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Dealing with neonatal emergencies in low-resource settings

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ABSTRACT

We describe the development and delivery of neonatal care including trends and impacts of major interventions on neonatal mortality particularly in low-resource settings. Low- and middle-income countries continue to be major contributors to neonatal mortality. Although there has been progress in reducing neonatal mortality, neonatal deaths are contributing an increasing percentage of childhood mortality. Several interventions targeting neonatal care such as neonatal resuscitation and essential newborn care have contributed to improved outcomes. However, there are still many neonatal deaths that are preventable with known effective interventions. This review addresses interventions proven effective in reducing neonatal mortality, challenges to implement them, and future directions of implementing these interventions in low- and middle-income countries.

1. History of global neonatal mortality and morbidity

Childhood mortality approached 50% in the 18th and 19th century in some countries in Europe [1]. Advances in medicine and recognition of child and newborn mortality as a problem led to a gradual decline in child and newborn mortality in developed countries in the early 20th century [2]. Earlier data on neonatal mortality are incomplete, and comprehensive data on global neonatal mortality including data trends from different countries are available only since 1990 [1,3]. Neonatal mortality rates have been improving during the last few decades, but the rate of decrease has been slower as compared to the decline in under 5 mortality [4,5]. Therefore, the proportion of neonatal mortality to under 5 mortality has increased to 45% [6,7].

2. Chronology of neonatal resuscitation

The earliest account of neonatal resuscitation was described in texts dating back to 6th century BC [8,9]. Resuscitation as an intervention that could save lives was identified only in the late 18th century, beginning the era of formalized resuscitation training and certification [9]. This led to the formation of various societies focused on resuscitation guidelines [10]. One of the first efforts directed at formal neonatal resuscitation training was in mid-1970s and was called Neonatal Educational Program [11]. In 1987, the American Academy of Pediatrics developed the Neonatal Resuscitation Program (NRP) [11]. By 1989, the program was adopted across North America, and early international dissemination began [12]. This was followed by a rapid global adoption period in which many hospitals and teaching institutes across the world implemented neonatal resuscitation program [13]. In 1992, the International Liaison Committee on Resuscitation (ILCOR) began an international collaborative effort to form an international consensus on resuscitation including neonatal resuscitation [14]. Evidence-based neonatal resuscitation guidelines began to be formulated every 5 years with the most recent one in 2015 [15,16]. There has been a universal uptake of NRP and subsequent improvement in neonatal resuscitation practice and outcomes in high-income countries [12].

3. Challenges to neonatal resuscitation in low- and middle income countries

Approximately 98% of all perinatal and neonatal deaths occur in low- and middle-income countries [17]. Neonatal mortality is about 50 times higher in low- and middle-income countries compared to high-income countries [18]. Although global under 5 mortality has decreased substantially, the decrease in neonatal mortality has been more modest [19]. Failure to initiate spontaneous breathing is a major cause of perinatal mortality and morbidity [20–22]. Approximately 13 million neonates require resuscitation [18] and of them, 3–6 million neonates require assistance to initiate respirations [23]. Neonates who require respiratory support, if not assisted promptly, decompensate rapidly resulting in death [24]. Delivery of prompt and effective neonatal resuscitation is the only intervention that could potentially prevent mortality in such scenarios [25–32]. In an observational study, 94% of neonates requiring resuscitation responded to basic steps like

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suctioning and bag and mask ventilation; delay in the administration of basic resuscitation was associated with the corresponding rise in the risk of death [33].

Low- and middle-income countries continue to have high neonatal mortality secondary to high rates of home births with lack of trained birth attendants as well as lack of prompt and effective basic neonatal resuscitation facilities [18,34,35]. About 60 million births/year happen outside birthing facilities mainly at home or the birth attendants' homes. Rates of home births are as high as 50–90% in some countries [18,36]. In the 60 million births that occur outside of birthing facilities, close to 52 million deliveries occur without a trained birth attendant [37,38]. Additionally, health care facilities are ill-equipped, and many of them lack trained neonatal resuscitation providers [18]. In a survey from 6 African countries, only 2%–12% of birthing hospitals had trained neonatal resuscitation providers and only 8%–22% of the facilities had neonatal resuscitation equipment [39].

NRP and ILCOR guidelines were based on clinical research mostly originating from developed countries [40]. As NRP and ILCOR guidelines were based on best scientific evidence and did not consider resource and personnel constraints, application of AAP and ILCOR neonatal resuscitation guidelines was constrained in resource-limited settings from low- and middle-income countries [18].

4. Resuscitation guidelines for low- and middle-income countries

Neonatal resuscitation was assumed to require expertise and resources available only in neonatal intensive care units [13,41]. Soon after the implementation of NRP, growing evidence suggested that most of the neonates who required resuscitation could be saved by simple interventions such as drying, stimulation, and bag and mask ventilation [39,42–44]. Due to the constraints in implementation of NRP/ILCOR guidelines in resource-limited settings and the evidence suggesting that most of the neonates who require resuscitation can be saved by simple interventions, World Health Organization (WHO) initiated training and implementation of Essential Newborn Care (ENC) in 1994 [45] which also included basic neonatal resuscitation. Focused Basic Newborn Resuscitation guidelines were issued by WHO in 1998 [46]. These guidelines were revised by WHO in 2012 in the publication Basic Neonatal Resuscitation [47] and Early Essential Newborn Care (EENC) guidelines in 2014 [48]. In 2006, the American Academy of Pediatrics constituted a global implementation task force to develop a simulation-based training package for neonatal resuscitation for low- and middle-income countries [49]. AAP together with partners including WHO, the US Agency for International Development, Save the Children's Saving Newborn Lives program, the National Institute of Child Health and Human Development, and the Laerdal Global Health Group introduced neonatal resuscitation guidelines for low- and middle-income countries named Helping Babies Breathe (HBB) in 2010 [13] which was revised in 2016 [50] (see Fig. 1). AAP has also issued general newborn care guidelines for low- and middle-income countries called Essential Care for Every Baby (ECEB) in 2014 [51] and Essential Care for Small Babies (ECSB) in 2015 [52]. A summary of the guidelines covered in these educational programs is included in Table 1.

5. Evidence of the impact of neonatal resuscitation programs in low- and middle-income countries

Although there have been several large trials for assessing the effectiveness of basic resuscitation in low- and middle-income countries, most of the research has been observational or quasi-randomized due to the ethical challenges associated with an obviously life-saving intervention such as neonatal resuscitation.

In an interventional multicenter trial (N = 71,689 neonates), early neonatal (< 7 day) mortality decreased from 36.6/1000 to 25.1/1000 live births following ENC training of midwives in health clinics ($p < 0.001$) and to 15.9/1000 live births following NRP training [28]. A large multi-country study with active baseline before and after study and cluster randomized controlled design (First Breath Trial) (N = 120,009 births, birthweight > 1500 g) assessed the impact of essential newborn care and basic neonatal resuscitation training in rural community birth attendants of six countries (Argentina, Democratic Republic of Congo, Guatemala, India, Pakistan, and Zambia) [25]. ENC implementation resulted in a significant decrease in the stillbirth rate (RR 0.69; CI 0.54, 0.88; $p < 0.01$) and perinatal mortality. However, after ENC training, NRP training was not associated with a significant reduction in neonatal mortality or stillbirth rate in clusters that were randomized to NRP training compared to control clusters. The findings of this trial indicate that neonates who were stillborn before ENC training were surviving due to the provision of basic resuscitation. Additional NRP training after ENC training was not associated with significant improvement in perinatal/neonatal mortality suggesting that ENC was equally effective to NRP in these low-resource settings [25]. Similar to ENC training trials, large multicenter trials of training birth attendants from low- and middle-income countries in Helping Babies Breathe (HBB) have shown to significantly decrease stillbirth rate and neonatal mortality [30,53,54]. The systematic review and meta-analysis of interventional trials of basic neonatal resuscitation training of birth attendants from low- and middle-income countries has shown a significant decrease in the incidence of fresh stillbirth (RR 0.74, CI 0.61 to 0.90), perinatal mortality (RR 0.82, 95% CI 0.74 to 0.91), and neonatal mortality (RR 0.58, 95% CI 0.42 to 0.82) [55]. The reduction is stillbirth from a postnatal intervention indicates that resuscitation can be effective even when there are no signs of being alive at birth.

6. Neonatal emergencies in low-resource settings

As per recent estimates, there are close to 3 million neonatal deaths per year with the overwhelming majority of them (~98%) happening in low- and middle-income countries [6,7]. Leading causes of neonatal mortality include prematurity (29–35% of neonatal deaths), birth asphyxia or intrapartum-related events (23%), sepsis (21–36%) and congenital anomalies (11.3%) [7,56]. It should be noted that assignment of a single cause of neonatal mortality is difficult to ascertain as many of the neonatal illnesses have overlapping features. Causes of neonatal mortality are often misclassified [57]. As noted earlier, the neonatal mortality burden is largely concentrated in low- and middle-income countries which lack vital registries that can provide reliable data. Neonatal mortality data are often based on verbal autopsy, estimations, and surveys that are inherently riddled with high risk for inaccuracies [56–59]. However, the interventions to prevent the aforementioned complications when administered as a package of care have shown notable effectiveness in preventing neonatal mortality [25,28,30,53–55].

6.1. Resuscitation

The majority of neonates who require resuscitation respond to simple interventions such as drying, stimulation, and bag and mask ventilation [39,42–44]. Delay in providing basic resuscitation steps results in a rapid increase in the risk of mortality and morbidity [33]. The meta-analysis of studies on basic neonatal resuscitation in resource-limited settings shows a decrease in birth asphyxia/intrapartum-related deaths (RR = 0.70, 95% CI 0.59–0.84) [60] fresh stillbirth (RR 0.74, CI 0.61 to 0.90), neonatal (RR 0.58, 95% CI 0.42 to 0.82), and perinatal mortality (RR 0.82, 95% CI 0.74 to 0.91) [55]. It should be noted that the major focus of basic neonatal resuscitation guidelines for low- and middle-income countries has been on providing immediate drying, stimulation, maintaining open airway, and bag and mask ventilation [47,48,50]. NRP [15] and ILCOR [16] guidelines recommend the presence of two NRP trained providers as well as instruments and supplies like heart rate monitoring, saturation monitoring, oxygen source with

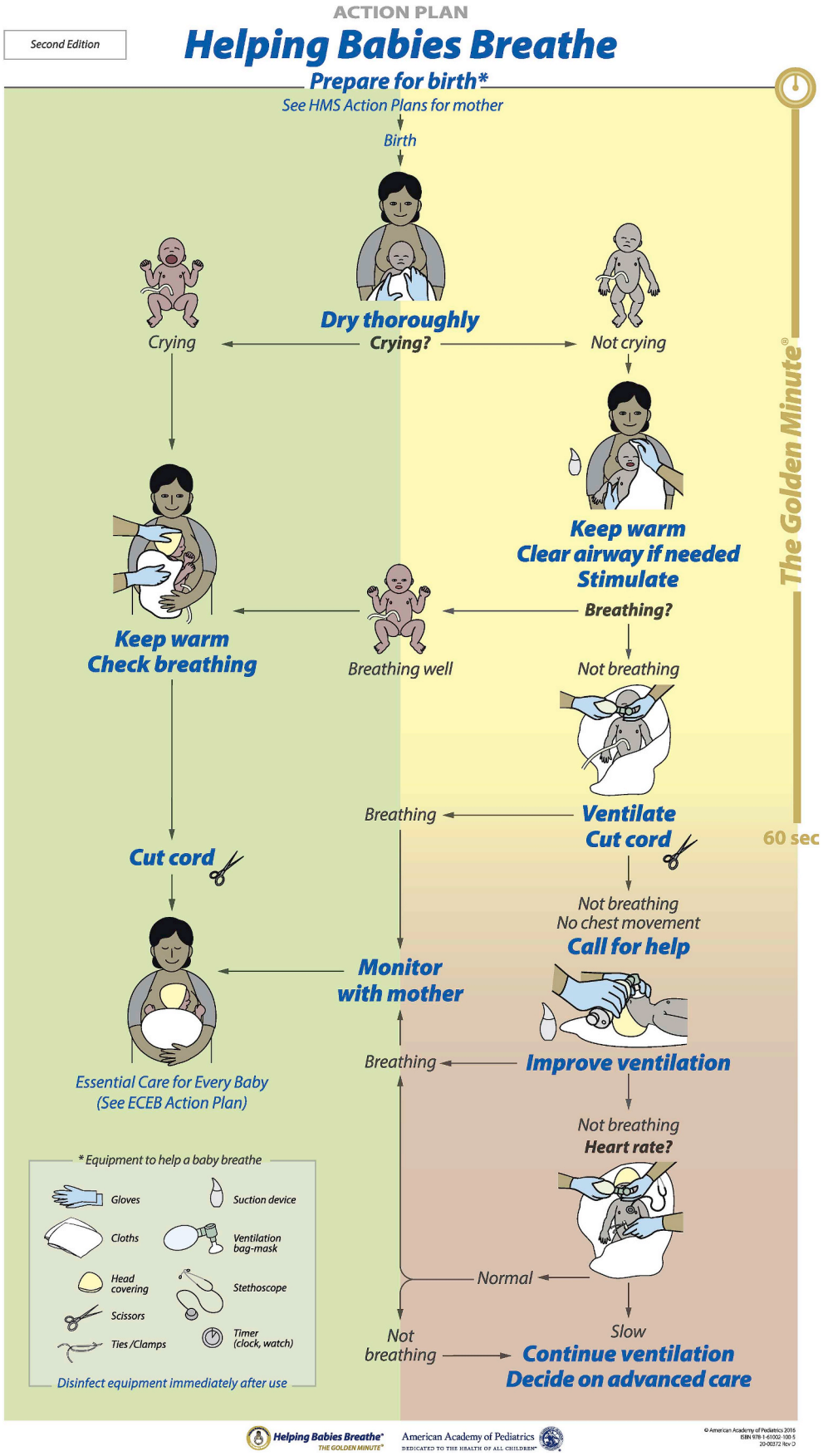

Fig. 1. Helping babies breathe second edition action plan. Abbreviations: ECEB, essential care for every baby; HMS, helping mothers survive.
Source: Niermeyer S, Kamath-Rayne B, Keenan W, Little G, Singhal N, Visick M, eds. (2016).7 Reprinted with permission from the American Academy of Pediatrics.

Table 1
Neonatal care guidelines for low and middle-income countries.

Guideline	Antenatal education	Delayed Cord Clamping	Skin to skin care	Resuscitation	Early breast feeding	Prematurity	Infection prevention Clean delivery practices	Follow up	Newborn care education including danger signs
Essential Newborn Care (ENC), WHO, 1994 [45]			+	+	+	+	+		+
Basic Newborn Resuscitation, WHO, 1998 [46]				+			+		
Helping Babies Breathe (HBB), AAP, 2010 [13]		+	+	+	+		+		
Basic Neonatal Resuscitation, WHO, 2012 [47]		+		+					
Early essential newborn care guidelines, WHO, 2014 [48]	+	+	+	+	+	+	+	+	+
Essential Care for Every Baby (ECEB), AAP, 2014 [51]			+		+	+	+	+	+

Timeline and components of major neonatal care guidelines for low- and middle-income countries, + indicates that the intervention was present in the guideline. WHO = World Health Organization, AAP = American Academy of Pediatrics.

blender, CPAP, laryngoscope, endotracheal tube, laryngeal mask, intubation supplies, umbilical line supplies, IV line supplies, epinephrine, normal saline and other medications. However, most neonates respond well to basic neonatal resuscitation which can be administered by a single provider with minimal equipment like bag-mask device, clean cloth, a sterile cord tie and blade/scissors [13,47,48,50]. Neonatal resuscitation should be followed by basic neonatal care as described in Early Essential Newborn Care, Essential Care for Every Baby [51], and Essential Care for Small Babies [52] as applicable.

6.2. Prematurity

Prematurity-related complications is the leading contributor to neonatal mortality [7,61]. The incidence of prematurity has been steadily increasing. In 2015, there were an estimated 15 million premature births and 1 million premature neonatal deaths [7,61,62]. Many premature neonates who survive suffer from long term complications. Prematurity-related neonatal deaths are concentrated in low- and middle-income countries. About 75% of the prematurity-related neonatal deaths and the majority of the morbidities can be prevented by implementing low-cost interventions like essential neonatal care, antenatal corticosteroids, kangaroo mother care and exclusive breastfeeding, and early identification and treatment of neonatal illnesses [61].

Antenatal corticosteroids have been proven to be effective in reducing several adverse outcomes in high-income countries. In a meta-analysis of studies conducted in high-income countries, antenatal corticosteroids decreased perinatal deaths (aRR 0.72, 95% CI 0.58 to 0.89), neonatal deaths (RR 0.69, 95% CI 0.59 to 0.81), respiratory distress syndrome (aRR 0.66, 95% CI 0.56 to 0.77), moderate/severe respiratory distress syndrome (aRR 0.59, 95% CI 0.38 to 0.91), intraventricular hemorrhage (aRR 0.55, 95% CI 0.40 to 0.76), necrotising enterocolitis (RR 0.50, 95% CI 0.32 to 0.78), need for mechanical ventilation (RR 0.68, 95% CI 0.56 to 0.84), and systemic infections in the first 48 h after birth (RR 0.60, 95% CI 0.41 to 0.88) [63]. However, the large cluster-randomized trial conducted in low- and middle income countries of antenatal corticosteroids (ACT Trial, N = 4778) there was no benefit in neonatal mortality or any other major outcomes and suspected maternal infection increased in the intervention group (OR 1·67, 1·33-2·09, $p < 0·0001$) [64] The results of this study led to a cautious approach by WHO by restricting antenatal corticosteroids to hospital settings in women with high risk for preterm delivery between 24 and 34 weeks of gestation [61,65,66]. The WHO sponsored clinical trial of antenatal steroids in low- and middle-income countries (WHO ACTION Trials) will provide additional information on the impact of antenatal corticosteroids and neonatal maternal outcomes. Antenatal magnesium sulfate for preterm neuroprotection has not been studied in low and middle-income countries. Thus, although antenatal magnesium sulfate for preterm neuroprotection is a standard of care in high-income countries based on multiple trials and meta-analyses [67–71], it is not recommended by WHO to be used outside of hospital settings in low and middle-income countries [66]. WHO additionally recommends antenatal antibiotic treatment for preterm labor and surfactant therapy for treatment of infants intubated for respiratory distress syndrome that specifically take place in hospital settings [66].

Prematurity-related deaths continue to happen well beyond the immediate delivery and resuscitation period [72]. Therefore, it is important for healthcare providers to closely follow up preterm neonates for early identification of danger signs and referral [72,73]. Mothers and immediate caregivers should be educated with programs such as Essential Care for Small Babies [52] and about identification of neonatal danger signs. Efforts should be made to strengthen local infrastructure to provide facility-based care for preterm neonates until they can be safely discharged to home in mother or family's care as medical care to preterm neonates has a high impact on premature neonatal survival [73].

6.3. Sepsis and infection prevention

Sepsis contributes to about one third of neonatal mortality worldwide [7,56]. About half of the sepsis-related deaths happen secondary to early-onset sepsis (within 3–7 days of life) and the rest is due to late-onset sepsis (> 7days of life) [72]. [74]. Close attention should be paid to the antenatal/perinatal history and maternal high-risk factors for sepsis [75]. Low birth weight and premature neonates are at 3–10 times higher risk for sepsis than term neonates because of limited host defenses, immune immaturity/dysfunction, and lack of transplacental maternal antibody transfer [75]. Neonatal care providers should be aware of the increased risk for sepsis in premature and low birth weight neonates, and a close follow-up of such neonates should be ensured.

It is important for the provider to educate the mother and the family about clean postnatal care practices as late onset sepsis accounts for about half of the sepsis related neonatal mortality. In a systematic review on the effect of various practices on neonatal mortality, it was found that there was a significant reduction in neonatal mortality with resuscitation provider handwashing (19%, 95% C.I. 1–34%), maternal handwashing (44%, 95% C.I. 18–62%), clean delivery practices (at home (15%, IQR 10–20%) or in a facility (27%, IQR 24–36)), and clean postnatal practices (40%, IQR 25–50%) [76]. There have been studies from different parts of the world indicating the wide scale prevalence of harmful postnatal care practices which predispose the neonates to the risk of sepsis [77–81]. Neonatal sepsis secondary to harmful cultural practices is an area with considerable scope for providing population-based educational initiatives. In addition to education about neonatal care practices, population-based initiatives should also be targeted for education regarding early identification of neonatal sepsis signs. Close follow-up of all neonates, especially the ones with risk factors for sepsis should be done to facilitate early identification, prompt treatment, and referral of sick neonates [72,73].

6.4. Prevention of hypothermia

As neonates have limited capacity to thermoregulate, normothermia is critical for neonatal survival [82]. The transition from the fetal environment to the extrauterine environment is associated with marked thermodynamic changes which can result in hypothermia unless active efforts are made to prevent it [83]. As their immature thermoregulatory mechanisms get easily overwhelmed, hypothermia is especially dangerous to premature and low birth weight neonates and it can rapidly result in multisystem compromise if left untreated [84]. Additionally, neonates with growth restriction, asphyxia, feeding difficulties, and hypoglycemia are also at increased risk of hypothermia and related complications [85]. Neonatal hypothermia can lead to multisystem symptoms like breathing difficulty, feeding difficulty, lethargy, and shock. Moreover, neonatal hypothermia has been shown to be independently associated with increased risk of mortality, intraventricular hemorrhage, respiratory diseases, hypoglycemia and late-onset sepsis [86]. Therefore, it is difficult to attribute the possible impact on neonatal mortality to hypothermia. In a meta-analysis of observational studies, the reported hypothermia incidence was found to be very high (as high as 90% in a few studies from low and middle-income countries) [85]. Neonatal hypothermia-related case fatality rates have been described in the range from 8.5% to 80% with fatality rates increasing proportionally to the degree of hypothermia [85,87–89] Prevention of hypothermia is one of the first and most important interventions for ensuring the optimal neonatal outcome. Care should be taken to ensure that the delivery room is > 25*C [90]. Immediate drying and early skin to skin care by placing the neonate on mother's chest should be ensured [13,48,50–52]. Additionally, caps, plastic wraps, infant radiant warmers, and exothermic mattress should be used whenever necessary and feasible [90–94].

6.5. Delayed cord clamping

Delayed cord clamping is a simple intervention that provides benefits for term [95,96] and preterm neonates [97–100]. In term neonates, delayed cord clamping has been shown to increase the neonatal iron stores and about 50% decrease in the risk for subsequent anemia [95,96]. In preterm neonates, there is a decrease in mortality, anemia, blood transfusion requirement, hemodynamic instability, IVH, and necrotising enterocolitis [97–100]. Delayed cord clamping may improve neurodevelopmental outcomes [101,102]. As delayed cord clamping is an inexpensive and easy to administer intervention, it has been recommended in all neonatal resuscitation guidelines since 2010 [13,15,16,47,48,50].

6.6. Early and continued skin to skin care

Skin to skin care immediately after birth has also been advocated continuously in neonatal resuscitation guidelines for low- and middle-income countries [13,45,48,50–52]. Early skin to skin care immediately after birth promotes better thermoregulation in neonates and significantly decreases the chances of hypothermia [103–105]. Early skin to skin care enhances cardiorespiratory stability and decreases the incidence of hypoglycemia [106,107]. Early skin to skin care decreases the time taken to initiate breastfeeding, increases the breast milk supply, increases the chances of exclusive breastfeeding and breastfeeding duration [106–110]. Early skin to skin care decreases maternal pain due to episiotomy, pain during the third stage of labor and also decreases the duration of the third stage of labor [105,108]. Early skin to skin care increases maternal satisfaction and mother-infant bonding [110]. Skin to skin care continued beyond the immediate delivery period offers important benefits to the neonate including decrease in neonatal mortality and morbidity rates, decrease in rates of serious infection, increasing rates of exclusive breastfeeding, improving neonatal growth, decreasing hospital admission rates, improving maternal satisfaction, improving maternal-infant bonding and improving maternal competence [111–115]. The benefits of neonatal skin to skin care are particularly remarkable for preterm and low birth weight neonates [111,113–115]. Skin to skin care should be given to all neonates following birth. Mothers and other care providers should be encouraged to continue skin to skin care as long as feasible.

7. Future directions

Unattended home deliveries and deliveries that are attended by untrained birth attendants continue to be painfully frequent in low- and middle-income countries [18,36–38,116–118]. Many health care facilities in low- and middle-income countries are poorly equipped and staffed to provide adequate neonatal care [18,119,120]. Serious and sustained efforts are required to fill these life-threatening gaps in neonatal care. Institutional delivery should be promoted wherever feasible. Where home delivery is the only option, it should be made sure that a trained birth attendant is present for every delivery as perinatal mortality can be decreased with adequate training [121]. Several studies have shown that the competence of trained birth attendants decreases over time [122–124] so continued efforts should be made for retraining of traditional birth attendants to ensure optimal competency [123–126]. Individualized neonatal referral and emergency preparedness plans should be crafted for each village/cluster, and health providers should receive training in how to deal with common neonatal emergencies including prompt and safe neonatal transport. Transport networks and transport infrastructure (teams, ambulances, triage helpline) connecting community-level health centers to tertiary health centers should be devised for individual regions. Health promotion and neonatal care education during the antenatal period and post-natal period should be strengthened. As neonatal deaths continue to happen well beyond the immediate post-delivery period [72,73], follow up of

all neonates and a close follow-up of at-risk neonates once or twice during the first week should be ensured. This would also provide an educational opportunity to reinforce components of essential newborn care and early identification of danger signs as well as identify and educate care providers about harmful neonatal care practices. Community-level education about essential newborn care, neonatal care practices, and early identification of neonatal danger signs should be implemented to raise mass awareness.

Last but not least, antenatal care including antenatal screening should be strengthened to identify high risk pregnancies and neonates with congenital anomalies during the antenatal period. Screening for maternal hypertension/pre-eclampsia and diabetes should be conducted. Identification and management of preterm labor is essential. Congenital anomalies contribute to about 11.3% [7,56] of total neonatal mortality. Currently, there seems to be little effort by neonatal health policymakers regarding tackling neonatal mortality burden associated with congenital anomalies. Delayed recognition of congenital anomalies precludes optimal planning and referral of neonates with these conditions.

8. Conclusions

Although remarkable progress has been made in neonatal care in low- and middle-income countries, much remains to be achieved. Low- and middle-income countries continue to contribute disproportionally to neonatal mortality. Simple and inexpensive interventions like prompt and effective basic resuscitation, clean delivery and handwashing by care providers, early and exclusive breastfeeding, essential care for preterm and small babies, early and continued skin to skin care, ensuring normothermia, and delayed cord clamping are critical for improving neonatal outcomes in low- and middle-income countries. Key preventative neonatal care interventions such as mother and family education about essential newborn care, education about danger signs, early follow up of all neonates and closer follow up of at-risk neonates should be ensured. Anticipation and early identification of neonatal illness with a prompt transfer to a higher care center is essential for the survival of sick neonates.

Disclosures

Waldemar A. Carlo is on the Board of Mednax

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