La patologia pneumococcica: conoscerla per prevenirla

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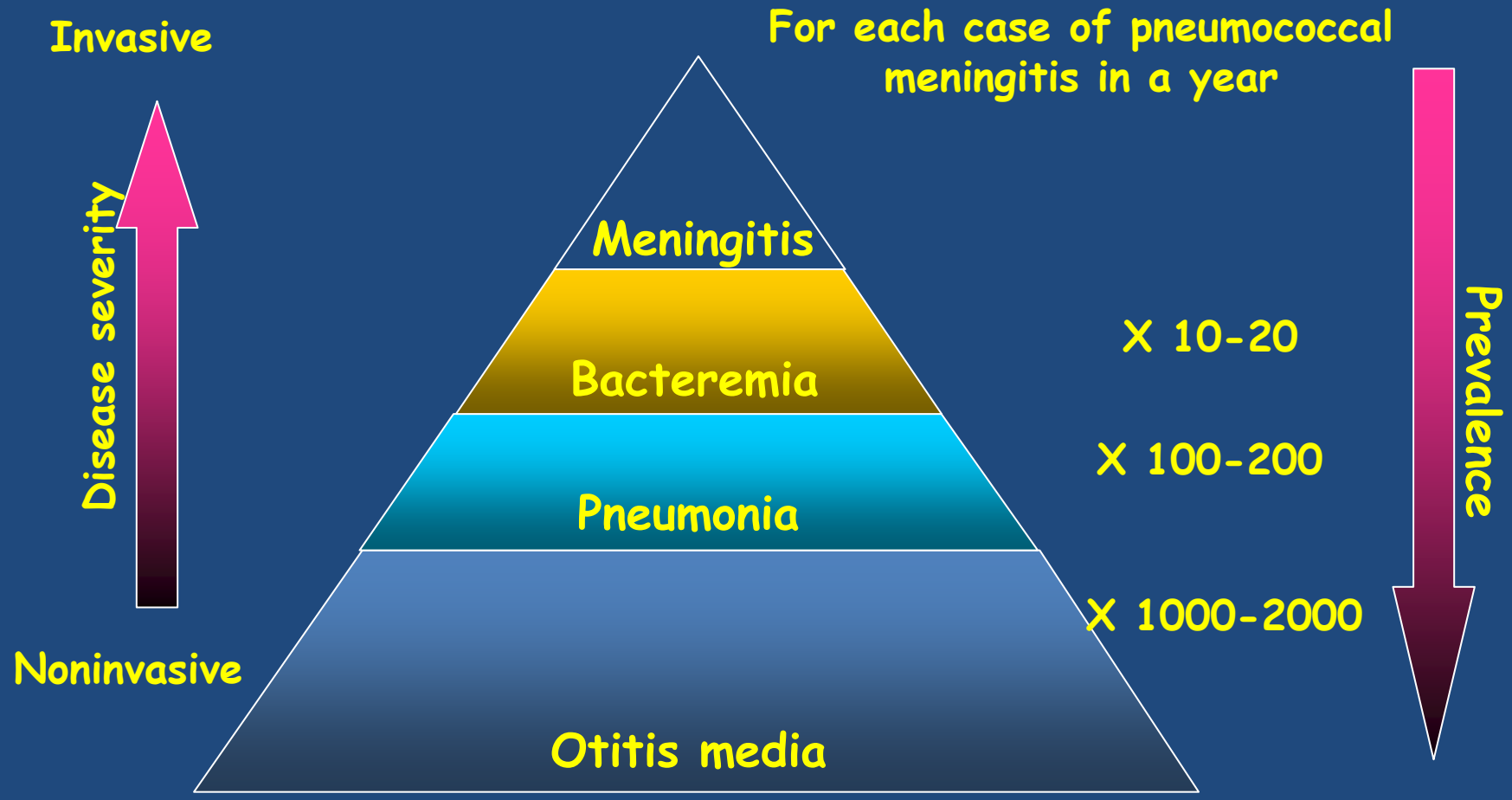
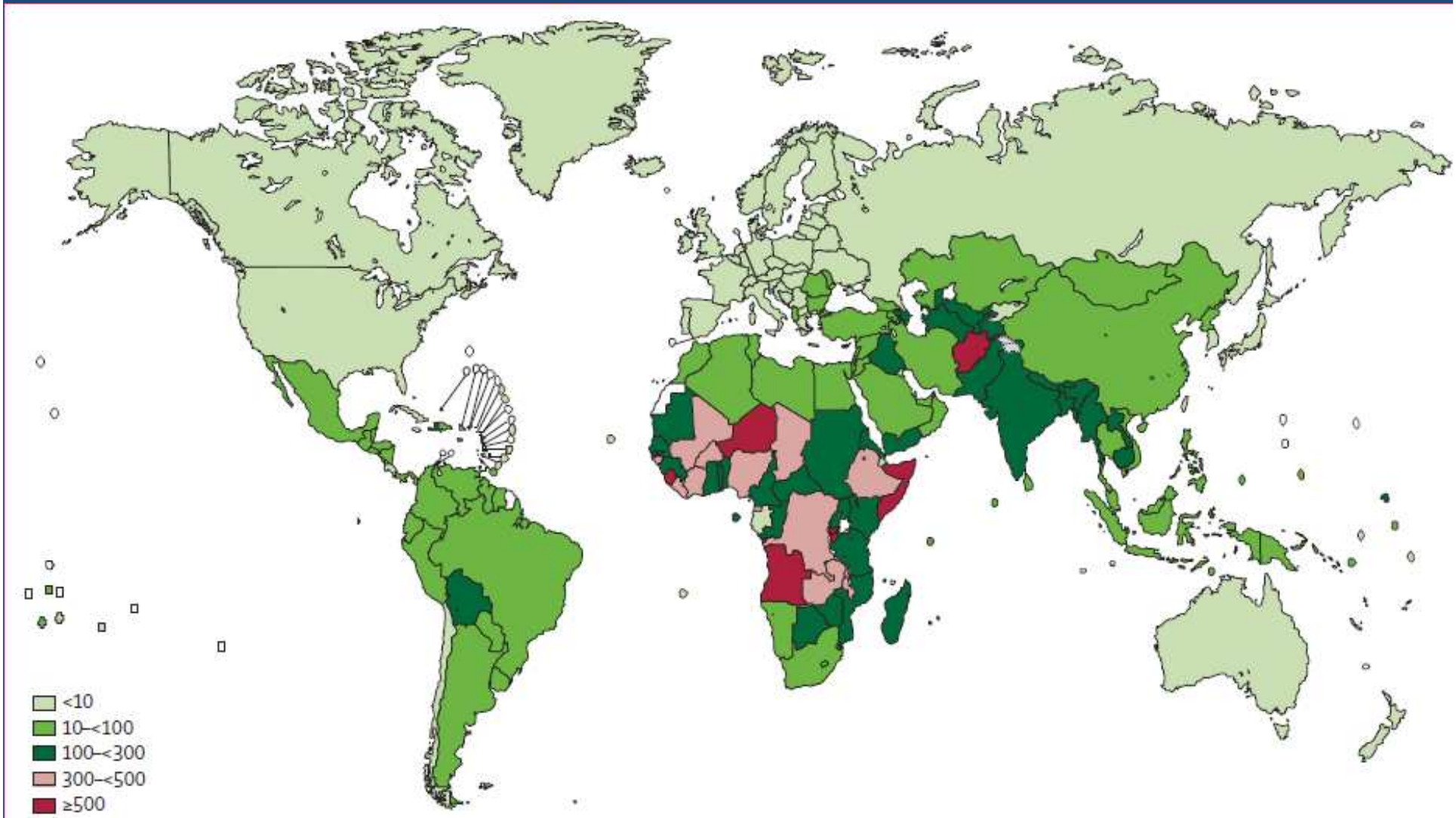
Streptococcus pneumoniae Disease Burden in Children

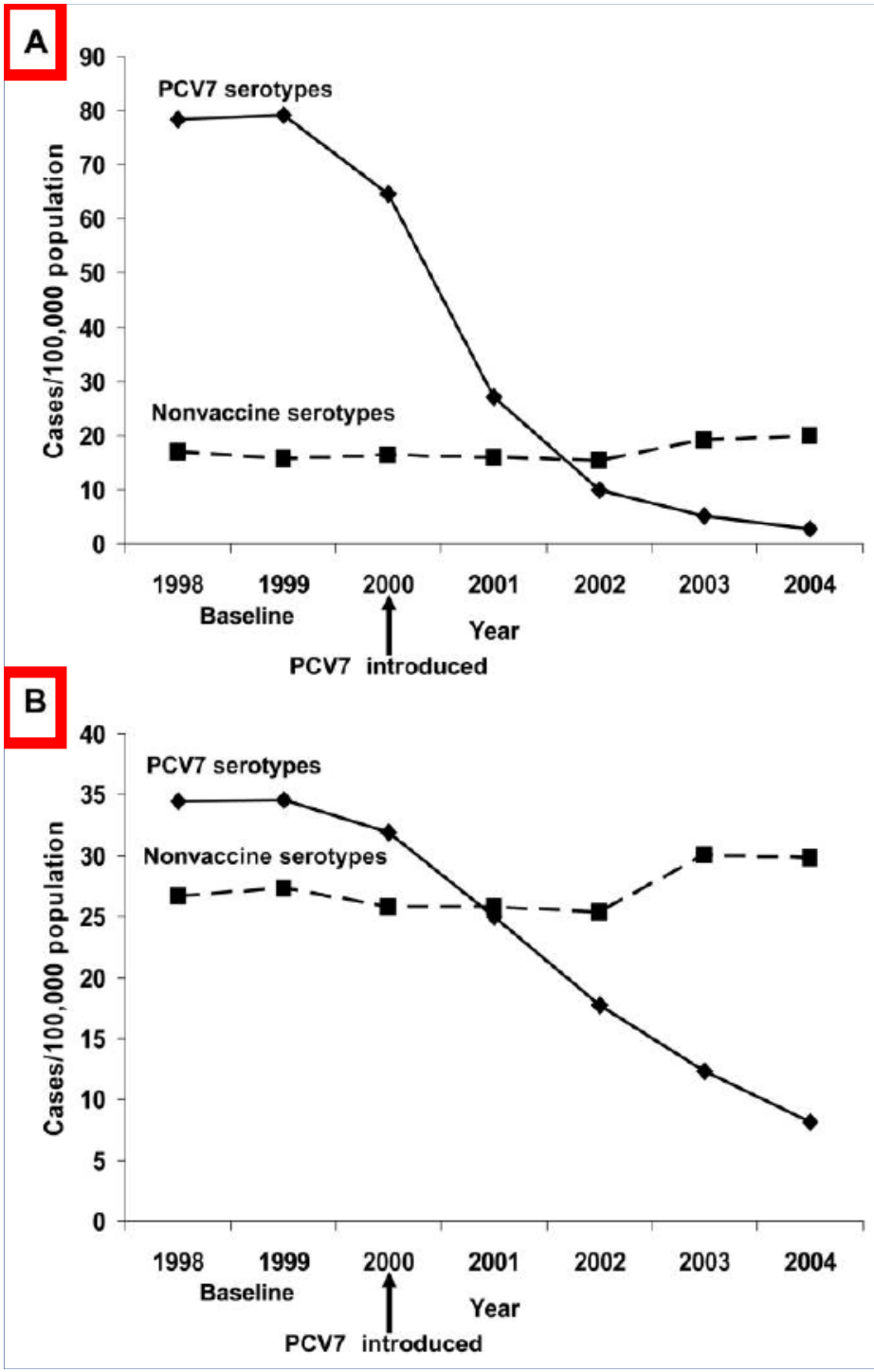


Adapted from: American Academy of Pediatrics. *Pediatrics*. 2000;106:367-376
MMWR. 1997;46:1-24.

Pneumococcal deaths in children 1-59 mos per 100 000 children of the same age

(from O'Brien KL, et al. Lancet 2009)





Incidenza delle IPD negli U.S.A. prima e dopo l'impiego di PCV-7

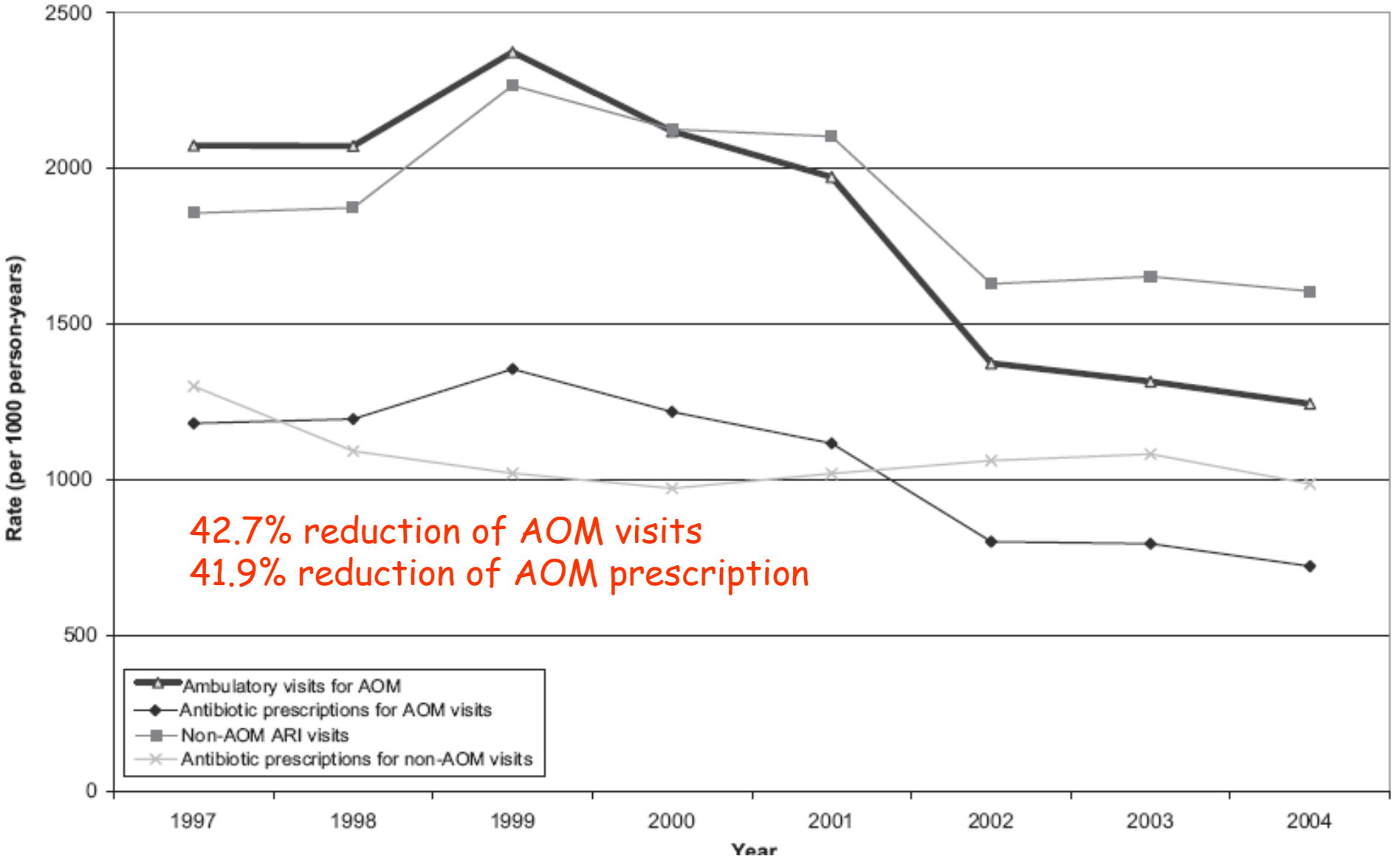
A = Bambini < 5 anni
B = Soggetti ≥ 65 anni

(da Hicks LA, J Infect Dis 2007)

Trends in Acute Otitis Media-Related Health Care Utilization by Privately Insured Young Children in the United States, 1997 2004

Fangjun Zhou, Abigail Shefer, Yuan Kong and J. Pekka Nuorti

Pediatrics 2008;121;253-260

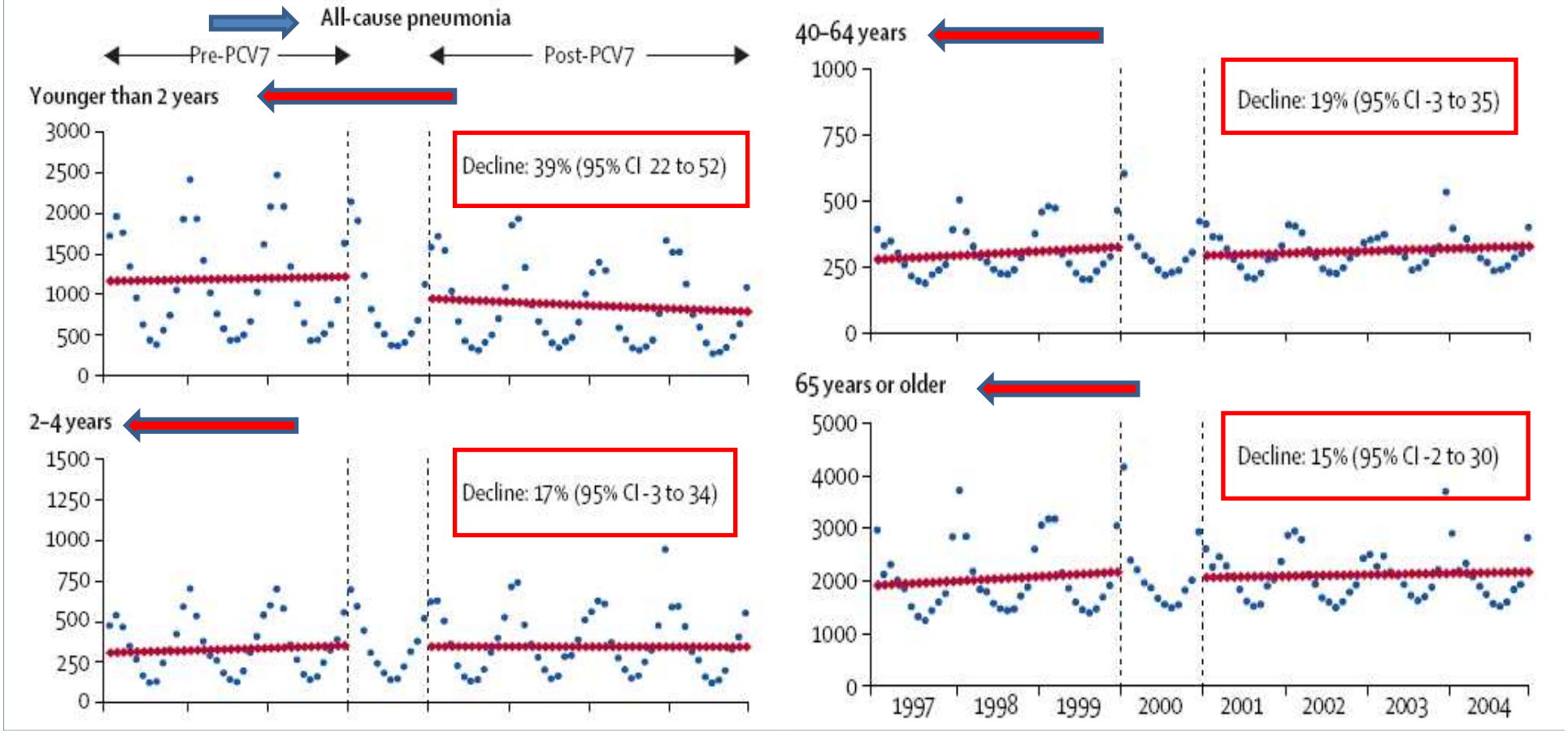


Andamento della ospedalizzazione per CAP negli U.S.A. prima e dopo l'introduzione di PCV-7

(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

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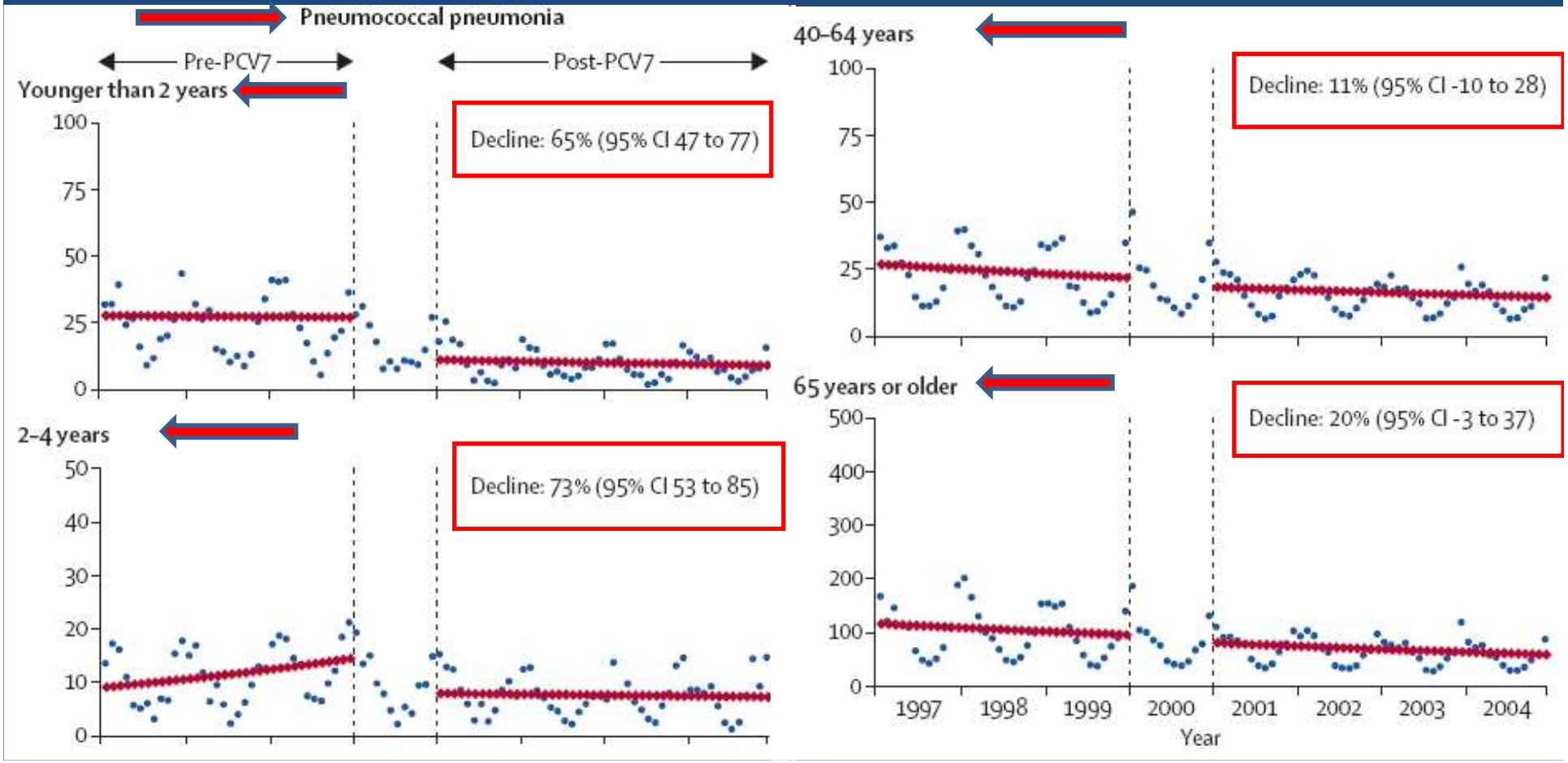
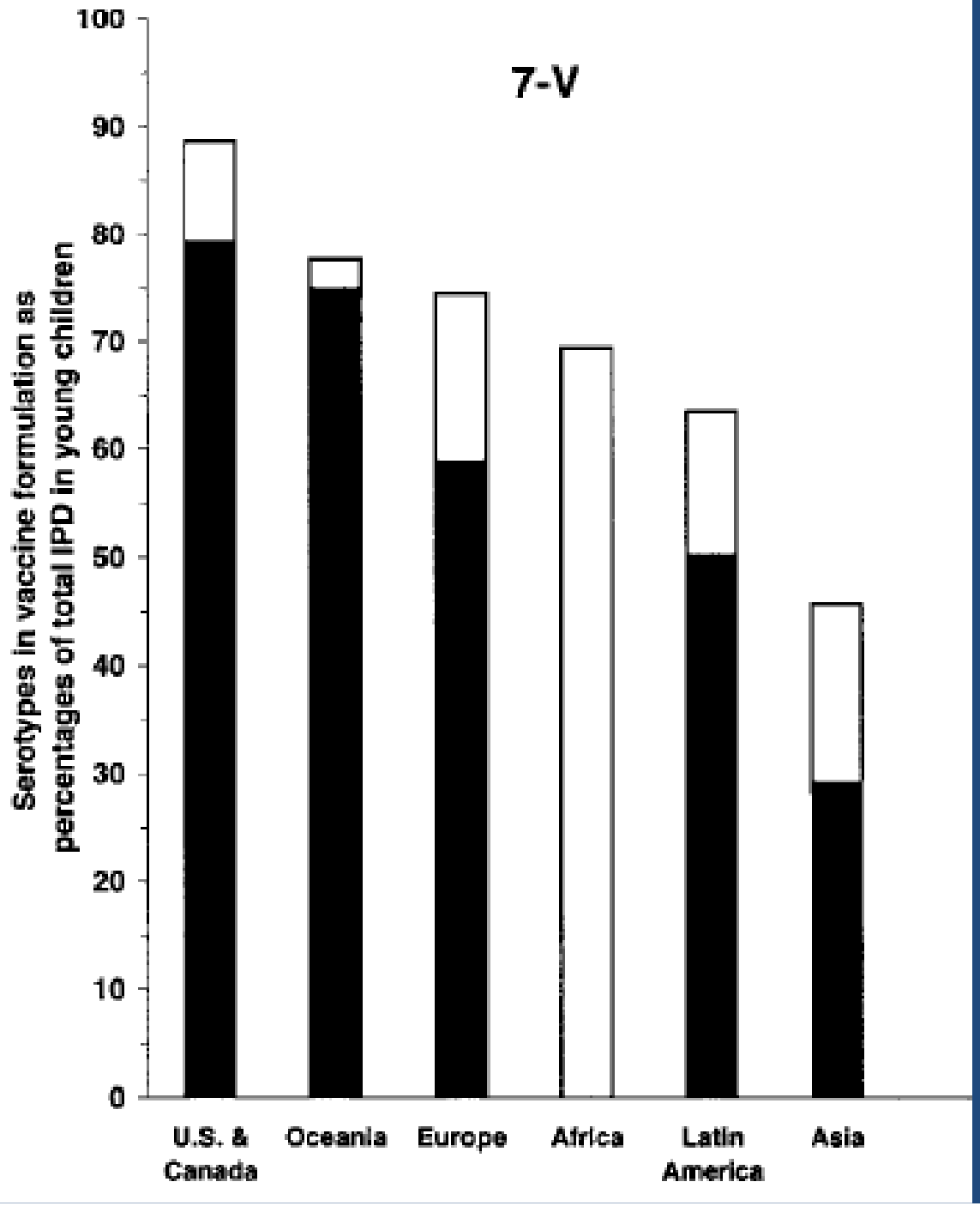


CARATTERISTICHE DI PCV-7

Formulazione basata sui sierotipi:

- a) più importanti negli U.S.A.
- b) responsabili di patologia invasiva
- c) prevalenti nei bambini più piccoli



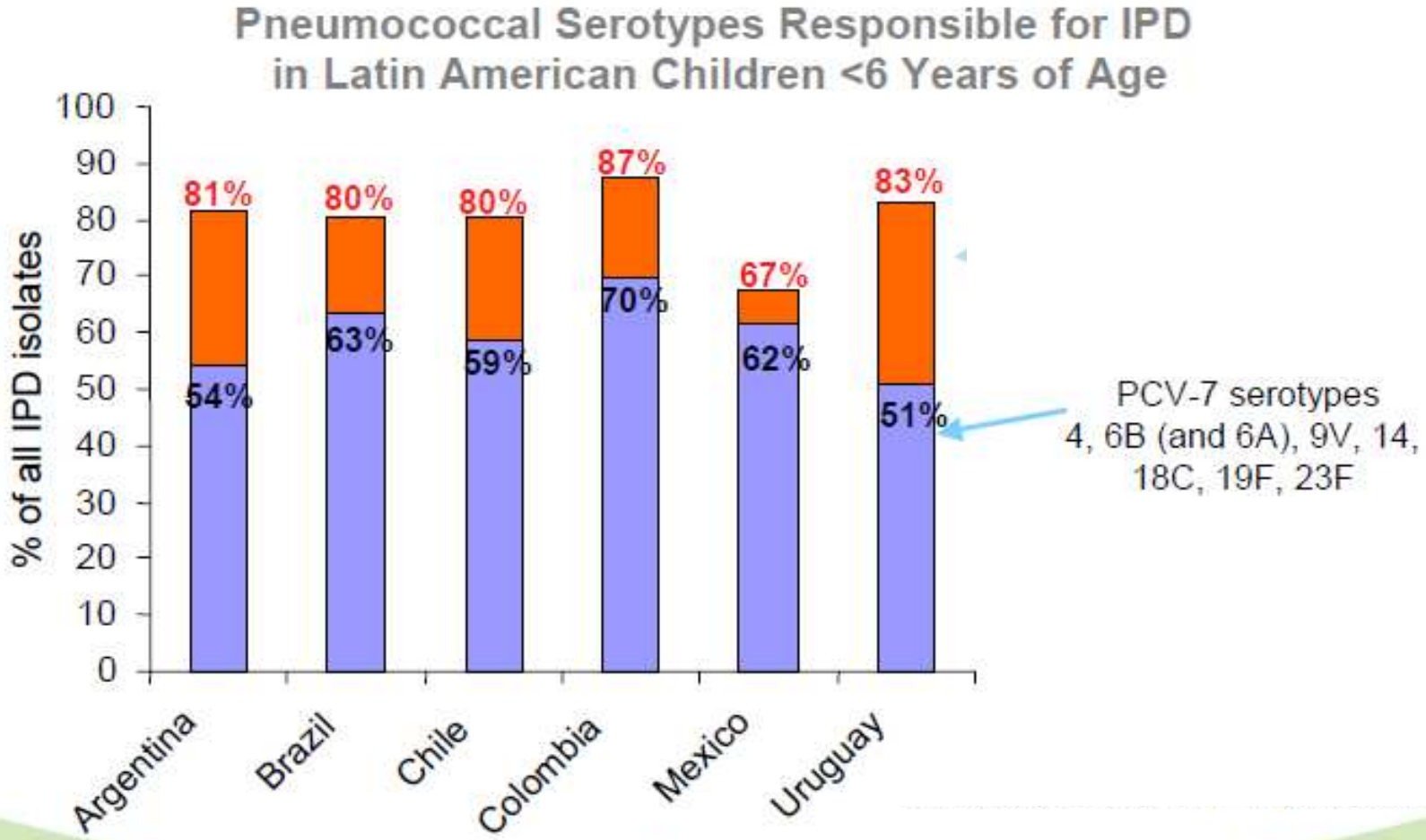
COPERTURA TEORICA OFFERTA DA PCV-7 CONTRO LE IPD NEL BAMBINO PICCOLO

(da Hausdorff WP et al. Clin Infect Dis 2000)

Nero = sierotipi inclusi in PCV-7
Bianco = sierotipi cross-reattivi
Colonna interamente bianca = dati teorici

1, 3, 5 e 7F sono i sierotipi non presenti in PCV-7 isolati di frequente al di fuori di Nord America e Australia

The critical importance of serotypes 1, 5, and 7F



Sources: Argentina, Brazil, Mexico (1993-99): SIREVA: (DiFabio et al PIDJ 2001)
Colombia (1994-2004): Agudelo et al (Biomedica 2006)
Chile (2003-mid-2006): Lagos et al (pers. comm.)
Uruguay (1994-2001): Camou et al (Vaccine 2003)

PROBLEMI DI PCV-7 INSORTI DOPO L'USO (I)

- L'uso di PCV-7 causa una modificazione dello stato di portatore e delle circolazione dei diversi tipi di *Sp*, con sostituzione di quelli contenuti nel vaccino con altri non inclusi (fenomeno del rimpiazzo)

- Ciò ha limitato valore per le IPD, perché i nuovi ceppi hanno modeste proprietà invasive

- Può, però, avere significato per le OMA e le CAP non batteriemiche perché la frequenza di comparsa di queste dipende dall'entità dell'esposizione e non dalla invasività. In altre parole, è possibile che, con il tempo l'efficacia di PCV-7 in queste patologie si riduca

PROBLEMI DI PCV-7 INSORTI DOPO L'USO (II)

- Il fenomeno del rimpiazzo ha provocato un aumento della frequenza di comparsa di OMA e dei casi di CAP gravi dovute a sierotipi non inclusi (ancora i sierotipi 1, 3, 5 e 7F)
- In ogni parte del mondo sono emersi problemi per il sierotipo 19A, in questo caso, probabilmente, anche per modificazioni spontanee delle caratteristiche di invasività e sensibilità agli antibiotici di questo sierotipo

MODIFICAZIONI INDOTTE DA PCV-7 SULL'EZIOLOGIA PNEUMOCOCCICA DELL'OMA

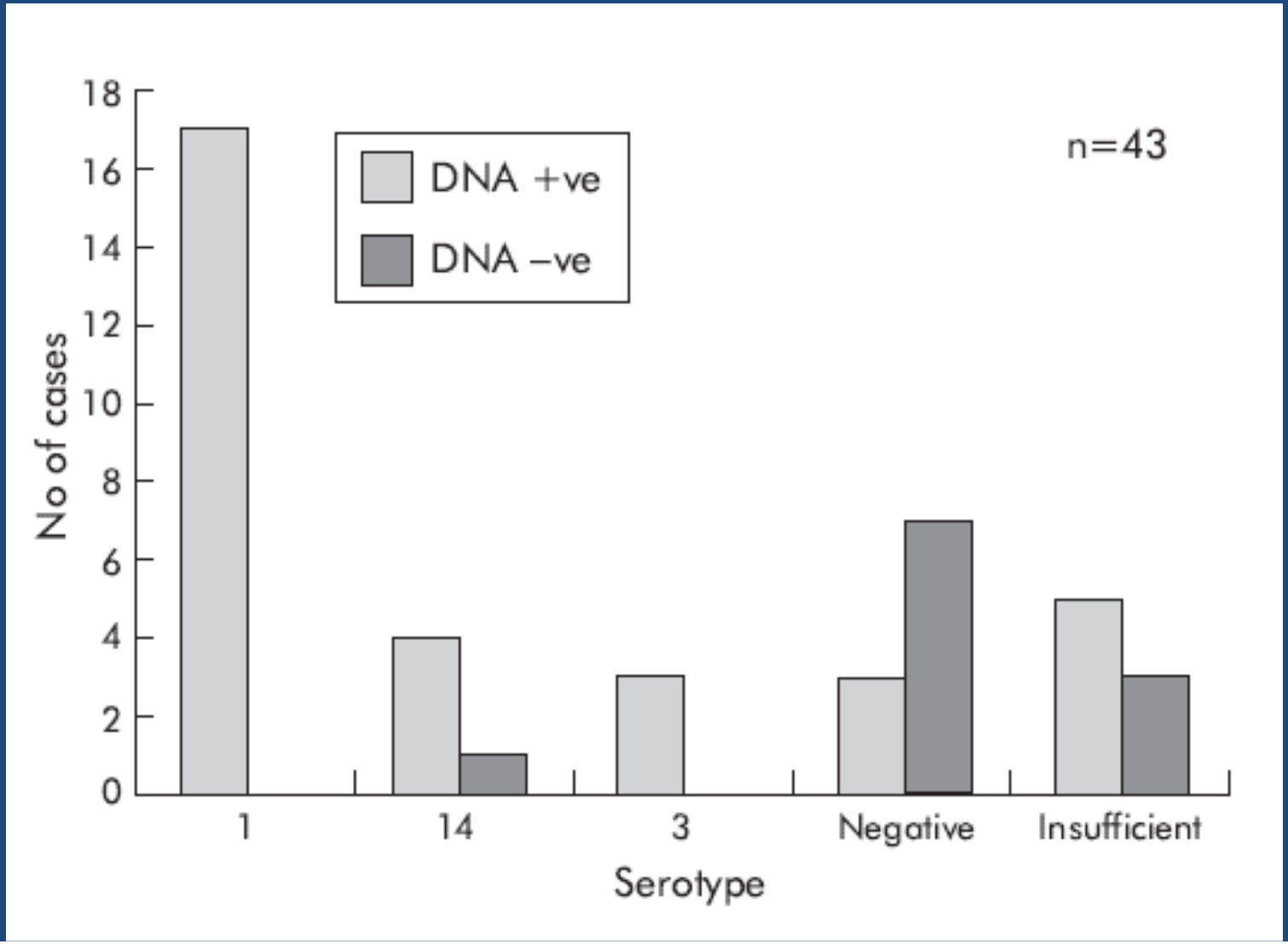
(da Block SL et al. Pediatr Infect Dis J 2004)

Sierotipi	Pre PCV-7	Post PCV-7
PCV-7	92/132 (70%)	8/22 (36%)
Cross reattivi con PCV-7	11/132 (8%)	7/22 (32%)
Non PCV-7	29/132 (22%)	7/22(32%)*
Totale	132 (100%)	22 (100%)

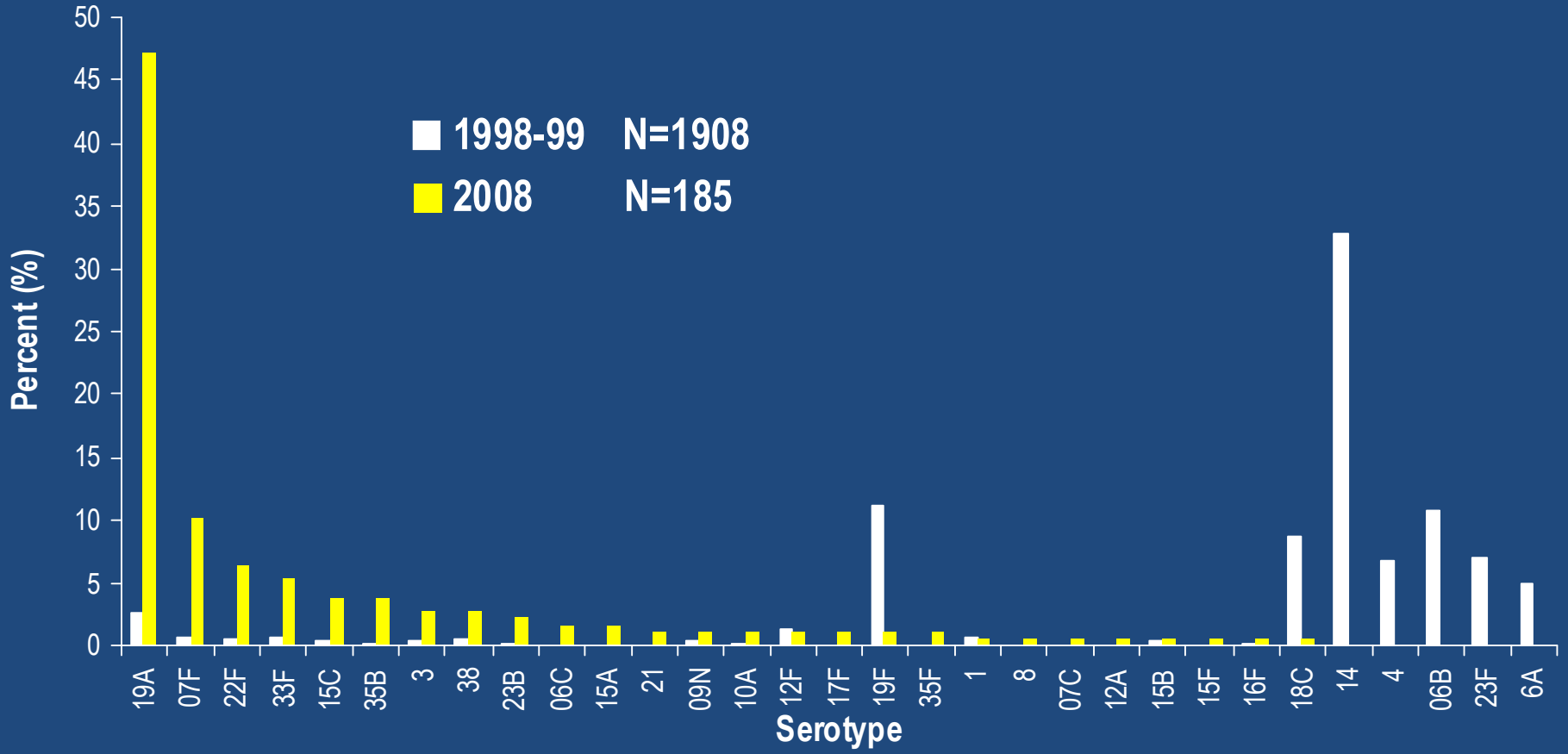
* Sierotipi 1 (1), 11A (2), 15A (1), 29 (2), 33F (2)

Sierotipi di pneumococco associati ad empiema pleurico

(da Eastham et al. Thorax 2004)

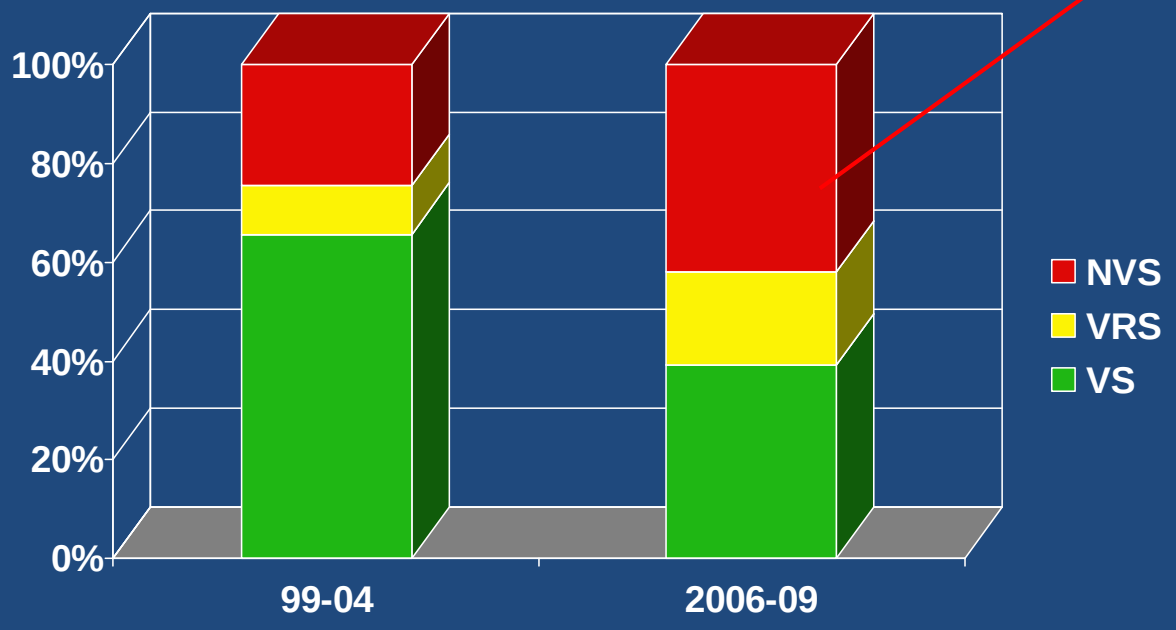


Serotype distribution of invasive pneumococcal disease isolates among children <5 years of age, Active Bacterial Core surveillance areas, 2008 vs. 1998-1999



(CDC, 2010)

Variazione sierotipi 0-4 anni

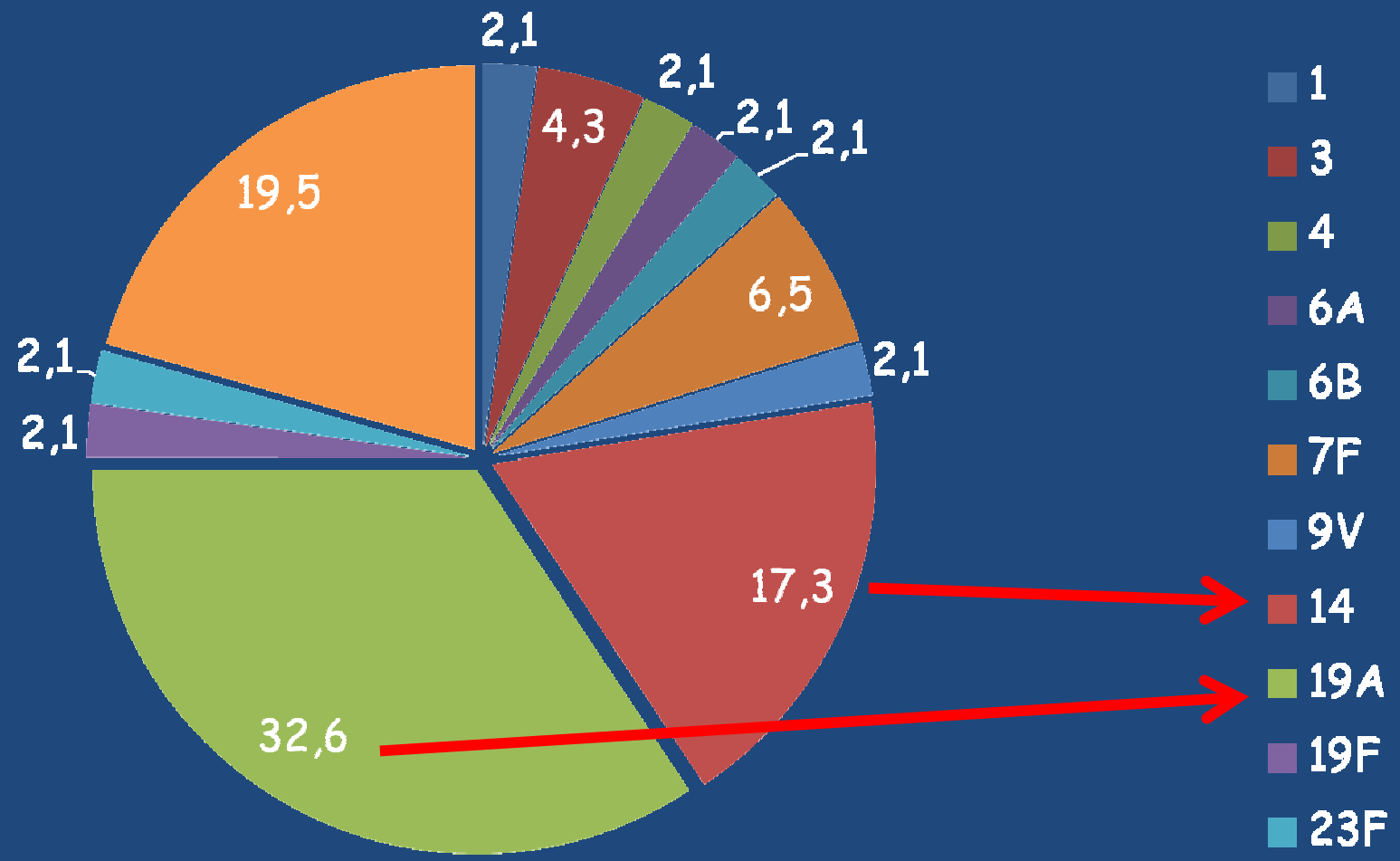


Sierotipo	n° ceppi
14	30
19A	17
1	13
7F	12
23F	10
19F	7
6A	6
15B	5
24F	5
3	4
18C	3
10A	3
22F	3
33F	3
38	3
6B	2
23A	2
15C	2
Altro	2
4	1
9V	1
23B	1
17	1
20	1
29	1

Per cortesia della prof.ssa Pantosti

Polmoniti batteriemiche da *Sp*: importanza dei vari sierotipi

(da Esposito S, et al. SIMRI 2010)



Serotype Composition of new pneumococcal vaccines

PCV-7	4	6B	9V	14	18C	19F	23F						
PCV-10	4	6B	9V	14	18C	19F	23F	1	5	7F			
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A

PCV13 contains the same carrier protein – CRM_{197}

THEORETICAL ADVANTAGES OF PCV-D

- Coverage against a greater number of serotypes in comparison to PCV-7
- Coverage against infections due to non-typable Haemophilus influenzae

Efficacy of PCV-D in prevention of AOM

(from Prymula et al. Lancet 2007)

	Pneumococcal vaccine		Control vaccine		Vaccine efficacy* % (95% CI)
	Number of children	Incidence per 1000 person-years	Number of children	Incidence per 1000 person-years	
Per-protocol cohort	2455		2452		
Vaccine pneumococcal serotypes	57	14·4	118	30·4	52·6% (35·0 to 65·5)
Non-typable *H influenzae*	39	9·8	56	14·2	31·1% (−3·7 to 54·2)
Intention-to-treat cohort	2489		2479		
Vaccine pneumococcal serotypes	64	14·2	132	29·8	52·6% (36·1 to 64·9)
Non-typable *H influenzae*	43	9·5	63	14·0	32·7% (0·77 to 54·3)

IMPACT OF PCV-D ON CARRIER STATE OF RESPIRATORY PATOGENS IN CHILDREN 15 -18 MOS OLD

(from Prymula R, et al. Lancet 2007)

	Pneumococcal vaccine (N=177)		Control vaccine (N=175)		Vaccine efficacy*		p†
	n	%	n	%	%	95% CI	
S pneumoniae	30	16·9	39	22·3	23·9	−16·6 to 50·4	0·228
S pneumoniae vaccine serotypes	11	6·2	19	10·9	42·8	−16·7 to 71·9	0·130
S pneumoniae non-vaccine serotypes‡	12	6·8	14	8·0	15·3	−78·0 to 59·7	0·689
H influenzae	18	10·2	31	17·7	42·6	1·3 to 66·6	0·046
Non-typable *H influenzae*	16	9·0	27	15·4	41·4	−4·9 to 67·3	0·075

N=number of swabs collected. n/%=number/percentage of swabs positive for *S pneumoniae* or *H influenzae*. *Vaccine efficacy was estimated as 1 minus relative risk. †Two-sided Fisher's Exact test. ‡Excluding vaccine-related cross reactive serotypes.

CRITICISM FOR THE STUDY REGARDING AOM PREVENTION WITH PCV-D

- Diagnosis of AOM was debatable
- Incidence of AOM in control patients significantly lower than expected
- The vaccine used was similar but not identical to the licensed 10-valent vaccine. It contained 11 serotypes and had differences in carrier protein because all the serotypes were conjugate with D protein.

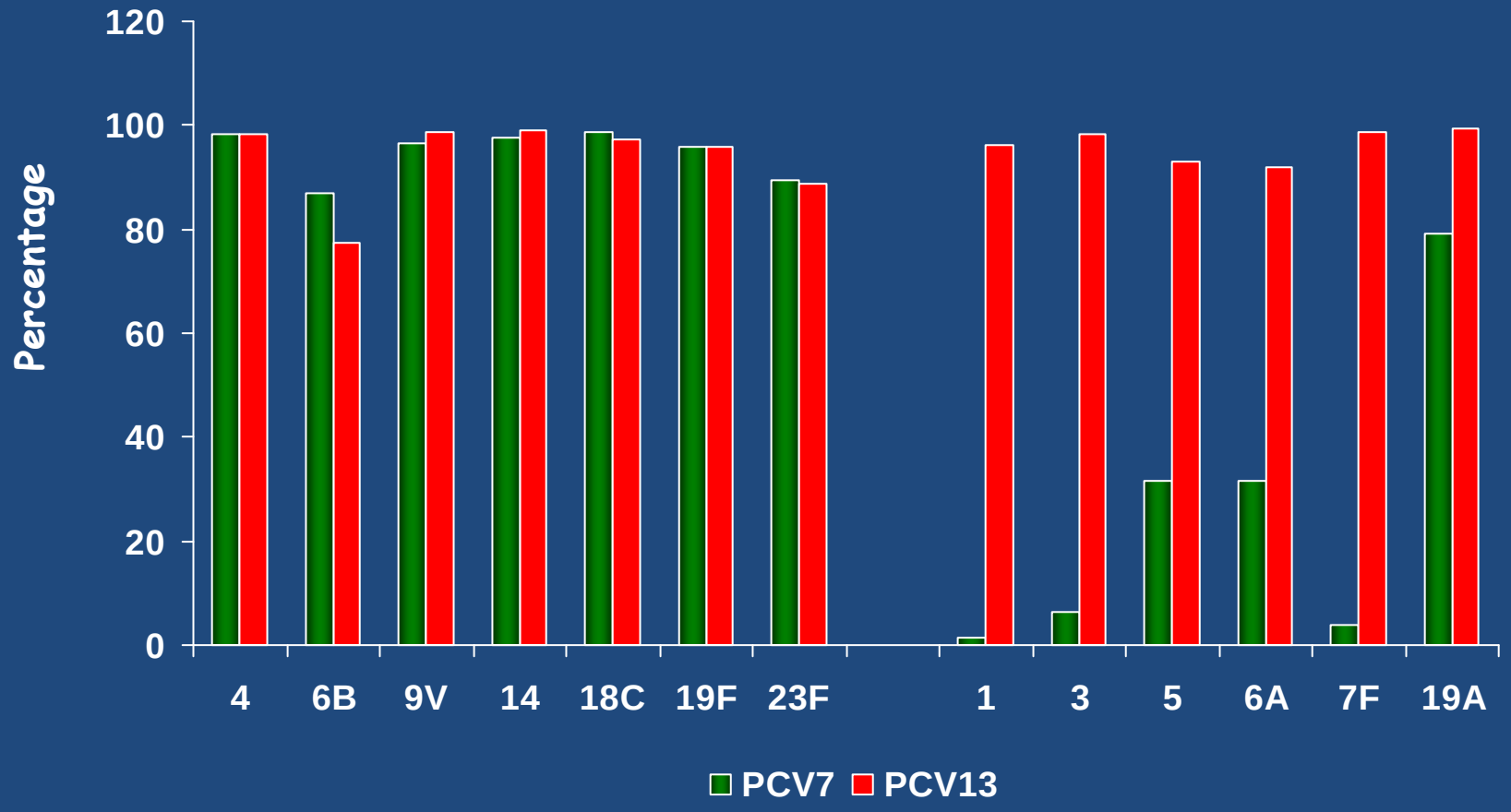
TABLE 3. Comparative Analysis Between the PHiD-CV and 7vCRM Vaccines for ELISA and OPA Responses 1 Month After the Third Primary Vaccine Dose (ATP Cohort for Immunogenicity)

Antibody	ELISA			OPA		
	Difference in % ≥0.2 μg/mL(7vCRM minus PHiD-CV)			Difference in % ≥8 (7vCRM minus PHiD-CV)		
	%	96.5% CI		%	95% CI	
Anti-4	2.89	1.71	4.16	0.37	−3.81	2.09
Anti-6B	13.12	7.53	18.28	3.14	−3.80	8.03
Anti-9V	1.37	−0.28	2.56	0.00	−4.14	1.41
Anti-14	−0.08	−1.66	0.71	−0.75	−5.73	1.14
Anti-18C	2.92	0.88	4.57	1.85	−5.09	6.52
Anti-19F	3.83	1.87	5.50	4.45	−3.72	10.61
Anti-23F	12.72	8.89	16.13	3.83	−2.20	7.96

From Vesikary et al. Pediatric Infectious Disease Journal 2009

German Study: Post-Infant Series Immunogenicity

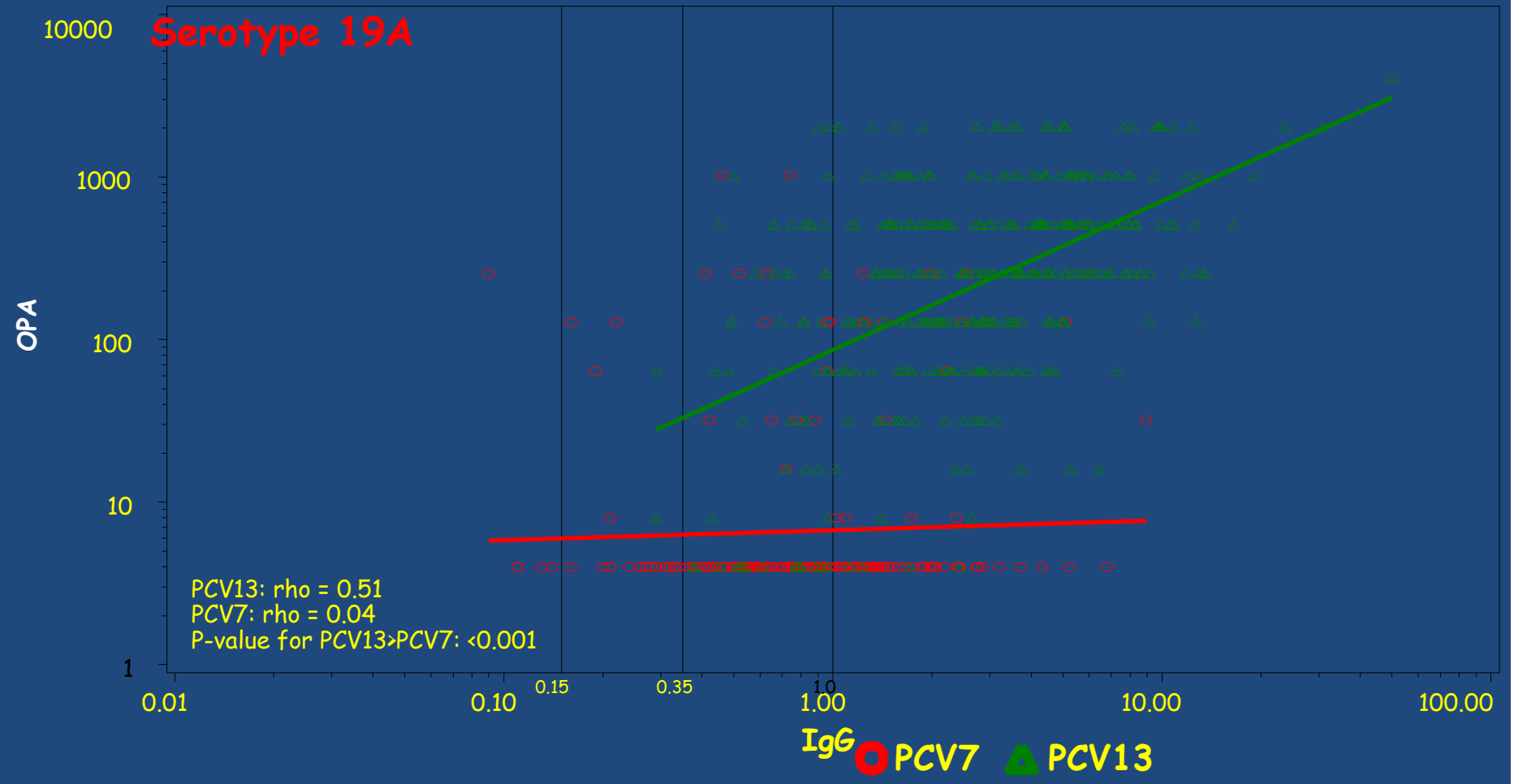
Infants Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 μg/mL After Primary Series



Kieninger D.M. et al, 48th ICAAC/46th IDSA 2008

Additional Serotype: 19A

Plot of polysaccharide-binding IgG vs OPA assay data



Kieninger D.M. et al, 48th ICAAC 2008

Pneumococcal OPA GMTs After the Infant Series in the German study

Serotype	PCV13 GMTs	PCV7 GMTs	Ratio (95% CI)
4	1573.29	1860.79	0.85
6B	744.43	1160.76	0.64
9V	4937.84	5379.51	0.92
14	2139.65	3345.19	0.64
18C	1509.65	1780.26	0.85
19F	150.12	165.69	0.91
23F	1089.92	1070.83	1.02
[illegible]	[illegible]	[illegible]	12.09
[illegible]	[illegible]	[illegible]	40.87
5	162.02	4.64	34.95
6A	1228.45	122.40	10.04
7F	11544.75	115.45	100.0
19A	442.48	6.70	66.02

10 to 100 fold higher functional activity for the 6 Additional Serotypes with PCV13

GMT=Geometric Mean Titre
Study 006; 48th ICAAC/46th IDSA
2638

Italian Study

(Esposito S, et al.)

- 602 subjects were randomly assigned in a 1:1 ratio to receive either PCV13 (n=301) or PCV7 (n=301) at 3, 5 and 11-12 months of age
- All the children received Infanrix Hexa concomitantly with pneumococcal vaccine
- Evaluable immunogenicity population included randomly assigned subjects who met all the inclusion criteria, has at least 1 valid and determinate assay result for the proposed analysis, and had no major protocol violations
- Safety population included all subjects who received at least 1 dose of study vaccines
- Immunogenicity of pneumococcal vaccines and of Hinfanrix Hexa was evaluated 1 months after the second dose and 1 months after the booster dose
- Distribution of demographic characteristics was not notably different in the 2 groups

Percentage of Subjects With Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL 1 Month After the Infant Series and After the Toddler Dose

(From Esposito S, et al. ESPID 2009)

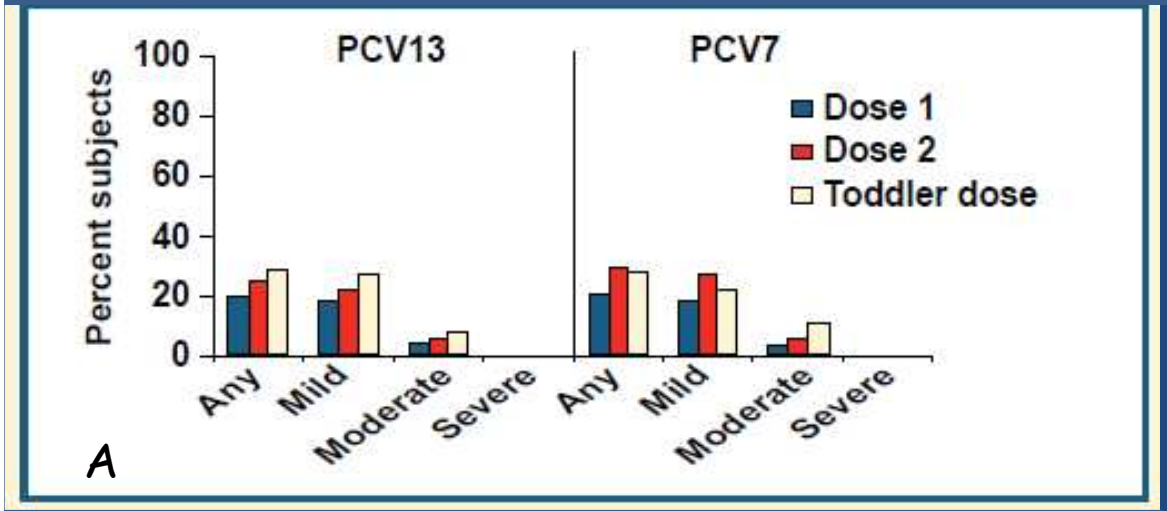
Serotype	After dose 2	After toddler dose	
	PCV13 % (95% CI) (n=261-264)	PCV13 % (95% CI) (n=232-237)	PCV7 % (95% CI) (n=240-245)
Included in PCV7			
4	96.6 (93.6, 98.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)
6B	58.4 (52.2, 64.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)
9V	94.7 (91.2, 97.1)	100.0 (98.4, 100.0)	100.0 (98.5, 100.0)
14	94.2 (90.6, 96.7)	99.6 (97.7, 100.0)	99.6 (97.7, 100.0)
18C	92.4 (88.5, 95.3)	99.2 (97.1, 99.9)	99.6 (97.8, 100.0)
19F	95.1 (91.7, 97.3)	98.8 (96.4, 99.7)	98.4 (95.9, 99.6)
23F	68.6 (62.6, 74.1)	99.2 (97.0, 99.9)	98.8 (96.4, 99.7)
Additional in PCV13			
1	96.6 (93.6, 98.4)	99.6 (97.7, 100.0)	3.3 (1.4, 6.5)
3	92.8 (89.0, 95.6)	93.9 (90.1, 96.5)	6.7 (3.9, 10.6)
5	91.6 (87.5, 94.6)	100.0 (98.5, 100.0)	70.2 (63.6, 76.2)
6A	86.5 (81.8, 90.4)	99.6 (97.7, 100.0)	86.4 (81.5, 90.5)
7F	98.5 (96.2, 99.6)	99.6 (97.7, 100.0)	4.9 (2.6, 8.5)
19A	98.5 (96.1, 99.6)	100.0 (98.5, 100.0)	99.6 (97.7, 100.0)

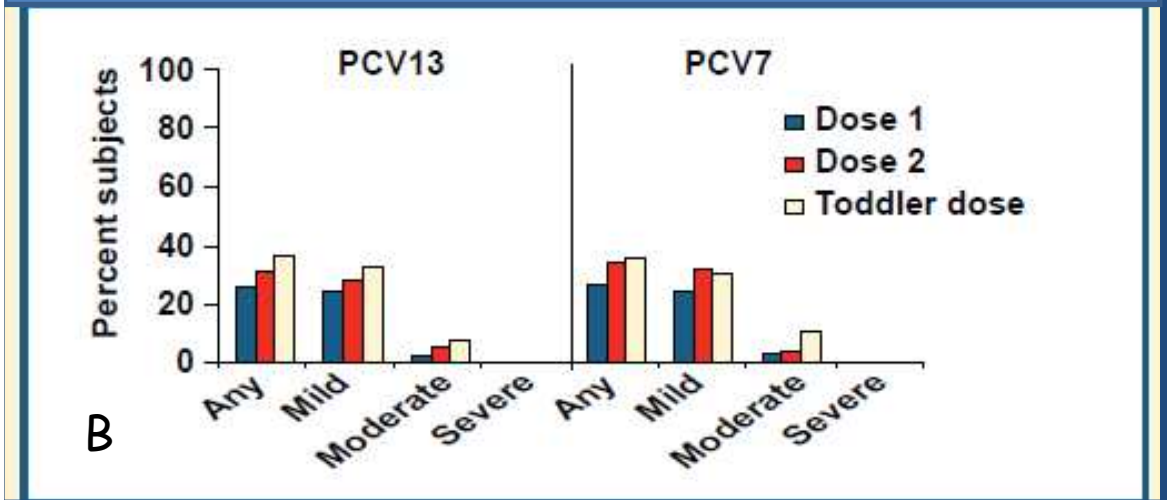
Percentage of Subjects with Prespecified Antibody Concentrations for Concomitant Vaccine Antigens 1 Month After the Infant Series and After the Toddler Dose

(From Esposito S, et al. ESPID 2009)

Vaccine antigen		Comparison level	After dose 2			After toddler dose		
			PCV13, % (n=155-273)	PCV7, % (n=214-276)	*Difference, % (95% CI%)	PCV13, % (n=125-252)	PCV7, % (n=96-255)	*Difference, % (95% CI)
Hepatitis B		10.0 mIU/mL	93.8	93.1	0.7 (-3.6, 5.0)	98.4	98.8	-0.4 (-3.0, 2.0)
Hib (PRP)		0.15 µg/mL	87.0	90.3	-3.2 (-9.1, 2.4)	99.6	98.2	1.4 (-0.8, 4.2)
		1.0 µg/mL	49.4	48.7	0.7 (-8.2, 9.5)	96.2	92.2	4.0 (-0.4, 8.7)
Pertussis	PT	≥5 EU/mL	99.6	100.0	-0.4 (-2.2, 1.0)	100.0	100.0	0.0 (-1.6, 1.7)
		≥16 EU/mL Infant	95.2	95.2	-0.0 (-4.0, 3.8)	—	—	—
		≥21 EU/mL Toddler	—	—	—	92.8	95.4	-2.7 (-7.3, 1.8)
	FHA	≥5 EU/mL	100.0	100.0	0.0 (-1.6, 1.4)	100.0	100.0	0.0 (-1.6, 1.7)
		≥7.82 EU/mL	100.0	100.0	0.0 (-1.6, 1.4)	100.0	100.0	0.0 (-1.6, 1.7)
		≥31 EU/mL Infant	94.7	95.6	-0.9 (-5.0, 2.9)	—	—	—
		≥162 EU/mL Toddler	—	—	—	95.2	95.3	-0.1 (-4.3, 4.1)
	Pertactin	≥5 EU/mL	100.0	100.0	0.0 (-1.5, 1.4)	100.0	100.0	0.0 (-1.6, 1.7)
		≥40 EU/mL Infant	91.9	95.2	-3.2 (-7.8, 1.0)	—	—	—
		≥106 EU/mL Toddler	—	—	—	94.9	95.4	-0.5 (-4.7, 3.7)
Diphtheria		0.01 IU/mL	100.0	100.0	0.0 (-1.8, 1.6)	100.0	100.0	0.0 (-2.3, 2.0)
		0.1 IU/mL	92.8	96.3	-3.5 (-8.3, 0.8)	100.0	100.0	0.0 (-2.3, 2.0)
Tetanus		0.1 IU/mL	94.2	92.5	1.7 (-3.9, 7.1)	97.6	93.8	3.8 (-1.7, 10.9)
Polio	Type 1	≥1:8	99.5	99.6	-0.1 (-2.3, 1.7)	100.0	100.0	0.0 (-2.4, 2.1)
	Type 2	≥1:8	95.6	96.6	-1.0 (-5.0, 2.8)	100.0	100.0	0.0 (-2.4, 2.1)
	Type 3	≥1:8	99.5	98.9	0.7 (-1.6, 2.9)	100.0	100.0	0.0 (-2.4, 2.1)

Hib=*Haemophilus influenzae* type b; PRP=polyribosylribitol phosphate; PT=pertussis toxoid; FHA=filamentous hemagglutinen; *% responders PCV13 - % responders PCV7





Percentuale di bambini con gonfiore (A) o arrossamento (B) in sede di iniezione di PCV-7 o PCV-13

Da Esposito et al. Espid 2009

Adverse events due to PCV-7 and PCV-13

From Esposito et al. ESPID 2009