NEC FREE NICU

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Quality Improvement Initiative to Reduce the Necrotizing Enterocolitis Rate in Premature Infants

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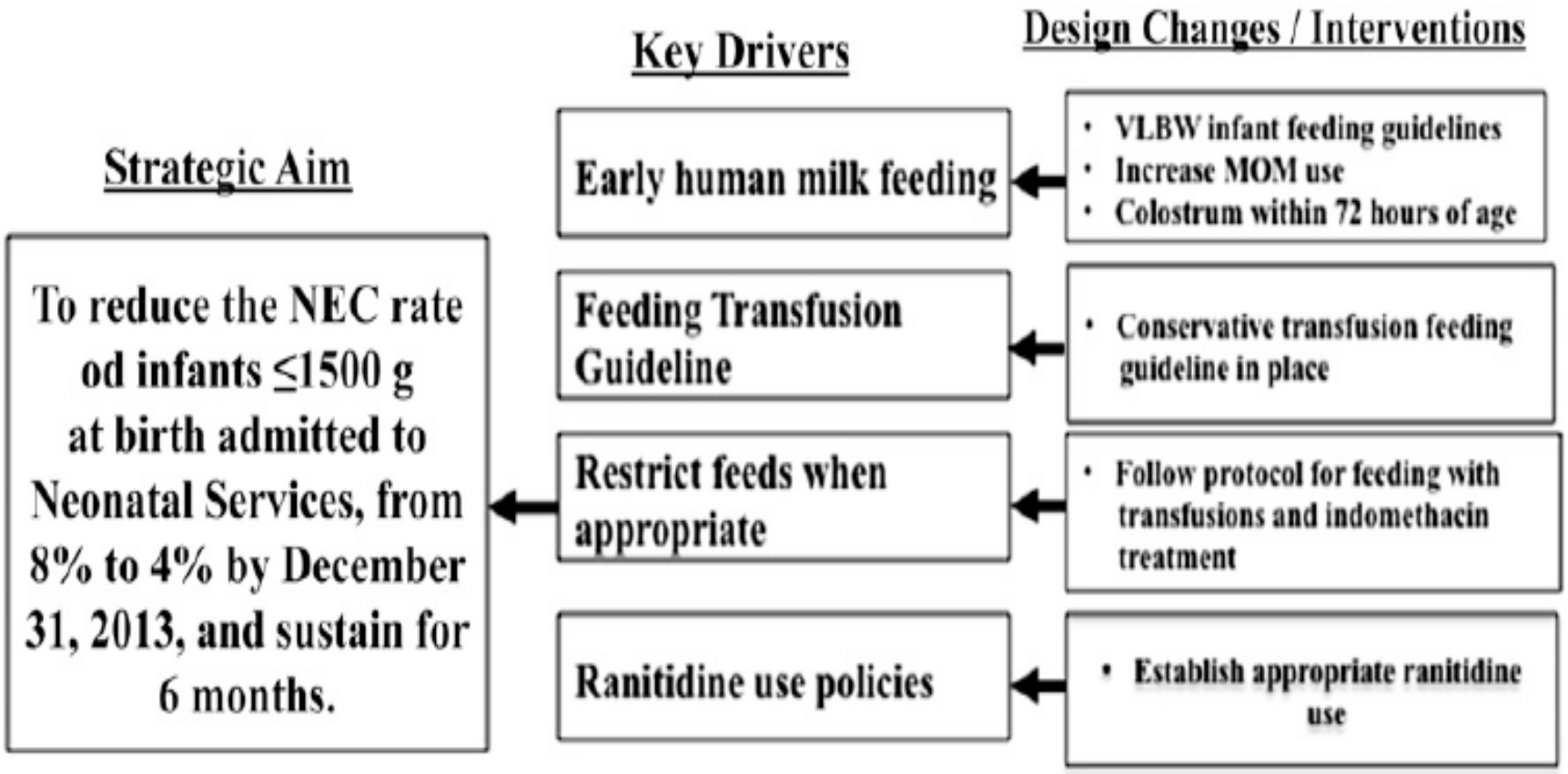


FIGURE 1

Key driver diagram summarizing specific interventions driving key baseline changes aimed at achieving the specific aim of NEC rate reduction by 50%. Key driver diagram based on Institute for Healthcare Improvement model of improvement.

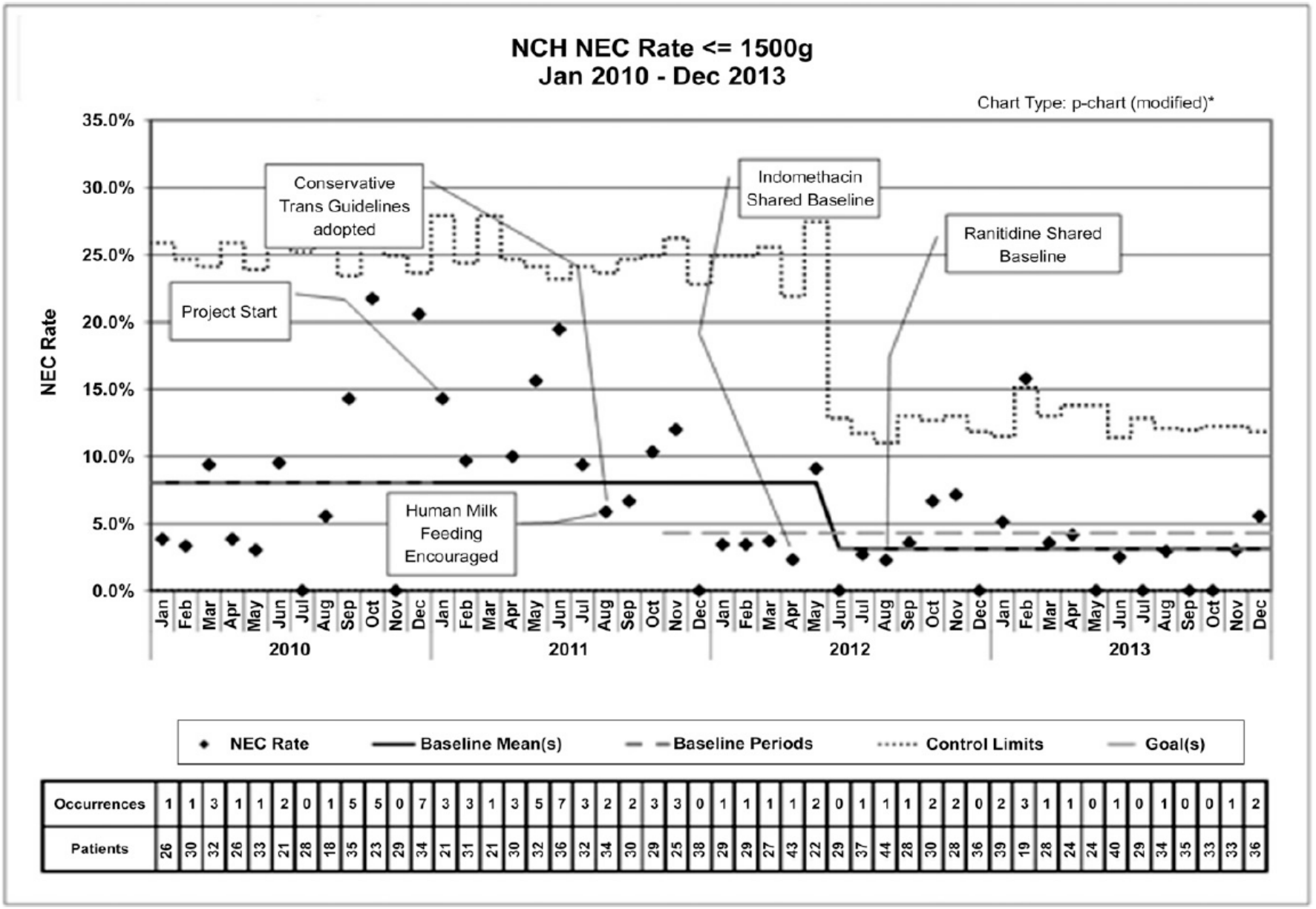


FIGURE 2

Overall NEC rate in VLBW infants from January 2010 to December 2013. Annotated p-chart showing change by month in proportion of patients ≤1500 g birth weight who developed NEC during admission to a Neonatal Services nursery. Callout indicates timing of improvement interventions. Control limits deviated from the standard because data dispersion (i.e., variation) is too large or too small to meet usual p-chart statistical assumptions.

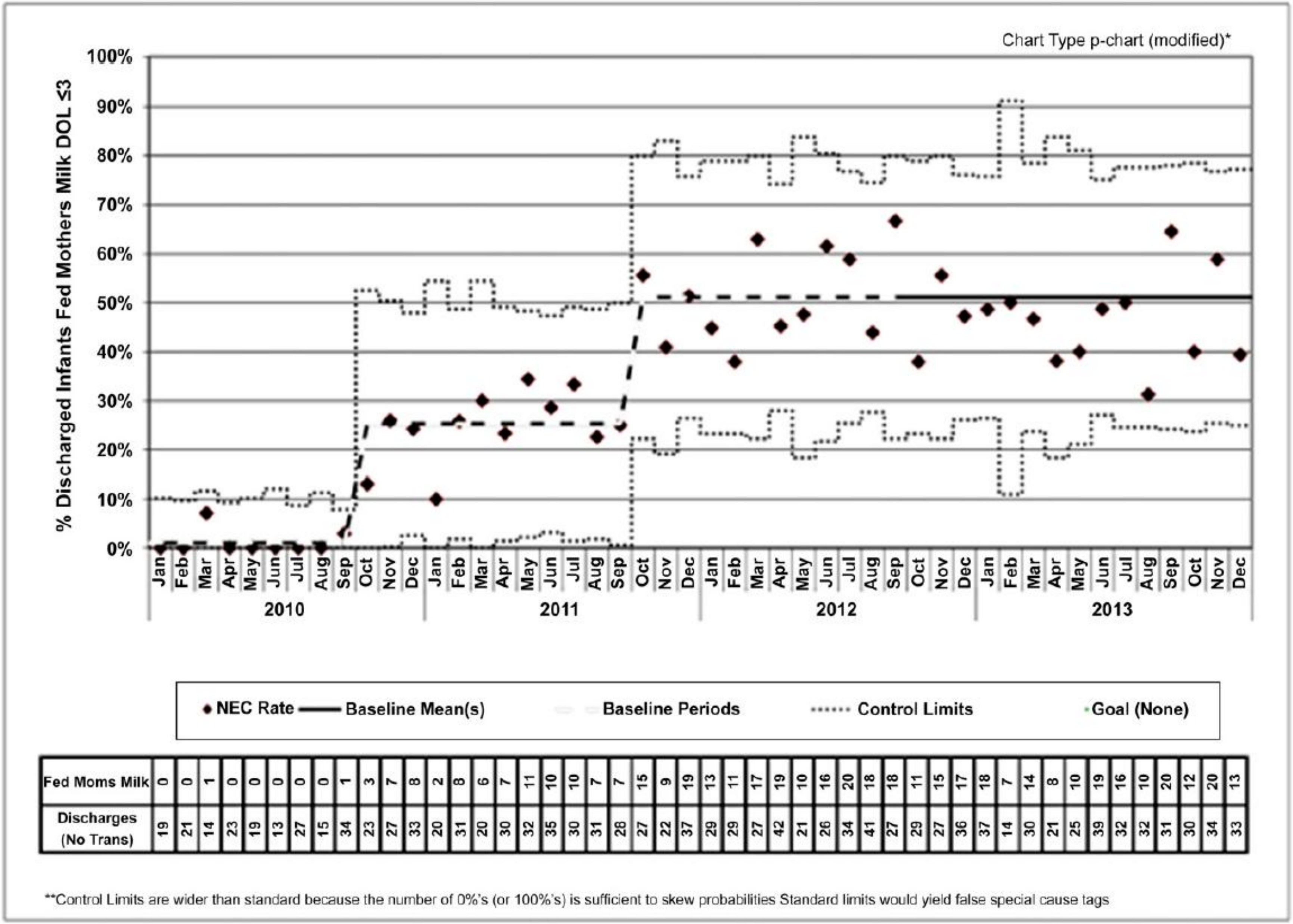
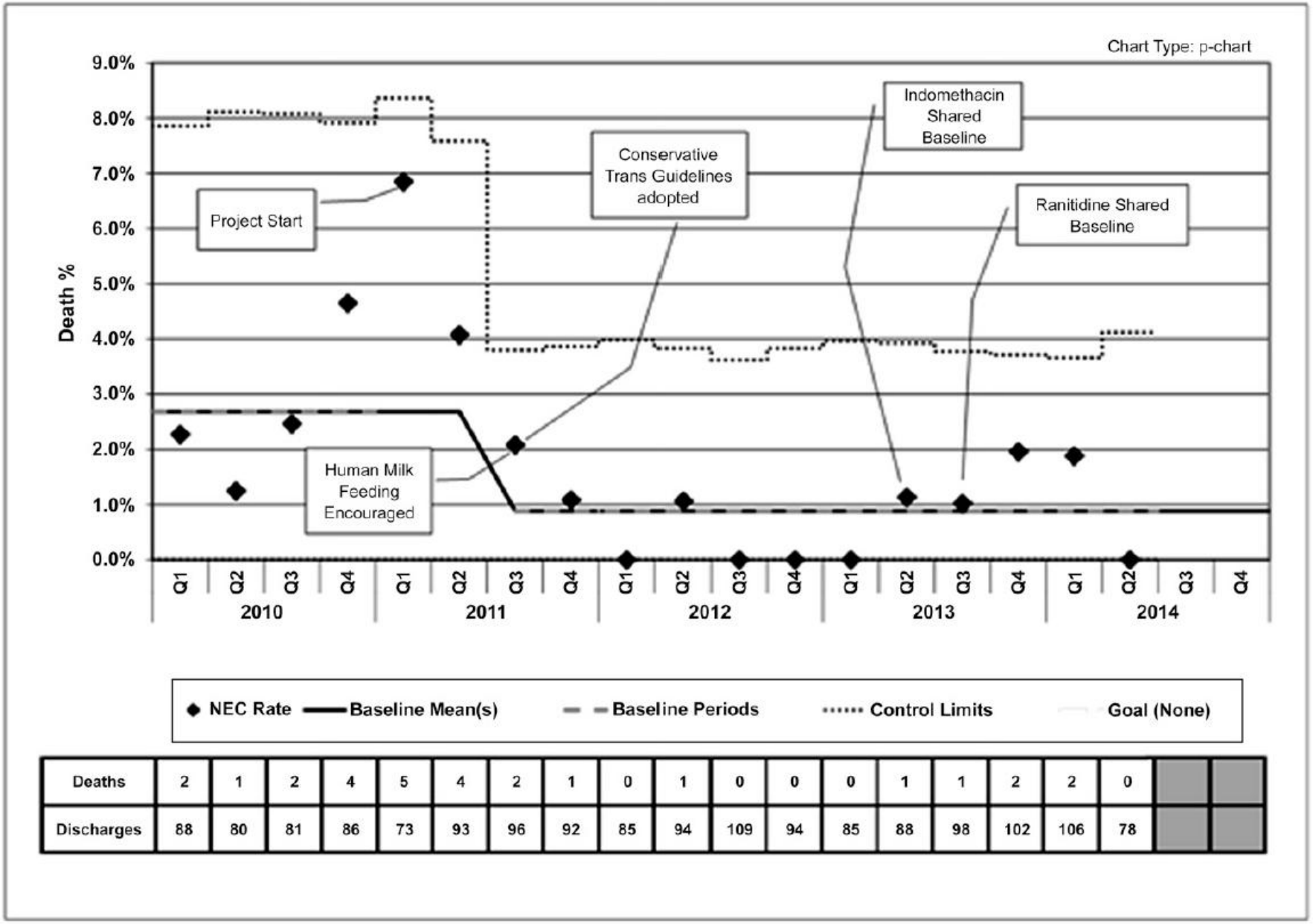


FIGURE 3

Annotated p-chart for percent of VLBW infants (≤1500 g) at birth who were fed MOM by day of life 3 and discharged. Control limits are wider than standard because the number of 0% (or 100%) is sufficient to skew probabilities. Standard limits would yield false special cause flags.



Deaths	2	1	2	4	5	4	2	1	0	1	0	0	0	1	1	2	2	0		
Discharges	88	80	81	86	73	93	96	92	85	94	109	94	85	88	98	102	106	78		

FIGURE 4

NEC mortality among Neonatal Services nurseries for VLBW (≤1500 g) infants. Annotated p-chart of death of patients ≤1500 g at birth who developed NEC while hospitalized in a Neonatal Services nursery. Denominator represents total admissions of patients weighing ≤1500 g at birth.

ORIGINAL ARTICLE

Impact of standardised feeding regimens on incidence of neonatal necrotising enterocolitis: a systematic review and meta-analysis of observational studies

S K Patole, N de Klerk

Arch Dis Child Fetal Neonatal Ed 2005;**90**:F147–F151. doi: 10.1136/adc.2004.059741

Variable	Studies Patole *et al*	Kamitsuka *et al*	O'Reilly *et al*	Premji *et al*	Brown *et al*	Spritzer *et al*
Timing to start feeds	No respiratory assistance or MAP<10 cm, no PDA or sepsis, no need for cardiovascular support	Day 4, 3, 2 (or longer if needed) for neonates weighing 1250–1500 g (A), 1502–2000 g (B) and 2001–2500 g (C) respectively	1–8 days	Started at day 5–6 of life	Feeds delayed for 5–7 days or longer in complicated deliveries with fetal distress	As soon as possible in well neonates. Delayed by 1 week in presence of ventilation, IUGR or complicated labour/delivery
Feeding method	Intermittent bolus gavage feeds by nasogastric tube	Intermittent bolus gavage feeds by nasogastric tube	Intermittent bolus gavage feeds, by gastric tube	Intermittent bolus gavage feeds by nasogastric tube	Intermittent 3 hourly bolus feeds by nasogastric tube	Not clear
Feeding type	Expressed breast milk (preferred) or 20 kcal/oz formula (later increased to 24 kcal/oz)	Expressed breast milk (preferred) or half strength formula (later increased to full strength)	Expressed breast milk (preferred) or 20 kcal/oz iron fortified formula	Expressed breast milk (preferred) or 24 kcal/oz formula	Sterile water followed by formula (0.45 cal/ml graded up to 0.80 cal/ml)	Dilute formula, graded gradually to full strength
Feed volume at start	0.5 ml/hour (<28 weeks) or 1 ml/hour (≥28 weeks)	Group A and B: 3 ml 3 hourly. Group C: 4 ml 3 hourly	Started as minimal enteral feeds (<10–20 ml/kg/day) for 3–4 days and then upgraded by 10–20 ml/kg/day	Maximum ≥24 ml/kg/day. For <750 g: 1 ml/2 h For ≥750–<1000 g: 2 ml/2 h. For ≥1000–<1500 g: 1 ml every 2 h	For <1250 g: 2 ml/2 h. For 1250–1500 g: 3 ml/2 h. For >1500 g: 4 ml/2 h	20 ml/kg
Increment volume	Start with 0.5 ml/12 h for <28 weeks, and 1 ml/12 h for ≥28 weeks. Increase by 1 ml 8 hourly after reaching 100 ml/kg/day (maximum: 24 ml/kg/day)	Not more than 20 ml/kg/day	10–20 ml/kg/day	Maximum: ⩽30 ml/kg/day. For <750 g: 1 ml every24 h. For ≥750–<1000 g: 1 ml every24 h. For ≥1000–<1500 g: 1 ml every 12 h	Detailed plan provided for reaching 20 ml/8 h (<1250 g), 25 ml/8 h (1250–1500 g), 29 ml/8 h (>1500 g)	20 ml/kg/day
Total maximum volume	170 ml/kg/day	150 ml/kg/day	150 ml/kg/day or 120 kcal/kg/day	Not clear	See above	Not specified
Minimal enteral feeds (volume and duration)	Not used	Not used	<10–20 ml/kg/day, continued for 3–4 days (breast milk or preterm formula)	Used only for neonates<1 kg at <24 ml/kg/day, Start within 48 hours of birth, and continued for 5–6 days	Not used	Not used
Definition of "feed intolerance"	Specified	Not specified	Specified	Specified	Not specified Plan of action given for apnoea, bradycardia, abdominal distension, gastric retention of formula, occult blood in stools, and for "NEC" or "shock"	Not specified
Plan of action for sepsis	Stop feeds for 48 h or until haemodynamic stability	Not specified	Not specified	Not specified	Not specified (see above)	Not specified
Plan of action for PDA and indomethacin	Stop feeds until 24 h after completing indomethacin therapy	Not specified	Not specified	Stop feeds during indomethacin therapy	Not specified (see above)	Not specified
Plan of action for "large" gastric aspirates	Stop feeds if such aspirates are persistent	Not specified	Stop feeds	Guidelines provided for contacting clinician for decision making	Stop feeds "for a week or two or more till resolution of the problem"	Not specified
Plan of action for bile stained gastric aspirates	Stop feeds if such aspirates are persistent	Not specified	Stop feeds	Guidelines provided for contacting clinician for decision making	Not specified	Not specified
Policy for umbilical catheters	Catheters were retained as long as they were needed	Not specified	Not specified	Not specified	Not specified	Not specified

MAP, Mean arterial pressure; PDA, patent ductus arteriosus; IUGR, intrauterine growth retardation; NEC, necrotising enterocolitis.

STANDARDIZED FEEDING STRATEGIES

- Timing to start feed
- Feeding method
- Feeding type
- Feed volume to start
- Increment volume
- Total maximum volume
- MEN
- Definition of feed intolerance

Feeding strategies

- Plan of action for sepsis
- Plan of action for PDA and indomethacin
- Plan for action for large gastric aspirates
- Plan of action for bile stained aspirate
- Plan of action for umbilical catheters

Other strategies

Table 1 Characteristics of studies included in the analysis

Ref	Authors and year	Weight group	NEC incidence before SFR	NEC incidence after SFR
7	Brown *et al* 1978	LBW	14/1745	1/932
8	Spritzer *et al* 1988	<2 kg	51/529	0/604–3/937
9	Kamitsuka *et al* 2000	LBW	23/477	5/467
		VLBW	3/68	3/77
10,11	Patole *et al* 2000	VLBW	30/250	1/298
15	Premji *et al* 2002	VLBW	2/100	0/100
16	Kuzma-O'Reilly *et al* 2003*	VLBW	62/828	94/2041

NEC, Necrotising enterocolitis; SFR, standardised feeding regimen; LBW, low birth weight; VLBW, very low birth weight.
*Data from three participating centres .

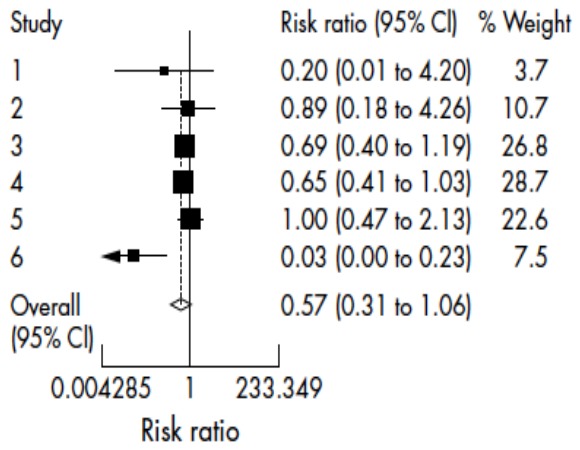


Figure 2 Subgroup analysis for very low birthweight neonates from four studies: 1, Premji *et al*[15]; 2, Kamitsuka *et al*[9]; 3, Kuzma-O'Reilly *et al*[16]; 6, Patole *et al*.[10 11] The data from the three participating centres in Kuzma-O'Reilly *et al* are presented separately (studies 3–5). CI, Confidence interval

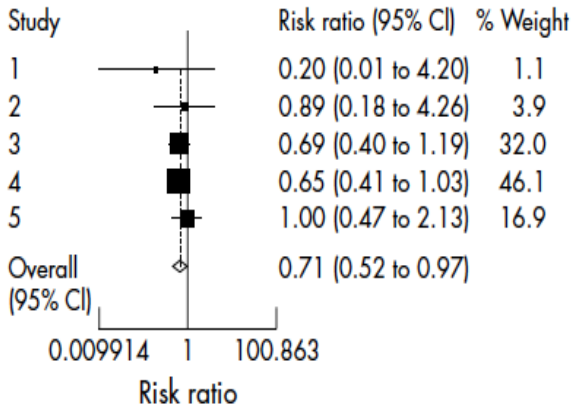


Figure 3 Subgroup analysis for very low birthweight neonates excluding the data from Patole *et al*. Studies: 1, Premji *et al*[15]; 2, Kamitsuka *et al*[9]; 3, Kuzma-O'Reilly *et al*.[16] The data from the three participating centres in Kuzma-O'Reilly *et al* are presented separately (studies 3–5). CI, Confidence interval.

Reduction in the incidence of NEC by 87% by introduction of a standardized feeding regimen

OTHER INTERVENTIONS

- Antenatal steroids
- Delayed cord clamping
- Improving gut colonization
- Blood transfusion strategies
- Probiotics
- Lactoferrin

ANTENATAL STEROIDS AND NEC

- 21 randomized trials (3885 women/4269 infants)
- No increased risk – maternal deaths, chorioamnionitis or puerperal sepsis
- **ACS associated with overall reduction in**
  - Neonatal death
  - RDS, IVH, **NEC**
  - Respiratory support, NICU admissions
  - Systemic infections in the first 48 h of life

Cochrane Review (2006)

DELAYED CORD CLAMPING AND NEC

- Rabe et al
- 15 studies (738 infants)
- 24 to 36 wks GA, delay of 30-180 secs
- Delayed cord clamping:
  - **Lower risk for NEC (RR 0.62, 95% CI 0.43 to 0.90)**

Cochrane Review (Preterm infants)

IMPROVE GUT COLONIZATION

- Intervention that can improve adequate colonization of neonatal gut
  - Vaginal delivery
  - EBM
  - Do not keep NPO for long
  - Restrict antibiotic to mother and baby (NICHD; NEC 61% vs 51% in prolonged Ab group)
  - No H2 blockers in NICU (NICHD ; More NEC in H2 blocker group ; OR 1.71; CI 1.34-2.19)

Guillet. Association of H2 blocker therapy and higher NEC in VLBW. Pedairics 2006;114e137
Cotton . Prolonged duration of empiric antibiotic treatment is associated with increased rate of NEC and death in ELBW. Pediatrics 2009; 123:58

FEEDING BLOOD TRANSFUSION AND NEC

- A retrospective chart review over a 3-year period

- **No decrease in NEC if withheld feeds during blood transfusions**. (NEC – Not fed (7.8%) vs fed (13.8%); p = 0.33)

- HOLDING FEEDS - need for **IV access, additional fluids & disruption of optimum nutrition.**

Doty M[1], Wade C[2], Farr J[2], Gomezcoello VC[3], Martin G[4], Nasr T[5] Feeding during Blood Transfusions and the Association with Necrotizing Enterocolitis. Am J Perinatol. 2016 Jul;33(9):882-6. doi: 10.1055/s-0036-1579651. Epub 2016 Mar 31.

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FEEDING BLOOD TRANSFUSION AND NEC

RESEARCH PAPER

Relationship between Packed Red Blood Cell Transfusion and Severe Form of Necrotizing Enterocolitis: A Case Control Study

*PARVESH M GARG, *SRIKANTH RAVISANKAR, HUI BIAN, *SCOTT MACGILVRAY AND #PREM S SHEKHAWAT

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Received: March 13, 2015; Initial review: May 01, 2015; Accepted: October 08, 2015.

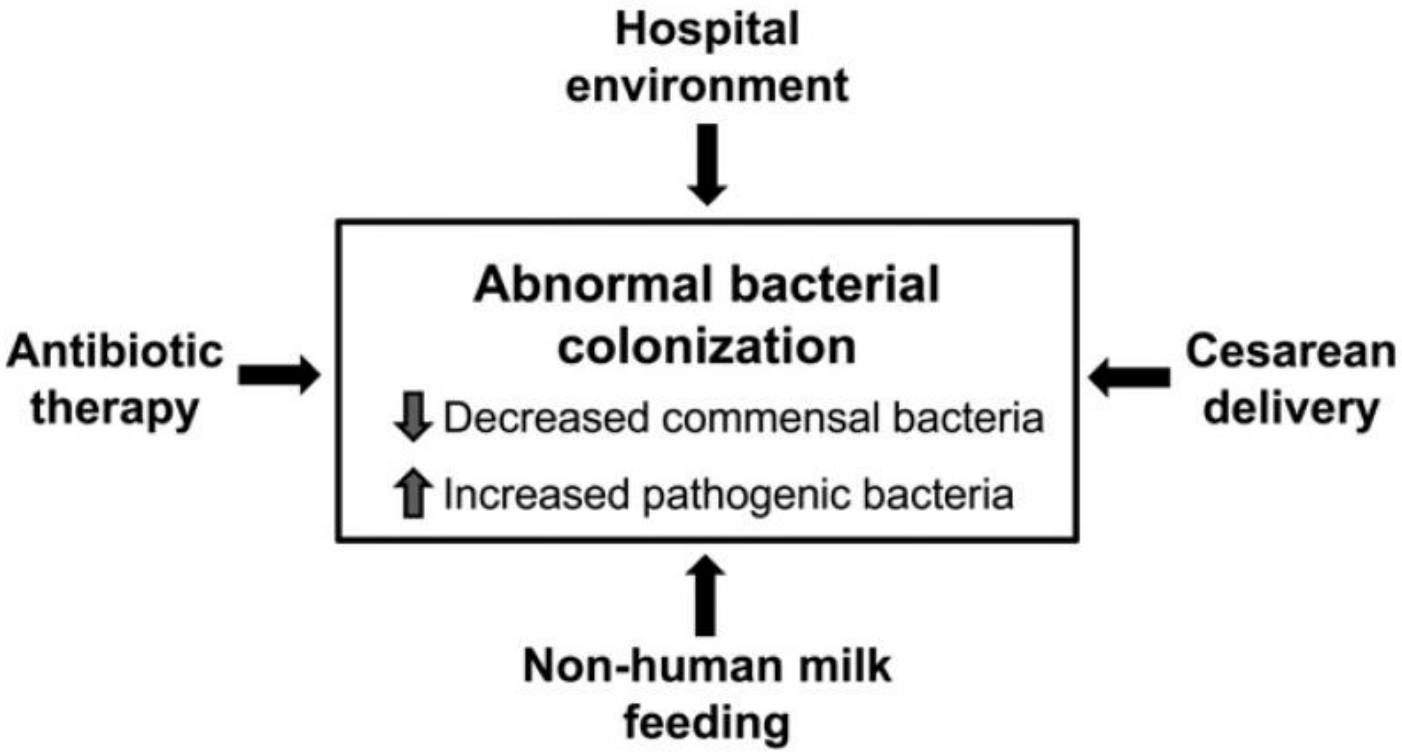
FEEDING BLOOD TRANSFUSION AND NEC

What is Already Known?

- Onset of Necrotizing enterocolitis is preceded by blood transfusion in some cases and it leads to a severe form of disease with high morbidity and mortality.

What This Study Adds?

- Blood transfusion-associated Necrotizing enterocolitis seems to be a severe form of disease and withholding feedings around the time of transfusion does not seem to prevent this entity.



FACTORS INFLUENCING ABNORMAL INTESTINAL BACTERIAL COLONIZATION IN PRETERM INFANTS

PROBIOTICS AND NEC

EVIDENCE-BASED CHILD HEALTH: A COCHRANE REVIEW JOURNAL
Evid.-Based Child Health **9**: 672–674 (2014)
Published online in Wiley Online Library (http://www.evidence-basedchildhealth.com). **DOI:** 10.1002/ebch.1977

Commentary

Cochrane in context: Probiotics for prevention of necrotizing enterocolitis in preterm infants

Cochrane Review: Probiotics for prevention of necrotizing enterocolitis in preterm infants AlFaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database of Systematic Reviews* 2014, Issue 4. Art. No.: CD005496. DOI: 10.1002/14651858.CD005496.pub4.

RESULT

- 24 eligible trials were included.
- Probiotics reduced severe NEC (>stage II) (RR 0.43 [0.33-0.56]
- No systemic infection

PROBIOTICS AND NEC

Aceti *et al. Italian Journal of Pediatrics* (2015) 41:89
DOI 10.1186/s13052-015-0199-2

ITALIAN JOURNAL OF PEDIATRICS

REVIEW Open Access

Probiotics for prevention of necrotizing enterocolitis in preterm infants: systematic review and meta-analysis

Arianna Aceti[1*], Davide Gori[2], Giovanni Barone[3], Maria Luisa Callegari[4], Antonio Di Mauro[5], Maria Pia Fantini[2], Flavia Indrio[5], Luca Maggio[3], Fabio Meneghin[6], Lorenzo Morelli[4], Gianvincenzo Zuccotti[6], Luigi Corvaglia[1] and on behalf of the Italian Society of Neonatology

RESULT IN OVERALL POPULATION

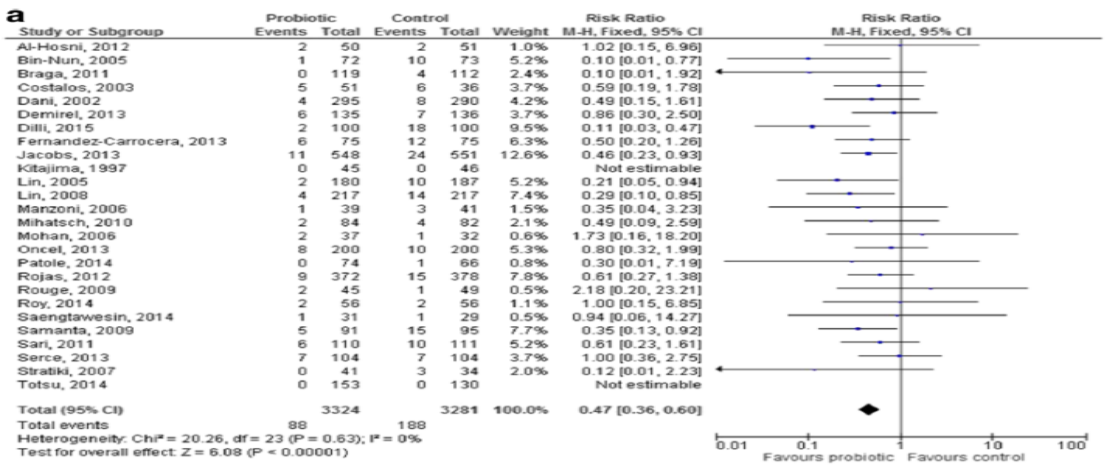


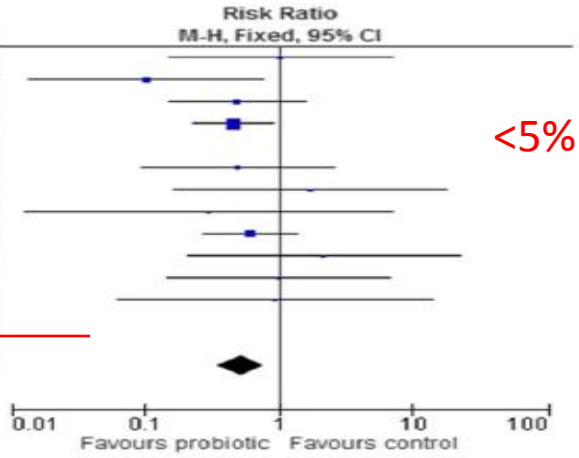
Fig. 2 Forest plot (2**a**) and funnel plot (2**b**) of the included studies. The forest plot shows the association between the use of probiotics and necrotizing enterocolitis in the overall population of preterm infants. The funnel plot does not show any clear visual asymmetry. M-H: Mantel-Haenszel method

RESULLT ACCORDING TO INCIDENCE

a

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Al-Hosni, 2012	2	50	2	51	2.8%	1.02 [0.15, 6.96]
Braga, 2011	1	72	10	73	14.3%	0.10 [0.01, 0.77]
Dani, 2002	4	295	8	290	11.6%	0.49 [0.15, 1.61]
Jacobs, 2013	11	548	24	551	34.4%	0.46 [0.23, 0.93]
Kitajima, 1997	0	45	0	46		Not estimable
Mihatsch, 2010	2	84	4	82	5.8%	0.49 [0.09, 2.59]
Mohan, 2006	2	37	1	32	1.5%	1.73 [0.16, 18.20]
Patole, 2014	0	74	1	66	2.3%	0.30 [0.01, 7.19]
Rojas, 2012	9	372	15	378	21.4%	0.61 [0.27, 1.38]
Rouge, 2009	2	45	1	49	1.4%	2.18 [0.20, 23.21]
Roy, 2014	2	56	2	56	2.9%	1.00 [0.15, 6.85]
Saengtawesin, 2014	1	31	1	29	1.5%	0.94 [0.06, 14.27]
Totsu, 2014	0	153	0	130		Not estimable
Total (95% CI)		1862		1833	100.0%	0.52 [0.35, 0.78]
Total events	36		69			

Heterogeneity: Chi² = 6.36, df = 10 (P = 0.78); I² = 0%
Test for overall effect: Z = 3.20 (P = 0.001)

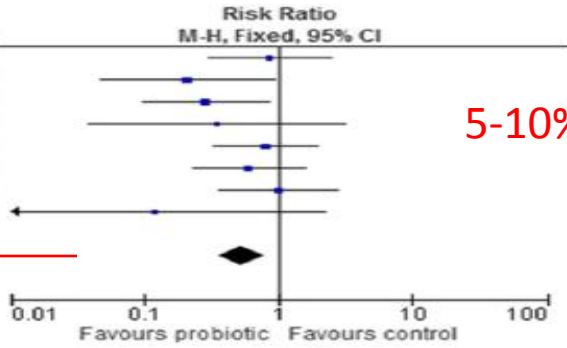


<5%

b

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Demirel, 2013	6	135	7	136	10.8%	0.86 [0.30, 2.50]
Lin, 2005	2	180	10	187	15.2%	0.21 [0.05, 0.94]
Lin, 2008	4	217	14	217	21.7%	0.29 [0.10, 0.85]
Manzoni, 2006	1	39	3	41	4.5%	0.35 [0.04, 3.23]
Oncel, 2013	8	200	10	200	15.5%	0.80 [0.32, 1.99]
Sari, 2011	6	110	10	111	15.4%	0.61 [0.23, 1.61]
Serce, 2013	7	104	7	104	10.9%	1.00 [0.36, 2.75]
Stratiki, 2007	0	41	3	34	5.9%	0.12 [0.01, 2.23]
Total (95% CI)		1026		1030	100.0%	0.54 [0.36, 0.80]
Total events	34		64			

Heterogeneity: Chi² = 6.98, df = 7 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.03 (P = 0.002)

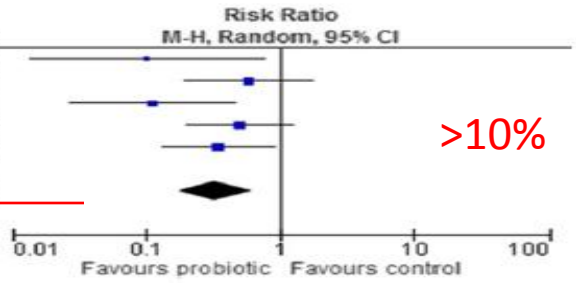


5-10%

c

Study or Subgroup	Probiotic Events	Probiotic Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bin-Nun, 2005	1	72	10	73	8.5%	0.10 [0.01, 0.77]
Costalos, 2003	5	51	6	36	22.2%	0.59 [0.19, 1.78]
Dilli, 2015	2	100	18	100	15.2%	0.11 [0.03, 0.47]
Fernandez-Carrocera, 2013	6	75	12	75	27.8%	0.50 [0.20, 1.26]
Samanta, 2009	5	91	15	95	26.3%	0.35 [0.13, 0.92]
Total (95% CI)		389		379	100.0%	0.33 [0.17, 0.62]
Total events	19		61			

Heterogeneity: Tau² = 0.15; Chi² = 5.68, df = 4 (P = 0.22); I² = 30%
Test for overall effect: Z = 3.45 (P = 0.0006)



>10%

SINGLE STRAIN PRODUCT AND NEC

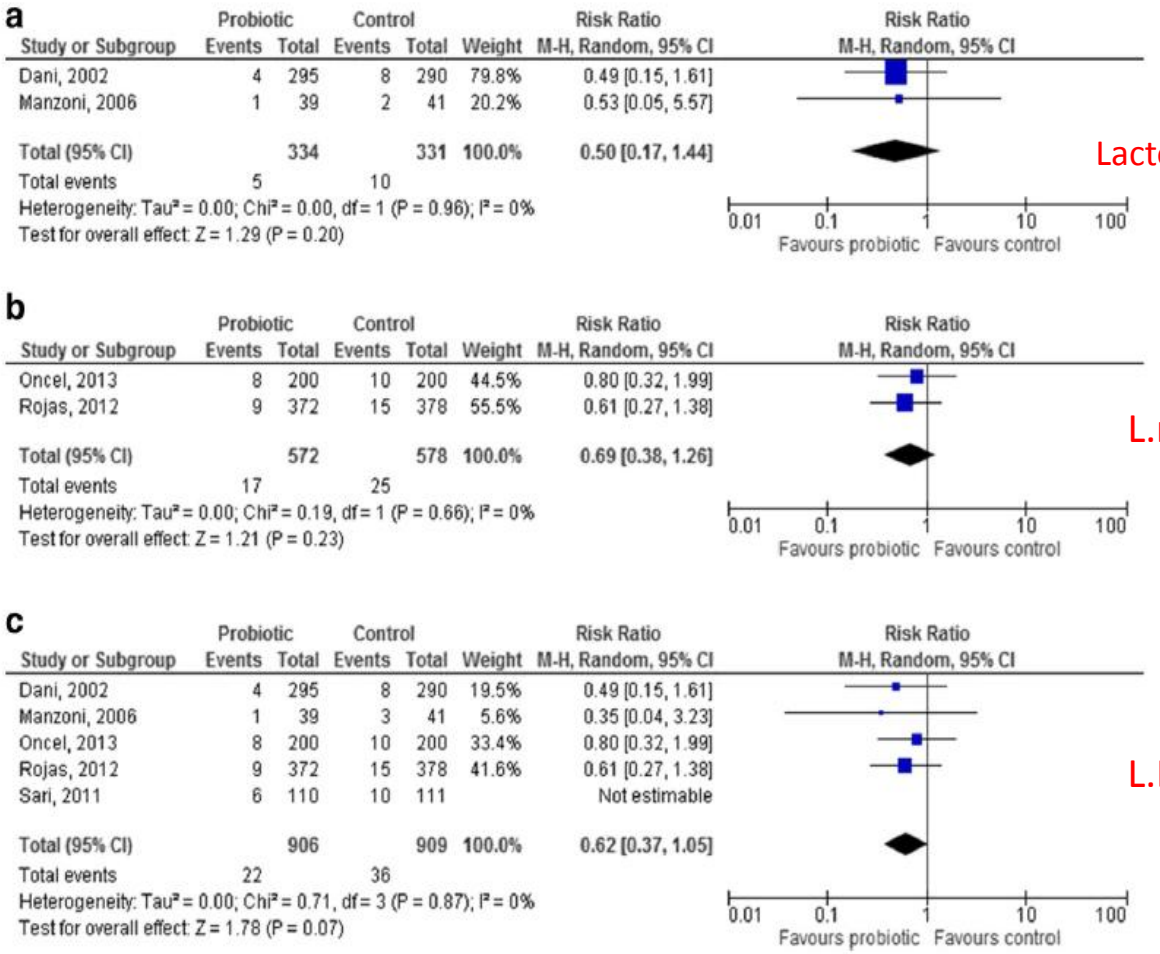


Fig. 4 Forest plot showing the association between probiotics and necrotizing enterocolitis in the studies which used a single-strain product containing *Lactobacilli* ((4**a**). *L. reuteri*; (4**b**). *L. GG*; (4**c**). pooled analysis of all the studies using *Lactobacilli*). M-H: Mantel-Haenszel method

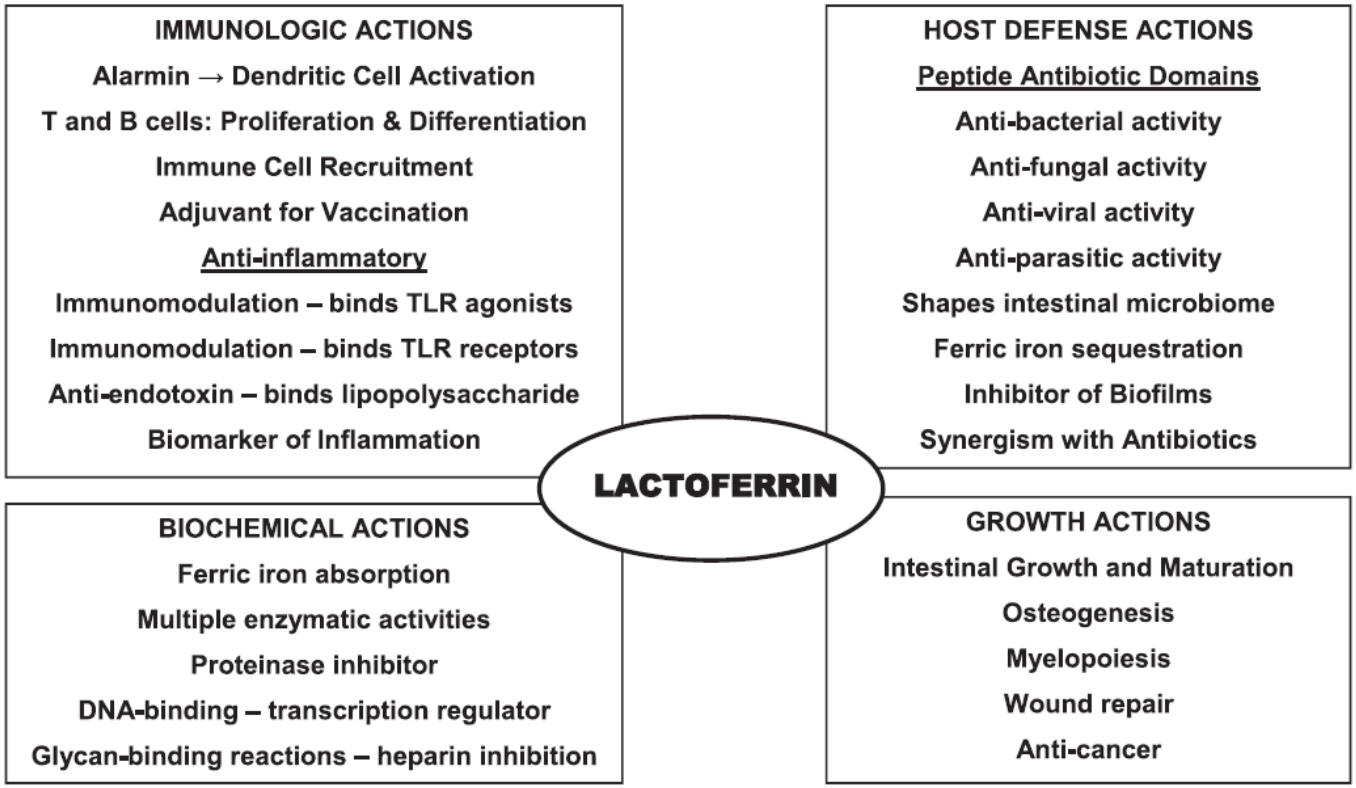
PROBIOTICS AND NEC : SUMMARY

- Current evidence suggests that probiotics are effective in decreasing NEC in preterm infants.
- Concerns regarding safety and optimal dosing have limited the routine clinical use of probiotics in preterm infants.
- Prebiotics and postbiotics are potential alternatives or adjunctive therapies to the administration of live microorganisms, although studies demonstrating their clinical efficacy in preventing NEC are currently lacking.

Ravi Mangal Patel, Patricia Wei Denning Therapeutic Use of Prebiotics, Probiotics, and Postbiotics to Prevent NEC. What is the Current Evidence? Clinics of Perinatology 2012

LACTOFERRIN ,ARGININE AND GLUTAMINE AND NEC

LACTOFERRIN AND NEC

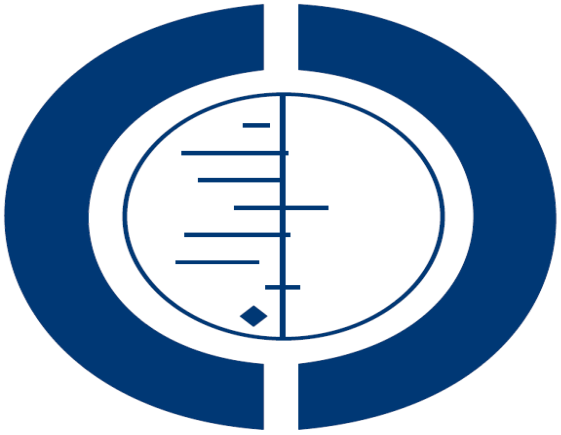


Vogel HJ. Lactoferrin, a bird's eye view. Biochem Cell Biol 2012;90(3):233–44.

LACTOFERRIN AND NEC

Oral lactoferrin for the prevention of sepsis and necrotizing enterocolitis in preterm infants (Review)

Pammi M, Abrams SA



THE COCHRANE COLLABORATION®

LACTOFERRIN AND NEC

Figure 2. Forest plot of comparison: 1 Lactoferrin alone versus placebo, outcome: 1.2 NEC ≥ stage II.

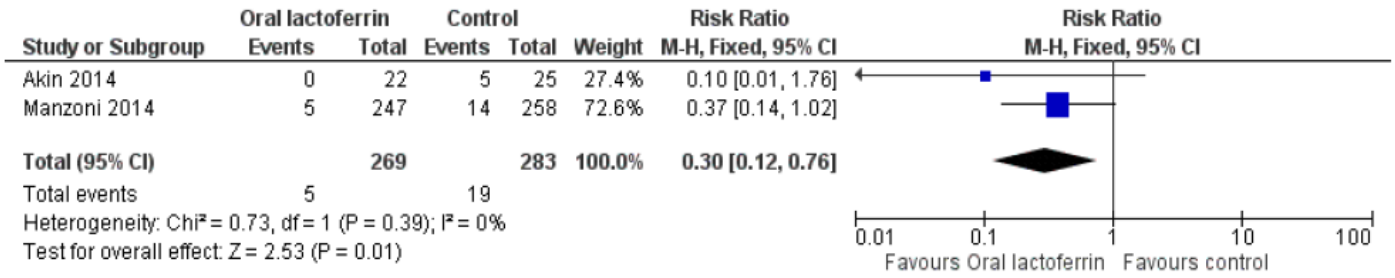
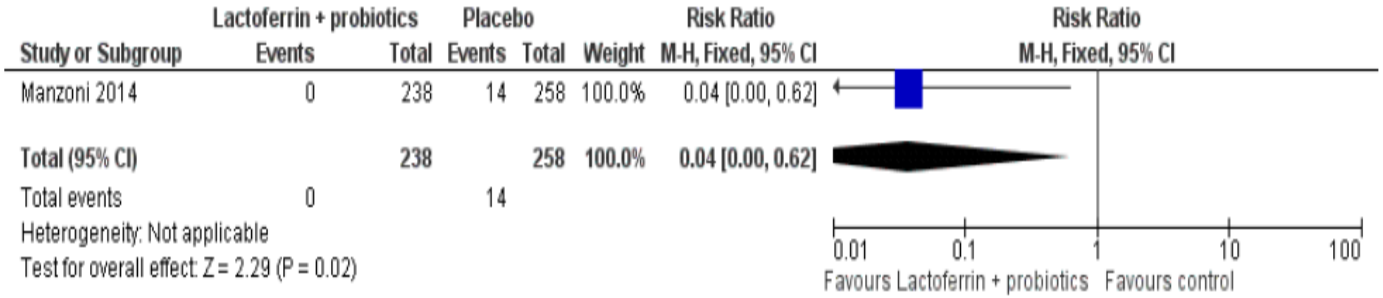


Figure 6. Forest plot of comparison: 2 Lactoferrin + LGG versus placebo, outcome: 2.5 NEC ≥ stage II.



ONGOING STUDIES WITH BOVINE LACTOFERRIN

- Optimal dose?
- Bovine/human recombinant?
- Food additive/medicine?

Study	Target sample size
Oral Lactoferrin Supplementation for Prevention of Sepsis in preterm neonates	180
ELFIN (UK)	2200
NEOLACTO	414
LIFT (Australia)	1100
Total	Around 4000

ARGININE , GLUTAMINE AND IMMUNOGLOBULIN

- Arginine
  - Meta-analysis (2studies)
  - NEC >II: Lower (RR 0.41 ; CI 0.20-0.85)
- Glutamine
  - RCT
  - NEC: Same
- Immunoglobulin
  - Cochrane metanalysis : NO role
- Human milk oligosaccharides : protective animal model

KEY POINTS

- Avoid prematurity ?????
- Antenatal steroids
- Delayed cord clamping
- Antibiotic stewardship
- Standardized feeding regimens

KEY POINTS

- No H2 blockers
- Probiotics
- Strict blood transfusion protocols
- Colostrum/Lactoferrin may be tried
- Arginine, glutamine and immunoglobulin no role

THANK YOU