

Evidence-based interventions to reduce mortality among preterm and low-birthweight neonates in low-income and middle-income countries: a systematic review and meta-analysis

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ABSTRACT

Background Preterm birth is the leading cause of under-five-mortality worldwide, with the highest burden in low-income and middle-income countries (LMICs). The aim of this study was to synthesise evidence-based interventions for preterm and low birthweight (LBW) neonates in LMICs, their associated neonatal mortality rate (NMR), and barriers and facilitators to their implementation. This study updates all existing evidence on this topic and reviews evidence on interventions that have not been previously considered in current WHO recommendations.

Methods Six electronic databases were searched until 3 March 2020 for randomised controlled trials reporting NMR of preterm and/or LBW newborns following any intervention in LMICs. Risk ratios for mortality outcomes were pooled where appropriate using a random effects model (PROSPERO registration number: CRD42019139267).

Results 1236 studies were identified, of which 49 were narratively synthesised and 9 contributed to the meta-analysis. The studies included 39 interventions in 21 countries with 46 993 participants. High-quality evidence suggested significant reduction of NMR following antenatal corticosteroids (Pakistan risk ratio (RR) 0.89; 95% CI 0.80 to 0.99; Guatemala 0.74; 0.68 to 0.81), single cord (0.65; 0.50 to 0.86) and skin cleansing with chlorhexidine (0.72; 0.55 to 0.95), early BCG vaccine (0.64; 0.48 to 0.86; I^2 0%), community kangaroo mother care (OR 0.73; 0.55 to 0.97; I^2 0%) and home-based newborn care (preterm 0.25; 0.14 to 0.48; LBW 0.42; 0.27 to 0.65). No effects on perinatal (essential newborn care 1.02; 0.91 to 1.14; neonatal resuscitation 0.95; 0.84 to 1.07) or 7-day NMR (essential newborn care 1.03; 0.83 to 1.27; neonatal resuscitation 0.92; 0.77 to 1.09) were observed after training birth attendants.

Conclusion The findings of this study encourage the implementation of additional, evidence-based interventions in the current (WHO) guidelines and to be selective in usage of antenatal corticosteroids, to reduce mortality among preterm and LBW neonates in LMICs. Given the global commitment to end all preventable neonatal deaths by 2030, continuous

Key questions

What is already known?

- ▶ Preterm birth and low birth weight in low-income and middle-income countries (LMICs) are responsible for one of the highest preventable neonatal deaths and disability-adjusted life years (DALYs) globally.
- ▶ In 2015, the WHO published recommendations on interventions to improve preterm birth outcomes, focusing on nine antenatal, perinatal and postnatal interventions, and their maternal and neonatal outcomes.
- ▶ To date, the vast majority of published research on interventions for preterm and low-birthweight (LBW) neonates has been conducted in high-income countries.

What are the new findings?

- ▶ To our knowledge, this is the first systematic review and meta-analysis that updates all existing evidence and provides an overview of new evidence regarding mortality outcomes for preterm and LBW neonates in LMICs.
- ▶ Four effective interventions currently not included in the WHO guidelines were identified: cord and skin cleansing with chlorhexidine, community kangaroo mother care for all LBW neonates <2500 g, home-based newborn care and early BCG vaccination for LBW neonates.
- ▶ Antenatal corticosteroids are effective under certain circumstances.
- ▶ A reporting gap for neonatal mortality outcomes for studies with a focus on antenatal and population-based interventions for preterm and LBW neonates was identified.

evaluation and improvement of the current guidelines should be a priority on the agenda.

BACKGROUND

Globally, an estimated 15 million infants are born prematurely each year.¹ Complications in

Key questions

What do the new findings imply?

- ▶ The novel findings of this study encourage the implementation of additional, evidence-based methods to reduce the neonatal mortality rate among preterm and LBW neonates.
- ▶ Optimal use of maternal and newborn healthcare practices, such as accurate gestational age dating, birth and death registration, and a health system in which continuous knowledge generation is embedded in daily practice, remain priorities to inform future practice.
- ▶ The findings highlight the importance of disaggregated data presentation to increase the availability of neonatal mortality outcomes for preterm and LBW neonates in LMICs.

preterm birth are the leading cause of death in children under 5 years of age globally and accounted for approximately 35% of 2.5 million deaths among all newborn babies in 2018.² An estimated 81.1% of preterm births occurred in Asia and sub-Saharan Africa and >80% of all newborn deaths among preterm and low-birthweight (LBW) neonates occurred in these countries.^{1 3} Low-income and middle-income countries (LMICs) are disproportionately affected due to their lack of available, affordable, acceptable and sufficient-quality maternal and newborn care. Moreover, LMICs continue to deal with shortages of trained health personnel and healthcare technology such as incubators and respiratory support systems. This may cause an increased incidence of disability among preterm and LBW babies, who survive the neonatal period.⁴

Addressing the global burden of preterm birth and LBW babies is crucial to achieve Sustainable Development Goal (SDG) 3.2 and end the preventable deaths of newborns and children under 5 years of age. About 84% of preterm births are moderate and late preterm (32–37 weeks), whose deaths could be prevented with supportive care and feasible interventions.⁵ In 2014, the WHO and UNICEF launched the Every Newborn Action Plan (ENAP), a global roadmap with strategic actions to end preventable newborn mortality and stillbirth by 2035.³ In 2015, the WHO published recommendations on interventions to improve preterm birth outcomes.⁴ This recommendation focused on improving maternal and neonatal outcomes associated with preterm birth. Evidence for nine interventions, identified through a scoping exercise among international stakeholders, was synthesised into a guideline.

Gestational age determination in LMIC settings is known to be challenging. Because of this, a proportion of labelled preterm babies are in fact growth-restricted term neonates. LBW babies are at increased risk of early mortality. They need different strategies and approaches than preterm babies. Neonates that are both preterm and growth retarded are at even higher risk of complications and adverse outcomes.^{6 7} In the current WHO guidelines, fetal growth restriction is not addressed. Interventions aimed at optimising outcomes for LBW neonates were therefore included in this study.

This manuscript updates *all* existing evidence on reduction of neonatal mortality among preterm *and/or*

LBW neonates in LMICs and reviews evidence on interventions that have not been previously considered in the current WHO recommendations.

METHODS

Search strategy and selection criteria

This systematic review and meta-analysis was registered with the PROSPERO registry for systematic reviews (CRD42019139267), conducted according to the Cochrane methodology,⁸ and reporting adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁹ Ethics approval was not required for this literature research. No human or animal participants were involved.

Randomised controlled trials (RCTs) of interventions for preterm and LBW neonates in LMICs with reported neonatal mortality outcomes were eligible for inclusion. These included studies on maternal and neonatal interventions preconception, antepartum, intrapartum or postpartum up to 28 days of life. Given the circumstances and challenges accompanied with conducting an RCT in a low-resource setting and the high number of pre-post intervention studies (before–after design) in our search results, we decided to also include this research design in our review. Exclusion criteria were conference abstracts, reports, editorials, presentations, project protocols, full text unavailable in English or Spanish. We did not include reviews from high-income settings. The rationale behind this is the fact that interventions effective in high-income settings cannot be translated to low-resource settings untested, and circumstances are too different to compare results. Preterm and LBW neonates were defined as <37.0 weeks of gestation and birth weight <2500 g, respectively.³ Mortality definitions were according to WHO (online supplemental appendix 2).¹⁰ LMICs were defined according to the World Bank classification.¹¹ Meta-analysis was performed for studies reporting on the same intervention with similar mortality outcomes.

The search was conducted by MS and MK in six electronic databases from database inception to 3 March 2020: Pubmed/MEDLINE, The Cochrane Library, EMBASE, POPLINE, The Global Health Library and African Journals Online. For every database, a search string was developed with the support of a librarian. Predefined search (title/abstract), MeSH terms, text words and word variants were used to identify preterm and LBW neonates combined with perinatal, neonatal, or infant mortality or survival. The Cochrane Highly Sensitive Search Strategies were used to identify randomised trials in MEDLINE⁸ and BMI Search Blocks¹² to identify LMICs. References were manually searched for additional studies (snowballing). Limits were only applied for the Global Health Library (English). The full search strings are available in .

Endnote reference software (V.X9) was used to remove duplicates both automatically and manually. Subsequently, MS and MK independently screened articles

based on title and abstract using the web application Rayyan.¹³ Studies screened in full text were exported as pdfs to Endnote. Full-text screening was performed by MS and checked by MK. In disagreements, JLB was consulted and articles discussed until consensus was reached. Authors were contacted once when full texts were inaccessible.

Data analysis

MS and MK conducted data extraction supported by JLB. A standardised, piloted data extraction sheet was created with the following information: study design, country and setting, sample size, mean gestational age,

mean birth weight, neonatal mortality outcome and secondary outcomes. Outcome measurements were noted as percentages and relative risk ratios (RR). The corresponding author was emailed once when there were incomplete data. A statistician was consulted in the case of statistical or methodological uncertainties.

Bias was assessed using the Revised Cochrane Risk-of-Bias tool for randomised trials (RoB 2) and the Risk Of Bias In Non-randomised Studies of Interventions (ROBINS-I) tool for before–after studies.^{14 15} As mortality estimates are suggested to be unaffected by lack of blinding,¹⁶ risk of bias of open-label studies was not

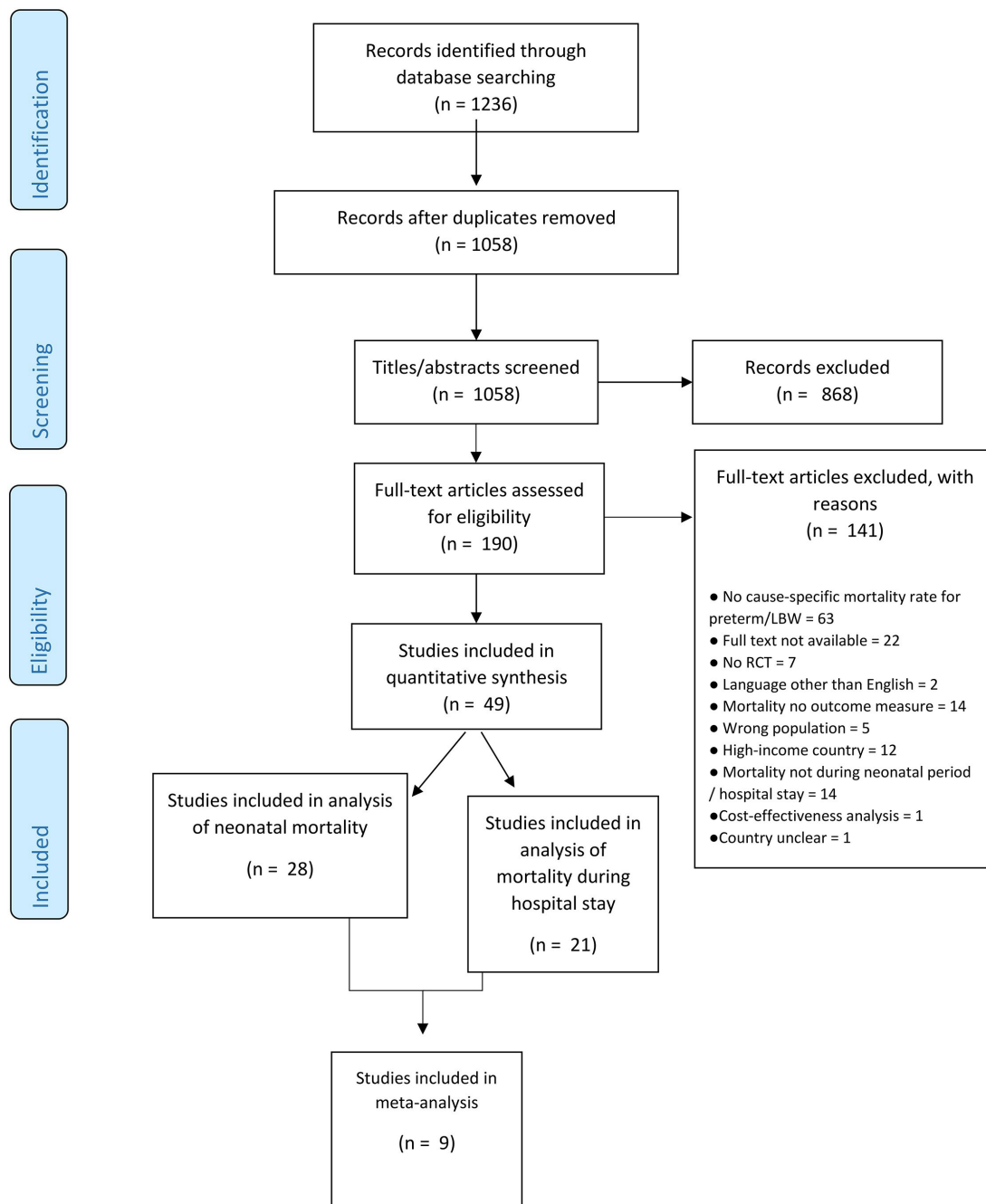


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart study selection. RCT, randomised controlled trial.

increased solely due to unblinded participants, carers or outcome assessors. Cluster RCTs were also assessed on bias arising from the recruitment of individual participants after randomisation with clearly defined inclusion criteria established prior to randomisation considered as low risk of bias. Bias assessment was conducted by MS, with random samples double-checked for accuracy (MK), supported by JLB and/or an external statistician. The evidence quality was assessed across studies according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.¹⁷ An explanation of the GRADE certainty ratings can be found in online supplemental appendix 7.

Quantitative results of (neonatal) mortality rates (NMRs) were summarised in an evidence table with counts, frequencies including, RR with 95% CI and p value, according to intervention. RRs of cluster RCTs retrieved from the study results and RRs of individually randomised studies were computed using RevMan V.5.3.¹⁸ For comparable interventions and outcomes, the RRs were pooled in a meta-analysis using the random-effects model with RevMan V.5.3.¹⁸ A post hoc analysis of studies on in-hospital mortality was performed because of the uncertainty in outcome definition, but there was a high likelihood that these studies predominantly incorporated the neonatal period in their mortality outcome measure. Likewise, RRs with 95% CI and p value of in-hospital mortality were computed using RevMan V.5.3.¹⁸ RRs of in-hospital mortality reported in the stepped-wedge cluster RCT were retrieved from the study results.

In addition to the Cochrane methodology for conducting a systematic review, a strengths, weaknesses, opportunities and threats (SWOT) analysis was done by MS with support from MK and JLB. The rationale behind conducting a SWOT analysis was the analytical framework it provides for the identification of internal (strengths and weaknesses) and external factors (opportunities and threats) that influence the effect of interventions and thereby translate research into practice.¹⁹ The SWOT analysis for each intervention was predominantly based on the included articles.

Patient and public involvement

Due to the nature of this literature study, patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

RESULTS

In total, 1058 articles were identified through database searching after removing duplicates (figure 1). After title and abstract screening, 190 articles were screened in full text, of which 49 were included reporting on 39 different interventions. Of these, 41 were (cluster) randomised trials, 7 were before–after studies, and 1 was both combined. Twenty-eight studies were included in the primary analysis on neonatal mortality^{20–47}; in-hospital mortality was reported from the other 21. This subgroup

of studies was included in a post hoc analysis.^{48–68} Nine studies reported on five similar interventions: early BCG vaccine, community kangaroo mother care (KMC), topical ointment with sunflower seed oil, topical ointment with Aquaphor and bubble CPAP. The results were pooled into a meta-analysis.^{23 24 31 34 35 40 45 60 66}

Tables 1 and 2 present an overview of study characteristics. The included studies were published in 1989–2020 and included 46 993 participants. Studies were conducted in 21 different countries, of which 8 were in low-income countries, 30 were in lower middle-income countries and 7 were in upper middle-income countries (online supplemental appendix 7). Two studies were conducted in multiple LMICs, including a main publication and two subanalyses of the same study.^{20 22 36 39}

Thirty-nine interventions were identified in 49 articles. The interventions were related to the antenatal period (n=2),^{20 21 36 39 43} infection and sepsis prevention (n=11),^{23 24 26 27 31 34 35 37 38 46 48 62 64} feeding (n=3),^{25 42 67} newborn care strategies (n=5),^{22 28–30 40 41 45 47 49 53} prevention and treatment of respiratory morbidity (n=12),^{51 52 54–61 63 65 66} and others (n=5).^{32 33 44 50 68}

Different definitions of mortality were studied. Two studies reported on the rate of stillbirths,^{20 22} three studies included perinatal mortality,^{20–22} two studies reported on 7-day neonatal mortality^{20 22} and one study reported on 21-day neonatal mortality.²³ Twenty-five studies included mortality at 28 days of postnatal age.^{20 24–47} Twenty studies reported in-hospital mortality and death at 36 weeks and one study recorded the gestational age from the last menstrual period.^{48–68}

Table 3 presents an overview of the quantitative results including studies' quality of evidence assessing neonatal mortality, table 4 presents in-hospital mortality, and figure 2 presents meta-analyses (online supplemental appendix 10). Figures 3 and 4 show a visual overview of interventions, study characteristics and quality of evidence. Interventions showing results with high or moderate certainty evidence are narratively discussed in detail. Studies yielding (very) low-quality results are not discussed in detail. figures 3 and 4

Neonatal mortality and in-hospital mortality results are described separately. Studies of high, moderate and low quality are highlighted under different subheadings.

Neonatal mortality

High quality

Thirteen studies were considered of high quality. They evaluated antenatal corticosteroids treatment, skin cleansing with chlorhexidine, early BCG, community KMC, home-based newborn care and training birth attendants.^{20 22 24 27–31 36 39 40 45 46}

Antenatal corticosteroids (ACS) treatment for pregnant women at 24^{0/7}–35^{6/7} weeks of gestation versus standard care was studied in six MICs.²⁰ No significant differences were found in stillbirth, perinatal mortality or 7-day NMR rates. The 28-day NMR varied among the six different study sites. Two subanalyses reported 28-day NMR for

Table 1 Study characteristics of studies assessing neonatal mortality

Author (year) [†] +Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Study definition of mortality
ANTENATAL INTERVENTIONS								
Althabe <i>et al</i> ²⁰ (2015), Garces <i>et al</i> ²⁶ (2016) Klein <i>et al</i> ²⁹ (2016) Argentina, Zambia, Guatemala, India, Pakistan, Kenya	Cluster RCT	18	Women at risk of preterm birth* from 24 ⁺⁰ to 35 ^{+6/7} weeks of gestation/intervention: 2520, control: 2258 <5th percentile birth weight births/intervention: 3268, control: 2997	709 health facilities: 520 clinics and 189 primary health centres, community health clinics or dispensaries	Multifaceted: health-provider training, posters, pregnancy disc and uterine height tape to facilitate identification of women at risk of preterm birth, one course of four doses of 6 mg of dexamethasone intramuscular every 12 hours, referral recommendation for women identified as at high risk of preterm birth	Standard care	Yes	≤28 days post birth
Rasool <i>et al</i> ⁴³ (2017) Pakistan	RCT	1	Pregnant women 28–36 weeks of gestation, admitted to the hospital because of premature contractions or risk of preterm delivery/intervention: 25 (analysed: 24), control: 25 (analysed: 24)	NICU of a teaching hospital	Four doses of 6 mg dexamethasone 12 hours apart (route of admission not reported)	Two doses of 12 mg of dexamethasone 24 hours apart (route of admission not reported)	No	Neonatal death
Aggarwal <i>et al</i> ²¹ (2018) India	RCT	18	Pregnant women between 26 and 33 ^{+6/7} weeks of gestation and arrested preterm labour/intervention: 25, control: 25 Preterm deliveries/intervention: 18 control: 23	Tertiary hospital	Maintenance tocolysis with oral nifedipine 20 mg 8 hourly for 12 days in established preterm labour	Standard care	No	Perinatal mortality
POSTNATAL INTERVENTIONS								
Feeding interventions								
Donor human milk Adhisivam <i>et al</i> ²⁵ (2018) India	RCT	NA	Preterm neonates/intervention: 40, control: 40	NICU of a tertiary hospital	Fortified pasteurised donor human milk (PDHM)	Unfortified PDHM	No	≤28 days post birth or discharge whichever was earlier
Formula feeding Nandakumar <i>et al</i> ⁴² (2020) India	RCT	21	Preterm neonates born between 27 and 32 weeks of gestation; and birth weight <1500 g/intervention: 62, control: 59	Level II NICU of a referral hospital	Hybrid milk feeds: mother's milk supplemented with formula milk	Mother's milk alone	No	Most likely simultaneously measured with oxygen dependency at 28 days. (author did not respond)
Infection prevention								

Continued

Table 1 Continued

Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Study definition of mortality
Arifeen <i>et al</i> ²⁷ (2012) Bangladesh	Cluster RCT	28	LBW† live births/intervention: 3374 (multiple), 3173 (single), control: 3058 Preterm live births/intervention: 2188 (multiple), 1933 (single), control: 2073	Three rural subdistricts of northern Bangladesh	(1) Single cleansing on the cord: 4% aqueous chlorhexidine solution once at birth. (2) Multiple cleansing: at birth plus daily for 7 days.	Dry cord care	Yes	≤28 days post birth
Tielsch <i>et al</i> ⁴⁶ (2007) Nepal	Cluster RCT	31	All live births in the study area Birth weight <2500 g/ intervention: 2448, control: 2491	A rural district where >95% of births occur at home	Wiping of the total body excluding the eyes and ears with infant wipes that released a 0.25% free chlorhexidine solution	Placebo	Yes	≤28 days post birth
Darmstadt <i>et al</i> ²⁴ (2004) Egypt	RCT	NA	Preterm infants with gestational age <34 weeks/intervention: 51, control: 52	NICU of a tertiary hospital	Three times daily topical application of sunflower seed oil (SSO) for the first 14 days, then twice daily until 28 days post birth	Standard skin care	No	Beyond 2 days post birth until 28 days or discharge.
Darmstadt <i>et al</i> ²⁵ (2008) Bangladesh	RCT	68	Preterm infants ≤72 hours after birth ≤33 weeks of gestation/intervention: 157 Aquaphor, 159 SSO, control: 181	Special care nursery of a children's hospital	(1) Topical high-linoleate SSO. (2) Aquaphor original emollient topical ointment.	Standard skin care	No	≤28 days post birth
Erdemir <i>et al</i> ²³ (2015) Turkey	RCT	24	Preterm infants ≤34 weeks of gestation/intervention: 100, control: 97	Level III NICU of a tertiary hospital	Aquaphor original emollient topical ointment	Standard skin care	No	Not reported. The infants were studied for a period of 3 weeks
Aggarwal <i>et al</i> ²⁶ (2016) India	RCT	14	VLBW† infants with gestational age <32 weeks/intervention: 49 (analysed: 45), control: 50 (analysed: 45)	Neonatology department of a tertiary hospital	Supplementation with 10 µg selenium (SE) powder	100 mg Glucon-D powder alone	No	≤28 days post birth; during hospital stay or follow-up
Kaur <i>et al</i> ²⁷ (2015) India	RCT	15	LBW neonates <2000 g/intervention: 65 (analysed: 63), control: 67	Level III NICU of a tertiary hospital	Bovine lactoferrin supplementation	Placebo	No	After the first 72 hours up to 28 days post birth
Aaby <i>et al</i> ²⁴ (2011) Guinea-Bissau	RCT	39	LBW infants/intervention: 1182 (analysed: 1168), control: 1161 (analysed: 1152)	Six districts with a population of around 102 000, including 30% of the inhabitants of the capital	Early BCG vaccine administered directly after birth	Late BCG (when a normal birth weight was obtained or with the first DTP vaccination at 6 weeks of age)	Yes	At 1 month of age
Biering-Sørensen <i>et al</i> ²¹ (2017) Guinea-Bissau	RCT	79	LBW infants/intervention: 2062 (analysed: 2059), control: 2071 (analysed: 2061)	Six districts with a population of around 102 000, including 30% of the inhabitants of the capital	Early BCG vaccine administered directly after birth	Late BCG	Yes	≤28 days post birth

Continued

Table 1 Continued

Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Study definition of mortality
Kirpal <i>et al</i> ²⁸ (2016) India	RCT	19	VLBW neonates receiving broad spectrum IV antibiotics for >3 days/ intervention: 40 (analysed: 38), control: 40 (analysed: 37)	NICU of a tertiary hospital	Intravenous fluconazole (6 mg/kg) every other day for 7 days, then daily until day 28 post birth or discharge	Placebo	No	≤28 days post birth
Strategies of newborn care								
Nagai <i>et al</i> ⁴¹ (2010) Madagascar	RCT	14	LBW neonates/intervention: 37, control: 36	A university referral hospital	Earlier kangaroo mother care (KMC): begin as soon as possible within 24 hours post birth	Conventional care	Yes	≤28 days post birth
Worku <i>et al</i> ⁴⁷ (2005) Ethiopia	RCT	12	Neonates with birth weight <2000 g/intervention: 62, control: 61	Neonatal unit of a tertiary university hospital	Earlier KMC: begin as soon as possible within 24 hours post birth	Conventional care	Yes	Not reported. The mean age at exit from the study was 4.6 days for KMC and 5.4 days for CMC
Mazumder <i>et al</i> ⁴⁰ (2019) India	RCT	39	Neonates weighing 1500–2250 g at home within 72 hours of birth, stable and feeding/intervention: 4480 (4470 analysed), control: 3922 (3914 analysed)	Rural and semiurban areas in two districts	Community-based KMC	Standard home-based care	Yes	≤28 days post birth
Sloan <i>et al</i> ⁴⁵ (2008) Bangladesh	Cluster RCT	15	All women aged 12–50 years/ intervention: 20 516, control: 19 337 Live births ≤2500 g/intervention: 408, control: 333 Live births ≤2000 g/intervention: 95, control: 71	Four rural subdistricts	Community-based KMC	Standard home-based care	Yes	≤28 days post birth
Home-based neonatal care								
Bang <i>et al</i> ²⁹ (1999) India	Pre-post intervention trial	60	LBW live births/observation year: 320, last intervention year: 321 Preterm births/observation year: 75, last intervention year: 93	A rural, underdeveloped subdistrict of India	Package of home-based neonatal care including management of sepsis	Preintervention period	Yes	≤28 days post birth
Bang, Baitule <i>et al</i> ²⁸ (2005) India	Pre-post intervention trial	108	LBW live births/observation year: 320, last three intervention years: 825 Preterm neonates/observation year: 75, last three intervention years: 226	A rural, underdeveloped subdistrict of India	Package of home-based neonatal care including management of sepsis	Preintervention period	Yes	≤28 days post birth
Bang, Reddy <i>et al</i> ³⁰ (2005) India	Pre-post intervention trial	120	Preterm neonates/observation year: 75, last two intervention years: 142	A rural, underdeveloped subdistrict of India	Package of home-based neonatal care including management of sepsis	Preintervention period	Yes	≤28 days post birth

Continued

Table 1 Continued

	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Study definition of mortality
Training of traditional birth attendants	Carlo <i>et al</i> ²² (2010) Argentina, Democratic Republic of Congo, Guatemala, India, Pakistan, Zambia	ENC: pre-post intervention trial, NRP: cluster RCT	24 (ENC)/26 (NRP)	VLBW infants/ENC pre-trial: 169, post-trial: 359 NRP intervention: 273, control: 295	ENC: 96 rural communities, NRP: 88 rural communities	Essential Newborn Care (ENC) training and Neonatal Resuscitation Programme (NRP) training	ENC: preintervention period, NRP: no additional training	Yes	7-day neonatal mortality, perinatal mortality and stillbirths
Others									
DCC	Chopra <i>et al</i> ²³ (2018) India	RCT	16	Pregnant women with gestational age at delivery of ≥35 weeks and an SGA infant <10th percentile/intervention: 55, control: 58	Tertiary hospital	DCC after 60 s	ECC immediately after birth	No	Neonatal mortality
Hypothermia prevention	Sarman <i>et al</i> ⁴⁴ (1989) Turkey	RCT	10	Neonates weighing between 1000 and 2000 g, <7 days of age/intervention: 28, control: 32	Neonatal care unit of a university hospital	Hypothermia prevention with heated, water-filled mattress incubators	Air-heated incubators	No	Neonatal death
Quality improvement intervention	Cavicchiolo <i>et al</i> ²² (2016) Mozambique	Pre-post intervention trial	24	All newborns admitted to the NICU admission for prematurity/preintervention: 447, postintervention: 605	Obstetrical department and NICU of a large public hospital	Quality improvement intervention focused on infrastructure, equipment and clinical protocols	Preintervention period	Yes	Neonatal mortality

*Preterm birth/neonate=<37 weeks of gestation.

†LBW=low birth weight (< 2500 g).

‡VLBW=very low birth weight (< 1500 g).

CMC, conventional method of care; DCC, delayed cord clamping; DTP, diphtheria, tetanus, pertussis; ECC, early cord clamping; ENC, essential newborn care; IV, intravenous; KMC, kangaroo mother care; NICU, neonatal intensive care unit; NRP, neonatal resuscitation program; PDHM, pasteurised donor human milk; RCT, randomised controlled trial; Se, selenium; SGA, small for gestational age; SSO, sunflower seed oil.

Table 2 Study characteristics of studies assessing in-hospital mortality

	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Duration of hospital stay in days (mean±SD)
POSTNATAL INTERVENTIONS									
Feeding interventions									
Feeding schedule	Tali <i>et al</i> ⁶⁷ (2016) India	RCT	NA	Neonates weighing 501–1500 g/intervention: 60, control: 60	Level III NICU	3-hour feeding schedule (eight feeds daily)	2-hour feeding schedule (12 feeds daily)	No	Intervention: 46±21.5, control: 43.7±20.2
Infection prevention									
Granulocyte stimulation	Aktas <i>et al</i> ⁶⁸ (2015) Turkey	RCT	24	Neutropenic preterm neonates* with culture-proven or suspected sepsis/intervention: 33, control: 23	Teaching hospital	Recombinant human granulocyte-macrophage colony-stimulating factor (rhG-CSF) 10 mg/kg/day in 5% dextrose until absolute neutrophil count reached >1.0×10 ⁹ /L	Empirical antibiotics alone	Yes	Not reported
Pro/synbiotic supplements	Nandhini <i>et al</i> ⁶² (2016) India	RCT	NA	Enterally fed preterm neonates with gestational age 28–34 weeks and birth weight >1000 g/intervention: 110 (analysed: 108), control: 110	Paediatrics department of a tertiary hospital	Synbiotics supplement: <i>Lactobacillus acidophilus</i> , <i>Bifidobacterium longum</i> , <i>Lactobacillus rhamnosus</i> , <i>Lactobacillus plantaris</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus bulgaricus</i> , <i>Bifidobacterium infantis</i> , <i>Bifidobacterium breve</i> and 100 mg of fructo-oligosaccharide (prebiotic)	Standard care	No	Intervention: 8.3±4.5, control: 8.4±5.1
Prevention and treatment of respiratory morbidity	Sari <i>et al</i> ⁶⁴ (2011) Turkey	RCT	9	Preterm neonates with a gestational age <33 weeks or birth weight <1500 g, who survived to feed enterally/intervention: 121 (analysed: 110), control: 121 (analysed: 111)	NICU of a training hospital	Feeding with oral probiotic <i>Lactobacillus sporogenes</i> 350 000 colony-forming unit once a day	Breast milk or formula alone	Yes	Death >7 days intervention: 43.5, control: 30

Continued

Table 2 Continued

CPAP	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Duration of hospital stay in days (mean±SD)
	Bhatti <i>et al</i> ⁶² (2015) India	RCT	19	Preterm neonates <34 weeks of gestation with respiratory distress within 6 hours of life/intervention: 80, control: 90	Two level III NICU's	Nasal-jet CPAP device: a variable flow CPAP device with a Benveniste valve that generates CPAP at the level of the nostril with a short binasal prong as nasal interface	Bubble CPAP	No	Not reported
	Mazmanyan <i>et al</i> ⁶⁰ (2016) Armenia	RCT	NA	Preterm neonates/ intervention: 66, control: 59	Neonatal unit	Bubble CPAP	Flow driver CPAP	No	Not reported
	Okello <i>et al</i> ⁶³ (2019) Uganda	Pre-post intervention trial	32	VLBW† neonates/ preintervention: 158, postintervention: 219	Neonatal unit of a regional referral hospital	Bubble CPAP	Preintervention period	Yes	Median (IQR) preintervention: 8 (2, 17), postintervention: 9.5 (4, 19)
	Say <i>et al</i> ⁶⁵ (2016) Turkey	RCT	7	Preterm infants with gestation 26–32 weeks and IRDS/intervention: 75, control: 74	NICU of a teaching hospital	Binasal prong for applying CPAP	Nasal mask for applying nasal CPAP	No	Median (IQR) intervention: 18 (10–21), control: 25 (20–28)
	Tagare <i>et al</i> ⁶⁶ (2013) India	RCT	13	Preterm neonates with IRDS and oxygen requirement >30% within first 6 hours of life/intervention: 57, control: 57	NICU of a tertiary hospital	Bubble CPAP	Ventilator-derived CPAPNot reported	No	Not reported

Continued

Table 2 Continued

	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Duration of hospital stay in days (mean±SD)
Exogenous surfactant replacement therapy	Gharehbaghi <i>et al</i> ⁶⁴ (2010) Iran	RCT	13	Preterm infants with IRDS that required exogenous surfactant replacement therapy/intervention: 79, control: 71	Level III NICU of a university hospital	Poractant alfa 200 mg/kg in two divided doses	Beractant 100 mg/kg in four divided doses	No	Intervention: 24.9±26.4, control: 29.1±23.5
	Halim <i>et al</i> ⁶⁵ (2018) Pakistan	RCT	8	Preterm neonates at <34 weeks of gestation with IRDS/intervention: 50, control: 50	Neonatal unit of a tertiary hospital	Less invasive surfactant administration (LISA) method: surfactant was administered at a dose of 100 mg/kg of Survanta with the help of size 6Fr nasogastric tube	Conventional INSURE method: Intubation SURfactant and Extubation	No	Median (IQR) intervention: 7 (5), control: 6 (4)
	Jain <i>et al</i> ⁶⁷ (2019) India	RCT	19	Preterm neonates born at 26–32 weeks' gestation with clinical features of IRDS ≤6 hours of birth and fulfilled criteria for surfactant therapy ≤24 hours of birth/intervention: 53 (analysed: 52), control: 48 (analysed: 46)	NICUs of seven tertiary care centres	Goat lung surfactant extract	Beractant	Yes	Intervention: 31.6±32.0, control: 31.7±21.9
Feeding supplementation	Basu <i>et al</i> ⁵¹ (2019) India	RCT	20	VLBW neonates requiring respiratory support in the form of oxygen inhalation, CPAP, high flow nasal cannula (HFNC), or mechanical ventilation at the age of 24 hours/intervention: 98, control: 98	NICU of a tertiary care teaching hospital	Oral vitamin A 1 mL of syrup (10 000 IU of retinol/dose) on alternate day for 28 days, starting at 24 hours of life	Placebo	No	Death was recorded at 36 weeks post menstrual age

Continued

Table 2 Continued

	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Duration of hospital stay in days (mean±SD)
Oxygen systems other than CPAP	Graham <i>et al</i> ⁶⁵ (2019) Nigeria	Stepped-wedge cluster RCT	44	All children (aged <15 years), admitted to participating hospitals. LBW±, preterm/preintervention: 1883, pulse oximetry: 688, full O ₂ system: 1137	Twelve general, paediatric, and maternity hospitals in southwest Nigeria	<p>▲ Pulse oximetry to improve clinical use of oxygen targeting hypoxaemic neonates</p> <p>▲ Full O₂ system involving (1) a standardised oxygen equipment package, (2) clinical education and support, (3) technical training and support, and (4) infrastructure and systems support</p>	Preintervention period	Yes	Not reported
	Krishna <i>et al</i> ⁶⁸ (2019) India	RCT	17	Preterm neonates with gestational age of 27–34 weeks, ventilated within the first week of life for IRDS/intervention: 40, control: 41	Level III NICU of a tertiary hospital	Volume-guaranteed ventilation (VGV)	Pressure-controlled ventilation	No	Not reported
	Murki <i>et al</i> ⁶¹ (2018) India	RCT	13	Preterm infants with gestational age of ≥28 weeks and birth weight ≥1000 g, with respiratory distress/intervention: 133, control: 139	NICUs of two tertiary care hospitals	High-flow nasal cannula (HFNC) as a primary non-invasive respiratory support	Nasal CPAP	No	Intervention: 18±13, control: 17±14
Prophylactic methylxanthines	Kumar <i>et al</i> ⁶⁹ (2017) India	RCT	24	Preterm neonates with gestational age of ≤30 weeks, who were intubated for ≥24 hours/intervention: 78 (analysed: 70), control: 78 (analysed: 73)	NICU of a tertiary hospital	Aminophylline: loading dose of 5 mg/kg, followed by a maintenance dose of 1.5 mg/kg Q8h via injection and oral preparation of 10 mg/mL of theophylline	Caffeine: a loading dose of 20 mg/kg of caffeine citrate and continued on a maintenance dose of 5 mg/kg Q24h via (IV or oral)	No	Duration of NICU stay median (25th percentile, 75th percentile)/intervention: 34 (14.8, 48.3), control: 38 (21, 55)

Strategies of newborn care

Continued

Table 2 Continued

	Author (year)+Country	Study design	Duration of study (months)	Study participants and sample size	Setting	Intervention	Control	Mortality as primary outcome	Duration of hospital stay in days (mean±SD)
Maternal nursing care	Arif <i>et al</i> ⁴⁹ (1999) Pakistan	RCT	6	Babies weighing 1000–2000 g on admission irrespective of sex or age/intervention: 160 (analysed: 151), control: 240 (analysed: 211)	Neonatal ward of a government children's hospital	Maternal nursing care	Special care baby unit, looked after entirely by nurses	Yes	Not reported
	Bhutta <i>et al</i> ⁵³ (2004) Pakistan	Pre-post intervention trial	98	VLBW infants/intervention: 318, control: 191	Neonatal unit of a tertiary hospital	A stepdown unit (involvement of maternal nursing care)	Preintervention period	Yes	Intervention: 15.4±15.7, control: 22.2±21.7
Others									
Strategies for PDA closure	Balachander <i>et al</i> ⁵⁰ (2018) India	RCT	16	Preterm neonates with PDA of size ≥1.5 mm and left to right shunt after 24 hours of life/intervention: 55, control: 55	Neonatal unit of a tertiary hospital	Oral paracetamol for PDA closure: 15 mg/kg/dose 6-hourly by oro-gastric tube or paladai for 2 days	Oral ibuprofen: 10 mg/kg stat on day 1 followed by 5 mg/kg 24 hours for 2 days	No	Intervention: 21.4±11.8, control: 25.7±15.1
Hypothermia prevention	Van Den Bosch <i>et al</i> ⁵⁸ (1996) Malawi	RCT	4	Neonates with a birth weight of 800–1500 g and Apgar score >7/intervention: 33 (analysed: 15), control: 32 (analysed: 11)	Neonatal nursery of a tertiary hospital	Polythene tobacco-wrap folded double with one thickness above and two thicknesses tucked below the baby	Standard nursing procedure	No	Intervention: 29.4 (95% CI 1.0 to 57.8), control: 14 (–9.6 to 37.6)

*Preterm neonate=<37 weeks of gestation.

†VLBW=very low birth weight (<1500 g).

‡LBW=low birth weight (<2500 g).

CPAP, continuous positive airway pressure; HFNC, high flow nasal cannula; INSURE, intubation surfactant administration and Extubation; IRDS, infant respiratory distress syndrome; IV, intravenous; LISA, less invasive surfactant administration; NICU, neonatal intensive care unit; PDA, patent ductus arteriosus; RCT, randomised controlled trial; rhG-CSF, recombinant human granulocyte-macrophage colony-stimulating factor; VGV, volume-guaranteed ventilation.

Table 3 Neonatal mortality rates and calculated risk ratios

Intervention	Control	Mortality definition	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95%CI	P value	GRADE quality of evidence
ANTENATAL INTERVENTIONS									
Four doses of dexamethasone 6 mg 12 hours apart	Standard care	Stillbirths	Althabe <i>et al</i> ²⁰ (2015)	748 (22.9)	739 (24.7)	0.99	0.90–1.09	0.81	⊕⊕⊕⊕ High
		Perinatal mortality	Althabe <i>et al</i> ²⁰ (2015)	1203 (36.8)	1172 (39.1)	0.97	0.91–1.04	0.46	⊕⊕⊕⊕ High
		7-day neonatal mortality	Althabe <i>et al</i> ²⁰ (2015)	455 (13.9)	433 (14.4)	0.94	0.84–1.06	0.30	⊕⊕⊕⊕ High
		28-day neonatal mortality	Althabe <i>et al</i> ²⁰ (2015)	566 (22.4)	524 (23.2)	0.96	0.87–1.06	0.65	⊕⊕⊕⊕ High
			Garces <i>et al</i> ⁸⁶ (2016)	36 (18.3)	39 (23.5)	0.74	0.68–0.81	<0.0001	⊕⊕⊕⊕ High
			Klein <i>et al</i> ³⁹ (2016)	133 (25)	158 (25.6)	0.96	0.75–1.22	NA	⊕⊕⊕⊕ Moderate*
			Nagpur, India	109 (30.5)	84 (32.9)	0.94	0.72–1.23	NA	⊕⊕⊕⊕ Moderate*
			Pakistan	172 (22.6)	172 (25)	0.89	0.80–0.99	NA	⊕⊕⊕⊕ High
			Zambia	30 (15.2)	27 (12.7)	1.43	0.90–2.28	NA	⊕⊕⊕⊕ Moderate*
			Kenya	45 (19.2)	27 (14.3)	1.30	0.94–1.81	NA	⊕⊕⊕⊕ Moderate*
Two doses of 12 mg of dexamethasone 24 hours apart	Standard care	Guatemala	Guatemala	57 (16.5)	39 (23.5)	0.75	0.69–0.82	NA	⊕⊕⊕⊕ High
		Argentina	Argentina	20 (22)	17 (13)	1.60	0.99–2.58	NA	⊕⊕⊕⊕ Moderate*
		Rasool <i>et al</i> ⁴³ (2017)	0 (0)†	2 (8.4)†	0.20	0.01–3.96	0.29	⊕⊕⊕⊕ Very low‡§¶**	
Maintenance tocolysis with nifedipine	Standard care	Perinatal mortality	Aggarwal <i>et al</i> ²¹ (2018)	2 (11.1)	3 (13)	0.85	0.16–4.57	0.85	⊕⊕⊕⊕ Low**
POSTNATAL INTERVENTIONS									
Feeding interventions									

Continued

Table 3 Continued

Intervention	Control	Mortality definition	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95%CI	P value	GRADE quality of evidence
Fortified pasteurised donor human milk (PDHM)	Unfortified PDHM	28-day neonatal mortality	Adhivam <i>et al</i> ²⁵ (2018)	3 (7.5)	3 (7.5)	1.00	0.21–4.66	1.00	⊕⊕○○ Low**
Hybrid milk feeds	Mother's milk alone		Nandakumar <i>et al</i> ⁴² (2020)	4 (6.4)	5 (8.4)	0.76	0.21–2.70	0.67	⊕○○○ Very low††††**
Infection prevention									
Single cord cleansing with chlorhexidine	Dry cord care	28-day neonatal mortality	Arifeen <i>et al</i> ²⁷ (2012)	LBW: 121 (3.8) Preterm: 78 (4.0)	145 (4.7)	0.82	0.63–1.06	NA	⊕⊕⊕⊕ High
Multiple cord cleansing with chlorhexidine				LBW: 159 (4.7) Preterm: 119 (5.4)	145 (4.7)	1.00	0.79–1.27	NA	⊕⊕⊕⊕ High
Skin cleansing with chlorhexidine	Placebo		Tielsch <i>et al</i> ⁴⁷ (2007)	83 (3.4)	117 (4.7)	0.72	0.55–0.95	NA	⊕⊕⊕⊕ High
Topical ointment SSO	Standard skin care		Darmstadt <i>et al</i> ²⁴ (2004)	12 (23.5)	18 (34.6)	0.68	0.37–1.26	0.29	⊕⊕○○ Low*\$††\$
SSO and Aquaphor			Darmstadt <i>et al</i> ³⁵ (2008)	SSO: 105 (65.8)	128 (70.6)	SSO: 0.93	SSO: 0.81–1.08	SSO: 0.36	⊕⊕○○ Low*\$††\$
Aquaphor		21-day neonatal mortality	Erdemir <i>et al</i> ²³ (2015)	10 (10)	4 (4.1)	2.43	0.79–7.47	0.12	⊕⊕○○ Low*\$††\$
Supplementation Selenium	Glucon-D powder alone	28-day neonatal mortality	Aggarwal <i>et al</i> ²⁶ (2016)	2 (4.4)	3 (6.7)	0.67	0.12–3.80	0.65	⊕○○○ Very low****
Bovine lactoferrin	Placebo		Kaur <i>et al</i> ³⁷ (2015)	0 (0)	5 (7.5)	0.10	0.01–1.71	0.11	⊕⊕○○ Low**
Early BCG vaccine	Late BCG		Aaby <i>et al</i> ²⁴ (2011)	27 (2.3)	48 (4.2)	0.55	0.35–0.88	0.01	⊕⊕⊕⊕ High\$
Prophylactic fluconazole	Placebo		Biering Sorensen <i>et al</i> ⁶¹ (2017)	44 (2.1)	62 (3.0)	0.71	0.49–1.04	0.08	⊕⊕⊕⊕ High\$
			Kirpal <i>et al</i> ⁸⁸ (2016)	7 (18.4)	12 (32.4)	0.57	0.25–1.28	0.17	⊕⊕⊕○ Moderate*
Strategies of newborn care									

Continued

Table 3 Continued

Intervention	Control	Mortality definition	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95%CI	P value	GRADE quality of evidence
Early KMC	Late KMC	28-day neonatal mortality	Nagai <i>et al</i> ⁴¹ (2010)	2 (5.4)	1 (2.8)	1.95	0.18–20.53	0.58	⊕⊕○○ Low**
Community KMC	Conventional care	Standard home-based care	Worku <i>et al</i> ⁴⁷ (2005)	14 (22.5)	24 (38)	0.57	0.33–1.00	0.05	⊕⊕⊕○ Moderate*
			Sloan <i>et al</i> ⁴⁵ (2008)	≤2500 g: 22 (5.4) ≤2000 g: 9 (9.5)	20 (6) 16 (22.5)	0.87††† 0.37†††	0.43–1.74††† 0.16–0.86†††	0.69††† 0.02†††	⊕⊕⊕⊕ High§§ ⊕⊕⊕○ Moderate*
Home-based neonatal care	Preintervention period		Mazumder <i>et al</i> ⁴⁰ (2019)	73 (1.6)	90 (2.3)	0.71	0.52–0.96	0.03	⊕⊕⊕⊕ High§§
			Bang <i>et al</i> ²⁹ (1999)	LBW: 13 (4) Preterm: 9 (9.7)	36 (11.3) 25 (33.3)	0.36 0.29	0.20–0.67 0.14–0.58	0.0011 0.0005	⊕⊕⊕⊕ High
			Bang, Baitule <i>et al</i> ²⁸ (2005)	Preterm: 23 (10.2)	25 (33.3)	0.31	0.18–0.50	0.00	⊕⊕⊕⊕ High
			Bang, Reddy <i>et al</i> ³⁰ (2005)	LBW: 39 (4.7) 12 (8.5)	36 (11.3) 25 (33.3)	0.42 0.25	0.27–0.65 0.14–0.48	0.0001 0.0000	⊕⊕⊕⊕ High
Training of traditional birth attendants	ENC: preintervention period NRP: No additional training	Stillbirths	Carlo <i>et al</i> ²² (2010)	ENC: 157 (43.7) NRP: 91 (33.3)	ENC: 72 (42.6) NRP: 101 (34.2)	ENC: 1.03 NRP: 0.97	ENC: 0.80–1.31 NRP: 0.57–1.67	NA NA	⊕⊕⊕○ Moderate*
		Perinatal mortality		ENC: 283 (78.8) NRP: 198 (72.5)	ENC: 133 (78.7) NRP: 225 (76.3)	ENC: 1.02 NRP: 0.95	ENC: 0.91–1.14 NRP: 0.84–1.07	NA NA	⊕⊕⊕⊕ High
		7-day neonatal mortality		ENC: 126 (35.1) NRP: 107 (39.2)	ENC: 61 (36.1) NRP: 124 (42)	ENC: 1.03 NRP: 0.92	ENC: 0.83–1.27 NRP: 0.77–1.09	NA NA	⊕⊕⊕⊕ High

Others

Continued

Table 3 Continued

Intervention	Control	Mortality definition	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95%CI	P value	GRADE quality of evidence
Delayed cord clamping	Early cord clamping	28-day neonatal mortality	Chopra <i>et al</i> ⁶³ (2018)	1 (1.8)	0	3.16	0.13–75.98	0.48	⊖○○○ Very low**‡‡‡
Heated mattress	Air-heated incubators		Sarman <i>et al</i> ⁴⁴ (1989)	6 (21.4)	11 (34.4)	0.62	0.26–1.47	0.28	⊕⊕⊕○ Moderate*
Quality improvement intervention	Preintervention period		Cavicchiolo <i>et al</i> ³² (2016)	200 (33.0)	192 (43.0)	0.77	0.66–0.90	0.001	⊕⊕⊕○ Moderate\$\$\$

*Insufficient sample to meet optimal information size (OIS) criteria and/or 95% CI close to or crosses line of no effect or fails to exclude important benefit or harm.

†The mortality event rate is based on the number of women per study arm who received the intervention.

‡Identification and recruitment of individual participants occurred after randomisation.

§Method of randomisation is not reported, baseline differences suggest a problem with randomisation.

¶Information about blinding of participants and carers is not provided.

**Insufficient sample to meet OIS criteria with very few events and 95% CI fails to exclude important benefit or harm.

††Allocation concealment is not reported.

‡‡Method of ascertainment of mortality outcome measure is not reported.

§§Derived from the meta-analysis pooling the results of both studies.

¶¶I² of 76%, p value of 0.04, minimal overlapping 95% CIs and one study showing benefit while the other study shows harm suggest serious inconsistency of results.

***Loss to follow-up and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available.

†††OR; adjusted for cluster design effect.

‡‡‡Substantial loss to follow-up in relation to the number of events and failure to adhere to the intention-to-treat principle.

§§§Confounding due to baseline differences cannot be excluded and is not controlled for in the study.

Table 4 Mortality rates during hospitalisation and calculated risk ratios

Intervention	Control	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95% CI	P value	GRADE quality of evidence
Feeding interventions								
3-hour feeding schedule	2-hour feeding schedule	Tali <i>et al</i> ⁶⁷ (2016)	0	0	NA	NA	NA	⊕⊕○○ Low*
Infection prevention								
rhG-CSF	Empirical antibiotics alone	Aktas <i>et al</i> ⁴⁸ (2015)	10 (30.3)	6 (26.1)	1.16	0.49–2.74	0.73	⊕⊕○○ Low*
Synbiotics	Standard care	Nandhini <i>et al</i> ⁶² (2016)	10 (9.3)	9 (8.2)	1.13	0.48–2.68	0.78	⊕⊕○○ Low*
<i>Lactobacillus sporogenes</i>	Breast milk or formula alone	Sari <i>et al</i> ⁶⁴ (2011)	3 (2.7)	4 (3.6)	0.76	0.17–3.30	0.71	⊕⊕○○ Low*
Prevention and treatment of respiratory morbidity								
Nasal-jet CPAP	Bubble CPAP	Bhatti <i>et al</i> ⁵² (2015)	20 (25)	16 (18)	1.41	0.78–2.52	0.25	⊕⊕○○ Moderate†
Bubble CPAP	Flow driver CPAP	Mazmanyan <i>et al</i> ⁶⁰ (2016)	3 (4.5)	1 (1.7)	2.68	0.29–25.08	0.39	⊕○○○ Low*‡
	Preintervention period	Okello <i>et al</i> ⁶³ (2019)	58 (26.5)	62 (39.2)	0.68	0.50–0.91	0.01	⊕○○○ Low\$
	Ventilator-derived CPAP	Tagare <i>et al</i> ⁶⁶ (2013)	4 (7)	5 (8.8)	0.80	0.23–2.83	0.73	⊕○○○ Low*
	Nasal mask for applying nasal CPAP	Say <i>et al</i> ⁶⁵ (2016)	4 (5.4)	7 (9.3)	0.56	0.17–1.85	0.34	⊕○○○ Low*
Surfactant	Beractant	Gharehbaghi <i>et al</i> ⁵⁴ (2010)	21 (26.6)	15 (21.1)	1.26	0.70–2.25	0.44	⊕⊕○○ Moderate†
► Poractant alfa	Conventional INSURE method	Halim <i>et al</i> ⁵⁶ (2018)	19 (38)	28 (56)	0.68	0.44–1.04	0.08	⊕⊕○○ Moderate†
► LISA method	Beractant	Jain <i>et al</i> ⁵⁷ (2019)	21 (40.4)	14 (30.4)	1.33	0.77–2.30	0.31	⊕⊕○○ Moderate†

Continued

Table 4 Continued

Intervention	Control	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95% CI	P value	GRADE quality of evidence
Vitamin A supplementation	Placebo	Basu <i>et al</i> ⁶¹ (2019)	9 (9.2)	16 (16.3)	0.56	0.26–1.21	0.14	⊕⊕⊕○ Moderate†
Pulse oximetry	Preintervention period	Graham <i>et al</i> ⁶⁵ (2019)	82 (13.4)	326 (17.4)	1.12	0.56–2.26¶	0.76¶	⊕⊕⊕○ Moderate†
Full O ₂ system	Preintervention period		203 (19.5)	326 (17.4)	0.99¶	0.61–1.59¶	0.96¶	⊕⊕⊕○ Moderate†
Volume-guaranteed ventilation	Pressure-controlled ventilation	Krishna <i>et al</i> ⁶⁸ (2019)	4 (10)	5 (12.2)	0.82	0.24–2.84	0.75	⊕⊕○○ Low*
Aminophylline	Caffeine	Kumar <i>et al</i> ⁶⁹ (2017)	16 (21.9)	15 (21.4)	1.02	0.55–1.91	0.94	⊕⊕○○ Low†**
High flow nasal cannula	Nasal CPAP	Murki <i>et al</i> ⁶¹ (2018)	4 (3.0)	3 (2.1)	1.39	0.32–6.11	0.66	⊕⊕○○ Low*
Strategies of newborn care								
Maternal nursing care	Special care baby unit	Arif <i>et al</i> ⁴⁹ (1999)	43 (28.5)	141 (66.8)	0.43	0.33–0.56	0.0000	⊕⊕⊕○ Moderate**
Stepdown unit	Preintervention period	Bhutta <i>et al</i> ⁶³ (2004)	55 (17.3)	63 (33)	0.52	0.38–0.72	0.0001	⊕⊕⊕○ Moderate§
Others								
Oral paracetamol for PDA closure	Oral ibuprofen	Balachander <i>et al</i> ⁶⁰ (2018)	12 (21.8)	11 (20)	1.10	0.53–2.26	0.81	⊕⊕○○ Low*
Polythene tobacco wrap	Standard nursing procedure	Van Den Bosch <i>et al</i> ⁶⁸ (1996)	0	6 (54.5)	0.06	0.0036–0.93	0.04	⊕⊕○○ Low†**

*Insufficient sample to meet optimal information size (OIS) criteria with very few events and 95% CI fails to exclude important benefit or harm.

†Insufficient sample to meet OIS criteria and/or 95% CI close to or crosses line of no effect or fails to exclude important benefit or harm.

‡Derived from the meta-analysis pooling the results of both studies.

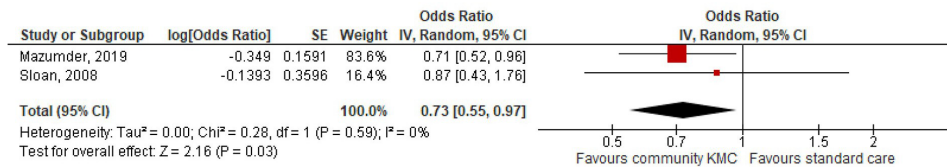
§Serious risk of selection bias.

¶Mixed-model odds ratio; accounted for the clustering of patients within hospitals and adjusted for time trends.

**Substantial loss to follow-up in relation to the number of events and failure to adhere to the intention-to-treat principle.



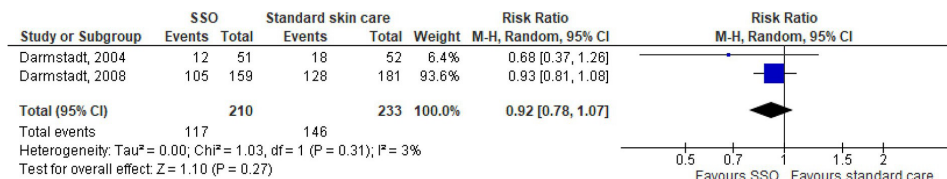
Meta-analysis addressing the effect of early versus late BCG on 28-day neonatal mortality among LBW neonates.



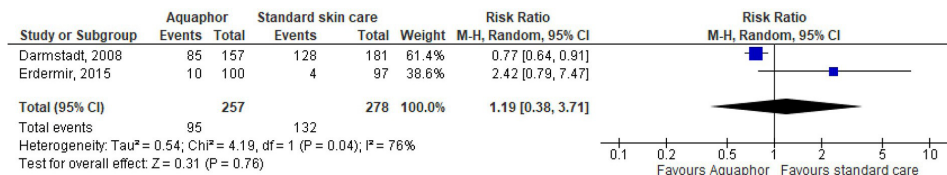
Meta-analysis addressing the effect of community KMC versus standard home-based care on 28-day neonatal mortality among LBW neonates.



Meta-analysis addressing the effect of Bubble CPAP versus conventional CPAP on mortality during hospital stay among preterm neonates.



Meta-analysis addressing the effect of topical ointment therapy with Sunflower Seed Oil versus standard skin care on 28-day neonatal mortality among preterm neonates.



Meta-analysis addressing the effect of topical ointment therapy with Aquaphor versus standard skin care on 28-day and 21-day neonatal mortality among preterm neonates.

Figure 2 Forest plots. BCG, bacille calmette-guérin; CPAP, continuous positive airway pressure; KMC, kangaroo mother care; LBW, low birth weight.

their individual study sites. Significant reductions in 28-day NMR among <5th percentile births were only observed in Guatemala and Pakistan study sites.^{36 39}

Skin cleansing with chlorhexidine versus placebo was studied in rural Nepal. Significantly reduced NMR was recorded among LBW neonates (RR 0.72; 95% CI 0.55–0.95).⁴⁶ Likewise, *single cord cleansing with chlorhexidine* versus standard care led to significantly reduced NMR among preterm neonates (0.65; 0.50–0.86) in rural Bangladesh.²⁷

Two studies assessed the effect of *early versus late BCG* vaccination among LBW neonates in urban districts

of Guinea-Bissau consecutively. Both studies showed a significant reduction in NMR (0.55; 0.35–0.88) (0.71; 0.49–1.04).^{24 31}

Community KMC versus standard home-based care was studied among LBW neonates. In rural and semiurban areas of India, a significant reduction in 28-day NMR was reported (0.71; 0.52–0.96).⁴⁰ Similarly, in rural Bangladesh 28-day NMR decreased significantly among LBW neonates weighing ≤2000 g (OR 0.37; 0.16–0.86). The same study did not find a significant difference in 28-day NMR among neonates weighing ≤2500 g (OR 0.87; 0.43–1.74).⁴⁵ A before–after study of *home-based newborn*

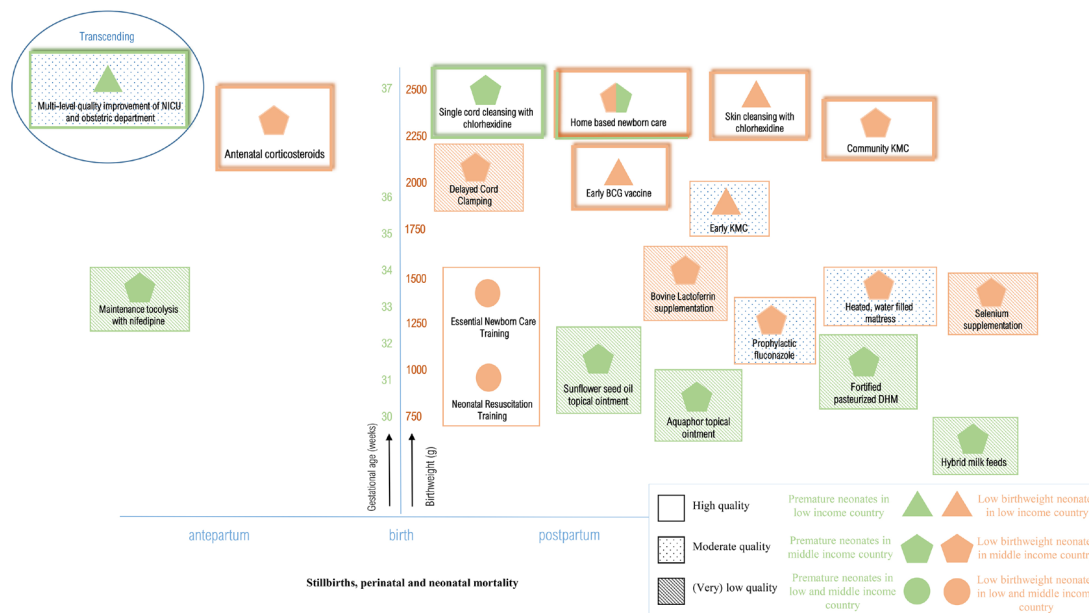


Figure 3 Summary of main findings. BCG; bacille calmette-guérin; DHM, donor human milk; KMC, kangaroo mother care; NICU, neonatal intensive care unit

care in rural India showed a significant reduction in NMR among LBW neonates (0.42; 0.27–0.65) and preterm neonates (0.25; 0.14–0.48).^{28–30}

Essential newborn care (ENC) training and *neonatal resuscitation programme (NRP)* were delivered to birth attendants in six MICs. No significant differences in perinatal (ENC: 1.02; 0.91–1.14/NRP: 0.95; 0.84–1.07) and 7-day NMR (ENC: 1.03; 0.83–1.27/NRP: 0.92; 0.77–1.09) were observed.²²

Meta-analysis

Pooled estimates of two studies assessing the effects of *early versus late BCG* vaccination among LBW neonates

in urban districts of Guinea-Bissau showed a significant reduction in NMR (0.64; 0.48–0.86).^{24 31}

The pooled mortality estimates of *community KMC* showed a significantly lower 28-day NMR in the intervention group (OR 0.73; 0.55–0.97).^{40 45}

Moderate quality

Four studies on neonatal mortality were considered of moderate quality. These studies assessed the effect of a quality improvement intervention introduction in the obstetric department and neonatal intensive care unit (NICU), heated mattress, prophylactic fluconazole, and early KMC on NMR.^{32 38 44 47}

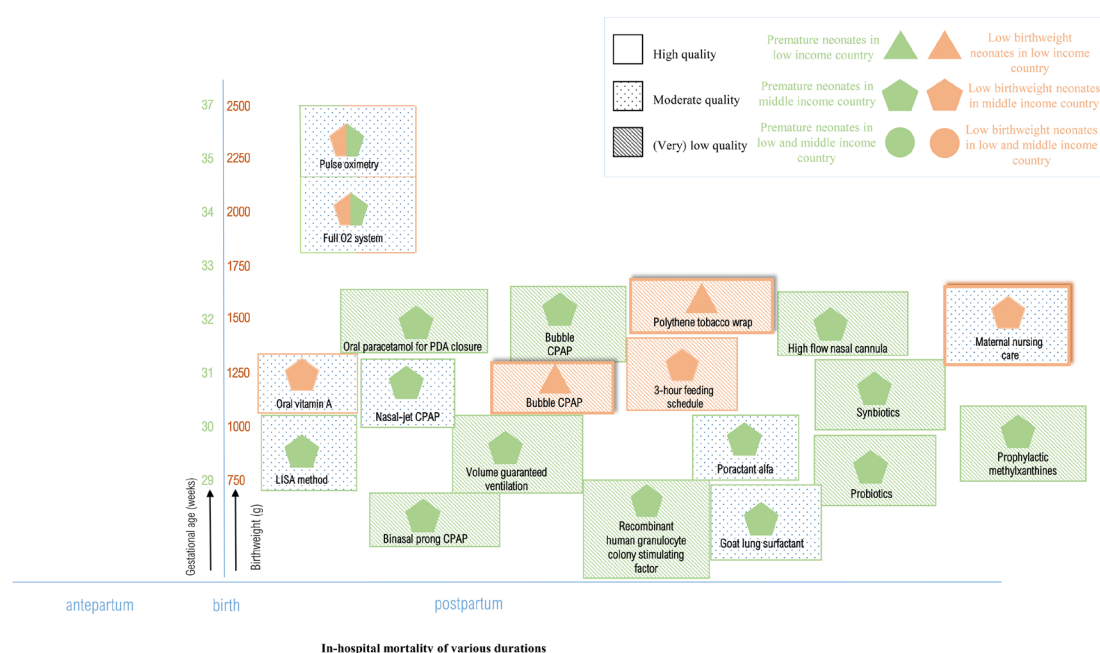


Figure 4 Summary of findings post hoc analysis. CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus.



Figure 5 infographic. This infographic tells the story of a health professional in a low-resource setting. She explains to her patient, a woman in her early pregnancy, that there is an increased risk of neonatal mortality in case her newborn is born preterm or growth-restricted. She shows a set of evidence-based interventions and recommendations she is about to implement to reduce this risk, strengthen newborn health care, and ultimately reduce under-five mortality (SDG 3.2).

The *multilevel quality improvement intervention* implemented protocols for the infrastructure, equipment and daily clinical routine at the NICU and obstetric department of a large public hospital in Mozambique. This resulted in a significant decline of NMR in premature neonates (0.77; 0.66–0.90).³²

Heated, water-filled mattresses were evaluated in a study by Sarman *et al* to prevent hypothermia among LBW neonates at a neonatal care unit in Turkey. Neonatal mortality rate

did not change significantly in comparison with air heated incubators (21.4% vs 34.4%; 0.62; 0.26–1.47).⁴⁴

Prophylactic fluconazole versus placebo in very LBW neonates was studied at a NICU in India. No significant difference in neonatal mortality rate was observed (18.4% vs 32.4%; RR 0.57, 95% CI 0.25–1.28).³⁸

Early KMC versus conventional care in LBW neonates was implemented by Worku *et al* in a tertiary hospital in Ethiopia. The neonatal mortality rate showed a trend

towards a significant decline (22.5% vs 38%; 0.57; 0.33–1.00).⁴⁷

Low or very low quality

Eight studies reported low-quality or very low-quality results. Corresponding studies addressed the effect of maintenance tocolysis, feeding supplements, and delayed cord clamping, all versus standard care or placebo.^{21 26 33 37}

The same applies to fortified versus unfortified pasteurised donor human milk, hybrid milk versus mother's milk alone, and sunflower seed oil and Aquaphor versus standard care.^{23 25 34 35 42}

Meta-analysis

The meta-analyses of topical ointment with *sunflower seed oil* versus standard care (0.92; 0.78–1.07) and *Aquaphor* versus standard care (1.19; 0.38–3.71) showed high heterogeneity and no significant differences in NMR.^{23 34 35}

Post hoc analysis of in-hospital mortality

First, eight studies of moderate quality are described, assessing nasal-jet versus bubble CPAP, less-invasive surfactant administration (LISA) versus conventional intubation surfactant administration and extubation (INSURE), surfactant agents of porcine, bovine and caprine origin, vitamin A, introducing pulse oximetry, full oxygen system, maternal nursing and a stepdown unit involving maternal nursing.^{49 51–57} Studies with low-quality evidence are briefly mentioned.

Moderate quality

Bhatti *et al* studied *nasal-jet CPAP* versus bubble CPAP in neonates with gestational age <34 weeks at two NICUs in India. No significant effect on in-hospital mortality was observed (25% vs 18%; 1.41; 0.78–2.52).⁵²

Two different surfactant agents of porcine and bovine origin for preterm neonates with IRDS were introduced by Gharehbaghi *et al* (*poractant alfa* vs beractant: 26.6% vs 21.1%; 1.26; 0.70–2.25) and Jain *et al* (*goat lung surfactant extract* vs beractant: 40.4% vs 30.4%; 1.33; 0.77–2.30) at NICUs in Iran and India. No significant difference in mortality rate was reported.^{54 57} LISA, studied versus the INSURE method, did not affect mortality rate among preterm neonates at a neonatal unit in Pakistan (38% vs 56%; 0.68; 0.44–1.04).⁵⁶

Basu *et al* administered *oral vitamin A* versus placebo to VLBW neonates at a NICU in India which did not result in a significant different mortality rate (9.2% vs 16.3%; 0.56; 0.26–1.21).⁵¹

Two oxygen systems were studied in a before–after study by Graham *et al* in 12 hospitals in Nigeria. Introduction of *pulse oximetry* to improve oxygen practices did not show a significant difference in mortality among LBW and preterm neonates (13.4% vs 17.4%; OR 1.12; 0.56–2.26). Likewise, introduction of a multifaceted, *full oxygen system*, did not alter the mortality significantly (19.5% vs 17.4%; 0.99; 0.61–1.59).⁵⁵

LBW neonates weighing 1000–2000 g on admission were randomised to *maternal nursing care* or conventional

nursing care at a neonatal ward in Pakistan. A significantly declined mortality rate until hospital discharge was observed in the maternal nursing group (28.5% vs 66.8%; 0.43; 0.33–0.56).⁴⁹

In a before–after study, Bhutta *et al* introduced a step-down unit at a neonatal ward in Pakistan. The unit had a nursing ratio of 1:5 compared with 1:3 at the conventional ward. Co-bedding was established, number of visitors was minimalised and mothers were involved in regular monitoring of vital signs and temperature. A significant lower mortality rate was observed after the unit was created (17.3% vs 33%; 0.52; 0.38–0.72).⁵³

Low or very low quality

Thirteen studies reported low or very low quality results of in-hospital mortality following different interventions. Among these, six interventions were compared with standard care or placebo: a 3-hour feeding schedule, probiotics and synbiotics, granulocyte stimulating agent, volume guaranteed ventilation and polythene tobacco wrap.^{48 58 62 64 67 68} Other interventions with (very) low quality results studied high-flow nasal cannula versus nasal CPAP, binasal prong versus nasal mask for applying CPAP, aminophylline versus caffeine for extubation failure, oral paracetamol versus ibuprofen for patent ductus arteriosus (PDA) closure, introduction of bubble CPAP, and bubble versus conventional CPAP.^{50 59–61 63 65 66}

Risk of bias

Tables 7–9 (online supplemental appendix) show the risk of bias assessment of individual studies. Overall, the risk of bias in randomised studies was considered 'some concerns' in 30 studies and 'high risk' in 13. Only one study scored low risk for all domains.⁴⁰ Most studies failed to report on the use of a prespecified analysis plan in the methods section. The studies generally performed well in terms of outcome measurement (96% low risk) and missing outcome data (88% low risk). Several studies displayed a moderate or high risk of bias in the randomisation process (44%) and deviations from intended interventions (74%). The bias risk in before–after studies varied from low to critical risk, particularly due to the risk of confounders and selection bias.^{22 28–30 32 53 63}

Quality of evidence

The GRADE evidence profiles are provided in tables 5 and 6 of the online supplemental appendix. The summarised results are listed in tables 3 and 4 of the manuscript.

SWOT analysis

Table 10 (online supplemental appendix) provides SWOT analysis.^{69–78}

The strengths of the interventions addressed in this study generally pertain to their accessibility, acceptability, applicability, affordability and scale-up ability without disrupting mother–infant bonding.

The weaknesses of the interventions are the requirements of the minimal clinical infrastructure, for example, gestational age determination, adequate neonatal care,

skills retainment or adequate follow-up system to evaluate long-term effects.

Opportunities are conducting implementation studies to determine the most effective strategy, subsequent implementation and scale-up of interventions including smooth embedding in the existing (inter)national guidelines. Many interventions such as chlorhexidine are widely available, listed as essential drugs or already culturally accepted.

Barriers to implementation generally pertain to limited availability of equipment, resources or skilled health personnel, cultural or traditional unacceptability, dysfunctional safety measures and limited access to tertiary health centres/NICUs.

DISCUSSION

This systematic review summarises the evidence on 38 interventions evaluated in 49 studies among 46 993 participants across 21 LMICs. The 12 studies with high quality of evidence showed lower neonatal mortality rates among preterm and LBW neonates with the use of skin and cord cleansing with chlorhexidine, early BCG vaccination, community KMC and home-based newborn care.^{24 27–31 40 45 46} The effects on NMR of antenatal corticosteroids varied. No effects on mortality rates were observed among VLBW neonates following training of birth attendants in neonatal resuscitation and essential newborn care.^{20 22 36 39} Remaining studies showed significant shortcomings in quality and diverse impacts on mortality rates.

In 2015, the WHO published recommendations on interventions to improve preterm birth outcomes.⁴ This WHO report was based on priority questions formulated by experts in the field of maternal and neonatal care. These questions resulted in eleven PICO's (Patient, Intervention, Control, Outcome), addressing nine different antenatal, perinatal and postnatal interventions. The available evidence concerning the selected interventions was reviewed and synthesised into a guideline, focusing on maternal and neonatal mortality and morbidity outcomes related to preterm birth.

In our study, we reviewed *all* existing evidence on interventions to reduce, *specifically*, neonatal mortality among preterm *and/or* LBW neonates. We did not focus on a preliminary selection of interventions, and included preterm *and* growth-restricted neonates. We were therefore able to identify a larger number of interventions, among which some were not previously considered in the WHO guideline.

The 2015 WHO guideline recommends antenatal corticosteroid therapy for women at risk of preterm birth at 24^{0/7}–34^{0/7} weeks of gestation. In the ACT trial, corticosteroids increased neonatal mortality among the intervention group.²⁰ Absence of effect in the intervention group could be due to the outcome definition with birth weight <5th percentile as a proxy for preterm birth. As such, the intervention group may have partially consisted

of growth-restricted and near-term neonates for whom corticosteroids are not recommended. The Guatemalan and (to a lesser extent) Pakistan sites showed a significant reduction in NMR among <5th percentile neonates, which might be attributed to the higher level of care and greater ACS use.³⁶ These controversial findings emphasise the need to implement the use of antenatal corticosteroids solely in areas where gestational age dating and adequate maternal and newborn care can be guaranteed. Effectuation should be dependent on these conditions, and results carefully monitored. This is supported by the recently published WHO Antenatal Dexamethasone for Early Preterm Birth in Low-Resource Countries (ACTION) trial that showed a positive effect of antenatal dexamethasone treatment on stillbirth and neonatal mortality in early preterm neonates in secondary and tertiary hospitals in India, Pakistan, Kenya, Nigeria and Bangladesh (NMR: 19.6% vs 23.5%; RR 0.84 (0.72–0.97) | stillbirth or NMR: 25.7% vs 29.2%; RR 0.88 (0.78–0.99)).⁷⁹

KMC is strongly recommended for newborns of birth weight ≤ 2000 g in the WHO guideline and the 2016 Cochrane review.^{4 80} Likewise, the ENAP states that by 2025 $\geq 75\%$ of stable preterm newborns or babies <2000 g should receive KMC.³ Our meta-analysis on community KMC shows a reduced neonatal mortality for *all* LBW neonates (ie, <2500 g) at the community level (high certainty of evidence).

In view of the large number of neonatal deaths caused by infant respiratory distress syndrome, CPAP therapy is strongly recommended by the WHO despite the low-quality evidence in LMICs.⁴ Thukral *et al* expressed the urgent need for high-quality studies on CPAP therapy among LMICs.⁸¹ The results of the studies included in our review addressing different CPAP devices are in line with these studies. Our SWOT analysis identifies bubble CPAP as the most cost-effective, easy-to-use and safe device in settings with trained staff but limited resources.

We found high-quality evidence based on two community trials for reducing the NMR among premature and LBW neonates after skin and cord chlorhexidine application. This finding aligns with the Cochrane review of term or late preterm neonates >2500 g, suggesting reduced neonatal mortality in the community setting.⁸² Likewise, the WHO recommends daily chlorhexidine application for home births in settings with high neonatal mortality.⁸³ Based on our findings, the WHO could consider to extend this recommendation to LBW and preterm neonates.

The strengths of this review are the comprehensiveness reflected in the large number of interventions and included participants, the SWOT analysis and meta-analysis where appropriate. Several limitations must be considered in the interpretation of findings. First, the inherent limitation linked to the overall moderate-to-low quality of included studies, not always powered for neonatal mortality endpoints or within the same timeframe. This may be explained by the resource constrictions of many healthcare settings in LMICs but also underlines the urgency of strengthening the research

infrastructure to answer urgent clinical questions in real-life contexts using optimal scientific approaches. Second, publication bias may be present because studies performed in low-resource settings may go unpublished and unindexed by international journals or databases. This could partly explain the scarcity of studies from low-income countries. The scarcity of studies is also represented in the meta-analysis, which is limited in quality due to the few number of studies included. Third, our SWOT analysis was primarily based on study author-reported characteristics of interventions, which may lead to under-reporting of weaknesses and barriers to implementation.

Relatively few studies that address antenatal interventions to prevent preterm birth could be included. These studies' outcomes usually focus on incidence of prematurity rather than perinatal mortality, while this can be included relatively easily in future study reports. Similarly, presentation of mortality disaggregated by prematurity and/or LBW incidence or availability of study datasets⁸⁴ would allow more interventions to be evaluated in future (individual participant data) systematic reviews.

CONCLUSION

Given the global commitment to end preventable deaths of newborns and children less than 5 years old in SDG 3.2, ongoing preventable mortality among preterm and LBW neonates needs urgent attention. This manuscript provides sufficient high-quality evidence to consider implementation of additional low-cost, high-benefit interventions in current guidelines; cord and skin cleansing with chlorhexidine, community KMC for LBW neonates, home-based newborn care and early BCG vaccination for LBW neonates. These interventions are accessible, acceptable, applicable and affordable.

These practices are currently not recommended in most countries. Given the circumstances and possibilities in research in LMICs, evidence is sufficient although not high in quantity (in relation to the quantity and quality of data from high-income countries related to this topic) to discourage current underutilisation of health practices and opportunities and consider to update present guidelines.

We highlight the importance of accurately imbedding or optimal usage of maternal and newborn healthcare practices such as gestational age dating and birth and death registration in order to benefit from and investigate any intervention. Antenatal corticosteroid treatment should be implemented if adequate gestational age dating is available and adequate maternal and neonatal care is provided.

There is an urgent need for high-quality evidence to guide clinical and public health practice in LMICs. These should focus on strategies to prevent and manage common complications in preterm and LBW neonates.¹ Beyond classic RCTs, relatively novel scientific approaches such as stepped-wedge RCTs,⁸⁵ implementation-evaluation studies and learning health system research based on

routinely collected (electronic) patient data should be considered.

An infographic that summarizes the main outcomes and recommendations of this study is provided in figure 5.

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