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Appendix 1: Search strategy

MEDLINE: 802 articles

Scopus: 226 articles

Web of Science: 398 articles

Clinicaltrials.gov: 121 articles

CENTRAL: 47 articles

Additional sources (Google Scholar/snowball method): 6 articles

Total: 1,600 articles

Duplicates: 418 articles

Screened: 1,182 articles

Retrieved in full-text: 43 studies

Excluded with reasons: 7 studies

Included in the qualitative and quantitative synthesis: 36 studies

Intervention:

-Thin catheter administration: 28 studies

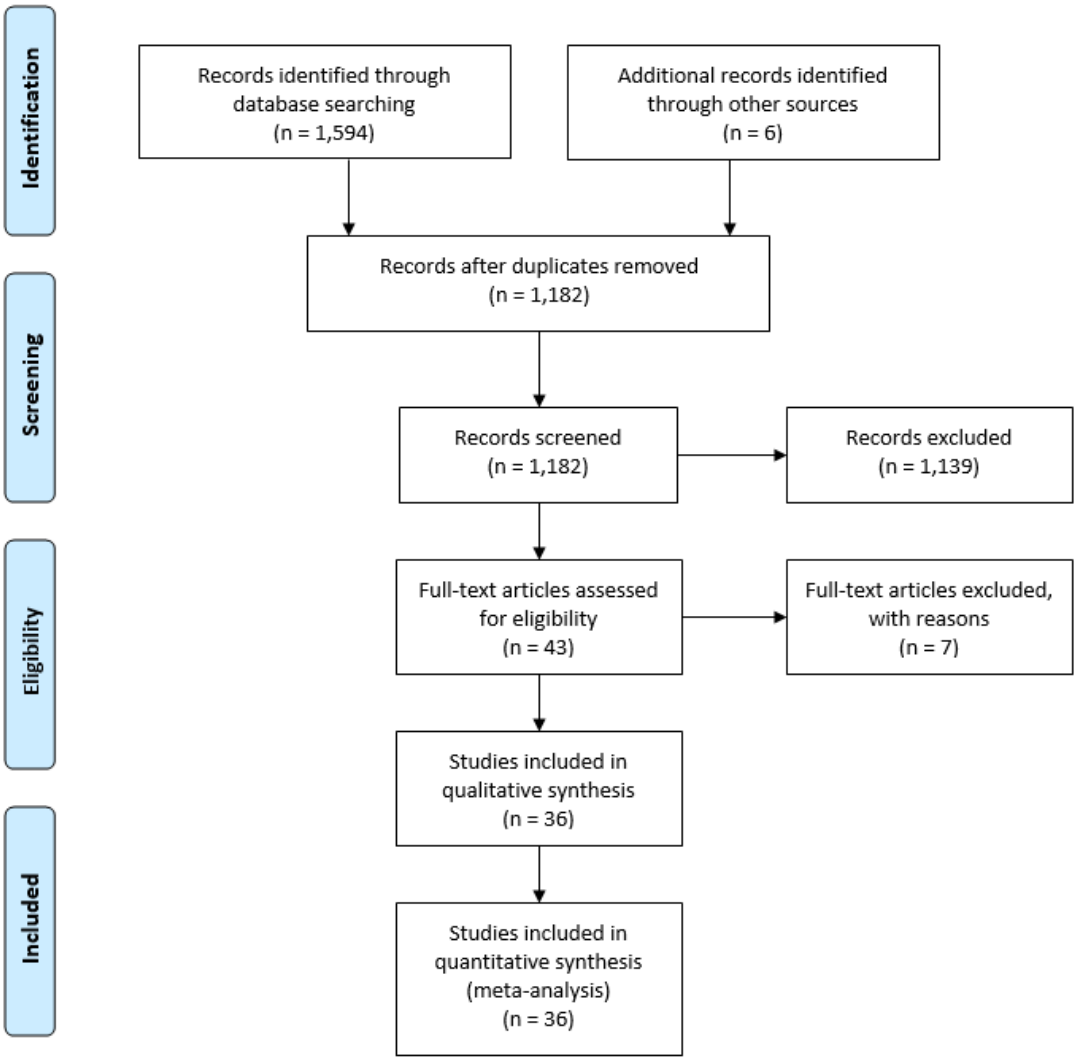
-Laryngeal mask: 5 studies

-Nebulization: 2 studies

-InSurE: 32 studies

-Pharyngeal instillation: 1 study

-No surfactant: 5 studies



Suppl. Figure 1. Search plot diagram

Appendix 2: Study characteristics

Year; Author	Study design	Inclusion criteria	Exclusion criteria	Method of SURE	Use of forceps	Pre-medication	Surfactant dose	Use of nCPAP	Comparator	Outcomes of interest
2019; Minocchieri	RCT	•Gestational age: 29-34 weeks •RDS diagnosis	•Major congenital abnormalities •Cardiopulmonary failure •History of intubation or surfactant •Pneumothorax at enrollment	Nebulization	NA	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h •BPD •Pneumothorax •IVH grade III/IV
2019; Legge	RC	•Birth weight >500 g •Gestational age >24 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter	NR	NR	NR	Yes	InSurE	•Mortality •Pneumothorax • IVH grade >II •NEC •hs-PDA
2019; Jena	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube or 16G Angiocath	No	No	Neosurf®, 5 ml/kg	Yes	InSurE	•Mortality •MV within 72h •BPD •Pneumothorax •IVH grade ≥II •NEC stage ≥2 •hs-PDA
2019; Isidro	RC	•Gestational age <32 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter	NR	NR	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •MV within 72h •NEC •hs-PDA •Repeat dose
2019; Hanke	PC	•Gestational age: 26-32 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Repeat dose
2019; Halim	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube	No	No	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •MV •Pneumothorax •hs-PDA
2019; Buyuktiryaki	RC	•Gestational age: 25-29 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2019; Berneau	RC	•Gestational age <30 weeks	•Major congenital abnormalities	Thin catheter/ 4F suction catheter	Yes	Atropine/ Ketamine	200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w •Pneumothorax •PVL •Repeat dose
2018; Seo	RC	•Gestational age >30 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 4-5F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV •BPD at 36w •Pneumothorax

									•IVH grade ≥II •NEC stage ≥2 •hs-PDA •Repeat dose
2018; Ramos-Navarro	PC	•Gestational age <32 weeks •RDS diagnosis	•No surfactant administration	Thin catheter/ 5F nasogastric tube	No	No	Survanta®, 200 mg/kg	Yes	InSurE	•Repeat dose
2018; Langhammer	Cross-sectional	•Birth weight <1500 g	•No surfactant administration	Thin catheter/ nasogastric tube	Yes	No	Curosurf® or Survanta®	Yes	InSurE	•MV •BPD at 36w •Pneumothorax •IVH grade >II •PVL •NEC stage ≥2 •hs-PDA
2018; Hartel	PC	•Birth weight <1500 g •Gestational age: 22-29 weeks	•Major congenital abnormalities	Thin catheter/ 5F nasogastric tube	NR	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •BPD at 36w •IVH grade ≥II •NEC stage≥2 •PVL •hs-PDA
2018; Dargaville	RC	•Gestational age: 29-32 weeks •RDS diagnosis	•Major congenital abnormalities •PPROM ≥14 days	Thin catheter	NR	NR	Curosurf®,100 - 200 mg/kg	Yes	No surfactant	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II
2017; Tomar	PC	•Gestational age: 24-34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Survanta®, 100 mg/kg	Yes	InSurE	•Mortality •BPD at 36w •Pneumothorax •IVH •NEC stage ≥2 •PDA •Repeat dose
2017; Templin	PC	•Gestational age: 24-26 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter/ 5F suction catheter	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2017; Roberts	RCT	•Gestational age: 28-36 weeks •Birth weight >1250 g •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score <5 •History of intubation or surfactant	Laryngeal mask	NA	Atropine, sucrose	Curosurf®, 200 mg/kg	Yes	No surfactant	•Mortality •MV •Pneumothorax •IVH grade >II •PVL •Repeat dose
2017; Olivier	RCT	•Gestational age: 32-37 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation •Pneumothorax at enrollment	Thin catheter/ 5F nasogastric tube	Yes	Atropine/ Fentanyl	Survanta®, 100 mg/kg	Yes	InSurE	•MV •Pneumothorax •Repeat dose

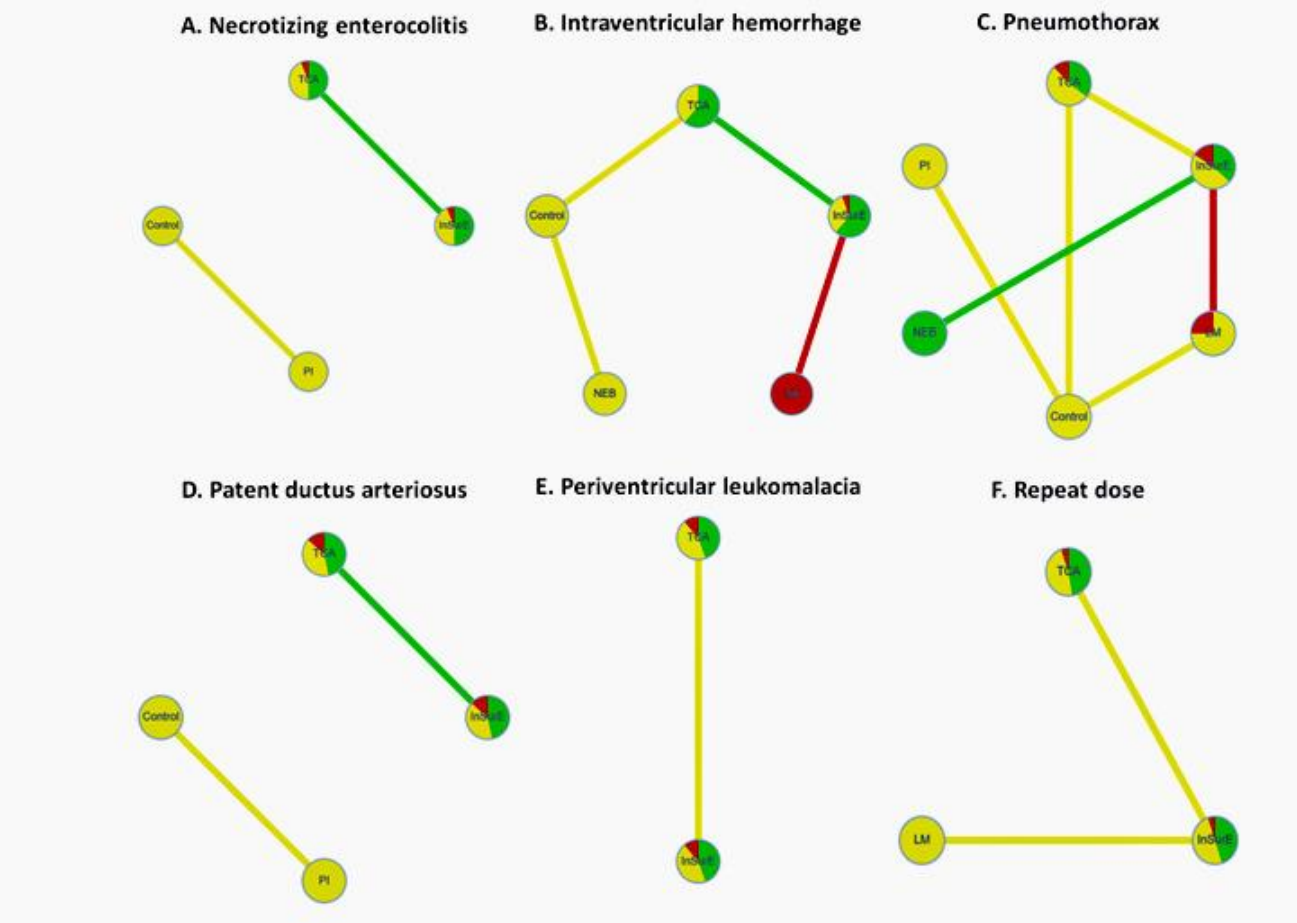
2017; Bertini	PC	•Gestational age ≤33 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade >II
2017; Barbosa	RCT	•Birth weight >1000 g •Gestational age: 28-35 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation •5-minute Apgar score <3 •History of chorioamnionitis •Fever/rupture of membranes >18 h	Laryngeal mask	NR	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h •Pneumothorax •IVH •Repeat dose
2016; Li	RC	•Gestational age: 27-32 weeks •RDS diagnosis	•Major congenital abnormalities •Perinatal asphyxia	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •BPD •IVH •NEC •PVL
2016; Canals Candela	RC	•Gestational age <34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ Angiocath	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•MV within 72h
2015; Teig	RC	•Gestational age <29 weeks •RDS diagnosis	•Major congenital abnormalities	Thin catheter/ 4F suction catheter	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •hs-PDA •Repeat dose
2015; Pinheiro	RCT	•Gestational age: 29-37 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score ≤3 •History of intubation or surfactant •Birth weight <1000 g •Severe RDS	Laryngeal mask	NA	Atropine	Infasurf®, 3 ml/kg	Yes	InSurE	•Mortality •BPD at 36w •Pneumothorax
2015; Mohammadizadeh	RCT	•Birth weight: 1000-1800 g •Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score ≤4 •History of chorioamnionitis •Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	No	Atropine	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •IVH •Repeat dose
2015; Kribs	RCT	•Gestational age: 23-26 weeks •RDS diagnosis	•Major congenital abnormalities •Cardiopulmonary failure	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •NEC stage >2 •PVL •hs-PDA
2015; Göpel	PC	•Birth weight <1500 g •Gestational age <32 weeks	•Need of intubation for resuscitation	Thin catheter/ nasogastric tube	Yes	No	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade >II •PVL •NEC stage >2
2015; Bao	RCT	•Gestational age: 28-32 weeks •RDS diagnosis	•Major congenital abnormalities •History of intubation	Thin catheter/ 16G Angiocath	No	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV within 72h •BPD at 36w •Pneumothorax •Repeat dose

2014; Krajewski	RC	•Gestational age <36 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade ≥II •NEC •PDA
2014; Aguar	PC	•Gestational age: 24-35 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 6F nasogastric tube	Yes	Atropine	Curosurf®, 100 mg/kg	Yes	InSurE	•Mortality •MV •BPD •IVH grade >II •NEC •PDA •Repeat dose
2013; Sadeghnia	RCT	•RDS diagnosis	•Major congenital abnormalities •Perinatal asphyxia	Laryngeal mask	NA	No	Survanta®, 100 mg/kg	Yes	InSurE	•MV •Pneumothorax •Repeat dose
2013; Mirnia	RCT	•Gestational age: 27-32 weeks •RDS diagnosis	•Major congenital abnormalities •5-minute Apgar score <6	Thin catheter/ 5F nasogastric tube	No	Atropine	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •BPD at 36w •Pneumothorax •IVH grade ≥II •NEC stage ≥2 •PDA •Repeat dose
2013; Klebermass-Schrehof	RC	•Gestational age: 23-27 weeks •RDS diagnosis	•Need of intubation for resuscitation	Thin catheter/ 4F nasogastric tube	Yes	No	Curosurf®, 200 mg/kg	Yes	InSurE	•Mortality •MV •Pneumothorax •IVH grade >II •NEC stage ≥2 •PVL •hs-PDA •Repeat dose
2013; Kanmaz	RCT	•Gestational age ≤34 weeks •RDS diagnosis	•Major congenital abnormalities •Need of intubation for resuscitation	Thin catheter/ 5F nasogastric tube	No	No	Curosurf®, 100 mg/kg	Yes	InSurE	•MV •BPD at 36w •Pneumothorax •Repeat dose
2013; Attridge	RCT	•RDS diagnosis •Birth weight >1200 g	•Major congenital abnormalities •History of intubation or surfactant •Pneumothorax at enrollment	Laryngeal mask	N/A	No	Infasurf®, 3 ml/kg	Yes	No surfactant	•MV •Pneumothorax
2000; Berggren	RCT	•Gestational age <36 weeks •RDS diagnosis	•Major congenital abnormalities •a/A p_aO_2 <15	Nebulization	NA	No	480 mg	Yes	No surfactant	•MV •IVH
1987; Ten Centre Study Group	RCT	•Gestational age: 25-29 weeks •RDS diagnosis	•Major congenital abnormalities	Pharyngeal instillation	NA	No	100 mg	No	No surfactant	•Mortality •Pneumothorax •NEC •PDA

Suppl. Table 1. Methodological characteristics of the included studies. *nCPAP: nasal continuous positive airway pressure; NEC: necrotizing enterocolitis; PVL: periventricular leukomalacia; BPD: bronchopulmonary dysplasia; hs-PDA: hemodynamically significant patent ductus arteriosus; InSurE:*

intubation, surfactant administration and extubation; IVH: intraventricular hemorrhage; MV: mechanical ventilation; NA: not applicable; NR: not reported; PC: prospective cohort; PROM: premature rupture of membranes; RC: retrospective cohort; RCT: randomized controlled trial; RDS: respiratory distress syndrome; SURE: surfactant administration without extubation;

Appendix 3: Network plots

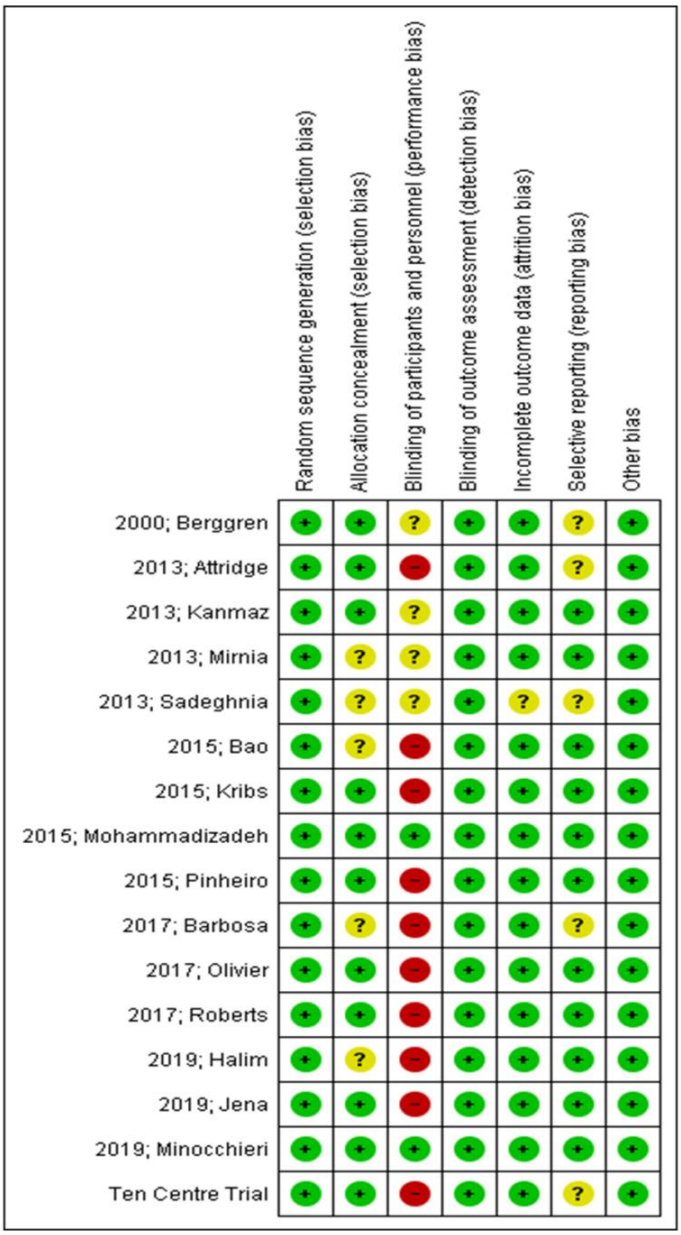


Suppl. Figure 2. Network plots of the secondary outcomes.

The colors of circles are proportional to the risk of bias in studies including the treatment. Control refers to no surfactant administration.

InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration

Appendix 4: Risk of bias evaluation



Suppl. Figure 3. Quality assessment of randomized controlled trials.

Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool								
Year; Author	***Bias due to confounding***	***Bias in selection of participants into the study***	***Bias in classification of interventions***	***Bias due to deviations from intended interventions***	***Bias due to missing data***	***Bias in measurement of outcomes***	***Bias in selection of the reported result***	***Overall bias***
2019; Legge	**Moderate**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**	**Moderate**
2019; Isidro	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2019; Hanke	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Moderate**
2019; Buyuktiryaki	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2019; Berneau	**Low**	**Low**	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Moderate**
2018; Seo	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2018; Ramos-Navarro	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Moderate**
2018; Langhammer	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2018; Hartel	**High**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**High**
2018; Dargaville	**Moderate**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2017; Tomar	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2017; Templin	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2017; Bertini	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2016; Li	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**
2016; Canals Candela	**Low**	**Low**	**Low**	**Low**	**NI**	**Low**	**Low**	**Low**
2015; Teig	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2015; Göpel	**Low**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**
2014; Krajewski	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2014; Aguar	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
2013; Klebermass-Schrehof	**Moderate**	**Moderate**	**Low**	**Low**	**Low**	**Low**	**Low**	**Moderate**

Suppl. Table 2. Quality assessment of observational studies.
NI: no information

Appendix 5: Meta-regression analysis

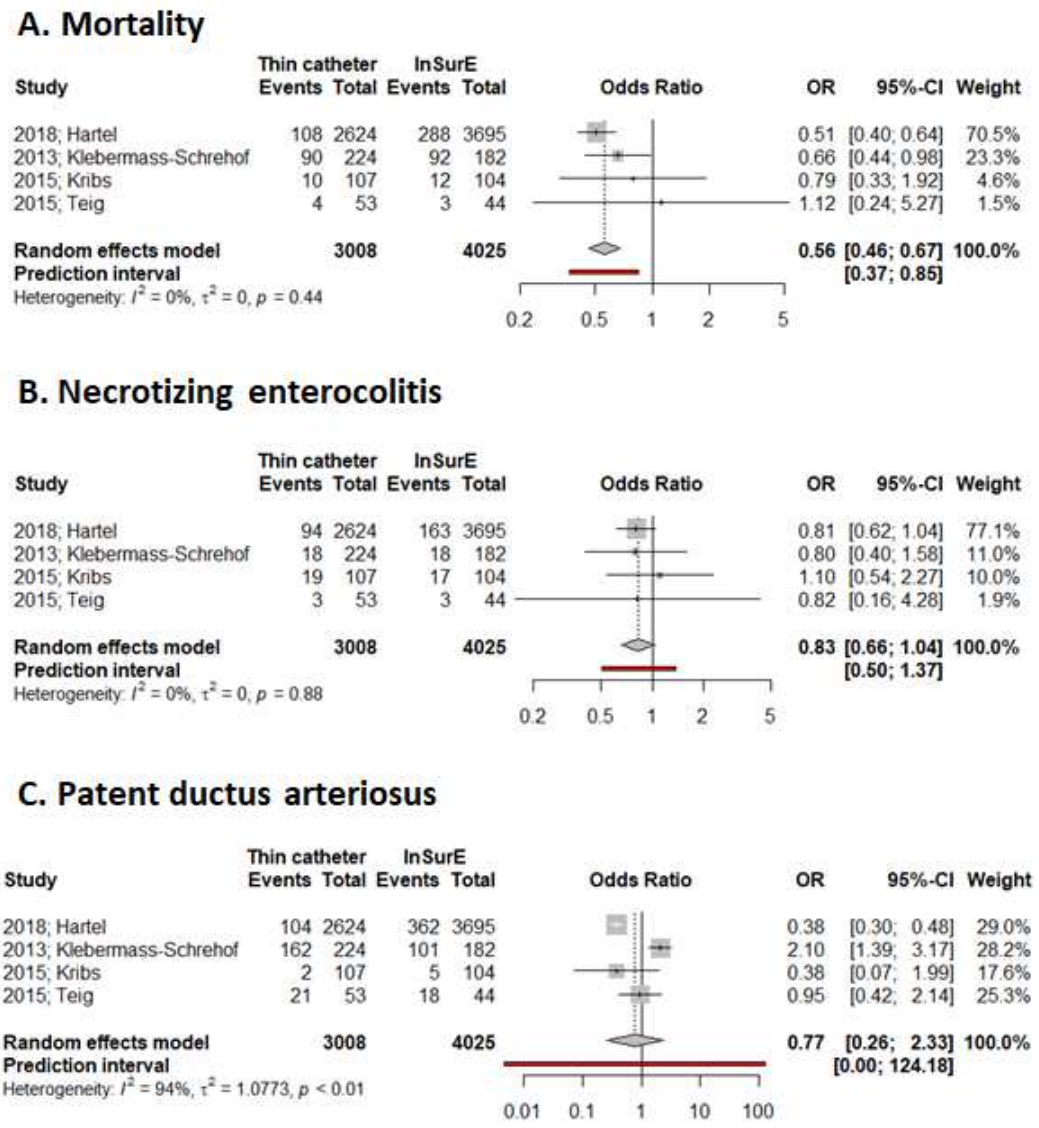
Comparison	RCT	Sample size	Type of surfactant	Premedication	Use of forceps
Mortality	-0.196 (-0.859 to 0.366)	0.459 (-0.288 to 1.200)	-0.094 (-0.805 to 0.615)	-0.275 (-1.018 to 0.327)	0.088 (-0.536 to 0.823)
Need of MV	-0.339 (-1.594 to 0.817)	0.484 (-0.674 to 1.713)	-0.747 (-2.451 to 0.983)	0.404 (-0.901 to 1.637)	-0.523 (-1.741 to 0.789)
BPD	-0.145 (-0.907 to 0.604)	0.673 (-0.112 to 1.464)	-0.525 (-2.975 to 1.303)	0.778 (-0.081 to 1.628)	0.443 (-0.360 to 1.268)
NEC	-0.313 (-1.434 to 0.459)	0.086 (-0.822 to 1.130)	0.097 (-0.689 to 1.122)	-0.835 (-2.487 to 0.320)	0.873 (-0.096 to 1.963)
IVH	-0.099 (-0.927 to 0.732)	0.772 (-0.143 to 1.669)	-0.344 (-1.327 to 0.457)	0.322 (-0.545 to 1.213)	-0.124 (-0.850 to 0.719)
Pneumothorax	-0.374 (-1.123 to 0.380)	0.353 (-0.537 to 1.287)	-0.604 (-1.764 to 0.527)	0.217 (-0.732 to 1.177)	0.418 (-0.407 to 1.258)
PVL	0.153 (-0.721 to 0.974)	-0.170 (-1.792 to 1.259)	0.011 (-14.825 to 15.767)	0.780 (-0.326 to 2.054)	0.039 (-1.012 to 1.128)
PDA	0.098 (-0.697 - 0.876)	0.178 (-0.579 to 0.923)	0.202 (-0.563 to 1.010)	0.100 (-0.646 to 0.849)	-0.092 (-0.806 to 0.554)
Repeat dose	-0.587 (-1.690 to 0.589)	0.186 (-1.021 to 1.397)	-0.158 (-1.270 to 0.980)	0.104 (-1.099 to 1.347)	-0.109 (-1.427 to 1.143)

Suppl. Table 3. Outcomes of the meta-regression analysis.

Data expressed as β coefficient (95% confidence intervals). InSurE was set to be the reference treatment. No significant associations were noted.

PVL: periventricular leukomalacia; IVH: intraventricular hemorrhage; MV: mechanical ventilation; BPD: bronchopulmonary dysplasia; NEC: necrotizing enterocolitis; PDA: patent ductus arteriosus; RCT: randomized controlled trials

Appendix 6: Gestational age <28 weeks



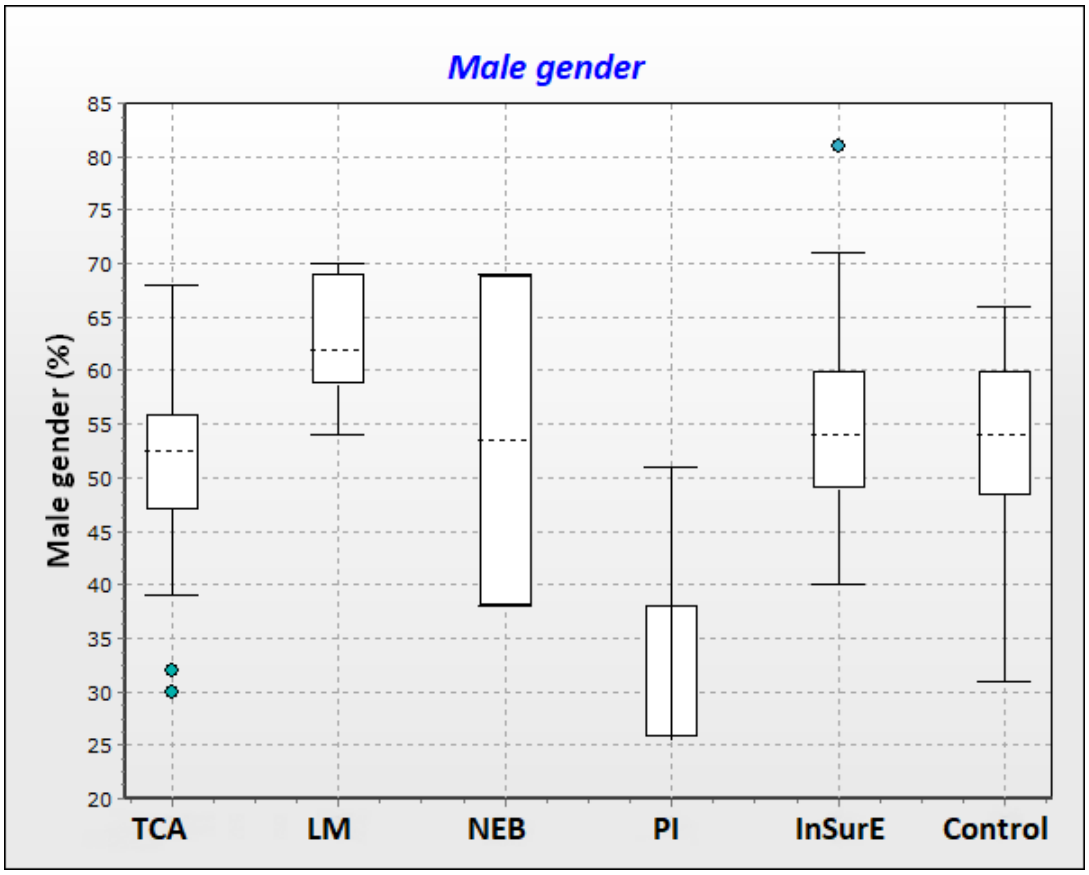
Suppl. Figure 4. Outcomes of sensitivity analysis examining neonates with gestational age <28 weeks. Analysis was based on direct evidence.

Appendix 7: Randomized vs. non-randomized evidence

Outcome	Randomized controlled trials	Observational studies
Mortality	0.62 (0.36-1.06)	0.64 (0.53-0.76) *
Mechanical ventilation	0.39 (0.26-0.60) *	0.46 (0.24-0.88) *
Bronchopulmonary dysplasia	0.54 (0.29-1.01)	0.54 (0.43-0.68) *
Necrotizing enterocolitis	0.33 (0.05-2.02)	0.77 (0.62-0.96) *
Periventricular leukomalacia	N/A	0.65 (0.52-0.81) *
Pneumothorax	0.59 (0.33-1.03)	0.91 (0.63-1.33)
Intraventricular hemorrhage	0.70 (0.40-1.23)	0.84 (0.54-1.29)
Patent ductus arteriosus	1.05 (0.62-1.77)	0.86 (0.50-1.49)
Repeat surfactant dose	0.90 (0.55-1.46)	1.65 (0.77-3.53)

Suppl. Table 4. Outcomes of randomized controlled trials and observational studies regarding the comparison of thin catheter administration and InSurE.
*Data expressed as odds ratio (95% confidence intervals). *p-value <0.05; N/A: not applicable*

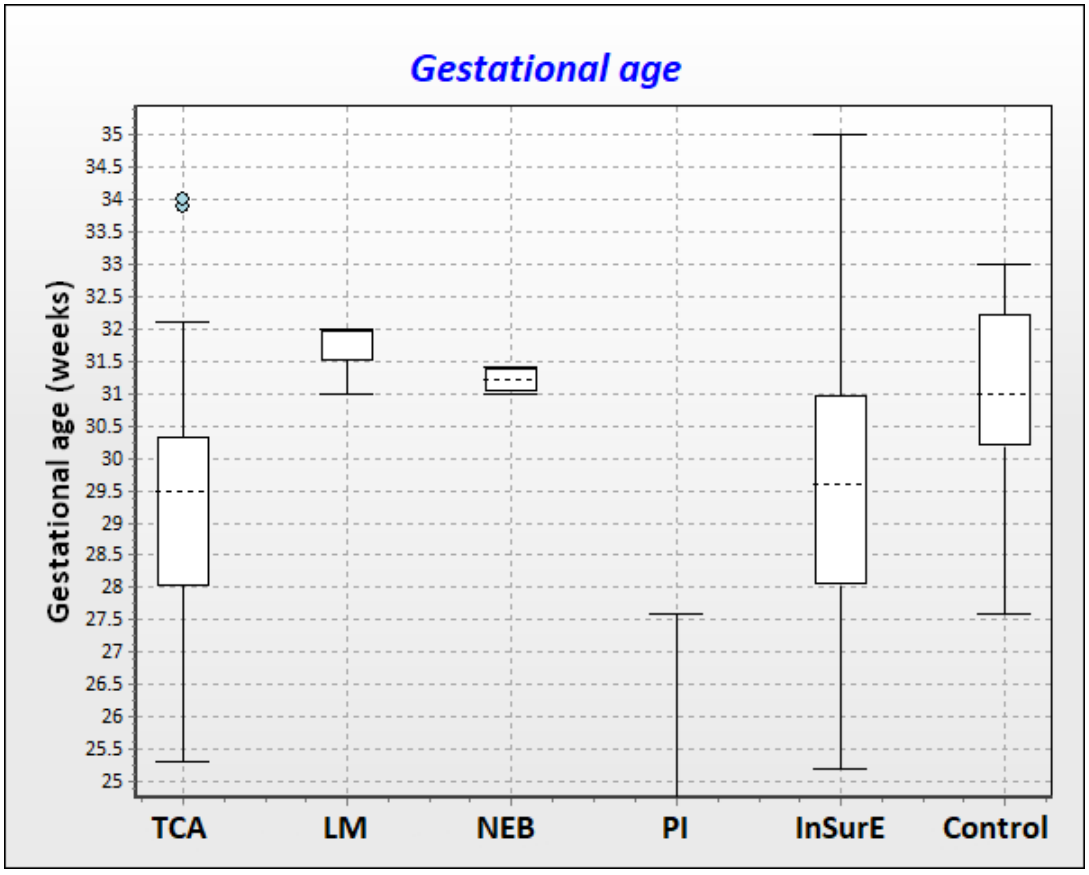
Appendix 8: Transitivity assessment



Suppl. Figure 5. Boxplot of gender distributions among different interventions.

No significant difference was noted (overall median: 54, χ^2: 7.16, *p-value*=0.21).

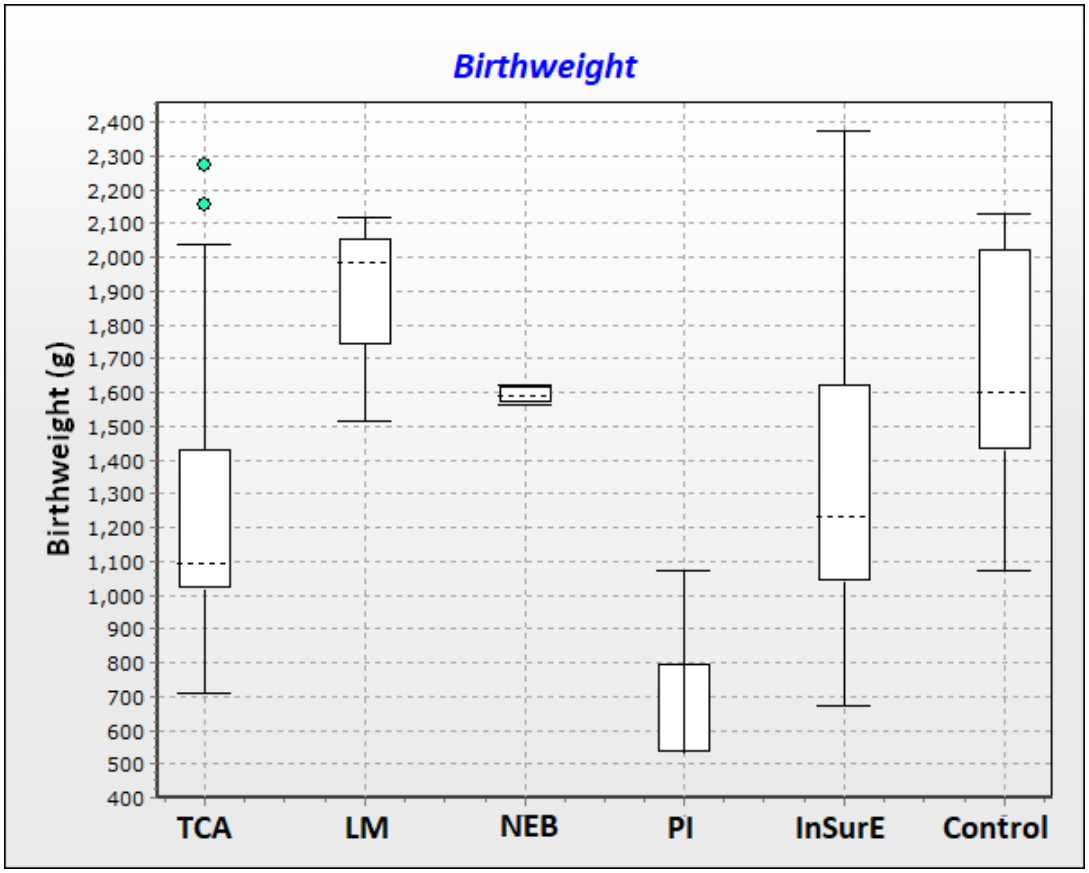
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 6. Boxplot of gestational age distributions among different interventions.

No significant difference was noted (overall median: 29.6, χ^2: 10.38, *p-value*=0.07).

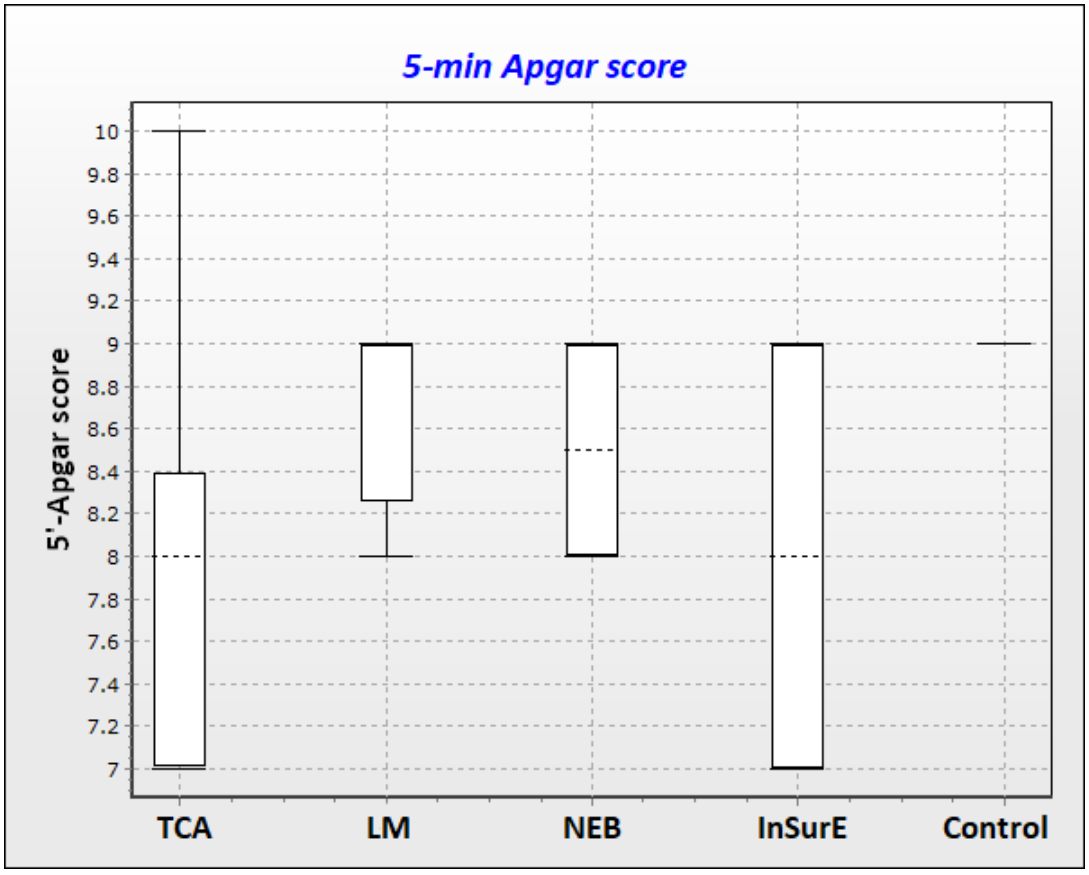
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 7. Boxplot of birthweight distributions among different interventions.

No significant difference was noted (overall median: 1.29, χ^2: 10.37, *p-value*=0.07).

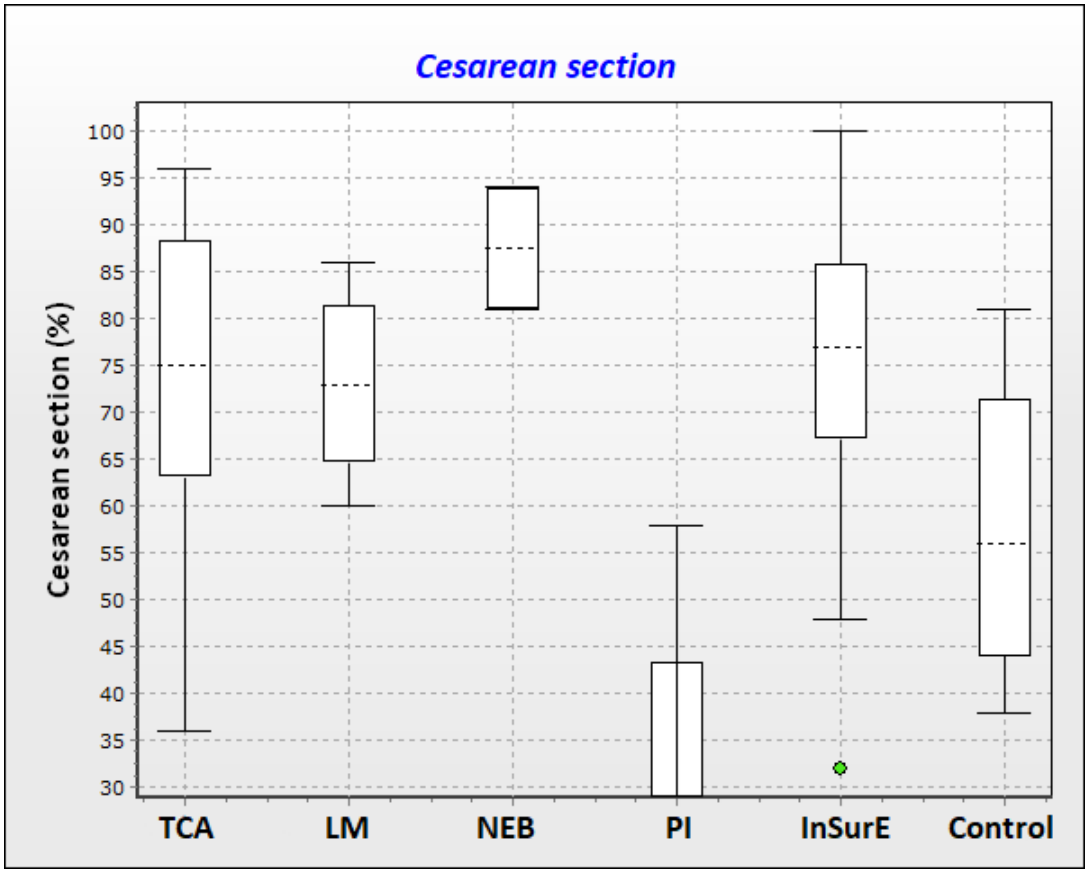
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 8. Boxplot of 5-min Apgar score distributions among different interventions.

No significant difference was noted (overall median: 8, χ^2: 10.01, *p-value*=0.16).

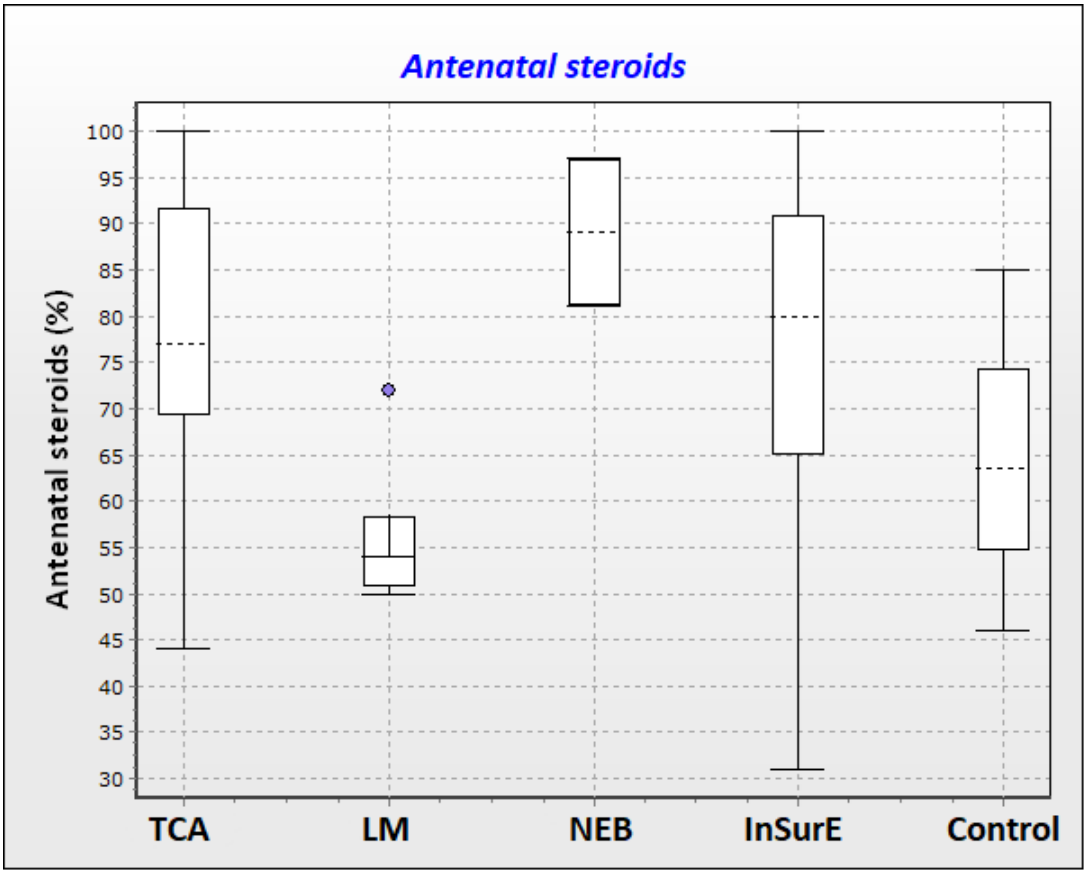
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 9. Boxplot of cesarean section distributions among different interventions.

No significant difference was noted (overall median: 77, χ^2: 4.54, *p-value*=0.34).

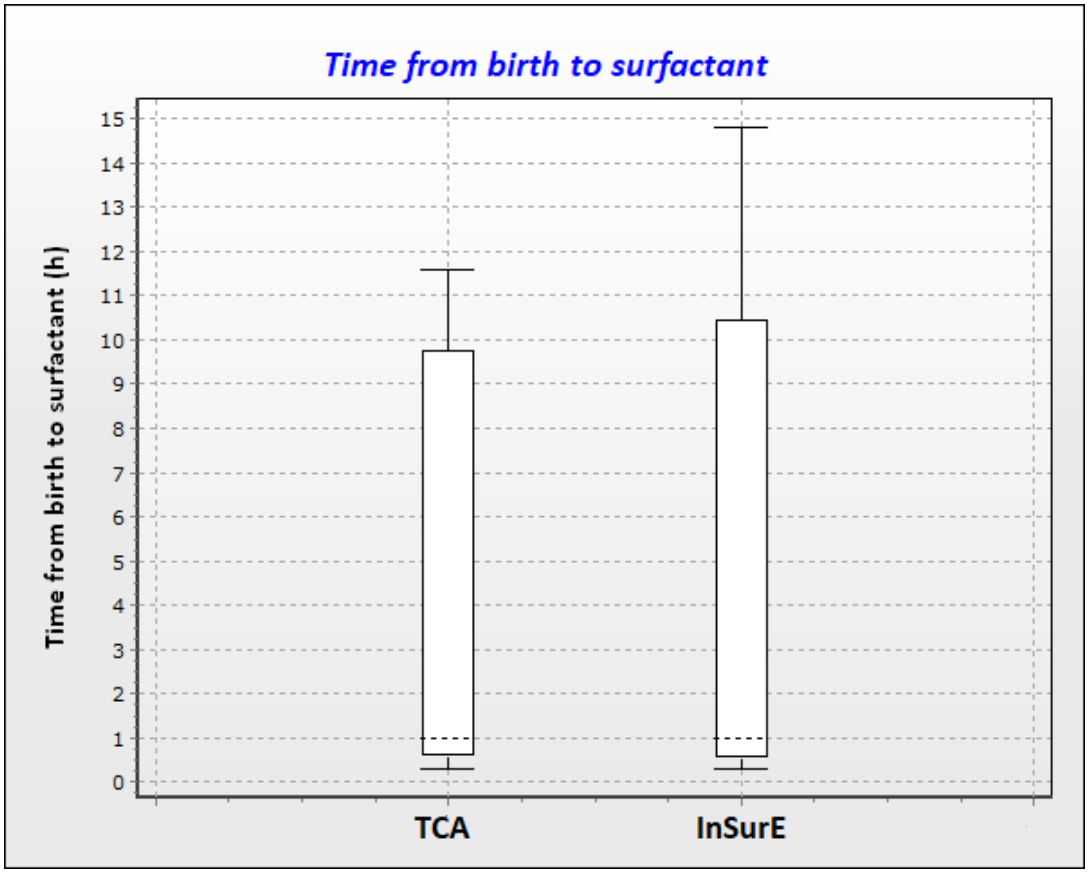
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 10. Boxplot of antenatal steroid administration distributions among different interventions.

No significant difference was noted (overall median: 76.5, χ^2: 8.65, *p-value*=0.07).

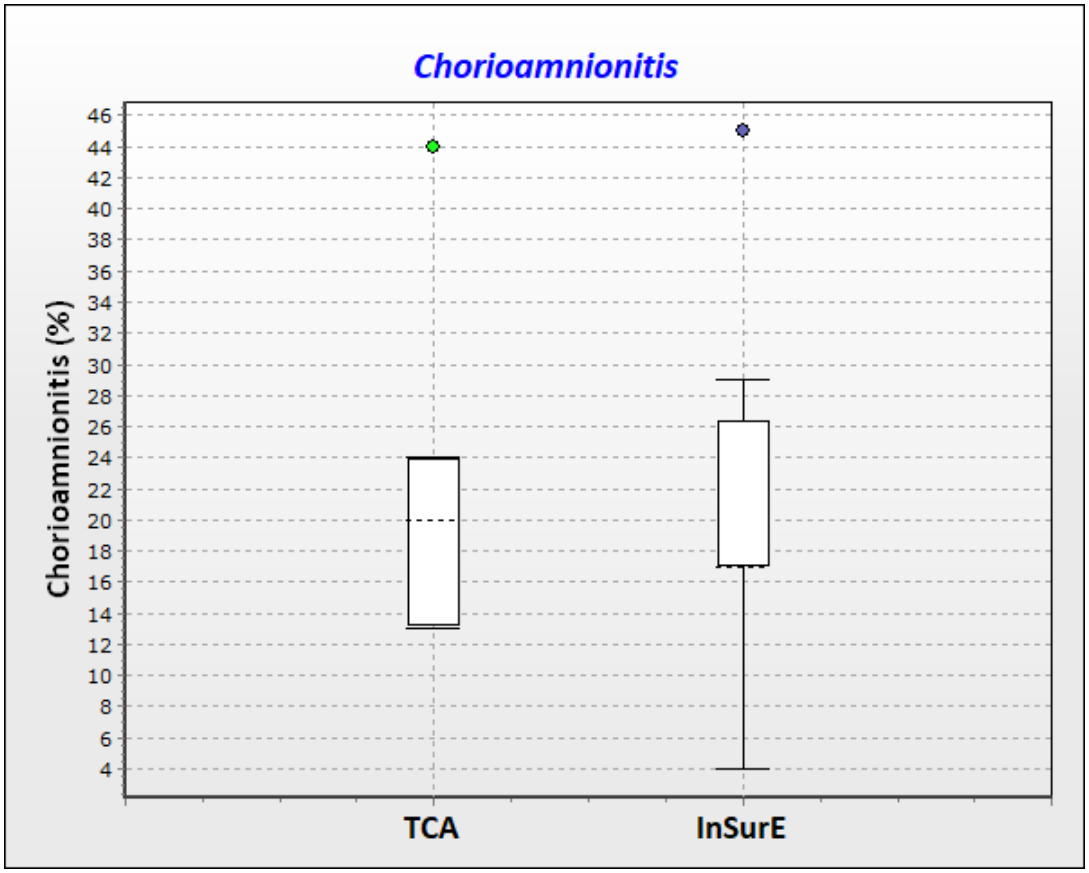
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation;



Suppl. Figure 11. Boxplot of time from birth to surfactant distributions among different interventions.

No significant difference was noted (overall median: 1, χ^2: 0.29, *p-value*=0.59).

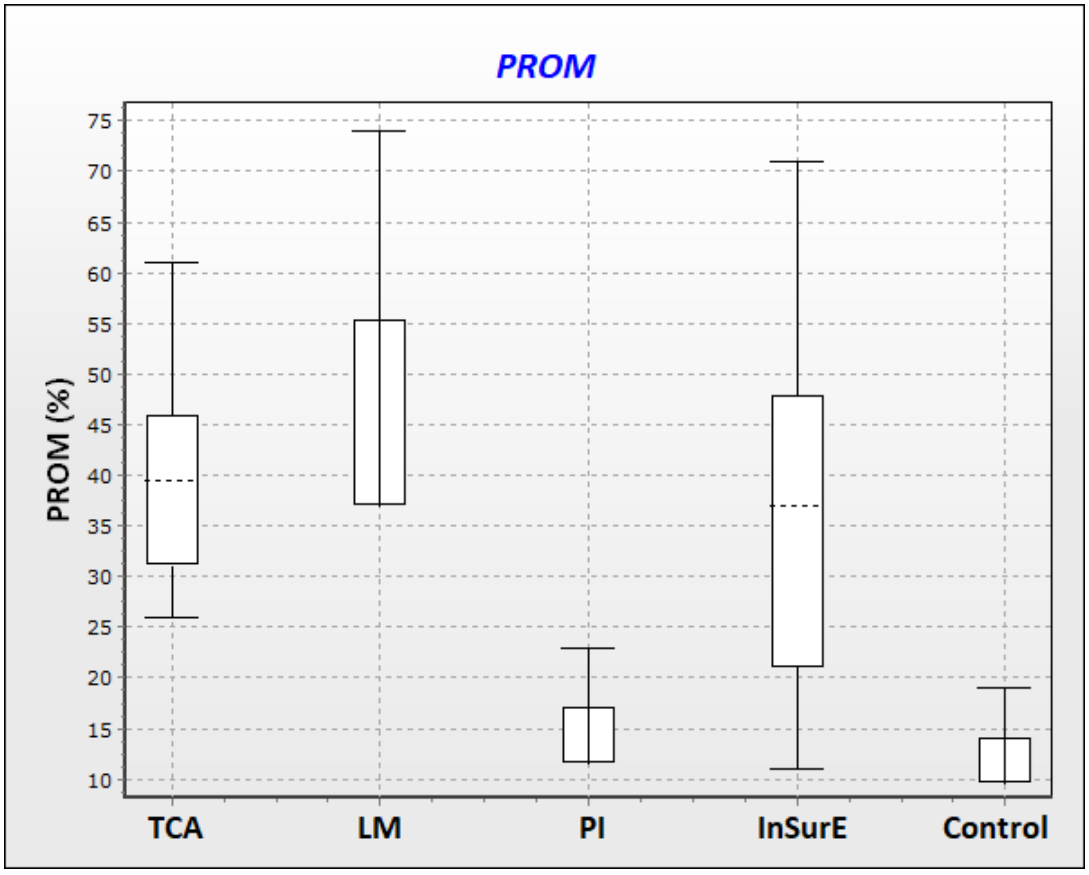
InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration



Suppl. Figure 12. Boxplot of chorioamnionitis distributions among different interventions.

No significant difference was noted (overall median: 17, χ^2: 0.14, *p-value*=0.71).

InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration



Suppl. Figure 13. Boxplot of premature rupture of membrane distributions among different interventions.

No significant difference was noted (overall median: 17, χ^2: 0.14, *p-value*=0.71).

InSurE: intubation, surfactant administration, extubation; TCA: thin catheter administration; LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation; PROM: premature rupture of membranes

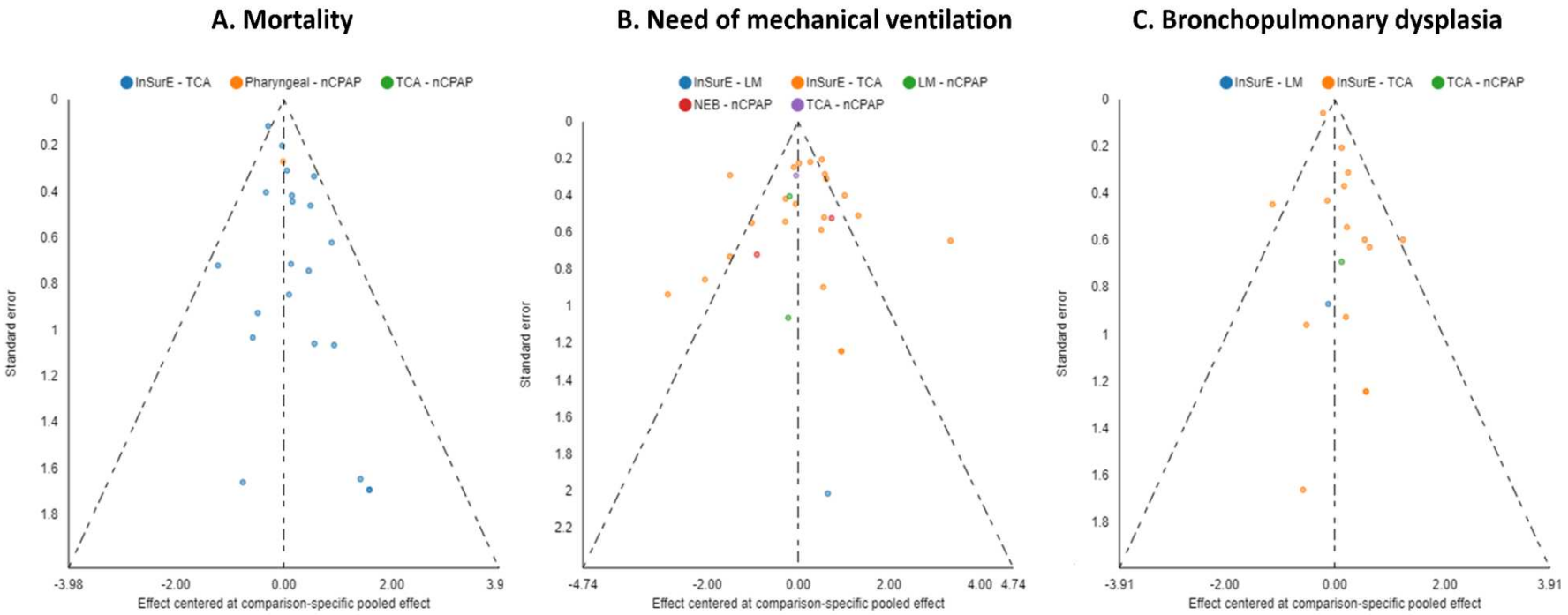
Appendix 9: Inconsistency assessment

Comparison	Direct odds ratio	Indirect odds ratio	Ratio of odds ratios	*p-value*
Need of mechanical ventilation				
InSurE vs. TCA	2.36 (1.59-3.51)	1.44 (0.01-167.7)	1.64 (0.014-194.2)	0.839
Control vs. TCA	4.44 (0.88-22.41)	7.28 (0.08-650.2)	0.61 (0.005-72.24)	0.839
InSurE vs. LM	1.00 (0.02-68.51)	1.64 (0.18-15.09)	0.61 (0.005-72.24)	0.839
Control vs. LM	3.09 (0.71-13.38)	1.88 (0.02-177.1)	1.64 (0.014-194.2)	0.839
Control VS. NEB	2.00 (0.50-7.99)	-	N/A	N/A
InSurE vs. NEB	-	1.00 (0.12-8.07)	N/A	N/A
Control vs. InSurE	-	2.00 (0.42-9.53)	N/A	N/A
LM vs. NEB	-	0.68 (0.10-4.85)	N/A	N/A
LM vs. TCA	-	1.60 (0.23-11.13)	N/A	N/A
NEB vs. TCA	-	2.35 (0.30-18.38)	N/A	N/A
Pneumothorax				
InSurE vs. TCA	1.25 (0.92-1.71)	1.29 (0.18-9.35)	0.97 (0.13-7.24)	0.978
Control vs. TCA	3.54 (1.38-9.06)	3.44 (0.59-20.28)	1.03 (0.14-7.65)	0.978
InSurE vs. LM	0.57 (0.16-2.04)	0.56 (0.12-2.63)	1.03 (0.14-7.65)	0.978
InSurE vs. NEB	5.32 (0.25-115.5)	-	N/A	N/A
Control vs. LM	1.57 (0.48-5.18)	1.61 (0.32-8.09)	0.97 (0.13-7.24)	0.978
Control vs. PI	1.17 (0.71-1.92)	-	N/A	N/A
LM vs. TCA	-	2.22 (0.82-5.99)	N/A	N/A
NEB vs. TCA	-	0.24 (0.01-5.19)	N/A	N/A
PI vs. TCA	-	3.01 (1.14-7.94)	N/A	N/A
Control vs. InSurE	-	2.81 (1.19-6.64)	N/A	N/A
InSurE vs. PI	-	0.42 (0.15-1.13)	N/A	N/A
LM vs. NEB	-	9.43 (0.37-238.4)	N/A	N/A
LM vs. PI	-	0.74 (0.25-2.17)	N/A	N/A
NEB vs. PI	-	0.08 (0.01-1.98)	N/A	N/A
Control vs. NEB	-	14.95 (0.61-364.75)	N/A	N/A

Suppl. Table 5. Outcomes of the SIDE-splitting test, suggesting no inconsistency.

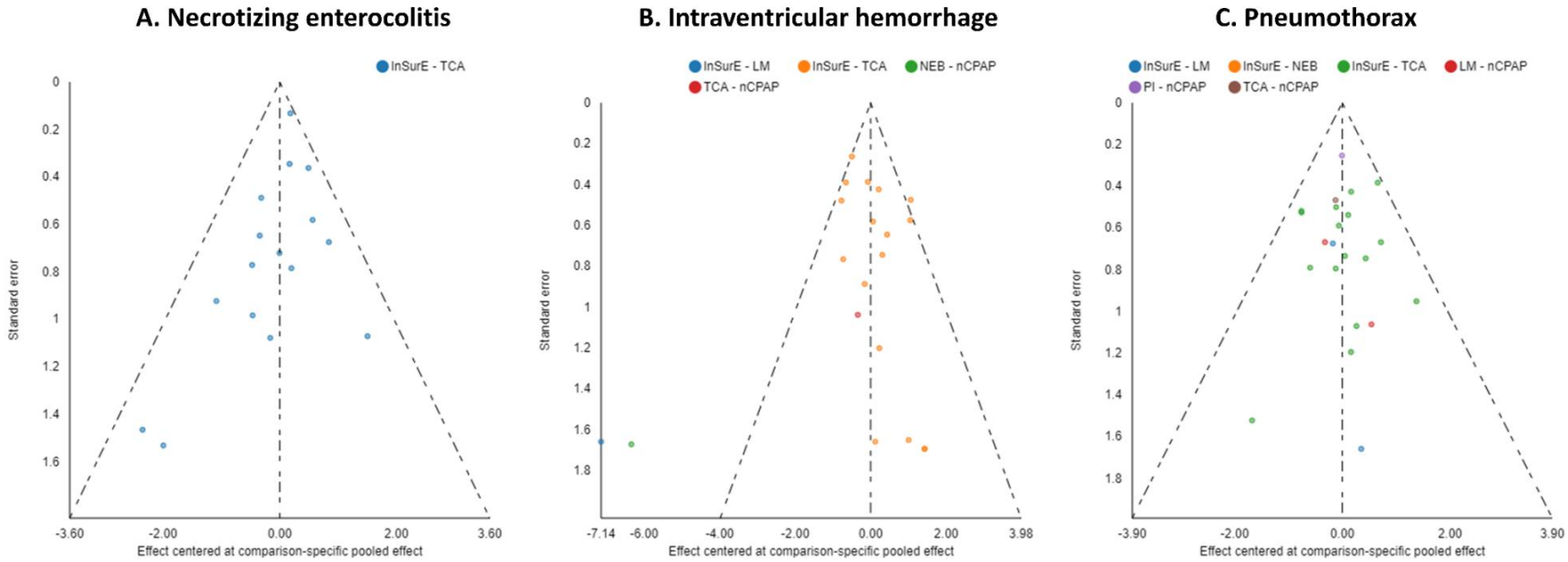
InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; N/A: not applicable; NEB: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration;

Appendix 10: Publication bias assessment



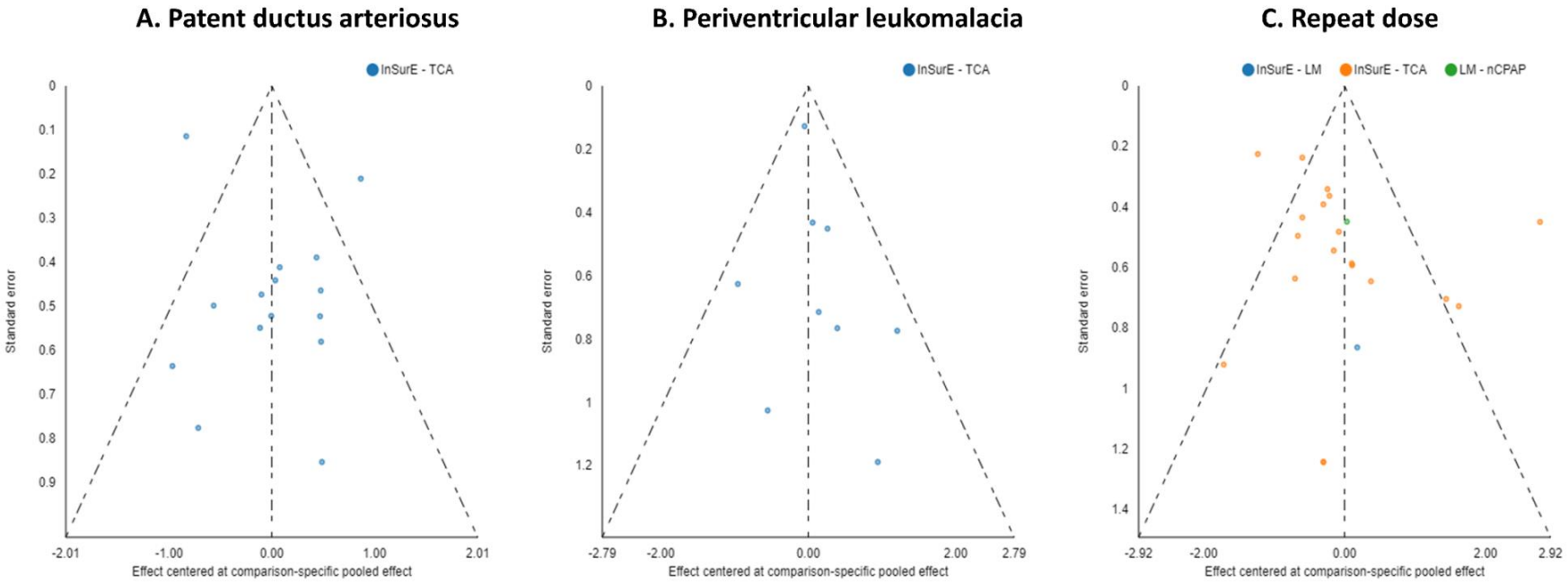
Suppl. Figure 14. Comparison-adjusted funnel plots of primary outcomes.

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*



Suppl. Figure 15. Comparison-adjusted funnel plots of necrotizing enterocolitis (A), intraventricular hemorrhage (B) and pneumothorax (C).

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*



Suppl. Figure 16. Comparison-adjusted funnel plots of patent ductus arteriosus (A), periventricular leukomalacia (B) and repeat dose of surfactant (C).

nCPAP: nasal continuous positive airway pressure; *InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; TCA: thin catheter administration*

Appendix 11: Confidence In Network Meta-Analysis (CiNeMA)

	Comparison	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Overall quality
	Intraventricular hemorrhage							
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	TCA vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	InSurE vs. LM	Major concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	NEB vs. Control	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
Indirect evidence	*TCA vs. LM*	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	TCA vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	InSurE vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	InSurE vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	LM vs. NEB	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	LM vs. Control	Some concerns	Suspected	No concerns	Major concerns	No concerns	Major concerns	**Very low**
	Pneumothorax							
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	**Moderate**
	TCA vs. Control	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	InSurE vs. NEB	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	LM vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
Indirect evidence	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	TCA vs. NEB	No concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	TCA vs. PI	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. Control	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	**Moderate**
	InSurE vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	LM vs. NEB	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	LM vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	NEB vs. PI	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	NEB vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Repeat dose							
Mixed evidence	TCA vs. InSurE	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	InSurE vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
Indirect evidence	TCA vs. LM	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	Necrotizing enterocolitis							
Direct evidence	TCA vs. InsurE	Some concerns	Undetected	No concerns	Some concerns	No concerns	Major concerns	**Low**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Patent ductus arteriosus							
	TCA vs. InsurE	Some concerns	Undetected	No concerns	Major concerns	No concerns	Major concerns	**Low**
	PI vs. Control	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	**Moderate**
	Periventricular leukomalacia							
	TCA vs. InsurE	Some concerns	Undetected	No concerns	No concerns	No concerns	Major concerns	**Moderate**

Suppl. Table 6. Credibility of evidence of secondary outcomes. Control refers to no surfactant administration.

InSurE: intubation, surfactant administration, extubation; LM: laryngeal mask; NEB: nebulized; PI: pharyngeal instillation; TCA: thin catheter administration

Appendix 12: PRISMA checklist

Section/Topic	Item #	Checklist Item	Reported on page
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	**1**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	**2**
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	**3**
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	**4**
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	**4**
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly*	**4-5**

		describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	**5**
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	**5**
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	**5-6**
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	**6**
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	**6**
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	**6**
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	**7**
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	**6**
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	**6-7**

Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	**7**
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	**6-7**
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	**6-7**
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	**8, Appendix 1**
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	**Figure 1, Appendix 3**
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	**8**
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	**9, Appendix 2, Table 1**
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	**10, Appendix 4**
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	**9**
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger*	**9-10**

		networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons. If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	**10, Appendix 8-9**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	**10-11, Appendix 10**
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	**9-10, Appendix 5-7**
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	**14-15**
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	**16**
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	**16-17**
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	**17**