New technologies for essential newborn care in under-resourced areas: what is needed and how to deliver it

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Globally, the largest contributors to neonatal mortality are preterm birth, intrapartum complications and infection. Many of these deaths could be prevented by providing temperature stability, respiratory support, hydration and nutrition; preventing and treating infections; and diagnosing and treating neonatal jaundice and hypoglycaemia. Most neonatal health-care technologies which help to accomplish these tasks are designed for high-income countries and are either unavailable or unsuitable in low-resource settings, preventing many neonates from receiving the gold standard of care. There is an urgent need for neonatal health-care technologies which are low-cost, robust, simple to use and maintain, affordable and able to operate from various power supplies. Several technologies have been designed to meet these requirements or are currently under development; however, unmet technology needs remain. The distribution of an integrated set of technologies, rather than separate components, is essential for effective implementation and a substantial impact on neonatal health. Close collaboration between stakeholders at all stages of the development process and an increased focus on implementation research are necessary for effective and sustainable implementation.

Keywords: Neonatal health-care, Low-resource settings, Global health technologies, Preterm birth, Neonatal infection, Intrapartum complications

Introduction

Despite worldwide advances in overall health-care quality and access, neonatal survival remains a global challenge. Over 3 million neonatal deaths occur annually, and these deaths comprise more than 40% of under-5 mortality.[1] Globally, neonatal deaths are unevenly distributed – 99% occur in low- and middle-income countries (LMICs).[2] There is also an increased burden of morbidity among survivors, and it is estimated that over 200 million children under 5 years are not reaching their developmental potential.[3]

One factor contributing to this inequality is a lack of basic neonatal care technologies in low-resource settings. Over the last century, with a focus on basic technologies and improved care regimens, neonatal mortality rates (NMRs) in the United States and United Kingdom decreased from 40 to less than 15 deaths per 1000 births; the NMR further decreased with the development of neonatal intensive care units (NICUs) and more complex technology.[4] While the NMR in some LMICs has begun to fall in recent decades, it remains above 30 in the World Health Organization (WHO)-defined LMIC regions of Africa, South-east Asia and the Eastern Mediterranean, where even basic technology and improvements in care have not been successfully introduced.[5] Although most neonatal technologies have simple functional objectives, they are marketed for high-resource settings and can be prohibitively costly and largely unavailable to low-resource hospitals.[6–8] Even when made available through donations or other funding, most health-care technologies are designed for use in high-resource settings and can be inappropriate for other settings. In addition to being prohibitively expensive,[9] they can be overly complex in operation with built-in obsolescence, and may require a constant supply of consumables, climate control, uninterrupted electric power supply, and frequent manufacturer support and maintenance.[6–8] According to WHO, up to

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three-quarters of these commercial devices do not function properly in low-resource settings and remain unused.[8] Lack of regular maintenance and lack of spare parts are key contributors to this problem.

Without new approaches to global neonatal care, inequality in neonatal outcomes will persist. The development of newborn care technologies which are appropriate, affordable, accessible and available in low-resource settings can help reduce this disparity.[6,8] A review by Thairu *et al.*[6] contains a comprehensive list of neonatal care devices designed for low-resource settings and concludes that the majority are in development and often face major challenges in scale-up.[6] Here, the physiological background of the primary causes of neonatal death, the gold standard for managing them in high-resource settings, and the current challenges and solutions associated with this management in low-resource settings are outlined. While reduction in neonatal mortality can result from interventions throughout the maternal-infant continuum of care and in a variety of care settings, this review focuses on facility-based, post-natal interventions. Finally, we advocate for technological innovation in neonatal health-care as well as innovation in delivery – with a focus on providing a complete suite of technologies which address the majority of health challenges faced by newborns.

Causes of Newborn Death

Globally, 82% of neonatal deaths can be attributed to three causes – prematurity and low birthweight (LBW) (35%), intrapartum-related complications, including birth asphyxia and birth trauma (24%), and infection (23%)[10,11] (Fig. 1). The physiological background and standard management of these three causes are outlined below.

Premature birth

A premature newborn is not sufficiently mature to achieve optimum independent physiological function and is vulnerable to increased morbidity and mortality. Special attention to factors which endanger the preterm newborn is needed to improve the chance of survival and full development. Pulmonary surfactant levels are inadequate and respiratory bronchioles are not fully developed until approximately 36 weeks of gestation,[12] making premature babies prone to develop respiratory distress syndrome (RDS). Immaturity of other physiological systems such as the nervous, cardiovascular, immune, musculoskeletal, gastro-intestinal, endocrine and renal systems, as well as the skin, puts pre-term newborns at particular risk of infection, poor thermoregulation, hypoglycaemia, apnoea of prematurity, intraventricular haemorrhage, anaemia, jaundice, haemorrhagic disease of the newborn and necrotizing enterocolitis.[4,13–15]

Careful monitoring and support of the neonate's physiological functions are required in order to prevent, detect and treat specific complications of prematurity. These include good resuscitation procedures, provision of adequate warmth, fluids and feeds, and monitoring of oxygenation, body temperature, weight, glucose and bilirubin levels, as well as close monitoring for clinical signs of disease. Careful oxygen therapy, continuous positive airway pressure (CPAP) or mechanical ventilation are required for respiratory distress whether owing to RDS or other causes. When indicated, surfactant therapy is provided. Direct skin-to-skin contact between mother and newborn (kangaroo mother care, KMC) or external heating are used to prevent and treat hypothermia. Monitoring is required to detect apnoeic episodes in infants with apnoea of prematurity (AOP). Treatment of AOP includes resuscitation steps

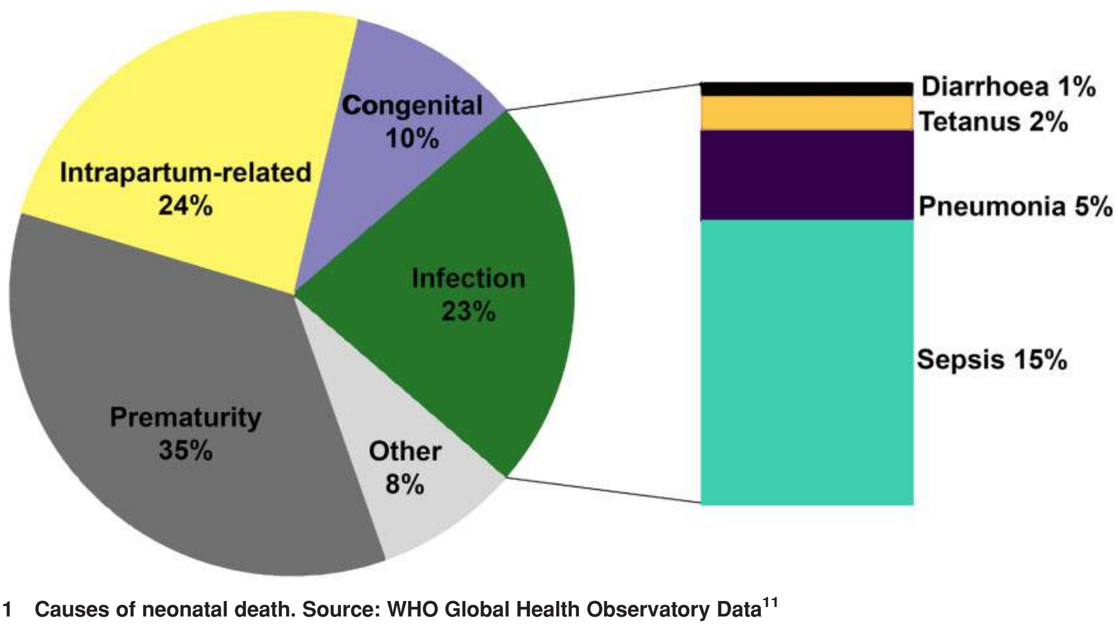

Figure 1 Causes of neonatal death. Source: WHO Global Health Observatory Data[11]

such as stimulation and manual ventilation, and respiratory stimulants such as caffeine, CPAP and mechanical ventilation. All these are coupled with steps to identify and treat the underlying cause.[16–18]

Intrapartum-related complications

Birth asphyxia occurs when an infant does not receive sufficient oxygen before, during or immediately after birth. Hypoxic-ischaemic encephalopathy (HIE) is a common neonatal complication that occurs when the infant's brain is deprived of oxygen.[19] HIE results from poor delivery of oxygen to the neural tissue,[19] leading to tissue hypoxia and metabolic acidosis.[18] This culminates in tissue injury from direct hypoxic insult as well as indirect injury from free radicals during re-oxygenation.[18–22] These processes evolve over time, destroy essential components of the cell and lead to cell death.[20,23,24] The resultant neonatal complications include multi-organ failure, neonatal encephalopathy and death.[25] Symptoms change with time and depend on the severity, timing and duration of the initial injury.[19]

Management begins with prevention through good antenatal care, skilled birth attendants and emergency obstetric care, which significantly reduce intrapartum-related deaths in term infants.[20,26] 'Neonatal resuscitation' encompasses the set of interventions to establish breathing and circulation at birth and is the next step in reducing birth asphyxia.[27,28] It is critical to quickly identify infants at risk of neonatal encephalopathy and determine the time and extent of hypoxic-ischaemic brain injury.[23,24] Current recommendations for HIE management include cooling, fluid restriction, seizure control, management of acid-base and electrolyte imbalance and vital organ support.[29] Therapeutic hypothermia is an effective neuro-protective intervention in moderate-to-severe HIE in infants <6 hours of age.[19,22,23,30]

Infection

Neonates are particularly prone to infections owing to their poor innate and adaptive immune systems. Infection can be transmitted from the mother antenatally through the placenta or vaginal canal as well as by bacterial contact during peri-natal and post-natal periods. Various factors predispose neonates to infection, including prematurity, maternal infection and prolonged rupture of membranes. Some infections are acquired in hospital or in the community after discharge.

Neonatal infections can manifest as urinary tract infection, tetanus, pneumonia, meningitis, sepsis and diarrhoea. Management may require supportive measures to maintain oxygenation, perfusion and vital organ function as well as investigations to identify causative organisms and rule out complications. Specific treatment constitutes parenteral antibiotics, mainly first-line penicillin and gentamicin, aiming to target the most common causative organisms.[25] Where cultures are available, antibiotic therapy is tailored to growth and sensitivity results.

Technologies for Essential Newborn Care in Low-Resource Settings

The three main causes of neonatal death are complex and require an array of tools for diagnosis and treatment. Moreover, the causes are interconnected and have considerable overlap.[31] Fig. 2 illustrates the links between the causes of death, their resulting complications and the tools required for management. The overlapping nature of the complications and management tools is clear – a single tool can be useful in addressing multiple root causes of death, and each cause of death requires multiple tools for management.[4,7,32–35] The tools have been classified into six main functions: (i) provide hydration and nutrition, (ii) prevent and treat infections, (iii) provide temperature stability, (iv) provide breathing support, (v) monitor and treat jaundice, and (vi) monitor and treat hypoglycaemia. A set of technologies which accomplishes these six functions would enable a low-resource facility to address the majority of cases of neonatal death. The gold standard of care for each of these six functions is reviewed in the next section, and the challenges and potential solutions to improve care in low-resource settings are discussed.

Provide hydration and nutrition

Gold standard of care

Sick, small-for-gestational-age (SGA) and preterm babies have special fluid and nutritional requirements.[36,37] Intravenous (IV) infusions of water, electrolytes and glucose are given to the neonate during the first weeks of life to maintain fluid and electrolyte balances and to provide carbohydrates for basic metabolic processes.[38] Treatment is meticulously managed through weight monitoring, fluid intake/output recording and urine and blood analyses.[37,38]

Breastfeeding is the goal for all infants, but those who are sick and premature may initially require alternative feeding methods.[39] Total parenteral nutrition (TPN) is the exclusive management of nutrition through IV delivery of macro- and micronutrients, and is reserved for very premature or sick infants.[38,40] When an infant can tolerate intragastric feeding, it receives the mother's pump-expressed breast-milk with an infusion pump or a gravity-fed drip.[41] Once an infant can swallow, it transitions to mouth feeding with a cup or spoon. Finally, when proper sucking and attachment is learned, the infant breastfeeds exclusively.[39,41] Breast-milk may be supplemented with various macro- and micronutrients if an infant is not receiving proper nutrition.[36,41] Donor milk or special formula is used when a mother's own milk is not available or safe.[41,42]

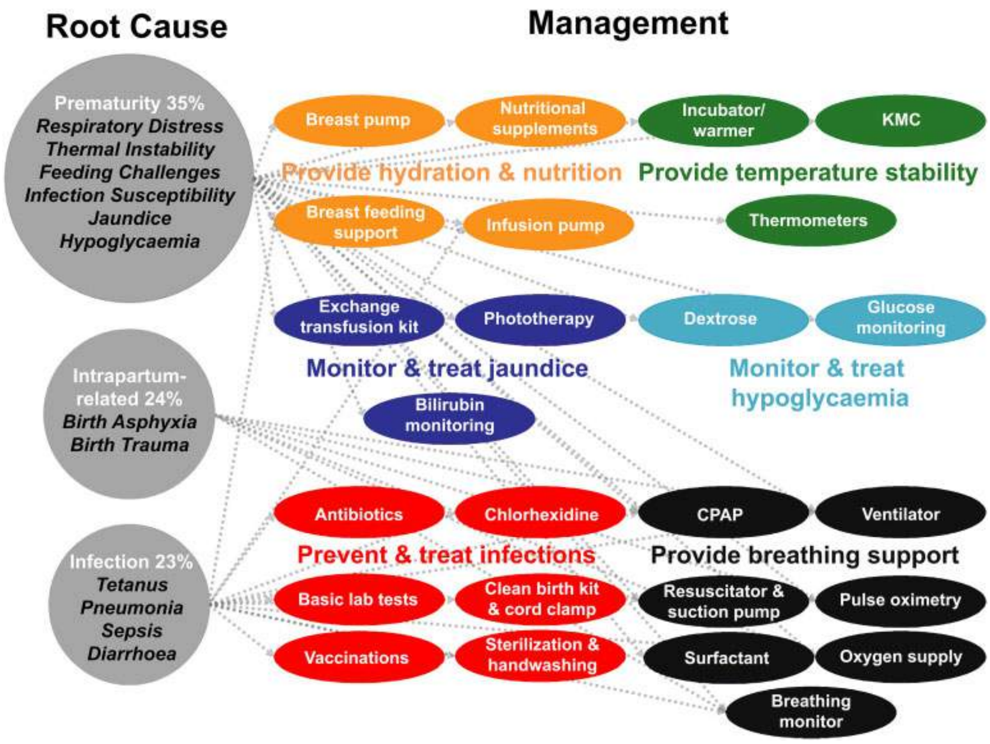

Figure 2 Primary causes of neonatal death and their corresponding management tools. Tools are grouped into general intervention categories, although some tools may be useful in multiple categories. Sources: Mandate,[32] March of Dimes et al.,[4] Bhutta et al.,[33] The Partnership for Maternal, Newborn & Child Health,[34] Wyatt,[7] Lawn et al.[35]

Challenges and solutions in low-resource settings

Fluid therapy requires delivery at precise volumes and flow rates, and fluid overload can be life-threatening.[38] When a pump is not available, a basic drip set is used.[38] This increases the risk of over-infusion, especially if the drip set does not have a burette.[38] TPN is extremely rare in low-resource settings owing to the high risk of infection, insufficient training, high cost, inaccurate fluid delivery methods and insufficient laboratory-based monitoring.[38,41,43] To our knowledge, technologies designed to address fluid delivery in low-resource settings are limited. Currently in development, the Maji device is a mechanical volume regulator that prevents over-infusion during gravity-driven fluid therapy.[44] Also in development, the DripAssist device monitors flow rates during gravity-driven fluid therapy.[45] A low-cost, versatile syringe or infusion pump is still needed to help with IV delivery of fluids and electrolytes, as well as enteral and parenteral feeding.[4] An interactive job aid, whether electronic or physical, could also help overburdened nurses manage the book-keeping and calculations required in providing hydration and nutrition; performing calculations mentally significantly decreases accuracy.[46] An accurate, convenient and low-cost weighing method is needed for managing fluid balance and monitoring growth.[38]

Expression and storage of human milk are difficult in low-resource settings.[43] Inadequate breast pumps can lead to difficulty in expressing milk and, ultimately, decreased production;[47] sterile containers and methods of refrigeration, freezing and pasteurization are also required for breast-milk management.[43] Bottle-feeding is dangerous in low-resource settings because of the difficulties of sterilization.[38,41] Safe administration of formula or donor milk is a challenge because wet nurses must be properly screened for infection and formula must be prepared hygienically.[38] Breast-milk fortifiers can also be prohibitively costly.[48,49]

Appropriate and more affordable tools are needed for the expression, storage and delivery of breast-milk for the non-breastfed infant. One technology being developed is the JustMilk Nipple Shield Delivery System, which would allow a mother to provide drugs and supplemental nutrition through a dissolvable tablet absorbed during breastfeeding.[50] Innovative designs are needed for an appropriate, affordable and efficient breast-pump.[38] New methods to refrigerate and freeze milk without a constant power supply would be ideal. Finally, re-usable feeding accessories with appropriate methods of sterilization would be beneficial in settings where a constant supply of consumables is not feasible.

Prevent and treat infections

Gold standard of care

Prevention of infection is key and begins during pregnancy, when the mother is tested for Group B Streptococcus between the 35th and 37th week of pregnancy; if infection is detected, she is treated with antibiotics when labour commences to prevent the infection being passed to the infant during delivery.[51] Tetanus toxoid vaccinations are given routinely to pregnant women to prevent mother-to-child transmission of tetanus. Neonatal nosocomial infection is prevented by frequent hand-washing and sterilization of equipment and instruments. If an infection develops, laboratory and radiographic tests are used for diagnosis.[52] Depending on cause, common treatment options include antibiotics, resuscitation with IV fluids, blood transfusions and oxygen or other means of respiratory support.[52,53]

Challenges and solutions in low-resource settings

Neonatal infections are more common where access to basic health services is limited and hygiene is poor.[35] The most important protective interventions for nosocomial infections are frequent hand-washing, exclusive breastfeeding and facility cleanliness,[54,55] but widespread implementation of these interventions is challenging in low-resource settings. Infants (and their mothers) who are malnourished or have a chronic illness are at risk of infection because of immunosuppression and a susceptibility to preterm birth.[56] Passive transfer of maternal antibodies does not occur until 29 weeks of gestation.[57] Thus, preterm infants, 92% of whom are born in developing countries, may have an increased risk of infection, regardless of the mother's antibody status.[4]

Tetanus often results from unhygienic handling of the umbilical cord at birth, but can be prevented by ante-natal immunization. The United Nations Children's Fund (UNICEF) estimates that a complete tetanus toxoid vaccine course costs ~US$1.20 per woman,[58] which includes operational costs and funds to promote clean birthing practices. Cleansing the umbilical stump with chlorhexidine (US$0.03/ml) also substantially reduces sepsis and deaths.[53]

Diarrhoea results in increased losses of water, electrolytes and/or nutrients, making fluid and electrolyte replacement therapy essential.[59] Frequent breastfeeding provides nutrients and fluid and in many cases can stabilize the neonate without further intervention. In some cases, however, IV fluid administration is required. This can be challenging in settings where controlled delivery of fluids is not available.

Clinical signs of pneumonia and sepsis overlap and require similar empirical treatment regimens,[51,54] including supportive care and antibiotics. The aims of supportive care are to regulate the infant's temperature, carefully manage fluids and energy requirements through oral or gastric milk feeds and/or IV support, and provide oxygen therapy.[60] While antibiotics to treat pneumonia and sepsis are relatively inexpensive,[61] factors limiting treatment are disease recognition and diagnostic capability,[62] as well as the increasing anti-microbial resistance in NICUs.[63] When gold standard diagnostics are unavailable, careful clinical assessment in concert with inexpensive commercial point-of-care monitors, such as pulse oximeters and hand-held portable whole-blood lactate analyzers (as used in fitness applications), have been shown to help determine severity of illness and appropriate treatment.[52,64–66] Other tests to diagnose sepsis are being developed, including an inexpensive device (US$0.60/strip) for measuring blood levels of histones, which have been shown to be major mediators of thrombosis, inflammation and death in sepsis.[67] An international team of technical experts has recommended two priorities for improving infection interventions: the development of new oral antibiotics and interventions to prevent infection transmission during childbirth.[68]

Provide temperature stability

Gold standard of care

WHO has defined hypothermia as a body temperature of <36.5°C and it is further divided into three levels: mild (36.0–36.5°C), moderate (32.0–35.9°C) and severe (<32.0°C).[69] To prevent hypothermia, WHO recommends provision of a 'warm chain', including warming the delivery room, immediate drying of the neonate, skin-to-skin contact for the infant, early and exclusive breastfeeding, postponing bathing, use of appropriate clothing and bedding, placing the mother and baby together, provision of warmth in transport and resuscitation areas, and training to raise awareness of the importance of hypothermia.[70] In high-resource settings, these steps are easily accomplished through advanced infrastructure, technologies and training. Delivery rooms and NICUs are tightly controlled for temperature and humidity, and hypothermic infants can be placed in incubators or overhead radiant warmers. Incubators have automated temperature and humidity control, and can also help reduce risk of infection as they separate infants from each other and from the open NICU environment. Overhead radiant warmers also have automated temperature control and are often used immediately after birth during Apgar scoring and/or resuscitation, as they still allow easy access to the infant.

Challenges and solutions in low-resource settings

Hypothermia is extremely common in LMICs; in studies in Ethiopia, Zambia and Zimbabwe, over half of newborns evaluated were hypothermic.[71] Unfortunately, there are several obstacles to preventing hypothermia in low-resource settings: hospitals are often minimally insulated and room temperatures are not tightly controlled; incubators and commercial radiant warmers are not affordable and require physical infrastructure that might not be available.[70] Alternative approaches to managing hypothermia include preventing heat loss and providing external sources of warmth.[70,72]

A number of studies have shown that the simple practice of wrapping a newborn's wet body from the shoulders downward in a plastic bag immediately after delivery significantly lowers hypothermia rates in pre-term and LBW infants.[72–75] These occlusive wraps reduce evaporative and convective heat loss, and are affordable and available in low-resource settings.[73] Similarly, topical emollients such as mineral oil and lanolin may help reduce water and heat loss in pre-term newborns.[71]

The simplest source of external warmth is KMC. A recent Cochrane review concluded that KMC for LBW infants is an effective alternative to conventional newborn care.[76] KMC is less expensive than conventional methods,[77] reduces risk of mortality, sepsis and hypothermia, and increases growth, breastfeeding and mother-to-infant attachment.[76] KMC can be continued at home.

In cases of severe maternal or neonatal illness, re-warming infants on a heated mattress has proven to be a simple and effective alternative to incubators and radiant warmers.[72,78,79] In one design, a plastic bag filled with 10 L of water is heated using a heating pad; temperature can be electronically regulated between 35–38°C.[78] Hypothermic neonates assigned to the heated mattress returned to normothermia more rapidly and were more likely to survive than those treated in an air-heated incubator.[78] Electrical power failures occurred almost every day during the study; the high heat capacity of the water-filled mattress may have resulted in higher, more stable temperatures than in the incubator. The Embrace Warmer is a similar alternative source of external warmth designed for newborns in low-resource environments.[70] The device is an infant-sized sleeping bag that contains a reheatable phase change material which maintains near constant temperature over several hours.

Traditional incubators often fail owing to harsh environments in low-resource settings: a programme in Nigeria developed a local capacity to recycle obsolete incubator casings and restore warming capacity at less than 25% of the cost of purchasing new incubators.[80] Several low-cost incubators (projected costs of US$80–625) have been designed explicitly for low-resource settings, including the LifeRaft Infant Incubator, m.kat, NeoNurture, and a disposable incubator.[70,81]

There are promising early-stage alternatives for providing external warmth, but more clinical data are needed to assess their efficacy. There is also a substantial need for better tools to reliably monitor for hypothermia in settings where the ratio of caregivers to infants is low. Better tools are needed to implement and maintain a chain of warmth from delivery to discharge, especially for premature babies.

Provide respiratory support

Gold standard of care

At birth, an unresponsive infant is immediately resuscitated, often involving endotracheal intubation.[82] To test for respiratory conditions caused by infection such as pneumonia and sepsis, blood or other bodily fluids are sent to the laboratory.[52] Common respiratory conditions not caused by infection include transient tachypnoea of the newborn, meconium aspiration syndrome, birth asphyxia and RDS. Chest radiography, CT scans or other imaging modalities are employed as standard procedure for all infants who exhibit respiratory distress in order to diagnose complications such as a collapsed lung or material within the lungs.[52] Blood gas analysis and pulse oximetry provide information on blood acidity and oxygen and carbon dioxide content to determine the treatment required.[83] Depending on the diagnosis, treatment options for respiratory distress include antibiotics, supplemental oxygen, invasive and non-invasive ventilation and surfactant replacement.[53,84]

Challenges and solutions in low-resource settings

Caregivers in low-resource settings have often not been properly trained in resuscitation procedures.[35] Although endotracheal intubation is commonly used for resuscitation, initial ventilation with a bag and mask is sufficient for the majority of infants.[82,85,86] UNICEF's partnership with Laerdal Global Health offers their resuscitation product along with training materials to low-income countries at a low price (< US$16.00).[87] Trained birth attendants using quality resuscitation devices can decrease mortality by up to 30%.[88]

In low-resource settings, oxygen cylinders or concentrators often deliver almost pure oxygen to infants struggling to breathe. While the delivery of oxygen improves survival rates,[84] excessive blood oxygen levels may result in oxygen toxicity and retinopathy.[89] The development of low-cost flow-splitters and air-oxygen mixers for use in these settings could improve the efficiency and safety of oxygen therapy, respectively. Moreover, to reduce the risk of retinopathy, treatment with supplemental oxygen must be synchronised with pulse oximetry.[90] One promising technology is the Kenek Edge[91,92] (< US$50) which measures peripheral oxygen saturation (SpO_2) by connecting to supported mobile phones and tablets through the audio port.[93] However, this device is not yet suitable for neonates and has not been tested clinically. Lifebox®[94] is an affordable (US$250), commercially available SpO_2 monitor[6,95] which exceeds the WHO device design specifications.[95]

Many infants with respiratory distress require positive pressure to be directed to the alveoli in the lungs.[96] When mechanical ventilation is employed, the endotracheal tube connects the sterile lower respiratory system with the infant's external environment, increasing the possibility of nosocomial infection, especially in hospitals with poor infection control.[54,97,98] Non-invasive ventilation with CPAP can help manage respiratory distress, particularly in these settings,[54,98,99] as it is simpler than full ventilation and does not require intubation. The Pumani device is a low-cost (~US$400) CPAP which is safe, durable and simple to use and repair.[99,100] Another device, Diamedica Baby CPAP, incorporates an oxygen concentrator as an integral part of the CPAP unit for a price much lower than average (~US$2750).[101] In addition to CPAP, surfactant is highly successful in treating infants with RDS; however, it is expensive and intubation is required for administration.[83] Promising research is being conducted on the delivery of surfactant using Aerosurf®, an aerosol technology.[102]

Monitor and treat jaundice

Gold standard of care

Neonatal jaundice is assessed by measuring the concentration of bilirubin in the blood. Laboratory analysis determines the total serum bilirubin (TSB) and therefore the degree of jaundice. TSB measurement helps determine the effectiveness and appropriate cessation of jaundice therapy. Transcutaneous bilirubinometry (TcB) is often used for non-invasive, bedside estimation of bilirubin levels.[103]

Phototherapy is the use of blue light to break down bilirubin into non-toxic metabolites. It is the safest, most convenient and most common method for treating moderate levels of neonatal jaundice.[104] Although phototherapy is simple, it needs specific characteristics to be most effective: (i) a light emission spectrum of 400–520 nm, peaking at 450 ± 20 nm, (ii) direct light exposure on at least one horizontal body surface plane, and (iii) an irradiance level of ≥ 30 μW/cm^2/nm.[105–109] Phototherapy is provided by commercial devices containing LEDs, fluorescent tubes, halogen/tungsten lamps or fibre-optic systems.[110] LED devices are becoming most popular because of their narrow blue light spectrum, minimal heat production, power efficiency, low cost and long bulb lifetime.[111] A blood exchange transfusion is performed only when an infant does not respond to phototherapy or if initial TSB levels are above a threshold.

Challenges and solutions in low-resource settings

Although jaundice-induced brain damage (kernicterus) is considered largely preventable, it is still a leading cause of morbidity and mortality in developing countries.[38,105,112–116] Where TSB/TcB measurements are unavailable, visual estimation of bilirubin levels is used to diagnose and manage jaundice. Although adequate for initial screenings, visual estimation does not allow accurate determination of overall risk, especially in pre-term or dark-skinned infants.[104,105,117,118] A low-cost, point-of-care method of measuring bilirubin concentration would increase diagnostic capabilities, especially when laboratory analysis is not available.

Commercial phototherapy devices are often too expensive for low-resource settings.[110,119] Even when donated, the devices are difficult to maintain. Several studies have shown that donated devices are quick to break down owing to harsh operating conditions (heat/humidity, power surges, etc.) or provide sub-optimal therapy owing to burned-out or broken bulbs.[106,119–123] Inadequate training also contributes to improper clinical set-up and technical maintenance.[110] 'Homemade' phototherapy is common but poses safety risks and often provides insufficient irradiance.[110,124] In the absence of a reliable device or power supply, hospitals may use direct sunlight phototherapy which poses risks of sunburn, overheating, and dehydration. When phototherapy is ineffective, exchange transfusions become much more common but carry an added risk of infection, especially when performed in sub-optimal conditions.[125,126]

Several low-cost LED phototherapy devices[127–131] designed specifically for use in low-resource settings are under development or have recently entered the market (Table 1). Some settings need devices which do not require continuous electricity and these are not yet widely available.[119,125] Outdoor canopies equipped with ultraviolet/infrared filters are being evaluated and could allow safe sunlight phototherapy where conventional phototherapy is unavailable.[132–135] Beyond technological innovation, Cline *et al.* have posited that clinical training programmes for best practices and a uniform maintenance checklist are essential for increased effectiveness of phototherapy in low-resource settings.[124]

Monitor and treat hypoglycaemia

Gold standard of care

Hypoglycaemia is the presence of abnormally low glucose levels in the blood. Neonatal hypoglycaemia is generally characterized by a plasma glucose concentration <2.6 mmol/L; however, it must be noted that this value does not have strong scientific justification, which can present challenges for diagnosis.[136] Screening is recommended for newborns who have a heightened risk of hypoglycaemia from a broad range of conditions. These newborns should be regularly screened until they have had normal blood glucose measurements for at least three feed-fast cycles.[136] The standard screening method is a laboratory enzymatic test (e.g. glucose oxidase, hexokinase or dehydrogenase) to determine blood glucose concentration.[136] Although brief periods of hypoglycaemia are normal in newborns, persistent or recurrent hypoglycaemia can cause brain injury or other morbidities and requires prompt management.[137]

Table 1 Examples of recently-developed low-cost LED phototherapy technologies

Product	Designer	Manufacturer	Cost	Key features	Current status
Brilliance[127]	D-Rev	Phoenix Medical Systems	US$500	CE Mark	Commercially available
Firefly[120,128]	Design that Matters	Medical Technology Transfer & Services	US$1.50/infant	Double-sided to increase surface area receiving treatment	Commercially available
Billights[129]	Rice University	University of Malawi – Polytechnic	< US$110 (parts only)	Simple, open-source design to encourage local production	Pilot implementation, ongoing local production
BluLine[119]	Duke University	Tackle Design	US$45 (parts only)	Battery-powered	Pilot implementation
Bili-Hut[130,131]	Boston Children's Hospital	Little Sparrows Technologies	US$400	Battery-powered, portable	Prototype

Management depends on the clinical state of the infant and may include increasing feeds, intravenous dextrose and, in some cases, the use of drugs such as glucagon and hydrocortisone.[138]

Challenges and solutions in low-resource settings

Hypoglycaemia is widespread in low-resource settings and is interconnected with other common complications such as pre-term birth, hypothermia and malaria.[4,139–142] A key barrier to the management of hypoglycaemia is under-diagnosis and therefore under-treatment.[139,141,143] When laboratory diagnosis is not readily available, bed-side screening is performed using whole-blood glucose analysers and reagent test strips.[136] These readings correlate fairly well with actual plasma glucose concentrations, but may vary by 0.5–1.1 mmol/L,[144–147] and are most inaccurate at the lower concentrations, as seen in hypoglycaemic newborns.[136] Because of these inaccuracies, glucose concentrations should ideally be confirmed by expedited laboratory testing,[136] which is not feasible in many settings.

In addition to challenges in accuracy and logistics, comprehensive hypoglycaemia screening of high-risk newborns with bedside kits and laboratory confirmation is too expensive in some settings. Test strips are unique to their glucometer and a constant supply of specific strips may be difficult to maintain. Thus, there is a real need for durable, affordable and accurate bedside blood glucose test kits, as well as universal test strips.

Even when a hypoglycaemic infant is identified, treatment can be challenging. IV access for infusions of dextrose can be difficult in small infants, and a syringe pump or other accurate infusion method may not be available.[148] Oral dextrose gel and sugar powder have shown initial promise as simple, low-cost alternatives.[142,148,149] These non-invasive techniques would not require the mother and baby to be separated.[149]

Recommendations

Unmet technology needs

In order to address the discrepancies in health-care between the gold standard and low-resource settings, technological innovation and implementation must be strategically executed. According to the United Nations Secretary General's Global Strategy for Women's and Children's Health, innovation in product development and efficient health service delivery are key components in achieving the Millennium Development Goals.[150] Appropriate health-care technologies, as defined by WHO, are scientifically valid, adapted to local needs, accepted by users and recipients and maintainable with local resources.[151] As such, implementation in low-resource settings generally requires technologies to have specific characteristics beyond what is inherent in commercial technologies developed for high-resource settings (Table 2).

Table 2 Recommended characteristics of technologies in low-resource settings

Characteristic	Details/rationale
Low-cost/affordable[6,7,9]	Very limited healthcare budgets in low-resource settings
Robust[6,7]	Will be subjected to harsh environmental conditions including large temperature fluctuations, increased humidity, and high risk of physical damage
Simple to operate[6,7]	Shortages of adequately-trained healthcare professionals; a clear user interface with only essential features is desirable
Safe[7]	If sub-standard or perceived as sub-standard, will not be acceptable to healthcare workers or procurement agencies
Environmentally friendly[7]	
Reliable[7]	
Meets international regulatory standards[7]	
No requirement for constant supply of consumables[6,7]	Extreme difficulty in consistently procuring consumable parts
No requirement for regular maintenance; simple maintenance procedures[6,7,9]	Lack of trained maintenance personnel and tools
Can operate from various power sources, long battery life[6,7,9]	Frequent interruptions of mains electrical supply or complete lack of electrical power
Lifespan of at least 5 years[7]	Limited healthcare budgets and maintenance capabilities
Culturally appropriate	Local beliefs and practices could go against safe use of technology

The diversity and extent of resource constraints must be recognized. Developing countries are not homogenous; a challenge faced at one clinic may not be present in a hospital in an adjacent region. District hospitals are often better positioned than larger central hospitals to provide preventive medicine and timely emergency treatment. In many instances, policymakers and other stakeholders are training health workers at district hospitals for increased responsibilities which has led to improved care of newborns.[152] While this is encouraging, the balance between the risks and benefits of each technological intervention must be considered on a case-by-case basis,[153] a lesson that was recently learned through the widespread distribution of ante-natal corticosteroids.[154] Thus, when technologies for low-resource settings are being developed, it is important that the general level of infrastructure and human resources for which a solution is intended be identified.

As seen throughout this review, there are still significant technological gaps in each area of neonatal care. In some cases a new methodology or technology is required to meet the needs of low-resource settings; in other cases, currently available technologies must simply be revised for a new context. Table 3 provides some examples of technologies which would address major gaps in neonatal health-care in low-resource settings.

The importance of an integrated set of technologies

The multiplicity of causes of infant mortality must be kept in mind.[155,156] Effective strategies should combine interventions into packages, instead of offering single interventions in a vertical manner.[157] Programmes which address the many causes of neonatal mortality are more likely to yield improved results.[158] This paper reviews the technological needs for comprehensive newborn care; additionally, multiple researchers and international health organizations have published evidence-based packages for essential and emergency newborn care and have advocated comprehensive implementation of these packages.[4,33,34]

Some institutions have begun to implement comprehensive technology packages for neonatal care. The Breath of Life Program at the East Meets West Foundation provides a set of low-cost, locally manufactured neonatal technologies for hospitals in Africa and Asia. The package includes CPAP, resuscitation station with overhead warmer, pulse oximetry, phototherapy and hand sanitizers.[120] The Centre for Global Child Health at The Hospital for Sick Children in Toronto, Canada created a low-cost, community-based neonatal kit comprising a clean delivery kit (sterile blade, cord clamp, clean plastic sheet, surgical gloves and hand soap), sunflower oil emollient, chlorhexidine, ThermoSpot™ temperature indicator, Mylar® infant sleeve and a re-usable instant heat pack. The Centre is co-ordinating with the Lady Health Worker Programme in rural Pakistan to implement the kit, and its impact is being evaluated in a cluster randomized trial.[159]

The maternal-infant continuum of care is also critical, and efforts to reduce neonatal mortality should include maternal care.[157,160] While it has been estimated that implementation of a postnatal care package alone at 90% coverage could reduce neonatal mortality by up to 39%, the inclusion of ante-natal and intrapartum packages increases the potential reduction to 69%.[157] The most basic components of essential and advanced care at each stage of childbirth are illustrated in Fig. 3.

Essential ante-natal care components include tetanus toxoid vaccination, screening for pre-eclampsia, anaemia, malaria, tuberculosis and HIV, screening and treatment of asymptomatic bacteriuria and syphilis, and provision of supplemental vitamins, anti-malarial prophylaxis and bed-nets.[160] Ante-natal corticosteroids

Table 3 Technologies in development and unmet technological needs

Category of care	Technology	In development or unmet need?	Details
Provide hydration and nutrition	Syringe/infusion pump[4]	Unmet need	Low-cost, low-maintenance device to control IV fluid flow
	Breast pump[43,47]	Unmet need	Low-cost, low-maintenance design for assisted expression of breast milk
Prevent and treat infections	Sepsis diagnostic test[71]	In development	Low-cost test strip to indicate blood levels of histones
	Oral antibiotics[73]	Unmet need	To prevent infection transmission during childbirth
Provide temperature stability	Real-time temperature monitor[70]	Unmet need	Low-cost, low-maintenance monitor for neonates at risk of hypothermia
Provide breathing support	Surfactant aerosol delivery[102]	In development	Uses aerosol technology to deliver surfactant to the lungs
	Pulse oximeter[99]	In development	Low-cost, SpO_2 adaptor for mobile phones
Monitor and treat jaundice	Bilirubin monitor[104,105,117,118]	Unmet need	Low-cost, accurate, point-of-care test for jaundice
	Phototherapy independent from power grid[119,130–135]	In development	Phototherapy techniques that employ battery power or sunlight
Monitor and treat hypoglycaemia	Bedside blood glucose test kits[139,141,143]	Unmet need	Accurate, durable and affordable screening tool for hypoglycaemia; universal test strips

in preterm labour, antibiotics in premature rupture of membranes, fetal heart rate monitoring and caesarean section, if required, also have the potential to dramatically reduce neonatal mortality.[7,27,161–163] Community-based antenatal care packages are cost-effective; to have the greatest impact, however, there must also be high-quality clinical care.[160]

Keys to comprehensive implementation of integrated technologies

Effective and sustainable implementation of technologies is a major challenge in improving neonatal survivial.[6,164,165] When developing medical technologies, clinicians, public health experts and engineers often work together to identify problems and address technology gaps in particular settings. Likewise, similar interdisciplinary effort is required to effectively implement and evaluate neonatal technologies. Clinicians, engineers, industry, academics, government officials, non-governmental organizations and public health experts must collaborate to develop plans for implementation and for evaluating outcomes.[166] Public/private partnerships are critical to ensure that once the technologies have been proven, there is a realistic means of reaching a satisfactory market.[167,168] Ideally, technologies should be commercially viable so as to have a significant and sustained impact on neonatal mortality and morbidity.[167] Moreover, ancillary services for technology implementation, such as training new clinical staff and maintaining supply chains for spare parts and consumables, must be thoroughly integrated into local systems to achieve a long-term impact.

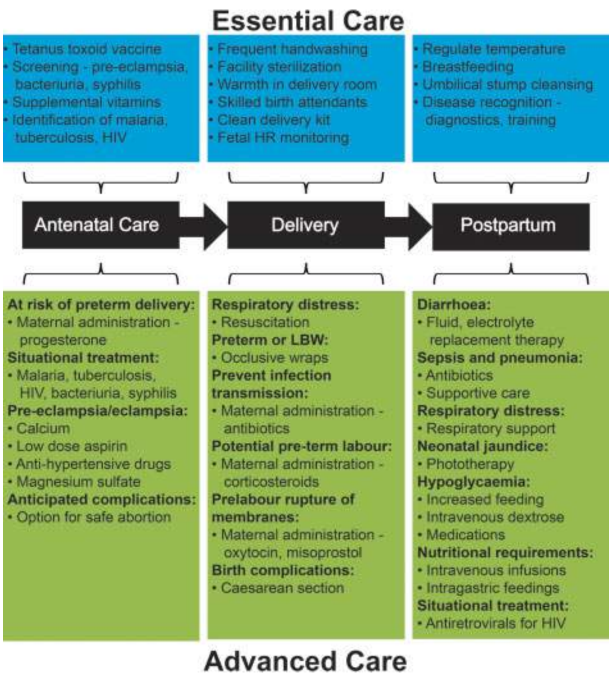

Figure 3 The maternal-infant continuum of care with corresponding interventions for essential and advanced care. Sources: March of Dimes et al.,[4] The Partnership for Maternal, Newborn & Child Health[34]

It is important that local innovators and other stakeholders are not left out of the development and implementation process, and local capacity-building of human resources and infrastructure should be a focus. Local education systems can expand to include programmes for the design, manufacture and maintenance of life-saving technologies, which will help create a path toward long-term sustainability and independence in health-care technology.

It is critical that implementation research be conducted and outcomes evaluated in order to develop not only the best possible package of technologies, but also the most effective training materials and implementation methods. Many expert panels have emphasized the need for sound implementation research into overcoming the remaining barriers to reducing neonatal mortality.[4,41,166]

Finally, in order for the international development community to move its focus toward complete technology packages, interdisciplinary collaboration, in-country innovation and capacity-building, and implementation optimization, funding priorities might also have to be reconsidered. While technological innovation is a key first step, support must continue beyond the initial stages in order to facilitate optimal and comprehensive impact.

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References

1 Liu L, Oza S, Hogan D, Perin J, Rudan I, Lawn JE, *et al.* Global, regional, and national causes of child mortality in 2000–13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet. 2014;385:430–40.
2 Lawn JE, Cousens S, Zupan J. 4 million neonatal deaths: When? Where? Why? Lancet. 2005;365:891–900.
3 Grantham-McGregor S, Bun Cheung Y, Cueto S, Glewwe P, Richter L, Strupp B, *et al.* Developmental potential in the first 5 years for children in developing countries. Lancet. 2007;369:60–70.
4 March of Dimes, PMNCH, Save the Children, World Health Organization. Born Too Soon: The Global Action Report on Preterm Birth. Geneva: WHO, 2012.
5 Oestergaard MZ, Inoue M, Yoshida S, Mahanani WR, Gore FM, Cousens S, *et al.* Neonatal mortality levels for 193 countries in 2009 with trends since 1990: a systematic analysis of progress, projections, and priorities. PLoS Med. 2011;8:e1001080.
6 Thairu L, Wirth M, Lunze K. Innovative newborn health technology for resource-limited environments. Trop Med Int Health. 2013;18:117–28.
7 Wyatt J. Appropriate medical technology for perinatal care in low-resource countries. Ann Trop Paediatr. 2008;28:243–51.
8 World Health Organization. Medical Devices: Managing the Mismatch: an Outcome of the Priority Medical Devices Project. Geneva: WHO, 2010.
9 Riviello ED, Letchford S, Achieng L, Newton MW. Critical care in resource-poor settings: Lessons learned and future directions. Crit Care Med. 2011;39:860–7.
10 Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, *et al.* Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375:1969–87.
11 World Health Organization. Global Health Observatory Data Repository, 2014. Available from: http://apps.who.int/ghodata/.
12 Taneja B. Physiological and anaesthetic considerations for the preterm neonate undergoing surgery. J Neonat Surg. 2012;1:14.
13 Henderson-Smart D. The effect of gestational age on the incidence and duration of recurrent apnoea in newborn babies. Aust Paediatr J. 1981;17:273–6.
14 Pillekamp F, Hermann C, Keller T, von Gontard A, Kribs A, Roth B. Factors influencing apnea and bradycardia of prematurity–implications for neurodevelopment. Neonatology. 2006;91:155–61.
15 Perlman JM, McMenamin JB, Volpe JJ. Fluctuating cerebral blood-flow velocity in respiratory-distress syndrome: relation to the development of intraventricular hemorrhage. N Engl J Med. 1983;309:204–9.
16 Osborn DA, Henderson-Smart DJ. Kinesthetic stimulation for treating apnea in preterm infants. Cochrane Database Syst Rev. 1999:CD000373.
17 Sreenan C, Lemke RP, Hudson-Mason A, Osiovich H. High-flow nasal cannulae in the management of apnea of prematurity: a comparison with conventional nasal continuous positive airway pressure. Pediatrics. 2001;107:1081–3.
18 Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Cochrane Database Syst Rev. 2000;2:CD000273.
19 Verklan MT. The chilling details: hypoxic-ischemic encephalopathy. J Perinat Neonatal Nurs. 2009;23:59–68.
20 Zupan SV. Definition of intrapartum asphyxia and effects on outcome. J Gynecol Obstet Biol Reprod (Paris). 2008;37:S7–15.
21 Herrera-Marschitz M, Neira-Peña T, Leyton L, Gebicke-Haerter P, Rojas-Mancilla E, Morales P. Short- and long-term consequences of perinatal asphyxia: looking for neuroprotective strategies. Adv Neurobiol. 2015;10:169–98.
22 Chaudhari T, McGuire W. Allopurinol for preventing mortality and morbidity in newborn infants with suspected hypoxic-ischaemic encephalopathy. Cochrane Database Syst Rev. 2012;7:CD006817.
23 Wachtel EV, Hendricks-Muñoz KD. Current management of the infant who presents with neonatal encephalopathy. Curr Probl Pediatr Adolesc Health Care. 2011;41:132–53.
24 Buonocore G, Perrone S, Turrisi G, Kramer BW, Balduini W. New pharmacological approaches in infants with hypoxic-ischemic encephalopathy. Curr Pharm Des. 2012;18:3086–100.
25 Zaidi AK, Tikmani SS, Warraich HJ, Darmstadt GL, Bhutta ZA, Sultana S, *et al.* Community-based treatment of serious bacterial infections in newborns and young infants: a randomized controlled trial assessing three antibiotic regimens. Pediatr Infect Dis J. 2012;31:667–72.
26 Lawn J, Kerber K, Enweronu-Laryea C, Massee Bateman O. Newborn survival in low resource settings — are we delivering? BJOG. 2009;116:49–59.
27 Lee AC, Cousens S, Wall SN, Niermeyer S, Darmstadt GL, Carlo WA, *et al.* Neonatal resuscitation and immediate newborn assessment and stimulation for the prevention of neonatal deaths: a systematic review, meta-analysis and Delphi estimation of mortality effect. BMC Public Health. 2011;11:S12. doi: 10.1186/1471-2458-11-S3-S12.
28 Boyle D, Kattwinkel J, eds. Textbook of Neonatal Resuscitation, 5th edn. Elk Grove Village, IL: American Academy of Pediatrics and American Heart Association, 2006.
29 Alonso-Spilsbury M, Mota-Rojas D, Villanueva-García D, Martínez-Burnes J, Orozco H, Ramírez-Necoechea R, *et al.* Perinatal asphyxia pathophysiology in pig and human: a review. Anim Reprod Sci. 2005;90:1–30.
30 Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG. Cooling for newborns with hypoxic ischaemic encephalopathy. Cochrane Database Syst Rev. 2013;1:CD003311.
31 Freeman JV, Christian P, Khatry SK, Adhikari RK, LeClerq SC, Katz J, *et al.* Evaluation of neonatal verbal autopsy using physician review versus algorithm-based cause-of-death assignment in rural Nepal. Paediatr Perinat Epidemiol. 2005;19:323–31.
32 MANDATE. Mandate Model, 2014. Available from: http://www.mandate4mnh.org/.
33 Bhutta ZA, Black RE. Global maternal, newborn, and child health—so near and yet so far. N Engl J Med. 2013;369:2226–35.
34 The Partnership for Maternal, Newborn & Child Health. A Global Review of the Key Interventions Related to Reproductive, Maternal, Newborn and Child Health (RMNCH). Geneva: PMNCH, 2011.
35 Lawn JE, Kerber K, Enweronu-Laryea C, Cousens S. 3.6 million neonatal deaths—what is progressing and what is not? Semin Perinatol. 2010;34:371–86.
36 World Health Organization. The Low-Birth-weight Infant. WHO Bull OMS Suppl. 1989;67:68–84.
37 Chawla D, Agarwal R, Deorari AK, Paul VK. Fluid and electrolyte management in term and preterm neonates. Indian Pediatr. 2008;75:255–9.
38 Slusher T, Vaucher Y, Zamora T, Curtis B. Feeding and fluids in the premature and sick newborns in the low-middle income countries. In: Özdemir Ö, ed. Contemp Pediatr. Available from: http://www.intechopen.com/books/contemporary-pediatrics/feeding-and-fluids-in-the-premature-and-sick-newborn-in-the-low-middle-income-countries.
39 American Academy of Pediatrics. Essential Care for Every Baby, 2014. Available from: http://www.aap.org/en-us/Documents/global_eceb_providerguide_english.pdf.
40 Chawla D, Thukral A, Agarwal R, Deorari A, Paul V. Parenteral nutrition. Indian Pediatr. 2008;75:377–83.

41 Edmond K, Bahl R. Optimal Feeding of Low-birth-weight Infants: Technical Review. Geneva: WHO, 2006.
42 World Health Organization. Guidelines on Optimal Feeding of Low Birth Weight Infants in Low and Middle Income Countries. Geneva: WHO, 2011.
43 Murguia-Peniche T, Kirsten GF. Meeting the challenge of providing neonatal nutritional care to very or extremely low birth weight infants in low-resource settings. World Rev Nutr Diet. 2014;110:278–96.
44 Shah K, Skerrett E, Nojoomi M, Walker T, Maynard K, Pan M, *et al.* Maji: A new tool to prevent over-hydration of children receiving intravenous fluid therapy in low-resource settings. Am J Trop Med Hyg. [In press].
45 ShiftLabs. Hacking Innovation. Available from: www.shiftlabs.com.
46 Crass RE, Vance JR. In vivo accuracy of gravity-flow i.v. infusion systems. Am J Hosp Pharm. 1985;42:328–31.
47 Hill PD, Aldag JC, Demirtas H, Naeem V, Parker NP, Zinaman MJ, *et al.* Association of serum prolactin and oxytocin with milk production in mothers of preterm and term infants. Biol Res Nurs. 2009;10:340–9.
48 Hamosh M. Lipid metabolism in premature infants. Biol Neonate. 1987;52 (Suppl 1):50–64.
49 Mehta NR, Hamosh M, Bitman J, Wood DL. Adherence of medium-chain fatty acids to feeding tubes during gavage feeding of human milk fortified with medium-chain triglycerides. J Pediatr. 1988;112:474–6.
50 JustMilk. Available from http://justmilk.org/.
51 Centers for Disease Control. Group B Streptococcus, 2015. Available from: www.cdc.gov.
52 Becker JU, Theodosis C, Jacob ST, Wira CR, Groce NE. Surviving sepsis in low-income and middle-income countries: new directions for care and research. Lancet Infect Dis. 2009;9: 577–82.
53 World Health Organization. Maternal, Newborn, Child and Adolescent Health: Recommendations on Newborn Health. 2013. Available from: http://www.who.int/maternal_child_adolescent/documents/mnca-recommendations/en/.
54 Duke T. Neonatal pneumonia in developing countries. Arch Dis Child Fetal Neonatal Ed. 2005;90:F211–19.
55 Bhutta ZA, Yusuf K, Khan IA. Is management of neonatal respiratory distress syndrome feasible in developing countries? Experience from Karachi (Pakistan). Pediatr Pulmonol. 1999; 27:305–11.
56 Beck S, Wojdyla D, Say L, Betran AP, Merialdi M, Requejo JH, *et al.* The worldwide incidence of preterm birth: a systematic review of maternal mortality and morbidity. Bull WHO. 2010;88:31–8.
57 Srivastava S, Shetty N. Healthcare-associated infections in neonatal units: lessons from contrasting worlds. J Hosp Infect. 2007;65:292–306.
58 Vandelaer J, Birmingham M, Gasse F, Kurian M, Shaw C, Garnier S. Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative. Vaccine. 2003;21:3442–5.
59 O'Ryan M, Prado V, Pickering LK. A millennium update on pediatric diarrheal illness in the developing world. Semin Pediatr Infect Dis. 2005;16:125–36.
60 World Health Organization. Pocket Book of Hospital Care for Children: Guidelines for the Management of Common Illnesses with Limited Resources, 2nd edn. Geneva: WHO, 2013.
61 Coffey P, Kelly K, Baqui A, Bartlett A, Bhutta Z, Hedman L, *et al.* Case study: Injectable antibiotics for treatment of newborn sepsis. 2012. Available from: http://www.everywomaneverychild.org/images/FINAL_UN_Commission_ReportInjectable_Antibiotics_February_2012.pdf.
62 Cohen GM. Access to diagnostics in support of HIV/AIDS and tuberculosis treatment in developing countries. AIDS. 2007;21:S81–7.
63 Sheth KV, Patel TK, Tripathi CB. Antibiotic sensitivity pattern in neonatal intensive care unit of a tertiary care hospital of India. Asian J Pharm Clin Res. 2012;5:46–50.
64 Karon BS, Scott R, Burritt MF, Santrach PJ. Comparison of lactate values between point-of-care and central laboratory analyzers. Am J Clin Pathol. 2007;128:168–71.
65 Moore CC, Jacob ST, Pinkerton R, Meya DB, Mayanja-Kizza H, Reynolds SJ, *et al.* Point-of-care lactate testing predicts mortality of severe sepsis in a predominantly HIV type 1-infected patient population in Uganda. Clin Infect Dis. 2008;46:215–22.
66 Mtove G, Nadjm B, Hendriksen IC, Amos B, Muro F, Todd J, *et al.* Point-of-care measurement of blood lactate in children admitted with febrile illness to an African District Hospital. Clin Infect Dis. 2011;53:548–54.
67 Saving Lives at Birth: A Grand Challenge for Development. HIST-BIRTH: Innovative and rapid point-of-care histone test strips for early diagnosis of sepsis in pregnancy and childbirth, 2011. Available from: http://savinglivesatbirth.net/summaries/281
68 Bahl R, Martines J, Ali N, Bhan MK, Carlo W, Chan KY, *et al.* Research priorities to reduce global mortality from newborn infections by 2015. Pediatr Infect Dis J. 2009;28:S43–8.
69 Mullany LC. Neonatal hypothermia in low-resource settings. Semin Perinatol. 2010;34:426–33.
70 Lunze K, Hamer DH. Thermal protection of the newborn in resource-limited environments. J Perinatol. 2012;32:317–24.
71 Kumar V, Shearer JC, Kumar A, Darmstadt GL. Neonatal hypothermia in low resource settings: a review. J Perinatol. 2009;29:401–12.
72 McCall EM, Alderdice F, Halliday HL, Jenkins JG, Vohra S. Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants. Cochrane Database Syst Rev. 2010:CD004210.
73 Leadford AE, Warren JB, Manasyan A, Chomba E, Salas AA, Schelonka R, *et al.* Plastic bags for prevention of hypothermia in preterm and low birth weight infants. Pediatrics. 2013;132:e128–34.
74 Rohana J, Khairina W, Boo NY, Shareena I. Reducing hypothermia in preterm infants with polyethylene wrap. Pediatr Int. 2011;53:468–74.
75 Smith J, Usher K, Alcock G, Buettner P. Application of plastic wrap to improve temperatures in infants born less than 30 weeks gestation: a randomized controlled trial. Neonatal Netw. 2013;32:235–45.
76 Conde-Agudelo A, Diaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2014;4:CD002771.
77 Cattaneo A, Davanzo R, Worku B, Surjono A, Echeverria M, Bedri A, *et al.* Kangaroo mother care for low birthweight infants: a randomized controlled trial in different settings. Acta Paediatr. 1998;87:976–85.
78 Sarman I, Can G, Tunell R. Rewarming preterm infants on a heated, water filled mattress. Arch Dis Child. 1989;64:687–92.
79 Boo NY, Selvarani S. Effectiveness of a simple heated water-filled mattress for the prevention and treatment of neonatal hypothermia in the labour room. Singapore Med J. 2005;46:387–91.
80 Amadi HO, Osibogun AO, Eyinade O, Kawuwa MB, Uwakwem AC, Ibekwe MU. Challenges and frugal remedies for lowering facility based neonatal mortality and morbidity: a comparative study. Int J Pediatr. 2014;2014:986716.
81 Tran K, Gibson A, Wong D, Tilahun D, Selock N, Good T, *et al.* Designing a Low-Cost Multifunctional Infant Incubator. J Lab Autom. 2014;19:332–7.
82 Wall SN, Lee AC, Niermeyer S, English M, Keenan WJ, Carlo W, *et al.* Neonatal resuscitation in low-resource settings: what, who, and how to overcome challenges to scale up? Int J Gynaecol Obstet. 2009;107:S47–64.
83 Vidyasagar D, Velaphi S, Bhat VB. Surfactant replacement therapy in developing countries. Neonatology. 2011;99:355–66.
84 Kamath BD, MacGuire ER, McClure EM, Goldenberg RL, Jobe AH. Neonatal mortality from respiratory distress syndrome: lessons for low-resource countries. Pediatrics. 2011;127:1139–46.
85 Palme-Kilander C. Methods of resuscitation in low-Apgar-score newborn infants—a national survey. Acta Paediatr. 1992;81:739–44.
86 Palme-Kilander C, Tunell R. Pulmonary gas exchange during facemask ventilation immediately after birth. Arch Dis Child. 1993;68:11–16.
87 UNICEF. Neonatal Resusciation Devices: Market & Supply Update. 2014. Available from: http://www.unicef.org/supply/files/Resuscitation_Devices_Market_Supply_Update.pdf.
88 Coffey P, Kak L, Narayanan I, Lockwood JB, Singhal N, Wall S, *et al.* Case study: newborn resuscitation devices. United Nations Commission on Life-Saving Commodities for Women and Children, 2012. Available from: http://www.everywomaneverychild.org/images/UN_Comission_Report_ Resuscitation_Devices_COMPLETE_reduced.pdf.
89 Silverman WA. The lesson of retrolental fibroplasia. Sci Am. 1977;236:100–7.

90 Berger T, Fontana M, Stocker M. The journey towards lung protective respiratory support in preterm neonates. Neonatology. 2013;104:265–74.
91 Ansermino M. Compendium of New and Emerging Technologies that Address Global Health Concerns: Mobile Phone Pulse Oximeter. Available from: http://www.who.int/medical_devices/en/.
92 Hudson J, Nguku S, Sleiman J, Karlen W, Dumont G, Petersen C, *et al.* Usability testing of a prototype Phone Oximeter with healthcare providers in high-and low-medical resource environments. Anaesthesia. 2012;67:957–67.
93 LGT Medical. Kenek Edge. Available from: http://lgtmedical.com/kenekedge/.
94 Lifebox. Acare Technology: Lifebox. Available from: http://www.lifebox.org/about-lifebox/our-product/.
95 Herbert LJ, Wilson IH. Pulse oximetry in low-resource settings. Breathe. 2012;9:90–8.
96 Richardson CP, Jung A. Effects of continuous positive airway pressure on pulmonary function and blood gases of infants with respiratory distress syndrome. Pediatr Res. 1978;12:771–4.
97 Narasimhan R, Krishnamurthy S. A review of non-invasive ventilation support in neonates. Paediatr Child Health. 2014;24:7–11.
98 Mahmoud RA, Roehr CC, Schmalisch G. Current methods of non-invasive ventilatory support for neonates. Paediatr Respir Rev. 2011;12:196–205.
99 Brown J, Machen H, Kawaza K, Mwanza Z, Iniguez S, Lang H, *et al.* A high-value, low-cost bubble continuous positive airway pressure system for low-resource settings: technical assessment and initial case reports. PLoS One. 2013;8:e53622.
100 Kawaza K, Machen HE, Brown J, Mwanza Z, Iniguez S, Gest A, *et al.* Efficacy of a low-cost bubble CPAP system in treatment of respiratory distress in a neonatal ward in Malawi. PLoS One. 2014;9:e86327.
101 Diamedica. Baby CPAP. Available from: http://www.diamedica.co.uk/english/product_details.cfm?id=202.
102 Finer NN, Merritt TA, Bernstein G, Job L, Mazela J, Segal R. An open label, pilot study of Aerosurf® combined with nCPAP to prevent RDS in preterm neonates. J Aerosol Med Pulm Drug Deliv. 2010;23:303–9.
103 Lo SF, Doumas BT. The status of bilirubin measurements in U.S. laboratories: why is accuracy elusive? Semin Perinatol. 2011;35:141–7.
104 Ives NK. Management of neonatal jaundice. Paediatr Child Health. 2011;21:270–6.
105 American Academy of Pediatrics Subcommittee on Hyperbilirubinemia. Management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. Pediatrics. 2004;114:297.
106 Maisels MJ. Why use homeopathic doses of phototherapy? Pediatrics. 1996;98:283–7.
107 Tan K. The nature of the dose-response relationship of phototherapy for neonatal hyperbilirubinemia. J Pediatr. 1977;90:448–52.
108 Tan K. The pattern of bilirubin response to phototherapy for neonatal hyperbilirubinaemia. Pediatr Res. 1982;16:670–4.
109 Ennever J, McDonagh A, Speck W. Phototherapy for neonatal jaundice: optimal wavelengths of light. J Pediatr. 1983;103:295–9.
110 Bhutani VK, Cline BK, Donaldson KM, Vreman HJ. The need to implement effective phototherapy in resource-constrained settings. Semin Perinatol. 2011;35:192–7.
111 Seidman DS, Moise J, Ergaz Z, Laor A, Vreman HJ, Stevenson DK, *et al.* A prospective randomized controlled study of phototherapy using blue and blue-green light-emitting devices, and conventional halogen-quartz phototherapy. J Perinatol. 2003;23:123–7.
112 National Quality Forum. Serious Reportable Events in Healthcare: A Consensus Report. 2002. Available from: http://www.qualityforum.org/projects/hacs_and_sres.aspx.
113 Bhutani VK. Kernicterus as a 'never-event': a newborn safety standard? Indian J Pediatr. 2005;72:53–6.
114 Simini F. Clinical signs that predict severe illness in children under age 2 months: a multicentre study. Commentary. Lancet. 2008;371:135–42.
115 Slusher T, Olusanya B. Neonatal jaundice in low-and middle-income countries. In: Stevenson D, Maisels J, Watchko J, editors. Care of the Jaundiced Neonate. 1st edn. New York, NY: McGraw-Hill; 2012.
116 Mwaniki MK, Atieno M, Lawn JE, Newton CR. Long-term neurodevelopmental outcomes after intrauterine and neonatal insults: a systematic review. Lancet. 2012;379:445–52.
117 Johnson L, Bhutani VK. Guidelines for management of the jaundiced term and near-term infant. Clin Perinatol. 1998; 25:555–74.
118 Keren R, Tremont K, Luan X, Cnaan A. Visual assessment of jaundice in term and late preterm infants. Arch Dis Child Fetal Neonatal Ed. 2009;94:F317–22.
119 Malkin R, Anand V. A novel phototherapy device. IEEE Eng Med Biol Mag. 2010;29:37–43.
120 The East Meets West Foundation. Expanding Organizational Capacity. 2012. Available from: https://www.gsb.stanford.edu/sites/default/files/documents/EMW-ExpandingOrganizationalCapacity.pdf.
121 Pejaver RK, Vishwanath J. An audit of phototherapy units. Indian J Pediatr. 2000;67:883–4.
122 Ferreira ALC, Nascimento RMd, Veríssimo RCSS. Irradiance of phototherapy equipment in maternity wards in Maceió. Rev Lat Am Enfermagem. 2009;17:695–700.
123 Djokomuljanto S, Quah B-S, Surini Y, Noraida R, Ismail N, Hansen TWR, *et al.* Efficacy of phototherapy for neonatal jaundice is increased by the use of low-cost white reflecting curtains. Arch Dis Child Fetal Neonatal Ed. 2006;91:F439–42.
124 Cline BK, Vreman HJ, Faber K, Lou H, Donaldson KM, Amuabunosi E, *et al.* Phototherapy device effectiveness in Nigeria: irradiance assessment and potential for improvement. J Trop Pediatr. 2013;:fmt027.
125 Slusher TM, Zipursky A, Bhutani VK. A global need for affordable neonatal jaundice technologies. Semin Perinatol. 2011;35:185–91.
126 Owa JA, Ogunlesi TA. Why we are still doing so many exchange blood transfusion for neonatal jaundice in Nigeria. World J Pediatr. 2009;5:51–5.
127 D-Rev. Newborn Health Impact Dash Board. Available from: http://d-rev.org/impact/brilliance/.
128 DtM. Design That Matters. Available from: http://www.designthatmatters.org/.
129 Viau Colindres J, Rountree C, Destarac MA, Cui Y, Valdez MP, Castellanos MH, *et al.* Prospective randomized controlled study comparing low-cost LED and conventional phototherapy for treatment of neonatal hyperbilirubinemia. J Trop Pediatr. 2011;58:178–83.
130 Little Sparrows. Bili-Hut. Available from: http://little-sparrows-tech.com/.
131 New Scientist. Portable jaundice therapy could save infants' lives. 2013. Available from: http://www.newscientist.com/article/dn24396-portable-jaundice-therapy-could-save-infants-lives.html#.VS3TcfnF8uc.
132 Olusanya BO, Imam ZO, Mabogunje CA, Emokpae AA, Slusher TM. Maternal satisfaction with a novel filtered-sunlight phototherapy for newborn jaundice in Southwest Nigeria. BMC Pediatr. 2014;14:180.
133 Slusher TM, Olusanya BO, Vreman HJ, Wong RJ, Brearley AM, Vaucher YE, *et al.* Treatment of neonatal jaundice with filtered sunlight in Nigerian neonates: study protocol of a non-inferiority, randomized controlled trial. Trials. 2013;14:446.
134 Slusher TM, Vreman HJ, Olusanya BO, Wong RJ, Brearley AM, Vaucher YE, *et al.* Safety and efficacy of filtered sunlight in treatment of jaundice in African neonates. Pediatrics. 2014;133:e1568–74.
135 Vreman HJ, Slusher TM, Wong RJ, Schulz S, Olusanya BO, Stevenson DK. Evaluation of window-tinting films for sunlight phototherapy. J Trop Pediatr. 2013;59:496–501.
136 Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. Pediatrics. 2011;127:575–9.
137 Su J, Wang L. Research advances in neonatal hypoglycemic brain injury. Transl Pediatr. 2012;1:108–15.
138 Sweet CB, Grayson S, Polak M. Management strategies for neonatal hypoglycemia. J Pediatr Pharmacol Ther. 2013;18: 199–208.
139 Osier F, Berkley J, Ross A, Sanderson F, Mohammed S, Newton C. Abnormal blood glucose concentrations on admission to a rural Kenyan district hospital: prevalence and outcome. Arch Dis Child. 2003;88:621–5.
140 De L, Costello AM, Pal DK, Manandhar DS, Rajbhandari S, Land JM, Patel N. Neonatal hypoglycaemia in Nepal 2. Availability of alternative fuels. Arch Dis Child Fetal Neonatal Ed. 2000;82:F52–8.

141 Anderson S, Shakya KN, Shrestha LN, De L, Costello AM. Hypoglycaemia: a common problem among uncomplicated newborn infants in Nepal. J Trop Pediatr. 1993;39:273–7.
142 Barennes H, Valea I, Nagot N, Van de Perre P, Pussard E. Sublingual sugar administration as an alternative to intravenous dextrose administration to correct hypoglycemia among children in the tropics. Pediatrics. 2005;116:e648–53.
143 Allen CW, Jeffery H. Implementation and evaluation of a neonatal educational program in rural Nepal. J Trop Pediatr. 2006;52:218–22.
144 Altimier L, Roberts W. One Touch II hospital system for neonates: correlation with serum glucose values. Neonatal Netw. 1996;15:15–18.
145 Giep TN, Hall RT, Harris K, Barrick B, Smith S. Evaluation of neonatal whole blood versus plasma glucose concentration by ion-selective electrode technology and comparison with two whole blood chromogen test strip methods. J Perinatol. 1995;16:244–9.
146 Maisels MJ, Lee CA. Chemstrip glucose test strips: correlation with true glucose values less than 80 mg/dL. Crit Care Med. 1983;11:293–5.
147 Hussain K, Sharief N. The inaccuracy of venous and capillary blood glucose measurement using reagent strips in the newborn period and the effect of haematocrit. Early Hum Dev. 2000;57:111–21.
148 Graz B, Dicko M, Willcox ML, Lambert B, Falquet J, Forster M, *et al.* Sublingual sugar for hypoglycaemia in children with severe malaria: a pilot clinical study. Malar J. 2008;7:242.
149 Harris DL, Weston PJ, Signal M, Chase JG, Harding JE. Dextrose gel for neonatal hypoglycaemia (the Sugar Babies Study): a randomised, double-blind, placebo-controlled trial. Lancet. 2014;382:2077–83.
150 Ban K-M. Global Strategy for Women's and Children's Health. New York: United Nations; 2010.
151 World Health Organization. Essential Antenatal, Perinatal and Postpartum Care. Geneva: WHO; 2002.
152 Bhutta ZA, Lassi ZS, Pariyo G, Huicho L. Global Experience of Community Health Workers for Delivery of Health Related Millennium Development Goals: a Systematic Review, Country Case Studies, and Recommendations for Integration into National Health Systems. Geneva: WHO, Global Health Workforce Alliance; 2010. Available from: http://www.who.int/workforcealliance/knowledge/resources/chwreport/en/.
153 De L, Costello AM, Azad K. Scaling up antenatal corticosteroids in low-resource settings? Lancet. 2014;385:585–7.
154 Althabe F, Belizán JM, McClure EM, Hemingway-Foday J, Berrueta M, Mazzoni A, *et al.* A population-based, multifaceted strategy to implement antenatal corticosteroid treatment versus standard care for the reduction of neonatal mortality due to preterm birth in low-income and middle-income countries: the ACT cluster-randomised trial. Lancet. 2014;385:629–39.
155 Gupta R, Sachdev H, Shah D. Evaluation of the WHO/UNICEF algorithm for integrated management of childhood illness between the ages of one week to two months. Indian Pediatr. 2000;37:383–90.
156 Mulholland K. Commentary: comorbidity as a factor in child health and child survival in developing countries. Int J Epidemiol. 2005;34:375–7.
157 Darmstadt GL, Bhutta ZA, Cousens S, Adam T, Walker N, de Bernis L. Evidence-based, cost-effective interventions: how many newborn babies can we save? Lancet. 2005;365:977–88.
158 Sachdev H. Commentary: Utilizing information on causes of neonatal deaths in less-developed countries. Int J Epidemiol. 2006;35:718–9.
159 Turab A, Pell LG, Bassani DG, Soofi S, Ariff S, Bhutta ZA, *et al.* The community-based delivery of an innovative neonatal kit to save newborn lives in rural Pakistan: design of a cluster randomized trial. BMC Pregnancy Childbirth. 2014;14:315.
160 Adam T, Lim SS, Mehta S, Bhutta ZA, Fogstad H, Mathai M, *et al.* Cost effectiveness analysis of strategies for maternal and neonatal health in developing countries. Br Med J. 2005;331:1107.
161 Cousens S, Blencowe H, Gravett M, Lawn JE. Antibiotics for pre-term pre-labour rupture of membranes: prevention of neonatal deaths due to complications of pre-term birth and infection. Int J Epidemiol. 2010;39:i134–43.
162 Mwansa-Kambafwile J, Cousens S, Hansen T, Lawn JE. Antenatal steroids in preterm labour for the prevention of neonatal deaths due to complications of preterm birth. Int J Epidemiol. 2010;39:i122–33.
163 Lee AC, Cousens S, Darmstadt GL, Blencowe H, Pattinson R, Moran NF. Care during labor and birth for the prevention of intrapartum-related neonatal deaths: a systematic review and Delphi estimation of mortality effect. BMC Public Health. 2011;11:S10.
164 Blencowe H, Cousens S. Review: Addressing the challenge of neonatal mortality. Trop Med Int Health. 2013;18:303–12.
165 Howitt P, Darzi A, Yang G-Z, Ashrafian H, Atun R, Barlow J. Technologies for global health. Lancet. 2012;380:507–35.
166 Peterson HB, Haidar J, Merialdi M, Say L, Gülmezoglu AM, Fajans PJ. Preventing maternal and newborn deaths globally: using innovation and science to address challenges in implementing life-saving interventions. Obstet Gynecol. 2012;120:636–42.
167 Free MJ. Achieving appropriate design and widespread use of health care technologies in the developing world.: Overcoming obstacles that impede the adaptation and diffusion of priority technologies for primary health care. Int J Gynaecol Obstet. 2004;85:S3–13.
168 World Health Organization. Every Newborn: An action Plan to End Preventable Deaths. Geneva: WHO; 2014.