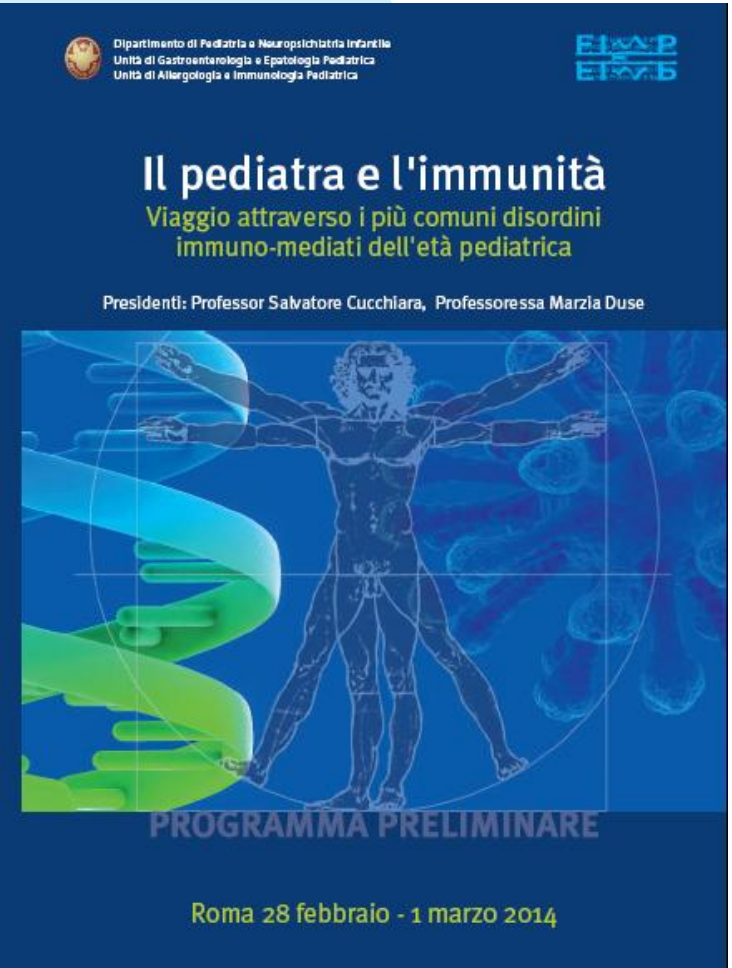
Profilo del microbiota intestinale nelle prime epoche della vita e sviluppo di patologia immuno-mediata



Mauro Calvani

Azienda Ospedaliera S. Camillo-Forlanini
U.O.C. per il Governo Clinico in Pediatria
ed Ematologia Pediatrica
Roma

Il microbiota intestinale

Sviluppo del microbiota intestinale

Funzioni del microbiota intestinale

Rapporti con le patologie immunomediate

Possibili implicazioni terapeutiche

Il microbiota intestinale

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Microbiota Intestinale

Precedentemente chiamata “flora batterica intestinale” o “microflora”, è l’insieme dei microorganismi che si trovano nel tubo digerente

Microbioma Intestinale

Il genoma collettivo di tutti i microrganismi che si trovano nel tubo digerente

Noi esseri umani, come altri mammiferi, viviamo in associazione con una enorme quantità di microorganismi commensali residenti sulle nostre superfici esterne o interne. Il rapporto tra numero di cellule del microbiota e le nostre cellule somatiche oscilla tra 10-100/1

Microbiota predominante

Phyla

Classe

Ordine

Famiglia

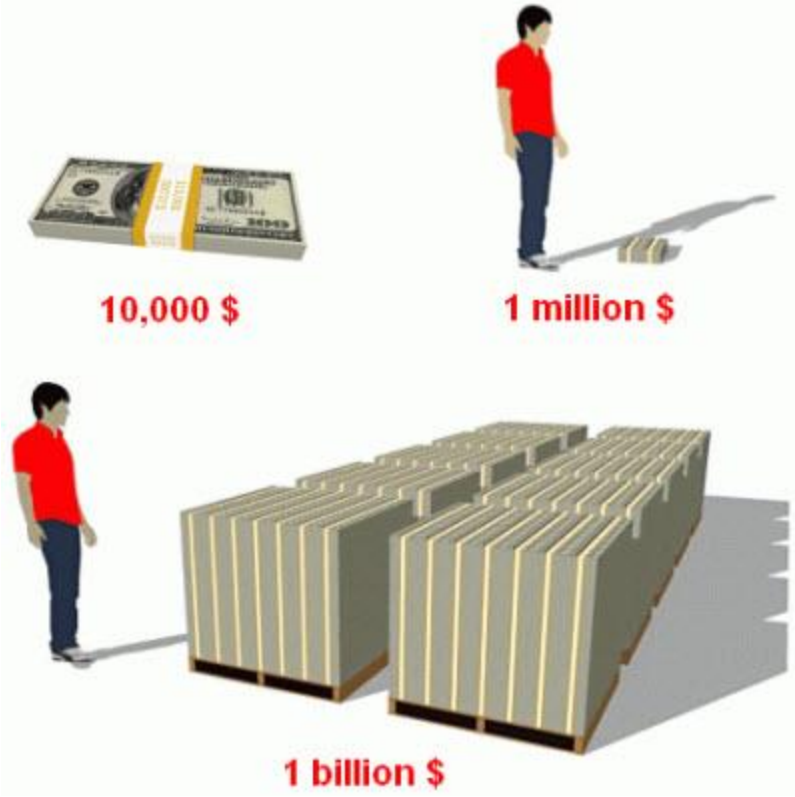
Genere

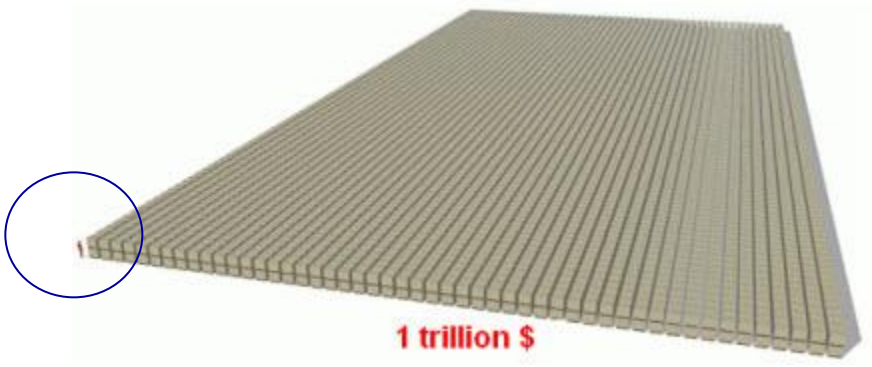
Specie

Sito	**Phyla**
Cute	Actinobacteria Firmicutes Proteobacteria
Cavità orale	Bacteroides Firmicutes Fusobacteria Proteobacteria
Vie aeree	Bacteroides Firmicutes Proteobacteria
Gastrointestinale	**Bacteroides** **Firmicutes** Actinobacteria
Urogenitale	Firmicutes

L’ecosistema intestinale è costituito da 3 milioni di specie o oltre 100 trilioni di microorganismi)

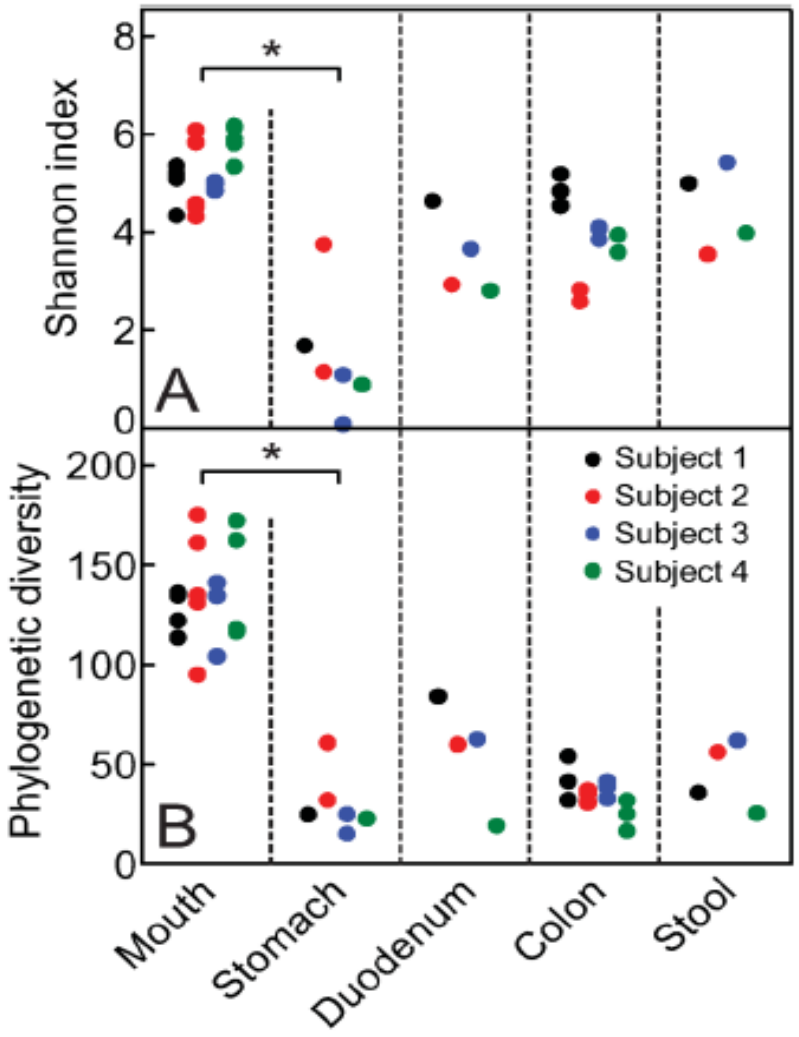
Nell’intestino sono presenti soprattutto 2 delle 55 Phyla oggi conosciute (Firmicutes e Bacteroides) e circa il 15% delle oltre 1000 specie conosciute





Bacterial biogeography of the human digestive tract

La bocca e l'intestino (in particolare il colon) contengono il maggior numero di specie batteriche, lo stomaco il minor numero

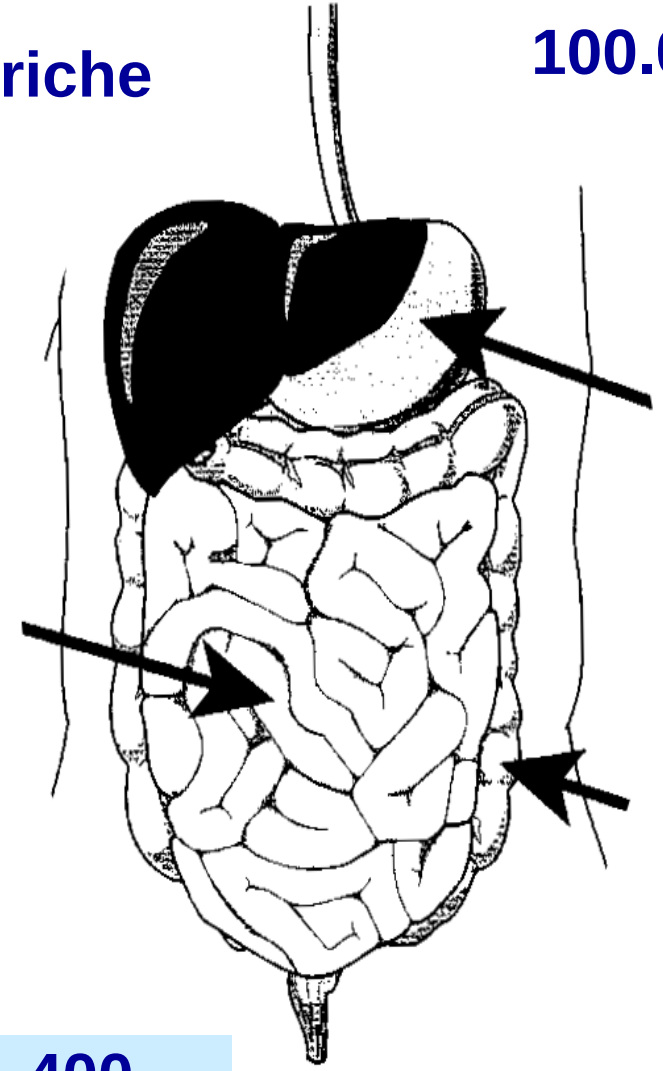


Steams JC et al, www nature.com Scientific Report 2011: 1; 170

Microflora Intestinale

10^{14} cellule batteriche

100.000.000.000.000



Stomaco 10^3/ml
H.pylori

Piccolo intestino
10^4 - 10^6
Lactobacilli e cocci Gram +

Colon 10^{12}/g
Bacteroides
Bifidobacter
Peptostreptococci
Fusobacteri
Lctobacilli
Enterobacteri
Enterococchi
Clostridi

400 specie

Intestinal microbiota in functional bowel disorders: a Rome foundation report

La composizione del microbiota intestinale varia in funzione di fattori Intrinseci e Estrinseci

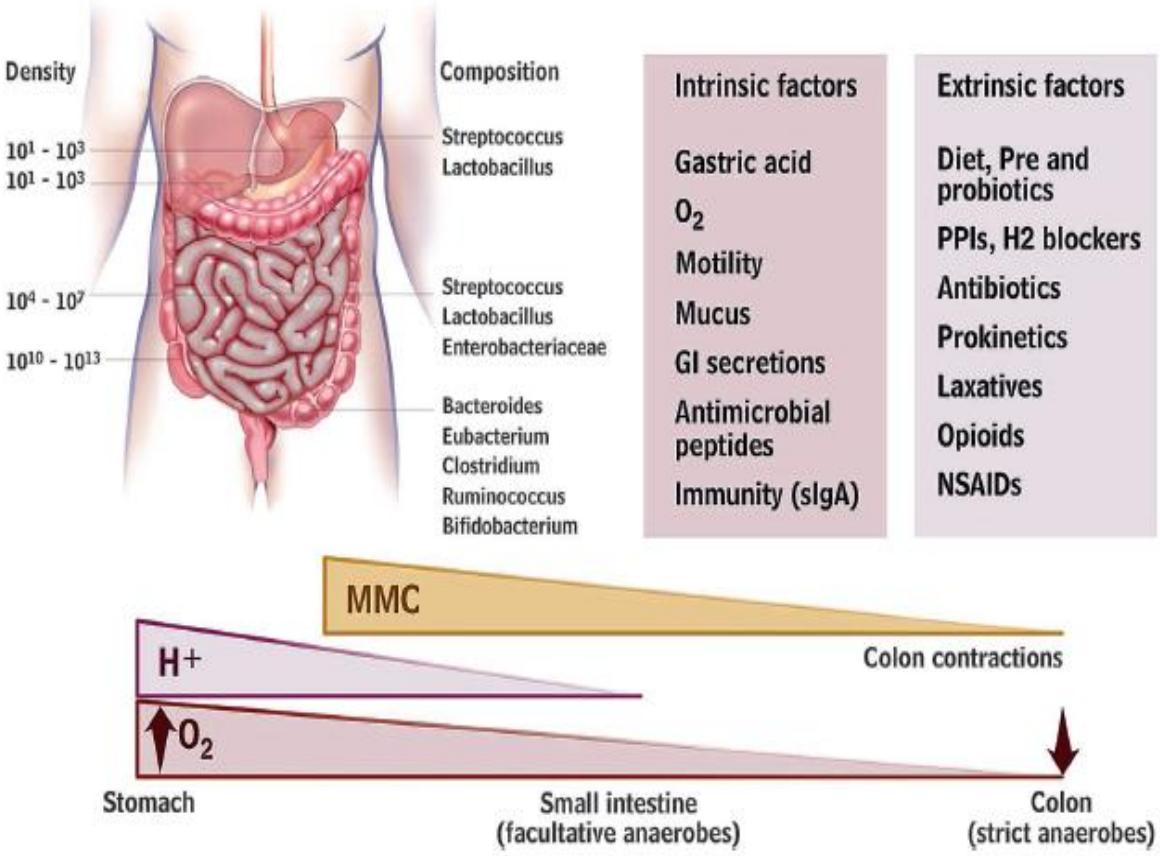


Figure 1 Gut microbiota and the intrinsic and extrinsic factors that can affect its distribution and composition. A

Simren M et al, Gut 2013; 62: 159-76

microbiota intestinale

Sviluppo del microbiota intestinale

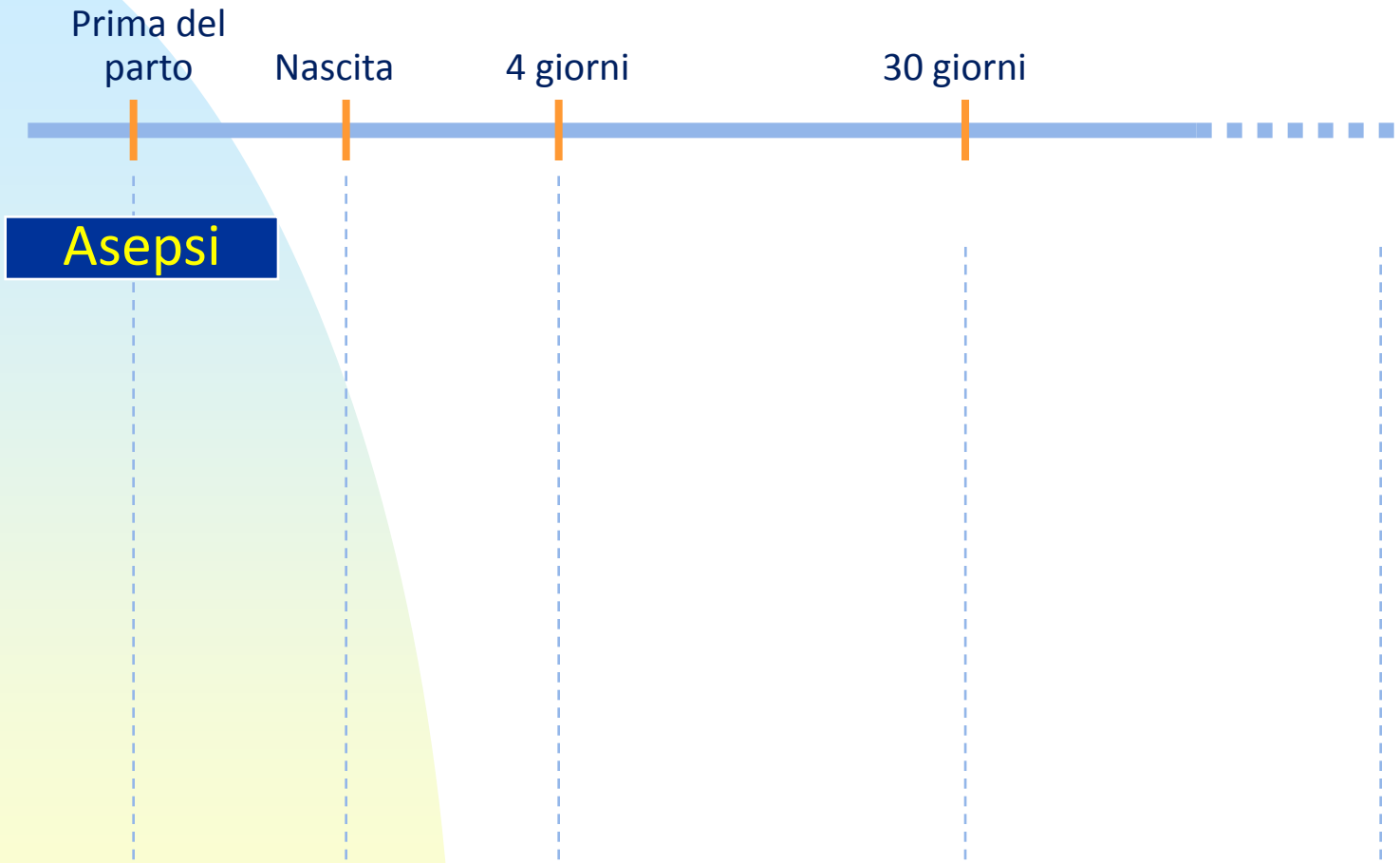
Funzioni del microbiota intestinale

Rapporti con le patologie immunomediate

Possibili implicazioni terapeutiche

Sviluppo della flora batterica intestinale

L'intestino del neonato alla nascita è sterile



Development of the Human Infant Intestinal Microbiota

Metodi: 14 bambini sani nati a termine (di cui 2 gemelli) sono stati seguiti dalla nascita fino all'età di 1 anno indagando il profilo batterico dei campioni fecali con una metodica basata su sequenze di DNA ribosomiale a piccole subunità.

Risultati:

1) La diversità di Phila è molto limitata. 3 gruppi batterici sono responsabili di oltre il 95% degli isolamenti
2) A livello individuale vi è una notevole differenza nel processo di colonizzazione
3) Vi è una notevole stabilità nella popolazione microbica nel tempo

Palmer C et al, Plos Biology 2007; 5: 1556-73

Development of the Human Infant Intestinal Microbiota

Risultati:

4) Nei primi giorni di vita si assiste ad una colonizzazione peculiare per ogni bambino e dipendente dal tipo di parto

5) Dal 5 giorno di vita in poi il profilo del microbiota inizia a somigliare a quello di un adulto

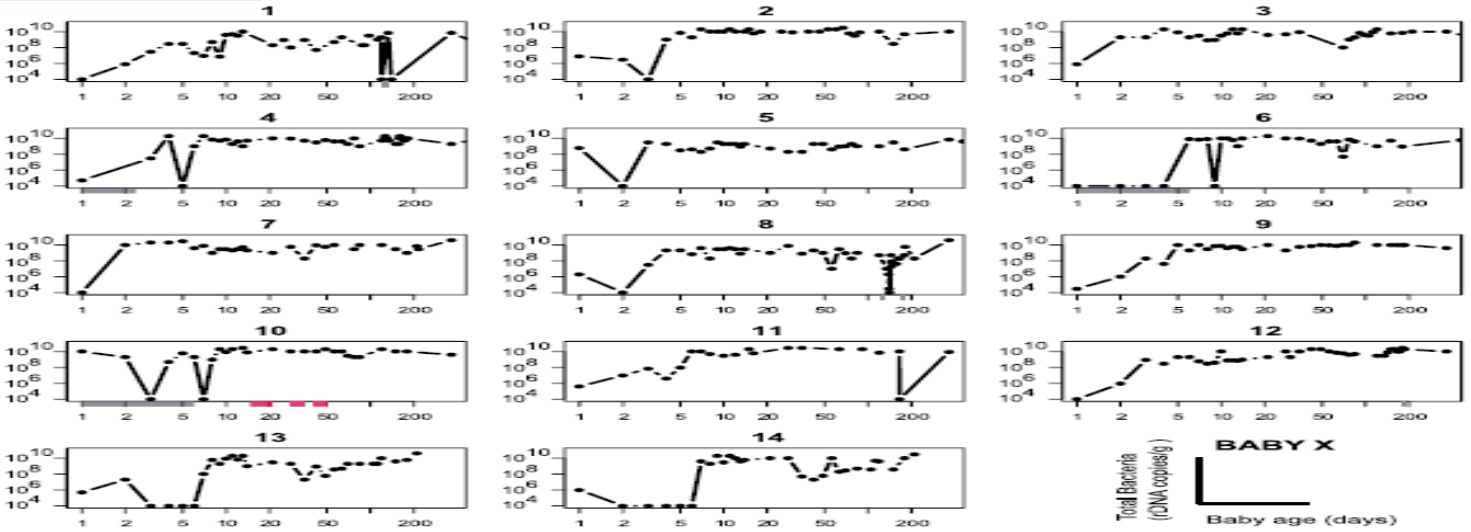
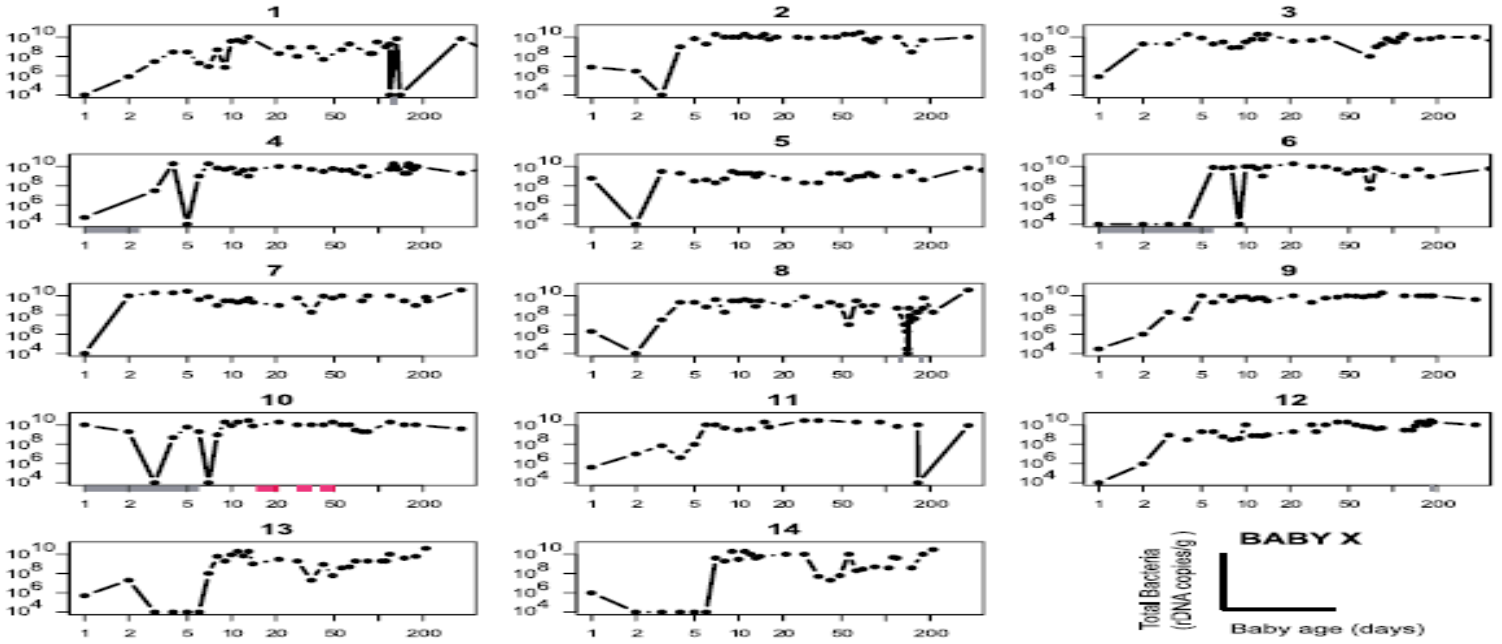


Figure 2. Variation in the Overall Density of Fecal Bacteria during the First Year of Life.
For each baby sample, bacterial abundance was estimated by TaqMan real-time PCR with universal bacterial primers. Estimated rRNA gene copies per gram of feces (*y*-axis) are plotted as a function of days of life (*x*-axis). Both axes are on a logarithmic scale. Abundance measurements are truncated on the lower end at the value corresponding to the 95th percentile of the extraction (negative) controls (copy number corrected by median stool mass). Episodes of antibacterial or antifungal (nystatin) treatment are indicated on the temporal axis by gray or pink bars, respectively (see Table 1 for additional information).

Palmer C et al, Plos Biology 2007; 5: 1556-73

Development of the Human Infant Intestinal Microbiota

A livello individuale vi è una notevole differenza da bambino a bambino nel profilo temporale della colonizzazione, che è invece molto simile nei gemelli



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Palmer C et al, Plos Biology 2007; 5: 1556-73

Bacterial Community Variation in Human Body Habitats Across Space and Time

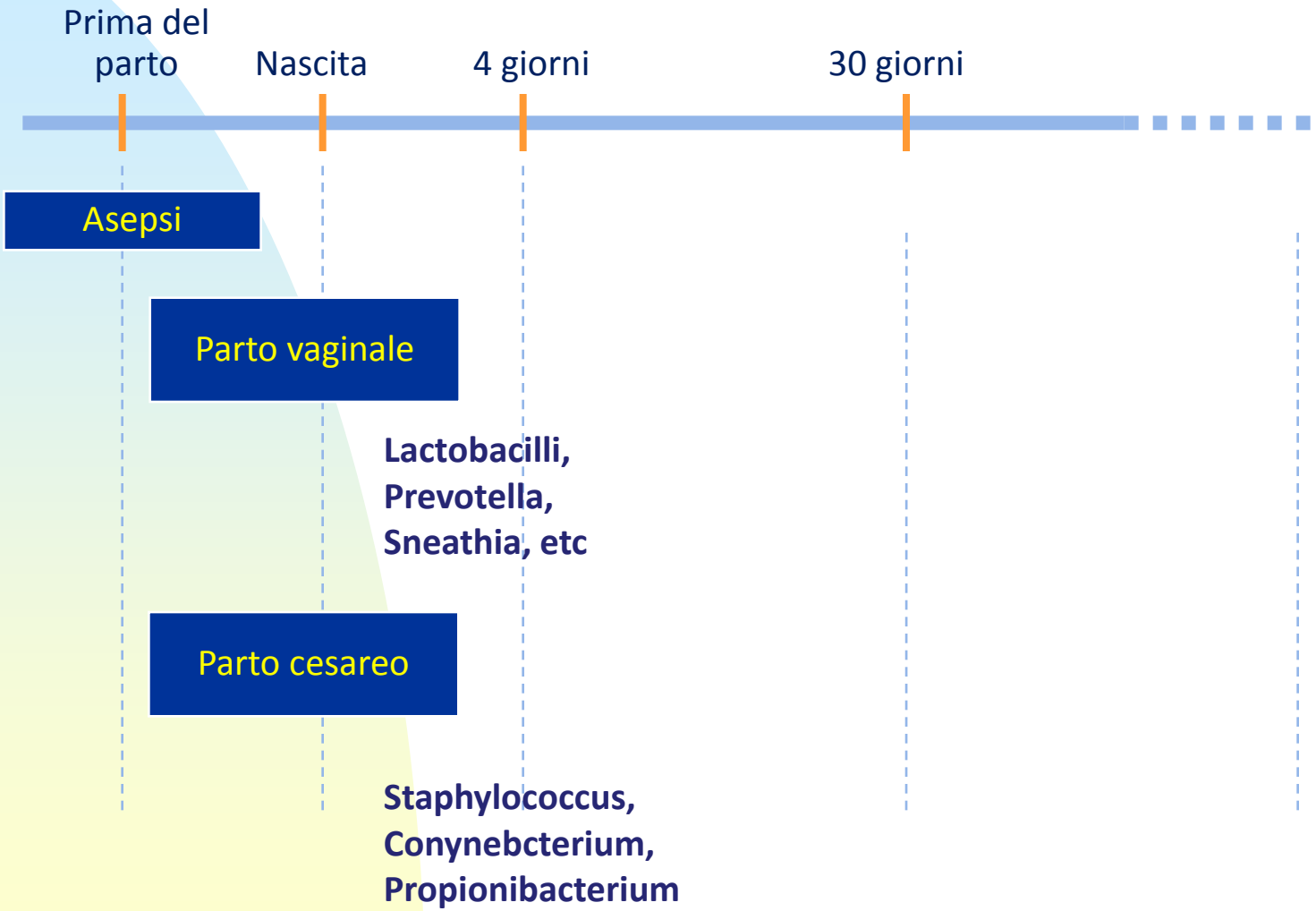
Our work also ties together two emerging themes from studies of human-associated microbial communities:

1) high levels of variability among individuals in every body habitat studied to date, including the gut, skin, and oral cavity, and
2) relative stability within individuals.

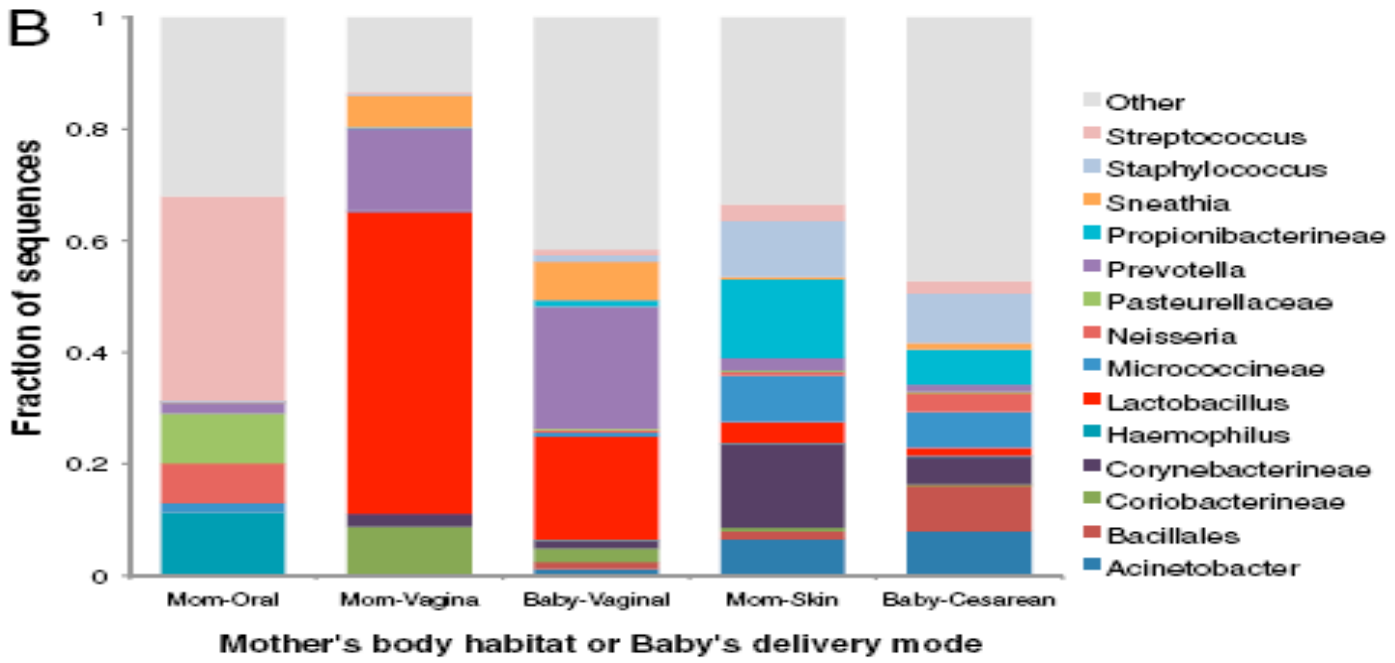
Costello EK et al, Science 2009; 326: 1694-1697

Sviluppo della flora batterica intestinale

Il tipo di parto condizione la colonizzazione microbica del neonato



Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns



A 4 giorni il microbiota dei neonati da parto vaginale somiglia a quello vaginale materno, da cesareo al microbiota cutaneo della mamma

Dominguez Bello MG, PNAS 2010; 107: 11971

Sviluppo della flora batterica intestinale

Il tipo di latte condizione la colonizzazione intestinale del neonato

Prima del parto | Nascita | 4 giorni | 30 giorni

Asepsi

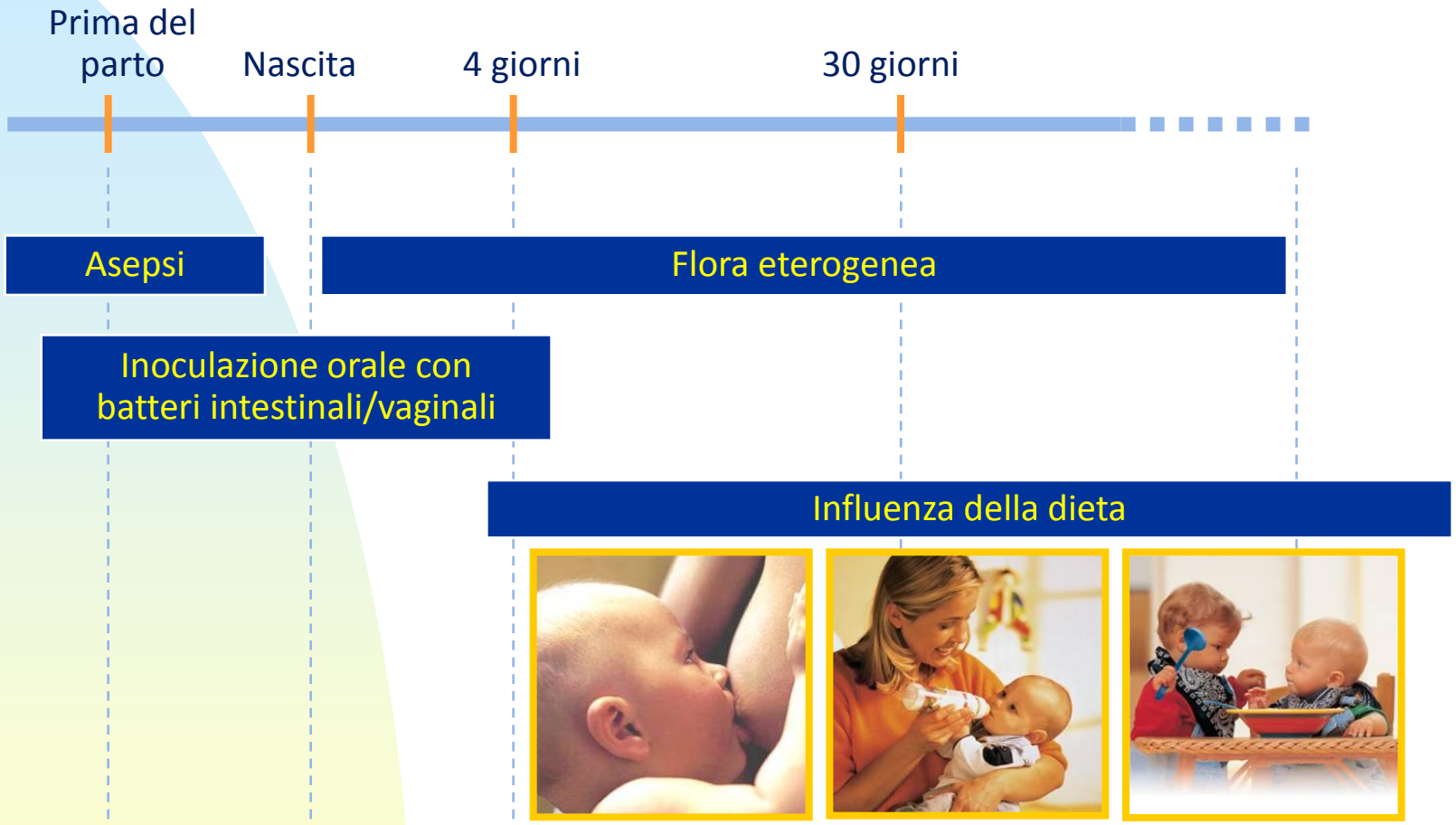
90-99% bifidobatteri

Inoculazione orale con batteri intestinali/vaginali

E.Coli, Clostridium difficile, Bacteroides fragilis, Lactobacilli

Orrhage & Nord, 1999; Harmsen et al.

Sviluppo della flora batterica intestinale



Orrhage & Nord, 1999; Harmsen et al.

Factors Influencing the Composition of the Intestinal Microbiota in Early Infancy

Disegno: Studio prospettico. I campioni di feci di 1032 neonati di 1 mese sono stati analizzati per la ricerca dei batteri, correlandone la presenza con il tipo di parto, alimentazione, età gestazionale, ospedalizzazioni, uso di antibiotici, etc

Risultati: a 1 mese tutti i bambini erano colonizzati soprattutto da bifidobatteri, E Coli e B fragilis, meno da Clostridium difficilis e da lactobacilli

TABLE 2 Median Counts and Prevalence of Selected Gut Bacteria in Feces of Infants 1 Month of Age ($n = 1032$)

	Bifidobacteria	*E coli*	*C difficile*	*B fragilis* Group	Lactobacilli	Total
Median counts (range), $\log_{10}$ CFU/g feces	10.68 (6.84–11.56)	9.35 (5.91–10.79)	5.32 (2.70–9.57)	9.28 (5.74–10.44)	8.66 (7.92–10.73)	11.12 (9.43–12.14)
Prevalence, %	98.6	87.7	25.0	81.6	32.4	100

Penders J et al, Pediatrics 2006; 118: 511

Factors Influencing the Composition of the Intestinal Microbiota in Early Infancy

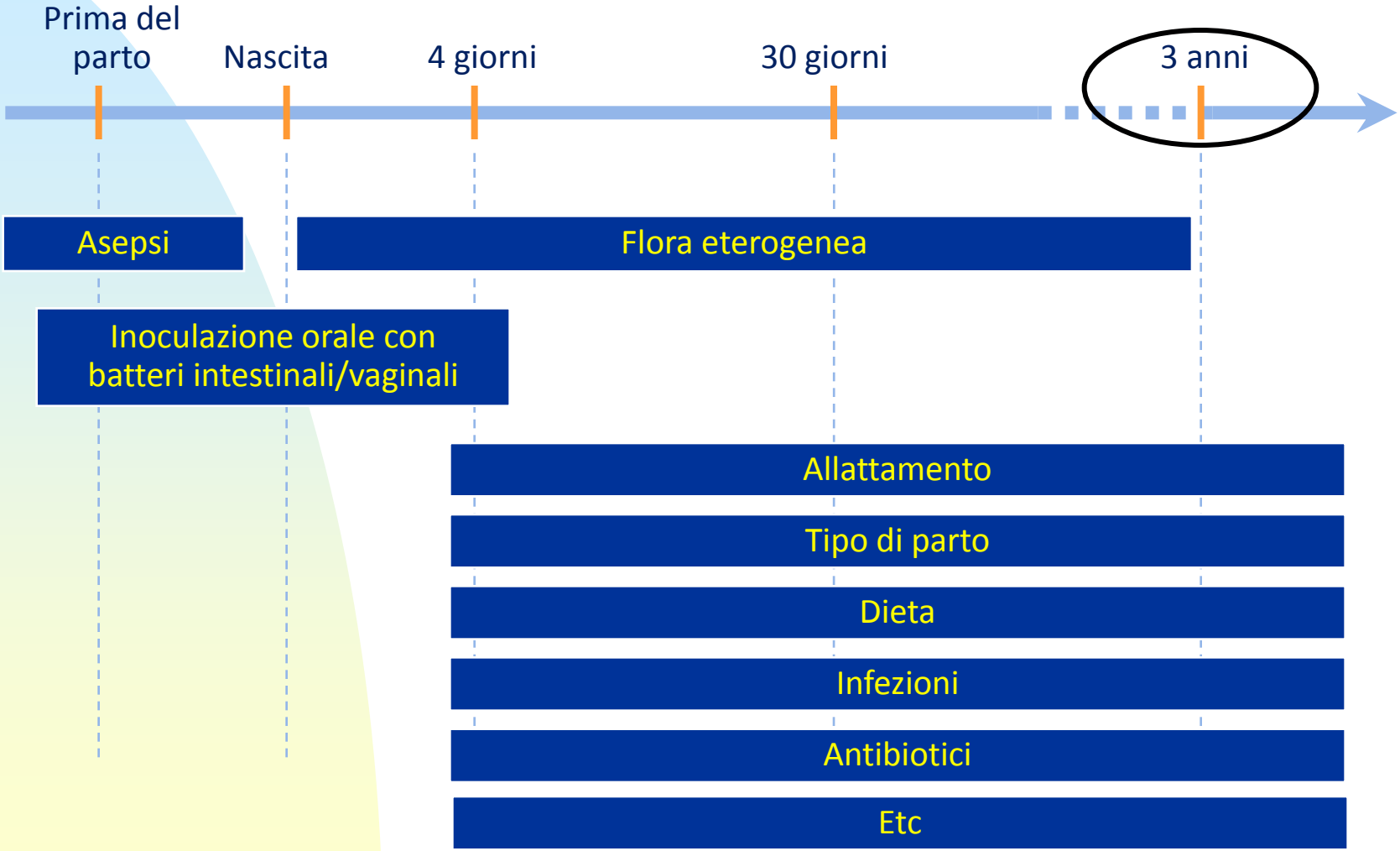
Il cesareo si associa a un ridotto numero di bifidobatteri e di B.fragilis e a un maggio numero di Clostridium difficile.
La ospedalizzazione a un maggior numero di Clostridium difficile
L'allattamento artificiale si associa a un maggior numero di clostridium difficile, E Coli e b. Fragilis e a meno lattobacilli
L'uso di antibiotici riduce i bifidobatteri e il b. fragilis

TABLE 5 Linear Regression Coefficients for Bacterial Counts and ORs for Presence of Gut Bacteria, With Respect to Determinants in Multivariate Analyses

	Bifidobacteria		*E coli*		*C difficile*		*B fragilis* Group		Lactobacilli	
	Coefficient (*P*)	OR (99% CI)	Coefficient (*P*)	OR (99% CI)	Coefficient (*P*)	OR (99% CI)	Coefficient (*P*)	OR (99% CI)	Coefficient (*P*)	OR (99% CI)
Cesarean section (compared with vaginal delivery)	−0.34 (.003)[a]	ND	0.07 (.677)	1.04 (0.38–2.83)	0.88 (.24)	2.07 (1.01–4.25)[a]	−1.36 (<.001)[a]	0.28 (0.13–0.61)[a]	0.31 (.032)	0.84 (0.42–1.70)
Hospitalization (d)	−0.01 (.365)	ND	0.04 (.108)	1.00 (0.86–1.17)	0.06 (.364)	1.13 (1.01–1.25)[a]	0.01 (.621)	1.02 (0.90–1.16)	0.02 (.306)	1.02 (0.92–1.12)
Prematurity (compared with term infants)	0.38 (.282)	ND	−0.81 (.109)	0.11 (0.01–1.15)	2.83 (.007)[a]	4.47 (0.48–41.85)	0.38 (.432)	0.96 (0.09–10.38)	−0.23 (.580)	0.68 (0.09–5.25)
Exclusive formula-fed (compared with exclusively breastfed)	−0.10 (.233)	ND	0.24 (.031)	2.90 (1.22–6.89)[a]	1.03 (.003)[a]	1.88 (1.13–3.11)[a]	0.25 (.027)	2.22 (1.16–4.24)[a]	0.056 (.564)	1.64 (1.03–2.60)[a]
Antibiotic use by infant (yes/no)	−0.66 (.001)[a]	ND	0.06 (.825)	0.57 (0.12–2.66)	0.94 (.324)	0.59 (0.13–2.75)	−1.10 (<.001)[a]	1.30 (0.27–6.19)	−0.16 (.470)	1.11 (0.34–3.63)
Miconazole use by infant (yes/no)	−0.59 (.003)[a]	ND	0.41 (.142)	0.60 (0.13–2.90)	0.04 (.965)	1.01 (0.25–4.09)	0.174 (.506)	1.49 (0.27–8.20)	0.17 (.468)	1.27 (0.38–4.25)
Siblings (yes/no)	0.25 (.001)[a]	ND	0.21 (<.025)	1.45 (0.82–2.57)	−0.32 (.277)	1.01 (0.66–1.56)	0.004 (.907)	1.09 (0.68–1.74)	0.01 (.923)	0.88 (0.59–1.29)

Penders J et al, Pediatrics 2006; 118: 511

Sviluppo della flora batterica intestinale



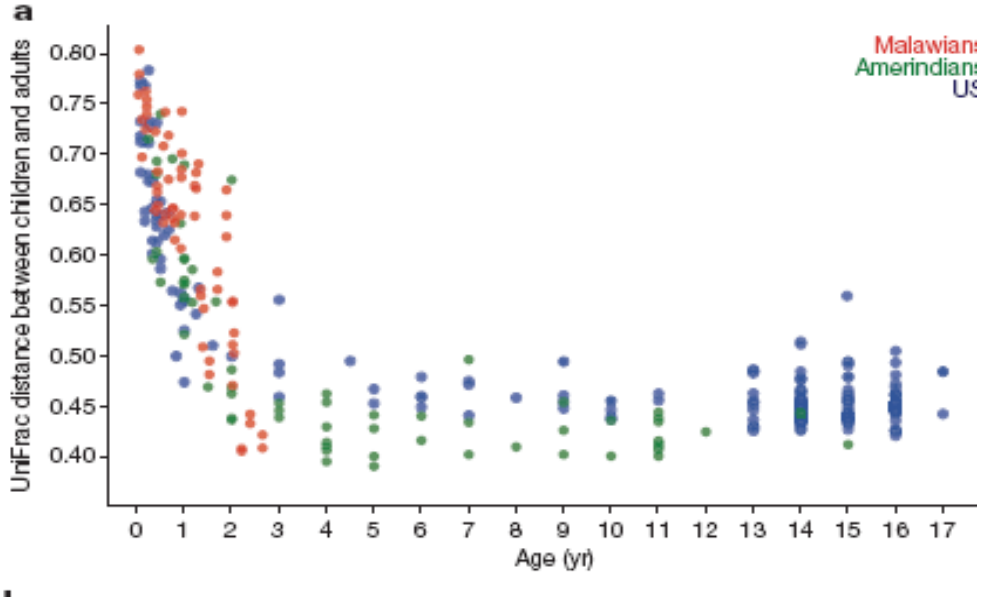
Human gut microbiome viewed across age and geography

Obiettivo: Esaminare eventuali differenze nel microbioma in diverse popolazioni e età.

Disegno: hanno caratterizzato le specie batteriche in campioni fecali di 531 soggetti sani di differenti aree geografiche.

Risultati

1: In tutte le popolazioni la composizione del microbioma **si stabilizza verso i 3 anni di vita**.



Yatsunenko T et al, Nature 2012; 486: 222-8

Human gut microbiome viewed across age and geography

Risultati

2 : le variazioni interpersonali sono maggiori nei bambini rispetto agli adulti in tutte le popolazioni (Fig. b)

3: le aree geografiche comportano una variazione nel microbioma, evidenti in tutte le età (Fig c)

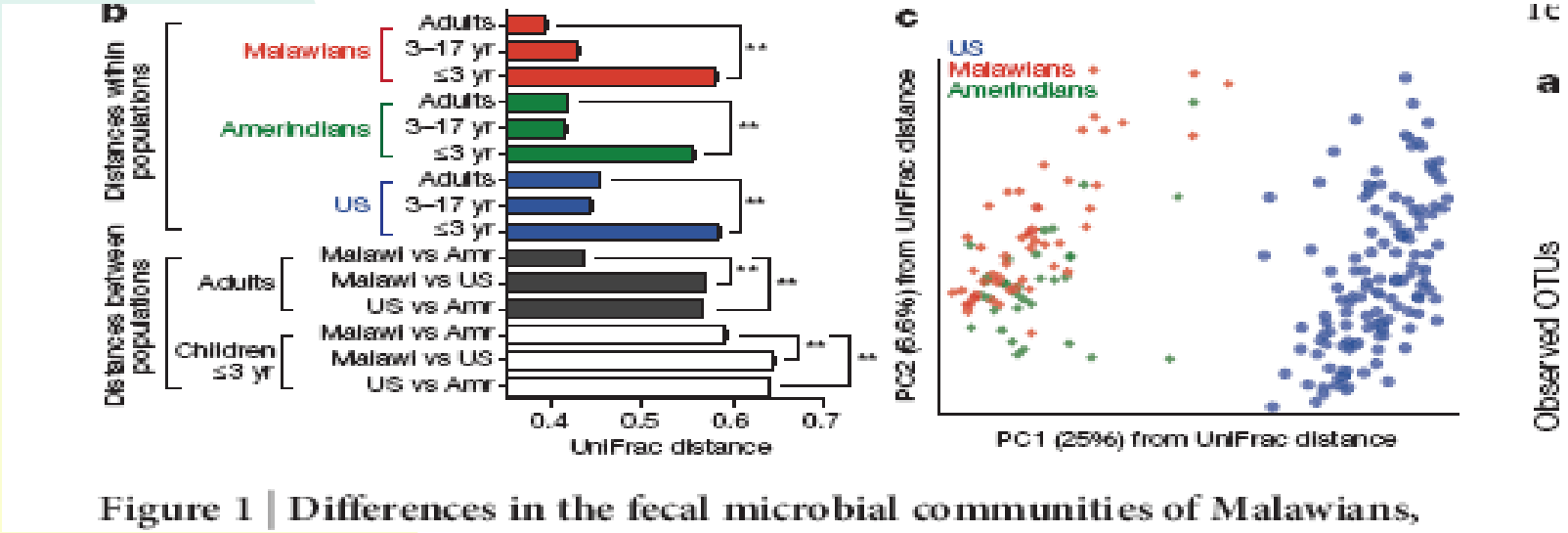


Figure 1 | Differences in the fecal microbial communities of Malawians,

Yatsunenko T et al, Nature 2012; 486: 222-8

microbiota intestinale

Sviluppo del microbiota intestinale

Funzioni del microbiota intestinale

Rapporti con le patologie immunomediate

Possibili implicazioni terapeutiche

Funzioni del Microbioma Intestinale

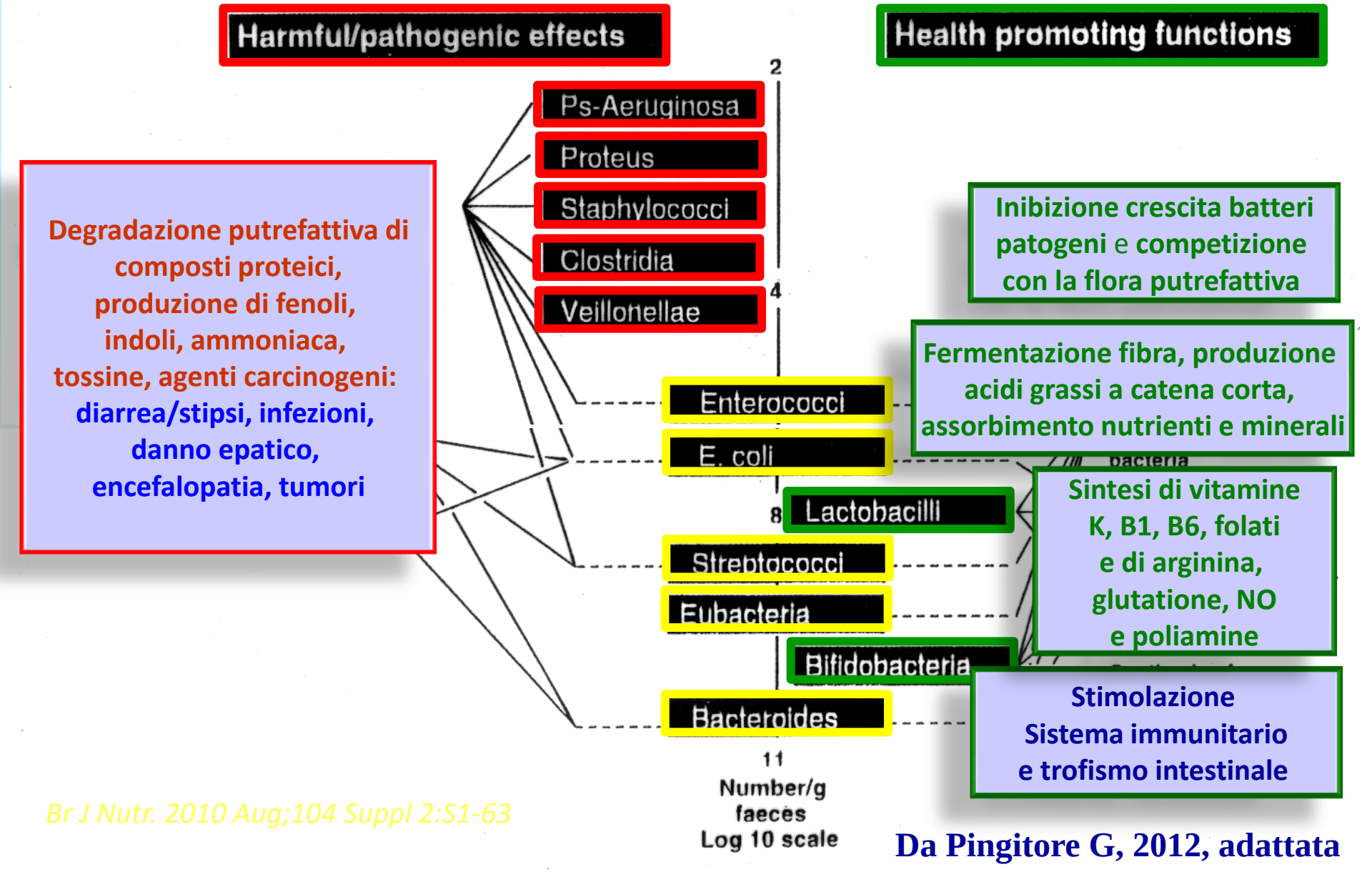
Difesa dalla colonizzazione da parte di patogeni
(produzione di sostenze anti microbiche)

Rinforzo della barriera intestinale
(stimolo alla sintesi di IgA)

Facilita l'assorbimento di nutrienti
(metabolizzando composti indigeribili)

Guida nella maturazione e indirizzo funzionale del sistema immune dell'ospite

La microflora dell'intestino crasso



Br J Nutr. 2010 Aug;104 Suppl 2:S1-63

Da Pingitore G, 2012, adattata

microbiota intestinale

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Role of the intestinal microbiome in health and disease: from correlation to causation

Principali patologie correlate con variazioni del microbiota intestinale

Table 1 **Intestinal microbiota-associated diseases, syndromes, or other aberrations, with summaries of multiple studies that support an association between the microbiota and the indicated aberration.**

Aberration	Most relevant observations and potential correlation	References
Crohn's disease	Diversity decrease – reduced *F. prausnitzii*	Kaser et al. 2010[51]; Sokol et al. 2009[52]; Willing et al. 2010[53]
Ulcerative colitis	Diversity decrease – reduced *A. muciniphila*	Png et al. 2010[54]; Kaser et al. 2010[51]; Lepage et al. 2011[55]
Irritable bowel syndrome	Global signatures – increased *Dorea* and *Ruminococcus*	Salonen et al. 2010[36]; Saulnier et al. 2011[56]; Rajilić-Stojanović et al. 2011[13]
Clostridium difficile infection	Strong diversity decrease – presence of *C. difficile*	Grehan et al. 2010[57]; Khoruts et al. 2010[58]
Colorectal cancer	Variation in *Bacteroides* spp. – increased fusobacteria	Sobhani et al. 2011[59]; Wang et al. 2012[60]; Marchesi et al. 2011[61]
Allergy/atopy	Altered diversity – specific signatures	Stsepetova et al. 2007[62]; Bisgaard et al. 2011[63]; Storrø et al. 2011[64]
Celiac disease	Altered composition, notably in small intestine	Nistal et al. 2012[65]; Di Cagno et al. 2011[66]; Kalliomäki et al. 2012[67]
Type 1 diabetes	Signature differences	Vaarela 2011[68]; Giongo et al. 2011[69]; Brown et al. 2011[70]
Type 2 diabetes	Signature differences	Larssen et al. 2010[71]; Wu et al. 2010[72]; Kootte et al. 2012[73]
Obesity	Specific bacterial ratios (*Bacteroidetes*/*Firmicutes*)	Ley et al. 2006[74]; Turnbaugh et al. 2009[10]; Musso et al. 2011[75]

De Vos WM, et al Nutr Rev 2012; 7: s45-56

Role of the intestinal microbiome in health and disease: from correlation to causation

Table 2 **Indications for associations between the microbiota and health aberrations, provided as an alphabetical listing of the aberrations suggested to be associated with the intestinal microbiota, along with support for such an association.**

Disease or aberration	Type of support	Reference*
Alzheimer's disease	Microbiota in a mouse model of Alzheimer's disease	Karri et al. 2010[103]
Atherosclerosis	Analysis of plaques in humans	Koren et al. 2011[104]
Autistic spectrum disorders	Analysis of mucosa in children with autism spectrum disorders	Williams et al. 2011[105]
Chronic fatigue syndrome	Cultured microbiota in patients with chronic fatigue syndrome	Sheedy et al. 2009[106]
Colic babies	Longitudinal analysis of colic babies cohort	de Weerth et al. 2012 unpublished data
Cardiovascular disease	Cardiovascular-diseased mice and microbial metabolism	Wang et al. 2011[48]
Depression and anxiety	Probiotic intervention in stressed mice	Bravo et al. 2011[34]
Frailty	Analysis of elderly and high frailty scores	van Tongeren et al. 2005[107]
Graft-vs-host disease	Review of human data on graft-vs-host disease	Murphy et al. 2011[108]
Multiple sclerosis	Involvement of microbiota in mice with multiple sclerosis	Berer et al. 2011[109]
Nonalcoholic fatty liver disease	Effect of choline depletion in humans	Spencer et al. 2011[101]
Parkinson's disease	Role of enteric nervous system and review of Parkinson's disease development	Braak et al. 2003[110]
Rheumatoid arthritis	Microbiota as predisposing factor in rheumatoid arthritis	Scher and Abramson 2011[111]
Retrovirus infection	Mouse retrovirus infection relies on microbiota	Kane et al. 2011[112]
Poliovirus infection	Mouse microbiota promotes poliovirus infection	Kuss et al. 2011[113]

* The most recent single reference is given.

De Vos WM, et al Nutr Rev 2012; 7: s45-56

Role of the intestinal microbiome in health and disease: from correlation to causation

In most instances, however, this has simply meant an analysis of associations with disease or functional disturbances, and only in special cases are specific correlations described in which specific microbial groups relate to a healthy or a diseased state in a manner that implies a linear relationship. Finally, there are only a handful of examples in which the cause-and-effect relations satisfying Koch's postulates apply, but even these relate mainly to studies in animal models, thereby providing hypotheses for human disease and human intervention tests.

De Vos WM, et al Nutr Rev 2012; 7: s45-56

Effect of barrier microbes on organ-based inflammation

Le MICI potrebbero trarre origine da una inappropriata risposta immune verso il microbiota intestinale e verso l'intestino in soggetti geneticamente predisposti, in conseguenza di fattori ambientali ancora poco definiti.

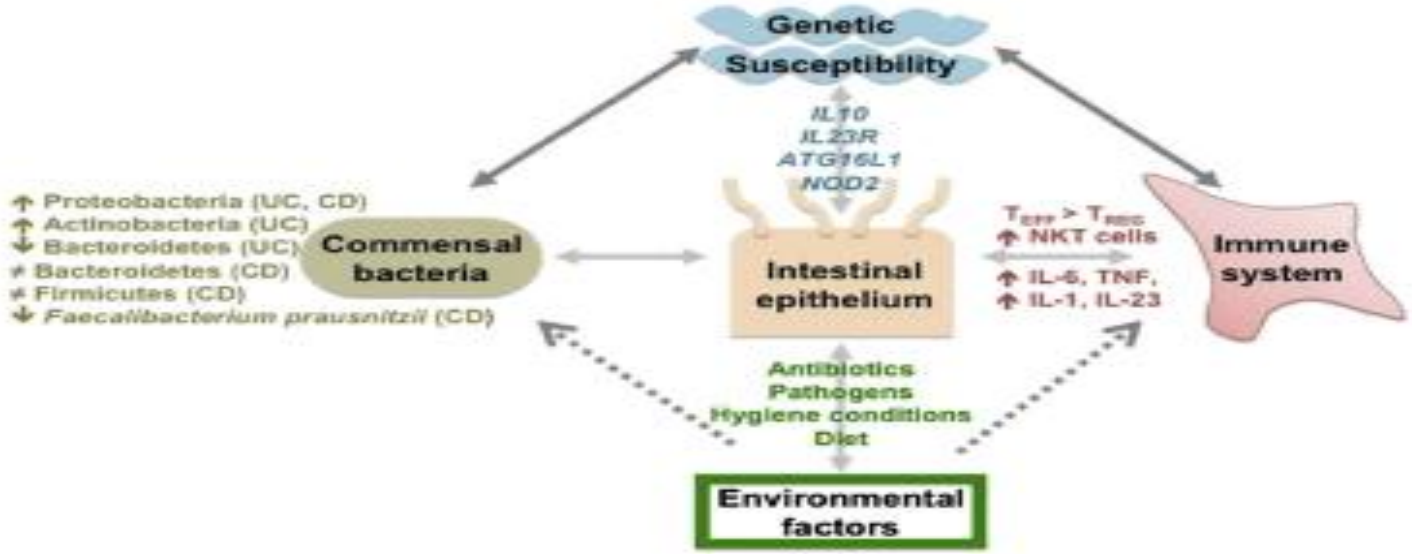

FIG 2. Factors that influence IBD development. IBD is caused by dysfunction in the composition of and interactions between the commensal microbiota, the intestinal epithelium, and the immune system. Each of these factors is under the influence of genetic and environmental factors. *NKT*, Natural killer T cells; T_{EFF}, T effector cell; T_{REG}, T regulatory cell.

Garn H et al, JACI 2013; 131: 1465-78

Effect of barrier microbes on organ-based inflammation

Allo sviluppo delle malattie allergiche potrebbero contribuire oltre ai fattori genetici diversi fattori ambientali che, condizionando lo sviluppo di una dversa flora batterica intestinale, orientano la risposta immunologica in senso Th-2

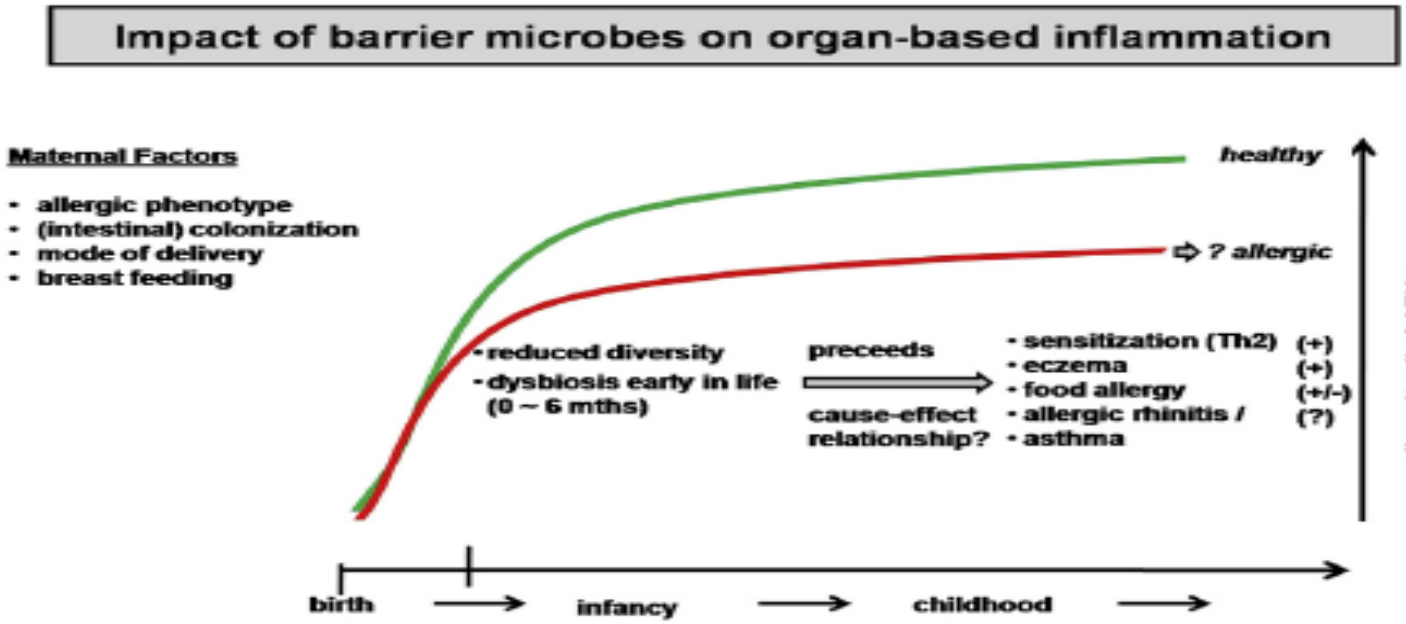

FIG 4. Effect of barrier microbes on organ-based inflammation. Fundamental differences exist between the normal homeostatic colonization pattern and the pattern identified in healthy children *(green)* and intestinal colonization in allergic children *(red)*. However, the detailed qualitative and quantitative changes are still inconsistent and might differ for various allergic phenotypes. A common pattern, which is currently emerging, is reduced diversity in allergic subjects that precedes the onset of allergic diseases later on in life. However, a cause-effect relationship needs to be formally established. *OTUs*, Operational taxonomic units.

Garn H et al, JACI 2013; 131: 1465-78

The 'microflora hypothesis' of allergic diseases

As an extension of the hygiene hypothesis, the '**microflora hypothesis of allergic disease**' was postulated to highlight the role of the gut in modulating host immunity in early life and possibly in later life

Noverr MC, et al. Clin Exp Allergy 2005;35:1511-20

Effect of barrier microbes on organ-based inflammation

TABLE III. Open questions

- Does a cause-effect relationship exist between dysbiosis and allergic phenotypes/intestinal inflammation?
- What causes dysbiosis? Candidates include host genetics, environmental factors, or both.
- Is dysbiosis the result of a loss of protective microbes or the acquisition of disease-promoting strains?
- How can dysbiosis be corrected?
- Does intestinal dysbiosis contribute to allergic manifestations outside the gut, and, if so, how?
- Does lung dysbiosis contribute to allergic manifestations outside the lung and perhaps to intestinal inflammation?
- How stable is dysbiosis over time?
- What are the reasons for heterogenic results between the studies?

Garn H et al, JACI 2013; 131: 1465-78

microbiota intestinale

Sviluppo del microbiota intestinale

Funzioni del microbiota intestinale

Rapporti con le patologie immunomediate

Possibili implicazioni terapeutiche

Intestinal microbiota in functional bowel disorders: a Rome foundation report

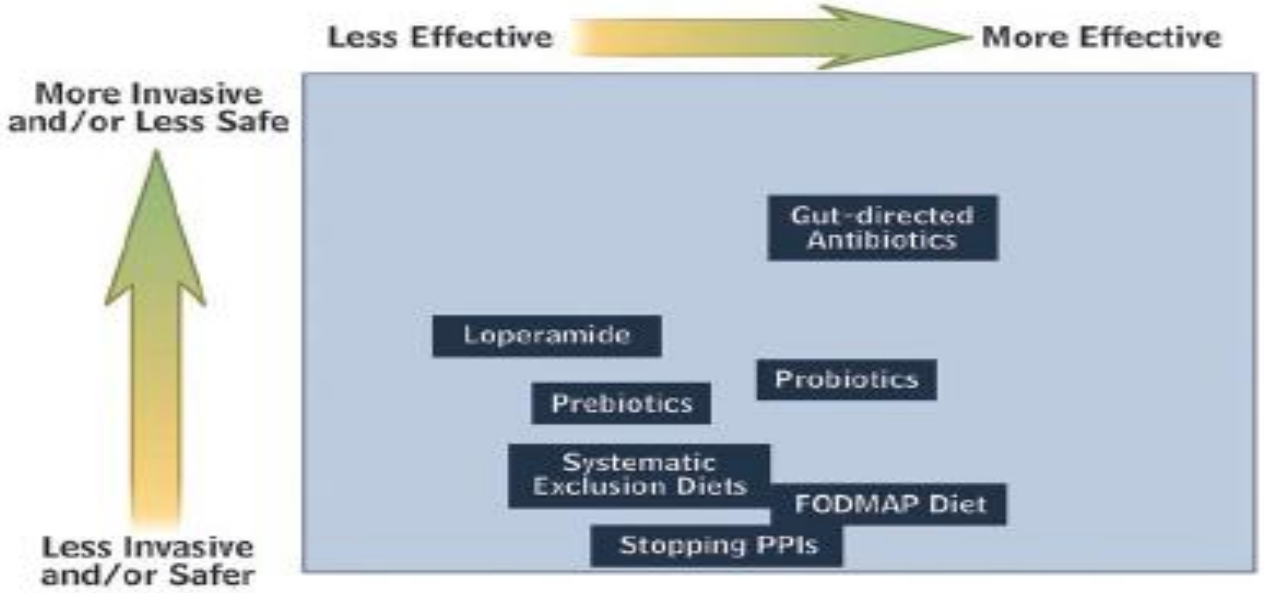

Figure 4 Plot chart of currently available strategies for modifying gut microbiota aiming to demonstrate the relationship between the effectiveness and invasiveness/safety of the proposed approach. FODMAP, fermentable oligo-, di- and mono-saccharides and polyols; PPI, proton pump inhibitor.

Simren M et al, Gut 2013; 62: 159-76

LINEE GUIDA PROBIOTICI E PREBIOTICI

Probiotici

quei microrganismi che, introdotti con l'alimento, siano in grado di raggiungere l'intestino in condizioni di vitalità ed esercitare una azione salutistica sull'organismo

Prebiotici

Sono parti di alimenti non digeribili o non completamente digeribili, che stimolano selettivamente la crescita e le attività dei lattobacilli o dei bifidobatteri, principali costituenti dell'ecosistema intestinale nei bambini allattati al seno

Simbiotici

Associazione di un probiotico con prebiotici

Da Pingitore G 2012, adattata

Actual concept of "probiotics": Is it more functional to science or business?

Today probiotics represent a very big business. The global functional food market has been recently estimated at up to $50 billion annual share, while the world probiotic market is estimated at $15 billion. Today, this market is growing at a pace of 5%-30% depending on the country and product type.

The European Commission has recognized probiotic bacteria as having the status of nutrients; in addition probiotics in powder, capsule or tablet form are in most European countries regarded as “food supplements”..

Thus, in most cases, these products reach the market without being tested in the expensive three phases required for approval of a new drug.

Caselli G et al, World J Gastroenterol 2013; 19: 1527-40

Actual concept of "probiotics": Is it more functional to science or business?

Table 3 Results of clinical trials with probiotics in patients with Crohn's disease

Ref.	Patients (*n*)	Duration of therapy	Probiotic strains	Dose (CFU/d)	Outcomes
Malchow *et al*[135]	24	3 mo	*Escherichia coli* Nissle 1917	2.5×10^{10}	Maintaining the remission
Guslandi *et al*[136]	32	6 mo	*Saccharomyces boulardii*	1 g	Postsurgical prevention of CD recurrence (relapse rate probiotic+ 5-ASA *vs* 5-ASA alone)
Prantera *et al*[137]	45	1 yr	*Lactobacillus GG*	12×10^{9}	Postsurgical prevention of CD recurrence (no effects)
Schultz *al*[138]	11	6 mo	*Lactobacillus GG*	2×10^{9}	Probiotics are not superior to placebo in maintaining remission
Bousvaros *et al*[139]	75	1 yr	*Lactobacillus GG*	2×10^{10}	Probiotics are not superior to placebo in maintaining remission
Marteau *et al*[140]	98	6 mo	*Lactobacillus johnsonii*	4×10^{9}	Postsurgical prevention of CD recurrence (recurrence rate decreased *vs* placebo)
Chermesh *et al*[141]	30	24 mo	Synbiotic 2000 (*Pediococcus pentoseceus*, *Lactobacillus raffinolactis*, *Lactobacillus paracasi* susp paracsei, *Lactobacillusplantarum 2362*) and 4 fermentable fibers *vs* placebo	10^{11}	Postsurgical prevention of CD recurrence (NS)
Van Gossum *et al*[142]	70	12 wk	*Lactobacillus johnsonii* or placebo	10^{10}	Postsurgical prevention of CD recurrence (NS)
Rolfe *et al*[143]	7 RCTs				No benefit of probiotics in the maintenance of remission of CD
Rahimi *et al*[144]	8 RCTs				None benefit for probiotic treatment in the maintenance of clinical remission of CD

Caselli G et al, World J Gastroenterol 2013; 19: 1527-40

Actual concept of "probiotics": Is it more functional to science or business?

Table 2 Results of clinical trials with probiotics in ulcerative colitis

Ref.	Patients (*n*)	Duration of therapy	Probiotic strains	Dose (CFU/d)	Outcomes
Kruis *et al*[118]	120	12 wk	*Escherichia coli* Nissle 1917	50×10^{10}	Maintaining the remission (similar to 5-ASA)
Rembacken *et al*[119]	116	1 yr	*Escherichia coli* Nissle 1917	5×10^{10}	Induction of remission (similar to 5-ASA); maintaining of relapses (similar to 5-ASA)
Venturi *et al*[120]	20	1 yr	VSL3®	5×10^{11}	Maintaining the remission
Ishikawa *et al*[121]	21	1 yr	Milk with bifidobacteria	10×10^{8}	Maintaining the remission
Guslandi *et al*[122]	25	4 wk	*Saccharomyces boulardii*	250 mg × 3	Induction of remission
Kruis *et al*[123]	327	1 yr	*Escherichia coli* Nissle 1917	$2.5\text{-}25 \times 10^{9}$	Induction of remission (5-ASA better than probiotic)
Tursi *et al*[124]	90	8 wk	Balsalazide/VSL3®	900×10^{8}	Induction of remission
Cui *et al*[125]	30	8 wk	Bifidobacteria	1.26 g/d	Maintaining of remission
Kato *et al*[126]	20	12 wk	*Bifidobacterium*-fermented milk *vs* placebo	10^{9}	CDAI lower in Bifidobacterium fermented milk that in placebo
Furrie *et al*[127]	18	4 wk	*Bifidobacterium longum* + prebiotic (Synergy 1)	4×10^{11}	Induction of remission
Bibiloni *et al*[128]	32	6 wk	VSL3®	1800 billion × 2	Induction of remission
Zocco *et al*[129]	187	12 mo	*Lactobacillus GG vs* mesalazina	18×10^{9}	No difference between the treatment groups
Henker *et al*[130]	34	12 mo	*Escherichia coli* Nissle 1917	5×10^{10}	Maintenance of remission
Miele *et al*[131]	29	12 mo	VSL3®	$450\text{-}1800 \times 10^{9}$	Induction of remission (92.8% in treated with VSL3® and 36.4% in the placebo group)
Sood *et al*[132]	147	12 wk	VSL3®	3.6×10^{12}	Induction of remission (42.9% against 15.7% in the placebo group)
Matthes *et al*[133]	57	4 wk	*Escherichia coli* Nissle 1917	$10\text{-}40 \times 10^{8}$	Induction of remission
Sang *et al*[134]	13 RCTs				Heterogenity between the studies in their methodology and results

Caselli G et al, World J Gastroenterol 2013; 19: 1527-40

Guidance for Substantiating the Evidence for Beneficial Effects of Probiotics: Probiotics in Chronic Inflammatory Bowel Disease and the Functional Disorder Irritable Bowel Syndrome

"Selected probiotics strains have been proven to be clinically effective in maintaining remission in patients with ulcerative colitis. None of the probiotics thus far tested has been shown to be effective in induction of remission or in maintenance of remission in patients with Crohn's disease.…"

Haller D et al, J Nutr 2010; 140: 690s-9s

Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases

Metodo: studio effettuato mediante questionari su una coorte di 108.000 bambini Norvegesi, indagando il consumo materno durante la gravidanza di alimenti contenenti probiotici e il consumo del bambino di probiotici dopo i primi 6 mesi di vita.

TABLE II. Association between maternal probiotic milk and yogurt consumption in patients with pregnancy and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa whose mothers had completed the 6-, 18-, and 36-month postnatal questionnaires

	Cases (no.)	Cases (%)*	Unadjusted RR (95% CI)	Adjusted† RR (95% CI)	Adjusted‡ RR (95% CI)
Atopic eczema at 6 mo	4,849	12.2	0.94 (0.89-1.00)	0.93 (0.88-0.99)	0.94 (0.89-0.99)
Current atopic eczema at 18 mo	5,440	13.6	0.99 (0.94-1.04)	1.00 (0.94-1.05)	1.00 (0.95-1.05)
Rhinoconjunctivitis at 18-36 mo	1,425	3.6	0.85 (0.76-0.95)	0.90 (0.81-1.00)	0.87 (0.78-0.98)
Current asthma at 36 mo with asthma medication	2,260	5.7	0.97 (0.90-1.05)	0.99 (0.91-1.08)	0.99 (0.91-1.08)

*There were missing outcome data for the following: atopic eczema at 6 months (2.1%), current atopic eczema at 18 months (1.3%), rhinoconjunctivitis at 18 to 36 months (2.9%), and current asthma at 36 months with asthma medication (2.6%). The case percentage is calculated with the total N in the denominator with no missing information.
†Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, and dietary fiber intake (in grams per 10 MJ).
‡Additional adjustment for total energy intake (in MJ per day), breast-feeding, maternal history of allergic disease, parity, infant's sex, and mode of delivery (cesarean section vs vaginal).

Il consumo materno durante la gravidanza avrebbe un debole effetto protettivo verso l'eczema a 6 mesi e rinocongiuntivite a 18-36 mesi

Bertelsen RJ et al, JACI 2014; 133: 165-71

Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases

TABLE III. Association between consumption of probiotic milk products by the child only, mother only (in pregnancy), and both the mother and child and atopic eczema, rhinoconjunctivitis, and asthma among 40,614 children in MoBa who had completed the 6-, 18-, and 36-month postnatal questionnaires

		Current atopic eczema at 18 mo		Rhinoconjunctivitis at 18-36 mo		Current asthma with asthma medication at 36 mo	
Probiotic milk products	No.	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)	Cases (%)	Adjusted* RR (95% CI)
No intake (reference)	18,572	13.6	1	3.9	1	5.8	1
Child intake only	7,000	13.6	1.01 (0.94-1.08)	3.7	0.98 (0.85-1.13)	5.9	1.08 (0.96-1.21)
Mother intake only	7,437	14.6	1.08 (1.01-1.15)	3.6	0.94 (0.81-1.08)	5.3	0.96 (0.85-1.08)
Mother and child	7,605	12.5	0.93 (0.86-1.00)	3.0	0.80 (0.68-0.93)	5.8	1.07 (0.95-1.19)

*Adjusted for maternal age, smoking in pregnancy, maternal education, prepregnancy BMI, dietary fiber intake (grams per 10 MJ), total energy intake (MJ per day), breast-feeding, maternal history of allergic disease, parity, infant's sex, and mode of delivery.

Solo il consumo sia materno in gravidanza che del bambino dopo il sesto mese avrebbero un lieve effetto protettivo sullo sviluppo di eczema a 18 mese e di rinocongiuntivite a 18-36 mesi

Bertelsen RJ et al, JACI 2014; 133: 165-71

Primary Prevention of Allergic Disease Through Nutritional Interventions

SELECTION OF INFANT FORMULA FOR PRIMARY PREVENTION OF ALLERGIC DISEASE IN THE CHILDREN

pHFs versus extensive casein or extensive whey hydrolysate formulas (ehF). A meta-analysis of 2 studies found no significant difference between a pHF and an eHF in the development of infant allergic diseases, including asthma and food allergy.65,66 One large study found that hydrolyzed formulas, especially the extensively hydrolyzed casein formulas, have the potential to reduce the risk of atopic dermatitis up to age 6 years when used as a supplement or substitute to breast milk instead of conventional cow's milk formulas during the first 4 months of life. No effect was observed on asthma and food allergy.67-69 Additional prospective trials, also in high-risk infants, are needed to confirm the potential benefits of pHFs or eHFs and to determine whether the benefits persist later into childhood, adolescence, or adulthood

Fleisher DM et al, J Allergy Clin Immunol in Practice 2013; 1: 29-36

Primary Prevention of Allergic Disease Through Nutritional Interventions

SELECTION OF INFANT FO[illegible]ARY PREVENTION O[illegible] CHILDREN

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E le formule con i probiotici?

Fleisher DM et al, J Allergy Clin Immunol in Practice 2013; 1: 29-36

Probiotics and allergy in children
An update review

We reviewed recent randomized, double-blinded, placebo-controlled clinical trials using probiotics for allergic diseases of children and evaluated their clinical efficacy, possible mechanisms, dosage, and safety for managing allergic diseases of children. The current data **are insufficient to strongly recommend probiotics as a standard treatment or preventative measure for pediatric allergic disease.** More studies are needed to standardize study designs, bacterial strains, dosages, and durations for different allergic diseases of children

Pan SJ et al, Pediatr Allergy Immunol 2010; 21: e659-66

Clinical Use of Probiotics in Pediatric Allergy: A World Allergy Organization Position Paper

Conclusions: Probiotics do not have an established role in the prevention or treatment of allergy. No single probiotic supplement or class of supplements has been demonstrated to efficiently influence the course of any allergic manifestation or long-term disease or to be sufficient to do so.

Fiocchi A et al, WAO Journal 2012; 5: 148-67

Probiotic supplementation during pregnancy or infancy for the prevention of asthma and wheeze: systematic review and meta-analysis

Conclusions We found no evidence to support a protective association between perinatal use of probiotics and doctor diagnosed asthma or childhood wheeze. Randomised controlled trials to date have not yielded sufficient evidence to recommend probiotics for the primary prevention of these disorders. Extended follow-up of existing trials, along with further clinical and basic research, are needed to accurately define the role of probiotics in the prevention of childhood asthma

Banting MBA et al, BMJ 2013; 347:6471

Grazie per l’attenzione…