Risk Factors for Birth Asphyxia Mortality in a Community-based setting in Southern Nepal

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ABSTRACT

Background: The majority of the 1 million annual neonatal deaths attributed to birth asphyxia occur in non-hospital settings in low-middle income countries. There is little information on potentially preventable risk factors for birth asphyxia in this setting.

Objective: To identify antepartum, intrapartum, and infant risk factors for birth asphyxia mortality in a community-based setting in Southern Nepal.

Design, Setting, and Patients: A prospective cohort study conducted between September 2002 – January 2006 in Sarlahi, Nepal of 23,662 live-born infants, of whom ninety percent were born at home.

Main Outcomes Measures: Adjusted Relative Risk (RR) estimates for antepartum, intrapartum, and infant risk factors for neonatal death from birth asphyxia.

Results: The birth asphyxia mortality rate was 9.7/1,000 live births. Birth asphyxia accounted for 30% of neonatal deaths, and 70% of asphyxia deaths occurred in the first 24 hours of life. Antepartum risk factors for birth asphyxia mortality included low paternal education (RR 2.70), lower caste (RR 1.72), Madeshi ethnicity (RR 2.52), and primiparity (RR: 1.49). Maternal fever (RR 2.03) and multiple births (RR 4.94) were significant intrapartum risk factors for birth asphyxia mortality. Maternal swelling, convulsions, vaginal bleeding, and prolonged rupture of membranes were associated with higher risk for birth asphyxia, although they were not statistically significant in the adjusted analysis. Births attended by doctors or auxiliary nurse midwives were associated with increased risk of asphyxia mortality than non-attended births (RR: 2.51). Premature infants (< 37 weeks) were more likely to die of birth asphyxia (RR: 2.28), and the combination of maternal fever and prematurity resulted in a synergistic elevation in risk for birth asphyxia mortality (RR: 7.53).

Conclusions: Risk factors for perinatal asphyxia during childbirth in low-income, home based births are similar to those observed in hospitals, with maternal infections, multiple births, and prematurity playing an important role in the community based setting. Low socioeconomic status is highly associated with perinatal asphyxia and the proximal mechanisms leading to mortality need to be further elucidated. Furthermore, the interaction between maternal infections and prematurity may be an important target for future community-based interventions to reduce the impact of birth asphyxia on neonatal mortality.

INTRODUCTION

Burden of birth asphyxia

Of the four million annual neonatal deaths, ninety-nine percent occur in low-middle income countries where the majority of births occur in the home without a skilled attendant [1,2]. Birth asphyxia is defined by the World Health Organization as "the failure to initiate and sustain breathing at birth" [3] and accounts for 23% of neonatal mortality [1]. A substantial proportion (estimated at 26%) of the 1 million annual intrapartum stillbirths result from birth asphyxia [4]. Another one million children who survive birth asphyxia live with chronic neuro-developmental morbidity, including cerebral palsy, mental retardation, and learning disabilities, although there is significant uncertainty regarding this estimate [5]. In 2003, WHO estimated that the number of disability adjusted life years (DALYs) attributed to birth asphyxia surpassed those due to all illnesses preventable by childhood vaccination [6].

Accurate estimates of the global burden of birth asphyxia are difficult to establish because of limited information, including nearly absent vital registration in communities where the majority of neonatal deaths occur. Ellis et al [7]conducted a prospective cross-sectional survey of hospital births in Katmandu, Nepal between 1995-1996 and estimated that the perinatal mortality rate attributable to birth asphyxia, based on rates of neonatal encephalopathy and fresh stillbirths, was 10.8 per 1,000 births, accounting for 24% of perinatal deaths. In the first national perinatal care survey of South African hospitals conducted in 2000[8], intrapartum-related birth asphyxia accounted for 14.3% of perinatal mortality (asphyxia specific mortality rate: 4.8/1000 births). In rural regions, however, the contribution of asphyxia to perinatal mortality was substantially higher at 26.4% (8.2/1,000 births). These rates may underestimate the scope of the problem, given that in many regions in southeast Asia and sub-Saharan Africa, over two thirds of

births occur at home without a skilled birth attendant [2], and many neonatal deaths, particularly when they occur early, go unreported. In a rural district of Uttar Pradesh, India without adequate vital registration, Baqui et al [9] utilized verbal autopsy data to determine that birth asphyxia or injury accounted for 23% of neonatal deaths with an estimated asphyxia specific mortality rate of 11.3/1,000 live births. Finally, in a prospective community-based study of home deliveries in Gadchiroli, India, Bang et al [10] reported the incidence of mild birth asphyxia at 14.2% and severe birth asphyxia at 4.6%, with a 3.7% and 38.5% case fatality rate, respectively. The asphyxia mortality rate was 10.5/1,000 live births in this setting [10].

Ascertainment of birth asphyxia

The lack of a standard case definition for birth asphyxia, particularly in the community setting, is another fundamental challenge to understanding its global public health impact. The American Association of Obstetrics and Gynecology and American Academy of Pediatrics position paper (1996) [11] defines a newborn to have suffered birth asphyxia if it has: 1) Umbilical cord arterial pH <7.0, 2) Apgar score of 0-3 at greater than 5 minutes, 3) Neonatal neurological manifestations (seizure, coma, or hypotonia) and 4) Multi-system organ dysfunction (cardiovascular, gastrointestinal, hematologic, pulmonary, or renal). However, Apgar scores and acidosis have low sensitivity and positive predictive value for neurological injury and morbidity [11, 12]. While laboratory data and monitoring is available in hospitalized settings, it is not feasible for the majority of births occurring in communities without skilled attendants. Therefore, community based definitions of birth asphyxia must utilize more general symptom and sign-based definitions such as those developed by the World Health Organization, or national standards like those developed by the National Neonatology Forum of India – "gasping and

ineffective breathing or lack of breathing at one minute after birth [13]." Presently, there is no community-based standard for birth asphyxia, and studies often utilize varying definitions which may affect the assignment and distribution of neonatal deaths attributed to birth asphyxia.

The verbal autopsy is a practical method to establish estimates of cause of death in community settings where vital registration is lacking and deaths occur outside hospital facilities. Verbal autopsy techniques rely on caregivers to recall and describe the clinical symptoms and events surrounding their child's death. However, assigning cause of death in neonates is particularly challenging in verbal autopsy given the non-specific and overlapping clinical symptoms of major causes of neonatal deaths [14]. In the first validation study of verbal autopsy, Kalter et al [15] developed a standardized verbal autopsy instrument to interview caregivers of infants who died in hospitals in Dhaka, Bangladesh (n=149). Four symptom based definitions of birth asphyxia were tested, with the two best performing definitions achieving a sensitivity of 87% and specificity of 76%. These definitions were incorporated into the World Health Organization standard methods for verbal autopsy [16]. A few additional studies have attempted to validate neonatal verbal autopsy. In Karachi, Pakistan [14], field and hospital diagnoses of birth asphyxia were compared with symptom modules and verbatim open histories. The validity of the method using both the symptom modules and open history was weak for birth asphyxia, with a sensitivity of 58%, specificity of 78%, and positive predictive value of 57%. Finally, in an evaluation of neonatal verbal autopsy conducted in rural Nepal by Freeman et al[17], performance of computer based symptom defined algorithms compared to physician assigned causes of death (based on review of the open narrative and questionnaire-based data) was low, with a kappa score of 0.17. These studies highlight the complexities of using verbal autopsy to establish cause of death due to birth asphyxia in the community.

Risk factors for birth asphyxia

Risk factors for birth asphyxia have been studied in several hospital based settings in developing countries. Established antepartum risk factors for asphyxia include nulliparity[18,19], maternal fever[20], maternal anemia[20], pregnancy induced hypertension[18, 21], antepartum hemorrhage[18, 20], and history of prior neonatal death[18]. Intrapartum risk factors for birth asphyxia are malpresentation[8, 20,21], prolonged 1st and 2nd stages of labor[21,22], meconium stained amniotic fluid[8, 18, 20, 22], pre-eclampsia[20], premature rupture of membranes[20], oxytocin augmentation of labor[20], and umbilical cord prolapse[8, 21]. Post-partum and infant factors include prematurity [23], low birth weight [20, 24], and intrauterine growth restriction [19, 21].

Given the challenge in precisely defining birth asphyxia, the clinical syndrome of neonatal encephalopathy has been used as a direct marker and consequence of intrapartum hypoxia [7, 25-27]. Ellis et al [7] conducted a matched case control study in the principal maternity hospital in Katmandu, Nepal, and identified the following significant risk factors for neonatal encephalopathy: maternal short stature, increased maternal age, multiple births, lack of antenatal care, non-cephalic presentation, prolonged rupture of membranes, oxytocin induction of labor, particulate meconium, and clinically obstructed labor. While we speculate that hospital-based and home-based risk factors for birth asphyxia may be similar, this has not been assessed in the literature.

Objectives

In this study, we aim to first identify birth asphyxia cases in the community-based setting by comparing several accepted verbal autopsy case definitions of birth asphyxia and developing a consensus definition by analyzing verbal autopsy closed and open histories using computer

algorithms, physician and independent review. Subsequently, we identify antepartum, intrapartum, and infant risk factors for birth asphyxia mortality in Sarlahi, Nepal, a low-resource setting where 90% of deliveries occur in the home.

METHODS

Data Collection

The data for this analysis were collected during a cluster randomized, double-masked, community-based trial of the impact of newborn skin washing and umbilical cord cleansing on neonatal mortality and morbidity in Sarlahi, Nepal [28, 29]. The Nepal Nutrition Intervention Project, Sarlahi (NNIPS) conducted the trial between September 2002 – January 2006 and the study procedures have been reported in detail previously [28, 29]. Pregnant women were enrolled during the 6th month of pregnancy and provided education regarding nutrition during pregnancy, clean delivery, and essential newborn care, including breastfeeding, clean cord care and thermal care. All women enrolled received albendazole (400 mg), iron-folate, and vitamin A supplementation. A household level survey was conducted to gather data on socioeconomic status, household structure, and maternal reproductive history. All infants born after September 2002 in 413 monitored sectors within the study site were eligible for enrollment.

Newborns were randomized by sector according to a factorial study design for treatment with total body skin cleansing, as soon as possible after birth, with 0.25% chlorhexidine vs. sterile wipes [29]. Nested within each skin cleansing group, infants were then randomly assigned to a cord cleansing regimen (umbilical stump cleansing with 4% chlorhexidine, soap and water, vs. dry cord care/education) [28]. During the initial phase, 17,530 infants were enrolled and

randomized to treatment from September 2002 – March 2005, after which randomization to placebo skin cleansing was discontinued due to Data Safety and Monitoring Board recommendations to extend chlorhexidine cord and skin cleansing treatments to the placebo clusters. Thereafter, an additional 6,132 infants were enrolled to chlorhexidine full body skin treatment until January 2006.

For each live birth, data regarding maternal morbidity before, during, and after childbirth was collected. During the neonatal period, newborns were visited on 11 occasions (days 1-4, 6, 8, 10, 12, 14, 21, 28) to assess for vital status and morbidity, including umbilical cord and skin infection. In the event of a neonatal death, a verbal autopsy was conducted by the study area coordinators, or their supervisors, at the earliest possible time after the death (median time 2 days) in order to gather information about the circumstances surrounding the event. All study area coordinators had completed secondary school education, were trained in verbal autopsy techniques, and had 3-12 years experience in conducting verbal autopsy. The newborn washing study verbal autopsy form was based on the World Health Organization standard verbal autopsy form [16] with minor modifications. The verbal autopsy instrument was pre-tested in the field, translated and reverse-translated in several iterations and has been used by the Nepal Nutrition Intervention Study for over 5 years. For all neonatal deaths during the study period, the verbal autopsy forms and open histories were reviewed by 2 independent Nepali physicians (SKK and RA) to determine physician consensus on the proximal causes of death.

Case Definition of Birth Asphyxia

Given the lack of a standardized community-based definition for birth asphyxia, and because few studies have validated verbal autopsy definitions of birth asphyxia [15, 30] a literature

review was conducted to identify verbal autopsy definitions used in prior studies to assign birth asphyxia cause of death. We identified four verbal autopsy based definitions for use in this analysis: the World Health Organization Standard Verbal Autopsy Methods (3rd and 4th definitions) [16], the definition used by Baqui et al [31], and the definition used by the Newborn Washing Study [29] (Table 1). The verbal autopsy data for the 759 neonatal deaths in the Newborn Washing Study were analyzed by computer algorithms to identify cases meeting these four definitions of birth asphyxia. Alternate definitions considered but not utilized in this analysis were those described by Marsh et al [30] due to the weak performance of the birth asphyxia algorithm (sensitivity 58%, specificity 78%); Bang et al[32] due to the combined definition of asphyxia with birth injury; and Christian et al[33] due to the lack of testing of specific symptoms in prior validation studies.

Application of Cause-of-Death Hierarchy

Verbal autopsy algorithms may apply a hierarchal classification to assign a single proximate cause of death [9, 34]. Neonatal deaths were analyzed to identify those attributed to birth asphyxia using the four computer-based algorithms with the application of a hierarchy. In the hierarchal approach, deaths were first assigned to tetanus and congenital malformations before assignment to birth asphyxia as the primary cause of death. An additional hierarchical model was explored which also placed deaths due to prematurity above those due to birth asphyxia. This fixed hierarchal classification has been utilized by the Child Health Epidemiology Reference Group (CHERG) to establish global estimates of the burden of neonatal deaths [35] and is based on the Wigglesworth [36]and NICE [37] classifications of neonatal death.

Review of the verbal autopsy data, particularly the open history section, and consensus among the investigators (ACL, LCM, GLD) was required to confirm the hierarchical cause of death assignments for tetanus and congenital malformations. Upon review of verbal autopsy histories and given the universal study administration of tetanus toxoid, no neonatal deaths were assigned to neonatal tetanus. All causes of deaths attributed to congenital malformations were also independently reviewed by the investigators to determine whether the congenital malformation was the likely proximate cause of death and not simply an associated, non-lethal minor congenital malformation. Of the 61 infants identified with any congenital malformation, 30 (50%) were assigned as having a probable lethal congenital malformation. Probable lethal congenital malformations were considered those with any back lesion which could be consistent with a neural tube defect (n=3), any gross malformations of the head (missing eyes, ears, or forehead) (n=6), significant genital or urinary tract malformations (n=4), any midline cleft given the potential association with cardiac defects [38, 39] (n=14), absent extremities (n=2), and potential clinical genetic syndromes [40] (craniofacial dysmorphism and clinodactyly) (n=1). The non-lethal congenital malformations (n=31) included: molding/caput, polydactyly, syndactyly, curved extremities, and club foot.

The verbal autopsy definition of prematurity was assigned as those infants whose mothers' self reported the infant "being born early" which has been validated and utilized in the World Health Organization Standard Verbal Autopsy Methods (sensitivity 79-90%, specificity 78-85%) [16].

Assignment of Consensus Cause of Death (Figure 1)

All 759 neonatal deaths were assigned a birth asphyxia algorithm agreement score from zero to four, calculated as the sum of the number of algorithms assigning birth asphyxia as the primary cause of neonatal death. A hierarchal definition of birth asphyxia was utilized for this score assignment, which placed neonatal tetanus (no cases) and congenital malformations above birth asphyxia. The birth asphyxia agreement score was compared to the independent Nepali physician assignment of cause of death utilizing patient records and review of verbal autopsy information.

Neonates who received a birth asphyxia definition agreement score of 4 (n=170) or 3 (n=44) were assigned birth asphyxia as the cause of death. The investigators (ACL, LCM, GLD) reviewed a random subset of 20 verbal autopsy open histories for neonates who were assigned an agreement score of 4 or 3 by computer algorithm, but who were not assigned birth asphyxia as cause of death by the reviewing Nepalese physicians. These infants were assigned alternate diagnoses by the Nepali physician reviewers such as prematurity, lower respiratory infection, and malnutrition. In none of these cases, however, were the study investigators able to rule out birth asphyxia as a cause of death; thus, all cases meeting the definition of birth asphyxia by 3 or 4 algorithms were retained as cases of death due to birth asphyxia.

For all neonates who received birth asphyxia algorithm agreement scores of 0 (n=351) or 1 (n=187), Nepali physician-assigned proximal cause of death was reviewed. For those newborns assigned birth asphyxia by Nepali physician consensus (0 score, n=4; 1 score, n=12), verbal autopsy open histories were reviewed. In all 16 cases, the verbatim histories were suggestive of birth asphyxia as the proximal cause of death, and these cases were assigned birth asphyxia as the primary cause of death.

Seven newborns were assigned a birth asphyxia algorithm agreement score of 2. All of these cases were not assigned birth asphyxia as proximal cause of death by Nepali physician consensus. Open histories were determined not to be consistent with birth asphyxia by the investigators and these infants were not assigned to birth asphyxia as cause of death.

After this review process, a total of 230 (30%) of the 759 neonatal deaths in the study cohort were assigned birth asphyxia as the consensus cause of death.

Data Analysis

Risk factors for birth asphyxia mortality were grouped into antepartum, intrapartum, and infant variables. For each potential risk factor, the risk ratio (RR) for birth asphyxia death was calculated in univariate analysis utilizing log binomial regression. Cluster analysis was used to control for non-independence of events for mothers contributing more than one child to the cohort. Linearity of continuous covariates was tested. Risk factors that were associated with birth asphyxia death with a p value <0.10 were considered for testing in the multivariate model.

A core model of antepartum covariates was constructed using maternal age, given its pre-existing association with neonatal mortality [27, 41], and adding additional significant covariates ($p<0.05$) by forward selection. For collinear covariates, the most significant variable was added to the model. The same antepartum model was achieved with backward selection.

For the intrapartum risk factors, we included risk factors that temporally preceded the asphyxial event in order to focus on potentially preventable risk factors. Therefore, we excluded measures that may have been undertaken as a result of labor complications potentially attributable to birth asphyxia (e.g., resuscitative measures, assisted delivery, C-section). A future analysis will separately assess the risk of these factors on birth asphyxia mortality. All

intrapartum covariates passing the initial screen by univariate analysis ($p<0.10$) were included in the final model with a few exceptions (discussed in the results section), given that they were established risk factors in prior studies and we wanted to determine the independent adjusted association of each intrapartum risk factor with case status.

Gestational age was calculated at the time of study enrollment and also reported by the mother after the delivery. The gestational age variable utilized for analysis was the average of these values. Gestational age scale was modeled as a continuous, continuous with spline, categorical and dichotomous variables in exploratory analyses. Interaction was tested between prematurity with maternal fever, swelling, convulsions, and prolonged rupture of membranes.

STATA, version 9.0 software (StatCorp LP, College Station, Texas) was used to conduct all analyses. The study was approved by the Nepal Health Research Council (Katmandu, Nepal) and Johns Hopkins Bloomberg School of Public Health Committee on Human Research (Baltimore, MD).

RESULTS

In the Sarlahi study region between September 2002 and January 2006, there were 23,662 live births and 759 neonatal deaths. Verbal autopsies were completed on 99% (n=750) of neonatal deaths. The overall characteristics of the study population have been previously described [28]. Nine percent of live births occurred in a hospital or clinic facility, and 91% were born in the home, *maiti* or outdoors. Twenty five percent of births were attended by either a

doctor[a] or auxiliary nurse midwife. The overall prevalence of low birth weight was 28.7%. Two hundred and thirty infants met our birth asphyxia case definition for an asphyxia-specific mortality rate of 9.7 per 1,000 live births. Of the birth asphyxia deaths, 158 (69%) occurred within the first 24 hrs of life and 228 (99%) within the first week of life (Figure 2). The median time to death for birth asphyxia cases was 11 hours.

Birth Asphyxia Cause of Death Assignment by Verbal Autopsy

Non-hierarchal

Figure 3 depicts the assignment of birth asphyxia as cause of death utilizing the four non-hierarchal verbal autopsy definitions. Fifty-seven percent of the neonatal deaths were assigned to birth asphyxia by at least one algorithm. The non-hierarchal definition of birth asphyxia used by Baqui *et al* (2006) was the broadest, assigning 54% of the neonatal deaths to birth asphyxia. The WHO-4 definition was the narrowest, assigning 25% of deaths to birth asphyxia, given the inclusion of convulsions which may only present in cases of severe asphyxia. The WHO-3, WHO-4 and Newborn Washing Study non-hierarchal definitions received percentage agreement scores greater than 90% and excellent inter-algorithm agreement (kappa 0.82-0.93). The Baqui *et al* algorithm had weaker agreement with percentage agreement scores ranging from 70-76% and fair inter-algorithm agreement (kappa 0.35 -0.42).

Hierarchal

For each of the four definitions of birth asphyxia, the number of birth asphyxia deaths and proportionate mortality assigned after applying each step of the hierarchy are shown in Table

[a] The term "doctor" in this survey may have been open to wide interpretation, ranging from a formally trained physician, traditional medical practitioner, to local shopkeeper selling medications.

2 and Figure 4. While no infants were assigned tetanus as a cause of death, removal of the lethal congenital malformations reduced birth asphyxia proportionate mortality by 4-6% and removal of deaths attributable to prematurity reduced the birth asphyxia proportionate mortality by 30-38 % among the four definitions.

Antepartum Risk Factors

Socioeconomic and antenatal maternal factors tested in univariate analysis are shown in Table 3, while Tables 6 and 7 reflect the adjusted Relative Risk (RR) for factors included in the multivariate models. Young maternal age (< 20 years) was a significant risk factor for birth asphyxia mortality in univariate analysis (RR 1.85, Confidence Interval (CI) 1.25 to 2.70, reference: 25-29 years old); however the significance of this effect was attenuated after controlling for maternal parity. Parental literacy, education, and occupation were significant risk factors for birth asphyxia mortality in univariate analysis. These covariates were highly collinear, however, and when adjusted for the other factors, the most significant predictor was paternal education, which resulted in a 42% reduction in birth asphyxia risk for education 1-10 years (RR CI: 0.42, 0.80, reference: no education), and 63% reduction in those educated more than 10 years (RR CI: 0.22, 0.61). Caste and ethnicity were significant independent risk factors for asphyxia mortality after adjusting for the other socioeconomic indicators, with a RR 0.58 for high vs. low caste (CI: 0.35, 0.94) and RR 2.52 for Madeshi vs. Pahmadi ethnicity (CI: 1.60, 3.98). Infants of primiparous mothers had a 49% increased risk for birth asphyxia mortality compared to multiparous mothers (CI: 1.01, 2.20). Unlike prior studies, history of a prior child death did not significantly predict birth asphyxia mortality (RR 1.00, CI: 0.70, 1.40).

Intrapartum Risk Factors

In univariate analysis (Table 4), facility-based delivery was associated with a higher risk of birth asphyxia mortality (RR: 1.93, CI: 1.32, 2.81); however this association was likely confounded by clinical condition and became insignificant when adjusted for intrapartum complications in the multivariate analysis (RR: 1.10, CI: 0.67, 1.81) (Table 7). Delivery outdoors or on the way to a health facility was significantly associated with birth asphyxia death RR 2.82 (CI: 1.32, 6.05). Type of birth attendant was an independently significant risk factor for birth asphyxia mortality. Deliveries attended by a doctor or auxiliary nurse midwife were at 2.51 times increased risk for birth asphyxia than those attended by family members or no one (CI: 1.73, 3.64), after adjusting for other factors. Those births attended by health workers not formally trained in conducting deliveries (community health volunteer or maternal child health worker) had 2.22 times greater risk (CI: 1.3, 3.81). Of maternal intrapartum complications, maternal fever was significantly associated with increased birth asphyxia risk, leading to a 2.03 increased risk for birth asphyxia death (CI: 1.25, 3.28, Model 5). Prolonged rupture of membranes and symptoms of pre-eclampsia, eclampsia, and vaginal bleeding were associated with higher risk of birth asphyxia mortality, however, these effects were non-significant after adjusting for the remaining intrapartum risk factors. Finally, multiple birth was strongly associated with birth asphyxia mortality with a RR of 4.94 (CI 2.86, 8.52) for twin (n=360) or triplet (n=6) deliveries vs. singleton deliveries.

Prolonged labor was defined, as in prior studies [41], as labor lasting longer than 24 hrs in a primiparous mother and longer than 12 hours in a multiparous mother. There was an independent association of prolonged labor and birth asphyxia mortality in univariate analysis (RR 1.31, CI: 1.00, 1.73), however, this effect was attenuated after adjusting for other covariates.

This was likely due to the fact that prolonged labor may have been acting as an intermediate variable, mediating the effects of primiparity and multiple birth [42]. Prolonged labor was therefore not included in the final multivariate model given the potential for partial mediation of the other intrapartum risk factors.

Meconium was not directly inquired about in the survey; however color of amniotic fluid was reported. In univariate analysis, "green" presumably meconium stained amniotic fluid had a 32% non-significant increased risk of birth asphyxia death, however, the sample size was small and precision of the estimate was low (CI: 0.19, 2.16). "Red" amniotic fluid had a significant 58% increased risk for birth asphyxia mortality (CI: 1.15, 2.16), however, this was clinically difficult to distinguish from vaginal bleeding and was therefore not included in the final multivariate modeling.

Infant Factors

Female sex was associated with decreased risk for birth asphyxia death in the univariate (Table 5) and multivariate analyses (RR: 0.74, CI: 0.56, 0.97) (Table 7). Washing treatment allocation was not included in the multivariate analysis, given that it did not reach statistical significance in univariate analysis.

A substantial proportion of birth weight information was missing on the early neonatal deaths (78%) because death occurred prior to the first visit by the health worker. The median time to birth asphyxia death was 11 hours, while the mean time to the health worker visit was 19 hours. Of the 230 birth asphyxia deaths, birth weight information was gathered on 51 infants (22%). The average birth weight for the birth asphyxia cases was 2.22 kg (n=51) vs. non-birth asphyxia cases 2.70 kg (n=22,711) ($p<0.01$). The risk for birth asphyxia mortality was 11.88

times higher in the lowest weight category of < 2 kg (n=1,146) as compared to the 2.5-2.9 kg weight category (CI: 6.09, 23.14) (n=10,211). However, due to the considerable differential missing data for birth asphyxia cases, birth weight was not included in the final multivariate model.

The mean gestational age for birth asphyxia cases was 37.0 wks vs. 39.2 weeks for non-birth asphyxia cases ($p<0.01$). Gestational age was modeled as a continuous, categorical and dichotomous variable in exploratory analysis; however the choice of scale did not significantly affect the coefficients of the other covariates in the development of the multivariate model. Given the inaccuracy of the mother's gestational age estimation, gestational age was categorized as dichotomous -- premature (<37 wks gestation) vs. full term (>=37 weeks) in the final model. Prematurity resulted in a 2.28 times increased risk of birth asphyxia mortality, adjusted for other risk factors (CI: 1.67, 3.09), compared to term infants of gestational age >37 weeks.

In the development of the multivariate model, prematurity was noted to attenuate the effect of maternal fever, and confounding and interaction were tested. Maternal fever did not reach criteria for confounding the relationship between prematurity and birth asphyxia mortality; however, it did modify the effect of prematurity on birth asphyxia mortality (Table 7, $p=0.02$). In premature infants, maternal fever significantly increased the risk of birth asphyxia mortality by 7.53 times compared to full term infants without exposure to maternal fever (CI: 4.42, 12.83). In non-premature infants this effect was not significant.

DISCUSSION

Limited vital registration data in developing countries and the lack of standard case definitions for birth asphyxia present major challenges to understanding the global burden of birth asphyxia. In this study, we identify birth asphyxia deaths in Sarlahi, Nepal by triangulating 1) the consensus of four established verbal autopsy algorithms, 2) local physician case review, and 3) an independent review of verbal autopsy open histories. From these cases, we assessed antepartum, intrapartum, and infant risk factors for birth asphyxia mortality. While there are limitations to this method, to our knowledge, this is the first study of risk factors for birth asphyxia mortality in a community-based, low-resource setting.

Defining Birth Asphyxia in the Community Based Setting

Comparing four established non-hierarchal case definitions of birth asphyxia, we identified a birth asphyxia proportionate mortality ranging from 24% (World Health Organization 4 algorithm[16]) to 54% (Baqui *et al* algorithm[9]) of neonatal deaths. While all four definitions incorporate the basic WHO definition of "failing to sustain breathing at birth", the definitions differ with respect to timing of death (requirement of death in first week of life) and co-existing infant clinical symptoms (seizures, poor feeding). Alternate definitions published in the literature but not tested in this study have included other pre-existing risk factors for birth asphyxia such as prolonged labor[14], breech presentation [14,32], meconium[32], IUGR[32], or twin pregnancy[32]. This study demonstrates that the distribution of neonatal deaths attributed to birth asphyxia may vary substantially based on the choice of verbal autopsy definition of birth asphyxia, which, in turn, may influence resulting policy and resource allocation. Furthermore, limitations to these definitions include the lack of validation studies using physiologic or

physician criteria to confirm cause of death [43]. The only validated definitions of birth asphyxia among these four definitions were the World Health Organization algorithms which were validated on a sample of 105 infants, of which 19 were birth asphyxia cases [15].

Standard approaches to establishing cause-of-death estimates assign single as opposed to overlapping causes of neonatal death by applying a hierarchy [34]. In applying the standard hierarchy described by the Child Health Epidemiology Reference Group [34], the proportion of neonatal deaths attributed to birth asphyxia was reduced by approximately 5% with the assignment of lethal congenital malformations and an additional 30% with the assignment of prematurity. The overlap in clinical symptoms between premature and asphyxiated infants make it difficult to differentiate them by verbal autopsy methods which utilize non-specific symptoms such as "failing to cry at birth" or "failing to breathe." As demonstrated in this study, removing those premature infants who are often identified by "being small at birth", may significantly underestimate the proportionate birth asphyxia mortality.

Community Based Risk Factors for Birth Asphyxia Mortality

Socioeconomic status was a significant risk factor for birth asphyxia mortality in Sarlahi, Nepal. This is consistent with a study of neonatal encephalopathy from Perth, Western Australia, where maternal socioeconomic status defined by maternal unemployment and lack of private health insurance were independent risk factors for moderate to severe neonatal encephalopathy [27]. In our study, parental education, literacy, and occupation were individually associated with birth asphyxia mortality, with paternal education being the most significant predictor in the multivariate model. Caste and ethnicity were additional independent significant risk factors for birth asphyxia mortality. These distal risk factors of lower socioeconomic status

remained significant after adjustment for pre-established intrapartum risk factors for birth asphyxia mortality. Potential proximal mechanisms by which these factors may lead to increased risk for birth asphyxia may include maternal nutritional status, antepartum care and treatment, and access to and care seeking of health care services during delivery. These factors need to be explored in greater depth.

Unlike previous studies, maternal age was not an independent risk factor for birth asphyxia mortality in this setting. In Ellis et al [41] and Badawi et al's [27] studies of hospital based neonatal encephalopathy, high maternal age was associated with increased risk of neonatal encephalopathy. In contrast, in our cohort, lower maternal age was associated with increased risk of birth asphyxia mortality; however, this covariate was highly associated with parity, and the relationship was not significant after adjusting for parity.

Maternal intrapartum complications – antepartum hemorrhage, maternal fever, pre-eclampsia, eclampsia, prolonged rupture of membranes, and obstructed labor – have been associated with increased risk of birth asphyxia and neonatal encephalopathy in multiple studies [18, 20-22, 44]. In the Sarlahi cohort, measures of clinical symptoms reflecting these disease processes (maternal fever, swelling, vaginal bleeding, convulsions, prolonged rupture of membranes) were significant in initial univariate analysis, however, after adjusting for the other intrapartum factors, only maternal fever remained a significant predictor of birth asphyxia death. Given the potential association between prolonged rupture of membranes and maternal fever, these factors were tested independently in separate models for both confounding and interaction, and not found to be significant. The lack of significance of the clinical symptoms "maternal swelling" and "convulsions" of pre-eclampsia or eclampsia may be due to recall bias or the non-specificity of the survey symptoms, as compared to hospital based diagnoses of pre-eclampsia or eclampsia,

which may be verified by clinicians, blood pressure measurements, urinalysis and laboratory testing. In addition, as opposed to prior studies [27, 41] we chose to adjust for the other intrapartum risk factors to obtain the most conservative estimate of the effect of each individual risk factor.

An unexpected finding of this analysis was the increased risk of birth asphyxia mortality for deliveries attended by doctors or auxiliary nurse midwives. The survey question and categories regarding birth attendant may have been subject to misclassification in this study, as some participants may have selected "doctor" referring to a traditional Nepali doctor or pharmacist as opposed to a provider formally trained to assist childbirth. This increased risk also may be attributed to confounding by indication, i.e., in complicated childbirths, higher level medical care was sought. This association persisted, however, even after adjusting for common intrapartum complications. These findings suggest the need to further assess the training of doctors and nurse midwives to recognize risk factors and clinical symptoms of birth asphyxia, and manage birth asphyxia in the home-based setting.

Low birth weight is a well established risk factor for birth asphyxia [20, 24] and neonatal encephalopathy [27]. In the Katmandu study [41], birth weight was not significantly associated with risk for neonatal encephalopathy. A limitation of our study was the substantial differential missing data on birth weight of asphyxiated infants due to the timing of data collection and birth asphyxia mortality in this community setting. We postulate that infants who died from birth asphyxia may be of lower birth weight and/or lower gestational age due to their decreased energy reserves. If this were the case, we expect our univariate RR estimates might underestimate the true association of low birth weight with birth asphyxia mortality.

The strongest predictor for birth asphyxia mortality in this study was the combined, synergistic effect of maternal fever and prematurity (RR: 7.53, CI: 4.42, 12.83). In an analysis of

the Nepal Nutrition Intervention project from an earlier study period (January 2000-April 2001), the risk of 6-month mortality was 86.4 times higher in infants with symptoms of birth asphyxia, prematurity, and sepsis as opposed to those with only sepsis (OR: 3.3), asphyxia (OR 4.9) or prematurity (OR 3.5) [45]. In the Gadchiroli field trial of home based neonatal care, case fatality rates for preterm infants in combination with other morbidities were significantly higher than those with single morbidities or prematurity alone [46]. In that study, the case fatality for preterm infants with sepsis was 51.9% versus preterm (11.1%) or sepsis (0%) alone while the case fatality for asphyxiated premature infants was 66.7% versus birth asphyxia alone (25%) [46].

The synergy between birth asphyxia, infection and prematurity may be explained by a common inflammatory pathway of neonatal brain injury. Hypoxic-ischemic insult in immature rats results in the induction of cytokine and chemokine mRNA expression in brain cells, followed by the acute recruitment of neutrophils, macrophages, and expression of adhesion molecules (β2-Integrin); and eventual chronic inflammation by the activation of CD4 lymphocytes, microglia and astroglia [47]. In asphyxiated neonates, elevation of interleukin-6 (IL-6) is markedly elevated in cerebrospinal fluid and is related to the severity of hypoxic ischemic encephalopathy [48]. Elevations in cytokines (IL6, IL-1β, ICAM-1) and chemokines (IL-8) have been reported in the serum of asphyxiated neonates [49-51]. Increases in inflammatory mediators are also found in infants with neonatal infections (IL-6, IL-1β, ICAM-1, IL-8)[49, 51], infants of mothers with intrauterine infection (IL-6) [52], and the amniotic fluid of mothers with preterm birth (IL-6, TNF-α, PGE) [53]. Cytokines are postulated to induce fetal brain damage by directly causing white matter injury, weakening the germinal matrix endothelium leading to intra-ventricular hemorrhage, and inducing further inflammatory reactions by microglia and astrocytes

[54]. Furthermore, premature infants are more vulnerable to cytokine induced damage due to the immaturity of their blood-brain barrier.

These findings suggest that targeting the community-based treatment of maternal infections during pregnancy may be an important intervention to reduce birth asphyxia specific and overall neonatal mortality. Maternal infections have been long associated with preterm labor and stillbirths, and are hypothesized to mediate preterm labor via increased prostaglandin production[55]. Maternal chorioamnionitis [56], bacterial vaginosis [57], and urinary tract infections [58, 59] are significantly associated with increased risk for preterm delivery. While the prevention of prematurity has been challenging to address in public health interventions, the improved recognition and treatment of maternal infections during pregnancy at the community level may help reduce neonatal morality.

Furthermore, while we only addressed early, birth asphyxia specific mortality in this study, the inter-relationships between maternal infection, prematurity and neonatal mortality highlighted by these findings raise the potential consideration of intrapartum risk factors in the community-based treatment of neonatal infections. While neonatal sepsis protocols in industrialized countries frequently utilize maternal risk factors to empirically manage neonates at risk for Group B Strep infection [60], present protocols for community-based recognition and treatment of infections in low income settings rely primarily on postnatal clinical symptoms of newborns, and do not incorporate maternal or intrapartum risk factors [61-63]. In a recent Neonatal Cochrane review, investigators concluded that there was insufficient data to make conclusions regarding prophylactic antibiotic treatment versus selective antibiotics for infants of mothers with risk factors for neonatal infection, and called for large randomized trials[64]. The findings from this study raise for consideration that these intrapartum risk factors should also be

considered in the development of community-based infection recognition and treatment protocols of neonatal sepsis in low-resource settings.

Conclusions

This study highlights the critical need to develop and validate a standardized community-based verbal autopsy definition for birth asphyxia. We established that risk factors for perinatal asphyxia during childbirth in low-income, home-based births are similar to those observed in hospitals, with maternal infections, multiple births, and prematurity playing an important role in the community. Low socioeconomic status is highly associated with perinatal asphyxia and the proximal mechanisms leading to mortality need to be further elucidated. Finally, the interaction between maternal infections and prematurity may be an important target for future community-based interventions to reduce the impact of birth asphyxia on neonatal mortality.

TABLE 1. Comparison of Verbal Autopsy Definitions of Birth Asphyxia

	BIRTH ASPHYXIA DEFINITION			
Sign/Symptom	**Definition 1:** WHO Algorithm 3 [16]	**Definition 2:** WHO Algorithm 4 [16]	**Definition 3:** Baqui [29]	**Definition 4:** Newborn Washing Study [31]
Death in first 7 days of life			X	X
Infant Failed to Cry at Birth	X	X	*	X
Not able to breathe at birth	*		*	
Not able to breathe in first 2 min				*
Convulsions in first 2 days				*
Convulsions/Spasms at any time		*		
Unable to suckle normally after birth	*	*	*	
Difficulty sucking in first 2 days				*

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

FIGURE 1: Assignment of Birth Asphyxia as the Cause of Death

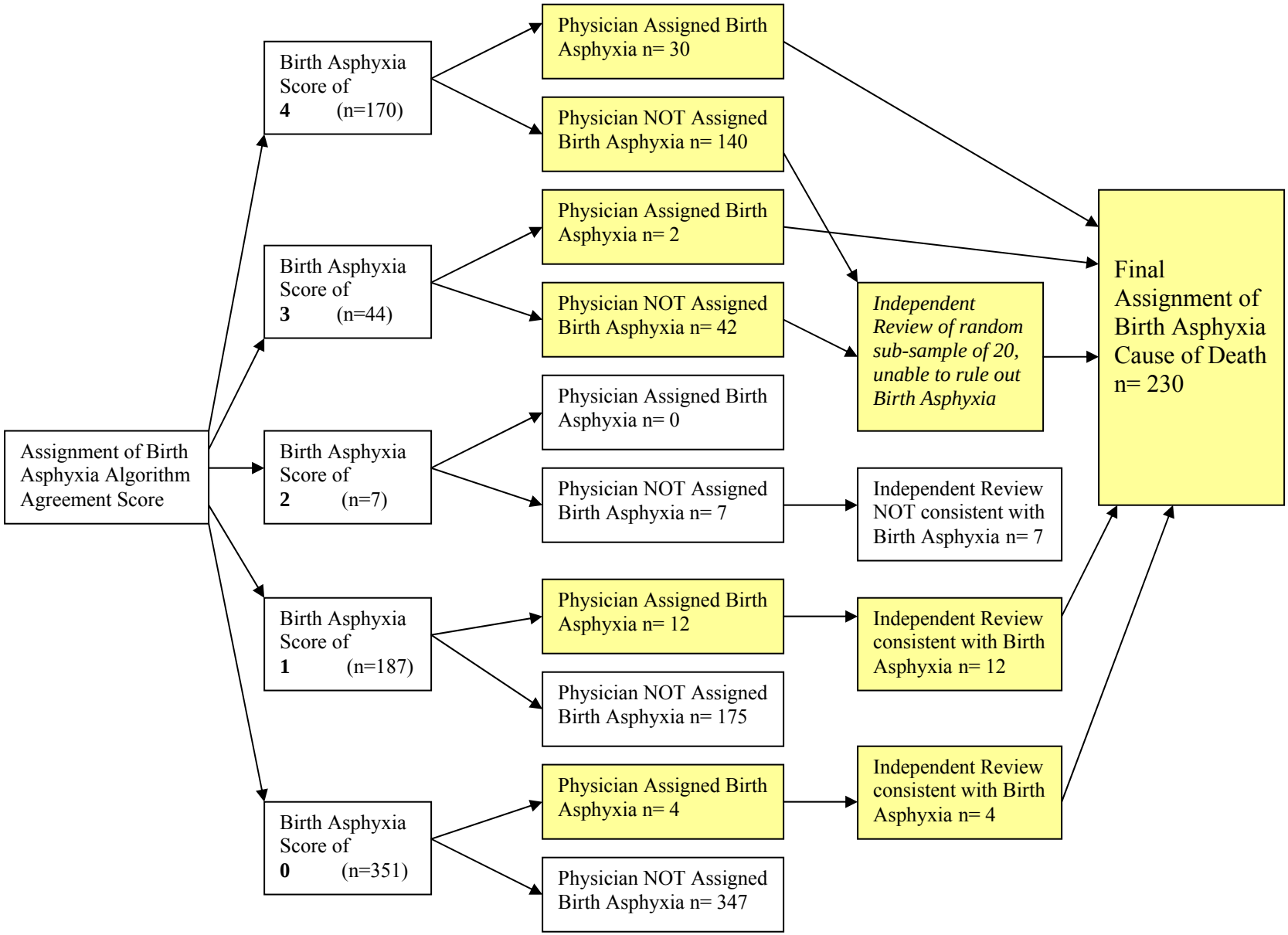

FIGURE 2: Distribution of Timing of Birth Asphyxia Deaths

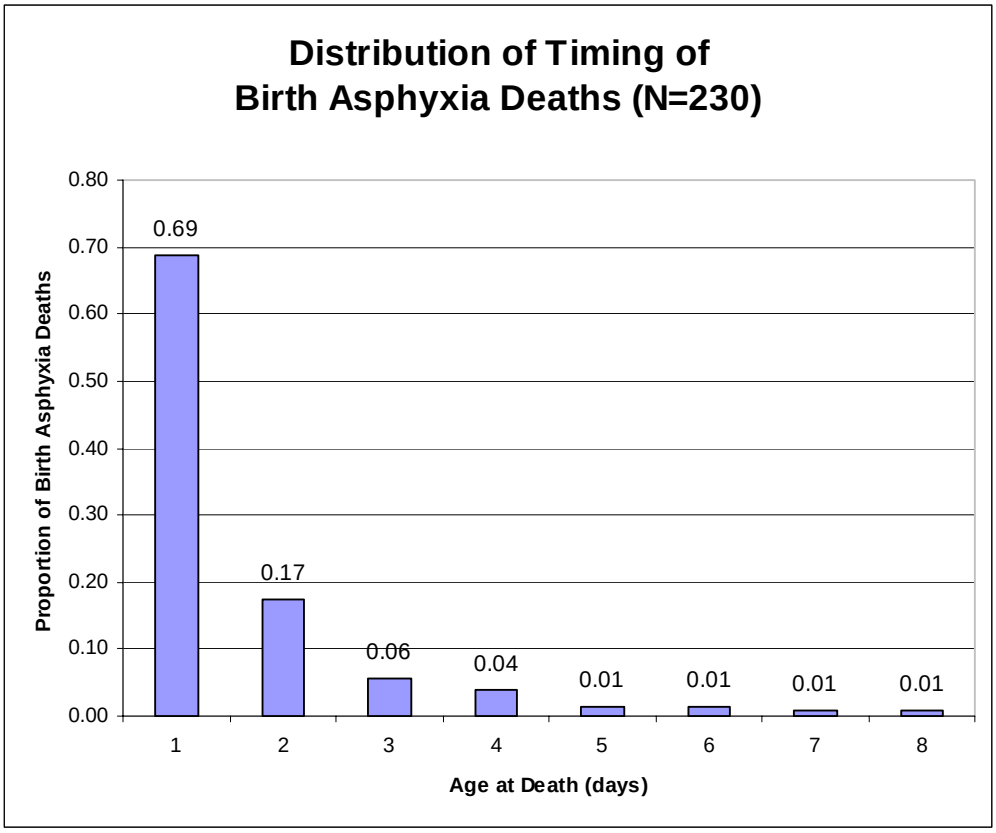

FIGURE 3: Venn Diagram of Non-Hierarchal Birth Asphyxia Definitions (N=759 total Neonatal Deaths)

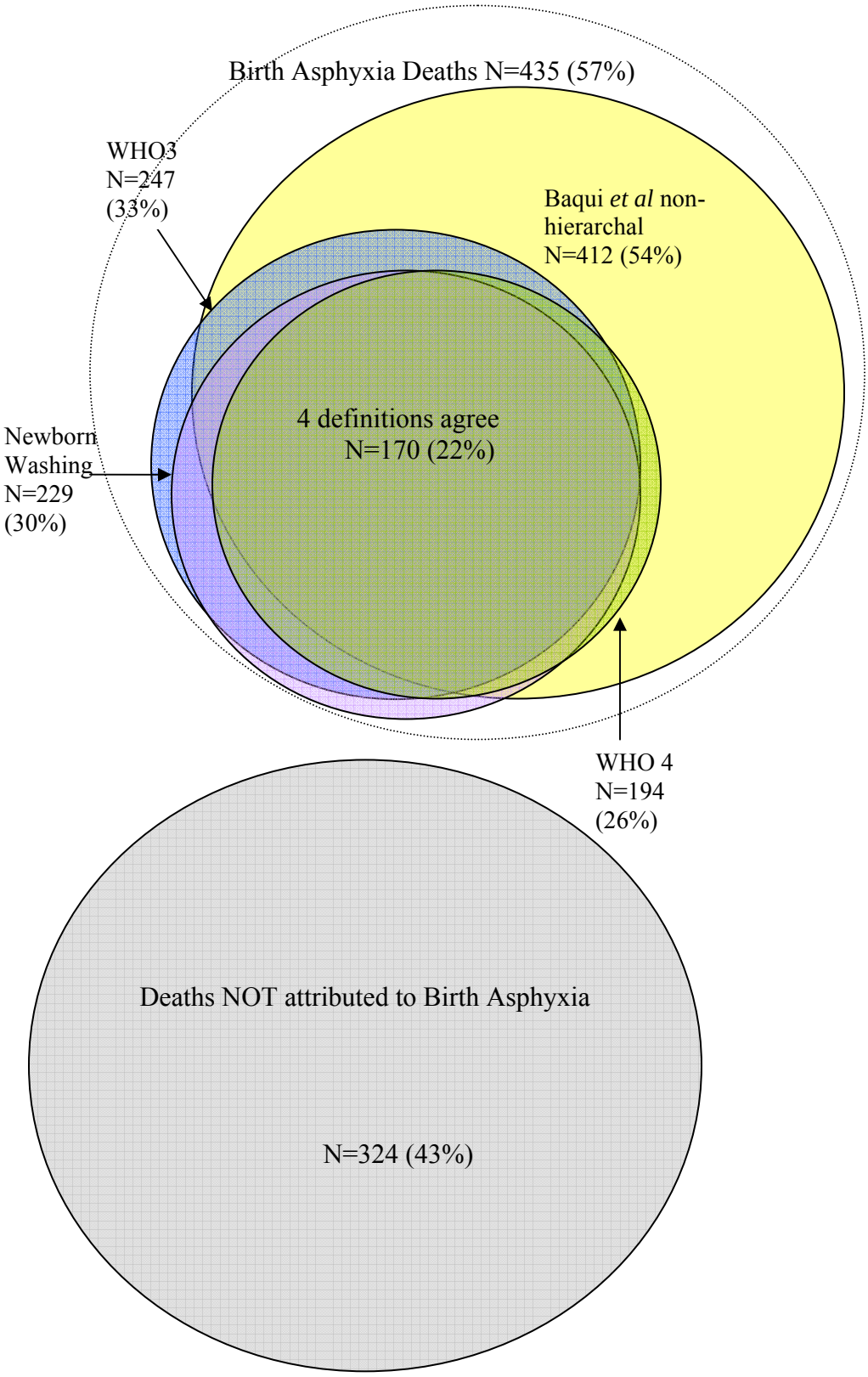

TABLE 2: Birth Asphyxia Deaths and Proportionate Mortality with Utilization of Standard Hierarchy[34] for Cause of Death Assignment for 759 Neonatal Deaths

Algorithm	Non-Hierarchal Assignment		Hierarchal 1*		Hierarchal 2**	
	No. Birth Asphyxia Deaths	Proportionate Neonatal Mortality	No. Birth Asphyxia Deaths	Proportionate Neonatal Mortality	No. Birth Asphyxia Deaths	Proportionate Neonatal Mortality
WHO3	247	33%	231	30%	163	21%
WHO4	194	26%	180	24%	126	17%
Baqui	412	54%	389	51%	244	32%
New Born Washing	229	30%	213	28%	147	19%

* (Minus Tetanus, Congenital Malformations Deaths)

** (Minus Tetanus, Congenital Malformations, and Prematurity Deaths)

FIGURE 4

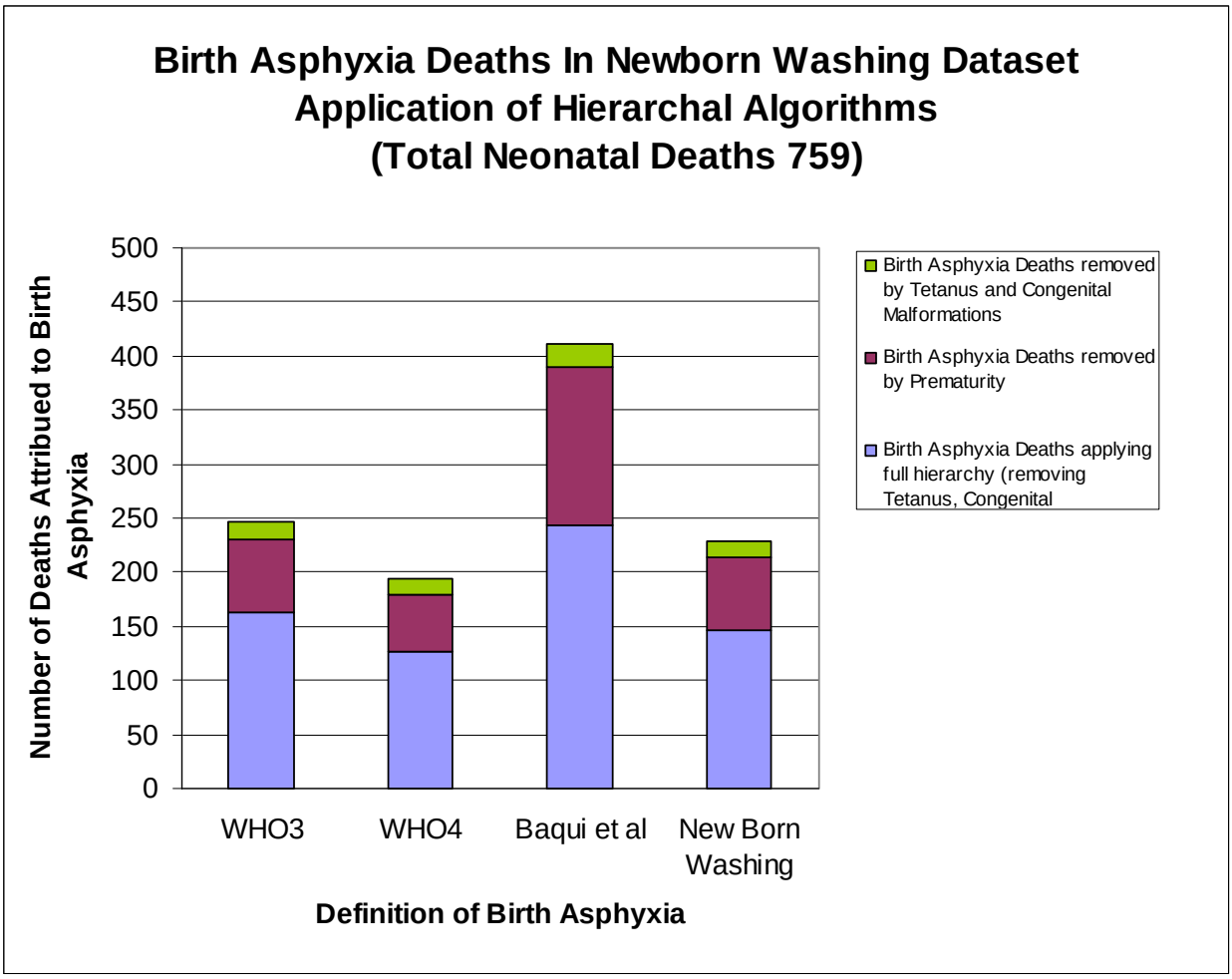
Birth Asphyxia Deaths In Newborn Washing Dataset
Application of Hierarchal Algorithms
(Total Neonatal Deaths 759)
Number of Deaths Attribued to Birth Asphyxia
500
450
400
350
300
250
200
150
100
50
0
WHO3
WHO4
Baqui et al
New Born Washing
Definition of Birth Asphyxia
Birth Asphyxia Deaths removed by Tetanus and Congenital Malformations
Birth Asphyxia Deaths removed by Prematurity
Birth Asphyxia Deaths applying full hierarchy (removing Tetanus, Congenital

TABLE 3. UNIVARIATE ANALYSIS: Antepartum Risk Factors for Birth Asphyxia

ANTEPARTUM Risk Factor	Category	Total Number	No. Died Birth Asphyxia	RR	95% CI	P
Maternal Age	<20	5,989	79	1.00		
	20-24	9,396	85	0.69	0.51, 0.93	0.02
	25-29	5,159	37	0.54	0.36, 0.81	0.00
	30-34	2,156	21	0.74	0.45, 1.21	0.23
	>35	950	8	0.64	0.31, 1.32	0.22
Maternal Literacy	Illiterate	17,569	194	1.00		
	Literate	6,081	36	0.54	0..37. 0.77	0.00
Maternal Education	None	17,988	195	1.00		
	1-3 yrs	513	1	0.18	0.03, 1.28	0.09
	4-6 yrs	1,765	13	0.68	0.39, 1.19	0.18
	7-9 yrs	1,508	9	0.55	0.28, 1.07	0.08
	>=10 yrs	1,866	12	0.59	0.32, 1.11	0.10
Maternal Occupation	Home	19,940	201	1.00		
	Farmer	2,120	10	0.47	0.25, 0.88	0.02
	Unskilled Laborer	1,267	16	1.25	0.76, 2.18	0.45
	Contracted Laborer	11	0	0.00	0.00	0
	Business	182	2	1.09	0.27, 4.36	0.93
	Private	76	1	1.31	0.19, 9.19	0.79
Paternal Literacy	Illiterate	10,308	137	1.00		
	Literate	13,329	93	0.52	0.40, 0.69	0.00
Paternal Education	None	10,939	143	1.00		
	1-3 yrs	974	12	0.94	0.52, 1.69	0.84
	4-6 yrs	3,552	23	0.50	0.32, 0.77	0.00
	7-9 yrs	3,560	27	0.58	0.38, 0.88	0.01
	>=10 yrs	4,382	25	0.44	0.29, 0.68	0.00
Paternal Occupation	Farmer	10,359	96	1.00	1.00	
	Unskilled Laborer	6,624	85	1.38	1.03, 1.87	0.03
	Contracted Laborer	1,258	14	1.20	0.69, 2.10	0.52
	Business	2,908	26	0.96	0.61, 1.52	0.88
	Private	1,713	8	0.50	0.25, 1.03	0.06
	Home	212	0			
Caste	Brahmin	1,523	9	1.00	1.00	
	Chetri	1,551	15	1.64	0.72, 3.72	0.24
	Vaishya	14,707	134	1.54	0.79, 3.02	0.21
	Shudra	3,270	40	2.07	1.00, 4.29	0.05
	Muslim	2,208	22	1.69	0.76, 3.72	0.20
Ethnic Group	Pahadi	6,627	30	1.00		
	Madeshi	16,646	189	2.51	1.71, 3.68	0.00
Parity	>=1 prior liveborn	17,704	145	1.00		
	0 prior liveborn	5,955	85	1.74	1.33, 2.28	0.00
History of Child Death	No prior child death	18,786	183	1.00		
	>=1 child death	4,873	47	0.99	0.70, 1.40	0.95
Electricity	No Electricity	17,611	168	1.00		
	Electricity	5,662	50	0.95	0.68, 1.28	0.64

TABLE 4. UNIVARIATE ANALYSIS: Intrapartum Risk Factors for Birth Asphyxia

INTRAPARTUM RISK FACTOR	CATEGORY	TOTAL NUMBER	NO. DIED BIRTH ASPHYXIA	RR	95% CI	P
Place of Delivery	Home	16,288	143	1.00		
	Maiti	3,737	40	1.22	0.86, 1.73	0.27
	Health Facility (Hospital or Clinic)	2,069	35	1.93	1.32, 2.81	0.00
	On way to clinic/outdoors	270	6	2.53	1.13, 5.67	0.02
Birth Attendant Type	Family member	9,112	54	1.00		
	No attendant	540	5	1.56	0.63, 3.89	0.34
	Dhami/Jankri	38	0			
	Traditional Birth Attendant	4,502	31	1.16	0.75, 1.80	0.50
	CHV/MCH	1,263	19	2.54	1.47, 4.38	0.00
	Auxillary Nurse Midwife	1,568	24	2.58	1.60, 4.20	0.00
	Doctor	4,381	84	3.24	2.28, 4.60	0.00
Maternal Fever [•]	No fever	21,577	200	1.00		
	Fever	784	24	3.30	2.15, 5.07	0.00
Vaginal Bleeding [*]	No bleeding	21,464	208	1.00		
	Bleeding	876	17	2.00	1.23, 3.27	0.01
Swelling [*]	No swelling	18,348	162	1.00		
	Swelling	4,019	63	1.78	1.33, 2.37	0.00
Convulsions [*]	No convulsions	22,263	221	1.00		
	Convulsions	85	4	4.74	1.80, 12.46	0.00
Prolonged Labor	Labor <24 hrs primip, <12 hrs multip	16,117	149	1.00		
	Labor >24 hrs primip, >12 hrs multip	6,172	75	1.31	1.00, 1.73	0.05
Multiple Pregnancy	Singleton	23,296	211	1.00		
	Twin	360	17	5.21	3.02, 9.00	0.00
	Triplet	6	2	26.15	9.14, 148.13	0.00
Prolonged Rupture of Membranes	ROM <24hrs	20,577	194	1.00		
	ROM>24 hrs	1,564	27	1.83	1.22, 2.76	0.00
Amniotic Fluid	Clear	14,595	126	1.00		
	Green	88	1	1.32	0.19, 9.32	0.78
	Red	4,100	56	1.58	1.14, 2.19	0.01
C-section	No C-section	23,440	227	1.00		
	C-section	222	3	1.40	0.45, 4.33	0.56
Episiotomy	No Episiotomy	22,996	223	1.00		
	Episiotomy	666	7	1.08	0.51, 2.29	0.83
Injection during Childbirth	No Injection	16,554	109	1.00		
	Received Injection	7,108	121	2.59	1.99, 3.37	0.00
Baby pulled	Baby not pulled	23,454	220	1.00		
	Baby pulled	208	10	5.13	2.76, 9.53	0.00
External Pressure	No External pressure	18,129	170	1.00		
	External pressure	5,533	60	1.16	0.86, 1.55	0.34
External Massage	No External Massage	11,535	97	1.00		
	External Massage	12,127	133	1.30	1.00, 1.69	0.05

[*] Symptoms within 7 days prior to delivery

TABLE 5. UNIVARIATE ANALYSIS: Infant and Post Partum Factors

INFANT FACTORS	Category	Total N	No. Died BA	RR	CI	p
Birth Weight	<2 kg	1,146	20	11.88	6.09, 23.14	0.00
	2.0-2.4 kg	5,638	10	1.21	0.54, 2.69	0.64
	2.5-2.9 kg	10,211	15	1.00		
	3.0-3.4 kg	4,895	5	0.70	0.25, 1.91	0.48
	>3.5kg	872	1	0.78	0.1, 5.9	0.81
Gestational Age	Pre-term: <37 wks	4,320	93	3.07	2.33, 4.05	0.00
	Term: 37-42 wks	16411	115	1.00		
	Post-term: >42wks	2918	22	1.07	0.69, 1.67	0.75
Infant Sex	Male	12,195	135	1.00		
	Female	11,467	95	0.75	0.58, 0.97	0.03
Washing Treatment Allocation	Placebo	8,880	81	1.00		
	Washing Treatment	14,782	149	0.90	0.69, 1.19	0.48

TABLE 6: MULTIVARIATE MODELS

RISK FACTORS		MODEL 1 (N=22.968)			MODEL 2 (N=21,147)			MODEL 3 (N= 23,649)		
ANTEPARTUM	**CATEGORY**	**RR**	**CI**	**P**	**RR**	**CI**	**P**	**RR**	**CI**	**P**
Maternal Age (ref: <20yo)	20-24yo	1.01	0.68, 1.49	0.96						
	25-29yo	0.78	0.48, 1.29	0.34						
	30-34yo	0.97	0.54, 1.77	0.93						
	>35yo	0.85	0.39, 1.87	0.69						
Paternal Education (ref: None)	1-10 years	0.59	0.43, 0.81	0.00						
	>10 years	0.37	0.23, 0.62	0.00						
Caste (ref: Vaishya, Shudra, or Muslim)	Brahmin/Chetri	0.48	0.31, 0.74	0.00						
Ethnicity (ref: Pahmadi)	Madeshi	2.86	1.91, 4.28	0.00						
Parity (ref: Multiparous)	Nulliparous	1.91	1.32, 2.77	0.00						
INTRAPARTUM										
Place of Delivery (ref: Home)	Maiti				1.04	0.73, 1.5	0.82			
	Facility Delivery				0.87	0.56, 1.35	0.52			
	Outdoors/way to clinic				2.45	1.1, 5.48	0.03			
Birth Attendant (ref: No attendant)	TBA or Dhami/Jankri				1.11	0.71, 1.74	0.64			
	CHV/MCH				2.42	1.41, 4.16	0.00			
	Skilled Attendant (Doctor or Midwife)				2.92	2.02, 4.21	0.00			
Maternal Fever (ref: afebrile)	Fever				2.66	1.69, 4.17	0.00			
Maternal Swelling (ref: no swelling)	Swelling				1.34	0.97, 1.86	0.08			
Convulsions (ref: no convulsions)	Convulsions				1.41	0.33, 5.97	0.64			
Vaginal Bleeding (ref: no bleeding)	Bleeding				1.57	0.93, 2.65	0.12			
Rupture of Membranes (ref: <24hr)	Prolonged (>24hr)				1.22	0.79, 1.9	0.37			
Multiple birth (ref: singleton)	Twin or Triplet				5.26	3.02, 9.17	0.00			
INFANT										
Prematurity (ref: >37wks)	<37wks							3.03	2.32, 3.96	0.00
Infant Sex (ref: male)	Female							0.75	0.58, 0.98	0.03

TABLE 7: MULTIVARIATE MODELS

RISK FACTORS		MODEL 4 (N=20,529)			MODEL 5 (N=20,524)			MODEL 6 (N=20,524)		
ANTEPARTUM	**CATEGORY**	**RR**	**CI**	**P**	**RR**	**CI**	**P**	**RR**	**CI**	**P**
Maternal Age (ref: <20yo)	20-24yo	0.89	0.59, 1.33	0.56	0.91	0.61, 1.36	0.66	0.94	0.62, 1.41	0.76
	25-29yo	0.69	0.42, 1.13	0.14	0.70	0.42, 1.16	0.17	0.72	0.43, 1.19	0.20
	30-34yo	0.71	0.37, 1.33	0.28	0.70	0.37, 1.32	0.27	0.71	0.38, 1.36	0.30
	>35yo	0.66	0.29, 1.52	0.33	0.64	0.28, 1.5	0.31	0.64	0.27, 1.5	0.30
Paternal Education (ref: None)	1-10 years	0.57	0.41, 0.79	0.00	0.58	0.42, 0.8	0.00	0.58	0.42, 0.8	0.00
	>10 years	0.35	0.21, 0.59	0.00	0.37	0.22, 0.61	0.00	0.37	0.22, 0.61	0.00
Caste (ref: Vaishya, Shudra, or Muslim)	Brahmin/Chetri	0.57	0.35, 0.93	0.03	0.57	0.35, 0.94	0.03	0.58	0.35, 0.94	0.03
Ethnicity (ref: Pahmadi)	Madeshi	2.94	1.87, 4.63	0.00	2.51	1.59, 3.96	0.00	2.52	1.6, 3.98	0.00
Parity (ref: Multiparous)	Nulliparous	1.55	1.06, 2.27	0.02	1.47	1, 2.15	0.05	1.49	1.01, 2.2	0.04
INTRAPARTUM										
Place of Delivery (ref: Home)	Maiti	0.73	0.49, 1.09	0.12	0.74	0.5, 1.1	0.13	0.72	0.49, 1.08	0.11
	Facility Delivery	1.11	0.68, 1.8	0.69	1.13	0.69, 1.85	0.62	1.10	0.67, 1.81	0.71
	Outdoors/way to clinic	2.93	1.33, 6.48	0.01	2.75	1.29, 5.89	0.01	2.82	1.32, 6.05	0.01
Birth Attendant (ref: No attendant)	TBA or Dhami/Jankri	0.90	0.57, 1.42	0.64	0.90	0.57, 1.42	0.66	0.89	0.56, 1.41	0.62
	CHV/MCH	2.03	1.18, 3.51	0.01	2.23	1.3, 3.82	0.00	2.22	1.3, 3.81	0.00
	Skilled Attendant (Doctor or Midwife)	2.44	1.67, 3.56	0.00	2.48	1.71, 3.6	0.00	2.51	1.73, 3.64	0.00
Maternal Fever (ref: afebrile)	Fever	2.21	1.35, 3.6	0.00	2.03	1.25, 3.28	0.00	0.83	0.31, 2.23	0.71
Maternal Swelling (ref: no swelling)	Swelling	1.28	0.9, 1.81	0.17	1.33	0.94, 1.87	0.11	1.32	0.94, 1.86	0.11
Convulsions (ref: no convulsions)	Convulsions	1.21	0.28, 5.27	0.80	1.01	0.24, 4.27	0.98	1.00	0.25, 3.97	1.00
Vaginal Bleeding (ref: no bleeding)	Bleeding	1.52	0.87, 2.65	0.15	1.54	0.89, 2.67	0.12	1.55	0.9, 2.66	0.11
Rupture of Membranes (ref: <24hr)	Prolonged (>24hr)	1.20	0.75, 1.9	0.45	1.19	0.75, 1.9	0.46	1.17	0.73, 1.86	0.52
Plurality (ref: singleton)	Twin or Triplet	5.58	3.15, 9.88	0.00	4.91	2.84, 8.47	0.00	4.94	2.86, 8.52	0.00
INFANT										
Prematurity (ref: >37wks)	<37wks				2.58	1.95, 3.4	0.00	2.28	1.67, 3.09	0.00
Infant Sex (ref: male)	Female				0.74	0.56, 0.98	0.04	0.74	0.56, 0.99	0.04
Interaction Term (ref: full term, no history of maternal fever)	Premature (<37wks) and Maternal Fever							7.53	4.42, 12.83	0.02

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