

# Original Article

## Why Do Neonates Die in Rural Gadchiroli, India? (Part I): Primary Causes of Death Assigned by Neonatologist Based on Prospectively Observed Records

**Abhay T. Bang, MD, MPH**  
**Vinod K. Paul, MD, PhD**  
**Hanimi M. Reddy, PhD**  
**Sanjay B. Baitule, DHMS**

prematurity. Infections cause a larger proportion of deaths in neonates in the community compared to the reported proportion in hospital-based studies.

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### OBJECTIVE:

To determine the primary causes of death in home-cared rural neonates by using prospectively kept health records of neonates and a neonatologist's clinical judgment.

### STUDY DESIGN:

In the first year (1995 to 1996) of the field trial in Gadchiroli, India, trained village health workers observed neonates in 39 villages by attending home deliveries and making eight home visits during days 0 to 28. The recorded data were validated in the field by a physician. An independent neonatologist assigned the most probable single primary cause of death based on these recorded data.

### FINDINGS:

A total of 763 neonates were observed, of whom 40 died (NMR 52.4/1000). The primary causes of death were sepsis/pneumonia 21 (52.5%), asphyxia 8 (20%), prematurity <32 weeks 6 (15%), hypothermia 1 (2.5%), and other/not known 4 (10%). Most of the prematurity or asphyxia deaths occurred during the first 3 days of life. All 21 sepsis/pneumonia deaths occurred during days 4 to 28. A similar picture existed in England before the antibiotic era.

### CONCLUSION:

Sepsis/pneumonia is the primary cause in half the deaths in rural neonates cared for at home in Gadchiroli, followed by asphyxia and

### INTRODUCTION

*Although the causal analysis can be extended far beyond medical factors, we shall limit this inquiry into "Why do neonates die in rural homes?" only to medical causes of death. The purpose is to estimate the contribution of the main diseases in causing neonatal deaths, and, thereby, to estimate the potential for preventing deaths by preventing or treating these diseases and finally, to select the correct priorities for action. We do this in two parts:*

*Part I. Primary causes of death, assigned by a neonatologist.*

*Part II. We find that most often, death results not due to a single morbidity but due to multiple morbidities. Hence, using a multicausal analysis, we estimate the population attributable fractions of six major causes of death, and also identify different combinations of morbidities causing neonatal deaths. We estimate the proportion of deaths that would be prevented by addressing some of the main causes. We finally identify priorities based on this analysis. We also propose a hypothesis on how neonatal mortality can be reduced.*

In the absence of access to hospital care, most neonatal births and deaths in rural areas in developing countries occur at home.<sup>1</sup> Hence, for selecting the appropriate interventions to reduce neonatal mortality, it is essential to know the causes of neonatal deaths in rural homes. However, most available studies are hospital based.<sup>2–4</sup> The situation of neonatal health in rural homes cannot be extrapolated from the hospital-based studies because the conditions are radically different. Besides, only selected neonates reach hospitals. Therefore, we need information from population-based studies.

Population-based studies have invariably used retrospective inquiry or "verbal autopsy" to determine the cause of death.<sup>5–7</sup> However, this method has not been validated for neonatal deaths, except for neonatal tetanus.<sup>8</sup> The diagnosis of birth asphyxia as the cause of death, based on history alone, may be invalid, since

SEARCH (Society for Education, Action and Research in Community Health), (A.T.B., H.M.R., S.B.B.), Gadchiroli, India; and Department of Pediatrics (V.K.P.), All India Institute of Medical Sciences, New Delhi, India.

The financial support for this work came from The John D. and Catherine T. MacArthur Foundation, The Ford Foundation and Saving Newborn Lives Initiative, Save the Children, USA, and the Bill and Melinda Gates Foundation.

Address correspondence and reprint requests to Abhay T. Bang, MD, MPH, SEARCH, Gadchiroli 442-605, India.

E-mail: search@satyam.net.in

mothers may not be able to correctly report the condition of the baby at birth. Determining that low birth weight (LBW), sepsis or hypothermia is the cause of death needs ante-mortem clinical observations and measurements, which are not available in verbal autopsy. Thus, the currently available community-based information on causes of neonatal deaths is of questionable validity.

This lack of valid information may affect the choice of interventions. To determine causes of death, the neonates in rural homes need to be prospectively observed, their medical data recorded, and the causes of death determined from such medical record review. Prior to the field trial in Gadchiroli, India,<sup>9,10</sup> such studies have not been conducted because of absence of any observer and of prospectively recorded data on neonates in rural homes.

During the first year of our field trial of Home-based Neonatal Care in rural Gadchiroli, we prospectively observed the neonates in 39 villages.<sup>9-11</sup> This study was conducted to answer the question: "What are the primary causes of deaths in home-cared neonates in a rural community?"

## METHODS

The first year of the intervention (1995 to 1996) in the field trial was devoted primarily to observing neonatal health with few interventions. The present study is an outcome of this observation period. The study design, area, and the methods of data collection have been extensively reported.<sup>9-11</sup> Therefore, their presentation here is brief.

After appropriate training, female village health workers (VHWs), one each in 39 villages, collected data on mothers during pregnancy by making three home visits. Most women in the area delivered at home, attended by traditional birth attendants (TBAs). The VHWs were also present at the home deliveries and made observations, including assessment of neonates at 1 and 5 minutes after birth. Subsequently, they visited mothers and neonates on eight fixed days (1, 2, 3, 5, 7, 15, 21, and 28) during the neonatal period, taking history, examining the baby, and recording the findings. They made additional visits on other days if the baby was sick and they were informed.

The record filled by VHWs included four sections:

- (a) information during pregnancy,
- (b) information during labor,
- (c) first examination of newborn within 6 hours after birth, and
- (d) information about mother and newborn, collected during eight or more postnatal home visits.

Altogether, information on 18 maternal and 28 neonatal variables was recorded.

In the first year of intervention, VHWs were not trained in the treatment of sick neonates. The newborns received care from the family and TBA and, if invited by the family, also from a government nurse or private doctor. The VHWs recorded the findings until the baby reached 28 days, or left the village, or died. In case of death, VHWs made efforts to collect information from the family about the circumstances before death, symptoms in the neonate, and the treatment provided. The data collection started on April 1, 1995, and continued for 1 year, until March 31, 1996.

A supervisory physician from the study team (S.B.B.) visited each neonate at home once in 2 weeks, verified the data recorded by the VHW, and noted any other observations. If a newborn was found to be sick, the family was advised to hospitalize the baby; SEARCH offered free ambulance service for transporting the sick baby; but the final decision was left to the family, who most often decided not to go to hospital. The care seeking behavior has been described earlier.<sup>10,11</sup>

Records of the 40 neonates who died during 1 year of the study period were reviewed by a neonatologist (V.K.P.) at the All India Institute of Medical Sciences, New Delhi, who assigned the most probable cause of death. The primary cause of death was defined as "the disease or injury which initiated the train of morbid events leading directly to death".<sup>12</sup> Although many conditions/ complications contribute to death, in view of the difficulties and uncertainty involved in assigning the cause of death in neonates, we selected a limited number of principal entities as the primary causes of neonatal death: (i) prematurity, (ii) birth asphyxia, (iii) sepsis/pneumonia, (iv) tetanus neonatorum, (v) hypothermia, and (vi) others. LBW per se was not considered as the primary cause of death.

The neonatologist carefully evaluated the information in the case record. The assignment of the primary cause was based on the answer to the following question: "Which of the six categories of primary causes of death fits best with the clinical course of the baby?" In spite of the overlapping clinical features of various primary causes, the evolution of the clinical picture and the course of events allowed assigning a primary cause to most of the deaths. Since we were determining the primary cause as against the contributory causes, prematurity was considered only if the period of gestation was less than 32 weeks, and hypothermia (skin temperature <95°F) only if it was persistent (recorded more than once) in the absence of any other major cause. Tetanus neonatorum was diagnosed if the baby of an unimmunized mother died at any time from the fourth day onwards because of inability to feed, trismus, and spasms. Sepsis was diagnosed if the baby died with features suggestive of systemic bacterial infections manifesting as septicemia, meningitis, or pneumonia. Birth asphyxia was diagnosed if the baby had failed to establish breathing at birth with subsequent features suggestive of hypoxic ischemic encephalopathy or hypoxic damage to other

organ systems. "Others" included congenital malformations or any other cause, or where a definite cause could not be established.

A vital statistics surveillance system involving male village health workers and supervisors independently recorded births and deaths in the study area. This system was earlier evaluated to be 98% complete.<sup>9,10</sup>

The ethical clearance for the study was granted by an external committee.<sup>9</sup>

**RESULTS**

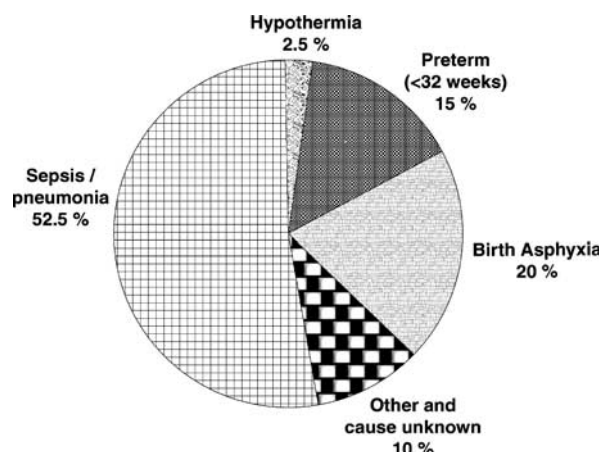
The vital statistics surveillance system recorded a total of 1016 live births in the 39 villages during the 1-year of study, and 52 of these babies died during the neonatal period. Out of the total live births, 763 neonates (75.1%) were studied by female VHWs, and 253 were not studied. A total of 40 neonates died from among the 763 studied; and 12 died from among the 253 not studied. The neonatal mortality rate in the two groups was 52.4 and 47.4, respectively ( $p > 0.5$ ). The still birth rate (SBR) in the births observed was 24/1000 births and 25/1000 in the unobserved births ( $p > 0.5$ ). Hereafter, the 763 observed neonates constitute the study population. Socio-demographic characteristics of the population in the 39 villages, the completeness of recording births and deaths, and the lack of selection bias in the neonates included in this study population have been published.<sup>10,11,13</sup>

Nearly 95% of mothers delivered at home and 81% were delivered by TBAs. VHWs were present during labor (74.7%) and within 6 hours of the birth (92.4%). Data on maternal and labor characteristics and the incidence of various neonatal morbidities and the associated case fatality have been published.<sup>10,13</sup> In all, 42% neonates were LBW (<2500 g), 75 (9.8%) were preterm (<37 weeks), 130 (17%) had clinical features suggestive of infection, and 26 (4.6%) had severe asphyxia at birth. Only

three (0.4%) neonates were hospitalized for sickness. None of them died.

A total of 40 neonatal deaths occurred in the 763 study neonates, giving the neonatal mortality rate of 52.4 per 1000 live births (95% CI: 36.6 to 68.2). Of this, early NMR (during days 1 to 7) was 30.1 per 1000 live births (23/763), and late NMR (during days 8 to 28) was 22.3 per 1000 live births (17/763).

The primary causes of death are shown in Figure 1. Sepsis 21 deaths (52.5%, 95% CI 37.0 to 69.0), asphyxia 8 deaths (20%, 95% CI 7.6 to 32.4), and prematurity <32 weeks 6 deaths (15%, 95% CI 3.9 to 26.1) were the most common primary causes. The temporal distribution of neonatal deaths by the primary cause is presented in Table 1. Almost all deaths due to asphyxia and prematurity occurred in the first 3 days, while all sepsis deaths occurred after 3 days of life. Out of the 17 deaths in the late neonatal period, 16 occurred due to sepsis. The mean day of death due to sepsis was 12.5.



**Figure 1.** Proportion of neonatal deaths by the primary cause of death.

Primary cause	Day of death				% Deaths (95% CI)	Mean age at death (days)	CSNMR/1000 live births*	
	1-3	4-7	8-14	15-28				Total
Preterm <32 weeks	6	—	—	—	6	15.0 (3.9-26.1)	2.0	7.9
Birth asphyxia	7	1	—	—	8	20.0 (7.6-32.4)	1.8	10.5
Sepsis/pneumonia	—	5	11	5	21	52.5 (37.0-69.0)	12.5	27.5
Tetanus neonatorum	—	—	—	—	—	—	—	—
Hypothermia	—	1	—	—	1	2.5 (-2.3-7.3)	5.0	1.3
Other and cause not known	1	2	—	1	4	10.0 (0.7-19.3)	8.5	5.2
<b>Total</b>	<b>14</b>	<b>9</b>	<b>11</b>	<b>6</b>	<b>40</b>	<b>100.0</b>	<b>7.9</b>	<b>—</b>

\*Cause specific neonatal mortality rate/1000 live births.

## DISCUSSION

This is the first study in which the neonates in rural homes were prospectively observed, including during home-delivery and at birth, and the causes of death determined from these ante-mortem records. It revealed that sepsis was the primary cause in half of the deaths, with most of the sepsis deaths occurring during 4 to 28 days of life. This picture is quite different from the one gained from hospital-based studies. The primary causes of neonatal deaths reported in the hospital-based National Neonatal Perinatal Database, India (1996)<sup>2</sup> were prematurity (31.0%), birth asphyxia (26.0%), infections (22.0%), and malformations (9.6%). Similarly, the World Health Organization estimates (in 2001) that, globally, the causes of neonatal deaths are: birth asphyxia/injury 29%, complications of prematurity 24%, and infections: (sepsis + pneumonia) 26%, tetanus 7%; congenital malformations 11%. LBW was an important secondary factor in 40 to 80% of neonatal deaths.<sup>1</sup> The proportion of deaths due to sepsis observed in this study was twice these estimates.

### Are Our Findings an Artifact?

The study area and the socio-demographic characteristics were similar to most villages in India.<sup>9–11</sup> The NMR of 52.4 in the study population during 1995 to 1996 was virtually identical to the 52.3 reported by the Sample Registration System of the Govt. of India in 1995.<sup>7</sup> The reporting of births and deaths in the study area was 98 to 99% complete.<sup>9</sup> Although not all neonates born in the 39 study villages could be studied, there was no apparent selection bias in the neonates studied and not studied,<sup>10,13</sup> and the quality of data collected was verified in the field by a physician and also validated by parallel observations.

The date of last menstrual period was recorded by VHWs during early pregnancy. Hence, the period of gestation could be estimated based on history. Only deaths in neonates <32 weeks were considered for prematurity as the primary cause of death. Therefore, prematurity as an associated cause of death in neonates >32 weeks is not represented in this analysis. (It is included in the next article, "Why do neonates die in rural homes, part II".)

As the VHWs were present at the time of home deliveries and recorded the cry and breathing at 1 and 5 minutes after birth, this cohort of neonates provides a reliable estimate of the incidence of birth asphyxia in home-delivered neonates. Of the 10 neonatal deaths that occurred in severely asphyxiated neonates, asphyxia was assigned as the primary cause in eight deaths. Thus, the estimated proportion of deaths due to asphyxia (20%) in this cohort seems reliable.

The diagnosis of sepsis in this study was based on data prospectively collected by the VHW as interpreted by a neonatologist. Some degree of inaccuracy is inherent in an approach that is based on clinical findings only and not on laboratory workup including bacterial cultures. Many conditions in neonates may mimic sepsis.

We recognize this limitation of the study. However, radiological and bacteriological investigations are unlikely to be available in the near future to the population of interest, that is, home-cared rural neonates. Hence within these limitations, the method adopted in this study appears to be the best available.

In our study, sepsis/pneumonia was not identified as the cause of death for infants who died in the first 3 days of life. It is quite possible we misclassified these early deaths and hence missed some cases of early-onset sepsis. Based on the onset, it is customary to classify neonatal sepsis into early (onset within 3 days) or late (onset after 3 or more days) varieties. Early-onset sepsis may occur as pneumonia presenting as respiratory distress, which may be, quite often, indistinguishable from that due to lung immaturity (hyaline membrane disease), aspiration syndromes, or metabolic disease. Out of 14 deaths on days 1 to 3, 13 were assigned to prematurity and asphyxia (Table 1). Infection may have contributed to death in premature neonates, or may result in failure to establish breathing at birth mimicking asphyxia. Hence, early-onset sepsis may be a cause of death in some of the deaths occurring during 1 to 3 days of life. It is also possible that sepsis may have had an early onset, but it actually killed the infant after 3 days of life, and hence the death was included in the later time period.

### How can the Finding of the High Proportion of Neonatal Deaths due to Sepsis be Explained?

A high proportion of LBW (42%) and preterm (10%) babies in the neonates exposed to unhygienic conditions and care, resulting in a large proportion acquiring infections (umbilical infection, skin infection, and clinically suspected sepsis), and lack of access to medical care seem to be the main reasons for such a high proportion of deaths due to infections.<sup>10,11,13</sup>

The study population being community-based may be another explanation for this observed difference. Since hospital-born neonates receive hygienic care and early treatment with antibiotics on the slightest suspicion of infection, the incidence of sepsis as well as deaths due to sepsis are expected to be low in them. Moreover, hospital-delivered neonates are very often discharged within a few days after birth,<sup>14</sup> but almost all sepsis deaths in this study occurred after 3 days of birth. Hence, it is likely that hospital-based information selectively underrepresents sepsis deaths. In a global review, the proportion of neonatal deaths attributed to infections (including tetanus) were reported to be 4 to 56% in hospital-based studies vs 8 to 85% in community-based studies.<sup>15</sup> This supports our contention.

This view is also supported by the causes of neonatal admissions to the peripheral hospitals. Sepsis is the most common indication for neonatal admissions to the district and subdistrict hospitals.<sup>16</sup> In a district hospital in Himachal Pradesh, India, 96% of neonates were admitted with the clinical diagnosis of septicemia or pneumonia.<sup>17</sup> Similarly, 82% neonates admitted to a subdistrict

hospital had septicemia, pneumonia, meningitis, or cellulitis as the main diagnosis.<sup>18</sup> Thus, it appears that if the study population is community-based or from peripheral hospitals, infections predominate as the cause of illness or death.

The probable reasons for such a high proportion of deaths due to infections in our study were poor hygiene in rural homes,<sup>11,13</sup> a high proportion of reproductive tract infections in mothers,<sup>19</sup> 42% of neonates being LBW, and the traditional custom of not breast feeding for the first 3 days, thus depriving the baby of colostrum. The observed incidence of umbilical infection was 19.8% and of skin infections was 11.5%. All these factors predispose the neonates to infections and could explain the high (17%) incidence of suspected sepsis in the 763 observed neonates.<sup>11,13</sup>

As many as 54.4% of the observed 763 home-cared neonates in this study had indications for medical attention. However, only 2.6% of neonates were seen by a doctor, most often an unqualified village doctor, and only 0.4% were hospitalized.<sup>13</sup> Parents were either unwilling or unable to hospitalize the sick neonates, and existing primary health care essentially did not provide neonatal care. The lack of medical care certainly contributed to deaths due to infection.

Most community-based studies used retrospective inquiry to determine the causes of death.<sup>5–7</sup> The clinical manifestations of systemic infections, except tetanus, may be subtle, varied, and insidious,<sup>20</sup> and hence missed in the retrospective inquiry. Our study, based on a detailed recording of prospective observations made at home, is more likely to detect infection as the cause of death. However, even a recent community-based study in rural Gambia, using retrospective inquiry, estimated that 57% deaths in neonates were due to infections.<sup>21</sup>

A recent global review of infections in neonates estimated that 30 to 40%, that is, approximately 1.2 to 1.6 million, neonatal deaths occur each year due to infections.<sup>15</sup> Our study supports this, and puts the proportion of deaths due to sepsis at nearly 50%. Yet, our estimate is not unique, and the reported proportion in community-based estimates has ranged from 8% to as high as 85%.<sup>15</sup>

A similar pattern existed in developed countries before the antibiotic era. The Royal College of Obstetricians and Gynaecologists and the British Paediatric Association appointed a Joint Committee to investigate the causes of the high infant mortality rate in England (47/1000 live births) in 1945. It reported on a large series of necropsies on neonates in 1943, which showed that 36.5% of dead neonates had infections, and this proportion was 73.6% in the neonatal deaths occurring during 8 to 28th days of life.<sup>22</sup>

The limitations of this study must be kept in mind. Nearly 25% of births and neonatal deaths in the area were not observed by VHWs and hence not included in the study. Moreover, this is a relatively small size study, in one area. Hence, the estimates have wide confidence intervals. Other prospective observational studies

on home-cared neonates need to be conducted in other areas to confirm our findings. The pattern of cause of death seen in this study may vary with the different levels of NMR. The proportion of deaths due to infection may be smaller at the lower levels of NMR. However, the picture reported in this study may be relevant to a large number of developing countries, including the Indian subcontinent, where NMR remains high.

We have already mentioned the limitations of diagnosis based only on history and physical examination, without laboratory investigations. Attributing death to a single primary cause is convenient but arbitrary. In reality, most deaths were associated with multiple, overlapping morbidities and mean number of morbidities per 763 observed neonates was 2.2. Hence, although this analysis provides very useful information it does not provide the complete picture. In a subsequent analysis, we attempt to take into consideration multiple morbidities as the cause of death.

## CONCLUSIONS

This prospective observational study of home-cared neonates in a poor, rural community suggests that infections are the most important cause of neonatal deaths. Infections contribute a larger proportion of neonatal deaths at a high level of NMR such as is prevalent in rural India, and in the community-based estimates. No death occurred due to tetanus — probably because 79% of mothers received tetanus toxoid<sup>10</sup> and because TBAs were trained and provided with clean blades and thread. Since all sepsis deaths occurred from day 4 onwards, we see an opportunity for reducing the incidence of acquired infection by providing health education, improving hygiene, and promoting early breast feeding. And finally, those who develop clinical features suggestive of sepsis need early treatment with antibiotics. Since the mean day of death due to sepsis was 12.5, most of these neonates are likely to be at home. If monitored for sepsis, it may be possible to detect and treat them in time.

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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

**Abhay T. Bang, MD, MPH**

**Hanimi M. Reddy, PhD**

**Rani A. Bang, MD, MPH**

**Mahesh D. Deshmukh, MSc**

### 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<sup>1</sup> 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%.<sup>2</sup>

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<sup>3</sup> for assigning the primary or underlying cause of death, the selection of one cause from among many does involve a subjective judgment.<sup>4–6</sup> 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.

SEARCH (Society for Education, Action and Research in Community Health), Gadchiroli, India

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Address correspondence and reprint requests to Abhay T. Bang, MD, MPH, SEARCH, Gadchiroli 442-605, India.

E-mail: search@satyam.net.in

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This was consistent with the current multicausal understanding of the causal mechanism as described by Rothman and Greenland.<sup>7</sup> 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.<sup>8,9</sup> 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.<sup>10–12</sup> 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%.<sup>12,13</sup>

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,<sup>10,13</sup> 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  $\geq 60$  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.<sup>10</sup> 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:<sup>14</sup>

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

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,<sup>15–17</sup> 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  $\times$  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 hierarchical 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.<sup>8,9</sup>

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)

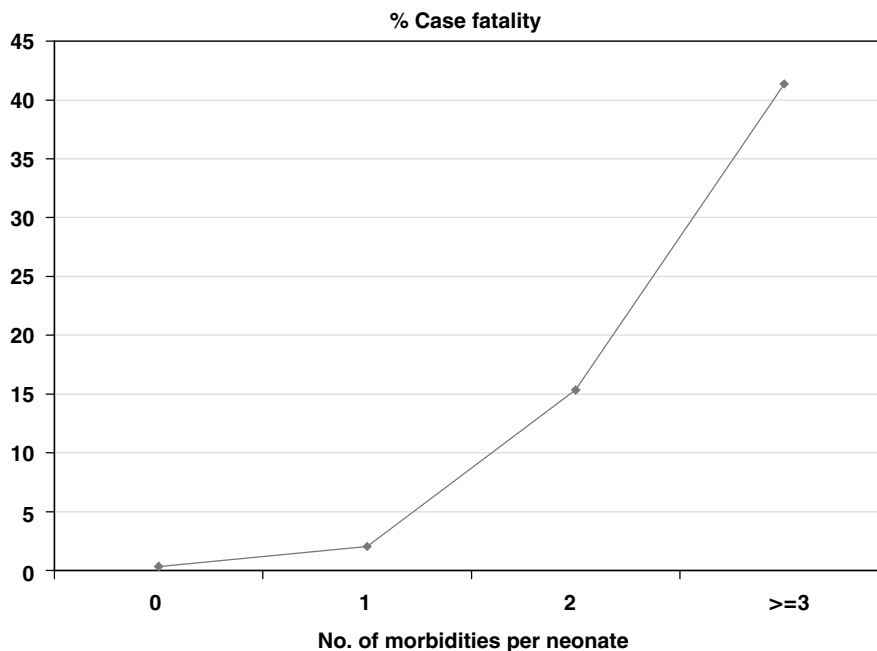
Morbidity	Sick neonates		Deaths		RR <sup>†</sup> of death (95% CI)	Proportion of total deaths (40)*
	N*	% Incidence	N*	% Case fatality		
Preterm (<37 weeks)	75	9.8	25	33.3	15.3 (8.4–27.7)	62.5
Clinical sepsis	130	17.0	24	18.5	7.3 (4.0–13.4)	60.0
Intrauterine growth restriction (IUGR) <sup>‡</sup>	253	33.2	11	4.3	0.8 (0.4–1.5)	27.5
Severe birth asphyxia	26 <sup>§</sup>	4.6	10	38.5	8.0 (4.4–14.9)	25.0
Hypothermia <sup>¶</sup>	106	13.9	9	8.5	1.8 (0.9–3.7)	22.5
Feeding problems <sup>¶</sup>	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.  
<sup>†</sup>Relative risk.  
<sup>‡</sup>Full term (37 completed weeks or more) with birth weight <2500 g.  
<sup>§</sup>Observed in 570 neonates.  
<sup>¶</sup>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 <sup>†</sup>
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) <sup>‡</sup>	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.  
<sup>†</sup>A neonate having more than one morbidity is counted in each category. Hence, the sum of PARs is more than 1.  
<sup>‡</sup>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) <i>No morbidity</i>	308	2741 <sup>a</sup>	281 <sup>b</sup>	40.4	1	0.3	2.5
(B) <i>Single morbidity</i>	289	2388 <sup>c</sup>	276 <sup>d</sup>	37.9	6	2.1	15.0
Only asphyxia without other morbidity <sup>†</sup>	8	—	—	1.0	2	25.0	5.0
Only IUGR <sup>1</sup> without other morbidity	155	—	—	20.3	1	0.6	2.5
Only preterm <sup>2</sup> without other morbidity	27	—	—	3.5	3	11.1	7.5
Only sepsis <sup>3</sup> without other morbidity	40	—	—	5.2	0	0.0	0.0
Only hypothermia <sup>4</sup> 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) <i>Only two morbidities</i>	137	2191 <sup>e</sup>	268 <sup>f</sup>	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) <i>Three or more morbidities</i>	29	1911	258	3.8	12	41.4	30.0
Total	763	2472 <sup>g</sup>	276 <sup>h</sup>	100.0	40	5.2	100.0
(E) <i>Morbidities in combination with preterm<sup>§</sup></i>							
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) <i>Morbidities in combination with IUGR<sup>§</sup></i>							
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.

<sup>†</sup>Severe asphyxia.

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

<sup>§</sup>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<sup>2</sup> 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

Birth weight (g)	Without sepsis			With sepsis			Absolute difference in % CF*	p	Relative risk <sup>†</sup>	PAR <sup>‡</sup>	Expected deaths in sepsis cases <sup>§</sup>	Estimated excess deaths <sup>¶</sup>
	Neonates	Deaths	% CF*	Neonates	Deaths	% CF*						
≥ 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 <sup>†</sup>	0.52 <sup>‡</sup>	6.42	17.58

\*Case fatality.  
<sup>†</sup>Of death for sepsis.  
<sup>‡</sup>Population attributable risk for sepsis.  
<sup>§</sup>Expected deaths in sepsis cases if sepsis was prevented, and hence CF in neonates without sepsis would apply.  
<sup>¶</sup>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			Ranking
	Primary cause (assigned by neonatologist)*	PAR <sup>†</sup> in multicausal analysis <sup>‡</sup>	Proportion of all deaths <sup>§</sup>	
<i>(A) Individual morbidity</i>				
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	—	—	—
<i>(B) Combinations of morbidities</i>				
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
<i>(C) Deaths preventable by preventing/managing sepsis, even if LBW persisted</i>		Preventable deaths <sup>¶</sup> 17.58	Proportion of total deaths(40) preventable 44.0%	
*Bang, Paul and Reddy, Why do neonates die in rural homes? Part I.				
<sup>†</sup> Population attributable risk.				
<sup>‡</sup> Table 2 in the present paper.				
<sup>§</sup> Table 3 in the present paper.				
<sup>¶</sup> 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,<sup>7</sup> 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.<sup>10–12</sup> As to the quality and completeness of data, and the definitions and validity of diagnoses of morbidities, these have been discussed elsewhere.<sup>10–12</sup> 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.<sup>18</sup>

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<sup>1</sup> 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<sup>19</sup> 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.<sup>20,21</sup>

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.<sup>9</sup> 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.<sup>22,23</sup> 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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