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Review

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Immediate Care for Common Conditions in Term and Preterm Neonates: The Evidence

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Immediate care · Newborn · Low- and middle-income countries

Abstract
Background: Several interventions provided to newborns at birth or within 24 h after birth have been proven critical in improving neonatal survival and other birth outcomes. We aimed to provide an update on the effectiveness and safety of these interventions in low- and middle-income countries (LMICs). ***Summary:*** Following a comprehensive scoping of the literature, we updated or re-analyzed the LMIC-specific evidence for included topics. Ninety-four LMIC studies were identified. Delayed cord clamping with immediate neonatal care after cord clamping resulted in a lower risk of blood transfusion in newborns <32–34 gestational weeks and a lower occurrence of anemia in term newborns but did not have significant effect on neonatal mortality or other common morbidities both in preterm and term newborns. Immediate thermal care using plastic wrap/bag led to a 38% lower risk of hypothermia and a higher axillary temperature in preterm newborns without increasing the risk of hyperthermia. Kangaroo mother care initiated immediately (iKMC) or early after birth (eKMC, within 24 h) significantly reduced neonatal mortality and the occurrence of hypothermia in preterm or low-birth-weight neonates. For delayed first bath in newborns, no pooled estimate was generated due to high heterogeneity of included studies. Trials from high-income countries demonstrated anti-D's effectiveness in lowering the incidence of Rhesus D alloimmunization in subsequent pregnancy if given within 72 h postpartum. ***Key Messages:*** We generated the most updated LMIC evidence for several immediate newborn care interventions. Despite their effectiveness and safety in improving some of the neonatal outcomes, further high-quality trials are necessary.

Introduction

In 2020, more than two million newborns died within the first month of life globally [1]. Despite the substantial decline in the number of neonatal deaths since 1990, its rate of decline has been much slower than that of postneonatal under-five mortality [1, 2]. Three quarters of neonatal deaths occur during the first week of life,

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while about one million newborns died within the first 24 h of life in 2019 [1]. Furthermore, there are still significant disparities in neonatal mortality across regions and countries. Country-level neonatal mortality rates in 2020 ranged from 1 to 44 deaths per 1,000 live births, with the risk of dying before the 28th day of life for a child born in the highest-mortality country approximately 56 times higher than the lowest-mortality country [1].

To improve neonatal survival and short- and long-term birth outcomes, the World Health Organization (WHO) recommended providing essential newborn care to all babies in the first few days of life [3], with immediate care at the time of birth and initiated within the first 24 h of the life being a critical component of the package. Immediate newborn care is the initial and key step of newborns stepping into their independent life. In the past decade, the concept of the "Golden Hour"in newborn care [4] has received increasing attention because the first 60 min of life plays an important role in both short- and long-term outcomes [5]. Based on a growing body of evidence of their beneficial effects, a number of professional organizations such as the WHO, the American College of Obstetricians and Gynecologists, recommend delayed cord clamping (DCC), kangaroo mother care (KMC) and thermal protection/care to be provided to newborns immediately at birth or shortly after birth [6–8]. Moreover, these three key interventions of immediate newborn care are simple and of low-cost, making them applicable to resource-limited areas. There are several interventions that are recommended to be provided early after delivery: providing newborns with vitamin K within 8 h after birth to prevent vitamin K deficiency bleeding [9]; hepatitis B vaccination birth dose (ideally within 24 h of birth) to prevent perinatal transmission of hepatitis B [10]; and administrating anti-D immunoglobulin to Rhesus (Rh) negative women after delivering Rh positive newborns (within 72 h of delivery) to reduce the risk of RhD alloimmunization [11]. Despite long-proven effectiveness and safety, these interventions still face various barriers in their implementation or scale-up nowadays.

Currently, with the majority of immediate newborn care studies being conducted in developed countries, evidence specifically targeting low- and middle-income countries (LMICs), conflict-affected, and/or resource-restricted countries and areas is still scarce. There is great inequity between the adaptation and coverage of evidence-based newborn care interventions and the great disease burden in LMICs. DCC, thermal protection/care and immediate KMC are of no exception. Anemia, which could lead to increased morbidity and mortality, affects about 293 million preschool age children globally, with two-thirds of these cases in LMICs [12]. Despite the mounting evidence of the benefit of DCC on reducing anemia in infants as a result of increased placental transfusion, the uptake of the practice has been slow in many LMICs [13, 14]. Concerns regarding DCC effectiveness and safety among health practitioners serve as a major obstacle due to the lack of LMIC-specific evidence regarding the relationship between DCC and improved hematological outcomes, such as a reduction in infant anemia, polycythemia, and jaundice [12].

Closing the great gaps in evidence-based immediate newborn care strategies in LMICs is necessary to help achieve the global Sustainable Development Goal (SDG) for reducing newborn mortality (Goal 3.2) and to improve their function and quality of life in the long run. Therefore, we conducted this review to provide a comprehensive and robust update describing the highest quality and most recently available evidence from LMIC settings for the effectiveness and safety of DCC, immediate KMC and thermal protection/care to improve immediate care for newborns.

Methods

This paper forms part of a supplement describing an extensive synthesis on effective newborn interventions in LMICs. The objective of this paper was to describe the evidence on three effective and safe strategies/interventions for immediate newborn care (DCC, KMC, thermal care/protection), delayed first bath and anti-D immunoglobulin to Rh-negative mothers. Other important immediate/early neonatal interventions (neonatal resuscitation, therapeutic hypothermia for perinatal asphyxia, care for newborns with respiratory conditions, Vit K injection in preterm newborns, breastfeeding teaching/training and any supplementation, and prevention of infection) have been covered in six other manuscripts of this supplement. Different methodological approaches were taken to synthesize the evidence in its totality. In this section, we provide a high-level overview of the evidence synthesis methodology for each topic included in this manuscript. The rationale and the general methodology applied to this review and other reviews of the upcoming 2024 *Lancet Global Newborn Care Series* related to newborn interventions have been described in the methods paper for this series [15].

Update of Systematic Reviews

Search and Selection of Studies

We updated existing systematic reviews for interventions in immediate newborn care if the last search date of the review of a specific intervention was before 2020. Based on this rationale, the following topics were updated based on existing but outdated reviews [16–18]: (1) thermal protection/care in preterm and/or low birth weight (LBW) newborns; (2) DCC in preterm newborns; and (3) DCC in term newborns. We used the original search syntax and list of databases where possible described in the existing systematic review to identify new trials. The detailed search strategies for each topic can be found in the online supplementary appendix (for all online suppl. material, see https://doi.org/10.1159/000541037). For all three topics, searches were executed in Medline, Embase, and Cochrane CENTRAL. Additional databases searched were review specific and can be found in the online supplementary appendix as well. The date of last search ranged from July 2022 to March 2023. The search results are screened for relevance against the existing reviews' inclusion criteria shown in Table 1.

Data Synthesis

Data were collected and synthesized as described [15]. Revman 5.0 was used to general the pooled estimates and corresponding forest plots. The updated effect measures for outcomes of interest were calculated by pooling the effect estimates from new LMIC studies with the existing estimates from the LMIC studies already included in the source reviews. Models and methods used for each topic are listed in Table 2.

Reanalysis of Existing Reviews

Selection of Studies

For the topic of immediate/early initiated KMC and delayed first bath, we identified an existing systematic review with the most up-to-date, synthesized evidence for KMC's effectiveness and safety [19, 20]. The inclusion criteria reported by the original review's authors can be found in Table 1, while the search strategies and databases searched can be found in the online supplementary appendix. For the KMC topic, we further narrowed the inclusion criteria to studies investigating the effect of KMC initiated immediately (generally within the first 3 h) or early (within 24 h) after birth versus late-initiated KMC (initiated after stabilization of the neonates, generally after 24 h). The administration of anti-D immunoglobulin to RhD negative women after delivering a RhD positive baby has been the standard of care for decades, with one Cochrane review serving as the backbone of the evidence [21]. We, therefore, used this Cochrane review as our source for potential LMIC-specific evidence for the anti-D immunoglobulin topic.

Data Collection and Synthesis

Data were extracted from studies conducted in LMICs only, as defined by the current World Bank classification. Data were extracted from the forest plots of the source systematic review and re-analyzed for each outcome of interest by one author (L.J.). They were then verified against the original review by another author (L.H.). We adopted the same statistical method described in the existing review to generate the pooled effect estimate, as listed in Table 2.

Results

Immediate newborn care interventions play an important role in helping babies' safe transition between intrauterine and neonatal life, especially for the preterm and LBW neonates (Fig. 1). Some of the salient findings are summarized in the following paragraphs and are further detailed in online supplementary Tables 2–6 (appendix p. 80–113).

Selection of Studies

Across the intervention topics reviewed, a total of 25,566 records were identified. After removing duplicates, the titles and abstracts of 17,506 records were screened, and 580 were included for full-text screening. Ninety-seven studies with LMIC-specific data or with disaggregated data for LMICs were eligible for inclusion for these four topics. One study from DCC in preterm newborns was a multicenter study conducted both in high-income countries (HICs) and in Pakistan. We had the access to Pakistan data and included this LMIC data into our analysis. Among 97 included studies, three studies fit in the inclusion criteria for both the immediate thermal care and the KMC topic. Therefore, 94 individual studies were included in our final analysis. For the topic of anti-D administration, no eligible LMIC study was identified; thus, we leveraged HICs evidence for this topic from six studies (PRISMA diagrams per topic are listed in Fig. 2).

Study Characteristics

Table 3 provides a high-level summary of included study characteristics for each topic. The majority of topics only included randomized controlled trials (RCTs). Three

Table 1. Eligibility criteria per included review

Topic	Participant	Intervention	Comparator	Primary outcomes	Study design	Setting
DCC in preterm infants	Preterm infants born before 37 completed weeks' gestation and their mothers	Cord clamped after 30 s or more after birth	Cord clamped less than 30 s after birth	• Neonatal mortality • Neonatal morbidities • Manual removal of the placenta • PPH (blood loss 500 mL or more)	RCT and cluster RCT Quasi-randomized studies were excluded	LMICs
DCC in term infants	Term infants (equal to or greater than 37 completed weeks' gestation, single pregnancy, and cephalic presentation) and their mothers; Cephalic presentation; Singleton	Umbilical cord clamped greater than 1 min after birth or when cord pulsation has ceased	Umbilical cord clamped within 60 s of the birth of the infant	• Neonatal mortality before discharge • Growth and nutrition parameters • Neonatal morbidities • Severe PPH (blood loss 1,000 mL or more) • PPH (blood loss 500 mL or more) • Mean blood loss (mL) • Maternal postpartum Hb	Randomized comparisons were included Quasi-randomized studies were excluded	LMICs
Thermal care	Preterm infants <37 weeks' gestation or LBW infants weighing ≤2,500 g	Any intervention applied at and/or immediately after birth to prevent hypothermia, and interventions to promote hypothermia risk awareness	Routine thermal care as defined based on WHO recommendations (single or any combination)	• Hypothermia • Mortality • Neonatal morbidities • Length of stay • Any adverse outcome due to the intervention (i.e., hyperthermia, burns) • Developmental outcomes (i.e., cerebral palsy)	RCT and quasi-RCT	LMICs
KMC	Mothers and their preterm (<37 gestational weeks) or LBW (birth weight ≤2,500 g, regardless of gestational age) newborn infants	KMC initiated immediately or early after birth (with 24 h)	Late-initiated KMC or conventional care	• Neonatal mortality • Infant mortality by 6 months of follow-up • Nosocomial sepsis • Hypothermia • Exclusive breastfeeding • Growth parameters	RCT and cluster RCT Quasi-RCT and cross-,over trials were excluded	LMICs

Table 1 (continued)

Topic	Participant	Intervention	Comparator	Primary outcomes	Study design	Setting
Anti-D immunoglobulin administration after child birth	Rhesus negative women without anti-D antibodies who gave birth to a Rhesus positive baby	Anti-D immunoglobulin given after birth irrespective of parity, ABO compatibility, size of feta-maternal hemorrhage, dose or timing	No treatment or placebo	• Subsequent development of Rhesus D alloimmunization • Neonatal morbidity in a subsequent pregnancy • Adverse effects of treatment • Maternal concerns	RCT and quasi-RCT	HICs
Timing of first bath	Term neonates up to 28 completed days of life	Delayed first bath (after 24 h of life)	Early first bath (different timing within 24 h)	• Neonatal mortality • Hypothermia	RCTs and observational studies (if RCT inadequate or the optimal information size not met)	LMICs

KMC, kangaroo mother care; LBW, low birth weight; LMICs, low- and middle-income countries; PPH, postpartum hemorrhage; RCT, randomized controlled trials; WHO, World Health Organization.

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Table 2. High-level summary of analysis methods per topic

Topic	Source SR	Data synthesis	Comparisons	Subgroup analysis	Sensitivity analysis
Update to systematic reviews					
Immediate thermal care	McCall E.M., Alderdice F., Halliday H.L., Vohra S., Johnston L. Interventions to prevent hypothermia at birth in preterm and/or low birth weight infants *Cochrane Database of Systematic Reviews*. 2018, Issue 2. Art. No.: CD004210. DOI: 10.1002/14651858.CD004210.pub5	All meta-analyses were performed using the fixed-effect model. If substantial heterogeneity was detected from I^2 statistic, we performed sensitivity and subgroup analyses. Mantel-Haenszel method was used for estimates of RR and risk difference. For measured quantities (ex: body temperature, heart rate etc.), inverse variance method was used. Risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes. When both study arms had 0 events, additionally calculated risk difference (RD). Calculated mean differences (MDs), standardized mean difference (SMD) and 95% confidence limits for continuous outcomes. SMD was calculated when outcome was reported using different scales. When analyzing continuous data, the possibility of skewed data was considered. If standard deviation was missing, it was imputed from standard error of MD extracted from study	1. Plastic wrap/bag versus routine care 2. Plastic wrap versus routine care during interhospital neonatal transport 3. Plastic bag with previous drying versus routine care 4. Plastic bag with previous drying versus plastic bag without previous drying 5. Polyvinyl bag versus polythene wrap 6. Plastic wrap versus cloth wrap 7. Cap versus no cap/routine care 8. Woolen cap versus no cap 9. Plastic cap versus routine care 10. Plastic wrap + plastic cap versus plastic wrap + cotton cap 11. Plastic wrap + plastic cap versus routine care 12. Plastic wrap + cotton cap versus routine care 13 Novel heating device versu routine thermal care (radiant warmer)	1. By study design: RCT, quasi-RCT; 2. By country's income: middle-income country, low-income country; 3. By facility level: secondary, tertiary; 4. By geographic region	N/A

Table 2 (continued)

Topic	Source SR	Data synthesis	Comparisons	Subgroup analysis	Sensitivity analysis
Preterm cord clamping	Rabe H., Gyte G.M.L., Díaz-Rossello J.L., Duley L. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. *Cochrane Database of Systematic Reviews*. 2019, Issue 9. Art. No.: CD003248. DOI: 10.1002/14651858.CD003248.pub4	We carried out statistical analysis using the Review Manager software (RevMan 2014). M-H random-effect model was used for combining data as it was considered to be reasonable to assume that there was clinical heterogeneity due to the large variation in the timing of DCC between the included studies and where the baby was placed during this time. There was also variation in how umbilical cord milking was undertaken, either before or after cutting the cord	1. Delayed cord clamping (DCC) with immediate neonatal care after cord clamping versus early cord clamping (ECC) 2. DCC with immediate neonatal care with cord intact versus ECC 3. DCC with immediate neonatal care after cord clamping versus UCM 4. UCM versus ECC; 5. DCC with immediate neonatal care after cord clamping OR UCM versus ECC.	1. By gestational age (GA): <32–34 GA, ≥32–34 GA, and mixed gestation; 2. By intervention: DCC <1 min with baby level with uterus, or with baby held low; DCC 1–2 min with baby level with uterus, or with baby held low; DCC >2 min with baby level with uterus or baby held low; mixed interventions or unclear	Done for comparison 1–4
Term cord clamping	McDonald SJ., Middleton P., Dowswell T., Morris P.S. Effect of timing of umbilical cord clamping of term infants on maternal and neonatal outcomes. *Cochrane Database of Systematic Reviews*. 2013, Issue 7. Art. No.: CD004074. DOI: 10.1002/14651858.CD004074.pub3	We carried out statistical analysis using the Review Manager software (RevMan 2011). M-H fixed-effect model for combining data in the absence of significant heterogeneity and when trials were sufficiently similar. If heterogeneity was found, this was explored by sensitivity analysis followed by random-effects analysis if required	DCC versus ECC	1. By the timing of uterotonic used: uterotonic at or after clamping, uterotonic not specified; 2. By facility level	N/A
Reanalysis of existing systematic reviews					
Immediate and early initiated Kangaroo mother care (KMC)	Sivanandan S, Sankar MJ. Kangaroo mother care for preterm or low birth weight infants: a systematic review and meta-analysis. *BMJ Global Health*. 2023; 8:e010728	The effect estimates – RR or MD were synthesized using RevMan version 5.4. Results were pooled using fixed-effect meta-analyses using the Mantel-Haenszel method. The heterogeneity of the pooled studies was assessed using the test of homogeneity of study-specific effect sizes and the I^2 statistic, in addition to visual confirmation from forest plots. If substantial heterogeneity was detected, the reasons for heterogeneity were explored. If there was no critical clinical or methodological heterogeneity among the studies, we pooled their results using the random-effects model. We evaluated the likelihood of potential publication bias using funnel plots	Immediate KMC versus late-initiated KMC	N/A	N/A

Table 2 (continued)

Topic	Source SR	Data synthesis	Comparisons	Subgroup analysis	Sensitivity analysis
Anti-D immunoglobulin after child birth	Anti-D administration after childbirth for preventing Rhesus alloimmunization *Cochrane Database of Systematic Reviews*. 1997, Issue 2. Art. No.: CD000021. DOI: 10.1002/14651858.CD000021	Categorical data were compared using RRs and 95% CIs. Statistical heterogeneity between trials was tested for using the χ^2 test with *n* (the number of trials contributing data) minus one degrees of freedom. With no significant heterogeneity ($p > 0.10$), data were pooled using a fixed-effects model. If significant heterogeneity was found, the random-effects model was used	Anti-D immunoglobulin versus no treatment or placebo	N/A	N/A
Timing of first bath	Priyadarshi M., Balachander B., Gupta S., Sankar MJ. Timing of first bath in term healthy newborns: A systematic review. *J Glob Health*. 2022;12:12004	No quantitative analysis was performed due to great difference in study design, intervention definition and outcome reporting	Delayed first bath versus early first bath	N/A	N/A

quasi-RCTs were also included in thermal care. One pilot RCT was included for delayed first bath, while the remaining three studies for this topic were observational studies (case-control or cross-sectional studies). The topics of DCC in preterm newborns, immediate, or early initiated KMC and thermal protection/care restricted the analysis to studies in preterm/LBW newborns only, while DCC in term newborns and delayed first bath focused on term-only neonatal population. A detailed study characteristics table of all included LMIC studies can be found in online supplementary appendix p. 13–79; online supplementary Table 1.

Quality Assessments

Of the 87 RCTs total included in this review, 47 (54.0%) were rated as having a high risk of bias (ROB), 31 (35.6%) as having moderate ROB, and only nine (10.4%) were rated as having a low ROB. Of the three quasi-RCTs included in thermal care, two were of critical ROB and one of moderate ROB. For the three observational studies included in delayed first bath, one was of critical ROB, and two were at serious ROB. The pilot RCT on delayed first bath was of high ROB. Please see online supplementary Figures 1–3 for detailed quality assessment tools used and the ratings for each included study.

DCC for Term and Preterm Newborns

In the WHO's 2014 guideline for cord clamping in neonates [22] and 2022 guideline for preterm infants' care [23], DCC was recommended for improved maternal and infant health and nutrition outcomes based previous evidence. In this review, we updated the evidence related to DCC in LMIC settings for preterm and term newborns, respectively.

In the population of preterm neonates with a gestational age of <32–34 weeks, compared to early cord clamping (ECC), DCC with immediate neonatal care after cord clamping led to a significantly lower risk of receiving blood transfusion (risk ratio [RR] 0.31, 95% confidence interval [CI] 0.15–0.67), using inotropes for low blood pressure (RR 0.32, 95% CI 0.13–0.82). For preterm neonates, the risk of developing late sepsis (after 3 days or as defined by trialists) was lower for those received DCC (RR 0.65, 95% CI 0.45–0.95) (Table 4), but no significant difference was seen for neonatal mortality (RR 0.99, 95% CI 0.47–2.06) or neonatal hemoglobin (Hb) within 24 h after birth. There was also no difference in neonatal morbidities (hypothermia, intraventricular hemorrhage [IVH], respiratory distress syndrome, necrotizing enterocolitis

[NEC], retinopathy of prematurity, patent ductus arteriosus), and the risk of developing hyperbilirubinemia requiring phototherapy between the DCC and the ECC group. Subgroup analysis by facility levels revealed similar findings in preterm newborns whether DCC was performed in secondary-level or in tertiary-level facilities. However, when we restricted analysis to studies with low ROB, there was no significant difference between DCC and ECC for all the outcomes of interest in preterm newborns (online suppl. Table 2, appendix p. 80–98). In terms of maternal outcomes, mothers of preterm newborns who received DCC were not at a higher risk of developing postpartum hemorrhage (RR 1.72, 95% CI 0.22–13.71).

Compared to ECC, umbilical cord milking (UCM) led to a higher level of Hb (g/dL) within the first 24 h of birth (mean difference [MD] 1.51, 95% CI 0.76–2.26) in preterm newborns, particularly for those with a GA of less than 32–34 weeks (MD 1.18, 95% CI 0.07–2.29) (Table 4). The comparison between DCC with immediate neonatal care after cord clamping and UCM did not show any significant difference across all outcomes of interest. No LMIC study has been identified investigating the long-term neurodevelopmental outcomes in newborns who received UCM (online suppl. Table 2, appendix p. 80–98).

In term newborns and infants, compared to ECC, DCC (cord clamped at least 1 min after birth) led to: a significantly higher level of cord and newborn Hb (g/dL) (MD 0.36, 95% CI 0.28–0.45; MD 1.09, 95% CI 0.11–2.07, respectively); a significantly lower risk of low infant hematocrit (<45%) at 24–48 h (RR 0.39, 95% CI 0.24–0.66) and infant iron deficiency at three to 6 months (RR 0.71, 95% CI 0.53–0.96); but a significantly higher risk of developing clinical jaundice (RR 1.58, 95% CI 1.36–1.84) or polycythemia (RR 2.68, 95% CI 1.58–4.55) (Table 4). For infants' neurodevelopment at 4 months, participants who received DCC had a significantly higher Age and Stage Questionnaires (ASQ) communication score (MD 2.20, 95% CI 0.41–3.99) and ASQ problem-solving score (MD 12.43, 95% CI 11.28–13.58). No difference was shown between ECC and DCC in ASQ gross motor, fine motor and personal-social score (online suppl. Table 3, appendix p. 99–101). Similarly, no difference was found between ECC and DCC in term babies and their mothers regarding the occurrence of postpartum hemorrhage, maternal Hb 24–72 h postpartum, breastfeeding, neonatal mortality, severe infant jaundice, or infant Hb at 3 to 6 months of age (online suppl. Table 3, appendix p. 99–101).

Immediate Thermal Care

Studies investigating the effectiveness and safety of measures to reduce heat loss and maintain newborns' temperature mainly fall into two groups [18]: (1) barriers to heat loss, including wraps and/or head coverings of different materials to reduce evaporative heat losses; and (2) external heat sources, mainly including heated mattress and novel heating technologies. We only included studies investigating the effect of thermal protection/care measures provided immediately or early after birth (within the first hour or the first 24 h) in this manuscript. If thermal care interventions were not provided within the first 24 h after birth, we presented these results and relevant discussion in another manuscript focusing on interventions for small and vulnerable newborns [24].

Barriers to Heat Loss

Our results showed that, compared to routine care (i.e., drying, placed under a radiant warmer, covered with sterile cloth only), thermal care using plastic wrap/bag led to a 38% lower risk of developing hypothermia (RR 0.62, 95% CI 0.55–0.70). Among them, eight studies were conducted in middle-income countries, demonstrating a significant effect on preventing hypothermia by using plastic wrap/bags (RR 0.63, 95% CI 0.55–0.71). Only one study with 104 participants was conducted in a low-income country without estimable findings. Furthermore, two studies with 158 participants reported mild hypothermia and moderate hypothermia, respectively. The pooled estimates suggested plastic wrap/bag had a significant effect in preventing moderate hypothermia (RR 0.58, 95% CI 0.44–0.77, I^2 = 4%) but not in preventing mild hypothermia (RR 1.15, 95% CI 0.56–2.35, I^2 = 79%) upon admission to neonatal intensive care unit (NICU) (Table 4). The body temperature (axillary) of newborns receiving plastic wrap/bag was taken at various time points in different studies. Eight studies measured the participants' axillary temperature at admission to NICU/nursery and found a significantly higher body temperature of the plastic bag/wrap group (MD 0.43, 95% CI 0.35–0.51). The plastic bag/wrap group also demonstrated a higher axillary temperature when the temperature was measured post-admission to NICU/nursery (MD 0.29, 95% CI 0.20–0.38), post-stabilization (MD 0.50, 95% CI 0.13–0.87), and at 1 h of life (MD 0.16, 95% CI 0.09–0.23). However, the difference in neonates' axillary temperate at 2 h of life was not significant between the plastic wrap/bag group and the control group (p = 0.25), unless restricting the

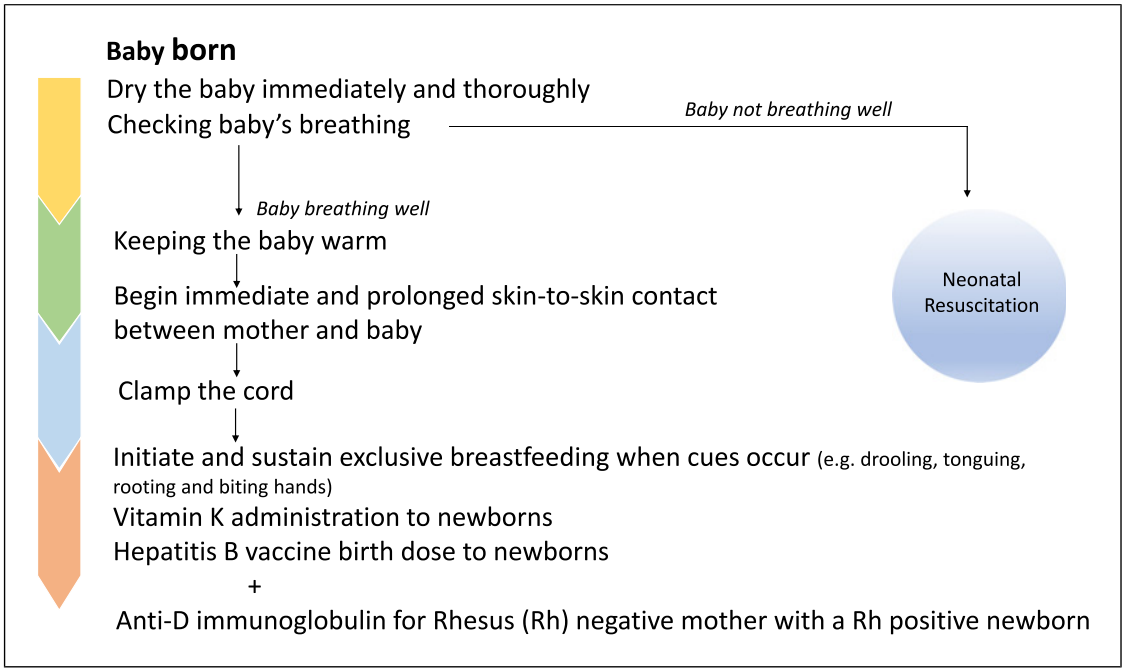

Fig. 1. Timeline of the interventions given immediately or early after child birth.

analysis to RCTs only (MD 0.23, 95% CI 0.13–0.33). Regarding its safety, plastic wrap/bag did not show a significant effect in reducing neonatal/infant mortality (death before discharge or at 6 months' corrected age if the infant remains in hospital) (RR 0.84, 95% CI 0.49–1.44) or common neonatal morbidities (including hypoglycemia, respiratory distress syndrome, NEC, patent ductus arteriosus, and culture-proven sepsis). It did not increase the risk of hyperthermia (RR 0.63, 95% CI 0.22–1.81) either (online suppl. Table 4, appendix p. 102–110).

The pooled estimate from two studies showed that plastic wrap during interhospital transport resulted in a lower risk of developing hypothermia (RR 0.75, 95% CI 0.58–0.96) and a higher axillary temperature (MD 0.56, 95% CI 0.35–0.78) for the preterm newborns, while not increasing hyperthermia risk (RR 2.94, 95% CI 0.31–27.79). Plastic wrap had a better effect in preventing hypothermia versus cotton/cloth wrap (RR 0.22, 95% CI 0.10–0.48) but with great heterogeneity (I^2 = 74%) (Table 4). No difference between plastic wrap+ plastic cap versus plastic wrap+ cloth/cotton cap in axillary temperature upon admission to NICU and post-stabilization in NICU (online suppl. Table 4, appendix p. 101–109). For other twelve comparisons, the results were all based on single estimates and can be found in online supplementary Table 4 (appendix p. 102–110).

External Heat Sources

Eight studies compared the effect of novel heating technology (cocoon warmer, heated water-filled mattress, thermal blanket, and intelligent heating box) with traditional thermal care methods (incubator or radiant warmer). Only four of them provided interventions to participating newborns immediately after birth. Due to the limited number of studies and participants, no significant difference was found between novel heating device and the conventional thermal care devices in the incidence of hypothermia (regardless of the severity of hypothermia), newborns' body temperature or the occurrence of neonatal morbidities (Table 4).

Two studies [25, 26] compared the effect of skin-to-skin contact (SSC) initiated immediately after birth with conventional thermal care (i.e., warm delivery room, newborns dried with cloth, dressed properly and transferred to prewarmed incubator) in keeping neonates warm and physiologically stable. Bergman et al. [25] compared the effect of SSC immediately after birth with conventional incubator care in 31 LBW infants (birth weight between 1,200 and 2,199 g). They found SSC significantly reduced the risk of hypothermia within 6 h of birth (RR 0.09, 95% CI 0.01–0.64; RD −0.56, 95% CI −0.84 to −0.27) without any adverse effect. Luong et al. [26] also found neonates received SSC immediately after birth showed a better transition to extrauterine life,

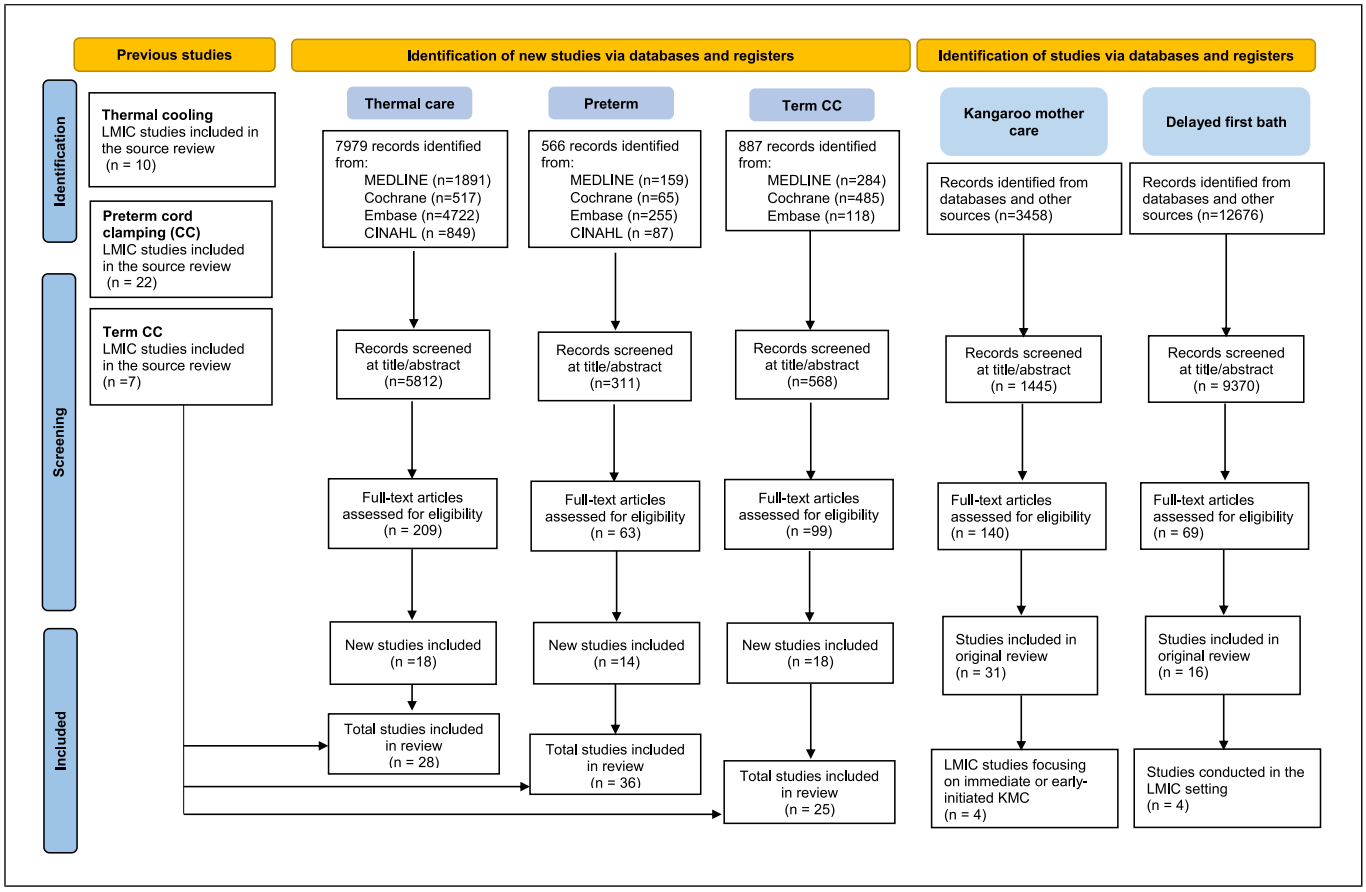

Fig. 2. PRISMA flowchart for included immediate newborn care interventions.

demonstrated by lower risk of developing hypothermia (1/50 vs. 35/50, $p < 0.001$) and hypoglycemia (2/50 vs. 12/50, $p < 0.001$) at 3 h after birth, higher score related to the stability of the cardiorespiratory system, less intravenous fluid requirement, and less antibiotic use during the subsequent hospital stay.

Immediate and Early Initiated KMC

In addition to SSC, KMC had several other components. It has been recommended as a simple and cost-effective intervention in keeping the babies warm and for reducing mortality and morbidity of preterm and LBW newborns. However, there is still lack of evidence in the LMIC setting and on the effectiveness of KMC when initiated immediately after birth.

According to our reanalysis of the LMIC-specific data from the most updated review on KMC [19], we only identified a single study [27] investigating the effect of KMC provided immediately to newborns after birth. Two studies compared the effect of early initiated KMC versus late-initiated KMC [28, 29]. The pooled estimates from these three studies showed early initiated KMC significantly improved mortality by discharge or 28 days of life (RR 0.78, 95% CI 0.66–0.92), exclusive breastfeeding at discharge (RR 1.05, 95% CI 1.02–1.07), hypothermia at discharge or 28 days of life (RR 0.74, 95% CI 0.61–0.90) when comparing to late-initiated KMC. There was no difference in their effect on mortality by 6 months of age, and exclusive breastfeeding at 4 weeks and 6 months of age. Although early initiated KMC showed a significant improvement in nosocomial sepsis till 28 days of life (RR 0.85, 95% CI 0.76–0.96) compared to late-initiated KMC, the effect was restricted to clinical sepsis (RR 0.85, 95% CI 0.75–0.95) (Table 4; online suppl. Table 5, appendix p. 111). Subgroup analysis could not be assessed as there were insufficient studies.

Delayed First Bath after Birth

Among the four LMIC studies identified, their study design, definition of delayed and early bath, and reported outcomes varied greatly. Therefore, their

Table 3. Study characteristics summary table

Topic	Methodology	# of LMIC studies	Study setting details	Study design details	Participants	Intervention	Literature search date
Cord clamping in preterm newborns	Updated	36	India (11) China (6) Thailand (4) Turkey (4) Iran (3) South Africa (3) Pakistan (3) Egypt (1) Kenya (1)	All included studies are RCTs; 27 studies of high ROB; 9 of unclear ROB	Preterm infants born before 37 completed weeks' gestation	Umbilical cord clamped after 30 s or more after birth	Last search conducted in Feb 2023
Cord clamping in term newborns	Updated	25	India (6) Turkey (6) Iran (3) China (2) Pakistan (2) Argentina (1) Egypt (1) Libya (1) Mexico (1) Nigeria (1) Zambia (1)	All studies are RCTs; 6 studies of high ROB; 12 of unclear ROB; 7 of low ROB	Term, singleton infant with cephalic presentation	Umbilical cord clamped greater than 1 min after birth or when cord pulsation has ceased	Last search conducted in Mar 2023
Immediate thermal care	Updated	28 (with 3 studies overlapping with studies included in immediate or early initiated KMC)	India (6) Turkey (3) Iran (3) China (3) Malaysia (2) Thailand (2) Ethiopia (1) Madagascar (1) Mexico (1) Pakistan (1) South Africa (1) Vietnam (1) Zambia (1) Multi-center studies: Gana, India, Malawi, Nigeria and Tanzania (1)	24 were RCTs; 3 were quasi-RCTs; Of the 24 RCTs, 15 were of high ROB, 7 of some concerns, and 2 of low ROB; For the 3 non-RCTs, 2 were of critical ROB and 1 of moderate ROB	Preterm and/or LBW infants	Any intervention applied at and/or immediately after birth to prevent hypothermia, and interventions to promote hypothermia risk awareness	Last search conducted in Jul 2022
Immediate or early initiated KMC	As-is	4	Gambia (1) Madagascar (1) A multicenter study conducted in Ghana, India, Malawi, Nigeria, and Tanzania (1)	All of high ROB	Mothers and their preterm or LBW newborns	Immediate or early KMC (initiated within the first 24 h), including skin-to-skin care and/or exclusive breastfeeding and/or follow-up of the mothers and newborns after discharge	Literature search conducted in Mar 2022
Timing of first bath	As-is	4	Ethiopia (1) Lebanon (1) Nepal (1) Nepal and Bangladesh (1)	2 of critical ROB; 2 of serious ROB	Term neonates (up to 28 completed days of life)	Delayed first bath (after 24 h of life)	Last literature search conducted on 30th Nov 2021

KMC, kangaroo mother care; LBW, low birth weight; RCT, randomized controlled trial; ROB, risk of bias.

data could not be pooled together. Three studies focused on the outcomes of our interests. A cross-sectional study from Nepal and Bangladesh [30] found no significant difference in neonatal mortality between early (at 2 or 6 h of age) and delayed (at 24 h of age) bath groups. Another case-control study from Nepal [31] compared early bath (different timing within 24 h of birth) and delayed bath (first bath after 24 h of birth) and found no effect of bath timing on hypothermia. A matched case-control study (matched for date of birth and lived in the same kebele) from Ethiopia recruited 789 neonates and found that delaying the first bath for at least for 24 h was significantly associated with a lower infant mortality (adjusted odds ratio 0.46, 95% CI 0.28–0.77) compared to early bath (within 24 h after birth) [32].

Anti-D Immunoglobulin Prophylaxis

No LMIC study was identified for anti-D immunoglobulin prophylaxis. Six HIC trials with over 10,000 women demonstrated that anti-D lowered the incidence of RhD alloimmunization 6 months after birth (RR 0.04, 95% CI 0.02–0.06, random-effect model; Peto OR 0.08, 95% CI 0.06–0.11) and in a subsequent pregnancy (RR 0.14, 95% CI 0.06–0.35, random-effect model; Peto OR 0.12, 95% CI 0.07–0.19) regardless of the ABO status of the mother and baby, if anti-D was given within 72 h of birth (online suppl. Table 6, appendix p. 112).

Discussion

Despite the global decline in neonatal mortality across all regions, its reduction rate was still slower than that among children aged 1–59 months [33]. To help further improve neonatal survival, adopted from the adult trauma term [34], the "Golden Hour" concept was first implemented in neonatal care in 2009 [4] focusing on providing essential care to newborns immediately after their birth [35, 36]. In 2023, WHO published the second edition of its Essential Newborn Care (ENC) course. Its first part, ENC 1 (Immediate Care and Helping Babies Breathe at Birth) focused on essential newborn care provided from birth to 60 min after birth. After drying the babies thoroughly, interventions provided to newborns who are breathing well include [37]: keeping warm by positioning the baby skin-to-skin with mother, covering with a dry cloth and a head covering), waiting 1–3 min before clamping and cutting cord, continue skin-to-skin care and monitor, and helping initiate breastfeeding. For newborns not breathing well, they will receive stimulation, resuscitation and further respiratory support within 60 s after birth ("The Golden Minute"). Despite that prevention of infection is not listed as an action step within the "Golden Hour/Minute," it is an essential activity that healthcare providers must think about throughout the whole process. Among the ENC 1 package, we updated or summarized the LMIC evidence of the effectiveness and safety of four key immediate or early initiated newborn care interventions in this paper (Table 5).

Preterm newborns often suffer from fluctuating and low blood pressure during the first days of life, which contributes to a risk of IVH, long-term neurodevelopmental disabilities, and/or death [38, 39]. However, delaying umbilical cord clamping extends blood flow between the baby and the placenta and may stabilize blood pressure, support cardiovascular changes and improve overall resilience as newborns transition from fetal to neonatal circulation [40, 41]. This umbilical flow may improve their resilience during the transition. DCC, therefore, has been investigated based on the abovementioned hypothesis and the belief that immediate cord clamping may inhibit the newborn's ability to endure this transition. Previous evidence has shown fewer preterm babies died before discharge or had any bleeding in the brain when DCC (with immediate neonatal care after cord clamping) was performed [17]. In the WHO's two guidelines related to DCC [22, 23], it is recommended for term and preterm newborns based on evidence predominantly from the HIC setting. For preterm newborns, although there was no difference in mortality risk between neonates receiving DCC and ECC, they report that DCC led to a lower risk of developing NEC and IVH and a significant reduction in the need for blood transfusion without increasing the risk of jaundice requiring treatment. In our updated review, we found that DCC with immediate newborn care after cord clamping showed no significant effect on neonatal mortality and the majority of morbidities in preterm or LBW infants in LMICs except that it significantly lowered the preterm neonates' risk of receiving blood transfusion or developing late-onset sepsis. The most recent systematic review on DCC, cord milking and ECC [42] found DCC reduced death before discharge in preterm neonates (OR 0.68, 95% CI 0.51–0.91; 20 studies, 3,260 infants), compared to ECC. However, their data were also predominantly based on HICs studies, and their LMIC-only data did not show a significant benefit of DCC over ECC on neonatal

Table 4. Pooled effect estimates of immediate care interventions for newborns

Outcome	Group	Studies, *n* (participants, *n*)	Effect estimate (95% CI)	Heterogeneity (I^2), %	Test for subgroup differences
DCC in preterm newborns					
DCC with immediate neonatal care after cord clamping versus ECC					
Neonatal mortality before discharge	<32–34 GA	3 (249)	RR 1.59 (0.68 to 3.73)	0	0.29
	≥32–34 GA	3 (310)	RR 1.38 (0.09 to 20.31)	34	
	Mixed gestation	4 (300)	RR 0.56 (0.20 to 1.54)	18	
	Total	10 (859)	RR 0.99 (0.47 to 2.06)	28	
	Sensitivity analysis	3 (344)	RR 1.17 (0.46 to 2.93)	0	
Inotropics for low blood pressure	<32–34 GA	2 (132)	**RR 0.32 (0.13 to 0.82)**	–	0.16
Blood transfusion in infant	<32–34 GA	4 (328)	**RR 0.31 (0.15 to 0.67)**	28	0.09
Late sepsis (after 3 days or as defined by trialists)	Total	7 (574)	**RR 0.65 (0.45 to 0.95)**	5	0.67
DCC with immediate neonatal care with cord intact versus ECC					
Neonatal mortality before discharge	Total	2 (161)	RR 1.33 (0.33 to 5.45)	–	NA
UCM versus ECC					
Neonatal mortality before discharge	Total	3 (348)	RR 0.96 (0.41 to 2.26)	0	0.60
	Sensitivity analysis	3 (348)	RR 0.96 (0.41 to 2.26)	0	
Hyperbilirubinemia treated by phototherapy	≥32–34 GA	1 (200)	**RR 3.67 (1.85 to 7.26)**	–	0.003
Blood transfusion in infant	Mixed gestation	1 (102)	**RR 0.41 (0.20 to 0.83)**	–	0.15
	Total	3 (393)	RR 0.65 (0.39 to 1.08)	73	
Hb within 1st 24 h of birth (g/dL)	<32–34 GA	3 (382)	**MD 1.18 (0.07 to 2.29)**	75	0.68
	≥32–34 GA	2 (400)	MD 1.83 (−0.38 to 4.03)	95	
	Mixed gestation	1 (102)	**MD 1.71 (1.23 to 2.19)**	–	
	Total	6 (884)	**MD 1.51 (0.76 to 2.26)**	84	
DCC in term newborns					
DCC with immediate neonatal care after cord clamping versus ECC					
Neonatal mortality	Total	3 (719)	RR 0.95 (0.21 to 4.19)	47	0.17
Clinical jaundice	Uterotonic at or after clamping	1 (102)	RR 0.85 (0.46 to 1.56)	–	0.04
	Use of uterotonic not specified	7 (2,317)	**RR 1.65 (1.41 to 1.93)**	85	
	Total	8 (2,419)	**RR 1.58 (1.36 to 1.84)**	84	
Polycythemia	Uterotonic at or after clamping	5 (492)	RR 2.04 (0.57 to 7.35)	0	0.64
	Use of uterotonic not specified	5 (850)	**RR 2.86 (1.60 to 5.12)**	29	
	Total	10 (1,342)	**RR 2.68 (1.58 to 4.55)**	0	

Table 4 (continued)

Outcome	Group	Studies, *n* (participants, *n*)	Effect estimate (95% CI)	Heterogeneity (I^2), %	Test for subgroup differences
Cord Hb (g/dL)	Uterotonic at or after clamping	1 (382)	**MD −0.50 (−0.81 to −0.19)**	–	< 0.00001
	Use of uterotonic not specified	5 (1,107)	**MD 0.44 (0.35 to 0.53)**	94	
	Total	6 (1,489)	**MD 0.36 (0.28 to 0.45)**	95	
Newborn Hb (g/dL)	Use of uterotonic not specified	2 (626)	**MD 1.09 (0.11 to 2.07)**	86	NA
Infant Hb at 24–48 h (g/dL)	Uterotonic at or after clamping	3 (242)	**MD 0.85 (0.37 to 1.34)**	90	0.002
	Use of uterotonic not specified	5 (1,200)	**MD 1.64 (1.50 to 1.79)**	98	
	Total	8 (1,442)	**MD 1.58 (1.44 to 1.72)**	97	
Low infant hematocrit (<45%) at 24–48 h	Uterotonic at or after clamping	1 (159)	RR 0.56 (0.25 to 1.27)	–	0.26
	Use of uterotonic not specified	3 (702)	**RR 0.31 (0.16 to 0.60)**	73	
	Total	4 (861)	**RR 0.39 (0.24 to 0.66)**	58	
Infant iron deficiency at 3–6 months	Uterotonic at or after clamping	1 (78)	RR 0.96 (0.72 to 1.29)	–	0.03
	Use of uterotonic not specified	2 (567)	**RR 0.47 (0.26 to 0.85)**	47	
	Total	3 (645)	**RR 0.71 (0.53 to 0.96)**	73	
Mean maternal blood loss (mL)	Use of uterotonic not specified	2 (568)	**MD −21.72 (−39.45 to −4.00)**	90	0.44
	Total	4 (1,447)	**MD −17.23 (−30.75 to −0.71)**	72	
Immediate thermal care					
Plastic wrap/bag versus routine care					
Hypothermia	Middle-income countries	8 (710)	**RR 0.63 (0.55 to 0.71)**	78	0.82
	Low-income countries	1 (104)	**RR 0.59 (0.39 to 0.91)**	NA	
	Total	9 (814)	**RR 0.62 (0.55 to 0.70)**	75	
Mild hypothermia	–	2 (160)	RR 1.15 (0.56 to 2.35)	79	NA
Moderate hypothermia	–	2 (160)	**RR 0.58 (0.43 to 0.78)**	3	NA
Body temperature (axillary temperature)	At admission to NICU/nursery	8 (625)	**MD 0.43 (0.35 to 0.51)**	87	<0.00001
	Post-admission in NICU/nursery	5 (417)	**MD 0.29 (0.20 to 0.38)**	84	
	Post-stabilization	1 (110)	**MD 0.50 (0.13 to 0.87)**	NA	
	At 1 h of life	5 (576)	**MD 0.16 (0.09 to 0.23)**	95	
	At 2 h of life	3 (271)	MD 0.05 (−0.03 to 0.12)	98	
Clinical sepsis	–	2 (251)	**RR 0.24 (0.06 to 0.89)**	0	NA

Table 4 (continued)

Outcome	Group	Studies, *n* (participants, *n*)	Effect estimate (95% CI)	Heterogeneity (I^2), %	Test for subgroup differences
Culture-proven sepsis	–	2 (251)	RR 0.74 (0.44 to 1.22)	0	NA
Mortality	Middle-income countries	4 (238)	RR 0.61 (0.33 to 1.14)	0	0.05
	Low-income countries	1 (104)	RR 2.62 (0.72 to 9.58)	NA	
	Total	5 (342)	RR 0.84 (0.49 to 1.44)	0	
Plastic wrap versus routine care during interhospital transport					
Hypothermia	–	2 (204)	**RR 0.75 (0.58 to 0.96)**	79	NA
Axillary temperature	–	2 (204)	**MD 0.56 (0.35 to 0.78)**	0	NA
Hyperthermia	–	2 (204)	RR 2.94 (0.31 to 27.79)	0	NA
Plastic wrap versus cotton/cloth wrap					
Hypothermia	–	2 (220)	**RR 0.22 (0.10 to 0.48)**	74	0.10
Novel heating technology versus standard care (incubator/room warming)					
Hypothermia (any severity)	–	2 (237)	RR 0.90 (0.73 to 1.12)	NA	NA
Body temperature post intervention	–	2 (237)	**SMD 0.51 (0.25 to 0.77)**	70	NA
Hyperthermia	–	1 (199)	Not estimable	NA	NA
Immediate and early initiated KMC					
Mortality by discharge or 28 days of life or 40 weeks PMA	–	3 (3,533)	**RR 0.78 (0.66 to 0.92)**	0	NA
Nosocomial sepsis till 28 days of life	Clinical sepsis	2 (3,415)	**RR 0.85 (0.75 to 0.95)**	71	0.35
	Culture-proven sepsis	1 (279)	RR 1.53 (0.44 to 5.31)	NA	
	Total	2 (3,694)	**RR 0.85 (0.76 to 0.96)**	54	
Exclusive breastfeeding	At discharge	2 (2,717)	**RR 1.05 (1.02 to 1.07)**	82	**NA**
	At 4 weeks of age	2 (2,804)	RR 1.01 (0.98 to 1.04)	43	
Hypothermia	–	3 (3,553)	**RR 0.74 (0.61 to 0.90)**	25	NA

DCC, delayed umbilical cord clamping; ECC, early umbilical cord clamping; GA, gestational age; Hb, hemoglobin; KMC, kangaroo mother care; PMA, post-menstruation age; MD, mean difference; NA, not applicable; NICU, neonatal intensive care unit; RCT, randomize controlled trial; RR, risk ratio; SMD, standardized mean difference; UCM, umbilical cord milking. Bold values represent the effect estimates are statistically significant.

mortality before discharge. Due to very limited number of studies on UCM, we did not find clear evidence regarding its effect on neonatal mortality and morbidities compared to either ECC or DCC, which is consistent with other studies on this topic [42]. No LMIC evidence is available for the long-term neurodevelopmental outcomes in newborns who received UCM, either.

Placental transfusion refers to the net transfer of blood to the baby between birth and cord clamping. For term newborns, the additional plasma from placental transfusion is quickly lost during circulation, leaving a high red cell mass which is broken down later. It was reported that DCC improved iron storage at age six to 12 months for term newborns [16, 43]. Similarly, we

Table 5. Summary of findings related to immediate newborn care interventions

WHO ENC 1 package [37] (Immediate Care and Helping Babies Breathe at Birth)	Summary of our findings	Outcomes	Pooled estimates	Number of participants (studies)	Quality of evidence (GRADE)
1. Dry thoroughly 2. Assess crying/breathing					
3. Keep warm	KMC provided to preterm or LBW infants immediately or early after delivery can lead to a lower rate in mortality, sepsis and hypothermia	Neonatal mortality by discharge or 28 days of life	**RR 0.78 (0.66 to 0.92)**	3,533 (3 studies)	High
		Sepsis by discharge or 28 days of life	**RR 0.85 (0.76 to 0.96)**	3,694 (3 studies)	Moderate
		Hypothermia by discharge or 28 days of life	**RR 0.74 (0.61 to 0.90)**	3,553 (3 studies)	High
	Plastic wrap or bag for immediate thermal protection/care may help lowering the occurrence of hypothermia and improving infants' core temperature at 1 h of life for preterm or LBW infants, without increasing the risk of hyperthermia. But it may not have effect on neonatal mortality in this population	Hypothermia	**RR 0.62 (0.55 to 0.70)**	814 (9 studies)	Very low
		Axillary temperature at 1-h of life	**MD 0.16 (0.09 to 0.23)**	576 (5 studies)	Very low
		Hyperthermia	RR 0.63 (0.22 to 1.81)	416 (7 studies)	Low
		Mortality before discharge or at 6-month's corrected age	RR 0.84 (0.49 to 1.44)	342 (5 studies)	Low
4. Check breathing					
5. Clamp and cut cord	For term neonates, DCC may result in a higher level of Hb in neonates and infants till 3–6 months after birth, as well as a lower rate of infant iron deficiency. But it may also increase the occurrence of clinical jaundice and polycythemia	Neonatal mortality	RR 0.95 (0.21 to 4.19)	719 (3 studies)	Very low
		Clinical jaundice	**RR 1.58 (1.36 to 1.84)**	2419 (8 studies)	Low
		Jaundice requiring phototherapy	RR 1.03 (0.83 to 1.29)	2346 (12 studies)	Moderate
		Polycythemia	**RR 2.68 (1.58 to 4.55)**	1342 (10 studies)	Low
		Cord Hb	**MD 0.36 (0.28 to 0.45)**	1489 (6 studies)	Very low
		Infant Hb at 24–48 h of life	**MD 1.58 (1.44 to 1.72)**	1442 (8 studies)	Very low
		Low infant hematocrit (<45%) at 24–48 h of life	**RR 0.39 (0.24 to 0.66)**	861 (4 studies)	Moderate
		Infant iron deficiency at 3–6 months	**RR 0.71 (0.53 to 0.96)**	645 (3 studies)	Low
		Low infant Hb at 3–6 months	RR 0.94 (0.68 to 1.29)	501 (3 studies)	Low
	For preterm infants, DCC (with immediate neonatal care either with cord intact or after cord clamping) may not help with improving neonatal survivals	Mortality by discharge for DCC with immediate neonatal care after cord clamping	RR 0.99 (0.47 to 2.06)	859 (10 studies)	Very low
		Mortality by discharge for DCC with immediate neonatal care with cord intact	RR 1.33 (0.33 to 5.45)	161 (2 studies)	Low
6. Continue SSC and monitor 7. Help initiate breastfeeding					

ENC, essential neonatal care; KMC, kangaroo mother care; LBW, low birth weight; MD, mean difference; RR, risk ratio; SSC, skin-to-skin contact.

found that in term newborns in LMICs, DCC resulted in a higher Hb and hematocrit level in the first few days of life (not lasting till 3 to 6 months of assessment) and a lower risk of infant iron deficiency at 3 to 6 months. Several included studies [43–46] also revealed a higher ferritin level in DCC term newborns with a follow-up duration ranging from 6 weeks to 3 months. In contrast, these newborns were at a higher risk of developing clinical jaundice and/or polycythemia. The physiology of placenta transfusion at preterm birth is not well understood. The mechanisms for the circulatory changes may not be fully developed and the process may take longer [46]. The relative contribution to blood volume and red cell mass of DCC may be greater than for those born at term as a higher proportion of the intrauterine blood volume is sequestered in the placenta [47, 48]. Given that the vast majority of our included LMIC studies did not report newborns and infants' level of Hb and hematocrit as their outcomes of interest, we were not able to synthesize relevant evidence on DCC's effect on preterm or LBW babies' Hb, hematocrit, and iron reserves. The long-term effect of DCC on infants' or children's neurodevelopmental outcomes is still unknown due to scarce evidence.

Once out of the uterus, maintaining normothermia is a major challenge and of vital importance to the newborns, especially for the preterm or LBW infants due to their immature thermoregulation and greater susceptibility to the adverse effects of hypothermia [49]. Prediction models from a systematic review identified normal temperature upon admission to the NICU to be one of eight predictors of survival in infants born at <32 weeks gestation and/or <1,500 g birth weight [50]. Hypothermia is defined as a core body temperature of <36.5°C or a skin temperature of <36°C [6]. Despite years of efforts in newborn thermal care globally, hypothermia remains a challenge in both HIC and LMIC settings with different resource levels and across all climates. A systematic review in 2013 reported the prevalence of hypothermia in LMICs and revealed widely varied rates both in hospital and community settings. Hospital rates of hypothermia ranged from 8% (<34.5°C) within 12 h of birth in Guinea-Bissau to 85% (<36°C) upon admission in Zimbabwe, while community rates ranged from 11% (<35.6°C) on the first day of life in India to 92% (<36.5°C) during the first month in Nepal [51]. The Vermont Oxford Network collected data from nearly 1,000 centers across 28 HICs or upper middle-income countries and found that, even though there had been an improvement in admission hypothermia rates since 2009, nearly four in ten infants in 2016 were still hypothermic upon admission to the NICU [52]. Not only has an independent association between hypothermia and neonatal mortality been shown consistently in the literature [53–58], but also a link has been suggested between hypothermia and an increased risk for neonatal morbidities in preterm infants [56, 59], such as IVH, respiratory disease, hypoglycemia, late-onset sepsis, and hospital admission. Although the mechanisms associated with increased mortality and morbidity are not clear, it has been postulated that alterations of normal metabolic functions associated with hypothermia predispose newborns to hypoxia, impaired fluid balance, hypoglycemia, hyperkaliemia, or an accumulation of toxic metabolic by-products that may not be compatible with life [60].

Consequently, understanding how to best identify and implement evidence-based thermal care strategies is always a focus in immediate newborn care. Appropriate thermal care is mandatory in the delivery room and involves minimization of heat loss alongside optimization of heat supply [61, 62]. Previous evidence has shown plastic wraps improved preterm newborns' core temperature and reduced the incidence of hypothermia upon admission or up to 2 h after birth in the NICU [18]. According to our analysis of LMIC settings, thermal care using plastic wrap/bag could lead to a 38% lower risk of developing hypothermia in preterm or LBW neonates when compared to routine thermal care immediately started in the delivery room (i.e., providing a warm delivery room with prewarmed contact surfaces, drying the infant immediately after birth, wrapping in a prewarmed, dry blanket, avoiding draughts, and using radiant warmers or incubators) [6]. This thermal care intervention also demonstrated a significantly favorable effect on improving core body temperature at and post-admission to the NICU/nursery. In contrast to previous findings on this topic [18], we found plastic bag/wrap may not increase the risk of hyperthermia based on the evidence available in LMIC settings. There was still insufficient evidence to suggest that plastic wrap/bag could significantly reduce mortality during hospitalization, or the occurrence of major neonatal morbidities. Evidence was also very limited for other barriers-to-heat-loss methods, such as polythene bag, polyvinyl bag, and cotton/cloth wrap.

Considered as one important and easy-to-apply approach to increase heat supply, KMC is defined as early, continuous, and prolonged SSC between the mother and preterm babies; exclusive breastfeeding or breast milk feeding; early discharge after hospital-initiated KMC

with continuation at home; and adequate support and follow-up for mothers at home [63]. However, there is significant heterogeneity across KMC studies regarding the time of KMC initiation and duration. Furthermore, a large number of studies did not report a definition of KMC but equated KMC with SSC [64]. Early initiation of breastfeeding is a pivotal part of the KMC package because it can significantly reduce neonatal mortality [65]. However, in real practice, more than half of newborns in LMICs did not receive the benefit of early initiation of breastfeeding according to the UNICEF and WHO 2016 report [66]. This is a result of multiple factors: inadequate support from the health workers around the time of birth, lack of empowerment toward mothers and families, local culture, and policies [66]. Furthermore, there are also significant variations in other details of KMC, like the timing of initiation, duration of SSC, positioning, and necessary equipment and supplies. Evidence specifically related to KMC initiated immediately after birth for preterm and/or LBW babies is still scarce. According to three LMIC studies of early KMC (within 24 h) that we identified from the source reviews, immediate or early initiated KMC had a significantly more favorable effect over KMC initiated after 24 h of age in preventing hypothermia and nosocomial sepsis, as well as reducing neonatal mortality by 28 days or life. These findings could provide public health practitioners with practical details for implementing KMC programs targeting preterm and/or LBW newborns in the real world: SSC can be initiated in the health-care facility or at home, should be started as soon as possible at birth, and should be given for as many hours as possible, while early initiation of breastfeeding should be supported at the same time. This was in accordance with previous systematic reviews and reports not restricted to LMIC settings [19, 23, 67, 68]. However, evidence related to bonding and attachment with the mother, pain management of the mother, and the neurological development of these preterm or LBW infants who received immediate KMC in the LMIC setting was lacking.

Delayed bath beyond 24 h may play a role in keeping babies warm because it has been shown to be associated with vernix caseosa retention on newborns' skin, which may help with their thermoregulation [69] and adequate time of SSC between newborns and their mothers [70]. Due to the limited number of LMIC studies and their great heterogeneity in study designs, we could not come to a conclusion regarding the effect of delayed first bath on neonatal mortality and morbidities, such as hypothermia. A similar dilemma exists in the area of novel heating technology applied at birth or immediately afterward. Despite years of efforts in developing novel heating technologies to keep babies warm, there was still insufficient evidence suggesting these innovative interventions are superior in preventing hypothermia or other neonatal morbidities compared with conventional methods (i.e., prewarmed incubator, room warming), particularly scarce in the LMIC setting. It is possibly due to the fact that these novel technologies were not readily available in resource areas. Therefore, there are still great research gaps either in developing affordable innovative thermal care technologies/devices for resource-limited areas or in testing existing novel technologies' effectiveness in keeping babies warm.

The most common form of hemolytic disease of the fetus and newborn is caused by the transplacental transfer of anti-Rh antibodies directed at red blood cell surface RhD antigens from sensitized mothers to their fetus. Since the 1960s, the empirical use of anti-D immunoglobulin in Rh-negative women after giving birth to Rh positive babies (within 72 h) has been shown to reduce RhD alloimmunization dramatically [21, 71] Given the high-quality evidence from studies conducted in the HIC setting, no further RCT has been identified since 2000. In recent years, routine antenatal anti-D prophylaxis in the last trimester of pregnancy has been widely adopted in many developed countries [11, 72, 73] because it can lead to a significant decline in the residual numbers of women becoming sensitized. However, in LMIC settings, routine antenatal anti-D prophylaxis programs are still out of reach as a result of limited resources and access to care. Anti-D immunoglobulin after birth still plays a critical role in the prophylaxis of Rh alloimmunization among Rh-negative women in LMICs and the associated fetal and neonatal morbidities in their subsequent pregnancies, but there are some barriers in its implementation and scale-up. Common barriers include, but are not limited to, the following: lack of information about previous pregnancies and termination of pregnancy due to poor data management [74, 75], unaffordability of anti-D immunoglobulin [75], absence of a universal access program for all Rh-negative women [74, 75].

Gaps and Future Challenges

There are still great gaps existing in the research, application and scale-up of immediate newborn care across the world. Some routine immediate care at birth (i.e., drying thoroughly, checking crying/breathing,

stimulation as needed) is critical component of essential newborn care package and is usually provided as part of the package. We were not able to identify qualified evidence reviews or trials for an individual routine immediate care. Current recommendations related to routine immediate care are mainly based on the basis of existing WHO guidelines and practice. It could be a subject for further investigation and analysis in the future. Innovations in developing and implementing effective and affordable neonatal care interventions can become game changers in reducing neonatal mortality and morbidities. One major barrier for LMICs with a high neonatal disease burden is the lack of various resources, including medication, devices, and health workforces. In our search, we found limited LMIC studies investigating the effectiveness of novel thermal care approaches, which may be partly explained by the resource restriction regarding device availability and health personnel required for maintaining and operating novel thermal care devices. Similar with DCC with immediate newborn care with cord intact. Only two LMIC studies with a total of 161 participants were identified for this topic, probably due to the very limited availability of life supporting trolleys in the LMIC setting. Even for interventions not requiring a lot resources, evidence is still lacking. KMC is an important intervention in preventing hypothermia and the resulting morbidities in preterm and/or LBW newborns and was shown to result in earlier physiological stabilization in this population. Although 23 RCTs investigating the effect of KMC in LMIC settings were identified from the source review, only one study was successful in providing KMC to newborns immediately after birth, while the median time for initiating KMC in the remaining studies ranged from several hours to more than 24 h after birth. In recent years, there have been a lot of research investigating the details in performing UCM in newborns, including its short-term effect and safety in newborns with different gestational ages (extreme preterm newborns <28 weeks, newborns of 28–32 weeks, near-term and term newborns) [76–78], as well as its potential effect on newborns' long-term neurodevelopmental outcomes [79]. Despite this simple intervention's potential implication, no such study has been conducted in the LMIC setting yet. Evidence-based interventions are the foundation of effective neonatal programs to reduce neonatal mortality and morbidities. However, studies conducted in LMICs are often limited in both quantity and quality. There is great demand for high-level evidence to guide future actions and to inform policy-making in these countries and areas.

With effective interventions, the bottlenecks most frequently identified as very major or significant for implementation and scaling up by countries with a high burden of neonatal death were: families' and caregivers' perception, health financing, health workforce, health service delivery, medical products and technologies [80]. Furthermore, bottlenecks for specific interventions might differ across countries and areas. To translate evidence into practice and to systematically scale-up interventions, future projects should focus on examining neonatal outcomes; adapting existing evidence and recommendations to different countries, local culture and contexts; identifying sustainable investments; and promoting the partnership of multiple stakeholders at both the national and community level.

Strengths and Limitations

Our study reviewed the most recent evidence on immediate newborn care interventions to inform practice in LMIC settings. Included topics were identified based on previous high-profile reviews and in consultation with our technical advisory group of global experts in newborn care. However, our findings do have several limitations that should be recognized. The quality of LMIC evidence for many of the interventions is unsatisfactory due to one or more of the following reasons: various risks of bias within included studies (for all interventions reviewed and discussed), small sample size and/or number of events (for DCC in preterm neonates and the majority of comparisons in immediate thermal care/protection), great heterogeneity among studies (the majority of outcomes in early KMC as well as in anti-D management), and limited number of studies included (the majority of comparisons in immediate thermal care/protection). To be noteworthy, although the quality assessment tools used (ROB, ROB-2, and ROBINS-I (Risk Of Bias In Non-randomised Studies-of Interventions)) are all well-established and widely-accepted, they may not be able to really differentiate the quality of included studies due to the nature of our interventions. For example, blinding participants and healthcare personnels is not feasible in KMC studies; therefore, all included KMC trials were rated as of high ROB, even for well-designed ones. It requires extra considerations when interpreting the quality assessment results and assessing the certainty of evidence. Furthermore, our included studies focused on the effectiveness and safety of immediate newborn care but did not evaluate the implementation process, financial cost, human force input, or the perception of the newborns' families.

Conclusion

Our review covered key interventions of immediate newborn care, especially for preterm and/or LBW infants. By identifying or providing updated evidence on these immediate neonatal interventions, we found that, despite limitations such as high heterogeneity and varying study quality for certain interventions: (1) KMC provided to preterm or LBW newborns immediately or early (with 24 h) after birth can lead to a lower mortality rate and a lower risk of sepsis and hypothermia; (2) plastic bag or wrap may help reducing hypothermia risk in preterm or LBW neonates and improve their core temperature without increasing the risk of hyperthermia; (3) DCC may improve neonatal Hb and iron storage in term newborns but did not show significant effect for preterm newborns. Efforts are needed to implement and to scale-up these interventions in LMICs, conflict-affected, and resource-limited areas via appropriate delivery platforms in a continuous fashion to help achieve SDG 3.2.

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Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.H. and Z.A.B. conceptualized and designed the study. G.D., O.M., A.C., and L.H. conducted the updated systematic literature search and designed the data collection form for DCC and thermal care. G.D., O.M., and A.C. extracted data from literature and carried out the data analysis for these topics. L.J. designed the data collection form, extracted data from analysis, and performed data analysis for KMC and drafted the initial manuscript. L.H., T.V., and Z.A.B. supervised the whole process, and critically reviewed and revised the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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