**Risk of Mortality Associated With Neonatal Hypothermia in Southern Nepal**

Luke C. Mullany, PhD; Joanne Katz, ScD; Subarna K. Khatry, MD; Steven C. LeClerq, MPH; Gary L. Darmstadt, MD; James M. Tielsch, PhD

**Objective:** To quantify the neonatal mortality/hypothermia relationship and develop evidence-based cutoffs for global definitions of neonatal hypothermia.

**Design:** Cohort study. Field workers recorded neonatal axillary temperature at home and recorded vital status at 28 days.

**Setting:** Rural Nepal.

**Participants:** Twenty-three thousand two hundred forty infants in Sarlahi, Nepal.

**Main Exposure:** Hypothermia.

**Outcome Measures:** Mortality risk was estimated using binomial regression models. Infants were classified using (1) World Health Organization (WHO) cutoffs for mild, moderate, and severe hypothermia; (2) quarter-degree intervals from 32.0°C to 36.5°C; and (3) continuous temperatures. Estimates were adjusted for age, ambient temperature, and other potential confounders.

**Results:** Mortality increased among mild (relative risk [RR], 1.70; 95% confidence interval [CI], 1.23-2.35), moderate (RR, 4.66; 95% CI, 3.47-6.24), and severe (RR, 23.36; 95% CI, 4.31-126.70) hypothermia cases. Within the WHO’s moderate classification, risk relative to normothermic infants ranged from 2 to 30 times. Adjusted mortality risk increased 80% (95% CI, 63%-100%) for each degree decrease, was strongly associated with temperatures below 35.0°C (RR, 6.11; 95% CI, 3.98-9.38), and was substantially higher among preterm infants (RR, 12.02; 95% CI, 6.23-23.18) compared with full-term infants (RR, 3.12; 95% CI, 1.75-5.57). Relative risk was highest in the first 7 days, but remained elevated through 28 days.

**Conclusions:** A new hypothermia classification system should be considered by the WHO for global guidelines. We recommend that grade 1 be equivalent to the current mild category (36.0°C), restricting and splitting the moderate category into grades 2 (35.0°C-36.0°C) and 3 (34.0°C-35.0°C), and expanding severe hypothermia to less than 34.0°C (grade 4). Reducing hypothermia may dramatically decrease the global neonatal mortality burden.

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**Journal Club**

Annually, 4 million newborns die during the neonatal period. Sufficient information is not available regarding the role that hypothermia plays in these deaths, and there are few data available that provide evidence on effectiveness of measures to reduce hypothermia-related mortality risk.

Community and hospital-based data from developing countries indicate that the proportion of infants experiencing hypothermia is high. Estimates of the relationship between hypothermia and risk of neonatal mortality risk are limited largely to small hospital-based studies that lack a population base and inadequately control for the most important covariates: age and ambient temperature. Both mortality and hypothermia are strongly correlated with age of the infant, and overall risk of hypothermia can vary substantially by season.

A recent investigation from Guinea-Bissau provided supportive evidence for a relationship between hypothermia and neonatal mortality and controlled for both ambient temperature at measurement (infants were hospital born; temperature range within the maternity ward, 26°C-30°C) and age at measurement (axillary temperature taken within 12 hours of birth). Infants were followed up in the community. Among 2926 newborns, 8% had axillary temperatures of less than 34.5°C, and 7-day mortality was 4.8 times higher among this subgroup.

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The World Health Organization (WHO)\(^1\) currently divides newborn hypothermia into 3 categories: mild (36.0°C-36.5°C), moderate (32.0°C-36.0°C), and severe (<32.0°C). Under these definitions, almost all infants in low-resource community settings experience some degree of mild or moderate hypothermia (among 23,240 infants in rural Sarlahi, Nepal, where >90% of babies are born at home, 92.3% had axillary temperatures <36.5°C ±1 times during the neonatal period\(^2\)), yet almost none are classified as severely hypothermic, primarily because the cutoff for severe hypothermia is so low (32°C). Epidemiological data presented with an evidence-based public health perspective are required to either (1) provide justification for continued use of these cutoffs or (2) support alternative cutoffs. The investigators from the Guinea-Bissau study\(^3\) rightly pointed out the apparent arbitrariness of both these WHO cutoffs and those used in previous hospital-based studies; they arrived at their 34.5°C cutoff by examining the crude mortality risk across a range of temperatures from 32°C to 37°C.

Our recent community-based trials of chlorhexidine cleansing interventions in southern Nepal\(^11,13\) included repeated in-home visits by project workers to collect 213,616 axillary temperatures from 23,240 infants. We used these data to quantify associations between neonatal hypothermia and subsequent risk of mortality during the first month of life and explored variation in the hypothermia/mortality relationship across gestational age strata. We examined the impact of varying the hypothermia cutoff definition on the observed association between exposure and mortality and propose new cutoffs for neonatal hypothermia.

**METHODS**

**DATA COLLECTION**

Between August 2002 and January 2006, 23,662 live-born infants in Sarlahi, Nepal, were eligible to participate in a previously reported trial of the impact of 2 chlorhexidine interventions (newborn skin and umbilical cord cleansing) on neonatal mortality and morbidity.\(^11,13\) Women were identified mid-pregnancy, study procedures were explained to the women, informed consent was obtained, and the women were given counseling on early and exclusive breastfeeding and rapid warming and drying of the infant.

At each home visit after birth (days 1-4, 6, 8, 10, 12, 14, 21, and 28), project workers measured axillary temperature of the newborn using a locally available, low-reading digital thermometer accurate to 0.1°C. At the start of the study, all workers had 7 to 12 years of experience collecting axillary temperatures from newborns and infants, and all were retrained at baseline and provided with supervision via direct observation at regular intervals. The project workers reiterated basic messages about the importance of keeping the infant warm if temperatures less than 36.5°C were observed and recommended that caretakers seek care for their infants if the temperature was below 35.5°C.

Daily ambient temperature recordings were available from Sitamar (27°00′34″N, 84°58′47″E, 137 m above sea level) and Janakpur (26°42′39″N, 85°55′27″E, 78 m above sea level) airports, which are approximately 52 km east and 60 km west, respectively, of the geographical center of the study area (approximately 400 km²). Ambient temperature on each day of the study period was defined as the mean minimum temperature recorded from the 2 airports. The study site and adjacent airports are at or near sea level with little topographical variability.

**STATISTICAL ANALYSIS**

Infants first measured within the first 72 hours after birth were included in the analysis. The first axillary temperature observed was examined in relation to mortality risk in 3 distinct ways. Infants were classified according to the standard WHO cutoffs for mild (36.0°C-36.5°C), moderate (32.0°C-36.0°C), and severe (<32.0°C) hypothermia. In each category, the neonatal mortality rate (expressed as deaths per 1000 live births) was compared with infants who were normothermic at first measurement (≥36.5°C and <37.5°C). Second, each infant was classified into quarter-degree (ie, 0.25°C) exposure intervals across the entire WHO-defined range of hypothermia (≥36.5°C), with the lowest category including all infants at less than 32.0°C. Neonatal mortality rate risk estimates were calculated relative to the normothermic category. Results for both analyses are presented with and without adjustment for age (in hours) and ambient temperature at the time of axillary measurement. For the third analysis, the interval-specific relative risk (RR) estimates and 95% confidence intervals (CIs) were plotted to visually examine the relationship between decreasing axillary temperature and mortality and to assess appropriateness of modeling mortality risk as a function of the continuous axillary temperature measure. Locally weighted regression smoothing\(^15\) of the risk of neonatal mortality across the range of observed temperatures was used to confirm that the relationship of the log risk of mortality and axillary temperature was approximately linear. Subsequently, a binomial risk regression model with exposure defined continuously and adjusted for age and ambient temperature was used to estimate the incremental risk of mortality for each degree decrease in body temperature.

Following results suggested by these analyses, new cutoffs for neonatal hypothermia based on mortality risk were proposed, termed grades 1 through 4, in increasing order of severity. All infants were reclassified into 1 of these 4 new categories or a fifth normothermic category, which encompasses a temperature range (36.5°C-37.5°C) similar to the current WHO classification scheme. Neonatal mortality rate for each new category and the risk of death relative to the normothermic category was estimated with 95% CIs.

As the relationship between mortality and hypothermia may be modified substantially by gestational age of the infant, weight at measurement, and/or small-for-gestational-age status, separate models that were adjusted for age and ambient temperature at observation were estimated with interaction terms for these 3 factors. Weight was measured at the time of the first home visit using a digital neonatal scale; gestational age was estimated from the woman’s report of last menstrual period collected upon enrollment at mid-pregnancy; and small for gestational age was defined as having a weight less than the tenth percentile for gestational age by sex, using Alexander’s US national reference standards.\(^14\) Among these, only preterm birth status modified the mortality/hypothermia relationship; thus, we present models separately for preterm and full-term infants. The overall and stratified models were further examined for residual confounding by variables that we have previously shown\(^11,12,13,16\) to be related to mortality in this context, including sex, weight, ethnicity,\(^17\) timing of initiation of breastfeeding,\(^18\) hand-washing status of birth attendant and mother,\(^19\) parent (original) trial allocation,\(^11,12\) facility birth, and a composite variable indicating illness at the time of axillary temperature measurement. An infant was considered ill if 2 or more of the following conditions were present: (1) difficulty breathing; (2) stiffening of the back or convulsions; (3) dysentery; (4) 5 or more watery stools within 24 hours; (5) severe chest indrawing; (6) umbilical cord infection; and (7) a respiratory rate of more than 70 breaths/minute. The final multivariate model was examined for reverse causality, by sequentially restricting deaths if they occurred within
Table 1. Associations Between Mortality and First Temperature Observed for Standard WHO Categories

<table>
<thead>
<tr>
<th>Temperature Category, °C</th>
<th>Live Births</th>
<th>Deaths</th>
<th>NMR, /1000 Live Births</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, 36.5-37.5</td>
<td>8378</td>
<td>79</td>
<td>9.4</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Mild, 36.0-36.5</td>
<td>5016</td>
<td>69</td>
<td>13.8</td>
<td>1.46 (1.06-2.01)</td>
<td>1.70 (1.23-2.35)</td>
</tr>
<tr>
<td>Moderate, 32.0-36.0</td>
<td>6188</td>
<td>182</td>
<td>29.4</td>
<td>3.12 (2.40-4.05)</td>
<td>4.66 (3.47-6.24)</td>
</tr>
<tr>
<td>Severe, &lt;32.0</td>
<td>4</td>
<td>1</td>
<td>250.0</td>
<td>26.51 (4.79-146.81)</td>
<td>23.36 (4.31-126.70)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NMR, neonatal mortality rate; RR, relative risk; WHO, World Health Organization.

a Adjusted for age and ambient temperature at measurement.

RESULTS

Of the 23,662 live-born infants eligible for the parent trial, 23,257 (98.2%) were encountered alive at 1 or more home visits during the neonatal period. Seventeen had no axillary temperature measurements, while the remaining 23,240 contributed 213,636 measurements (mean 9.2 measurements/infant) to the analytic data set. Median age at first in-home measurement was 19 hours; the proportion measured within 6, 12, 24, 48, and 72 hours was 12.4%, 32.7%, 62.7%, 82.4%, and 87.7%, respectively. Among the 20,382 (87.7%) infants measured within the first 72 hours, the temperature exceeded 37.5°C in 796 (3.9%) infants, leaving 19,586 with exposure measures in the hypothermic (<36.5°C) or normothermic (≥36.5°C-37.5°C) range. Observed minimum ambient temperatures ranged from 3.8°C to 29.3°C.

EXPOSURE DEFINED USING WHO CATEGORIES

Among all infants, 8378 (42.8%) had normothermic first temperature readings, while approximately 25.6% and 31.6% were classified as mildly or moderately hypothermic, respectively (Table 1). Relative to the normothermic group in which neonatal mortality was 9.4 per 1000 births, the subsequent mortality risks were significantly elevated in all hypothermia categories: among infants with mild and moderate hypothermia, risk of death was 1.46 (95% CI, 1.06-2.01) and 3.12 (95% CI, 2.40-4.05) times higher, respectively. After adjustment for age and ambient temperature at measurement, these RR estimates increased to 1.70 (95% CI, 1.23-2.35) and 4.66 (95% CI, 3.47-6.24), respectively. In the severe category, risk was also substantially higher, but numbers were very small; of 4 infants with body temperatures less than 32.0°C, 1 died.

EXPOSURE DEFINED USING QUARTER-DEGREE INTERVALS

For every quarter-degree interval from 36.5°C to 32°C and below, the crude and adjusted mortality risk exceeded that for infants in the normothermic category (Table 2); there was a steady exponential increase in mortality risk with lower first temperature (Figure). Between 36.0°C and 35.0°C, the risk was elevated approximately 2 to 3 times, while between 35.0°C and 34.0°C, the risk relative to normothermic infants was 8 to 15 times higher. Below 34.0°C, risk was elevated more than 10-fold and in some categories exceeded 30-fold, but the overall number of infants in these lower intervals was small (<200).

MODELING RISK AS A FUNCTION OF CONTINUOUS AXILLARY MEASURES

Risk of death increased by approximately 75% for every 1°C decrease in axillary temperature (RR, 1.75; 95% CI, 1.69-1.81), with adjustment for age and ambient temperature at measurement. The risk of subsequent mortality for an infant with an initially observed temperature that is 3°C lower than a normal temperature of 36.5°C would be elevated approximately 5.36 (95% CI, 4.85-5.91) times.

NEW PROPOSED CUTOFFS FOR NEONATAL HYPOTHERMIA

New cutoffs were selected to define 4 hypothermia grades of increasing severity (Table 3). Under this classification, the most severe category (grade 4, <34.0°C) includes both the lower end of the moderate WHO classification and the WHO severe group; infants in this category were at substantially higher mortality risk compared with normothermic infants (adjusted RR, 24.74; 95% CI, 16.67-36.72). Grades 2 (35.0°C-35.9°C) and 3 (34.0°C-34.9°C) divide the WHO moderate classification into 2 further grades and are associated with 3.04 (95% CI, 2.17-4.25) and 10.00 (95% CI, 6.83-14.64) times the risk of normothermic infants, respectively. Under this new proposed classification, grade 1 hypothermia is equivalent to the WHO mild classification; mortality risk was elevated 1.84 (95% CI, 1.33-2.54) times.

EFFECT MODIFICATION AND MULTIVARIATE ADJUSTMENT

Low weight (<2500 g), small for gestational age, and preterm status were examined as potential effect modifiers.
Weight and small for gestational age did not modify the relationship (terms for interaction with temperature <35.0°C, RR, 1.33; 95% CI, 0.78-2.26; P = .30; and small for gestational age, RR, 0.89; 95% CI, 0.53-1.51; P = .68), while gestational age (RR, 2.15; 95% CI, 1.36-3.39; P < .001) significantly modified the relationship between mortality and hypothermia. A multivariate model adjusted for age and ambient temperature at measurement, sex, ethnicity, timing of breastfeeding initiation, hand-washing status of birth attendant and mother, weight, parent trial allocation, facility delivery, and illness at the time of axillary temperature measurement and stratified by preterm status (<37 weeks vs ≥37 weeks) is shown in Table 4. In this adjusted model, mortality

### Table 2. Associations Between Mortality and First Temperature Observed in Quarter-Degree Intervals

<table>
<thead>
<tr>
<th>Temperature Category, °C</th>
<th>No. of Cases</th>
<th>Live Births</th>
<th>Deaths</th>
<th>NMR, /1000 Live Births</th>
<th>RR (95% CI)</th>
<th>Adjusted RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal, 36.50-37.50</td>
<td>8378</td>
<td>79</td>
<td>9.4</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36.25-36.50</td>
<td>2240</td>
<td>24</td>
<td>10.7</td>
<td>1.14 (0.72-1.79)</td>
<td>1.36 (0.87-2.15)</td>
<td></td>
</tr>
<tr>
<td>36.00-36.25</td>
<td>2776</td>
<td>45</td>
<td>16.2</td>
<td>1.72 (1.20-2.47)</td>
<td>2.29 (1.59-3.30)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35.75-36.00</td>
<td>1341</td>
<td>21</td>
<td>15.7</td>
<td>1.66 (1.03-2.68)</td>
<td>2.54 (1.56-4.11)</td>
<td></td>
</tr>
<tr>
<td>35.50-35.75</td>
<td>1358</td>
<td>24</td>
<td>17.7</td>
<td>1.87 (1.19-2.95)</td>
<td>3.15 (1.98-5.01)</td>
<td></td>
</tr>
<tr>
<td>35.25-35.50</td>
<td>776</td>
<td>14</td>
<td>18.0</td>
<td>1.91 (1.09-3.36)</td>
<td>3.69 (2.07-6.59)</td>
<td></td>
</tr>
<tr>
<td>35.00-35.25</td>
<td>663</td>
<td>11</td>
<td>16.6</td>
<td>1.78 (0.94-3.39)</td>
<td>3.65 (1.92-6.94)</td>
<td></td>
</tr>
<tr>
<td>34.75-35.00</td>
<td>401</td>
<td>18</td>
<td>44.9</td>
<td>4.76 (2.88-7.86)</td>
<td>10.48 (6.18-17.75)</td>
<td></td>
</tr>
<tr>
<td>34.50-34.75</td>
<td>389</td>
<td>18</td>
<td>46.5</td>
<td>4.91 (2.97-8.10)</td>
<td>11.42 (6.75-19.31)</td>
<td></td>
</tr>
<tr>
<td>34.25-34.50</td>
<td>276</td>
<td>9</td>
<td>32.6</td>
<td>3.46 (1.75-6.82)</td>
<td>8.67 (4.29-17.53)</td>
<td></td>
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<tr>
<td>34.00-34.25</td>
<td>285</td>
<td>10</td>
<td>35.1</td>
<td>3.72 (1.95-7.11)</td>
<td>9.59 (4.89-18.81)</td>
<td></td>
</tr>
<tr>
<td>33.75-34.00</td>
<td>154</td>
<td>8</td>
<td>51.9</td>
<td>5.51 (2.71-11.20)</td>
<td>15.42 (7.37-32.28)</td>
<td></td>
</tr>
<tr>
<td>33.50-33.75</td>
<td>169</td>
<td>17</td>
<td>100.6</td>
<td>10.67 (6.46-17.61)</td>
<td>30.52 (17.65-52.76)</td>
<td></td>
</tr>
<tr>
<td>33.25-33.50</td>
<td>110</td>
<td>6</td>
<td>54.5</td>
<td>5.78 (2.58-12.98)</td>
<td>18.80 (8.05-43.94)</td>
<td></td>
</tr>
<tr>
<td>33.00-33.25</td>
<td>91</td>
<td>3</td>
<td>33.0</td>
<td>3.50 (1.12-10.87)</td>
<td>10.96 (3.44-34.93)</td>
<td></td>
</tr>
<tr>
<td>32.75-33.00</td>
<td>63</td>
<td>6</td>
<td>95.2</td>
<td>10.10 (4.57-22.30)</td>
<td>32.48 (14.20-74.30)</td>
<td></td>
</tr>
<tr>
<td>32.50-32.75</td>
<td>41</td>
<td>4</td>
<td>97.6</td>
<td>10.35 (3.98-26.93)</td>
<td>32.08 (11.98-85.91)</td>
<td></td>
</tr>
<tr>
<td>32.25-32.50</td>
<td>44</td>
<td>11</td>
<td>250.0</td>
<td>26.51 (15.19-46.27)</td>
<td>77.18 (43.35-137.38)</td>
<td></td>
</tr>
<tr>
<td>32.00-32.25</td>
<td>27</td>
<td>2</td>
<td>74.1</td>
<td>7.85 (2.03-30.35)</td>
<td>19.41 (5.18-72.78)</td>
<td></td>
</tr>
<tr>
<td>Severe, &lt;32.00</td>
<td>4</td>
<td>1</td>
<td>250.0</td>
<td>26.51 (4.79-146.81)</td>
<td>21.28 (4.01-112.98)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NMR, neonatal mortality rate; RR, relative risk.

*a* World Health Organization categories.

*b* Adjusted for age and ambient temperature at measurement.

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**Note:**

- **Figure:** Association between first temperature observed and mortality, adjusted for age and ambient temperature at measurement. Error bars indicate 95% confidence interval; *normal temperature*.

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risk associated with hypothermia grades 2, 3, or 4 among preterm infants remained significantly elevated compared with normothermic infants, and the magnitude of the relationship in each of these 3 categories was substantially higher than among full-term infants. Among full-term infants, significantly elevated mortality risks after adjustment were seen only for grade 3 (RR, 2.47; 95% CI, 1.27-4.80) and grade 4 (adjusted RR, 4.80; 95% CI, 2.34-9.81) hypothermia. If grades 3 and 4 are combined, mortality risk associated with temperature below 35.0°C was elevated 6.11 (95% CI, 3.98-9.38) times relative to normothermic infants and was substantially higher among preterm infants (RR, 12.02; 95% CI, 6.23-23.18) compared with full-term infants (RR, 3.12; 95% CI, 1.75-5.57).

The binomial regression model that used the continuous auxiliary measures was also adjusted for all the variables listed previously (adjusted RR, 1.80; 95% CI, 1.63-2.00) and examined separately by gestational age. For preterm infants, the adjusted risk of mortality was 1.99 (95% CI, 1.70-2.34) times higher for every 1°C decrease in axillary temperature; for full-term infants, incremental risk per degree was lower, but remained significantly elevated (RR, 1.56; 95% CI, 1.31-1.86).

### REVERSE CAUSALITY AND INTERVAL BETWEEN EXPOSURE AND OUTCOME

The full multivariate model was reestimated after excluding deaths that occurred soon after the first observed axillary temperature measurement. Three cutoffs were examined separately: requiring that the infant survived for at least 12, 24, or 48 hours after observation did not change the adjusted RR or mortality for each grade of hypothermia relative to normothermic infants. Finally, the association between hypothermia and mortality was examined separately for the early (first week) and late (last 3 weeks) neonatal periods. The full multivariate model for the first week of life and conditioned on survival to 7 days is shown in Table 5. For each hypothermia grade, both the magnitude and statistical strength of association were lower in the late neonatal period relative to the early period. However, for grades 3 and 4, adjusted mortality risk remained elevated relative to normothermic infants throughout the entire period.

### COMMENT

Pathophysiologic mechanisms by which cold stress may lead to subsequent mortality have been well described, but population-based data on incidence and consequences of neonatal hypothermia from community settings have been lacking. These data from southern Nepal...
demonstrate that initial observed body temperature of newborns is strongly correlated with subsequent mortality, especially among preterm babies. Absolute mortality risk rose exponentially with decreasing initial axillary temperature, after adjustment for age and ambient temperature, as indicated by the linear relationship on the log risk scale. The risk of mortality subsequent to hypothermia was higher in the first week of life, but temperatures less than 35.0°C remained associated with mortality throughout the neonatal period.

Given the high magnitude and substantial variation of the risk relationship within the current 3-tiered WHO hypothermia classification system, we propose new cutoffs to address 2 important problems associated with the current scheme. First, the existing cutoff for severe hypothermia (≤32.0°C, “grave prognosis; urgent skilled care needed”) is too restrictive. Under this criterion, approximately two-tenths of 1% (4 of 19,268) of infants met this cutoff, though some severely hypothermic newborns may have died before a measurement could be recorded. The rarity of such levels and the noninclusion of infants with very low body temperature may contribute to underestimation of the seriousness of cold injury. Under the new cutoffs, grade 4 hypothermia extends up to 34°C and included 3.6% of newborns. Second, the existing moderate category (32.0°C-36.0°C, “immediate warming of baby necessary”) is too wide, encompassing both “near severe” hypothermia cases with extremely high mortality risk and “near mild” cases with substantially lower, albeit still elevated, mortality risk. Approximately half of all hypothermic infants in this study fell into this category, while the other half were in the mild category (36.0°C-35.9°C, “advise warming the baby”). Under the new cutoffs, the most severely hypothermic infants previously classified as moderate are now classified in grade 4. The remainder is split into 2 categories, allowing an improved division of subsequent mortality risk and targeted intervention by grade and preterm status. For example, in a community-based neonatal health program with outreach workers conducting postnatal visits, estimates from the fully adjusted model suggest that preterm grade 3 and grade 4 infants require urgent and skilled care plus referral, while preterm grade 2 infants and full-term grade 3 infants might be targeted with immediate in-home demonstration of improved thermal care plus daily home visits for observation. Furthermore, our suggested classification fits more closely with more recent WHO guidelines. For care of normal infants, WHO recommends referral for inpatient care for those with a temperature of less than 35.0°C and inpatient hospital care for sick newborns presenting with temperature of less than 35.5°C.

A previous small community-based study of neonatal body temperature indicated that mortality was approximately 3 times higher among infants with temperatures of less than 35.0°C, but no further information was available or risk in other temperature ranges. Similar temperature-dependent risk was demonstrated in Guinea-Bissau, but, unlike the current findings, no excess risk of mortality in the first week or 2 months after birth was found among infants with first observed temperatures in the upper end of the hypothermia severity scale (ie, 34.6°C-36.5°C). While all newborns have immature thermoregulatory control, premature or low-weight infants are particularly susceptible to heat loss in part owing to their reduced deposits of brown adipose tissue, required for nonshivering thermogenesis, their high surface area to weight ratio, and their compromised skin barrier function leading to increased transepidermal water loss.

Study strengths include large sample size, inclusion of 3 calendar years of data, measures taken among a population-based sample from a community setting, and the availability of age and ambient temperature data for every axillary measurement. Mortality among newborns peaks in South Asia during the hot season prior to monsoon season, while hypothermia peaks in the cold winter months. Thus, crude examination of the mortality/hypothermia relationship without taking into account seasonality will underestimate the relationship.

Age of first observation varied in this analysis and as a result, we chose to restrict analysis to infants first observed within 72 hours of birth. If all infants are included, regardless of timing of observation, similar conclusions are drawn, with slightly lower-magnitude risk ratios for each hypothermia cutoff (data not shown). Gestational age measures based on mother’s report of last menstrual period can lead to some misclassification, potentially reducing our ability to correctly estimate the degree to which this factor modifies the overall relationship. Some infants (1.8%) were excluded; most were deaths prior to our arrival (n = 378, 90% of the missing infants). As most of these deaths presumably occurred among the highest risk preterm and/or low-birth-weight infants, it is possible that the mortality/hypothermia relationship may have been further strengthened had they been included. While axillary recordings were chosen given the ease and safety of placement in this nonclinical setting, accuracy of readings might have been slightly improved if rectal temperature measures had been possible. Despite the large overall sample size, small numbers for some of the hypothermia categories or quarter-degree intervals led to wide CIs. Finally, the new classification scheme suggested herein might be further refined through research that allows examination of prognosis in the context of adequate management of infants identified with hypothermia.

Further attention to the high prevalence and adverse consequences of neonatal hypothermia in community settings is needed. The exposure is easily measured by community-based workers and is one of the most important indicators of subsequent survival of the infant. Revaluation of the WHO cutoffs for severity of hypothermia holds relevance for more appropriately classifying risk and emphasizing the urgent nature of moderate hypothermia. However, the programmatic take-home message is of greater import. All cold infants are at increased risk of death; in both home and facility settings, prevention of cold stress starting immediately at birth is critical and when exposure occurs, early identification of at-risk infants and contextually appropriate steps for warming must be initiated. Simple, low-cost interventions for thermal protection, an essential component of newborn care, exist and include immediate drying, wrapping, delayed bathing, early breastfeeding initiation, and skin-to-skin contact. Coverage or adherence to these practices is low in Sarlahi; infants are bathed almost immediately, less...
than half of infants are breastfed within 24 hours, and less than 5% report skin-to-skin contact in the first 2 weeks of life. Although challenging, improvements are possible through innovative and intensive efforts to change behaviors. A package of behavioral change communications focused largely, though not exclusively, on improved thermal care, led to substantial reductions in newborn mortality in Uttar Pradesh. By incorporating such efforts into existing neonatal health programs and prioritizing implementation, reductions in prevalence of neonatal hypothermia in low-resource communities is possible and can contribute greatly to reducing the global burden of neonatal deaths.

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