Online Only Material

eMethods – Search Strategy

1) The Central Register of Controlled Trials (CENTRAL) in the Cochrane Library
Searched from inception to March 2020
Search strategy:

1	MeSH descriptor: [Infant, Very Low Birth Weight] explode all trees
#2	MeSH descriptor: [Infant, Newborn] explode all trees
#3	MeSH descriptor: [Infant, Extremely Low Birth Weight] explode all trees
#4	MeSH descriptor: [Infant, Low Birth Weight] explode all trees
#5	MeSH descriptor: [Infant, Premature] explode all trees
#6	MeSH descriptor: [Infant, Extremely Premature] explode all trees
#7	MeSH descriptor: [Premature Birth] explode all trees
#8	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#9	Birth, Premature OR Births, Premature OR Premature Births OR Preterm Birth OR Birth, Preterm OR Births, Preterm OR Preterm Births OR Infants, Premature OR Premature Infant OR Preterm Infants OR Infant, Preterm OR Infants, Preterm OR Preterm Infant OR Premature Infants OR Neonatal OR Prematurity OR Prematurity, Neonatal OR Extremely Premature Infant OR Infants, Extremely Premature OR Premature Infant, Extremely OR Premature Infants, Extremely OR Extremely Preterm Infants OR Extremely Preterm Infant OR Infant, Extremely Preterm OR Infants, Extremely Preterm OR Preterm Infant, Extremely OR Preterm Infants, Extremely OR Extremely Premature Infants OR Extremely Low Birth Weight OR Extremely Low Birth Weight Infant OR (Extremely AND low AND birth AND weight) OR Very Low Birth Weight OR (Very AND low AND birth AND weight) OR Very Low Birth Weight Infant OR Low Birth Weight Infant OR Low Birth Weight OR Birth Weight, Low OR Birth Weights, Low OR Low Birth Weights Infants, Newborn OR Newborn Infant OR Newborn Infants OR Newborns OR Newborn OR Neonate OR Neonates OR Infants, Premature OR Premature Infant OR Preterm Infants OR Infant, Preterm OR Infants, Preterm OR Preterm Infant OR Premature Infants OR Neonatal Prematurity OR Prematurity, Neonatal OR ELBW OR VLBW OR Extreme prematurity
#10	#8 OR #9
#11	MeSH descriptor: [Surface-Active Agents] explode all trees
#12	MeSH descriptor: [Pulmonary Surfactants] explode all trees
#13	Agents, Surface-Active OR Surface Active Agents OR Active Agents, Surface OR Agents, Surface Active OR Tensides OR Surfactants OR Surfactant OR Amphiphilic Agents OR Agents, Amphiphilic OR Surfactants, Pulmonary OR Pulmonary Surfactant OR Surfactant, Pulmonary
#14	#11 OR #12 OR #13
#15	#8 AND #14

2) MEDLINE (PubMed)
Searched from inception to March 2020
Search strategy:

a) <u>Population – neonates</u>
"Infant, Newborn"[Mesh]
"Infant, Extremely Low Birth Weight"[Mesh]
"Infant, Low Birth Weight"[Mesh]
"Infant, Very Low Birth Weight"[Mesh]
"Infant, Premature"[Mesh]
“Extremely Premature"[Mesh]
"Premature Birth"[Mesh]

Entry terms:
Birth, Premature
Births, Premature

Premature Births
Preterm Birth
Birth, Preterm
Births, Preterm
Preterm Births
Infants, Premature
Premature Infant
Preterm Infants
Infant, Preterm
Infants, Preterm
Preterm Infant
Premature Infants
Neonatal Prematurity
Prematurity, Neonatal
Extremely Premature Infant
Infants, Extremely Premature
Premature Infant, Extremely
Premature Infants, Extremely
Extremely Preterm Infants
Extremely Preterm Infant
Infant, Extremely Preterm
Infants, Extremely Preterm
Preterm Infant, Extremely
Preterm Infants, Extremely
Extremely Premature Infants
Extremely-Low-Birth-Weight [all fields] OR
Extremely Low Birth Weight [all fields] OR
Extremely Low Birth Weight Infant
Extremely AND low AND birth AND weight [all fields] OR
Very Low Birth Weight [all fields] OR
Very Low-Birth-Weight [all fields] OR
Very AND low AND birth AND weight OR
Infant, Very-Low-Birth-Weight [all fields] OR
Infants, Very-Low-Birth-Weight [all fields] OR
Very Low Birth Weight Infant [all fields] OR
Very-Low-Birth-Weight Infants [all fields] OR
Low-Birth-Weight Infant
Infant, Low-Birth-Weight
Infants, Low-Birth-Weight
Low Birth Weight Infant
Low-Birth-Weight Infants
Low Birth Weight
Birth Weight, Low
Birth Weights, Low
Low Birth Weights
Infants, Newborn [all fields] OR
Newborn Infant [all fields] OR
Newborn Infants [all fields] OR
Newborns [all fields] OR
Newborn [all fields] OR
Neonate [all fields] OR
Neonates [all fields] OR
ELBW [all fields] OR
VLBW [all fields] OR
Extreme prematurity [all fields]

b) Intervention – Surfactant

34 "Surface-Active Agents"[Mesh]
35 "Pulmonary Surfactants"[Mesh]

Entry terms
36 Agents, Surface-Active [all fields] OR
37 Surface Active Agents [all fields] OR
38 Active Agents, Surface [all fields] OR
39 Agents, Surface Active [all fields] OR
40 Tensides [all fields] OR
41 Surfactants [all fields] OR
42 Surfactant [all fields] OR
43 Amphiphilic Agents [all fields] OR
44 Agents, Amphiphilic [all fields] OR
45 Surfactants, Pulmonary [all fields] OR
46 Pulmonary Surfactant [all fields] OR
47 Surfactant, Pulmonary [all fields]

The population and intervention search strategies above were combined with boolen operator 'AND'. The pubmed controlled clinical trials filter was applied.

3) EMBASE

Searched from inception to March 2020
Search strategy:

1. infant newborn.mp. or exp newborn/
2. extremely low birth weight.mp. or exp low birth weight/ or exp very low birth weight/ or exp extremely low birth weight/ or exp newborn/ or exp prematurity/
3. extremely-low-birth-weight.mp.
4. (extremely and low and birth and weight).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
5. very low birth weight.mp. or exp very low birth weight/
6. very-low-birth-weight.mp.
7. (very and low and birth and weight).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
8. newborn infant.mp.
9. neonate.mp.
10. premature.mp.
11. exp premature labor/ or preterm.mp. or exp gestational age/
12. elbw.mp.
13. vlbw.mp.
14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
15. exp surfactant associated protein/ or exp surfactant/ or surfactant.mp.
16. pulmonary surfactant.mp. or exp lung surfactant/
17. surface active agents.mp. or surfactant/
18. surfactant/ or tensides.mp.
19. surfactants.mp. or surfactant/
20. 15 or 16 or 17 or 18 or 19
21. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).af.
22. exp crossover-procedure/ or exp double-blind procedure/ or exp randomized controlled trial/ or exp single-blind procedure/
23. 21 or 22
24. 14 and 20 and 23

4) Science Citation Index Expanded (Web of Science)
Searched from inception to March 2020
Search strategy:

TI = (Surface-Active Agents OR Pulmonary Surfactants OR Agents, Surface-Active OR Active Agents, Surface OR Agents, Surface Active OR Surfactants OR Surfactant OR Surfactants, Pulmonary OR Pulmonary Surfactant OR Surfactant, Pulmonary)

TI = (Infant, Extremely Low Birth Weight OR Infant, Low Birth Weight OR Infant, Very Low Birth Weight OR Infant, Premature OR Extremely Premature)

TI = (Infants, Premature OR Premature Infant OR Preterm Infants OR Infant, Preterm OR Preterm Infant OR Premature Infants OR Neonatal Prematurity OR Prematurity, Neonatal OR Extremely Premature Infant OR Infants, Extremely Premature OR Premature Infant, Extremely OR Premature Infants, Extremely OR Extremely Preterm Infants)

TI = (Extremely Preterm Infant OR Extremely Premature Infants OR Extremely-Low-Birth-Weight OR Extremely Low Birth Weight [all fields] OR(Extremely AND low AND birth AND weight) OR Very Low Birth Weight OR Very Low-Birth-Weight OR Neonate OR Neonates OR ELBW OR VLBW OR extreme prematurity)

TS=(random* OR rct* OR crossover OR masked OR blind* OR placebo* OR meta-analysis OR systematic review* OR meta-analys*)

5) ClinicalTrials.gov
Searched from inception to March 2020
Condition: prematurity
Intervention: Surfactant

6) World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/)
Searched from inception to March 2020
Condition: neo*
Intervention: surfactant

eMethod – Data extraction and Management

Two authors independently extracted the data below in a pre-piloted data extraction form:

- Outcome data (for each outcome and each intervention group):
  - Number of participants randomised
  - Number of participants included for the analysis
  - Number of participants with events for binary outcomes, mean and standard deviation for continuous outcomes, number of events and the mean follow-up period for count outcomes and number of participants with events and the mean follow-up period for time-to-event outcomes
  - Natural logarithm of hazard ratio and its standard error if this was reported rather than the number of participants with events and the mean follow-up period for time-to-event outcomes
- Data on potential effect modifiers:
  - Participant characteristics such as sex, gestational age, birthweight, use of antenatal steroids
  - Details of the intervention and control
  - Length of follow-up
  - Information related to 'Risk of Bias' assessment
- Other data:
  - Year and language of publication
  - Country
  - Year(s) in which the trial was conducted
  - Inclusion and exclusion criteria

We collected data at maximum follow-up provided and also at shorter (up to three months) and medium-term follow-up (three months to 1 year) where applicable. We attempted to contact trial authors in the case of unclear or missing information. Any differences in opinion were resolved by discussion.

eMethods – Data Synthesis

A network meta-analysis was conducted to compare thresholds of FiO2 simultaneously for each of the primary and secondary outcomes. Network meta-analysis combines direct evidence within trials and indirect evidence across trials [1]. Our analysis was based on guidance by the National Institute for Clinical Excellence (NICE) Decision Support Unit (DSU).[1-4]

We obtained a network plot to ensure that the trials were connected by interventions [3]. We excluded any trials unconnected to the network from the meta-analysis and reported only the direct pair-wise meta-analysis for such comparisons.

We conducted a Bayesian network meta-analysis using the Markov chain Monte Carlo method.

We used a fixed-effect model and random-effects model for the network meta-analysis. For each pair-wise comparison in a table, we reported the fixed-effect model if the two models reported similar results; otherwise, we reported the more conservative model.

We used a hierarchical Bayesian model using three different initial values, employing codes provided by NICE DSU [5]. We used a normal distribution with large variance (10,000) for treatment effect priors (vague or flat priors). For the random-effects model, we used a prior distributed uniformly (limits: 0 to 5) for between-trial standard deviation but assumed the same between-trial standard deviation across treatment comparisons [5]. We used a 'burn-in' of 10,000 simulations, checked for convergence (of effect estimates and between-study heterogeneity) visually (i.e. whether the values in different chains mix very well by visualisation) and ran the models for another 10,000 simulations to obtain effect estimates. If we did not obtain convergence, we increased the number of simulations for the 'burn-in'.

We estimated the probability that each intervention ranks at one of the possible positions using the NICE DSU codes [5].

Analysis was carried out using OpenBUGS, version 3.2.3

We assessed inconsistency (statistical evidence of the violation of transitivity assumption) by fitting both an inconsistency model and a consistency model. We used inconsistency models employed in the NICE DSU manual, as we used a common between-study standard deviation [2].

In the presence of inconsistency, we assessed whether the inconsistency was due to clinical or methodological heterogeneity.

We performed the direct comparisons using the same codes and the same technical details

Subgroup/sensitivity analysis: Subgroup analysis was planned based on 1) trials at low risk of bias compared to trials at high risk of bias, 2) gestational age, 3) Current best practice – use of antenatal steroids and NCPAP. Due to a paucity of data these could not be carried out. A sensitivity analysis of current best practice was performed. No trials reported only per-protocol analysis results, therefore no best-worst case scenario/worst-best case scenario analyses as sensitivity analyses were required. No imputations were required for mean or standard deviation, therefore sensitivity analysis excluding same was not required.

eResults – Risk of Bias Assessment

eTable 1 – Risk of Bias Assessment

	Bev.	DuW	Dilm	Dunn	Egb	Finer	Kand	Katt	Kend	Lefor	Merr	Roja	Sand	Walti
Randomisation process	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Deviations from intended interventions	Low	SC	High	Low	SC	Low	SC	High	Low	SC	Low	Low	Low	SC
Missing outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Measurement of the outcome	SC	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Selection of the reported result	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC
Overall risk of bias	SC	SC	High	SC	SC	SC	SC	High	SC	SC	SC	SC	SC	SC

eTable 1a – Risk of bias in each domain for each included study, Author 1. SC some concerns

	Bev.	**DuW.**	**Dilm**	**Dunn**	**Egb.**	**Finer**	**Kand**	**Katt.**	**Kend**	**Lefor**	**Merri**	**Roja**	**Sand**	**Walti**
Randomisation process	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Deviations from intended interventions	Low	SC	High	Low	SC	Low	SC	High	Low	SC	Low	Low	Low	SC
Missing outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Measurement of the outcome	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Selection of the reported result	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC
Overall risk of bias	SC	SC	High	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC	SC

eTable 1b – Risk of bias in each domain for each included study, Author 2. SC some concerns

eResults – Excluded Studies

None of the excluded studies met the inclusion criteria.

5 of the studies were identified as review articles or systematic reviews [6-10]. 1 study is an ongoing trial assessing surfactant thresholds for treatment [11]. We were unable to translate 2 studies and the abstracts did not provide sufficient information for inclusion [12,13]. 23 were not randomised control trials [14-36]. 6 trials met the inclusion criteria but did not list an fio2 for treatment with selective surfactant [37-42]. 55 did not meet the inclusion criteria of a trial assessing prophylactic treatment with surfactant vs selective treatment with surfactant [43-96]. 10 of the references are trial register or published abstracts of an included trial: [97-106]. 3 references were abstracts without a published trial found despite attempts to contact the author [107-109].

eResults – Primary Outcome Mortality

A random-effect model was used for the network meta-analysis because it was more conservative.
Deviance Information Criteria (DIC) for fixed model was 171.1, random 172.3.
Median between-study standard deviation for the random-effect model 0.23 (95% CrI 0.011, 0.742), variance 0.055.
Model used for direct comparisons are included in Table 1 with the odds ratio for each comparison.

eTable 2. Odds ratio for both the direct and network comparison of the primary outcome

Mortality	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.88[0.25,16.51] *	1.52[0.87,2.52] *	0.8[0.62,1.04] #	1.1[0.67,1.78] #
Threshold 30%	1.81[1.00,3.44]		-	-	-
Threshold 40%	1.52[0.94,2.40]	0.84[0.37,1.77]		-	-
Threshold 50%	0.82[0.50,1.41]	0.45[0.20,1.01]	0.54[0.28,1.13]		-
Threshold 60%	1.16[0.63,2.29]	0.64[0.27,1.60]	0.76[0.36,1.80]	1.41[0.64,3.31]	

eTable 2. Odds ratio for both the direct and network comparison of the primary outcome
Network Meta-analysis comparisons are below the greyed line, direct comparisons are above the line. Comparisons that did not reach statistical significance (credibility intervals for the odds ratio cross 1) are highlighted in yellow. Comparisons that do reach statistical significance are highlighted in blue.
Most conservative method of analysis was used in each case. * denotes fixed-effect model, # denotes random effect model for direct comparisons.

eResults – Sensitivity Analysis of Current Best Practice

Six studies met the criteria. This included 2554 patients. 1268 were in the combined prophylaxis arm and were compared with 138 (one study) in the 30% threshold arm, 183 (2 studies) in the 40% arm, 727 (two studies) in the 50% arm and 216 (one study) in the 60% arm.

eTable 4 shows the odds ratio for each comparison within the analysis, along with the model of comparison used. Most conservative model was used in each case.

Fixed-effects model was used for all outcomes, except pneumothorax, where random-effects model was used. DIC, between-study variance with 95% CrI and variance where applicable are shown in eTable 5.

There was no statistically significant difference seen in mortality, BPD, pneumothorax, or grade 3/4 IVH.

There was an increased rate of major morbidity in the 60% threshold group– 31 more per 1000 (95% CrI intervals 136 more to 572 more).

Each comparison was deemed to be at very-low quality of evidence.

eTable 3. Odds Ratio for Sensitivity Analysis

Mortality	Prophylaxis	30% Threshold	40% Threshold	50% Threshold	60% Threshold
Prophylaxis		1.02[0.45,2.34] &	1.33[0.69,2.6] *	0.81[0.61,1.07] *	0.55[0.23,1.29] &
30% Threshold	1.03[0.45,2.35]		-	-	-
40% Threshold	1.32[0.69,2.61]	1.30[0.45,3.77]		-	-
50% Threshold	0.81[0.61,1.07]	0.79[0.33,1.90]	0.61[0.29,1.24]		-
60% Threshold	0.56[0.23,1.29]	0.54[0.16,1.77]	0.42[0.14,1.22]	0.69[0.27,1.66]	

eTable 3a. Odds ratio for sensitivity analysis for mortality

Bronchopulmonary Dysplasia	Prophylaxis	30% Threshold	40% Threshold	50% Threshold	60% Threshold
Prophylaxis		1.39[0.87,2.23]	0.83[0.39,1.7]	0.93[0.74,1.16]	1.3[0.84,2.02]
30% Threshold	1.40[0.88,2.24]		-	-	-
40% Threshold	0.83[0.39,1.70]	0.59[0.24,1.40]		-	-
50% Threshold	0.93[0.74,1.16]	0.66[0.39,1.11]	1.12[0.53,2.44]		-
60% Threshold	1.29[0.84,2.02]	0.93[0.49,1.76]	1.57[0.68,3.74]	1.40[0.86,2.30]	

eTable 3b. Odds ratio for sensitivity analysis for bronchopulmonary dysplasia

Pneumothorax	Prophylaxis	30% Threshold	40% Threshold	50% Threshold	60% Threshold
Prophylaxis		4.78[1.42,22.97] &	3.73[0.01,3209.92]#	1.07[0.71,1.62] *	1.73[0.67,4.82] &
30% Threshold	4.99[0.00,6953.50]		-	-	-
40% Threshold	3.09[0.02,2455.29]	0.65[0.00,14472.42]		-	-
50% Threshold	1.52[0.01,324.08]	0.31[0.00,2426.00]	0.48[0.00,754.46]		-
60% Threshold	1.73[0.00,2151.67]	0.36[0.00,8681.94]	0.54[0.00,2972.03]	1.13[0.00,8391.71]	

eTable 3c. Odds ratio for sensitivity analysis for pneumothorax

Major Morbidity	Prophylaxis	30% Threshold	40% Threshold	50% Threshold	60% Threshold
Prophylaxis		1.21[0.87,1.7] &	1.15[0.8,1.66] *	1.06[0.93,1.21] *	2.05[1.45,2.92] &
30% Threshold	1.20[0.86,1.68]		-	-	-
40% Threshold	1.16[0.81,1.66]	0.96[0.58,1.57]		-	-
50% Threshold	1.06[0.93,1.21]	0.88[0.62,1.26]	0.92[0.63,1.34]		-
60% Threshold	2.05[1.46,2.93]	1.70[1.05,2.78]	1.77[1.07,2.95]	1.92[1.34,2.83]	

eTable 3d. Odds ratio for sensitivity analysis for major morbidity

Grade 3 or 4 Intraventricular Haemorrhage	Prophylaxis	30% Threshold	40% Threshold	50% Threshold	60% Threshold
Prophylaxis		1.62[0.24,14.17] &	2.16[0.86,5.88] *	1.28[0.93,1.78] *	0.71[0.23,2.12] &
30% Threshold	1.64[0.24,14.41]		-	-	-
40% Threshold	2.16[0.87,5.98]	1.32[0.12,11.55]		-	-
50% Threshold	1.28[0.93,1.78]	0.78[0.09,5.46]	0.59[0.21,1.56]		-
60% Threshold	0.71[0.23,2.09]	0.43[0.04,3.90]	0.33[0.07,1.36]	0.55[0.17,1.71]	

eTable 3e. Odds ratio for sensitivity analysis for grade 3 or 4 Intraventricular Haemorrhage

eTable 3 (a-e) above shows the odds ratio for the network and direct comparisons for each outcome in the sensitivity analysis.
Network meta-analysis comparisons are below the greyed line, direct comparisons are above the line.
Comparisons that did not reach statistical significance (credibility intervals for the odds ratio cross 1) are highlighted in yellow. Comparisons that do reach statistical significance are highlighted in blue.
Most conservative model of analysis was used in each case.
*denotes fixed-effect model, # denotes random effect model for the direct comparison, & denotes only one study in comparison leading to use of the random effects model,
^ denotes zero events in at least one arm of one study leading to use of the fixed effect model.

eTable 4. Models used for outcomes for sensitivity analysis

Outcome	DIC – Fixed	DIC - Random	Model Used	SD	95% CrI	Variance
Mortality	74.72	76.47	Fixed			
BPD	76.01	76.54	Fixed			
Pneumothorax	75.86	63.82	Random	3.424	1.22, 4.92	11.72
Major Morbidity	89.54	89.58	Fixed			
Grade 3/4 IVH	66.33	67.54	Fixed			

eTable 4. Models used for outcomes for sensitivity analysis

DIC – Deviance Information Criteria, Fixed – Fixed effect model, Random – Random effect model

SD – between study standard deviation, CrI – Credible interval, BPD – bronchopulmonary dysplasia, IVH – intraventricular haemorrhage

eResults – Secondary Outcomes

1. Bronchopulmonary Dysplasia

Network meta-analysis was performed using a fixed-effects model as it was more conservative. DIC for the fixed-effect model was 91.45, random-effect model 92.9.
Model used for the direct comparisons along with odds ratio for each comparison, both network and direct are shown in eTable 3a.

eTable 5. Odds Ratio for Both the Direct and Network Comparisons For Secondary Outcomes

Bronchopulmonary Dysplasia	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.4[0.87,2.23] &	0.77[0.37,1.61] ^	0.93[0.74,1.16] *	1.02[0.71,1.45] *
Threshold 30%	1.39[0.87,2.24]		-	-	-
Threshold 40%	0.77[0.37,1.58]	0.55[0.23,1.30]		-	-
Threshold 50%	0.93[0.74,1.16]	0.66[0.39,1.12]	1.20[0.57,2.61]		-
Threshold 60%	1.02[0.72,1.45]	0.73[0.40,1.32]	1.32[0.60,3.01]	1.10[0.72,1.67]	

eTable 5a. Odds ratio for both the direct and network comparison for the outcome bronchopulmonary dysplasia.
Network meta-analysis comparisons are below the greyed line, direct comparisons are above the line.
Comparisons that did not reach statistical significance (credibility intervals for the odds ratio cross 1) are highlighted in yellow. Comparisons that do reach statistical significance are highlighted in blue.
Most conservative method of analysis was used in each case.
*denotes fixed effect model, # denotes random effect model for direct comparisons, & denotes only one study in comparison with no convergence of random effect model – fixed effect used, ^ denotes zero events in one arm of one study leading to use of the fixed effect model

2. Chronic Lung Disease

Network meta-analysis was performed using a random-effects model, as the most conservative model.
DIC for the fixed-effect model was 109, random-effect model 110.7. Median between-study standard deviation 0.1751 (95% CrI 0.0078, 0.8729), variance 0.031.
Models used in the direct comparisons with odds ratio for each comparison are shown in table 3.

Chronic Lung Disease	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.47[0.07,30.69] #	1.07[0.8,1.43] *	3.97[0.88,30.78] &	0.6[0.33,1.06] *
Threshold 30%	1.48[0.82,2.63]		-	-	-
Threshold 40%	1.05[0.63,1.64]	0.71[0.32,1.48]		-	-

Threshold 50%	4.08[0.77,35.45]	2.75[0.46,25.87]	3.90[0.69,35.98]		-
Threshold 60%	0.59[0.28,1.22]	0.40[0.16,1.01]	0.56[0.23,1.36]	0.14[0.01,0.91]	

eTable 5b. Odds ratio for both the direct and network comparisons for CLD. Description of table as per table 3a

3. Bronchopulmonary Dysplasia or Chronic Lung Disease at maximal follow up
For this outcome, a random-effect model was used for the network meta-analysis as the more conservative choice.
DIC for the fixed model was 152.9, random model 154.7. Median between study deviation 0.1619 (95% CrI 0.0071, 0.678), variance 0.26.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3c.

CLD or BPD	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.45[1.09,1.93] *	0.94[0.68,1.29] ^	0.93[0.74,1.16] ^	0.91[0.65,1.26] *
Threshold 30%	1.45[0.95,2.21]		-	-	-
Threshold 40%	0.91[0.54,1.41]	0.63[0.32,1.13]		-	-
Threshold 50%	0.96[0.59,2.00]	0.66[0.36,1.58]	1.06[0.57,2.75]		-
Threshold 60%	0.86[0.47,1.34]	0.59[0.28,1.06]	0.94[0.46,1.81]	0.90[0.32,1.64]	

eTable 5c. Odds ratio for the comparisons of both the direct and network comparisons for CLD or BPD. Description of table as per eTable 3a

4. Pneumothorax (or other air-leak)
Network meta-analysis was performed using a random-effects model, as the most conservative model.
DIC for the fixed-effect model was 159.5, random-effect model was 154.3. Between study standard deviation was 0.859 (95% CrI 0.197, 2.115), variance 0.74.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3d.

Pneumothorax	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		2.36[0.29,22.15] #	1.38[0.89,2.17] *	0.92[0.63,1.35] *	1.67[0.88,3.19] *
Threshold 30%	2.41[0.61,10.48]		-	-	-
Threshold 40%	1.26[0.42,3.97]	0.52[0.08,3.13]		-	-
Threshold 50%	0.81[0.19,3.47]	0.33[0.04,2.49]	0.64[0.10,3.99]		-
Threshold 60%	2.05[0.50,10.72]	0.85[0.11,7.42]	1.62[0.27,12.07]	2.54[0.35,23.13]	

eTable 5d. Odds ratio for the comparisons of both the direct and network comparisons for pneumothorax. Description of table as per eTable 3a

5. Surfactant Treatment (proportion requiring surfactant)
Network meta-analysis not performed.
Proportions receiving surfactant (binary): 99.07% of the prophylaxis group received any surfactant
41.54% in the 30% group
53.82% in the 40% group
64.42% in the 50% group
46.22% of 60% group.

6. Number of Surfactant Doses Required
Network meta-analysis was performed using a random-effects model, as the most conservative model.
DIC for the fixed-effect model was 270, random-effect model 269. Between study standard deviation 2.504 (95% CrI 0.1212, 4.879), variance 6.27.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3f.

Surfactant - Number of Doses	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		0.51[0.46,0.56] *	0.71[0.63,0.8] *	0.65[0.58,0.73] *	0.26[0.21,0.32] *
Threshold 30%	0.51[0.46,0.56]		-	-	-
Threshold 40%	0.71[0.63,0.81]	1.41[1.20,1.65]		-	-
Threshold 50%	0.65[0.58,0.73]	1.29[1.10,1.51]	0.91[0.77,1.08]		-
Threshold 60%	0.26[0.21,0.32]	0.52[0.41,0.65]	0.37[0.29,0.47]	0.40[0.32,0.51]	

eTable 5e. Odds ratio for the comparisons of both the direct and network comparisons for number of surfactant doses required. Description of table as per eTable 3a

7. Total Number of Major Morbidities
Network meta-analysis was performed using a fixed-effects model, as the most conservative model. DIC for the fixed-effect model was 168.5, random-effect model 168.5.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3g.

Major Morbidity	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.14[0.93,1.4] *	1.18[0.89,1.56] *	1.04[0.92,1.18] *	1.02[0.81,1.28] *
Threshold 30%	1.14[0.94,1.40]		-	-	-
Threshold 40%	1.18[0.89,1.56]	1.03[0.73,1.45]		-	-
Threshold 50%	1.04[0.92,1.18]	0.91[0.72,1.16]	0.89[0.65,1.20]		-

Threshold 60%	1.02[0.81,1.28]	0.89[0.65,1.21]	0.86[0.60,1.24]	0.97[0.75,1.27]	

eTable 5f. Odds ratio for the comparisons of both the direct and network comparisons for total number of major morbidities. Description of table as per eTable 3a

8. Grade 3 or 4 Intraventricular Haemorrhage

Network meta-analysis was performed using a random-effects model, as the most conservative model.

DIC for the fixed-effect model was 138.3, random-effect model 137.8. Between study standard deviation 0.449 (95% CrI 0.326, 1.281), variance 0.2.

Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3h.

Grade 3 or 4 Intraventricular Haemorrhage	Prophylaxis	Threshold 0.3	Threshold 0.4	Threshold 0.5	Threshold 0.6
Prophylaxis		2.16[0.14,34.19] #	1.59[0.91,2.84] *	1.21[0.9,1.63] &	0.67[0.32,1.32] &
Threshold 0.3	2.01[0.83,5.46]		-	-	-
Threshold 0.4	1.69[0.77,4.10]	0.84[0.24,2.93]		-	-
Threshold 0.5	1.11[0.44,2.47]	0.55[0.14,1.75]	0.65[0.18,1.94]		-
Threshold 0.6	0.68[0.22,2.03]	0.34[0.07,1.35]	0.40[0.09,1.52]	0.61[0.16,2.60]	

eTable 5g. Odds ratio for the comparisons of both the direct and network comparisons for grade 3 or 4 intraventricular haemorrhage. Description of table as per eTable 3a

9. Periventricular Leukomalacia

Network meta-analysis was performed using a fixed-effect model, as the most conservative model. DIC for the fixed-effect model was 78.82, random-effect model 80.17.

Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3i.

Periventricular Leucomalacia	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		0.81[0.51,1.28] *	0.63[0.07,4.18] *	0.81[0.22,2.77] *	0.58[0.2,1.5] *
Threshold 30%	0.81[0.51,1.28]		-	-	-
Threshold 40%	0.64[0.07,4.25]	0.79[0.09,5.53]		-	-
Threshold 50%	0.80[0.21,2.81]	0.98[0.25,3.79]	1.26[0.13,14.92]		-
Threshold 60%	0.58[0.19,1.50]	0.71[0.22,2.06]	0.91[0.10,9.56]	0.72[0.14,3.64]	

eTable 5h. Odds ratio for the comparisons of both the direct and network comparisons for periventricular leukomalacia. Description of table as per eTable 3a

10. Necrotising Enterocolitis

Network meta-analysis was performed using a fixed-effects model, as the most conservative model. DIC for the fixed-effect model was 112.5, random-effect model 114.4.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3j.

Necrotising Enterocolitis	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		0.86[0.54,1.36] *	1.27[0.81,2] ^	1.27[0.92,1.77] *	1.15[0.61,2.08] &
Threshold 30%	0.86[0.55,1.35]		-	-	-
Threshold 40%	1.27[0.81,2.01]	1.48[0.78,2.80]		-	-
Threshold 50%	1.27[0.91,1.77]	1.48[0.84,2.59]	1.00[0.57,1.74]		-
Threshold 60%	1.15[0.61,2.10]	1.33[0.61,2.84]	0.90[0.41,1.91]	0.90[0.44,1.80]	

eTable 5i. Odds ratio for the comparisons of both the direct and network comparisons for necrotising enterocolitis. Description of table as per eTable 3a

11. Retinopathy of Prematurity

Network meta-analysis was performed using a random-effects model, as the most conservative model.
DIC for the fixed-effect model was 65.68, random-effect model 67.53. Between study standard deviation 0.517 (95% CrI 0.0198, 3.845), variance 0.27.
Models used in the direct comparisons along with odds ratio for each comparison are shown in eTable 3k.

Retinopathy of Prematurity > Stage 2	Prophylaxis	Threshold 30%	Threshold 40%	Threshold 50%	Threshold 60%
Prophylaxis		1.02[0.03,37.98] &	0.9[0.34,2.31] *	1.01[0.72,1.41] *	2.35[1.02,5.42] &
Threshold 30%	1.01[0.01,96.83]		-	-	-
Threshold 40%	0.87[0.09,7.05]	0.85[0.01,117.92]		-	-
Threshold 50%	0.99[0.12,6.96]	0.97[0.01,121.39]	1.14[0.06,23.17]		-
Threshold 60%	2.36[0.13,40.29]	2.31[0.01,464.98]	2.69[0.07,101.80]	2.38[0.07,76.63]	

eTable 5j. Odds ratio for the comparisons of both the direct and network comparisons for retinopathy of prematurity greater than stage 2. Description of table as per eTable 3a

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