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Map Babies' Brains
Evaluating the location and volume of brain lesions in very premature infants may help predict later problems in their neurodevelopment, suggests new imaging research. A study of 216 preterm neonates with an average gestational age of 28 weeks showed that those with greater white matter injury (WMI) volume in the frontal lobe were 79 times more likely to develop adverse cognitive outcomes by age 18 months, and 64 times more likely to develop adverse motor outcomes, compared with those without such injuries. Greater parietal and temporal lobe volumes also predicted poor motor outcomes but were not significantly associated with cognitive outcomes. “My recommendation is that if you’re looking at scans of babies who are born preterm and see white matter injury, it’s important to consider not only how much injury there is but where the injury is occurring,” principal investigator Steven P Miller, MDCM, head of neurology at the Center for Brain and Mental Health at The Hospital for Sick Children in Toronto, Ontario, Canada, said.

Getinge Unifies its Brands
Getinge has announced that it has unified all its current brands under the single brand of Getinge to better convey its customer offering. As part of this new brand structure, the company has rolled out a new brand identity, which all its products will carry. In line with our ongoing transformation to make our company even more customer-centric, we have taken the next step of unifying all of our brands under the single brand of Getinge. This new brand structure will further strengthen our position as a leading global medtech company. Some of these brands, such as Maquet, will become product family names under the Getinge master brand,” said Raoul Quintero, President of the Americas at Getinge. “As a single-brand company, we will also be better able to convey our full customer offering, which is designed to help healthcare institutions address the challenges they face in today’s ever-changing healthcare environment of expanding healthcare reform initiatives, financial pressures and accelerated hospital consolidation.” As healthcare institutions are being challenged to provide quality care in a leaner, more efficient manner, they are seeking partners who deliver smart, cost-saving solutions that maintain the highest standards in clinical excellence. Getinge has refocused its resources to develop and deliver more innovative healthcare solutions that will address its customers’ most complex healthcare challenges and ultimately improve the daily lives of patients.

Neo Medical Device Helps Save Baby Hippo
It turns out medical devices designed for premature infants can help save other lives too. The Cincinnati Zoo & Botanical Garden staff were flummoxed when having to deal with baby hippopotamus Fiona — who was dehydrated and in desperate need of intravenous fluid. That’s when the Cincinnati’s Children’s Vascular Access Team stepped into action, employing a Neo Magic device manufactured by Neo Medical Inc. “Preemies have very tiny and unstable veins, and even though our vet team was able to get multiple IVs placed, the veins could not sustain the IV and would blow,” said curator of mammals Christina Gorsuch. Fiona weighed 29 pounds when she was born — a healthy hippo typically weighs 55-100 pounds. In dire need of fluids, the VAT team members placed a life-saving Neo Magic IV catheter in her leg. Ultimately, this saved her life. The Neo Magic line of vascular access devices and accessories were designed specifically for neonatal and pediatric patients … until now. “At Neo Medical, we value input from clinicians and focus our efforts on creating more innovative solutions that will address the challenges our customers face.”

In the future. The rapid growth of what was previously known as Getinge Group over the last 25 years, primarily through acquisitions, has resulted in an extensive brand portfolio, including ArjoHuntleigh, Maquet, Lancer, Atrium and others. “In line with our ongoing transformation to make our company even more customer-centric, we have taken the next step of unifying all of our brands under the single brand of Getinge. This new brand structure will further strengthen our position as a leading global medtech company. Some of these brands, such as Maquet, will become product family names under the Getinge master brand,” said Raoul Quintero, President of the Americas at Getinge. “As a single-brand company, we will also be better able to convey our full customer offering, which is designed to help healthcare institutions address the challenges they face in today’s ever-changing healthcare environment of expanding healthcare reform initiatives, financial pressures and accelerated hospital consolidation.” As healthcare institutions are being challenged to provide quality care in a leaner, more efficient manner, they are seeking partners who deliver smart, cost-saving solutions that maintain the highest standards in clinical excellence. Getinge has refocused its resources to develop and deliver more innovative healthcare solutions that will address its customers’ most complex healthcare challenges and ultimately improve the daily lives of patients.
considered in the context of organizational factors, burnout prevalence was positively and significantly associated with average daily admission rates \( (r = 0.53; P < .001) \) and with the number of NICU beds \( (r = 0.55; P < .001) \). Burnout prevalence was also significantly higher in NICU units with the highest vs the lowest occupancy \( (28.1\% \pm 8.1\% \text{ vs } 19.9\% \pm 8.4\%; P = .02) \). Notably, NICUs with 2 or more years of EHR use had significantly higher burnout prevalence than those that did not use EHRs \( (28.3\% \pm 10.1\% \text{ vs } 18.4\% \pm 6.6\%; P = .015) \), independent of the number of licensed beds or average daily admissions, the authors report. “EHR use was associated with higher burnout prevalence, particularly among NICUs with the most long-standing EHR use, suggesting against unfamiliarity and initial inefficiency as primary drivers of any such association,” the authors write. “Beyond the increased time necessary for documentation, reliance on an EHR for health care delivery may limit providers’ experience with interpersonal interactions or direct patient care.”

**Black Babies More At-Risk**

Even as infant mortality rates are declining nationwide, there are some US states where black babies are much more likely to die than white infants, a study suggests. Overall, infant mortality rates decreased 13 percent in the US from 2000 to 2013, the study found. By the end of this period, however, the black infant mortality rate was 11.1 deaths for every 1,000 live births, compared with just 5.1 deaths for every 1,000 white newborns. The rate is calculated based on the number of babies who die before their first birthday. Eliminating this gap would have saved almost 65,000 black babies during the study period, according to lead study author Dr Joedrecka Brown Speights.
of Florida State University College of Medicine in Tallahassee. For the study, researchers used government records to calculate infant mortality rates in 35 states; some states had too few deaths to analyze meaningful differences between the groups of babies. By the end of the study, state-level black infant mortality rates ranged from 6.65 to 13.77 deaths for every 1,000 live births. All states improved infant mortality rates for black babies during the study period, though none achieved equality. The three states with the biggest improvements were Arizona, Iowa and Massachusetts, which reduced infant mortality by at least 30 percent during the study period. Based on the rate of improvement in each state, researchers calculated that 18 states would achieve equal infant mortality rates for black and white babies by 2050.

Researchers also looked at how black babies fared relative to white infants and found wide variation among states. Massachusetts reduced the racial gap in infant mortality by 24 percent during the study period, followed by Tennessee with a 23 percent reduction and Arizona with a 22 percent decline. The gap widened in three states, expanding by less than 1 percent in New Jersey and Illinois and increasing almost 12 percent in Kansas. The leading causes of black infant mortality for newborns are low birth weight, preterm deliveries, birth defects and pregnancy complications. Over the first year of life, the leading causes of death for black babies are birth defects, sudden infant death syndrome or accidental injuries.

Benefit of Iodide Supplementation Questioned
Iodide supplementation of preterm infants born at <31 weeks’ gestation conferred no overall benefit on neurodevelopment at two years in a pragmatic randomized controlled trial conducted in the UK. “Preterm infants are vulnerable to iodide insufficiency and thyroid dysfunction,” Dr Fiona Williams from the University of Dundee and colleagues note in their report on the study. “The link between suboptimal neurodevelopment and the early iodide status of preterm infants is not well known. It is also unknown whether iodide supplementation can confer a benefit to later outcome,” they point out. The team designed their trial to see whether iodide supplementation leads to improved neurodevelopmental outcome in extreme preterm infants at two years of age. “The impetus for this trial was the accumulating evidence from observational studies that hypothyroxinemia is associated with compromised neurodevelopment,” they write. They recruited 1,273 infants born at <31 weeks’ gestation from 21 U.K. neonatal units. Of these, 131 died and neurodevelopmental assessments were available for 498 infants supplemented with iodide 30 mcg/kg started within 42 hours of birth to the equivalent of 34 weeks’ gestational age and 499 placebo-supplemented infants. No adverse consequences were associated with iodide supplementation at 30 mcg/kg per day. The iodide-supplemented group had slightly higher levels of TSH (but not T4 or TBG) than the placebo group, the researchers report. There was no marked difference between iodide and placebo in the primary outcome of neurodevelopmental status at age two measured with the Bayley Scales of Infant Development-III.

Impact of Glucocorticoids Studied
Fetal exposure to repeat doses of glucocorticoids does not adversely affect bone mass of six-to-eight year olds, researchers say. Dr Christopher McKinlay of the University of Auckland, New Zealand says that treatment of women at risk of preterm...
birth with repeat doses of antenatal glucocorticoids reduces neonatal morbidity, but uptake has been limited by concern about long-term adverse effects. For example, animal studies suggest that repeat doses of glucocorticoids may impair fetal calcium uptake and bone mineralization, alter skeletal growth and increase the risk of osteoporosis. In the ACTORDS study, mothers at risk for preterm birth were randomized to a single dose of betamethasone or placebo a week or more after an initial course of the drug, to be repeated weekly while the risk of preterm birth persisted. Altogether, 185 children were assessed: 91 in the repeat betamethasone group and 94 in the placebo group. The mean gestational age at birth in both groups was 31 weeks, with 93% of children born preterm. Mothers had received a median of two doses of study drug, in addition to the prerandomization course of antenatal glucocorticoids. Both groups of children had similar whole-body bone mineral content — a median of 553 g for the repeat betamethasone group and 567 g for placebo. Bone area was also similar, at a median 832 cm² for the repeat betamethasone group and 822 cm² for placebo. There were no differences between the groups in spinal bone mineral content and body segment proportions, and the incidence of fractures was similar, at 13% in the group exposed to repeat betamethasone and 11% in the placebo group (p=0.65).

Higher Risk of Preterm Birth Among Cancer Survivors
Pregnant women who have survived cancer in adolescence or young adulthood have an increased risk of giving birth preterm, researchers have found. Dr Hazel B Nichols and colleagues from the University of North Carolina, Chapel Hill, conducted a case-control cohort study to compare birth outcomes of survivors of adolescent-and-young-adult (AYA) cancer and women without a history of cancer. They used the North Carolina Central Cancer Registry to identify all women diagnosed with incident cancer at ages 15 to 39 from 2000 to 2013 and data extracted from statewide birth certificates on live births occurring between 2000 and 2014. Commonly diagnosed included breast, melanoma/skin carcinoma, non-Hodgkin lymphoma, Hodgkin lymphoma and gynecologic-site groupings. Data extracted from randomly selected statewide birth certificates included birth weight, gestational age, infant sex, mode of delivery, plural birth, and Apgar score. Maternal characteristics included race/ethnicity, parity, smoking during pregnancy, education and marital status. The final analyses included nearly 2,600 births to AYA-cancer survivors and more than 12,900 births to women without a cancer diagnosis.

Mean maternal age was 31.1 years, with 78% of the cancer cohort non-Hispanic white versus 59% of those without the disease. Overall, preterm births (<37 weeks) were significantly more common among cancer survivors (prevalence ratio, 1.52), as were early preterm birth (<34 weeks) and low birth weight (<2500 g). Survivors also had a small but statistically significant increase in Cesarean deliveries.

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need to set the desired CPAP/PEEP. The flow is subsequently adjusted automatically based on the patient condition and potential leaks. This prevents unintended peak pressures and guarantees highly efficient leak compensation. In addition to the standard nCPAP mode, the HAMILTON-C1 neo also features the biphasic nCPAP-PC (pressure controlled) mode. This mode allows you to set two pressure levels as well as the rate and inspiratory time. Its versatility makes the HAMILTON-C1 neo an ideal companion for your smallest patients in various situations such as the delivery room and intensive care unit, as well as during intrahospital transport.

Benefits of Antenatal Steroids
Among mothers at risk for preterm delivery, corticosteroid treatment from as early as 23 weeks of pregnancy leads to a lower rate of death and serious illness for their babies, a new study suggests. Colm P Travers, MD, from the University of Alabama at Birmingham, and colleagues published the study. “Among infants born from 23 to 34 weeks’ gestation, antenatal exposure to corticosteroids compared with no exposure was associated with lower mortality and morbidity at most gestations,” the authors write. “The effect size of exposure to antenatal corticosteroids on mortality seems to be larger in infants born at the lowest gestations.” Clinical practice guidelines currently recommend that women at risk for preterm delivery receive antenatal corticosteroid treatment from 24 to 34 weeks of pregnancy. Guidelines also encourage clinicians to consider extending this treatment recommendation to women from 23 0/7 to 23 6/7 weeks of pregnancy. However, this extension is based on limited data from observational studies and consensus, and the benefits of using corticosteroid treatment during the 23rd week have been less clear. Dr Travers and colleagues therefore aimed to investigate whether exposure to corticosteroids during pregnancy is associated with a lower rate of death among infants at each gestational age at which the therapy is recommended. In their prospective cohort study, the researchers analyzed data collected at 300 neonatal intensive care units in the United States from 2009 to 2013. They included 117,941 infants born between 23 and 34 weeks of gestation, 81,832 of whom were exposed to antenatal corticosteroids. According to the researchers, infants’ exposure to antenatal corticosteroids was associated with a significantly lower rate of death before hospital discharge at each gestational age (29 weeks or younger, 31 weeks, and 33 - 34 weeks) compared with infants without exposure (range of adjusted odds ratios [AOR], 0.32 - 0.55).

Touch Can Help Shape Babies’ Brains
For newborns, skin-to-skin contact with parents and caregivers may help shape how their brains respond to touch, a sense necessary for social and emotional connections, a new study suggests. Plenty of previous research has linked skin-to-skin touch with developmental benefits for both premature and full-term babies, ranging from improved growth and sleep to better motor development. Research has also tied breastfeeding and other forms of supportive touch to less discomfort during from needle sticks and other painful medical procedures. In the current study, researchers tested how 125 premature and full-term infants responded to gentle touch. Overall, the preemies were more likely than the full-term babies to have a reduced response to this contact, the study found. But preemies who had more gentle contact with parents and caregivers had a
stronger response to touch than the preterm infants who didn’t get this type of support. The preterm babies who had more exposure to painful medical procedures also had a reduced response to touch. “Our findings add to our understanding that more exposure to these types of supportive touch can actually impact how the brain processes touch, a sense necessary for learning and social-emotional connections,” said lead study author Dr Nathalie Maitre of Nationwide Children’s Hospital in Columbus, Ohio. “What is surprising is that painful procedures which are known to impact processing of pain in the brain also impact processing of touch, in a negative way,” Maitre said. The preemies in the study were born between 24 and 36 weeks gestation, while the full-term infants arrived between 38 and 42 weeks. They all participated in the touch experiment before they were discharged from the hospital where they were born. Newborn development, especially in the first few months, is heavily shaped by touch and sound, as the visual system is still very immature, Maitre said. Touch is a way for infants to learn about their surroundings and an early way to communicate with their parents. To evaluate how newborns respond to touch, researchers exposed all of the infants in the study to a light puff of air and a “fake” puff of air and measured their brain responses. Researchers chose a puff of air because it does not generate enough pressure to activate any pain receptors, Maitre said. If the infant brain can respond to this touch, babies can also learn how to tell the difference between different textures, for example the difference between their mother’s skin and a hard object, or even their father’s stubby cheek and their sister’s soft one.

Smoking During Pregnancy Tied to Retinal Damage
When women smoke during pregnancy or have underweight babies their children have a greater risk of retinal nerve fiber layer thinning, a Danish study suggests. Thinning of the retinal nerve fiber layer may raise the risk of vision impairment and glaucoma, the researchers note. Previous studies have linked maternal smoking to underweight babies, Hakan Ashina of Rigshospitalet in Copenhagen and colleagues point out. Because low birth weight is also associated with having a thinner retinal nerve fiber layer, smoking could have a direct and indirect effect on the optic nerve and its connections to the retina, they note. They examined data from eye exams on 1,323 children at age 11 or 12 and found both smoking and low birth weight independently associated with thinner retinal nerve fiber. “Smoking for a relatively short time interval during pregnancy can have lifelong consequences to the exposed fetus,” said Dr Christopher Kai-Shun Leung, a researcher at the Chinese University of Hong Kong and author of an editorial accompanying the study. In the study, 80 percent of the mothers didn’t smoke during pregnancy. Another 2 percent of mothers stopped smoking during pregnancy and about 18 percent continued to smoke throughout pregnancy. Roughly 4 percent of their babies were born at a low birth weight. Eye exams for all of the kids found they had an average retinal nerve fiber thickness of 104 micrometers. Children of mothers who smoked during pregnancy had retinal nerve fiber that was typically 5.7 micrometers thinner than in kids whose mothers didn’t smoke at all while pregnant.

Not All Screenings Predict Preemies
Quantitative fetal fibronectin screening and transvaginal cervical length measurement do not accurately predict preterm birth in first-time pregnant women at low risk for the outcome, new data show. In a multisite prospective study designed to
had spontaneous preterm birth before 32 weeks, the authors report. However, on the basis of a cervical length threshold of 25 mm, which is often used in practice, only 35 of 439 women (8.0%) with spontaneous preterm birth before 37 weeks screened positive at visit 2 and 94 of 403 (23.3%) women screened positive at visit 3.

Maternal Obesity May Increase Cerebral Palsy Risks
Among Swedish women, being overweight or obese in early pregnancy is associated with a greater risk of giving birth to a child with cerebral palsy, a new study from Eduardo Villamor, MD, DrPH, from the University of Michigan suggests. “In this nationwide Swedish study, maternal overweight and increasing grades of obesity were associated with increasing rates of cerebral palsy,” the authors write. “The association was restricted to children born at full term and was partly mediated through asphyxia-related neonatal complications.” Despite improvements in perinatal care, an increasing prevalence of cerebral palsy has been reported from 1998 through 2006 among children born at full term. Whereas maternal obesity is a significant risk factor for obstetric complications and asphyxia-related neonatal morbidities, it has been unclear if it is a risk factor for cerebral palsy in the offspring. Dr Villamor and colleagues therefore investigated the relationship between maternal obesity in early pregnancy and risk for cerebral palsy in the offspring, as well as possible mechanisms for any such association. They performed a nationwide retrospective cohort study of 1,423,929 singleton births by using data recorded in the Swedish Medical Birth Register from 1997 through 2011. They also used national registries to follow the children for a cerebral palsy diagnosis through 2012. Overall, 3029 of the children were

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diagnosed with cerebral palsy over a median 7.8 years of follow-up. The authors also found that maternal overweight (body mass index [BMI] of 25 to 29.9) and increasing grades of obesity (BMI 30 or greater) in early pregnancy were associated with increasing rates of cerebral palsy in the offspring. This association was statistically significant only for children born at full term, who accounted for 71% of all children with cerebral palsy, the authors say. Compared with children born to mothers of normal weight, the adjusted hazard ratios (aHRs) for cerebral palsy were 1.22 (95% confidence interval [CI], 1.11 - 1.33) for mothers who were overweight, 1.28 (95% CI, 1.11 - 1.47) for those with grade 1 obesity, 1.54 (95% CI, 1.24 - 1.93) for those with grade 2 obesity, and 2.02 (95% CI, 1.46 - 2.79) for those with grade 3 obesity.

PDA Ligation Does Not Worsen Outcomes
Ligation of a patent ductus arteriosus (PDA) in extremely preterm infants is not associated with increased morbidity or mortality, contrary to earlier reports. “This study is most relevant for the population of extremely preterm infants with persistent hemodynamically significant PDA after failure or contraindications of medical therapy,” Dr Dany E Weisz from Sunnybrook Health Sciences Center in Toronto said. “The results of this study suggest that clinicians should not avoid surgical ligation in extremely preterm infants with persistent large PDA out of fear that the surgery itself is the cause of increased morbidity or neurodevelopmental impairment.” “For the past decade, multiple large observational studies have associated PDA ligation with neurodevelopmental impairment in preterm infants,” she explained. “In the absence of data from randomized controlled trials, the publication of these studies has led to a reduction in the number of infants treated with surgical PDA ligation.” None of the earlier observational studies, however, adjusted for such confounders as survival bias and major neonatal morbidities arising before exposure to ligation. Dr Weisz’s team evaluated the association of PDA ligation with neonatal and neurodevelopmental outcomes after accounting for antenatal, perinatal, and postnatal confounders in their retrospective study of 754 preterm infants with hemodynamically significant PDA. About a quarter (184) of the infants were treated with surgical ligation; the rest received medical treatment only.

“Safe” Insecticides Not So Safe
Prenatal and childhood exposure to pyrethroid insecticides may adversely affect neurobehavioral development in children up to age 6 years, new research shows. A group of French researchers led by Jean-François Viel, MD, PhD, and Prof Andreas G Franke, MD, both of the University of Mainz, Germany, investigated the associations between exposure to pyrethroid insecticides and behavioral skills in 6-year-olds. Pyrethroids are synthetic chemicals that are widely used in agricultural settings. They are also found in an array of products, including mosquito repellents and treatments for head lice, scabies, and fleas. The general population is exposed to pyrethroids via diet and indoor residential uses (ie, through ingestion and dermal and inhalational pathways). Using a longitudinal design, the researchers assessed pyrethroid exposure in children prenatally and at age 6 years. They found that in 6-year-old children, increased prenatal concentrations of the cis-dimethylcyclopropane carbolic acid metabolite were associated with internalizing difficulties. A positive association was also found between the presence of childhood 3-phenoxybenzoic acid (3-PBA) and externalizing difficulties.

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Low Birthweight a Risk Factor For Adult Psychiatric Disorders
Low birthweight, both term and preterm, is a substantial risk factor for adult psychiatric morbidity and lower overall functioning, according to new research. “This underscores the need for long-term follow-up of low-birthweight survivors through adolescence and adulthood, as well as continued promotion of healthy pregnancies and improvement of perinatal treatment,” first author Dr Astrid Lærum of Norwegian University of Science and Technology in Trondheim said. In a prospective cohort study, the study team examined psychiatric morbidity and overall functioning in 44 adults born preterm with very low birthweight (VLBW, <= 1500 g), 64 adults born small for gestational age at term (term SGA, <10th percentile) and 81 term born control adults (>= 10th percentile). In the control group, 11 (14%) adults had a psychiatric disorder, of whom seven had anxiety disorders and five had substance use disorders. None had mood disorders.

From adolescence to adulthood, the term SGA group had a “marked increase” in the estimated probability of psychiatric disorders from 9% to 39%, the authors report. At age 26, psychiatric disorders were significantly more prevalent in the VLBW group (16 of 44, 36%), including anxiety (27%), mood (18%), and somatoform disorders (9%). Four of the eight VLBW adults with mood disorders had bipolar disorder and all of those with somatoform disorders had body dysmorphic disorder.

Influenza Antivirals Safe During Pregnancy
Using neuraminidase inhibitors during pregnancy is not associated with adverse neonatal outcomes or congenital malformations, researchers have found. “Our study is the largest to date on the use of neuraminidase inhibitors during pregnancy and the association with adverse pregnancy outcomes,” Dr Sophie Graner from Karolinska Institutet in Stockholm, Sweden, said. “We were relieved but perhaps not surprised to find that our results confirmed and expanded on the knowledge from previously published studies that there seems to be no increased risks with exposure during fetal life (for) stillbirth, neonatal

Levothyroxine Benefits Unclear
Treating subclinical hypothyroidism and hypothyroxinemia during pregnancy does not significantly improve cognitive outcomes in offspring compared with no treatment, according to new data. “On the basis of a comprehensive battery of tests through 5 years of age, we did not find significantly better neurodevelopmental outcomes in children whose mothers had received thyroxine treatment for subclinical hypothyroidism or hypothyroxinemia during pregnancy than in children whose mothers did not receive such treatment,” write Brian Casey, MD, of the University of Texas Southwestern Medical Center, and colleagues. The study also found that receiving levothyroxine did not significantly improve pregnancy or neonatal outcomes. Whether to treat subclinical hypothyroidism during pregnancy is a matter of debate. The American College of Obstetricians and Gynecologists (ACOG) says a recommendation for routine screening is premature due to lack of clinical trials demonstrating improved outcomes with levothyroxine treatment.
Safe Sleep NICU Program Increases Parents’ Awareness

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Janice Preuit BSN, RNC-NIC, at St Luke’s Magic Valley.

Neonatal Intensive Care: How did you learn about the “HALO Safer Way to Sleep” program and when did you introduce it in the NICU?
Janice Preuit: We heard about the “Safer Way to Sleep” program from SL Neonatology group; we introduced it to our NICU last Summer. There have been multiple avenues from conferences to educational offerings that have supported the safe sleep practices.

NIC: Did the introduction of the program provide you with an opportunity to review safe sleep techniques with the nursing staff? Were they excited about the program?
JP: Yes, it opened the discussion regarding safe sleep techniques and when to start practicing back to sleep with our preterm population. The staff were excited to learn more. It also assisted conversation for planning for discharge.

NIC: How did you review safe sleep with parents before the program was in place?
JP: Pamphlets were distributed to the parents and the nursing staff would discuss the importance of placing baby on its back to sleep, keeping toys or pillows out of the crib, not cobedding with their baby and other safe sleep practices.

NIC: How has the program and use of the HALO SleepSack Swaddle changed the way the parents handle their baby in the NICU? Were they more comfortable with their baby in the NICU?
JP: Parents and staff have commented on how nice and soft the HALO SleepSacks are and how much easier it is to swaddle the babies using HALO SleepSack. It has become a standard practice of the unit.

NIC: Did you get the sense that parents were gaining the confidence to take care of the baby at home because the safe sleep techniques you were using in the NICU could easily be implemented at home?
JP: The parents have verbalized their appreciation of the safe sleep education. This education becomes an awareness for the parents and they are very receptive to the information.

NIC: Has the NICU experience of the parent changed as a result of the program?
JP: There is more awareness about safe sleep practices.

NIC: Are you a Cribs 4 Kids Safe Sleep Certified hospital?
JP: We are not at this time and plan to investigate how we can become a Safe Sleep Certified hospital through Cribs 4 Kids.

Janice Preuit BSN, RNC-NIC is a Unit Based Clinical Educator, NICU and Women and Children at St Luke’s Magic Valley. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.
The Benefits of an Exclusive Human Milk-based Diet for Very Low Birth Weight Babies

In this feature, Neonatal Intensive Care interviews clinicians and healthcare providers about the actual application of specific products and therapies. This interview is with Amy B. Hair, MD, at Texas Children's Hospital.

Neonatal Intensive Care: You have done an extensive amount of research and have numerous publications focused on neonatal nutrition, specifically growth and the use of human milk in very low birth weight (VLBW) infants. For our readers, can you please define an exclusive human milk-based diet (EHMD)?

Amy B. Hair: An EHMD is a special diet designed for VLBW infants. It is mother's own milk, donor human milk, and fortified with a donor human milk-derived fortifier. Babies born < 1500 gram birth weight (VLBW) need additional protein and minerals to optimize growth and help build strong bones. Extremely premature babies are born very early and do not get the full transfer of nutrients from the placenta, which usually occurs in the 3rd trimester of pregnancy.

NIC: How do you define and measure growth for VLBW infants on an EHMD?

AH: Appropriate growth is defined as 15 g/kg/day weight gain velocity or growth averaged over 7 days with length gain of 1 cm/week. We also measure head circumference and monitor to make sure the baby’s head is growing at least 1 cm/week. All 3 measurements are plotted weekly on a premature infant growth curve and we track the “curve” or percentile of the growth curve that the babies are growing on. We want to make sure babies are growing in all 3 parameters. Weight is usually plotted on this special growth curve daily. The most recently updated Fenton curves for premature infants are based on national birth data as well as international data and were published by Fenton et al in 2013. The Fenton 2013 growth curves offer the best estimate of postnatal growth for infants, which is supposed to match intrauterine growth rates (if babies weren’t born yet).

NIC: Are there other factors that clinicians should be aware of that impact growth for VLBW?

AH: Growth is impacted by early parenteral or intravenous nutrition prior to initiation of feeds. It is important to give adequate protein in parenteral IV nutrition early on once a premature infant is born (VLBW infant). These infants are born with an immediate protein deficiency because they are born so early. Then, once enteral feeds are started, it is important to start fortification of feeds early to start providing adequate protein enterally. Premature infants are born with a protein deficiency and need adequate early nutrition so they don’t get behind in growth. Also, medical factors may limit growth such as electrolyte abnormalities, anemia, steroids, diuretics, and inadequate calories due to fluid restriction.

NIC: In one study, you examined the impact of feeding tubes and delivery of nutrition. What was your finding?

AH: We found that breast milk fat (mother’s milk and donor human milk fat) stick to the walls of the inside of the feeding tubes. This leads to inadequate delivery of breast milk fat which is high in calories. If fat is not optimally delivered, these tiny premature infants will not receive the full calories they need to grow. We found that a syringe tip “up” position provides the best fat delivery. We are conducting further research to investigate which materials of tubing are preferred to deliver the most fat to babies.

NIC: Can you elaborate on how an EHMD provides a high protein diet?

AH: An EHMD allows for the delivery of high protein in enteral feeds. Because the fortifier is from donor human milk, the babies are receiving an all human milk protein diet. No cow protein. The fortifiers whether they are 24 kcal/oz or 30 kcal/oz contain the same osmolarity so they are gentle on the intestines and well tolerated by the babies. With the wide variety of fortifiers available with an EHMD, you can provide optimal protein even if you are limited in the amount of volume or milk you can feed a baby. Because the fortifiers are gentle on the intestines, studies have shown that you can increase calories and protein early in the diet and have theoretically less of a protein deficiency once the infant is on full enteral feeds.

NIC: There is evidence suggesting high variability in mom’s milk. In your opinion, how does that impact growth?

AH: Studies show that mom’s milk varies in fat content which effects overall energy content of the milk. We always want to use mom’s milk first because of the special immune factors and prebiotics but we need to be aware that the milk may be low in fat. This is important when you are calculating the calories a baby is receiving because if the milk is low in fat, the baby may not be receiving adequate calories and nutrition. You can adjust this low fat milk with the use of donor human milk cream or fat which has been shown in studies to improve weight gain and length growth. The bottom line is that babies may not be receiving the full amount of calories we calculate due to fat loss in the feeding

Amy B. Hair, MD is Assistant Professor, Program Director of Neonatal Nutrition, Program Director of NICU Intestinal Rehab Team, Section of Neonatology, Department of Pediatrics, Baylor College of Medicine at Texas Children's Hospital. If you would like to participate in this feature, as a company or healthcare provider, please contact Steve Goldstein at s.gold4@verizon.net.
requiring surgery. This has not changed over the past 8 years. Now it is consistently 2-3 percent with rare cases of NEC necrotizing enterocolitis rate was 16% before we started an
less central venous catheter line days. We have also seen
aH:
We have seen a decline in TPN or IV nutrition days and
your feeding approach that you can share with our readers?
nic:
Have you seen other favorable outcomes associated with
earlier you can provide enteral protein, the better you can deliver
at 60 ml/kg/day, studies would suggest that it is safe (because
thousand premature infants with this diet. While we fortify early
an EHMD at Texas Children’s since 2009 and have fed over a
decide what will work in their population. We have been using
protocols from units that successfully fortify feeds early and then
aH:
you recommend?
most hospitals are hesitant to follow, what would
much earlier. Some hospitals are hesitant to follow, what would
Aspirin May Curb Risks
Aspirin may reduce the risk of spontaneous preterm birth
in pregnant women at risk for preeclampsia, according to a
new systematic review and meta-analysis. “Low-dose aspirin
might be an effective treatment in pregnancy to prevent
spontaneous preterm birth, one of the major problems in
modern day obstetrics,” senior author Dr Martijn Oudijk of
the Academic Medical Center in Amsterdam, the Netherlands,
said. “While there have been suggestions of an effect of aspirin
on spontaneous preterm birth from translational research and
smaller studies, it was important to do this study to obtain more
knowledge on the effect of aspirin and to have a sound base
investigate this treatment for other indications to improve
pregnancy outcome,” he said. Dr Oudijk and colleagues drew
on data from a meta-analysis of studies evaluating the effect of
antiplaeterles to reduce preeclampsia (the Perinatal Antiplatelet
Review of International Studies Individual Participant Data).
They analyzed results from more than 27,000 women who had
participated in 17 randomized trials, 15 of which compared
low-dose aspirin with placebo/no treatment. In two small trials,
some women received aspirin in combination with dipyridamole
or dipyridamole alone. The authors investigated spontaneous
birth before 37 weeks, before 34 weeks, and before 28 weeks of
gestation. Women who received antiplatelets were at lower risk
of having a spontaneous birth before 37 weeks (relative risk,
0.93; 95% confidence interval, 0.86 to 0.996) and before 34 weeks
(OR, 0.86; 95% CI, 0.76 to 0.99) than were women on placebo/
no treatment. The relative risk of having a spontaneous preterm
birth prior to 37 weeks of gestation was 0.83 (95% CI, 0.73 to
0.95) for women who had previously been pregnant and 0.98
(95% CI, 0.89 to 1.09) for those pregnant for the first time.

Treatment Option for Opioid-Addicted Infants
With US birthrates of infants exposed in the womb to heroin
and other opioids soaring, physicians are stepping up research
into the best treatment methods. Because the babies became
dependent on the drugs their mothers were taking, doctors often
give them medication to ease the painful withdrawal symptoms
they undergo after birth. Typically doctors administer morphine.
A new study in the New England Journal of Medicine shows
that a different drug, buprenorphine—a medication used to
curb opioid cravings in adult addicts—might actually be a better
Continued on page 20...
Reducing Loss of Prolacta Fortified Human Breast Milk in Enteral Delivery

Windí Bowman, BA; Ty Bourquin, BS; Lili Cruchelow, BSN; Melinda Smith, MS; RAC; CBA

This case study was taken at a hospital that is among the largest purchasers of Prolacta in the United States. The Milk Preparation Technicians, Nurse Manager, and Educator have expressed concerns about Prolacta loss throughout milk preparation, storage, and delivery of Prolacta fortified HBM. Approximately 10 mL of Prolacta was lost for every 30 mL during the preparation and feeding processes. This represented a significant nutrition loss for the baby and a great financial impact to the hospital, since on average, the fortifier costs $6.25/mL.

Observations Before NeoMed Conversion
• 100 bed, Level III NICU using a competitor's enteral delivery systems to deliver nutrition to NICU babies by both pump and gravity feeds.
• Nurses reported that approximately 80% of the feeds for this NICU are via pump, and approximately 20% are via gravity.
• This NICU uses Medfusion 3500, Baxter AS50, and BBraun syringe pumps.
• For very-low-birthweight infants, the Neonatologist typically fortifies using Prolacta 4, 6, and Cream HBM.

Observations After NeoMed Conversion
• After a two-week trial of NeoMed products, the hospital converted to NeoMed’s complete Enteral Safety Delivery System including Transfer Lids, Straws, Syringes, Feeding Tubes, and Extension Sets. They also standardized pump delivery with NeoMed Medfusion 3500 Enteral Only pumps.
• The hospital also decided to change their extension set protocols, changing extension sets with every feed (4 hours) instead of once every 24 hours.
• The hospital believes that a full conversion to NeoMed will result in reduced process volume loss of Prolacta HBM Fortifier, more calories and fats delivered to their babies, better compliance with ADA Guidelines and Joint Commission Best Practices, and greater nursing satisfaction.

Volume Loss Observations Before NeoMed Conversion
• Clinical staff reported ongoing issues with tip caps falling off of the current catheter-style syringes, causing leaking into the transport bags before nurses could initiate delivery. Milk preparation added volume to the syringe to compensate for this expected loss.
• Nurses at bedside reported unexpected spray exposure from current catheter style syringes when tip caps were removed. Some competitive syringe sizes did not have a tactile stop to signal plunger removal, and nurses sometimes pulled the plunger out, spilling Prolacta and HBM during preparation and at bedside. Manpower needs are impacted while exposed nurses go to the ER, receive an eye flush, and take blood tests to ensure nothing has been contracted from the HBM.
• The NICU has a dedicated milk preparation room for Prolacta. Nutrition is pulled up into syringes in this room for all patients receiving Prolacta or any variation. The Prolacta is poured into a medicine cup, then a syringe is placed directly into the Prolacta for filling. Afterwards, the tip of the syringe is wiped clean and the tip cap is attached, then the syringe is bagged for refrigeration until needed.
• The ISO 7886-1 standard defines how much dead space is acceptable per syringe size. Catheter style syringes have larger tip volumes that exceed that maximum allowable dead space, regardless of syringe size (Figure 1).

Windí Bowman holds a Bachelors of Business Administration from the University of Alabama and she has a background in nutritional delivery product research, development, and launch for the neonatal market. She began her career in sales over 20 years ago working specifically with Labor and Delivery and Neonatal Intensive Care medical devices. Windí started with NeoMed in May of 2014 as a Territory Manager and is now a Regional Director of Sales.
After NeoMed Conversion
• NeoMed's plugged tip caps are designed to help reduce failure and leakage into storage bags.
• NeoMed syringe tips have less dead space and therefore should not waste as much nutrition as the competitive product.
• The ADA Guidelines recommends use of a straw or transfer lid during milk preparation to enhance aseptic techniques.
• This should reduce Prolacta HBM Fortifier and HBM loss by eliminating waste caused when nurses must wipe down the syringe tip after transferring into a cup and placing the syringe tip directly into the nutrition.

Extension Set Observations
Before NeoMed Conversion
• Extension sets were typically changed once daily.
• Separation was also reported at the extension set/syringe connection site, causing loss. This was likely caused by a combination of hub stretching due to larger catheter style syringe tips and higher fat content of fortifiers.
• Priming volume (2.3 mL) in competitive extension sets was flagged as a major concern, so the extension sets were changed at 24-hour intervals in an effort to reduce loss. Nurses observed that residue in the extension sets between feeds thickened over time.
• Buildup of HBM and thick medications can compromise connections.

After NeoMed Conversion
• NeoMed extension sets being used have 22% less priming volume than the competitor (1.8 versus 2.3 mL) to help reduce loss of costly fortified HBM.
• NeoMed recommended that extension sets should be changed every 4 hours, per the ADA Guidelines. This should help minimize buildup and help mitigate bacterial colonization. The Nurse Manager was encouraged to speak with other facilities about their extension set protocols to validate our recommendation.1
• Changing extension sets every 4 hours (per ADA) should reduce disconnections and/or leaking at the connection site.

Feeding Tube Observations
Before NeoMed Conversion
• Feeding tubes were typically changed every 7-10 days.
• Nurses reported clogged feeding tubes and extension sets, and attributed this to the viscosity of thick medications introduced through the bifurcated extension set.
• Feeding tubes are sometimes observed to have residue between the last side port and the distal tip.

After NeoMed Conversion
• Open distal tips in NeoMed's polyurethane and silicone feeding tubes help eliminate accumulation and consequently, help mitigate concern for possible breast milk colonization and bacterial growth.2

Gravity Feed Observations
Before NeoMed Conversion
• Gravity feeds were observed being delivered using an “open” syringe hanging at the bedside with the plunger removed. Leaking was occasionally noted between the feeding tube and syringe connection site.

After NeoMed Conversion
• Gravity feeds can be administered using more closed and aseptic techniques with NeoMed’s GravityPro. Large bore
extension sets used with a gravity feed may help administer thick nutrition into smaller feeding tubes more easily.

**Pump Feed Observations Before NeoMed Conversion**

- Medfusion pumps were tilted in a way that might void the warranty if there is leakage from the back of the syringe.
- Baxter pumps were oriented syringe-tip-down, so lipids were delivered last and sometimes left in the tubing. BBraun pumps delivered horizontally, but center-tip syringes delivered lipids last if there was phase separation.
- Some pumps observed for enteral feeding were not expressly labeled or color coordinated for dedicated enteral-only feeds.

**After NeoMed Conversion**

- NeoMed recommended that the NICU use dedicated Medfusion 3500 pumps to standardize enteral delivery. These should be labeled for enteral use only and have colored faceplates.²
- Using NeoMed offset tip syringes, pumps can be positioned as the manual recommends (see warranty information). NeoMed's offset tip syringes are designed to deliver lipids first, helping maximize lipid delivery.⁴

**Conclusion**

Since converting to NeoMed's Enteral Safety System the NICU and its staff have observed:

- A reduction in the purchase volume and use of Human Milk Fortifiers
- A reduction in the number of patients with growth restrictions
- Virtual elimination of spray exposure of nutrition that occurs during removal of tip caps and while disengaging syringes from sets
- No HBM volume loss reported due to failing tip caps
- No HBM volume loss resulting from failing connections between sets and syringes
- Elimination of material accumulated at the distal tip of feeding tubes
- Over-filling syringes no longer needed to compensate for expected tip cap failure and syringe tip priming volume loss
- A reduction in reported cases of occluded or clogged enteral systems
- Clinical staff reports an improvement in operation efficiencies

**References**


**High Frequency Ventilator Unveiled**

Bunnell Incorporated has announced the upcoming release of the new LifePulse High Frequency Ventilator — Model 204! Since 1988, the Life Pulse HFJV has been used for treating premature babies in acute respiratory failure in hospitals in the US and Canada. Bunnell continues a tradition of providing proven, unique High-Frequency Jet Ventilation technology in the new Model 204 LifePulse for the treatment of critically ill infants with ventilator-induced lung injuries. The new LifePulse, also known as the “Jet” ventilator, features many upgrades and benefits. More information can be found at www.bunl.com. The Model 204 LifePulse will be available for distribution beginning in September. Health Canada approval is pending. As a committed partner in effective and quality healthcare, Bunnell offers free trials, training and education, and industry-leading customer support including 24/7-hotline support at 800-800-4358.
Steps to Optimal Care: Use of Barcoding, Milk Technicians, and Centralized Milk Preparation for a Better NICU

Bri Ziganti of Paragon Data Systems

Abstract
Hospitalized preemies require attentive, precise care. Unfortunately, each nurse’s attention must be split between several different tasks and patients, leaving them vulnerable to breastmilk misappropriation. Gray et al found that NICU patients are already at a higher, more frequent risk for misidentification errors than other hospitalized patient groups when they have similar surnames or MRNs. Factor in multiple bottles of human milk being prepared and stored for each patient, and the likelihood for error rises.

Implementing a barcode validation and tracking system is a smart way to eliminate many of the errors from manual data entry. However, a barcoding system is only the first step. Implementing a centralized milk preparation lab and creating a milk technician role dedicated to managing NICU inventory and preparing feeds will save a hospital money, time, and product. Most importantly, the additional efficiency allows nurses to focus on providing direct, hands-on care to their patients, improving patient safety and satisfaction.

Currently, many hospitals ask their nursing staff to juggle patient care and the delicate process of milk preparation at the same time. Besides the risk of misidentification and giving the wrong milk to the wrong child, mishandled feedings could become contaminated, causing life-threatening infections to a vulnerable preemie, or transmit viruses such as HIV, Hepatitis B, or Cytomegalovirus.

Even simple mathematical errors can result in fortification mistakes, which can harm the baby or delay recovery.

Additionally, parents may experience unnecessary stress, anxiety, and less confidence in the NICU’s competency if they learn their child was given the wrong feed.

To combat this, hospitals have developed extensive safety protocols. The administration of human fluids like blood and breastmilk typically require a two-person “double check,” where a staff member will ask another qualified employee to confirm that the patient name and medical record number on the fluid product matches the same information on the patient’s wristband, before dispensing the treatment or feed.

This failsafe procedure is cumbersome, requires a greater number of staff or disruptions to workflow, and still relies on human oversight.

To truly eliminate the risk of human error, many hospitals have begun to replace the manual double check protocol with an automated process.

Review of Literature
A study performed at the Children’s Hospital of Orange County in 2013 confirmed that using a barcoded patient identification and breastmilk labeling and inventory system increased efficiency and safety by allowing for automated confirmation of identity and milk expiration. Three timing studies were conducted to gauge the effectiveness of the system as a double check method and determine whether barcoding decreased time spent prepping feeds.

Three data sets were collected: one before barcode scanning was implemented, one three weeks after system implementation, and one three months after implementation. The data considered included the total time per day spent on the four primary categories of breastmilk handling: updating and reviewing EMR orders, receiving and storing expressed breastmilk from mothers, thawing specific milk volumes for batch preparation, and finally, prepping individual feeds for each patient. The study then compared the average time each duty would usually take a nurse to perform manually versus the average time each duty took using the barcoded system.

Timing Results
Barcoded breastmilk tracking and validation produced a statically significant reduction in the time needed to manually handle breastmilk and perform other administrative tasks such as the two-nurse check above. The average time saved was approximately one hour per day, which was able to be reallocated to hands-on patient care.

Scanning also reduced staffing hours from two dietetic technicians on all shifts to one technician for all but peak times, eliminating 20 hours of shifts per week. This resulted in a decreased annual labor cost of $30,000.00 in salary and benefits.

The barcoding system was able to decrease the amount of time (and therefore, money), spent on nursing activities as well, as RNs did not have to find and interrupt another RN to perform...
The Next Step Towards Patient Safety and Efficiency in the NICU: Implementing Milk Technicians and Centralized Human Milk Prep

**Improvements from Implementing a Milk Technician Role**

Once a NICU has the means to track and validate their milk inventory more accurately, the next step to safer care is eliminating the need for nurses to prepare feeds at all. A busier nurse is more likely to commit an error than a nurse who can focus on their patient.5

Not all hospitals have the space or funding for a separate milk lab. However, real improvements to both inventory quality and safety as well as time spent on direct patient care can be reached by outsourcing feed preparation and inventory maintenance to milk technicians.

**Review of Literature**

Boston Children’s Hospital implemented a milk technician role in 2011 after determining that their feed practices needed to improve. In reviewing SERS reports from January 2005 to April of 2009, they found that there were 16 instances of feeding errors from patient misidentification, improper fortification, or improper milk storage5. NICU staff were performing more than 100 measurements per day to prep feeds, and were preparing more than one feed at a time, greatly increasing each nurse’s workload, and therefore, the chance for error. Each breastmilk feed took between 5 to 10 minutes to prepare, a process which had to be repeated a minimum of 3 to 4 times per day.

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**Figure 1.** Steele, et al, 2015.

### TOTAL TIME SPENT PER DAY ON BREASTMILK HANDLING BEFORE AND AFTER BARCODE TRACKING

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<tr>
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<tr>
<td>Updating Orders</td>
<td>1.3</td>
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<tr>
<td>Receiving/Storing</td>
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<td>0.8</td>
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<td>Thawing</td>
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<td>0.51</td>
<td>0.46</td>
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<tr>
<td>Preparation</td>
<td>3.9</td>
<td>3.3</td>
<td>3.4</td>
</tr>
<tr>
<td>Total Time</td>
<td>6.19</td>
<td>5.15</td>
<td>5.31</td>
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Daily total centralized breast milk preparation time and time for each duty category (displayed in hours). * Denotes statistical significance (P<0.05). (Steele, et al, 2015).
The Next Step Towards Patient Safety and Efficiency in the NICU: Implementing Milk Technicians and Centralized Human Milk Prep

BOSTON CHILDREN’S NURSE SURVEY RESPONSES ON EFFECTIVENESS OF MILK TECHNICIANS

Table 1. Staff survey responses on the effectiveness of milk preparation by milk technicians. Yes Response (N = 120), % (Barbas, 2013).

<table>
<thead>
<tr>
<th>QUESTION</th>
<th>YES RESPONSES</th>
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<tr>
<td>Does the preparation of feeds by the mother’s milk technician save you time?</td>
<td>89.60</td>
</tr>
<tr>
<td>Do you feel confident that the breast milk is prepared accurately according to nutrition orders?</td>
<td>91.64</td>
</tr>
<tr>
<td>Do you feel confident that the breast milk is prepared using a sanitary technique?</td>
<td>92.76</td>
</tr>
<tr>
<td>Was the feeding clearly labeled and easy to understand?</td>
<td>100.00</td>
</tr>
<tr>
<td>Have you had to call the mother’s milk technician to communicate order changes or other information?</td>
<td>58.19</td>
</tr>
<tr>
<td>If yes, was the mother’s milk technician responsive to your needs?</td>
<td>84.52</td>
</tr>
<tr>
<td>If no, do you know how to contact the mother’s milk technician when necessary?</td>
<td>64.70</td>
</tr>
<tr>
<td>Do you feel the preparation of breast milk feedings by the mother’s milk technician improves the safety of breast milk administration?</td>
<td>85.12</td>
</tr>
</tbody>
</table>

Figure 2. Barbas, 2013.

Decreasing the margin of error meant decreasing the amount of manual steps needed to feed a child, and, if possible, removing that responsibility from the nursing staff entirely. They determined that 60% of the steps to prepare a fortified feed could be eliminated if a trained technician prepared the milk instead of a nurse.5

Milk technicians were trained to use the hospital’s barcoding system to scan and record inventory. They were educated on breast anatomy and milk production, breastmilk fortifiers, and centrifuge usage. They also received training that met with standard food safety and infection control procedures as well as the American Dietetic Association breastmilk preparation guidelines.

Once trained, the technicians were tasked with maintaining NICU inventory, measuring creatinine of modified milk and milk fortifiers, and finally, preparing and labeling individual feeds for use in the NICU. Nurses were no longer required to leave their patients’ bedsides to manage nutrition.

Timing Results
Staff nurses were surveyed anonymously six months after the milk technician role was fulfilled. 90% of respondents said they felt the milk technicians saved them time. 92% felt confident that the breastmilk was prepared accurately. 85% agreed that milk technicians improve the safety of expressed breastmilk feed administration.5 Overall, the milk technician role allows nurses to spend more time taking care of patients without reducing feed quality.

Increased Results from Implementing a Centralized Prep Lab
Though the work of milk technicians alone increases accuracy and the amount of time RNs can spend with their patients, NICUs can improve care even more drastically by investing in a centralized milk preparation lab.

Before the Human Milk Lab at The Children’s Hospital of Colorado opened in 2007, the NICU relied on decentralized milk storage and preparation by their nursing staff. An extensive evaluation found that their existing workflow was inefficient, overwhelming, and far more likely to allow for contamination. By implementing a barcoding inventory and validation system as well as a centralized milk preparation and storage lab, this hospital was able to ensure that the right milk was delivered at the right time to the right patient, with the right additives.6

Timing Results
Nurses were able to spend more time verifying and administering feeds and less time prepping and retrieving milk or formula, minimizing the time they were away from their patients.

At Children’s Colorado, the milk lab also served as a dropoff point for parents to deliver expressed breastmilk to the NICU, pick up new bottles and labels, and request updates on their current inventory.5 This provides a natural “barrier” that makes
it less likely nurses will be interrupted by parents for unrelated administrative tasks, allowing the RNs to focus on direct patient care and speaking with parents who have questions or concerns about their child’s treatment.

Maximizing Milk Safety and Quality
Before Children’s Colorado implemented their milk lab, their milk thawing and warming procedures were inconsistent; in fact, 77% of the time milk was outside the temperature range recommended by the CDC and the Academy of Breastfeeding Medicine.5,7,8,9

The areas where feeds were prepared were not consistently tested to ensure aseptic preparation. Perhaps worst of all, because the nurses were distracted or busy with other tasks, fortified milk wasn’t routinely double checked, meaning misfeeds and contamination could easily slip through the standard safeguards.4

Finally, nurses at both Children’s Colorado and Boston Children’s did not typically wear the same level of PPE as milk technicians do when they are preparing feeds at the bedside. In a milk lab, most technicians always wear gloves, surgical caps, and even masks when preparing bottles or fortifications, providing a more sterile environment.

Contamination Elimination Results
At Children’s of Orange County, Steele et al. found that ready-to-feed formulas prepared at the patient’s bedside by nursing staff were 24 times more likely to be contaminated than feeds prepared by technicians in a centralized milk prep room.2 In addition, powdered formulas were 14 times more likely to be contaminated than ready-to-feed formulas.2 This study suggests that NICUs that use centralized milk prep rooms will see a significant decrease in feed contamination.

Other Benefits of Milk Technicians
Cost Savings
Because milk technicians are not required to have the same level of education as RNs or other clinical staff, labor expenses could be reduced. According to the latest U.S. Bureau of Labor Statistics Occupational Employment and Wages Report, the average hourly wage of a RN in the United States is $34.14.10 The Bureau of Labor Statistics doesn’t have salary information for milk technicians, but the average wage of a similar occupation, a nursing assistant, is $13.40 an hour. Additionally, various hospitals with Level III NICUs have advertised milk technician jobs between $11.50 - $13.50 per hour in 2016. This means that employing more milk technicians instead of more RNs can cut a NICU’s labor costs in half.

Reduced Waste
Roles dedicated to maintaining clean, organized refrigerators and freezers prevents breastmilk from being wasted through early expiration, improper storage, or unnecessary preparation when the patient is NPO.5

Consistency
The nursing staff at Boston Children’s felt that standardization of the fortification process kept the feeds far more consistent, helped avoid adverse reactions to unnecessary feed variation, and allowed their patients to adjust to recommended changes in calorie intake.5 In hospitals around the country, inconsistent management and distribution of inventory have resulted in misappropriation, risk of infection, and family dissatisfaction.5

Keeping care consistent by appointing specific employees to focus on feed preparation, setting clear policies for milk management, and employing risk reduction strategies leads to better outcomes.5, 11

Brand Reputation
Increased accuracy and accountability ensures compliance and avoids causing mistrust between parents of preemies and the hospital.5 Parents who experienced the stress of a misfeed may be motivated to file a lawsuit or defame the hospital in the media.5 Negative publicity can cause many thousands of dollars of damage to a brand and demoralize staff. Keeping patient safety at the forefront of operations allows for a better interaction between parents and the NICU.
CLINICAL PROTOCOL FOR STORAGE DURATION OF FRESH HUMAN MILK

<table>
<thead>
<tr>
<th>LOCATION</th>
<th>TEMPERATURE</th>
<th>DURATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>COUNTERTOP OR TABLE</td>
<td>Room temperature (up to 77° F)</td>
<td>6 - 8 hours</td>
</tr>
<tr>
<td>INSULATED COOLER BAG</td>
<td>5° F - 39° F</td>
<td>24 hours</td>
</tr>
<tr>
<td>REFRIGERATOR</td>
<td>39° F</td>
<td>5 days</td>
</tr>
<tr>
<td>FREEZER:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Freezer compartment of a refrigerator</td>
<td>5° F</td>
<td>2 weeks</td>
</tr>
<tr>
<td>• Freezer compartment of a refrigerator with separate doors</td>
<td>0° F</td>
<td>3 - 6 months</td>
</tr>
<tr>
<td>• Chest or upright deep freezer</td>
<td>-4° F</td>
<td>6 - 12 months</td>
</tr>
</tbody>
</table>

Conclusion
In summary, implementing automated barcode verification practices, milk technicians, and a centralized milk preparation lab can significantly improve workflow, feed accuracy, and patient safety, reducing waste of time, milk, and money. Eliminating the need for a two-nurse check through automated milk validation is the first step to providing safer care without increasing staffing hours or taking time away from attending patients. However, there are other strategies NICUs should use to exceed these original safety and efficiency goals. Centralizing the storage and processing of human milk feeds with dedicated space and staff provides statistically significant improvements to patient care.

Unlike refrigerators contained within the NICU, milk labs are specifically designed to store human milk at the recommended safe temperature, and provides a separate, sterile environment in which feed preparation can take place uninterrupted by other care needs. Milk labs are also organized to prevent milk misappropriation and accidental contamination. Using the NICU’s barcoding validation and recording system, trained milk technicians are responsible for the identification, management, and preparation of each feed, resulting in increased time nurses can provide direct care to their preemie patients. The need for multiple dietician shifts is reduced or eliminated, lowering labor costs to the hospital. Risk of family dissatisfaction from less personalized and safer care is drastically reduced. Finally, clinical employees feel more secure knowing they have less demands on their time.

When NICUs invest in trained staff specifically concerned with the proper storage and preparation of expressed and fortified breastmilk feeds, RNs can focus on providing hands-on care without compromising feed safety or quality.

References

Figure 4. Eglash, 2010.
Making a U-Turn in the NICU – Creating Change to Promote Infant-Driven Feedings and Sustainable Use of Human Milk

Lori Wood MSN, CNS, RNC-NIC, IBCLC

Introduction
Infant-Driven Feeding® (IDF), frequently thought to be synonymous with Cue-based Feeding, is a rapidly growing segment of developmentally appropriate care in the Neonatal Intensive Care Unit (NICU). Among the many lifesaving interventions our tiniest of babies receive, we nestle in the promotion and attainment of feedings. While eating is pleasurable and comforting for most, oral aversion, experienced by many premature infants, can devastate and spoil this enjoyable task. While our unit’s quest began with seeking more of mother’s own milk (MOM) for feeding and the start of an oral care with colostrum program, we found the journey to be more inclusive. Soon a Baby Friendly designation, donor human milk, and the continued promotion of human milk was becoming the norm. One practice still needed to change: the way in which we fed our babies. With such convincing evidence available to support the need for this huge culture adjustment, our 30-bed level III community NICU set to change our course.

Developing in a Foreign Land – Extraterrestrial Gestation
Much is known about the culture and environment of the NICU as well as the effects of the clinician on the outcomes of premature infants. Brain development is the combination of the interaction of both genetic makeup and exposure (Garner et al, 2012). Physical, emotional, and social experiences, both positive and negative, encountered in early life are deeply represented and are “biologically embedded” in the growing brain (Hertzman, 2012). Premature and sick infants are exposed to many painful and/or noxious stimuli during the course of a day in the NICU. Intubations, suctioning, nasal prongs, oro/nasogastric tubes, and the removal of tape are but a few of the interventions that take place on or around the mouth and face. These procedures can lead to hypersensitivity of the facial area and contribute to lack of feeding progression (Amaizu et al, 2008). Additional painful procedures, pokes, and sticks as well as the interruption of sleep and rest contribute to the negative experiences that are a premature infant’s life.

Brain circuits critical for the development of touch (somatic), motion (kinesthetic), position (proprioception), smell, taste, hearing (auditory), vision, emotion (limbic), socialization, and memory begin developing at 28 weeks gestational age. These circuits are highly influenced by sleep. Deep rapid eye movement (REM) sleep is necessary for long-term circuitry to develop and progress higher learning and the proper development of these senses (Gravens & Browne, 2008). Brain plasticity responsible for continued adaptation and learning in response to environmental stimuli, as well as long-term memory creation, are also supported and enhanced by protecting sleep (Gravens & Browne, 2008). Studies of the effects of preterm birth and post-delivery experiences on brain development and cortical folding demonstrate decreased gyri and sulci as well as decreased circumference. These alterations in development for low birth weight and preterm infants disrupt cortical development in a regionally specific fashion. Experiences of the infant can ripple into poor outcomes and abnormalities (Coughlin, 2015).

Language development and feeding skills are based in shared cortical areas tying the two together. A complex study with the inclusion of 1447 infants born ≤ 26 weeks gestation studied the tie between infants displaying feeding difficulties at 18 months corrected gestation and language delays. While a definitive association is still poorly understood, researchers hypothesize that developmental pathways responsible for feeding competence are intertwined with pathways responsible for language. After variances to account for issues such as extended ventilator days, sepsis, periventricular leukomalacia, and intraventricular bleeds, babies with moderate to severe feeding problems are more likely to have language delay and abnormalities. Of the 1447 infants enrolled in this study, 13% had feeding difficulties at 18 months of age. Of the 13% with dysfunctional feeding behaviors, 47% were noted to have language delays as compared to 11% of infants without feeding issues. Of the 47% of infants with language issues, 95% of these children have severe language problems. Bayley Scores for Infant Development were used to assess these babies and all infants were followed in Developmental Clinics through 18 months corrected gestation (Adams-Chapman et al, 2013).

Negative experiences and over stimulation can contribute to delays in attaining goals such as the safe and effective ability of infants to develop oral feedings. Extended feeding problems after discharge and into childhood are often seen. In a review by Shaker, multiple reports of infants with extended feeding problems at corrected ages of 18-24 months are listed with numbers of children varying between 19-80% (Shaker, 2012)! Physical challenges prove to be barriers in the acquisition of feeding competence, but negative sensory stimulation can cause stress as well. As preterm infants are storing feeding experiences

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in their memory, they establish physical behaviors and reactions which can be triggered by the act of feeding (Shaker, 2013). The experience and exposure of the preterm infant during feedings must be considered when developing protocols and education for both staff and parents. Every caregiver partnered with the infant must develop strong assessment skills and techniques geared at assisting babies during their feeding encounter.

Past feeding techniques and strategies employed by staff have included practices now known to both interfere with feeding maturation and competence as well as degrade the infant’s ability to maintain physical stability. As a baby experiences stress or tires while feeding; suck, swallow, and even sleep can be affected. An infant may begin to fall into a light sleep pattern, show signs of autonomic stress such as color and saturation changes, change suck and swallow patterns, or begin to show signs of fatigue (Shaker, 2012). As an infant adjusts its feeding behaviors in response to stress or tiring, the astute caregiver must assess each change and adjust his/her response to the infant. True partnering and communication must occur to ensure positive feedings each and every time. By learning to read infant communication and response, changes in physiologic stability such as apnea, bradycardia, and aspiration can be avoided keeping infant feedings safe. Understanding infant response both physiologically and behaviorally, leads to the provision of safe and enjoyable experiences (Shaker, 2013).

Journey and Change
As our unit sought to move to an infant-driven feeding model, the extensive research and understanding surrounding this topic came into play as we strategized a plan to make this change. Our NICU was looking to re-educate staff and sway culture from volume driven to satisfying and safe feedings for our compromised infants. A new process and relationship with each infant needed to be learned. Our NICU had already been involved in an incredible and successful journey to embrace human milk for our babies and families:

- Baby Friendly status in 2010
- Commitment to helping every mother to provide human milk for her baby
- Ability to pump with novel, evidence-based pump technology
- Realizing higher volumes of pumped milk
- Providing colostrum and human milk via Oropharyngeal Administration or Oral Care
- Reducing ventilator associated pneumonia (VAP) with the use of human colostrum and human milk for oral care and administration
- Providing donor human milk
- Ongoing support and education to families and staff

Changing to an infant-driven method of feeding babies seemed the next logical step in progressing our infants and their families to a natural, developmentally appropriate, evidence-based, process.

Human Milk – The Platform
Our unit’s journey began with seeking more of Mom’s Own Milk (MOM). We wanted more human milk for feedings and mom’s colostrum and human milk to provide oral colostrum care. We struggled with sufficient volumes to provide both feedings and oral care. Our goal was to gain enough human milk to begin a trial of oral care to reduce VAP. Theoretical information was available surrounding the concept of the provision of colostrum and activation of an immunostimulatory cascade protecting infants from VAP (Wood, 2013). In an effort to increase our volumes of human milk, we researched and provided documentation and support to attain approval for new technology in our breast pumps.

Our research led us to the Symphony® breast pump (Medela LLC) with its innovative and advanced pump technology (Symphony Pump with Preemie+™ technology). This novel pump pattern based on the research of Paula Meier was just what our unit needed to increase volumes of pumped milk. With an exclusive, research-based pumping pattern, the Symphony pump uses a pattern based on the sucking behavior of newly born infants. Initially trialed with moms of preterm infants, the research has extended into the term population and proves to bring lactogenesis II quicker with more milk volume (Meier, et al, 2010; Torowicz, 2015, Post, 2016).

- We saw an increase in our pumping volumes in only two months
- We reduced the use of galactogogues in our setting by 20%
- We incorporated the practice of oral care with colostrum with our increased amounts of human milk
- We reduced our incidence of VAP
  - From 2-4 cases/year to 0
- We transitioned to oropharyngeal administration of colostrum (Wood, 2013).

After our success, we researched and provided documentation to support the use of Donor Human Milk in our hospital

- Significant progress was made toward increasing the amount of human milk used in our infant’s diet
- Progress was needed in the percentage of human milk at discharge
- Progress was needed in infants nursing from the breast at discharge

A Necessary U-Turn
Current practice in the NICU was volume-driven feeding. Research and education needed to be the center of change. Change is a slow process, especially when the process, methods, and understanding of the progression of oral feeds in premature infants requires drastic altering. Volume driven culture and timed feedings promote an around-the-clock mentality of what each feeding should be, allowing infants to experience hunger, be ready for feeds and process experiential learning (Bingham, 2009). Feedings are dynamic in children and adults. A large breakfast may be followed by a smaller lunch. Hunger and desire dictate the amount of food consumed; we allow no development of this reaction in infants when we push consistent or increasing amounts on a timed schedule. Faster attainment of full oral feedings is also noted with an infant-driven process (Kirk, et al, 2007; Pickler, et al, 2009). Much was needed to change to embrace a new way of interacting with and feeding our babies. The NICU staff practice included:

- multiple nipple changes
- moving the nipple in the mouth to “encourage” extended feeding times
- ignoring subtle changes in infant behavior which clearly showed disinterest
- pushing for every last milliliter
- assisting parents to learn this method and become “better feeders” of their infants
These “techniques” have been the cornerstone to progressing feedings in premature infants. Neonatal nurses and staff have been taught to use these methods to move babies toward full oral feeds and begin the discharge process. Education on infant-driven feeding theory, techniques, and culture change had begun, but many of our staff were not yet convinced. We needed to shift our culture and place emphasis on:

- Quality of feedings
- A validated scoring tool
- Watching for infant’s cues before:
  - Initiating oral feeds (weeks gestation don’t tell us where to go)
  - Progressing the number of oral feedings
  - Discontinuing the NG/OG tube
  - Moving to full ad lib feeds
- Pairing with the infant and using relationship-based care
- Progressing feeds as “driven” by the baby

**Assisting Parents to Make the Connection**

Parents also have educational needs to acquire the necessary skills and confidence to feed their baby. Understanding of infant cues and communication, as well as skills and feeding techniques, are often new to the parents of a preterm infant. When paired with the physiologic state of the baby, understanding how long to feed and how to carry out the task, can seem a daunting, intimidating piece of NICU life. For parents who are feeling comfortable, engaged and eager to participate in cares, the act of feeding the baby is a nurturing and life-giving task; one that many parents have longed to do. Some families may be scared and lacking necessary confidence to move forward with feeding their infant.

When qualitative questions were asked of families in one study, recurrent themes of being immersed in an emotional experience, learning as one goes, and the technical aspects of feeding and assessing were expressed. Approaching discharge and feeling confident to continue progressing their infant along the feeding continuum without staff help can prove to be a mountain many parents feel unready to climb (Stevens, 2014). The NICU proves to be a formidable opponent to parents and infants by nature of the setting, busy staff, and individual opinions and practice. Nurses and other NICU staff may also be unprepared to offer the best evidence-based practice to promote optimal feeding procedures and elicit the desired outcomes. Lack of individualization to family and baby specific needs can lead to a one-way-fits-everybody approach by staff. This can create feelings of parental insecurity (McGrath, 2007). We need to assist parents to understand and create a relationship with the baby. Focusing on feeding experiences, rather than numbers and empty bottles, can help families to create positive feedings and gain skill. Once both staff and parents are able to approach feedings as dynamic instead of static, a change from volume-based to infant-driven feeding can begin (Holloway, 2014.) Staff are in the position to partner with parents and the baby to create relationships and educate (Wood, 2015). Attainment of this process involves a complete change in understanding, procedure, and culture to overcome outdated and previously adopted practice. Education, evidence-based protocols, standardized tools and evaluations, as well as unit competencies are effective in leading the charge to create this change.

**Knowledge Surrounding Infant Feeding**

Early preterm birth alone can be enough to interrupt the acquisition of oral feedings. The ability to coordinate respiratory patterns, suck and swallow coordination, awake states, and stamina takes time and experience. Even at discharge, many babies still lack consistent feeding skills and the ability to change and adapt according to situations (Shaker, 2013). Attainment of feeding competency is a complex set of skills!

Feeding competence takes time to develop. Information is available to demonstrate that the type of feeding an infant is exposed to impacts the development of facial structure and muscles. Decreased masseter muscle activity is demonstrated in bottle-fed infants along with perioral muscle function differences (Franca, et al, 2014; Jacinto-Goncalves, et al, 2004). Inhibited mandible growth has been observed in bottle-fed mice. These variances are thought to be due to the physiologic differences between breast and bottle feeding. Bottle feeding is a non-physiologic process while breast feeding uses muscles and oral/intra-oral structures as designed (Geddes, et al, 2007).

Ultrasound and pressure measurements studies give us an understanding of the true physiologic process of breastfeeding thanks to studies from the University of Western Australia. Bottle/nipple feeding relies on cupping, compression, and stripping of the nipple. Compression and stripping uses muscles differently, accounting for variances in facial and jaw development. Milk is easily expressed from a nipple without using vacuum in preterm infant feeding. Boluses of milk cannot be controlled as compression and stripping can offer a larger amount of fluid in the oral cavity in relation to the effort exerted. Safety in feeding is reliant on the ability to control the bolus of milk in the mouth (Geddes, et al, 2007).

In comparison, breastfeeding uses intra-oral vacuum to obtain milk from the breast. Infants are physiologically made to use the mouth to compress the breast and nipple and create vacuum to release milk into the mouth. During a breastfeeding cycle, the infant presses the nipple against the hard palate with the tongue. After compression, the posterior tongue is dropped while the tip of the tongue remains up against the palate. This action causes a negative vacuum, pulling a bolus of milk into the mouth. The amount of vacuum created is individual to each suck. The bolus of milk pulled into the mouth is dependent on the amount of vacuum created (Geddes, 2007). This process is physiologically supported by oral and facial structure and results in a safer transfer of bolus to the infant. Intra-oral vacuum applied during breastfeeding is quite different from the physiology used in bottle/nipple feeding. Additionally, positive feeding behaviors have been noted earlier when infants are breastfeeding than when they are bottle fed. This seems to suggest that mom’s breast and the baby have an innate and co-regulatory relationship not seen with a bottle (Nyquist, 2008; Nyquist, 2013). This information was helpful to our unit as we studied the process of infant-driven feeding and pondered how to create the necessary change to move us from a volume-driven feeding culture.

**A Useful Tool!**

Learning to assess and feed as well as transition to an environment where it was acceptable to stop a feeding before a specific volume had been consumed proved to be difficult! Our previous model of success was determined by the infant’s intake regardless of the baby’s response. Also, caregivers learn to use manipulation and “techniques” to “encourage” feeds. This
struggle and culture change is described as a consistent theme when moving to an infant-driven feeding model (Ludwig & Waitzman, 2007).

A novel new premature nipple (Calmita™ by Medela LLC) which had been trialed extensively in Australia and was implemented in Europe, became available as a product trial for our unit. Calmita was created using the principles of intra-oral vacuum and had proven to improve breastfeeding rates of preterm infants in the hospital. By promoting a more natural feeding response and supporting innate infant feeding behavior, Calmita was also credited with earlier discharge home (Simmer, 2016) Calmita:

- Uses infant created intra-oral vacuum while feeding
- An integrated vacuum-controlled valve allows the infant to suck, swallow, pause, and breathe
- Mimics breastfeeding behaviors
- Milk only flows when the infant creates intra-oral vacuum – Safety!

The integrated vacuum-controlled valve in the Calmita nipple allows the infant to suck, swallow, pause, and breathe while feeding, letting the infant to decide when to drink and when to pause (Simmer, 2016). Milk could not be “forced” on an infant as the intra-oral vacuum had to be created by the infant with each suck. Our unit thought perhaps this new technology would break volume-driven “techniques” and support infant-driven feeding.

We began a limited trial with a small group of nurses and our occupational therapist. We had training and education on the Calmita nipple and first feedings were observed and assisted to ensure that staff understood how the Calmita worked. Our initial infant-driven feeding had just begun and our unit had not yet shifted to our new cue-based protocol. Because of this huge change in process, initial response was mixed. Some staff preferred standard nipples as “infants took more volume.” This response was based on old understanding and volume-driven practice. We were experiencing difficulty in breaking old behavior! Over time, and with more education, staff began to feel driven practice. We were experiencing difficulty in breaking old

What’s Happening Now?
What began with one facet of promoting human milk has become a fabulous journey with many noted benefits! By first seeking to increase the amount of mom’s own human milk and researching before implementing new technology and practice, our unit has been able to fuel an evidence-based approach to change. We have:

- Increased the use of human milk in the NICU by 20%
- Human milk is the preferred choice and few parents refuse this knowledge
- All infants:
  - not being fed
  - on ventilator, positive airway pressure, or high flow nasal cannulas
  - receiving feeds by oro/nasogastric tube
  - are receiving oropharyngeal administration of colostrum as soon as colostrum is available. This process continues until the infant is taking oral feeds
- Reduced Ventilator Associated Pneumonia – one case after our oral care protocol began was attributed to the lack of colostrum care initiation
- Began our Cue-based Feeding Protocol
  - Still working out differences in practice – change is hard
  - Calmita trial will be expanded now that the principles of infant driven feeding are better understood

Conclusion
Mindful feeding and partnering with the baby are the foundation for consistent and positive feeding experiences for preterm infants. With the understanding that positive and consistent change takes time, education, champion change agents, and follow-up, moving to a new culture and evidence-based practice can occur. As the undisputed gold standard, human milk must be the future of each and every NICU. Infant-driven feedings and relationship-based care paired with the use of human milk can increase positive outcomes by avoiding negative experiences. Along with the expectation of nurses and NICU staff to practice evidence-based care, true empathetic, individualized, and responsible actions must become the norm. Each and every person responsible for continuing the extraterine gestation of these tiniest of patients must hold their personal integrity to the highest level. Every NICU caregiver holds the future and development of the preterm population in their hands. By using an infant-driven feeding model and listening to the cues and communication of the patient, we can shape and influence the outcomes of babies.

References


Medela’s holistic approach to human milk handling and delivery in the NICU reflects our decades of investment in human milk research. Our neonatal feeding system is specifically designed to preserve the integrity of human milk for neonates. And our education and clinical support is here to help ensure that the gold standard in infant food is matched by gold standard NICU practices.

Because for neonates, human milk is more than food—human milk is medicine.
Effect Of Maternal Skin-To-Skin Contact On Decolonization Of Methicillin-Oxacillin-Resistant Staphylococcus In Neonatal Intensive Care Units: A Randomized Controlled Trial

Fernando Lamy Filho¹, Silvia Helena Cavalcante de Sousa¹, Isolina Januária Sousa Freitas¹, Zeni Carvalho Lamy¹, Vanda Maria Ferreira Simões¹, Antônio Augusto Moura da Silva¹ and Marco Antônio Barbieri²

Abstract

Background: Decolonization with topical antibiotics is necessary to control outbreaks of multidrug-resistant bacterial infection in the Neonatal Intensive Care Unit (NICU), but can trigger bacterial resistance. The objective of this study was to determine whether skin-to-skin contact of newborns colonized with Methicillin-Oxacillin Resistant Staphylococcus aureus or Methicillin-Oxacillin-Resistant Coagulase-Negative Staphylococcus aureus (MRSA/MRSE) with their mothers could be an effective alternative to promote bacterial decolonization of newborns’ nostrils.

Methods: We performed a randomized clinical trial with 102 newborns admitted to the NICU in three hospitals in São Luís, Brazil. Inclusion criteria were birth weight of 1300 to 1800 g, more than 4 days of hospitalization, newborns with positive nostril cultures for MRSA and/or multidrug-resistant coagulase-negative Staphylococcus and mothers not colonized by these bacteria. We used a random number algorithm for randomization. Allocation was performed using sealed opaque envelopes. Skin-to-skin contact was given twice a day for 60 minutes for seven consecutive days. The control group received routine care without skin-to-skin contact. There was no masking of newborn’s mothers or researchers but the individuals who carried out bacterial cultures and assessed results were kept blind to group allocation. The primary outcome was colonization status of newborns’ nostrils after 7 days of intervention. The directional hypothesis was that more newborns who receive skin-to-skin contact holding 2 hours/day for 7 days than newborns who receive normal care will be decolonized.

Results: Decolonization of MRSA/MRSE was greater in the intervention group (Risk Ratio = 2.27; 95% CI 1.27–4.07, p-value = 0.003). Number Needed to Treat (NNT) was 4.0 (95% CI 2.2 – 9.4). After adjustment for the possible confounding effects of small for gestational age birth, antibiotic use, need for resuscitation, sex and cesarean delivery, skin-to-skin contact remained strongly associated with decolonization of newborns’ nostrils from MRSA/MRSE bacteria (p = 0.007). There was no need to interrupt the trial for safety reasons.

Conclusion: Skin-to-skin contact might be an effective and safe method for promoting decolonization of newborns’ nostrils colonized by MRSA/MRSE.

Background

Staphylococcus resistant to methicillin-oxacillin is one of the most frequent pathogens colonizing newborns (NB) admitted to Neonatal Intensive Care Units (NICU) [1]. They are identified as being primarily responsible for outbreaks of nosocomial infection especially in situations of overcrowding and understaffing [2,3]. Mupirocin promotes decolonization of these bacteria, but does not prevent outbreaks of infection and can trigger bacterial resistance [4-6].

Studies suggest that the presence of nonpathogenic bacteria can inhibit MRSA growth. Uehara et al. [7] showed that colonization by MRSA could be inhibited by the presence of methicillin non-resistant bacteria (Streptococcus viridans group) in the oral cavity of newborns admitted to neonatal units. Shimizu et al. [8] also showed the same effect on preterm infants admitted to the NICU of Nagano Children’s Hospital.

Other studies have indicated the possibility of transmission of MRSA from mother to newborn through skin-to-skin contact. In 2003, Kawada et al. postulated that transmission of MRSA from mother to infant could occur through breastfeeding [9]. Sakaki et al. [10] found an association between skin-to-skin contact and newborn MRSA infection.

Several studies have also shown that certain bacteria of the normal flora of human skin and mucous membranes have the ability to take the place of multiresistant bacteria that are already installed, through a competitive mechanism termed bacterial interference [11,12]. This mechanism has been used to promote healing of infections by multiresistant bacteria mainly in the fields of urology and otorhinolaryngology [13,14]. It is also possible that this mechanism could be responsible for the ability of the Kangaroo Mother Care to reduce infection rates of newborns undergoing this method, as demonstrated by Lawn et al. in 2010 [15] and Conde-Agudelo, et al., 2011, in a Cochrane database meta-analysis [16].

Kangaroo mother care (KMC) is an effective and safe alternative to conventional neonatal care in low birthweight (LBW) infants...
that was found to reduce mortality at discharge or 40–41 weeks' postmenstrual age and at latest follow up, severe infection/ sepsis, nosocomial infection/ sepsis, hypothermia, severe illness, lower respiratory tract disease, and length of hospital stay. The major component of KMC is skin-to-skin contact (SSC) between a mother and her newborn. Recently Lawn et al. [15] demonstrated that Kangaroo mother care is effective in preventing neonatal deaths due to preterm birth complications [17].

As literature points to an association between KMC and reduction of infections in preterm newborns, we tested the hypothesis of whether skin-to-skin contact between newborns colonized by MRSA/MRSE and their mothers is associated with decolonization of newborns’ nostrils.

Methods

Trial design and settings

We performed a controlled parallel randomized and single-blind clinical trial, conducted at the NICU of three public maternity hospitals in São Luís, northeastern Brazil: Hospital of the Federal University of Maranhão (HUMI), Marly Sarney Maternity Hospital (MMS) and Benedito Leite Maternity Hospital (MBL).

Sample

A target sample of 100 patients (including possible losses to follow-up) was calculated considering a 30% difference in the percentage of decolonization between the intervention and control groups, with 80% power and 5% probability of type I error, assuming that percentage of decolonization in the control group is 20% and setting the ratio between groups at 1:1.

Participants

Eligible subjects were singleton neonates, born at the three institutions of the study, weighing 1300 to 1800 g and clinically stable. They had been hospitalized for more than 4 days and their nostrils were colonized by Staphylococcus aureus or coagulase-negative Staphylococcus resistant to meticillin-oxacillin. Mothers were not colonized in their nostrils by these bacteria and did not present skin diseases.

Included infants and hospital participation

A total of 247 (21 from HUMI; 180 from MMS; 46 from MBL) dyads (mother and newborn) were assessed for eligibility from April 2008 to December 2010. The different number of patients assessed for eligibility in the three study hospitals was due to differences in size and number of hospitalizations in these units. Moreover, in the HUMI unit, data collection had to be discontinued because the skin-to-skin position was instituted as routine care, making randomization impossible. A total of 102 dyads were found to be eligible for the study.

Excluded infants

The remaining 145 newborns were not included in the study, 121 because they were not colonized with MRSA/ MRSE and/or because their mothers were colonized with MRSA/MRSE at their first nostrils’ culture. One mother refused to participate and 23 did not participate for other reasons (Figure 1).

We did not include infants below 1300 g because they were often subjected to routine umbilical catheterization. Infants over 1800 g were excluded because they remained, in general, less than four days in the NICU. Those who underwent surgery for congenital problems, ostomy and urethral catheter drainage were not included as well.

Allocation

For allocation of participants, a computer-generated random number list was used. The allocation sequence was concealed by using sealed opaque black envelopes. After identification of each eligible dyad the chief researcher in the presence of the mother in the NICU opened an envelope. Groups were then formed (intervention group, n = 53; control n = 49).

Mothers and researchers were aware of group allocation (intervention or control), whereas the individuals who carried out the bacterial cultures and assessed the results were kept blind to the allocation.

Interventions

Mothers in the study group were instructed to have skin-to-skin contact with their newborns in the NICU twice a day (morning and evening) for 60 minutes, for seven days (including weekends). Adherence to the intervention was verified daily and
recorded on sheets. Skin-to-skin contact consisted of placing the infant wearing only a diaper in prone decubitus, upright against his mother’s chest, between the breasts. The infant was restrained in position by a strap that tied him/her to his/her mother [18] and was covered with the mother’s clothes. NICU had its temperature maintained at 26 degrees Celsius.

All mothers underwent a routine hand washing procedure before entering the NICU. They did not have their chests scrubbed before skin-to-skin contact. The mother sat in a chair positioned by the side of the infants’ bed. Standing nurses transferred the babies to sitting mothers. A team member who accompanied the intervention monitored infant temperature, heart rate and oxygen saturation to ensure babies’ safety [19,20]. Both groups received routine nursing care such as nutrition, hygiene, bathing and diapering, organization of parents’ visit, breastfeeding and administration of drugs. Mothers were encouraged to touch, breast feed her baby and get him/her as soon as possible in her lap, under staff supervision. Fathers did not hold infants in skin-to-skin contact.

All mothers in the intervention group successfully completed 60 minutes of skin-to-skin contact for just one hour twice a day.

Outcomes

The primary endpoint for testing the efficacy of intervention was colonization status of newborns’ nostrils after 7 days of intervention (decolonization of the infants’ nostril from multi-drug resistant Staphylococcus). Birth weight (measured at birth using digital scales with 5 gram precision), gestational age (according the the last menstrual date), type of delivery (vaginal/cesarean section), sex (male/female), birth weight for gestational age (classified according to Alexander’s curve) [21], 5th min Apgar score and need for resuscitation (at delivery room) and antibiotic use (from birth to the end of data collection) were compared between groups.

Interim analysis and protocol of interruption

No interim analysis was performed. There was no need to interrupt the trial for safety reasons.

Table 3. Adjusted analysis of MRSA/MRSE decolonization of the nostrils of preterm infants admitted to the NICU (intervention vs. control group)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Risk ratio*</th>
<th>95% CI**</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small for gestational age birth</td>
<td>1.26</td>
<td>0.86-1.85</td>
<td>0.228</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>1.54</td>
<td>0.98-2.39</td>
<td>0.056</td>
</tr>
<tr>
<td>Skin-to-skin contact</td>
<td>2.30</td>
<td>1.30-4.06</td>
<td>0.004</td>
</tr>
<tr>
<td>Need for resuscitation</td>
<td>1.65</td>
<td>1.08-2.51</td>
<td>0.020</td>
</tr>
<tr>
<td>Born by cesarean delivery</td>
<td>0.81</td>
<td>0.57-1.15</td>
<td>0.245</td>
</tr>
</tbody>
</table>


Data collection

The material for the first bacterial culture was collected at baseline from both mothers and their newborns by a nasal swab performed on the fourth, fifth or sixth day of hospitalization, by a lab technician using a cotton swab soaked in sterile saline solution that was introduced into the nasal cavity of newborns and their mothers. The results of the culture from the first collection of nasal swabs determined the eligibility of the dyads for randomization.

Decolonization was checked by a second swab collection seven days after the beginning of the intervention. The second culture was collected only from infants. No other site of culture collection was considered in addition to the nostrils. Collected materials were placed in Stuart transport medium and sent to the laboratory for seeding in 5% Agar sheep blood and Brain Heart Infusion (BHI) for 24 to 48 h at 35 °C. Cultures were considered to be positive when Staphylococcus was isolated by the catalase, coagulase and VitekbioMerieux® automated method. Antimicrobial susceptibility testing was performed by Kirby Bauer disc diffusion, following recommendations from the CLSI/2008. For the samples considered to be “methicillin-oxacillin resistant” the E-test was used for confirmation of sensitivity to vancomycin.

All newborns who remained colonized after the second nostril culture, performed 7 days after randomization, were decolonized according to the recommendations of the Hospital Infection Control Committee of each unit at the end of the 7 days.

Statistical analysis

Following CONSORT guidelines, we did not perform a statistical test comparing differences in baseline characteristics because of randomization.

For the analysis of primary outcome, we first applied the Mantel-Haenszel chi-square test for two proportions. In a second analysis we fitted a generalized linear model for the binomial family with a log link to control for possible confounding effects of small for gestational age birth, antibiotic use, need for resuscitation, sex and cesarean delivery. These variables were chosen based on the magnitude of differences in their distributions between the intervention and the control group. A p-value of less than 0.05 was considered statistically significant. All tests were two-tailed. To evaluate the clinical relevance of the outcome we calculated the Number Needed to Treat (NNT). Intention to treat analysis was not performed because there were no losses to follow-up.

Ethical considerations

The study was approved by the Ethics Research Committee of the University Hospital, Federal University of Maranhão, Brazil,
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under No. 33104-1504/07 on behalf of all three participating hospitals. Each hospital's director gave institutional permission for the study. All newborns' mothers read a Plain Language Statement, written in plain, simple language, explaining the purpose, methods, demands, risks and potential benefits of the research and signed a written informed consent form. This trial was registered with ClinicalTrials.gov under number NCT01498133.

Results
Mother-newborn dyads were recruited from April, 2008 through December, 2010. The flowchart in Figure 1 shows selection, allocation, intervention, monitoring and analysis of the patients enrolled in the study.

We assessed 247 newborns for eligibility. The eligible dyads (102) were distributed as follows: 25 at the University Hospital Unit, 175 at the Marly Sarney Maternity Hospital and 47 at the Benedito Leite Maternity Hospital. Among the 102 randomized patients, 83 infants had MRSA in the first culture and 19 had MRSE. Prevalence of MRSA/MRSE was 66.9%.

No participants were lost to treatment or follow-up after assignment to study groups and none of the newborns had changes in vital signs that required team interventions or stopping the procedure.

Baseline variables for the study groups are displayed in Table 1. The variables cesarean section, small for gestational age, need for resuscitation in the delivery room and antibiotics use were unbalanced between groups.

Outcomes and estimation
Decolonization rates were significantly different between groups, as illustrated in Table 2. Infants receiving skin-to-skin care were 2.35 times more likely to decolonize than the control group.

Number Needed to Treat (NNT) was 4 (95% CI 2.2 – 9.4).

Even after adjustment for confounders skin-to-skin contact remained strongly associated with decolonization of newborns' nostrils from MRSA/MRSE bacteria (Risk ratio = 2.30, 95% CI 1.30-4.06, p = 0.004) (Table 3).

It is worth noting that among those infants who decolonized from MRSA/MRSE, the same genera of bacteria that had grown in their mother's baseline culture was identified in the infant's second culture in 84.2% of cases (data not shown).

Discussion
More than half of the newborns who received skin-to-skin holding intervention from their mothers who were not colonized with MRSA/MRSE were decolonized at the end of the seven days of treatment, but the mechanism for decolonization is unclear.

Several researchers have suggested that the presence of non-pathogenic flora [8] or strains of Streptococcus [7] inhibit growth of MRSA, possibly by acting on or interfering with some stage of the colonization process. A similar mechanism, replacement of newborn's multiresistant flora with mothers' non-pathogenic flora, may also be implicated.

A possible explanation for this finding is the phenomenon of bacterial interference, through which mothers' sensitive bacteria replace newborn's MRSA/ MRSE. This possibly occurs through changes in bacterial microenvironment that include competition for nutrients and production of antagonistic substances by mother's bacteria such as bacteriocins. Recent works, especially in the area of urology and otorhinolaryngology, have shown that it is possible to induce exchange of multiresistant bacterial flora by introducing certain strains of antibiotic-sensitive bacteria [11-13]. It is possible that such mechanism could also explain the effect of skin-to-skin contact in reducing the incidence and severity of infection episodes in preterm infants, as observed in several studies [15,16].

In our study we found that children who decolonized from MRSA / MRSE had the same genera of bacteria of his mother's culture in 84.2% of cultures performed seven days after the beginning of the intervention. This increases the likelihood that replacement of infant's multiresistant bacteria had occurred with their mother's non-MRSA/MRSE bacteria.

The intensity of the effect of decolonization was demonstrated by the number needed to treat (NNT). Just four newborns had to undergo skin-to-skin contact for one decolonization to be observed, a potentially huge effect.

Decolonization of the control group could have been due to other factors present in the NICU. It is plausible that this fact occurred spontaneously or was influenced by other types of babies' manipulation during routine care in the NICU. Kohler et al. describes spontaneous clearance rate (MRSA decolonization) of 22% [22]. Decolonization of 50% of infants who underwent skin-to-skin contact is of great importance since other methods of decolonization, such as the use of topical antibiotics and bathing with chlorhexidine, pose risk for premature babies, as shown by Nelson et al. in 2014 [4].

Limitations
The impossibility of blinding mothers and researchers to the intervention could have led to differences in neonatal care between groups. However, the individuals who carried out the bacterial cultures and assessed the results were kept blind to the allocation. These differences are unlikely to have provoked changes in the results of bacterial cultures of nasal mucosa.

Colonization with non-pathogenic bacteria could also have been mediated through the individuals who moved the infant from the NICU bed to the skin-to-skin contact position with their mothers. However, contact time between these personnel and the newborns was short. In addition, all newborns had similar manipulation. Mothers and babies had not had any previous experience with skin-to-skin contact before the study, a fact that reduces the likelihood that mothers in the control group had performed skin-to-skin-contact during the study. Although data on breastfeeding have not been collected, breastfeeding routine was similar in both groups. Although colonization of the newborns' nostrils in the intervention group could have occurred by any skin-to-skin contact, most skin-to-skin contact was provided by the kangaroo position.

No site of culture collection other than the nostrils was used in this work. While PCR for mecA is considered the gold standard assay for the detection of MRSA, the Vitek automated method used in our work is also reliable to detect MRSA, with sensitivity ranging from 90% to 99% and specificity close to 100% [23,24]. It is known that nasal swabs could be not so sensitive
in assessing CA-MRSA colonization and that a negative test for nasal colonization does not rule out MRSA [25]. It is also known that colonization and/or culture yield can result in intermittently positive samples [26].

Conclusions

Replacement of non-MRSA/MRSE bacteria from mothers to newborns through skin-to-skin contact could have occurred to explain a more than two-fold higher decolonization rate in the intervention group compared to the control group. The phenomenon of bacterial interference might be a possible mechanism explaining this finding.

The current methods of controlling bacterial outbreaks in the NICU are not effective in preventing endemic multiresistant Staphylococcus infection and can increase bacterial resistance [2,4,27,28]. The findings of this study might be a possible alternative to the decolonization of MRSA/MRSE from the infants’ nostrils because the procedure proved to be safe and effective and the number needed to decolonize one patient (NNT = 4.0) is superior to other methods of decolonization [28]. However, it is necessary to ensure that mothers eligible to practice skin-to-skin position with their babies are not carriers of MRSA/MRSE, since there is evidence in the literature that points to the possibility of transmission of this pathogen from mother to newborn [8,9].

Neonatal mortality by nosocomial infection remains one of the greatest challenges of public health [29-31]. Skin-to-skin contact between mothers and their newborns might be a safe and cost-effective strategy of biological control to promote decolonization of multiresistant bacteria and a possible reduction of nosocomial infections in the NICU.

References


Diaper Dermatitis in Infant Skin: Causes and Mitigation

Josh Gregorio, PhD, and Karien Rodriguez, PhD

Introduction

Infants under the age of two, especially preterm neonates, are vulnerable to developing skin irritation in the diapered region. Overhydration or prolonged skin contact with urine and feces can result in breakdown of the skin barrier (the protective outer layer of the skin), leading to irritation and the appearance of a rash. This event is known as diaper rash or diaper dermatitis, general terms describing skin inflammation in the diaper region.

Diaper dermatitis is among the most common skin disorders of infancy. It accounts for 10-20% of all skin disorders treated by pediatricians and the highest incidence occurs in children between 9 and 12 months of age.1,2 If left untreated, progressive skin irritation in the diapered region can lead to secondary infections, including Candida albicans (candida dermatosis) and bacterial infections, that require additional treatment by a physician.

Types of Diaper Dermatitis

Although there are many types of diaper dermatoses (Table 1), most incidences arise from a nonallergic rash resulting from chemical, physical, or mechanical irritation called irritant contact dermatitis.

Table 1. Loosely defined categories of dermatitis occurring in the diaper area.1

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>This category includes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rashes that are directly or indirectly caused by the wearing of diapers.</td>
<td>Dermatoses: such as irritant contact dermatitis, miliaria, intertrigo, candidal diaper dermatitis, and granuloma gluteal infantum</td>
</tr>
<tr>
<td>Rashes that appear elsewhere but can be exaggerated in the groin area due to the irritating effects of wearing a diaper.</td>
<td>Atopic dermatitis, seborrheic dermatitis, and psoriasis</td>
</tr>
<tr>
<td>Rashes that appear in the diaper area irrespective of diaper use.</td>
<td>Rashes associated with bullous impetigo; Langerhans cell histiocytosis, acrodermatitis enteropathica (zinc deficiency); congenital syphilis; scabies; and HIV</td>
</tr>
</tbody>
</table>

Classifications of Diaper Dermatitis

Diaper dermatitis can be classified as mild, moderate, or severe, and is dependent on skin involvement and the degree of inflammation (Figure 1). Characteristics of mild diaper dermatitis include shiny erythema with or without scales, whereas more severe cases have intense erythema, ulcerations, and pustule and vesicle eruptions.

Figure 1. Representative images of diaper dermatitis severity range: (A) healthy skin, (B) slight, (C) mild, (D) severe.

Causes and Risk Factors

The exact cause or etiology of diaper dermatitis is not fully understood. However, we know that many factors within the diapered environment contribute to the manifestation of diaper dermatitis. Extensive research has demonstrated that factors including chemical and mechanical irritants, skin pH, diet, skin overhydration, skin occlusion, diarrhea, gestational age and medication contribute to the occurrence and severity of diaper dermatitis.4-7

Factors Contributing to Diaper Dermatitis

- skin overhydration
- skin occlusion
- feces and fecal enzymes
- infrequent diaper changes
- incomplete cleaning and drying of the skin in the diaper area
- infant’s diet

Additionally, caretaker behavior and practices such as infrequent diaper changes, incomplete cleaning and drying of the skin in the diaper area, diet (breast fed babies have been shown to have...
infections. An illustration of diaper dermatitis induction is depicted in Figure 2. Preterm Infants

It is also known that preterm infants are at increased risk of developing diaper dermatitis because their skin barrier (stratum corneum) is not yet fully formed. In fact, infants born at gestational ages of less than 25 weeks only have half the thickness of both the stratum corneum and the underlying epidermis as compared with full term neonates (Figure 3).8-10 Moreover, premature infants skin is very permeable to both water and irritants.11 Additionally, infants born at less than 28 gestational weeks lack an outer protective layer called the vernix caseosa and suffer from increased water evaporation from their skin.7 It is estimated to take 2-9 weeks after birth for the skin to fully form in preterm neonates.7

Mitigation

Although diaper dermatitis has not been shown to be completely avoidable, there is ample evidence that preventive care can be effectively implemented to reduce the incidence and severity of diaper dermatitis. Maintenance of dry skin in the diapered area can effectively reduce skin damage due to overhydration. Strategies including frequent diaper changes, airing out the skin in between diaper changes, and use of diapers with increased wicking and superabsorbent materials help in keeping the skin dry. Additionally, the use of creams and ointments that provide barrier protection between the skin and the external environment can help mitigate diaper dermatitis by preventing direct skin contact. Mechanical irritation due to overwiping can also lead to compromised skin and should be avoided. It is important to note that clinical studies have demonstrated the use

- infections. An illustration of diaper dermatitis induction is depicted in Figure 2.

- Preterm Infants

- Mitigation
of disposable wipes that contain emollient cleansers to be less irritating on infant skin than water and cloth.12-13

Moreover, advances in diaper technology have helped mitigate the effects of elevated moisture retention and occlusion to address some of the moisture-induced skin irritation and keep baby more comfortable.14-16 Enhanced breathable outer cover materials allow air to pass into the diaper and minimize the moisture trapped inside. More hydrophilic and sophisticated materials are used to quickly take fluid in and channel it away from skin into moisture trapping regions. Advanced absorbent systems are now designed to be more thin and flexible, yet also retain more liquid and lock moisture away from the skin-diaper interface.14-16 A general diagram highlighting the balance of interacting forces between healthy and irritated diapered skin is shown in Figure 5.

![Figure 5: There is an intricate balance between healthy and compromised diapered skin. Environmental and caretaker practices heavily influence the incidence of diaper dermatitis.](image)

References

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Abstract
Background: Each year, about 5.3 million babies die in the perinatal period. Understanding of causes of death is critical for prevention, yet there is no globally acceptable classification system. Instead, many disparate systems have been developed and used. We aimed to identify all systems used or created between 2009 and 2014, with their key features, including extent of alignment with the International Classification of Diseases (ICD) and variation in features by region, to inform the World Health Organization’s development of a new global approach to classifying perinatal deaths.

Methods: A systematic literature review (CINAHL, EMBASE, Medline, Global Health, and PubMed) identified published and unpublished studies and national reports describing new classification systems or modifications of existing systems for causes of perinatal death, or that used or tested such systems, between 2009 and 2014. Studies reporting ICD use only were excluded. Data were independently double-extracted (except from non-English publications). Subgroup analyses explored variation by extent and region.

Results: Eighty-one systems were identified as new, modifications of existing systems, or having been used between 2009 and 2014, with an average of ten systems created/modified each year. Systems had widely varying characteristics: (i) comprehensiveness (40 systems classified both stillbirths and neonatal deaths); (ii) extent of use (systems were created in 28 countries and used in 40; 17 were created for national use; 27 were widely used); (iii) accessibility (three systems available in e-format); (iv) underlying cause of death (64 systems required a single cause of death); (v) reliability (10 systems tested for reliability, with overall Kappa scores ranging from .35-.93); and (vi) ICD alignment (17 systems used ICD codes). Regional databases were not searched, so system numbers may be underestimated. Some non-differential misclassification of systems was possible.

Conclusions: The plethora of systems in use, and continuing system development, hamper international efforts to improve understanding of causes of death. Recognition of the features of currently used systems, combined with a better understanding of the drivers of continued system creation, may help the development of a truly effective global system.

Background
Each year, approximately 2.6 million babies are stillborn in their third trimester, about half of these during labour (intrapartum stillbirths). Another 2.7 million are born alive only to die within their first month [1, 2]. With 5.3 million deaths a year, perinatal death is a tragedy on a par with under-5 deaths (5.9 million [1]), and has far-reaching effects for bereaved families, caregivers, and ultimately society at large [3]. Understanding the causes of stillbirths and neonatal deaths is critical for prevention. Systems that classify causes are thus indispensable tools for researchers, policy makers and caregivers working to reduce the numbers of these deaths.

Classification systems for causes of stillbirth and neonatal death are roughly a century old. The first systems originated in Scotland to classify causes based on clinically observable factors [4]. In 1941, Baird developed what has become one of the most widely used classification systems, referred to as the “Aberdeen,” which aimed to reduce the percentage of unexplained deaths [5]. Early modifications to the Aberdeen added categories, provided definitions to increase consistency of interpretation, and incorporated World Health Organization (WHO) definitions for low birthweight. A new family of systems with more focus on autopsy results was established in 1956 by Bound [6]. This system was modified for use by the British Perinatal Mortality Survey, with several other subsequent modifications [4]. In 1980,
Systems:
- **System**: Any approach to classifying causes of neonatal deaths and/or stillbirths described by authors of included publications as a “system” or “approach”, and/or that included a clearly delineated list of causes separate from the data.
- **Modified system**: One created as a result of changing an existing system, where:
  - the system presented was described by the authors as a modification, or
  - it was apparent the system had been modified (e.g. different number of levels or categories at the top level, different meaning of categories), despite the authors’ stating that the system had not been changed.
- **New system**: One created without modifying an existing system.
- **Used system**: One used for any purpose (e.g. clinical, research) other than purely developmental (e.g. testing for reliability).
- **Global system**: One used to classify or estimate causes of stillbirths and neonatal deaths in all countries with available data.
- **National system**: One used by a government for annual reporting of causes for the majority (>50%) of SB and/or NND nationwide, or
  - used by any organization (e.g. the United States Agency for International Development, USAID, or the United Nations Children’s Fund, UNICEF) to classify causes of death
    - as reported by Demographic and Health Surveys (DHS) in at least one year, where
      - DHS data was assumed to be nationally representative, or
    - of the majority (>50%) of SB and/or NND in a country in at least one year, or
  - otherwise stated to be a system developed for government use.
- **Widely used system**: One used to classify 1000+ perinatal deaths and/or in two or more countries between 2009 and 2014.

Characteristics:
- **Level**: Some systems have a single “level” of causes while others have several, with the top level listing general causes and each lower level listing sub-categories within a given general cause. For example, classifying the cause of a SB or NND in a system with multiple levels requires selecting a set of causes, from most general (from the top level) to most specific (from the lowest level), e.g. “congenital anomaly” from the top level and “trisomy 13” at the next level down.
- **Completely hierarchical system**: One requiring that causes be assigned via consideration of each cause in sequence, such that if a death could be assigned to the first cause in the list, then none of the subsequent causes would be considered, and if the death could not be assigned to the first cause but could be assigned to the second cause in the list, then none of the subsequent causes would be considered, and so on.
- **Partially hierarchical system**: One in which hierarchy is optional or incompletely defined.

Wigglesworth launched a third family using categories that were simple to apply, clinically actionable, and did not require autopsy [7]. The Wigglesworth system has been used and adapted widely [8]. Numerous other types of systems have been developed to classify causes of both stillbirth and neonatal deaths, for instance systems based on placental pathology [9], distinguishing between immediate and underlying causes [10, 11], combining autopsy results with clinical data [12], incorporating deaths both before birth and through infancy [13], and exploring preventability rather than causality [14].

There is a recognized need to rationalize approaches to cause-of-death classification. The Lancet’s 2011 stillbirth series called for the creation of a “universal classification system” for causes of stillbirth [15, 16], and the United Nations-endorsed Every Newborn Action Plan (2014) identified cause of death as a key gap in the available data, proposing registration of all stillbirths and neonatal deaths together with identification of cause of death as one of the plan’s global indicators [17].

While it is improving, under-reporting of perinatal deaths (particularly stillbirths) in some of the highest-burden regions is still problematic [2]. In recognition of the need to increase accurate data capture and reporting, the WHO is currently developing a new approach to perinatal death classification for global use, the “WHO Application of the ICD-10 to perinatal deaths” (ICD-Perinatal Mortality or ICD-PM) [18]. Having a separate ICD module for perinatal deaths which incorporates both maternal and fetal/neonatal conditions, in recognition of the mother-baby dyad, is intended to increase reporting of perinatal deaths globally, as well as improving data accuracy.

Several reviews of classification systems for causes of stillbirth and neonatal death have been undertaken, yet all have been limited by one or more factors, including type of death (most were stillbirth-only) and scope (time period, languages included, etc.) [8, 19-21]. The aim of this systematic review was to gain an understanding of classification systems that have been developed or used recently in order to inform the ICD-PM and plans for its implementation. Specific objectives were to:

1. identify classification systems for causes of stillbirth and neonatal death which have been developed as new systems, modified from existing systems, or used between 2009 and 2014;
2. describe the characteristics of these systems, including any reliability testing performed;
3. describe the alignment of these systems with the ICD; and
4. examine variation in Objectives 1-3 according to country economic region as defined by the World Bank [22].

This paper presents findings from the first of a two-part study. The second part presents an assessment of alignment of the systems identified and reported on in the present paper with expert-identified characteristics for a globally acceptable system,
and is also reported in the BMC Ending Preventable Stillbirths series [23].

Methods
A systematic literature review was undertaken using principles of the Cochrane Collaboration [24], including a comprehensive search, and study selection and data extraction independently undertaken by two authors. The senior author resolved differences; otherwise, system developers who are co-authors were excluded from selection of studies, data extraction and analysis. See Additional file 1 for the PRISMA checklist.

Inclusion criteria
We included published and unpublished studies reporting classification systems for stillbirths (SB) and/or neonatal deaths (NND) that were created, modified, and/or used between 2009 and 2014. The inclusion criteria were:

1. All publications between 2009 and 2014 that:
   a. described at least one new and/or modified classification system for causes of SB and/or NND or
   b. reported data on causes of SB and/or NND using any classification system, regardless of when that system was created or modified.
2. For any systems that were found to be used between 2009 and 2014, as in (1-b) above, we also included the publication that was provided as the reference for that system, regardless of whether it was published in 2009-2014 or earlier.
3. All publications between 2009 and 2014 that reported on reliability testing of any systems included via (1) and (2) above.
4. The most recent publication between 2009 and 2014 in English that described a national system.

The original search period was the ten years from 2004-2013; this was halved (to 2009-2013) due to resource limitations, and because data extraction extended into 2014, a sixth year was added to the search period. Systems classifying SB were included regardless of the gestation at which SB was defined in included publications. Systems classifying both early (0-7 days) and late (8-28 days) NND were included, as well as systems classifying perinatal deaths without separation into SB and NND.

The rationale for including modifications of original systems was twofold. First, even slight modification of a system may render its data less compatible with other systems, and second, modification may reflect users' perceptions of the inadequacy of available systems. See Fig. 1 for definitions of terms used.

Exclusion criteria
Systems developed for specific populations (e.g., unexplained SB at term, low birthweight babies) were excluded. Systems for which data on SB, NND, and/or perinatal deaths could not be separated from data on deaths before or after the perinatal period (e.g., miscarriages, late infant deaths) were excluded. Because our ultimate aim was to inform development and optimize successful uptake of a new global system, we needed to gain an understanding of the context of systems development beyond the ICD. This meant our focus was on understanding the features of systems developed by users, and thus which reflected their needs. Hence, papers describing use of only the ICD were also excluded.

Search strategy and study selection
Five electronic databases (CINAHL, EMBASE, Global Health, MEDLINE, and PubMed) were searched for the period January 1, 2009, to December 31, 2014, with no language limits (see Fig. 2 for search string). In addition, an English-language search was carried out to identify all national systems in use. Searches were supplemented by contacting expert informants.

Every English-language paper was independently screened for inclusion by two authors in two stages—abstract review and full text review—with final decisions made by the senior author in the event of disagreement (see Additional file 2 for decision tree on inclusion/exclusion). Screening of non-English papers at the abstract stage was performed in the same way, but full-text review was done by one of three researchers (depending on language) with guidance by the first author.

Data collection
A data collection tool was purpose-built and pilot tested for data extraction of 48 variables (see Additional file 3), including:

1. 21 variables to describe basic system features such as year of publication, whether systems were new or modified, whether authors intended to create or modify systems or merely to use existing systems, and authors' descriptions of reasons for system creation;
2. 26 variables to enable assessment of alignment with expert-identified characteristics for a globally acceptable system (see [23]), including variables for:
   a. Comprehensiveness (e.g. whether both SB and NND were included, and whether associated factors were recorded);
   b. Extent of use (e.g. regions of origin and use, number of deaths classified, and whether national or not);
   c. Accessibility and relevance (e.g. whether available in e-format and multiple languages and whether guidance for accessing data was provided; also, although verbal autopsy is a data collection tool, we recorded whether systems had been used with verbal autopsy as one proxy for a system's relevance in low-resource settings);
   d. Identification of underlying causes (e.g. maximum % "other" recorded by any use of the systems in included papers, number of causes in top "level", number of levels, and whether fully, partially, or not hierarchical; see Fig. 1
for definitions of terms);
e. Reliability (including whether rules for assigning cause of
death and definitions of causes were provided);
3. One variable to record whether ICD codes were used. This
variable was included in data extraction as it was known to
be important for development of the ICD-PM.

Data for variables relating to basic system features were taken
both from publications that introduced new or modified systems
between 2009 and 2014, and from older publications if they had
been cited as the source of a system used within 2009-2014,
regardless of year of publication. Data relating to the use of
the systems (included in #2 above), for instance number of
deaths classified, countries in which used, and percent of deaths
classified as “other”, were taken from publications within 2009-
2014 that described use of these systems. Therefore, a system
described in a publication from 1970 would be included only if
it had been used at least once in a publication between 2009 and
2014; all data relating to use of this system would be taken only
from the latter publication, while all data relating to the system’s
basic features would be taken from the former publication.

Data from English publications were independently double-
extracted; any disagreements were resolved by the senior
author. Data from non-English publications were extracted by
the same researchers who had performed full-text review of
these publications, with the guidance of the first author. Where
multiple systems were included in a single publication, each was
extracted separately.

Data management and analysis
Data were entered into Microsoft Excel 2013. Coding was
independently checked by a second researcher, and then
imported to Stata/IC 12.1 for analysis of frequency distributions.
Subgroup analyses were performed to explore differences in
frequencies according to extent of use (whether widely used,
region in which used, and use in highest-burden countries). A
sensitivity analysis was carried out to explore the implications of
cut-offs for identification of widely used systems (see Additional
file 4 for method). For a copy of the study protocol, please
contact the author.

Results
Search results
In total, 4,948 publications were screened for eligibility, 764
were assessed for eligibility, and 146 were included (Fig. 3).
Some included publications met more than one inclusion
criterion (e.g., included both a description of a new system
and use of an existing system) (see Additional file 5 for all
included publications with reasons for inclusion). Of included
publications, 11 presented systems that were newly created, 40
presented systems that were modified, 81 presented system use
(including 17 systems that had been created prior to 2009), and
15 presented the results of reliability testing for one or more
included systems.

120 non-English publications in 16 languages were screened
via English abstracts, with publications in eight non-English
languages identified for full-text review. Eight publications

Fig. 3 Classification systems for causes of stillbirths and neonatal deaths, 2009-2014: PRISMA flow diagram
System creation and use

Number and year of creation of systems

A total of 81 systems were created, modified, and/or used between 2009 and 2014. The oldest system in use was Wigglesworth 1980, while two systems created in 2014 had no published record of use (McClure 2014-GLOBAL Network and Gardosi 2014-MAIN). An average of 10 systems were created or modified annually between 2009 and 2014 (see Additional file 6).

New and modified systems compared to author intent

The majority of systems (n = 59, 73%) were modifications of existing systems. Of the 14 systems that we defined as new, 10 were also intended by their authors as new systems. Of the remaining four, two were intended as new approaches rather than new systems, one was intended as a use of an existing system, and one was not intended as a use or creation of any system. Just 22 of the 59 systems defined by us as modifications were intended by their authors as such. A further 27 were intended as uses of existing systems, with the modifications that we found going unmentioned by the authors; five were intended as new systems, and the remaining five had other intents. We were unable to determine whether eight systems were new or modified; of these, six were intended as uses of existing systems, while author intent for the remaining two could not be determined (see Table 1 and Additional file 5).

Reasons for system creation

Authors of 27 of the 73 systems which we were able to identify as either new or modified provided no rationale for the creation or modification of the systems. Reasons provided for the remainder focused on adding features [25] and missing categories [26, 27], accommodating new knowledge on causation and increasing accuracy [28], reaching new audiences (e.g. in low- and middle-income countries, LMIC) [29], addressing underlying causes [5, 8, 11, 30, 31], providing rules and/or definitions [7, 8, 26, 29, 32-35], or reducing the proportion of “unexplained” deaths [27, 32, 35-38]. Some found the inclusion of both SB and NND to be a shortcoming to be addressed (through creation of SB-only or NND-only systems) [33], while others felt that limiting systems to SB only or NND only was a shortcoming to be addressed (through creation of a system for both SB and NND) [8, 35]. There was a similar difference of opinion regarding whether hierarchy was a shortcoming to be addressed through creation of a non-hierarchical system [39], or a useful feature to incorporate into a new system [29].

Overview of system characteristics

Characteristics of the 81 included systems are presented in Table 1. The characteristics that were most common among the systems regardless of whether used in high-income countries (HIC) only or LMIC only were: (i) exclusion of fetal growth restriction (FGR), intrauterine growth restriction (IUGR) and small-for-gestational age (SGA) from the list of causes (75% and 88% of HIC-only and LMIC-only systems, respectively); (ii) requiring a single cause of death to be recorded (81% and 72%); (iii) ten or fewer causes at the top level (72% and 88%); (iv) not requiring recording of the type of data used to assign causes (81% and 100%); (v) not using ICD codes (92% and 75%); (vi) not having been tested for reliability (86% and 88%); (vi) use in just one country (83% and 94%); (viii) unavailable in e-format (94% and 97%); and (viii) unavailable in multiple languages (97% and 100%).

In addition to these, the characteristics that were most common among the 36 systems used only in HIC were: (i) non-hierarchical; and (ii) not having been used with verbal autopsy. Characteristics most common among the 32 systems used only in LMIC included: (i) lack of rules for assigning causes of death; (ii) lack of guidance on how to access data from systems; (iii) no inclusion of associated factors; and (iv) used to classify fewer than 500 deaths (among publications included in our search 2009-2014).

Comprehensiveness of systems

Types of deaths included

Systems classifying both SB and NND were most common, with just under half the systems classifying both types of death. Next
most common were systems classifying just NND (around one-third of systems) (see Table 1). There was a difference in type of death classified according to region of use. Of the 36 systems used in HIC only, over half classified both types of death, and one quarter classified SB only. SB-only systems were less common among the 32 systems used in LMIC only: 14 systems classified both SB and NND death and 14 classified NND only, while just four classified SB only.

Of the 55 systems that included SB, a minority (n = 16, 29%) required distinguishing between antepartum (AP) and intrapartum (IP) SB, with similar results across HIC and LMIC settings. For the 40 systems including both SB and NND, more than half (n = 22) provided no guidelines or rules for distinguishing between SB and NND, and 11 had no categories that were clearly either SB or NND (see Table 1).

**Associated factors**

Twenty-three systems (28%) allowed associated factors to be recorded (see Table 1). This feature was more common among HIC-only systems (13 of the 36 systems) than LMIC-only systems (six of the 32 systems). Less than half (n = 11) of systems allowing associated factors clearly distinguished them from causes of death.

**Extent of use of all systems**

**Regions of origin and use**

Systems were created or modified in 28 countries on six continents, the majority (65%) in HIC, and were used in a total of 40 countries (see Fig. 4). Of the 53 systems created in HIC, most (68%) were used only in HIC. Of the 28 systems created in LMIC, the majority (86%) were used only in LMIC. Half of the 81 systems were used only in the publications which presented them. Most systems (74%) were used in just one country, and five systems were described but not used. Four systems were used to report global data; other than these, the largest number of countries in which any system was used was seven (by Wigglesworth 1980 and Gardosi 2005-ReCoDe) (see Additional file 7). About one-fifth of the 81 systems (n = 17) were national, including 13 systems used in eight HIC and five systems used in five countries in Asia, Africa, and South America (see Additional file 8).

**Systems used in highest-burden settings**

Included systems were used in only about half of the highest-burden countries (six of the top 11 highest-NND burden countries and six of the top 10 highest-SB burden countries) (see Additional file 9). This included just one national system, used in Bangladesh. Specifically, no systems were found to be used in the two highest-burden countries, China and India (though the ICD has been used to classify perinatal deaths in China [40]). Other than systems used to estimate global causes, only two systems were used in more than one highest-burden country: Engmann 2012 [39] (in Pakistan and the Democratic Republic of the Congo, DRC) and Wigglesworth 1980 [7] (in Pakistan and Bangladesh).

**Number of deaths classified**

According to published reports of system use, 49 of 81 systems (60%) had been used to classify fewer than 500 deaths, including 17 of the 36 systems used only in HIC (47%) and 26 of the 32 systems used only in LMIC (81% see Table 1). Just under one-third of systems (28%) were used to classify 1000 or more deaths: 12 of the 36 systems used only in HIC (33%) and just four of the 32 systems used only in LMIC (13%) (see Table 1).

Other than global systems and systems that were not used, systems classified between 14 and 47,238 deaths. The total deaths classified by systems (excluding global systems) between 2009 and 2014 was just under 234,000, representing less than 1% of all SB and NND globally in this period (assuming 2.6 million stillbirths and 2.7 million neonatal deaths annually [1, 2]) (see Table 2 for data on numbers of deaths classified by widely used systems; other data not shown).

**Most widely used systems and their selected characteristics**

Systems used in more than one country and/or to classify 1000 or more deaths were considered to be “widely used” (see Additional file 4 for the results of sensitivity analysis of these cut-offs). It is worth noting that national systems in countries with small numbers of perinatal deaths, such as Bhutan and Wales, were thus not considered to be widely used, though they may cover a high percentage of deaths within their context. By this definition, 27 systems (33%) were widely used, including almost half of the 17 national systems (see Table 2). Thirteen of the 27 most widely used systems classified both SB and NND, 10 classified NND only and four classified SB only. Most (about 70%) of the widely used systems were not hierarchical. Nearly one-third of the 17 widely used systems which included SB did not distinguish at all between AP and IP SB.

The majority of the widely used systems (78%) required identifying a single cause of death. Ten allowed associated factors to be recorded, although this varied depending on which types of deaths were classified, with two of the four widely used SB-only systems and two of the 10 widely used NND-only systems allowing associated factors. Most of the 27 widely used systems (70%) provided definitions for at least some causes of death, though only eight systems provided definitions for all causes. About half gave some description of how cause of death should be assigned (see Table 2).

Widely used systems differed from less used systems in several respects. They were more likely to: (i) be used in both HIC and LMIC (eight of 27 systems, or 30%, as opposed to none of the 54 less used systems); (ii) have been tested for reliability (22% vs 7% respectively); (iii) be available in e-format (11% vs none); (iv) record the degree of certainty of the cause of death assigned (48% vs 39%); (v) record the type of data available for assigning cause of death (19% vs 4%); (vi) provide definitions for some or all causes of death (70% vs 50%); (vii) provide rules for assigning cause of death (52% vs 35%); and (viii) allow associated factors (37% vs 24%). Widely used systems that included both SB and NND were also more likely to clearly distinguish the two types of death (six of the 13 widely used systems including both SB and NND vs seven of the 27 less used systems including both types of deaths).

Widely used systems were less likely to: (i) be used in LMIC only (22% of widely used systems versus 48% of less used systems); and (ii) have recorded a maximum proportion of deaths classified as “unexplained” that was less than 20% (22% vs 35%) (data not shown).

**Accessibility and relevance**

The majority of systems (n = 66, 82%) provided no guidance on
how potential users might access data from their systems. Three systems were available in e-format (as defined by availability of a form that could be filled in online). Just one system was available in more than one language (English and Lithuanian). Fourteen systems (17%) had been used with verbal autopsy (see Table 1).

**Identification of underlying causes**

**Number of causes and levels**

Systems had from one to four levels (see Fig. 1 for definition of this term), with a mean of 1.8 levels. Just over half had more than one level. Nine of the 36 HIC-only systems (25%) versus three of the 32 LMIC-only systems (10%) had three or more levels. The range of number of causes at the top level was two to 40, with a median of 8.2 causes. Most systems (n = 67, 83%) had 10 or fewer causes at the top level. Of the 14 systems with more than 10 causes at the top level, 10 were used only in HIC. Most systems (n = 64, 79%) required that a single cause of death be recorded, with

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All systems, n (%)</th>
<th>Systems used in HIC only, n (%)</th>
<th>Systems used in LMIC only, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For systems including any type of death (SB, NND, or both)</td>
<td>81 (100%)</td>
<td>36 (100%)</td>
<td>32 (100%)</td>
</tr>
<tr>
<td>Type of system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New</td>
<td>14 (17%)</td>
<td>6 (17%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Modified</td>
<td>59 (73%)</td>
<td>28 (78%)</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (10%)</td>
<td>2 (6%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Uses ICD codes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17 (21%)</td>
<td>3 (8%)</td>
<td>8 (25%)</td>
</tr>
<tr>
<td>No</td>
<td>62 (77%)</td>
<td>33 (92%)</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Includes definitions for all causes of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (28%)</td>
<td>9 (25%)</td>
<td>11 (34%)</td>
</tr>
<tr>
<td>No</td>
<td>35 (43%)</td>
<td>14 (39%)</td>
<td>16 (50%)</td>
</tr>
<tr>
<td>Some causes only</td>
<td>23 (28%)</td>
<td>13 (36%)</td>
<td>5 (16%)</td>
</tr>
<tr>
<td>Includes a description of how COD are to be assigned</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (41%)</td>
<td>16 (44%)</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>No</td>
<td>47 (58%)</td>
<td>20 (56%)</td>
<td>23 (72%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Number of deaths classified using this system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not used</td>
<td>5 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&lt; 500</td>
<td>44 (54%)</td>
<td>17 (47%)</td>
<td>26 (81%)</td>
</tr>
<tr>
<td>500-999</td>
<td>9 (11%)</td>
<td>7 (19%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>1000+</td>
<td>23 (28%)</td>
<td>12 (33%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Includes guidance on how potential users might access data from the system</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8 (10%)</td>
<td>5 (14%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>No</td>
<td>66 (82%)</td>
<td>24 (67%)</td>
<td>30 (94%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>7 (9%)</td>
<td>7 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Available in e-format</td>
<td>3 (4%)</td>
<td>2 (6%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Available in more than 1 language</td>
<td>1 (1%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Type of death classified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both SB and NND</td>
<td>40 (49%)</td>
<td>20 (56%)</td>
<td>14 (44%)</td>
</tr>
<tr>
<td>NND only</td>
<td>26 (32%)</td>
<td>7 (19%)</td>
<td>14 (44%)</td>
</tr>
<tr>
<td>SB only</td>
<td>15 (19%)</td>
<td>9 (25%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Number of countries in which used</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>60 (74%)</td>
<td>30 (83%)</td>
<td>30 (94%)</td>
</tr>
<tr>
<td>2+</td>
<td>13 (16%)</td>
<td>6 (17%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Used to report global data</td>
<td>3 (4%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Tested for reliability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (12%)</td>
<td>4 (11%)</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>No</td>
<td>68 (84%)</td>
<td>31 (86%)</td>
<td>28 (88%)</td>
</tr>
<tr>
<td>Unclear</td>
<td>3 (4%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
</table>
Percent “other” and “unexplained”

Around two-thirds of systems (n = 54) had at least one category for grouping causes not defined elsewhere in the system as “other” (see Table 1). For most of these systems (72 %), the maximum proportion of deaths classified as “other” was less than 20 %, a finding that was similar for both HIC-only and LMIC-only systems (see Table 1).

Hiearchy

Most systems (n = 53, 65 %) were not hierarchical, while just under one-quarter were completely hierarchical. Hierarchy was more common among the 32 systems used only in LMIC (just under one-third of these were completely hierarchical) than among the 36 systems used only in HIC (14 % were completely hierarchical) (see Fig. 1 for definition of terms and Table 1 for data).

Table 1 Selected characteristics of classification systems for causes of stillbirth and neonatal death, 2009–2014 (Continued)

<table>
<thead>
<tr>
<th>Hierarchical</th>
<th>Yes</th>
<th>No</th>
<th>Partially</th>
<th>Unclear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18 (22)</td>
<td>53 (65)</td>
<td>7 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Requires that a single cause of death be recorded</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>64 (79)</td>
<td>12 (15)</td>
<td>7 (9)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>List of causes does not include FGR, IUGR or SGA</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>65 (80)</td>
<td>16 (20)</td>
<td>7 (9)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Allows associated factors to be recorded</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>23 (28)</td>
<td>57 (70)</td>
<td>5 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Number of categories in top level</td>
<td>≤ 10</td>
<td>&gt; 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>67 (83)</td>
<td>14 (17)</td>
<td>26 (72)</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Number of levels</td>
<td>&gt; 1</td>
<td>1</td>
<td>Unclear</td>
<td></td>
</tr>
<tr>
<td></td>
<td>44 (54)</td>
<td>35 (43)</td>
<td>2 (3)</td>
<td>14 (17)</td>
</tr>
<tr>
<td>Used with verbal autopsy</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>14 (17)</td>
<td>12 (20)</td>
<td>7 (9)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Maximum percent of deaths classified as “other” using this system</td>
<td>&lt; 20 %</td>
<td>≥ 20 %</td>
<td>No “other” category</td>
<td>“Other” category but no data available</td>
</tr>
<tr>
<td></td>
<td>39 (48)</td>
<td>10 (12)</td>
<td>27 (33)</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Maximum percent of deaths classified as “unexplained” using this system</td>
<td>&lt; 20 %</td>
<td>≥ 20 %</td>
<td>No “unexplained” category</td>
<td>“Unexplained” category but no data available</td>
</tr>
<tr>
<td></td>
<td>25 (31)</td>
<td>38 (47)</td>
<td>11 (14)</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Allows the type of data available for assigning COD to be recorded</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>34 (42)</td>
<td>55</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Requires recording whether the stillbirth was antenatal vs intrapartum</td>
<td>Yes</td>
<td>No</td>
<td>Partially</td>
<td>Unclear</td>
</tr>
<tr>
<td></td>
<td>16 (29)</td>
<td>14 (26)</td>
<td>25 (46)</td>
<td>8 (28)</td>
</tr>
</tbody>
</table>
only systems. The range of the maximum proportion of deaths classified as “other” was 0 % [41] to 68 % [47], with an average of 14 % and a median of 8 % (for systems with at least one “other” category and available data). The range of proportion of deaths classified as “other” was somewhat narrower for SB-only (1-48 %) and NND-only systems (0-54 %) than for systems including both types of deaths (1-68 %) (see Additional file 10).

The majority of systems (n = 70, 86 %) also had categories for “unexplained” deaths. Of these 70 systems, just 36 % had a maximum proportion of deaths classified as “unexplained” that was less than 20 %. Slightly more LMIC-only systems than HIC-only had this relatively low proportion of deaths classified as “unexplained” (46 % of LMIC-only versus 38 % for HIC-only systems, including only systems with at least one “unexplained” category). The range was 0 % [42] to 100 % (the FIGO system as used in [27]); with an average of 29 % and a median of 23 %. (The mean and median were virtually unchanged when the outlier of 100 % was excluded.) The range of proportion of deaths classified as “unexplained” was narrowest for NND-only systems (0-30 %) and widest for systems including both types of deaths (6-100 % excluding the slight outlier of 100 %, the range was 0-81 %). See Additional file 10 for details and a list of terms that were included in the assessment of the proportion of deaths classified as “other” and “unexplained”.

Reliability

Reliability testing

Only 10 systems (12 %) were tested for reliability between 2009 and 2014 (see Table 1), about half of these only internally (by the teams which had developed the systems). Eight of the 10 tested systems originated in HIC. Three groups tested systems other than their own, and four systems were tested more than once. The overall Kappa ranged from -.35 (poor agreement) (for Cole 1986 [26]) to .93 (excellent agreement) (for Korteweg 2006-Tulip [35]); all but one of the Kappa values were over .50 (fair to excellent) (see Additional file 11).

The range for external Kappas (Kappa values from testing by teams which had not developed the systems being tested) was .35-.93 and the range for internal Kappas (Kappa values from testing by teams which had developed the systems being tested) was .51-.89. The 59 modified systems were much less likely to have been tested for reliability than the 14 new systems (9 % v 36 %, respectively).

Availability of definitions and rules

Just 23 of the 81 systems (28 %) provided definitions for all causes of death, and 33 (41 %) provided some description of how to assign causes of death (see Table 1). Sixteen of the 32 systems used only in LMIC (50 %), and 14 of the 36 systems used only in HIC (39 %), provided no definitions for causes. The majority of LMIC-only systems (n = 23, 72 %) and HIC-only systems (n = 20, 56 %) provided no guidance on assigning cause of death. Only seven of 81 systems (9 %) allowed recording of the type of data used to assign cause of death, all of them HIC-only systems.

System alignment with the ICD

Seventeen of the included systems (21 %) used ICD codes; this was more common among LMIC-only systems (25 %) than HIC-only systems (8 %) (see Table 1).

Discussion

We reviewed contemporary classification systems used for causes of stillbirths and neonatal deaths globally, to inform development of the new ICD-PH. We found a large number of systems in addition to the ICD, with widely varying characteristics and limited reach in terms of numbers of deaths classified, especially in highest-burden countries.

The most comprehensive review of classification systems prior to this one, by Gordijn et al., described 35 systems published in English developed between 1954 and 2006 [8]. In 2009, Flenady et al. identified and tested six contemporary systems commonly used for stillbirth in HIC using independent teams across a number of countries [20]; a publication by Fraen et al. on challenges of data collection reviewed 11 systems [19]. In 2014, a systematic review of studies reporting factors associated with stillbirth in LMIC found just seven systems used [21]. We identified far more systems developed and used than these previous reviews. While our comprehensiveness (including no language restriction) may partially explain this difference, the inclusion of “modifications”, even if minor, is likely the major reason. We did this both because even slight modification may affect data comparability, and because modification may reflect
users’ perceptions of the inadequacy of available systems. We also included systems for both stillbirth and neonatal death, whereas most previous reviews focused on stillbirth.

While the overarching aim of all perinatal death classification systems is to understand causes to enable prevention, systems had multiple specific purposes and rationales, including national tracking (e.g., MRC 2002-PPIP [50]), in-depth research (e.g., Flenady 2009-PSANZ-PDC [28]), or more generally to overcome shortcomings of existing systems and meet context-specific needs [4, 31, 33] (see Additional file 12). Numerous incompatible systems reduce the utility of the data of each [43], yet few papers describing new or modified systems mentioned other systems. Only one-third of systems were “widely used” by our definition (see Table 2), and systems collectively classified only a small proportion of perinatal deaths globally between 2009 and 2014 (other than those estimating global causes, e.g. CHERG for NND only); none were classified in six of the 12 highest-burden (LMIC) countries. National systems were used in only a few countries (see Additional file 8), and there were none in the two highest-burden HIC (the US and Russia). Low coverage may be due to lack of the required data or poor system accessibility, both of which may reflect systems’ unsuitability, especially for low-resource settings. The size of the burden itself, requiring allocation of scarce resources to healthcare, may place a high opportunity cost on the resources required for classification, even in high-resource settings. Coverage may also be hampered by a silo effect, with over half of systems only used by the teams that created or modified them, and most only used in the regions where they were created, possibly because many systems are context-specific. For instance, there are more NND-only systems in LMIC, a situation which may be driven by the relative lack of SB data and attention to SB in LMIC. With nearly twice as many systems created in HIC as in LMIC, this suggests potential LMIC users may also have less choice in terms of available, locally relevant systems. In particular, limited diagnostic capacity in low-resource settings may make some systems based on pathology findings impossible to use.

The multiple systems reflect many challenges for the uptake of a system aimed at global application. This review suggests ways to increase global uptake. Characteristics found to be common among all systems (e.g. requiring a single cause of death and lacking hierarchy), and among the most widely-used systems (e.g. availability of rules and definitions), could be considered proxies for what users expect in an effective system. The characteristics that were rarest (e.g. using ICD codes and having been tested for reliability) may reflect not only user preferences, but also the resources available to users. A globally acceptable system might also benefit from incorporating the most common characteristics of systems used only in LMIC (to increase uptake across settings), and from exploring in greater depth than was possible in this study the reasons why certain features (e.g. reliability testing) were quite uncommon. A global system must accommodate not only low levels of data in poorer settings but also more detailed data in HIC settings, or other regions with access to better diagnostics [44]. Disseminating a system widely, removing language barriers, offering electronic as well as paper-based data collection, training users, assessing system reliability, and addressing users’ concerns with established systems would increase acceptance and uptake of any system intended for global use, including by governments. Systems’ broad albeit thin reach also presents opportunities; for instance, a new global system could be introduced through existing channels for classification.

The ICD is the global standard for assigning diagnoses. It is used for reporting deaths in 117 countries, sometimes including perinatal deaths, for example in three of the highest burden countries—China, Tanzania and Bangladesh [32, 40, 45]. However, perinatal deaths, in particular stillbirths, remain poorly captured and classified; this is a driving factor in the WHO’s work to create the ICD-PM. Many systems are incompatible with the ICD’s key principles, such as identification of a single cause of death, use of ICD codes, incorporation of associated factors, and distinguishing between IP and AP, and between SB and NND. This may be in part due to low awareness of its importance, but is more likely to be due to the ICD’s limited utility for classification of stillbirths. It is hoped that future revisions of the ICD will address this limitation. A particular concern is the low percentage of systems that require recording the timing of deaths (IP vs AP). This information is among the most basic and is obtainable even in low-resource settings, yet was only required by 16 of the 55 systems that include SB, reflecting the larger issue of insufficient data on IP stillbirths worldwide, despite the huge burden and preventability of most of these deaths [2].

This review had some limitations. The comprehensive search notwithstanding, some systems may not have been identified; no regional databases were searched. This would have led to an underestimate of the true number of systems, possibly weighted toward those in LMIC. The quality of included publications was not assessed, so data used to assign values for percent of deaths classified as “other” and “unexplained” and number of deaths classified was likely of varying quality. For national systems, since only the most recent publication within 2009-2014 was included, the number of deaths classified may be an underestimate. However, this would likely not have affected our findings significantly. Data for some variables were difficult to ascertain, for instance the number of languages in which a system was available, possibly leading to non-differential misclassification of systems for some variables. We were unable to review findings with system authors or double-extract data from non-English publications (6 % of included publications).

**Conclusions**

Stillbirth and neonatal death deprive millions of babies of their right to grow and develop, bereaving their parents and other family members and affecting millions of caregivers. Though this burden is decreasing, progress is slow. Greater effort must be made, through increased attention from policy-makers, bolder partnerships across the reproductive, maternal, and child health spectrum, country leadership, and innovative programs to scale up effective interventions. Classification of causes is critical to this effort. Whether directly or indirectly, the ultimate aim of classification is to provide data that can be useful in reducing stillbirth and neonatal death. A prime example of how classification systems can be useful is in the recording of stillbirth timing—whether antepartum or intrapartum. This data should be generally available even in low-resource settings and is actionable, even amidst the chaos of multiple systems.

This systematic review provides a comprehensive summary of the landscape of contemporary classification systems for stillbirths and neonatal deaths to inform the development of a globally acceptable approach for the accurate determination of causes of death. In part two of the study, we assess the alignment...
of the 81 identified systems with expert-identified characteristics for a globally acceptable classification system [23]. We hope that this study will ultimately prove useful not only to researchers and practitioners, but also to bereaved families in all countries who want to know “what happened”.

Endnotes

1There was not a one-to-one correspondence between included publications and included systems (many publications included more than one system; multiple publications used the same system); hence search results do not demonstrate the total number of systems found.

2The system was National Services Scotland 2013-FIGO, [27] which only allocates stillbirths to one of two “causes”, SB weighing 1000 g + and normally formed SB weighing 500 g +, both of which were included as “unexplained” causes in the BMC Supplement companion paper that we used as our guide.

Table 2 Widely used classification systems for causes of stillbirth and neonatal death, 2009–2014: Selected characteristics

<table>
<thead>
<tr>
<th>Systems classifying both SB and NND</th>
<th>Country of origin</th>
<th>Region and countries of use (2009–2014)</th>
<th># deaths classified (2009–2014)</th>
<th># causes classified</th>
<th># levels</th>
<th>Ass’d factors vs causes</th>
<th>Ass’d factors vs causes</th>
<th>Defs</th>
<th>Rules</th>
<th>Max % unexp</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMACE 2010-maternal &amp; fetal [36]</td>
<td>UK</td>
<td>HIC (UK)</td>
<td>6,804</td>
<td>13</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Some</td>
<td>Yes</td>
<td>39%</td>
</tr>
<tr>
<td>CMACE 2011-maternal &amp; fetal [46]</td>
<td>UK</td>
<td>HIC (UK, Wales)</td>
<td>9,786</td>
<td>12</td>
<td>3</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>51%</td>
</tr>
<tr>
<td>Cole 1986 [26]</td>
<td>UK</td>
<td>Both (Nigeria, Netherlands)</td>
<td>345</td>
<td>10</td>
<td>2</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>55%</td>
</tr>
<tr>
<td>Engemann 2012 [30]</td>
<td>USA</td>
<td>LMC (Guatemala, DRC, Zambia, Pakistan)</td>
<td>252</td>
<td>7.5</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>No</td>
<td>12%</td>
</tr>
<tr>
<td>Flewady 2009-PSANZ-PDC [28]</td>
<td>Australia</td>
<td>Both (Australia, Vietnam, New Zealand, Madagascar)</td>
<td>13,416</td>
<td>7</td>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>Some</td>
<td>Yes</td>
<td>54%</td>
</tr>
<tr>
<td>Freen 2009-Codac [11]</td>
<td>Norway</td>
<td>HIC (Norway, Italy, Wales)</td>
<td>872</td>
<td>3</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>53%</td>
</tr>
<tr>
<td>Kerteweg 2006-Tulip [35]</td>
<td>Neth.</td>
<td>HIC (Netherlands)</td>
<td>3,603</td>
<td>6</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>23%</td>
</tr>
<tr>
<td>Mananath 2010 [47]</td>
<td>Nepal</td>
<td>LMC (Nepal)</td>
<td>1,272</td>
<td>9</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>10%</td>
</tr>
<tr>
<td>National Services Scotland 2013-FIGO [27]</td>
<td>Scotland</td>
<td>HIC (Scotland)</td>
<td>1,249</td>
<td>4</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>No</td>
<td>100%2</td>
</tr>
<tr>
<td>MRC 2002-PPIP [48]</td>
<td>South Africa</td>
<td>LMC (South Africa)</td>
<td>47,238</td>
<td>9.5</td>
<td>1</td>
<td>Yes</td>
<td>Yes</td>
<td>Some</td>
<td>No</td>
<td>35%</td>
</tr>
<tr>
<td>Wigglesworth 1980 [7]</td>
<td>UK</td>
<td>Both (Turkey, Bangladesh, UK, Ireland, Nepal, Pakistan, Brazil)</td>
<td>4,558</td>
<td>5</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>56%</td>
</tr>
<tr>
<td>Winbo 1998-NICE [31]</td>
<td>Sweden</td>
<td>LMC (Tanzania)</td>
<td>2,494</td>
<td>13</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>46%</td>
</tr>
<tr>
<td>Wood 2012 [40]</td>
<td>UK</td>
<td>HIC (Scotland)</td>
<td>8,332</td>
<td>2</td>
<td>2</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>60%</td>
</tr>
<tr>
<td>Systems classifying SB only</td>
<td>Dudley 2010-INCODE [34]</td>
<td>USA (Canada, USA)</td>
<td>1,075</td>
<td>4</td>
<td>7</td>
<td>No</td>
<td>n/a</td>
<td>Some</td>
<td>n/a</td>
<td>26%</td>
</tr>
<tr>
<td>Gardosi 2005-ReCoDe [37]</td>
<td>UK</td>
<td>Both (Italy, UK, France, Portugal, New Zealand, Germany, Brazil)</td>
<td>25,779</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>n/a</td>
<td>Some</td>
<td>Yes</td>
<td>26%</td>
</tr>
<tr>
<td>Seaton 2012 [50]</td>
<td>UK</td>
<td>HIC (UK)</td>
<td>21,352</td>
<td>1</td>
<td>9</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>No</td>
<td>41%</td>
</tr>
<tr>
<td>Varti 2008-Stockholm [33]</td>
<td>Sweden</td>
<td>HIC (Sweden)</td>
<td>1,089</td>
<td>17</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>19%</td>
</tr>
<tr>
<td>Systems classifying NND only</td>
<td>Black 2010-CHERS [51]</td>
<td>USA (Global)</td>
<td>&gt;1 million</td>
<td>8</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Some</td>
<td>Yes</td>
<td>23%</td>
</tr>
<tr>
<td>CMACE 2010-neonatal [36]</td>
<td>UK</td>
<td>HIC (UK, Ireland)</td>
<td>7,717</td>
<td>10</td>
<td>2</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>6%</td>
</tr>
<tr>
<td>Cole 1989-ICE [52]</td>
<td>UK</td>
<td>HIC (Canada, USA)</td>
<td>38,692</td>
<td>8</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>15%</td>
</tr>
<tr>
<td>Flewady 2009-PSANZ-NID [28]</td>
<td>Australia</td>
<td>HIC (Australia, New Zealand)</td>
<td>3,449</td>
<td>11</td>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Some</td>
<td>n/a</td>
<td>4%</td>
</tr>
<tr>
<td>Lawn 2006-CHERS [53]</td>
<td>South Africa</td>
<td>Both (sub-Saharan Africa, Laos, Uganda); also global</td>
<td>&gt;1 million</td>
<td>7</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>Yes</td>
<td>Yes</td>
<td>23%</td>
</tr>
<tr>
<td>Lawn 2012 [54]</td>
<td>South Africa</td>
<td>Global</td>
<td>&gt;1 million</td>
<td>5</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>No</td>
<td>11%</td>
</tr>
<tr>
<td>Lawn 2015 [55]</td>
<td>South Africa</td>
<td>Global</td>
<td>&gt;1 million</td>
<td>5</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>No</td>
<td>11%</td>
</tr>
<tr>
<td>Rocha 2011 [56]</td>
<td>Brazil</td>
<td>LMC (Brazil)</td>
<td>2,893</td>
<td>Unclear</td>
<td>6</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Smith 2010 [57]</td>
<td>UK</td>
<td>HIC (UK)</td>
<td>18,524</td>
<td>10</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Winter 2013-Rwanda [58]</td>
<td>Rwanda</td>
<td>LMC (Bhutart, Rwanda)</td>
<td>628</td>
<td>7</td>
<td>1</td>
<td>No</td>
<td>n/a</td>
<td>No</td>
<td>n/a</td>
<td>0%</td>
</tr>
</tbody>
</table>

Her Hierarchical or not, IP vs AP Requires distinguishing antepartum from intrapartum stillbirth, SB vs NND cats Includes separate categories for stillbirths and neonatal deaths, Single cause Requires single cause to be identified, # causes Number of causes at top level, Ass’d factors Allows associated factors to be recorded, Ass’d factors vs causes Requires associated factors and causes to be distinguished from one another, Defs Includes definitions for all causes, Rules Includes guidelines for assigning cause of death, Max % unexp Maximum percent of deaths classified as “unexplained” (see Additional file 10 for more detail)

NOTE: All data other than region/countries of use and number of deaths classified was taken from reference papers for included systems, which are cited in the first column. "Widely used" is defined as used to classify >1000 deaths and/or in 2+ countries between 2009 and 2014

1Defined as country of first affiliation of first author of reference paper
2Region and countries of use and numbers of deaths classified all taken exclusively from included papers between 2009 and 2014 that reported use of the included systems
3Average taken when there was more than one set of levels (e.g. one for stillbirths and one for neonatal deaths)
4The system only allocates stillbirths to one of two “causes”, both of which are considered to be “unexplained”; see Additional file 10 for more detail
5The system has a category for “unexplained” but there was no data reported
6These systems have no category for “unexplained”

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**Abbreviations**


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**Availability of data and materials**


**Authors’ contributions**

VF and FF conceptualized the study. SHL and VF designed the study; SHL, ZT and HR carried out data extraction; VF acted as arbiter for disagreements on data extraction; SHL coordinated the study, conducted all data analysis and drafted the paper; VF, AW, FK, HB, JJE, GS, OT, MG, EA, RP, and EM reviewed early drafts of the manuscript. All authors (SHL, ZT, HR, EA, HB, JJE, JFF, JG, SG, AMG, AEHP, FK, JL, EMM, RP, GCSS, ÖT, AMW, VF) read and approved the final manuscript.

**Competing interests**

The lead author, SHL, has no competing interests. ZT, HR and AW have no competing interests. The remaining authors have been involved in the development or evaluation of existing perinatal death classification systems.

**Consent for publication**

Not applicable, as no individual person’s data has been reported in this paper.

**Ethics approval and consent to participate**

Not applicable, as no individual person’s data has been reported in this paper.

**References**


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