BMJ Global Health

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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To cite: Kleinhout MY, Stevens MM, Osman KA, *et al*. 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 . *BMJ Global Health* 2021;**6**:e003618. doi:10.1136/bmjgh-2020-003618

Handling editor Seye Abimbola

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Received 3 August 2020
Revised 23 December 2020
Accepted 25 December 2020

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

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.

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 MEDLINE[8] and BMI Search Blocks[12] 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

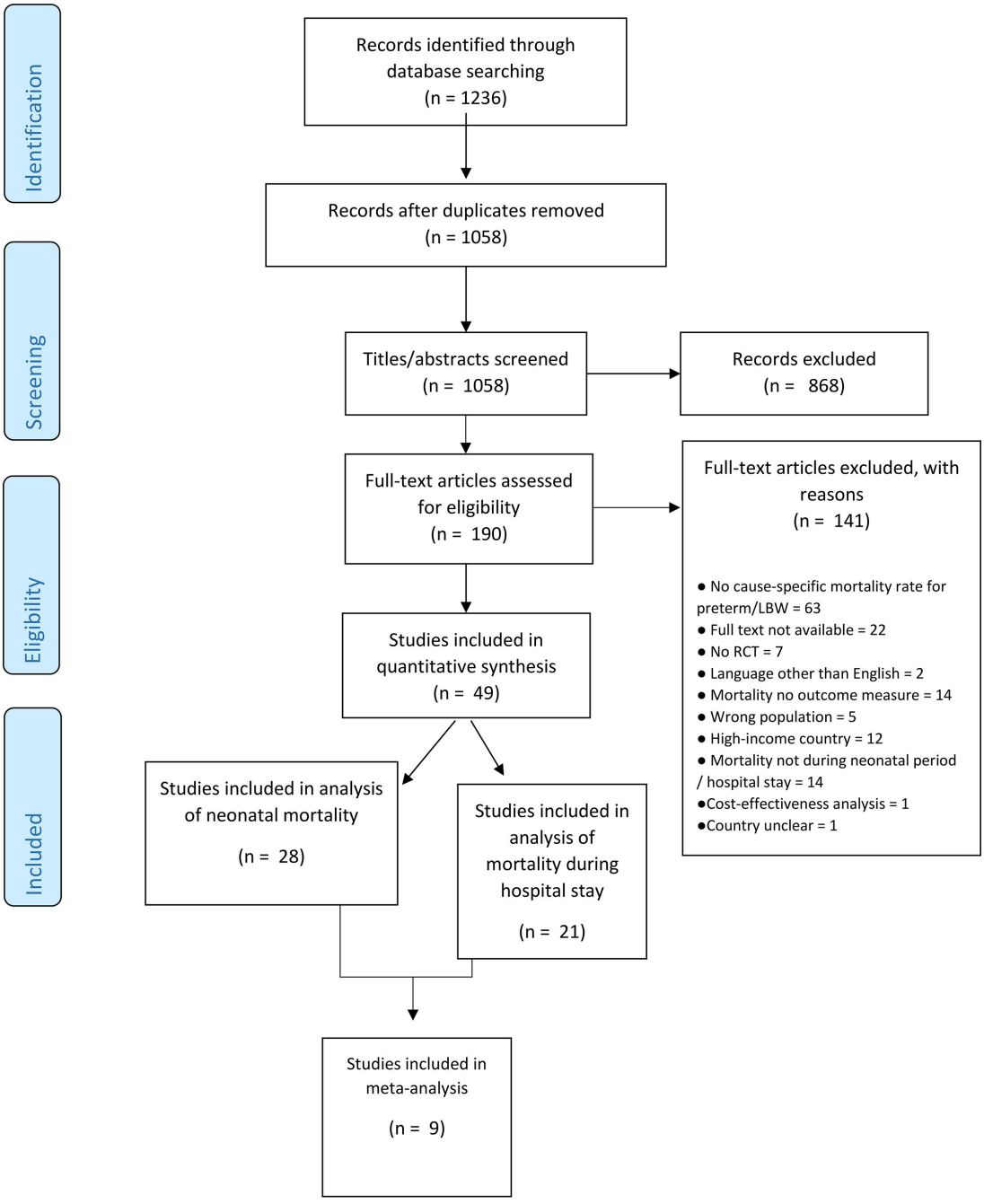


Figure 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart study selection. RCT, randomised controlled trial.

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 corticosteroid*s (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									
Antenatal corticosteroids	Althabe *et al*[20] (2015), Garces *et al*[36] (2016) Klein *et al*[39] (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 *et al*[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
Maintenance tocolysis	Aggarwal *et al*[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 nidefipine 20 mg 8 hourly for 12 days in established preterm labour	Standard care	No	Perinatal mortality
POSTNATAL INTERVENTIONS									
Feeding interventions									
Donor human milk	Adhisivam *et al*[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 *et al*[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
Cord cleansing with chlorhexidine	Arifeen *et al*[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
Skin cleansing with chlorhexidine	Tielsch *et al*[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
Topical emollient ointment therapy	Darmstadt *et al*[34] (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 *et al*[35] (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 *et al* [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
Feeding supplements	Aggarwal *et al*[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 *et al*[37] (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
BCG	Aaby *et al* [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 *et al*[31] (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
Antifungal therapy	Kirpal *et al*[38] (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									
Kangaroo mother care	Nagai *et al*[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 *et al*[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 *et al*[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 *et al*[45] (2008) Bangladesh	Cluster RCT	15	All women aged 12–50 years/ intervention: 20516, control: 19337 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 *et al*[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 *et al*[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 *et al*[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 *et al*[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 *et al*[33] (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 *et al*[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	Air-heated incubators	No	Neonatal death
Quality improvement intervention	Cavicchiolo *et al*[32] (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, diphteria, 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 *et al*[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 *et al*[48] (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 *et al*[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: *Lactobacillus acidophilus*, *Bifidobacterium longum*, *Lactobacillus rhamnosus*, *Lactobacillus plantaris*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Bifidobacterium infantis*, *Bifidobacterium breve* and 100 mg of fructo-oligosaccharide (prebiotic)	Standard care	No	Intervention: 8.3±4.5, control: 8.4±5.1
	Sari *et al*[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 *Lactobacillus sporogenes* 350 000 000 colony-forming unit once a day	Breast milk or formula alone	Yes	Death >7 days intervention: 43.5, control: 30
Prevention and treatment of respiratory morbidity									

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)
CPAP	Bhatti *et al*[52] (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 *et al*[60] (2016) Armenia	RCT	NA	Preterm neonates/ intervention: 66, control: 59	Neonatal unit	Bubble CPAP	Flow driver CPAP	No	Not reported
	Okello *et al*[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 *et al*[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 *et al*[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 *et al*[54] (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 *et al*[56] (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 administration and Extubation	No	Median (IQR) intervention: 7 (5), control: 6 (4)
	Jain *et al*[57] (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 *et al*[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 *et al*[55] (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	▶ Pulse oximetry to improve clinical use of oxygen targeting hypoxaemic neonates ▶ Full O_2 system involving (1) a standardised oxygen equipment package, (2) clinical education and support, (3) technical training and support, and (4) infrastructure and systems support	Preintervention period	Yes	Not reported
	Krishna *et al*[58] (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 *et al*[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 *et al*[59] (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 *et al*[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 *et al*[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 *et al*[60] (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 *et al*[68] (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 *et al*[20] (2015)		748 (22.9)	739 (24.7)	0.99	0.90–1.09	0.81	⊕⊕⊕⊕ High
		Perinatal mortality	Althabe *et al*[20] (2015)		1203 (36.8)	1172 (39.1)	0.97	0.91–1.04	0.46	⊕⊕⊕⊕ High
		7-day neonatal mortality	Althabe *et al*[20] (2015)		455 (13.9)	433 (14.4)	0.94	0.84–1.06	0.30	⊕⊕⊕⊕ High
		28-day neonatal mortality	Althabe *et al*[20] (2015)		566 (22.4)	524 (23.2)	0.96	0.87–1.06	0.65	⊕⊕⊕⊕ High
			Garces *et al*[36] (2016)		36 (18.3)	39 (23.5)	0.74	0.68–0.81	<0·0001	⊕⊕⊕⊕ High
			Klein *et al*[39] (2016)	Belgaum, India	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*
				Guatemala	57 (16.5)	39 (23.5)	0.75	0.69–0.82	NA	⊕⊕⊕⊕ High
				Argentina	20 (22)	17 (13)	1.60	0.99–2.58	NA	⊕⊕⊕◯ Moderate*
	Two doses of 12 mg of dexamethasone 24 hours apart		Rasool *et al*[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 *et al*[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	Adhisivam *et al*[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 *et al*[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*et al*[27] (2012)	LBW: 121 (3.8)	145 (4.7)	0.82	0.63–1.06	NA	⊕⊕⊕⊕ High
				Preterm: 78 (4.0)	128 (6.2)	0.65	0.50–0.86	NA	⊕⊕⊕⊕ High
Multiple cord cleansing with chlorhexidine				LBW: 159 (4.7)	145 (4.7)	1.00	0.79–1.27	NA	⊕⊕⊕⊕ High
				Preterm: 119 (5.4)	128 (6.2)	0.88	0.69–1.12	NA	⊕⊕⊕⊕ High
Skin cleansing with chlorhexidine	Placebo		Tielsch *et al*[47] (2007)	83 (3.4)	117 (4.7)	0.72	0.55–0.95	NA	⊕⊕⊕⊕ High
Topical ointment SSO	Standard skin care		Darmstadt *et al*[34] (2004)	12 (23.5)	18 (34.6)	0.68	0.37–1.26	0.29	⊕⊕◯◯ Low*§¶§§
SSO and Aquaphor			Darmstadt *et al*[35] (2008)	SSO: 105 (65.8)	128 (70.6)	SSO: 0.93	SSO: 0.81–1.08	SSO: 0.36	⊕⊕◯◯ Low*§¶§§
				Aquaphor: 85 (54.2)	128 (70.6)	Aquaphor: 0.77	Aquaphor: 0.64–0.91	Aquaphor: 0·0023	⊕⊕◯◯ Low*¶¶§§
Aquaphor		21-day neonatal mortality	Erdemir *et al*[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 *et al*[26] (2016)	2 (4.4)	3 (6.7)	0.67	0.12–3.80	0.65	⊕◯◯◯ Very low*****
Bovine lactoferrin	Placebo		Kaur *et al*[37] (2015)	0 (0)	5 (7.5)	0.10	0.01–1.71	0.11	⊕⊕◯◯ Low**
Early BCG vaccine	Late BCG		Aaby *et al*[24] (2011)	27 (2.3)	48 (4.2)	0.55	0.35–0.88	0.01	⊕⊕⊕⊕ High§§
			Biering Sorensen *et al*[31] (2017)	44 (2.1)	62 (3.0)	0.71	0.49–1.04	0.08	⊕⊕⊕⊕ High§§
Prophylactic fluconazole	Placebo		Kirpal *et al*[38] (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 *et al*[41] (2010)	2 (5.4)	1 (2.8)	1.95	0.18–20.53	0.58	⊕⊕◯◯ Low**
	Conventional care		Worku *et al*[47] (2005)	14 (22.5)	24 (38)	0.57	0.33–1.00	0.05	⊕⊕⊕◯ Moderate*
Community KMC	Standard home-based care		Sloan *et al*[45] (2008)	≤2500 g: 22 (5.4)	20 (6)	0.87†††	0.43–1.74†††	0.69†††	⊕⊕⊕⊕ High§§
				≤2000 g: 9 (9.5)	16 (22.5)	0.37†††	0.16–0.86†††	0.02†††	⊕⊕⊕◯ Moderate*
			Mazumder *et al*[40] (2019)	73 (1.6)	90 (2.3)	0.71	0.52–0.96	0.03	⊕⊕⊕⊕ High§§
Home-based neonatal care	Preintervention period		Bang *et al*[29] (1999)	LBW: 13 (4)	36 (11.3)	0.36	0.20–0.67	0·0011	⊕⊕⊕⊕ High
				Preterm: 9 (9.7)	25 (33.3)	0.29	0.14–0.58	0·0005	⊕⊕⊕⊕ High
			Bang, Baitule *et al*[28] (2005)	Preterm: 23 (10.2)	25 (33.3)	0.31	0.18–0.50	0.00	⊕⊕⊕⊕ High
				LBW: 39 (4.7)	36 (11.3)	0.42	0.27–0.65	0·0001	⊕⊕⊕⊕ High
			Bang, Reddy *et al*[30] (2005)	12 (8.5)	25 (33.3)	0.25	0.14–0.48	0·0000	⊕⊕⊕⊕ High
Training of traditional birth attendants	ENC: preintervention period NRP: No additional training	Stillbirths	Carlo *et al*[22] (2010)	ENC: 157 (43.7)	ENC: 72 (42.6)	ENC: 1.03	ENC: 0.80–1.31	NA	⊕⊕⊕◯ Moderate*
				NRP: 91 (33.3)	NRP: 101 (34.2)	NRP: 0.97	NRP: 0.57–1.67	NA	⊕⊕⊕◯ Moderate*
		Perinatal mortality		ENC: 283 (78.8)	ENC: 133 (78.7)	ENC: 1.02	ENC: 0.91–1.14	NA	⊕⊕⊕⊕ High
				NRP: 198 (72.5)	NRP: 225 (76.3)	NRP: 0.95	NRP: 0.84–1.07	NA	⊕⊕⊕⊕ High
		7-day neonatal mortality		ENC: 126 (35.1)	ENC: 61 (36.1)	ENC: 1.03	ENC: 0.83–1.27	NA	⊕⊕⊕⊕ High
				NRP: 107 (39.2)	NRP: 124 (42)	NRP: 0.92	NRP: 0.77–1.09	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 *et al*[33] (2018)	1 (1.8)	0	3.16	0.13–75.98	0.48	⊕◯◯◯ Very low**‡‡‡
Heated mattress	Air-heated incubators		Sarman *et al*[44] (1989)	6 (21.4)	11 (34.4)	0.62	0.26–1.47	0.28	⊕⊕⊕◯ Moderate*
Quality improvement intervention	Preintervention period		Cavicchiolo *et al*[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.
¶¶I^2 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

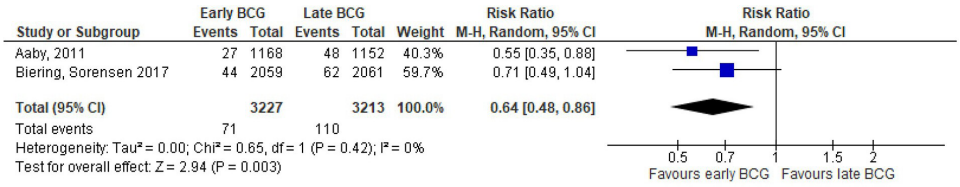
Intervention	Control	Author (year)	Mortality outcome intervention, n (%)	Mortality outcome control, n (%)	RR	95% CI	P value	GRADE quality of evidence
Feeding interventions								
3-hour feeding schedule	2-hour feeding schedule	Tali *et al*[67] (2016)	0	0	NA	NA	NA	⊕⊕◯◯ Low*
Infection prevention								
rhG-CSF	Empirical antibiotics alone	Aktas *et al*[48] (2015)	10 (30.3)	6 (26.1)	1.16	0.49–2.74	0.73	⊕⊕◯◯ Low*
Synbiotics	Standard care	Nandhini *et al*[62] (2016)	10 (9.3)	9 (8.2)	1.13	0.48–2.68	0.78	⊕⊕◯◯ Low*
Lactobacillus sporogenes	Breast milk or formula alone	Sari *et al*[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 *et al*[52] (2015)	20 (25)	16 (18)	1.41	0.78–2.52	0.25	⊕⊕⊕◯ Moderate†
Bubble CPAP	Flow driver CPAP	Mazmanyan *et al*[60] (2016)	3 (4.5)	1 (1.7)	2.68	0.29–25.08	0.39	⊕⊕◯◯ Low*‡
	Preintervention period	Okello *et al*[63] (2019)	58 (26.5)	62 (39.2)	0.68	0.50–0.91	0.01	⊕⊕◯◯ Low§
			VLBW 36 (19.7)	41 (31.5)	0.62	0.42–0.92	0.02	⊕⊕◯◯ Low§
			ELBW 22 (61.1)	21 (75)	0.82	0.58–1.14	0.23	⊕◯◯◯ Very low†§
	Ventilator-derived CPAP	Tagare *et al*[66] (2013)	4 (7)	5 (8.8)	0.80	0.23–2.83	0.73	⊕⊕◯◯ Low*
Binasal prong	Nasal mask for applying nasal CPAP	Say *et al*[65] (2016)	4 (5.4)	7 (9.3)	0.56	0.17–1.85	0.34	⊕⊕◯◯ Low*
Surfactant ► Poractant alfa	Beractant	Gharehbaghi *et al*[54] (2010)	21 (26.6)	15 (21.1)	1.26	0.70–2.25	0.44	⊕⊕⊕◯ Moderate†
► LISA method	Conventional INSURE method	Halim *et al*[56] (2018)	19 (38)	28 (56)	0.68	0.44–1.04	0.08	⊕⊕⊕◯ Moderate†
► Goat lung surfactant extract	Beractant	Jain *et al*[57] (2019)	21 (40.4)	14 (30.4)	1.33	0.77–2.30	0.31	⊕⊕⊕◯ Moderate†

Continued

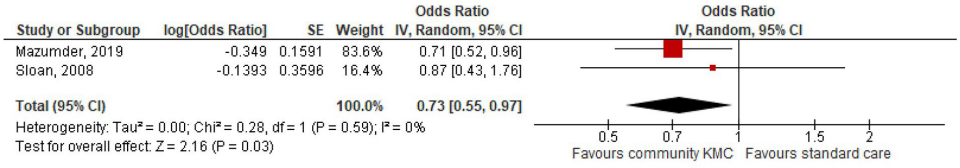
Table 4 Continued

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 *et al*[51] (2019)	9 (9.2)	16 (16.3)	0.56	0.26–1.21	0.14	⊕⊕⊕◯ Moderate†
Pulse oximetry	Preintervention period	Graham *et al*[55] (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 *et al*[58] (2019)	4 (10)	5 (12.2)	0.82	0.24–2.84	0.75	⊕⊕◯◯ Low*
Aminophylline	Caffeine	Kumar *et al*[59] (2017)	16 (21.9)	15 (21.4)	1.02	0.55–1.91	0.94	⊕⊕◯◯ Low†**
High flow nasal cannula	Nasal CPAP	Murki *et al*[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 *et al*[49] (1999)	43 (28.5)	141 (66.8)	0.43	0.33–0.56	0·0000	⊕⊕⊕◯ Moderate**
Stepdown unit	Preintervention period	Bhutta *et al*[53] (2004)	55 (17.3)	63 (33)	0.52	0.38–0.72	0·0001	⊕⊕⊕◯ Moderate§
Others								
Oral paracetamol for PDA closure	Oral ibuprofen	Balachander *et al*[50] (2018)	12 (21.8)	11 (20)	1.10	0.53–2.26	0.81	⊕⊕◯◯ Low*
Polythene tobacco wrap	Standard nursing procedure	Van Den Bosch *et al*[68] (1996)	0	6 (54.5)	0.06	0·0036–0.93	0.04	⊕⊕◯◯ Low†**

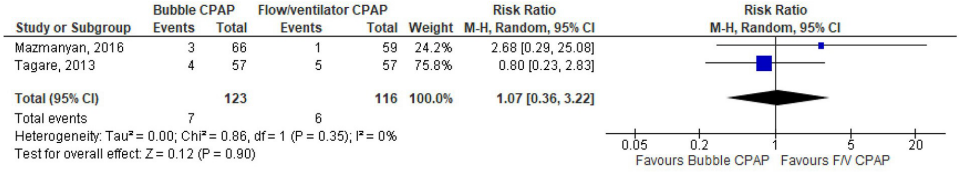
*Insufficient sample to meet optimal information size (OIS) criteria with very few events and 95% CI fails to exclude important benefit or harm.
†Insufficient sample to meet OIS criteria and/or 95% CI close to or crosses line of no effect or fails to exclude important benefit or harm.
‡Derived from the 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*

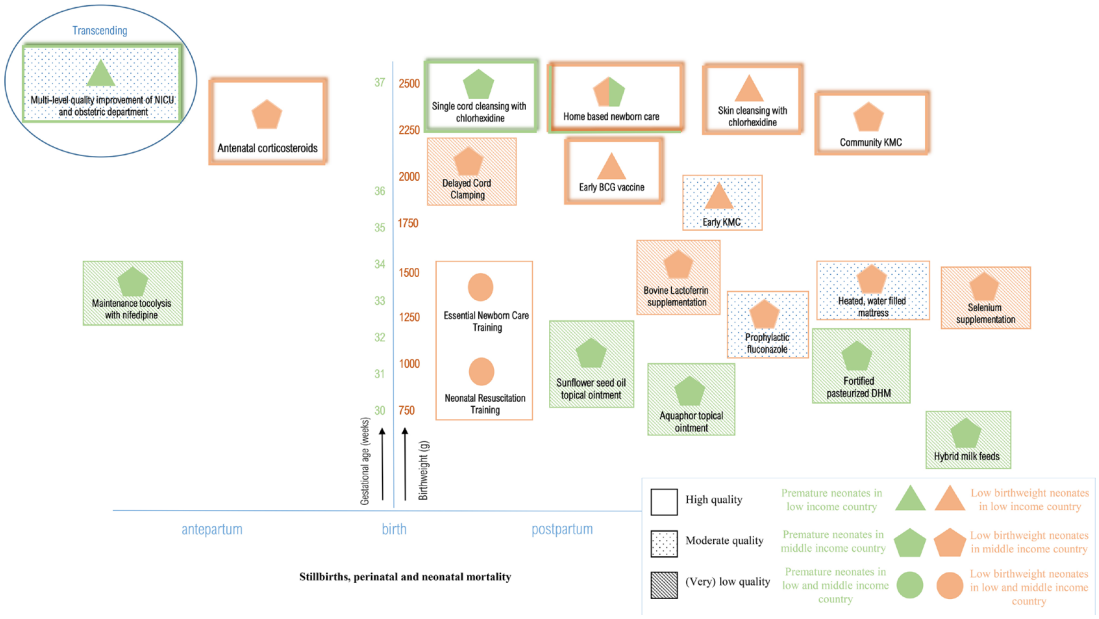


Figure 3 Summary of main findings. BCG; bacille calmette-guérin; DHM, donor human milk; KMC, kangaroo mother care; NICU, neonatal intensive care unit

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]

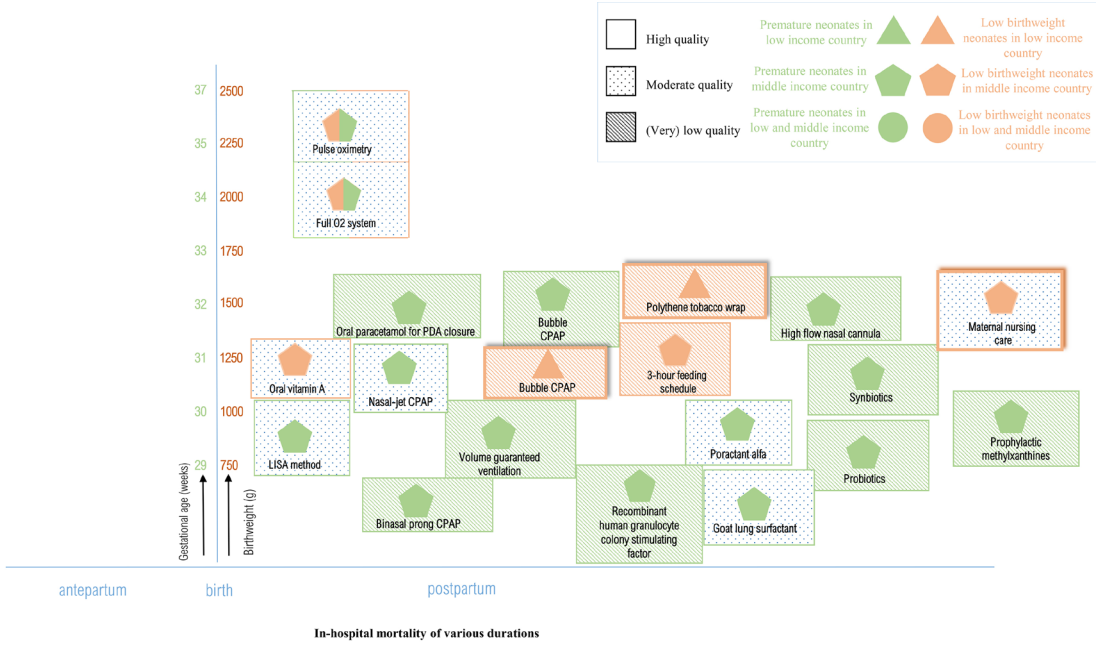


Figure 4 Summary of findings post hoc analysis. CPAP, continuous positive airway pressure; PDA, patent ductus arteriosus.

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 stepdown 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 ≥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 datasets[84] 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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Acknowledgements We would like to thank information specialist, Dr Paulien Wiersma, who supported us in developing our search strategy. We would like to thank Professor Dr Rob Scholten and Dr Peter Zuithoff for their statistical advice on the Results and Meta-analysis sections. We would like to thank medical illustrator, Anna Sieben, for the design of a visual summary that supports our study.

Contributors *Joint first authors: MK and MS contributed equally to this paper and would like to be stated as joint first authors in the published version of the manuscript in BMJ Global Health. MK proposed the research question and MK, MS and JLB designed the study. MS and MK performed the literature search, study selection and data extraction with support of JLB. MS performed statistical analysis and designed tables and figures. FG aided in the statistical analysis. MS wrote the first draft of the manuscript, with continuous input from MK. All authors critically and equally reviewed and edited the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon request. All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information. Additional data extracted from the included studies, but not directly relevant to the study, are available upon request from the corresponding author (ORCID-ID 0000-0001-9323-4436, e-mail: merel.stevens@hotmail.com).

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APPENDIX

List of abbreviations and definitions

Abbreviation	Meaning
ACS	Antenatal corticosteroids
ACT	Antenatal corticosteroids in developing countries
ACTION	Antenatal CorticosTeroids for Improving Outcomes in preterm Newborns
BCG	Bacillus Calmette-Guérin
BPD	Bronchopulmonary dysplasia
CI	Confidence interval
CKMC	Community kangaroo mother care
CPAP	Continuous positive airway pressure
DCC	Delayed cord clamping
DHM	Donor human milk
DTP	Diphteria, tetanus, pertussis
ECC	Early cord clamping
ENAP	Every Newborn Action Plan
ENC	Essential newborn care
GLSE	Goat lung surfactant extract
HBNC	Home based neonatal care
HBNC	Home based newborn care
HFNC	High flow nasal cannula
INSURE	Intubation surfactant administration and extubation
IQR	Interquartile range
IRDS	Infant respiratory distress syndrome
IV	Intravenous
KMC	Kangaroo mother care
LBW	Low birthweight
LHS	Learning health system
LICs	Low-income countries
LISA	Less invasive surfactant administration
LMICs	Low- and middle-income countries
MICs	Middle-income countries
nCPAP	Nasal continuous positive airway pressure
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
NMR	Neonatal mortality rate
NRP	Neonatal resuscitation program
PDA	Patent ductus arteriosus
PDHM	Pasteurized donor human milk
PPROM	Preterm premature rupture of membranes
PRISMA	Preferred Reporting Items for Systematic Reviews
RCT	Randomized controlled trial
rhG-CSF	Recombinant human granulocyte-macrophage colony-stimulating factor
RoB	Risk of Bias
RR	Risk ratio
Se	Selenium

SGA	Small for gestational age
SSO	Sunflower seed oil
SWOT	Strengths, Weaknesses, Opportunities, Threats
UNICEF	United Nations International Children's Emergency Fund
VAS	Vitamin A supplementation
VGV	Volume guaranteed ventilation
VLBW	Very low birthweight
WHO	World Health Organization
Neonatal mortality	Death from birth to 28 days of life
Perinatal mortality	Death from 22 competed weeks of gestation to seven days of life
Stillbirth	Death prior to complete extraction of a product of conception, irrespective of the pregnancy duration

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((((("Premature Birth"[Mesh] OR prematur*[Title/Abstract] OR preterm*[Title/Abstract] OR "Infant, Premature"[Mesh]))))) OR (((((((("Infant, Low Birth Weight"[Mesh]) OR small for gestational age[Title/Abstract]) OR small for date[Title/Abstract]) OR sga[Title/Abstract]) OR low birthweight[Title/Abstract]) OR low birth weight[Title/Abstract]) OR vlbw[Title/Abstract]) OR elbw[Title/Abstract])) AND ((((((((((("Perinatal Mortality"[Mesh]) OR "Perinatal Death"[Mesh]) OR "Infant Mortality"[Mesh]) OR "Survival"[Mesh]) OR premature surviv*[Title/Abstract]) OR preterm surviv*[Title/Abstract]) OR Preterm Mortalit*[Title/Abstract]) OR Preterm Death*[Title/Abstract]) OR neonatal mortalit*[Title/Abstract]) OR neonatal surviv*[Title/Abstract])) AND (("Developing Countries"[Mesh] OR developing countr*[tiab] OR developing nation*[tiab] OR developing population*[tiab] OR developing econom*[tiab] OR undeveloped countr*[tiab] OR undeveloped nation*[tiab] OR "undeveloped economy"[tiab] OR "undeveloped economies"[tiab] OR least developed countr*[tiab] OR least developed nation*[tiab] OR "least developed economy"[tiab] OR "least developed economies"[tiab] OR less-developed countr*[tiab] OR less-developed nation*[tiab] OR "less-developed population"[tiab] OR "less-developed populations"[tiab] OR less-developed econom*[tiab] OR lesser developed countr*[tiab] OR lesser developed nation*[tiab] OR "lesser developed population"[tiab] OR "lesser developed populations"[tiab] OR "lesser developed economy"[tiab] OR "lesser developed economies"[tiab] OR under-developed countr*[tiab] OR under-developed nation*[tiab] OR underdeveloped countr*[tiab] OR underdeveloped nation*[tiab] OR underdeveloped population*[tiab] OR underdeveloped econom*[tiab] OR low income countr*[tiab] OR middle income countr*[tiab] OR low income nation*[tiab] OR middle income nation*[tiab] OR low income population*[tiab] OR middle income population*[tiab] OR low income econom*[tiab] OR middle income econom*[tiab] OR lower income countr*[tiab] OR lower income nation*[tiab] OR lower income population*[tiab] OR "lower income economy"[tiab] OR "lower income economies"[tiab] OR resource limited[tiab] OR low resource countr*[tiab] OR lower resource countr*[tiab] OR low resource nation*[tiab] OR low resource population*[tiab] OR "low resource economy"[tiab] OR "low resource economies"[tiab] OR underserved countr*[tiab] OR underserved nation*[tiab] OR underserved population*[tiab] OR "underserved economy"[tiab] OR "underserved economies"[tiab] OR "under-served country"[tiab] OR "under-served countries"[tiab] OR "under-

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(prematur*):ti,ab,kw OR (preterm*):ti,ab,kw OR (small for gestational age):ti,ab,kw OR (small for date*):ti,ab,kw OR ("SGA"):ti,ab,kw OR (low birth weight):ti,ab,kw OR (low birthweight):ti,ab,kw OR (vlbw):ti,ab,kw OR (elbw):ti,ab,kw) AND (premature surviv*):ti,ab,kw OR (preterm surviv*):ti,ab,kw OR (preterm mortalit*):ti,ab,kw OR (preterm death*):ti,ab,kw OR (neonatal mortalit*):ti,ab,kw OR (neonatal surviv*):ti,ab,kw) AND (developing countr*):ti,ab,kw OR (developing nation*):ti,ab,kw OR (developing population*):ti,ab,kw OR (developing econom*):ti,ab,kw OR (undeveloped countr*):ti,ab,kw OR (undeveloped nation*):ti,ab,kw OR (undeveloped economy):ti,ab,kw OR (undeveloped economies):ti,ab,kw OR (least developed countr*):ti,ab,kw OR (least developed nation*):ti,ab,kw OR (least developed economy):ti,ab,kw OR (least developed countr*):ti,ab,kw OR (less-developed nation*):ti,ab,kw OR (less-developed population*):ti,ab,kw OR (less-developed econom*):ti,ab,kw OR (lesser developed countr*):ti,ab,kw OR (lesser developed nation*):ti,ab,kw OR (lesser developed population*):ti,ab,kw OR (lesser developed econom*):ti,ab,kw OR (under-developed countr*):ti,ab,kw OR (under-developed nation*):ti,ab,kw OR (underdeveloped countr*):ti,ab,kw OR (underdeveloped nation*):ti,ab,kw OR (underdeveloped population*):ti,ab,kw OR (underdeveloped econom*):ti,ab,kw OR (low income countr*):ti,ab,kw OR (middle income countr*):ti,ab,kw OR (low income nation*):ti,ab,kw OR (middle income nation*):ti,ab,kw OR (low income population*):ti,ab,kw OR (middle income population*):ti,ab,kw OR (low income econom*):ti,ab,kw OR (middle income econom*):ti,ab,kw OR (lower income countr*):ti,ab,kw OR (lower income nation*):ti,ab,kw OR (lower income population*):ti,ab,kw OR (lower income econom*):ti,ab,kw OR (resource limited):ti,ab,kw OR (low resource countr*):ti,ab,kw OR (lower resource countr*):ti,ab,kw OR (low resource nation*):ti,ab,kw OR (low resource population*):ti,ab,kw OR (low resource econom*):ti,ab,kw OR (underserved countr*):ti,ab,kw OR (underserved nation*):ti,ab,kw OR (underserved population*):ti,ab,kw OR (underserved econom*):ti,ab,kw OR (under-served countr*):ti,ab,kw OR (under-served nation*):ti,ab,kw OR (under-served population*):ti,ab,kw OR (under-served econom*):ti,ab,kw OR (deprived countr*):ti,ab,kw OR (deprived nation*):ti,ab,kw OR (deprived population*):ti,ab,kw OR (deprived

econom*):ti,ab,kw OR (poor countr*):ti,ab,kw OR (poor nation*):ti,ab,kw OR (poor population*):ti,ab,kw OR (poor econom*):ti,ab,kw OR (poorer countr*):ti,ab,kw OR (poorer nation*):ti,ab,kw OR (poorer population*):ti,ab,kw OR (poorer econom*):ti,ab,kw OR (lmic):ti,ab,kw OR (lmics):ti,ab,kw OR (lami):ti,ab,kw OR (transitional countr*):ti,ab,kw OR (transitional nation*):ti,ab,kw OR (transition econom*):ti,ab,kw OR (low resource setting*):ti,ab,kw OR (lower resource setting*):ti,ab,kw OR (middle resource setting*):ti,ab,kw OR (Third World):ti,ab,kw OR (south asia):ti,ab,kw OR (southeast asia):ti,ab,kw OR (borneo):ti,ab,kw OR (cambodia):ti,ab,kw OR (indonesia):ti,ab,kw OR (laos):ti,ab,kw OR (myanmar):ti,ab,kw OR (papua new guinea):ti,ab,kw OR (thailand):ti,ab,kw OR (timor-leste):ti,ab,kw OR (viet nam):ti,ab,kw OR (yemen):ti,ab,kw OR (turkey):ti,ab,kw OR (iraq):ti,ab,kw OR (africa south of the sahara):ti,ab,kw OR (egypt):ti,ab,kw OR (mauritania):ti,ab,kw OR (morocco):ti,ab,kw OR (tunisia):ti,ab,kw OR (fiji):ti,ab,kw OR (philippines):ti,ab,kw OR (samoan islands):ti,ab,kw OR (tonga):ti,ab,kw OR (vanuatu):ti,ab,kw OR (kiribati):ti,ab,kw OR (armenia):ti,ab,kw OR (ukraine):ti,ab,kw OR (bolivia):ti,ab,kw OR (el salvador):ti,ab,kw OR (guatemala):ti,ab,kw OR (honduras):ti,ab,kw OR (nicaragua):ti,ab,kw OR (haiti):ti,ab,kw OR (kosovo):ti,ab,kw OR (kyrgyzstan):ti,ab,kw OR (tajikistan):ti,ab,kw OR (uzbekistan):ti,ab,kw OR (federated states of micronesia):ti,ab,kw OR (mongolia):ti,ab,kw OR (north korea):ti,ab,kw OR (sao tome and principe):ti,ab,kw OR (solomon islands):ti,ab,kw OR (syrian arab republic):ti,ab,kw OR (palestine):ti,ab,kw OR (south east asia*):ti,ab,kw OR (middle east*):ti,ab,kw OR (afghan*):ti,ab,kw OR (angola*):ti,ab,kw OR (armenia*):ti,ab,kw OR (bangladesh*):ti,ab,kw OR (benin*):ti,ab,kw OR (bhutan*):ti,ab,kw OR (birma*):ti,ab,kw OR (boliv*):ti,ab,kw OR (botswan*):ti,ab,kw OR (burkina faso*):ti,ab,kw OR (burundi*):ti,ab,kw OR (cabo verde*):ti,ab,kw OR (cambod*):ti,ab,kw OR (cameroon*):ti,ab,kw OR (cape verd*):ti,ab,kw OR (central africa*):ti,ab,kw OR (chad*):ti,ab,kw OR (comoro*):ti,ab,kw OR (congo*):ti,ab,kw OR (cote d ivoire*):ti,ab,kw OR (djibouti*):ti,ab,kw OR (east africa*):ti,ab,kw OR (eastern africa*):ti,ab,kw OR (egypt*):ti,ab,kw OR (el salvador*):ti,ab,kw OR (equatorial guinea*):ti,ab,kw OR (eritre*):ti,ab,kw OR (ethiopia*):ti,ab,kw OR (gabon*):ti,ab,kw OR (gambia*):ti,ab,kw OR (gaza*):ti,ab,kw OR (ghan*):ti,ab,kw OR (guatemal*):ti,ab,kw OR (guinea*):ti,ab,kw OR (haiti*):ti,ab,kw OR (hondur*):ti,ab,kw OR (india*):ti,ab,kw OR (indones*):ti,ab,kw OR (ivory coast*):ti,ab,kw OR (kenya*):ti,ab,kw OR (kiribati*):ti,ab,kw OR (kosovo*):ti,ab,kw OR (kyrgyz*):ti,ab,kw OR (lao pdr*):ti,ab,kw OR (lesotho*):ti,ab,kw OR (liberia*):ti,ab,kw OR (madagascar*):ti,ab,kw OR (malaw*):ti,ab,kw OR (mali):ti,ab,kw OR (mauritan*):ti,ab,kw OR (mauriti*):ti,ab,kw OR (micronesi*):ti,ab,kw OR (mocambiqu*):ti,ab,kw OR (moldov*):ti,ab,kw OR (mongolia*):ti,ab,kw OR (morocc*):ti,ab,kw OR (mozambiqu*):ti,ab,kw OR (myanmar*):ti,ab,kw OR (namibia*):ti,ab,kw OR (nepal*):ti,ab,kw OR (nicaragua*):ti,ab,kw OR (niger*):ti,ab,kw OR (northern korea*):ti,ab,kw OR (north korea*):ti,ab,kw OR (pakistan*):ti,ab,kw OR (palestin*):ti,ab,kw OR (papua new guinea*):ti,ab,kw OR (philippine*):ti,ab,kw OR (principe*):ti,ab,kw OR (republic of korea*):ti,ab,kw OR (rhodesia*):ti,ab,kw OR (rwanda*):ti,ab,kw OR (samoa*):ti,ab,kw OR (sao tome*):ti,ab,kw OR (senegal*):ti,ab,kw OR (sierra leone*):ti,ab,kw OR (solomon islands*):ti,ab,kw OR (somalia*):ti,ab,kw OR (south africa*):ti,ab,kw OR (south sudan*):ti,ab,kw OR (southern africa*):ti,ab,kw OR (sri lanka*):ti,ab,kw OR (sub saharan africa*):ti,ab,kw OR (subsaharan africa*):ti,ab,kw OR (sudan*):ti,ab,kw OR (swaziland*):ti,ab,kw OR (syria*):ti,ab,kw OR (tajikist*):ti,ab,kw OR (tanzan*):ti,ab,kw OR (timor*):ti,ab,kw OR (togo*):ti,ab,kw OR (tonga*):ti,ab,kw OR (tunis*):ti,ab,kw OR (ugand*):ti,ab,kw OR (ukrain*):ti,ab,kw OR (uzbekistan*):ti,ab,kw OR (vanuatu*):ti,ab,kw OR (vietnam*):ti,ab,kw OR (west africa*):ti,ab,kw OR (west bank*):ti,ab,kw OR (western africa*):ti,ab,kw OR (yemen*):ti,ab,kw OR (zaire*):ti,ab,kw OR (zambia*):ti,ab,kw OR (zimbabw*):ti,ab,kw)

Popline

((('premature birth' OR 'premature' OR 'prematurity' OR 'preterm' OR 'preterms' OR 'low birth weight' OR 'small for gestational age' OR 'small for date' OR 'sga' OR 'low birthweight' OR 'low birth weight' OR 'vlbw' OR 'elbw'))) AND ((('infant mortality' OR 'survival' OR 'premature survival' OR 'preterm survival' OR 'premature mortality' OR 'premature death' OR 'premature deaths' OR 'preterm mortality' OR 'preterm mortalities' OR 'preterm death' OR 'preterm deaths' OR 'neonatal mortality' OR 'neonatal mortalities' OR 'neonatal survival'))) AND ((('low income countries' OR 'low income country' OR 'middle income countries' OR 'middle income country' OR 'developing country' OR 'developing countries' OR 'low resource setting' OR 'low resource settings' OR 'third world' OR 'poor country' OR 'poor countries'))) AND (((random OR randomized OR randomised) AND (controlled OR control OR placebo OR versus OR vs OR group OR groups OR comparison OR compared OR arm OR arms OR crossover OR cross\-over) AND (trial OR study OR single OR double OR triple) AND (masked OR blind OR blinded)))

African Journals OnLine

('premature birth' OR prematur* OR preterm* OR 'small for gestational age' OR 'small for date' OR 'sga' OR 'low birthweight' OR 'low birth weight' OR vlbw OR elbw) AND ('mortality' OR 'survival')

Global Health Library

(tw:('premature birth' OR 'premature' OR 'prematurity' OR 'preterm' OR 'preterms' OR 'small for gestational age' OR 'small for date' OR 'sga' OR 'low birthweight' OR 'low birth weight' OR 'vlbw' OR 'elbw')) AND (tw:('perinatal mortality' OR 'perinatal death' OR 'infant mortality' OR 'survival' OR 'premature survival' OR 'preterm survival' OR 'preterm mortality' OR 'preterm death' OR 'preterm deaths' OR 'neonatal mortality' OR 'neonatal survival')) AND (instance:"ghl") AND (instance:"ghl") AND (la:("en"))

GRADE CERTAINTY RATINGS

Certainty	What it means
Very low	The true effect is probably markedly different from the estimated effect
Low	The true effect might be markedly different from the estimated effect
Moderate	The authors believe that the true effect is probably close to the estimated effect
High	The authors have a lot of confidence that the true effect is similar to the estimated effect

COUNTRIES AND CORRESPONDING STUDIES

LOW-INCOME COUNTRIES*		
Democratic Republic of Congo	Carlo *et al* [22] (2010)	Training of birth attendants
Ethiopia	Worku *et al* [47] (2005)	Earlier KMC

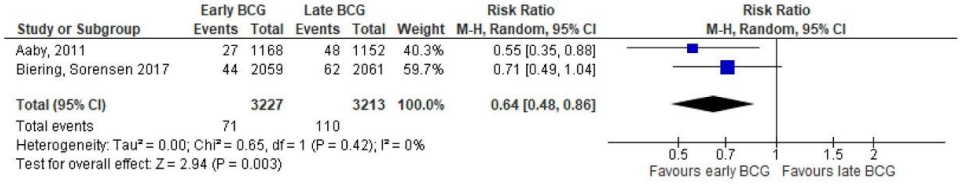
Guinea-Bissau	Aaby *et al* [24] (2011)	Early BCG
	Biering-Sorensen [31] (2017)	
Madagascar	Nagai *et al* [41] (2010)	Earlier KMC
Malawi	Van den Bosch *et al* [68] (1996)	Polythene tobacco wrap
Mozambique	Cavicchiolo *et al* [32] (2016)	Quality improvement intervention of NICU and obstetric department
Nepal	Tielsch *et al* [46] (2007)	Skin-cleansing with chlorhexidine
Uganda	Okello et al [63] (2019)	Bubble CPAP
LOWER MIDDLE-INCOME COUNTRIES*		
Bangladesh	Arifeen *et al* [27] (2012)	Single and multiple cord cleansing with chlorhexidine
	Darmstadt *et al* [35](2008)	Topical ointment with Aquaphor and SSO
	Sloan *et al* [45] (2008)	Community KMC
Egypt	Darmstadt *et al* [34] (2004)	Topical ointment with SSO
India	Adhisivam *et al* [25] (2018)	Fortified pasteurized donor human milk
	Aggarwal *et al* [26] (2016)	Selenium supplementation
	Aggarwal *et al* [21] (2018)	Maintenance tocolysis with nidefipine
	Althabe *et al* [20] (2015)	Antenatal corticosteroids
	Balachander *et al* [50] (2018)	Oral paracetamol for PDA closure
	Bang *et al* [29] (1999)	Home based newborn care
	Bang, Baitule *et al* [28](2005)	Home based newborn care
	Bang, Reddy *et al* [30] (2005)	Home based newborn care
	Basu *et al* [51] (2019)	Oral vitamin A supplementation
	Bhatti *et al* [52] (2015)	Nasal-jet CPAP device
	Carlo *et al* [22] (2010)	Training of birth attendants
	Chopra *et al* [33] (2018)	Delayed cord clamping
	Garces *et al* [36] (2016)	Antenatal corticosteroids
	Jain *et al* [57] (2019)	Goat lung surfactant extract
	Kaur *et al* [37] (2015)	Bovine lactoferrin supplementation
	Kirpal *et al* [38] (2016)	Prophylactic fluconazole
	Klein *et al* [39] (2016)	Antenatal corticosteroids
	Krishna *et al* [58] (2019)	Volume-guaranteed ventilation
	Kumar *et al* [59] (2017)	Aminophylline
	Mazumder *et al* [40] (2019)	Community KMC
	Murki *et al* [61] (2018)	High-flow nasal cannula
	Nandakumar *et al* [42] (2020)	Hybrid milk feeds
	Nandhini *et al* [62] (2016)	Synbiotics supplementation
	Tagare *et al* [66] (2013)	Bubble CPAP

	Tali *et al* [67] (2016)	3-hour feeding schedule
Kenya	Althabe *et al* [20] (2015) Garces *et al* [36] (2016) Klein *et al* [39] (2016)	Antenatal corticosteroids
Nigeria	Graham *et al* [55] (2019)	Pulse oximetry and full O_2 system
Pakistan	Althabe *et al* [20] (2015)	Antenatal corticosteroids
	Arif *et al* [49] (1999)	Maternal nursing care
	Bhutta *et al* [53] (2004)	Stepdown unit involving maternal nursing care
	Carlo *et al* [22] (2010)	Training of birth attendants
	Garces *et al* [36] (2016)	Antenatal corticosteroids
	Halim *et al* [56] (2018)	Less invasive surfactant administration
	Klein *et al* [39] (2016)	Antenatal corticosteroids
	Rasool *et al* [43] (2017)	Antenatal corticosteroids
Zambia	Althabe *et al* [20] (2015)	Antenatal corticosteroids
	Carlo *et al* [22] (2010)	Training of birth attendants
	Garces *et al* [36] (2016)	Antenatal corticosteroids
	Klein *et al* [39] (2016)	Antenatal corticosteroids
UPPER MIDDLE-INCOME COUNTRIES*		
Argentina	Althabe *et al* [20] (2015)	Antenatal corticosteroids
	Carlo *et al* [22] (2010)	Training of birth attendants
	Garces *et al* [36] (2016)	Antenatal corticosteroids
	Klein *et al* [39] (2016)	Antenatal corticosteroids
Armenia	Mazmanyan *et al* [60] (2016)	Bubble CPAP
Guatemala	Althabe *et al* [20] (2015)	Antenatal corticosteroids
	Carlo *et al* [22] (2010)	Training of birth attendants
	Garces *et al* [36] (2016)	Antenatal corticosteroids
	Klein *et al* [39] (2016)	Antenatal corticosteroids
Iran	Gharehbaghi *et al* [54] (2010)	Poractant alfa
Turkey	Aktas *et al* [48] (2015)	rhG-CSF
	Erdemir *et al* [23] (2015)	Topical ointment with Aquaphor
	Sari *et al* [64] (2011)	Lactobacillus sporogenes
	Sarman *et al* [44] (1989)	Heated, water filled mattress
	Say *et al* [65] (2016)	Binasal prong for applying CPAP

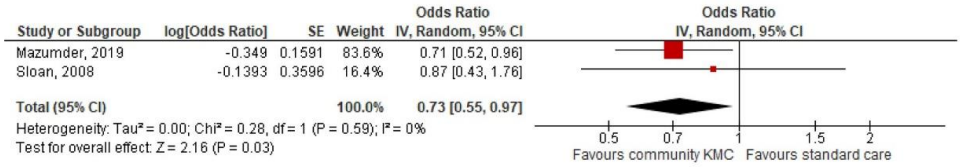
*According to the World Bank Classification [11]

KMC=kangaroo mother care. BCG=Bacillus Calmette-Guérin. NICU=neonatal intensive care unit. CPAP=continuous positive airway pressure. SSO=sunflower seed oil. PDA=patent ductus arteriosus. rhG-CSF=recombinant human granulocyte-macrophage colony-stimulating factor

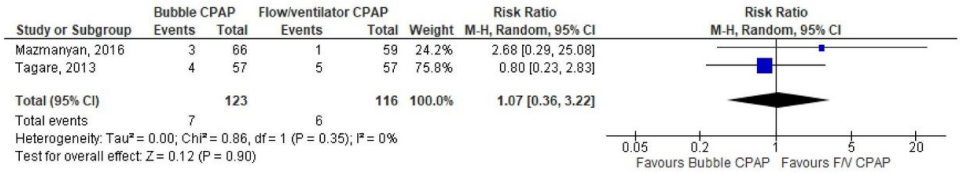
FIGURE 2: META-ANALYSES



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

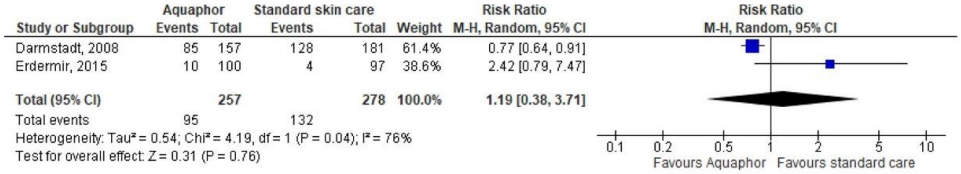


Meta-analysis addressing the effect of community KMC versus standard home-based care on 28-day neonatal mortality among LBW neonates.



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.

GRADE EVIDENCE PROFILES

Table 5. QUALITY ASSESSMENT							SUMMARY OF FINDINGS				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute	
Antenatal corticosteroids vs. standard care on stillbirths											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	748/3268	739/2997	0.99 (0.90-1.09)	-	⊕⊕⊕⊕ HIGH
Antenatal corticosteroids vs. standard care on perinatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	1172/2997	1203/3268	0.97 (0.91- 1.04)	-	⊕⊕⊕⊕ HIGH
Antenatal corticosteroids vs. standard care on 7-day neonatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	455/3268	433/2997	0.94 (0.84-1.06)	-	⊕⊕⊕⊕ HIGH
Antenatal corticosteroids vs. standard care on 28-day neonatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	566/3268	524/2997	0.96 (0.87-1.06)	-	⊕⊕⊕⊕ HIGH
1 (Garces et al.)	cluster-RCT	not serious	not serious	not serious	not serious	none	36/197	39/166	0.74 (0.68-0.81)	-	⊕⊕⊕⊕ HIGH
1 (Klein et al., Belgaum)	cluster-RCT	not serious	not serious	not serious	serious	none	133/533	158/618	0.96 (0·75 – 1·22)	-	⊕⊕⊕◯ MODERATE [a]
1 (Klein et al., Nagpur)	cluster-RCT	not serious	not serious	not serious	serious	none	109/357	84/255	0.94 (0·72 – 1·23)	-	⊕⊕⊕◯ MODERATE [a]
1 (Klein et al., Pakistan)	cluster-RCT	not serious	not serious	not serious	not serious	none	172/760	172/687	0.89(0·80 – 0·99)	-	⊕⊕⊕⊕ HIGH
1 (Klein et al., Zambia)	cluster-RCT	not serious	not serious	not serious	serious	none	30/198	27/212	1.43 (0·90 – 2·28)	-	⊕⊕⊕◯ MODERATE [a]

1 (Klein et al., Kenya)	cluster-RCT	not serious	not serious	not serious	serious	none	45/235	27/189	1.30 (0·94 – 1·81)	-	⊕⊕⊕◯ MODERATE [a]
1 (Klein et al., Guatemala)	cluster-RCT	not serious	not serious	not serious	not serious	none	57/346	39/166	0.75 (0·69 – 0·82)	-	⊕⊕⊕⊕ HIGH
1 (Klein et al., Argentina)	cluster-RCT	not serious	not serious	not serious	serious	none	20/91	17/131	1.60 (0·99 – 2·58)	-	⊕⊕⊕◯ MODERATE [a]
Antenatal corticosteroids; four doses of 6 mg versus two doses of 12 mg dexamethasone on 28-day neonatal mortality											
1 (Rasool)	RCT	very serious	not serious	not serious	very serious	none	0/24	2/24	0.20 (0·01 – 3·96)	-	⊕◯◯◯ VERY LOW [b,c,d,e,]
Maintenance tocolysis with nifedipine versus standard care on perinatal mortality											
1	RCT	not serious	not serious	not serious	very serious	none	2/18	3/23	0.85 (0.16-4.57)	-	⊕⊕◯◯ LOW [e]
Fortified versus unfortified pasteurized donor human milk on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	very serious	none	3/40	3/40	1.00 (0·21 – 4·66)	-	⊕⊕◯◯ LOW [e]
Hybrid milk feeds versus mother's milk alone on 28-day neonatal mortality											
1	RCT	serious	not serious	not serious	very serious	none	4/62	5/59	0.76 (0·21 – 2·70)	-	⊕◯◯◯ VERY LOW [d,e,f,g]
Single and multiple cord cleansing with chlorhexidine versus dry cord care on 28-day neonatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	280/6547	145/3058	Single LBW: 0.82(0·63-1·06) / Single preterm: 0.65(0·50-0·86) / Multiple LBW: 1.00(0·79-1·27) / Multiple preterm: 0.88(0·69-1·12)	-	⊕⊕⊕⊕ HIGH
Skin cleansing with chlorhexidine versus placebo on 28-day neonatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	83/2448	117/2491	0.72 (0·55–0·95)	-	⊕⊕⊕⊕ HIGH
SSO versus standard skin care on 28-day neonatal mortality											
2	RCT	serious	not serious	not serious	serious	none	117/210	146/233	0.92 (0.78-1.07)	-	⊕⊕◯◯ LOW [a.c,d †]
Aquaphor versus standard skin care on 21- and 28-day neonatal mortality											

2	RCT	not serious	serious	not serious	serious	none	95/257	132/278	1.19 (0.38-3.71)	-	⊕⊕◯◯ LOW [a,h †]
Selenium supplementation versus Glucon-D powder alone on 28-day neonatal mortality											
1	RCT	serious	not serious	not serious	very serious	none	2/45	3/45	0.67 (0·12 – 3·80)	-	⊕◯◯◯ VERY LOW [e,i]
Bovine lactoferrin versus placebo on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	very serious	none	0/63	5/67	0.10 (0·01 – 1·71)	-	⊕⊕◯◯ LOW [e]
Early versus late BCG vaccine on 28-day neonatal mortality											
2	RCT	not serious	not serious	not serious	not serious	none	71/3227	110/3213	0.64 (0.48-0.86)	-	⊕⊕⊕⊕ HIGH [†]
Prophylactic fluconazole versus placebo on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	serious	none	7/38	12/37	0.57 (0·25 – 1·28)	-	⊕⊕⊕◯ MODERATE [a]
Early versus late KMC on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	very serious	none	2/37	1/36	1.95 (0·18 – 20·53)	-	⊕⊕◯◯ LOW [e]
Early KMC versus conventional care on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	serious	none	14/62	24/61	0.57 (0·33 – 1·00)	-	⊕⊕⊕◯ MODERATE [a]
Community KMC versus standard home-based care											
2	(cluster)-RCT	not serious	not serious	not serious	not serious	none	104/4973	126/4318	0.73 (0.55-0.97)	-	⊕⊕⊕⊕ HIGH [†]
Home based neonatal care versus pre-intervention period											
1 (Bang et al.)	Before-after design	not serious	not serious	not serious	not serious	none	LBW:13/321 Preterm:9/93	LBW:36/320 Preterm:25/75	LBW: 0.36 (0·20 – 0·67) Preterm: 0.29 (0·14 – 0·58)	-	⊕⊕⊕⊕ HIGH
1 (Bang, Baitule et al.)	Before-after design	not serious	not serious	not serious	not serious	none	LBW:39/825 Preterm:23/226	LBW:36/320 Preterm: 25/75	LBW: 0.42 (0·27 – 0·65) Preterm: 0.31 (0·18 – 0·50)	-	⊕⊕⊕⊕ HIGH

1 (Bang, Reddy et al.)	Before-after design	not serious	not serious	not serious	not serious	none	12/142	25/75	0.25 (0·14 – 0·48)	-	⊕⊕⊕⊕ HIGH
Training of traditional birth attendants versus pre-intervention period on stillbirths											
1	Before-after design	not serious	not serious	not serious	serious	none	157/359	72/169	1.03 (0·80–1·31)	-	⊕⊕⊕◯ MODERATE [a]
Training of traditional birth attendants versus no additional training on stillbirths											
1	cluster-RCT	not serious	not serious	not serious	serious	none	91/273	101/295	0.97 (0·57 – 1·67)	-	⊕⊕⊕◯ MODERATE [a]
Training of traditional birth attendants versus pre-intervention period on perinatal mortality											
1	Before-after design	not serious	not serious	not serious	not serious	none	283/359	133/169	1.02 (0·91 – 1·14)	-	⊕⊕⊕⊕ HIGH
Training of traditional birth attendants versus no additional training on perinatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	198/273	225/295	0.95 (0·84 – 1·07)	-	⊕⊕⊕⊕ HIGH
Training of traditional birth attendants versus pre-intervention period on 7-day neonatal mortality											
1	Before-after design	not serious	not serious	not serious	not serious	none	126/359	61/169	1.03 (0·83 – 1·27)	-	⊕⊕⊕⊕ HIGH
Training of traditional birth attendants versus no additional training on 7-day neonatal mortality											
1	cluster-RCT	not serious	not serious	not serious	not serious	none	107/273	124/295	0.92 (0·77 – 1·09)	-	⊕⊕⊕⊕ HIGH
Delayed versus early cord clamping on 28-day neonatal mortality											
1	RCT	serious	not serious	not serious	very serious	none	1/55	0/58	3.16 (0·13 – 75·98)	-	⊕◯◯◯ VERY LOW [e,k]
Heated mattress versus air heated incubators on 28-day neonatal mortality											
1	RCT	not serious	not serious	not serious	serious	none	6/28	11/32	0.62 (0.26 – 1.47)	-	⊕⊕⊕◯ MODERATE [a]
Quality improvement intervention of NICU and obstetric department versus pre-intervention period on 28-day neonatal mortality											
1	Before-after design	serious	not serious	not serious	not serious	none	200/605	192/447	0.77 (0·66 – 0·90)	-	⊕⊕⊕◯ MODERATE [j]

† Derived from the meta-analysis pooling the results of both studies.
‡ Odds ratio; adjusted for cluster design effect.

RR=risk ratio. CI=confidence interval. GRADE = Grading of Recommendations Assessment, Development, and Evaluation system. PDHM=pasteurized donor human milk. LBW=low birthweight. SSO=sunflower seed oil. BCG=Bacillus Calmette-Guérin. KMC=kangaroo mother care. ENC=Essential Newborn Care. NRP=Neonatal Resuscitation Program.

a=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.
b= identification and recruitment of individual participants occurred after randomization.
c= method of randomization is not reported, baseline differences suggest a problem with randomization.
d=information about blinding of participants and carers is not provided.
e=insufficient sample to meet optimal information size (OIS) criteria with very few events and 95% CI fails to exclude important benefit or harm.
f=allocation concealment is not reported.
g=method of ascertainment of mortality outcome measure is not reported.
h=I^2 of 76%, p-value of 0,04, minimal overlapping 95% CI's and one study showing benefit while the other study shows harm suggest serious inconsistency of results.
i=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.
j=confounding due to baseline differences cannot be excluded and is not controlled for in the study.
k=substantial loss to follow-up in relation to the number of events and failure to adhere to the intention-to-treat principle.

Table 6. QUALITY ASSESSMENT IN-HOSPITAL MORTALITY							SUMMARY OF FINDINGS				
							No of patients		Effect		Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Control	Relative (95% CI)	Absolute	
3-hour versus 2-hour feeding schedule on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	0/60	0/60	NA	-	⊕⊕◯◯ LOW [a]
rhG-CSF versus empirical antibiotics alone on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	10/33	6/23	1.16 (0·49 – 2·74)	-	⊕⊕◯◯ LOW [a]
Synbiotics versus standard care on in-hospital mortality											

1	RCT	not serious	not serious	not serious	very serious	none	10/108	9/110	1.13 (0·48 – 2·68)	-	⊕⊕◯◯ LOW [a]
Lactobacillus sporogenes versus breast milk or formula alone on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	3/110	4/111	0.76 (0·17 – 3·30)	-	⊕⊕◯◯ LOW [a]
Nasal-jet CPAP versus bubble CPAP on in-hospital mortality											
1	RCT	not serious	not serious	not serious	serious	none	20/80	16/90	1.41 (0·78 – 2·52)	-	⊕⊕⊕◯ MODERATE [b]
Bubble CPAP versus flow driver CPAP on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	3/66	1/59	2.68 (0·29 – 25·08)	-	⊕⊕◯◯ LOW [a] *
Bubble CPAP versus pre-intervention period											
1	Before-after design	very serious	not serious	not serious	not serious	none	58/219	62/158	0.68 (0·50 – 0·91)	-	⊕⊕◯◯ LOW [c]
Bubble CPAP versus ventilator-derived CPAP on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	4/57	5/57	0.80 (0·23 – 2·83)	-	⊕⊕◯◯ LOW [a] *
Binasal prong versus nasal mask for applying nasal CPAP on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	4/75	7/74	0.56 (0·17 – 1·85)	-	⊕⊕◯◯ LOW [a]
Poractant alfa versus beractant on in-hospital mortality											
1	RCT	not serious	not serious	not serious	serious	none	21/79	15/71	1.26 (0·70 – 2·25)	-	⊕⊕⊕◯ MODERATE [b]
LISA method versus conventional INSURE method on in-hospital mortality											
1	RCT	not serious	not serious	not serious	serious	none	19/50	28/50	0.68 (0·44 – 1·04)	-	⊕⊕⊕◯ MODERATE [b]
Goat lung surfactant extract versus beractant on in-hospital mortality											
1	RCT	not serious	not serious	not serious	serious	none	21/52	14/46	1.33 (0·77 – 2·30)	-	⊕⊕⊕◯ MODERATE [b]
Vitamin A supplementation versus placebo on in-hospital mortality											

1	RCT	not serious	not serious	not serious	serious	none	9/98	16/98	0.56 (0·26 – 1·21)	-	⊕⊕⊕◯ MODERATE [b]
Pulse oximetry versus pre-intervention period on in-hospital mortality											
1	cluster-RCT	not serious	not serious	not serious	serious	none	82/611	326/1876	1.12 (0·56 – 2·26)[†]	-	⊕⊕⊕◯ MODERATE [b]
Full O_2 system versus pre-intervention period on in-hospital mortality											
1	cluster-RCT	not serious	not serious	not serious	serious	none	203/1042	326/1876	0.99 (0·61 – 1·59)[†]	-	⊕⊕⊕◯ MODERATE [b]
Volume-guaranteed ventilation versus pressure-controlled ventilation on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	4/40	5/41	0.82 (0·24 – 2·84)	-	⊕⊕◯◯ LOW [a]
Aminophylline versus caffeine on in-hospital mortality											
1	RCT	serious	not serious	not serious	serious	none	16/73	15/70	1.02 (0·55 – 1·91)	-	⊕⊕◯◯ LOW [b,d]
High flow nasal cannula versus nasal CPAP on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	4/133	3/139	1.39 (0·32 – 6·11)	-	⊕⊕◯◯ LOW [a]
Maternal nursing care versus special care baby unit on in-hospital mortality											
1	RCT	serious	not serious	not serious	not serious	none	43/151	141/211	0.43 (0·33 – 0·56)	-	⊕⊕⊕◯ MODERATE [d]
Stepdown unit versus pre-intervention period on in-hospital mortality											
1	Before-after design	serious	not serious	not serious	not serious	none	55/318	63/191	0.52 (0·38 – 0·72)	-	⊕⊕⊕◯ MODERATE [c]
Oral paracetamol versus oral ibuprofen for PDA closure on in-hospital mortality											
1	RCT	not serious	not serious	not serious	very serious	none	12/55	11/55	1.10 (0·53 – 2·26)	-	⊕⊕◯◯ LOW [a]
Polythene tobacco wrap versus standard nursing procedure on in-hospital mortality											
1	RCT	serious	not serious	not serious	serious	none	0/15	6/11	0.06 (0·0036 – 0·93)	-	⊕⊕◯◯ LOW [b,d]

*** Derived from the meta-analysis pooling the results of both studies.**
† Mixed-model odds ratio; accounted for the clustering of patients within hospitals and adjusted for time trends

RR=risk ratio. CI=confidence interval. rhG-CSF=Recombinant human granulocyte-macrophage colony-stimulating factor. CPAP=continuous positive airway pressure. VLBW=very low

birthweight. ELBW=extremely low birthweight. LISA=less invasive surfactant administration. INSURE=INtubation SURfactant administration and Extubation. PDA=patent ductus arteriosus

a=insufficient sample to meet optimal information size (OIS) criteria with very few events and 95% CI fails to exclude important benefit or harm.
b=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.
c=serious risk of selection bias.
d=substantial loss to follow-up in relation to the number of events and failure to adhere to the intention-to-treat principle.

RISK OF BIAS OF INDIVIDUAL STUDIES

Table 7. Risk of bias assessment of randomized controlled trials and pre-post intervention analyses according to the Cochrane RoB 2 tool (n = 36)

Author (year)	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall judgement
Aaby *et al* [24] (2011)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Adhisivam *et al* [25] (2018)	Low risk	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Aggarwal *et al* [21] (2018)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Aggarwal *et al* [26] (2016)	Low risk	Some concerns	High risk	Low risk	Some concerns	**High risk**
Aktas *et al* [48] (2015)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Arif *et al* [49] (1999)	Some concerns	Some concerns	High risk	Low risk	Some concerns	**High risk**
Balachander *et al* [50] (2018)	Low risk	Some concerns	High risk	Low risk	Some concerns	**High risk**
Basu *et al* [51] (2019)	Low risk	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Bhatti *et al* [52] (2015)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Biering Sorensen et al [31] (2017)	Some concerns	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Chopra *et al* [33] (2018)	Low risk	High risk	High risk	Low risk	Some concerns	**High risk**
Darmstadt *et al* [34] (2004)	High risk	Some concerns	Low risk	High risk	Some concerns	**High risk**
Darmstadt *et al* [35] (2008)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Erdemir *et al* [23] (2015)	Low risk	Some concerns	Low risk	Some concerns	Some concerns	**Some concerns**
Gharehbaghi *et al* [54] (2010)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Halim *et al* [56] (2018)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Jain *et al* [57] (2019)	Low risk	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Kaur *et al* [37] (2015)	Low risk	Low risk	High risk	Low risk	Some concerns	**High risk**
Kirpal *et al* [38] (2016)	Some concerns	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Krishna *et al* [58] (2019)	Low risk	High risk	Low risk	Low risk	Some concerns	**High risk**

Kumar *et al* [59] (2017)	Some concerns	High risk	High risk	Low risk	Some concerns	**High risk**
Mazmanyan *et al* [60] (2016)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Mazumder *et al* [40] (2019)	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Murki *et al* [61] (2018)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Nagai *et al* [41] (2010)	Some concerns	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Nandakumar *et al* [42] (2020)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Nandhini *et al* [62] (2016)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Rasool *et al* [43] (2017)	High risk	High risk	Low risk	Low risk	Some concerns	**High risk**
Sari *et al* [64] (2011)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Sarman *et al* [44] (1989)	Some concerns	High risk	Low risk	Low risk	Some concerns	**High risk**
Say *et al* [65] (2016)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Tagare *et al* [66] (2013)	Low risk	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Tali *et al* [67] (2016)	Low risk	High risk	Low risk	Low risk	Some concerns	**High risk**
Van den Bosch *et al* [68] (1996)	Some concerns	High risk	High risk	Low risk	Some concerns	**High risk**
Worku *et al* [47] (2005)	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**

Table 8. Risk of bias assessment of cluster-randomized controlled trials according to the Cochrane RoB 2 tool (n = 8)

Author (year)	Randomization process	Timing of identification and recruitment of participants	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall judgement
Althabe *et al* [20] (2015)	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Arifeen *et al* [27] (2012)	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Carlo *et al* [22] (2010) NRP trial	Some concerns	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Garces *et al* [36] (2016)	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**

Graham *et al* [55] (2019)	Low risk	Some concerns	Some concerns	Low risk	Low risk	Low risk	**Some concerns**
Klein *et al* [39] (2016)	Low risk	Some concerns	Some concerns	Low risk	Low risk	Some concerns	**Some concerns**
Sloan *et al* [45] (2008)	Some concerns	Some concerns	Low risk	Low risk	Low risk	Some concerns	**Some concerns**
Tielsch *et al* [46] (2007)	Low risk	Low risk	Low risk	Low risk	Low risk	Some concerns	**Some concerns**

	Table 9. Risk of bias assessment of non-randomized, before-after designs according to the ROBINS-I tool (n = 7)							
Author (year)	**Confounding**	**Selection bias**	**Classification of interventions**	**Deviations from intended intervention**	**Missing outcome data**	**Measurement of the outcome**	**Selection of reported results**	**Overall judgement**
Bang *et al* [29] (1999)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Bang, Baitule *et al* [28] (2005)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Bang, Reddy *et al* [30] (2005)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Bhutta *et al* [53] (2004)	Low risk	Serious risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Serious risk**
Carlo *et al* [22] (2010) ENC trial	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low risk**
Cavicchiolo *et al* [32] (2016)	Serious risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Serious risk**
Okello *et al* [63] (2019)	Moderate risk	Critical risk	Serious risk	Low risk	Low risk	Low risk	Low risk	**Critical risk**

SWOT ANALYSIS

Table 10. SWOT analysis of interventions to reduce mortality among preterm and LBW neonates

Intervention	Strengths (S)	Weaknesses (W)	Opportunities (O)	Threats (T)
	ANTENATAL INTERVENTIONS			
Antenatal corticosteroids (ACS)	Among the most effective hospital-based interventions to reduce neonatal mortality associated with preterm birth.[20,36,39]	ACS might increase risk of infectious morbidity for women and their infants delivered in community settings. [20,36,39]	How and to whom ACS can be safely and effectively delivered in low-resource settings should be investigated before the scale-up of ACS takes place. [20]	Birth attendants in low-resource settings might not have the skills necessary to assess risk of preterm birth or to safely administer ACS and do often not have ultrasound dating or last menstrual period available.[20,36,39]
		The most effective corticosteroid regimen is not established and therefore different agents in various dosages and frequencies are currently used in clinical practice.[43]	Scale-up strategies should explore the minimum maternal and neonatal care needed to attend infants exposed to ACS in such settings.[20]	ACS might have little effect in settings without neonatal intensive care.[20,36,39]
		Risk of morbidity increases with inaccurate gestational age determination.[20,36,39]		Access to tertiary care with availability of ACS is poor in LICs.[20,36,39]
Maintenance tocolysis with nifedipine in established preterm labour	Ease of administration, high-efficacy and less side-effects compared to other tocolytics.[21]	Accurate determination of gestational age is required.[21]	Multicentre trials and collaboration among hospitals to gather high numbers of data may help to assess the effectiveness of maintenance tocolysis.[21]	If gestational age is not accurately determined nifedipine could do more harm than good.[21]
	FEEDING INTERVENTIONS			
Fortified pasteurized donor human milk (PDHM)	PDHM is associated with a lower risk of necrotizing enterocolitis (NEC) compared to formula feeding	PDHM is likely to have a lower protein content than own mother's milk.[25]	An exclusively human milk–based diet is associated with lower rates of NEC and	Lack of availability, accessibility in terms of cost and distribution substantially limits DHM use.[25]

	in the absence of own mother's milk.[25]		DHM should therefore be made available in low resource settings.[25]	
	Fortifiers enrich breast milk with important nutrients and thereby improve growth of preterm infants.[25]	PDHM might cause feed intolerance or increase risk of NEC through interfering with gastric emptying and intestinal peristalsis.[25]	It is possible to supply PDHM according to established guidelines with no adverse events even in resource limited settings.[25]	The number of available donor human milk bank facilities is minuscule compared to the number of NICUs and eligible babies in resource limited settings.[25]
		Immunological components specific for preventing NEC may be lost during pasteurization.[25]		Dietary, cultural or ethical convictions might limit the use of fortifiers from bovine origin, whilst human-derived fortifiers are often unavailable in low-resource settings.[25]
Hybrid feeding (mother milk and formula supplementation)	Hybrid feeding requires less skills and is associated with a lower risk of infection compared to parenteral nutrition.[42]	Formula milk is associated with higher risk of feed intolerance and NEC.[42]	More cost effective and easier in terms of distribution than use of donor human milk.[42]	Maternal complications underlying preterm birth and neonatal complications managed at a NICU often create a barrier for early initiation of breastfeeding.[76]*
			Breast milk with formula supplementation is a solution in settings where donor human milk banks are not available, which is often the case in LMICs.[42]	
			Intensive efforts to improve breast pumping practices could result in improvement of breastmilk feeding in NICUs.[42]	
3-hour feeding schedule	A 3-hour feeding schedule is associated with significantly less feeding time.[67]	In neonates weighing ≤ 1000 gram a 3-hour feeding schedule might not be tolerated due to larger volumes per feed.[67]	A less frequent feeding schedule would reduce neonate handling and workload on nursing staff, hence reducing	Considering the risk of hypoglycaemia is still unsure, neurological damage could be a potential result of a 3-hour feeding

	Neonates who are fed only 8 times a day (3-h) are less likely to be handled or disturbed.[65]	The risk of hypoglycaemia in unstable neonates following a 3-hour feeding schedule is yet to be studied.[65]	infection rate and length of hospital stay.[67]	schedule, and neurological complications in preterm infants are difficult to deal with in resource-limited settings.[67]
	INFECTION PREVENTION			
Cord and skin cleansing with chlorhexidine	Safe, simple to deliver and inexpensive.[27,46]	The wetting action of wipes is associated with risk of hypothermia, when skin-wiping promptly followed by wrapping of the newborn is not performed adequately.[46]	Pragmatic implementation in countries with restricted resources and high neonatal mortality, where most deliveries occur at home in unhygienic conditions.[27,46]	Traditional umbilical practices involving harmful substances are widespread and therefore adaptation of the intervention could be difficult.[27]
			Application of chlorhexidine can act as a behaviour change agent. In many cultures where applying agents to cord and skin are common practice, a policy of chlorhexidine application may accelerate change by substituting a harmful substance for a helpful one.[34,35]	
			Chlorhexidine is listed on the WHO Essential Drug List and should therefore be made available in all countries.[77]*	
			WHO recommends cleansing with chlorhexidine for newborns who are born at home. The use of chlorhexidine in health facilities is one of the top research priorities as stated in the Every Newborn Action Plan.[3,27]	
Topical ointment therapy with Aquaphor and	Emollient therapy is readily available worldwide, inexpensive and technologically simple.[34,35]	Topical ointment changes the bacterial flora of the skin and therefore affects the prevalence of bacterial colonization.[23]	Considering the rising rates of antibiotic resistance, there is an urgent need to develop effective measures to prevent neonatal infections.[34]	Organisms attributable to the development of sepsis differ among countries and therefore one agent might not suit all settings.[34]

Sunflower Seed Oil (SSO)			Applying products to the newborn skin is commonplace in many cultures which facilitates implementation and acceptance of the intervention.[34,35]	
Supplementation with pro- and synbiotics and selenium	Safe intervention, no adverse effects noted.[37,62,64]	Not studied in neonates weighing < 1000 g or less.[26,37]	Pro- and synbiotics increase weight gain and therefore potentially reduce time until NICU discharge which is cost-effective.[60]	Careful consideration should be given to the differences in effectivity of various probiotic strains before its use is translated to clinical practice.[60]
	Neonates who received pro- or synbiotics showed a better tolerability towards feeds.[37,62,64]	Adverse effects on the long term are unknown.[26,37]		
	L. sporogenes presents advantages over other probiotic strains, such as low cost and ease of preparation.[64]	There is a theoretical risk of septicaemia due to probiotics, especially in immunocompromised neonates.[62]		
	Administration of pro- and synbiotics showed to lower the risk of NEC, late-onset sepsis and sepsis-attributable mortality in preterm neonates.[26,37,62]			
Early BCG vaccine	BCG seems to non-specifically enhance protection against important infections killing neonates, thereby reducing mortality.[22,29,77]	The immunological mechanisms underlying the nonspecific effect on overall mortality is poorly understood.[24,31,78]	The national immunization programme should be redesigned so that LBW neonates receive BCG at birth.[24,78]	BCG is very often delayed in low-income countries. Failing to vaccinate children with BCG at birth lowers the coverage for BCG among LBW children.[24,78]
	If early BCG vaccine reduces the risk and severity of infectious diseases, it could promote childhood growth.[22,77]		BCG vaccine could be promoted not only as a tuberculosis vaccine but also as a vaccine against neonatal infections.[31]	Extending early BCG vaccination to deliveries at home might be challenging in the absence of an adequate immunization program.[31]

Prophylactic fluconazole	Fluconazole treats candida species, which have a major contribution to the incidence of late onset sepsis in VLBW infants.[38]	There is a potential risk of resistance to fluconazole which could limit its effectivity. In this study, 60% of Candida tropicalis were resistant to fluconazole.[38]	Invasive fungal infection causes substantial morbidity and mortality in VLBW infants and treatment with fluconazole could be a step towards improved care.[38]	The implementation is limited to NICU settings. However, in low resource settings there is often a lack of equipment, supplies and resources to care for VLBW infants.[38]
	No significant adverse events were observed. [38]	Length of therapy course and parenteral route of administration contribute to the high costs and risk of complications associated with prophylactic fluconazole.[38]		
Recombinant human granulocyte-macrophage colony-stimulating factor (rhG-CSF)	Treatment-related side effects and toxic effects attributable to rhG-CSF were not detected.[48]	Theoretical concerns exist stating that rhG-CSF worsens IRDS and BPD by overactivating systemic inflammatory response.[48]	Sepsis is a leading cause of morbidity and mortality among premature neonates. Effective treatment is vital to reduce mortality.[48]	Resources needed to detect neutropenia to effectively implement rHG-CSF are not widely available in low-resourced settings.[48]
				Evidence is insufficient to support routine use for treatment or prophylaxis of neonatal sepsis.[48]
	PREVENTION AND TREATMENT OF RESPIRATORY MORBIDITY			
CPAP	Relatively simple to apply and low-cost health technology that can be delivered safely in LMICs.[63,65,66]	CPAP can only be applied in a hospital setting.[52,60,63,65,66]	The simplicity and low cost of Bubble CPAP is of particular benefit in LMICs where management and referral to tertiary care centres impose a significant economic burden.[52,60,63,66]	Ventilatory support needs to be provided within a hospital setting with trained staff who can identify the neonates that will benefit most, considering the supportive equipment, such as an oxygen source, that is needed but not always available or accessible in LMICs. [52,60,63,65,66]
	CPAP reduces the need for mechanical ventilation which is scarce in low-resource settings.[60,63,65]		Previous studies have shown successful implementation of CPAP in rural hospitals with limited resources.[60,63]	
			CPAP was readily accepted and effectively delivered by medical and nursing staff.[60]	

Exogenous surfactant replacement therapy	Easy to administer and proven to be effective in treating a large cause of death among preterm babies: respiratory distress syndrome.[54,57]	Costly intervention that can only be used in well-resourced NICU settings with availability of respiratory support systems and management of complications. [54,57]	There is an urgent need to develop a low-cost surfactant variant that can be implemented in LMICs.[57,79]	The ongoing changing pathogenesis of BPD and the multiplicity of factors involved prevent surfactant from being the ultimate solution to prevent BPD.[54]
	LISA can avoid the need for sedation and tracheal intubation; and has shown promising results with reduced need and duration of mechanical ventilation.[56]		Before wide uptake is recommended, studies should assess the additional lives saved by surfactant once antenatal corticosteroids or CPAP are used.[79]	Considering its animal-derived nature, dietary, cultural or ethical convictions might create a barrier to implementation of surfactant therapy.[54,57]
			LISA method potentially reduces the cost of hospital stay and complications of mechanical ventilation by avoiding intubation.[56]	
			LISA method can even be implemented at a level II NICU where nasal CPAP is available.[56]	
Feeding supplementation with vitamin A (VAS)	Cost-effective strategy to improve the clinical outcome in VLBW neonates with respiratory distress.[51]	Long term follow-up is necessary to document the effect of high-dose VAS on respiratory, growth, and neurodevelopmental outcome.[51]	Considering the discomfort, high cost and limited availability of vitamin A injections, oral supplementation is the preferable option.[51]	Consensus on the adequate dosing and effects of vitamin A remains unclear and a standard regimen is not available, which challenges its implementation in daily practice.[51]
Oxygen systems other than CPAP	VGV is associated with a lower risk of ventilation-induced lung injuries and associated morbidities.[58]	The major challenge is the risk of leak which is higher in infants because of using uncuffed tubes. Therefore, success of VGV in infants, especially extreme preterm newborns depends upon the amount of present leak.[58]	VGV potentially reduces the duration of ventilation, risk of lung injury and associated long term complications such as BPD, hence shortening the length of hospital stay and reducing costs.[58]	Mechanical ventilation systems require a higher level of skills and are associated with higher costs compared to, for example, CPAP. This challenges the feasibility of its implementation in a low-resource setting.[58]

	Pulse oximetry is key to improving oxygen use and relatively affordable.[55]	Excessive oxygen administration can cause harm. This has the greatest implications for preterm neonates, particularly for their developing eyes and lungs. For this reason, neonatal guidelines recommend targeting oxygen saturations in preterm neonates receiving oxygen.[55]	When oxygen supplies are limited, objective evidence of high hypoxaemia through the use of pulse oximetry enables hospitals to mobilise additional oxygen supplies to those who would benefit most.[55]	The challenges to oxygen access include many factors, such as weak equipment maintenance systems, poor power supplies, staff shortages, lack of clinical guidelines, and challenges of interdisciplinary cooperation.[55]
	Lower incidence of nasal trauma, patient and parent friendly nasal prongs, and ease of use are the advantages of HFNC device over nasal CPAP.[61]	HFNC was inferior to nasal CPAP in preventing the failure of the support mode within the first 72 h of birth.[61]	The challenges to oxygen access simultaneously provide opportunities to use oxygen access as a means to reveal systemic weaknesses and incrementally improve the broader hospital system for improved patient outcomes.[55]	
Prophylactic methylxanthines to prevent extubation failure	Methylxanthine therapy is beneficial in increasing the possibility of successful extubation in preterm neonates.[59]	The intervention focuses on intubated preterm infants only. [59]	The intervention is cheap and caffein is widely available. Therefore, scale-up in low-resource settings should be highly feasible.[80]*	A NICU and ventilatory support equipment need to be available which is challenging in resource-poor settings.[59]
	Caffeine is the safest option to prevent extubation failure.[59]			
	STRATEGIES OF NEWBORN CARE			
Kangaroo Mother Care (KMC)	Can be applied in any setting, including rural places with a high number of home deliveries.[40,41,45,47]	According to the conventional method, KMC can only be initiated once complete clinical stabilization is established.[41] However, as most	An adequate way of implementing early KMC for newborns requiring intensive care is needed to benefit these infants,	The newborns suffering from severe conditions who would benefit most from earlier KMC face many obstacles for KMC performance

	KMC prevents hypothermia and severe infections including sepsis and promotes exclusive breastfeeding while it strengthens the mother-infant bond.[38,39,43]	neonatal mortality occurs prior to stabilization, a substantial decline in NMR will only be achieved if unstable LBW neonates are included.[47]	considering that earlier KMC is not a substitute.[41]	including adequate technique, mother-infant separation reliable relationship between family and staff.[41]
	Early KMC appears to reduce weight loss in the early days after birth, thereby improving early survival of fragile LBW infants.[39]		Stabilization for LBW infants was faster and better following early KMC. Therefore it could be an effective and safe intervention in the community setting, especially in countries with a high number of home deliveries.[45,47]	Implementation and effect depend on the quality of CKMC training and the mother's behaviour modification, making it difficult to ensure optimal uptake.[40,45]
	Cost-effective intervention by appropriately using human and material resources.[45]		Integrating KMC into essential newborn baby care programmes that are currently operational in most countries should be a high priority.[40]	Instruction of clinicians and family members on the KMC method is necessary to effectively implement community KMC.[45]
				Providing KMC at home might be challenging in settings where women do household chores or start work outside home soon after delivery.[40]
Home-based newborn care (HBNC)	HBNC is a way to overcome major barriers to receiving adequate care (lack of infrastructure and financial means).[28-30]	A major concern is whether it is ethical to allow a village health worker, rather than a doctor, to diagnose and treat a potentially fatal disease such as neonatal sepsis.[28-30]	The major challenge is to provide HBNC on a larger scale. Methods for scaling need to be developed, and effectiveness of HBNC in the health services setting need to be tested.[28-30]	An established referral system is needed to increase effectiveness of a home based intervention package and to prevent harm. [28-30]
	Cost-effective and less resources required.[28-30]			

	Treating sick preterm neonates at home is very effective in a setting where most births occur at home and health facilities are not accessible.[28-30]			
Training of birth attendants	Birth attendants were trained to report outcomes of all pregnancies, which allowed ascertainment of the contributions of stillbirths and very early neonatal deaths to perinatal mortality rates.[22]	A study showed that neonatal resuscitation competency dropped to an unsatisfactory level three months after training, indicating that training alone is not adequate to retain the knowledge and skills.[81]*	Promising solution to reduce neonatal mortality in the absence of advanced care or infrastructure for referrals to advanced facilities.[22]	The main concern is whether the outcomes of VLBW infants, who are at high risk of death, improve through training of birth attendants when maternal and neonatal referral and advanced care remain unavailable. [22]
	Training improves midwives' skills and knowledge. This is a long-lasting and therefore sustainable way of improvement.[22]		Effectivity of training can be enhanced through implementation of a high frequent, low impact system of refreshment training to prevent loss of health workers' knowledge and skills.[81,82]*	Unless there is a structure of quality improvement cycles integrated in the health system, quality and effectiveness cannot be guaranteed. [81,82]*
Maternal nursing care	There is no disruption of mother–infant bonding and the mother gains confidence in handling her LBW baby after discharge which results in better management at home.[49]	Continuously taking care of a (sick) newborn might be challenging for mothers who have multiple responsibilities. Therefore a supportive family and a safe and hygienic living environment are required after discharge from the hospital.[84]*	The hospital stay, burden on nursing staff, and overcrowding of the special care unit can all be reduced, which is especially beneficial for NICU's in LMICs.[49,53]	Fear of infection and aspiration and a lack of confidence in the mother's ability to tube-feed, clean the LBW baby and handle the incubator prevents her from adequate participation.[51]
	A good alternative to mother–infant separation traditionally practiced in neonatal intensive care which contributes to morbidity in both.[49]	Mothers need adequate training and strict follow-up by nursing professionals. Mothers may not detect changes in their infant's condition that require prompt medical attention.[49,83]	Maternal nursing prevents prolonged hospital stay which potentially reduces the economic burden on families and third parties.[53]	The training of mothers should be thoroughly to ensure safe management of the LBW infant at home. This requires staff to invest their time and, in the worst case,

	Increasing skin to skin contact, providing rooming-in facilities, and involving mothers actively in the care of high-risk newborns improves their survival and weight gain due to breastmilk.[49]		In view of the rising costs of neonatal intensive care, implementation of maternal nursing may also be of relevance to high resource settings.[53]	might not even outweigh the benefit of reduced burden on staff.[49,53]
	OTHERS			
Delayed cord clamping (DCC)	Simple, cost-effective intervention as no additional resources are needed.[33]	DCC theoretically increases the risk of hyperbilirubinemia, polycythaemia and respiratory distress. Scientific support of these concerns is lacking. [33]	DCC improves long-term outcomes, including cognition, and reduces the need for blood transfusion. This lowers the risk of transmission of diseases. Additionally, blood transfusion is not always readily available in low-resource settings.[33]	DCC prevents immediate transfer of the newborn to the neonatologist and therefore potentially delays resuscitation.[33]
	DCC improves iron stores leading to reduction in iron deficiency, which commonly occurs in LBW infants.[33]			
Hypothermia prevention with heated mattress and polythene wrap	A cheap, safe, freely available and effective compromise between a complex heat supply and the more primitive method of using the mother's skin.[44,68]	The air temperature cannot be closely monitored which poses a risk of overheating.[44,68]	Effective alternative in settings with lack of continuous supply of electricity. [44,68]	Resources for accurate measurement of body temperature are needed to prevent hyperthermia. [44,68]
	Physical mother-child contact is still possible as opposed to an incubator. [44,68]		Can be implemented both inside the hospital and at home. [44,68]	
	Polythene wrap is not associated with risk of burns.[68]			
Multi-level quality improvement intervention of NICU and obstetric department	Different aspects of care at the obstetric department and NICU are tackled by a comprehensive multi-level intervention.[32]	Implementing different improvement strategies simultaneously makes it difficult to determine the role of each intervention on the final outcome.[32]	Future quality improvement interventions will focus on implementing the actual program and progressively introducing new strategies.[32]	Aspects including improvement of electricity supply and increasing the healthcare providers' salaries should be taken into account alongside the implementation of a quality improvement intervention.[32]
Oral paracetamol for closure of PDA	Safer option with fewer side effects compared to ibuprofen.[50]	Lack of echocardiogram in LMIC to confirm diagnosis and lack of a follow-	Widely available and therefore relatively easy to implement on a large	Lack of evidence that closure of PDA is superior to not closing it.[85]*

	In neonates with hyperbilirubinemia, paracetamol may be a better option.[50]	up system embedded in the local health system to ensure adequate follow-up.[84]*	scale.[50]	

* Additional consideration based on literature beyond included studies.

SWOT=Strengths, Weaknesses, Opportunities, Threats. ACS=antenatal corticosteroids. LICs=low-income countries. PDHM=pasteurized donor human milk. NEC=necrotizing enterocolitis. DHM=donor human milk. NICU=neonatal intensive care unit. LMICs=low- and middle-income countries. WHO=World Health Organization. SSO=sunflower seed oil. BCG=Bacillus Calmette-Guérin. LBW=low birthweight. VLBW= very low birthweight. rhG-CSF=recombinant human granulocyte-macrophage colony-stimulating factor. IRDS= infant respiratory distress syndrome. BPD=bronchopulmonary dysplasia.
CPAP=continuous positive airway pressure. LISA=less invasive surfactant administration. VAS=vitamin A supplementation. VGV=volume guaranteed ventilation. HFNC=high flow nasal cannula. KMC=kangaroo mother care. NMR=neonatal mortality rate. CKMC=community kangaroo mother care. HBNC=home based newborn care. DCC=delayed cord clamping. PDA=patent ductus arteriosus.