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# Original Article

## Why Do Neonates Die in Rural Gadchiroli, India? (Part II): Estimating Population Attributable Risks and Contribution of Multiple Morbidities for Identifying a Strategy to Prevent Deaths

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**OBJECTIVES:**

The understanding about why neonates die in rural areas in developing countries is limited. In the first year (1995 to 1996) of the field trial of home-based neonatal care in rural Gadchiroli, India, we prospectively observed a cohort of neonates in 39 villages. In Part I of this article, we presented the primary causes of death. The data were further analyzed:

1. To estimate the population attributable risk (PAR) of death for the main causes of neonatal mortality.
2. To evaluate the effect of a multiplicity of morbidities and to identify which morbidity combinations cause neonatal deaths.
3. To develop a hypothesis about how best to reduce neonatal mortality.

**STUDY DESIGN:**

We analyzed the observational data by logistic regression to estimate the PAR of death for six major morbidities. The effect of the number of morbidities per neonate on case fatality (CF) was estimated. Then we identified the main combinations of morbidities as the component causes leading to death. We estimated the excess deaths attributable to sepsis.

**RESULTS:**

This cohort included 763 neonates among whom 40 neonatal deaths occurred. Six major morbidities were associated with the following proportion of deaths: preterm, 62.5%; sepsis, 60%; intrauterine growth restriction (IUGR), 27.5%; asphyxia, 25%; hypothermia, 22.5%, and feeding problems, 15%. The estimated PARs were: preterm, 0.74; IUGR, 0.55; sepsis, 0.55; asphyxia, 0.35; hypothermia, 0.08, and feeding problems, 0.04. The CF associated with the number of morbidities per neonate was: with no morbidity, 0.3%; one morbidity, 2.1%; two morbidities, 15.3%; three or more morbidities, 41.4% ($p<0.001$). In all, 82.5% of all deaths occurred in neonates with two or more morbidities. The proportion of total deaths associated with only preterm was 7.5%, and with only IUGR was 2.5%; however, with the main morbidity combinations it was preterm + sepsis, 35%; IUGR + sepsis, 22.5%; preterm + asphyxia, 20%; preterm + hypothermia, 15%; and preterm + feeding problem, 12.5%. The % CF with low birth weight (LBW) <2500 g alone was 5.2% and with infection alone was 1.9%, but with LBW + infection it was 31.9%. The estimated excess deaths caused by sepsis over and above LBW was 44% of the total deaths.

**CONCLUSIONS:**

Preterm and IUGR are ubiquitous components, but usually not sufficient to cause death. Most deaths occur due to a combination of preterm or IUGR with other comorbidities. If preterm birth or IUGR cannot be prevented, the strategy should be to ensure neonatal survival by addressing comorbidities, that is, infections, asphyxia, hypothermia, and feeding problems in that order of priority. We hypothesize that the prevention and/or management of neonatal infections will reduce neonatal mortality by 40 to 50%.
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## INTRODUCTION

The World Health Organization has estimated[1] that the direct causes of neonatal deaths globally are: infections, 32%; asphyxia, 29%; complications of prematurity, 24%; congenital anomalies, 10%, and other, 5%. In the first year of the field trial of home-based neonatal care in rural Gadchiroli, India, the primary cause of death was sepsis/pneumonia, 52.5%, followed by asphyxia, 20%; prematurity, 15%; hypothermia, 2.5%, and other, 10%.[2]

A single primary cause of death makes for convenient analysis and presentation of data. However, it suffers from certain limitations. First, it oversimplifies the complex reality by ignoring the contribution of associated causes. Second, in spite of the guidelines[3] for assigning the primary or underlying cause of death, the selection of one cause from among many does involve a subjective judgment.[4–6] Hence, attributing death to a single cause may be difficult and even misleading. It also shrinks the opportunity for intervention by ignoring the contributory causes.

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This was consistent with the current multicausal understanding of the causal mechanism as described by Rothman and Greenland.[7] According to this, the ''one cause–one effect'' understanding is a simplistic misbelief. In reality, most outcomes — whether disease or death — are caused by a chain or web consisting of many component causes. A combination of multiple causes that results in disease or death is considered a ''sufficient cause.'' Some of its components are ''necessary'' but insufficient to cause the effect by themselves. When the causal mechanism includes the necessary components and also becomes sufficient, the effect is produced.

Which morbidities or combinations of morbidities constituted the causal web sufficient to cause neonatal deaths? What proportion of neonatal deaths were attributable to each of these component causes? In epidemiology, population attributable risk (PAR), also called attributable fraction, is used for estimating the proportion of disease or death in a population that can be ascribed to a cause or a combination of causes. It is also a useful measure of what proportion of disease or deaths can be prevented if that component cause is removed.[8,9] The purpose of this paper is to identify which morbidity or morbidities can be targeted to reduce neonatal mortality. The prospectively observed data on a cohort of rural neonates in the first year of the Gadchiroli trial offered a unique opportunity because it represented the natural history of rural neonates. We analyzed these data with the following objectives:

1. To estimate the population attributable risk (PAR) of death for the main causes of neonatal mortality.
2. To evaluate the effect of a multiplicity of morbidities and to identify which morbidity combinations cause neonatal deaths.
3. To identify the priority for action and to develop a hypothesis about how best to reduce neonatal mortality.

## METHODS

We conducted a field trial of home-based neonatal care in rural Gadchiroli (India), in a block of 39 intervention villages. Agriculture was the main occupation of the population, and deliveries occurred mostly at home, assisted by traditional birth attendants. The selection of the area, characteristics of the study population, the study design, and methods of data collection have been described earlier in detail.[10–12] Trained village health workers (VHWs) collected data on neonates born in 39 villages by making three home visits during pregnancy, attending home delivery, and eight home visits during days 1 to 28 of neonatal life. A supervisory physician who visited each village once in 15 days checked the quality of data. The births and neonatal deaths were recorded by VHWs as well as by an independent vital statistics surveillance system. The quality and the completeness of data was >90%.[12,13]

From the observational data prospectively collected in 39 villages in the first year of the trial (April 1995 to March 1996) on the incidence of various neonatal morbidities and the associated number of deaths in 763 neonates,[10,13] we selected the six morbidities associated with the most deaths. (We use the term ''morbidity'' to include risk factors such as low birth weight (LBW) or preterm birth as well as diseases.) These were (1) preterm birth (<37 weeks); (2) full term birth with intrauterine growth restriction (IUGR), that is, gestation of 37 weeks or more, but birth weight <2500 g; (3) clinical sepsis (when any two of the following six clinical criteria were simultaneously present in a neonate: (i) previously normal cry became weak/stopped or previously normal baby became drowsy/unconscious or previously normal sucking became weak or stopped, (ii) baby cold to touch or feverish (skin temperature >99°F), (iii) skin infection or umbilical infection, (iv) Vomiting or diarrhea or abdominal distension, (v) respiratory rate ≥60 and (vi) grunting or chest indrawing); (4) severe asphyxia (breathing not well established at 5 minutes after birth); (5) feeding problems; and (6) hypothermia (skin temperature <95°F). Birth defects were not a major cause of death in this cohort. The period of gestation was calculated from the date of last menstruation (which was recorded by the VHWs at the time of registering the pregnancy, usually in the 4th or 5th month). The birth weight was recorded in most neonates within 6 hours of birth using a spring balance (Salter, UK). The details of recording the data have been published earlier.[10] We assessed the validity of gestational age by cross-tabulating against the birth weight. In many neonates, feeding problems and hypothermia were not present initially, but appeared on later days as a part of the clinical diagnosis of sepsis. In such neonates, we decided to count these two as manifestations of sepsis and not as independent morbidities. But if these occurred independent of clinical sepsis in the same neonates or in different neonates, they were considered a morbidity per se.

By univariate analysis, we calculated the incidence, case fatality, and relative risk of death associated with each of these six morbidities. This being a multicausal analysis, a neonate was counted in each morbidity from which it suffered. When multiple morbidities occurred in the same neonate, such neonates were counted more than once.

To remove the confounding effect caused by the presence of multiple morbidities in the same neonate and to estimate the odds ratio (OR) of death associated with each morbidity, we performed logistic regression analysis. (An explanation of the statistical method is provided at the end of the Methods section.) From these ORs, we estimated the PAR of neonatal death attributable to each morbidity. The PAR was calculated by the equation:[14]

$$\text{PAR} = \frac{P(\hat{R}R - 1)}{1 + P(\hat{R}R - 1)}$$

To evaluate the effect of the multiplicity of morbidities, neonates were categorized by the number of morbidities they suffered from

during the first 28 days. We then analyzed the number of deaths associated with each category, the percent case fatality (% CF), and the distribution of the neonatal deaths in these categories.

To identify how the individual morbidities, alone and in combinations, affected neonatal survival, we tabulated the neonates: those with no morbidity, with a single morbidity, and with various combinations of morbidities, and the associated number of neonatal deaths. We also tabulated the mean birth weight and period of gestation of neonates in each category. From these, we identified five causal combinations that explained most deaths.

We further assessed the effect of the combination of LBW and infection, by analyzing % CF in LBW without sepsis, in sepsis without LBW, and in neonates with LBW + sepsis. We estimated by logistic regression the OR of death for LBW alone, sepsis alone, and for the interaction of these two.

Since the earlier reviews of field trials and programs have found that LBW or preterm birth are usually not preventable at the population level,[15–17] we explored how many deaths could be prevented by addressing the other component cause, namely, infection, even in the presence of LBW (which included most (62/75) preterm and all IUGR neonates). To do this, we estimated the excess number of deaths contributed by clinical sepsis by calculating the number of deaths with sepsis minus the number of deaths without sepsis in different birth weight strata. For example, the excess deaths caused by sepsis in neonates with birth weight 2000 to 2499 g were estimated from the deaths observed in neonates of birth weight 2000 to 2499 g with sepsis, minus deaths expected if sepsis was absent (the percent case fatality in neonates without sepsis × the number of neonates with sepsis in that birth weight group).

We then summarized in one table the various estimates we had arrived at by different methods and in a hierarchal order of magnitude.

We used SPSS PC + and the Epi-info softwares for data analysis.

[Statistical explanation: Strong correlations between independent variables in a logistic regression model may sometimes cause multicollinearity, which may even result in incorrect conclusions (Kleinbaum DG. Logistic Regression. New York: Springer-Verlag; 1994. p. 168). The independent variables in our models are six neonatal morbidities, and there is a possibility that the presence of one or more of them may be associated with the presence of one or more of the others. We used $\chi^2$ test to assess the associations among the different morbidities. We found statistically significant associations ($p<0.05$) of preterm birth with LBW as well as with birth asphyxia, sepsis, and feeding problems, and of LBW with sepsis. Hence, we further assessed the presence of any multicollinearity among the variables included in the logistic regression model by using a SAS Macro that outputs the condition indices (CI) and variance decomposition proportions (VDP). As is customary, a CI value of 20 or more was taken as an indicator of collinearity and VDP values of 0.5 or higher were used to identify specific variables involved in the collinearity (1. Kleinbaum DG. Epidemiologic Modeling. Course material for the course Epi 740, Rollins School of Public Health, Emory University, Atlanta; 2. David Garson. Quantitative Research in Public Administration. Course material for the course PA 765, North Carolina State University, Raleigh, North Carolina). No collinearity was identified in the model. The highest CI value was 7.34, much less than the cutoff value of 20.]

## RESULTS

Out of total 1016 live births in the year 1995 to 1996 in 39 villages, 763 neonates (75%) were studied, among whom 40 deaths occurred during the neonatal period. The number of neonates with different gestational age and their mean birth weight in parentheses was: <32 weeks: 11 (1484 g), 33 to 34 weeks: 15 (1742 g), 35 to 36 weeks: 46 (2188 g), 37 to 38 weeks: 189 (2416 g), 39 to 40 weeks: 302 (2549 g), and >40 weeks: 162 (2613 g). The date of last menstruation of the mother or birth weight of the neonate was not recorded in 38 cases.

The six main morbidities (those associated with most of the deaths), their incidence, associated case fatality, proportion of deaths, and the relative risk of death are presented in Table 1. In this cohort, the incidence of LBW was high, 41.9%. Since the incidence of preterm birth was 9.8%, the majority of the LBW neonates were IUGR. The incidence of sepsis (clinical) and hypothermia was also >10%. In this univariate analysis, most deaths were associated with preterm (62.5%), sepsis (60%), IUGR (27.5%), and asphyxia (25%).

Univariate analysis does not take into consideration the confounding effect caused by the presence of multiple morbidities in a neonate. The logistic regression adjusts for such an effect and provides the estimates of risk, as ORs, associated with individual morbidities. The ORs estimated by logistic regression and the estimated PAR associated with these six morbidities are presented in Table 2. The ORs of preterm birth, sepsis, IUGR, and asphyxia are highly significant, but not for hypothermia and feeding problems.

PAR is highest, 0.74, for preterm, followed by 0.55 for sepsis, 0.55 for IUGR, and 0.35 for asphyxia. PAR for hypothermia and feeding problems is low. Since neonates having multiple morbidities were counted with each morbidity, the sum total of PARs was more than 1. This is an accepted and expected phenomenon with multicausal situations.[8,9]

The effect of a multiplicity of morbidities in a neonate was assessed by estimating the percent case fatality in neonates with different numbers of morbidities. Case fatality steeply and progressively increased with the increase in the number of morbidities per neonate (Figure 1).

To assess the effect of individual morbidities and their combinations, neonates were tabulated according to morbidities, singly and in various combinations. Table 3 shows their incidence,

**Table 1** Case Fatality and Relative Risk of Death Associated with Selected Neonatal Morbidities: Univariate Analysis (1995–1996, $n = 763$, neonatal deaths = 40)

| Morbidity | Sick neonates | | Deaths | | RR† of death (95% CI) | Proportion of total deaths (40)* |
|---|---|---|---|---|---|---|
| | *N** | % Incidence | *N** | % Case fatality | | |
| Preterm (<37 weeks) | 75 | 9.8 | 25 | 33.3 | 15.3 (8.4–27.7) | 62.5 |
| Clinical sepsis | 130 | 17.0 | 24 | 18.5 | 7.3 (4.0–13.4) | 60.0 |
| Intrauterine growth restriction (IUGR)‡ | 253 | 33.2 | 11 | 4.3 | 0.8 (0.4–1.5) | 27.5 |
| Severe birth asphyxia | 26§ | 4.6 | 10 | 38.5 | 8.0 (4.4–14.9) | 25.0 |
| Hypothermia¶ | 106 | 13.9 | 9 | 8.5 | 1.8 (0.9–3.7) | 22.5 |
| Feeding problems¶ | 63 | 8.3 | 6 | 9.5 | 2.0 (0.9–4.5) | 15.0 |

*A neonate having more than one morbidity is counted in each category. Hence, the sum may be more than the total neonates or deaths in the study population.
†Relative risk.
‡Full term (37 completed weeks or more) with birth weight <2500 g.
§Observed in 570 neonates.
¶Excluding when present in neonates with sepsis.

**Table 2** Odds Ratio (OR) and Population Attributable Risk (PAR) of Death for Individual Morbidities ($n = 763$, deaths = 40)

| Morbidity | Odds ratio* (95% CI) | Significance | Population attributable risk† |
|---|---|---|---|
| Preterm (<37 weeks) | 29.79 (9.4–94.5) | <0.001 | 0.74 |
| Clinical sepsis | 8.17 (3.6–18.6) | <0.001 | 0.55 |
| Intrauterine growth restriction (IUGR)‡ | 4.69 (1.4–15.4) | <0.011 | 0.55 |
| Severe birth asphyxia | 12.80 (3.8–43.6) | <0.001 | 0.35 |
| Hypothermia | 1.61 (0.6–4.2) | NS | 0.08 |
| Feeding problems | 1.47 (0.5–4.7) | NS | 0.04 |

*Adjusted OR determined by logistic regression.
†A neonate having more than one morbidity is counted in each category. Hence, the sum of PARs is more than 1.
‡Full term (37 completed weeks or more) with birth weight <2500 g.
NS = not significant.

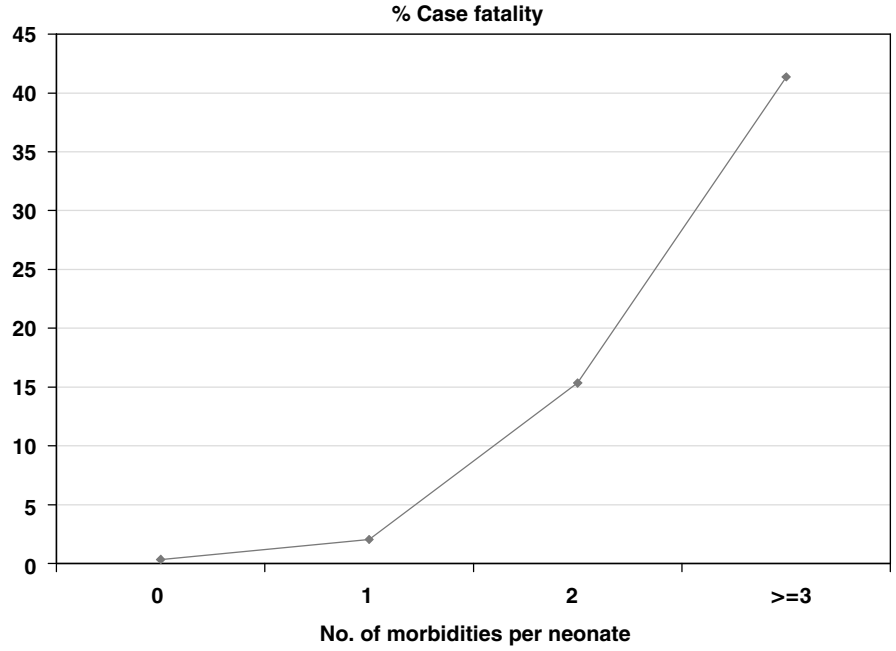


**Figure 1.** Effect of the number of morbidities per neonate on case fatality.

**Table 3** Combinations of Neonatal Morbidities: Incidence, Case Fatality and Presence in Neonatal Deaths (1995–1996, $n = 763$, neonatal deaths = 40)

| Morbidity categories* | No. | Mean birth weight (g) | Mean days of gestation | % Incidence | Deaths | % CF | % of deaths (40) |
|---|---|---|---|---|---|---|---|
| (A) *No morbidity* | 308 | 2741[a] | 281[b] | 40.4 | 1 | 0.3 | 2.5 |
| (B) *Single morbidity* | 289 | 2388[c] | 276[d] | 37.9 | 6 | 2.1 | 15.0 |
| Only asphyxia without other morbidity[†] | 8 | — | — | 1.0 | 2 | 25.0 | 5.0 |
| Only IUGR[1] without other morbidity | 155 | — | — | 20.3 | 1 | 0.6 | 2.5 |
| Only preterm[2] without other morbidity | 27 | — | — | 3.5 | 3 | 11.1 | 7.5 |
| Only sepsis[3] without other morbidity | 40 | — | — | 5.2 | 0 | 0.0 | 0.0 |
| Only hypothermia[4] without other morbidity | 40 | — | — | 5.2 | 0 | 0.0 | 0.0 |
| Only feeding problems without other morbidity | 19 | — | — | 2.5 | 0 | 0.0 | 0.0 |
| (C) *Only two morbidities* | 137 | 2191[e] | 268[f] | 17.9 | 21 | 15.3 | 52.5 |
| IUGR+sepsis | 41 | — | — | 5.4 | 7 | 17.1 | 17.5 |
| IUGR+feeding problems | 16 | — | — | 2.1 | 1 | 6.3 | 2.5 |
| Preterm+severe asphyxia | 6 | — | — | 0.8 | 4 | 66.7 | 10.0 |
| Preterm+sepsis | 15 | — | — | 2.0 | 7 | 46.7 | 17.5 |
| Preterm+feeding problem | 6 | — | — | 0.8 | 1 | 16.7 | 2.5 |
| Sepsis+hypothermia | 8 | — | — | 1.0 | 1 | 12.5 | 2.5 |
| Other combinations of two morbidities | 45 | — | — | 5.9 | 0 | 0.0 | 0.0 |
| (D) *Three or more morbidities* | 29 | 1911 | 258 | 3.8 | 12 | 41.4 | 30.0 |
| Total | 763 | 2472[g] | 276[h] | 100.0 | 40 | 5.2 | 100.0 |
| (E) *Morbidities in combination with preterm*[§] | | | | | | | |
| Only preterm | 27 | 2228 | 244 | 3.5 | 3 | 11.1 | 7.5 |
| Preterm+sepsis | 27 | 1899 | 246 | 3.5 | 14 | 51.9 | 35.0 |
| Preterm+asphyxia | 12 | 1617 | 237 | 1.6 | 8 | 66.7 | 20.0 |
| Preterm+hypothermia | 14 | 1856 | 251 | 1.8 | 6 | 42.9 | 15.0 |
| Preterm+feeding problems | 14 | 1815 | 247 | 1.8 | 5 | 35.7 | 12.5 |
| (F) *Morbidities in combination with IUGR*[§] | | | | | | | |
| Only IUGR | 155 | 2181 | 278 | 20.3 | 1 | 0.6 | 2.5 |
| IUGR+sepsis | 49 | 2094 | 275 | 6.4 | 9 | 18.4 | 22.5 |
| IUGR+asphyxia | 3 | 2083 | 278 | 0.4 | 0 | 0.0 | 0.0 |
| IUGR+hypothermia | 38 | 2193 | 276 | 5.0 | 2 | 5.3 | 5.0 |
| IUGR+feeding problems | 20 | 2141 | 276 | 2.6 | 1 | 5.0 | 2.5 |

*A,B,C,D are exclusive categories. Under E and F, neonates from B,C,D are included, the combinations are overlapping, and same neonate may be included in more than one category.

a: 290, b: 296, c: 284, d: 287, e: 134, f: 136, g: 737, h: 748 are the corresponding neonates.

[†]Severe asphyxia.

1 = intrauterine growth restriction; 2 = <37 weeks, 3 = clinical diagnosis of sepsis, 4 = skin temperature <95°F.

[§]A neonate may have multiple morbidities simultaneously, and is included in each combination. Hence the total is more than 100%. Similarly, neonates from the earlier categories A, B, C, and D are also included under categories E and F, when appropriate.

the percent case fatality, and the percent of deaths associated with each category. A, B, C, and D, are exclusive categories. The percent case fatality is very low in neonates without morbidity. Among the single morbidities, only asphyxia and preterm have a high CF of 25 and 11%, respectively. The CF increases especially with two or more morbidities in a neonate, and when morbidities occur in combination with preterm or IUGR. Under E and F are presented various morbidities in combination with preterm and IUGR. Percent case fatality was very high in neonates with preterm and any other morbidity. On the other hand, CF in the

presence of IUGR was high only in combination with sepsis (18.4%). The maximum number of deaths, 23/40 or 57.5%, were caused when sepsis occurred in the presence of preterm or IUGR.

Also seen in Table 3 is that the mean birth weight and the period of gestation decrease as the number of other morbidities increases. In other words, neonates with lower birth weight or shorter period of gestation suffer from more comorbidities. The higher case fatalities are, thus, a total effect of lower birth weight/gestation and number of comorbidities.

Effect of the interaction between LBW and infection on CF was analyzed. As compared to the zero % CF in neonates without LBW or infection, the % CF was 1.9% in neonates with clinical sepsis without LBW, 5.2% in neonates with LBW without sepsis, and increased to 31.9% when these two occurred together. The interaction showed in logistic regression an OR of 3.8, and was not statistically significant.

The excess deaths contributed by the addition of sepsis are presented in Table 4. The % CF in neonates with and without sepsis is compared in different birth weight strata. The net difference is presented as the absolute difference in % CF. The second-to-last column presents the estimated number of residual deaths expected to occur when sepsis is prevented and, hence, the estimated excess deaths contributed by sepsis are shown in the last column. The total excess deaths caused by sepsis are thus estimated to be 17.58 or 44% of the total deaths in this cohort of neonates. We also note that the PAR for sepsis estimated by this method (0.52) comes very close to the PAR estimated by the logistic regression (0.55).

Table 5 compares the results of four different methods we used to assess the contribution of different morbidities to neonatal deaths in the two papers (including the present one), titled ''Why do neonates die in rural homes? Parts I and II''. The data on the primary cause of death[2] assigned by neonatologist are based on the same cohort of neonates in Gadchiroli. The remaining three estimates are drawn from different tables in the present paper. Although the absolute values of PARs and the proportion of deaths vary depending on the method used, the rankings show a fairly consistent pattern.

In Table 5, section A, the PARs are presented for individual morbidities. Preterm ranks highest, followed by sepsis and IUGR, having equal ranking, followed by asphyxia, hypothermia, and feeding problems. When morbidity combinations are seen as the cause of death, section B, preterm or IUGR are the ubiquitous components, and their combination with sepsis occupies the first two ranks.

The contribution of sepsis to total deaths is estimated by different methods to be 52.5, 55, 57.5, and 44% (Table 5).

## DISCUSSION

Although most neonatal deaths occur in neonates with preterm or IUGR birth, when these morbidities occur alone without other comorbidities, the case fatality is low and these contribute only a small proportion (10%) of deaths. By contrast, most deaths occur when preterm or IUGR is of a more severe degree and is combined with other morbidities: sepsis, asphyxia, hypothermia, or feeding problems, in that order. Hence, LBW (preterm or IUGR) in combination with one of these four morbidities constitutes sufficient cause of death. The most important among these combinations is the combination of LBW and sepsis. The case fatality increases many fold when these two occur together. We estimate that nearly three-fourths of neonatal deaths can be attributed to preterm birth and nearly half to sepsis, and that LBW

**Table 4** Case Fatality in Different Birth Weight Groups With and Without Clinical Sepsis, and Estimating the Number of Excess Deaths Caused by Sepsis

| | Without sepsis | | | With sepsis | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Birth weight (g) | Neonates | Deaths | % CF* | Neonates | Deaths | % CF* | Absolute difference in % CF* | *p* | Relative risk† | PAR‡ | Expected deaths in sepsis cases§ | Estimated excess deaths¶ |
| ≥2500 | 363 | 0 | 0.0 | 54 | 1 | 1.9 | 1.9 | <0.130 | — | — | 0.00 | 1.00 |
| 2000–2499 | 201 | 3 | 1.5 | 45 | 6 | 13.3 | 11.8 | <0.002 | — | — | 0.67 | 5.33 |
| <2000 | 47 | 10 | 21.3 | 27 | 17 | 63.0 | 41.7 | <0.001 | — | — | 5.74 | 11.26 |
| Not recorded | 22 | 3 | 13.6 | 4 | 0 | 0.0 | — | — | — | — | — | — |
| Total | 633 | 16 | 2.5 | 130 | 24 | 18.5 | 15.9 | <0.001 | 7.3† | 0.52† | 6.42 | 17.58 |

*Case fatality.
†Of death for sepsis.
‡Population attributable risk for sepsis.
§Expected deaths in sepsis cases if sepsis was prevented, and hence CF in neonates without sepsis would apply.
¶Excess deaths caused by sepsis.

**Table 5** Summary of the Proportion of Deaths Attributed to Different Causes by Different Methods of Estimation and Proportion of Deaths Preventable

| Cause of death | % of deaths attributed | | | |
|---|---|---|---|---|
| | Primary cause (assigned by neonatologist)* | PAR† in multicausal analysis‡ | Proportion of all deaths§ | Ranking |
| *(A) Individual morbidity* | | | | |
| Preterm | 15.0 | 0.74 | — | 1 |
| Sepsis | 52.5 | 0.55 | — | 2 |
| Intrauterine growth restriction | NR | 0.55 | — | 2 |
| Asphyxia | 20.0 | 0.35 | — | 4 |
| Hypothermia | 2.5 | 0.08 | — | 5 |
| Feeding problems | NR | 0.04 | — | 6 |
| Not known | 10.0 | — | — | — |
| *(B) Combinations of morbidities* | | | | |
| Preterm+sepsis | — | — | 35.0 | 1 |
| IUGR+sepsis | — | — | 22.5 | 2 |
| Preterm+asphyxia | — | — | 20.0 | 3 |
| Preterm+hypothermia | — | — | 15.0 | 4 |
| Preterm+feeding problems | — | — | 12.5 | 5 |
| *(C) Deaths preventable by preventing/ managing sepsis, even if LBW persisted* | Preventable deaths¶ 17.58 | | Proportion of total deaths(40) preventable 44.0% | |

*Bang, Paul and Reddy, Why do neonates die in rural homes? Part I.
†Population attributable risk.
‡Table 2 in the present paper.
§Table 3 in the present paper.
¶Table 4 in the present paper.
NR: not recorded as the primary cause.

(preterm or IUGR) + sepsis combined is responsible for nearly 60% of deaths.

Since the causal web can be interrupted by addressing one of the component causes, sepsis, asphyxia, hypothermia, and feeding problems, in that order, provide opportunity for preventing neonatal deaths, even if LBW or preterm continues at the current level. Of these, sepsis ranks as the highest priority. It is unlikely that, with the current state of knowledge, we will be able to reduce significantly the incidence of preterm or IUGR births in developing countries. Hence, the strategy of choice will be to address infections. We hypothesize that prevention and/or treatment of infections will reduce neonatal mortality by 40 to 50%.

This is an observational study showing associations between selected morbidities and neonatal deaths. It cannot be considered to provide irrefutable evidence of a cause-and-effect relationship. However, of the various causal criteria provided by Hill and further commented on by Rothman,[7] morbidities as a cause of neonatal death meet, in this study, the criteria of temporality, strength of association, and plausibility.

Other limitations of the study are that the observations are only from one site and made only in 1 year. Sample size is relatively small. Although 25% neonates in the area, among whom 12 died, were not studied, as we have earlier published, the studied and unstudied groups had similar neonatal mortality rate.[10–12] As to the quality and completeness of data, and the definitions and validity of diagnoses of morbidities, these have been discussed elsewhere.[10–12] The mean birth weight closely followed the gestational age (Results text) indirectly validating the assessment of gestational age. The diagnosis of sepsis was entirely clinical, without any laboratory backup. Hence there is bound to be substantial imprecision, and false-positive diagnosis. This is reflected in Tables 3 and 4 in which the case fatality of sepsis in some categories is very low. We have estimated the sensitivity, specificity, and positive predictive value of these criteria.[18]

The strength of this analysis is that it is based on prospectively observed, community-based data on neonates in rural homes. In addition, the observations cover all major morbidities in neonates. Hence, these data represent the natural history of neonates in the rural community and allow a comprehensive assessment of the interactions of various morbidities and their contribution to death. To our knowledge, this is the first such comprehensive and

quantitative assessment on neonates in a community setting in a developing country.

The proportion of neonatal deaths attributable to different causes, especially to infections, is different in this assessment than the global assessment[1] in which the direct causes of death are infections, 32%; asphyxia, 29%; complications of prematurity, 24%; and congenital anomalies, 10%. Why this difference? The limitations of this study, mentioned earlier, may be responsible for some of this difference. However, the alternative explanations are: (1) The global data are presented in the form of single cause of death. In this analysis, we have included all major causes and, moreover, analyzed deaths by combinations of morbidities. (2) This analysis was performed on a community-based situation in a rural area setting. Many of the global or national estimates[19] use hospital-based data. (3) And, finally, this analysis is based on prospective observations compared to the retrospective inquiries about probable cause of death that are the bases for estimating the causes of death in rural infants in many national estimates.[20,21]

We found in this analysis, presented in Figure 1 and Table 3, that, in rural Gadchiroli, neonatal deaths are caused not by a single morbidity but by a combination of multiple morbidities. Most deaths occurred when LBW (preterm or IUGR) was complicated by sepsis, asphyxia, hypothermia, or a feeding problem. This is consistent with the current causal understanding.

Using the multicausal model, the logistic regression yielded the estimated risks of death (represented by the OR) and PAR for each morbidity (Table 2). Preterm birth emerged at the top, followed by sepsis and IUGR. The sum total of PARs was more than 1. This is inevitable when multiple causes are assigned to each death.[9] However, each PAR represents the proportion of deaths that can be attributed to that cause. Does this imply that we could prevent more than 100% deaths if we prevented all causes — an impossible proposition? It only means that there is more than one way of preventing the same death, and hence, that death is counted in both the categories.

If there is more than one pathway for preventing deaths, then which pathway or morbidity should be selected?

An important insight from this analysis is the quantitative assessment of the contribution of infection to neonatal deaths. The excess neonatal mortality caused by sepsis was estimated to be 17.6/40 or 44% (Tables 4 and 5). There is a remarkable consistency in the results by different methods (Table 5). Preterm births showed the highest PAR. Sepsis ranked second. Sepsis with preterm or IUGR birth formed the causal combinations accounting for a total of 57.5% of deaths.

## SIGNIFICANCE

This analysis presents the complex web of causes of deaths in rural neonates more faithfully than do single-cause estimates. In line with current thinking about causality, it looks at neonatal morbidities in combinations and brings out the fact that, among the neonates in rural settings, neonatal deaths occur most often when sepsis, asphyxia, hypothermia, or feeding problems occur in combination with LBW (preterm or IUGR). This is what physicians have always known and, hence, in caring for neonates — whether LBW/preterm or normal — the emphasis has been on ensuring air, warmth, milk, and prevention or treatment of infections.[22,23] If these morbidities are prevented or treated, an LBW or preterm baby has better chances of survival.

This analysis provides evidence leading to a hypothesis that despite continued high rates of preterm or IUGR, a large proportion of these neonates can be saved. It also provides a quantitative estimate that nearly half of the neonatal mortality in rural settings can be reduced by addressing infections. This provides a hypothesis for testing in intervention trials, as well as a strategy for preventing neonatal deaths. The order of priority for efforts to prevent neonatal deaths should be sepsis, asphyxia, hypothermia, and feeding problems. A comprehensive approach addressing all four problems should achieve maximum results.

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