IRR: perché alcuni bambini si ammalano più spesso di altri

F. Cardinale

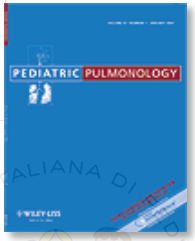
UOC di Pediatria ad indirizzo Immuno-Reumatologico e Allergo-Pneumologico

Azienda Ospedaliero - Universitaria "Policlinico – Giovanni XXIII" - Bari

IRR nel bambino: verso una nuova visione

- Che cosa si sapeva
- Nuovi aspetti eziopatogenetici
- Una ipotesi unificante
- Conclusioni

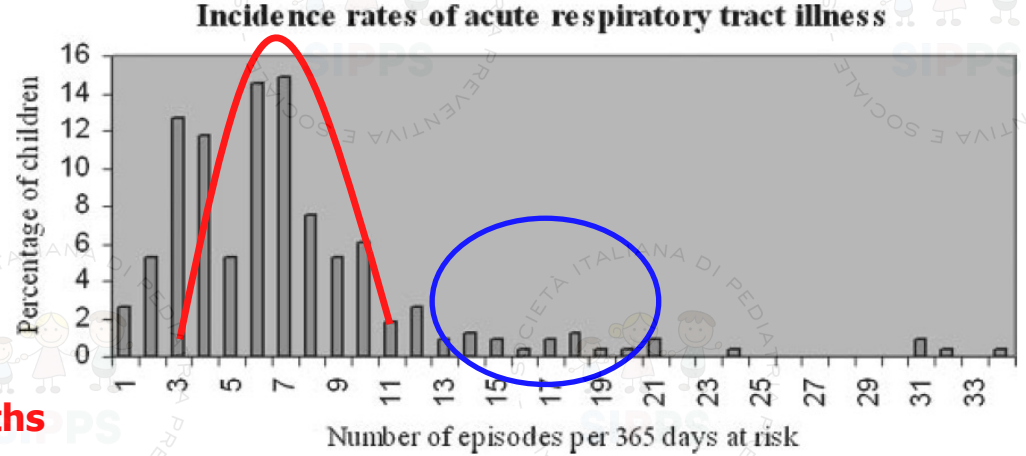
Acute Respiratory Symptoms and General Illness During the First Year of Life: A Population-Based Birth Cohort Study



Von Listow, Ped Pulmonol 2008;44:554

228 healthy infants from Copenhagen, Denmark followed from **birth** to **1 year** of age during 2004–2006

daily diaries and monthly home visits



Symptoms of **ARTI** for a **mean** of **3.5 months**

Mean 6.3 episodes (M: 5.1, IQR: 3.3–7.8) of **ARTI** per 365 days at risk

Determinants for ARTI: increasing age, winter season, household size, size of residence, day-care attendance, siblings aged 1–3 years attending a day nursery

Population-Based Study of the Impact of Childcare Attendance on Hospitalizations for Acute Respiratory Infections

Kamper-Jorgensen, Pediatrics 2006;118:1439

Studio *register-based* su **138.821 ricoveri ospedalieri** per **ARTI** in una coorte di **bb Danesi** di **età 0-5 aa**

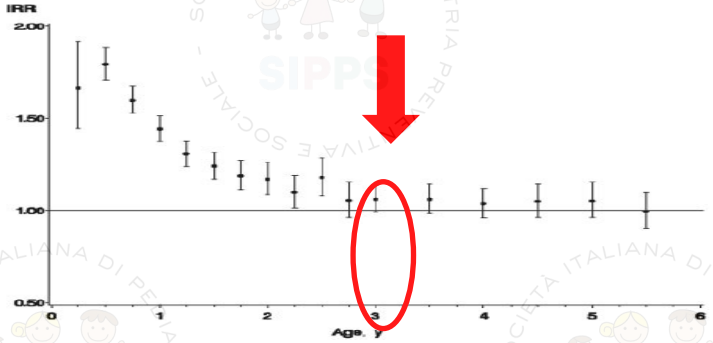
TABLE 1 IRR and 95% CIs of Hospitalization for ARI in Children Aged 0, 1, 2, and ≥3 Years, According to Time Since Enrollment Into First and Second Child Care Facility, Respectively

Variable	Short (≤5 mo)	Medium (6–11 mo)	Long (≥12 mo)	Home Care (Ref)
Time since first enrollment				
Age 0 y	1.69 (1.63–1.74)	1.60 (1.38–1.86)	NE	1
Age 1 y	1.47 (1.42–1.52)	1.24 (1.19–1.28)	1.01 (0.95–1.07)	1
Age 2 y	1.41 (1.31–1.52)	1.34 (1.25–1.43)	1.02 (0.97–1.06)	1
Age ≥3 y	1.08 (1.01–1.16)	1.18 (1.10–1.27)	1.04 (1.00–1.09)	1
Time since second enrollment				
Age 0 y	1.61 (1.40–1.84)	NE	NE	1
Age 1 y	1.40 (1.31–1.49)	1.30 (1.18–1.42)	0.89 (0.68–1.18)	1
Age 2 y	1.21 (1.10–1.33)	1.28 (1.16–1.41)	1.02 (0.92–1.12)	1
Age ≥3 y	1.06 (1.00–1.13)	1.02 (0.96–1.09)	0.98 (0.93–1.03)	1

In bb <12 mesi, primi 6 mesi di day-care associati a **+69%** rischio di ricovero ospedaliero

Rischio di ricovero **↑ 4x** per bb età 0-2 aa inseriti nel **day-care senza fratelli**

Dopo 1 anno di frequenza day-care e **dopo i 3 aa rischio uguale** agli home-care



Burden of Recurrent Respiratory Tract Infections in Children

A Prospective Cohort Study

Toivonen, PIDJ 2016;36:e332

STEP Study

Prospective study on **1089** children followed from birth to 2 yrs of age for **RTI** by a daily symptom diary and nasal swabs for viruses (n=714)

TABLE 3. Risk Factors for Recurrent Respiratory Tract Infections

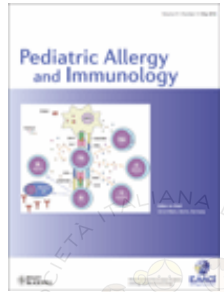
	Children With Recurrent Infections (n = 109), n (%)	Children Without Recurrent Infections (n = 980), n (%)	OR (95% CI), Unadjusted	*P*, Unadjusted	OR (95% CI), Adjusted	*P*, Adjusted
Characteristic*						
Male sex	62 (57)	502 (51)	1.26 (0.84–1.87)	0.26	1.17 (0.77–1.77)	0.46
Older siblings	76 (70)	422 (43)	3.05 (1.99–4.67)	<0.001	3.03 (1.94–4.74)	<0.001
Higher educational level of the mother	73/109 (67)	612/955 (64)	1.14 (0.75–1.73)	0.55	1.33 (0.85–2.06)	0.21
Living in the nonurban area	57/109 (52)	389/957 (41)	1.60 (1.08–2.38)	0.02	1.34 (0.88–2.04)	0.17
Breast-fed at least for 6 months	70/106 (66)	566/937 (60)	1.28 (0.84–1.95)	0.26	1.20 (0.78–1.85)	0.41
Parental smoking at the time of pregnancy or birth	9/106 (9)	158/893 (18)	0.43 (0.21–0.87)	0.02		
Nasopharyngeal bacterial colonization at 2 months of age†						
Streptococcus pneumoniae	9/33 (27)	29/281 (10)	3.26 (1.38–7.68)	0.007	2.44 (0.93–6.39)	0.07
Moraxella catarrhalis	12/33 (36)	61/281 (22)	2.06 (0.96–4.42)	0.06	1.71 (0.75–3.88)	0.20

*Binary logistic regression analysis was performed using sex, siblings, mother's educational level, living environment and breast-feeding as predictors.
†The logistic regression analysis was performed for nasopharyngeal bacteria, adjusting for sex, siblings, mother's educational level, living environment and breast-feeding.

Older siblings (≥1) was the only risk factor for **recurrent RTI**

No s.s. effect for **day care** attendance and **parental smoking** for recurrent RTI

The child with recurrent respiratory infections: normal or not?



De Martino, Pediatr Allergy Immunol 2007:18:3

Fattori Ambientali
(fumo, scuola materna,…)

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Immunodeficit secondario post-virale

Infezioni virali

IRR nel bambino: verso una nuova visione

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- Nuovi aspetti eziopatogenetici
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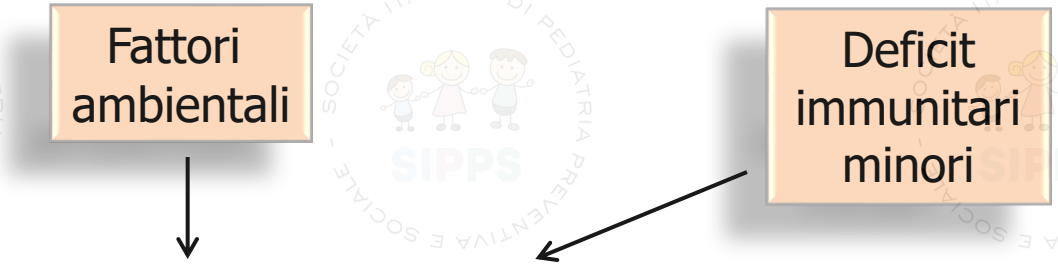
Perché alcuni bambini ammalano di IRR?



[…] **RRI children** have no significant alteration of immunity […]

De Martino, PAI 2007:18:3

DEFICIT SELETTIVI DI RISPOSTA ANTICORPALE (SPAD)

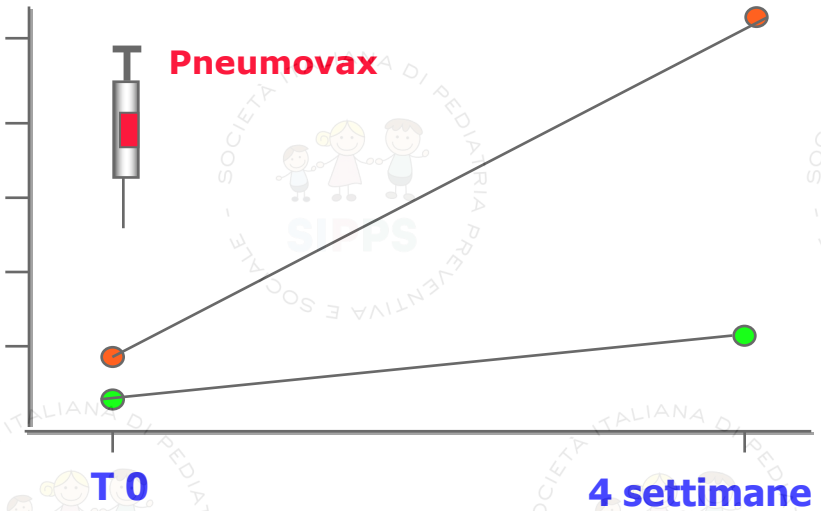
Selective defect in the antibody response to Haemophilus Infl. type B in children with recurrent infections and normal serum IgG subclass levels

Ambrosino DM et al. , J Allergy Clin Immunol 1988;81:1175-9

Defective antipneumococcal polysaccharide antibody response in children with recurrent respiratory tract infections

Sanders LA et al., J Allergy Clin Immunol 1993;91:110 -9

IgG anti-polisaccaride Pneumococcico (U. ELISA)



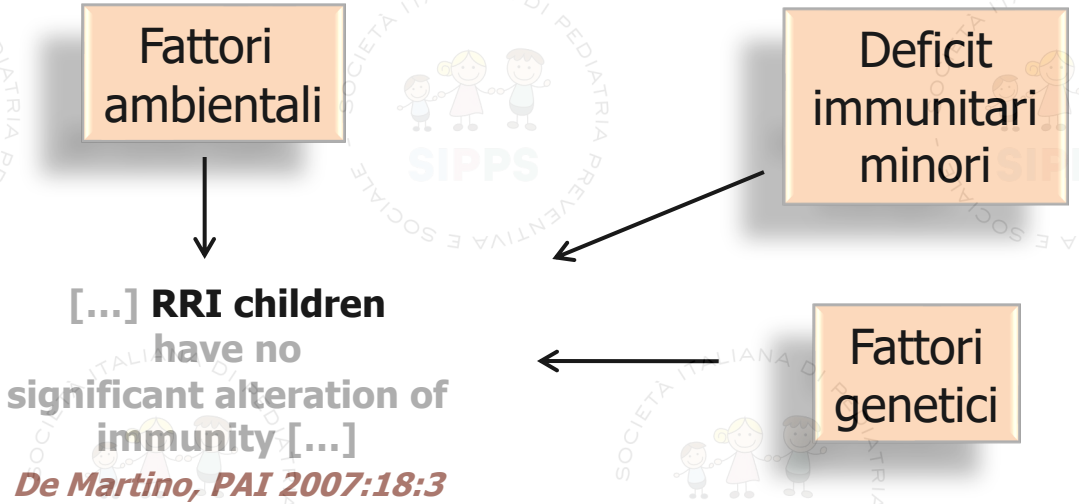
ESID Registry – Working Definitions for Clinical Diagnosis of PID

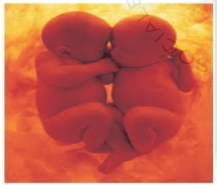
These criteria are only for patients with **no genetic diagnosis***.
*Exceptions: Atypical SCID, DiGeorge syndrome – a known genetic defect and confirmation of criteria is mandatory.

Deficiency of specific IgG (Specific antibody deficiency - SPAD)	3. Predominantly antibody deficiencies	102582	ORPHA:169443		Nizar Mahlaoui, David Edgar, Stephan Ehl, Helen Chapel, Isabella Quinti, Esther de Vries	Infections (recurrent or severe bacterial) **AND** normal serum/plasma IgG, A and M and IgG subclass levels **AND** Profound alteration of the antibody responses to *S.* pneumoniae (or other polysaccharide vaccine) either after documented invasive infection or after test immunization. **AND** Exclusion of T cell defect	**Unclassified antibody deficiencies**

https://esid.org/Working-Parties/Registry-Working-Party/Diagnosis-criteria

Perché alcuni bambini ammalano di IRR?





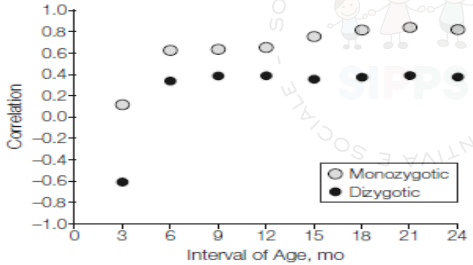
The Heritability of Otitis Media
A Twin and Triplet Study

Casselbrant, JAMA 1999;282:2125-2130

Prospective twin and triplet cohort study with enrollment from 1982 through 1995.

168 healthy same-sex **twin** and **7 triplet** sets recruited within the first 2 mo of life; zygosity results available for 140 sets 99% followed up for **1 yr** and 90% for **2 yrs**

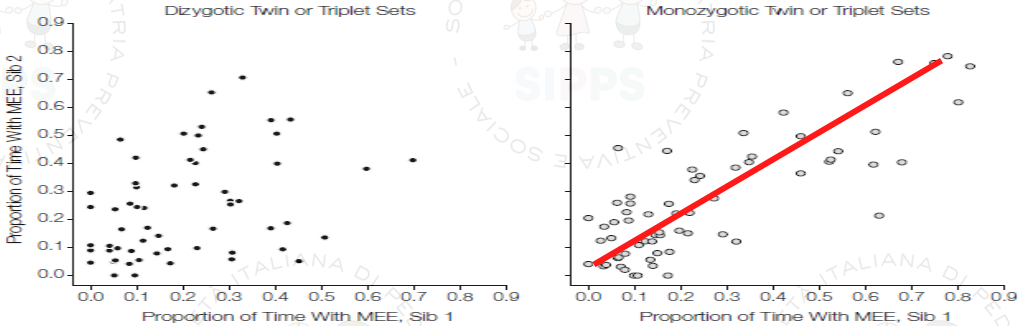
Figure 1. Correlation of Time With MEE Between 2 Sibs in a Twin or Triplet Set



Estimate of **heritability** of time with middle ear effusion **0.73** (*P=.001).*

Estimate of discordance of an episode of AOM in monozygotic twins **0.04** compared with **0.49** in dizygotic twins (*P = .005).*

Figure 2. Proportion of Time With MEE by 24 Months of Age for Sib 1 vs Sib 2 Within a Twin or Triplet Set



ARTICLE
Received 29 Jan 2016 | Accepted 2 Aug 2016 | Published 28 Sep 2016
DOI: 10.1038/ncomms12792 OPEN

Genome-wide association study for acute otitis media in children identifies *FNDC1* as disease contributing gene

Van Ingen, Nature Comm 2016;Sep 28;7:12792

Genome-wide association study
Two cohorts of **AOM children** (age of onset <3 years old) [825 cases + 7,936 controls and 1,219 cases + 1067 controls]

Table 1 | Genome-wide significant association of 6q25.3 with acute otitis media.

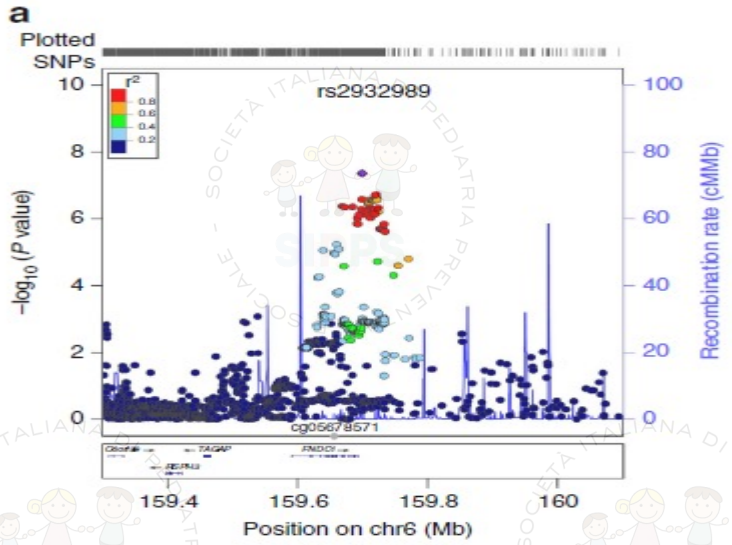
SNP	Chr	Pos (hg19)	Gene	A1/A2	MAF cases/controls	Stage	OR_{CHOP} (95% CI)	P_{CHOP}	OR_{GenR} (95% CI)	P_{GenR}	P_{meta}
rs2932989	6	159699284	*FNDC1*	T/G	0.17/0.13	Discovery	1.41 (1.23, 1.62)	$1.46e^{-06}$	1.25 (1.05, 1.48)	$1.02e^{-02}$	$4.36e^{-08*}$
						Replication	1.35 (1.05, 1.73)	$1.55e^{-02}$			
						Combined					$2.15e^{-09\dagger}$

A1, minor allele; A2, major allele; Chr, chromosome; CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; P, *P* value; Pos, position; SNP, single-nucleotide polymorphism.
*P value of meta-analysis at discovery stage.
†P value of meta-analysis of all cohorts.

Significant association at a locus on **6q25.3**

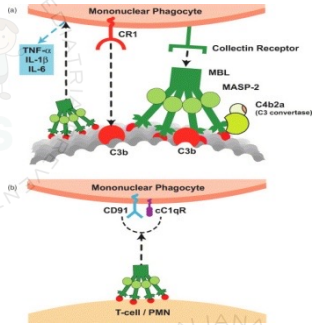
One variant (rs2932989) surpassed the genome-wide significance threshold

Correlation found between the variant and the expression levels and methylation status of the **fibronectin type III domain containing 1 (FNDC1)** gene



Acute Respiratory Tract Infections and Mannose-Binding Lectin Insufficiency During Early Childhood

Koch A, JAMA 2001;285:1316



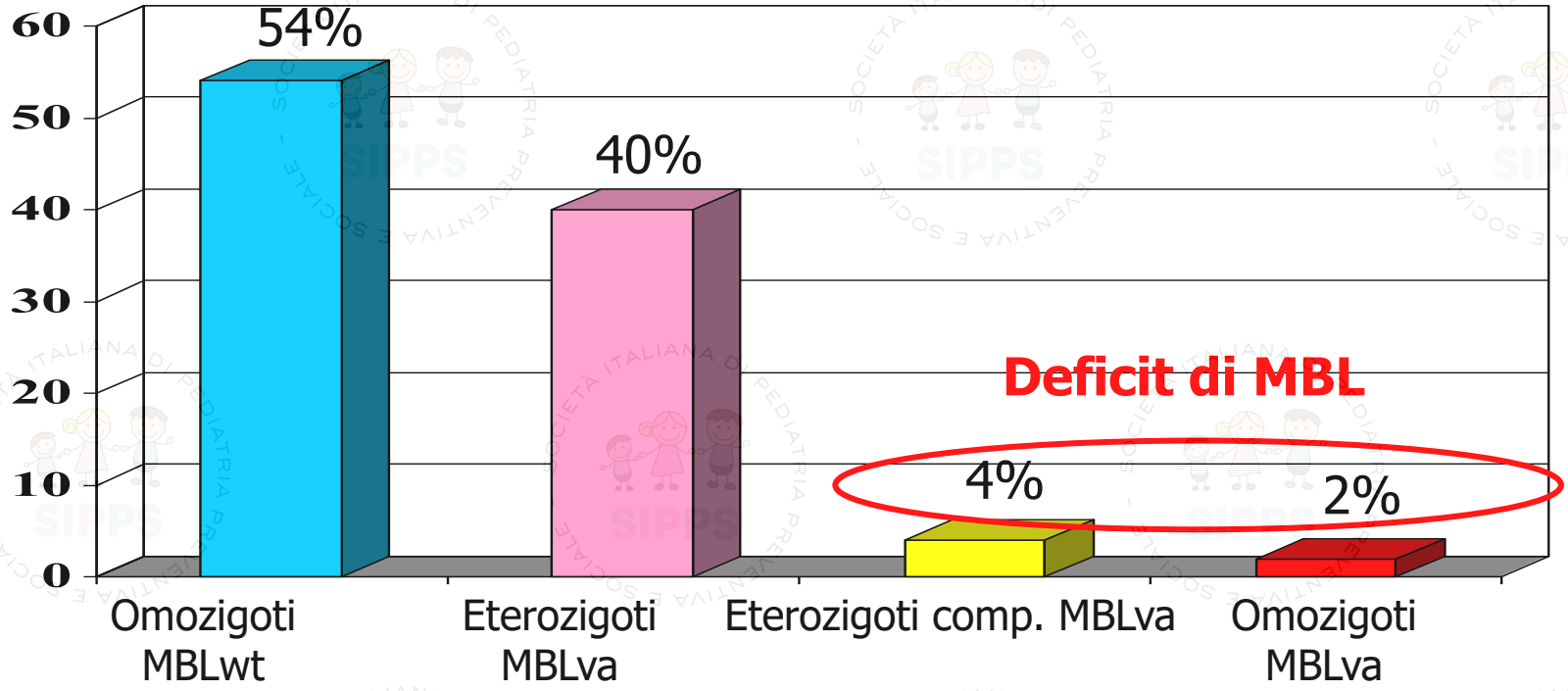
Bambini di età **6-17 mesi** con **deficit di MBL** (genotipo XA/O e O/O) presentano una frequenza di infezioni vie aeree superiori **≈ 3 volte maggiore** rispetto a individui con genotipo normale

Table 2. Association Between Mannose-Binding Lectin Genotypes and Risk of Acute Respiratory Tract Infections (ARI) in 252 Children From Sisimiut, Greenland

		ARI		
	Days at Risk	No. of Episodes	RR (95% CI)*	*P* Value
Genotypes, structural alleles				
A/A	22 619	548	1.00	.02†
A/O (A/B, A/C, A/D)	6026	149	1.41 (0.96-2.06)	
O/O	605	14	2.09 (1.16-3.75)	
A/A	22 619	548	1.00	<.05
A/O + O/O	6631	163	1.46 (1.01-2.10)	
Genotypes, promotor alleles included				
YA/YA	17 246	402	1.00	.003
YA/XA	4423	127	0.98 (0.58-1.66)	
XA/XA	950	19	0.94 (0.41-2.14)	
YA/O	5453	129	1.26 (0.85-1.85)	
XA/O	573	20	2.70 (1.63-4.49)	
O/O	605	14	1.93 (1.11-3.35)	
A/A (YA/YA, YA/XA, XA/XA)	22 619	548	1.00	<.001
YA/O	5453	129	1.26 (0.87-1.82)	
XA/O	573	20	2.70 (1.64-4.44)	
O/O	605	14	1.91 (1.10-3.32)	
Sufficient (*A/A + YA/O*)	28 072	677	1.00	<.001
Insufficient (*XA/O + O/O*)	1178	34	2.08 (1.41-3.06)	

*Relative risk (RR) estimated in generalized estimating equation model with 6 banded Toeplitz correlation structure and adjusted for sex, age, ethnicity, and calendar time. CI indicates confidence interval.
†*P* values test for homogeneity. Test for trend *P* = .02.

Prevalenza del deficit di MBL nella popolazione



Cardinale F, Int J Immunopathol Pharmacol 2008;21:735-8

Vitamin D Receptor Polymorphisms and the Risk of Acute Lower Respiratory Tract Infection in Early Childhood

Roth, J Infect Dis 2008;197:676

- **56 bb età 1-24 mesi** ospedalizzati per LRTI (bronchiolite, polmonite)
- **64 controlli**

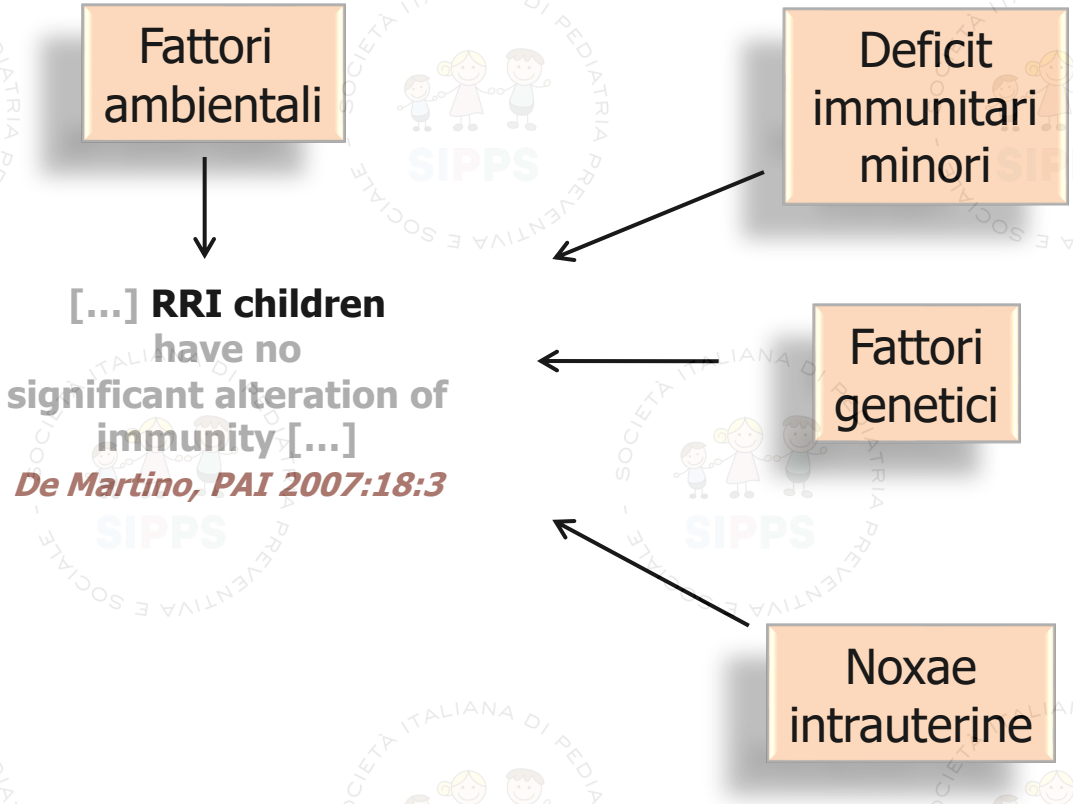
Studiati per polimorfismi del **Vitamin D Receptor** (*Taq*1 e *Fok*1)

VDR locus, model, genotype	Overall (n = 120) OR (95% CI)	*P*	Subsample (n = 81) OR (95% CI)	*P*
*Fok*I				
Crude				
FF	1		1	
Ff	1.34 (0.59–3.05)	.480	1.87 (0.59–5.92)	.289
ff	7.43 (1.80–30.67)	.006	26.40 (2.58–271.09)	.006
Ethnicity adjusted				
FF	1		N/A	
Ff	1.40 (0.55–3.58)	.481	. . .	
ff	6.16 (1.31–28.95)	.021	. . .	
Fully adjusted[a]				
FF	1		1	
Ff	1.04 (0.29–3.77)	.955	1.83 (0.32–10.39)	.493
ff	7.38 (1.17–46.55)	.033	29.90 (1.93–463.72)	.015

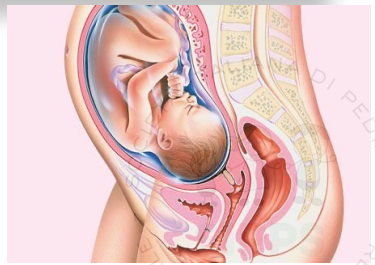
Genotipo *Fok*1 associato ad un rischio **7x** di **infezioni delle basse vie respiratorie**

Associazione più debole con polimorfismi di *Taq*1

Perché alcuni bambini ammalano di IRR?



Neonatal total IgE and respiratory tract infections in children with intrauterine smoke exposure



Ruskamp, Arch Dis Child 2010;95:427–431

Data from **2863 children** collected from birth to the age of **4 yrs**

Neonatal total IgE available from 914 children +questionnaires

In children with **↑ tIgE** or **atopic dermatitis** and **prenatal tobacco** exposure higher risk of **frequent RTI (OR 6.18)**

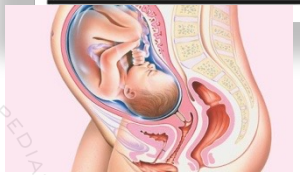
Similar results seen for **lower RTI** and **otitis**

The effect was less evident for postnatal ETS

Table 2 Association between frequent RTI* and risk factors (n=2863)

	Crude OR† (95% CI)	aOR‡ (95% CI)
Maternal smoking during pregnancy	1.64 (1.06 to 2.55)	1.46 (0.85 to 2.49)
ETS exposure at 3 months	1.32 (0.88 to 1.97)	0.96 (0.59 to 1.58)
ETS exposure at 1 year	0.99 (0.66 to 1.49)	1.53 (0.93 to 2.50)
Atopic dermatitis at 3 months	2.21 (1.31 to 3.72)	1.84 (1.07 to 3.17)
Elevated neonatal tIgE§	1.38 (0.53 to 3.60)	1.11 (0.41 to 3.01)
Parental allergy¶	1.61 (1.11 to 2.34)	1.56 (1.06 to 2.29)
Frequent wheeze**	4.65 (2.96 to 7.30)	4.05 (2.55 to 6.44)
Breastfeeding for <12 weeks	1.76 (1.21 to 2.56)	1.56 (1.06 to 2.31)
Low level of parental education††	2.24 (1.31 to 3.82)	2.06 (1.18 to 3.57)

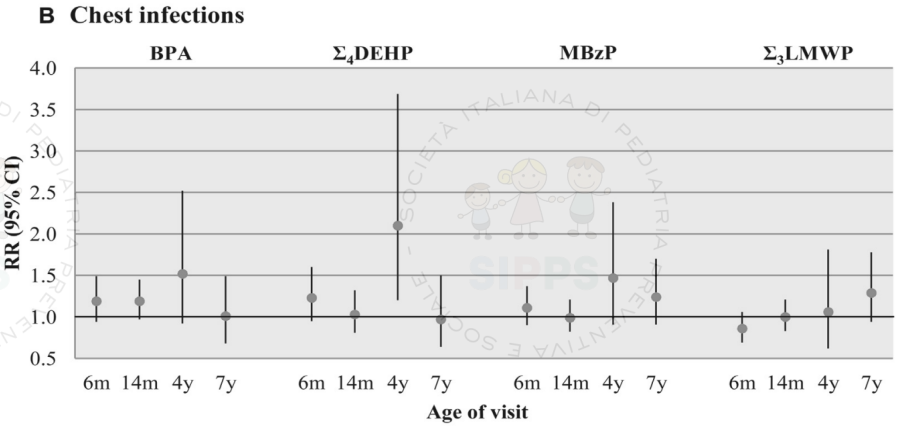
Prenatal exposure to bisphenol A and phthalates and childhood respiratory tract infections and allergy



Gascon, JACI 2015;135:370

INMA Study (Spain)
657 pregnant women
Levels of bisphenol A and metabolites of high- and low molecular weight phthalates (*Σ4DEHP, MBzP, Σ3LMWP*) measured in urine during the **1th** and **3rd trimester**

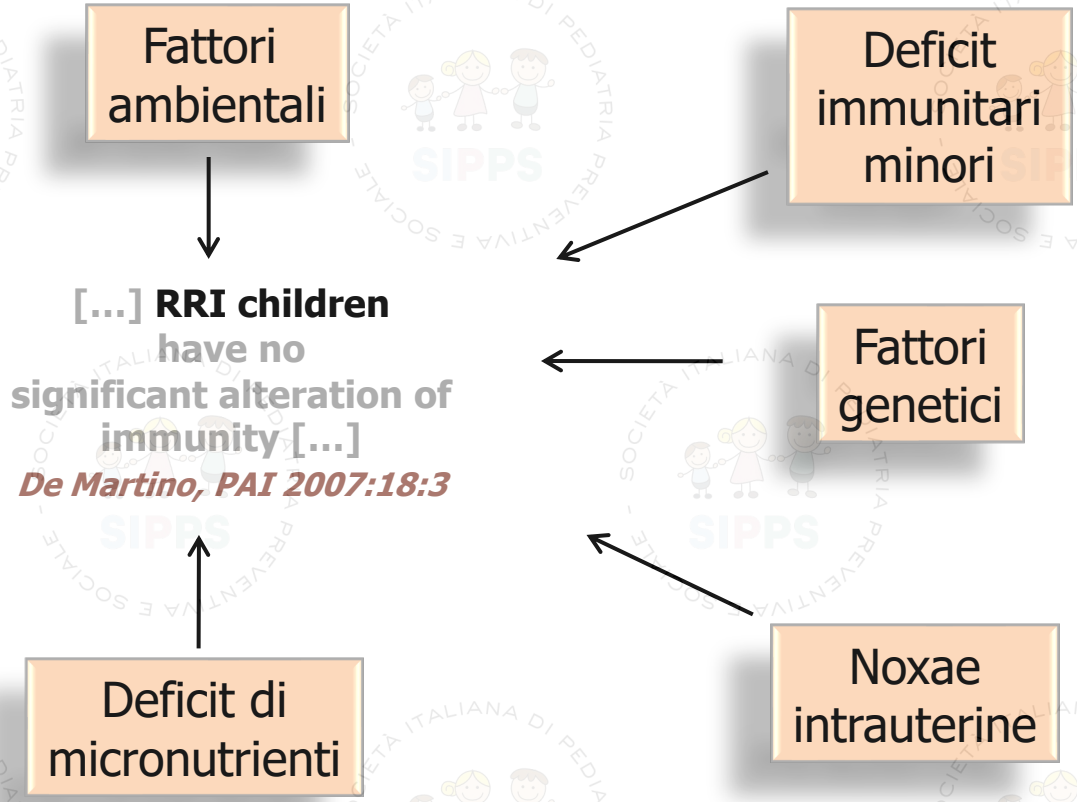
Questionnaires at 6 + 14 mo, 4 + 7 yrs + **sIgE**



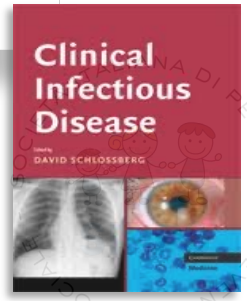
↑ **risk** at any age for **each doubling** in maternal urinary **BPA** and **Σ4DEHP** for:

- **wheeze** (RR 1.20 - 1.25)
- **chest infections** (RR, 1.15 – 1.15)
- **bronchitis** (RR 1.18 – 1.20)

Perché alcuni bambini ammalano di IRR?



Low Serum 25-Hydroxyvitamin D Level and Risk of Upper Respiratory Tract Infection in Children and Adolescents



Science, Clin Infect Dis 2013;57:392–7

Prospective study

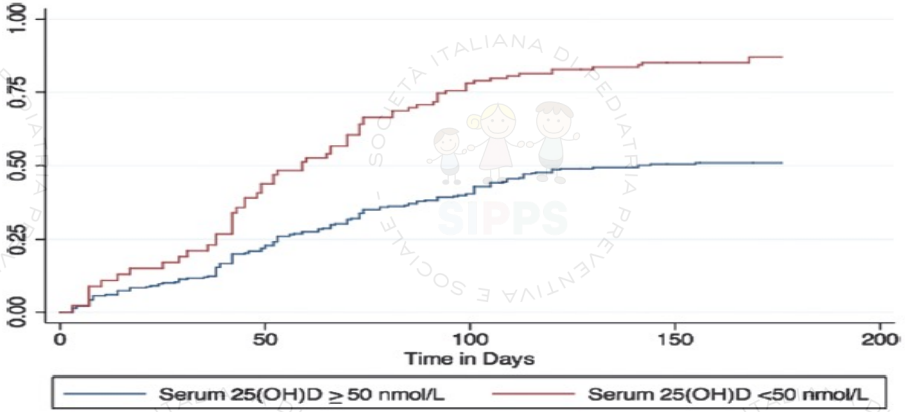
743 children (3-15 yrs) followed between Dec 2008 and June 2009

Nasopharyngeal swabs tested for respiratory viruses

229 participants (31%) developed at least 1 laboratory-confirmed viral RTI

Serum **Vit D** levels **<30 ng/mL** increased the risk of viral RTI by **50%**

Serum **Vit D** levels **<20 ng/mL** increased the risk by **70%**



Hair Zinc and Selenium Levels in Children With Recurrent Wheezing

Razi, Ped Pulmonol 2012;47:1185

65 pts with **recurrent wheezing** (RW) and 65 **healthy children** (HC)
hair Zn^{++} and **Se^{++}** levels measured

TABLE 4—The Results of Bivariate Correlations Between Levels of TAC (mmol/L), Hair Zn (μg/g), and Hair Se (μg/g), in RW Group

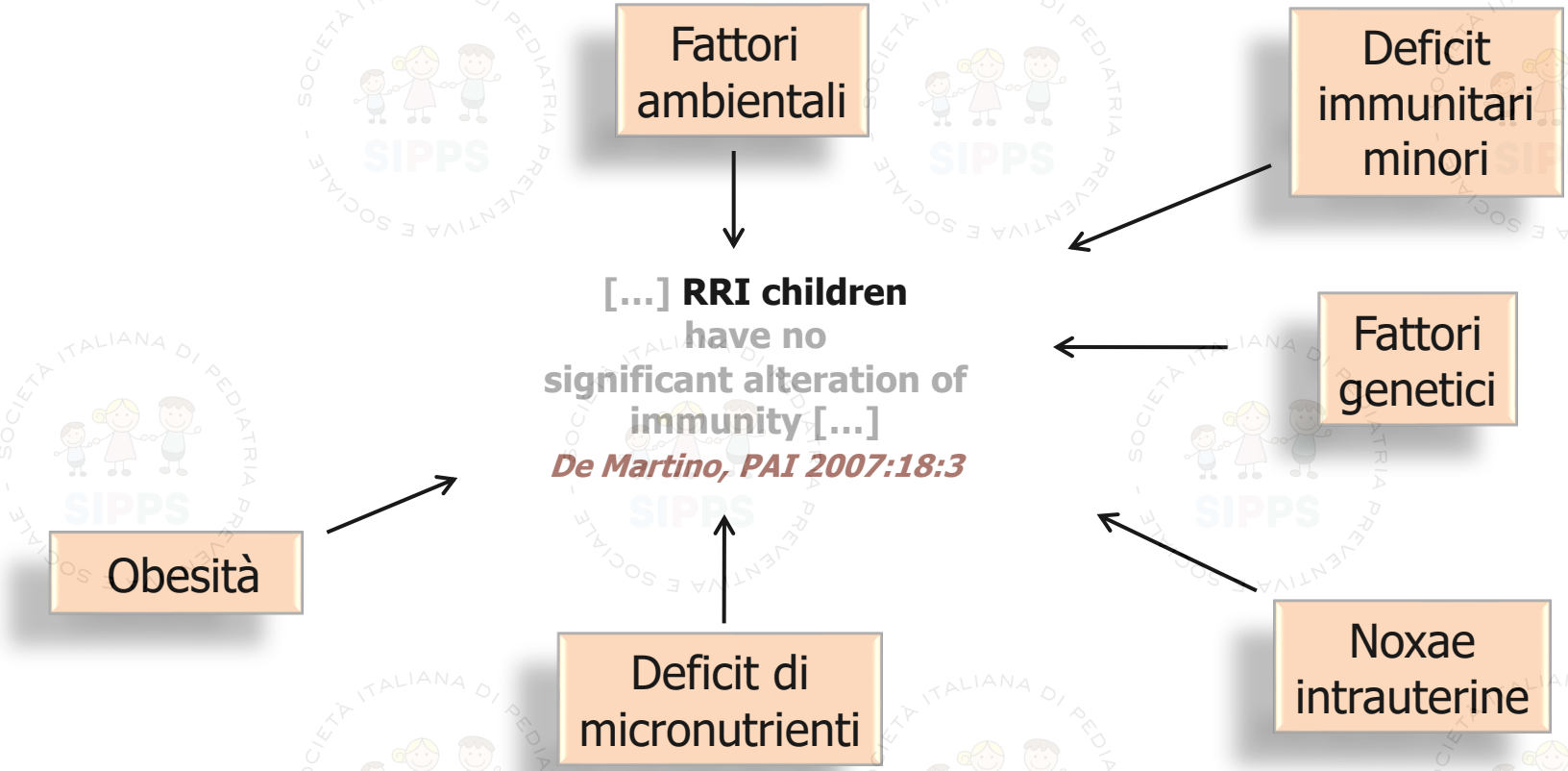
	TAC		Hair Zn level		Hair Se level	
	r*	*P*-value	r*	*P*-value	r*	*P*-value
Hair Zn level	0.426	<0.001	1	—	0.675	<0.001
Hair Se level	0.266	0.002	0.675	<0.001	1	—
Wheezy attacks in the past 6 months	−0.291	0.001	−0.209	0.017	−0.206	0.019
ARTIs in the past 6 months	−0.316	<0.001	−0.196	0.025	−0.146	0.098

Zn^{++} and **Se^{++}** levels **lower** in the RW group

N° of **wheezing** episodes (last 6 mo) negatively correlated with **Zn^{++}** and **Se^{++}** in RW group

N° of **ARTI** (last 6 mo) negatively correlated with **Zn^{++}** in RW group

Perché alcuni bambini ammalano di IRR?



Predisposition to acute respiratory infections among overweight preadolescent children: an epidemiologic study in Poland

Jerwcoski, Publ Health 1999;112:185

Studio cross-sectional con questionari
su **1129** preadolescenti (9 aa) in Cracovia

Suscettibilità alle **ARTI** correlata con il BMI

BMI ≥20 correlata con un rischio
2x di **ARTI**

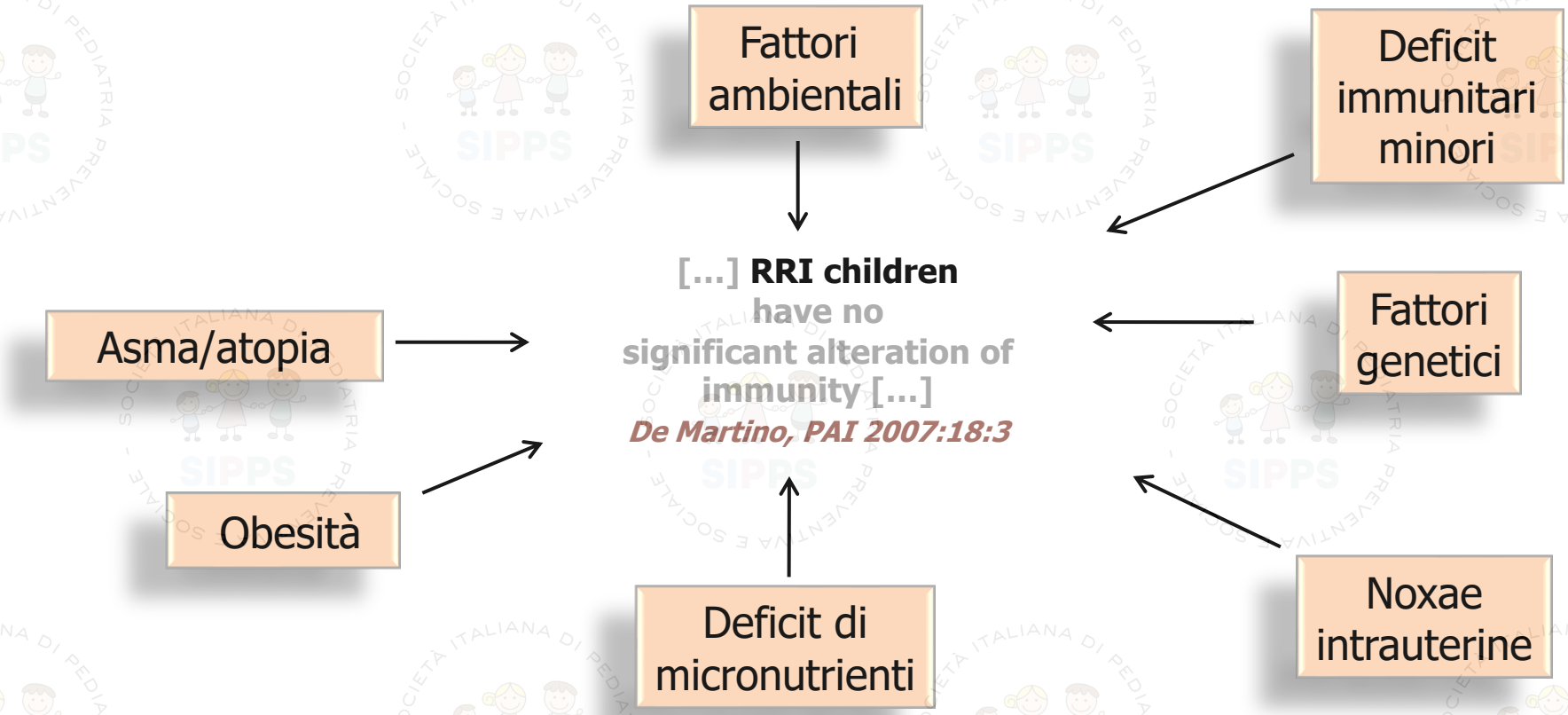
Altri fattori indipendenti di rischio per ARTI:

- Storia di sintomi respiratori cronici
- Allergia
- Fumo passivo

Table 1 Characteristics of children with various body mass index (BMI), and the occurrence of acute respiratory infections in the last 12 months

Variables	BMI < 15 $n = 240$	BMI 15–20 $n = 774$	BMI ≥ 20 $n = 101$	
Gender:				
Boys	19.2%	71.1%	9.8%	$\chi^2 = 4.282$
Girls	24.1%	67.6%	8.3%	2 df, $P = 0.118$
Parental education:				
Elementary	25.7%	69.2%	5.1%	$\chi^2 = 9.654$
Middle or higher	20.1%	69.6%	10.3%	2 df, $P = 0.008$
Allergy	18.3%	23.1%	30.7%	OR: 1.0 1.3 2.0 $\chi^2 = 6.113$, $P = 0.013$
Number of chronic respiratory symptoms:				
0 or one	89.2%	86.0%	75.2%	
Two or more	10.8%	14.0%	24.8%	OR: 1.0 1.3 2,8 $\chi^2 = 9.800$, $P = 0.002$
Spells of acute respiratory infections:				
0	52.5%	43.8%	34.7%	
One or two	31.8%	32.3%	33.7%	$\chi^2 = 14.866$
Three or more	5.7%	23.9%	31.7%	4 df, $P = 0.005$

Perché alcuni bambini ammalano di IRR?



Allergic patients have more numerous and prolonged respiratory infections than nonallergic subjects

Cirillo & Marseglia, Allergy 2007:62:1087

624 adults studied (**202** suffering from **allergic rhinitis**).
Number of **ARTI** as well as the duration of the disease recorded for 2 yrs

Higher rate of **ARTI** episodes in **allergic subjects** (adjusted incidence IRR = **2.16**)

Number of mild ARTI episodes slightly higher **(IRR = 1.68)**

Number of **severe episodes** markedly higher **(IRR = 15.71)**

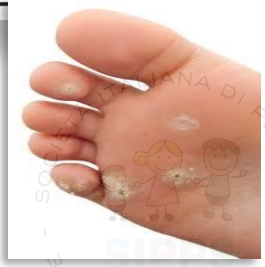
Longer total **duration of ARTI** (mean **difference of 17.4 days**)

Table 1. Association of allergy with the primary and secondary endpoints over the 2-year follow-up

Endpoint	Allergy	Rate (95% CI)	IRR (95% CI)	*P*-value	Sensitization	Rate (95% CI)	IRR (95% CI)	*P*-value
Primary endpoint								
Total RI count	No	1.6 (1.5–1.7)	1	< 0.001	None	1.6 (1.5–1.7)	1	< 0.001
	Yes	3.5 (3.3–3.9)	2.16 (1.94–2.41) *		Mono	3.3 (2.7–4.1)	2.06 (1.66–2.56) *	
					Poly	3.5 (3.3–3.8)	2.18 (1.94–2.44) *	
Secondary endpoints								
Severe RI count	No	0.06 (0.04–0.09)	1	< 0.001	None	0.06 (0.04–0.09)	1	< 0.001
	Yes	0.9 (0.8–1.1)	15.71 (10.35–23.84)		Mono	0.8 (0.5–1.2)	13.39 (7.60–23.58)	
					Poly	0.9 (0.8–1.1)	16.10 (10.57–24.52)	
Mild RI count	No	1.5 (1.4–1.7)	1	< 0.001	None	1.5 (1.4–1.7)	1	< 0.001
	Yes	2.6 (2.4–2.8)	1.68 (1.50–1.89)		Mono	2.5 (2.0–3.2)	1.66 (1.30–2.11)	
					Poly	2.6 (2.4–2.8)	1.69 (1.50–1.90)	
		Median (IQR)	Mean difference (95%CI)	*P*-value		Median (IQR)	Mean difference (95%CI)	*P*-value
Total RI duration (days)	No	7 (5–10)	17.4 (15.5–19.4)	< 0.001	None	7 (5–10)		< 0.001
	Yes	23 (13–34)			Mono	17 (10–28)	13.8 (89.0–18.7)	
					Poly	24 (13–34)	18.0 (15.9–20.2)	
Severe RI duration (days)	No	0 (0–0)	11.6 (10.1–13.1)	< 0.001	None	0 (0–0)		< 0.001
	Yes	12 (0–17)			Mono	8 (0–15)	8.4 (5.0–11.9)	
					Poly	12 (0–18)	12.1 (10.5–13.8)	
Mild RI duration (days)	No	6 (5–9)	5.8 (5.0–6.7)	< 0.001	None	6 (5–9)		< 0.001
	Yes	11 (8–17)			Mono	10 (8–15)	5.4 (3.0–7.8)	
					Poly	12 (8–17)	5.9 (5.0–6.9)	

Childhood atopic dermatitis and warts are associated with increased risk of infection: A US population-based study

Silverberg, JACI 2014;1331:1041



The **2007 National Health Interview Survey** representative sample of **9417 children** age 0-17 years

[…] Children with **AD + other atopic disease** had a higher number of infections than those with either disorder by itself…

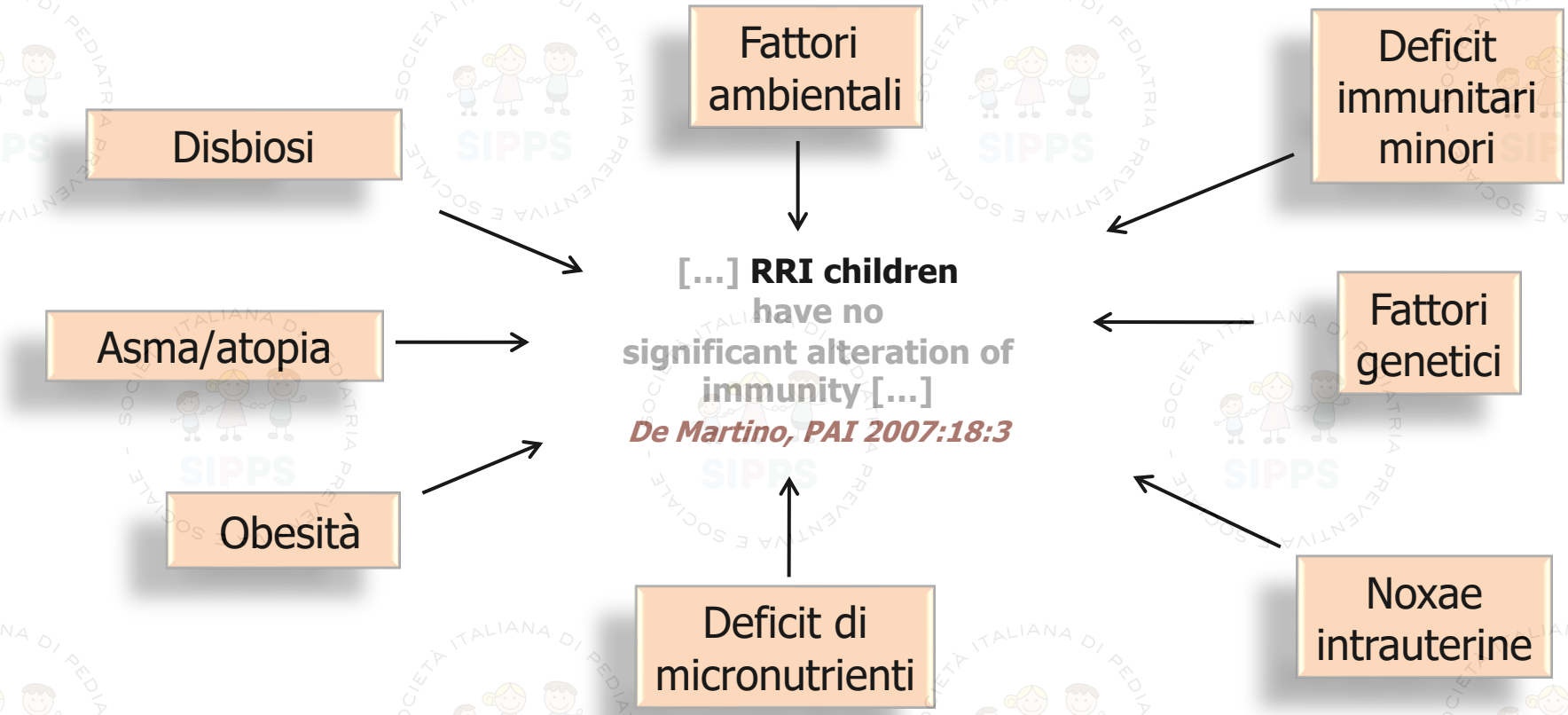
Children with **AD** and [illegible] disease had OR of **wart**

Children with **AD** had higher OR

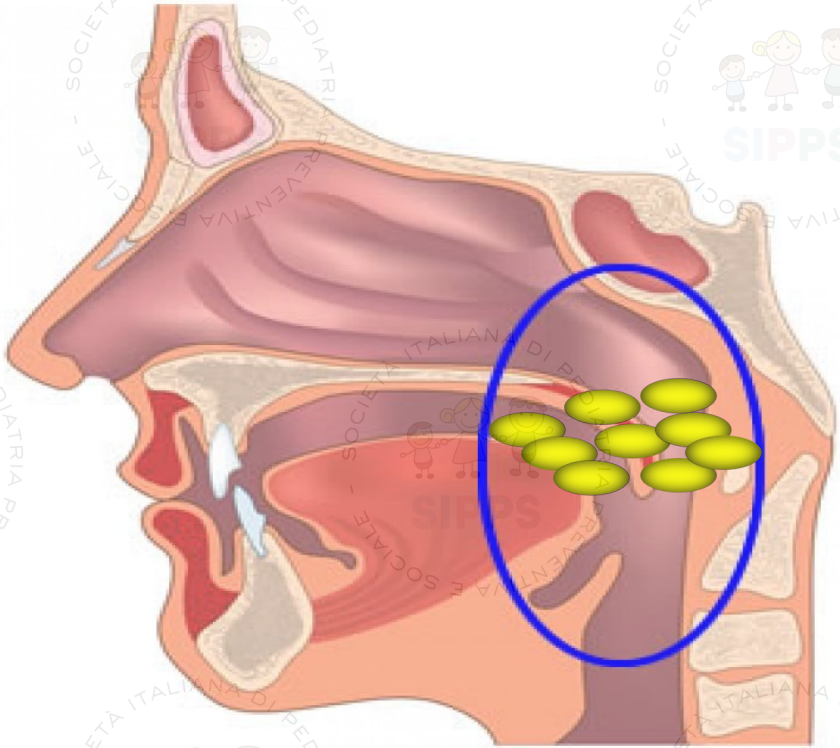
- **sore throat**
- head or **chest cold**
- **influenza/pneumonia**
- **sinus infections**
- **ear infections**
- **chickenpox**
- **urinary tract infections**

						17)				
						AD (n = 856)				
							With other atopic disease (n = 396)			
					alue	Frequency	% Prevalence (95% CI)	aOR (95% CI)	*P* value	
					—	370	92.3 (89.0-95.6)	1.00 (reference)	—	
					<.0001	26	7.7 (4.4-11.0)	1.83 (1.82-1.84)	<.0001	
				1.00 (reference)	—	314	77.3 (71.7-82.8)	1.00 (reference)	—	
				1.56 (1.54-1.57)	<.0001	81	22.7 (17.2-28.3)	1.47 (1.46-1.47)	<.0001	
				1.00 (reference)	—	193	47.2 (41.2-53.2)	1.00 (reference)	—	
				1.91 (1.91-1.92)	<.0001	201	52.8 (46.8-58.8)	1.61 (1.61-1.62)	<.0001	
				1.00 (reference)	—	303	77.7 (72.8-82.6)	1.00 (reference)	—	
Yes	1195	13.5 (12.6-14.3)	90	18.9 (14.7-23.2)	1.48 (1.47-1.48)	<.0001	92	22.3 (17.4-27.2)	1.47 (1.46-1.47)	<.0001
Influenza/pneumonia										
No	8064	93.9 (93.3-94.6)	423	92.4 (89.5-95.2)	1.00 (reference)	—	349	88.0 (84.1-91.8)	1.00 (reference)	—
Yes	487	6.1 (5.4-6.7)	37	7.6 (4.8-10.5)	1.67 (1.66-1.67)	<.0001	47	12.0 (8.2-15.9)	1.24 (1.23-1.24)	<.0001
Sinus infections										
No	8028	93.7 (93.1-94.3)	420	91.5 (88.4-94.7)	1.00 (reference)	—	299	73.7 (68.0-79.3)	1.00 (reference)	—
Yes	526	6.3 (5.7-6.9)	40	8.5 (5.3-11.6)	2.59 (2.58-2.60)	<.0001	97	26.3 (20.7-32.0)	2.18 (2.18-2.19)	<.0001
Recurrent ear infections										
No	8139	95.2 (94.6-95.8)	426	93.7 (91.2-96.2)	1.00 (reference)	—	358	90.5 (87.0-93.9)	1.00 (reference)	—
Yes	412	4.8 (4.2-5.4)	34	6.3 (3.8-8.8)	1.33 (1.32-1.34)	<.0001	38	9.5 (6.1-13.0)	1.41 (1.40-1.41)	<.0001
Chickenpox infections										
No	6132	71.6 (70.3-72.8)	348	77.2 (72.5-82.0)	1.00 (reference)	—	274	67.7 (61.8-73.6)	1.00 (reference)	—
Yes	2318	28.4 (27.2-29.7)	104	22.8 (18.0-27.5)	1.19 (1.19-1.20)	<.0001	118	32.3 (26.4-38.2)	1.33 (1.32-1.33)	<.0001
Urinary tract infections										
No	8454	98.8 (98.5-99.1)	449	97.2 (95.3-99.1)	1.00 (reference)	—	384	97.1 (95.3-98.9)	1.00 (reference)	—
Yes	102	1.2 (0.9-1.5)	11	2.8 (0.9-4.7)	3.12 (3.10-3.14)	<.0001	12	2.9 (1.1-4.7)	1.72 (1.70-1.73)	<.0001

Perché alcuni bambini ammalano di IRR?



La disbiosi delle vie aeree come causa di IRR



Maturation of the Infant Respiratory Microbiota, Environmental Drivers, and Health Consequences

A Prospective Cohort Study

Bosch, AJRCCM 2017 Dec 15;196:1582

112 infants prospectively followed

Nasopharyngeal microbiota longit… characterized from bi… 1,2,3,4,6,9, **12 m**…

Children wit… first year of … **microbial c**… the 1th month of life

This was associated with prolonged ↓ of **Corynebacterium/ Dolosigranulum** and **↑ of Moraxella** very early in life, followed by later **↑ of Neisseria** and **Prevotella spp.**

[…] drivers of these aberrant developmental trajectories of respiratory microbiota members were mode of delivery, infant feeding, crowding, and **recent antibiotic use**…

Bosch, AJRCCM 2017 Dec 15;196:1582

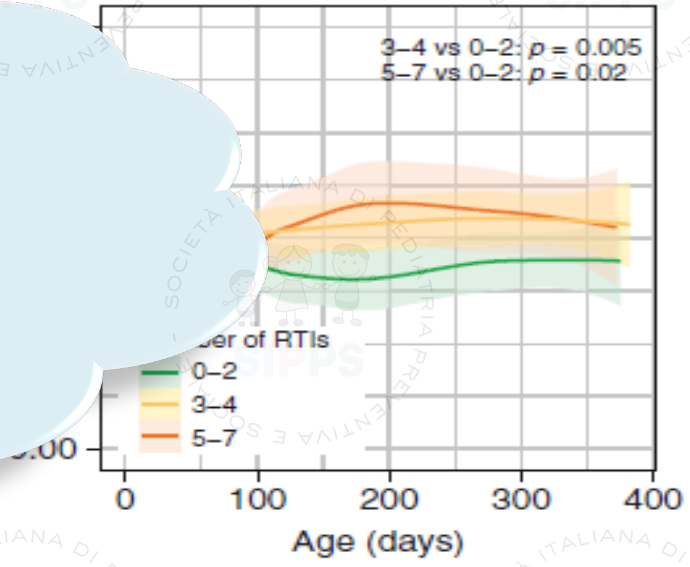


Figure 5. Microbiota stability over time stratified by respiratory tract infection (RTI) susceptibility.

ORIGINAL ARTICLE

Early nasal microbiota and acute respiratory infections during the first years of life

Toivonen, Thorax;2019;0:1-8

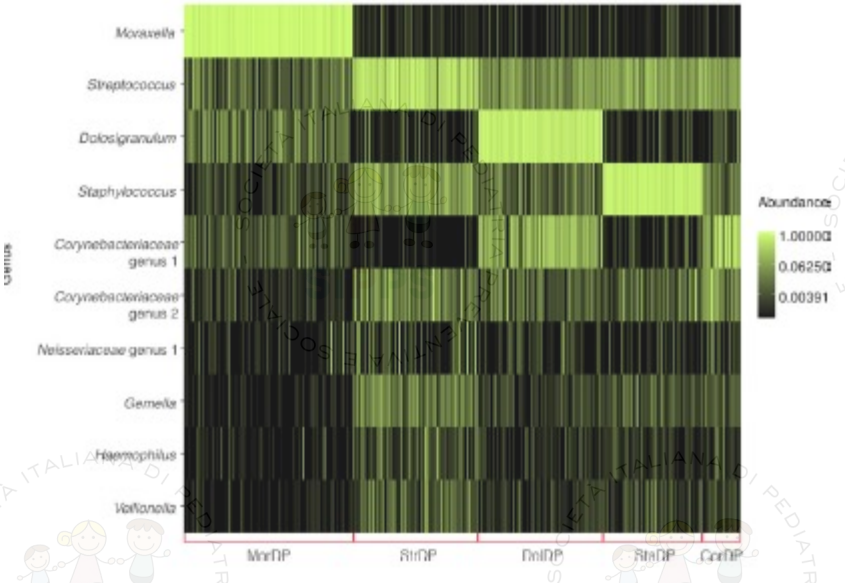
839 healthy infants tested at age **2 mo** for **nasal microbiota** using **16S rRNA** gene sequencing

Follow-up for ARIs from birth to **age 24 months**

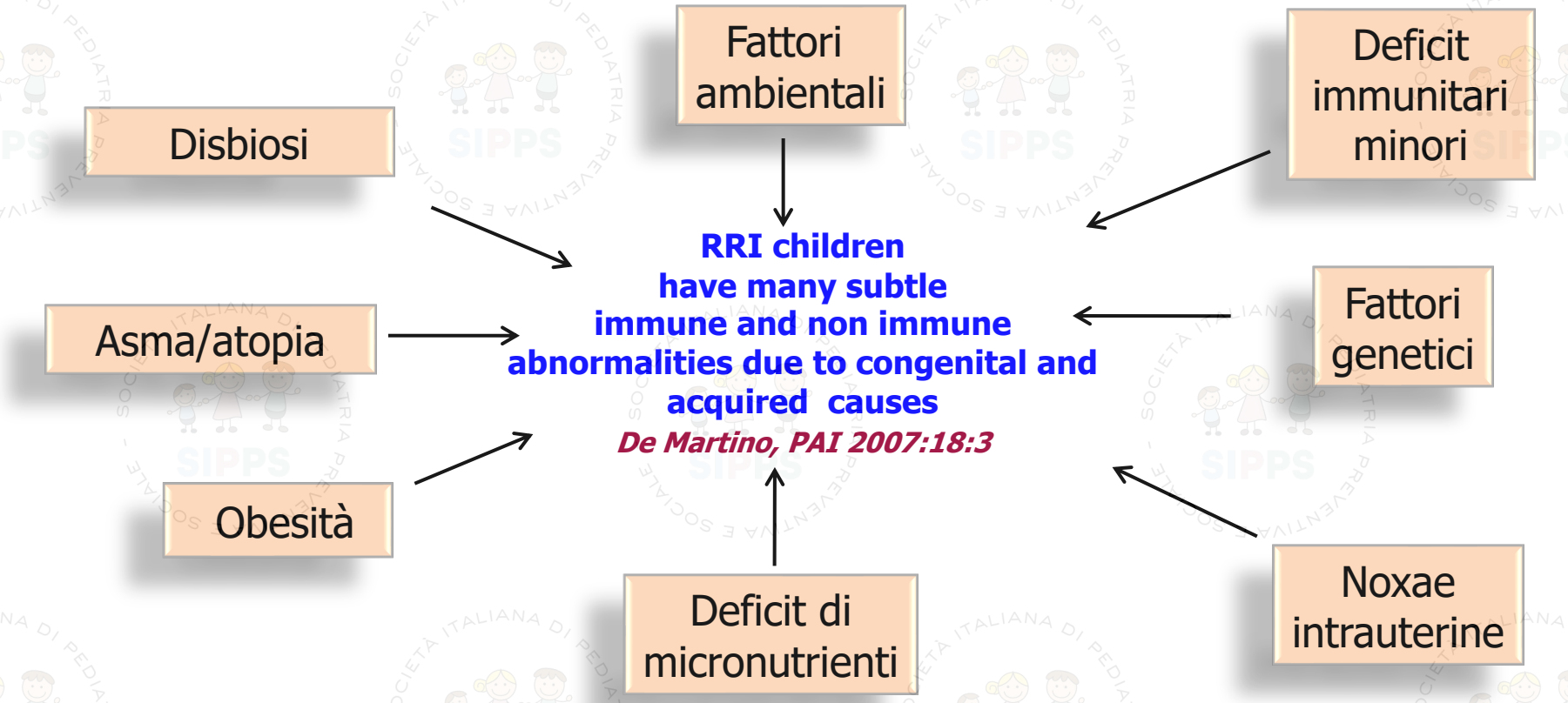
5 nasal microbiota profile identified

Incidence rate of **ARIs** highest in children with an early **moraxella-dominant** profile **(aIRR 1.19; p<.01)**

The risk was **higher** for **LRTI (aIRR 2.79)**



Perché alcuni bambini ammalano di IRR?




WHAT
ELSE?

Effetti dei CS nella bronchiolite da RSV

The New England
Journal of Medicine

Volume 315 JULY 10, 1986 Number 2

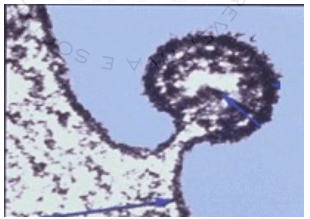
RESPIRATORY SYNCYTIAL VIRAL INFECTION IN CHILDREN WITH COMPROMISED IMMUNE FUNCTION

Breese-Hall, NEJM 1986;315:77

Table 3. Shedding Patterns of RSV in Children with Compromised Immune Function as Compared with Those in Children with Normal Immune Function Matched for Type of Illness (Pneumonia) and Age.*

	Cancer	Controls	Steroid Therapy	Controls	Immuno-deficiency	Controls
No. of patients	20	40	22	41	5	10
Mean peak titer ($log_{10}TCID_{50}$/ml)	4.7	2.8	3.6	2.2	5.2	3.1
	P<0.01		P<0.01		P<0.02	
Duration of shedding in days — mean (range)	16 (4–47)	6 (1–20)	9 (3–22)	4 (1–21)	26 (14–46)	7 (3–15)
	P = 0.01		P = 0.05		P = 0.01	
No. (%) shedding ≥20 days	11 (55)	1 (2.5)	3 (14)	2(5)	4 (80)	0
	P = 0.001		NS		P = 0.001	

I **cortisonici** aumentano l'**entità** e la **durata** dello **shedding** del **VRS**

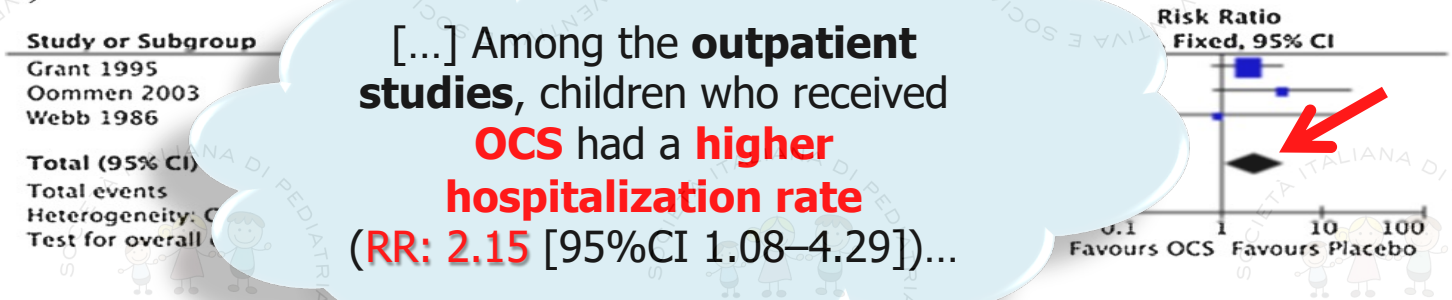


Efficacy of Oral Corticosteroids in the Treatment of Acute Wheezing Episodes in Asthmatic Preschoolers: Systematic Review With Meta-Analysis

Castro-Rodriguez, Ped Pulmonol 2016;51:868

RR hospital admission

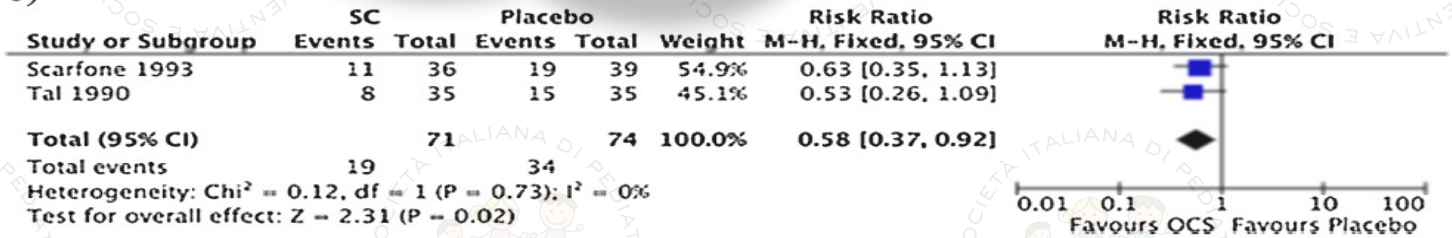
b)



[…] Among the **outpatient studies**, children who received **OCS** had a **higher hospitalization rate** (RR: 2.15 [95%CI 1.08–4.29])…

Outpatients studies

c)



ED studies

Choosing Wisely®

An initiative of the ABIM Foundation

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Five Things Physicians and Patients Should Question

2012–2014

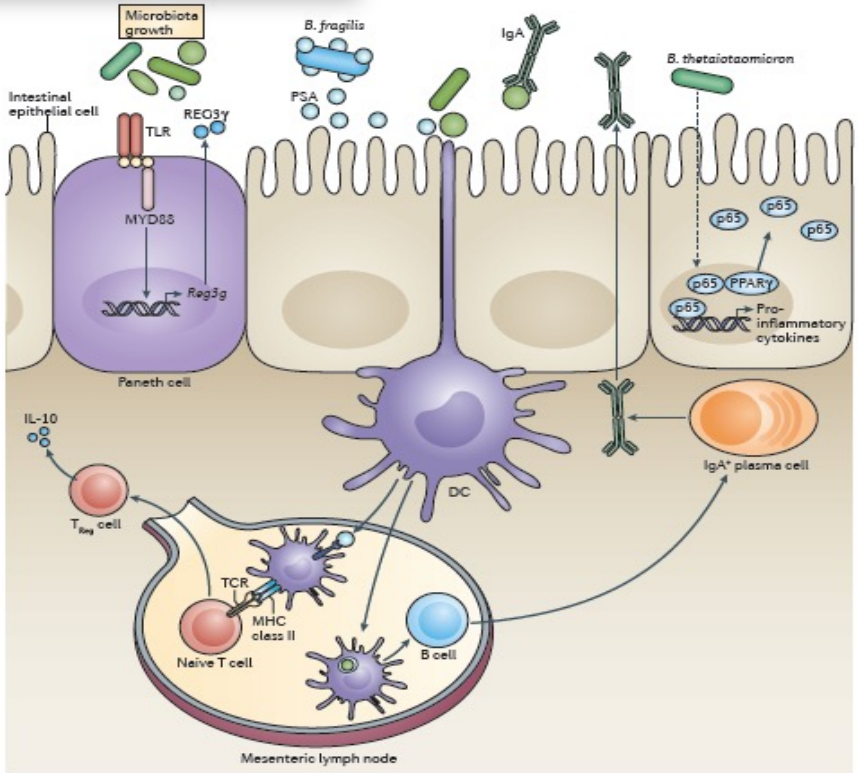
1

Antibiotics should not be used for apparent viral respiratory illnesses (sinusitis, pharyngitis, bronchitis).

Although overall antibiotic prescription rates for children have fallen, they still remain alarmingly high. Unnecessary medication use for viral respiratory illnesses can lead to antibiotic resistance and contributes to higher health care costs and the risks of adverse events.

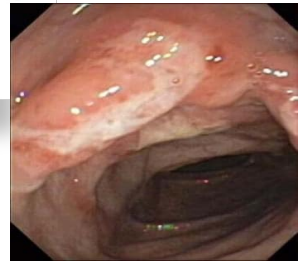
http://www.choosingwisely.org/doctor-patient-lists/american-academy-of-pediatrics/

Mucosal immunity to pathogenic intestinal bacteria



Perez-Lopez, Nature Rev Immunol 2016

Antibiotic Exposure and IBD Development Among Children: A Population-Based Cohort Study

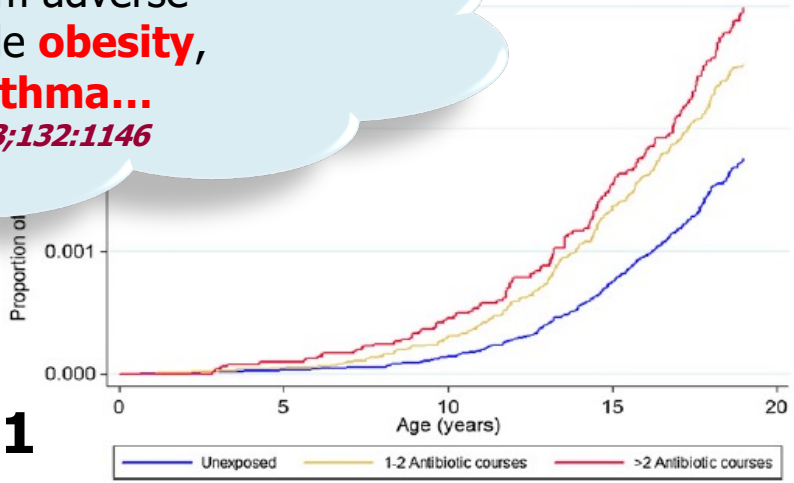


464 UK ambulatory practices

1.072.426 children enrolled
6.6 million person-years of f

[…] Other long-term adverse health effects include **obesity**, **eczema**, and **asthma…**
Hersh, Pediatrics 2013;132:1146

Exposure throughout childhood to **antianerobic antibiotics** (including amoxicillin) was associated with developing **IBD (HR +84%)**



Exposure **<1 year of age** had an adjusted HR of **5.51**

Each antibiotic course increased the **IBD** hazard by **6%**

Kronman, Pediatrics 2012;130:e794

STUDY

Antibiotic Treatment of Acne May Be Associated With Upper Respiratory Tract Infections

David J. Margolis, MD, PhD; Whitney P. Bowe, BS; Ole Hoffstad, MA; Jesse A. Berlin, ScD

Arch Dermatol. 2005;141:1132-1136

La probabilità di sviluppare una **infezione respiratoria** nei 12 mesi successivi ad un **trattamento antibiotico** per **acne** è **aumentata** di **2.23** volte (95% CI, 2.12-2.34; P<.001).

CURRENT OPINION

The liver-gut-axis: initiator and responder to sepsis

Michael Bauer

Bauer, Curr Opin Crit Care 2022 Apr; 28(2): 216–220.

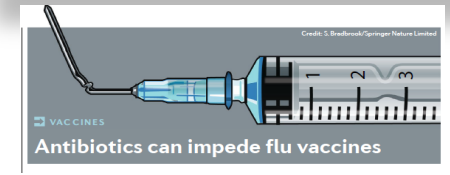
Summary

Characterization of liver function beyond bilirubin and the microbiome can be achieved with contemporary sequencing and metabolomic techniques. Such studies are essential to understand how gut-liver crosstalk and 'dysbiosis' affect susceptibility to and outcome of sepsis.

Article

Cell

Antibiotics-Driven Gut Microbiome Perturbation Alters Immunity to Vaccines in Humans



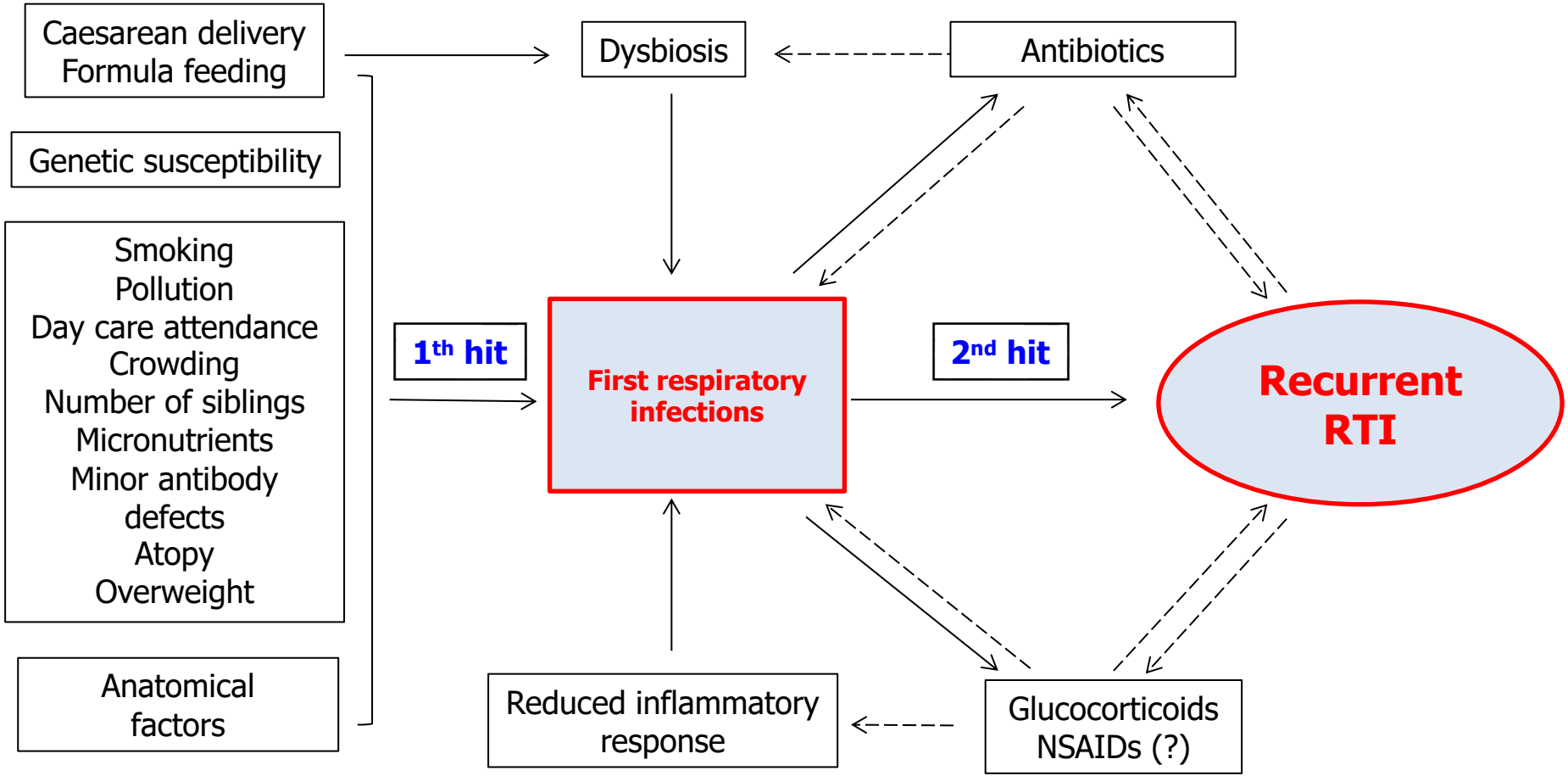
Hagan, Cell 2019;178:1313
Gordon, Nature Rev Immunol 2019;19:663

affected. However, in a second trial of subjects with low pre-existing antibody titers, there was significant impairment in H1N1-specific neutralization and binding IgG1 and IgA responses. In addition, in both studies antibiotics treatment resulted in (1) enhanced inflammatory signatures (including AP-1/NR4A expression), observed previously in the elderly, and increased dendritic cell activation; (2) divergent metabolic trajectories, with a 1,000-fold reduction in serum secondary bile acids,

IRR nel bambino: verso una nuova visione

- Che cosa si sapeva
- Nuovi aspetti eziopatogenetici
- Una ipotesi unificante
- Conclusioni

The "sum & vicious cycle" hypothesis

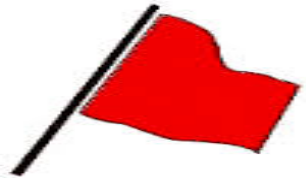


Cardinale, Curr Pediatr Rev 2023

IRR nel bambino: verso una nuova visione

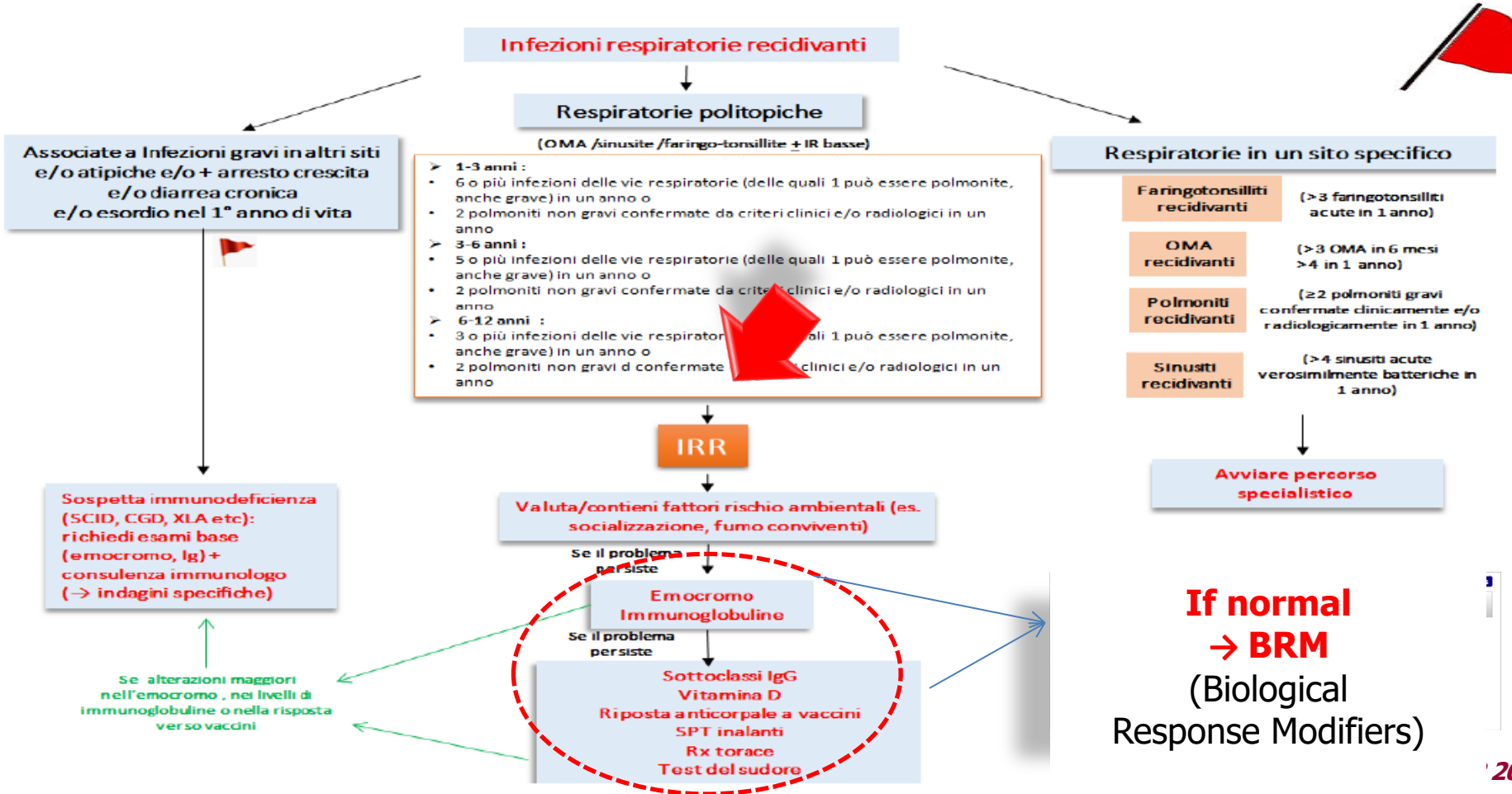
- Che cosa si sapeva
- Nuovi aspetti eziopatogenetici
- Una ipotesi unificante
- Conclusioni

Possibili patologie di base nelle IR recidivanti delle alte e basse vie



Patologia/sintomo	Sospetto
Infezioni polmonari croniche, complicate o atipiche (diffuse)	Deficit immunitari, FC, DCP, bronchiectasie, malformazioni
Infezioni polmonari ricorrenti (localizzate)	Bronchiectasie, malformazioni, corpo estraneo,
Infezioni politopiche e/o immunodisregolazione (autoimmunità multipla etc.)	Deficit immunitari
Esordio primi 6 mesi, IgE >2000 U/l, DA severa, ridotto accrescimento, diarrea cronica…	Deficit immunitari
Sinusite ricorrente-cronica/ severa / complicata	Deficit immunitari, DCP, fattori anatomici
OMA ricorrente-cronica/ severa / complicata	Deficit immunitari, DCP, fattori anatomici

...when everything is negative consider BRM



If normal
→ BRM
(Biological Response Modifiers)

2021

Take home messages

- Il bambino con IRR è nella maggior parte dei casi un bambino immunocompetente
- I fattori ambientali sono solo una parte dei fattori predisponenti
- Importanza fattori genetici
- In bambino con IRR particolarmente frequenti eseguire comunque esami di screening (emocromo, IgG A M)
- Un periodo di sospensione dell'asilo di 3-6 mesi può servire in molti casi a risolvere il quadro clinico
- Antibiotici, FANS e corticosteroidi plausibilmente possono peggiorare il quadro clinico
- Nei casi in cui non esistano fattori ambientali, escluse patologie d'organo e sistemiche, possibile spazio per immunomodulatori

fabiocardinale1961@gmail.com