Experiences of Centers Routinely Using Probiotics

Probiotics and the Prevention of NEC, Death, and Sepsis

NEC SOCIETY

Save the dates!

- **Monday, May 6 at 12pmET**

  Practical Considerations and Consent

  - UC Davis
  - Emory University
  - Patient-family perspective

- **June 2 – 5, 2019**

  NEC Symposium in Ann Arbor, MI

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JUNE 2-5
ANN ARBOR MI

NEC SYMPOSIUM 2019

NURSE PRACTITIONERS PED. SURGEONS
NEONATOLOGISTS INDUSTRY SCIENTISTS
NON-PROFITS NURSES PATIENT-FAMILIES

HIGHLIGHTS:

Prevention and early detection of NEC
Human milk and NEC
Patient-family centered care in NEC prevention
Animal models of NEC
Probiotics and NEC
NEC registry and biorepository
Treatment and neurodevelopmental outcomes

TO REGISTER
& FOR THE FULL AGENDA:
https://necsymposium.eventbrite.com

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C.S. MOTT CHILDREN'S HOSPITAL
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Disclaimer:

This an educational webinar series.

The NEC Society and invited speakers are not marketing any probiotic products, which are not currently FDA approved for the prevention of necrotizing enterocolitis or other neonatal diseases.

NEC SOCIETY

- Jennifer Canvasser with son, Micah
- Founder, Director of NEC Society
- Vision: create a world without NEC
- Jennifer@NECsociety.org

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Indian Ocean

Webinar Faculty

Jennifer Canvasser, MSW
Founder, Director
NEC Society

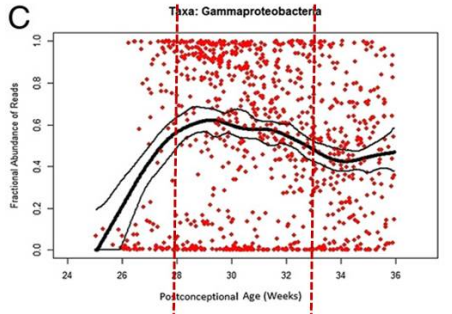
Mark Undewood, MD, MAS
Professor of Pediatrics
UC Davis, CA
Scientific Advisor, NEC Society

Ravi Patel, MD, MSc
Associate Professor of Pediatrics
Emory University, Atlanta, GA
Scientific Advisor, NEC Society

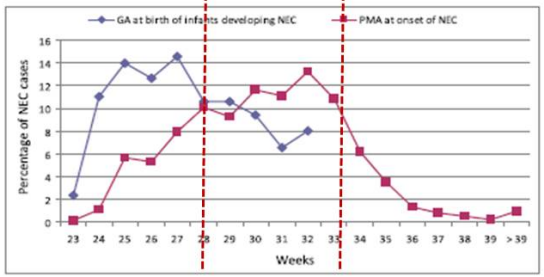
THLs from webinar #1

Intestinal dysbiosis is common and plays a central role in NEC pathogenesis

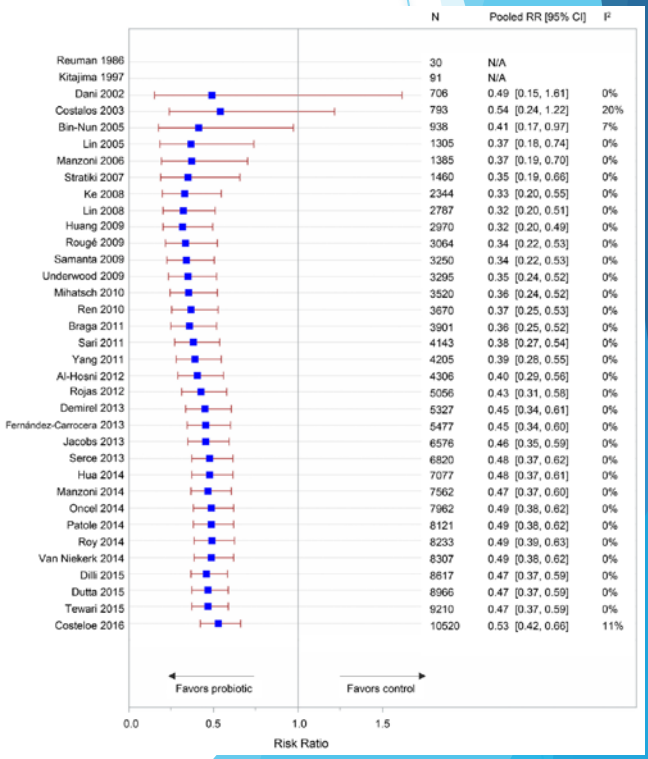
Gut Microbiota



922 samples from 58 preemies
La Rosa, PNAS 2014



16,669 infants < 33 weeks
Yee WH, Pediatrics 2012



Probiotics decrease the risk of NEC, death and sepsis in VLBW and ELBW infants

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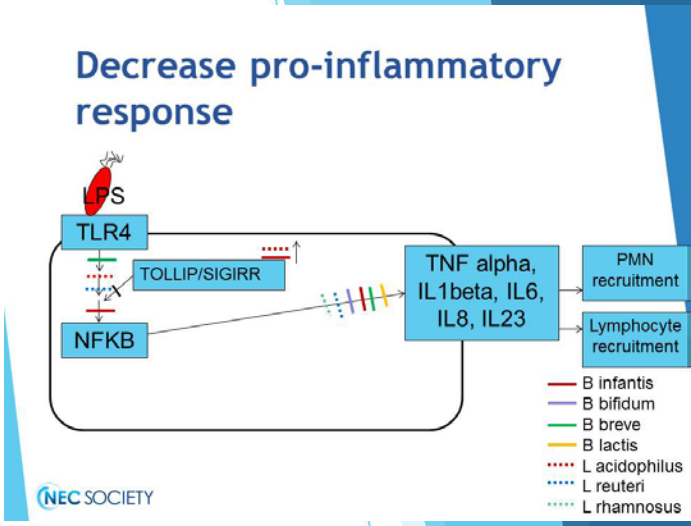
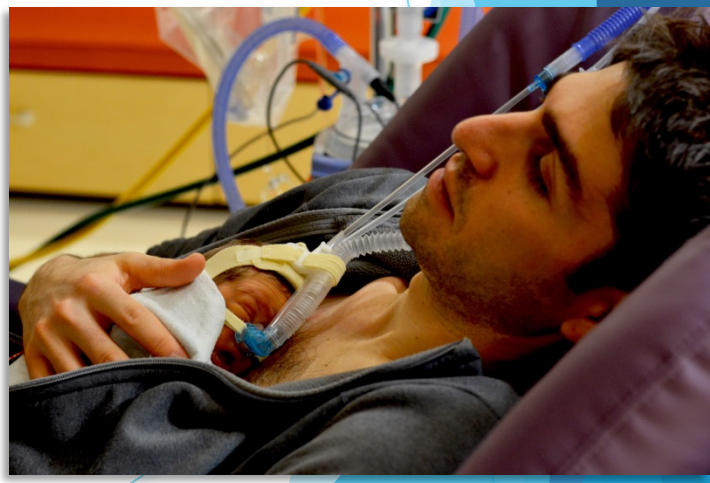
THLs from webinar #1

Mechanisms: alter microbiota, decrease inflammation, decrease intestinal permeability



No clear best product choice



Parents want to discuss NEC, human milk and probiotics (resources available at NECSociety.org)

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Overview of today's webinar

Welcome and introduction

- Jennifer Canvasser, MSW and Mark Underwood, MD, MAS

Experiences of centers:

- University of Utah
  - Maggie Sekhon, MD and Brad Yoder, MD
- Northern California Kaiser Permanente
  - Allen Fischer, MD
- Southern California Kaiser Permanente
  - David Braun, MD
- Emory University
  - Ravi Patel, MD, MSc

Q&A with speakers

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Today's Guest Faculty Speakers

Dr. Bradley Yoder
University of Utah

Dr. David Braun
Kaiser Permanente,
Southern California

Dr. Maggie Sekhon
University of Utah

Dr. Allen Fischer
Kaiser Permanente,
Northern California

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Reducing rates of NEC using a probiotic protocol: the University of Utah experience

Maggie K Sekhon & Bradley A Yoder

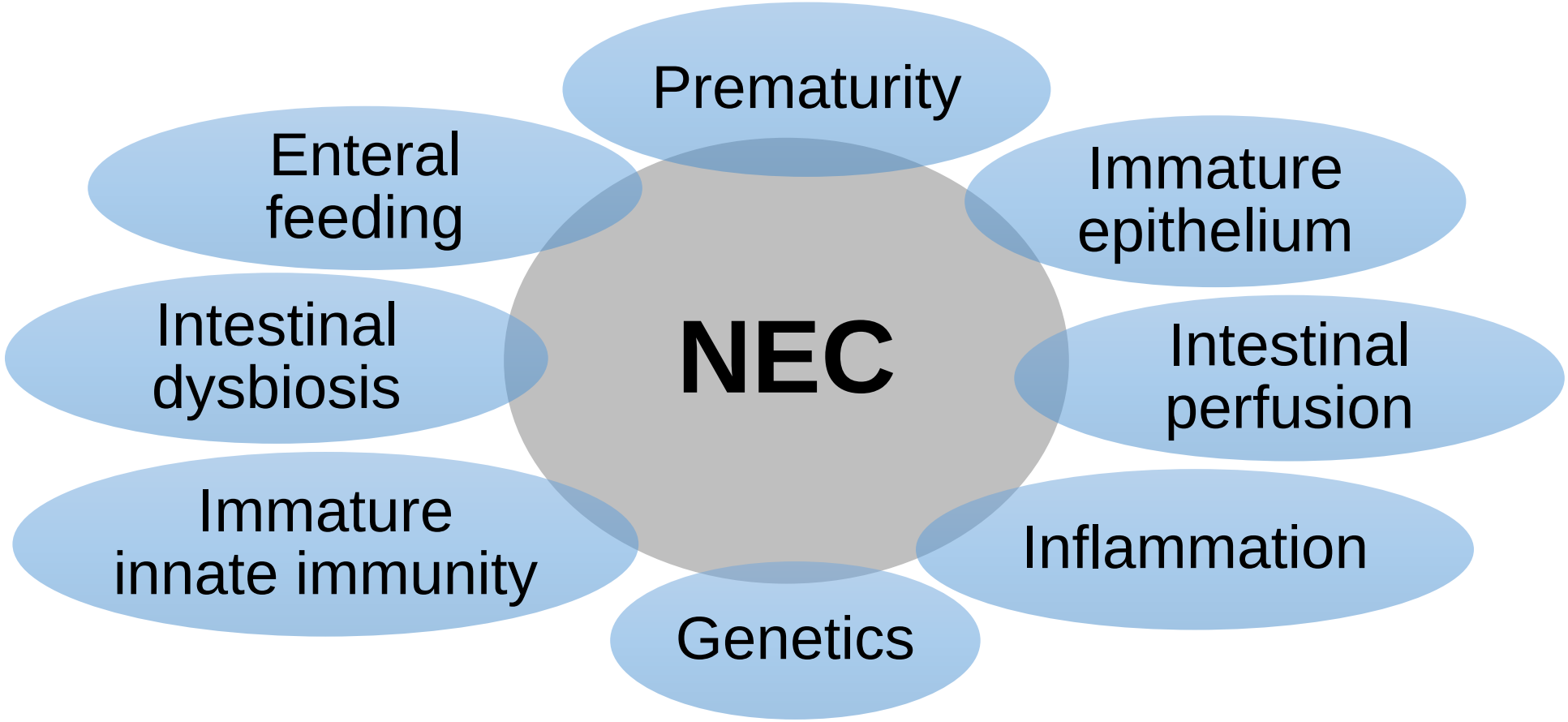
Division of Neonatology

University of Utah School of Medicine

Intermountain Primary Children's Hospital

HEALTH UNIVERSITY OF UTAH

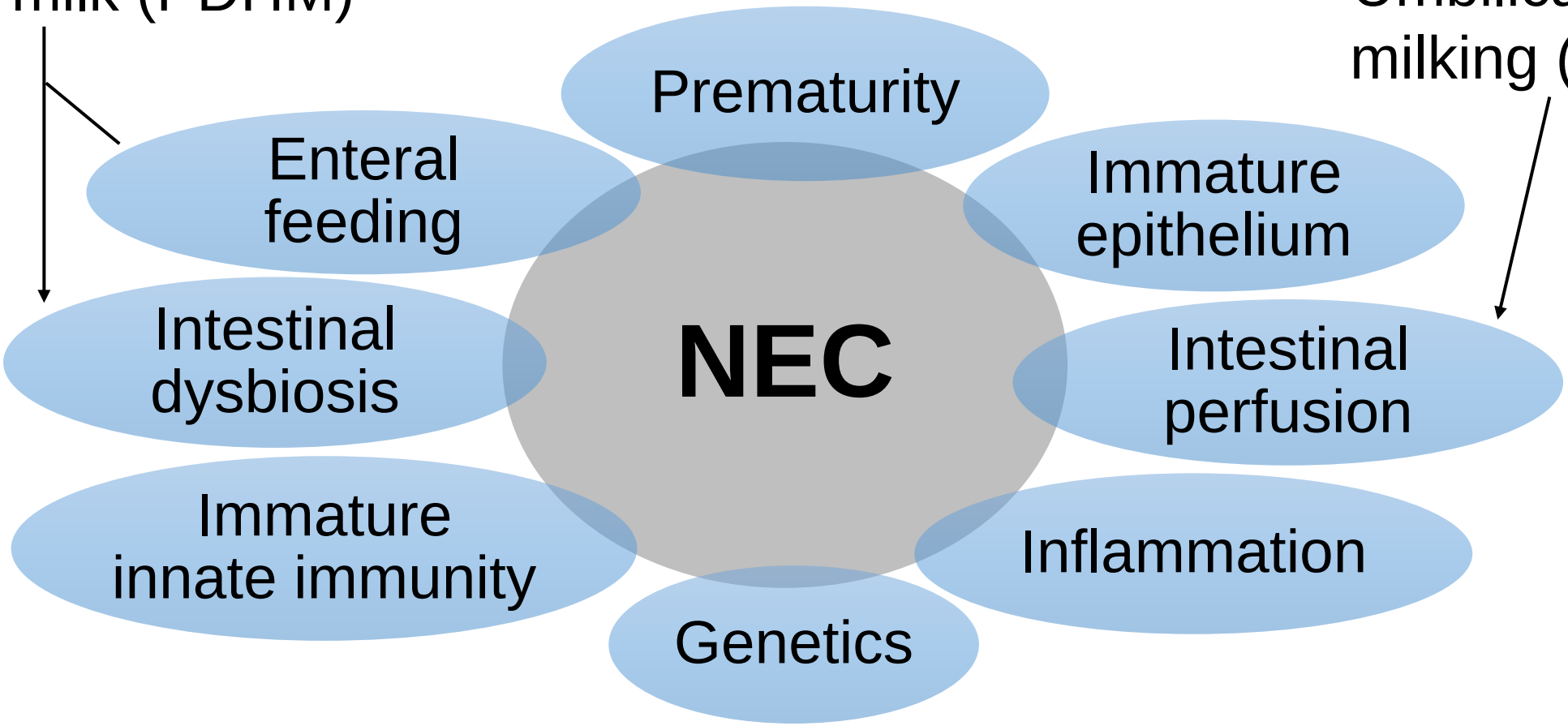
What contributes to NEC risk?



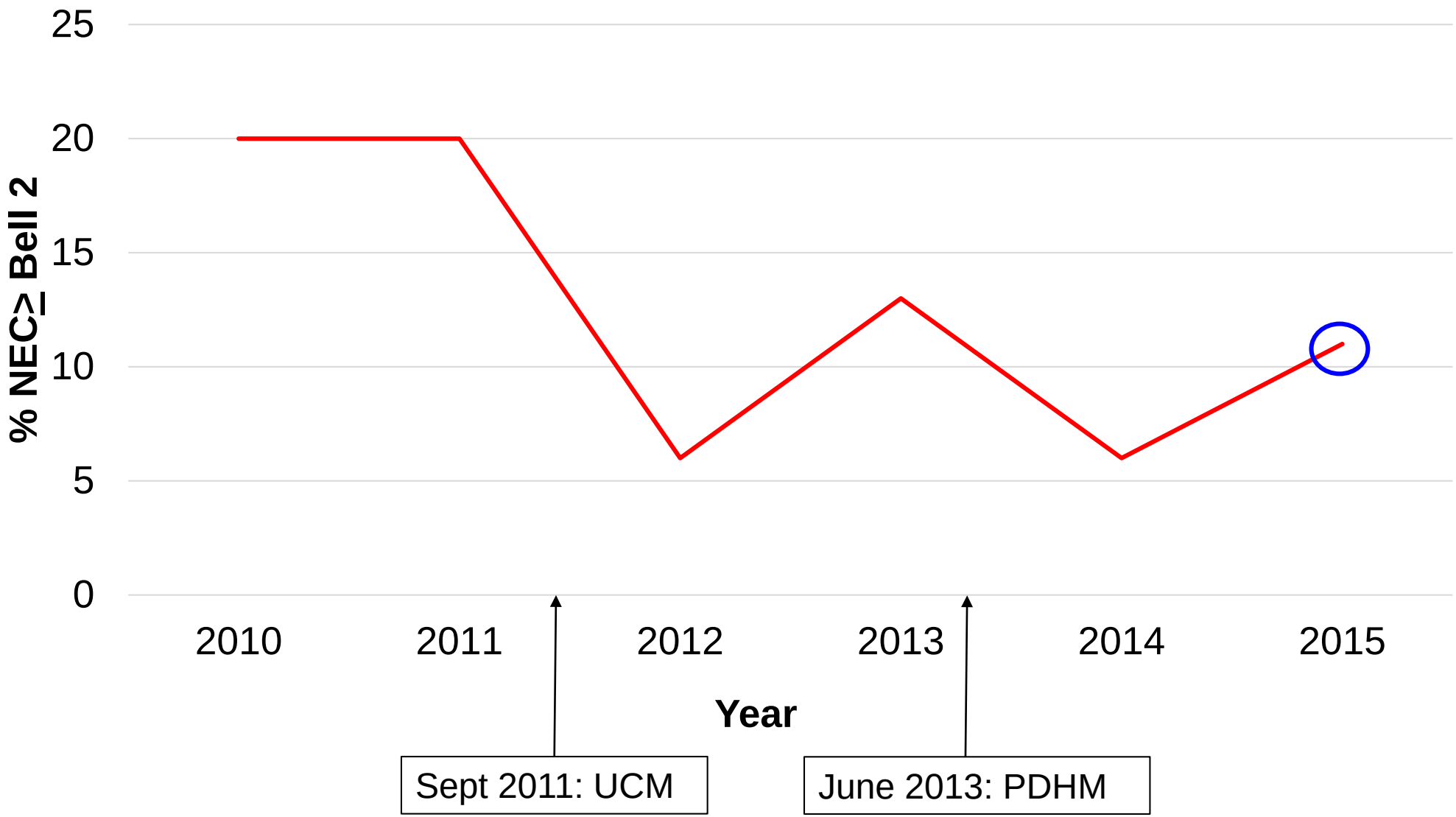
Interventions to decrease NEC

June 2013:
Pasteurized donor human milk (PDHM)

Sept 2011:
Umbilical cord milking (UCM)



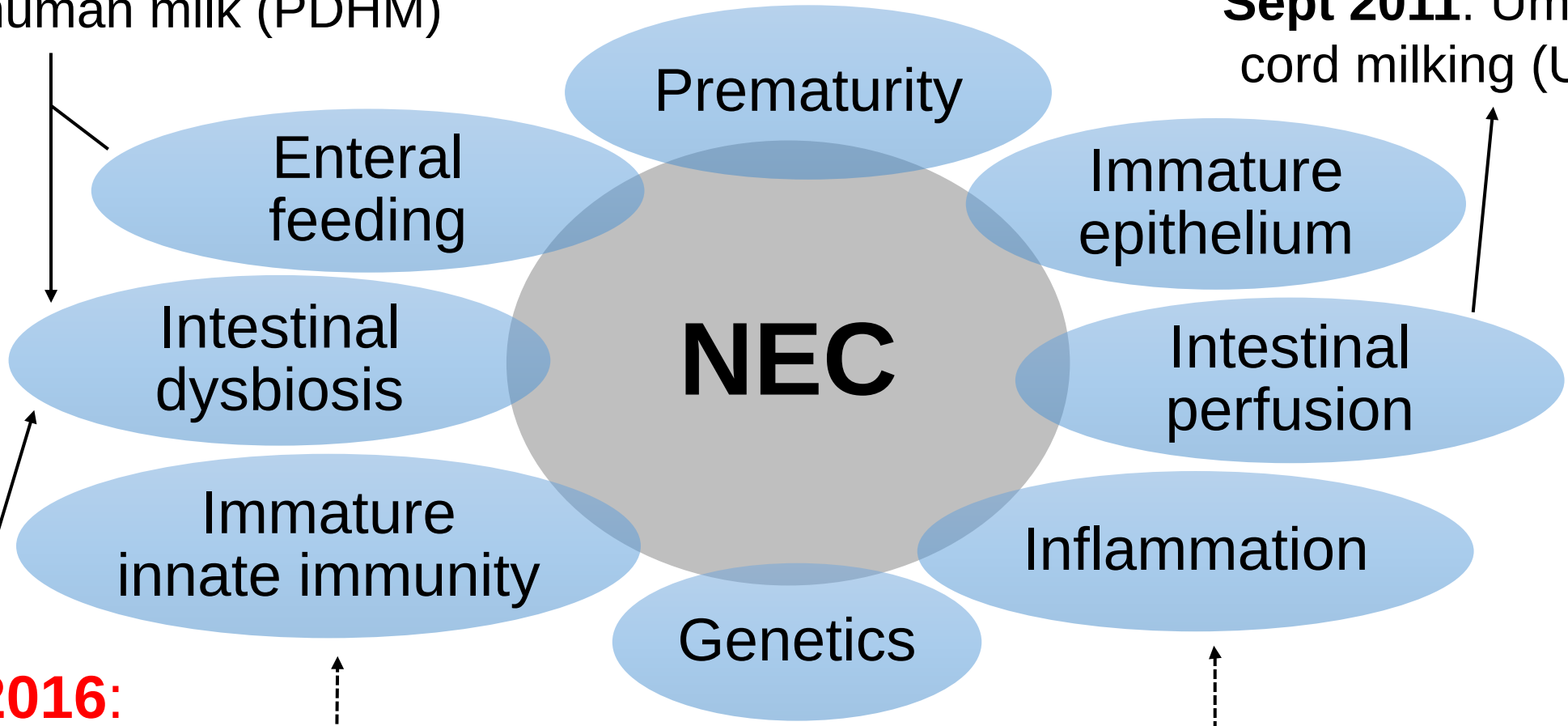
Decrease in NEC in <30 weeks gestation with UCM & PDHM



What next?

June 2013: Pasteurized donor human milk (PDHM)

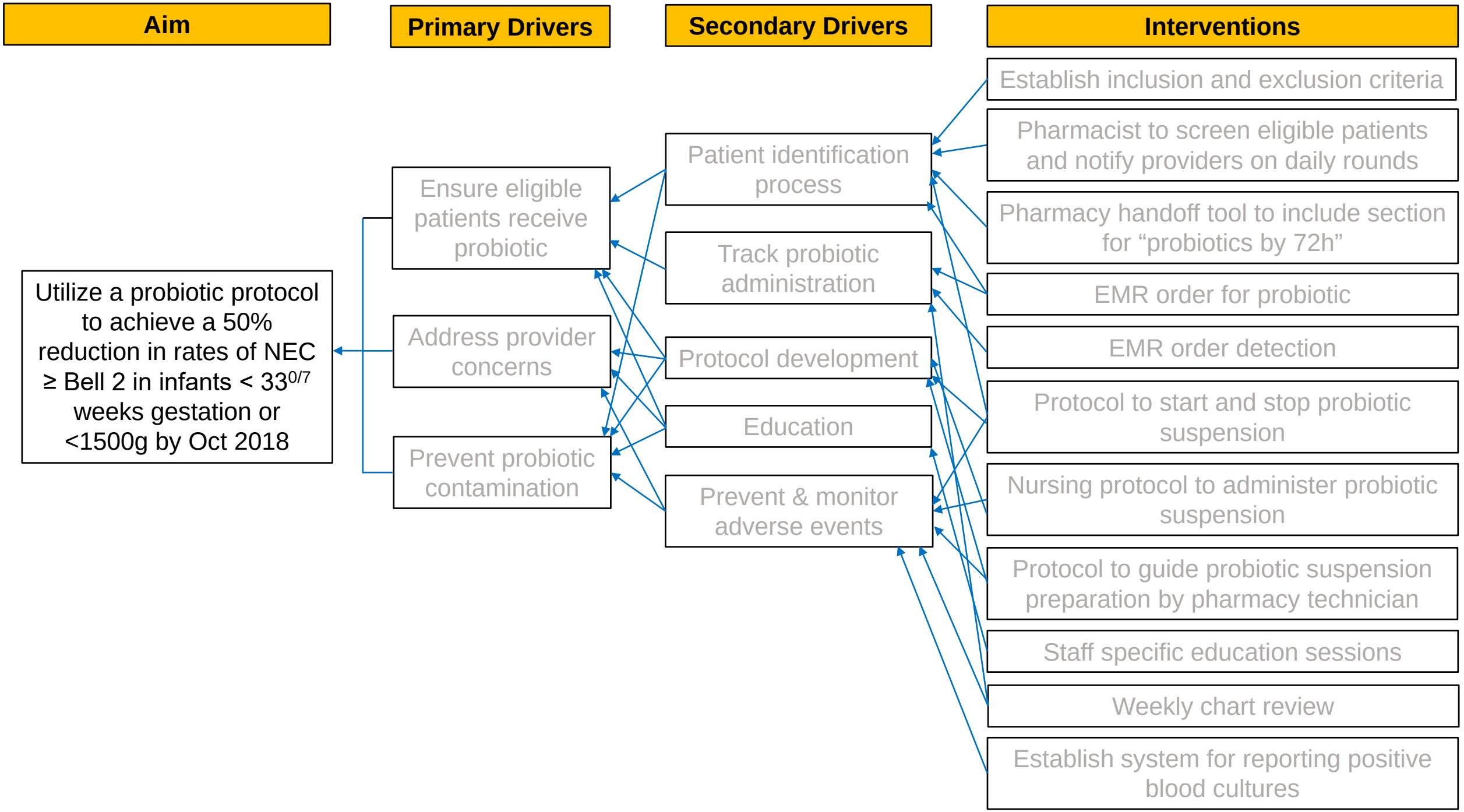
Sept 2011: Umbilical cord milking (UCM)



Oct 2016: Probiotics

Aim Statement

To achieve a 50% reduction in NEC Bell Stage ≥ 2 by Oct 2018 in infants born <33 weeks gestation or <1500g


Aim
Primary Drivers
Secondary Drivers
Interventions
Utilize a probiotic protocol to achieve a 50% reduction in rates of NEC ≥ Bell 2 in infants < 33^0/7 weeks gestation or <1500g by Oct 2018
Ensure eligible patients receive probiotic
Address provider concerns
Prevent probiotic contamination
Patient identification process
Track probiotic administration
Protocol development
Education
Prevent & monitor adverse events
Establish inclusion and exclusion criteria
Pharmacist to screen eligible patients and notify providers on daily rounds
Pharmacy handoff tool to include section for “probiotics by 72h”
EMR order for probiotic
EMR order detection
Protocol to start and stop probiotic suspension
Nursing protocol to administer probiotic suspension
Protocol to guide probiotic suspension preparation by pharmacy technician
Staff specific education sessions
Weekly chart review
Establish system for reporting positive blood cultures

Product

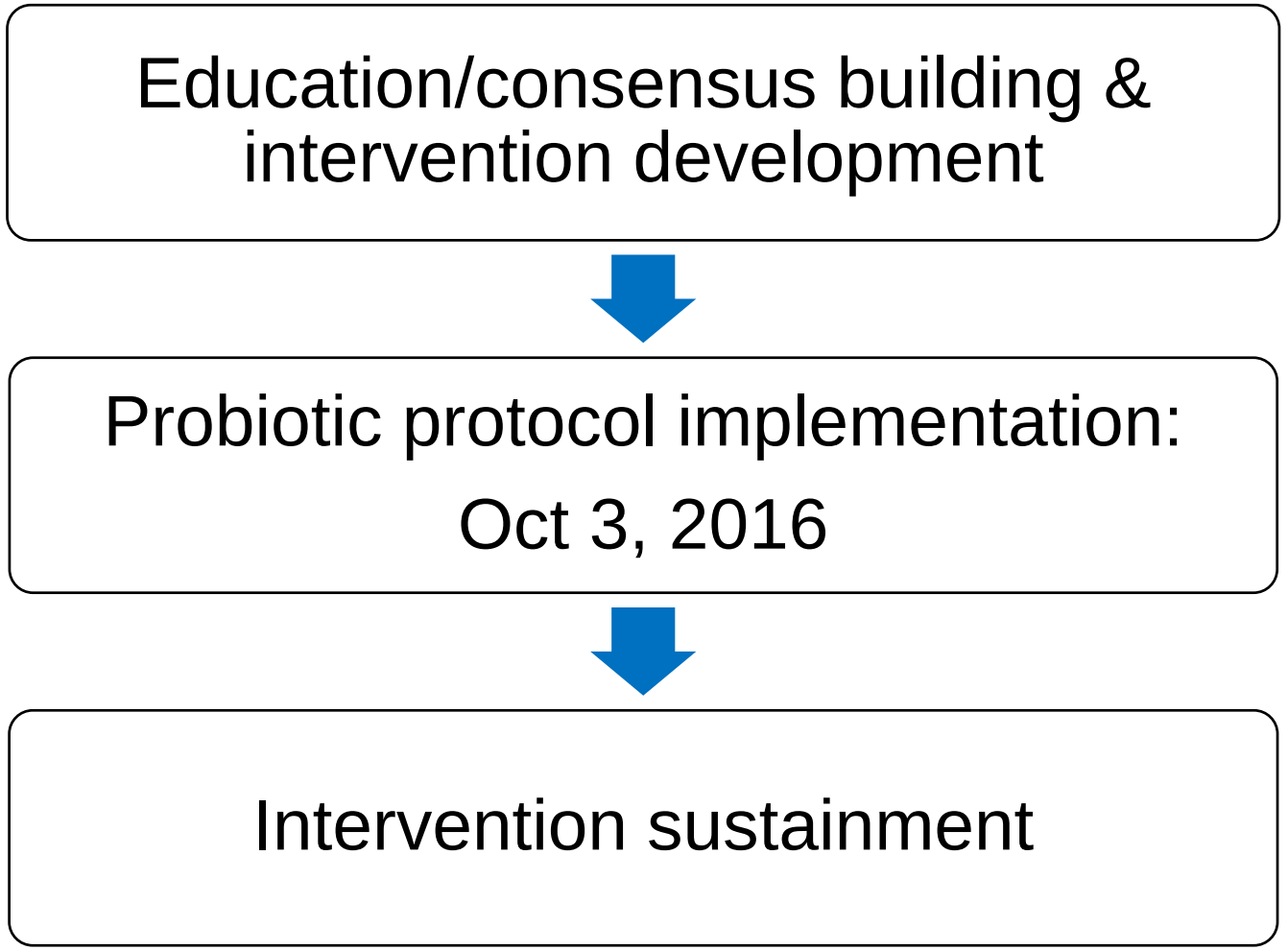
- *Ultimate Flora*
  - 4 *Bifidobacteria (B.breve, B.bifidum, B.infantis, & B.longum)*
  - *Lactobacillus rhamnosus*
  - 4 x 10^9 live cultures/1g
- Quality assurance:
  - Natural Health Products Regulations under Health Canada
  - Independent validation of component bacteria at the University of Iowa

Protocol Summary

- Eligibility criteria:
  1. <$33^{0/7}$ weeks gestation OR <1500g
  2. Post-menstrual age ≥ $24^{0/7}$ weeks
  3. 72 hours of age
  4. ≥ 6 ml/day enteral feedings for 24 hours
  5. No lethal anomalies/conditions or significant GI anomalies

- Discontinued at $36^{0/7}$ weeks corrected gestational age

PDSA cycles


Education/consensus building & intervention development
Probiotic protocol implementation:
Oct 3, 2016
Intervention sustainment

Measures

1. Monthly rate of NEC ≥ Bell Stage 2 per 100 patient days
   - U chart with Laney correction

2. Process measure: protocol compliance

3. Balancing measure: probiotic sepsis

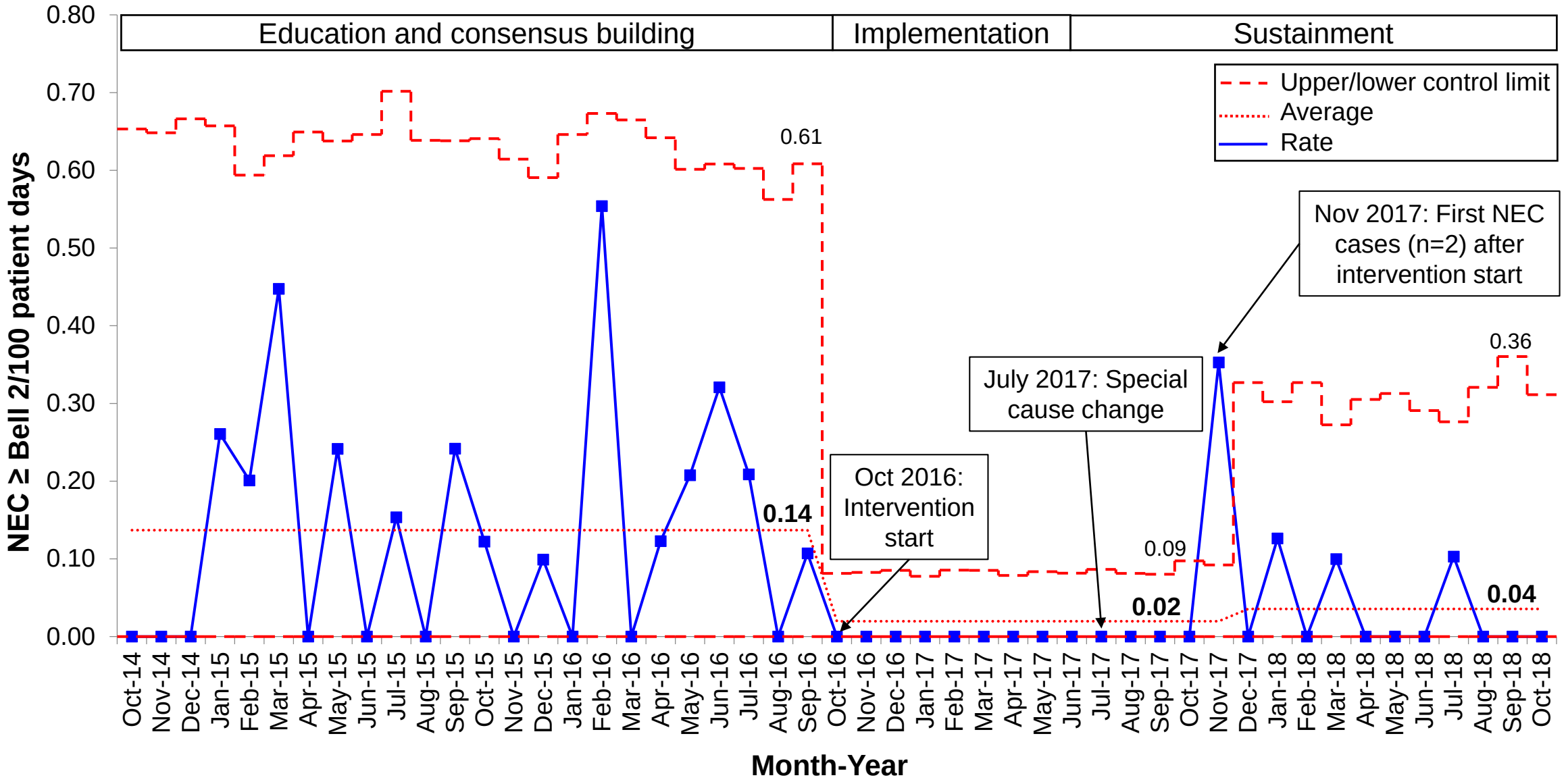
Results

- 290 infants received probiotic (Oct 3, 2016 – Oct 31, 2018)

- Protocol compliance:
  - 1 (0.3%) ineligible patient received the probiotic
    - Post-natal diagnosis of coarctation of the aorta
  - 5 (1.5%) eligible patients were missed
    - No missed patients were diagnosed with NEC

- Balancing measure: No cases of probiotic sepsis

Monthly NEC ≥ Bell 2 per 100 patient days



NEC in probiotic period

GA	Birth weight	NEC Mon-Year	NEC Day of life	NEC Class	Survived?	On probiotics?
25 5/7	965	Nov-2017	15	Surgical	N	Yes
28 2/7	520	Nov-2017	11	Surgical	Y	Yes
28 5/7	1030	Jan-2018	3	Surgical	Y	No
26 2/7	705	Mar-2018	8	Bell 2	N	No
32 0/7	2010	Jul-2018	16	Bell 2	Y	Yes

Conclusion

- Implementation of a probiotic protocol was associated with decreased rates of NEC ≥ Bell Stage 2

- Factors key to success:
  - Informatics support to build a probiotic monitoring report
  - NICU pharmacist assigned role of patient identification
  - Routine monitoring of compliance & adverse outcomes

The University of Utah

Division of Neonatology

Bringing Probiotics into the NICUs of Kaiser Permanente SCAL

David Braun, MD
Regional PIC, Neonatology
Feb 23, 2019

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SCPMG

Where KP SCAL was in 2015

- Babies
  - 41,000 births
  - 600 little babies (GA < 32 wk or BW <= 1500 g)
- NICUs
  - 5 surgical level 3 NICUs
  - 4 medical level 3 NICUs
  - 4 level 2 NICUs
- Neonatologists
  - 65
- NICU directors' committee
  - 1
- # of centers using probiotics
  - 1

2015: How it started

- 2015
  - KP EBM study surveillance team concluded: time for probiotics
  - 2015-2017
    - Numerous discussions
      - NICU opinion leader ad hoc group
      - CME sessions
      - NICU directors' committee discussions
      - Outside experts brought in for formal consultation (eg Underwood)
      - 1:1 discussions
      - Pharmacy discussions

2015-2017: Should we try probiotics at all?

What generated discomfort	Response
Fear of that there isn't enough data to support probiotic use	Tens of thousands of patients, dozens of RCTs, multiple meta-analyses. Much better literature support than most any intervention
AAP says not to use them till FDA approves	Quirks of US (FDA) treatment of probiotics (food vs drug) is practical obstacle to approve probiotics as drug
Fear of nosocomial infection from contaminants (FDA issue 1)	Overall nosocomial infection rate LOWER with probiotics. FDA was basically case report. Use high quality product
Fear that organisms in products not of proper ID, viability, or titer (FDA issue 2)	Publications distinguish between poor and high quality products
Our NEC rates are already low	Studies with similar starting NEC rates still show further drop in NEC
Don't we need RCT to adopt probiotics into practice? We're not allowed to arbitrarily change standard of care.	**Got formal legal opinion**: wide latitude allowed if plausible rationale **Change**: the only perfectible practice is consistent practice **Let's up our game**: choose changes in care rationally, implement consistently and then assess

2017: Which probiotic?

Criteria	FloraBaby	ABC Dophilus	Natren (B infantis)	Biogaia Protectis (L reuteri)	Evivo (B infantis ss)
Product quality (titer, constituent consistency)			+	++	++
Safety (no contaminants)	?		?	+	+
Not a powder (FDA issue)				+	+
Not a powder (ease of administration in NICU setting)				+	+
Efficacy (NEC)	+	+	++	+	++
Efficacy (nosocomial inf)			+	++	+
Efficacy (colonization, outcompeting pathogens)	+	+	++	+	+++
Safety/efficacy (gut-trophic metabolites)	+	+	+	+	+++

2017:

Agreed to encourage use of Biogaia Protectis or Gerber Soothe
Tentative plan to change to Evivo when available

- Rationale for
  - Most appealing of products available at time
  - Probably change to Evivo (B infantis) when available
  - Would "break the ice" for using probiotics at all
- Target babies
  - VLBW or GA < 32 wk while feeding and GA < 34 wk
- Results:
  - Marked increase in use
  - No subjective complaints
  - No objective change in NEC, infection, length of stay, death

year	NICUs using Probiotics	Little Babies receiving Probiotics
2016	1 (7%)	3%
2017	10 (77%)	40%

2018:
Evivo now available
Discomfort (MD and Pharmacy) with changing to Evivo

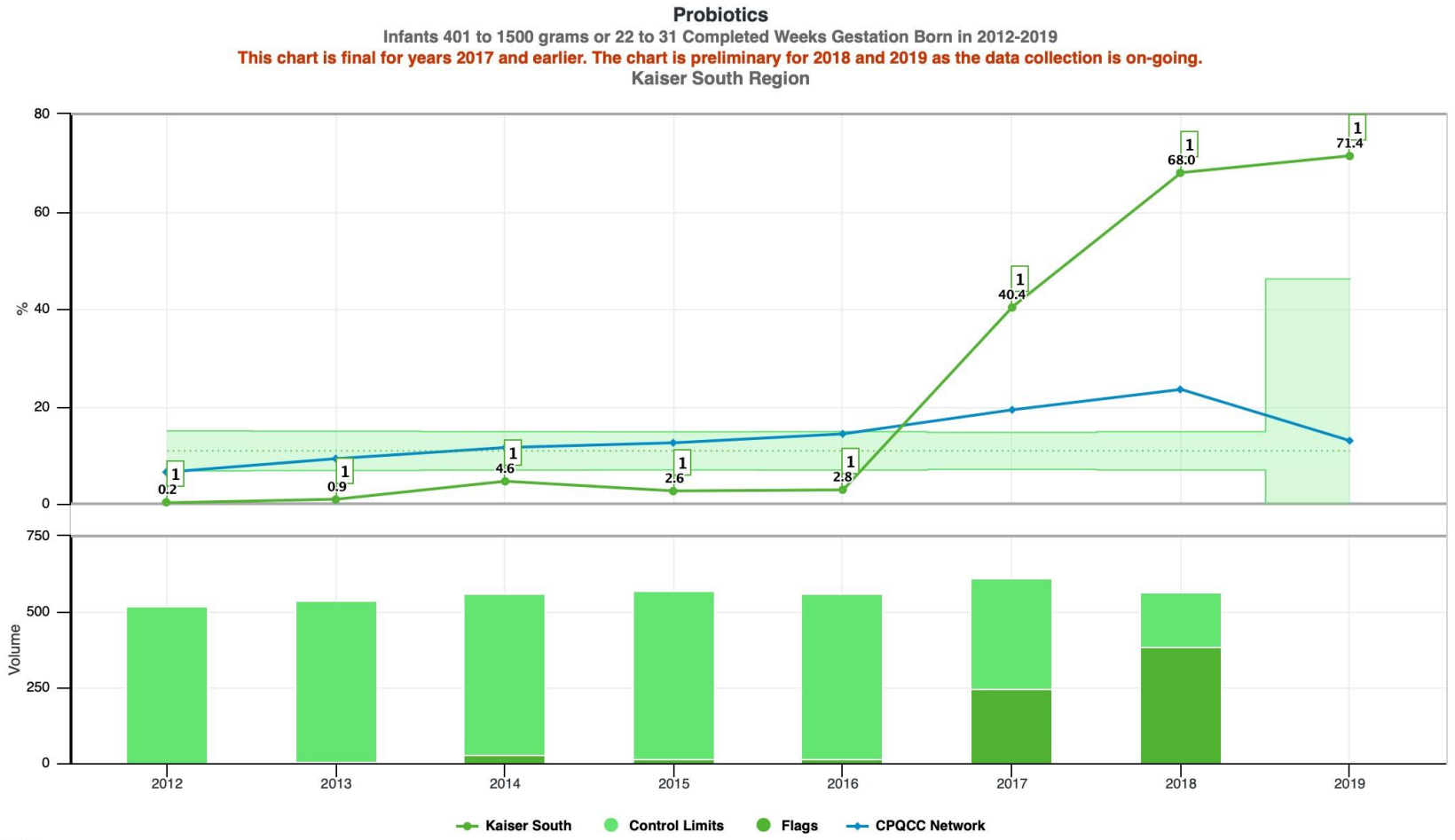
What generated discomfort	Response
Biogaia is going well: why change?	"Well"=ease of use, no obvious problems Expect as "well" or with Evivo
Biogaia has efficacy: why change?	Evivo likely to have significantly more efficacy
Evivo is not on formulary and not on contract	Got on formulary Got contract
Heavy marketing by Evivo: are we caving to marketing?	Marketing doesn't mean product is worse Worked with Evolve Biosystem to decrease marketing
Evivo much more expensive	KP cost benefit analysis (drug costs vs acute hospital costs of NEC) Conclusion: same $ for less disease
Cost benefit analysis is just theoretical: why not wait for future studies	Studies won't be out for years at very least Likely form of study: Pragmatic (QI) trial So why don't we be one of those pragmatic (QI) trials?
We don't do studies; we use our personal experience	Personal experience is just a mediocre form of a study Why not up our game individually and as a profession? Let's combine our efforts, let's coordinate on this "The only perfectible practice is consistent practice"

Late 2018:
Agreement to use Evivo exclusively for now

- **QI initiative (pragmatic trial)**
  - **Product:**
    - Evivo liquid
  - **Population**
    - GA< 32 wk or BW<=1500 g or GI baby
  - **Dose:**
    - unit dose (8B CFU) daily
  - **Days to dose**
    - any day an enteral feeding is given
  - **Days not to dose**
    - Days baby not fed a feeding
    - Postmenstrual age >= 34 wk
  - **When to reassess this regimen**
    - N=2000 babies dosed
      - 80% power to pick up drop of NEC from 3% to 2%

Implementation so far: per eligible baby

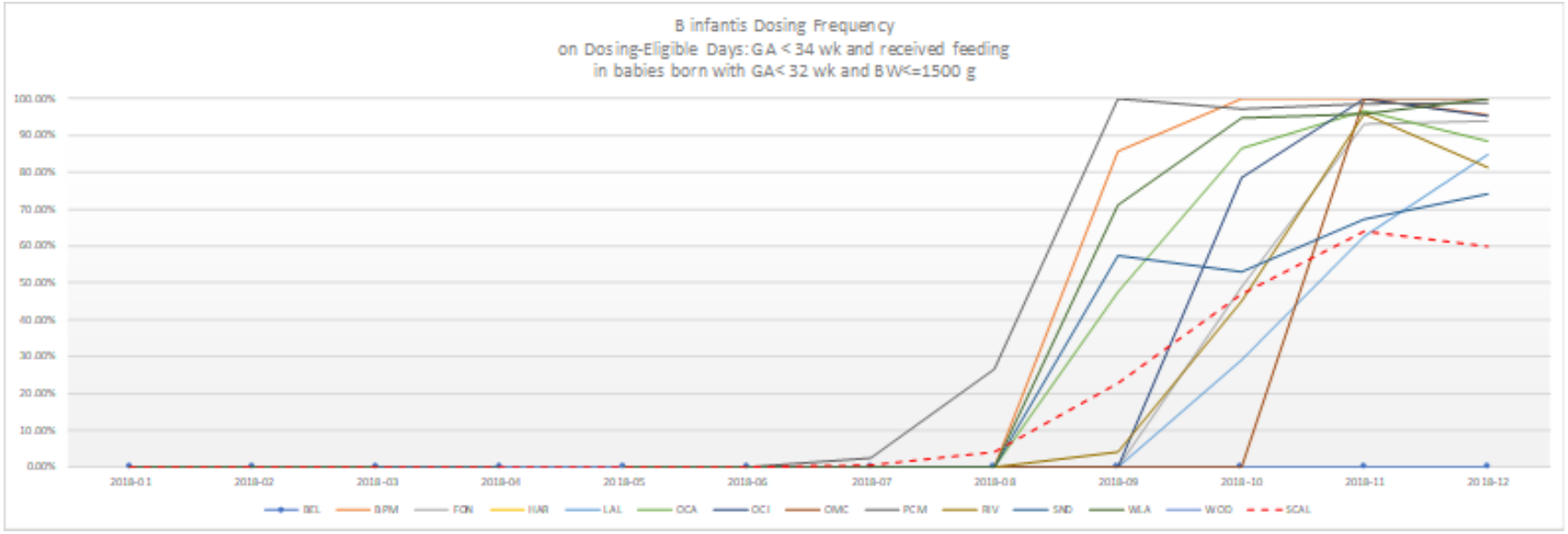
Biogaia or Evivo

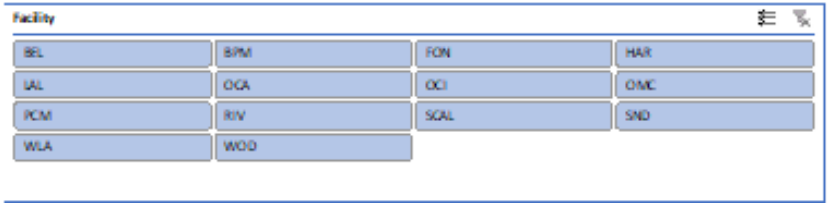


CPQCC

Implementation so far: per eligible day

for Evivo





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Our Center's Experience with Routine Use of Probiotics

Ravi Mangal Patel, MD, MSc
Associate Professor of Pediatrics
Emory University School of Medicine and
Children's Healthcare of Atlanta

rmpatel@emory.edu

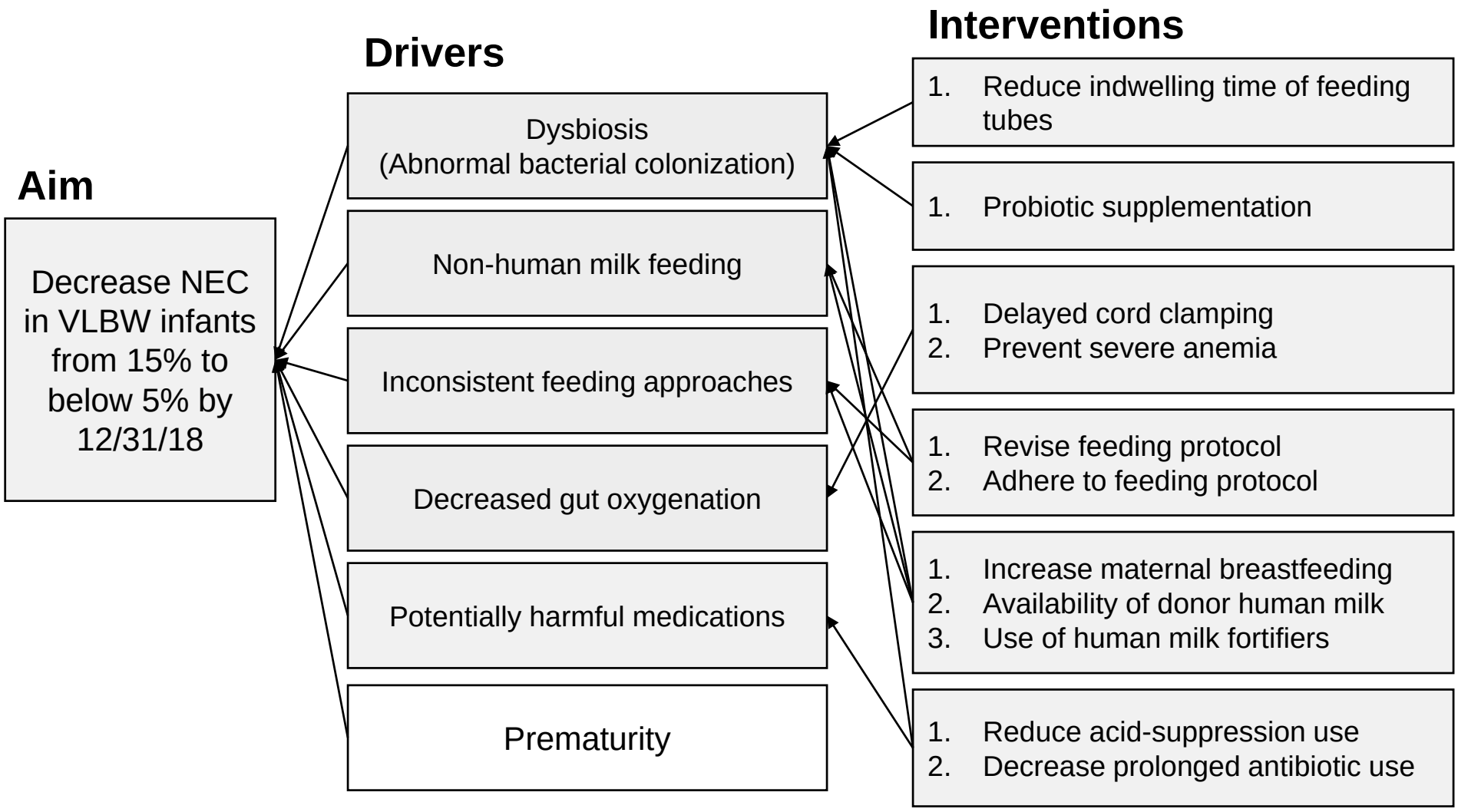
@ravimpatelmd
#preventNEC

Disclosure: Probiotics are not approved by the US Food and Drug Administration for the prevention of NEC or other diseases in preterm infants. This webinar is intended to be educational in nature only.

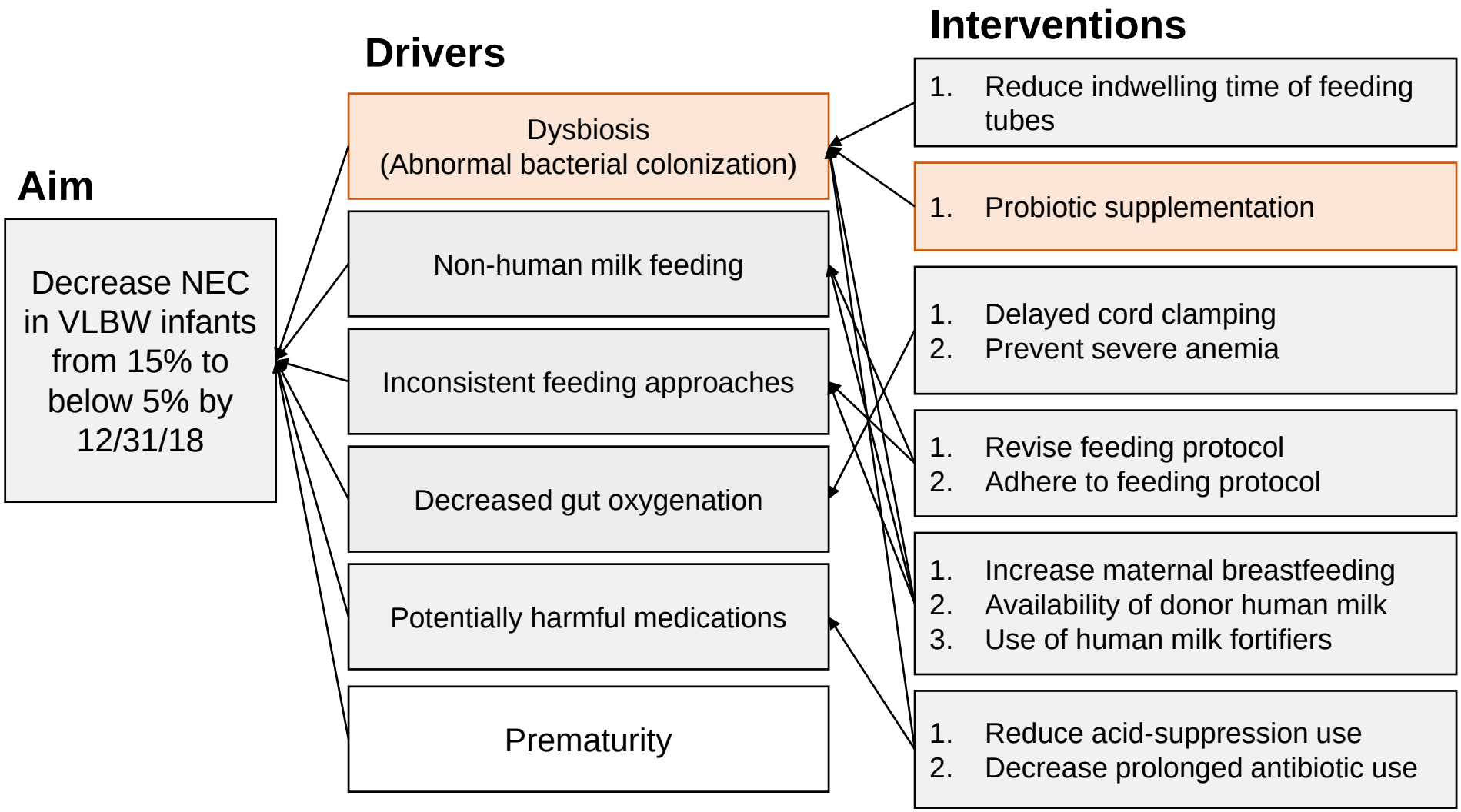
Context

- In 2013, we had a NEC incidence of 15% in very low birth weight (VLBW) infants (based on VON definition).
- Our center had started routine use of donor human milk as part of efforts to decrease NEC and we had began discussions regarding the use of probiotics.
- In Nov of 2013, the ProPrems trial was published, which was important in our center's decision to begin routine use of probiotics as part of overall QI efforts to prevent NEC.

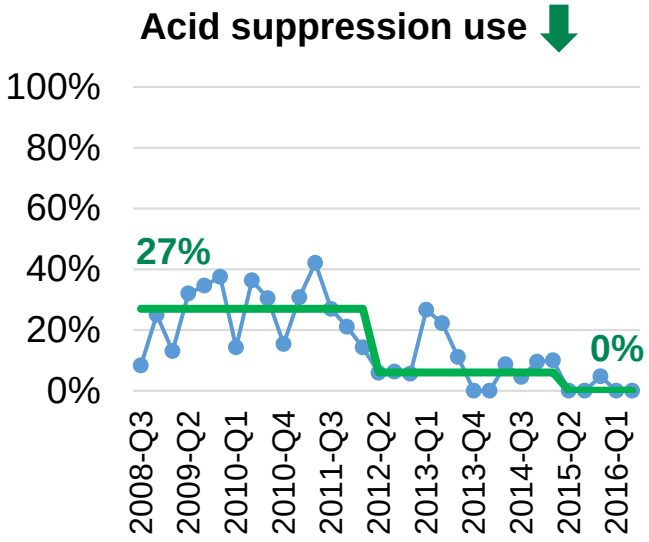
Decreasing NEC

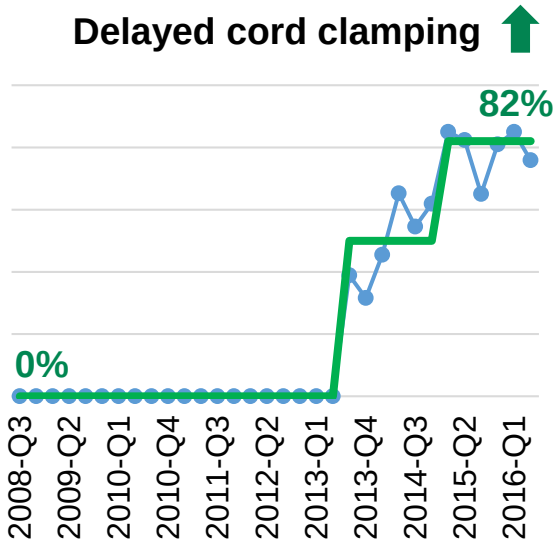


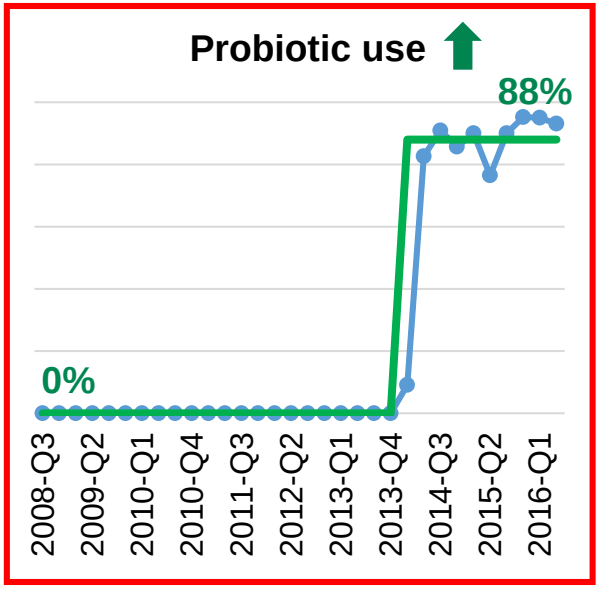
Decreasing NEC

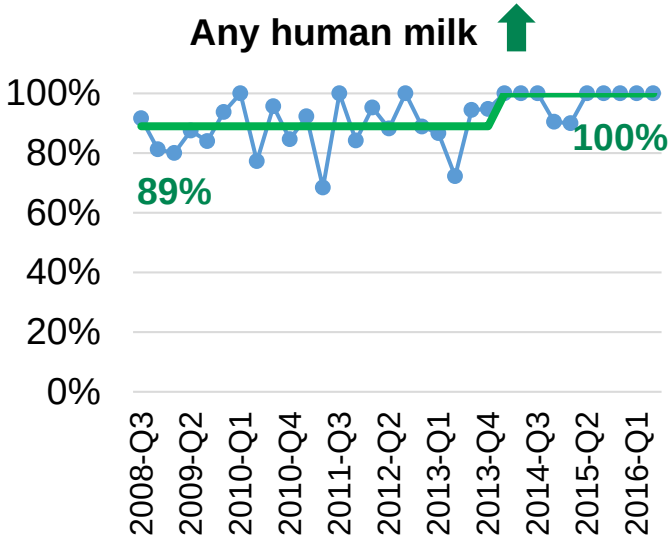


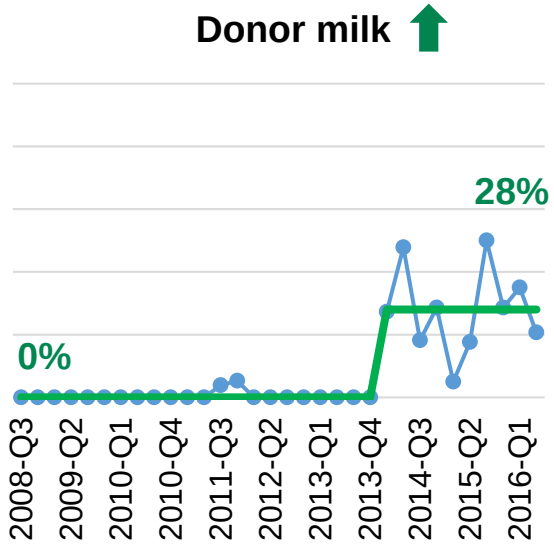
Process measures (interventions)

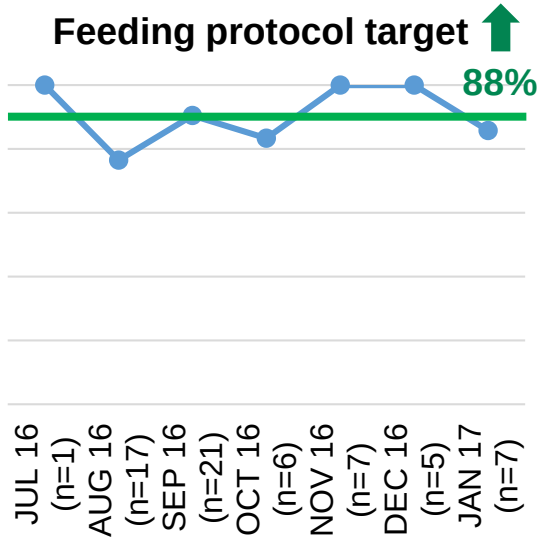




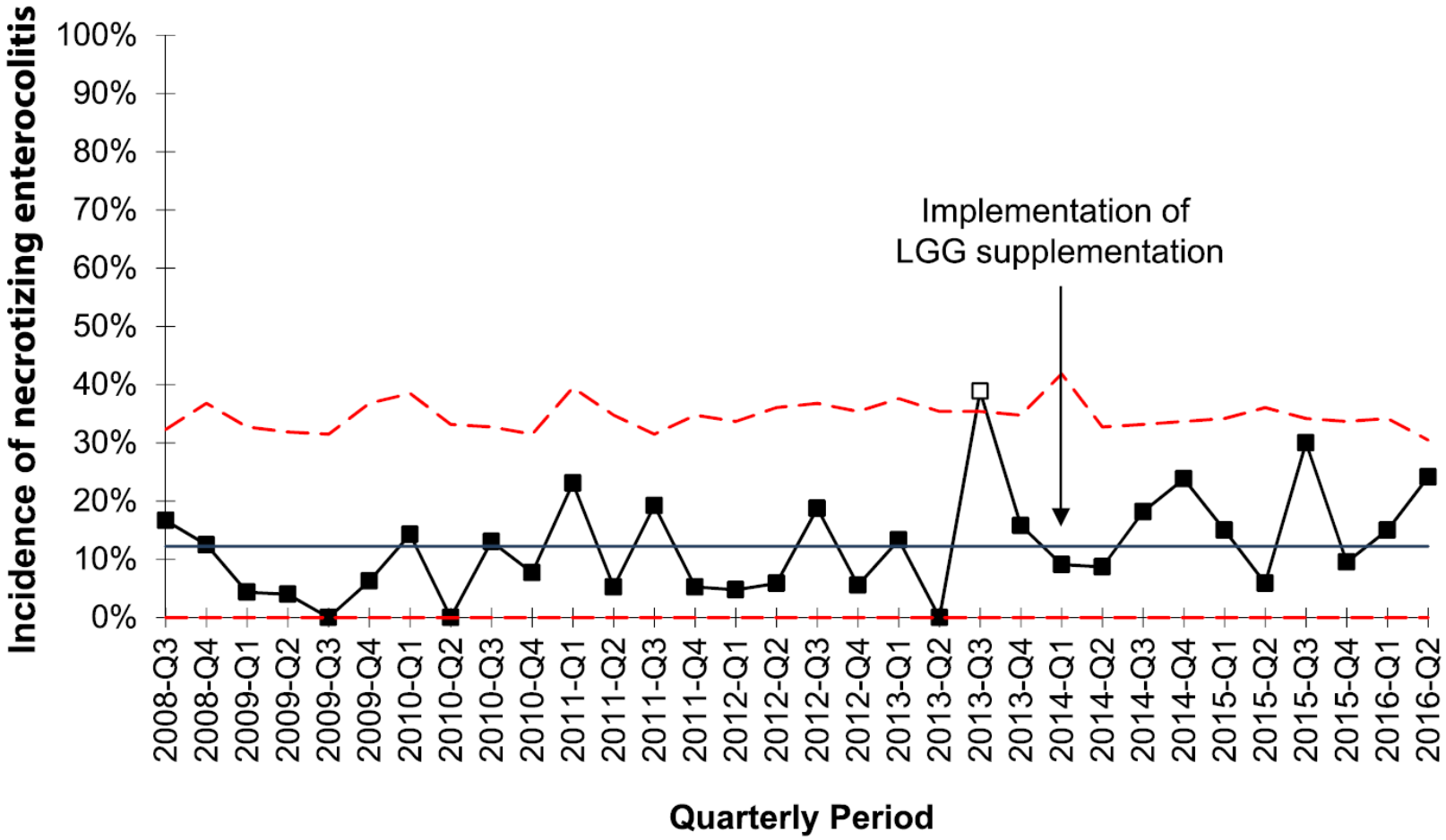








Comparison of NEC incidence before and after routine probiotic (LGG) supplementation



Kane et al. *J Pediatr.* 2018

Comparison of NEC incidence before and after routine probiotic (LGG) supplementation

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

Next steps

- We have continued to address other drivers of NEC, including reducing prolonged empiric antibiotic use.
- We changed to using BioGaia Protectis, a *Lactobacillus reuteri-containing* liquid preparation in 2018.
- Our experience highlights the uncertainty regarding the influence of population characteristics (e.g. antibiotic use) on probiotic effects and choice of specific products.

More information can be found on the NEC Society webpage at www.NECsociety.org

Contact: Jennifer@NECsociety.org