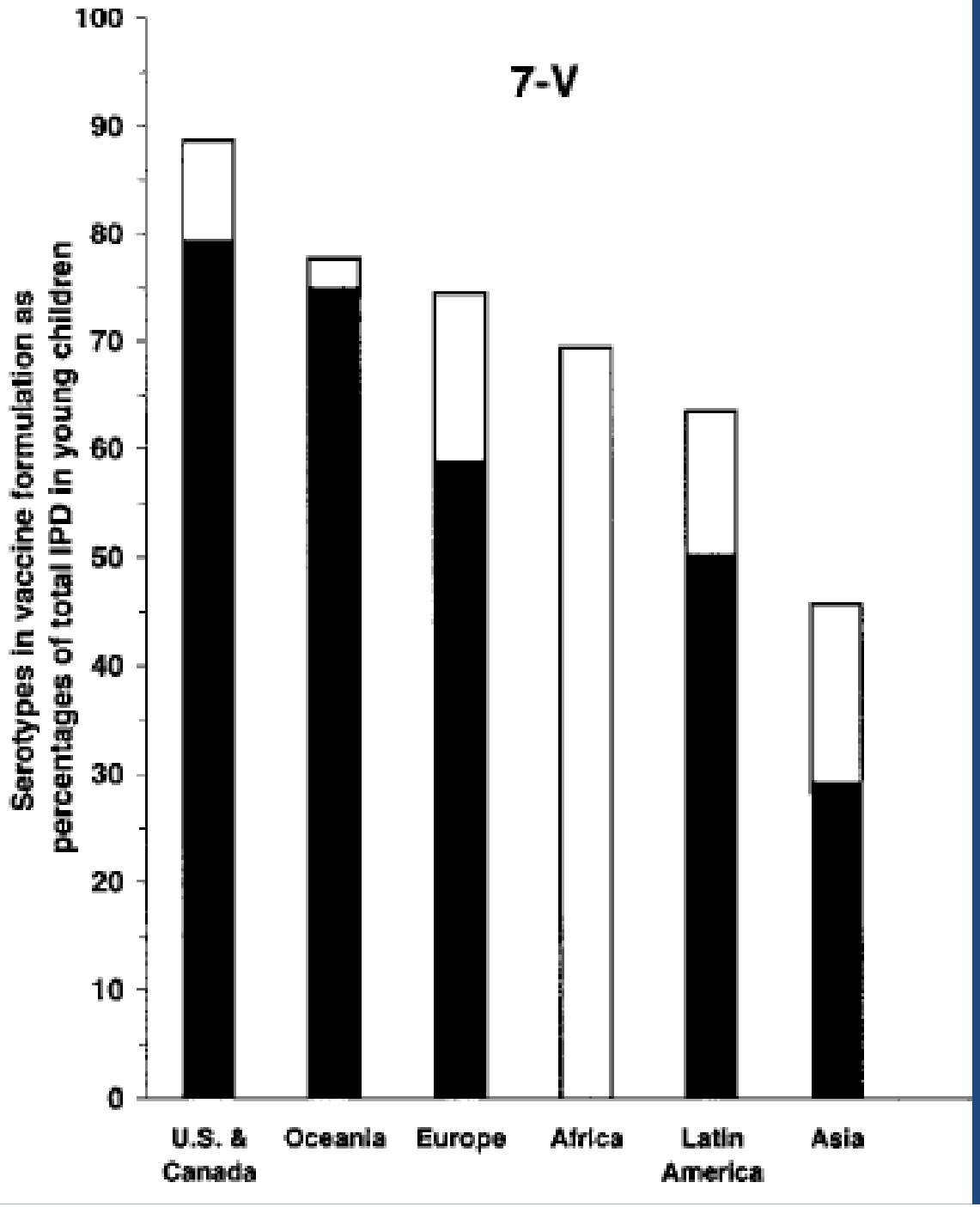
POSSIBILE IMPATTO DI PCV-13

Nicola Principi

LIMITI DI PCV-7 PRESENTI IN ORIGINE

- La composizione di PCV-7, ottima per il Nord America e l'Australia e buona per l'Europa, trascura alcuni sierotipi (1, 3, 5, 7F) responsabili di parte delle IPD diagnosticate in Sud America e in Asia
- OMA e CAP in molte aree geografiche, incluse gli U.S.A. e l' Europa, sono dovute a sierotipi di *Sp* non inclusi in PCV-7 (6A)
- Alcuni sierotipi non inclusi in PCV-7 (1 e 3, in particolare) causano CAP gravi



THEORETIC COVERAGE OFFERED BY PCV-7 AGAINST IPD IN YOUNG CHILDREN

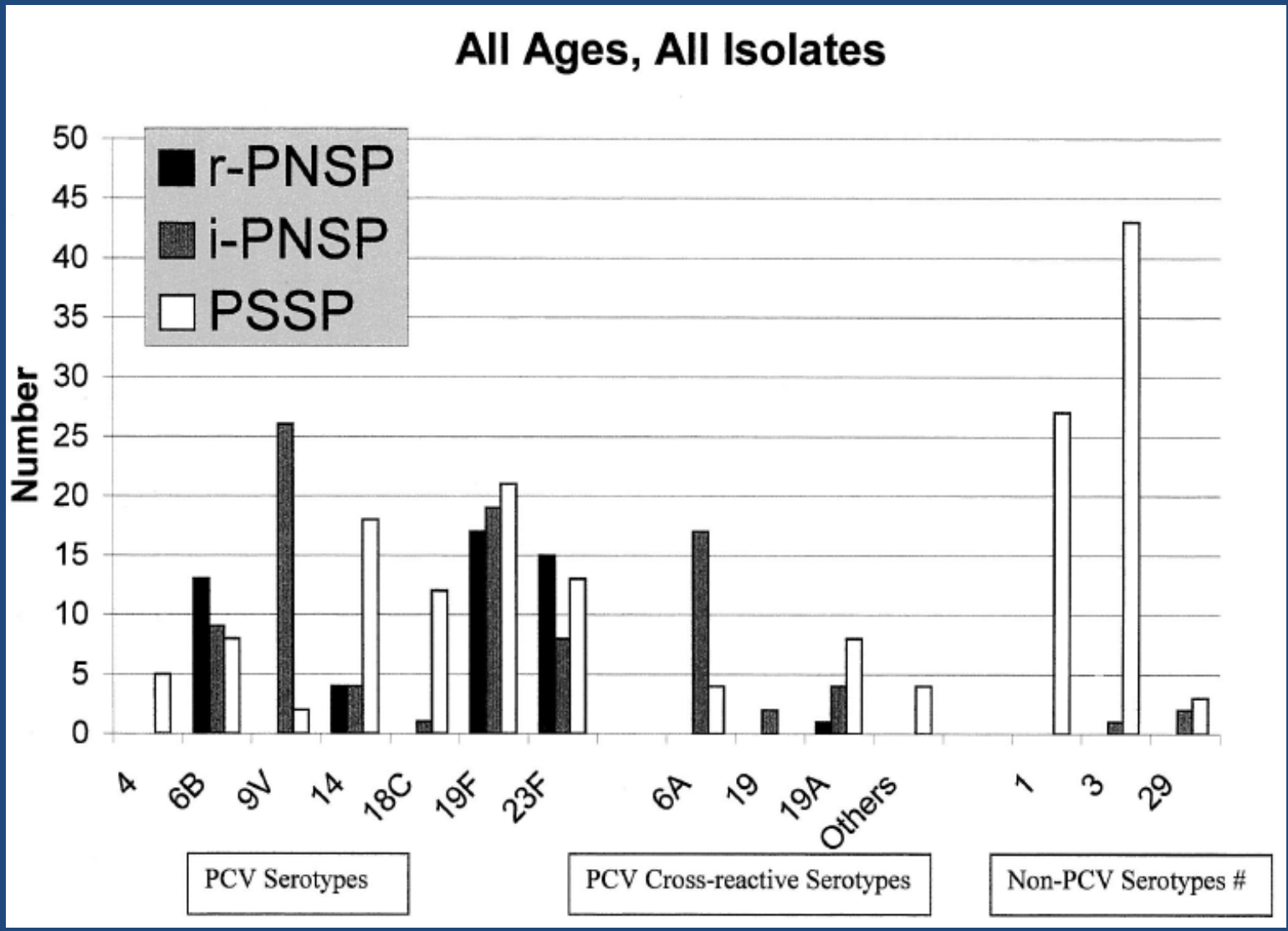
(From Hausdorff WP et al. Clin Infect Dis 2000)

Black = serotypes included in PCV-7
White = cross-reactive serotypes
Totally white column = theoretic data

1, 3, 5 and 7F are serotypes not included in PCV-7 often isolated outside USA and Australia

PNEUMOCOCCAL SEROTYPES ASSOCIATED WITH OMA IN KENTUCKY FROM 1992 TO 1998

(From Block SL et al. Pediatr Infect Dis J 2002)



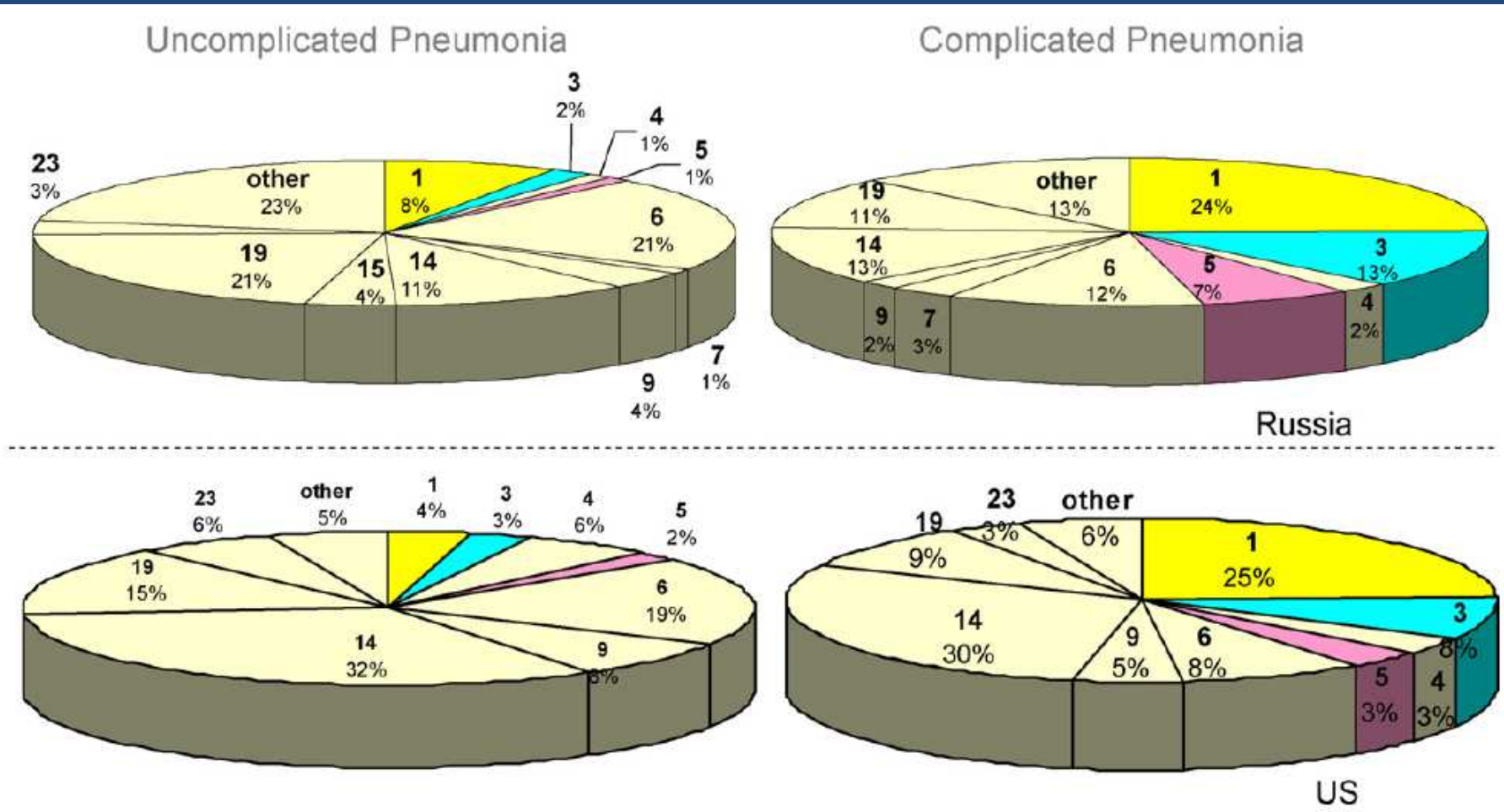
SEROTYPES ASSOCIATED WITH CAP IN 48 CHILDREN WITH PNEUMOCOCCAL CAP

(From Esposito S et al. Vaccine 2003)

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)

PNEUMOCOCCAL SEROTYPES AND CAP SEVERITY

(From Le Monnier A et al., Clin Infect Dis 2006, and Katosova LK, Zh Mikrobiol Epidemiol Immunobiol 1994)



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

- L'uso di PCV-7 ha determinato una modificazione delle caratteristiche dello stato di portatore e una significativa modificazione della 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, almeno in parte, per modificazioni spontanee delle caratteristiche di invasività e sensibilità agli antibiotici di questo sierotipo

Age, serotype[a]	Total no. of cases 1998–1999	Total no. of cases 2004	No. of cases/ 100,000 population 1998–1999	No. of cases/ 100,000 population 2004	Relative risk (95% CI)[b]	P
<5 years						
Overall	1150	297	95.2	22.6	0.2 (0.2–0.3)	<.01
PCV7[c]	953	36	78.9	2.7	0.03 (0.02–0.05)	<.01
Nonvaccine						
Overall	197	261	16.3	19.9	1.2 (1.1–1.4)	.01
3	5	13	0.4	1.0	2.5 (1.1–5.7)	.03
6A	59	12	4.8	0.9	0.2 (0.1–0.3)	<.01
7F	8	12	0.6	0.9	1.4 (0.6–2.9)	.42
12F	16	7	1.3	0.5	0.4 (0.2–0.9)	.03
15	11	31	0.9	2.4	2.7 (1.5–4.6)	<.01
19A	30	103	2.5	7.8	3.2 (2.3–4.4)	<.01
22F	7	20	0.5	1.5	2.8 (1.4–5.5)	<.01
33F	9	21	0.7	1.6	2.3 (1.2–4.4)	.01
38	6	8	0.5	0.6	1.3 (0.5–3.1)	.62
≥65 years						
Overall	1213	788	61.5	38.0	0.6 (0.6–0.7)	<.01
PCV7	681	171	34.5	8.2	0.2 (0.2–0.3)	<.01
Nonvaccine						
Overall	532	617	27.0	29.8	1.1 (1.0–1.2)	.05
3	72	84	3.6	4.1	1.1 (0.9–1.5)	.4
6A	77	67	3.9	3.3	0.8 (0.6–1.1)	.21
7F	24	21	1.2	1.0	0.8 (0.5–1.4)	.51
9N	14	8	0.7	0.4	0.5 (0.3–1.2)	.13
11A	30	33	1.5	1.6	1.1 (0.7–1.6)	.8
12F	42	15	2.1	0.7	0.3 (0.2–0.6)	<.01
15	16	29	0.8	1.4	1.8 (1.1–3.0)	.02
16F	9	19	0.4	0.9	2.1 (1.1–4.1)	.02
19A	44	83	2.2	4.0	1.8 (1.3–2.4)	<.01
22F	54	72	2.7	3.5	1.3 (0.9–1.7)	.12
23A	8	34	0.4	1.6	4.0 (2.2–7.2)	<.01
31	11	11	0.5	0.5	1.0 (0.5–2.1)	.94
33F	12	30	0.6	1.5	2.5 (1.5–4.3)	<.01
35	20	43	1.0	2.1	2.0 (1.3–3.1)	<.01
38	11	14	0.6	0.7	1.1 (0.6–2.3)	.64

Differences in the role of different pneumococcal serotypes in causing IPD in USA before and after PCV-7 introduction

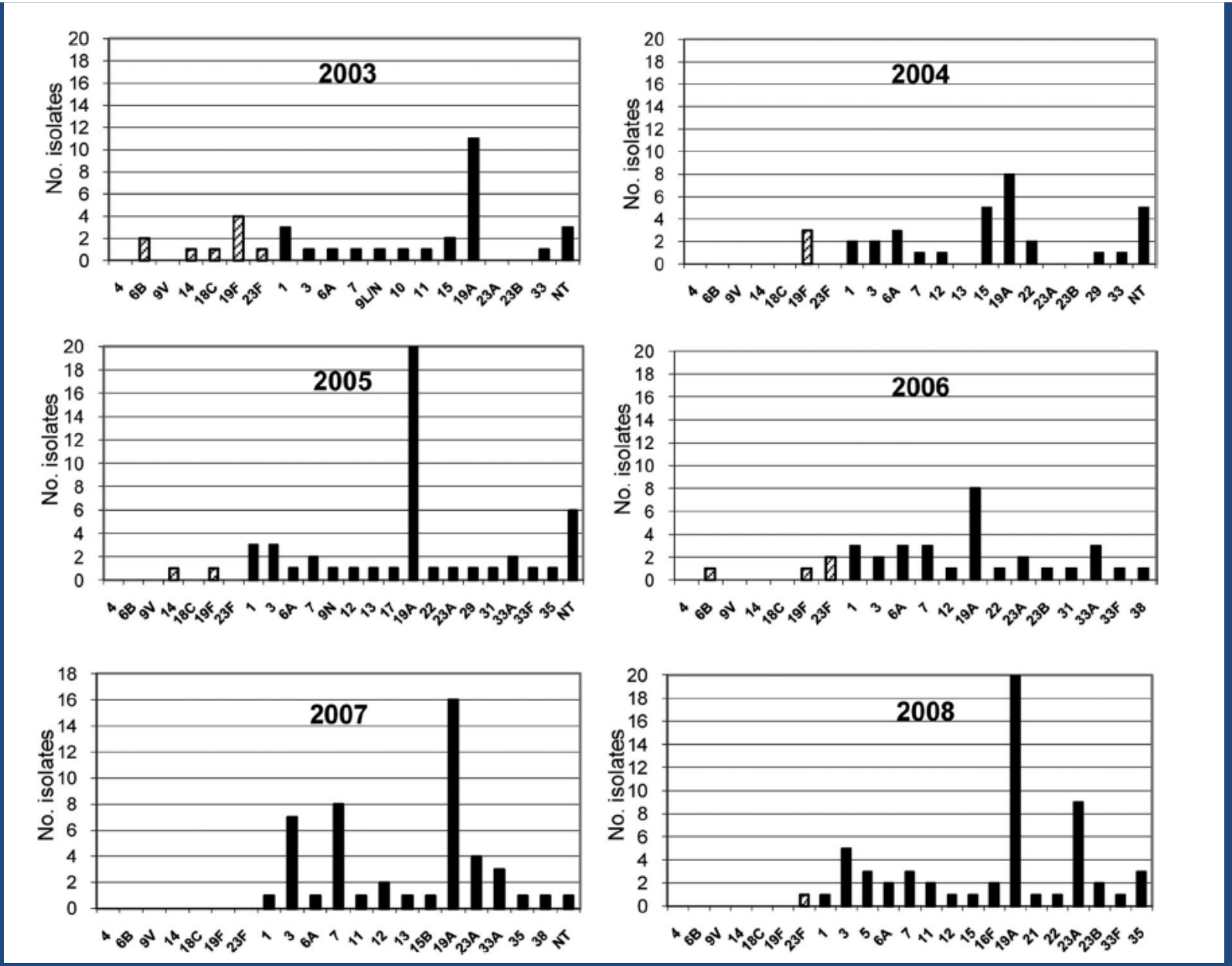
PNEUMOCOCCAL SEROTYPES IN PLEURAL EFFUSION BEFORE AND AFTER PCV-7 INTRODUCTION

(From 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.



Serotypes isolated from IPDs in Dallas

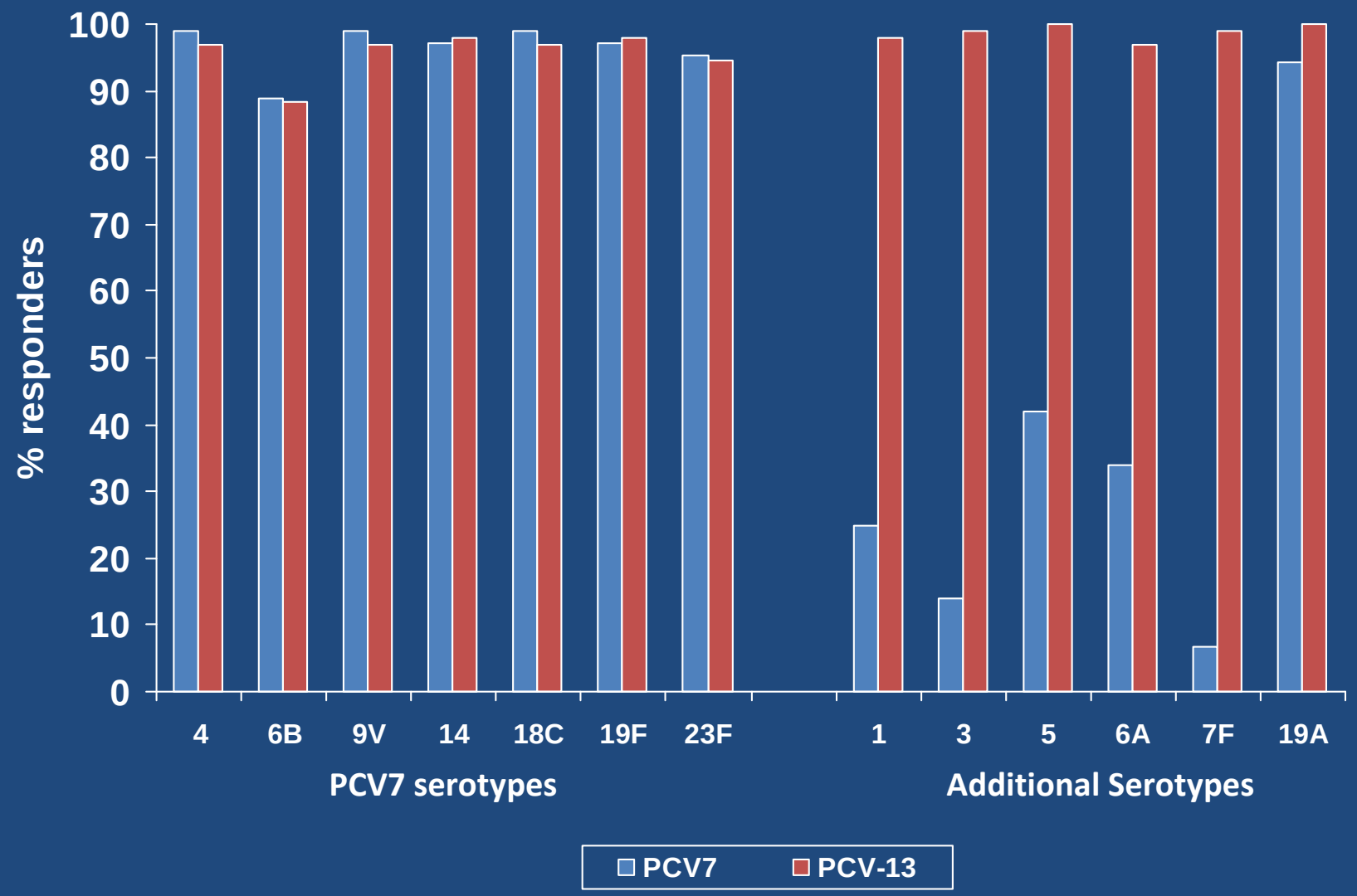
(from Techasaensiri C, et al. Pediatr Infect Dis J 2010)

Serotype Composition of new pneumococcal vaccines

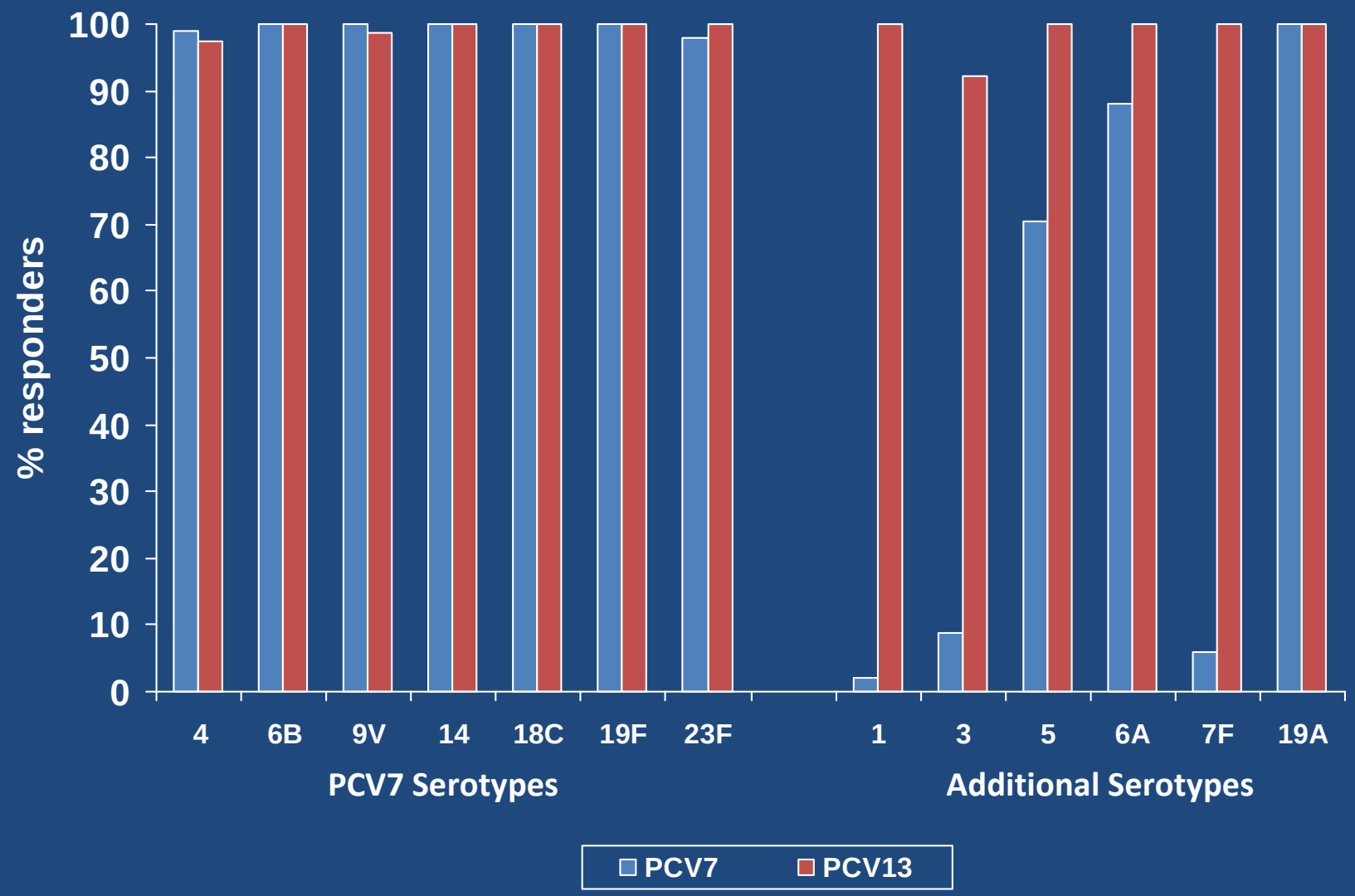
PCV-7	4	6B	9V	14	18C	19F	23F						
PCV-10	4	6B	9V	14	18C	19F	23F	1	5	7F			
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A

PCV13 contains the same carrier protein – CRM_{197}

Phase 1-2 Study: Percentage of Subjects Achieving Antibody Concentration of ≥0.35 µg /mL: Post-primary Series



Phase 1-2 Study: Percentage of Subjects Achieving Antibody Concentration of ≥0.35 μg/mL: Post-booster Dose



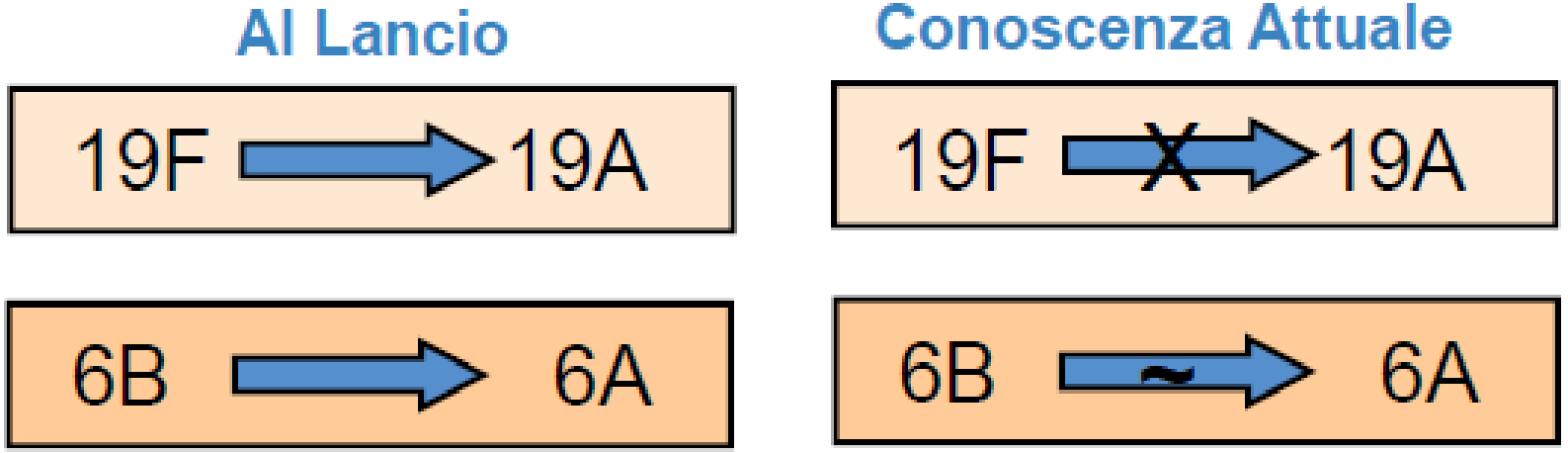
Percentage of Subjects With Pneumococcal IgG Antibody Concentration ≥0.35 µg/mL 1 Month After the Infant Series and After the Toddler Dose

(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)

La Cross-Protezione non è dimostrata

Deduzioni di Cross-Protezione Basate sulle IgG ELISA



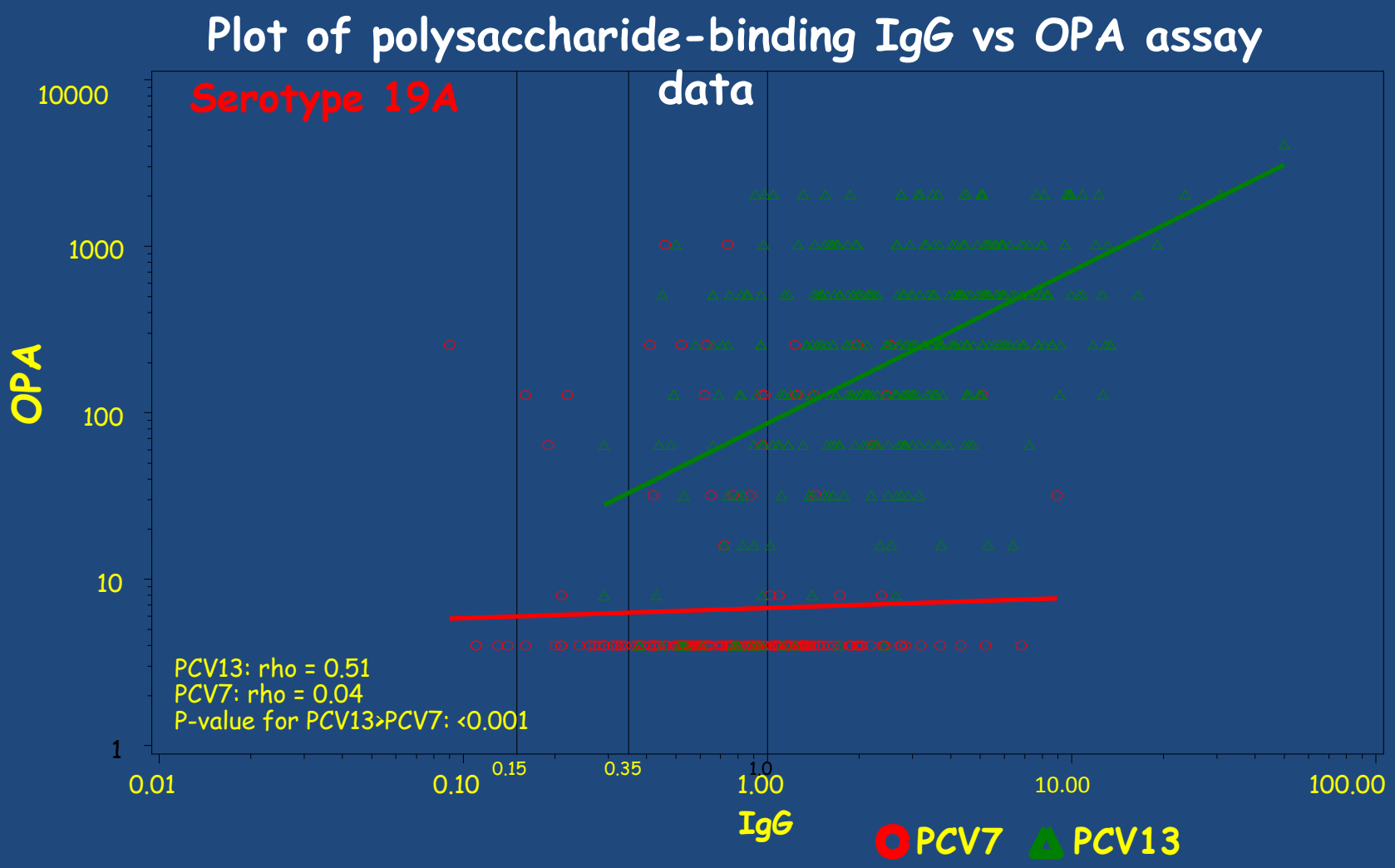
Nessuna protezione di sierogruppo per il 19A, parziale per il 6A

Revisione degli stampati di Prevenar per rispecchiare i dati clinici

La protezione diretta (sierotipo-specifica) è la strategia preferibile

La cross-protezione può essere stabilita solo tramite l'effectiveness clinica del vaccino utilizzato in un programma nazionale di immunizzazione

Additional Serotype: 19A



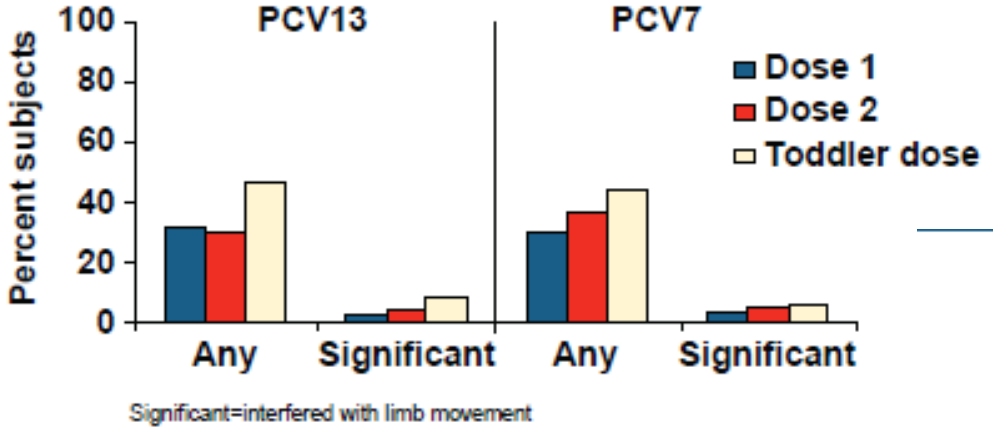
Kieninger D.M. et al, 48th ICAAC 2008

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)

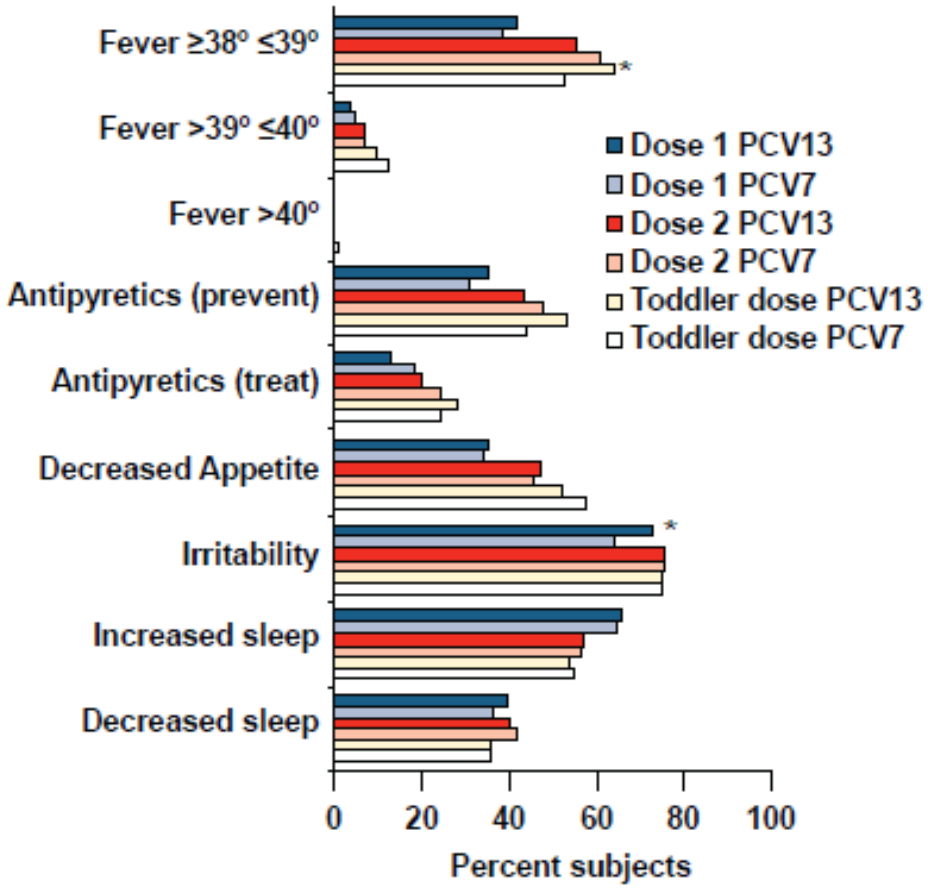
Vaccine antigen		Comparison level	After dose 2			After toddler dose		
			PCV13, % (n=155-273)	PCV7, % (n=214-276)	*Difference, % (95% CI%)	PCV13, % (n=125-252)	PCV7, % (n=96-255)	*Difference, % (95% CI)
Hepatitis B		10.0 mIU/mL	93.8	93.1	0.7 (-3.6, 5.0)	98.4	98.8	-0.4 (-3.0, 2.0)
Hib (PRP)		0.15 µg/mL	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



From Esposito et al. Clin Vacc Immunol 2010

EVENTI AVVERSI SISTEMICI DA PCV-7 E DA PCV-13



CAP batteriemica *da Streptococcus pneumoniae* in bambini italiani (I)

Centri coinvolti:

- Clinica Pediatrica I – Milano (Principi – Esposito)
- Clinica Pediatrica – Novara (Bona)
- Clinica Pediatrica – Padova(Da Dalt)
- Ospedale Gaslini – Genova (Rossi)
- Ospedale Bambino Gesù – Roma (Tozzi)

CAP batteriemica *da Streptococcus pneumoniae* in bambini italiani (II)

- Casi arruolati = 510
- Positivi per pneumococco (colture e/o PCR) = 72 (14.1%)
- Positivi con complicanze 19 (26.3%)
- Forme clinicamente gravi (Sat $O_2 \leq 92\%$) = 6 (8.3%)

SIEROTIPI ASSOCIATI A CAP BATTERIEMICA

Sierotipo	Tutti i casi (n=72)	Casi non complicati (N=53)	Casi complicati (n=19)
19A	17 (23.6%)	12 (22.6%)	6 (31.6%)
14	10 (13.9%)	9 (17.3%)	1 (5.3%)
4	5 (6.9%)	4 (7.7%)	1 (5.3%)
3	4 (5.6%)	2 (3.8%)	2 (10.5%)
7F	3 (4.2%)	2 (3.8%)	1 (5.3%)
19F	3 (4.2%)	3 (5.8%)	----------
1	1 (1.4%)	----------	1 (5.3%)
6A	1 (1.4%)	1 (1.9%)	----------
6B	1 (1.4%)	1 (1.9%)	----------
9V	1 (1.4%)	1 (1.9%)	----------
23F	1 (1.4%)	----------	----------
Diversi da PCV13	19 (26.4%)	13 (25.0%)	6 (31.6%)
Non tipizzabili	6 (8.3%)	5 (9.6%)	1 (5.3%)

COPERTURA ASSICURATA DAI VACCINI PNEUMOCOCCICI CONIUGATI CONTRO LE CAP BATTERIEMICHE IN ITALIA

- PCV-7: 29.1% (forme complicate 11.1%)
- PCV10. 37.9% (forme complicate 16.6%)
- PCV13 :71.2% (forme complicate 72.9%)

Estimated disease incidence and fatality rates from pneumococcal infections in the USA

(from Rubin JL et al. Vaccine 2010)

Parameter	Age group (years)									
	<1	1–<2	2–<3	3–<4	4–<5	5–17	18–34	35–49	50–64	65+
Annual baseline (2007) incidence rates/100,000[a]										
Simple otitis media (all-cause)[b]	88,523	98,440	64,856	52,272	40,656	–	–	–	–	–
Complex otitis media (all-cause)[b]	11,573	8946	3249	2662	2078					
Clinically diagnosed outpatient pneumonia (all-cause)[c]	5839	10,055	8746	5223	4570	1628	522	748	1820	4935
Clinically diagnosed inpatient pneumonia (all-cause)[d]	810	810	390	390	390	74.3	77.9	161.3	328.1	2162.7
IPD[e]	40.15	34.72	20.13	13.09	9.34	2.42	4.34	11.46	19.82	37.85
Percent of invasive disease that is meningitis[f]	9.5%	9.5%	6.9%	6.9%	6.9%	11.1%	10.5%	8.7%	6.9%	6.3%
Percent of meningitis that results in deafness[g]	13%	13%	13%	13%	13%	6%	13%	13%	13%	13%
Percent of meningitis that results in disability[g]	7%	7%	7%	7%	7%	5%	7%	7%	7%	7%
Case-fatality rates										
Meningitis[h]	6.9%	6.9%	4.0%	4.0%	4.0%	10.0%	10.0%	11.0%	11.4%	23.8%
Bacteremia[i]	1.8%	0.1%	0.4%	0.4%	0.4%	4.2%	4.7%	8.0%	11.3%	15.7%
Clinically diagnosed all-cause inpatient pneumonia[j]	0.8%	0.1%	0.2%	0.2%	0.2%	0.3%	0.7%	1.7%	2.5%	6.3%

Estimated direct and indirect effects of PCV13

(from Rubin JL et al. Vaccine 2010)

Parameter	<1[a]	1–<2	2–<5[b]	5–17	18–34	35–49	50–64	65+
Direct effects (% reduction in disease at time of vaccination)								
IPD[c]	39.8%	59.8%	67.6%	–	–	–	–	–
All-cause outpatient pneumonia[d]	3.0%	4.6%	5.2%	–	–	–	–	–
All-cause hospitalized pneumonia[e]	12.9%	19.4%	22.0%	–	–	–	–	–
All-cause simple AOM[f]	4.0%	5.9%	6.7%	–	–	–	–	–
All-cause complex AOM[g]	6.1%	9.1%	10.3%	–	–	–	–	–
Indirect effects (% reduction in disease)								
IPD[h]	43.9%	21.5%	39.4%	34.4%	37.1%	31.5%	24.5%	27.4%
Non-IPD[i]								
All-cause outpatient pneumonia[j]	6.2%	6.2%	0.0%	4.3%	4.5%	5.8%	3.2%	3.4%
All-cause inpatient pneumonia	22.5%	22.5%	0.0%	8.4%	10.3%	9.0%	7.5%	6.8%
All-cause simple AOM	14.4%	0.0%	0.0%	–	–	–	–	–
All-cause complex AOM	15.1%	15.1%	0.0%	–	–	–	–	–

PCV13 vs. PCV7	
Cases (avoided)	
IPD	(106,381)
Hospitalized pneumonia	(947,989)
Non-hospitalized pneumonia	(1,934,407)
Otitis media	(16,298,782)
Deaths (avoided)	(40,519)
Costs (savings) in millions	
Medical	($11,433)
Non-medical	($3,610)
Vaccination program	$3,432
Total	($11,610)
QALYs gained	499,177
Life-years saved	501,921
Cost-effectiveness in dollars	
Cost/QALY gained	Cost-saving
Cost/LY saved	Cost-saving
Cost (savings) per child vaccinated[b] in dollars	($294)

Clinical and economical impact of PCV13 vs PCV7

(from Rubin JL et al. Vaccine 2010)

	16–23	16–35	16–59
Cases (avoided)			
IPD	(1034)	(1996)	(2929)
Hospitalized pneumonia	(9686)	(19,857)	(32,308)
Non-hospitalized pneumonia	(33,781)	(73,150)	(115,610)
Otitis media	(418,080)	(837,190)	(1,197,581
Deaths (avoided)	(20)	(45)	(82)
Costs (savings) in millions			
Medical	($148)	($293)	($445)
Non-medical	($105)	($209)	($305)
Vaccination program	$262	$653	$1,426
Cost(savings)/additional child			
Vaccinated[a]	$4	$25	$51
QALYsgained	2931	6020	9178
Totals by catch-up program			
Total cost (savings) in millions			
16–23	$10	–	–
16–35	–	$151	–
16–59	–	–	$675
Cost/QALY gained			
16–23	$3,399	–	–
16–35	–	$25,052	–
16–59	–	–	$73,564

Estimated advantages of a catch-up program with PCV13

(from Rubin JL et al. Vaccine 2010)