Infant Bacterial Therapeutics

May 6, 2019

Staffan Strömberg

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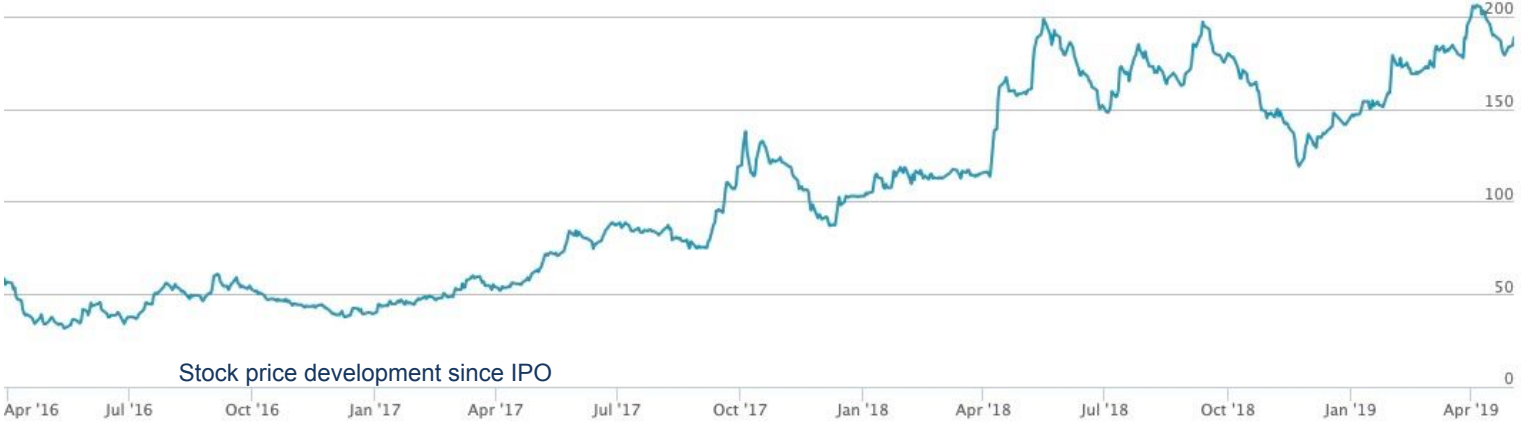
Infant Bacterial Therapeutics AB

Corporate overview

- Founded in 2013 in Stockholm, Sweden as a subsidiary of BioGaia
- IPO in 2016, currently listed on Nasdaq Stockholm Mid-Cap
- Cash end of Q1 2019 MSEK 540, sufficient to fund development to market
- Planned Phase III start during H1 2019
- Market cap: MSEK 2 000



Stock price development since IPO

Corporate development since 2018 AGM

- List change to regulated market **Nasdaq Stockholm Mid-Cap** in September 2018

- Analyst coverage: SEB (Sweden) and Chardan (US) (not commissioned research)

First distribution deal for IBP-9414 in place

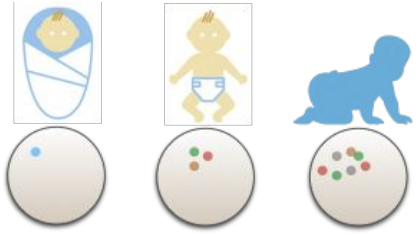
With Megapharm for IBP-9414 for the Israeli market and the Palestinian Authority's territories.

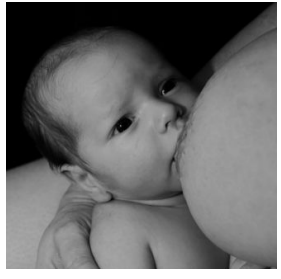
- Megapharm responsible for local registration, price negotiation and marketing
- IBT will receive 70% of revenue after an initial period
- Potential to include Israeli medical centers in Phase III trial

The IBT concept

Altering the human microbiome to treat diseases related to poor gut function

Newborn infant microbiome is dynamic





Human bacterial strains derived from human breast milk

Published proof-of-concept clinical signal

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

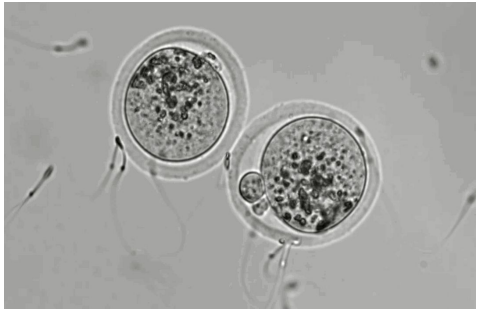
Prophylactic Probiotics to Prevent Death and Nosocomial Infection in Preterm Infants

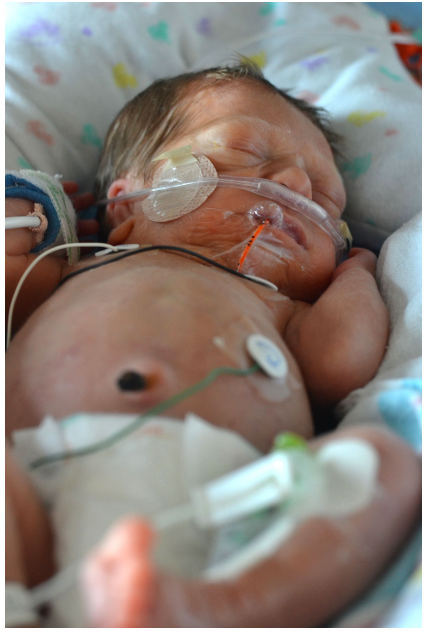
Mario A. Rojas, Juan M. Lozano, Maria X. Rojas, Viviana A. Rodriguez, Martin A. Rondon, Jaime A. Bastidas, Luis A. Perez, Catherine Rojas, Oscar Ovalle, Jorge E. Garcia-Harker, Maria E. Tamayo, Gloria C. Ruiz, Adriana Ballesteros, Maria M. Archila and Mauricio Arevalo

Pediatrics 2012;130;e1113; originally published online October 15, 2012; DOI: 10.1542/peds.2011-3584

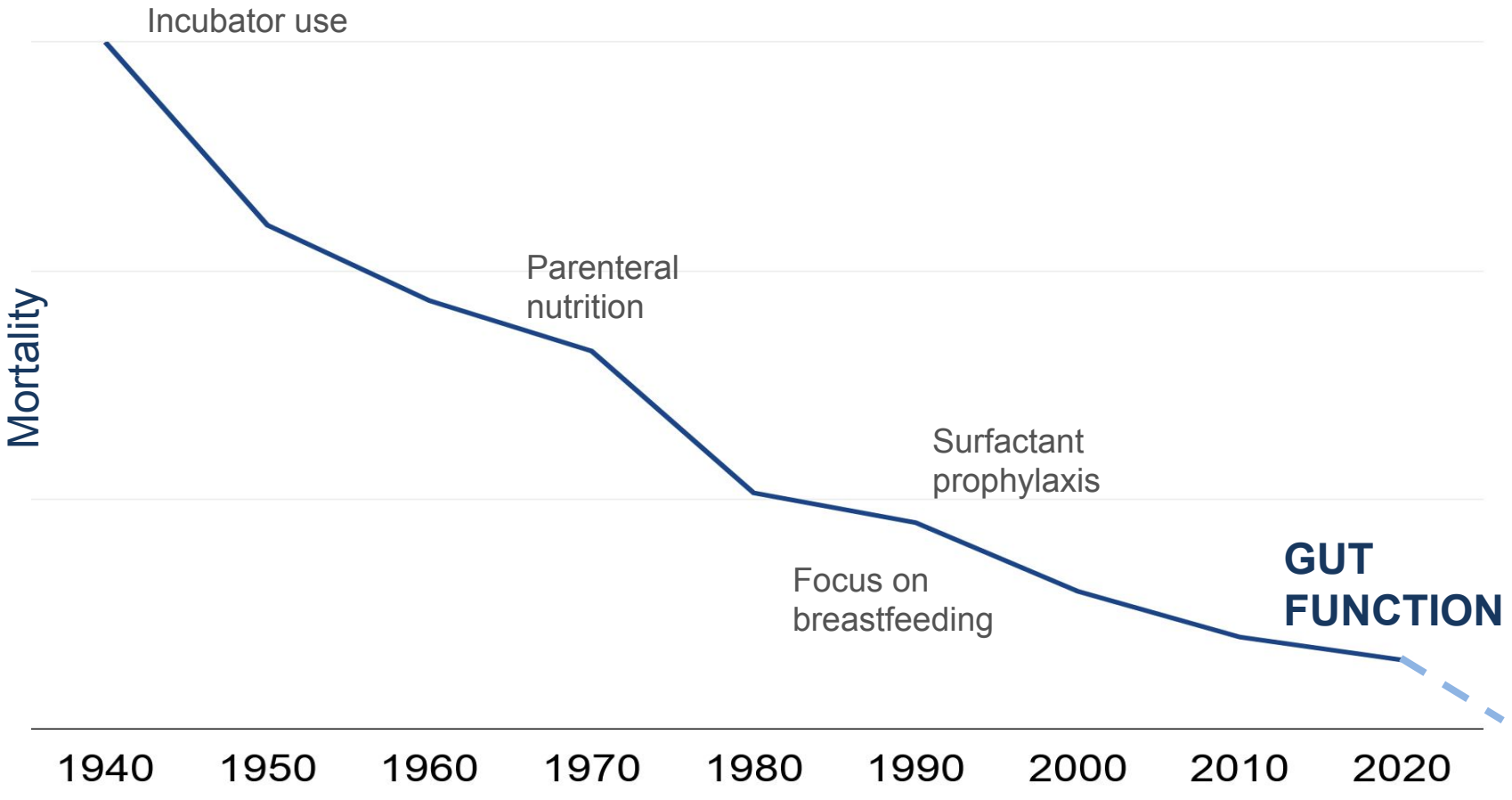

High unmet medical need

Our patients



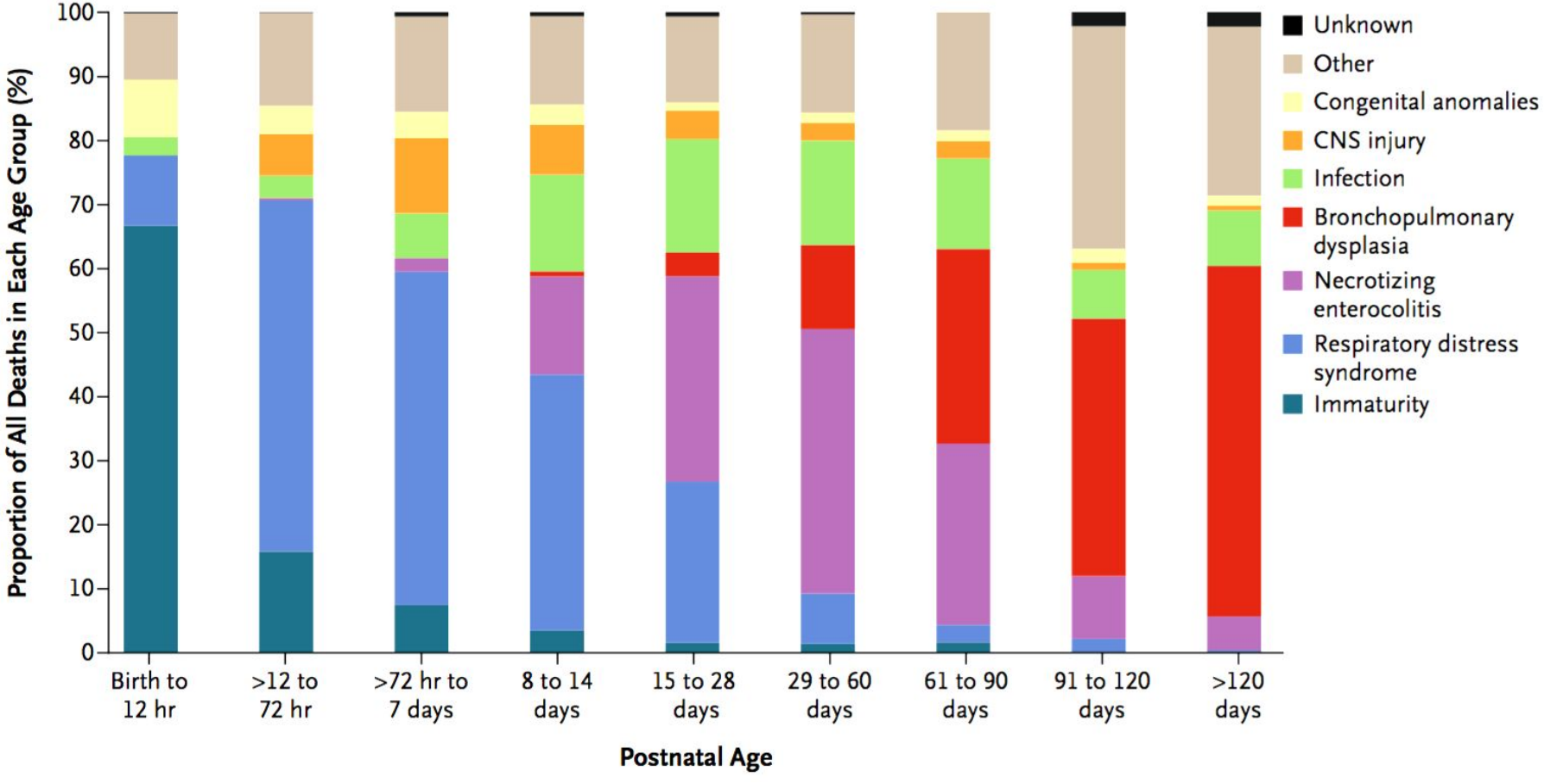


GI tract left untreated in preterm infants



CDC/NCHS, National Vital Statistics System

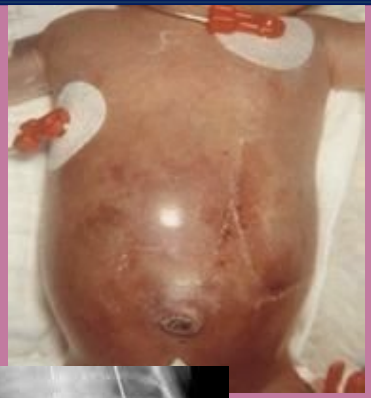
Causes of death

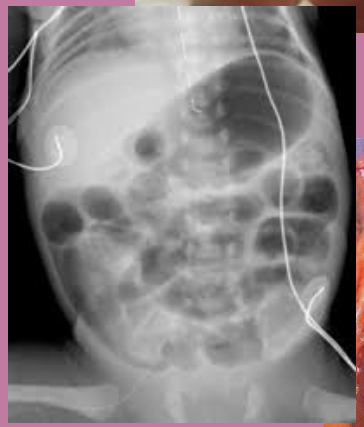


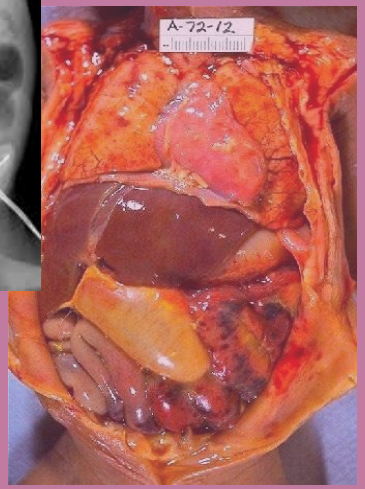
Patel 2015

Necrotizing enterocolitis (NEC)

- NEC is severe inflammation of the bowel in preterm infant where 20-40% need complicated and costly surgery
- Survivors have long-term consequences such as short-bowel syndrome, abnormal growth, cognitive, visual and hearing impairments
- There is no therapy available today
- **NEC is one of the leading causes of death in the Neonatal intensive care unit (NICU) with up to 40% morbidity rate killing 1500 US and 3700 EU infants each year**



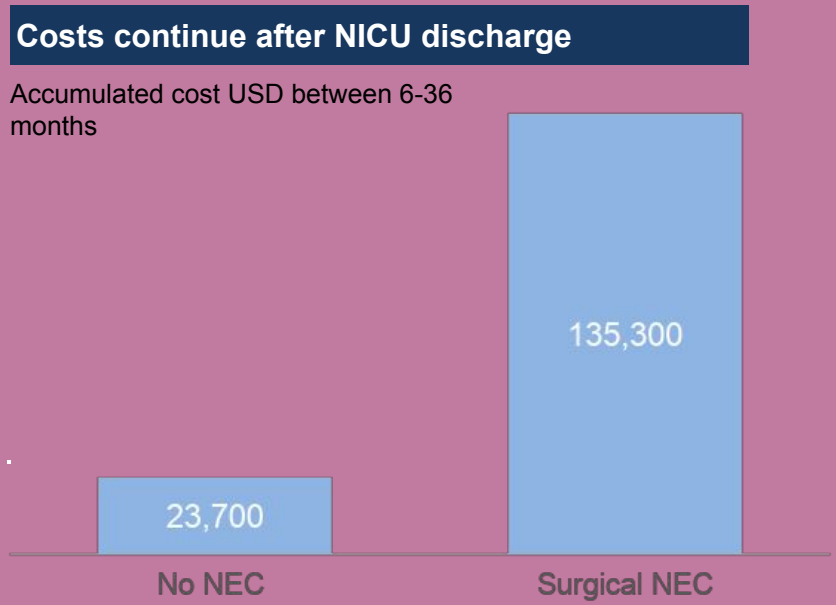




Simpson 2010, Clark 2012

Economic burden of NEC

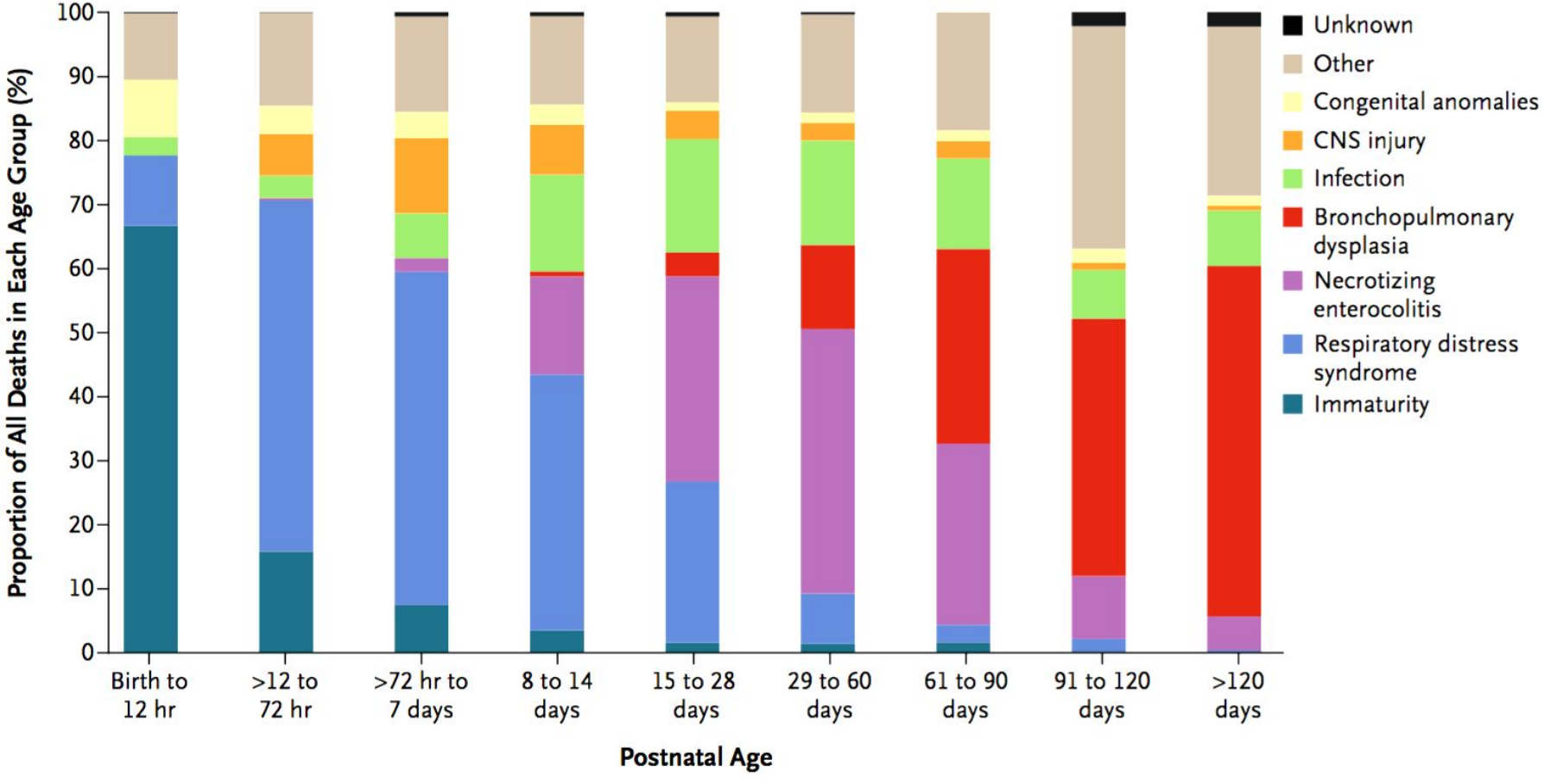
NEC Economic Burden is estimated to be 20% of the total cost of initial care and USD 5 Billion spent annually on NEC in the US.



Long term costs associated with sequelae such as impaired growth, short bowel syndrome and poor neurodevelopment

Ganapathy 2011, 2013

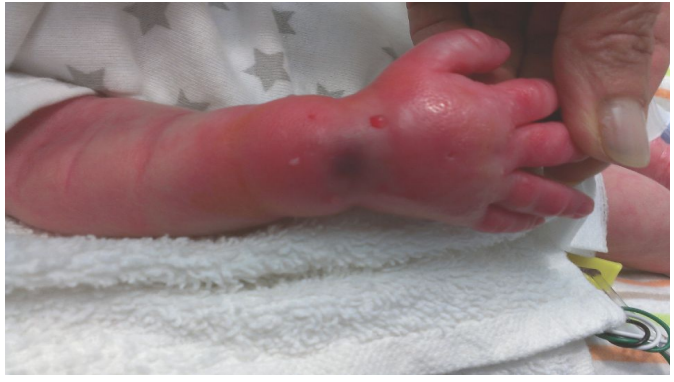
Causes of death



Patel 2015

Feeding the preterm infant

- Establishing enteral (mouth) feeding in preterm infants to establish “catch up growth” that is important for e.g. cognitive development.

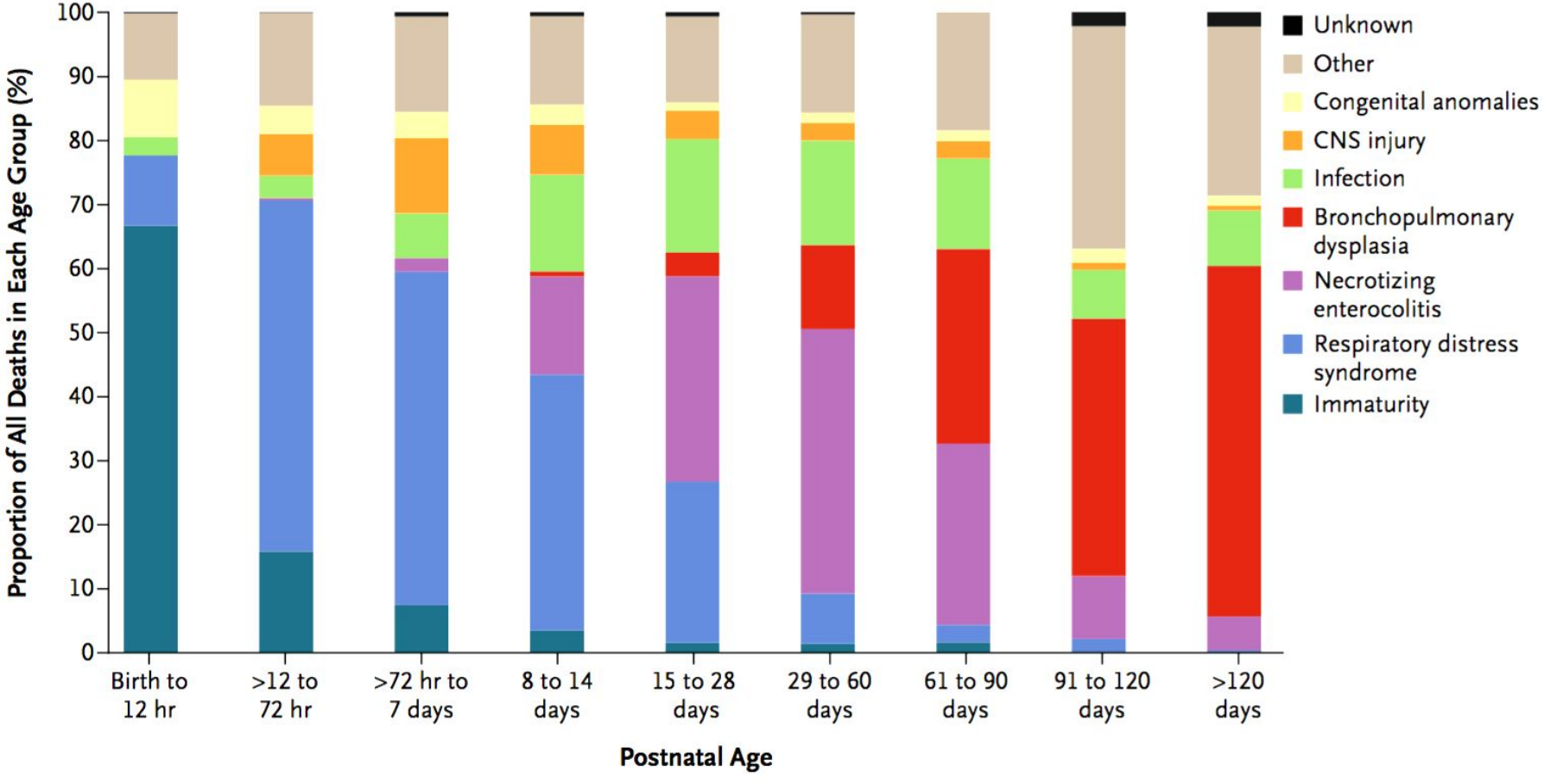


- Prolonged parenteral (needle feeding) nutrition increases cost and causes complications: cholestasis, increased risk of BPD, pulmonary vascular resistance, infections and sepsis.

Despite intensive nutritional strategies for premature infants, growth failure remains a major problem

Murgas-Torrazza, 2013; Agostoni, 2010

Causes of death



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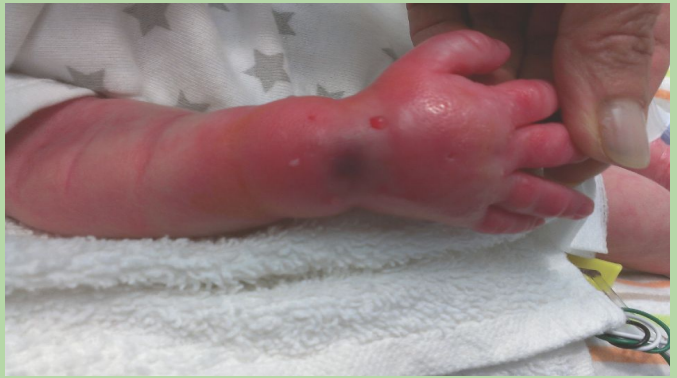


- Establishing enteral (mouth) feeding is one important goal in preterm infants
for “catch up growth”, for development and to combat intestinal damage.

Despite intensive nutritional strategies for premature infants, growth failure remains a major problem

Murgas-Torrazza, 2013; Agostoni, 2010

Feeding the preterm infant

- Prolonged hospital stay of the preterm infant is associated with a high direct cost burden - $3,200 per day

- Long Term: Improved growth velocity improves neurodevelopmental outcomes in extremely low birth weight infants

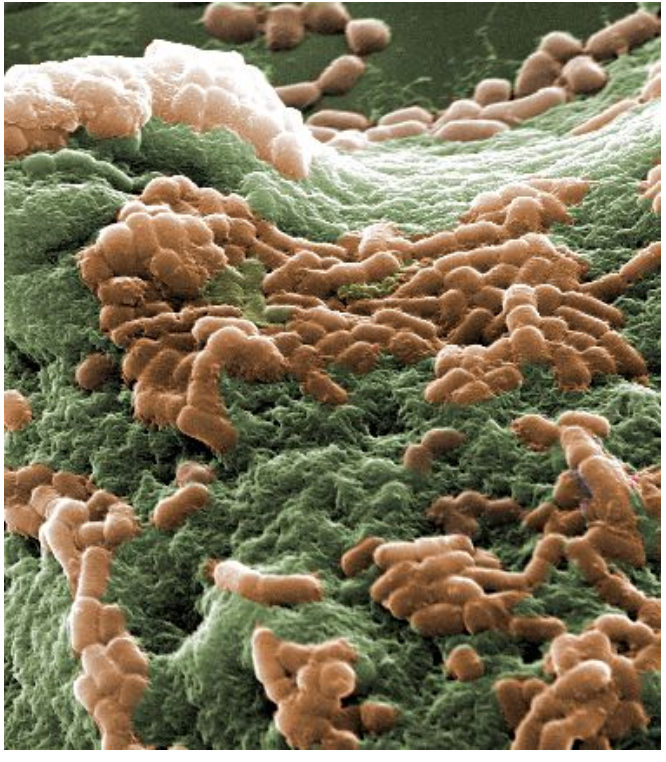
Ganapathy, 2011 and Ehrenkranz et al 2006

MECHANISM OF ACTION –*Lactobacillus reuteri*

Lactobacillus reuteri

Active substance of IBP-9414

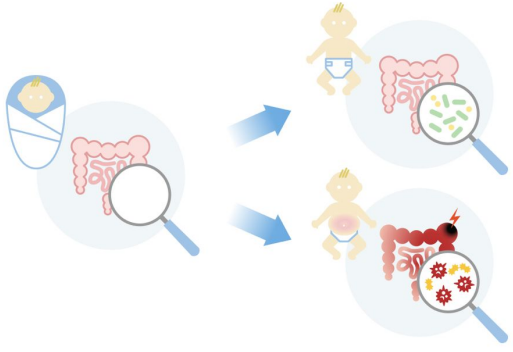
Lactobacillus reuteri present on women's breasts

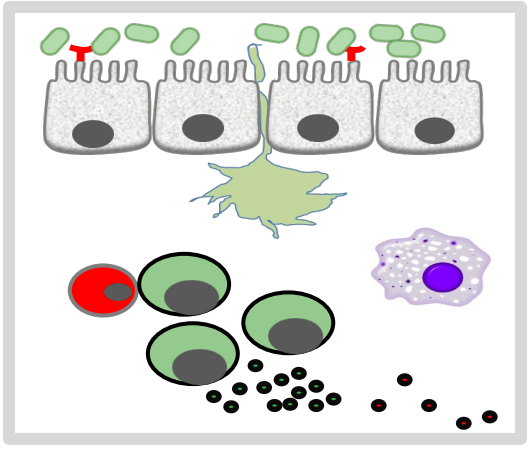


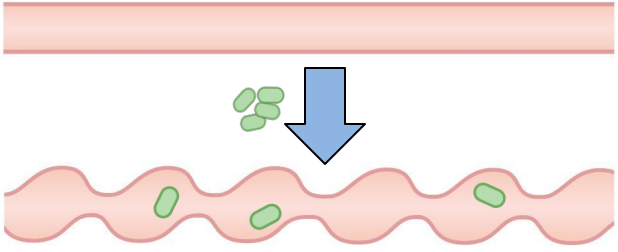
Lactobacillus reuteri (orange) adhering to intestinal mucus

Picture with the permission Versalovic

L. reuteri mechanisms of action







Combats dysbiosis

Reduces inflammation

Improves gut motility

Improved GUT function!

Short term: reduction of NEC and Sepsis

Long term: catch up growth for preterm leading to e.g. better cognitive function

CLINICAL EFFICACY SIGNAL – *L. reuteri*

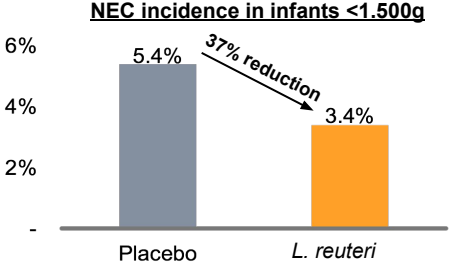
9 studies show clinically significant reduction of NEC

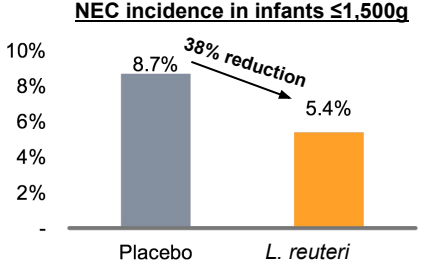
Study	Number of patients	Reduction in NEC incidence
Rojas et al. (2012)	▪ 750 patients	▪ 40% in the total study population ▪ 37% in infants ≤1,500g
Oncel et al. (2014)	▪ 400 patients	▪ 20% in the total study population ▪ 38% in infants ≤1,000g
Spreckels et al. (2018)	▪ 104 patients	▪ 53% in infants ≤1,000g
Hunter et al. (2012) & Dimaguila et al. (2013)	▪ 354 patients	▪ 89% in the total study population
Sanchez Alvarado (2017)	▪ 225 patients	▪ 64% in infants ≤1,500g
Rolnitsky et al. (2017)	▪ 937 patients	▪ 49% in the total study population
Jerkovic Raguz et al. (2016)	▪ 100 patients	▪ 50% in the total study population
Shadkam et al. (2015)	▪ 60 patients	▪ 82% in the total study population
Hernandez-Enriquez et al. (2016)	▪ 44 patients	▪ 92% in the total study population

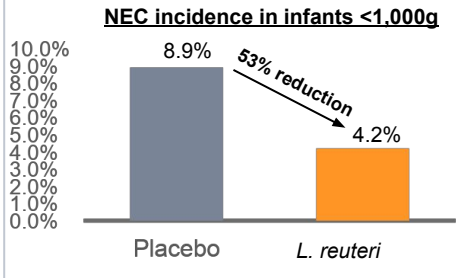
Clear clinical signal (1/4)

Randomised double-blind placebo-controlled clinical studies indicate reduction of NEC

	1 Rojas et al. (2012)	2 Oncel et al. (2014)	3 Spreckels et al. (2018)
Aim of the study	▪ Determine whether prophylactic administration of *L. reuteri* to pre-term infants reduces the incidence of the composite outcome of death or nosocomial infection	▪ Evaluate the effect of administration of *L. reuteri* on the incidence and severity of NEC and sepsis in very low-birth-weight infants	▪ Measure the colonization rate of *L. reuteri* and relate the colonization rate to antibiotic treatment and clinical outcomes
Target population	▪ Infants ≤2,000 g birth weight split into <1,500 and 1,501g-2,000g	▪ Infants ≤32 GA weeks and ≤1,500g birth weight	▪ Infants ≤28 GA weeks and <1,000g birth weight
Method	▪ Placebo-controlled trial conducted in 9 Columbian NICUs between 2008-2011	▪ Placebo-controlled trial conducted in Turkey between Feb-12 – Feb-13	▪ Placebo-controlled trial conducted in Sweden between 2012-2015
# of patients	▪ 750 patients (372 *L. reuteri* and 378 placebo)	▪ 400 patients (200 *L. reuteri* and 200 placebo)	▪ 104 patients (48 *L. reuteri* and 56 placebo)
Results	▪ 40% reduction in NEC incidence in the total study population ▪ 37% reduction in NEC incidence in infants ≤1,500g ▪ No infections and no adverse effects	▪ 20% reduction in NEC incidence in the total study population ▪ 38% reduction in NEC incidence in infants ≤1,000g ▪ No infections and no adverse effects	▪ 53% reduction in NEC incidence in infants ≤1,000g

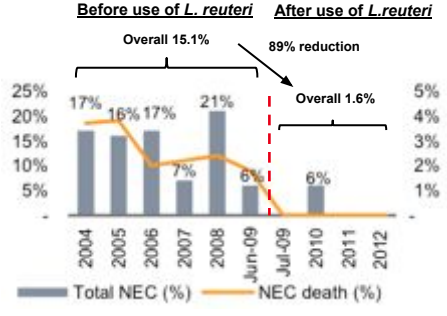
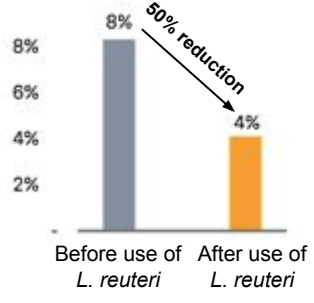






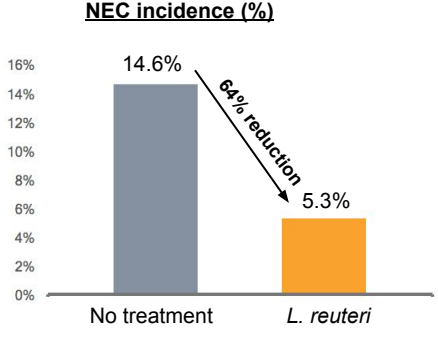
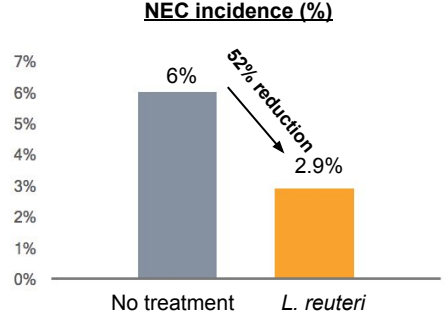
Clear clinical signal (2/4)

Retrospective cohort clinical studies indicate reduction of NEC

	4 Hunter et al. (2012) & Dimaguila et al. (2013)	5 Jerkovic Raguz et al. (2016)
Aim of the study	▪ Examine the potential benefit of administering *L. reuteri* on the rate of NEC in extremely low-birth-weight infants	▪ Analyse the treatment, course and outcome of premature infants treated with *Lactobacillus reuteri*
Target population	▪ Infants ≤1,000g birth weight	▪ Premature infants of GA between 30-34 weeks
Method	▪ Retrospective comparison of the rates of NEC in neonates before and after the introduction of *L. reuteri* routine use	▪ Retrospective cohort study with comparison of outcomes before and after the introduction of *L. reuteri*.
# of patients	▪ 354 patients (232 before and 122 after the introduction of *L. reuteri)*	▪ 100 patients (50 before and 50 after the introduction of *L. reuteri*)
Results	▪ Reduction in NEC incidence in neonates who received *L. reuteri* (2.5%) vs. others (15.1%) ▪ Additional data from Dimaguila et al. (2013) (1.6% vs. 15.1%) ▪ No infections and no adverse effects 	▪ The incidence of NEC was reduced from 8% to 4% after the initiation of *L. reuteri* use **NEC incidence in all enrolled infants** 

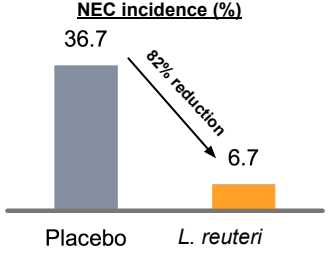
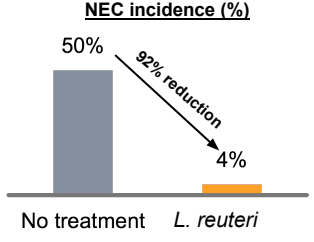
Clear clinical signal (3/4)

Retrospective cohort clinical studies indicate reduction of NEC

	6 Sanchez Alvarado (2017)	7 Rolnitsky et al. (2017)
Aim of the study	▪ Demonstrate that the use of *Lactobacillus reuteri* prevents NEC in premature infants <1,500g birth weight	▪ Quality improvement study to reduce NEC rates in infants in the NICU by treating with *Lactobacillus reuteri*
Target population	▪ Infants ≤1,500g birth weight	▪ Premature infants of GA <33 weeks
Method	▪ Retrospective comparison of medical records of infants treated or not treated with *L. reuteri*	▪ Retrospective cohort study with comparison of outcomes before and after the introduction of *L. reuteri*.
# of patients	▪ 225 patients (75 on *L. reuteri* and 150 controls)	▪ 937 patients (330 before and 607 after the introduction of *L. reuteri*)
Results	▪ NEC incidence was reduced from 14.6% to 5.3% with *L. reuteri* use ▪ Number needed to treat (NNT): 11 	▪ NEC incidence was reduced from 6.0% to 2.9% in infants <1,500g birth weight after the initiation of *L. reuteri* use 

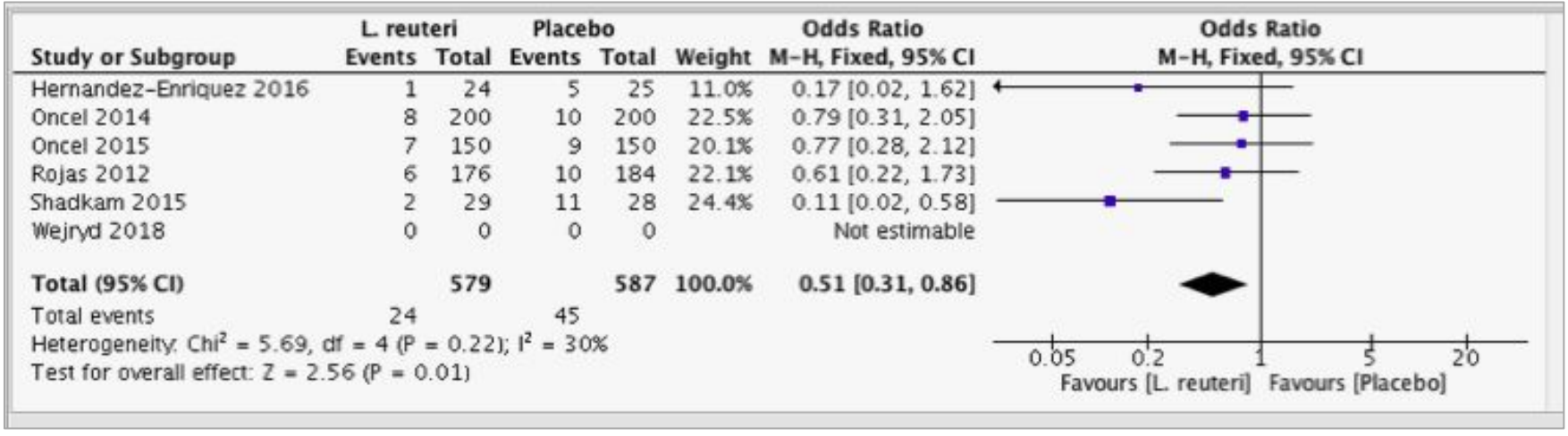
Clear clinical signal (4/4)

Other studies indicating reduction of NEC

	8 Shadkam et al. (2015)	9 Hernandez-Enriquez et al. (2016)
Aim of the study	▪ Evaluate the effects of *Lactobacillus reuteri* on the gastrointestinal complications and feeding tolerance in premature infants	▪ Evaluate the effectiveness of the use of *Lactobacillus reuteri* to reduce the incidence of NEC in infants with very low birth weight
Target population	▪ Premature infants with weight between 1,000 – 1,800g	▪ Very low birth weight infants < 1,500g and GA < 34 weeks
Method	▪ Randomised blinded clinical trial conduced at NICU between October 2012 – March 2013	▪ Randomised controlled trial conducted in a Mexican NICU between May 2012 and May 2013
# of patients	▪ 60 patients (30 *L. reuteri* and 30 placebo)	▪ 44 patients (24 *L. reuteri* and 20 no treatment)
Results	▪ Incidence of NEC in infants administered with *L. reuteri* (6.7%) was lower than the placebo group (36.7%) 	▪ The incidence of suspected NEC was much lower in the group that received *L reuteri* (1/24, 4%) vs. the group that received no treatment (10/20, 50%) 

NEC clinical signals

Incidence of NEC



Meta-analysis: NEC <1500g all randomized controlled trials gives an Odds Ratio of 0.51

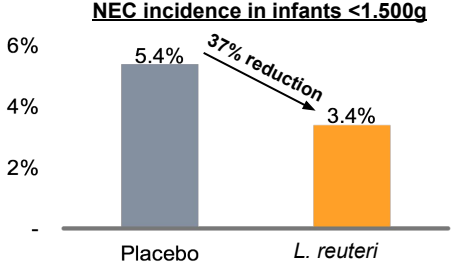
L. reuteri demonstrates clear signal on improved feeding tolerance

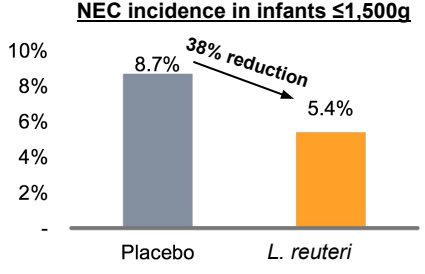
Study	Number of patients	Results
Rojas et al. (2012)	▪ 750 patients	▪ 34% reduction in episodes of feeding intolerance (p=0.08)
Oncel, et al. (2014)	▪ 400 patients	▪ 29% reduction in episodes of feeding intolerance (p=0.015)
Oncel et al. (2015)	▪ 300 patients	▪ 36% reduction in episodes of feeding intolerance (p=0.004)
Rolnitsky et al. (2018)	▪ 937 patients	▪ 52% reduction in episodes of feeding intolerance (p<0.01)

Clear clinical signal (1/2)

Randomised double-blind placebo-controlled clinical studies indicate improved feeding tolerance

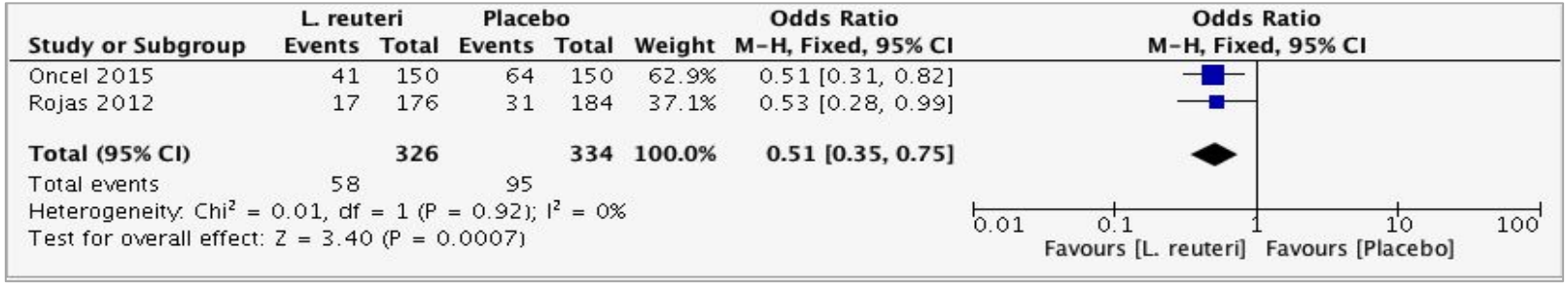
	1 Rojas et al. (2012)	2 Oncel et al. (2014)
Aim of the study	▪ Determine whether prophylactic administration of *L. reuteri* to pre-term infants reduces the incidence of the composite outcome of death or nosocomial infection	▪ Evaluate the effect of administration of *L. reuteri* on the incidence and severity of NEC and sepsis in very low-birth-weight infants
Target population	▪ Infants ≤2,000 g birth weight split into <1,500 and 1,501g-2,000g	▪ Infants ≤32 GA weeks and ≤1,500g birth weight
Method	▪ Placebo-controlled trial conducted in 9 Columbian NICUs between 2008-2011	▪ Placebo-controlled trial conducted in Turkey between Feb-12 – Feb-13
# of patients	▪ 750 patients (372 *L. reuteri* and 378 placebo)	▪ 400 patients (200 *L. reuteri* and 200 placebo)
Results	▪ 40% reduction in NEC incidence in the total study population ▪ 37% reduction in NEC incidence in infants ≤1,500g ▪ No infections and no adverse effects	▪ 20% reduction in NEC incidence in the total study population ▪ 38% reduction in NEC incidence in infants ≤1,000g ▪ No infections and no adverse effects





Feeding tolerance – clinical signals

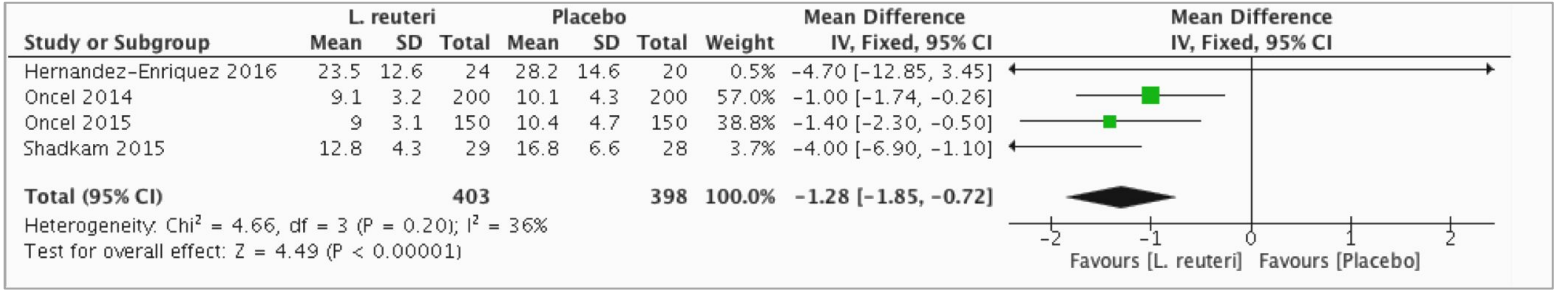
Reported feeding intolerance events



Study or Subgroup	L. reuteri Events	L. reuteri Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Oncel 2015	41	150	64	150	62.9%	0.51 [0.31, 0.82]
Rojas 2012	17	176	31	184	37.1%	0.53 [0.28, 0.99]
Total (95% CI)		**326**		**334**	**100.0%**	**0.51 [0.35, 0.75]**
Total events	58		95			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%
Test for overall effect: Z = 3.40 (P = 0.0007)

Time to full enteral feeding



Study or Subgroup	L. reuteri Mean	L. reuteri SD	L. reuteri Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Hernandez-Enriquez 2016	23.5	12.6	24	28.2	14.6	20	0.5%	-4.70 [-12.85, 3.45]
Oncel 2014	9.1	3.2	200	10.1	4.3	200	57.0%	-1.00 [-1.74, -0.26]
Oncel 2015	9	3.1	150	10.4	4.7	150	38.8%	-1.40 [-2.30, -0.50]
Shadkam 2015	12.8	4.3	29	16.8	6.6	28	3.7%	-4.00 [-6.90, -1.10]
Total (95% CI)			**403**			**398**	**100.0%**	**-1.28 [-1.85, -0.72]**

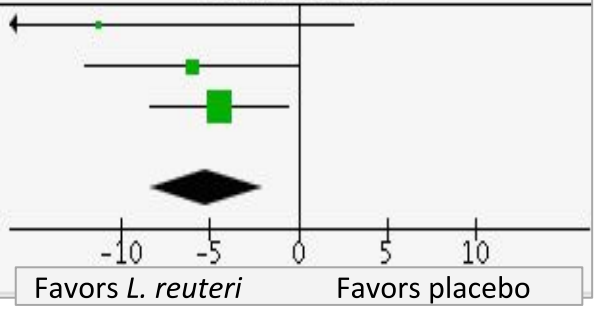
Heterogeneity: Chi² = 4.66, df = 3 (P = 0.20); I² = 36%
Test for overall effect: Z = 4.49 (P < 0.00001)

Hospital stay – clinical signal

Study or Subgroup	L. reuteri Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Hernandez-Enriquez 2016	39.3	22.8	24	50.6	25.4	20	4.9%	-11.30 [-25.69, 3.09]
Oncel 2015	42.4	24.1	150	48.4	29.2	150	27.9%	-6.00 [-12.06, 0.06]
Rojas 2012	32.5	17	176	37	20.7	184	67.2%	-4.50 [-8.41, -0.59]
Total (95% CI)			**350**			**354**	**100.0%**	**-5.25 [-8.46, -2.05]**

Heterogeneity: $Chi^2 = 0.88$, $df = 2$ ($P = 0.64$); $I^2 = 0\%$

Test for overall effect: $Z = 3.22$ ($P = 0.001$)



PLAN ENDORSED BY STAKEHOLDERS – Regulatory agencies and KOLs

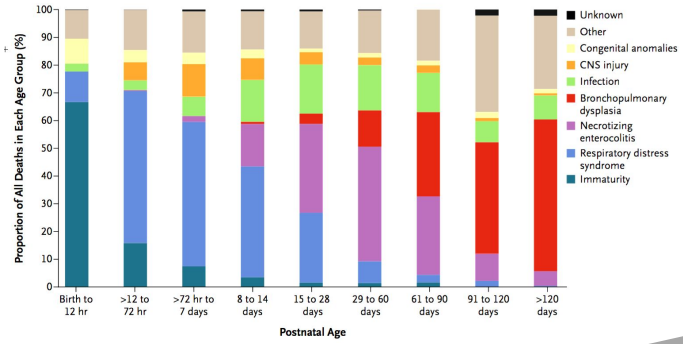
Network of KOLs

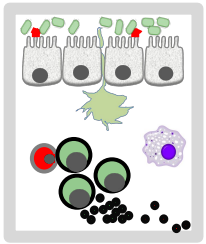
IBT has developed the IBP-9414 program with deep considerations of KOLs experience and clinical practice

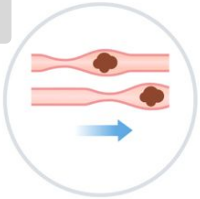
Some of the external medical experts

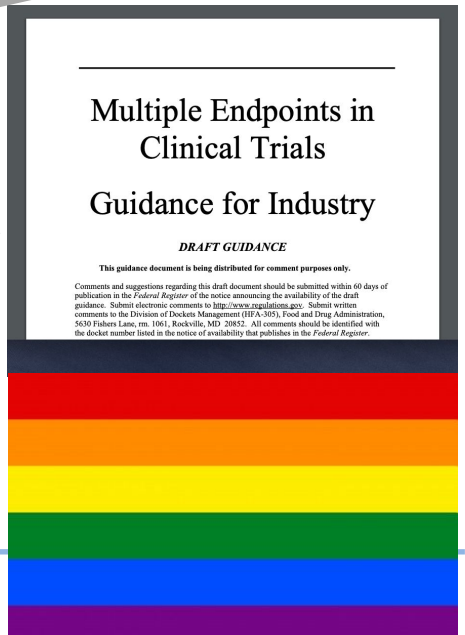
Aideen Moore, The Hospital for Sick Children, Toronto, Canada.
Alexandre Lapillonne, Necker Hospital for Sick Children, Paris, France
Andreas Repa, Medical University of Vienna, Austria
Hans van Goudoever, VU University Medical Center and Emma Children's Hospital, Amsterdam, the Netherlands
Jae Kim, University of California San Diego, CA
Josef Neu, University of Florida College of Medicine, Gainesville, FL
Kara Calkins, University of California Los Angeles School of Medicine, CA
Lawrence Moss, Nationwide Children's Hospital, Columbus, OH
Mario Rojas, University of Wake Forest University School of Medicine, NC
Mark Underwood, University of California Davis Children's Hospital, CA
Michael Caplan, North Shore Research Institute, Chicago, IL
Miguel Sáenz de Pipaon, University Hospital "La Pa", Madrid, Spain
Robert White, Memorial Hospital, South Bend MI
Teresa del Moral, University of Miami School of Medicine, FL
Thomas Abrahamsson, Linköping University Hospital, Sweden
Walter Mihatsch, Harlaching Hospital, Munich, Germany

FDA meeting - November 20









Two Primary Endpoint

"NEC and/or Feeding tolerance"

Additional Endpoints **NEC**	Additional Endpoints **Feeding**
Medical NEC Surgical NEC	Time to full feed
etc	Hospital days
	etc


STRONG INTEREST FROM THE MARKET

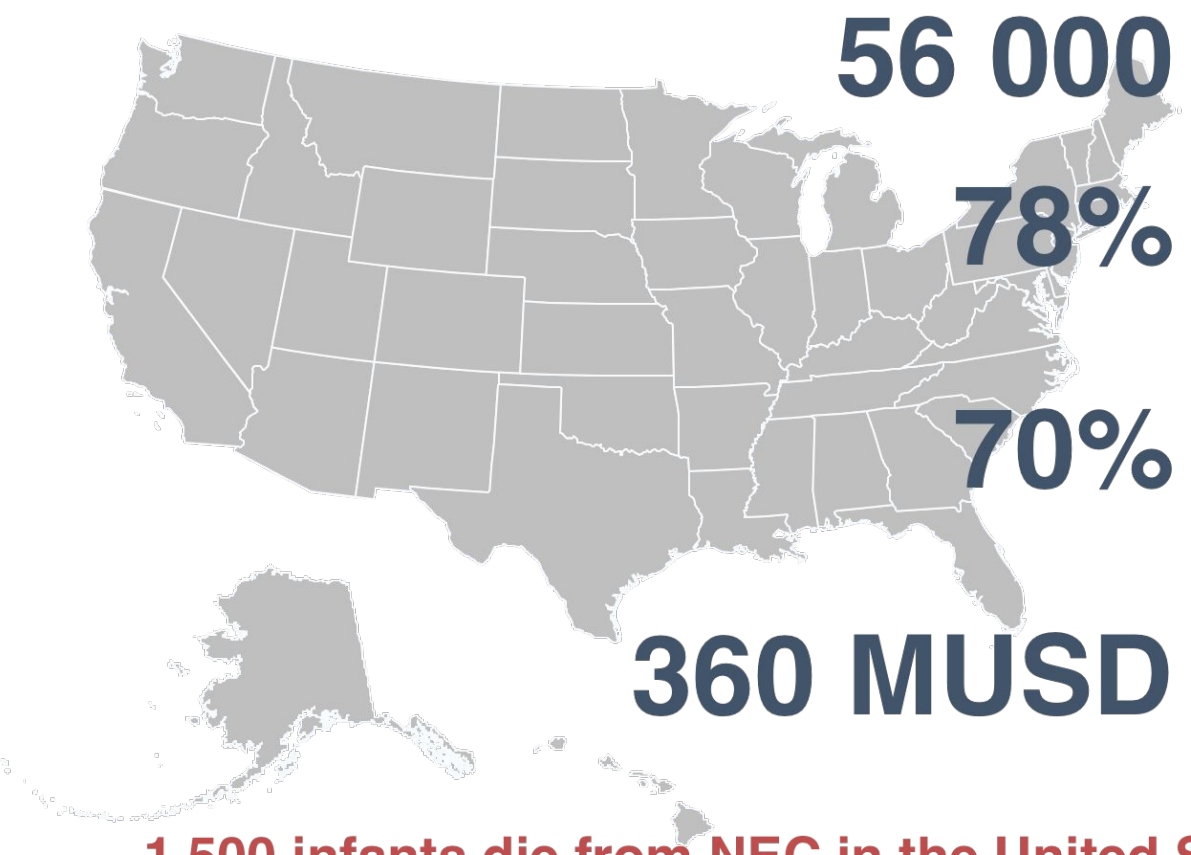
IBP-9414 Target Product Profile

For the prevention of necrotizing enterocolitis

Product description	▪ Oral suspension ▪ Supplied as a freeze-dried powder in a prefilled, clear, glass vial ▪ To be reconstituted in sterile water and delivered in enteral syringe
Administration	▪ Once daily until gestational age 34 weeks ▪ Administered enterally through the nasogastric or orogastric tube
Product efficacy	▪ Demonstrates 33% reduction in the incidence of NEC compared to standard of care alone
Safety profile	▪ Well tolerated with no known side effects ▪ No increase in risk of sepsis or multi-resistance to antibiotics ▪ No known contraindications

A valuable pharmaceutical

Results of market analysis by ClearView Healthcare Partners



56 000

Number of infants born under 1,500 grams in the United States annually

78%

Physician preference share demonstrates neonatologists show high willingness to prescribe IBP-9414

70%

Of addressable patients are anticipated to receive care at an institution that includes IBP-9414 on formulary

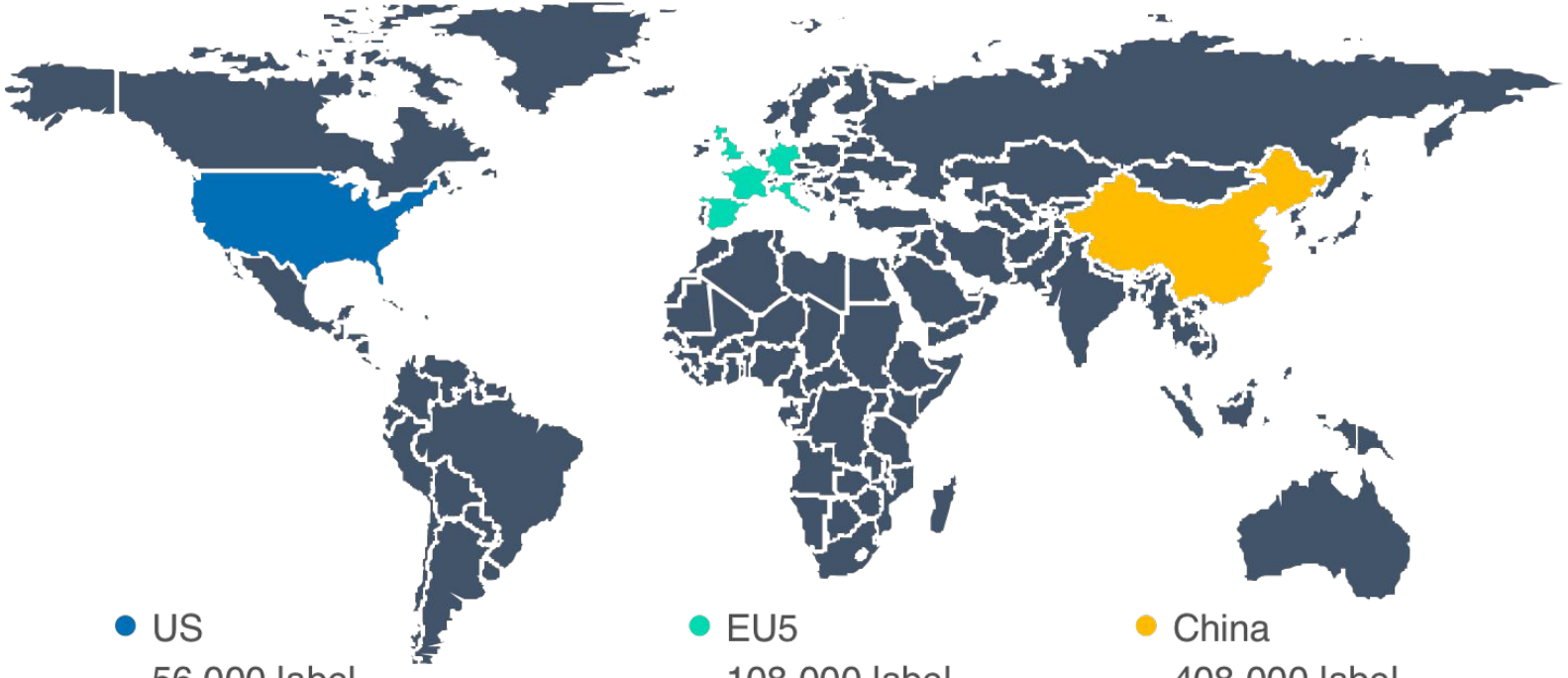
360 MUSD

Estimated annual revenue potential in US based on ClearView market research

1 500 infants die from NEC in the United States each year

A global need

15 Million Pre-term births annually



- US
  56 000 label population = 360 MUSD annual sales for NEC prevention
- EU5
  108 000 label population
- China
  408 000 label population

Plan for 2019 and beyond

- Commence Phase III - “The Connection Study” that IBT needs to register the IBP-9414 drug to allow sales of product (CTA/IND filed in US, UK, FR, SP, HU and hopefully this week in Israel)

- Finding good partners, e.g. like Megapharm in Israel, for distribution of the IBP-9414 drug around the world.

- Market research to better understand the markets behavior around “poor gut function and feeding problems in preterm babies”

- Progress the Gastroschisis project, IBP-1016, and possibly two additional possible indications based on *L. reuteri*

- Explore New Live Bacterial Platforms: New patent possibilities, not necessarily involving the use of *L. reuteri* bacteria

IBP-9414 our lead Phase III program

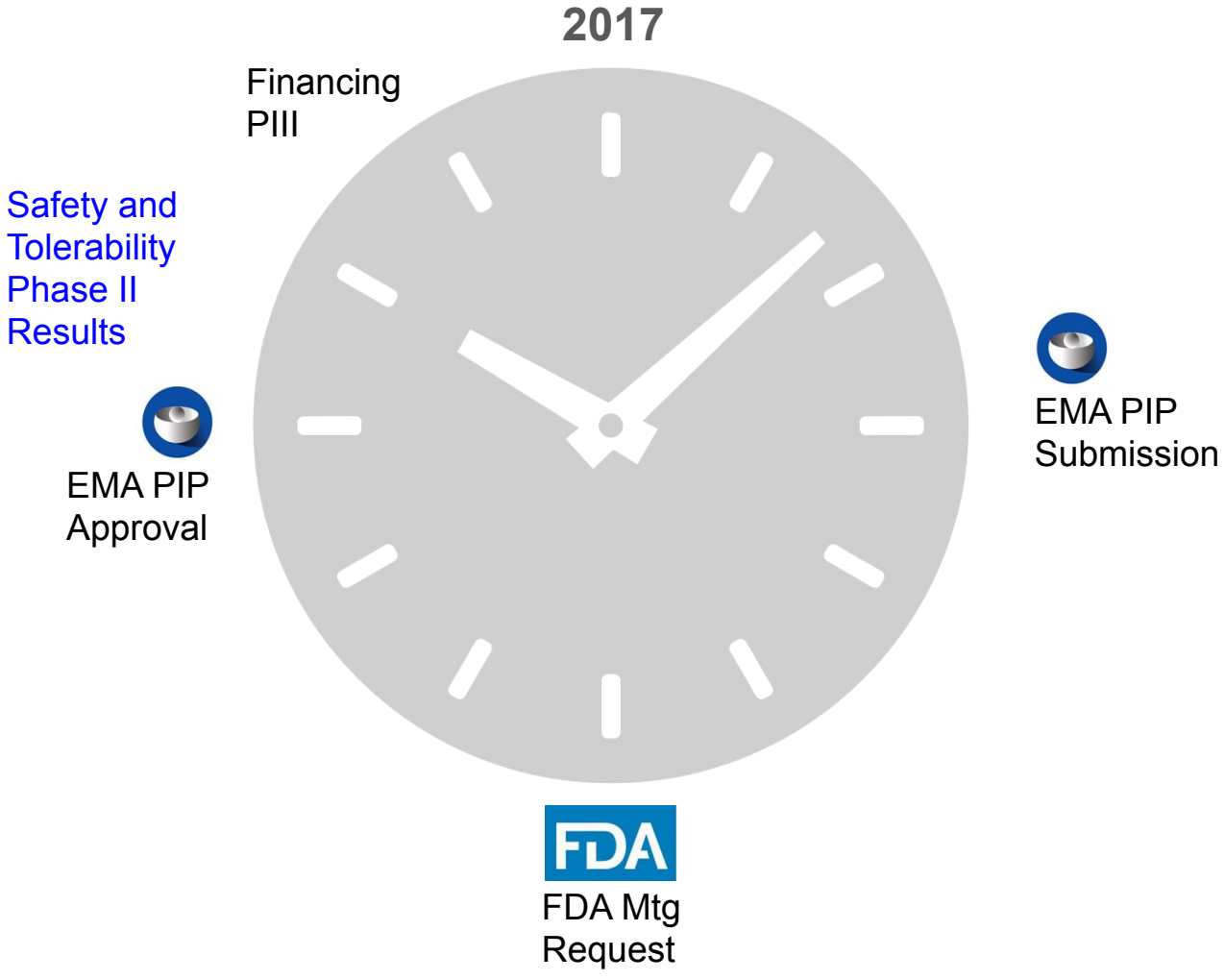
Ticks all relevant pillars for the development of a successful drug

Medical need	✓
Mechanism of action	✓
Clinical data	✓
Safe	✓
Aligned regulatory agencies	✓
GMP manufacture	✓
Market exclusivity	✓
Aligned payers	✓

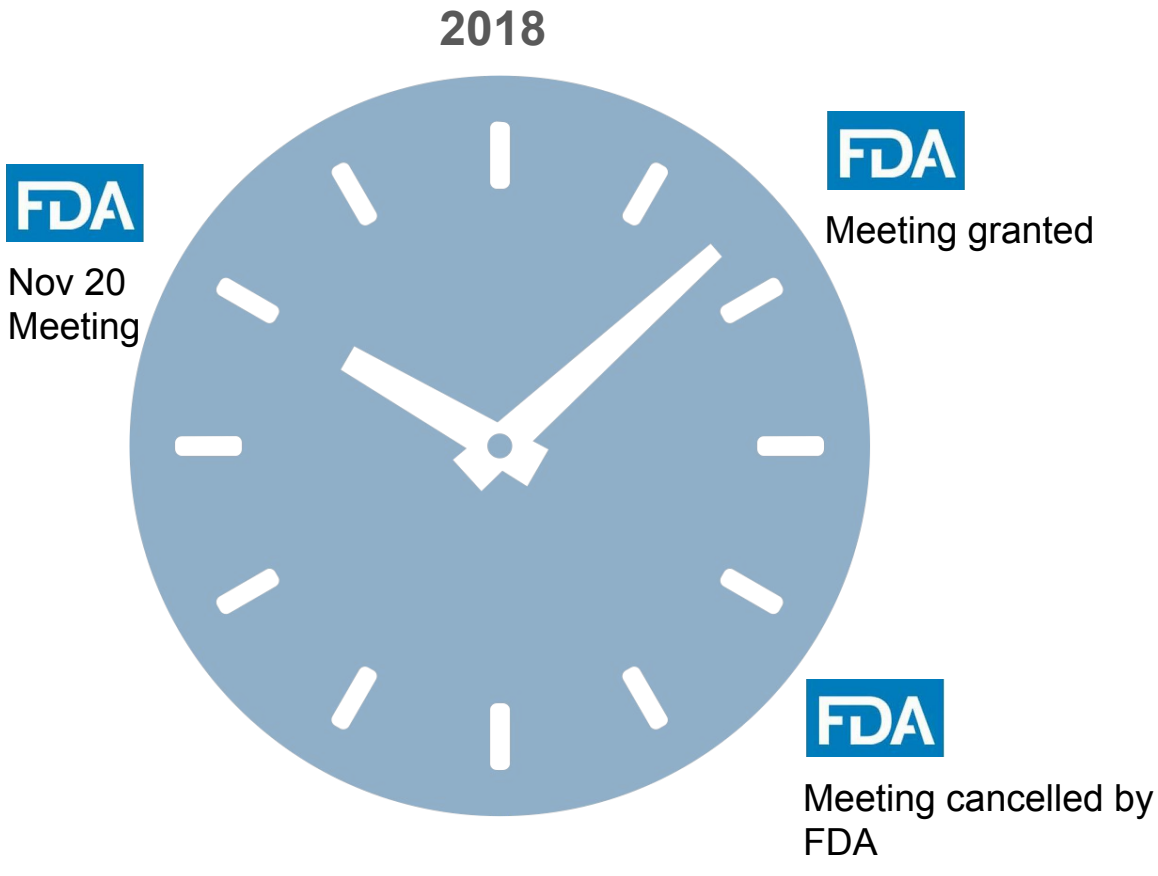
Thank you

Infant Bacterial Therapeutics AB
+46 (0) 8 410 145 55
www.ibtherapeutics.com

Continuous interactions with regulators



Continuous interactions with regulators



Continuous interactions with regulators

2019

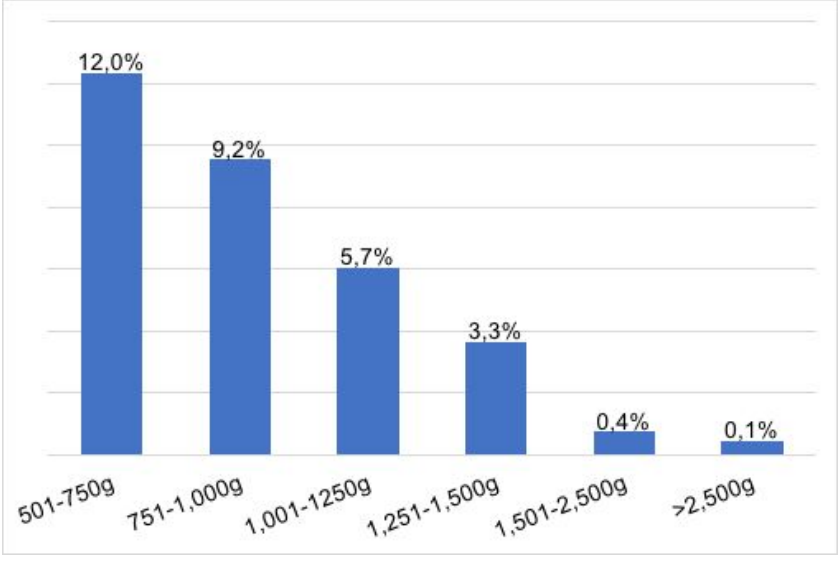
FDA Interactions and Submissions UK, FR, ES, HU IL

Planned study start

NEC – a devastating disease

The smaller the premature infant is at birth, the more likely he/she will die

NEC incidence rate



NEC mortality rate

501-750g	42.0%
751-1,000g	29.4%
1,001-1250g	21.3%
1,251-1,500g	15.9%
1,501-2,500g	12,7%

Shelley 2012, Bolisetty 2000, Llanos 2002, Fitzgibbons 2009, Abdullah 2010, Christensen 2010

Infant Bacterial Therapeutics

Overview

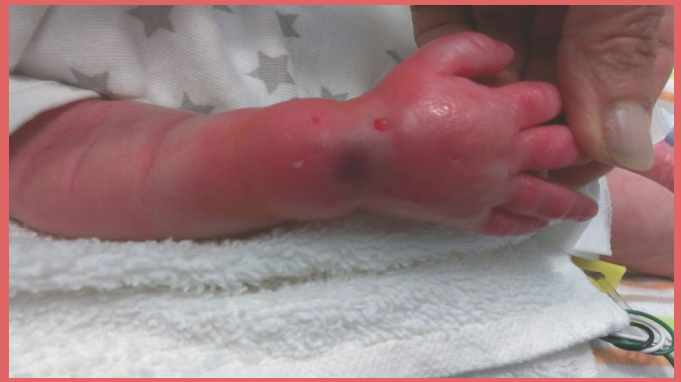
- Pharmaceutical microbiome company focused on areas of unmet medical need
- Lead drug candidate IBP-9414, to prophylactically prevent necrotizing enterocolitis ("NEC"), a fatal, rare disease that afflicts premature infants and reduce feeding intolerance in the same patient group
- Opportunity for second rare disease program IBP-1016 for the treatment of an unmet medical need in gastroschisis, a severe disease in infants

- Orphan Drug Designation from FDA and EMA
- Rare Pediatric Disease Designation granted
- Exclusive royalty free worldwide license to patents
- Market Approval for IBP-9414 target 2021

- Financial resources sufficient finance development to application for market approval
- Listed on Nasdaq Stockholm Mid-Cap IBTB:SS,
- Third party assessed opportunity - USD 360m in US market for IBP-9414
- Priority Review Voucher eligible

Feeding the preterm infant

- Prolonged parenteral (needle feeding) nutrition increases cost and causes complications: cholestasis, increased risk of BPD, pulmonary vascular resistance, infections and sepsis.

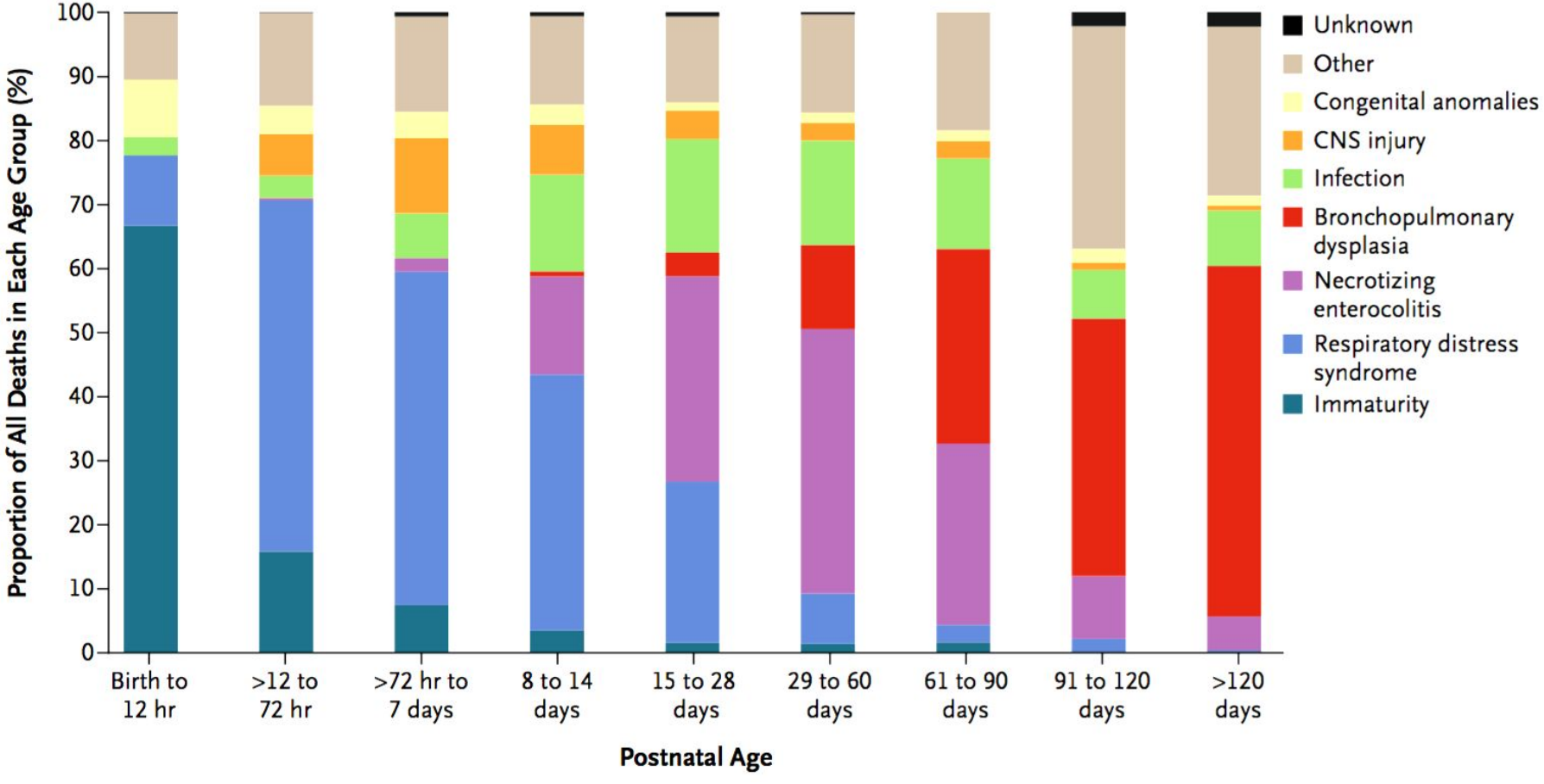


- Establishing enteral (mouth) feeding is one important goal in preterm infants
for “catch up growth”, for development and to combat intestinal damage.

Despite intensive nutritional strategies for premature infants, growth failure remains a major problem

Murgas-Torrazza, 2013; Agostoni, 2010

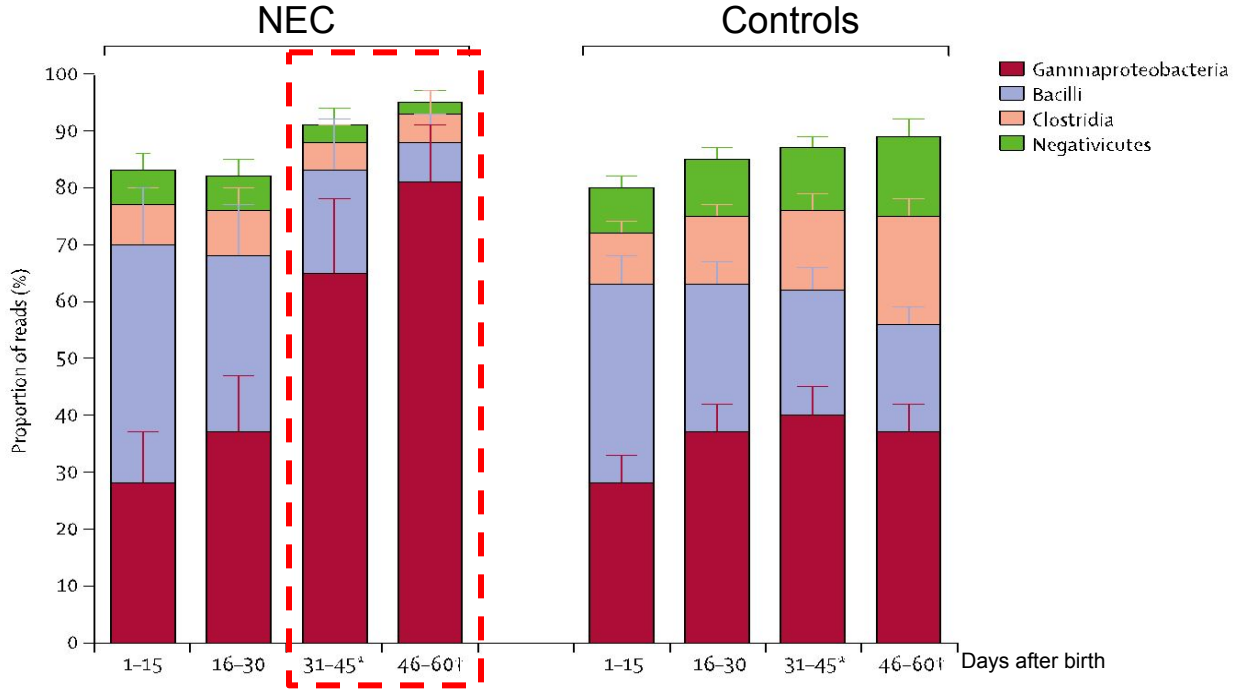
Causes of death



Patel 2015

Dysbiosis in NEC

Dysbiosis with pathogen blooms in the microbiota can contribute to necrotizing enterocolitis in preterm infants



Bloom of pathogen-rich gamma proteobacteria prior to onset of NEC

Microbiome optimization may provide a novel strategy for preventing NEC

Warner et al, 2016, Pammi et al. 2017

Anti-pathogen effects *in vitro*

L. reuteri produces species-specific antimicrobial substance called reuterin

Bacteria

- *Bacillus subtilis*
- *Listeria monocytogenes*
- *Campylobacter jejuni*
- *Porphyromonas gingivalis*
- *Clostridium perfringens*
- *Prevotella intermedia*
- *Clostridium difficile*
- *Pseudomonas fluorescens*
- *Escherichia coli (patogena)*
- *Salmonella typhimurium*
- *Enterobacter sakazakii*
- *Shigella spp*
- *Fusobacterium nucleatum*
- *Staphylococcus aureus*
- *Helicobacter pylori*
- *Streptococcus mutans*

Yeast and fungi

- *Candida albicans*
- *Aspergillus flavus*
- *Fusarium samiaciens*

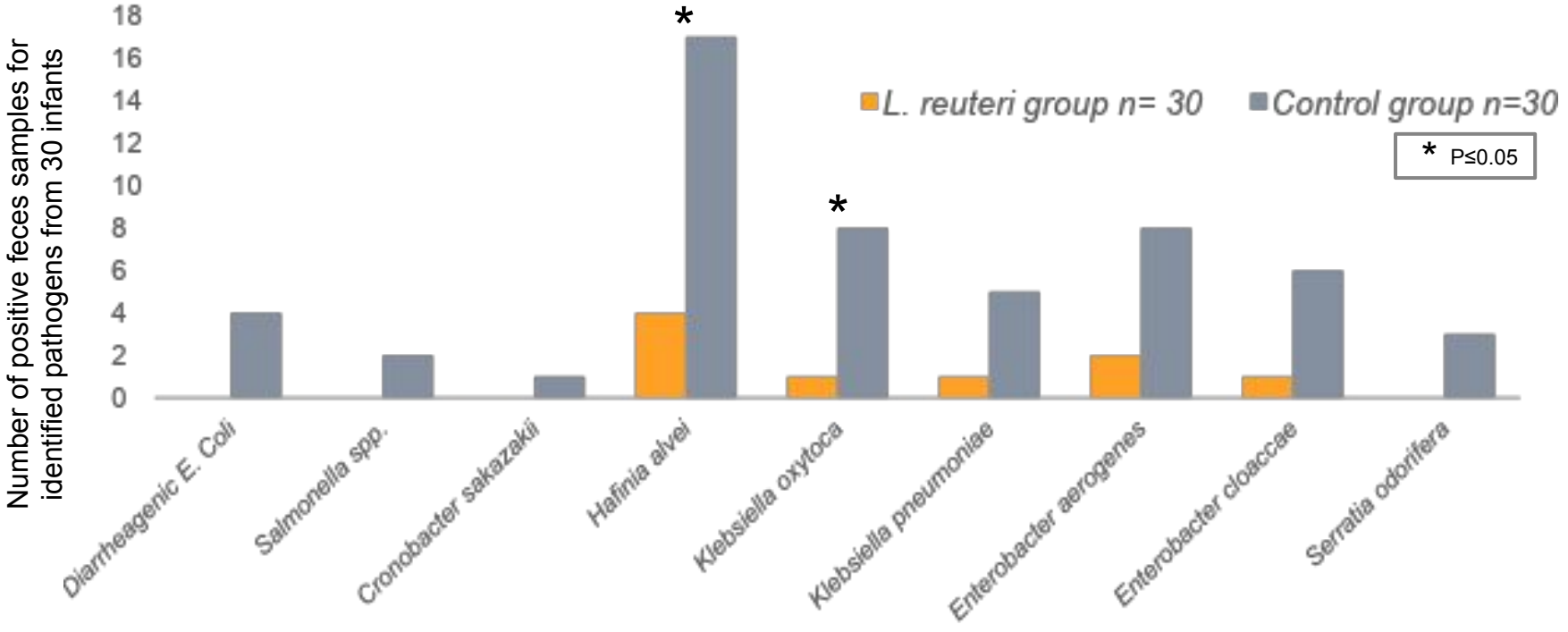
L. reuteri* inhibits *S. aureus

L. reuteri inhibits the growth of pathogens

Talarico 1988; Axelsson, 1989; Morita, 2008; Spinler 2008; Schaefer 2010; Savino 2015

Anti-pathogen effects in infants

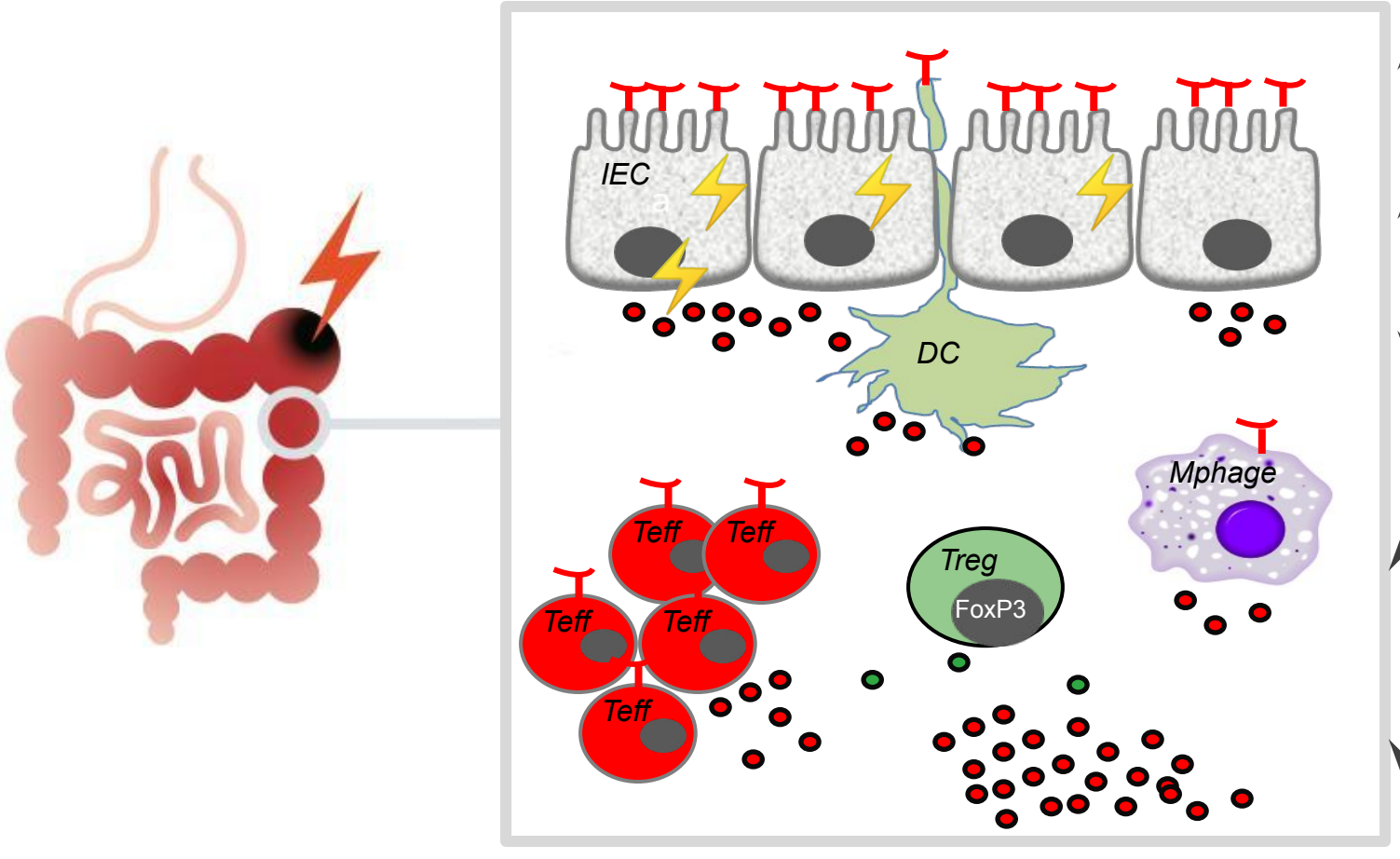
Infant fecal pathogens after 1 month *L. reuteri* treatment



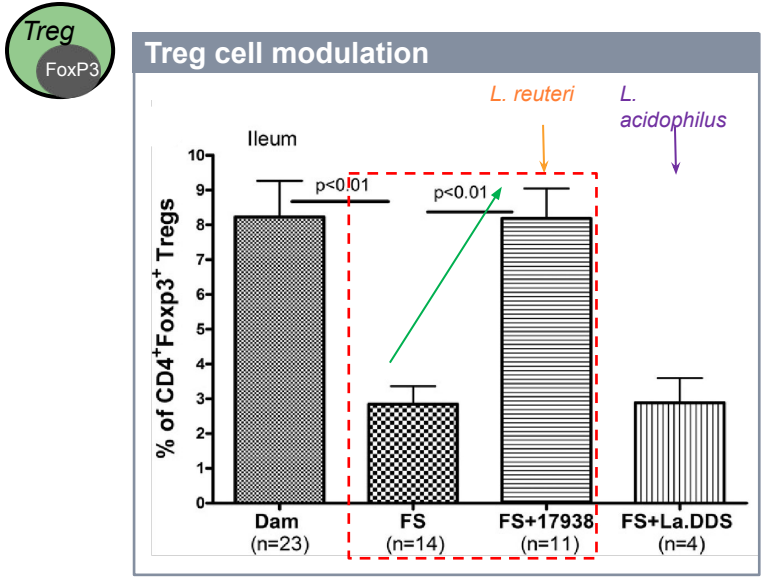
***L. reuteri* decreased gut pathogen colonization in infants**

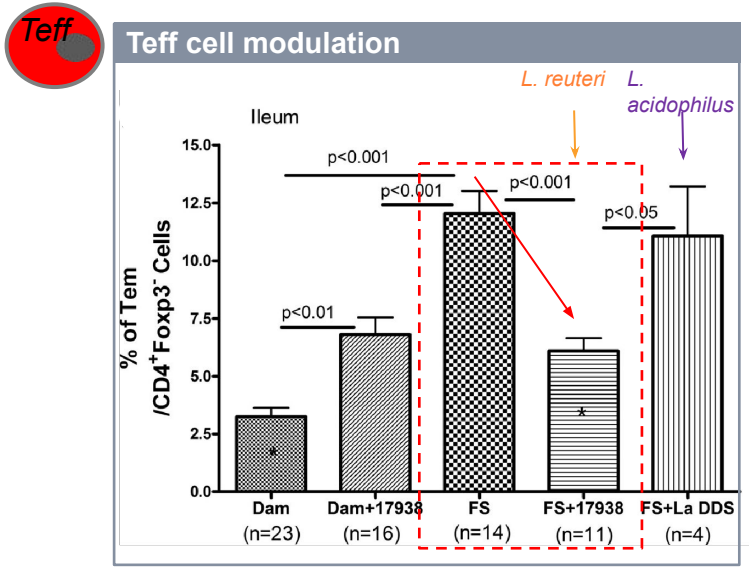
Savino 2015

Inflammation



Strain specific anti-inflammation in rodents



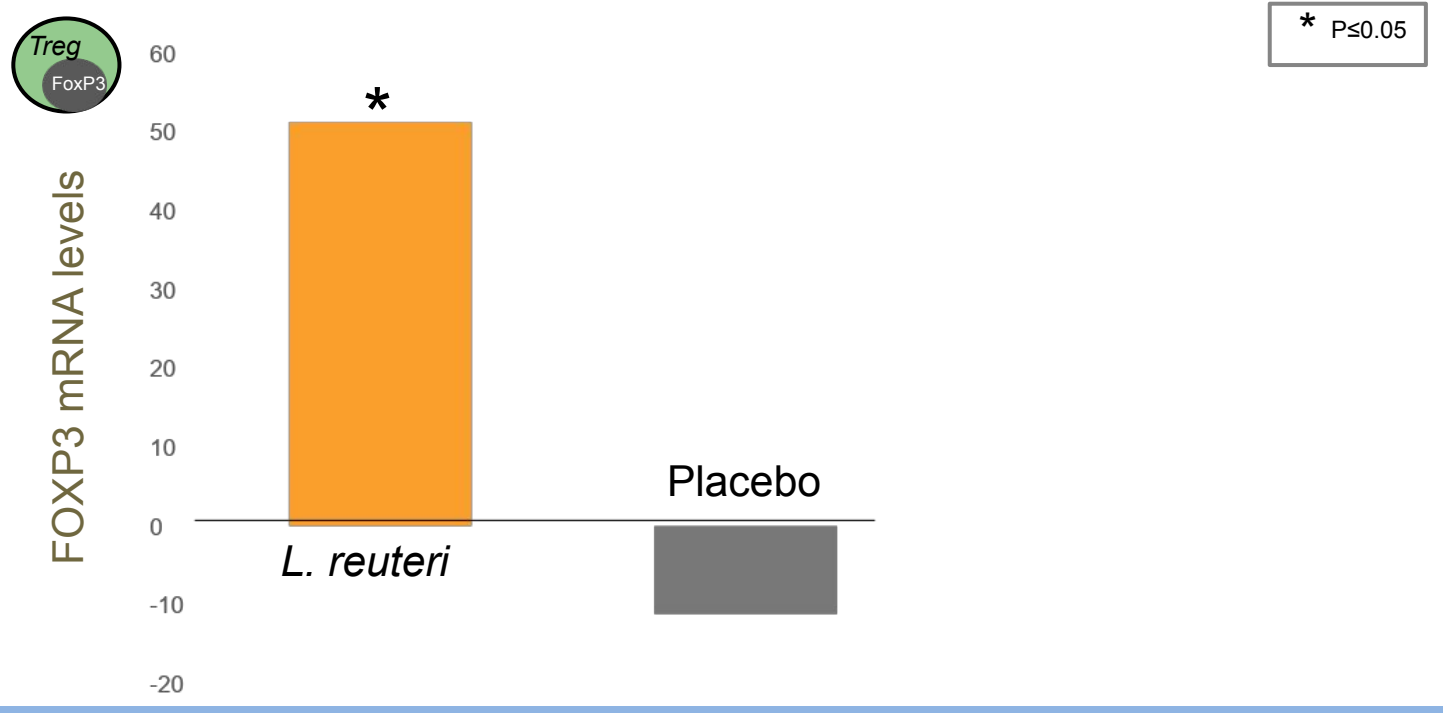


***L. reuteri has* strain specific anti-inflammatory activity through recruitment of Treg cells and down regulation of Teff cells**

Liu 2014

Anti-inflammatory in infants

Treg cells increase in infant blood after *L. reuteri* administration

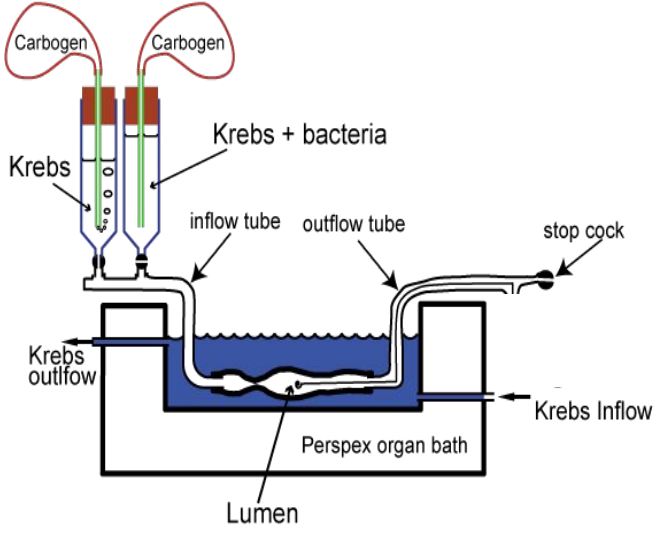


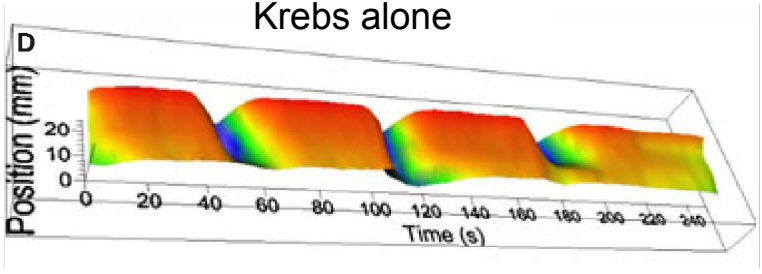
***L. reuteri* recruitment of Treg cells now shown in infants**

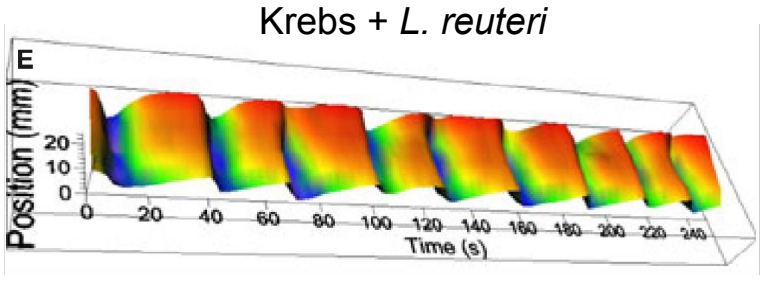
Savino 2017

L. reuteri improves gut motility *ex vivo*

Spatiotemporal mapping of mouse gut motility







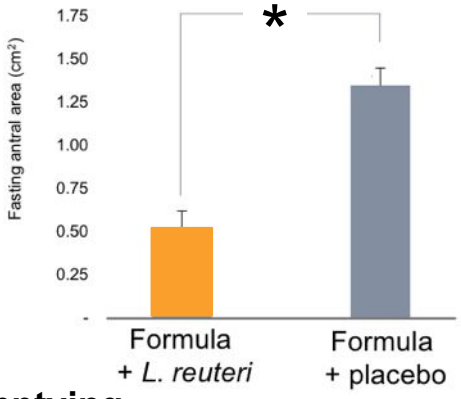
Colon motility increased within minutes of *L. reuteri* addition

Effect is strain specific and gut region specific

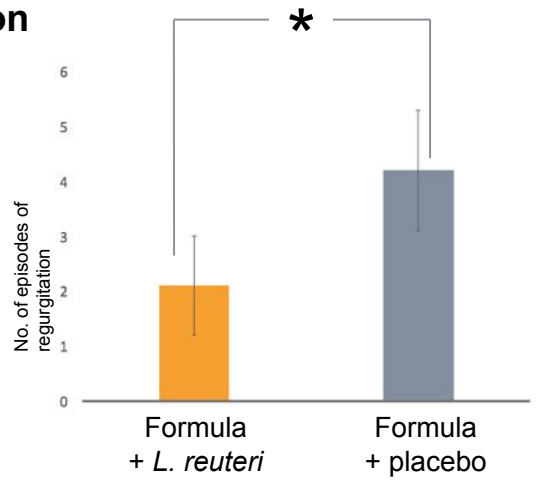
Wu 2013

Modulation of gut motility in preterm infants

Fasting antral area

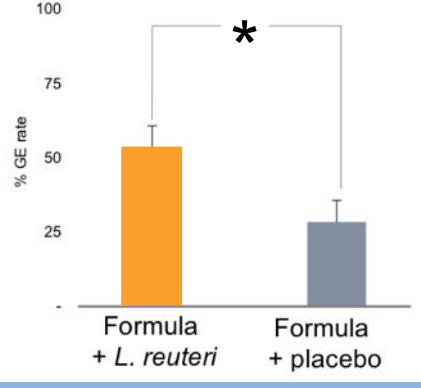


Regurgitation

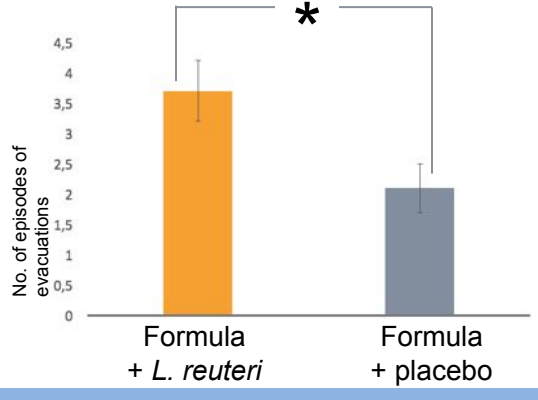


* P≤0.05

Gastric emptying



Stooling



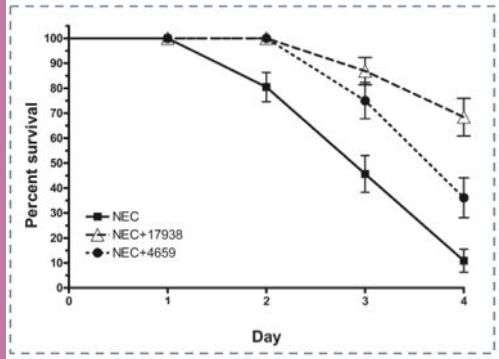
Preterm infants given *L. reuteri* show improved gut emptying

Indrio 2008

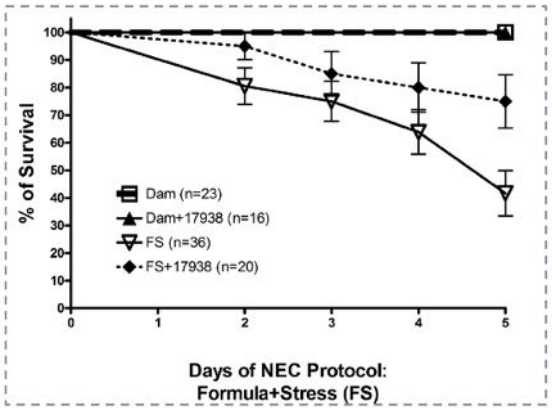
Protection against NEC in animal models

L. reuteri increases survival reproducibly in NEC model

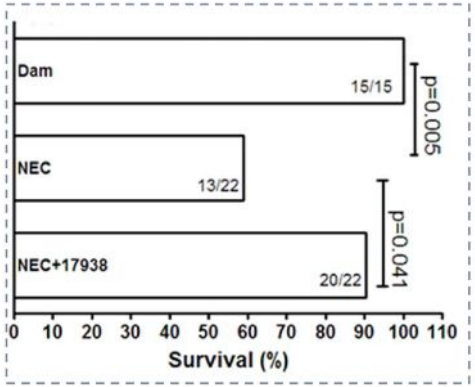
Experiment 1 in rat, 2012



Experiment 2 in mouse, 2013



Experiment 3 in rat, 2014



L. reuteri reduces NEC in rodent models

Liu, 2012 & Liu 2013 (rat), Liu 2014 (mouse)