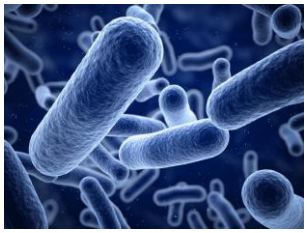


Gut Instinct: how the way you're born and fed affect your immune system

Dr Vincent Ho
Senior Lecturer and Gastroenterologist
Western Sydney University School of Medicine

Immune fitness – the key ability to be fit for the future

Immune fitness refers to a resilient immune system with an inbuilt capacity to adapt to challenges by establishing, maintaining and regulating an appropriate immune response

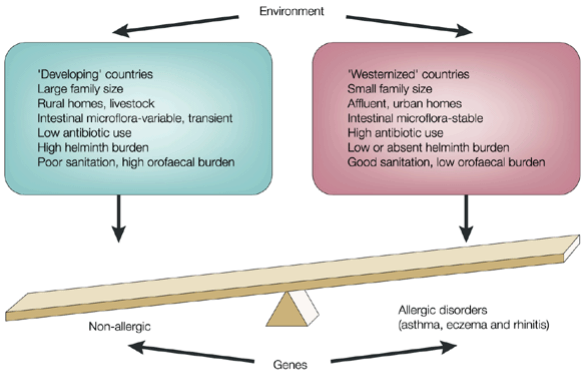
Immune system:
Resilient or even transformative

Impact on wellbeing:
Quick and integral recovery, energetic, healthier after infection

"Healthy and Happy"

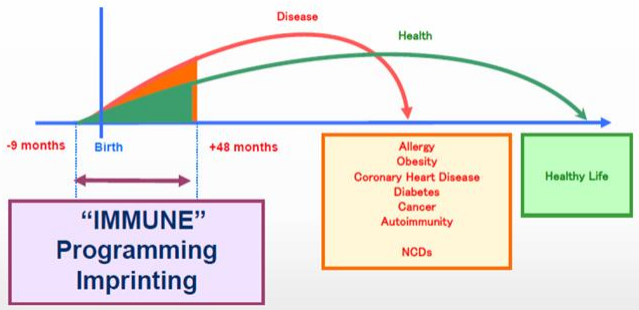
ADAPTED FROM IMMUNOWELL.COM
https://www.ncbi.nlm.nih.gov/medlineplus/ency/article/000821.htm

Immune fitness and the ability to adapt – Hygiene hypothesis

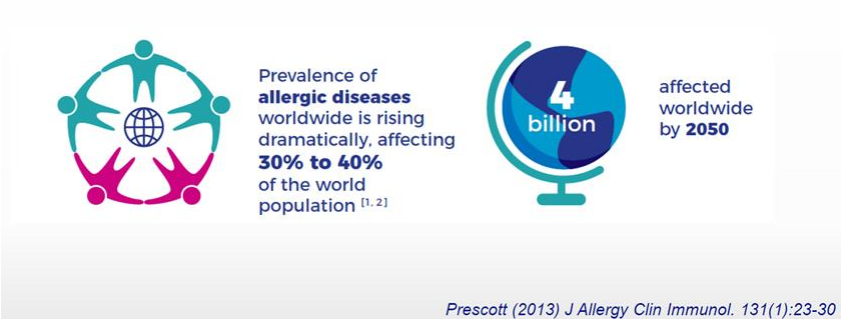


Nature Reviews | Immunology

Prevention of non-communicable diseases – early life changes preparing for later life

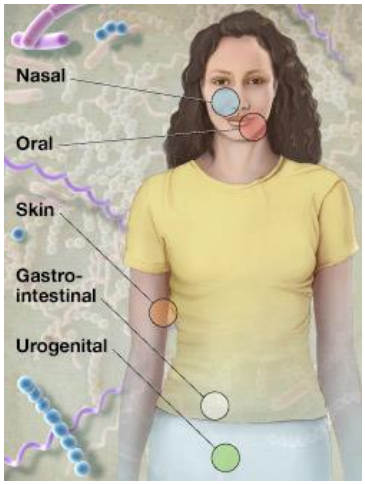


Prevalence of allergic diseases rising



Sites that harbor a normal bacterial flora:

- Skin and mucous membranes
- Upper respiratory tract
- Gastrointestinal tract
- Outer opening of urethra
- External genitalia
- Vagina
- External ear canal
- External eye (lids, conjunctiva)



Benefits of normal bacterial flora

1. Synthesize and excrete vitamins
Vitamin K and Vitamin B12

2. Prevent colonization by pathogens
competing for attachment sites or for essential nutrients

3. May antagonize other bacteria
the production of substances which inhibit or kill non-indigenous species(nonspecific fatty acids, peroxides, bacteriocins).

4. Stimulate the development of certain tissues
i.e., intestines, certain lymphatic tissues, capillary density

5. Stimulate the production of cross-reactive antibodies.
Low levels of antibodies produced against components of the normal flora are known to cross react with certain related pathogens, and thereby prevent infection or invasion.

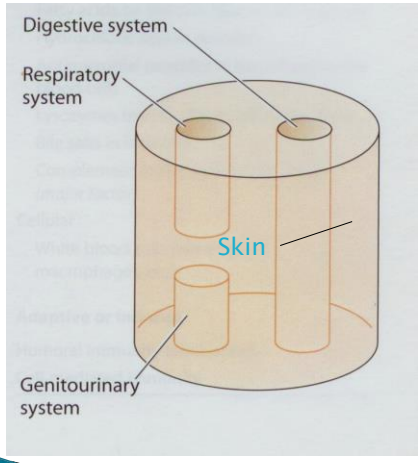
A healthy microbial community is essential

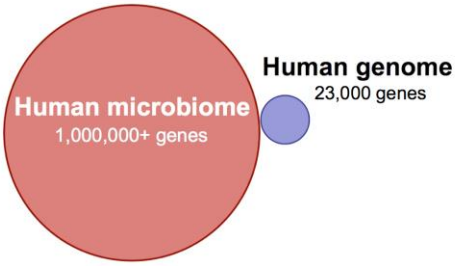
Mice raised in a germ-free environment display:

- Decreased nutrient absorption
- Less developed intestines
- Vitamin deficiency
- Underdeveloped immune system
- Heighted sensitivity to pathogens

(Hooper et al. 2001 *Science*)

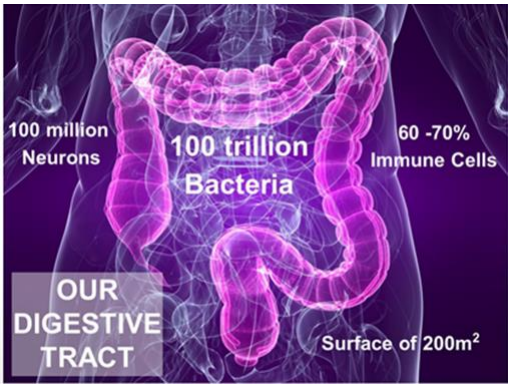
A microbe's view of us





Bacterial cells outnumber your body cells 10:1 and comprise up to 2.5 kg of your body mass

The GUT



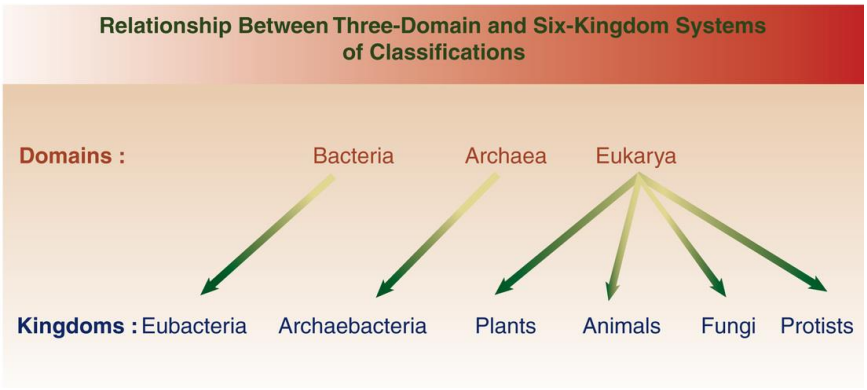
Definition of gut microbiome

- The human microbiota consists of a wide variety of bacteria, viruses, fungi, and other single-celled animals that live in the body.
- The microbiome is the name given to all of the genes inside these microbial cells.
- These two terms “microbiota” and “microbiome” are often used interchangeably

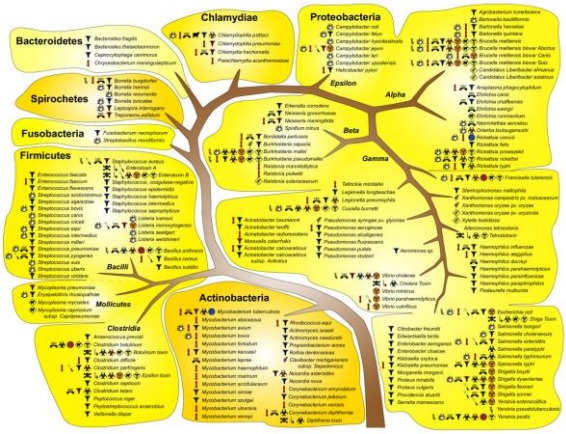
Features of a healthy gut microbiota

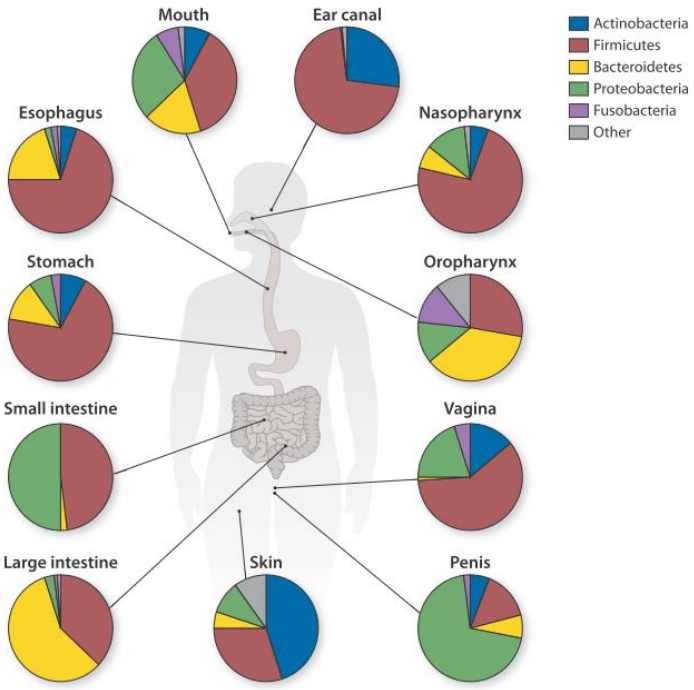
- High level of diversity
- High level of stability
- Resistance to stress-related change (antibiotics, infections and immunosuppression)
- High level of redundancy of metabolic pathways

Classification of living things

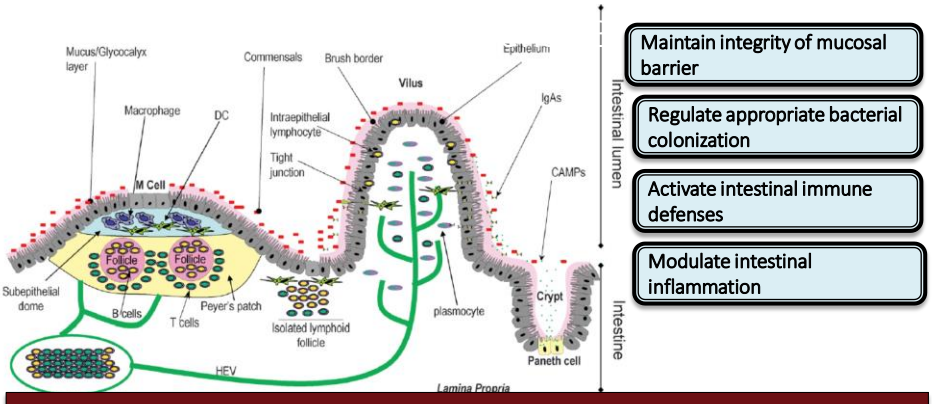


Bacterial tree – Phyla





Intestinal Tract: The largest immune organ (70% of the immune system) and defense barrier



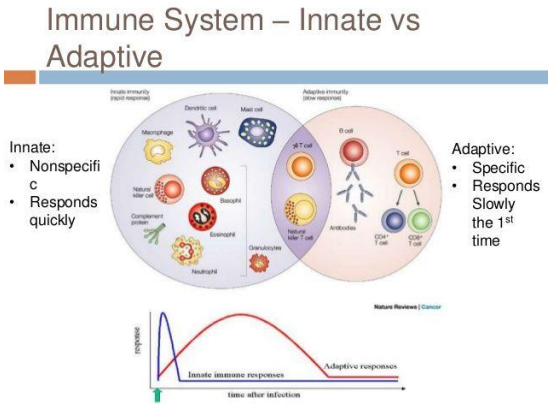
- Maintain integrity of mucosal barrier
- Regulate appropriate bacterial colonization
- Activate intestinal immune defenses
- Modulate intestinal inflammation

Balance between appropriate tolerance & inflammatory attack

- Non-specific intestinal barrier defenses
- Epithelial cell layer
- Gut-associated lymphoid tissue (GALT)

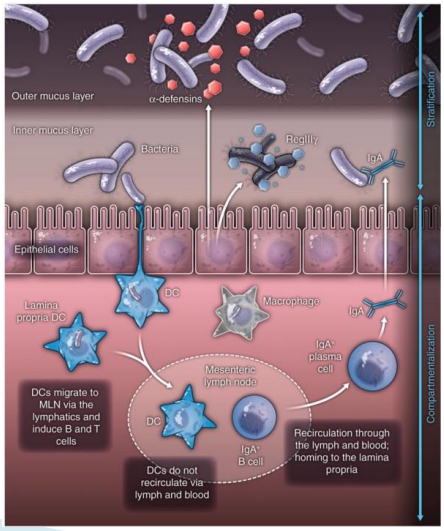
From Magalhaes JG, Tattoli I, Girardin SE. The intestinal epithelial barrier: how to distinguish between the microbial flora and pathogens. Semin Immunol. Apr 2007;19(2):106-115.

How the immune system works

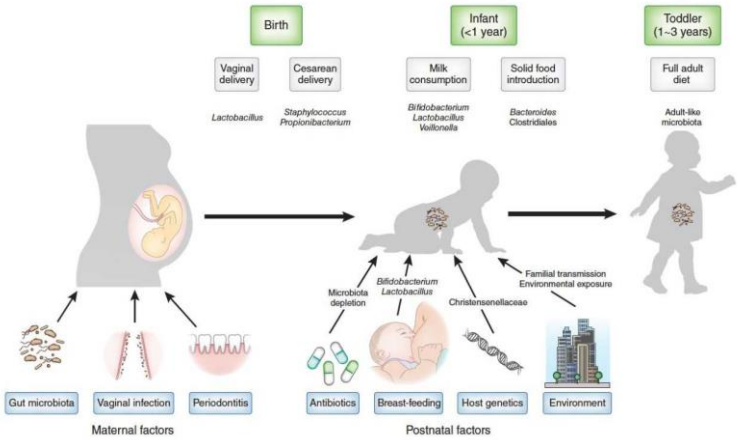


Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004;4:11–22.

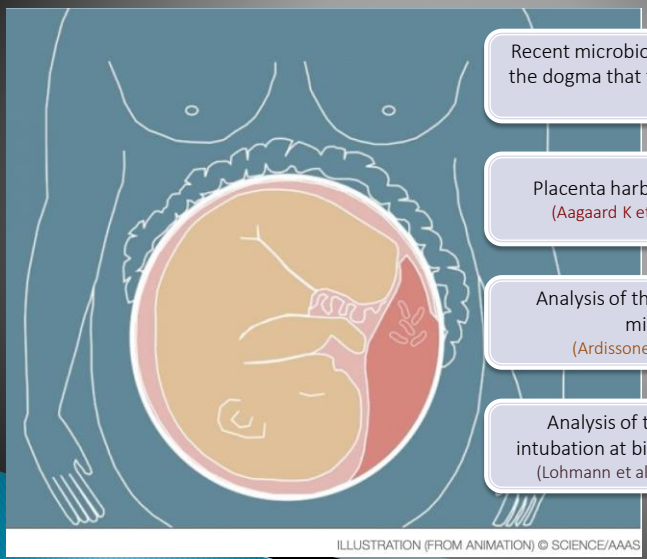
How commensal bacteria function within the gut immune system



The first 1000 days of life



Maternal foetal microbiota



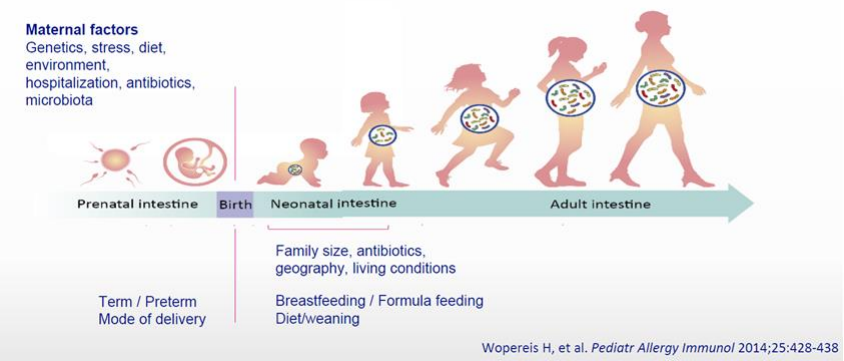
Recent microbiota studies have challenged the dogma that the the Maternal-Fetal unit is sterile.

Placenta harbors a unique microbiota
(Aagaard K et al, Sci Transl Med. 2014)

Analysis of the first meconium reveal microorganisms
(Ardissone et al., Plos one 2014)

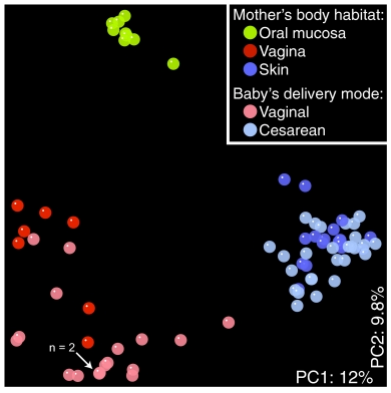
Analysis of tracheal aspirates after intubation at birth reveal microorganisms
(Lohmann et al., Pediatric Research 2014)

Factors influencing the early microbiota development



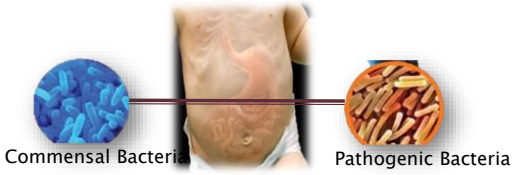
Wopereis H, et al. *Pediatr Allergy Immunol* 2014;25:428-438

The first microbiotas of newborns are primarily structured by delivery mode



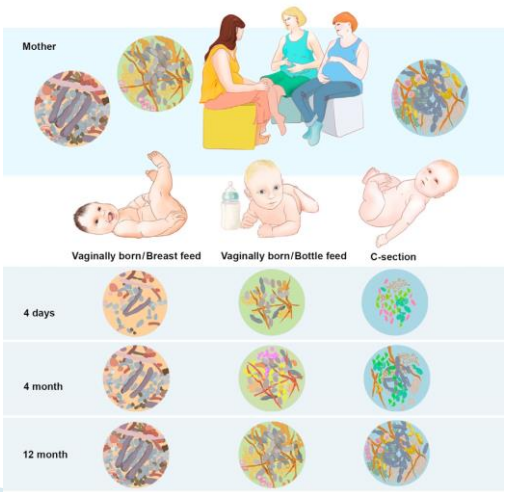
Dominguez-Bello M.G., Costello E.K., Contreras M., Magris M., Hidalgo G., Fierer N., Knight R. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc. Natl. Acad. Sci. USA. 2010;107:11971-11975.

Colonisation Patterns in the Newborn

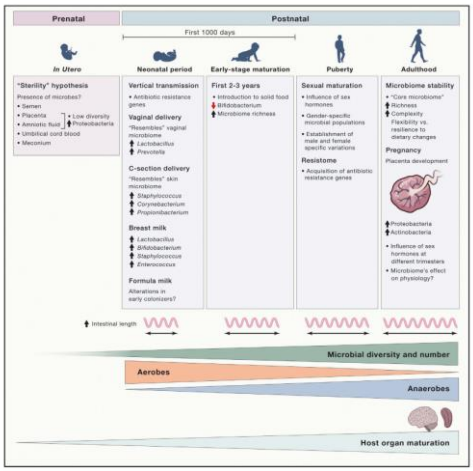


Exposure	Bifidobacterium, Lactobacillus	Enterococci, Clostridium, Coliforms
Delivery Mode	Vaginal	Caesarean Section
Diet	Breast Milk	Formula
Hospitalization		✓
Medications		
Antibiotics H2 Blockers		✓ ✓
Prematurity		✓

Delivery mode, feeding and infant microbiome



Gut microbiome changes from infancy to adulthood



Kundu, Parag et al. Our Gut Microbiome: The Evolving Inner Self Cell , Volume 171 , Issue 7 , 1481 – 1493

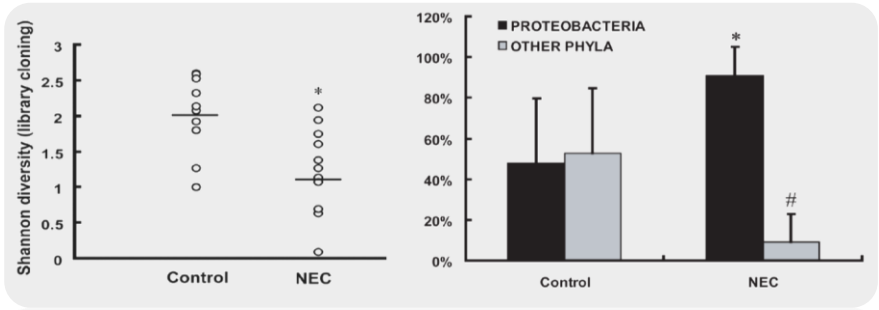
What happens when it goes wrong?

Features of a unhealthy gut microbiota

- Low level of diversity
- Low level of stability
- Low resistance to stress-related change (antibiotics, infections and immunosuppression)
- Low level of redundancy of metabolic pathways

Necrotising enterocolitis: Reduced diversity, increased proteobacteria

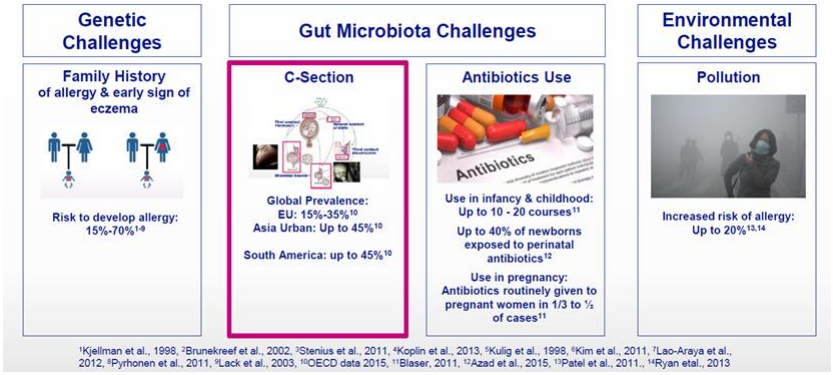
Reduced diversity, increased proteobacteria



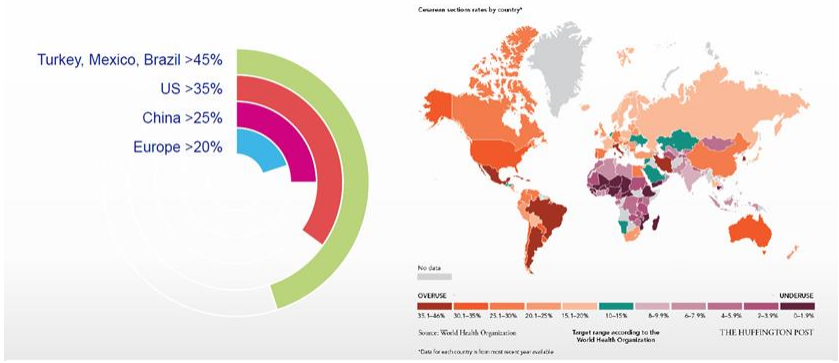
Microbiome is altered in ALL preterm infants!

Wang et al. ISME J, 2009

Immune system under challenge..



C-section rate increasing globally



Delivery mode shapes microbiota acquisition in newborns and may increase the risk of allergies

Infants born by C-section have a different microbiota composition than those born by vaginal delivery

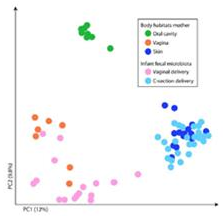
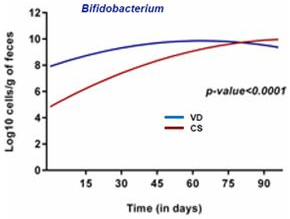


Figure based on Dominguez-Bello et al. (2010) PNAS 107: 11971–11975

Infants born by C-section have a delayed colonization by Bifidobacterium



Martin et al, (2016) PlosOne 11(6)

Infants born by C-section may have higher risk of asthma

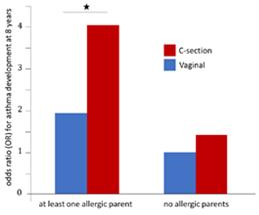


Figure based on Rodult et al. (2009) Thorax 64:107-113

C-section may increase the risk of allergies

Danish Cohort: IRRs by Cesarean Delivery in the 35-Year Period 1977-2011

- Following 1.9 Million Term
- Children in the Age Span 0 to 15 Years

Children delivered by C-section had significantly increased risk of **asthma, inflammatory bowel disease and immune deficiencies**

	Cases	aIRR (95% Confidence Interval); *P*	PARF (Cases)
Asthma[a]	103 822	1.23 (1.21–1.25); *P* < .0001	3.07 (3187)
Asthma >5 y[b]	48 858	1.16 (1.13–1.19); *P* < .0001	2.19 (1070)
Systemic connective tissue disorders	7498	1.11 (1.04–1.19); *P* = .0021	1.53 (115)
Juvenile arthritis	6946	1.10 (1.02–1.18); *P* = .0117	1.34 (93)
Diabetes type 1	6136	1.01 (0.93–1.10); *P* = .82	—[d]
Inflammatory bowel diseases	2697	1.20 (1.06–1.36); *P* = .004	2.70 (73)
Immune deficiencies	2589	1.48 (1.32–1.62); *P* < .0001	6.09 (158)
Celiac disease	1944	0.99 (0.87–1.14); *P* = .89	—[d]
Leukemia	1631	1.17 (1.00–1.36); *P* = .048	2.31 (38)
Psoriasis	1306	0.98 (0.81–1.18); *P* = .81	—[d]
Arm fracture[b,c]	77 490	0.99 (0.96–1.01); *P* = .19	—[d]

Cases are defined by first in- or outpatient admission to a hospital in Denmark. IRRs are adjusted for age, calendar year, birth weight, parity, gender, season of birth, maternal age, and maternal illness. The PARF is calculated based on an overall prevalence of 14% cesarean deliveries for diseases with significant association to cesarean delivery.

[a] Attained age and calendar year included in 1-y categories.

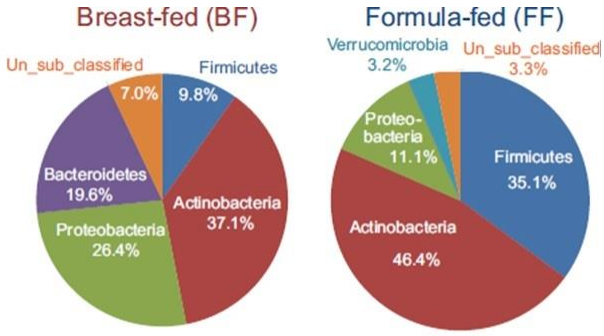
[b] Attained calendar year included in 3-y and age in 6-y categories.

[c] Not adjusted for maternal disease.

[d] PARF is not calculated for insignificant associations.

Sevelsted A et al. Pediatrics. 2015 Jan;135(1):e92-8

Changes with formula feeding

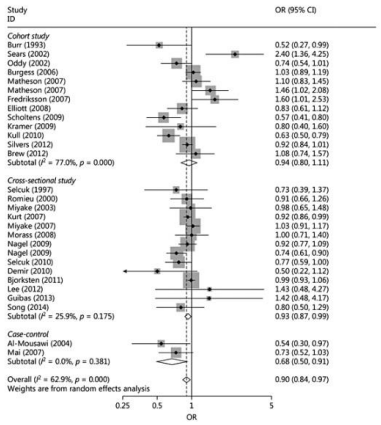


- BF had more total Proteobacteria and Bacteriodetes
- FF had more Firmicutes and no Bacteriodetes

Donovan, S. M., M. Wang, M. Li, I. Friedberg, S. L. Schwartz, and R. S. Chapkin. 2012. Host-microbe interactions in the neonatal intestine: Role of human milk oligosaccharides. *Advances in Nutrition* 3(3):450S-455S.

Breast feeding reduces risk of asthma in children

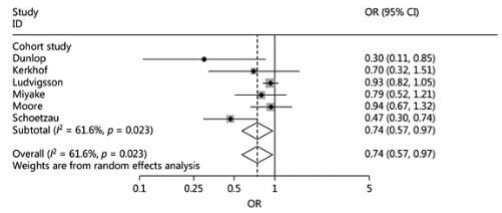
Meta-analysis: more versus less breastfeeding and risk of asthma in children aged 5-18 years. OR, odds ratio; CI, confidence interval.



Lodge CJ, Tan DJ, Lau MXZ, Dai X, Tham R, Lowe AJ, et al: Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatrica 2015;104:38-53.

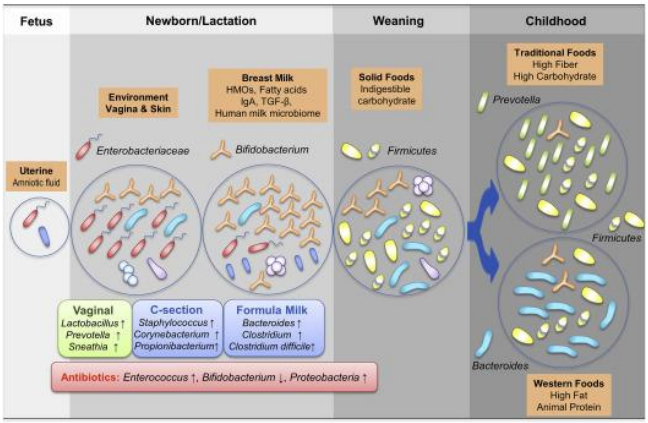
Breast feeding reduces risk of eczema

Meta-analysis: exclusive breastfeeding >3- 4 months compared with less and risk of eczema up to 2 years of age. OR, odds ratio; CI, confidence interval.



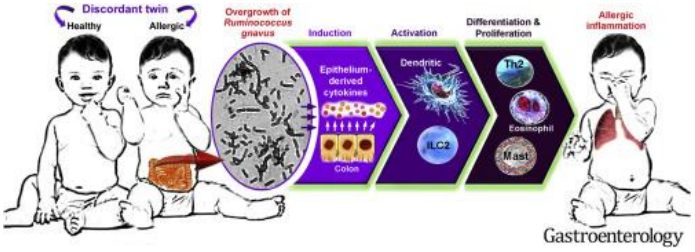
Lodge CJ, Tan DJ, Lau MXZ, Dai X, Tham R, Lowe AJ, et al: Breastfeeding and asthma and allergies: a systematic review and meta-analysis. Acta Paediatrica 2015;104:38-53.

Changes in microbiota in infancy/childhood



J Allergy Clin Immunol 2001;107:153e9. 5. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. Allergol Int 2017;66:515e22

How early life disruption of the gut microbiome (dysbiosis) can lead to increased allergy risk



Chua H. H., Chou H. C., Tung Y. L., et al. Intestinal dysbiosis featuring abundance of Ruminococcus gnavus associates with allergic diseases in infants. *Gastroenterology*. 2018;154(1):154-167

Early life disruption of the gut microbiota is associated with increased risks of allergies

Beneficial Microbes, 2017 online ARTICLE IN PRESS

Ratio of *Klebsiella*/*Bifidobacterium* in early life correlates with later development of paediatric allergy

J.S.Y. Low[1], S.-E. Soh[2,3,#], Y.K. Lee[4], K.Y.C. Kwek[5#], J.D. Holbrook[2,6], E.M. Van der Beek[7,8], L.P. Shek[2,3#], A.E.N. Goh[5#], O.H. Teoh[5#], K.M. Godfrey[9#], Y.-S. Chong[2,10#], J. Knol[7,11] and C. Lay[1,3*]

Time is also important!
Differences precede the onset

Table S2. Ratio of relative abundances of *Klebsiella* to *Bifidobacterium* (K/B ratio) of allergic and healthy infants at age 3 weeks, 3 months and 6 months respectively.

Timepoint	*Klebsiella*/*Bifidobacterium* ratio		
	Healthy controls	Allergic cases	*P*-value
Week 3	0.23 (0.01-213.07)	1.70 (0.01-1408.00)	0.12
Month 3	0.03 (0.00-0.68)	0.52 (0.00 – 2281.33)	*0.01
Month 6	0.01 (0.00-62.00)	0.05 (0.00-910.50)	0.26

The values were expressed in median (range). Differences in medians of *Klebsiella*/*Bifidobacterium* ratio between the two groups were performed using non-parametric Mann-Whitney U test. Single asterisk (*) indicate $P \leq 0.05$.

Interpreting the gut microbiota

Real life example – my son Brandon

Brandon's 3 week faecal microbial assay

Collection Date: 4/12/2017 Receipt Date: 6/12/2017 Process Date: 6/12/2017 Completed Date 18/12/2017

Name: Ho, Brandon
Address:

Referred by: Ho, Vincent

Sample ID: 138758 DOB: 9/11/2017

Ho, Brandon

Total Count	cfu/gm	Hi	Lo	Normal Range	% Distribution	Normal Distribution
Total Bacterial Count	1.92×10^{10}					
Aerobe:Anaerobe Ratio	43.82					
Aerobes						
Total Aerobe Count	8.06×10^{8}					
E.coli coliform	1.78×10^{8}					
Escherichia coli	1.78×10^{8}					
Enterococcus (Total)	6.07×10^{6}					
Enterococcus faecalis	6.07×10^{6}					
Staphylococcus (Total)	2.09×10^{7}					
Staphylococcus aureus	2.09×10^{7}					
Yeast (Total)	$<1.00 \times 10^{7}$					

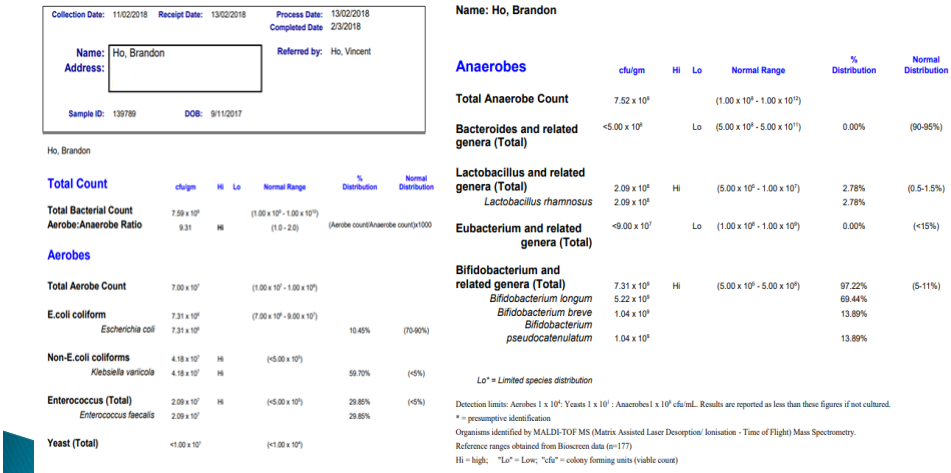
Name: Ho, Brandon

Anaerobes	cfu/gm	Hi	Lo	Normal Range	% Distribution	Normal Distribution
Total Anaerobe Count	1.84×10^{10}					
Bacteroides (Total)	$<1.00 \times 10^{8}$					
Lactobacillus and related genera (Total)	5.23×10^{8}					
Lactobacillus paracasei	5.23×10^{8}					
Bifidobacterium and related genera (Total)	1.57×10^{10}					
Bifidobacterium breve	1.57×10^{10}					
Clostridium and related genera (Total)	7.32×10^{7}					
Clostridium perfringens	7.32×10^{7}					
Other anaerobes						
Propionibacterium acnes	2.09×10^{9}					

Lo = Limited species distribution*

Detection limits: Aerobes 1 x 10^{6}: Yeasts 1 x 10^{5} : Anaerobes1 x 10^{8} cfu/mL. Results are reported as less than these figures if not cultured.
* = presumptive identification
Organisms identified by MALDI-TOF MS (Matrix Assisted Laser Desorption/ Ionisation - Time of Flight) Mass Spectrometry.
Reference ranges obtained from Bioscreen data (n=177)
Hi = high; "Lo" = Low; "cfu" = colony forming units (viable count)

Brandon's 3 month faecal microbial assay



Collection Date: 11/02/2018 Receipt Date: 13/02/2018 Process Date: 13/02/2018 Completed Date 2/3/2018

Name: Ho, Brandon
Address:

Referred by: Ho, Vincent

Sample ID: 139789 DOB: 9/11/2017

Ho, Brandon

Total Count	cfu/gm	Hi	Lo	Normal Range	% Distribution	Normal Distribution
Total Bacterial Count	7.59×10^{9}			(1.00×10^{8} - 1.00×10^{10})		
Aerobe:Anaerobe Ratio	9.31	Hi		(1.0 - 2.0)	(Aerobe count/Anaerobe count)x1000	
Aerobes						
Total Aerobe Count	7.00×10^{7}			(1.00×10^{7} - 1.00×10^{8})		
E.coli coliform	7.31×10^{8}			(7.00×10^{8} - 9.00×10^{8})		
Escherichia coli	7.31×10^{8}				10.45%	(70-90%)
Non-E.coli coliforms	4.18×10^{7}	Hi		($<5.00 \times 10^{6}$)		
Klebsiella varricola	4.18×10^{7}	Hi			59.70%	(<5%)
Enterococcus (Total)	2.09×10^{7}	Hi		($<5.00 \times 10^{6}$)	29.85%	(<5%)
Enterococcus faecalis	2.09×10^{7}				29.85%	
Yeast (Total)	$<1.00 \times 10^{7}$			($<1.00 \times 10^{6}$)		

Name: Ho, Brandon

Anaerobes	cfu/gm	Hi	Lo	Normal Range	% Distribution	Normal Distribution
Total Anaerobe Count	7.52×10^{9}			(1.00×10^{9} - 1.00×10^{12})		
Bacteroides and related genera (Total)	$<5.00 \times 10^{9}$		Lo	(5.00×10^{9} - 5.00×10^{11})	0.00%	(90-95%)
Lactobacillus and related genera (Total)	2.09×10^{8}	Hi		(5.00×10^{6} - 1.00×10^{7})	2.78%	(0.5-1.5%)
Lactobacillus rhamnosus	2.09×10^{8}				2.78%	
Eubacterium and related genera (Total)	$<9.00 \times 10^{7}$		Lo	(1.00×10^{8} - 1.00×10^{9})	0.00%	(<15%)
Bifidobacterium and related genera (Total)	7.31×10^{8}	Hi		(5.00×10^{8} - 5.00×10^{9})	97.22%	(5-11%)
Bifidobacterium longum	5.22×10^{8}				69.44%	
Bifidobacterium breve	1.04×10^{8}				13.89%	
Bifidobacterium pseudocatenulatum	1.04×10^{8}				13.89%	

Lo = Limited species distribution*

Detection limits: Aerobes 1 x 10^{6}: Yeasts 1 x 10^{5} : Anaerobes1 x 10^{8} cfu/mL. Results are reported as less than these figures if not cultured.
* = presumptive identification
Organisms identified by MALDI-TOF MS (Matrix Assisted Laser Desorption/ Ionisation - Time of Flight) Mass Spectrometry.
Reference ranges obtained from Bioscreen data (n=177)
Hi = high; "Lo" = Low; "cfu" = colony forming units (viable count)

Dysbiosis and correlation with increased allergy risk – can it be measured?

Beneficial Microbes, 2017 online ARTICLE IN PRESS

Ratio of *Klebsiella/Bifidobacterium* in early life correlates with later development of paediatric allergy

J.S.Y. Low[1], S.-E. Soh[2,3†], Y.K. Lee[4], K.Y.C. Kwek[3†], J.D. Holbrook[2,5], E.M. Van der Beek[7,8], L.P. Shek[3,3†], A.E.N. Goh[3†], O.H. Teoh[3†], K.M. Godfrey[9†], Y.-S. Chong[2,10†], J. Knol[7,11] and C. Lay[1,3*]

Time is also important!
Differences precede the onset

Table S2. Ratio of relative abundances of *Klebsiella* to *Bifidobacterium* (K/B ratio) of allergic and healthy infants at age 3 weeks, 3 months and 6 months respectively.

Timepoint	*Klebsiella/Bifidobacterium* ratio		
	Healthy controls	Allergic cases	*P*-value
Week 3	0.23 (0.01-213.07)	1.70 (0.01-1408.00)	0.12
Month 3	0.03 (0.00-0.68)	0.52 (0.00 – 2281.33)	*0.01
Month 6	0.01 (0.00-62.00)	0.05 (0.00-910.50)	0.26

The values were expressed in median (range). Differences in medians of *Klebsiella/Bifidobacterium* ratio between the two groups were performed using non-parametric Mann-Whitney U test. Single asterisk (*) indicate $P \leq 0.05$.

What could this mean?

Collection Date: 11/02/2018 Receipt Date: 13/02/2018 Process Date: 13/02/2018 Completed Date 2/3/2018

Name: Ho, Brandon
Address:

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Sample ID: 139789 DOB: 9/11/2017

Ho, Brandon

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Escherichia coli	7.31×10^8				10.45%	(70-90%)
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Yeast (Total)	$<1.00 \times 10^7$			$(<1.00 \times 10^8)$		

Name: Ho, Brandon

Anaerobes	cfu/gm	Hi	Lo	Normal Range	% Distribution	Normal Distribution
Total Anaerobe Count	7.52×10^8			$(1.00 \times 10^8 - 1.00 \times 10^{10})$		
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Lactobacillus rhamnosus	2.09×10^8				2.78%	
Eubacterium and related genera (Total)	$<9.00 \times 10^7$		Lo	$(1.00 \times 10^8 - 1.00 \times 10^9)$	0.00%	(<15%)
Bifidobacterium and related genera (Total)	7.31×10^8	Hi		$(5.00 \times 10^7 - 5.00 \times 10^8)$	97.22%	(5-11%)
Bifidobacterium longum	5.22×10^8				69.44%	
Bifidobacterium breve	1.04×10^8				13.89%	
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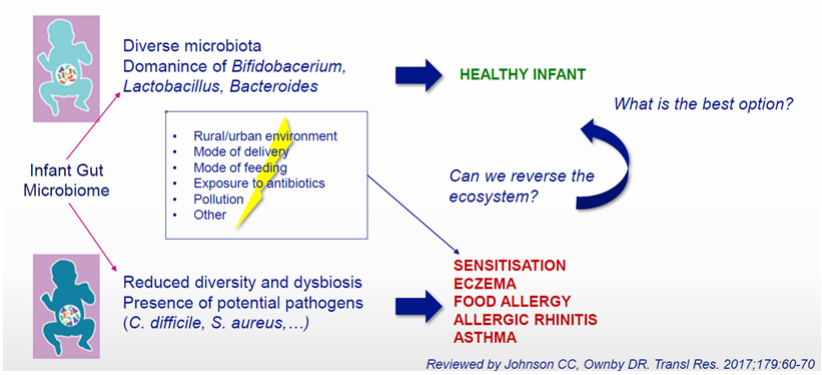
Detection limits: Aerobes 1×10^5. Yeasts 1×10^7 / Anaerobes1 $\times 10^8$ cfu/mL. Results are reported as less than these figures if not cultured.
* = presumptive identification
Organisms identified by MALDI-TOF MS (Matrix Assisted Laser Desorption/ Ionisation - Time of Flight) Mass Spectrometry.
Reference ranges obtained from Biosceren data (n=177)
Hi = high; "Lo" = Low; "cfu" = colony forming units (viable count)

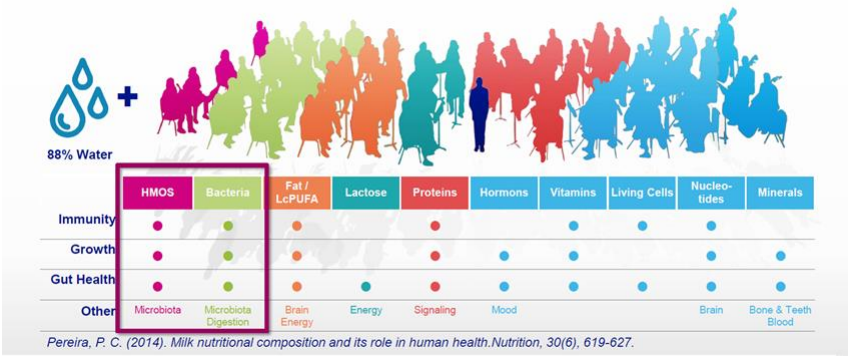
Ratio of Klebsiella to Bifidobacterium = 4.18/731 = 0.005
In Healthy Control Range but this is only based upon one study
We need more studies to find out what this all means

Is the early gut microbiota then a potential target?



Interventions

What is in human breast milk?



Pereira, P. C. (2014). Milk nutritional composition and its role in human health.Nutrition, 30(6), 619-627.

Human milk influences not only gut microbiota composition but also functionality

Table 2 Relative gene expression levels in breast-fed (BF) versus formula-fed (FF) infants following a 3-month feeding period

Gene	BF/FF	*P*-value	q-value
TACR1	1.80	0.0189	0.1670
REL	1.62	0.0047	0.1026
DUOX2	1.45	0.0215	0.1670
VAV2	1.36	0.0088	0.1404
NDST1	0.79	0.0103	0.1477
AOC3	0.78	0.0202	0.1670
SP2	0.76	0.0030	0.0860
IL1A	0.71	0.0089	0.1389
ALOX5	0.69	1.40E-05	0.0008
BPIL1	0.37	1.43E-05	0.0008
KLRF1	0.35	3.16E-05	0.0015

Fold change represents relative expression level in BF divided by FF infants for the 11 genes exhibiting the strongest multivariate relationships to microbiota virulence characteristics.

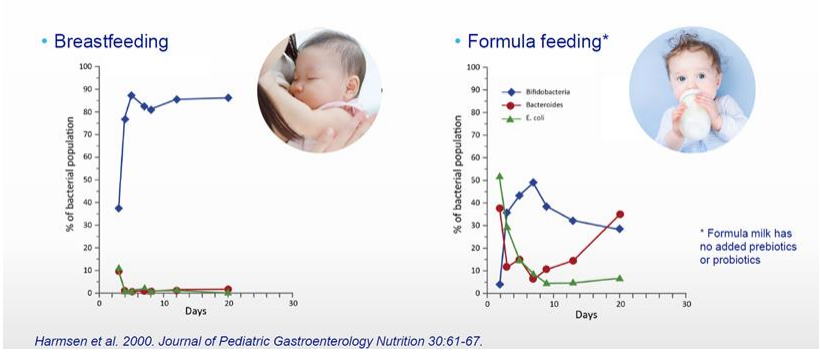
Genes that modulate gut motility and epithelial homeostasis

Genes that prime mucosal inflammatory responses

Breastfeeding facilitates the adaptive and functional changes required for optimal transition from intrauterine to extrauterine life

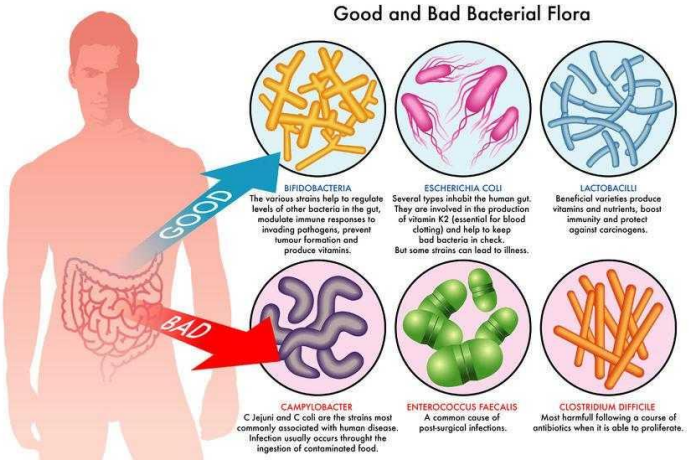
Schwartz et al., 2012., Genome Biology

Breastfed infants have a bifidobacteria dominated microbiota



Harmsen et al. 2000. Journal of Pediatric Gastroenterology Nutrition 30:61-67.

Common probiotic strains



Probiotics – what are they?

PROBIOTICS

"live microorganisms that, when administered in adequate amounts, confer a health benefit on the host"

Hill et al., 2014
Nature Reviews Gastroenterology & Hepatology 11, 506–514 (2014)

Fiocchi et al. World Allergy Organization Journal (2015) 8:4
DOI 10.1186/s40413-015-0055-2

WAO journal
WORLD ALLERGY ORGANIZATION

POSITION ARTICLE AND GUIDELINES — Open Access

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics

Alessandro Fiocchi[1†], Ruby Pawankar[2†], Carlos Cuello-Garcia[3,4], Kangmo Ahn[5], Suleiman Al-Hammadi[6], Arnav Agarwal[3,7], Kirsten Beyer[8], Wesley Burks[9], Giorgio W Canonica[10], Motohiro Ebisawa[11], Shreyas Gandhi[3,7], Rose Kamenwa[12], Bee Wah Lee[13], Haiqi Li[14], Susan Prescott[15], John J Riva[16], Lanny Rosenwasser[17], Hugh Sampson[18], Michael Spigler[19], Luigi Terracciano[20], Andrea Vereda-Ortiz[22], Susan Waserman[21], Juan José Yepes-Nuñez[3], Jan L Brozek[3,21*] and Holger J Schünemann[3,21]

The WAO guideline panel suggests: a) using probiotics in pregnant women at high risk for having an allergic child; b) using probiotics in women who breastfeed infants at high risk of developing allergy; and c) using probiotics in infants at high risk of developing allergy. All recommendations are conditional and supported by very low quality evidence.

Sometimes dead bacteria can play a role in modulating the immune system!

RESEARCH ARTICLE

Differences between live and heat-killed bifidobacteria in the regulation of immune function and the intestinal environment

H. Sugahara ⓘ, R. Yao ⓘ, T. Odamaki ⓘ, J.Z. Xiao ⓘ
*h-sugahara@morinagamilk.co.jp

Beneficial Microbes: 8 (3) - Pages: 463 - 472

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https://doi.org/10.3920/BM2016.0158

Published Online: April 26, 2017

Abstract | References | Supplementary Materials | Cited by | PDF

Abstract

Probiotics are live microorganisms that confer a health benefit on the host, such as improvement of the intestinal environment, modulation of immune function and energy metabolism. Heat-killed probiotic strains have also been known to exhibit some physiological functions; however, the differences between live and heat-killed probiotics have not been well elucidated. In this study, we investigated the differences between live and heat-killed *Bifidobacterium breve* M-16V, a probiotic strain, in the regulation of immune function, intestinal metabolism and intestinal gene expression of the host using gnotobiotic mouse model and omics approaches. Both live and heat-killed cells of *B. breve* M-16V showed immune-modulating effects that suppressed pro-inflammatory cytokine production in spleen cells and affected intestinal metabolism; however, live cells exhibited a more remarkable effect in the regulation of intestinal metabolism and intestinal gene expression involved in nutrient metabolism. Our findings are valuable for considering the health benefits of live and heat-killed bacteria and the usefulness of different forms of probiotics.

Keywords: cytokine, transcriptome, metabolome, *Bifidobacterium*, probiotics

Probiotics can help prevent allergy in children born from Caesarean section

J Allergy Clin Immunol. 2009 Feb;123(2):335-41. doi: 10.1016/j.jaci.2008.11.019. Epub 2009 Jan 8.

Probiotics prevent IgE-associated allergy until age 5 years in cesarean-delivered children but not in the total cohort.

Kuitunen M[1], Kukkonen K, Juntunen-Backman K, Korpela R, Poussa T, Tuure T, Haahtela T, Savilahti E.

Author information

Abstract

BACKGROUND: Less microbial exposure in early childhood is associated with more allergic disease later. Allergic children have a different fecal microflora, with less lactobacilli and bifidobacteria. Beneficial effects regarding the development of allergy have been suggested to come through probiotic supplementation.

OBJECTIVE: We sought to study the effect of probiotic and prebiotic supplementation in preventing allergies.

METHODS: In a double-blinded, placebo-controlled study we randomized 1223 mothers with infants at high risk for allergy to receive a probiotic mixture (2 lactobacilli, bifidobacteria, and propionibacteria) or placebo during the last month of pregnancy and their infants to receive it from birth until age 6 months. Infants also received a prebiotic galacto-oligosaccharide or placebo. At 5 years, we evaluated the cumulative incidence of allergic diseases (eczema, food allergy, allergic rhinitis, and asthma) and IgE sensitization.

RESULTS: Of the 1018 intent-to-treat infants, 891 (88%) attended the 5-year visit. Frequencies of allergic and IgE-associated allergic disease and sensitization in the probiotic and placebo groups were similar: 52.6% versus 54.9% and 29.5% versus 26.6%, respectively, and 41.3% in both. No significant difference appeared in frequencies of eczema (39.3% vs 43.3%), atopic eczema (24.0% vs 25.1%), allergic rhinitis (20.7% vs 19.1%), or asthma (13.0% vs 14.1%) between groups. However, less IgE-associated allergic disease occurred in cesarean-delivered children receiving probiotics (24.3% vs 40.5%; odds ratio, 0.47; 95% CI, 0.23% to 0.96%; P = .035).

CONCLUSIONS: No allergy-preventive effect that extended to age 5 years was achieved with perinatal supplementation of probiotic bacteria to high-risk mothers and children. It conferred protection only to cesarean-delivered children.

PMID: 19135235 DOI: 10.1016/j.jaci.2008.11.019

Probiotics and eczema

Allergy. 2015 Nov;70(11):1356-71. doi: 10.1111/all.12700. Epub 2015 Aug 13.

Probiotics for prevention of atopic diseases in infants: systematic review and meta-analysis.

Zuccotti G[1], Meneghin F[2], Aceti A[3], Barone G[4], Callegari ML[5], Di Mauro A[6], Fantini MP[7], Gori D[7], Indrio F[6], Maggio L[4], Morelli L[5], Corvaglia L[3]; Italian Society of Neonatology.

Author information

Abstract

Growing evidence underlines the pivotal role of infant gut colonization in the development of the immune system. The possibility to modify gut colonization through probiotic supplementation in childhood might prevent atopic diseases. The aim of the present systematic review and meta-analysis was to evaluate the effect of probiotic supplementation during pregnancy and early infancy in preventing atopic diseases. PubMed, Embase and Cochrane Library were searched for randomized controlled trials evaluating the use of probiotics during pregnancy or early infancy for prevention of allergic diseases. Fixed-effect models were used, and random-effects models where significant heterogeneity was present. Results were expressed as risk ratio (RR) with 95% confidence interval (CI). Seventeen studies, reporting data from 4755 children (2381 in the probiotic group and 2374 in the control group), were included in the meta-analysis. Infants treated with probiotics had a significantly lower RR for eczema compared to controls (RR 0.78 [95% CI: 0.69-0.89], P = 0.0003), especially those supplemented with a mixture of probiotics (RR 0.54 [95% CI: 0.43-0.68], P < 0.00001). No significant difference in terms of prevention of asthma (RR 0.99 [95% CI: 0.77-1.27], P = 0.95), wheezing (RR 1.02 [95% CI: 0.89-1.17], P = 0.76) or rhinoconjunctivitis (RR 0.91 [95% CI: 0.67-1.23], P = 0.53) was documented. The results of the present meta-analysis show that probiotic supplementation prevents infantile eczema, thus suggesting a new potential indication for probiotic use in pregnancy and infancy.

KEYWORDS: atopic diseases; infant; meta-analysis; probiotic

Comment in

Probiotics and prevention of eczema: have we enough data to draw conclusions? [Allergy. 2016]

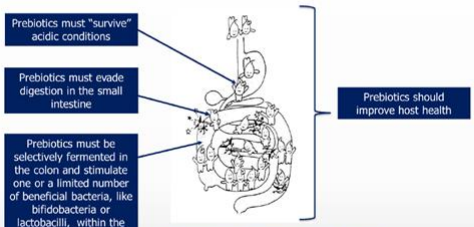
Reply. [Allergy. 2016]

PMID: 26198702 DOI: 10.1111/all.12700

[Indexed for MEDLINE]

Prebiotics

Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon that can improve host health



Fuller & Gibson, 1997, Scand J Gastroenterol Suppl

Promising' results in general allergy outcomes (eczema, asthma) in high-risk populations

Osborne & Sinn. Cochrane Review (2013

Types of prebiotics

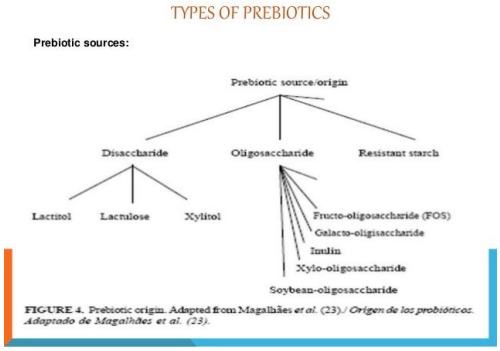
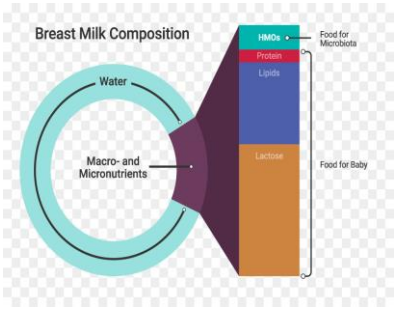
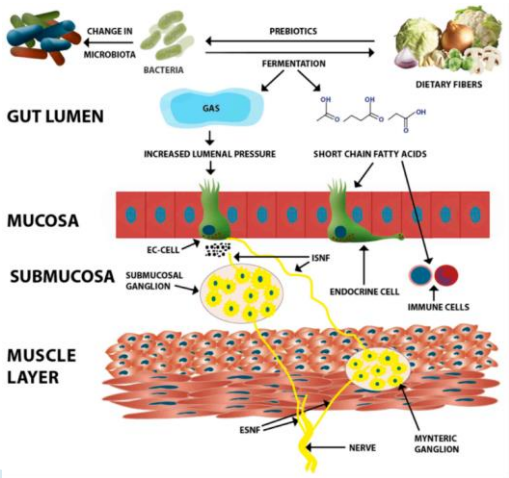


FIGURE 4. Prebiotic origin. Adapted from Magalhães *et al.* (23)./ *Origen de los probióticos. Adaptado de Magalhães et al. (23).*



Mechanisms in which dietary fibre can affect the functions of the gastrointestinal tract



Evidence for the use of prebiotics for the prevention of allergy

Question: Prebiotics compared to no prebiotics for the prevention of allergies
Settings: ambulatory care
Author(s): Carlos Cuello, Juan J. Yepes, Yuan Zhang, Gian Paolo Morgano, Jan Brozek, Holger Schünemann
Date: January 2015
Bibliography (systematic reviews): Cuello-Garcia, et al. 2015 (in process).

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prebiotics	no prebiotics	Relative (95% CI)	Absolute (95% CI)		
Development of eczema (any eczema) (follow up: range 3 to 24 months)												
5	randomised trials	serious [1]	not serious	not serious	serious [4]	none	47/683 (6.9%)	75/630 (11.9%)	**RR 0.57** (0.3 to 1.08)	51 fewer per 1000 (from 83 fewer to 10 more)	⊕⊕◯◯ LOW	CRITICAL
Development of allergic rhinitis												
0	–	–	–	–	–	–	–	–	–	–	–	CRITICAL
Development of asthma and/or recurrent wheezing (follow up: range 18 to 24 months)												
2	randomised trials	serious [2]	not serious	serious [10]	serious [11]	none	8/128 (6.3%)	21/121 (17.4%)	**RR 0.37** (0.17 to 0.8)	109 fewer per 1000 (from 35 fewer to 144 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Development of food allergy (follow up: median 18 months)												
1	randomised trials	serious [3]	not serious	very serious [10]	serious [12]	none	3/62 (4.8%)	9/53 (17.0%)	**RR 0.28** (0.08 to 1.00)	122 fewer per 1000 (from 0 fewer to 156 fewer)	⊕◯◯◯ VERY LOW	CRITICAL
Development of any allergy												
0	–	–	–	–	–	–	–	–	–	–	–	IMPORTANT
Adverse events (follow up: range 1 to 12 months)												
7	randomised trials	serious [2]	not serious	not serious	serious [9]	none	350/970 (36.1%)	329/948 (34.7%)	**RR 1.03** (0.93 to 1.14)	21 more per 1000 (from 17 fewer to 68 more)	⊕⊕◯◯ LOW	CRITICAL
Nutritional status (follow up: range 1 to 12 months; assessed with: mean weight gained per day or the final weight assessed by clinicians; better indicated by higher values)												
12	randomised trials	serious [3]	not serious	not serious	not serious	none	1162	1136	-	SMD **0.06 higher** (0.02 lower to 0.15 higher)	⊕⊕⊕◯ MODERATE	CRITICAL

SMD – standardised mean difference; RR – relative risk

1. Random sequence generation was unclear in 4 studies and in 2 studies 20% to 30% of participants were lost to follow-up
2. 95% CI does not exclude an appreciable clinical benefit or no difference.
3. 20% and 30% of patients lost to follow-up in both studies; there is a concern about blinded assessment of outcomes and inadequate description of the allocation concealment
4. Only 29 events.
5. Only one study with 30% lost to follow-up and inadequate description of blind outcome assessment
6. Only 12 events.
7. There was 20 to 30% lost to follow-up in 4 studies; 5 studies did not describe blinded outcome assessment, and random sequence generation and allocation concealment were not adequately described (in 2 and 3 studies, respectively).
8. 95% confidence interval does not exclude an appreciable harm
9. Blind outcome assessment was not described in 6 studies and in 2 studies there was large number of patients lost to follow-up
10. There is a concern that only one study reported this outcome and did not describe how the outcome was measured (it seems to be a self-reported adverse reaction to food); there is very serious concern that this outcome does not reflect allergic reactions at all.
11. Development of asthma was not directly measured and the guideline panel was uncertain whether recurrent wheezing is an appropriate proxy for development of asthma

Cuello-Garcia CA, Brozek JL, Fiocchi A, Pawankar R, Yepes-Nunez JJ, et al. Probiotics for the prevention of allergy: A systematic review and meta-analysis of randomized controlled trials. J Allergy Clin Immunol. 2015; 136(4): 952-961

WHO recommendations in regards to prebiotics and allergy prevention in infants

World Allergy Organ J. 2016 Mar 1;9:10. doi: 10.1186/s40413-016-0102-7. eCollection 2016.

World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Prebiotics.

Cuello-Garcia CA[1,2], Fiocchi A[#3], Pawankar R[#4], Yepes-Nuñez JJ[1,5], Morgano GP[1], Zhang Y[1], Ahn K[6], Al-Hammadi S[7], Agarwal A[8], Gandhi S[8], Beyer K[9], Burks W[10], Canonica GW[11], Ebisawa M[12], Kamenwa R[13], Lee BW[14], Li H[15], Prescott S[16], Riva JJ[1,17], Rosenwasser L[18], Sampson H[19], Spigler M[20], Terracciano L[21], Vereda A[22], Waserman S[23], Schünemann HJ[1,23], Brożek JL[1,23].

Author information

Abstract

BACKGROUND: The prevalence of allergic diseases in infants, whose parents and siblings do not have allergy, is approximately 10 % and reaches 20-30 % in those with an allergic first-degree relative. Intestinal microbiota may modulate immunologic and inflammatory systemic responses and, thus, influence development of sensitization and allergy. Prebiotics - non-digestible oligosaccharides that stimulate growth of probiotic bacteria - have been reported to modulate immune responses and their supplementation has been proposed as a preventive intervention.

OBJECTIVE: The World Allergy Organization (WAO) convened a guideline panel to develop evidence-based recommendations about the use of prebiotics in the prevention of allergy.

METHODS: The WAO guideline panel identified the most relevant clinical questions about the use of prebiotics for the prevention of allergy. We performed a systematic review of randomized controlled trials of prebiotics, and reviewed the evidence about patient values and preferences, and resource requirements (up to January 2015, with an update on July 29, 2015). We followed the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to develop recommendations.

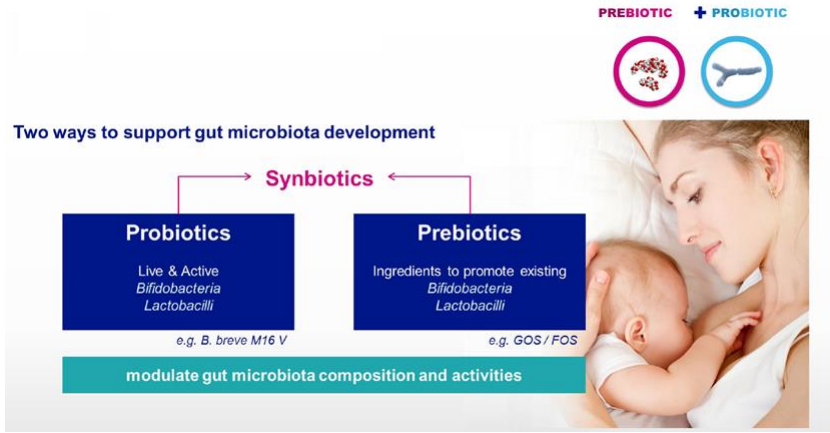
RESULTS: Based on GRADE evidence to decision frameworks, the WAO guideline panel suggests using prebiotic supplementation in not-exclusively breastfed infants and not using prebiotic supplementation in exclusively breastfed infants. Both recommendations are conditional and based on very low certainty of the evidence. We found no experimental or observational study of prebiotic supplementation in pregnant women or in breastfeeding mothers. Thus, the WAO guideline panel chose not to provide a recommendation about prebiotic supplementation in pregnancy or during breastfeeding, at this time.

CONCLUSIONS: WAO recommendations about prebiotic supplementation for the prevention of allergy are intended to support parents, clinicians and other health care professionals in their decisions whether or not to use prebiotics for the purpose of preventing allergies in healthy, term infants.

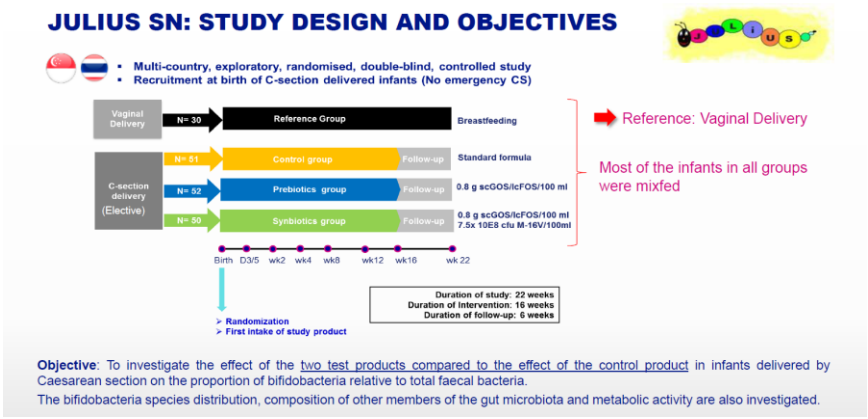
PMID: 26962387 PMCID: PMC4772464 DOI: 10.1186/s40413-016-0102-7

Free PMC Article

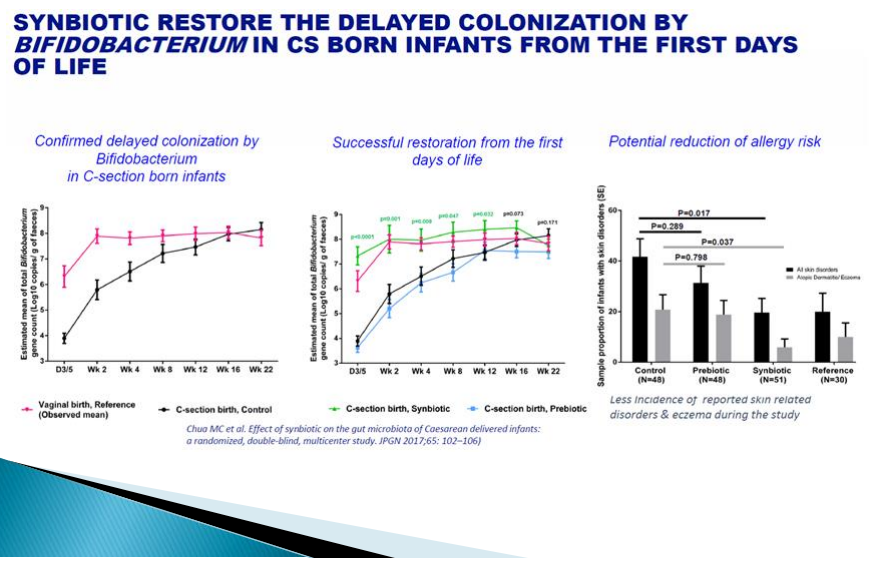
Synbiotic concept



Synbiotics as an intervention



Synbiotics and their effect



Synbiotics and atopic dermatitis

JAMA Pediatr. 2016 Mar;170(3):236-42. doi: 10.1001/jamapediatrics.2015.3943.

Synbiotics for Prevention and Treatment of Atopic Dermatitis: A Meta-analysis of Randomized Clinical Trials.

Chang YS[1], Trivedi MK[2], Jha A[3], Lin YF[4], Dimaano L[4], García-Romero MT[5]

⊕ **Author information**

Erratum in
JAMA Pediatr. 2016 Mar;170(3):299.

Abstract

IMPORTANCE: Atopic dermatitis (AD) is a highly prevalent condition that may be associated with an altered gastrointestinal microbiota that promotes an immune environment more susceptible to allergic disease. Synbiotics, a mixture of prebiotics and probiotics, have been used for the prevention and treatment of AD.

OBJECTIVE: To investigate the efficacy of synbiotics for primary prevention and treatment of AD.

DATA SOURCES: PubMed/MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and the CAB Abstracts Archive searchable database were searched from the inception of all databases to October 15, 2015, with no language restrictions.

STUDY SELECTION: We included all published randomized clinical trials of synbiotics for prevention and/or treatment of AD. To be included, a publication needed to clearly define the intervention as oral administration of synbiotics (combination of probiotics and prebiotics) and must have included an assessment of AD disease severity, such as the Severity Scoring of Atopic Dermatitis (SCORAD) index, or the incidence of AD as an outcome measure. Only 8 of 257 initially identified studies (3%) met selection criteria.

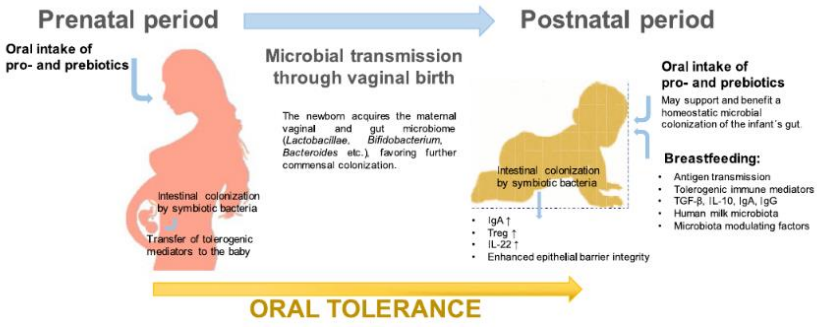
DATA EXTRACTION AND SYNTHESIS: Data extraction was independently done by multiple observers and cross-checked to avoid errors. The quality of the selected studies was critically examined following the Cochrane guidelines. Data were pooled using a random-effects model.

MAIN OUTCOMES AND MEASURES: The primary outcomes were the SCORAD index (treatment studies) and the relative risk of AD (prevention studies). The hypothesis was formulated before data collection.

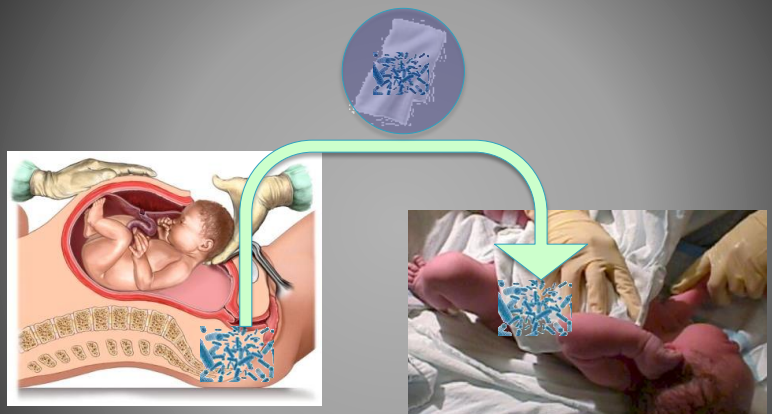
RESULTS: A total of 257 abstracts were screened to identify 6 treatment studies (369 children enrolled; aged 0 months to 14 years) and 2 prevention studies (1320 children enrolled; up to age 6 months in one study and term neonates aged <3 days in the other). From the 6 treatment studies included for random-effects meta-analysis, the overall pooled change in SCORAD index in those treated with synbiotics at 8 weeks of treatment was -6.56 (95% CI, -11.43 to -1.68; P = .008). Heterogeneity was significant ($I(2) = 77.1\%$; P = .001). Subgroup analysis showed that the beneficial effect was significant only when using mixed strains of bacteria (weighted mean difference, -7.32; 95% CI, -13.98 to -0.66; P = .03) and when used in children aged 1 year or older (weighted mean difference, -7.37; 95% CI, -14.66 to -0.07; P = .048). From the 2 prevention studies included, the pooled relative risk ratio of AD in those treated with synbiotics compared with placebo was 0.44 (95% CI, 0.11 to 1.83; P = .26).

CONCLUSIONS AND RELEVANCE: This meta-analysis shows evidence that supports the use of synbiotics for the treatment of AD, particularly synbiotics with mixed strains of bacteria and for children aged 1 year or older. Further studies are needed to evaluate the effectiveness of synbiotics for primary prevention of AD.

Prenatal and postnatal intake of probiotics/prebiotics



Restoring the Natural Microbiome



From: http://commonhealth.wbur.org/2014/06/birth-canal-bacteria-c-section

Partial restoration of gut microbiota in Caesarean born infants?

Nat Med. 2016 Mar;22(3):250-3. doi: 10.1038/nm.4039. Epub 2016 Feb 1.

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer.

Dominguez-Bello MG[1,2], De Jesus-Laboy KM[2], Shen N[3], Cox LM[1], Amir A[4], Gonzalez A[4], Bokulich NA[1], Song SJ[4,5], Hoashi M[1,6], Rivera-Vinas JI[7], Mendez K[7], Knight R[4,8], Clemente JC[3,9].

Author information

Abstract

Exposure of newborns to the maternal vaginal microbiota is interrupted with cesarean birthing. Babies delivered by cesarean section (C-section) acquire a microbiota that differs from that of vaginally delivered infants, and C-section delivery has been associated with increased risk for immune and metabolic disorders. Here we conducted a pilot study in which infants delivered by C-section were exposed to maternal vaginal fluids at birth. Similarly to vaginally delivered babies, the gut, oral and skin bacterial communities of these newborns during the first 30 d of life was enriched in vaginal bacteria--which were underrepresented in unexposed C-section-delivered infants--and the microbiome similarity to those of vaginally delivered infants was greater in oral and skin samples than in anal samples. Although the long-term health consequences of restoring the microbiota of C-section-delivered infants remain unclear, our results demonstrate that vaginal microbes can be partially restored at birth in C-section-delivered babies.

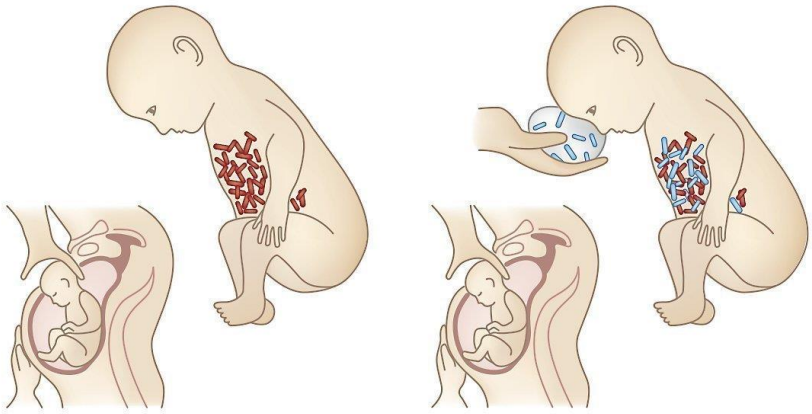
Comment in

First microbial encounters. [Nat Med. 2016]

PMID: 26828196 PMCID: PMC5062956 DOI: 10.1038/nm.4039

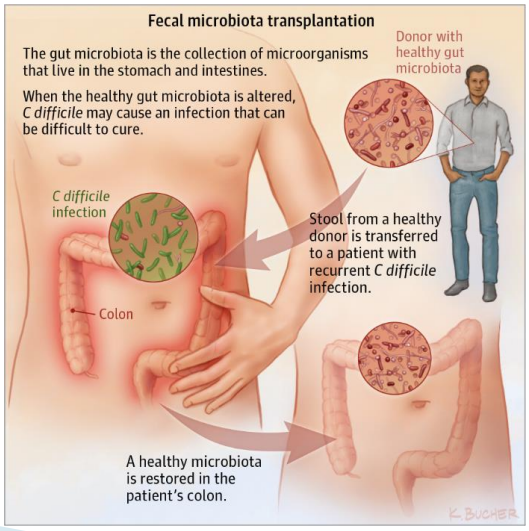
[Indexed for MEDLINE] Free PMC Article

Potential microbiota transplant from vaginal seeding

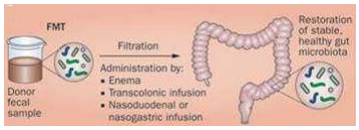


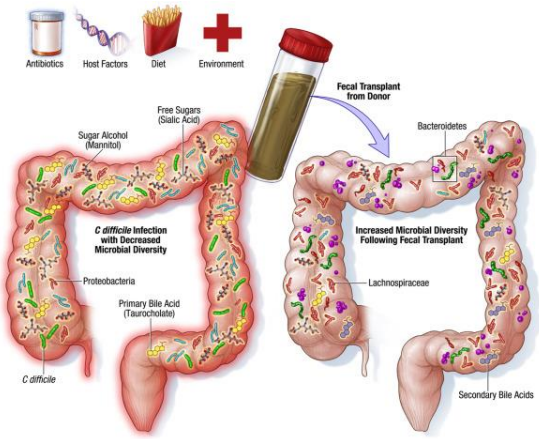
Inoculation of the newborn with maternal microbiota restructures the microbiome after caesarean birth. Left: C-section babies get a microbiome (small red rods) upon delivery. Right: Swabbing the babies with gauze that has been in the mother's vagina transfers her vaginal microbiome (small blue rods) to her baby, resulting in a mixture of both types. (/ Kim Caesar/Nature Publishing Group)

Faecal microbial transplantation



Faecal microbial transplantation and what happens





Take home messages

- Microbial colonisation following birth is essential for establishing a symbiosis with our immune system and influences health throughout life
- An interruption of microbial colonisation (Dysbiosis) is associated with the development of allergic diseases
- Specific pre, pro and synbiotic interventions in early life can help modulate early microbial colonisation and influences immune development and allergy risk. We need more quality studies in this area.
- Other interventions such as vaginal swabbing and faecal microbial transplantation are still experimental as early life interventions
- Early life nutrition represents a fundamental basis for the strong relationship between the gut microbiota, the immune system and health

Questions?