Research priorities for care of preterm or low birth weight infants: health policy

Care of Preterm or Low Birthweight Infants Group[a]

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Summary

Research priorities for preterm or low birth weight (LBW) infants were advanced in 2012, and other research priority-setting exercises since then have included more limited, context-specific research priorities pertaining to preterm infants. While developing new World Health Organization (WHO) guidelines for care of preterm or LBW infants, we conducted a complementary research prioritisation exercise. A diverse, globally representative guideline development group (GDG) of experts – all authors of this paper along with WHO steering group for preterm-LBW guidelines – was assembled by the WHO to examine evidence and consider a variety of factors in intervention effectiveness and implementation, leading to 25 new recommendations and one good practice statement for care of preterm or LBW infants. The GDG generated research questions (RQs) based on contributions to improvements in care and outcomes of preterm or LBW infants, public health impacts, answerability, knowledge gaps, feasibility of implementation, and promotion of equity, and then ranked the RQs based on their likelihood to further change or influence the WHO guidelines for the care of preterm or LBW infants in the future. Thirty-six priority RQs were identified, 32 (89%) of which focused on aspects of intervention effectiveness, and the remaining four addressed implementation ("how") questions. Of the top 12 RQs, seven focused on further advancing new recommendations – such as family involvement and support in caring for preterm or LBW infants, emollient therapy, probiotics, immediate KMC for critically ill newborns, and home visits for post-discharge follow-up of preterm or LBW infants – and three RQs addressed issues of feeding (breastmilk promotion, milk banks, individualized feeding). RQs prioritised here will be critical for optimising the effectiveness and delivery of new WHO recommendations for care of preterm or LBW infants. The RQs encompass unanswered research priorities for preterm or LBW infants from prior prioritisation exercises which were conducted using Child Health and Nutrition Research Initiative (CHNRI) methodology.

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Keywords: Research priorities; Prioritisation; Newborn health; Preterm infant; Low birth weight; Neonatal mortality

Introduction

The top cause of mortality for under-five children is complications of preterm birth, which accounted for an estimated 17.7% of child deaths (0.94 million) in 2019.[1,2] Given new evidence for interventions to avert deaths in preterm or low birth weight (LBW) infants,[3] the World Health Organization (WHO) engaged a Guideline Development Group (GDG) of 25 international experts – all authors of this paper along with WHO steering group for preterm-LBW guidelines – in 2020 to develop new evidence-based recommendations for care of preterm or LBW infants. Twenty-five new or updated WHO recommendations were made by the GDG in November 2022.[4,5] These recommendations complement or replace prior WHO recommendations made in 2011, 2012, and 2015.[6–8]

Alongside the development of the recommendations for interventions to be implemented in the care of preterm or LBW infants, the GDG formulated research questions (RQs) related to the 25 recommendations and the good practice statement. We then prioritised the RQs according to their likelihood of leading to additional change or influence in future guideline updates and ultimately to improve survival, health and development of preterm or LBW infants. Here we present the priority RQs and discuss their implications.

Methods

Guideline Development Group

The WHO Secretariat identified the external experts for the GDG from the six WHO regions, seeking to achieve geographic representation and gender balance while avoiding conflicts of interest. To ensure broad representation, the GDG was comprised of experts in public health, maternal and child health and nutrition, policy-making, programme planning and implementation,

[a]Author group details are provided at the end of the manuscript.
Corresponding author. Department of Maternal, Newborn, Child and Adolescent Health and Ageing, World Health Organization, Geneva, Switzerland.
E-mail address: guptashu@who.int (S. Gupta).

Key messages

- Our method for identifying research priorities utilised many criteria in common with CHNRI methodology, however, in addition to these criteria, we added a new element to prioritise RQs based on the likelihood that answering the RQ would lead to change or influence recommendations from WHO on the care of preterm or LBW infants in the future.
- The majority of RQs (32 of 36; 89%) focus on generating additional evidence for aspects of intervention effectiveness; four (11%) address questions of how to implement recommended interventions; and 7 of the 12 highest-scoring RQs are on effectiveness of newly recommended interventions (e.g., family involvement and support in caring for preterm or LBW infants, emollient therapy, probiotics, immediate KMC for critically ill newborns, home visits for post-discharge follow-up).
- Many previously proposed RQs for care of preterm of LBW infants have been answered to date, yet the burden of disease remains high; thus, expanding the evidence based for interventions for preterm or LBW infants is of great public health importance.
- New WHO recommendations for care of preterm or LBW infants will require adaptation for implementation, and many of the RQs prioritised here will lead to further optimisation of the effectiveness and delivery of these new interventions.
- Investment in these prioritised RQs along with RQs yet unanswered from prior prioritisation exercises will lead to additional advances in the care, survival and health of preterm or LBW infants around the world.

research methodology and statistics; included representatives from government, non-governmental organisations, academia, private healthcare institutions, parent groups and consumers; and had global representation from high-, middle-, and low-income countries.

Formulation of recommendations for care of preterm or LBW infants

Formulation of the recommendations for care of preterm or LBW infants involved review of evidence of impact of interventions on all-cause mortality, morbidity, growth, and neurodevelopment [3]; assessment of the quality of the scientific evidence; and expert judgements on various criteria important for effective implementation and impact, such as the balance of benefits and harms on preterm or LBW infant outcomes, certainty of the evidence, values of families and health workers, acceptability, resource requirements, feasibility and equity.

Formulation of research questions

As each recommendation was formulated, the GDG collectively identified key research gaps in intervention effectiveness and implementation. In addition to RQs generated during discussions of the guidelines, the WHO Secretariat for the GDG solicited RQs individually from the GDG members based on the following criteria, which were weighted equally: the research will: 1) Contribute to improvements in care and outcomes of preterm or LBW infants, 2) Be likely to result in significant public health impacts, 3) Be answerable, 4) Fill an important knowledge gap, 5) Be feasible to implement, and 6) Be likely to promote equity. These RQs were clarified and refined by the Secretariat, eliminating duplicates, resulting in a list of 43 RQs, plus one more which was added on evaluating the cost-effectiveness of the 'strong' recommendations which are applicable widely to all preterm or LBW infants. The GDG members then voted independently for their top five questions based on the criterion: 'How likely is the research question to change or influence the WHO preterm or LBW guidelines in the future?' The RQs were then prioritised based on their score determined by the number of GDG members who selected them[b]; members of the WHO Secretariat did not vote. Each GDG member had an equal vote. The maximum possible score for an individual question was 25, i.e., all GDG members choose a given RQ among their top five choices; there was no weighting by rank order among the top five choices by a given GDG member. The minimum score was zero, i.e., none of the GDG members choose that RQ among their top five.

Search strategy and selection criteria

We conducted a search in Pubmed for studies in English over the past decade which focused on research priorities for care of preterm or LBW infants. Search terms included neonatal, perinatal, newborn, newborn infant, preterm, preterm infant(s), LBW, research, and priorities. We also searched the reference lists of identified articles for additional pertinent literature.

Ethical approval

This did not constitute human subjects research; ethical approvals or consent to participate were not needed.

Role of the funding source

There was no funding source for this study. GLD and SG had full access to the data set and made the decision to submit the paper for publication. All authors had full access to all the data in the study and accept responsibility for the decision to submit the paper for publication.

Results

A total of 36 RQs were prioritised (Table 1, Table 2); eight received no votes and were eliminated (Table 2). Overall, 32 RQs (89%) focused on aspects of intervention effectiveness ("what" questions) and four RQs (11%) aimed to address implementation ("how" questions).

The four top-tier RQs each received seven votes and focused on strategies (how) to increase family

[b]A total of 24 GDG members selected their choice of the top five RQs, of which 21 were included as scoring by three authors was invalid.

participation in the care of preterm or LBW infants, approaches (how) to promote exclusive breastmilk feeding, effectiveness of topical emollient therapy, and effectiveness of CPAP compared with humidified high-flow nasal cannulae (Table 1).

The second tier of RQs comprised three which received five votes each, including effectiveness of immediate Kangaroo Mother Care (KMC) for critically ill preterm or LBW infants; effectiveness, safety, and feasibility of setting up human milk banks; and effectiveness and safety of probiotics (Table 1). Rounding out the top twelve RQs were a third tier of five questions which each received four votes (Table 1). These RQs included the effectiveness of KMC on longer-term outcomes, how to scale up immediate KMC, effectiveness of individualised early feeding strategies, effectiveness of family support interventions, and effectiveness and feasibility of virtual compared to in-person post-discharge home visits.

An additional 14 RQs received lower prioritisation (Table 2). Seven RQs, forming a fourth tier, received three votes each, including development of an implementation model (how) for prolonged KMC in high-income countries, effectiveness of multicomponent fortification of human milk, long-term impacts of exclusive breastfeeding, effectiveness of prophylactic immediate CPAP, dosing of caffeine therapy for prevention and treatment of apnea, and effectiveness of m-health approaches to supporting families in caring for preterm or LBW infants. Also prioritised in this fourth tier of RQs was research on cost effectiveness of the recommendations. Several other RQs which received two or one vote were captured in a fifth tier listed in Table 2.

Discussion

A prioritisation process among global experts on the WHO GDG for care of preterm or LBW infants resulted in an extensive list of 44 RQs which were considered to be most important for further advancing WHO recommendations for care of preterm or LBW infants; eight received no support and were eliminated. Among the top 12 RQs, seven pertain to new interventions which appeared for the first time in WHO recommendations.[5] These include family participation in the care of preterm or LBW infants and emollient therapy, which were prioritised in the top tier (i.e., the top four RQs), along with immediate KMC for critically ill newborns, probiotics, and home visits for post-discharge follow-up of preterm or LBW infants. Ten of the top 12 RQs focus on intervention effectiveness, and two are on approaches to implementation. Three of the top 12 RQs address

Research implications	Total score
Tier 1	
What strategies can be used to increase family participation in the care of their preterm or LBW infants in intensive and special care units, and in settings without dedicated newborn units?	7
How can exclusive breastfeeding be promoted, supported and scaled-up for preterm or LBW infants, especially those who are very preterm or very LBW?	7
What is the effectiveness of emollients on thermoprotection, growth, microbiome development, invasive infection/sepsis, mortality, and longer-term neurodevelopment in preterm or LBW infants, especially in low- and lower-middle-income settings, including Africa? • Which emollients (which oils, which composition) are most effective and safe? • What is the optimal regime (dose, frequency, duration) and mode of application (e.g., non-touch applications) for very or extremely preterm infants?	7
What is the effectiveness of continuous positive airway pressure (CPAP) compared with humidified high-flow nasal cannulae and other forms of non-invasive ventilation in improving mortality and morbidity in preterm or LBW infants with respiratory distress syndrome?	7
Tier 2	
What is the effectiveness of immediate Kangaroo Mother Care (KMC) in improving mortality, morbidity, growth and neurodevelopmental outcomes for critically ill preterm or LBW infants, such as infants who are mechanically ventilated or on vasopressor support?	5
What is the effectiveness, safety, and feasibility of setting up human milk banks in low- and middle-income countries?	5
What is the effectiveness and safety of probiotics on mortality, morbidity, growth, immunological status, microbiome development, and neurodevelopmental outcomes in human milk fed preterm or LBW infants? • What are the most optimal probiotic compositions or combinations of genera, species and strains? • What is the optimal dosage and duration of probiotics? • What is the effectiveness of probiotics alone compared with a combination of probiotics and prebiotics? • What is the role of probiotics in prevention and management of postnatal growth restriction in preterm infants?	5
Tier 3	
What is the effectiveness of KMC on longer-term (i.e., up to two years of age, school-age, adolescence) growth, neuro-cognitive development, behavior, mental health, and disability outcomes?	4
How can immediate KMC be scaled-up in routine health systems?	4
What are the most effective early feeding strategies for very preterm or very LBW infants, infants with illnesses (e.g., post surgery), and infants with other conditions (e.g., doppler abnormalities, severe growth restriction)?	4
What is the most effective type of family support (e.g., education, counselling, discharge preparation by health providers, peer support) for families of preterm or LBW infants?	4
What is the effectiveness on mortality, morbidity, growth, and neurodevelopment of "in-person" home visits compared with "digital" home visits (e.g., online video, mobile application [app], mHealth) for post-discharge follow-up of preterm or LBW infants?	4

Table 1: **Prioritised research questions to inform WHO recommendations for care of preterm or low birth weight (LBW) infants: top three tiers of questions.**

Tier 4	
What are the key components of an implementation model that achieves high population-level coverage of Kangaroo Mother Care (KMC) for more than eight hours per day in high-income countries?	3
What is the effect of multicomponent fortification of human milk on exclusive breastfeeding rates at six months of age in human milk-fed preterm or LBW infants?	3
What is the effect of the duration of exclusive breastfeeding on long-term (i.e., up to two years of age, school age, adolescence) health, growth, neurodevelopment, and metabolic (e.g., blood sugar, lipid profile) outcomes of preterm or LBW infants?	3
What is the effectiveness of starting CPAP immediately after birth regardless of respiratory distress in improving mortality and morbidity in preterm or LBW infants? If effective, infants of what gestational age?	3
What is the optimal timing of initiation, dosage, and duration of caffeine therapy for prevention and treatment of apnea in preterm infants <34 weeks of gestation?	3
What is the effectiveness on mortality, morbidity, growth, and neurodevelopment of digital health interventions (e.g., online video, mobile-application [app], mHealth based support) in supporting parents of preterm or LBW infants in the care of their infants?	3
What is the cost-effectiveness of the interventions strongly recommended by the World Health Organization for the care of preterm or LBW infants (KMC including immediate KMC, mother's own milk, early enteral feeding, exclusive breastfeeding for six months, enteral iron supplementation, continuous positive airway pressure [CPAP] for respiratory distress syndrome, caffeine for treatment of apnea and extubation, family involvement, home visits for family support)?	3
Tier 5	
What is the effectiveness of KMC provided by the mother plus other family members compared with KMC provided only by the mother for as long as possible, on daily duration of KMC, breastfeeding, maternal rest and self-care, maternal and paternal physical and mental health and bonding with the infant, and inter-personal relationships between parents?	2
When mother's own milk is not available, what is the effectiveness and safety of pasteurised compared with unpasteurised donor human milk for feeding preterm or LBW infants?	2
What is the effect of responsive feeding compared with different schedules of feeding (e.g., 2- or 3-hourly) until term corrected age on mortality, morbidity, growth, and neurodevelopment in preterm or LBW infants?	2
What is the effect of different doses, timing, and duration of zinc supplementation in human milk-fed preterm or LBW infants?	2
What is the effect of prolonged skin-to-skin contact beyond the first hour of birth in newborns born at term gestation (≥37 weeks) with normal birth weight (≥2500 grams)?	1
What is the effect of KMC on the physical and mental health and childcare practices of the mothers, fathers, partners and family members?	1
What is the effectiveness and safety of KMC during transport of a preterm or LBW infant from the community to hospital, between hospitals, and within the hospital compared with standard methods of transport (e.g., transport incubator) on hypothermia at arrival, hypoglycemia, morbidity, and mortality?	1
What is the effectiveness of KMC compared with other approaches (e.g., oral sucrose) with no KMC in reducing pain during procedures that are likely to be painful?	1
What is the effect of higher compared with lower increments in feeding volume (e.g., 40 vs 30 ml/kg/day) in preterm infants who need to be fed by an alternate feeding method to breastfeeding (e.g., gastric tube feeding or cup feeding)?	1
What is the effect of different doses, timing, and duration of supplementation with iron on clinical outcomes (e.g., mortality, anemia, sepsis, necrotising enterocolitis, neurodevelopment) and iron-related biomarkers (e.g., soluble transferrin receptor) in human-milk fed preterm or LBW infants? • What is the optimal dose and duration of supplementation at different gestational ages, birth weights, and soluble transferrin receptor concentrations?	1
What is the effect of different doses, timing of initiation and duration of supplementation with vitamin D on mortality, morbidity and bone health in human milk-fed preterm or LBW infants? • What is the optimal dose and duration of supplementation at different gestational ages, birth weights, 25-hydroxyvitamin D [25-(OH)D] concentrations, and alkaline phosphatase levels?	1
What is the effect of different doses, timing of inititation and duration of vitamin A supplementation on mortality and morbidities, including infections, in human milk-fed preterm or LBW infants? • What is the optimal dose and duration of supplementation at different gestational ages, birth weights and retinol levels?	1
What is the optimal timing/schedule of caffeine administration for extubation in preterm infants <34 weeks of gestation?	1
How can social care services support parents or families of preterm or LBW infants?	1
What is the effectiveness of home visits from health workers who are specially trained in preterm and LBW care compared with home visits from routinely trained health workers, including community health workers for the follow-up care of preterm or LBW infants on their mortality, morbidity, growth and neurodevelopmental outcomes?	1
What is the optimal content, duration and frequency of home visits for preterm or LBW infants?	1
What is the effectiveness of parental entitlements including financial incentives and additional leave from work in improving infant outcomes (e.g., mortality, morbidity, exclusive breastfeeding, duration of hospital stay) and family outcomes (e.g., physical and mental health, couple's relationship, catastrophic health expenditure)? • Which type of entitlements are most effective? • Which type of entitlements are most desirable for families? • What should be the duration of parental leave and entitlements? • What are the most effective ways to operationalise these policies in public and private (formal and informal) sectors?	1
Research questions which received no votes and were deprioritised	
What is the effectiveness of standard infant formula compared to preterm infant formula with different caloric densities on mortality, morbidity, growth, and neurodevelopment outcomes in preterm or LBW infants, when mother's own milk and donor human milk are not available?	0
What is the effectiveness and cost-effectiveness of liquid preterm formula (ready-to-use and liquid concentrate formula) compared to powder preterm formula on feeding intolerance, necrotising enterocolitis, infection-related morbidity and mortality, and growth, especially in lower income settings and settings with high infection rates when mother's own milk and donor human milk are not available?	0
What is the effectiveness of different feeding volume increments by milk type (e.g., exclusively formula-fed vs. exclusive breastmilk-fed infants), gestational age or birth weight subgroups (e.g., extremely preterm or LBW infants vs. very preterm or very LBW or ≥1500 g/≥32-week infants) and presence of illness or other conditions (e.g., surgical gut, doppler abnormalities, severe small-for-gestational-age, etc.) on mortality, morbidity, growth, and development outcomes of preterm infants who need to be fed by an alternate feeding method to breastfeeding (e.g., gastric tube feeding or cup feeding)?	0
What is the effectiveness of calcium and phosphorous supplementation compared to no supplementation on bone health in human milk-fed preterm or LBW infants? What is the optimal dose and duration of calcium and phosphorous supplementation at different gestational ages and birth weights?	0

(Table 2 continues on next page)

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What is the effectiveness of multiple micronutrient supplementation (different doses, timing of initiation and duration) compared to multi-component fortification of human milk and no supplementation on mortality, morbidity, biochemical markers, and neurodevelopmental outcomes in human milk-fed preterm or LBW infants?	0
Which CPAP interface is most effective and safe for use preterm infants who require CPAP?	0
What is the effectiveness of starting early CPAP (i.e., after the onset of respiratory distress but before the diagnosis of respiratory distress syndrome is made) compared to oxygen therapy and other supportive care in preterm infants?	0
What is the effectiveness and safety of caffeine compared to other methylxanthines for the treatment of apnoea in preterm infants?	0

Table 2: **Research questions prioritised, in the lower tiers or deprioritised, to inform WHO recommendations for care of preterm or low birth weight (LBW) infants.**

family involvement and support, a new set of recommendations for care of preterm or LBW infants; three of the top 12 RQs address issues of feeding (breastmilk promotion, milk banks, individualized feeding), and two focus on KMC (in critically ill infants and long-term impacts). Among the 24 fourth- and fifth-tier RQs, 22 were questions of intervention effectiveness and two aimed to inform implementation.

Our research priorities for preterm or LBW infants are heavily oriented toward effectiveness of interventions for preterm infants, perhaps in part because considerations of intervention effectiveness were front-and-center in the guideline development process. Nearly half (n = 11) of the 25 recommendations were new,[5] for interventions not featured previously by WHO (i.e., probiotics, emollients, caffeine, family involvement, family support, home visits), while some involved new applications of intervention already on WHO's lists (e.g., KMC started immediately after birth, CPAP started immediately after birth, Bubble CPAP). Fourteen of the new recommendations were also conditional, often on the basis of a need for additional, generalisable evidence for impact. In this context and as directed by the final question framing our prioritisation of RQs (i.e., selection of research which would further advance the guidelines), our RQs focused on areas where additional evidence for effectiveness is needed. Beyond consideration of effectiveness, however, formulation of the recommendations also involved examination of issues related to implementation such asvalues of families and health workers, and the acceptability, resource requirements, feasibility and equity implications of introducing the intervention into health systems. The new WHO recommendations for care of preterm or LBW infants will require adaptation for implementation at regional and country levels and the training of multiple cadres of healthcare providers. Therefore, some RQs prioritised here will be critical for optimising the effectiveness and delivery of these new interventions.

Most prior systematic research prioritisation exercises for newborn health have utilised the Child Health and Nutrition Research Initiative (CHNRI) methodology for setting priorities in health research investments,[9,10] and several of these efforts have identified RQs for preterm or LBW infants (Table 3).[11–19] The CHNRI process engages topic experts to propose RQs, typically spanning the spectrum of epidemiological research, health policy and systems research, improvement of existing interventions, and development of new interventions. RQs are then assessed for answerability, effectiveness, deliverability, maximum potential for mortality reduction and the effect on equity. The research prioritisation process followed by the GDG was similar to CHNRI, involving the generation of a broader set of RQs which the GDG then prioritised based on criteria that resemble those used by CHNRI, e.g., answerability, effectiveness, deliverability (i.e., feasibility for implementation), potential for significant public health impacts, and effect on equity. In addition, we explicitly considered contribution to improvements in care and outcomes of preterm or LBW infants and to filling a knowledge gap that would inform new recommendations or change an existing WHO recommendation for care of preterm or LBW infants. Furthermore, our discussion of research priorities followed immediately upon broad discussion of a set of judgements regarding each intervention, including certainty of the evidence, values of families and health workers, acceptability, resource requirements, feasibility and equity. Ultimately, in this context, and unlike the CHNRI process, our prioritization of RQs was based on an assessment of the likelihood that answering the RQ would lead to change or influence the existing WHO preterm/LBW infant guidelines.

Prior research prioritisation exercises that have encompassed care for preterm or LBW infants have had various primary remits, including neonatal infections,[11] birth asphyxia,[12] newborn health,[13,14] maternal and perinatal health,[15] India,[16] humanitarian conflict settings,[17] and Covid-19.[18] We found one prior report from a decade ago (2012) on a research prioritisation exercise exclusively focused on preterm or LBW infants, particularly research for reduction of mortality.[19] The top ten research priorities identified then were predominantly health systems and policy research questions (Table 3). These research questions remain pertinent today – and are echoed in several of our research priorities – although the focus has shifted for some. Identification of LBW infants at home is now central to the new WHO recommendation for home initiation of KMC, optimal home care practices is now a focus of the new recommendation on home visits, and implementation of approaches to increase the use of antenatal corticosteriods in preterm

Reference	Title	Research questions[a]
Bahl R, et al. Pediatr Infect Dis J 2009; 28 (1 Suppl):S43-8.	Research priorities to reduce global mortality from newborn infections by 2015.	• What is the feasibility and effectiveness of simpler, cheaper technology be developed to improve supportive care of neonates with infections in low resource settings (such as robust pulse oximeter, oxygen condensors, low-cost continuous positive airway pressure (CPAP), warm mattress, transport bassinet etc.)?
Lawn JE, et al. PLoS Med. 2011; 8 (1):e1000389	Setting research priorities to reduce almost one million deaths from birth asphyxia by 2015	• What is the prevalence of babies requiring resuscitation in various settings? What is the prevalence for preterm and term babies? (ranked 19 of 61)
Bahl R, et al. J Glob Health. 2012; 2 (1):010403	Setting research priorities to reduce global mortality from preterm birth and low birth weight by 2015	Top ten research priorities • Identification of LBW infants within 24–48 h of birth for additional care among those born at home • Approaches to improve quality of care of LBW infants in health facilities • Identification of current behaviors, and barriers and supports for optimal home care practices, including care seeking for illness • Effective interventions for achieving early initiation of breastfeeding including feeding mode and techniques for those unable to suckle directly from the breast • Approaches to improve access to care for the subset of LBW infants who need hospital care • Improved criteria for identifying LBW infants who need to be cared for in a hospital • Effectiveness of improved cord care (eg, chlorhexidine application) • Comparison of Kangaroo Mother Care (KMC) and alternative methods of keeping the LBW infant warm in community settings
Yoshiha S, et al. Lancet 2014; 384 (9938):e27–e29	Newborn health research priorities beyond 2015	Top ten research priorities: Delivery • How can facility-based initiation of KMC or continuous skin-to-skin contact be scaled up? • Can community-based extra care for preterm/LBW babies delivered by community health workers (CHWs) reduce neonatal morbidity and mortality in settings with poor access to facility care? Top five research priorities: Development • Can community-based initiation of KMC reduce neonatal mortality of clinically stable preterm and LBW babies? Top five research priorities: Discovery • Can stable surfactant with simpler novel modes of administration increase the use and availability of surfactant for preterm babies at risk of respiratory distress syndrome? • Can strategies for prevention and treatment of intrauterine growth restriction be developed?
Souza JP, et al. Reprod Health 2014; 11:61	Maternal and perinatal health research priorities beyond 2015: an international survey and prioritization exercise	Top 20 research questions • Evaluate the effectiveness and cost of a package of community level interventions for preterm babies (e.g., implementing and providing guidelines for KMC, home visits by CHWs, infection prevention strategies)
Yoshida S, et al. J Glob Health 2016; 6 (1):010508	Setting research priorities to improve global newborn health and prevent stillbirths by 2025	Top ten research priorities • Can community–based initiation of KMC reduce neonatal mortality of clinically stable preterm and LBW babies? • How can facility-based initiation of KMC or continuous skin–to–skin contact be scaled up? • Can community based "extra care" for preterm/LBW babies delivered by CHWs reduce neonatal morbidity and mortality in settings with poor accessibility to facility care? Top ten development research priorities • Can community–based initiation of KMC reduce neonatal mortality of clinically stable preterm and LBW babies? • Can low–cost devices for facility care of newborns be developed and tested for the effectiveness at various levels of the health system (eg, CPAP devices, syringe drivers, IV giving sets, phototherapy units, oxygen concentrators, oxygen saturation monitors incubators, ventilators, therapeutic hypothermia technology)? • Can surfactant reduce preterm morbidity and mortality in low and middle income countries? Top ten discovery research priorities • Can stable surfactant with simpler novel modes of administration increase the use and availability of surfactant for preterm babies at risk of respiratory distress syndrome? • Can strategies for prevention and treatment of intrauterine growth restriction be developed? • Can the new method identify intrauterine growth restriction at the early stage (including biomarkers) and predict abnormal postnatal growth and body composition?

(Table 3 continues on next page)

Reference	Title	Research questions[a]
(Continued from previous page)		
Arora N, et al. Indian J Med Res 2017; 145 (5):611-622	Research priorities in maternal, newborn, & child health & nutrition for India: An Indian Council of Medical Research-INCLEN initiative	Top 10 newborn health priorities • Engaging and empowering family members and community in the care of newborn (including family centred care): barriers, strategies to overcome, impact, cost-effectiveness • Low cost, feasible, portable technological innovations in equipment to improve capacity (diagnosis, identification and management) and outreach for foetal and neonatal care (especially, LBW, preterm: CPAP, surfactant therapy, etc.) at various levels of the health system and their impact evaluation
Kobeissi L, et al. Confl Health. 2021; 15 (1):16	Setting research priorities for sexual, reproductive, maternal, newborn, child and adolescent health in humanitarian settings	• In acute and protracted conflict-affected contexts (*to specify), what are the most effective models to care for vulnerable newborns (small and sick)?
COVID-19 Research Prioritization Group on MNCAH. J Glob Health 2021; 11:04071	Global research priorities on COVID-19 for maternal, newborn, child and adolescent health	Top ten research priorities for newborn health • What is the most effective way to prevent the transmission of SARS-CoV-2 to preterm newborns receiving KMC? • What are the major risk and/or protective factors (eg, breastfeeding, skin-to-skin care or KMC, LBW, Bacillus Calmette Guerin or other existing vaccinations, HIV-1 exposure, etc.) for the acquisition of SARS-CoV-2 infection or development of COVID-19 disease or severe disease in newborns of SARS-CoV-2 infected mothers? • What is the impact of maternal SARS-CoV-2 infection on newborn health outcomes (eg, intrauterine growth restriction, prematurity, and birth asphyxia), and how can this be mitigated?

[a]Research questions were identified which focused directly on the care of preterm or LBW infants; questions pertaining to the prevention of preterm birth, or to broader aspects of care provision for newborn infants who are not necessarily preterm or LBW were not included.

Table 3: **Research priority setting exercises which identified questions pertaining to the care of preterm or low birth weight (LBW) infants.**

labor is an area of focus stemming from the new WHO guidelines on use of antenatal corticosteroids.[20,21] The question on KMC effectiveness in community settings has since been answered,[22] and WHO has updated guidelines on cord care with chlorhexidine.[23] The top-ranked epidemiological question – improving criteria for identifying LBW infants who need to be cared for in a hospital – is also important now for appropriate referral to hospital of infants receiving KMC at home.

WHO led a prioritisation exercise reported in 2014 on research priorities for improving newborn health outcomes (Table 3).[13] A recent analysis of the attention given subsequently to these priorities indicated that both delivery domain questions related to preterm infants (e.g., scale up of facility-based KMC, and effectiveness of extra community-based care for preterm infants) received high attention, and the one development domain question (effectiveness of community-initiated KMC) and the two discovery domain questions (surfactant administration, and prevention and treatment of intrauterine growth restriction) received moderate attention.[24] Thus, action to address the RQs posed regarding preterm infants was substantial and advanced knowledge since the research priorities were issued. For example, questions on the effectiveness of facility-based KMC and on the effectiveness of community-based extra care for preterm/LBW babies have been addressed. Now, the priority is on (as identified in our RQs) the effectiveness of in-person compared with digital home visits for post-discharge follow-up, the effectiveness of home visits from health workers specially trained in preterm and LBW care compared with more generalist community health workers, and the optimal content, duration and frequency of home visits. A similar report in 2016 on research priorities for improving newborn health built on the 2014 report,[14] adding a question on effectiveness of community-based initiation of KMC which has since been answered and is now recommended. Two additional development research priorities were directed at technology development such as low-cost devices for facility care of newborns and evaluation of surfactant effectiveness. Discovery priorities included novel modes of surfactant administration, and early identification (e.g., biomarkers), prevention and treatment of intrauterine growth restriction. These remain important areas of investigation.

Within a broader maternal and perinatal health research priority setting exercise reported in 2014, the following RQ was ranked in the top 20: "Evaluate the effectiveness and cost of a package of community level interventions for preterm babies (e.g. implementing and providing guidelines for kangaroo mother care, home visits by CHWs, infection prevention strategies)."[15] These are now encompassed in the new WHO recommendations.

Among ten priority newborn care research priorities identified through an adapted CHNRI process in India, several could influence care of preterm/LBW infants, but two are directly relevant to the new WHO recommendations, including technological innovations in equipment to improve foetal and neonatal care (and engaging and empowering family members and communities in newborn care.[16] Implementation research was noted as an important area for consideration.

While addressing research priorities for sexual, reproductive, maternal, newborn, child and adolescent health in humanitarian settings, Kobeissi et al. included a research priority on the most effective models to care for vulnerable newborns (small and sick) in acute and protracted conflict-affected contexts. Additional priorities pertinent to the care of preterm or LBW infants, and overlapping with our RQs included strategies/approaches (task shifting, selfcare, community health workers, mobile clinics, digital technologies) to provide maternal and perinatal health services and delivery of nutrition interventions for high-risk infants/children (e.g., preterm, LBW) in refugee camps. Finally, MNCH research priorities for Covid-19 included one research priority focused on how to prevent the transmission of SARS-CoV2 to preterm newborns receiving kangaroo mother care.

Our research prioritisation process had several strengths. It was based on a number of standard criteria similar to those used in the CHNRI research prioritization method, and took place within a highly rigorous, systematic process of evidence review as well as consideration of issues important for implementation. Moreover, the GDG process enabled extensive discussions and sharing of diverse perspectives in identifying and refining relevant RQs. The RQs were also prioritised with a focus on generating additional global improvements in survival and health or preterm or LBW infants.

The number of experts on the GDG who prioritised the RQs was relatively small compared to typical CHNRI processes; the set of RQs prioritised by another group of experts of similar size convened by a similar process might have differed from ours; however, the GDG members were selected based on their experience and expertise in this area and the benefit of involving experts in research prioritisation is well documented.[25] While the criteria for our assessment of RQs was similar to CHNRI, we did not use a formal framework for prioritisation but left it to the broader discretion of the experts. The prioritisation was based on an overall judgement by GDG members considering all of the prioritisation criteria; we did not ask them to rank or score each RQ on each criterion (rather based on an overall assessment of likelihood that answering the RQ would change or influence the new WHO preterm/LBW guidelines), nor did we use a summative scoring system based on all the different criteria, as optimal methods for doing this are unclear. We also did not use more formal, quantitative methods such as value-of-information analyses to assist with prioritisation. Given the nature of several new interventions that were recommended and the conditional nature of several recommendations, the focus of our RQs may have been biased toward effectiveness questions over questions of implementation. Experts in the GDG were selected based on a number of factors, including their expertise, and they may be actively involved in research on the identified priorities. This could have affected their suggestions for the RQs to be included, but since the RQs were prioritised based on the scoring by all members, it is unlikely to have affected the final selection. Our review of literature for research priorities for preterm or LBW infants was not exhaustive and may have missed other presentations or research priorities that are embedded within larger bodies of work. Cost effectiveness of interventions also requires additional emphasis.

Conclusions

While a broad armamentarium of interventions is available to improve the care and ultimately the survival and health of preterm or LBW infants, many pressing RQs pertaining to preterm/LBW infant care remain. Review of prior research prioritisation exercises for preterm/LBW infants suggests that action has ensued to answer many key questions posed in the past, contributing to an expansion of evidence-based interventions for preterm/LBW infants. Here, along with RQs yet unanswered from other prioritisation exercises, we propose a robust, diverse research agenda for advancing preterm/LBW infant care. We call on governments, non-governmental organizations, research institutes, and donors to evaluate and support the top-ranked priorities to improve care and outcomes for every preterm and LBW infant.

Contributors

G.L.D. and S.G. conceptualised the paper; G.L.D. led literature review; methodology was devised by S.G., R.B., K.E., G.L.D. and R.C.; S.G. and R.B. managed project administration and resources; R.B. provided supervision; K.E. and G.L.D. validated study findings; S.G. and G.L.D. led data visualization; G.L.D. led writing of the original draft; R.C. provided critical input; all authors contributed to writing review and editing. All authors contributed intellectual content and approved the final draft for publication. S.G. and G.L.D. had full access to the data in the study and take responsibility for the integrity and accuracy of the underlying data (verification) and the data analysis; S.G. and G.L.D. had responsibility for the decision to submit the manuscript for publication. All authors had full access to all the data in the study and accept responsibility for the decision to submit the paper for publication.

Data sharing statement

All data used in developing this paper are contained within the paper or are available publicly.

Declaration of interests

MB is board member, MSF, Sweden. RC reports receiving consulting fees from the World Health Organization to serve as methodologist for the development of the guidelines on which this manuscript is based. SM is a member of European Foundation for the Care of Newborn Infants (EFCNI) Trustee Board and the EFCNI Executive Board; participation in both EFCNI boards is nonpaid. Other authors declare no other competing interests.

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Authors

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Care of Preterm or Low Birthweight Infants Group

The members of the Care of Preterm or Low Birthweight Infants Group are: Gary L Darmstadt, Nafisa Hamoud Al Jaifi, Shabina Ariff, Rajiv Bahl, Mats Blennow, Vanessa Cavallera, Doris Chou, Roger Chou, Liz Comrie-Thomson, Karen Edmond, Qi Feng, Patricia Fernandez Riera, Laurence Grummer-Strawn, Shuchita Gupta, Zelee Hill, Ayede Adejumoke Idowu, Carole Kenner, Victoria Nakibuuka Kirabira, Reinhard Klinkott, Socorro De Leon-Mendoza, Silke Mader, Karim Manji, Rhonda Marriott, Monica Morgues, Sushma Nangia, Suman Rao, Mohammod Shahidullah, Hoang Thi Tran, Andrew D Weeks, Bogale Worku, Khalid Yunis.

Prematurity Research Center, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, USA (GLD); Sana'a University, Sana'a, Yemen (NHAJ); Aga Khan University, Karachi, Pakistan (SA); World Health Organization, Geneva, Switzerland (RB, DC, VC, KE, LG-S, SG, SR); Karolinska Institutet and University Hospital, Stockholm, Sweden (MB); Oregon Health and Science University, Portland, OR, USA (RC); Monash, Melbourne, Australia (LC-T); Department of Pediatrics, Peking University First Hospital, Beijing, China (QF); Ministry of Health, Buenos Aires, Argentina (PFR); University College London, London, UK (ZH); University of Ibadan, Ibadan, Nigeria (AAI); Council of International Neonatal Nurses, Inc, Yardley, PA, USA (CK); Nsambya Hospital, Entebbe, Uganda (VNK); Klinikum Garmisch-Partenkirchen, Garmisch-Partenkirchen, Germany (RK); Kangaroo Mother Care Foundation, Manila, Philippines (SDL-M); European Foundation for the Care of Newborn Infants, Munich, Germany (SM); Muhimbili University of Health and Allied Sciences, Dar Es Salaam, Tanzania (KM); Murdoch University, Perth, Australia (RM); Universidad de Chile, Santiago, Chile (MM); Lady Hardinge Medical College and Kalawati Saran Children's Hospital, New Delhi, India (SN); Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh (MS); Da Nang Hospital for Women and Children, Da Nang, Viet Nam (HTT); University of Liverpool, Liverpool, UK (ADW); Ethiopian Pediatric Society, Addis Ababa, Ethiopia (BW); American University of Beirut, Beirut, Lebanon (KY).

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