**NLS 5101 Consensus on Science**

## Consensus on Science

In the following paragraphs, where meaningful meta-analysis was possible, results are expressed as;

* relative risk (RR) with 95% confidence interval (95% CI)
* outcome/1000 infants with 95% CI when there are small differences (<1%)
* absolute risk difference (ARD) with 95% CI when there are larger differences
* number needed to treat or number needed to harm when the differences are statistically different and clinically meaningful.

***Comparison 1. Increased room temperature ≥23.0°C vs lower room temperature.***

Two RCTs {Duryea 2016 505.e1, Jia 2013 264} and three observational studies {de Almeida 2014 271, Kent 2008 325, Johannsen 2017 235} addressed whether higher ambient temperature vs. lower ambient temperature contributed to maintaining normal temperature in preterm infants. The data could not be combined in meta-analysis because the boundaries of higher and lower temperatures in each study differed (and overlapped) and because of differences in study design. Therefore, the results are summarized in narrative form, and no Evidence to Decision table was developed.

One RCT enrolling infants of all gestations compared operating room temperatures of 23°C (I) to 20°C (C). {Duryea 2016 505.e1} From enquiry to the authors, subgroup data were available for infants <28 weeks (n=8), 28-31 weeks’ (n=14) and 32-36 weeks’ gestation (n=124). The data for the first two subgroups (n=22) were evaluated for the current review and **could not exclude benefit or harm** for any outcome relevant to this review, **very low certainty evidence** downgraded for very serious risk of bias and very serious imprecision. Reported outcomes included death, mean body temperature, hypothermia <36.5°C and <36°C, hyperthermia >37.5°C, IVH any grade and >grade 2 and delivery room intubation. Nevertheless, the study as a whole (all gestations, including late preterm and term infants) found improved body temperatures and reduced rates of hypothermia when a temperature of 23°C was used. Of interest, rates of hypothermia were strikingly lower in the two groups of lower gestation than in the study as a whole. The authors suggested that this was likely to be because of more use of other measures to prevent hypothermia in infants of lower gestation, thereby masking an effect of ambient temperature.

In one study of infants of ≤32 weeks’ gestation, births were randomly assigned to a room with an ambient temperature of 24 to 26°C vs another with an ambient temperature of 20 to 23°C. {Jia 2013 264}. Among outcomes relevant to the review, the study reported only secondary outcomes. **Use of the higher temperature range increased body temperature on admission** (mean difference 0.5°C higher with higher room temperature 95% CI 0.15 to 0.85°C higher) and **reduced rates of moderate hypothermia <36°C** (RR 0.51 95% CI 0.32 to 0.80, 337 fewer per 1,000 were hypothermic 95% CI from 467 fewer to 137 fewer), **very low certainty evidence** downgraded for very serious risk of bias and serious imprecision from 1 study including 91 infants. {Jia 2013 264}. This study did not report rates of hyperthermia.

A cohort study compared outcomes for infants ≤31 weeks’ gestation during an epoch when ambient operating room temperatures were 20°C (n=73) with those during an epoch when operating room temperatures were 25 to 28°C (n=35), and reported mean body temperature, hypothermia <36.5°C, NEC, IVH>grade 2 and late onset neonatal sepsis. The study found that **rates of hypothermia <36.5°C were lower with use of higher room temperatures** (RR 0.69, 95% CI 0.51-0.94), **very low certainty evidence** downgraded for risk of bias and very serious imprecision. {Kent 2008 325} None of the other findings were statistically significant.

A retrospective observational study used logistic regression to examine risk factors for admission hypothermia <36.0°C in inborn infants of 23 to 33 weeks’ gestation. {de Almeida 2014 271} The study reported that **DR temperature <25°C** was among the variables that were **independently associated with risk of hypothermia** (odds ratio 1.44, 95% CI 1.10-1.88) ungraded observation from 1 retrospective study including 1764 infants. {de Almeida 2014 271}

One observational study compared ambient temperatures of **34°C to 28°C** and found **higher admission temperatures** (MD 0.4°C higher, 95% CI 0.24 to 0.5°C higher in infants exposed to the 34°C ambient temperatures) and **increased risk of hyperthermia** (RR 11.48 95% CI 1.54 to 85.54, ARD 115 more infants were hyperthermic per 1000 95% CI 6 more to 92 more), **very low certainty evidence** from 1 observational study including 202 infants. {Johannsen 2017 235}

***Comparison 2. Thermal mattress vs no thermal mattress***

The systematic review found four RCTs that examined use of a thermal mattress; because of critical differences in the comparator they were meta-analysed as:

*Two RCTs enrolling 174 participants that compared use of a thermal mattress vs no thermal mattress.* {Chawla 2011 780, McCarthy 2013 e135} In these studies, a plastic bag or wrap was used (by hospital protocol) for all infants {McCarthy 2013 e135} or for those <28 weeks’ gestation. {Chawla 2011 780} and all other measures to maintain normal temperature were also similar in both study arms.

*Two RCTs enrolling 77 infants that compared use of a thermal mattress vs use of a plastic bag or wrap.* {Mathew 2013 317, Simon 2011 33} The difference in exposure of the infants in each arm of these studies to plastic bags or wraps would have confounded the assessment of the effect of the thermal mattress itself. Therefore, for the purposes of this comparison, the evidence from these trials was downgraded for very serious indirectness and they were meta-analysed separately.

For the critical primary outcome **survival to hospital discharge**:

From the studies that assessed thermal mattress vs no thermal mattress, **clinical benefit or harm cannot be excluded** (RR 1.02, 95% CI 0.98 to 1.06), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Chawla 2011 780, McCarthy 2013 e135}

From the studies that assessed thermal mattress vs plastic bag or wrap, **clinical benefit or harm cannot be excluded** (RR 0.96, 95% CI 0.87 to 1.05), **very low certainty evidence** downgraded for very serious indirectness and serious imprecision from two RCTs enrolling 77 participants. {Mathew 2013 317, Simon 2011 33}

The important primary outcome **normothermia on admission** was reported by only one study which reported **possible clinical harm**  from use of a thermal mattress vs no thermal mattress (RR 0.53, 95% CI 0.34 to 0.81, ARD 363 fewer infants per 1000 were normothermic on admission 95% CI 147 fewer to 509 fewer infants per 1000, number needed to treat to harm (NNTH) 3 infants), **moderate certainty evidence** downgraded for serious imprecision from one RCT including 72 participants. {McCarthy 2013 e135}

*Secondary outcomes:*

For **mean body temperature on admission**, from the studies that assessed thermal mattress vs no thermal mattress, there was **possible clinical benefit** (mean body temperature was 0.46°C higher with use of a thermal mattress than with no thermal mattress, 95% CI 0.22°C higher to 0.6°C higher), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Chawla 2011 780, McCarthy 2013 e135}

For **mean body temperature on admission**, from the studies that assessed thermal mattress vs plastic bag or wrap, **clinical benefit or harm could not be excluded** (mean body temperature was 0.1°C higher with use of a thermal mattress than with a plastic bag or wrap, 95% CI 0.6°C lower to 0.8°C higher), **very low certainty evidence** downgraded for serious risk of bias and serious imprecision from two RCTs enrolling 174 participants. {Mathew 2013 317, Simon 2011 33}

For the important adverse outcome **hyperthermia** (temperature on admission > 37.5°C) there was **possible clinical harm** from use of a thermal mattress vs no thermal mattress (RR 2.77 95% CI 1.24 to 6.17, ARD 126 more infants were hyperthermic per 1000, 95% CI 17 more to 369 more, NNTH 8 infants) **low certainty evidence**, downgraded for risk of bias and imprecision from two RCTs enrolling 174 participants that compared thermal mattress to no thermal mattress {Chawla 2011 780, McCarthy 2013 e135}. In the RCTs comparing a thermal mattress without a plastic bag or wrap to a plastic bag or wrap without a thermal mattress, only one reported this outcome but the confidence intervals were so wide as to preclude any conclusion; (RR 12.29 95% CI 0.02 to 77700.79), **very low certainty evidence** downgraded for indirectness and imprecision from one RCT enrolling 36 participants. {Simon 2011 33}

**For other secondary outcomes**, only the evidence from the studies that compared thermal mattress to no thermal mattress is described here, {Chawla 2011 780, McCarthy 2013 e135} For these other secondary outcomes the results reported in either of the studies comparing thermal mattress with plastic bag or wrap, the very low certainty evidence from these studies {Mathew 2013 317, Simon 2011 33} would not have changed the conclusions of the review. Additional data for these studies is shown in the Evidence to Decision table.

For hypothermia on admission, BPD, IVH>grade 2, and NEC, confidence intervals crossed the line of no effect and were so wide that no conclusions can be drawn about clinical benefit or harm, **moderate or** **low certainty evidence** downgraded for serious risk of bias and imprecision). {Chawla 2011 780, McCarthy 2013 e135}

The systematic review also found **5 observational studies** that examined use of a thermal mattress combined with use of a plastic bag or wrap compared to use of a plastic bag or wrap alone in a total of 1027 infants, which contributed evidence for some of the systematic review outcomes. {Ibrahim 2010 795, Lewis 2011 160, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45}

For beneficial outcomes, the observational studies did not change the outcomes of the review, so they are not described further. Of note, for the **important adverse outcome** of **hyperthermia on admission** there was **evidence of possible harm** (RR 3.44 95% CI 1.91 to 6.20, ARD 113 more per 1,000 infants 95% CI from 42 more to 241 more infants, NNTH 9 infants), **moderate certainty evidence** from 4 studies including 703 infants, downgraded for very serious risk of bias. {Ibrahim 2009 256, McCarthy 2011 1534, Pinheiro 2011 357, Singh 2010 45}

***Comparison 3. Plastic bag or wrap vs no plastic bag or wrap***

For the critical primary outcome of **survival to hospital discharge,** there was **probable clinical benefit** from use of a plastic bag or wrap (RR 1.05 95% CI 1.00 to 1.10, ARD 41 more infants per 1,000 95% CI 0 fewer to 82 more infants per 1000, survived, number needed to treat to benefit (NNTB) 24 infants), **high certainty evidence** from 11 RCTs enrolling 1419 infants. {Ahmed 2013 169, Bhavsar 2015 23, Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Smith 2013 235, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750}

For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** from use of a plastic bag or wrap (RR 2.86 95% CI 1.66 to 4.91, ARD 238 more infants per 1,000 were normothermic, 95% CI 85 more to 501 more infants per 1000, NNTB 4 infants), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from 5 RCTs enrolling 449 infants. {Chantaroj 2011 S32, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}

*Secondary outcomes:*

For **mean body temperature on admission** to a neonatal unit, **there was possible clinical benefit** from use of a plastic bag or wrap.Mean temperaturemeasured by axilla was 0.65°C higher (95% CI 0.44 to 0.86°C ), and measured by rectum was 0.77°C (95% CI 0.44 to 0.86°C ), **low certainty evidence** downgraded for serious risk of bias and suspected publication bias from 12 RCTs enrolling 821 infants {Ahmed 2013 169, Bhavsar 2015 23, Chantaroj 2011 S32, Farhadi 2012 19, Gathwala 2010 24, Knobel 2005 304, Nimbalkar 2019 122, Reilly 2019 37, Rohana 2011 468, Smith 2013 235, Talakoub 2015 322, Trevisanuto 2010 914, Vohra 1999 547, Vohra 2004 750}

For **hypothermia < 36.5°C on admission** to a neonatal unit **there was probable clinical benefit** from use of a plastic bag or wrap (RR 0.64, 95% CI 0.50 to 0.82, ARD 313 fewer infants were hypothermic per 1000 95% CI 435 fewer to 157 fewer infants per 1000, NNTB 3 infants), **moderate certainty evidence** downgraded for serious risk of bias from 6 RCTs enrolling 489 infants. {Chantaroj 2011 S32, Farhadi 2012 19, Knobel 2005 304, Nimbalkar 2019 122, Rohana 2011 468, Trevisanuto 2010 914}

For **moderate hypothermia on admission** to a neonatal unit there was **possible clinical benefit** from use of a plastic bag or wrap (RR 0.40 ,95% CI 0.19 to 0.81, ARD 142 fewer infants had moderate hypothermia per 1000, 95% CI 192 fewer to 45 fewer infants per 1000, NNTB 5 infants), **very low certainty evidence** downgraded for serious risk of bias, serious indirectness and serious imprecision from 4 RCTs enrolling 1055 infants. {Bhavsar 2015 23, Reilly 2015 262, Rohana 2011 468, Smith 2013 235}

For **IVH >grade 2**, **clinical benefit or harm could not be excluded** (RR 0.76 95% CI 0.37 to 1.55), **moderate certainty evidence** downgraded for serious imprecision from 4 RCTs enrolling 972 infants. {Knobel 2005 304, Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **NEC, clinical benefit or harm could not be excluded** (RR 0.95, 95% CI 0.61 to 1.50), **low certainty evidence** downgraded for serious indirectness and imprecision from 3 RCTs enrolling 935 infants. {Reilly 2015 262, Reilly 2019 37, Rohana 2011 468}

For **late onset sepsis**, **clinical benefit or harm could not be excluded** (RR 0.92, 95% CI 0.76 to 1.11), **low certainty evidence** downgraded for serious inconsistency and serious imprecision from 3 RCTs enrolling 853 infants. {Reilly 2015 262, Reilly 2019 37, Smith 2013 235}

For **intubation in the delivery room,** **clinical benefit or harm could not be excluded** (RR 1.02, 95% CI 0.82 to 1.26), **low certainty evidence** downgraded for serious risk of bias and serious imprecision from 2 RCTs enrolling 174 infants. {Rohana 2011 468, Trevisanuto 2010 914}

For the **important adverse outcome** **hyperthermia (> 38.0****°C**) there was **probable harm** (RR 3.73 95% CI 1.81 to 7.69 ARD 29 more infants were hyperthermic per 1000, 95% CI 9 to 72 infants, NNTH 34), **moderate certainty evidence**, downgraded for serious risk of bias from 12 RCTs enrolling 1652 infants. {Bhavsar 2015 23, Farhadi 2012 19, Gathwala 2010 24, Knobel 2005 304, Lyu 2015 e150277, Nimbalkar 2019 122, Reilly 2015 262, Rohana 2011 468, Smith 2013 235, Trevisanuto 2010 914, Vohra 2004 750}

***Comparison 4. Cap vs no cap***

*Plastic cap (no bag) compared to no bag or cap:*

The systematic review found a single small three-arm RCT (with no serious risk of bias) that compared use of a plastic cap (similar to a shower cap) with use of a plastic bag (no cap, only head dried) or with no plastic cap or bag. {Trevisanuto 2010 914} For both the plastic cap and the no bag or cap groups, the infants’ bodies were dried and they were placed on prewarmed towels. All other interventions, including use of a prewarmed radiant warmer, were similar in both groups.

For the critical primary outcome of **survival**, **clinical benefit or harm could not be excluded** for the use of a plastic cap compared to no plastic cap. (RR 0.97 95% CI 0.84 to 1.12), **moderate certainty evidence** from 1 RCT including 64 participants. {Trevisanuto 2010 914}

For the important primary outcome of **normothermia on admission** to a neonatal unit, there was **possible clinical benefit** with the use of a plastic cap compared to no plastic cap (RR 6.00 95% CI 1.96 to 18.38, ARD 469 more infants per 1000 were normothermic, 95% CI 90 more to 1000 infants more, NNTB 2 infants), **moderate certainty evidence** from 1 RCT enrolling 64 participants. {Trevisanuto 2010 914}

*Secondary outcomes:*

For **mean body temperature** there was **probable clinical benefit** (MD 0.8°C higher (0.41 to 1.19°C higher with the use of a plastic cap compared to no plastic cap), **moderate certainty evidence** downgraded for imprecisionfrom 1 RCT with 64 participants {Trevisanuto 2010 914}

For **hypothermia < 36.5°C** there was **probable clinical benefit** (RR 0.48 95%CI 0.32 to 0.73, ARD 471 fewer infants were hypothermic per 1,000 95% CI 616 fewer to 245 fewer per 1000 infants) **moderate certainty evidence** downgraded for imprecisionfrom 1 RCT with 64 participants (RR 0.48 95%CI 0.32 to 0.73) {Trevisanuto 2010 914}

For the **outcome of delivery room intubation clinical benefit or harm cannot be excluded, (**RR 0.82 95% CI 0.49 to 1.37, ARD 96 fewer infants were intubated per 1000, 95% CI 271 fewer to 197 more per 1000), **moderate certainty evidence** downgraded for imprecisionfrom 1 RCT with 64 participants. {Trevisanuto 2010 914}

For the important adverse outcome **hyperthermia** **(> 37.5°C),** there were no events in either arm of the study, so the effect is not estimable. {Trevisanuto 2010 914}

*Cloth cap compared to no cap:*

An observational study compared the use of various interventions that included use of a plastic bag or wrap, a linen or woollen cap and a transport incubator. All infants were cared for under radiant warmers in the DR, and thermal mattresses were not used.  After adjustment for maternal and neonatal characteristics at birth, variables related to care in the DR and variables related to transport from the DR to the NICU, **not using a cloth cap was an independent risk factor for hypothermia <36.0°C at NICU admission**(adjusted odds ratio 0.55, 95% CI 0.39-0.78), ungraded observation from 1 retrospective study including 1764 infants. {de Almeida 2014 271}

***Comparison 5. Heating and humidification of gases used for resuscitation, vs no heating and humidification***

For the critical primary outcome of **survival to hospital discharge**, **clinical benefit or harm cannot be excluded** (RR 1.00 95% CI 0.94 to 1.0 ARD 0 fewer per 1,000 infants 95% CI 95% CI 55 fewer to 46 more per 1000 infants), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} This result was supported by an observational study enrolling 112 participants, which also produced evidence of very low certainty, downgraded for serious risk of bias and very serious imprecision. {te Pas 2010 e1427}

For the important primary outcome of **normothermia on admission** to a neonatal unit **clinical benefit or harm cannot be excluded** (RR 1.23 95% CI 0.93 to 1.62, ARD 305 more per 1,000 infants 95% CI 78 fewer to 791 more per 1000 infants), **very low certainty evidence** downgraded for serious risk of bias and inconsistency, and very serious imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245} An observational study enrolling 112 participants found **possible clinical benefit** from use of heated and humidified gases (RR 3.53, 95% CI 1.65 to 7.55), **low certainty evidence** downgraded for serious risk of bias and serious imprecision. {te Pas 2010 e1427}

*Secondary outcomes:*

For **mean body temperature on admission**, **there was possible benefit although the clinical significance is uncertain** (mean body temperature was 0.15°C higher 95% CI 0.03 to 0.26°C higher), **moderate certainty evidence** downgraded for serious risk of bias from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **any hypothermia <36.5°C** there was **possible clinical benefit** (RR 0.67 95% CI 0.51 to 0.87, ARD 128 fewer infants were hypothermic per 1,000, 95% CI 191 fewer to 51 fewer, NNTB 8 infants), **low certainty evidence** downgraded for serious risk of bias and imprecision from 2 RCTs enrolling 476 participants). {McGrory 2018 47, Meyer 2015 245}

For **mild hypothermia clinical benefit or harm cannot be excluded** (RR 0.61 95% CI 0.35 to 1.05), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **moderate hypothermia <36°C** there was **possible clinical benefit** (RR 0.58 95% CI 0.36 to 0.94 ARD 72 fewer infants were moderately hypothermic per 1,000, 95% CI 110 fewer to 10 fewer, NNTB 14 infants), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **RDS requiring surfactant clinical benefit or harm cannot be excluded** (RR 0.91 95% CI 0.76 to 1.09), **low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **delivery room intubation, clinical benefit or harm cannot be excluded** (RR 1.10 95% CI 0.88 to 1.39), **low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **BPD,** **clinical benefit or harm cannot be excluded** (RR 0.89 95% CI 0.70 to 1.13), **very low certainty evidence** downgraded for risk of bias, indirectness and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For **IVH >Grade 2,** there was **probable clinical benefit** (RR 0.39 95% CI 0.17 to 0.91, ARD 24 fewer infants had IVH >grade 2 per 1000 95% CI 68 fewer to 7 fewer infants per 1000, NNTB 42 infants), **moderate certainty evidence** downgraded for imprecision from 2 RCTs enrolling 476 participants). {McGrory 2018 47, Meyer 2015 245}

For **NEC** **clinical benefit or harm cannot be excluded** (RR1.55 CI 95% 0.45 to 5.31), **very low certainty evidence** downgraded for risk of bias and imprecision from 2 RCTs enrolling 476 participants. {McGrory 2018 47, Meyer 2015 245}

For the important adverse outcome of **hyperthermia (> 37.5°C**), **clinical benefit or harm could not be excluded** (RR 1.46 95% CI 0.60 to 3.52, ARD 41 more infants per 1000 were hypothermic with use of heated and humidified gases, 95% CI 36 fewer to 227 more), **very low certainty evidence** downgraded for risk of bias, inconsistency, and imprecision from 2 RCTs enrolling 476 infants). {McGrory 2018 47, Meyer 2015 245} The observational study provided low certainty evidence also supporting that clinical benefit or harm cannot be excluded. {te Pas 2010 e1427}

For other secondary outcomes, (receipt of positive pressure ventilation in the delivery room, late onset neonatal sepsis) outcome data were not reported.

***Comparison 6. Radiant warmer (with or without servo control)***

For this comparison, no studies were found that compared the use of a radiant warmer to no radiant warmer. The only study found for inclusion compared a servo-controlled radiant warmer to manual control. Evidence from the study showed that **when a servo-controlled radiant warmer was used compared to using a radiant warmer in manual mode** for preterm infants in the delivery room:

For the critical primary outcome of **survival to hospital discharge**, **clinical benefit or harm could not be excluded** (RR 1.05, 95% CI 0.99 to 1.11, ARD 44 more infants per 1000 survived with the use of servo control 95% CI 9 fewer to 97 more per 1000 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

For the important primary outcome of **normothermia on admission to a neonatal unit**, **clinical benefit or harm could not be excluded** (RR 0.94, 95% CI 0.75 to 1.17, ARD 25 fewer infants per 1000 were normothermic on admission with use of servo control, 95% CI 106 fewer to 72 more per 1000 infants), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

*Secondary outcomes:*

For **mean body temperature on admission, there was probable clinical harm** (mean difference (MD) 0.2°C lower 95% CI 0.33 to 0.07 lower with use of servo control), **moderate certainty evidence** downgraded for imprecision from 1 RCT enrolling 450 participants. {Cavallin 572}

For **any hypothermia < 36.5°C there was probable clinical harm** (RR 1.20 95% CI 1.01 to1.42, ARD 100 more per 1,000 had hypothermia <36.5°C with use of servo control, 95% CI 5 more to 209 more infants per 1000, NNTH 10 infants), **moderate certainty evidence** downgraded for imprecision from 1 trial enrolling 450 infants. {Cavallin 572} As shown by the next two outcomes, the main contribution to this outcome was from infants who had mild hypothermia/cold stress (36.0 to 36.4°C).

For **mild hypothermia (36.0 to 36.4°C)** there was **probable clinical harm** (RR 1.48 (95% CI 1.09 to 2.01, ARD 107 more per 1,000 had mild hypothermia with use of servo control 95% CI 20 more to 224 more per 1000, NNTH 9 infants), **moderate certainty evidence**, downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572}

For **moderate hypothermia < 36.0**°**C, clinical benefit or harm cannot be excluded** (RR 0.97 (95% CI 0.71 to 1.31, ARD 8 fewer infants per 1000 were hypothermic with use of servo control, 95% CI 80 fewer to 85 more per 1000), **moderate certainty evidence,** downgraded for serious imprecision from 1 RCT enrolling 450 infants) {Cavallin 572}

For **IVH > grade 2,** **clinical benefit or harm cannot be excluded** (RR 0.87 95% CI 0.42 to 1.78, ARD 9 fewer infants per 1000 had IVH with use of servo control 95% CI 39 fewer to 52 more per 1000 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants). {Cavallin 572}

For **late onset neonatal sepsis, clinical benefit or harm cannot be excluded** (RR 1.39 95% CI 0.89 to 2.18, ARD 49 more infants per 1000 had sepsis with use of servo control 95% CI 14 fewer to 147 more per 1000), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants). {Cavallin 572}

For **bronchopulmonary dysplasia, clinical benefit or harm cannot be excluded** (RR 0.98 95%CI 0.68 to 1.41, ARD 4 fewer per 1000 had BPD with use of servo control 95% CI 67 fewer to 86 more per 1000), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572}

For **delivery room intubation, there was possible clinical benefit** (RR 0.67 95%CI0.46 to 0.93, ARD 79 fewer infants per 1000 were intubated 95% CI 130 fewer to 7 fewer per 1000, NNTB 13 infants), **moderate certainty evidence** downgraded for serious imprecision from 1 RCT enrolling 450 infants. {Cavallin 572} However, there was no difference in the use of delivery room nasal positive pressure ventilation or in the combined outcome of intubation plus nasal positive pressure ventilation.

***For the following comparisons***, or for any combination of these interventions, the systematic review found no RCTs or observational studies that allowed assessment of the effectiveness of the intervention.

***Comparison 7: Early monitoring of temperature***

This comparison aimed to determine whether early or frequent checking of temperature during or immediately after initial resuscitation improved temperatures on admission to a NICU (e.g., by allowing prompt initiation of other interventions to improve temperature. No RCTs or observational studies that addressed this comparison were found. Early measuring of temperature was a component of several QI studies, but the design and reporting of the studies precluded assessment of the magnitude of effect of this specific intervention.

***Comparison 8. Warm bags of fluid vs no warm bags of fluid***

No RCTs or observational trials provided data for this comparison.

***Comparison 9. Swaddling vs no swaddling***

No RCTs or observational trials provided data for this comparison.

***Comparison 10. Skin to skin care vs no skin to skin care***

Only two small RCTs were identified, and they reported only secondary outcomes. {Bergman 2004 779, Linnér 2020 697} Therefore an evidence to decision table and treatment recommendations were not developed.

For the **outcome of mean body temperature** **clinical benefit or harm cannot be excluded** (MD 0.59°C higher with use of skin to skin care 95% CI 1.17°C lower to 2.36°C higher) **very low certainty evidence** downgraded for very serious risk of bias and inconsistency, and serious imprecision from 2 RCTs enrolling 62 infants. {Bergman 2004 779, Linnér 2020 697}

One of these trials including 55 infants found no difference in rates of RDS treated with surfactant. {Linnér 2020 697}

***Subgroup analyses***

The only comparison for which there were sufficient data for formal subgroup analysis was use of a **plastic bag or wrap vs no plastic bag or wrap;**

*For subgroup analysis by gestational age groups: (<28 weeks vs 28-33+6 weeks)* a plastic bag or wrap was more efficacious in preventing moderate hypothermia in the lower gestation subgroup (test for subgroup differences (random effects): χ2 = 5.27, df = 1 (p = 0.02)). For all other outcomes results of tests for subgroup differences were not statistically significant.

*For subgroup analysis high income vs middle income country setting* a plastic bag or wrap was more efficacious in preventing moderate hypothermia inhigh income countries, (test for subgroup differences (random effects): χ2 = 5.20, df =1 (p =0.02)). For all other outcomes results of tests for subgroup differences were not statistically significant.

*For subgroup analysis by setting high resource vs low resource setting* there were no data.

*For subgroup analysis by site (inborn vs outborn)* the tests for subgroup differences were not statistically significant.

***Observational studies and quality improvement studies***

In addition to the RCTs or observational studies described above, the systematic review found 29 studies that used quality improvement (QI) methodology. {Aley-Raz 2020 476, Ashmeade 2016 73, Billimoria 2013 455, Caldas 2018 368, Castrodale 2014 9, Choi 2018 239, Cleator 2022 75, Croop 2020 530, DeMauro 2013 e1018, Ferretti 2021 e240, Frazer 2018 520, Frazer 2021 , Godfrey 2013 311, Harer 2017 1242, Harriman 2018 462, Keir 2022 375, Lee 2008 754, Manani 2013 8, Peleg 2019 387, Pinheiro 2014 e218, Reuter 2014 , Russo 2014 31055, Sharma 2020 1851, Sivanaridan 2016 , Sprecher 2021 270, Vinci 2018 e125, Wlodaver 2016 182, Yip 2017 922, Young 2021 } Most of the (QI) studies demonstrated improvements.

Some examined multifaceted interventions either as a bundle of care or sequentially introduced using ‘plan-do-study-act’ cycles. These studies did not allow any definite conclusions to be drawn about the effectiveness of any component intervention. Any assessment of component interventions would have been at critical risk of bias because of confounding from other co-interventions. Because of this and a high degree of heterogeneity in the interventions used, no meta-analyses could be performed, and individual studies are difficult to interpret.

Nevertheless, taken together, these QI studies suggest that hypothermia can be a common problem among preterm infants in both low-income and high-income settings. They also suggest that multidisciplinary teams, working together to recognize local place, people, policy and procedure contributors to risk, and to test the effect of locally devised solutions, may be an effective way to reduce rates of hypothermia.