we decided to start from the other end, ie, dead neonates. In the preantibiotic era, there was 90% case fatality in neonatal sepsis.[16,17] We deduced, therefore, that in a setting without treatment, the neonatal deaths would include almost all but 10% of neonates with sepsis. The clinical judgment was then necessary to exclude deaths from other causes. Therefore the diagnostic standard in this study was neonatal deaths which an experienced neonatologist judged as due to sepsis.

Analysis. We analyzed the data from the preintervention period (1995–1996) to identify the signs in live neonates that were associated with the diagnostic standard and evaluated their ability to predict it by standard methods.[18,19] The signs thus selected were then tested on the 1996–1999 data to further evaluate their validity during the intervention phase and were modified to improve their performance. Sensitivity was the overriding consideration because the diagnostic standard was death.

We selected 10 maternal and 21 neonatal signs from the neonatal records as potential criteria. The association of each with sepsis death was estimated in the data from 1995–1996 by the odds ratio and the 95% confidence intervals (CI). Those with significant association (lower limit of CI, >1.0) were selected for further analysis. (Information on 6 variables was available from 2 sources, mother's report and VHW's observation. When both were significantly associated with the outcome, the one with the higher odds ratio was selected; if they had similar odds ratios, the mother's information was preferred because of its

ease of data collection and greater availability.) The sensitivity and specificity of the 16 signs thus selected, to predict sepsis deaths, were calculated, first individually and then for a prediction rule of the simultaneous presence of any 1, any 2, any 3, any 4 or any 5 signs.

To reduce the number of criteria to make the final instrument manageable for use in the field, and to focus on those signs that were independently associated with sepsis death, we did logistic regression with backward elimination, using SPSS PC, and identified 5 signs. A rule based on "simultaneous presence of any 2" of the 5 signs thus selected was evaluated for sensitivity, specificity and predictive values,[18,19] using the same 1995–1996 data set. To improve the sensitivity, we then added the other criteria one at a time and evaluated the performance of the rule of "any 2" of each set of 6. The best set of 6 that emerged was then evaluated on the data from the period 1996–1999. To further improve the performance, the signs of respiratory system were added, one at a time, to the previously selected 6 signs, and the best set of 7 criteria was finally selected. Its performance was evaluated on the data set of 1995–1996 and on the entire data set of 1995–1999.

The individual contribution of each of the finally selected 7 criteria was assessed by estimating the proportion of sepsis deaths in which each criterion was present, the number of days it manifested before death and the number of sepsis deaths that would be missed by deleting it.

We finally estimated the lead time gained,[19] ie, number of days before death at which the diagnosis of sepsis could be made for initiating appropriate management, using the rule of "any 2 of the selected 7 criteria."

Because the 7 finally selected criteria required reporting of signs by mothers and observation by VHWs, we evaluated by similar methods a set of neonatal signs based only on mothers' reports to identify the danger signals presence of any 1 of which a mother could use for seeking care.

Consent and Ethical Approval. The field trial was given ethical approval by an external committee of pediatricians and public health experts.[12] Written consent to conduct the trial was obtained from the village councils of 39 intervention villages and from the parents of neonates who were treated for sepsis.[12,13]

RESULTS

During 1995–1996, 1016 neonates were born in the 39 study villages, of whom 763 (75.1%) were observed at home by VHWs. Forty of the 763 died (NMR 52.4/1000), and 22 deaths were assigned to sepsis/pneumonia. The 253 neonates not observed by the VHWs had an NMR of 47.4/1000, not significantly different from that in the observed neonates. Forty-three percent of the observed neonates had low birth weight (<2500 g), and 10% were born preterm. The mean agreement between data recorded by VHWs and by the physician on 47 variables was 92.3%.[12]

Association of the 10 maternal and 21 neonatal signs/symptoms with sepsis deaths in the 1995–1996 data were estimated. Those that showed significant association (lower limit of 95% CI of odds ratio, >1.0) are shown in Table 1. Only 2 of the 10 maternal variables (premature rupture of membranes and persistent cough) but 14 of the 21 neonatal variables showed significant association. Sixteen neonatal signs with significant association were selected for further analysis. Umbilical and skin sepsis did not show significant association, but they were included for further exploration because of their well-known association with sepsis, giving a total of 18 neonatal variables.

Table 1 also indirectly shows the sensitivity (percent among sepsis deaths) and the specificity (100 − percent among survivors) of each sign to identify sepsis death. The performance of any 1 of the selected 16 signs was sensitivity 100%, specificity 53.6%; that of any 2 signs was sensitivity 100%, specificity 81.0%; that of any 3 signs was sensitivity 86.4%, specificity 91.8%; that of any 4 signs was sensitivity 72.7%, specificity 94.6%; and that of any 5 signs was sensitivity 68.2%, specificity 97.2%. The respective yield (percent of neonates selected as sepsis) was 48.0, 21.4, 10.5, 7.3 and 4.7%. A receiver operating characteristics curve was plotted (not shown) in which the point closest to the upper left corner gives the best performance in the sense of balancing sensitivity and specificity. On the basis of the receiver operating characteristics curve, we selected "any 2" rather than "any 3" because of its 100% sensitivity.

The logistic regression analysis identified 5 criteria that independently showed significant or almost significant association with sepsis death. These, with their odds ratios (the 95% CI in parentheses), were: cry reduced or stopped, 14.3 (3.9, 52.1); sucking weak/reduced/stopped, 7.9 (1.8, 34.2); vomiting or abdominal distension, 6.8 (1.7, 27.2); limbs limp, 3.3 (0.9, 12.0); baby cold to touch, 3.5 (1.0, 12.4).

The performance of these 5 core clinical criteria in predicting sepsis deaths in the neonatal population of 1995–1996 is shown in Table 2. "Any 2" of the 5 criteria gave 90.9% sensitivity. When the other criteria were added, one at a time, addition of 'umbilical sepsis' to the 5 core criteria gave 100% sensitivity (Table 2). This combination of 6 was selected as the best set of criteria on the basis of the 1995–1996 data.

From April 1996 to October 1999, 3052 neonates were born in the study villages, of whom 2804 (92%) were observed by VHWs. Among these, 169 were treated with antibiotics for suspected sepsis, using the presence of any 2 of a similar set of signs.[12] Seventy-five neonates died (NMR 26.7/1000), including 21 with sepsis (determined subsequently, as described under the "diagnostic standard" of this paper), of whom 6 had been treated for sepsis.

Performance of the 6 criteria selected from 1995–1996 was evaluated on the neonatal population in 1996–1999 with the 21 sepsis deaths (Table 3). Although specificity improved to 95.7%, the sensitivity was 81%, with 4 sepsis deaths missed by

TABLE 1. Frequency of Signs and Symptoms and Their Association With Neonatal Sepsis Deaths in Gadchiroli: 1995–96, n = 763, Sepsis Deaths = 22

Sign/Symptom	Source of Information	Present in Sepsis Deaths (22)		Present in Survivors (741)		Odds Ratio
		No	%	No	%	
Maternal						
a. In the last trimester of pregnancy						
Vaginal discharge	Mother	3	13.6	89	12.0	1.2 (0.3–4.2)*
Bacterial skin infection	Mother	0	0.0	26	3.5	0.0
Burning in urine	Mother	1	4.5	41	5.5	0.8
Fever during 7 days before delivery	Mother	3	13.6	49	6.6	2.2 (0.5–8.4)
b. During labor						
Premature rupture of membranes†	Mother	4	18.2	34	4.6	4.6 (1.3–15.6)
Prolonged labor	Mother	4	18.2	71	9.6	2.1 (0.6–6.8)
c. During 0–28 d postpartum						
Foul smelling/purulent vaginal discharge	Mother	6	27.3	235	31.7	0.8 (0.3–2.2)
Fever	Mother	3	13.6	87	11.7	1.2 (0.3–4.4)
Diarrhea	Mother	2	9.1	46	6.2	1.5
Persistent cough†	Mother	10	45.5	149	20.1	3.3 (1.3–8.4)
Neonatal (0–28 d)						
Drowsy/unconscious†	Mother	15	68.2	29	3.9	52.6 (18.3–156.1)
Drowsy/unconscious	VHW	11	50.0	18	2.4	40.2 (14.0–116.6)
Cry abnormal or weak	Mother	12	54.5	59	8.0	13.9 (5.3–36.4)
Cry weak or stopped†	VHW	15	68.2	20	2.7	77.3 (25.9–238.7)
Sucking weak/reduced/stopped†	Mother	19	86.4	79	10.7	53.1 (14.4–230.8)
Limbs became limp†	Mother	12	54.5	24	3.2	35.9 (12.9–100.9)
Mother feels baby has fever	Mother	1	4.5	88	11.9	0.4 (0.1–2.5)
Temperature >99°F	VHW	3	13.6	117	15.8	0.8 (0.2–3.1)
Mother feels baby is cold†	Mother	13	59.0	58	7.8	17.0 (6.5–45.4)
Temperature <95°F	VHW	12	54.5	70	9.4	11.5 (4.5–30.0)
Neonatal (0–28 d)						
Urine diminished or stopped†	Mother	6	27.3	22	3.0	12.3 (3.9–37.7)
Diarrhea	Mother	0	0.0	42	5.7	0.0
Vomiting†	Mother	4	18.2	32	4.3	4.9 (1.3–16.7)
Abdominal distension†	VHW	3	13.6	12	1.6	9.6 (2.0–41.1)
Cough	Mother	2	9.1	150	20.2	0.4 (0.1–1.8)
Nasal discharge	VHW	1	4.5	90	12.1	0.3 (0.1–2.5)
Mother feels baby has fast breathing†	Mother	5	22.7	56	7.6	3.6 (1.1–10.9)
Respiratory rate ≥60	VHW	3	13.6	59	8.0	1.8 (0.4–6.8)
Grunt†	VHW	8	36.4	56	7.6	7.0 (2.6–18.7)
Mother feels baby had chest indrawing	Mother	3	13.6	50	6.7	2.2 (0.5–8.2)
Chest indrawing†	VHW	5	22.7	47	6.3	4.3 (1.3–13.3)
Stops breathing intermittantly†	VHW	5	22.7	2	0.3	7108.7 (16.9–881.1)
Tongue blue†	VHW	4	18.2	4	0.5	41.1 (7.8–217.6)
Pustules in skin	VHW	2	9.1	38	5.1	1.9 (0.0–8.7)
Umbilical sepsis	VHW	4	18.2	148	20.0	0.9 (0.3–2.9)
Hemorrhage†	VHW	3	13.6	5	0.7	23.2 (4.0–124.0)
Seizures	Mother	0	0.0	1	0.1	0.0

*Numbers in parentheses, 95% CI.
†Variable selected for further analysis (total, 16).

TABLE 2. Evaluation of Various Sets of Clinical Criteria to Predict Sepsis Death: 1995–1996, n = 763, Sepsis Deaths = 22

Clinical Criteria (Simultaneous Presence of any 2 or More)	True Positive	False Negative	False Positive	True Negative	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Yield (% Neonates Selected as Sepsis)
Clinical core criteria 1. Cry weak or stopped* 2. Sucking reduced or stopped† 3. Limbs loose† 4. Baby was cold† 5. Vomiting† or abdominal distension*	20	2	40	701	90.9	94.6	33.3	99.7	7.9
5 core criteria and fast breathing†	20	2	51	690	90.9	93.1	28.2	99.7	9.3
5 core criteria and drowsy/unconscious†	21	1	46	695	95.5	93.8	31.3	99.5	8.8
‡5 core criteria and umbilical sepsis*	22	0	46	695	100.0	93.8	32.4	100.0	8.9

*Observed by village health worker.
†History given by mother
‡The set of criteria selected for further testng.

TABLE 3. Evaluation of Criteria in Neonatal Populations During Different Periods

Clinical Criteria (Simultaneous Presence of Any 2 or More)	True Positive	False Negative	False Positive	True Negative	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)	Yield (% Neonates Selected as Sepsis)
				April 1996–October 1999, n = 2804, sepsis deaths = 21					
Core criteria 1. Cry weak or stopped* 2. Sucking reduced or stopped† 3. Limbs loose† 4. Baby was cold† 5. Vomiting† or abdominal distension* 6. Umbilical sepsis*	17	4	120	2663	81.0	95.7	12.4	99.9	4.9
6 core criteria and respiratory rate ≥60†	18	3	151	2632	85.7	94.6	10.7	99.9	6.0
6 core criteria and grunt*	19	2	150	2633	90.5	94.6	11.2	99.9	6.0
6 core criteria and chest indrawing*‡	20	1	146	2637	95.2	94.8	12.0	100.0	5.9
6 core criteria and grunt[a] or chest indrawing*	20	1	159	2624	95.2	94.3	11.2	100.0	6.4
6 core criteria and respiratory rate ≥60* or chest indrawing*	20	1	155	2628	95.2	94.4	11.4	100.0	6.2
				April 1995–March 1996, n = 763, sepsis deaths = 22					
6 core criteria and chest indrawing*	22	0	59	682	100.0	92.0	27.2	100.0	10.6
				April 1995–October 1999, n = 3567, sepsis deaths = 43					
6 core criteria and chest indrawing	42	1	205	3319	97.7	94.2	17.0	100.0	6.9

*Observed by village health worker.
†History given by mother.
‡Finally chosen criteria.

the criteria. Some of these missed deaths had grunt, chest indrawing or increased respiratory rate. The performance of the 6 criteria with these 3 signs added singly and in combination is also presented in Table 3. A rule of any 2 of the 6 criteria plus chest indrawing showed high sensitivity and specificity and lower yield. The performance of these 7 criteria when evaluated again on the data of 1995–1996 and on the entire data of 1995–1999 continued to show the high performance (Table 3). Hence they were selected as the final set.

The clinical definitions of the 7 selected criteria were as follows: mother states that (1) baby who earlier sucked well was now sucking less, or weakly or did not suck for 8 hours or more; (2) baby's limbs, previously normal, have become limp; (3) baby's body has become cold to touch. The village health worker observed that: (4) baby who previously cried well has stopped crying, or the cry has become weak; (5) baby's abdomen was distended; (6) baby developed subcostal chest indrawing; and (7) there was pus in or from the umbilicus.

The contribution of each criterion (proportion of sepsis deaths in which it was present), the lead time (the mean number of days it manifested before death) and the number of sepsis deaths missed if the criterion was deleted (1995–1999) are presented in Table 4.

The lead time gained[19] using the final set of 7 screening criteria in the year 1995–1996 was 5.4 days; in 1996–1999, it was 1.8 days. In 1995–1996, it was <24 hours in 2 deaths and 24–48 hours in 2 deaths, but in 1996–1999 it was <24 hours in 11 deaths and 24–48 hours in 5 deaths. Inspection of the records in which the lead time was short did not reveal another clinical variable that could have predicted the deaths earlier.

TABLE 4. Contribution, Lead Time and Essentiality of Each Selected Criteria in Predicting Sepsis Deaths: 1995–1999, Sepsis Deaths = 43

Criteria	No. Present in Sepsis Deaths	Lead Time (Manifested Before Death) in Days	Deaths Missed if the Criteria Are Deleted
Cry weak or stopped*	23 (53.5)†	3.9 ± 1.2‡	5
Sucking reduced or stopped§	32 (74.4)	3.2 ± 0.9	14
Limbs loose§	15 (34.9)	3.3 ± 1.1	5
Mother felt that baby was cold to touch§	18 (41.9)	4.0 ± 0.9	9
Vomiting§ or abdominal distension*	10 (23.3)	2.6 ± 0.8	6
Umbilical sepsis*	5 (11.6)	7.0 ± 1.7	4
Chest indrawing*	12 (27.9)	2.6 ± 1.2	5

*Observed by village health worker.
†Numbers in parentheses, percent.
‡Mean ± SE.
§History given by mother.

With a selection rule of any 3 of the 7 criteria, the sensitivity fell to 77.3% in 1995–1996 and to 52.4% in 1996–1999, although specificity improved to 96.9 and 97.9%, respectively.

Five neonatal signs reported by mothers were identified as the danger signals: (1) sucking reduced or stopped; (2) drowsy or unconscious; (3) baby cold to touch; (4) fast breathing; (5) chest indrawing. The presence of any 1 of these 5 signals predicted sepsis death in 1995–1996 (1996–1999 in parentheses) with sensitivity 100% (100%), specificity 78.4% (87.1%), positive predictive value 12.1% (5.5%), negative predictive value 100% (100%) and yield 23.9% (13.6%).

DISCUSSION

This retrospective analysis identified a decision rule, and a set of 7 clinical criteria for detecting neonates in rural homes likely to die of sepsis, which showed 100% sensitivity, 92% specificity and 27% predictive value. With these criteria, 10.6% of the neonates from the community in the preintervention phase would have been identified as suspected sepsis for management. The criteria performed well during the intervention phase also. Five signs reported by mothers were identified for use as danger signals to seek care for sepsis.

We avoided selection bias in the study population by using the community-based population. However, in the absence of laboratory investigations, how valid was our diagnostic standard? Without treatment, only 10% of sepsis cases can be expected to survive[16,17]; therefore restricting to dead neonates ensures that all sepsis cases in the study population, except for these 10%, were included. However, among the dead neonates, there could be some misclassification in assigning the cause of death based on the clinical judgment. Because clinical judgment in our study was used only in neonates with fatal outcome, the chance of misclassifying normal neonates as septic is minimum. The clinical criteria that emerged (Table 3) closely agree with the established description of neonatal sepsis.[20–22] The neonatologist was certain that he would have started treatment of sepsis if these cases were seen before death. Thus the diagnostic standard is appropriate for identifying sick neonates in whom death may be preventable by treatment of sepsis.

Even a diagnostic standard of blood culture is less than definitive.[20] Moreover clinical judgment is involved even with the interpretation of seemingly objective diagnostic standards such as chest radiographs or bacterial culture.[10,23] Hence the dictum that management of neonatal sepsis should ultimately be guided by clinical judgment[21,22] was used.

The clinical data collected by VHWs showed 92% agreement with the physician. Because these clinical criteria are meant for use in the community by nonphysician health workers, our data collection closely represented the real life situation.

The respiratory signs of rate, chest indrawing and grunt were not significant in the logistic regression. This could be the result of using trimethoprim-sulfamethoxazole in neonates with suspected pneumonia in the study population.[12,13] Because such treatment reduces case fatality in neonates with respiratory signs,[14] prediction of sepsis/pneumonia deaths by these signs might be underestimated. This probable imbalance was corrected in the finally selected set of criteria by including chest indrawing.

There are no earlier studies for comparison of community-based neonatal screening for sepsis. The study in Bangladesh found that the IMCI criteria to identify sick babies, 7–59 days old, for hospital admission had sensitivities of 79–84% and specificities of 54-to 69%.[9] This study was in a clinic setting, with the physician's judgment as the diagnostic standard. Our diagnostic standard was more rigorous, and the sensitivity of 100% and specificity of 92% are satisfactory.

The investigators of the WHO multicentric study reported that the specificity of the simpler clinical predictors was not satisfactory.[11] The clinical variables identified in these and some other studies[10,11,24] and ours are, to some extent, similar; but our set of 7 signs and the decision rule of "any 2 signs" showed better performance.

The positive predictive value of the finally selected criteria was 27.2% in 1995–1996 and 12% in 1996–1999. Because the 1996–1999 data are postintervention, in which fewer deaths occurred, the predictive value is underestimated. Hence the performance in 1995–1996 is the more realistic estimate.

With these criteria, nearly 10% of the neonates in the community will be identified for treatment with antibiotics; at the 27% predictive value, 1 fatal illness will be treated for 4 treated neonates. This compares favorably with the neonatal care practice in Boston, MA, where 4.4–10.5% of neonates in nurseries were treated with antibiotics on the clinical suspicion of sepsis but only 4–7% of the treated cases showed positive bacterial culture.[25] Another study from the United States reported that of the 18,299 neonates born in hospitals during 1995–1996, 15.2% were evaluated but only 2.2% of those evaluated had infection (true positive); yet 10.9% of the asymptomatic and 38–79% of those with clinical signs received antibiotics.[26] Standard textbooks of neonatology recommend commencing antibiotics even on slight suspicion of sepsis.[21,22] Our clinical criteria follow the same principle, but with fewer overtreatments.

The lead time to commence treatment before death was satisfactory (5.4 days) in 1995–1996. It was less (1.8 days) in 1996–1999, probably because in the postintervention data many of the deaths were residual, more serious and more rapid. We did not find any earlier clinical features in these neonates to further improve the criteria.

There are certain limitations of our criteria. Some signs, such as convulsions and jaundice, were probably underreported by VHWs and hence were not well-represented in this data set. Of the 5 clinical criteria identified by logistic regression, 2 (limbs limp and baby cold to touch) were of borderline significance. Because most deaths in the diagnostic standard in 1995–

1996 occurred beyond 3 days after birth, these criteria may not be adequate for detecting early onset sepsis. Clinical manifestation of neonatal sepsis is protean and illusive. In spite of the reassuring validity here, these criteria are likely to miss some sepsis cases. That is an inherent limitation of the nature of the problem and of the imperfect nature of any clinical criteria.[11,20–22] The validity of the criteria may be lesser in populations other than on which these criteria are based.[19]

Usefulness of screening neonates for sepsis using similar criteria and treating with antibiotics was tested in the field trial in Gadchiroli. The case fatality in the neonates diagnosed as suspected sepsis and treated by VHWs, fell from 16.6% to 2.8%; and the sepsis related NMR in 39 villages declined by 76%.[12] The improved criteria developed in this paper should give better results because they identify additional sepsis deaths missed by the criteria used in the Gadchiroli field trial.

The cost of septic workup in developed countries is prohibitively high, reported as $71.48 per mother-baby pair investigated or $1066.77 per septic neonate detected.[27] Cost estimates of such procedures are not available in India, but the cost of home-based monitoring of neonates and providing care to suspected septic neonates and other sick babies was only $5 per neonate in our study.[12]

For some of the clinical variables, the mother's history was equally or more predictive as the VHW's observations (Table 1), probably because the mother observed the baby more sensitively and for longer hours. This finding suggests the possibility of educating mothers to identify danger signals in neonates and seek care even if any 1 danger signal is present. We identified 5 such signs based on mother's history (see "Results") that showed satisfactory performance.

To obtain reliable information from mothers or VHWs, in-depth understanding of the words in their culture, proper phrasing of questions and adhering to the definitions of various criteria (see "Results") are important. Training VHWs to ask questions to mothers, identify signs and apply definitions correctly and subsequent field supervision are crucial.

These criteria shall enable the program managers in developing countries to train health workers to detect and either treat or refer neonates with suspected sepsis, thus substantially reducing neonatal deaths caused by sepsis/pneumonia.

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