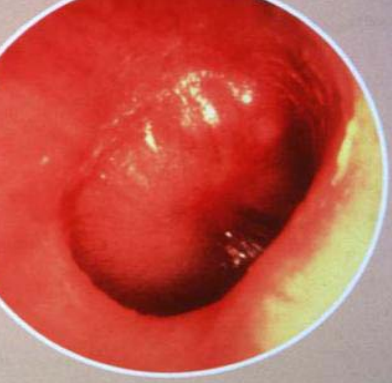


IL RUOLO DI PCV-7 NELLA PREVENZIONE DELL' OTITE MEDIA ACUTA E DELLA POLMONITE

NICOLA PRINCIPI
ISTITUTO DI PEDIATRIA
UNIVERSITA' DI MILANO



pe © <http://www.medscape.com>

EFFICACIA NELLE OTITI

PNEUMOCOCCAL CONJUGATE VACCINE STUDIES

Kaiser Study (Northern California)

- Randomized, prospective, placebo-controlled
- October 1995 to August 1998
- 37868 infants
- PCV7 given at 2,4,6 and 12 to 15 months

FinOM study

- 1662 infants
- PCV7 given at 2,4, 6 and 12 months
- Diagnosis of AOM made by investigators
- Tympanocentesis if AOM

Northern California Kaiser Permanente Efficacy Study Trial Design

- October 1995 – August 1998
- Healthy, 2-month-old infants
- Immunizations at 2, 4, 6 and 12-15 months of age
- Randomized, double-blind, controlled
 - Pneumococcal conjugate vaccine, 7-valent
 - versus meningococcal C conjugate vaccine as control ,
 - 1 : 1 randomization

Dose	No. children receiving this dose (Pneumo)	No. children receiving this dose (Control)
1	18,927	18,941
2	17,174	17,196
3	14,565	15,536
4	10,940	10,995

Pneumococcal conjugate vaccine efficacy for otitis media (Kaiser Study-Northern California - USA)



	Vaccine Efficacy %	95% CI
OM-physician visit	8,9	5.8; 11.8
Episodes OM	7	4,1; 9,7
OM 3/4	9,3	3,0; 15,1
OM 4/5	11,9	1,6; 21,1
OM 5/6	22,8	6,7; 36,2
Tube placement	20,1	1,5 35,2

37868 infants – PCV7 given at 2 4 6 and 12 to 15 months

Long-term impact of the pneumococcal conjugate vaccine on otitis media (Kaiser Study – 3.5 years follow-up)

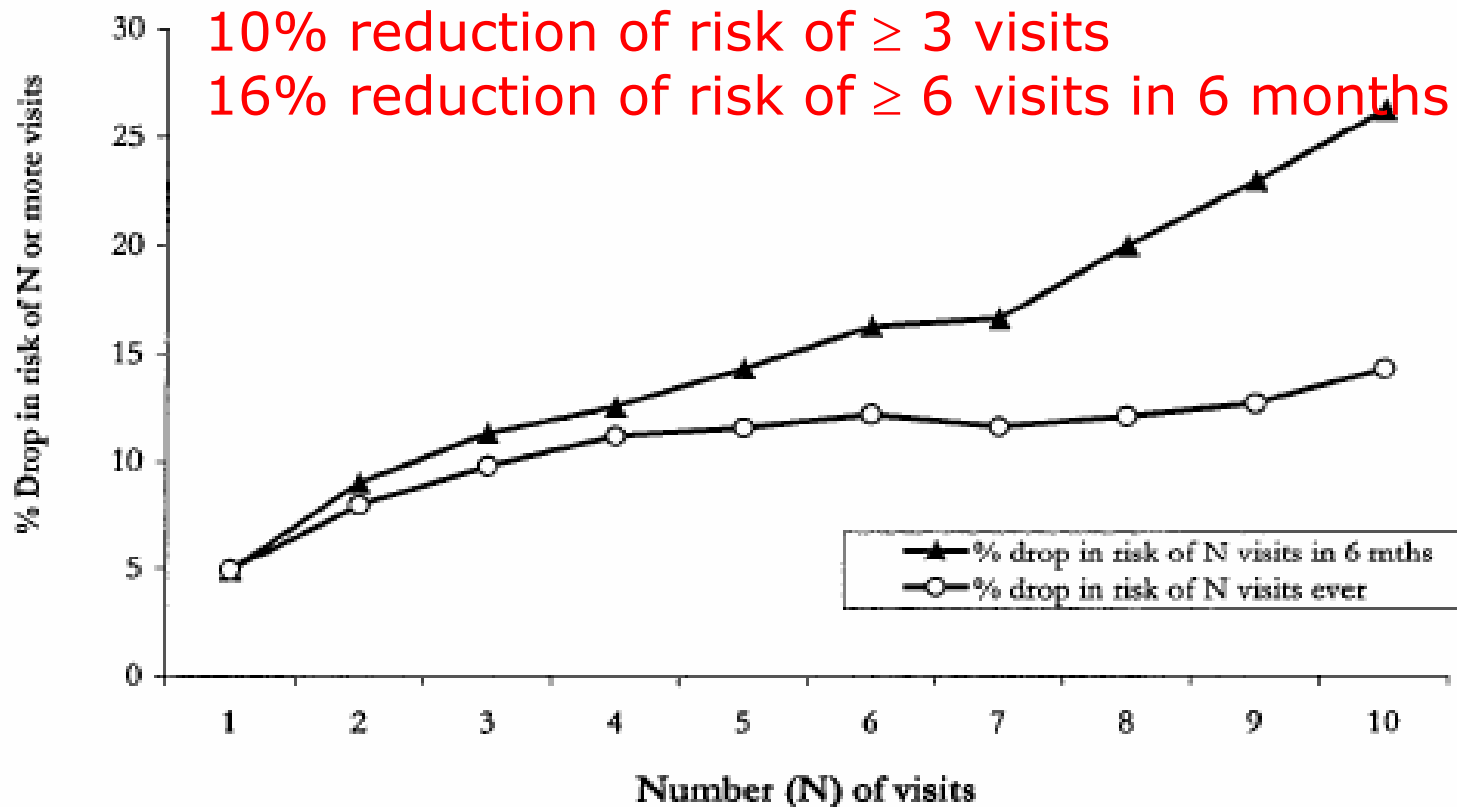
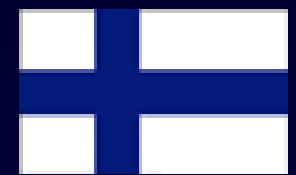


FIG. 2. Effect of the pneumococcal conjugate vaccine on frequent otitis media, by frequency of otitis visits.

Effect of pneumococcal vaccine on tympanostomy tube placement

Type of Analysis	Intention-to-Treat	Per Protocol
<i>N</i> with tube procedure (PCV/control)	325/426	288/380
% risk of tubes by age 3.5 yr (PCV/control)	2.9/3.8	2.9/3.9
Mean otitis visits before 1st tube (PCV, control)	11.9, 11.4	12.2, 11.3
PCV effect (% reduction in risk of 1st tube)	23.2	24.2
95% CI (lower, upper)	11.3, 33.5	11.7, 35.0

PCV-7: FINOM STUDY

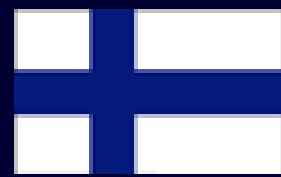


Effect on single episode or recurrent AOM

	Control Group (N = 353)	PncCRM Group (N = 403)	Vacc Effic
Children with at least 1 AOM after 24 mo of age (%)	72.7	67.3	8
Children with recurrent AOM* after 24 mo of age (%)	39.8	32.5	18
Children with follow-up for otitis media with effusion after 24 mo of age (%)	9.9	5.0	50
Diagnosis of otitis media at the visit (%)	12.5	11.4	9

*At least 3 episodes.

PCV-7: FINOM STUDY



Efficacy (95% CI)

All AOM

6% (-4, 16)

Pneumococcal
acute otitis media
(confirmed, all serotypes)

34% (21, 45)

Pneumococcal AOM
acute otitis media
(confirmed, vaccine serotypes)

57% (44, 67)

- 1662 infants - PCV7 given at 2,4, 6 and 12 months
- Diagnosis of AOM made by investigators
- Tympanocentesis if AOM

Eskola et al. N Engl J Med, 2001

Order of Authors: Susanna Esposito, MD; Alessandro Lizioli, MD; Annalisa Lastrico, MD; Nadia Faelli, MD; Alessandro Rognoni, MD; Claudia Tagliabue, MD; Laura Cesati, MD; Vittorio Carreri, MD; Nicola Principi, MD

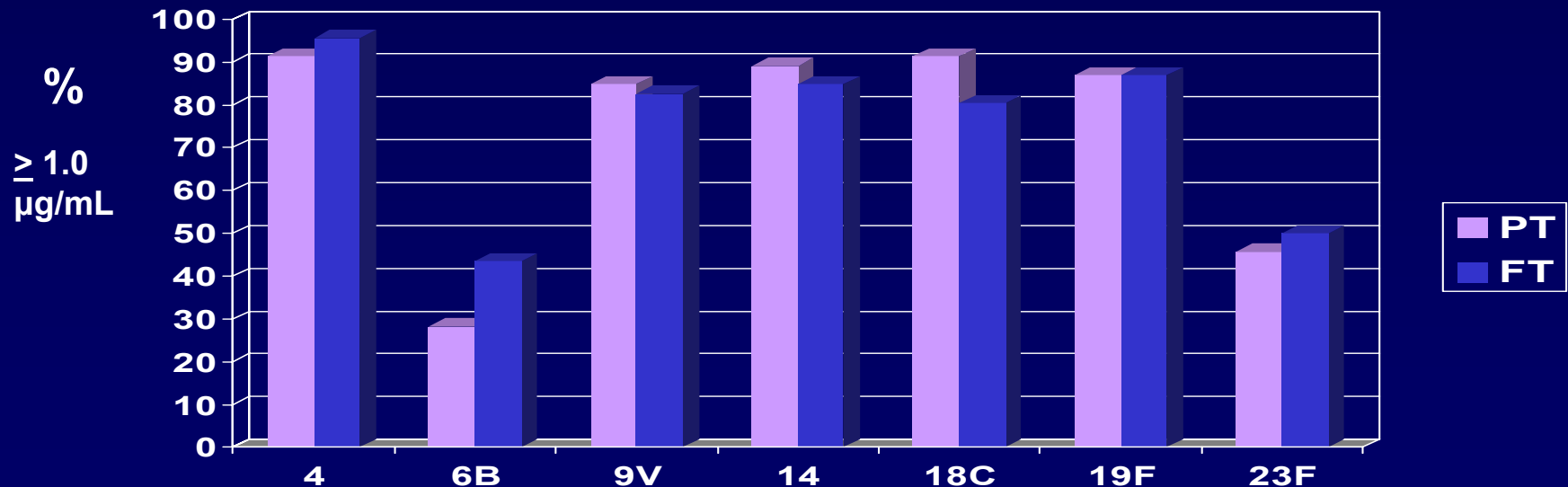
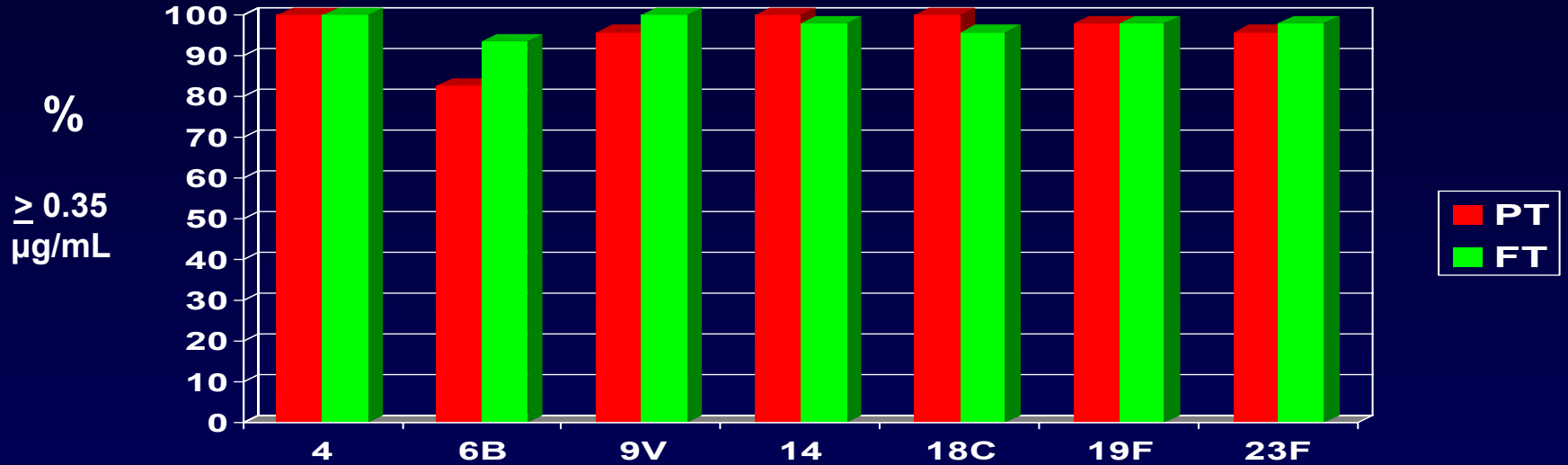
This study was designed to evaluate the impact of heptavalent pneumococcal conjugate vaccine (PCV-7) administered at 3, 5 and 11 months of age on respiratory tract infections in very young children. A total of 1,571 healthy infants (910 males) aged 75-105 days (median 82 days) were enrolled to receive a hexavalent vaccine and PCV-7 (n=819) or the hexavalent vaccine alone (n=752) at 3, 5 and 11 months of age. Among the 1,555 subjects (98.9%) who completed the study, the administration of PCV-7 significantly reduced the incidence of acute otitis media and radiologically confirmed community-acquired pneumonia, also leading to a significant reduction in antibiotic consumption.

**Respiratory
Research 2007;
8:12**

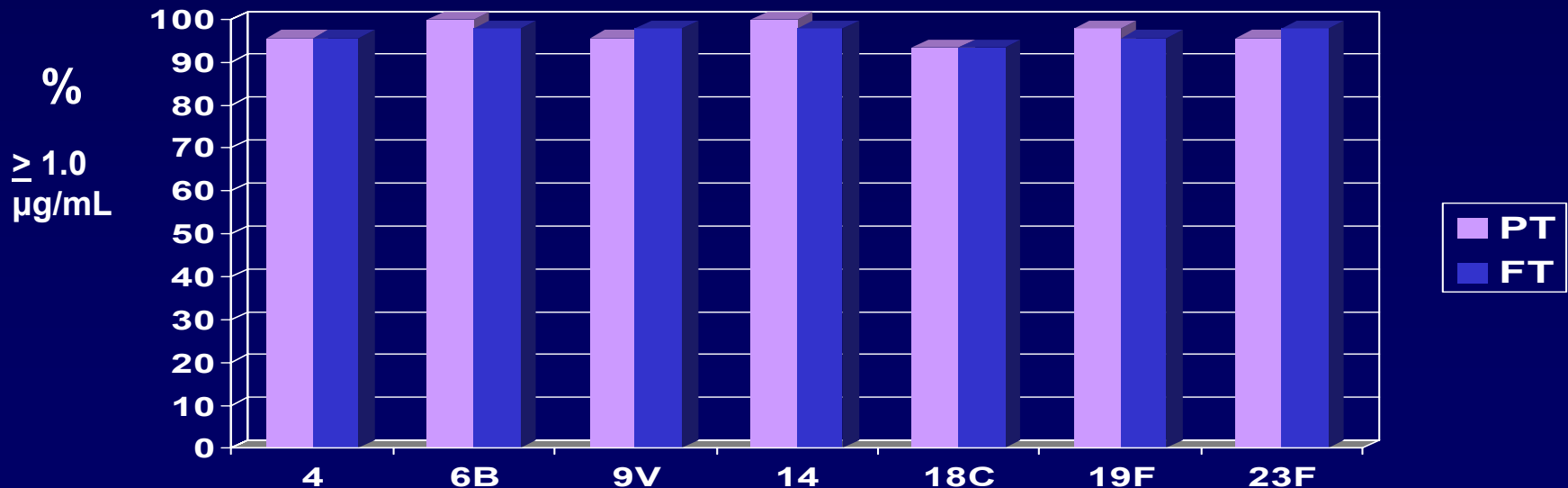
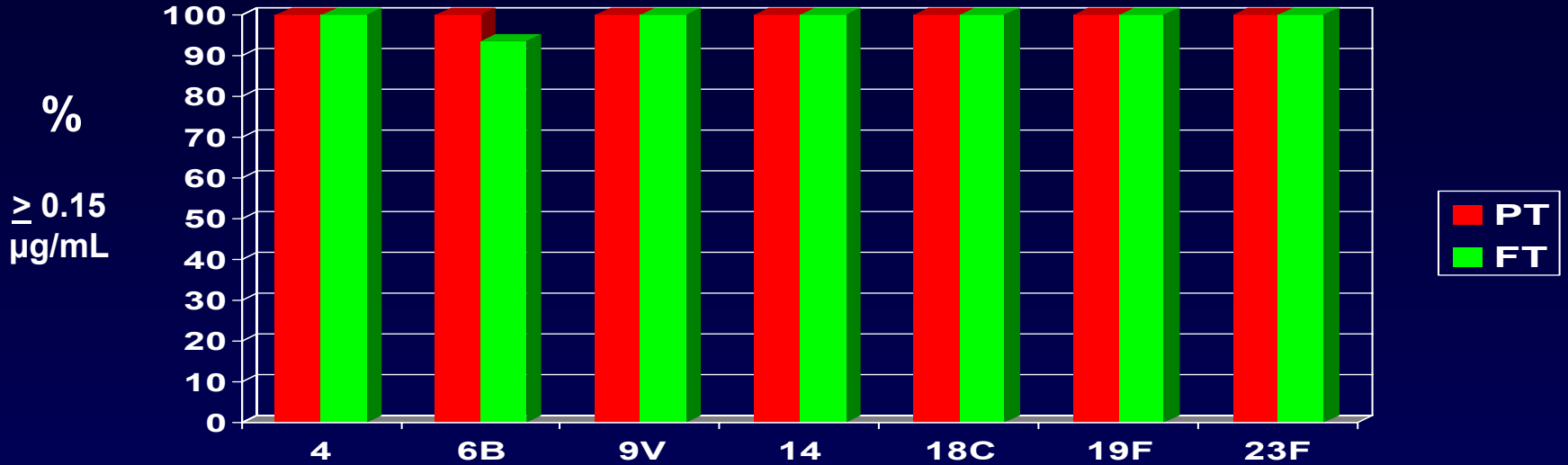
PCV7: REGIONE LOMBARDIA

Ai genitori dei bambini che si presentavano ai centri vaccinali per la somministrazione dell'esavalente è stata offerta la possibilità di essere vaccinati, secondo lo stesso calendario e nelle stesse sedute, anche con PCV-7

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



EVENTI AVVERSI SISTEMICI DA ESAVALENTI ASSOCIATI O MENO A PREVENAR (I DOSE)

EVENTO AVVERSO	HEXAVAC (N=534)	HEXAVAC + PREVENAR (N=572)	INFANRIX -HEXA (N=295)	INFANRIX-HEXA + PREVENAR (N=311)
Qualsiasi effetto sistemico	163 (30,5%)	214 (37,4%)*	81 (27,4%)	109 (35,0%)
Febbre > 39°C	49 (9,2%)	93 (16,3%)*	33 (11,2%)	62 (19,9%)*
Durata (gg)	2 (0,4%)	9 (1,6%)	1 (0,3%)	5 (1,6%)
	1 (2hh-2gg)	1 (1h-4gg)	1 (1g-4gg)	1 (6hh-2gg)
Dosi antipiretici	48	116*	42	81
Irritabilità	89 (16,7%)	95 (16,6%)	35 (11,9%)	37 (11,9%)
Inappetenza	9 (1,7%)	19 (3,3%)	3 (1,0%)	9 (2,9%)
Pianto inconsolabile	32 (6,0%)**	22 (3,8%)°	1 (0,3%)**	0°
Sonnolenza	14 (2,6%)	21 (3,7%)	16 (5,4%)	16 (5,1%)
Sonno agitato	1 (0,2%)	3 (0,5%)	1 (0,3)	0

STUDY CHILDREN

	PCV-7	CONTROLS
N. of children initially enrolled	845	779
N. of children who completed the protocol	811 (95.9%)	744 (95.5%)

CATEGORIES

- Total respiratory tract infections including:
 - a) upper respiratory tract infections (rhinitis, pharyngitis, sinusitis)
 - b) lower respiratory tract infections (bronchitis, infectious wheezing, cap)
- Acute otitis media
- Other infections

PCV7: REGIONE LOMBARDIA

- Controllo telefonico ogni 30 giorni presso la famiglia e, se del caso, presso il curante
- Valutazione di tutta la patologia occorsa fino al compimento del 30° mese di vita con registrazione della diagnosi e della terapia

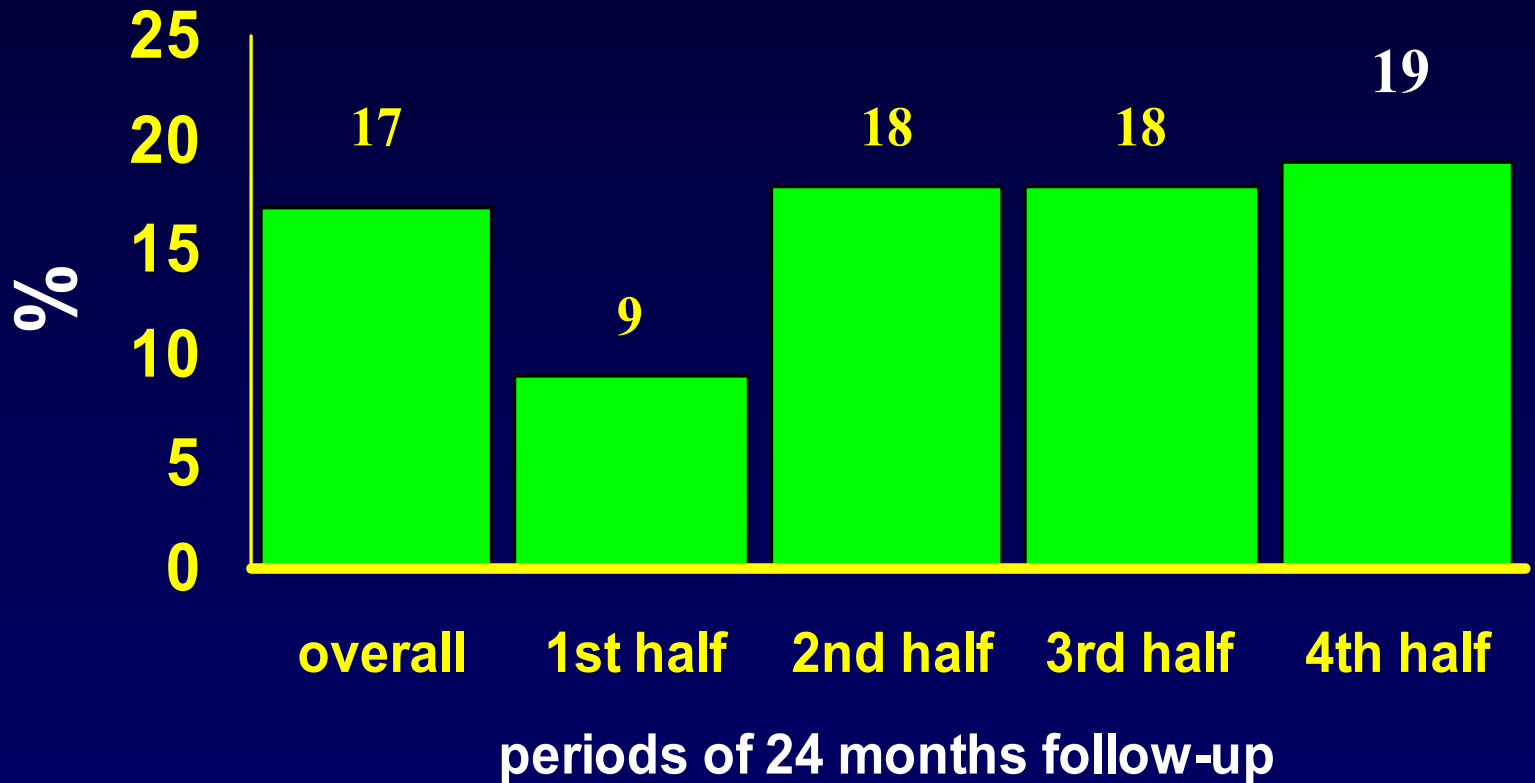
CHARACTERISTICS OF THE STUDY CHILDREN - I

CHARACTERISTIC	PCV-7	CONTROLS
Total number	811	744
Living in urban area	527 (65.0%)	498 (66.9%)
Number of family members (median, range)	3 (2-4)	3 (2-4)
Number of siblings (median, range)	1 (0-2)	1 (0-2)
Age of the mother (median, range)	33 (24-49)	33 (20-40)
Age of the father (median, range)	35 (21-50)	35 (21-51)

CHARACTERISTICS OF THE STUDY CHILDREN - II

CHARACTERISTIC	PCV-7	CONTROLS
No. of smokers in the family (mean \pm S.D.)	0 (0-2)	0 (0-3)
Breast-feeding for at least 3 months	551 (67.9%)	476 (64.1%)
Total no. of children attending day-care	284 (35.0%)	231 (30.1%)
Duration of attendance		
0-6 months	79 (9.7%)	65 (8.7%)
7-12 months	16 (2.0%)	44 (5.9%)
13-18 months	111 (13.7%)	94 (12.6%)
19-24 months	78 (9.6%)	28 (3.9%)

IMPACT ON OTITIS MEDIA OF PCV7 IN ITALIAN CHILDREN (3 doses, 3,5,11 m)



Effect of conjugate pneumococcal vaccine followed by polysaccharide pneumococcal vaccine on recurrent acute otitis media: a randomised study

Veenhoven RH et al, Lancet, 2003; 361:2189

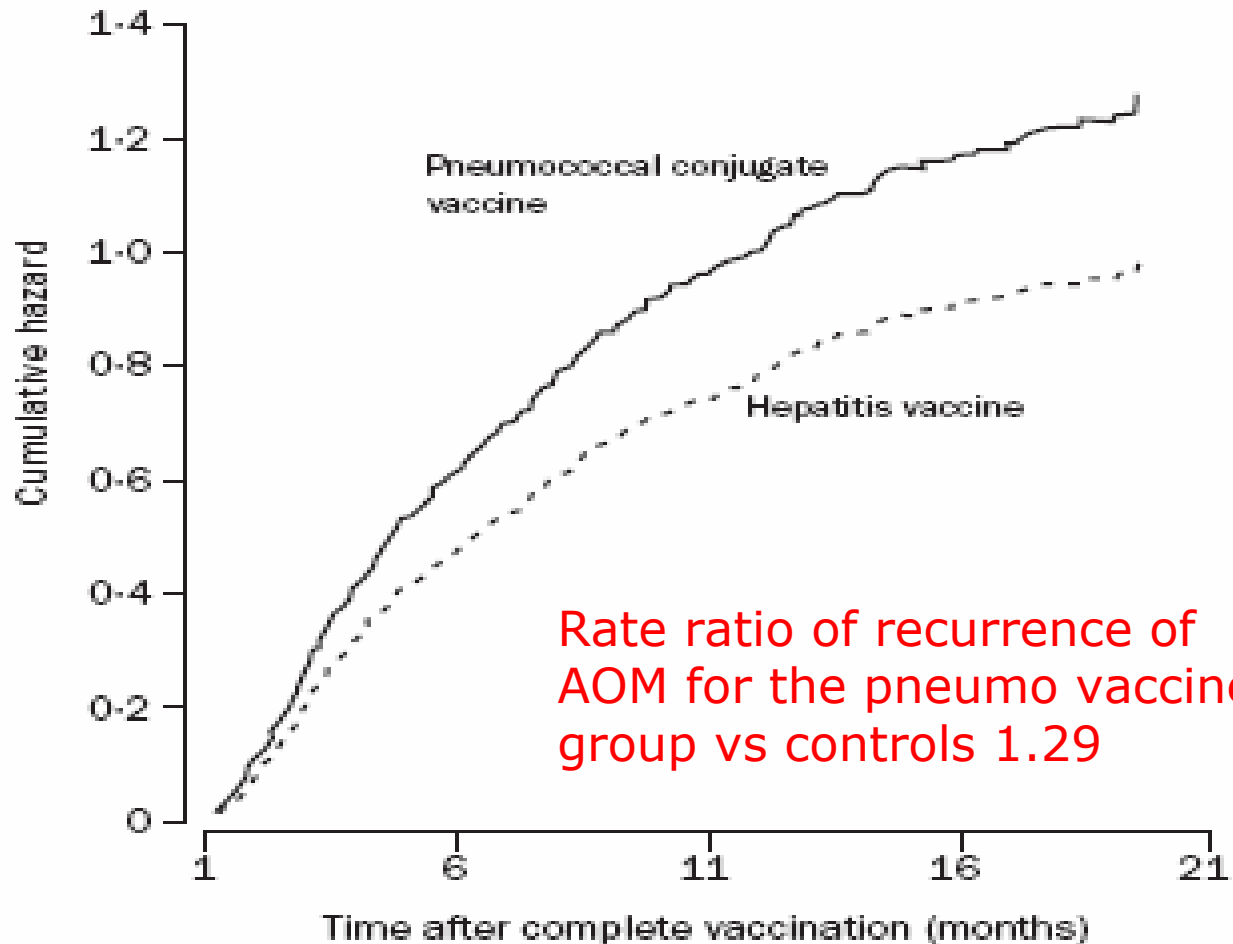


Figure 2: Cumulative hazard function for risk of AOM

Effect of Combined Pneumococcal Conjugate and Polysaccharide Vaccination on Recurrent Otitis Media With Effusion

Niels van Heerbeek, MD, PhD^a, Masja Straetemans, PhD^b, Selma P. Wiertsema, MSc^c, Koen J.A.O. Ingels, MD, PhD^a, Ger T. Rijkers, PhD^c, Anne G.M. Schilder, MD, PhD^d, Ellsabeth A.M. Sanders, MD, PhD^a, Gerhard A. Zielhuis, PhD^b

^aDepartment of Otorhinolaryngology, Radboud University Nijmegen Medical Centre, Nijmegen, Netherlands; ^bDepartment of Epidemiology and Biostatistics, Radboud University Nijmegen, Nijmegen, Netherlands; ^cLaboratory of Pediatric Immunology and Departments of ^dOtorhinolaryngology and ^ePediatric Immunology, Wilhelmina Children's Hospital, University Medical Centre Utrecht, Utrecht, Netherlands

The authors have indicated they have no financial relationships relevant to this article to disclose.

Pediatrics 2006 (March); 117: 603

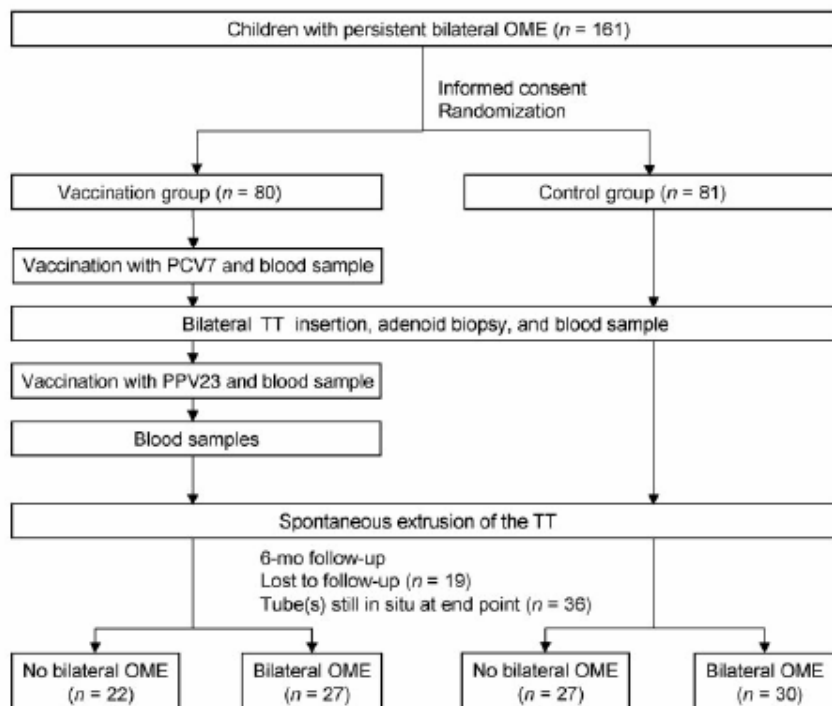


TABLE 3 Number of Children With Unilateral or Bilateral OME After Extrusion of TTs in the 2 Treatment Groups

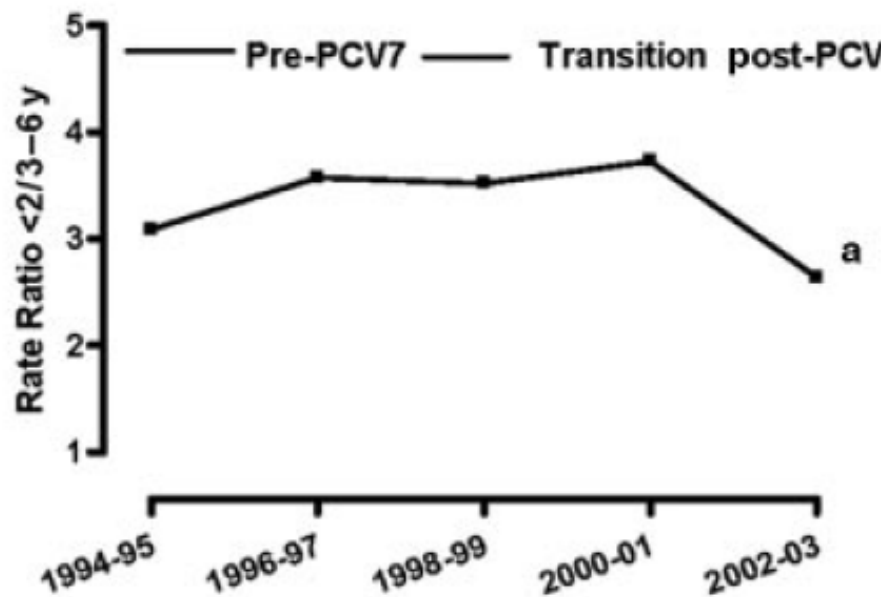
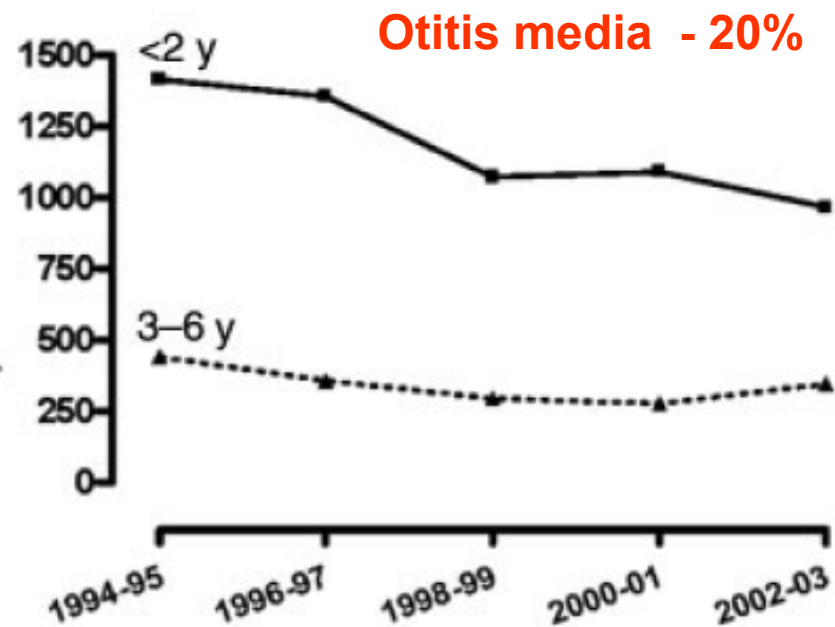
	n (%)	
	Vaccination + TT Group	TT Group
No recurrent OME	12 (15)	10 (12)
Unilateral OME	10 (13)	17 (21)
Bilateral OME	27 (34)	30 (37)
Incomplete follow-up data	31 (39)	24 (30)

PNEUMOCOCCAL VACCINE AND OTITIS MEDIA

the earlier the better

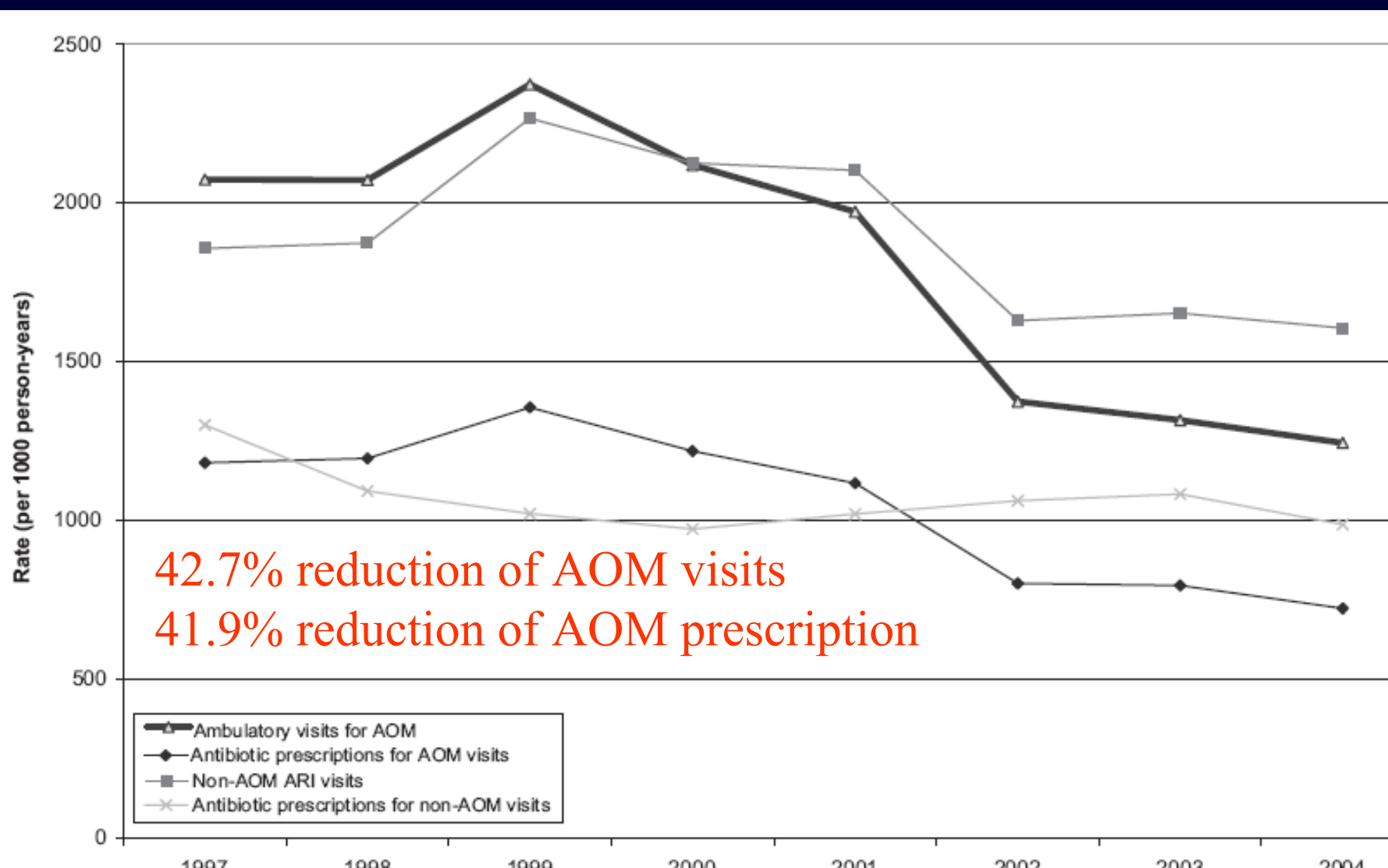
- the seven-valent pneumococcal conjugate vaccine given according to the routine infant schedule and administered early in life is effective in reducing the rate of acute otitis media at a small (but significant!!) rate.
- in older children with recurrent acute otitis media or otitis media with effusion, the vaccine does not appear to reduce subsequent episodes of otitis media

National impact of universal childhood immunization with pneumococcal conjugate vaccine on outpatients medical care visits in USA



Insured Young Children in the United States, 1997-2004

Fangjun Zhou, Abigail Shefer, Yuan Kong and J. Pekka Nuorti
Pediatrics 2008;121:253-260



Bacterial isolates from middle-ear aspirates in infants and children with acute otitis media

Bacterial pathogen	Percentage of children with pathogen			
	1952–1981		1985–1992	
	Mean	Range	Mean	Range
<i>Streptococcus pneumoniae</i>	33	26–53	38	27–52
<i>Haemophilus influenzae</i>	21	14–31	27	16–52
<i>Moraxella catarrhalis</i>	3	0–4	10	2–15
Streptococcus, group A	8	0.3–24	3	0–11
<i>Staphylococcus aureus</i>	2	0–3	2	0–16
Miscellaneous bacteria	1	0–2	8	0–24
None or nonpathogens	31	2–47	28	12–35

Middle ear pathogens (%) recovered from AOM pre-PCV7 (1992-1998) vs post –PCV7 (2000-2003) in vaccinees 7-24 m (> 3 doses PCV7)

Bacteria	Pre PCV 7	Post PCV7
S. pneumoniae	48	31
•Penicillin S	23	12
•Intermediate	16	13
•Resistant	9	6
H.Influenzae	41	56
•Beta lactamases +	23	36
•Beta lactamases –	18	20
M. Catarrhalis	9	11
GABS	2	2

Resistenza ai betalattamici degli isolati da OMA prima e dopo l'impiego di PCV-7

(da Block et al. *Diagnost Microbiol Infect Dis* 2007)

Study location (REF)	Pathogen	% N of isolates	
		Pre-PCV7	Post-PCV7
Kentucky (Block et al., 2004b)	<i>S. pneumoniae</i>		
	Penicillin susceptible	48 (77)	38 (10)
	Penicillin intermediate	33 (53)	42 (11)
	Penicillin resistant	19 (30)	19 (5)
	<i>H. influenzae</i>		
	β -Lactamase positive	56 (77)	63 (29)
β -lactamase negative	44 (60)	27 (17)	
New York (Casey and Pichichero, 2004)	<i>S. pneumoniae</i>		
	Penicillin susceptible	54 (27)	72 (20)
	Penicillin intermediate	12 (6)	14 (4)
	Penicillin resistant	34 (17)	14 (4)
	<i>H. influenzae</i>		
	β -Lactamase positive	46 (18)	55 (28)
β -Lactamase negative	54 (21)	45 (23)	

Empiric First-line Antibiotic Treatment of Acute Otitis in the Era of the Heptavalent Pneumococcal Conjugate Vaccine

Jane Garbutt, Isabel Rosenbloom, Jenny Wu and Gregory A. Storch

Pediatrics 2006;117;1087-1094

CONCLUSIONS. In our community, widespread use of heptavalent pneumococcal vaccine has reduced the prevalence of *S pneumoniae* nonsusceptible to penicillin, and the prevalence of *S pneumoniae* nonsusceptible to amoxicillin remains low (<5%). When antibiotic treatment is elected for children with uncomplicated acute otitis media, we recommend treatment with standard-dose amoxicillin (40–45 mg/kg per day) for children with ≥3 doses of heptavalent pneumococcal vaccine, regardless of age and child care status. High-dose amoxicillin should be used for children with <3 doses of heptavalent pneumococcal vaccine and those treated recently with an antibiotic.

EFFICACIA SU POLMONITE

PNC-CRM7: PREVENTION OF PNEUMONIA

Black at al. *Pediatr Infect Dis J* 2002; 21:810

TABLE 2. First episode of pneumonia in children with heptavalent pneumococcal vaccine vs. control group

Outcome	Intent to Treat			Per Protocol		
	Cases/1000 person-years.		Effectiveness (%)	Cases/1000 person-years		Effectiveness (%)
	Vaccine group	Control group		Vaccine group	Control group	
All clinical pneumonia	43.5	45.8	6.0 (-1.5-11.0)* <i>P</i> = 0.13	53.4	55.9	4.3 (-3.5-11.5) <i>P</i> = 0.27
Clinical pneumonia and radiograph obtained	26.3	28.9	8.9 (0.9-16.3) <i>P</i> = 0.03	30.9	34.2	9.8 (0.1-18.5) <i>P</i> = 0.05
Clinical pneumonia and perihilar findings only	3.0	3.4	11.1 (-13.8-30.6) <i>P</i> = 0.35	2.8	3.2	11.9 (-23.3-37.0) <i>P</i> = 0.46
Clinical pneumonia and positive film	8.3	10.1	17.7 (4.8-28.9) <i>P</i> = 0.01	8.7	11.0	20.5 (4.4-34.0) <i>P</i> = 0.02

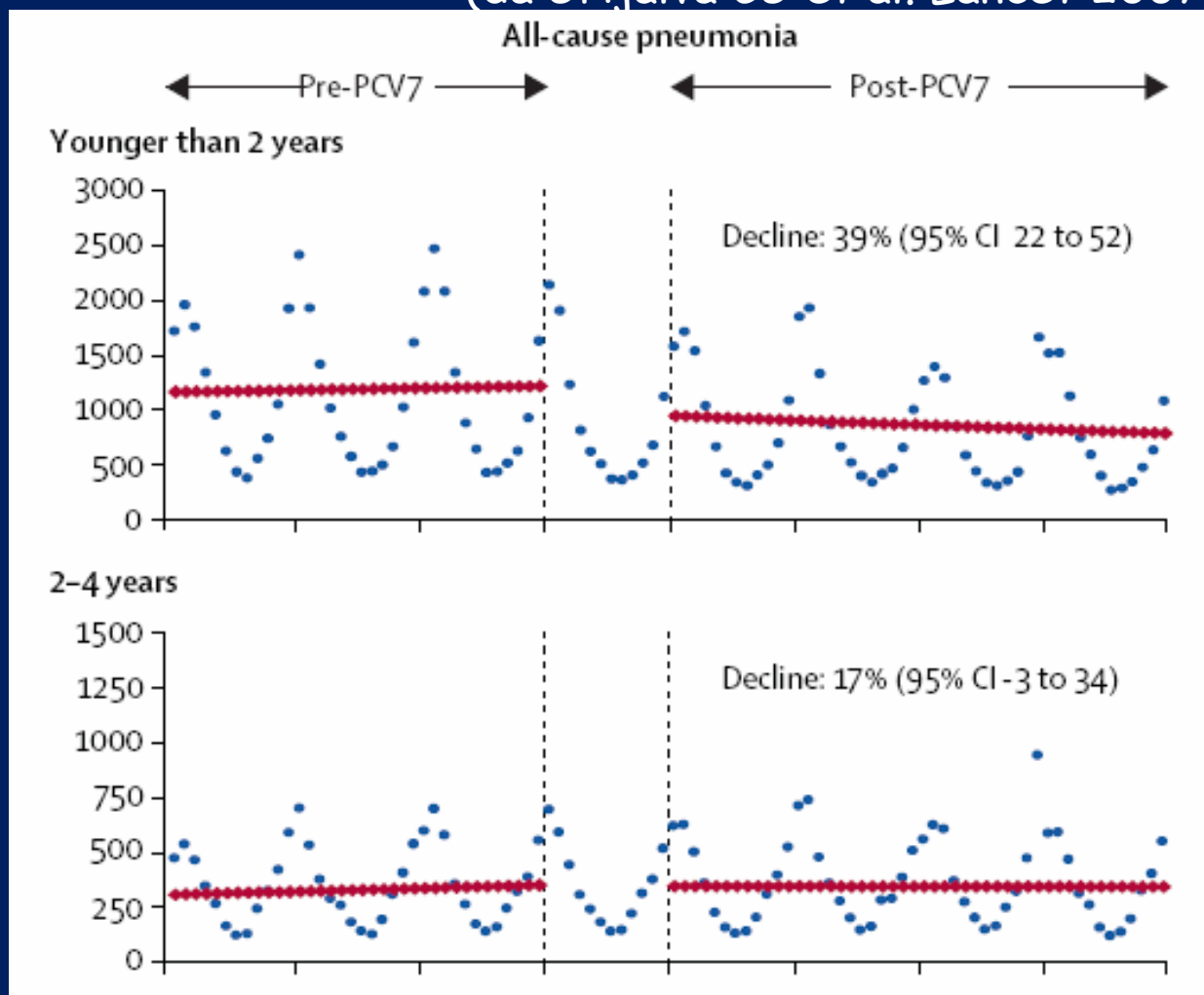
Table 4. Efficacy of the Vaccine against First Episodes of Radiologically Confirmed Pneumonia.*

Variable	Vaccinated Group	Control Group	P Value	Vaccine Efficacy (95% CI)
	<i>no. of episodes</i>			<i>%</i>
HIV-negative children	169	212	0.03	20 (2 to 35)
HIV-positive children	182	209	0.19	13 (-7 to 29)
All children	356	428	0.01	17 (4 to 28)

* CI denotes confidence interval, and HIV human immunodeficiency virus.

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)



Inpatient US
database

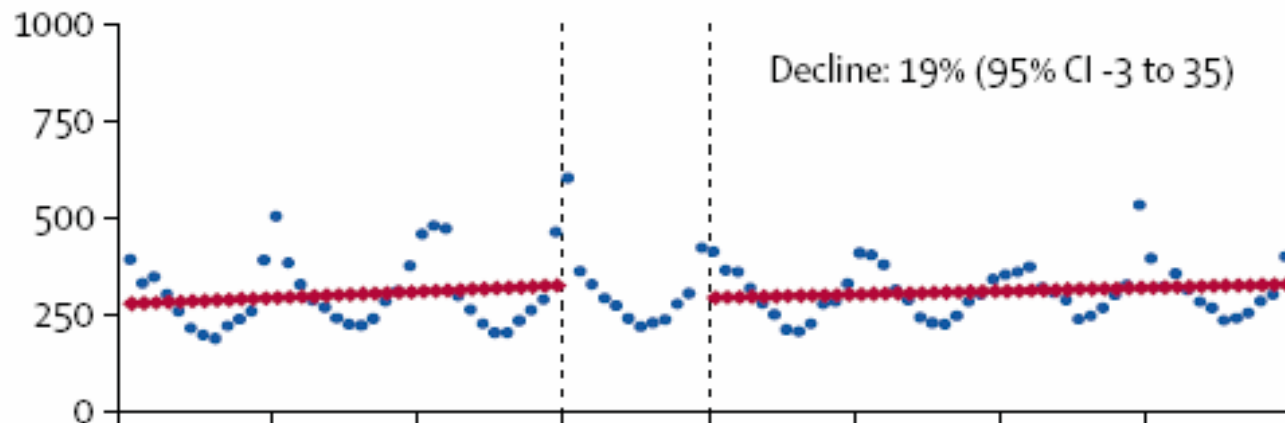
2001-2004
compared with
1997-1999

1012 hospitals
Over 38 millions
admissions

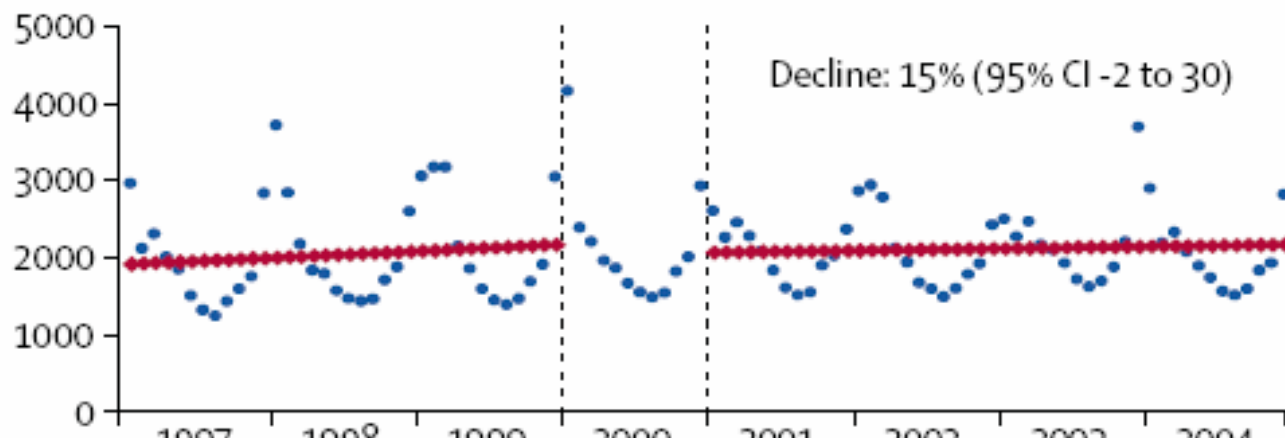
Andamento della ospedalizzazione per polmonite negli U.S.A. prima e dopo l'introduzione di PCV-7 (II)

(da Grijalva CG et al. Lancet 2007)

40-64 years

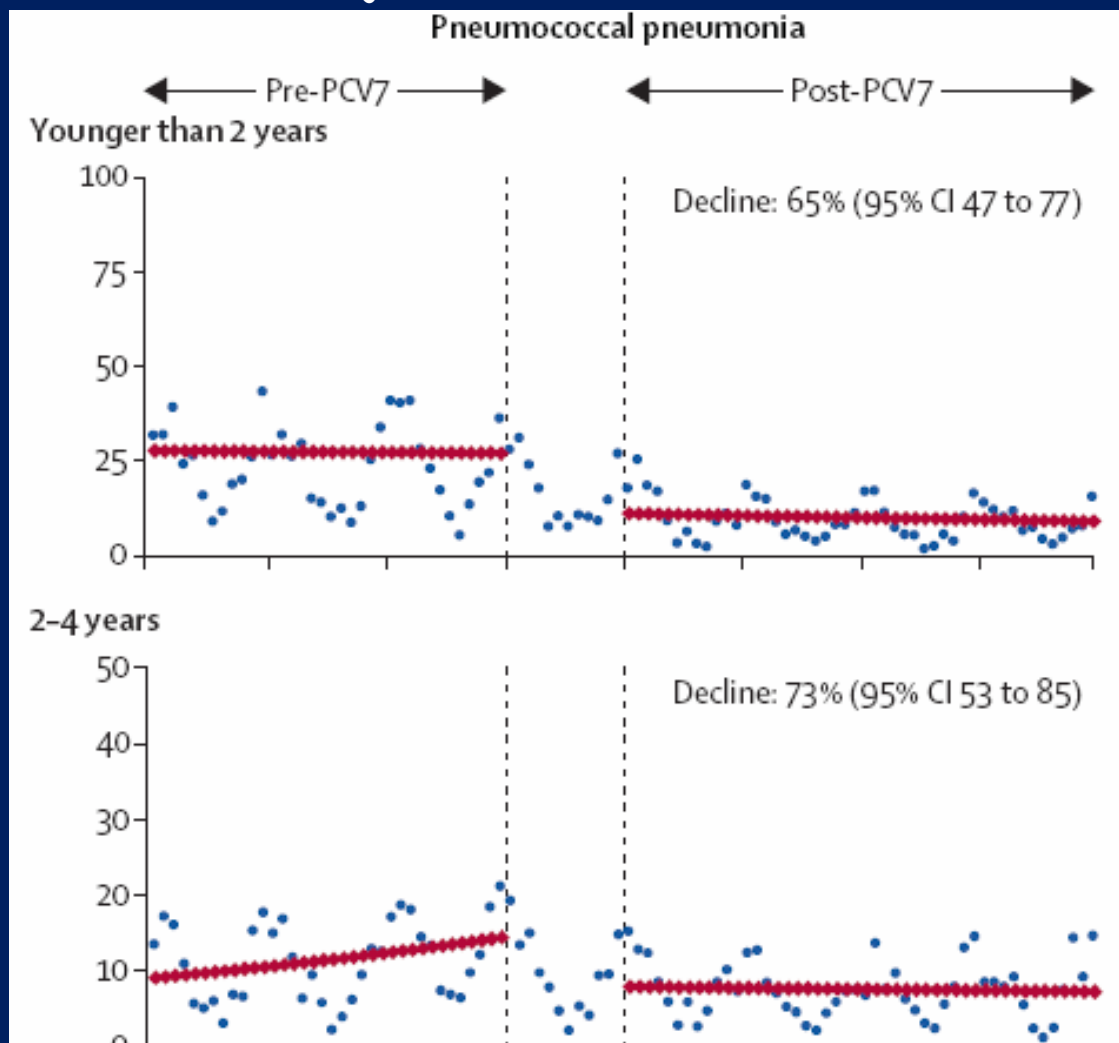


65 years or older



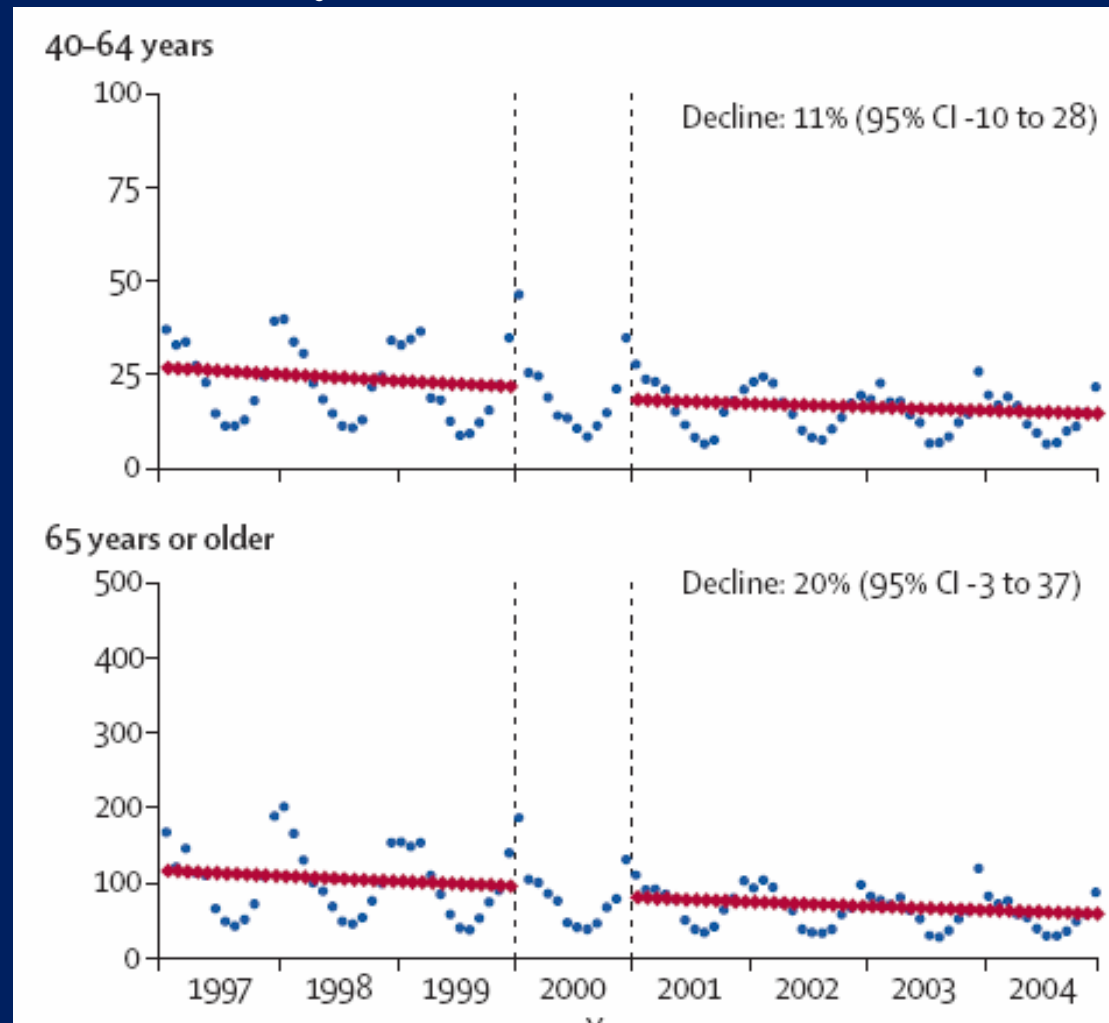
Andamento della ospedalizzazione per polmonite pneumococcica negli U.S.A. prima e dopo l'introduzione di PCV-7 (I)

(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)



Characteristics of the study population

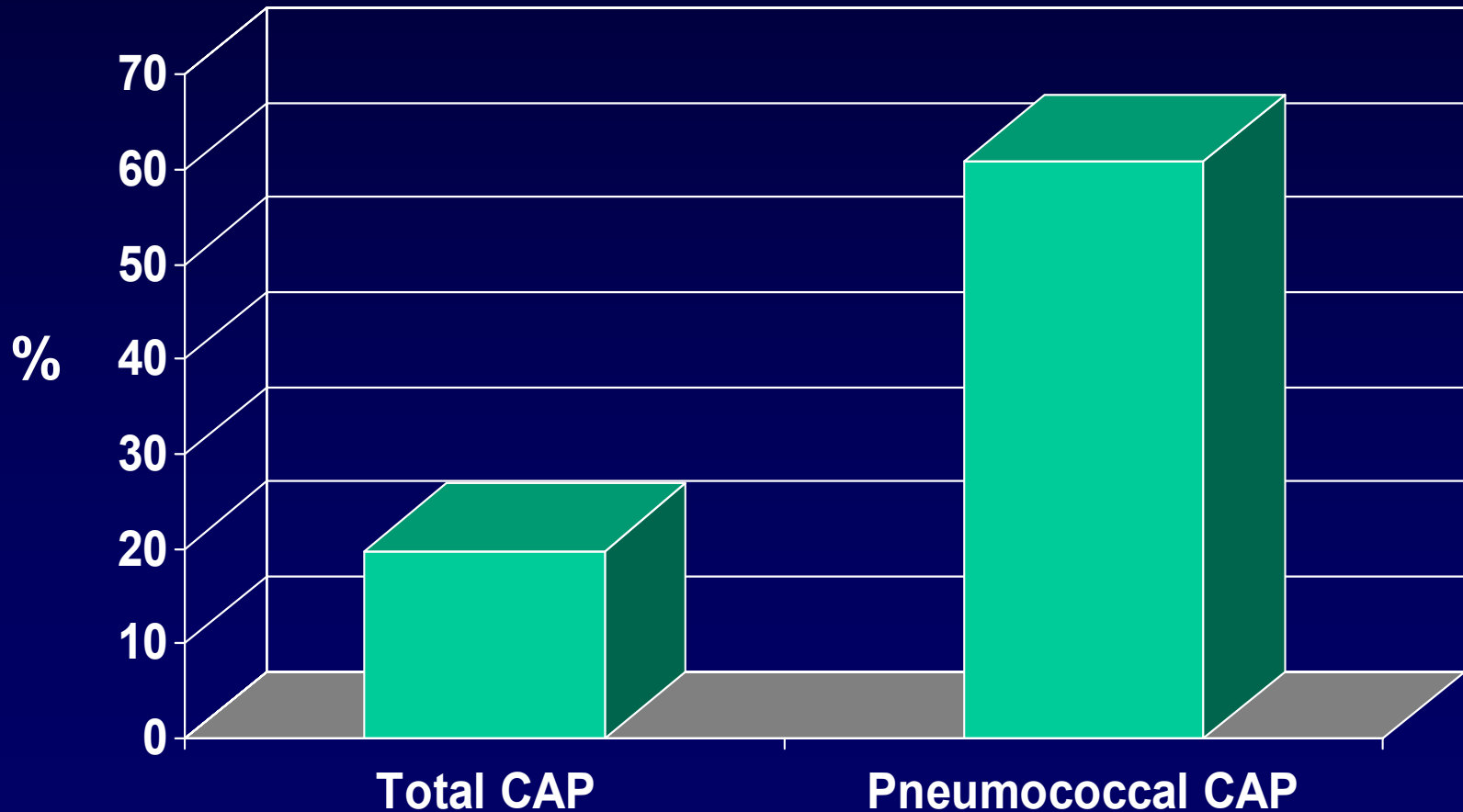
Esposito et al. *Clin Infect Dis* 2002.

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

Serotype distribution among the 48 children with community-acquired pneumococcal pneumonia

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)

PROTECTIVE COVERAGE OF PCV-7 FOR COMMUNITY ACQUIRED PNEUMONIA IN ITALIAN CHILDREN



Order of Authors: Susanna Esposito, MD; Alessandro Lizioli, MD; Annalisa Lastrico, MD; Nadia Faelli, MD; Alessandro Rognoni, MD; Claudia Tagliabue, MD; Laura Cesati, MD; Vittorio Carreri, MD; Nicola Principi, MD

This study was designed to evaluate the impact of heptavalent pneumococcal conjugate vaccine (PCV-7) administered at 3, 5 and 11 months of age on respiratory tract infections in very young children. A total of 1,571 healthy infants (910 males) aged 75-105 days (median 82 days) were enrolled to receive a hexavalent vaccine and PCV-7 (n=819) or the hexavalent vaccine alone (n=752) at 3, 5 and 11 months of age. Among the 1,555 subjects (98.9%) who completed the study, the administration of PCV-7 significantly reduced the incidence of acute otitis media and radiologically confirmed community-acquired pneumonia, also leading to a significant reduction in antibiotic consumption.

**Respiratory
Research 2007;
8:12**

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

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

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

	PCV-7 (N.811)	Control (N.744)	RR	95%CI	<i>P</i>
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