

# Probiotics, Prebiotics, Oral Tolerance

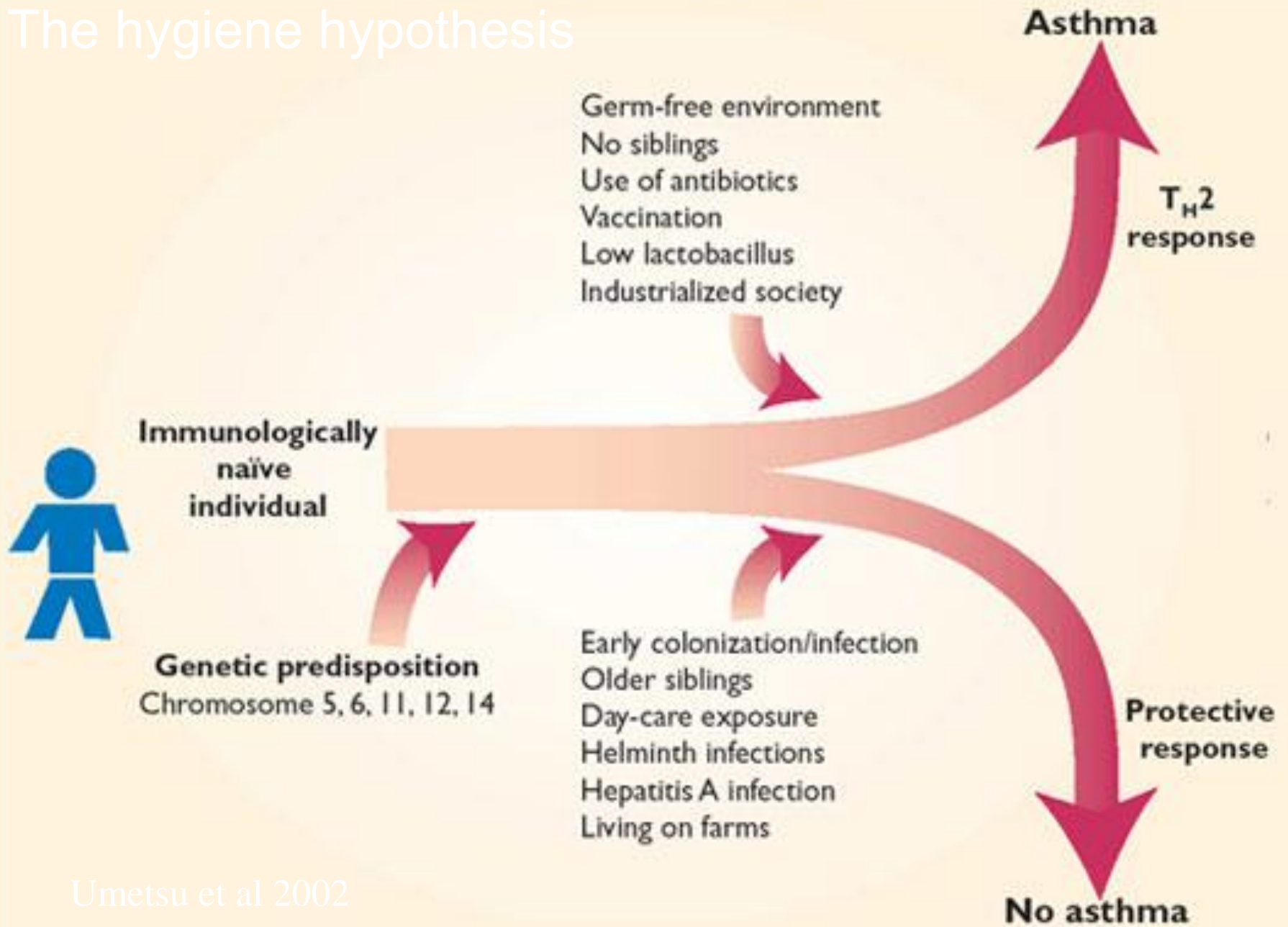


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# The hygiene hypothesis



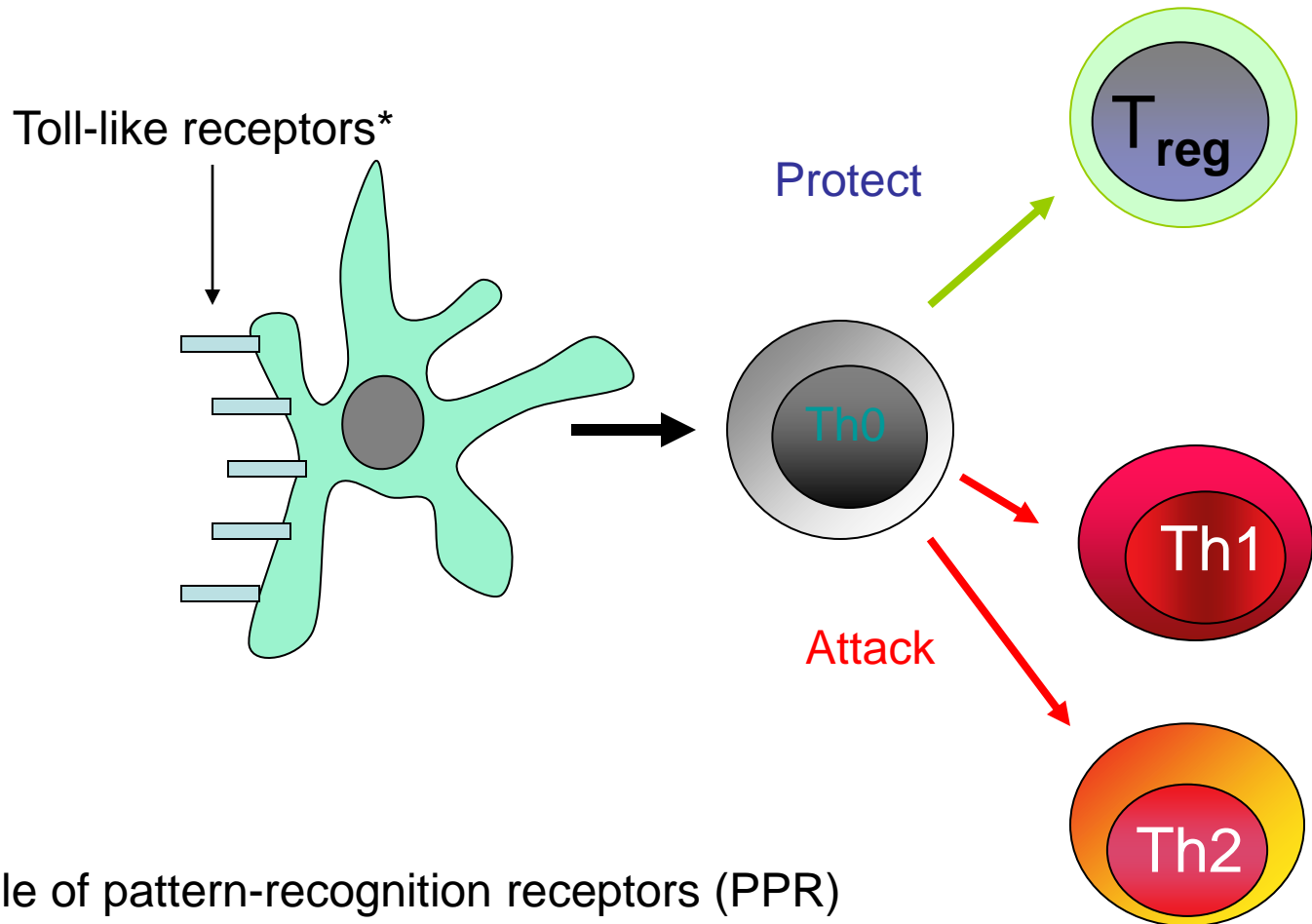
Umetsu et al 2002



1.0 μm

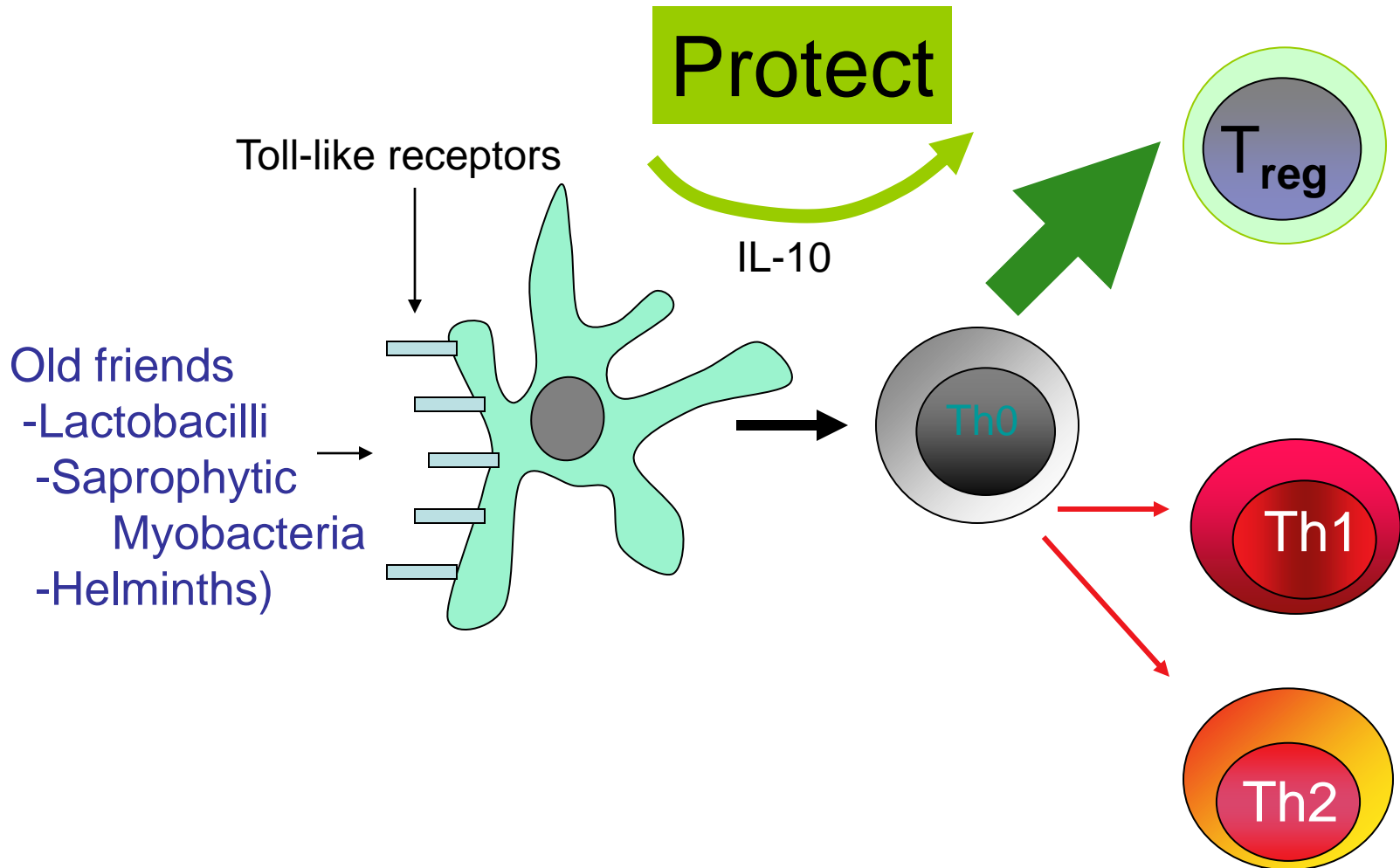


# Dendritic cells identify friend or foe

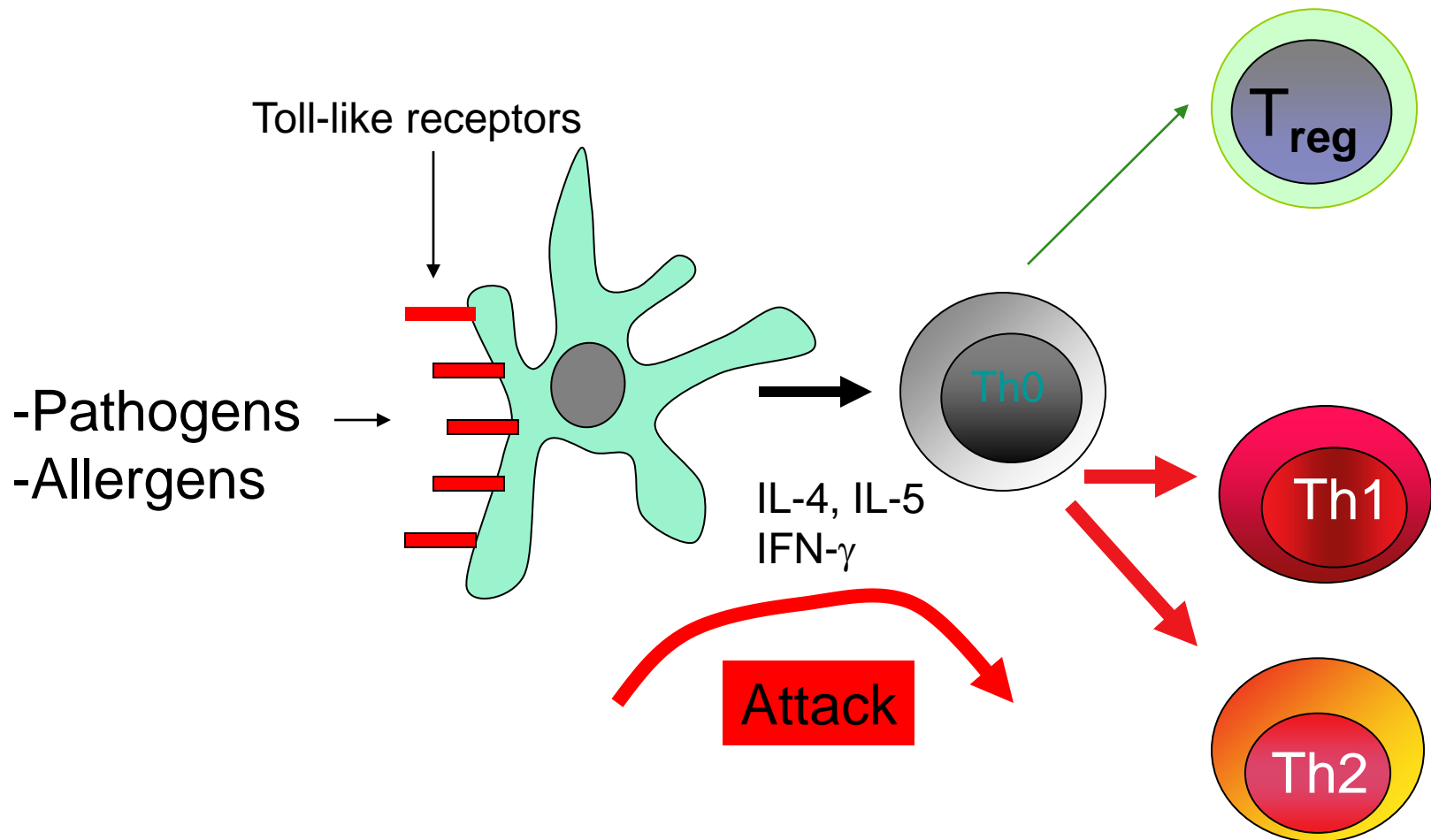


\*Example of pattern-recognition receptors (PPR)  
Recognise Pathogen-associated patterns (PAMP's)

# Dendritic cells identify friend or foe



# Dendritic cells identify friend or foe



# Probiotics and Prebiotics for Allergic Disease

**Probiotics** – live microorganisms which when administered in adequate amounts confer a health benefit on the host

**Prebiotic** – a selectively fermented ingredient that allows specific changes, in the composition and/or activity in the gastrointestinal microbiota, that confers benefits upon host well-being and health

**Synbiotic** – a combination of pro and prebiotic

# Health Benefits of Probiotics

The precocious old  
age of ruminants...  
coincides with an  
extraordinary  
richness of the  
intestinal flora<sup>1</sup>



## SCIENTIST'S BAN ON SOUR-MILK GERM

Bacillus Bulgaricus Lauded by  
Metchnikoff Is of No Value,  
a Yale Man Says.

<sup>1</sup>*Prolongation of Life: Optimistic Studies 1906*



# Health Benefits of Probiotics

- Treatment of infectious diarrhoea<sup>1</sup>
- Prevention of antibiotic associated diarrhoea<sup>2</sup>
- Prevention of flares of chronic pouchitis<sup>3</sup>
- Prevention of necrotising enterocolitis<sup>4</sup>

<sup>1</sup> Allen Cochrane Database Syst Rev. 2003:CD003048

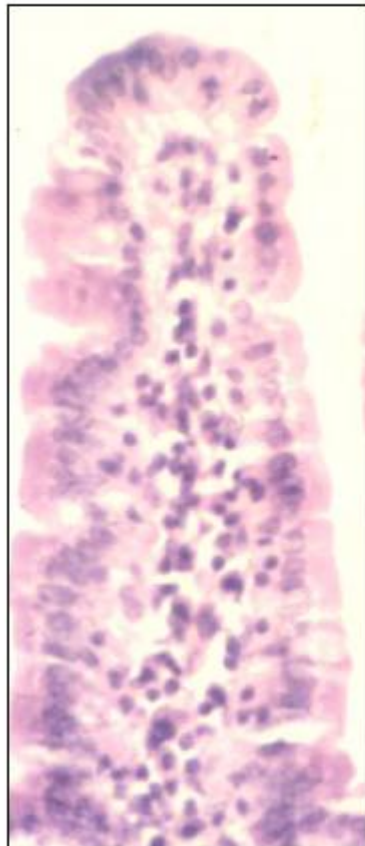
<sup>2</sup> D'Souza BMJ 2002;324:1361

<sup>3</sup> Gionchetti Gastroenterology 2000;119:305-9

<sup>4</sup> Alfaleh Cochrane Database Syst Rev. 2008:CD005496

# Intestinal Microbes and Immune Development

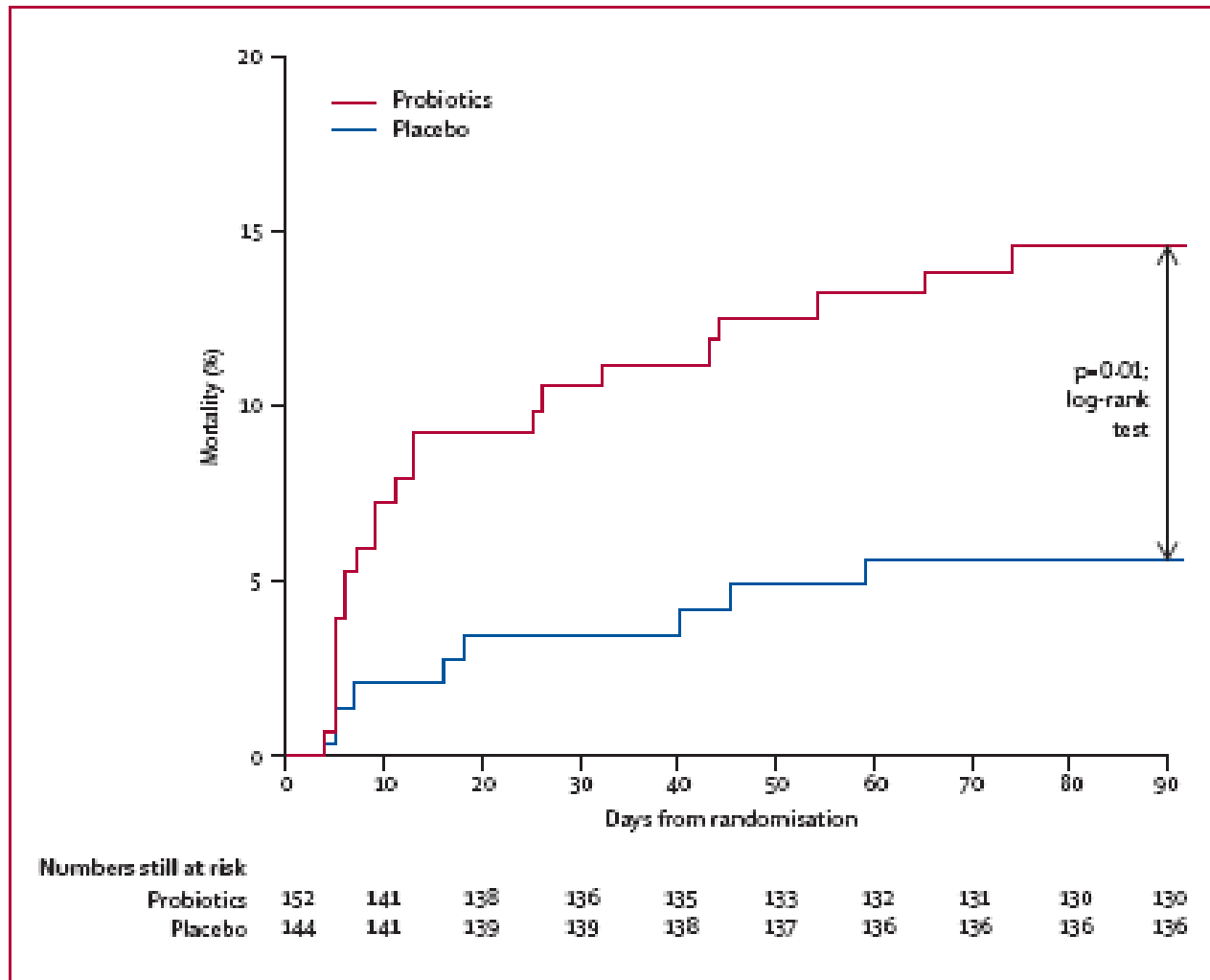
Normal mouse



Germ-free mouse



# Probiotic Safety – Fatal Bowel Ischaemia



# Intestinal Effects of Probiotic Bacteria

TLR signalling by microbes  epithelial repair<sup>1</sup>

Inhibit NF- $\kappa$ B activation in intestinal epithelial cells<sup>2</sup>

Reduce intestinal inflammation/permeability in eczema<sup>3</sup>

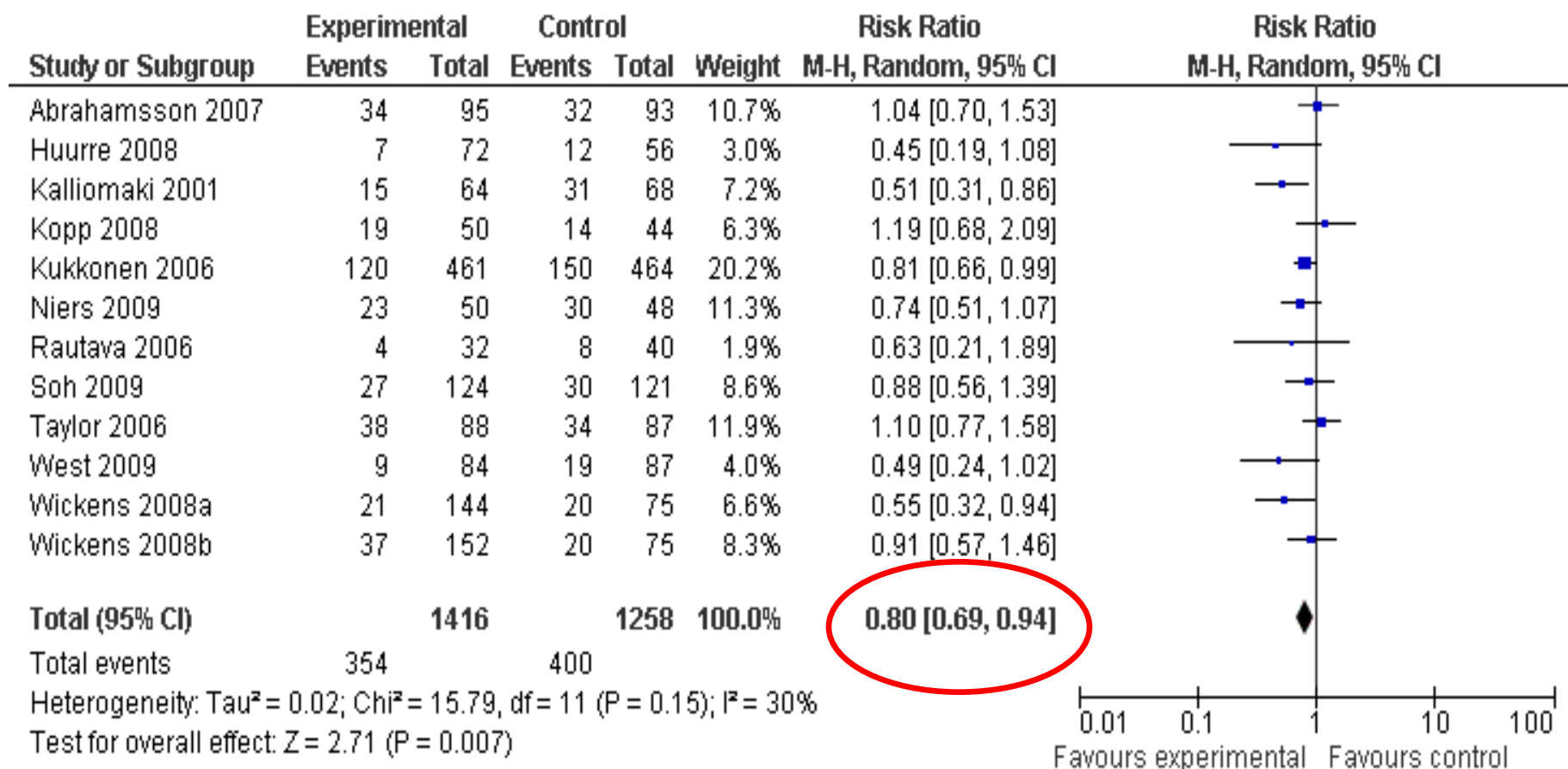
<sup>1</sup>Cell 2004;118:229-41 <sup>2</sup>Nat Immunol 2004;5:104-12

<sup>3</sup>J Pediatr 2004;134:612-6

# Systemic Immune Effects of Probiotics

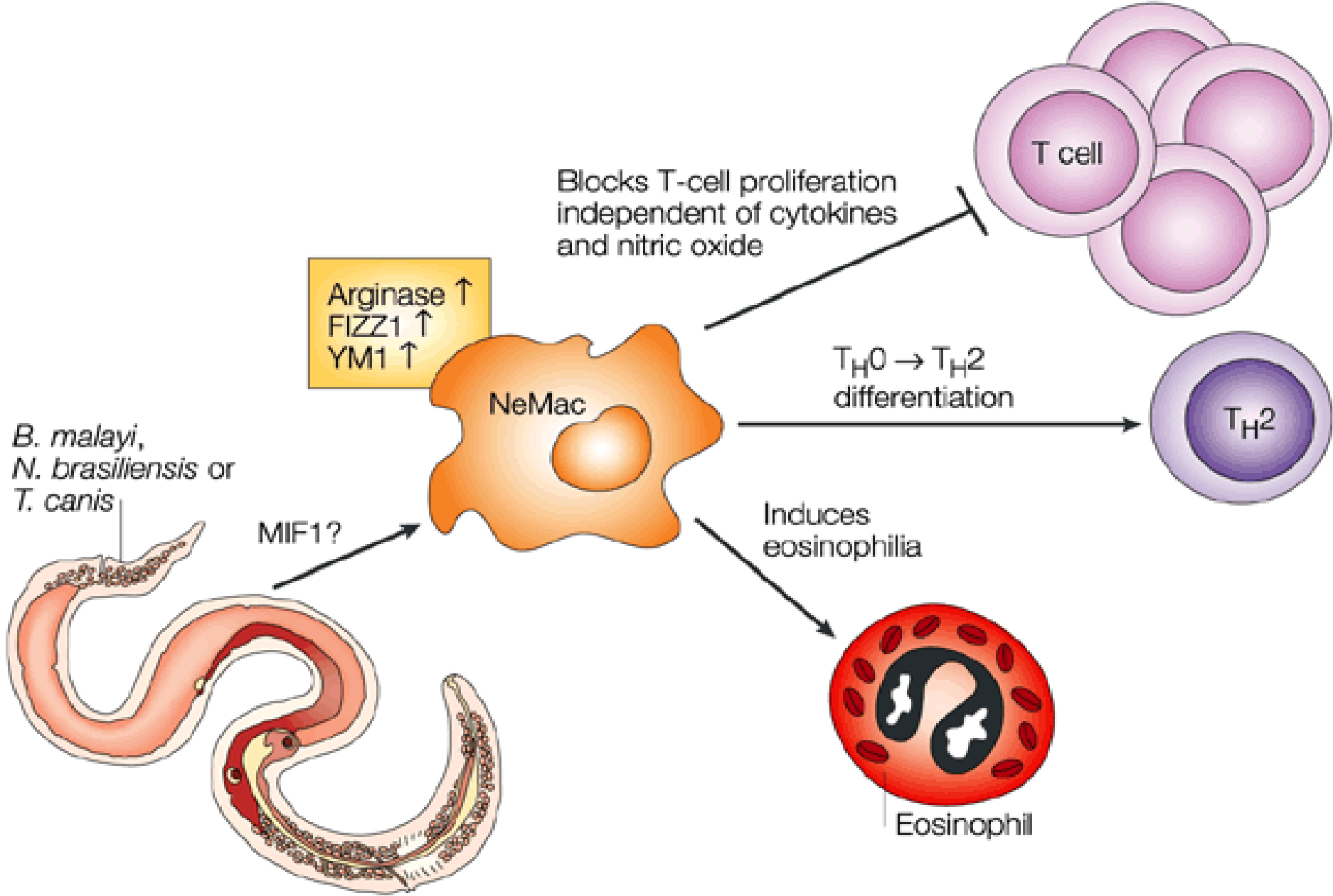
	Probiotic	Placebo	P value
Median CRP all infants	0.19	0.09	0.008
Median CRP infants with eczema	0.18	0.06	0.008

# Probiotics for Eczema Prevention ?









# Reduced helminth burden increases allergen skin sensitization but not clinical allergy: a randomized, double-blind, placebo-controlled trial in Vietnam

C. Flohr<sup>1,2</sup>, L. N. Tuyen<sup>3</sup>, R. J. Quinnell<sup>4</sup>, S. Lewis<sup>5</sup>, T. T. Minh<sup>3</sup>, J. Campbell<sup>2</sup>, C. Simmons<sup>2</sup>, G. Telford<sup>6</sup>, A. Brown<sup>6</sup>, T. T. Hien<sup>7</sup>, J. Farrar<sup>2</sup>, H. Williams<sup>8</sup>, D. I. Pritchard<sup>6</sup> and J. Britton<sup>5</sup>

Table 2. Effect of anti-helminthic treatment on study outcomes at 12 months' follow-up

	Anti-helminthic treatment, <i>N</i> (%)	Placebo, <i>N</i> (%)	Size of effect*	<i>P</i> -value
Children infected with <i>A. lumbricoides</i> at baseline				
Total	52 (50.5)	51 (49.5)	–	–
Skin sensitization				
Any allergen	20 (38.5)	9 (17.6)	4.90 (1.48–16.19)	0.009
Rhinitis since start of treatment (questionnaire)	50 (6.7)	36 (4.9)	1.39 (0.89–2.15)	0.1
Flexural dermatitis since start of treatment (skin examination)	7 (0.9)	6 (0.8)	1.15 (0.39–3.45)	0.8
Skin sensitization				
Any allergen	251 (33.4)	207 (28.1)	1.31 (1.02, 1.67)	0.03

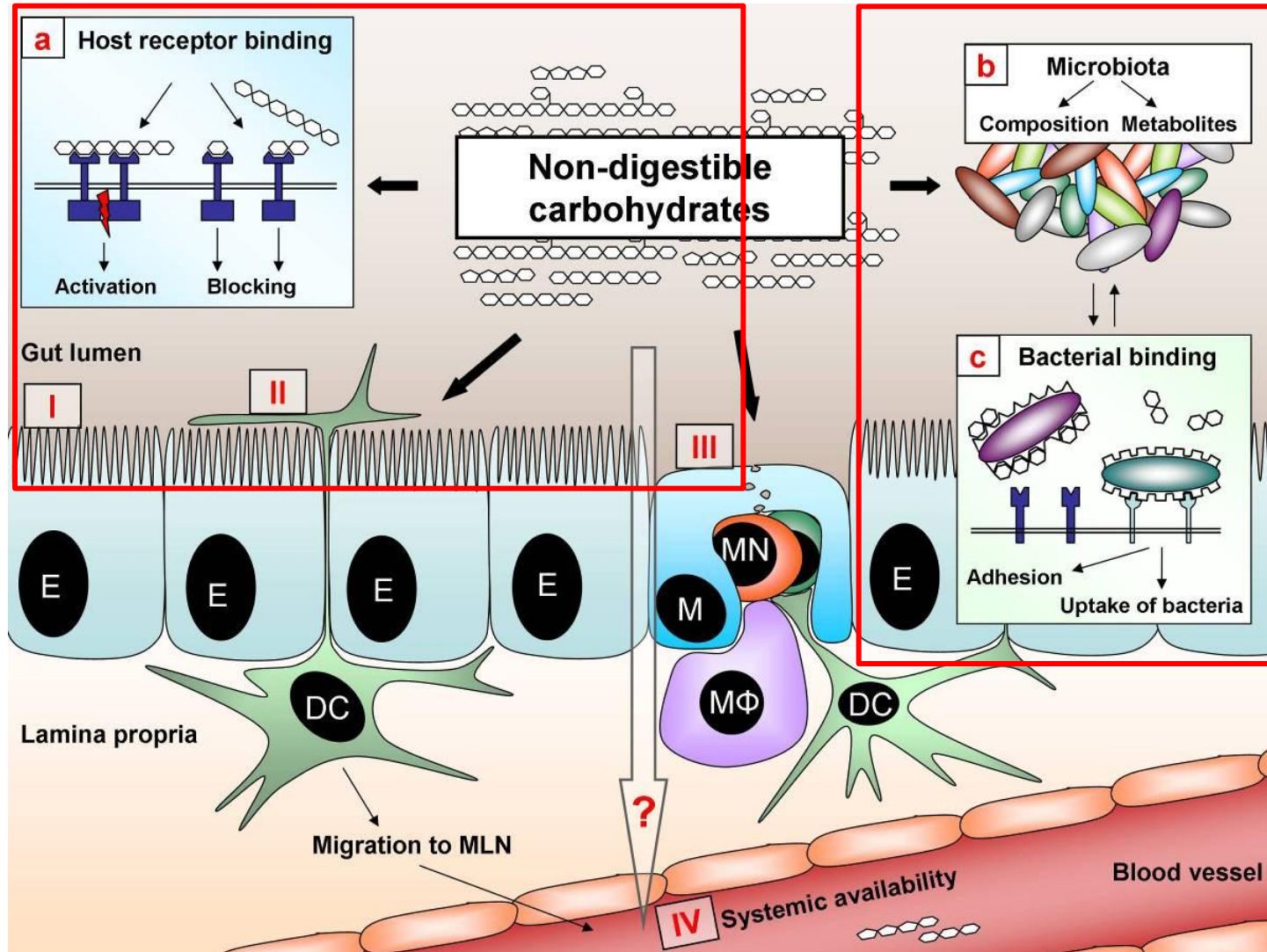
# PREBIOTICS

# Prebiotics

- Major Constituent of Human Breast Milk
- Present at 10g/l
- Encourage proliferation of bifidobacteria in the infant large intestine
- May also have direct immune effects on developing infant GALT

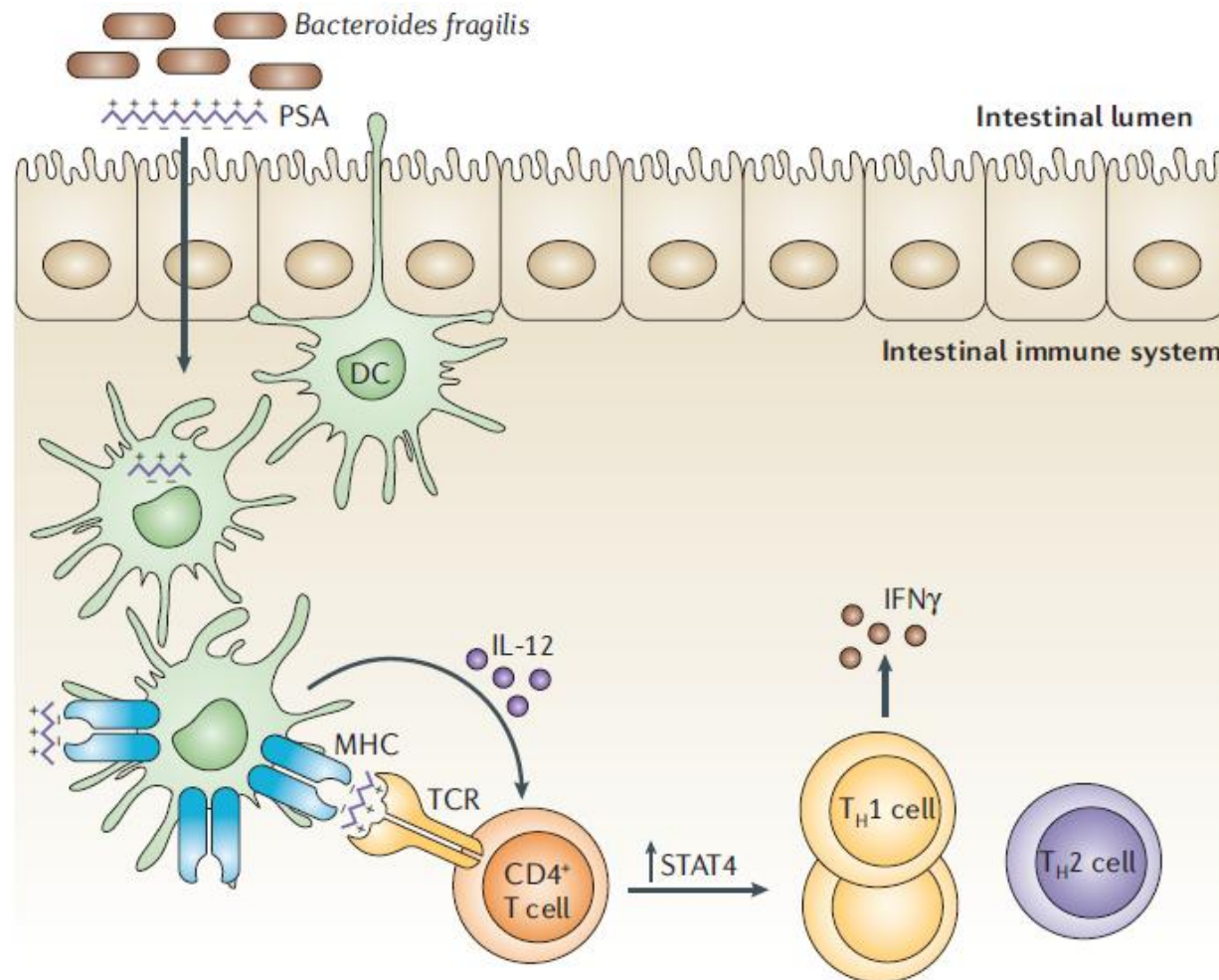


# Immune Modulation by Prebiotics

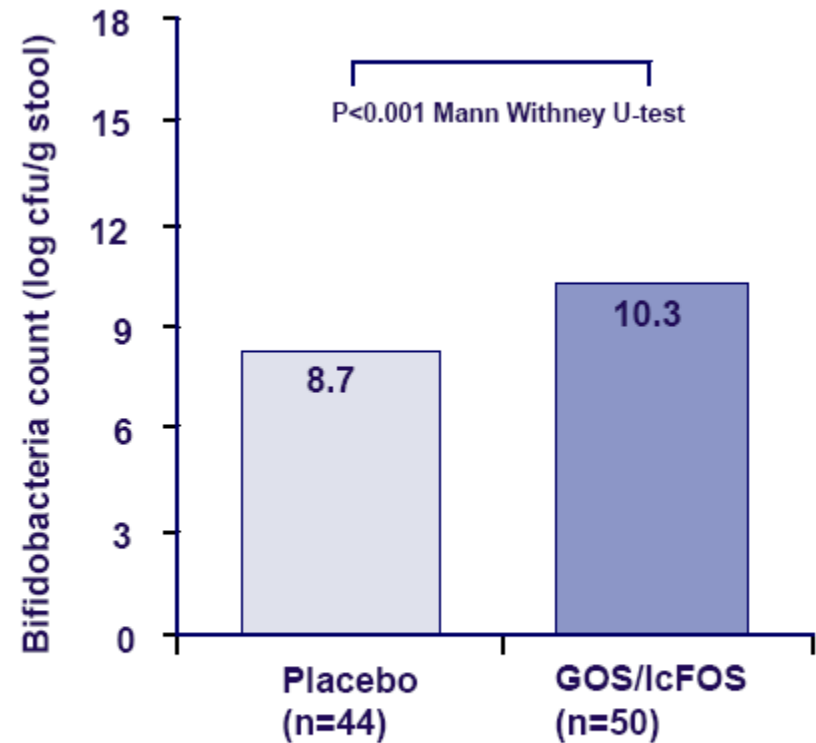
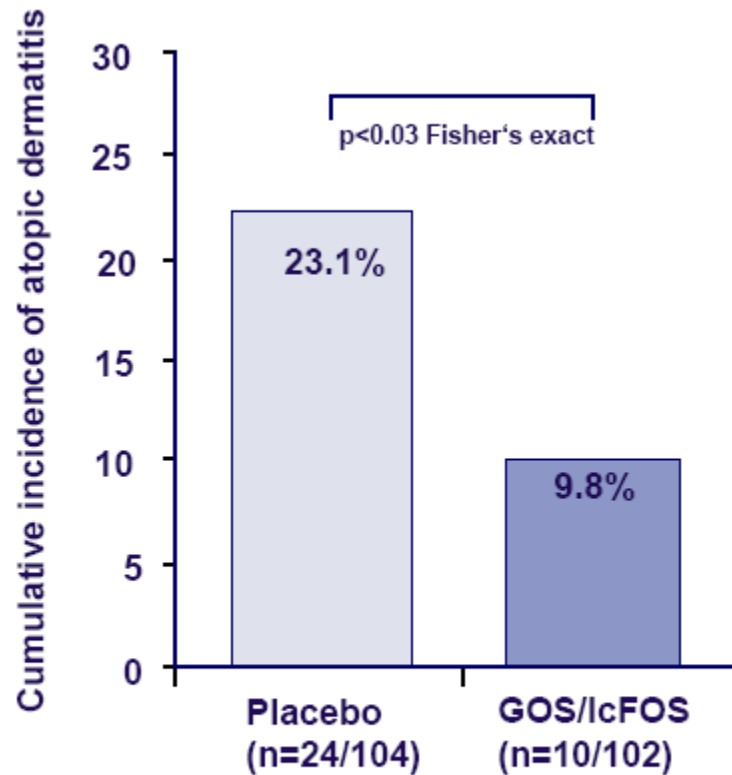


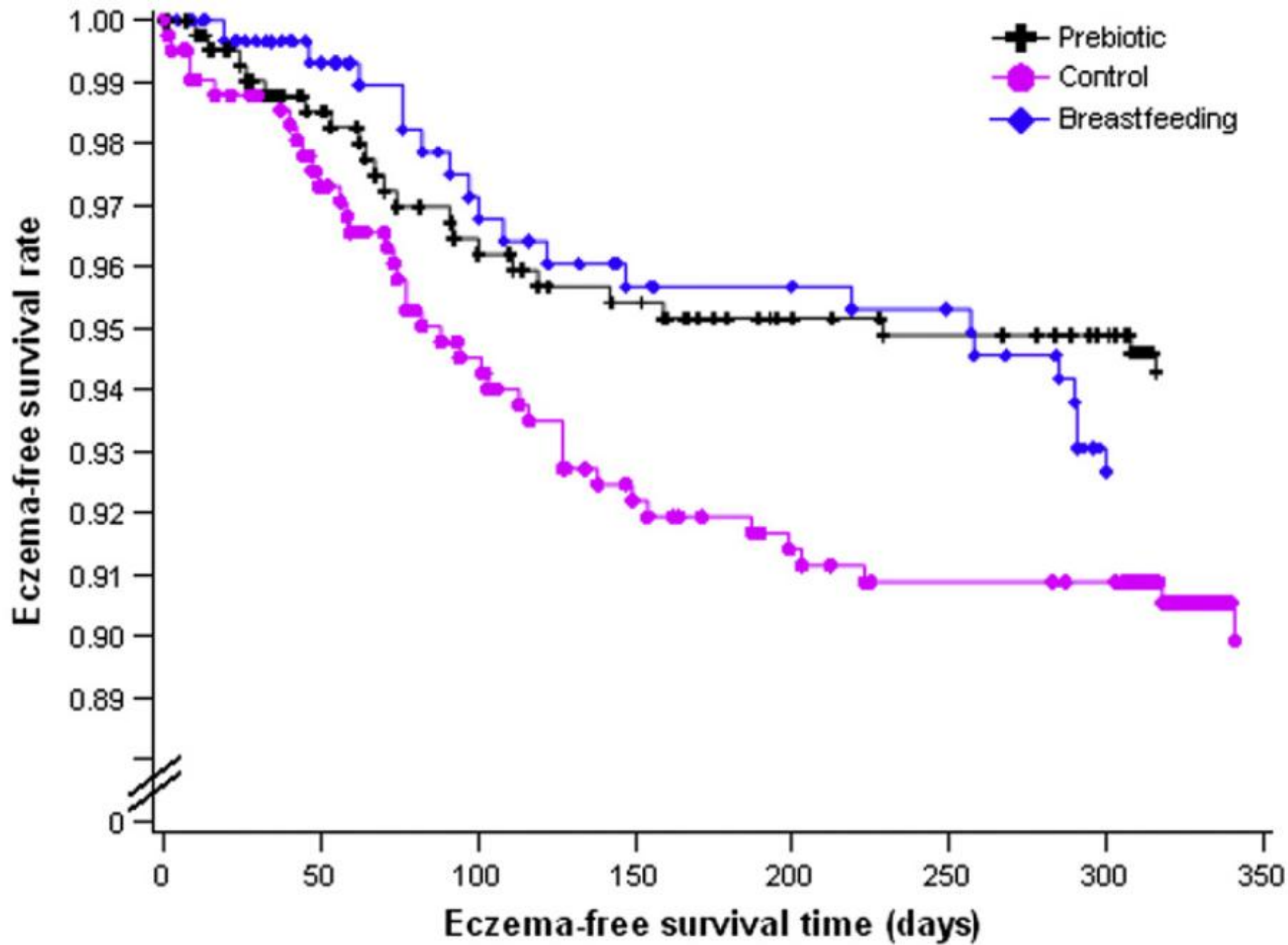


# Immune Modulation by Carbohydrates

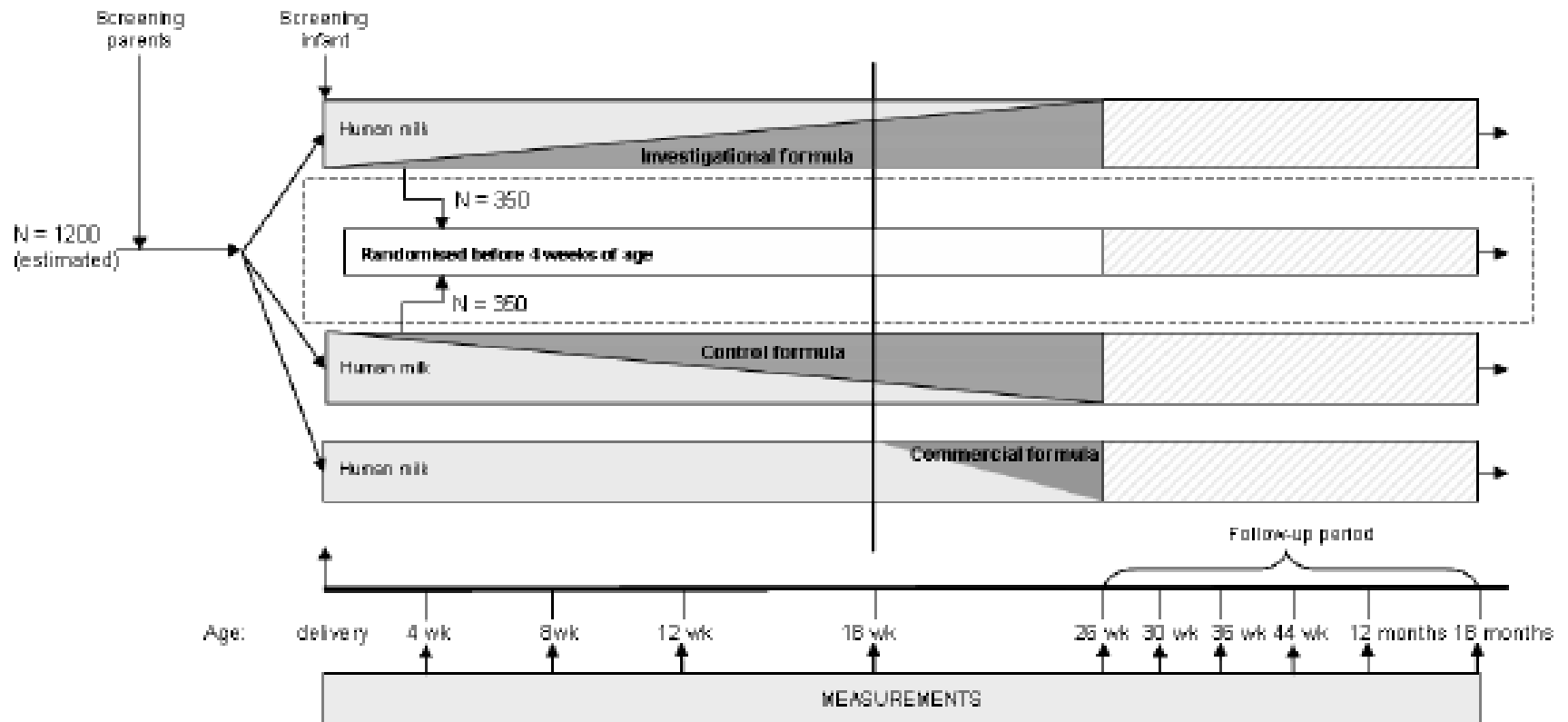


# Prebiotics alter Intestinal Microbiota





# PATCH – study design



# PATCH

## Participating sites



### United Kingdom

- Poole
- Salisbury
- London



### Ireland

- Cork

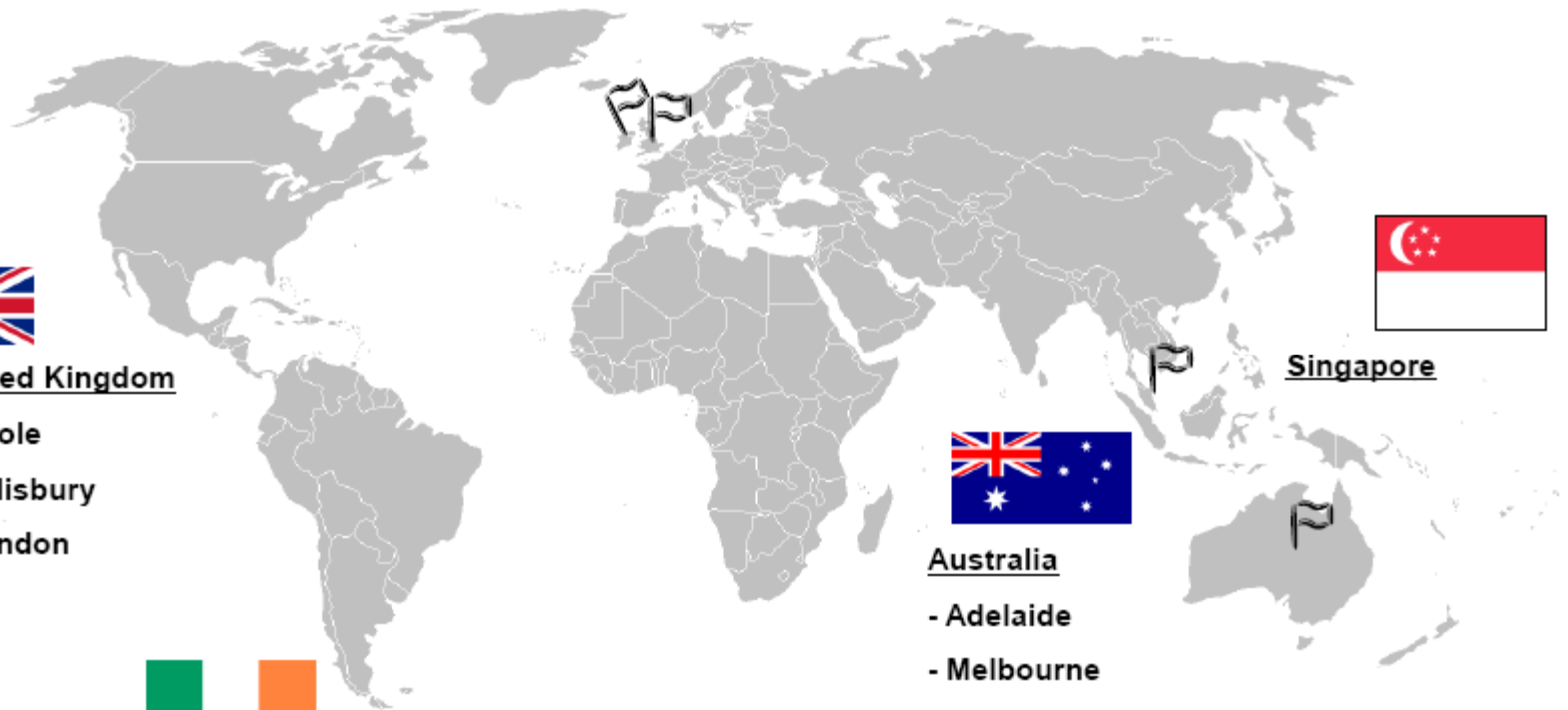


### Australia

- Adelaide
- Melbourne
- Gold Coast
- Brisbane
- Sydney



### Singapore



# Conclusions

- Microbial exposures may be important for preventing the onset of allergic sensitisation / disease
- Probiotics are relatively safe microbial exposures which may be helpful in this regard
- Prebiotics may reduce the risk of eczema in formula fed infants
- Treatment of helminth infestation increases skin prick test sensitivity