24º Congresso Brasileiro de
PERINATOLOGIA

Is It Possible to Prevent Necrotizing Enterocolitis?

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EMORY UNIVERSITY SCHOOL OF MEDICINE

Children's Healthcare of Atlanta

@ravimpatelmd

Disclosures

I will be discussed the use of probiotics for the prevention of NEC, which is not an approved indication by the US FDA.

I am not endorsing the use of any specific probiotic product.

Instituto PGG

Established in Brazil, in 2016, by a multidisciplinary group, including TV presenter and mother of extreme premature triplets Isabella Fiorentino, to raise awareness of NECROTIZING ENTEROCOLITIS.

- **Free and specialized psychological assistance to family members of affected babies available throughout Brazil.**
- **Creation of a NEC network for the spread of information and connection with foreign specialists and researchers.**
- **Building up of a database with information about NEC in Brazil, open to hospitals and doctors interested in participating.**

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Close working partnership with:

- We invite you to learn more about our project, join our network and refer affected family members to our psychologists: contato@pequenosgrandesguerreiros.org

www.pequenosgrandesguerreiros.org

- Join us at the NEC Society 2019 Symposium, 5 - 9 June, Ann Arbour, Michigan, US

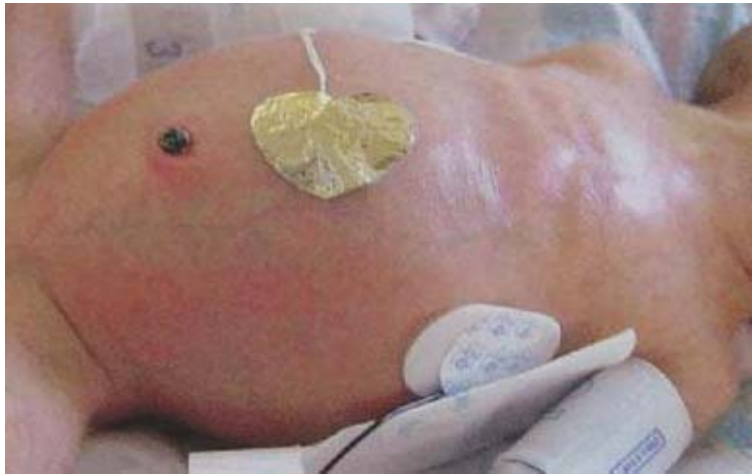
www.necsociety.org

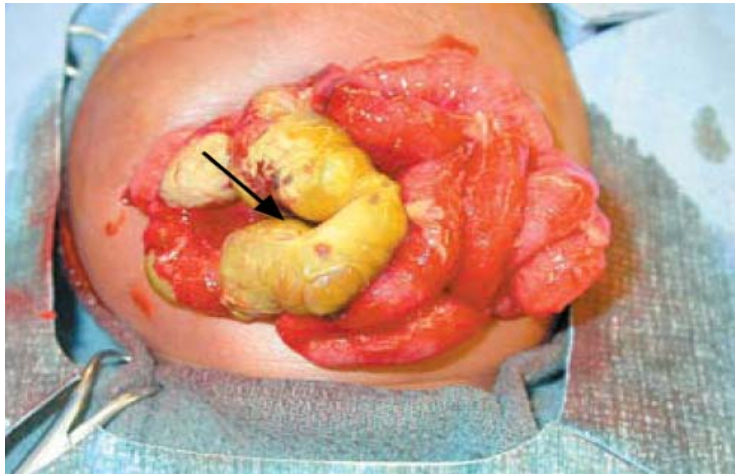
Overview

1. Discuss trends in the current incidence of NEC
2. Review risk factors for NEC
3. Highlight potential strategies to prevent NEC

Necrotizing enterocolitis (NEC)

- NEC is multifactorial disease, characterized by intestinal inflammation and necrosis although the exact pathogenesis is not fully elucidated
- Case-fatality rate of 15-30%





Neu and Walker, *NEJM.* 2011
Lin and Stoll, *Lancet.* 2006

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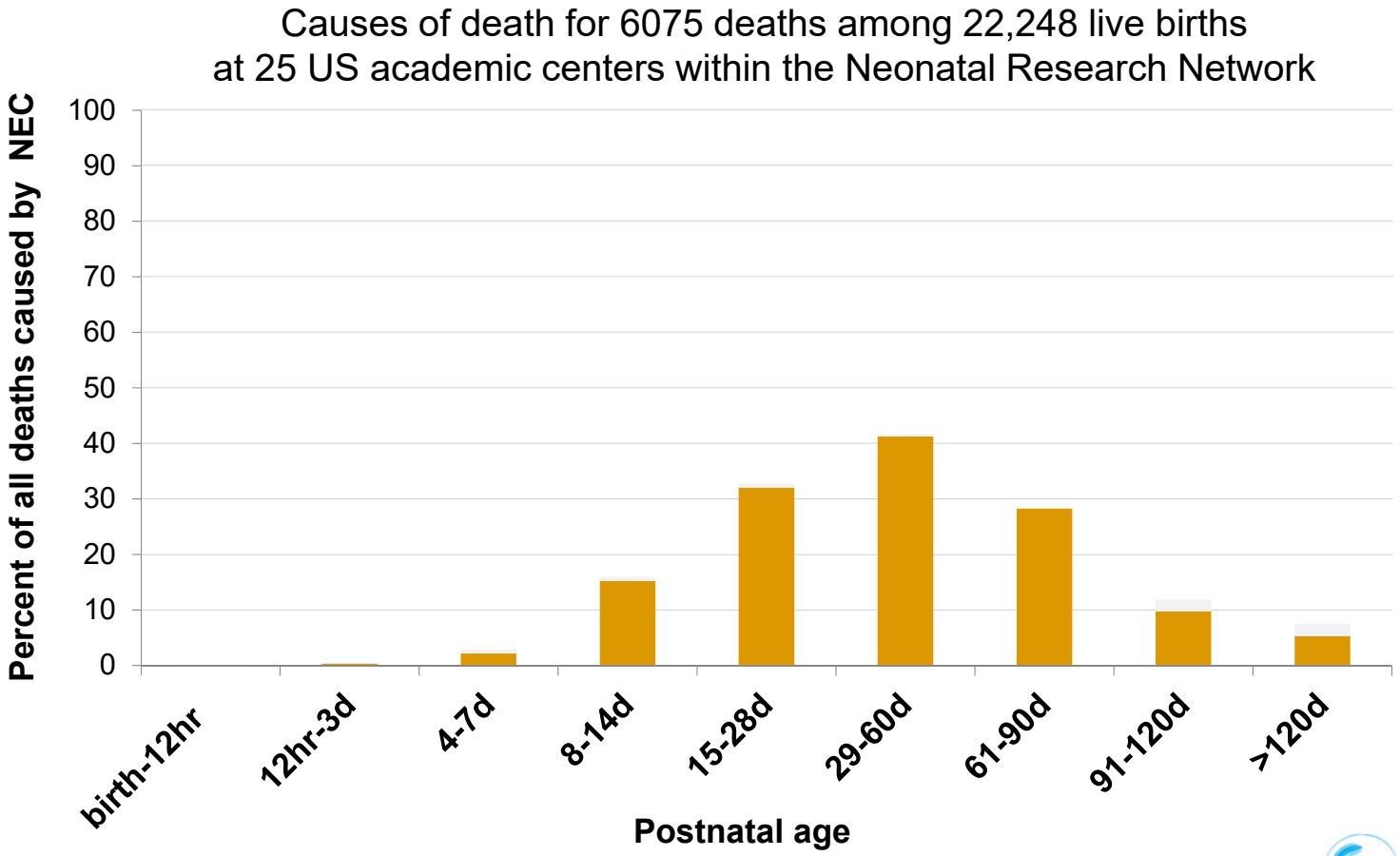
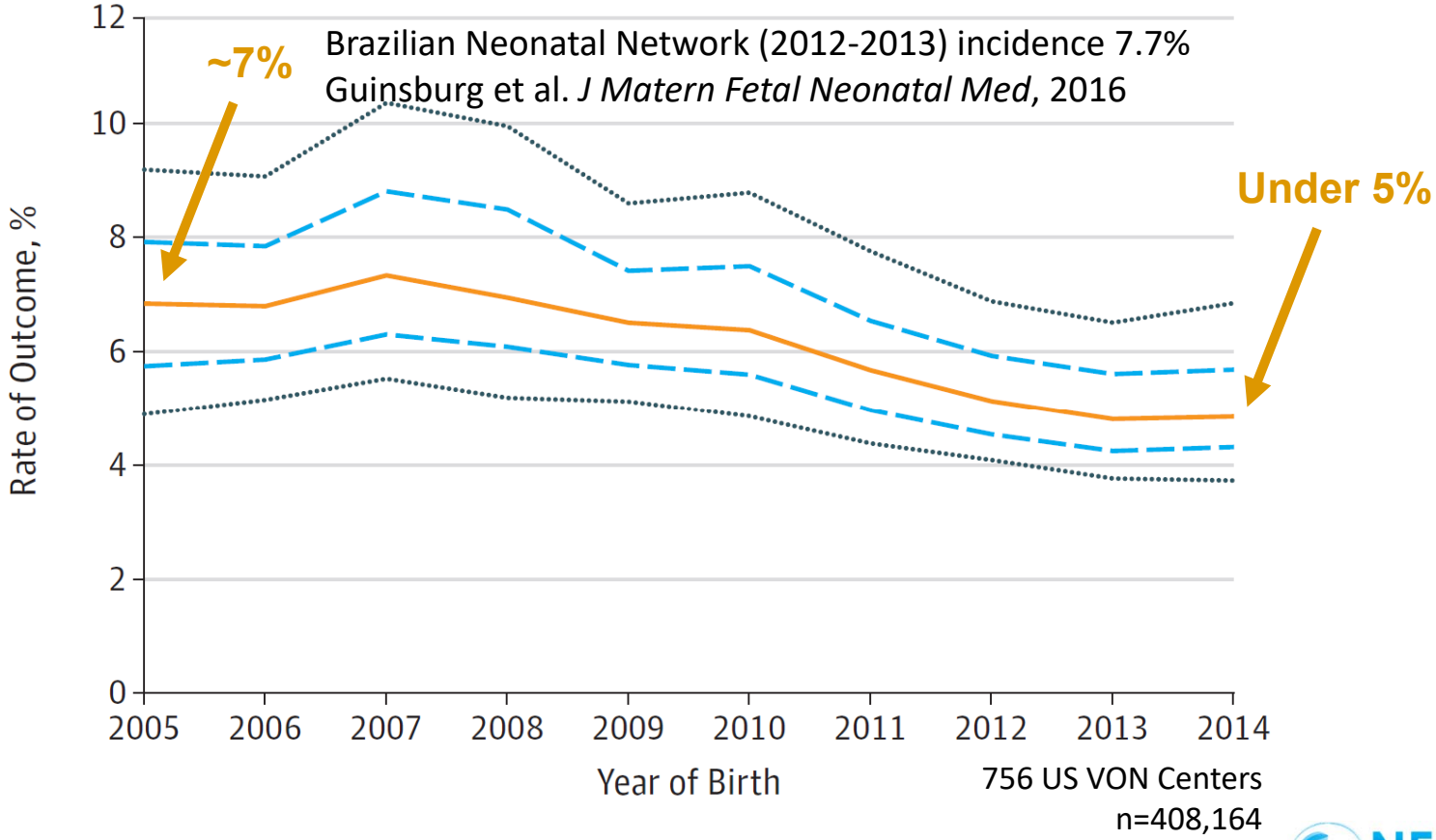
Deaths caused by NEC by postnatal age



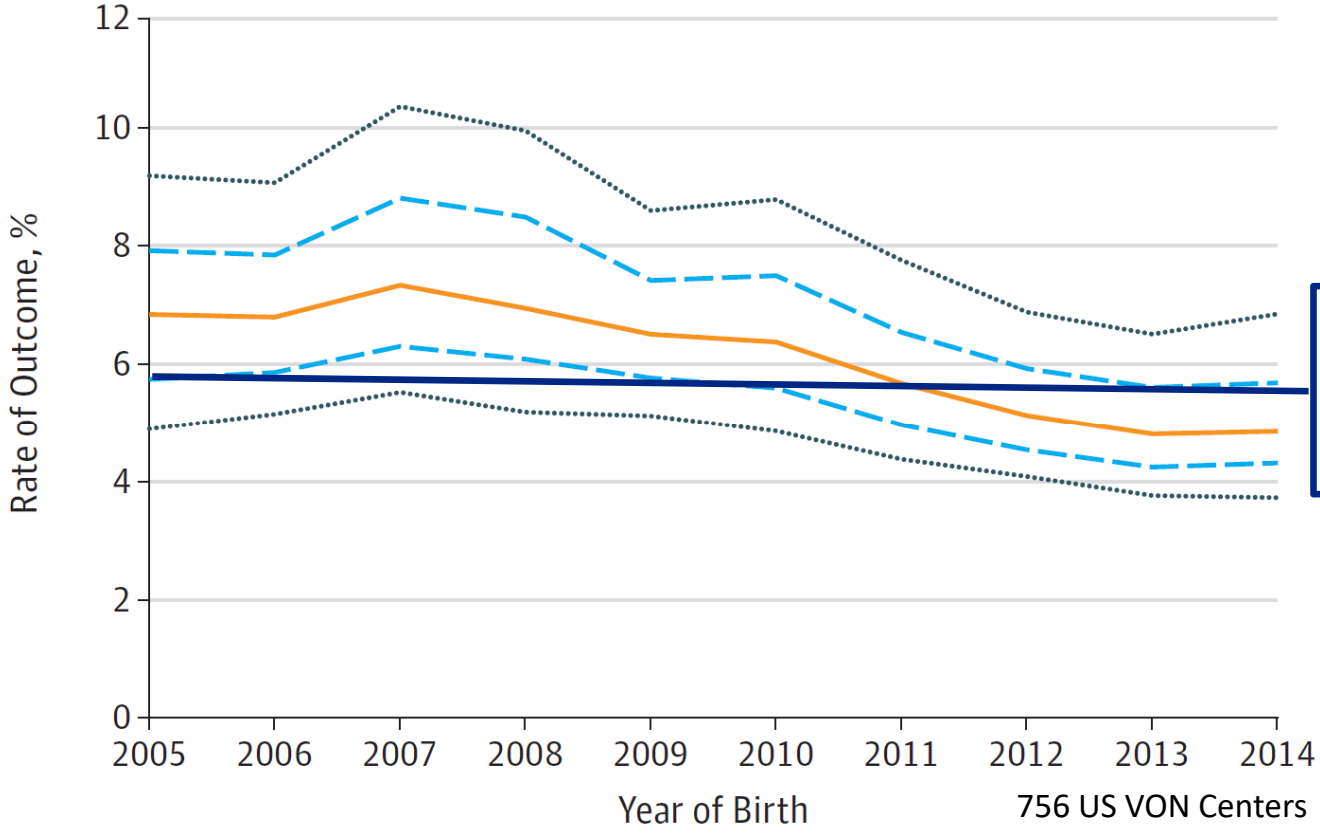
Patel RM, et al. *N Engl J Med.* 2015

Trends in incidence of NEC in US



Horbar et al. *JAMA Pediatr.* 2017

Trends in incidence of NEC in US



In 2014, 75% of NICUs achieved NEC rates of the best performing 25% of NICUs in 2005

756 US VON Centers
n=408,164

Horbar et al. *JAMA Pediatr.* 2017

To prevent NEC, need a framework to address the major causes (*drivers*)

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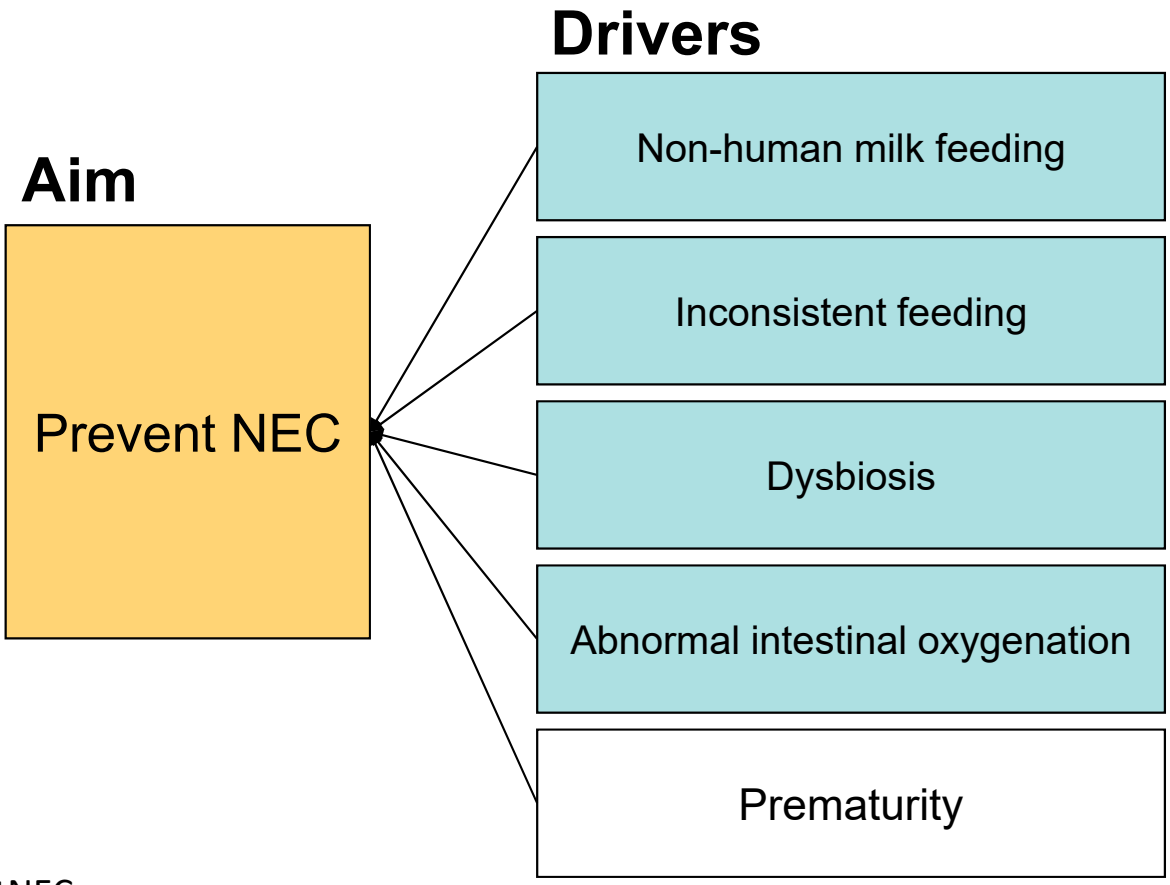
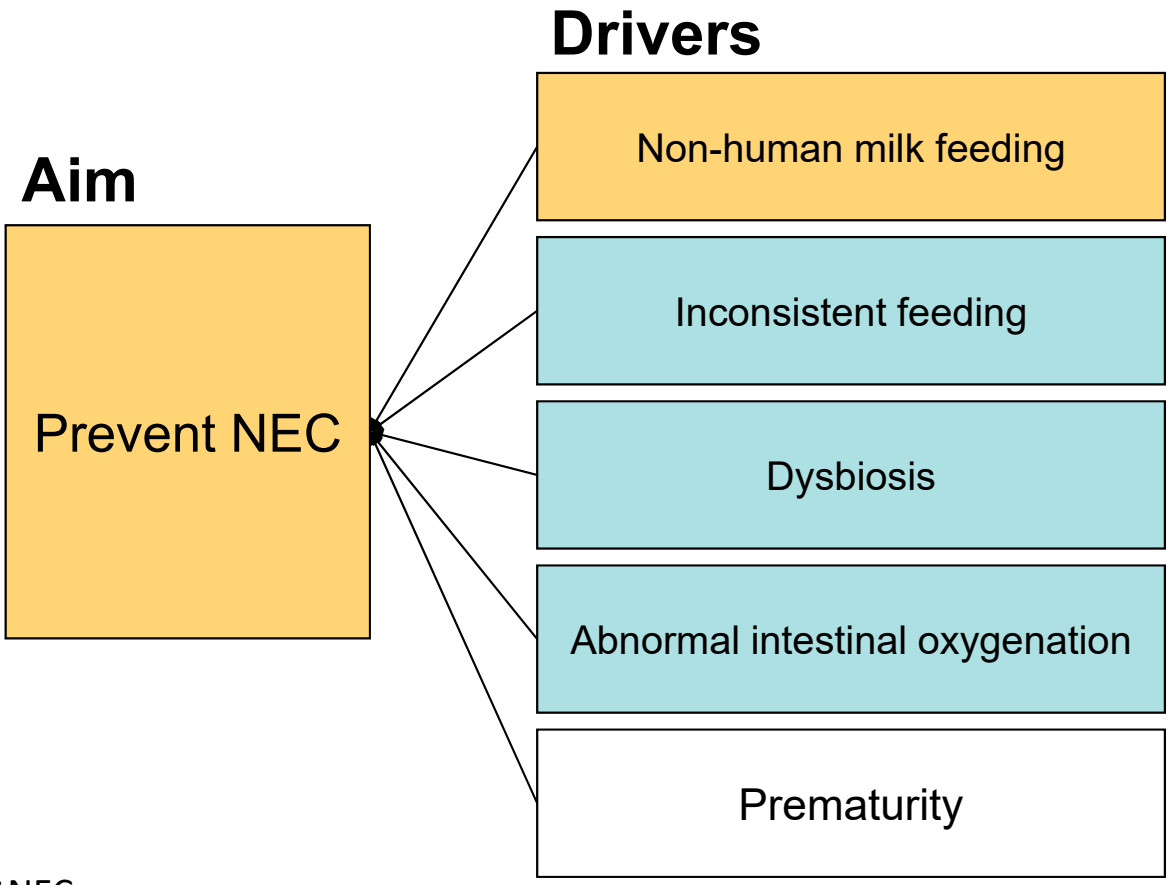
Framework for major drivers of NEC



Drivers of NEC



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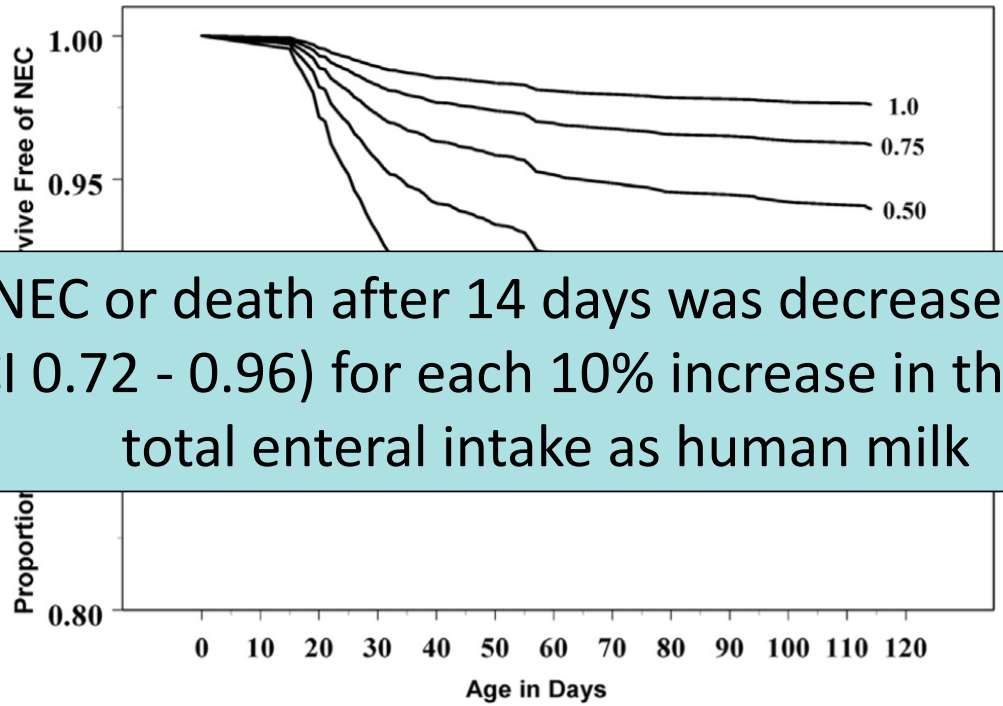
Feeding approaches and risk of NEC

Factor	Association with NEC	Observational study	Randomized controlled trial
Feeding			
Breast milk	↓	X	X
Preterm formula	↑	X	X
Donor human milk	↓	X	X
Delayed feeding	-		X
Slow feeding	-		X
Trophic feeding	-		X
Feeding protocol	↓	X	

Rose and Patel. *Sem Fetal Neo Med.* 2018

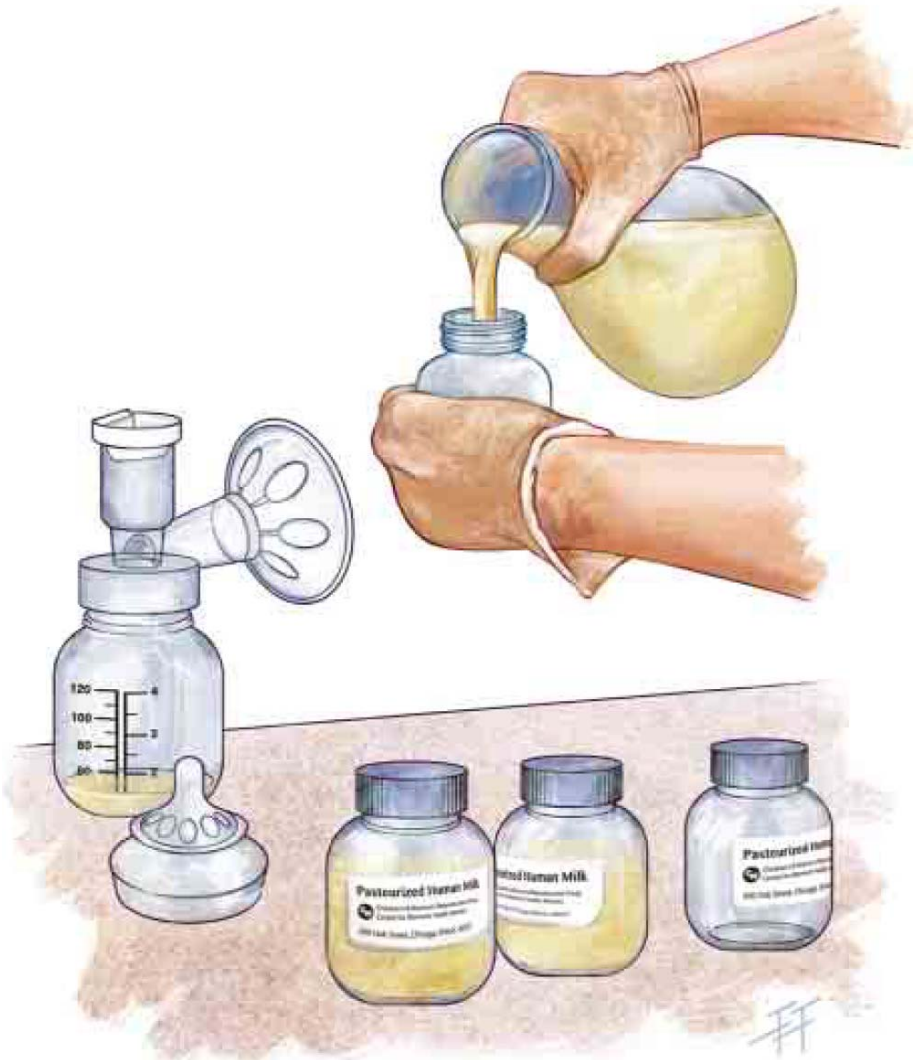
Effect of breastfeeding on NEC



The risk of NEC or death after 14 days was decreased by a factor of 0.83 (95% CI 0.72 - 0.96) for each 10% increase in the proportion of total enteral intake as human milk

Fig. 1. Adjusted survival curves for necrotizing enterocolitis (NEC) or death by proportion of human milk to total intake over the first 14 days of life. Survival

Meinzen-Derr et al. *J Perinatol* 2009



Moreno. *JAMA Pediatr.* 2016

Is donor milk, when mother's milk is not available, a safe and effective intervention to prevent NEC?

Effect of donor milk on NEC (DoMINO trial)

Outcome	**Donor Milk** (n=181)	**Preterm formula** (n=182)	**Risk difference** (95% CI)
NEC, Bell stage 2+	1.7%	6.6%	-5% (-9 to -1)*
Total weight gain	1551 g	1532 g	30 g (-98 to 158)
Mean cognitive score	93	95	-2 (-6 to 2)
Cognitive score <85	27%	16%	11% (2 to 20)*

*P <0.05

O'Connor et al. *JAMA*. 2016

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O'Connor et al. *JAMA*. 2016

MILK Trial (NICHD Neonatal Research Network)

P: Extremely preterm infants (< 29 wk) whose mothers unable to provide sufficient breastmilk (n=670)

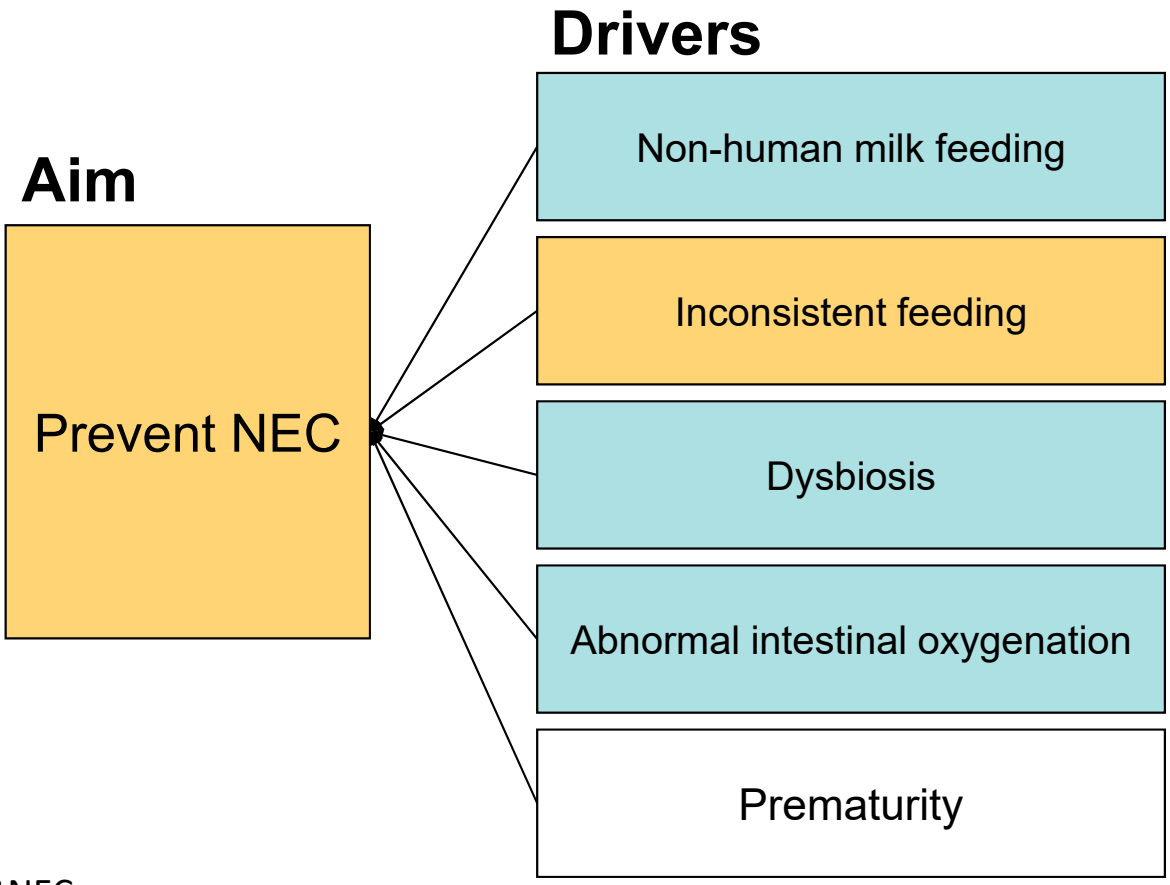
I: Donor human milk

C: Preterm formula

O: neurodevelopment at age 22-26 months of donor human milk as compared to preterm infant formula as the in-hospital diet for infants

https://clinicaltrials.gov/ct2/show/NCT01534481

Drivers of NEC



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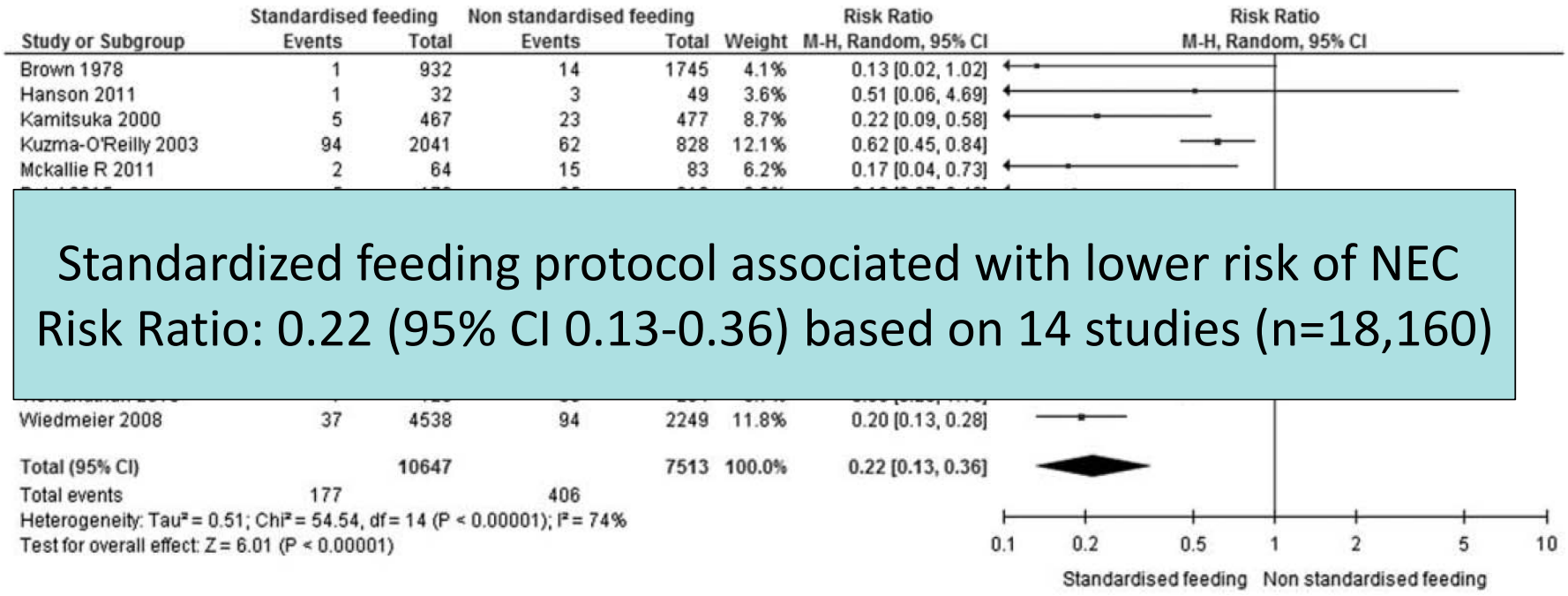
Rose and Patel. *Sem Fetal Neo Med.* 2018

Standardized feeding associated with less NEC



Standardized feeding protocol associated with lower risk of NEC
Risk Ratio: 0.22 (95% CI 0.13-0.36) based on 14 studies (n=18,160)

Figure 2. Association of standardized feeding regimen (SFR) and necrotizing enterocolitis (NEC) in preterm neonates.

Jasani and Patole. *J Perinatol.* 2017

Effect of slow vs. fast rates of advancement

Incidence of necrotising enterocolitis.

Study or Subgroup	Slow rate Events	Total	Fast rate Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Year
1.1.1 All infants							
Rayyis 1999	13	98	8	87	8.2%	1.44 [0.63, 3.32]	1999
Caple 2004	2	84	4	74	4.1%	0.44 [0.08, 2.34]	2004
Salho							
Krishr							
Karag							
Rabar							
Rabar							
Modi 2							
SIFT 2							
Jain 2016	1	15	2	15	1.9%	0.50 [0.05, 4.94]	2016
Subtotal (95% CI)		**1886**		**1856**	**100.0%**	**1.07 [0.83, 1.39]**	
Total events	112		102				
Heterogeneity: Chi² = 11.34, df = 9 (P = 0.25); I² = 21%							

Risk Ratio M-H, Fixed, 95% CI

0.01 0.1 1 10 100

Favours slow rates Favours faster rates

No reduction in risk of NEC with slower advancement of feeding (up to 24 ml/kg/day) compared to faster advancement

Risk Ratio: 1.07 (95% CI 0.83-1.39) based on 10 studies (n=3738)

Test for subgroup differences: Chi² = 1.38, df = 3 (P = 0.71), I² = 0%

Oddie et al. *Cochrane Database Syst Rev.* 2017

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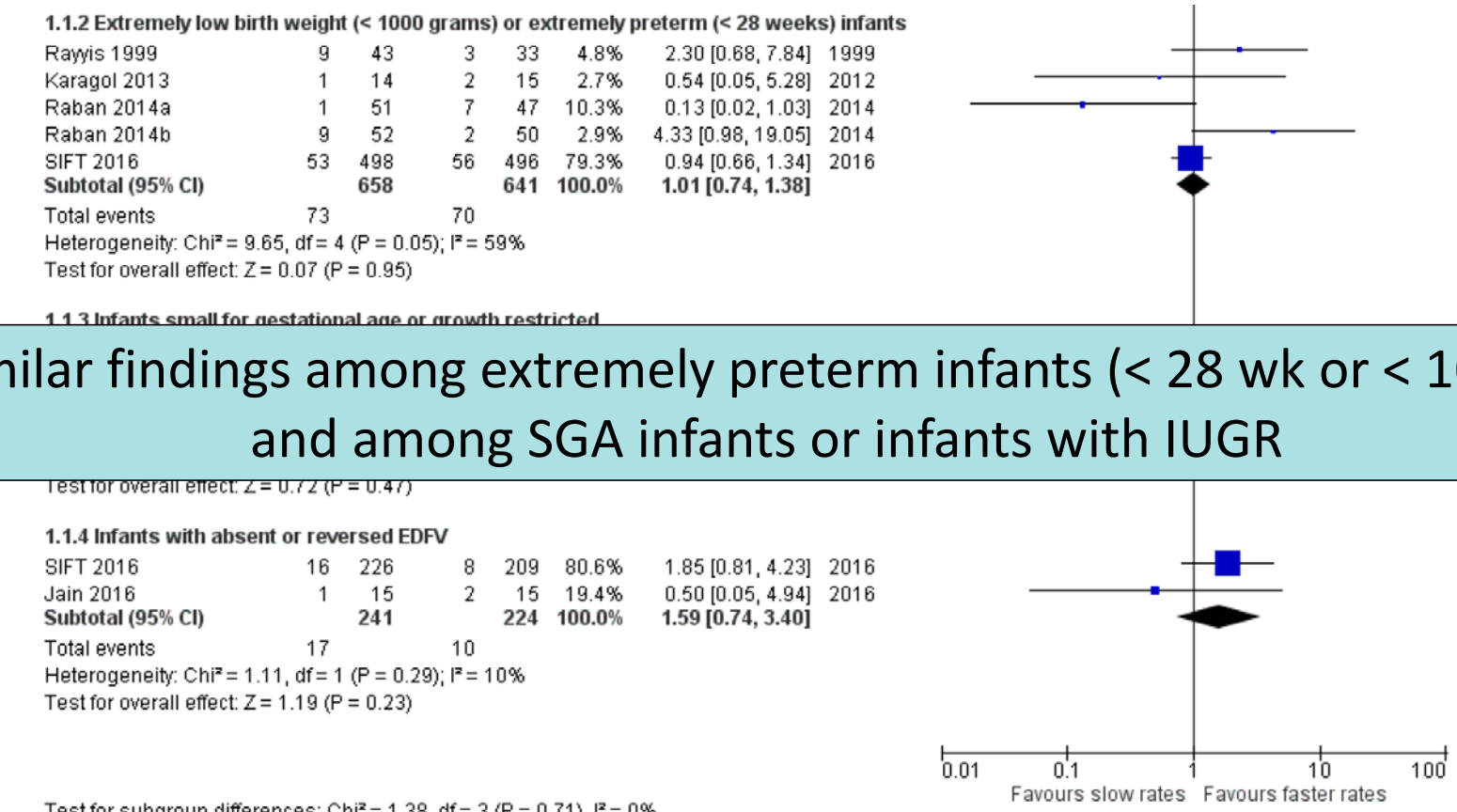
Effect of slow vs. fast rates of advancement



Similar findings among extremely preterm infants (< 28 wk or < 1000 g) and among SGA infants or infants with IUGR

Oddie et al. *Cochrane Database Syst Rev.* 2017

Is routine monitoring gastric residuals needed?

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

The Impact of Routine Evaluation of Gastric Residual Volumes on the Time to Achieve Full Enteral Feeding in Preterm Infants

Arieh Riskin, MD, MHA, Keren Cohen, MD, Amir Kugelman, MD, Arina Toropine, MD, Waseem Said, MD, and David Bader, MD, MHA

Objective evaluation to evaluate

Study de before (n =

Results T (*P* = .02). C from paren (*P* = .002). the selective gastric residual volume evaluation group compared with 3.3% in the historic control group (*P* = .4). Multiple regression analyses showed that the strongest predictor of time to full enteral feedings was GA. Routine evaluation of gastric residual volume and increasing time on noninvasive ventilation both prolonged the attainment of full enteral feedings. Findings were consistent in the subgroup with birth weights of <1500 g. Increased weight at discharge was most strongly associated with advancing postmenstrual, age but avoidance of routine evaluations of gastric residual volume also was a significant factor.

Conclusions Avoiding routine evaluation of gastric residual volume before every feeding was associated with earlier attainment of full enteral feedings without increasing risk for NEC. *(J Pediatr 2017;189:128-34).*

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Gastric Residual Volume in Feeding Advancement in Preterm Infants (GRIP Study): A Randomized Trial

Balpreet Singh, MD, MSc[1,2], Niels Rochow, MD[1], Lorraine Chessell, RD[1], Jennifer Wilson, MHSc[1], Kathy Cunningham, MHSc[1], Christoph Fusch, MD, PhD[1,3], Sourabh Dutta, MD, PhD[1,4], and Sumesh Thomas, MD[1,5]

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sidual volume. The primary outcome was the time to reach feeding volumes of 120 mL/kg per day. Secondary outcomes were time to regain BW, episodes of feeding interruptions, sepsis, and necrotizing enterocolitis.

Results Eighty-seven infants were enrolled. There were no differences between the study and control groups with respect to time to reach full feeds (6 days [95% CI, 5.5-6.5] vs 5 days [95% CI, 4.5-5.5]; *P* = .82), time to regain BW, episodes of feeding interruptions, or sepsis. Two infants in the control group developed necrotizing enterocolitis.

Conclusions Avoiding routine assessment of gastric residual volume before feeding advancement did not shorten the time to reach full feeds in preterm infants with BW between 1500 and 2000 g. *(J Pediatr 2018;200:79-83).*

Trial registration Clinicaltrials.gov: NCT01337622.

Although case-control studies suggest residual volumes increase prior to NEC, no studies have shown routine measurement of gastric residuals prevents NEC

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Example of feeding protocol at Emory

Birthweight (kg)	1.31				
Day of Enteral Feeding	Date	Goal volume (ml/kg)	Goal volume (ml)	Goal caloric density	Comments
1		20	3	20 kcal/oz	Trophic feeds (BM preferred)
2		50	8	20 kcal/oz	Daily advance
3		80	13	20 kcal/oz	
4		80	13	22 kcal/oz	If on formula, advance to 24kcal/oz
5		80	13	24 kcal/oz	
6		110	18	24 kcal/oz	Discontinue fluids/IV
7		140	22	24 kcal/oz	
8		150	25	24 kcal/oz	

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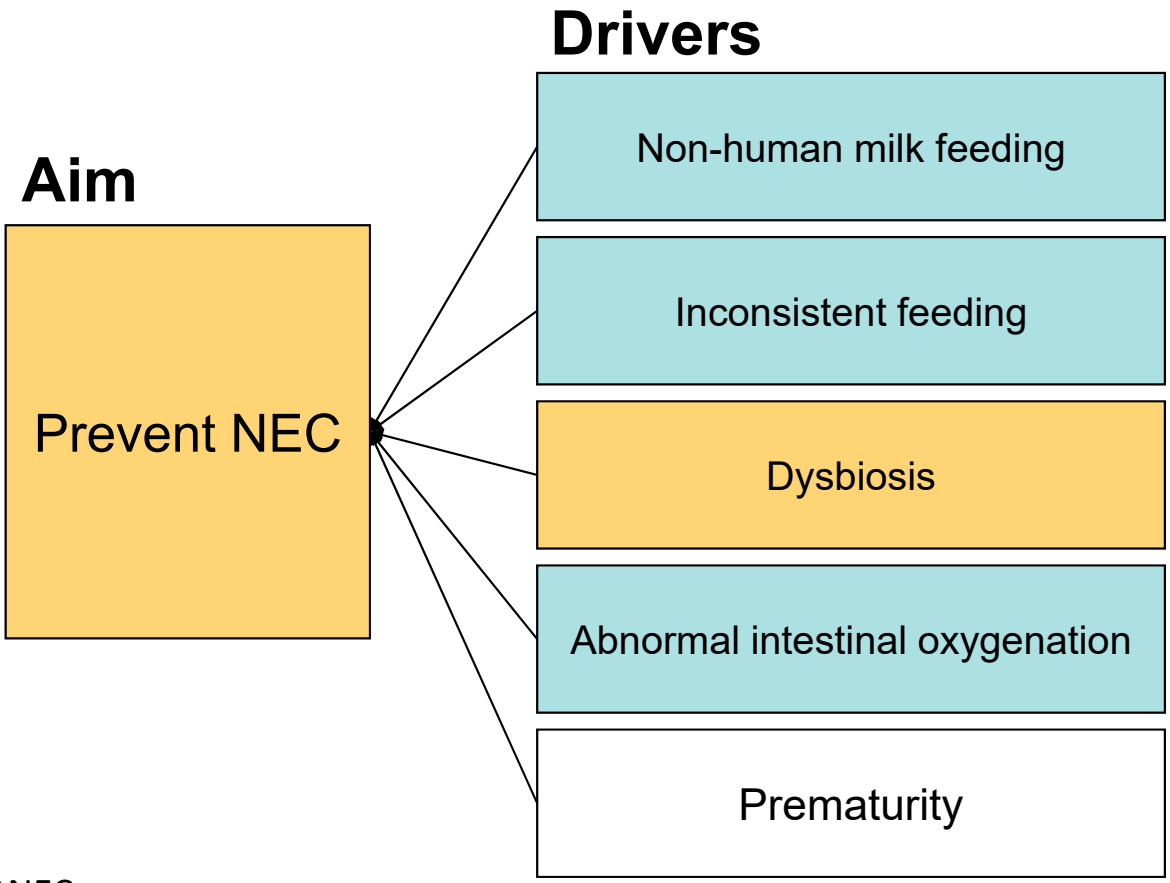
Drivers of NEC



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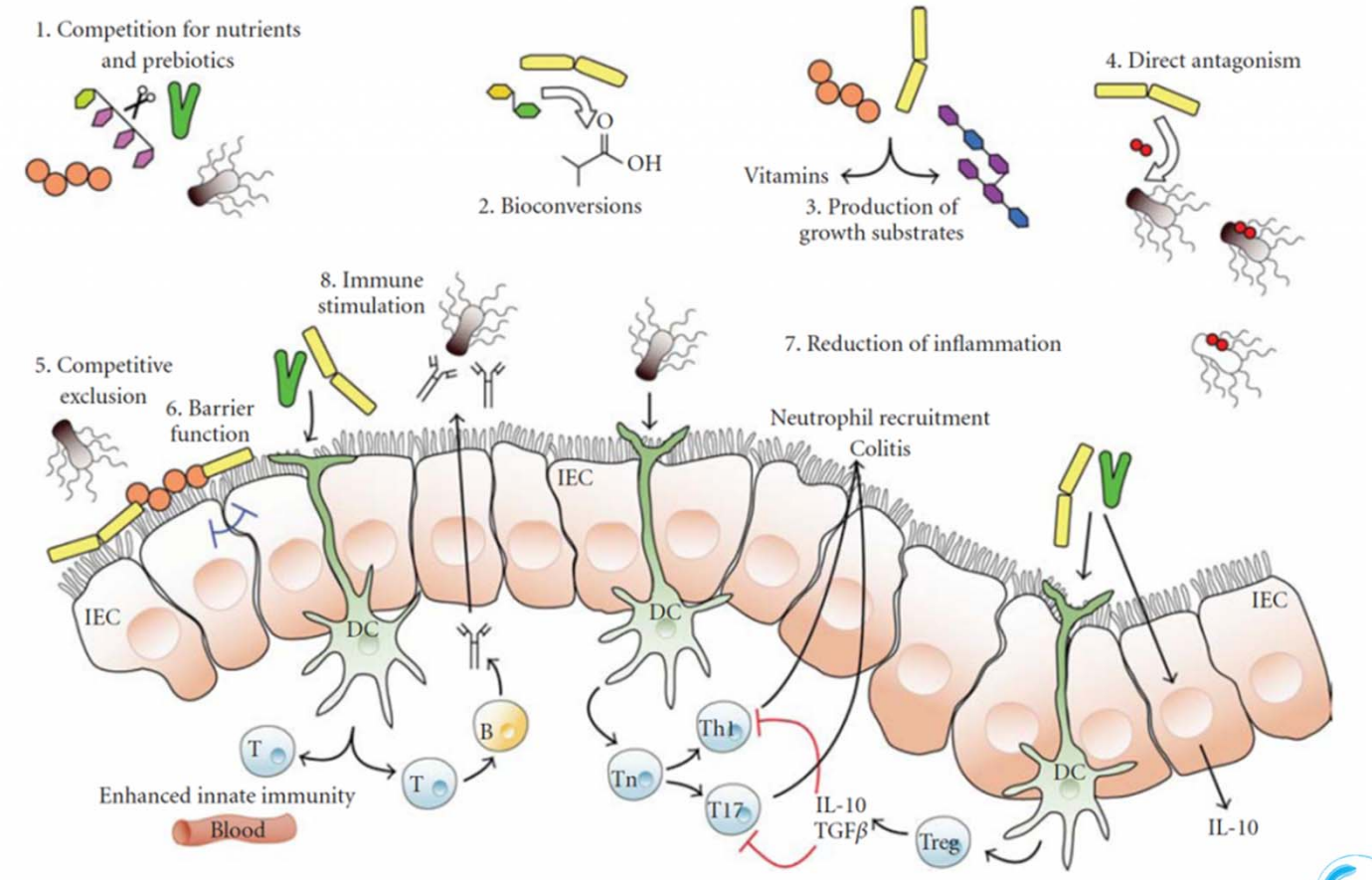
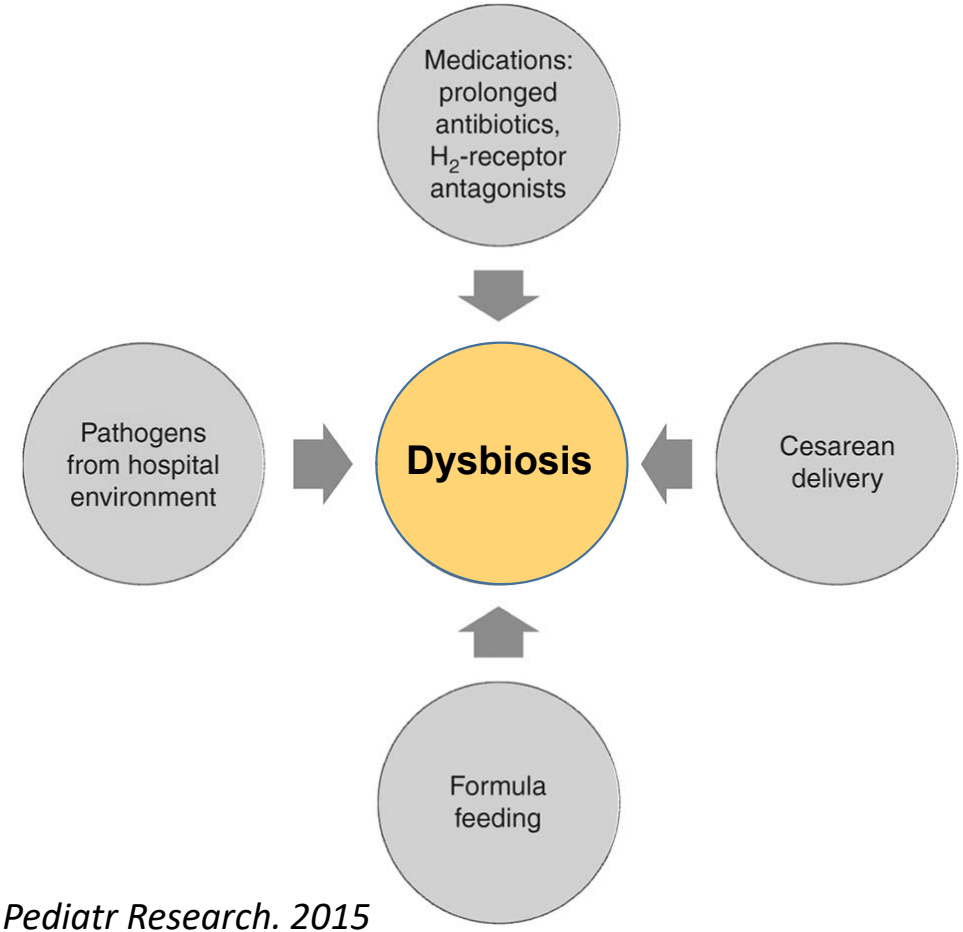
Importance of commensal bacteria

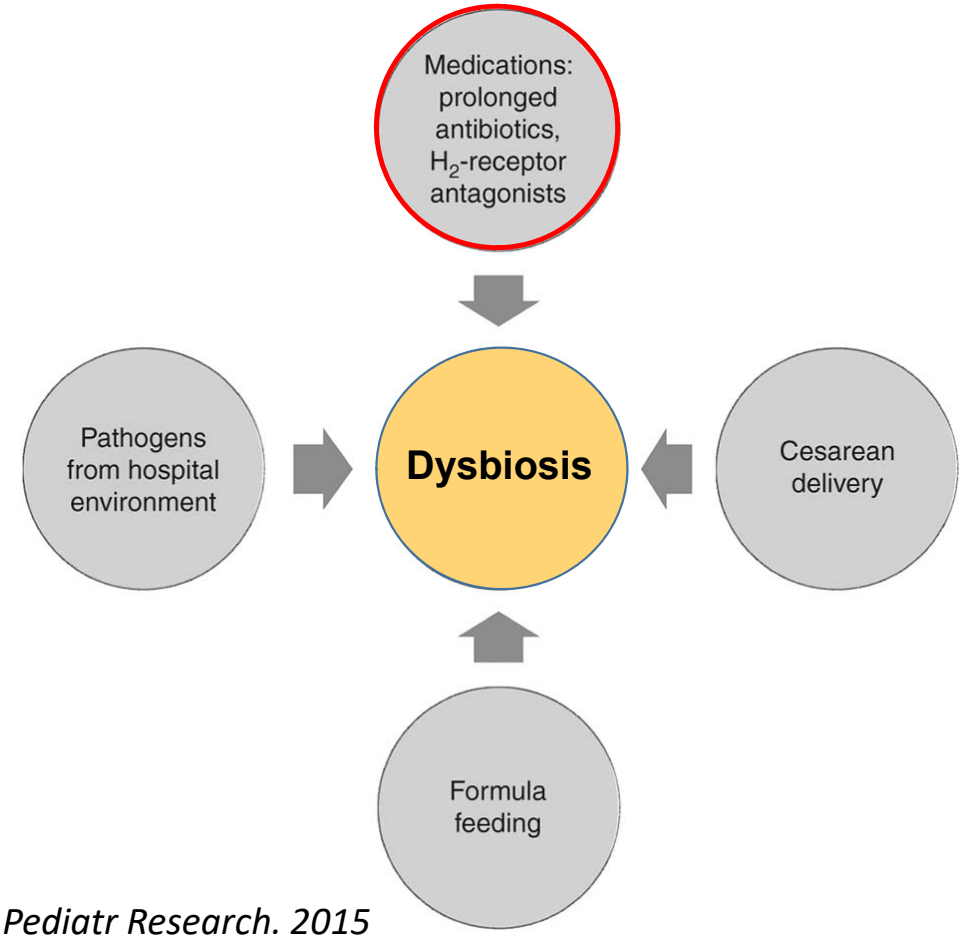


Dysbiosis in NEC



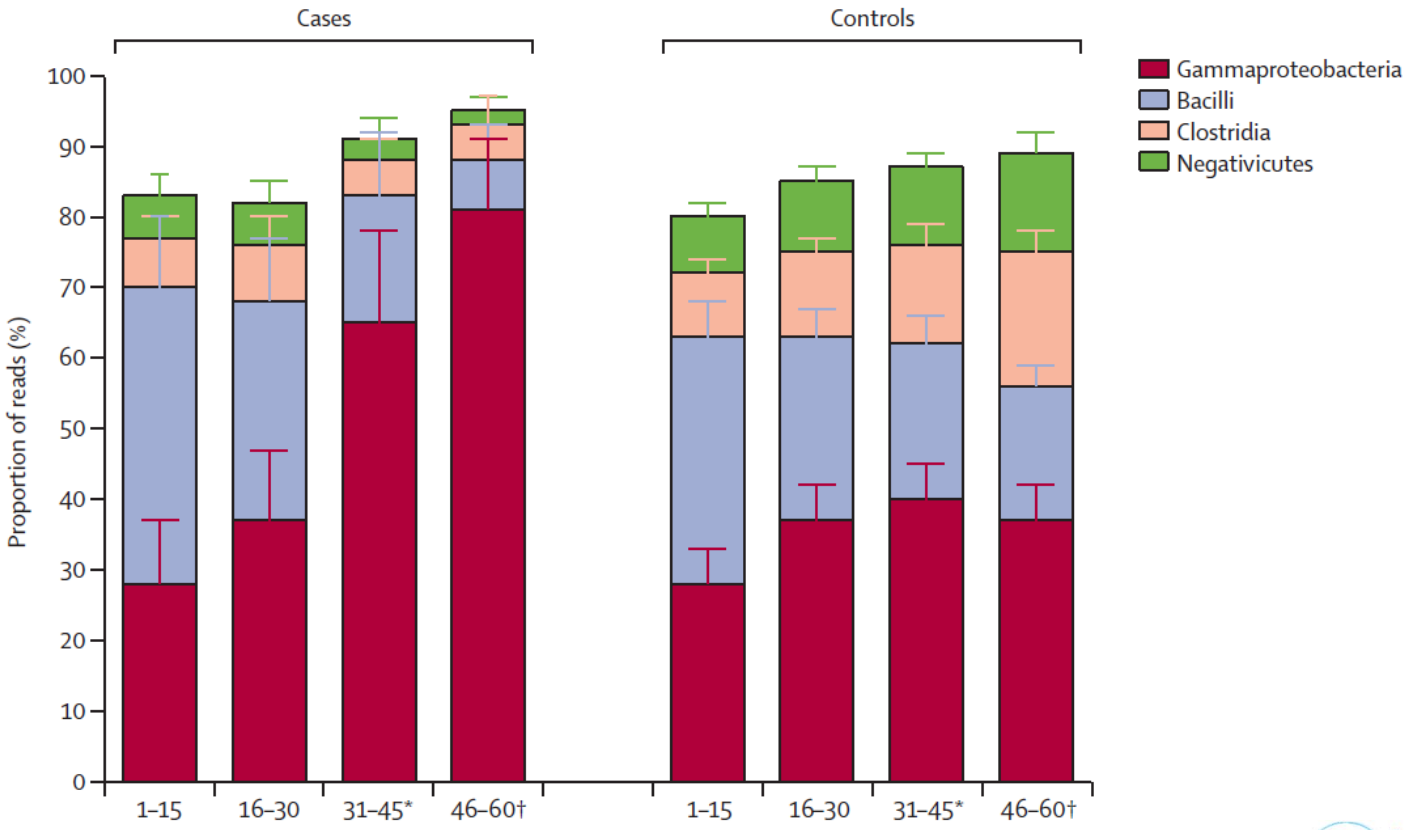
Patel and Denning. *Pediatr Research. 2015*

Dysbiosis in NEC

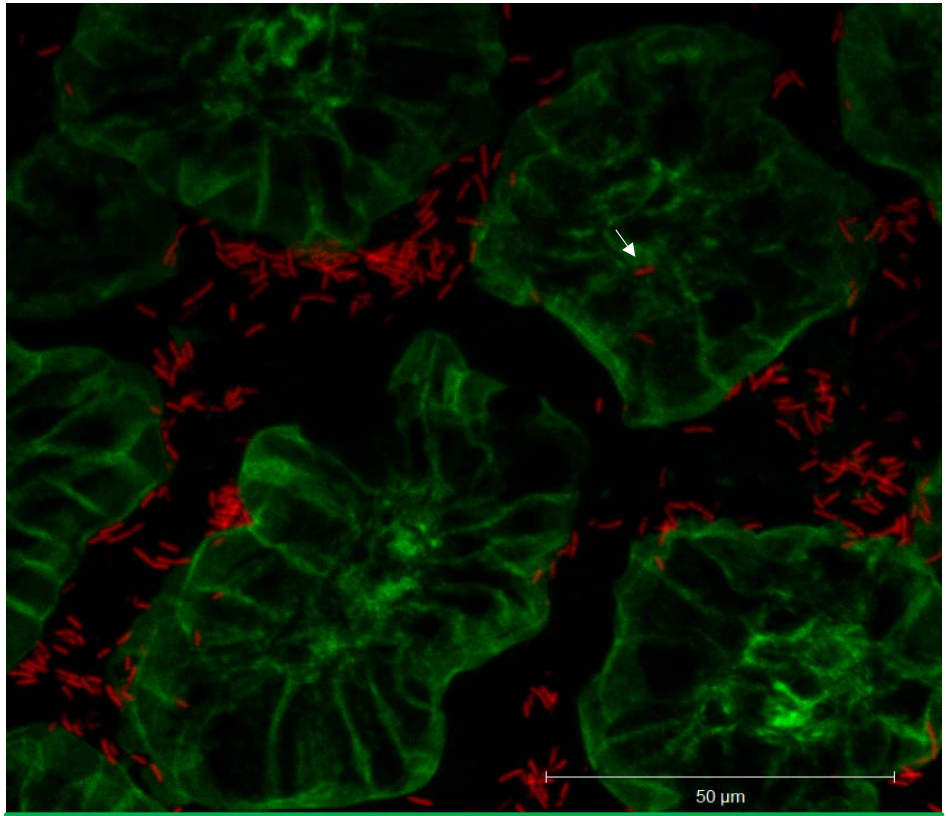


Patel and Denning. *Pediatr Research. 2015*

Dysbiosis before NEC



Warner et al. *Lancet.* 2016



Probiotic: a microorganism (such as lactobacillus) that when consumed (as in a food or a dietary supplement) maintains or restores beneficial bacteria to the digestive tract [source: Merriam-Webster]

Can probiotics prevent the potential consequences of dysbiosis?

Meta-analyses of probiotics in preterm infants

Summary of recent meta-analyses evaluating treatment effects of probiotics.

Outcome	Year	Trials, *n*	Patients, *n*	RR (95% CI)	I^2	Effects
NEC (Bell Stage 2 or 3)						
Sawh et al.[35]	2016	35	10520	0.53 (0.42–0.66)	11%	Random
Dermyshi et al.[39]	2017	29	8535	0.57 (0.47–0.70)	23%	Fixed
Chang et al.[62]	2017	25	7345	0.60 (0.48–0.74)	0%	Fixed
Thomas et al.[49]	2017	23	7325	0.57 (0.43–0.74)	22%	Random
Late-onset sepsis						
Sawh et al.[35]	2016	28	8707	0.88 (0.77–1.00)	31%	Random
Rao et al.[40]	2016	37	9416	0.86 (0.78–0.94)	35%	Fixed
Dermyshi et al.[39]	2017	28	7987	0.88 (0.80–0.97)	17%	Fixed
Death						
Sawh et al.[35]	2016	27	9507	0.79 (0.68–0.93)	0%	Random
Dermyshi et al.[39]	2017	27	8156	0.77 (0.65–0.92)	16%	Fixed
Chang et al.[62]	2017	21	6291	0.75 (0.60–0.92)	9%	Fixed
Thomas et al.[49]	2017	22	6954	0.72 (0.57–0.92)	17%	Random

Patel and Underwood. *Sem Ped Surg.* 2018

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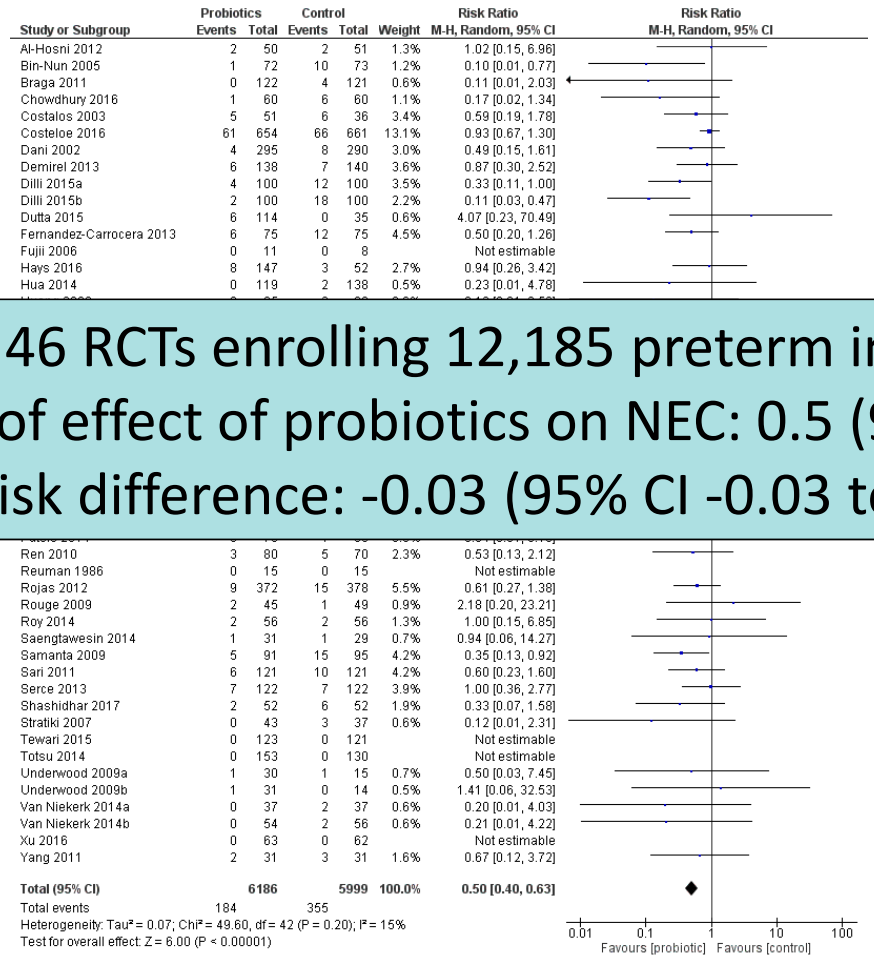
Probiotics and NEC



Study or Subgroup	Probiotics Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Al-Hosni 2012	2	50	2	51	1.3%	1.02 [0.15, 6.96]
Bin-Nun 2005	1	72	10	73	1.2%	0.10 [0.01, 0.77]
Braga 2011	0	122	4	121	0.6%	0.11 [0.01, 2.03]
Chowdhury 2016	1	60	6	60	1.1%	0.17 [0.02, 1.34]
Costalos 2003	5	51	6	36	3.4%	0.59 [0.19, 1.78]
Costeloe 2016	61	654	66	661	13.1%	0.93 [0.67, 1.30]
Dani 2002	4	295	8	290	3.0%	0.49 [0.15, 1.61]
Demirel 2013	6	138	7	140	3.6%	0.87 [0.30, 2.52]
Dilli 2015a	4	100	12	100	3.5%	0.33 [0.11, 1.00]
Dilli 2015b	2	100	18	100	2.2%	0.11 [0.03, 0.47]
Dutta 2015	6	114	0	35	0.6%	4.07 [0.23, 70.49]
Fernandez-Carrocera 2013	6	75	12	75	4.5%	0.50 [0.20, 1.26]
Fujii 2006	0	11	0	8		Not estimable
Hays 2016	8	147	3	52	2.7%	0.94 [0.26, 3.42]
Hua 2014	0	119	2	138	0.5%	0.23 [0.01, 4.78]
Ren 2010	3	80	5	70	2.3%	0.53 [0.13, 2.12]
Reuman 1986	0	15	0	15		Not estimable
Rojas 2012	9	372	15	378	5.5%	0.61 [0.27, 1.38]
Rouge 2009	2	45	1	49	0.9%	2.18 [0.20, 23.21]
Roy 2014	2	56	2	56	1.3%	1.00 [0.15, 6.85]
Saengtawesin 2014	1	31	1	29	0.7%	0.94 [0.06, 14.27]
Samanta 2009	5	91	15	95	4.2%	0.35 [0.13, 0.92]
Sari 2011	6	121	10	121	4.2%	0.60 [0.23, 1.60]
Serce 2013	7	122	7	122	3.9%	1.00 [0.36, 2.77]
Shashidhar 2017	2	52	6	52	1.9%	0.33 [0.07, 1.58]
Stratiki 2007	0	43	3	37	0.6%	0.12 [0.01, 2.31]
Tewari 2015	0	123	0	121		Not estimable
Totsu 2014	0	153	0	130		Not estimable
Underwood 2009a	1	30	1	15	0.7%	0.50 [0.03, 7.45]
Underwood 2009b	1	31	0	14	0.5%	1.41 [0.06, 32.53]
Van Niekerk 2014a	0	37	2	37	0.6%	0.20 [0.01, 4.03]
Van Niekerk 2014b	0	54	2	56	0.6%	0.21 [0.01, 4.22]
Xu 2016	0	63	0	62		Not estimable
Yang 2011	2	31	3	31	1.6%	0.67 [0.12, 3.72]
Total (95% CI)		**6186**		**5999**	**100.0%**	**0.50 [0.40, 0.63]**
Total events	184		355			

Heterogeneity: Tau² = 0.07; Chi² = 49.60, df = 42 (P = 0.20); I² = 15%
Test for overall effect: Z = 6.00 (P < 0.00001)

Risk Ratio M-H, Random, 95% CI
0.01 0.1 1 10 100
Favours [probiotic] Favours [control]

46 RCTs enrolling 12,185 preterm infants

Risk ratio of effect of probiotics on NEC: 0.5 (95% CI 0.4 - 0.6)

Risk difference: -0.03 (95% CI -0.03 to -0.02)

*unpublished

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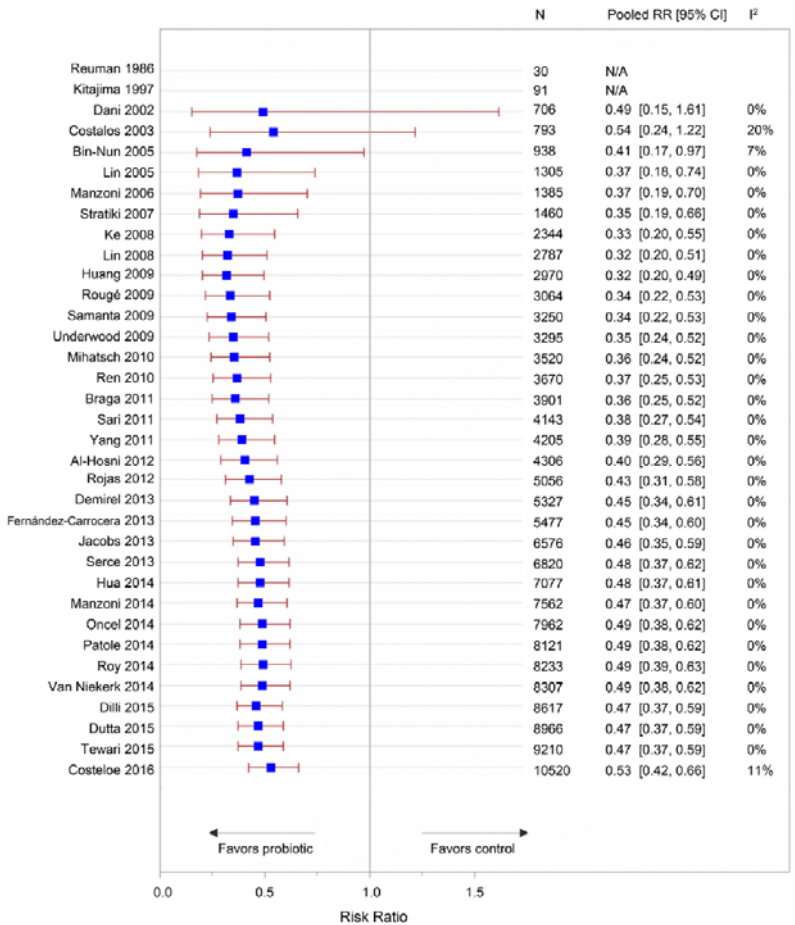
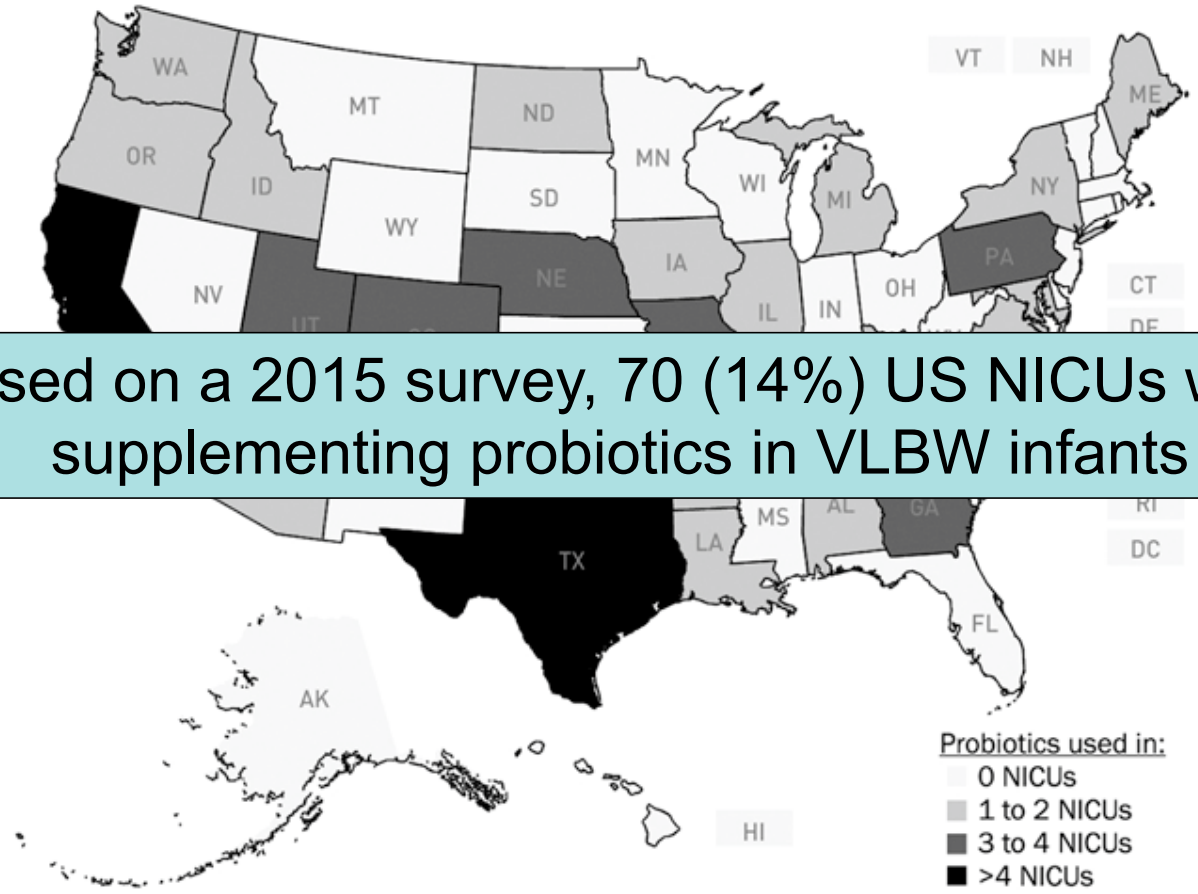
Cumulative meta-analysis



Patel and Underwood. *Sem Ped Surg.* 2018

Probiotic use in the US



Based on a 2015 survey, 70 (14%) US NICUs were supplementing probiotics in VLBW infants

Viswanathan et al. *J Perinatol.* 2016

Mostly commonly used probiotics in US

Probiotic brand	Strains	NICUs using probiotics, n (%)
Culturelle	*Lactobacillus rhamnosus GG*	19 (27%)
Biogaia	*Lactobacillus reuteri*	10 (14%)
Gerber Soothe	*Lactobacillus reuteri*	10 (14%)
Florababy	*Bifidobacterium breve, infantis, bifidum, longum, Lactobacillus rhamnosus*	6 (8%)

Viswanathan et al. *J Perinatol.* 2016

Which probiotic do I choose?

Which probiotic product to use remains uncertain, since the total body of evidence comprises a heterogeneous group of probiotics (individual species and combination products, and regimens). In the previous review, only the *Lactobacillus* and multispecies supplements were shown to be effective for this outcome. We would recommend a regulatory body-approved product and that quality assessment be requested from the manufacturer to validate the purity of product. The evidence of benefit was clear for *Lactobacillus* or *Bifidobacterium* species and multiple species products so any of these would be reasonable choices.

Sawh SC, et al. *Peer J*, 2016

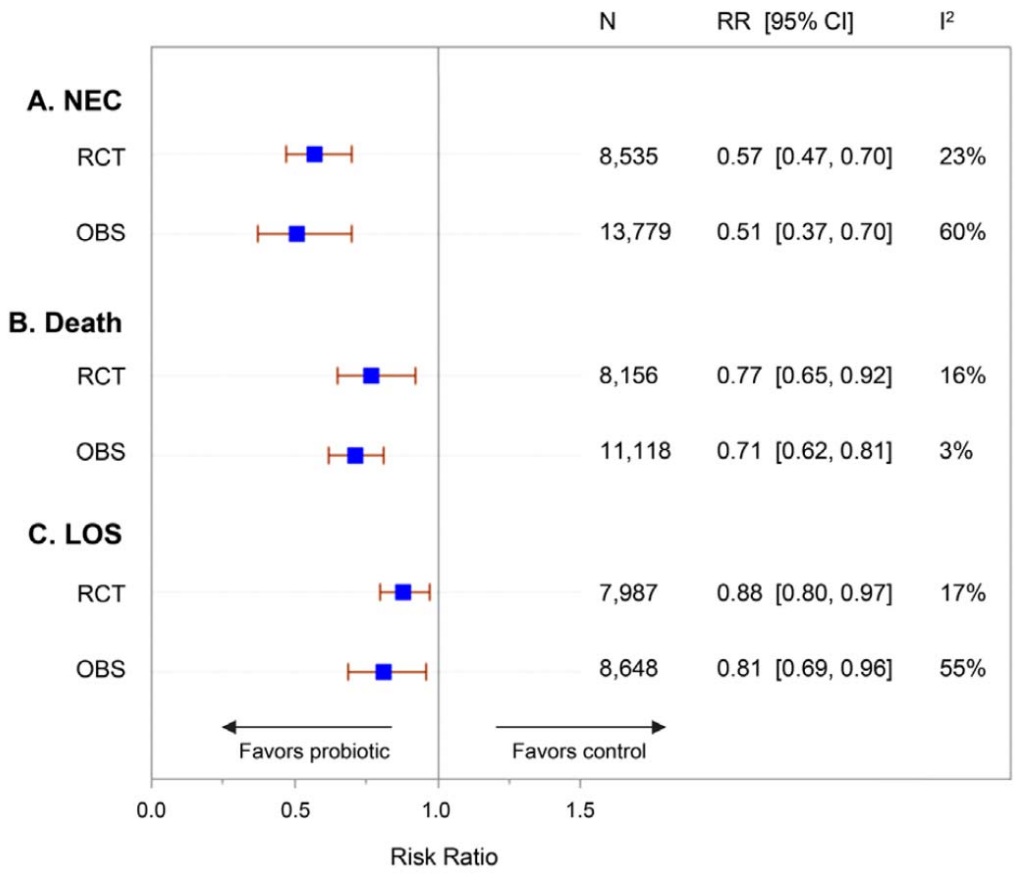
Label vs. actual content

Validating bifidobacterial species and subspecies identity in commercial probiotic products

Zachery T. Lewis[1,2], Guy Shani[1,2], Chad F. Masarweh[1,2], Mina Popovic[3], Steve A. Frese[1,2], David A. Sela[4], Mark A. Underwood[2,5] and David A. Mills[1,2]

- 16 probiotic products containing bifidobacterial species examined using DNA-based methods and confirmed using culture-based techniques.
- “many bifidobacterial probiotic products differ from the ingredient list … Only 1 of the 16 probiotics perfectly matched its bifidobacterial label claims in all samples tested, and both pill-to-pill and lot-to-lot variation were observed.”

Effectiveness of probiotics in preterm infants



Patel and Underwood. *Sem Ped Surg.* 2018

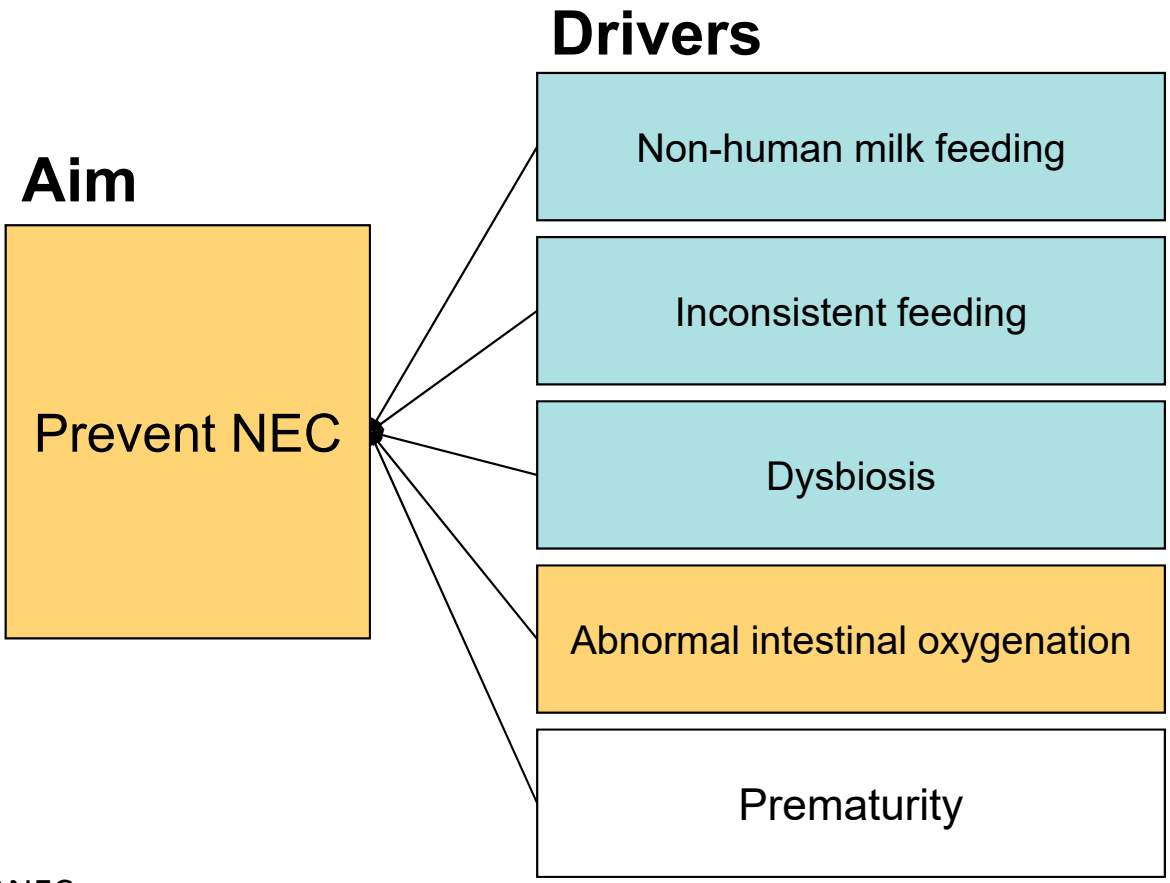
Routine supplementation of LGG

Table IV. Infant characteristics and outcomes before and after implementation of LGG supplementation

Characteristics or outcomes	Pre-LGG implementation epoch, 2008-2014 (n = 443)	Post-LGG implementation epoch, 2014-2016 (n = 197)	P*
Gestational age, wk	28.7 (26.4-30.6)	28.3 (26.3-30.6)	.26
Birth weight, g	1080 (820-1300)	1000 (740-1270)	.10
Receipt of any initial antibiotics	366/443 (83%)	156/197 (79%)	.30
Receipt of prophylactic indomethacin	164/443 (37%)	97/197 (49%)	.004
Receipt of any human milk	387/438 (88%)	193/197 (98%)	<.001
Age at first feed	2 (1-3)	2 (1-3)	.86
Necrotizing enterocolitis stage IIA or greater	45/443 (10%)	33/197 (17%)	.02
Necrotizing enterocolitis stage IIIA or IIIB	20/443 (5%)	11/197 (6%)	.56
Death	17/443 (4%)	13/197 (7%)	.13
Necrotizing enterocolitis (Stage IIA or greater) or death	53/443 (12%)	41/197 (21%)	.004
Blood culture-positive sepsis	86/440 (20%)	47/196 (24%)	.20
LGG-associated sepsis	0 (0%)	0 (0%)	-

Kane et al. *J Pediatr.* 2018

Drivers of NEC



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RBC transfusion, anemia and NEC

Original Investigation

Association of Red Blood Cell Transfusion, Anemia, and Necrotizing Enterocolitis in Very Low-Birth-Weight Infants

Ravi M. Patel, MD, MSc; Andrea Knezevic, MS; Neeta Shenvi, MS; Michael Hinkes, MD; Sarah Keene, MD; John D. Roback, MD, PhD; Kirk A. Easley, MApStat; Cassandra D. Josephson, MD

Primary objective: To test the hypothesis that the risk of NEC is greater in VLBW infants exposed to RBC transfusion compared to non-transfused VLBW infants

Secondary objective: To determine if exposure to severe anemia (hemoglobin ≤8 g/dL) is an independent risk factor for NEC in very low birth weight infants

Patel RM et al. *JAMA.* 2016

RBC transfusion not associated with NEC

Risk Factors	NEC		
	Cause-Specific HR (95% CI)[b]	*P* Value	% Reliability[c]
Model 1—Primary Analysis (N = 598)[d]			
Birth weight, per 100-g increase	0.72 (0.62-0.84)	<.001	98
Received RBC transfusion in a given week[e]	0.44 (0.17-1.12)	.09	45
Severe anemia in a given week (hemoglobin ≤8 g/dL)[e]	5.99 (2.00-18.0)	.001	70
Days of breast milk feeding in first 10 days of life, per 1-day increase	1.10 (1.01-1.21)	.04	37
SNAP on day of birth, per 1-point increase	1.00 (0.93-1.07)	.99	8
Days of antibiotic treatment in first 10 days of life, per 1-day increase	1.04 (0.93-1.16)	.50	8

Patel RM et al. *JAMA.* 2016

Severe anemia associated with NEC

Risk Factors	NEC		
	Cause-Specific HR (95% CI)[b]	*P* Value	% Reliability[c]
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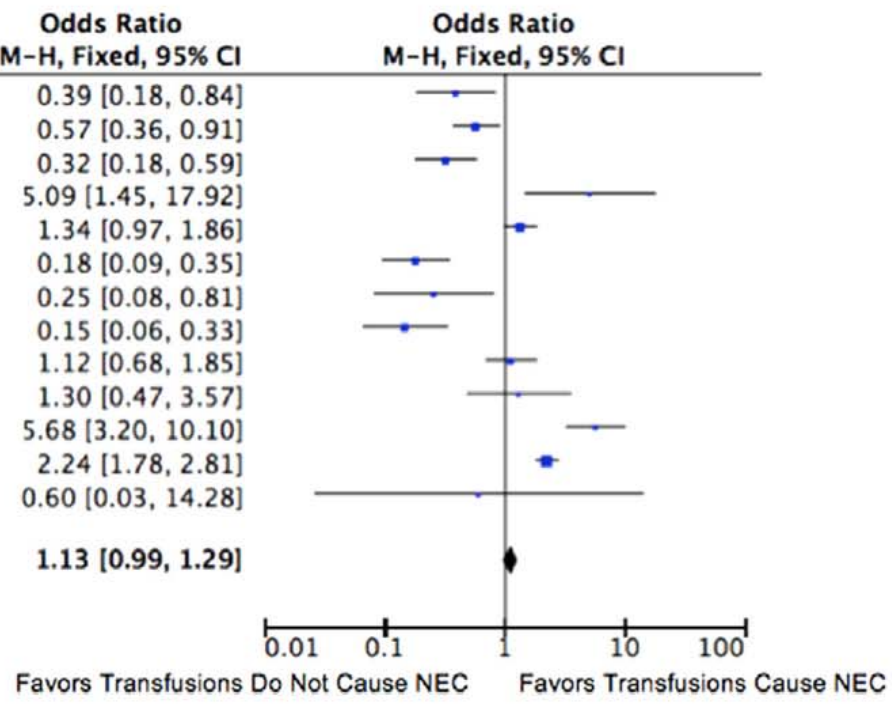
Patel RM et al. *JAMA.* 2016

Updated meta-analysis of transfusion and NEC

Study or Subgroup	Transfused Events	Transfused Total	Not Transfused Events	Not Transfused Total	Weight	Odds Ratio M-H, Fixed, 95% CI
AlFaleh 2014	23	110	17	42	4.8%	0.39 [0.18, 0.84]
Christensen 2010	40	162	72	198	12.0%	0.57 [0.36, 0.91]
Demirel 2012	15	296	50	351	10.7%	0.32 [0.18, 0.59]
El-Dib 2011	14	19	11	31	0.5%	5.09 [1.45, 17.92]
Elabiad 2013	116	1842	58	1218	16.1%	1.34 [0.97, 1.86]
Josephson 2010	18	70	75	114	10.4%	0.18 [0.09, 0.35]
Martin 2013	12	42	11	18	2.7%	0.25 [0.08, 0.81]
Patel 2016	7	319	37	279	9.5%	0.15 [0.06, 0.33]
Paul 2011	33	1149	30	1168	7.1%	1.12 [0.68, 1.85]
Sharma 2014	11	20	31	64	1.6%	1.30 [0.47, 3.57]
Singh 2011	44	67	67	266	2.3%	5.68 [3.20, 10.10]
Stritzke 2013	144	355	783	3350	22.0%	2.24 [1.78, 2.81]
Vallieva 2009	2	47	0	5	0.2%	0.60 [0.03, 14.28]
Total (95% CI)		**4498**		**7104**	**100.0%**	**1.13 [0.99, 1.29]**
Total events	479		1242			

Heterogeneity: $Chi^2 = 164.25$, $df = 12$ ($P < 0.00001$); $I^2 = 93\%$

Test for overall effect: $Z = 1.78$ ($P = 0.07$)



Hay S et al. *Semin Perinatol.* 2017

Transfusion of Prematures (TOP) Trial

Enrollment complete (n=1824) and follow-up ongoing

Table 2
Transfusion of Prematures trial hemoglobin transfusion thresholds

	High-Threshold (Liberal) Group		Low-Threshold (Restrictive) Group	
Time Period	Respiratory Support	No Support	Respiratory Support	No Support
Week 1	13.0	12.0	11.0	10.0
Week 2	12.5	11.0	10.0	8.5
Weeks ≥3	11.0	10.0	8.5	7.0

Hemoglobin values shown are g/dL. Respiratory support defined as mechanical ventilation, continuous positive airway pressure, fraction of inspired oxygen in excess of 0.35, or oxygen by nasal cannula in excess of 1 L/min.

ClinicalTrials.gov Identifier: NCT01702805

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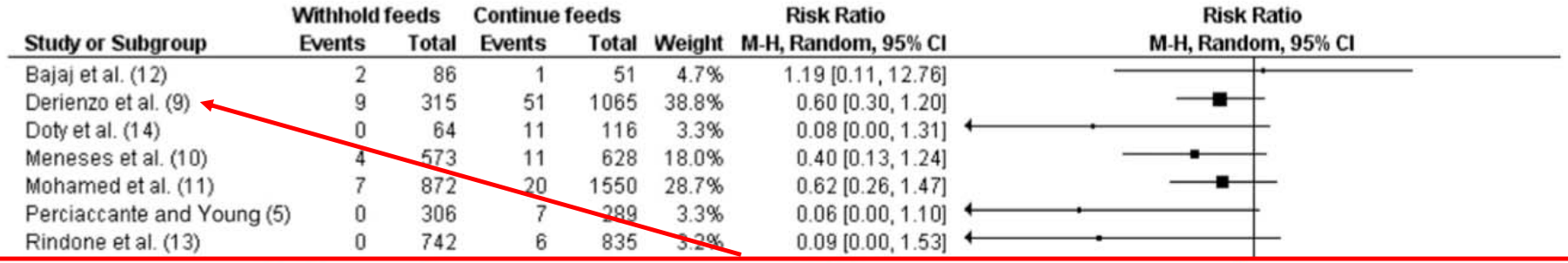
Feeding during RBC transfusion



Study or Subgroup	Withhold feeds Events	Total	Continue feeds Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Bajaj et al. (12)	2	86	1	51	4.7%	1.19 [0.11, 12.76]
Derienzo et al. (9)	9	315	51	1065	38.8%	0.60 [0.30, 1.20]
Doty et al. (14)	0	64	11	116	3.3%	0.08 [0.00, 1.31]
Meneses et al. (10)	4	573	11	628	18.0%	0.40 [0.13, 1.24]
Mohamed et al. (11)	7	872	20	1550	28.7%	0.62 [0.26, 1.47]
Perciaccante and Young (5)	0	306	7	289	3.3%	0.06 [0.00, 1.10]
Rindone et al. (13)	0	742	6	835	3.2%	0.09 [0.00, 1.53]

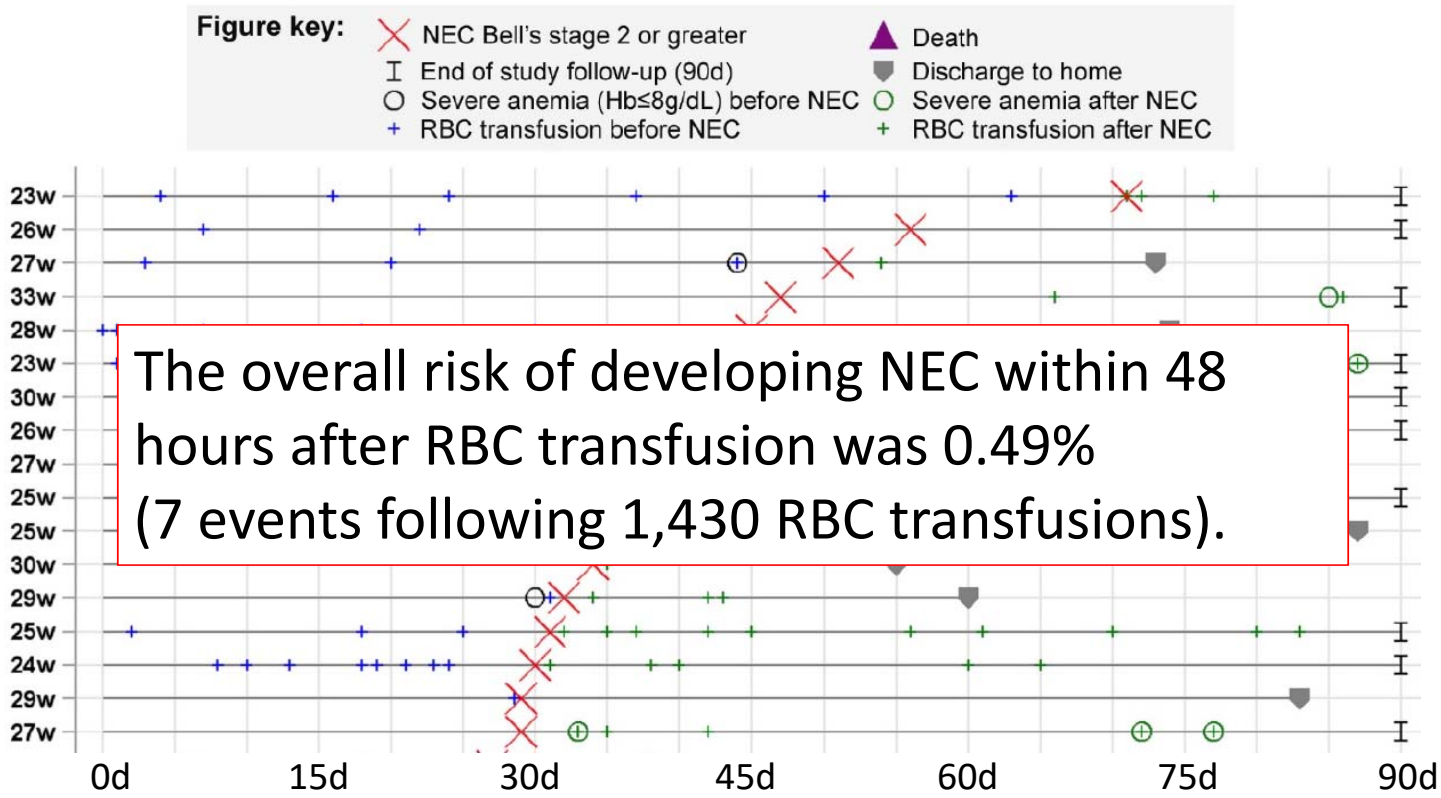
CONCLUSIONS: Pre-transfusion hematocrit is inversely related to risk of TANEC, which suggests that temporally maintaining a higher baseline hemoglobin in infants most at risk of NEC may be protective. The lack of difference in TANEC pre-/post-implementation of our peri-transfusion feeding protocol, despite an overall temporal decrease in NEC, suggests that other unmeasured interventions may account for the observed decreased incidence of NEC.

FIGURE 2 Association of withholding feeds peritransfusion and incidence of transfusion-associated necrotizing enterocolitis in preterm infants. M-H, Mantel-Haenszel.

Outcome	Absolute risk, *n* (%) Estimate without withholding feeds	Corresponding estimate with withholding feeds	Relative effect, RR (95% CI)	Participants, *n*	GRADE quality of evidence
TANEC	107 of 4534 (2.35)	22 of 2958 (0.74)	0.47 (0.28, 0.80), $P = 0.005$	7492	Moderate

Jasani et al. *Adv Nutr 2017*

Risk of NEC following transfusion

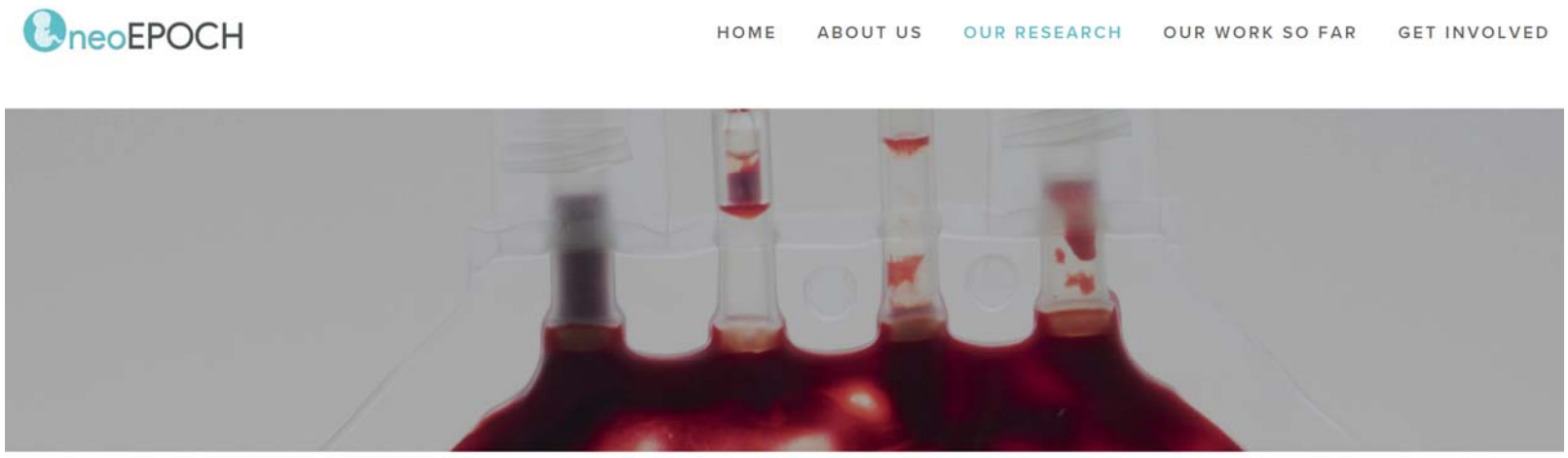


The overall risk of developing NEC within 48 hours after RBC transfusion was 0.49% (7 events following 1,430 RBC transfusions).

Patel RM et al. *JAMA.* 2016

Feeding during RBC transfusion

http://neoepoch.com/wheat-trial



Planned enrollment of 4,500 preterm infants

WHEAT TRIAL

WHEAT stands for Witholding Enteral feeds Around packed red cell Transfusion to prevent necrotising enterocolitis in preterm neonates. It is a multi-centre, randomised *point of care trial.* This means that WHEAT uses information that is already being collected by doctors and nurses as part of day to day care, which makes it much simpler and easier to take part in.

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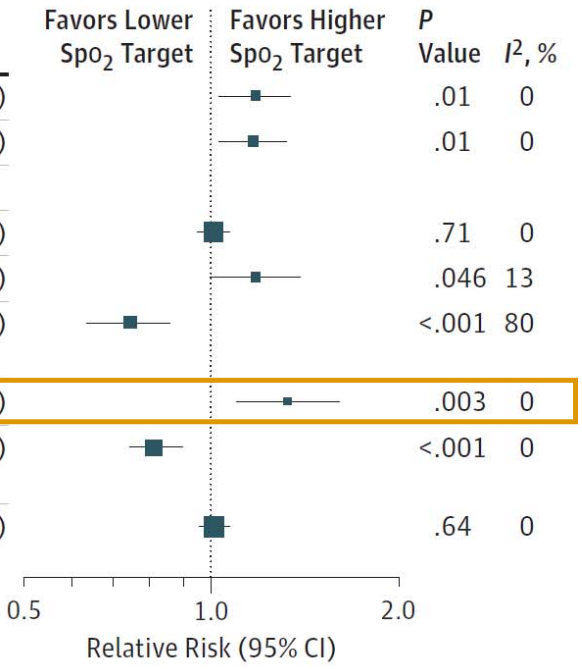
Oxygen targeting and risk of NEC

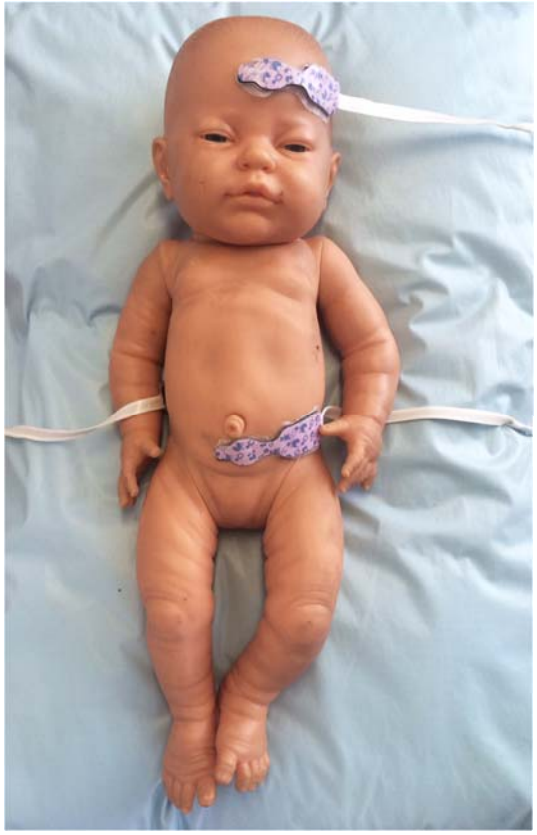
Figure 3. Effect of Oxygen Saturation as Measured by Pulse Oximetry (Spo_2) Target Levels on Secondary Outcomes

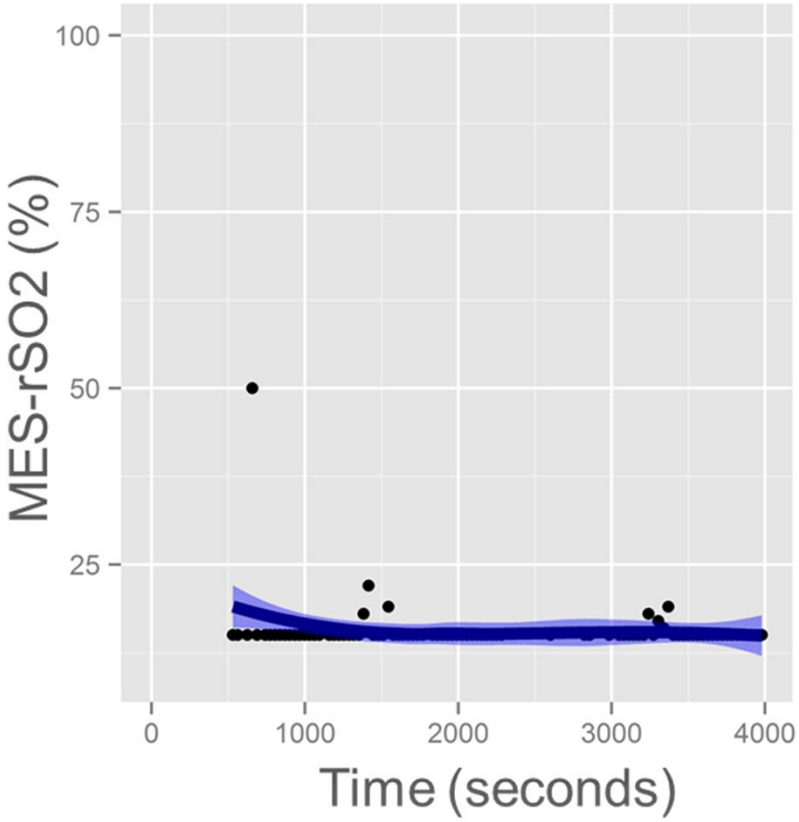
Dichotomous Outcomes	No. of Infants With Event/Total No. (%)[a] Lower Spo_2 Target	Higher Spo_2 Target	Risk Difference (95% CI), %	Relative Risk (95% CI)	*P* Value	I^2, %
Death before postmenstrual age of 36 wk	415/2478 (17)	354/2481 (14)	2.5 (0.5 to 4.5)	1.18 (1.03 to 1.34)	.01	0
Death before discharge from hospital	460/2478 (19)	397/2481 (16)	2.6 (0.5 to 4.7)	1.17 (1.03 to 1.32)	.01	0
Patent ductus arteriosus[b]						
Treated medically or surgically	1139/2456 (46)	1127/2463 (46)	0.5 (-2.3 to 3.3)	1.01 (0.95 to 1.07)	.71	0
Treated surgically	281/2462 (11)	240/2464 (10)	1.7 (0 to 3.4)	1.18 (1.00 to 1.39)	.046	13
Treated retinopathy of prematurity before corrected age of 18-24 mo	220/2020 (11)	308/2065 (15)	-4.0 (-6.1 to -2.0)	0.74 (0.63 to 0.86)	<.001	80
Severe necrotizing enterocolitis[c]	227/2464 (9)	170/2465 (7)	2.3 (0.8 to 3.8)	1.33 (1.10 to 1.61)	.003	0
Supplemental oxygen at postmenstrual age of 36 wk	459/1846 (25)	578/1910 (30)	-5.6 (-8.5 to -2.7)	0.81 (0.74 to 0.90)	<.001	0
≥1 Readmission to hospital	942/1754 (54)	967/1819 (53)	0.6 (-2.6 to 3.9)	1.01 (0.96 to 1.07)	.64	0



Askie et al. NeOProM collaboration. *JAMA.* 2018

Use of near infrared spectroscopy (NIRS)





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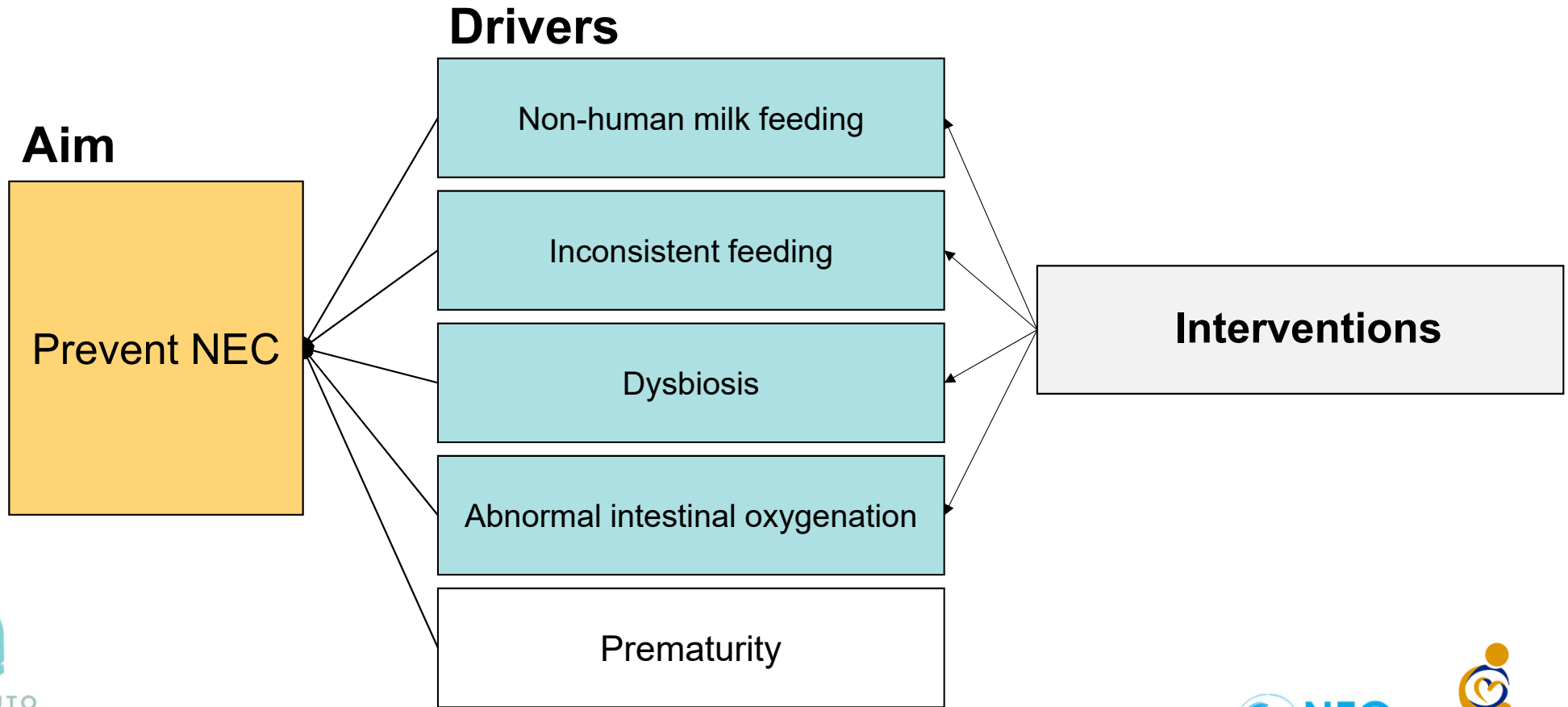
Drivers of NEC



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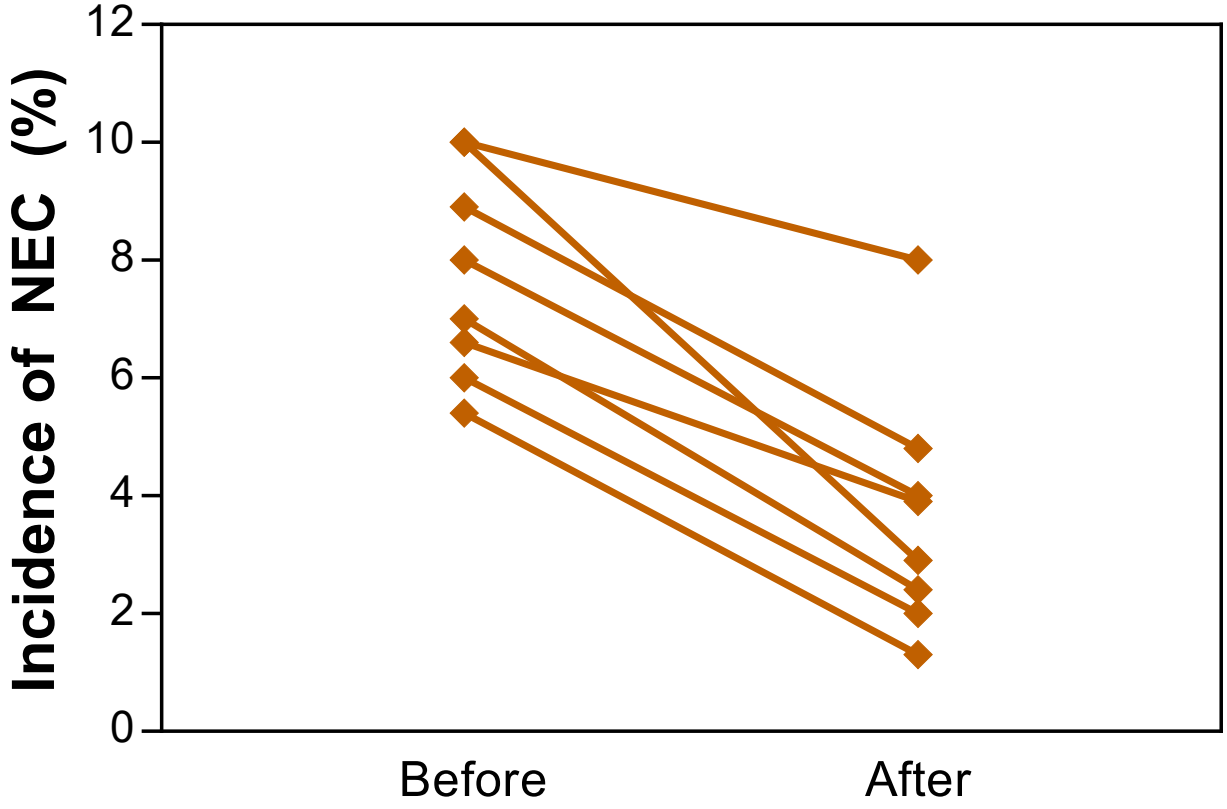
Effect of quality improvement on NEC



Published quality improvement initiatives involving 378 centers (n=60,485)

Patel et al. *Clin Perinatol.* 2017

Conclusions

- Experience from others centers supports the potential of efforts to prevent NEC
- Breastfeeding is the most important intervention to prevent NEC
- Suggest a long-term timeframe, given NEC is multifactorial and multiple drivers (potential causes) may need to be addressed
- Additional research is necessary to better understand causes of NEC and higher quality evidence to guide prevention efforts

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Obrigado !!

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