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Verbal Autopsy Methods to Ascertain Birth Asphyxia Deaths in a Community-based Setting in Southern Nepal

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Abstract

OBJECTIVES—1) Develop an approach to ascertain birth asphyxia deaths using verbal autopsy data from a community-based setting in Nepal, and 2) explore variations in birth asphyxia mortality fractions using different birth asphyxia case definitions and hierarchal classifications.

PATIENTS AND METHODS—Data were prospectively collected during a cluster-randomized, community-based trial of health interventions on neonatal mortality in Sarlahi, Nepal from 2002-2006. To assign cause of death, four computer-assigned, symptom-based asphyxia case definitions; Nepali physician classification; and our independent review of verbal autopsy open narratives were used. Varying hierarchal classification approaches to assign cause of death were also explored.

RESULTS—Birth asphyxia specific mortality ranged from 26%-54% depending on the computer case definition used. There was poor agreement between computer and physician classification of birth asphyxia (kappa 0.15). By comparing computer, physician, and our independent ascertainment of cause of death, we identified 246 cases of birth asphyxia (32% of neonatal deaths). Allowing for more than one cause of death, 30% and 42% of asphyxia cases also met criteria for prematurity and serious infection, respectively. When a hierarchy was used to assign a single cause of death, the birth asphyxia proportionate mortality was reduced to 12% when identification of deaths due to congenital anomalies, prematurity, and serious infections preceded birth asphyxia.

CONCLUSIONS—Use of varying verbal autopsy definitions and hierarchal approaches to assign cause of death may substantially affect estimates of birth asphyxia-specific mortality and analyses of risk factors. Verbal autopsy methods need to be standardized and validated in order to generate accurate global estimates to direct policy and resource allocation in low-middle income countries.

Keywords

asphyxia; neonatal mortality; newborn; Nepal; verbal autopsy

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ROLES OF AUTHORS

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INTRODUCTION

Birth asphyxia is estimated to account for 23% of the 4 million global neonatal deaths and an additional one million stillbirths annually.^{1, 2} The burden of asphyxia-related morbidity and mortality is concentrated in low-middle income countries, where 99% of neonatal deaths occur¹ and the majority of births occur without medical supervision.³ The lack of a standardized case definition for birth asphyxia, particularly in community-based settings, is a fundamental challenge to understanding its global public health impact and to identifying and redressing risk factors.² The World Health Organization (WHO) defines birth asphyxia as “the failure to initiate and sustain breathing at birth;”⁴ whereas the American Academy of Pediatrics⁵ classifies an asphyxiated infant with: 1) umbilical cord arterial pH < 7.0, 2) Apgar score of 0-3 at > 5 minutes, 3) neurological manifestations (seizure, coma, or hypotonia) and 4) multi-system organ dysfunction (cardiovascular, gastrointestinal, hematologic, pulmonary, or renal). Apgar scores and acidosis, however, have low sensitivity and low positive predictive value for neurological injury and morbidity.^{5, 6} Furthermore, laboratory data and monitoring are not feasible in resource-poor regions where the majority of births occur outside of health facilities, without skilled attendants, and many deaths occur before the infant survives long enough to develop neurological signs and organ system dysfunction. Therefore, community-level definitions of birth asphyxia must utilize information about an infant’s clinical condition surrounding the time of death that can be described by non-medical caretakers.^{1, 7}

Verbal autopsy is a tool used to determine causes of death in regions lacking vital registration systems and physician-assigned cause-of-death data. During a verbal autopsy, a trained interviewer asks the caretaker open and structured questions about the events and clinical symptoms surrounding their child’s death. The autopsy results are either reviewed by a physician to ascertain cause of death, or alternately, to generate larger-scale epidemiologic estimates of disease distribution, computer algorithms are used to determine cause of death from specific reported symptoms.^{8, 9} While verbal autopsy has been widely utilized in ascertaining causes of death in children,¹⁰ determining cause of death in neonates is particularly challenging given the non-specific and overlapping clinical symptoms of several major causes of neonatal deaths.¹¹

The methods and accuracy of ascertaining birth asphyxia using verbal autopsy have varied widely across studies. Kalter et al¹² developed and validated four symptom-based case definitions of birth asphyxia using computer algorithms; the best-performing algorithm had a sensitivity of 87% and specificity of 76%. Freeman et al utilized data from our study area in Nepal to compare these computer-based definitions with physician-assigned causes of death and found poor agreement for birth asphyxia (kappa = 0.17).¹³ Marsh et al used a different asphyxia case definition and found that the combination of computer and physician assignment performed poorly for birth asphyxia (sensitivity 58%, specificity 78%, positive predictive value 57%).¹¹

The WHO International Classification of Diseases and standard epidemiologic approaches classify single, underlying causes of death in order to estimate the distribution of diseases as a proportion of the total number of neonatal deaths.^{8, 9, 14} Computer-based methods use a hierarchy to assign cause of death when co-morbid states are present. The Child Health Epidemiology Reference Group (CHERG) developed a standard hierarchy that sequentially attributes deaths to congenital abnormalities, neonatal tetanus, preterm birth, birth asphyxia, sepsis/pneumonia, then diarrhea.⁹ Once a death is assigned to a specific cause, that case may not be assigned to another cause of death lower in the hierarchy. When this hierarchy was applied by Baqui et al to assign a single cause of death in India, the estimates of birth asphyxia mortality were substantially different than when multiple causes of death were allowed.¹⁵

These issues highlight the challenges of using verbal autopsy methods to ascertain the burden of birth asphyxia at the community level. Standardizing these methods is essential to establish accurate global estimates of birth asphyxia in order to direct and monitor public health programs. In this report, we describe the development of an approach to identify birth asphyxia deaths using verbal autopsy data from a low-resource, community-based setting in Nepal; explore variations in birth asphyxia mortality fractions using different birth asphyxia case definitions and hierarchical classifications; and propose a new case definition for birth asphyxia for future evaluation at the community level.

METHODS

Data Collection

Data for the Nepal Newborn Washing Study (NWS) were collected by the Nepal Nutrition Intervention Project, Sarlahi (NNIPS) during a community-based trial in 2002-2006 of the impact of newborn skin and umbilical cord cleansing with chlorhexidine on neonatal mortality and morbidity in southern Nepal.^{16, 17} Study procedures have been reported in detail previously.^{16, 17}

Pregnant women were enrolled during mid-pregnancy and received iron-folic acid, vitamin A, tetanus immunization, albendazole, a clean birth kit, and health education on prenatal and infant care. Newborns were randomized within clusters (n=413 sectors) in a factorial design to one of two full-body skin cleansing regimens (0.25% chlorhexidine or placebo)¹⁷ and one of three cord cleaning regimens (4% chlorhexidine, soap and water, or dry cord care).¹⁶

Household interviews were conducted to gather information on socioeconomic status, maternal reproductive history, labor and delivery, and the infant's postnatal course. Study staff collected data on newborn vital status and morbidity symptoms. Verbal autopsies were conducted on all neonatal deaths (median time of verbal autopsy administration: 2.0 days after death, 75% within 1 week, and 90% within 3 weeks) by supervisory workers who were trained in verbal autopsy techniques and had 3-12 years of experience in conducting verbal autopsies in this setting. The interview was conducted in Nepali using local terminology and consisted of open-ended questions to obtain a narrative of the newborn's death followed by close-ended questions. The verbal autopsy questionnaire was based on the WHO standard verbal autopsy form¹⁰ with minor modifications.¹³

Computer-based Assignment of Cause of Death

Computerized algorithms were developed for each cause of death based on previously reported case definitions described below. Each definition required the union or intersection of specific symptoms extracted from the structured questions on the verbal autopsy questionnaire; the computer algorithm assigned a cause of death if the criteria for the definition were met. A literature review was conducted to identify existing case definitions of the following conditions.

Case Definitions of Birth Asphyxia—Four case definitions were used in this analysis and are shown in Table 1: WHO Standard Verbal Autopsy Methods (definitions 3 and 4),¹⁰ the definition used by Baqui *et al.*¹⁵ and the definition used in the NNIPS-NWS.¹⁷ Because the computer algorithms generated separate results for each definition, for every neonatal death, we calculated a birth asphyxia score reflecting the sum of the number of definitions classifying the case as birth asphyxia (range 0-4) (Figure 1). Furthermore, a consensus definition was developed that was a union of the four pre-established definitions (Table 1).

Validation studies have been performed utilizing the two WHO definitions¹² (definition 3: sensitivity 73%, specificity 72%; definition 4: sensitivity 87%, specificity 69%). Although the Baqui et al and NNIPS-NWS algorithms have not been formally validated, both utilize symptoms from the WHO definitions. Alternate definitions considered but not used in this analysis were those described by Marsh et al¹⁸ due to the poor algorithm performance; Bang et al¹⁹ due to the combined definition of asphyxia with birth injury and lack of validation of the algorithm; and Christian et al²⁰ due to the lack of validation of specific symptoms.

Case Definitions of Congenital Abnormality and Tetanus—Congenital abnormality and neonatal tetanus were defined by the WHO Standard Verbal Autopsy Methods¹⁰ (Figure 2).

Case Definition of Preterm Birth—Preterm birth was defined according to the WHO Standard Verbal Autopsy Methods (Figure 2).¹⁰ Other definitions we investigated included gestational age (<37 and <33 weeks) by maternal report of last menstrual period (LMP) and low birth weight (<2500 grams). The WHO definition was chosen in order to use a validated definition with data available from standard verbal autopsy forms, which does not include data on LMP. Furthermore, maternal report of LMP is often imprecise,²¹ and birth weight data were missing for many early neonatal deaths. Data on the baby being “small at birth” was not available in this study.

Case Definition of Serious Neonatal Infection—The case definition of serious neonatal infections is described in Baqui et al (Figure 2).¹⁵ Several definitions of neonatal infections were reviewed^{10, 15, 17, 22, 23} and this definition was selected after considering the content, information available in our data set, limitations in data from community settings, and assessment of the sepsis proportionate mortality with each definition. We chose a definition reflecting serious neonatal infections as a group, including sepsis, pneumonia and meningitis, because of overlapping clinical signs of these conditions^{22, 24} and frequent co-existence of these infections in newborns.^{25, 26} Moreover, separate algorithms for these conditions have performed poorly in prior validation exercises.^{10, 27}

Assignment of Birth Asphyxia as a Final Cause of Death

In addition to the computer classification, causes of death were assigned during the study period by two Nepalese pediatricians (RKA, SKK). They independently reviewed data from both the structured questions and verbatim history and classified cause of death based on their clinical knowledge and judgment. Specific symptom-based criteria for birth asphyxia were not pre-established prior to their case review. Differences in case assignment were reconciled by discussion. While multiple causes of death were allowed, single causes were primarily assigned. A prior study by Freeman et al within our study area suggested that the Nepalese physicians were less comfortable assigning causes of death for early neonatal deaths with overlapping features and tended to under-recognize birth asphyxia.¹³

Given these limitations and the previously reported discordance between computer and physician classifications of cause of death,¹³ we attempted to best determine the final cause of death with a comprehensive approach utilizing all our available data. We considered the computerized classification of cause of death, Nepali physician assignment, as well as our (ACL, LCM, GLD) independent review of the verbal autopsy open histories using a tiered approach (Figure 1). For all of the infants who had a high computer-assigned birth asphyxia score (3 or 4), if Nepali physicians also classified the death as asphyxia, then birth asphyxia was assigned as a final cause of death. For those with a high asphyxia score who were not assigned birth asphyxia by physician review, we further reviewed the open narratives in order to classify the cause of death. For those with an intermediate asphyxia score (2), both physician

assignment and our independent review of the open narratives were also considered. For those with a low asphyxia score (0 or 1) but asphyxia classified by physician assignment, we further reviewed the open narrative histories.

The goal of this case identification was to have a high sensitivity to pick up all potential cases of birth asphyxia, given that these methods were utilized for a study of community-based risk factors of birth asphyxia.²⁸

Use of a Hierarchy to Assign Birth Asphyxia as Single Cause of Death

We explored variations in cause-specific mortality fractions attributed to birth asphyxia using three different hierarchal approaches depicted in Figure 2. Hierarchy 2 is the standard hierarchy developed by CHERG.⁹ Hierarchy 1 assigns cases to birth asphyxia prior to prematurity, similar to a hierarchical classification used in Winbo et al,⁸ and was tested in order to determine the broader contribution of birth asphyxia to disease burden, given the overlapping symptoms of preterm and asphyxiated infants. Hierarchy 3 removes cases of neonatal infections prior to asphyxia, since some hierarchical systems place antepartum infections before intrapartum asphyxia because congenitally acquired infections may be considered the underlying cause of death.²⁸⁻³⁰

RESULTS

Computer-based Classification of Birth Asphyxia as a Cause of Death

Fifty-seven percent (431/759) of the neonatal deaths were assigned to birth asphyxia by at least one definition. The non-hierarchal definition of birth asphyxia used by Baqui *et al* was the most inclusive, classifying 54% of the neonatal deaths to birth asphyxia, while the WHO-4 definition was the narrowest, assigning 26% of deaths to asphyxia, given its requirement for convulsions, which may only present in cases of severe asphyxia (Table 1). The WHO-3 definition classified 247 (33%) birth asphyxia cases, NNIPS-NWS 229 (50%) cases, and the new proposed consensus definition 249 (33%) cases. The WHO-3, WHO-4 and NNIPS-NWS definitions had excellent inter-algorithm agreement (kappa 0.82-0.93), while the Baqui *et al* algorithm had weaker agreement with the others (kappa 0.35 -0.42) (Table 2).

Out of 759 neonatal deaths, 230 (30%) infants met criteria for birth asphyxia by 3 or 4 case definitions, 7 met criteria by 2 definitions, and 194 (26%) by a single definition.

Comprehensive Assessment to Classify Birth Asphyxia

Of the infants who met criteria for birth asphyxia by 3 or 4 definitions, 196 (85%) were assigned alternate diagnoses by the reviewing Nepalese physicians (Figure 1). Thus, the agreement between physician-assigned and computer-assigned birth asphyxia (by 3 or 4 definitions) was weak, with 72% agreement and a kappa score of 0.15. We reviewed the verbal autopsy open histories of a random subset of 40 of these deaths not identified as birth asphyxia by the physicians, and were unable to rule out birth asphyxia as a cause of death in any of the cases; thus, all were retained as deaths due to birth asphyxia. None of the cases with an intermediate asphyxia score of 2 were classified as birth asphyxia by the Nepali physicians or our independent review, and thus were not included as cases of asphyxia. There was not sufficient evidence for including the infants who were attributed to birth asphyxia by a single computer definition. However, the physicians classified 12 of these infants as dying from birth asphyxia, as well as an additional 4 cases that were not assigned asphyxia by any of the computer definitions. Upon review of the structured questions for these infants which were drawn upon by the computer algorithms, 10 of the 16 had missing data for specific signs required by the algorithms, and 5 had “weak” as opposed to “no” cry. The narratives of death for these cases

were reviewed and consistent with birth asphyxia, and thus they were included among the final assignment of birth asphyxia cases.

After this extensive review process, a total of 246 (32%) of the 759 neonatal deaths received a final assignment of birth asphyxia as a cause of death (Figure 1).

Overlapping Causes of Death

Figure 3 shows the overlapping assignments of cause of death due to birth asphyxia, prematurity and serious infections, using a non-hierarchical approach allowing assignment of more than one cause of death. Of the birth asphyxia deaths, 29% also met criteria for death due to prematurity and 42% for serious infections. Only 98 infants (40% of cases assigned to birth asphyxia) exclusively met the criteria for birth asphyxia.

Classifying Single Causes of Death by Using a Hierarchy

In order to determine the effect of applying a hierarchy to assign single cause of death, we applied definitions for alternate major causes of neonatal deaths in standard sequential order, as per CHERG methodology (Figure 2).³¹

Congenital abnormality—Sixty-one (8%) neonatal deaths were classified as a congenital abnormality by the computer algorithm.¹⁰ We further reviewed the open narratives of these cases to determine whether the malformation was potentially lethal, rather than a minor, non-lethal abnormality. Thirty (4%) cases were classified as lethal malformations (Figure 2), i.e., back lesions consistent with a neural tube defect, gross malformations of the head (missing eyes, ears, or forehead), significant genital or urinary tract malformations, midline cleft (given the potential association with cardiac defects),^{32, 33} absent extremities, and potential clinical genetic syndromes³⁴ (craniofacial dysmorphism and clinodactyly). Non-lethal malformations (n=31) included molding/caput, polydactyly, syndactyly, curved extremities and club foot.

Tetanus—Thirty (4%) cases were classified as tetanus by the computer algorithm,¹⁰ however, given the universal administration of tetanus toxoid by the study and that none of these cases were classified as tetanus deaths by the physicians, no cases were classified as tetanus.

Prematurity—223 (29%) cases were classified as due to preterm birth¹⁰ when placed after congenital abnormalities and tetanus in the hierarchy (Figure 2, hierarchy 2).

Serious Neonatal Infection—225 (30%) cases were classified as due to serious infection¹⁵ when placed after congenital abnormalities, tetanus, and preterm birth in the hierarchy (Figure 2, hierarchy 3).

Birth Asphyxia—The birth asphyxia specific mortality fraction was reduced from 32% (based on non-hierarchical classification, Figure 1) to 30% with the hierarchical classification of congenital abnormalities before birth asphyxia (hierarchy 1); to 21% with the further classification of preterm births (hierarchy 2); and to 12% with the additional classification of serious neonatal infections before birth asphyxia in the hierarchy (hierarchy 3) (Figure 2).

DISCUSSION

Establishing accurate estimates of birth asphyxia in low-middle income countries is a key priority in order to guide public health programming. To generate epidemiologic estimates of disease burden, computer-based methods are commonly used to interpret verbal autopsy data.^{10,15} Comparing four established, case definitions of birth asphyxia, the birth asphyxia

mortality fraction ranged from 26% to 54%. While they each incorporate the basic WHO definition of “failing to sustain breathing at birth,” the definitions differ with respect to timing of death and co-existing infant clinical symptoms. Alternate definitions published in the literature have included pre-established risk factors for birth asphyxia such as prolonged labor,¹¹ breech presentation,^{11, 19} presence of meconium,¹⁹ IUGR,¹⁹ or twin pregnancy;¹⁹ however, verbal autopsy definitions incorporating these risk factors have not been validated. Furthermore, incorporation of risk factors may be inappropriate in a clinical case definition for birth asphyxia as they do not directly define the condition. Future research requires the validation and utilization of a standard community level case definition of birth asphyxia in order to generate consistent global estimates of birth asphyxia. We propose a definition (Table 1) for future evaluation which is a consensus of the four tested definitions.

We found poor agreement between computer and Nepali physician assigned cause of death, which has been reported in a prior verbal autopsy study.¹³ In order to most accurately ascertain cause of death, in addition to using computer algorithms, we incorporated data from physician-assigned cause of death and conducted an additional independent review of open narratives. The majority (85%) of infants assigned birth asphyxia by 3 or 4 algorithms were not identified as asphyxia deaths by physician review. The non-specific and vague symptoms of birth asphyxia may contribute to this discord. Physicians assigned a single cause of death to all but one infant, with their top two cause-of-death assignments being “uncertain” (40%) and preterm birth (22%). Hence, the physicians may have been more likely to assign alternate causes of death with more distinct signs that were easier to distinguish on verbal autopsy review, or not assign a cause at all in cases of ambiguity. This highlights the potential for the under-recognition of birth asphyxia by physician review of verbal autopsy data alone. In cases of birth asphyxia identified by physician review alone, the computer algorithms failed to classify birth asphyxia either due to missing data or the report of “weak” as opposed to “no” cry.

Current standards for classification of causes of death support the assignment of single as opposed to multiple causes of death in order to calculate cause-specific mortality fractions.^{8, 14} However, multiple disease processes may contribute to the complex patho-physiology leading to a newborn’s death. We have previously reported a significant synergistic relationship between prematurity and maternal infections in the risk for birth asphyxia mortality.²⁸ By classifying only a single cause of death, this interaction would not have been recognized. Furthermore, the overlapping clinical presentation of neonatal conditions presents challenges in discriminating cause of death with verbal autopsy methods which often utilize non-specific symptoms and rely on subtle differences that may not be discernable by caregivers. For example, a preterm or septic infant may be neurologically depressed at birth and also meet criteria for birth asphyxia by “failing to cry at birth,” “failing to breathe,” or being “unable to suck.” In this data, over half of the infants who were classified as birth asphyxia also met criteria for an alternate diagnosis. In many cases, a newborn may experience several co-morbidities which are furthermore challenging to differentiate by verbal autopsy; and thus, classifying only a single cause of death fails to acknowledge complex disease processes and inaccurately influences estimates of true disease burden.

To identify a single underlying cause of death, various hierarchical classification schemes have been devised. The fixed disease categories and hierarchy tested in this study were developed by CHERG⁹ in order to standardize approaches in classifying causes of neonatal death and produce disease estimates for programmatic relevance. Some hierarchical systems assign deaths based on categories indicating the timing of the events leading to death [e.g., antenatal, intrapartum, postnatal].³⁰ The Office of National Statistics in England uses such a hierarchal classification system in the International Classification of Diseases (ICD 10) which assigns neonatal deaths to congenital anomalies, antepartum infections, and immaturity related conditions before assigning deaths due to asphyxia.³⁵ However, in another classification

system used in Sweden described in Winbo et al,⁸ asphyxia is instead placed ahead of preterm birth defined as <33 weeks gestation or <2500 grams. We found that the asphyxia-specific proportionate mortality was reduced from 30% to 21% when the order of asphyxia was changed from before to after preterm birth in the hierarchy (Hierarchy 1 vs. 2). The Neonatal and Intrauterine Cause of Death by Etiology (NICE) classification system aims to identify underlying etiology of death and places specific conditions, including fetal infections, above most causes of birth asphyxia.²⁹ In our analysis, placing infections above asphyxia reduced the asphyxia proportionate mortality to 12%.

The non-specificity of computer algorithms for certain conditions may lead to misclassification,³⁶ and the placement of these conditions early in the hierarchy may result in the erroneous removal of cases from the pool of infants who would have been classified as birth asphyxia. For example, of the cases assigned by computer algorithm as congenital abnormalities, our independent review of narratives re-classified half of the cases as non-lethal malformations. Similarly for tetanus, upon physician review, all of the computer-assigned cases were eliminated due to the universal administration of tetanus toxoid and the lack of a clear description of classic signs of tetanus such as opisthotonus or trismus. In general, if hierarchical methods are to be utilized, specificity is of paramount importance for those algorithms near the top of the hierarchy; thus, congenital anomalies and tetanus, both of which have shown high specificity in prior neonatal verbal autopsy validation studies (specificity 95% and 89% respectively),¹⁰ typically appear at the top of hierarchical approaches (Figure 3). As the definition of preterm birth used here (“being born early”) had a low specificity of 78% in a prior validation study,¹⁰ positioning this above birth asphyxia in the hierarchy may have resulted in undue over-classification of preterm births and an apparent underestimate of birth-asphyxia proportionate mortality.³⁶

Given the frequent co-morbidity of neonatal diseases, current limitations in the accuracy of case definitions, and the substantial variations in estimates generated from different hierarchical approaches, we recommend allowing the classification of multiple causes of death, in order to generate more accurate and consistent estimates of disease distribution. Marsh et al also reported considerable changes in estimates of cause-of-death with single vs. multiple cause attribution in Karachi, Pakistan and recommended allowing multiple causes to better guide health program planning.³⁷ New verbal autopsy methods are being developed to analyze multiple causes of death that may simplify methods, reduce the assumptions required to make assignments, and improve the accuracy and reproducibility of estimates of cause-specific mortality rates.³⁸

Limitations to these methods include the lack of validation of cause of death using direct physiologic criteria or physician monitoring/measurements given that the majority of births and deaths occurred at home.³⁹ The WHO definitions of birth asphyxia were previously validated on a small sample of 105 infants, of which 19 were birth asphyxia cases.¹² Verbal autopsy methods also rely on retrospective recall and self-report of maternal and infant symptoms. About half of the verbal autopsies were conducted within 48 hours of death. Verbal autopsies conducted closer to the time of death are more accurate and less subject to recall bias, however, a short time for bereavement may also potentially distress the family and result in higher refusal rates.³⁹ The time between death and verbal autopsy here (75% within 1 week) may be shorter than in other settings, where a lag time of several weeks to a few months is more common. The longstanding relationship between the NNIPS project and the community (>20 years) and the extensive training and experience in conducting sensitive verbal autopsy interviews, however, likely facilitated the low refusal rate of 1%.

Conclusions

In interpreting burden of disease data based on verbal autopsy, it is critical to understand the underlying methodology which may substantially influence the estimates generated. We demonstrate that the distribution of neonatal deaths attributed to birth asphyxia may vary considerably based on 1) the choice of verbal autopsy case definition of birth asphyxia, 2) whether single or multiple causes of death are allowed, and 3) the order of hierarchical assignment of cause of death, particularly for diseases lower in the hierarchy and neonatal conditions with overlapping symptoms which are challenging to distinguish by verbal autopsy. Unfortunately, this applies to the three major causes of neonatal mortality: neonatal infections, preterm birth and birth asphyxia. In the case of birth asphyxia, the placement of preterm birth above asphyxia in standard hierarchies may substantially underestimate asphyxia-specific mortality by as much as 30%. Such misclassification might also undermine analyses to elucidate risk factors for birth asphyxia at the community level, and lead to under-estimation of the potential overall impact of interventions aiming to reduce mortality from birth asphyxia. Verbal autopsy methods for birth asphyxia need to be further standardized and validated in order to generate accurate global estimates to direct policy and resource allocation in communities which face the highest rates of neonatal mortality.

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Abbreviations

BA, Birth Asphyxia; CHERG, Child Health Epidemiology Research Group; LMP, Last Menstrual Period; NWS, Nepal Newborn Washing Study; NNIPS, Nepal Nutrition Intervention Project; WHO, World Health Organization.

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Figure 1.

Non-hierarchical Assignment of Birth Asphyxia as Consensus Cause of Death (cont)

^a Computer based algorithms: WHO3 definition, WHO4 definition, Baqui et al, NNIPS-NWS^b Local Nepali Physician (RKA, SKK) review of verbal autopsy interview and open verbatim histories to assign cause of death^c Investigators (ACL, GLD, LCM) review of open verbatim histories to verify cause of death

Figure 2.
Hierarchical Assignment of Neonatal Causes of Death

Figure 3. Venn Diagram of Overlapping Major Causes of Neonatal Mortality, Using a Non-hierarchical Approach to Assign Multiple Causes of Death. Total Number of Neonatal Deaths n=759.

Table 1
Signs and Symptoms from Verbal Autopsy Questionnaire Included in Computer Algorithms for Birth Asphyxia

Sign/Symptom	WHO Definition 3 ¹⁰	WHO Definition 4 ¹⁰	Birth Asphyxia Symptom-Based Case Definitions Baqui et al ¹⁵	Newborn Washing Study ¹⁷	Proposed Consensus Definition
Death in first 7 days of life			X	X	
Infant failed to cry at birth	X	X	*	X	X
Not able to breathe at birth	*		*	*	*
Convulsions or spasms		*		*	*
Unable to suckle normally after birth	*	*	*	*	*
Number (percentage) of Cases Assigned	247 (33%)	194 (26%)	412 (54%)	229 (50%)	249 (33%)
BA					

X = Required for definition
* = Need one of the conditions to meet criteria for birth asphyxia

Table 2
Inter-algorithm Agreement between Non-Hierarchical Birth Asphyxia Definitions

Algorithm 1	Algorithm 2	Percentage Agreement	Kappa Score
WHO-3	NNIPS-NWS	97%	0.93
WHO-4	NNIPS-NWS	93%	0.83
WHO-3	WHO-4	93%	0.82
NNIPS-NWS	Baqui et al	76%	0.42
WHO-3	Baqui et al	73%	0.37
WHO-4	Baqui et al	70%	0.35

WHO-3 = World Health Organization Standard 3rd Definition ¹⁰

WHO-4 = World Health Organization Standard 4th Definition ¹⁰

NNIPS-NWS = Nepal Newborn Washing Study Definition ^{17, 38}

Baqui et al = Baqui et al Definition ¹⁵