# Infant Bacterial Therapeutics

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# Infant Bacterial Therapeutics AB

## Founded in 2013 in Stockholm, Sweden

## IPO in 2016, listed on Nasdaq Stockholm

- Market cap SEK 1 800 M ($190 M)
- Cash position as of September 30, 2019 SEK 511 M ($53 M) sufficient to fund IBP-9414 development to market

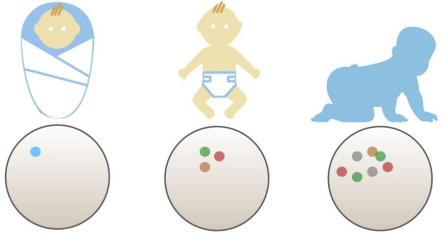
## Pivotal Phase III Trial for lead development program IBP-9414

- Patients recruited in EU and USA
- Orphan Drug Designation in EU and USA
- Rare Pediatric Disease Designation

# The IBT concept

- Establish the human microbiome to treat diseases related to poor gut function

- Newborn infant microbiome is dynamic



- Human bacterial strains derived from human breast milk

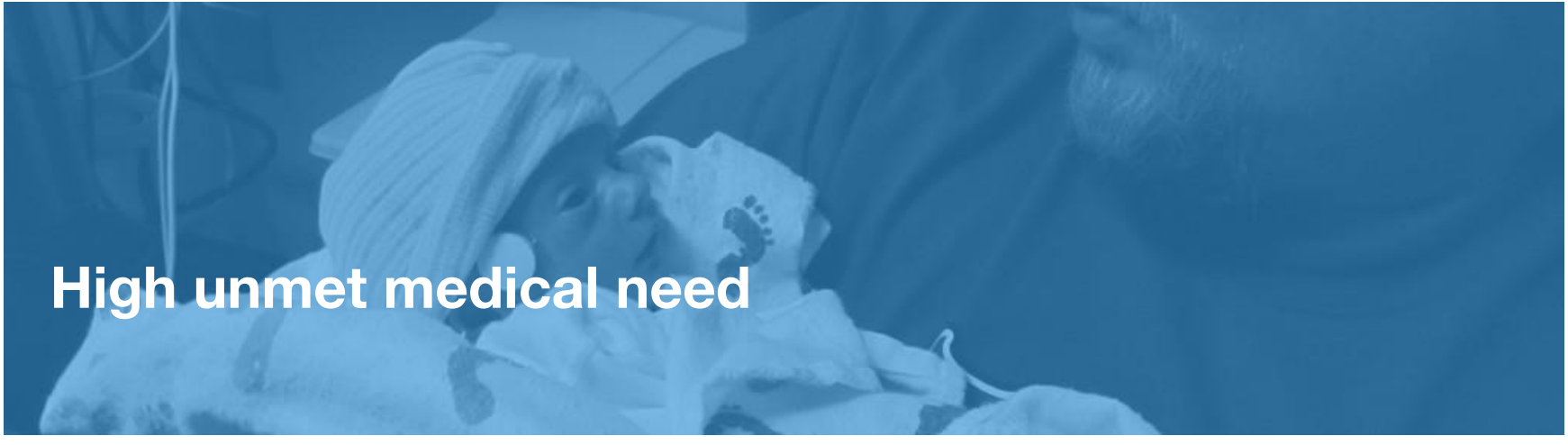
- Published clinical proof-of-concept signal

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

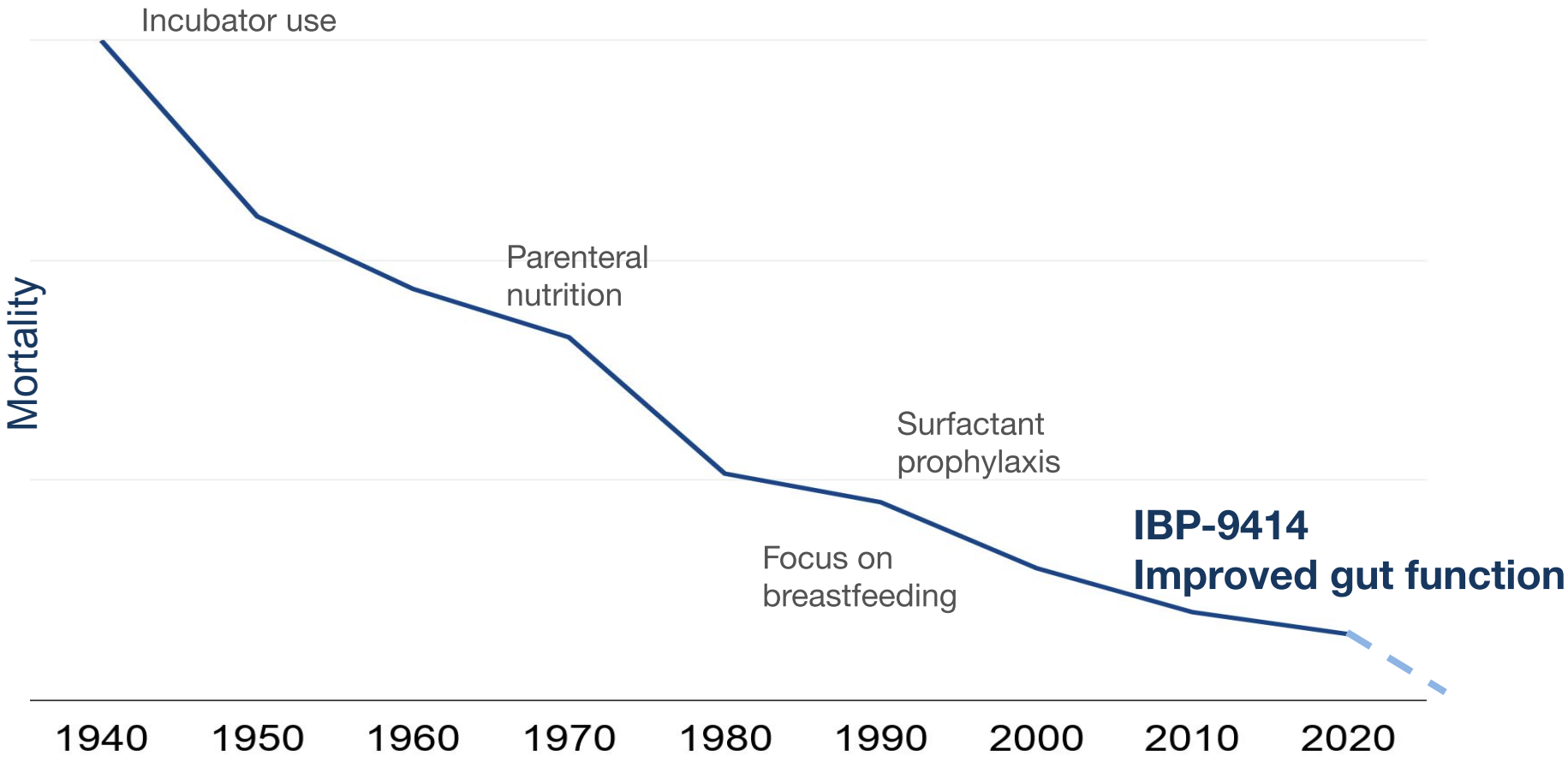
**Prophylactic Probiotics to Prevent Death and Nosocomial Infection in Preterm Infants**

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

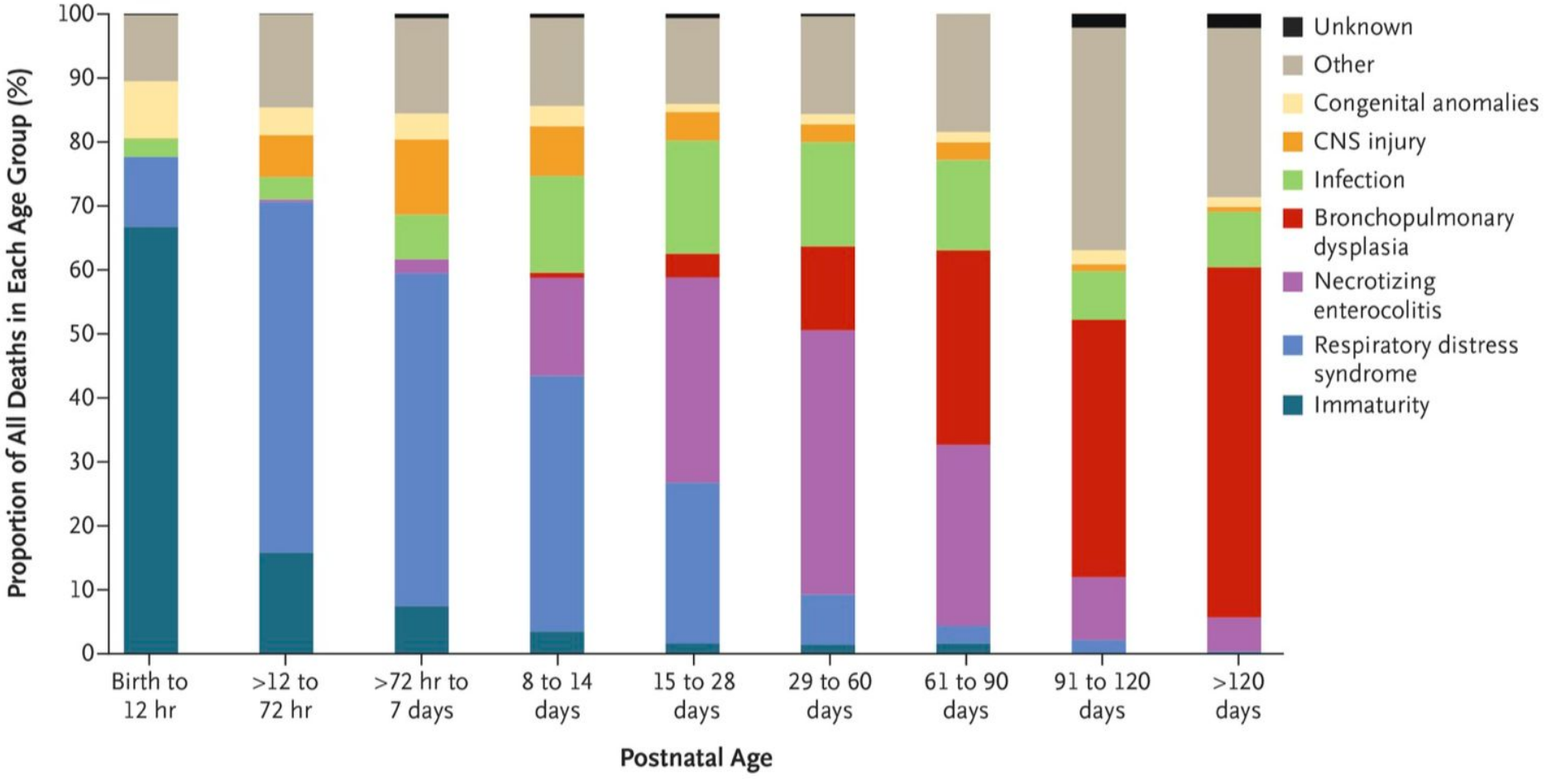

High unmet medical need

# Breakthroughs in preterm infant care




CDC/NCHS, National Vital Statistics System

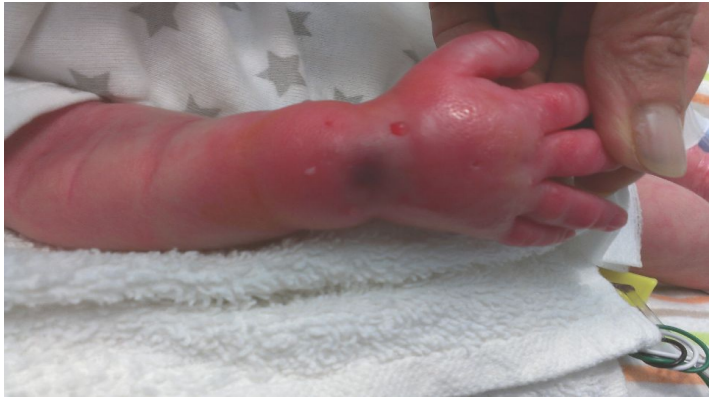
# Causes of death




Patel 2015

# Feeding the preterm infant

Establishing enteral (mouth) feeding in preterm infants is a primary clinical goal to **attain normal growth,** important for e.g. cognitive development.



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

Murgas-Torrazza, 2013; Agostoni, 2010

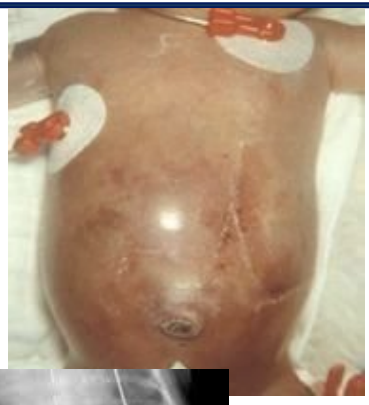
# Necrotizing enterocolitis (NEC)

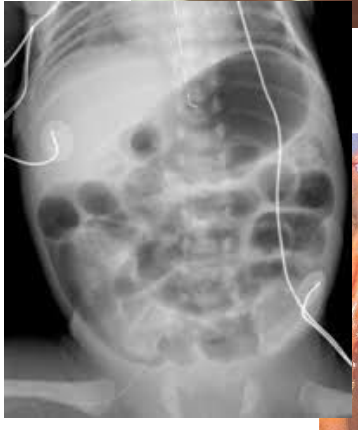
- NEC is severe inflammation of the bowel in preterm infants where 20-40% need complicated and costly surgery

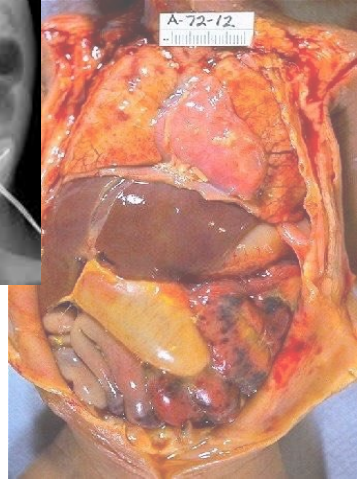
- Survivors have long-term consequences such as short-bowel syndrome, abnormal growth, cognitive, visual and hearing impairments

- 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% mortality rate killing 1500 USA and 3700 EU infants each year**





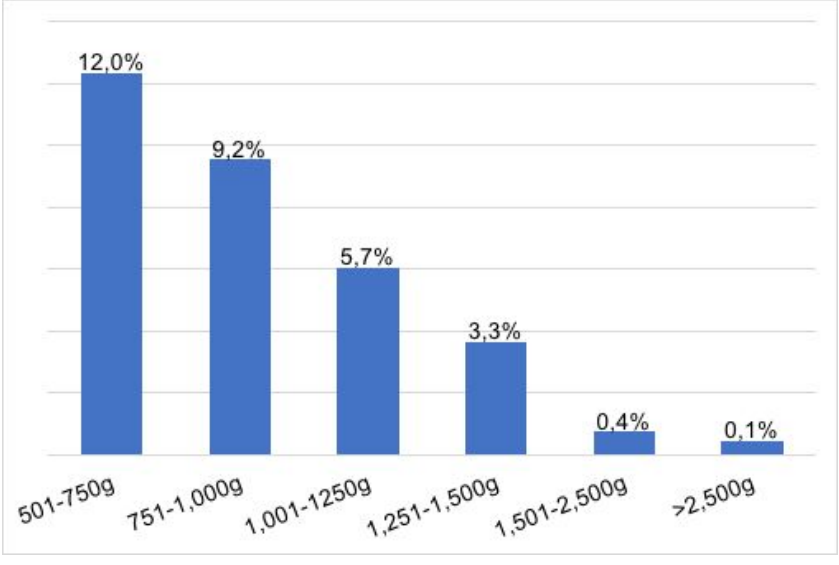



Simpson 2010, Clark 2012

# 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

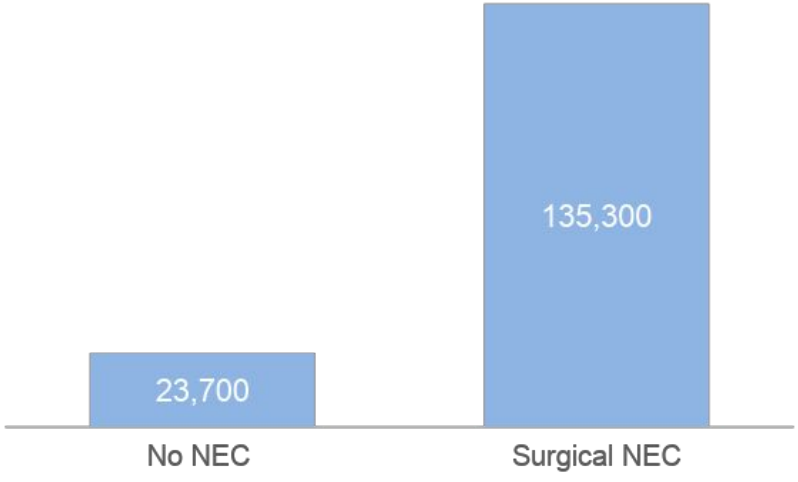
| | |
|---|---|
| 501-750g | 42.0% |
| 751-1,000g | 29.4% |
| 1,001-1250g | 21.3% |
| 1,251-1,500g | 15.9% |
| 1,501-2,500g | 12,7% |

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

# Economic burden of NEC

Average total treatment cost of NEC is $500,000 per patient in the USA

**Costs continue after NICU discharge**




Accumulated USD cost between 6-36 months

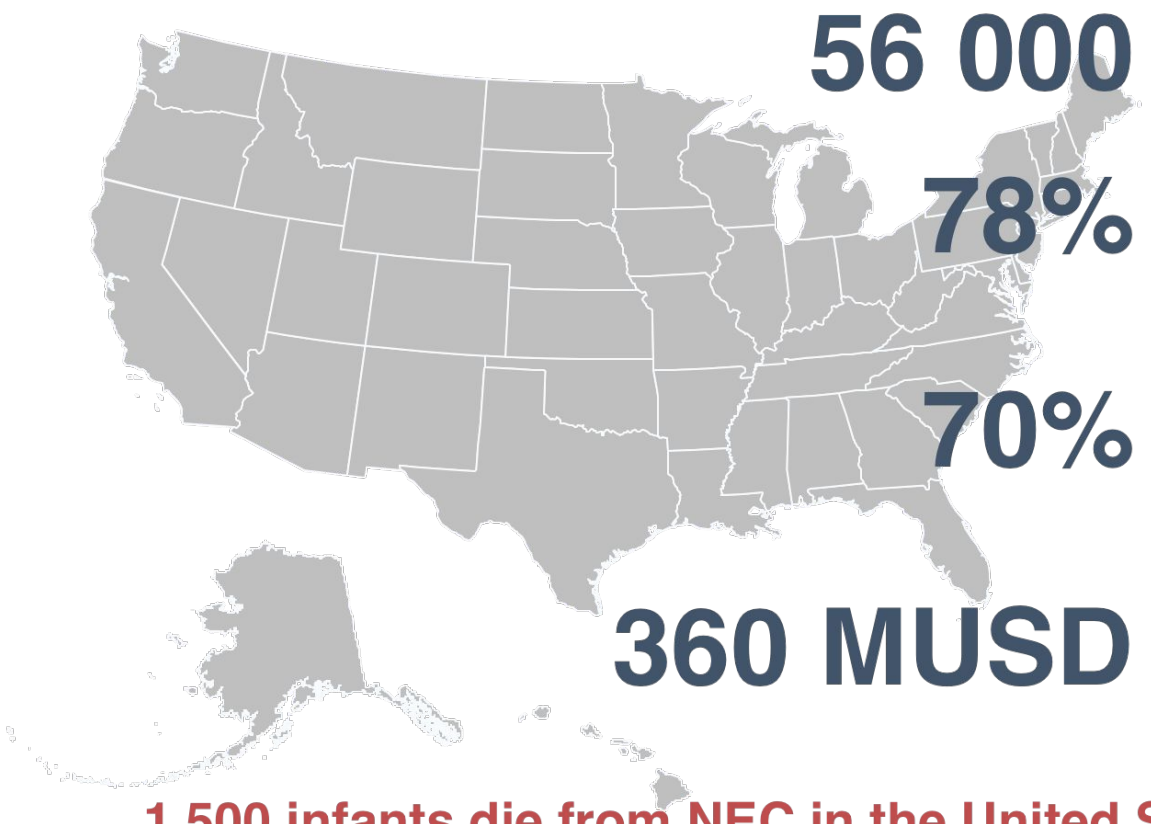
**NEC Economic Burden is estimated to be 20% of the total cost of initial care and $5 Billion spent annually on NEC in the USA**

Ganapathy 2011, Niño 2016


STRONG INTEREST FROM THE MARKET

# A valuable pharmaceutical

## Results of NEC 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

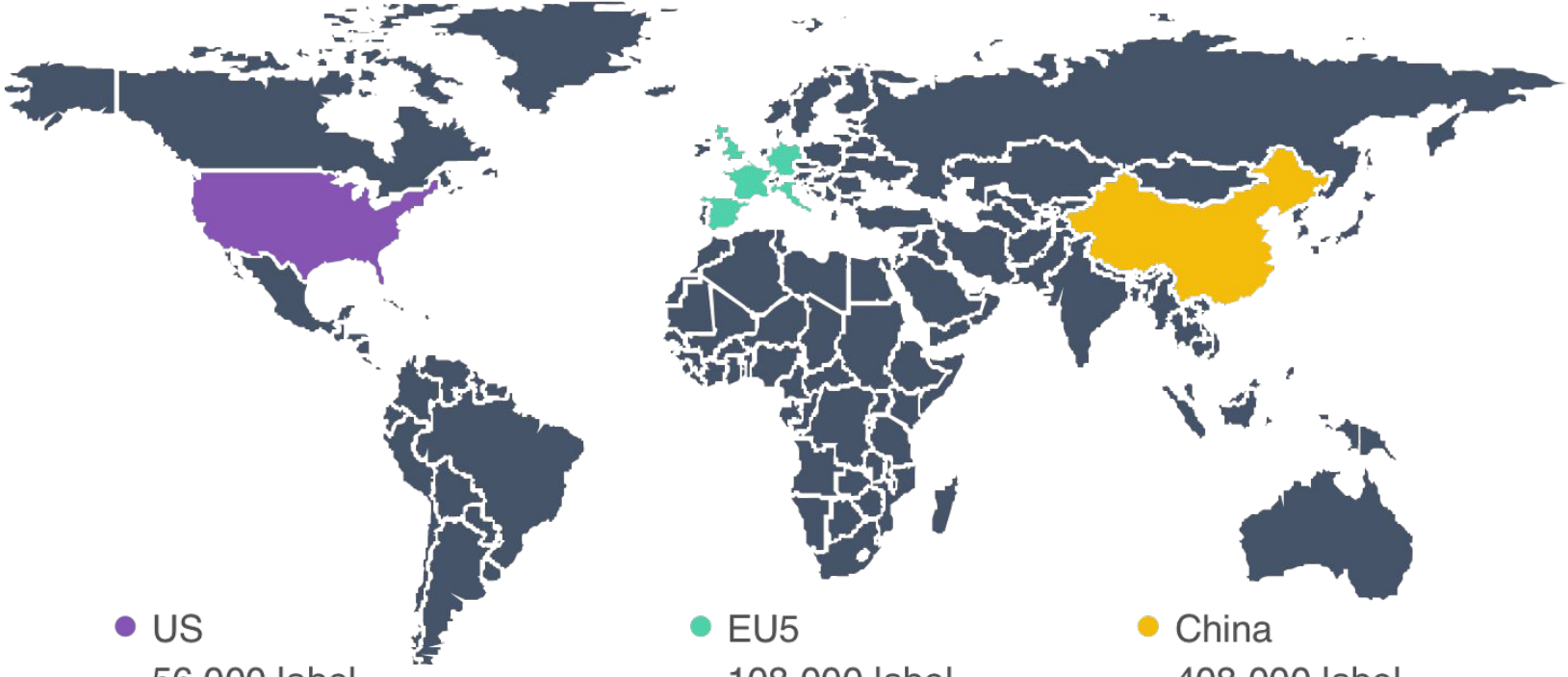
**360 MUSD**

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


The product

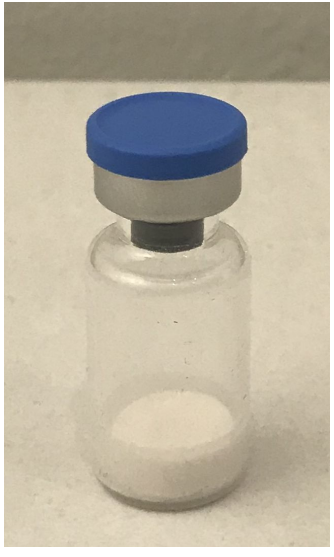
# Pharmaceutical drug candidate IBP-9414

- Rigorous pharmaceutical Chemistry-Manufacturing-Control standards in all steps with GMP according to 21 CFR Part 210

- Developed under IND

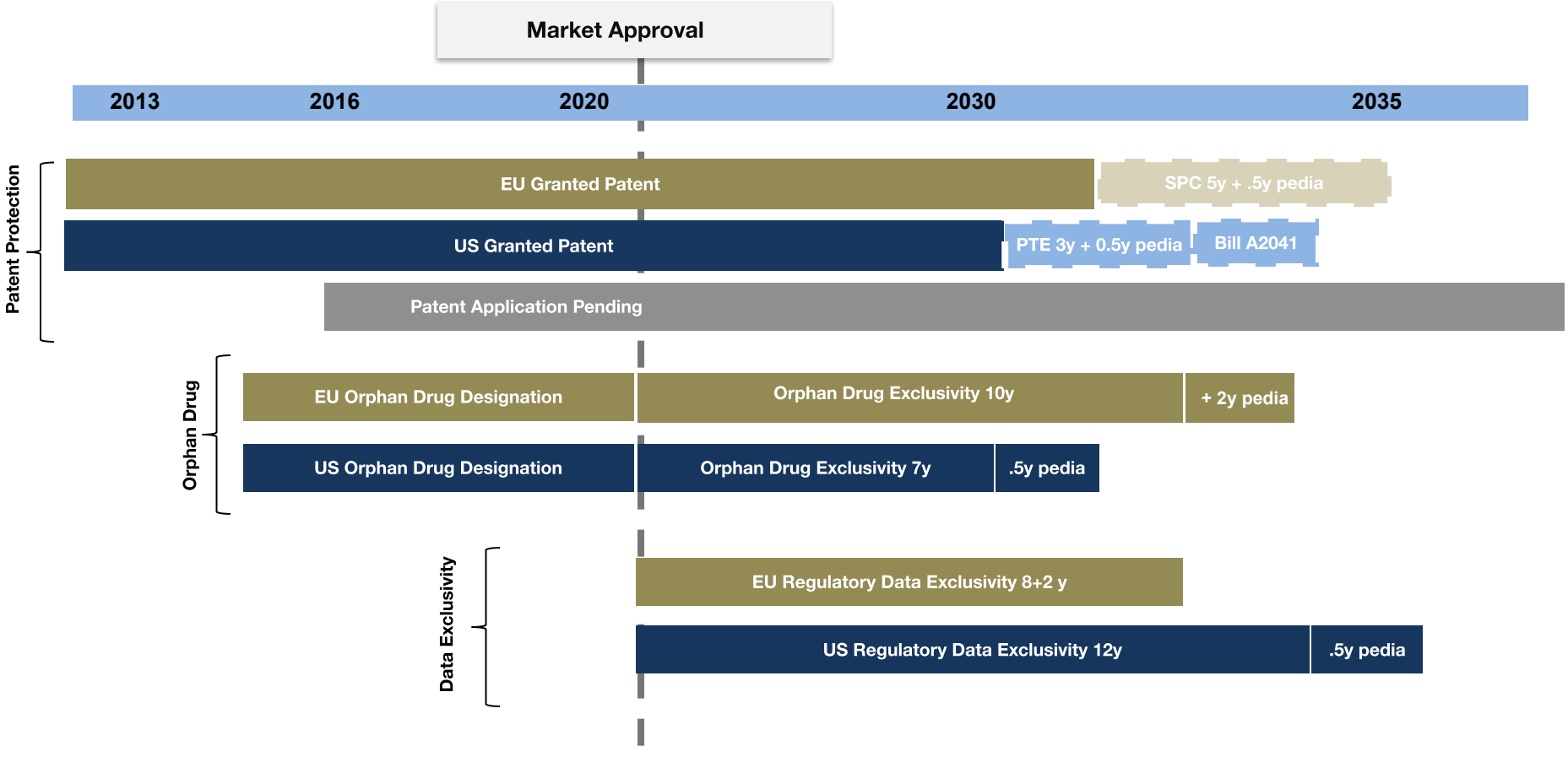
- Single dose vial with dose accuracy following ICH Guidelines for Pharmaceuticals

- Stringent control of bioburden and microbial purity on final product analysis according to USA and Eur Pharmacopeia



# IBP-9414 Market Exclusivity

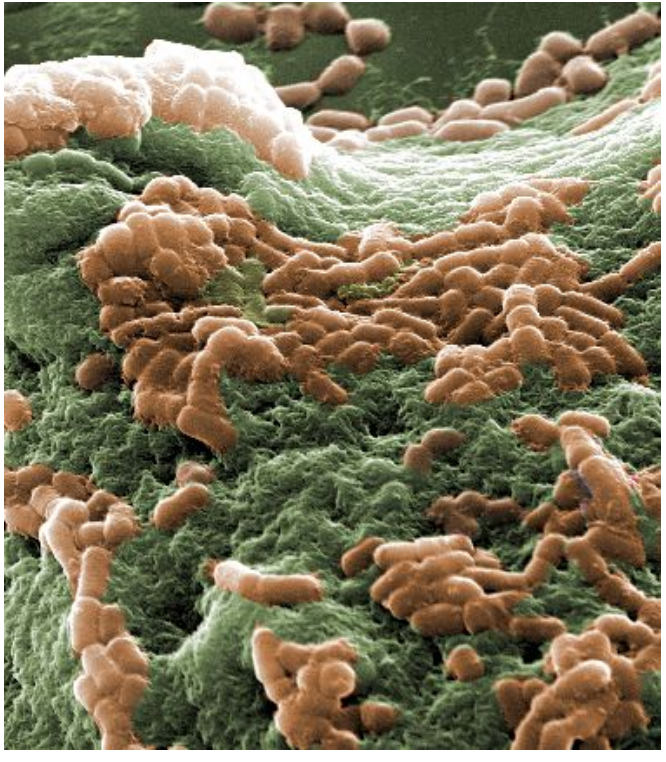
## Three layers of IP protection



# *Lactobacillus reuteri*

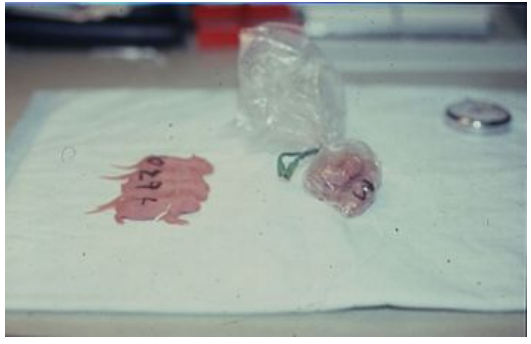
## Active substance of IBP-9414

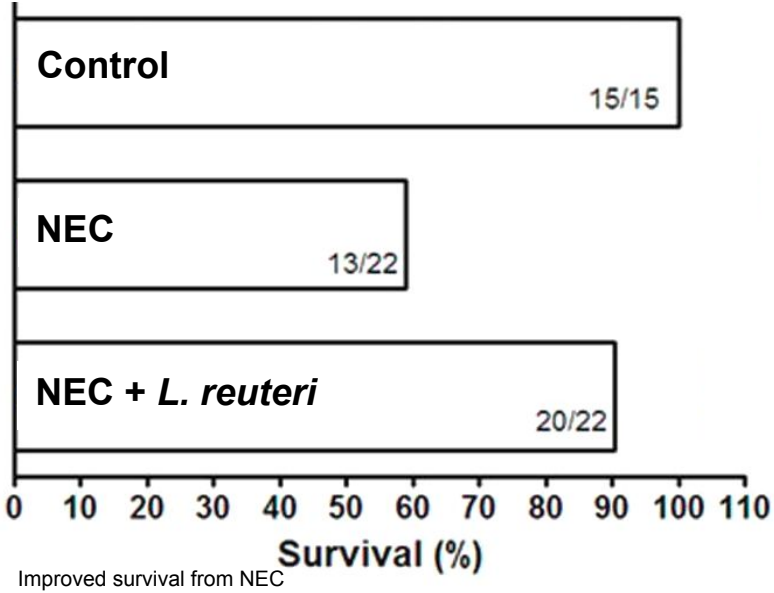
*Lactobacillus reuteri* present on women's breasts



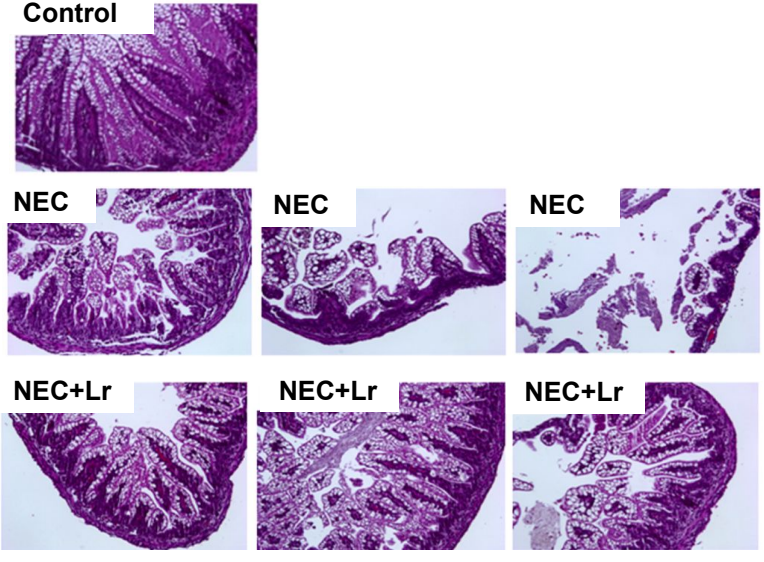
*Lactobacillus reuteri* (orange) adhering to intestinal mucus

# *L. reuteri* protects from NEC in animal models





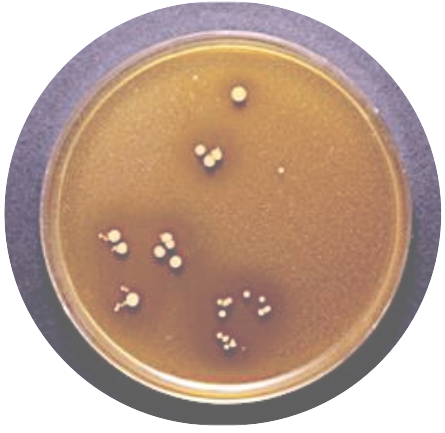

Improved survival from NEC

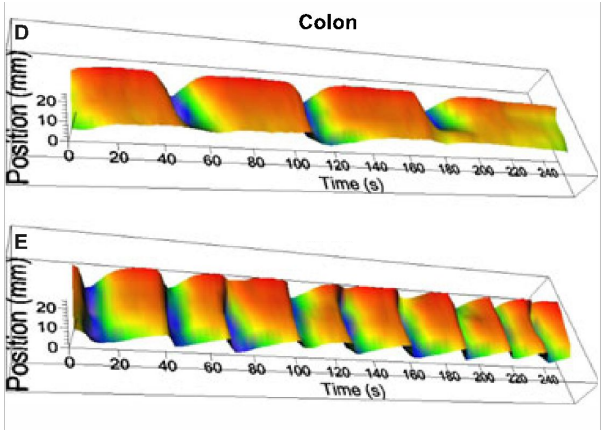



Reduced intestinal damage

Liu, 2012, 2013, 2014

# *L. reuteri* - mechanisms of action





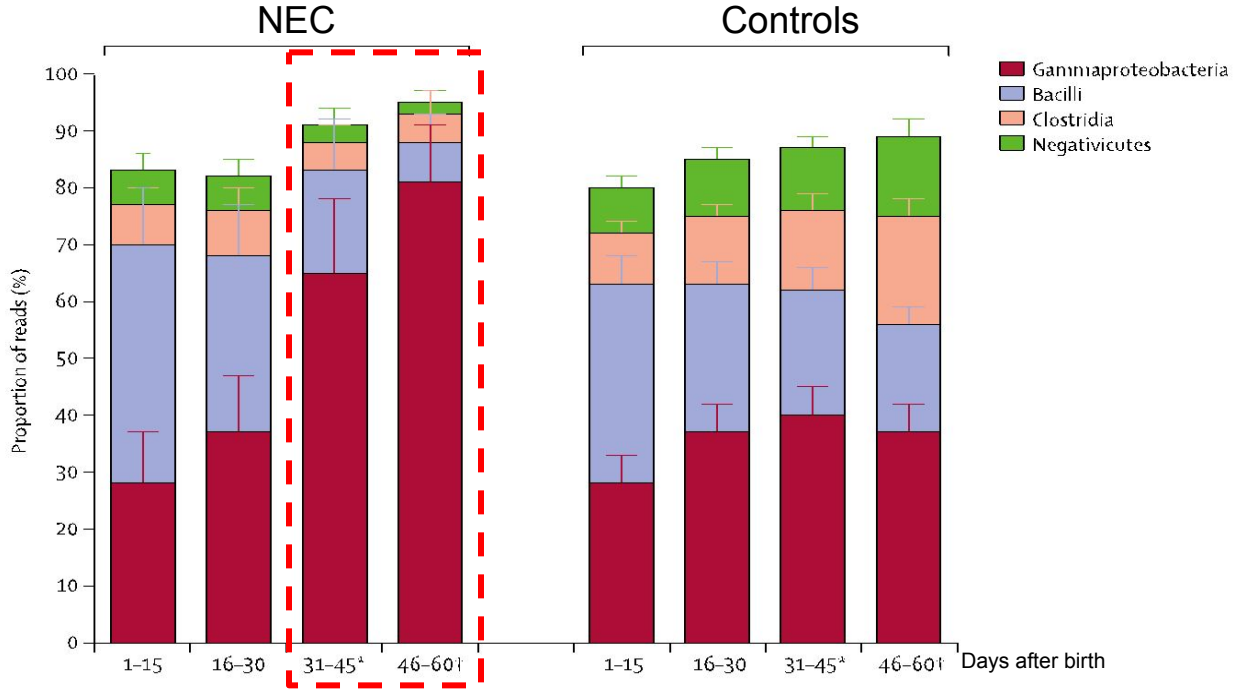

**Combats dysbiosis** **Reduces inflammation** **Improves gut motility**

## Improved gut function including prevention of NEC

Schaefer 2010, Walter 2011, Wu 2013, West 2020

# Clinical Signal - Dysbiosis

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



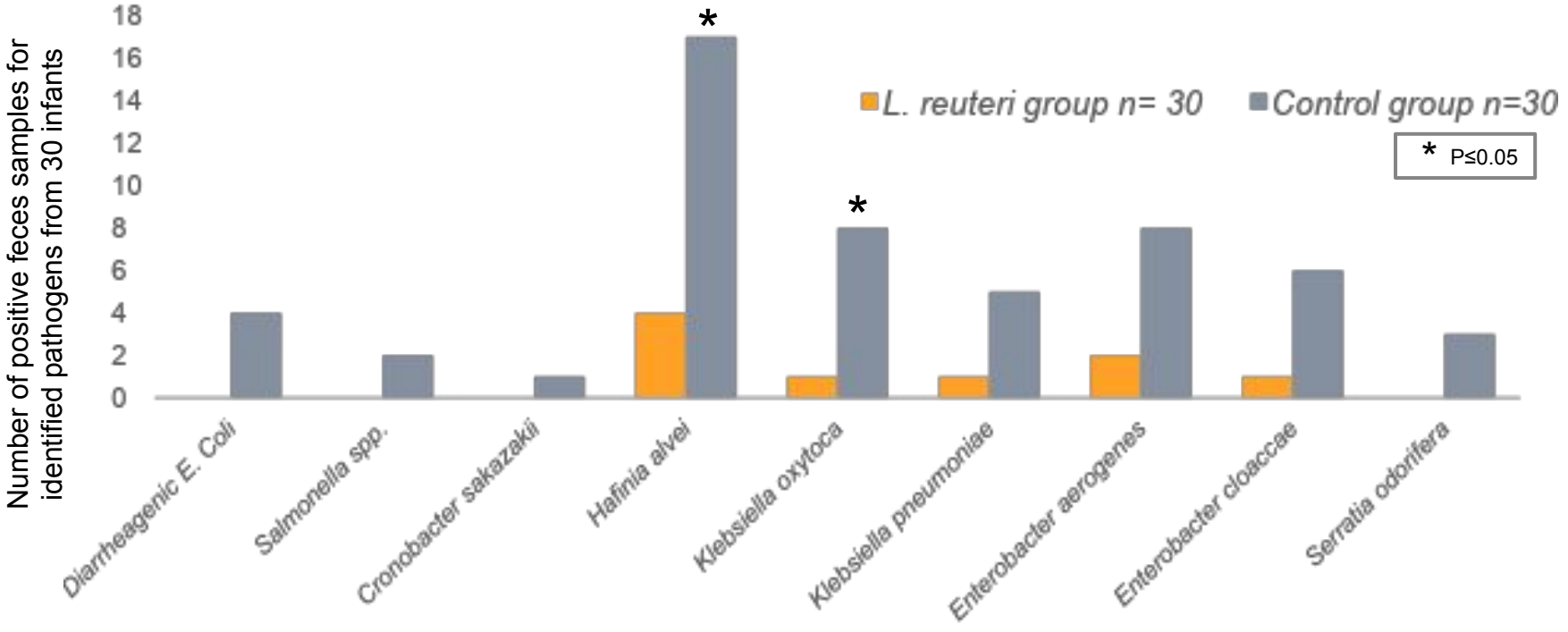

Bloom of pathogen-rich gamma proteobacteria prior to onset of NEC

Microbiome optimization may provide a novel strategy for preventing NEC

**Source** Warner et al, 2016, Pammi et al. 2017

# Clinical data - Anti-pathogen effects

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




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

**Source** Savino 2015

# Pre-clinical - Anti-pathogen effects

## *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*

***L. reuteri* inhibits *S. aureus***

**Yeast and fungi**

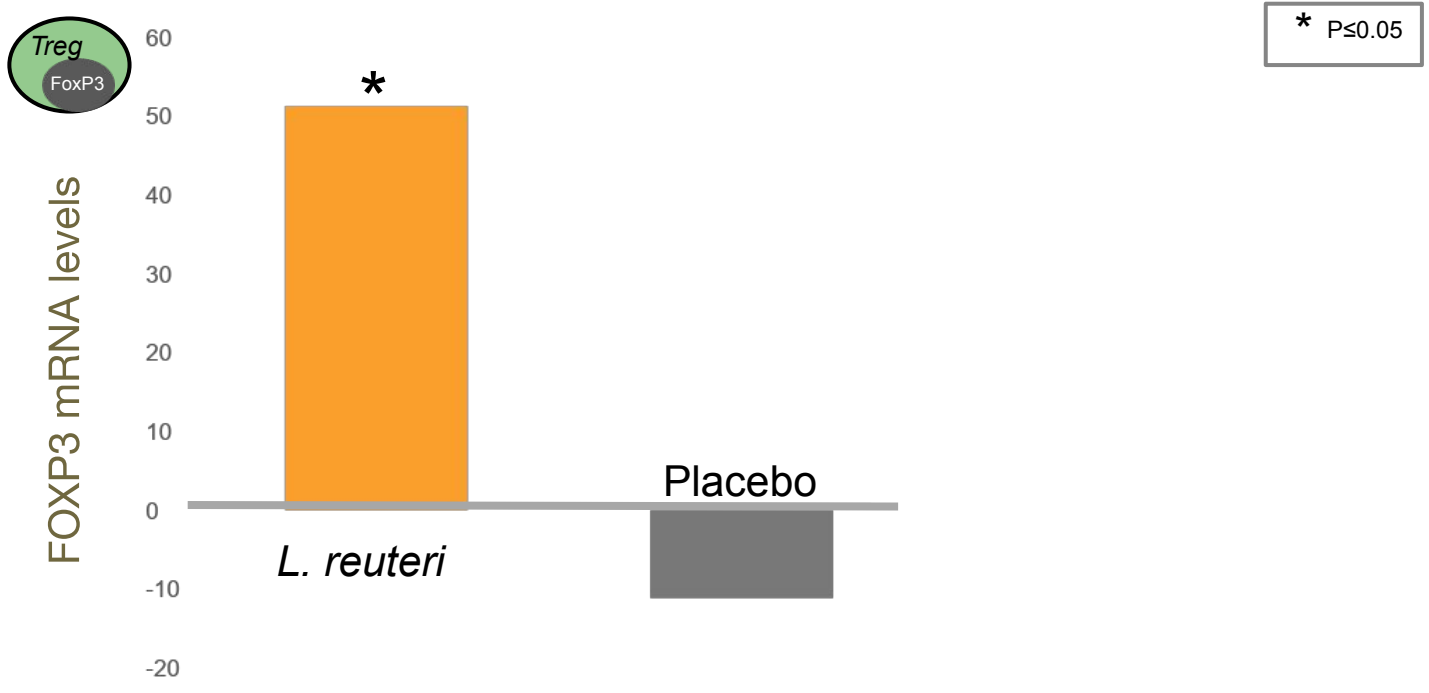
- *Candida albicans*
- *Aspergillus flavus*
- *Fusarium samiaciens*

***L. reuteri* inhibits the growth of pathogens**

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

# Clinical - Anti-inflammatory

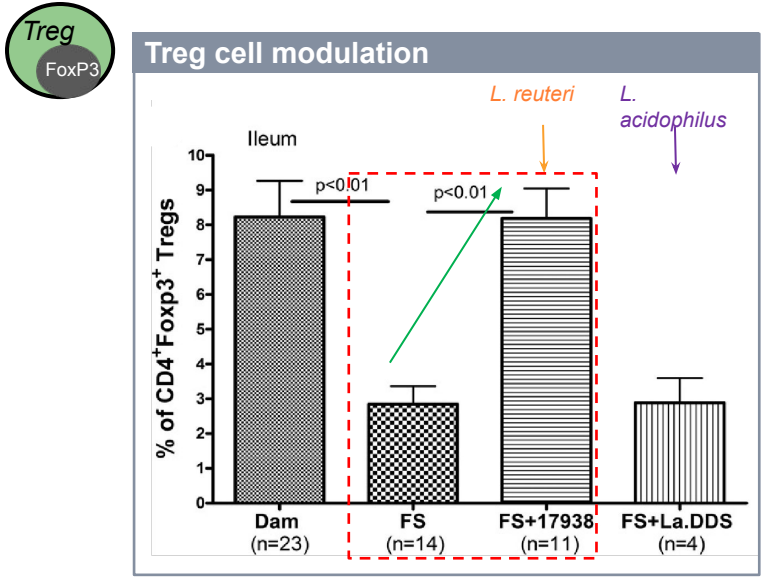
## Treg cells increase in infant blood after *L. reuteri* administration

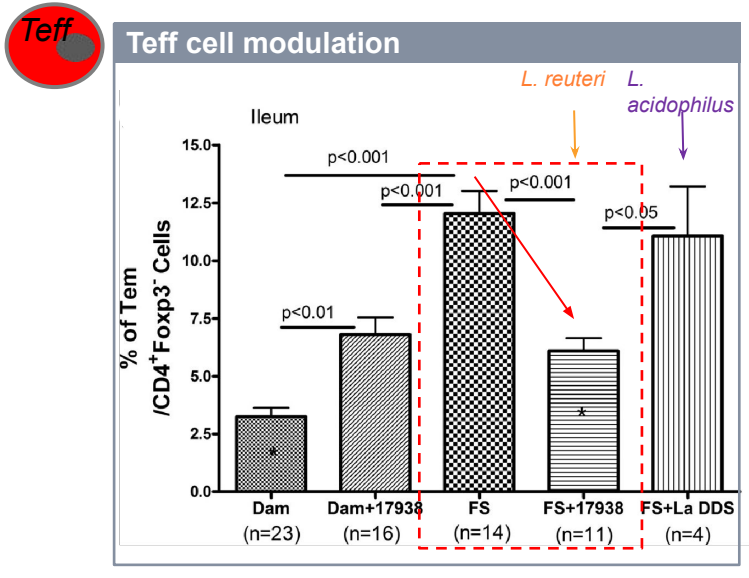



***L. reuteri* recruitment of Treg cells now shown in infants**

**Source** Savino 2017

# Pre-clinical - Strain specific anti-inflammation in NEC animal model



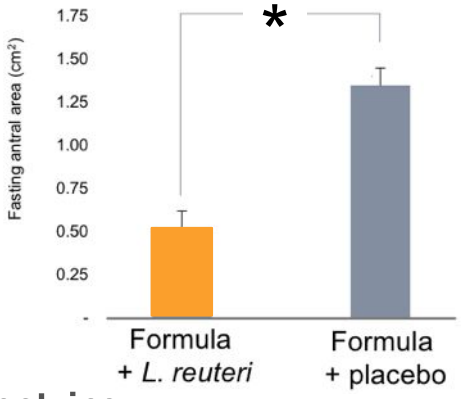




***L. reuteri has*** **strain specific anti-inflammatory activity through recruitment of Treg cells and down regulation of Teff cells**

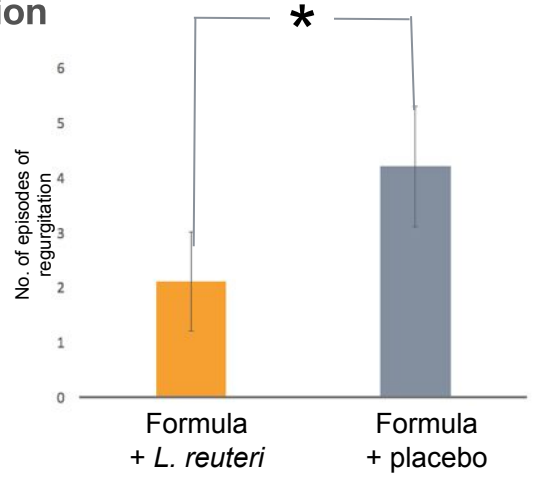
**Source** Liu 2014

# Clinical data - Modulation of gut motility

## Fasting antral area

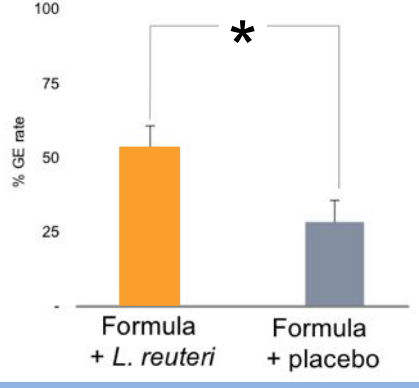



## Regurgitation

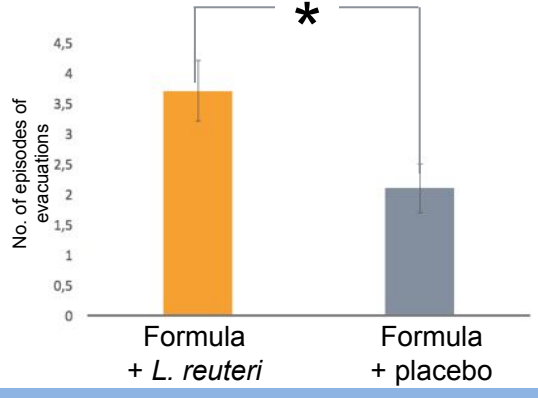



* P≤0.05

## Gastric emptying




## Stooling

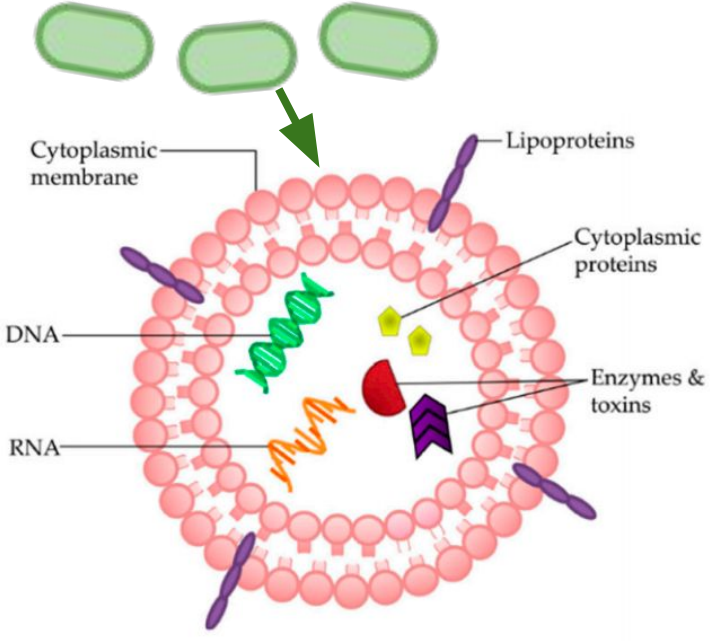



**Preterm infants given *L. reuteri* show improved gut emptying**

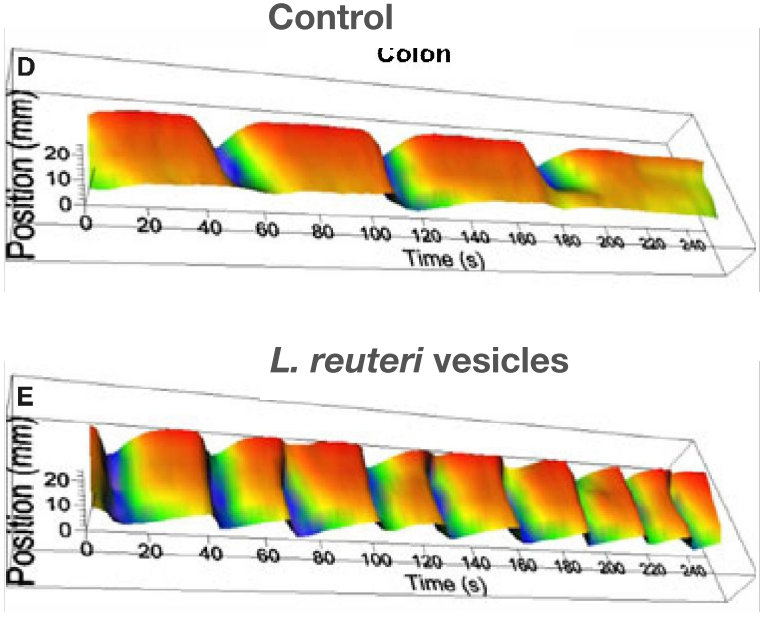
**Source** Indrio 2008

# Pre-clinical data - improved gut motility

## Microvesicles from *L. reuteri* completely reproduce gut motility modulation of the intact bacteria in mouse




Bacterial membrane vesicles produced by *L. reuteri*




Propagating contractile clusters in the colon

**Source** Wu 2013, West 2020

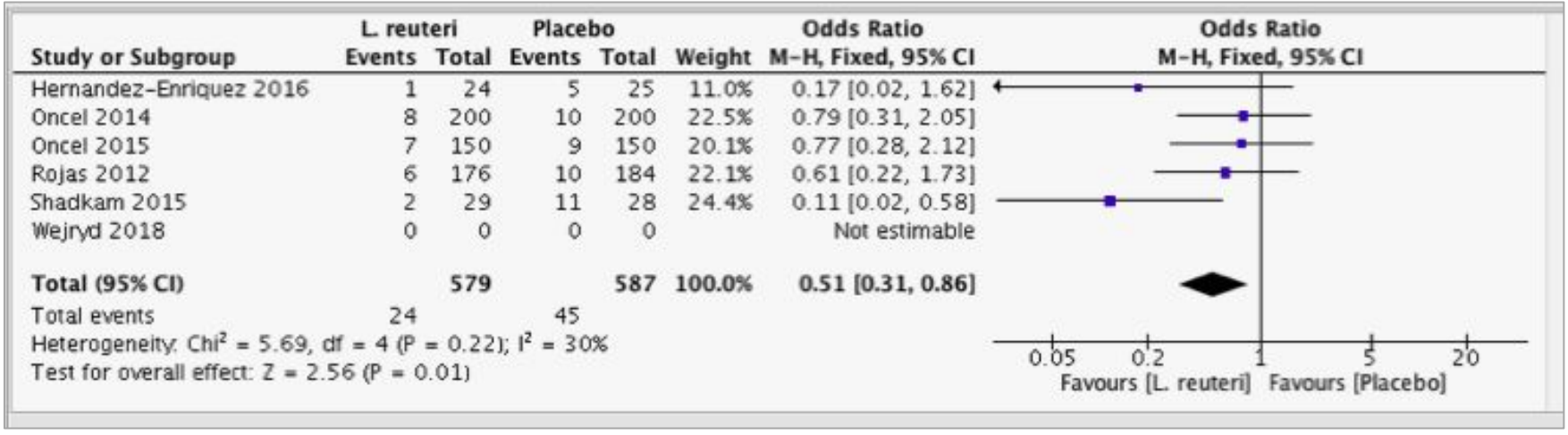

Clinical signal

# Publications with clinical signals

| NICU Study | Number of Patients | Reduction of NEC incidence | Reduction in episodes of feeding intolerance *or* reduction in time to full enteral feeding |
|---|---|---|---|
| Rojas et al. 2012 | 750 | **37 %** | **43% *** |
| Oncel et al. 2014 | 400 | **20 %** | **33% *** |
| Oncel et al. 2015 | 300 | **22 %** | **36% *** |
| Shadkam et al. 2015 | 60 | **82 %** | **24% **** |
| Hernandez-Enriquez et al. 2016 | 44 | **83 %** | **17% **** |
| Indrio et al. 2017 | 60 | | **44% **** |
| Spreckels et al. 2018 | 104 | **55 %** | |
| Wejryd et al. 2019 | 134 | **17 %** | No difference ** |
| | | | |
| Hunter et al. 2012/ Dimaquila et al. 2013 | 354 | **89 %** | |
| Jerkovic-Raguz et al. 2016 | 100 | **50 %** | |
| Sanchez-Alvarado 2017 | 225 | **64 %** | |
| Kaban et al. 2019 | 94 | **100 %** | **67% *** |
| Rolnitsky et al. 2019 | 1,357 | **55 %** | **52% *** |
| Cui 2019 | 93 | **79 %** | **18% **** |

* reduction in episodes of feeding intolerance
** reduction in time to full enteral feeding

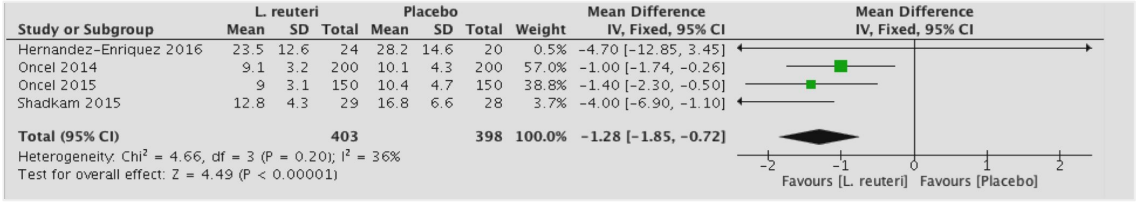
# NEC clinical signals



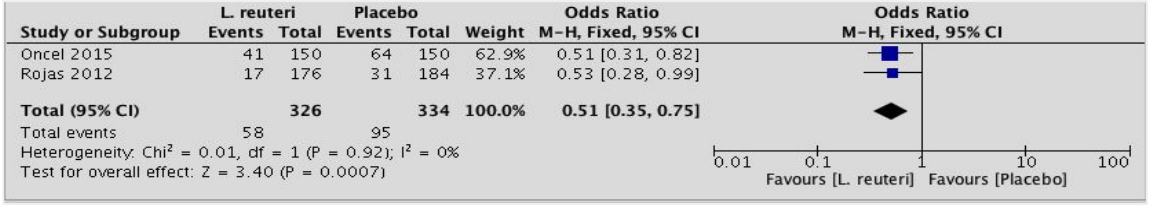

***Meta-analysis of 1166 patients <1500g all randomized controlled trials gives an Odds Ratio of 0.51***

# Feeding Tolerance - clinical signals and consequences

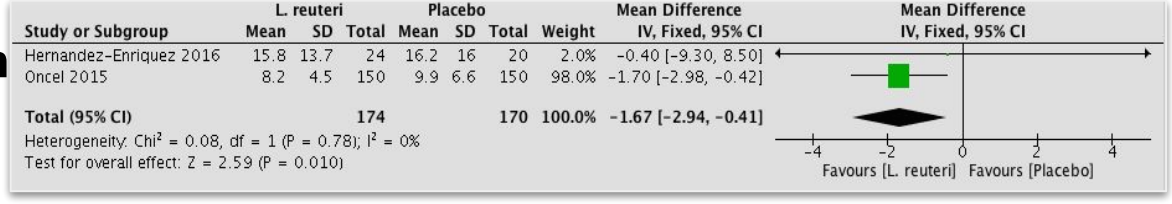
**Time to full enteral feeding**
*-1.28 days [-1.85, -0.72]*



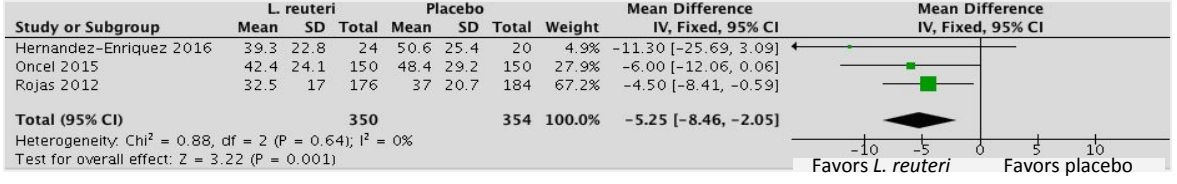

**Feeding intolerance events**
*OR 0.51 [0.35, 0.75]*




**Days on Parenteral Nutrition**
*-1.67 days [-2.94, -0.41]*




**Days in hospital**
*-5.25 days [-8.46, -2.05]*



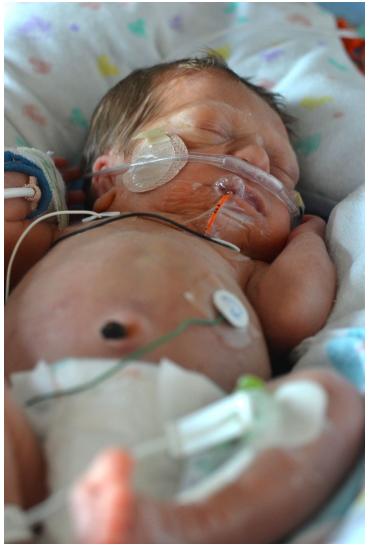
# Economics of NICU stay

Overall cost of of preterm births in the USA is estimated at $26 Billion

More than 65% of NICU admissions have an average LOS of about 20 days

Average NICU cost per day is $3,000

Cost of average NICU admission is similar to that of patients admitted for spinal cord injury and heart valve disorders



5 days * $3,000 * 65% (LOS 20 days) * 56,000 (VLBW USA/year) = $546 Million

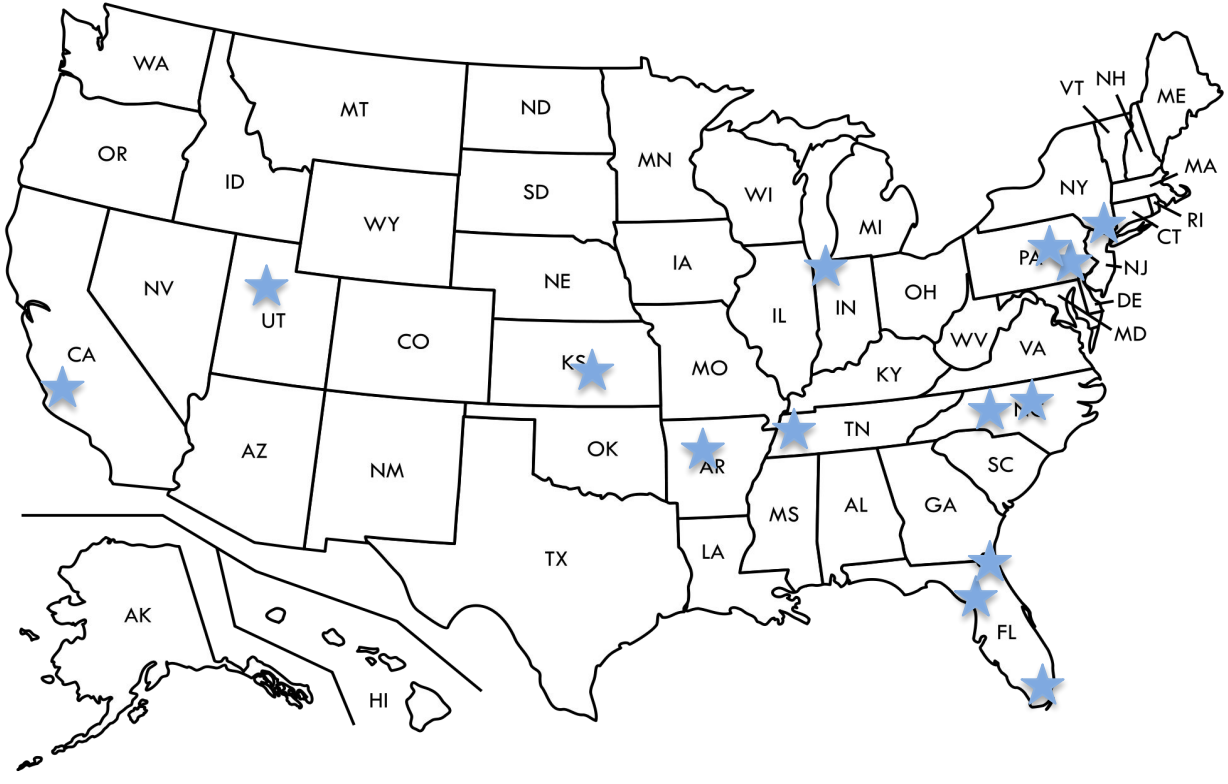
Kornhauser 2010


Clinical Development Program

# IBP-9414 Phase II: Safety & Tolerability Study

RCT; 120 infants 500g - 2000g; 14 days daily dosing from 48h; dose $10^8$ or $10^9$ CFU or placebo; follow up 1 & 6 months

**Dr. Neu, Gainesville FL, PI**
Dr. Ashley, Durham NC
Dr. Bloom, Wichita KS
Dr. Del Moral, Miami FL
Dr. Garg, Los Angeles CA
Dr. Gerstmann, Orem UT
Dr. Guthrie, Jackson TN
Dr. Hand, Brooklyn NY
Dr. Hirsch, Philadelphia PA
Dr. Hudak, Jacksonville FL
Dr. Kehinde, Philadelphia PA
Dr. Kona, Little Rock AR
Dr. Porcelli, Wake Forest NC
Dr. White, South Bend IN



# IBP-9414 Phase II Safety & Tolerability Study

- Similar AE and SAE profile in active and placebo groups
- No SAE related to study drug
- No evidence of cross-contamination with IBP-9414 in placebo treated infants
- Executed according to timeplan

Key conclusion: Safe and well-tolerated

http://ibtherapeutics.com/wp-content/uploads/2016/03/Hot-topics-poster-1128.pdf

# IBP-9414 Clinical Development Plan

## Phase 2
## Safety and Tolerability Trial

- Randomized, double blind, dose escalation, placebo-controlled
- Multicenter study
- Safety and tolerability of IBP-9414 in premature infants ≤2,000g birth weight
- 120 infants
- 15 sites in the USA

## Phase 3
## Efficacy and Safety Trial – Connection Study

- Randomized, double blind, placebo-controlled
- Multicenter study
- Efficacy and safety of IBP-9414 in premature infants 500-1500g birth weight for the prevention of necrotizing enterocolitis
- 2158 infants
- 100 sites in the USA, UK, Spain, France, Hungary, Israel

# Phase III Pivotal Trial

- IBT has developed the IBP-9414 program in cooperation with the regulators and with considerations of KOLs experience and clinical practice
- CTX/IND approval received in UK, Spain, Hungary, France and USA, application filed in Israel
- During the autumn focus has been on increasing the recruitment rate at open sites
- Recruitment rates at active sites has significantly improved
- Focus has now shifted towards contracting and activating additional sites

# 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 | ✔ |
| Orphan Drug and Rare Pediatric Disease designations | ✔ |


Thank you
Infant Bacterial Therapeutics AB
www.ibtherapeutics.com

# Thank you