SAP

SOCIEDAD ARGENTINA DE PEDIATRÍA

Why we don’t always do what trials tell us to do!

Roger F. Soll, M.D.
H. Wallace Professor of Neonatology,
University of Vermont
President, Vermont Oxford Network
Coordinating Editor, Cochrane Neonatal

roger.soll@uvmhealth.org

Why we don’t always do what trials tell us to do!

Disclosure

Dr. Soll is President of
The Vermont Oxford Network and
Coordinating Editor of Cochrane Neonatal

No other relevant financial issues to disclose.

Evidence Based Medicine

Improvement Formula

Do What?
Evidence Based Medicine

Do How?
Evidence Based Practice

Batalden, PB, Davidoff F. Qual Saf Health Care 2007;16:2-3

QSHC ONLINE

JAMA The Journal of the American Medical Association

Commentary

September 12, 2007

Limitations of Applying Summary Results of Clinical Trials to Individual Patients

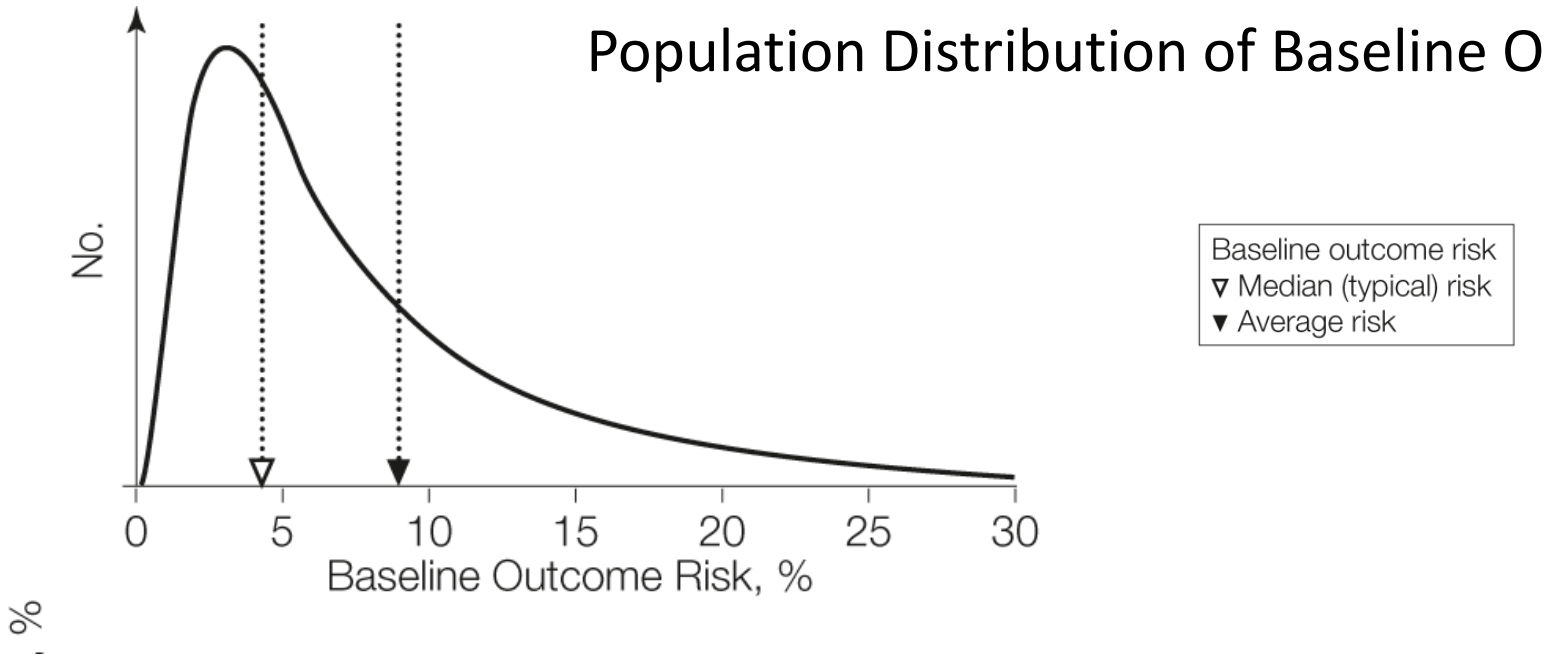
The Need for Risk Stratification

David M. Kent, MD, MS; Rodney A. Hayward, MD

JAMA. 2007;298(10):1209-1212. doi:10.1001/jama.298.10.1209

JAMA The Journal of the American Medical Association

Population Distribution of Baseline Outcome Risk

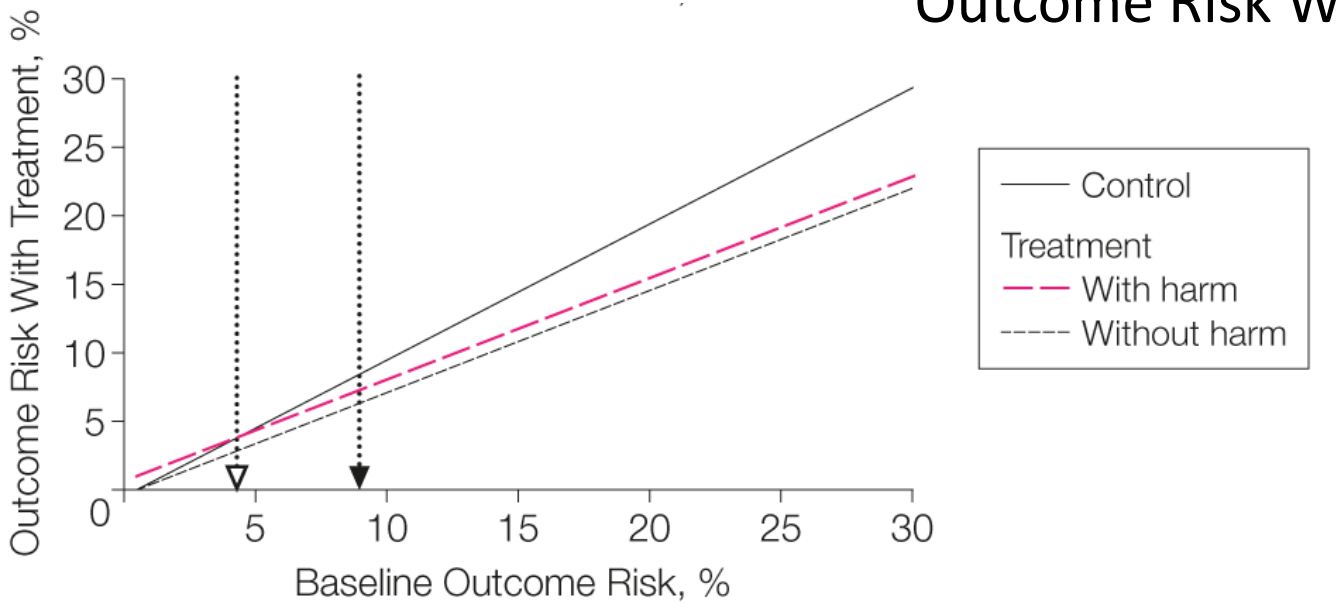


Patients enrolled in clinical trials often have greatly different baseline risks for the outcome of interest. The risk distribution is often skewed; a relatively small group of high risk patients with multiple risk factors account for a large number of the outcomes and the mean risk might be considerably higher than the risk in the typical (median) patient

David M. Kent, MD, MS; Rodney A. Hayward, MD. *JAMA.* 2007;298(10):1209-1212.

JAMA The Journal of the American Medical Association

Outcome Risk With Treatment



A constant relative risk reduction (25% in this case) leads to increasing benefits as baseline risk increases; treatment and control outcome rates progressively diverge at higher baseline risks.

When a therapy is associated with even a small amount of treatment-related harm, low-risk patients are unlikely to benefit at all.

David M. Kent, MD, MS; Rodney A. Hayward, MD. *JAMA*. 2007;298(10):1209-1212.

JAMA The Journal of the American Medical Association

Patients enrolled in clinical trials often have greatly different baseline risks for the outcome of interest…..

David M. Kent, MD, MS; Rodney A. Hayward, MD. *JAMA.* 2007;298(10):1209-1212.

Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants.

Cleminson J, Austin N, McGuire W. Cochrane Database of Systematic Reviews 2015, Issue 10. Art. No.: CD003850. DOI: 10.1002/14651858.CD003850.pub5.

Identified 15 eligible trials enrolling a total of 1690 infants.

Ten trials (1371 infants) compared systemic antifungal prophylaxis versus placebo or no drug.

These trials were generally of good methodological quality.

Cochrane Neonatal

Vermont Oxford NETWORK

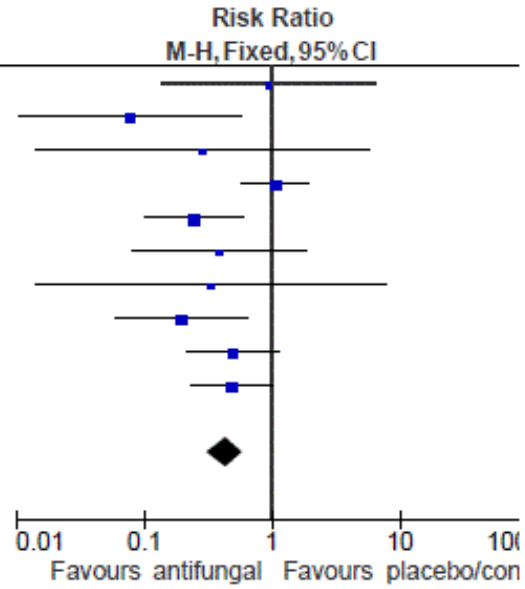
Prophylactic systemic antifungal agents to prevent mortality and morbidity in very low birth weight infants.

Invasive Fungal Infection (relative risk)

Study or Subgroup	Systemic antifungal Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
Kicklighter 2001	2	53	2	50	2.0%	0.94 [0.14, 6.44]	2001
Kaufman 2001	1	50	13	50	12.5%	0.08 [0.01, 0.57]	2001
Cabrera 2002	0	6	1	5	1.6%	0.29 [0.01, 5.79]	2002
Parikh 2007	16	60	15	60	14.4%	1.07 [0.58, 1.96]	2007
Manzoni 2007a	7	216	14	106	18.1%	0.25 [0.10, 0.59]	2007
Kim 2010	2	28	5	27	4.9%	0.39 [0.08, 1.82]	2010
Arrieta 2010	0	20	1	20	1.4%	0.33 [0.01, 7.72]	2010
Aydemir 2011a	3	93	15	91	14.6%	0.20 [0.06, 0.65]	2011
Benjamin 2014	8	188	15	173	15.0%	0.49 [0.21, 1.13]	2014
Kirpal 2015	8	38	16	37	15.6%	0.49 [0.24, 1.00]	2015
Total (95% CI)		752		619	100.0%	0.43 [0.31, 0.59]	
Total events	47		97				

Heterogeneity: Chi² = 15.59, df = 9 (P = 0.08); I² = 42%

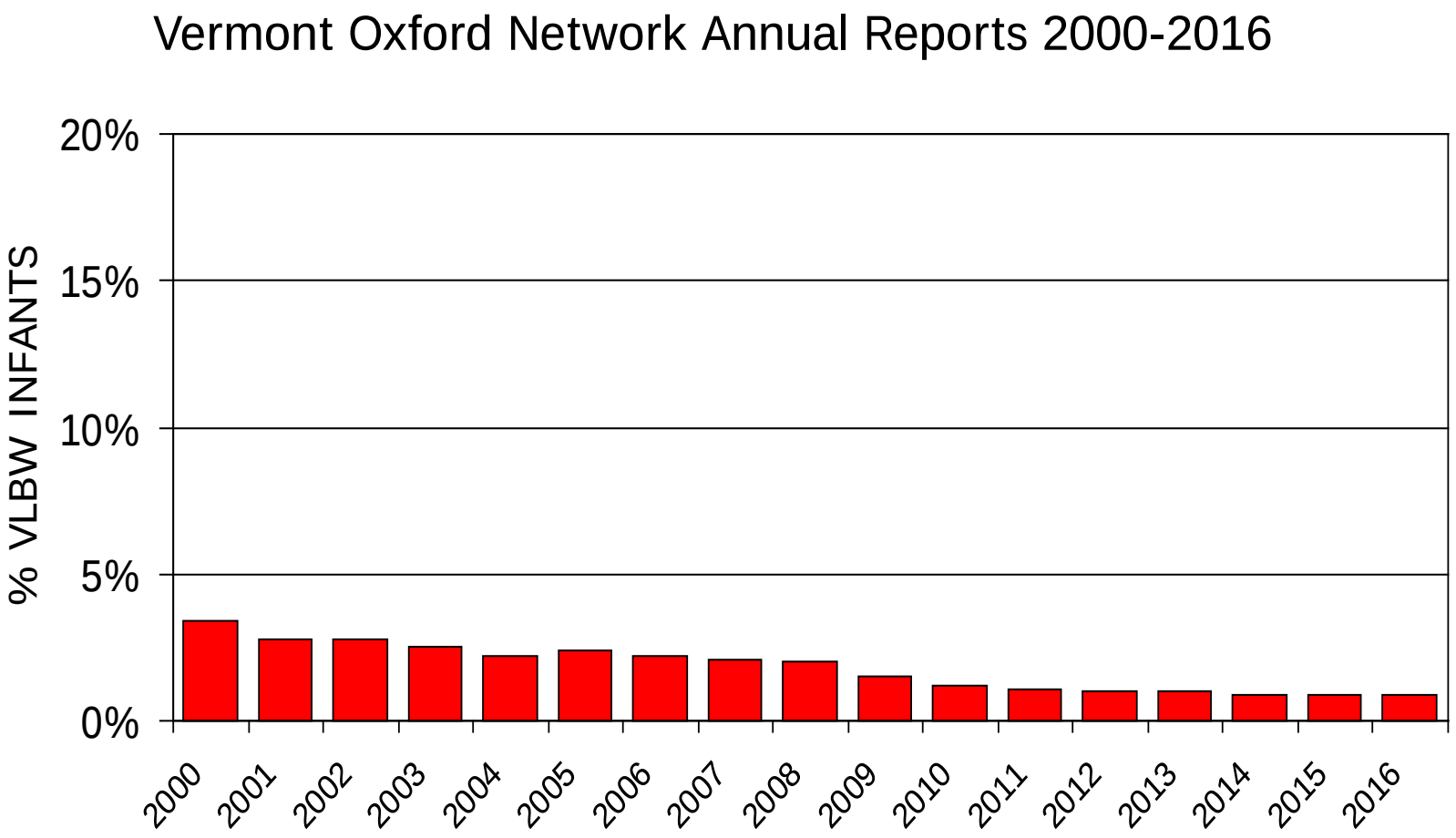
Test for overall effect: Z = 5.16 (P < 0.00001)



Cochrane Neonatal

Typical relative risk 0.43, 95% CI 0.31 to 0.59
Typical risk difference -0.09, 95% CI -0.12 to -0.06

Fungal Sepsis



Rates of Fungal Sepsis by Gestational Age Category
Vermont Oxford Network 2016

GA Category	N	Mean (%)	Q1	Q3
< 24 Weeks	2,249	3.9%	0.0%	0.0%
24 to 26 Weeks	13,212	1.9%	0.0%	0.0%
27 to 29 Weeks	22,625	0.6%	0.0%	0.0%
30 to 32 Weeks	16,240	0.3%	0.0%	0.0%
> 32 Weeks	4,820	0.1%	0.0%	0.0%
ALL INFANTS	59,146	0.9%	0.0%	0.7%

"It's hard to improve on zero!"

Prophylactic antifungal therapy

Authors' conclusions

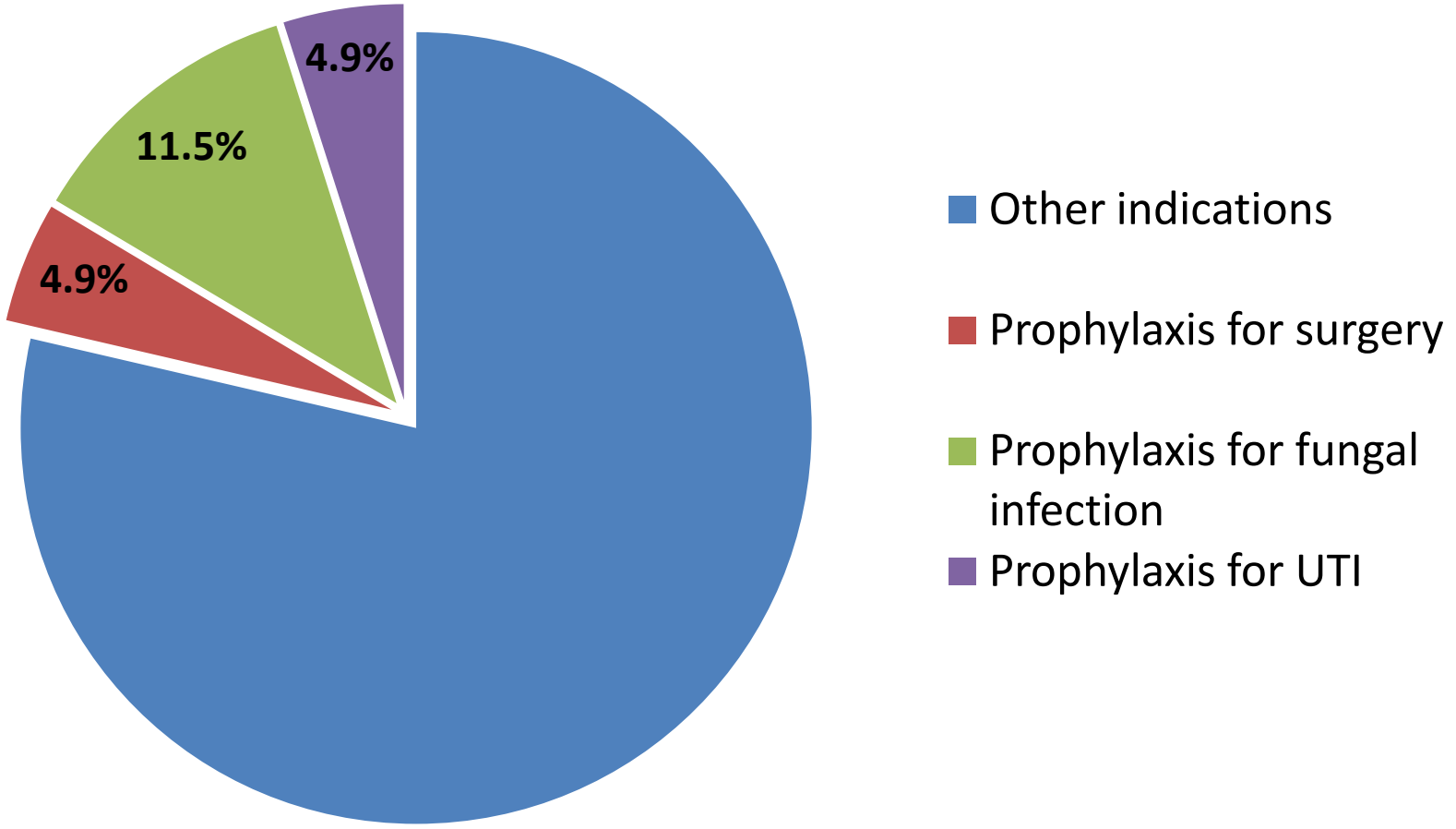
Prophylactic systemic antifungal therapy reduces the incidence of invasive fungal infection in very preterm or very low birth weight infants.

This finding should be interpreted and applied cautiously since the incidence of invasive fungal infection was very high in the control groups of many of the included trials.

Meta-analysis does not demonstrate a statistically significant effect on mortality. There are currently only limited data on the long-term neurodevelopmental consequences for infants exposed to this intervention**. In addition, there is a need for further data on the effect of the intervention on the emergence of organisms with antifungal resistance.**

Of infants on antibiotics….

22% were being treated "prophylactically"



Risk factors for fungal infection in preterm infants

Risk factor	Odds Ratio (95% CI)
Gestational age < 25 weeks	4.15 (3.12 to 6.12)
Male	1.28 (1.01 to 1.62)
Central catheter	3.94 (1.48 to 12.3)
Broad-spectrum antibiotics in week before culture	1.77 (1.33 to 2.29)
Cephalosporin use by day of life 3	1.77 (1.31 to 2.38)
H2 blockers	2.44 (1.11 to 5.29)

Hsieh, Emily, P. Brian Smith, and Daniel K. Benjamin. “Neonatal Fungal Infections: When to Treat?” Early human development 88.Suppl 2 (2012): S6–S10. PMC.

JAMA The Journal of the American Medical Association

A constant relative risk reduction leads to increasing benefits as baseline risk increases; treatment and control outcome rates progressively diverge at higher baseline risks.

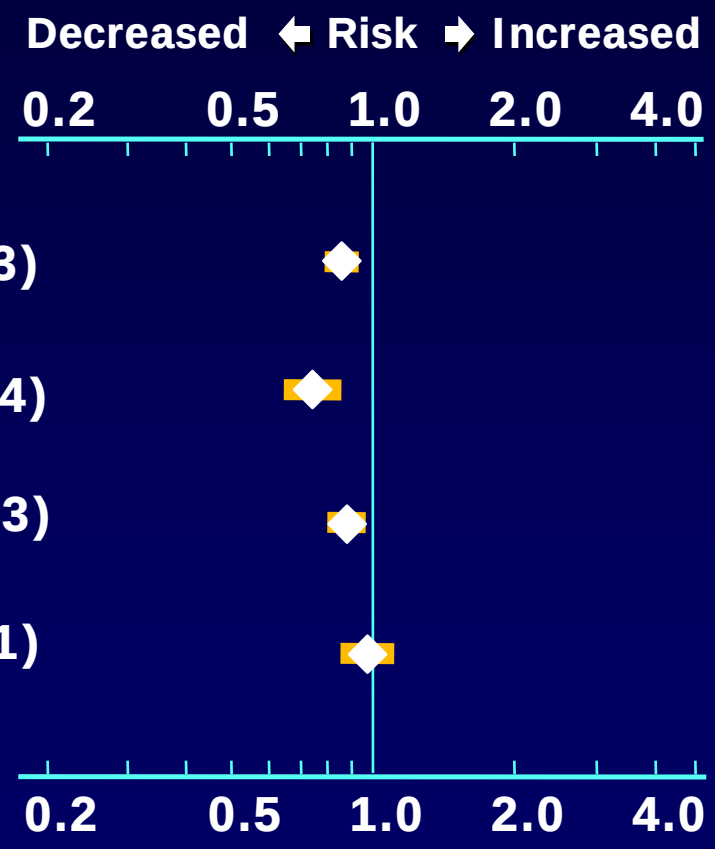
When a therapy is associated with even a small amount of treatment-related harm, low-risk patients are unlikely to benefit at all.

David M. Kent, MD, MS; Rodney A. Hayward, MD. *JAMA*. 2007;298(10):1209-1212.

EARLY (≤ 7 DAYS) POSTNATAL STEROID THERAPY

META-ANALYSIS OF 32 RANDOMIZED CONTROLLED TRAILS

Outcome (N Studies)	Typical Risk Difference (95% CI)
CLD @ 28 DAYS (17)	-0.07 (-0.10,-0.03)
CLD @ 36 WEEKS (24)	-0.07 (-0.09, -0.04)
DEATH/CLD @ 36 WKS (25)	-0.06 (-0.09, -0.03)
MORTALITY (30)	-0.01 (-0.03, 0.01)

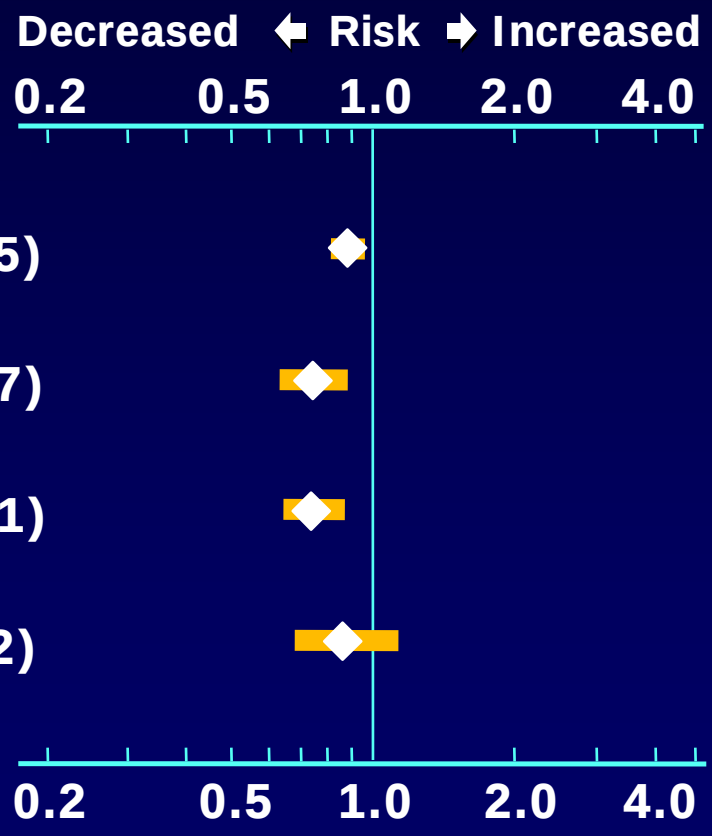


Doyle 2017

LATE (> 7 DAYS) POSTNATAL STEROID THERAPY

META-ANALYSIS OF 21 RANDOMIZED CONTROLLED TRAILS

Outcome (N Studies)	Typical Risk Difference (95% CI)
CLD @ 28 DAYS (6)	-0.11 (-0.17, -0.05)
CLD @ 36 WEEKS (11)	-0.15 (-0.22, -0.07)
DEATH/CLD @ 36 WKS (11)	-0.18 (-0.25, -0.11)
MORTALITY (19)	-0.03 (-0.07, 0.02)

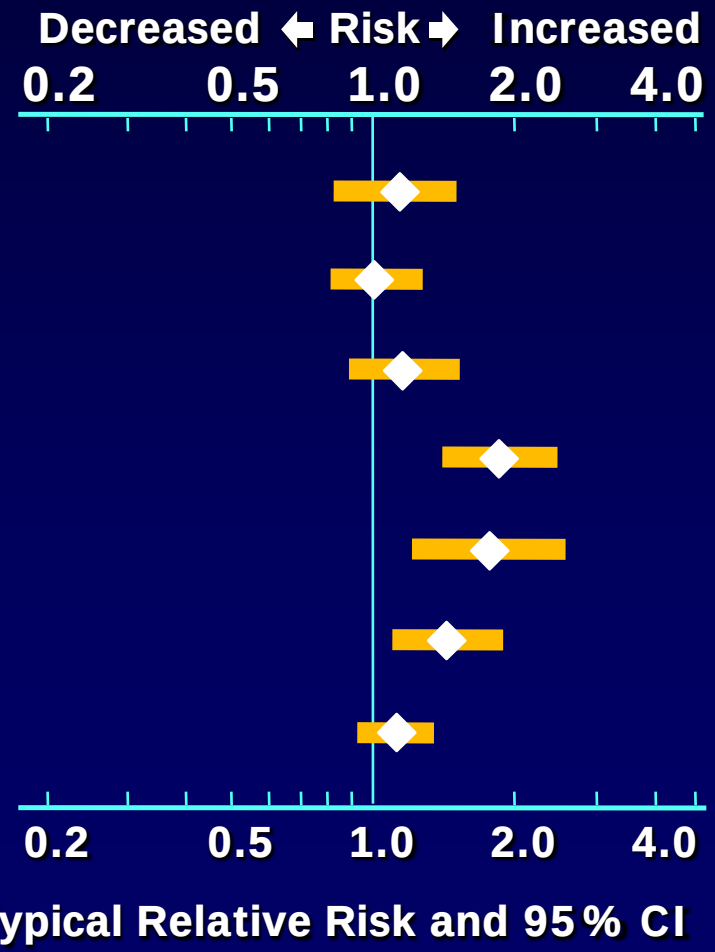


Doyle 2017

EARLY (≤ 7 DAYS) POSTNATAL STEROID THERAPY

NEURODEVELOPMENTAL OUTCOME IN SURVIVORS

OUTCOME (N Studies)	Typical Risk Difference (95% CI)
PVL (15)	0.00 (-0.01, 0.02)
BAYLEY MDI < 2SD (3)	0.01 (-0.06, 0.06)
BAYLEY PDI < 2SD (3)	0.02 (-0.02, 0.07)
ABNORMAL NEURO EXAM (5)	0.10 (0.05, 0.15)
DEVELOPMENTAL DELAY (1)	0.14 (0.03, 0.24)
CEREBRAL PALSY (13)	0.02 (-0.00, 0.05)
MOD/SEVERE IMPAIRMENT (7)	0.01 (-0.02, 0.05)

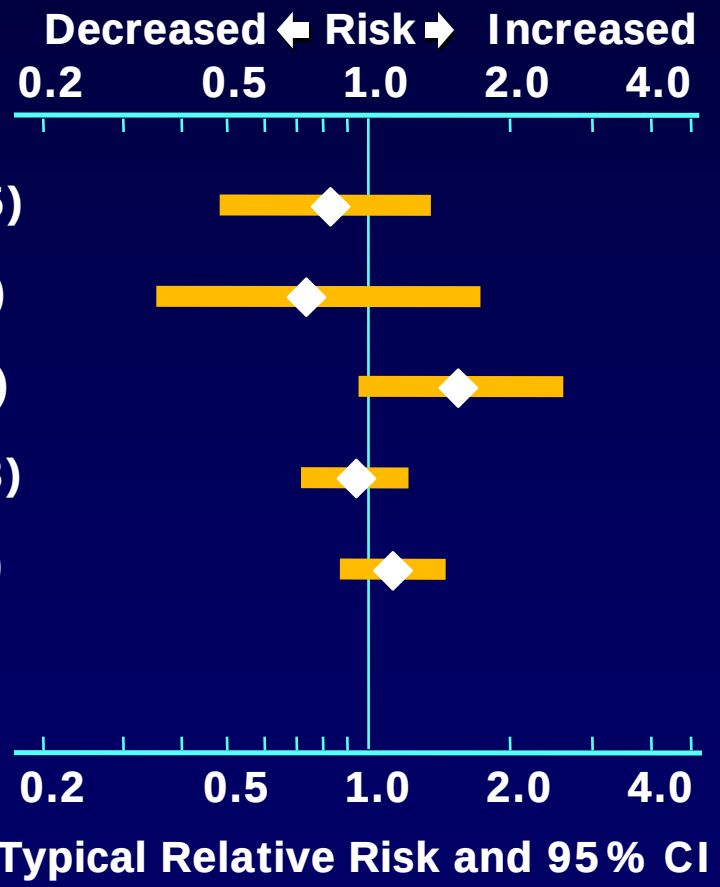


Doyle 2017

LATE (> 7 DAYS) POSTNATAL STEROID THERAPY

NEURODEVELOPMENTAL OUTCOME IN SURVIVORS

Outcome (N)	Typical Risk Difference (95% CI)
BAYLEY MDI < 2SD (7)	-0.03 (-0.10, 0.05)
BAYLEY PDI < 2SD (1)	-0.04 (-0.17, 0.09)
ABNORMAL NEURO EXAM (4)	0.15 (-0.00, 0.30)
CEREBRAL PALSY (15)	-0.02 (-0.08, 0.03)
MOD/SEVERE IMPAIRMENT (9)	0.03 (-0.03, 0.08)



Doyle 2017

POSTNATAL CORTICOSTEROIDS TO TREAT OR PREVENT CHRONIC LUNG DISEASE IN PRETERM INFANTS

RECOMMENDATIONS FROM THE COMMITTEE ON THE FETUS AND NEWBORN 2002

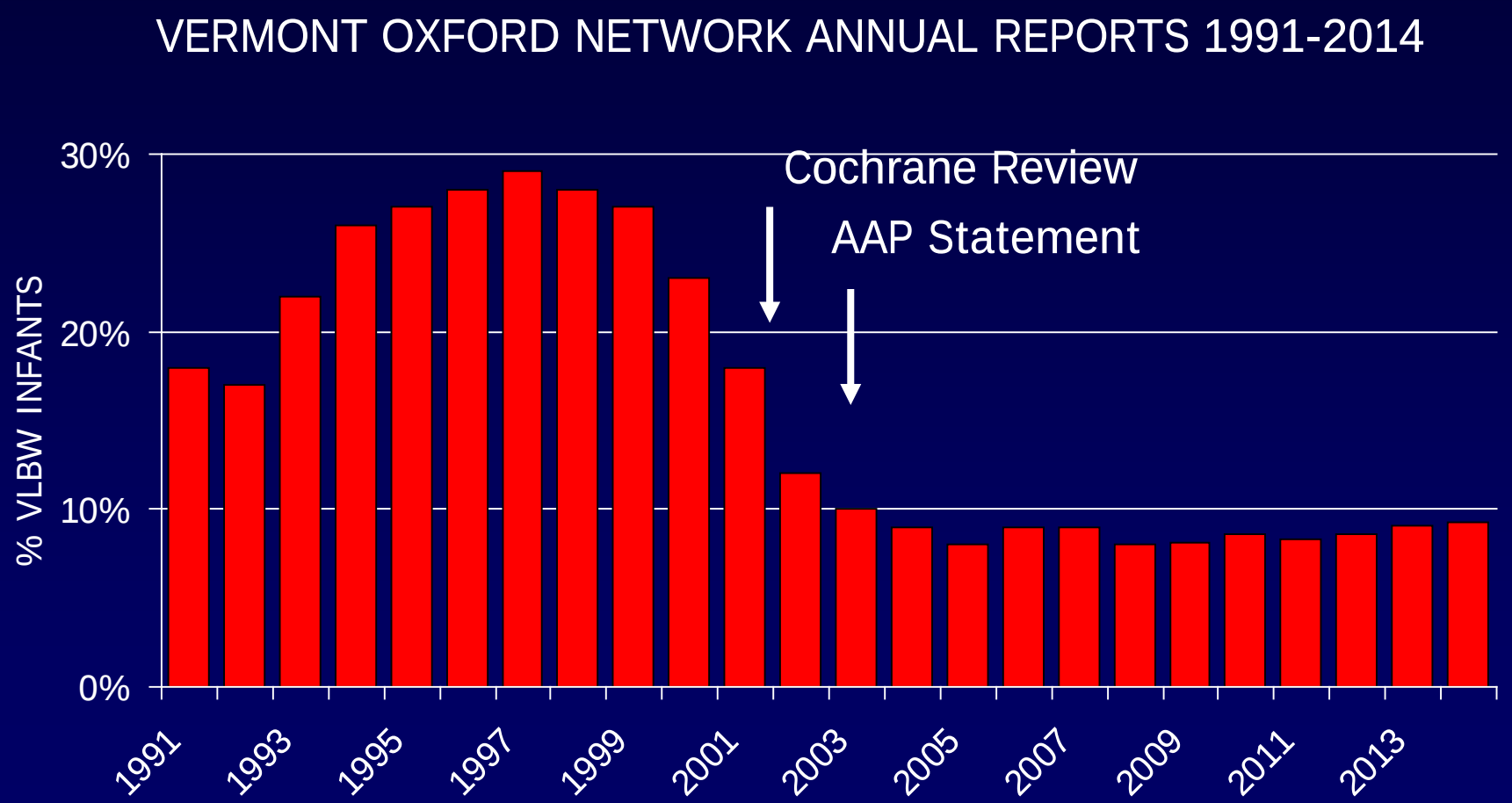
On the basis of limited short-term benefits, the absence of long-term benefits, and the number of serious short-term and long-term complications, the routine use of systemic dexamethasone for the prevention or treatment of chronic lung disease in infants with very low birth weight is not recommended.

POSTNATAL CORTICOSTEROIDS TO TREAT OR PREVENT CHRONIC LUNG DISEASE IN PRETERM INFANTS

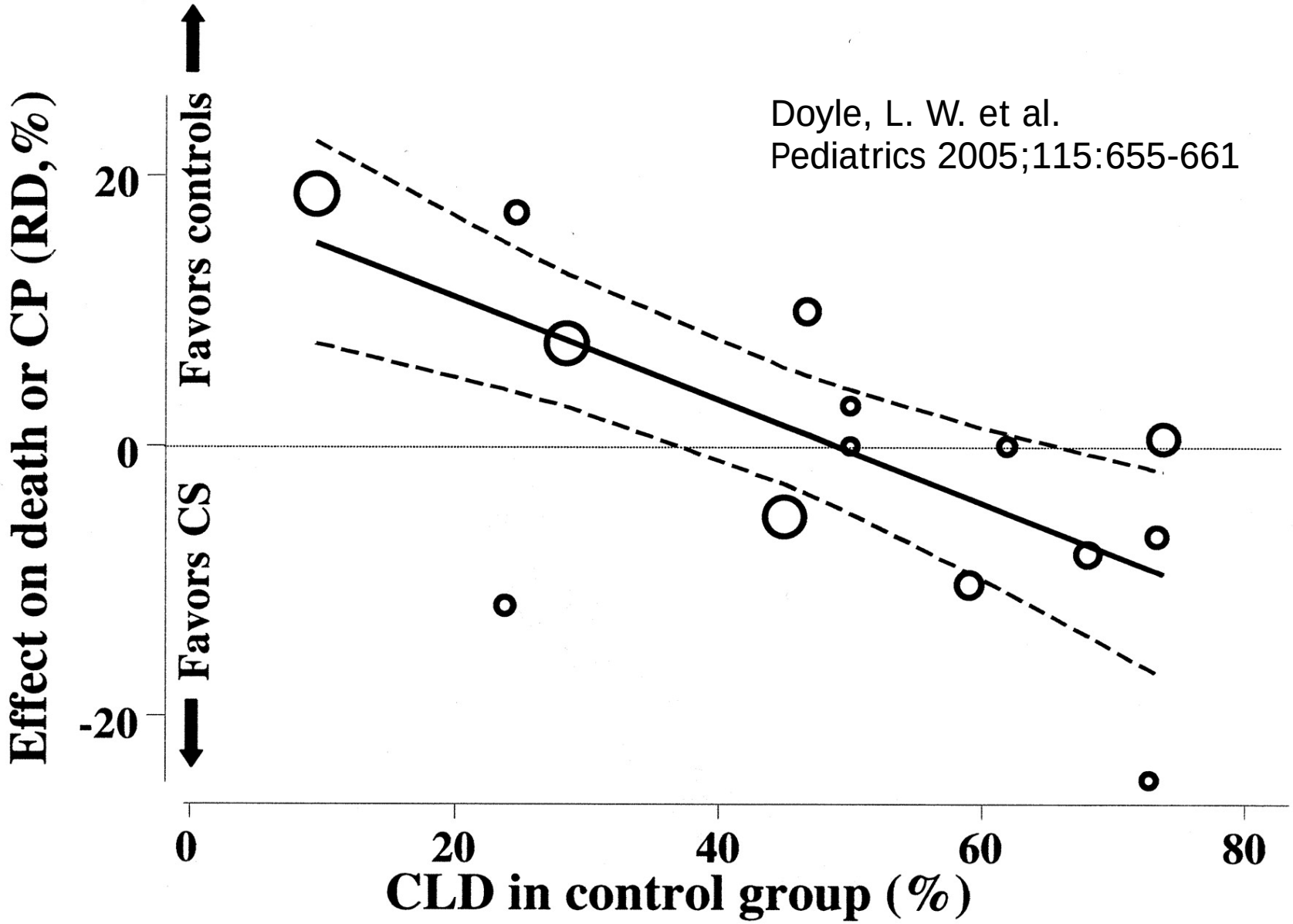
RECOMMENDATIONS FROM THE COMMITTEE ON THE FETUS AND NEWBORN 2002

Outside the context of a randomized controlled trial, the use of corticosteroids should be limited to exceptional clinical circumstances (e.g., an infant on maximal ventilatory and oxygen support). In those circumstances, parents should be fully informed about the known short- and long-term risks and agree to treat.

Postnatal Corticosteroid Use in VLBW Infants



Risk Difference (%) for Death or CP among all participants vs. rate of CLD (%) in the control group



Doyle, L. W. et al.
Pediatrics 2005;115:655-661

Competing Risks

Cochrane Neonatal

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Askie LM, Darlow BA, Davis PG, Finer N, Stenson B, Vento M, Whyte R.

Cochrane Database of Systematic Reviews 2017, Issue 4. Art. No.: CD011190.
DOI: 10.1002/14651858.CD011190.pub2.

NeOProM

Askie et al. BMC Pediatrics 2011, 11:6
http://www.biomedcentral.com/1471-2431/11/6

BMC Pediatrics

STUDY PROTOCOL Open Access

NeOProM: Neonatal Oxygenation Prospective Meta-analysis Collaboration study protocol

Lisa M Askie[1*], Peter Brocklehurst[2], Brian A Darlow[3], Neil Finer[4], Barbara Schmidt[5,6], William Tarnow-Mordi[7,8], for the NeOProM Collaborative Group[1]

Characteristics of randomized trials included in the NeoProM Collaboration

Trial acronym	**BOOST II-Australia**	**BOOST II-UK**	**BOOST-NZ**	**SUPPORT**	**COT**
Registration number	**ACTRN12605000055606**	**ISRCTN00842661**	**ACTRN12605000253606**	**NCT00233324**	**ISRCTN62491227**
Planned sample size	1200	1200	320	1310	1200
Countries of recruitment	Australia	United Kingdom	New Zealand	United States	Canada, USA, Argentina, Germany, Israel, Finland
Participants	Infants < 28 wks gestation inborn or outborn < 24 hrs old	Infants < 28 wks gestation < 12 hrs old (24 hrs if outborn)	Infants < 28 wks gestation inborn or outborn < 24 hrs old	Infants 24-27 wks gestation < 2 hrs old	Infants 23 0/7-27 6/7 wks gestation < 24 hrs old
Masked?	Yes	Yes	Yes	Yes	Yes
Intervention	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)	Lower oxygen saturation (85%-89%)
Comparator	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)	Higher oxygen saturation (91%-95%)
Intervention & comparator duration	Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO_2 > 96% in room air for 95% of time over 3 days.	Oximeter applied from randomisation until postmenstrual age (PMA) of 36 wks or until baby is breathing air. All monitoring at any time prior to 36 wks to be done using study oximeter. BPD defined at 36 wks using a physiological test.	Oximeter applied asap after admission to NICU, continued for minimum 2 wks. Thereafter continued until 36 wks corrected age or SpO_2 > 96% in room air for 95% of time over 3 days.	Oximeter applied within 2 hrs following admission to NICU until infant has been in room air for 72 hrs or until 36 wks corrected age, assessed by physiologic oxygen test.	Oximeter applied from day of birth until a minimum 36 wks PMA. If breathing room air without any form of respiratory assistance from 35 wks PMA onward, study oximetry discontinued at a 36 wks PMA. If receiving any form of respiratory assistance and/or oxygen therapy from 35 wks PMA onward study oximetry continues until 40 wks PMA. Study oximetry stopped at any time before 40 wks PMA if baby discharged home (with or without respiratory assistance and/or oxygen).

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Results:

- Five trials, which together enrolled 4965 infants, were eligible for inclusion.
- The investigators of these five trials had prospectively planned to combine their data as part of the NeOProM (Neonatal Oxygen Prospective Meta-analysis) Collaboration.

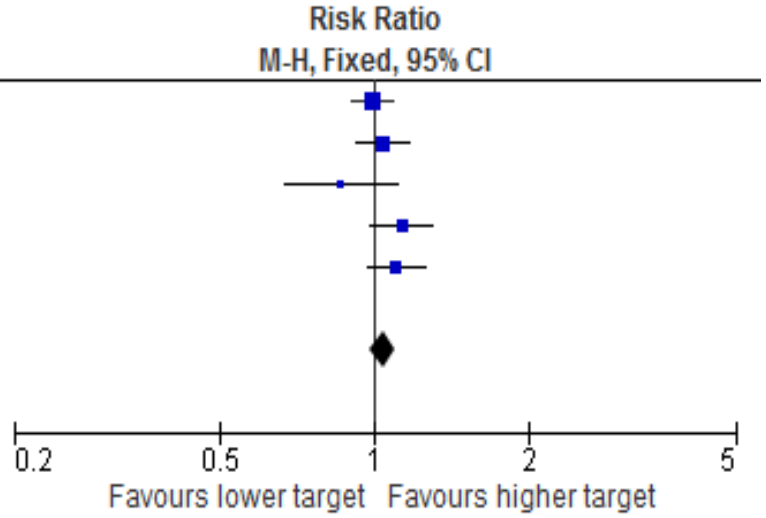
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Death or Major Disability to 18 to 24 months

	Lower oxygen saturation		Higher oxygen saturation			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	Year
Vaucher 2012	363	613	374	624	31.7%	0.99 [0.90, 1.08]	2012
Schmidt 2013	298	578	283	569	24.4%	1.04 [0.92, 1.16]	2013
BOOST NZ 2014	65	167	76	168	6.5%	0.86 [0.67, 1.11]	2014
BOOST-II Australia 2016	247	549	217	545	18.6%	1.13 [0.98, 1.30]	2016
BOOST-II UK 2016	245	473	220	468	18.9%	1.10 [0.97, 1.25]	2016
Total (95% CI)		**2380**		**2374**	**100.0%**	**1.04 [0.98, 1.10]**	
Total events	1218		1170				

Heterogeneity: Chi² = 5.50, df = 4 (P = 0.24); I² = 27%

Test for overall effect: Z = 1.35 (P = 0.18)



Typical RR 1.04 (95% CI 0.98 to 1.10)

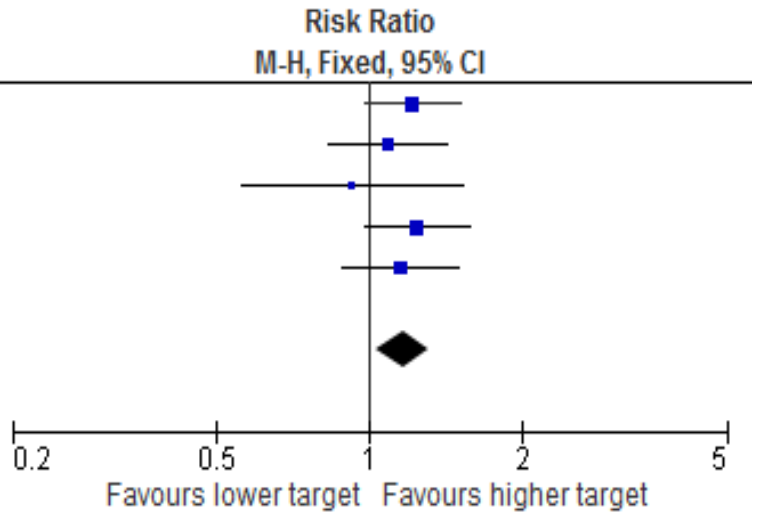
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Death to 18 to 24 months

Study or Subgroup	Lower oxygen saturation Events	Total	Higher oxygen saturation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vaucher 2012	140	633	118	648	27.9%	1.21 [0.98, 1.51]
Schmidt 2013	97	585	88	577	21.2%	1.09 [0.83, 1.42]
BOOST NZ 2014	25	170	27	170	6.5%	0.93 [0.56, 1.53]
BOOST-II UK 2016	122	484	98	483	23.5%	1.24 [0.98, 1.57]
BOOST-II Australia 2016	100	561	87	562	20.8%	1.15 [0.89, 1.50]
Total (95% CI)		**2433**		**2440**	**100.0%**	**1.16 [1.03, 1.31]**
Total events	484		418			

Heterogeneity: $Chi^2 = 1.51$, $df = 4$ ($P = 0.83$); $I^2 = 0\%$

Test for overall effect: $Z = 2.50$ ($P = 0.01$)



Typical RR 1.16 (95% CI 1.03 to 1.31)
Typical RD 0.03 (95% CI 0.01 to 0.05)

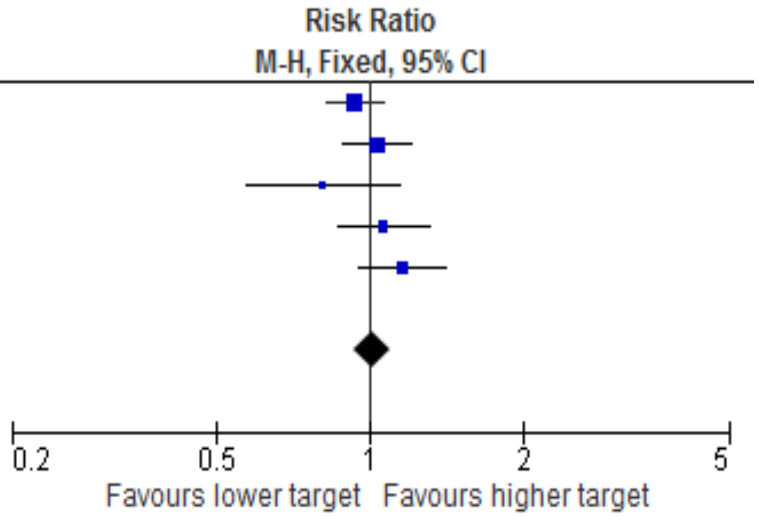
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Major Disability to 18 to 24 months

Study or Subgroup	Lower oxygen saturation Events	Total	Higher oxygen saturation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vaucher 2012	223	473	256	506	33.5%	0.93 [0.82, 1.06]
Schmidt 2013	201	488	195	489	26.4%	1.03 [0.89, 1.20]
BOOST NZ 2014	40	142	49	141	6.7%	0.81 [0.57, 1.15]
BOOST-II UK 2016	123	351	122	370	16.1%	1.06 [0.87, 1.30]
BOOST-II Australia 2016	147	449	130	458	17.4%	1.15 [0.95, 1.40]
Total (95% CI)		**1903**		**1964**	**100.0%**	**1.01 [0.93, 1.09]**
Total events	734		752			

Heterogeneity: Chi² = 5.13, df = 4 (P = 0.27); I² = 22%

Test for overall effect: Z = 0.25 (P = 0.80)



Typical RR 1.01 (95% CI 0.93 to 1.09)

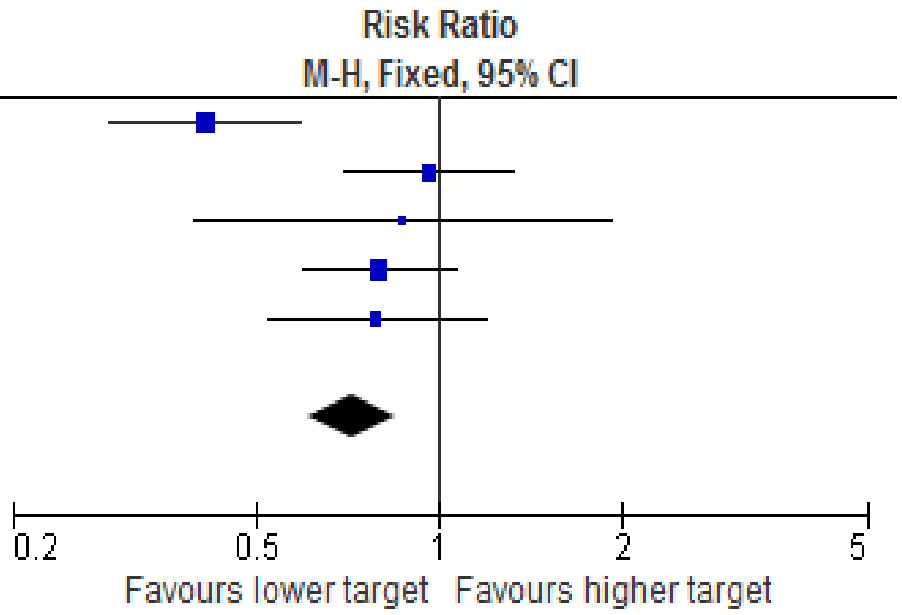
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Severe Retinopathy of Prematurity

Study or Subgroup	Lower targeting Events	Total	Higher targeting Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Vaucher 2012	36	482	93	514	29.9%	0.41 [0.29, 0.59]
Schmidt 2013	63	500	66	503	21.9%	0.96 [0.70, 1.33]
BOOST NZ 2014	11	158	12	150	4.1%	0.87 [0.40, 1.91]
BOOST-II UK 2016	67	395	86	403	28.3%	0.79 [0.60, 1.06]
BOOST-II Australia 2016	37	487	48	497	15.8%	0.79 [0.52, 1.19]
Total (95% CI)		**2022**		**2067**	**100.0%**	**0.72 [0.61, 0.85]**
Total events	214		305			

Heterogeneity: Chi² = 12.90, df = 4 (P = 0.01); I² = 69%

Test for overall effect: Z = 3.97 (P < 0.0001)



Typical RR 0.72 (95% CI 0.61 to 0.85)

Typical RD -0.04 (95% CI -0.06 to -0.02)

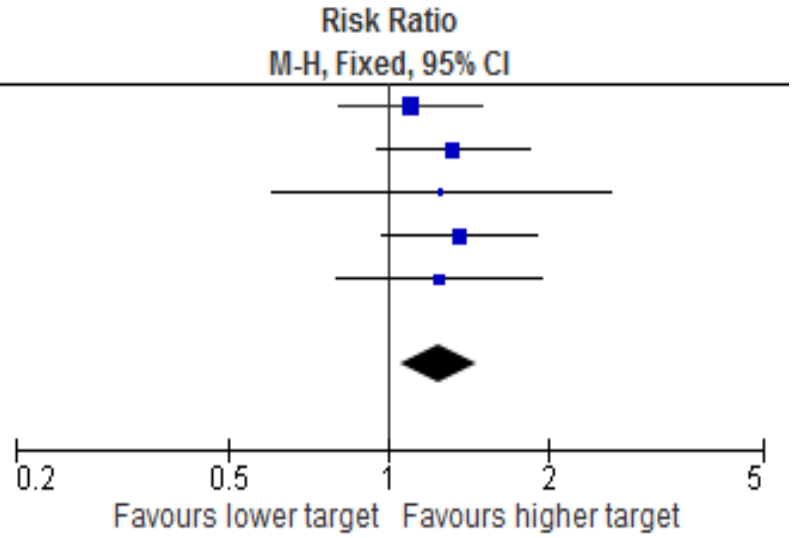
Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Effect on Necrotizing Enterocolitis

	Lower oxygen saturation		Higher oxygen saturation			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Vaucher 2012	76	641	70	649	31.2%	1.10 [0.81, 1.49]
Schmidt 2013	74	602	56	599	25.2%	1.31 [0.95, 1.83]
BOOST NZ 2014	15	170	12	170	5.4%	1.25 [0.60, 2.59]
BOOST-II UK 2016	71	484	52	480	23.4%	1.35 [0.97, 1.89]
BOOST-II Australia 2016	41	567	33	567	14.8%	1.24 [0.80, 1.94]
Total (95% CI)		**2464**		**2465**	**100.0%**	**1.24 [1.05, 1.47]**
Total events	277		223			

Heterogeneity: Chi² = 0.98, df = 4 (P = 0.91); I² = 0%

Test for overall effect: Z = 2.55 (P = 0.01)



Typical RR 1.24 (95% CI 1.05 to 1.47)
Typical RD 0.02 (95% CI 0.01 to 0.04)

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Author's Conclusions:

In extremely preterm infants, targeting lower (85% to 89%) SpO_2 compared to higher (91% to 95%) SpO_2 had no significant effect on the composite outcome of death or major disability or on major disability alone, including blindness, but increased the average risk of mortality by 28 per 1000 infants treated.

The trade-offs between the benefits and harms of the different oxygen saturation target ranges may need to be assessed within local settings (e.g. alarm limit settings, staffing, baseline outcome risks) when deciding on oxygen saturation targeting policies.

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

"The tradeoff between the potential benefits and risks of lower versus higher saturations may not be the same in each nursery."

Schmidt B, Whyte RK, Roberts RS. J Pediatr. 2014;165:6-8 .

Effects of targeting lower versus higher arterial oxygen saturations on death or disability in preterm infants

Outcome of concern	Appropriate choice of saturation range (SpO_2)
Composite outcome of death or major disability	lower (85% to 89%) *or* higher (91% to 95%)
Death	higher (91% to 95%)
Retinopathy of Prematurity	lower (85% to 89%)
Necrotizing Enterocolitis	higher (91% to 95%)

Values

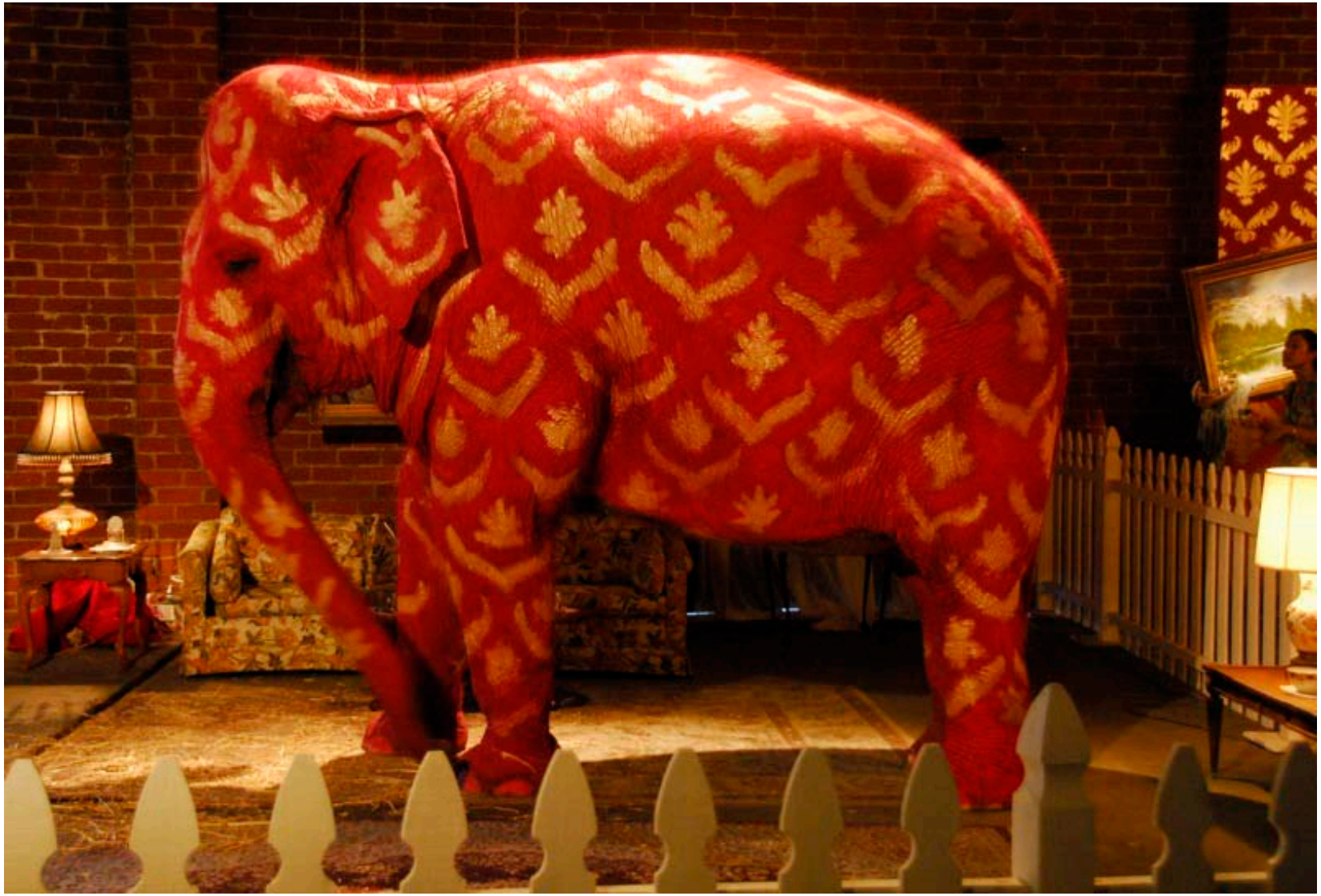
Prophylactic intravenous indomethacin for preventing mortality and morbidity in preterm infants.

Fowlie PW, Davis PG, McGuire W.

Cochrane Database Syst Rev. 2010 Jul 7;(7):CD000174.
doi: 10.1002/14651858.CD000174.pub2. PMID: 20614421

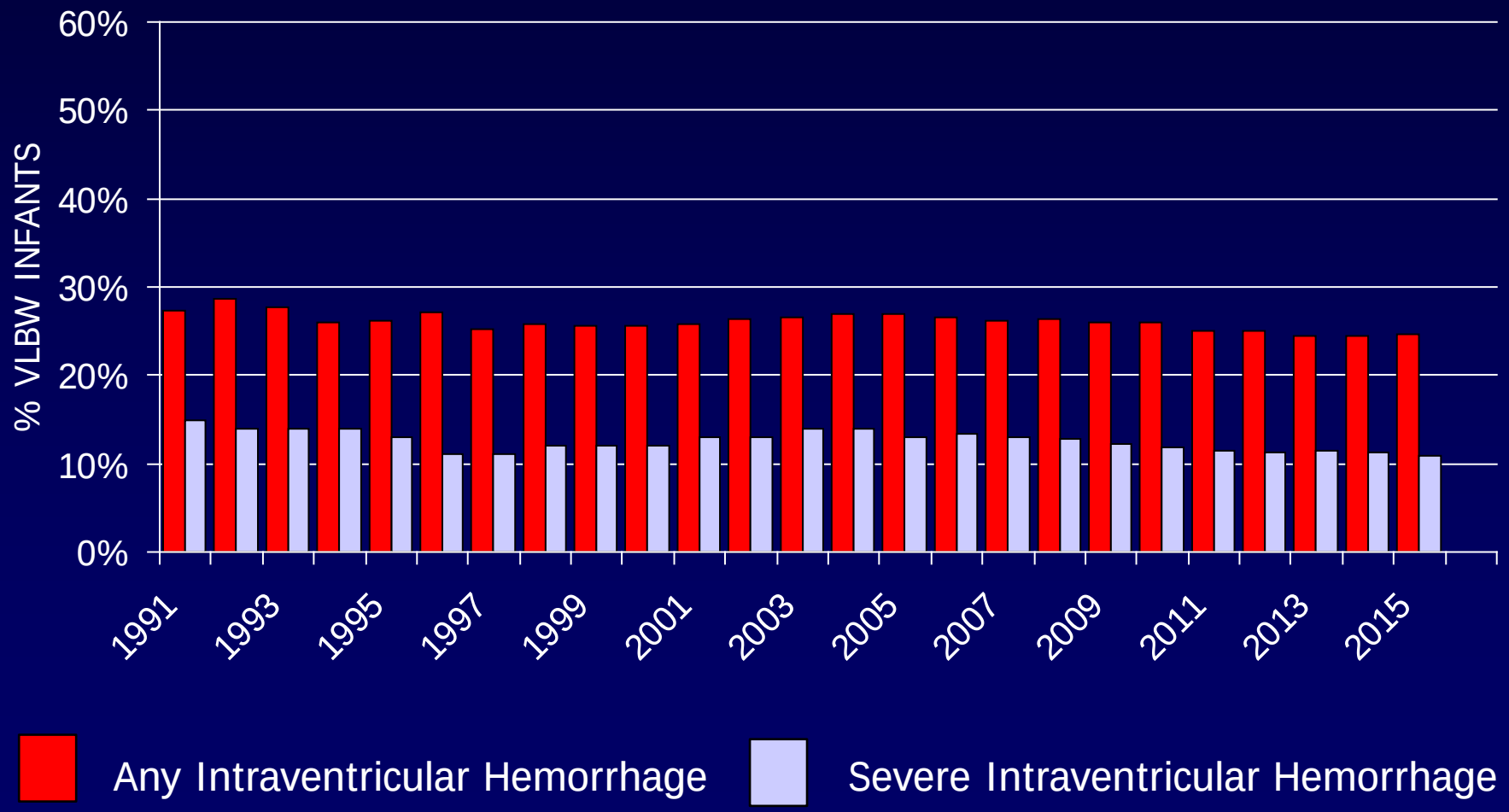
Cochrane Neonatal

Long-Term Effects of Indomethacin Prophylaxis in ELBW Infants
Schmidt B and colleagues. N Engl J Med 2001; 344:1966-1972



Intraventricular Hemorrhage

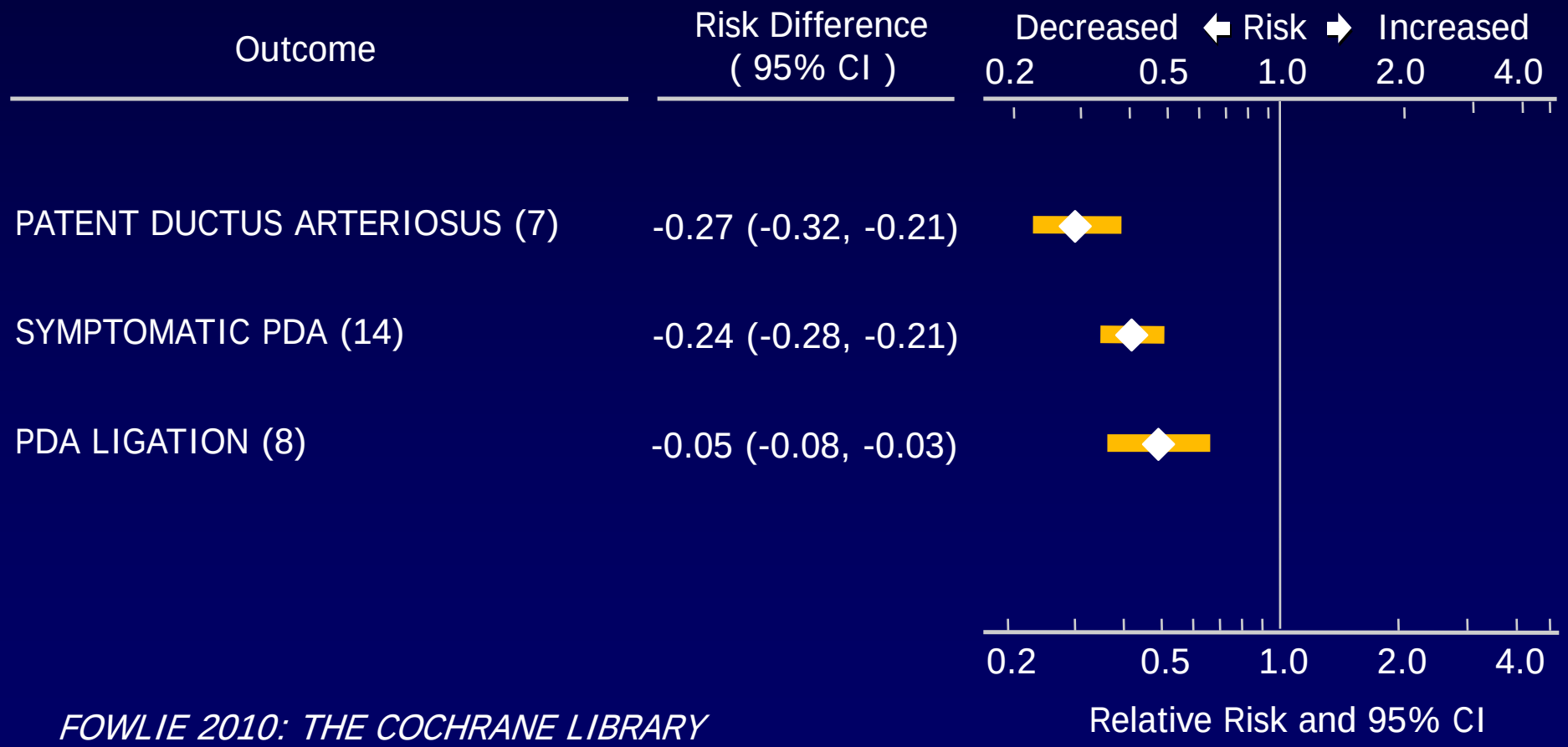
VERMONT OXFORD NETWORK ANNUAL REPORTS 1991-2015



Prophylactic Indomethacin

Meta-analysis of 19 trials

EFFECT ON PATENT DUCTUS ARTERIOSUS (PDA)



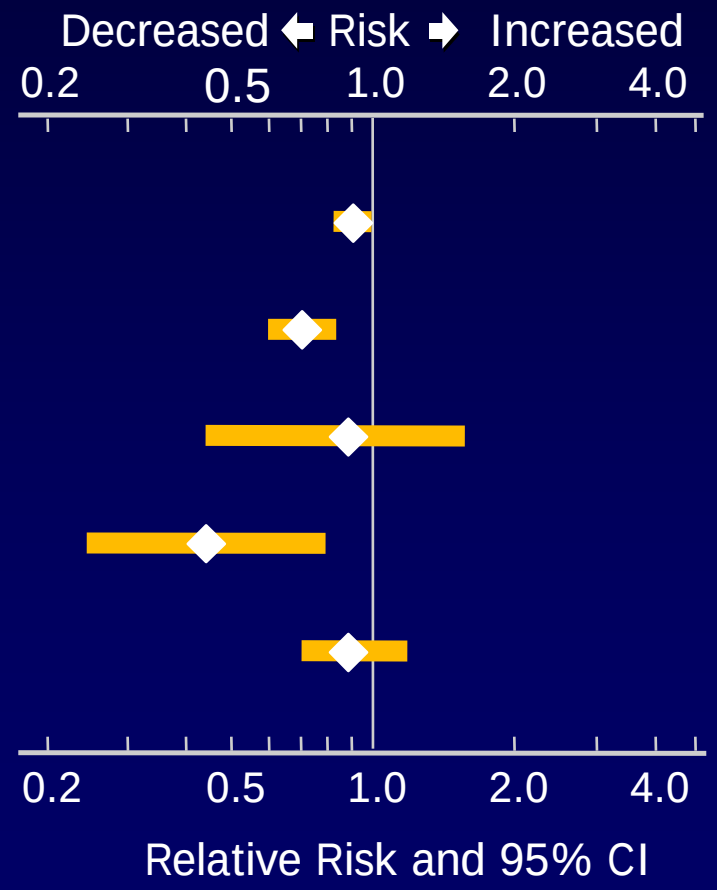
FOWLIE 2010: THE COCHRANE LIBRARY

Prophylactic Indomethacin

Meta-analysis of 19 trials

EFFECT ON CENTRAL NERVOUS SYSTEM INJURY

Outcome	Risk Difference (95% CI)
INTRAVENTRICULAR HEMORRHAGE (14)	-0.04 (-0.08, -0.01)
SEVERE IVH (14)	-0.05 (-0.07, -0.02)
PROGRESSIVE IVH (2)	-0.08 (-0.29, 0.13)
PERIVENTRICULAR LEUKOMALACIA (5)	-0.05 (-0.08, -0.01)
WHITE MATTER INJURY (1)	-0.04 (-0.07, 0.00)

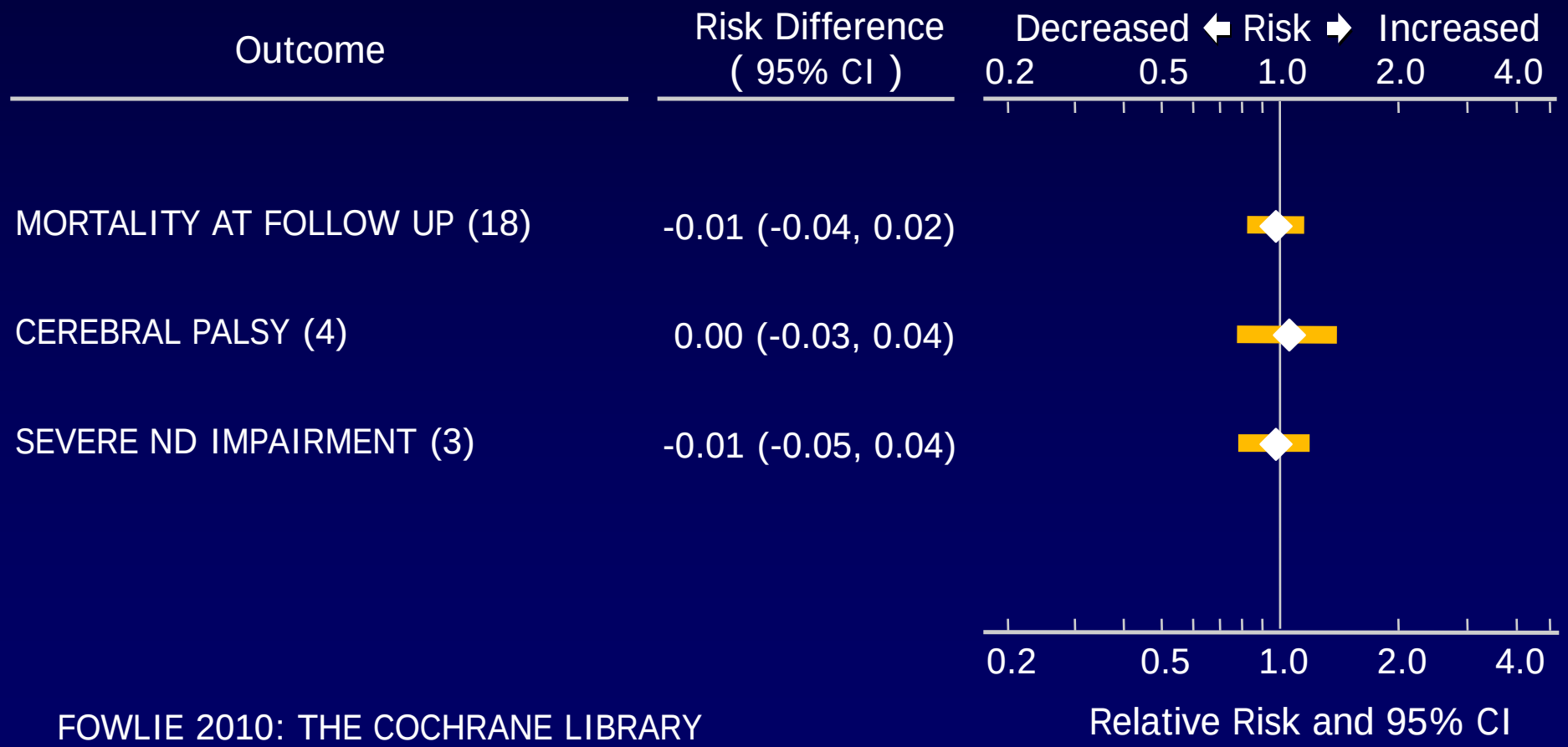


FOWLIE 2010: THE COCHRANE LIBRARY

Prophylactic Indomethacin

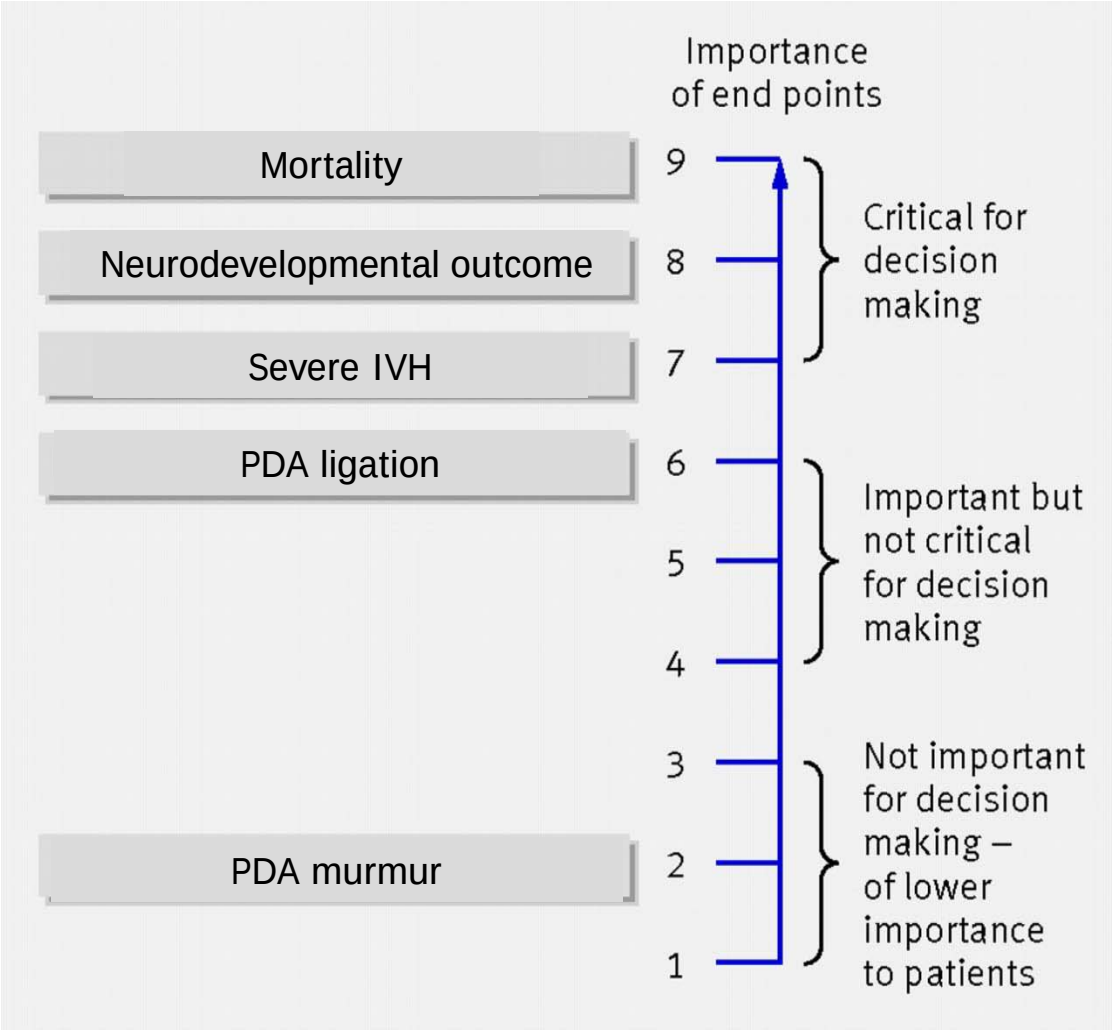
Meta-analysis of 19 trials

STATUS AT LATEST FOLLOW UP



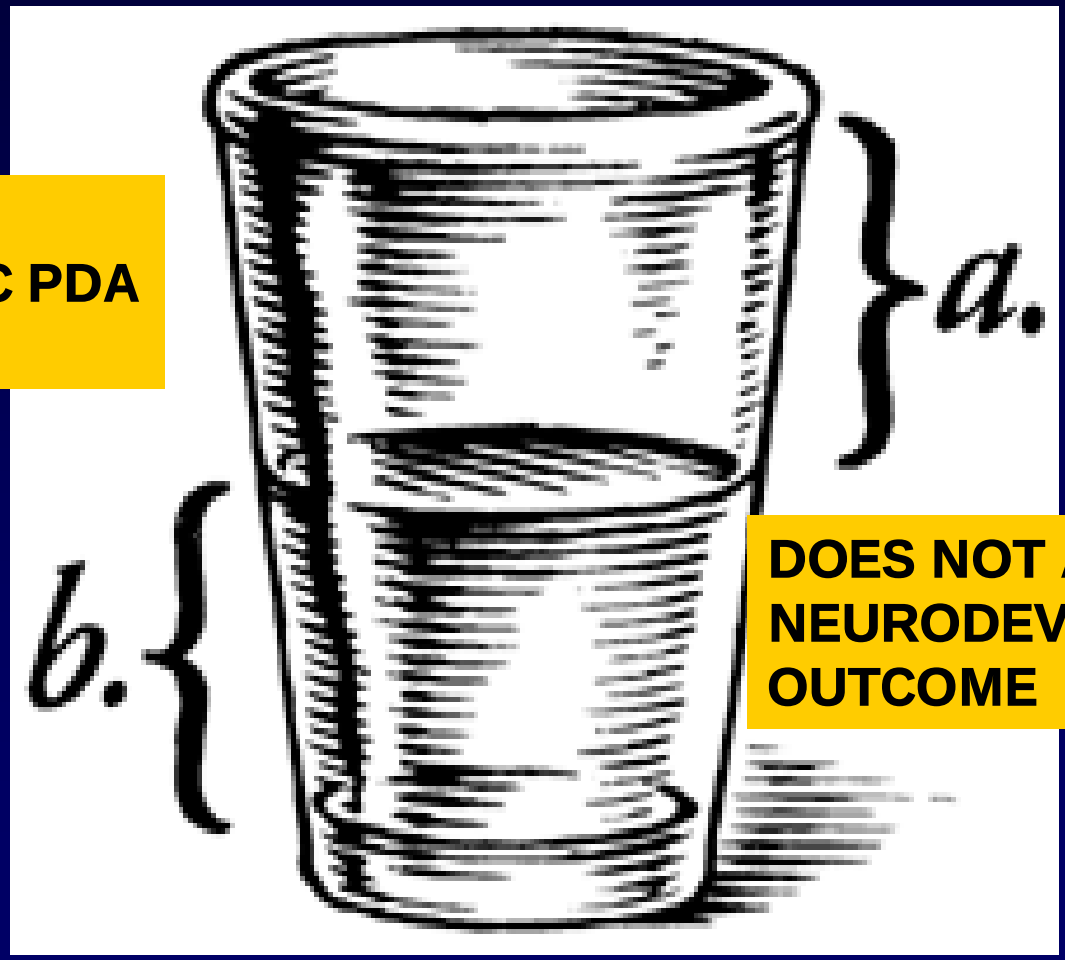
FOWLIE 2010: THE COCHRANE LIBRARY

Hierarchy of outcomes according to importance to patients to assess effect of prophylactic indomethacin



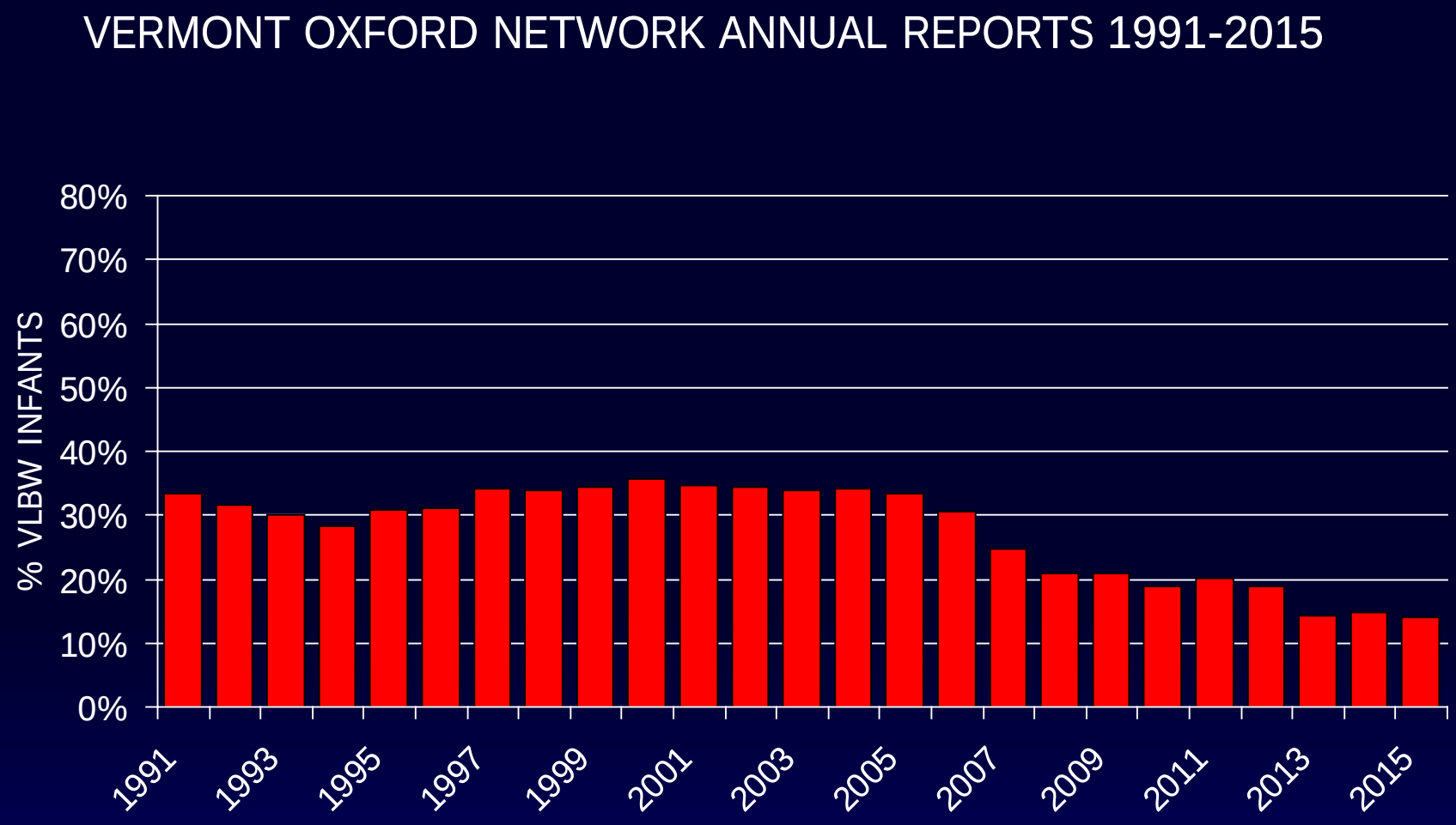
Prophylactic Indomethacin: Glass half full or half empty?

PREVENTS:
SYMPTOMATIC PDA
SEVERE IVH



DOES NOT ALTER NEURODEVELOPMENTAL OUTCOME

Indomethacin

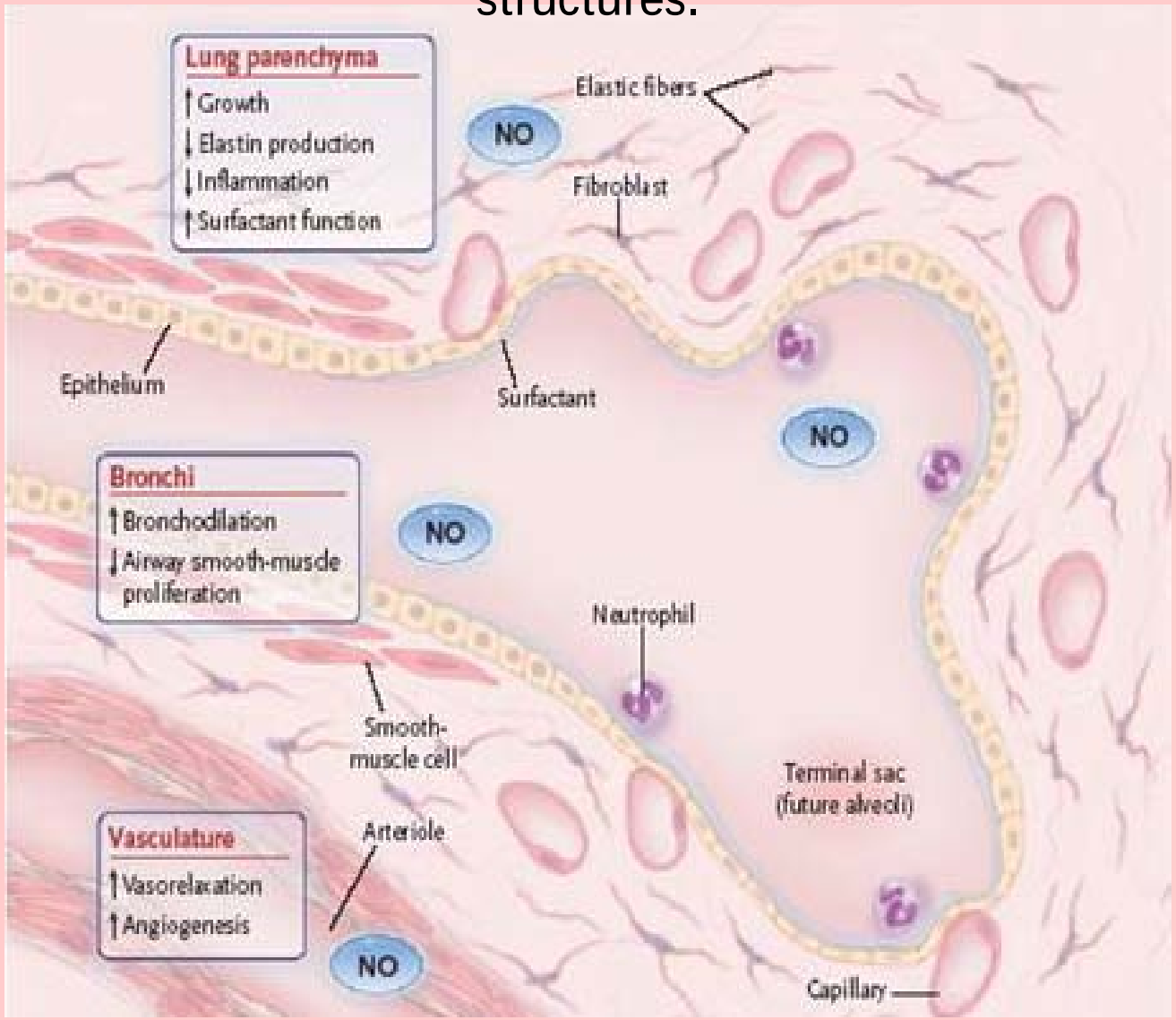


False precision / false optimism

Individual Patient Data Meta-analysis

“There must be a pony in here someplace!”

Nitric oxide may influence many facets of lung development, including lung parenchyma, bronchi, and vascular structures.



Martin RJ, Walsh MC. NEJM 2005

Inhaled nitric oxide for respiratory failure in preterm infants

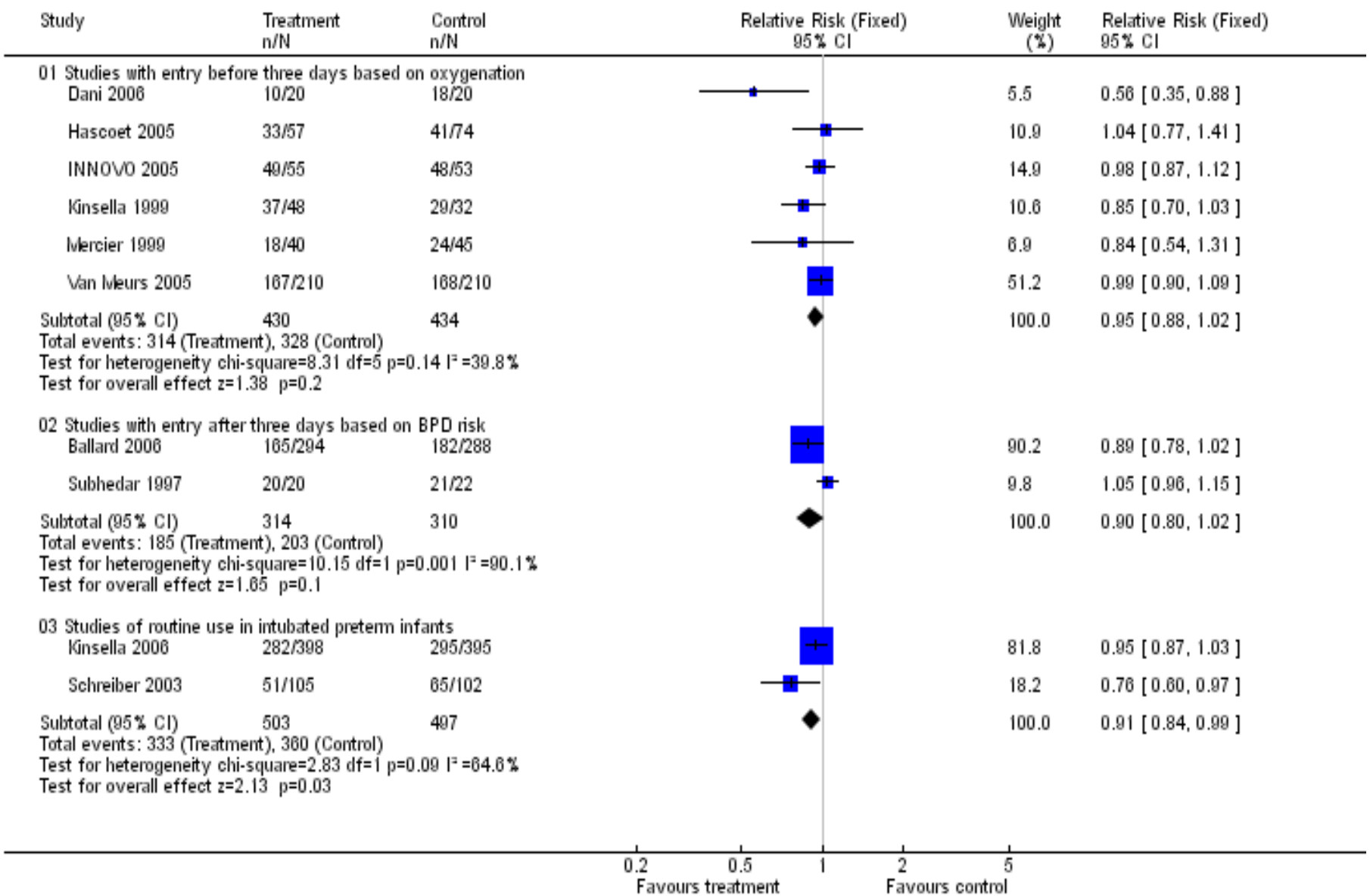
KJ Barrington, NN Finer

Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD000509. DOI: 10.1002/14651858.CD000509.pub3.

Cochrane Neonatal

NITRIC OXIDE FOR RESPIRATORY FAILURE IN PRETERM INFANTS

EFFECT ON DEATH OR BPD AT 36 WEEKS PMA



NIH Consensus Development Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants

Taken as a whole, the available evidence does not support use of iNO in early-routine, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks' gestation who require respiratory support.

There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants of <34 weeks' gestation.

In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

CLINICAL REPORT

Use of Inhaled Nitric Oxide in Preterm Infants

The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).

The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).

Pediatrics 2014

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Off-label use of inhaled nitric oxide after release of NIH consensus statement.

Ellsworth MA, Harris MN, Carey WA, Spitzer AR, Clark RH.

Pediatrics. 2015 Apr;135(4):643-8. doi: 10.1542/peds.2014-3290. Epub 2015 Mar 9.

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

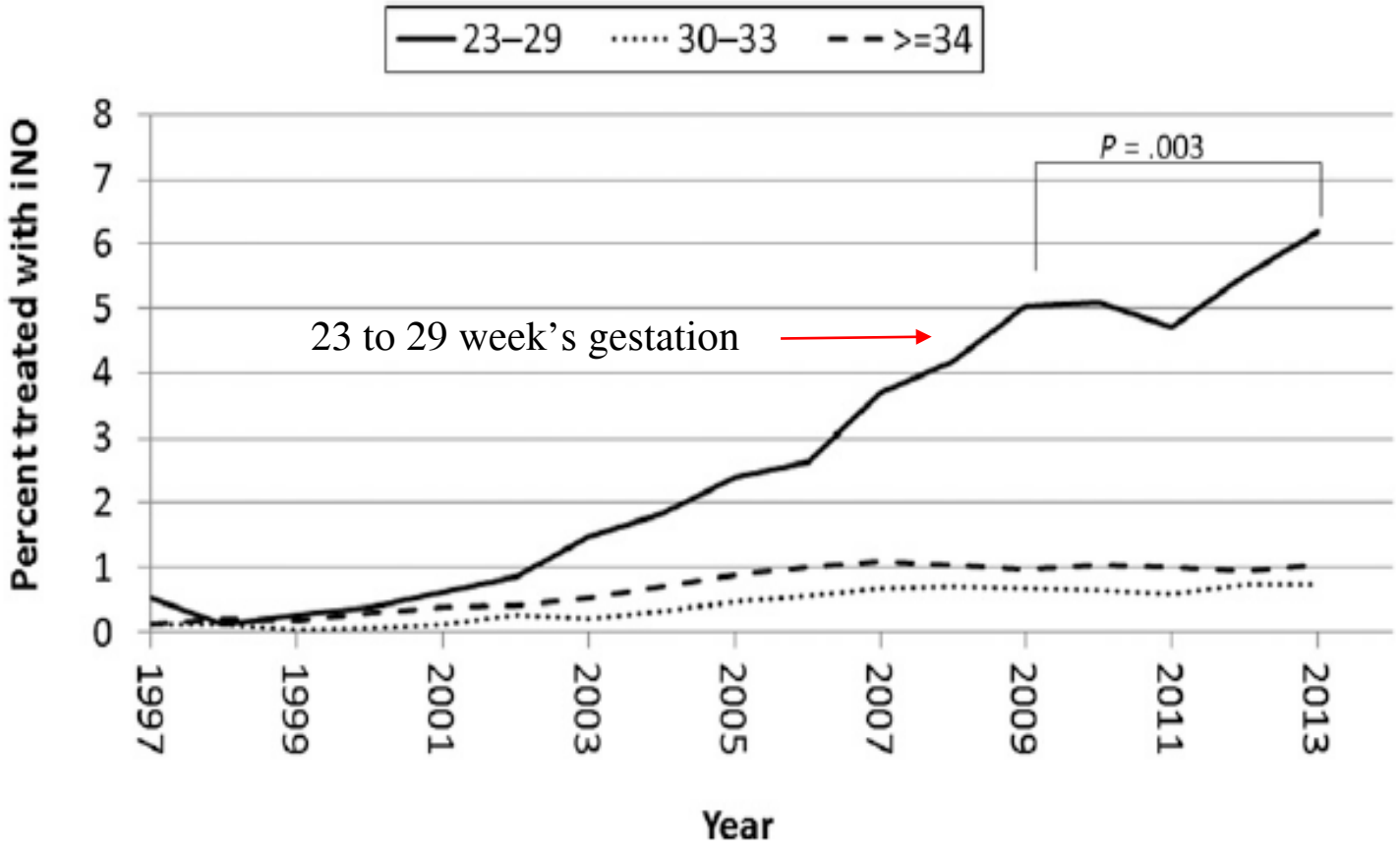
Ellsworth et al. Off-label use of inhaled nitric oxide after release of NIH consensus statement. Pediatrics. 2015 Apr;135(4):643-8.

The objective of this study was to describe utilization patterns of iNO in American NICUs in the years surrounding the release of the National Institutes of Health statement.

The Pediatrix Medical Group Clinical Data Warehouse was queried for the years 2009 to 2013 to describe first exposure iNO use among all admitted neonates stratified by gestational age.

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

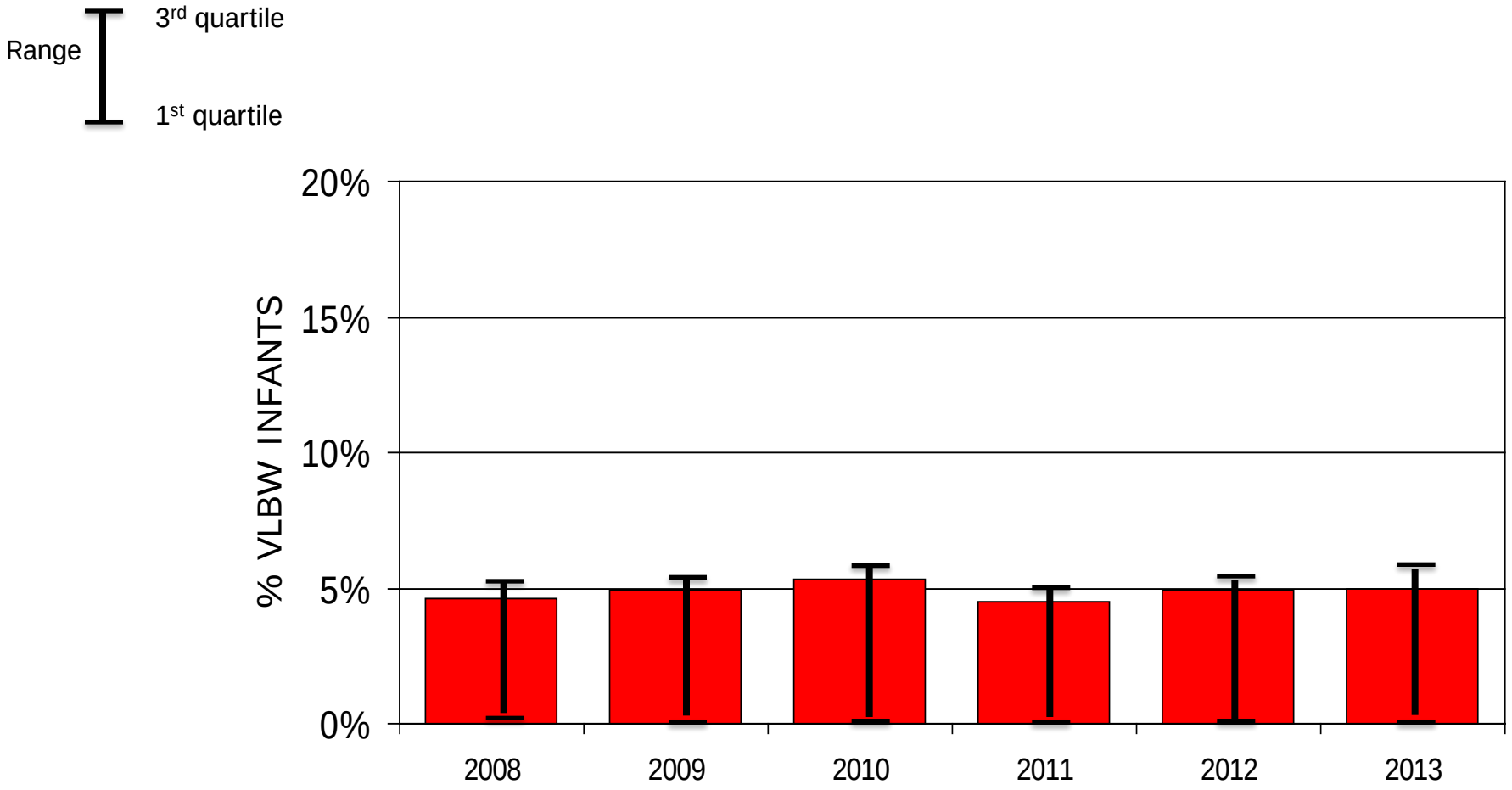
Change in percentage of infants treated with iNO from 1997 to 2013



Of all neonates who received iNO therapy in 2013, nearly half were < 34 weeks' gestation.

Inhaled Nitric Oxide in VLBW Infants

Vermont Oxford Network Annual Reports 2000-2012



The evidence does not extend far enough!

Cochrane Library

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth.

Roberts D, Brown J, Medley N, Dalziel SR.

Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017 Mar 21;3:CD004454. doi: 10.1002/14651858.CD004454.pub3. Review. PMID: 28321847

Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth.

This update includes 30 studies (7774 women and 8158 infants).

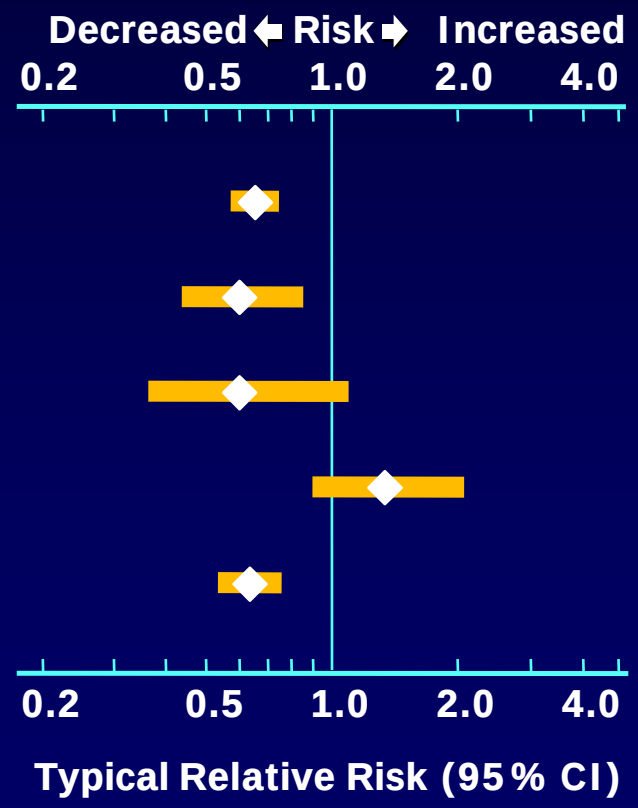
Risk of bias: Most studies are of low or unclear risk for most bias domains.

Roberts D, Brown J, Medley N, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2017 Mar 21;3:CD004454. doi: 10.1002/14651858.CD004454.pub3. Review. PMID: 28321847

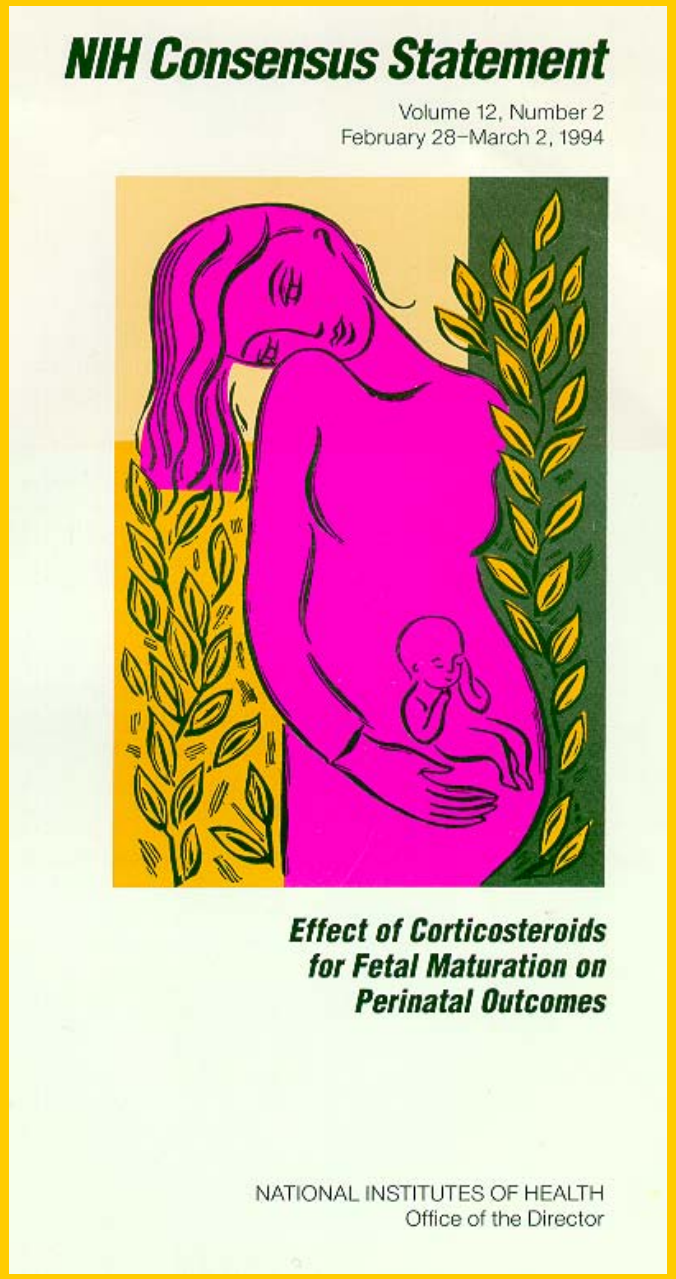
PROPHYLACTIC CORTICOSTEROIDS PRIOR TO PRETERM BIRTH

OVERVIEW OF 30 RANDOMIZED CONTROLLED TRIALS

Outcome (# of trials)	Typical Relative Risk (95% CI)
RDS (28)	0.66 (0.56, 0.77)
Intraventricular hemorrhage (16)	0.55 (0.40, 0.76)
Necrotizing enterocolitis (10)	0.50 (0.32, 0.78)
Bronchopulmonary dysplasia (6)	0.86 (0.42, 1.79)
Neonatal death (22)	0.69 (0.59, 0.81)



Roberts 2017



CORTICOSTEROIDS FOR PRETERM BIRTH

"Antenatal corticosteroid therapy is indicated for women at risk of premature delivery with few exceptions and will result in a substantial decrease in neonatal morbidity and mortality, as well as substantial savings in health care costs"

Current ACOG Guidelines

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

Society for Maternal-Fetal Medicine

	22 Weeks	23 Weeks	24 Weeks
Resuscitation	Consider	Consider	YES
Antenatal Steroids	NO	Consider	YES

(2017) Obstetric Care Consensus No. 6: Periviable Birth. *Obstet Gynecol.* Oct;130(4): e187-199.

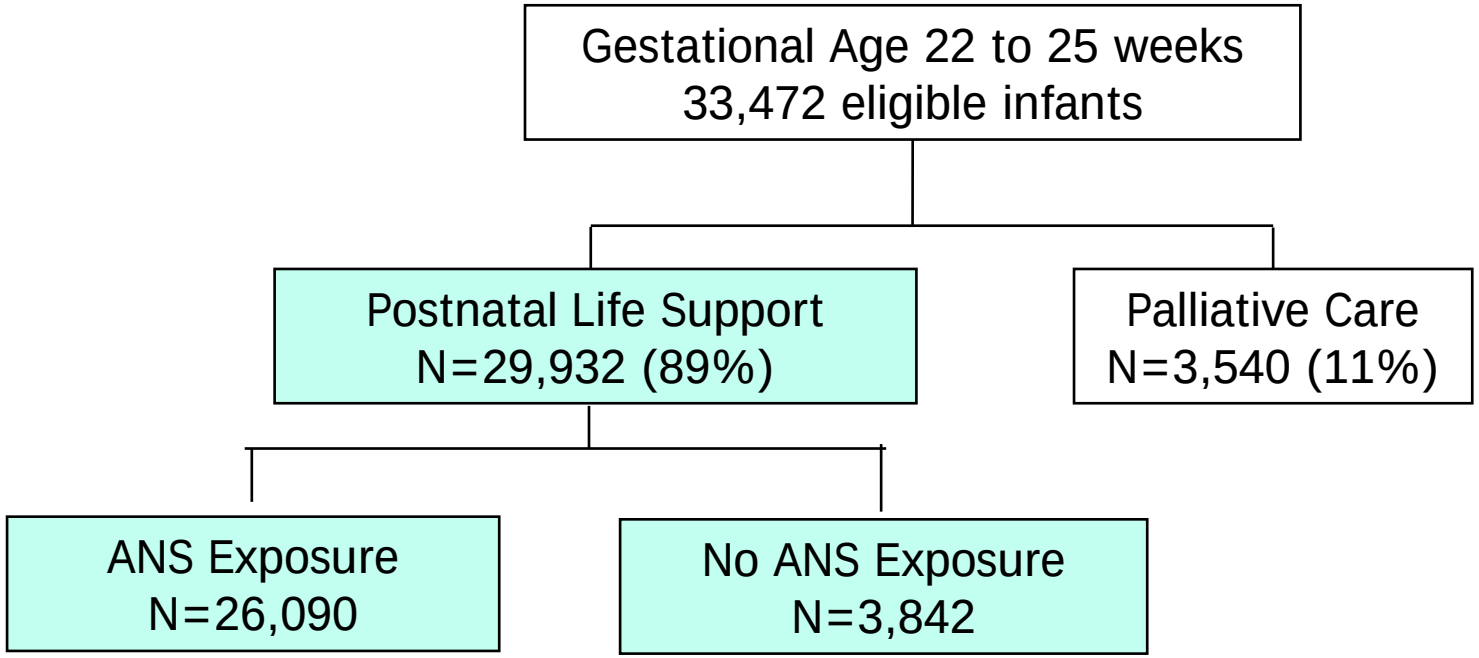
Original Investigation I Pediatrics

Association of Antenatal Steroid Exposure with Survival Among Infants Receiving Postnatal Life Support at 22 to 25 Weeks' Gestation

Danielle E. Y. Ehret, MD, MPH, Erika M. Edwards, PhD, MPH, Lucy T. Greenberg, MS, Ira M. Bernstein, MD, Jeffrey S. Buzas, PhD, Roger F. Soll, MD, Jeffrey D. Horbar, MD

JAMA Network Open 2018

Postnatal Life Support and Antenatal Steroids
Vermont Oxford Network 2012-2016



Exclusions: Outborn Infants; Infants with Major Congenital Anomalies

Postnatal Life Support and Antenatal Steroids
Vermont Oxford Network 2012-2016

Gestational Age	Proportion of infants receiving postnatal life support with ANS exposure
22 weeks	52%
23 weeks	83%
24 weeks	89%
25 weeks	91%

Postnatal Life Support and Antenatal Steroids
Vermont Oxford Network 2012-2016

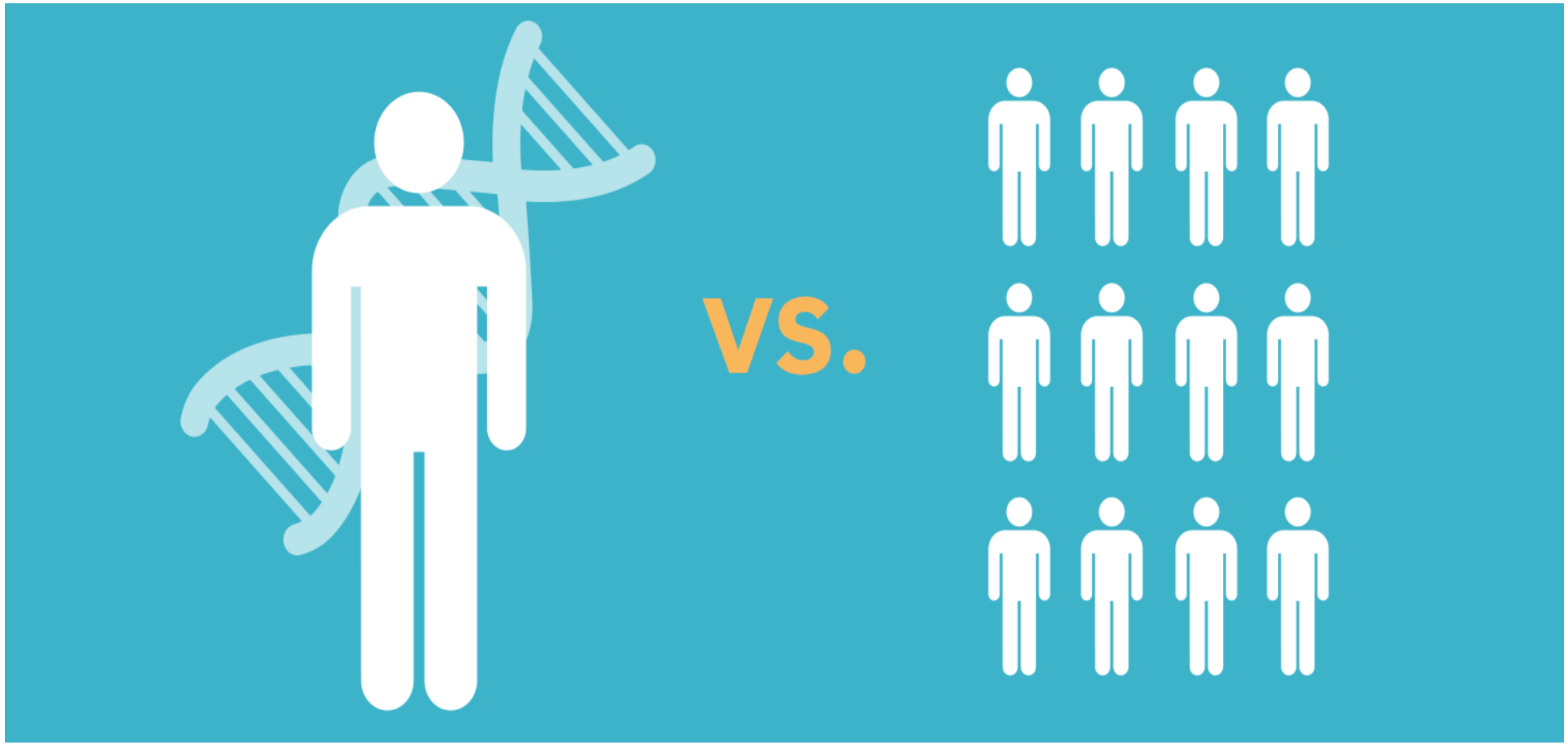
Survival			
Gestational Age	Postnatal Life Support Only	Postnatal Life Support with ANS Exposure	aRR (95% CI)
22 weeks	17.7%	38.5%	**2.11** (1.68-2.65)
23 weeks	35.6%	55.4%	**1.54** (1.40-1.70)
24 weeks	59.6%	71.3%	**1.18** (1.12-1.25)
25 weeks	75.7%	83.0%	**1.11** (1.07-1.14)
22-25 weeks	51.9%	72.3%	**1.37** (1.32-1.42)

Postnatal Life Support and Antenatal Steroids
Vermont Oxford Network 2012-2016

Survival without Major Morbidity			
Gestational Age	Postnatal Life Support Only	Postnatal Life Support with Antenatal Steroid Exposure	aRR (95% CI)
22 weeks	1.0%	4.4%	**4.35** (1.84-10.28)
23 weeks	2.8%	5.9%	**2.19** (1.48-3.25)
24 weeks	9.5%	11.4%	**1.27** (1.04-1.56)
25 weeks	18.8%	22.2%	**1.26** (1.10-1.44)
22-25 weeks	9.1%	14.6%	**1.67** (1.49-1.87)

Postnatal Life Support and Antenatal Steroids
Vermont Oxford Network 2012-2016

- Many infants born at 22 and 23 weeks' gestation received postnatal life support but lacked exposure to ANS
- Receipt of ANS was associated with higher survival and survival without major morbidities
- Should recommendations change?
- Should further trials be conducted?



Tension between treating individual patients and populations

Cochrane Neonatal