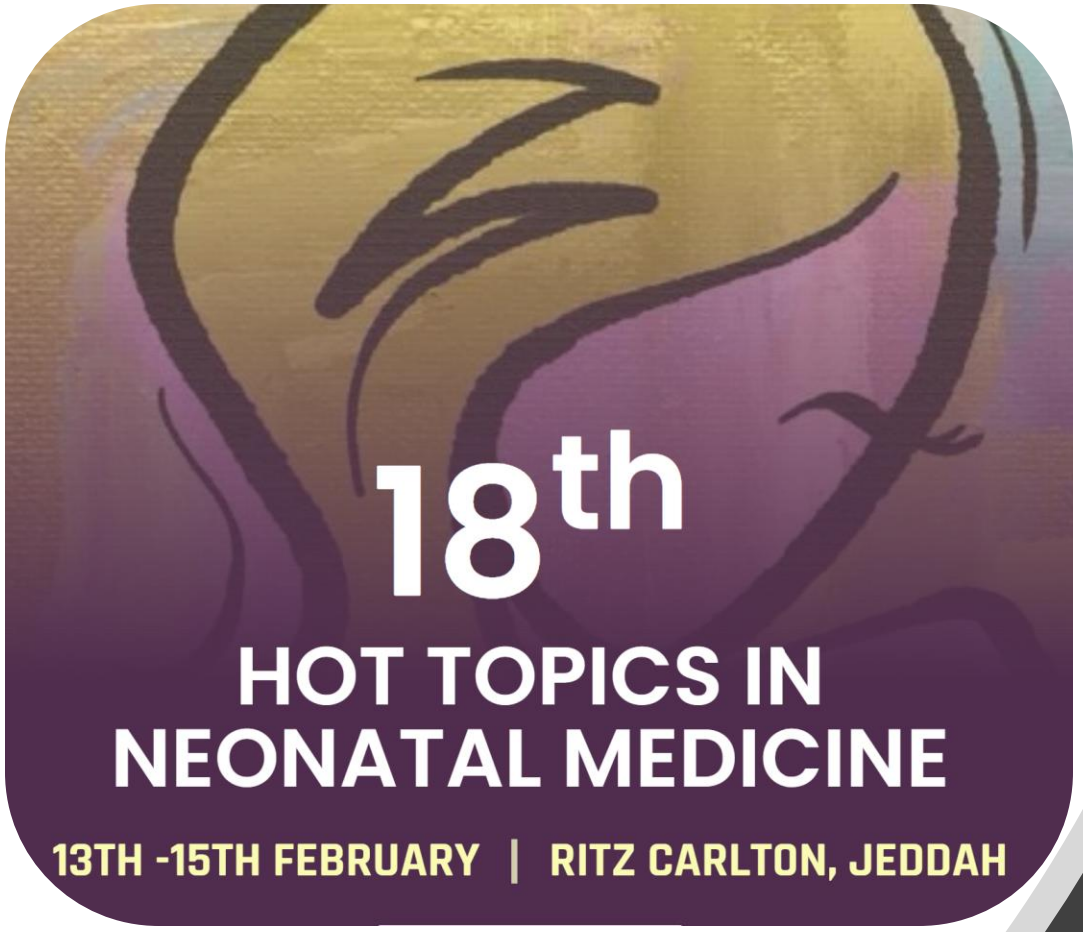


Postnatal steroids for preterm infants

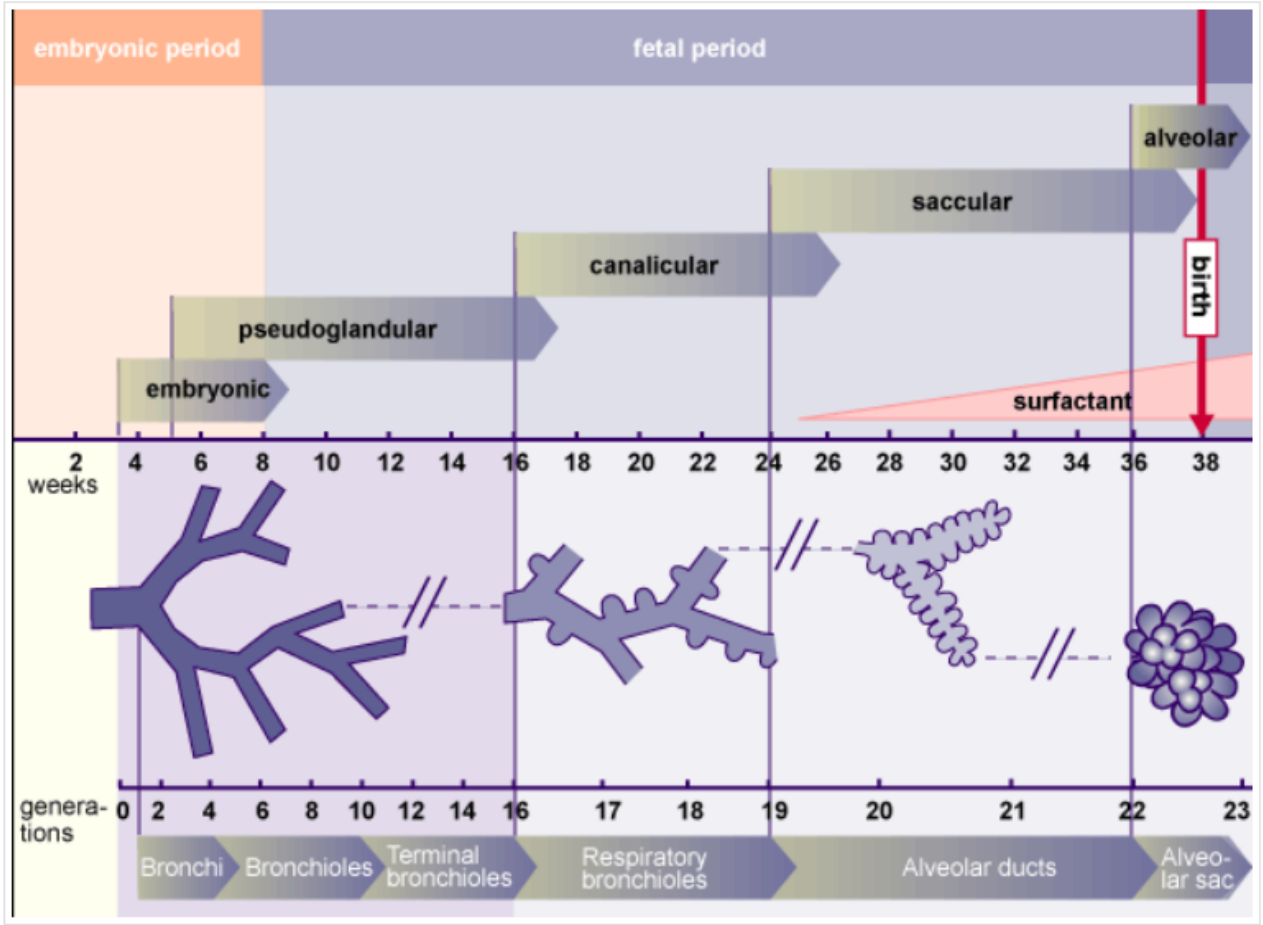
Peter Davis

The Royal Women's Hospital,

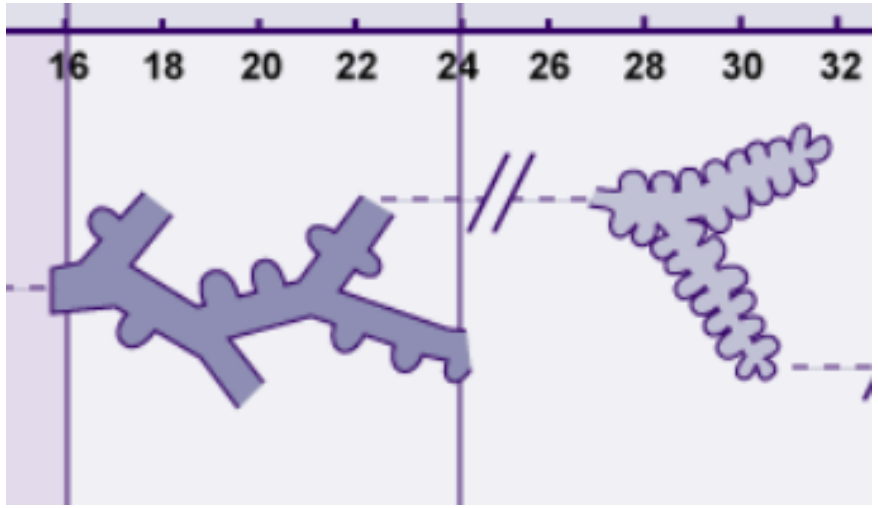
University of Melbourne

Pathogenesis of bronchopulmonary dysplasia (BPD)

- Exposure at canalicular phase of development



Pathogenesis



- Exposure at canalicular phase of development
- To:
  - Oxygen
  - Poor nutrition
  - Sepsis
  - PDA
  - …

Bronchopulmonary dysplasia (BPD)

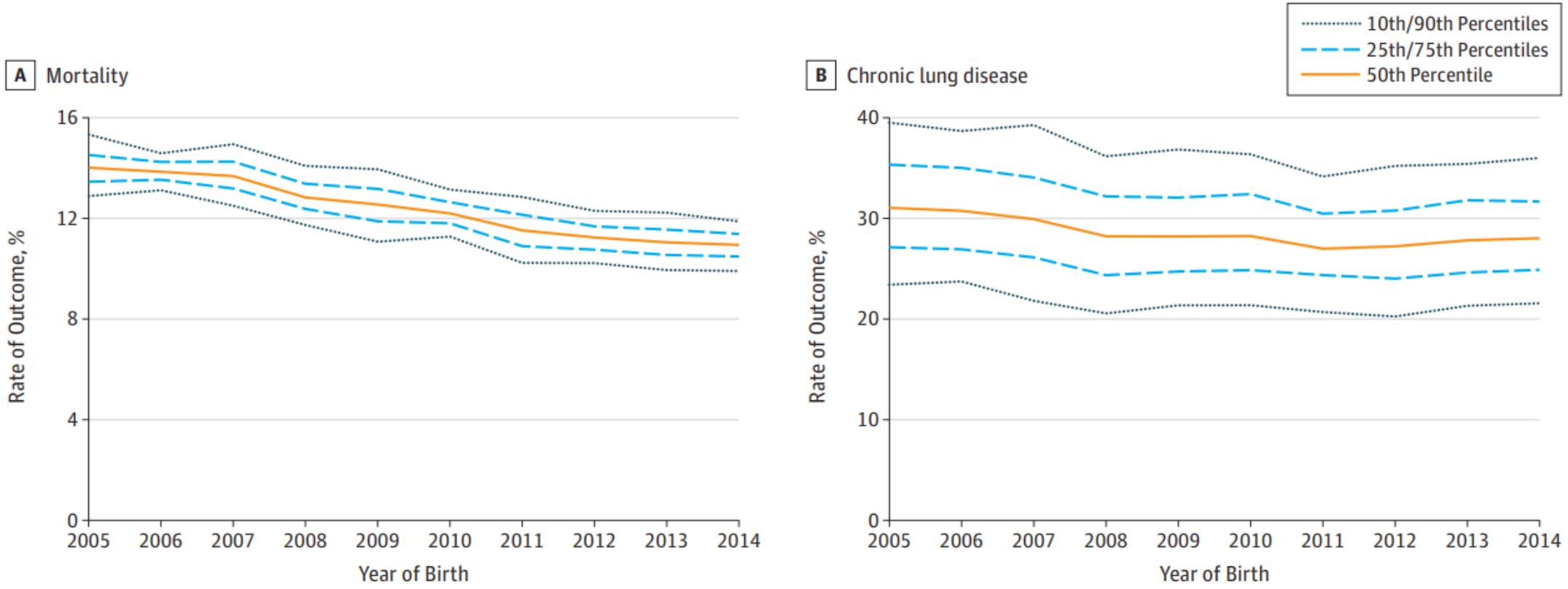
- “Old” BPD: Northway 1967
  - RDS + high pressures + oxygen toxicity= cystic emphysema and fibrosis
- “New” BPD: Jobe 1999
  - After antenatal steroids, surfactant, gentle ventilation
  - Arrested alveolarization and pulmonary vasculature development

“BPD is recognized as the end result of lung injury and repair in VLBW infants”

Consequences of BPD

- Respiratory health
  - More time in hospital during infancy
  - Higher rates of wheezing and asthma in childhood, and perhaps in adulthood
- Lung function
  - Airflow limitation: decreased $FEV_{1,}$ FEV_1/FVC
  - Decreased exercise capacity
- Neurodevelopment
  - Increased risk of cerebral palsy, cognitive deficits, behavioural problems

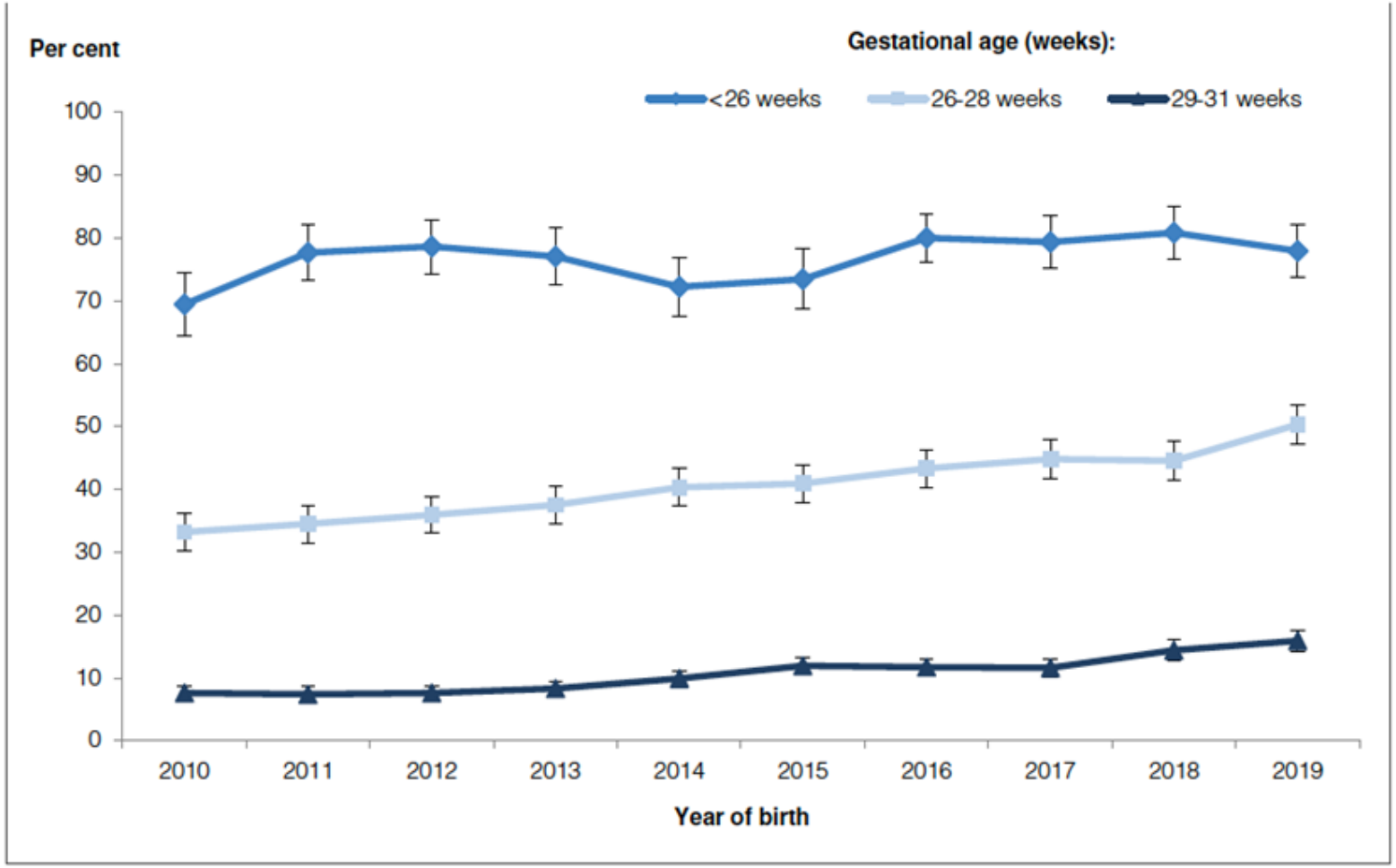
Rates of BPD over time



Variation in Performance of Neonatal Intensive Care Units in the United States. Horbar JD, et al. JAMA Pediatr. 2017. PMID: 28068438

Rates of BPD over time

FIGURE 22: Trends in chronic lung disease (with 95% CI) for level III registrants who survived to 36 weeks post menstrual age, ANZNN 2010–2019



Postnatal corticosteroids

- Potent synthetic steroids that are given in pharmacologic doses to decrease lung inflammation
  - but when given systemically have effects on the developing organs including lung and brain
- May be given as:
  - “prophylaxis” i.e. soon after birth to prevent BPD

or

  - “treatment” i.e. after 7 days to decrease the rate of BPD

Cochrane Library

Cochrane Database of Systematic Reviews

Early (<7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants (Review)

Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL

Systematic review includes:

- 32 studies
- 4395 infants
- Quality of evidence “high” for major outcomes

Results

- No difference in mortality rates
- Early steroids improve:
  - Early extubation
  - BPD
  - PDA

Results

- Associated adverse effects:
  - GI bleeding
  - Intestinal perforation
  - Hyperglycemia
  - Hypertension
  - Growth failure
- Long term neurological harm
  - Increased cerebral palsy (but not death or major disability)
  - Harm associated with dexamethasone, not hydrocortisone

Conclusions

- Benefits of early steroids may not outweigh the risks
- More long-term data are required
- More trials of hydrocortisone powered for long term outcomes are required

IPD meta-analysis

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis

Michele L. Shaffer, PhD[1], Olivier Baud, MD, PhD[2,3,4], Thierry Lacaze-Masmonteil, MD, PhD[5,6], Outi M. Peltoniemi, MD, PhD[7,8], Francesco Bonsante, MD[9], and Kristi L. Watterberg, MD[10]

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

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- 5 eligible RCTs, 4 included: N= 982
  - ➢40% open-label corticosteroid use

- Early low-dose hydrocortisone treatment for 10-15 days:
  - ➢Increased survival without BPD at 36 weeks

    46% vs. 53%, OR 1.45 (1.11-1.90)

    Death: 16% vs. 20%, OR 0.76 (0.54-1.07)

    BPD: 36% vs. 43%, OR 0.73 (0.54-0.98)
  - ➢Decreased death before discharge: OR 0.70 (0.51-0.97)
  - ➢Decreased PDA treatment: OR 0.72 (0.56-0.93)

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

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- 5 eligible RCTs, 4 included: N= 982
  - ➢40% open-label corticosteroid use

- Early low-dose hy t for 10-15 days:
  - ➢Increased sur weeks
    - 46% 1.90)
    - Death: -1.07)
    - BPD: 0.98)
  - ➢Decreased death before discharge: OR 0.70 (0.51-0.97)
  - ➢Decreased PDA treatment: OR 0.72 (0.56-0.93)

No difference in:
- ➢Days of ventilation
- ➢Days of CPAP
- ➢Days of oxygen
- ➢Home oxygen

THE JOURNAL OF PEDIATRICS • www.jpeds.com ORIGINAL ARTICLES

Effect of Prophylaxis for Early Adrenal Insufficiency Using Low-Dose Hydrocortisone in Very Preterm Infants: An Individual Patient Data Meta-Analysis

Michele L. Shaffer, PhD[1], Olivier Baud, MD, PhD[2,3,4], Thierry Lacaze-Masmonteil, MD, PhD[5,6], Outi M. Peltoniemi, MD, PhD[7,8], Francesco Bonsante, MD[9], and Kristi L. Watterberg, MD[10]

- Early low-dose hydrocortisone treatment for 10-15 days:
  - ➢ Increased spontaneous gastrointestinal perforation: OR 2.50 (1.33-4.69)
  - ➢ Increased late-onset sepsis: OR 1.34 (1.02-1.75)

  - ➢ No difference in longer-term neurodevelopment
    - Neurodevelopmental impairment: **OR 0.76 (0.52-1.12)**
    - Cerebral palsy: OR 0.95 (0.56-1.60)

A clinician’s interpretation

- A modest and imprecise treatment effect from the trial
- Lingering concerns about exposing all extremely preterm infants to early systemic corticosteroids

Cochrane Library

Cochrane Database of Systematic Reviews

Late(≥7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants (Review)

Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL

Systematic review includes:

- 21 studies
- 1424 infants
- Quality of evidence “high” for major outcomes

Results

- No difference in
  - Mortality
  - Cognitive delay
  - Cerebral palsy
- Steroids help
  - BPD
  - Home oxygen
- Steroids harm
  - Hyperglycemia
  - Hypertension
  - GI bleeding

Conclusions

- “Benefits of late steroids may not outweigh the risks”
- May reduce mortality without increasing long term neurodevelopmental risks
  - Quality of studies is limited
- Suggest reserve late steroids for infants unable to be weaned from mechanical ventilation
- Minimise dose and duration

Solving (partially) the riddle

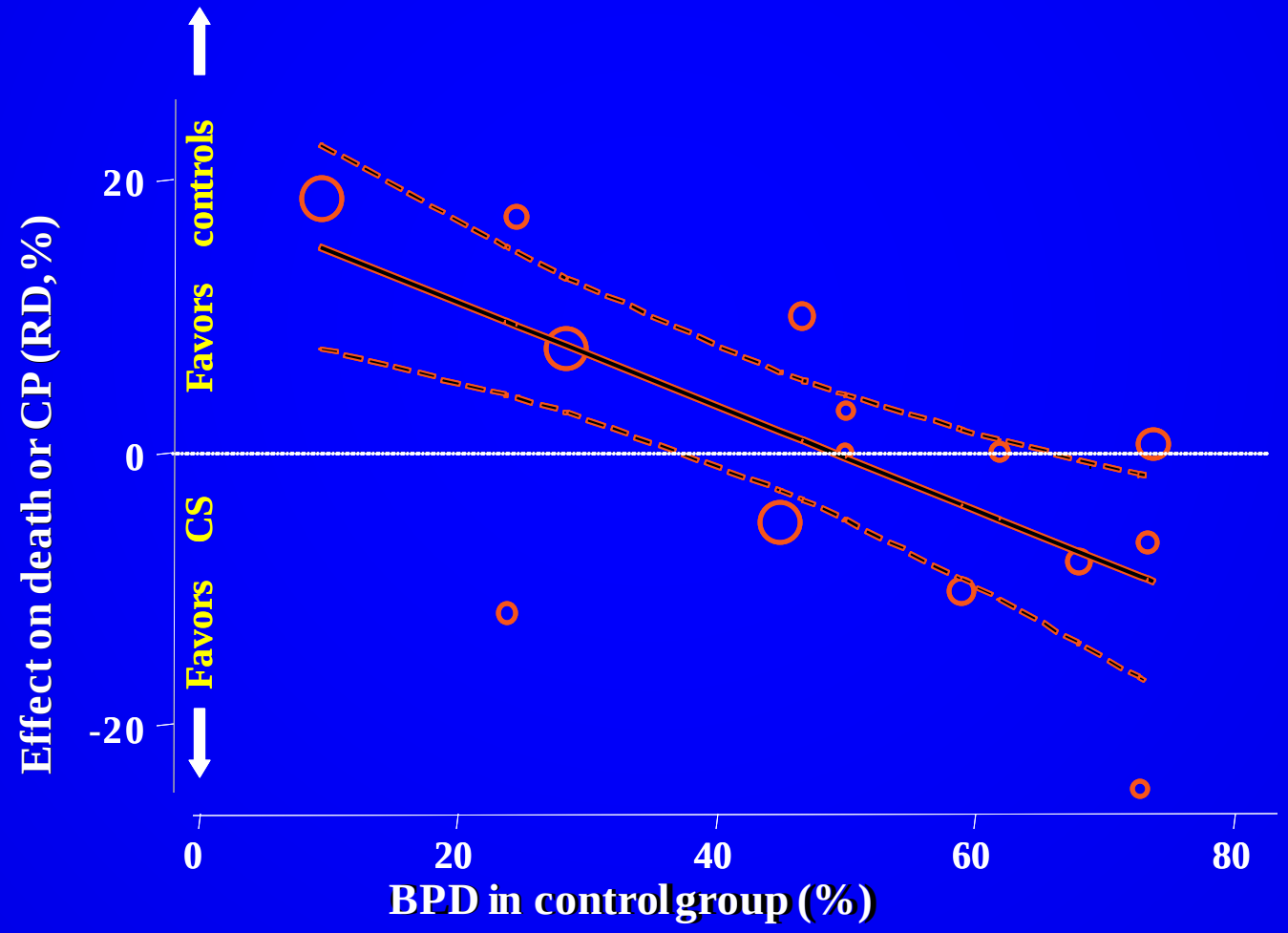
- Hypothesis
  - The baseline risk for BPD determines the treatment effect of dexamethasone on the combined outcome of death and cerebral palsy (CP)
  - i.e. steroids are more likely to do harm when the risk of BPD is small
- Methods
  - Weighted meta-regression analysis of the corticosteroid effect on the combined outcome death + CP and the rate of BPD in the control group

Doyle, Halliday, Ehrenkranz, Davis, Sinclair. Pediatrics 2005;115:655-661

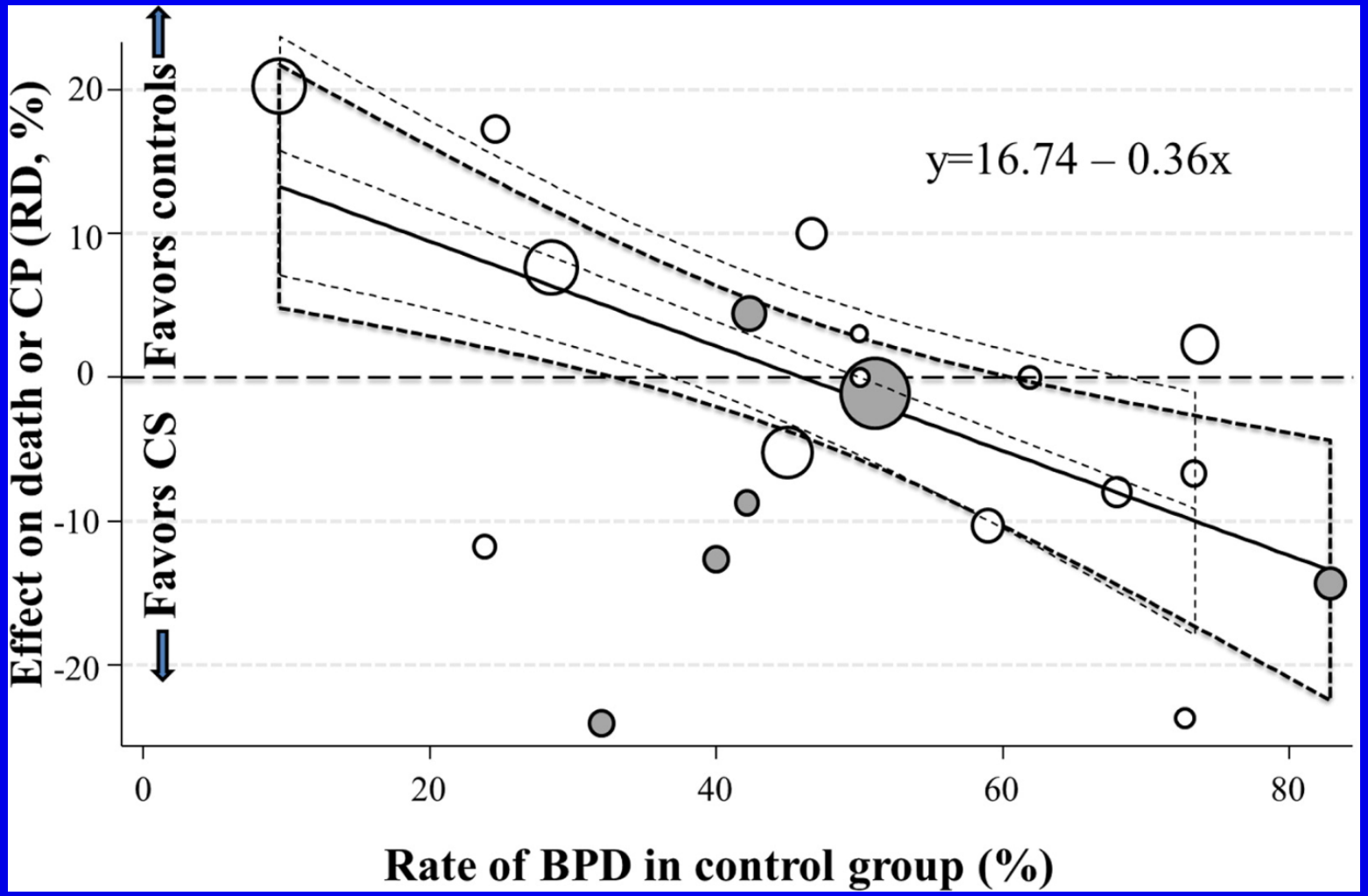
Results

- 20 studies (2064 infants) reporting death and BPD
- 9 early treatment - 1st week
- 11 later - > 1st week

Risk difference for Death or CP vs Rate of BPD



Updated: J Pediatr 2014



Other routes?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Long-Term Effects of Inhaled Budesonide for Bronchopulmonary Dysplasia

Dirk Bassler, M.D., Eric S. Shinwell, M.D., Mikko Hallman, M.D., Ph.D., Pierre-Henri Jarreau, M.D., Ph.D., Richard Plavka, M.D., Ph.D., Virgilio Carnielli, M.D., Christoph Meisner, Ph.D., Corinna Engel, Ph.D., Alexander Koch, M.D., Karen Kreutzer, M.D., Johannes N. van den Anker, M.D., Ph.D., Matthias Schwab, M.D., Henry L. Halliday, M.D., and Christian F. Poets, M.D., for the Neonatal European Study of Inhaled Steroids Trial Group*

N Engl J Med 2018;378:148-57.
DOI: 10.1056/NEJMoa1708831

Methods

- RCT n=863
- Infants 23-28 weeks
- Intervention: early (within 24 hours after birth) inhaled budesonide (vs placebo)
- Long term outcome – neurodevelopmental disability in survivors (CP, cognitive delay, deafness or blindness)

Death or disability

	Budesonide	Placebo	RR (95% CI)	P value
Death or disability	230/390 (59%)	223/379 (59%)	1.00 (0.89, 1.13)	0.97
Death	82/413 (20%)	58/400 (15%)	1.37 (1.01, 1.86)	0.04

Interpretation

- Inhaled steroids are not the solution!

Steroids+surfactant?

Seminars in Fetal and Neonatal Medicine
Available online 23 November 2023, 101499
In Press, Journal Pre-proof What's this?

Surfactant as a Drug Carrier

Arun Sett (Dr) [a b c d], Charles C. Roehr (Professor) [e f g], Brett J. Manley (Associate Professor) [a b c]

Pre-clinical studies

Study	Model	Surfactant	Results
Yang (2013)	Piglets (n=12)	Bovine (Survanta)	Improved oxygenation, reduced cytokines, less lung injury
Mikolka (2016)	Rabbit (n=33)	Porcine (Curosurf)	Reduced lung inflammation and oxidative damage
Kothe (2018)	Preterm lambs (n=38)	Porcine (Curosurf)	Increased lung maturation, better lung function, less injury
Kothe (2019)	Preterm lambs (n=37)	Porcine (Curosurf)	Improved mechanics, reduced inflammation, less lung injury
Hillman (2020)	Preterm lambs (n=23)	Porcine (Curosurf)	Reduced lung inflammation
Hillman (2021)	Preterm lambs (n=16)	Porcine (Curosurf)	Reduced lung and systemic inflammatory response

Yeh *et al*: 3 RCTs of 0.25mg/kg budesonide

	SURVANTA N=116	SURVANTA N=265	CUROSURF N=310
Population	BW <1500g, severe RDS, MV and FiO_2 >0.60 shortly after birth **Mean ~26.5w, 900g**	BW <1500g, severe RDS <4 hrs old, MV and FiO_2 >0.50 **Mean ~27w, 900g**	BW <1500g, ETT in DR, or failed CPAP/HF <4 hrs **Mean ~27w, 970 g**
Death or BPD @36w	32% vs. 61% P=0.003	42% vs. 66% P<0.001	42% vs 63% P<0.001
Death	17% vs. 32% P=0.08	13% vs 16% P=0.54	8% vs 9% P=NS
BPD @36w	15% vs. 29% P=0.12	29% vs 50% P<0.001	33% vs 54% P<0.001
	Pediatrics 2007	*AJRCCM 2016*	*Unpublished*

PICOT

P Extremely preterm infants born <28 weeks' gestation

I Intratracheal budesonide (0.25 mg/kg) mixed with surfactant

- *poractant alfa* (Curosurf®) 200mg/kg 1st intervention, 100mg/kg if 2nd intervention

C Surfactant alone (same doses)

O Survival free of physiological BPD

T 36 weeks' PMA

Inclusion criteria

1. Born before 28 weeks' gestation
2. <48 hours old
3. No more than one prior dose of surfactant
4. Receiving either:
    A. Mechanical ventilation (regardless of ventilation settings or oxygen requirement), or
    B. Non-invasive respiratory support (any type) and a clinical decision to treat with surfactant

Exclusion criteria

1. Postnatal corticosteroids for the prevention of lung disease
2. Unlikely to survive and/or not for admission to the NICU
3. Known or suspected major congenital anomaly
   (incl. severe pulmonary hypoplasia where survival is unlikely)
4. Likely to be transferred to a non-participating NICU within 24 hours

NO PREVIOUS SURFACTANT

Assess up to 48 hours of age:

1. Intubated, *or*
2. Non-invasive support and clinician decision to give surfactant

NO PREVIOUS SURFACTANT

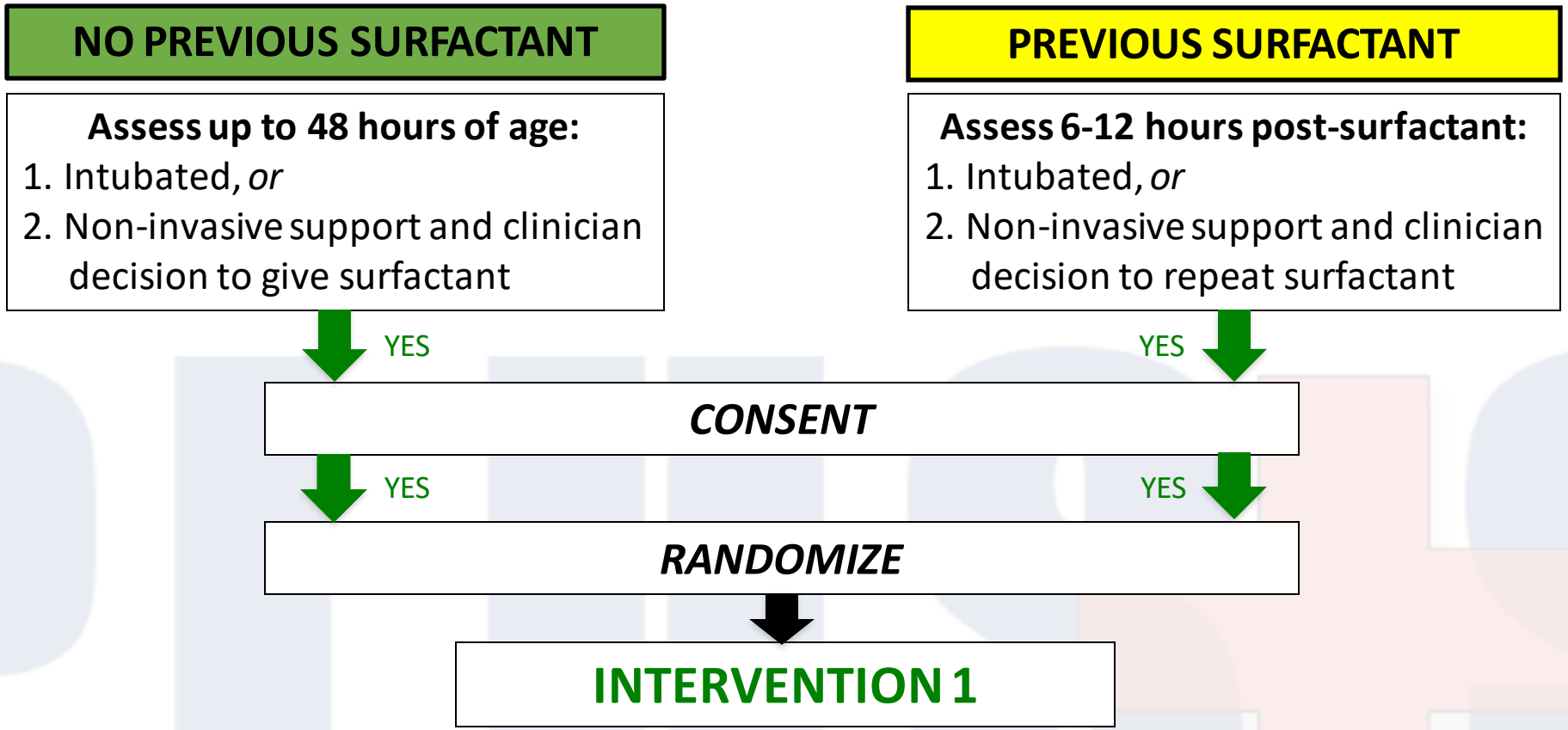
Assess up to 48 hours of age:

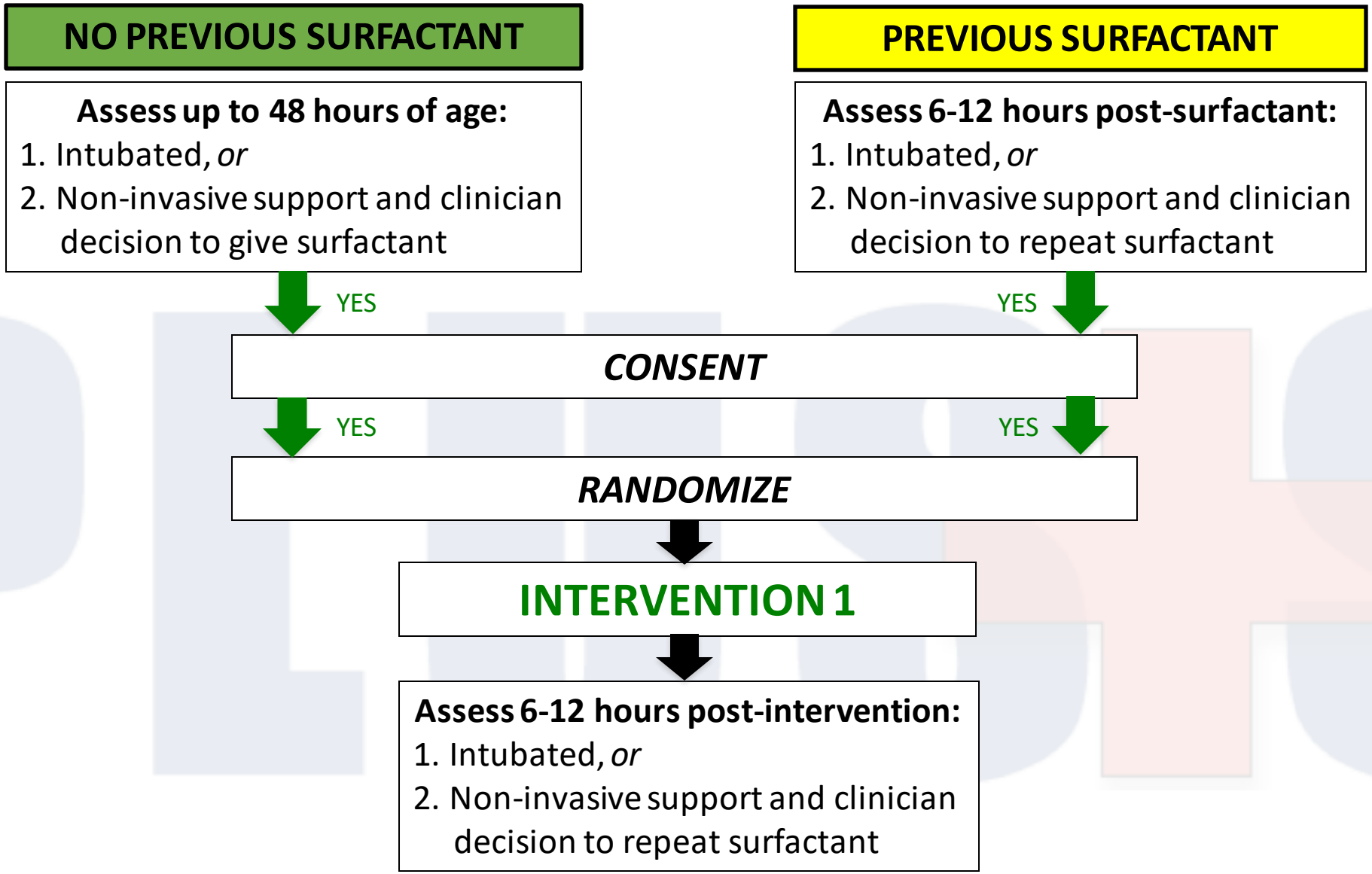
1. Intubated, *or*
2. Non-invasive support and clinician decision to give surfactant

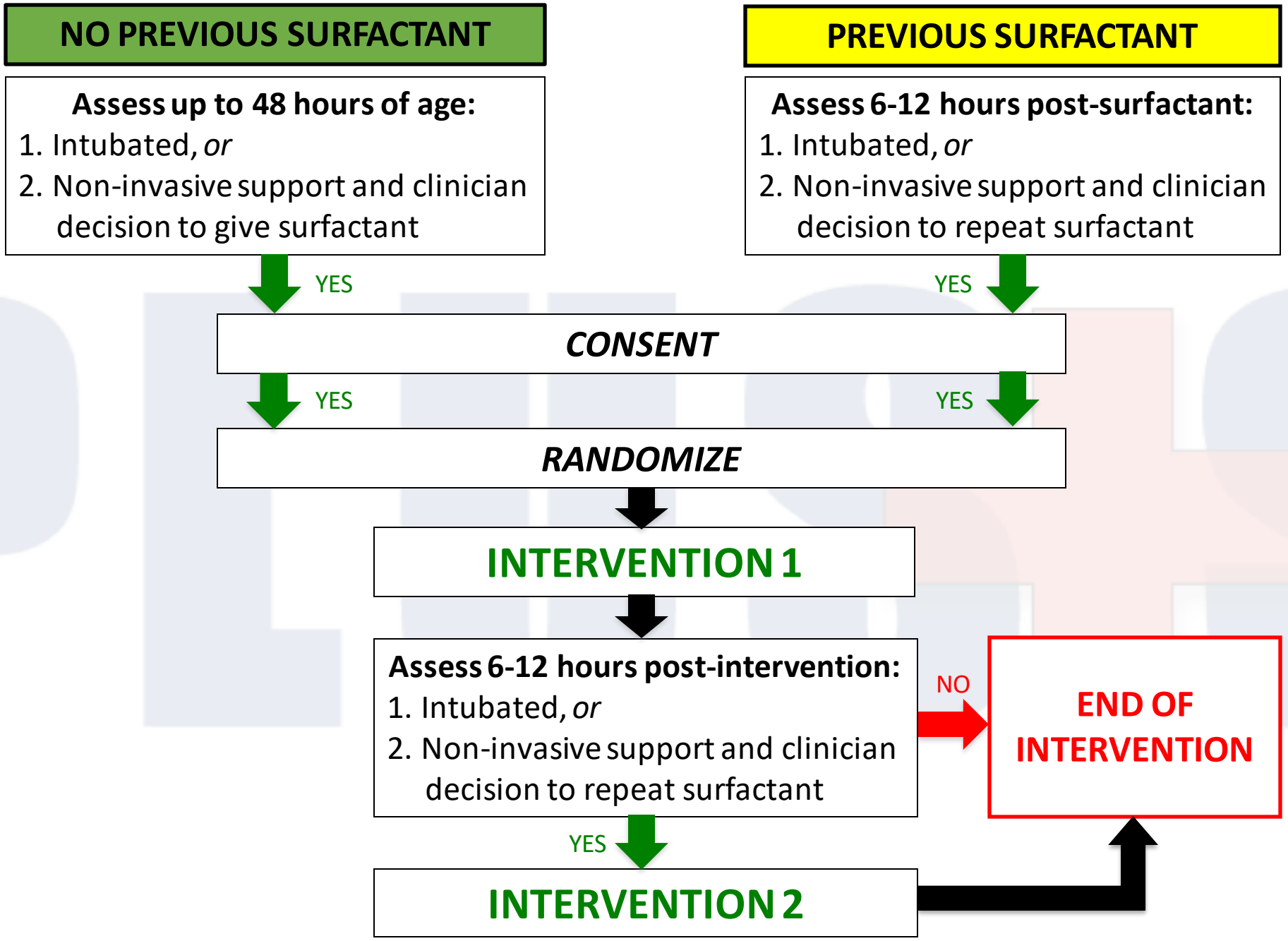
PREVIOUS SURFACTANT

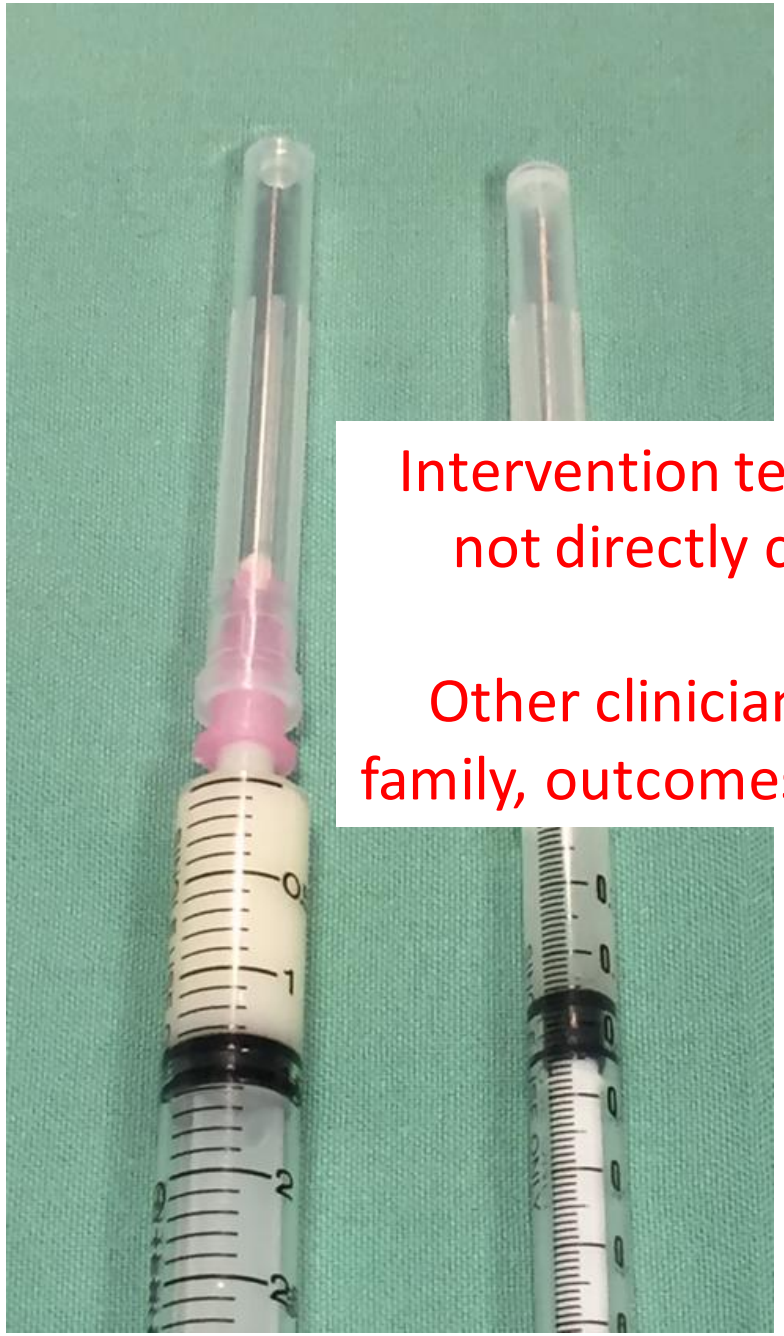
Assess 6-12 hours post-surfactant:

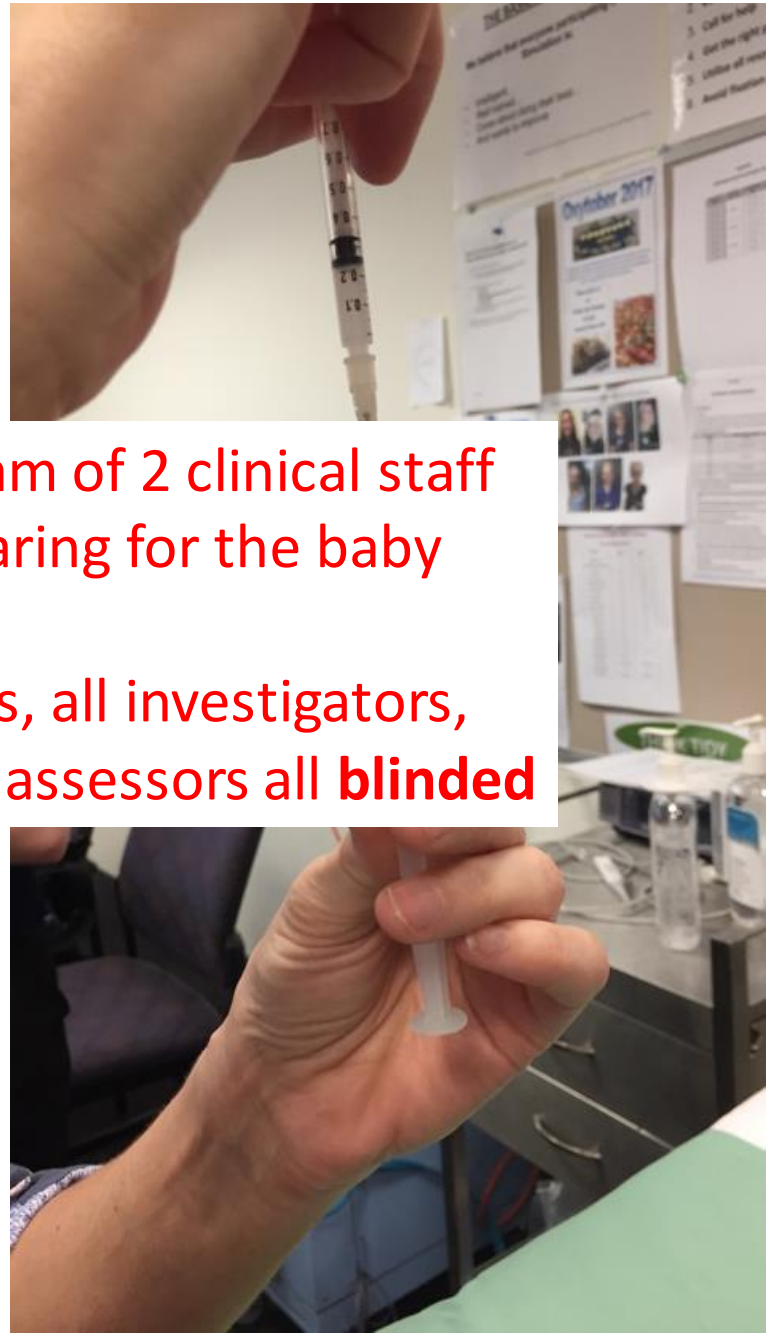
1. Intubated, *or*
2. Non-invasive support and clinician decision to repeat surfactant

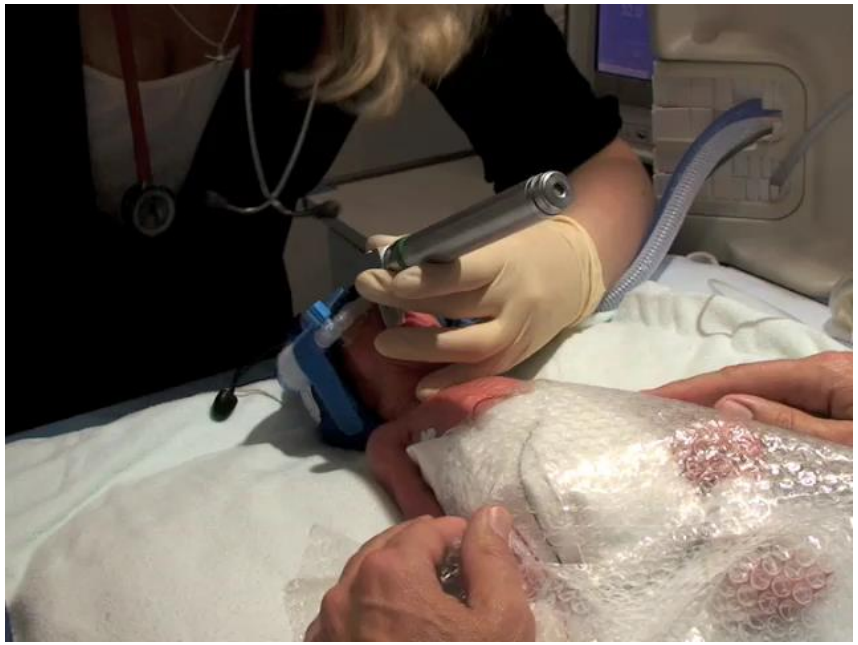

NO PREVIOUS SURFACTANT
Assess up to 48 hours of age:
1. Intubated, or
2. Non-invasive support and clinician decision to give surfactant
PREVIOUS SURFACTANT
Assess 6-12 hours post-surfactant:
1. Intubated, or
2. Non-invasive support and clinician decision to repeat surfactant
YES
YES
CONSENT
YES
YES
RANDOMIZE
INTERVENTION 1


NO PREVIOUS SURFACTANT
Assess up to 48 hours of age:
1. Intubated, or
2. Non-invasive support and clinician decision to give surfactant
PREVIOUS SURFACTANT
Assess 6-12 hours post-surfactant:
1. Intubated, or
2. Non-invasive support and clinician decision to repeat surfactant
YES
YES
CONSENT
YES
YES
RANDOMIZE
INTERVENTION 1
Assess 6-12 hours post-intervention:
1. Intubated, or
2. Non-invasive support and clinician decision to repeat surfactant


NO PREVIOUS SURFACTANT
Assess up to 48 hours of age:
1. Intubated, or
2. Non-invasive support and clinician decision to give surfactant
PREVIOUS SURFACTANT
Assess 6-12 hours post-surfactant:
1. Intubated, or
2. Non-invasive support and clinician decision to repeat surfactant
YES
YES
CONSENT
YES
YES
RANDOMIZE
INTERVENTION 1
Assess 6-12 hours post-intervention:
1. Intubated, or
2. Non-invasive support and clinician decision to repeat surfactant
NO
END OF INTERVENTION
YES
INTERVENTION 2







Intervention team of 2 clinical staff not directly caring for the baby

Other clinicians, all investigators, family, outcomes assessors all **blinded**

PLUS+S

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

BPD if any of the following:

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

BPD if any of the following:

1. Mechanical ventilation, CPAP, NIPPV, or nasal high-flow ≥2 L/min

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

BPD if any of the following:

1. Mechanical ventilation, CPAP, NIPPV, or nasal high-flow ≥2 L/min
2. Effective $FiO_2 \geq 0.30$ if receiving oxygen or nasal prong flow <2 L/min

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

BPD if any of the following:

1. Mechanical ventilation, CPAP, NIPPV, or nasal high-flow ≥2 L/min
2. Effective $FiO_2 \geq 0.30$ if receiving oxygen or nasal prong flow <2 L/min
3. Effective $FiO_2 < 0.30$ if receiving oxygen or nasal prong flow <2 L/min AND an unsuccessful air reduction trial

PLUS

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Assessed between **36^{+0} and 36^{+6} weeks' PMA**

BPD if any of the following:

1. Mechanical ventilation, CPAP, NIPPV, or nasal high-flow ≥2 L/min
2. Effective $FiO_2 \geq 0.30$ if receiving oxygen or nasal prong flow <2 L/min
3. Effective $FiO_2 < 0.30$ if receiving oxygen or nasal prong flow <2 L/min AND an unsuccessful air reduction trial

Infants discharged home <36+0 weeks' without respiratory support or oxygen = "no BPD"

PLUS+S

Sample size

Estimated incidence of primary outcome 50% (in 2017)

90% power to detect increase from **50% to 60%** requires **1038** infants

Aim to recruit a total of **1060 infants** **(530 each arm)**

Randomization

Online via RedCAP

Individually randomized

Randomly-permuted block sizes

1. Gestational age:
   <26 vs. 26-27 completed weeks'
2. Mode of respiratory support:
   MV vs. non-invasive support
3. Prior surfactant: yes/no

Consent

Prospective, written

- Antenatal
- Very early postnatal
- Later postnatal

PLUS+S

Protocol

Manley *et al. Trials* (2023) 24:320
https://doi.org/10.1186/s13063-023-07257-5

Trials

STUDY PROTOCOL Open Access

Intratracheal budesonide mixed with surfactant to increase survival free of bronchopulmonary dysplasia in extremely preterm infants: study protocol for the international, multicenter, randomized PLUSS trial

Brett J. Manley[1*], C. Omar F. Kamlin[1], Susan Donath[2], Li Huang[3], Pita Birch[4], Jeanie L. Y. Cheong[1], Peter A. Dargaville[5,6], Jennifer A. Dawson[1], Lex W. Doyle[1], Susan E. Jacobs[1], Rodney Wilson[7], Peter G. Davis[1] and Christopher J. D. McKinlay[8]

Statistical Analysis Plan

Francis *et al. Trials* (2023) 24:709
https://doi.org/10.1186/s13063-023-07650-0

Trials

UPDATE Open Access

Intratracheal budesonide mixed with surfactant to increase survival free of bronchopulmonary dysplasia in extremely preterm infants: statistical analysis plan for the international, multicenter, randomized PLUSS trial

Kate L Francis[1,2], Christopher J D McKinlay[3], C Omar F Kamlin[4], Jeanie L Y Cheong[1,4,5], Peter A Dargaville[6,7], Jennifer A Dawson[1,4], Lex W Doyle[4,5], Susan E Jacobs[4,5], Peter G Davis[1,4,5], Susan M Donath[1,2] and Brett J Manley[1,4,5*]

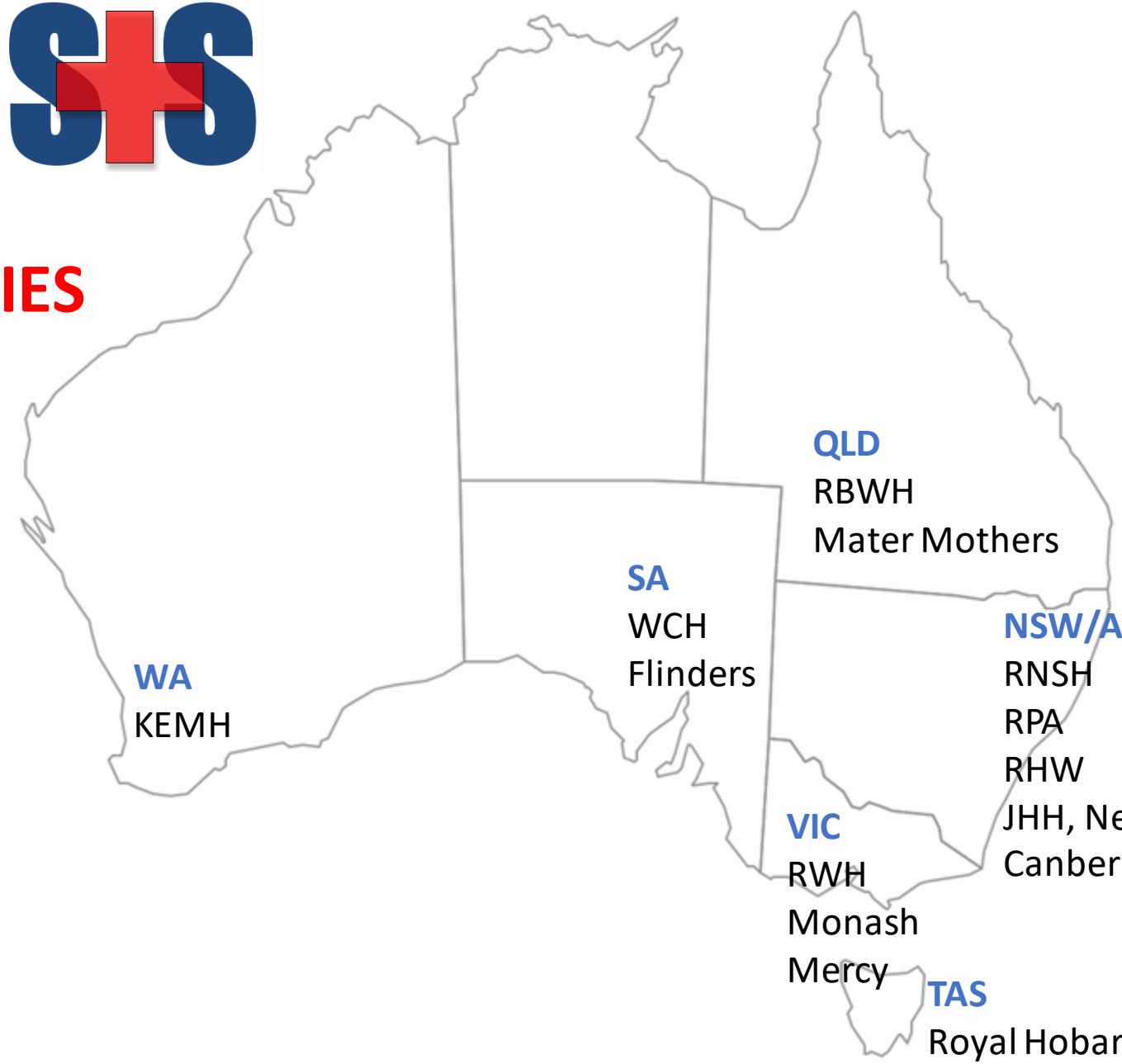
PLUSS


PLUSS
The PLUSS Trial - Preventing Lung
Disease Using Surfactant + Steroid

RESULTS

PLUS

21 NICUs
4 COUNTRIES



WA
KEMH

SA
WCH
Flinders

QLD
RBWH
Mater Mothers

NSW/ACT
RNSH
RPA
RHW
JHH, Newcastle
Canberra

VIC
RWH
Monash
Mercy

TAS
Royal Hobart

CANADA
RAH,
Edmonton

SINGAPORE
KK Women's and
Children's

NEW ZEALAND
Auckland
Middlemore
Christchurch
Wellington
Waikato

Demographics

Maternal Ethnicity	Surfactant + Budesonide	Surfactant alone
European (Caucasian)	60%	56%
Asian	18%	21%
Māori	8%	7%
Aboriginal or Torres Strait Islander	6%	6%
Pasifika	4%	5%
Canadian First Nations, Ink/Inuit, Metis	1%	2%
Other	4%	4%

Demographics

Maternal	Surfactant + Budesonide	Surfactant alone
Exposure to any antenatal corticosteroid	96%	96%
2+ doses of antenatal corticosteroid	67%	66%

Demographics

Maternal	Surfactant + Budesonide	Surfactant alone
Exposure to any antenatal corticosteroid	96%	96%
2+ doses of antenatal corticosteroid	67%	66%
Histological chorioamnionitis	40%	42%
Prolonged rupture of membranes >18 hours	29%	33%

Demographics

Maternal	Surfactant + Budesonide	Surfactant alone
Exposure to any antenatal corticosteroid	96%	96%
2+ doses of antenatal corticosteroid	67%	66%
Histological chorioamnionitis	40%	42%
Prolonged rupture of membranes >18 hours	29%	33%
Labor before birth	63%	62%
Cesarean section	63%	66%

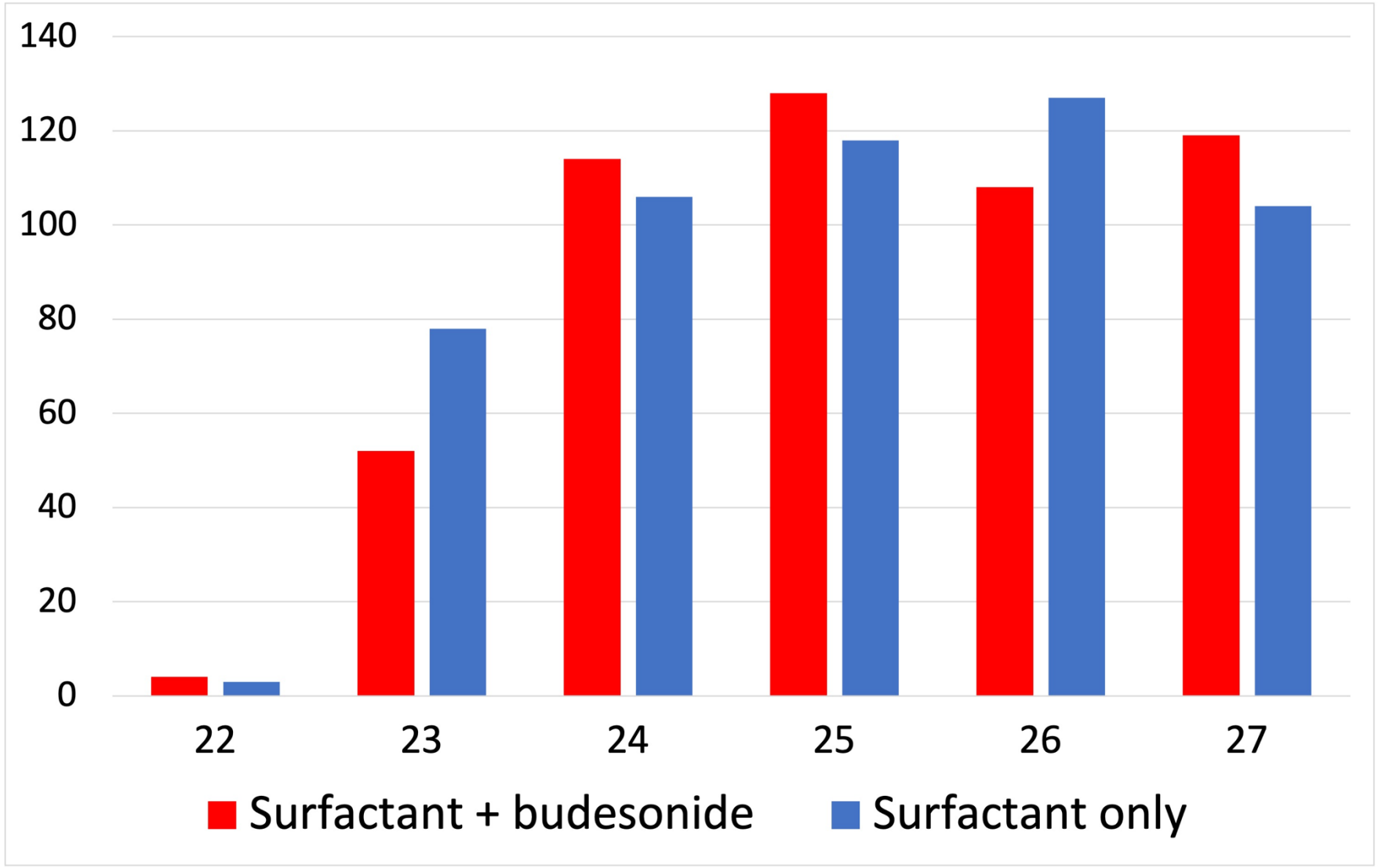
Demographics

Infants	Surfactant + Budesonide	Surfactant alone
GA at birth, weeks, mean (SD)	25.7 (1.3)	25.5 (1.4)
Birth weight, grams, mean (SD)	782 (198)	769 (196)

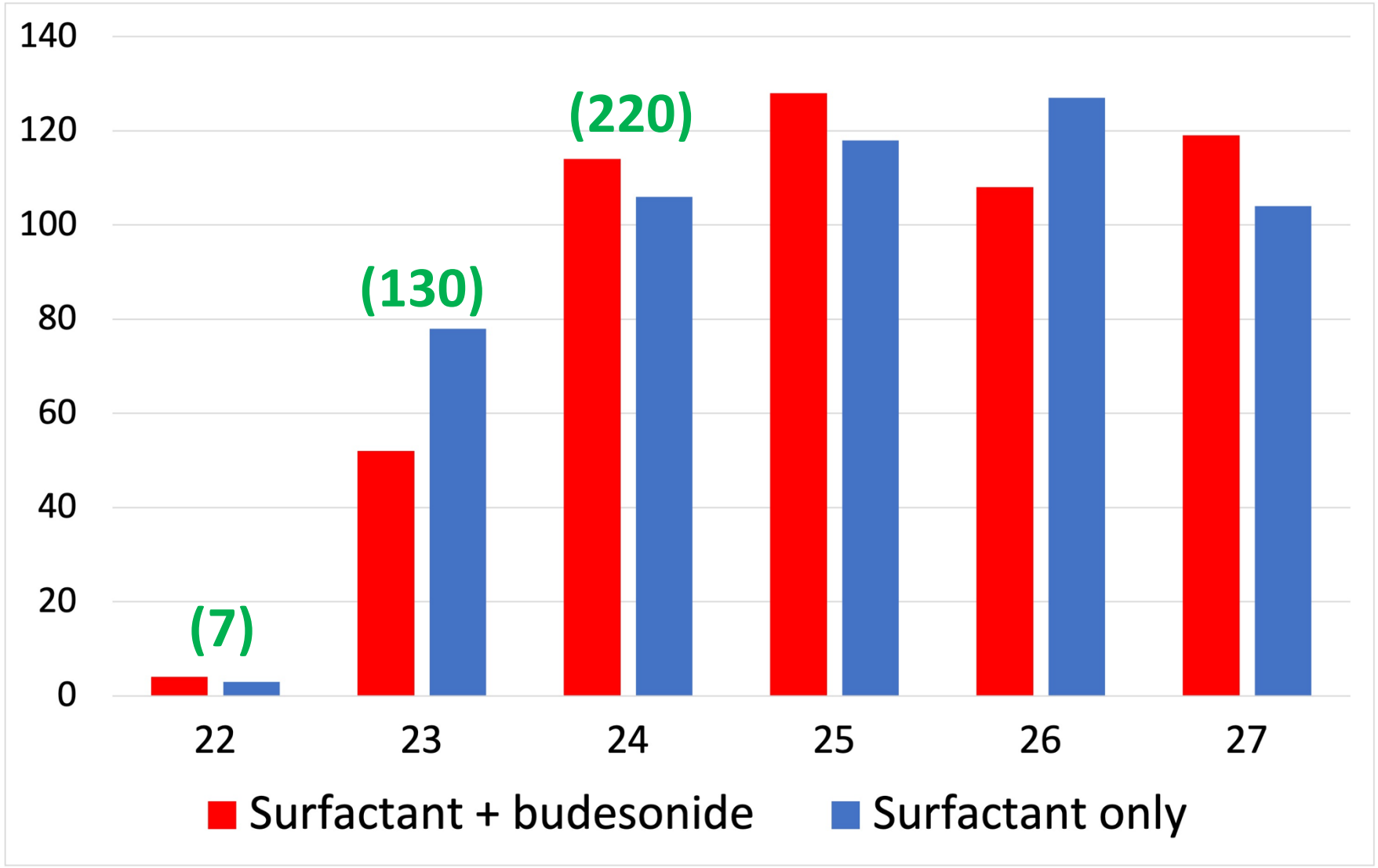
Demographics

Infants	Surfactant + Budesonide	Surfactant alone
GA at birth, weeks, mean (SD)	25.7 (1.3)	25.5 (1.4)
Birth weight, grams, mean (SD)	782 (198)	769 (196)
SGA <10th centile	14%	14%
Male	55%	56%
Multiple birth	26%	31%
Intubated in the DR	64%	61%
Apgar @5 mins, median (IQR)	7 (6-8)	7 (6-8)

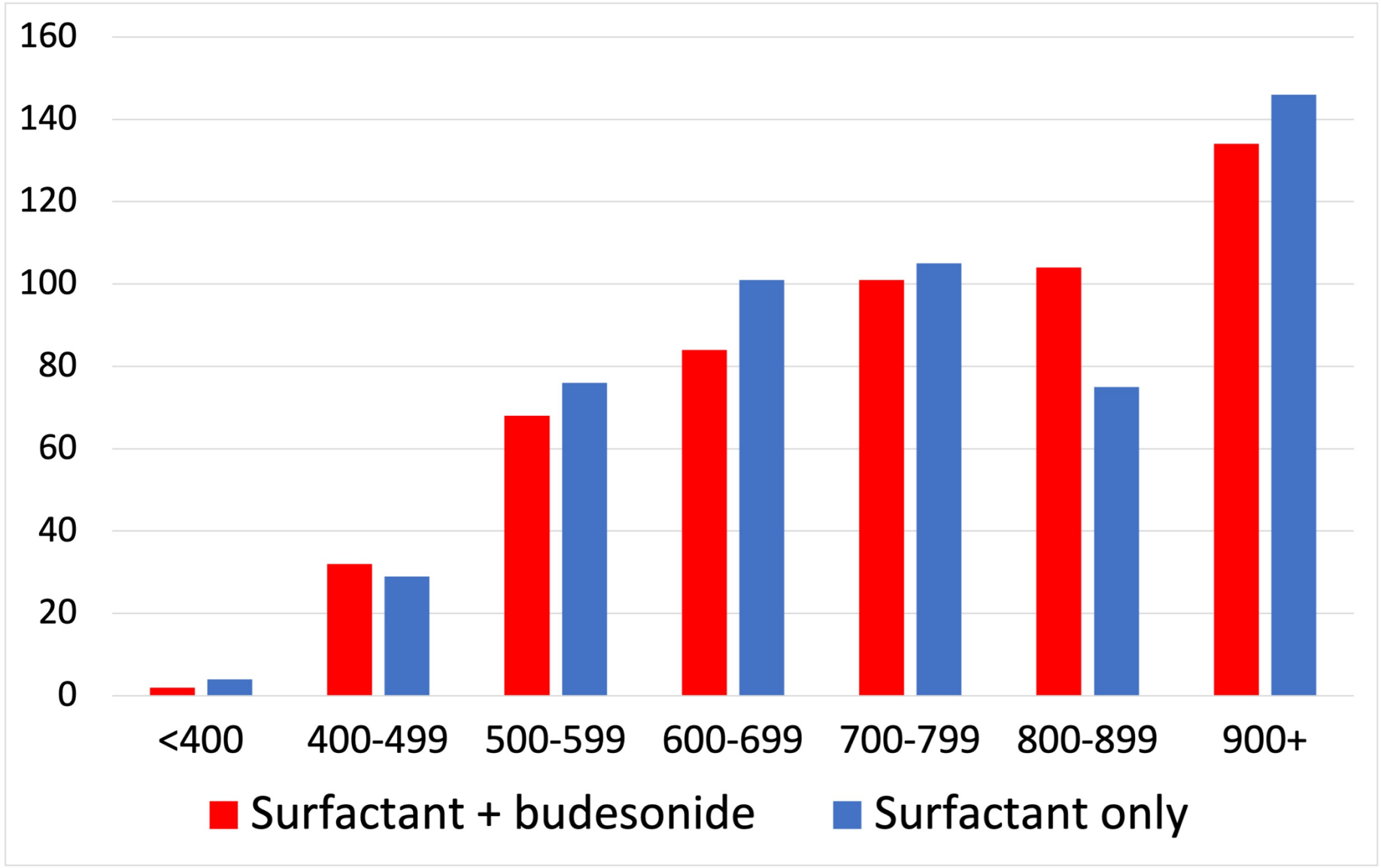
Gestational age, completed weeks, no.



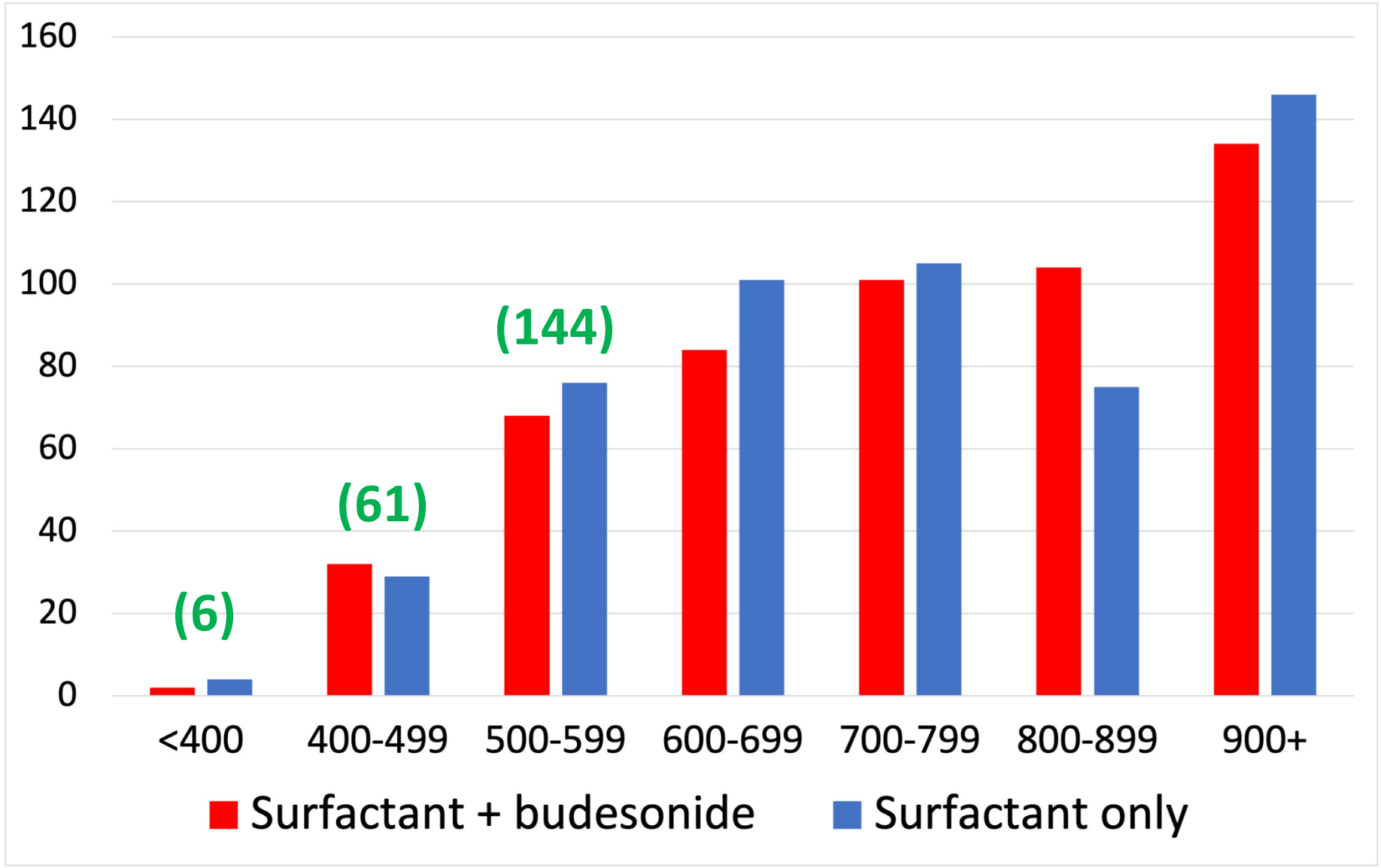
Gestational age, completed weeks, no.



Birth weight, grams, no.



Birth weight, grams, no.



Demographics

Infants	Surfactant + Budesonide	Surfactant alone
Previous surfactant	57%	57%

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pH, mean (SD)	7.29 (0.09)	7.30 (0.08)
pCO_2, mm Hg, mean (SD)	47.3 (10.5)	46.5 (11.3)
Blood glucose, mmol/L, mean (SD)	4.9 (2.3)	4.9 (2.4)

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pCO_2, mm Hg, mean (SD)	47.3 (10.5)	46.5 (11.3)
Blood glucose, mmol/L, mean (SD)	4.9 (2.3)	4.9 (2.4)
FiO_2, median (IQR)	0.30 (0.23-0.42)	0.30 (0.23-0.45)

Intervention

	Surfactant + budesonide	Surfactant alone
Age at randomisation, hours, median (IQR)	4.2 (1.0-8.0)	5.0 (1.0-8.0)
No intervention	0.8%	0.7%
One intervention	31%	27%
Two interventions	69%	73%

Primary outcome

Survival without physiological BPD at 36 weeks' PMA

Surfactant + Budesonide	VERSUS	Surfactant only
25.5% (134/525)		**22.6%** (121/536)

Adjusted risk difference (95% CI)*

2.7% (-2.1%, 7.4%)

*Adjusted for stratification variables (GA, prior surfactant, mode of respiratory support)

PLUS+S

Primary outcome

Death or BPD at 36 weeks' PMA

Surfactant + Budesonide	VERSUS	Surfactant only
74.5%		**77.4%**

Adjusted risk difference (95% CI)*

-2.7% (-7.4%, 2.1%)

*Adjusted for stratification variables (GA, prior surfactant, mode of respiratory support)

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	Surfactant + budesonide	Surfactant alone	Adjusted risk difference (95% CI)*
Alive at 36+0 weeks' PMA	83.2%	80.4%	1.5 (-2.8, 5.8)
BPD	69.3%	71.9%	-2.6 (-8.3, 3.1)

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Alive at hospital discharge*	81.3%	78.5%	2.0 (-2.6 to 6.5)

*A few babies remain in hospital

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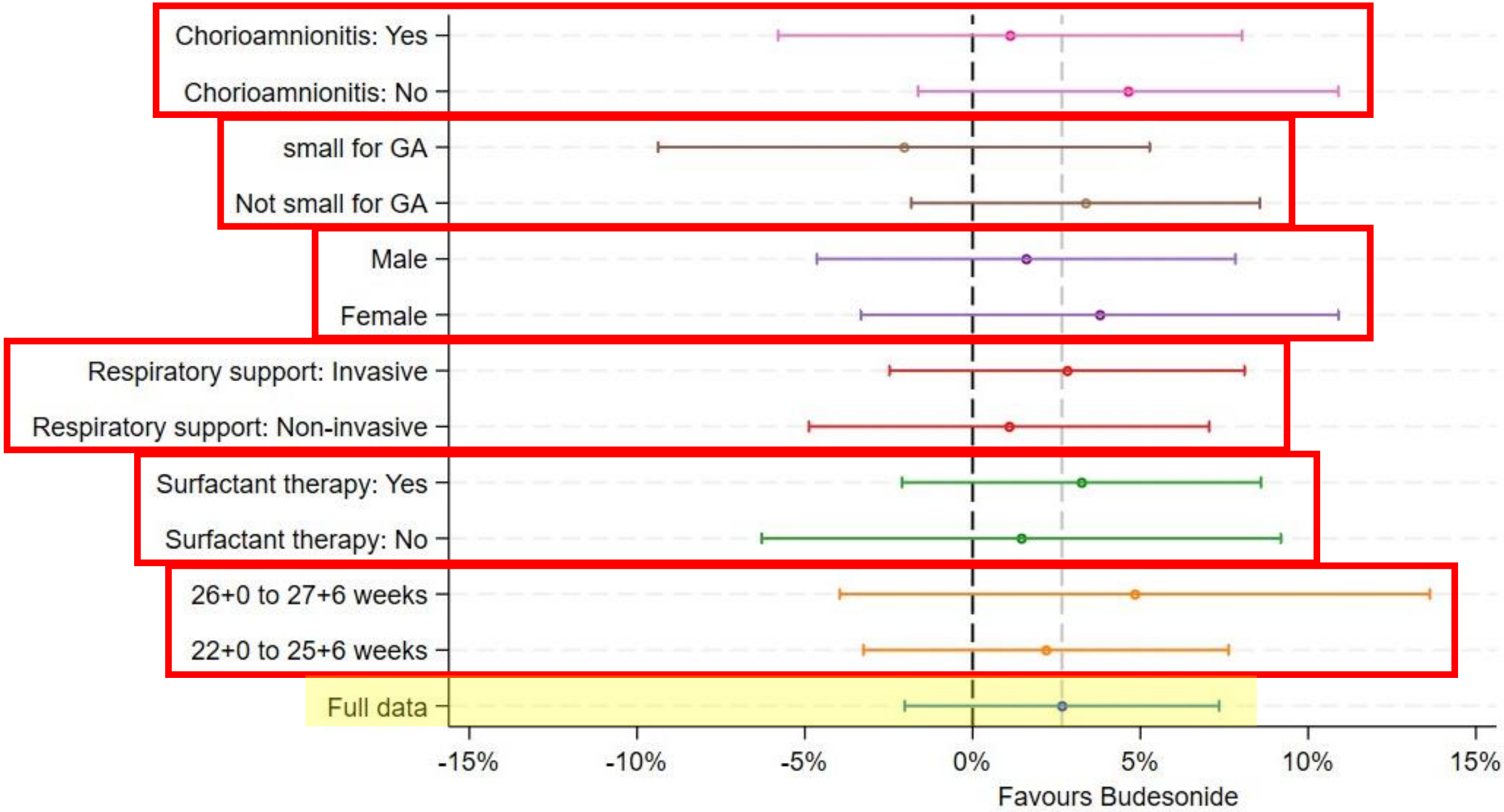
BPD severity (Jensen *et al* 2019)

None	30%	28%	ref
Mild (grade 1)	5%	7%	-4.1 (-12.5, 4.2)
Moderate (grade 2)	60%	62%	-3.0 (-9.5, 3.6)
Severe (grade 3)	5%	3%	3.3 (-4.0, 10.6)

PLUS+S


Chorioamnionitis: Yes
Chorioamnionitis: No
small for GA
Not small for GA
Male
Female
Respiratory support: Invasive
Respiratory support: Non-invasive
Surfactant therapy: Yes
Surfactant therapy: No
26+0 to 27+6 weeks
22+0 to 25+6 weeks
Full data
-15%
-10%
-5%
0%
5%
10%
15%
Favours Budesonide

Secondary outcomes

	Surfactant + budesonide	Surfactant alone
Respiratory support or oxygen at 40 weeks' PMA	42%	45%

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Secondary outcomes

	Surfactant + budesonide	Surfactant alone
Respiratory support or oxygen at 40 weeks' PMA	42%	45%
Systemic postnatal corticosteroids for lung disease	33%	33%
Discharged home on oxygen	34%	34%
Duration of MV, days, median (IQR)	10 (2-26)	10 (3-26)
PMA ceasing respiratory support, median (IQR)	36.6 (34.0-39.3)	36.4 (33.0-39.6)
PMA ceasing supplemental oxygen, median (IQR)	38.8 (32.0-42.0)	37.5 (32.3-41.9)
Duration of hospitalization, days, median (IQR)	110 (90-133)	110 (94-135)

Secondary outcomes

Neonatal morbidities	Surfactant + budesonide	Surfactant alone
IVH grade III or IV	16%	18%
ROP stage 2 or above (n=872)	56%	54%
NEC Bells stage 2 or above	8%	8%
PDA treated (anti-prostaglandin therapy or surgery)	26%	29%

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Growth Z-scores at 36 weeks' PMA	Surfactant + budesonide	Surfactant alone
Weight	-0.8 (1.2)	-0.9 (1.1)
Length	-2.3 (1.7)	-2.4 (1.6)
Head circumference	-1.1 (1.6)	-1.2 (1.4)
BMI	1.0 (1.2)	1.0 (1.2)

Potential adverse effects of budesonide

<14 days after first intervention	Surfactant + budesonide	Surfactant alone
Spontaneous intestinal perforation	4%	3%
Gastrointestinal hemorrhage	3%	4%
Pulmonary hemorrhage <48 hours*	7%	10%
Anti-hypertensive agents	0.4%	0.6%
Hyperglycemia >10 mmol/L or insulin	65%	62%
Late onset sepsis	14%	15%

*aRD -3.2 (-6.6, 0.2)

Conclusions

In this international, multicenter, randomized trial that recruited a population of extremely small and extremely immature infants, early intratracheal budesonide mixed with surfactant, compared with surfactant alone, did *not* result in an important increase in survival free of BPD

- Small but not "significant" increase of 2.7% (~12% relative increase)
- No difference in other respiratory outcomes or potential adverse effects
- Longer-term outcomes important
- Replication and meta-analysis important

PLUS+S2

Survival free of moderate-severe neurodisability at 2 years

- Bayley III/IV, cerebral palsy
- Growth
- Respiratory health
- Behaviour
- Quality of life
- Cost-effectiveness

357 children assessed at 2 years
566 primary outcomes (incl. deaths)



“BiB” NICHD Neonatal Research Network

- Very similar inclusion criteria
- Very similar intervention (Curosurf)
- Same primary outcome
- Similar sample size (~50% progress)

…Meta-analysis, IPDMA