

# LE POLMONITE DA *STREPTOCOCCUS PNEUMONIAE*

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# ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITALIZED CHILDREN

AGE (Years)	N°	VIRAL ETIOLOGY	BACTERIAL ETIOLOGY	MIXED ETIOLOGY	ALL*
<2	108	80	47	34	93
2-5	84	58	56	33	81
>5	62	37	58	19	76
TOTAL	254	62	53	30	85

\*Total with detected etiology.

Results expressed as percentages of patients.

Adapted from Juven et al. *Pediatr Infect Dis J* 2000

# CAP E *STREPTOCOCCUS PNEUMONIAE* (S.P.) IN ETA' PEDIATRICA (I)

STUDIO	N	PAESE	DURATA (MESI)	ETÀ MEDIA (MESI)	S.P. (%)
RAMSEY et al. 1986	162	USA	20	21	18
TURNER et al. 1987	98	USA	16	24	17
AUSINA et al. 1988	198	SPAGNA	12	60	15
CLAESSON et al. 1989	336	SVEZIA	14	60	13
NOHYNEK et al. 1991	121	FINLANDIA	12	20	16

# CAP E *STREPTOCOCCUS PNEUMONIAE* (S.P.) IN ETA' PEDIATRICA (II)

STUDIO	N	PAESE	DURATA (MESI)	ETÀ MEDIA (MESI)	S.P. (%)
RUUSKANEN et al. 1992	50	FINLANDIA	8	52	38
GENDREL et al. 1998	104	FRANCIA	30	66	13
HEISKANEN- KOSMA et al. 1998	201	FINLANDIA	12	60	28
WUBBEL et al. 1999	168	USA	23	48	21
JUVEN et al. 2000	254	FINLANDIA	36	48	37

# CHARACTERISTICS OF THE STUDY POPULATION

## Characteristics

	No. of patients (%) (n=196)
Males	99 (50.5)
Mean $\pm$ SD age, years	3.707 $\pm$ 0.870
Acute <i>Streptococcus pneumoniae</i> infection	48 (24.5)
Acute atypical bacteria infection	46 (23.5)
<i>Mycoplasma pneumoniae</i> infection	30 (15.3)
<i>Chlamydia pneumoniae</i> infection	6 (3.1)
Mixed <i>Mycoplasma pneumoniae</i> - <i>Chlamydia pneumoniae</i> infection	10 (5.1)
Mixed <i>Streptococcus pneumoniae</i> -atypical bacteria infection	16 (8.2)
Mixed <i>Streptococcus pneumoniae</i> - <i>Mycoplasma pneumoniae</i> infection	14 (7.1)
Mixed <i>Streptococcus pneumoniae</i> - <i>Chlamydia pneumoniae</i> infection	2 (1.1)

# SEROTYPE DISTRIBUTION AMONG THE 48 CHILDREN WITH COMMUNITY-ACQUIRED PNEUMOCOCCAL PNEUMONIA

(Da Esposito et al. Vaccine 2004)

Pneumococcal serotype	No. of patients (%)
1	16 (31.4)
14	11 (21.6)
9V	6 (11.8)
4	4 (7.8)
6B	4 (7.8)
19F	4 (7.8)
18C	3 (5.9)
23F	2 (3.9)
5	1 (2.0)

# POLMONITE DA *STREPTOCOCCUS PNEUMONIAE*: CLINICA

Tradizionalmente la CAP da pneumococco è identificata con la classica **polmonite franca lobare** caratterizzata da:

- ✓ Insorgenza brusca con febbre elevata
- ✓ Decorso contenuto in 7 giorni
- ✓ Quadro anatomopatologico di epatizzazione
- ✓ Reperto obiettivo di ipofonesi, crepitatio indux, respiro soffiante, crepitatio redux
- ✓ Quadro radiologico di consolidamento lobare o sublobare
- ✓ Notevole elevazione degli indici di flogosi
- ✓ Possibilità di risoluzione spontanea, ma alto rischio di evoluzione negativa in assenza di terapia antibiotica adeguata
- ✓ Pronta risposta alla terapia con penicillina

# CLINICAL CHARACTERISTICS OF CHILDREN WITH BACTERIAL CAP

(From Esposito et al. Clin Infect Dis 2002)

Characteristics	<i>S. Pneumoniae</i> infection (%) (N=48)	Atypical bacteria infection (%) (N=46)	Mixed <i>S. pneumo- atypical bacteria</i> infection (%) (N=16)
Males	25 (52.1)	22 (47.8)	8 (50.0)
Mean age $\pm$ SD, yrs	3.666 $\pm$ 0.899	3.759 $\pm$ 1.030	3.762 $\pm$ 1.030
Onset			
Gradual	23 (47.9)	26 (56.5)	8 (50.0)
Acute	25 (52.1)	20 (43.5)	8 (50.0)
Similar illness within the family	6 (12.5)	9 (19.5)	3 (18.7)
Cough	31 (64.5)	33 (71.7)	11 (68.7)
Tachypnea	12 (25.0)	11 (23.9)	4 (25.0)
Fever	42 (91.3)	39 (84.7)	14 (87.5)
Rales	45 (93.7)	41 (89.1)	15 (93.7)
Wheezes	6 (12.5)	7 (15.2)	2 (12.5)
Days of hosp. $\pm$ SD	6.857 $\pm$ 3.523	6.744 $\pm$ 2.672	7.110 $\pm$ 2.370
Days of illness $\pm$ SD	12.325 $\pm$ 6.065	13.307 $\pm$ 5.089	13.714 $\pm$ 5.517

*No significant differences were observed*

# LABORATORY DATA OF CHILDREN WITH BACTERIAL CAP

(From Esposito et al. Clin Infect Dis 2002)

Parameter	<i>S. pneumoniae</i> infection (%) (N=48)	Atypical bacteria infection (%) (N=46)	Mixed <i>S.pneumoniae</i> and atypical bacteria infect. (%) (N=16)
WBC (cells/ $\mu$ L)	16,669 $\pm$ 8,831 <sup>*°</sup>	12,554 $\pm$ 5,404 <sup>*</sup>	13,141 $\pm$ 4,540 <sup>°</sup>
Neutrophils, %	69 $\pm$ 17 <sup>*°</sup>	59 $\pm$ 18 <sup>*</sup>	63 $\pm$ 16 <sup>°</sup>
Lymphocytes, %	22 $\pm$ 15	28 $\pm$ 17	25 $\pm$ 16
Monocytes, %	7 $\pm$ 3	8 $\pm$ 3	7 $\pm$ 3
Eosinophils, %	1 $\pm$ 2	1 $\pm$ 1	1 $\pm$ 2
Basophils, %	0.3 $\pm$ 0.6	0.4 $\pm$ 0.7	0.3 $\pm$ 0.4
CRP ( $\mu$ g/dL)	109 $\pm$ 110 <sup>*°</sup>	59 $\pm$ 88 <sup>*</sup>	77 $\pm$ 79 <sup>°</sup>
ESR (mm/1h)	57 $\pm$ 28	47 $\pm$ 27	52 $\pm$ 44

Mean values  $\pm$  SD. \*p < 0.05 vs <sup>\*</sup>atypical bacteria infection and <sup>°</sup>mixed *S. pneumoniae*-atypical bacteria infection; no other significant differences were observed. WBC, white blood cell count; CRP, C-reactive protein, ESR, erythrocyte sedimentation rate

# BACTERIAL vs VIRAL PNEUMONIA

Virkki et al. Thorax 2002

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N=215	Bacterial %	Viral %
Alveolar infiltrates	71	29
Interstitial infiltrates	48	52
WBC >15 x 10 <sup>9</sup> /l	63	37
ESR > 30 mm/h	64	36
CRP > 40 mg/l	70	30
CRP > 80 mg/l	75	25

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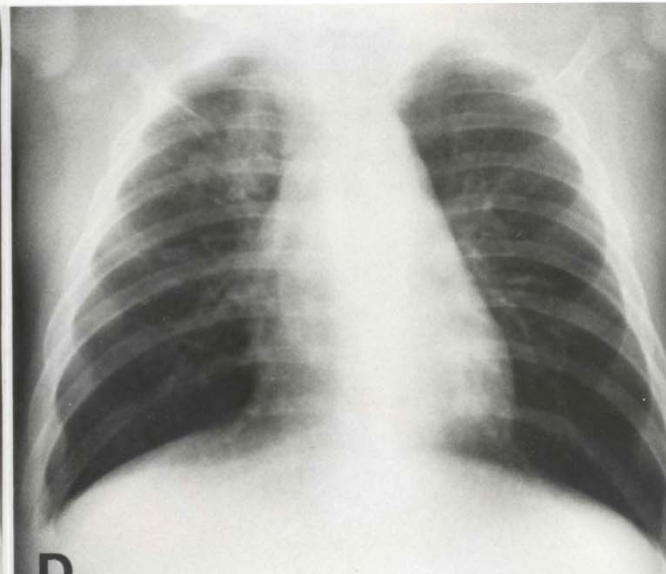
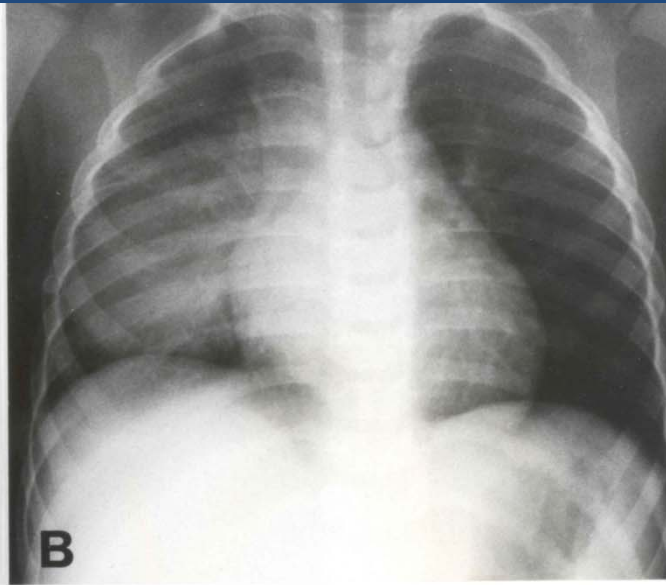
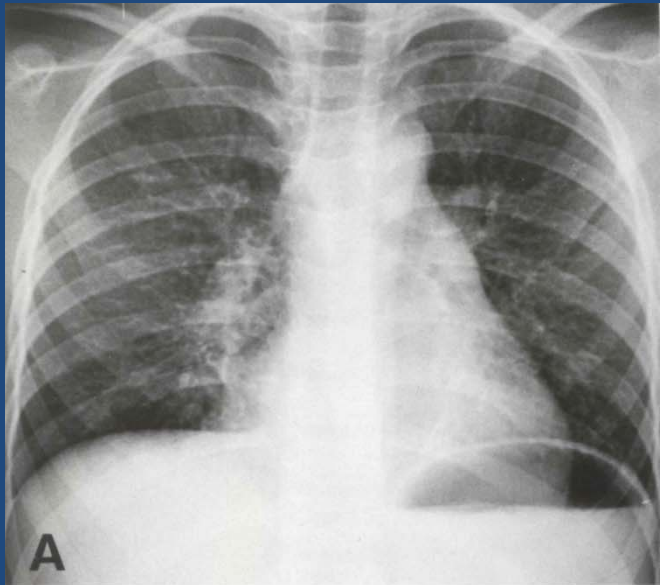
# COMPARISON OF RADIOGRAPHIC CHARACTERISTICS OF CHILDREN WITH CAP

(From Esposito et al. Clin Infect Dis 2002)

<b>Finding</b>	<b><i>S. pneumoniae</i> infection (%) (N=48)</b>	<b>Atypical bacteria infection (%) (N=46)</b>	<b>Mixed <i>S.pneumoniae</i> and atypical bacteria infect. (%) (N=16)</b>
Hyperinflation	5 (10.4)	6 (13.0)	2 (12.5)
Peribronchial wall thickening	3 (6.2)	4 (8.7)	1 (6.2)
Perihilar linear opacities	15 (31.2)	20 (43.5)	9 (56.6)
Reticulo-nodular infiltrate	13 (27.1)	21 (45.6)	5 (31.2)
Segmental or lobar consolidation	18 (37.5)	12 (26.1)	5 (31.2)
Bilateral consolidations	7 (14.6)	4 (8.7)	2 (12.5)
Pleural effusion	3 (6.2)	3 (6.5)	1 (6.2)

No significant differences were observed

# IMMAGINI RADIOLOGICHE DI CAP DA *STREPTOCOCCUS PNEUMONIAE*



# CARATTERISTICHE DISTINTIVE TRA POLMONITI PNEUMOCOCCICHE COMPLICATE E NON

(Da Tan TQ et al. Pediatrics 2002)

Characteristic	Uncomplicated ( <i>n</i> = 235)	Complicated ( <i>n</i> = 133)	<i>P</i> Value
Age (mo; median, range)	27 (0.067–311)	45 (0.25–215)	.0080
White race	85 (36%)	77 (58%)	<.0001
Underlying disease	114 (48.5%)	30 (22.6%)	<.0001
Antibiotic usage before diagnosis	30 (12.8%)	25 (19%)	.12
Chest pain	18 (7.7%)	39 (29.3%)	<.0001
Fever before diagnosis >3 d	70 (31.4%)	82 (65.1%)	<.0001
Penicillin-resistant isolates	22 (9.4%)	15 (11.3%)	NS
CXR findings			
≥2 lobes	87 (37%)	86 (65%)	<.0001
Consolidation	97 (41.3%)	120 (90.2%)	<.0001
Hospital duration (d; mean [median, range])	6.45 (4, 1–45)	17.70 (13, 1–176)	<.0001
Defervescence >2 d	53 (26.4%)	111 (86.1%)	<.0001
Oxygen requirement >2 d	46 (52.3%)	100 (88%)	<.0001

# SENSIBILITA' DELLO PNEUMOCOCCO E GRAVITA' DEL QUADRO CLINICO

(Da Wexler ID et al. *Pediatr Pulmunol* 2006)

Characteristic	Penicillin-sensitive (n = 84)	Penicillin-resistant (n = 16)	P-value
Age (years)			
Mean	4.3 ± 4.0	1.9 ± 2.0	0.02
Median	3.0	1.3	
P/F ratio	1.47	3.00	NS
Significant background disease (%)	41	50	NS
Respiratory distress (%) (dyspnea and/or retractions)	32	56	0.05
Weight ≤10% for age (%)	39	40	NS
Pulmonary complications (%)	37	44	NS
Days to defervescence (days)			
Mean	4.9 ± 4.9	6.9 ± 9.1	NS
Median	3	3	
Hospitalization duration (days)			
Mean	8.0 ± 8.4	11.2 ± 8.8	NS
Median	5	8	

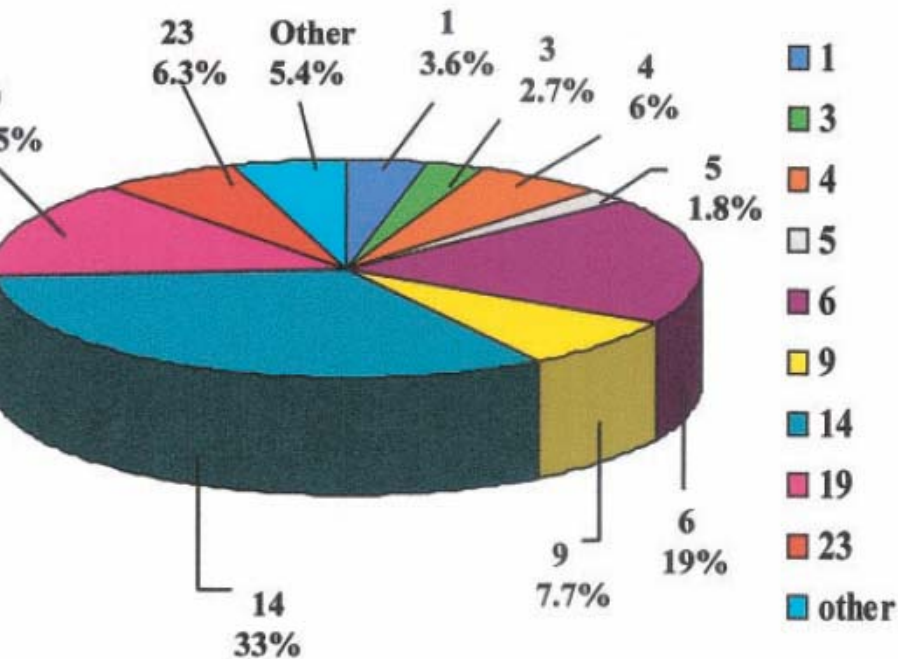


presence of penicillin resistance vs. penicillin sensitivity. NS, nonsignificant.

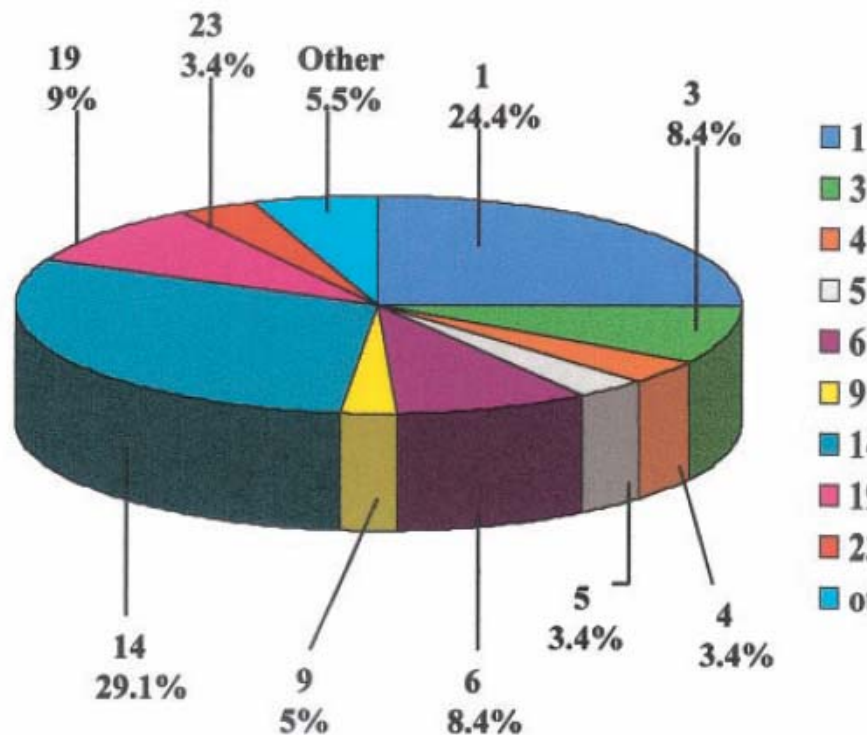
# SIEROTIPI DI PNEUMOCOCCO E GRAVITA' DELLA POLMONITE

(Da Tan TQ et al. Pediatrics 2002)

## Uncomplicated Pneumonia



## Complicated Pneumonia

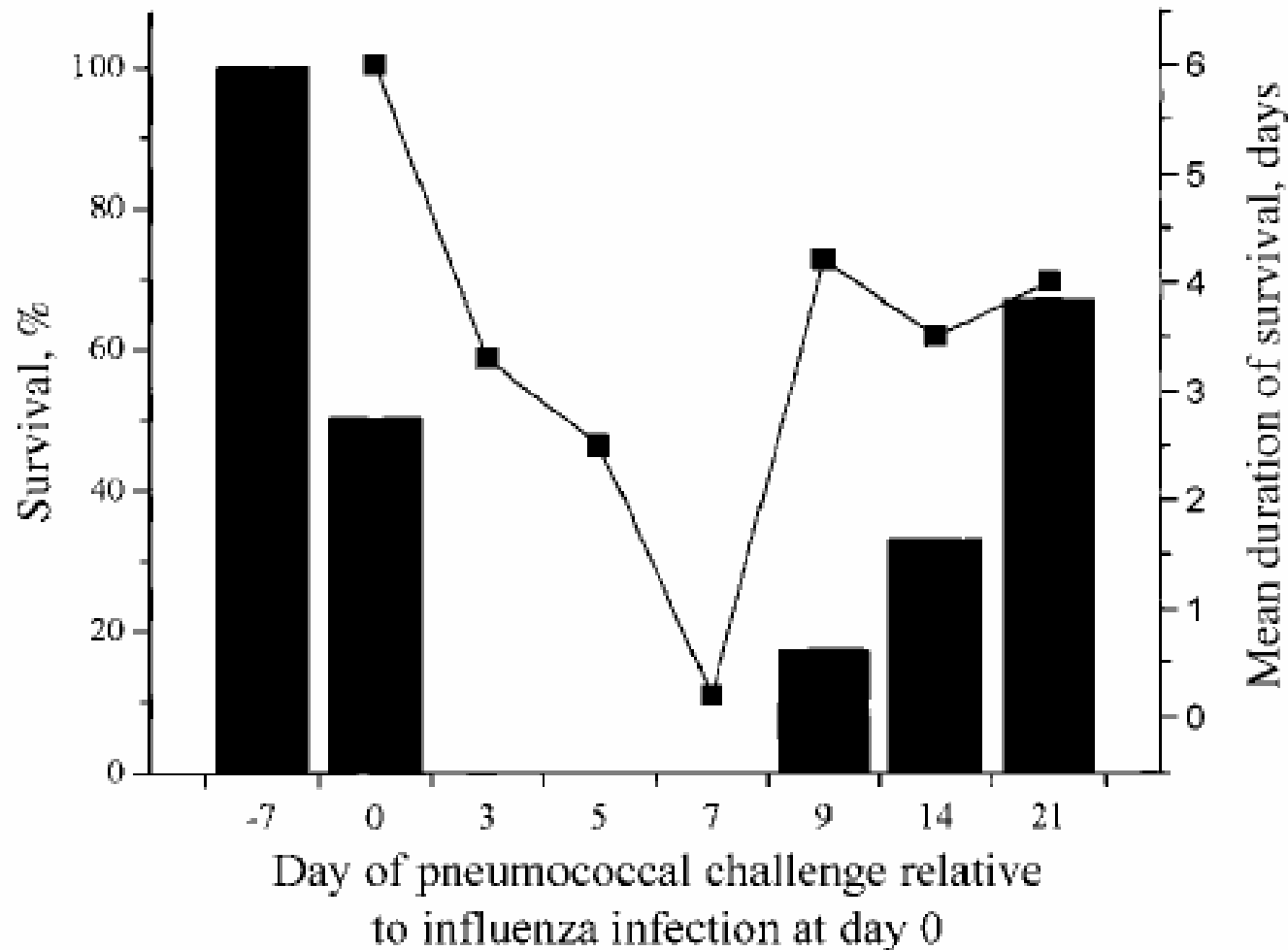


# SIEROTIPI DI PNEUMOCOCCO ASSOCIATI A POLMONITE NECROTIZZANTE

(Da Bender JM et al. Clin Infect Dis 2008)

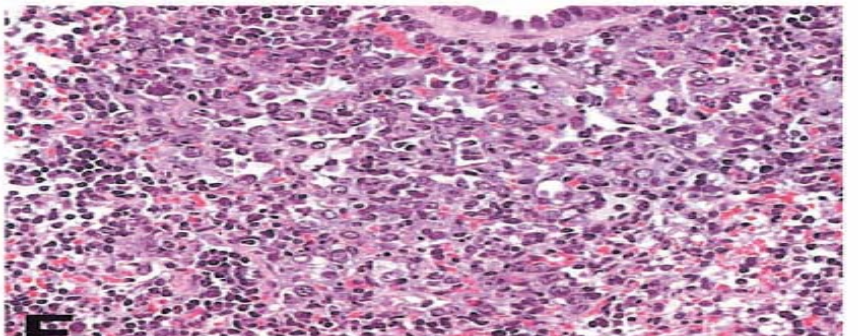
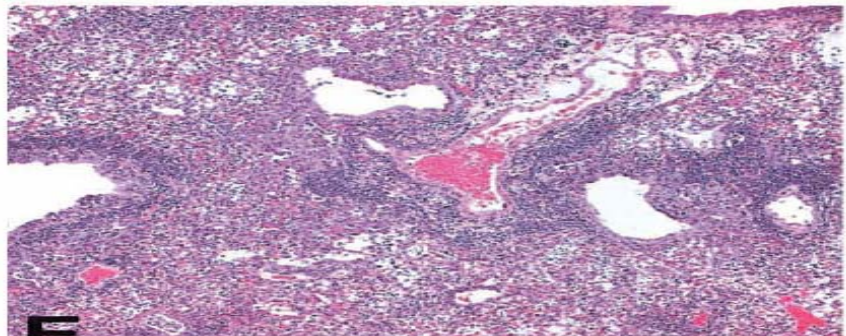
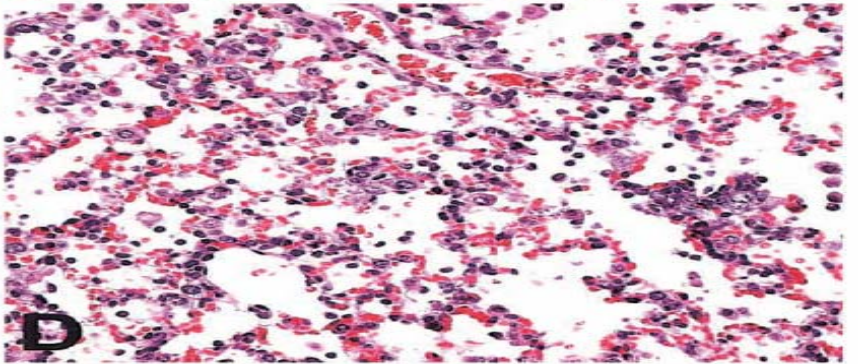
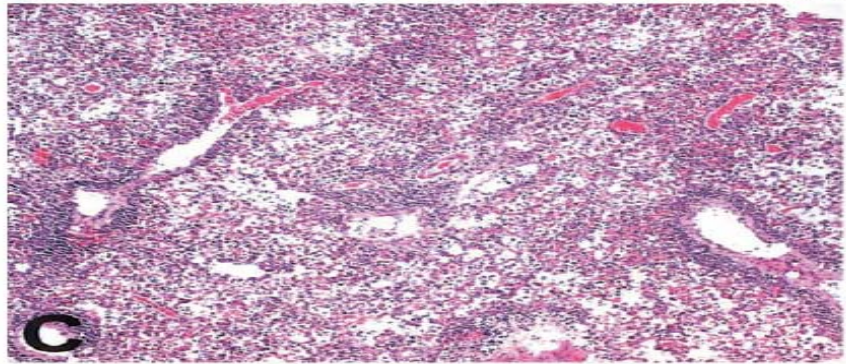
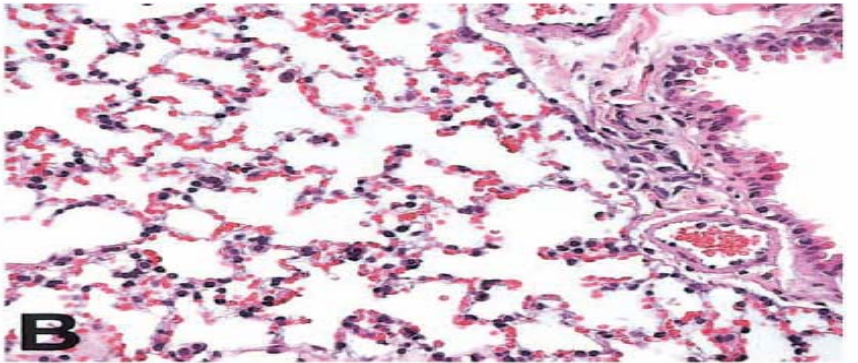
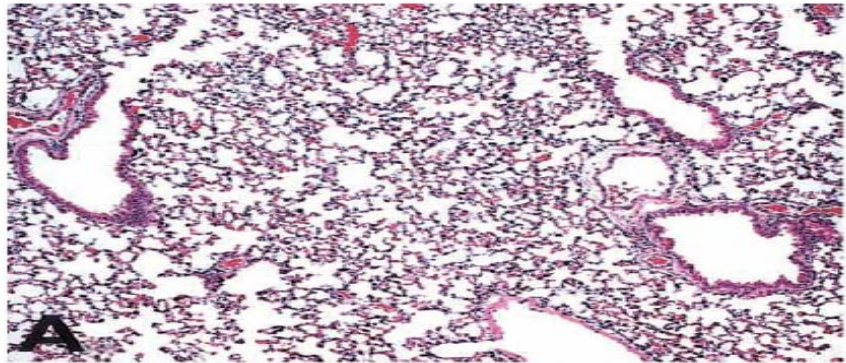
Serotype	No. of children with pneumonia due to the specified serotype	No. (%) of children with PNP due to the specified serotype
All serotypes	124	38 (23)
1	28	3 (11)
3	14	11 (79)
<b>4</b>	<b>2</b>	<b>1 (50)</b>
6A	2	1 (50)
<b>6B</b>	<b>6</b>	<b>2 (33)</b>
7	7	1 (4)
9	3	0
9N	2	0
<b>9V</b>	<b>5</b>	<b>0</b>
<b>14</b>	<b>7</b>	<b>0</b>
<b>18C</b>	<b>0</b>	NA
19	8	4 (50)
19A	13	4 (31)
<b>19F</b>	<b>6</b>	<b>1 (17)</b>
22	2	0
<b>23F</b>	<b>2</b>	<b>0</b>
NG	2	1 (50)
Other <sup>a</sup>	6	2 (33)

# TIMING OF SURVIVAL AFTER INFLUENZA AND *STREPTOCOCCUS PNEUMONIAE* (McCullers and Rehg, J Infect Dis 2002)



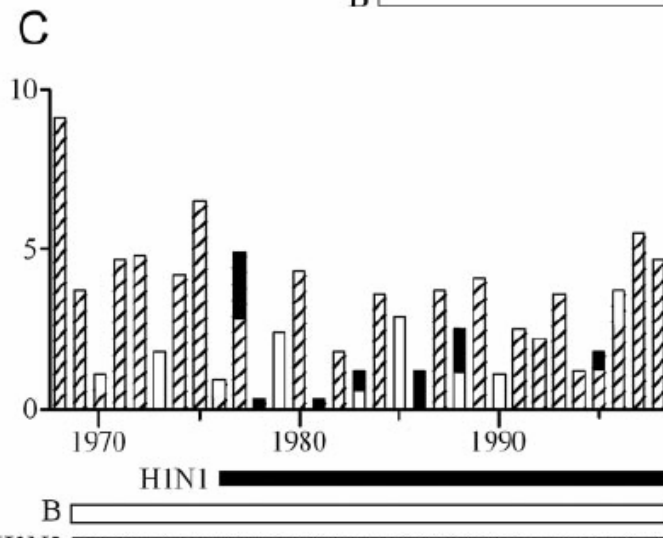
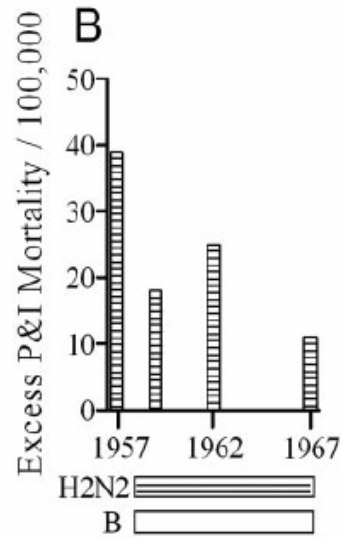
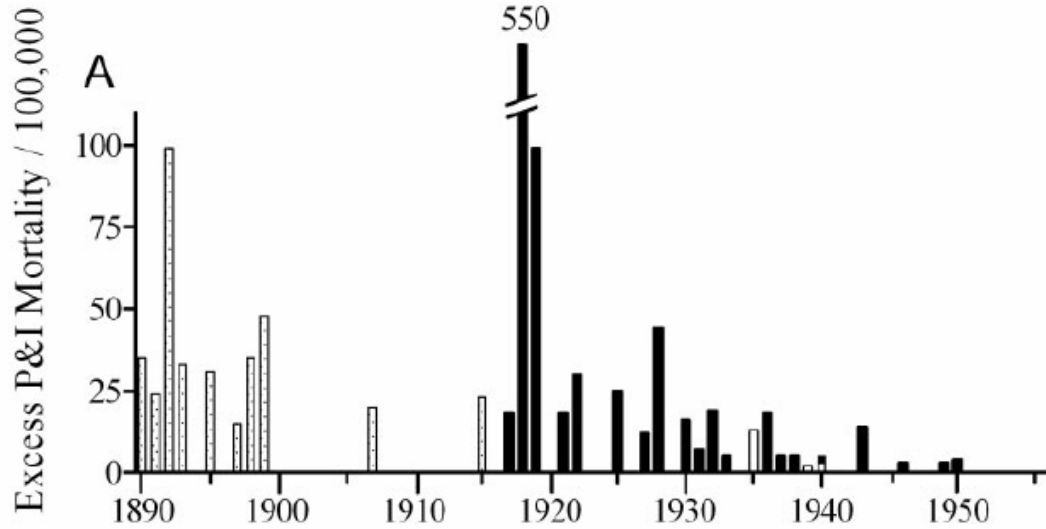
# PATHOLOGIC ANALYSIS OF SURVIVAL AFTER INFLUENZA AND *STREPTOCOCCUS PNEUMONIAE* INFECTION

(McCullers and Rehg, J Infect Dis 2002)

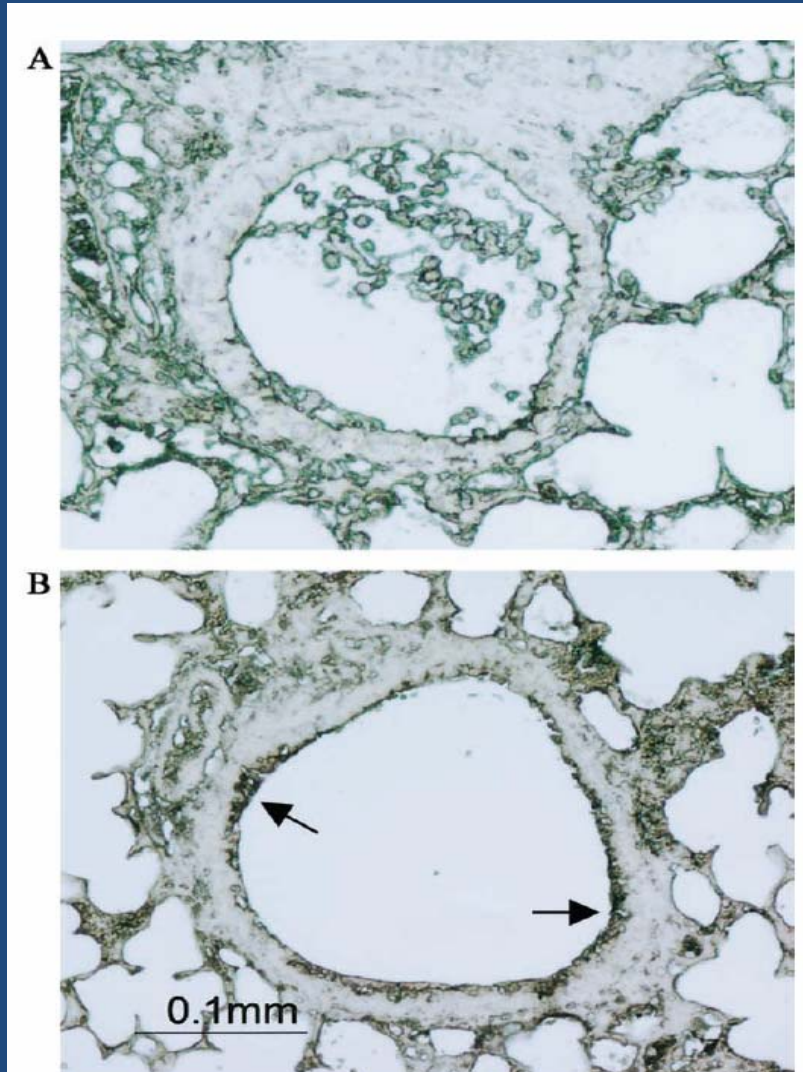


# EXCESS MORTALITY RATES BY YEAR

(McCullers JA, Clin Microbiol Rev 2006)

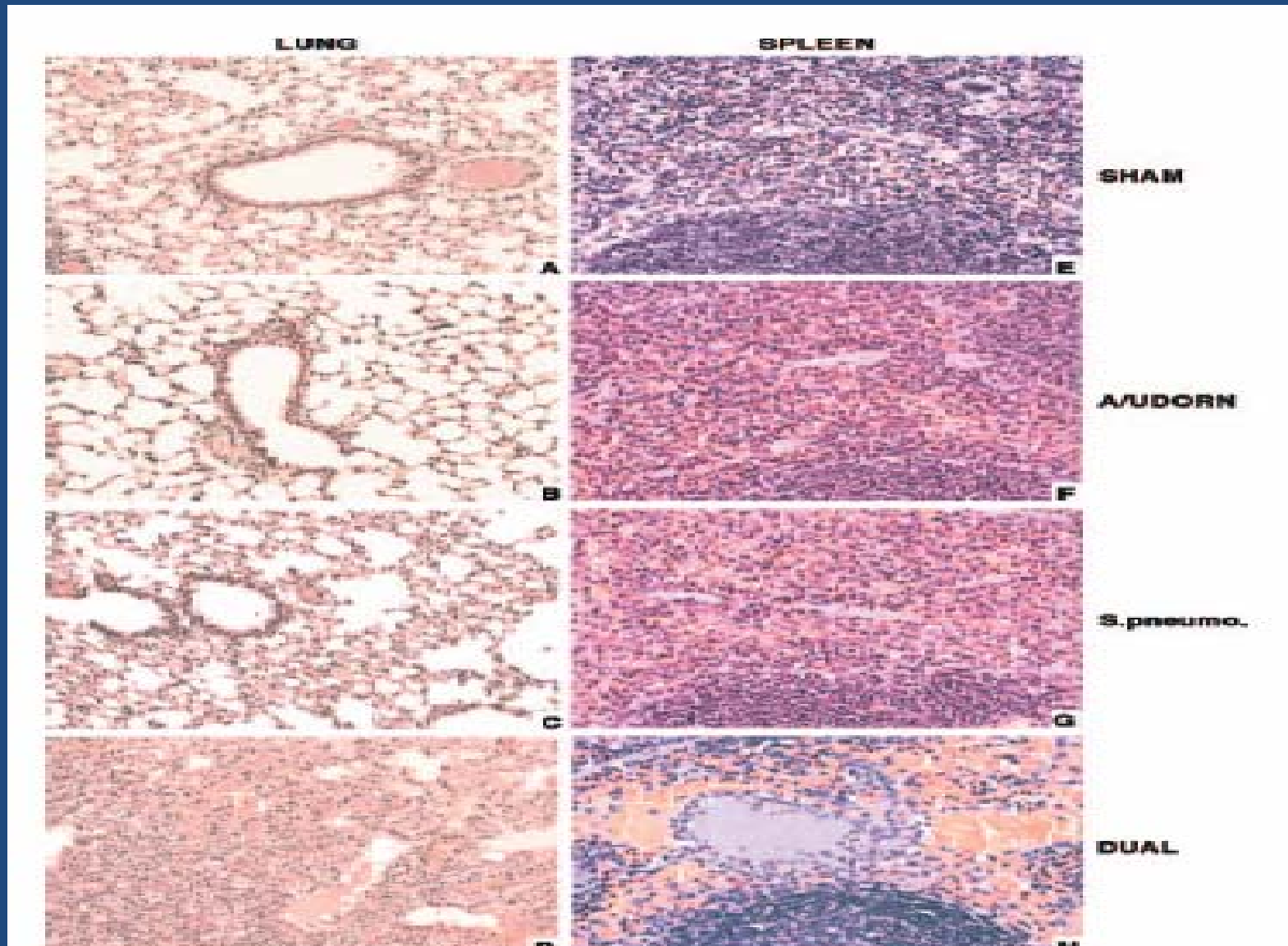


**ROLE OF NEUROMINIDASE IN LETHAL  
SYNERGISM BETWEEN INFLUENZA VIRUS AND  
*STREPTOCOCCUS PNEUMONIAE*  
(McCullers and Bartmess, J Infect Dis 2003)**



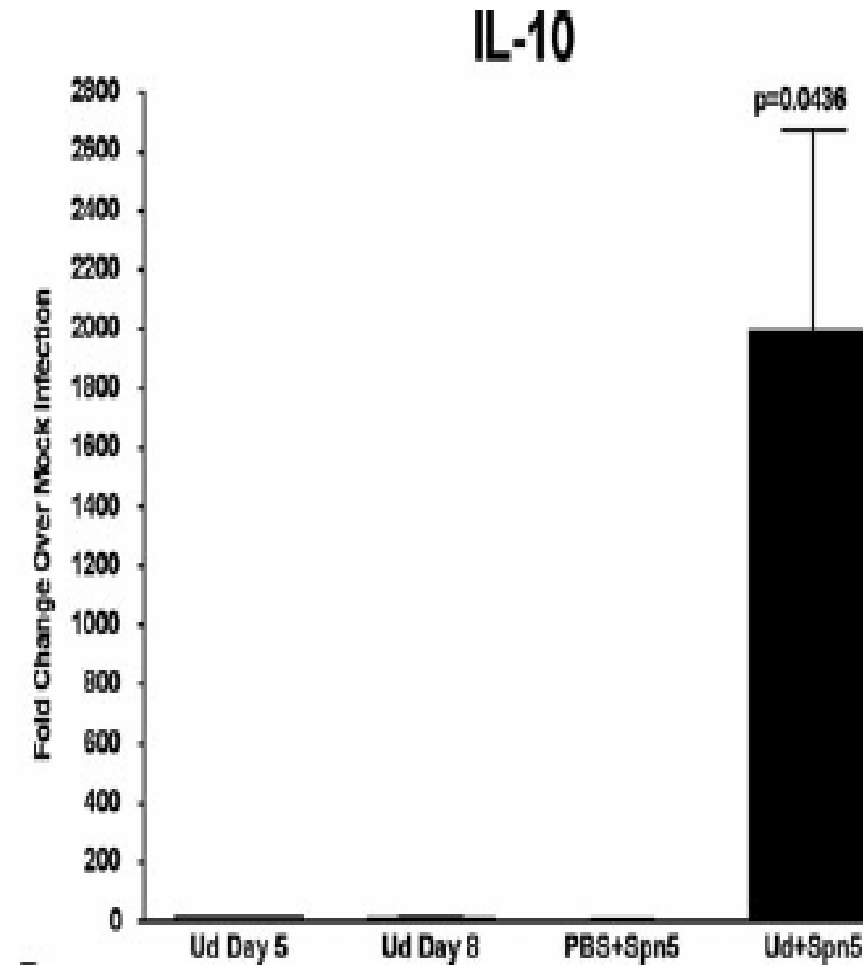
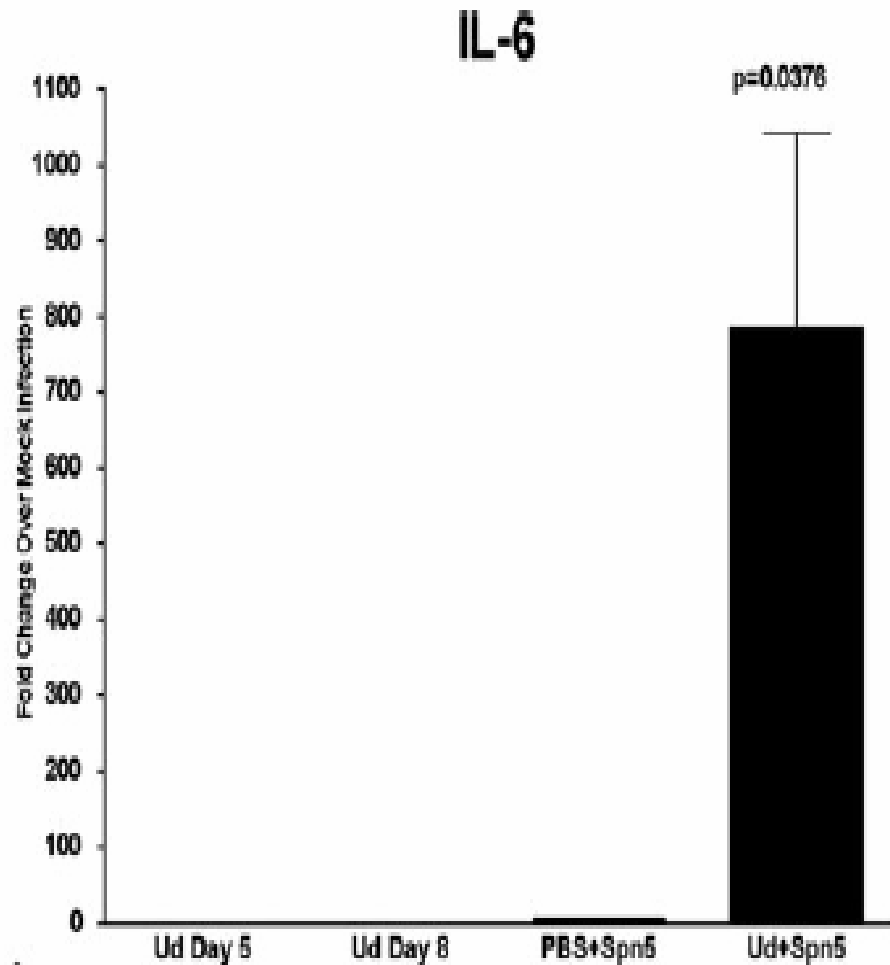
# HISTOPATHOLOGICAL FEATURES OF INFLUENZA-OR/AND PNEUMOCOCCAL INFECTED MICE

(Speshock et al. Infect Immun 2007)



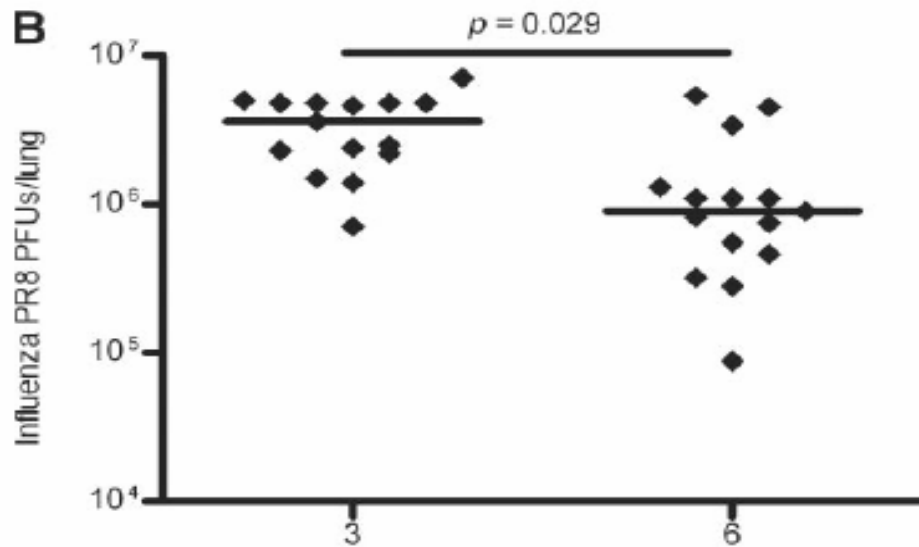
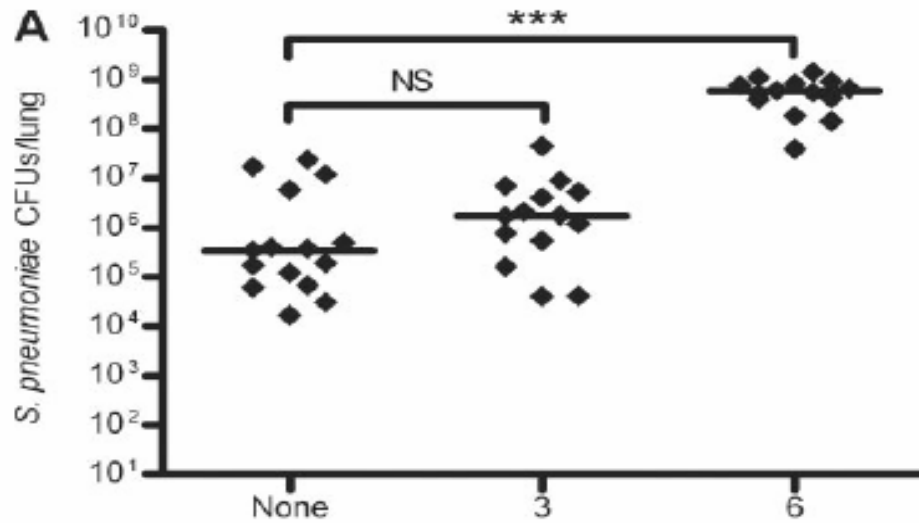
# CYTOKINE SECRETION IN INFLUENZA- OR/AND PNEUMOCOCCAL INFECTED MICE

(Speshock et al. Infect Immun 2007)



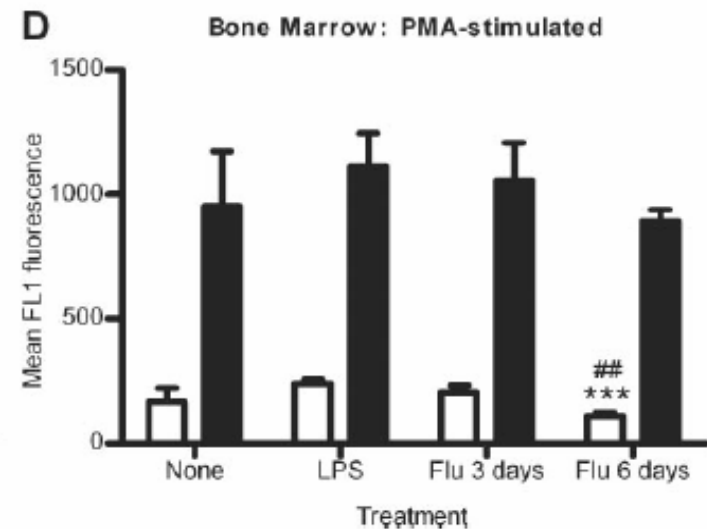
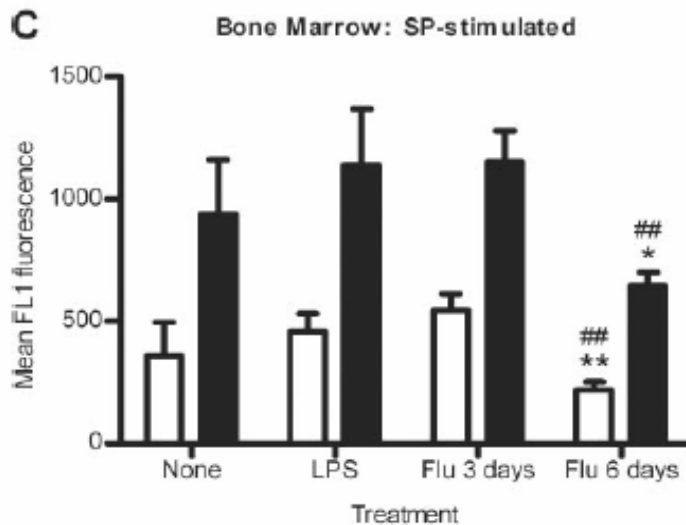
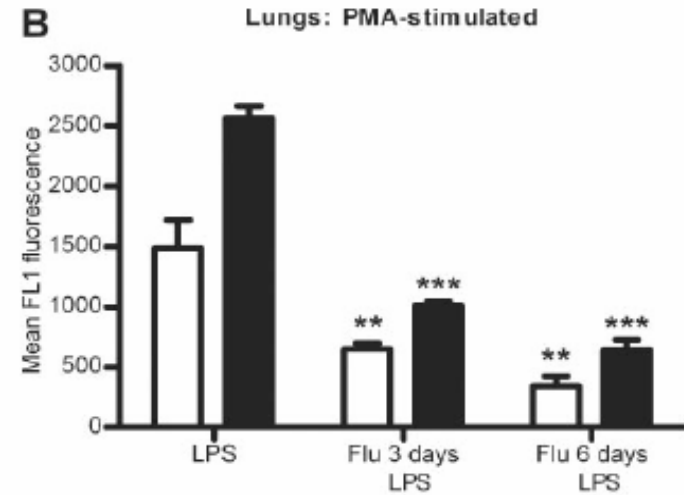
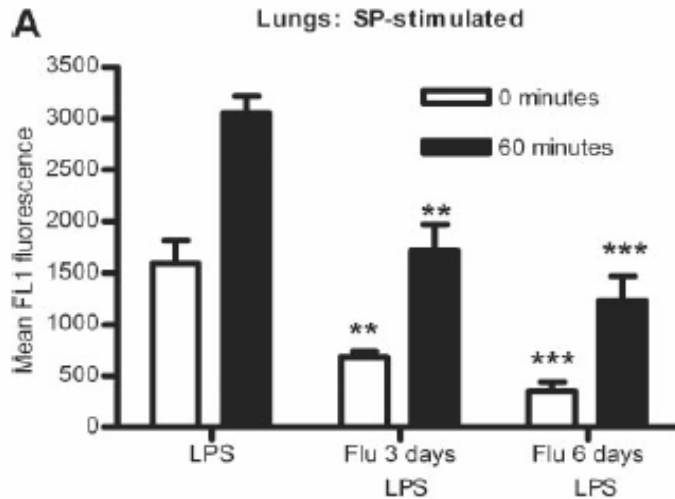
# INFLUENZA AND *S. PNEUMONIAE* IN MICE LUNGS

(McNamee et al., Infect Immun 2006)



# NEUTROPHIL FUNCTION IN INFLUENZA- INFECTED MICE

(McNamee et al., Infect Immun 2006)



# EFFICACY OF PCV IN FULLY IMMUNIZED INFANTS

(Madhi SA et al., Nat Med 2004)

Clinical diagnosis	All children <sup>e</sup>				HIV-uninfected children <sup>f</sup>				HIV-infected children <sup>f</sup>			
	Vaccine <i>n</i> = 18,245	Placebo <i>n</i> = 18,268	Efficacy (95% CI)	<i>P</i> value	Vaccine <i>n</i> = 17,065	Placebo <i>n</i> = 17,086	Efficacy (95% CI)	<i>P</i> value	Vaccine <i>n</i> = 1,180	Placebo <i>n</i> = 1,182	Efficacy (95% CI)	<i>P</i> value
Total number of pneumonia cases <sup>a</sup>	544	679	20 (10, 28)	0.00009	348	452	23 (11, 33)	0.0002	181	210	14 (-4, 28)	0.0002
Pneumonia with lobar consolidation <sup>b</sup>	251	303	17 (2, 30)	0.03	119	158	25 (4, 40)	0.02	128	140	8 (-15, 27)	0.02
Pneumonia without identified virus <sup>c</sup>	419	486	14 (2, 24)	0.03	252	299	16 (0, 29)	0.05	167	187	11 (-8, 26)	0.05
Identified virus-associated pneumonia <sup>d</sup>	160	231	31 (15, 43)	0.0004	111	167	33 (15, 48)	0.0008	44	57	0.2 (-14, 47)	0.0008
Influenza A	31	56	45 (14, 64)	0.01	21	32	34 (-14, 62)	0.1	9	21	57 (7, 80)	0.1
Adenovirus	90	115	22 (-3, 41)	0.08	64	94	32 (6, 50)	0.02	22	17	-30 (-143, 31)	0.02
Rhinovirus types 1-3	24	43	44 (8, 66)	0.02	16	27	41 (-10, 68)	0.09	8	16	50 (-17, 78)	0.09
Parainfluenza virus	14	15	7 (-0.4, 55)	0.9	9	13	31 (-62, 70)	0.4	5	2	-150 (-1, 188, 51)	0.4

# CAP DA *STREPTOCOCCUS PNEUMONIAE*: CONCLUSIONI EZIOPATOGENETICHE

- ✓ La CAP da pneumococco è molto comune
- ✓ I sierotipi più frequenti sono gli stessi responsabili delle infezioni invasive
- ✓ Le forme più gravi, che coprono circa il 10% del totale, sono prevalentemente dovute ai sierotipi 1 e 3
- ✓ La resistenza agli antibiotici non ha ruolo nel condizionare la gravità
- ✓ Il virus influenzale favorisce la sovrainfezione polmonare pneumococcica

# CAP DA *STREPTOCOCCUS PNEUMONIAE*: PRESUPPOSTI TERAPEUTICI

- ✓ La differenziazione eziologica tra forme virali e batteriche è, in pediatria, estremamente difficile
- ✓ Lo stesso si può dire tra le diverse forme batteriche
- ✓ Ciò spiega perché gran parte degli esperti consiglia di trattare tutte le CAP dei soggetti di età pediatrica con antibiotici
- ✓ La scelta della terapia deve essere tale da coprire i patogeni più probabilmente in causa

# BACTERIAL ETIOLOGY OF PNEUMONIA

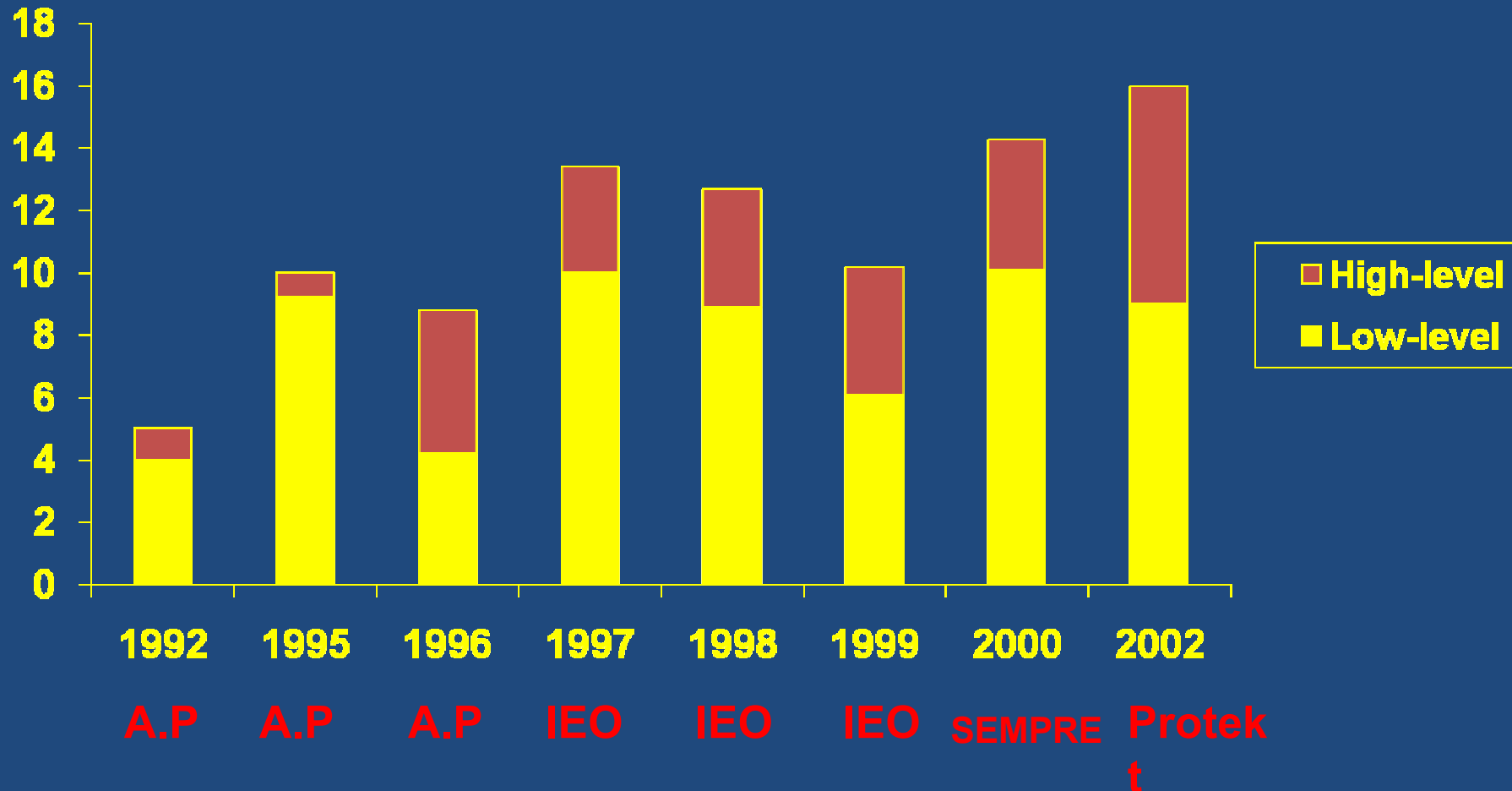
	2 wks-3 m	4 m-4 yrs	> 4 yrs
<i>S.pneumoniae</i>	++	+++	++
<i>H. influenzae</i>	+	++	+
<i>S. pyogenes</i>	-	+	+
<i>S.aureus</i>	++	+	+
<i>Strep B and D</i>	+++	-	-
Enteric bacilli	+++	-	-
<i>M.pneumoniae</i>	-	++	+++
<i>C. trachomatis</i>	++	-	-
<i>C. pneumoniae</i>	-	+	++
Anaerobes	-	-	+

1    ++++ very frequent    +++ frequent    ++ less frequent    + rare

# *S. pneumoniae*

## Evolution of penicillin-resistance in Italy

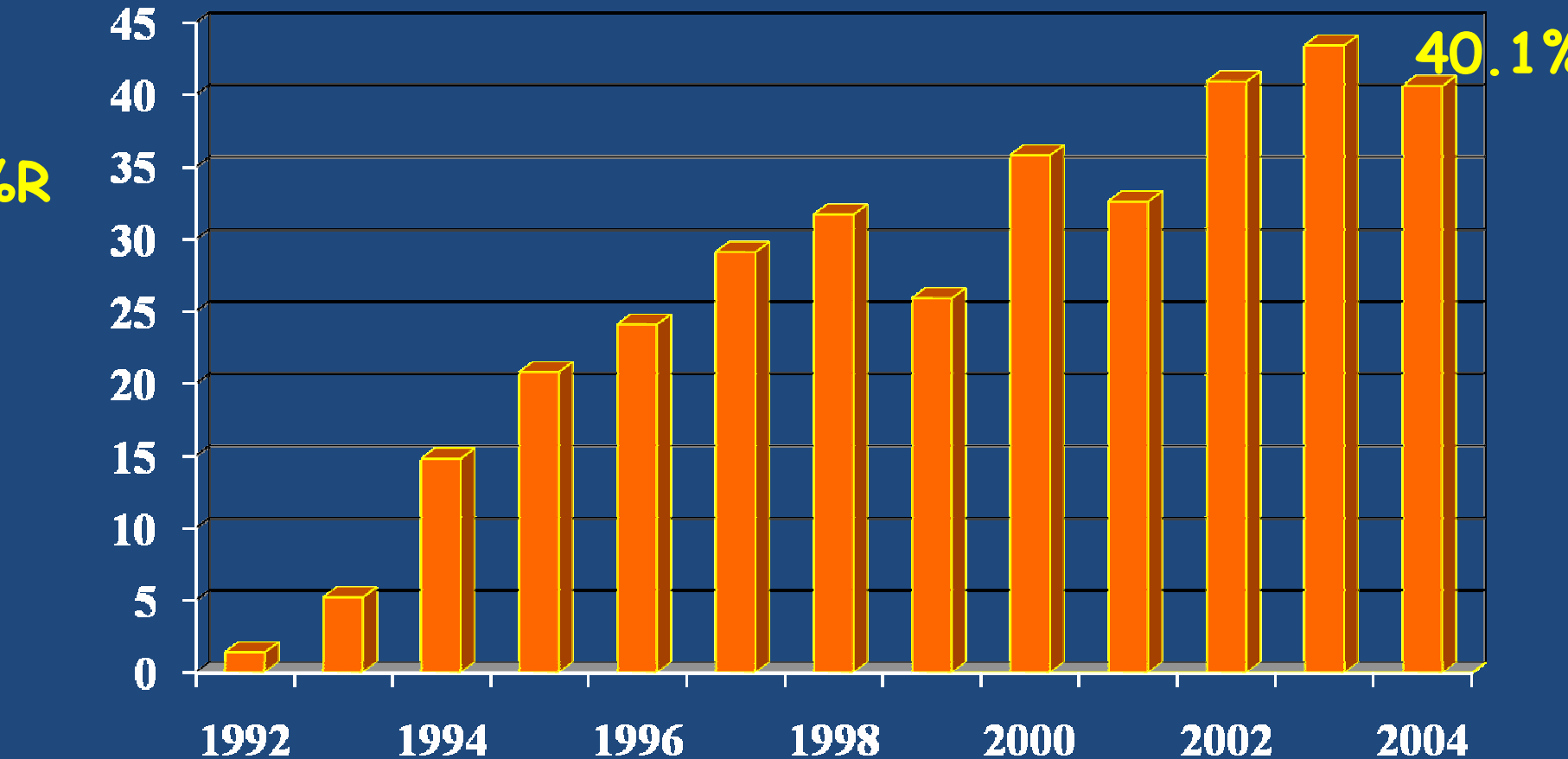
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Felmingham *et al.*, JAC, 2000; Marchese *et al.*, MDR, 2001; Schito *et al.*, 43<sup>rd</sup> ICCAC, 2003 ; Schito *et al.*, 43<sup>rd</sup> ICAAC, 2003.

# *S. pneumoniae*

## macrolide-resistance in Italy (%)



Felmingham *et al.*, 1996; Felmingham *et al.*, 2002; Marchese *et al.*, 2001; Schito *et al.*, 2002; Marchese *et al.*, 2005

# Comparison of the clinical outcome of the evaluable children according to the aetiological diagnosis and antimicrobial therapy

Clinical response	<i>S. pneumoniae</i> infection (%) (N=44)	Atypical bacteria infection (%) (N=42)	Mixed <i>S.pneumoniae</i> atypical bacteria infect. (%) (N=15)
Treated with a $\beta$ -lactam monotherapy	28 (63.6)	21 (50.0)	5 (33.3)
Cure or improvement	27 (96.4)*^	11 (52.4)*\$#	2 (50.0)^
Failures	1 (3.6)*^	10 (47.6)*\$#	2 (50.0)^
Treated with a $\beta$ -lactam plus a macrolide	9 (20.5)	7 (16.7)	6 (40.0)
Cure or improvement	9 (100.0)	7 (100.0)\$	6 (100.0)
Failures	0	0\$	0
Treated with a macrolide monotherapy	7 (15.9)	14 (33.3)	5 (33.3)
Cure or improvement	6 (85.7)	13 (92.9)#	5 (100.0)
Failures	1 (14.3)	1 (7.1)#	0

From Esposito et al. Clin Infect Dis 2002; 35:1345-52

\* $p=0.0003$  vs atypical bacteria infection, ^  $p=0.034$  vs mixed *S. pneumoniae*-atypical bacteria infection, \$ $p=0.030$  vs atypical bacteria infection treated with a  $\beta$ -lactam plus a macrolide, # $p=0.023$  vs atypical bacteria infection treated with a macrolide only; no other significant differences were observed

# SUGGESTED DRUG TREATMENT FOR CAP IN CHILDREN

(4 months to 4 years)

**ORAL AMOXICILLIN** (70-90 mg/kg/die in 3 doses)

If therapy seems to fail after 48-72 hrs,

**AN ORAL MACROLIDE** (30-40 mg/kg/die in 3-4 doses)

PARENTERAL DRUGS (cephalosporins) AND COMBINATION OF BOTH DRUGS ARE SUGGESTED FOR MORE SEVERE CASES

# SUGGESTED DRUG TREATMENT FOR CAP IN CHILDREN ( > 4 years)

**AN ORAL MACROLIDE** (dose according to the molecule)

If treatment seems to fail after 48-72 hrs,  
or for more severe diseases add:

**I.V. AMPICILLIN** (100-150 mg/kg/die in 3 doses) or **CEFOTAXIME** (100-150 mg/kg/die in 3 doses) or **CEFTRIAZONE** (100 mg/kg/die in one dose)