Delivery room interventions to reduce hypothermia soon after birth in preterm infants - A systematic review and network meta-analysis

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KEY POINTS

Question

Which is the most appropriate thermal care intervention in delivery room to reduce hypothermia and improve clinical outcomes in preterm infants?

Findings

Network meta-analysis of nine interventions studied in 34 trials including 3688 infants showed that a combination of plastic bag / wrap with plastic cap or with heated humidified respiratory gases reduced the risk of mortality before discharge and major brain injury respectively, whilst stabilizing the core body temperature soon after birth. Certainty of evidence for these interventions was moderate for temperature stabilization and low to moderate for other clinical outcomes.

Meaning

Delivery room use of a plastic bag / wrap along with plastic cap or with heated humidified gases appear to be the appropriate thermal care interventions for preterm infants.

ABSTRACT

Importance

Prevention of hypothermia in delivery room is a cost-effective, high impact intervention to reduce neonatal mortality, especially in preterm infants. Several interventions for preventing hypothermia in delivery room exist, of which the most effective one is currently unknown.

Objective

Assess the efficacy and safety of thermal care interventions initiated in the delivery room for preterm neonates ≤ 36 weeks' gestation.

Data sources

Medline, CENTRAL, Embase and CINAHL.

Study selection

Randomized and quasi-randomised controlled trials were included.

Data extraction and synthesis

Data synthesis with network meta-analysis using bayesian approach.

Main outcomes and measures

Primary outcomes were core body temperature on admission or within 2 h of life and incidence of moderate or severe hypothermia. Secondary outcomes were hyperthermia, major brain injury and mortality before discharge.

Results

34 studies (3688 neonates) evaluating nine interventions - plastic bag or wrap, thermal mattress, plastic cap, skin-to-skin care, plastic bag or wrap with thermal mattress, plastic bag or wrap with plastic cap, plastic bag or wrap with heated humidified respiratory gases, plastic bag or wrap with incubator transport and routine care were evaluated.

Compared to routine care alone, plastic bag or wrap with thermal mattress [MD (95% CrI): 0.98^{o}C (0.60-1.36)], plastic cap [0.83^{o}C (0.28-1.38)], plastic bag or wrap with heated humidified respiratory gases [0.76^{o}C (0.38-1.15)], plastic bag or wrap with plastic cap [0.62^{o}C (0.37-0.88)], thermal mattress [0.62^{o}C (0.33-0.93)] and plastic bag or wrap [0.56^{o}C (0.44-0.69)] resulted in greater core body temperature. Certainty of evidence was moderate for five comparisons and low for plastic bag or wrap with thermal mattress.When compared to routine care alone, plastic bag or wrap with heated humidified respiratory gases resulted in lesser major brain injury [0.23 (0.03-0.67)] (certainty of evidence - moderate) and plastic bag or wrap with plastic cap decreased the risk of mortality [0.19 (0.02-0.66)] (certainty of evidence – low).

Conclusions and relevance

Plastic bag or wrap along with plastic cap or heated humidified gases were associated with better core body temperature, which also translated to improved clinical outcomes. Certainty of evidence was low to moderate.

INTRODUCTION

Neonatal hypothermia (NH) is a significant problem in both developing and developed countries.[1,2,3] The dose-response effect between the severity of NH and the risk of mortality is well established.[3-6] Hence, prevention of NH in delivery room is touted as a cost-effective, high impact intervention to reduce neonatal mortality. The 2020 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) reiterated its previous recommendation of using additional thermal care interventions such as maintaining delivery room temperature at 23-25^{o}C, warm blankets, plastic wraps without drying, thermal mattress and cap for infants born at less than 32 weeks' gestation.[7] However, the CoSTR authors stress the weakness of the recommendations, based on the very low certainty of evidence, and indicate the need for an updated systematic review.[7] Apart from assessing efficacy, it is also essential to establish the safety of these interventions, as some studies have shown an increased risk of hyperthermia with their use.[8-10]

Currently existing systematic reviews compared several of the thermal care interventions in pair-wise meta-analyses.[8-11] However, faced with a rapidly evolving evidence-base and a choice of several competing interventions for which direct pair-wise comparisons are not available, a systematic review based on network meta-analysis (NMA) for data synthesis could be considered an appropriate evaluation strategy.[12] Hence, we compared the efficacy and safety of different delivery room thermal care interventions in a NMA, aiming to identify the most effective intervention for preterm infants in the delivery room to reduce NH and improve clinical outcomes.

METHODS

The protocol was registered with PROSPERO (CRD42020216008).[13] This SR is reported in accordance with the PRISMA – NMA extension.[14]

Inclusion criteria

Randomized controlled trials (RCTs) and quasi-RCTs evaluating thermal care interventions in delivery room in preterm neonates (< 37 weeks' gestation) were included. Studies published as peer-reviewed abstracts or in non-English language were also included. Studies that included term infants or infants > 2500 g birth weight were excluded.

Interventions

The following nine thermal care interventions were included:

- Plastic bag or plastic wrap covering the torso and limbs with head uncovered or covered with a cloth cap
- Plastic cap to cover the head
- Skin-to-skin contact
- Thermal mattress
- Plastic bag or plastic wrap covering the torso and limbs with head covered with plastic cap
- Plastic bag or plastic wrap covering the torso and limbs, along with use of a thermal mattress
- Plastic bag or plastic wrap covering the torso and limbs, along with use of heated humidified gas for resuscitation or to initiate invasive, non-invasive respiratory support in delivery room.
- Plastic bag or plastic wrap covering the torso and limbs, along with use of an incubator for transport from the delivery room.
- Routine care including drying and covering the body with warm blankets, with or without a cloth cap.

Outcomes

Primary outcomes were core body temperature (axillary or rectal) and incidence of moderate or severe hypothermia (defined as body temperature < 36^{o}C), at admission or within 2 h of life. While incidence of hypothermia was the *a priori* decided primary outcome, moderate or severe hypothermia was reported as the primary outcome in this systematic review. Secondary outcomes were incidence of hyperthermia (defined as body temperature > 37.5^{o}C), major brain injury (grade 3-4 intraventricular hemorrhage[15] or periventricular leukomalacia) and mortality before discharge.

Literature Search

Medline, CENTRAL, Embase and CINAHL were searched from their inception till 5th November 2020. Reference lists of included trials and published systematic reviews were also searched to identify additional studies. Two authors screened the title and abstract of all studies using Rayyan-QCRI software,[16] and independently assessed the full-text articles for potentially relevant trials. The search strategy is provided in eTable 1 in supplement.

Risk of bias assessment

Two authors independently assessed the risk of bias (low, high, or unclear) in all included trials using the Cochrane risk of bias tool 1.0.[17] Discrepancies were resolved by consulting a third author.

Data extraction and data synthesis

Two authors extracted data from the included trials independently and in duplicates using a structured proforma. Statistical analysis was done using R-software (R Foundation for Statistical Computing, Vienna, Austria). NMA with Bayesian random-effects model was used for data synthesis.[18,19] Non-informative priors and generalized linear models with four chains, burn-in of 50,000 iterations, followed by 1,00,000 iterations and 10,000 adaptations were utilized.[19] Geometry of networks for all outcomes was evaluated using network plots. Model convergence was assessed using Gelman-Rubin statistic, trace and density plots.[20] Fit of the model was analysed using leverage plots, total residual deviance and deviance information criterion. Node-splitting was utilised to detect inconsistency.[21] I^2 statistic and Cochran Q was used to evaluate heterogeneity in pair-wise meta-analysis for direct evidence. Publication bias was looked for using funnel plot when there were ten or more trials in a meta-analysis. Network estimates were expressed as risk ratio (RR) or mean difference (MD) with respective 95% credible intervals (CrI), and were illustrated using league plots and forest plots. Ranking of interventions for both efficacy and safety was done using surface under the cumulative ranking curve (SUCRA) plots.[22] SUCRA values when expressed in percentage can be between 0 and 100 %. The higher the SUCRA value, the better would be the ranking of the intervention. SUCRA values are prone for misinterpretation. SUCRA need to be interpreted along with the certainty of evidence for any intervention. Also, SUCRA can vary for an intervention for different outcomes. While an intervention is ranked higher for its efficacy, it could be ranked down for its side-effect profile. These things need to be considered by the clinician while interpreting SUCRA and prior to adopting any intervention to practice. Meta-regression with gestational age as covariate was performed for the primary outcome. Certainty of evidence for all the estimates was done according to GRADE working group recommendations for NMA.[23]

Sensitivity analyses

The following sensitivity analyses were performed: (1) effect of thermal care interventions on infants born at $\leq$ 30 weeks' gestation, (2) evaluating plastic bag and plastic wrap as separate interventions, (3) drying versus no drying prior to application of plastic bag or wrap, and (4) any hypothermia (defined as core body temperature < 36.5°C at admission or within 2 h of life).

RESULTS

A total of 6154 titles and abstracts were screened, of which 34 studies enrolling 3688 neonates were included (eFigure 1 in supplement).[24-57] There were four three-armed RCTs.[30,51,54,55] The mean gestational age and birth weight of studied neonates were 29 weeks and 1200 g respectively (eFigure 2-3 in supplement). The characteristics of included studies is given in Table 1. Some of the excluded studies are given in eTable 2 in supplement, with reasons for exclusion.[58-64] The characteristics of the networks for all the outcomes is given in eTable 3 in supplement.

Risk of bias

Amongst 34 included trials, four had high and eight had unclear risk of selection bias.[24-26,28,30-32,34-36,50,54] Masking of the interventions was not performed in most studies, except two studies in which outcome assessors alone were masked.[26,50] One trial had high risk of attrition bias.[30] Six studies had high risk of other bias.[26,27,30,40,43,50] The risk of bias assessment of individual trials is given in eFigure 4 in supplement.

Primary outcomes

1. Core body temperature at admission or within 2 h of life

Thirty two studies including 3568 neonates reported this outcome. Eight interventions including routine care were evaluated. Figure 1 shows the network plot, SUCRA plot and forest plots with routine care as the common comparator. Figure 2 shows the league plot depicting the network estimates for various comparisons. Forest plots for direct evidence is given in eFigure 5 in supplement**.** There was no inconsistency on node-splitting analysis (eFigure 6 in supplement). Certainty of evidence assessment for primary and secondary outcomes is given in Table 2.

Compared to routine care alone, plastic bag or wrap with thermal mattress [MD (95% CrI): 0.98^{o}C (0.60-1.36)], plastic cap [0.83^{o}C (0.28-1.38)], plastic bag or wrap with heated humidified respiratory gases [0.76^{o}C (0.38-1.15)], plastic bag or wrap with plastic cap

[0.62^{o}C (0.37-0.88)], thermal mattress [0.62^{o}C (0.33-0.93)] and plastic bag or wrap alone [0.56^{o}C (0.44-0.69)] resulted in greater core body temperature. Certainty of evidence was moderate for five comparisons and low for plastic bag or wrap with thermal mattress. SUCRA ranked plastic bag or wrap with thermal mattress as the most effective intervention (SUCRA 0.89).

1a. Sensitivity analysis on core body temperature - Plastic bag and plastic wrap as separate interventions

Both plastic bag and plastic wrap were found to have equally efficacy in maintaining core body temperature [MD 0.06^{o}C (−0.19, 0.30)]. Certainty of evidence was moderate. (eFigure 7-8 in supplement). Inconsistency was detected in the network for plastic bag versus routine care comparison. (eFigure 9 in supplement)

1b. Sensitivity analysis on core body temperature - Evaluating studies in which the mean gestational age of included neonates was ≤ 30 weeks

The results were similar to those of the primary analysis, except that incubator transport also resulted in greater core body temperature compared to routine care [MD 0.68^{o}C (0.16-1.22]). (eFigure 10-12 in supplement)

1c. Meta-regression with gestational age as covariate for core body temperature

The core body temperature was evaluated at three gestational ages – 24, 30 and 34 weeks. While all the interventions resulted in significantly greater core body temperatures at 24 weeks, some interventions namely, plastic cap, incubator transport, and plastic bag or wrap with heated humidified gas had imprecise estimates at 30-34 weeks (eFigure 13 in supplement).

1d. Sensitivity analysis on core body temperature - Drying versus no drying before applying plastic bag or wrap

Core body temperature was comparable between drying versus no drying for both plastic bag or wrap alone [-0.09 (-0.38, 0.19); certainty of evidence - moderate] and plastic bag or wrap with plastic cap [-0.37 (-0.90, 0.15); certainty of evidence – very low] (eFigure 14-15 in supplement).

2. Moderate or severe hypothermia at admission or within 2 h of life.

Eight interventions including routine care were evaluated. Figure 3 shows the network, SUCRA and forest plots. Plastic bag or wrap alone [RR 0.23 (0.04-0.55)], thermal mattress [0.12 (0.00-0.62)] and plastic bag or wrap with heated humidified gas [0.12 (0.00-0.47) reduced the risk of moderate to severe hypothermia when compared to routine care. These are depicted in a league plot in eFigure 16 in supplement. The certainty of evidence was moderate for plastic bag or wrap alone, low for thermal mattress and plastic bag or wrap with heated humidified gas. SUCRA ranked thermal mattress and plastic bag or wrap with heated humidified gas as the two best interventions. However, certainty of evidence was low for both. Direct estimates are depicted in eFigure 17 in supplement. There was no inconsistency in the network. (eFigure 18 in supplement).

The confidence intervals of network estimates were wider for many comparisons when compared to the direct evidence from pair-wise comparisons. Hence, a sensitivity analysis was performed based on frequentist method with random-effects approach. The results were similar, and the estimates for plastic bag or wrap with plastic cap, plastic bag or wrap with thermal mattress and skin to skin contact were more precise (Figure 3D).

2a. Sensitivity analysis - Any hypothermia

Interventions such as skin to skin contact, plastic bag or wrap with heated humidified gas, plastic bag or wrap with thermal mattress, plastic bag or wrap with plastic cap, thermal mattress and plastic bag or wrap alone reduced the risk of any hypothermia, compared to routine care (eFigure 19-22 in supplement)

Secondary outcomes

1. Mortality before discharge.

Plastic bag or wrap with plastic cap decreased the risk of mortality before discharge compared to plastic bag or wrap alone [0.26 (0.02-0.86)] and routine care [0.19 (0.02-0.66)] (certainty of evidence - low) (eFigure 23-26 in supplement).

2. Hyperthermia at admission or within 2 h of life.

Only direct evidence from pair-wise meta-analysis revealed an increased risk of hyperthermia for plastic bag or wrap alone versus routine care [3.39 (1.84, 6.25)], and plastic bag or wrap with thermal mattress versus plastic bag or wrap alone [2.25 (1.13, 4.50)]. (eFigure 27 - 30 in supplement).

3. Major brain injury

Plastic bag or wrap with heated humidified gas decreased the risk of major brain injury compared to routine care [0.23 (0.03-0.67)] and showed a trend towards lesser major brain injury compared to plastic bag or wrap alone [0.38 (0.08-1.08)] (Certainty of evidence – moderate) (eFigure 31 - 33 in supplement).

The results are summarised in eTable 4 in supplement. Certainty of evidence for the sensitivity analyses and the secondary outcomes are given in eTable 5 in supplement.

DISCUSSION

This systematic review and NMA included 34 trials studying nine thermal care interventions in 3688 preterm neonates to prevent hypothermia soon after birth in the delivery room. Most of the interventions were found to be better than routine care in stabilizing the core body temperature and reducing the risk of moderate to severe hypothermia. However, there were distinct differences between them for the secondary outcomes namely hyperthermia, mortality and major brain injury.

The Cochrane review by McCall et al. (2018) showed that plastic bag or wrap improves core body temperature at admission or within 2 h of life with the certainty of evidence being moderate.[8] The data for other interventions were small and the evidence was not graded. We found moderate certainty of evidence for four interventions (plastic bag or wrap alone, thermal mattress, plastic bag or wrap with heated humidified gas and plastic cap) to improve core body temperature. This could be due to an increase in statistical power by the addition of evidence from the indirect fraction as well as inclusion of additional nine studies in this NMA.

Due to the various thermal care interventions having different mechanisms of action of preventing heat loss, using a combination of interventions might be useful in the most vulnerable infant. SUCRA ranked plastic bag or wrap with thermal mattress as the most effective intervention to improve core body temperature at admission or within 2 h of life. However, direct evidence indicated that plastic bag or wrap with thermal mattress might be associated with higher risk of hyperthermia. Though these were not reflected in the final network estimates, these estimates were derived from a sparse network where bayesian analysis with random effects approach is known to present imprecise results when compared to the direct evidence.[65] Hence, plastic bag or wrap with thermal mattress might not be recommended as the first choice till further adequately powered studies reporting on hyperthermia are available.

The mean difference in the core temperature between the different thermal adjuncts and routine care varied from 0.56 – 0.98 degree Celsius. Though, these were statistically significant, how much of this translated into clinical benefits is an important question to ponder. While observational studies and quality improvement projects have indicated that better temperature profiles at NICU admissions result in decreased mortality and morbidity, meta-analysis of RCTs have failed to show clinical benefits of these thermal care interventions.[4,7,8] On the contrary, in this NMA important clinical benefits were seen for plastic bag or wrap along heated humidified gas which decreased the risk of major brain injury (certainty of evidence – moderate) and plastic bag or wrap with plastic cap which decreased the risk of mortality (certainty of evidence – low). Also, plastic bag or wrap and plastic bag or wrap with thermal mattress showed a trend towards reduction in mortality when compared to routine care (certainty of evidence - low).

We conducted a meta-regression for core body temperature with gestational age as a covariate. Though the meta-regression showed that the efficacy of additional interventions was greater at lower gestational ages, some of them were still effective at 34 weeks' gestation. The results of individual trials conducted in more mature infants are also in agreement with this finding.[26,30,51] We suggest further research in this group of infants especially in resource limited settings, where radiant warmers and transport incubators might not be available and low-cost interventions such as plastic bag or wrap and plastic cap may have a significant impact in reducing hypothermia and neonatal mortality. Further, pre-sterilized plastic bag or wrap and plastic cap might be the most feasible interventions during delayed cord clamping (DCC), which is now considered the standard of care in term and preterm infants[66]. None of the included studies had looked at thermal care interventions during DCC, which potentially constitutes a period of rapid heat loss in preterm infants.

Though plastic bags and wraps work by the same principle of reducing evaporative and convective heat loss and seem to be technically similar, there could be differences in thickness of the plastic material, ease of application, extent of infant's body coverage, risk of displacement and other factors. A recent systematic review on plastic bag or wrap suggested possible differences between plastic bags and wraps and recommended further studies to evaluate the efficacy of plastic bags versus wraps.[10] However, we found that that plastic bags and wraps are equally efficacious. CoSTR (2020) recommends applying plastic bag or wrap to the infant immediately after birth without prior drying.[7] This is due to the understanding that extreme preterm infants have high trans-epidermal water loss; keeping the infant wet inside the plastic bag or wrap creates a high-humidity micro-environment and reduces evaporative heat loss. However, this recommendation does not have a high-level evidence. We found drying or no drying prior to applying plastic bag or wrap may not make a difference in maintenance of core body temperature (certainty of evidence - moderate). The included studies have used a cut-off of < 36.5 or < 36°C for either rectal or axillary temperature to define hypothermia. Though we considered both rectal and axillary temperature as core body temperature as followed in the Cochrane review, a difference of ≥ 0.5°C have been reported between the two in neonates.[67,68] Hence, to avoid this variability and the risk of inconsistency secondary to intransivity, we analysed moderate to severe hypothermia (temperature < 36°C) as the primary outcome. Plastic bag or wrap reduced the risk of moderate to severe hypothermia at admission or within 2 h of life, when compared to routine care (certainty of evidence - moderate). Two other recent systematic reviews on plastic bag or wrap also found significant reduction in hypothermia with its use.[9,10] The frequentist analysis showed most thermal care interventions were efficacious in reducing the risk of moderate to severe hypothermia.

There were several limitations in this systematic review. The variation amongst demographic and other characteristics such as gestational age, varying delivery room care practices, underlying sickness profile of the included neonates between the included trials might have introduced intransivity in this network meta-analysis. Further, there was wide differences in the way temperature was measured (axillary versus rectal) between the included trials. Though we considered hypothermia as the primary outcome *a priori*, we analysed moderate to severe hypothermia as the primary outcome in the review. We did not analyse some *a priori* decided secondary outcomes due to availability of limited data. Many of the included

RCTs were single centre trials with small sample size and low event rates, making the effect estimates prone for selective reporting and publication bias. Finally, we were unable to access unpublished data from the included studies and relied upon the recent Cochrane review for the same.[8]

CONCLUSION

Most of the thermal care interventions used in the delivery room result in better core body temperature at admission or within 2 h (certainty of evidence - moderate) and decrease the risk of moderate to severe hypothermia (certainty of evidence – moderate for plastic bag or wrap, low to very low for others), when compared to routine care alone. A combination of plastic bag or wrap with heated humidified gas or plastic cap reduces the risk of major brain injury (certainty of evidence - moderate) and mortality (certainty of evidence - low) respectively. Further trials adequately powered to assess important clinical outcomes are warranted.

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FIGURE LEGENDS

Figure 1: Network plot; Surface Under the Cumulative Ranking **(**SUCRA) and Forest plot for core body temperature at admission or within 2 h of life.

A. The size of nodes representing the interventions in network plots is proportional to the number of neonates receiving the intervention, and the width of the lines connecting the nodes is proportional to the number of trials evaluating the two interventions in a pair-wise manner. The number of trials comparing any two interventions are indicated besides the lines.
B. SUCRA values (expressed in percentage) for each intervention were as follows - Plastic bag / wrap with thermal mattress (PBWrTM): 89.1, Plastic cap (PCAP): 71.6, Plastic bag / wrap with heated humidified respiratory gases (PBWrHHGAS): 66.5, Plastic bag / wrap with plastic cap (PBWrPCAP): 47.7, Thermal mattress (TM): 46.6, Plastic bag / wrap with incubator transport(INCUPBWr): 42.4, Plastic bag /wrap (PBWr): 35.5 and Routine care (RCARE): 4.7. Higher rankings are associated with larger outcome values.
C. Forest plot shows the mean difference in core temperature (MD) with 95% credible interval (CrI) of the different interventions with routine care as the common comparator.

Figure 2: League plot of the network estimates for core body temperature at admission or within 2 h of life**.** League plots compare the effect estimate for an intervention in the column versus another in a row. Network estimates are depicted as risk ratio (RR) with 95% credible interval (CrI). PBWrTM indicates plastic bag / wrap with thermal mattress, PCAP indicates plastic cap, PBWrHHGAS indicates plastic bag / wrap with heated humidified respiratory gases, PBWrPCAP indicates plastic bag / wrap with plastic cap, TM indicates thermal

mattress, INCUPBWr indicates plastic bag / wrap with incubator transport, PBWr indicates plastic bag /wrap and RCARE indicates routine care. ** values are statistically significant.

Figure 3: Network plot; Surface Under the Cumulative Ranking **(**SUCRA) and Forest plot (bayesian and frequentist approach) for moderate to severe hypothermia at admission or within 2 h of life.

A. The size of nodes representing the interventions in network plots is proportional to the number of neonates receiving the intervention, and the width of the lines connecting the nodes is proportional to the number of trials evaluating the two interventions in a pair-wise manner. The number of trials comparing any two interventions are indicated besides the lines.
B. SUCRA values are arranged from highest to lowest values, as follows: Thermal mattress (TM), Plastic bag / wrap with heated humidified respiratory gases (PBWrHHGAS), Skin to skin contact (SSC), Plastic bag / wrap with thermal mattress (PBWrTM), Plastic bag /wrap (PBWr), Plastic bag / wrap with plastic cap (PBWrPCAP), Plastic bag / wrap with incubator transport (INCUPBWr), and Routine care (RCARE). Higher rankings are associated with smaller outcome values.
C. Forest plot shows risk ratio (RR) with 95% credible interval (CrI) with different interventions with routine care as the common comparator for moderate to severe hypothermia at admission or within 2 h of life, when analyzed with bayesian approach.
D. Forest plot shows risk ratio (RR) with 95% confidence interval (CI) with different interventions with routine care as the common comparator for moderate to severe hypothermia at admission or within 2 h of life, when analyzed with frequentist approach

Table 1: Characteristics of included studies

Study.ID	Country	Intervention (n)	Comparator (n)	Drying (for PB Wr)	Gestational age (Weeks); mean ± SD		Birth weight (g); mean ± SD		Temperature used for analysis	Hypothermia Definition (ºC)	Moderate to severe hypothermia definition (ºC)	Components of routine care
					Intervention	Comparator	Intervention	Comparator				
Ahmed 2013[24]	Cairo	PBAG (25)	RCARE (25)	Wet	29.56 ± 1	30.04 ± 1.75	1190 ± 200	1250 ± 40	Rectal, Admission	NR	<35	Radiant warmer, cap, transport incubator
Almeida 2013[25]	Hawai	TM (26)	RCARE (14)	-	32 ± 0.91	32 ± 1.3	1989 ± 626	1906 ± 526	Axillary, Admission	NR	NR	Radiant warmer, cap, transport incubator
Bergman 2004[26]	South Africa	SSC (20)	RCARE (14)	-	34.2 ± 1.9	35.3 ± 1.9	1813 ± 260	1866 ± 258	NR	NR	Axillary < 35.5	Incubator. Cap, booties and heat shield if required
Bhavsar 2015[27]	India	PBWrPCAP (49)	RCARE (47)	Dry	32.6 ± 2.4	31.9 ± 2.8	1686 ± 446	1471 ± 446	Axillary, Admission	NR	Axillary < 35	Radiant warmer, transport incubator, inter-hospital transport
Brennan 1996[28]	USA	TM (12)	RCARE (12)	-	27.8	27.3	1033	1027	Axillary, Admission	Axillary < 36.5	Axillary < 36	Radiant warmer, and as per NRP
Caglar 2014[29]	Turkey	PBAG (22)	PWRAP (37)	Wet	29.27 ± 1.8	28.64 ± 2.05	1183 ± 520	1079 ± 336	Axillary, 1 h	Axillary < 36.5	Axillary < 36	Radiant warmer, cap, transport incubator

Cardona-Torres 2011[30]	Mexico	PWRAP-wet (30) & PWRAP-dry (30)	RCARE (30)	Wet & Dry	34.5 ± 2.6 & 35.2 ± 1.8	35.6 ± 1.68	1934 ± 456 & 2101 ± 319	2173 ± 275	Axillary, 1 h	Axillary < 36.5	NR	Radiant warmer, transport incubator
Chantaroj 2011[31]	Thailand	PBAG (19)	RCARE (19)	Wet	28 ± 6	29 ± 2	1263 ± 274	1200 ± 258	Rectal, Admission	Rectal < 36.5	NR	Radiant warmer, yarn cap, transport incubator
Chawla 2011[32]	USA	PBWrTM (53)	RCARE (49)	Wet	28.7 ± 3	28.7 ± 2.4	1151 ± 407	1175 ± 413	Axillary, Admission	Axillary < 36	Axillary < 35	Radiant warmer, cap, transport incubator
Doglioni 2014[33]	Italy	PBWrPCAP (50)	PBWr (50)	Wet	25.7 ± 1.7	25.8 ± 1.7	789 ± 214	770 ± 245	NR	Axillary < 36.5	Axillary < 36	Radiant warmer, transport incubator
Farhadi 2012[34]	Iran	PBAG (20)	RCARE (20)	Wet	28.8 ± 2	29.2 ± 2.3	1278 ± 518	1190 ± 492	Axillary, NR	NR	NR	Radiant warmer, cap
Gathwala 2010[35]	India	PBAG (30)	RCARE (30)	Dry	29.93 ± 1.08	29.46 ± 1.33	1120 ± 190	1110 ± 230	Rectal, Admission	NR	NR	Radiant warmer, cap, transport incubator
Hashim 2017[36]	Malaysia	PBWrPCAP (40)	PBWr (40)	Wet	30.9 ± 2	31.3 ± 2	1410 (1170-1605)	1642 (1260-1756)	Axillary, Admission	Axillary < 36.5	Axillary < 36	Radiant warmer, cotton cap, transport incubator
Hu 2017[37]	China	PBAG (54)	RCARE (54)	Dry	29.7 ± 2	30 ± 2	1185 ± 213	1225 ± 195	Axillary, Admission	Axillary < 36.5	Axillary < 36	Radiant warmer, cap, transport incubator, inter-hospital transport
Knobel 2005[38]	USA	PBAG (41)	RCARE (47)	Wet	26.5 ± 1.4	26.1 ± 1.4	918 ± 259	850 ± 253	Rectal, Admission	Rectal < 36.5	NR	Radiant warmer, warm blankets

Leadford 2013[39]	Zambia	PBAG (49)	RCARE (55)	Dry	34 (32-36)	34 (31-36)	2200 ± 560	2110 ± 520	Axillary, 1 h	Axillary < 36.5	NR	Radiant warmer or SSC, blanket
Leslie 2007[40]	India	PBWrTM (23)	RCARE (24)	Wet	26 (23-28)	26 (23-28)	805 (560-1320)	840 (530-1240)	Axillary, Admission	Axillary < 36.5	NR	Radiant warmer, woollen cap
Mathew 2012[41]	USA	PBAG (21)	TM (20)	Wet	26 ± 1.3	26 ± 1.2	768 ± 162	766 ± 186	NR	NR	NR	Radiant warmer, cotton cap, transport incubator
McCarthy 2013[42]	Ireland	PBWrTM (37)	RCARE (35)	Wet	28 ± 2	28 ± 2	1085 ± 360	1194 ± 386	Rectal, Admission	Axillary < 36.5	NR	Radiant warmer, cotton cap, transport incubator
McGrory 2017[43]	Australia	PBWrHH GAS (132)	PBWr (141)	Wet	27 ± 1.8	27 ± 1.8	973 ± 288	930 ± 272	Rectal, Admission	Axillary < 36.5	Axillary < 36	Radiant warmer, cotton woollen cap, transport incubator
Meyer 2007[44]	New Zealand	INCUPB Wr (30)	PBWr (32)	Wet	26 (24.9-27)	26 (25-27)	870 (751-1031)	902 (746-991)	Axillary, Admission	Axillary < 36.5	Axillary < 36	Plastic wrap, Radiant warmer, radiant warmer or incubator for transport
Meyer 2015[45]	New Zealand	PBWrHH GAS (100)	PBWr (100)	Wet	29 (27-30)	29 (26-30)	1158 (890-1460)	1190 (954-1396)	Axillary, Admission	NR	Axillary < 35.5	Radiant warmer, cap, Radiant warmer, radiant warmer or incubator for transport

Nimbalkar 2018[46]	India	PBAG (74)	RCARE (77)	Wet	NR	NR	1658 ± 358	1627 ± 425	Axillary, 1 h	Axillary < 36.5	NR	Radiant warmer, cap, transport in open trolley
Reilly 2015[47]	USA and Canada	PWRAP (404)	RCARE (397)	Wet	25.6	26.0	800 ± 205	821 ± 199	Axillary, Admission	Axillary < 36.5	Axillary < 34.5	Radiant warmer, cap, transport incubator+/-
Reilly 2019[48]	USA and Canada	PWRAP (14)	RCARE (14)	Wet	22.8	22.7	565	552	Axillary, Admission	NR	NR	Radiant warmer, cap, transport incubator+/-
Rohana 2011[49]	Malaysia	PWRAP (50)	RCARE (60)	Wet	29.7 ± 2.9	29.8 ± 2.7	1277 ± 462	1328 ± 459	Axillary, Admission	Axillary < 36.5	Axillary < 36	Radiant warmer, cotton, cap, transport incubator
Santos 2012[50]	Philippines	PBWrPCAP (28)	RCARE (30)	Dry	NR	NR	NR	NR	Axillary, Admission	NR	NR	Droplight, blankets
Shabeer 2018[51]	India	PBAG (101) & TM (99)	RCARE (100)	Wet	34.4 ± 1.9 & 34.9 ± 1.9	34.5 ± 2	1890 ± 242 & 1860 ± 184	1827 ± 208	Axillary, Admission	Axillary < 36.5	Axillary < 35	Radiant warmer, cotton cap, transport incubator
Simon 2011[52]	USA	TM (17)	PBWr (19)	Wet	26 ± 1.2	25.9 ± 1.3	812 ± 176	901 ± 248	NR	Axillary < 36.5	NR	Radiant warmer, cotton or polyester cap, transport incubator
Smith 2013[53]	Australia	PWRAP (43)	RCARE (49)	Wet	NR	NR	991 ± 299	982 ± 233	Axillary, Admission	NR	NR	Radiant warmer, cap, transport in radiant warmer

Talakoub 2015[54]	Iran	PBAG (32) & PBWrPCAP (32)	RCARE (32)	Wet	NR	NR	NR	NR	Axillary, Admission	NR	NR	Radiant warmer, cotton cap, transport incubator
Trevisanuto 2010[55]	Italy	PBAG (32) & PCAP (32)	RCARE (32)	Wet	25.8 ± 1.5 & 26.1 ± 1.4	26.3 ± 1	800 ± 223 & 834 ± 246	813 ± 225	Axillary, Admission	Axillary < 36.4	NR	Radiant warmer, transport incubator
Vohra 1999[56]	Canada	PWRAP (27)	RCARE (32)	Wet	NR	NR	NR	NR	Rectal, Admission	NR	NR	Radiant warmer, transport incubator
Vohra 2004[57]	Canada	PWRAP (27)	RCARE (26)	Wet	26 ± 1.5	26 ± 1.4	858 ± 199	825 ± 270	Rectal, Admission	NR	NR	Radiant warmer

Table 2: Certainty of evidence for different comparisons for the primary outcomes

Primary outcome - Mean core body temperature (axillary or rectal) at admission or within first 2 hours of life				
	Indirect Evidence	**Direct Evidence**	**Network Meta-analysis^**	
Comparison	**Certainty of evidence**	**Certainty of evidence**	**Mean difference (95% Credible Interval)**	**Certainty of evidence**
PBWrTM:PCAP	LOW[1, 2]	-	0.15 (−0.51, 0.81)	LOW
PBWrTM:PBWrHHGAS	LOW[1, 2]	-	0.22 (−0.29, 0.73)	LOW
PBWrTM:PBWrPCAP	LOW[1, 2]	-	0.36 (−0.09, 0.79)	LOW
PBWrTM: TM	LOW[1, 2]	-	0.36 (−0.11, 0.82)	LOW
PBWrTM: INCUPBWr	LOW[1, 2]	-	0.42 (−0.27, 1.10)	LOW
PBWrTM:PBWr	-	LOW[1, 2]	**0.42 (0.06, 0.77)**	LOW
PBWrTM:RCARE	LOW[1, 2]	-	**0.98 (0.60, 1.36)**	LOW
PCAP:PBWrHHGAS	LOW[3]	-	0.07 (−0.59, 0.73)	LOW
PCAP:PBWrPCAP	LOW[2, 5]	-	0.21 (−0.39, 0.80)	LOW
PCAP:TM	LOW[4, 7]	-	0.21 (−0.42, 0.82)	LOW
PCAP:INCUPBWr	LOW[3]	-	0.27 (−0.53, 1.06)	LOW
PCAP:PBWr	MODERATE[2]	LOW[3]	0.27(-0.29, 0.81)	MODERATE
PCAP:RCARE	LOW[3]	MODERATE[2]	**0.83 (0.28, 1.38)**	MODERATE
PBWrHHGAS:PBWrPCAP	LOW[2, 5]	-	0.14 (−0.31, 0.58)	LOW
PBWrHHGAS:TM	LOW[4, 7]	-	0.14 (−0.34, 0.60)	LOW
PBWrHHGAS:INCUPBWr	LOW[3]	-	0.20 (−0.49, 0.88)	LOW
PBWrHHGAS:PBWr	-	MODERATE[4, *]	0.20 (−0.17, 0.56)	MODERATE
PBWrHHGAS:RCARE	MODERATE[4, *]	-	**0.76 (0.38, 1.15)**	MODERATE
PBWrPCAP:TM	LOW[2, 5]	-	0.01 (−0.38, 0.38)	LOW
PBWrPCAP:INCUPBWr	LOW[2, 5]	-	0.06 (−0.58, 0.69)	LOW
PBWrPCAP:PBWr	LOW[2, 6, *]	LOW[2, 5]	0.06(-0.20, 0.32)	LOW
PBWrPCAP:RCARE	LOW[2, 6, *]	LOW[2, 6, *]	**0.62 (0.37, 0.88)**	LOW

TM:INCUPBWr	LOW[4, 7]	-	0.05 (−0.59, 0.71)	LOW
TM:PBWr	MODERATE[8, *]	LOW[4, 7]	0.06 (−0.23, 0.36)	MODERATE
TM:RCARE	LOW[4, 7]	MODERATE[8, *]	**0.62 (0.33, 0.93)**	MODERATE
INCUPBWr:PBWr	-	LOW[3]	0.00 (−0.58, 0.58)	LOW
INCUPBWr:RCARE	LOW[3]	-	0.56 (−0.03, 1.16)	LOW
PBWr:RCARE	LOW[2, 6, *]	MODERATE[9,*, #]	**0.56 (0.44, 0.69)**	MODERATE

[1]Downgraded by one level for serious risk of bias due to one study (Chawla 2011) with 45% weightage being quasi-randomised.
[2]Downgraded by one level for serious imprecision due to optimal information size (OIS) criterion not met.
[3]Downgraded by two levels for very serious imprecision due to small sample size and confidence interval including ‘no difference’.
[4]Downgraded by one level for serious imprecision due to confidence interval including ‘no difference’.
[5]Downgraded by one level for serious risk of bias due to possible selection bias in two studies (Doglioni 2014; Talakoub 2015).
[6]Downgraded by one level for serious risk of bias due to possible selection bias in two studies (Santos 2012; Talakoub 2015).
[7]Downgraded by one level for serious inconsistency due to heterogeneity.
[8]Downgraded by one level for serious risk of bias due to possible selection bias in two studies (Almeida 2013, Brennan 1996).
[9]Downgraded by one level for publication bias.
[*]Not downgraded for inconsistency, since the heterogeneity is due to differences between small and large beneficial effects.
[#]Not downgraded for risk of bias, Since the studies with possible risk of bias (Ahmed 2013; Gathwala 2010; Talakoub 2015, Cardona-Torres 2011, Chantaroj 2011, Farhadi 2012) contribute only 27% weightage, and 73% weightage of effect estimate is from good quality studies.
Note: The outcome is not downgraded for lack of blinding in any comparison, since it is an objective outcome and blinding is difficult for these interventions.

Primary outcome - Moderate or severe hypothermia [defined as core body temperature (axillary or rectal temperature) less than 36 degree Celsius] at admission or within 2 hours of life.

	Indirect Evidence	**Direct Evidence**	**Network Meta-analysis**	
Comparison	**Certainty of evidence**	**Certainty of evidence**	**Risk Ratio (95% Credible Interval)**	**Certainty of evidence**
SSC:PBWrHHGAS	LOW[1, 2]	-	72.86 (0.01, 53.37)	LOW
SSC:PBWrTM	LOW[1, 2]	-	118.59 (0.00, 38.80)	LOW

SSC:PBWrPCAP	VERY LOW[3, 5, 6]	-	3.16 (0.00, 9.51)	VERY LOW
SSC:TM	LOW[1, 2]	-	514.84 (0.01, 153.95)	LOW
SSC:PBWr	LOW[1, 2]	-	3.24 (0.01, 9.85)	LOW
SSC:INCUPBWr	LOW[1, 2]	-	18.85 (0.00, 10.38)	LOW
SSC:RCARE	-	LOW[1, 2]	0.29 (0.00, 1.20)	LOW
PBWrHHGAS:PBWrTM	LOW[3, *]	-	5.23 (0.02, 12.02)	LOW
PBWrHHGAS:PBWrPCAP	VERY LOW[3, 5, 6]	-	0.67 (0.02, 2.81)	VERY LOW
PBWrHHGAS:TM	LOW[3, *]	-	74.08 (0.04, 87.00)	LOW
PBWrHHGAS:PBWr	-	LOW[3, *]	0.54 (0.05, 2.01)	LOW
PBWrHHGAS:INCUPBWr	LOW[3, *]	-	1.10 (0.00, 3.35)	LOW
PBWrHHGAS:RCARE	LOW[3, *]	-	**0.12 (0.00, 0.47)**	LOW
PBWrTM:PBWrPCAP	VERY LOW[3, 5, 6]	-	3.40 (0.02, 8.65)	VERY LOW
PBWrTM:TM	LOW[3, 4]	-	280.82 (0.05, 215.42)	LOW
PBWrTM:PBWr	-	LOW[3, 4]	1.78 (0.05, 7.20)	LOW
PBWrTM:INCUPBWr	LOW[3, 4]	-	6.24 (0.01, 9.33)	LOW
PBWrTM:RCARE	LOW[3, 4]	-	0.43 (0.01, 1.46)	LOW
PBWrPCAP:TM	LOW[2]	-	286.92 (0.21, 257.36)	LOW
PBWrPCAP:PBWr	LOW[2]	VERY LOW[3, 5, 6]	1.65 (0.27, 5.91)	LOW
PBWrPCAP:INCUPBWr	VERY LOW[3, 5, 6]	-	3.57 (0.02, 11.03)	VERY LOW
PBWrPCAP:RCARE	VERY LOW[3, 5, 6]	LOW[2]	0.33 (0.04, 1.05)	LOW
TM: PBWr	LOW[8, 2]	LOW[7]	0.91 (0.01, 4.60)	LOW
TM:INCUPBWr	LOW[2,8]	-	5.17 (0.00, 5.45)	LOW
TM:RCARE	LOW[7]	LOW[2,8]	**0.12 (0.00, 0.62)**	LOW
PBWr:INCUPBWr	-	LOW[7]	1.39 (0.02, 5.92)	LOW
PBWr:RCARE	LOW[7]	MODERATE[2]	**0.23 (0.04, 0.55)**	MODERATE

INCUPBWr:RCARE	LOW[7]	-	2.27 (0.02, 9.31)	LOW

[1]Downgraded by one level for serious risk of bias due to possible selection bias in the included study (Bergman 2014).
[2]Downgraded by one level for serious imprecision due to OIS criteria not met.
[3]Downgraded by one level for serious imprecision due to confidence interval reaching ‘no difference’.
[4]Downgraded by one level for serious risk of bias due to possible selection bias in the included study (Chawla 2011).
[5]Downgraded by one level for serious risk of bias due to possible selection bias in one study (Hashim 2017).
[6]Downgraded by one level for serious inconsistency due to heterogeneity.
[7]Downgraded by two levels for very serious imprecision due to data from one study with small sample size and risk-benefit could not be decided.
[8]Downgraded by one level for serious risk of bias due to possible selection bias in the included study (Bergman 2014).
[*]Not downgraded for heterogeneity, since the heterogeneity is due to differences between small and large beneficial effects.
Note: The outcome is not downgraded for lack of blinding in any comparison, since it is an objective outcome and blinding is difficult for these interventions.