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

FULL SEARCH STRING

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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

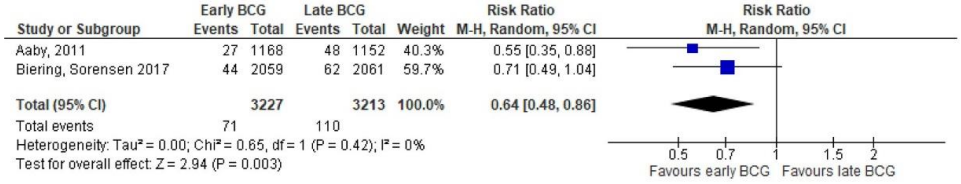
Guinea-Bissau	Aaby *et al* [24] (2011)	Early BCG
	Biering-Sorensen [31] (2017)	
Madagascar	Nagai *et al* [41] (2010)	Earlier KMC
Malawi	Van den Bosch *et al* [68] (1996)	Polythene tobacco wrap
Mozambique	Cavicchiolo *et al* [32] (2016)	Quality improvement intervention of NICU and obstetric department
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

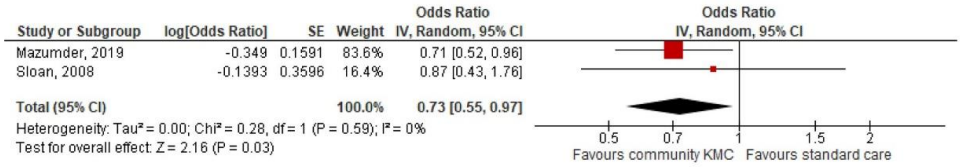
*According to the World Bank Classification [11]

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

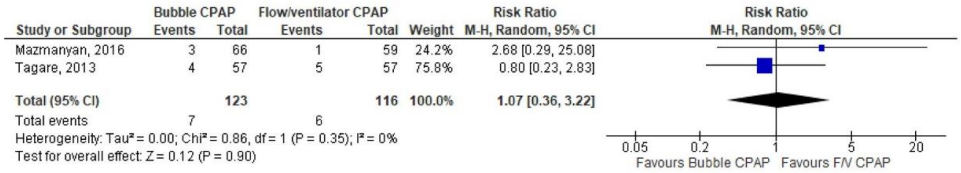
FIGURE 2: META-ANALYSES



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

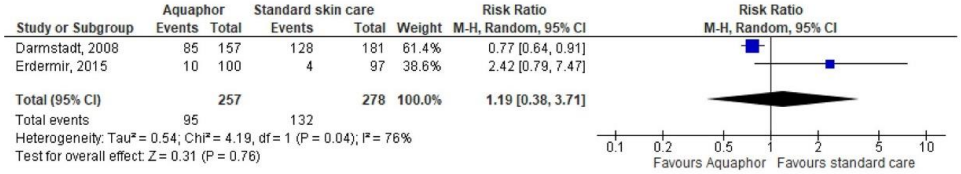


Meta-analysis addressing the effect of community KMC versus standard home-based care on 28-day neonatal mortality among LBW neonates.



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.