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Why Not Just One Bottle: The Art and Science of Exclusive Breastfeeding

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Oklahoma
Baby-Friendly Symposium
February 20, 2015

Disclosure

- I have no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider of commercial services discussed in this CME activity.
- I do not intend to discuss an unapproved/investigative use of a commercial product/device in my presentation.

Objectives

1. Describe how human milk affects the cellular and molecular development of the infant's immune system
2. Understand why supplementing interferes with breastfeeding
3. Elevate the threshold for supplementing a breastfed newborn

Disease Protection in Children

"Dose Dependent"

1. AOM 50% less **EBF**>3-6 months
2. Atopic dermatitis less 42% **EBF**>3 months
3. LRTI and hospitalization less 72% with **EBF**>4 months
4. Asthma less 40% for **EBF**>3 months
5. Obesity less 4-24%; with **EBF** less 34%
6. T1DM less 19-27% **EBF**>3 months
7. T2DM less 39% with any BF vs. None
8. Cancer:
    1. ALL less 19% with BF>6 months
    2. AML less 15% with BF>6 months
9. SIDS less 36% with any BF vs. None
10. Gastro less 64% with any BF vs. None

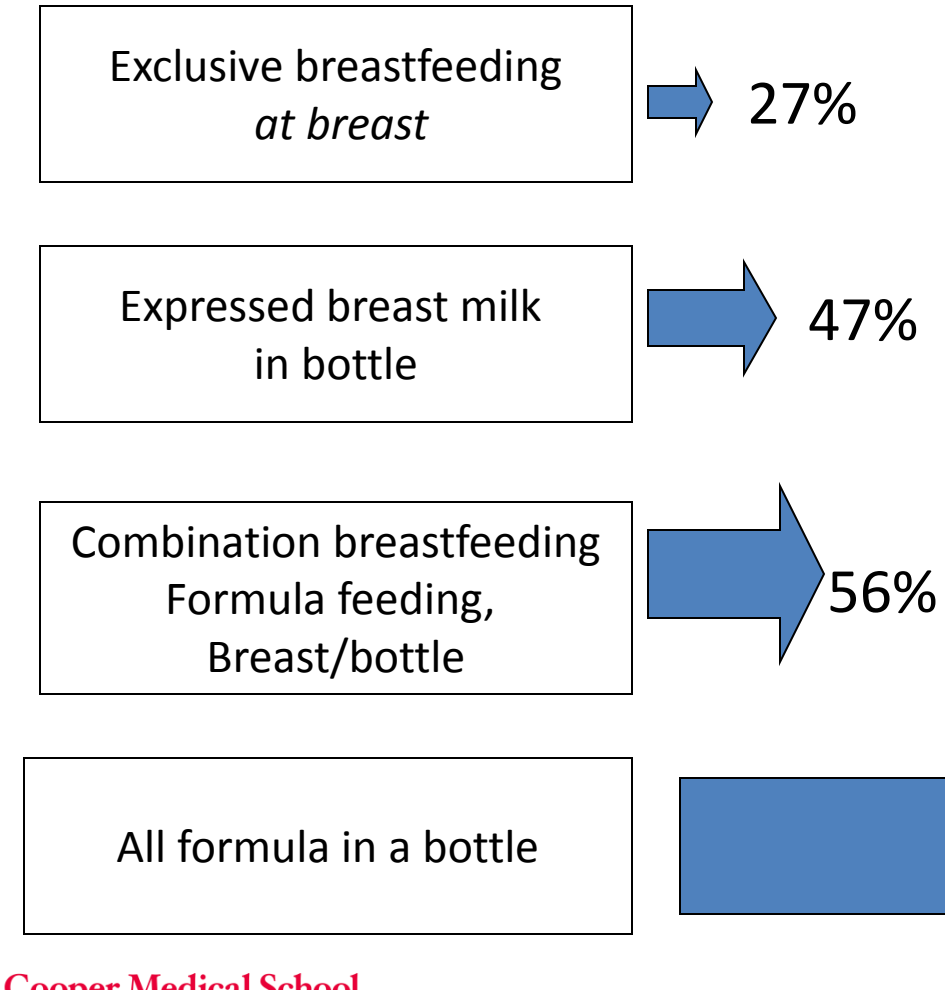
S. Ip, et al. AHRQ Review 2007

New Evidence Linking *Early* Supplementation with ALL

	Cases (%) (ALL) n=314	Controls (%) n=663	OR (95% CI)
Any Breastfeeding	35 (11) 279 (89)	40 (6) 623 (94)	Reference **0.52 (0.32-0.86)**
Age of formula introduction			
Never	75 (26)	191 (30)	Reference
≥ 6 Months	60 (21)	126 (20)	1.15 (0.76-1.75)
2-6 months	56 (19)	114 (18)	1.12 (0.73-1.71)
15 days – 2 months	27 (9)	92 (15)	0.65 (0.38-1.10)
< 14 days	**75 (26)**	**108 (17)**	**1.57 (1.03-2.37)**

Greenop KR. Nutrition and Cancer 2015

Breastfeeding Leads to Self-Regulation



How often does your infant
empty the bottle/cup after
7 months of age?

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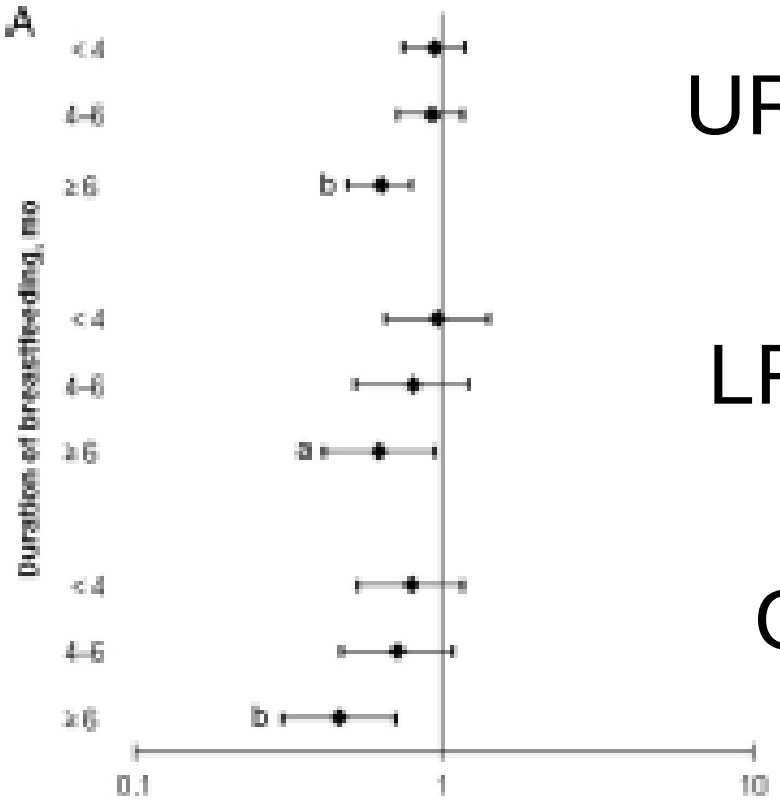
Pediatrics. 2010 Jun;125(6):e1386-93. 2010.

Exclusive 4 vs. 6 Months



URTI

LRTI

GI

Liesbeth D. et al. Pediatrics June 2010

Formula Supplementation Increases Risk of Ear, Sinus and Throat Infections Beyond Infancy

Formula Supplementation	N	%	AOR	95% CI
BF<6 mo with formula <6 mo	440	44.6	Ref	
BF ≥ 6 mo with formula < 6 mo	279	41.9	0.96	0.69-1.32
BF ≥ 6 mo **without formula < 6 mo**	389	34.2	0.70*	0.51-0.85
			*P<0.01	

Longitudinal data from the IFS II followed through age 6 years; AA and Hispanic mothers under-represented

Li R. Pediatrics September 2014

Epidemiological Evidence of Immune Modulation

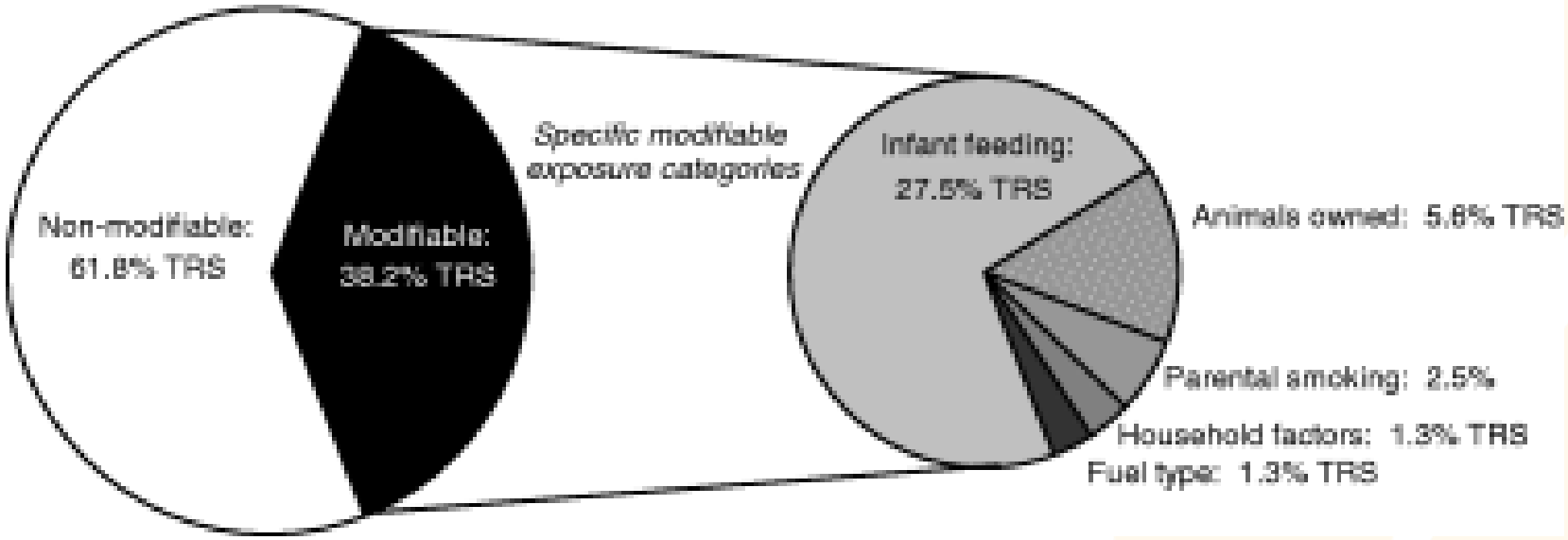
- Non-EBF results in risk of autoimmune diseases; long after breastfeeding
  - Atopy and Asthma (response to LRTI)
  - Crohn's and Ulcerative Colitis
  - Celiac
  - Leukemia
  - Type 1 DM

Prevalence of Modifiable Exposures Among Slovak Children by AE Status

Infant feeding	AE+	AE-	p-value
Any formula in the first year of life	178 (86.8)	892 (79.9)	0.02*
Exclusive breastfeeding for ≥4 months	5 (2.4)	86 (7.7)	0.006*
Introduction of solid food <4 months	103 (49.8)	632 (56.5)	0.07
Cow's milk in the first year of life	184 (90.2)	941 (84.6)	0.04*

Dunlop, Anne L. et al. 2006. *Pediatric Allergy and Immunology.*

% Regression Score Accounted for by Modifiable Exposures



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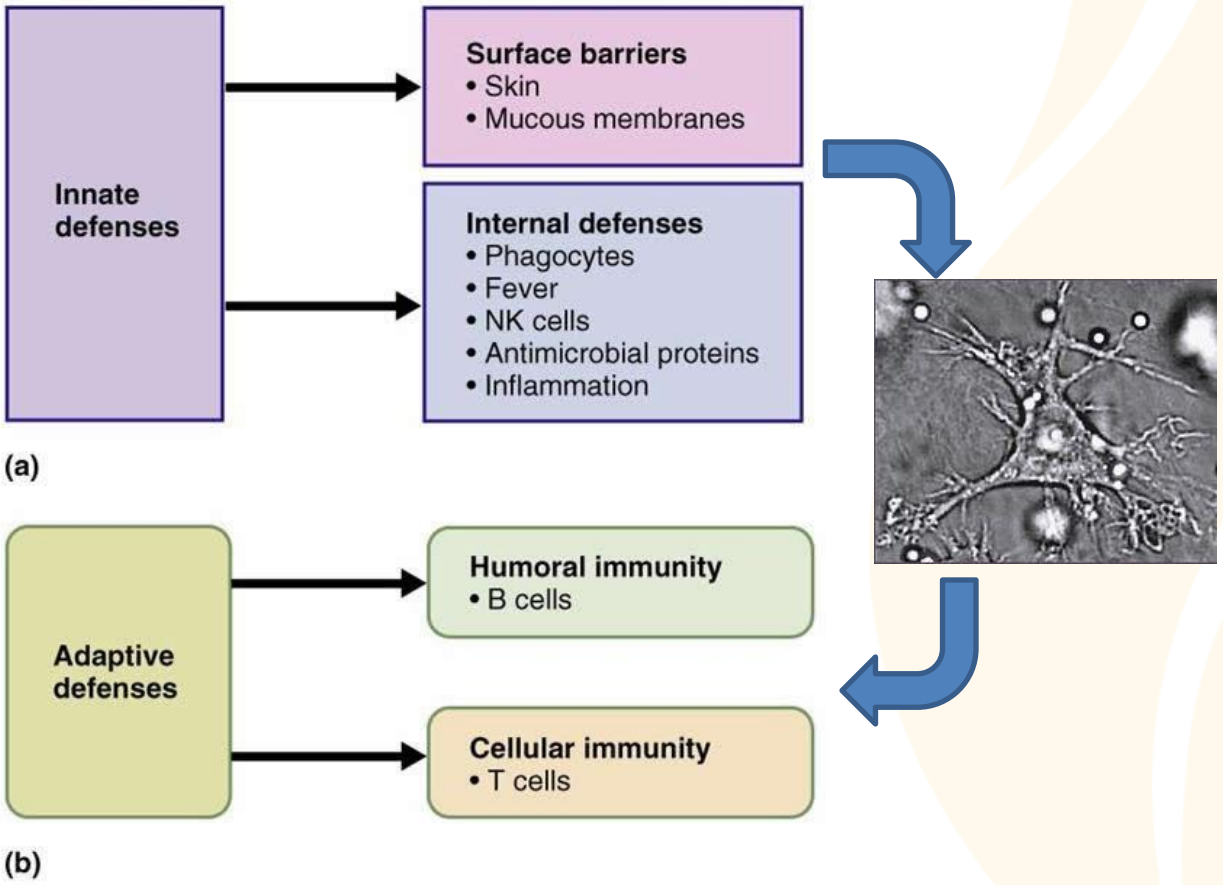
Dunlop, Anne L. et al. 2006. *Pediatric Allergy and Immunology.*

Human Milk Influences the Development of Immune System

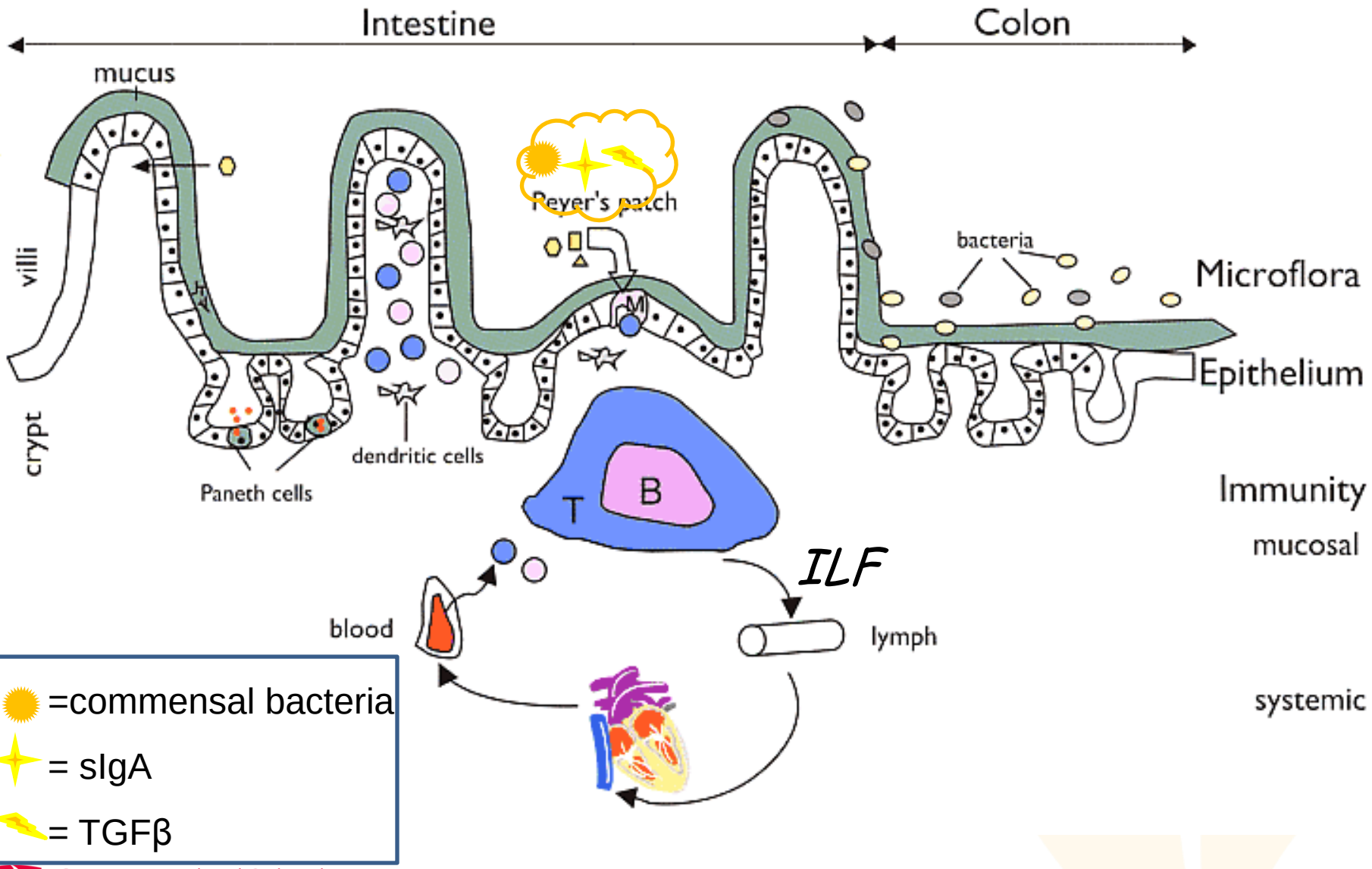


http://classes.midlandstech.edu/carterp/Courses/bio211/chap21/chap21.htm

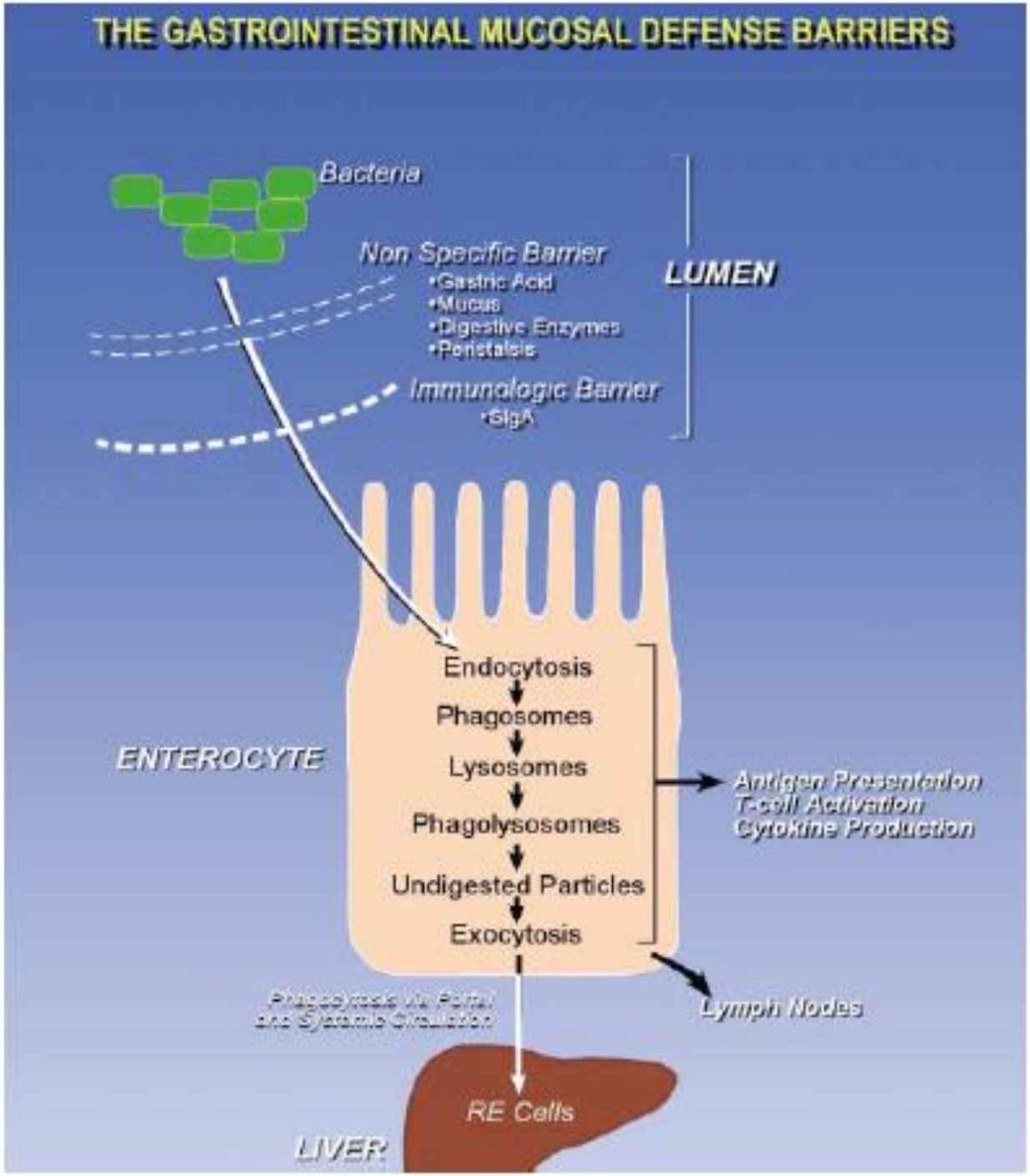
Gut Colonization Essential to Prevent Allergy and Establish Normal Function

- Newborn gut needs to be colonized shortly after birth
- Immune response to flora leads to:
  - Colonization with commensal bacteria
  - Development of immunologic tolerance
- Hygiene hypothesis
  - If not exposed and/or unable to properly handle flora (via HM) then allergy develops

Newborn Intestinal Immune System



http://www.customprobiotics.com/about_probiotics.htm



HM Provides Innate Host Defense:

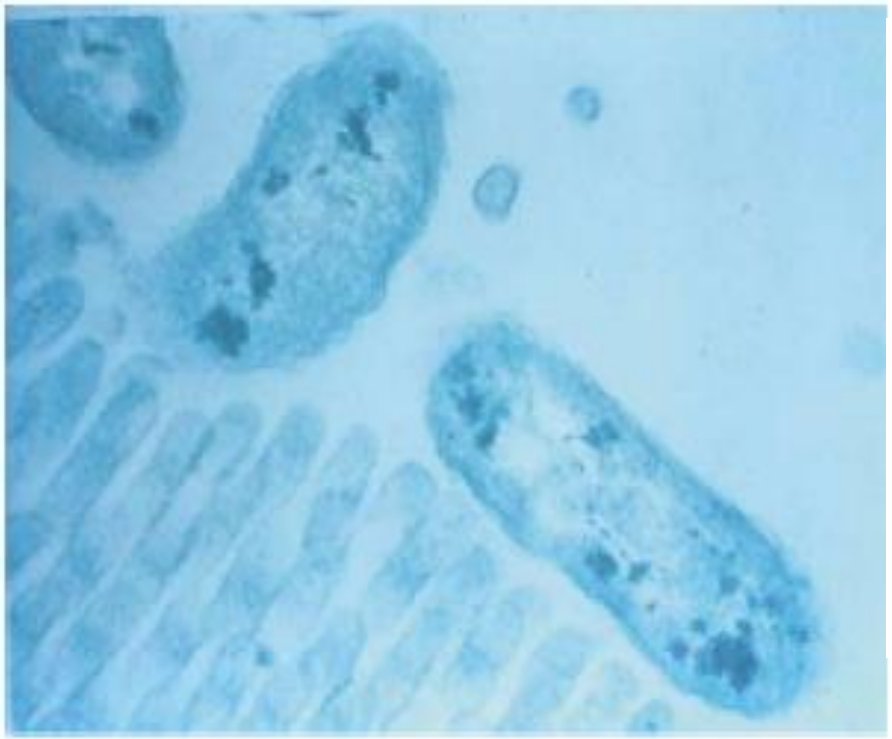
- Lipids
- Mucin
- Lactoferrin
- Lysozyme
- Complement
- Leukocytes

Specific Adaptive Immunity:

- sIgA
- Anti-idiotypic Ab
- Probiotic
- TLR signaling

Forchielli ML and Walker A. Br J Nutr. 2005 Apr;93 Suppl 1:S41-8.

Enteric Bacterium Interact with Intestinal Microvillus of the Small intestine

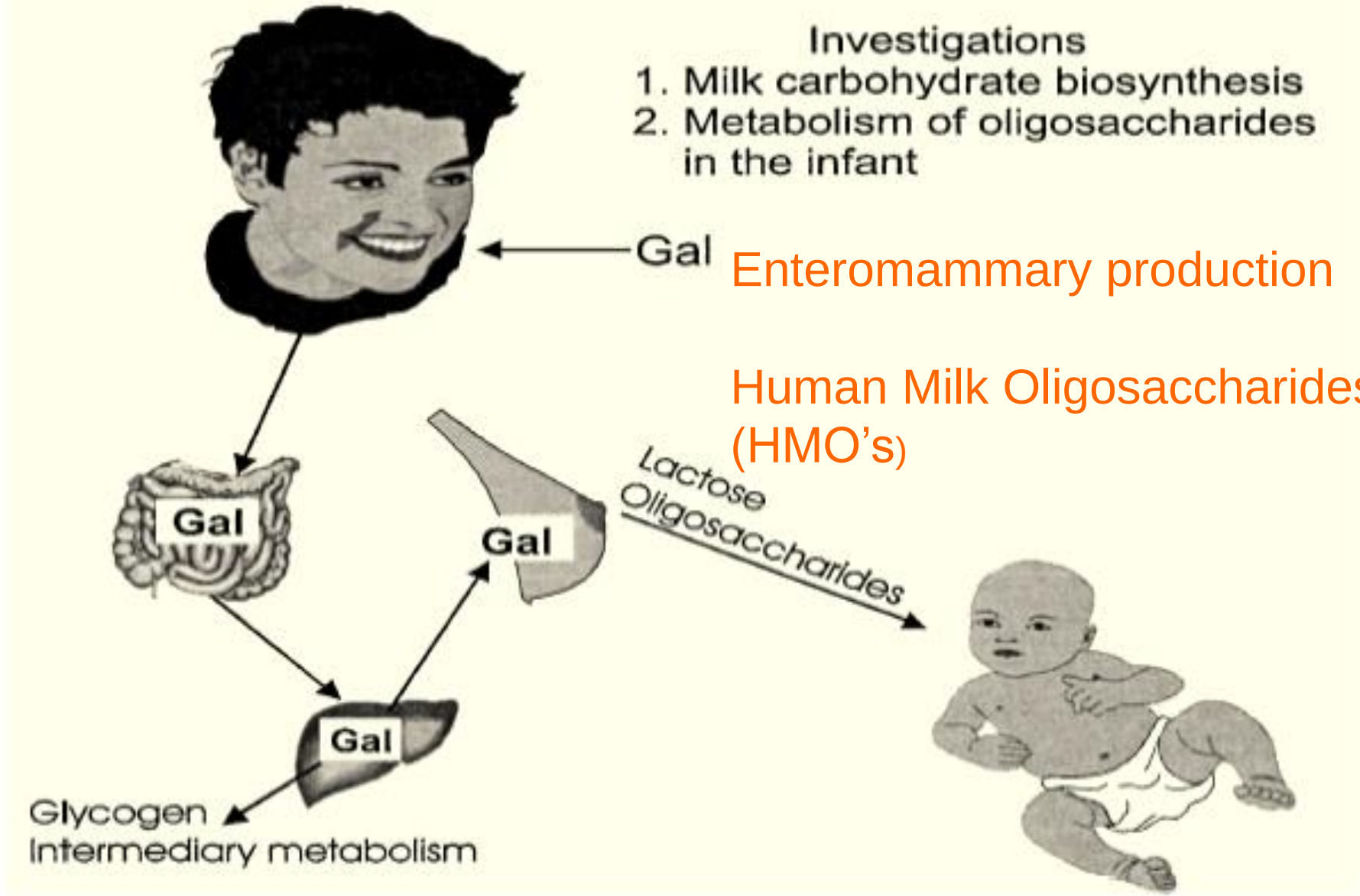


Bacterial-epithelial "cross-talk"

- Organizes B,T, Macrophages and dendritic cells
- Regulates Ag transport
- Drives Ag specific and non-specific pathways for recognition
- Responses are both pro and anti-inflammatory

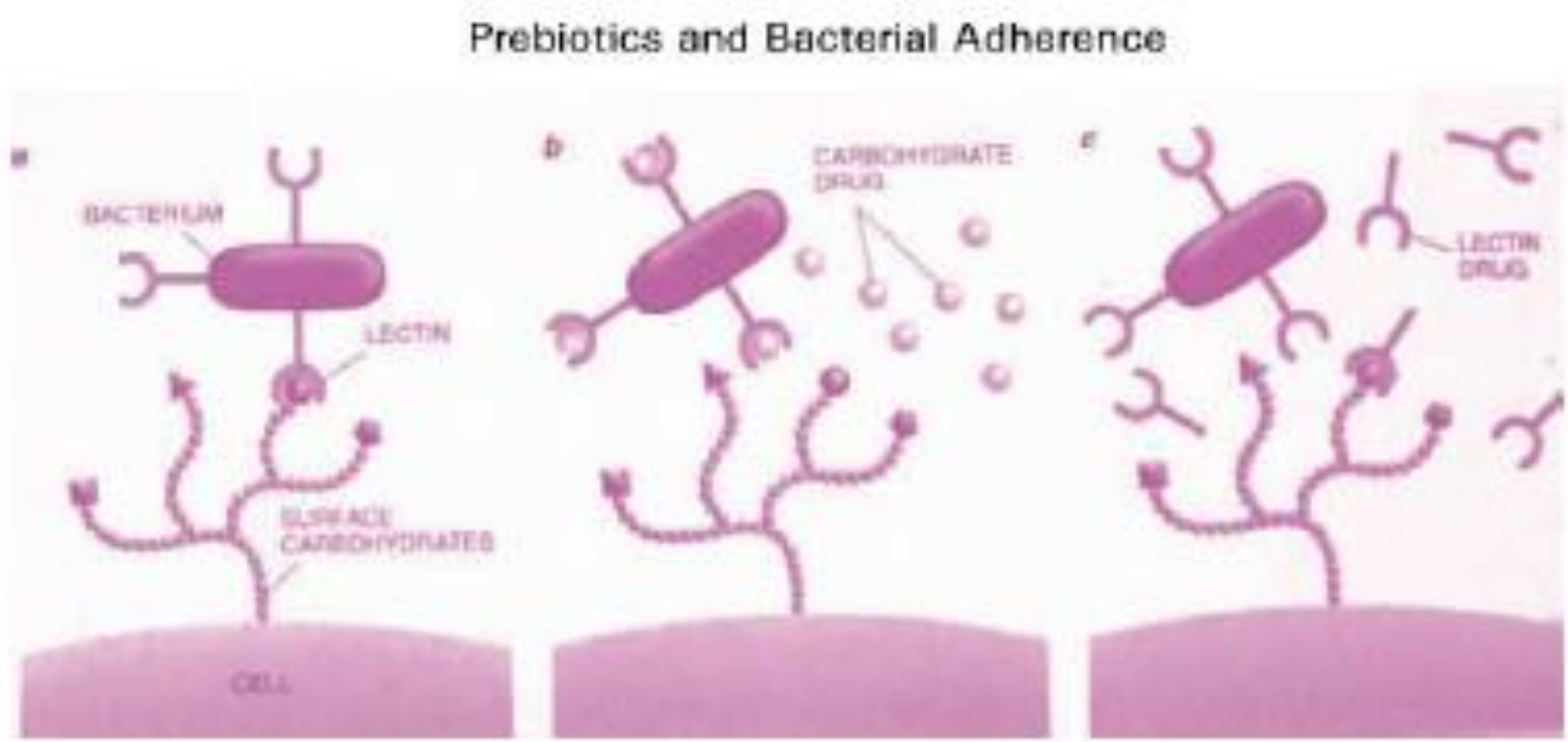
Forchielli ML and Walker A. Br J Nutr. 2005 Apr;93 Suppl 1:S41-8.

Studies with ^{13}C-labeled Monosaccharides



C. Kunz, et al. Ann Rev Nutrition 2000

How Prebiotics in Human Milk Work



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Forchielli ML and Walker A. Br J Nutr. 2005 Apr;93 Suppl 1:S41-8.

Oligosaccharides *necessary* to colonize commensal bacteria

Sugars on normal cell surfaces

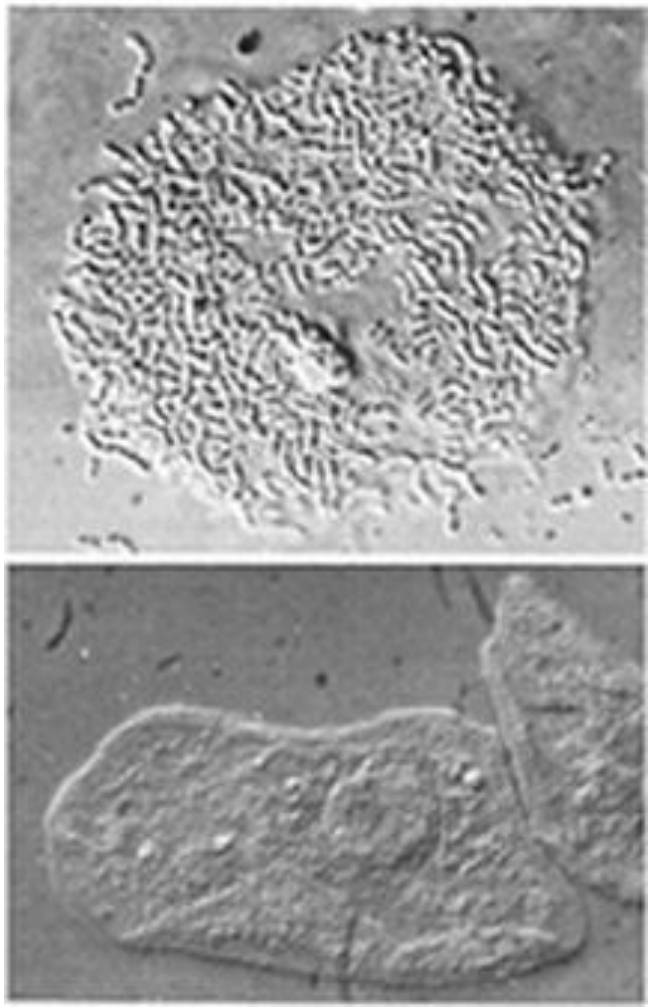
(throat) permit bacterial adhesion →

(pneumococci) and infection.

Oligosaccharides thwart attempt

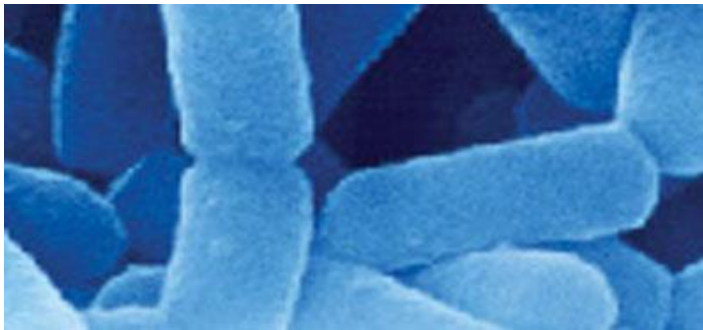
for bacteria to enter cell

By binding sugar receptors →



Immune System Priming

- Probiotic bacteria need an invitation to the environment that hosts them
  - Prebiotic - oligosaccharides, suppress of immune reaction to probiotic while participating in host defense against pathogenic bacteria
- Nature permits host defense without the need for an inflammatory response….protects the epithelium…reason to have a delayed immune system…



Stool PH as an Indicator of Normal Gut Fermentation

Table 2. *Value of stool pH*

	3rd day	1st month	2nd month	3rd month	4th month
BF	5.03 ± 0.7	5.05 ± 0.2	5.04 ± 0.7	5.06 ± 0.3	5.04 ± 0.4
FF	5.12 ± 1.4	5.13 ± 0.3	5.11 ± 0.3	5.12 ± 0.7	5.15 ± 0.6
SF	5.86 ± 1.7*	5.63 ± 0.5*	5.93 ± 0.7*	5.78 ± 0.6*	5.83 ± 0.7*

* vs breast-feed and FF feed $p < 0.001$.

BF-Exclusively HM-fed; FF-fermented formula;
SF-standard formula

Indrio F. et al. Pediatric Research 2007

Oligosaccharides are *necessary* but *not sufficient* to properly colonize the infant's intestine

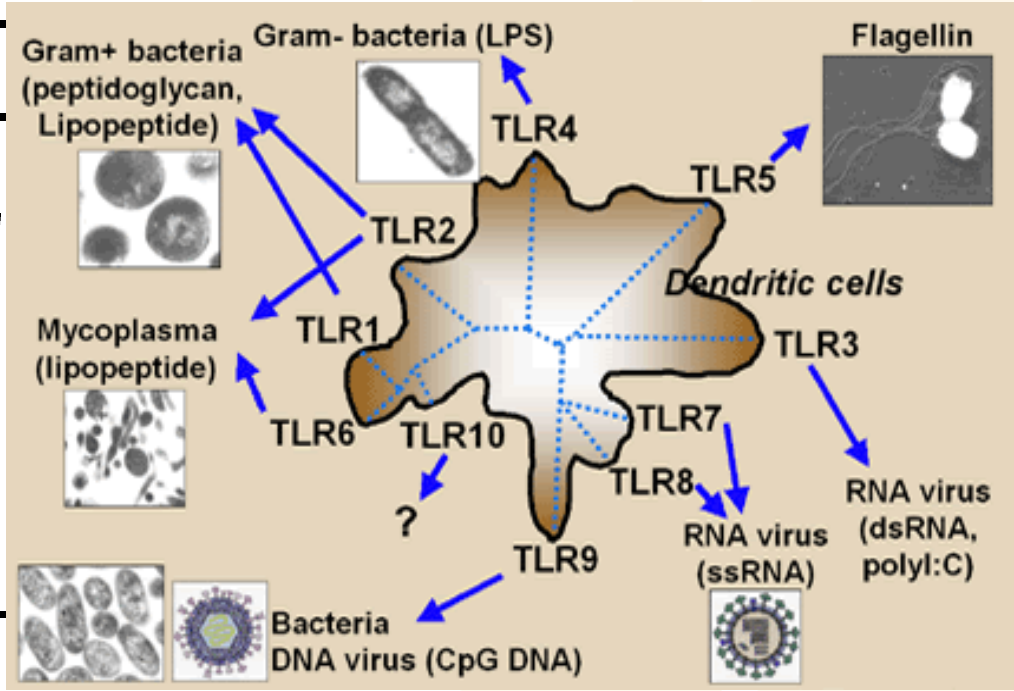
Toll like receptors (TLR) necessary to bind bacteria in concert with oligosaccharides
(LPS on gram - bacteria)

Need certain TLR's to be present

LeBoudier. *The Journal of Immunology*, 2006,176: 3742-3752.

Toll-like Receptors (TLR) and Their Ligands

TLR	Ligands
TLR1	Triacyl lipopeptides
TLR2	Lipoprotein/lipopeptides, peptidoglycan, lipoteichoic acid,
TLR3	Double-stranded RNA
TLR4	Lipopolysaccharide, HSP60 etc., commensal bacteria
TLR5	Flagellin
TLR6	Diacyl lipopeptides
TLR7	Synthetic compounds (the immune response modifiers)
TLR8	Unknown
TLR9	CpG DNA
TLR10	Unknown



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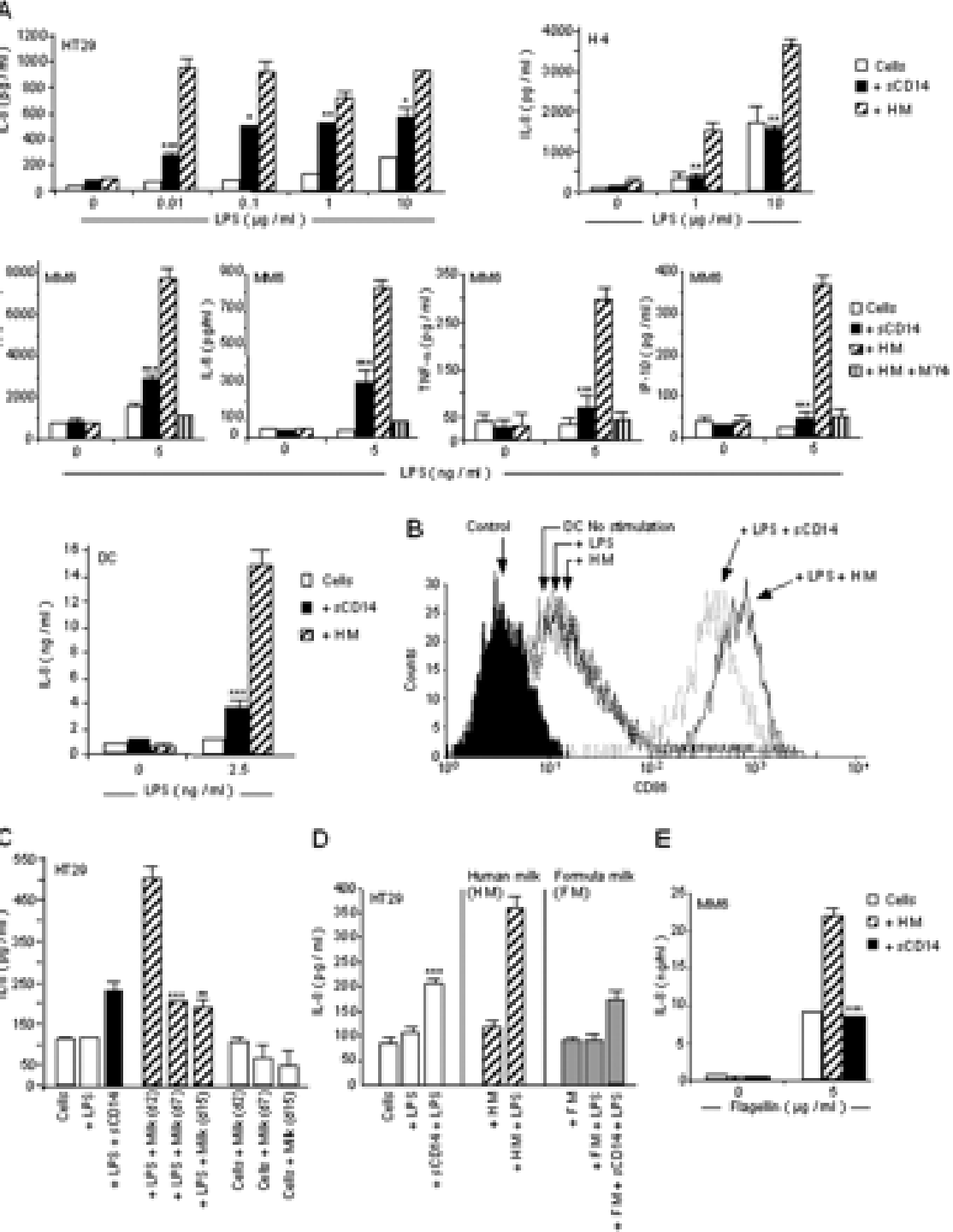
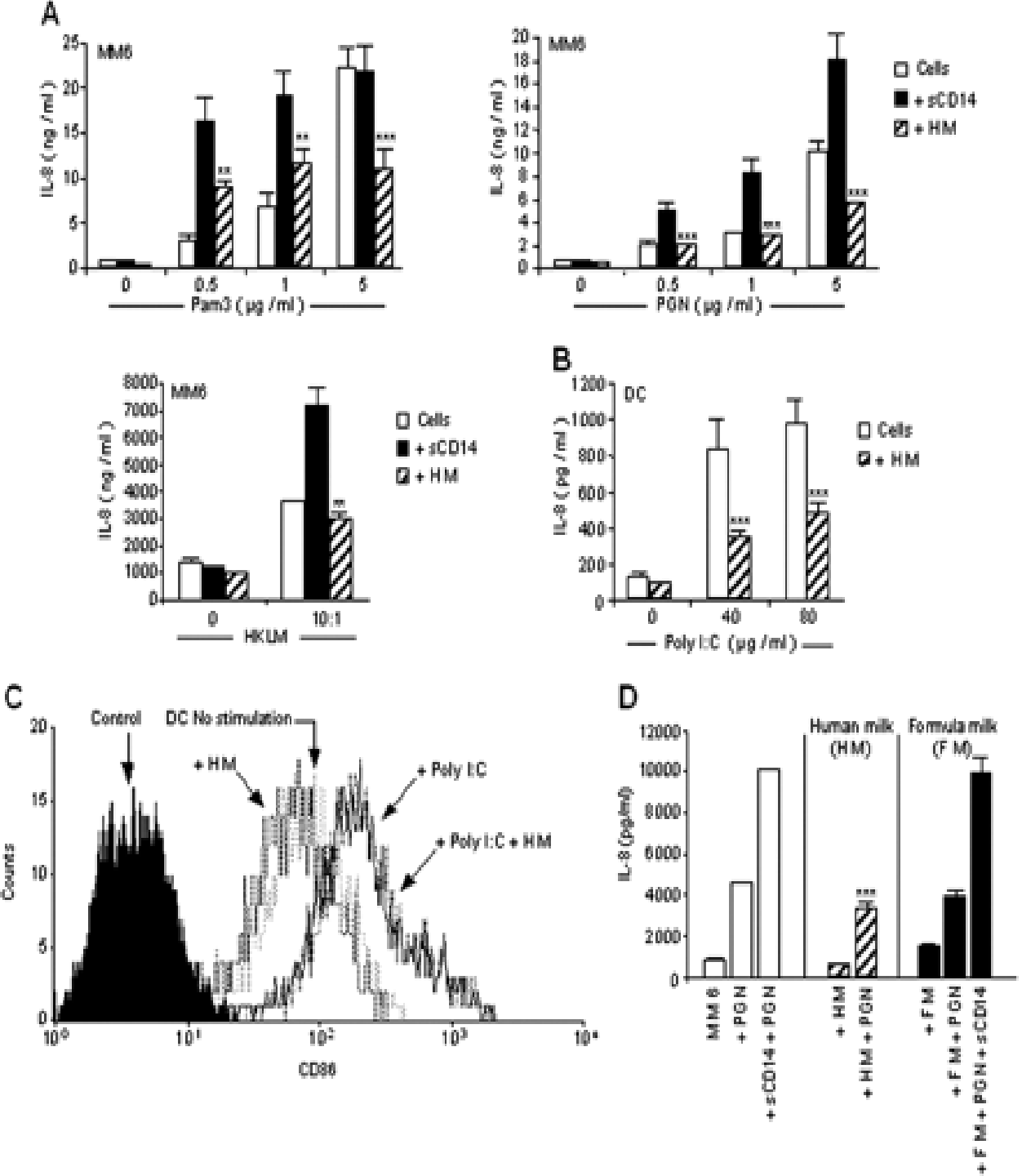
Forchielli ML and Walker A. Br J Nutr. 2005 Apr;93 Suppl 1:S41-8.



Human Milk, but Not Infant Formula Enhances TLR4- and TLR5-mediated responses

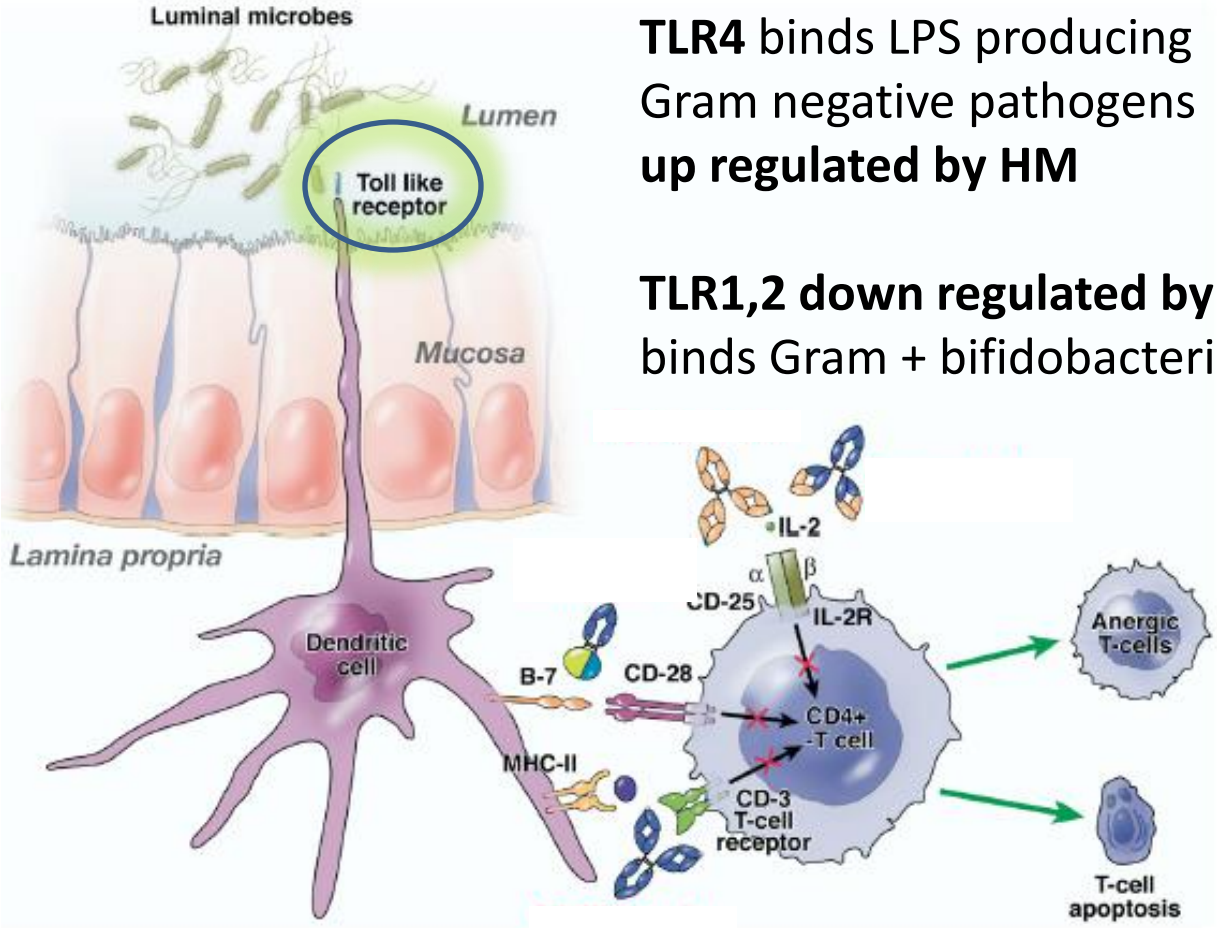
LeBoudier. The Journal of Immunology, 2006,176: 3742-3752.



Negative Effect of Human Milk, but Not Formula, on Cell Stimulation Via TLR2 and TLR3

The Journal of Immunology, 2006, 176: 3742-3752.

Specific Toll-like Receptors necessary for proper colonization



TLR4 binds LPS producing Gram negative pathogens **up regulated by HM**

TLR1,2 down regulated by HM binds Gram + bifidobacteria

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Rutgeerts P Gastroeneterology 2009

Exclusive Human Milk Necessary for Proper Colonization

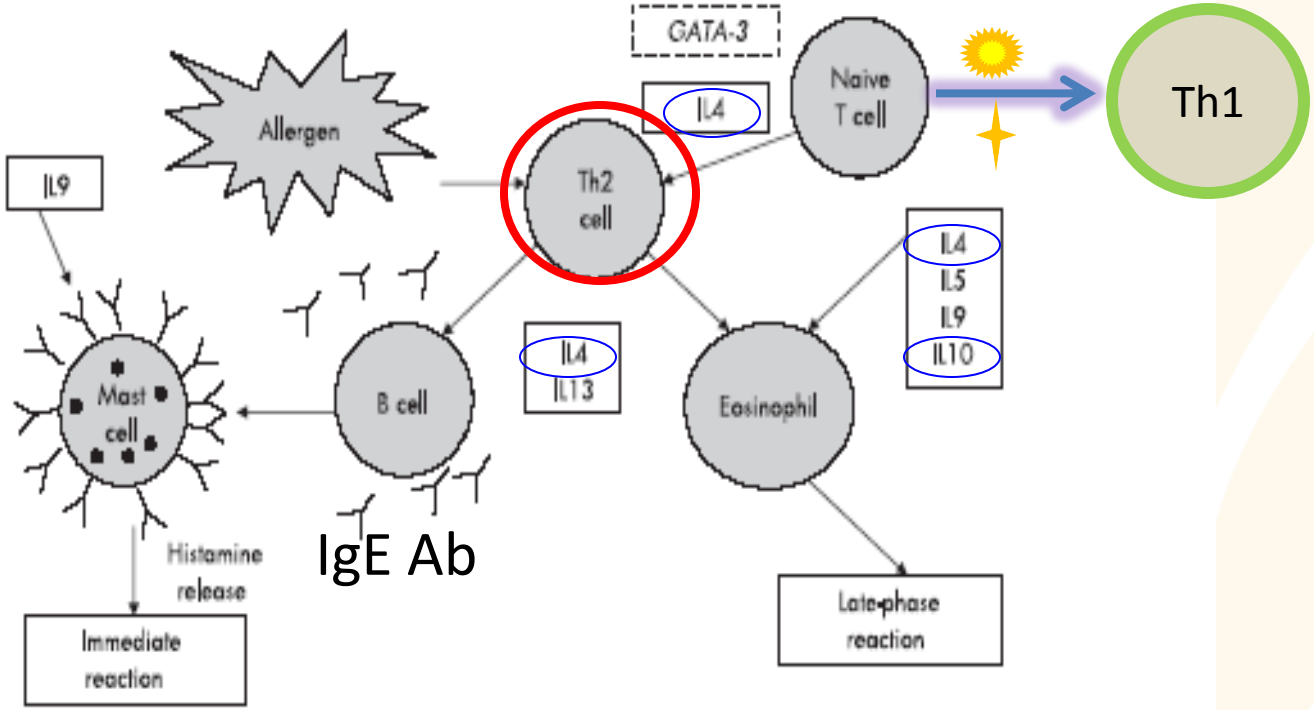
- Exclusive HM: probiotic/commensal bacteria- bifidobacteria, and lactobaccilus.
- Supported by complex system of HMO (not other prebiotics)
- Flora contribute to and are a marker of normal immune development, need certain toll-like receptors for hosting.
- Formula feeding: bacteroides, clostridia, streptococci.

just one bottle… leads to colonization with bacteria that induces an inflammatory response (enhanced by factors in human milk).

C. Kunz, et al. Ann Rev Nutrition 2000

HM Alters Allergic Response

- Newborn responses naturally skewed toward Th2>Th1
- Colonization helps drive Th1 and induce tolerance
- Cytokines in milk enhance/divert allergic response.
- Maternal sIgA diverts antigenic response.



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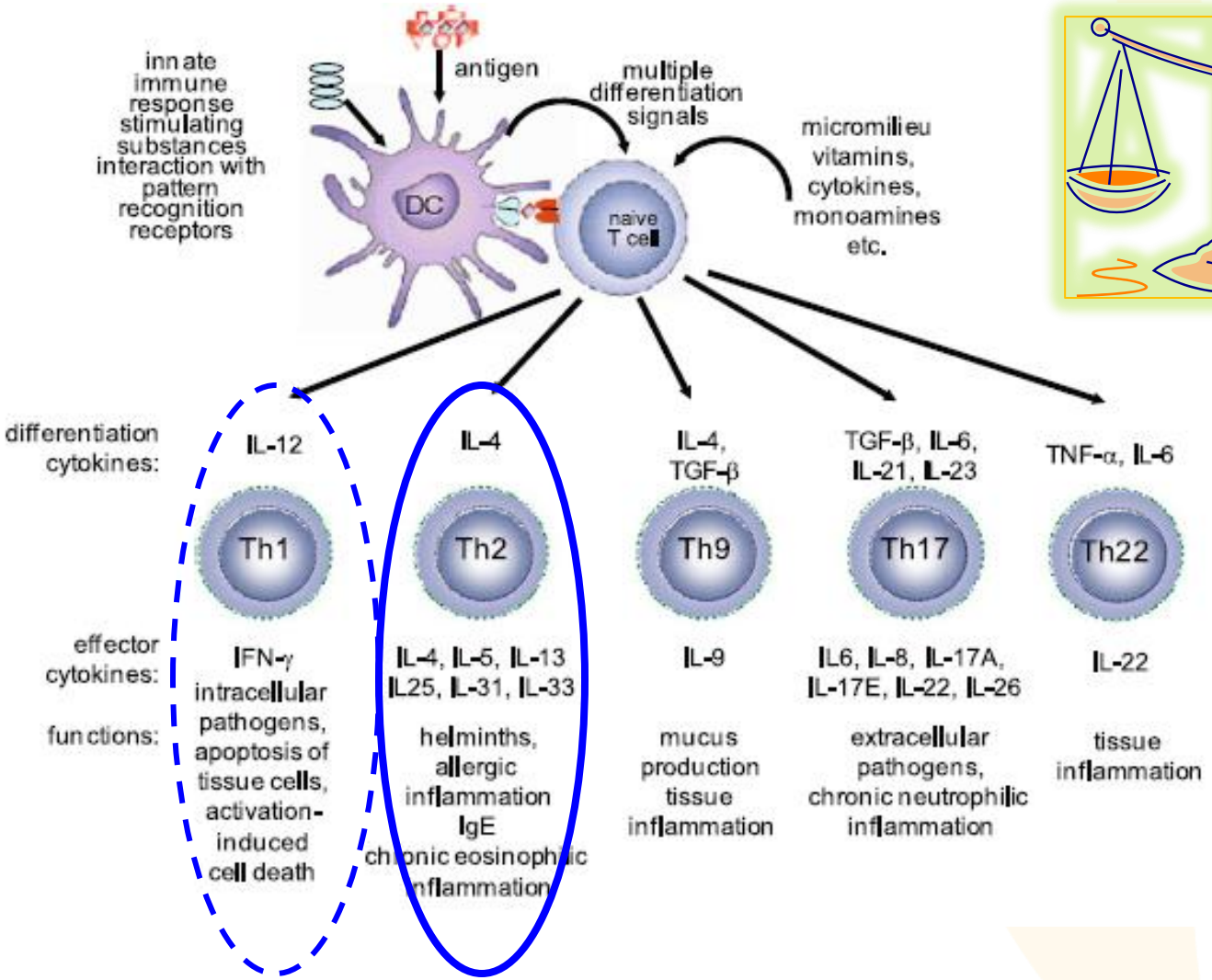
Chung EK et al. Arch Dis Child Fetal Neo Ed 2007

T Cell Ontogeny and Balance



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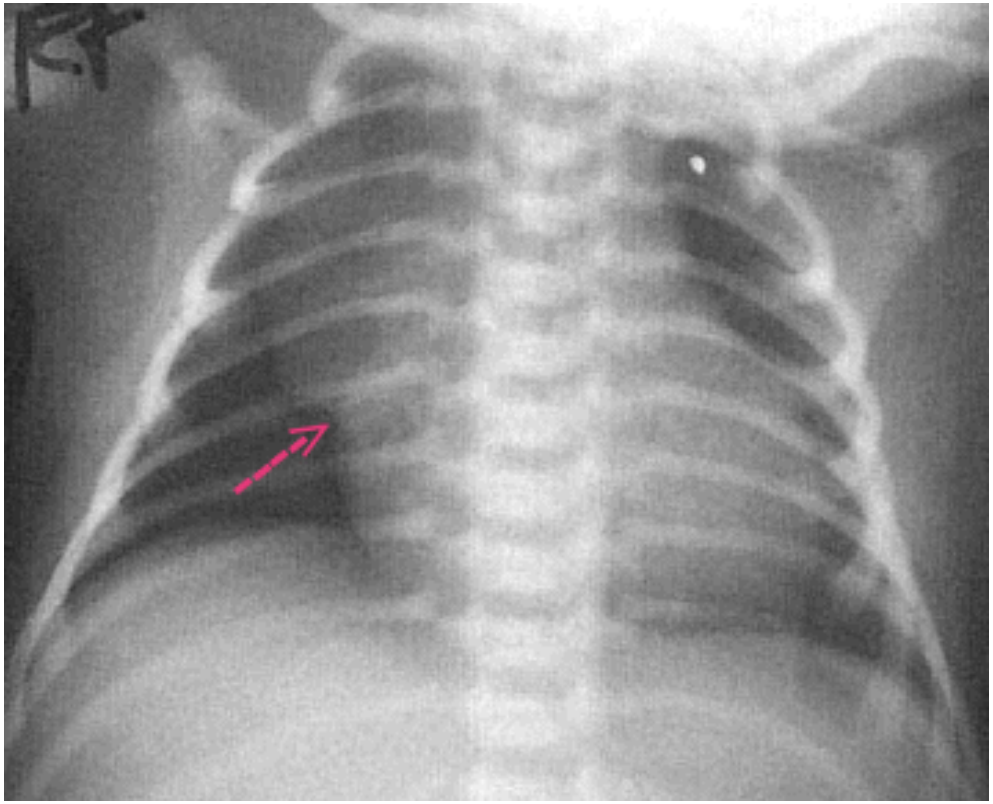
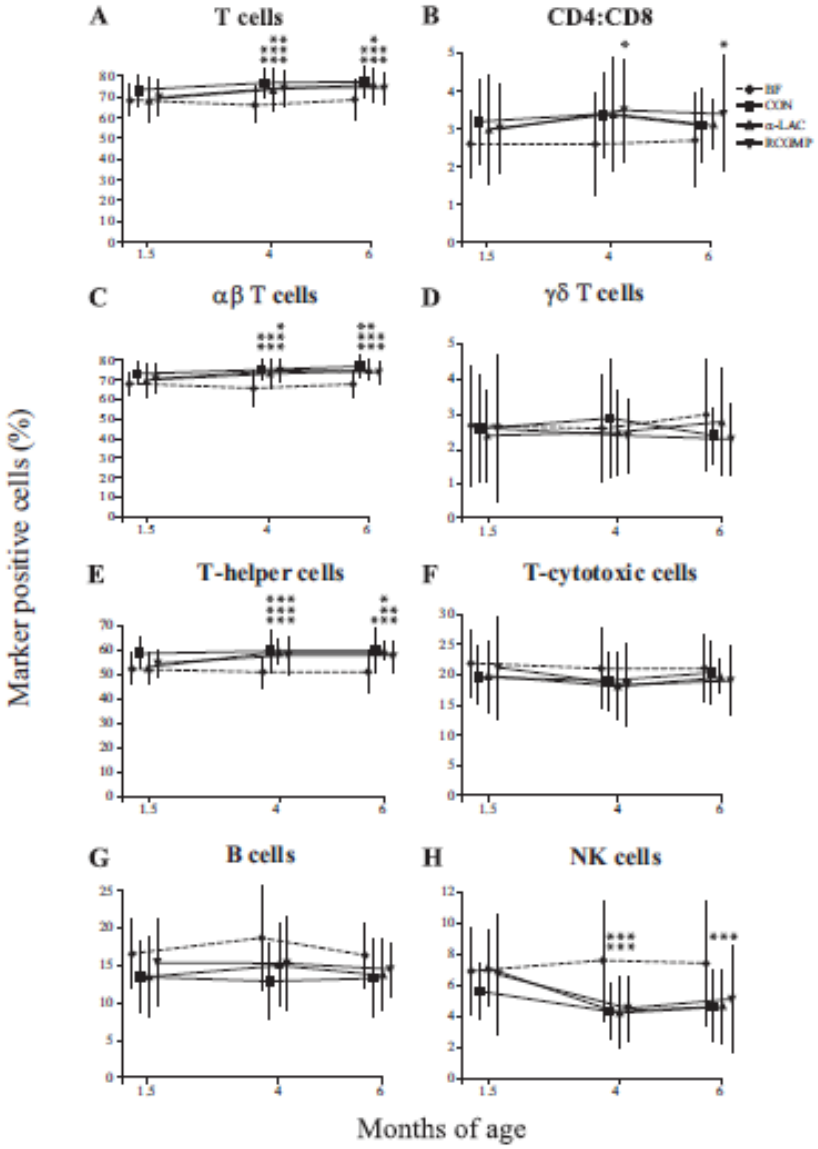
Jutel M. Current Allergy Asthma Rep. 2011

Ontogeny of T Cell Function



- Delayed T cell function.
- Breastfed infants have a thymus twice the size of formula fed infants.
- Immune properties of HM are priming (signaling) the resting thymus cells.
- T cells develop in GALT sent to thymus.

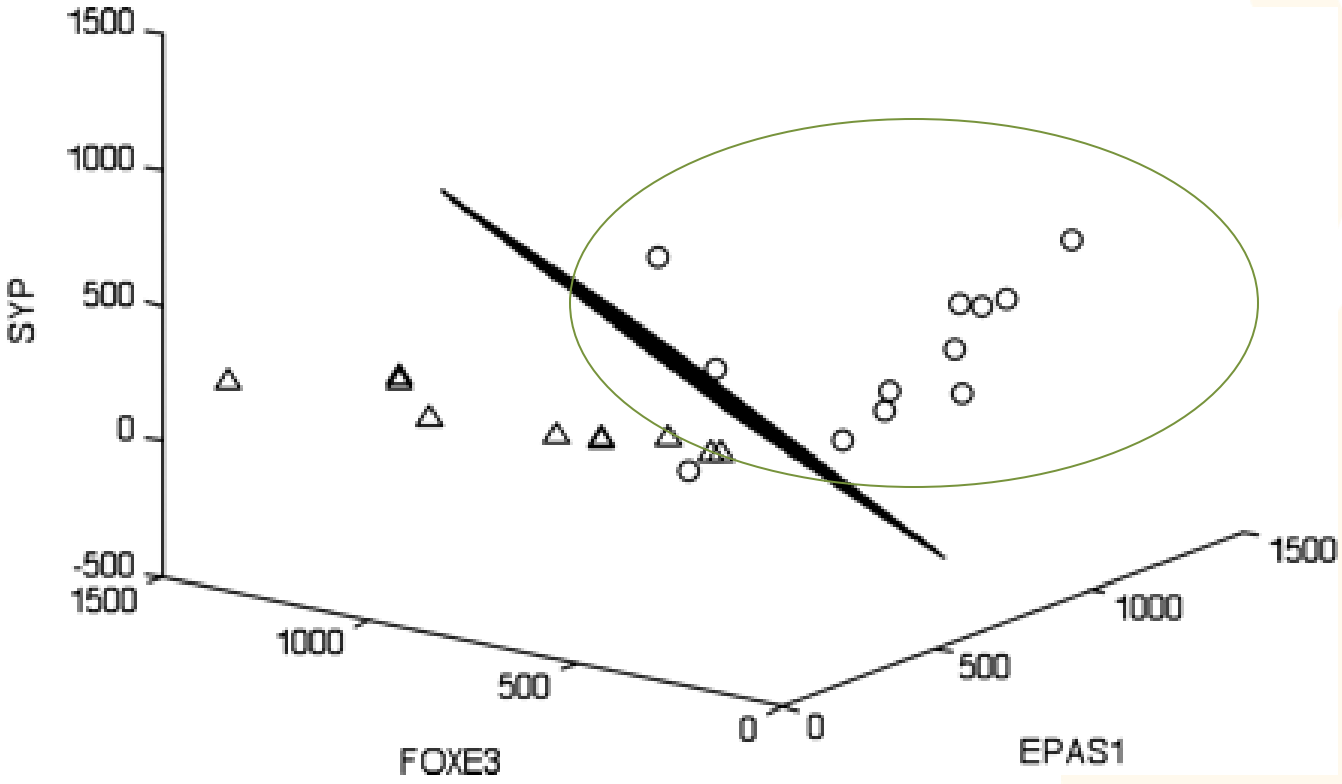
FF Skews Immune Cell Composition



- Distinct differences in circulating WBC at 6 mo.
- FF skewed toward naïve T cells, decrease in NK, CTL, and B cells, slower recruitment of T cells with effector functions for innate immunity
- If EBF were given IF at 4-6 mo. Pattern resembled FF infants

Andersson Y. et.al. J of Immunology 2009

Genes are Differentially Regulated by HM



3-dimensional bolstered gene expression discriminates between breast-fed (O) and formula-fed (Δ) infants

Master genes are transcription factors associated with angiogenesis and wound repair

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Chapkin RS, et al. *Am J Physiol Gastrointest Liver Physiol* 298: G582-G589, 2010

Human Milk Meta-genome

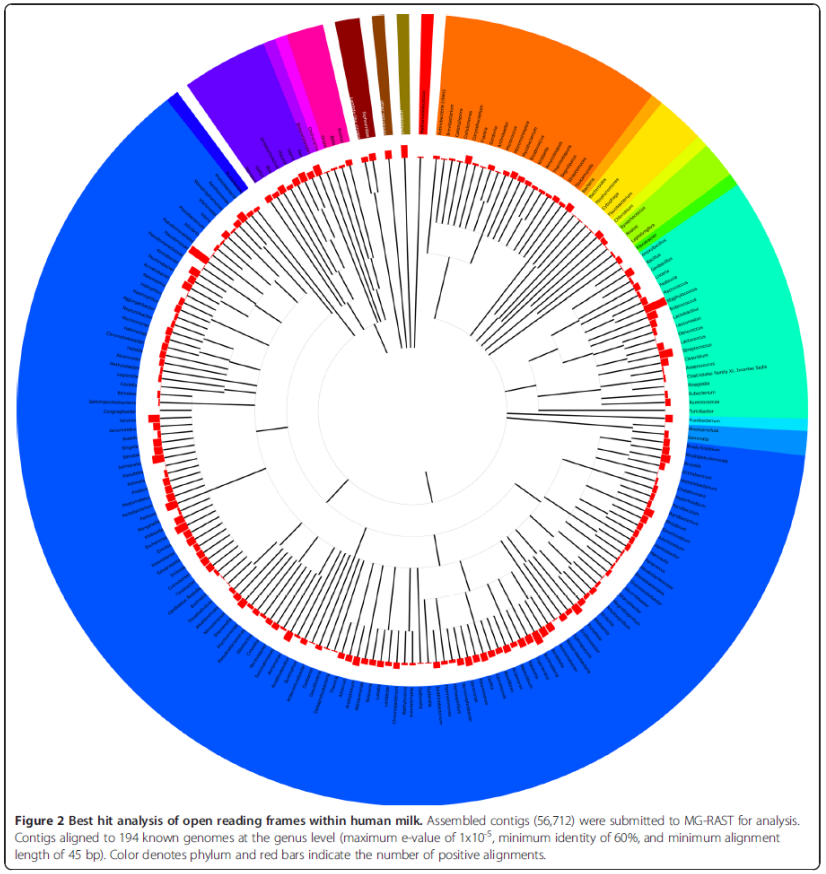
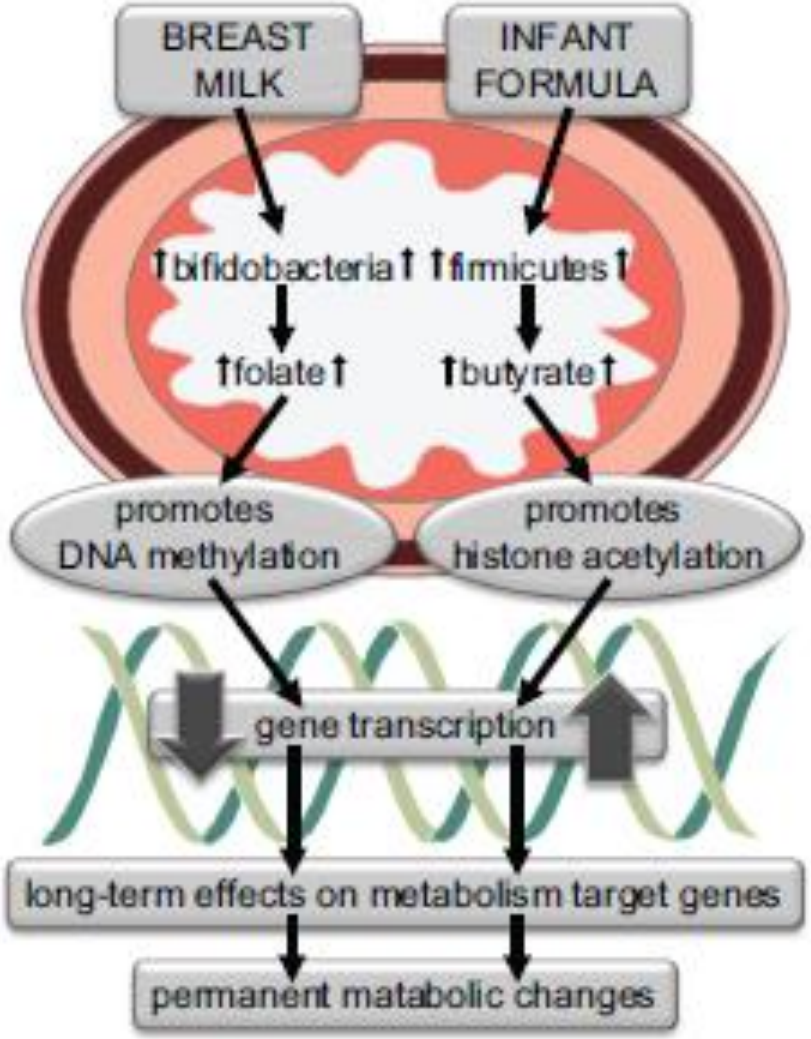


Figure 2 Best hit analysis of open reading frames within human milk. Assembled contigs (56,712) were submitted to MG-RAST for analysis. Contigs aligned to 194 known genomes at the genus level (maximum e-value of $1x10^{-5}$, minimum identity of 60%, and minimum alignment length of 45 bp). Color denotes phylum and red bars indicate the number of positive alignments.

- Pooled DNA from cells and bacteria in HM
- Open reading frames (ORF) in HM compared to stools of mom, BF infant, and FF infant
- Changes over time LI to LII
- HM DNA may contribute to colonization and immune modulation
- **Balance** of immune ***stimulatory*** effects of bacterial CpG's and immune ***suppressive*** effects of maternal and bacterial DNA present in HM

Ward TL et al BMC Microbiol. 2013 May 25;13:116

Link between nutrition, bacterial metabolites, and epigenetics



-Proposed mechanism between early nutrition and adult obesity

-Gut micro-flora produces differential metabolites

-methylation can enhance
-histone acetylation blocks

Mischke M. 2013
Jun 15;304(12):R1065-9

Functions of the Neonatal Microbiome

- Proper immune development
  - Balance of B, T cells
  - Tolerance, immunity, anti-inflammatory
  - Reduced risk of allergy and auto-immune diseases
- Signals neonatal cellular nuclei to transcribe specific genes
  - Toll-like receptors, leading to proper microbiome
  - Master genes to protect newborn
- Contributes to genes that signal normal metabolism

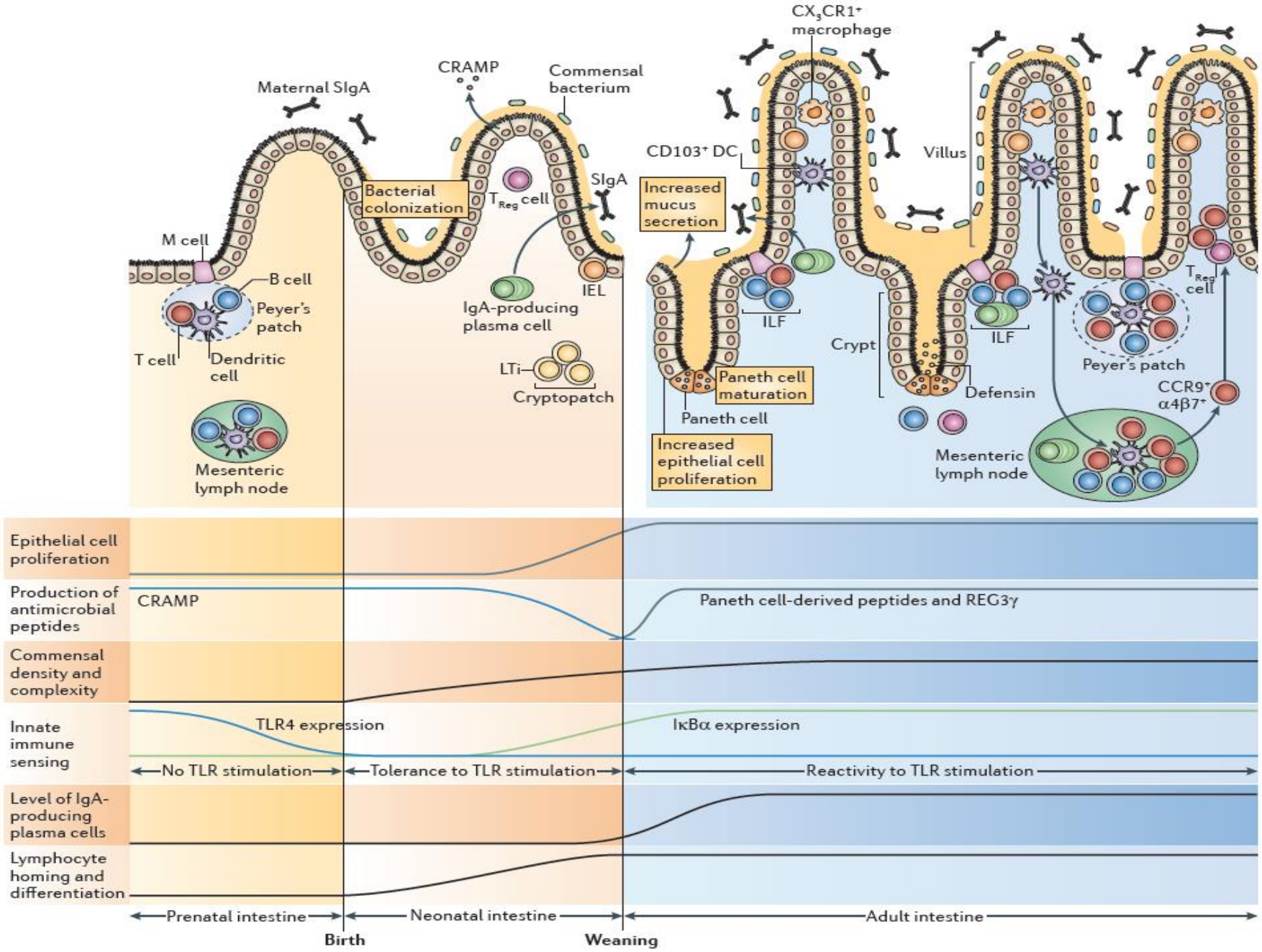
Mueller NT Trends in Molecular Medicine. Feb 2015

Normal Neonatal Microbiome

- Disruptors of the establishment of the normal neonatal microbiome include:
  - Any formula feeding
  - Maternal or neonatal antibiotics
  - Cesarean delivery
- Research Questions:
  - Can the normal microbiome be restored
  - Does restoration reduce risk of micro-biome related diseases?

Mueller NT Trends in Molecular Medicine. Feb 2015

Renz et al. Nature Reviews. 2012



EBF Influences Bacterial Diversity at Weaning

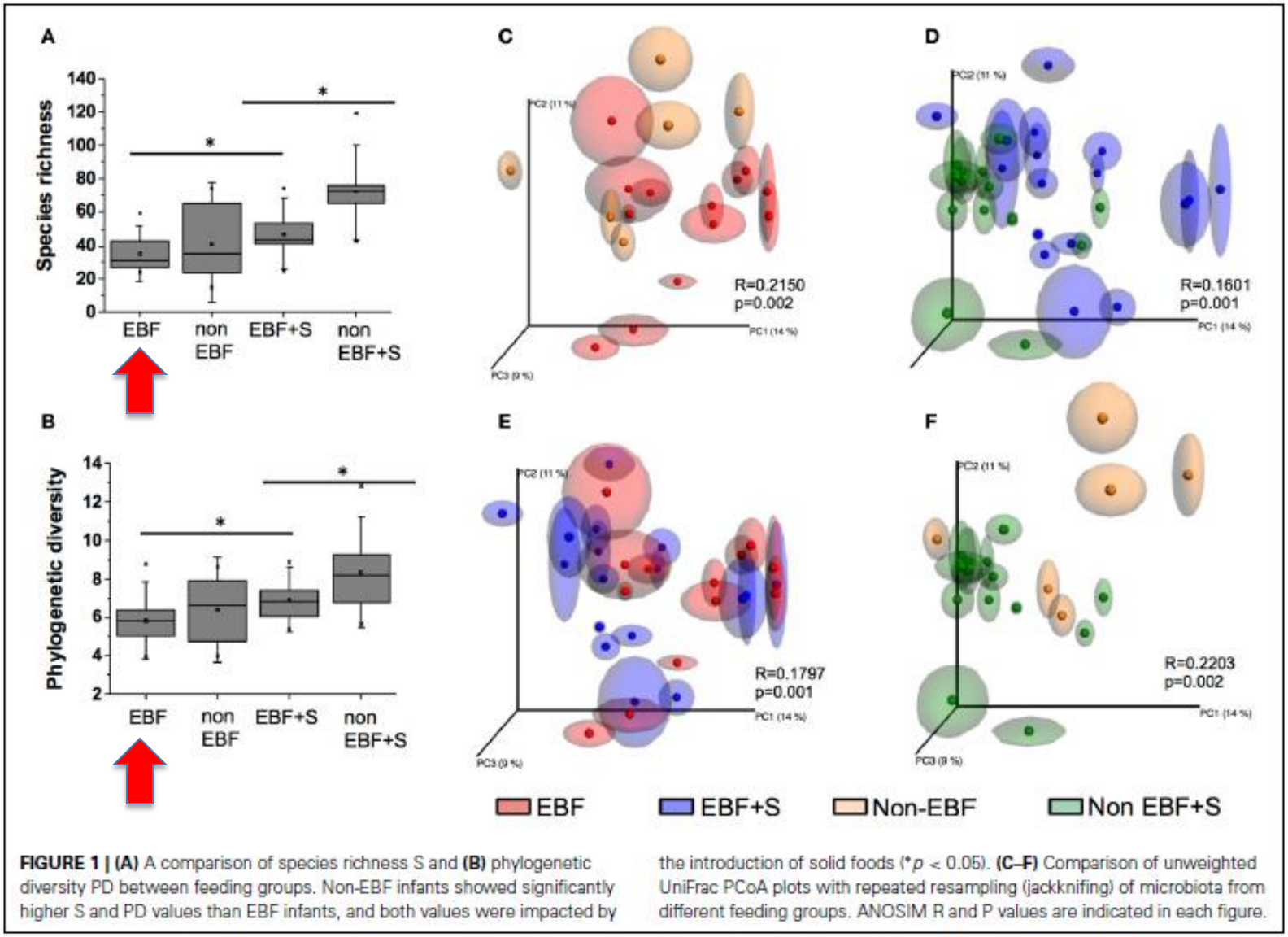


FIGURE 1 | (A) A comparison of species richness S and **(B)** phylogenetic diversity PD between feeding groups. Non-EBF infants showed significantly higher S and PD values than EBF infants, and both values were impacted by the introduction of solid foods (*$p < 0.05$). **(C–F)** Comparison of unweighted UniFrac PCoA plots with repeated resampling (jackknifing) of microbiota from different feeding groups. ANOSIM R and P values are indicated in each figure.

Azcarate-Peril A. *Frontiers in Cellular and Infection Microbiology Feb 2015*

Summary of Human Milk Influences on Gut Mucosa

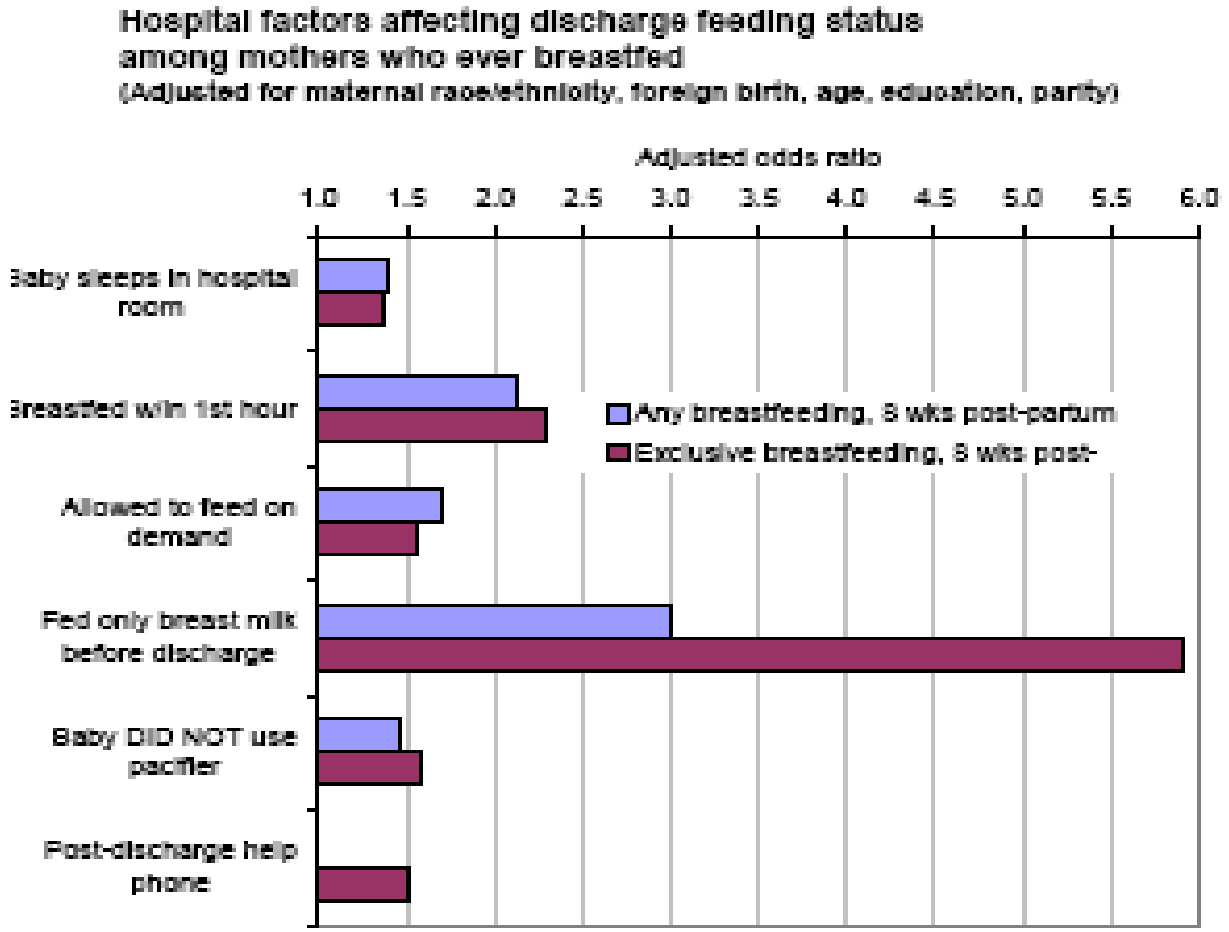
Oral Tolerance-necessary to prevent systemic hypersensitivity, mediated through regulatory T cells, T cell anergy and clonal deletion

Gut Colonization-via maternal milk and vaginal birth hosted by appropriate down regulation of Toll-like receptors

Microbiota-Epithelial Crosstalk-structurally arranges lymphoid cells and signaling mRNA transcripts for specific TLR expression

Induction of Intestinal Immune System-induction of ILF, peyer's patches and mesenteric lymph nodes

Supplementation in the Delivery Hospital Leads to Weaning by 6 weeks post-partum



NJ PRAMS

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Culture of Supplementation

- Market influence
- Nurse training and culture
- Physicians' worry…
  - Dehydration
  - Jaundice
  - Hypoglycemia
  - Litigation!

Reasons to Supplement

- Unresponsive hypoglycemia
- Severe maternal illness (psychosis, eclampsia, shock)
- Mother not available (maternal transfer)
- Galactosemia
- Infant unable to feed at breast (illness, congenital malformation)
- Few maternal medications
- LBW and sufficient milk is not available
- Delayed lactogenesis II (retained placenta, Sheehan), or primary glandular insufficiency
- Intolerable pain

When supplements are NOT Needed

- Colostrum QNS
- Teach how to use bottle
- Growth/appetite spurts, cluster feed
- Prevent Wt. loss
- Prevent hyperbilirubinemia
- Quiet a fussy baby
- Sleepy baby
- Let mother sleep
- Prevent hypoglycemia
- Breastfeeding “too” long to prevent damage and sore nipples

Another Reason NOT to Supplement

- Joint Commissions
- **Set Measure ID:** PC-05 & PC-05a
- **Performance Measure Name:** Exclusive Breast Milk Feeding
- **Description:** Exclusive breast milk feeding during the newborn's entire hospitalization

The Joint Commission PC-05 Mandate

Benchmark

Improving Performance on Perinatal Care Measures

Quality improvements in essential areas of patient safety, including perinatal care, rely on the performance of specific tasks. To help assess the effectiveness of patient care, The Joint Commission requires hospitals to submit data reports based on measures that meet certain criteria. These accountability measures are organized into "measure sets," which are a unique group of action items specifically selected to optimize the care provided in each area.

Currently, general medical/surgical hospitals are required to submit data for a minimum of 4 measure sets (out of 14) via a vendor that has been evaluated and listed by The Joint Commission. This will change, however, in 2014. Beginning January 1, hospitals must submit data for 6 measure sets. According to the new guidelines, some of these sets will be mandatory for hospitals. Others will be discretionary. A number of health care organizations that are involved in perinatal care supported adoption of the measure (*see* the box on page 18).

Perinatal care will fall under the mandatory column for hospitals with 1,100 or more births annually. The Joint

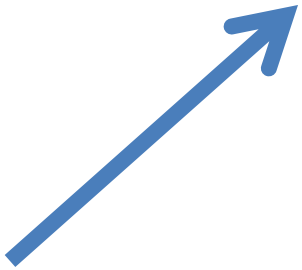
Beginning January 1, 2014, hospitals that see more than 1,100 births annually will be required to submit data on the Perinatal Care Measure Set.

- PC-03 Antenatal steroids
- PC-04 Health care–associated bloodstream infections in newborns
- PC-05 Exclusive breast milk feeding
- PC-05a Exclusive breast milk feeding considering mother's choice

A New Core Measure Set

The PC Core Measure Set comprises 5 main measures:

PC-01: Elective delivery
PC-02: Cesarean section
PC-03: Antenatal steroids
PC-04: Health care associated bloodstream infections in newborns
PC-05: Exclusive breast milk feeding



Mandatory in January 2014 PC-05 and PC-05a

- TJC defines exclusive breast milk feeding as newborn receiving only breast milk and no other liquids or solids except for drops or syrups consisting of vitamins, mineral, or medicines.
- Breast milk feeding includes expressed mother's milk as well as donor human milk, both of which may be fed to the infant by means other than suckling at the breast.

Mother's Intention to Breastfeed

- Ask on admission…How do you intend to feed your baby? (response options)
  - **Breastfeeding** (interpreted as exclusive breastfeeding, breast milk feeding)
  - **Combination** breastfeeding or breast milk feeding plus formula
  - **No breastfeeding** (formula only)
  - **Unsure**
- Then provide skin to skin care
  - If breastfeeding happens then revisit with question, how would you like your infant be fed while here in the hospital? (up to 4 hours)

Exclusive Human Milk Feeding – Considering Mothers' Intention (Joint Commission PC05a)

- **MEASURE: Percent of infants receiving human milk feedings exclusively throughout hospital stay (from birth to discharge), who do not have Joint Commission "allowable" reasons to be excluded (including intention)**

- **Exclusions: There is <u>MD/APN/CNM/IBCLC/CLC documentation</u> that:**
  - Infant's mother has medical contra-indication to breastfeeding (AV1)
  - Infant's mother stated intention not to breastfeed or to partially breastfeed at admission (AV2)
  - Infant has a a clinical "reason for not exclusively feeding breast milk" (AV3)
  - Infant's mother changed her intention to exclusively breastfeed to partial / no breastfeeding (AV3)

Summary of the Core Measure

- Numerator, all breast milk (at breast or breast milk given by another method-cup, syringe, sns, bottle)
- Denominator PC-05 – all term singleton newborns without a contraindication
- PC-05a same just mom has to say she wants to breastfeed (exclusively)
- Medical indications to supplement are NOT exclusions to denominator

What is the role of the clinician?

- Present data on dashboard and at departmental meetings
- Develop action plans to decrease supplementation
- Help write or revise hospital policies
- Educate on the risks of supplementation
- Provide or refer for breastfeeding management
- Use QI strategies

Supplementing Breastfeeding

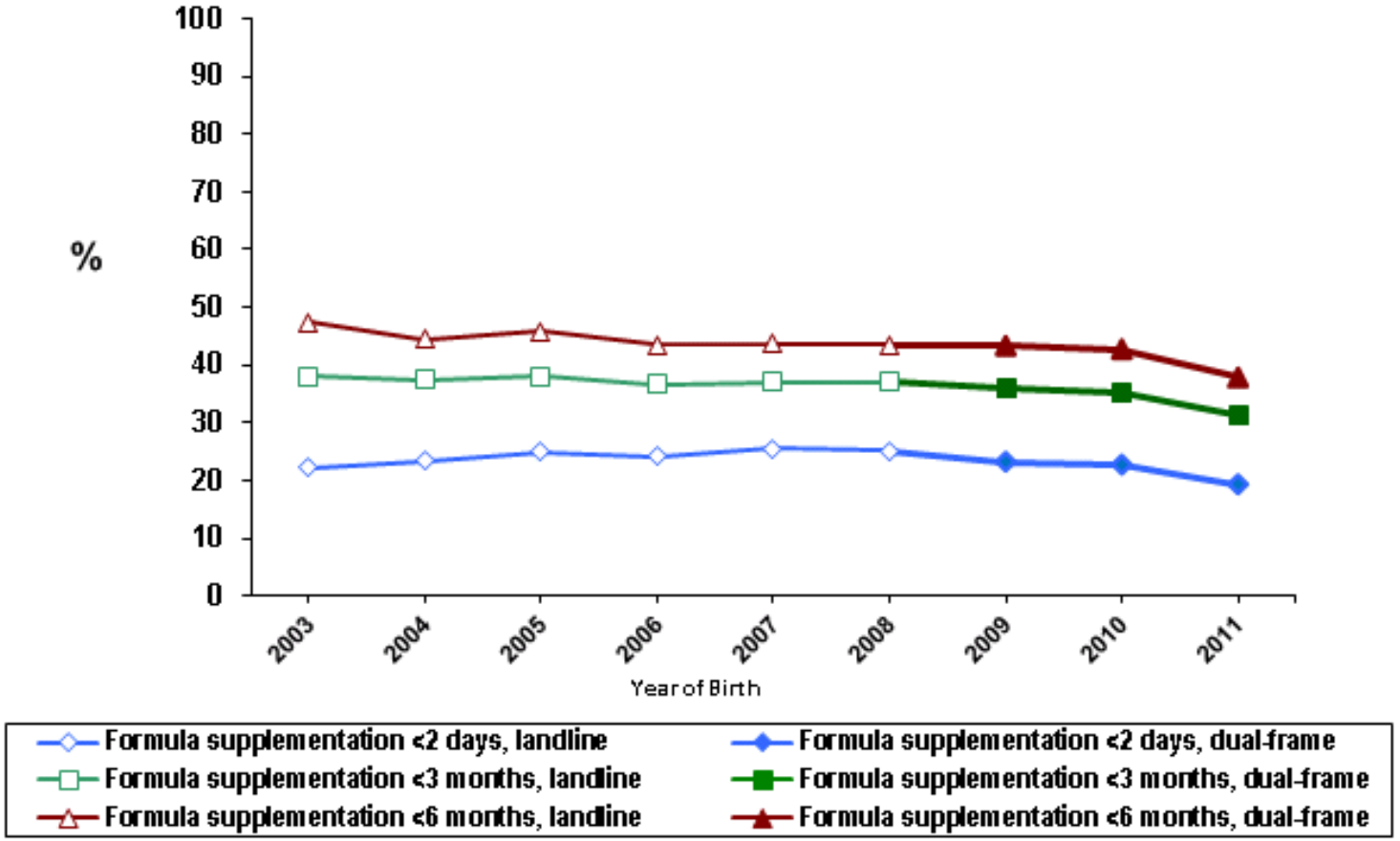
- What are medical indications for supplementation?
- Not the same as TJC defined reasons to use formula (these are medical *contraindications* to breastfeed)
- Weight loss?
- Jaundice?
- Hypoglycemia?
- Others?

Primum Non Noceri

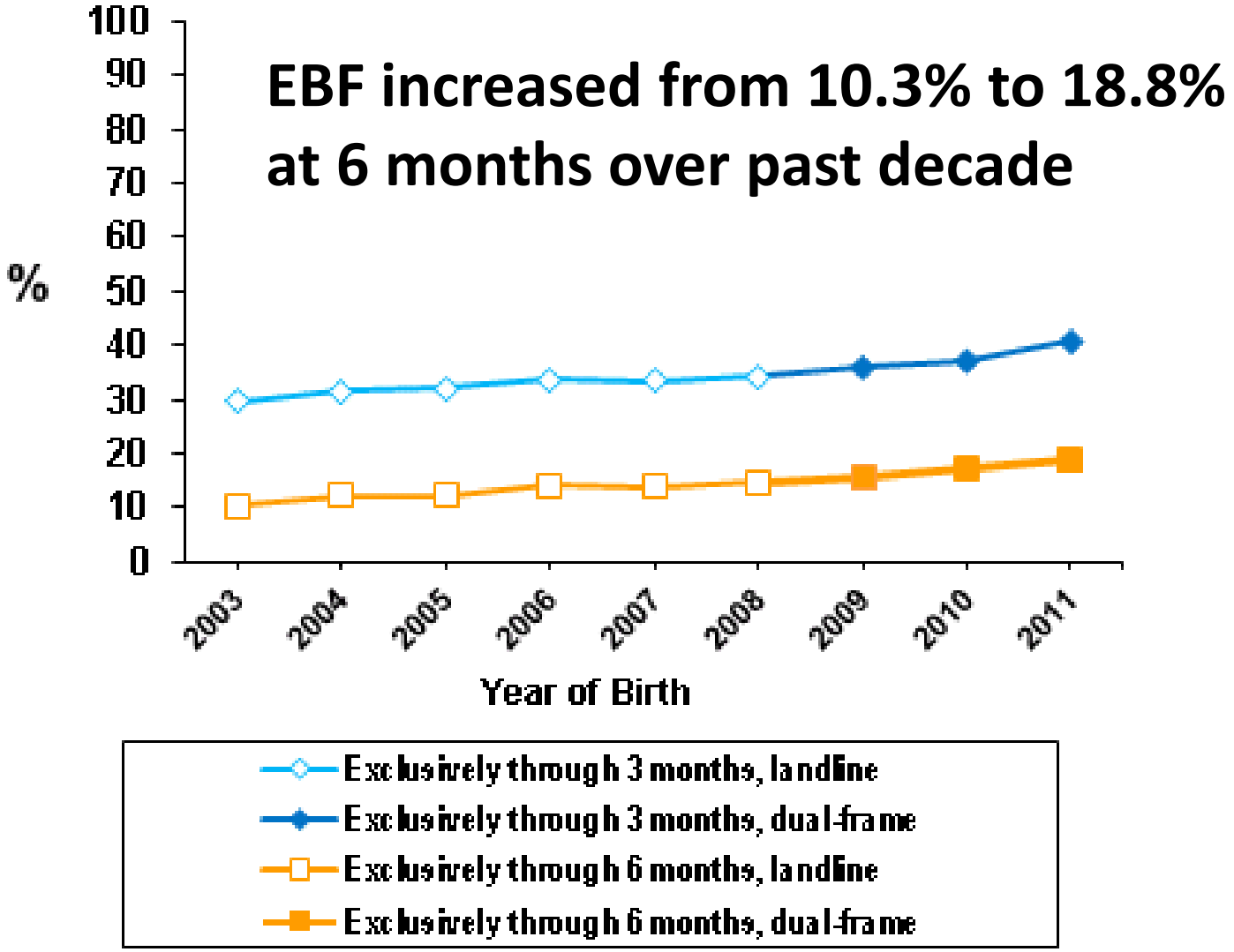
"First do no harm!"

Updated CDC NIS Data

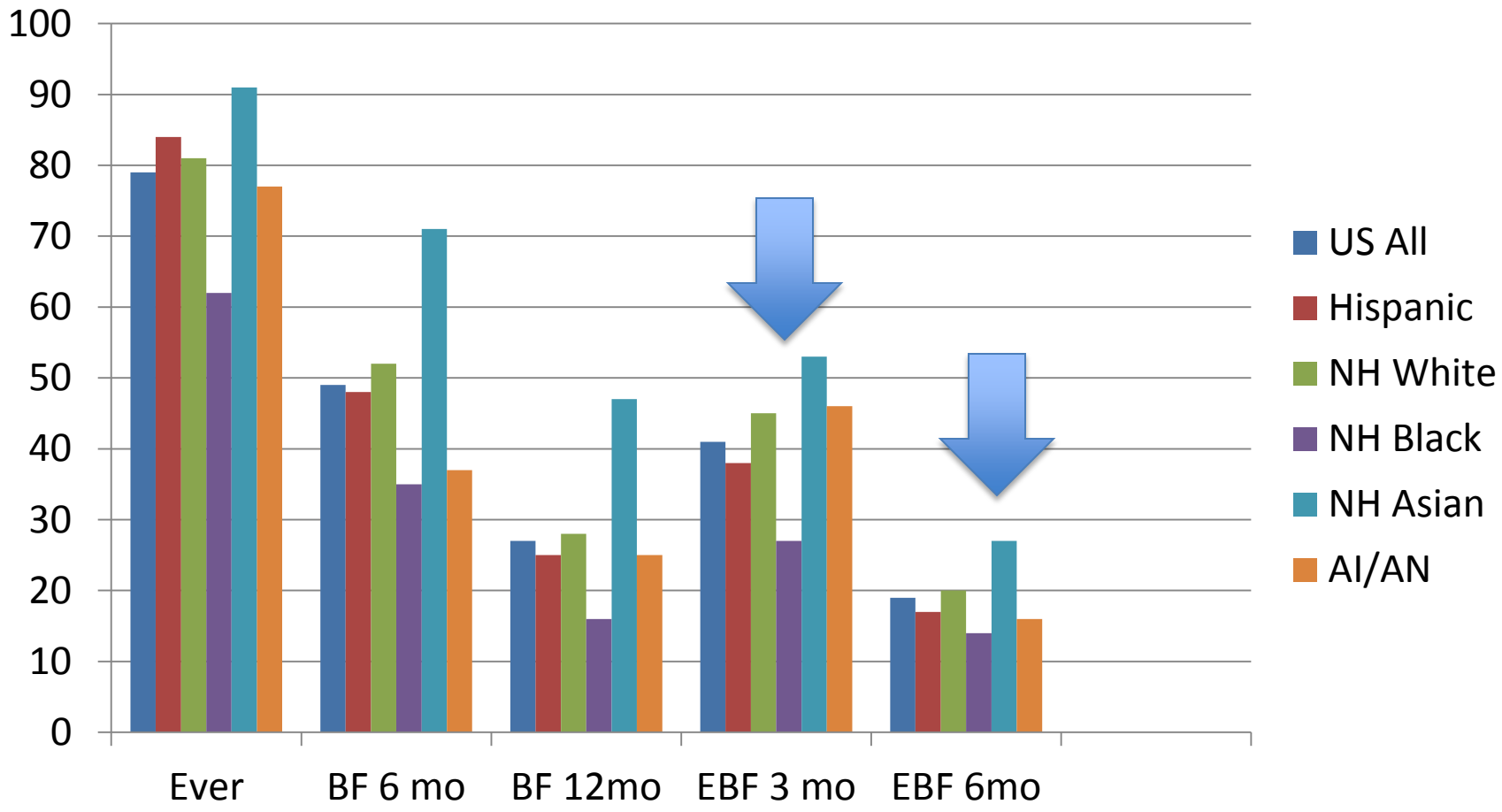
Less supplementation before 2 days from 22.3% to high of 25.6% now down to 19.4%



Updated CDC NIS Data



Focus on Disparities

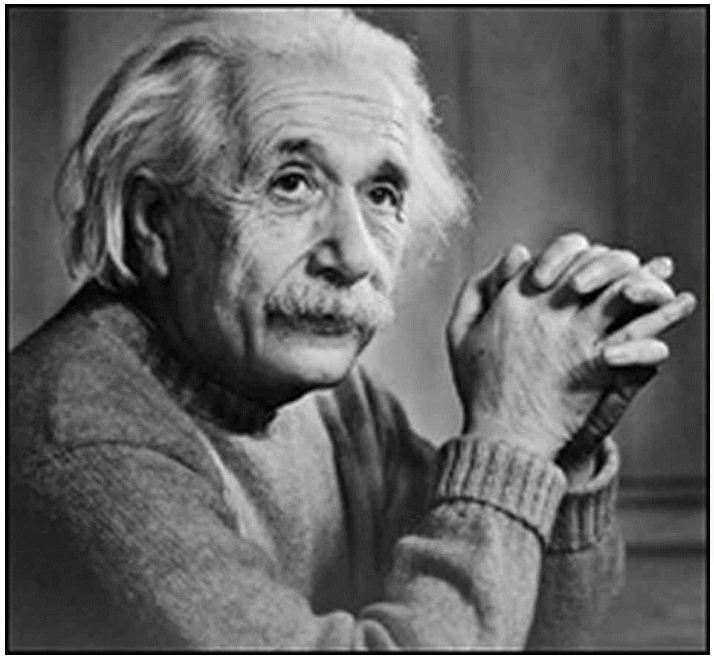


CDC NIS Data from 2011

Conclusions

- Exclusive breastfeeding produces optimal health outcomes-know the science
- Exclusive breastfeeding requires support in multiple dimensions
- Physicians are necessary to support exclusive breastfeeding
- The Baby-Friendly Hospital Initiative, using quality improvement methods, helps to support exclusive breastfeeding

"If you always do what you always did, you will always get what you always got."



-Albert Einstein