LA POSIZIONE OMS SUL VACCINO ANTIPNEUMOCOCCICO EPTAVALENTE CONIUGATO

Nicola Principi

Istituto di Pediatria – Università di Milano

ondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elen

Weekly epidemiological record
Relevé épidémiologique hebdomadaire

23 MARCH 2007, 82nd YEAR / 23 MARS 2007, 82e ANNÉE

No. 12, 2007, 82, 93–104

http://www.who.int/wer

ontents

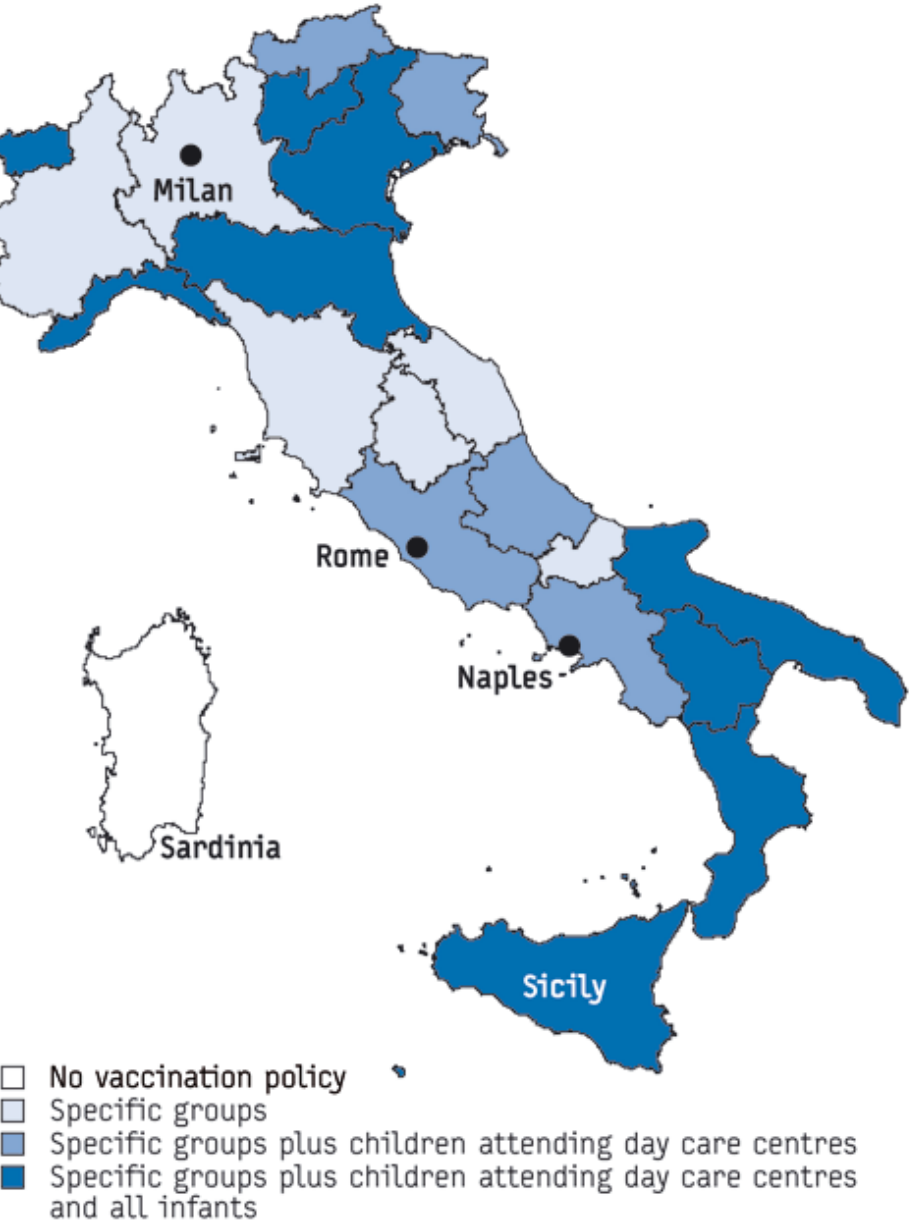
Pneumococcal conjugate vaccine for childhood immunization – WHO position paper

Vaccin antipneumococcique conjugué pour la vaccination infantile – note d'information de l'OMS

ecognizing the heavy burden of pneumococcal dis-
se occurring in young children and the safety and
ficacy of PCV-7 in this age group, WHO considers
at it should be a priority to include this vaccine in
tional immunization programmes, particularly
countries where mortality among children aged
years is >50/1000 live births or where >50 000 chil-
en die annually.

Reconnaissant l'ampleur de la charge de morbidité due aux
pneumococcies chez les jeunes enfants d'une part, et l'inno
cuité et l'efficacité du vaccin antipneumococcique conjugué 7
valent dans cette tranche d'âges d'autre part, l'OMS considère
comme prioritaire d'inclure ce vaccin dans les programme
nationaux de vaccination, notamment dans les pays où la mor
talité chez les moins de 5 ans est supérieure à 50 pour 1000 en
fants nés vivants et dans ceux où la moralité infantile annuelle
est supérieure à 50 000.

ian regions recommending free of charge PCV by target
pulation, as of May 2006



Vaccinazione antipneumo nelle diverse Regioni Italiane

PCV-7: ACQUISIZIONI RECENTI

- PCV-7 è efficace nella prevenzione delle infezioni invasive (IPD) e della patologia di superficie e l'effetto della sua somministrazione al bambino si estende a tutta la popolazione (herd immunity).
- L'herd immunity è estremamente rilevante, tanto che il numero assoluto di IPD prevenute è maggiore nei non vaccinati che nei vaccinati
- L'uso di PCV-7 è accompagnato, almeno in certe realtà, da un aumento delle IPD da sierotipi non contenuti nel vaccino
- Il rimpiazzo riduce solo in modo marginale i vantaggi della vaccinazione. Non è certo che questo fenomeno sia realmente dovuto all'uso del vaccino
- PCV-7 può essere somministrato con lo schema italiano a 3 dosi senza perdita di immunogenicità e di efficacia

PNC-CRM7:EFFICACIA NELLE PATOLOGIE INVASIVE

	Pnc-CRM7	Controlli	Efficacia (%)	95% CI
No. di bambini	18,927	18,941		
Casi				
Per protocol*	1	39	97.4	82.7-99.9
Intent to treat†	3	49	93.9	79.6-98.5
Tutti i sierotipi				
Intent to treat†	6	55	89.1	73.7-95.8 (p <0.001)

* Dopo 3 dosi.

† Dopo ciascun numero di dosi.

Black S, Shinefield H et al. *Pediatr Infect Dis J.* 2000;19:187-195

PNC-CRM7:EFFICACIA NELLE PATOLOGIE INVASIVE

SIEROTIPI	"Split" dei casi (controlli:vaccino)	EFFICACIA	95% LL di CI
19F	13:2	84.6	36.1
14	11:0	100	60.2
18C	9:0	100	49.3
6B	7:1	85.7	-11.2
23F	6:0	100	15
9V	3:0	100	-142
4	0:0	—	—

Black S, Shinefield H et al. *Pediatr Infect Dis J*. 2000;19:187-195.

PCV-7: EFFICACIA NELLE POLMONITI

OUTCOME (First Episode)	ITT (%)	PP
ANY PNEUMONIA VISIT	6; p=0.13	4.3; p=0.27
X-RAY ALSO OBTAINED	8.9; p= 0.03	9.8; p=0.047
POSITIVE X-RAY (ALL AGES)	22.7; p=0.002	23.4; p=0.014
POSITIVE (< 2 YRS)	17.7; p=0.009	20.5; p=0.015
POSITIVE (> 2 YRS)	-6.1; p=0.70	9.1; p=0.72

From Black S eta l. ESPID 2002

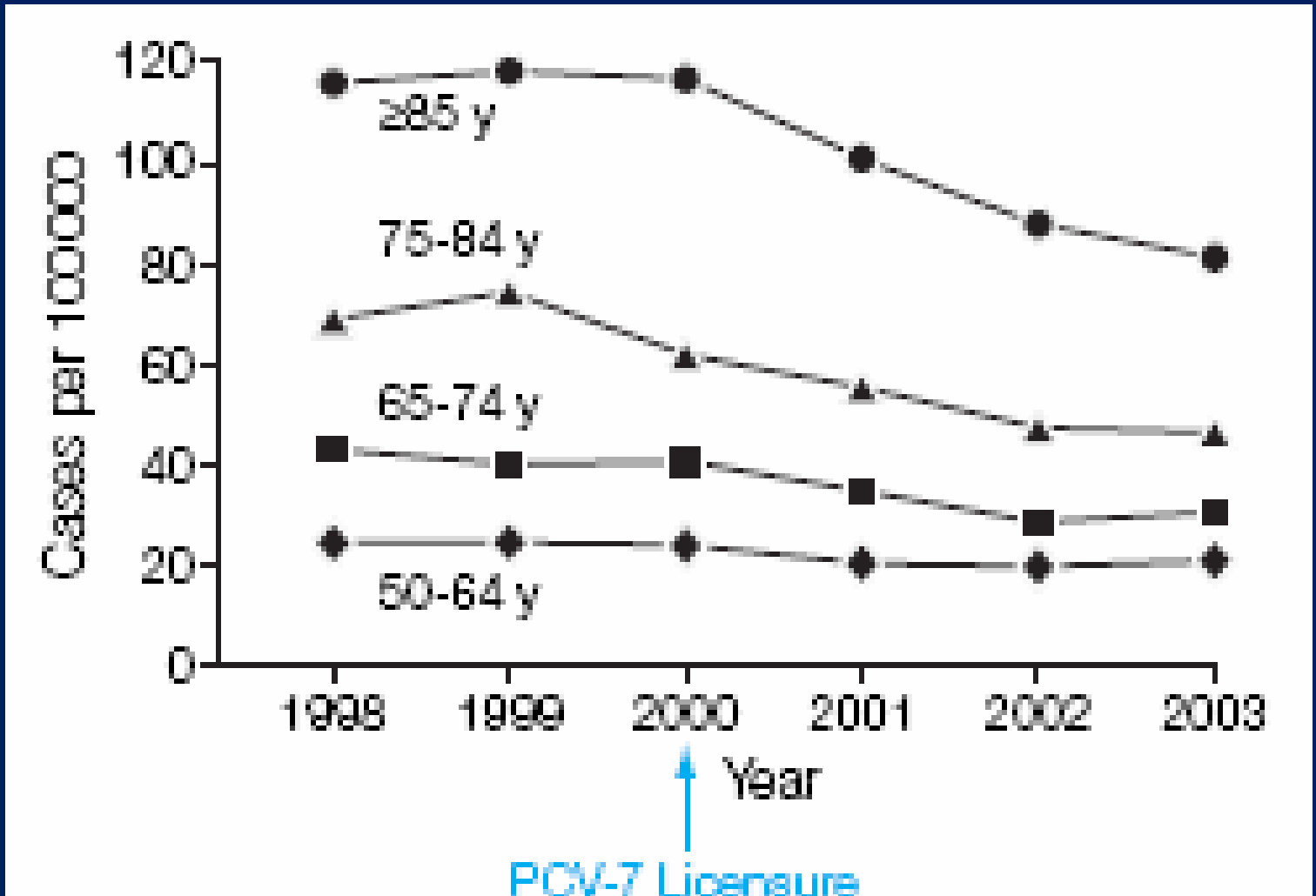
PCV-7: L'ESPERIENZA FINLANDESE SULLE AOM

Parametro	Efficacia (95% CI)
Tutti gli episodi	6% (-4, 16)
OM pneumococciche confermate (tutti i sierotipi)	34% (21, 45)
OM pneumococciche confermate (sierotipi vaccino)	57% (44, 67)

Eskola et al. N Engl J Med,2001

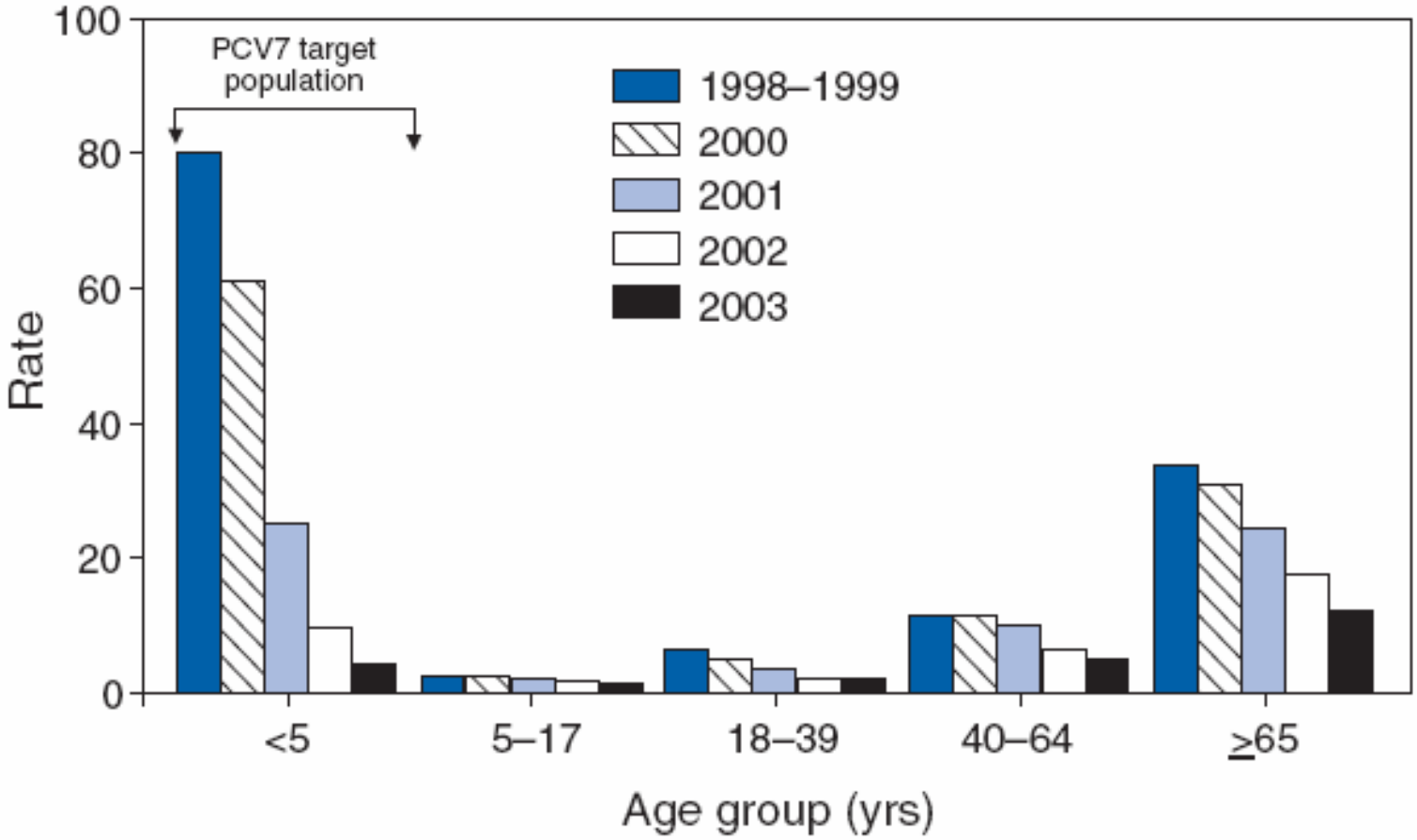
INCIDENZA DI IPD NEGLI ADULTI - ANZIANI DOPO L'INTRODUZIONE DI PCV-7 NEGLI U.S.A.

(da Lexau CA et al, Jama 2005)



FREQUENZA DI IPD DA VTP NEGLI U.S.A.

(da MMWR 2005)



* Per 100,000 population.

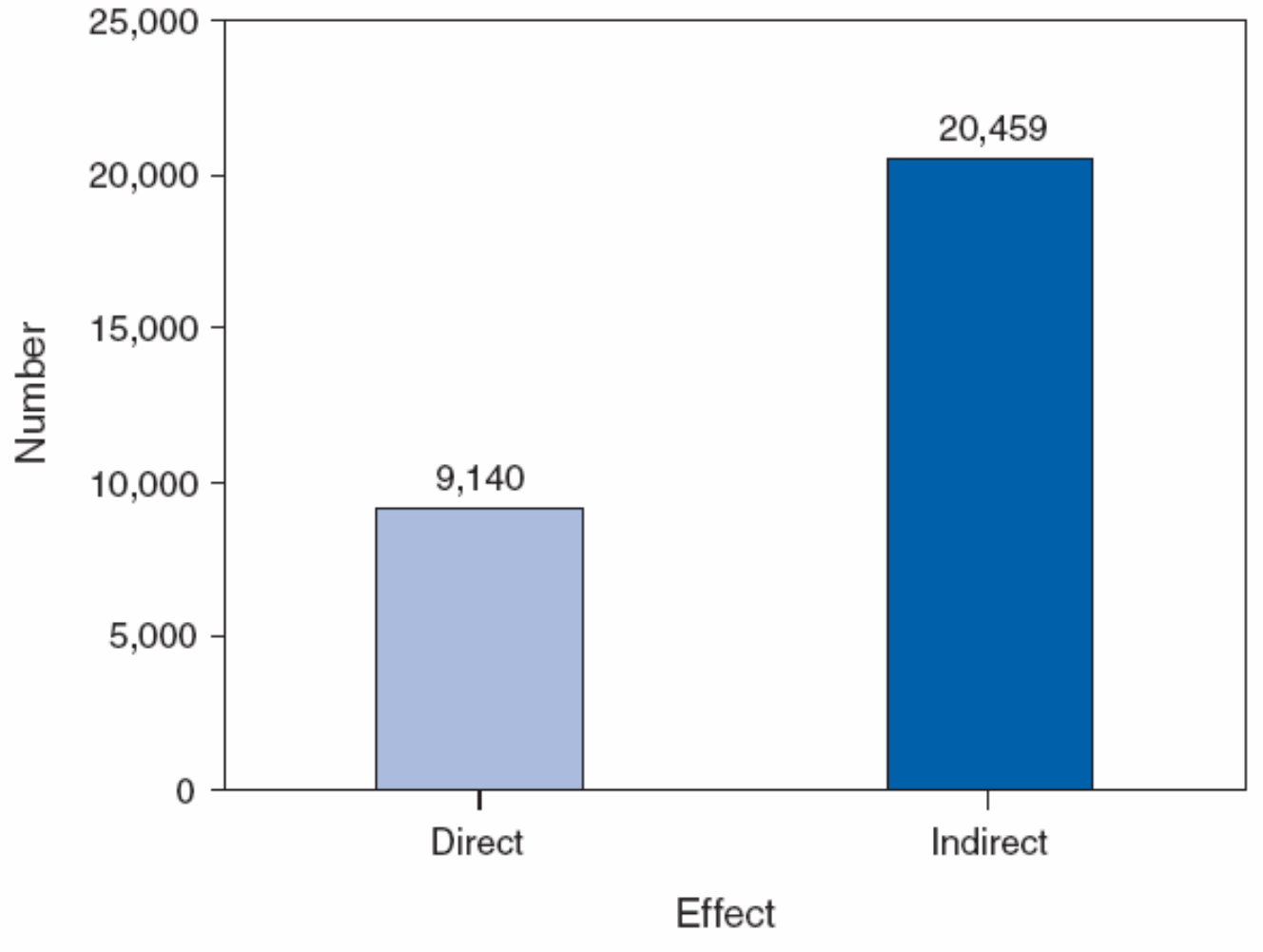
IMPATTO DI PCV-7 SU IPD NEGLI U.S.A.

(da MMWR, 2005)

Age group (yrs)	Serotype category*	1998–1999 average projected no. of cases†	2003 projected no. of cases†	Change in annual projected no. of cases
<5				
	Vaccine	14,293	876	-13,417
	Nonvaccine	2,947	3,578	631
	Total	17,240	4,454	-12,786
5–17				
	Vaccine	1,195	569	-626
	Nonvaccine	880	824	-56
	Total	2,075	1,393	-682
18–39				
	Vaccine	5,023	1,610	-3,413
	Nonvaccine	3,419	3,407	-12
	Total	8,442	5,017	-3,425
40–64				
	Vaccine	8,945	4,167	-4,778
	Nonvaccine	7,545	10,237	2,692
	Total	16,490	14,404	-2,086
≥65				
	Vaccine	11,595	4,230	-7,365
	Nonvaccine	9,169	10,635	1,466
	Total	20,764	14,865	-5,899
All ages				
	Vaccine	41,051	11,452	-29,599
	Nonvaccine	23,960	28,681	4,721

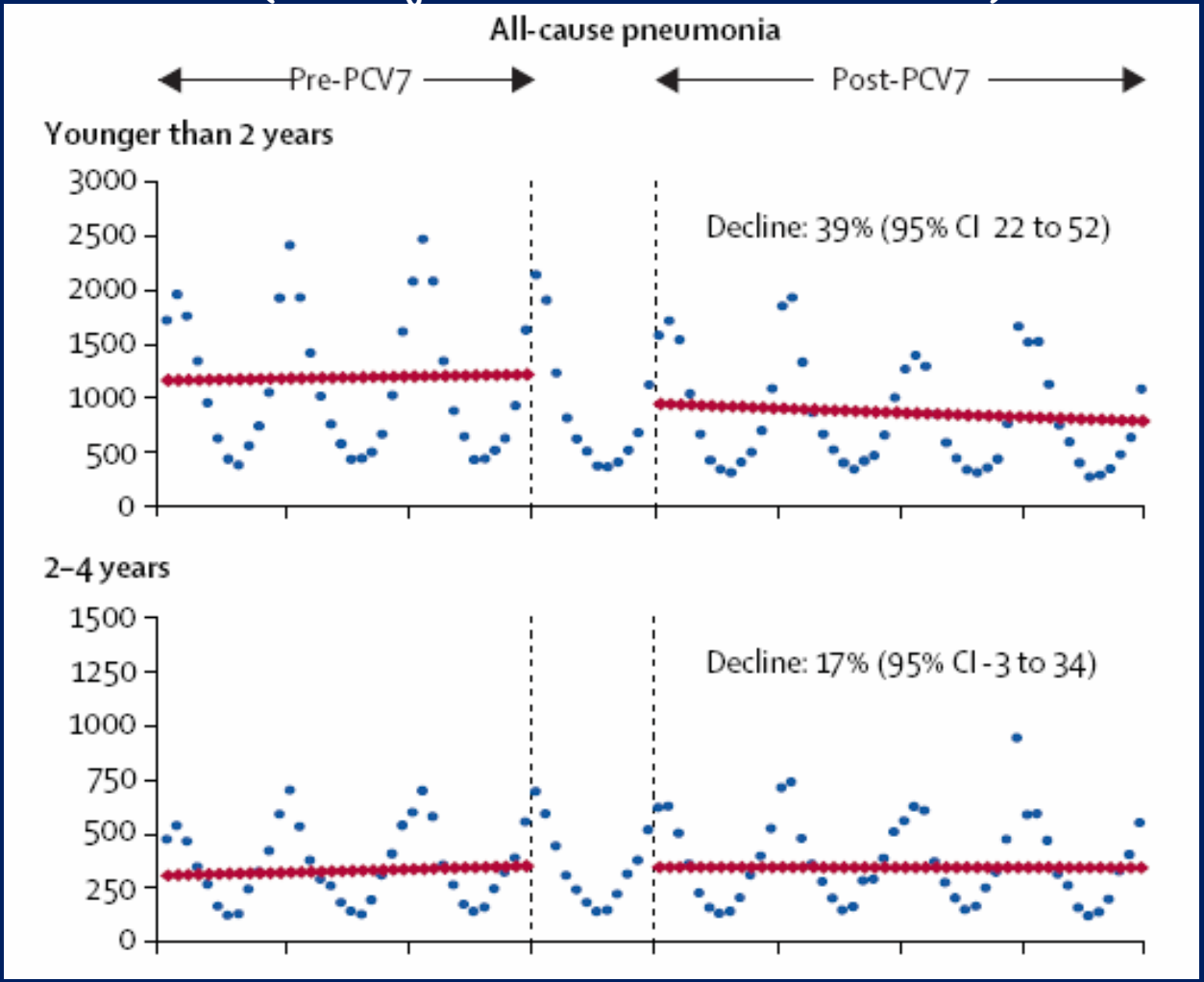
NUMERO STIMATO DI CASI DI IPD DOVUTI A VTP PREVENUTO DA PCV-7 NEGLI U.S.A NEL 2003

(da MMWR 2005)



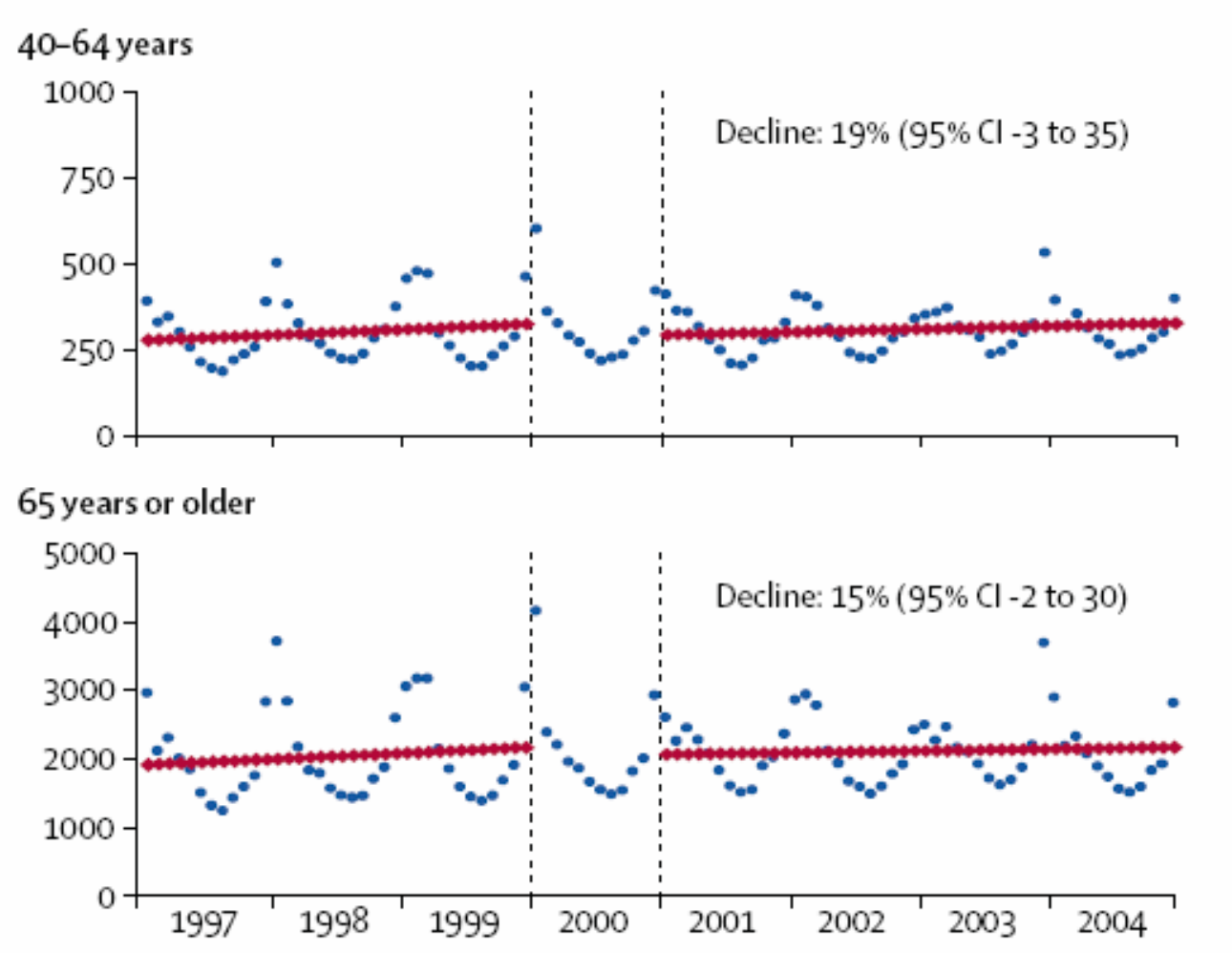
Andamento della ospedalizzazione per polmonite negli U.S.A. prima e dopo l'introduzione di PCV-7 (I)

(da Grijalva CG et al. Lancet 2007)



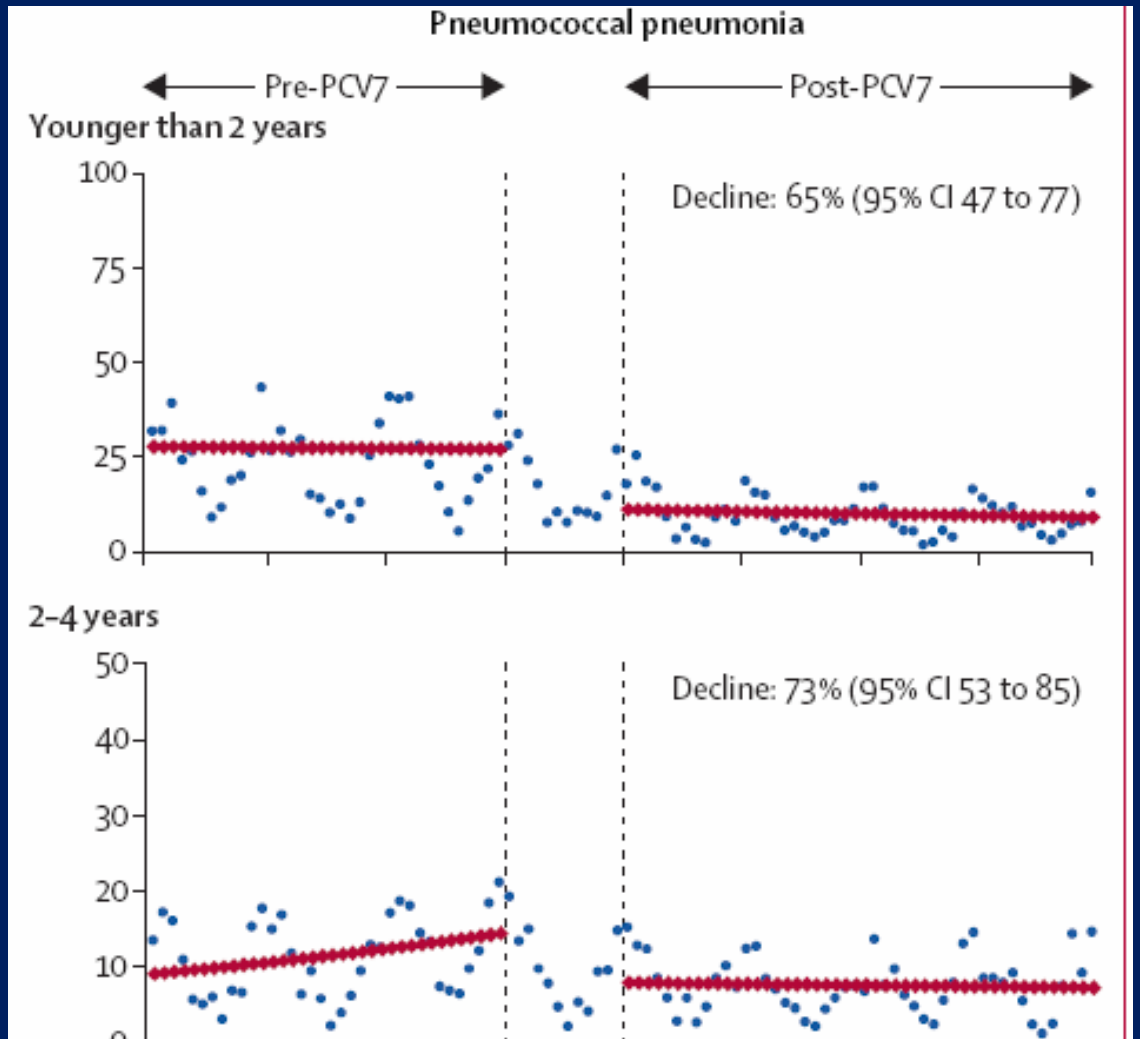
Andamento della ospedalizzazione per polmonite negli U.S.A. prima e dopo l'introduzione di PCV-7 (II)

(da Grijalva CG et al. Lancet 2007)



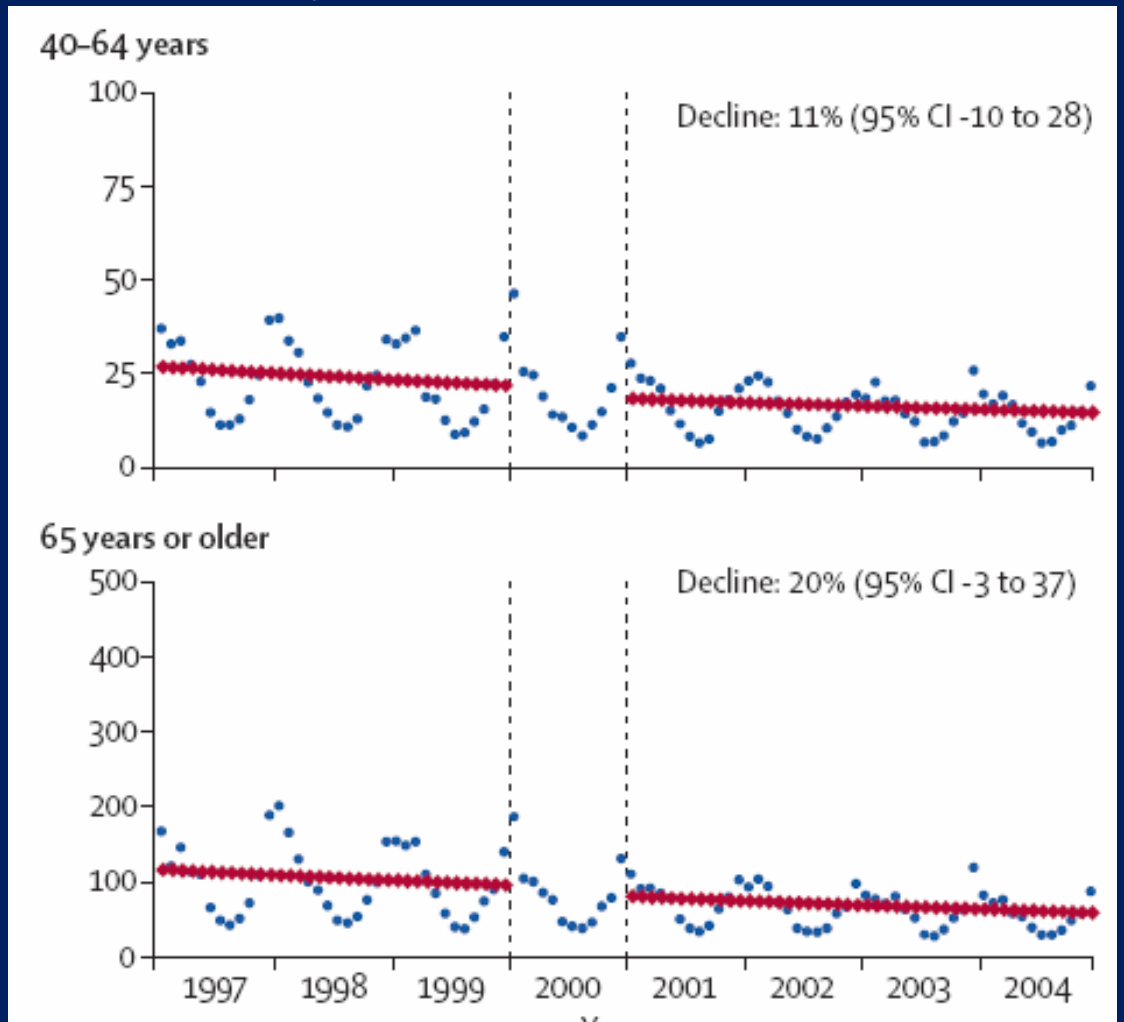
Andamento della ospedalizzazione per polmonite pneumococcica negli U.S.A. prima e dopo l'introduzione di PCV-7 (I)

(da Grijalva CG et al. Lancet 2007)

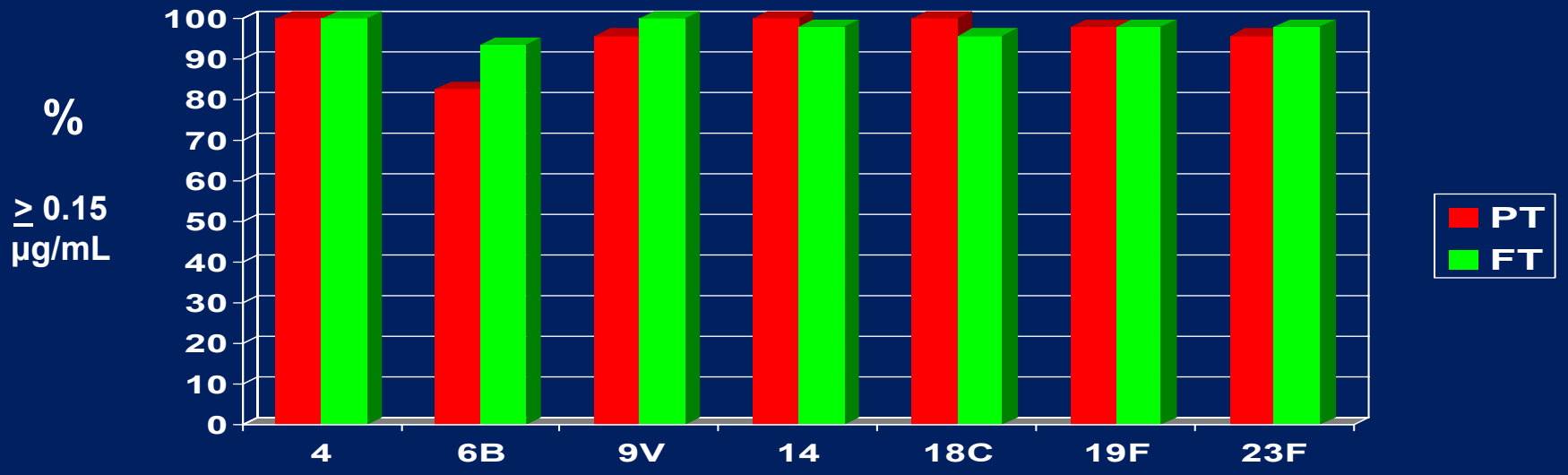


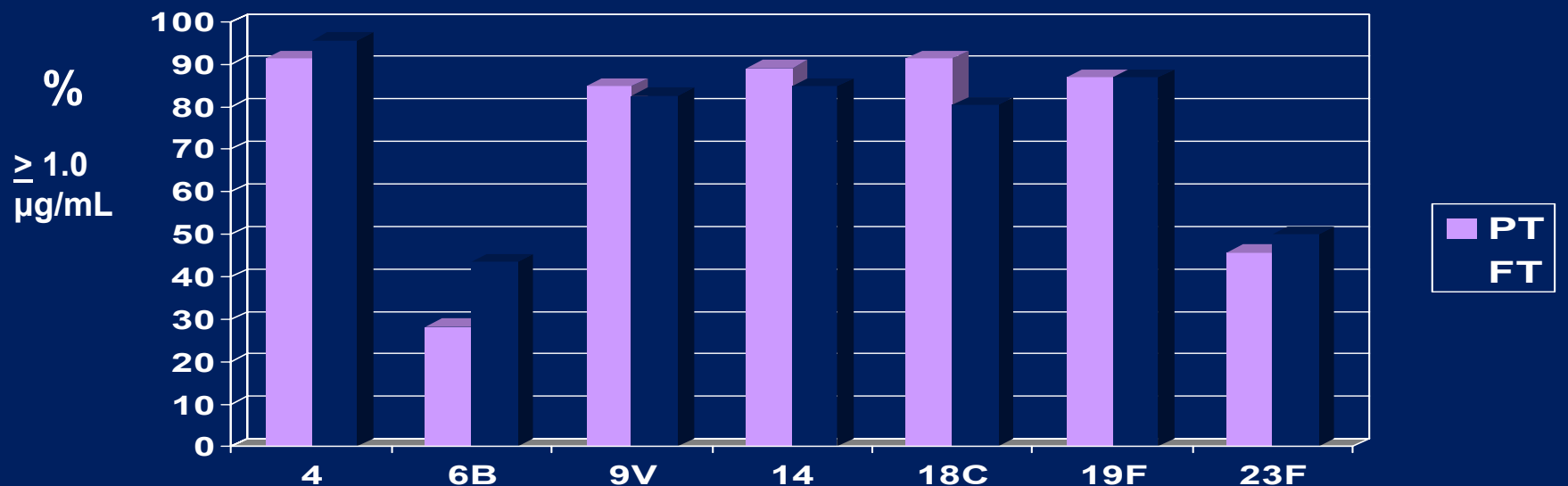
Andamento della ospedalizzazione per polmonite pneumococcica negli U.S.A. prima e dopo l'introduzione di PCV-7 (II)

(da Grijalva CG et al. Lancet 2007)

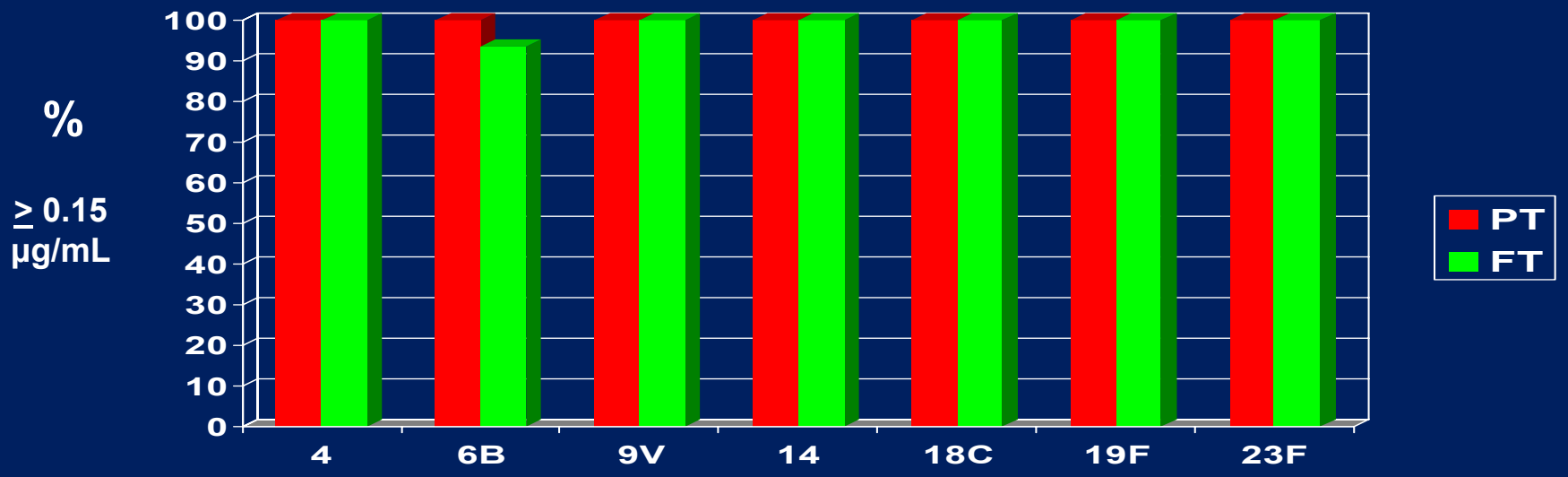


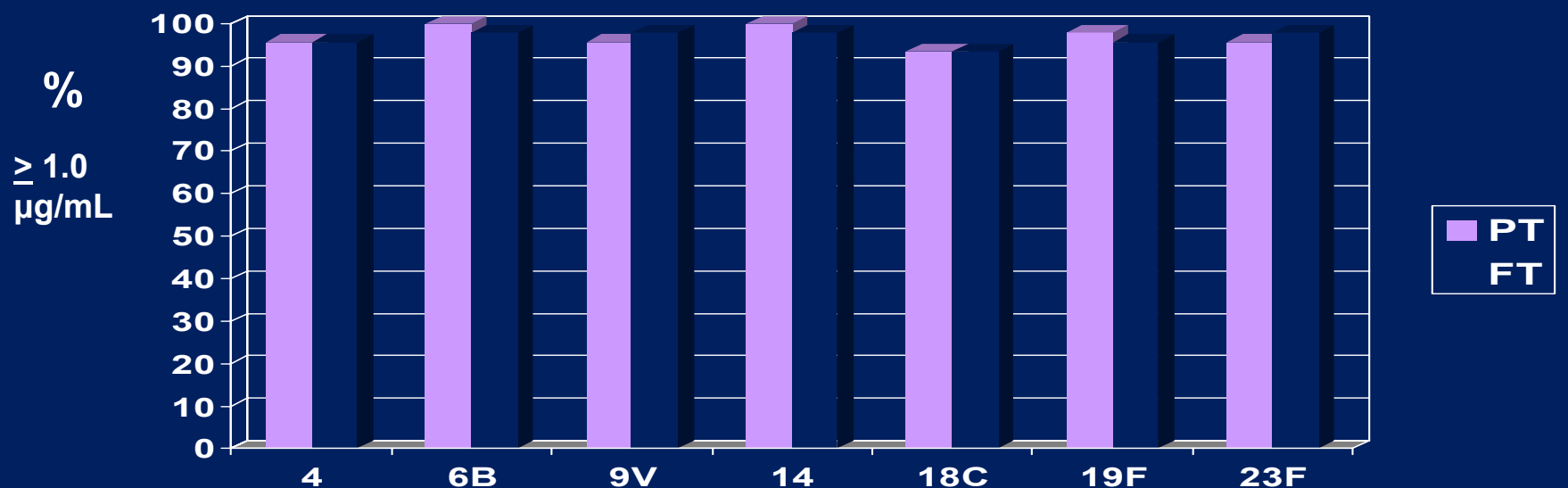
Pre-term (PT) and full-term (FT) infants that reach theoretic protective levels of type-specific IgG antibodies against pneumococcal disease one month after the 2nd dose of PCV





Pre-term (PT) and full-term (FT) infants that reach theoretic protective levels of type-specific IgG antibodies against pneumococcal disease one month after the 3rd dose of PCV





ITALIAN PNEUMO STUDY GROUP

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

From Esposito S. et al. Resp Research 2007

FREQUENCY OF ACUTE OTITIS MEDIA (AOM) DURING FOLLOW-UP

	PCV-7 (N.811)	Controls (N.744)	RR	95% CI	*P*
Total AOMs	637	698			
Episodes/ 100 child years	39.2	46.9	0.83	0.61-1.02	0.02

From Esposito S. et al. Resp Research 2007

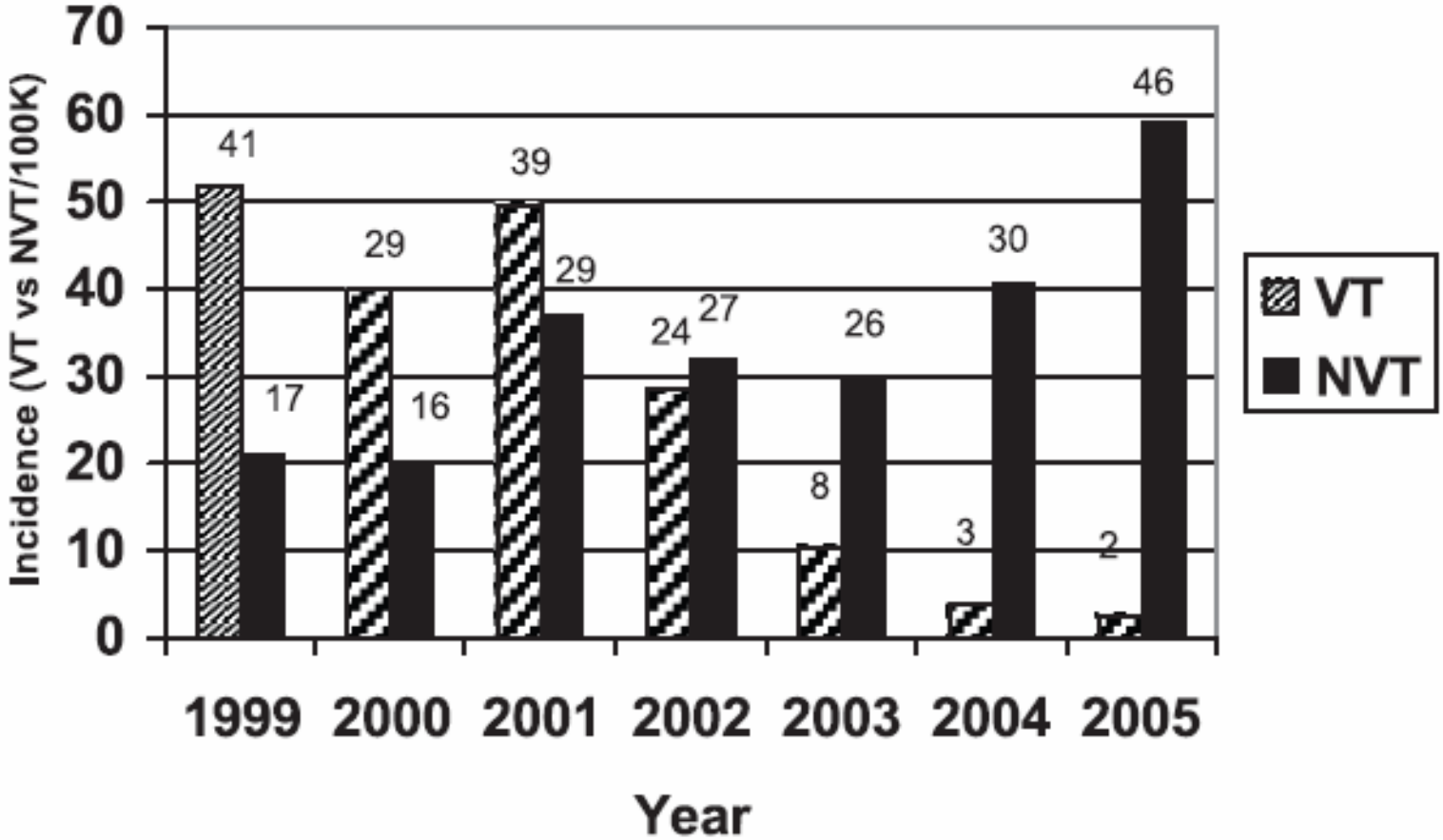
FREQUENCY OF COMMUNITY ACQUIRED PNEUMONIA (CAP) DURING FOLLOW-UP

	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 S. et al. Resp Research 2007

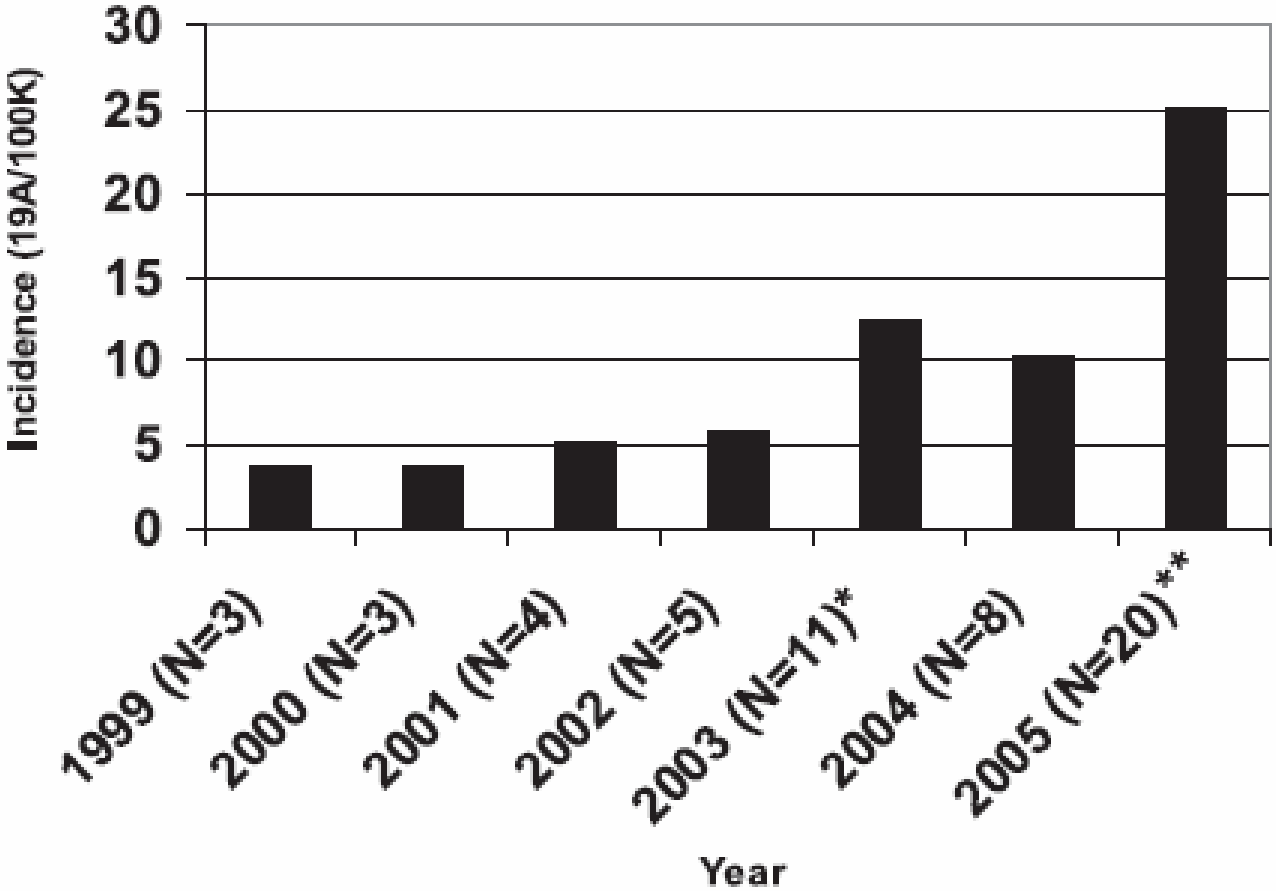
INCIDENZA DI IPD IN DALLAS PRIMA E DOPO PCV-7

(da Messina AF, Pediatr Infect Dis J 2007)



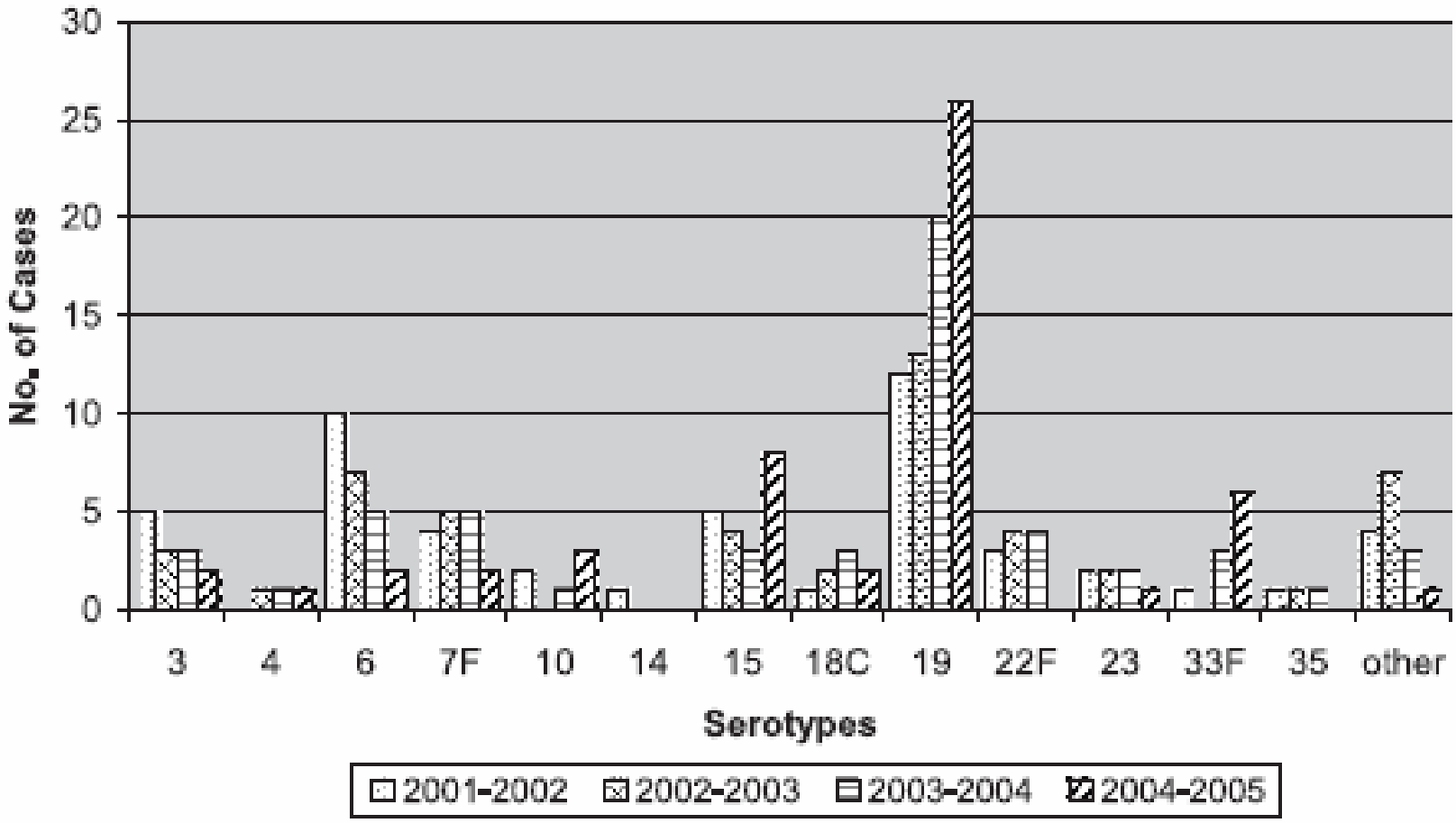
INCIDENZA DI IPD DA SIEROTIPO 19A IN DALLAS

(da Messina AF, Pediatr Infect Dis J 2007)



SIEROTIPI DI PNEUMOCOCCO RESPONSABILI DI IPD IN BOSTON

(da Pelton SI et al Pediatr Infect Dis J 2007)



Nasopharyngeal Colonization With Serotype 19A Among Persons Colonized With Streptococcus pneumoniae in 8 Rural Villages, 1998-2004*

le 3. Nasopharyngeal Colonization With Serotype 19A Among Persons Colonized With *Streptococcus pneumoniae* in 8 Rural Villages, 8-2004*

	No./Total (%) of Cases						
, y	1998	1999	2000	2001	2002	2003	2004
	1/43 (2.3)	0/40 (0)	0/43 (0)	0/48 (0)	1/63 (1.6)	2/58 (3.5)	12/73 (1
	0/93 (0)	0/73 (0)	0/85 (0)	0/106 (0)	0/113 (0)	8/107 (7.5)	32/117 (2
7	1/283 (0.3)	0/265 (0)	0/311 (0)	0/500 (0)	1/488 (0.2)	27/630 (4.3)	97/602 (1
3	0/101 (0)	0/68 (0)	0/106 (0)	0/266 (0)	0/266 (0)	4/413 (1.0)	28/377 (7

ults through 2003 were previously published.[10,19]

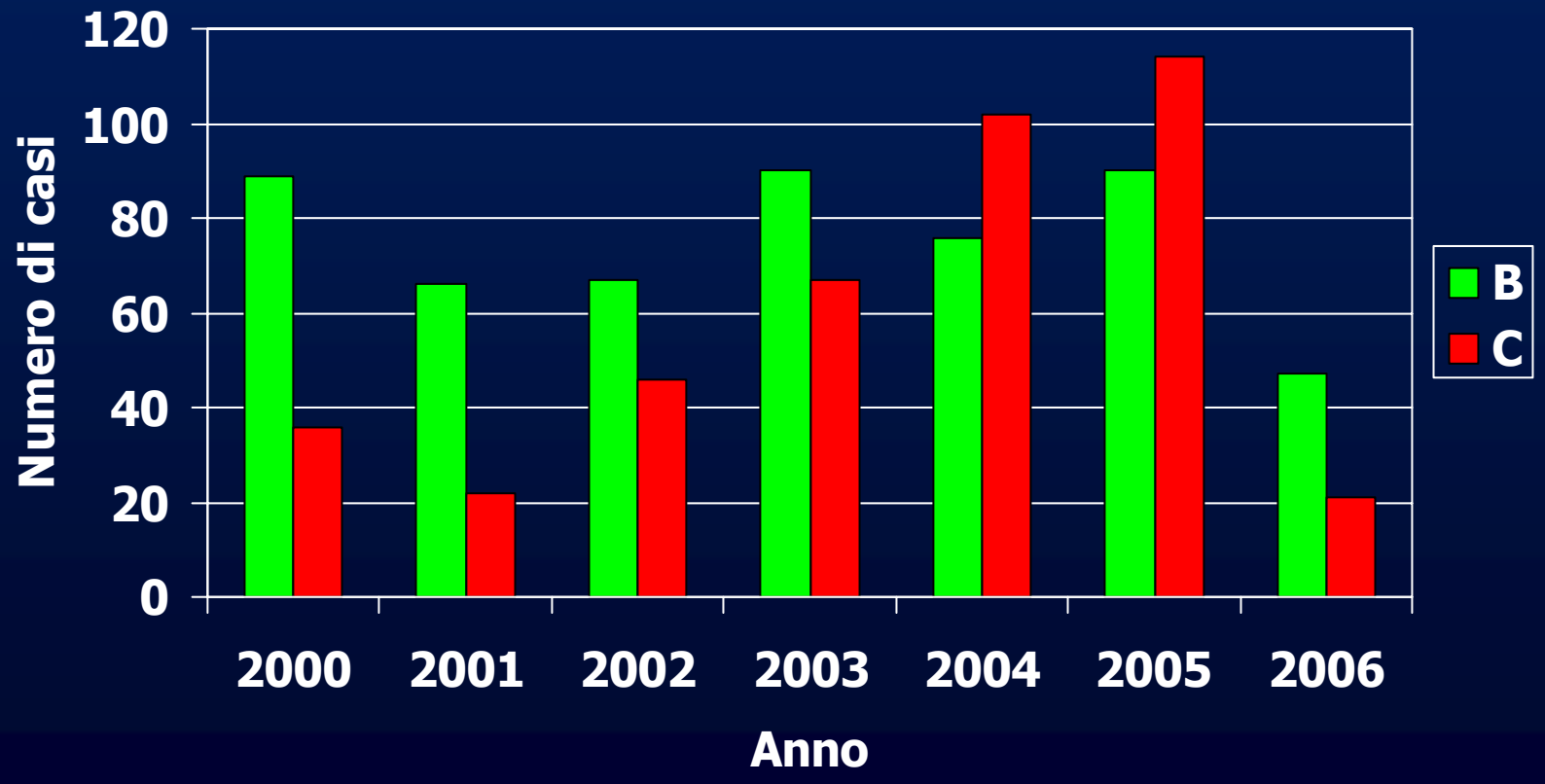
Singleton, R. J. et al. JAMA 2007;297:1784-1792.

JAMA

INCREMENTO DELLE FORME DA SIEROTIPI NON CONTENUTI

- Il calcolo della frequenza di comparsa delle IPD dopo l'introduzione di PCV-7 dimostra che l'incremento dei casi da sierotipi non contenuti riduce solo di poco i vantaggi legati alla caduta dei casi sostenuti dai sierotipi presenti
- Le valutazioni microbiologiche indicano la presenza nei ceppi più recenti di significative modificazioni genetiche. Ciò suggerisce la possibilità che il fenomeno sia spontaneo e non indotto dal vaccino
- Un attento monitoraggio della situazione è, comunque, necessario

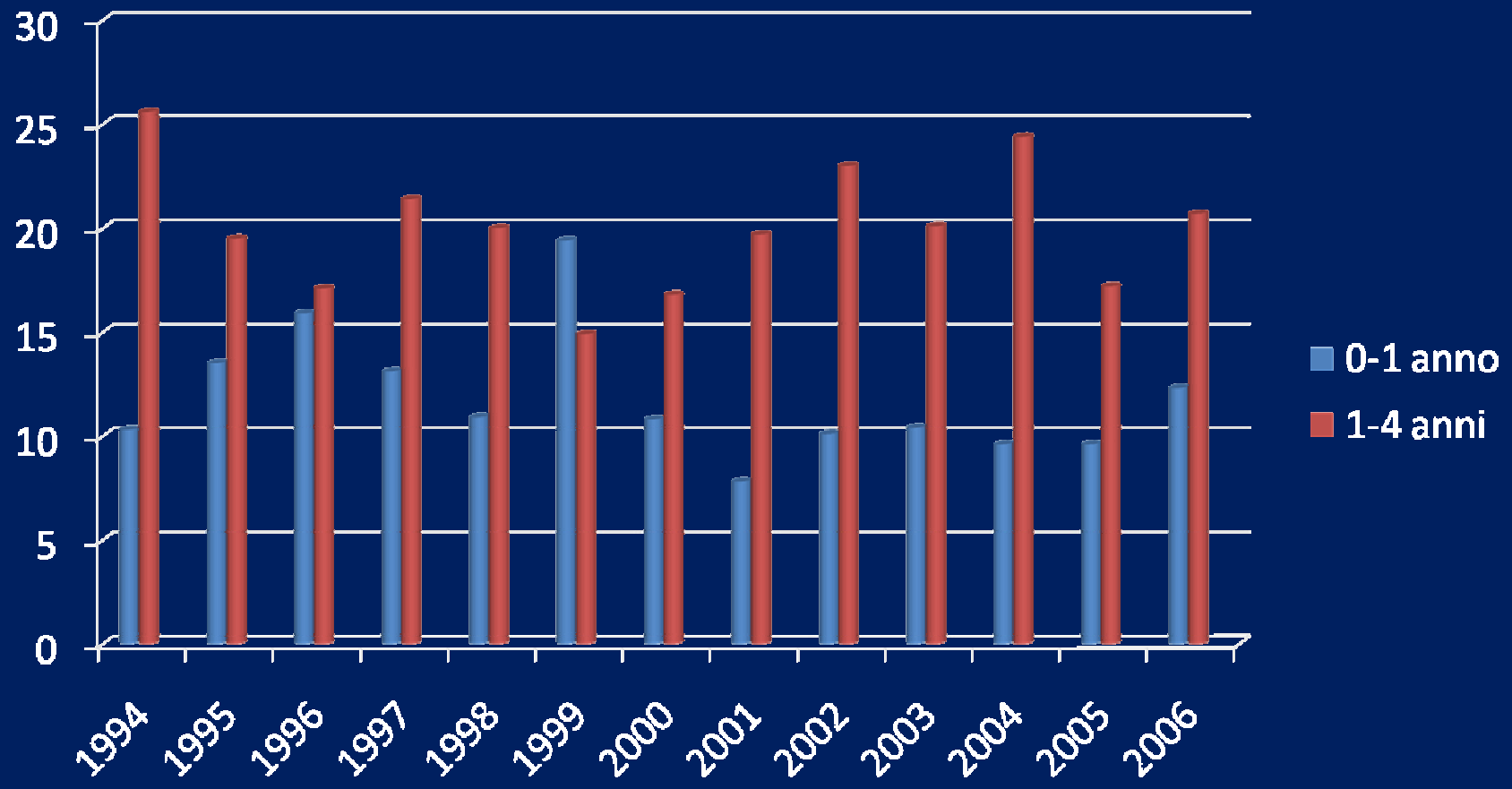
INCIDENZA DELLA PATOLOGIA INVASIVA DA MENINGOCOCCO DI SIEROGRUPPO B E C PER ANNO IN ITALIA



I dati 2005 -2006 non sono definitivi — Ministero della Salute - 2006

INCIDENZA (%) DI INFEZIONI MENINGOCOCCICHE INVASIVE IN ITALIA NEI PRIMI ANNI DI VITA

(Dati ISS, Italia)



From Trotter et al. Lancet 2004

	Age at vaccination	Doses scheduled*	Period of observation, by quarter year	Overall		Within 1 year of scheduled vaccination†		More than 1 year after scheduled vaccination†	
				Cases (vaccinated)	Vaccine effectiveness (95% CI)	Cases (vaccinated)	Vaccine effectiveness (95% CI)	Cases (vaccinated)	Vaccine effectiveness (95% CI)
ohort									
outine	2–4 months	3	Q1 2000–Q1 2004	28 (21)	66% (6 to 86)	9 (3)	93% (67 to 99)	19 (18)	–81% (–7430 to 71)
nfant catch-up	5–11 months	2	Q3 2000–Q1 2004	13 (5)	85% (46 to 96)	6 (2)	87% (11 to 99)	7 (3)	82% (–8 to 97)
oddlers catch-up	1–2 years	1	Q3 2000–Q1 2004	25 (10)	83% (60 to 93)	19 (6)	88% (65 to 96)	6 (4)	61% (–327 to 94)
re-school catch-up	3–4 years	1	Q3 2000–Q1 2004	37 (2)	98% (91 to 100)	45 (1)	98% (90 to 100)	19 (4)	93% (78 to 98)
nfant school catch-up	4–6 years	1	Q3 2000–Q1 2004	19 (0)	100% (71 to 100)				
unior school catch-up	7–10 years	1	Q3 2000–Q1 2004	8 (3)	88% (38 to 98)				
econdary school catch-up	11–16 years	1	Q2 2000–Q1 2004	40 (8)	96% (90 to 98)	45 (4)	96% (89 to 99)	39 (8)	90% (77 to 96)
ixth form catch-up	17–18 years	1	Q1 2000–Q1 2004	44 (4)	93% (82 to 98)				
otal				214 (53)		124 (16)		90 (37)	

quarter. *Vaccine effectiveness compares children eligible for complete vaccination who had received all scheduled doses versus no doses. Partly vaccinated children were excluded. †For the time change analysis, pre-school ant, and junior cohorts were combined, as were the secondary school and sixth form cohorts.

ble: MCC vaccine effectiveness in immunised cohorts to end of March, 2004

VACCINAZIONE CON MEN-C A 3, 5 E 11 MESI

(Esposito S et al., Vaccine 2007)

DOSE	ELISA, µg/mL		SBA, 1 per GMC	
	PT	FT	PT	FT
Pre-dose 1, No.				
GMC	0,17*	0,11°	2,06*	2,57°
95% IC	0,13-0,24*	0,08-0,16°	1,6-2,64*	2,0-3,3°
Post-dose 2, No.				
GMC	16	16	1.243	1.389
95% IC	13-19	13-20	807-1.915	902-2.139
Pre-dose 3, No.				
GMC	2,77**	3,1°°	54**	85°°
95% IC	2,29-3,36**	2,54-3,78°°	27-110**	41-176°°
Post-dose 3, No.				
GMC	21	27	1.992	2.435
95% IC	18-24	23-32	1.339-2.964	1.623-3.654

*$p<0,05$ *vs* PT post-dose 2, pre-dose 3 e post-dose 3; **$p<0,05$ *vs* PT post-dose 2 e post-dose 3; °$p<0,05$ *vs* FT post-dose 2, pre-dose 3 e post-dose 3; °°$p<0,05$ *vs* FT post-dose 2 e post-dose 3; non altre differenze significative tra i 2 gruppi

OSPEDALIZZAZIONE PER DIARREA DA ROTAVIRUS

(daVan Damme P et al. Lancet Infect Dis 2006)

tudy	Country	Years	Data sources	Age	Hospitalisation caused by rotavirus diarrhoea (incidence/ 1000 person-years)	Infants with rotavirus diarrhoea in all infants hospitalised for diarrhoea (%)
isser et al, 1999[20]	Spain	1989–1995	Lab and hospital data	<5	2·5	..
e Wit et al, 2000[21]	Netherlands	1996–1998	Lab and hospital data	<5	2·7	48
ischer, 2001[22]	Denmark	1995–1999	Hospital data	<5	2·8	19
ohansen et al, 1999[23]	Sweden	1993–1996	Lab and hospital data	<4	3·7	53
yan et al, 1996[24]	England and Wales	1993–1994	Lab and hospital data	<5	5·2	54
esikari et al, 1999[25]	Finland	1985–1995	Lab and hospital data	<5	..	54
oppe et al, 2002[26]	Germany	1997–1998	Hospital data	<4	7·7	43
ynch et al, 2001[27]	Ireland	1997–1998	Lab and hospital data	<5	12·0	50
zucs et al, 1999[28]	Hungary	1993–1996	Lab and hospital data	<4	8·4	21
il et al, 2004[29]	Spain	1999–2000	Lab and hospital data	<5	1·0 (2·5 during winter months)	14
rukowicz et al, 1999[30]	Poland	1994–1996	Lab and hospital data	<5	3·1	41
ourquet et al, 2003[31]	France	2003	Hospital data	<5	5·9	43

not reported.

ATTIVITA' MEDICA SUL TERRITORIO PER DIARREA DA ROTAVIRUS

(da Van Damme P et al. Lancet Infect Dis 2006)

Study	Country	Year	Health-care setting	Number of consultations with family doctors or pediatricians per 1000 person-years for rotavirus diarrhoea	% rotavirus of all diarrhoea
Ehlken et al, 2002[40]	Germany	1997–1998	Primary care	48·5	23·7
Frühwirth, Heininger et al, 2001[38]	Austria	1997–1998	Primary care and hospital	8·4	29·5
DeWit et al, 2000[21]	Netherlands	1996–1999	Primary care	Not available	21·0
Frühwirth, Karmaus et al, 2001[41]	Switzerland	1997–1998	Primary care and hospital	18	37·5
Cilla et al, 2000[42]	Spain	1991–1997	Primary care and hospital	21·7	..
Djuretic et al, 1999[43]	UK	1992–1996	Primary care	Not available	29·0

=not reported.

	Rotarix (GlaxoSmithKline)	RotaTeq (Merck)
	Monovalent vaccine	Pentavalent vaccine
riginal strain	Human rotavirus strain 89-12 P1A[8], G1	Bovine rotavirus strain WC3 P7[5], G6
inal vaccine	RIX4414	Five reassortants; G1_WC3 G2_WC3 G3_WC3 GA_WC3 P1A[8]_WC3
itre	$10^{5.8}$ focus-forming units	$6.7–12.4 \times 10^{7}$ plaque forming units
ethod of attenuation	Passaged 43 times	Animal strains naturally attenuated; passage varies by reassortant 7–69 tir
ell substrate	Vero cells	Vero cells
resentation and formulation	Dual-compartment device to reconstitute lyophilised virus with buffer	Liquid virus mixed with buffer; no reconstitution needed
uffer	Calcium carbonate (1 mL)	Citrate phosphate sucrose (2 mL)
ose regimen	Two oral doses	Three oral doses
	Dose 1: 6–14 weeks of age	Dose 1: 6–12 weeks of age
	Dose 2: ≥4 weeks later	Doses 2 and 3: at about 4–10-week intervals
helf life at 2–8°C	36 months	24 months
accine interference		
Diphtheria tetanus pertussis, inactivated polio vaccine, *Haemophilus influenzae* type b vaccine, Hepatitis B vaccine	None	None*
Pneumococcal conjugate†	..	..
Oral polio 1 vaccine†	..	..
Post-dose shedding	>50%	~10%

	Rotarix			RotaTeq		
Rota virus type	Vaccine (n/N)	Placebo (n/N)	RRR (95% CI)	Vaccine (n/N)	Placebo (n/N)	RRR (95% CI)
G1P[8]	2/2646	29/1348	96.5 (86–99.6)	32/34,035	414/34,003	92 (88–95)
G2P[4]	9/14,792	15/11,269	71.4 (20–91)	1/34,035	12/34,003	92 (35–99)
G3P[8]	0/2646	6/1348	100 (56.7–100)	3/34,035	20/34,003	85 (50–96)
G4P[8]	0/2646	7/1348	100 (64.7–100)	2/34,035	20/34,003	90 (57–98)
G9P[8]	2/2646	21/1348	95 (80.2–99.4)	2/34,035	25/34,003	92 (66–98)

RRR, relative risk reduction

Efficacy (RRR) of rotavirus vaccines against severe rotavirus gastroenteritis (Rotarix) or hospitalisations and emergency department visits (RotaTeq).

NUOVI VACCINI ANTIROTAVIRUS E INVAGINAZIONE INTESTINALE

	Site	Follow-up period post-vaccination	Number of participants		Intussusception cases			Relative risk (95% CI)
			Vaccinated	Placebo		Vaccinated	Placebo	
lonovalent (Rotarix, laxoSmithKline)	Europe, Asia,	31 days	~31 500	~31 500	Total	6	7	~0·86 (0·29–2·55)
	Latin America[77]				Dose 1	1	2	~0·50 (0·05–5·51)
					Dose 2	5	5	~1·00 (0·29–3·45)
	Latin America[78]	1 year	10 159	10 010	Total	4	14	0·28 (0·10–0·81)
entavalent (RotaTeq, Merck)	USA, others[84]	42 days	~35 150	~35 150	Total	6	5	~1·20 (0·37–3·93)
					Dose 1	0	1	~0 (0–17·30)
					Dose 2	4	1	~4·00 (0·45–35·79)
					Dose 3	2	3	~0·67 (0·11–3·99)
		1 year	~35 150	~35 150	Total	12	15	~0·80 (0·35–1·71)

ble 3: Summary of vaccine safety trials focused on intussusception. Risk of intussusception following receipt of rotavirus vaccine or placebo

Evidence-based recommendations

- Healthy infants:
  - It is recommended that the first dose of RV vaccine should be given between the age of 6 and 12 weeks, and the full schedule (Rotarix 2 doses; RotaTeq 3 doses) should be completed by the age of 6 months
    - High quality data, net benefit, strong recommendation: 1A
    - Insufficient data to describe the risk of ITSS when first dose is given t infants older than 3 months of age.
    - The peak of natural incidence of ITSS occurs at 4-9 months of age
    - Catch-up vaccination with the first dose of RV vaccine given to infants older than 3 months of age is therefore not recommended

FATTORI FAVORENTI L'ACCETTAZIONE DEL VACCINO ANTIROTAVIRUS

(da Staat MA, et al. Pediatr Infect Dis J 2006)

Risk Factor	Vaccine (n = 124) No. (%)	No Vaccine (n = 139) No. (%)	*P* Value
Sex			
Male	71 (50%)	71 (50%)	Referent
Female	53 (44%)	68 (56%)	0.23
Race/ethnicity			
Hispanic	3 (50%)	3 (50%)	
Non-Hispanic white	107 (51%)	101 (49%)	
Non-Hispanic black	9 (26%)	25 (74%)	
Other	5 (33%)	10 (67%)	
Non-Hispanic white	107 (51%)	101 (49%)	Referent
Nonwhite	17 (31%)	38 (69%)	<0.0001
Adults in household			
1	7 (30%)	16 (70%)	Referent
>1	117 (49%)	123 (51%)	0.03
Mother's age at possible immunization*			
<25 yr	10 (21%)	37 (79%)	Referent
≥25 yr	114 (53%)	101 (47%)	<0.0001
Mother's education*			
<High school	5 (24%)	16 (76%)	
High school only	19 (31%)	43 (69%)	
Some college/technical college or more	100 (56%)	79 (44%)	
<College/technical college	24 (29%)	59 (71%)	Referent
Some college/technical college or more	100 (56%)	79 (44%)	<0.0001
Insurance*			
None	0 (0%)	1 (100%)	
Medicaid	7 (21%)	26 (79%)	
Other	117 (51%)	111 (49%)	
None or Medicaid	7 (21%)	27 (79%)	Referent
Other	117 (52%)	111 (48%)	<0.0001