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Evidence for global health care interventions for preterm or low birth weight infants: An overview of systematic reviews

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Evidence for Global Health Care Interventions for Preterm or Low Birth Weight Infants: An Overview of Systematic Reviews

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abstract

CONTEXT : Twenty-four research questions (framed as population, intervention, comparator, and outcomes) for global health care interventions for preterm and low birth weight (LBW) infants were identified at a World Health Organization guideline development group expert meeting in December 2020.

OBJECTIVE: To describe which systematic reviews had addressed these research questions in the last 3 years.

DATA SOURCES: Medline (Ovid); the Cochrane Database of Systematic Reviews; the Cochrane Database of Systematic Review Protocols; and the PROSPERO International prospective register of systematic reviews databases from January 1, 2019 to December 31, 2021 were used. Randomized controlled trials or observational studies. Two reviewers independently extracted data.

RESULTS: We found 9 systematic reviews. Eight reviews of 121 studies and 25 465 preterm or LBW infants published in the last 36 months "fully" addressed 8 of our 24 research questions (donor human milk, multicomponent fortifier, formula milk, probiotics, emollients, continuous positive airways pressure [CPAP] any, CPAP early, CPAP prophylactic); and 1 systematic review found no trials (mother's own milk). All received a "high" AMSTAR quality rating. Fifteen research questions (kangaroo mother care, early initiation, responsive feeding, advancement, exclusive breastfeeding duration, iron, zinc, vitamin D, vitamin A, calcium and phosphorous, multiple micronutrients, CPAP pressure source, methyl xanthines, family involvement, and family support) had no systematic review. Limitations include that we restricted our search to those interventions identified as a priority at a World Health Organization scoping meeting. Other interventions that may be of importance to preterm or LBW infants were not able to be considered.

CONCLUSIONS: Almost a third of our research questions were addressed by high quality systematic reviews. We found gaps in thermal care, feeding, and familysupport interventions, which need to be addressed.

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Drs Edmond and Strobel conceptualized and designed the study, designed the data collection instruments, extracted data, and drafted the initial manuscript; and both authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Despite substantial progress over the last 10 years, the survival, morbidity, growth, and neurodevelopment of preterm and low birth weight (LBW) infants remains concerning in many countries.[1–3]

It is well recognized that preventive and promotive care through the first 2 years of life is critical for the preterm and LBW infant.[4–7] Key interventions include: the care that all babies need that may have a special impact on preterm and LBW babies, and the special care that only preterm and LBW infants need.[8] Care ranges from: delivery management, infection prevention, thermal care, responsive care, prevention of injury and pain, nutrition and probiotics, skin care, screening, discharge preparedness, post discharge care, and management of complications. Family support and involvement is required throughout care.[4–8]

Twenty-four research questions (framed as population, intervention, comparator, outcomes [PICOs]) were identified at a World Health Organization guideline development group expert meeting in December 2021 (Table 1).[9]

To understand the current evidence base for these research questions, we conducted an "overview of systematic reviews"[10] process to (1) understand which systematic reviews, if any, had addressed the 24 research questions in the last 3 years and (2) analyze the methodological quality of the reviews.

METHODS

We used standard Cochrane methods for overview of systematic reviews[10] to search for all published systematic reviews of randomized controlled trials (RCTs) and nonrandomized studies of interventions (NRSIs) for the 24 research questions listed in Table 1. We searched for both RCT and observational study systematic reviews. The review was registered in PROSPERO CRD42022309313.[11]

Search Strategy

The search strategy included terms for preterm and LBW and systematic review only, to avoid losing data we did not restrict the initial search terms on intervention type or PICO. The appendix lists the search strategies. The search was limited to the last 36 months, ie, from January 1, 2019 to December 31, 2021. We searched the following databases: Medline via Ovid; the Cochrane Database of Systematic Reviews; the Cochrane Database of Systematic Review Protocols; and the PROSPERO International prospective register of systematic reviews. We used the Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia,[12] to manage all stages.

Criteria for Screening Reviews for Inclusion

Reviews had to assess preterm (<37 weeks' gestation) or LBW infants (<2.5kg) from 0 to 24 months. They could be cared for in both the health facility and the home in all countries (ie, high, middle, and low income countries).

Only studies that examined the impact of the interventions in Table 1 (kangaroo mother care [KMC], feeding, micronutrients, probiotics, emollients, continuous positive airways pressure [CPAP], methyl xanthines, and family involvement and family support) were included. The intervention had to be administered to the infant from birth to 24 months chronological age.

The interventions had to be compared with placebo, no intervention, or usual care as defined by trial authors.

"Critical" outcomes for inclusion in the review were mortality, morbidity, growth, and neurodevelopment.

Reviews were excluded if they: did not address at least 1 of the 24 research questions; did not include preterm or LBW infants; did not assess all of the critical outcomes (ie, mortality, morbidity, growth, and neurodevelopment); if they included small subpopulations only (eg, very preterm or very LBW infants only); or if they did not include a meta-analysis.

Selection of Reviews

Two review authors (K.E. and N.S.) independently screened titles and abstracts, and assessed the full texts of all identified systematic reviews for eligibility. We assessed the reviews' objectives and methods, including outcomes and participants for relevance and included only those reviews that meet the criteria listed above. We resolved any disagreements through discussion until we reached a consensus.

Data Extraction and Management

We generated a data extraction form and pretested it. After verification, 2 review authors (K.E. and N.S.) independently extracted data from each review. We resolved any discrepancies through discussion until we reached a consensus, or, if necessary, by consulting another review author. We collected basic data on: design, year of publication, year of search, number of studies, number of participants, country, health facility type and predefined covariates: population (gestational age and birth weight); intervention characteristics (type, dose, and frequency); comparator characteristics (placebo, no intervention, usual care, and other); and outcomes (mortality, morbidity, growth, and neurodevelopment).[11]

TABLE 1 Research Questions (24) for Care of the Preterm or LBW Infant

Interventions	PICO
Thermal care	
Kangaroo mother care (KMC)	In preterm or LBW infants (P), what is the effect of KMC (I) compared with conventional neonatal care (C) on critical outcomes (O)? If KMC is effective, then what is the effect of early-onset KMC (I) compared with late-onset KMC (C) on critical outcomes (O)? What is the effect of short (I) compared with longer (C) durations of KMC on critical outcomes (O)?
Milk feeding	
Mother's own milk	In preterm or LBW infants (P), what is the effect of feeding mother's own milk (I) compared with feeding infant formula (C) on critical outcomes (O)?
Donor human milk	In preterm or LBW infants who cannot be fed mother's own milk (P), what is the effect of feeding donor human milk (I) compared with feeding infant formula (C) on critical outcomes (O)?
Infant formula	In preterm or LBW infants who cannot be fed mother's own milk or donor human milk (P), what is the effect of feeding nutrient enriched ('preterm') infant formula (I) compared with feeding standard infant ("term") formula (C) on critical outcomes (O)?
Fortification	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of multicomponent fortification of milk (I) compared with no fortification (C) on critical outcomes (O)?
Initiation of enteral feeding	In preterm or LBW infants (P) what is the effect of early initiation of enteral feeding (I) compared with delayed feeding (C) on critical outcomes (O)? If early, then when should feeding be initiated? Does this effect differ in infants given full enteral feeding compared with infants given restricted volumes including minimal enteral feeding?
Responsive feeding	In preterm or LBW infants who receive any enteral feeding (P), what is the effect of responsive feeding based on infants' cues (I) compared with scheduled feeding (C) on critical outcomes (O)?
Volume advancement	In preterm or LBW infants who receive any enteral feeding (P), what is the effect of fast advancement of enteral feeds (I) versus slower rates of feed advancement (C) on critical outcomes (O)?
Duration of exclusive breastfeeding	In preterm or LBW infants (P), what is the effect of exclusive breastfeeding for less than 6 mo (I) compared with exclusive breastfeeding for 6 mo (C) on critical outcomes (O)? If less than 6 mo, then what is the optimal duration?
Micronutrients	
Iron	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral iron supplementation (I) compared with no iron supplementation (C) on critical outcomes (O)?
Zinc	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral zinc supplementation (I) compared with no zinc supplementation (C) on critical outcomes (O)?
Vitamin D	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral vitamin D supplementation (I) compared with no vitamin D supplementation (C) on critical outcomes (O)?
Vitamin A	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral vitamin A supplementation (I) compared with no vitamin A supplementation (C) on critical outcomes (O)?
Calcium and phosphorous	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral CaP04 supplementation (I) compared with no CaP04 supplementation (C) on critical outcomes (O)?
Multiple micronutrient supplements	In preterm or LBW infants who are fed mother's own milk or donor human milk (P), what is the effect of enteral multiple micronutrient supplements (I) compared with no enteral multiple micronutrient supplements (C) on critical outcomes (O)?
Probiotics	
Probiotics	In preterm or LBW infants who receive any enteral feeding (P), what is the effect of probiotics (I) versus no probiotics (C) on critical outcomes (O)?
Skin care	
Emolients	In preterm or LBW infants (P) what is the effect of topical ointment, cream or oil applied to the skin (I) compared with routine skin care (C) on critical outcomes (O)?
CPAP respiratory support	
CPAP for respiratory distress	In preterm infants with respiratory distress syndrome (P), what is the effect of any CPAP therapy (I) versus supportive care with oxygen therapy by head box, facemask, or nasal cannula (C) on critical outcomes (O)?
Early CPAP	In preterm infants with respiratory distress syndrome (P), what is the effect of early CPAP (I) versus late CPAP(C) on critical outcomes (O)?
CPAP prophylaxis	In preterm infants less than 32w regardless of respiratory status (P) What is the effect of CPAP started immediately after birth (I) compared with supportive care with oxygen therapy by head box, face mask, or nasal cannula (C) on critical outcomes (O)? -what is the effect of CPAP started immediately after birth (I) compared with mechanical ventilation (C) on critical outcomes (O)?
CPAP pressure source	In preterm infants with respiratory distress syndrome, what is the effect of bubble (I) compared with other forms of CPAP (C) on critical outcomes (O)?

TABLE 1 Continued

Interventions	PICO
Methyl xanthine respiratory management	
Methyl xanthines	In preterm infants, what is the effect of any methyl xanthine compared with no methyl xanthine on critical outcomes? What is the effect by indication (any, prevention, or treatment), by type of methyl xanthine (eg, caffeine or theophylline) and by gestational age or birth wt.
Family care	
Family involvement	In hospitalized preterm or LBW infants (P) do interventions to involve families in the infant's routine health care (family involvement strategies, FIS) (I) compared with standard hospital or NICU care (C) improve critical outcomes (O)
Family support	In preterm or LBW infants (P), do interventions to support the family to care for the infant in the home (I) compared with no or different interventions (C) improve critical outcomes (O)

PICO, population, intervention, comparator, outcome questions.

Assessment of Methodological Quality of Included Reviews

We assessed the methodological quality of the systematic reviews using AMSTAR 2 (A Measurement Tool to Assess Systematic Reviews).[13] We resolved any discrepancies through discussion until we reached a consensus. AMSTAR 2 assesses the degree to which review methods avoid bias by evaluating the methods against specific criteria. There are 7 critical domains: apriori registration of the study protocol, adequacy of the literature search, justification for excluding studies, assessment of risk of bias including publication bias, appropriateness of meta-analytical methods, assessment of conflicts, and funding source. Each item is rated as high, moderate, low, or critically low.[13] We also collected data on the tool used to assess risk of bias and the tool used to assess certainty of evidence. We did not assess the quality of studies in network meta-analyses because of their different design.

Data Analysis

We described each systematic review by intervention and covariate (as defined above). We also assessed whether each systematic review addressed the research question "fully" (all 4 components of the PICO), "partially" (1 to 3 components of the PICO) or "did not address" (no components of the PICO). We also assessed the methodological quality of the reviews using AMSTAR2 criteria and the overall total quality rating.

RESULTS

We identified 1595 records (Fig 1). After removing duplicates and screening titles, abstracts, and full text articles we included 9 reviews.[14–22] Sixteen reviews were excluded because of wrong population (ie, included very LBW or very preterm infants only), 6 had the wrong study design (eg, were literature reviews without a systematic review or meta-analysis), 2 had the wrong intervention (eg, restricted on feed volume), and 15 had insufficient outcomes assessed (ie, 3 reviews only assessed necrotizing enterocolitis, 3 only assessed bronchopulmonary dysplasia, and 1 only assessed apnea, sepsis, growth, biomarkers). Characteristics of excluded reviews can be found in the appendix.

The characteristics of the 9 included reviews are shown in Table 2. There were a total of 121 studies and 25 465 preterm or LBW infants in the 9 reviews. One review included no studies (ie, was an "empty" review),[14] all the other reviews included only RCTs, and there was 1 network meta-analysis.[19] The number of studies in the reviews ranged from 4 (CPAP) to 45 (probiotics) (median 8, interquartile range [IQR] 5–18, mean 13, standard deviations [SD] 14). The number of participants ranged from 119 (CPAP) to 12 320 (probiotics) (median 1456, IQR 322–3201, mean 2829, SD 3987). Three reviews included under 1000 infants.[17,20,21] All reviews only included hospitalized infants. Only 1 review included studies from low income countries,[19] and 2 included only high income countries.[15,20]

All 9 systematic reviews "fully addressed" (ie, examined all components of the PICOs) of 9 research questions (mother's own milk, donor human milk, fortification, infant formula, emollients, probiotics, or any CPAP, early and prophylactic CPAP). Fifteen research questions (KMC, early initiation, responsive feeding, advancement, exclusive breastfeeding (EBF) duration, iron, zinc, vitamin D, vitamin A, calcium and phosphorous, multiple micronutrients, CPAP pressure source, methyl xanthines, family involvement, and family support) had no systematic review.

The AMSTAR quality assessment is summarized in Table 3. We were not able to assess the quality of 2 reviews; 1 was a network meta-analysis,[19] and 1 was an empty review[14] which found no trials. All the other 7 reviews were rated as high. All reviews used the Cochrane risk of bias (ROB) tool,[23] and the GRADE system for assessing the certainty of the body of evidence.[24,25] All used a comprehensive search strategy, all assessed the potential

TABLE 2 Characteristics of Included Reviews

Domain	Intervention	Review name	Designs	Network Meta-analysis	Year of Search	No Studies	No Infants	Countries	Setting	Type of Participants	Interventions	Comparisons	Outcomes
Thermal care	KMC	—	—	—	—	—	—	—	—	—	—	—	—
Human milk feeding	Mother's own milk	Brown, et al 2019[14]	RCTs only	No	2018	0	0	0	0	Any preterm or LBW	Mother's own milk	0	0
	Donor human milk	Quigley, et al 2019[15]	RCTs only	No	2019	12	1879	HIC	Hospitalized infants only	Any preterm or LBW	Donor	Formula	All critical outcomes
Fortification of human milk	Multi component fortifier	Brown, et al 2020[16]	RCTs only	No	2019	18	1456	HIC, MIC	Hospitalized infants only	Any preterm or LBW	Fortification	None	All critical outcomes
Formula feeding	Formula milk	Walsh, et al 2019[17]	RCTs only	No	2018	7	590	HIC, MIC	Hospitalized infants only	Any preterm or LBW	Formula	None	All critical outcomes
Feeding mechanisms	Early initiation	—	—	—	—	—	—	—	—	—	—	—	—
	Responsive feeding	—	—	—	—	—	—	—	—	—	—	—	—
	Advancement	—	—	—	—	—	—	—	—	—	—	—	—
	EBF duration	—	—	—	—	—	—	—	—	—	—	—	—
Micronutrients	Iron	—	—	—	—	—	—	—	—	—	—	—	—
	Zinc	—	—	—	—	—	—	—	—	—	—	—	—
	Vitamin D	—	—	—	—	—	—	—	—	—	—	—	—
	Vitamin A	—	—	—	—	—	—	—	—	—	—	—	—
	Calcium and phosphorous	—	—	—	—	—	—	—	—	—	—	—	—
	Multiple micronutrients	—	—	—	—	—	—	—	—	—	—	—	—
Probiotics	Probiotics	Chi, et al 2021[19]	RCTs only	Yes	2020	45	12320	HIC, MIC, LIC	Hospitalized infants only	Any preterm or LBW	Probiotics	None, placebo, or different probiotic	All critical outcomes
Skin care	Emollients	Cleminson, et al 2021[18]	RCTs only	No	2021	22	5578	HIC, MIC	Hospitalized infants only	Any preterm or LBW	Emollient	Usual care	All critical outcomes
Respiratory support	CPAP any	Ho, et al 2020[20]	RCTs only	No	2020	4	119	HIC	Hospitalized infants only	Any preterm or LBW	CPAP any	No CPAP	All critical outcomes
	CPAP early	Ho, et al 2020[21]	RCTs only	No	2020	5	322	HIC, MIC	Hospitalized infants only	Any preterm or LBW	CPAP early	Usual care, none or placebo	All critical outcomes
	CPAP prophylactic	Subramaniam, et al 2021[22]	RCTs only	No	2020	8	3201	HIC, MIC	Hospitalized infants only	Any preterm or LBW	CPAP prophylactic	Usual care, none or placebo	All critical outcomes
	CPAP pressure source	—	—	—	—	—	—	—	—	—	—	—	—
	Methyl xanthines	—	—	—	—	—	—	—	—	—	—	—	—
Family	Family involvement	—	—	—	—	—	—	—	—	—	—	—	—
	Family support	—	—	—	—	—	—	—	—	—	—	—	—

—, no data available; HIC, high income country; LIC, low income country; MIC, middle income country; RCTs, randomized control trials.

TABLE 3 Methodological Assessment of Included Studies

Category	Intervention	Review Name	Tool Used to Assess Risk of Bias	Tool Used to Assess Certainty of Evidence	AMSTAR Assessment	Addressed PICO
Human milk feeding	Mother's own milk	Brown, et al 2019[14]	ROB	GRADE	NA	Fully
Donor human milk	Donor	Quigley, et al 2019[15]	ROB	GRADE	High	Fully
Fortification	Fortification	Brown, et al 2020[16]	ROB	GRADE	High	Fully
Formula	Formula	Walsh, et al 2019[17]	ROB	GRADE	High	Fully
Probiotics	Probiotics	Chi, et al 2021[19]	ROB	GRADE	NA	Fully
Skin care	Emollient	Cleminson, et al 2021[18]	ROB	GRADE	High	Fully
Respiratory support	CPAP	Ho, et al 2020[20]	ROB	GRADE	High	Fully
Respiratory support	CPAP	Ho, et al 2020[21]	ROB	GRADE	High	Fully
Respiratory support	CPAP	Subramaniam, et al 2021[22]	ROB	GRADE	High	Fully

GRADE, Grading of Recommendations, Assessment, Development and Evaluations; NA, not applicable; ROB, Risk of Bias Tool.

impact of bias on the results of the meta-analysis, and accounted for bias in discussing the results, and all assessed heterogeneity and small study bias. Two reviews did not report if they performed study selection in duplicate and 5 reviews did not report on the funding of studies.

DISCUSSION

In our overview of systematic reviews, we found 9 systematic reviews of 121 studies and 25 465 preterm or LBW infants published in the last 36 months that addressed 9 of our 24 research questions. The remaining 15 research questions had no systematic review that addressed the research question. The included systematic reviews assessed mother's own milk, donor human milk, fortification, infant formula, emollients, probiotics, any CPAP, and early and prophylactic CPAP. However, important interventions such as KMC, early initiation, responsive feeding, advancement,

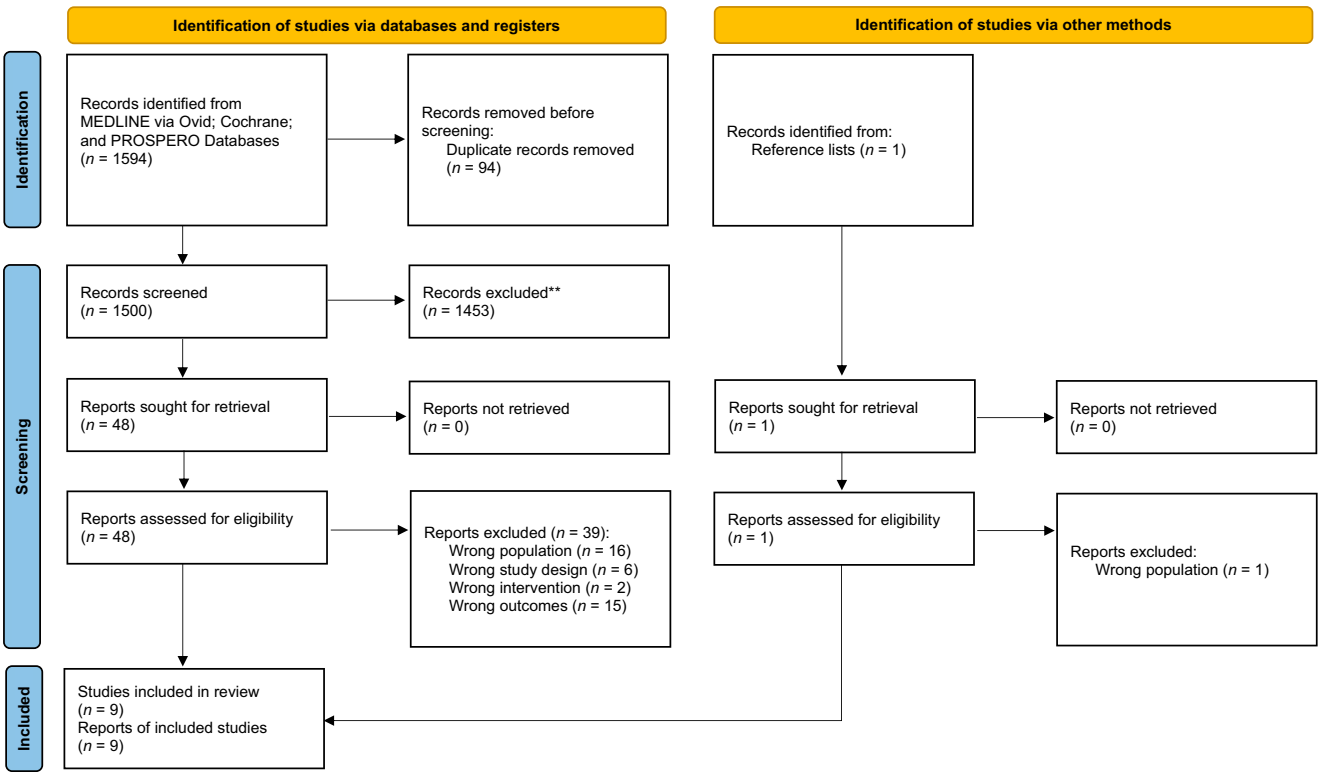

FIGURE 1
Prisma flow diagram. From Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

duration of EBF, iron, zinc, vitamin A, vitamin D, calcium and phosphorous, multiple micronutrients, methyl xanthines, family involvement, and family support did not have a recent systematic review that covered all PICO elements.

Thirty nine reviews met the inclusion criteria partially (ie, covered some element of each PICO) but were excluded from the analysis. Four reviews were excluded as they did not include meta-analyses, 2 reviews assessed the wrong interventions, and 15 did not assess all critical outcomes (mortality, morbidity, growth, and neurodevelopment) (eg, they reviewed only single morbidities such as necrotizing enterocolitis, bronchopulmonary dysplasia, apnea, sepsis, or biomarkers). We had decided apriori that each of the outcomes, mortality, morbidity, growth, and neurodevelopment, were separately "crucial" to the understanding of impact of interventions in preterm and LBW infants. Thus, we did not consider a review to be "complete" unless each of these outcomes were included. Sixteen reviews were excluded because they restricted their target populations to very LBW or very preterm infants. Infants between 32 and 36 weeks' gestation have higher risks of mortality and morbidity than term infants,[3,26] and we felt that that complete reviews should also assess effectiveness in these older infants. Encouragingly, most reviews included term LBW infants, highlighting the now well-known vulnerabilities of these infants.[2–4] However, all the reviews only included studies from hospitalized infants and only 1 study was from a low income country.

All the 9 reviews were rated as high quality and the authors used standard tools for assessing risk of bias and the certainty of the body of evidence, used a comprehensive search strategy, and assessed the potential impact of bias on the results of the meta-analysis and heterogeneity. The authors assessed small study bias if data were available, otherwise, they reported reasons for not completing this (ie, not enough studies available). The only reasons for rating the systematic reviews down were that 2 did not complete study selection in duplicate, and 5 reviews did not state the funding sources of included studies.

There are many current publications of the "estimates" of the prevalence of LBW and prematurity and the "risks" and burden of ill health in preterm and LBW infants.[1–5,26] However, to our knowledge, this is the first overview of systematic reviews of trials of health care interventions for the care of preterm and LBW infants.[10] This lack of "overview" of trials is concerning as we located 48 systematic reviews and 700 trials evaluating health care for preterm and LBW infants just in the last 36 months. In 2010, a global research priority setting exercise identified many research gaps for the care of the preterm and LBW infant.[6] Important questions about the efficacy and effectiveness of interventions for preterm and LBW infants have been answered over the last 10 years, yet our overview has also shown that important gaps in the global evidence base remain.

Our overview had some limitations. We restricted our search only to those interventions identified as a priority at a World Health Organization scoping meeting. Other interventions that may be of importance to preterm or LBW infants were not considered as they were out of scope for this review. We are planning an additional overview of systematic reviews using similar methods to assess these other interventions.

Overall, it is encouraging that almost a third of our research questions were addressed by high quality systematic reviews of over 120 trials and 26 000 infants. However, we found important gaps. Interventions, such as feeding of preterm and LBW infants, especially "what to feed" (micronutrient deficiencies), "how to feed" (ie, the mechanics of feeding young infants), and reviews of family involvement and support had no recent systematic reviews that fully addressed important research questions. All studies were from hospitalized infants and only 1 was from a low income country. These deficits are concerning and need to be urgently addressed.

Systematic reviews of intervention trials are a crucial component of the knowledge base for the health care of all populations. International agencies and the research community must maintain their focus on support of rigorous systematic assessment and meta-analysies of intervention studies. This is especially important for infants with the highest burden of ill health such as those who are born preterm and LBW.

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