I NUOVI VACCINI PNEUMOCOCCICI

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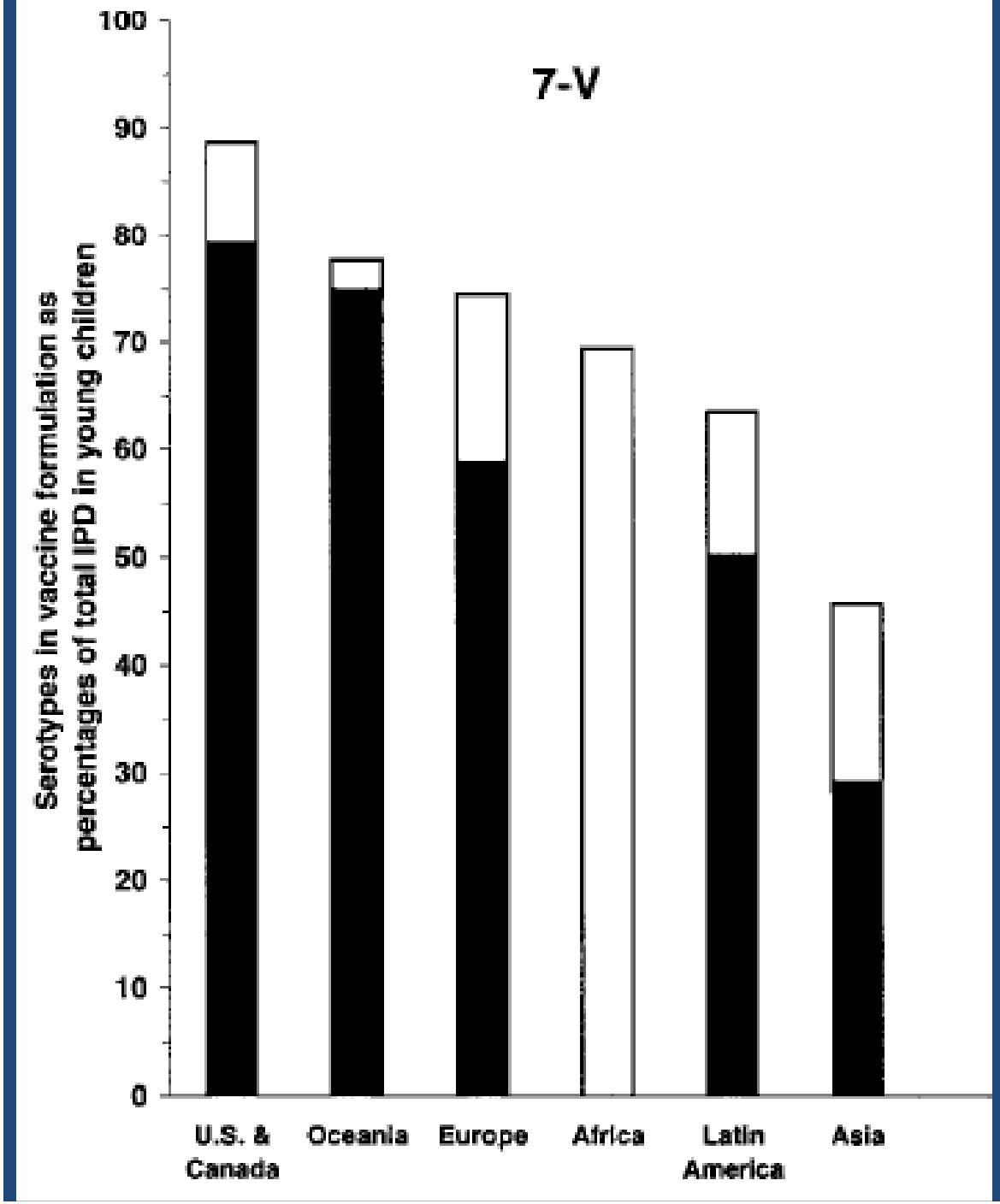
PCV-7: EFFICACIA

- Il vaccino pneumococcico eptavalente coniugato (PCV-7) si è dimostrato estremamente efficace tanto da essere raccomandato per tutta la popolazione pediatrica dall'OMS
- Il suo uso sistematico nel bambino dei primi mesi di vita ha ridotto in modo estremamente significativo tutta la patologia da *Streptococcus pneumoniae* nella popolazione vaccinata e ha indotto una immunità di gregge tanto rilevante da determinare una caduta dell'incidenza della patologia pneumococcica anche nei non vaccinati di ogni età

LIMITI DI PCV-7 PRESENTI IN ORIGINE

- La composizione ottima per il nord America e l'Australia e buona per l'Europa, trascura alcuni sierotipi (1, 3, 5, 7F) responsabili di parte di IPD in Sud America e in Asia
- OMA e CAP sono, anche negli U.S.A. ed in Europa, dovute a sierotipi di *Sp* non inclusi in PCV-7 in percentuali lievemente superiori a quelle che causano IPD
- Alcuni sierotipi non inclusi in PCV-7 (1 e 3, in particolare) causano CAP gravi



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

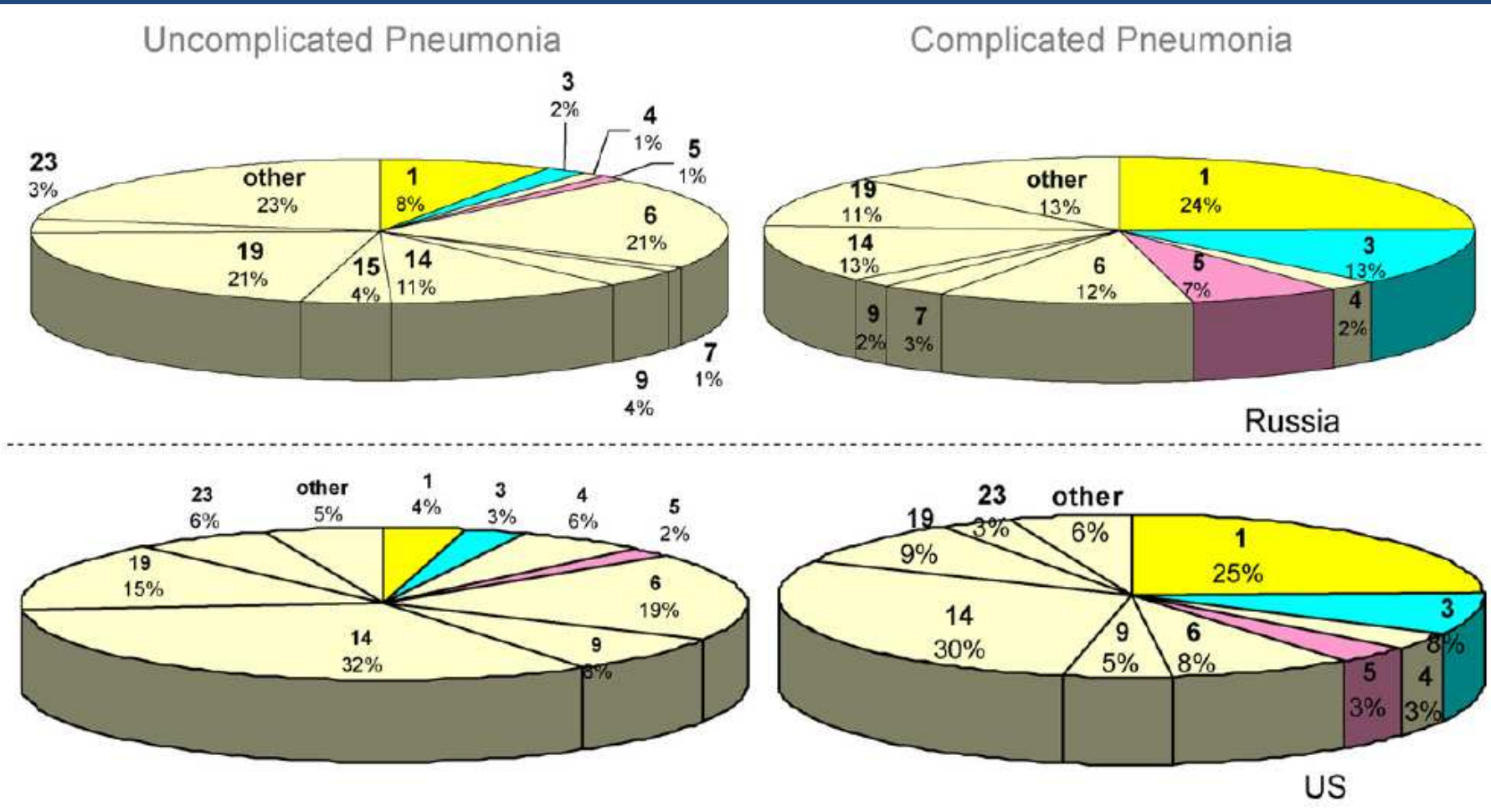
(da Hausdorff WP et al. Clin Infect Dis 2000)

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

SIEROTIPI DI SP E GRAVITA' DELLA CAP

(da Le Monnier A, et al. Clin Infect Dis 2006 e Katosova LK, Zh MikrobiolEpidemiol Immunobiol 1994)



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 è, almeno in parte, associato ad 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, 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 *SP* RESPONSABILI DI EMPIEMA PLEURICO PRIMA E DOPO L'INTRODUZIONE DI PCV-7

(da Byington CL et al Pediatr Infect Dis J 2006)

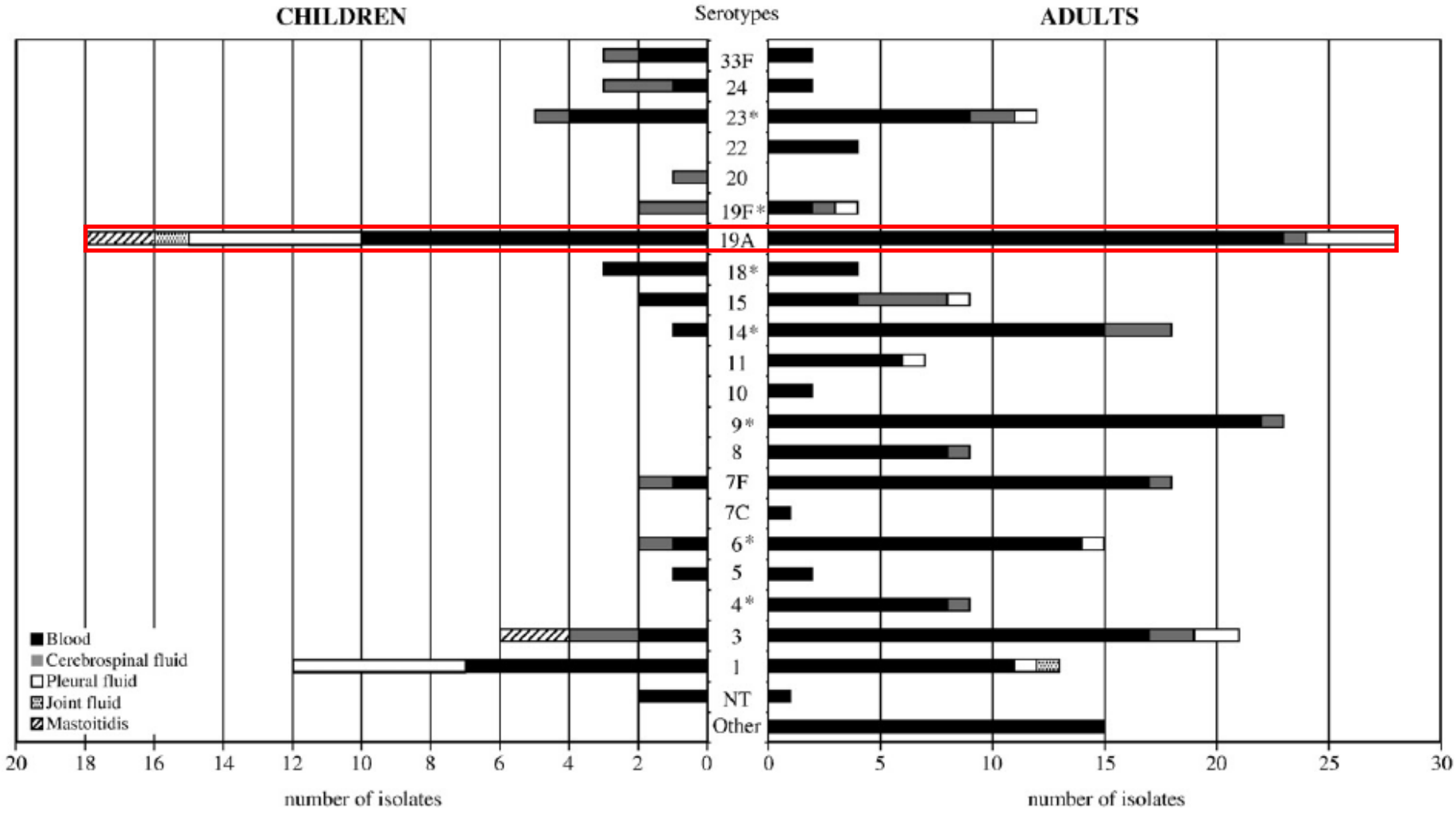
Serotypes	Total (N = 74)	Pre (N = 24)	Post (N = 50)	*P*
Vaccine serotypes				
4	1 (1)*	0 (0)	1 (2)	1.0
6B	2 (3)	2 (8)	0 (0)	0.10
9V	3 (4)	1 (4)	2 (4)	1.0
14	3 (4)	3 (13)	0 (0)	0.03
18C	1 (1)	0 (0)	1 (2)	1.0
19F	5 (7)	2 (8)	3 (6)	0.66
23F	1 (1)	1 (4)	0 (0)	1.0
Total vaccine serotypes	16 (21)	9 (37)	7 (14)	0.046
Nonvaccine serotypes				
1	28 (38)	11 (46)	17 (34)	0.47
3	10 (14)	0 (0)	10 (20)	0.025
6A	1 (1)	1 (4)	0 (0)	1.0
7	2 (3)	0 (0)	2 (4)	1.0
9N	1 (1)	0 (0)	1 (2)	1.0
19A	8 (11)	1 (4)	7 (14)	0.26
22	1 (1)	0 (0)	1 (2)	1.0
28	1 (1)	0 (0)	1 (2)	1.0
NT	6 (8)	2 (8)	4 (8)	1.0
Total nonvaccine serotypes	58 (78)	15 (63)	43 (86)	0.046

*Numbers in parentheses, percent.

NT indicates not tested.

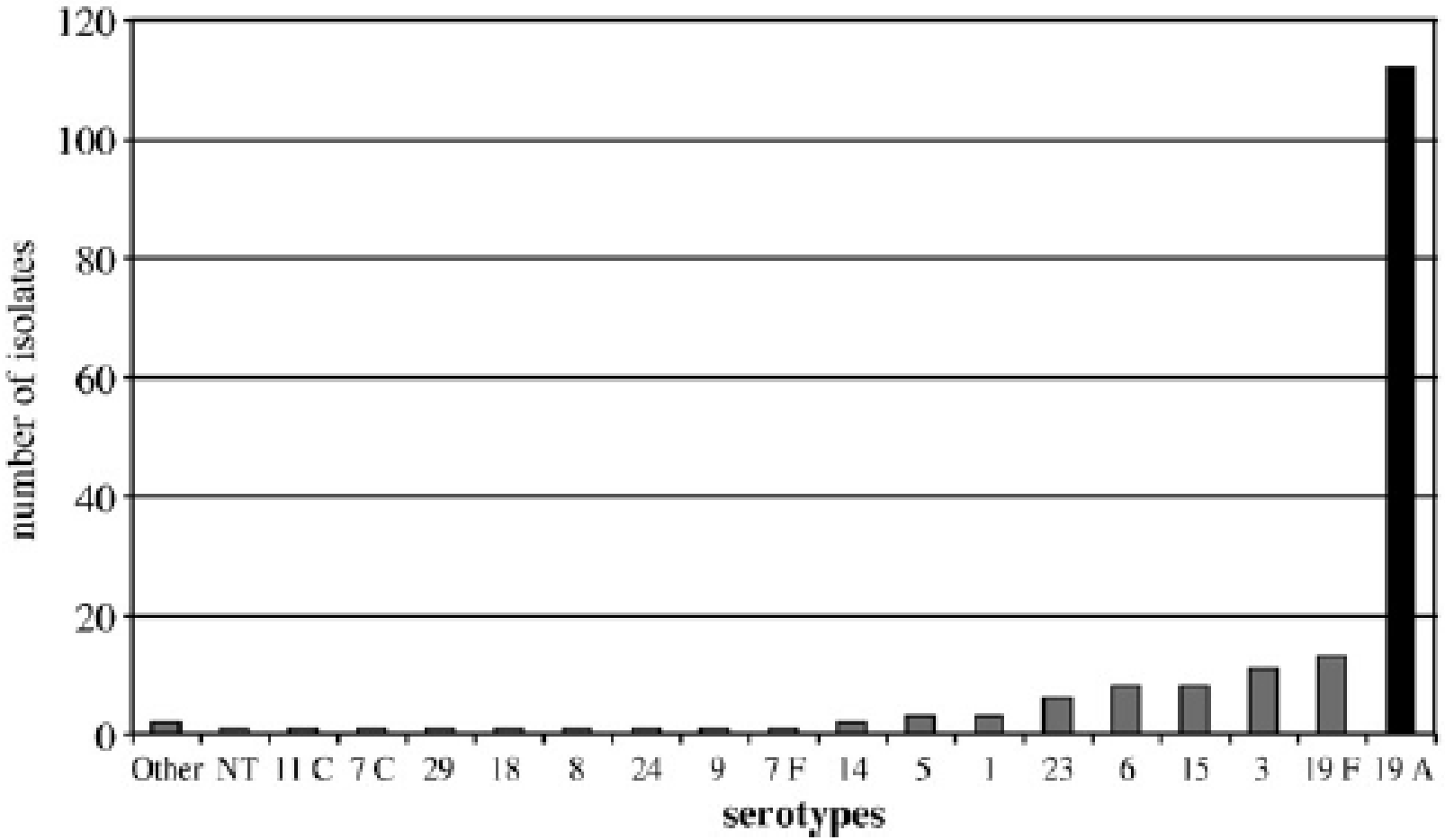
Serotype distribution of *Sp* isolated from invasive diseases in France

(from Dortet L, et al. Diagnos Microbiol Infect Dis 2009)



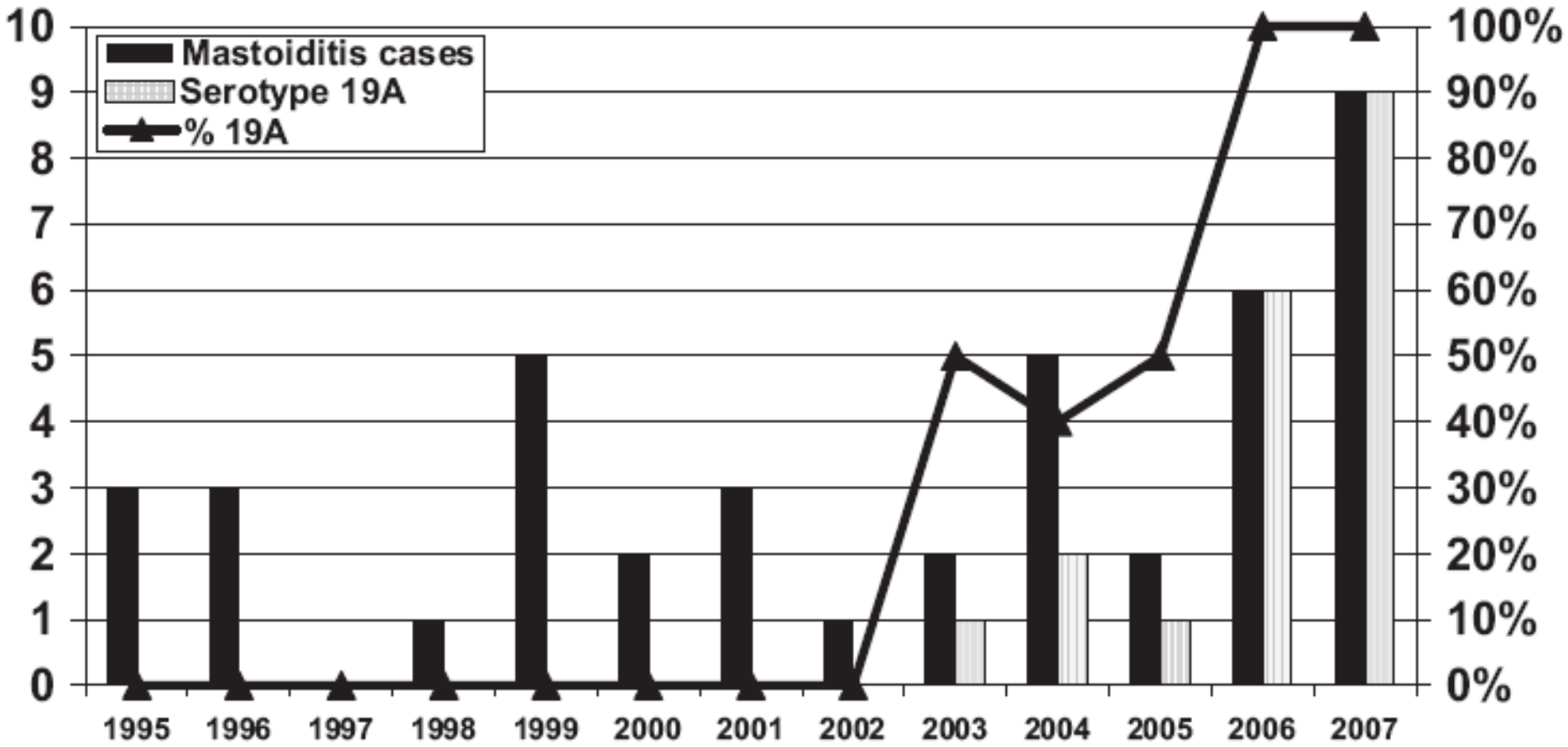
Serotype distribution of *Sp* isolated from acute otitis media in France

(from Dortet L, et al. Diagnos Microbiol Infect Dis 2009)

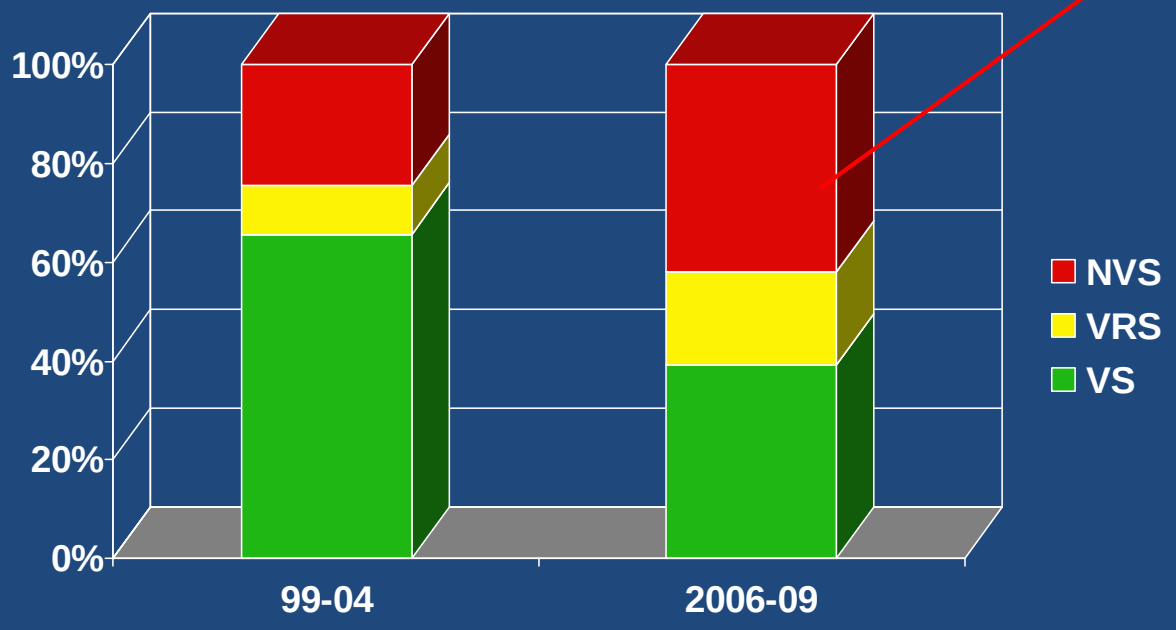


MASTOIDITE DA PNEUMOCOCCO 19A IN TEXAS

(da Ongkasuwan J et al. Pediatrics 2008)



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

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

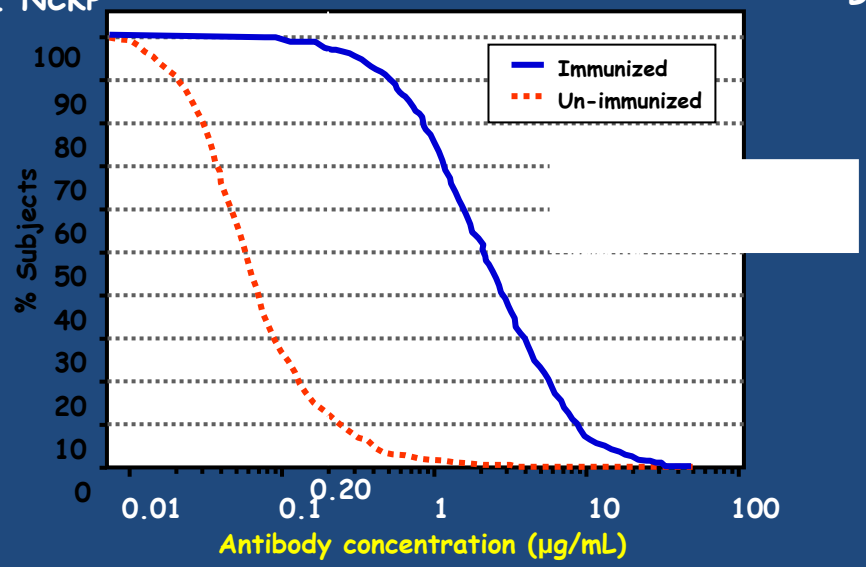
PCV13 contains the same carrier protein – CRM_{197}

Pneumococcal Conjugate Vaccines: Correlates of Immunity

- 2003 – **WHO working group estimated the protective concentration of anticapsular antibodies by correlating the anticapsular antibody levels of children with the clinical efficacy against IPD in three efficacy trials (PCV7 or 9v-PnC)**
  - Northern California Kaiser Permanente
  - South Africa
  - Navajo
- WHO working group concluded
  - 0.35 μg/mL of IgG class anticapsular antibodies to be the best estimate of the protective concentration applicable on a global level
  - The primary end point for comparing future PnC vaccines with PCV7 will be the proportion of infants achieving this concentration 1 month after primary immunization

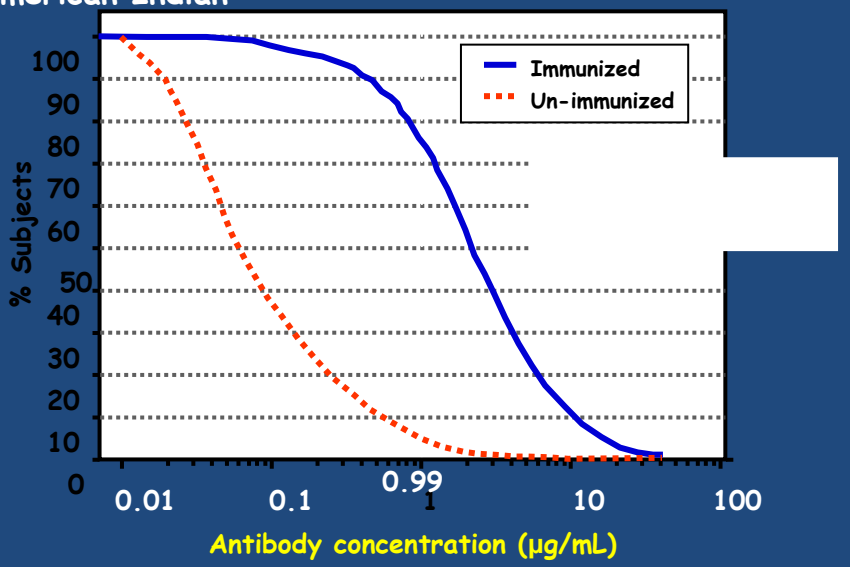
WHO. Technical Report Series No. 927. 2005.

A. NCKP



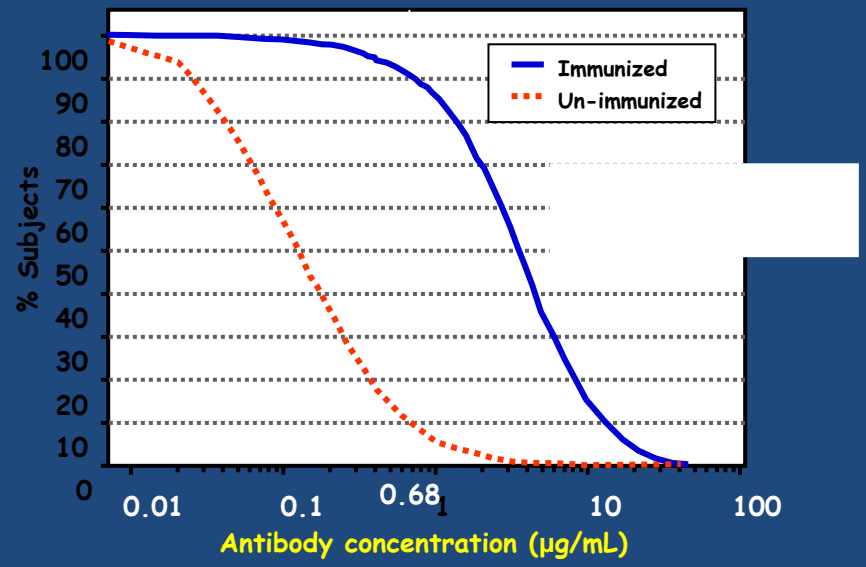
NCKP PP VE: 97.4%
Predicted VE with 0.2 µg/mL cut-off: 97.3%

B. American Indian

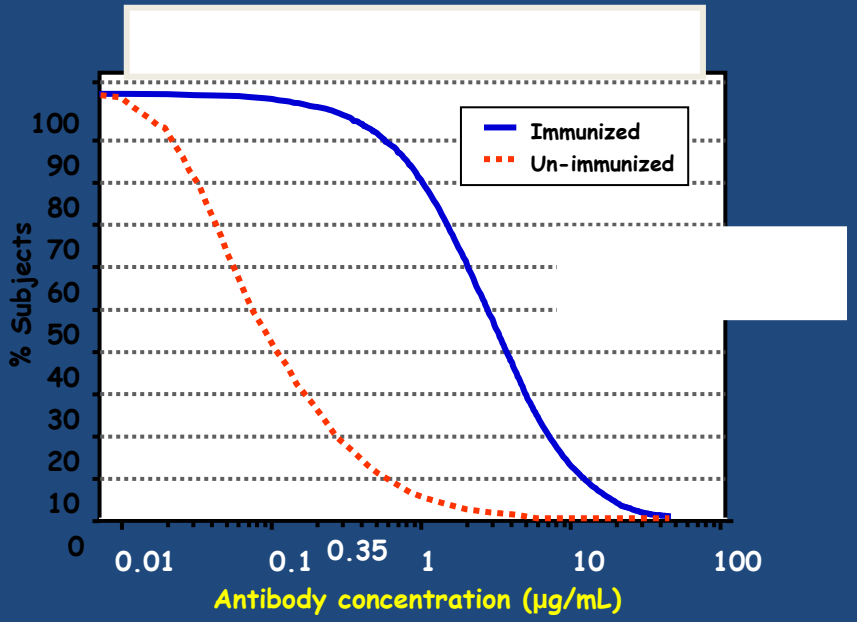


American Indian Trial VE: 76.8%
Predicted VE with 0.99 µg/mL cut-off: 76.7%

C. South African



South African Trial PP VE: 90%
Predicted VE with 0.68 µg/mL cut-off: 89.9%



Pooled VE: 93%
Predicted VE with 0.35 µg/mL cut-off: 92.5%

Adapted from Siber GR, et al. *Vaccine*. 2007;25:3816-3826.

WHO: Serological Criteria for Evaluation/Licensure of New PCVs

Primary Criteria (1 month after 3-dose primary series)

- IgG anticapsular antibody concentrations (ELISA) reported as geometric mean concentrations (GMCs)
- Percentage of responders achieving IgG anticapsular antibody threshold concentration (ELISA) of 0.35 μg/mL

Additional Criteria

- Functionality of antibodies measured by opsonophagocytic activity
- Immunological memory demonstrated by booster dose or avidity of antibodies

WHO (2005) Recommendations for the production and control of pneumococcal conjugate vaccines. WHO Technical Report Series No. 927

PCV-10: ATTUALI CONOSCENZE (I)

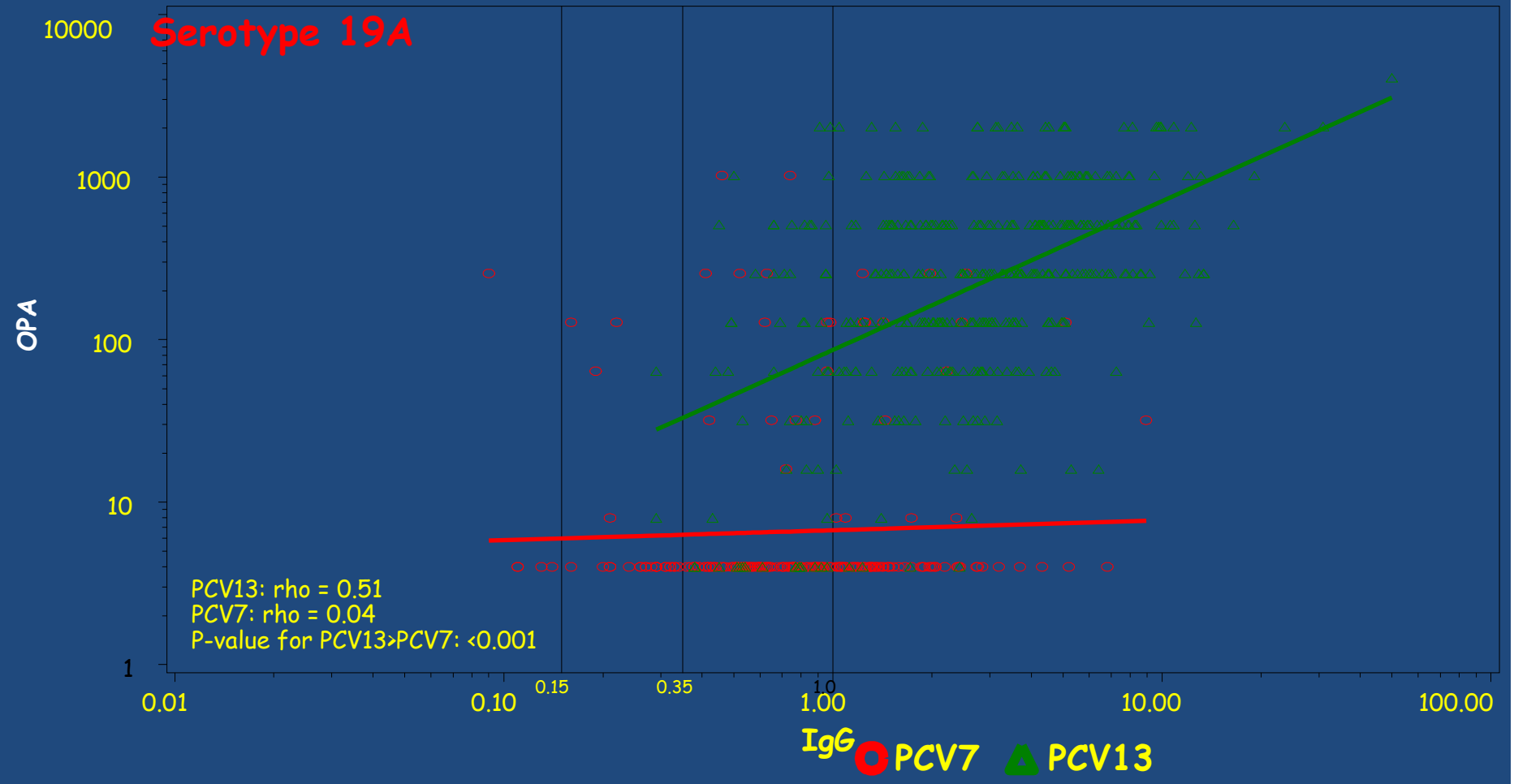
- Registrato dall'EMEA – Non registrato dall'FDA
- Studi di immunogenicità limitati alla schedula 3+1. L'uso dello schema 2+1 non è supportato dalla dimostrazione di adeguata immunogenicità
- Rispetto a PCV-7, dopo il ciclo primario, i criteri di non inferiorità non sono rispettati per 6B e 23 F, anche se la percentuali di soggetti con OPA $\geq$ 1:8 è simile nei 2 gruppi
- Rispetto a PCV-7, dopo la dose di richiamo, i livelli di anticorpi sono significativamente inferiori per tutti i sierotipi con l'eccezione del 19 F, anche se un simile numero di bambini ha raggiunto valori di OPA $\geq$ 1:8

PCV-10: ATTUALI CONOSCENZE (II)

- Il vaccino non contiene i sierotipi 3, 6A e 19A
- La elevata produzione di anticorpi contro 19A non è efficace
- Mancano studi clinici che ne avvalorino l'efficacia sul campo. L'unico studio disponibile è effettuato con un prototipo vaccinale diverso

Additional Serotype: 19A

Plot of polysaccharide-binding IgG vs OPA assay data



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

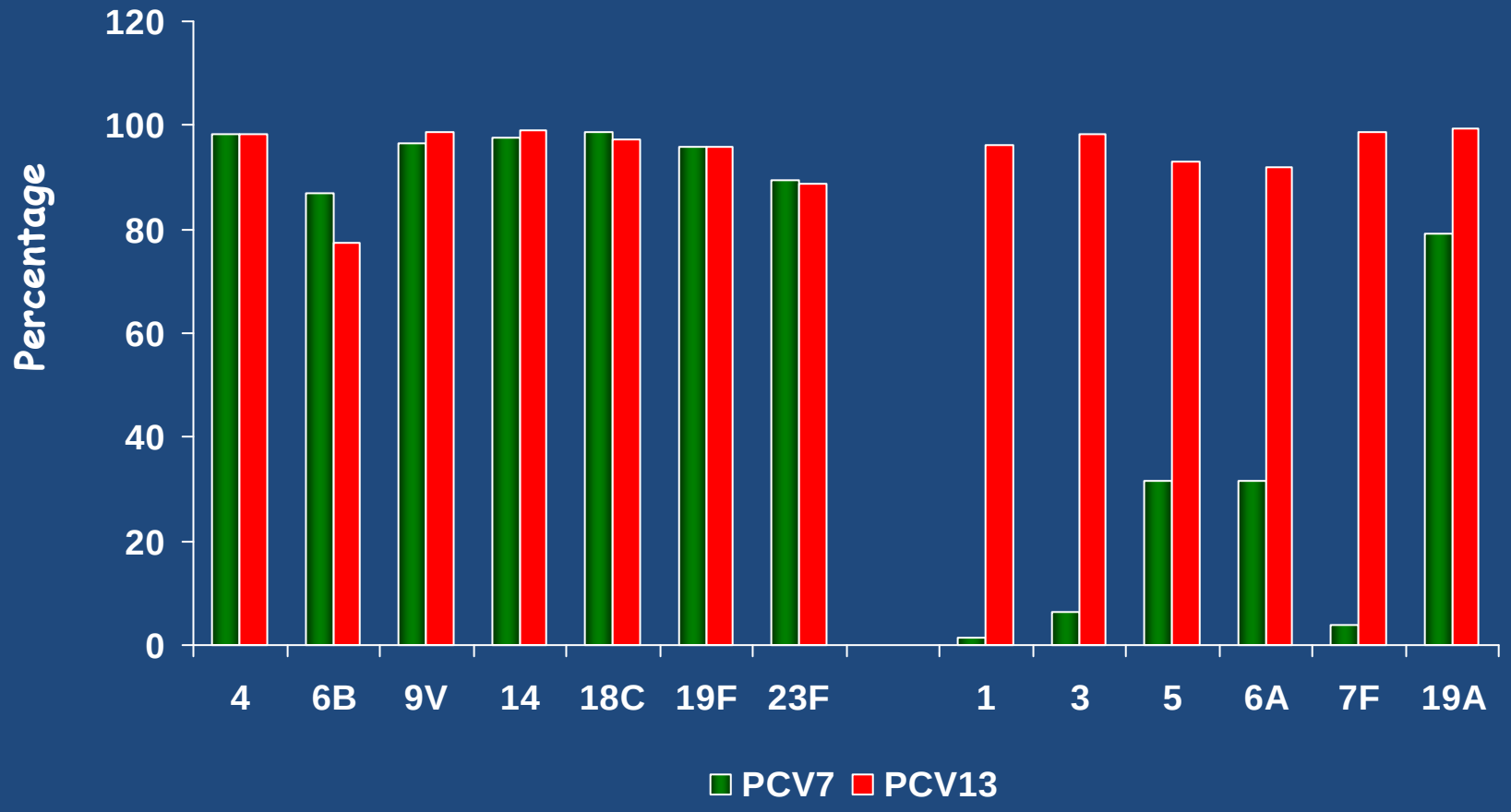
German Pivotal Non-inferiority Study Summary

In this pivotal controlled clinical study, PCV13

- Elicited IgG antibody responses by ELISA meeting all pre-defined non-inferiority criteria
  (% infants with IgG $\geq$ 0.35 μg/mL or GMC for all serotypes)
- Induced functional antibody activity
  - Comparable to PCV7 for the 7 common serotypes
  - 10-100 fold higher for the 6 additional serotypes
- Induced immunological memory suggested by higher post toddler GMCs

German Study: Post-Infant Series Immunogenicity

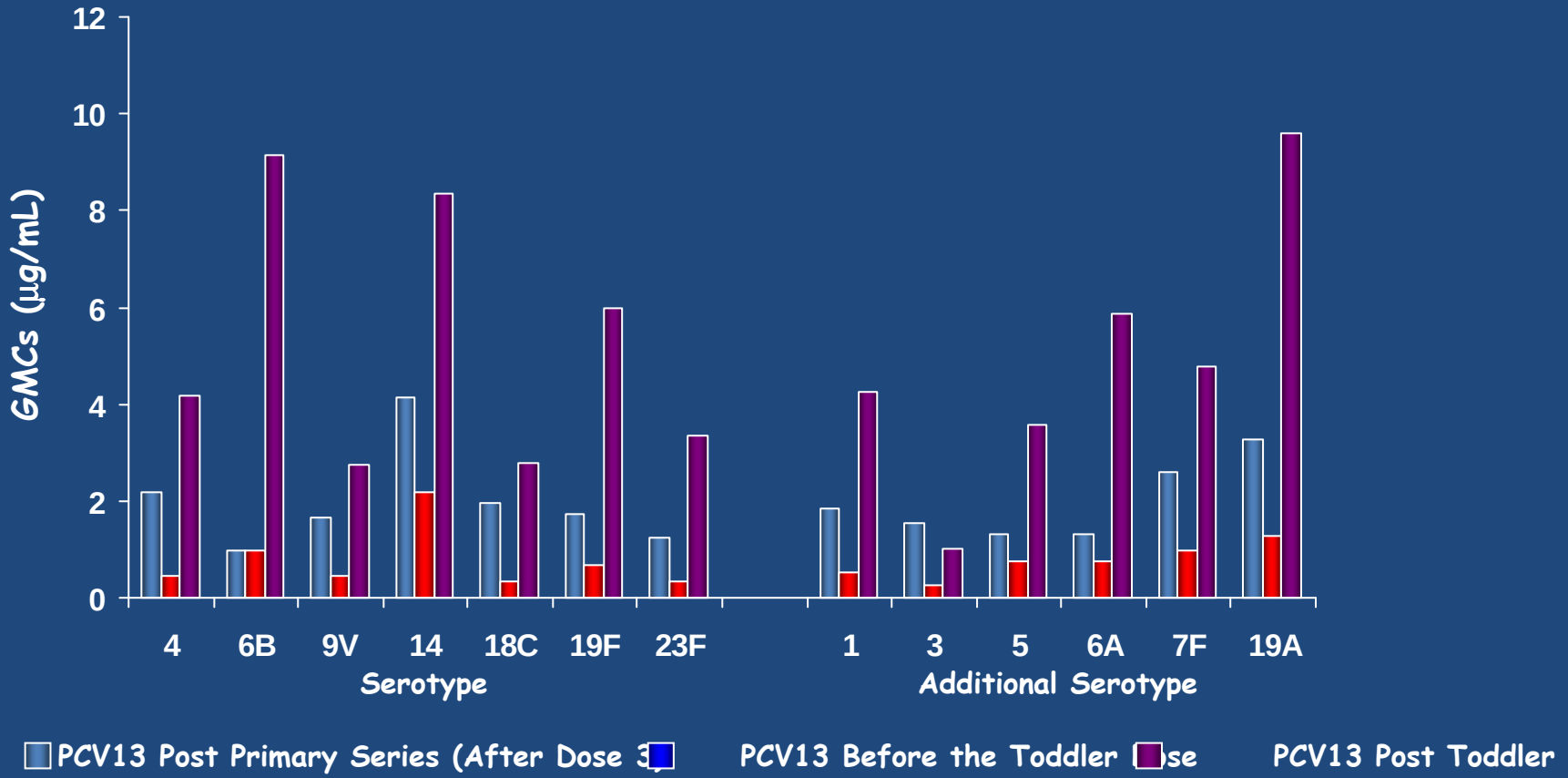
Infants Achieving a Pneumococcal IgG Antibody Concentration ≥0.35 μg/mL After Primary Series



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

German Study: ELISA IgG GMCs after Primary Series, Pre- and Post Booster Dose in PCV13 Group

Increase in IgG GMCs Post Booster Consistent With Establishment of Immunological Memory



48th ICAAC/46th IDSA 2008, Abst # 2638

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)

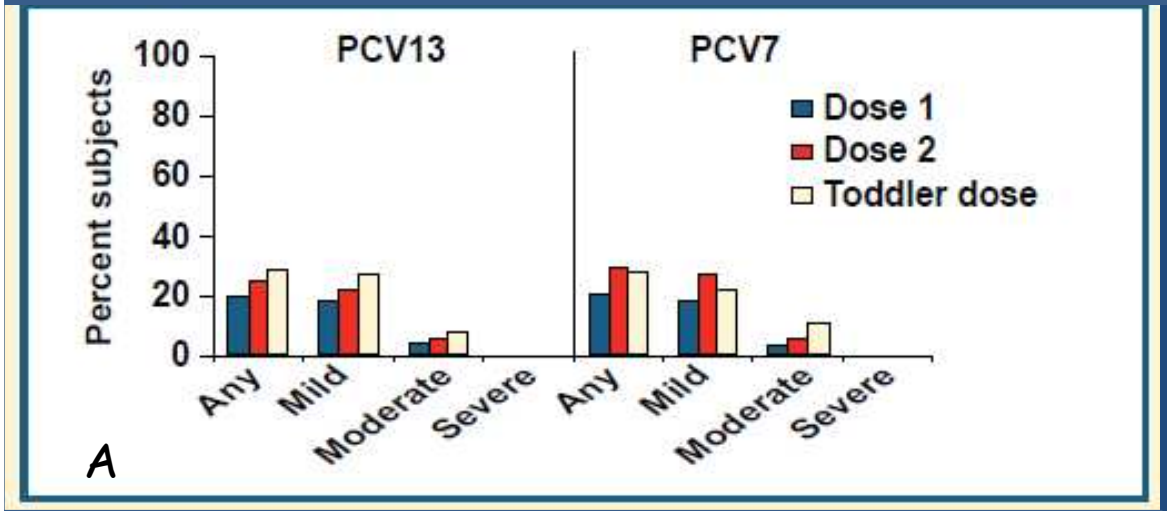
Serotype	After dose 2	After toddler dose	
	PCV13 % (95% CI) (n=261-264)	PCV13 % (95% CI) (n=232-237)	PCV7 % (95% CI) (n=240-245)
Included in PCV7			
4	96.6 (93.6, 98.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)
6B	58.4 (52.2, 64.4)	100.0 (98.5, 100.0)	100.0 (98.5, 100.0)
9V	94.7 (91.2, 97.1)	100.0 (98.4, 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)

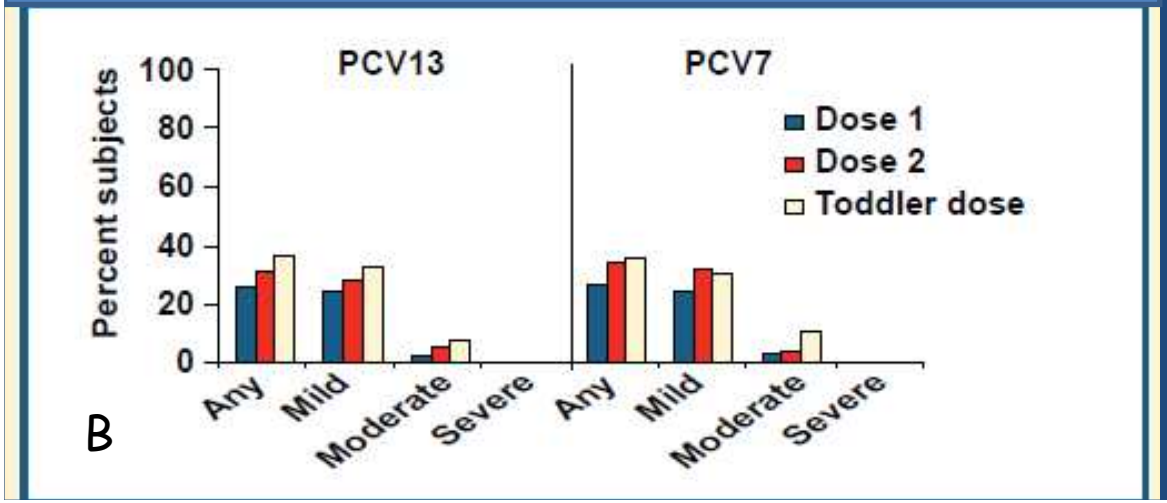
Percentage of Subjects with Prespecified Antibody Concentrations for Concomitant Vaccine Antigens 1 Month After the Infant Series and After the Toddler Dose

(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



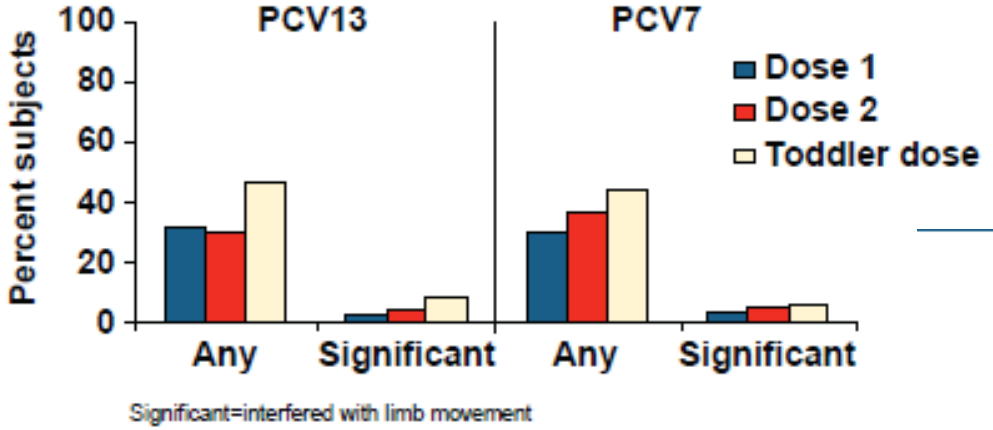


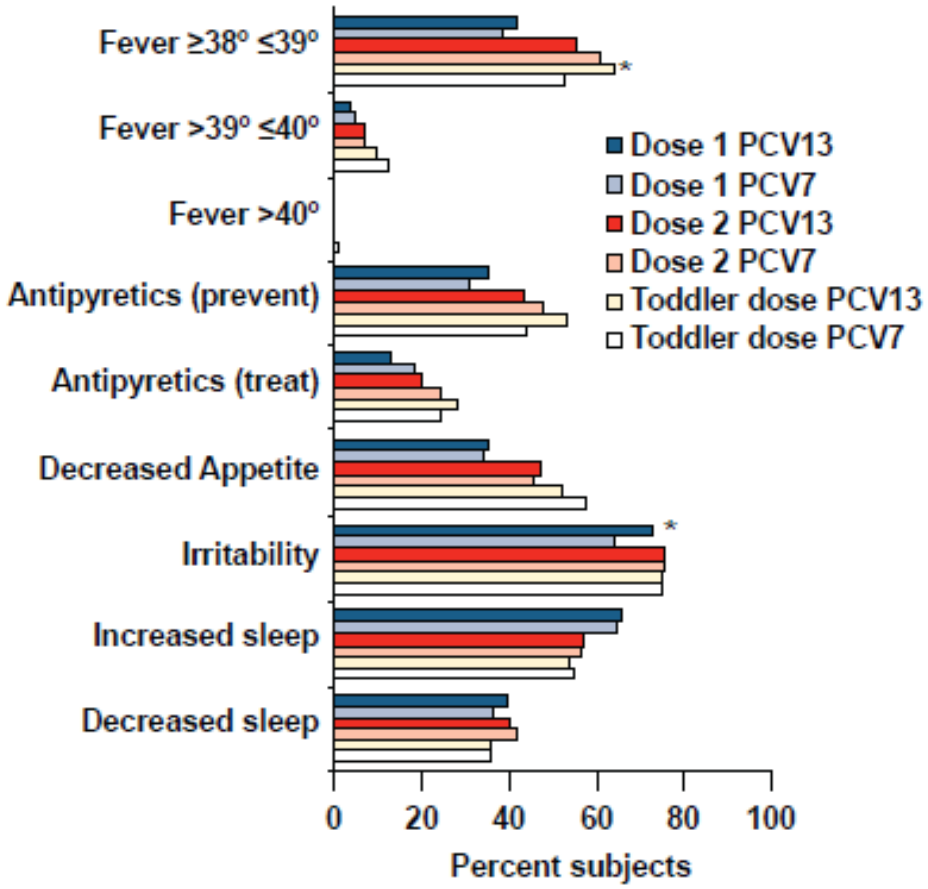
Percentuale di bambini con gonfiore (A) o arrossamento (B) in sede di iniezione di PCV-7 o PCV-13

Da Esposito et al. Espid 2009

Adverse events due to PCV-7 and PCV-13

From Esposito et al. ESPID 2009





Safety and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine Given With Routine Pediatric Vaccination to Healthy Children in France

E Grimprel,[1] F Laudat,[2] SA Baker,[3] MS Sidhu,[3] C Sekaran,[3] WC Gruber,[3] EA Emini,[3] DA Scott,[3] *on behalf of the 008 study group*[4]

[1]Hôpital Armand Trousseau, Paris, France; [2]Wyeth Vaccines Research, Paris, France; [3]Wyeth Vaccines Research, Pearl River, NY, USA; [4]Multiple investigational sites, France.

ESPID 2009

Table 2: Percent of Subjects Achieving Pneumococcal IgG Concentrations ≥0.35 µg/mL to the 7 Common Serotypes 1 Month After the Toddler Dose.

PCV7 Serotype	PCV13/PCV13 % ≥0.35 µg/mL N=230-236	PCV7/PCV13 % ≥0.35 µg/mL N=108-113	PCV7/PCV7 % ≥0.35 µg/mL N=111-127
4	100.0	99.1	100.0
6B	99.6	98.1	99.2
9V	100.0	100.0	100.0
14	99.6	99.1	100.0
18C	99.6	98.2	99.2
19F	97.9	97.3	97.6
23F	99.6	99.1	99.2

Table 3: Serum IgG and Functional (OPA) Responses to the 6 Additional Serotypes 1 Month After the Toddler Dose

Additional Serotype	PCV13/PCV13			PCV7/PCV13		
	% ≥0.35 µg/mL N=230-236	OPA N=86-88		% ≥0.35 µg/mL N=108-113	OPA N=89-90	
		% Titer ≥1:8	GMT		% Titer ≥1:8	GMT
1	100.0	100.0	126.0	95.5	98.9	61.6
3	94.8	100.0	345.3	93.8	97.8	428.9
5	100.0	100.0	244.2	90.1	97.8	131.0
6A	100.0	100.0	1346.8	89.9	98.9	891.4
7F	100.0	100.0	8126.2	100.0	100.0	17034.6
19A	100.0	98.8	804.1	100.0	97.8	1072.4

GMC = geometric mean concentration; OPA = opsonophagocytic assay; GMT = geometric mean titer