Ruolo dei prebiotici nella nutrizione infantile

G.E. Moro

Alba, 17 settembre 2016

BENEFICIAL EFFECTS OF HUMAN MILK

Breastfeeding represents the most appropriate nutrition for every infant because :

- reduces the number of infections and related morbidity and mortality
- prevents atopy and other allergies, *and*
- improves neurocognitive development

Compounds with Immunological Properties in Human Milk

Oligosaccharides

In breast milk

Not in cows' milk

Field, J Nutr, 2005

Oligosaccharides represent a major component of human milk

Lactose	53-61 g/l
Fat	30-50 g/l
Oligosaccharides	10-12 g/l
Protein	8-10 g/l

- Resistant to digestion in upper GI tract
- Fermented by gut flora
- Protect against attachment and invasion of pathogens
- Act as prebiotics – increasing beneficial bacteria

Elie Metchnikoff
(1845 – 1916)

Theodor Escherich
(1857 – 1911)

Elie Metchnikoff

(Charkiv, 1845 - Paris, 1916)
Nobel Prize Winner in 1908,
he used to say:

"When people have learnt how to cultivate a suitable flora in the intestine of children as soon as they are weaned from the breast, the normal life may extend to twice my 70 years"

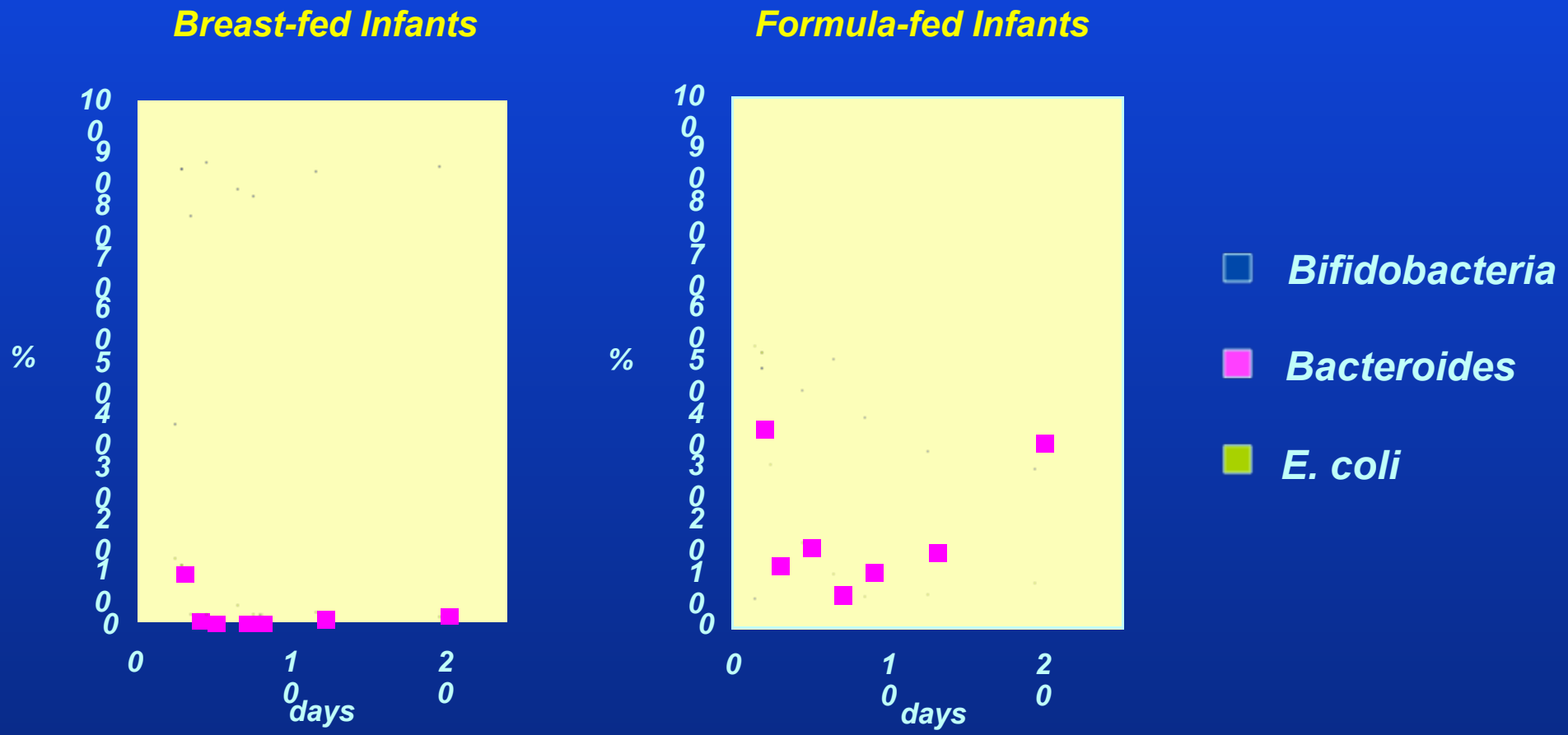
- **Theodor Escherich (1857–1911)**

  Chair of Pediatrics (1902-1911) at the University of Vienna

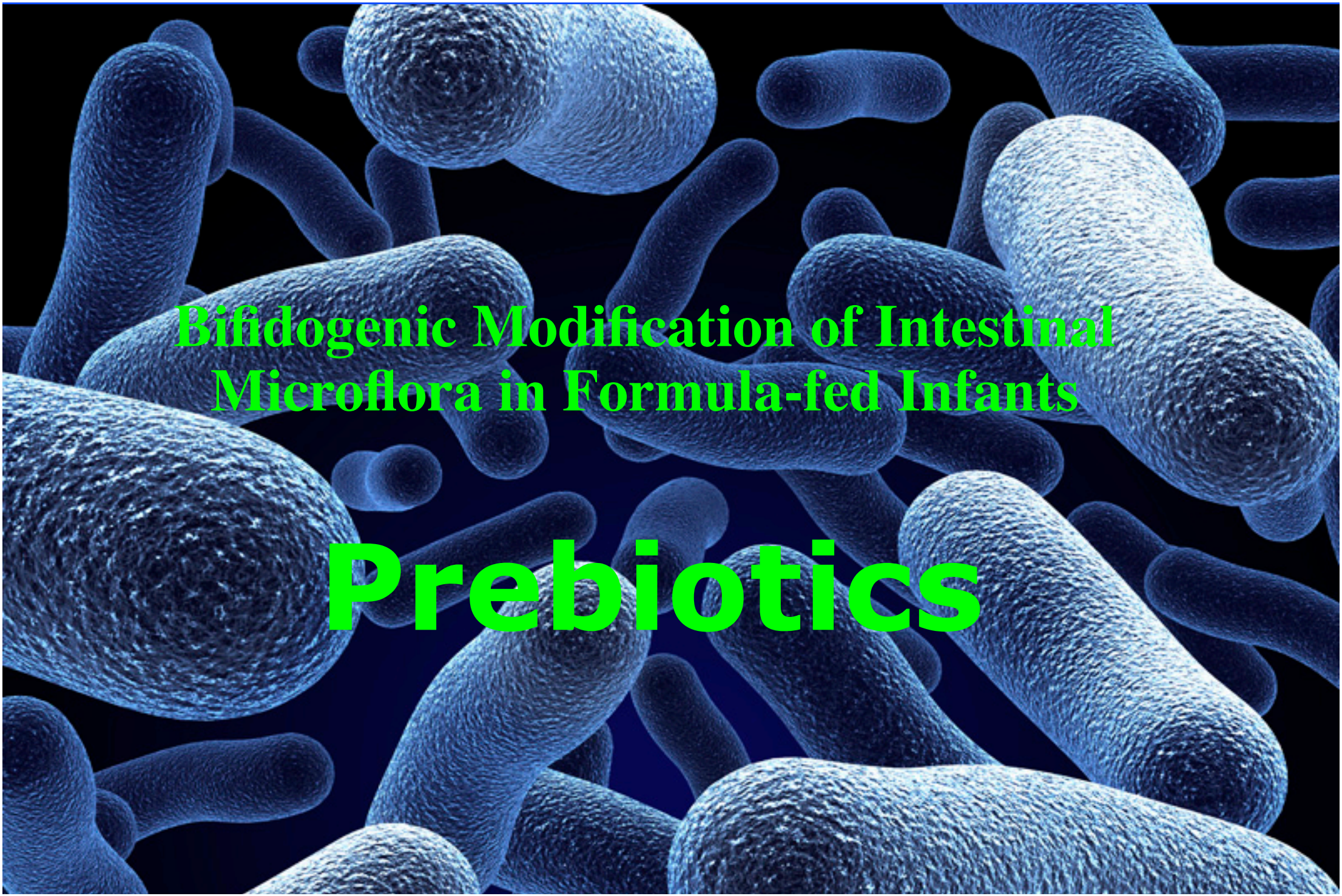
  Director of the St. Anna Childrens Hospital

- Indicated **that the intestinal bacteria of the breast fed neonates were significantly different from infants fed in other ways** (life saving properties of HM).
- His efforts resulted in eventual construction of the Imperial Institute for Maternal and Infant Care.

Intestinal Flora of Breast-fed Infants Versus Formula-fed Infants



Harmsen HJM, Wildeboer- Veloo ACM, Raangs GC, et al. J. Pediatr. Gastroenterol. Nutr. 2000; 30:61-67


Bifidogenic Modification of Intestinal Microflora in Formula-fed Infants
Prebiotics

Concept on a Specific Prebiotic Mixture:

Mimicking Size, Linkage, partly Building Blocks and Prebiotic function of HMOS

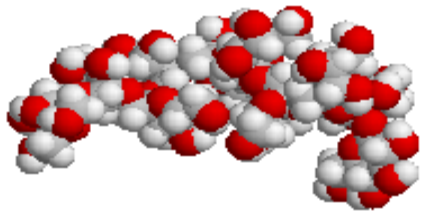
90 % scGOS: low molecular weight (short chain)
Galacto-oligosaccharides
(enzymatic from lactose)

[Gal(1-]1- 4 3/4/6)Gal(1-4)Glc

10% lcFOS: high molecular weight (long chain)

Lactose

Fructo-oligosaccharides
(fraction) from chicory



[Frc(2-]n≥8 1)Frc(2-1)Glc

Sucrose

Software:

Bohne A, Lang E, von der Lieth CW.

SWEET - WWW-based rapid 3D construction of oligo- and polysaccharides. Bioinformatics. 1999 Sep;15(9):767-8.

Clinical Studies

- Prebiotics and Intestinal Flora
- Prebiotics and Allergy
- Prebiotics and Infections
- Follow-up and Long Lasting Effects
- Costs of Allergic Diseases

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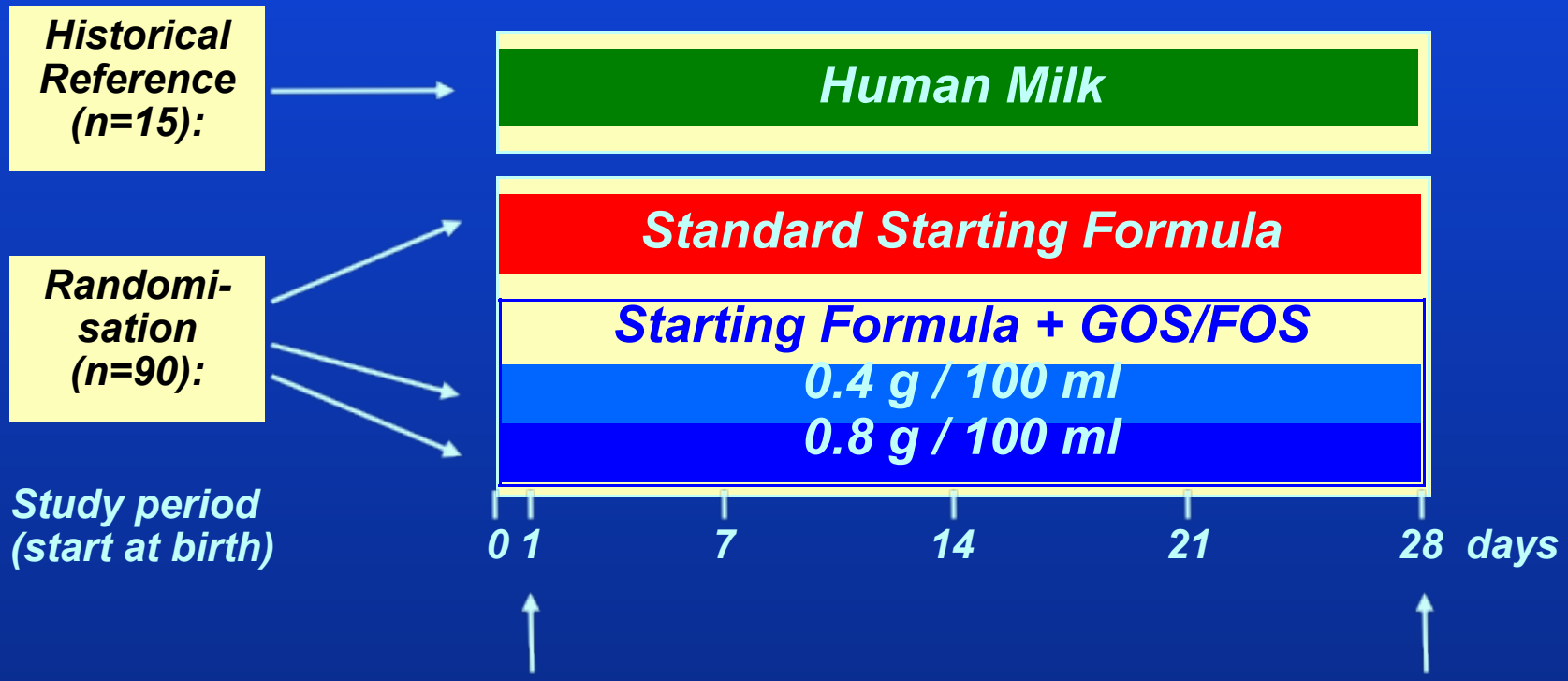
Influence of the GOS/FOS Mixture on the Faecal Flora in Term Infants

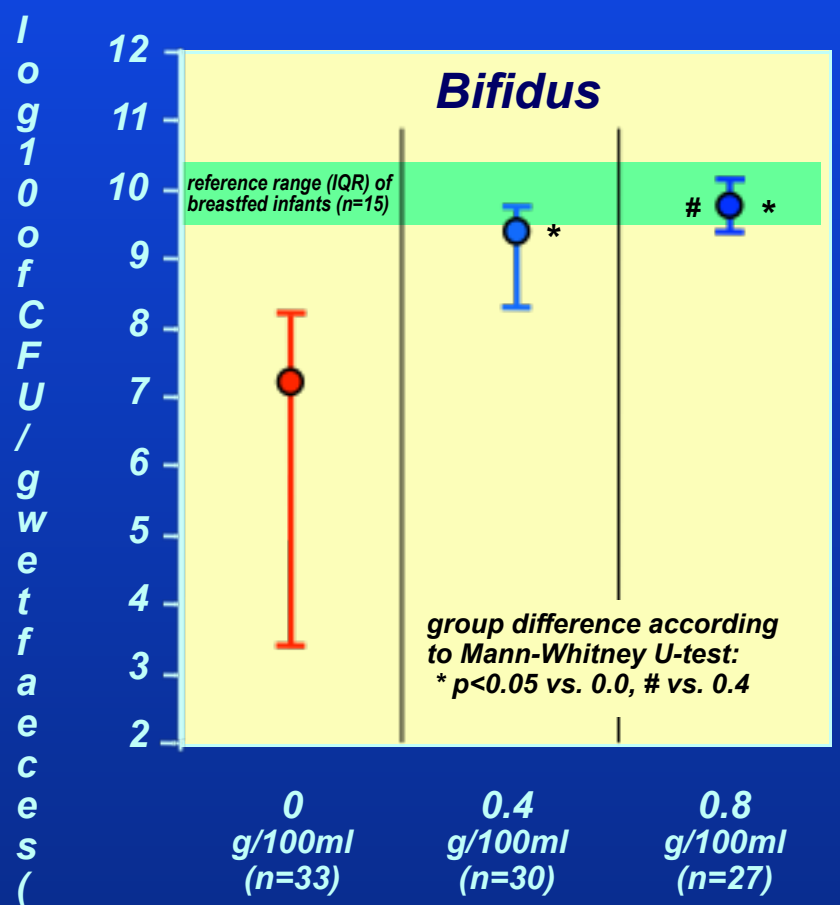
Study design: double blind, randomized, controlled study with parallel group design

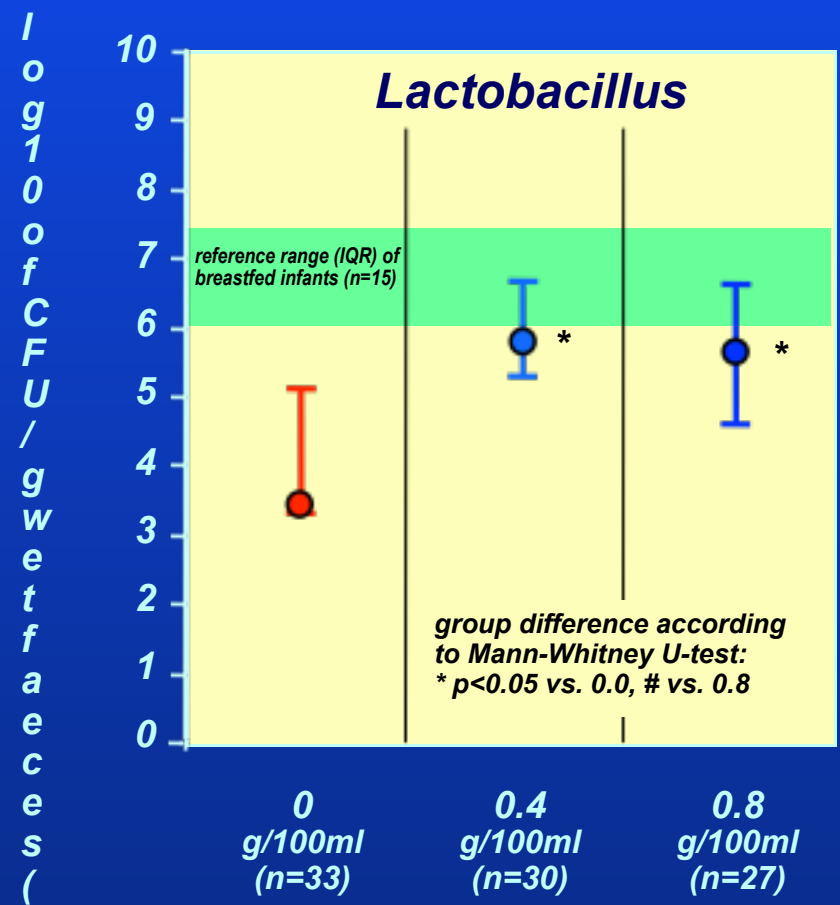


Main examination parameters: *anthropometrical parameters, acceptance and tolerance; quantitative and qualitative bacterial analysis of the faeces*

Study planned in 1999 and published in JPGN in 2002

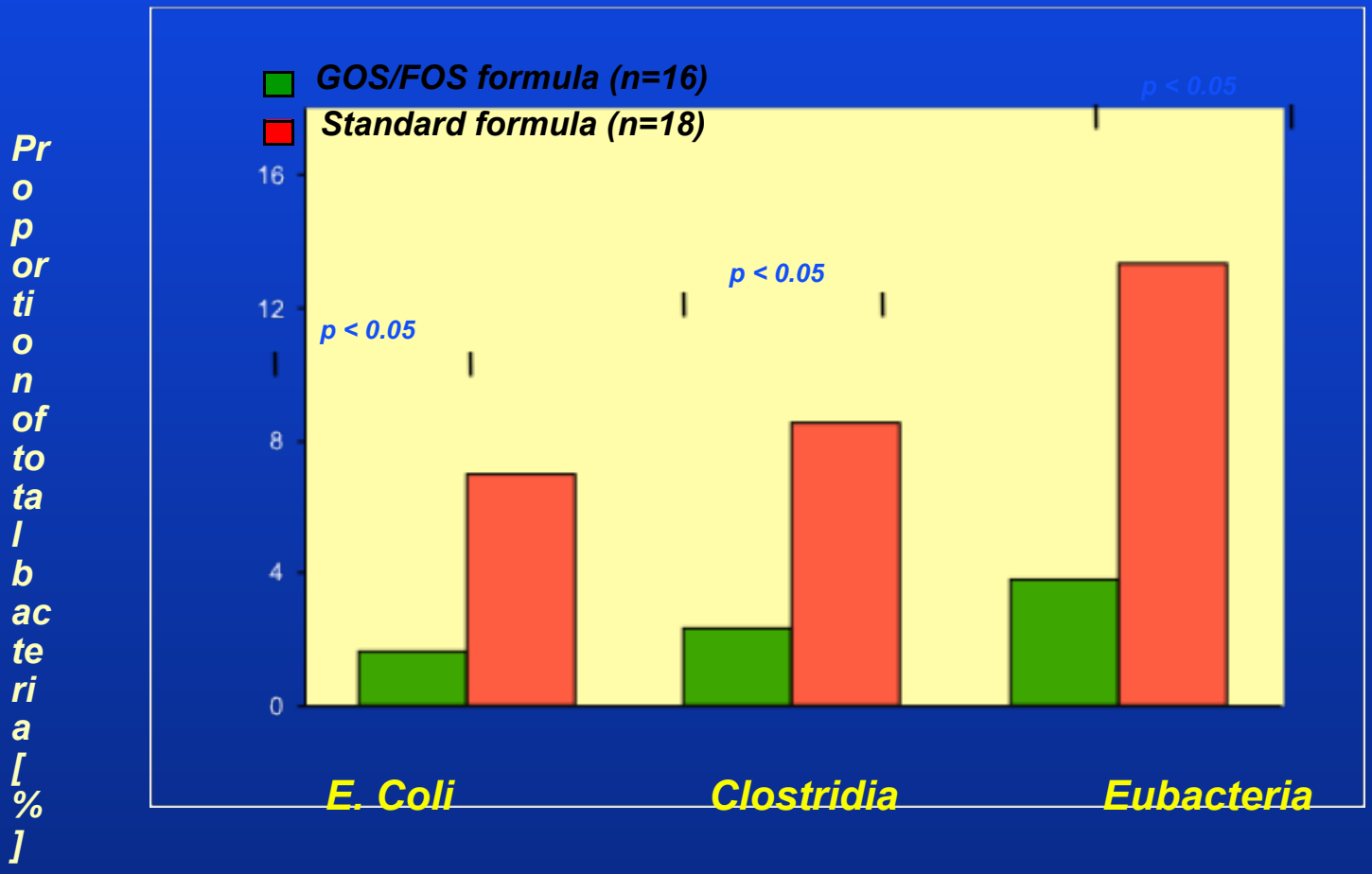
Effect of the GOS/FOS Mixture on the Faecal Flora in Term Newborns (Day 28)





Moro G, Minoli I, Mosca M, Jelinek J, Stahl B, Boehm G. Dosage related bifidogenic effects of galacto- and fructo-oligosaccharides in formula fed term infants. J Pediatr Gastroenterol Nutr 2002; 34:291-295

Reduction of Potential Pathogens
- Term Infants after 6 weeks -



Knol et al. 2003

Prebiotics and Intestinal Environment

The results of several RCT have shown that, in formula-fed infants, this GOS/FOS mixture is able to produce a significant

- *increase of Bifidobacteria*
- *decrease of pathogens*
- *appropriate SCF pattern*
- *decrease of fecal pH*
- *increase of secretory IgA*
- *increase of fecal lysozyme*
- *decrease of intestinal permeability*
- *improvement of stool characteristics*

reproducing an intestinal situation similar to BF infants

Clinical Studies

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New concepts on allergy

- ***Deficient exposure to non pathogenic microbes**, including those in gut microbiota, early in life is crucial for development of allergy.*
- ***Alterations in gut microbiota** precede development of allergy.*
- *Children with **allergy** have a **different intestinal flora** from healthy children, with higher levels of **clostridia** and lower levels of **bifidobacteria**.*

Prebiotics and Allergy Prevention

*At Macedonio Melloni Hospital in Milan, a placebo controlled study was performed to evaluate the cumulative incidence of Atopic Dermatitis (AD) in infants at high risk for allergy fed the GOS/FOS mixture (**at least one of the parents was positive for allergy**).*

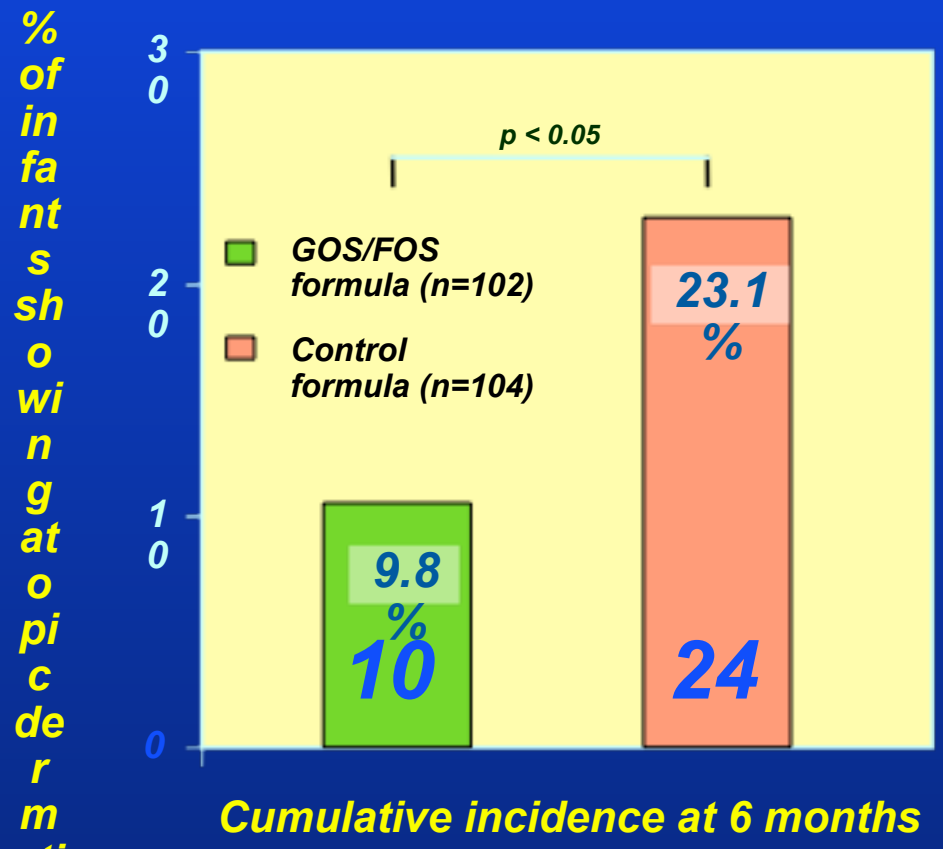
All the infants were fed with hydrolysed formula for the first 6 months of life

Bifidobacteria as CFU per g Fresh Stool at 3 Examination Days

	GOS/FOS (n=104)	Placebo (n=102)	P value
At start of the study:			
Bifidobacteria	8.17	8.33	ns
At 3 months of age:			
Bifidobacteria	9.56	8.30	< 0.0001
At 6 months of age:			
Bifidobacteria	10.28	8.65	< 0.0001

Moro, Arslanoglu et al. Arch Dis Child, 2006

Cumulative Incidence of Atopic Dermatitis



Evaluated by SCORAD index

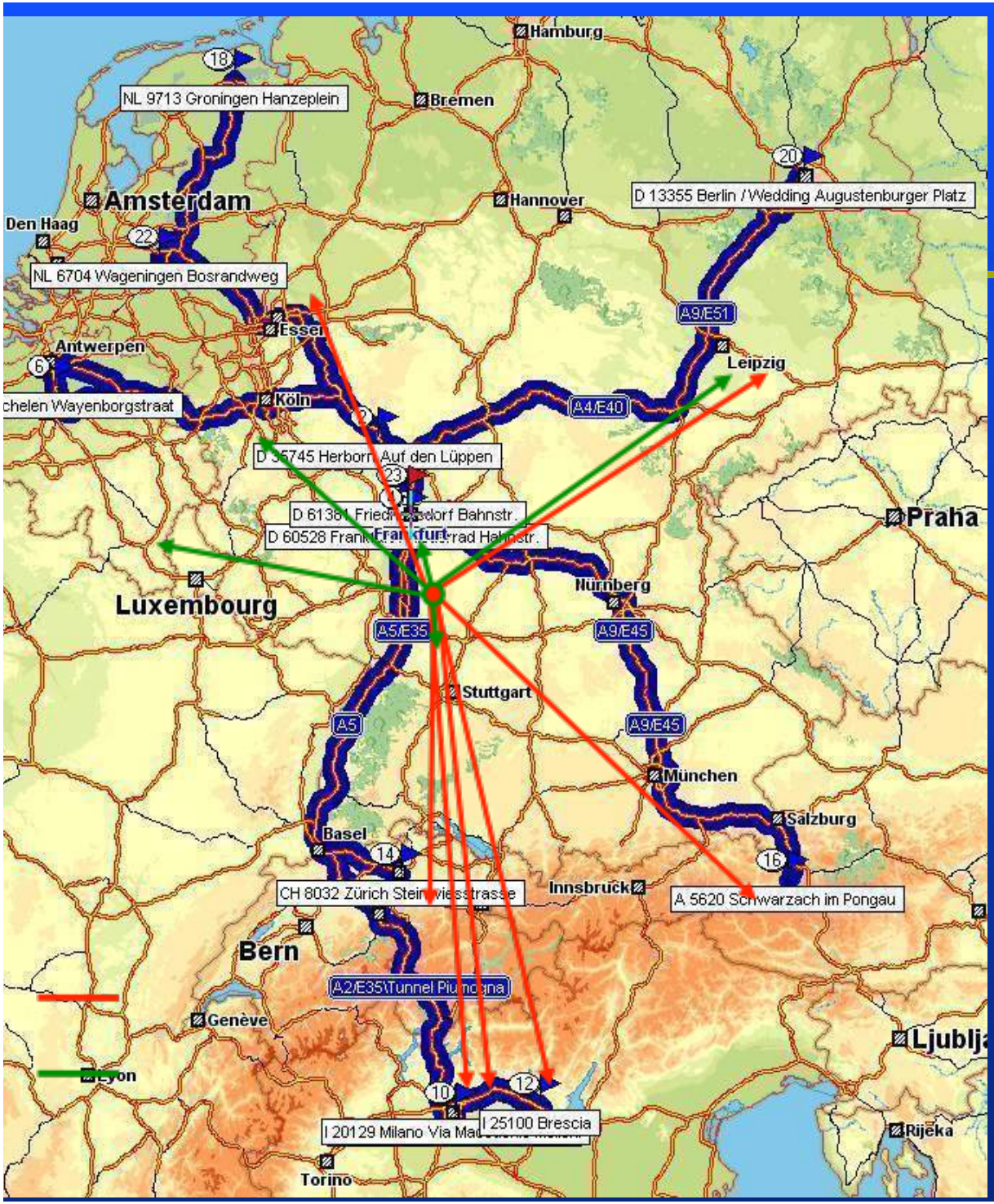
Boehm et al 2005

Moro, Arslanoglu et al. Arch Dis Child, 2006

Atopic Dermatitis : Results

1. Supplementation of infant formula with this prebiotic mixture reduced by 51% the incidence of AD in the first 6 months of life in infants at high risk of atopy

2. In this scenario, 7 infants should be treated to prevent one case of AD in the first 6 months of life



7 Centres in 5 Countries

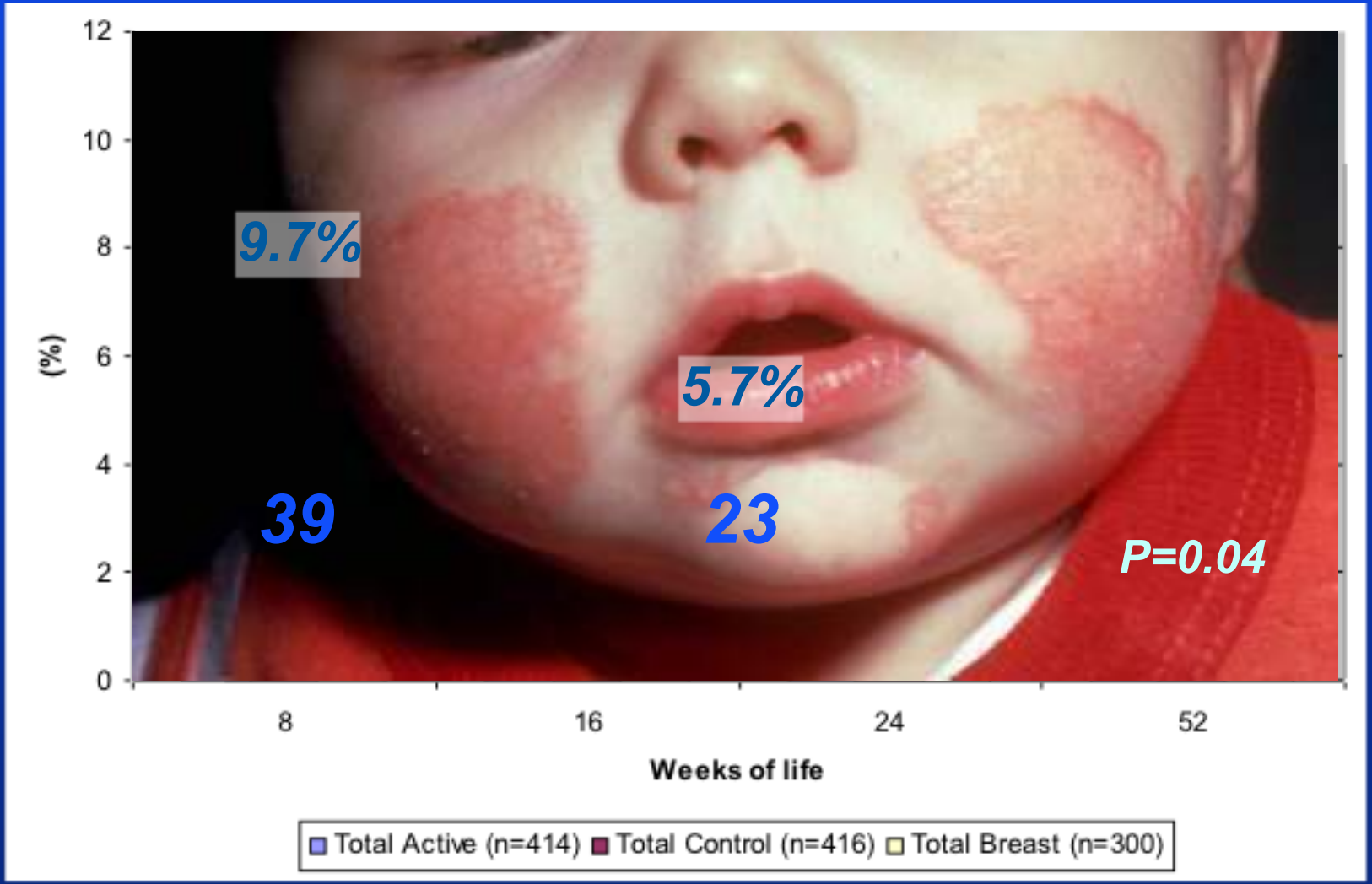
Multicentre Infection Preventive Study

Healthy term infants at low risk of atopy

STUDY DESIGN

- 830 healthy term infants with low atopy risk were recruited from 7 European centers.
- Infants were randomized to a formula with GOS/FOS (Prebiotics Group = PG, n=414) or without GOS/FOS (Control Group = CG, n=416) for the first year of life.
- A Breastfeeding Group (BG, n=300) was included as the non-randomized reference group.
- Infants were clinically examined at study entry, 2, 4, 6, and 12 months of life.
- The main aim of the study was to assess the occurrence of AD in the first year of life.

Cumulative Incidence of AD at 52 weeks



Clinical Implications

Formula supplementation with this specific mixture of oligosaccharides is effective as primary prevention of AD also in infants from low atopy risk population.

Clinical Studies

- Prebiotics and Intestinal Flora
- Prebiotics and Allergy
- **Prebiotics and Infections**
- Follow-up and Long Lasting Effects
- Costs of Allergic Diseases

Preventive Effects of GOS/FOS on Infections

Milan study :

Infants at high risk for allergy evaluated in the first 6 months of life for

number and severity of infections

(Moro, Arslanoglu et al. 2006)

Milan study : number of infections in the study population (first 6 months of life)

Milan study : number of infections requiring antibiotic therapy (first 6 months of life)

Prebiotics and Infections : Conclusions

Prebiotic supplementation in healthy term infants at high risk for allergy :

- ***Reduces the risk of infections***
  (mainly upper respiratory infections)
- ***Reduces the use of antibiotics***

Clinical Studies

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Long lasting effects

Bifidogenic effects

Clinical effects

Bifidogenic effects

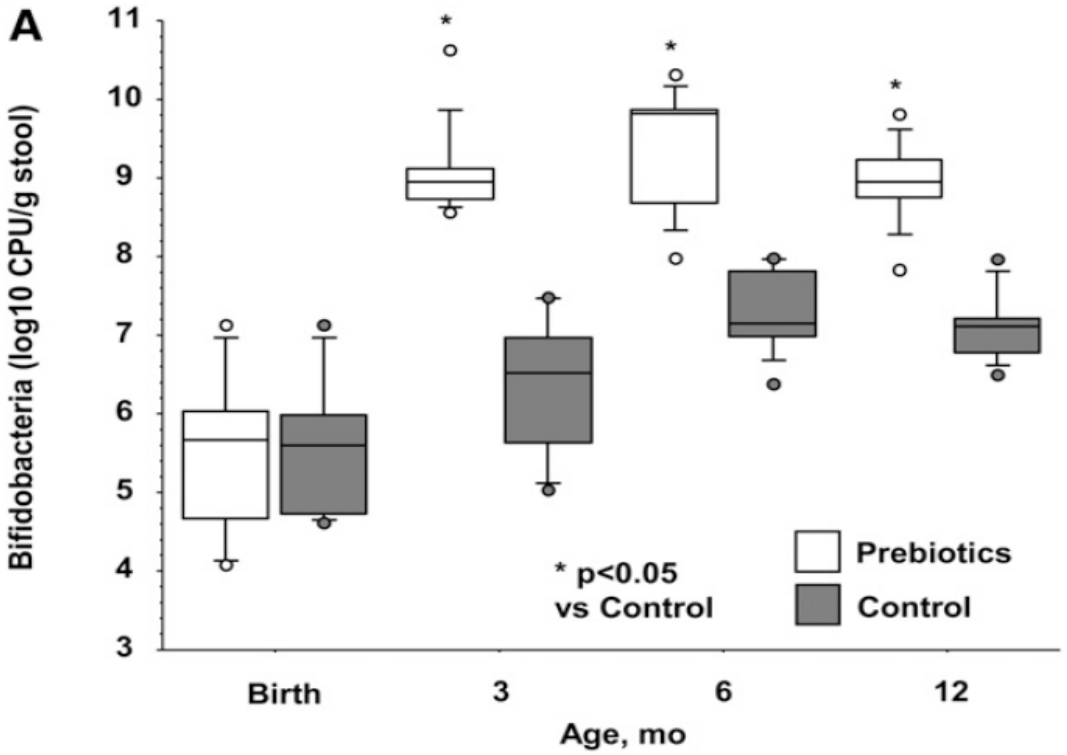
A Specific Prebiotic Mixture Added to Starting Infant Formula Has Long-Lasting Bifidogenic Effects[1–3]

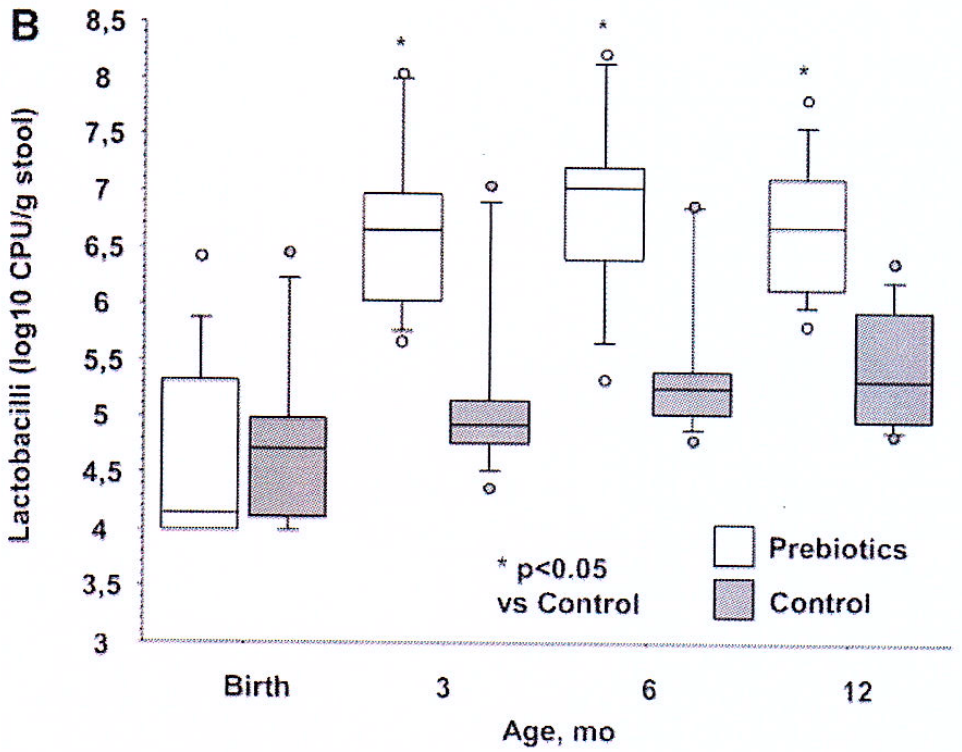
Filippo Salvini,[4]* Enrica Riva,[4] Elisabetta Salvatici,[4] Günther Boehm,[5,6] Jürgen Jelinek,[5] Giuseppe Banderali,[4] and Marcello Giovannini[4]

[4]Paediatric Department, University of Milan, San Paolo Hospital, Milan 20142, Italy; [5]Danone Research, Centre for Specialised Nutrition, Friedrichsdorf 61381, Germany; and [6]Sophia Children's Hospital, Erasmus University, Rotterdam 3015, The Netherlands

The Journal of Nutrition, 2011

A Specific Prebiotic Mixture Added to Starting Infant Formula Has Long-Lasting Bifidogenic Effects[1–3]





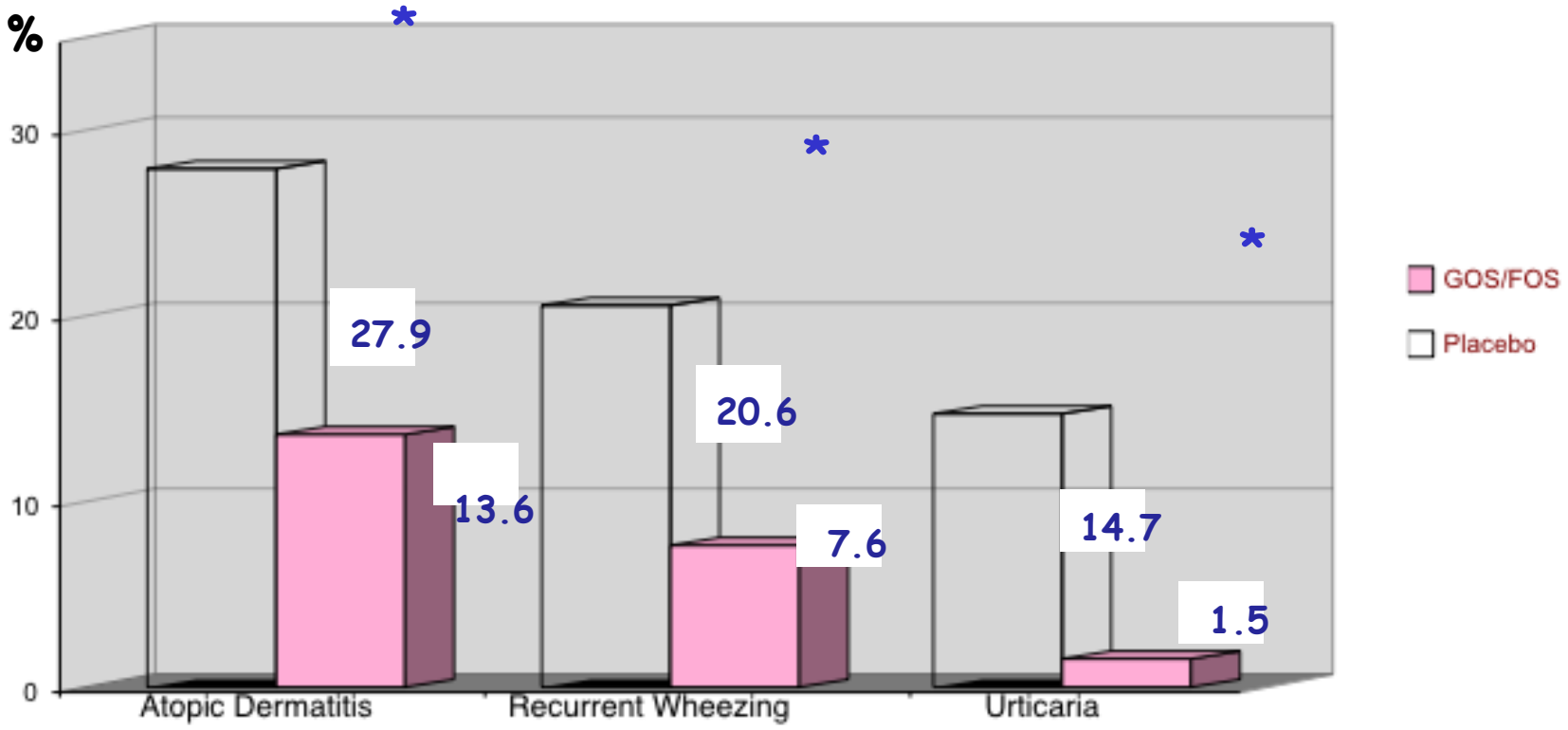
The data from this study indicate that early colonization of the intestine might have long-lasting effects on the composition of the intestinal microbiota.

Clinical effects

Long term clinical effect of prebiotics: 2 years follow up

Infants at high risk for allergy

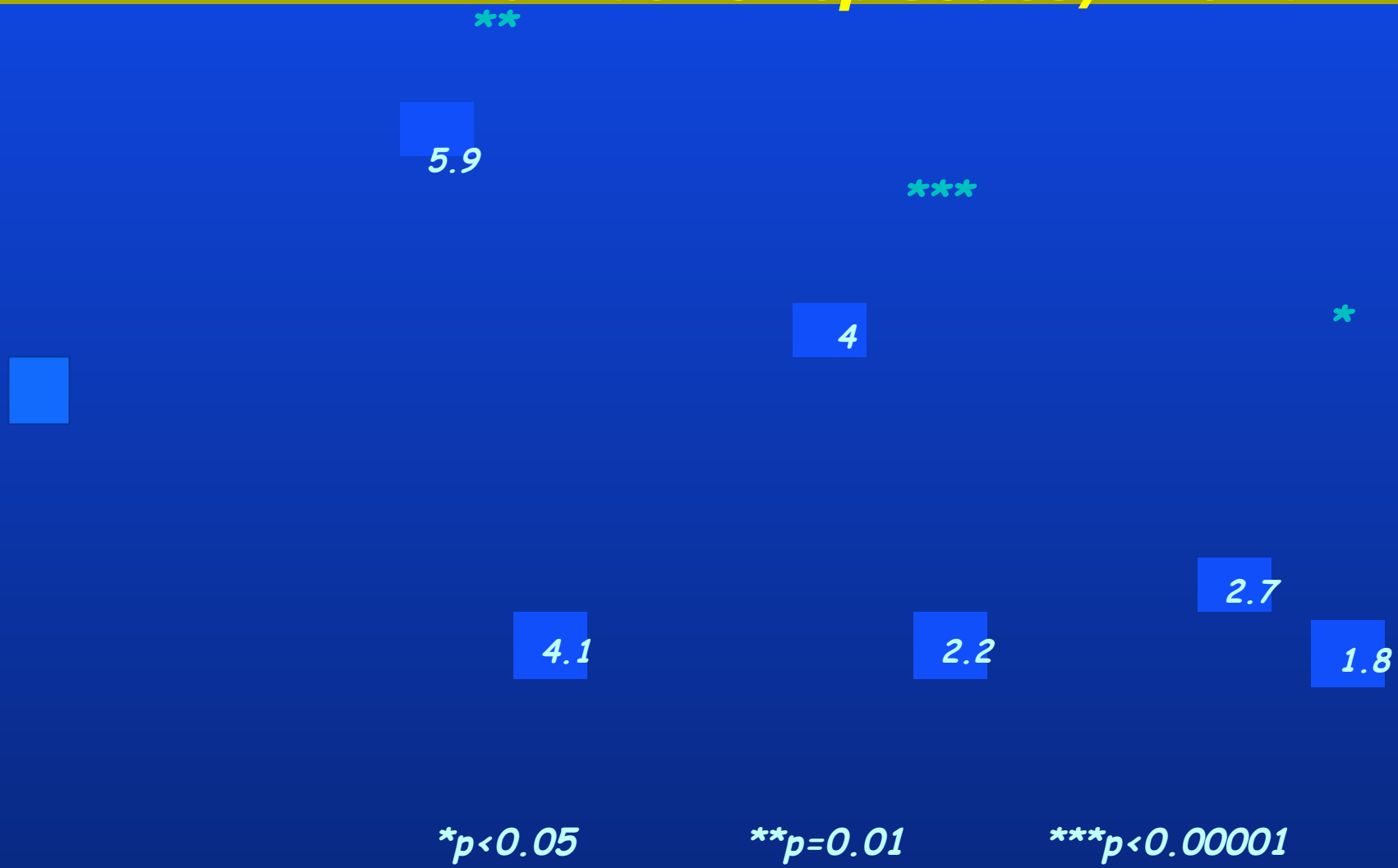
Cumulative Incidence of Allergic Diseases at 2 y



*p<0.05 for the difference between groups
Fisher's exact test

Number of Infectious Episodes

Number of episodes/infant



*p<0.05 **p=0.01 ***p<0.00001

Available online at www.sciencedirect.com
SciVerse ScienceDirect
2013

Table III – Comparative frequency of allergic reactions during the first 18 months of life depending on the type of feeding
Tabela III – Porównanie częstości występowania reakcji alergicznych u dzieci w ciągu pierwszych 18 miesięcy życie w zależności od rodzaju karmienia

	Group 1 n = 51	Group 2 n = 62	Group 3 n = 53	p
Allergic reactions to food*	3.92 (2)	4.84 (3)	16.98 (9)	<0.05
Allergic reactions to caw's milk protein*	1.96 (1)	3.23 (2)	15.09 (8)	<0.05
AD*	3.92 (2)	4.84 (3)	16.98 (9)	<0.05
Respiratory system allergic symptoms*	1.96 (1)	4.84 (3)	13.21 (7)	<0.05
Gastro-intestinal symptoms of food allergy*	1.96 (1)	3.23 (2)	13.21 (7)	<0.05

*percentage, number of children in brackets

Olena S. Ivakhnenko, Serhiy L. Nyankovskyy *
Lviv National Medical University, Lviv, Ukraine

Group 1 = breast-fed; Group 2 = GOS/FOS; Group 3 = standard formula

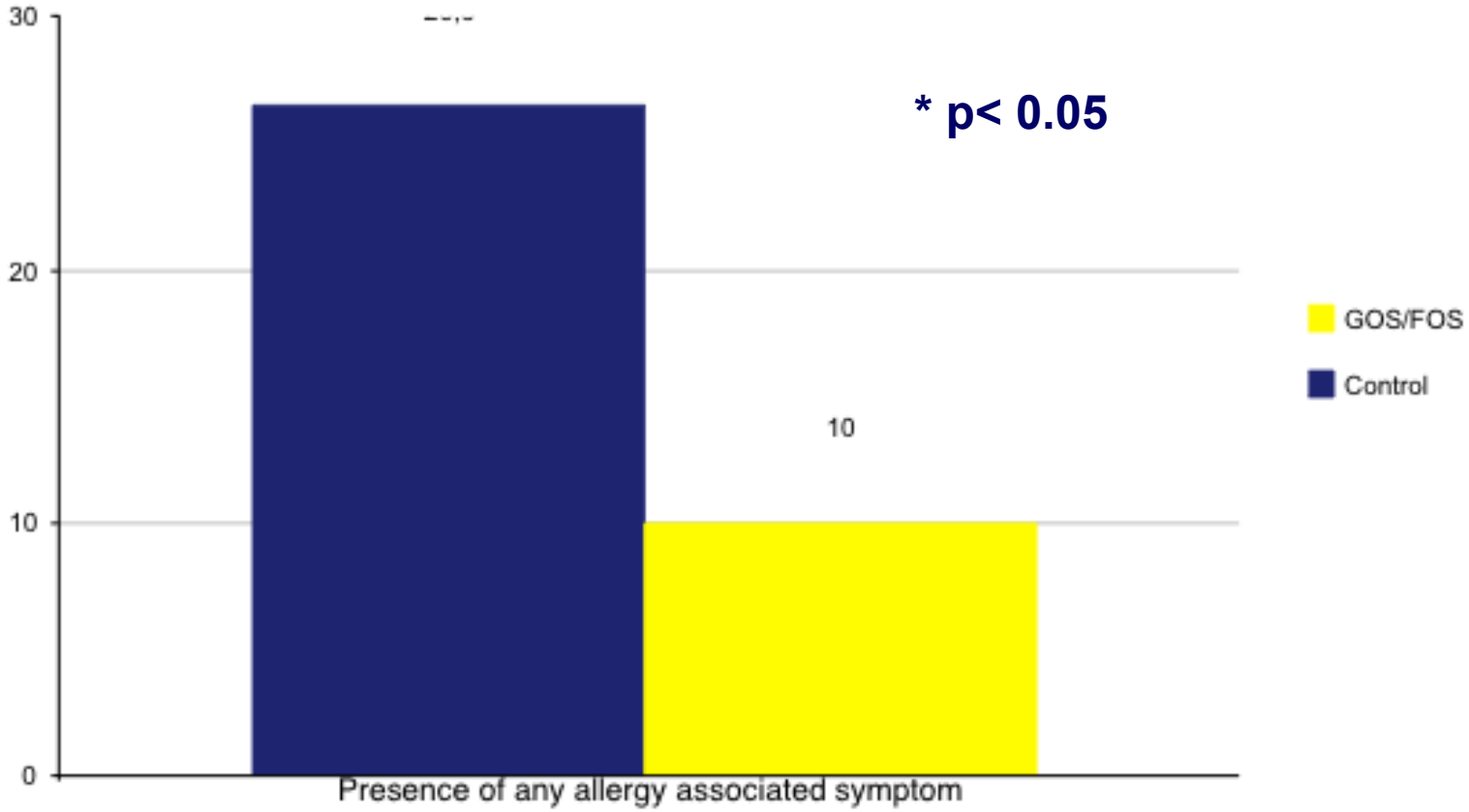
This study, performed in healthy term infants at low risk for atopy, confirms the long term benefits of the GOS/FOS mixture in the prevention of allergies at the age of 18 months.

Clinical effects

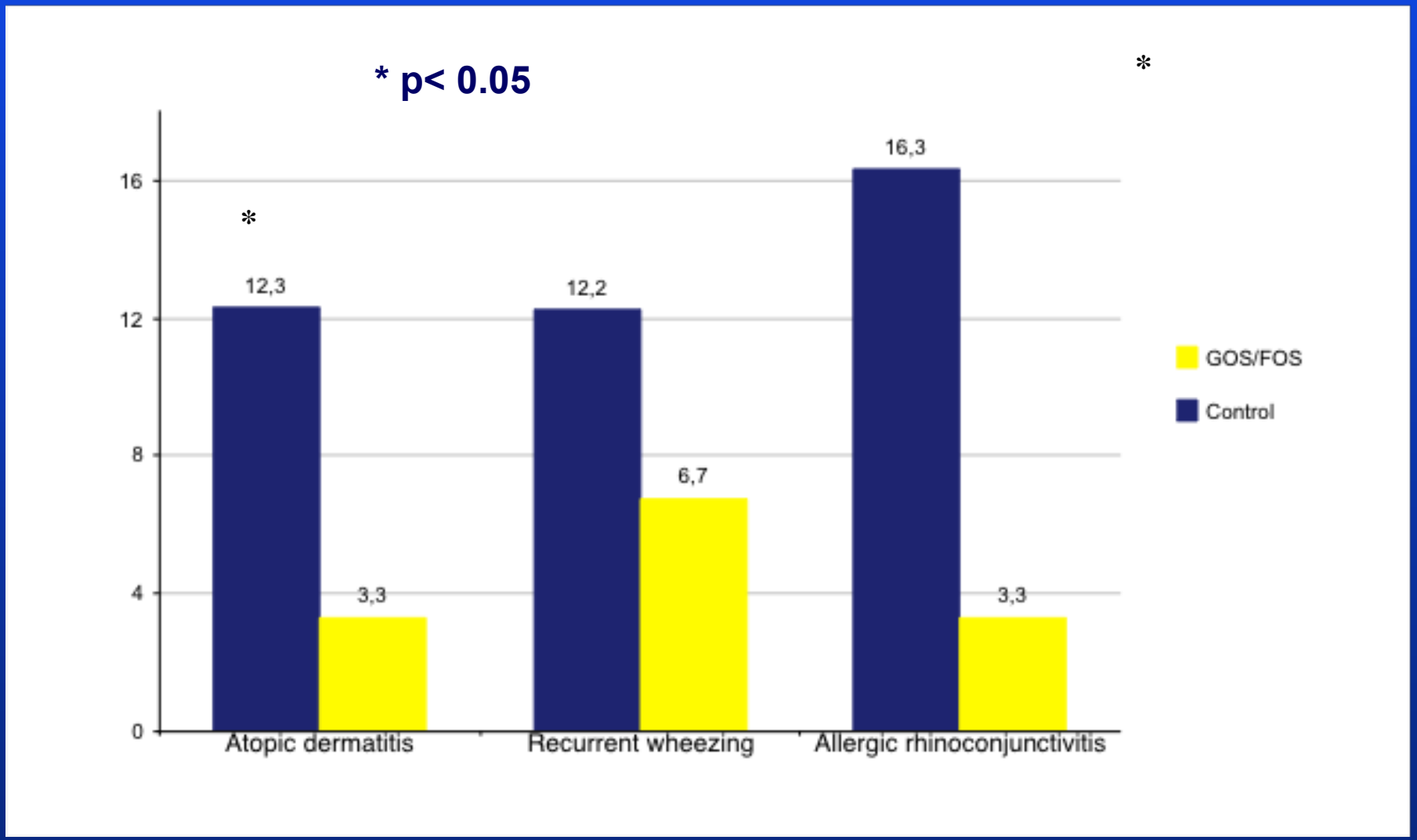
Long term clinical effect of prebiotics: 5 years follow up

Infants at high risk for allergy

ALLERGY ASSOCIATED SYMPTOMS AT 5 YEARS



ALLERGY ASSOCIATED SYMPTOMS AT 5 YEARS



Effect of Prebiotics on ATOPIC MARCH

Correlation between AD at 6 m and allergic manifestations at 5 y

Allergic manifestations at 5 years (%)	(+)AD at 6 m n=20	(-)AD at 6 m n=72	
Any persistent allergic manifestation (%)			
Persistent AD (%)			
Persistent wheezing (%)			
All. rhinoconjunctivitis (%)			

Correlation between AD at 6 m and allergic manifestations at 5 y

Allergic manifestations at 5 years (%)	(+)AD at 6 m n=20	(-)AD at 6 m n=72	OR P value
Any persistent allergic manifestation (%) *	40	9.7	6.2 0.003
Persistent AD (%) *	30	1.4	30.4 0.0001
Persistent wheezing (%)	20	5.6	4.3 0.065
All. rhinoconjunctivitis (%) *	25	4.2	7.7 0.01

* Statistically significant

AD and Atopic March: Conclusions

Occurrence of AD within the first 6 mo of life increases the onset and persistence of allergic manifestations in the first years of life (5 years)

In our study, the significant reduction of AD occurrence (57% reduction at 6 mo, 50% at 2 y) in the intervention group (scGOS/lcFOS, 9:1) has been accompanied by a marked reduction (≈80%) in allergic manifestations later

These two findings together imply that scGOS/lcFOS supplementation early in life is successful in avoiding the onset of the ***"atopic march"*** in a high risk group.

Clinical Studies

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Nutrition economic evaluation of allergy treatment in infants and children: background for probiotic studies

€ 425

Soili Alanne, MSc, SRD[1,2*]

[1]Department of Clinical Nutrition, Seinäjoki Central Hospital, Hospital District of South Osthrobothnia, Seinäjoki; [2]Functional Foods Forum, University of Turku, Finland

Microbial Ecology in Health & Disease, 2012

Atopic Dermatitis in Italian Children: Evaluation of Its Economic Impact

€ 312

Cost-effectiveness for a specific mixture of prebiotics in The Netherlands

Eur J Health Econ, 2010

Giampaolo Ricci, MD, Barbara I
Laura Pagliara, MD, Annalisa Pa
Massimo Masi, MD

J Pediatr Health Care, 2006

I. Lenoir-Wijnkoop · W. M. C. van Aalderen · G. Boehm · D. Klaassen · A. B. Sprikkelman · M. J. C. Nuijten

€ 472

Dutch Study

- The cost saving for AD in 100 infants at high risk of allergy receiving a formula with the GOS/FOS mixture of prebiotics, in the first 2 years of life is **€ 6749**

  (based on our 2 years follow up study)

- The total annual national cost saving may be at least **€ 4.2 millions**

  (based on Dutch data from high risk babies born in 2007)

Commonly used Prebiotics in Infant Formulas

PREBIOTIC	N of studies	N Infants in PG
SINGLE INGREDIENTS		
GOS	**2**	**146**
PDX	**1**	**25**
INULIN	**2**	**50**
scFOS	**5**	**374**
LACTULOSE	**1**	**15**
MIXTURES		
GOS/LACTULOSE	**1**	**150**
PDX/GOS	**1**	**27**
PDX/GOS/LACTULOSE	**1**	**27**
scFOS/lcFOS	**1**	**63**
scGOS/lcFOS	**20**	**1021**
scGOS/lcFOS/pAOS	**4**	**556**

Evaluated since more than 15 years, this GOS/FOS mixture represents the most studied compound in clinical trials and its safety and efficacy have been widely proven by scientific evidence

Moro and Boehm, Funct Review 4, 2012

FOS: Fructo-oligosaccharides; GOS: galacto-oligosaccharides; PDX: Polydextrose

Key Message 1:
Human Milk is the Gold Standard

Key Message 2:
When mother's milk is not available Formula with GOS/FOS should be used

Key Message 3:
This mixture mimics the GI effects of HM

Key Message 4:
Less allergies and infections

Key Message 5:
Long lasting effects

Thank you for your attention !