

# ASMA E INFEZIONI

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# VIRUS E BATTERI IMPLICATI NELLA DETERMINAZIONE DI WHEEZING

Patogeno	Frequenza (%)
Rhinovirus	2 - 37
Coronavirus	10 - 16
Influenza virus A e B	2 - 10
Parainfluenza virus 1, 2, 3	2 - 14
Adenovirus	1 - 4
Metapneumovirus	3 - 15
Virus respiratorio sinciziale	1 - 17
<i>Mycoplasma pneumoniae</i>	2 - 35
<i>Chlamydia pneumoniae</i>	2 - 25

# VIRUS E WHEEZING

(Da Jarriti T et al. Emerg Infect Dis 2004)

Virus	Total; n = 293
Respiratory syncytial virus (RSV)	80 (27)
Enterovirus	72 (25)
Rhinovirus	71 (24)
Rhino/enterovirus	46 (16)
Parainfluenza virus type 1	8 (3)
Parainfluenza virus type 2	0
Parainfluenza virus type 3	5 (2)
Parainfluenza virus type 1 or 3	4 (1)
Adenovirus	15 (5)
Human metapneumovirus	12 (4)
Influenza A virus	3 (1)
Influenza B virus	4 (1)
Coronavirus	4 (1)
Mixed viral infection	57 (19)
Total	258 (88)

# CLINICAL PRESENTATION OF THE STUDY CHILDREN IN WHOM A SINGLE INFECTIOUS AGENT WAS DEMONSTRATED (%)

(From Bosis S et al. J Med Virol 2005)

	hMPV (n=35)	RSV (n=141)	FLU (n=223)
FEVER $\geq$ 38°C	28 (80.0)*	66 (46.8)	179 (80.3)*
RESPIRATORY TRACT INFECTION	35 (100.0)	135 (95.7)	199 (89.2)
COMMON COLD	3 (8.6)	23 (16.3)	42 (18.8)
PHARYNGITIS	9 (25.7)	23 (16.3)	70 (31.4)
ACUTE OTITIS MEDIA	4 (11.4)	12 (8.5)	31 (13.9)
CROUP	3 (8.6)	7 (4.9)	7 (3.1)
ACUTE BRONCHITIS	3 (8.6)	16 (11.3)	19 (8.5)
WHEEZING	9 (25.7)*	33 (23.4)*	12 (5.4)
PNEUMONIA	4 (11.4)	21 (14.9)	18 (8.1)
GASTROENTERITIS	0	6 (4.3)	14 (6.3)
FEVER WITHOUT SOURCE	0	0	10 (4.5)

\* $P < 0.05$

# DIAGNOSTIC METHODS AND THERAPEUTIC APPROACHES TO THE STUDY CHILDREN IN WHOM A SINGLE INFECTIOUS AGENT WAS DEMONSTRATED (%)

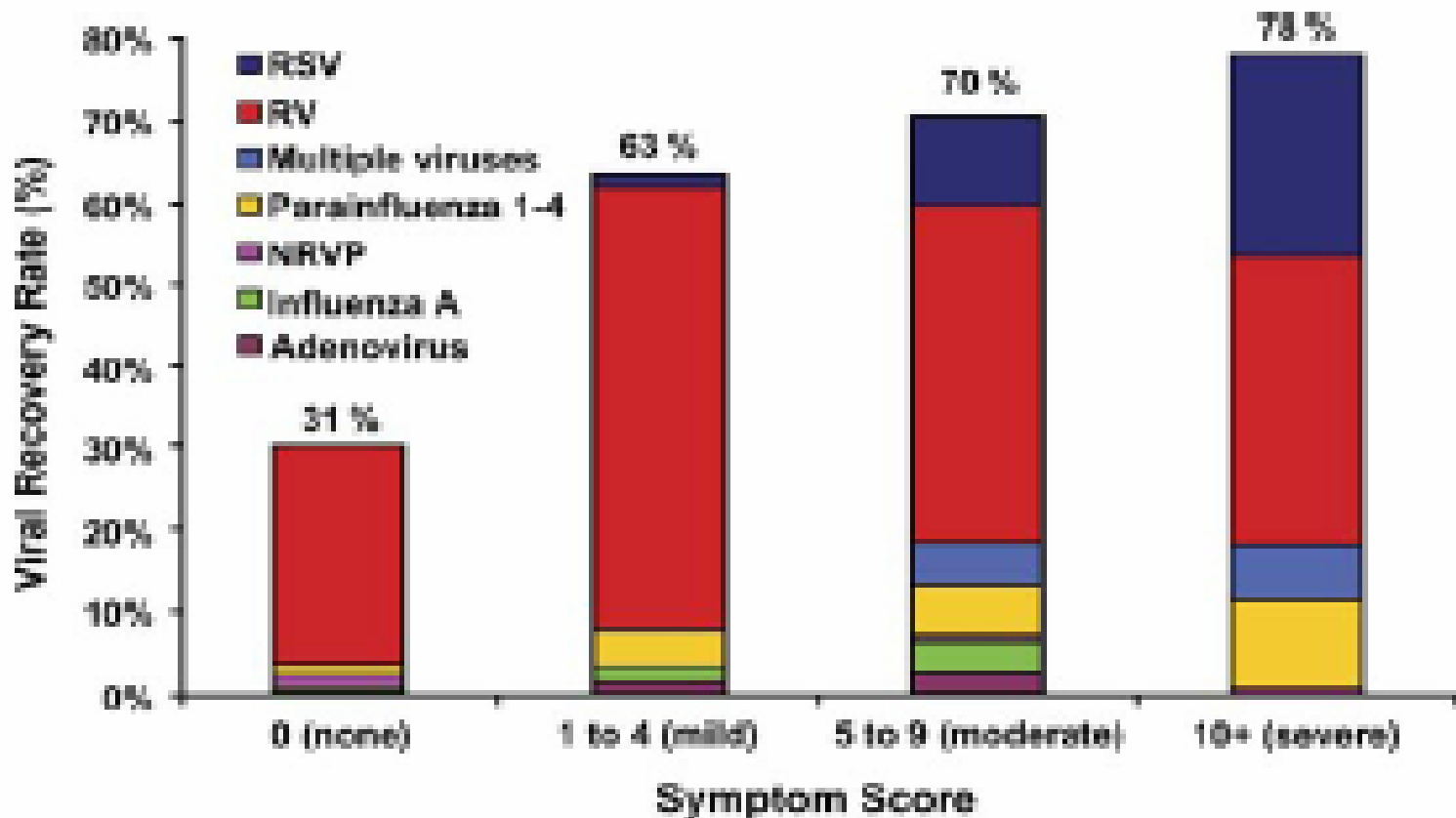
(From Bosis S et al. J Med Virol 2005)

	hMPV (n=35)	RSV (n=141)	FLU (n=223)
ROUTINE BLOOD EXAMINATION	2 (5.7)	12 (8.5)	10 (4.5)
MICROBIOLOGICAL TESTS	2 (5.7)	12 (8.5)	8 (3.6)
CHEST RADIOGRAPHY	5 (14.3)	<b>25 (17.7)*</b>	20 (8.9)
ANTIPYRETIC PRESCRIPTIONS	<b>26 (74.3)*</b>	65 (46.1)	<b>173 (77.6)*</b>
ANTIBIOTIC PRESCRIPTIONS	19 (54.3)	75 (53.2)	116 (52.0)
BRONCHODILATOR PRESCRIPTIONS	4 (11.4)	16 (11.3)	30 (13.5)
STEROID PRESCRIPTIONS	<b>11 (31.4)*</b>	<b>39 (33.3)*</b>	25 (11.2)

**\*P<0.05**

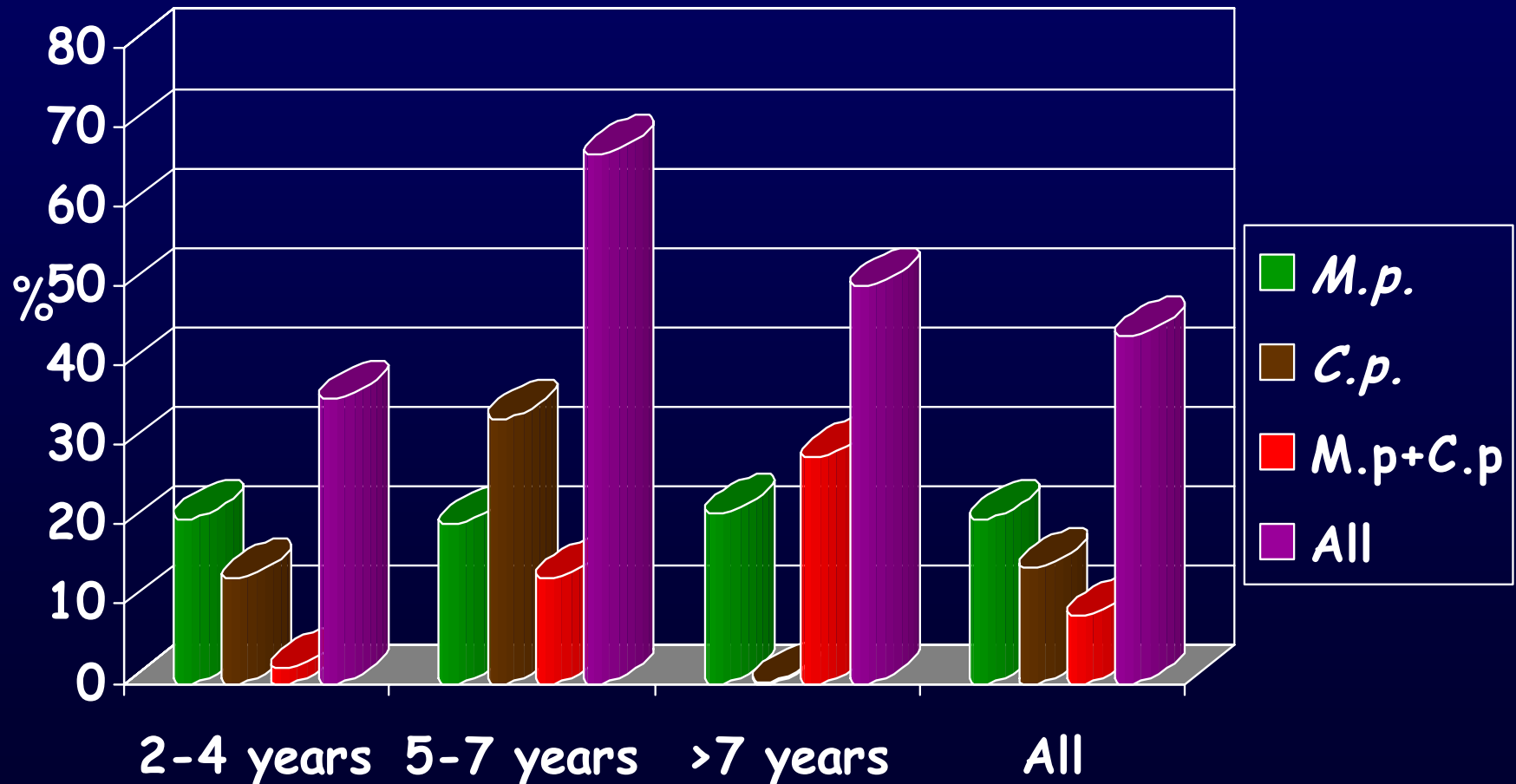
# INFEZIONI VIRALI E GRAVITÀ

(Da Lemanske RF Jr et al. J Allergy Clin Immunol 2005)



# ACUTE WHEEZING AND ATYPICAL BACTERIA IN 82 HOSPITALIZED CHILDREN

From Principi et al. Clin Infect Dis 2001



# WHEEZING STUDY PATIENTS AND CONTROLS

CHARACTERISTICS	WHEEZERS	CONTROLS
Number of patients	71	80
Sex, males (%)	32 (45.1)	38 (47.5)
Median age (range), years	4.5 (2-14)	5.4 (2-14)
Recurrent episodes of wheezing (%)	31 (43.7)	0
Atopy (%)	22 (31.0)	12 (15.0)

From Esposito S et al. Eur Resp J 2000; 16: 1142-6

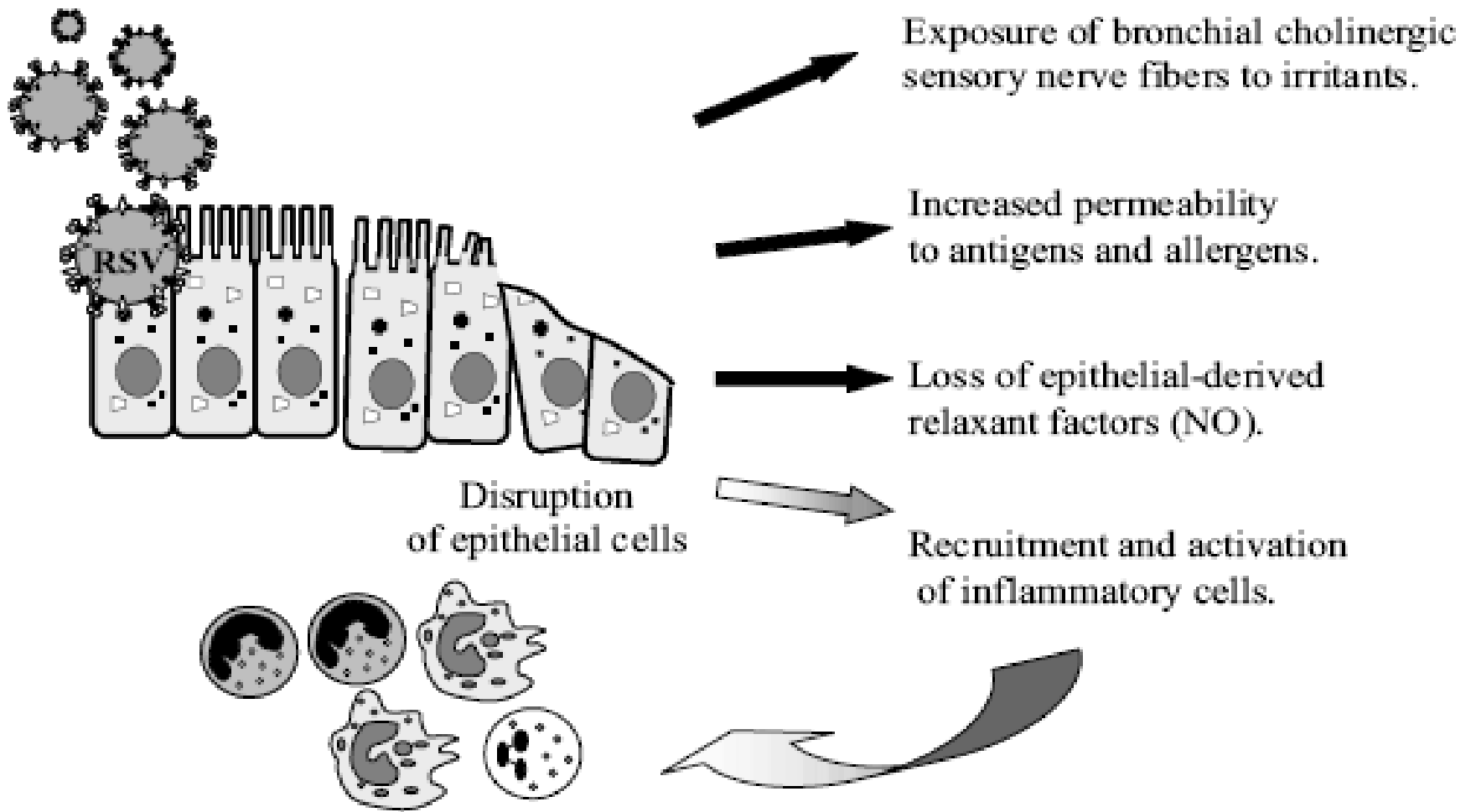


# INCIDENCE OF RECURRENT WHEEZING ACCORDING TO AGE

Age (years)	<i>M. pneumoniae</i> <i>C. pneumoniae</i> Infected	<i>M. pneumoniae</i> <i>C. pneumoniae</i> Not Infected	p value
2 - 4	8/8 (100.0%)	9/32 (28.1%)	0.003
≥ 5	12/16 (75.0%)	2/15 (13.3%)	0.002

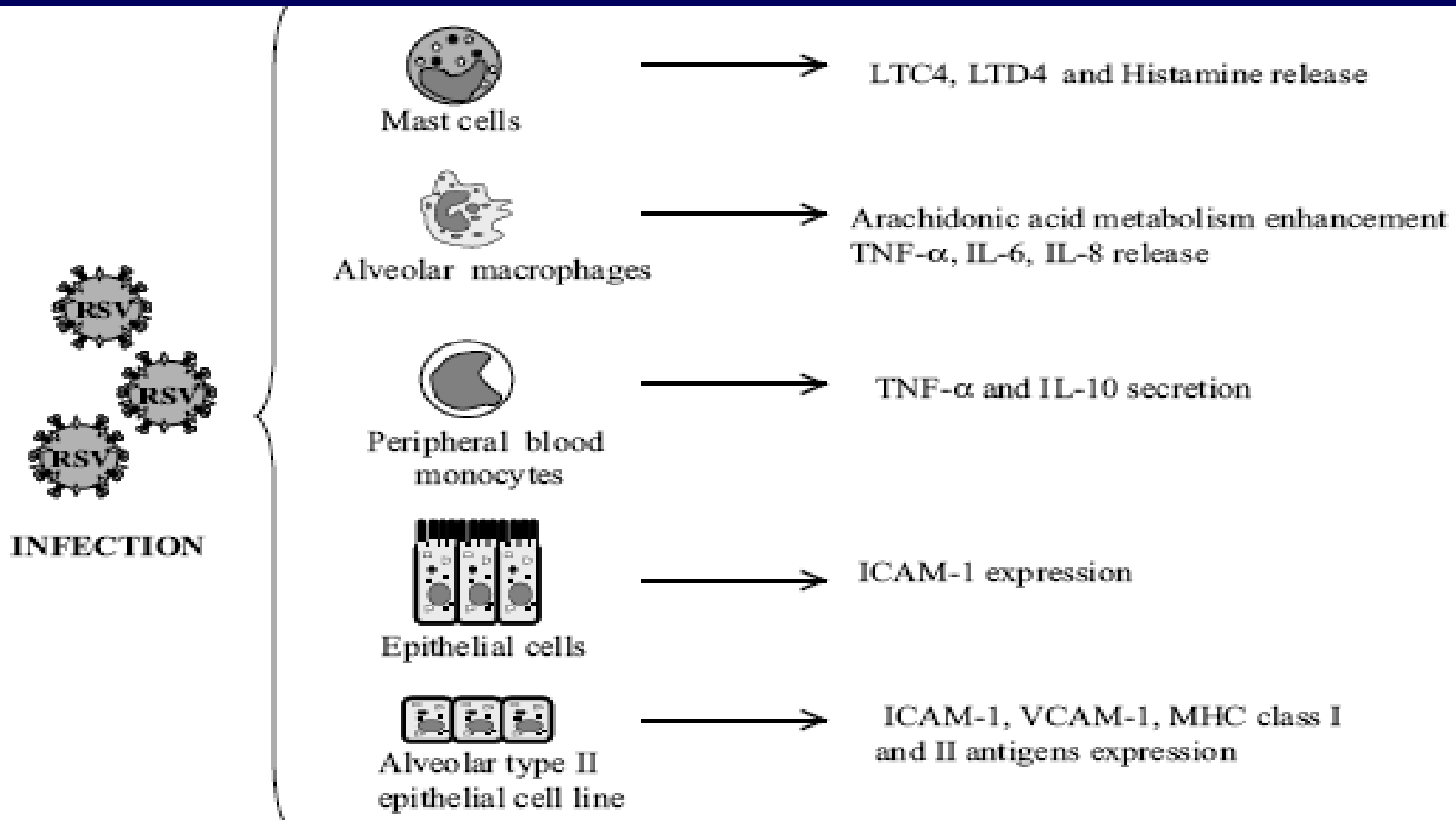
# DANNI DA RSV

(Da Silvestri M et al. Paediatric Resp Rev 2004)



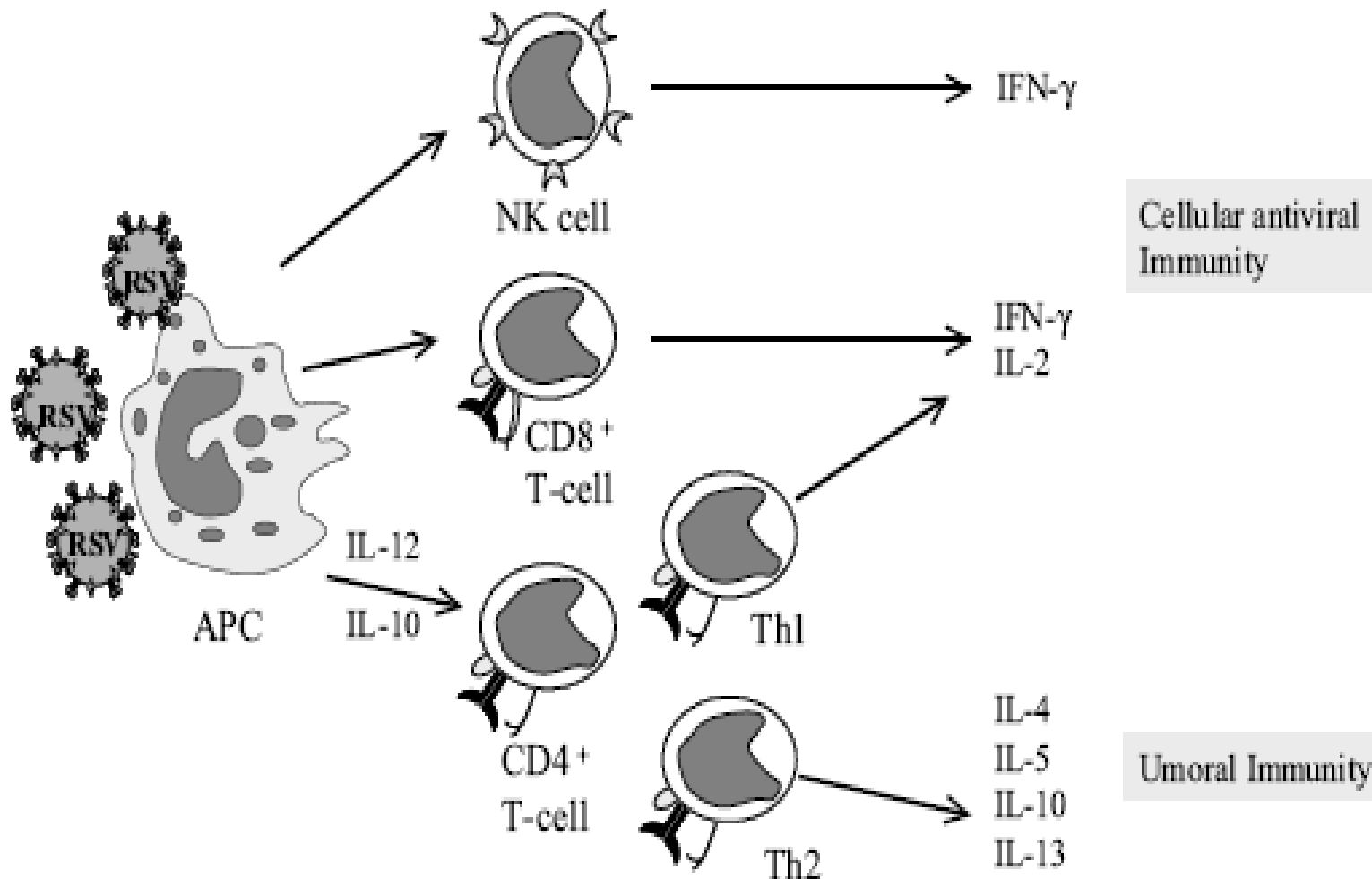
# CONSEGUENZE BIOCHIMICHE DEL DANNO CELLULARE DA RSV

(Da Silvestri M et al. Paediatric Resp Rev 2004)



# INFEZIONI RESPIRATORIE: ATTIVAZIONE IMMUNOLOGICA

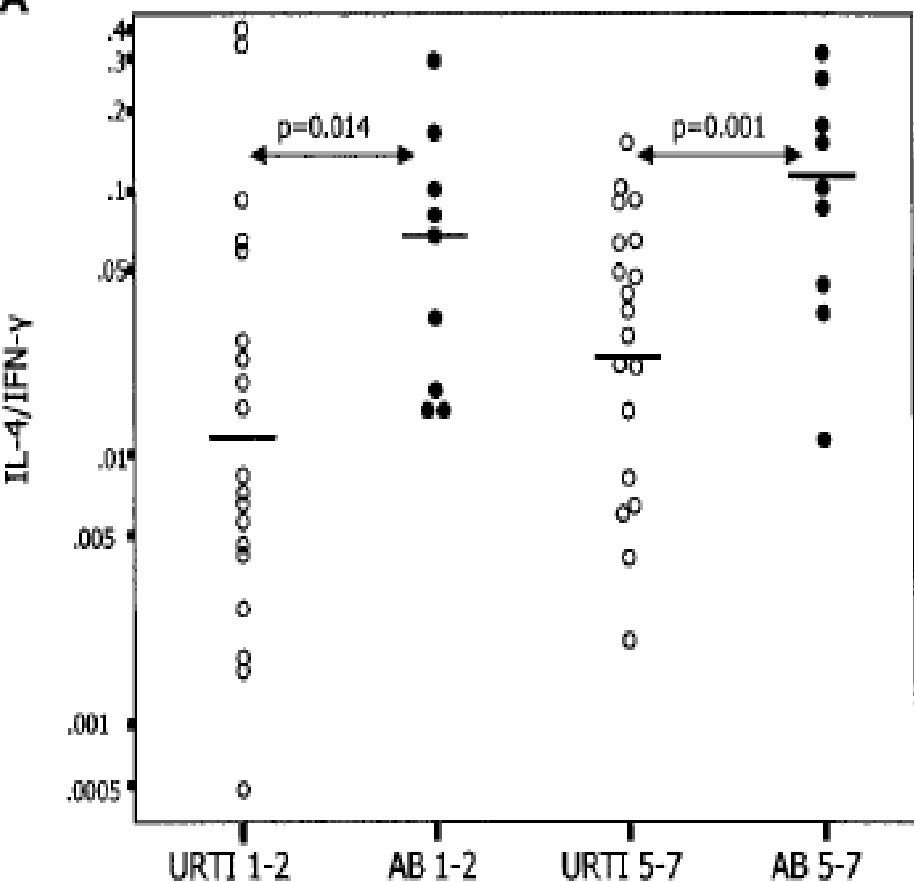
(Da Silvestri M et al. Paediatric Resp Rev 2004)



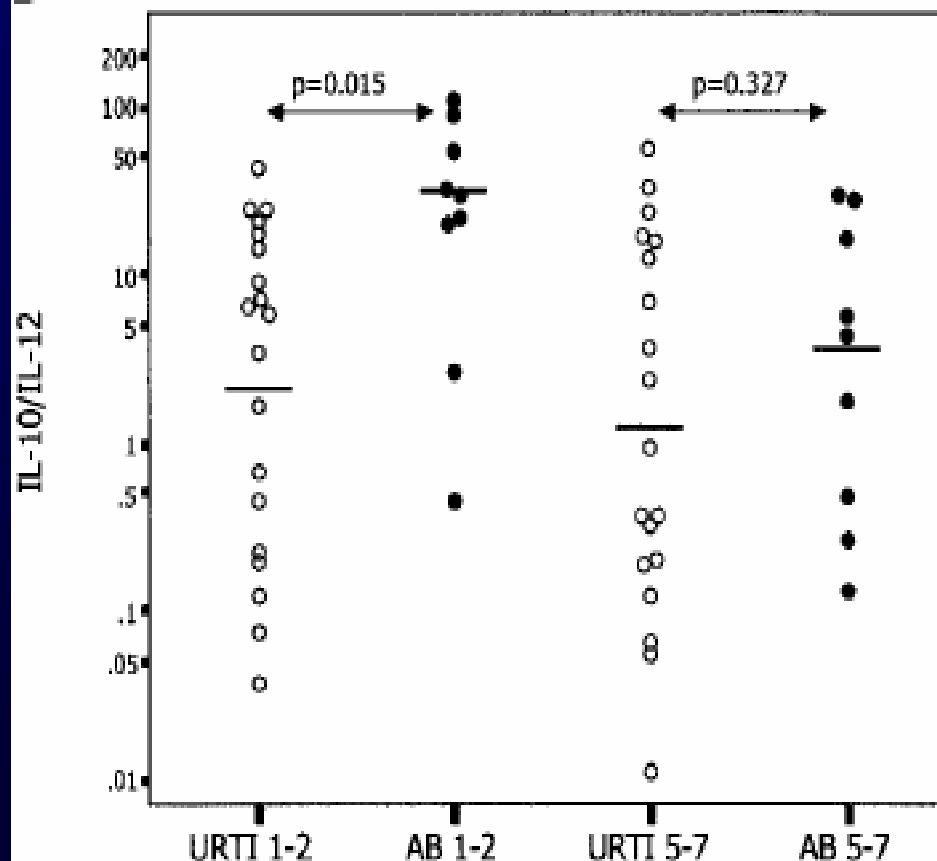
# IMPAIRED TYPE 1 AND TYPE 2 AIRWAY CYTOKINE PRODUCTION IN NASAL LAVAGE OF INFANTS WITH RSV BRONCHIOLITIS

(From Legg JP et al. *Am J Resp Crit Care Med* 2003)

A

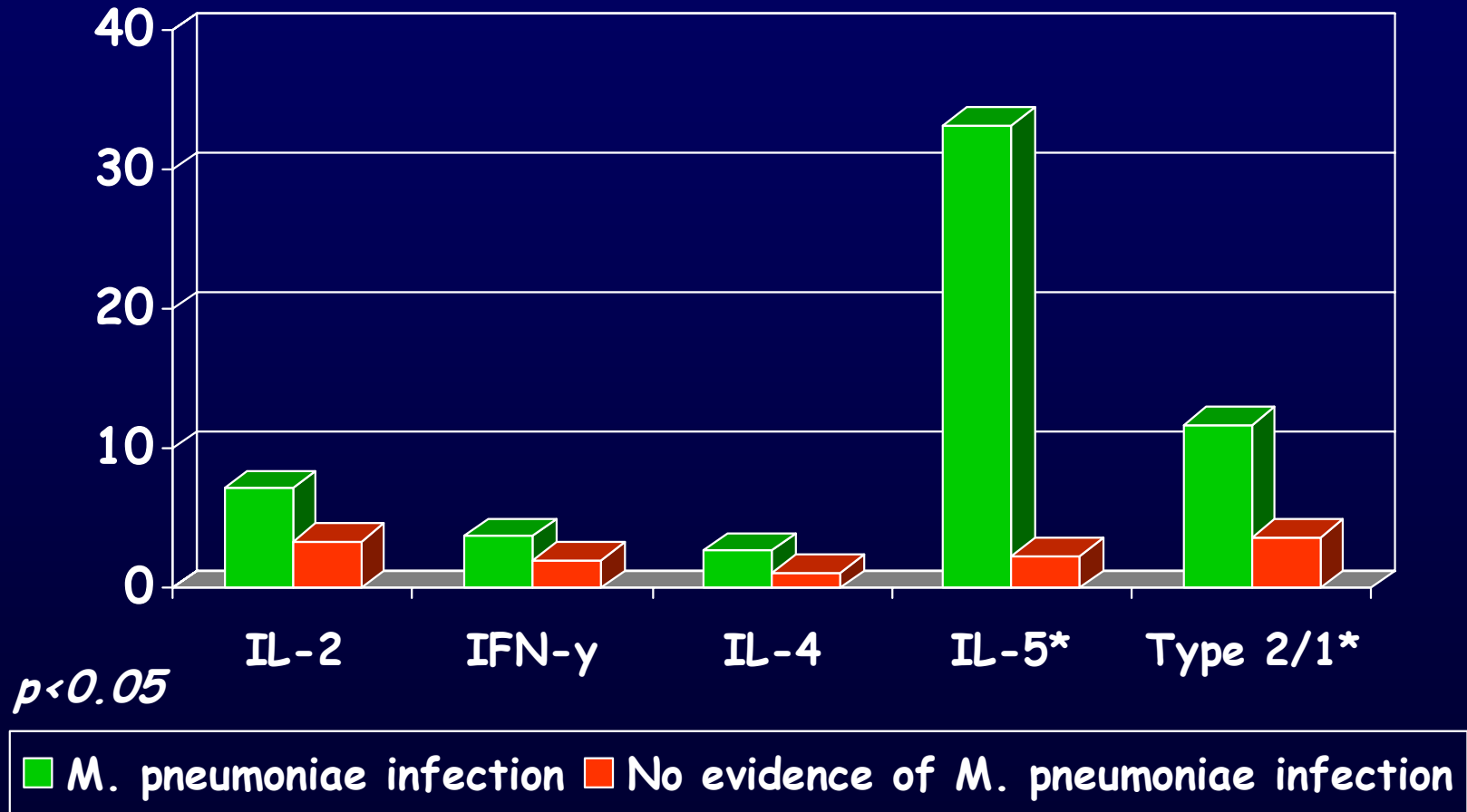


B



Circoli vuoti = URTI Circoli pieni = bronchiolite

# MEAN CYTOKINE SECRETION (PG/ML) IN CHILDREN WITH WHEEZING ACCORDING TO *M. PNEUMONIAE* INFECTION



From Esposito et al. *Pediatr Pulmonol* 2002; 34: 122-7

# INFEZIONE DA RSV E SVILUPPO DI ASMA A DISTANZA

(Da Sigurs N. Am J Resp Crit Care Med 2001)

	RSV Group (%)	Control Group (%)	p Value
Noble and coworkers			
Asthma at age 10 yr	39	13	0.004
Use of bronchodilator	33	3	
Sigurs and coworkers			
Any wheezing at age 7.5	38	2	< 0.0001
Asthma	23	2	< 0.001

# INFEZIONI RESPIRATORIE PRECOCI E RISCHIO DI WHEEZING

(Da Stein RT et al. *Lancet* 1999)

Lower respiratory tract illness before age 3 years	Infrequent wheeze after age 3 years			
	Age 6 (n=156/757)	Age 8 (n=125/614)	Age 11 (n=130/685)	Age 13 (n=97/517)
RSV	3.2 (2.0-5.0)*	2.5 (1.5-4.3)*	1.7 (1.0-2.9)†	1.4 (0.7-2.7)
Para-Influenza	1.7 (0.8-3.7)	1.6 (0.9-2.8)	0.5 (0.2-1.3)	1.2 (0.5-3.2)
Other agents	1.3 (0.6-2.9)	2.3 (1.1-4.8)†	1.1 (0.5-2.6)	2.8 (1.2-6.6)†
Negative tests	1.5 (0.8-2.6)	1.3 (0.7-2.5)	1.6 (0.9-2.9)	1.9 (1.0-4.0)†
None‡	1.0	1.0	1.0	1.0

Results adjusted for sex, maternal education, family history of asthma, allergy skin tests at Yrs 6, birthweight, and current maternal smoking. \*  $p < 0.001$ . †  $p < 0.05$ . ‡ Reference group.



# INFEZIONI RESPIRATORIE PRECOCI E RISCHIO DI WHEEZING

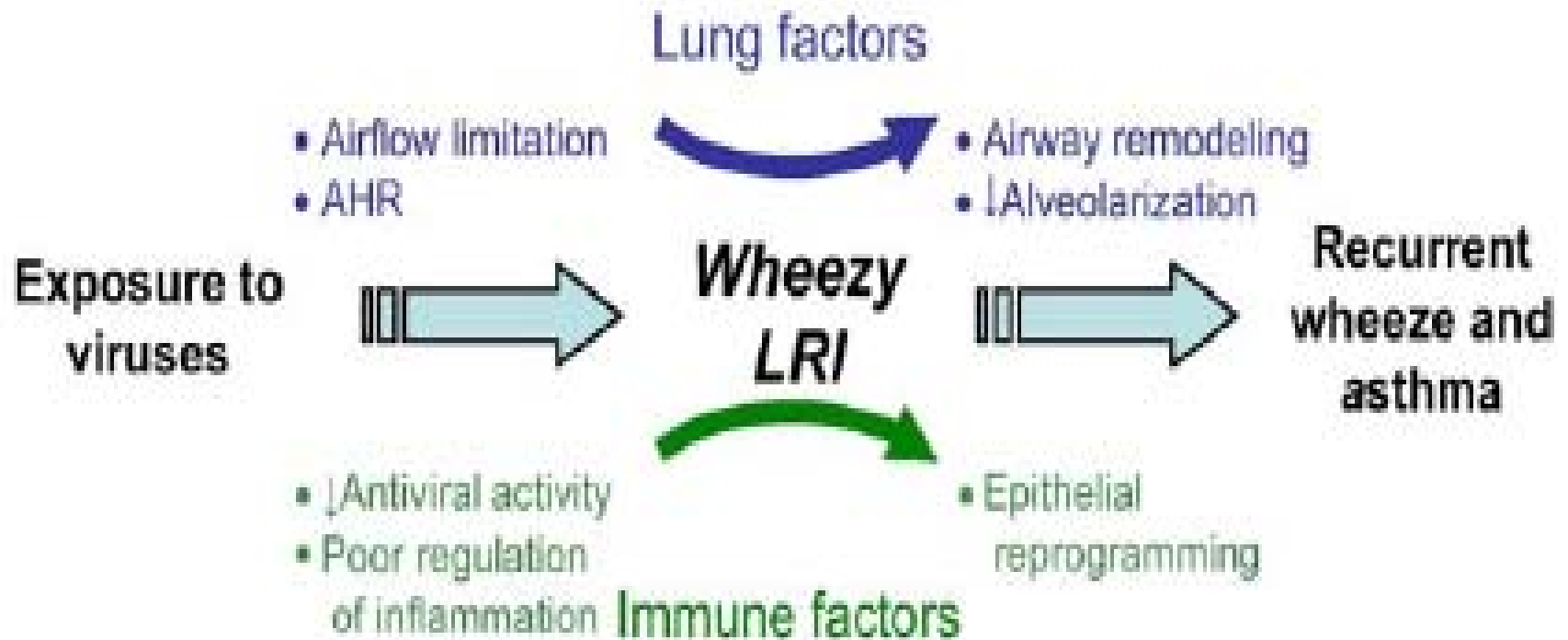
(Da Stein RT et al. *Lancet* 1999)

Lower respiratory tract illness before age 3 years	Frequent wheeze after age 3 years			
	Age 6 (n=68/669)	Age 8 (n=56/545)	Age 11 (n=79/634)	Age 13 (n=49/469)
RSV	4.3 (2.2-8.7)*	1.9 (0.9-4.2)	2.4 (1.3-4.6)†	1.4 (0.7-2.6)
Para-Influenza	2.4 (0.8-7.4)	0.4 (0.1-2.2)	2.3 (0.6-4.2)	1.3 (0.5-3.5)
Other agents	2.9 (1.1-7.8)‡	1.3 (0.4-4.4)	1.0 (0.3-3.2)	3.1 (1.3-7.6)†
Negative tests	1.9 (0.8-4.5)	2.3 (1.0-5.2)‡	2.0 (0.9-4.6)	2.1 (1.0-4.3)‡
None§	1.0	1.0	1.0	1.0

Results adjusted for sex, maternal education, family history of asthma, allergy skin tests at Yr6, birthweight, and current maternal smoking. \*p<0.001. †p<0.01. ‡p<0.05. All compared with No-LRIs subgroups. §Reference group.

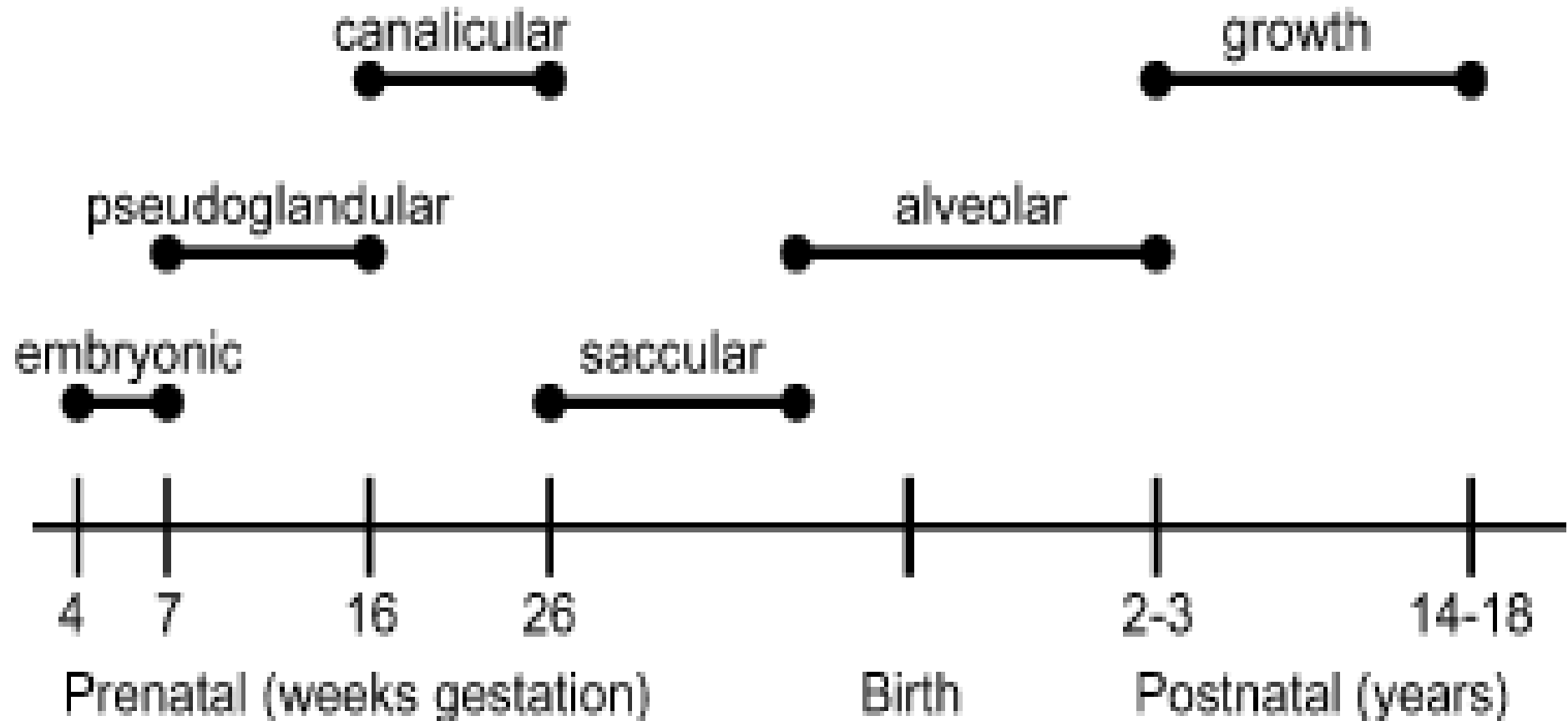
# INFEZIONI RESPIRATORIE: EFFETTO A DISTANZA

(Da Gern JE et al. J Allergy Clin Immunol 2005)



# STADI DELLO SVILUPPO POLMONARE

(Da Gern JE et al. J Allergy Clin Immunol 2005)



# INFEZIONI E SVILUPPO POLMONARE

- Il reclutamento e l'attivazione dei neutrofili provoca un aumento di elastasi che può portare al rimodellamento alveolare
- La presenza di citochine proinfiammatorie nel liquido amniotico è associata con un aumentato rischio di broncodisplasia
- Le infezioni possono indurre la sintesi di molti fattori, quali NO, TGF- $\beta$ , fattore di crescita dei fibroblasti, fattore di crescita vascolare endoteliale

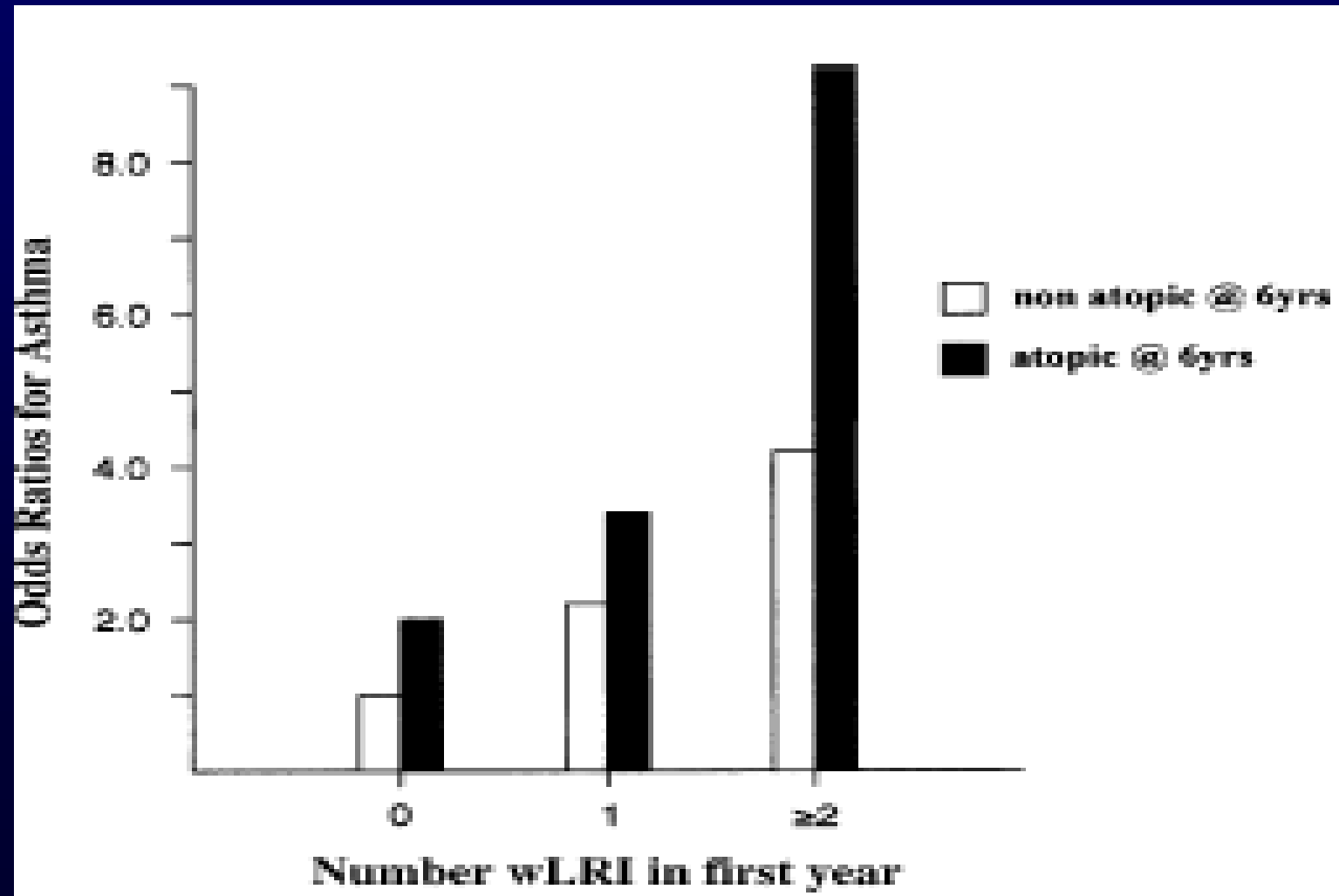
# MARKERS GENETICI ASSOCIATI CON BRONCHIOLITE GRAVE E WHEEZING RICORRENTE

(Da Mejias A et al. *Curr Opin Infect Dis* 2005)

Genetic markers (polymorphisms)	Associated outcomes
CCR5 (RANTES and MIP-1 $\alpha$ receptor)	Severe bronchiolitis
IL-4 and IL-4R $\alpha$	Hospitalization
IL-8 promoter	Severe bronchiolitis and increased wheezing at 6-year follow-up
IL-10	Hospitalization
Surfactant protein D	Severe bronchiolitis
TGF $\beta$ 1	Wheezing within first year of life
TLR4 mutations	Differences between mild and severe RSV bronchiolitis (hospitalization)

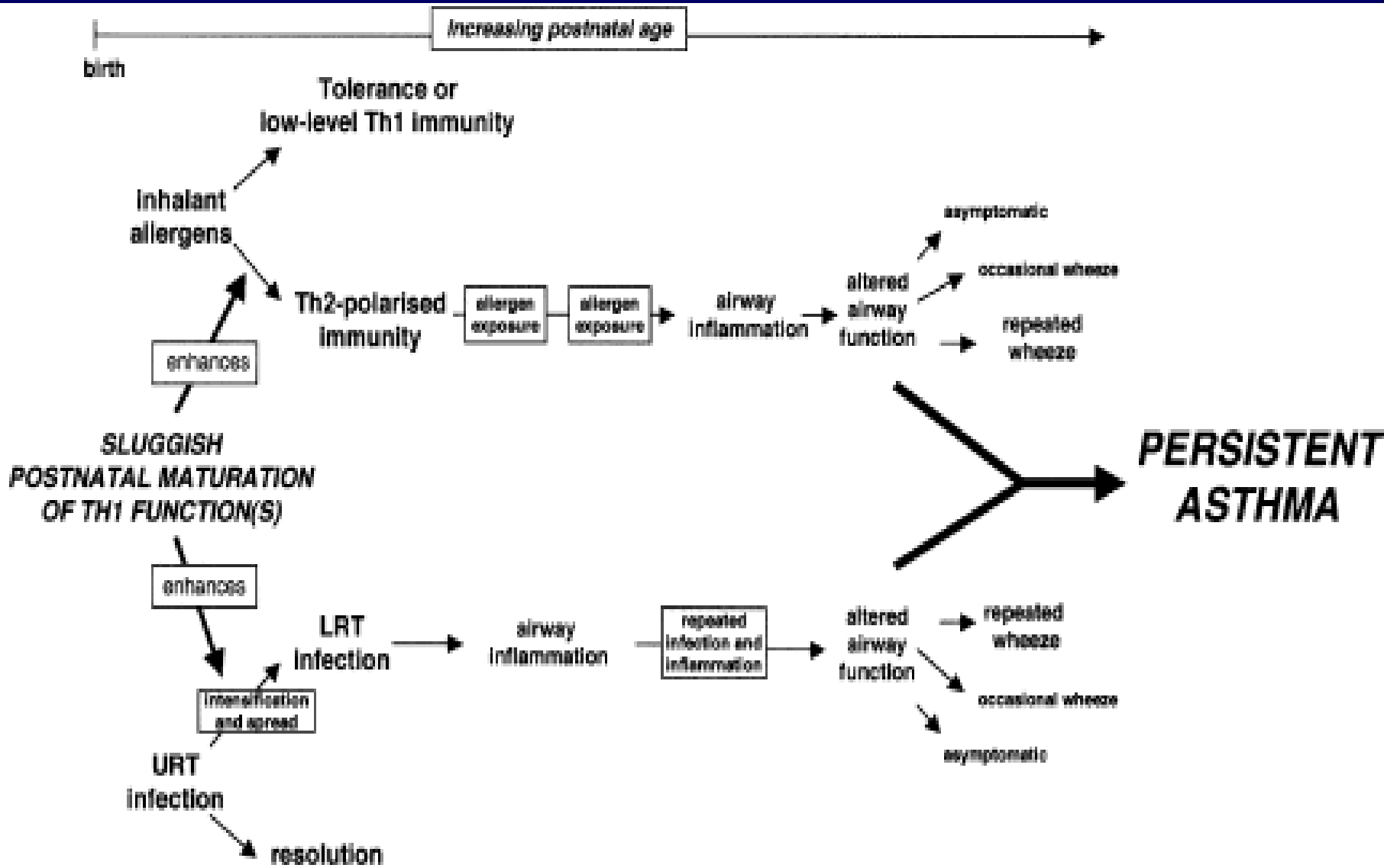
# RISCHIO DI ASMA A 6 ANNI IN FUNZIONE DELL'ATOPIA E DELLE INFEZIONI PRECOCI

(Da Holt PG et al. J Allergy Clin Immunol 2005)



# INTERAZIONI TRA DANNO DA INFEZIONE E ALLERGIA NELLA DETERMINAZIONE DELL'ASMA

(Da Holt PG et al. J Allergy Clin Immunol 2005)



# INFEZIONI ED ASMA

- Le infezioni respiratorie inducono, probabilmente in soggetti con predisposizione, broncostruzione
- Le infezioni precoci, specie se da RSV, possono alterare lo sviluppo polmonare e indurre situazioni favorevoli all'estrinsecazione dell'asma
- La persistenza dell'asma oltre l'adolescenza è, probabilmente, legata al coesistere di diversi fattori, genetici inclusi



# INFEZIONI ED ASMA: ASPETTI DI PREVENZIONE E DI TERAPIA

- Ridurre il rischio di infezioni virali precoci, specie nei prematuri e nei bambini con preesistenti alterazioni polmonari (anticorpi monoclonali anti-RSV, eliminazione di fattori domestici quali fumo passivo e frequenza in comunità, vaccino antinfluenzale)
- Diagnosticare e trattare le forme da batteri atipici

# INFLUENZA ED ASMA: EFFICACIA DEL VACCINO

(da Kramarz P et al. *J Pediatr* 2000)

	Influenza season		
	1993-1994*	1994-1995*	1995-1996†
No. of cases‡	577	969	2,075
No. of asthma exacerbations	710	1,146	2,564
Follow-up time (child-months)	3,904	6,520	14,067
Adjusted incidence rate ratio (95% CI)§	0.78 (0.55-1.10)	0.59 (0.43-0.81)	0.65 (0.52-0.80)
P value	.15	.001	.0001

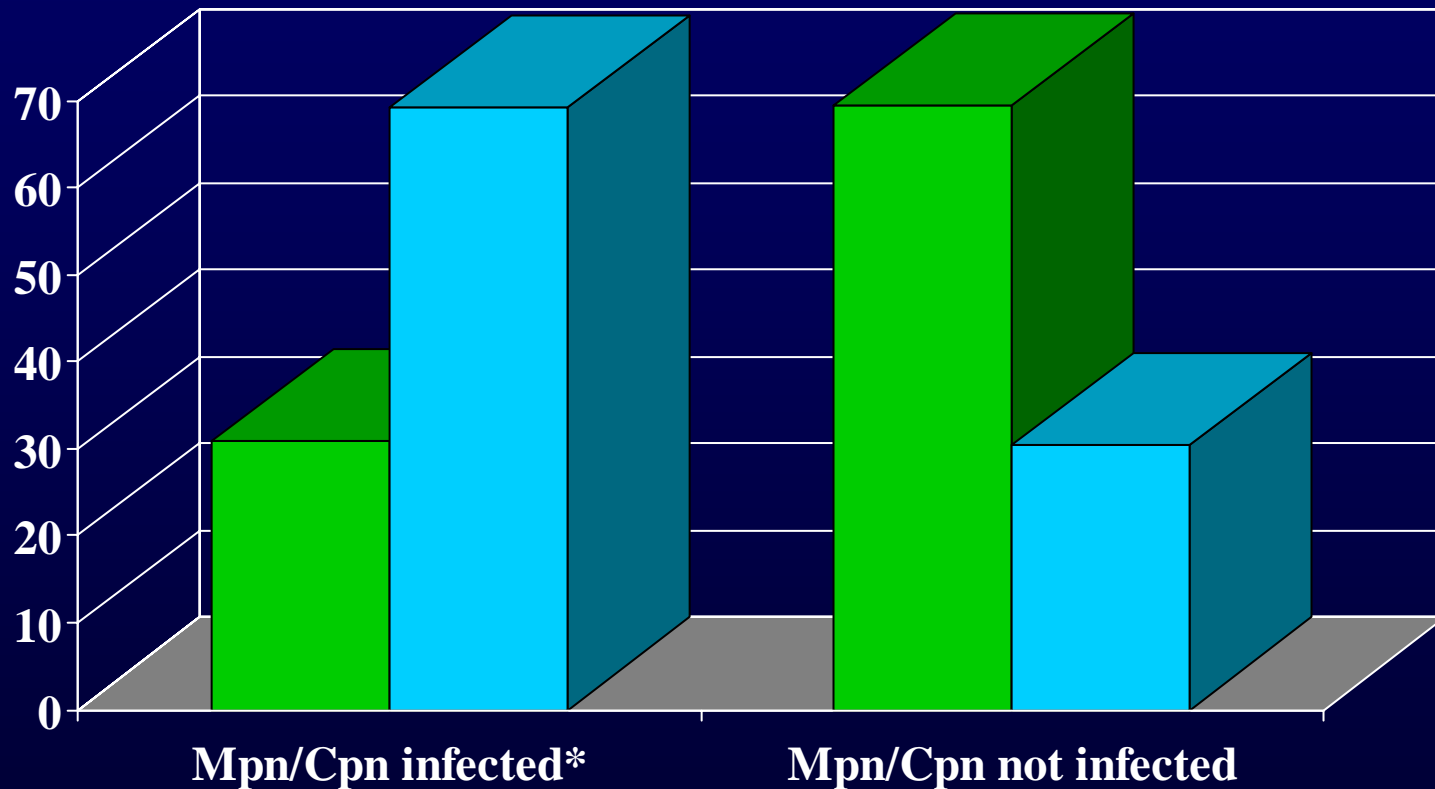
\*Three HMOs.

†Four HMOs.

‡Children with asthma who had at least one asthma exacerbation during the influenza season.

§Incidence rate ratio (95% CI) of asthma exacerbation occurring after influenza vaccination compared with the period before vaccination in the same individual; estimated by conditional Poisson regression models stratified by individual child and adjusted for 2-week periods of calendar time from October 1 through April 30 of each season.

# CLINICAL OUTCOME DURING THE 3-MONTH FOLLOW-UP IN CHILDREN WITH WHEEZING NOT TREATED WITH CLARITHROMYCIN, ACCORDING TO DIAGNOSIS



\* $p=0.03$

