A Remarkable Interrelationship between the Maternal Microbiota and the Microbiota of her Offspring : Breast-Feeding can help optimizing it…

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Perinatal Factors acting on the Bacterial Colonisation of the Neonate.

- Maternal Vaginal Microbiota during pregnancy
- Environmental factors in the Hospital
- Perinatal AB's - types of AB's which are used (narrow vs broad spectrum)
- Type of Delivery (vaginal or caesarean)
- Postnatal AB's and other drugs influence
- Nutrition by the end of the first week
- Milk processing and storage

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- Maternal Vaginal Microbiota during pregnancy

Influence of Pregnancy on Vaginal and Urethral Bacterial Colonisation : vulnerable ecosystem

Higher risk of Vaginal Dysbacteriosis

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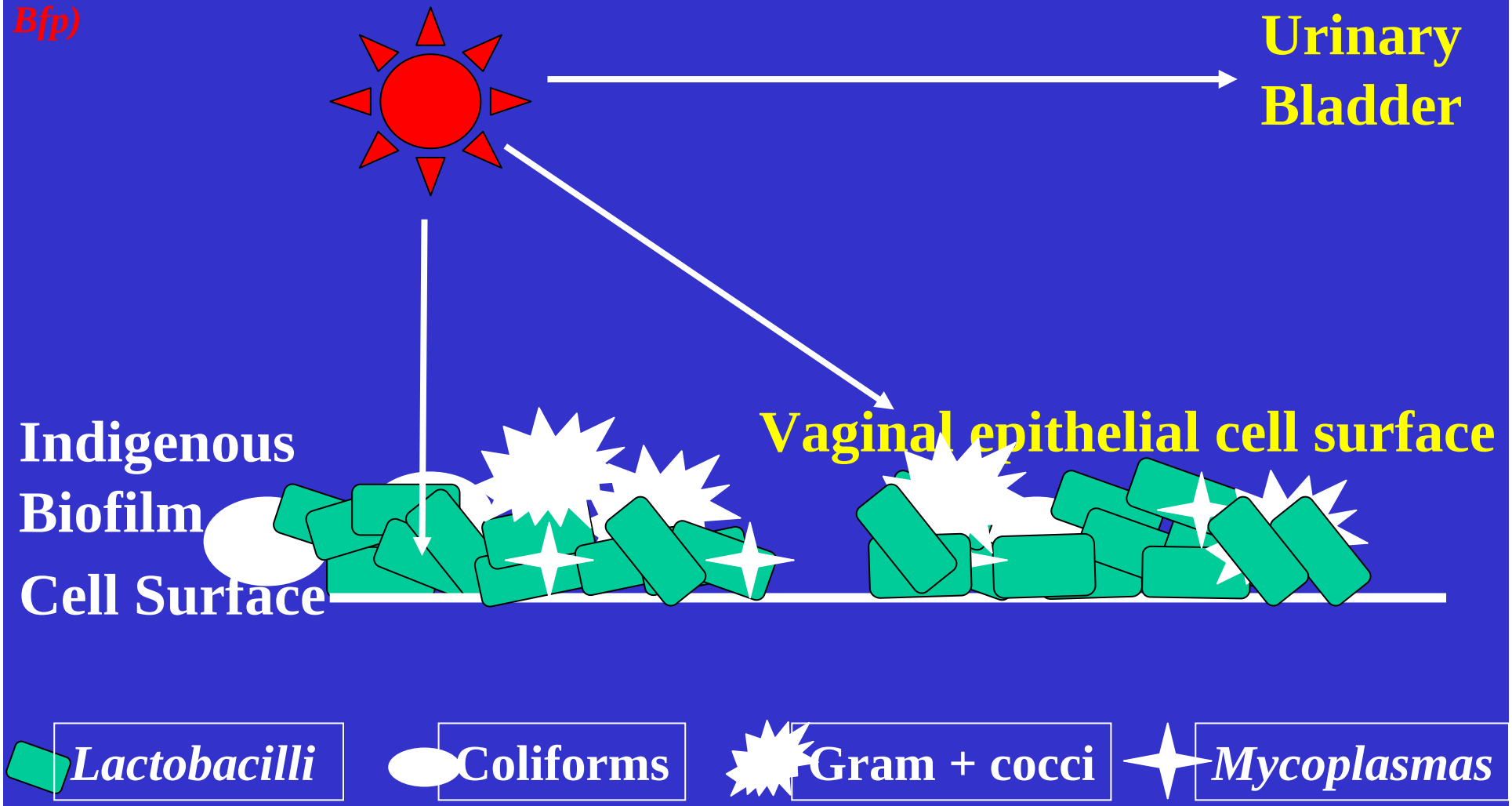
Fimbriated Uropathogenic E. coli

72 ECOR strains (A, B1 (commensal), B2,D (70% path),..K1), bundle-forming pili(P-Bfp)



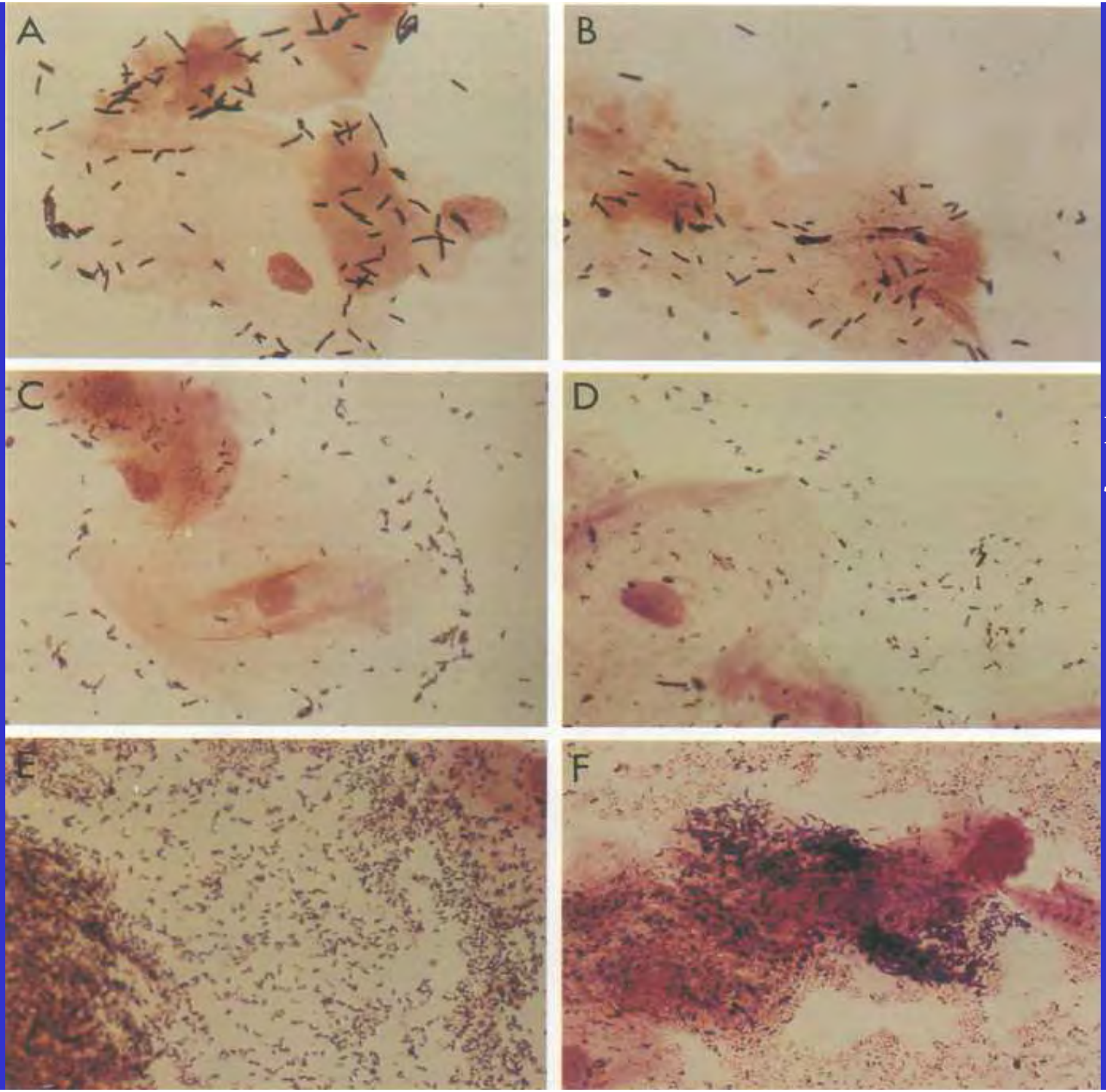
adapted from Reid G *Am J Clin Nutr* 2001;73:437S

Nugent ’s Scoring System

Score	Gram+ Rods (Lactobacillus)	Gram- to Variable Coccobacilli and Rods (rounded, pleomorphic; Gardnerella/Bacteroides)	Gram- Rods, Curved (Mobiluncus)
0	**> 30**	**0**	**0**
1	**5 - 30**	**< 1**	**1 - 5**
2	**1 - 4**	**1 - 4**	**> 5**
3	**< 1**	**5 - 30**	
4	**0**	**> 30**	

***HPF : High Power Field**

0 - 3 = normal flora; from 4 to 6 : intermediary flora; > 7 Vaginosis



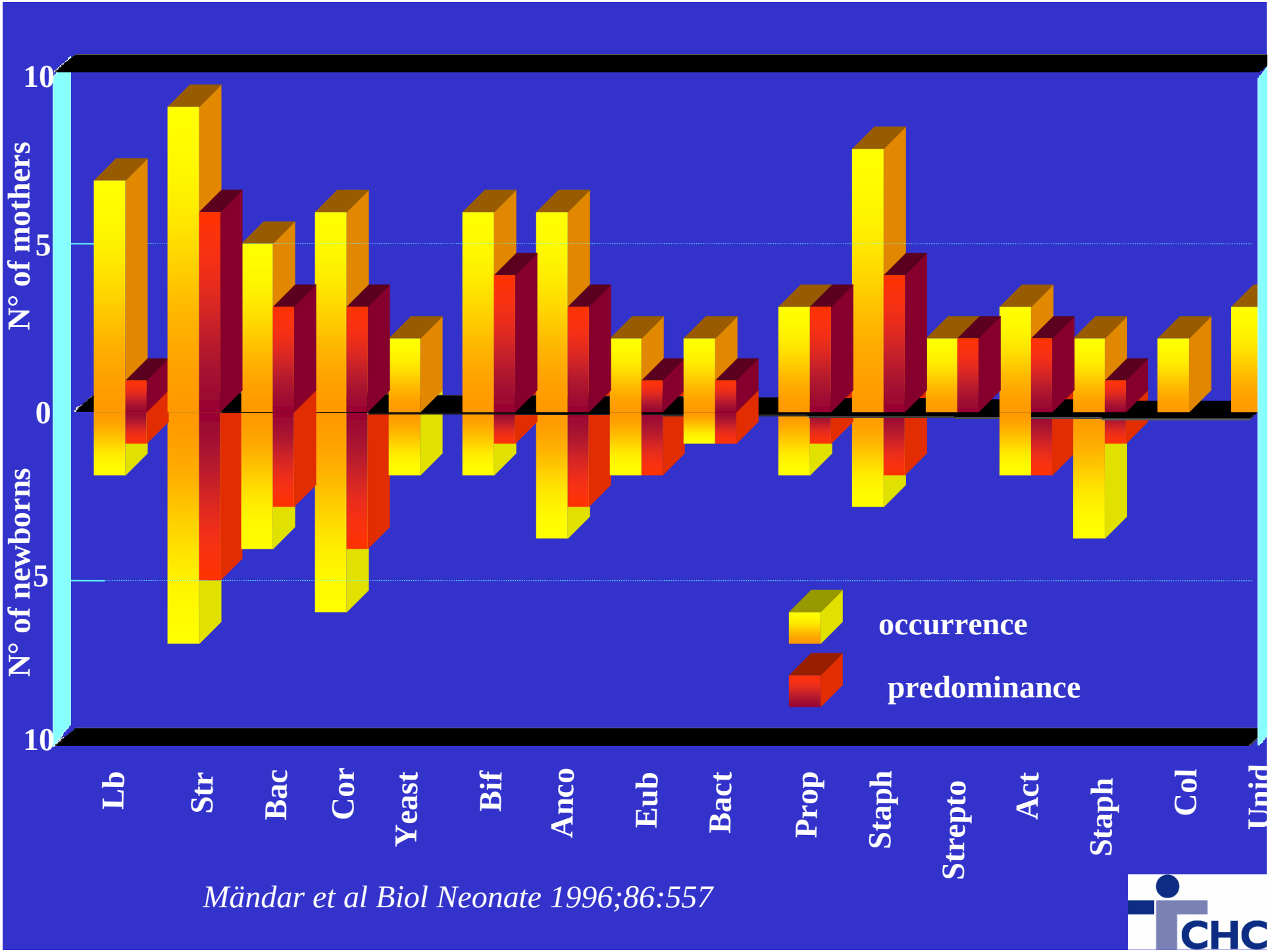
Nugent et al
J Clin Microbiol
1991;29:297.

	Lactobacillus present H_2O_2- positive	Lactobacillus present H_2O_2- negative	Lactobacillus absent	p	p
Chlamydia trachomatis	1/127 (1 %)	2/86 (2 %)	5/61 (8%)	0.57	0.01
Trichomonas	8/125 (6%)	10/85 (12 %)	8/62 (13 %)	0.17	0.14
Candidiasis (S)	3/125 (2 %)	8/85 (9 %)	0/62 (0 %)	0.05	0.55
Candidiasis (As)	21/122 (17 %)	19/77 (25 %)	7/62 (11 %)	0.20	0.30
Bacterialvaginosis	10/127 (8 %)	29/86 (34 %)	37/62 (60 %)	< 0.001	< 0.001
Gardnerella	55/127 (43 %)	55/85 (65%)	55/62 (89 %)	0.002	< 0.001
Bacteroides	62/125 (50 %)	62/83 (75 %)	46/61 (75 %)	< 0.001	0.001
Peptostreptococcus	35/125 (28 %)	34/83 (41 %)	29/61 (48 %)	0.05	0.01
Mycoplasmahominis	21/119 (18 %)	32/82 (39 %)	33/59 (56 %)	0.001	< 0.001
Ureaplasma urealyticum	86/120 (72 %)	68/80 (85 %)	51/60 (85 %)	0.03	0.05
GBS	20/126 (16 %)	19/85 (22 %)	9/61 (15 %)	0.23	0.84
Viridans streptococcus	38/125 (30 %)	39/86 (45 %)	28/62 (45 %)	0.03	0.05
Enterococcus	29/126 (23 %)	12/86 (14 %)	6/62 (10 %)	0.10	0.03
Escherichia coli	13/126 (10 %)	11/86 (13 %)	3/62 (5 %)	0.58	0.20

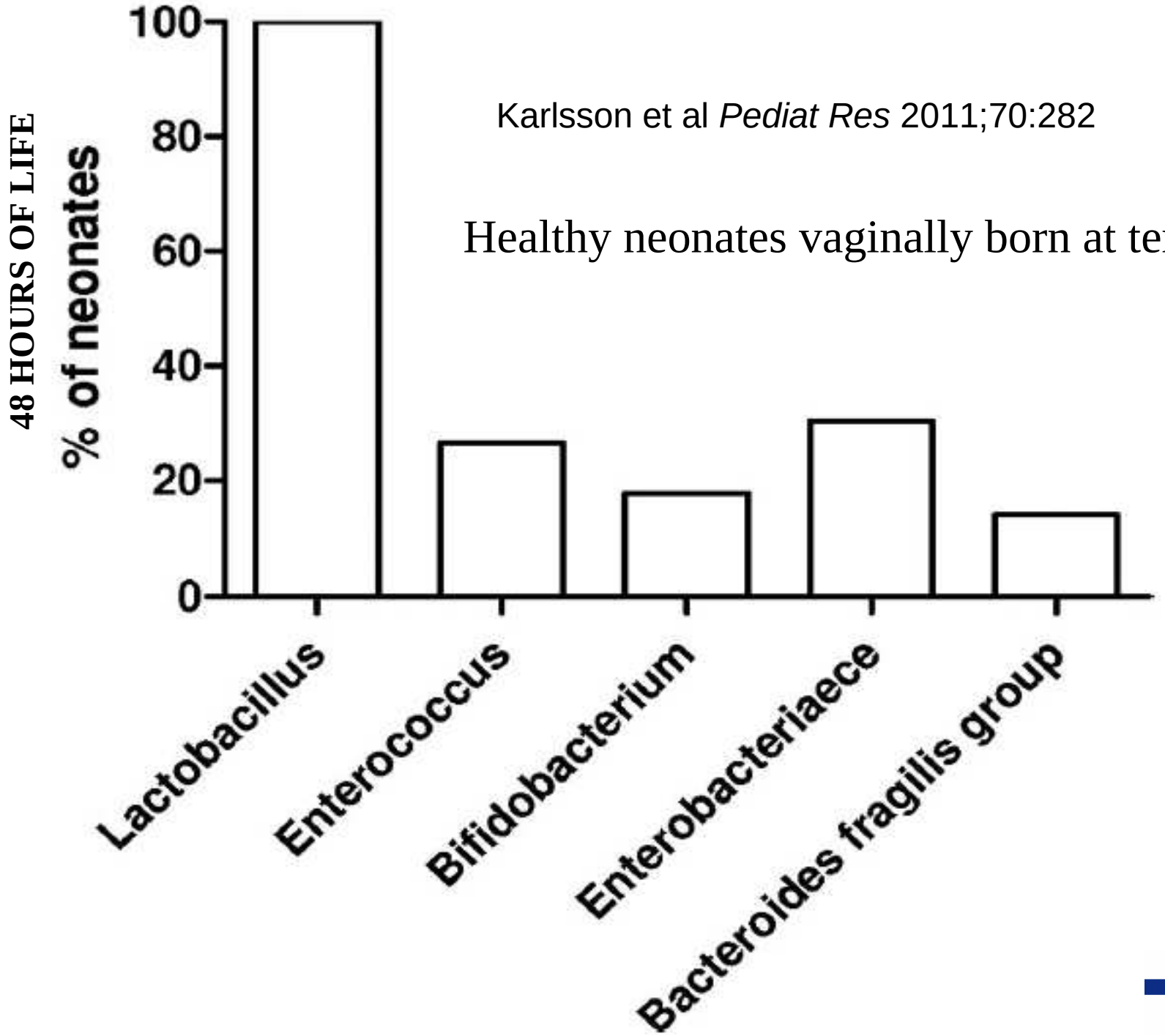
Hillier et al Obstetrics and Gynecology 1992;79

Both maternal recto-vaginal and environmental Microbiota at the time of birth….

...are the best major determinants of the Microbiota found in the intestine of the neonate at the Early Stage.

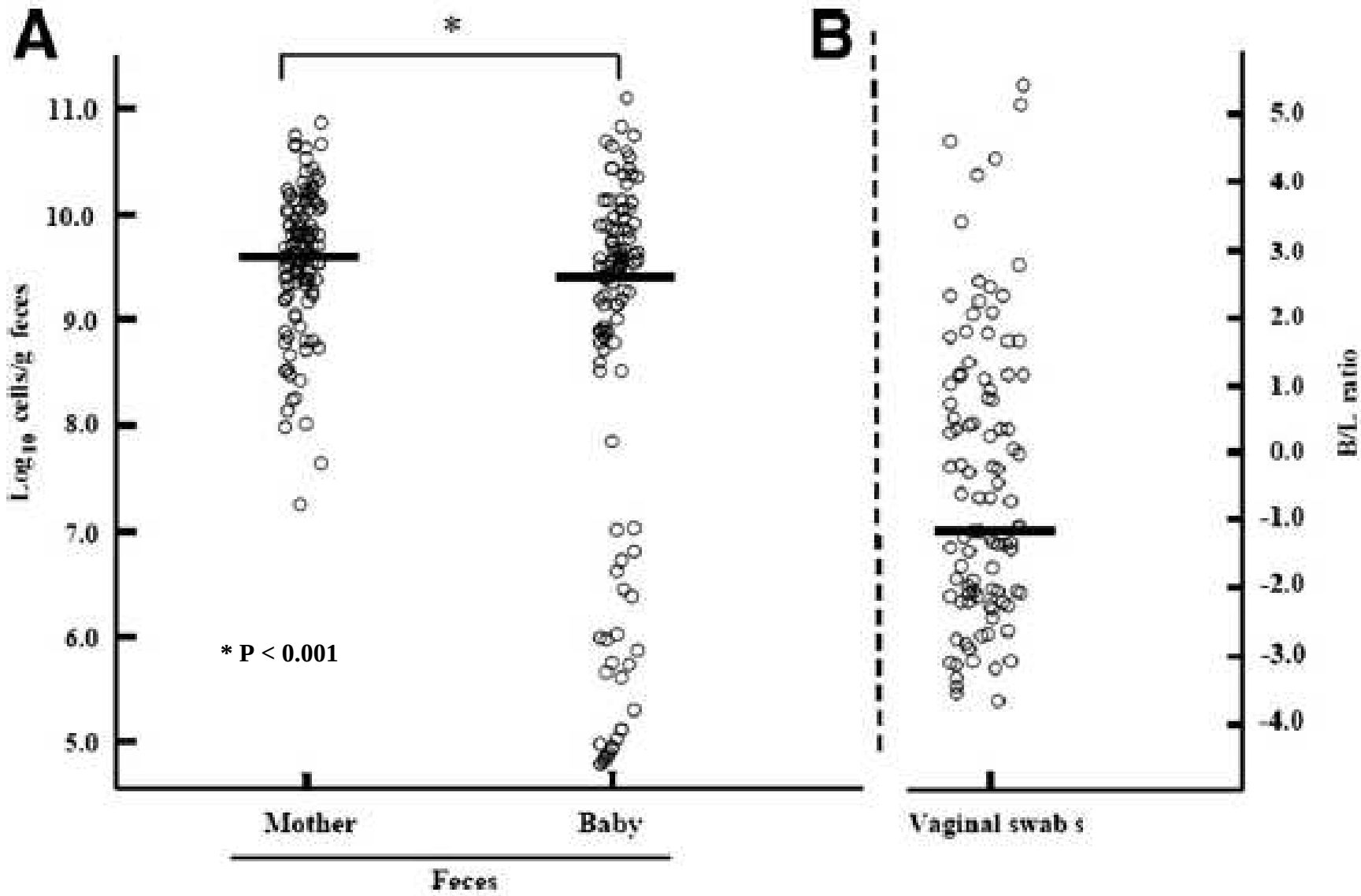


Mändar et al Biol Neonate 1996;86:557



Karlsson et al *Pediat Res* 2011;70:282

Healthy neonates vaginally born at term



diversity of bifidobacteria in the babies' feces. The most important determinants of intestinal bifidobacteria in infants were the colonization of *B. breve* in the mothers' gut and vaginal delivery. (*Pediatr Res* 65: 669–674, 2009) **Mikami et al et al**

Table 4: Bacteria detected in the samples of breast milk and feces of the breast- and formula-fed infants and percentage of sample which they were detected

Microorganism	Milk	Feces		P-value[a]
		Breast-fed infants	Formula-fed infants	
Staphylococcus epidermidis	100.00%	86.05%	13.33%	< 0.0001
Staphylococcus aureus	16.28%	16.28%	13.33%	NS[b]
Other *Staphylococcus* spp.	16.28%	6.98%	6.67%	NS
Enterococcus faecalis	20.93%	53.49%	100.00%	0.0011
Enterococcus faecium	ND[c]	2.33%	13.33%	NS
Other *Enterococcus* spp.	4.65%	9.30%	26.67%	NS
Streptococcus spp.	27.91%	13.95%	ND	NS
Other Gram-positive bacteria	20.93%	69.77%	33.33%	0.0130
Gram-negative bacteria	46.51%	97.62%	66.67%	0.0008

[a] Statistical significance between the breast-fed group and the formula-fed group (χ^2 test).
[b]NS, not significant ($P > 0.05$).
[c]ND, not detected.

Jimenez et al BMC *Microbiol* 2008.8/143.

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Antenatal AB's

Pregnant Women hospitalised in the MIC unit :

Higher risk of Vaginal Dysbacteriosis

Université de Liège
Faculté de Médecine
École de Santé Publique

ÉTUDE DE

LA FLORE VAGINALE DE LA MÈRE HOSPITALISÉE

DANS UN SERVICE DE GROSSESSES À HAUT-RISQUE

Mémoire présenté par
Catherine de Marneffe
en vue de l'obtention du titre de
Licenciée en Sciences de la Santé publique
orientation : promotion de la santé
section : épidémiologie et économie de la santé.

Année académique 2004-2005

Modification de la flore Vaginale en fonction des traitements de la Mère

		Modification de la flore vaginale	Modification des Lactobacilles	Modification des *Gardnerella vaginalis*	Modification des anaérobes
Antibiotiques	RR	**1.53**	**2.75**	1.53	1.27
	IC 95%	**[1.08; 2.17]**	**[1.18; 6.44]**	[0.59; 3.93]	[0.33; 4.85]
Corticoïdes	RR	*0.79*	*0.63*	0.87	0.96
	IC 95%	*[0.60; 1.04]*	*[0.34; 1.18]*	[0.36; 2.11]	[0.25; 3.65]
Thérapies locales	RR	**1.63**	**2.45**	*1.96*	1.31
	IC 95%	**[1.22; 2.19]**	**[1.23; 4.89]**	*[0.80; 4.81]*	[0.36; 4.74]
Examens vaginaux	RR	1.03	1.58	1.33	2.33
	IC 95%	[0.73; 1.46]	[0.64; 3.92]	[0.43; 4.10]	[0.31; 17.45]
Alitement obligatoire	RR	1.00	*1.89*	**4.33**	2.00
	IC 95%	[0.74; 1.35]	*[0.87; 4.10]*	**[1.07; 17.51]**	[0.44; 9.10]

de Marneffe C, Mémoire Lic Epidem Ulg 2005

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		Modification des BPO	Modification des agents mycotiques	Modification des mycoplasmes
Antibiotiques	RR	**4.40**	0.76	1.47
	IC 95%	**[1.73; 11.16]**	[0.31; 1.91]	[0.50; 4.35]
Corticoïdes	RR	1.38	2.12	**0.20**
	IC 95%	[0.73; 2.60]	[0.66; 6.80]	**[0.06; 0.66]**
Thérapies locales	RR	*1.41*	**7.85**	*2.54*
	IC 95%	*[0.81; 2.46]*	**[1.92; 32.05]**	*[0.86; 7.51]*
Examens vaginaux	RR	1.17	2.00	0.68
	IC 95%	[0.58; 2.34]	[0.50; 7.94]	[0.24; 1.94]
Alitement obligatoire	RR	*1.58*	1.20	*0.34*
	IC 95%	*[0.83; 3.02]*	[0.46; 3.15]	*[0.12; 1.01]*

de Marneffe C, Mémoire Lic Epidem Ulg 2005

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Wickramasinghe et al *Arch Dis Child Fet Neonat Ed* 2012;97:F234

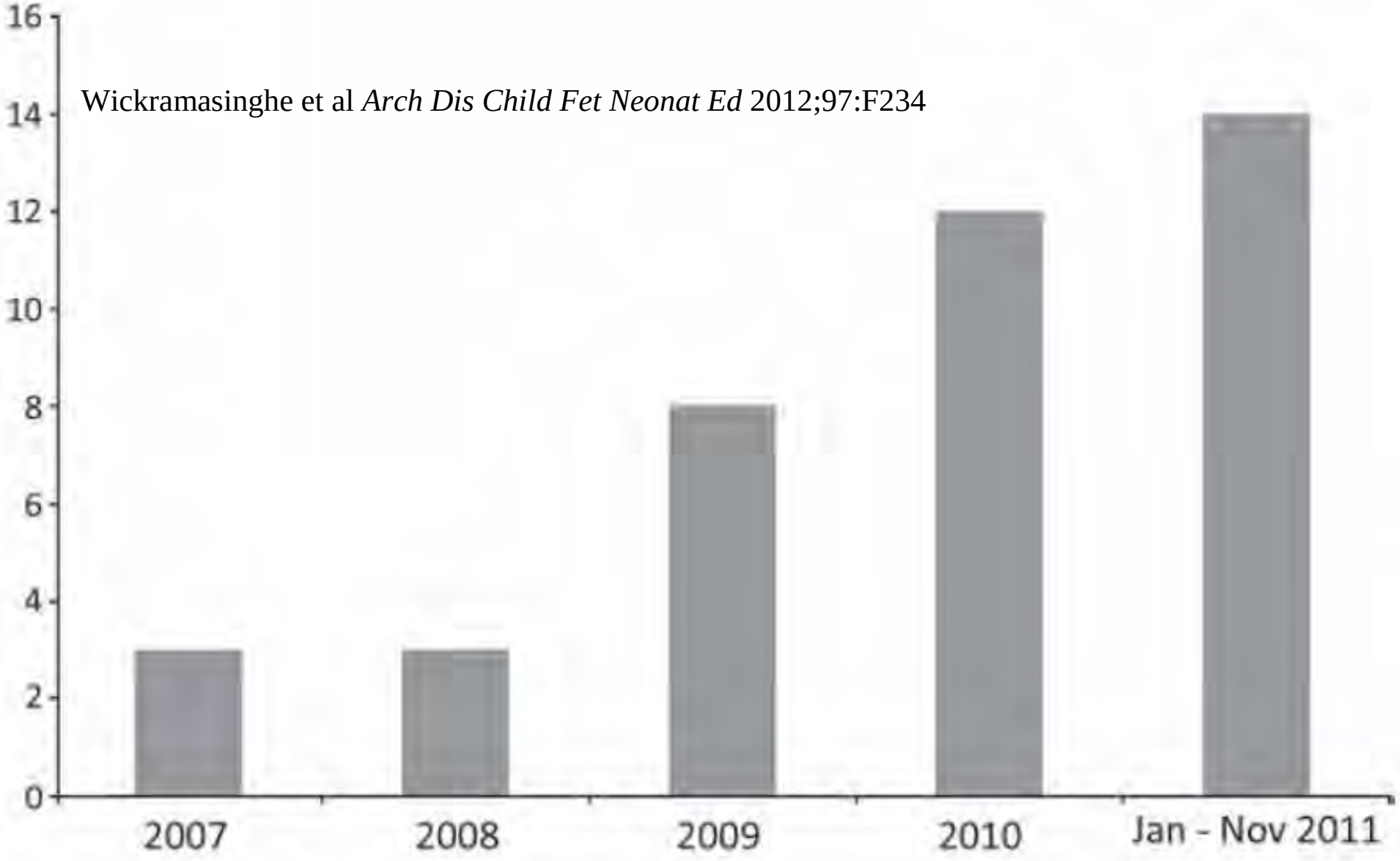
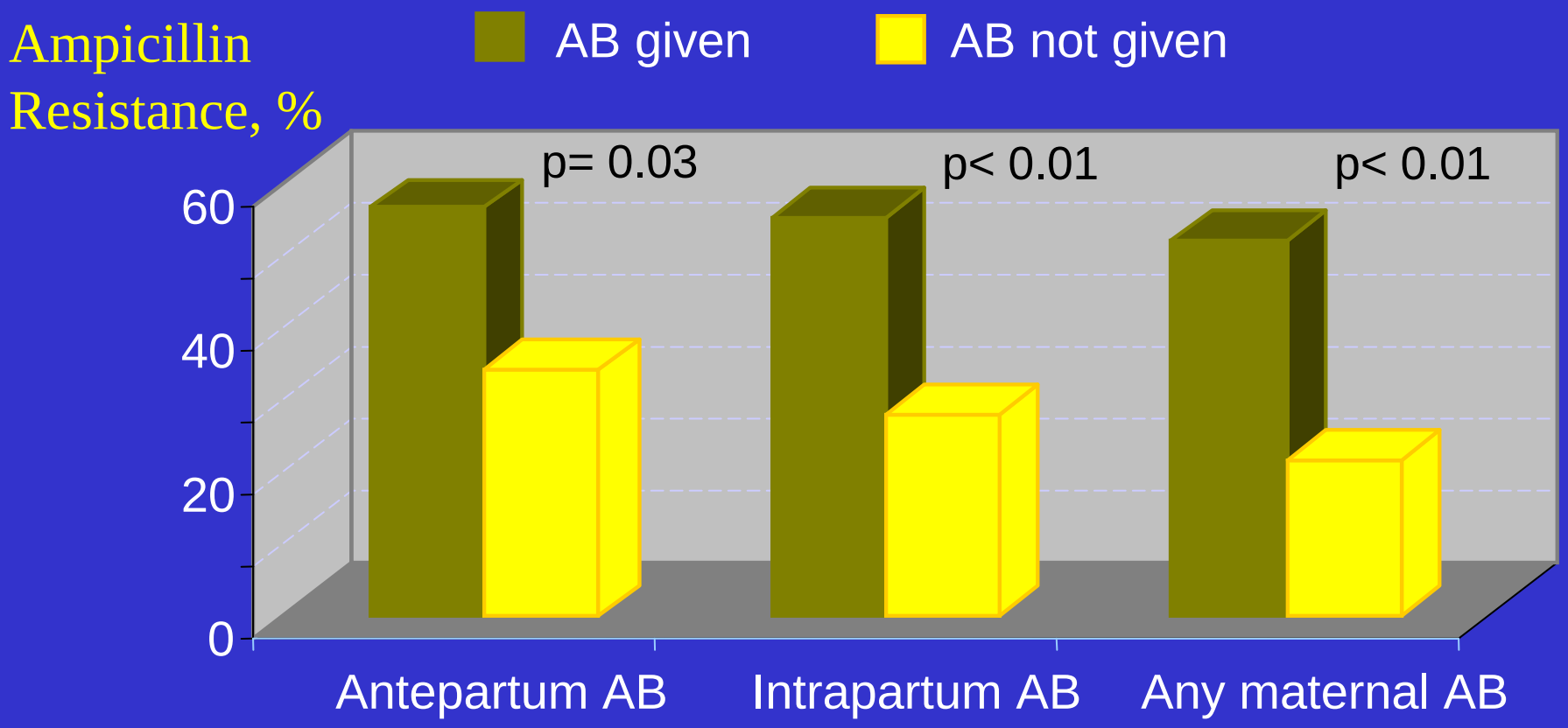


Figure 1 Number of multi-resistant gram-negative bacteria in antenatal patient urines since 2007.

AB use in pregnancy and drug-resistant infant sepsis



Mercer et al. Am J Obstet Gynecol 1999; 181:816

Intrapartum Antibiotics (IPA 's)
In Mothers of Case with SBI and Control infants

Exposure	*Case infants (N = 90)*	*Control Infants (N = 92)*	*OR (95% CI)*
Penicillin IPA	**10 (11%)**	**13 (14%)**	**0.95 (0.37-2.44)**
Broad-spectrum IPA*	**29 (32 %)**	**10 (11 %)**	**4.95 (2.04 – 11.98)**
Maternal chorioamnionitis	**1 (1%)**	**3 (3%)**	**0.12 (0.01 – 1.39)**
Breastfeading	**67 (74%)**	**74 (82%)**	**0.58 (0.29 – 1.18)**

* = significant

SBI = Serious Bacterial Infections

Glasgow et al *Pediatrics* 2005;116:696

Intrapartum Antibiotics (IPA 's) and Ampicillin-Resistant Organisms in Infants with SBI

Exposure	*Resistant,n (% ;N=37)*	*Non resistant,n (% ;N=53)*	*OR (95% CI)*
Any IPA	**24 (65)**	**13 (25)**	**5.7 (2.3-14.3)**
Penicillin IPA	**4 (11)**	**5 (9)**	**2.5 (0.6-10.6) ***
Ampicillin IPA	**12 (32)**	**6 (11)**	**6.2 (1.9-19.7)**
Other IPA agent	**8 (22)**	**2 (4)**	**12.3 (2.3-65.5)**

*** = NS**

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Glasgow et al *Pediatrics* 2005;116:696

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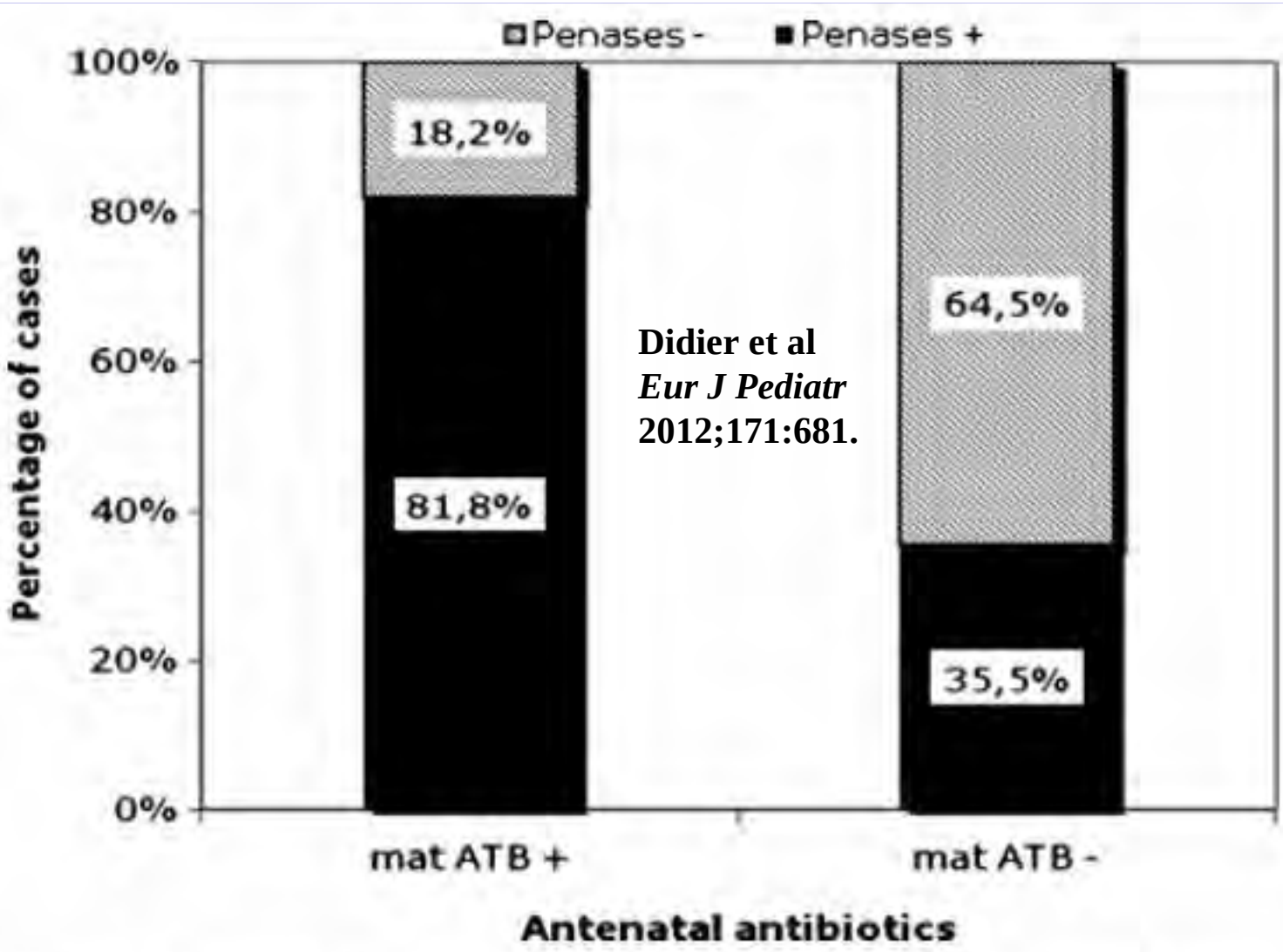

Didier et al
Eur J Pediatr
2012;171:681.

Fig. 1 Maternal antibiotic exposure and LONI due to penicillinases (Penases) producing *E. coli*. p=0.01. *MatATB*+infants exposed to maternal antibiotic treatment, *MatATB*−infants non exposed to maternal antibiotic treatment, *Penases*+penicillinases producing *E. coli*, *Penases*−penicillinases non-producing *E. coli*

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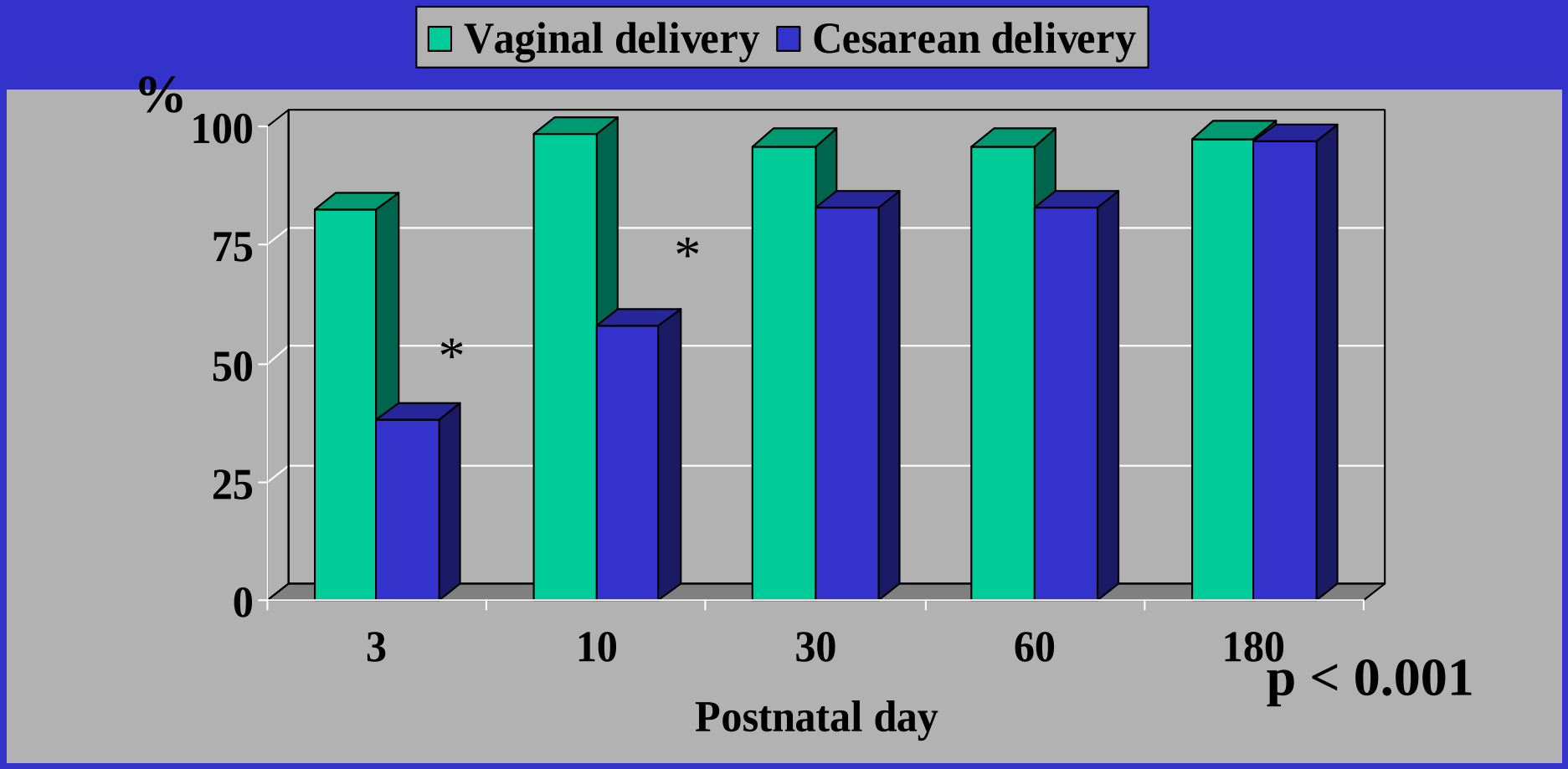
- Type of Delivery (vaginal or caesarean)

Percentage of *Bifidobacterium-like bacteria (BLB)* colonization in infants



Gronlund et al J Pediatr Gastroenterol Nutr 1999; 28:19-25

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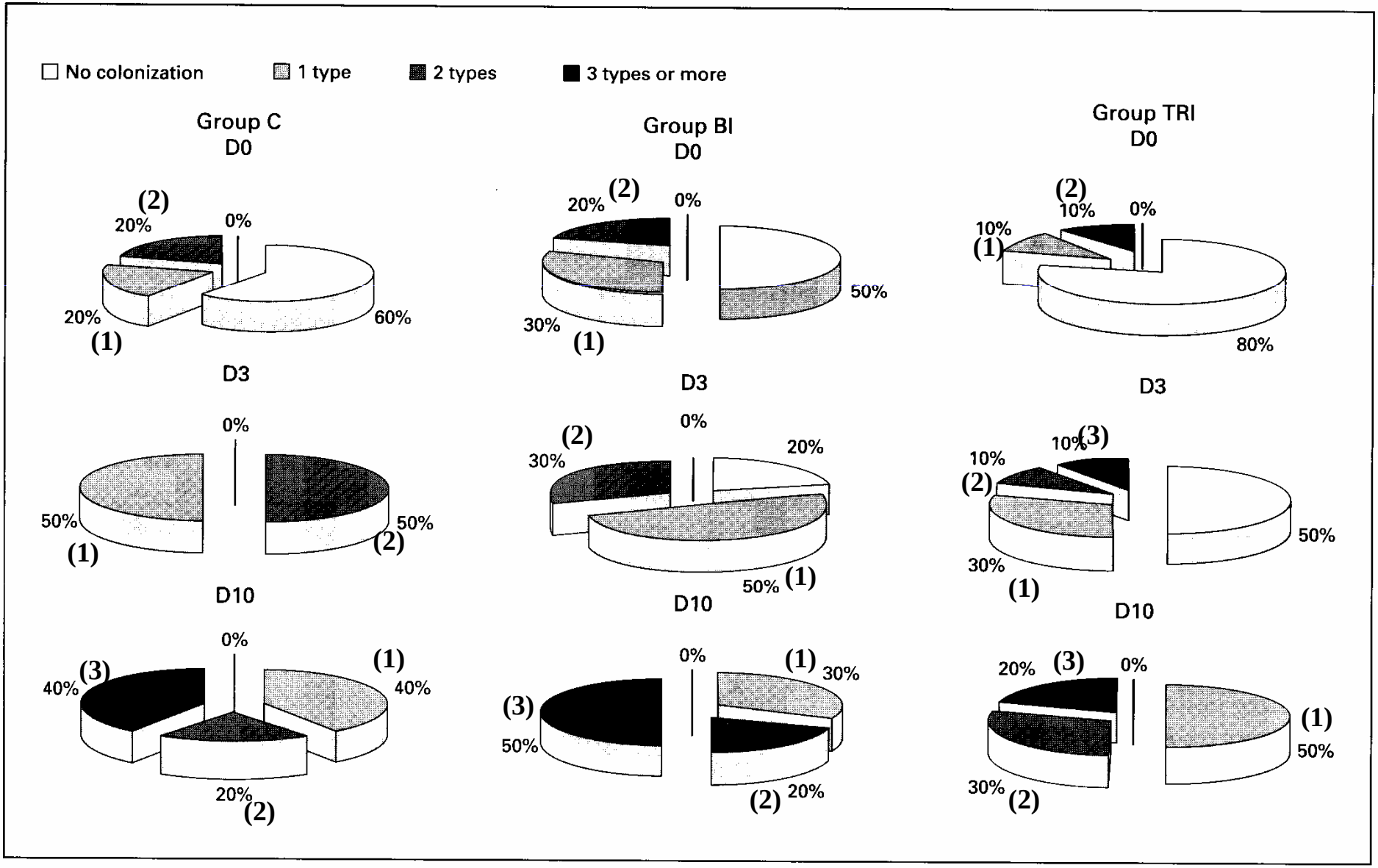
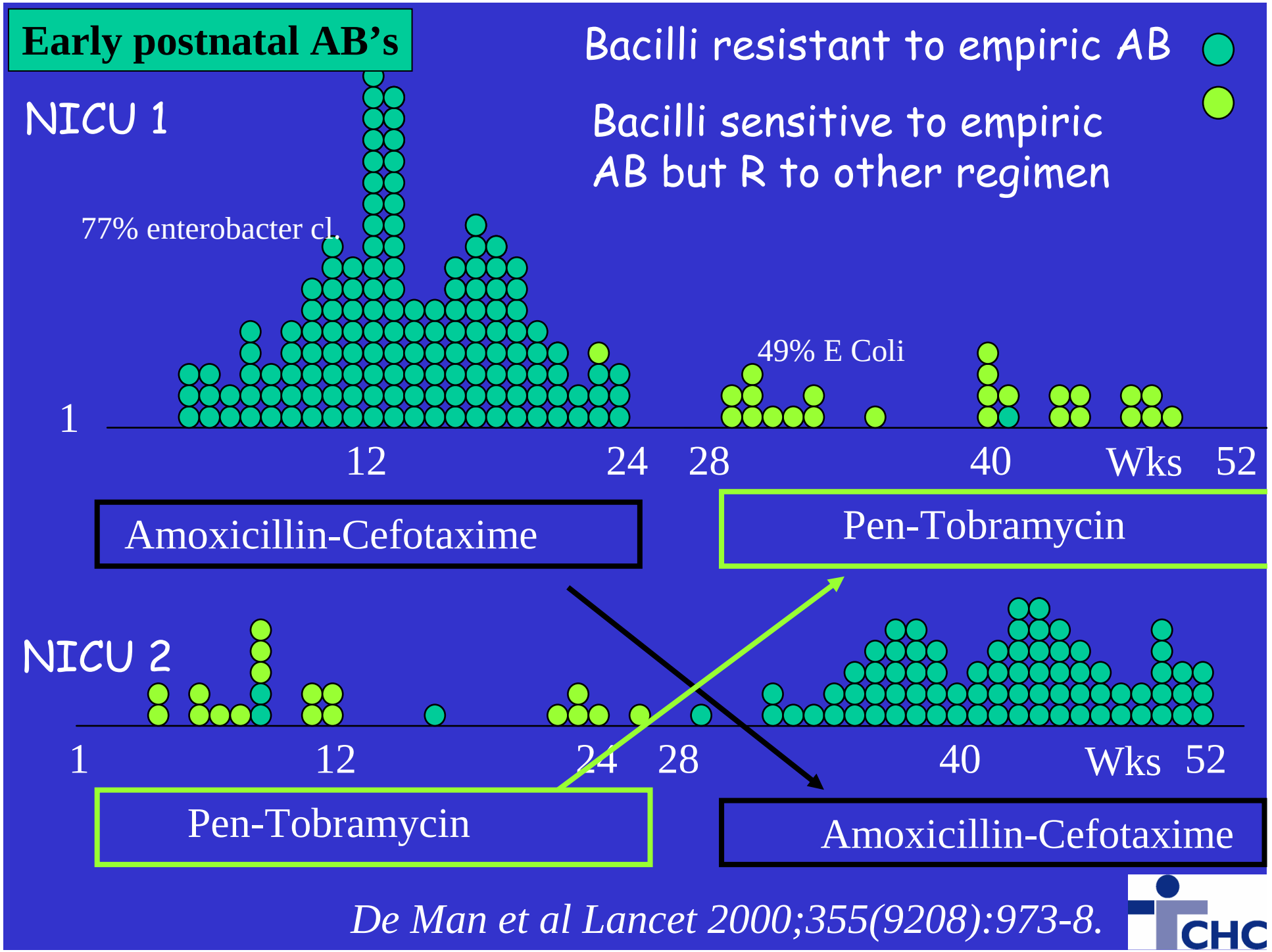


Bonnemaison et al

Biol Neonate 2003;85:304-310.



De Man et al Lancet 2000;355(9208):973-8.

Bacterial Ecology in the NICU influenced by:

- Cesarean Delivery
- Perinatal – Neonatal Antimicrobial Agents

- Quantitatively : decreasing total number and species
- Qualitatively : resistant *Enterobacteriacae, Clostridae,* Candida overgrowth.

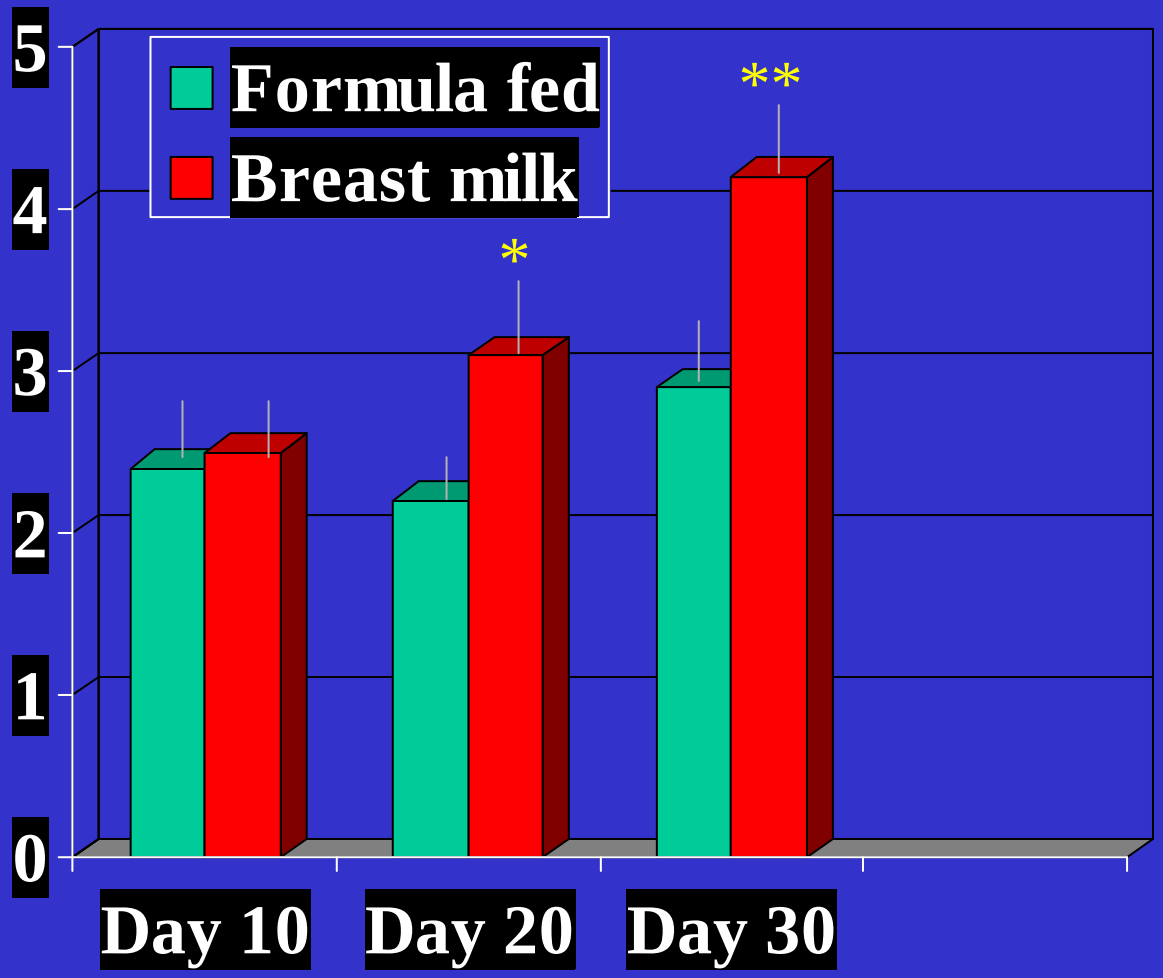
- Corticosteroids

- Candida overgrowth.

- H2 Blockers

- Increased gastric colonization.
- Increased risk of bacteriemia.

N° bacterial spp over time in breast milk and formula fed preterm infants



* p < 0.05
** p < 0.01

Gewolb et al
Arch Dis Child
1999;80:F167

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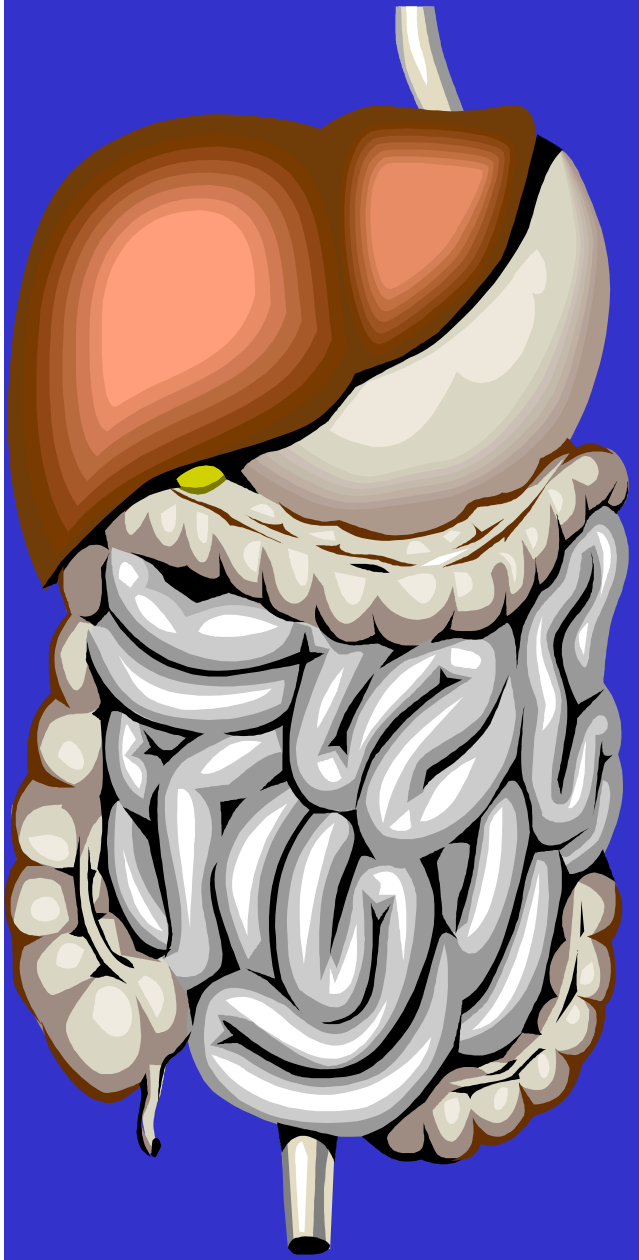
- Postnatal AB's and other drugs influence
- **Nutrition by the end of the first week**

Normal Development of the Intestinal Microflora during Infancy : Four different phases

- Initial acquisition of microorganisms from the maternal flora : *Lactobacilli*, Staphylococci (especially when breast-fed), Streptococci, *Enterobacteriacae*,…
- Influence of the Diet from day 4 : *Bifidobacteria* as well as Lactobacilli important dominance in exclusive breast-fed infants
- Dietary supplementation from month 6 : *Bacteroïdes* and Enterococci as well as *Enterobacteriacae* and clostridiae increase; correlated with increased faecal pH.
- Weaning and adult diet from 1 year : more diversified anaerobes flora and decrease in *Enterobacteriacae*



Stomach and Duodenum

(10^1 - 10^3 CFU/ml)

Lactobacilli

Streptococci

Yeasts

From Simon and Gorbach, 1982

Jejunum and Ileum

(10^4 - 10^8 CFU/ml)

Lactobacilli

Streptococci

Enterobacteriacae

Bacteroides

Bifidobacteria

Fusobacteria

Colon

(10^{10} - 10^{12} CFU/ml)

Bacteroides

Bifidobacteria

Streptococci

Fusobacteria

Enterobacteriacae

Clostridia

Veillonella

Lactobacilli

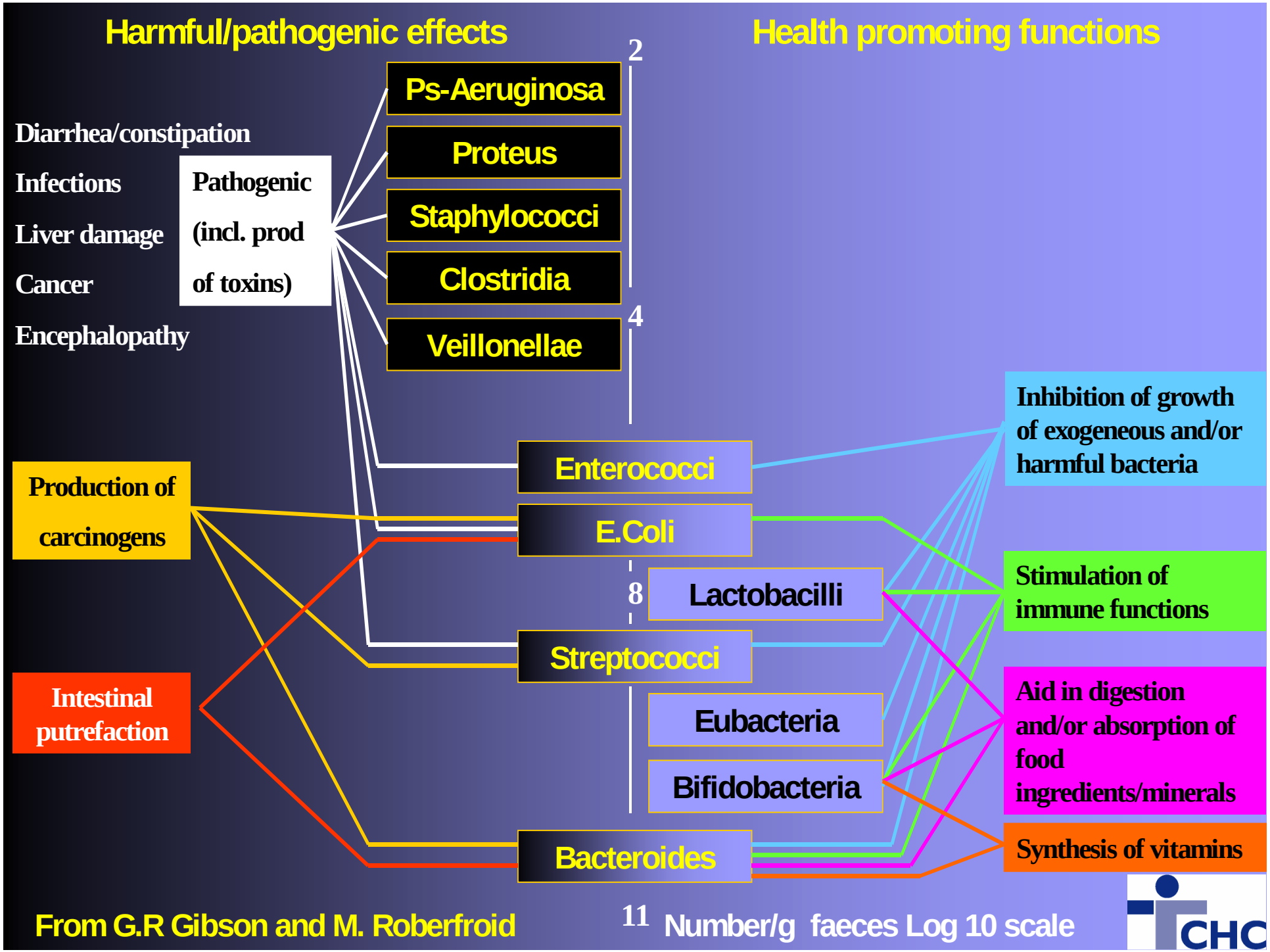
Proteus

Staphylococci

Pseudomonas

Yeasts

Protozoa


Harmful/pathogenic effects
Health promoting functions
Diarrhea/constipation
Infections
Liver damage
Cancer
Encephalopathy
Pathogenic (incl. prod of toxins)
2
Ps-Aeruginosa
Proteus
Staphylococci
Clostridia
4
Veillonellae
Enterococci
E.Coli
8
Lactobacilli
Streptococci
Eubacteria
Bifidobacteria
Bacteroides
Production of carcinogens
Intestinal putrefaction
Inhibition of growth of exogeneous and/or harmful bacteria
Stimulation of immune functions
Aid in digestion and/or absorption of food ingredients/minerals
Synthesis of vitamins
From G.R Gibson and M. Roberfroid
11 Number/g faeces Log 10 scale
CHC

Exclusive Breast-Feeding:

the best for Optimizing Bacterial/Mucosal Interface

Exclusive Breast-Feeding : the best for Optimizing Bacterial/Mucosal Interface

Bifidogenic Factors

- Glycoproteins {κ Casein (N-Acetyl-Glucosamine)}
- Mono-oligosaccharides, GOS, ….
- Low protein level
- High lactose concentration
- Low phosphate concentration

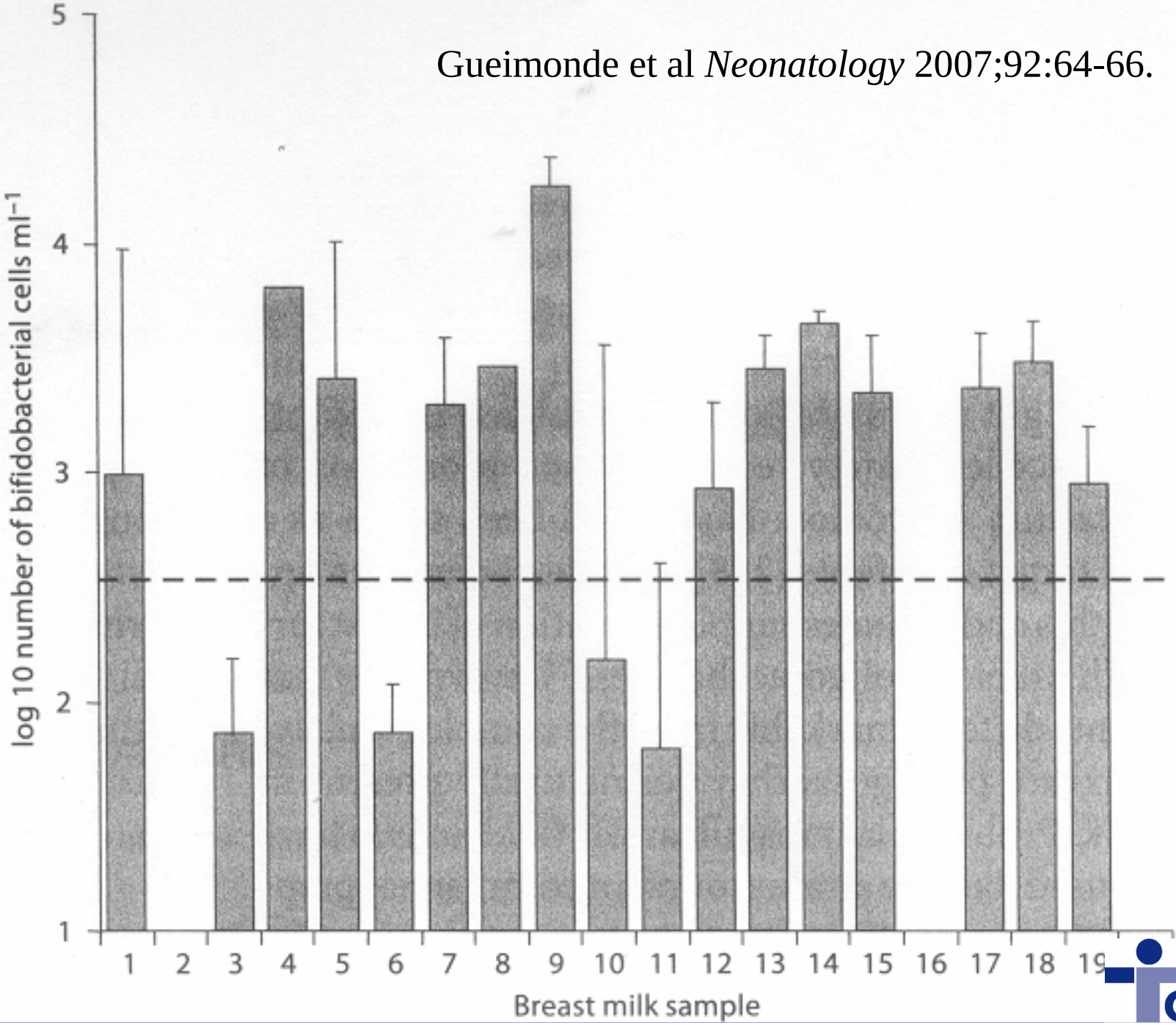
Immunomodulating Components

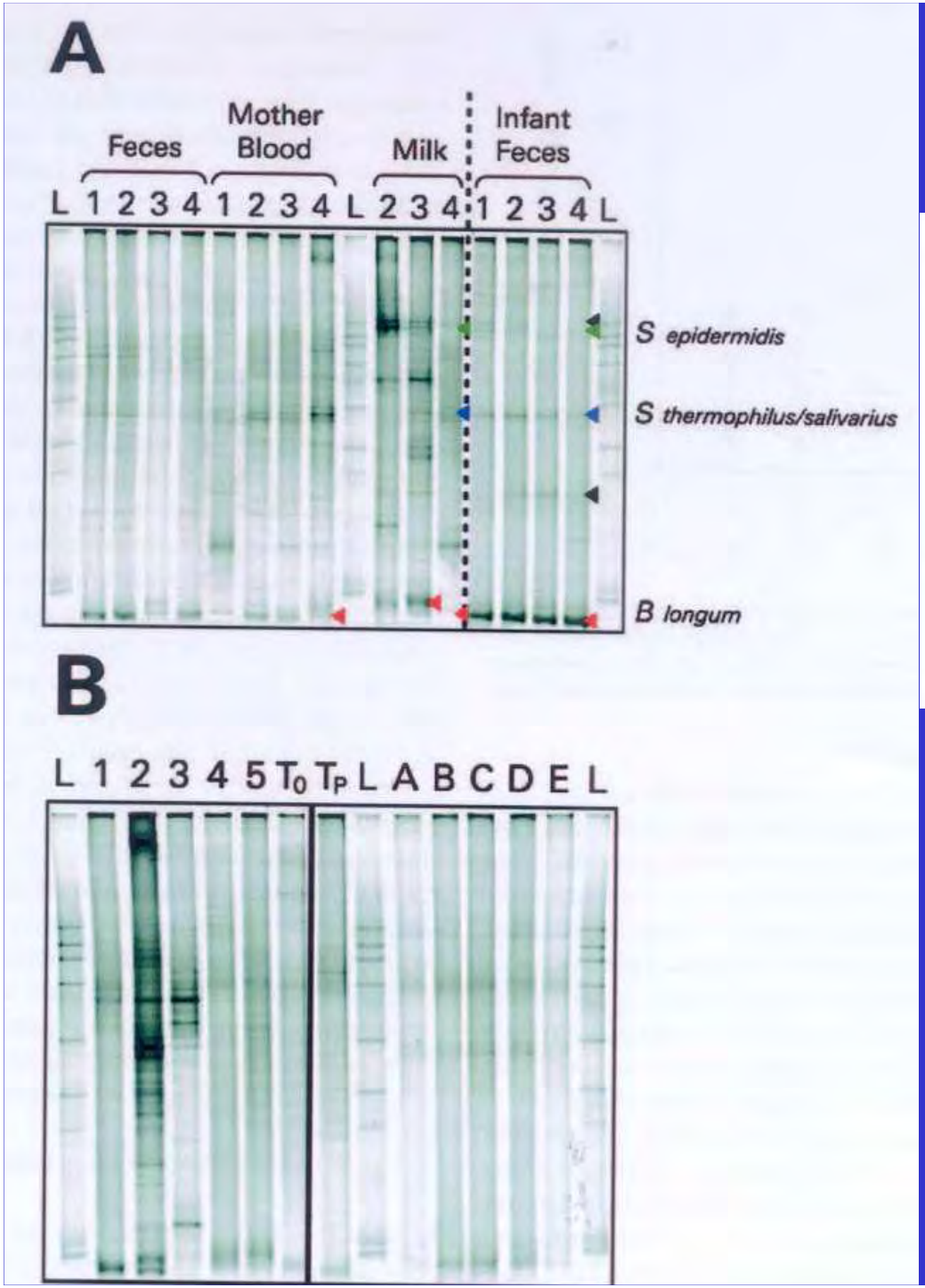
- Virtually all known immune components/nutriments found in HM are relevant for specific protective action on the epithelial cell
- Of outstanding interest: sCD14, Il-10, TGF-β, sTLR's. (S)IgA.

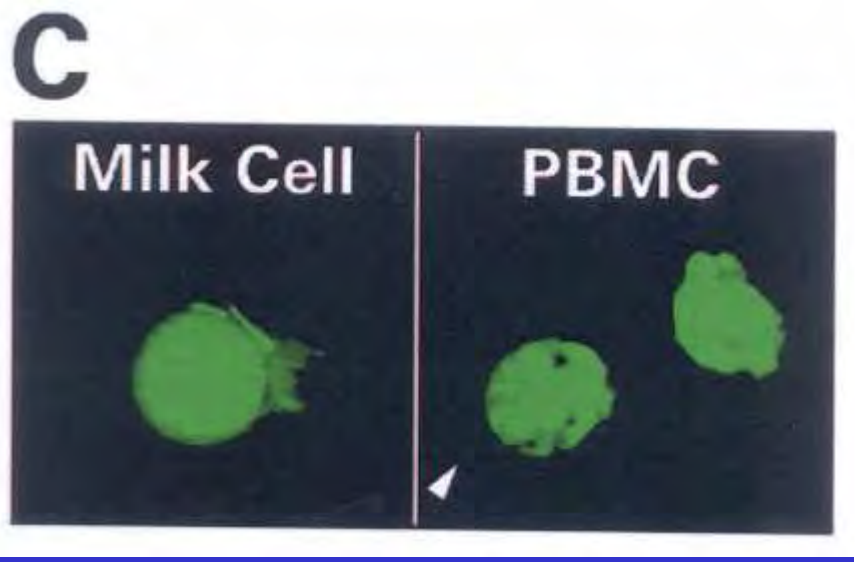
Biologically active Components

- Whey proteins (Lactoferrin, Lysozyme, Defensins, EGF, PAF-AH..
- Osteoprotegerin, adiponectin, alpha-lactalbumin
- PUFA's

Gueimonde et al *Neonatology* 2007;92:64-66.







Bacterial Imprinting of
the Neonatal Immune System :
Lessons from maternal cells
Perez et al
Pediatrics 2007; 119: e725.

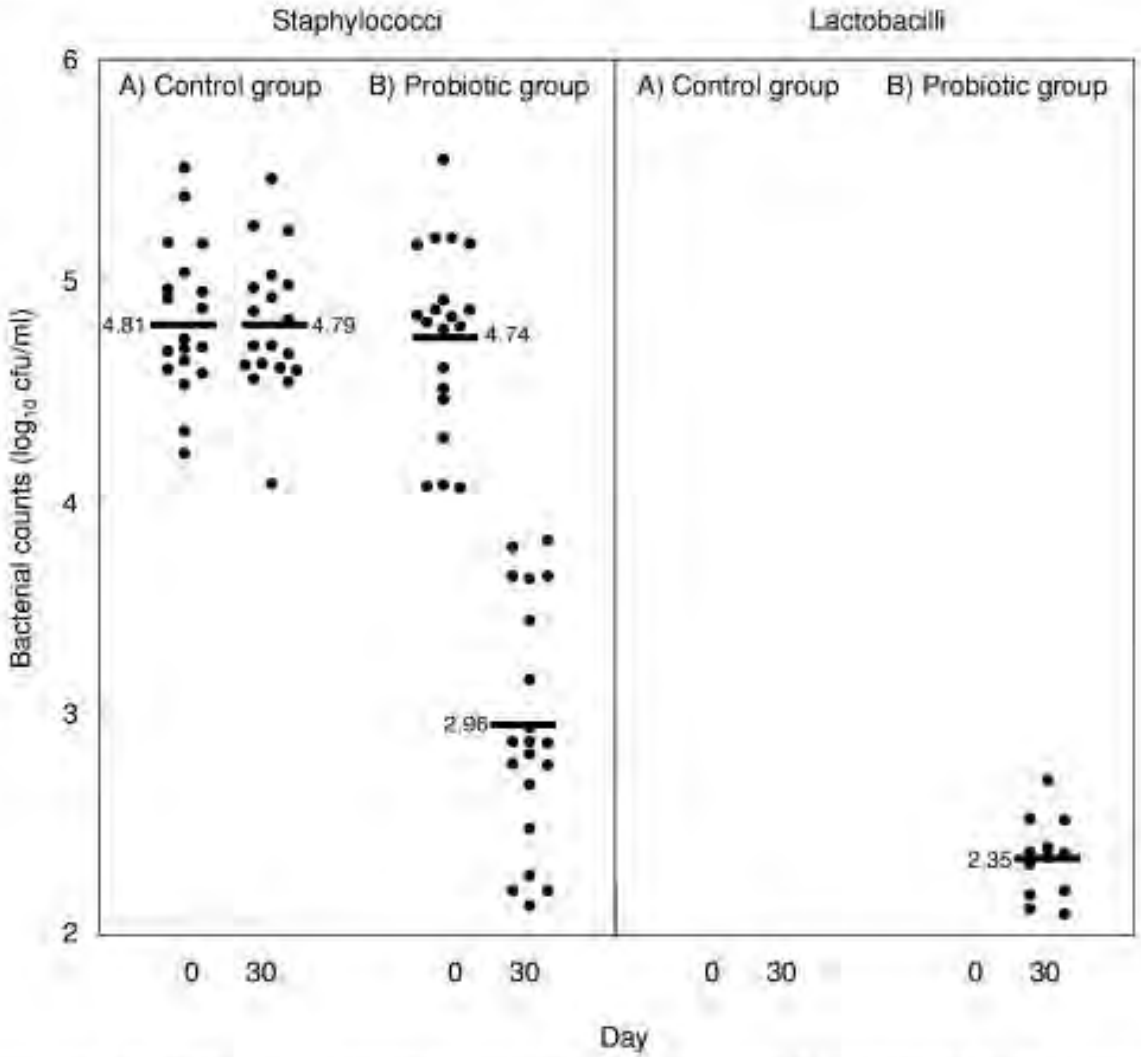


FIG. 1. Staphylococcal counts in the milk samples obtained from women of the control (A) and probiotic (B) groups at days 0 and 30. The black bars (and the associated number) indicate the mean of the values.

Perinatal Factors acting on the Bacterial Colonisation of the Neonate.

- Maternal Vaginal Microbiota during pregnancy
- Environmental factors in the Hospital
- Perinatal AB's - types of AB's which are used (narrow vs broad spectrum)
- Type of Delivery (vaginal or caesarean)
- Postnatal AB's and other drugs influence
- Nutrition by the end of the first week
- Milk processing and storage

	Storage (°C)		Heat-treated
	0-4	-20	56°C (30 min)
IgA	NC	NC	Stable (at 62°C ↓)
sIgA	NC	NC	Stable (at 62°C ↓)
Lactoferrin	NC	NC	NC (at 62°C ↓)
Lysozyme	NC	NC	NC (at 62°C ↓)
Fibronectin	NC	NC	
Mucid	NK	NK	
C3 complement	NC	NC	NC
Oligosaccharides	NC	NC	Stable
Glycoproteins			Stable
α-Tocopherol	Stable	Stable	
Cell count			
- number	NC	↓	↓↓
- function	NC	↓	↓↓
Bacterial growth	NC	NC	↓↓↓
Inhibition of *Ecoli*	Adherence to HEp-2 cells	NC	NC
Cytokines	NK	NK	
Nucleotides	Stable	Stable	

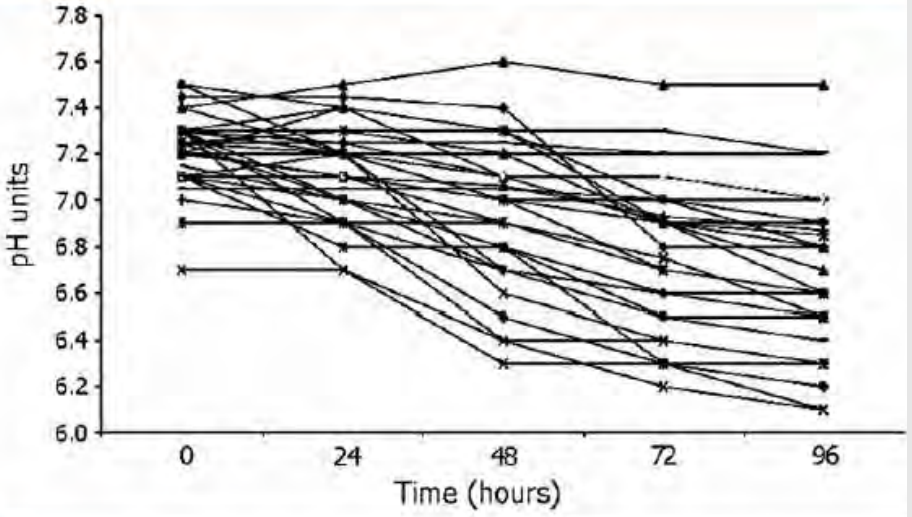


Figure 1. Milk pH declined over 96-hour refrigerator storage ($P < .001$). Each time point differs from the preceding value ($P < .05$).

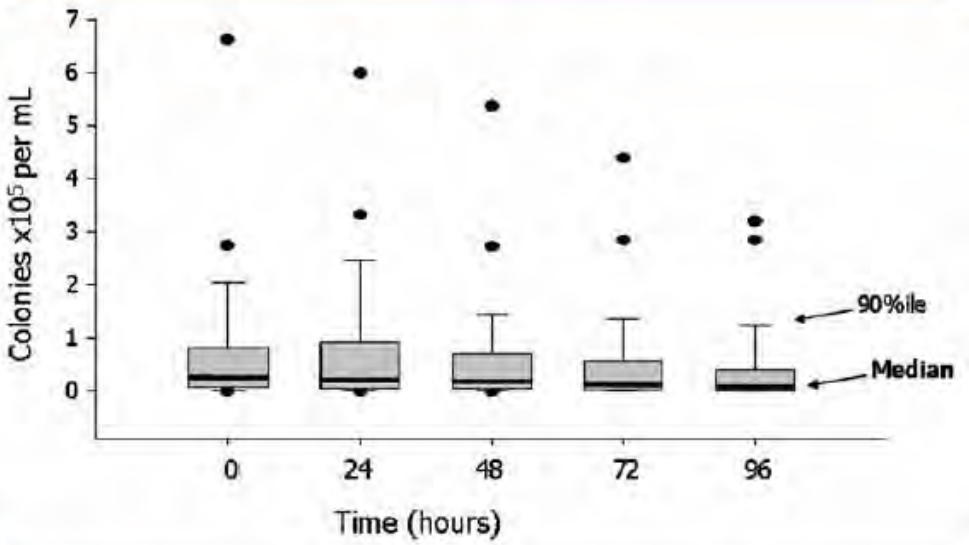
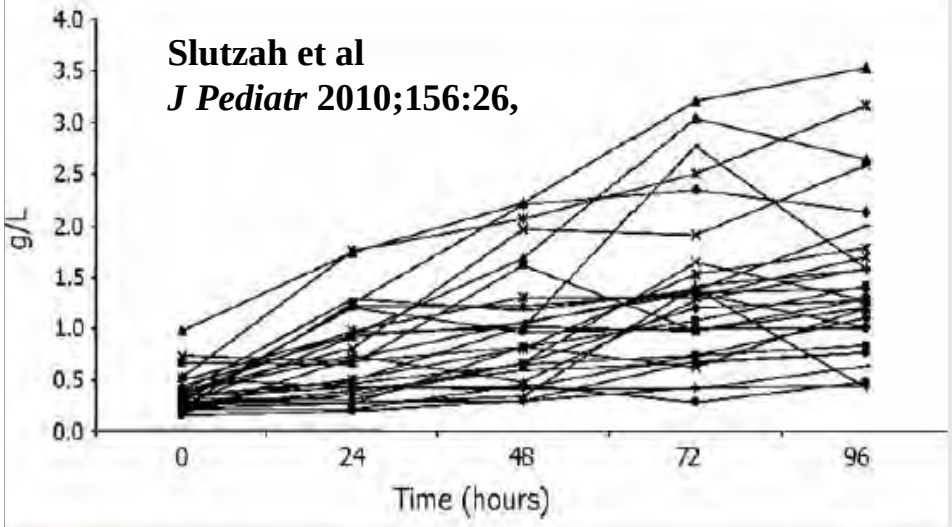


Figure 2. Gram positive bacterial colony counts declined over 96-hour storage ($P < .001$).



Slutzah et al
***J Pediatr* 2010;156:26,**

Figure 3. Free fatty acid concentrations increased 3-fold over 96-hour storage ($P < .001$).

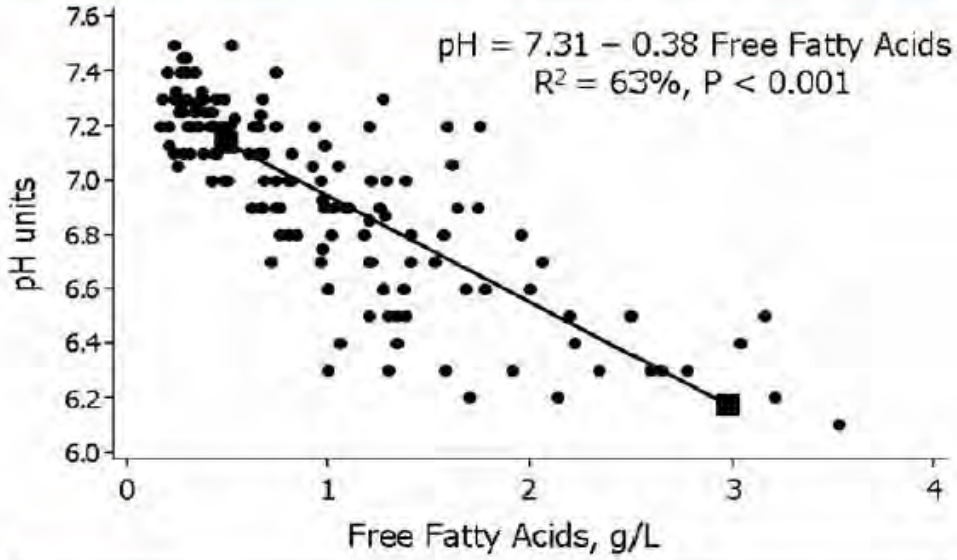
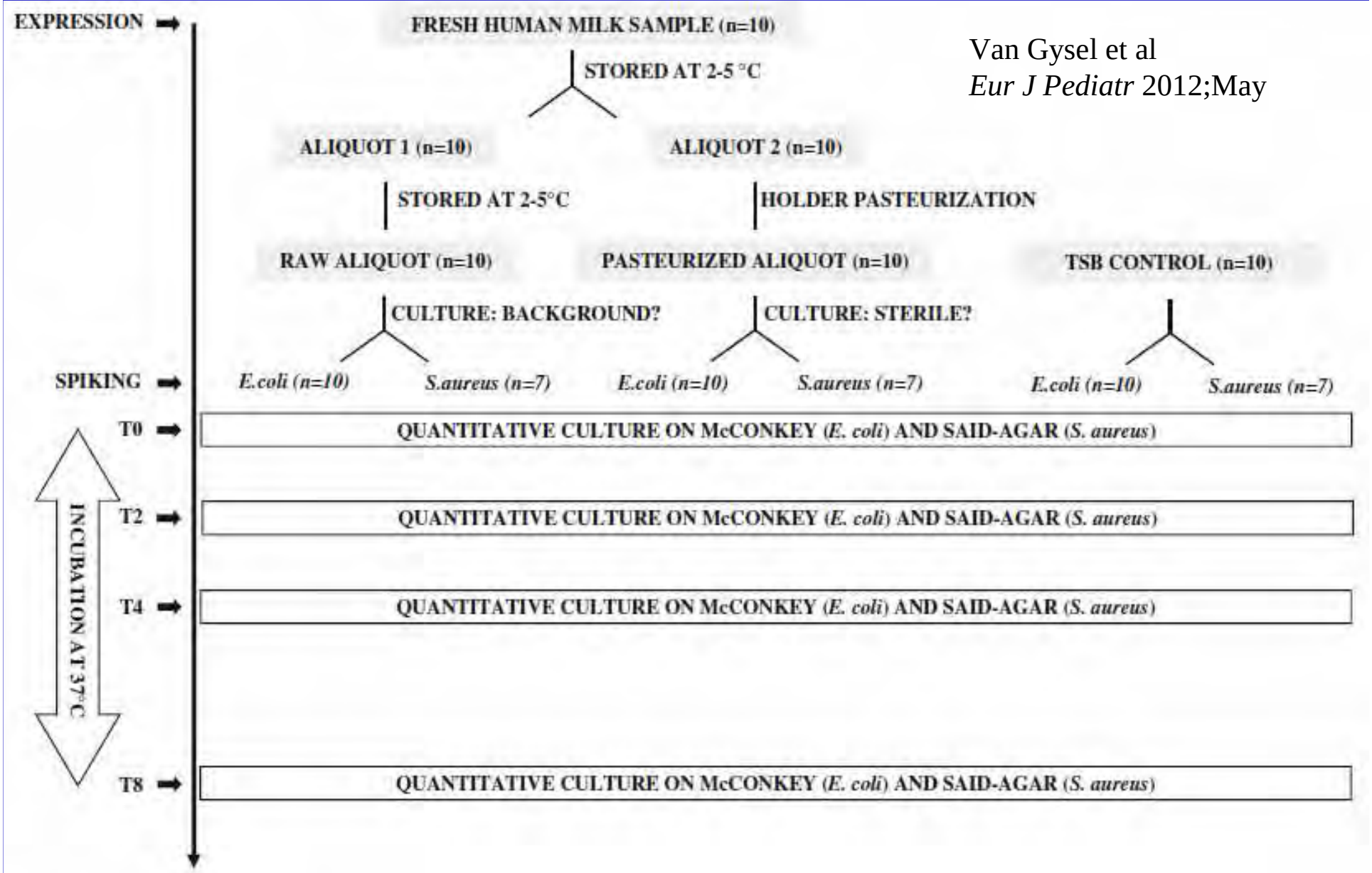
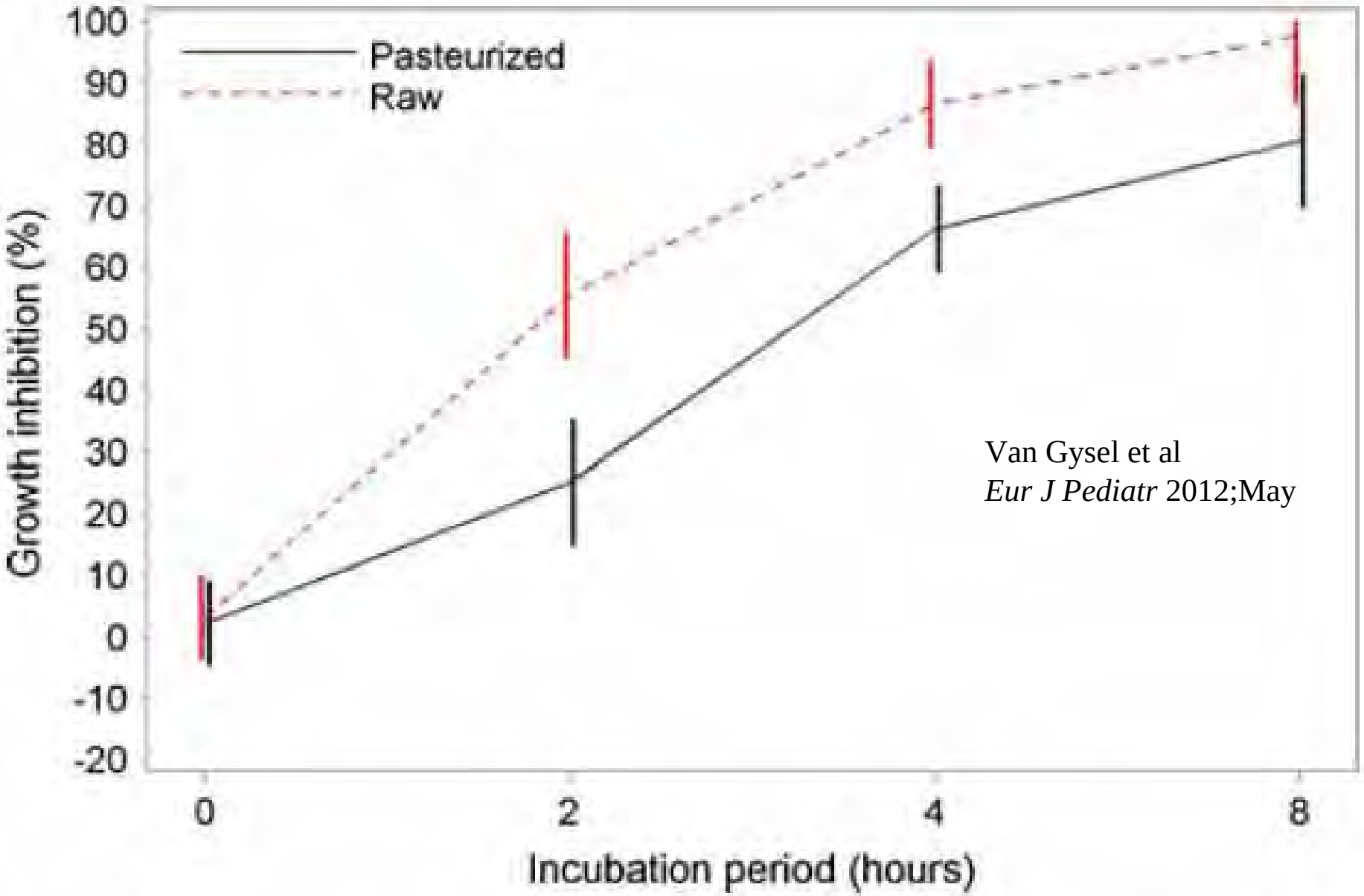


Figure 4. Inverse relationship between pH and f concentrations ($r = 0.79$, $P < .001$).



Van Gysel et al
Eur J Pediatr 2012;May



Van Gysel et al
Eur J Pediatr 2012;May

Fig. 3 Evolution of growth inhibition of *S. aureus* during incubation. Means and 95 % confidence intervals are plotted

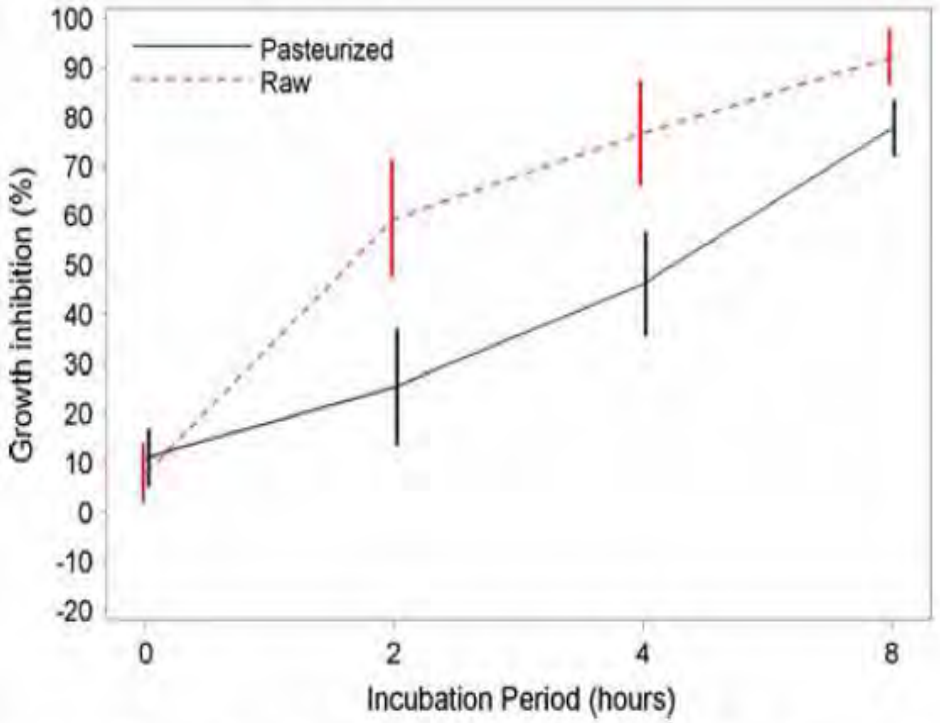
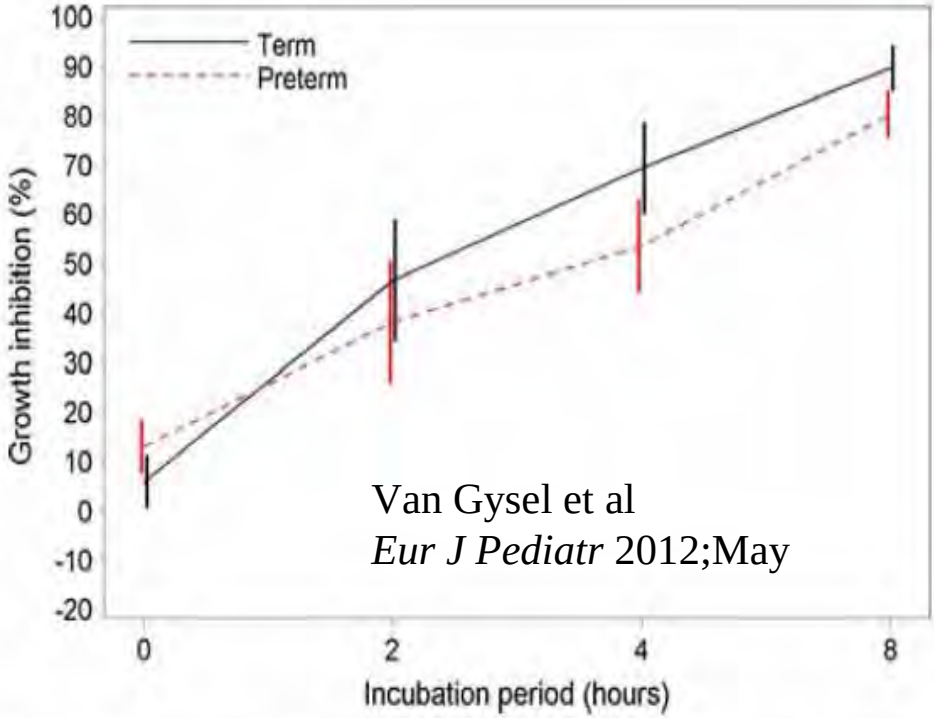


Fig. 2 Evolution of growth inhibition of *E. coli* during incubation. Means and 95 % confidence intervals are plotted



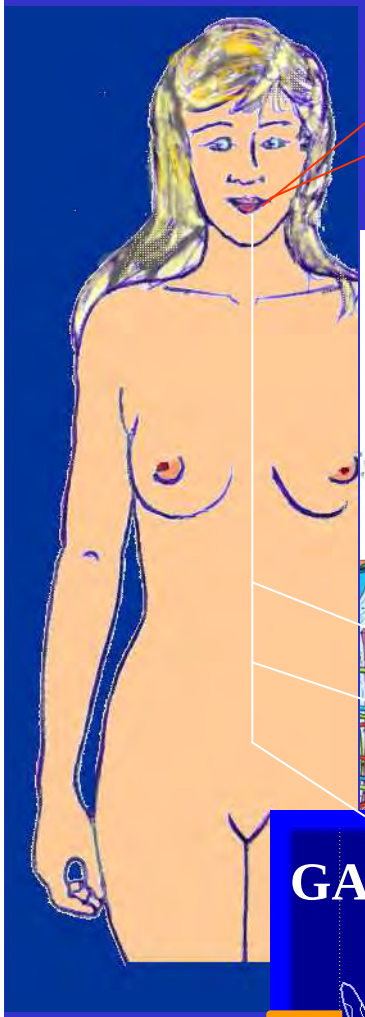
Van Gysel et al
Eur J Pediatr 2012;May

Fig. 4 Comparison of growth inhibition of *E .coli* between preterm and term milk. Means and 95 % confidence intervals are plotted

Mother

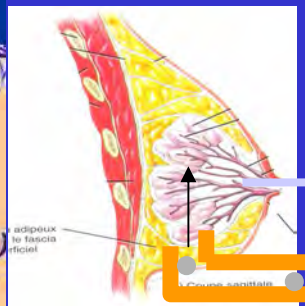
Child

Protection of upper respiratory tract mucosa and gastrointestinal mucosa, oral dietary antigen tolerance

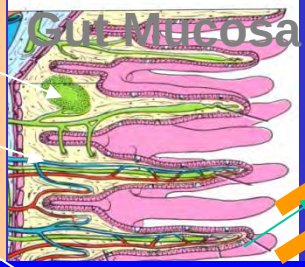


Microbes

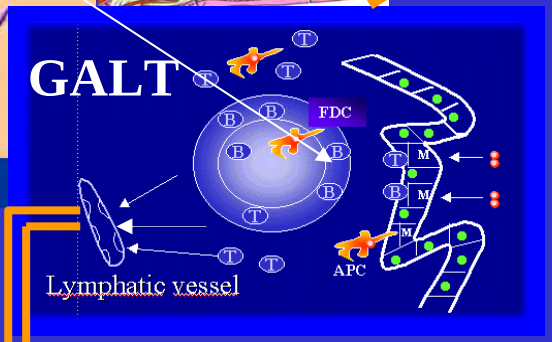
Food antigens



Breast milk



Peripheral blood



* sIGA, sIgM
* Natural defense factors (lactoferrin,..
* Controlled Bacterial translocation
* Maternal Dietary Atg Epitopes
* Immuno regulatory factors (TGF-β,..)
* *(Poluttants)*

Mesenteric lymph node

Thoracic duct

adapted from P.BRANDTZAEG, 1996

CHC

Recommendations ARE NEEDED to ameliorate NEONATAL BACTERIAL INTESTINAL COLONIZATION = PUBLIC HEALTH IMPACT IN ALLERGY PREVENTION

- **Prefer vaginal delivery when possible**
- **Exclusive breast feeding as long as possible**

⇒ optimal immune response after optimal mucosal microbial stimulation

⇒ allows low early diet antigen stimulation on immature mucosa

- **Progressive introduction of complementary foods**

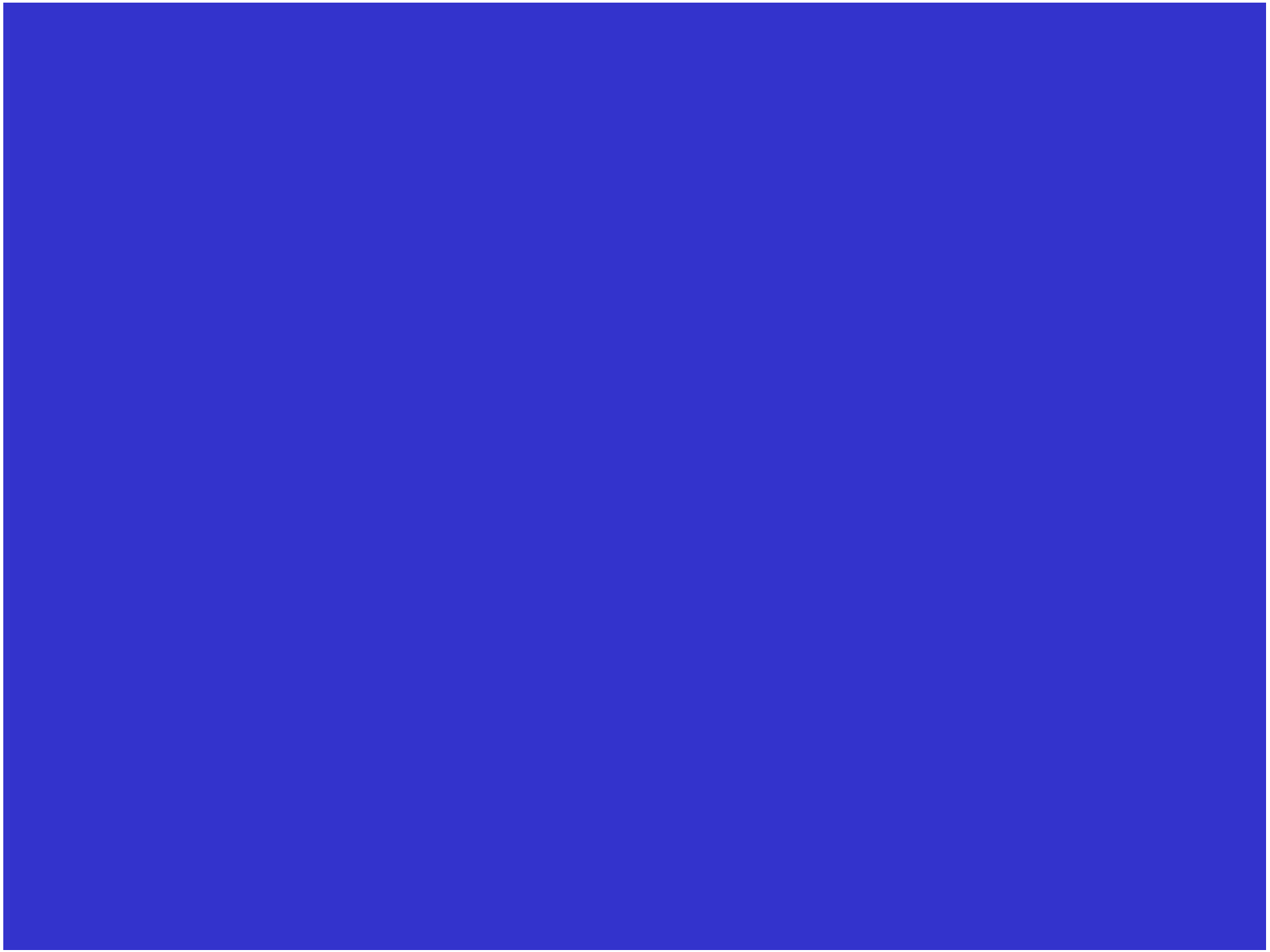
= not before four or six months = according to the 4 points rule

- **Rationale use of antibiotics and some other drugs :**

⇒ restriction in the early stage when possible

⇒ avoid excessive use of broad spectrum AB (esp. in prophylaxis)

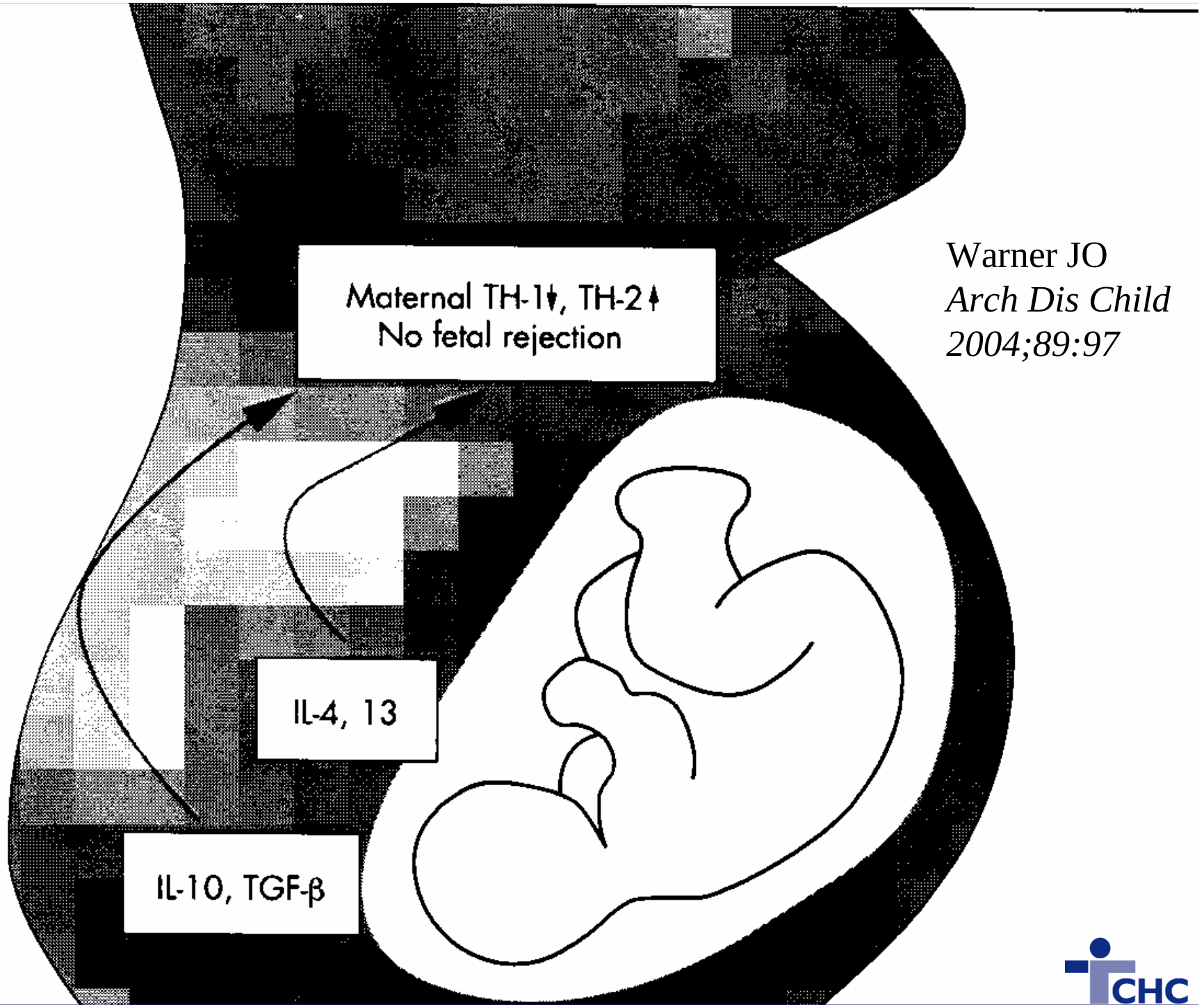
CHC



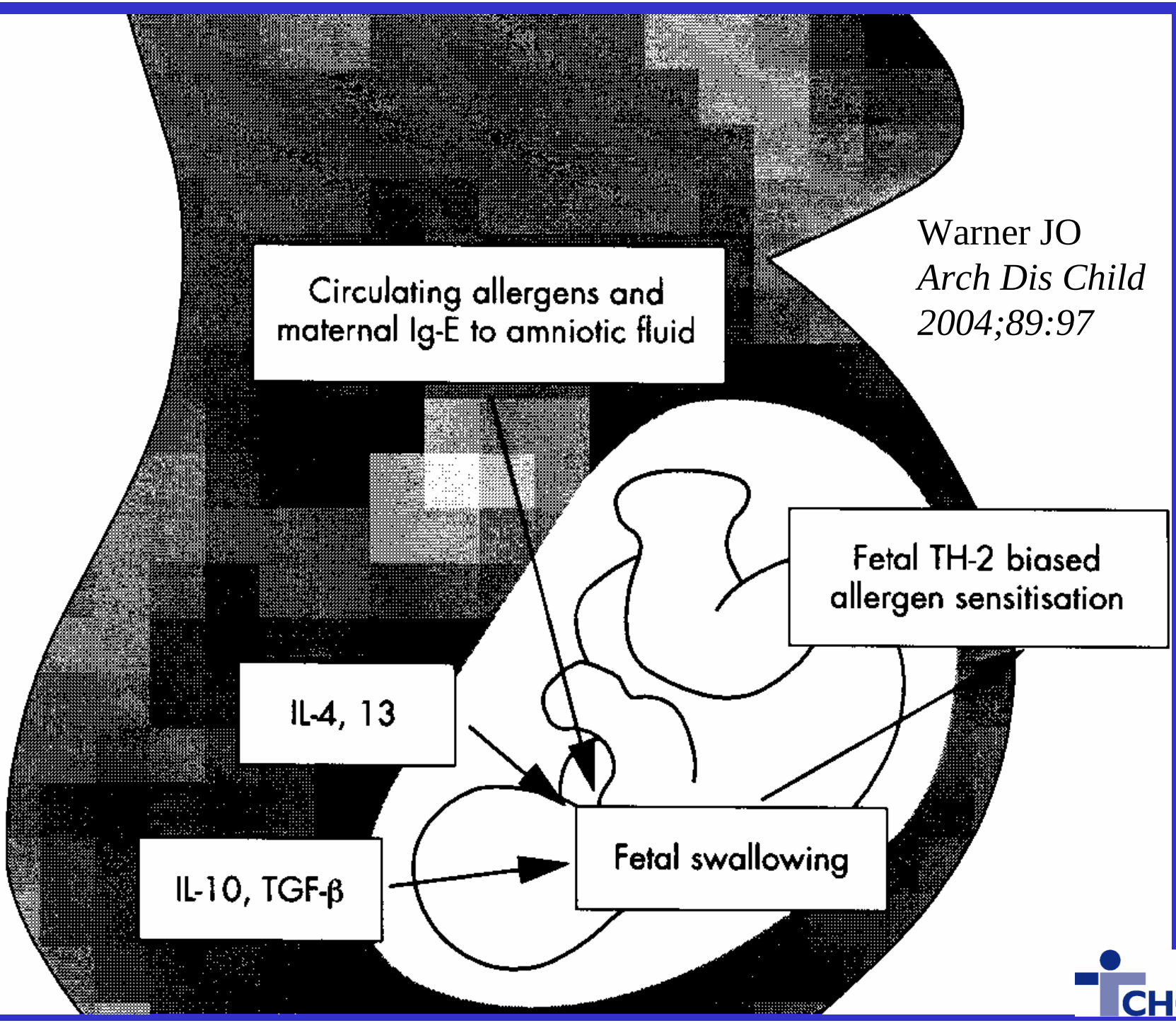
Major Nutrients of Human Milk : Multiple functions

Nutrients	Amount	Function
Protein		
- sIgA	50 - 100 mg/dL	Immune protection
- IgM	2 mg/dL	Immune protection
- IgG	1 mg/dL	Immune protection
- Lactoferrin	100 - 300 mg/dL	Anti-infective, iron carrier
- Lysozyme	5 - 25 mg/dL	Anti-infective
- alpha Lactalbumin	200 - 300 mg/dL	Ion carrier (Ca^{2+}), part of lactose synthase
- Casein	200 - 300 mg/dL	Ion carrier, inhibits microbial adhesion
Carbohydrates		
- Lactose	6.5 – 7.3 g/dL	Energy source
- Oligosaccharides	1.0 – 1.5 g/dL	Microbial ligands
- Glycoconjugates	-	Microbial and viral ligands
Fat		
- Triglyceride	3.0 – 4.5 g/dL	Energy source
- LC-PUFA	-	Essential for brain and retinal development
- FFA	-	Anti-infective

The Fetus and its Immunological protection

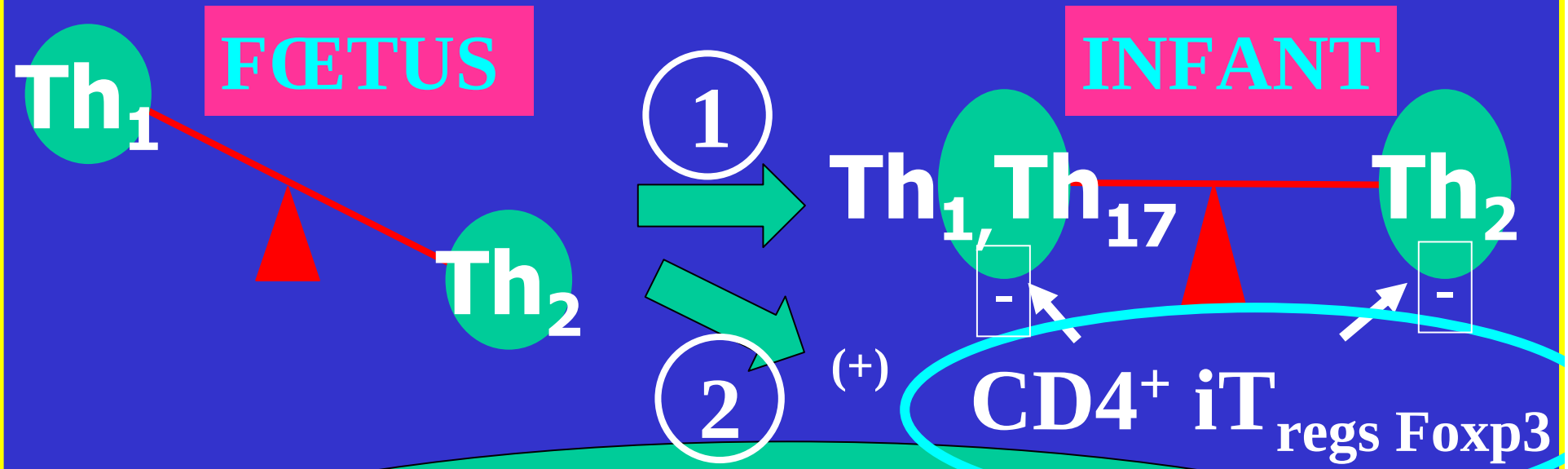


Warner JO
Arch Dis Child
2004;89:97



Warner JO
Arch Dis Child 2004;89:97

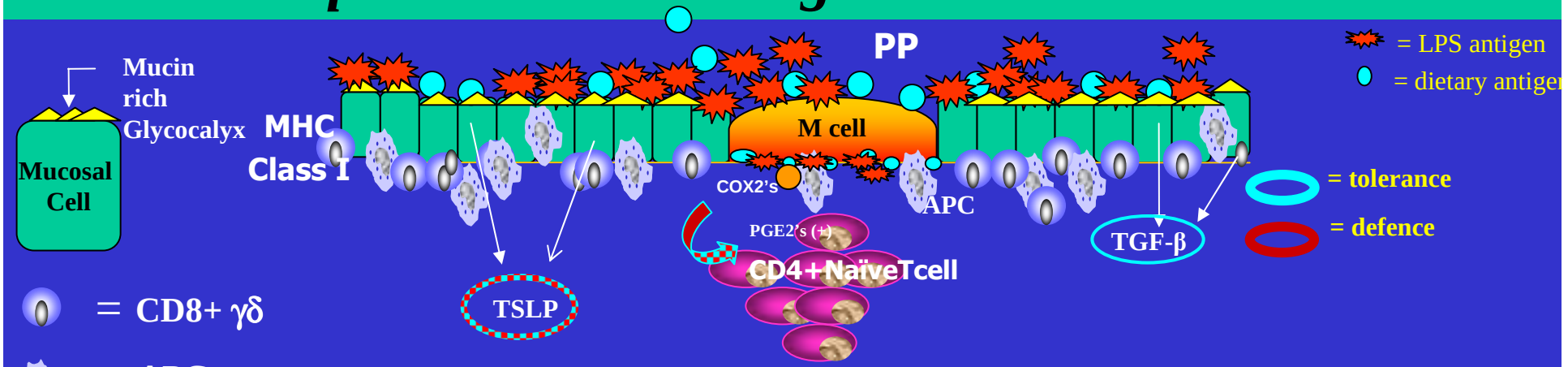
Physiological Fetal Immune Imbalance to be corrected and induced by invasive bacteria in the Early Stage



1 Th1,Th17 impulse and 2 up-regulation of $CD4^+$ iT_{reg} cells (Bystander Suppression) in a progressively increased TGF-β immune climate ($CD4^+CD25^+$ $_{Foxp3+}$, $Th3_{Foxp3-}$, $Tr1_{Foxp3-}$).

Crucial role of bacteria to induce **HOST DEFENSE** but also in the same time to get **DIET ANTIGEN TOLERANCE**……

Immune Equilibrium : To be got at the sub-Mucosa Level



= CD8+ γδ

= APC

= CD4 Naïve T Cell

Abreviations:

PP = Peyer Patch

LPS = Lipo-polysacharides

TGF = Transforming Growth Factor

TSLP = Thymic Stromal Lymphopoietin

APC = Antigen Presenting Cell

COX = Cyclo-oxygenases

CD = Cluster of Differentiation

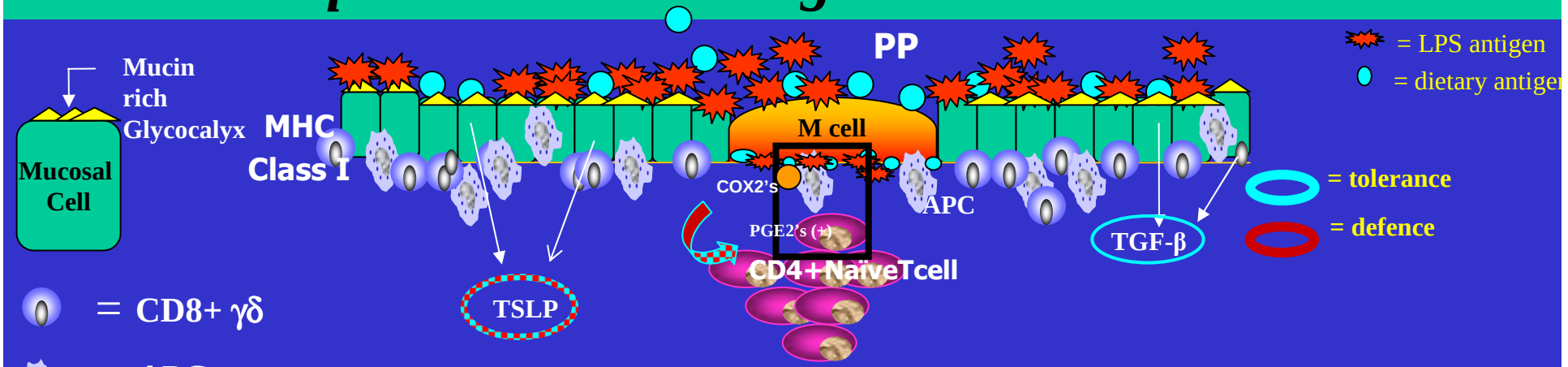
MHC = Major Histocompatibility Complex

PGE = Prostaglandins

CTLA = Cytotoxic T Lymphocyte Antigen

Dendritic Cell or Antigen Presenting Cell (APC)

Immune Equilibrium : To be got at the sub-Mucosa Level



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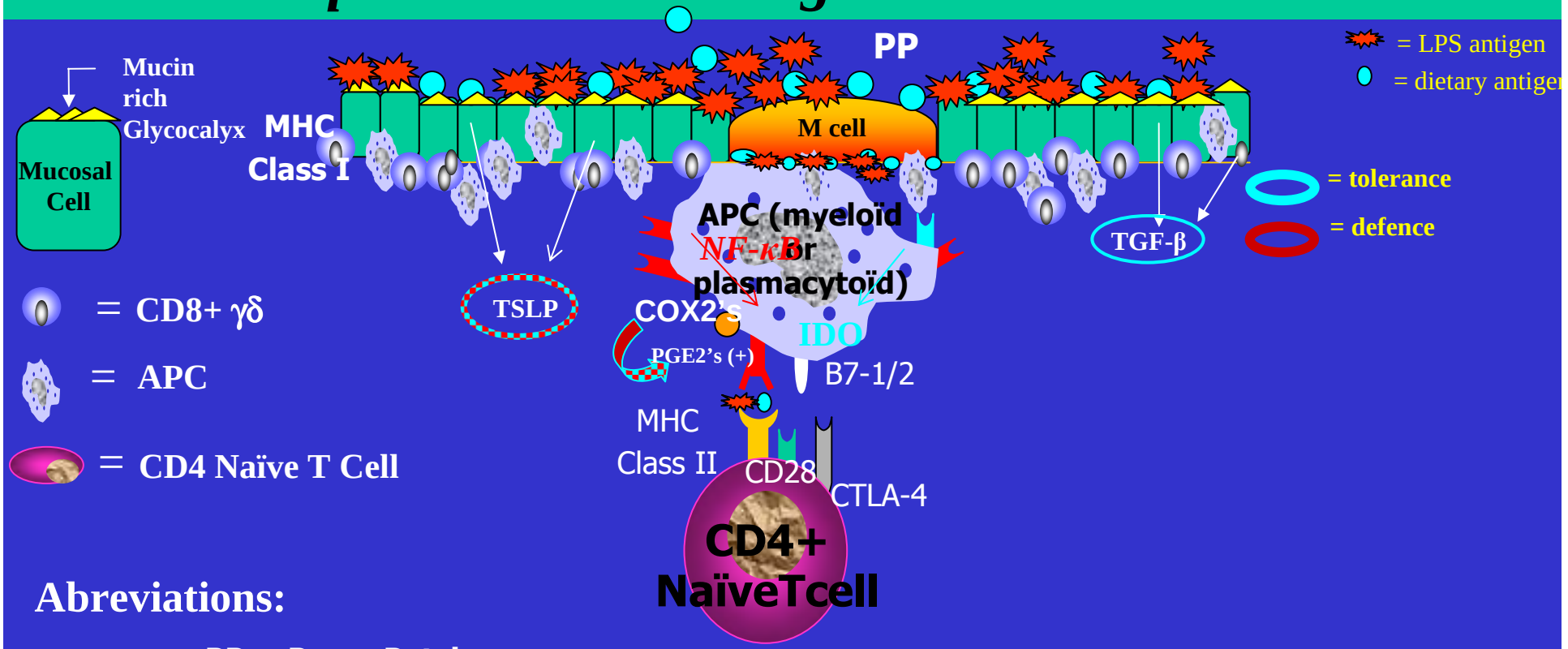

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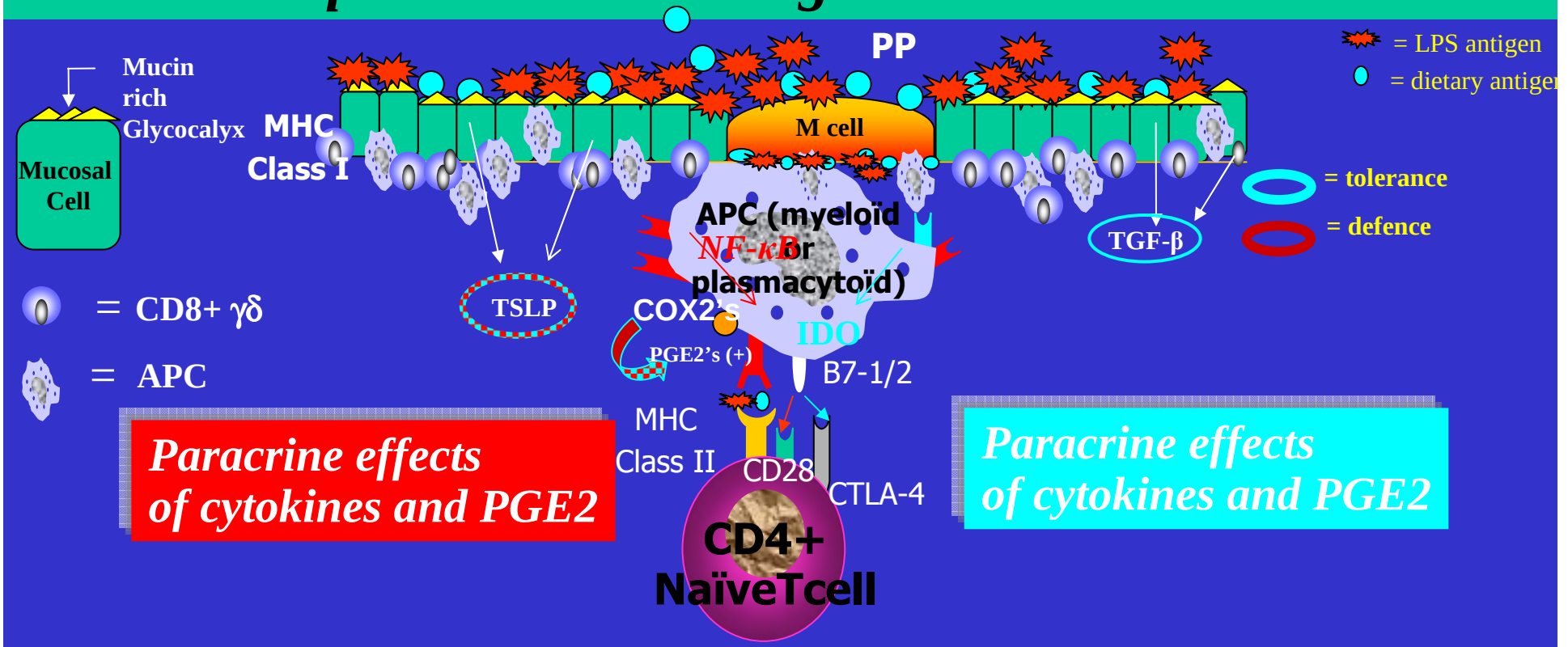
MHC = Major Histocompatibility Complex

PGE = Prostaglandins

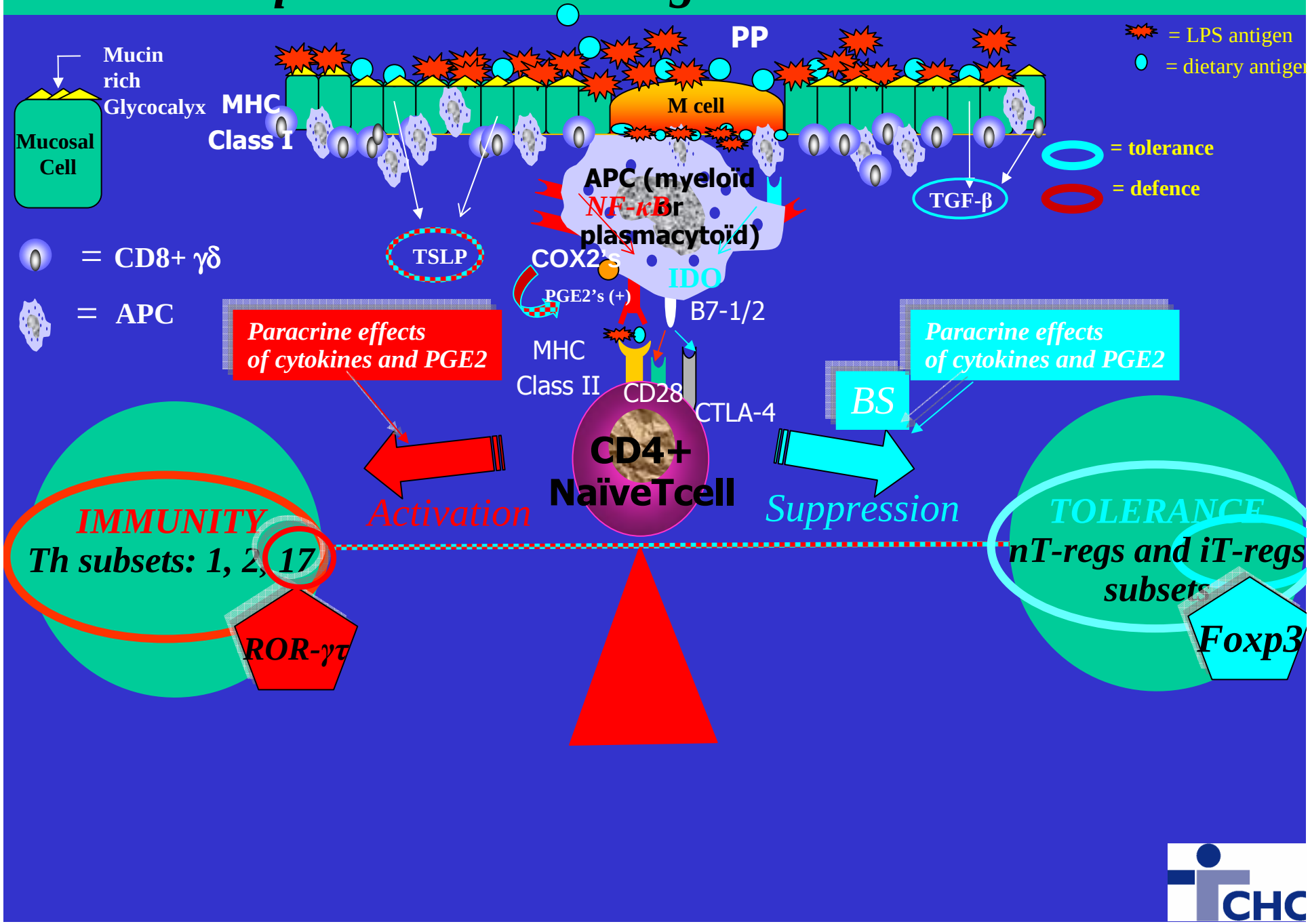
CTLA = Cytotoxic T Lymphocyte Antigen

IDO = Indoleamine-2,3 Dioxygenase

Immune Equilibrium : To be got at the sub-Mucosa Level



Immune Equilibrium : To be got at the sub-Mucosa Level



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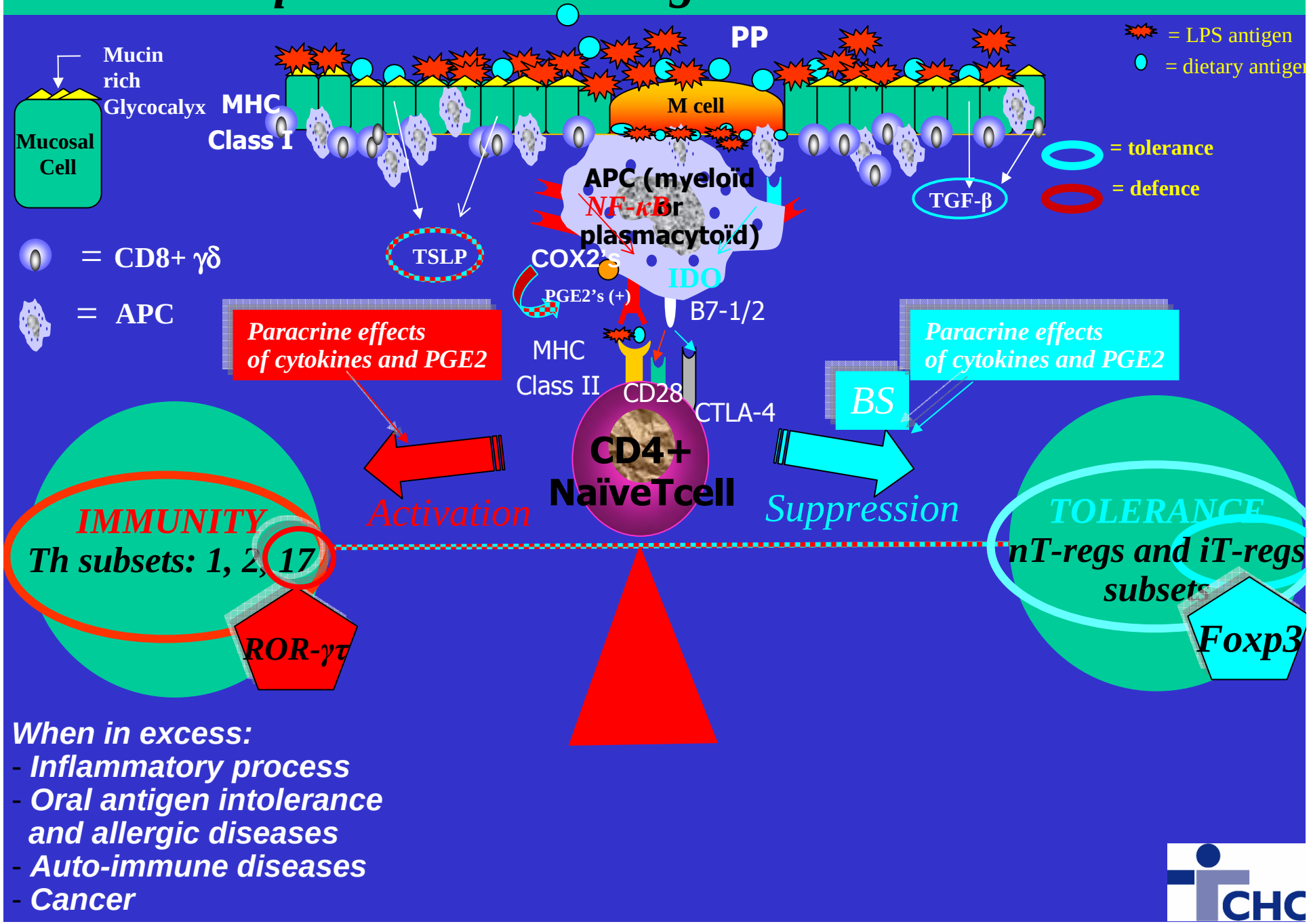
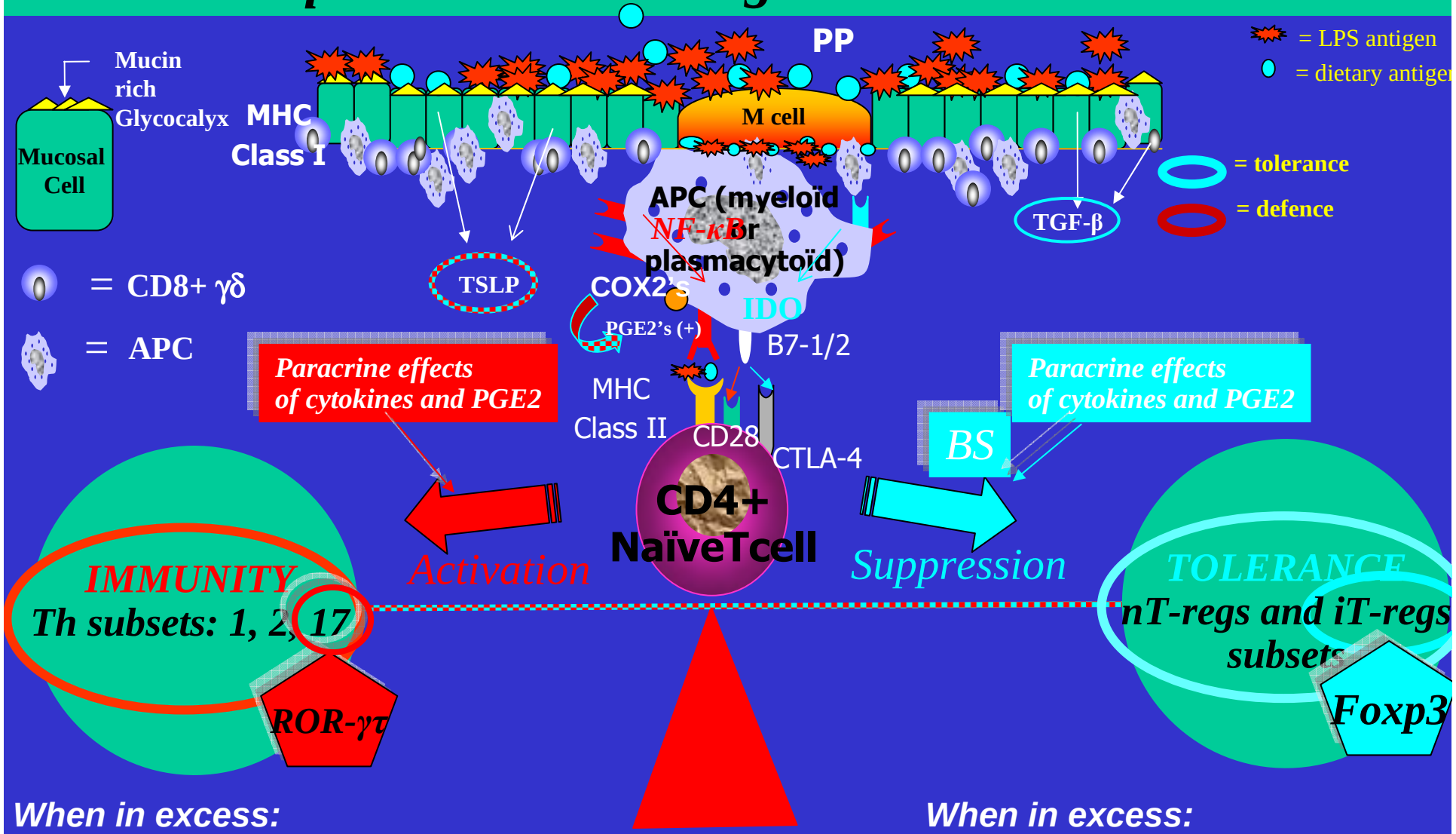


When in excess:

- ***Inflammatory process***
- ***Oral antigen intolerance and allergic diseases***
- ***Auto-immune diseases***
- ***Cancer***

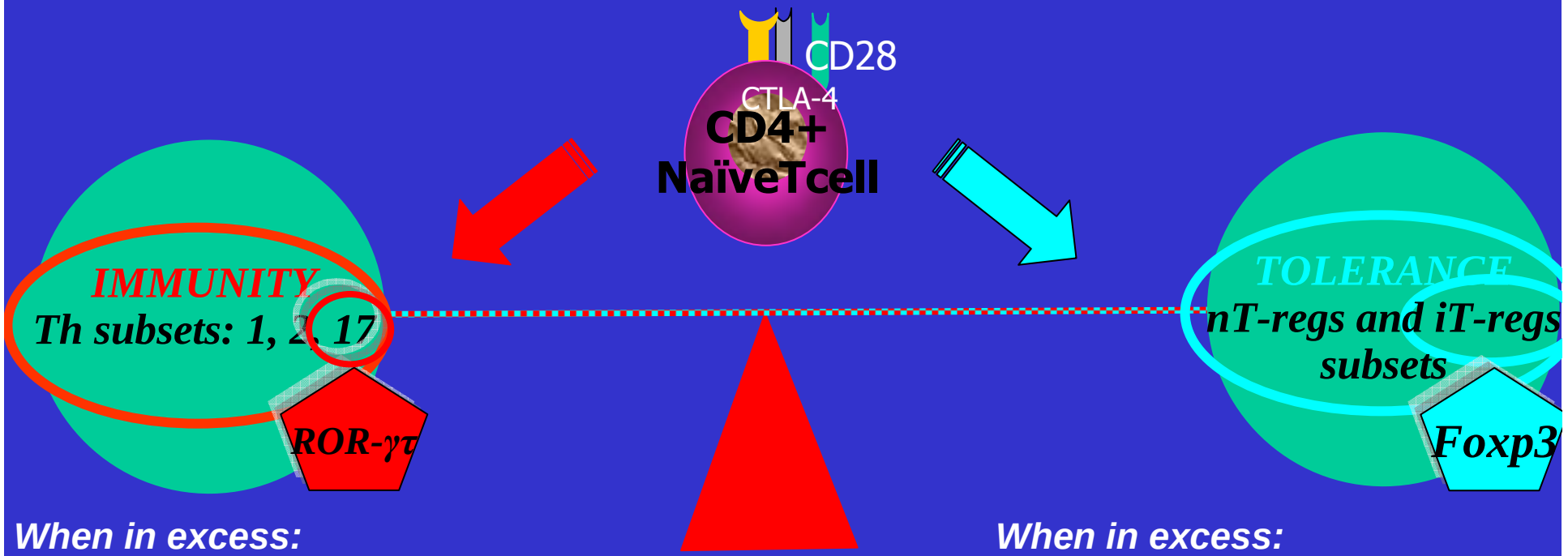
Immune Equilibrium : To be got at the sub-Mucosa Level



When in excess:
- ***Inflammatory process***
- ***Oral antigen intolerance and allergic diseases***
- ***Auto-immune diseases***
- ***Cancer***

When in excess:
- ***Infectious tolerance and chronic infections***
- ***Chronic inflammatory tolerance***
- ***Cancer***

Immune Equilibrium : to be got at the sub-Mucosa Level



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