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The Global Network Neonatal Cause of Death algorithm for low-resource settings

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Abstract

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Aim—This study estimated the causes of neonatal death using an algorithm for low-resource areas, where 98% of the world's neonatal deaths occur.

Methods—We enrolled women in India, Pakistan, Guatemala, the Democratic Republic of Congo, Kenya and Zambia from 2014–2016 and tracked their delivery and newborn outcomes for up to 28 days. Antenatal care and delivery symptoms were collected using a structured questionnaire, clinical observation and, or, a physical examination. The Global Network Cause of Death algorithm was used to assign the cause of neonatal death, analysed by country and day of death.

Results—One third (33.1%) of the 3,068 neonatal deaths were due to suspected infection, 30.8% to prematurity, 21.2% to asphyxia, 9.5% to congenital anomalies and 5.4% did not have a cause of death assigned. Prematurity and asphyxia-related deaths were more common on the first day of life (46.7% and 52.9%, respectively), while most deaths due to infection occurred after the first day of life (86.9%). The distribution of causes was similar to global data reported by other major studies.

Conclusions—The Global Network algorithm provided a reliable cause of neonatal death in low-resource settings and can be used to inform public health strategies to reduce mortality.

Keywords

Global Network Cause of Death algorithm; infection; low-middle income countries; preterm birth; neonatal mortality

BACKGROUND

An estimated 2.8 million neonatal deaths occur worldwide each year and 98% of these are in low and middle-income countries (LMIC) (1,2). In high-income countries, the rates of early neonatal death are often less than two per 1,000 and late neonatal deaths, between 7–28 days of life, are less than one per 1,000. In contrast, the rates of neonatal death are often 10 times higher - 20 per 1,000 - in LMIC for early neonatal deaths and seven per 1,000 for late neonatal deaths. The overwhelming majority of neonatal deaths are attributed to complications of preterm birth, infectious disease and asphyxia, which are all potentially preventable causes (3).

Most LMIC lack high-quality civil registry systems to record neonatal deaths and only 65% of births and 38% of all deaths are registered worldwide (3,4). In order to reduce avoidable deaths, we must understand the major causes of neonatal deaths and direct resources to prevent them (4–7). Because access to healthcare services is not universal in LMICs, and resources to ascertain the causes of neonatal deaths with diagnostic tools such as autopsies, placental histology, x-rays, ultrasound or bacterial cultures are limited, the cause of death (COD) assigned by clinicians might be inaccurate (1,2).

Methods to determine population-based causes of neonatal death worldwide vary from high-income countries, where vital registration systems are generally of a high quality, to LMIC, which frequently rely on estimates. A publication by Oza et al on worldwide causes of neonatal deaths was only able to obtain civil registration data for 65 of 194 countries to

estimate causes of death (8). The data for the remaining 129 countries were derived from mathematical models based on civil registry data from other countries or from literature reviews of small neonatal cause of death studies. In addition to modelling, verbal autopsies and expert algorithms have been applied to determine the causes of neonatal deaths in settings that lack high-quality civil registration systems (9–11).

In 2007, the World Health Organization developed a standard verbal autopsy methodology and questionnaire regarding diseases, signs, symptoms and the treatment of the deceased person, followed by physician certification, in which up to three trained physicians reviewed the data and assign a COD (12). Due to the considerable resources and training required for physician-certified verbal autopsy, several methods for computerised coding of verbal autopsy have been developed. These methods include the Tariff and the Artificial Neural Network methods, which are based on an algorithm to assign a single cause of death, as well as the InterVA method, which is based on probabilities and assigns multiple causes (13–15). One review found that the most common interpretation method of the verbal autopsy instruments was physician-certified, followed by probabilistic methods and algorithms (15).

A major concern with any classification system is the reliability of the COD determination across evaluators. When different clinicians determine the COD for any specific case, major differences often occur (16–19), as results may not only depend on the case data available, but also on the individual behavior of the classifiers. The use of physicians also poses a problem because of the required resources and training. The Bali Declaration, which was issued by a verbal autopsy expert group in 2011, stated that: “physician review of verbal autopsy data as the default method of choice for all verbal autopsy interpretations should be a thing of the past” (20). The World Health Organization neonatal death verbal autopsy instrument published in 2014 requires that the family or a community member must respond to more than 140 detailed questions and that the healthcare provider must access clinical information and diagnostics. This poses an additional challenge and makes it quite complicated and costly to incorporate into existing health systems (12).

To address the gaps in standardised systems to determine maternal and neonatal COD in LMIC, we developed the Global Network Cause of Death algorithm (21,22). We applied this algorithm to data available in community and clinic settings over an 18-month period as a tool to determine the causes of neonatal death. The application for determining the cause of stillbirths is described elsewhere (22). We compared the results obtained with this system to the clinician assigned causes of death, as well as to previous reports of causes of neonatal mortality.

METHODS

The study was conducted within the Global Network for Women’s and Children’s Health Research (Global Network), a multi-country research network with sites in the Democratic Republic of Congo, Kenya, Zambia, Belagavi and Nagpur, India, Pakistan and Guatemala. The network is funded by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (23,24).

Each site in the Global Network has between 10 and 20 geographically defined clusters, defined as communities with approximately 500 deliveries per year. These clusters participate in the Maternal Newborn Health Registry study, a population-based registry that aims to enroll all consenting women as early as possible during pregnancy. Basic demographic information is collected at enrollment and women are then visited by a registry administrator following delivery and at six weeks post-partum to obtain birth and child outcomes, including information on delivery care (24).

Causes of neonatal death

Neonatal deaths were defined as those that occurred before 28 days after live births. We obtained standardised data in the immediate neonatal period and, or, within two weeks after death using information obtained from the mother, family and caregivers and through clinical examinations that only required basic equipment, such as a scale for the birth weight determination, blood pressure cuff and thermometer. When available, we included hospital-based information from reviews of clinical records. In addition, for all neonatal deaths, the clinician-assigned cause of death was recorded, based on each site's local system for determining cause of death.

For the Global Network COD system, the information obtained for each neonatal death was analyzed using a computer-based, hierarchical algorithm (Figure 1).

The algorithm first determined whether a major congenital anomaly was present and, if so, whether this was the assigned cause of death. If there was no major congenital anomaly and an infection was present or suspected, such as tetanus, omphalitis, sepsis or pneumonia, then infection was determined to be the cause of death. If neither an anomaly nor infection was present, the algorithm then differentiated causes based on the gestational age at birth.

If there was no evidence of anomaly or infection among term infants, and if there was no crying or breathing difficulties at birth, asphyxia was assigned as the cause of death. If no signs of difficulties breathing at birth or respiratory distress were present, the cause of death was assigned as unknown. For preterm infants between 34 and 37 weeks, or over 2,000 grams, the algorithm assigned asphyxia as cause of death if a) the neonate breathed weakly, was resuscitated or had an early seizure or b) the mother had complications during pregnancy such as preeclampsia or eclampsia, obstructed or prolonged labour, fetal growth restriction, a twin pregnancy or a breech birth. If the infant was <34 weeks at birth and, or, <2,000 grams, and none of the above conditions were present, the algorithm assigned the cause of death as prematurity, regardless of whether respiratory distress was present, since respiratory distress syndrome is common and congenital anomalies and infections had previously been considered and rejected as a cause.

Statistical analyses

Data were entered at each study site where initial quality checks were performed. Data were transmitted to a central coordinating centre using a secure method, where additional data editing checks were performed. Data from all sites were combined for the analyses of the day of death and comparisons with the clinician assigned cause of death. Data from the two Indian sites and the two African sites were combined for the analysis of mortality rates and

cause specific mortality and we used Cohen's Kappa to assess the agreement between the algorithm and the clinician assigned cause of death. A Kappa range between 0 and 0.2 was considered to indicate minimal agreement, 0.21 to 0.4 fair agreement, 0.41 to 0.6 modest agreement, 0.61 to 0.8 substantial agreement and 0.81 to 1 exact agreement (25).

All analyses were performed in SAS version 9.3 (ASA Institute Inc, North Carolina, USA).

Ethical approval

We received ethical approval from the institutional review boards and ethics committee at the participating study sites (Aga Khan University, Pakistan; Kinshasa School of Public Health, Democratic Republic of Congo; Moi University, Kenya; Francisco Marroquin University, Guatemala; University of Zambia, Zambia; Lata Medical Research Foundation, Nagpur, India and KLE University, Belagavi, India) and their affiliated partner institutions in the USA (Columbia University, University of North Carolina at Chapel Hill, University of Indiana, University of Colorado, University of Alabama at Birmingham, Boston University and Thomas Jefferson University) and the data coordinating center (RTI International). The women provided informed consent prior to their participation in the study.

RESULTS

During the study period from 2014–2016, a total of 133,381 newborn infants were screened and 132,402 mother-infant dyads were eligible and the mothers agreed to participate. They included 122,799 women who delivered babies at more than 20 weeks of gestation (Figure 2). More than three-quarters (approximately 77%) of the births occurred in a hospital or clinic (Table 1). Guatemala had the lowest rate of facility births (55.3%), while the Indian sites had nearly all institutional deliveries. A total of 3,068 neonatal deaths were included in the analysis. The overall neonatal mortality rate was 25.5 deaths per 1,000 live births, which ranged from 16.3 per 1,000 in the African sites to 47.8 per 1,000 in Pakistan.

Based on the Global Network COD Algorithm, 33.1% of the neonatal deaths at all sites were due to infections, 30.8% to prematurity, 21.2% to asphyxia and 9.5% to congenital anomalies. A further 5.4% were classified as unknown (Figure 3). The Guatemalan and African sites had the highest proportion of deaths due to infection and the Indian sites at had the largest percentage due to congenital anomalies (17.7%). More than a quarter of the deaths at the African sites were due to asphyxia and about one-third of the deaths in Pakistan were due to prematurity.

We also analysed the cause of death in relation to the day of death. Prematurity and asphyxia-related deaths were more common on the first day of life, at 46.7% and 52.9%, respectively, while most deaths due to infection (86.9%) occurred after the first day of life (Figure 4).

Finally, we compared the results obtained through the Global Network COD algorithm and the clinician assigned cause of death. This showed that the clinicians and the algorithm agreed on the cause of death in 58% of cases and that the overall Kappa was 0.46, with a 95% confidence interval (CI) of 0.44–0.48), which was a moderate agreement between the

clinician and algorithm assigned causes of death. The data are presented for each specific cause of death in Table 2. Congenital anomalies showed a substantial agreement (0.73, 95% CI 0.69–0.76), while infections, prematurity, asphyxia and unknown causes showed a moderate agreement. The proportion of deaths that were classified as unknown was lower in the Global Network system (5.4%) than the clinician-based determination of cause of death (15.1%). The proportion of clinicians who described the cause of death as don't know or other ranged from 2% in Guatemala to nearly 50% in Kenya. Using the Global Network system, the proportion of unknown causes ranged from 5% to 7% for all sites, except Guatemala (1.3%) (data not shown).

DISCUSSION

We found that at all sites, nearly three-quarters of the deaths were attributed to infections, complications of prematurity and asphyxia irrespective of the number of live births, the neonatal mortality rate or the proportion of births occurring at home.

Approximately 10% of the deaths were attributed to congenital anomalies, ranging from about 18% of the deaths at the Indian sites to less than 5% at the African sites. The higher rate of anomalies at the Indian site has previously been reported. One study from this region in India observed a high rate of pregnant women (24%) who were in consanguineous partnerships, which increased the risk of birth defects (26).

When we used the Global Network Cause of Death algorithm to analyse data from this population-based community study, we found that the distribution of the causes of neonatal death were similar to that reported in the literature for the four main causes (3,26–28).

We found that deaths assigned to prematurity and asphyxia generally occurred earlier in the neonatal period and that infection-related deaths occurred later, which was also consistent with previous reports (29). The algorithm also revealed differences in the proportion of deaths assigned to different causes between the various sites.

The findings also showed some discrepancies between the algorithm and clinician-assigned cause of death and using the Global Network System reduced the number of deaths classified as unknown. The wide variation in rates of unknown causes between the sites was also reduced using the Global Network algorithm. The reasons for the differences in the types of causes, and the discrepancies between the algorithm and clinician-assigned cause of death, are unknown at this time.

Our study had several limitations. We recognise that this algorithm necessarily provides a simplification of the cause of death and that subtle or rare causes of neonatal death will be missed. In addition, a validation assessment of our algorithm would further strengthen it. However, determining a gold standard is challenging and, even when hospital-based cause of death data are available, the quality of the cause of deaths assignment in such settings needs to be carefully evaluated. Given these limitations, the Global Network Cause of Death algorithm provides data to inform the major causes and proportions of neonatal death.

The major strengths of this method were the consistency and transparency, with the ability to provide comparability across time or regions with minimal burden on the healthcare system. The algorithm uses major causes of death that have been well established and are commonly used for cause of death classifications, especially in low-resource settings. These attributes make this algorithm potentially useful, both for research and for public health policy purposes. In addition, our study employed the same methodology in different settings, allowing us to compare the cause of deaths profiles between them. The interpretation was not based on the physician's assignment and this avoided subjectivity during the diagnosis. The algorithm assigns a single cause of death, taking advantage of the hierarchical structure of the cause of deaths determination.

Implications

Other cause of death methodologies have used verbal autopsies conducted at community levels and these have been combined with physician's interpretations and consensus, machine learning or generating a set of probabilities of the cause of death. These methods can be subjective and have a number of disadvantages, depending on how and where they are implemented. Verbal autopsy can be time-consuming and costly and individual physicians are likely to classify the cause of death differently (30). The high proportion of neonatal deaths that are classified as unknown is also a major limitation of existing systems that limits how useful they are when it comes to informing interventions.

A reliable and reproducible classification system for the cause of neonatal deaths can advance research and inform public health strategies aimed at reducing neonatal mortality. The Global Network Cause of Death algorithm uses minimal, basic data from the mother, family or lay-health providers to determine the causes of the majority of neonatal deaths. Laboratory tests, placental examinations and autopsies are not necessary. This information can be used to analyse associations and generate hypotheses, and provide the basis for the design of future interventions. In addition, given the reliance of the system on minimal data, it should be feasible to use this system in broader clinical settings. Nevertheless, collecting the data for use in the algorithm requires some resources and ultimately requires a system that values knowledge about the causes of neonatal death in that setting. If the system can provide information on the distribution of causes of neonatal death, and that information can help to develop interventions that reduce deaths from certain conditions, that should increase the value that policy makers and clinicians place on the registration system.

CONCLUSION

We developed the Global Network Cause of Death algorithm to classify causes of neonatal deaths and our findings indicate that it is suitable for use across low-resource settings. It can be used to inform and provide a direction for public health strategies that reduce neonatal mortality. In these areas, where most of the global neonatal mortality occurs, the reliable and reproducible classification of maternal, fetal and neonatal death is needed, both to advance research and to inform public health strategies to reduce pregnancy-related mortality. A reliable system to determine cause of death will ultimately serve to inform the public health strategies necessary to reduce the high maternal, fetal and newborn mortality burden in low-

resource settings and assess the effects of interventions. The overall findings were consistent with other published studies on the causes of neonatal death in LMIC (1,2).

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Abbreviations

CI	Confidence interval
LMIC	low and middle income countries

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Key Notes

- We estimated the causes of neonatal death by using the Global Network algorithm in six low-resource countries: India, Pakistan, Guatemala, the Democratic Republic of Congo, Kenya and Zambia.
- A third (33.1%) of the 3,068 neonatal deaths were due to suspected infection, 30.8% to prematurity, 21.2% to asphyxia and 9.5% to congenital anomalies.
- The algorithm provided a reliable cause of neonatal death in low-resource settings and could help to reduce mortality.

Figure 1.
Global Network cause of neonatal death algorithm

Figure 2.
Screening and enrollment diagram

Figure 3.
Cause of neonatal deaths, overall and by region, by Global Network sites 2014–2016

Figure 4.
Day of death per specific cause of death

Characteristics of births and deaths at more than 20 weeks of gestation by region, 2014–2016

Table 1

	Total	Africa	India	Pakistan	Guatemala
Deliveries, n	122,799	40,824	39,676	22,324	19,975
Delivery location all births, n (%)					
Hospital	52,637 (42.9)	7,573 (18.6)	25,893 (65.3)	8,317 (37.3)	10,854 (54.3)
Clinic	42,504 (34.6)	23,372 (57.3)	12,750 (32.1)	6,189 (27.7)	193 (1.0)
Home/other	27,657 (22.5)	9,879 (24.2)	1,033 (2.6)	7,817 (35.0)	8,928 (44.7)
Neonatal deaths < 28 days, n (rate/1,000)	3,068 (25.5)	653 (16.3)	848 (21.7)	1,031 (47.8)	536 (27.2)
Delivery location for neonatal deaths, n (%)	3,068	653	848	1,031	536
Hospital	1,489 (48.5)	150 (23.0)	610 (71.9)	378 (36.7)	351 (65.5)
Clinic	843 (27.5)	335 (51.3)	195 (23.0)	308 (29.9)	5 (0.9)
Home/other	736 (24.0)	168 (25.7)	43 (5.1)	345 (33.5)	180 (33.6)
Skilled attendance for neonatal deaths, n (%)					
Skilled	2,054 (67.0)	441 (67.6)	815 (96.1)	433 (42.1)	365 (68.1)
Unskilled	1,011 (33.0)	211 (32.4)	33 (3.9)	596 (57.9)	171 (31.9)

Table 2

Comparison of cause of death assigned by the Global Network algorithm and by the clinician

Cause of neonatal death	Assigned by clinician, n (%)	Assigned by algorithm, n (%)	Assigned by both clinician and algorithm n (%) ^I	Cohen's Kappa (95% confidence Interval)
Congenital anomaly	187 (6.2)	287 (9.4)	178 (5.8)	0.73 (0.69 – 0.76)
Infection	543 (17.9)	1,001 (33.1)	450 (14.8)	0.45 (0.42 – 0.48)
Prematurity	892 (29.5)	932 (30.8)	574 (18.9)	0.46 (0.43 – 0.50)
Asphyxia	947 (31.3)	641 (21.2)	480 (15.8)	0.47 (0.43 – 0.50)
Unknown	454 (15.0)	162 (5.3)	101 (3.3)	0.27 (0.23 – 0.30)
Total	3,023 (100.0)	3,023 (100.0)	1,783 (58.9)	0.46 (0.44 – 0.48)

^I Percentages were estimated dividing the number of cases where there was agreement by the total sample size (n = 3,023)