

STATE-OF-THE-ART

Ascertaining causes of neonatal deaths using verbal autopsy: current methods and challenges

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Objective: 'Verbal autopsy' (VA) is used to ascertain cause of death in countries where vital registration systems are lacking. Current VA methods for neonatal deaths vary widely and suffer from several limitations. We aimed to: (1) review current neonatal VA methods, (2) identify gaps and limitations, (3) illustrate some limitations using VA data and (4) identify new approaches in methodology and analysis.

Study Design: Rolling techniques and database search terms were used to identify articles that described neonatal VA administration, validation and cause of death assignment.

Result: Current VA interviews include open and close-ended modules and are administered by trained interviewers. Causes of death are determined using physician review and/or computer algorithms for various neonatal causes of death. Challenges include lack of a standardized VA instrument and administration of methods, difficulty in identifying gold standards for validation studies, lack of validated algorithms for causes of death, poor existing algorithms, lack of standardized death classification terminology and the use of hierarchy to assign causes of death. Newer probabilistic methods of analysis such as Bayes Theorem or the Symptom Pattern method may improve accuracy for cause of death estimation and alleviate some of the challenges with traditional physician and algorithmic approaches, although additional research is needed.

Conclusion: Given the continued reliance on VA to determine cause of death in settings with inadequate registration systems, it is important to understand the gaps in current VA methods and explore how methods can be improved to accurately reflect neonatal disease burden in the global community.

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Background

Data on causes of death are important for health sector planning, including assessing programmatic needs, monitoring progress of interventions and reassessing health priorities. However, little is known about causes of death in many developing countries because vital registration systems are lacking. Many deaths occur at home, outside the formal health sector, and few are attended by qualified medical professionals. Verbal autopsy (VA) has been used to assign cause of death in such settings.

VA is a post-mortem in-depth interview with the primary caregiver of the deceased. In the case of child deaths, this is usually the mother. Underlying assumptions are that (1) each cause of death investigated has a set of observable symptoms that can be recognized and recalled by the primary caregiver, and (2) the characteristics of one cause of death can be distinguished from those of all others.

The majority of the estimated 4 million annual global neonatal deaths occur in developing countries outside of the formal health care system.¹ Previous research on cause of death for children <5 often excluded neonatal cases due to poor reporting and small numbers of neonatal deaths. Neonatal deaths were grouped with 'other' childhood or 'perinatal' causes, thus limiting opportunities to validate neonatal VA methods,^{2–5} or failed to identify specific causes of neonatal deaths.⁶ Neonatal causes of death are also particularly difficult to classify due to nonspecific signs and symptoms in sick newborns.^{2,7–9} Recently, several studies have focused exclusively on the use of VA in newborns, making this an opportune time to assess the current state of knowledge and provide direction for future research efforts.

We reviewed current literature on neonatal VA that (1) identified specific causes of death during the neonatal period, (2) described VA methodology used and/or (3) reported on validation of VA for neonatal deaths. Using this information, we aimed to: (1) identify current neonatal VA methods, including administration and cause-of-death assignment, (2) identify limitations of current methods, (3) illustrate limitations using examples from current VA data and (4) identify new methods to measure causes of neonatal death.

Current methods

VA instrument design and administration

Neonatal VA instruments consisted of open-history narratives and closed-ended questions about signs, symptoms and events leading to death. Social autopsy modules to assess care-seeking or other cultural influences were uncommon. Some studies reported care-seeking information from open histories¹⁰ and one recent VA instrument included a care-seeking module,¹¹ however, its use has not been validated. VA interviewer training ranged from several days to 1–3 weeks.^{12–15} Local women with secondary level schooling^{12–19} were primary interviewers, however, nurses, physicians^{20–24} and men^{14,23,25–27} were sometimes used. Interviews were conducted from several days²⁴ or weeks after the death^{10,12,13,15,19,20,23,25,26,28–30} to 5 years postmortem.³¹ The mother was generally the main respondent, however, interviews with the grandmother or other close relatives were also reported in cases where both the mother and baby had died.

VA cause of death assignment

Physician review with 2–3 physicians was the most common method used to assign cause of death from the VA.^{10,13,14,18,20–30,32–34} In the event of conflicting diagnoses among physician reviewers, discussions to reach consensus^{7,16,26,32} or a third party ‘majority rules’ were applied.^{22,25} In cases where all three disagreed, the cause was often labeled as ‘undetermined’.^{18,21}

Predefined diagnostic categories and clinical guidelines,^{7,21,24} prescribed lists of cause of death criteria,²⁶ and *International Classification of Disease*, 10th Edition (ICD-10) codes,^{23,29,34} or reference articles,¹³ helped guide cause of death assignment; however, in some studies, criteria to reach the diagnosis was left to the physician’s discretion.²⁸

Computer-programmed combinations of signs and symptoms (computer algorithms) of the fatal illness were also used to assign neonatal causes of death.^{12,15,26} Cases that met the algorithm’s definitions for each cause were identified.

Discrepancies between physician review and computer algorithms were common. Campbell *et al.*³² found that computer algorithms resulted in 48% of cases having an ‘unidentified’ cause of death compared with only 13% from the physician review. Physician review attributed more deaths to sepsis (20%) compared with computer algorithms (7%).³² This result was different from that reported by Freeman *et al.* who found that physicians assigned only 1.2% of deaths to sepsis, while computer algorithms attributed 52.2% of deaths to sepsis.¹⁶ Lee *et al.* also reported disagreement in birth asphyxia diagnosis between physician review and computer algorithms ($\kappa = 0.15$); 85% of birth asphyxia deaths identified by computer algorithm were unidentified by physician review.³⁵ For other causes of death such as prematurity and acute lower respiratory infection, Freeman *et al.* found that the percentage of deaths assigned was similar using both physician review and computer algorithms (26.4 and 20.4% versus 23.5 and 18.4%, respectively).¹⁶

Open histories were also used to assign causes of death.^{7,26} Freeman *et al.* reported that 12% of physician diagnoses relied exclusively on the open-history narrative; and for conditions such as sudden death and malnutrition, where computer algorithms were unavailable, the open history provided critical information for physician diagnosis.²⁶ The ability of physicians to incorporate open-history information into their review was indicated as a potential reason for the discrepancy between physician review and computer algorithms for certain conditions like sepsis.^{26,32} However, Freeman *et al.* developed computer algorithms that included coded symptoms from the open history and compared these diagnoses with those made by physician review. They found no increase in agreement between the computer algorithms and physician review,²⁶ raising questions about the usefulness of the open history. However, for conditions where computer-based algorithms were unavailable, such as sudden death, open histories provided important information. They also provided useful information about the social context of the fatal illness such as care-seeking and local beliefs, their conduct provided an opportunity to build rapport with the respondent, and may have even provided a cathartic effect for the mother after her loss of a newborn infant.

In addition to using algorithms and open histories, physician reviews often followed a hierarchy to assign a single cause of death.^{12,16,17,32,33} A hierarchy arranges causes of death in a particular order based primarily on the specificity of the causal definition or perceived certainty of each diagnosis, as well as the sensitivity of the causal definition and the presumed physiological precedence of each cause’s contribution to a death. The Child Health Epidemiology Research Group (CHERG) has identified a commonly used hierarchy (congenital abnormality → neonatal tetanus → preterm → birth asphyxia → sepsis/pneumonia → diarrhea → other) to estimate the cause distribution of neonatal deaths.³⁶ Conditions like congenital malformation and neonatal tetanus with highly specific symptoms (for example malformation, for the former and spasms, stiff neck and jaw for the latter) can be diagnosed by VA with reasonable certainty¹⁶ and are therefore often placed high in the hierarchy. As each cause of death is identified, cases assigned to the cause are sequentially removed from the sample and cannot be assigned another cause of death. Identifying single causes of death allows distribution of causes to be presented as a pie chart, common when depicting disease burden.

Despite progress to date, there are several limitations to current VA methods such as the administration, validation and methods to assess cause of death including terminology and hierarchy of causes.

Challenges

Lack of standardized VA instrument and administration

There is currently no commonly used VA instrument for neonatal deaths. The WHO (World Health Organization) has incorporated a

neonatal section into their VA for childhood deaths; however, its use has not been standardized. Administration of the VA instrument poses additional challenges. First, identifying deaths in the community where a VA is required is difficult. Though some communities without a functional vital registration system may operate informal surveillance through community leaders and health workers, obtaining accurate estimates about who has died and who requires a VA is a continuing challenge. VA administration requires substantial interviewer training and retraining in both clinical and bereavement issues as well as regular follow-up to obtain the VA from family members after a death. Reporting bias may occur due to cultural factors and stigma associated with death, whereby families may not wish to report deaths of infants <1 month old.¹⁰ This may be further biased with male interviewers. In addition, interviewers with some clinical background may unknowingly bias results to reflect the disease burden in their particular setting.³⁷ VA relies on the ability of caregivers to recall signs and symptoms exhibited by the newborn before death. Recall periods between 1 and 12 months have been accepted in adult studies³⁷ and the validity of mother's responses for a period up to 20 months after a child's death has remained high, possibly due to enhanced memory for details surrounding the tragedy of losing a child.⁶ Still, the possibility of recall bias may occur, especially in cases where a maternal death has also occurred. In these cases, validity of the caregiver response may be lessened due to the inability to recall specific events from two deaths (mother and newborn) or the inability to recall signs/symptoms in the same detail as the mother may have been able to.

Assigning cause of death using neonatal VA poses even more challenges. Identification of gold standard criteria for validation studies, lack of validated algorithms, overlapping signs and symptoms for different causes of death, use of a hierarchy to assign single cause of death, assigning single versus multiple causes of death, and varied cause of death terminology all contribute to the many challenges to assigning a cause of death using this method.

Identification of gold standards and validation

VA relies on the use of reference or 'gold' standard definitions to develop accurate diagnoses. Given that VA is based on subjective accounts from caregivers, validation studies are critical to determine how close to the 'truth' VA diagnoses are.

Validation studies compare the diagnosis made by VA with a reference standard diagnosis reached at the time of death. Medical autopsy is rarely available so reference standard diagnoses are made under conditions (i.e. in a hospital) in which the cause of death can be determined with a degree of certainty based on physician examination and laboratory testing. The validity of each algorithm for assigning cause of death is measured using sensitivity and specificity estimates and the reference standard diagnoses as gold standard.

Few validation studies for neonatal conditions have been conducted, and those that have included neonatal causes have not used comparable methods. Reported sensitivity and specificity for common neonatal conditions differ considerably across studies (Table 1). This may be due, in part, to varying definitions for the reference standards. For example, Kalter *et al.*¹⁵ developed reference standard criteria based on physicians' diagnoses combined with objective illness signs and laboratory and radiologic findings, whereas Setal *et al.*²⁹ provided physicians with ICD-10 codes to identify reference standard cases. Table 2 illustrates the variations in the reference standard diagnoses used for the three primary causes of neonatal death—sepsis, prematurity, and birth asphyxia.

Validation studies have also used different methods to assign the VA cause of death. Kalter *et al.*¹⁵ applied computer algorithms based on the closed-ended questions with the highest specificity and sensitivity profiles for each cause of death. In Pakistan, Marsh *et al.* had physicians review the open history alone, the open history plus closed-ended modules, and then the closed-ended modules alone. The open history was reviewed using a 'sign and symptom duration matrix' to guide the analysis, and diagnoses made from the closed-ended modules were based on predetermined field case definitions or algorithms.⁷ Setal *et al.*²⁹ employed

Table 1 Sensitivity and specificity of validated algorithms for stillbirths and neonatal causes of death

<i>Sensitivity (%)</i>	<i>Specificity (%)</i>	<i>Cases (n)</i>	<i>Reference country</i>
<i>Stillbirths</i>			
80	76	135	Iriya (2002) ¹⁴ Tanzania
61	84	243	Setal (2006) ²⁹ Tanzania
<i>Neonatal tetanus</i>			
84	99	19	Marsh <i>et al.</i> ⁷ Pakistan
90	79	30	Snow (1992) ³⁰ Kenya
83	89	20	Kalter (1999) ¹⁵ Bangladesh
<i>Prematurity</i>			
71	84	59	Marsh <i>et al.</i> ⁷ Pakistan
87	85	30	Kalter (1999) ¹⁵ Bangladesh
48	95	41	Setal (2006) ²⁹ Tanzania
<i>Sepsis</i>			
75	91	8	Kalter (1999) ¹⁵ Bangladesh
39	92	15	Marsh <i>et al.</i> ⁷ Pakistan
61	81	16	Snow (1992) ³⁰ Kenya
6	100	7	Setal (2006) ²⁹ Tanzania
<i>Birth asphyxia</i>			
58	78	52	Marsh <i>et al.</i> ⁷ Pakistan
87	69	19	Kalter (1999) ¹⁵ Bangladesh
54	93	91	Setal (2006) ²⁹ Tanzania

Table 2 Comparison of reference standard diagnoses for neonatal sepsis, prematurity/LBW, birth asphyxia from validation studies

	<i>Kalter et al. (1999)</i> ¹⁵	<i>Marsb et al.</i> ⁷	<i>Setal et al. (2006)</i> ²⁹
Neonatal sepsis	Rectal temperature >38 or <36 °C, plus: Positive blood culture, plus: Nonconsolable irritability, abnormally sleepy or difficult to wake, mottled and cool extremities, or pale and shocky on examination minus reference standard diagnosis of pneumonia, bacterial meningitis, acute or persistent diarrhea and local bacterial infection	Death after 1 day, plus: Any two symptoms of jaundice, fever or hypothermia, convulsions or vomiting	<i>ICD-10 Code P36</i> ^a Bacterial sepsis of newborn (congenital septicemia) Sepsis of newborn due to streptococcus, group B Sepsis of newborn due to other and unspecified streptococci Sepsis of newborn due to <i>Staphylococcus aureus</i> Sepsis of newborn due to other and unspecified staphylococci Sepsis of newborn due to <i>Escherichia coli</i> Sepsis of newborn due to anaerobes Other bacterial sepsis of newborn Bacterial sepsis of newborn, unspecified
Prematurity/low birth weight	Medically documented preterm birth (gestational age <37 weeks) Weight for age Z-score ≤3 on admission to hospital	Pregnancy <37 weeks gestation according to Ballard criteria Weight <2500 g at birth	<i>ICD-10 codes P05:P07</i> ^a Slow fetal growth and fetal malnutrition Light for gestational age (usually referred to as weight below but length above 10th centile for gestational age. Light-for-dates Disorders related to short gestation and LBW, not elsewhere classified Extremely LBW (birth weight ≤999 g) Other LBW (birth weight 1000–2499 g) Extreme immaturity [<28 completed weeks (<196 completed days) of gestation] Other preterm infants (28 weeks or more but <37 completed weeks (196 completed days but <259 completed days) of gestation) Prematurity NOS
Birth asphyxia	Medical history of birth asphyxia, evidenced by documented failure to breathe spontaneously at birth or 20-min Apgar score <4, plus: either lethargy, coma, hypotonia or seizures on examination, plus: 38 °C<rectal temperature never <36 °C	Persistent central nervous system depression, with or without a history of difficult labor or delivery, in the absence of hypoglycemia or demonstrated infection	<i>ICD-10 codes P20:P24</i> ^a Intrauterine hypoxia (includes: abnormal fetal heart rate, fetal or intrauterine: acidosis, anoxia, asphyxia, distress, hypoxia, meconium in liquor passage of meconium) Birth asphyxia Respiratory distress of newborn Congenital pneumonia due to viral agent Neonatal aspiration syndromes (includes: neonatal pneumonia resulting from aspiration)

^aWorld Health Organization (1993) *International Statistical Classification of Diseases and Related Health Problems*, 10th Revision, vol. 2. World Health Organization: Geneva, Switzerland.

physician review of the closed-ended modules and assignment of diagnoses based on current ICD-10 codes.

Findings from validation studies demonstrate high sensitivity and specificity for neonatal tetanus. However, algorithms for prematurity, neonatal sepsis and birth asphyxia, the top three causes of neonatal deaths, have variable validity. In Bangladesh, the VA algorithm for preterm, ‘pregnancy ended early or baby small or smaller than usual at birth,’ was validated against the reference standard with high sensitivity (97%), but lower specificity (65%).¹⁵ In part, this may be because the algorithm leaves room for subjectivity. A woman who is primigravida or living in an area with a high proportion of low birth weight (LBW) is unlikely to know if her baby was ‘smaller than usual at birth’.

All validation studies use hospital diagnoses to validate algorithms used in the community. Cases presenting in a hospital, however, are likely to have different socioeconomic status, health-seeking behaviors, disease symptomatology and possibly cause-of-death distribution than those dying without effective treatment in community. This raises further questions about the generalizability of findings from validation studies.³⁸

Lack of validated algorithms

Stillbirths account for an additional, estimated 3.2 million deaths globally each year,³⁹ however, there have been no well-validated algorithms to identify stillbirths from a VA interview, let alone specific causes of stillbirths. Setal *et al.*²⁹ included stillbirths in

their validation study; however, VA underestimated the stillbirth rate in this setting with relatively low sensitivity but good specificity (61 and 84% respectively). Iriya *et al.* also included stillbirths in their validation study and reported 80% sensitivity and 76% specificity,¹⁴ illustrating the need for additional research on stillbirth modules for use in VA. In addition, subcategorization of stillbirths according to their cause, such as infection or intrapartum hypoxia, is needed to help understand stillbirths as a cause of death. Stillbirths pose an additional challenge as misclassification can occur between stillbirths and early neonatal deaths, and between miscarriage and stillbirth.¹ In some settings, the underlying stigma of stillbirths may lead to underreporting.⁴⁰ In other settings, birth attendants may overreport stillbirths to protect their reputation as good delivery attendants in the community^{41,42} or to avoid investigation procedures required for neonatal deaths.²⁹

In addition to the lack of a validated algorithm for stillbirths, deaths due to some causes are often included as a subset of another condition due to a lack of cases. For example, birth injury is often grouped with birth asphyxia,^{12,18,21,32} Thus, the data for a single category of death may reflect more than one distinct condition with different risk factors. Similarly, deaths attributed to prematurity may involve a variety of disease processes including respiratory distress syndrome (RDS), intracranial hemorrhage, necrotizing enterocolitis, hypothermia and hypoglycemia, for which different interventions are needed. For many subcategories of prematurity, clear case definitions for use in VA have not been identified. Among these, RDS may be the most distinctive and thus amenable to identification with VA.

Poor existing algorithms

Existing algorithms remain poor, in part, due to overlapping signs and symptoms for many causes of neonatal deaths. Overlap of signs between pneumonia, sepsis and meningitis is common in newborns⁴³ and Kalter *et al.*¹⁵ reported that 'convulsions,' a sign of neonatal tetanus in VA, was also associated with other newborn causes of death such as birth asphyxia and neonatal sepsis. Other signs like 'fever' and 'difficulty breathing', associated with pneumonia and sepsis, may also be associated with other causes like tetanus. In a WHO memorandum, experts deduced that based on the few available validation studies, 'it would be almost impossible to distinguish between sepsis and pneumonia in the newborn based on verbal autopsy'.⁴⁴ Overlapping signs and symptoms relate to other challenges in neonatal VA such as misclassification of causes, assigning multiple causes and differentiating between direct, underlying and contributory causes of death.

Lack of standardized death classification terminology

Terminology used to classify cause of death has not been clearly standardized and makes cause of death identification confusing. Most current VA studies identify the direct cause of death, however,

some include antecedent or underlying causes. Trying to differentiate between direct, antecedent, and contributory causes remains a challenge, given the lack of standardized vocabulary and reporting in the literature. Currently, there are six recognized direct causes of neonatal deaths identifiable by VA: (1) serious infection (including sepsis, pneumonia), (2) birth asphyxia, (3) prematurity, (4) tetanus, (5) congenital malformation and (6) diarrhea.^{36,45} The ICD-10 specifies the listing of the following information on causes of death on the standard International Form of Medical Certification of Death:⁴⁶ (1) disease or condition directly leading to death, generally known as the direct cause of death, (2) antecedent causes (morbid conditions, if any, giving rise to the direct cause), otherwise known as the underlying cause(s), and (3) other significant conditions contributing to the death, but not related to the disease or conditions causing it, also known as the contributory cause(s).⁴⁷ These definitions can be difficult to interpret when we consider causes of neonatal death. For example, in the case of a premature, LBW infant dying of RDS, the death might be classified as follows: direct cause of death → RDS; antecedent (or underlying) cause of death → prematurity; contributory cause of death → LBW. However, given that RDS is not one of the six direct causes of neonatal deaths recognized by CHERG (that is prematurity not RDS), another classification might identify prematurity as the direct cause.

In Jordan, ICD-10 codes were assigned to 128 infant and neonatal deaths. Contributory causes were identified in 50% of deaths, and prematurity was identified as the contributory cause in 38% of deaths.⁴⁸ Conditions often associated with prematurity such as RDS, necrotizing enterocolitis and others were grouped into a category, 'conditions originating in the perinatal period,' which was the most common cause of neonatal death in this sample.⁴⁸ In this example, the authors considered prematurity a contributory cause; however, according to the ICD-10 definitions, contributory causes are 'not related to the disease causing it (death)'. This example highlights the confusion in terminology regarding the classification of neonatal deaths, particularly prematurity. In addition, although the International Form of Medical Certification of Death is most commonly used for all death certificates, there is another death certificate dedicated for use in cases of stillbirths and deaths occurring within 168 h (1 week) from birth, called the Certificate of Cause of Perinatal Death.⁴⁷ This form differs slightly from the standard death certificate in that it considers maternal factors in addition to the 'main' and 'other' diseases or conditions of the infant. This additional form uses slightly different terminology and its use is not standardized, adding to the confusion on how early neonatal deaths should be classified and the terminology used. In addition to the confusion with terminology, many physicians may not be properly trained on completing death certificates. This lack of standardized terminology and the challenges of death certification, including physician training, reflect limitations even among vital registration systems.

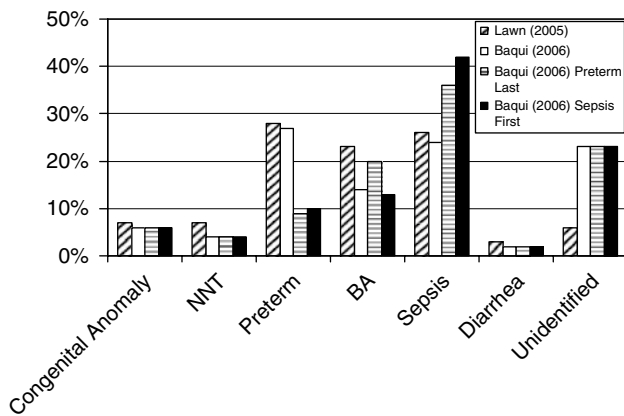


Figure 1 Changes in cause of neonatal death distributions based on modified hierarchies.

Limitations of hierarchy to assign causes of death

Use of a hierarchy has limitations, as the cause of death distribution can vary widely depending on how the hierarchy is selected. Using the CHERG hierarchy which was used to estimate 4 million causes of neonatal deaths³⁶ (congenital abnormality → neonatal tetanus → preterm → birth asphyxia → sepsis/pneumonia → diarrhea → other), Baqui *et al.*¹² found a similar cause of death distribution in India. However, using the same data, and reordering the hierarchy by placing prematurity last, we found that the percentage of deaths due to preterm birth decreased from 27 to 9%. When sepsis/pneumonia was placed first in the hierarchy, the percentage of deaths due to sepsis increased from 24 to 42% (all distributions; Figure 1). This highlights the variation in reporting that can occur depending on where each cause of death is placed in the hierarchy.

Other studies have applied different hierarchies, resulting in different cause-of-death distributions. For example, the recently published Nepal 2006 Demographic Health Survey used a hierarchy (neonatal tetanus, congenital abnormality, birth asphyxia, birth injury, diarrhea, acute respiratory infection, possible serious infection, preterm/LBW, and so on) which resulted in significantly lower estimates for prematurity (6% compared with 27% as reported by Lawn *et al.*¹).

Implications of current VA methods and limitations

Given the use of VA data for policy and program development, it is important to explore new methods to assign causes of death that overcome limitations in conventional VA methods. The influence of the hierarchy to assign cause of death, for example, has important implications. Those with specific disease interests may apply a hierarchy that results in a cause of death distribution with a larger number of deaths attributed to their disease of interest. For conditions such as birth asphyxia and serious infections, for which effective interventions have been proven to reduce mortality, the use of a hierarchy that illustrates their importance in neonatal cause of death distributions can help promote action.⁴⁹

Assigning multiple causes of death may alleviate this issue of assigning precedence to particular causes of death. In fact, researchers have recommended identifying multiple causes of death as many childhood deaths result from more than one cause and may be prevented if one of the causes is treated.³⁸ However, assigning multiple causes of death also presents challenges. Marsh *et al.* reported some differences in cause-of-death structure when multiple causes were assigned. For example, LBW increased from 26% of deaths when a single cause was assigned to 39% when multiple causes were allowed, but birth asphyxia showed little change, from 14 to 15%.²⁴ Physician assignment of multiple causes from VA may lack sensitivity due to the need for consensus among several physicians. Snow *et al.*³⁰ found that 27% of neonates were diagnosed with two causes of death based on hospital records, compared with only 7% assigned two causes through physician review of VA data. Assigning multiple causes can also result in overlapping causes of death. In Nepal, Lee *et al.*³⁵ reported that 29% of birth asphyxia deaths were classified as being premature and 42% also met criteria for serious infections. Baqui *et al.*¹² reported similar findings in India, where 23% of deaths attributed to sepsis or pneumonia also met criteria for preterm birth.

New methods to measure causes of neonatal death

New probabilistic models with the potential to overcome many of the biases of hospital-based validation studies and that allow for multiple causes of death have been used to analyze VA data.^{50–52} Fantahun *et al.* compared physician review of VA using ICD-10 codes to identify main and underlying causes of death with the InterVA probabilistic model. In this method, signs and symptoms, including patient history, were extracted from the VA closed-ended and open-history modules. Indicators were loaded into a computer database and the model was run to allow up to three causes of death, each with a probability estimate. Though they did not examine neonatal deaths exclusively, for deaths in infants under 1 year of age, physician review and the InterVA method resulted in similar cause-of-death estimates with the exception of ‘perinatal problems,’ which physicians reported more often than the InterVA model.⁵¹ King and Ying⁵² have also proposed a probabilistic model using symptom profiles to determine the mortality fractions for all causes of death in the community at once. In this model, multiple causes for an individual are handled by joining two or more causes together into a single category. Byass *et al.* reported another model based on Bayes theorem that identified various disease indicators and defined the probability of a particular cause based on the presence of specific indicators. This study reported consensus for 75% of cases between the model-assigned and physician review-assigned causes of death.⁵⁰ Finally, combining the methods of King and Byass, Murray *et al.*⁵³ validated the ‘Symptom Pattern’ (SP) method with the standard physician coded VA method and showed that SP correctly estimated cause specific mortality fractions with less error than physician

coded VA at both the population and individual level. These methods have advantages in that they do not rely on algorithms, require less time to analyze and do not require the time, effort and cost of physician reviewers. It is still unclear how these methods will vary across cultural and language barriers, however, validation studies are currently being conducted in multisite global field settings (www.gcgh.org).

Conclusion

International standards for VA methodology have been recommended.⁵⁴ These include improving and standardizing the VA questionnaire, applying methods for cause of death certification and coding of VA according to current ICD-10 classifications, and developing a cause of death list for VA according to the ICD-10.

With respect to neonatal deaths, additional methods to improve VA should be explored. The use of a social autopsy to address issues of care seeking should be incorporated. Research about the stigma behind stillbirths is needed to determine culturally sensitive ways to ascertain the burden of stillbirths and develop specific VA algorithms.

A standardized method of assigning causes of death should be adopted. Physician review can leave room for subjectivity, depending on who is making the diagnosis; and computer algorithms used vary considerably.

The use of a hierarchy to assign a single cause of death imposes further limitations, as a standard hierarchy has not been agreed upon, resulting in varied cause of death distributions depending on which hierarchy is used. Further research and clear guidelines are needed to define a standard approach to the use of a hierarchy to assign single cause-of-death estimates. The ability to assign multiple causes is also important. Many newborns die from multiple causes, and efforts to distinguish between direct, antecedent or underlying, and contributory causes should also be explored.

Larger validation studies of stillbirths and neonatal deaths in areas with diverse disease mixes should be conducted using standardized VA instruments and methods to help develop new algorithms and improve and validate existing algorithms. This could lead to improvements in assigning cause of death using computer algorithms. In addition, attempts should be made to conduct validation studies that do not rely solely on hospital gold standard diagnoses, which may reflect a biased cause of death profile. New probabilistic models for assigning cause of death from VA data overcome many of the biases of hospital-based validation studies, and also may improve the ascertainment of multiple and underlying causes of death. One possible method to address this issue is to create cause of death categories with multiple causes, for example preterm + birth asphyxia.

Given the implications for future programs and policies, it is important to further explore how VA methods can be improved

and/or explore other means of obtaining accurate cause of death estimates for newborn infants in settings with inadequate registration of vital events.

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