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. 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. A review by Thairu et al. 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. 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%). 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, making premature babies prone to develop respiratory distress syndrome (RDS). Immaturity of other physiological systems such as the nervous, cardiovascular, immune, musculoskeletal, gastrointestinal, 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, jaundice, haemorrhagic disease of the newborn and necrotizing enterocolitis.

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...
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.

**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. HIE results from poor delivery of oxygen to the neural tissue, leading to tissue hypoxia and metabolic acidosis. This culminates in tissue injury from direct hypoxic insult as well as indirect injury from free radicals during re-oxygenation. These processes evolve over time, destroy essential components of the cell and lead to cell death. The resultant neonatal complications include multi-organ failure, neonatal encephalopathy and death. Symptoms change with time and depend on the severity, timing and duration of the initial injury.

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

**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. 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. 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. 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. Treatment is meticulously managed through weight monitoring, fluid intake/output recording and urine and blood analyses.

Breastfeeding is the goal for all infants, but those who are sick and premature may initially require alternative feeding methods. 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. 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. 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. Breast-milk may be supplemented with various macro- and micronutrients if an infant is not receiving proper nutrition. Donor milk or special formula is used when a mother’s own milk is not available or safe.
Challenges and solutions in low-resource settings

Fluid therapy requires delivery at precise volumes and flow rates, and fluid overload can be life-threatening. When a pump is not available, a basic drip set is used. This increases the risk of over-infusion, especially if the drip set does not have a burette. In low-resource settings, TPN is extremely rare owing to the high risk of infection, insufficient training, high cost, inaccurate fluid delivery methods and insufficient laboratory-based monitoring. 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. Also in development, the DripAssist device monitors flow rates during gravity-driven fluid therapy. 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. 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. An accurate, convenient and low-cost weighing method is needed for managing fluid balance and monitoring growth.

Expression and storage of human milk are difficult in low-resource settings. Inadequate breast pumps can lead to difficulty in expressing milk and, ultimately, decreased production; sterile containers and methods of refrigeration, freezing and pasteurization are also required for breast-milk management. Bottle-feeding is dangerous in low-resource settings because of the difficulties of sterilization. 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. Breast-milk fortifiers can also be prohibitively costly.

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. Innovative designs are needed for an appropriate, affordable and efficient breast-pump. 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.\textsuperscript{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.\textsuperscript{52} Depending on cause, common treatment options include antibiotics, resuscitation with IV fluids, blood transfusions and oxygen or other means of respiratory support.\textsuperscript{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.\textsuperscript{35} The most important protective interventions for nosocomial infections are frequent hand-washing, exclusive breastfeeding and facility cleanliness,\textsuperscript{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.\textsuperscript{56} Passive transfer of maternal antibodies does not occur until 29 weeks of gestation.\textsuperscript{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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{53}

Diarrhoea results in increased losses of water, electrolytes and/or nutrients, making fluid and electrolyte replacement therapy essential.\textsuperscript{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,\textsuperscript{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.\textsuperscript{60} While antibiotics to treat pneumonia and sepsis are relatively inexpensive,\textsuperscript{61} factors limiting treatment are disease recognition and diagnostic capability,\textsuperscript{62} as well as the increasing anti-microbial resistance in NICUs.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{68}

**Provide temperature stability**

**Gold standard of care**

WHO has defined hypothermia as a body temperature of <36.5\degree C and it is further divided into three levels: mild (36.0–36.5\degree C), moderate (32.0–35.9\degree C) and severe (<32.0\degree C).\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{70} Alternative approaches to managing hypothermia
include preventing heat loss and providing external sources of warmth.\textsuperscript{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.\textsuperscript{72–75} These occlusive wraps reduce evaporative and convective heat loss, and are affordable and available in low-resource settings.\textsuperscript{73} Similarly, topical emollients such as mineral oil and lanolin may help reduce water and heat loss in pre-term newborns.\textsuperscript{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.\textsuperscript{76} KMC is less expensive than conventional methods,\textsuperscript{77} reduces risk of mortality, sepsis and hypothermia, and increases growth, breastfeeding and mother-to-infant attachment.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{82} To test for respiratory conditions caused by infection such as pneumonia and sepsis, blood or other bodily fluids are sent to the laboratory.\textsuperscript{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.\textsuperscript{52} Blood gas analysis and pulse oximetry provide information on blood acidity and oxygen and carbon dioxide content to determine the treatment required.\textsuperscript{83} Depending on the diagnosis, treatment options for respiratory distress include antibiotics, supplemental oxygen, invasive and non-invasive ventilation and surfactant replacement.\textsuperscript{53,84}

**Challenges and solutions in low-resource settings**

Caregivers in low-resource settings have often not been properly trained in resuscitation procedures.\textsuperscript{35} Although endotracheal intubation is commonly used for resuscitation, initial ventilation with a bag and mask is sufficient for the majority of infants.\textsuperscript{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).\textsuperscript{87} Trained birth attendants using quality resuscitation devices can decrease mortality by up to 30%.\textsuperscript{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,\textsuperscript{84} excessive blood oxygen levels may result in oxygen toxicity and retinopathy.\textsuperscript{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.\textsuperscript{90} One promising technology is the Kenek Edge\textsuperscript{91,92} (<US$50) which measures peripheral oxygen saturation (SpO\textsubscript{2}) by connecting to supported mobile phones and tablets through the audio port.\textsuperscript{93} However, this device is not yet suitable for neonates and has not been tested clinically. Lifebox\textsuperscript{94} is an affordable (US$250), commercially available SpO\textsubscript{2} monitor which exceeds the WHO device design specifications.\textsuperscript{95}

Many infants with respiratory distress require positive pressure to be directed to the alveoli in the lungs.\textsuperscript{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.\textsuperscript{54,97,98} Non-invasive ventilation with CPAP can help manage respiratory distress, particularly in these settings,\textsuperscript{54,98,99} as it is simpler than full ventilation and does not require intubation. The Pumani device is a low-cost (\textsim US$400) CPAP which is safe, durable and simple to use and repair.\textsuperscript{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 (\textsim US$2750).\textsuperscript{101} In addition to CPAP, surfactant is highly successful in treating infants with RDS; however, it is expensive and intubation is required for administration.\textsuperscript{83} Promising research is being conducted on the delivery of surfactant using Aerosurf\textsuperscript{®}, an aerosol technology.\textsuperscript{102}

\textit{Monitor and treat jaundice}

\textbf{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.\textsuperscript{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.\textsuperscript{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 \( \geq 30 \mu W/cm^2/nm \).\textsuperscript{105–109} Phototherapy is provided by commercial devices containing LEDs, fluorescent tubes, halogen/tungsten lamps or fibre-optic systems.\textsuperscript{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.\textsuperscript{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.

\textbf{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{106,119–123} Inadequate training also contributes to improper clinical set-up and technical maintenance.\textsuperscript{110} ‘Homemade’ phototherapy is common but poses safety risks and often provides insufficient irradiance.\textsuperscript{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.\textsuperscript{125,126}

Several low-cost LED phototherapy devices\textsuperscript{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.\textsuperscript{119,125} Outdoor canopies equipped with ultraviolet/infrared filters are being evaluated and could allow safe sunlight phototherapy where conventional phototherapy is unavailable.\textsuperscript{132–135} Beyond technological innovation, Cline \textit{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.\textsuperscript{124}

\textit{Monitor and treat hypoglycaemia}

\textbf{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.\textsuperscript{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.\textsuperscript{136} The standard screening method is a laboratory enzymatic test (e.g. glucose oxidase, hexokinase or dehydrogenase) to determine blood glucose concentration.\textsuperscript{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.\textsuperscript{137}
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.\textsuperscript{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.\textsuperscript{4,139–142} A key barrier to the management of hypoglycaemia is under-diagnosis and therefore under-treatment.\textsuperscript{139,141,143} When laboratory diagnosis is not readily available, bedside screening is performed using whole-blood glucose analysers and reagent test strips.\textsuperscript{136} These readings correlate fairly well with actual plasma glucose concentrations, but may vary by 0.5–1.1 mmol/L,\textsuperscript{144–147} and are most inaccurate at the lower concentrations, as seen in hypoglycaemic newborns.\textsuperscript{136} Because of these inaccuracies, glucose concentrations should ideally be confirmed by expedited laboratory testing,\textsuperscript{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.\textsuperscript{148} Oral dextrose gel and sugar powder have shown initial promise as simple, low-cost alternatives.\textsuperscript{142,148,149} These non-invasive techniques would not require the mother and baby to be separated.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Designer/Manufacturer</th>
<th>Key features</th>
<th>Cost</th>
<th>Current status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Brilliance127</strong></td>
<td>D-Rev Phoenix Medical Systems</td>
<td>CE Mark, Commercially available</td>
<td>US$500</td>
<td>Commercially available</td>
</tr>
<tr>
<td><strong>Firefly120,128</strong></td>
<td>Design that Matters Medical Technology Transfer &amp; Services</td>
<td>Double-sided to increase surface area receiving treatment; Simple, open-source design to encourage local production</td>
<td>US$50–500 (parts only)</td>
<td>Commercially available</td>
</tr>
<tr>
<td><strong>Bililights129</strong></td>
<td>Rice University University of Malawi – Polytechnic Services</td>
<td>Battery-powered, portable</td>
<td>US$110 (parts only)</td>
<td>Pilot implementation, ongoing local production</td>
</tr>
<tr>
<td><strong>BluLine119</strong></td>
<td>Tackle Design Little Sparrows Technologies</td>
<td>Battery-powered, portable</td>
<td>US$45 (parts only)</td>
<td>Pilot implementation, ongoing local production</td>
</tr>
<tr>
<td><strong>Bili-Hut130,131</strong></td>
<td>Boston Children’s Hospital</td>
<td>Battery-powered, portable</td>
<td>US$400</td>
<td>Prototype implementation, ongoing local production</td>
</tr>
</tbody>
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The diversity and extent of resource constraints must be recognized. Developing countries are not homogeneous; 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. While this is encouraging, the balance between the risks and benefits of each technological intervention must be considered on a case-by-case basis, a lesson that was recently learned through the widespread distribution of antenatal corticosteroids. 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. Effective strategies should combine interventions into packages, instead of offering single interventions in a vertical manner. Programmes which address the many causes of neonatal mortality are more likely to yield improved results. 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.

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. 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, Thermo-Spot® 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.

The maternal-infant continuum of care is also critical, and efforts to reduce neonatal mortality should include maternal care. 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%. The most basic components of essential and advanced care at each stage of childbirth are illustrated in Fig. 3.

**Table 2 Recommended characteristics of technologies in low-resource settings**

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

The multiplicity of causes of infant mortality must be kept in mind. Effective strategies should combine interventions into packages, instead of offering single interventions in a vertical manner. Programmes which address the many causes of neonatal mortality are more likely to yield improved results. 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.

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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. Ante-natal corticosteroids
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.\textsuperscript{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.\textsuperscript{160}

**Keys to comprehensive implementation of integrated technologies**

Effective and sustainable implementation of technologies is a major challenge in improving neonatal survival.\textsuperscript{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.\textsuperscript{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.\textsuperscript{167,168} Ideally, technologies should be commercially viable so as to have a significant and sustained impact on neonatal mortality and morbidity.\textsuperscript{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.

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 determine 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.\textsuperscript{4,41,166}

Finally, in order for the international development community to move its focus toward complete

### Table 3: Technologies in development and unmet technological needs

<table>
<thead>
<tr>
<th>Category of care</th>
<th>Technology</th>
<th>In development or unmet need?</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provide hydration and nutrition</td>
<td>Syringe/infusion pump\textsuperscript{9}</td>
<td>Unmet need</td>
<td>Low-cost, low-maintenance device to control IV fluid flow</td>
</tr>
<tr>
<td>Prevent and treat infections</td>
<td>Breast pump\textsuperscript{13,47}</td>
<td>Unmet need</td>
<td>Low-cost, low-maintenance design for assisted expression of breast milk</td>
</tr>
<tr>
<td></td>
<td>Sepsis diagnostic test\textsuperscript{17}</td>
<td>In development</td>
<td>Low-cost test strip to indicate blood levels of histones</td>
</tr>
<tr>
<td></td>
<td>Oral antibiotics\textsuperscript{73}</td>
<td>Unmet need</td>
<td>To prevent infection transmission during childbirth</td>
</tr>
<tr>
<td>Provide temperature stability</td>
<td>Real-time temperature monitor\textsuperscript{70}</td>
<td>Unmet need</td>
<td>Low-cost, low-maintenance monitor for neonates at risk of hypothermia</td>
</tr>
<tr>
<td>Provide breathing support</td>
<td>Sulfactant aerosol delivery\textsuperscript{102}</td>
<td>In development</td>
<td>Uses aerosol technology to deliver surfactant to the lungs</td>
</tr>
<tr>
<td>Monitor and treat jaundice</td>
<td>Pulse oximeter\textsuperscript{99}</td>
<td>In development</td>
<td>Low-cost, accurate, point-of-care test for jaundice</td>
</tr>
<tr>
<td></td>
<td>Bilirubin monitor\textsuperscript{104,105,117,118}</td>
<td>Unmet need</td>
<td>Phototherapy techniques that employ battery power or sunlight</td>
</tr>
<tr>
<td>Monitor and treat hypoglycaemia</td>
<td>Phototherapy independent from power grid\textsuperscript{119,130–135}</td>
<td>In development</td>
<td>Accurate, durable and affordable screening tool for hypoglycaemia; universal test strips</td>
</tr>
</tbody>
</table>

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**Figure 3** The maternal-infant continuum of care with corresponding interventions for essential and advanced care. Sources: March of Dimes et al.,\textsuperscript{4} The Partnership for Maternal, Newborn & Child Health\textsuperscript{114}
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**


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