3. Evidence and recommendations

This guideline includes 25 recommendations and 1 good practice statement (summarized in Table 1 in the executive summary and presented in detail in this chapter) for care of the preterm (born before 37 weeks' gestation) or low-birth-weight (LBW; < 2.5 kg) infant. Of the recommendations, 11 are new and 14 are updated, and the good practice statement is new. There are 11 strong recommendations for all preterm or LBW infants and 14 recommendations that are conditional on particular contexts or conditions.

Sixteen recommendations are for preventive and promotive care, six are for care for complications, and three are for family involvement and support. A good practice statement was made for parental leave and entitlements because the Guideline Development Group (GDG) determined that these have obvious benefits, although there was little evidence available.

The GDG provided remarks related to all the recommendations and the good practice statement, where needed. Users of the guideline should refer to these remarks, which are presented prominently along with the recommendations in this chapter.

The recommendations have been divided into the following categories, as presented in this chapter:

A. PREVENTIVE AND PROMOTIVE CARE (16 recommendations)

B. CARE FOR COMPLICATIONS (6 recommendations)

C. FAMILY INVOLVEMENT AND SUPPORT (3 recommendations, and 1 good practice statement)

A. Preventive and promotive care

A.1 KANGAROO MOTHER CARE

Recommendation and remarks

RECOMMENDATION A.1a (UPDATED)

Any KMC:
Kangaroo mother care (KMC) is recommended as routine care for all preterm or low-birth-weight infants. KMC can be initiated in the health-care facility or at home and should be given for 8–24 hours per day (as many hours as possible). *(Strong recommendation, high-certainty evidence)*

RECOMMENDATION A.1b (NEW)

Immediate KMC:
Kangaroo mother care (KMC) for preterm or low-birth-weight infants should be started as soon as possible after birth. (Strong recommendation, high-certainty evidence) *(Strong recommendation, high-certainty evidence)*

Remarks

- Any KMC
  - KMC can be given at home or at the health-care facility.
  - Infants who receive KMC should be secured firmly to the mother's chest with a binder that ensures a patent airway.
  - Whenever possible, the mother should provide KMC. If the mother is not available, fathers, partners and other family members can also provide KMC.
  - Infants who need intensive care should be managed in special units, where mothers, fathers, partners and other family members can be with their preterm or LBW infants 24 hours a day.
- Immediate KMC
  - At home, immediate KMC should be given to infants who have no danger signs *(22)*.
  - At health-care facilities, immediate KMC can be initiated before the infant is clinically stable unless the infant is unable to breathe spontaneously after resuscitation, is in shock or needs mechanical ventilation. The infant's clinical condition (including heart rate, breathing, colour, temperature and oxygen saturation, where possible) must be monitored.

Background and definitions

Kangaroo mother care (KMC) is defined by WHO as early, continuous and prolonged skin-to-skin contact between the mother (or other caregiver) and the baby, and exclusive breastfeeding *(20)*. In 2015, WHO recommended that KMC be given to hospitalized babies under 2.0 kg as soon as the babies were clinically stable *(20)*. However, there has been wide variation among care providers (i.e. parents/primary caregivers and health workers) in the timing and duration of KMC *(37,38)*. New studies have also been published that assess the effects of KMC provided before clinical stabilization and also KMC initiated in community settings *(39,40)*.

Summary of the evidence

Overview	A.1a Any KMC	A.1b Immediate KMC
PICO	**Population** – Preterm or LBW infants **Intervention 1** – KMC **Comparator 1** – Conventional newborn care **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up	**Population** – Preterm or LBW infants **Intervention 2** – KMC initiated early (within 24 hours of birth, also called immediate KMC) **Comparator 2** – Initiating KMC later (more than 24 hours after birth) **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Setting, timing, subgroups	**Setting** – Health-care facility or home in any country or setting **Timing of intervention** – From birth **Subgroups** • Gestational age at birth (< 34 weeks, ≥ 34 weeks) • Birth weight (< 2.0 kg, ≥ 2.0 kg) • Daily duration of KMC achieved (< 8 hours, 8–16 hours, > 16 hours)	

Effectiveness: Comparison 1 – KMC versus conventional newborn care

Sources and characteristics of the evidence

For the first comparison of KMC versus conventional newborn care, the effectiveness evidence was derived from a systematic review of 27 RCTs conducted between 1994 and 2021 that enrolled 11 956 infants *(41)*. Six studies were from high-income countries (Australia, the United Kingdom of Great Britain and Northern Ireland and the United States of America [USA]), four studies were from upper-middle-income countries (China, Colombia, Ecuador and Malaysia), 15 were from lower-middle-income countries (Bangladesh, India, Indonesia, Kenya and Nepal) and two studies were from a low-income country (Ethiopia). Twenty-five studies were conducted in health-care facilities and two were community-based. In all but one of the studies, the infants were stabilized before enrolment. KMC was started within 24 hours after birth in two studies, between 1 and 7 days after birth in 10 studies, and more than 7 days after birth in 12 studies, but 3 studies did not report the timing of initiation of KMC. The duration of KMC was less than 8 hours in nine studies, between 8 and 16 hours in nine studies and more than 16 hours in four studies, while five studies did not report the duration of KMC.

Critical outcomes

Sixteen trials reported all-cause mortality, 11 reported severe morbidity (9 reported severe infection, 11 hypothermia), 11 reported growth outcomes (weight gain) and 1 reported neurodevelopment (1 reported Griffith quotients, 1 reported Bayley Scales of Infant and Toddler Development, third edition [BSID-III]). No serious adverse events were reported. (Full details are provided in GRADE Table A.1a, in the Web Supplement.[3])

- **Mortality:** For KMC compared with conventional newborn care, high-certainty evidence from 12 trials of 10 505 participants suggests a decrease in all-cause mortality at discharge, at 40 weeks postmenstrual age (PMA; i.e. the baby's age when counted from the first day of the mother's last menstrual period before pregnancy – see Glossary) or at 28 days of age (relative risk [RR] 0.68, 95% confidence interval [CI] 0.53 to 0.86). High-certainty evidence from four trials of 8031 participants suggests a decrease in all-cause mortality at 6 months of age (RR 0.75, 95% CI 0.62 to 0.92).
- **Morbidity**: Moderate-certainty evidence from nine trials of 9847 participants suggests a decrease in severe infection or sepsis at 40 weeks PMA or at 28 days after birth (RR 0.85, 95% CI 0.79 to 0.92). Moderate-certainty evidence from 11 trials of 1169 participants suggests a decrease in hypothermia at discharge, at 40 weeks PMA or at 28 days after birth (RR 0.32, 95% CI 0.19 to 0.53).
- **Growth:** Low-certainty evidence from 11 trials of 1198 participants suggests an increase in weight gain (in grams per day) at 28 days after birth (mean difference [MD] 4.08, 95% CI 2.30 to 5.86).
- **Neurodevelopment:** Very-low-certainty evidence from one trial of 579 participants suggests little or no effect on Griffith quotients for psychomotor development (all subscales) at 12 months corrected age (i.e. the chronological age [age since birth or "postnatal age"] minus the number of weeks or months born preterm –

3 Available online: https://apps.who.int/iris/bitstream/handle/10665/363699/9789240060050-eng.pdf

see Glossary) (MD 1.05, 95% CI -0.75 to 2.85). Very-low-certainty evidence from one trial of 516 participants suggests little or no effect on cognitive neurodevelopment at 12 months of age using the BSID-III (MD 0.21, 95% CI -1.84 to 2.27) and other neurodevelopment measures (language, motor).

Other outcomes

There was an increase in exclusive breastfeeding at discharge, at 40 weeks PMA or at 28 days of age (RR 1.48, 95% CI 1.44 to 1.52; 9 trials, 9983 participants) and at 1–3 months follow-up (RR 1.39, 95% CI 0.99 to 1.97; 7 trials, 8139 participants). There was an increase in any breastfeeding at discharge, at 40 weeks PMA or at 28 days of age (RR 1.15, 95% CI 1.07 to 1.23; 12 studies, 10 146 participants) and at three months follow-up (RR 1.03; 95% CI 1.02 to 1.04; I^2 = 70%; 7 studies, 8463 participants). There was also a decrease in the length of hospital stay (MD -0.39 days, 95% CI -0.79 to 0.0; 12 studies, 1214 participants).

Subgroup analyses

Subgroup differences for morbidity, growth and neurodevelopmental outcomes could not be assessed as there were insufficient studies. For all-cause mortality, no subgroup differences were seen for setting (health-care facility, community), gestational age (mean gestational age < 34 weeks, ≥ 34 weeks), birth weight (birth or enrolment weight < 2.0 kg, ≥ 2.0 kg) or daily duration of KMC achieved (< 8 hours/day, 8–16 hours/day and > 16 hours/day), although the analysis for daily duration of less than 8 hours was limited by small sample size and imprecision.

Effectiveness: Comparison 2 – KMC initiated early versus later

Sources and characteristics of the evidence

For the second comparison of KMC initiated early (< 24 hours after birth) versus KMC initiated late (≥ 24 hours after birth), the effectiveness evidence was derived from a systematic review of four RCTs totalling 3603 infants *(41)*. One study was from a high-income country (Sweden), two were from low-income countries (Gambia and Madagascar) and one was a multicountry study conducted in Ghana, India, Malawi, Nigeria and the United Republic of Tanzania. All studies were conducted in health-care facilities. Two studies enrolled babies irrespective of clinical stability, while one study enrolled only stable infants and one study enrolled only unstable babies. KMC was started as soon after birth as possible in all studies. The mean age at initiation of KMC was 1.3 hours, 13.6 hours and 19 hours after birth in three studies, while one study did not report the age of initiation of KMC. The duration of KMC was less than 8 hours in one study, more than 16 hours in two studies and not reported in one study.

Critical outcomes

For the comparison of KMC initiated early compared with KMC initiated late, three trials reported all-cause mortality, three reported morbidity (2 reported severe infection, 3 hypothermia), one reported growth (weight gain) and none reported neurodevelopment outcomes. (Full details are provided in GRADE Table A.1b, in the Web Supplement.)

- **Mortality:** High-certainty evidence from three trials of 3533 participants suggests a decrease in all-cause mortality by 28 days of age (RR 0.78, 95% CI 0.66 to 0.92).
- **Morbidity:** Low-certainty evidence from two trials of 3415 participants suggests a decrease in the risk of sepsis by 28 days (RR 0.85, 95% CI 0.76 to 0.96). High-certainty evidence from three trials of 3513 participants suggests a decrease in the risk of hypothermia by discharge or 28 days (RR 0.74, 95% CI 0.61 to 0.90).
- **Growth:** Low-certainty evidence from one trial of 204 participants suggests little or no effect on weight gain by 28 days follow-up (measured in grams per day) (MD 2.20, 95% CI -5.26 to 0.86).

Other outcomes

There was an increase in exclusive breastfeeding (EBF) by hospital discharge (RR 1.12, 95% CI 1.07 to 1.16; 3 trials, 3464 participants). There was little or no effect on EBF by 28 days of age (RR 1.01, 95% CI 0.98 to 1.04; 3 trials, 2841 participants). There was a decrease in length of hospital stay (in days) (MD -0.30, 95% CI -0.31 to -0.29; 3 studies, 3498 participants).

Subgroup analyses

Differences for morbidity, growth and neurodevelopment could not be assessed as there were insufficient studies. For all-cause mortality, no subgroup differences were seen for setting (facility, community), gestational age (mean gestational age < 34 weeks, ≥ 34 weeks), birth or enrolment weight (< 2.0 kg, ≥ 2.0 kg) or daily duration of KMC (< 8 hours/day, 8–16 hours/day and > 16 hours/day).

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see

Table 1.1) reported that families want to be involved in delivering care to infants and want to take an active role in deciding what interventions are given to infants, including skin-to-skin contact and feeding *(14)*. A systematic review of caregivers' perspectives on KMC reported that social support, access to care and cultural norms were important drivers of family perceptions, practices, attitudes and values about KMC *(38)*. Important elements included: services free of charge for users; support from health workers; parents allowed unlimited visiting hours at the health-care facility; a private, quiet space in the hospital to provide KMC; and involvement of fathers and partners. Another synthesis of qualitative studies suggested that providing KMC can be restorative as well as energy-draining for mothers, fathers and partners *(37)*.

Resources required and implementation considerations

Organization of care

KMC can be implemented at home and at all levels of newborn care (primary, secondary and tertiary) *(42)*. Health services should ensure family involvement in the care of their preterm or LBW infant, irrespective of the infant's clinical condition. This should include a policy of "zero separation" between families and their preterm or LBW infant. This needs close collaboration between families and newborn and maternity care providers. Health-care facilities should ensure that families have access to beds, food, bathing and toilet facilities throughout the infant's hospital stay.

KMC is ideally initiated immediately after birth, or after initial resuscitation if that is needed. When it is not possible for the mother to provide KMC, other family members should provide it. To prepare for this situation, family members should be identified before delivery, counselled and allowed access to maternity and newborn care areas. If the infant needs to be transferred to a special or intensive care unit, the infant should be transported safely in KMC with the mother or another family member.

Choice of the best location for further management should be guided by the clinical condition of the infant. Stable larger infants could receive KMC in postnatal wards, while smaller ones could receive KMC in special care units (e.g. "step down" units, special care nurseries), and infants with complications could receive KMC in intensive care units. Many babies who need special or intensive care (e.g. level 2 or 3 care) are often separated from their mothers, although KMC is essential for these babies. Units that care for preterm babies and mothers with zero separation are needed (e.g. maternal–neonatal intensive care units [M-NICU] *[43]* or "couplet care" units *[44]*).

Health-care facilities should provide support so that mothers and families can continue KMC at home after discharge. All preterm and LBW infants must be followed up after discharge, ideally through home visits.

Preterm or LBW infants born at home should receive immediate KMC if they do not have danger signs, and should be transferred to a health-care facility if needed.

Infrastructure, equipment and supplies

A binder may help to keep the infant in skin-to-skin contact with the mother's or caregiver's chest. The infant should also have a warm hat, socks and a diaper/nappy. The mother or caregiver should wear whatever is comfortable, provided the clothes accommodate the baby.

Other arrangements can also make the baby and mother more comfortable, e.g. reclining beds and chairs. Other equipment and supplies needed are the same as for other newborn and maternal care, including a thermometer suitable for measuring body temperature down to 35°C.

If M-NICUs or couplet care units are used, they should have all the infrastructure, equipment and supplies that NICUs have for small or sick babies and that maternity wards have for mothers. For babies, this includes continuous positive airway pressure (CPAP) machines, pulse oximeters and radiant warmers or incubators if the infant is not in KMC. For mothers, this includes adult beds and an examination area where she can receive the health care she needs.

Workforce, training, supervision and monitoring

Health workers at all levels can provide KMC support to mothers and families. Training includes helping mothers keep infants in skin-to-skin contact, helping them with breastfeeding, and providing other neonatal care. Health workers should record the duration of KMC provided per day in a clinical register (or in home-based records in the community) and should monitor this on a regular basis.

Scale-up

KMC should be scaled up as an integrated intervention within programmes, not as a stand-alone programme. Scaling up means ensuring all preterm and LBW babies receive KMC across the whole country and across all countries. It needs multiple high-intensity (i.e. high-frequency and quality) interventions in the different domains described above (i.e. organization of care, health workforce, and infrastructure, equipment and supplies), but it also needs leadership and governance, financing, and health information systems.

- Leadership and governance can include: high-level leadership from national and subnational policy-makers, programme managers and facility directors; policies to enable zero separation; licensing standards for health-care facilities; pre-service education of health workers; and engagement with professional organizations.
- Health financing can include: dedicated line items in national budgets for KMC and expanded health insurance that includes KMC.
- Health information systems can include: monitoring of coverage and quality of KMC in routine health systems in health-care facilities and at the district and national levels.
- More detailed guidance on scaling up based on the results of implementation research *(43,45-50)* is being developed and will be published separately.

Feasibility and equity

Facility-based studies have shown that KMC can be provided to small babies, for more than 8 hours per day, and that it can be initiated immediately after birth irrespective of clinical stability *(39,43,45,46)*. These studies were conducted in poor, remote and urban communities in "real world pragmatic" settings *(40,51)*. However, community-initiated KMC and KMC for unstable babies have not been implemented outside research settings and global coverage remains low *(52,53)*.

Summary of judgements

	Comparison 1: KMC vs conventional newborn care (A.1a)	Comparison 2: Immediate KMC vs later KMC (A.1b)
Justification	• Evidence of large benefits: decreased mortality (*high-certainty evidence*), decreased infection (*moderate-certainty evidence*), decreased hypothermia (*moderate-certainty evidence*), increased weight gain (*low-certainty evidence*) and increased breastfeeding (*very-low-certainty evidence*) • No evidence of harms	• Evidence of large benefits: decreased mortality (*high-certainty evidence*), decreased hypothermia (*high-certainty evidence*), decreased infections and increased weight gain (*low-certainty evidence*) • No evidence of harms
Evidence-to-Decision summary		
Benefits	Large	Large
Harms	Trivial or none	Trivial or none
Certainty	Moderate	Moderate
Balance	Favours KMC	Favours immediate KMC
Values	No uncertainty or variability about outcomes	No uncertainty or variability about outcomes
Acceptability	Varies	Varies
Resources	Low to moderate	Low to moderate
Feasibility	Probably feasible	Probably feasible
Equity	Probably equitable	Probably equitable

A.2 MOTHER'S OWN MILK

Recommendation and remarks

RECOMMENDATION A.2 (UPDATED)

Mother's own milk is recommended for feeding of preterm or low-birth-weight (LBW) infants, including very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants. *(Strong recommendation, low-certainty evidence)*

Remarks

- The GDG made a strong recommendation despite low-certainty evidence because of the consistent harm from infant formula on two critical outcomes (necrotizing enterocolitis and infection) and lack of evidence of benefit from infant formula.
- The GDG also considered that providing mother's own milk is the standard of care across all countries and the core of many national policies and programmes.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

Mother's own milk confers important immune and nutritional advantages for preterm and LBW infants *(54-56)*. Artificial formulas can be manipulated to contain higher amounts of important nutrients (such as protein) than mother's own milk *(55,57)*. However, formula milks do not contain the antibodies and immune modulators and primers present in human milk that protect the immature gastro intestinal tract' of preterm and LBW infants *(19,58,59)*. In 2011, WHO recommended that mother's own milk should be given to all preterm and LBW infants *(19)*.

Summary of the evidence

OVERVIEW	A.2 Mother's own milk
PICO	**Population** – Preterm or LBW infants **Intervention** – Infant formula (term or preterm) **Comparator** – Mother's own milk **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Setting, timing, subgroups	**Timing of the intervention** – From birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Type of milk in the control group (mother's own milk as the sole diet, mother's own milk not the sole diet)

Effectiveness: Comparison – Any formula milk versus mother's own milk

Sources and characteristics of the evidence

The effectiveness evidence was derived from an updated systematic review of 42 studies reporting on 89 638 preterm or LBW infants from 20 countries (Australia, Belgium, Chile, China, Germany, Ghana, Greece, India, Israel, Italy, Japan, Nepal, the Netherlands, New Zealand, Poland, Romania, Spain, Sweden, the United Kingdom and the USA) *(60)*.

Studies were included if they compared infants who received formula as the sole or predominant (> 50%) diet (intervention group) with infants who received mother's own milk as the sole or predominant (> 50%) diet (comparison group) in the first 28 days after birth. Of the 89 638 participants, approximately 87% of infants were very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg). Studies typically excluded infants with congenital anomalies or gastrointestinal or neurological problems.

All the included studies were observational; there were no RCTs. Thirty-six studies were from hospitals and six were from the "whole population" (all infants born in the study area regardless of whether they

were admitted to hospital). The largest study (72 997 participants) was an observational study of all infants under 32 weeks' gestation admitted to 777 neonatal intensive care units (NICUs) in the USA. The studies used a combination of milks in the intervention and comparison groups.

In the intervention group, all 42 studies used formula milk as the sole or predominant (> 50%) diet. Among these studies, 24 studies gave formula milk as the sole diet, 13 mixed formula with mother's own milk, 5 mixed formula with donor milk and mother's own milk, and 6 did not state whether they mixed formula milk with other milks. Twenty-one studies used preterm formula, 5 used term formula, 2 used a combination of preterm and term formula, and 14 did not state which type of formula was used.

In the comparison group, all 42 studies used mother's own milk as the sole or predominant (> 50%) diet. Among these studies, 9 studies gave mother's own milk as the sole diet, 17 mixed mother's own milk with donor human milk, and the remainder did not state if they mixed mother's own milk with other milks. Twenty studies used fortifier, 6 did not use fortifier and 16 did not state whether fortifier was provided.

Babies all received their feeds from birth until discharge or 28 days of age. Twenty-five used parenteral nutrition, 10 did not use parenteral nutrition and the remainder did not state if parenteral nutrition was used.

Critical outcomes

For the comparison of any formula milk with mother's own milk, 5 studies reported all-cause mortality, 15 studies reported morbidity (15 reported necrotizing enterocolitis, 15 severe infection), 7 studies reported growth (3 reported weight-for-age z score [WAZ], 3 WAZ change, 9 length, 3 length-for-age z score [LAZ], 9 head circumference) and 8 studies reported neurodevelopment (8 reported cognitive outcomes, 3 language outcomes). (Full details are provided in GRADE Table A.2, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from five observational studies of 9673 participants suggests little or no effect on all-cause mortality at latest follow-up (mean 116 days) (OR 1.26, 95% CI 0.91 to 1.76).
- **Morbidity:** Low-certainty evidence from 15 observational studies totalling 3013 participants suggests an increase in necrotizing enterocolitis at latest follow-up (mean 44 days) (OR 2.99, 95% CI 1.75 to 5.11). Very-low-certainty evidence from 15 observational studies totalling 2562 participants suggests an increase in severe infection at latest follow-up (mean 31 days) (OR 1.52, 95% CI 0.98 to 2.37).
- **Growth:** Very-low-certainty evidence from three observational studies totalling 271 participants suggests little or no effect on weight (weight-for-age z score [WAZ]) between 39 and 416 weeks (MD 0.02, 95% CI -0.28 to 0.31). Very-low-certainty evidence from four observational studies totalling 74 130 participants suggests little or no effect on weight (WAZ change) from birth to discharge (mean 52 days) (MD 0.14, 95% CI -0.76 to 1.05). Very-low-certainty evidence from nine observational studies totalling 1048 participants suggests little or no effect on length (in centimetres) at latest follow-up (mean 58 days) (MD 0.33, 95% CI -0.4 to 1.05). Very-low-certainty evidence from three observational studies totalling 271 participants suggests little or no effect on length (LAZ) at 39 to 416 weeks (MD 0.06, 95% CI -0.81 to 0.92). Very-low-certainty evidence from nine observational studies totalling 1550 participants suggests little or no effect on head circumference (in centimetres) at latest follow-up (mean 45 days) (MD 0.26, 95% CI -0.35 to 0.87).
- **Neurodevelopment:** Very-low-certainty evidence from eight observational studies totalling 1560 participants suggests little or no effect on cognitive development at follow-up (range: 91 to 416 weeks) (standardized mean difference [SMD] 1.3 standard deviation [SD] lower, 95% CI -3.53 to 0.93). Very-low-certainty evidence from three observational studies totalling 587 participants suggests little or no effect on language development at follow-up (range: 39–104 weeks) (SMD 0.02 SD lower, 95% CI -0.39 to 0.43).

Subgroup analyses

There was no evidence of a subgroup difference by gestational age, birth weight, or type of milk in the control group for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding

what interventions are given to infants, including what and how they are fed *(14)*. Two qualitative reviews reported that parents understood the importance of expressing breast-milk for the care of their baby but also found it challenging to express breast-milk unless supported by hospital staff and adequately informed about resources *(61,62)*. Reviews also report that families value having formula available if their circumstances demand it – for example, work commitments, maternity leave, night-time feeding, father/partner support *(14)*.

Resources required and implementation considerations

Organization of care

Mother's own milk should be provided through direct breastfeeding wherever possible. If direct breastfeeding is not possible, then breast-milk can be expressed and provided using cups and gastric tubes.

Infrastructure, equipment and supplies

Breastfeeding requires no specific infrastructure, equipment or supplies. If expressed breast-milk is needed, milk can be expressed by hand or using a manual breast pump. Supplies are also needed for cup and gastric tube feeding. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can provide breastfeeding support to mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

Difficulties related to breastfeeding and expressing breast-milk in hospitals can include lack of privacy, inadequate training from busy health workers, and feelings of stress and inadequacy from mothers and families *(63)*. There are also studies that report difficulties in providing mother's own milk when the mother and baby return home from hospital, including difficulties balancing work commitments, maternity leave, night-time feeding and father and partner support *(14)*. There are many studies that report problems in sourcing clean water to reconstitute infant formula and wash receptacles in resource-limited settings *(64,65)*.

Summary of judgements

Comparison: Any formula milk vs mother's own milk (A.2)	
Justification	• No evidence of benefits of infant formula • Evidence of moderate harms from using infant formula instead of mother's own milk: increased necrotizing enterocolitis *(low-certainty evidence)* and increased infections *(very-low-certainty evidence)* • Evidence of little or no effect of using infant formula on mortality *(low-certainty evidence)*, weight gain *(very-low-certainty evidence)* and neurodevelopment *(very-low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Benefits of infant formula are trivial or none
Harms	Harms of infant formula are moderate
Certainty	Low
Balance	Does not favour infant formula, favours mother's own milk
Values	Probably no important uncertainty or variability about outcomes
Acceptability	Acceptability of infant formula varies, acceptability of mother's own milk does not vary
Resources	Low to moderate (costs of infant formula), negligible (costs of mother's own milk)
Feasibility	Feasibility of infant formula varies, feasibility of mother's own milk does not vary, where it is available
Equity	Equity of infant formula varies, equity of mother's own milk does not vary

A.3 DONOR HUMAN MILK

Recommendation and remarks

RECOMMENDATION A.3 (UPDATED)

When mother's own milk is not available, donor human milk may be considered for feeding of preterm or low-birth-weight (LBW) infants, including very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants. *(Conditional recommendation, moderate-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The potential harm of necrotizing enterocolitis from infant formula was considered by the GDG to be more clinically important than the benefit of increased growth from infant formula.
- Donor human milk was pasteurized in all but one trial, so the GDG was not able to make a recommendation on the use of unpasteurized milk.
- Safe and affordable milk-banking facilities are needed for the provision of donor human milk.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

When mother's own milk is not available, preterm or LBW infants must be given other milks. Donor human milk is provided through human milk banks (i.e. places where human milk is collected, treated and/or distributed) *(56,66)*. Donor milk has differences in immune composition to mother's own milk. Human milk banks also usually pasteurize milk to remove infective organisms, which further alters milk components *(56,66)*. WHO LBW feeding guidelines in 2011 recommended feeding donor human milk rather than infant formula to preterm or LBW babies who cannot be fed mother's own milk *(19)*. However, new studies have been published since that time.

Summary of the evidence

OVERVIEW	A.3 Donor human milk
PICO	**Population** – Preterm or LBW infants **Intervention** – Infant formula **Comparator** – Donor human milk **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Amount of donor milk in the control arm (donor milk provided as the sole diet, mixed with infant formula)

Effectiveness: Comparison – Infant formula versus donor human milk

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review published in 2019 of 12 RCTs enrolling 1879 preterm or LBW infants from neonatal units in eight countries (Austria, Canada, Finland, Hungary, Italy, the Netherlands, the United Kingdom and the USA) *(67)*. An updated search conducted on 1 October 2021 located no new trials. Participants were clinically stable preterm or LBW infants. Most were below 32 weeks' gestational age or below 1.8 kg at birth. Many trials excluded infants who were small for gestational age at birth and infants with congenital anomalies or gastrointestinal or neurological problems. The

trials varied according to whether formula or donor milk was provided as the sole diet (5 trials) or as a supplement to mother's own milk (7 trials). A mix of term and preterm formula was used. The donor milk was a mix of preterm and term donor milk and a mix of fortified and unfortified milk. In all trials except one, the donor human milk was pasteurized. In general, feeds were allocated for several weeks, or until participating infants reached a specified body weight (generally > 2 kg). One trial used the allocated feed for less than 10 days after birth. Infants then received preterm formula if their mother's own milk was insufficient.

Critical outcomes

For infant formula compared with donor human milk, seven trials reported all-cause mortality, nine reported morbidity (9 reported necrotizing enterocolitis, 5 invasive infection), nine reported growth (9 reported weight gain, 8 length, 8 head growth) and two reported neurodevelopment (neurodevelopmental disability). (Full details are provided in GRADE Table A.3, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from seven trials totalling 1527 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 1.1, 95% CI 0.8 to 1.5).
- **Morbidity:** Moderate-certainty evidence from nine trials totalling 1675 participants suggests an increase in risk of necrotizing enterocolitis by hospital discharge (RR 1.87, 95% CI 1.23 to 2.85). Moderate-certainty evidence from five trials totalling 1025 participants suggests little or no effect on risk of invasive infection by hospital discharge (RR 0.94, 95% CI 0.79 to 1.12).
- **Growth:** Moderate-certainty evidence from nine trials totalling 1028 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 2.51, 95% CI 1.93 to 3.08). Moderate-certainty evidence from eight trials totalling 820 participants suggests an increase in linear growth (crown–heel length, measured in millimetres per week) by hospital discharge (MD 1.21, 95% CI 0.77 to 1.65). Moderate-certainty evidence from eight trials totalling 894 participants suggests an increase in head growth (in millimetres per week) by hospital discharge (MD 0.85, 95% CI 0.47 to 1.23).
- **Neurodevelopment**: Moderate-certainty evidence from two trials totalling 400 participants suggests little or no effect on neurodevelopmental disability by 18 months of age (RR 1.21, 95% CI 0.62 to 2.35).

Two studies in the review also reported on long-term growth outcomes. Neither individual study nor meta-analyses of data from both studies showed differences in weight, length or head circumference at follow-up at 9 months, 18 months or 7.5–8 years of age. For the latest follow-up at 7.5–8 years of age, there was no difference in growth parameters between infants fed formula milk or donor human milk (weight [kg], MD -0.56, 95% CI -1.42 to 0.29; length [cm], 0.05, 95% CI -1.12 to 1.23; and head circumference [cm], MD -0.19, 95% CI -0.54 to 0.16; 2 studies, 420 participants).

Other outcomes

There was higher risk of feeding intolerance in the formula-fed group compared with the donor milk group (moderate-certainty evidence) (RR 4.92, 95% CI 1.17 to 20.70; 2 trials, 148 participants).

Subgroup analyses

For the analyses by gestational age and birth weight and amount of donor milk in the control arm, differences for all critical outcomes could not be assessed as there were insufficient studies.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. A number of studies report the facilitators and barriers to donating and receiving donor human milk *(68-71)*. These include preferences for receiving human rather than artificial milk, concerns about the effect of pasteurization and transportation, and concerns that the mother's own breast-milk supply will reduce *(68-71)*. A large cross-sectional survey among health workers in urban Zimbabwe reported that the concept of donor human milk banking was acceptable, and that the participants would accept donor human milk for their children, and many would encourage their clients to donate human milk *(68)*.

Resources required and implementation considerations

Organization of care

The provision of donor human milk requires access to a human milk bank where milk can be tested, pasteurized and transported safely.

Infrastructure, equipment and supplies

Infrastructure, equipment and supplies are needed for donor assessment (screening, informed consent, serological testing), milk expression, handling, storage, transport, pre-pasteurization testing, pasteurization, and post-pasteurization testing. Supplies are also needed for safe cup and gastric tube feeding.

Workforce, training, supervision and monitoring

Specialized staff are needed for the operation of donor human milk banks. Standardized packages are needed for training, supervision and monitoring. More detailed guidance on the operation of donor human milk banks is being developed and will be published separately. Health workers at all levels can provide feeding support.

Feasibility and equity

A census of milk banks from a systematic literature review reported 572 milk banks globally in 60 countries, with the majority in high-income countries *(68)*. It is well known that safe and affordable milk-banking facilities are needed for the provision of donor human milk. However, the base resources for donor milk feeding (i.e. donor recruitment, donor assessment [screening, informed consent, serological testing], milk expression, handling, storage, transport, pre-pasteurization testing, pasteurization, post-pasteurization testing) are much less available in low- and middle-income countries (LMICs), especially in smaller towns and villages *(66,72)*. The use of donor milk varies widely within and between countries and is influenced by cultural practices, access, costs, awareness, supportive policies and resources *(66,72)*.

Summary of judgements

Comparison: Infant formula vs donor human milk (A.3)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefits from using infant formula instead of donor human milk: increased in-hospital weight gain, length and head circumference (*moderate-certainty evidence*) • Evidence of moderate harms from using infant formula instead of donor human milk: increased necrotizing enterocolitis and feed intolerance (*moderate-certainty evidence*) • Evidence of little or no effect of using infant formula on mortality and neurodevelopment (*moderate-certainty evidence*) • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Benefits of infant formula are small
Harms	Harms of infant formula are moderate
Certainty	Moderate
Balance	Probably does not favour infant formula, probably favours donor human milk
Values	Probably no important uncertainty or variability about outcomes
Acceptability	Acceptability of infant formula and donor human milk varies
Resources	Resources for infant formula and donor human milk vary
Feasibility	Feasibility of infant formula and donor human milk varies
Equity	Equity of infant formula and donor human milk varies

A.4 MULTICOMPONENT FORTIFICATION OF HUMAN MILK

Recommendation and remarks

RECOMMENDATION A.4 (UPDATED)

Multicomponent fortification of human milk is not routinely recommended for all preterm or low-birth-weight (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)*

Remarks

- The potential harm of mortality and necrotizing enterocolitis from fortification was considered by the GDG to be very uncertain due to the low quality of the included trials. The GDG also considered that the benefits of multicomponent fortifier were clinically important for the weight, length and head circumference of very preterm (< 32 weeks) or very-low-birth-weight (VLBW) (< 1.5 kg) infants. Thus, the GDG decided not to routinely recommend multicomponent fortifier for all preterm or LBW infants and suggested that fortification may be considered for very preterm or VLBW infants. This recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there were limited data on the type of fortifier used in the studies. Based on most trials included in the evidence review, the GDG suggests that commercially available multicomponent fortifiers specifically formulated for preterm infants may be considered.
- The GDG also noted that there were limited data on the timing of initiation and duration of fortification in the studies. The GDG suggests that the initiation and duration of multicomponent fortification should be based on clinical judgement.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

Commercially available multicomponent fortifiers for infant human milk feeding can be human or animal (often cows' milk) protein based, and contain carbohydrate, fat, protein, multivitamins, iron, zinc, calcium and phosphorous in varying amounts *(56,73)*. They are provided as liquid or powder and mixed with mother's own or donor human milk *(74,75)*. Some health workers advise families to add multicomponent fortifier to human milk feeds for preterm and LBW infants with the intent to increase nutrient accretion *(76,77)*. However, there are concerns that multicomponent fortifiers are associated with adverse events such as feed intolerance and necrotizing enterocolitis *(56)*. WHO guidelines in 2011 recommended against the use of multicomponent fortifiers for all preterm and LBW babies but to use them for very-low-birth-weight (VLBW) babies (< 1.5 kg) or very preterm babies (< 32 weeks' gestation) who fail to gain weight *(19)*. There have been new trials since that time.

Summary of the evidence

OVERVIEW	A.4 Multicomponent fortification of human milk
PICO	**Population** – Preterm or LBW infants **Intervention** – Human milk with multicomponent fortifier (human derived or non-human derived) **Comparator** – Human milk without multicomponent fortifier **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Type of fortifier (human milk protein based, non-human milk protein based)

Effectiveness: Comparison – Multicomponent fortification versus unfortified breast-milk

Sources and characteristics of the evidence

The effectiveness evidence was derived from a 2019 Cochrane review of 18 small trials totalling 1456 preterm infants *(78)*. An updated search conducted on 1 October 2021 located no new trials. All trials were conducted in specialist paediatric hospitals, typically in NICUs. The trials were conducted in 11 countries (Brazil, Canada, Denmark, Egypt, India, Italy, Oman, South Africa, Sweden, the United Kingdom and the USA). Babies were mostly very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg).

Trials used a range of different "base" milks to feed the infants which were identical in the intervention and the control arms. Six trials used only mother's own milk, one trial used only donor human milk, seven trials used a mixture of mother's own milk and donor milk, and four trials used a mixture of mother's own milk, donor milk and preterm formula. Participants received the intervention once they were tolerating a specified quantity of milk feeding, typically at least 100 ml/kg per day, or when receiving "full" enteral feeds, typically 150 ml/kg per day.

In the intervention arm in all trials, multicomponent fortifier was mixed into the base milk and was provided according to the manufacturer's specifications. Fourteen trials used a commercially available, bovine-milk-based, powdered preparation and four trials used preterm formula powder as the multicomponent fortifier. No trials used human-milk-derived fortifier. The fortifier was provided until a prespecified body weight was attained (most commonly, 1.8–2.0 kg), until a prespecified PMA (most commonly 34–36 weeks) or until discharge home from hospital.

In the control arm, eight trials gave infants multiple supplements (i.e. multivitamins, iron, zinc, calcium and phosphorus) in similar quantities to the nutrients in multicomponent fortifier, five trials gave infants only vitamin D, and five trials gave no supplements at all. No trials gave infants additional carbohydrate or protein in the control arm.

Critical outcomes

For multicomponent fortification compared with unfortified breast-milk, two trials reported all-cause mortality, 13 reported morbidity (13 reported necrotizing enterocolitis), 14 reported growth (14 reported weight gain, 10 length gain, 11 head growth) and 1 reported neurodevelopment (Mental Development Index [MDI, BSID-II] and Psychomotor Development Index [PDI, BSID-II]). (Full details are provided in GRADE Table A.4, in the Web Supplement.)

- **Mortality:** Very-low-certainty evidence from two trials totalling 375 participants suggests an increase in all-cause mortality by discharge (RR 2.33, 95% CI 0.16 to 34.76).
- **Morbidity:** Low-certainty evidence from 13 trials totalling 1110 participants suggests an increase in necrotizing enterocolitis by hospital discharge (RR 1.37, 95% CI 0.72 to 2.63).
- **Growth:** Low-certainty evidence from 14 trials totalling 951 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 1.76, 95% CI 1.30 to 2.22). Low-certainty evidence from 10 trials totalling 741 participants suggests an increase in length gain (in centimetres per week) by hospital discharge (MD 0.11, 95% CI 0.08 to 0.15). Moderate-certainty evidence from 11 trials totalling 821 participants suggests an increase in head growth (in centimetres per week) by hospital discharge (MD 0.06, 95% CI 0.03 to 0.08).
- **Neurodevelopment:** Moderate-certainty evidence from one trial with 245 participants suggests little or no effect on MDI (BSID-II) by 18 months of age (MD 2.20, 95% CI -3.35 to 7.75). Moderate-certainty evidence from one trial totalling 245 participants suggests little or no effect on PDI (BSID-II) by 18 months of age (MD 2.40, 95% CI -1.90 to 6.70).

Other outcomes

There was little or no effect on length of hospital stay in weeks (MD -0.07, 95% CI -0.35 to 0.21; 6 trials, 526 infants), or feed intolerance (RR 1.05, 95% CI 0.65 to 1.67; 7 trials, 453 infants).

Subgroup analyses

The effect of gestational age and birth weight and type of fortifier could not be assessed as there were insufficient studies.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. No other specific evidence was located about whether families value fortified feeds rather than unfortified feeds for their preterm or LBW baby, or find fortified feeds more or less acceptable than unfortified feeds.

Resources required and implementation considerations

Organization of care

Health-care facilities can provide multicomponent fortifier for preterm or LBW infants.

Infrastructure, equipment and supplies

The main commodity required is the fortifier, which should be a standard, nationally approved, multicomponent fortifier specially formulated for preterm or LBW infants. Commonly used fortifiers have similar amounts of carbohydrate, protein and micronutrients. Facilities for expressing breast-milk are also needed, as are facilities for the safe mixing of fortifier into expressed breast-milk. Supplies are also needed for cup or gastric tube feeding.

Workforce, training, supervision and monitoring

Health workers at all levels can provide support to mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing multicomponent fortifier for preterm or LBW infants.

Summary of judgements

Comparison: Multicomponent fortification vs unfortified breast-milk (A.4)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefits: increase in in-hospital weight, length and head circumference *(moderate- to low-certainty evidence)* • Evidence on harms uncertain: mortality *(very-low-certainty evidence)*, necrotizing enterocolitis *(low-certainty evidence)* • Evidence of little or no effect on neurodevelopment *(moderate-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small
Harms	Unknown
Certainty	Low
Balance	Varies
Values	Uncertainty or variability about outcomes
Acceptability	Unknown
Resources	Low to moderate
Feasibility	Varies
Equity	Not equitable

A.5 PRETERM FORMULA

Recommendation and remarks

RECOMMENDATION A.5 (UPDATED)

When mother's own milk and donor human milk are not available, nutrient-enriched preterm formula may be considered for very preterm (< 32 weeks' gestation) or very low-birth-weight infants. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG was not able to recommend a particular type of preterm formula. Based on most trials included in the evidence review, the GDG suggests that commercially available nutrient-enriched formulas specifically formulated for preterm infants may be considered.
- There was insufficient evidence to make a recommendation for infants who were born at 32–36 weeks' gestation or with birth weight of 1.5–2.4 kg. For these infants, the GDG considered that standard term formula or nutrient-enriched preterm formula may be considered, depending on clinical judgement.
- The GDG also noted that there was limited information on the timing of initiation and duration of preterm formula in the studies. The GDG suggests initiation and duration should be based on clinical judgement.
- Mothers should also be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

If human milk is not available, then preterm and LBW infants need to be given infant formula in the first six months after birth *(56)*. Some studies suggest that feeding preterm infants with nutrient-enriched formula (or preterm formula) rather than formula developed for term infants (also called term formula, or non-nutrient-enriched formula) might increase nutrient accretion, growth and neurodevelopmental outcomes *(76,79,80)*. Preterm formula often has energy content over 72 kcal/100 ml and protein content over 1.7 g/100 ml *(56,81)*. Term formula milks have varying energy and protein content, usually below these values *(56,81)*. In 2011, WHO did not recommend preterm formula for feeding preterm and LBW infants *(19)*.

Summary of the evidence

OVERVIEW	A.5 Preterm formula
PICO	**Population** – Preterm or LBW infants **Intervention** – Nutrient-enriched formula (or preterm formula) **Comparator** – Non-nutrient-enriched formula (or term formula) **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Preterm formula versus term formula

Sources and characteristics of the evidence

The effectiveness evidence was derived from a 2019 Cochrane systematic review of seven trials including 590 infants *(81)*. An updated search conducted on 1 September 2021 located no new trials. The trials were undertaken during the 1970s and 1980s in neonatal units in South Africa, Thailand, Türkiye, the United Kingdom and the USA. All infants were clinically stable preterm infants. Most were very low birth weight (< 1.5 kg). Few participants were extremely preterm (< 28 weeks), extremely low birth weight (< 1.0 kg) or growth restricted. The

trials excluded infants with congenital anomalies, or respiratory, gastrointestinal or neurological problems.

Preterm formula was defined in the systematic review as a formula with both energy content over 72 kcal/100 ml and protein content over 1.7 g/100 ml and term formula was defined as a formula with both energy content below 72 kcal/100 ml and protein content below 1.7 g/100 ml. In six trials, the formula was the sole diet while in one trial the formula was used in addition to human milk. The milk feeds were started when infants were clinically stable and able to tolerate enteral feeds in all trials. Trial participants continued to receive the intervention or control formula for two weeks or until they reached 2.0 kg. The target volume of milk intake for both groups was 150–180 ml/kg per day.

Critical outcomes

For preterm formula compared with term formula, two trials reported all-cause mortality, three reported morbidity (3 reported necrotizing enterocolitis), five reported growth (6 reported weight gain, 5 length gain, 5 head circumference) and two reported neurodevelopment (both reported MDI and PDI). (Full details are provided in GRADE Table A.5, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from two trials totalling 424 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 1.12, 95% CI 0.65 to 1.93).
- **Morbidity:** Low-certainty evidence from three trials totalling 489 participants suggests a decreased risk of necrotizing enterocolitis by hospital discharge (RR 0.72, 95% CI 0.41 to 1.25).
- **Growth:** Low-certainty evidence from six trials totalling 440 participants suggests an increase in weight gain (in grams per kilogram per day) by hospital discharge (MD 2.43, 95% CI 1.60 to 3.26). Low-certainty evidence from five trials totalling 386 participants suggests little or no effect on length gain (in millimetres per week) by hospital discharge (MD 0.22, 95% CI -0.70 to 1.13). Low-certainty evidence from five trials totalling 399 participants suggests an increase in head circumference gain (in millimetres per week) by hospital discharge (MD 1.04, 95% CI 0.18 to 1.89).
- **Neurodevelopment:** Moderate-certainty evidence from two trials totalling 310 participants suggests an increase in MDI (BSID-II) at 18 months (MD 2.81, 95% CI -1.44 to 7.06). Low-certainty evidence from two trials totalling 310 participants suggests an increase in PDI (BSID-II) at 18 months (MD 6.56, 95% CI 2.87 to 10.26).

Subgroup analyses

For the analysis by gestational age and birth weight, differences for all critical outcomes could not be assessed as there were insufficient studies.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. No other specific evidence was located about whether families value preterm formula rather than term formula for their preterm or LBW baby, or find preterm formula more or less acceptable than term formula.

Resources required and implementation considerations

Organization of care

Health workers and staff at other care facilities can provide preterm (nutrient-enriched) formula for preterm or LBW infants.

Infrastructure, equipment and supplies

The main commodity required is the preterm formula, which should be a standard, nationally approved formula, specially formulated for preterm or LBW infants. Facilities are needed for safe reconstitution of preterm formula. Supplies are also needed for cup or gastric tube feeding.

Workforce, training, supervision and monitoring

Health workers at all levels can provide support to mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing preterm formula for preterm or LBW infants.

Summary of judgements

Comparison: Preterm formula vs term formula (A.5)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefits: increased in-hospital weight, head circumference, neurodevelopment *(low-certainty evidence)* • No evidence of harms • Evidence of little or no effect on mortality and necrotizing enterocolitis *(low-certainty evidence)*

Evidence-to-Decision summary	
Desirable	Small
Undesirable	Trivial or none
Certainty	Low
Balance	Probably favours preterm formula
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Moderate
Feasibility	Probably not feasible
Equity	Probably not equitable

A.6 EARLY INITIATION OF ENTERAL FEEDING

Recommendation and remarks

RECOMMENDATION A.6 (UPDATED)

Preterm and low-birth-weight (LBW) infants, including very preterm (< 32 weeks' gestation) and very LBW (< 1.5 kg) infants, 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 as soon as it becomes available. If mother's own milk is not available, donor human milk should be given wherever possible. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- Enteral feeding includes direct breastfeeding and feeding by cups, naso- or orogastric tubes.
- The trials included in the systematic review mostly did not state the stability of the babies, so careful consideration is needed in applying these recommendations to unstable babies. The GDG considers that initiation of enteral feeding in unstable babies should be based on clinical judgement.
- Infants should be given mother's own milk wherever possible. The provision of colostrum is especially important. If mother's own milk is not available, then donor human milk should be given wherever possible. 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 effectiveness by volume of initial feed, so a recommendation was not made on restricting the volume of feed.
- In all but one of the trials, the control group received parenteral nutrition. The benefits of early initiation of enteral feeding may be even greater when the alternatives are intravenous fluids or dextrose water rather than parenteral nutrition.

Background and definitions

WHO and UNICEF recommend early initiation of breastfeeding within 1 hour of birth for all healthy term infants *(63)*. Clinicians continue to debate the optimal timing of feeding initiation for preterm and LBW infants for fear of potential health complications, including necrotizing enterocolitis *(13,82,83)*. Additionally, women in communities around the world may delay feeding due to the cultural practices of discarding colostrum, pain and discomfort after delivery, and concern about the developmental maturity of the infant, including the infant's inability to digest milk feeds *(84,85)*. In 2011, WHO recommended early initiation of enteral feeding for stable preterm or LBW infants *(19)*. However, there have been new studies since that time.

Summary of the evidence

OVERVIEW	A.6 Early initiation of enteral feeding
PICO	**Population** – Preterm or LBW infants **Intervention** – Early initiation of enteral feeding (< 72 hours) **Comparator** – Delayed initiation of enteral feeding (> 72 hours) **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 1 month of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Timing of feed initiation (days 1, 2, 3) • Milk volume (< 15 ml/kg per day, ≥ 15 ml/kg per day) • Milk type (human milk, formula, and mixed human milk with formula)

Effectiveness: Comparison – Early versus delayed initiation of enteral feeding

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 14 trials enrolling 1511 preterm or LBW infants, which compared early initiation of enteral feeding (< 72 hours) with delayed initiation of enteral feeding (≥ 72 hours). The trials were from nine countries (Canada, Chile, Colombia, India, the Netherlands, Spain, the United Arab Emirates, the United Kingdom and the USA) *(86)*. All trials were based in hospital NICUs. Ten trials restricted enrolment to very preterm infants (< 32 weeks' gestation) or VLBW infants (< 1.5 kg) and five enrolled all preterm or LBW infants. Three studies enrolled only small-for-gestational-age (SGA) infants. Early initiation time ranged from 1 to 3 days after birth and delayed initiation time ranged from 4 to 15 days after birth. Two studies initiated feeding by day 1 (i.e. < 24 hours), eight studies initiated by day 2 (i.e. < 48 hours) and five studies initiated by day 3 (i.e. < 72 hours). Enteral feed volumes ranged from 5 to 25 ml/kg per day. Only two studies provided babies with feed volumes > 15 ml/kg per day. Only one trial provided direct breastfeeding while the remaining 13 gave feeds by naso- or orogastric tube. Three studies gave the babies formula milk, one gave mother's own milk and the remaining 10 gave a mixture of milks (i.e. mother's own, donor human milk and/or formula). All infants received supplemental parenteral nutrition in the delayed initiation group, except for one study which did not specify.

Critical outcomes

For early feeding compared with delayed feeding for preterm or LBW infants, 12 studies reported all-cause mortality outcomes, 14 reported morbidity (14 reported necrotizing enterocolitis, 6 sepsis, 1 intraventricular haemorrhage), 7 reported growth outcomes (7 reported time to regain birth weight, 1 weight, 1 length and 3 head circumference). None of the trials reported on neurodevelopment. (Full details are provided in GRADE Table A.6, in the Web Supplement.)

- **Mortality**: Moderate-certainty evidence from 12 trials totalling 1292 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.69, 95% CI 0.48 to 0.99).
- **Morbidity:** Low-certainty evidence from 13 trials totalling 1484 participants suggests little or no effect on necrotizing enterocolitis by hospital discharge (RR 1.05, 95% CI 0.75 to 1.46). Low-certainty evidence from five trials totalling 626 participants suggests little or no effect on sepsis by discharge (RR 0.90, 95% CI 0.54 to 1.52). Very-low-certainty evidence from one trial with 84 participants suggests a decrease in intraventricular haemorrhage by hospital discharge (RR 0.48, 95% CI 0.18 to 1.25).
- **Growth:** Low-certainty evidence from seven trials totalling 569 participants suggests little or no effect on time to regain birth weight (in days) (MD 0.26, 95% CI -0.63 to 1.15). Low-certainty evidence from three trials totalling 142 participants suggests little or no effect on weight (in grams) at latest follow-up (at chronological age 6–12 weeks) (MD -49.02, 95% CI -149.62 to 51.61). Very-low-certainty evidence from one trial with 40 participants suggests an increase in weight gain (in grams) from enrolment to 30 days follow-up (MD 51, 95% CI 32.4 to 69.6). Low-certainty evidence from two trials totalling 82 participants suggests little or no effect on length gain (in centimetres) at latest follow-up (at chronological age 32 weeks) (MD -0.62, 95% CI -1.51 to 0.27). Very-low-certainty evidence from two trials totalling 82 participants suggests little or no effect on head circumference (in centimetres) at latest follow-up (at discharge or chronological age 32 weeks) (MD -0.56, 95% CI -1.18 to 0.06).

Other outcomes

There was little or no effect on feed intolerance at discharge (RR 1.03, 95% CI 0.66 to 1.60; 2 trials, 187 participants) or length of hospital stay (days to discharge) (MD -3.2, 95% CI -5.74 to -0.66; 10 trials, 1100 participants).

Subgroup analyses

For the analyses by gestational age and birth weight, subgroup differences could not be assessed as there were insufficient studies on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There have been studies of the barriers, facilitators, preferences, values and acceptability of early and late initiation of enteral feeding for preterm or LBW infants *(84,85)*. Reasons for delay in initiation of feeding include cultural practices of discarding colostrum, pain and

discomfort after delivery, and concern about the developmental maturity of the baby, including the baby's inability to digest milk feeds. Reasons for early initiation include the importance of providing nurturing care to the baby as soon as possible, and concerns about the use of intravenous lines, dextrose water, total parenteral nutrition and lack of other nutritional support *(84,85)*.

Resources required and implementation considerations

Organization of care

Early initiation of enteral feeding from the first day of life (the day of birth) can be implemented at home and at all levels of newborn care (primary, secondary and tertiary).

Infrastructure, equipment and supplies

National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can provide early initiation support to mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of early initiation of feeding for preterm or LBW infants.

Summary of judgements

Comparison: Early vs delayed initiation of enteral feeding (A.6)	
Justification	• Evidence of moderate benefits: decreased mortality *(moderate-certainty evidence)*, decreased length of hospital stay *(moderate-certainty evidence)*, decreased intraventricular haemorrhage *(very-low-certainty evidence)* • No evidence of harms • Evidence of little or no effect on: necrotizing enterocolitis *(low-certainty evidence)*, sepsis *(low-certainty evidence)*, growth, i.e. time to regain birth weight, weight in grams, weight gain in grams, length at discharge *(low- to very-low-certainty evidence)*, feed intolerance *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours early initiation
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Negligible
Feasibility	Feasible
Equity	Equitable

A.7 RESPONSIVE AND SCHEDULED FEEDING

Recommendation and remarks

RECOMMENDATION A.7 (UPDATED)

In health-care facilities, scheduled feeding may be considered rather than responsive feeding for preterm infants born before 34 weeks' gestation, until the infant is discharged. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- In making this decision, the GDG considered that the harms from responsive feeding (i.e. poor weight gain) outweighed the benefits (i.e. decreased length of hospital stay).
- Most data were about infants born before 34 weeks' gestation, so recommendations could not be made for infants born at or after 34 weeks' gestation.
- The included trials used a range of different feeding schedules and it was not possible to recommend a particular schedule. The GDG suggests 2–3 hourly scheduled feeding may be used for infants born before 34 weeks' gestation as this is a commonly used and feasible schedule.
- All studies were in hospitalized infants, so the GDG could not make a recommendation on feeding outside the hospital.
- Nurturing care and responsive caregiving are critical to the well-being of every preterm and LBW infant and should be implemented regardless of the type of feeding regime.

Background and definitions

Responsive feeding is often defined as feeding in response to infant visual and auditory cues (or signals) of hunger and satiety *(87-89)*. Infant cues include crying, hand–mouth motions, suckling and awakeness. Scheduled feeding is defined in many studies as enteral feeding at regularly timed intervals, irrespective of infant cues *(87-89)*. A 2016 Cochrane review suggested that responsive feeding led to slower weight gain, but decreased the transition time from enteral tube to oral feeding *(90)*. However, another systematic review reported that responsive feeding decreased the length of hospitalization and increased weight gain in infants *(91)*. In 2011, WHO recommended that LBW infants who are orally fed but not breastfed should be fed based on infants' hunger cues, except when the infant remains asleep beyond three hours since the last feed *(19)*.

Summary of the evidence

OVERVIEW	A.7 Responsive and scheduled feeding
PICO	**Population** – Preterm or LBW infants who receive any enteral feeding **Intervention** – Responsive feeding based on infant cues **Comparator** – Scheduled feeding **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Responsive feeding versus scheduled feeding

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of eight RCTs reporting on 455 preterm or LBW infants from four countries (Canada, the Islamic Republic of Iran, Israel and the USA) *(92)*. The studies were all conducted in NICUs and the responsive feeding was provided by health staff and not by families – that is, the health workers directly implemented a protocol of scheduled or responsive feeding regardless of whether a family member was present. The scheduled feeding regimes were mostly 2- to 3-hourly and the feeding volumes ranged from 120 to 180 ml/kg per day. The studies implemented the intervention for variable durations, with the minimum being 3 days and the maximum lasting until hospital discharge. Only one study recruited very preterm infants (< 32 weeks' gestation) while the remainder recruited preterm infants.

Critical outcomes

For responsive feeding compared with scheduled feeding for preterm or LBW infants, seven studies assessed growth outcomes (7 reported weight gain, 3 weight). No studies assessed mortality, morbidity or neurodevelopment outcomes. (Full details are provided in GRADE Table A.7, in the Web Supplement.)

- **Growth:** low-certainty evidence from two trials totalling 213 participants suggests a decrease in weight (in grams per day) by hospital discharge (MD -2.8, 95% CI -3.39 to -2.22). Low-certainty evidence from three trials totalling 183 participants suggests little to no effect on weight (in grams) by hospital discharge (MD -22.21, 95% CI -130.63 to 86.21). Very-low-certainty evidence from five trials totalling 372 participants suggests little to no effect on weight gain (in grams per kg per day) by hospital discharge (MD -0.99, 95% CI -2.45 to 0.46).

Other outcomes

Very-low-certainty evidence from three trials totalling 342 participants suggests a decrease in duration of hospitalization (days to discharge) (MD -1.42, 95% CI -5.43 to 2.59).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient studies.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. No other specific evidence was located about whether families value responsive feeding more than scheduled feeding for their preterm or LBW baby or whether they find it more or less acceptable.

Resources required and implementation considerations

Organization of care

In facilities, infants born before 34 weeks' gestation can be fed every 2–3 hours. Infants born at 34 weeks' gestation or more can be fed every 3–4 hours or by responsive feeding. At home, there is no recommended scheduling; families and health workers can decide together, depending on clinical judgement and their preferences.

Infrastructure, equipment and supplies

National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

Administration of scheduled feeds for preterm and LBW babies varies markedly but common scheduling is 2- to 3-hourly feeding with volumes of 80–200 ml/kg per day for babies born before 34 weeks' gestation. Responsive feeding requires sensitivity and careful observation of the baby's behaviour and is more commonly implemented in settings with well staffed special care nurseries and NICUs *(87)*. There was no specific evidence on the feasibility and equity of responsive and scheduled feeding for preterm or LBW infants.

Summary of judgements

Comparison: Responsive feeding vs scheduled feeding (A.7)	
Justification	In trials where most participants are hospitalized infants born < 34 weeks' gestation: • Evidence of small benefits from responsive feeding: decreased length of hospital stay *(very-low-certainty evidence)* in trials of infants born < 34 weeks' gestation • Evidence of small harms from responsive feeding: decreased weight gain velocity in grams per day, and grams per kilogram per day *(low- to very-low-certainty evidence)*, decreased weight gain in grams at discharge *(very-low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Benefits of responsive feeding are trivial to none
Harms	Harms of responsive feeding are small
Certainty	Very low to low
Balance	Probably does not favour responsive feeding, probably favours scheduled feeding
Values	Uncertainty or variability about outcomes
Acceptability	Acceptability of responsive feeding and scheduled feeding varies
Resources	Resources needed for responsive feeding and scheduled feeding vary
Feasibility	Feasibility of responsive feeding and scheduled feeding varies
Equity	Equity of responsive feeding and scheduled feeding varies

A.8 FAST AND SLOW ADVANCEMENT OF FEEDING

Recommendation and remarks

RECOMMENDATION A.8 (UPDATED)

In preterm or low-birth-weight (LBW) infants, including very preterm (< 32 weeks' gestation) or very LBW (< 1.5 kg) infants, who need to be fed by an alternative 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)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that the trials enrolled infants immediately after birth (i.e. day 1 – within 24 hours of birth) so results are generalizable to very early feeding of LBW infants from this time.
- All trials excluded babies with congenital anomalies and birth asphyxia, so careful consideration is needed in applying these recommendations to infants with these conditions. Feed advancement should be based on clinical judgement for these infants.
- All trials compared fast advancement (increments of 30–40 ml/kg per day) with slow advancement (increments of 15–25 ml/kg per day). So the GDG took the conservative value of 30 ml/kg per day as the threshold for fast feed advancement. This value is also consistent with many national guidelines.
- All studies were in hospitalized infants, so the GDG could not make a recommendation on feeding outside the hospital.
- The GDG did not make separate recommendations for babies fed formula milk versus human milk as there was insufficient evidence (only one trial gave formula as the sole diet while the remainder gave human milk only or a mix of human milk and formula).
- The GDG considered that advancement should continue until full maintenance feed volumes are reached. These volumes should be based on local guidelines.
- The GDG noted that further research is needed to understand the neurodevelopmental effects of fast feed advancement.

Background and definitions

There is substantial variation in the definitions of fast and slow advancement of enteral feeding volumes for preterm and LBW babies in the first weeks after birth. Advancement increments commonly vary between 10 and 40 ml/kg per day *(93,94)*. Up to the 1990s, the standard of care was a conservative ("slow rate") approach because of concerns about feed intolerance (e.g. gagging, vomiting and apnoea post-feed) and necrotizing enterocolitis *(56)*. In 2011, WHO recommended that feeds could be advanced by up to 30 ml/kg per day with careful monitoring for feed intolerance in infants weighing under 1.5 kg *(19)*. However, there have been new studies published since that time *(95)*.

Summary of the evidence

OVERVIEW	A.8 Fast and slow advancement of feeding
PICO	**Population** – Preterm or LBW infants **Intervention** – Fast advancement of enteral feeds (≥ 30 ml/kg per day) **Comparator** – Slow advancement of enteral feeds (< 30 ml/kg per day) **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Type of milk (human milk, formula milk)

Effectiveness: Comparison – Fast versus slow advancement of enteral feeds

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 12 RCTs enrolling 4084 preterm or LBW infants *(96)*. The trials were conducted in Bangladesh, Colombia, India, the Islamic Republic of Iran, Ireland, South Africa, Türkiye, the United Kingdom and the USA. The United Kingdom Speed of Increasing Milk Feeds trial (SIFT) was the largest trial (n=2973) *(97)*. Most studies included clinically stable infants and excluded those with perinatal asphyxia or haemodynamic instability. The infants were typically randomized on days 1–4 after birth. Intervention (fast advancement) increments ranged from 30 to 40 ml/kg per day. Comparator (slow advancement) increments ranged from 10 to 25 ml/kg per day. The target volume of full feeding ranged from 120 to 180 ml/kg per day. Seven studies enrolled very preterm infants born before 32 weeks' gestation. Three studies used human milk, one used infant formula, and seven used a combination of the two.

Critical outcomes

For fast compared with slow advancement of enteral feeding for preterm or LBW infants, 11 trials reported all-cause mortality, 12 reported morbidity (12 reported necrotizing enterocolitis, 9 sepsis, 2 apnoea), 6 reported growth outcomes (6 reported time to regain birth weight, 1 WAZ at discharge, 1 weight at discharge, 1 weight gain, 1 head circumference) and 1 reported neurodevelopmental outcomes (disability). (Full details are provided in GRADE Table A.8, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from 11 trials with a total of 4132 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.93, 95% CI 0.73 to 1.18).
- **Morbidity:** Low-certainty evidence from two trials totalling 153 participants suggests a decrease in apnoea by hospital discharge (RR 0.72, 95% CI 0.47 to 1.12). Moderate-certainty evidence from 12 trials totalling 4291 participants suggests little or no effect on necrotizing enterocolitis by hospital discharge (RR 0.89, 95% CI 0.68 to 1.15). Moderate-certainty evidence from nine trials totalling 3648 participants suggests little or no effect on sepsis by hospital discharge (RR 0.92, 95% CI 0.83 to 1.03).
- **Growth:** High-certainty evidence from six trials totalling 993 participants suggests a decrease in time to regain birth weight by hospital discharge (MD -3.69, 95% CI -4.44 to -2.95). Low-certainty evidence from one trial with 2793 participants suggests little or no effect on WAZ by hospital discharge (MD 0.0, 95% CI -0.08 to 0.08). Low-certainty evidence from one trial with 131 participants suggests little or no effect on weight gain (in grams per kilogram per day) by hospital discharge (MD 0.5, 95% CI -1.19 to 2.19). Low-certainty evidence from one trial with 100 participants suggests little or no effect on weight in grams by hospital discharge (MD -29.0, 95% CI -74.89 to 16.89). Low-certainty evidence from one trial with 2793 participants suggests little or no effect on head circumference (head circumference z score) by hospital discharge (MD -0.1, 95% CI -0.22 to 0.02).
- **Neurodevelopment:** Low-certainty evidence from one trial of 2325 participants suggests little or no effect on neurodevelopment (neurodevelopmental disability measured using a validated test) at 24 months corrected age (RR 1.12, 95% CI 0.98 to 1.27).

Other outcomes

There was a decrease in length of hospital stay (days to discharge) (MD -3.08, 95% CI -4.34 to -1.81; 7 trials, 3864 participants) and little or no effect on feed intolerance by hospital discharge (RR 0.92, 95% CI 0.77 to 1.10; 8 trials, 1114 participants).

Subgroup analyses

No subgroup differences were seen for gestational age and birth weight for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. No specific evidence was located about whether families value fast versus slow feed advancement for their preterm or LBW baby or whether they find the different rates more or less acceptable.

Resources required and implementation considerations

Organization of care

Feed advancement should be based on clinical judgement for all infants at home and in health-care facilities. In facilities, there can be fast advancement of feed volumes by up to 30 ml/kg per day.

Infrastructure, equipment and supplies

National or local guidance on infrastructure, equipment and supplies for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

No specific evidence was located about the feasibility and equity of providing slow or fast feed advancement to preterm or LBW babies.

Summary of judgements

Comparison: Fast vs slow advancement of enteral feeds (A.8)	
Justification	• Evidence of moderate benefits: decrease in apnoea *(moderate-certainty evidence)*, decrease in time to regain birth weight *(high-certainty evidence)*, decreased length of hospital stay *(moderate-certainty evidence)* • Evidence on harms uncertain: impaired neurodevelopment *(low-certainty evidence)* • Evidence of little or no effect on: mortality, necrotizing enterocolitis, sepsis, weight gain, head circumference *(low-certainty evidence)*, feed intolerance *(moderate-certainty evidence)*

Evidence-to-Decision summary	
Desirable	Small
Undesirable	Unknown
Certainty	Moderate
Balance	Probably favours fast feed advancement
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Negligible
Feasibility	Probably feasible
Equity	Equitable

A.9 DURATION OF EXCLUSIVE BREASTFEEDING

Recommendation and remarks

RECOMMENDATION A.9 (UPDATED)

Preterm or low-birth-weight infants should be exclusively breastfed until 6 months of age. *(Strong recommendation, very-low-certainty evidence)*

Remarks

- The GDG made strong recommendation in favour of exclusive breastfeeding (EBF) until 6 months of age despite the very-low-certainty evidence because they considered the potential harms of less than 6 months of EBF to outweigh the potential harms of having at least 6 months of EBF.
- In making the decision, the GDG also considered the results of a systematic review of 42 studies (89 638 infants) comparing mother's own milk with infant formula in babies aged 0–6 months *(60)*. This review showed consistent harm from the use of infant formula on a critical outcome (morbidity: necrotizing enterocolitis) in the first 6 months after birth. It also reported no evidence of benefit from infant formula over the same period.
- The GDG also considered that EBF until 6 months of age is the standard of care for preterm and LBW infants across many high-, middle- and low-income countries and is the foundation of many national policies and programmes.
- The GDG also felt that mothers should be encouraged and supported before and after birth to provide their own breast-milk (including colostrum) for their infants.

Background and definitions

WHO defines exclusive breastfeeding (EBF) as feeding no other foods or fluids (not even water) except breast-milk, medicines, vitamins and minerals *(22)*. EBF until 6 months of age is recommended for full-term, normal-birth-weight infants *(22)*. However, preterm and LBW infants are more vulnerable to nutritional deficiencies *(13,56)*. The risks of contamination of complementary foods and early infant formula feeding are also well known *(98)*. In 2011, WHO recommended EBF until 6 months of age for preterm and LBW babies *(19)*, but new studies have been published since that time.

Summary of the evidence

OVERVIEW	A.9 Duration of exclusive breastfeeding (EBF)
PICO	**Population** – Preterm or LBW infants **Intervention** – EBF to < 6 months of age **Comparator** – EBF until 6 months of age **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Exclusive breastfeeding for less than six months versus for six months

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of two RCTs reporting on a total of 307 preterm or LBW infants from two countries (Honduras and India) *(99)*. The trial in Honduras randomized 119 term SGA EBF infants (mean birth weight in the intervention group was 2364 g [SD 137], mean birth weight in the control group was 2327 g [SD 183]) to receive nutrient-rich complementary foods starting from 4 months chronological age. The other study in India randomized 403 infants born before 34 weeks' gestation (mean birth weight in the intervention group was 1479 g [SD 308],

mean birth weight in the control group was 1492 g [SD 344]) to receive nutrient-rich complementary foods starting from 4 months corrected age. Fifty per cent (202/403) of these infants were EBF (104 intervention and 98 control) and 93% (188/202) of those EBF infants had WAZ outcome data (95 intervention and 93 control).

Critical outcomes

For EBF less than six months compared with EBF for six months for preterm or LBW infants, one trial reported morbidity (percentage of days with diarrhoea and/or fever), two trials reported growth outcomes (1 reported weight gain, 1 WAZ, 1 length gain) and one trial reported neurodevelopment (time to achieve motor developmental milestones). No trials reported mortality. (Full details are provided in GRADE Table A.9, in the Web Supplement.)

- **Morbidity:** Very-low-certainty evidence from one trial with 119 participants suggests a decrease in the percentage of days with diarrhoea from 16 to 26 weeks of chronological age (MD -2.6, 95% CI -5.2 to 0.0). Very-low-certainty evidence from one trial with 119 participants suggests little or no effect on the percentage of days with fever from 16 to 26 weeks chronological age (MD -0.7, 95% CI -3.4 to 2.0).
- **Growth:** Very-low-certainty evidence from one trial with 119 participants suggests a decrease in weight gain (in grams) from 4 to 6 months of chronological age (MD -13, 95% CI -143 to 117). Low-certainty evidence from one trial with 188 participants suggests little or no effect on WAZ at 12 months corrected age (MD 0.1, 95% CI -0.2 to 0.4). Very-low-certainty evidence from one trial with 119 participants suggests a decrease in the rate of length gain (in centimetres) from 4 to 6 months of chronological age (MD -0.2, 95% CI -0.6 to 0.2).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 108 participants suggests little or no effect on motor development milestones at specified chronological ages (in months) (raise head, MD 0.0, 95% CI -0.3 to 0.3; raise chest, MD -0.1, 95% CI -0.7 to 0.5; roll over, MD 0.0, 95% CI -0.7 to 0.7; able to crawl, MD 0.6, 95% CI -0.1 to 1.3; able to sit from lying position, MD 0.6, 95% CI 0.0 to 1.2). Very-low-certainty evidence from one trial with 99 participants suggests an increase in the percentage of infants who can walk by the chronological age of 12 months (RR 1.47, 95% CI 0.69 to 3.13).

Other outcomes

There was a decrease in anaemia (haemoglobin level < 10.5 g/dl) (RR 0.10, 95% CI 0.01 to 0.77, 1 trial, 104 participants) but not in infants who received iron supplements (RR 1.07, 95% CI 0.22 to 5.28; 1 trial, 29 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*.

There are studies that report the difficulties in providing mother's own milk when the mother and baby return home, including difficulties balancing work commitments, maternity leave, night-time feeding and father/partner support *(14)*. There are also studies that report family concerns with infant formula, including concerns about nutrient composition, water supply, contamination and cost *(64,65)*. Studies also report families valuing having formula available if their circumstances demand it, such as work commitments, maternity leave, night-time feeding, father and partner support *(64,65)*. No specific evidence was located about whether families value EBF for up to 6 months of age for their preterm or LBW baby or whether they find the different durations of EBF more or less acceptable.

Resources required and implementation considerations

Organization of care

Promotion of exclusive breastfeeding for six months should be done at the community and facility level and be integrated within standard national programmes. This should occur throughout the antenatal and postnatal periods and up until the infant reaches 6 months of age.

Infrastructure, equipment and supplies

National or local guidance for infrastructure, equipment and supplies for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can promote exclusive breastfeeding for six months. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of duration of EBF for preterm or LBW infants.

Summary of judgements

Comparison: Exclusive breastfeeding (EBF) for less than six months vs for six months (A.9)	
Justification	• Evidence of small benefits: decrease in percentage of days with diarrhoea *(very-low-certainty evidence)*, increase in neurodevelopment, i.e. percentage of infants who can walk by the age of 12 months *(very-low-certainty evidence)* • Evidence of small harms: decrease in weight gain in grams at 26 weeks *(very-low certainty evidence)* • Evidence of little or no effect on other morbidity (percentage of days with fever), other growth (weight-for-age z score [WAZ], length in centimetres), and other neurodevelopmental milestones (raise head, raise head and chest, roll over, crawl, sit from lying position) *(very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary	
Benefits	Benefits of EBF to < 6 months are small
Harms	Harms of EBF to < 6 months are small
Certainty	Very low
Balance	Does not favour EBF to < 6 months, favours EBF to 6 months
Values	Uncertainty or variability about outcomes
Acceptability	Acceptability of EBF to < 6 months varies
Resources	Resources for EBF to < 6 months are low to moderate
Feasibility	Feasibility of EBF to < 6 months varies
Equity	Equity of EBF to < 6 months varies

A.10 MICRONUTRIENT SUPPLEMENTATION

A.10a Iron supplementation

Recommendation and remarks

RECOMMENDATION A.10a (UPDATED)

Enteral iron supplementation is recommended for human milk-fed preterm or low-birth-weight infants who are not receiving iron from another source. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that there were limited data on dose, timing of initiation and duration of iron supplementation.
- Based on most trials included in the evidence review, the GDG suggests a daily dose of 2–4 mg/kg per day of elemental iron may be initiated when enteral feeds are well established, and may be continued until the infant receives iron from another source.

Background and definitions

Iron deficiency is associated with poor growth and development outcomes in term and preterm babies *(100,101)*. Human milk may not meet the nutritional requirements of preterm or LBW infants because of their low iron stores, red blood cell expansion, catch-up growth and iatrogenic blood loss. The most recent systematic reviews of RCTs and non-randomized studies reported that enteral iron supplementation may improve haematological outcomes in preterm and LBW babies but that there was insufficient evidence to assess effects on growth and neurodevelopmental outcomes *(100,101)*. The optimal dose, optimal timing of initiation and the level and types of morbidity associated with iron supplementation were also unclear. In 2011, WHO recommended that VLBW infants fed mother's own milk or donor human milk should be given iron supplementation of 2–4 mg/kg per day starting at 2 weeks and continuing until 6 months of age *(19)*.

Summary of the evidence

OVERVIEW	A.10a Iron supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Iron supplementation **Comparator** – No iron supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Iron supplementation versus no iron supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of eight trials (11 publications) reporting on a total of 1093 infants from seven countries (Canada, Germany, India, the Netherlands, Sweden, the United Kingdom and the USA) *(102)*. Most trials enrolled babies with birth weight below 1.5 kg or born before 32 weeks' gestation. The trials used iron supplementation doses ranging from 1 to 7 mg/kg per day, median 2.2 (IQR 1.97–2.55) mg/kg per day. Supplementation commenced between 14 and 56 days chronological age. The mean duration of supplementation was 81 (SD 57) days and the median duration was 53 (IQR 40–98) days. One trial gave iron with multivitamin supplements and compared this with infants who received multivitamins alone. The remaining seven trials gave iron supplementation alone and compared this with placebo or no iron supplementation.

Critical outcomes

For enteral iron supplementation compared with no iron supplementation, four trials reported morbidity (4 reported sepsis, 2 necrotizing enterocolitis), five reported growth outcomes (5 reported weight, 3 length, 3 head circumference) and one reported on neurodevelopment (cognitive outcomes). No studies reported all-cause mortality. (Full details are provided in GRADE Table A.10, in the Web Supplement.)

- **Morbidity:** Very-low-certainty evidence from four trials totalling 270 participants suggests little or no effect on sepsis prevalence at latest follow-up (median 8 [IQR 8–9] weeks) (RR 1.08, 95% CI 0.56 to 2.07). Very-low-certainty evidence from two trials totalling 194 participants suggests little or no effect on necrotizing enterocolitis prevalence at latest follow-up (median 9 [IQR 8.5–9.5] weeks) (RR 1.54, 95% CI 0.69 to 3.46).
- **Growth:** Low-certainty evidence from five trials totalling 574 participants suggests an increase in weight in grams at latest follow-up (median 26 [IQR 8–36] weeks) (MD 35.31, 95% CI -64.53 to 135.15). Moderate-certainty evidence from three trials totalling 384 participants suggests an increase in length in centimetres at latest follow-up (median 26 [IQR 8–183] weeks) (MD 0.69, 95% CI 0.01 to 1.37). Low-certainty evidence from three trials totalling 385 participants suggests little or no effect on head circumference at latest follow-up (median 26 [IQR 8–183] weeks) (MD 0.09, 95% CI -0.4 to 0.21).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 199 participants suggests little or no effect on cognitive development (measured using the Wechsler Intelligence Scale for Children, fourth edition [WISC-IV]) at latest follow-up (mean 365 weeks) (RR 0.31, 95% CI 0.09 to 1.02).

Other outcomes

Moderate-certainty evidence from two trials totalling 381 participants suggests a decrease in anaemia prevalence at latest follow-up (RR 0.25, 95% CI 0.10 to 0.62). Moderate-certainty evidence from five trials totalling 506 participants suggests an increase in haemoglobin prevalence at latest follow-up (mean 26 weeks) (MD 4.79, 95% CI 2.9 to 6.69). Very-low-certainty evidence from six trials totalling 607 participants suggests little or no effect on ferritin levels at latest follow-up (median 14 [IQR 8–26] weeks) (MD 8.76, 95% CI -0.85 to 18.37). Very-low-certainty evidence from two trials totalling 238 participants suggests little or no effect on feed intolerance at latest follow-up (mean 8 weeks) (RR 1.05, 95% CI 0.49 to 2.27).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value iron supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Iron supplements are commonly provided to LBW and preterm infants as oral liquid solution. Infants are commonly prescribed 2–4 mg/kg of elemental iron per day for the prophylaxis of iron deficiency anaemia. Concentrations of 5 mg of elemental iron per millilitre of liquid are often used (e.g. 1 ml/day to a 2 kg baby will provide 2.5 mg of elemental iron per day). Droppers or syringes can be used to administer the supplement to the infant. Doses are different for the treatment of iron deficiency anaemia. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility of providing iron supplements to preterm or LBW babies.

Summary of judgements

Comparison: Iron supplementation vs no iron supplementation (A.10a)	
Justification	• Evidence of small-to-moderate benefit: decreased anaemia, increased weight and length *(low-certainty evidence)* • No evidence of harms • Evidence of little or no effect on sepsis and necrotizing enterocolitis *(very-low-certainty evidence)*, and on weight, head circumference and neurodevelopment *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours iron supplementation
Values	No uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

A.10b Zinc supplementation

Recommendation and remarks

RECOMMENDATION A.10b (UPDATED)

Enteral zinc supplementation may be considered for human milk-fed preterm or low-birth-weight infants who are not receiving zinc from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (decreased neurodevelopment) was uncertain due to very-low-certainty evidence and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of supplementation. Based on most trials included in the evidence review, the GDG suggests a daily dose of 1–3 mg/kg per day of elemental zinc. The GDG also suggests that zinc may be initiated when enteral feeds are well established, and may be continued until the infant receives zinc from another source.

Background and definitions

Zinc is a trace element essential for physiological functions of the human body *(103)*. Zinc deficiency is associated with dysfunction in epidermal, gastrointestinal, central nervous, immune, skeletal and reproductive systems *(104,105)*. Human milk may not be able to meet the nutritional requirements of preterm or LBW infants because of their low zinc stores and catch-up growth *(104-106)*. A recent (2021) Cochrane review of enteral zinc supplementation in hospitalized preterm infants fed any type of milk (i.e. infant formula or human milk) reported that zinc supplementation reduced all-cause mortality and was associated with a probable improvement in short-term weight gain and linear growth, but had little or no effect on common morbidities of prematurity *(107)*. However, there have been no recent systematic reviews of zinc supplementation in babies born at home or in the hospital or on babies fed human milk only. The optimal dose and timing of initiation are also unclear.

Summary of the evidence

OVERVIEW	A.10b Zinc supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Zinc supplementation **Comparator** – No zinc supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Dose of elemental zinc (< 3 mg/day, 3–5 mg/day and > 5 mg/day)

Effectiveness: Comparison – Zinc supplementation versus no zinc supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 14 RCTs totalling 9940 preterm or LBW infants from 11 countries (Bangladesh, Brazil, Chile, Egypt, India, the Islamic Republic of Iran, Italy, the Republic of Korea, Nepal, Spain and the United Republic of Tanzania) *(108)*. Most infants had a birth weight of at least 1.5 kg or were born at 32 weeks' gestation or later. Among these, two large RCTs assessed the effects of zinc supplementation in a total of 2748 term LBW infants in Brazil and India. Zinc supplementation dosages across all 14 RCTs ranged from 1 mg/day up to 10 mg/day and commenced between birth and 35 days of age. Most

studies used a zinc dose of 3–5 mg/day. The mean duration of supplementation was 182 (SD 142) days and the median duration was 141 (IQR 98–183) days.

Critical outcomes

For zinc supplementation compared with no zinc supplementation, six trials reported all-cause mortality, six reported morbidity (2 reported hospitalization, 6 diarrhoea, 2 acute respiratory infection, 2 sepsis), eight reported growth outcomes (8 reported weight gain, 6 length gain, 5 head circumference) and two reported neurodevelopment (MDI and PDI [BSID-II]). (Full details are provided in GRADE Table A.11, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from six trials totalling 8801 participants suggests a decrease in all-cause mortality at latest follow-up (median 26 [IQR 14–152.1] weeks) (RR 0.73, 95% CI 0.46 to 1.16). There was a similar effect on all-cause mortality when the two trials with term LBW infants were excluded (RR 0.68, 95% CI 0.43 to 1.09; 4 trials, 7192 participants).
- **Morbidity:** Moderate-certainty evidence from six trials totalling 1947 participants suggests a decrease in diarrhoea (events) at latest follow-up (median 26 [IQR 20.1–52.1] weeks) (RR 0.81, 95% CI 0.68 to 0.97). Very-low-certainty evidence from two trials totalling 172 participants suggests a decrease in acute respiratory infection at latest follow-up (median 13 [IQR 6–20] weeks) (RR 0.32, 95% CI 0.09 to 1.17). Low-certainty evidence from two trials totalling 265 participants suggests little to no effect on sepsis at latest follow-up (median 17 [IQR 14 to 20] weeks) (RR 1.12, 95% CI 0.62 to 2.02).
- **Growth:** Moderate-certainty evidence from 8 trials totalling 798 participants suggests an increase in weight (in grams) at latest follow-up (median 22 [IQR 13.5–39] weeks) (MD 378.57, 95% CI 275.26 to 481.88). Low-certainty evidence from six trials totalling 529 participants suggests an increase in length (in centimetres) at latest follow-up (median 36.1 [IQR 20–52.1] weeks) (MD 2.92, 95% CI 1.53 to 4.31). Low-certainty evidence from five trials totalling 466 participants suggests an increase in head growth (in centimetres) at latest follow-up (median 20 [IQR 13–24] weeks) (MD 0.56, 95% CI 0.23 to 0.9).
- **Neurodevelopment:** Very-low-certainty evidence from two trials totalling 301 participants suggests a decrease in MDI (BSID-II) scores at latest follow-up (52 weeks) (MD -4.18, 95% CI -1.85 to -6.51). Very-low-certainty evidence from two trials totalling 301 participants suggests an increase in PDI (BSID-II) scores at latest follow-up (52 weeks) (MD 5.75, 95% CI -4.83 to 16.33).

Other outcomes

There was a decrease in hospitalization (at least one hospitalization) at latest follow-up (RR 0.70, 95% CI 0.24 to 2.00; 2 trials, 277 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome. For the dose of elemental zinc, no subgroup differences were seen for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value zinc supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Zinc supplements are often provided as either 5 mg zinc capsules that are then opened and mixed with 5 ml of water (1 mg elemental zinc per ml) or zinc-containing multinutrient syrups (5 mg elemental zinc in 120 mls) (i.e. 42 µg elemental zinc per ml). Babies are often prescribed 1–5 mls of these formulations daily. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing zinc supplements to preterm or LBW babies.

Summary of judgements

Comparison: Zinc supplementation vs no zinc supplementation (A.10b)	
Justification	• Evidence of small-to-moderate benefit: decreased mortality *(low-certainty evidence)*, decreased diarrhoea *(moderate-certainty evidence)*, decreased respiratory infection *(very-low-certainty)*, increased weight, length, head circumference *(moderate-certainty evidence)* and increased psychomotor development scores *(very-low-certainty evidence)* • Evidence on harms uncertain: decreased mental development scores *(low-certainty evidence)* • Evidence of little or no effect on sepsis *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Unknown
Certainty	Low
Balance	Probably favours zinc supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

A.10c Vitamin D supplementation

Recommendation and remarks

RECOMMENDATION A.10c (UPDATED)

Enteral vitamin D supplementation may be considered for human milk-fed preterm or low-birth-weight infants who are not receiving vitamin D from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (increased mortality) was uncertain due to low-certainty evidence and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG also noted improvements in vitamin D deficiency and alkaline phosphatase levels but there were no data on other markers of bone health such as osteopenia or rickets.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of supplementation. Based on most trials included in the evidence review, the GDG suggests a daily dose of 400–800 IU may be initiated when enteral feeds are well established, and may be continued until the infant receives vitamin D from another source.

Background and definitions

Vitamin D increases intestinal absorption of calcium and phosphorus, and enhances bone mineralization *(42)*. Low vitamin D levels are associated with seizures, irritability, rickets (swollen, deformed, painful joints and bones), bone fractures, osteopenia (radiological evidence of thin bones) and metabolic bone disease (radiological evidence of widened or deformed bones) *(109-111)*. Vitamin D deficiency has also been associated with increased risk of respiratory and diarrhoeal disease. Human milk may not be able to meet the nutritional requirements of preterm or LBW infants because of their low vitamin D stores and catch-up growth *(56)*. Babies born to darker-skinned mothers are at higher risk of vitamin D deficiency, especially those born in higher latitudes and in the winter months *(112)*. In 2011, WHO recommended that VLBW infants with birth weight below 1.5 kg should be given vitamin D supplements (400–1000 IU per day) until 6 months of age *(19)*. A systematic review published in 2020 reported improvements in vitamin D biomarkers (vitamin D levels, calcium levels, parathyroid hormone) after vitamin D supplementation was provided to all preterm infants *(113)*.

Summary of the evidence

OVERVIEW	A.10c Vitamin D supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Vitamin D supplementation **Comparator** – No vitamin D supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Vitamin D supplementation versus no vitamin D supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of three RCTs totalling 2479 preterm or LBW infants from two countries (India and the USA) *(114)*. One trial in India enrolled 2079 (84%) of these infants. Most had a birth weight of at least 1.5 kg or were born at 32 weeks' gestation or later. The trials used a dose of vitamin D supplementation ranging from 200 IU to 800 IU per day. Two trials compared vitamin D with placebo, while the third trial compared vitamin D plus multivitamins with multivitamins alone. Vitamin D supplementation began between birth and 7 days chronological age in all trials. The mean duration of supplementation was 19 (SD 19) days and the median duration was 26 (IQR 4 to 26) days.

Critical outcomes

For vitamin D supplementation compared with no vitamin D supplementation, two trials reported all-cause mortality, five reported morbidity (1 reported bronchopulmonary dysplasia, 1 reported "at least one serious morbidity"), two reported growth (2 reported WAZ, 2 LAZ/HAZ, 1 head circumference z scores) and two reported neurodevelopment (cognitive development and neurodevelopmental impairment). (Full details are provided in GRADE Table A.10c, in the Web Supplement.)

- **Mortality**: Low-certainty evidence from two trials totalling 2179 participants suggests an increase in all-cause mortality at latest follow-up (RR 1.81, 95% CI 0.92 to 3.56).
- **Morbidity:** Very-low-certainty evidence from one trial with 100 participants suggests a decrease in bronchopulmonary dysplasia at 8 weeks of age (RR 0.77, 95% CI 0.47 to 1.27). Very-low-certainty evidence from two trials totalling 2179 participants suggests little or no effect on any (at least one) serious morbidity at latest follow-up (median 17 [IQR 8–26] weeks) (RR 0.94, 95% CI 0.72 to 1.24). "At least one serious morbidity" is defined as any (at least one) serious morbidity assessed with: any severe morbidity (hospital admission, or outpatient visits with diagnoses selected based on clinical judgement that represented severe illness: pneumonia, persistent diarrhoea, dysentery, severe fever, severe protein energy malnutrition, ear infections, meningitis and septicaemia), RDS, early-onset sepsis (≤ 72 hours), late-onset sepsis (> 72 hours) and culture-positive meningitis *(115)*.
- **Growth:** Moderate-certainty evidence from one trial with 1273 participants suggests an increase in WAZ at 6 months (MD 0.12, 95% CI 0.01 to 0.23). Low-certainty evidence from one trial with 912 participants suggests little or no effect on WAZ scores between 3 and 6 years of age (MD -0.07, 95% CI -0.18 to 0.04). Moderate-certainty evidence from one trial with 1258 participants suggests an increase in LAZ at 6 months (MD 0.12, 95% CI 0.03 to 0.21). Low-certainty evidence from one trial with 912 participants suggests little or no effect on height-for-age z scores (HAZ) between 3 and 6 years of age (MD 0.07, 95% CI -0.05 to 0.19). Low-certainty of evidence from one trial with 1259 participants suggests little or no effect on head circumference z scores at 6 months (MD -0.08, 95% CI -0.17 to 0.01).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 70 participants suggests little or no effect on cognitive scores assessed at 104 weeks (RR 0.85, 95% CI 0.45 to 1.59). Very-low-certainty evidence from one trial with 71 participants suggests a decrease in neurodevelopmental impairment assessed at 104 weeks (RR 0.69, 95% CI 0.41 to 1.17).

Other outcomes

There was little or no effect on hospitalization (at least one hospitalization) at latest follow-up (6 months) (RR 0.84, 95% CI 0.42 to 1.66; 2 trials, 1468 participants). There was a decrease in serum alkaline phosphatase (ALP) (measured in IU per litre) (note: ALP should be ≥ 500 IU/L) at 6 months follow-up (RR 0.37, 95% CI 0.10 to 1.36; 1 trial, 265 participants). There was a decrease in vitamin D deficiency (< 20 µg/ml) at latest follow-up (6 months) (RR 0.58, 95% CI 0.49 to 0.68; 2 trials, 504 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including

what and how they are fed *(14)*. There was no specific evidence available about whether families value vitamin D supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common methods of providing enteral vitamin D for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group). Many formulations contain 400 IU vitamin D per 0.45–0.6 ml. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing vitamin D supplements to preterm or LBW babies.

Summary of judgements

Comparison: Vitamin D supplementation vs no vitamin D supplementation (A.10c)	
Justification	• Evidence of small benefit: decreased bronchopulmonary dysplasia *(very-low-certainty evidence)*, increased weight and length *(moderate-certainty evidence)* and decreased neurodevelopmental impairment *(very-low-certainty evidence)* • Evidence on harms uncertain: mortality *(low-certainty evidence)* • Evidence of little or no effect on infections *(moderate-certainty evidence)*, hospital admissions *(very-low-certainty evidence)*, head circumference *(low-certainty evidence)*, weight *(low-certainty evidence)* and length *(moderate-certainty evidence)*

Evidence-to-Decision framework	
Benefits	Moderate
Harms	Unknown
Certainty	Moderate
Balance	Probably favours vitamin D supplementation
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Varies
Equity	Varies

A.10d Vitamin A supplementation

Recommendation and remarks

RECOMMENDATION A.10d (UPDATED)

Enteral vitamin A supplementation may be considered for human milk-fed very preterm (< 32 weeks' gestation) or very-low-birth-weight (< 1.5 kg) infants who are not receiving vitamin A from another source. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- There were no trials in infants born ≥ 32 weeks' gestation or ≥ 1.5 kg birth weight, so the GDG did not make a recommendation for those infants.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of supplementation. Based on most trials included in the evidence review, the GDG suggests a daily dose of 1000–5000 IU may be initiated when enteral feeds are well established, and may be continued until the infant receives vitamin A from another source.

Background and definitions

Vitamin A regulates cellular growth and helps to maintain the integrity of the mucosa and epithelium of the respiratory and gastrointestinal tracts *(116,117)*. Vitamin A may also boost immune function *(118,119)*. Preterm infants are born with low cord blood and liver storage of vitamin A *(117)*. Supplementation with vitamin A has been reported to reduce bronchopulmonary dysplasia in studies of very preterm infants (born before 32 weeks' gestation) *(116,120,121)*.

Summary of the evidence

OVERVIEW	A.10d Vitamin A supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Vitamin A supplementation **Comparator** – No vitamin A supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Vitamin A supplementation versus no vitamin A supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of RCTs of "low" daily dose (< 10 000 IU/day) enteral vitamin A supplementation for preterm and/or LBW infants, which included four trials and 800 participants from three countries (China, India and the United Kingdom) *(122)*. All infants in the included trials had gestational age below 32 weeks or birth weight below 1.5 kg and most were born before 28 weeks' gestation (extremely preterm) or with birth weight below 1.0 kg (extremely LBW). Doses ranged from 1500 to 10 000 IU/day and initiation of supplementation was between 1 and 4 days of age in the trials. Two trials provided supplementation until 28 days after birth while the other two trials continued until 34–36 weeks PMA.

Critical outcomes

For vitamin A supplementation compared with no vitamin A supplementation, four trials reported all-cause mortality, five reported morbidity (4 reported bronchopulmonary dysplasia, 1 pneumothorax, 1 pulmonary haemorrhage, 4 retinopathy

of prematurity, 2 patent ductus arteriosis, 1 periventricular leukomalacia, 3 sepsis, 1 seizures, 3 necrotizing enterocolitis, 2 intraventricular haemorrhage) and one reported growth (weight gain). No trials reported neurodevelopment. (Full details are provided in GRADE Table A.10d, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from four trials totalling 800 participants suggests a decrease in all-cause mortality at latest follow-up (mean 10.3 weeks) (RR 0.74, 95% CI 0.53 to 1.02).
- **Morbidity:** Low-certainty evidence from four trials totalling 746 participants suggests a decrease in bronchopulmonary dysplasia at latest follow-up (mean 11.75 weeks) (RR 0.77, 95% CI 0.50 to 1.16). Low-certainty evidence from one trial with 154 participants suggests a decrease in pneumothorax at latest follow-up (10 weeks) (RR 0.75, 95% CI 0.46 to 1.21). Low-certainty evidence from one trial with 154 participants suggests a decrease in pulmonary haemorrhage at latest follow-up (10 weeks) (RR 0.60, 95% CI 0.30 to 1.21). Low-certainty evidence from four trials totalling 742 participants suggests a decrease in retinopathy of prematurity at latest follow-up (mean 11.75 weeks) (RR 0.69, 95% CI 0.37 to 1.30). Low-certainty evidence from two trials totalling 350 participants suggests a decrease in patent ductus arteriosus at latest follow-up (mean 7 weeks) (RR 0.66, 95% CI 0.21 to 2.06). Low-certainty evidence from one trial with 262 participants suggests a decrease in periventricular leukomalacia at latest follow-up (17 weeks) (RR 0.66, 95% CI 0.38 to 1.14). Low-certainty evidence from three trials totalling 646 participants suggests little to no effect on sepsis at latest follow-up (mean 12.3 weeks) (RR 0.87, 95% CI 0.64 to 1.19). Low-certainty evidence from one trial with 154 participants suggests little to no effect on seizures at latest follow-up (10 weeks) (RR 0.82, 95% CI 0.54 to 1.25). Very-low-certainty evidence from three trials totalling 604 participants suggests little to no effect on necrotizing enterocolitis at latest follow-up (mean 12.3 weeks) (RR 1.05, 95% CI 0.71 to 1.51). Very-low-certainty evidence from two trials totalling 450 participants suggests little to no effect on intraventricular haemorrhage at latest follow-up (mean 13.5 weeks) (RR 1.00, 95% CI 0.46 to 2.17).
- **Growth:** Low-certainty evidence from one trial with 188 participants suggests little to no effect on weight gain at latest follow-up (by hospital discharge or 16 weeks) (MD 0.02, 95% CI -0.2 to 0.24).

Other outcomes

There was a decrease in length of hospital stay (mean 6.3 weeks) (MD -8.76, 95% CI -32.1 to 14.58; 2 trials, 450 participants) and an increase in serum retinol concentration (measured in µg/ml) at latest follow-up (mean 8 weeks) (MD 4.7, 95% CI 1.2 to 8.2; 1 trial, 36 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value vitamin A supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common methods of providing enteral vitamin A for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group) in 30–50 ml bottles. Many formulations contain 1000–5000 IU vitamin A per 0.45–0.6 ml. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing vitamin A supplements to preterm or LBW babies.

Summary of judgements

Comparison: Vitamin A supplementation vs no vitamin A supplementation (A.10d)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of small benefit: decreased mortality *(moderate-certainty evidence)*, decreased bronchopulmonary dysplasia, pneumothorax, pulmonary haemorrhage, retinopathy of prematurity, patent ductus arteriosis and periventricular leukomalacia *(low-certainty evidence)* • No evidence of harm • Evidence of little or no effect on sepsis, seizures, weight *(low-certainty evidence)* and on necrotizing enterocolitis and intraventricular haemorrhage *(very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary	
Benefits	Small or trivial to none
Harms	Trivial or none
Certainty	Low
Balance	Probably favours vitamin A supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Feasible
Equity	Probably equitable

A.10e Calcium and phosphorous supplementation

Recommendation and remarks

NO RECOMMENDATION

Remark

- The GDG decided not to make a recommendation on calcium or phosphorous supplementation as there was little evidence of benefits or harms on any critical outcome.

Background and definitions

Preterm and LBW infants have low skeletal stores of calcium and phosphorus *(123)*. Previous systematic reviews have reported that calcium and phosphorous supplements given to human-milk-fed preterm or LBW infants had no effect on growth (weight, length, head circumference) but improved bone biomarkers (serum alkaline phosphatase) *(123,124)*. No effects have been reported on mortality, morbidity or neurodevelopment and no evidence was found on the optimal dose or timing of initiation.

Summary of the evidence

OVERVIEW	A.10e Calcium and phosphorous supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Calcium and phosphorous supplementation **Comparator** – No calcium and phosphorous supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Calcium and phosphorous supplementation versus no calcium or phosphorous supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of three trials (2 RCTs and 1 non-randomized trial) reporting on a total of 162 preterm and/or LBW infants from two countries (the Islamic Republic of Iran and the United Kingdom) *(125)*. Most babies in the trials had birth weight below 1.5 kg and/or had been born before 32 weeks' gestation. Two trials assessed the effect of phosphorus supplementation only (dose of 15 mg/kg per day in 1 trial and 25 mg/kg per day in 1 trial) and the third trial assessed the effect of supplementation with calcium and phosphorous combined (calcium 45 mg/kg per day, phosphorus 25 mg/kg per day). All three trials gave supplements enterally, via naso- or orogastric tubes. Supplementation commenced between birth and 10 days chronological age in all three trials. The duration of supplementation was between 10 and 42 days in one trial and it could not be assessed in the other two.

Critical outcomes

For calcium and phosphorous supplementation compared with no calcium or phosphorous supplementation, three trials reported morbidity (2 reported rickets, 1 osteopenia) and one trial reported growth (length and head circumference). No trials reported all-cause mortality or neurodevelopment, and no trials reported on serious adverse events. (Full details are provided in GRADE Table A.10e, in the Web Supplement.)

Morbidity: Very-low-certainty evidence from three trials totalling 159 participants suggests a decrease in osteopenia or rickets at latest follow-up (mean 38.3 weeks) (RR 0.68, 95% CI 0.46 to 0.99).

Growth: Very-low-certainty evidence from one trial with 40 participants suggests little to no effect on weight (in grams) at 6 weeks of age (MD 138.5, 95% CI -82.16 to 359.16). Very-low-certainty evidence from one trial with 40 participants suggests little to no effects on length (in centimetres) at 6 weeks of age (MD 0.77, 95% CI -0.92 to 2.46). Very-low-

certainty evidence from one trial with 40 participants suggests little to no effect on head circumference (in centimetres) at 6 weeks of age (MD 0.33, 95% CI -0.3 to 0.96).

Other outcomes

There was little or no effect on serum alkaline phosphatase (IU/L) at 6 weeks of age (MD -126.11, 95% CI -298.5 to 46.27; 2 trials, 122 participants), serum calcium (mg/dl) at 6 weeks of age (MD 0.54, 95% CI -0.19 to 1.27; 1 trial, 40 participants), or serum phosphorus (IU/L) at 6 weeks of age (MD 0.07, 95% CI -0.22 to 0.36; 1 trial, 40 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value calcium and phosphorous supplements for their preterm or LBW baby or whether they find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common methods of providing enteral calcium and phosphorous for preterm and LBW infants include a 5 ml suspension containing 125 mg of calcium, 55 mg of phosphorus and 200 IU of vitamin D, which is given three times a day at a dose of 2 ml/kg. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing calcium and phosphorous supplements to preterm or LBW babies.

Summary of judgements

Comparison: Calcium and phosphorous supplementation vs no calcium or phosphorous supplementation (A.10e)	
Justification	• Evidence of small benefit: decreased osteopenia, rickets *(very-low-certainty evidence)* • Evidence of little or no effect on weight, length, head circumference *(very-low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Unknown
Harms	Unknown
Certainty	Very low
Balance	Does not favour calcium and phosphorous supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

A.10f Multiple micronutrient (MMN) supplementation

Recommendation and remarks

NO RECOMMENDATION

Remark

- The GDG decided not to make a recommendation on MMN supplementation as there was no evidence of benefits or harms on any critical outcome.

Background and definitions

Many health workers advise families to give MMN supplements to human-milk-fed preterm and LBW infants *(76,123)*. The supplements commonly include A, D, E, B group vitamins, and some contain iron, zinc, folate and magnesium *(56)*. However, there has been no systematic review of the effect of MMN supplements on health and developmental outcomes in preterm and LBW infants.

Summary of the evidence

OVERVIEW	A.10f MMN supplementation
PICO	**Population** – Preterm or LBW infants who are fed mother's own milk or donor human milk **Intervention** – Enteral MMN supplementation **Comparator** – No MMN supplementation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – MMN supplementation versus no MMN supplementation

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of the effectiveness of MMNs defined as three or more micronutrients (vitamins A, D, E, B group, iron, zinc, folate or magnesium). Two RCTs were included, which enrolled a total of 414 preterm or LBW infants from two countries (Mexico and the United Republic of Tanzania) *(126)*. The United Republic of Tanzania trial recruited 339 preterm or LBW infants. The Mexico trial recruited 75 preterm or LBW infants. The United Republic of Tanzania trial intervention was vitamin C, E, B group, folate and vitamin B12, which was compared with no MMN in the control group. The Mexico trial gave the same nutrients to the intervention group plus zinc, magnesium, vitamin D, vitamin A and iron, and compared this with vitamin A and iron in the control group. The United Republic of Tanzania trial initiated supplementation at 66 weeks of age and continued until 18 months of age, while the Mexico trial started supplementation at 3 months, continuing until 24 months of age.

Critical outcomes

For enteral MMN supplementation compared with no MMN supplementation, two trials reported growth outcomes (weight-for-height z score [WHZ], HAZ, WAZ) and one trial reported neurodevelopmental outcomes (cognition, receptive language, expressive language, fine motor, gross motor). No trials reported mortality or morbidity outcomes, and no trials reported on serious adverse events. (Full details are provided in GRADE Table A.10f, in the Web Supplement.)

- **Growth:** Low-certainty evidence from two trials totalling 398 participants suggests little or no effect on wasting (WHZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 0.86, 95% CI 0.50 to 1.48). Low-certainty evidence from two trials totalling 399 participants suggests little or no effect on stunting (HAZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 1.17, 95% CI 0.83 to 1.66). Low-certainty evidence from two trials totalling

396 participants suggests little or no effect on underweight (WAZ < -2 SD) at latest follow-up (mean 91 weeks) (RR 1.22, 95% CI 0.85 to 1.22). There was also little or no effect on change in WHZ, HAZ or WAZ scores from baseline to endline in the studies.

- **Neurodevelopment:** At latest follow-up, very-low-certainty evidence from one trial with 27 participants suggests little or no effect on: cognition scores (78 weeks) (MD 2.64, 95% CI -0.48 to 5.67); receptive language scores (78 weeks) (MD 1.19, 95% CI -0.33 to 2.71); expressive language scores (78 weeks) (MD 0.94, 95% CI -1.13 to 3.01); fine motor scores (78 weeks) (MD 1.03, 95% CI -1.13 to 3.19); and gross motor scores (78 weeks) (MD 1.14, 95% CI -0.56 to 2.84). All of these neurodevelopment outcomes were measured using BSID-III.

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials reporting on any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting nutrition, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. There was no specific evidence available about whether families value MMN supplements for their preterm or LBW baby or find them acceptable.

Resources required and implementation considerations

Organization of care

The supplements can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common methods of providing enteral MMN supplements for preterm and LBW infants include infant multivitamin formulations (e.g. vitamins D, A, C, B group with added iron) in 30–50 ml bottles. Droppers or syringes can be used to administer the supplement to the infant. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing MMN supplements to preterm or LBW babies.

Summary of judgements

Comparison: MMN supplementation vs no MMN supplementation (A.10f)	
Justification	• Evidence of little or no effect on weight, length and neurodevelopment *(low- to very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary	
Benefits	Unknown
Harms	Unknown
Certainty	Low to very low
Balance	Does not favour MMN supplementation
Values	Uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

A.11 PROBIOTICS

Recommendation and remarks

RECOMMENDATION A.11 (NEW)

Probiotics may be considered for human-milk-fed very preterm infants (< 32 weeks' gestation).
(Conditional recommendation, moderate-certainty evidence)

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there are many infant probiotic formulations available in the public domain that have variable quality control and formulation *(127,128)*.
- The GDG considered that only probiotics especially formulated for preterm or LBW infants that meet regulatory standards should be used, and clear instructions for safe use should be given to health workers.
- The GDG did not make a recommendation for infants born after 32 weeks' gestation because the data were insufficient.
- Only five trials (254 participants) included infants fed formula as the sole diet, so the GDG did not make a recommendation for these infants.
- The GDG was not able to make a recommendation on type (i.e. genera, species or strain), formulation (e.g. powder or drops), dose, timing or duration of probiotic administration as there was insufficient evidence. The GDG considered that type, formulation, dose, timing and duration should be based on clinical judgement.

Background and definitions

Probiotics are formulations given by the enteral route that contain bacteria (e.g. *Bifidobacterium* spp. or *Lactobacillus* spp.) or fungi (e.g. *Saccharomyces* spp.) *(129,130)*. A range of probiotic supplements are available commercially. Probiotics colonize the mucosal surface of the human gastrointestinal tract, modulate the intestinal microbiome and promote mucosal barrier functions *(129,130)*. Probiotics have been used to prevent and treat infectious or inflammatory gastrointestinal conditions primarily in adults, with only low-certainty evidence of any benefit for most conditions *(131-133)*. There have also been many trials of probiotics in preterm and LBW infants in the last 10 years showing varying effects, including reductions in sepsis and necrotizing enterocolitis *(134-137)*, but also increases in bacteraemia and fungaemia *(134,138,139)*.

Summary of the evidence

OVERVIEW	A.11 Probiotics
PICO	**Population** – Preterm or LBW infants **Intervention** – Any probiotics **Comparator** – No probiotics **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Probiotic species (*Bifidobacterium* spp., *Lactobacillus* spp., other spp.) • Type of enteral feed (human milk, formula, mixed)

Effectiveness: Comparison – Any probiotics versus no probiotics

Sources and characteristics of the evidence

The effectiveness evidence was derived from a Cochrane systematic review of 56 trials totalling 10 812 very preterm (< 32 weeks' gestation) or VLBW infants (< 1.5 kg) *(127)*. An updated search conducted on 1 October 2021 located no new trials.

The average birth weight was 1.0–1.2 kg and average gestation at birth was 28–32 weeks. Four trials excluded infants who were born with birth weight below the 10th percentile for the reference population (i.e. small for gestational age, or SGA). Most trials were conducted during the past 20 years (4 trials were conducted pre-2000). The trials were from 21 countries (Australia, Bangladesh, Brazil, China, France, Germany, Greece, India, the Islamic Republic of Iran, Israel, Italy, Japan, Mexico, Pakistan, Poland, Slovenia, South Africa, Thailand, Türkiye, the United Kingdom and the USA). Fifty-five trials were individually randomized and one was cluster randomized. Twenty-one trials enrolled fewer than 100 participants, 20 enrolled 100–199, 12 enrolled 200–499 participants and 3 enrolled 500 participants or more. In most trials, participating infants were given human milk or formula feeding. Seven trials enrolled infants who received human milk only and five enrolled only formula-fed participants. The probiotic preparations varied, though were mostly lyophilized (freeze dried) or liquid commercially available products supplied by the manufacturer for use in the trial. Thirty-three trials used single-genus probiotics (most commonly, *Bifidobacterium* spp. or *Lactobacillus* spp.) and 23 used multi-genus combinations (most commonly, *Bifidobacterium* spp. plus *Lactobacillus* spp.). Most trials initiated supplementation during the first week after birth, typically with the first enteral feed. In most trials, the intervention period was at least six weeks, typically lasting until discharge from hospital. Eleven of the trials administered the intervention for a shorter period (7–30 days). One trial continued the intervention until the infant reached 2.0 kg body weight.

Critical outcomes

For probiotics compared with no probiotics, 51 trials reported all-cause mortality, 54 reported morbidity (54 reported necrotizing enterocolitis, 47 culture-confirmed infection) and 6 reported neurodevelopment (severe neurodevelopmental impairment). No trials reported growth. (Full details are provided in GRADE Table A.11, in the Web Supplement.)

- **Mortality**: Moderate-certainty evidence from 51 trials totalling 10 170 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.76, 95% CI 0.65 to 0.89).
- **Morbidity:** Low-certainty evidence from 54 trials totalling 10 604 participants suggests a decrease in necrotizing enterocolitis by hospital discharge (RR 0.54, 95% CI 0.45 to 0.65). Moderate-certainty evidence from 47 trials totalling 9762 participants suggests a decrease in invasive infection by hospital discharge (RR 0.89, 95% CI 0.82 to 0.97).
- **Neurodevelopment:** Low-certainty evidence from five trials totalling 1518 participants suggests little or no effect on neurodevelopment (severe neurodevelopmental impairment assessed using a validated test) between 18 months and 3 years (RR.1.03, 95% CI 0.84 to 1.26).

Other outcomes

There was a decrease in length of hospital stay (in days) (MD -1.93, 95% CI -3.78 to -0.08; 22 trials, 5458 infants).

Subgroup analyses

Subgroup differences for growth and neurodevelopment could not be assessed as there were insufficient studies. No difference was found for mortality, necrotizing enterocolitis or sepsis for any of the subgroups: gestational age and birth weight, probiotic species or type of enteral feed.

Other studies

Eight studies (3080 participants) recruited infants with gestational age 32–36 weeks (mean 33 weeks (SD 4 weeks) and showed decreases in all-cause mortality (RR 0.50, 95% CI 0.43 to 1.17; 4 trials, 2334 participants, low-certainty evidence), necrotizing enterocolitis (RR 0.32, 95% CI 0.16 to 0.66; 6 trials, 1493 participants, low-certainty evidence), sepsis (RR 0.50, 95% CI 0.29 to 0.85; 6 trials, 2708 participants, low-certainty evidence) and neurodevelopmental impairment (RR 0.48, 95% CI 0.29 to 0.80; 1 trial, 249 participants, very-low-certainty evidence).

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, and want to take an active role in deciding what interventions are given to infants, including what and how they are fed *(14)*. A study from the United Kingdom reported that families are willing to consider use of probiotics for their preterm or LBW infants if there is evidence of benefit and safety *(140)*. There was no other specific evidence available about whether families value probiotic supplements for their preterm or LBW baby or find them acceptable.

Resources required and implementation considerations

Organization of care

Probiotics can be provided in the health-care facility or at home. The family needs accurate information on the dose and how to administer the supplement. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Common probiotic preparations are either single-genus or multi-genus probiotic combinations (including *Bifidobacterium* spp. plus *Lactobacillus* spp). Dosing, amounts, frequency and duration vary. Probiotics can be provided as powder or liquids in bottles or mixed with infant milk or sterile water. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of providing probiotics to preterm or LBW babies.

Summary of judgements

Comparison: Any probiotics vs no probiotics (A.11)	
Justification	In trials where most participants are very preterm (< 32 weeks' gestation) or VLBW (< 1.5 kg): • Evidence of moderate benefit: decreased mortality, necrotizing enterocolitis and invasive infection *(moderate-certainty evidence)* • No evidence of harms • Evidence of little or no effect on neurodevelopment *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Probably favours probiotics
Values	No uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Varies
Equity	Varies

A.12 EMOLLIENTS

Recommendation and remarks

RECOMMENDATION A.12 (NEW)

Application of topical oils to the body of preterm or low-birth-weight infants may be considered.
(Conditional recommendation, moderate-certainty evidence)

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that there were limited data on the type, dose, timing of initiation and duration of oil use. Based on most of the trials included in the evidence review, the GDG suggested that sunflower or coconut oils may be used and that initiation and duration of use may be based on clinical judgement. The GDG also felt that application of oils should be done gently to avoid disrupting skin integrity.
- The GDG decided not to make a recommendation on the use of ointments or creams due to little or no effect on mortality and morbidity (invasive infection, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity) and no evidence on other critical outcomes.

Background and definitions

Emollients are moisturizing treatments applied topically, i.e. directly to the skin. They include ointments (water-in-oil suspensions), creams (oil-in-water suspensions) and natural vegetable or plant topical oils (e.g. sunflower and coconut oils). The skin of preterm infants is developmentally immature *(141,142)* and can be easily abraded, which can allow entry of pathogenic organisms *(143)*. Topical emollients can improve skin integrity and barrier (protective) functions but they can also disrupt skin integrity, remove normal flora and microorganisms and increase colonization with other microorganisms *(142)*. Emollients also contain fatty acids and other fluids that can be absorbed through the skin *(141)*. However, there have been no recent systematic reviews of the effectiveness of topical ointments, creams or oils in preterm and LBW infants.

Summary of the evidence

OVERVIEW	A.12a Topical oil	A.12b Topical ointment or cream
PICO	**Population** – Preterm and LBW infants **Intervention 1** – Topical oil **Comparator 1** – No topical oil **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up	**Population** – Preterm and LBW infants **Intervention 2** – Topical ointment or cream **Comparator 2** – No topical ointment or cream **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)	

Effectiveness: Comparison 1 – Topical oil versus no topical oil

Sources and characteristics of the evidence

For this comparison, the effectiveness evidence was derived from a systematic review of 15 RCTs enrolling a total of 3718 infants *(144)* from nine countries (Bangladesh, Brazil, Egypt, France, Germany, India, the Islamic Republic of Iran and Pakistan). All trials used natural vegetable or plant oils: sunflower (8 trials), coconut (4 trials), and soybean, almond, vegetable and olive oil (1 trial each). The population was very preterm babies (< 32 weeks' gestation) in three trials. The intervention generally commenced within a few days of birth and continued until about 1–4 weeks chronological age or until hospital discharge. The oils were applied 2–6 times each day onto the whole skin surface (except the face and head) by the family or health worker.

Critical outcomes

For topical oil compared with no topical oil, 11 trials reported all-cause mortality, 9 reported morbidity (9 reported invasive infection, 1 necrotizing enterocolitis, 1 bronchopulmonary dysplasia, 1 retinopathy of prematurity), 7 reported growth (7 weight gain, 6 length, 6 head circumference) and 1 reported neurodevelopment (cognitive, language, motor and socioemotional outcomes [BSID-III]). No trials reported on serious adverse events. (Full details are provided in GRADE Table A.12a, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from 11 trials totalling 1119 participants suggests little to no effect on all-cause mortality by hospital discharge (RR 0.94, 95% CI 0.82 to 1.08).
- **Morbidity:** Low-certainty evidence from nine trials totalling 3256 participants suggests a decrease in invasive infection by hospital discharge (RR 0.71, 95% CI 0.52 to 0.96). Very-low certainty evidence from one trial with 72 participants suggests a decrease in necrotizing enterocolitis by hospital discharge (RR 0.20, 95% CI 0.01 to 4.03). Very-low-certainty evidence from one trial with 72 participants suggests little to no effect on bronchopulmonary dysplasia at 26 weeks PMA (RR 0.93, 95% CI 0.53 to 1.64). Very-low-certainty evidence from one trial with 72 participants suggests little to no effect on retinopathy of prematurity by hospital discharge (RR 1.00, 95% CI 0.27 to 3.69).
- **Growth:** Low-certainty evidence from seven trials totalling 433 participants suggests an increase in the rate of weight gain (in grams per kilogram per day) by hospital discharge (MD 2.93, 95% CI 2.11 to 3.76). Moderate-certainty evidence from six trials totalling 358 participants suggests an increase in crown–heel length (millimetres per week) by hospital discharge (MD 1.34, 95% CI 0.2 to 2.74). Low-certainty evidence from six trials totalling 358 participants suggests little to no effect on change in head circumference (in millimetres per week) by hospital discharge (MD 0.66, 95% CI 0.54 to 1.85).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with 51 participants suggests little to no effect on cognitive developmental delay at 24 months of age (RR 0.25, 95% CI 0.06 to 1.11). Very-low-certainty evidence from one trial with 51 participants suggests little to no effect on language developmental delay at 24 months of age (RR 0.48, 95% CI 0.21 to 1.11). Very-low-certainty evidence from one trial with 51 participants suggests little to no effect on motor developmental delay at 24 months of age (RR 0.25, 95% CI 0.06 to 1.11). Very-low-certainty evidence from one trial with 51 participants suggests little to no effect on socio-emotional developmental delay at 24 months of age (RR 0.30, 95% CI 0.07 to 1.33). All neurodevelopmental outcomes were measured using BSID-III.

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Other studies

One additional trial also reported a decrease in infection-specific mortality by 28 days of age (adjusted odds ratio 0.72, 95% CI 0.39 to 1.34; 1 trial, 103 participants) and a decrease in nosocomial infections by 28 days of age (adjusted incidence ratio 0.46, 95% CI 0.26 to 0.81; 1 trial, 103 participants) *(145)*.

Effectiveness: Comparison 2 – Topical ointment or cream versus no topical ointment or cream

Sources and characteristics of the evidence

For the second comparison, the effectiveness evidence was derived from a systematic review of eight RCTs including 2086 preterm or LBW infants from five countries *(144)* (Austria, Bangladesh, Saudi Arabia, Türkiye and the USA). Most trials enrolled very preterm babies born at gestational ages up to 30 weeks while others enrolled babies born before 31 weeks (1 study), before 33 weeks (3 studies), before 34 weeks (1 study) or up to 36 weeks' gestation (2 studies). The trials used commercially available ointments or creams. The intervention generally commenced within a few days after birth and continued until about 1–4 weeks postnatal age or until hospital discharge. The ointments or creams were applied 2–6 times each day onto the whole skin surface (except the face and head) by the family or health worker.

Critical outcomes

For topical ointment or cream compared with no topical ointment or cream, seven trials reported all-cause mortality and eight reported morbidity (8 reported invasive infection, 4 necrotizing enterocolitis, 2 bronchopulmonary dysplasia, 1 retinopathy of prematurity). Growth and neurodevelopment outcomes were not reported. (Full details are provided in GRADE Table A.12b, in the Web Supplement.)

- **Mortality**: Low-certainty evidence from seven trials totalling 2067 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.87, 95% CI 0.75 to 1.03).
- **Morbidity:** Low-certainty evidence from eight trials totalling 2086 participants suggests little or no effect on invasive infection (at least one infection with any organism) by hospital discharge (RR 1.13, 95% CI 0.97 to 1.31). Low-certainty evidence from four trials totalling 1472 participants suggests little or no effect on necrotizing enterocolitis by hospital discharge (RR 1.25, 95% CI 0.89 to 1.76). Low-certainty evidence from two trials totalling 1009 participants suggests little or no effect on bronchopulmonary dysplasia by hospital discharge (RR 1.00, 95% CI 0.88 to 1.14). Very-low-certainty evidence from one trial with 952 participants suggests little or no effect on retinopathy of prematurity by hospital discharge (RR 0.99, 95% CI 0.77 to 1.28).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, and want to take an active role in deciding what interventions are given to infants, including what and how they receive skin care *(14)*. There was no specific evidence available about whether families value emollients for their preterm or LBW baby or find them more or less acceptable.

Resources required and implementation considerations

Organization of care

Emollients can be provided in the health-care facility or at home. They can be spread gently over the infant's abdomen, back and limbs. The family needs accurate information on how to apply the emollients gently. National or local guidance for health-care facilities should be used.

Infrastructure, equipment and supplies

Emollient preparations include sunflower and coconut oils. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

There was no specific evidence available about the feasibility and equity of topical emollient application for preterm or LBW babies.

Summary of judgements

	Comparison 1. Topical oil vs no topical oil (A.12a)	Comparison 2. Topical ointment or cream vs no topical ointment or cream (A.12b)
Justification	• Evidence of moderate benefits: decreased severe infection *(low-certainty evidence)*, increased weight *(low-certainty evidence)* and increased length *(moderate-certainty evidence)* • No evidence of harms • Evidence of little or no effect on: mortality *(low-certainty evidence)*, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity *(low-certainty evidence)*, head circumference *(low-certainty evidence)* and neurodevelopment *(very-low-certainty evidence)* • No evidence on other critical outcomes	• Evidence of little or no effect on all-cause mortality, invasive infection, necrotizing enterocolitis, bronchopulmonary dysplasia and retinopathy of prematurity *(low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary		
Benefits	Moderate	Trivial or none
Harms	Trivial or none	Trivial or none
Certainty	Low	Low
Balance	Probably favours topical oils	Does not favour ointments or creams
Values	No uncertainty or variability about outcomes	No uncertainty or variability about outcomes
Acceptability	Probably yes	Probably yes
Resources	Low to moderate	Low to moderate
Feasibility	Probably yes	Varies
Equity	Probably equitable	Probably equitable

B. Care for complications

B.1 CONTINUOUS POSITIVE AIRWAY PRESSURE FOR RESPIRATORY DISTRESS SYNDROME

Recommendation and remarks

RECOMMENDATION B.1 (UPDATED)

Continuous positive airway pressure (CPAP) therapy is recommended in preterm infants with clinical signs of respiratory distress syndrome. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that the evidence on harms (increased pneumothorax) was of uncertain clinical significance and the overall certainty of the body of evidence was low due to imprecision and indirectness.
- The GDG noted that there were limited data on the timing of initiation and duration of CPAP. Based on most of the trials included in the evidence review, the GDG suggests that CPAP may be considered as soon as the diagnosis of respiratory distress syndrome (RDS) is clinically suspected, and that duration should be based on clinical judgement.
- The GDG also noted that CPAP implementation must be done with skilled staff, quality equipment and quality consumables (including humidified blended oxygen–air and monitors).
- The GDG decided not to make a separate recommendation on the timing of CPAP for infants with RDS.

Background and definitions

Respiratory distress syndrome (RDS) is a major cause of morbidity and mortality in preterm infants *(146)*. RDS commonly develops in the first hours after birth and develops or "becomes established" over the first few days after birth *(146-148)*. Until the 1970s, initial therapy for RDS was traditionally oxygen given through a head box or nasal prongs, and infants with severe disease received mechanical ventilation.

Continuous positive airway pressure (CPAP) involves connecting a nasal "interface" (prongs, face mask or head box) via tubing to a pressure source with an air–oxygen mix *(149,150)*. CPAP provides distending pressure into the upper and lower airways preventing collapse, especially during expiration. CPAP devices were adapted for use in preterm babies in the 1970s and CPAP is now routinely used for preterm babies with RDS in many health-care facilities globally.

Summary of the evidence

OVERVIEW	B.1a Any CPAP	B.1b Early CPAP
PICO	**Population** – Preterm infants with RDS **Intervention 1** – Any CPAP **Comparator 1** – Usual supplemental oxygen therapy by head box, face mask or nasal cannula **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up	**Population** – Preterm infants with RDS **Intervention 2** – Early CPAP **Comparator 2** – Delayed CPAP **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – From birth **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)	

Effectiveness: Comparison 1 – Any CPAP versus supplemental oxygen

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a Cochrane systematic review of five RCTs conducted in the 1970s and 1980s reporting on a total of 322 preterm infants *(151)*. An updated search conducted on 1 October 2021 located no new trials.

Four studies were conducted in high-income settings (Australia, the United Kingdom and the USA) and one in a low-resource setting (the United Republic of Tanzania). Infants were included if they had RDS (defined as an infant needing FiO_2 [fraction of inspired oxygen] > 0.30). All trials used traditional CPAP as the intervention, none used "bubble" or newer types of CPAP. The comparator in all the trials was supplemental oxygen. No infants received mechanical ventilation in the control group. The mean age at study entry ranged from 10 to 150 hours post-birth. The mean birth weight of infants was 1.7–2.0 kg, with two trials excluding infants weighing less than 1.0 kg at birth.

Critical outcomes

For any CPAP compared with supplemental oxygen for RDS, five trials reported all-cause mortality outcomes, five trials reported morbidity (3 reported use of mechanical ventilation, 5 "failed treatment", 4 pneumothorax, 2 bronchopulmonary dysplasia). No trials reported growth or neurodevelopment outcomes. (Full details are provided in GRADE Table B.1a, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from five trials totalling 322 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.53, 95% CI 0.34 to 0.83).
- **Morbidity:** Very-low-certainty evidence from three trials totalling 233 participants suggests a decrease in the use of mechanical ventilation by hospital discharge (RR 0.72, 95% CI 0.54 to 0.96). Very-low-certainty evidence from five trials totalling 322 participants suggests a decrease in "failed treatment" (a composite outcome of death or the use of mechanical ventilation) by hospital discharge (RR 0.64, 95% CI 0.50 to 0.82). Low-certainty evidence from four trials totalling 270 participants suggests an increase in pneumothorax by hospital discharge (RR 2.48, 95% CI 1.16 to 5.30). Very-low-certainty evidence from two trials totalling 209 participants suggests little or no effect on bronchopulmonary dysplasia (defined as oxygen dependency at 28 days) by 36 weeks PMA (RR 1.04, 95% CI 0.35 to 3.13).

Other outcomes

One trial reported a decrease in the composite outcome of death or abnormal blood gases by hospital discharge (RR 0.53, 95% CI 0.32 to 0.90; 1 trial, 24 infants). One trial reported a decrease in the outcome of "transfer to an NICU" by hospital discharge (RR 0.49, 95% CI 0.30 to 0.78; 1 trial, 24 infants). One trial reported a decrease in the duration of oxygen therapy by hospital discharge (MD 0.20 days, 95% CI –2.47 to 2.87; 1 trial, 24 infants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Effectiveness: Comparison 2 – Early versus delayed CPAP

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a systematic review of four trials (2 RCTs and 2 quasi-RCTs) that recruited 119 preterm infants with RDS (mean birth weight 1.5–2.1 kg, mean gestational age 31–34 weeks) conducted in the United Kingdom and the USA in the 1970s or the early 1980s *(152)*. An updated search conducted on 1 October 2021 located no new trials. Infants were eligible for inclusion if they were given a diagnosis of RDS (based on clinical and radiological criteria) and were breathing spontaneously. Infants were randomized to receive CPAP immediately as soon as the diagnosis of RDS was made ("early group") or for treatment to be delayed until deterioration as defined by the study ("delayed group"). The early CPAP group received CPAP at a mean age of 7–18 hours post-birth and required FiO_2 0.30 to 0.60. The delayed CPAP group required FiO_2 from 0.60 to 1.0 but the mean age of receipt of CPAP was not stated in any trial.

Critical outcomes

For early compared with delayed CPAP for RDS, four trials reported all-cause mortality, four trials reported morbidity (4 reported the use of mechanical ventilation, 3 pneumothorax, 1 bronchopulmonary dysplasia). No trials reported growth or neurodevelopment outcomes. (Full details are provided in GRADE Table B.1b, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from four trials totalling 119 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.93, 95% CI 0.43 to 2.03).
- **Morbidity:** Very-low-certainty evidence from four trials totalling 119 participants suggests a decrease in the use of mechanical ventilation by hospital discharge ((RR 0.77, 95% CI 0.43 to 1.38). Low-certainty evidence from two trials totalling 98 participants suggests little or no effect on pneumothorax (RR 1.09, 95% CI 0.39 to 3.04). Very-low-certainty evidence from one trial with 29 participants suggests an increase in bronchopulmonary dysplasia at 36 weeks PMA (RR 1.42, 95% CI 0.10 to 20.49).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Other studies

Two studies assessing the effect of continuous negative pressure *(153,154)* were included in the previous Cochrane review *(155)* but not in the updated Cochrane review *(152)*, due to a change in the PICO intervention from negative pressure to continuous positive airway pressure (CPAP). The Cochrane review also excluded two RCTs *(156,157)* because they provided very early CPAP at 5 minutes of age, which was considered to be earlier that RDS could be established in the babies. These two RCTs were included in the 2021 Cochrane review of prophylactic and very early CPAP by Subramaniam et al. (see Recommendation B.1) *(158)*.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that carers want assistance in interacting with their babies, especially when they are undergoing therapies that make it difficult to have physical contact *(14)*. They want to learn about the health-care setting where they need to stay and care for their baby. They want to understand what medical equipment is being used and why. Studies report that families can find mechanical ventilation and CPAP intimidating and frightening and that these therapies can accentuate their feelings of inadequacy and lack of control over their baby's health care *(147,159)*. Families also worry about the pain and discomfort their baby is experiencing in NICUs *(14)*. No other specific evidence was located about whether families value CPAP rather than supplemental oxygen for their preterm or LBW baby or whether they find CPAP more or less acceptable than other supplemental oxygen.

Resources required and implementation considerations

Organization of care

CPAP for preterm or LBW infants should be done in special or intensive care units (level 2 or 3 facilities).

Infrastructure, equipment and supplies

CPAP devices include a pressure source with an air–oxygen mix . CPAP devices include "bubble" (underwater, water-seal) CPAP, ventilator CPAP and "Infant Flow Driver" CPAP. CPAP also requires an "interface", which is commonly a mask or nasal prongs. Disposable tubes and suction catheters are also needed. National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers who are qualified to work in level 2 (special newborn care units, special care nurseries) and level 3 (intensive care) facilities can support the provision of CPAP. Standardized packages are needed for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing CPAP for preterm or LBW infants.

Summary of judgements

	Comparison 1. Any CPAP vs supplemental oxygen (B1.a)	Comparison 2. Early vs delayed CPAP (B1.b)
Justification	• Evidence of moderate benefits: decreased mortality *(moderate-certainty evidence)*, decreased mechanical ventilation *(very-low-certainty evidence)* and decreased "failed treatment", i.e. death or use of mechanical ventilation *(very-low-certainty evidence)* • Evidence of small harms: increased pneumothorax *(low-certainty evidence)* • Evidence of little or no effect on bronchopulmonary dysplasia *(very-low-certainty evidence)*	• Evidence of small benefits: decrease in use of mechanical ventilation *(very-low-certainty)* • Evidence of small harm: increase in bronchopulmonary dysplasia *(very-low-certainty evidence)* • Evidence of little or no effect on mortality and air leak (pneumothorax) *(low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary		
Benefits	Moderate	Unknown
Harms	Small	Unknown
Certainty	Low	Very low
Balance	Favours CPAP	Unknown
Values	No uncertainty or variability about outcomes	Unknown
Acceptability	Probably yes	Unknown
Resources	Large	Negligible
Feasibility	Varies	Probably feasible
Equity	Varies	Probably equitable

B.2 CONTINUOUS POSITIVE AIRWAY PRESSURE IMMEDIATELY AFTER BIRTH

Recommendation and remarks

RECOMMENDATION B.2 (NEW)

Continuous positive airway pressure (CPAP) therapy may be considered immediately after birth for very preterm infants (< 32 weeks' gestation), with or without respiratory distress. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that duration of CPAP (i.e. when to stop CPAP) should be based on clinical judgement.
- The GDG also noted that skilled staff and quality equipment (including humidified blended oxygen–air) are needed for the administration of CPAP to preterm and LBW infants.

Background and definitions

The benefits of CPAP for RDS in preterm infants are well established *(151,155)*. However, it can be difficult to ascertain respiratory status in preterm babies soon after birth and to accurately predict the prognosis. Preterm babies with respiratory failure may not show signs of respiratory distress in the first hours after birth and babies with early respiratory distress may improve *(147)*. Thus, health workers in NICUs sometimes administer CPAP immediately after birth to all babies at risk, regardless of respiratory status (sometimes called immediate CPAP), rather than assessing for RDS. Benefits and harms of this practice have been unclear *(147,148,150)*. However, recent trials have assessed the effectiveness of immediate CPAP compared with both supplemental oxygen and mechanical ventilation.

Summary of the evidence

OVERVIEW	B.2a Immediate CPAP vs supplemental oxygen	B.2b Immediate CPAP vs mechanical ventilation
PICO	**Population** – Preterm infants immediately after birth **Intervention 1** – CPAP commencing immediately after birth **Comparator 1** – Supplemental oxygen by head box, face mask or nasal cannula **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up	**Population** – Preterm infants immediately after birth **Intervention 2** – CPAP commencing immediately after birth **Comparator 2** – Mechanical ventilation **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Immediately after birth **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • and birth weight (< 1.5 kg, ≥ 1.5 kg)	

Effectiveness: Comparison 1 – Immediate CPAP versus supplemental oxygen

Sources and characteristics of the evidence

For this comparison, the effectiveness evidence was derived from a Cochrane systematic review of four trials enrolling a total of 765 infants under 32 weeks' gestation at birth from seven countries (Argentina, Brazil, Canada, Italy, Paraguay, Peru and Uruguay) *(158)*. An updated search conducted on 1 October 2021 located no new trials. The review found two types of trial: (i) trials that provided CPAP within 15 minutes of birth regardless of respiratory status, and (ii) trials that provided CPAP between 15 and 60 minutes after birth prior to the onset of RDS.

Critical outcomes

For comparison 1, four trials reported all-cause mortality, four reported morbidity (4 reported "failed treatment", 4 bronchopulmonary dysplasia, 1 a composite outcome of death or bronchopulmonary dysplasia, 3 pneumothorax, 2 intraventricular haemorrhage). No trials reported growth or neurodevelopment. (Full details are provided in GRADE Table B.2a, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from four trials totalling 765 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 1.09, 95% CI 0.60 to 1.96).
- **Morbidity:** Very-low-certainty evidence from four trials totalling 765 participants suggests a decreased risk of "failed treatment" (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement, or the need for mechanical ventilation) by hospital discharge (RR 0.60, 95% CI 0.49 to 0.74). Moderate-certainty evidence from three trials totalling 683 participants suggests decreased bronchopulmonary dysplasia by 36 weeks PMA (RR 0.76, 95% CI 0.51 to 1.14). Low-certainty evidence from one trial with 256 participants suggests decreased death or bronchopulmonary dysplasia by 36 weeks PMA (RR 0.69, 95% CI 0.40 to 1.19). Low-certainty evidence from three trials totalling 568 participants suggests decreased pneumothorax by hospital discharge (RR 0.75, 95% CI 0.35 to 1.61). Low-certainty evidence from two trials totalling 486 participants suggests little or no effect on intraventricular haemorrhage grade 3 or 4 by hospital discharge (RR 0.96, 95% CI 0.39 to 2.37).

Other outcomes

Three trials reported a decrease in surfactant use by hospital discharge (RR 0.75, 95% CI 0.58 to 0.96; 3 trials, 683 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Effectiveness: Comparison 2 – Immediate CPAP versus mechanical ventilation

Sources and characteristics of the evidence

For this comparison, the effectiveness evidence was derived from the same Cochrane systematic review *(158)*. Three trials were included, which enrolled a total of 2364 very preterm infants (< 32 weeks' gestation) from 17 countries (Argentina, Australia, Belgium, Brazil, Canada, Chile, France, Germany, Greece, Italy, the Islamic Republic of Iran, New Zealand, Norway, Paraguay, Peru, Uruguay and the USA). An updated search conducted on 1 October 2021 located no new trials. The review included the same two types of trials as described above.

Critical outcomes

For comparison 2, four trials reported all-cause mortality, four trials reported morbidity (4 reported "failed treatment", 3 bronchopulmonary dysplasia, 1 a composite outcome of death or bronchopulmonary dysplasia, 3 pneumothorax, 2 intraventricular haemorrhage) and one trial reported on neurodevelopment (neurodevelopmental impairment). No trials reported growth. (Full details are provided in GRADE Table B.2b, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from three trials totalling 2358 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.82, 95% CI 0.66 to 1.03).
- **Morbidity:** Moderate-certainty evidence from two trials totalling 1042 participants suggests a decrease in risk of "failed treatment" (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement, or the need for mechanical ventilation) by hospital discharge (RR 0.49, 95% CI 0.45 to 0.54). Moderate-certainty evidence from three trials totalling 2150 participants suggests a decrease in bronchopulmonary dysplasia at 36 weeks PMA (RR 0.89, 95% CI 0.80 to 0.99). Moderate-certainty evidence from three trials totalling 2358 participants suggests a decrease in the combined outcome of all-cause mortality and bronchopulmonary dysplasia at 36 weeks PMA (RR 0.89, 95% CI 0.81 to 0.97). Low-certainty evidence from three trials totalling 2357 participants suggests little or no effect on pneumothorax by hospital discharge (RR 1.24, 95% CI 0.91 to 1.69). Moderate-certainty evidence from three trials totalling 2301 participants suggests little or no effect on intraventricular haemorrhage grade 3 or 4 by hospital discharge (RR 1.09, 95% CI 0.86 to 1.39).
- **Neurodevelopment:** Moderate-certainty evidence from one trial with 976 participants suggests little or no effect on neurodevelopmental impairment (defined as cerebral palsy, developmental delay, intellectual impairment, blindness or sensorineural deafness) by 18–22 months of age (RR 0.91, 95% CI 0.62 to 1.32).

Other outcomes

There was decrease in surfactant use (RR 0.60, 95% CI 0.57 to 0.63; 3 trials, 2354 infants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that carers want assistance in interacting with their babies, especially when they are undergoing therapies that make it difficult to have physical contact *(14)*. They want to learn about the health-care setting where they need to stay and care for their baby. They want to understand what medical equipment is being used and why. Studies report that families can find mechanical ventilation and CPAP intimidating and frightening and that these therapies can accentuate their feelings of inadequacy and lack of control over their baby's health care *(147,159)*. Families also worry about the pain and discomfort their baby is experiencing in NICUs *(14)*. No other specific evidence was located about whether families value immediate CPAP for their preterm or LBW baby or whether they find it more or less acceptable than supplemental oxygen.

Resources required and implementation considerations

Please refer to the information on this topic in section B.1.

Feasibility and equity

As described in section B.1, there was no specific evidence on the feasibility and equity of providing CPAP for preterm or LBW infants.

Summary of judgements

	Comparison 1. CPAP immediately after birth for very preterm infants vs supplemental oxygen (B2.a)	**Comparison 2. CPAP immediately after birth for very preterm infants vs mechanical ventilation (B2.a)**
Justification	In trials where most participants are very preterm (< 32 weeks' gestation): • Evidence of small benefits: decreased "failed treatment" (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation), decreased bronchopulmonary dysplasia *(moderate-certainty evidence)* and decreased pneumothorax *(low-certainty evidence)* • No evidence of harms • Evidence of little or no effect on mortality and intraventricular haemorrhage *(moderate-certainty evidence)* • No evidence on other critical outcomes	In trials where most participants are very preterm (< 32 weeks' gestation): • Evidence of moderate benefits: decreased "failed treatment" (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation), decreased bronchopulmonary dysplasia *(moderate-certainty evidence)* • No evidence of harms • Evidence of little or no effect on mortality *(moderate-certainty evidence)* pneumothorax *(low-certainty evidence)*, intraventricular haemorrhage *(moderate-certainty evidence)* and neurodevelopment *(moderate-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary		
Benefits	Small	Moderate
Harms	Trivial or none	Trivial or none
Certainty	Low	Moderate
Balance	Probably favours CPAP immediately after birth for very preterm infants (< 32 weeks' gestation)	Probably favours CPAP immediately after birth for very preterm infants (< 32 weeks' gestation)
Values	No uncertainty or variability about outcomes	Probable uncertainty or variability about outcomes
Acceptability	Varies	Varies
Resources	Vary	Vary
Feasibility	Varies	Varies
Equity	Varies	Varies

B.3 CONTINUOUS POSITIVE AIRWAY PRESSURE SOURCE

Recommendation and remarks

RECOMMENDATION B.3 (NEW)

For preterm infants who need continuous positive airway pressure (CPAP) therapy, bubble CPAP may be considered rather than other pressure sources (e.g. ventilator CPAP). *(Conditional recommendation, low-certainty evidence)*

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- Evidence was derived from trials that compared underwater (water-seal) "bubble" CPAP with mechanical ventilator CPAP or Infant Flow Driver (IFD) CPAP. All trials used commercially available devices and all used humidified blended oxygen–air.
- The GDG noted that the evidence on harms (increased nasal injury) was of uncertain clinical significance and the certainty of the body of evidence was low due to bias and imprecision.
- The GDG suggested that the nasal interfaces (i.e. prongs and cannulas) used with bubble CPAP machines should be carefully selected and that skilled nursing care is needed for the prongs and cannulas.
- The GDG also considered that careful selection, maintenance and monitoring of bubble CPAP devices is needed. Only commercially available bubble CPAP devices should be used; locally-manufactured or locally-adapted bubble CPAP devices should not be used.

Background and definitions

There are many different types of CPAP machines and pressure generation for ventilatory support of preterm infants. There is also considerable variation in practice and differing reports of benefits and harms *(150,160,161)*. The older-style CPAP pressure sources were mechanical ventilators; newer types include Infant Flow Driver (IFD) and bubble CPAP. Bubble CPAP uses an underwater water-seal method and is commonly used for providing CPAP to babies in LMICs *(150,160,161)*.

Summary of the evidence

OVERVIEW	B.3 Continuous positive airway pressure source
PICO	**Population** – Preterm infants with respiratory distress syndrome or post-extubation **Intervention** – Bubble CPAP pressure source **Comparator** – Other CPAP pressure sources (ventilator CPAP or Infant Flow Driver CPAP) **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Immediately after birth **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Bubble CPAP versus other CPAP pressure sources

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 15 RCTs including a total of 1437 preterm infants *(162)*. Most trials were small (median number of participants 88 [IQR 39–140]). They were conducted over the past 25 years in neonatal centres in seven countries (Albania, Armenia, Brazil, India, the Islamic Republic of Iran, Italy and the United Kingdom). The inclusion criteria were infants who required primary treatment for RDS after birth or following a period of mechanical ventilation (post-extubation). Most infants were born before 32 weeks' gestation (very preterm). Thirteen trials included both RDS and post-extubation infants, two trials included infants with RDS only and no trials included post-extubation infants only. All trials compared bubble CPAP with ventilator or IFD CPAP devices. The devices were all commercially manufactured; no locally manufactured or locally adapted devices were used. The interfaces in all trials were short nasal prongs. All infants received standard supportive care (i.e. supplemental oxygen).

Critical outcomes

For bubble CPAP compared with ventilator or IFD nasal CPAP, 10 trials reported all-cause mortality, 14 reported morbidity (13 reported "treatment failure", 14 pneumothorax, 7 bronchopulmonary dysplasia and 8 nasal injury). No trials reported growth or neurodevelopment. (Full details are provided in GRADE Table B.3, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from 10 trials totalling 1189 participants suggests little or no effect on all-cause mortality by hospital discharge (RR 0.93, 95% CI 0.64 to 1.36).
- **Morbidity/adverse events:** Low-certainty evidence from 13 trials totalling 1230 participants suggests a decrease in "treatment failure" (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement, or the receipt of mechanical ventilation within 72 hours after initiation of nasal CPAP) by hospital discharge (RR 0.76, 95% CI 0.60 to 0.95). Low-certainty evidence from 14 trials totalling 1340 participants suggests a decrease in pneumothorax (RR 0.73, 95% CI 0.40 to 1.34). Low-certainty evidence from seven trials totalling 603 participants suggests a decrease in bronchopulmonary dysplasia (oxygen dependency at 28 days) (RR 0.76, 95% CI 0.53 to 1.10). Low-certainty evidence from eight trials of 753 participants suggests an increase in nasal injury (defined as ulceration, bleeding, septal injury and scarring but excluding hyperaemia and erythema) by hospital discharge (RR 2.29, 95% CI 1.37 to 3.82).

Other outcomes

There was a decrease in length of hospital stay (in days) (MD -3.27, 95% CI -4.99 to -1.56 days; 5 trials, 591 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (Table 1.1) reported that carers want assistance in interacting with their babies, especially when they are undergoing therapies that make it difficult to have physical contact *(14)*. They want to learn about the health-care setting where they need to stay and care for their baby. They want to understand what medical equipment is being used and why. Studies report that families can find mechanical ventilation and CPAP intimidating and frightening and that these therapies can accentuate their feelings of inadequacy and lack of control over their baby's health care *(147,159)*. Families also worry about the pain and discomfort their baby is experiencing in NICUs *(14)*. Studies from LMICs indicate that bubble CPAP is both valued and acceptable to families and health workers *(163,164)*. No other specific evidence was located about whether families value bubble CPAP rather than other types of CPAP for their preterm or LBW baby or whether they find bubble CPAP more or less acceptable.

Resources required and implementation considerations

Please refer to the information on this topic in section B.1.

Feasibility and equity

Studies from LMICs *(165-168)* report the low cost and feasibility of establishing bubble CPAP services. There was no other specific evidence on the feasibility and equity of providing CPAP for preterm or LBW infants.

Summary of judgements

Comparison: Bubble CPAP vs other CPAP pressure sources (B.3)	
Justification	• Evidence of small-to-moderate benefits: decreased pneumothorax, decreased bronchopulmonary dysplasia and decreased failed treatment (defined as recurrent apnoea, hypoxia, hypercarbia, increasing oxygen requirement or the need for mechanical ventilation) *(low-certainty evidence)* • Evidence of small harms: increased nasal injury (defined as ulceration, bleeding, septal injury and/or scarring but excluding hyperaemia and erythema) *(low-certainty evidence)* • Evidence of little or no effect on mortality *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Small
Certainty	Low
Balance	Probably favours bubble CPAP
Values	Uncertainty or variability about outcomes
Acceptability	Varies
Resources	Moderate
Feasibility	Varies
Equity	Varies

B.4 METHYLXANTHINES FOR TREATMENT OF APNOEA

Recommendation and remarks

RECOMMENDATION B.4 (NEW)

Caffeine is recommended for the treatment of apnoea in preterm infants. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that evidence was available for all preterm infants, so caffeine (or other methylxanthines) is recommended for treatment of apnoea in preterm infants.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of administration. Based on the largest trial *(169)* included in the evidence review, the GDG suggested a 20 mg/kg loading dose and a 5 mg/kg per day maintenance dose for six weeks. The duration of caffeine administration should be based on clinical judgement.
- If caffeine is not available, other methylxanthines (aminophylline or theophylline) may be considered.

Background and definitions

Apnoea (temporary cessation of breathing) is common in preterm infants *(170,171)*. The frequency of apnoea is inversely related to gestational age, and it occurs in almost all infants born before 28 weeks' gestation (extremely preterm) *(170,171)*. Episodes of apnoea can result in hypoxaemia and bradycardia requiring mechanical ventilation. Intermittent hypoxic episodes in the first two months after birth are associated with increased risk of chronic conditions, such as retinopathy of prematurity, and adverse neurodevelopmental outcomes *(172,173)*. Since the 1970s, methylxanthine medicines such as theophylline, aminophylline and caffeine have been used to manage apnoea. More recently, large pragmatic studies have included methylxanthine treatment for a variety of indications, including the treatment and prevention of apnoea *(174)*. Studies have also assessed the use of methylxanthines to prevent apnoea before and after extubation *(169,175)*.

Summary of the evidence

OVERVIEW	B.4 Methylxanthines for treatment of apnoea
PICO	**Population** – Preterm infants **Intervention** – Any methylxanthine (aminophylline, theophylline, caffeine) at any dose **Comparator** – Placebo or no methylxanthine treatment **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Methylxanthine for treatment of apnoea versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from a Cochrane review of 18 RCTs enrolling a total of 2705 preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for treatment of apnoea), the inclusion criteria for infants were gestational age at birth below 37 weeks and evidence of apnoea. Six RCTs were included, enrolling a total of 959 preterm infants from six countries (Australia, Canada, France, India, the United Kingdom and the USA). The largest study, the Caffeine for Apnoea of Prematurity (CAP) trial *(169)*, enrolled 767 participants (birth weight 0.5–1.2 kg) from nine countries who received methylxanthines for

treatment of apnoea and conducted follow-up after five years. The other five trials were small, with fewer than 100 infants in each trial.

Critical outcomes

For methylxanthines for treatment of apnoea compared with placebo or no methylxanthine treatment, three trials reported all-cause mortality, five reported morbidity (1 reported apnoea, 5 use of mechanical ventilation, 1 bronchopulmonary dysplasia) and one trial reported a composite outcome of death or major neurodevelopmental disability. No trials reported growth outcomes. (Full details are provided in GRADE Table B.4, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from three trials totalling 154 participants suggests a decrease in all-cause mortality by hospital discharge (RR 0.49, 95% CI 0.14 to 1.78).
- **Morbidity:** Very-low-certainty evidence from one trial with 43 participants suggests a decrease in any apnoeic episodes by hospital discharge (RR 0.70, 95% CI 0.30 to 1.62). Low-certainty evidence from five trials totalling 192 participants suggests a decrease in the use of mechanical ventilation by hospital discharge (RR 0.34, 95% CI 0.12 to 0.97). Moderate-certainty evidence from one trial with 805 participants suggests a decrease in bronchopulmonary dysplasia at 36 weeks PMA (RR 0.72, 95% CI 0.58 to 0.89).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 767 participants suggests little or no effect on the composite outcome of death or major neurodevelopmental disability by the latest follow-up (5 years) (RR 0.85, 95% CI 0.71 to 1.01). This composite outcome was defined as death or survival to 5 years with one or more of the following: motor impairment (defined as a gross motor function classification system level of 3–5), cognitive impairment (defined as a full-scale IQ < 70), behaviour problems, poor general health, deafness and/or blindness, all measured using validated tests.

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported (within a theme on the health-care environment) that carers want mechanisms and initiatives to help them to interact with their babies, especially when they are undergoing therapies that make it difficult to have physical contact with the infant *(14)*. They also want to learn about the health-care setting (including the equipment in use) where they need to stay and care for the infant. No other specific evidence was located about whether families value methylxanthines for their preterm or LBW baby or whether they find them more or less acceptable than other medicines or no treatment.

Resources required and implementation considerations

Organization of care

Methylxanthines (caffeine, theophylline and aminophylline) must be dispensed by a health worker. They can be provided in the health-care facility or at home. Caffeine is given once a day and theophylline and aminophylline are given three times a day.

Infrastructure, equipment and supplies

Methylxanthines are available as intravenous and oral formulations. Caffeine citrate is available as 20 mg/ml and 10 mg/ml for intravenous and oral use, respectively. Oral caffeine comes as a ready-to-use formulation that needs no mixing. Theophylline is available as 50–60 mg/5 ml liquid. Aminophylline is available as 25 mg/ml ampoules.

Workforce, training, supervision and monitoring

Health workers at all levels can support mothers and families. Standardized packages are needed for training, supervision and monitoring. Dispensing needs to be documented in clinical records.

Feasibility and equity

Studies report that availability and cost are barriers for the use of caffeine citrate formulations in LMICs *(176)*. Theophylline and aminophylline are more widely available than caffeine in LMICs *(31,176)*. There was no specific evidence on the feasibility and equity of providing methylxanthines for preterm or LBW infants.

Summary of judgements

Comparison: Methylxanthine for the treatment of apnoea in preterm infants vs placebo or no methylxanthine treatment (B.4)	
Justification	• Evidence of moderate benefits: decreased death, bronchopulmonary dysplasia *(moderate-certainty evidence)*, decreased mechanical ventilation *(low-certainty evidence)* and decreased neurodevelopmental disability *(moderate-certainty evidence)* • No evidence of harms

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours methylxanthines for treatment of apnoea in infants < 37 weeks
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

B.5 METHYLXANTHINES FOR EXTUBATION

Recommendation and remarks

RECOMMENDATION B.5 (NEW)

Caffeine is recommended for the extubation of preterm infants born before 34 weeks' gestation. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- The GDG noted that evidence was available only for preterm infants born before 34 weeks' gestation, but suggests that caffeine (or other methylxanthines) may also be considered for extubation of preterm infants born at or after 34 weeks and before 37 weeks, depending on clinical judgement.
- The GDG noted that there were limited data on the timing of initiation and duration of administration. Based on the largest trials *(169,175)* included in the evidence review, the GDG suggested starting caffeine 24 hours before a planned extubation. If the extubation is unplanned, the infant should receive the caffeine as soon as possible after the extubation and within 6 hours, and should continue to receive it for six days.
- The GDG noted that there were limited data on the dosage. Based on the largest trials *(169,175)* included in the evidence review, the GDG suggested a 20 mg/kg loading dose and 5 mg/kg per day maintenance dose for six days.
- If caffeine is not available, other methylxanthines (aminophylline or theophylline) may be considered.

Background and definitions

Please refer to the information in section B.4.

Summary of the evidence

OVERVIEW	B.5 Methylxanthines for extubation
PICO	**Population** – Preterm infants (< 34 weeks) **Intervention** – Any methylxanthine (aminophylline, theophylline, caffeine) at any dose **Comparator** – Placebo or no methylxanthine treatment **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Methylxanthine for extubation versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived from the same Cochrane review of preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for extubation), the inclusion criteria for infants were gestational age at birth below 34 weeks and planned extubation. Seven RCTs enrolling a total of 870 preterm infants were included from five countries (Australia, Canada, Spain, the United Kingdom and the USA). The largest study was also the CAP trial *(169)*, which followed up 676 participants who received methylxanthines for extubation. The other six trials were small, with fewer than 100 infants in each trial.

Critical outcomes

For methylxanthines for extubation compared with no methylxanthine treatment, six trials reported morbidity (6 reported "failed extubation", 2 bronchopulmonary dysplasia) and one trial reported a composite outcome of death or major neurodevelopmental disability. No trials reported growth outcomes. (Full details are provided in GRADE Table B.5, in the Web Supplement.)

- **Morbidity:** Moderate-certainty evidence from six trials totalling 197 participants suggests decreased failed extubation (defined as the infant having to be re-intubated) by hospital discharge (RR 0.48, 95% CI 0.32 to 0.71). Moderate-certainty evidence from two trials totalling 704 participants suggests a decrease in bronchopulmonary dysplasia (defined as a need for supplemental oxygen) by 36 weeks PMA (RR 0.81, 95% CI 0.70 to 0.92).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 676 participants suggests decreased death or major neurodevelopmental disability (see section B.4 for the definition of the composite outcome) by the latest follow-up (5 years) (RR 0.85, 95% CI 0.73 to 0.99).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability, resources, feasibility and equity

Please refer to the information on these topics in section B.4.

Summary of judgements

Comparison: Methylxanthine for extubation in preterm infants vs placebo or no methylxanthine treatment (B.5)	
Justification	In trials where most participants are infants born < 34 weeks' gestation: • Evidence of moderate benefits: decreased death, bronchopulmonary dysplasia, failed extubation and neurodevelopmental disability *(moderate-certainty evidence)* • No evidence of harms

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Moderate
Balance	Favours methylxanthines for extubation in infants < 34 weeks
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

B.6 METHYLXANTHINES FOR PREVENTION OF APNOEA

Recommendation and remarks

RECOMMENDATION B.6 (NEW)

Caffeine may be considered for the prevention of apnoea in preterm infants born before 34 weeks' gestation. *(Conditional recommendation, low-certainty evidence)*

Remarks

- The GDG noted that the evidence on increased mortality came from three small trials totalling 129 infants *(177-179)* and was uncertain due to very low quality, and imprecision. Also, data on "death alone" were not available from a large trial of 423 infants *(169)*, which reported no effect on a combined outcome of death and neurodevelopmental disability. The GDG also noted that the evidence on harms from increased use of mechanical ventilation was uncertain due to very low quality, and imprecision.
- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that evidence was available only for preterm infants born before 34 weeks' gestation, but suggests that caffeine (or other methylxanthines) may also be considered for prevention of apnoea in preterm infants born at or after 34 weeks and before 37 weeks if there is clinical indication.
- The GDG noted that there were limited data on the dose, timing of initiation and duration of administration. Based on the largest trial *(169)* included in the evidence review, the GDG suggested a 20 mg/kg loading dose and a 5 mg/kg per day maintenance dose for six weeks. The duration of caffeine administration should be based on clinical judgement.
- If caffeine is not available, other methylxanthines (aminophylline or theophylline) may be considered.

Background and definitions

Please refer to the information in section B.4.

Summary of the evidence

OVERVIEW	B.6 Methylxanthines for prevention of apnoea
PICO	**Population** – Preterm infants (< 34 weeks) **Intervention** – Any methylxanthine (aminophylline, theophylline, caffeine) at any dose **Comparator** – Placebo or no methylxanthine treatment **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Methylxanthines for prevention of apnoea versus placebo or no methylxanthine treatment

Sources and characteristics of the evidence

The effectiveness evidence for this comparison was derived the same Cochrane review of preterm infants who received methylxanthines for any indication *(174)*. For the indication relevant to this comparison (for prevention of apnoea), the inclusion criteria for infants were gestational age at birth below 34 weeks and no evidence of apnoea. Seven RCTs enrolling a total of 706 preterm infants were included from six countries (Australia, Canada, the Islamic Republic of Iran, Switzerland, the United Kingdom and the USA). The largest study was also the CAP trial, which followed up 423 participants who received methylxanthines for prevention of apnoea *(169)*. The other six trials were small, with fewer than 100 infants in each.

Critical outcomes

For methylxanthines for prevention of apnoea compared with no methylxanthines, three trials reported all-cause mortality, four reported morbidity (2 reported apnoea, 4 use of mechanical ventilation, 3 bronchopulmonary dysplasia) and one reported a composite outcome of death or neurodevelopmental disability. No trials reported growth outcomes. (Full details are provided in GRADE Table B.6, in the Web Supplement.)

- **Mortality:** Low-certainty evidence from three trials *(177-179)* totalling 129 participants suggests little or no effect on mortality by hospital discharge (RR 2.19, 95% CI 0.85 to 5.68).
- **Morbidity:** Low-certainty evidence from two trials totalling 104 participants suggests a decrease in any apnoeic episodes by hospital discharge (RR 0.19, 95% CI 0.09 to 0.41). Low-certainty evidence from four trials totalling 208 participants suggests little or no effect on the use of mechanical ventilation by hospital discharge (RR 1.33, 95% CI 0.48 to 3.72). Moderate-certainty evidence from three trials totalling 541 participants suggests a decrease in bronchopulmonary dysplasia (defined as the use of supplemental oxygen at 36 weeks PMA) (RR 0.78, 95% CI 0.63 to 0.97).
- **Mortality or neurodevelopment:** Moderate-certainty evidence from one trial with 423 participants suggests no effect on the composite outcome of death or neurodevelopmental disability (see section B.4 for the definition of the composite outcome) by latest follow-up (5 years) (RR 1.00, 95% CI 0.80 to 1.24). Data on death alone and neurodevelopmental disability alone were not available for this trial.

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability, resources, feasibility and equity

Please refer to the information on these topics in section B.4.

Summary of judgements

Comparison: Methylxanthine for the prevention of apnoea in preterm infants vs placebo or no methylxanthine treatment (B.6)	
Justification	In trials where most participants are infants born < 34 weeks' gestation: • Evidence of small-to-moderate benefit: decreased bronchopulmonary dysplasia *(moderate-certainty evidence)* and decreased apnoeic episodes *(low-certainty evidence)* • Evidence of harms uncertain: little or no effect on mortality *(low-certainty evidence)*, little or no effect on combined outcome of neurodevelopment or death *(moderate-certainty evidence)* and increase in use of mechanical ventilation *(low-certainty evidence)* • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Small to moderate
Harms	Unknown
Certainty	Low
Balance	Probably favours methylxanthines for prevention of apnoea in infants < 34 weeks
Values	Uncertainty or variability about outcomes
Acceptability	Varies
Resources	Low to moderate
Feasibility	Probably feasible
Equity	Probably equitable

C. Family involvement and support

C.1 FAMILY INVOLVEMENT IN ROUTINE CARE

Recommendation and remarks

RECOMMENDATION C.1 (NEW)

Family involvement in the routine care of preterm or low-birth-weigh infants in health-care facilities is recommended. *(Strong recommendation, low- to moderate-certainty evidence)*

Remarks

- The trials in the systematic review varied widely in intervention content, intensity and effect but all showed consistent and similar effects.
- The GDG noted that the resources needed for and the feasibility of implementing family involvement strategies vary according to setting but that simple family involvement interventions such as the delivery of direct bedside care and involvement in medical decision-making could be implemented in all settings. Other components that can be provided include chairs near the infant's cot, even in busy and crowded hospital wards.
- The GDG also noted that family involvement strategies reduced the length of hospital stay, improved breastfeeding and reduced parental anxiety and stress.

Background and definitions

Preterm and LBW infants commonly require specialized care, close monitoring and medical interventions *(2,180)*. In some health-care facilities, families are not allowed any physical access to their infants and receive only intermittent verbal updates from health workers *(181-184)*. Family involvement is often defined as the participation of mothers, fathers/partners and other family members in routine care of the newborn while the baby is in the health-care facility *(180,185,186)*. It may include promotion of direct bedside care from the family (e.g. feeding and administration of medicines), inclusion of the family in medical decision-making, infrastructure changes (e.g. beds and chairs near the baby's cot, family rooms), health-care facility culture change and health worker behaviour change. Strategies to increase family involvement have typically focused on packages of one or more of these interventions with the overall aims of increasing the amount of direct hands-on care that parents provide for their infant and empowering families to collaborate in health-care decision-making. Well known packages that are implemented in high-, middle- and low-income countries include family-centred care, family-participatory care and family-integrated care *(180,185,186)*.

Summary of the evidence

OVERVIEW	C.1 Family involvement
PICO	**Population** – Hospitalized preterm or LBW infants **Intervention** – Interventions to involve families in their infant's routine health care **Comparator** – Usual hospital care **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Hospital in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg) • Intensity of interventions (high intensity ≥ 12 hours per day, low intensity < 12 hours per day)

Effectiveness: Comparison – Family involvement in routine care versus usual hospital care

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of 15 RCTs enrolling a total of 5240 preterm or LBW infants from nine countries (Australia, Canada, China, India, the Islamic Republic of Iran, New Zealand, the Republic of Korea, Sweden and the USA) *(187)*. Most infants were born before 32 weeks' gestation or had birth weight below 1.5 kg, and most trials excluded infants with major congenital anomalies. All trials were conducted in NICUs.

All trials evaluated the effect of family-centred models or packages for the hospital care of preterm or LBW infants on infant and parental outcomes. No studies of infrastructure or behaviour change interventions were located. The family-centred packages were heterogeneous, but their common core content was the involvement of family members in the provision of direct bedside care. Skin-to-skin care or kangaroo mother care (KMC) was included in nine trials, though frequency and duration were not described. Other common components included neurodevelopmental care (8 trials), preparation for transition to home (6 trials) and the involvement of parents in medical decision-making (4 trials).

Critical outcomes

For family involvement strategies compared with usual hospital care, four trials reported all-cause mortality outcomes, eight reported morbidity (6 reported serious infection, 6 necrotizing enterocolitis, 7 bronchopulmonary dysplasia, 8 retinopathy of prematurity and 5 intraventricular haemorrhage), three reported growth (weight gain) and two reported neurodevelopment. (Full details are provided in GRADE Table C.1, in the Web Supplement.)

- **Mortality:** Very-low-certainty evidence from four trials totalling 2378 participants suggests little or no effect on all-cause mortality by hospital discharge (OR 1.05, 95% CI 0.53 to 2.09).
- **Morbidity:** Low-certainty evidence from six trials totalling 2843 participants suggests a decrease in serious infection by hospital discharge (OR 0.79, 95% CI 0.53 to 1.16). Low-certainty evidence from six trials totalling 2809 participants suggests little or no effect on necrotizing enterocolitis by hospital discharge (OR 0.81, 95% CI 0.46 to 1.44). Low-certainty evidence from seven trials totalling 3085 participants suggests decreased bronchopulmonary dysplasia by hospital discharge (OR 0.74, 95% CI 0.53 to 1.03). Moderate-certainty evidence from eight trials totalling 2551 participants suggests decreased retinopathy of prematurity by hospital discharge (OR 0.52, 95% CI 0.34 to 0.80). Very-low-certainty evidence from five trials totalling 2555 participants suggests decreased intraventricular haemorrhage by hospital discharge (OR 0.74, 95% CI 0.36 to 1.54).
- **Growth:** Moderate-certainty evidence from three trials totalling 2215 participants suggests increased in-hospital growth velocity (grams per day) (MD 2.09, 95% CI 1.27 to 2.91).
- **Neurodevelopment:** Low-certainty evidence from two trials totalling 422 participants suggests increased neurodevelopment (measured using the Neonatal Neurobehavioral Examination – Chinese version [NNE-C] test) by hospital discharge or term corrected age, i.e. 37 weeks PMA (MD 1.11, 95% CI 0.21 to 2.01) *(187)*.

Other outcomes

There was a decrease in length of hospital stay (in days) (MD -2.91, 95% CI -5.15 to -0.68; 11 trials, 4452 participants). There was an increase in the proportion of infants predominantly or exclusively breastfeeding by hospital discharge (OR 1.34, 95% CI 1.10 to 1.65; 3 trials, 1739 participants). There was an increase in "any" breastfeeding by hospital discharge (OR 2.60, 95% CI 0.77 to 8.79; 5 trials, 2546 participants).

Subgroup analyses

For gestational age and birth weight, differences for weight gain and neurodevelopment could not be assessed as there were insufficient studies. For the other outcomes there was no evidence of a subgroup difference.

For the intensity of intervention, differences for intraventricular haemorrhage, weight gain and neurodevelopment could not be assessed as there were insufficient studies. For the other outcomes there was no evidence of a subgroup difference except for bronchopulmonary dysplasia, which decreased after high-intensity interventions (RR 0.18, 95% CI 0.05 to 0.66; 1 study, 366 participants) but not after low-intensity interventions (RR 1.04, 95% CI 0.68 to 1.58; 6 studies, 2719 participants) (test for subgroup differences, Chi^2 =7.22, *P*=0.007).

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, and want to take an

active role in deciding what interventions are given to infants, in the routine care of the newborn, in direct bedside care, including feeding their baby and in medical decision-making, and that they value hospital infrastructure changes (e.g. beds and chairs near the baby's cot, family rooms) *(14)*. No other specific evidence was located.

Resources required and implementation considerations

Organization of care

Family involvement strategies can be implemented at all levels of newborn care (primary, secondary and tertiary). Health-care facilities should ensure that families have access to beds, food, bathing and toilet facilities throughout the infant's hospital stay.

Infrastructure, equipment and supplies

No special infrastructure, equipment or supplies are needed to support family involvement in the care of their preterm or LBW infants. However, many arrangements can make the infant and mother more comfortable, e.g. reclining beds and chairs. More structured packages may include infrastructure changes such as beds and chairs near the infant's cot, and family rooms.

If couplet care or maternal–newborn intensive care units (M-NICUs) are used, they should have all the infrastructure, equipment and supplies that NICUs have for small or sick babies and that maternity wards have for mothers. For infants, this includes CPAP machines, pulse oximeters, and radiant warmers or incubators if the infant is not in KMC. For mothers, this includes adult beds and an examination area where she can receive the health care she needs.

Workforce, training, supervision and monitoring

Health workers at all levels can support family involvement in the routine care of their preterm or LBW infant. Standardized packages can be used for training, supervision and monitoring. This can include the promotion of direct bedside care from the family (e.g. feeding and administration of medicines), inclusion of the family in medical decision-making, health-care facility culture change, health worker behaviour change and infrastructure change.

Feasibility and equity

There was no specific evidence on the feasibility and equity of promoting family involvement for preterm or LBW infants.

Summary of judgements

Comparison: Family involvement in routine care vs usual hospital care (C.1)	
Justification	• Evidence of moderate benefits: decreased morbidity (infection, intraventricular haemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia), increased weight and length, and increased neurodevelopment *(low- to moderate-certainty evidence)* • No evidence of harms • Evidence of little or no effect on: mortality, necrotizing enterocolitis, and weight and head circumference *(low- to very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Low to moderate
Balance	Favours family involvement strategies
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Vary
Feasibility	Varies
Equity	Probably equitable

C.2 FAMILY SUPPORT

Recommendation and remarks

RECOMMENDATION C.2 (NEW)

Families of preterm or low-birth-weight 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 by health workers, and peer support.
(Conditional recommendation, very-low-certainty evidence)

Remarks

- The recommendation is conditional on shared decision-making with parents; this includes informing parents about the benefits and risks and the need for further research.
- The GDG noted that **education and counselling** also had important effects in improving parent-to-infant interaction, improving breastfeeding and decreasing parental anxiety, stress and depression, though these were not critical outcomes.
- The GDG noted that there were limited data on frequency, duration and intensity of **education and counselling**.
- The GDG noted that **discharge preparation** also had important effects in improving parent-to-infant interaction, improving breastfeeding and decreasing parental anxiety, stress and depression, though these were not critical outcomes.
- The GDG noted that there were limited data on the frequency, duration and intensity of **discharge preparation**.
- Preterm and LBW infants often require care from multiple health workers so the GDG also noted that careful coordination of care is needed post-discharge.
- The GDG made a conditional recommendation on **peer support,** although there were no data on critical outcomes; this was because of the effects on maternal anxiety and the importance of the intervention.
- The GDG noted that there were limited data on frequency, duration and intensity of **peer support**.
- The GDG decided not to make a recommendation on **digital information systems** as there was no evidence of benefits or harms on any critical outcome.

Background and definitions

Supporting families to care for their sick, vulnerable, preterm or LBW infant is a basic and integral component of any health system. However, many families still feel ill-equipped to care for their preterm or LBW newborn infant at home *(188,189)*. Families need support at all stages, starting from before conception, and including at the identification of a high-risk pregnancy, at the birth of the baby, in the health-care facility, at discharge and when the baby reaches home. Much of the support that families need to care for their preterm and LBW infants is provided through social services in high-, middle- and low-income countries. However, "what the health system can do" and the "health system building blocks" they can use (i.e. service delivery, workforce, digital information systems, medical products and technologies, financing, leadership and governance) *(190)* are often overlooked. Two systematic reviews have recently assessed the effectiveness of communication and peer-support interventions for families of preterm infants *(191,192)*. However, there have been no recent systematic reviews of the effects of other health system "building blocks" on infant mortality, morbidity, growth and neurodevelopmental outcomes.

Overall, the effectiveness evidence was derived from a systematic review of 37 trials (35 RCTs and 2 non-randomized) enrolling a total of 11 758 preterm or LBW infants from 18 countries *(193)* (Australia, Bangladesh, Canada, China, Denmark, Egypt, Finland, Greece, India, the Islamic Republic of Iran, Jamaica, the Netherlands, Norway, the Philippines, the Republic of Korea, Sweden, the United Kingdom and the USA). No studies were based in low-income settings. Interventions commenced either in the facility (24 trials) or in the home (13 trials). All

began after birth; no intervention started during pregnancy. No studies assessed the effect of the "usual support" that is provided to all babies, while all studies assessed only "extra support" (i.e. additional or strengthened support) needed for preterm and LBW infants. The interventions included in the studies were education and counselling (18 trials), peer support (2), discharge preparation (1), digital information systems (4) and home visits by a trained health worker or volunteer (9). No studies on the other health system building blocks – including financing, leadership or governance – were identified. The education and counselling, peer support and discharge preparation interventions are described below. Home visiting interventions are described in section C.3. Parental leave, financing and entitlements are described in section C.4.

Summary of the evidence

OVERVIEW	C.2a Education and counselling	C.2b Peer support	C.2c Discharge preparation	C.2d Digital information
PICO	**Population** – Families of preterm or LBW infants			
	Intervention 1 – Education and counselling interventions	**Intervention 2** – Peer support interventions	**Intervention 3** – Discharge preparation interventions	**Intervention 4** – Digital information interventions
	Comparator – Usual care **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up			
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)			

Effectiveness: Comparison 1 – Education and counselling versus usual care

Sources and characteristics of the evidence

For comparison 1, the effectiveness evidence was derived from the systematic review, which included four trials enrolling a total of 312 preterm or LBW infants *(193)*. The interventions included individual or group education or training (provided by health workers) of families to care for their preterm or LBW infant. Content included well-being strategies (e.g. strategies for managing stress, anxiety, depression, self-efficacy) and basic newborn-care practices (e.g. positioning, bathing, breastfeeding, thermal care, responsiveness and sensitivity). The interventions began in the facility, with some continuing at home following discharge.

Critical outcomes

For education and counselling compared with usual care, two trials reported growth (weight gain, length gain) and three reported neurodevelopment (cognitive and motor development). No trials reported mortality or morbidity. (Full details are provided in GRADE Table C.2a, in the Web Supplement.)

- **Growth:** Very-low-certainty evidence from one trial with 184 participants suggests an increase in infant weight (in grams) at 60 days (MD 305, 95% CI 228 to 382). Very-low-certainty evidence from one trial with 57 participants suggests an increase in infant weight (in grams) at 120 days (MD 410, 95% CI 406.03 to 413.97). Very-low-certainty evidence from one trial with 184 participants suggests an increase in infant length (in centimetres) at 60 days (MD 1.5, 95% CI 1.08 to 1.92). Very-low-certainty evidence from one trial with 57 participants suggests an increase in infant length (in centimetres) at 120 days (MD 1.2, 95% CI 0.2 to 2.6).
- **Neurodevelopment:** Very-low-certainty evidence from one trial with seven participants suggests little or no effect on motor development (BSID-III) at 6 months of age (MD 0.38, 95% CI -1.1.15 to 1.19). Low-certainty evidence from three trials totalling 64 participants suggests an increase in cognitive development (BSID-III) at 4–6 months of age (SMD 0.67, 95% CI 0.16 to 1.17).

Other outcomes

There was little or no effect on infant temperament at 6 months of age (SMD 0.26, 95% CI -0.29 to 0.81; 2 trials, 155 participants). There was an increase in mother–infant interaction at 6 weeks (MD 1.8, 95% CI 0.21 to 3.81; 1 trial, 142 participants), 3 months (MD 0.8, 95% CI 0.6 to 2.2; 1 trial, 196 participants) and 6 months of age (MD 0.21, 95% CI 0.11 to 0.67; 1 trial, 63 participants), but there was little to no effect at follow-up at 12 months of age (MD 0.1, 95% CI -0.01 to 0.21; 1 trial, 93 participants). There was little to no effect on duration of exclusive breastfeeding (EBF) (MD 2.0, 95% CI -5.48 to 9.48; 1 trial, 128 participants), but there was an increase in EBF at 2–3 months (RR 1.71, 95% CI 1.26 to 2.31; 2 trials, 244 participants).

Effectiveness: Comparison 2 – Peer support versus usual care

Sources and characteristics of the evidence

For comparison 2, the effectiveness evidence was derived from the systematic review, which included two trials enrolling a total of 118 preterm or LBW infants *(193)*. The peer supporters were all women who had cared for a preterm or LBW infant in a similar environment and were willing to use their experiences to support others. The interventions all commenced in the facility and took place either following agreement from the parent or were initiated by the parent. Content included well-being strategies and newborn-care practices.

Critical outcomes

For peer support compared with usual care, no trials reported mortality, morbidity, growth or neurodevelopment. (Full details are provided in GRADE Table C.2b, in the Web Supplement.)

Other outcomes

There was a decrease in maternal anxiety when the baby reached 4 months of age (SMD 0.74 lower, 95% CI 1.32 lower to 0.16 lower; 1 trial, 49 participants). There was little or no effect on EBF (intervention group: median 3 months [range 0–14]; control group: median 4.3 [range 0–13]; 1 trial, 69 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Effectiveness: Comparison 3 – Discharge preparation versus usual care

Sources and characteristics of the evidence

For comparison 3, the effectiveness evidence was derived from the systematic review, which included one trial enrolling 173 preterm or LBW infants *(193)*. The interventions were delivered by health workers in the days just prior to hospital discharge and focused specifically on preparing parents for the discharge of their infant. The content included well-being strategies and newborn-care practices, but also "anticipatory guidance" (i.e. what to expect), financial and social support information, and referral pathways.

Critical outcomes

For discharge preparation compared with usual care, one trial reported morbidity (emergency department presentations). No trials reported mortality, growth or neurodevelopment outcomes. (Full details are provided in GRADE Table C.2c, in the Web Supplement.)

- **Morbidity:** Very-low-certainty evidence from one observational study with 173 participants suggests a decrease in emergency hospital visits by 2 months of age (RR 0.62, 95% CI 0.39 to 1.00).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Effectiveness: Comparison 4 – Digital information systems versus usual care

Sources and characteristics of the evidence

For comparison 4, the effectiveness evidence was derived from the systematic review, which included four trials enrolling a total of 902 preterm or LBW infants *(193)*. The interventions used electronic web-based applications, including Skype, audiovisual workshops and telephone media. Content included well-being strategies and newborn-care practices. The interventions commenced either in the facility or at home.

Critical outcomes

One trial reported morbidity (emergency department presentations). No trials reported mortality, growth or neurodevelopment outcomes. (Full details are provided in GRADE Table C.2d, in the Web Supplement.)

- **Morbidity:** Very-low-certainty evidence from one trial with 89 participants suggests little to no effect on emergency hospital visits by two months post-discharge (usual care group: median 1 visit [range 0–6 visits] versus digital information systems group: median 1 visit [range 0–7 visits]).

Other outcomes

There was little or no effect on maternal–infant interaction by 1 month of age (MD -0.8, 95% CI -1.84 to 0.24; 1 trial, 129 participants) or by 4 months of age (MD -0.9, 95% CI -2.09 to 0.29; 1 trial, 85 participants). There was little or no effect on EBF by 2 months of age (RR 1.02, 95% CI 0.89 to 1.16; 2 trials, 688 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting all newborn-care practices, and want to take an active role in deciding what interventions are given to infants, including what newborn-care practices they receive and how they are implemented *(14)*. No specific evidence was located about the kinds of support families of preterm or LBW babies value or find acceptable.

Resources required and implementation considerations

Organization of care

Families may need education, counselling, discharge preparation and peer support at all levels of health facility care. Education, counselling and peer support may be needed at home. Support and planning should be started in the antenatal period where possible. Services should follow national and local guidance for health-care facilities.

Infrastructure, equipment and supplies

National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can provide family support. Standardized packages can be used for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence on the feasibility and equity of providing family support for preterm or LBW infants.

Summary of judgements

	Comparison 1. Education and counselling vs usual care (C.2a)	Comparison 2. Peer support vs usual care (C.2b)	Comparison 3. Discharge preparation vs usual care (C.2c)	Comparison 4. Digital information systems vs usual care (C.2d)
Justification	• Evidence of moderate benefits: increase in weight, length and neurodevelopment *(very-low-certainty evidence)* • No evidence of harms • No evidence on other critical outcomes	• Evidence of small benefits: decrease in maternal anxiety *(very-low-certainty evidence)* • No evidence of harms • No evidence on critical outcomes	• Evidence of small benefits: decrease in emergency department presentations *(very-low-certainty evidence)* • No evidence of harms • No evidence on other critical outcomes	• Evidence of little to no effect on emergency hospital visits *(very-low-certainty evidence)* • No evidence on other critical outcomes
Evidence-to-Decision summary				
Benefits	Moderate	Small	Small	Unknown
Harms	None	None	None	Unknown
Certainty	Very low	Very low	Very low	Very low
Balance	Probably favours education and counselling	Probably favours peer support	Probably favours discharge preparation	Unknown
Values	No uncertainty or variability about outcomes	No uncertainty or variability about outcomes	No uncertainty or variability about outcomes	No uncertainty or variability about outcomes
Acceptability	Probably acceptable	Probably acceptable	Probably acceptable	Probably acceptable
Resources	Moderate	Moderate	Moderate	Moderate
Feasibility	Probably feasible	Probably feasible	Probably feasible	Varies
Equity	Probably equitable	Probably equitable	Probably equitable	Varies

C.3 HOME VISITS

Recommendation and remarks

RECOMMENDATION C.3 (NEW)

Home visits by trained health workers are recommended to support families to care for their preterm or low-birth-weight infant. *(Strong recommendation, moderate-certainty evidence)*

Remarks

- Trained health workers can include nurses, midwives, doctors and community health workers.
- The GDG noted that there were limited data on the content, frequency, duration and intensity of home visits for preterm and LBW infants. Based on the trials included in the evidence review, the GDG recommended that extra home visits (i.e. additional to the routine scheduled postnatal contacts for all infants *[22]*) should be made, and that their content, frequency, duration and intensity should be based on clinical judgement.
- The GDG noted that home visits also increased exclusive breastfeeding, immunization visits and parental–infant attachment and decreased parental stress, though these were not critical outcomes.

Background and definitions

Families need support at all stages, from before conception, and including at the identification of a high-risk pregnancy, at the birth of the baby, in the health-care facility, at discharge, and especially when the baby reaches home *(189,194)*. Studies over the last 10 years in high-, middle- and low-income countries have shown that home visiting during the antenatal and postnatal periods can improve both the demand for and the use of antenatal, delivery and postnatal services and reduce maternal and newborn mortality *(22,195)*. However, there is limited information on the effects of home visiting for preterm and LBW infants.

Summary of the evidence

OVERVIEW	C.3 Home visits
PICO	**Population** – Families of preterm or LBW infants **Intervention** – Home visits to support families to care for their preterm or LBW infant in the home **Comparator** – Usual care **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Home visits to support families to provide care versus usual care

Sources and characteristics of the evidence

The effectiveness evidence was derived from a systematic review of nine trials enrolling a total of 8742 preterm or LBW infants from India, the Netherlands, Taiwan (China) and the USA *(193)*. The interventions were delivered by health workers, community health workers, trained intervention workers or trained volunteers. They started and continued in the home, immediately following

discharge from the facility. The content included well-being strategies and newborn-care practices but also "anticipatory guidance" (i.e. what to expect), financial and social support information, and referral pathways.

Critical outcomes

For home visits to support families to provide care compared with usual care, two trials reported all-cause mortality, one trial reported morbidity (hospitalizations) and two trials reported neurodevelopment (cognitive and motor neurodevelopment). No trials reported growth outcomes. (Full details are provided in GRADE Table C.3, in the Web Supplement.)

- **Mortality:** Moderate-certainty evidence from one trial with 6984 participants suggests decreased all-cause mortality by 180 days of age (RR 0.71, 95% CI 0.57 to 0.89). Low-certainty evidence from one observational study with 970 participants suggests decreased all-cause mortality by 12 months (RR 0.14, 95% CI 0.02 to 1.16).
- **Morbidity:** Low-certainty evidence from one observational study with 970 participants suggests a decrease in hospitalizations by 12 months (MD 0.34, 95% CI 0.16 to 0.52).
- **Neurodevelopment:** Moderate-certainty evidence from two trials totalling 652 participants suggests little or no effect on cognitive neurodevelopment (BSID-III) by 12 months (SMD 0.03, 95% CI -0.12 to 0.19). Low-certainty evidence from one trial with 136 participants suggests little or no effect on motor neurodevelopment (BSID-III) by 12 months (MD 0.02, 95% CI -0.35 to 0.32).

Other outcomes

There was little or no effect on infant temperament at 6 months of age (MD 0.70, 95% CI -0.60 to 1.46; 1 trial, 161 participants) or parent–infant attachment at 6 months of age (MD -1.20, 95% CI -2.79 to 0.39; 1 trial, 136 participants).

There was an increase in EBF at 6 months (RR 4.48, 95% CI 0.28 to 72.9; 3 trials, 7221 participants) and an increase in immunization visits in the first year (MD 1.21, 95% CI 0.93 to 1.49; 1 trial, 970 participants).

Subgroup analyses

The effect of gestational age and birth weight could not be assessed as there were insufficient trials for any critical outcome.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want to be involved in delivering care to infants, including supporting all newborn-care practices, and want to take an active role in deciding what interventions are given to infants, including what newborn-care practices they receive and how they are implemented *(14)*. No specific evidence was located about whether families value home visiting for their preterm or LBW baby or whether they find it more or less acceptable than other care.

Resources required and implementation considerations

Organization of care

A minimum of four postnatal care contacts is recommended for all infants *(22)*. Extra home visits (i.e. additional to the routine scheduled postnatal contacts for all infants) are needed for preterm and LBW babies. Their content, frequency, duration and intensity should follow national and local guidance for health-care facilities and should be based on clinical judgement.

Infrastructure, equipment and supplies

National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can provide home visits. However, standardized packages are needed for training, supervision and monitoring. Further guidance on follow-up care is being developed and will be published separately.

Feasibility and equity

There was no specific evidence about the feasibility and equity of home visiting interventions for preterm or LBW infants. Home visiting is a core part of the health programmes for both term and preterm infants in many high-, middle- and low-income countries *(22,195)*.

Summary of judgements

Comparison: Home visits to support families to provide care vs usual care (C.3)	
Justification	• Evidence of moderate benefits: moderate decrease in mortality *(moderate-certainty evidence)* and small decrease in number of hospitalizations *(very-low-certainty evidence)* • Evidence of little or no effect on cognitive or motor neurodevelopment *(low- to moderate-certainty evidence)* • No evidence of harms • No evidence on other critical outcomes

Evidence-to-Decision summary	
Benefits	Moderate
Harms	Trivial or none
Certainty	Low to moderate
Balance	Favours home visits
Values	No uncertainty or variability about outcomes
Acceptability	Probably acceptable
Resources	Moderate
Feasibility	Probably feasible
Equity	Probably equitable

C.4 PARENTAL LEAVE AND ENTITLEMENTS

Good practice statement and remarks

GOOD PRACTICE STATEMENT C.4 (NEW)

Parental leave and entitlements should address the special needs of mothers, fathers and other primary caregivers of preterm or low-birth-weight infants.

Remarks

- The GDG made this good practice statement in recognition of the costs and burdens to parents and families of implementing preterm and LBW infant care.
- Based on the studies in the review, the GDG considered that parental leave and entitlements should include additional days of leave from work and additional financial payments. However, there was insufficient information available to enable the GDG to make recommendations 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 the special needs of mothers and fathers/partners of preterm and LBW infants vary according to individual preferences and setting. They include: support for long hospital stays, multiple medical appointments, transport and equipment; support to help manage stress and anxiety about the infant; and support for caring for other children and family members.
- The GDG noted that parental leave and entitlements are in place in some countries but recommended that they should be expanded globally across high-, middle- and low-income countries.

Background and definitions

Families of preterm and LBW infants are well known to have increased risks of financial impoverishment, stress, anxiety and depression *(188,195,196)*. Leave from work is needed to help families care for the infant. Families may also need financial support for transport and equipment as well as for the costs of the hospitalization and caring for other children or family members *(189,191,197)*. Government and regulatory policies and entitlements are important ways to ensure families receive the financial and workplace support they need. However, there have been few reviews of policies for parental leave and entitlements for families of preterm or LBW infants across high-, middle- and low-income countries.

Summary of the evidence

OVERVIEW	C.4 Parental leave and entitlements
PICO	**Population** – Preterm or LBW infants **Intervention** – Parental leave and entitlements **Comparator** – Usual care **Outcomes** – All-cause mortality, morbidity, growth, neurodevelopment at latest follow-up
Timing, setting, subgroups	**Timing of the intervention** – Birth to 6 months of age **Setting** – Health-care facility or home in any country or setting **Subgroups** • Gestational age at birth (< 32 weeks, ≥ 32 weeks) • Birth weight (< 1.5 kg, ≥ 1.5 kg)

Effectiveness: Comparison – Parental leave and entitlements versus usual care

Sources and characteristics of the evidence

A systematic review of 37 trials (35 RCTs and 2 non-randomized studies) located no studies of the effectiveness of parental leave and entitlements in terms of critical infant outcomes (mortality, morbidity, growth, neurodevelopment) or family outcomes (stress, anxiety, depression) *(193)*.

An additional policy review was done of the most recent relevant policy reports:

(i) WHO sexual, reproductive, maternal, newborn, child and adolescent health policy survey, 2018–2019 (2018) *(198)*;
(ii) International Labour Organization database on conditions of work and employment programmes (2022) *(199)*;
(iii) International Network on Leave Policies and Research (2021) *(200)*.

One hundred and forty countries had policies for parental leave for childhood illness or complications. Twenty-eight countries had a parental leave policy specifically formulated for families of preterm infants: 20 high-income countries (Austria, Canada, Chile, Croatia, Cyprus, Finland, France, Germany, Hungary, Israel, Romania, Italy, Latvia, Lithuania, Luxembourg, New Zealand, Portugal, Slovenia, Spain and the United Kingdom), 6 upper-middle-income countries (Argentina, Belarus, Bulgaria, India, South Africa and Uruguay), 1 lower-middle-income (India) and 1 low-income country (Yemen). Seventeen countries only had policies for maternity leave (Argentina, Austria, Bulgaria, Canada, Chile, Croatia, Finland, France, Hungary, India, Italy, Latvia, Lithuania, Luxembourg, New Zealand, South Africa and Spain) and six had policies for both maternity and paternity leave (Cyprus, Germany, Portugal, Slovenia, the United Kingdom and Uruguay). Five countries did not specify whether the leave was maternal, paternal or both (Belarus, Israel, Romania, Türkiye and Yemen). The amount of leave time was equivalent to the number of weeks early that the baby was born in most cases.

Two countries – Canada and Germany – reported that they provided families with additional financial support for their preterm infants, called "parental allowance", but details were not available.

Values and acceptability

The systematic review about what matters to families about the care of the preterm or LBW infant (see Table 1.1) reported that families want workplace support, parental leave and financial incentives – especially support for the costs of accommodation, treatment, hospitalization and transport *(14)*. No other specific evidence was located about what types of policies and entitlements for parental leave and financial support families value or find acceptable.

Resources required and implementation considerations

Organization of care

Families need leave and entitlements when the infant is in the health-care facility and also at home, after discharge. Support and planning should be started in the antenatal period where possible or from the time of birth. Services should follow national and local guidance for health-care facilities.

Infrastructure, equipment and supplies

National or local guidance for health-care facilities should be used.

Workforce, training, supervision and monitoring

Health workers at all levels can provide support and referral for parental leave and entitlements, though detailed discussions are often managed by social care staff. Services should follow national and local guidance for health-care facilities. Standardized packages can be used for training, supervision and monitoring.

Feasibility and equity

There was no specific evidence about the feasibility and equity of parental leave and entitlements for preterm or LBW infants.

Summary of judgements

Comparison: Parental leave and entitlements vs usual care (C.4)	
Justification	• There were no studies comparing the benefits and harms of parental leave and entitlements. • This good practice statement was based on a review of 27 global policies for parental leave and entitlements for families of preterm and LBW Infants.

Evidence-to-Decision summary	
Benefits	Large
Harms	None
Certainty	Unknown
Balance	Favours parental leave and entitlements
Values	No uncertainty or variability about outcomes
Acceptability	Acceptable
Resources	Moderate
Feasibility	Varies
Equity	Equitable