New World Health Organization recommendations for care of preterm or low birth weight infants: health policy

Care of Preterm or Low Birthweight Infants Group[a]

eClinicalMedicine
2023;63: 102155
Published Online 16 August 2023
https://doi.org/10.1016/j.eclinm.2023.102155

Summary

Approximately 11% of infants are born preterm, and complications of prematurity are the most common cause of death in children aged under five years. Almost one million preterm infants die each year across low, high and middle income countries. In 2021, the World Health Organization (WHO) convened a Guideline Development Group (GDG) to examine evidence and formulate recommendations for care of preterm or low birthweight (LBW) infants according to WHO Guideline Review Committee (GRC) criteria. GRADE methods were used to assess the certainty of evidence and the GDG developed judgements using the DECIDE (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence) framework. Twenty-five recommendations were made; 11 recommendations were new, and 16 were for preventive and promotive care. Kangaroo Mother Care (KMC) was recommended to start immmediately after birth as routine care for all preterm or LBW newborns (except for critically ill infants who are in shock, unable to breath spontaneously after resuscitation, or require ventilatory support) both in the facility and at home. New recommendations were also made for caffeine to treat apnoea and for extubation; family involvement in routine care for preterm or LBW infants; and for post-discharge home-visit follow-up care. New recommendations were also made to consider use of probiotics, emollient therapy, caffeine for prevention of apnoea, continuous positive airway pressure (CPAP) immediately after birth (with or without respiratory distress) in infants less than 32 weeks gestational age; and for family support to enable the care of preterm or LBW infants. The recommendations confirm the pivotal role of preventive and promotive care for preterm and LBW infants, especially the importance of keeping the baby and mother together, and empowering and supporting families to care for their preterm or LBW infant. WHO is now working to help scale up care for small and sick newborns, including organizational shifts in all 'health system building blocks' such as infrastructure, commodities, workforce and monitoring.

Funding Nil.

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Keywords: Evidence; Guidelines; Health system organization; Maternal and newborn care; Preventive care; Promotive care; Sick newborn care

Introduction

The most important cause of death in children aged under five years is complications from preterm birth at a gestational age below 37 weeks.[1] Preterm birth occurred in an estimated 10.9% of live births in 2019, totalling 15.2 million infants globally.[2] The cause-specific fatality rate among all major causes of under-five and neonatal deaths is highest for preterm birth, leading to nearly 1 million deaths—about one-third (36.1%) of deaths in the neonatal period.[3] Low birthweight (LBW, <2500 g, without regard to gestational age) is a closely related categorisation of newborn infants that overlaps substantially with preterm birth and also encompasses infants who are full-term but small for gestational age (SGA) at birth.[4] Infants born too soon and too small are at particularly high risk for mortality.[5,6] Here we report on new global recommendations from the World Health Organization (WHO) for care of preterm or LBW infants,[7,8] briefly summarise evidence upon which the recommendations are based, and discuss implications of the recommendations for the organisation and provision of care.

Three WHO guidelines have been published previously on the care of preterm or LBW infants, most recently in 2015.[9–11] A body of new evidence has emerged since then on the effectiveness and implementation of interventions for care of preterm or LBW infants. The recommendations reported here were formulated during 2021–2022 to inform the advancement of national and subnational health policies, clinical protocols and programmatic guidance.

Methods

Standard WHO procedures were followed including the development of workstreams and establishment of an international Guideline Development Group (GDG) of

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Key messages

- Twenty-five recommendations for care of preterm or low birthweight (LBW) infants were made by a WHO Guideline Development Group of experts; 11 were new, eight were changed and six were updated.
- Eleven interventions had strong recommendations for global implementation, while 11 interventions were recommended conditionally as implementation may vary with context; two interventions were not recommended.
- New recommendations included preventive and promotive care (e.g., community and immediate KMC, probiotics, emollient therapy) as well as care for complications (continuous positive airway pressure and caffeine for respiratory support) and family involvement and support. A good practice statement was also made, based on more limited evidence, that parental leave policies and entitlements should address the special needs of mothers and fathers of a preterm or LBW infant.
- The recommendations confirm the pivotal role of preventive and promotive care for preterm and LBW infants, especially the importance of keeping the baby and mother together, and empowering and supporting families to care for their preterm or LBW infant.
- These new recommendations are being integrated into care for small and/or sick newborns—including WHO tools such as the Integrated Management of Childhood Illness chartbooklet and the WHO Pocket Book of Hospital Care For Children—and will be adapted for regional and country-level implementation.

experts (all of whom are authors of this paper).[12] The GDG was selected based on their expertise across public health, maternal and child health and nutrition, policy-making, programme planning and implementation, research methodology and statistics, and their broad representation of governments, non-governmental organisations, academia, private healthcare institutions, and parent groups, and diversity of high-, middle- and low-income countries.

Evidence review

The GDG defined the scope which included all interventions needed for the care of preterm or LBW infants (Supplementary Fig. S1). The GDG then listed the priority questions for care of preterm or LBW infants (PICO questions; Population, Intervention, Comparator, Outcome questions) (Supplementary Table S1). Interventions were then prioritised by the GDG: (i) that addressed a significant clinical or public health condition; (ii) for which guidance was non-existent or conflicting; (iii) for which new evidence was likely to change or update recommendations; and/or (iv) for which a recommendation would lead to a change in clinical practice or program design globally. Interventions that were already described in existing guideline documents were not included in this guideline as shown in Supplementary Fig. S1.[7] Outcomes of primary interest were all-cause mortality, morbidity, growth, and neurodevelopment, and subanalysis was done, where possible, for infants <32 weeks gestation or <1.5 kg birth weight.

Consistent with Cochrane review methods for assessing evidence to inform decision-making, the GDG process utilised available systematic reviews which summarised the latest evidence. A systematic search for existing systematic reviews and meta analyses was performed using 'Overviews of systematic reviews' methodology.[13] For interventions for which important new evidence was available since a previous systematic review was published, or if a systematic review was not available, a new systematic review was comissioned. Seventeen new systematic reviews were commissioned to assess topics not addressed in existing reviews and 21 additional existing systematic reviews and meta analyses were assessed by the GDG (Supplementary Table S2).[7,14–39] The quality of the scientific evidence for each intervention was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE),[40] and evidence was categorised as high, moderate, low and very low certainty. The Confidence in the Evidence from Reviews of Qualitative research (CERQual)[41] approach was used for qualitative evidence.

Evidence-to-decision and recommendation process

The WHO GDG process used the DECIDE (Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence) evidence-to-decision tool (Supplementary Table S3).[40–45] This included assessing the effects (benefits, harms) of the interventions on infant outcomes, certainty of the evidence, values of families and health workers, acceptability, resource requirements, feasibility and equity. Thus, a structured guideline process was applied which ensured consideration of all domains in the evidence-to-decision framework (including but not limited to intervention benefits and harms) (Supplementary Table S4).

A review was also conducted of the values of families in low-, middle- and high-income country studies in caring for their preterm infants—"what matters" to them.[38] Families indicated that they want a positive outcome for their baby, to be involved in delivering care, and to take an active role in deciding what interventions are given to their baby (Table 1). Consideration of these values was integrated when applying the DECIDE framework.

Recommendations were developed using Guideline Review Committee criteria.[7,12] Strong recommendations were if the intervention was applicable to all or almost all preterm or LBW infants; conditional recommendations were if the intervention is recommended under certain conditions which could be shared decision making or certain populations or settings (Supplementary Table S4).[7] Good practice statements also describe actions that should be routinely done under all or almost all circumstances and were developed when the GDG judged that benefits of

Domain	Descriptor
Positive outcome	Positive outcome for the child
Active involvement in care	Delivering care
	Fathers involved
	Opportunities for parenting
	Shared decision making and consent
Coping at home	Accessing support in a crisis
	Autonomy
	Extended family support and community resources
	Healthcare professional expertise in the community
	Preparation for discharge
	Transition arrangements
Emotional support for family	Support for all parents
	Additional support for mothers and fathers acknowledging that they may have different emotional support needs
	Support from the wider family
	Support from other parents in similar situations
Healthcare environment	Access to babies
	Orientation and familiarity with NICU
	Privacy vs monitoring
	Staffing and equipment levels
Information needs met	Information about the baby
	Frequent updates
	How information is given
	Matching needs with information
Logistical support	Accommodation (comfort and facilities)
	Broader family support and impact
	Costs of treatment
	Parental leave
Positive relationships with staff	Compassion and sensitivity
	Consistency in care and communication
	Healthcare professional expertise and care
	Respect, collaboration and trust

Table 1: **Family values about the care of their preterm or low birth weight infant.**[38]

interventions clearly outweighed harms, but for which direct evidence showing benefits was lacking and would be difficult to obtain.

Ethical review

No human subjects research was conducted and thus ethical clearance was not required.

Role of the funding source

There was no funding source for this study. K.E. and G.L.D. had full access to the data in the study and take responsibility for the integrity and accuracy of the data; K.E., and G.L.D. had responsibility for the decision to submit the manuscript for publication.

Results

Recommendations

Interventions

Twenty-five recommendations and one good practice statement were developed (Table 2). Eleven recommendations were new, as was the one good practice statement; eight were changed (plus another—calcium and phosphorus supplementation—was changed to not recommended), and six were updated with revised language. There were 11 strong recommendations and 11 conditional recommendations. Two interventions were not recommended. Most (n = 16) recommendations were for preventive and promotive care of preterm or LBW infants, six were for management of complications, and three were for involvement and support of families in caring for preterm or LBW infants.

Preventive and promotive care.

Kangaroo Mother Care (KMC). High-certainty evidence was found for KMC—defined as continuous and prolonged skin-to-skin contact of the baby with the mother and support for exclusive breastfeeding or breastmilk feeding—for reduction in mortality (high certainty evidence), decreased infection and hypothermia (moderate certainty evidence), increased weight gain (low certainty evidence), and increased breastfeeding (very low certainty evidence), and no evidence of harm.[17]

Recommendations were updated to extend KMC from use in health facilities for medically stable preterm or LBW infants to initiation in community settings for preterm or LBW infants born at home. Emphasis was placed on continuing KMC for at least 8 h per day. It was noted that whenever possible the mother should provide KMC; fathers and other family members can also provide KMC. A new strong, high certainty recommendation was also made for initiation of KMC as soon as possible after birth (including for hospitalised infants who are not yet clinically stabilised) unless the baby is critically sick, i.e., unable to breathe spontaneously even after resuscitation, is in shock, or requires mechanical ventilation. This recommendation for immediate KMC was based on large benefits of decreased mortality and hypothermia (high certainty evidence), decreased infections and increased weight gain (low certainty evidence), and no evidence of harms. Close monitoring of infants, especially when receiving immediate KMC, was considered to be important, including heart rate, breathing, colour, temperature, and where possible, oxygen saturation. The GDG supported implementation of KMC globally, including in high income settings, and provision by fathers and other caregivers. It was recognised that immediate KMC. i.e., initiation of KMC as soon as possible after birth, required mother-newborn care units in which mothers, fathers and other family

Domain	New recommendations	Old recommendations	Changes
Preventive and promotive care			
KMC	Kangaroo mother care (KMC) is recommended as routine care for all preterm or LBW infants. KMC can be initiated in facilities or at home and should be given for 8–24 h per day (as many hours as possible). *(Strong recommendation, high-certainty evidence)* Kangaroo mother care (KMC) for preterm or LBW infants should be started as soon as possible after birth. *(Strong recommendation, high-certainty evidence)*	Kangaroo mother care is recommended for the routine care of newborns weighing 2000 g or less at birth, and should be initiated in health-care facilities as soon as the newborns are clinically stable. *(Strong recommendation, moderate-certainty evidence)* Newborns weighing 2000 g or less at birth should be provided as close to continuous Kangaroo mother care as possible. *(Strong recommendation, moderate-certainty evidence)* Intermittent Kangaroo mother care, rather than conventional care, is recommended for newborns weighing 2000 g or less at birth, if continuous Kangaroo mother care is not possible. *(Strong recommendation, moderate-certainty evidence)* Unstable newborns weighing 2000 g or less at birth, or stable newborns weighing less than 2000 g who cannot be given Kangaroo mother care, should be cared for in a thermoneutral environment either under radiant warmers or in incubators. *(Strong recommendation, moderate-certainty evidence)*	- Recommendation changed: KMC recommended for all preterm or LBW infants - Can be initiated in facilities or at home - Requirement of being clinically stable before initiation removed - Duration of 8–24 h per day - Certainty of evidence high New recommendation
Feeding			
- Mother's own milk	Mother's own milk is recommended for feeding of preterm or LBW infants, including those <32 weeks' gestation. *(Strong recommendation, low-certainty evidence)*	LBW (LBW) infants, including those with very low birth weight (VLBW), should be fed mother's own milk. *(Strong recommendation, moderate-certainty evidence)*	- Recommendation re-worded - Certainty of evidence low
- Donor human milk	When mother's own milk is not available, donor human milk may be considered for feeding of preterm or LBW infants, including those <32 weeks' gestation. *(Conditional recommendation, moderate-certainty evidence)*	LBW infants, including those with VLBW, who cannot be fed mother's own milk should be fed donor human milk (recommendation relevant for settings where safe and affordable milk-banking facilities are available or can be set up). *(Conditional recommendation, high-certainty evidence)*	- Recommendation re-worded - Certainty of evidence moderate
- Multicomponent fortification of human milk	Multicomponent fortification of human milk is not routinely recommended for all preterm or LBW infants but may be considered for very preterm (<32 weeks' gestation) or very LBW (<1.5 kg) infants who are fed mother's own milk or donor human milk. *(Conditional recommendation, low-to-moderate-certainty evidence)*	VLBW infants who are fed mother's own milk or donor human milk should not routinely be given bovine milk-based human- milk fortifier (recommendation relevant for resource-limited settings). VLBW infants who fail to gain weight despite adequate breast- milk feeding should be given human-milk fortifiers, preferably those that are human milk based. *(Conditional recommendation, low-certainty evidence)*	- Recommendation changed: Multicomponent fortification of human milk may be considered for very preterm (<32 weeks' gestation) or very LBW (<1.5 kg) infants - Certainty of evidence low to moderate
- Preterm formula	When mother's own milk and donor human milk are not available, preterm formula may be considered for babies <32 weeks' gestation. *(Conditional recommendation, low-certainty evidence)*	LBW infants, including those with VLBW, who cannot be fed mother's own milk or donor human milk should be fed standard infant formula (recommendation relevant for resource-limited settings). VLBW infants who cannot be fed mother's own milk or donor human milk should be given preterm infant formula if they fail to gain weight despite adequate feeding with standard infant formula. *(Conditional recommendation, low-certainty evidence)*	- Recommendation changed: Preterm formula may be considered for babies <32 weeks' gestation
- Early initiation of enteral feeding	Preterm and LBW infants, including those <32 weeks' gestation or <1.5 kg at birth, should be fed as early as possible from the first day after birth. Infants who are able to breastfeed should be put to the breast as soon as possible after birth. Infants who are unable to breastfeed should be given expressed mother's own milk. If mother's own milk is not available, donor human milk should be given wherever possible. *(Strong recommendation, moderate-certainty evidence)*	LBW infants who are able to breastfeed should be put to the breast as soon as possible after birth when they are clinically stable. *(Strong recommendation, low-certainty evidence)* VLBW infants should be given 10 ml/kg per day of enteral feeds, preferably expressed breast milk, starting from the first day of life, with the remaining fluid requirement met by intravenous fluids (recommendation relevant for resource-limited settings. *(Conditional recommendation, low-certainty evidence)*	- Recommendation re-worded - Certainty of evidence moderate

(Table 2 continues on next page)

Domain	New recommendations	Old recommendations	Changes
(Continued from previous page)			
- Responsive and scheduled feeding	In health-care facilities, scheduled feeding may be considered rather than responsive feeding for preterm infants <34 weeks' gestation until the infant is discharged. *(Conditional recommendation, low-certainty evidence)*	LBW infants who are fully or mostly fed by an alternative oral feeding method should be fed, infants' hunger cues, except when the infant remains asleep beyond 3 h since the last feed (recommendation relevant to settings with an dequate number of health-care providers). *(Conditional recommendation, moderate-certainty evidence)*	- Recommendation changed: Favour scheduled feeding for preterm infants <34 weeks gestation - Certainty of evidence low
- Advancement of feeding	In preterm or LBW infants, including those <32 weeks' gestation or <1.5 kg at birth, who need to be fed by an alternate feeding method to breastfeeding (e.g., gastric tube feeding or cup feeding), feed volumes can be increased by up to 30 ml/kg per day. *(Conditional recommendation, moderate-certainty evidence)*	In VLBW infants who need to be fed by an alternative oral feeding method or given intragastric tube feeds, feed volumes can be increased by up to 30 ml/kg per day with careful monitoring for feed intolerance. *(Conditional recommendation, moderate-certainty evidence)*	- Recommendation re-worded
- Duration of exclusive breastfeeding	Preterm or LBW infants should be exclusively breastfed (EBF) until 6 months of age. *(Strong recommendation, very-low-certainty evidence)*	Optimal duration of exclusive breastfeeding. LBW infants should be exclusively breastfed until 6 months of age. *(Strong recommendation, low-certainty evidence)*	- Recommendation re-worded - Certainty of evidence very low
Micronutrients			
- Iron supplementation	Enteral iron supplementation is recommended for human milk-fed preterm or LBW infants who are not receiving iron from another source. *(Strong recommendation, moderate-certainty evidence)*	VLBW infants fed mother's own milk or donor human milk should be given 2–4 mg/kg per day iron supplementation starting at 2 weeks until 6 months of age. *(Conditional recommendation, low-certainty evidence)*	- Recommendation changed: Iron supplementation recommended for all human milk-fed LBW infants - Strength of recommendation strong -Certainty of evidence moderate
- Zinc supplementation	Enteral zinc supplementation may be considered for human milk-fed preterm or LBW infants who are not receiving zinc from another source. *(Conditional recommendation, low-certainty evidence)*	Routine zinc supplementation for LBW infants who are fed mother's own milk or donor human milk is not recommended at the present time, because there is not enough evidence of benefits to support such a recommendation. *(Conditional recommendation, moderate-certainty evidence)*	- Recommendation changed: Zinc supplementation may be considered for human milk-fed preterm or LBW infants - Certainty of evidence low
- Vitamin D supplementation	Enteral vitamin D supplementation may be considered for human milk-fed preterm or LBW infants who are not receiving vitamin D from another source. *(Conditional recommendation, low-certainty evidence)*	VLBW infants should be given vitamin D supplements at a dose ranging from 400 i.u to 1000 i.u. per day until 6 months of age. *(Conditional recommendation, very low-certainty evidence)*	- Recommendation changed: Vitamin D supplementation may be considered for all human milk fed LBW; - Certainty of evidence low
- Vitamin A supplementation	Enteral vitamin A supplementation may be considered for human milk-fed preterm or LBW infants <32 weeks' gestation or <1.5 kg at birth who are not receiving vitamin A from another source. *(Conditional recommendation, low-certainty evidence)*	Daily oral vitamin A supplementation for LBW infants who are fed mother's own milk or donor human milk is not recommended at the present time, because there is not enough evidence of benefits to support such a recommendation. *(Conditional recommendation, low-certainty evidence)*	- Recommendation changed: Vitamin A supplementation may be considered for human milk-fed preterm or LBW infants <32 weeks' gestation or <1.5 kg at birth
- Calcium and phosphorous supplementation	Not recommended	VLBW infants who are fed mother's own milk or donor human milk should be given daily calcium (120–140 mg/kg per day) and phosphorus (60–90 mg/kg per day) supplementation during the first months of life. *Conditional recommendation, low-certainty evidence)*	Recommendation changed: No recommendation for calcium and phosphorus supplementation
- Multiple micronutrient supplementation	Not recommended	–	New, no recommendation
Probiotics	Probiotics may be considered for human-milk-fed preterm infants <32 weeks' gestation. *(Conditional recommendation, moderate-certainty evidence)*	–	New recommendation
Emollients	Application of topical oils to the body of preterm or LBW infants may be considered. *(Conditional recommendation, low-certainty evidence)*	–	New recommendation
Management of complications			
Continuous positive airway pressure (CPAP)			
- CPAP for respiratory distress syndrome	Continuous positive airway pressure (CPAP) therapy is recommended in preterm infants <37 weeks' gestation with clinical signs of respiratory distress syndrome. *(Strong recommendation, moderate-certainty evidence)*	Continuous positive airway pressure therapy is recommended for the treatment of preterm newborns with respiratory distress syndrome. *(Strong recommendation, low-certainty evidence)* Continuous positive airway pressure therapy for newborns with respiratory distress syndrome should be started as soon as the diagnosis is made. *(Strong recommendation, low-certainty evidence)*	- Recommendation re-worded - Certainty of evidence moderate

(Table 2 continues on next page)

Domain	New recommendations	Old recommendations	Changes
(Continued from previous page)			
- CPAP immediately after birth	CPAP may be considered immediately after birth for very preterm infants <32 weeks' gestation, with or without respiratory distress. *(Conditional recommendation, low-certainty evidence)*		New recommendation
- CPAP pressure source (Bubble CPAP)	For preterm infants <37 weeks' gestation who need CPAP, Bubble CPAP may be considered rather than other pressure sources (e.g., ventilator CPAP). *(Conditional recommendation, low-certainty evidence)*	–	New recommendation
Methylxanthines			
- Methylxanthines for treatment of apnoea	Caffeine is recommended for treatment of apnoea in preterm infants <37 weeks' gestation. *(Strong recommendation, moderate-certainty evidence)*	–	New recommendation
- Methylxanthines for extubation	Caffeine is recommended for extubation of preterm infants <34 weeks' gestation. *(Strong recommendation, moderate-certainty evidence)*	–	New recommendation
- Methylxanthines for prevention of apnoea	Caffeine may be considered for prevention of apnoea in preterm infants <34 weeks' gestation. *(Conditional recommendation, low-certainty evidence)*	–	New recommendation
Family involvement and support			
Family involvement	Family involvement in routine care of preterm or LBW babies in health-care facilities is recommended *(Strong recommendation, low- to moderate-certainty evidence)*	–	New recommendation
Family support	Families of preterm or LBW infants should be given extra support to care for their infants, starting in health-care facilities from birth, and continued during follow-up post-discharge. The support may include education, counselling, and discharge preparation from health workers, and peer support. *(Conditional recommendation, very-low-certainty evidence)*	–	New recommendation
Home visits	Home visits by trained health workers are recommended to support families to care for their preterm or LBW infant. *(Strong recommendation, moderate-certainty evidence)*	–	New recommendation
Parental leave and entitlements	Parental leave and entitlements should address the special needs of mothers and fathers of preterm or LBW infants. *(Good practice statement)*	–	New best practice statement

Table 2: **WHO recommendations for the care of preterm or low birth weight infants which are included in the new guideline.**

members can be with their preterm or LBW babies 24 h per day.

Probiotics. A new, conditional recommendation based on moderate-certainty evidence was made that probiotics may be considered for human-milk-fed preterm infants <32 weeks gestation. The balance of evidence showed moderate benefits for decreased mortality, necrotising enterocolitis, and invasive infection in trials of preterm infants <32 weeks gestation, with no evidence of harms.[36] There was some uncertainty related to the variability in the probiotic species evaluated in the studies, and evidence on long-term harms was limited. The GDG did not make a recommendation regarding probiotic type, formulation (e.g., powder or drops), dose, timing or duration of probiotic administration, but suggested that only probiotics especially formulated for preterm or LBW infants that have received national regulatory approval, with clear instructions for safe use, should be used, with shared decision making with parents. Given limited data, a recommendation was not made for infants above 32 weeks, nor for exclusively formula fed infants.

Emollient therapy. A new conditional recommendation based on low-certainty evidence was made for the application of 'natural' oils (eg sunflower and coconut oil) to the body of preterm or LBW infants, based on moderate benefits of decreased severe infection and increased weight gain (low certainty evidence) and increased length (moderate certainty evidence), with no evidence of harms.[37] A recommendation was not made on the use of ointments or creams as the GDG considered there was no evidence of benefit of these products on critical outcomes. The GDG suggested that the natural oils that should be used are sunflower or coconut oils based on evidence indicating efficacy for these specific formulations. The GDG considered that duration of use may be based on clinical judgement, and

application of oils should be done gently to avoid disrupting skin integrity.

Feeding. No change was made to the strong recommendation for *exclusive breastfeeding* of preterm or LBW infants until 6 months of age, consistent with prior recommendations for all infants.[39] Seven other updated recommendations were made regarding aspects of milk feeding (Table 2).

Feeding mother's own milk was strongly recommended based on low-certainty evidence for moderate benefits of decreased mortality, decreased necrotising enterocolitis, and decreased infections, with no evidence of harms and lack of evidence to support changing the recommmendation.[18] While the importance of offering support to mothers to enhance the provision of their own breastmilk was noted, when mother's own milk is not available, a conditional recommendation based on moderate certainty evidence was made to consider *donor human milk* for feeding of preterm or LBW infants, including those <32 weeks gestation.[19] Evidence of moderate benefits for donor human milk compared with infant formula included decreased necrotising enterocolitis and feed intolerance (moderate certainty evidence) in trials of infants <32 weeks gestation or <1.5 kg; evidence was also found for small harms in growth, including decreased in-hospital weight gain, length and head circumference (moderate certainty evidence). Donor human milk was pasteurised in all but one trial, so a recommendation could not be made on the use of unpasteurised milk.

Multicomponent fortification of human milk was not routinely recommended for preterm or LBW infants, but a conditional recommendation based on low-to moderate-certainty evidence was made for very preterm (<32 weeks) or very LBW (<1.5 kg) infants who are fed mother's own milk or donor human milk. Evidence was found for small benefits of increased in-hospital weight, length and head circumference and was uncertain for harms of mortality and necrotising enterocolitis (low certainty evidence).[20] The GDG considered that commercially available multicomponent fortifiers specifically formulated for preterm infants may be considered and should commence when enteral feeds are well established (e.g., ≥100 ml/kg per day; "full" enteral feeds typically referred to 150 ml/kg per day) and the duration should be based on clinical judgement.

When mother's own milk and donor human milk are not available, the GDG made a conditional recommendation based on low-certainty evidence that *preterm formula*, i.e., commercially available nutrient-enriched formulas specifically formulated for preterm infants may be considered for babies <32 weeks gestation or <1.5 kg at birth. This was informed by evidence of small benefits, including increased in-hospital weight gain and head circumference growth and increased psychomotor development, and no evidence of harms for feeding preterm infants with nutrient-enriched formula (protein and energy plus minerals, vitamins, or other nutrients) compared with standard formula.[21] The GDG suggested that initiation and duration should be based on clinical judgement.

It was strongly recommended based on moderate-certainty evidence that *enteral feeding*—feeding via the enteral route including direct breastfeeding and by cup, naso- or oro-gastric tube—be initiated as early as possible from the first day after birth of preterm or LBW infants, including those <1.5 kg or <32 weeks gestation. This was based on evidence of moderate benefits of decreased mortality and length of hospital stay (moderate certainty), and decreased intra-ventricular haemorrhage (very low certainty) in trials (n = 14) of infants <37 weeks gestation or <2.5 kg birth weight, including 6 trials in infants <32 weeks <1.5 kg; there was no evidence of harms.[22] Infants who are able to breastfeed should be put to the breast as soon as possible after birth; infants who are unable to breastfeed should be given expressed mother's own milk whenever possible and put to breast for non-nutritive sucking. The guideline emphasised the need for careful consideration in applying these recommendations to unstable babies; initiation of enteral feeding in unstable babies should be based on clinical judgement. All infants should always be fed human milk whenever possible, but if human milk is not available, infants can be fed formula as this is preferable to delayed initiation of enteral feeding and the use of parenteral nutrition. There was no difference in effect by volume of initial feed; thus, a recommendation was not made on restricting volume of feed.

In health facilities, a conditional recommendation based on low-certainty evidence was made that *scheduled feeding* may be considered for preterm infants <34 weeks gestation until they are discharged, rather than responsive feeding. This decision was informed by evidence of small benefits from responsive feeding on decreased length of hospital stay (very low certainty) but also small harms from responsive feeding on decreased weight gain until discharge (low certainty).[23] The trials included in the review used various feeding schedules; the GDG suggested that 2–3 hourly scheduled feedings may be used, as this is a commonly used and feasible schedule. A recommendation could not be made on feeding after hospital discharge. It was emphasised that nurturing care and responsive caregiving are critical to the well-being of every preterm or LBW infant and should be implemented regardless of the type of feeding regime.

In preterm infants, including those <32 weeks gestation or <1.5 kg who need to be fed by an alternate feeding method to breast-feeding (e.g., gastric tube feeding or cup feeding), a conditional recommendation based on moderate-certainty evidence was made that *feeding advancement* may be increased by volumes up to 30 ml/kg per day. Evidence of moderate benefits was found on time to regain birth weight (high certainty), decreased length of hospital stay and decrease in apnoea

(moderate certainty) in trials (n = 12) of infants <37 weeks gestation or <2.5 kg birth weight, including 6 trials in infants <32 weeks or <1.5 kg.[24] The evidence on harm of neurodevelopmental disability was considered to be low certainty. All trials compared fast advancement (increments of 30–40 ml/kg per day) with slow advancement (increments of 10–25 ml/kg per day). The GDG took the conservative value of 30 ml/kg per day as the threshold for fast feed advancement, consistent with many national guidelines.[46,47]

Micronutrients. Enteral *iron supplementation* was strongly recommended based on moderate certainty evidence for human milk fed preterm or LBW infants who were not receiving iron from another source. This was based on evidence of small to moderate benefits of increased length (low certainty evidence), decreased anaemia prevalence (moderate certainty evidence), and increased ferritin (very low certainty evidence), and no evidence of harms.[25] The GDG suggested the initiation of a daily dose of 2–4 mg/kg/day of elemental iron when enteral feeds are fully established and continuation of administration until the infant receives iron from another source. In addition, zinc, vitamin A and vitamin D were conditionally recommended and calcium, phosphorous and multiple micronutrients were not recommended (Table 2).

A conditional recommendation based on low-certainty evidence was made that enteral *zinc supplementation* may be considered for human milk fed preterm or LBW infants who are not receiving zinc from another source. Evidence was found for small to moderate benefits of decreased mortality (low certainty evidence), and decreased diarrhoea and increased weight, length and head circumference (moderate certainty evidence), and uncertain evidence was found of harms for mental development (low certainty evidence).[26] The GDG suggested that a daily dose of 1–3 mg/kg/day of elemental zinc be initiated when enteral feeds are fully established and continued until the infant receives zinc from another source.

A conditional recommendation based on low-certainty evidence was also made that enteral *vitamin D supplementation* may be considered for human milk fed preterm or LBW infants who are not receiving vitamin D from another source. Evidence review indicated that there were small benefits of decreased bronchopulmonary dysplasia at 2 months and decreased developmental delay at 2 years (very low certainty evidence) and increased weight and length at 6 months (moderate certainty evidence).[27] Evidence was uncertain for mortality (low certainty evidence). It was suggested that a daily dose of 400–800 IU could be initiated when enteral feeds are fully established and continued until the infant receives vitamin D from another source.

Enteral *vitamin A supplementation* was recommended conditionally, based on low certainty evidence, and may be considered for human milk fed preterm or LBW infants <32 weeks gestation or <1.5 kg at birth who are not receiving vitamin A from another source. Evidence showed small benefit of decreased mortality, bronchopulmonary dysplasia, and patent ductus arteriosus (low certainty evidence), as well as retinopathy of prematurity (very low certainty evidence), with no evidence of harm.[28,48] The GDG suggested that a daily dose of 1000–5000 IU be initiated when enteral feeds are fully established and continued until the infant receives vitamin A from another source.

No recommendation was made for *calcium and phosphorus supplementation* or for *multiple micronutrient supplementation*, as there was insufficient evidence for preterm or LBW infants.[29,30]

Management of complications. Among interventions for management of complications in preterm or LBW infants, two respiratory interventions were prioritised: continuous positive airway pressure (CPAP) for respiratory distress and methylxanthines for apnoea (Table 2). Recommendations for other interventions were maintained unchanged (Table 2).

CPAP for respiratory distress syndrome. A strong recommendation based on moderate-certainty evidence was made for *CPAP for clinical signs of respiratory distress syndrome* (RDS) in preterm infants <37 weeks gestation. Evidence of moderate benefits included decreased mortality and decreased mechanical ventilation.[31,32] Evidence of small harms of unclear clinical significance was found for increased pneumothorax. It was recommended by the GDG that CPAP should be initiated as soon as the diagnosis of RDS is clinically suspected or made. A conditional recommendation based on low-certainty evidence was also made by the GDG that *CPAP therapy may be considered immediately after birth*. The GDG considered that there were small to moderate benefits from immediate CPAP. Benefits included decreased 'failed treatment' (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation] and decreased bronchopulmonary dysplasia in trials of preterm infants <32 weeks.[33] There was no evidence of harms.

The GDG also considered that CPAP implementation must be done with skilled staff, and quality equipment and consumables, including humidified, blended oxygen-air and monitors. Examination of specific *CPAP pressure sources*—comparing underwater (water-seal) 'bubble' CPAP with mechanical ventilator CPAP or infant flow driver CPAP, all commercially manufactured (no locally manufactured or locally adapted devices were used) using humidified blended oxygen-air and short nasal prong interfaces—led to a conditional recommendation for bubble CPAP based on low-certainty evidence for preterm infants <37 weeks gestation. This decision was based on evidence of small to moderate benefits of decreased pneumothorax, decreased

bronchopulmonary dysplasia, and decreased failed treatment (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation) in trials of preterm infants <37 weeks gestation.[34] Evidence of small harm was also found, consisting of increased nasal injury, defined as ulceration, bleeding, septal injury, scarring, excluding hyperaemia or erythema, mostly minor and of unclear cause. The GDG reccommended that the nasal interface (i.e., prongs and cannulas) used with bubble CPAP machines should be carefully selected and that skilled nursing care of the baby while on prongs and cannulas is needed.

Methylxanthines for apnoea. *Caffeine for treatment of apnoea* in all preterm infants <37 weeks gestation was strongly recommended based on moderate-certainty evidence. Inclusion criteria for the six RCTs relevant to this comparison were gestational age at birth below 37 weeks and evidence of apnoea. Evidence of moderate benefits included decreased death, bronchopulmonary dysplasia and neurodevelopmental disability (moderate certainty evidence) and decreased mechanical ventilation (low certainty evidence) in trials of caffeine in preterm infants, with no evidence of harms.[35] The GDG considered that c*affeine for prevention of apnoea* may be considered in preterm infants <34 weeks gestation, based on low certainty evidence. Inclusion criteria for the seven RCTs relevant to this comparison were gestational age at birth below 34 weeks and no evidence of apnoea. Evidence of small to moderate benefits was found for decreased bronchopulmonary dysplasia (moderate certainty evidence) and decreased apnoeic episodes (low certainty evidence) in trials of preterm infants <34 weeks gestation, and uncertain evidence of harms was found for increased mortality and mechanical ventilation (low certainty evidence).[35] The GDG recommended that if caffeine is not available, other methylxanthines (aminophylline or theophylline) may be considered, given decreased apnoea and need for mechanical ventilation in infants given aminophylline and theophylline. While evidence for use of methylxanthines for prevention of apnoea was available only for preterm infants <34 weeks gestation, the GDG suggested that caffeine (or other methylxanthines) may also be considered for prevention of apnoea in preterm infants 34– <37 weeks depending on clinical judgement. Based on the largest trial included in the evidence review,[49] the suggested dosing of caffeine was a 20 mg/kg loading dose and 5 mg/kg/day maintenance doses for 6 weeks. The GDG also noted that caffeine is often given until corrected gestational age of >34 weeks gestation and the baby is event free for at least 5 days.

A strong recommendation based on moderate-certainty evidence was also made for *caffeine for extubation* of preterm infants <34 weeks gestation, based on evidence of moderate benefits of decreased death, bronchopulmonary dysplasia, failed extubation, and neurodevelopmental disability and no evidence of harms.[35] Based on the largest trials included in the evidence review,[49,50] the GDG suggested that caffeine be started 24 h before a planned extubation. If the extubation is unplanned, the infant should receive caffeine as soon as possible after the extubation and within 6 h. A 20 mg/kg loading dose and 5 mg/kg/day maintenance doses continued for 6 days were suggested.

Family involvement and support. A series of recommendations were formulated for involvement of, and support of families in caring for preterm/LBW infants (Table 2). Family involvement was defined as participation of mothers, fathers, and other family members in routine care of the newborn infant while in the newborn care unit. It may include mothers, fathers and family members providing direct bedside care, family involvement in medical decision making, hospital culture change, and hospital infrastructure changes (e.g., rooming in, couplet care or zero-separation of mother and infant, family rooms). Other interventions (sometimes called 'cointerventions') which were implemented in the studies included neurodevelopmental and neurobehavioural care, skin-to-skin care, KMC, infant massage, psychosocial support, and financial incentives.

A strong recommendation based on low-to moderate-certainty evidence was made for *family involvement in routine care* of preterm or LBW babies in health facilities. This recommendation was made on the basis of evidence of moderate benefits, including decreased morbidity (infection, intraventricular haemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia), increased weight and length at hospital discharge, increased length at 18 months, increased neurodevelopment, decreased length of hospital stay, and increased breastfeeding in trials of infants <37 weeks gestation or <2.5 kg birth weight, with no evidence of harms.[14] Family involvement strategies also reduced parental anxiety and stress, although these were not critical outcomes of the review.

Assessment of the effectiveness of five different types of interventions to support families to care for their preterm or LBW infant (education and counselling, peer-to-peer support, home visiting, digital communication, discharge preparation) indicated that evidence was strongest for home visits.[15] *Home visits* by trained health workers were strongly recommended, based on moderate certainty evidence, to support mothers, fathers and families to care for their preterm or LBW infant. Evidence of benefits of home visits included a moderate decrease in mortality (moderate certainty evidence) and a small decrease in number of hospitalisations (very low certainty evidence) in trials of infants <37 weeks gestation or <2.5 kg birth weight, with no evidence of harms. Home visits also increased non-critical outcomes of exclusive breastfeeding rates, immunisation visits,

parental-infant attachment and decreased parental stress. The GDG suggested that extra home visits (i.e., additional to the routine scheduled postnatal contacts for all babies) should be made and that their content, frequency, duration and intensity should be established given that there is limited data on these features.

A conditional recommendation was made based on very low certainty evidence, that mothers, fathers and other family members should be given *extra* support to care for their preterm or LBW infant, starting in health facilities from birth, and continued during follow-up post-discharge. Support can be provided through education, counselling, and discharge preparation by health providers and peer support. Education and counselling and discharge preparation had important effects on non-critical oucomes including improving parent-to-infant interaction, improving breastfeeding, and decreasing parental anxiety, stress and depression.

A good practice statement was made based on a review of 20 current global parental leave policies and entitlements for parents of preterm or LBW infants.[15] No studies were identified comparing benefits and harms of policies and entitlements. It was determined that *parental leave policies and entitlements* should address the special needs of mothers and fathers of preterm or LBW infants. The GDG suggested that parental policies and entitlements should be expanded globally across high, middle-and low-income countries, and include additional days of leave from work and additional financial entitlements. However, there was insufficient information available to make statements about the number of days of leave parents should be given or what type of financial entitlements they should receive. The GDG also noted that special needs of mothers and fathers of preterm or LBW infants vary according to individual preferences and setting, but include support for long hospital stays and multiple medical appointments, stress and anxiety about the infant, caring for other children and family members, transport and equipment.

Discussion

The WHO guidelines development process used systematic methodology to update and develop new recommendations for care of preterm or LBW infants across all low, middle and high income countries. It involved rigorous new systematic reviews of evidence, meta-analyses, appraisal of quality, assessment of the balance of benefits and harms, and consideration of the values of families and health workers, intervention acceptability, resource requirements and feasibility of implementation, and equity of access and impact. This led to the formulation of 25 recommendations and one good practice statement, including 11 new recommendations. Two additional interventions were not recommended. The new recommendations were primarily in the areas of preventive and promotive care (i.e., community and immediate KMC, probiotics, emollient therapy), care for complications (CPAP and caffeine for respiratory support), and family involvement and support. In addition, recommendations for a number of interventions, particularly feeding interventions, underwent substantial revision and updating; revisions for micronutrient interventions were relatively minor.

High certainty evidence for benefits, without evidence of harm, was found for KMC. The scope was substantially expanded with a strong recommendation for KMC for routine care of all preterm or LBW newborns in health facilities. In addition, a strong, high-certainty recommendation was also made for immediate KMC to be initiated even before an infant is medically stable, provided that the baby is not in shock, is able to breathe spontaneously, and does not require mechanical ventilation. KMC was also recommended for all infants without danger signs cared for at home. These recommendations have important ramifications for health programming because mothers and newborns must remain together at all times. All the WHO health system 'building blocks' are needed including: a skilled workforce, infrastructure, commodities, financing, monitoring, governance, and government committment.[51] A recent WHO multi-country implementation research study showed that all of these 'building blocks' are needed to achieve coverage of more than 80%.[52] Guidance for KMC implementation is being prepared by the KMC Working Group of the WHO Strategic Technical Advisory Group of Experts in Maternal, Newborn, Child and Adolescent Health and Nutrition.[53]

Recommendations for family involvement and support in caring for preterm or LBW infants also call for substantial shifts in the organisation of care. The GDG considered that resources and feasibility for implementing family involvement strategies vary according to setting but that simple family involvement interventions such as provision of direct bedside care can be implemented now in low-income, low-resource settings. The family involvement and support recommendations call for shared care with families, ensuring their rightful place within care facilities. Health care providers are asked to empower families and to extend support from facilities to communities through home visits by front-line health workers.

Several other significant additions to global recommendations for care of preterm or LBW infants were made. Moderate certainty evidence for reduction in mortality and serious infections with probiotic administration to human milk-fed infants <32 weeks gestational age was reported. Understanding of the role of gut microbiota in health is advancing, and new discoveries are being made in how to promote health using

probiotics. However, this review also highlighted the need for rigorous quality control, assessment of safety, ongoing monitoring and regulatory approval processes.[8]

Emollient therapy is another intervention for which new evidence has emerged. This is the only intervention among those recommended which targets the immature skin barrier of preterm infants. The systematic review considered by the GDG showed important benefits of natural oils—principally sunflower seed oil and coconut oil—in prevention of sepsis and promotion of growth, without obvious harm. Application of natural oil products to the skin of newborn infants is a widespread practice, especially in South Asia.[54] Natural vegetable oil products vary widely in composition and many can be harmful.[55,56] Thus, there is need for quality assurance and to further define optimal composition, dose, timing of initiation and duration of emollient use.[8] Ointments and creams were not recommended; these substances are comprised primarily of biologically inert substances, whereas natural oils are comprised of fatty acids that can be absorbed and can also exert metabolic and biological effects.

New respiratory care recommendations included the use of CPAP beyond respiratory distress syndrome to immediate use as preventive therapy in infants <32 weeks gestational age, even before onset of respiratory distress. Furthermore, bubble CPAP was identified as the preferred pressure source. Caffeine was also recommended for treatment of apnoea in all preterm infants as well as prevention of apnoea and for extubation of preterm infants <34 weeks gestational age.

Conclusions

Overall, the new WHO recommendations affirm the central role of family involvement and support and the importance of high quality care for preterm term and LBW infants. The next steps are for adaptation to the needs of different countries and local contexts. WHO is also working to scale up care for small and sick newborns which includes updating 'derivative tools' including the WHO Integrated Management of Childhood Illness (IMCI) chartbooklet and the WHO Pocket Book of Hospital Care For Children) and the development of implementation guidance for global, regional and country levels.

Contributors

G.L.D., K.E., and R.B. conceptualised the paper; G.L.D. reviewed the literature for this paper; methodology was devised by K.E., G.L.D., and R.C.; K.E. and R.B. managed project administration and resources; K.E. and G.L.D. verified study findings; G.L.D. and K.E. led data visualization; G.L.D. led writing of the original draft; all authors contributed to writing review and editing. All authors contributed intellectual content and approved the final draft for publication. K.E. and G.L.D. had full access to the data in the study and take responsibility for the integrity and accuracy of the data; K.E., and G.L.D. had responsibility for the decision to submit the manuscript for publication.

Data sharing statement

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

Declaration of interests

RC reports consulting fees from WHO and the payments made to him and his institution. 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. The authors declare no other competing interests.

Acknowledgements

Funding: None.

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The authors include members of an independent, international panel of experts convened by WHO (Guideline Development Group [GDG]) that formulated the WHO recommendations for care of preterm or low birthweight infants discussed in this paper (GLD [co-chair], NHAJ, SA, MB, LC-T, QF, PFR, ZH, AAI, CK, VNK, RK, SDL-M, SM, KM, RM, MM, SN, SR, MS, HTT, ADW, BW, KY); the WHO Secretariat (RB, DC, VC, KE, LG-S, SG, AP, SR), who supported the GDG but did not take part in the formulation of the recommendations; and the external methodologist (RC) who provided external independent advice to the GDG and secretariat.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2023.102155.

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