LA POLMONITE DI COMUNITA'

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CASO CLINICO – FEDERICA 3 anni

- Anamnesi fisiologica e patologica negativa
- Frequenta la scuola materna da 3 mesi
- Comparsa di rinite e tosse catarrale e, dopo 3 giorni, febbre non remittente al paracetamolo (TA 40°C) e marcata inappetenza
- All'esame obiettivo riscontro di tachipnea, alitamento delle pinne nasali, MV ridotto in campo medio destro e qualche rantolo crepitante nella stessa sede
- Sospetto diagnostico???

POLMONITE - EPIDEMIOLOGIA

La polmonite di comunità (CAP) è una delle più comuni malattie dell'età pediatrica

- **La CAP è la seconda causa di morte nei bambini che vivono nei Paesi in via di sviluppo**
- **La CAP rappresenta una delle più frequenti ragioni di richiesta di assistenza ospedaliera nei Paesi industrializzati**

DIAGNOSI DI CAP

- *Sospetto diagnostico* -> VALUTAZIONE CLINICA (ipofonesi plessica, modificazioni del FVT, alterazioni del MV, polipnea)

- *Certezza diagnostica* -> RADIOGRAFIA DEL TORACE (presenza di infiltrati alveolari o interstiziali con o senza versamento pleurico)

FREQUENZA RESPIRATORIA E PRESENZA DI CAP NEL BAMBINO

Età	Frequenza respiratoria/min
< 2 mesi	> 60
2 – 12 mesi	> 50
> 12 mesi	> 40

I dati in Tabella risultano avere una sensibilità del 74% e una specificità del 67% per la diagnosi di CAP

CASO CLINICO – FEDERICA 3 anni

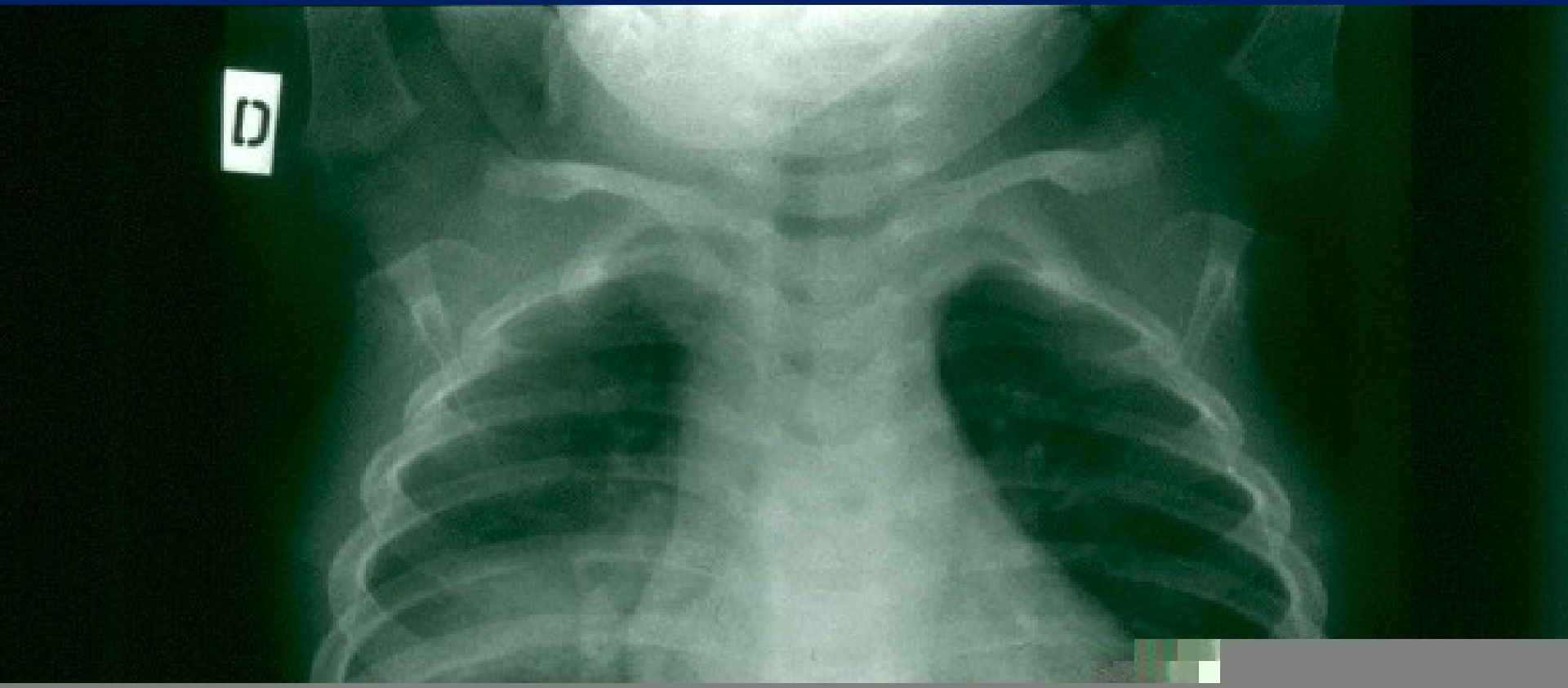
E' necessario eseguire la radiografia del torace?

E' necessario ricoverare la paziente?

E' SEMPRE NECESSARIO ESEGUIRE LA RADIOGRAFIA DEL TORACE PER PORRE DIAGNOSI DI CAP?

- No nei casi di lieve o media gravità con sintomatologia clinica ben espressa
- Sì nei casi dubbi, per evitare inutili trattamenti antibiotici
- Sì nei casi gravi, per definire la situazione di partenza della malattia
- Sì nei casi inseriti in protocolli di ricerca per definire i rapporti esistenti tra le variabili in studio e i tipi di alterazione polmonare

RADIOGRAFIA DEL TORACE DI FEDERICA



VALUTAZIONE DI GRAVITA' DELLA CAP DEL BAMBINO

- Temperatura corporea > 39°C
- Frequenza respiratoria > 50 atti/min
- Rientramenti intercostali di grado medio-alto o dispnea grave
- Alitamento delle pinne nasali
- Cianosi
- Apnea intermittente
- Difficolta' ad alimentarsi o segni di disidratazione
- Versamento pleurico esteso
- Segni di sepsi

CASO CLINICO – FEDERICA 3 anni

Quale sarà il più probabile agente eziologico?

E' possibile diagnosticarlo sulla base della clinica, dei comuni esami di laboratorio e della radiografia del torace?

ETIOLOGY OF PNEUMONIA IN CHILDREN

BACTERIA	30-50%
VIRUSES	30-50%
VIRAL-BACTERIAL	10-30%
TOTAL	50-90%

Ruuskanen O, Cap Ferrat 2002

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

BACTERIAL CO-INFECTIONS IN VIRAL PNEUMONIA
Juvén et al. Pediatr Infect Dis J 2002

	Rhinovirus %	RSV %	Adenovirus %	Parainflu %
S. pneumoniae	33	25	11	28
H. influenzae	10	18	11	4
M. pneumoniae	3	3	11	0
M. catarrhalis	9	0	11	12
Total	52	44	47	44

BACTERIAL ETIOLOGY OF PNEUMONIA

	1 wks - 3 m	4 m - 4 yrs	> 4 yrs
St.pneumoniae	++	+++	++
H. influenzae	+	+	+
St. pyogenes	-	+	+
Staph.aureus	++	+	+
Strep B and D	+++	-	-
Enteric bacilli	+++	-	-
Myc.pneumoniae	-	++	+++
Chl. trachomatis	++	-	-
Chl. pneumoniae	-	+	++
Anaerobes	-	-	+

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

INCIDENCE OF PNEUMONIA DUE TO *M. PNEUMONIAE* OR *C. PNEUMONIAE** VS. AGE

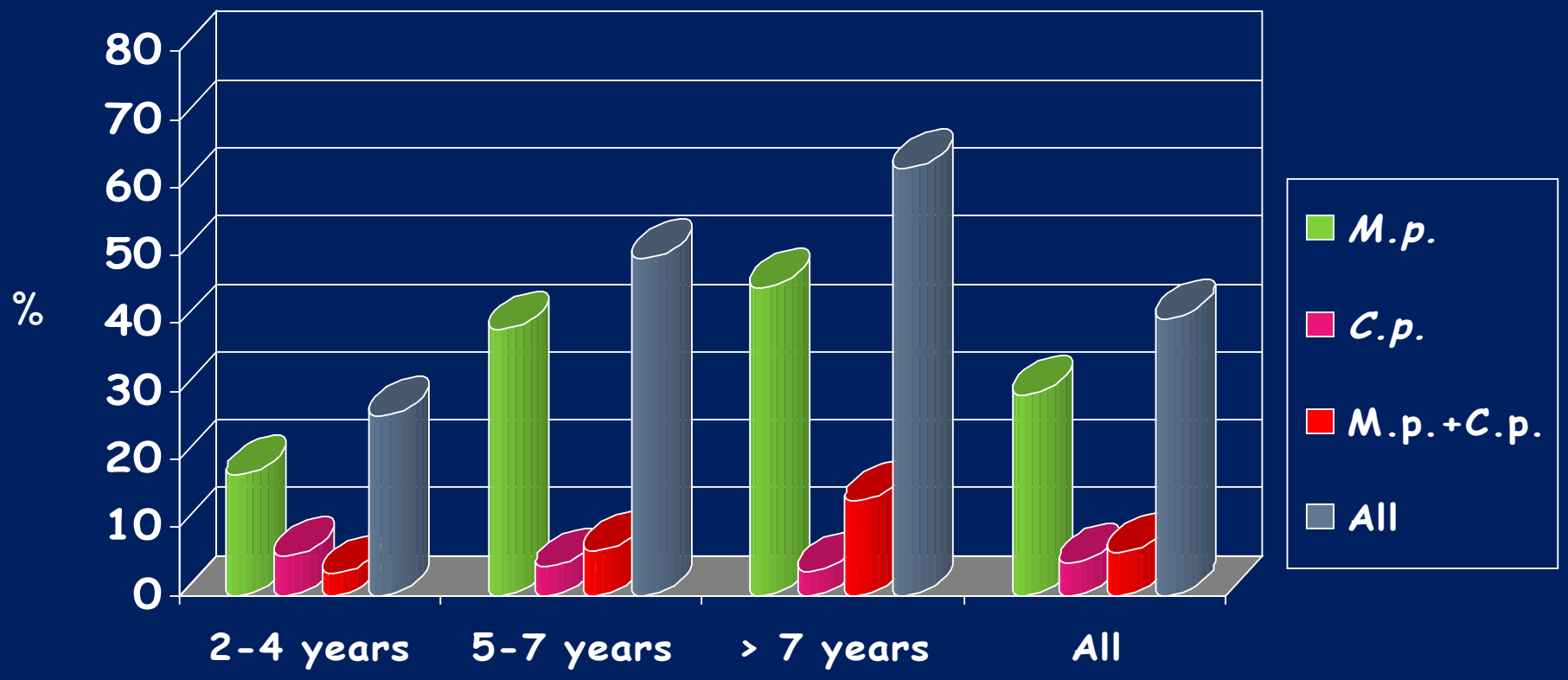
	Number of Patients (%)	
Age (yrs)	*M. pneumoniae*	*C. pneumoniae*
3 - 4	21/90 (23)	21/90 (23)
5 - 7	32/98 (33)	25/98 (26)
8 - 12	20/72 (28)	28/72 (39)

* As detected by culture, PCR, or serology.

Block et al., *Pediatr Infect Dis J* 1995;14:471-477.

CAP AND ATYPICAL BACTERIA IN 418 CHILDREN

From Principi et al. Clin Infect Dis 2001



CURRENT CONCEPT UNTIL 1995
BACTERIAL VS ATYPICAL PNEUMONIA: CLINICAL DIFFERENTIAL DIAGNOSIS (I)

	TYPICAL BACTERIAL	ATYPICAL
AGE	ALL, BUT > IN YOUNG CHILDREN	ALL AGES
FEVER	> 39°C	< 39°C
ONSET	ABRUPT	GRADUAL
URTI IN FAMILY	RARE	FREQUENT
ASSOCIATED SYMPTOMS	RARE (possible otitis,meningitis,arthritis)	FREQUENT (miringitis,conjuntivitis, pharyngitis, buccal ulcers)

CURRENT CONCEPT UNTIL 1995
BACTERIAL VS ATYPICAL PNEUMONIA: CLINICAL DIFFERENTIAL DIAGNOSIS (II)

	TYPICAL BACTERIAL	ATYPICAL
COUGH	PRODUCTIVE	NON PRODUCTIVE
PLEURITIC PAIN	COMMON	RARE
AUSCULTATION	FROM ALMOST NORMAL TO << BREATH SOUNDS; FINE, CRACKLING RALES	BILATERAL RALES; WHEEZING (possible)
PLEURAL EFFUSION	FREQUENT	VERY RARE

CHILDREN ENROLLED IN *THE PNEUMO STUDY*

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

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

Clinical characteristics of the study population at enrollment

Characteristics	*S. pneumoniae* infection (%) (N=48)	Atypical bacteria infection (%) (N=46)	Mixed *S. pneum.*-atypical bacteria infection (%) (N=16)
Males	25 (52.1)	22 (47.8)	8 (50.0)
Mean age ± SD, yrs	3.66 ± 0.899	3.75 ± 1.030	3.76 ± 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	6 (12.5)	9 (19.5)	3 (18.7)
the family	31 (64.5)	33 (71.7)	11 (68.7)
Cough	12 (25.0)	11 (23.9)	4 (25.0)
Tachypnea	42 (91.3)	39 (84.7)	14 (87.5)
Fever	45 (93.7)	41 (89.1)	15 (93.7)
Rales	6 (12.5)	7 (15.2)	2 (12.5)
Wheezes	6.857 ± 3.523	6.744 ± 2.672	7.110 ± 2.370
Days of hosp. ± SD	12.325 ± 6.065	13.307±5.089	13.714±5.517

No significant differences were observed

Laboratory data in the various aetiological groups

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

Mean values ± SD. *$p < 0.05$ vs *atypical bacteria infection and °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

Comparison of radiographic characteristics of the study population

Finding	*S. pneumoniae* infection (%) (N=48)	Atypical bacteria infection (%) (N=46)	Mixed *S.pneum.*-atypical bacteria infect. (%) (N=16)
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)

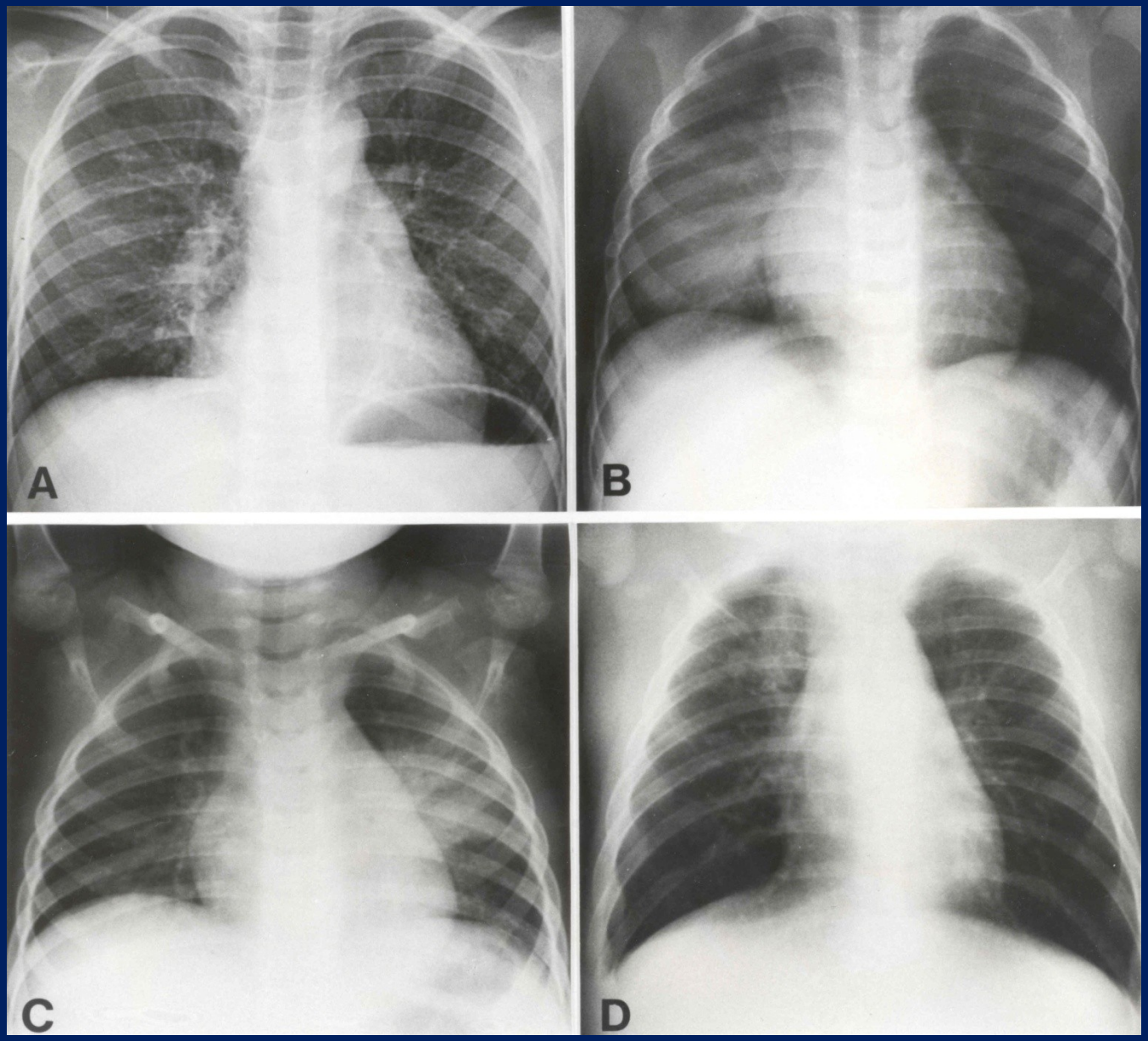
No significant differences were observed

BACTERIAL *vs* VIRAL PNEUMONIA

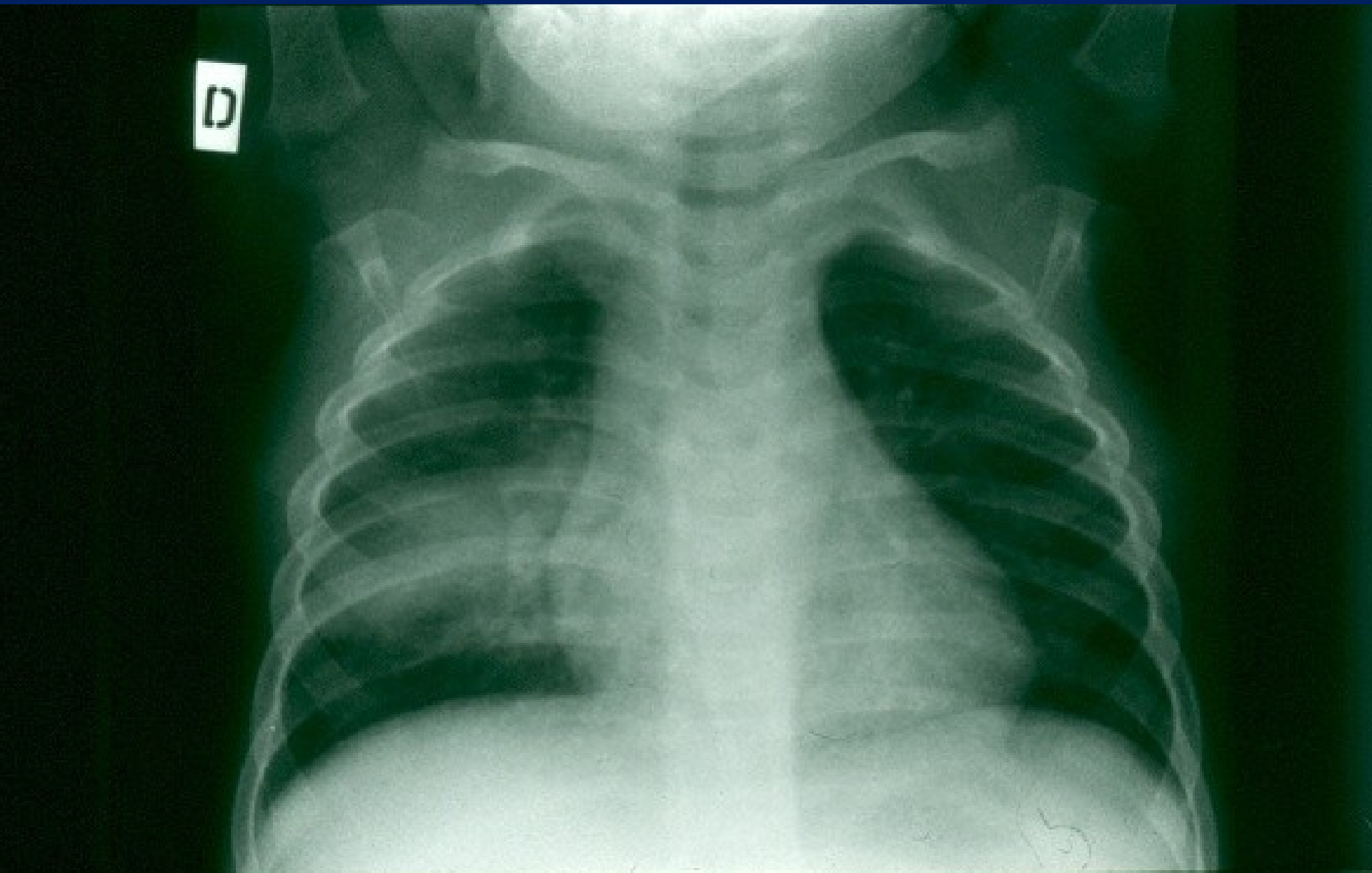
Virkki et al. Thorax 2002

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

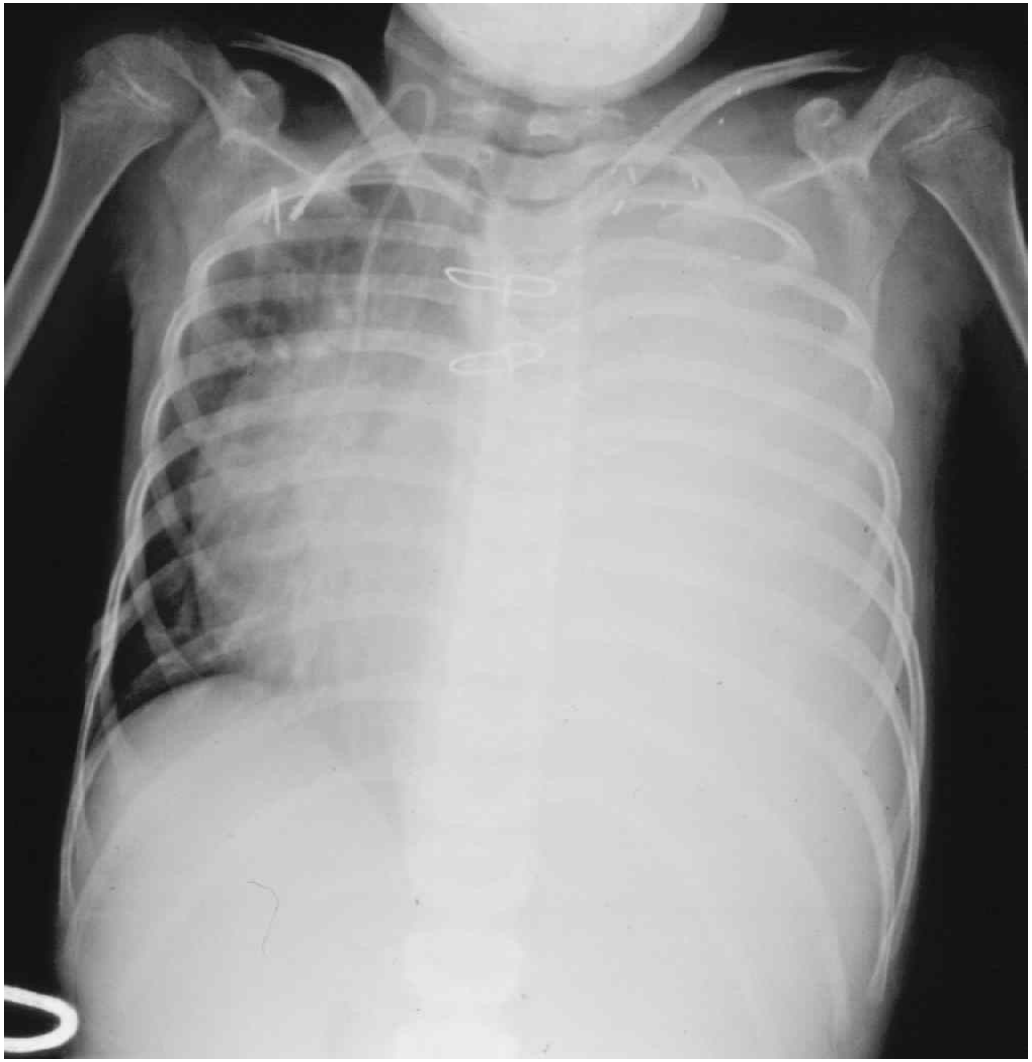
IMMAGINI RADIOLOGICHE DI CAP DA RSV



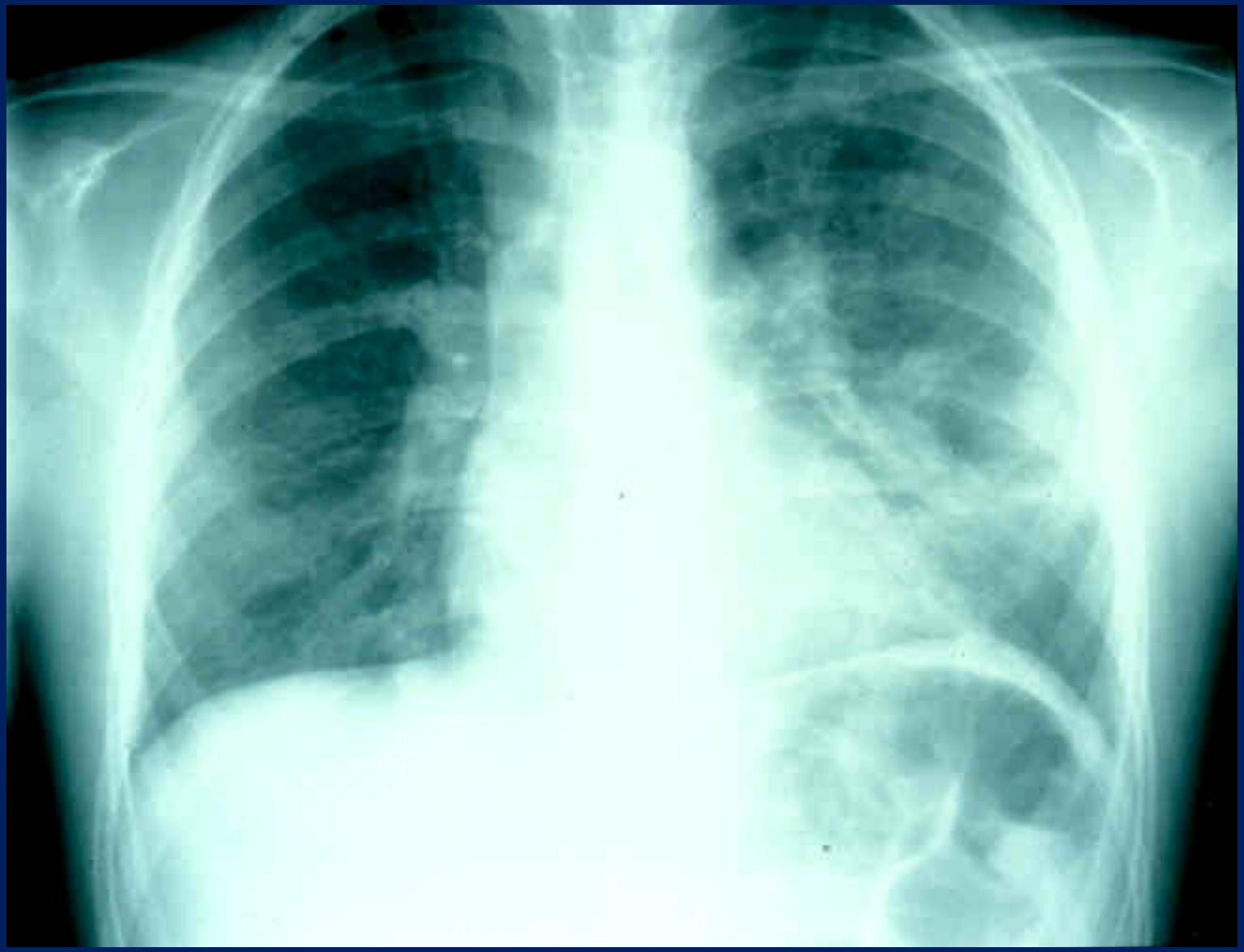
RADIOGRAFIA DEL TORACE DI CAP DA *MYCOPLASMA PNEUMONIAE*



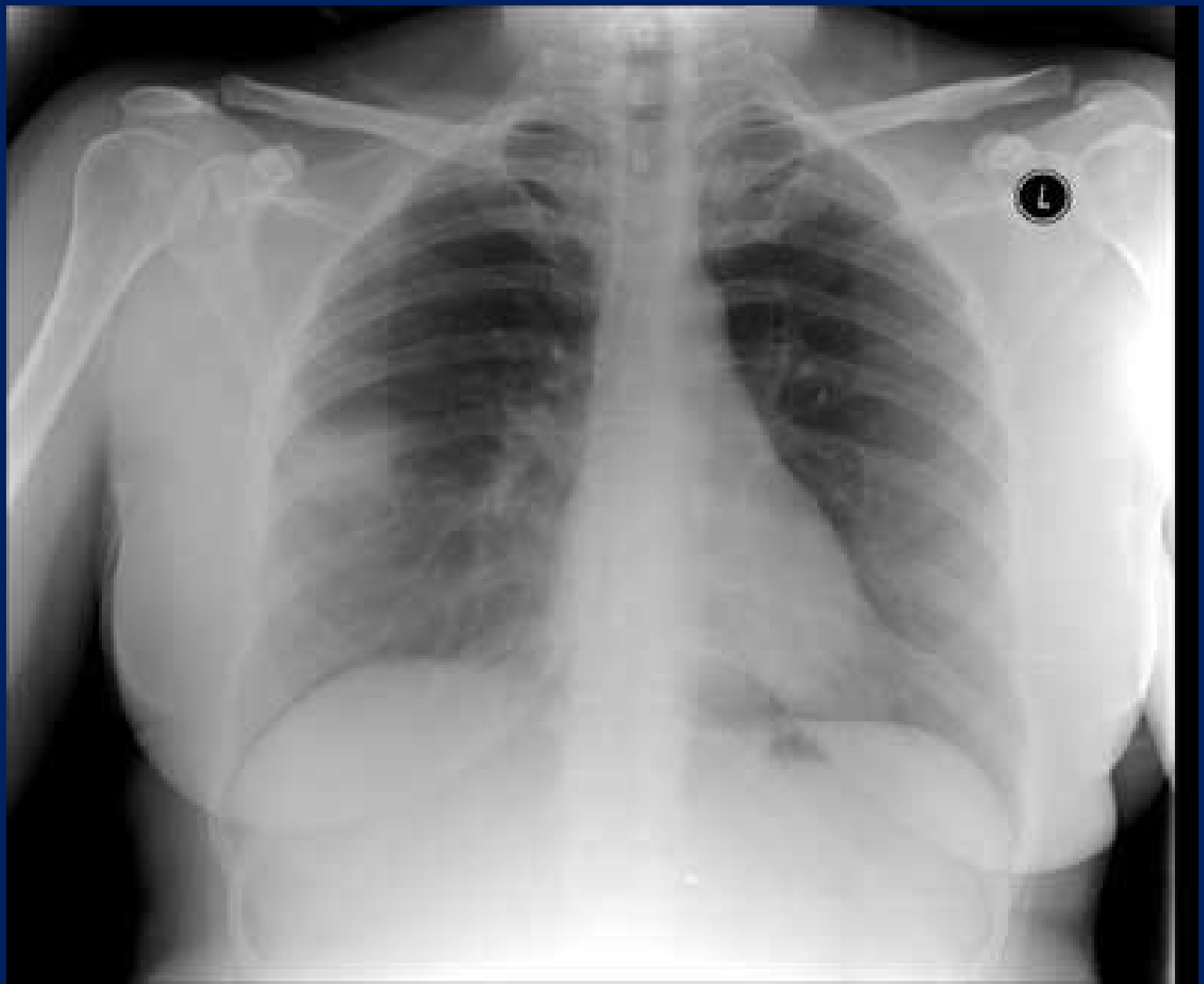
RADIOGRAFIA DEL TORACE DI CAP DA *MYCOPLASMA PNEUMONIAE*



RADIOGRAFIA DEL TORACE DI CAP DA *STREPTOCOCCUS PNEUMONIAE*



RADIOGRAFIA DEL TORACE DI CAP DA SARS CoV



ADVANTAGES AND LIMITS OF PROCALCITONIN IN CLINICAL PRACTICE

Tests	Group 1: Bacterial Septicemia or Meningitis				Group 2: Bacterial Localized Infections				Group 3: Viral Infections			
	PCT (n = 46)	CRP (n = 46)	IL-6 (n = 29)	INF-α (n = 23)	PCT (n = 78)	CRP (n = 78)	IL-6 (n = 50)	INF-α (n = 45)	PCT (n = 236)	CRP (n = 236)	IL-6 (n = 156)	INF-α (n = 172)
Median	17.75	143.50	495.00	0.00	2.00	65.50	59.50	0.00	0.20	10.00	28.50	11.00
Mean	45.9	148.4	880.3	2.1	4.2	82.8	206.8	9.9	0.4	19.5	105.6	30.1
25th percentile	6.46	78.00	167.00	0.00	1.00	25.00	37.50	0.00	0.10	4.00	15.25	2.00
75th percentile	49.40	204.00	1350.00	0.00	4.92	142.00	185.00	0.00	0.40	21.00	55.00	25.00
Minimum	0.15	9.00	5.00	0.00	0.10	0.00	2.00	0.00	0.00	4.00	0.00	0.00
Maximum	432.60	400.00	3200.00	50.00	44.00	400.00	1680.00	200.00	5.20	220.00	4516.00	400.00

From Gendrel D et al. Pediatr Infect Dis J 1999

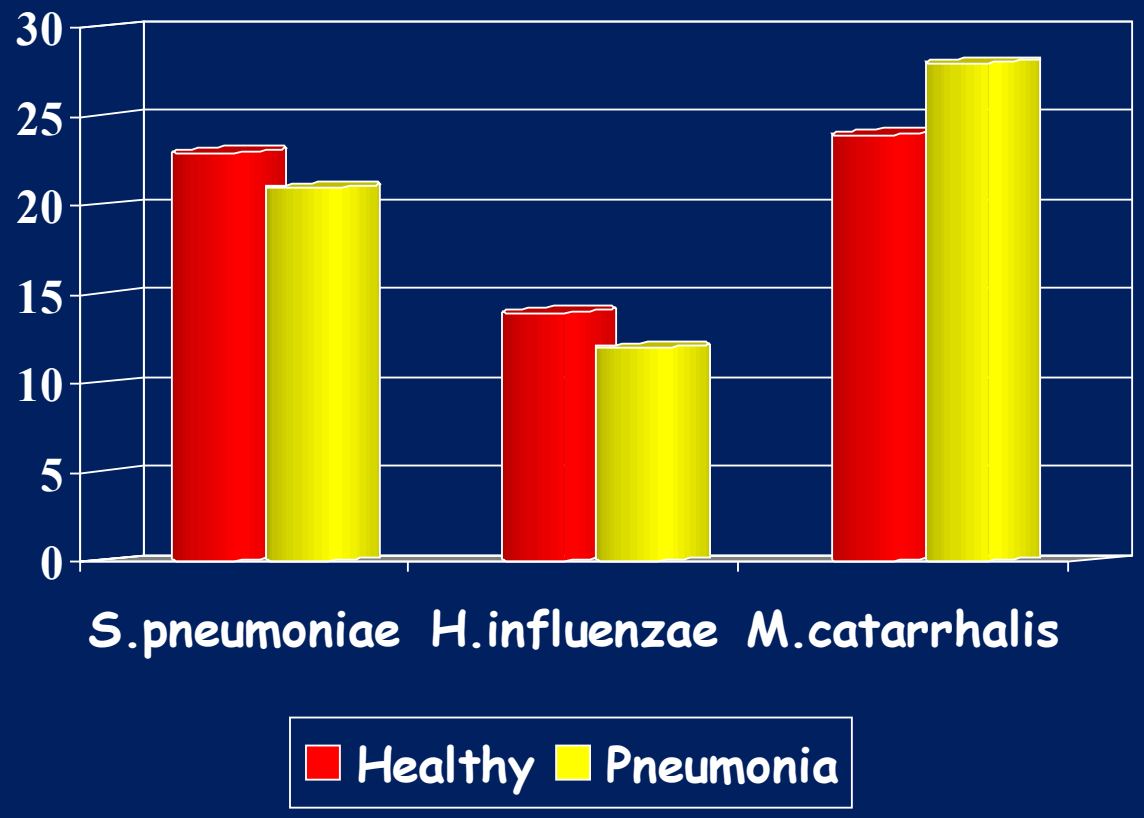
CASO CLINICO – FEDERICA 3 anni

E' giusto fare esami microbiologici per tentare di inquadrare l'eziologia della forma in atto?

TEST MICROBIOLOGICI PER LA DIAGNOSI EZIOLOGICA DI CAP

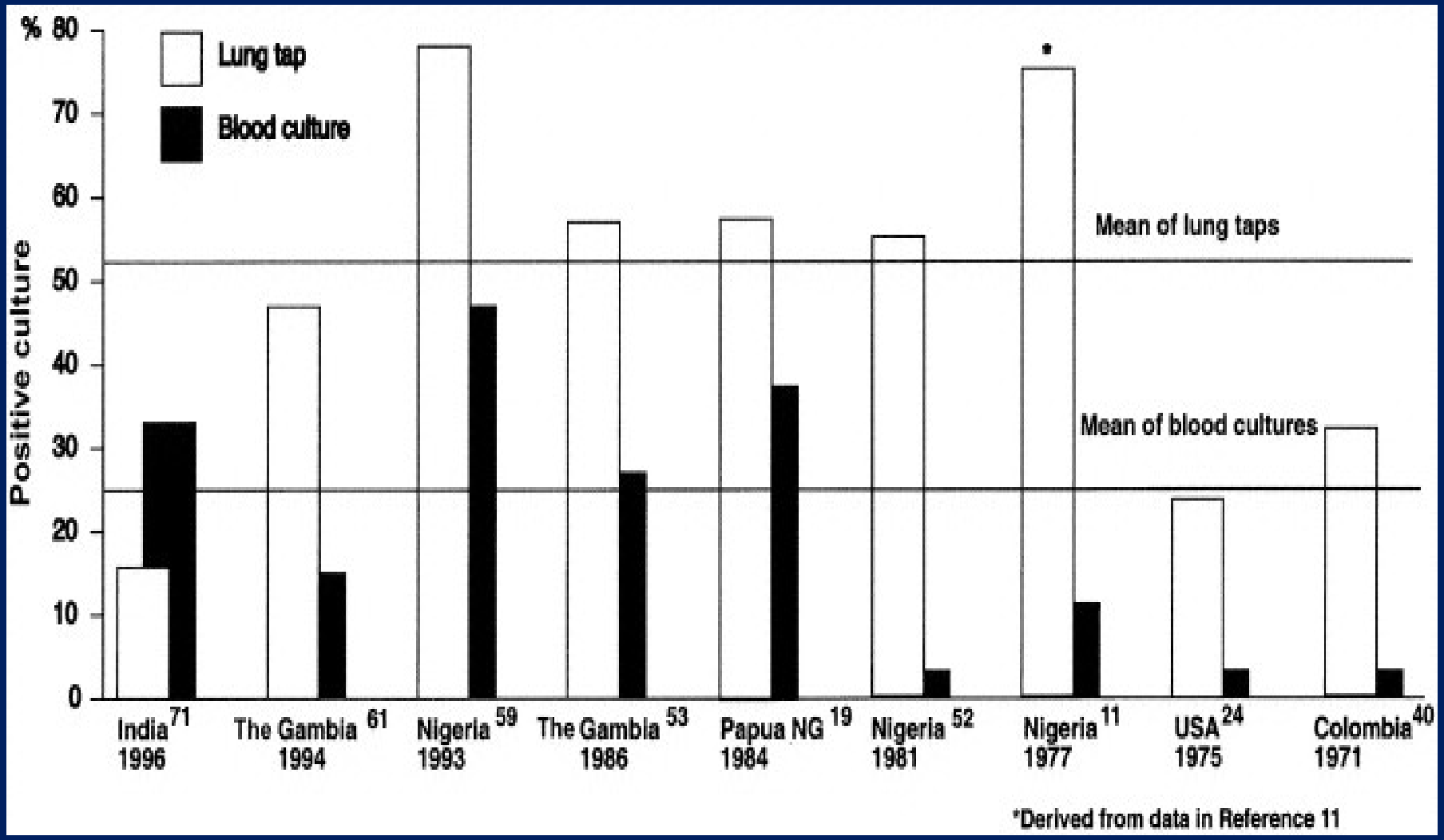
TEST	VANTAGGI	LIMITI
Tampone nasofaringeo	Facile esecuzione	Non correla con i dati polmonari se non per virus e batteri atipici
Coltura dell´espettorato	Buona sensibilitá	Non attendibile nel bambino piccolo
Emocoltura	Facile esecuzione	Bassa sensibilitá
Puntura polmonare	Facile esecuzione, buona sensibilitá	Media invasivitá
Puntura cricoidea	Buona sensibilitá	Alta invasivitá
BAL	Buona sensibilitá	Alta invasivitá

NASOPHARYNGEAL COLONIZATION (%) IN PNEUMONIA *VS* HEALTHY CHILDREN



From Nohynek et al. Pediatr Infect Dis J 1995

BACTERIAL YIELD OF LUNG TAP VS BLOOD CULTURE



From Vuori-Holopainen E and Peltola H, Clin Infect Dis 2001

PNEUMONIA: TRANSTHORACIC NEEDLE ASPIRATION

Vuori-Holopainen et al. Clin Infect Dis 2002

34 children with CAP and alveolar consolidation

2 (6%) patients with blood culture positive for *S. pneumoniae*

Needle aspiration disclosed etiology in 20/34 59 %

S. pneumoniae	17
M. catarrhalis	1
Parainfluenza/RSV	1
Enterovirus	1

IDEAL CHARACTERISTICS OF A DIAGNOSTIC TESTS FOR INFECTIOUS DISEASE

- ✓ IMMEDIATE RESULT
- ✓ EASY TO PERFORM
- ✓ HIGH SENSITIVITY AND SENSIBILITY
- ✓ COST/EFFECTIVE

EFFICIENCY OF IMMUNOFLUORESCENCE IN IDENTIFICATION OF RSV IN NASOPHARYNGEAL SECRETIONS

BECTON DICKINSON DIRECTIGEN RSV COMPARED TO CULTURE HAS:

- ✓ SENSITIVITY 93-97%
- ✓ SPECIFICITY 90-97%
- ✓ POSITIVE PREDICTIVE VALUE 82%
- ✓ NEGATIVE PREDICTIVE VALUE 98%

HOWEVER, IT IS CONSIDERED MODERATELY COMPLEX

IMPACT OF RAPID TEST FOR RSV DETECTION IN CLINICAL PRACTICE

- ✓ MARGINAL REDUCTION IN HOSPITAL STAYS
- ✓ 52% REDUCTION IN ANTIMICROBIAL USE
- ✓ 26% REDUCTION IN THE COST OF HOSPITAL CARE

From Woo PCY. J Clin Microbiol 1997

IMPACT OF RAPID TEST FOR RSV DETECTION IN CLINICAL PRACTICE

- ✓ REDUCTION OF ALBUTEROL USE
- ✓ REDUCTION IN HOSPITAL STAY
- ✓ SIGNIFICANT COST SAVING

From Williams et al. Infect Med 2002

RAPID DIAGNOSTIC TESTS FOR FLU VIRUSES

(From CDC. Pediatr Infect Dis J 2003)

TEST	DIRECTIGEN FLU A + B	Z STAT FLU	QUICKVUE INFLUENZA TEST	FLU OIA	NOW FLU A, NOW FLU B
COMPANY	BECTON DICKINSON	ZYME TX, INC.	QUIDEL	THERMO BIOSTAR	BINAX
DETECTION	FLU A, B	FLU A, B	FLU A, B	FLU A, B	FLU A, B
EASE TO PERFORM	MODERATELY COMPLEX; HOSPITAL OR LABORATORY	CLIA-WAIVED; PHYSICIAN OFFICE	CLIA-WAIVED; PHYSICIAN OFFICE	MODER. COMPLEX; HOSPITAL OR LAB.	MODER. COMPLEX; HOSPITAL OR LAB.
COST/TEST	$ 20.50	$ 14.50	$ 13.80	$16.50	$14.50
TIME FOR RESULT	15 min	30 min	10 min	15 min	15 min

EFFICIENCY OF RAPID DIAGNOSTIC TESTS FOR INFLUENZA VIRUSES IN OFFICE PRACTICE

TEST	DIRECTIGEN FLU A+B	Z STAT FLU	QUICKVUE INFLUENZA TEST	FLU OIA
COMPANY	BECTON DICKINSON	ZYME TX, INC.	QUIDEL	BIOSTAR
SENSITIVITY (%)	67 (T)	62 (T)	73 (N)	62 (T)
SPECIFICITY (%)	92 (T)	99 (T)	95-99 (N)	79.5 (T)

T= Throat Swab; N= Nasal Swab

Benjamin J. Contemp Pediatr 2000

IMPACT OF RAPID INFLUENZA TEST ON PEDIATRICIAN DECISION-MAKING

(From Esposito S et al. Arch Dis Child 2003)

	CASES (n=43)	CONTROL GROUP 1 (n=435)	P VALUE	CONTROL GROUP 2 (n=479)	P VALUE
Routine blood examination	1 (2.3)	63 (14.5)	0.045	72 (15.0)	0.038
Chest radiograph	2 (4.6)	50 (11.5)	0.207	56 (11.7)	0.208
Antibiotic use	14 (32.6)	282 (64.8)	<0.0001	296 (61.8)	0.0003
Days of antib.					
Median	7	7	0.944	7	0.961
Range	4-10	3-20		5-14	
Antiviral use	0	0		0	
Admitted	0	20 (4.6)	0.240	28 (5.8)	0.154

Percentages in parentheses

RATIONAL USE OF RAPID TEST FOR INFLUENZA VIRUSES AND RSV IDENTIFICATION

- ✓ SOME RAPID TESTS FOR INFLUENZA VIRUSES AND RSV IDENTIFICATION MEET THE CONDITIONS REQUIRED FOR THEIR USE IN CLINICAL PRACTICE

- ✓ SOME OF THE MOST EFFECTIVE TESTS ARE NOT EASY TO PERFORM SO THAT THEIR USE CAN BE SUGGESTED ONLY IN HOSPITAL OR REFERENCES LABORATORIES

EVALUATION OF BINAX NOW IN ADULTS WITH COMMUNITY ACQUIRED PNEUMONIA

PATIENT CONDITION GROUP	No. WITH POSITIVE TEST/TOTAL No. (%)
PNEUMOCOCCAL PNEUMONIA	19/27 (70.4)
BACTEREMIC	10/13 (76.9)
NONBACTEREMIC	9/14 (64.3)
NONPNEUMOCOCCAL PNEUMONIA	16/156 (10.3)
PNEUMONIA BUT NO PATHOGEN IDENTIFIED	64/269 (25.7)

Gutierrez et al. Clin Infect Dis 2003; 36: 286-92.

POSITIVE RESULTS OF BINAX NOW AMONG PEDIATRIC SUBJECTS

PATIENTS	WITH PNEUMOCOCCI IN NASOPHARYNX	WITHOUT PNEUMOCOCCI IN NASOPHARYNX	*P*
CHILDREN WITH PNEUMONIA	25/41 (61%)	6/47 (13%)	0.001
CONTROL CHILDREN	43/80 (54%)	25/118 (21%)	0.001

Dowell et al. Clin Infect Dis 2001; 32:824-5.

RISULTATI DEL TEST RAPIDO BINAX NOW

Popolazione	Tot. con Binax NOW positivo (%)	Binax NOW pos e colonizzaz. NF (%)	Binax NOW pos e assenza di colonizzaz. NF (%)
Casi con IPD	5/5 (100,0)*	2/2 (100,0)*	3/3 (100,0)*
Casi senza IPD	29/150 (19,3)	16/28 (57,1)°	13/122 (10,7)
Controlli	35/200 (17,5)	26/53 (49,1)°	9/147 (6,1)

*$p<0,05$ *vs* casi senza IPD e controlli

°$p<0,0001$ *vs* casi senza IPD e controlli senza colonizzaz. NF

Esposito S et al. Pediatr Infect Dis J 2004

CARATTERISTICHE DEL TEST PER L'IDENTIFICAZIONE DI IPD

Parametro	Formula	Valore
Sensibilità	VP/VP+FN	100%
Specificità	VN/VN+FP	80,6%
Valore predittivo positivo	VP/VP+FP	14,7%
Valore predittivo negativo	VN/VN+FN	100%

Esposito S et al. Pediatr Infect Dis J 2004

DIAGNOSIS OF ACUTE PNEUMOCOCCAL INFECTION

A 3-FOLD OR HIGHER INCREASE IN TYPE-SPECIFIC ANTI-CAPSULAR IgG CONCENTRATION TO ONE OF THE NINE MOST COMMON PNEUMOCOCCAL SEROTYPES (1, 4, 5, 6B, 9V, 14, 18C, 19F, 23F) BETWEEN PAIRED SERA

CONFRONTO TRA PCR E COLTURA PER LA IDENTIFICAZIONE DI *STREPTOCOCCUS PNEUMONIAE* NEL SANGUE

(da Azzari C et al. J Med Microbiol 2008)

	Patients (n=92)	PCR results for *S. pneumoniae* n (%)	Culture results for *S. pneumoniae* n (%)
Arthritis	4	Positive 2/4 (50) Negative 2/4 (50)	Positive 1/4 (25) Negative 3/4* (75)
Pneumonia	80	Positive 16/80 (20) Negative 64/80 (80)	Positive 1/80 (1.25) Negative 79/80 (98.75)
Meningitis/sepsis	8	Positive 4/8 (50) Negative 4/8 (50)†	Positive 2/8 (25) Negative 6/8 (75)‡

*One was positive for *Staphylococcus aureus*.

†Four were positive for *N. meningitidis*.

‡One was positive for *N. meningitidis*.

DIAGNOSTIC TESTS FOR *M. PNEUMONIAE* AND *C. PNEUMONIAE*

TEST	*SPECIMEN*	*COMMENTS*
CULTURE	Throat or NP swab, sputum, bronchial washing, tissue	Requires tissue culture; not routinely available; requires several days of incubation
PCR	Throat or NP swab, sputum, bronchial washing, tissue	No FDA-approved kits; available from research laboratories; potential for rapid diagnosis
SEROLOGY	Serum	Paired acute-convalescent sera preferred; IgM may take up to 4-6 weeks to appear (therefore retrospective)

DIAGNOSIS OF ACUTE *MYCOPLASMA PNEUMONIAE* INFECTION

- IgM to *M. pneumoniae* ≥ 1:100 (ELISA assay)

OR

- IgG to *M. pneumoniae* ≥ 1:400 (ELISA assay)

OR

- Four-fold rise in IgG specific titre (ELISA assay)

OR

- PCR positive for *M. pneumoniae* DNA in presence of acute respiratory symptoms*

* Abele-Horn et al., *J Cin Microbiol* 1998; 36: 548-551.

DIAGNOSIS OF ACUTE *CHLAMYDIA PNEUMONIAE* INFECTION

- IgM to *C. pneumoniae* ≥ 1:16 (MIF assay)

OR

- IgG to *C. pneumoniae* ≥ 1:512 (MIF assay)

OR

- Four-fold rise in IgG specific titre (MIF assay)

OR

- PCR positive for *C. pneumoniae* DNA in presence of acute respiratory symptoms*

* Blasi et al., *J Infect Dis* 1999; 180: 2074-2076.

REAL-TIME PCR IN THE DETECTION OF *M. PNEUMONIAE*

RESULT OF THE TEST	REAL-TIME PCR	CONVENTIONAL PCR
POSITIVE	68	72
NEGATIVE	79	75

From Hardegger D et al. J Microbiol Methods 2000

QUINDI, COME PUO' ESSERE FATTA LA DIAGNOSI EZIOLOGICA DI UNA CAP NELLA PRATICA QUOTIDIANA?

L'identificazione dell'agente infettivo responsabile di una CAP in età pediatrica nella pratica quotidiana può essere effettuato:

- con l'emocoltura per i batteri tradizionali (a breve disponibile la PCR?)
- con i test rapidi per RSV e influenza

CASO CLINICO – FEDERICA 3 anni

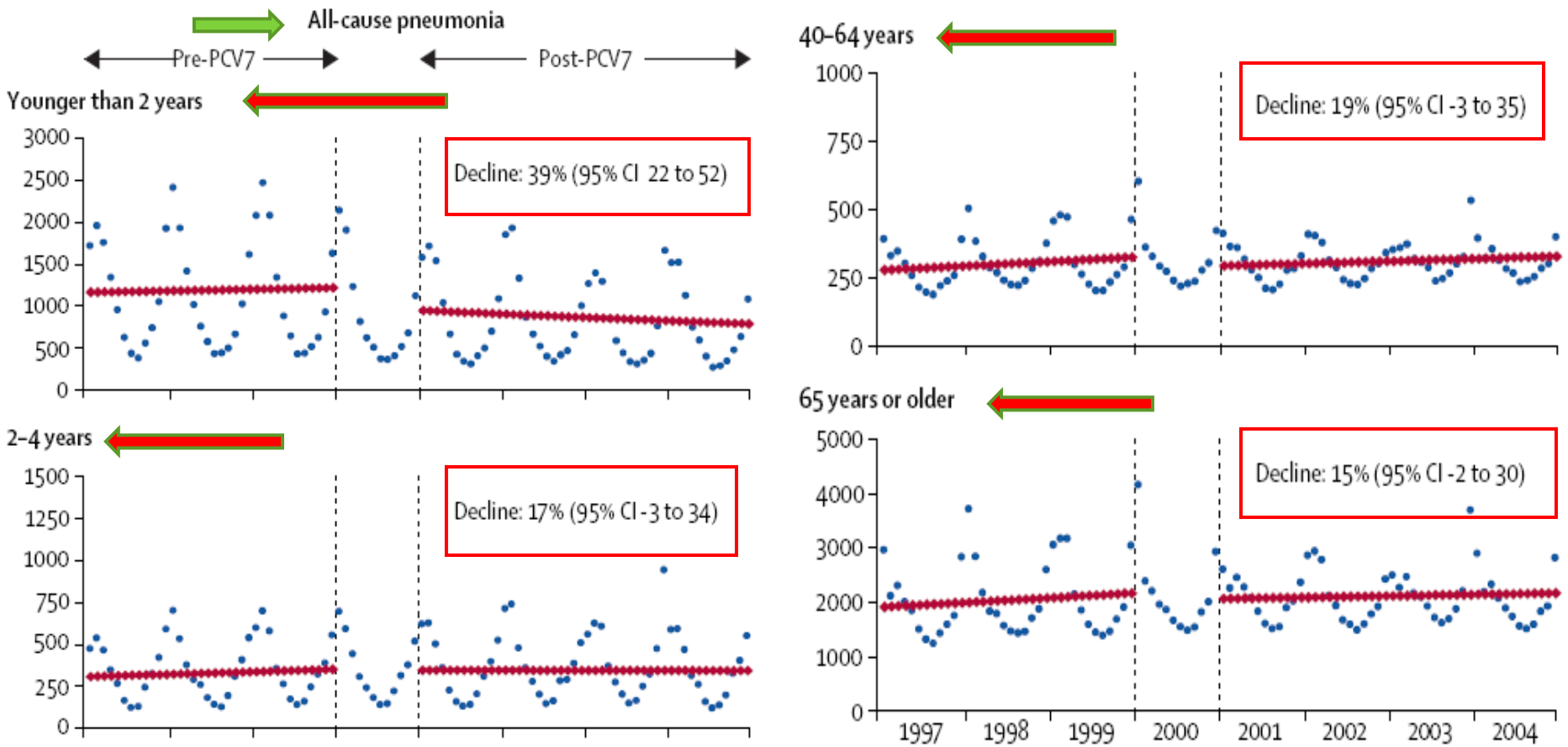
Avrebbe potuto essere prevenuta la CAP da cui è affetta Federica?

Andamento della ospedalizzazione per CAP negli U.S.A. prima e dopo l'introduzione di PCV-7

(da Grijalva CG et al. Lancet 2007)

1012 ospedali, più di 38 milioni di ricoveri

Confronto tra 2001-2004 e 1997-1999



Andamento della ospedalizzazione per CAP pneumococcica negli U.S.A. prima e dopo l'introduzione di PCV-7

(da Grijalva CG et al. Lancet 2007)

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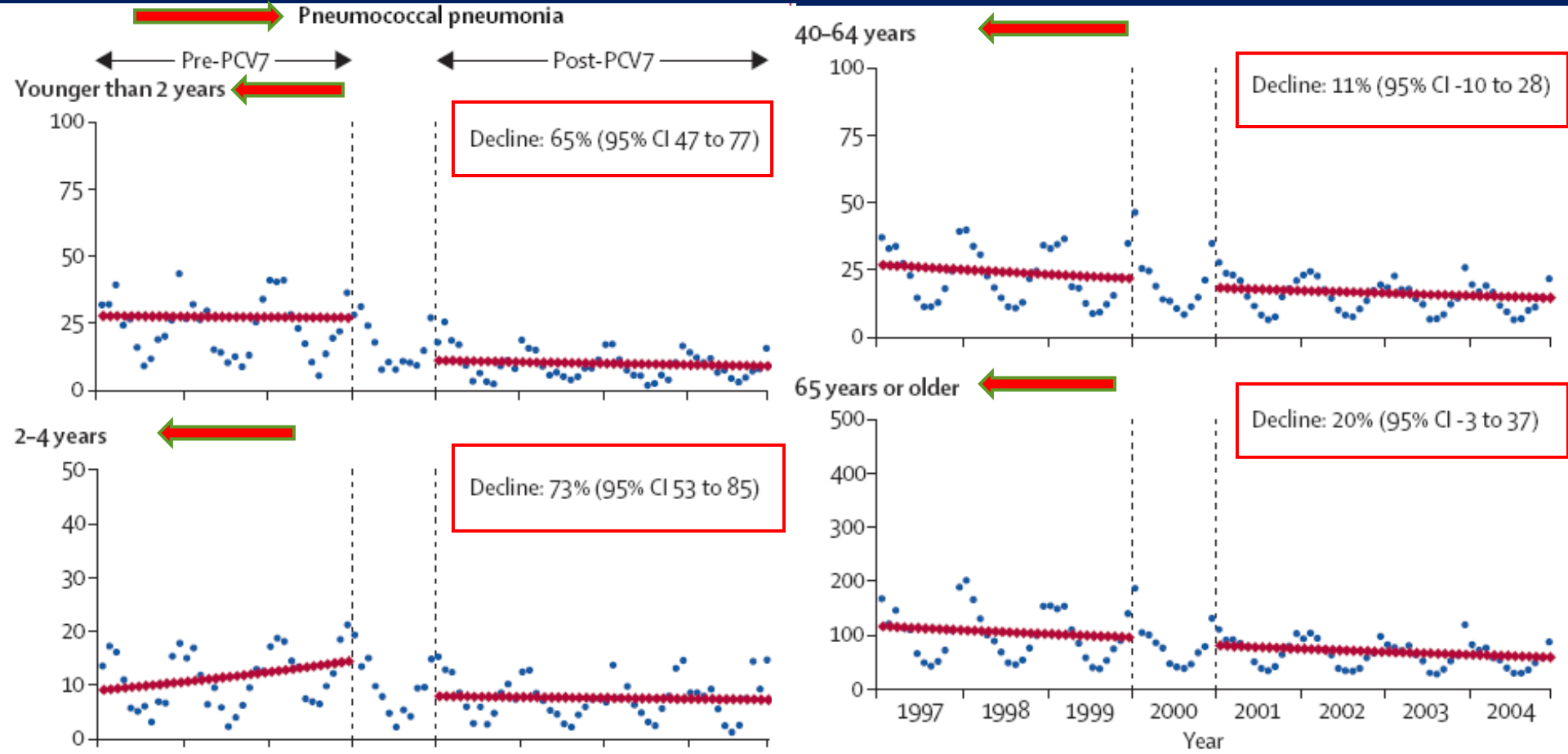


ITALIAN PNEUMO STUDY GROUP

(from Esposito et al. Resp Research 2007)

	PCV-7	CONTROLS
No. of children initially enrolled	845	779
No. of children who completed the protocol	811 (95.9%)	744 (95.5%)

FREQUENCY OF COMMUNITY ACQUIRED PNEUMONIA (CAP) DURING FOLLOW-UP

	PCV-7 (N.811)	Controls (N.744)	RR	95% CI	*P*
Total CAPs	27	72			
Episodes/ 100 child years	1.7	4.8	0.35	0.22-0.53	<0.001

From Esposito et al. Res Research 2007

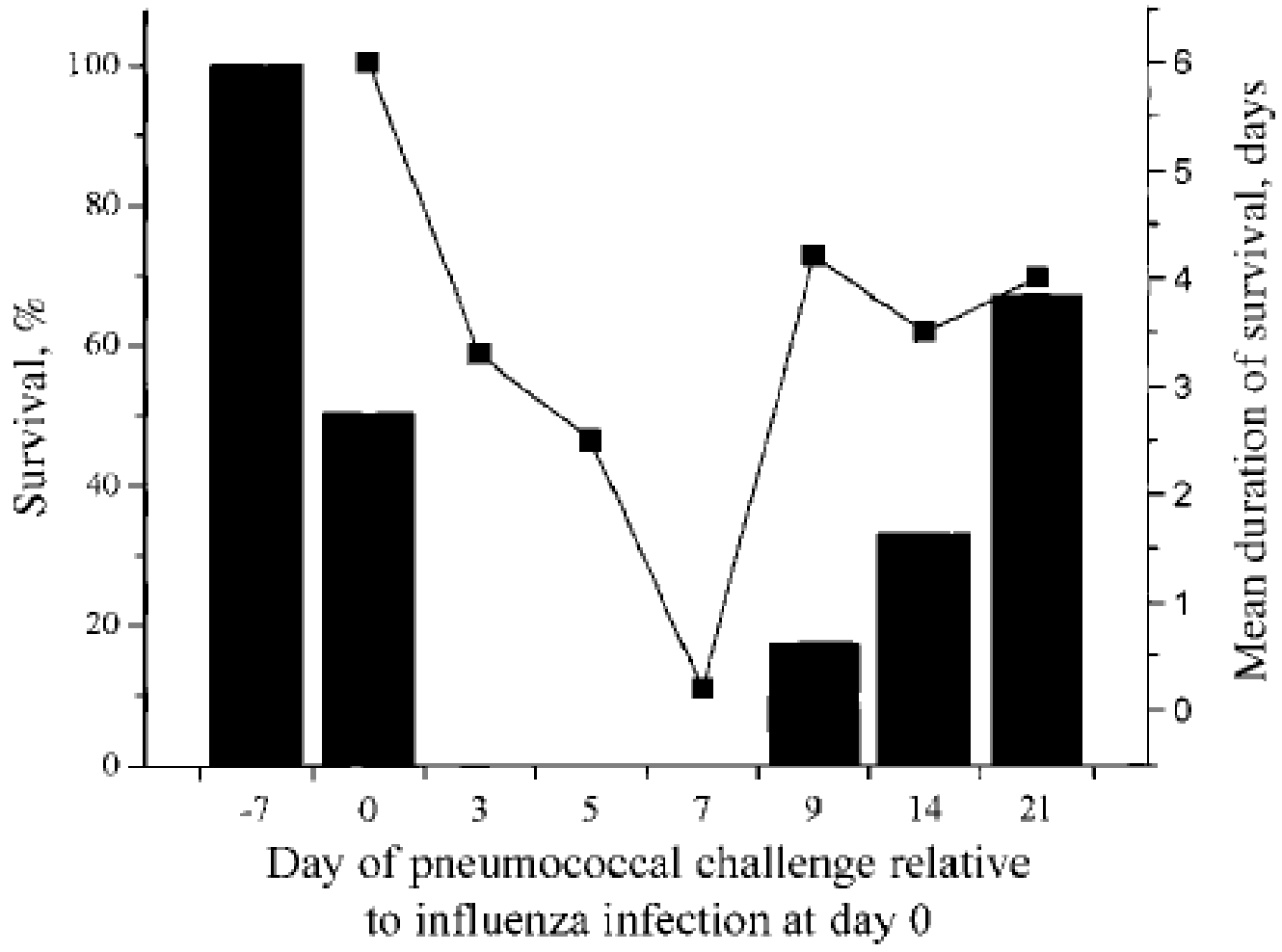
FREQUENCY OF COMMUNITY ACQUIRED PNEUMONIA (CAP) DURING EACH HALF YEAR OF FOLLOW-UP

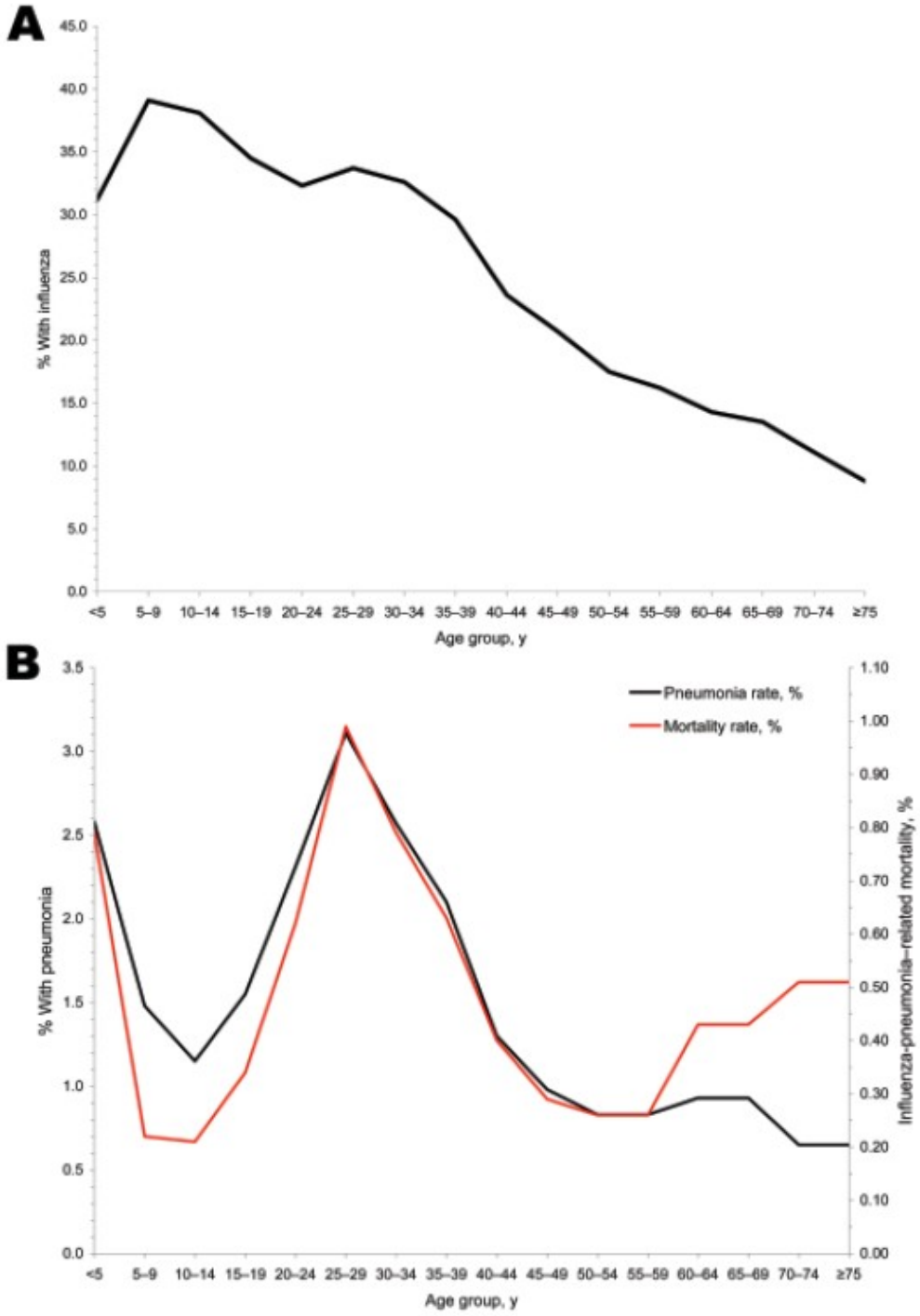
(from Esposito et al. Resp Research 2007)

	PCV-7 (N.811)	Control (N.744)	RR	95% CI	*P*
CAPs in the I half year of follow-up	9	7			
Episodes/100 child years	2.2	1.9	1.17	0.44-3.16	0.74
CAPs in the II half year of follow-up	3	9			
Episodes/100 child years	0.7	2.4	0.29	0.08-1.11	0.07
CAP in the III half year of follow-up	7	16			
Episodes/100 child years	1.72	4.30	0.40	0.16-0.97	0.04
CAPs in the IV half year of follow-up	8	40			
Episodes/100 child years	1.97	10.7	0.18	0.09-0.39	<0.001

TIMING OF SURVIVAL AFTER INFLUENZA AND *STREPTOCOCCUS PNEUMONIAE*

(McCullers and Rehg, J Infect Dis 2002)





Frequenza dell'influenza per età (A) e Frequenza di polmonite e mortalità per età (B) durante l'epidemia di influenza 1918-1919

(Da Brundage JF and Shanks GD. Emerg Infect Dis 2008

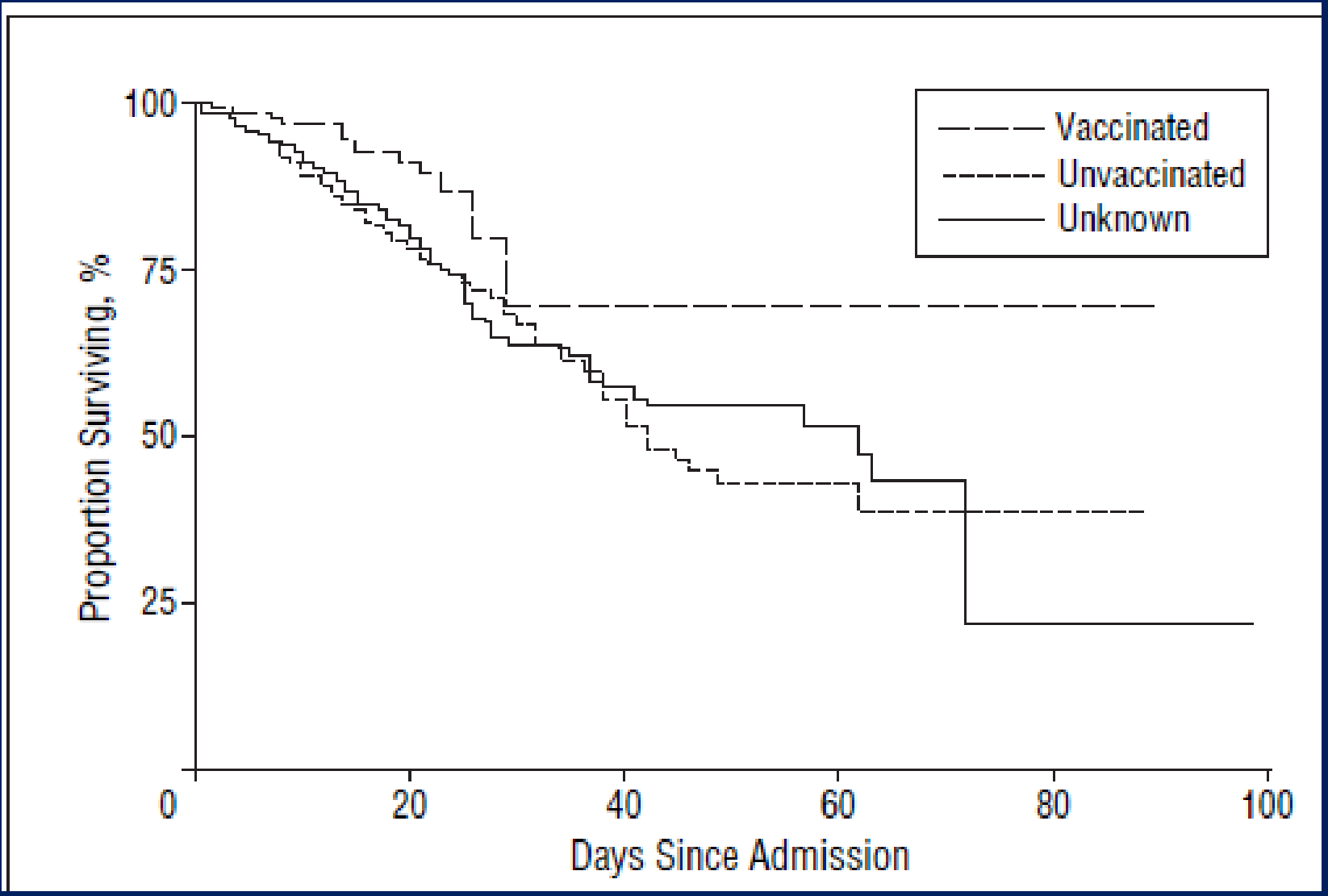
BATTERI COLTIVATI DA FRAMMENTI AUTOPTICI DI SOGGETTI DECEDUTI DURANTE LA PANDEMIA INFLUENZALE DEL 1918-1919

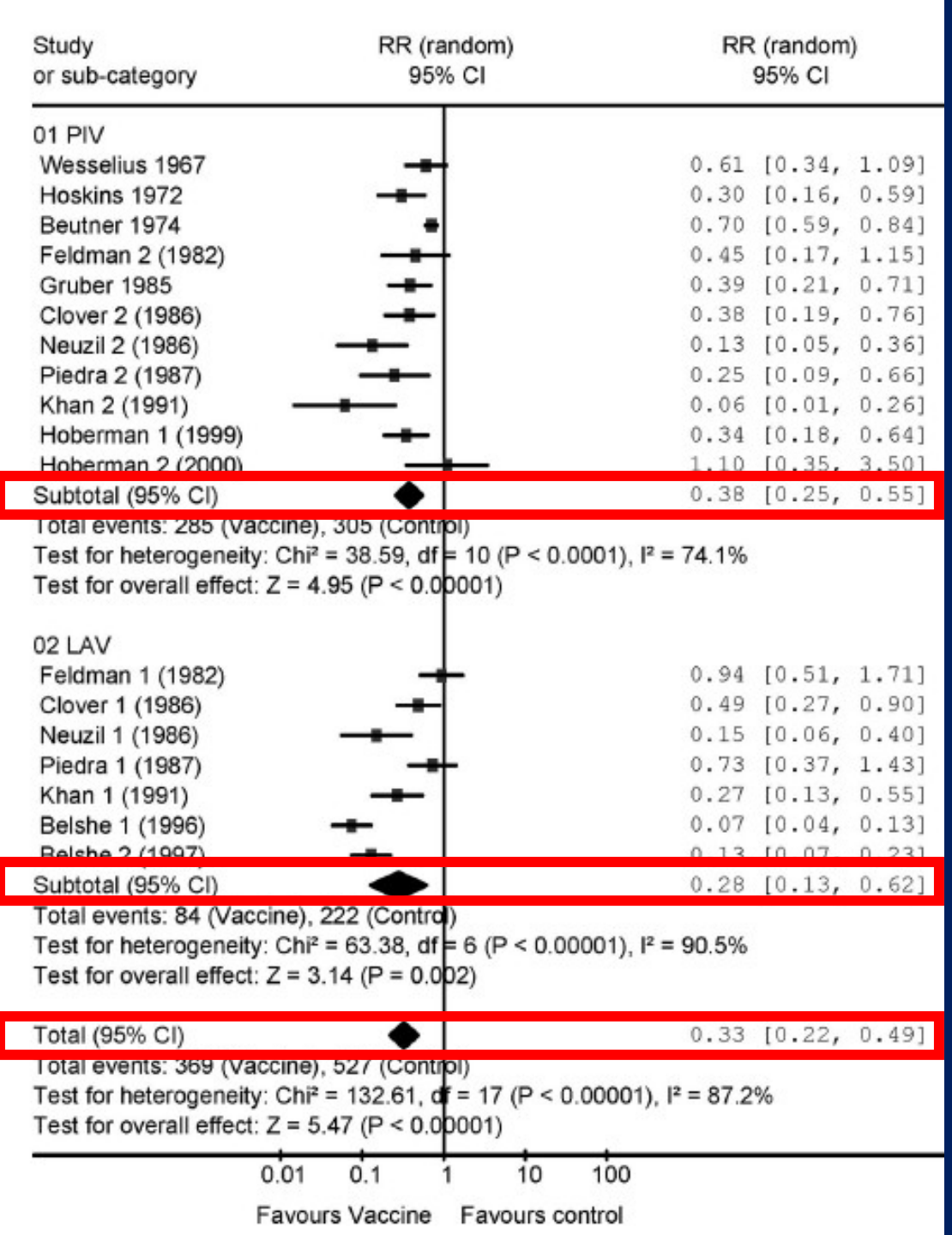
(da Morens DM et al. J Infect Dis 2008)

		No. (%) of cultures from which organism was recovered, by organism							
Type of autopsy series	No. of results	*Streptococcus pneumoniae*	*Streptococcus hemolyticus*	*Staphylococcus aureus*	*Diplococcus intracellulare meningitidis*	Mixed pneumopathogens	*Bacillus influenzae*	Other bacteria	No growth
All military (n = 60)	3515	**855 (24.3)**	615 (17.5)	263 (7.5)	40 (1.1)	707 (20.1)	387 (11.0)	484 (13.8)	164 (4.7)
All civilian (n = 36)	1751	380 (21.7)	281 (16.0)	164 (9.4)	1 (<0.1)	**398 (22.7)**	132 (7.5)	339 (19.4)	56 (3.2)
All military and civilian (n = 96)	5266	**1235 (23.5)**	896 (17.0)	427 (8.1)	41 (0.8)	1105 (21.0)	519 (9.9)	823 (15.6)	220 (4.2)
All higher- quality military and civilian[a] (n = 68)	3074	712 (23.2)	553 (18.0)	238 (7.7)	21 (0.7)	**828 (26.9)**	144 (4.7)	353 (11.5)	225 (7.3)
Predominance of pneumopathogens not confirmed (n = 14)	1115	209 (18.7)	132 (11.8)	52 (4.7)	0 (0.0)	24 (2.2)	210 (18.8)	**402 (36.1)**	86 (7.7)

SOPRAVVIVENZA IN ADULTI RICOVERATI PER CAP IN FUNZIONE DELLA PREGRESSA VACCINAZIONE ANTINFLUENZALE

(da Spaude KA, et alk. Arch Intern Med 2007)





EFFICACIA IN PEDIATRIA DELLA VACCINAZIONE CONTRO L'INFLUENZA

(diagnosi di laboratorio)

(da Manzoli L et al Vaccine 2007)

Quindi, che prevenzione è possibile della CAP?

- A) Vaccinazione antipneumococcica
- B) Vaccinazione antinfluenzale

CASO CLINICO – FEDERICA 3 anni

Quale sarà la terapia di scelta per Federica?

BACTERIAL ETIOLOGY OF PNEUMONIA

	1 wks - 3 m	4 m - 4 yrs	> 4 yrs
St.pneumoniae	++	+++	++
H. influenzae	+	+	+
St. pyogenes	-	+	+
Staph.aureus	++	+	+
Strep B and D	+++	-	-
Enteric bacilli	+++	-	-
Myc.pneumoniae	-	++	+++
Chl. trachomatis	++	-	-
Chl. pneumoniae	-	+	++
Anaerobes	-	-	+

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

TERAPIA DELLA CAP NEL NEONATO

- Considerati i batteri più frequentemente in causa, farmaci di scelta sono ampicillina+gentamicina
- I dosaggi dei farmaci variano in funzione dell'età gestazionale e/o del peso
- La terapia deve essere somministrata per via parenterale
- Il trattamento deve essere mantenuto per 10 giorni

TERAPIA DELLA CAP NEL LATTANTE DI 1-3 MESI

ASSENZA DI FEBBRE, TOSSE IMPORTANTE, INFILTRATO INTERSTIZIALE

↓

VEROSIMILMENTE *CHLAMYDIA TRACHOMATIS* E *BORDETELLA PERTUSSIS*

↓

ERITROMICINA O CLARITROMICINA PER 14 GIORNI O AZITROMICINA PER 3 GIORNI

PRESENZA DI FEBBRE, CONSOLIDAMENTO LOBARE

↓

VEROSIMILMENTE *STREPTOCOCCUS PNEUMONIAE*

↓

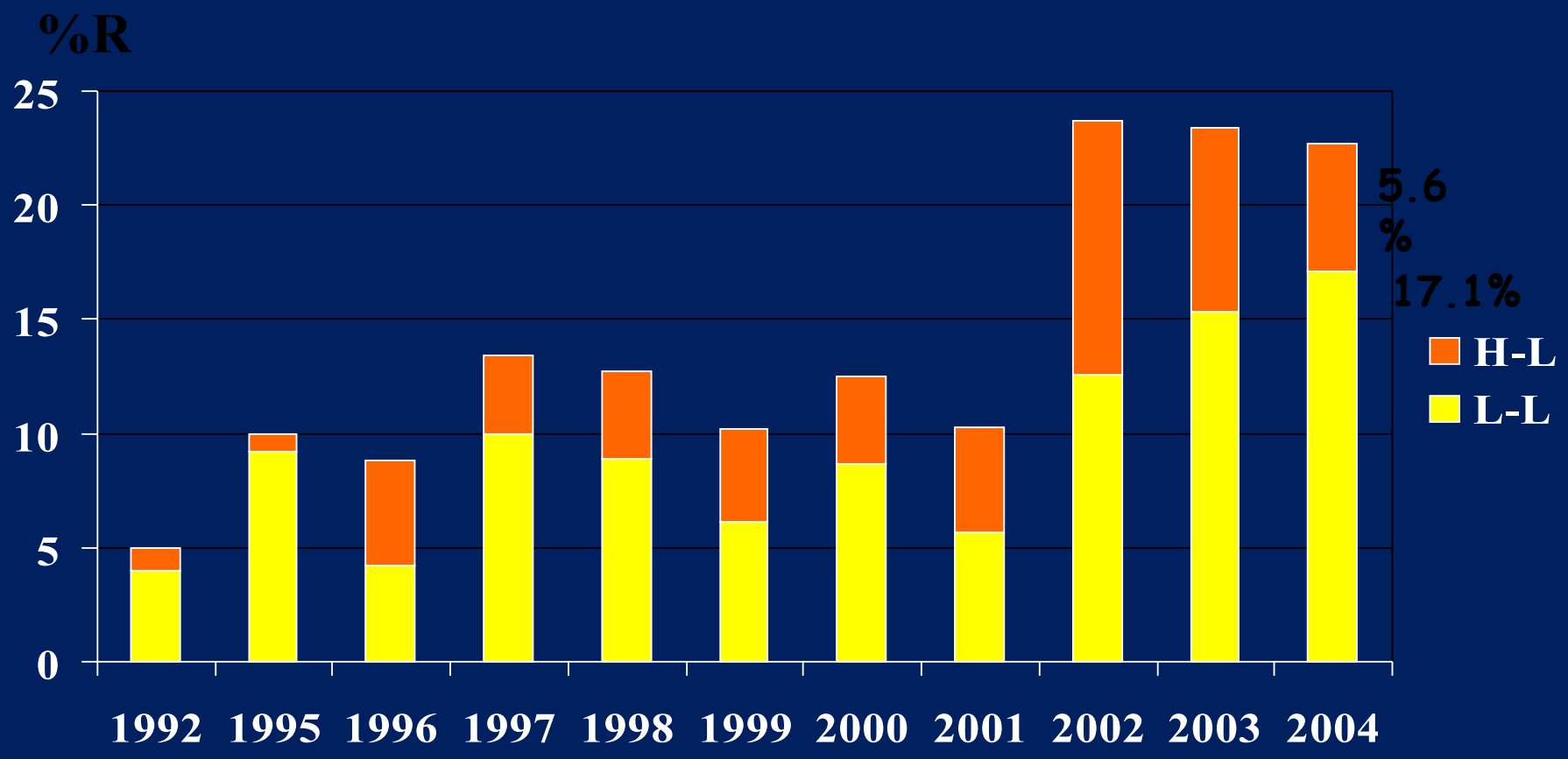
AMOXICILLINA ORALE O, NEI CASI PIU' GRAVI, AMPICILLINA EV O CEFOTAXIMA EV PER 10 GIORNI

ANTIBIOTIC THERAPY OF CAP OF INFANTS AND CHILDREN ≥ 4 MONTHS OF AGE

- *STREPTOCOCCUS PNEUMONIAE* AND ATYPICAL BACTERIA ARE THE MOST FREQUENT CAUSE OF CAP IN CHILDREN ≥ 4 MONTHS OF AGE
- DIFFERENTIATION OF PNEUMOCOCCAL FROM ATYPICAL BACTERIA CASES IS VERY DIFFICULT
- ANTIBIOTIC THERAPY MUST COVER ALL THE MOST FREQUENT ETIOLOGIES

S.pneumoniae

penicillin-resistance in Italy (%)



Felmingham *et al.*, 1996; Felmingham *et al.*, 2002; Marchese *et al.*, 2001 Schito *et al.*, 2003; Marchese *et al.* 2005.

S. pneumoniae
Variazioni locali della Penicillino-resistenza in Italia nel 2002

	n°	%
▪ NORD	85	19.6
▪ CENTRO	15	15.3
▪ SUD	35	35.7 ↑

Schito *et al.*, ICAAC, 2003

S. pneumoniae (835)
Comparative activity of penicillin and other beta-lactams

antibiotic	MIC_{50}	MIC_{90}	Range	%S	I%	R%
penicillin	0.03	0.25	≤0.008-4	77.3	17.1	5.6
amoxicillin	0.03	0.5	≤0.008-4	97.8	1.1	1.1
ceftriaxone	0.03	0.5	≤0.008-4	97.2	1.9	0.9

PROTEKT ITALY 2004

*S. pneumoniae**

Comparative activity of penicillin and other beta-lactams

	All (2093)	Children (779)
drug	%S	%S
Amoxi-clav	97.5	92.6
cefpodoxime	80.6	67.4
cefuroxime	80.6	67.0
penicillin	73.2	56.7
cefaclor	70.2	56.0

* Collected worldwide

PROTEKT INTERNATIONAL

MECHANISMS OF *S. PNEUMONIAE* BETA-LACTAM RESISTANCE

- THE RESISTANCE OF *S. PNEUMONIAE* TO BETA-LACTAMS IS RELATED TO TARGET-MEDIATED CHANGES IN THE SIZE AND CONFIGURATION OF THE PBPs.

- *S. PNEUMONIAE* HAS 5 PBPs: THE LEVEL OF RESISTANCE DEPENDS ON HOW MANY OF PBPs ARE MODIFIED AND TO WHAT EXTENT

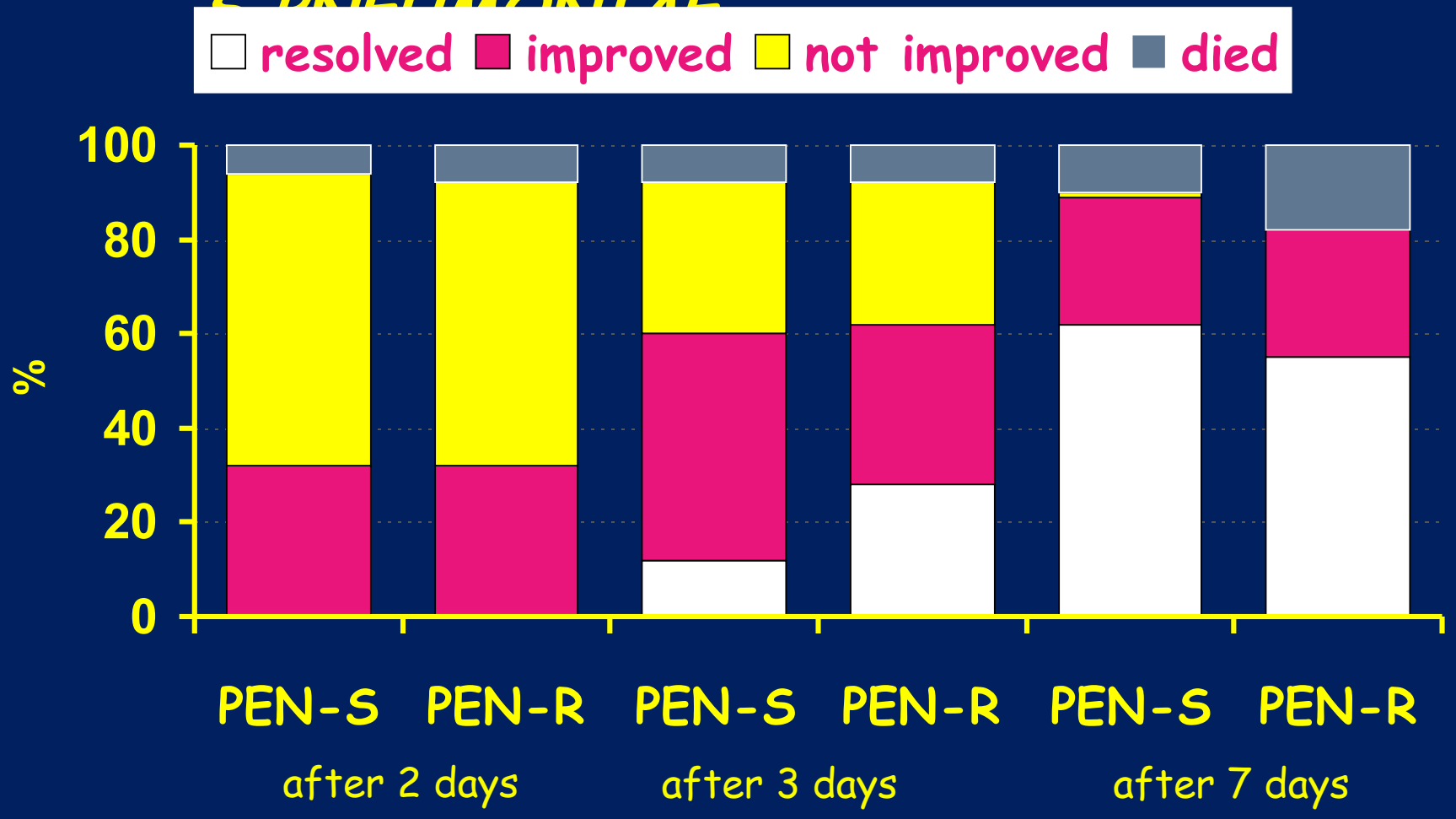
MECHANISMS OF *S. PNEUMONIAE* BETA-LACTAM RESISTANCE

- ✓ RESISTANCE TO PENICILLIN G IS MAINLY CAUSED BY CHANGES IN PBP2b, WHEREAS ALTERATIONS IN PBP2x ARE RELATED TO RESISTANCE TO CEPHALOSPORINS
- ✓ THE BETA-LACTAMS WHICH HAVE RETAINED A GOOD ACTIVITY ARE AMOXICILLIN, CEFUROXIME AND CEFPODOXIME (ORAL); CEFTRIAXONE, CEFOTAXIME, CEFPIROME AND CEFEPIME (PARENTERAL)
- ✓ IMIPENEM OR MEROPENEM ARE EVEN MORE ACTIVE THAN CEPHALOSPORINS

CLINICAL RELEVANCE OF *S. PNEUMONIAE* BETA-LACTAMS RESISTANCE

ALL THE BETA-LACTAMS, EVEN THOSE CONSIDERED *IN VITRO* NOT ACTIVE, WITH USUAL DOSES REACH IN BLOOD AND IN THE EPITHELIAL LINING FLUID CONCENTRATIONS HIGH ENOUGH TO ERADICATE ALL THE INTERMEDIATE AND ALMOST ALL THE RESISTANT STRAINS OF *S.PNEUMONIAE*

OUTCOME OF PNEUMONIA IN RELATION TO PENICILLIN RESISTANCE OF *S. PNEUMONIAE*



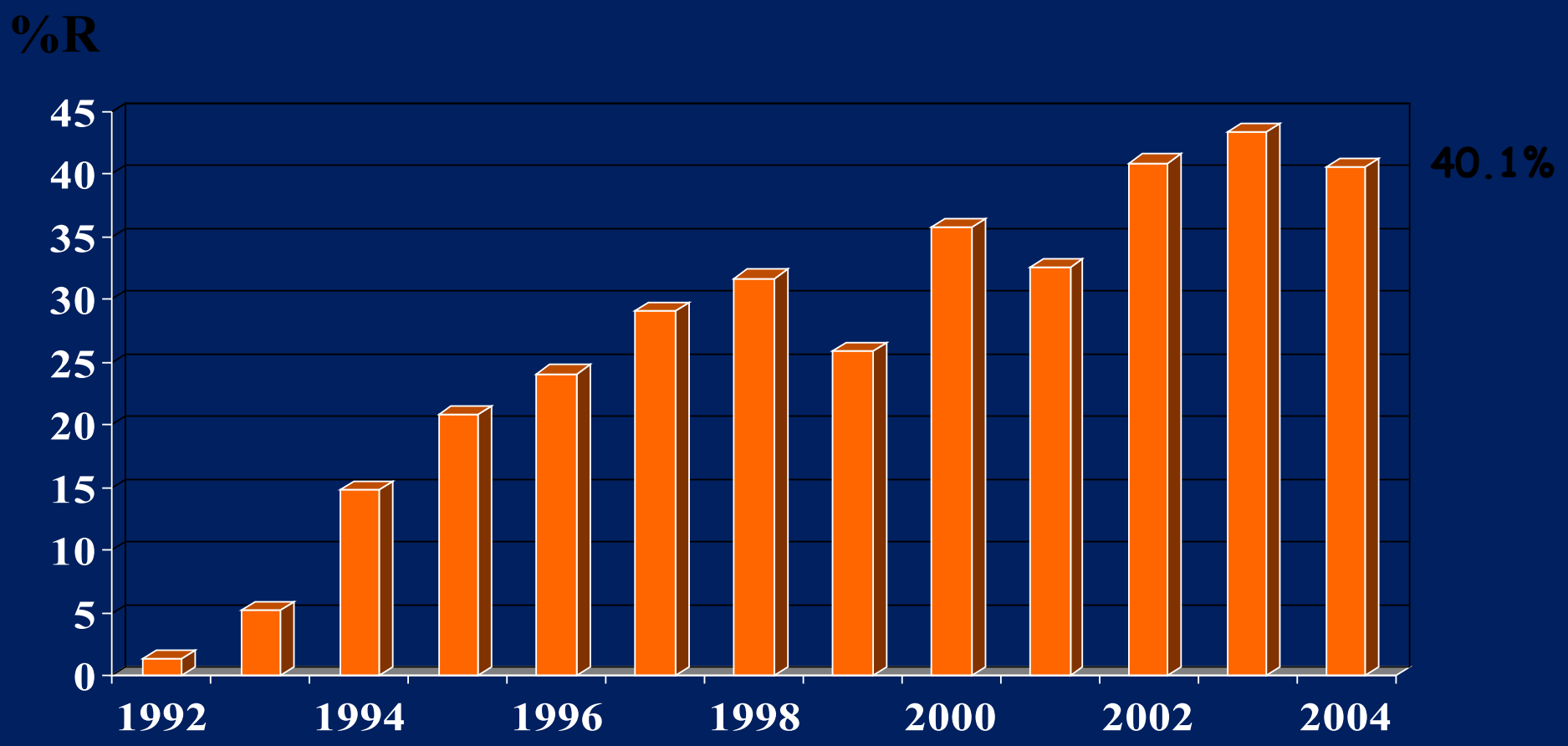
Ruolo della resistenza di *Sp* alla penicillina sul decorso della CAP

Treatment outcome	Susceptible	Intermediate	Resistant	Total	P
All children (n = 240)					0.75*
Success	94 (78)	49 (77)	46 (82)	189 (79)	
Failure	26 (22)	15 (23)	10 (18)	51 (21)	
Children without pleural effusion on admission (n = 111)					0.87*
Success	48 (86)	29 (91)	20 (87)	97 (87)	
Failure	8 (14)	3 (9)	3 (13)	14 (13)	
Children with pleural effusion on admission (n = 129)					0.37*
Success	46 (72)	20 (63)	26 (79)	92 (71)	
Failure	18 (28)	12 (37)	7 (21)	37 (29)	

*Fisher's exact test.

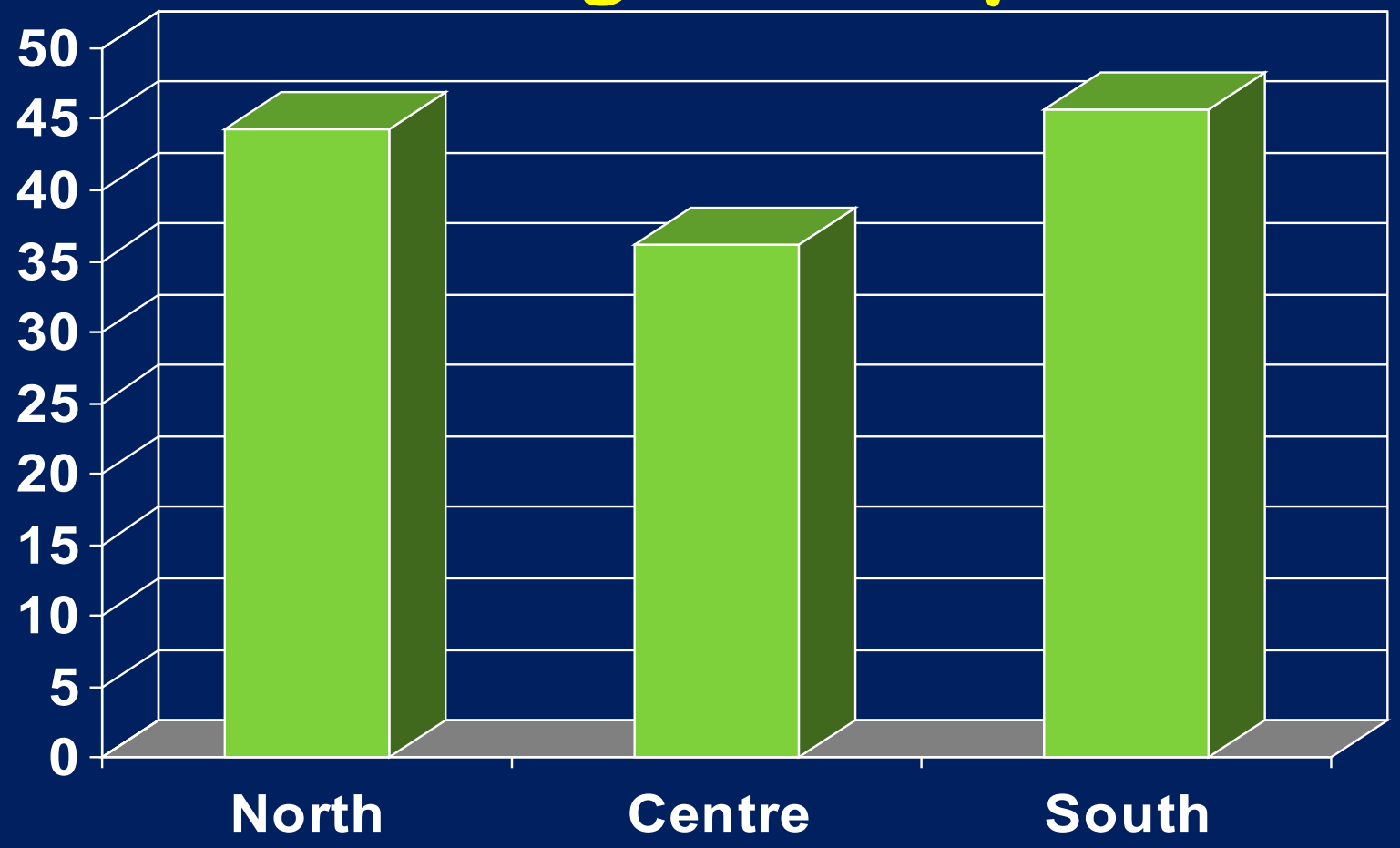
S.pneumoniae

macrolide-resistance in Italy (%)



Felmingham *et al*., 1996; Felmingham *et al.*, , 2002; Marchese *et al.*, 2001; Schito *et al*., 2003; Marchese *et al*., 2005

Macrolide-resistant *S. pneumoniae* %R circulating in Italy (2004)



MAIN MECHANISMS of MACROLIDE RESISTANCE

- Target alteration

  ermB → cross-resistance MLS_B

  (H-L)

- efflux

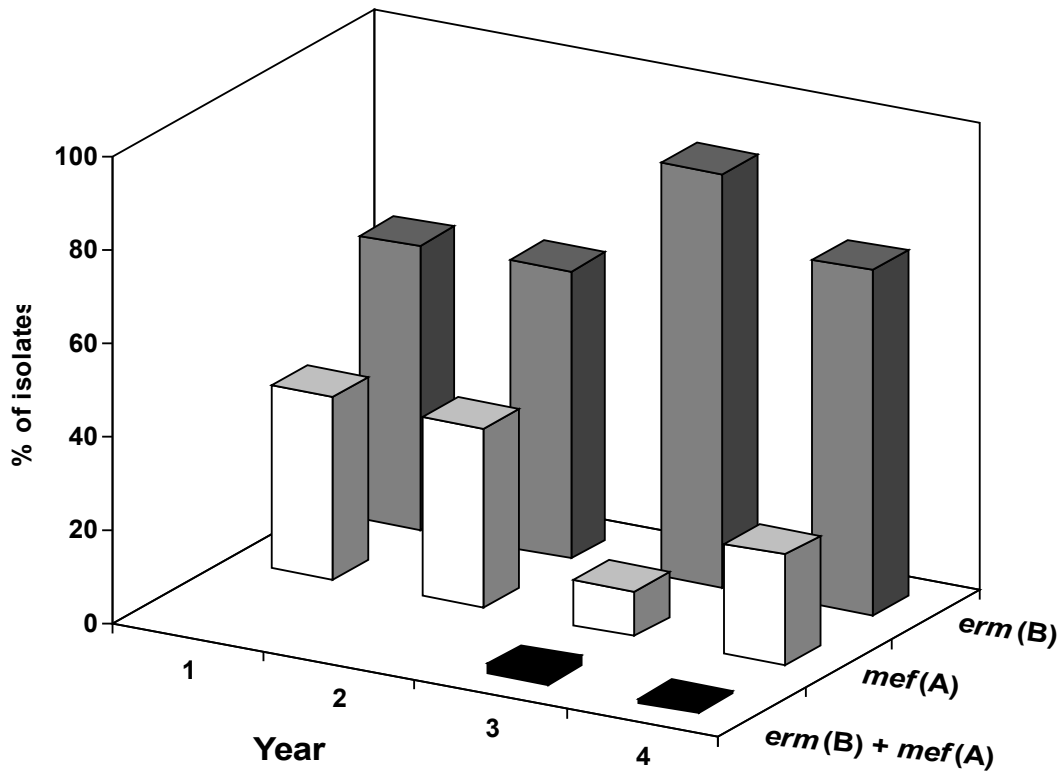
  mefA → M phenotype (L-L)

. Weisblum, AAC, 1995; Sutcliffe *et al.*, AAC, 1996; Farrell *et al* AAC 2005

MACROLIDE MIC IN ERYTHROMYCIN-RESISTANT *STREPTOCOCCUS PNEUMONIAE*

	ERYTHRO-MYCIN	CLARITHRO-MYCIN	AZITHRO-MYCIN
ERM B			
MIC 90	>32	>128	>32
RANGE	0.25 to>32	0.25 to >128	1 to >32
MEF E			
MIC 90	8	4	8
RANGE	0.5 to >32	0.06-8	0.5 to >32

Genotypes of mac-R *S. pneumoniae* circulating in Italy 1999-2003



Schito e Farrell, submitted, 2005

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

(from Esposito S. et al. Clin Infect Dis 2003)

Clinical response	*S. pneumoniae* infection (%) (N=44)	Atypical bacteria infection (%) (N=42)	Mixed *S.pneum.*-atypical bacteria infect. (%) (N=15)
Treated with a β-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 β-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

*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 β-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, add

ORAL ERYTHROMYCIN (30-40 mg/kg/die in 3-4 doses) OR CLARITHROMYCIN (15 mg/kg/die in 2 doses) OR AZITHROMYCIN (10 mg/kg/die in 1 dose)

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

SUGGESTED DRUG TREATMENT FOR CAP IN CHILDREN (4-18 years)

ORAL ERYTHROMYCIN (30-40 mg/kg/die in 3-4 doses) OR CLARITHROMYCIN (15 mg/kg/die in 2 doses) OR AZITHROMYCIN (10 mg/kg/die in 1 dose)

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

ORAL AMOXICILLIN (80-90 mg/kg/die in 2-3 doses), I.V. AMPICILLIN (100-150 mg/kg/die in 3 doses) or I.V. CEFOTAXIME (100-150 mg/kg/die in 3 doses)

CAP: DURATA DELLA TERAPIA

- Schemi tradizionali:

Forme lievi : 7 – 10 giorni

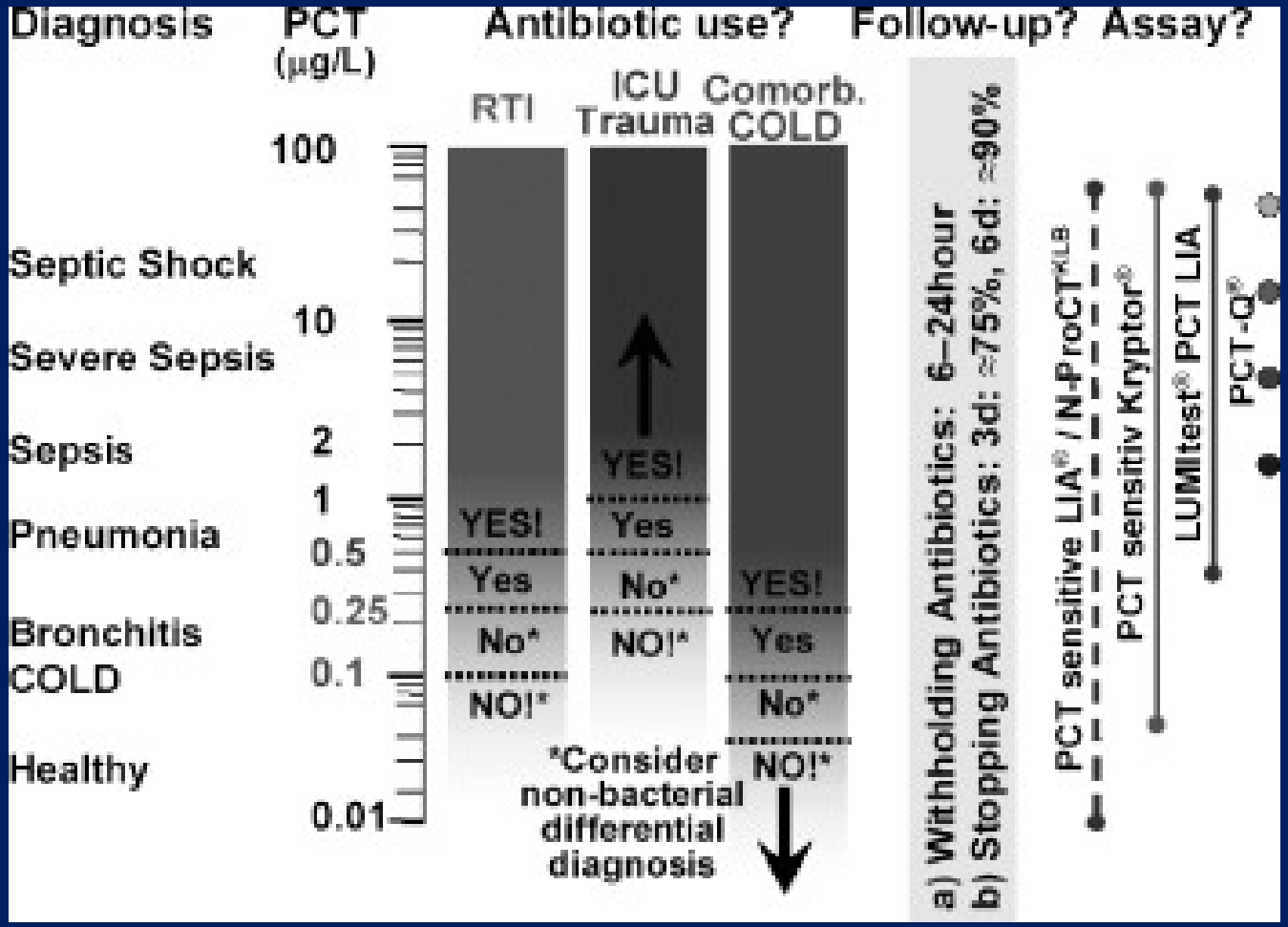
Forme gravi o complicate 14 giorni

- Schemi futuribili:

Durata in rapporto a specifici parametri biologici

USO DELLA PROCALCITONINA NELLA GESTIONE DELLA POLMONITE (I)

(da Muller e Prat. Clin Microbiol Infect 2006)



USO DELLA PROCALCITONINA NELLA GESTIONE DELLA POLMONITE (II)

(da Muller e Prat. Clin Microbiol Infect 2006)

PCT level

<0.1 µg/L	0.1–0.25 µg/L	0.25–0.5 µg/L	>0.5 µg/L
NO!	No	Yes	YES !

PCT re-assessed after 6–24hours
Antibiotic therapy given (i.e. protocol over-ruled) if:

- Respiratory or haemodynamic instability, severest comorbidity, ICU admission
- PCT <0.1 µg/L in patients with: CAP with PSI group V / CURB score >3, or COLD with GOLD stage IV
- PCT 0.1–0.25 µg/L in patients with: CAP with PSI IV & V / CURB score >2, empyema, complicated pneumonia*, COLD GOLD stage III, SaO_2<90% after 30 days intensive therapy

If on antibiotic therapy:
Re-evaluation on days 4, 6, 8

→ PCT measurement
→ Stop antibiotics according to cut offs above
→ Outpatients: antibiotic duration (0–7 days) based on last PCT level
→ Initially very high PCT: stop antibiotics when levels fall to 80–90% of peak

TERAPIA DI SUPPORTO NELLA CAP

BAMBINI SEGUITI A DOMICILIO

- Rivalutazione clinica dopo 48 ore in caso di persistenza della febbre o in caso di mancato miglioramento clinico

BAMBINI RICOVERATI IN OSPEDALE

- Monitoraggio dei parametri vitali
- Ossigenoterapia
- Adeguata somministrazione di liquidi

CASO CLINICO – FEDERICA 3 anni

Può essere utile far fare a Federica della fisioterapia respiratoria?

E' necessario eseguire un controllo radiologico?

CHILDREN WITH RECURRENT CAP

Recurrent CAP has been defined as two episodes of CAP in 1 year or > 3 episodes during any time frame, with radiographic clearing between episodes

An underlying cause is usually identified in > 80% of cases

Timing, location and prodromes to recurrence can all provide important clues to the aetiology of infection

DIAGNOSTIC CONSIDERATIONS FOR RECURRENT PNEUMONIA AT A SINGLE SITE

PERSISTENT OR PROGRESSIVE	PERSISTENT OR RECURRENT
Untreated common acute infection	Atelectasis
Unresolved common acute infection	Segmental bronchiectasis
Complication of acute infection	Intraluminal obstructing lesions
Tuberculosis	Extrinsic obstructing lesions
Uncommon infection	Congenital abnormalities
	Tracheobronchial cysts
	Pulmonary sequestration

ASPETTI RADIOLOGICI DELLA TUBERCOLOSI IN ETA' PEDIATRICA