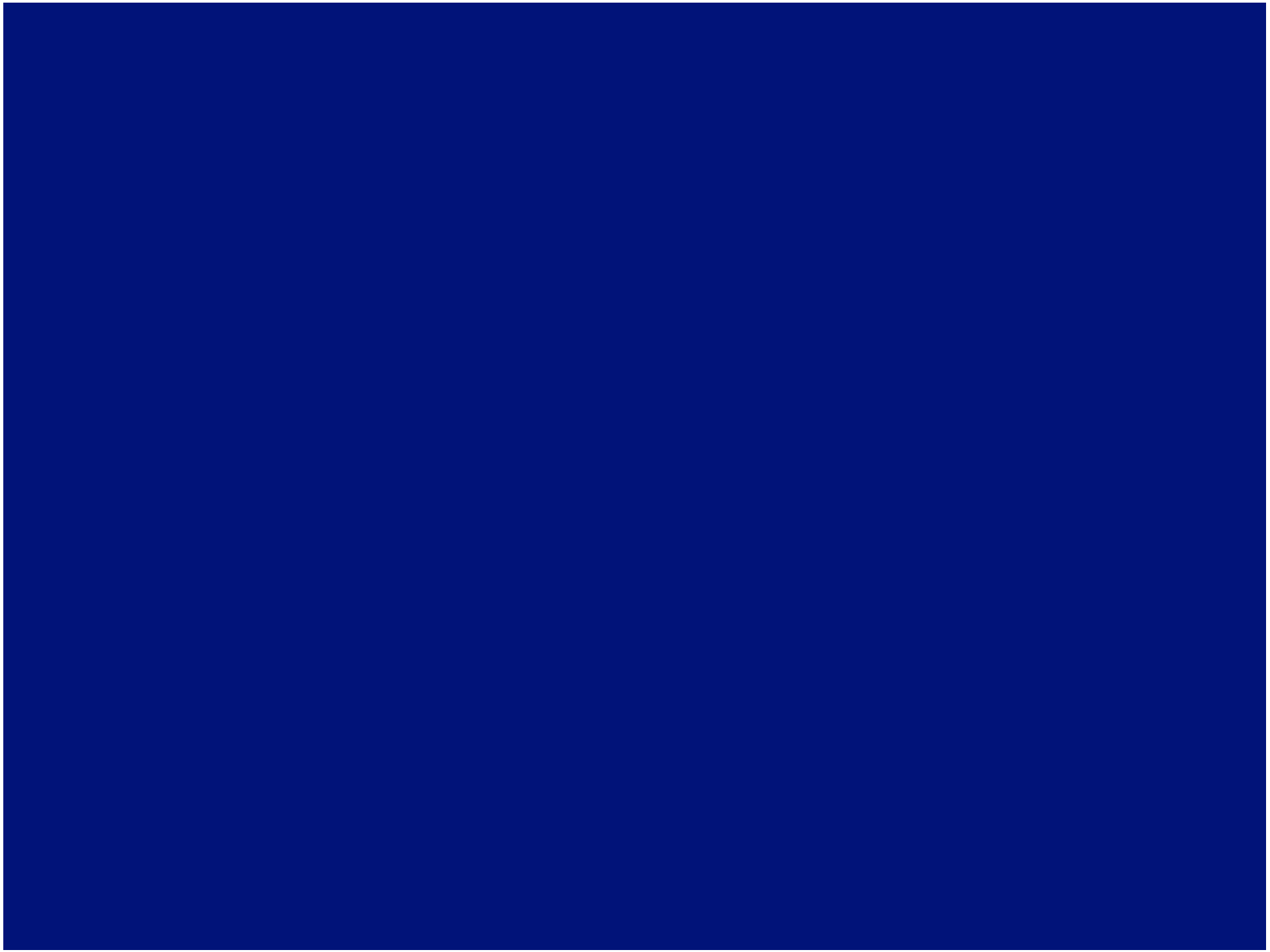
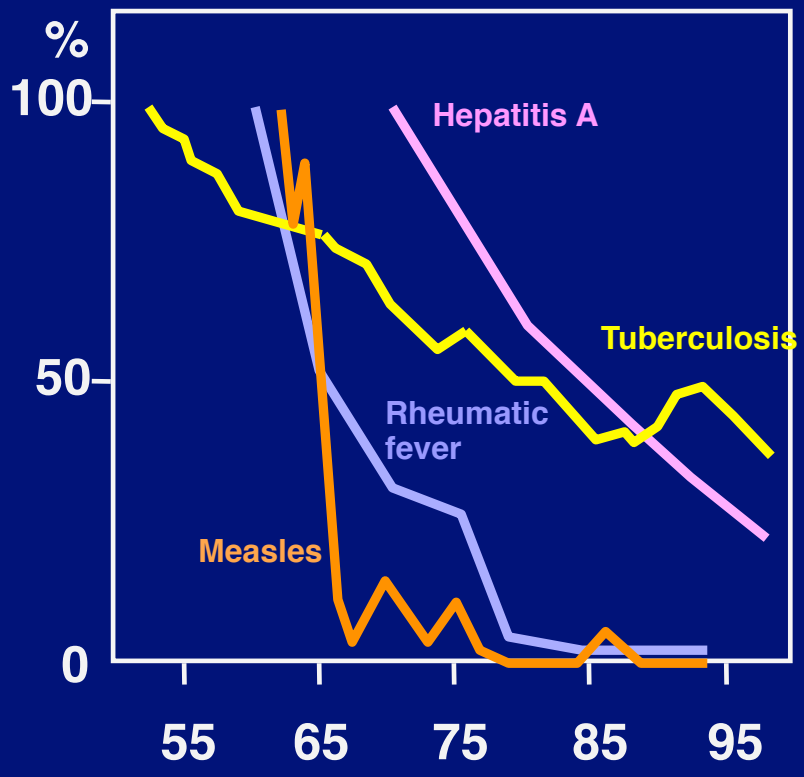
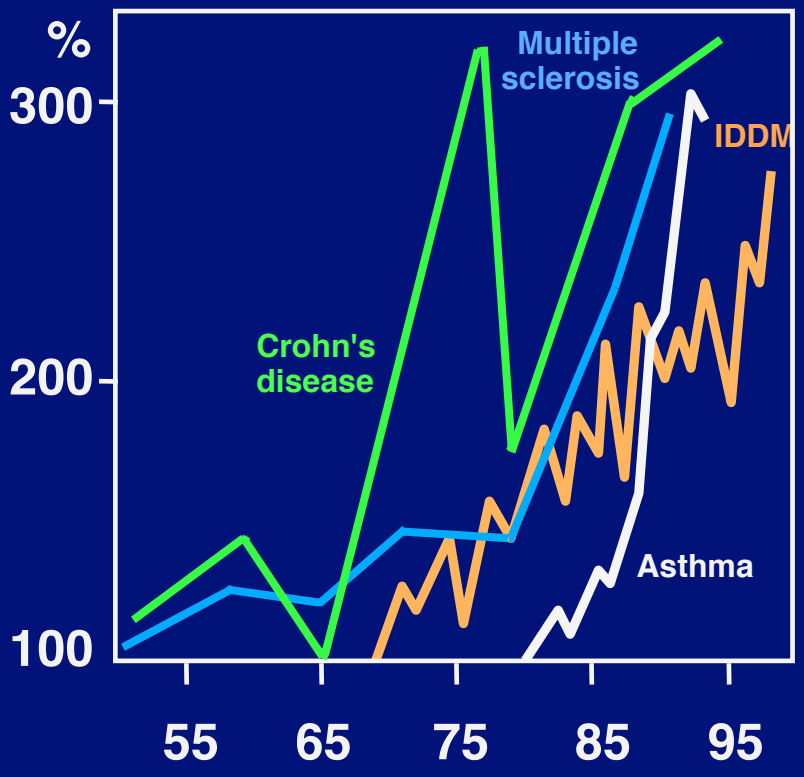


Incidence of prototype infectious diseases and immune disorders over 4 decades



Infectious disease



Immune disorders

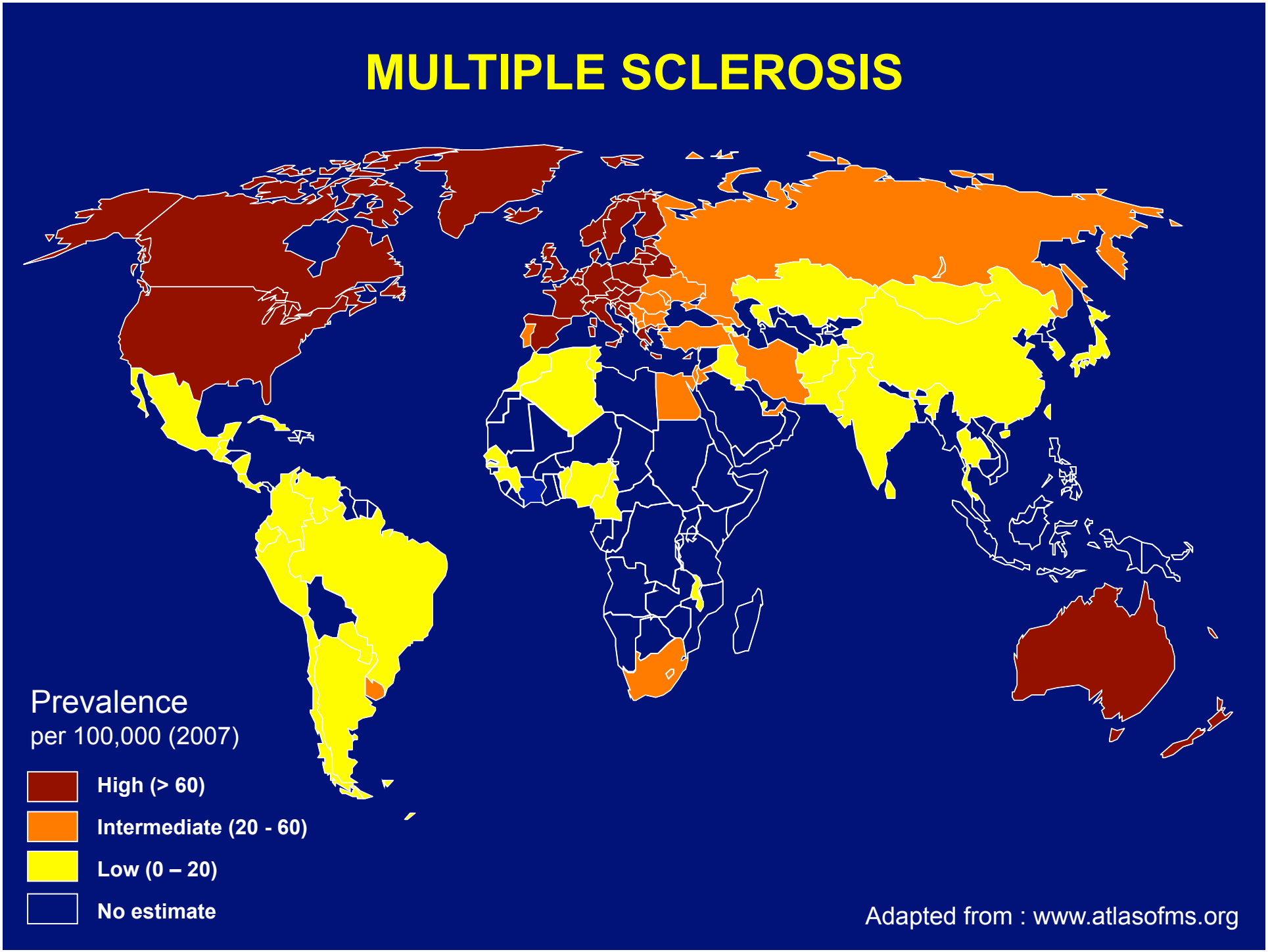
JF Bach N Engl J Med 2002, 347: 911- 920

Epidemological data

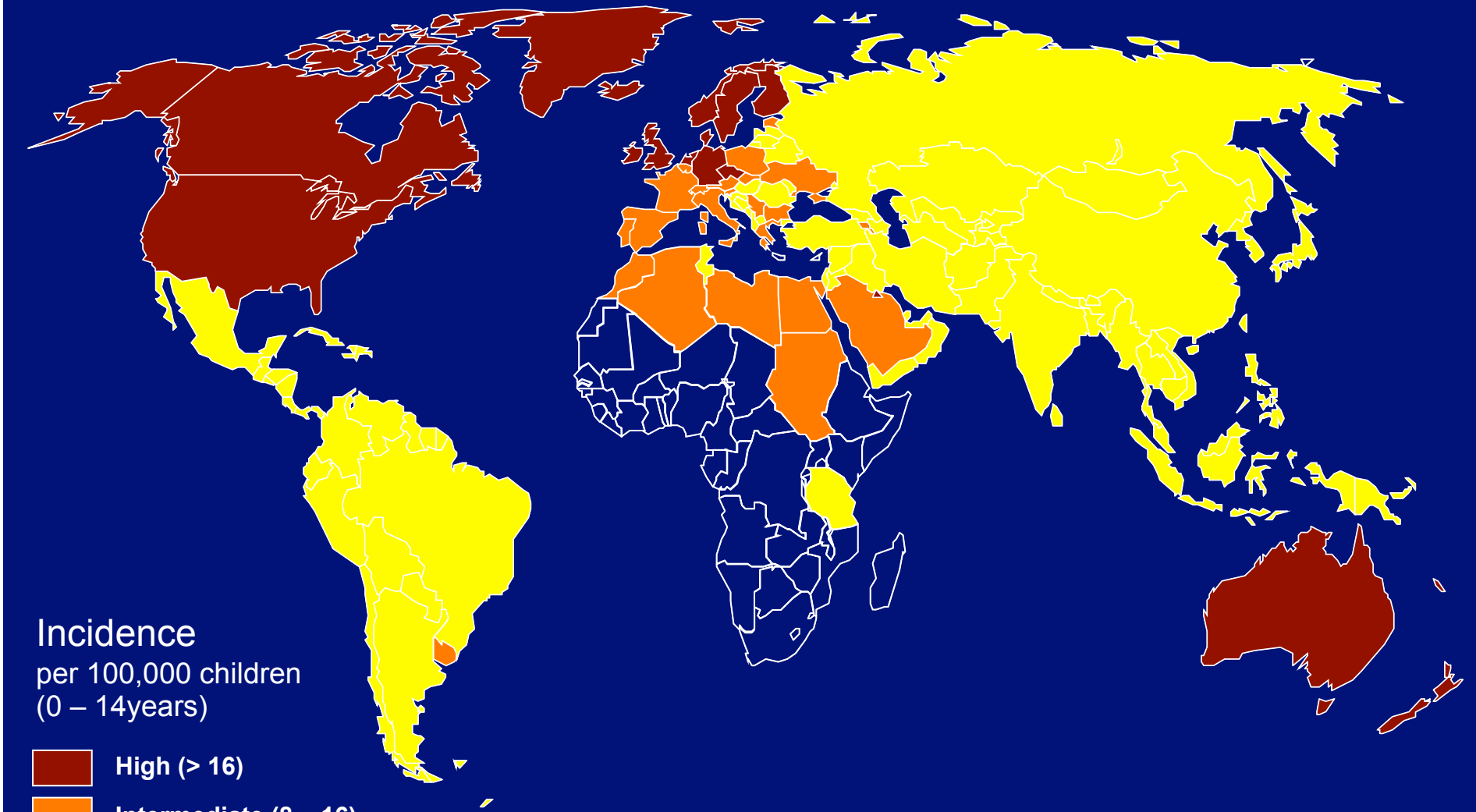
Epidemiological approaches of the hygiene hypothesis

1. Geographical distribution
   - Countries/ Regions/Cities
   - Migrants
   - Correlation with socioeconomical factors (notably, sanitary conditions)
   - Effect of farming and pets
2. Order of birth (modalities of delivery)
3. Number of infections

MULTIPLE SCLEROSIS

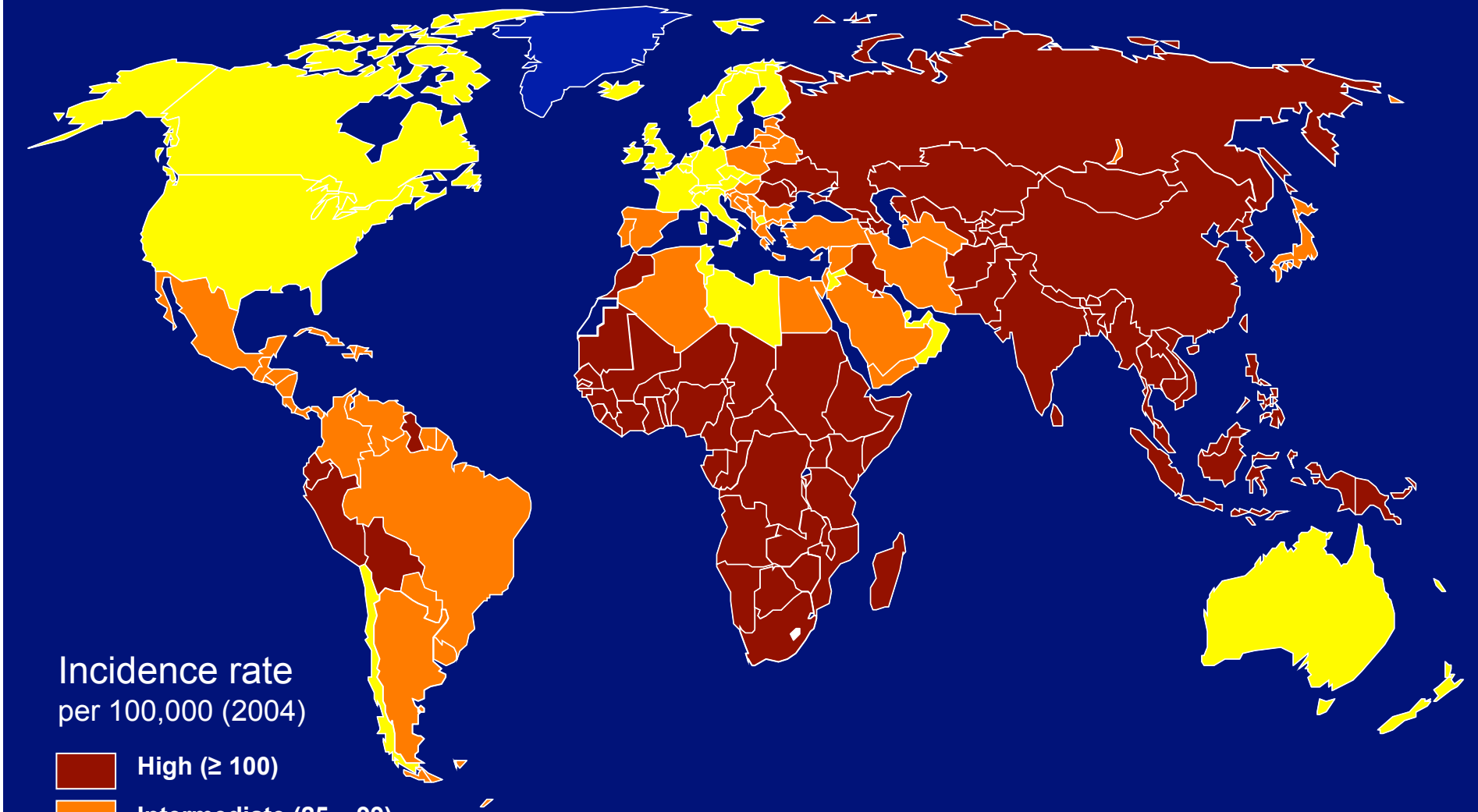


TYPE 1 DIABETES (INCIDENCE IN CHILDREN 0 – 14 YEARS)



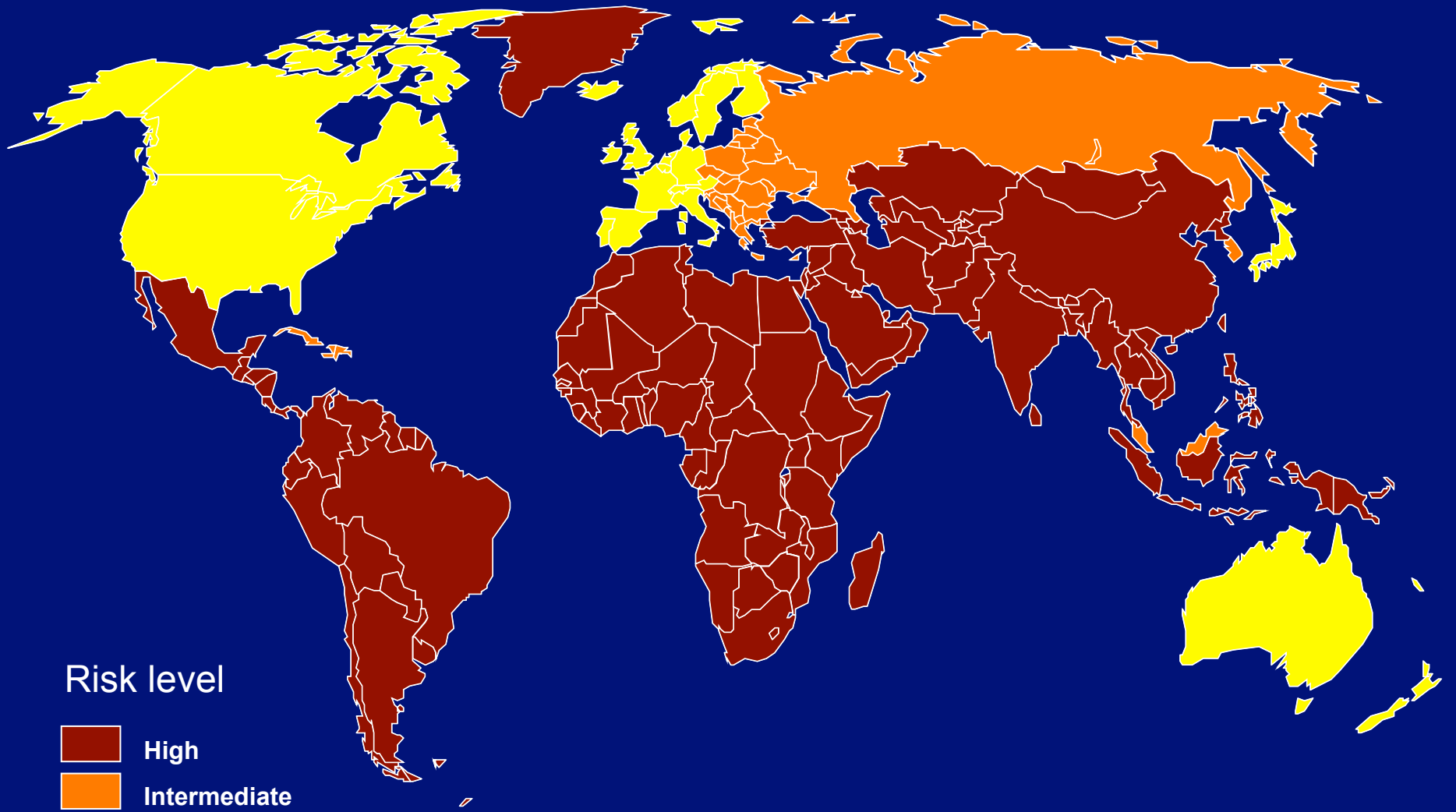
Adapted from : www.eatlas.idf.org

TUBERCULOSIS INCIDENCE RATE



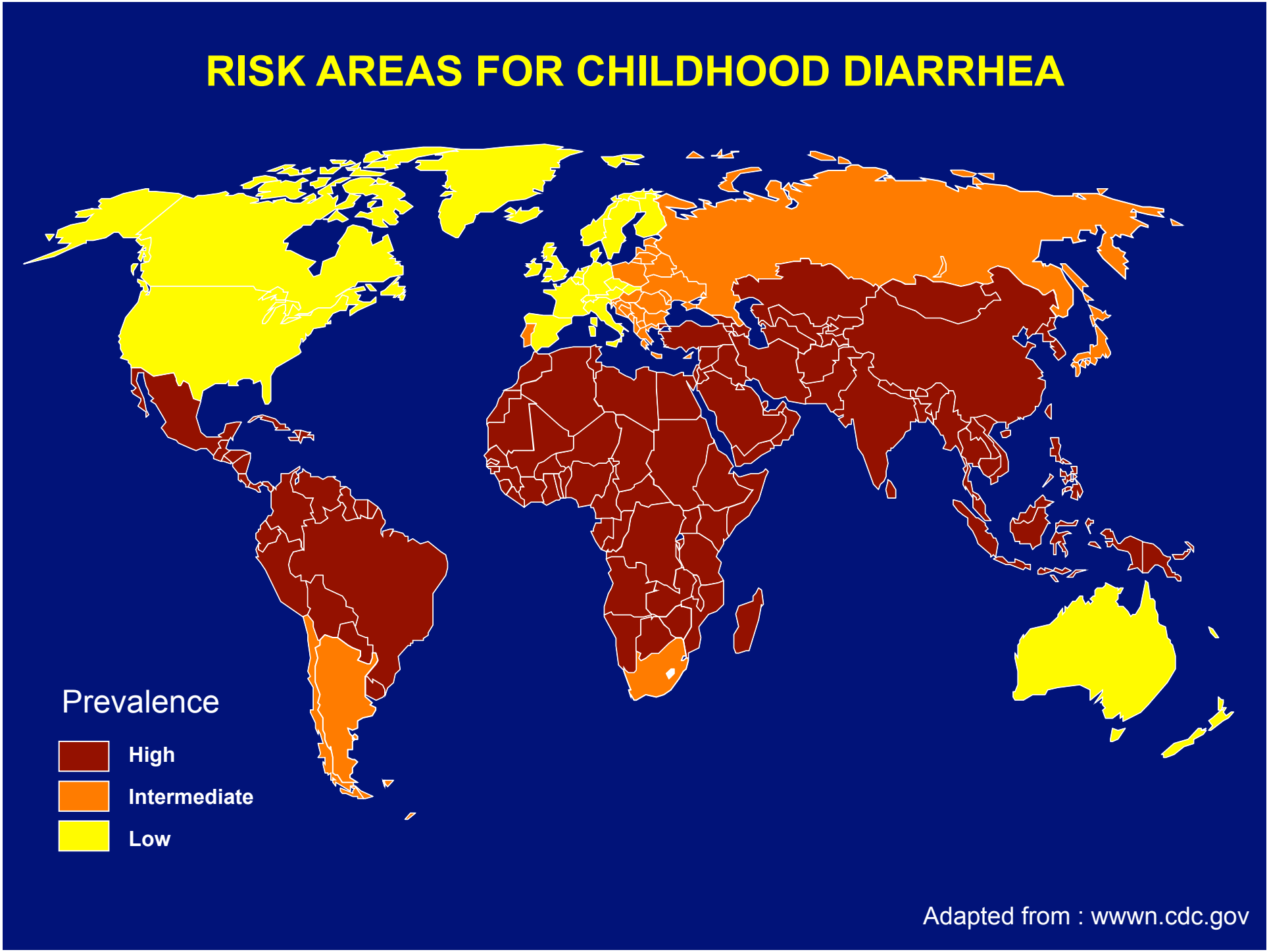
Adapted from : wwwn.cdc.gov

HEPATITIS A VIRUS ANTIBODIES PREVALENCE

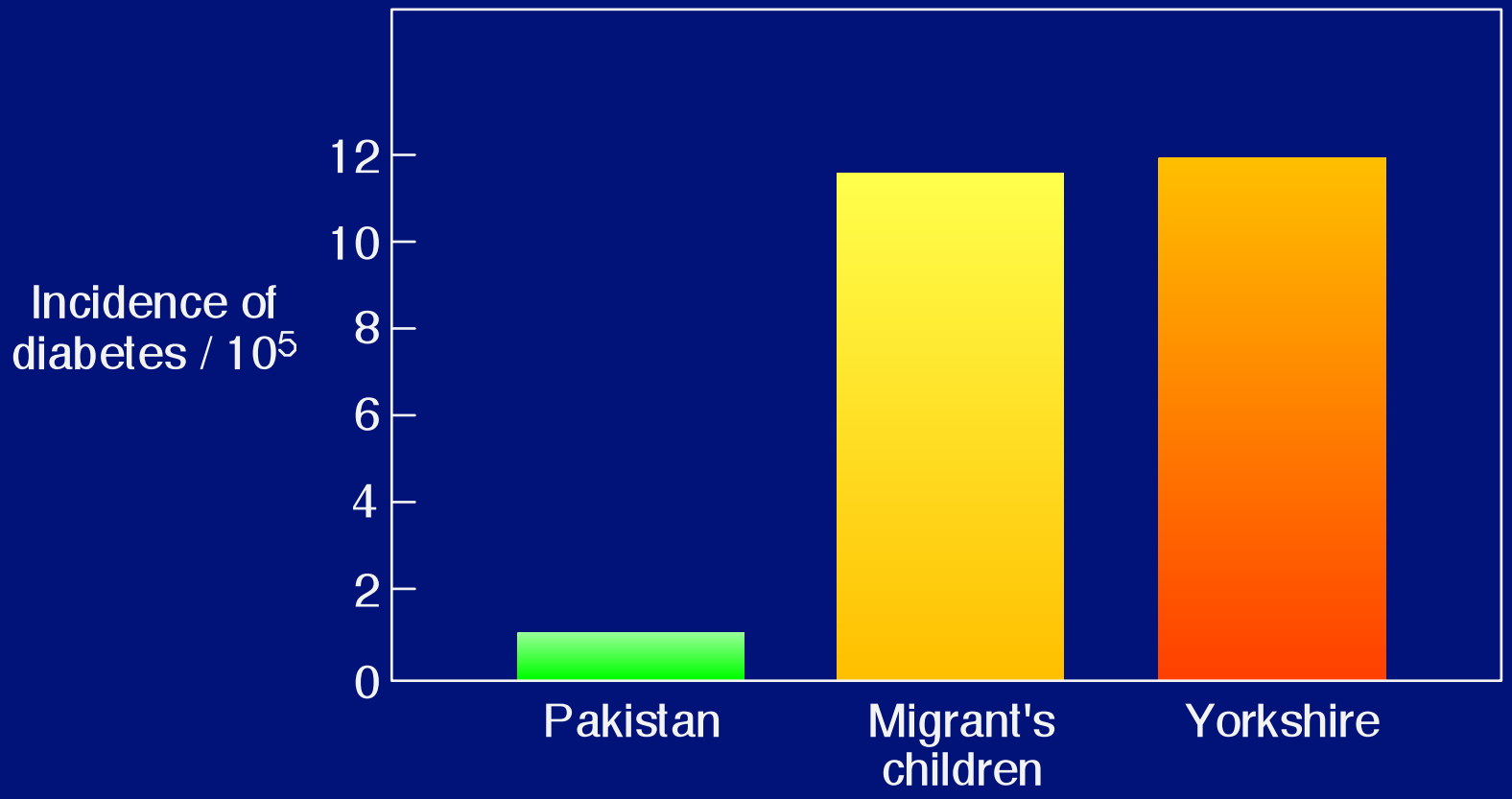


Adapted from : wwwn.cdc.gov

RISK AREAS FOR CHILDHOOD DIARRHEA



IDDM incidence in children of migrants from Pakistan to Yorkshire



Staines A. (1997) and Bodansky H.J. (1992)

PREVALENCE OF SELF-REPORTED LIFETIME ASTHMA IN YOUNG WHITE AND SOUTH ASIAN WOMEN

		Unadjusted data		
	*N**	%	OR	(95 CI)
All women				
White women	4848	21.8	1	
South Asian women	1712	10.9	0.44	(0.37–0.52)
Among south Asian women				
Born in the UK or immigrated before 5 years of age	349	16.0	1	
Immigrated aged 5 years or older	477	6.5	0.36	(0.23–0.58)

**N*, number of subjects with available data

C.E. Kuehni et al. Clin Exp All 2007, 37: 47

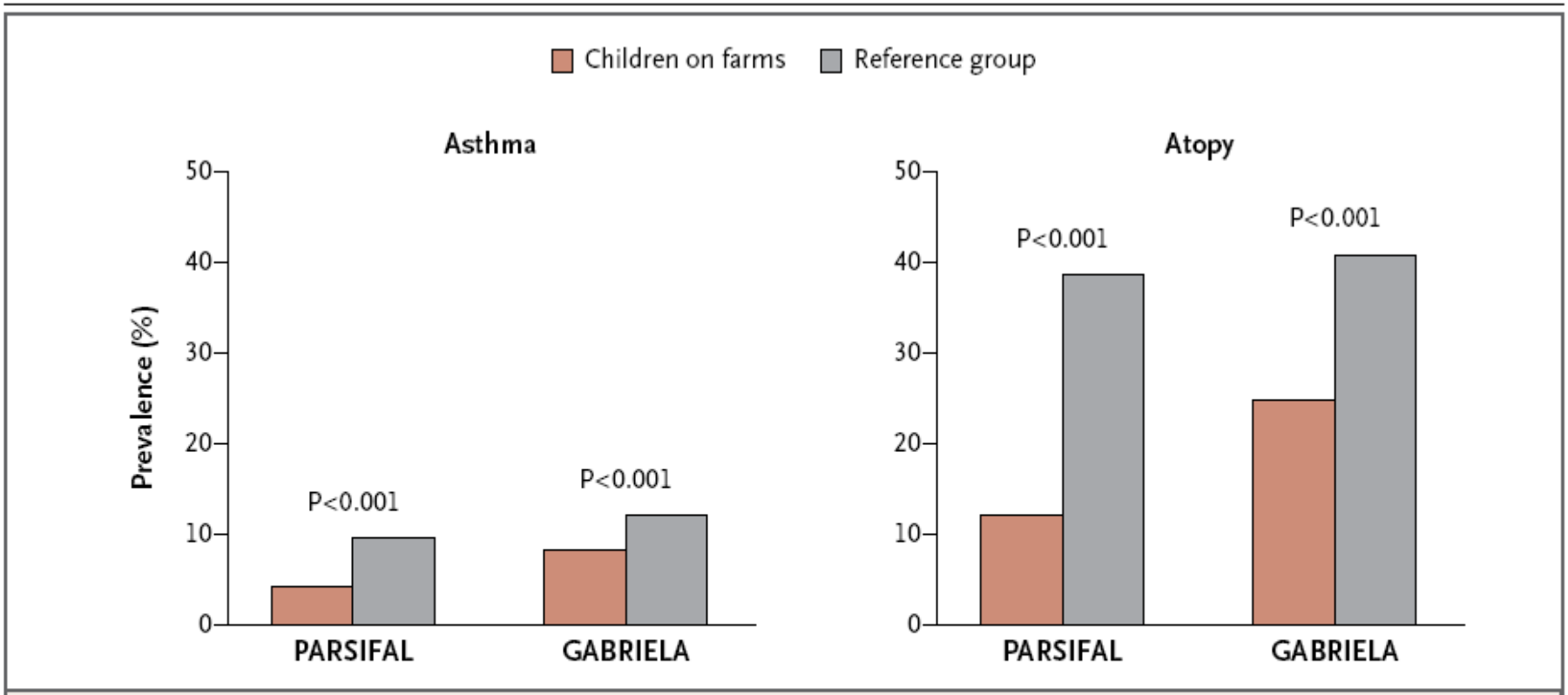


Figure 1. Prevalence of Asthma and Atopy among Children Living on Farms as Compared with Reference Groups.

The PARSIFAL study population included 6843 school-age children 6 to 13 years of age, and the GABRIELA study population included 9668 children between 6 and 12 years of age. Calculations of prevalence in GABRIELA were weighted on the basis of the total number of children who were eligible for inclusion in the study (34,491 children).

MJ Ege et al. New Engl J Med 2011; 364:701-9

The role of hygiene on establishment of the gut microbiota

IMPACT OF DIET IN SHAPING GUT MICROBIOTA REVEALED BY A COMPARATIVE STUDY IN CHILDREN FROM EUROPE AND RURAL AFRICA

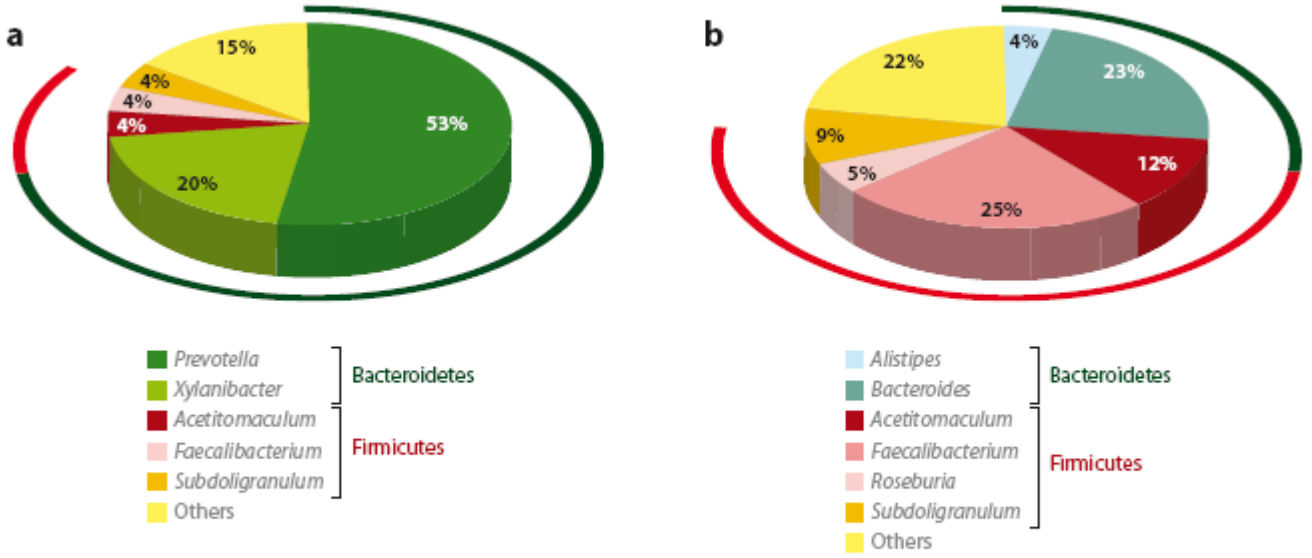
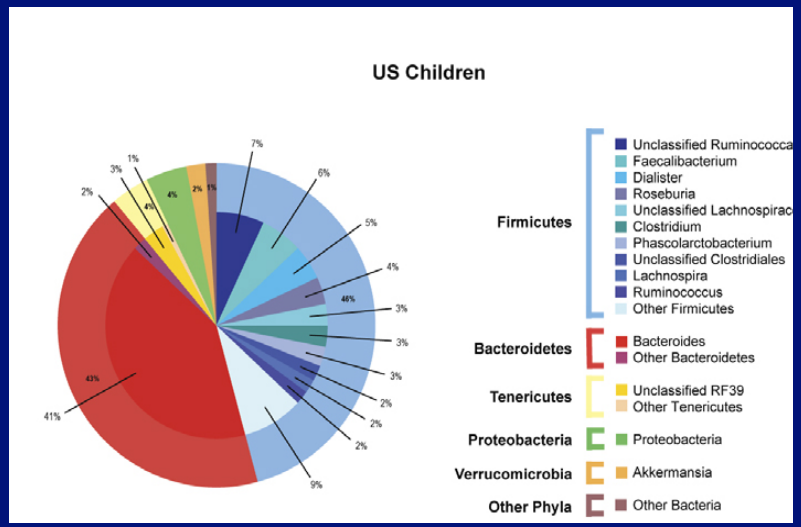
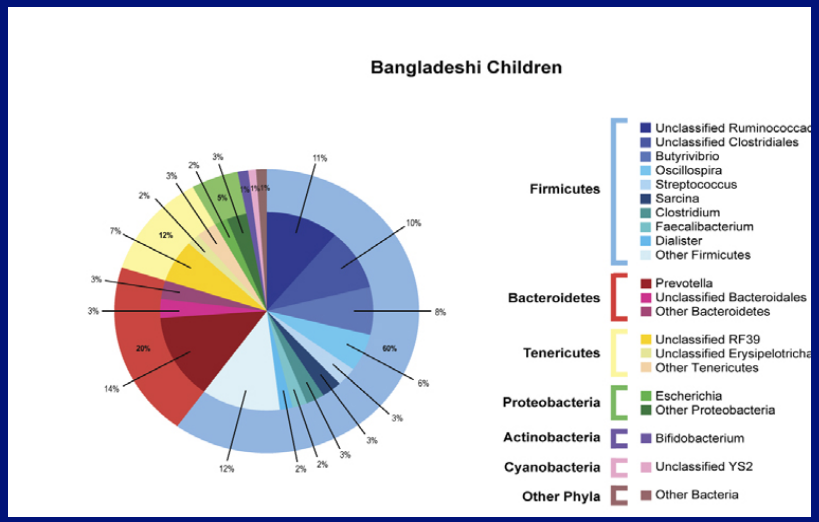


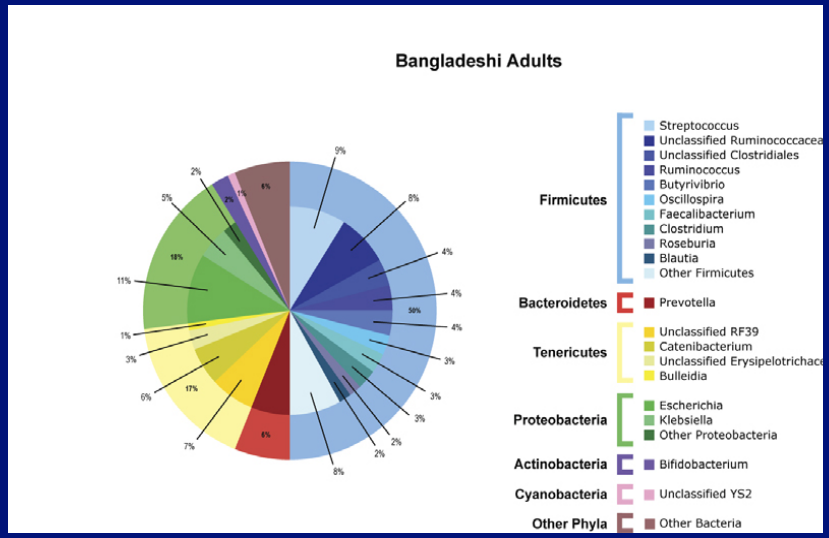
Figure 1

Bacterial taxa of the intestinal microbiota differ depending on diet. Taxa identified using 16S ribosomal RNA sequencing of DNA from fecal samples of children from (*a*) Burkina Faso and (*b*) Italy. The colors indicate differential distribution of classes of bacteria, including Firmicutes (*red*) and Bacteroidetes (*green*). Figure reproduced from Reference 14.

C De Filippo et al. Proc. Natl. Acad. Sci. USA 2010; *107:14691–96*







Lin *et al*. PLoS ONE 2012; 8: e53838

nature International weekly journal of science

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- Cut
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Published online 2 December 2009 | *Nature* **462**, 558 (2009) | doi:10.1038/462558a

News

Dirty pigs beat disease

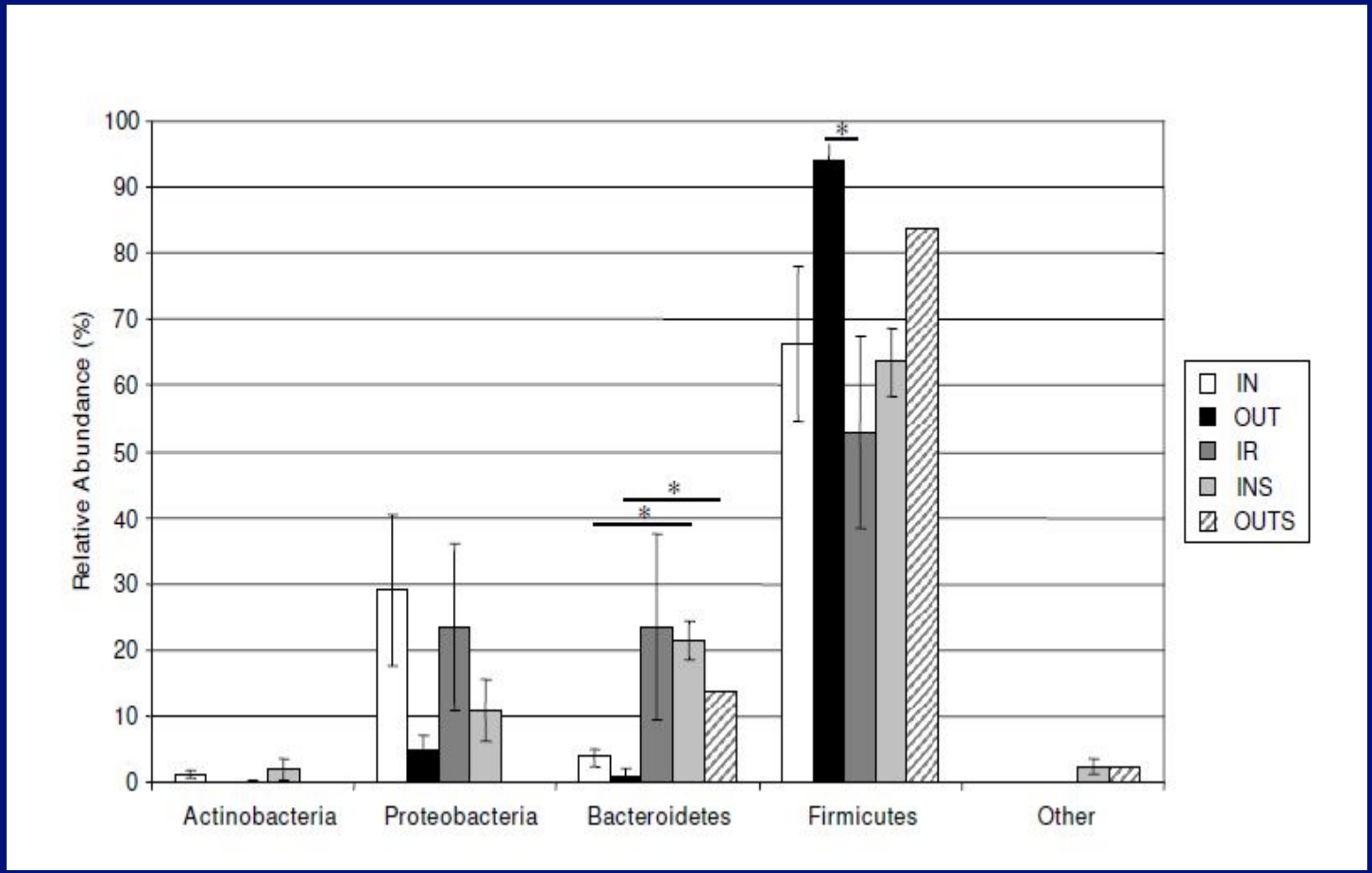
Immune system gets a boost from early exposure to bacteria.

Natasha Gilbert

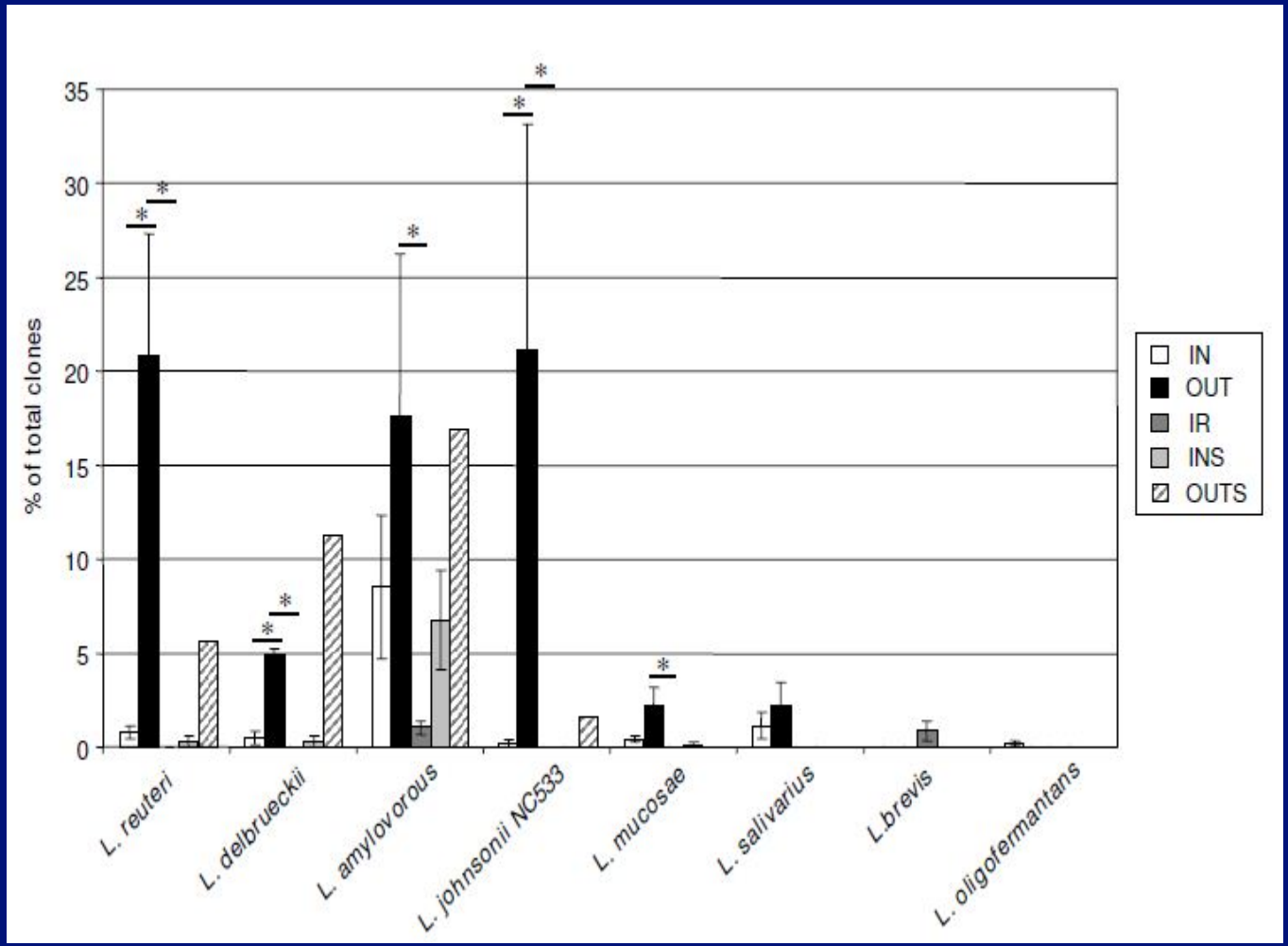
Living like a pig could be good for you, according to research showing that dirty piglets pick up 'friendly' bacteria that help them to develop robust immune systems later in life.

The results provide support for the hygiene hypothesis, which suggests that a lack of exposure to microbes in early life can affect development of the immune system and increase susceptibility to certain

Outdoor pigs had more 'friendly' gut bacteria than indoor pigs.



Mulder et al. BMC Biology 2009; 7:79



Mulder et al. BMC Biology 2009; 7:79

FACTORS AFFECTING MICROBIOTA COMPOSITION IN EARLY LIFE

Diet

- carbohydrate vs Fat
- calories
- breast feeding

Hygiene/Sanitation

- perinatal antibiotics
- mode of delivery

Other factors

- geography
- climate
- life style
- genetics

LETTER

doi:10.1038/nature12820

Diet rapidly and reproducibly alters the human gut microbiome

Lawrence A. David[1,2]†, Corinne F. Maurice[1], Rachel N. Carmody[1], David B. Gootenberg[1], Julie E. Button[1], Benjamin E. Wolfe[1], Alisha V. Ling[3], A. Sloan Devlin[4], Yug Varma[4], Michael A. Fischbach[4], Sudha B. Biddinger[3], Rachel J. Dutton[1] & Peter J. Turnbaugh[1]

Nature. 2014 Jan 23;505(7484):559-63. doi: 10.1038/nature12820. Epub 2013 Dec 11.

FACTORS CONTRIBUTING TO THE APPEARANCE OF INFECTIONS

Sources of pathogenic agents

- drinking water
- food (cold storage)
- climate
- housing conditions

Anti-infectious defense

- genetic factors
- nutrition
- antibiotics
- vaccination

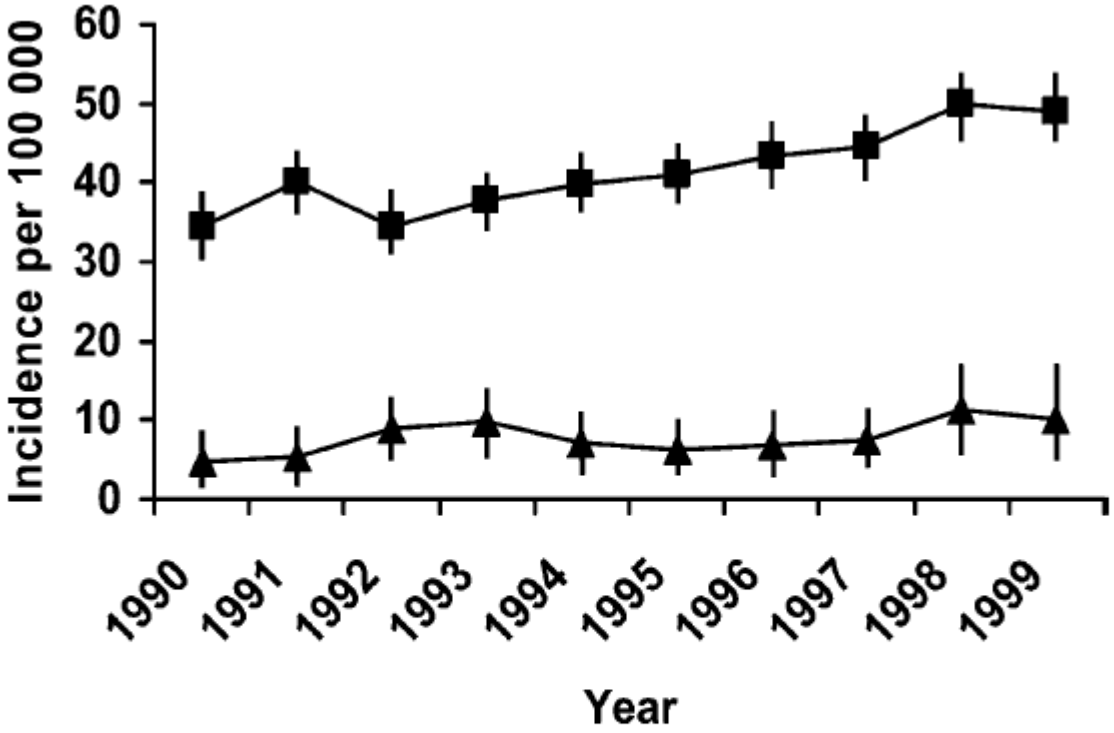


Figure 1. Age-adjusted mean annual incidence of type 1 diabetes in 0–14 year-old children in Russian Karelia and in Finland during the years 1990–99. Black triangles=Russian Karelia; black squares=Finland; vertical bars=95% confidence intervals.

***A Kondrashova et al. Ann Med* 2005;37:67-72**

Microbial content of drinking water in Finnish and Russian Karelia – implications for atopy prevalence

Table 3. Occurrence of atopy (skin prick test positivity to one or more allergens) according to DAPI categories (total cell counts/ml) among Finnish and Russian Karelian children

	DAPI*			
	Low	Intermediate	High	*P*-value
Atopy†, *n* (%)	43 (41.1)	39 (21.8)	48 (17.1)	<0.0001

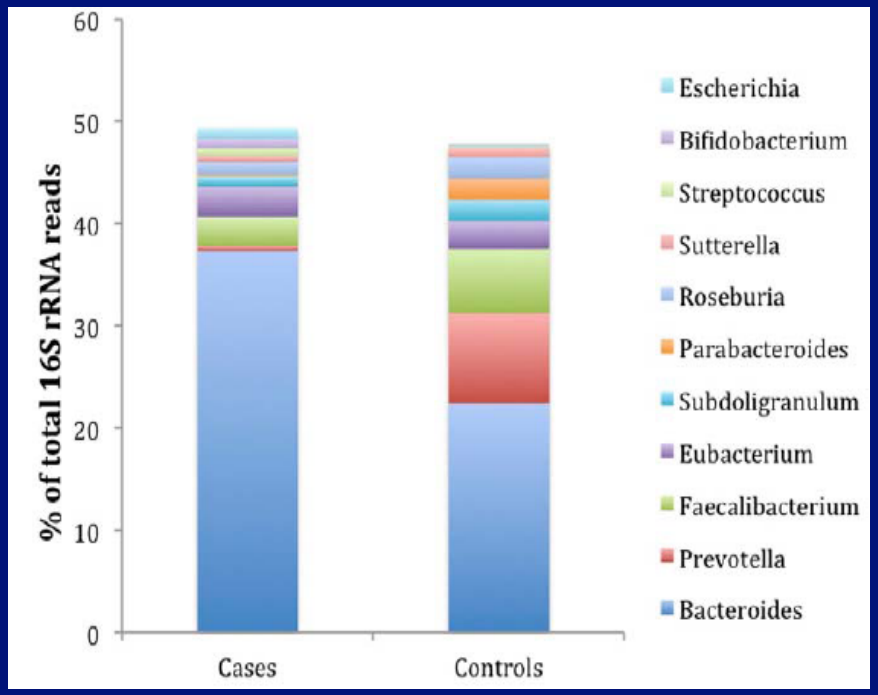
* DAPI low, $<10^5$ cells/ml; intermediate, 10^5–10^6 cells/ml; high; $>10^6$ cells/ml. Each child had been linked with the DAPI value of his/her school.

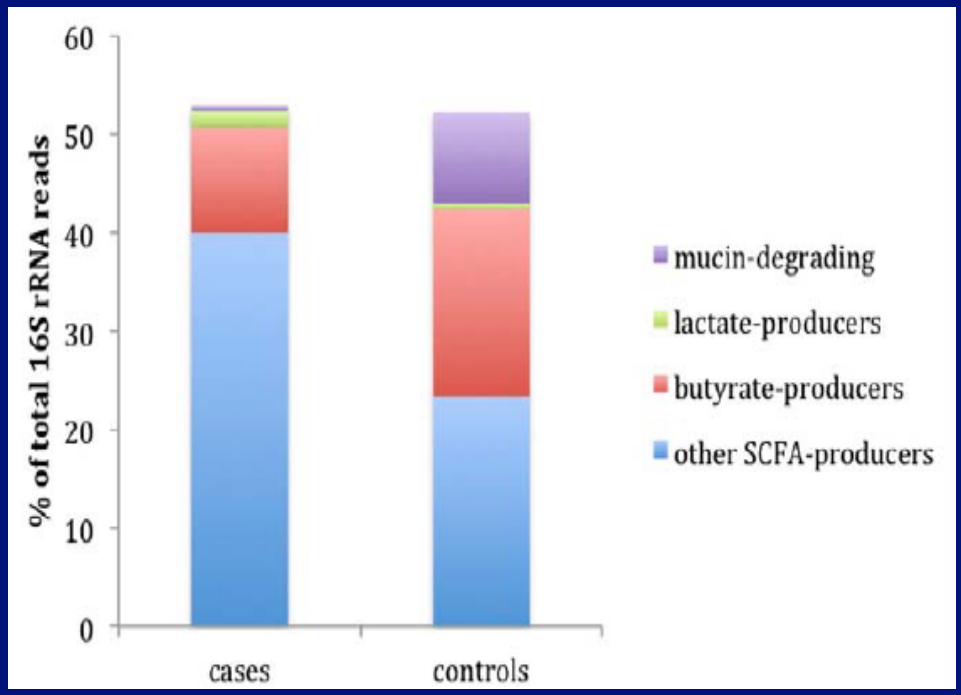
† Atopy = at least one positive skin prick test result.

L von Hertzen et al. Allergy 2007; 62: 288–92

Correlation between gut microbiota reduced diversity and dysimmune diseases

GUT MICROBIOME METAGENOMICS ANALYSIS AND DEVELOPMENT OF AUTOIMMUNITY : THE CASE OF TYPE 1 DIABETES





C.T. Brown et al., PLoS ONE 2011, 6: e25792

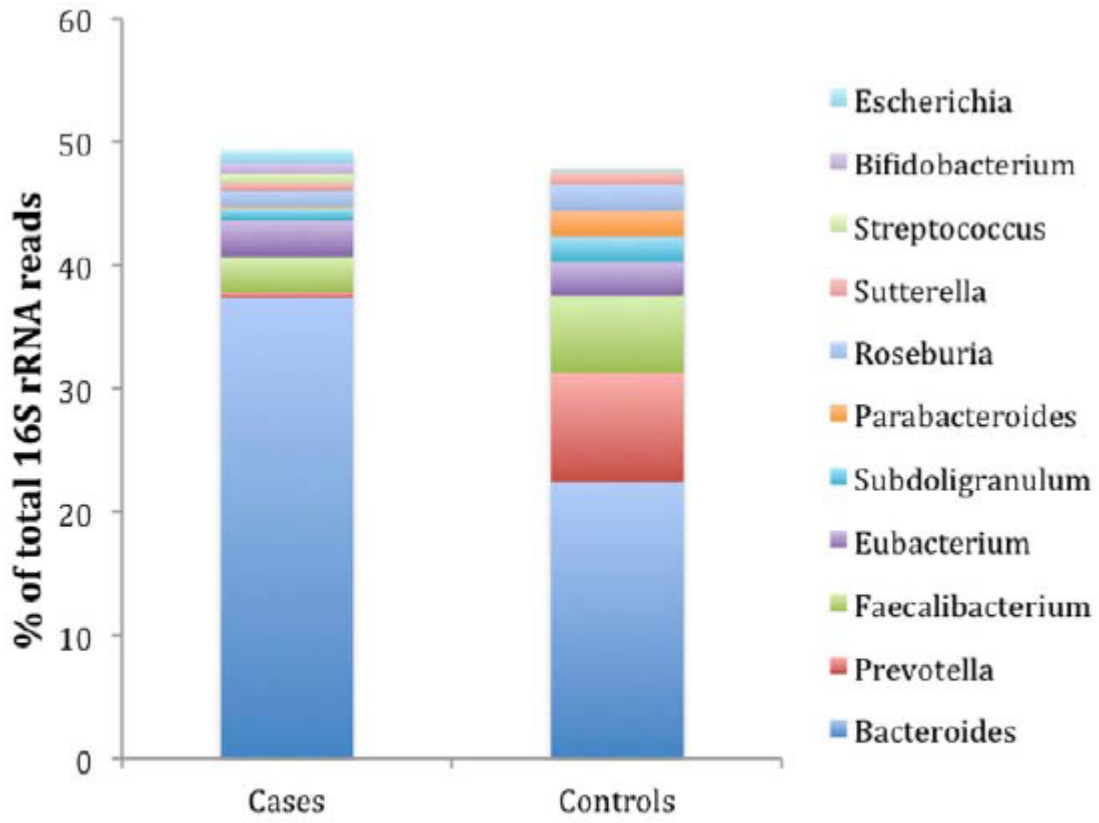


Figure 3. Mean proportion of the 11 most abundant genera that differ significantly between cases and controls (p value≤0.01).

C. Brown et al. PLoS ONE 2011;6:e25792

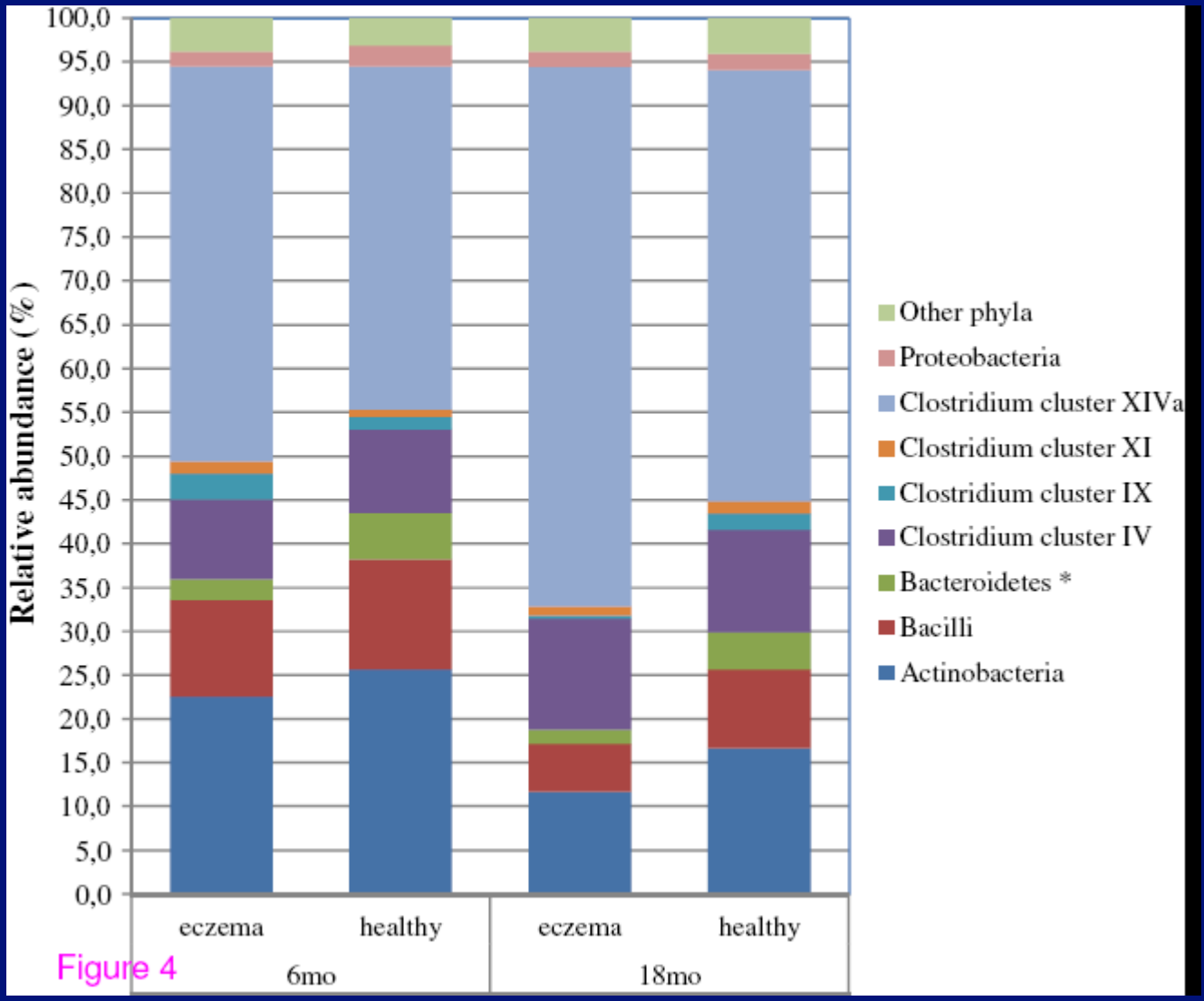


Figure 4

Nylund et al. BMC Microbiology 2013, 13:12

Spontaneous IDDM in NOD mice

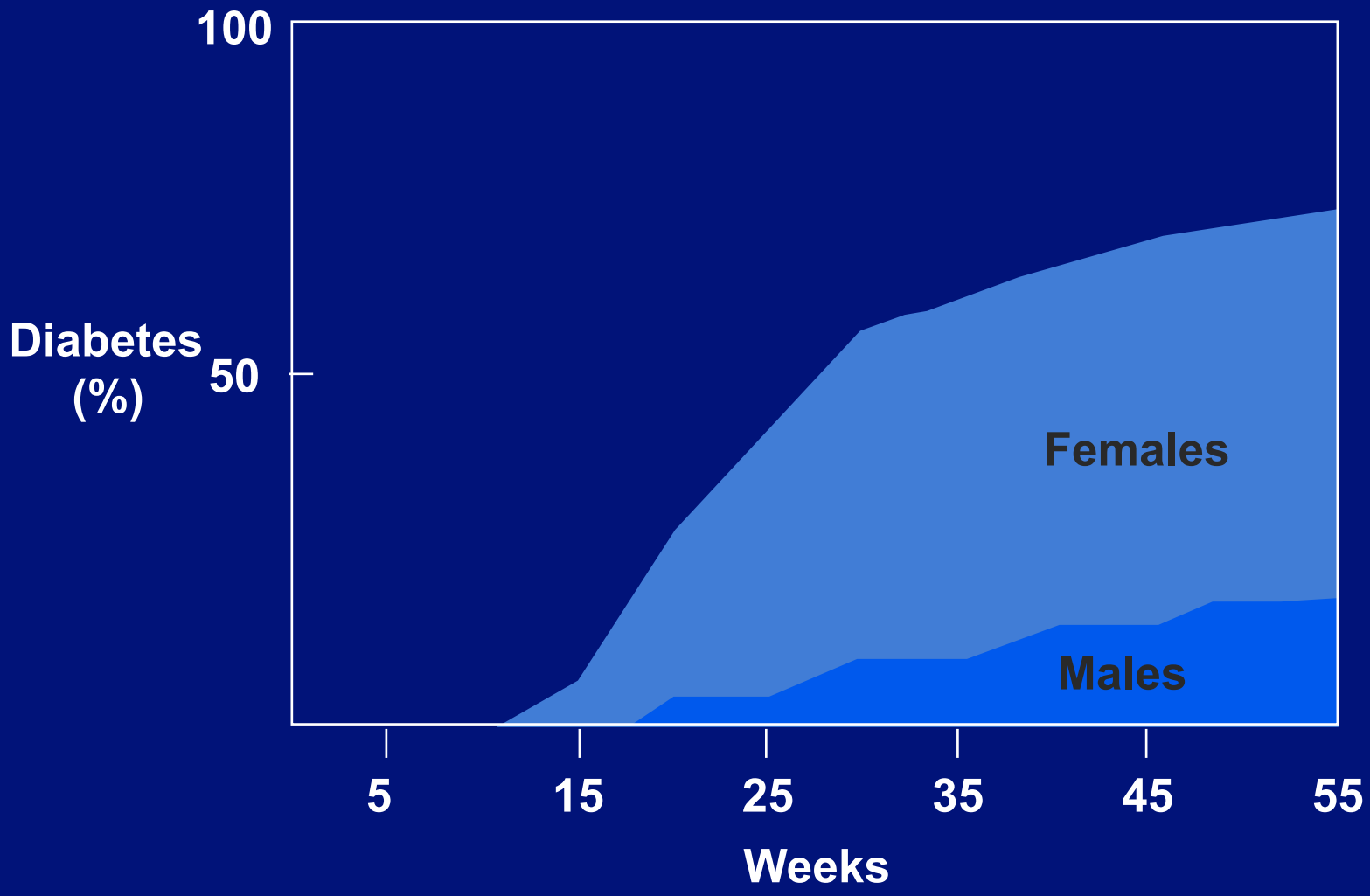


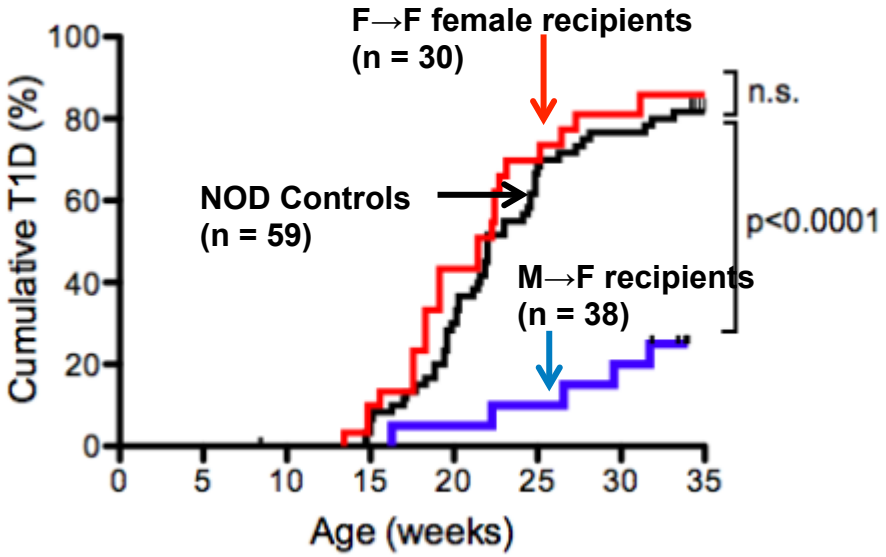
Table 1. Gender Bias of T1D in NOD Colonies

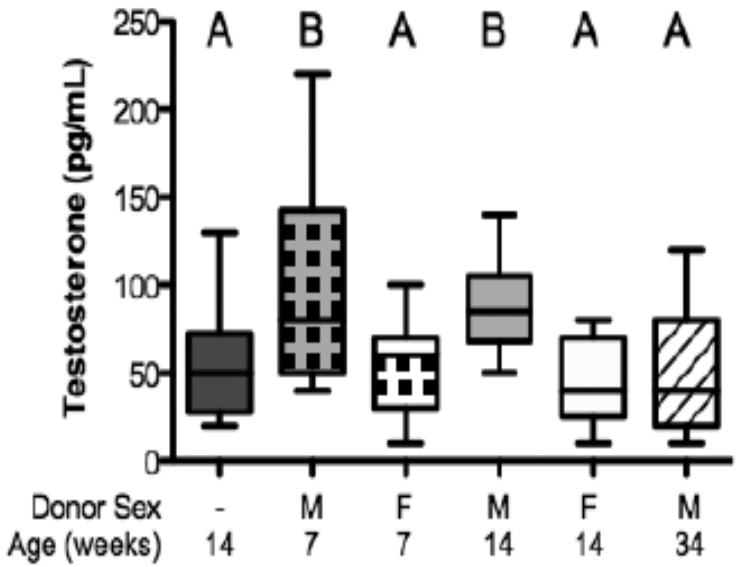
Institution	Female (F)	Male (M)	Ratio F/M
SPF Facilities			
U of Chicago	60%	25%	2.4
Yale 2008 (Wen et al., 2008)	90%	70%	1.3
Taconic 2009[a]	80%	50%	1.6
Harvard 2011 (Kriegel et al., 2011)	50%–60%	10%–15%	4.4
2002[b]	75%	50%	1.5
2003[b]	85%	60%	1.4
2004[b]	90%	45%	2.0
2005[b]	80%	40%	2.0
2006[b]	65%	35%	1.9
2007[b]	100%	65%	1.5
2008[b]	90%	85%	1.1
2009[b]	90%	65%	1.4
Germ-Free Facilities			
Taconic 2008 (Wen et al., 2008)	100%	85%	1.2
U of Chicago 2012	95%	84%	1.1

Cumulative incidence of diabetes in NOD mice at 30 weeks of age.

L Yurkovetskiy et al. Immunity 2013; 39: 400-12

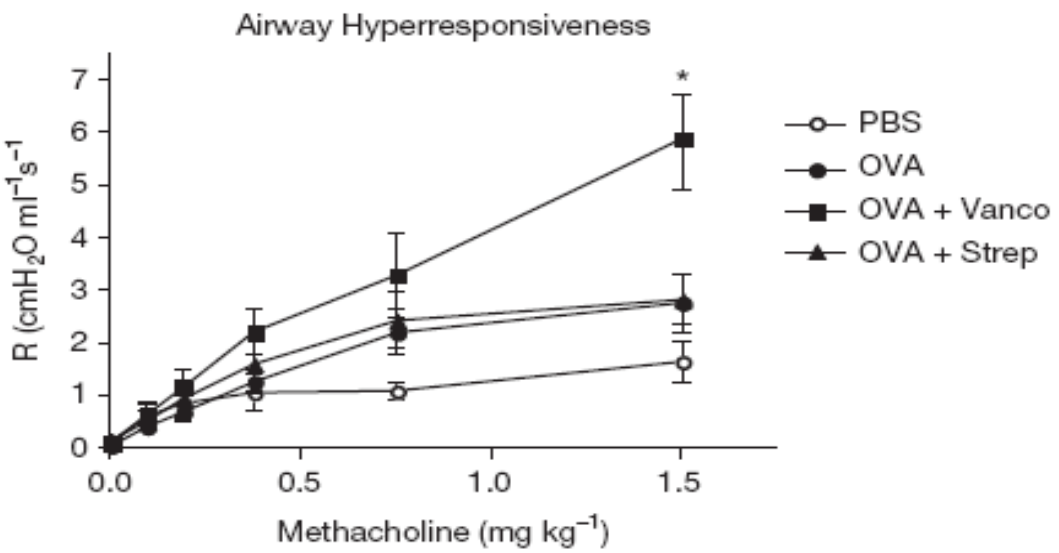
Gavage of female NOD pups with male NOD-derived intestinal microbiome

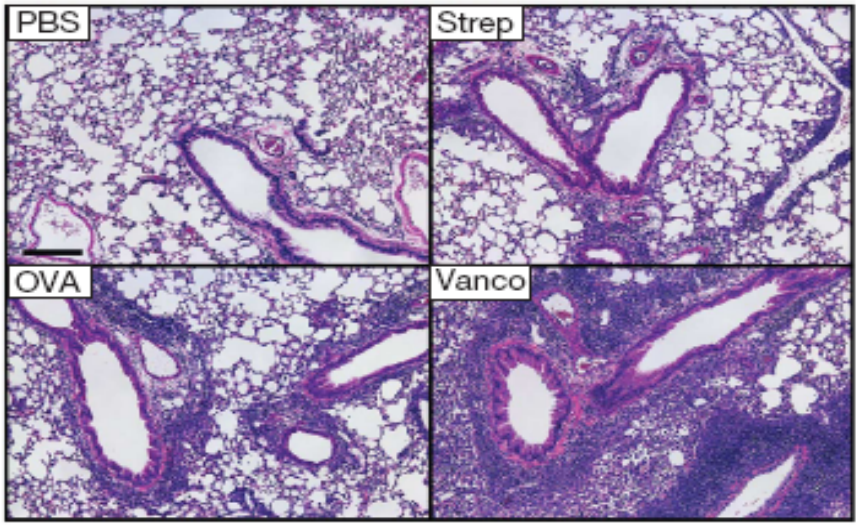




JGM Markle et al. Science 2013;339:1084-8

Direct evidence for a role of gut microbiota in the control of dysimmune diseases





Russell et al. **EMBO Reports 2012, 13: 440-447**

EFFECTS OF THE GERM FREE STATUS ON AUTOIMMUNE DISEASES

Diabetes (NOD mice)	Variable	
EAE	Conventional	↘
	Transgenic TCR	↘
Arthritis	CIA	↗
	KBxN	↘

PROBIOTICS IN GF MICE

Segmented Filamentous Bacteria	TH17 cells (IL-17)
Clostridium **Bacteroides fragilis**	Treg, IL-10
VSL#3	No Effect

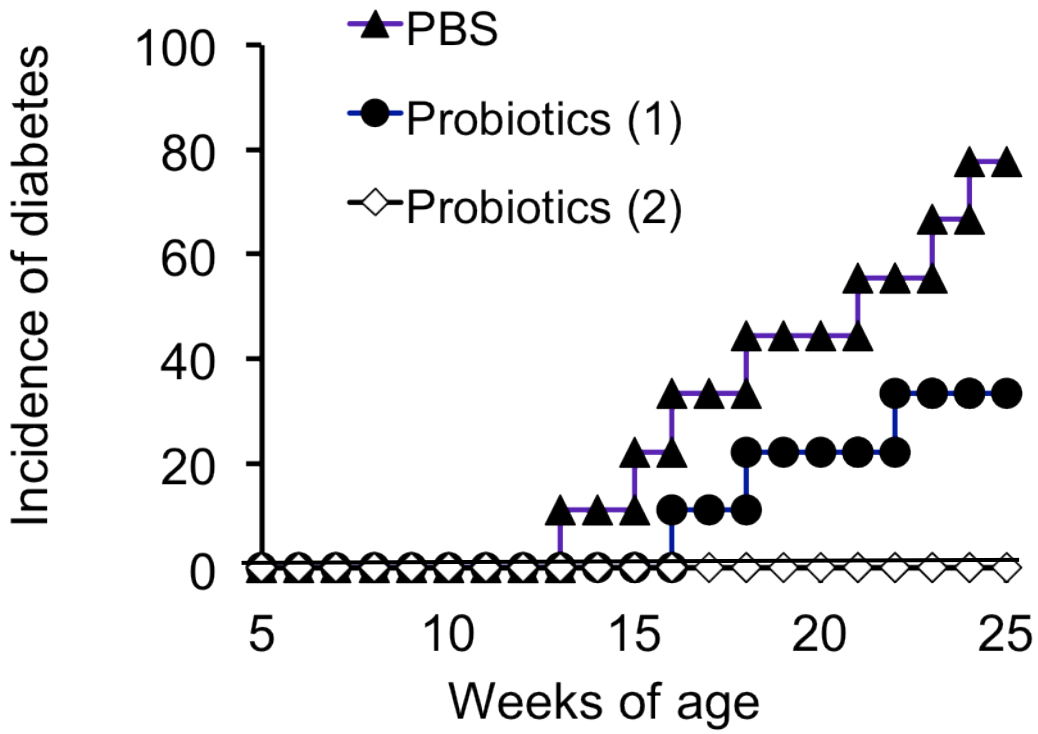
Table 2 | **Bacteria shown to be protective in inflammatory bowel disease**

Bacterial strain	Model system	Disease type or model	Mechanism of disease suppression
VSL#3*	Human and mouse	Pouchitis, ulcerative colitis and TNBS-induced colitis	Induction of IL-10- and TGFβ-expressing T cells
Bifidobacteria lactis	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS
Bifidobacteria infantis	Mouse	*Salmonella enterica*-induced enteritis	Induction of T_{Reg} cells and inhibition of NF-κB activation
Escherichia coli Nissle 1917	Human and mouse	Ulcerative colitis and DSS-induced colitis	Decreased colonic inflammation induced by TLR2 and TLR4 activation
Lactobacillus rhamnosus GG	Mouse and rat	TNBS-induced colitis and HLA-B27-associated colitis	Induction of T_{Reg} cells
Lactobacillus salivarius	Mouse	TNBS-induced colitis	Decreased colonic inflammation
Lactobacillus reuteri	Mouse	IL-10-deficient mice	Upregulation of NGF and decreased levels of IL-8 and TNF in cell lines
Lactobacillus plantarum 299v	Mouse	IL-10-deficient mice	Decreased levels of IFNγ and IL-12p40
Lactobacillus fermentum	Rat	TNBS-induced colitis	Decreased levels of colonic TNF and iNOS
Lactobacillus casei	Rat	TNBS-induced colitis	Decreased levels of colonic cyclooxygenase 2
Bacteriodes thetaiotaomicron	Rat	*S. enterica*-induced enteritis	Decreased levels of IL-8 and TNF in colorectal adenocarcinoma cell line
Bacteriodes fragilis	Mouse	T cell transfer and TNBS-induced colitis	Production of $CD4^+$ T cell-derived IL-10
YO-MIX Y109 FRO 1000‡	Mouse	TNBS-induced colitis	ND
Faecalibacterium prausnitzii	Mouse	TNBS-induced colitis	Decreased levels of NF-κB, IL-8 and TNF and increased IL-10 production

PREVENTION OF EXPERIMENTAL AUTOIMMUNE DISEASES BY PROBIOTICS

NOD Mice	**VSL#3**
BB Rats	***Lactobacillus Johnsonii***
EAE	***Bifidobacterium animalis***
	Lactobacillus plantarum + Lactobacillus casei
CIA	***Lactobacillus rhamnosus***

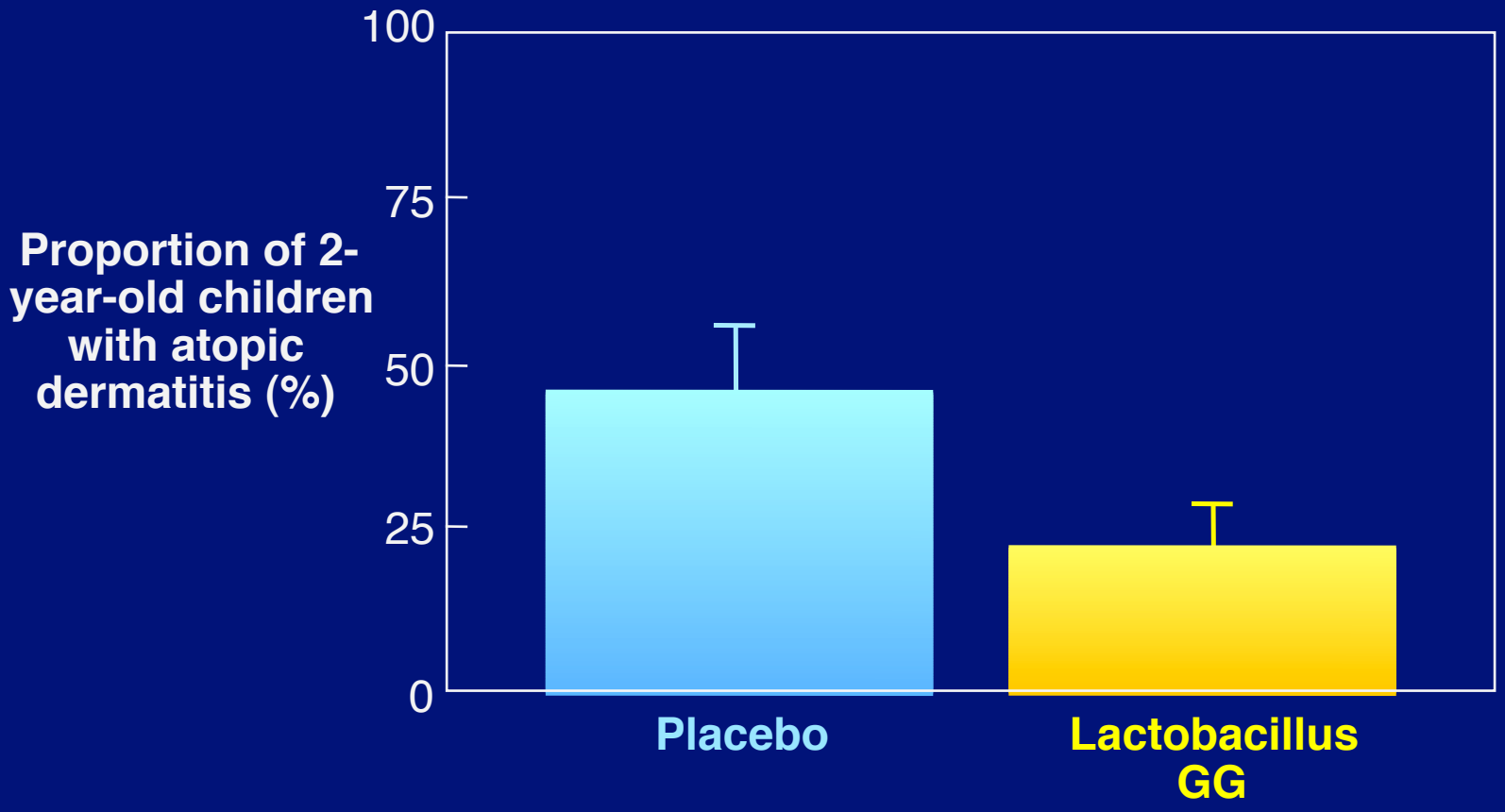
PROBIOTICS PROTECT FROM AUTOIMMUNE DIABETES



Daily administration of Probiotics: (1) 1.10^9 bacteria/mouse

(2) 5.10^9 bacteria/mouse

Treatment effect of Lactobacillus GG on atopic dermatitis



The Lancet, 2001

REVIEW ARTICLE

Probiotics Supplementation During Pregnancy or Infancy for the Prevention of Atopic Dermatitis

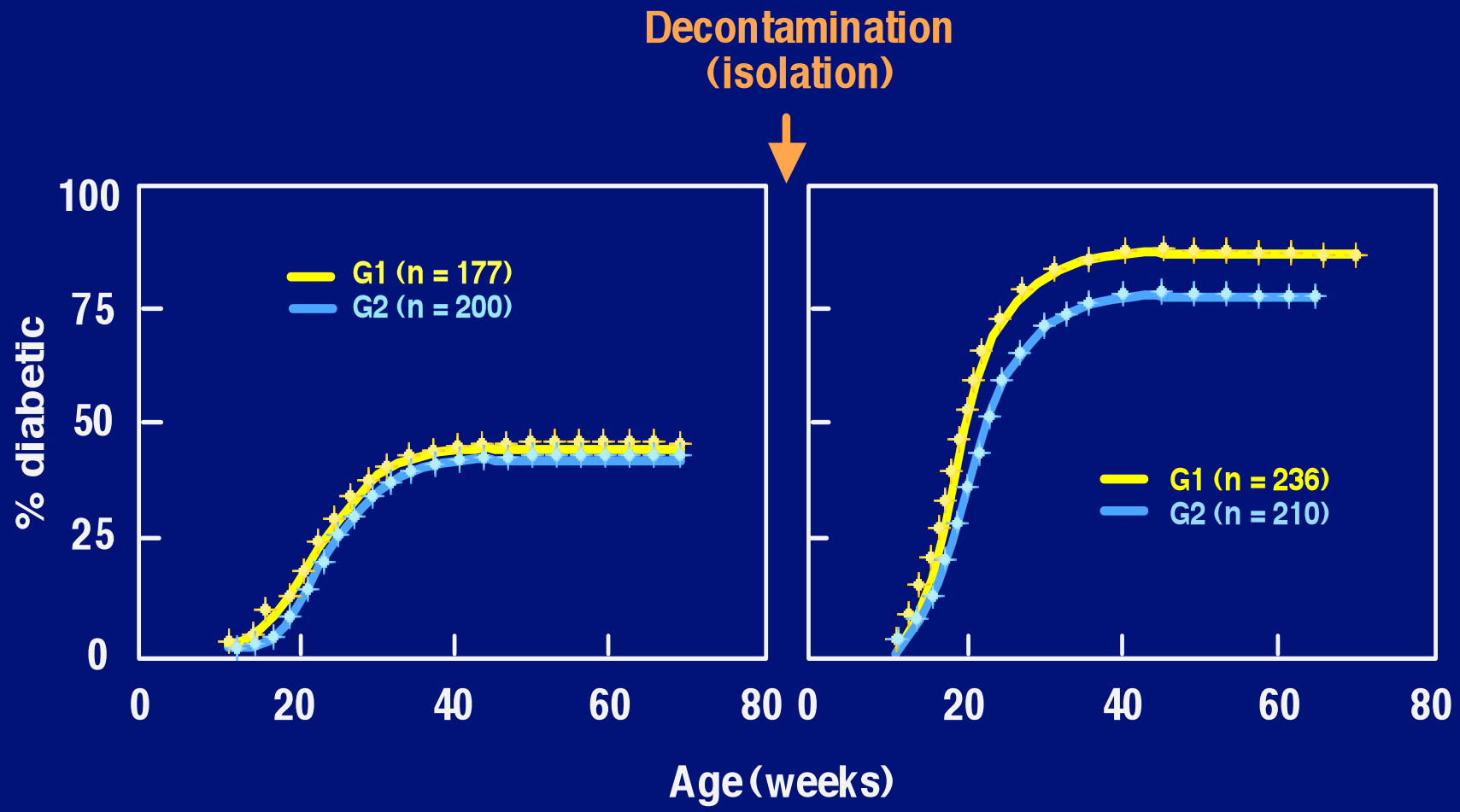
A Meta-analysis

Claudio Pelucchi,[a] *Liliane Chatenoud,*[a] *Federica Turati,*[a,b] *Carlotta Galeone,*[a,b] *Lorenzo Moja,*[a,c] *Jean-François Bach,*[d,e] *and Carlo La Vecchia*[a,b]

Epidemiology • Volume 23, Number 3, May 2012

The major role of pathogens

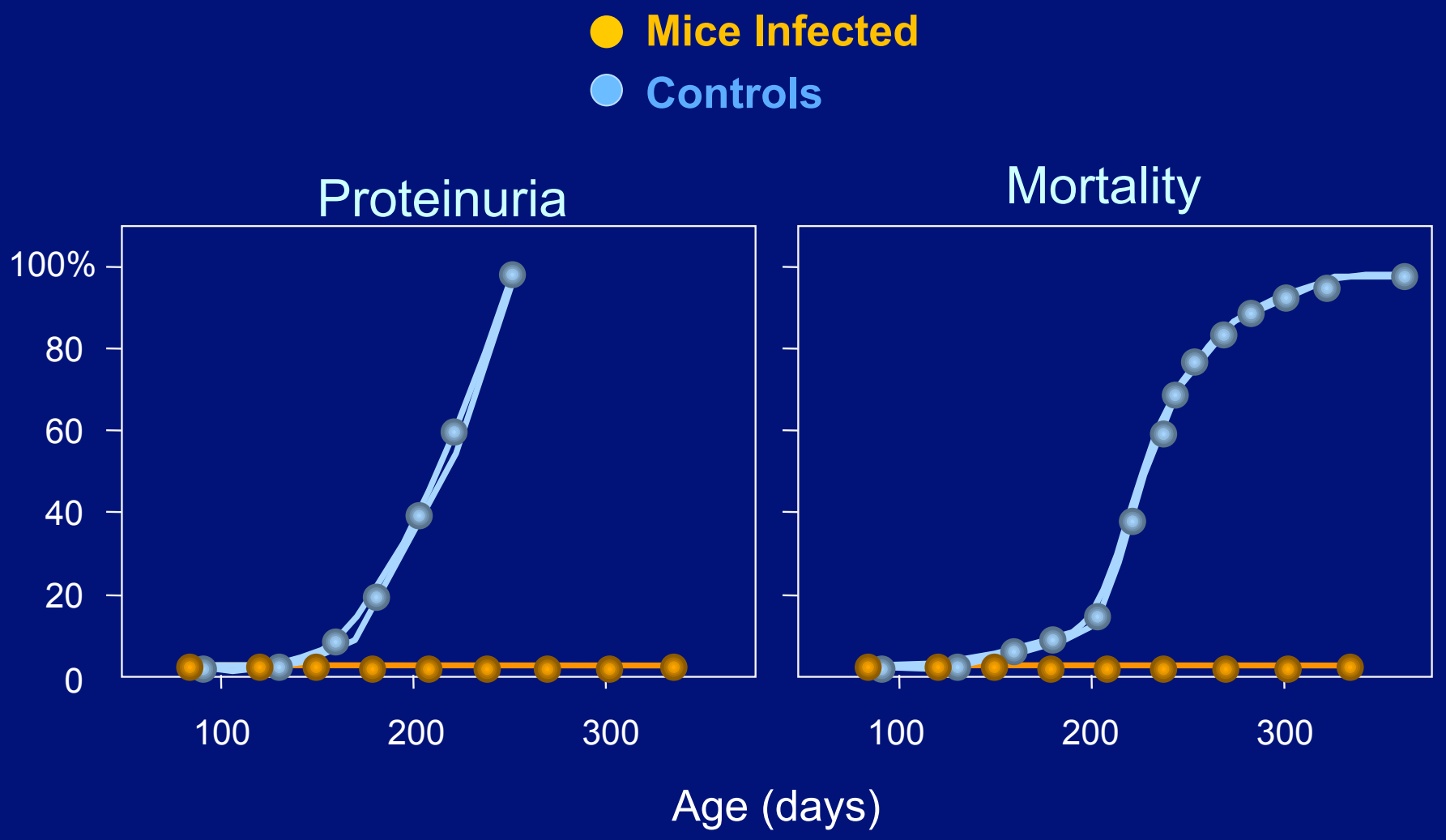
Effect of infections on diabetes incidence in female NOD mice



PREVENTION OF IDDM IN NOD MICE BY INFECTIOUS AGENTS

Bacteria	streptococci
	salmonella
	mycobacteria (CFA, BCG, …)
Viruses	LCMV
	MHV
	LDHV
Parasites	schistosoma
	pimworms

Effect of malaria in B / W mice



B. M. Greenwood et al, Science, 1970

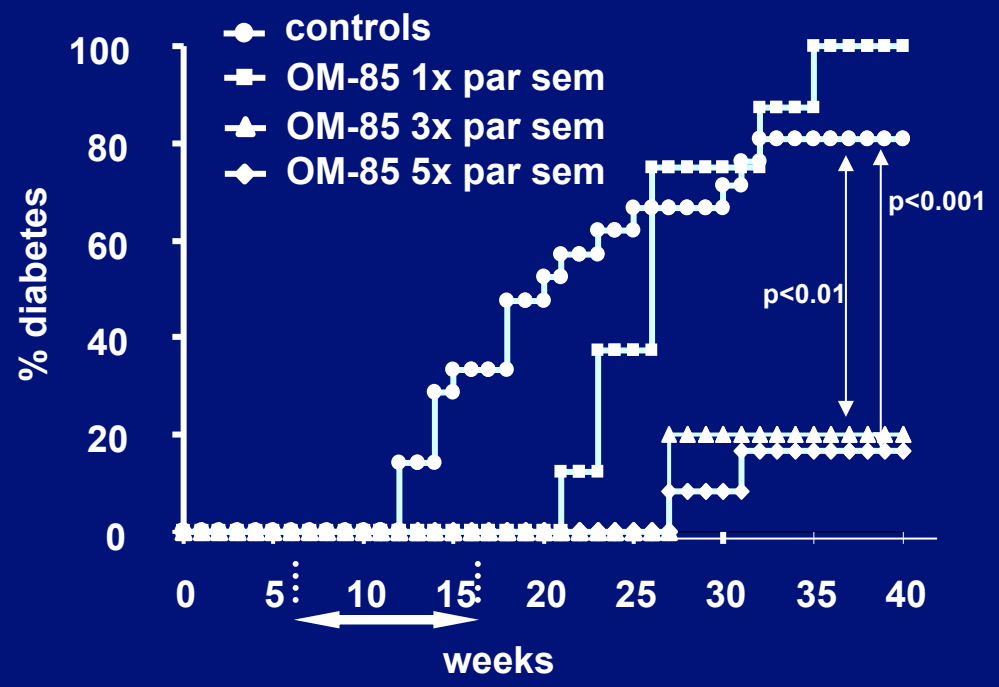
OM-85 : A BACTERIAL EXTRACT

OM-85 (OM-PHARMA, Suisse) :
plusieurs espèces bactériennes responsables d'infections du tractus respiratoire chez l'homme:

- *Haemophilus influenzae*
- *Diplococcus (Streptococcus) pneumoniae*
- *Klebsiella pneumoniae and ozaenae*
- *Staphylococcus aureus*
- *Streptococcus pyogenes* and *viridans*
- *Neisseria (Branhamella) catarrhalis*

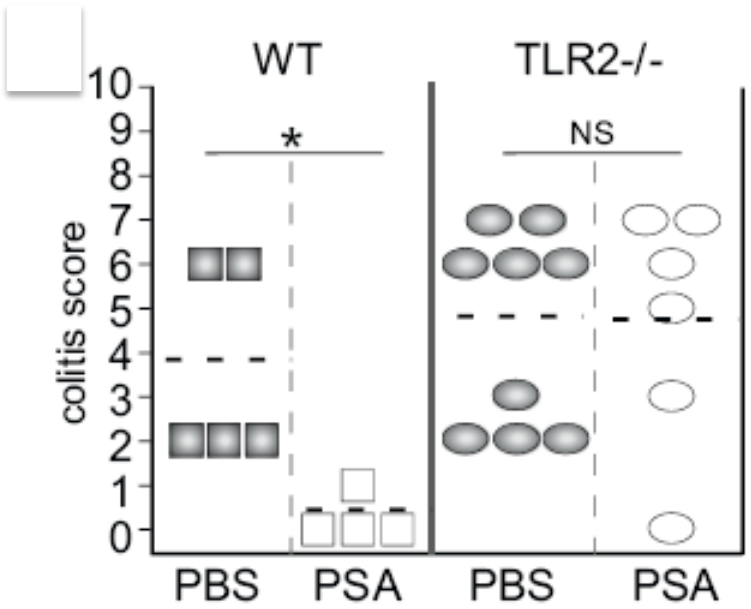
Alyanakian et al. Diabetes. 2006, 55:179-185

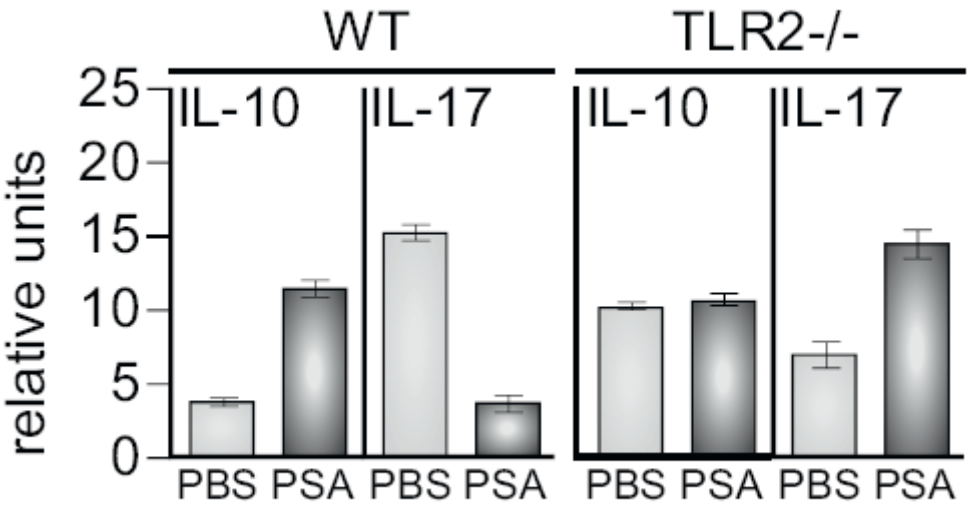
DIABETES PROTECTION BY OM-85



Underlying mechanisms : the major role of Toll-like receptors

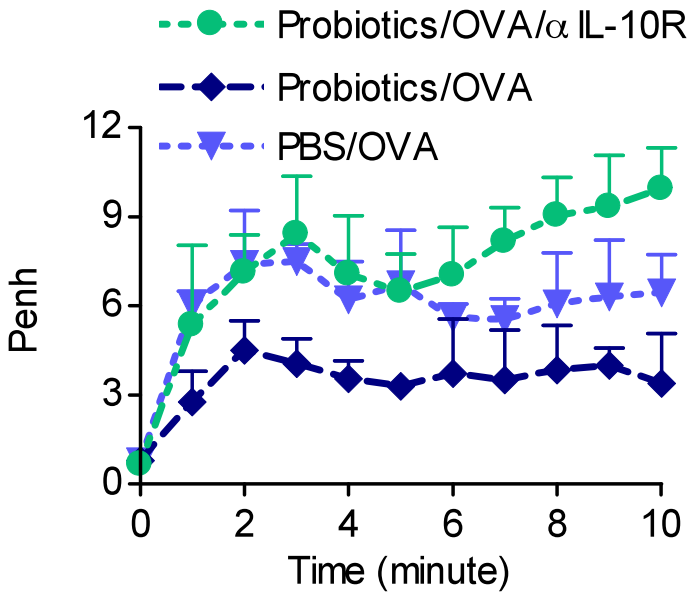
TLR2 DEPENDENCY OF THE PROTECTIVE EFFECT OF PSA ON COLITIS AND CYTOKINE PRODUCTION

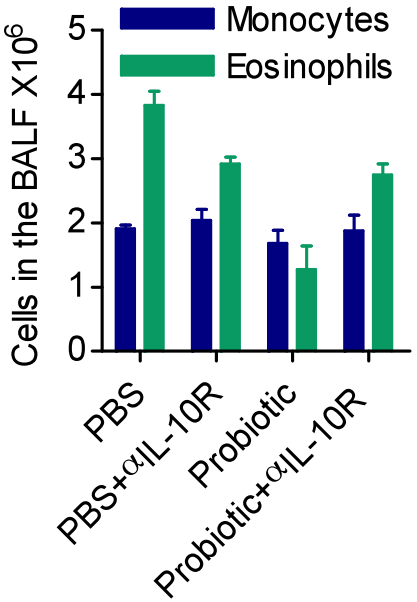


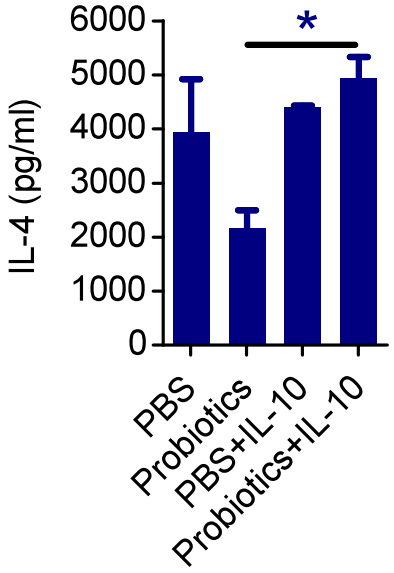


Proc. Natl. Acad. Sci (USA) 2010;107:12204-209

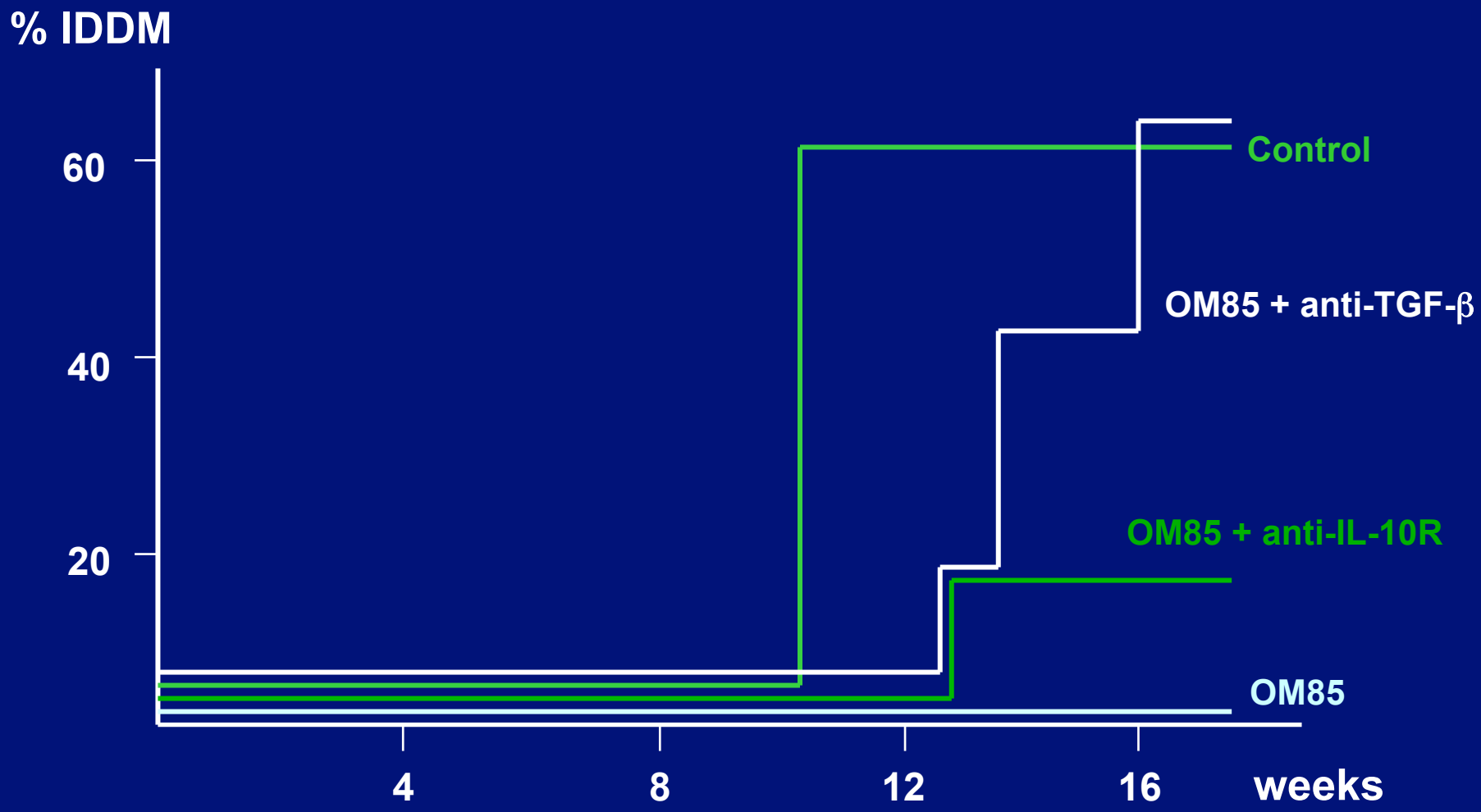
PROBIOTICS PROTECTION FROM ALLERGIC ASTHMA IS IL-10-DEPENDENT



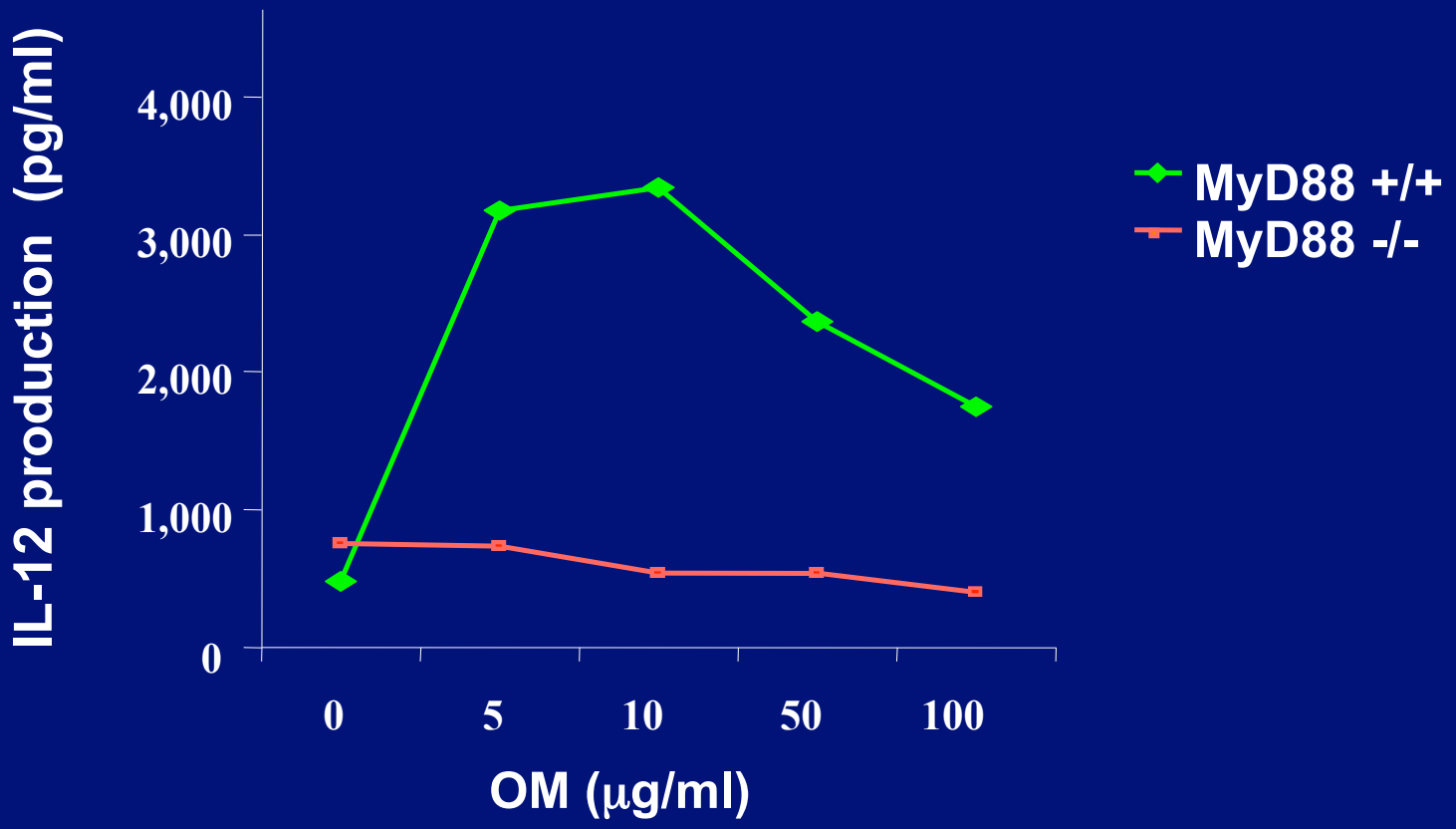




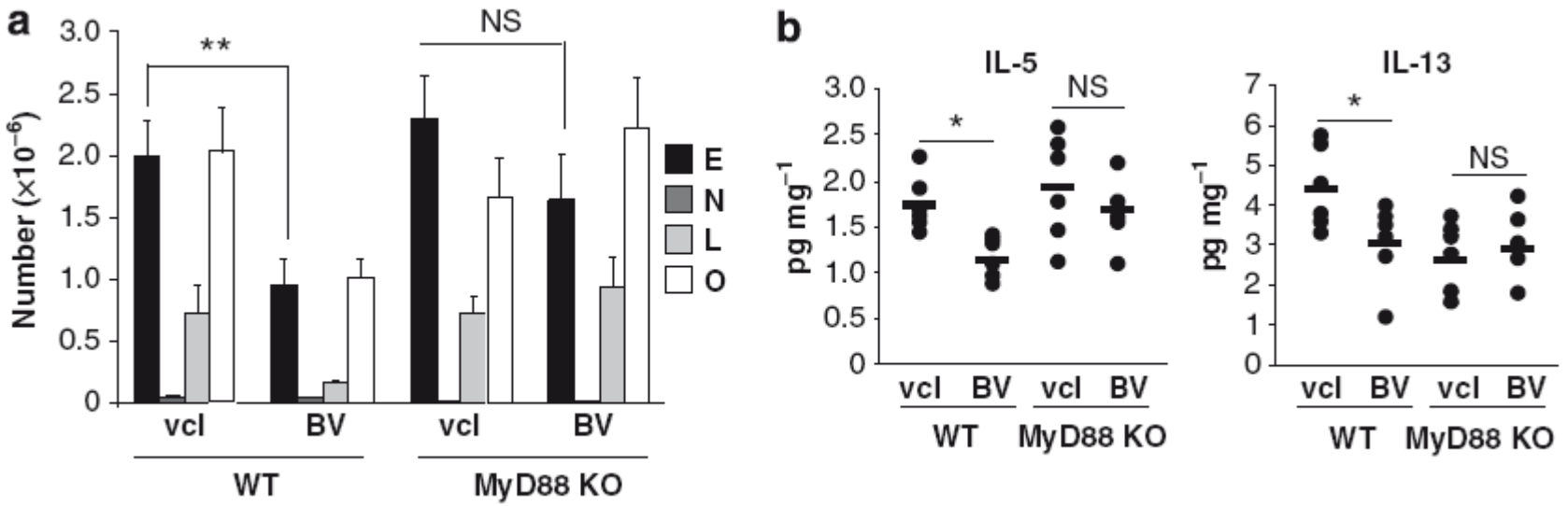
CYTOKINE DEPENDENCY OF THE OM85-INDUCED DIABETES PROTECTION



PRODUCTION OF IL-12 BY OM-85 IS ABOLISHED IN DENDRITIC CELLS FROM MYD88-DEFICIENT MICE

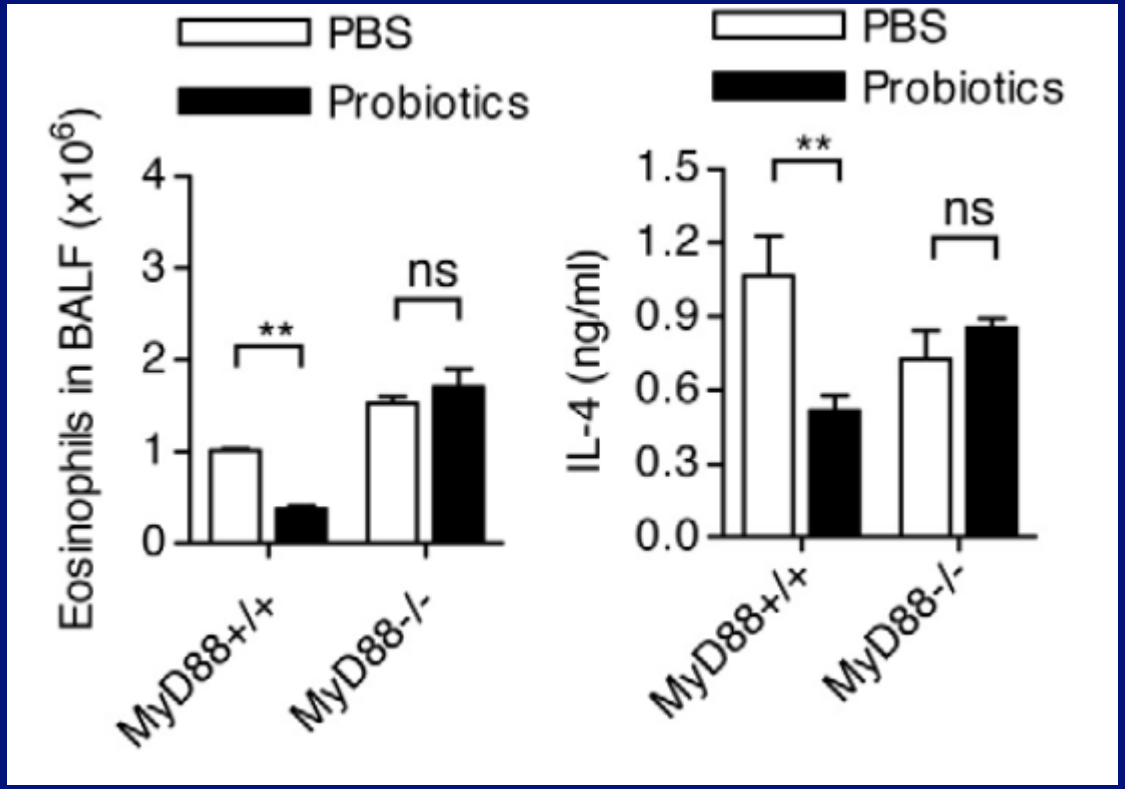


THE PROTECTIVE EFFECT OF om-85 (BV) ON ALLERGIC ASTHMA IS TLR-DEPENDENT

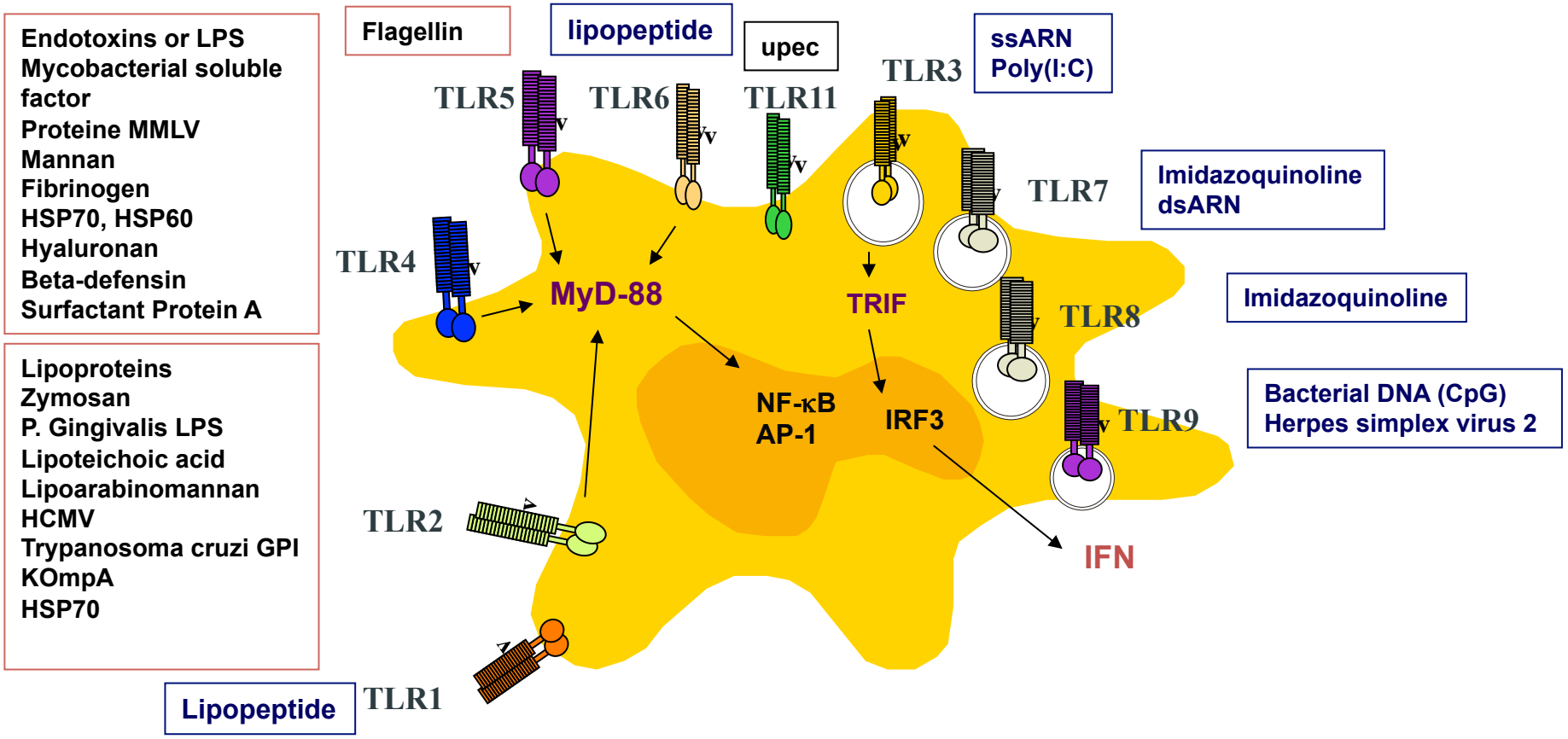


S Navarro et al. Mucosal Immunology 2011; 4: 53-65

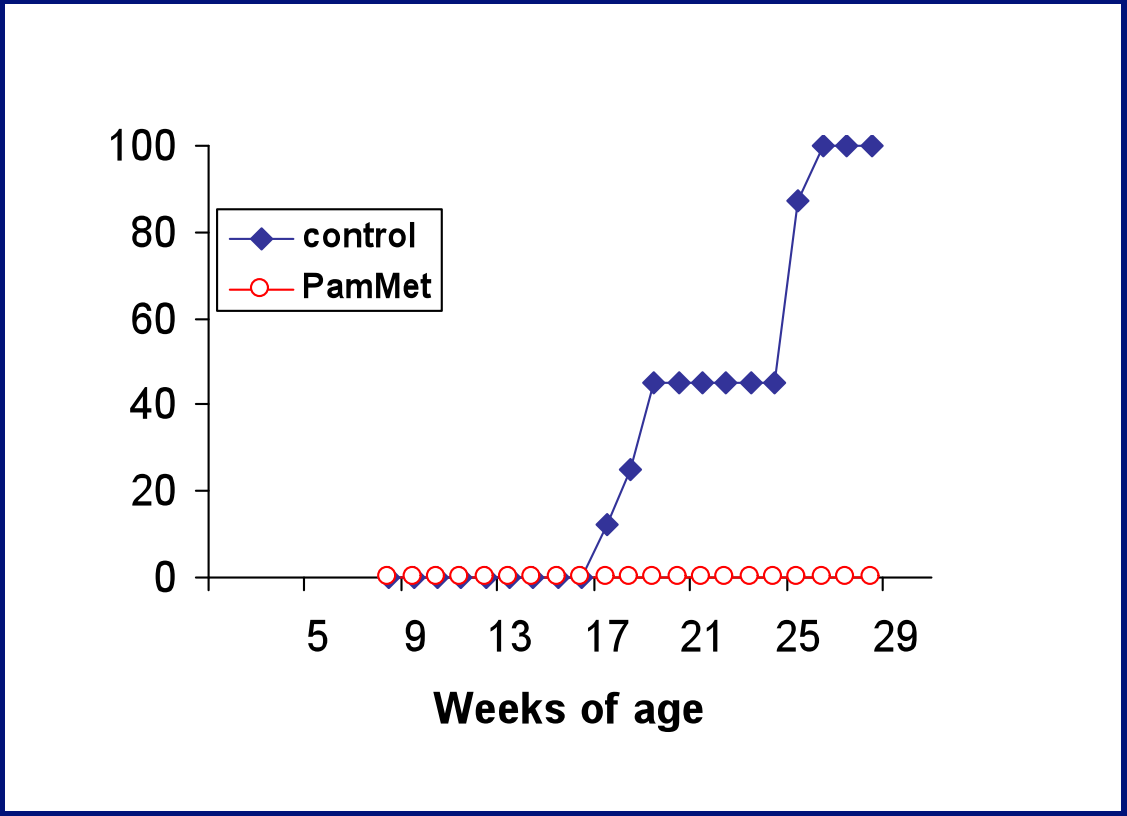
PROBIOTICS-INDUCED PROTECTION IS MyD88-DEPENDENT



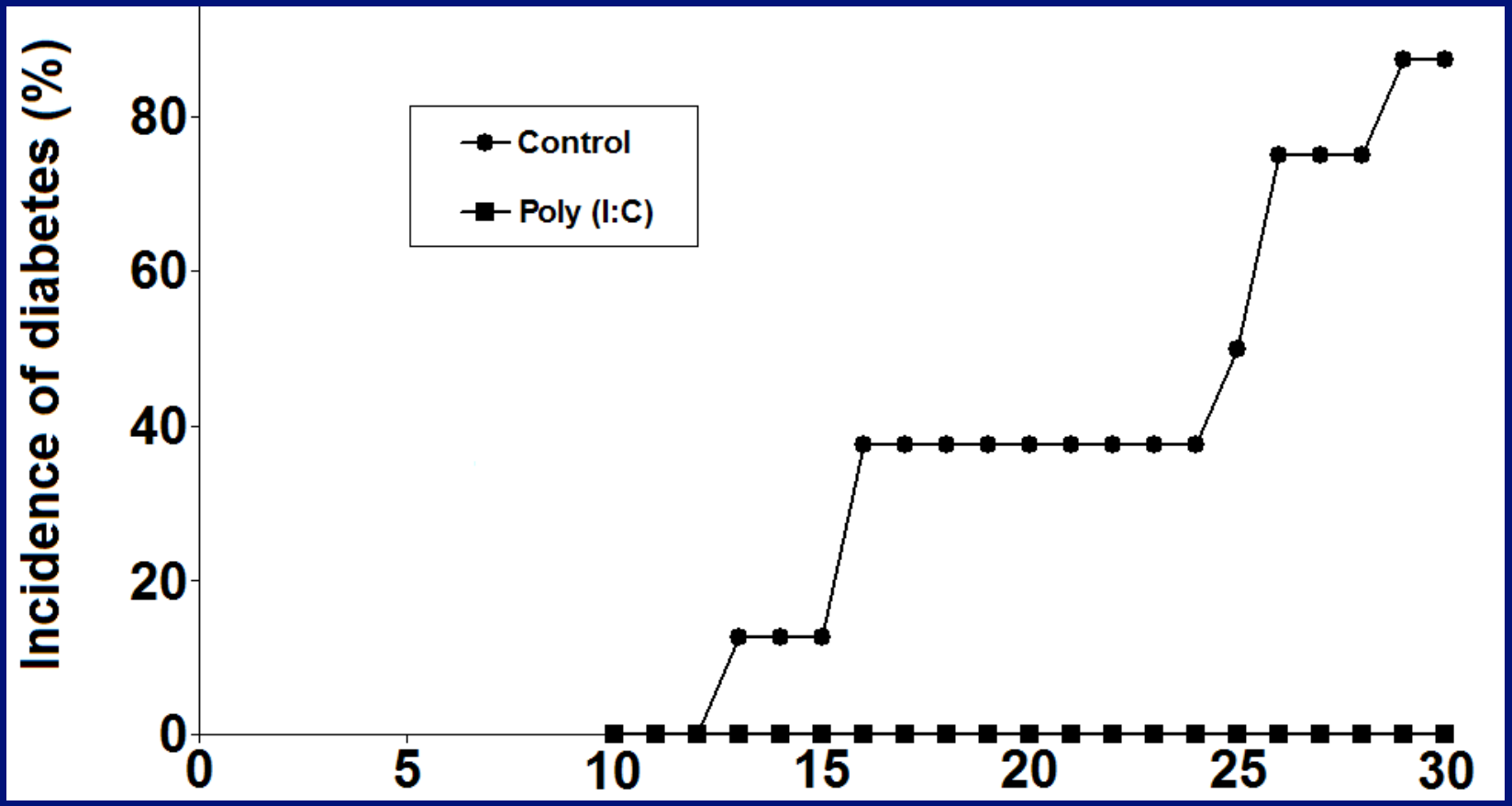
Immune response of dendritic cell to TLR agonists



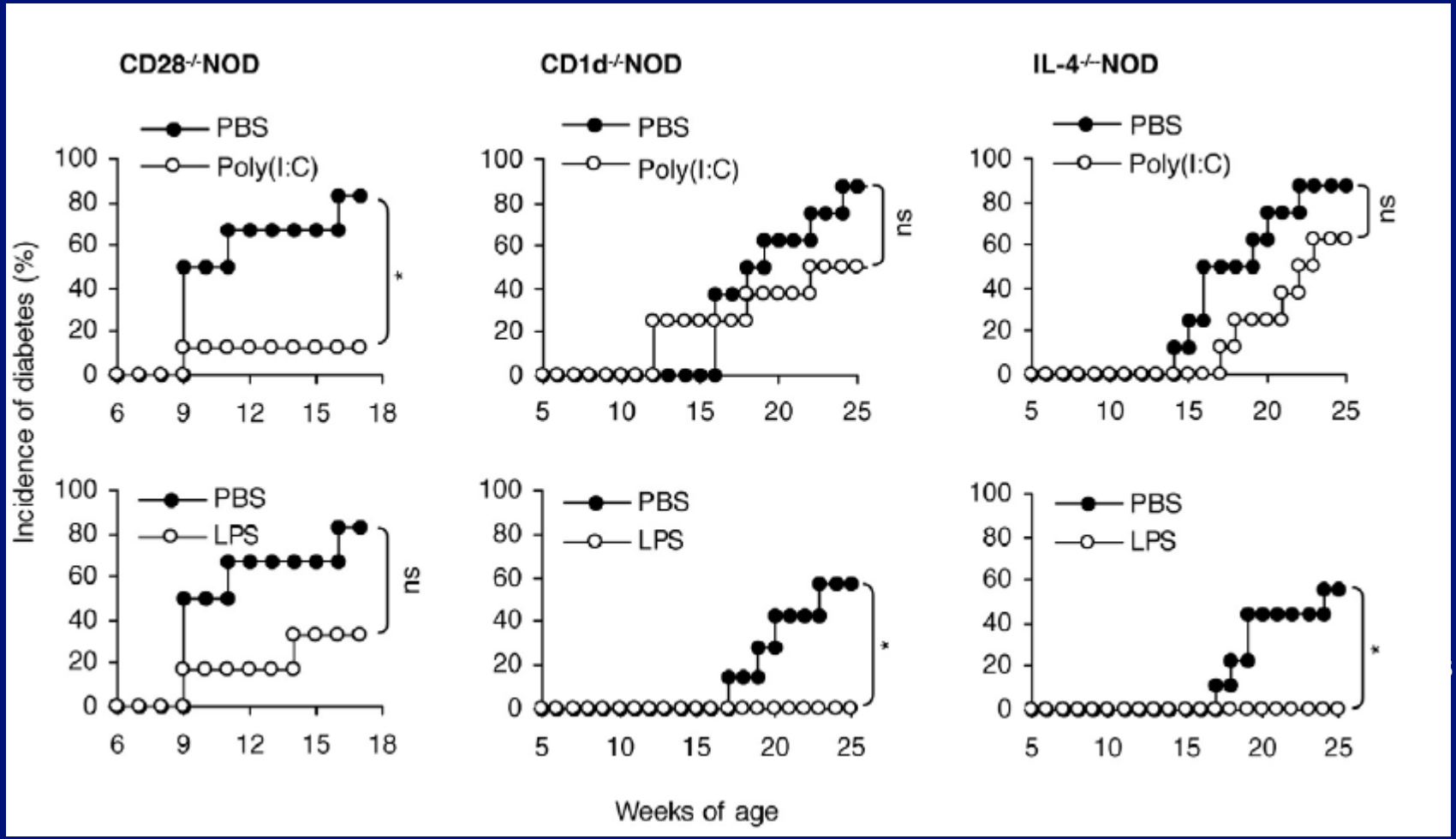
EFFECT OF PAMMET TREATMENT ON THE INCIDENCE OF DIABETES IN FEMALE NOD MICE



EFFECT OF POLY (I:C) TREATMENT ON THE INCIDENCE OF DIABETES IN FEMALE NOD MICE

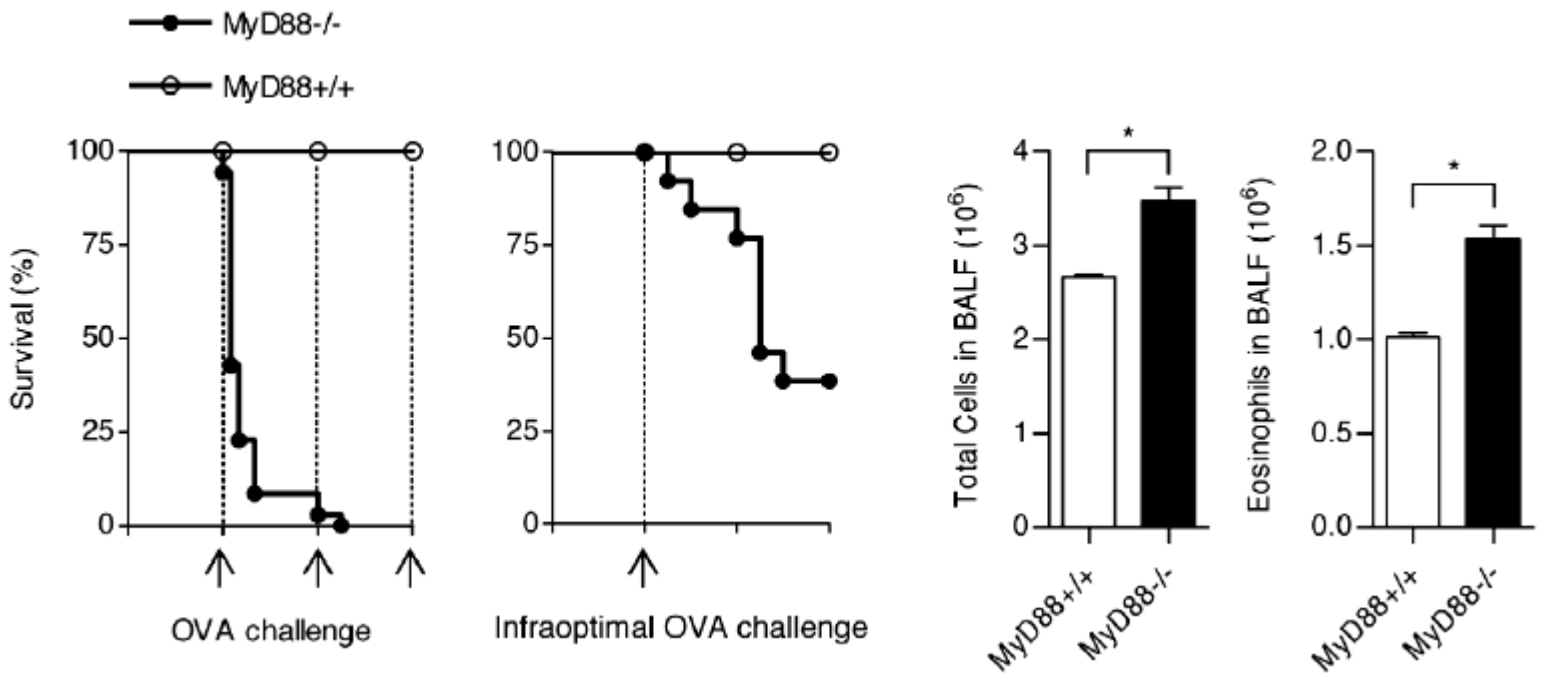


PROTECTION BY TLR AGONISTS AND IMMUNOREGULATION



Thieblemont N et al. PLoS ONE 2010, 5(7): e11484

EXACERBATION OF ALLERGIC ASTHMA IN MyD88 INVALIDATED NOD MICE



Thieblemont N et al. PLoS ONE 2010, 5(7): e11484

Conclusions

1. High hygiene predisposes to the development of autoimmune, allergic and inflammatory bowel diseases

2. The respective role of commensals and pathogens is ill-defined but most likely both of them are involved

3. A common major mode of action of commensals and pathogens involves TLR stimulation