PCV Impact on Carriage Leading to Herd Effects on Disease and Resistance; Replacement; Impact on Influenza and Controversies About PCV in Adults

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COI

- I have consulted in the past for the following companies all of whom make or hope to make a pneumococcal vaccine: Pfizer; Merck; GSK; Novartis; Sanofi; Biovac
- I have also consulted to the following companies who have products to diagnose or treat pneumococcal infections: Pfizer, GSK; Bayer; Alere
- I am now working for the Gates Foundation, directing their pneumonia strategy, so I no longer do paid industry consultations

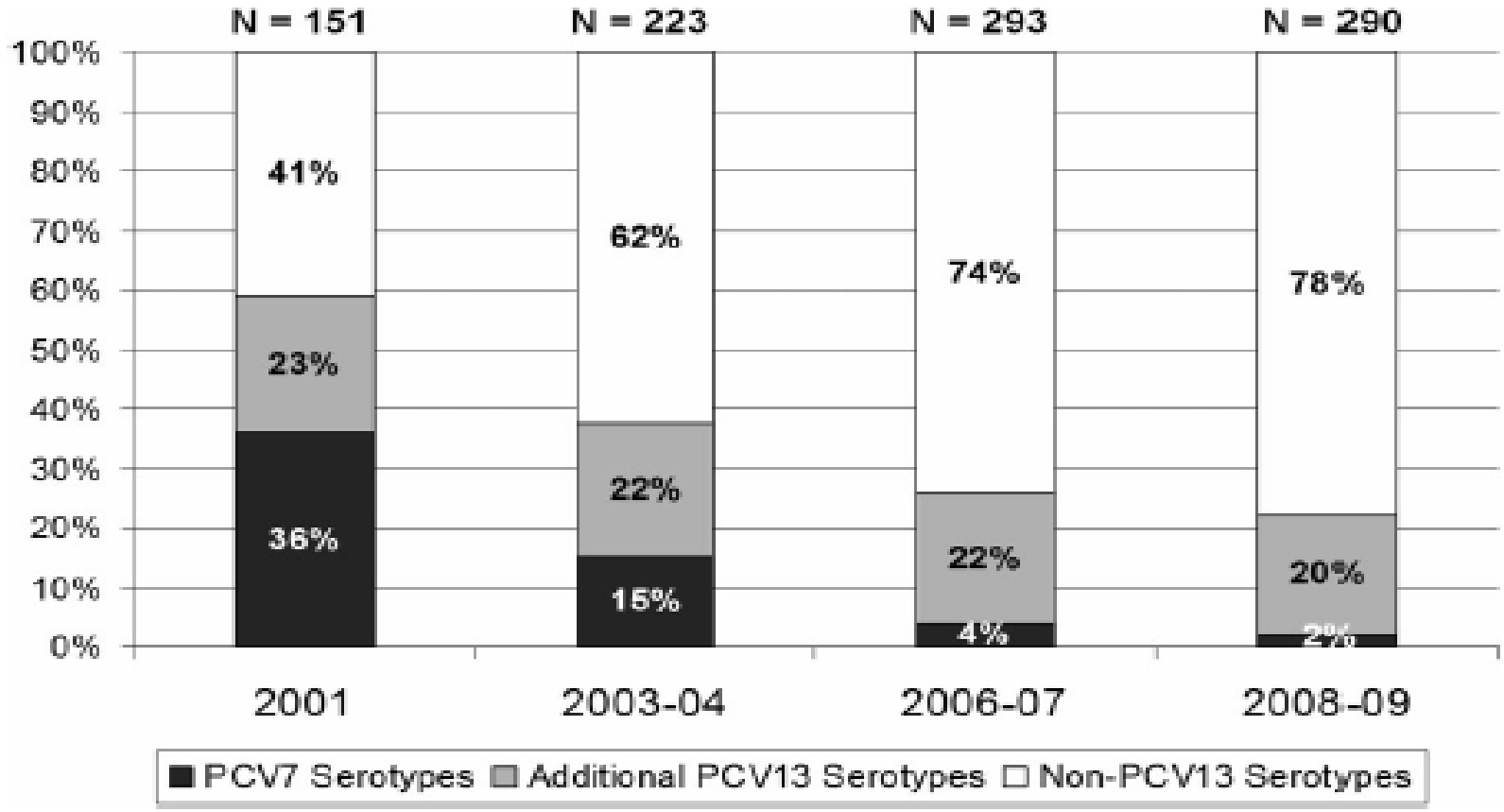
PCV9 Reduced Carriage of Vaccine Types By 50% After Primary Immunization of Infants in 1st Year of Life

	PCV9 n=242 (n [%])	**Control n=239** (n [%])	***P*-value**
Carriage of vaccine serotypes	43 (18)	86 (36)	6.5×10^{-6}
Carriage of nonvaccine serotypes	87 (36)	59 (25)	0.0007
Overall carriage	130 (54)	145 (61)	0.123

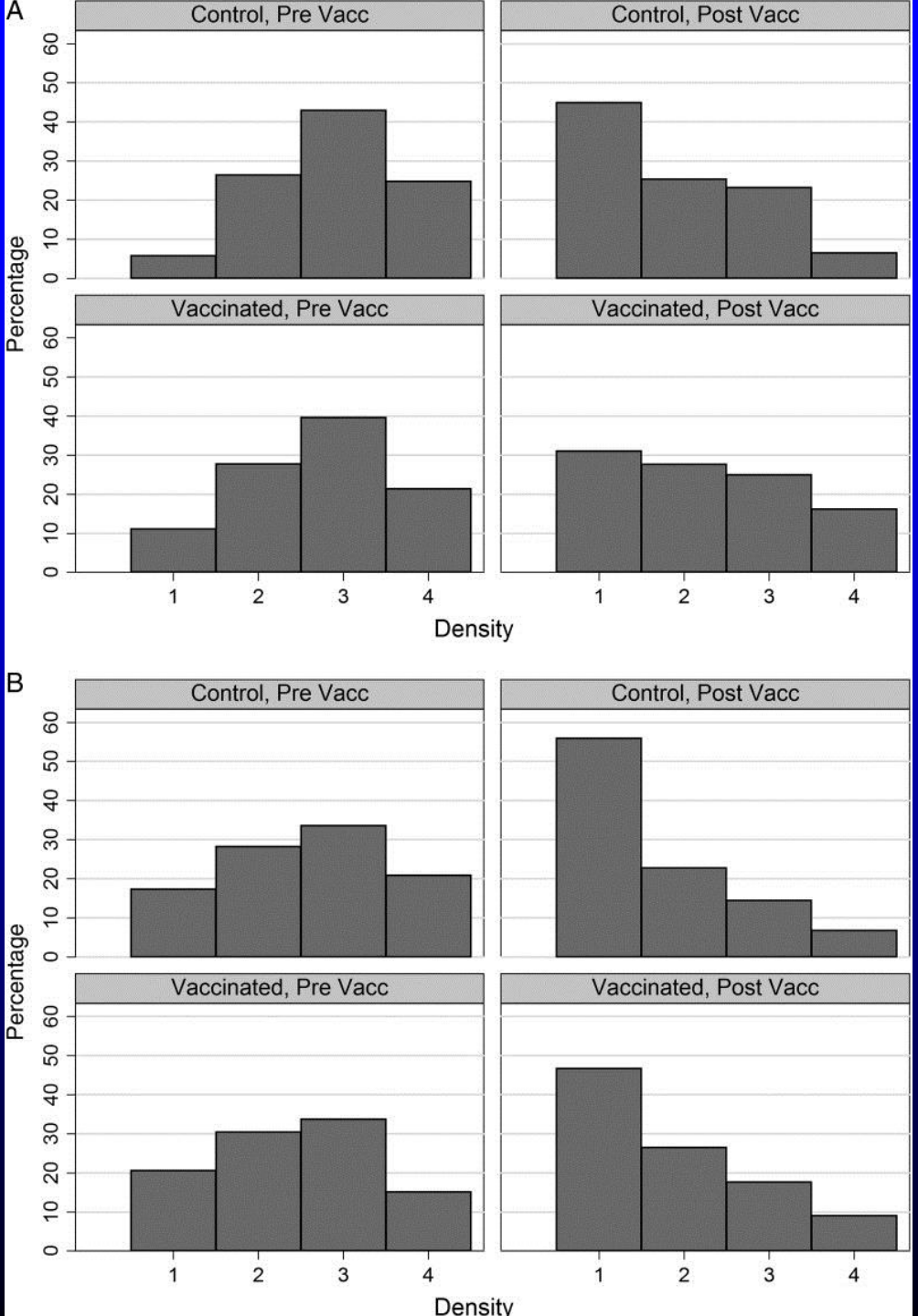
* Vaccination at 6, 10, and 14 weeks; carriage measured at 9 months.

Mbelle *et al.* JID 1999; **180**:1171–6

Reduction in PCV7 Types Carried by Children in MA, USA Post 2000



Wroe at el, Pediatr Infect Dis J. 2012 Mar;31(3):249-54



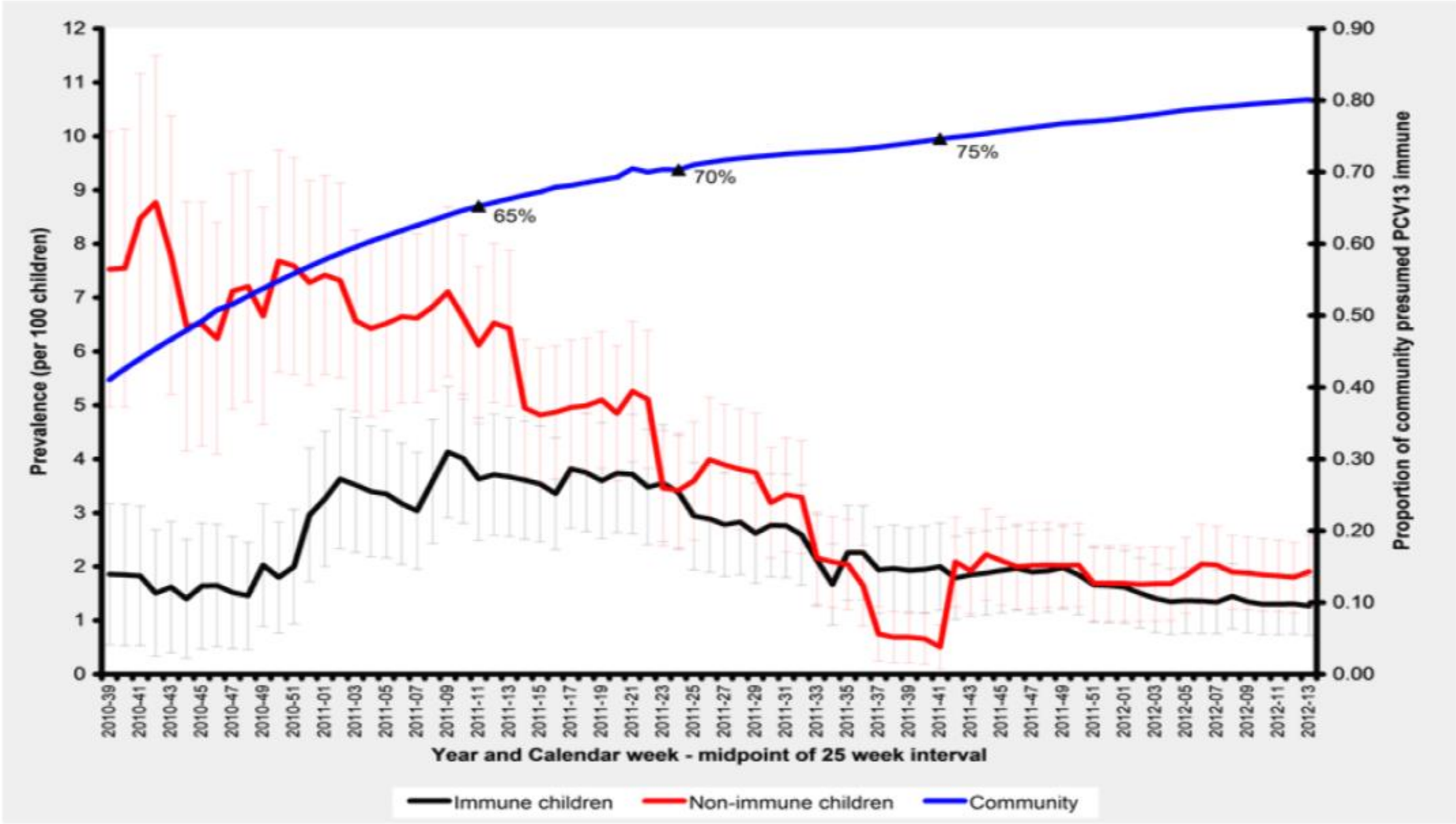
PCV7 Given Just to Kids or to All Ages in Gambia was Associated with Reduced Density In Carriage of All serotypes in All Ages

A: Ages < 5

B: Ages > 5

Roca et al, Clin Infect Dis 2012, 55, 816–824.

Carriage of PCV13 Serotypes by Children < 5 Yrs in Boston Family Practice

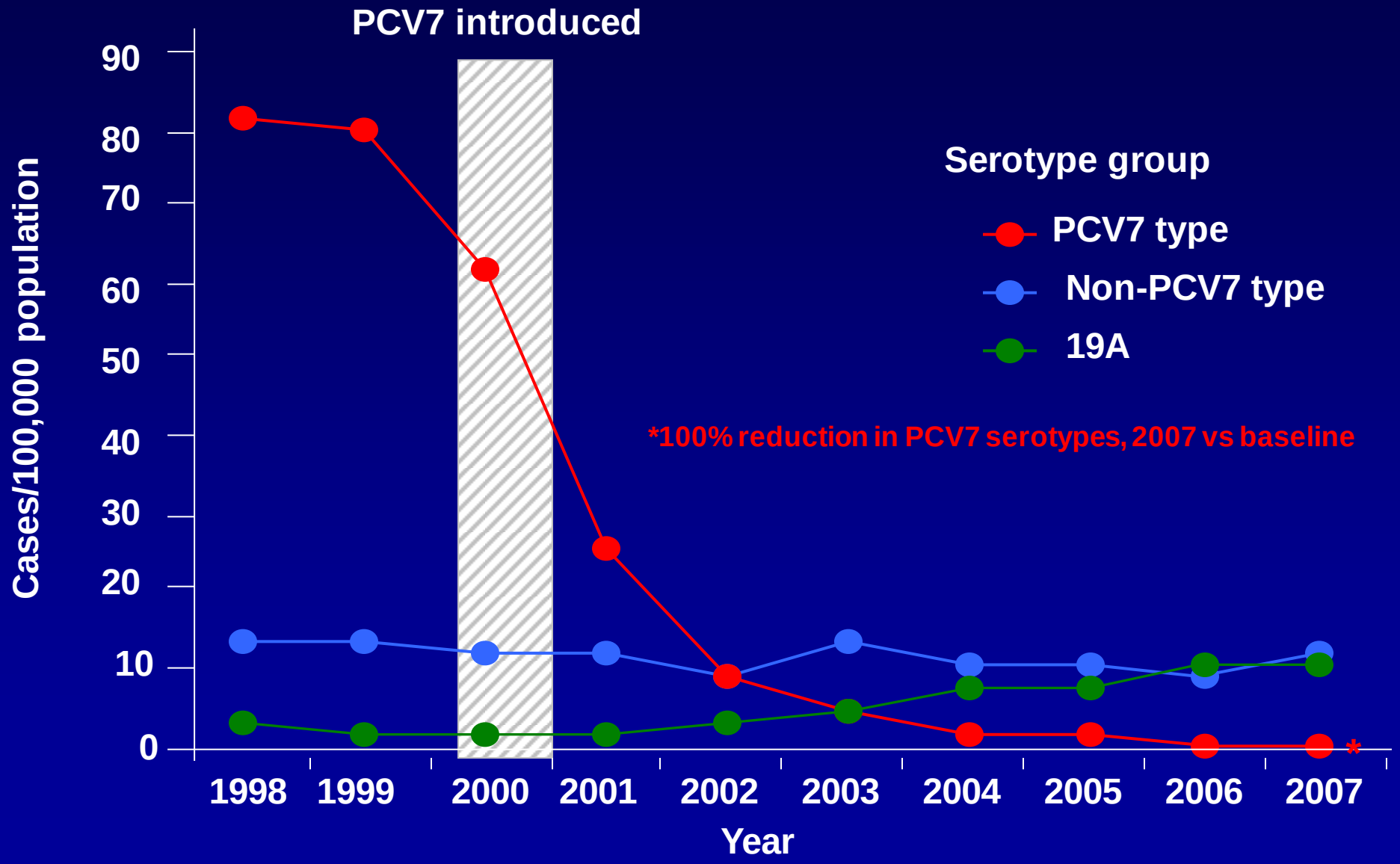


Loughlin et al, 2014, 33, 504 - 10

Data on Herd Protection Measured By Carriage from Kenya With and Without Catchup

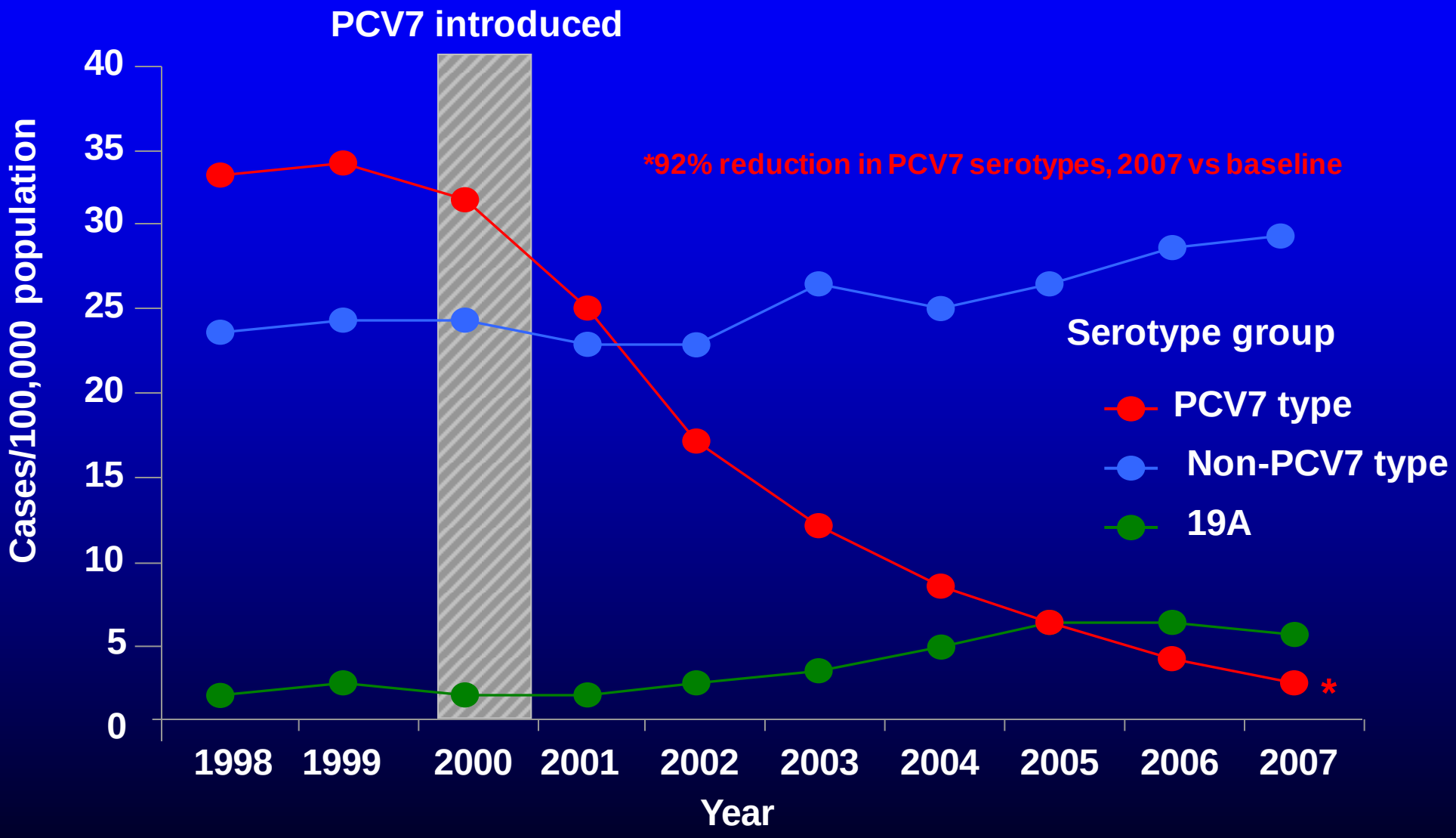
- Among individuals ≥5 years in Kilifi with catchup to age 5, the adjusted prevalence ratio 2 years post PCV10 for VT pneumococci was 0.34 (95%CIs: 0.18-0.62) (Hammitt et al, pneumonia 2014, 3,12)
- In Kibera, Nairobi, without catchup < 2 years post PCV10 in 85 unvaccinated children 1–4 years old, PCV10 serotypes decreased by 61% ($p < 0.001$) (Kim et al, pneumonia 2014, 3, 35)

Direct Effect of Vaccination: Invasive Pneumococcal Disease Among Children < 5 Years, 1998/99–2007



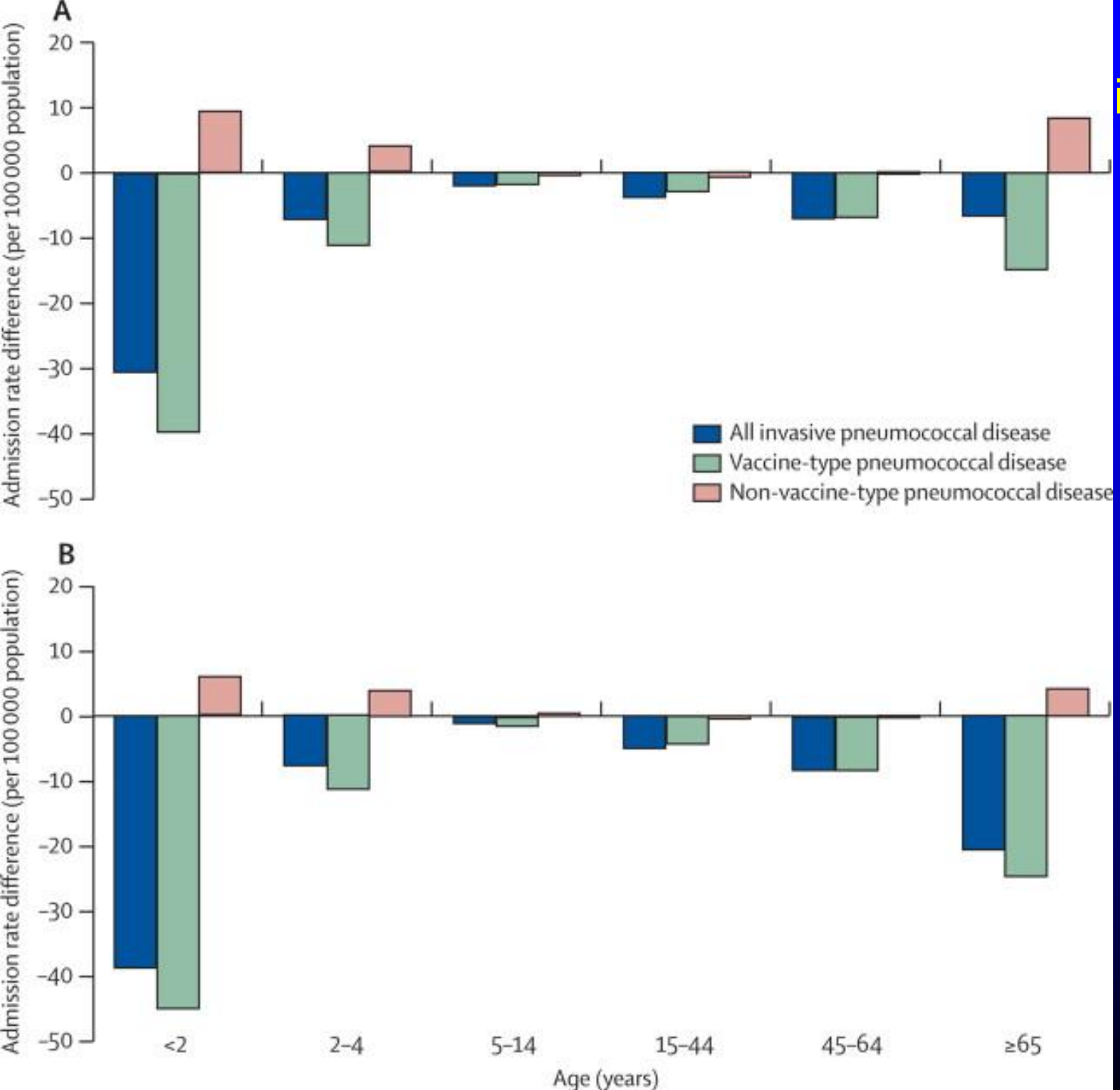
Pilishvili T, et al. *J Infect Dis*. 2010;201:32-41.

Invasive Pneumococcal Disease Among Adults ≥ 65 Years, 1998/99–2007



Pilishvili T, et al. *J Infect Dis*. 2010;201:32-41.

Absolute Rate Changes in IPD 4 years post PCV Introduction

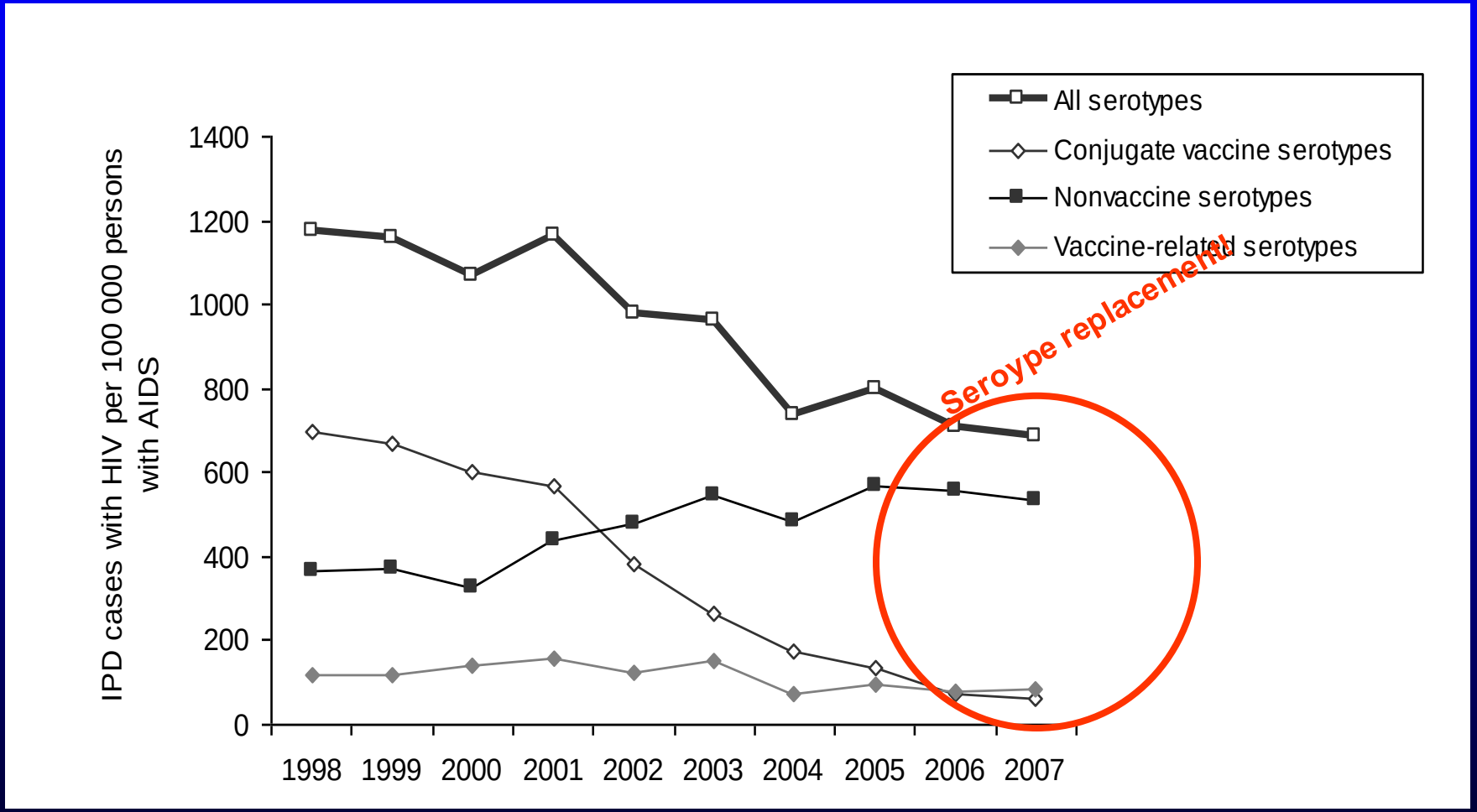


UK

US

Grijalva, Moore, Griffin, Lancet ID, 2011, 11, 724-6

IPD caused by PCV7 & NonPCV7 serotypes among adults aged 18-64 years with HIV/AIDS

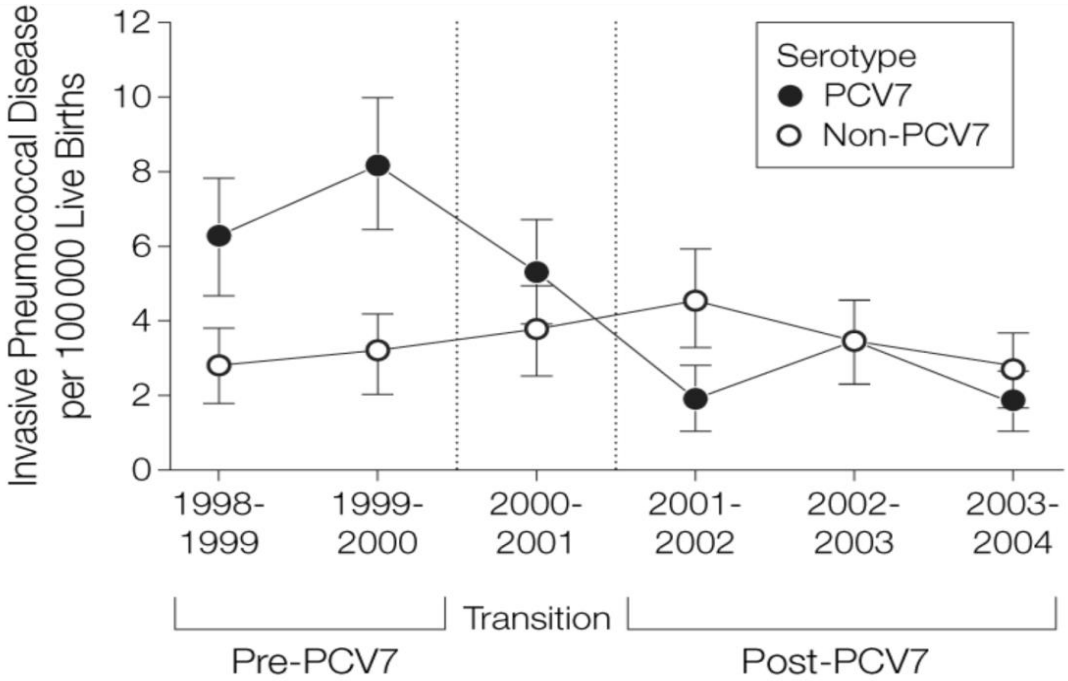


Cohen et al, 2010 , AIDS, 24, 2253-62

From: **Invasive Pneumococcal Disease Among Infants Before and After Introduction of Pneumococcal Conjugate Vaccine**

JAMA. 2006;295(14):1668-1674. doi:10.1001/jama.295.14.1668

Rates of Invasive Pneumococcal Disease for Infants Aged 0 to 90 Days by Year



Notably, the rate of IPD among infants aged 0 to 60 days decreased from 7.3 (95% CI, 5.6-9.5) per 100 000 live births in the pre-PCV7 years to 4.2 (95% CI, 3.0-5.9; P = .01) per 100 000 live births in the post-PCV7 years, although PCV7 is not recommended until infants reach 2 months of age.

Early Post PCV 7 (2009) And PCV 13 (2011) Impact in Kids and Middle Age (Mostly HIV Infected) Adults in South Africa

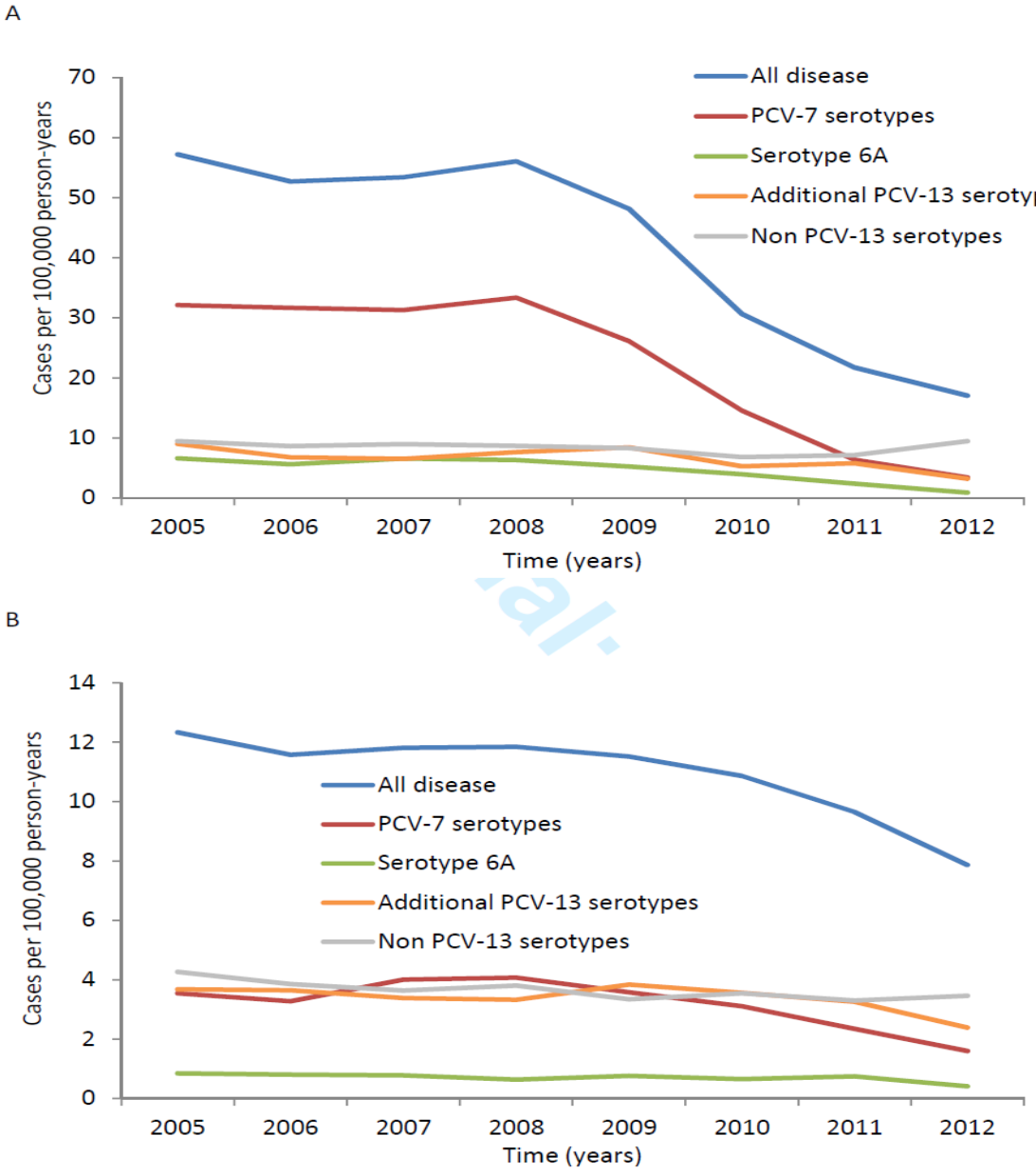
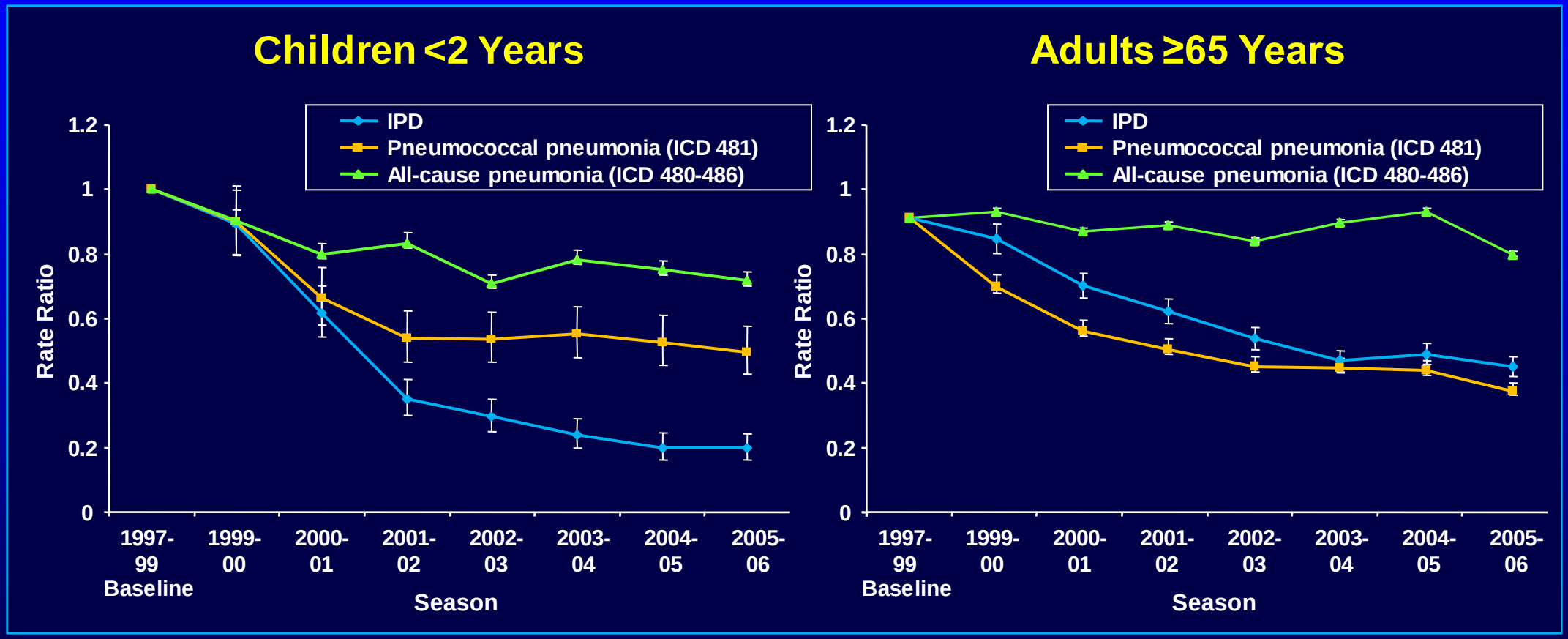


Figure 2. Incidence of invasive pneumococcal disease reported by year and serotype group among those (A) <2 years and (B) 25–44 years of age, South Africa, 2005 through 2012. PCV-7 and PCV-13 were introduced in 2009 and 2011, respectively.

Anne von Gottberg et al, 2014, unpublished

US Observational Study of PCV7 Impact on IPD and Pneumococcal Pneumonia



Simonsen L et al, Mbio, 2011, 2, e00309-10.

US Cases of Hospitalization Prevented, 2000-2006

	IPD			Nonbacteremic pneumococcal pneumonia (ICD9 481 with no IPD codes)		
Age Group	Estimate	Lower 95% CI	Upper 95% CI	Estimate	Lower 95% CI	Upper 95% CI
<2	8440	8101	8752	3399	4119	2572
2-4	2025	1766	2244	934	1590	188
5-17	1528	1257	1772	3977	4595	3305
18-39	8592	7658	9432	21808	23411	20094
40-64	7270	5428	9004	24614	26976	22169
65+	20046	16851	23014	99415	110428	87565
Total	**47899**	**41060**	**54218**	**154147**	**171118**	**135893**
% Adults	**75%**			**95%**		

Simonsen L et al, Mbio, 2011, 2, e00309-10.

TABLE 3 Estimated PCV7-associated reductions[a] in the U.S. burden of mortality while hospitalized for IPD, pneumococcal pneumonia, or all-cause pneumonia, 1999–2000 through 2005–2006 seasons

Age group	Estimated IPD reduction	95% CI	Estimated pneumococcal pneumonia (ICD9 481) reduction	95% CI	Estimated all-cause pneumonia reduction	95% CI
<2	212	81–275	34	–66–67	548	425–646
2–4	46	12–62	26	–3–38	191	136–235
5–17	103	65–130	13	–14–29	350	252–431
18–39	810	674–922	1,088	888–1,245	2,495	2,220–2,754
40–64	1,045	709–1,349	2,304	1,990–2,596	8,513	7,674–9,312
≥65	4,007	3,246–4,693	10,895	9,772–11,934	71,556	61,644–81,013
Total	6,222	4,788–7,431	14,360	12,568–15,908	83,653	72,351–94,391

[a] Number of deaths prevented.

Simonsen L et al, Mbio, 2011, 2, e00309-10

Herd Protection Through Interruption of Carriage

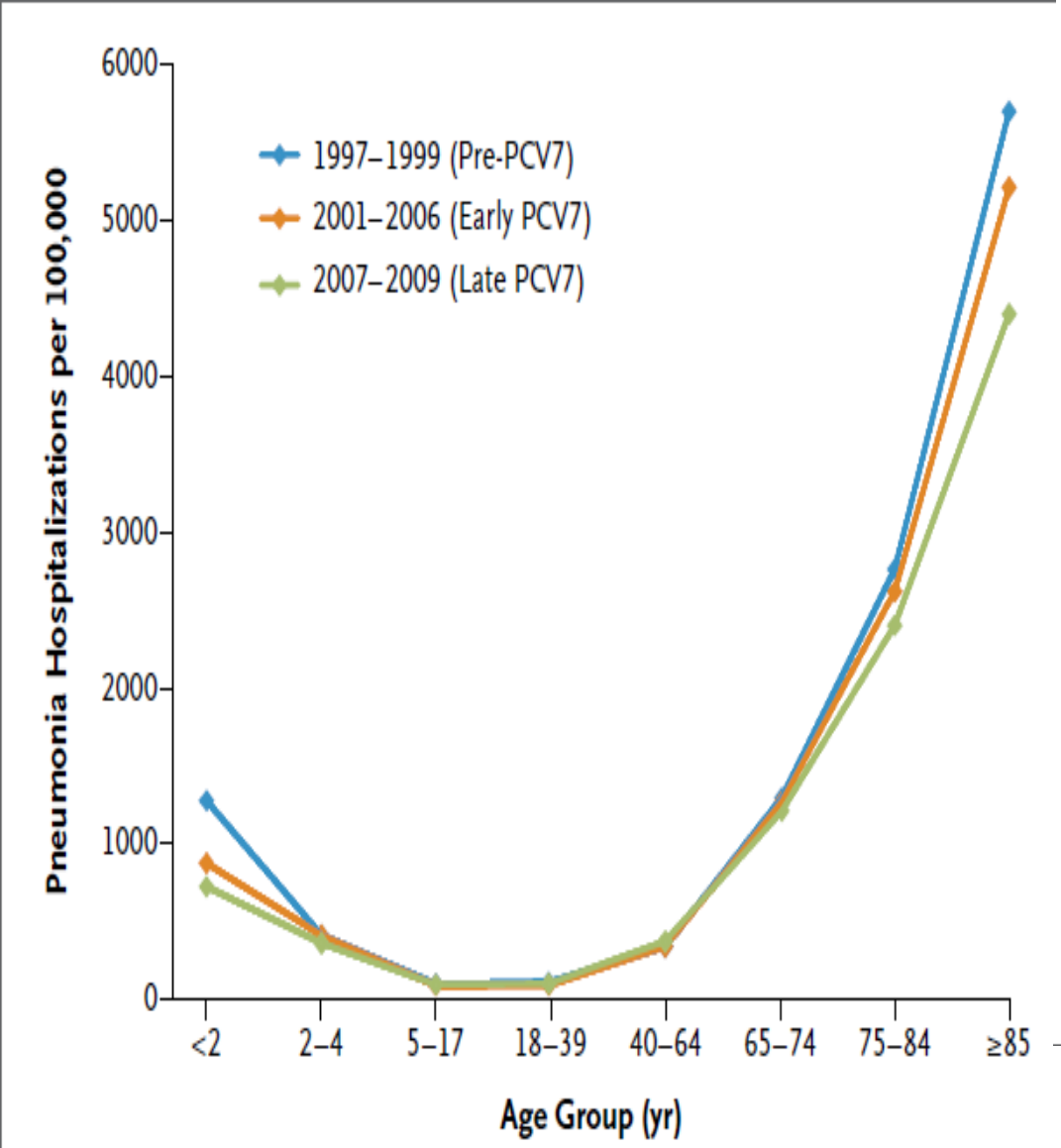
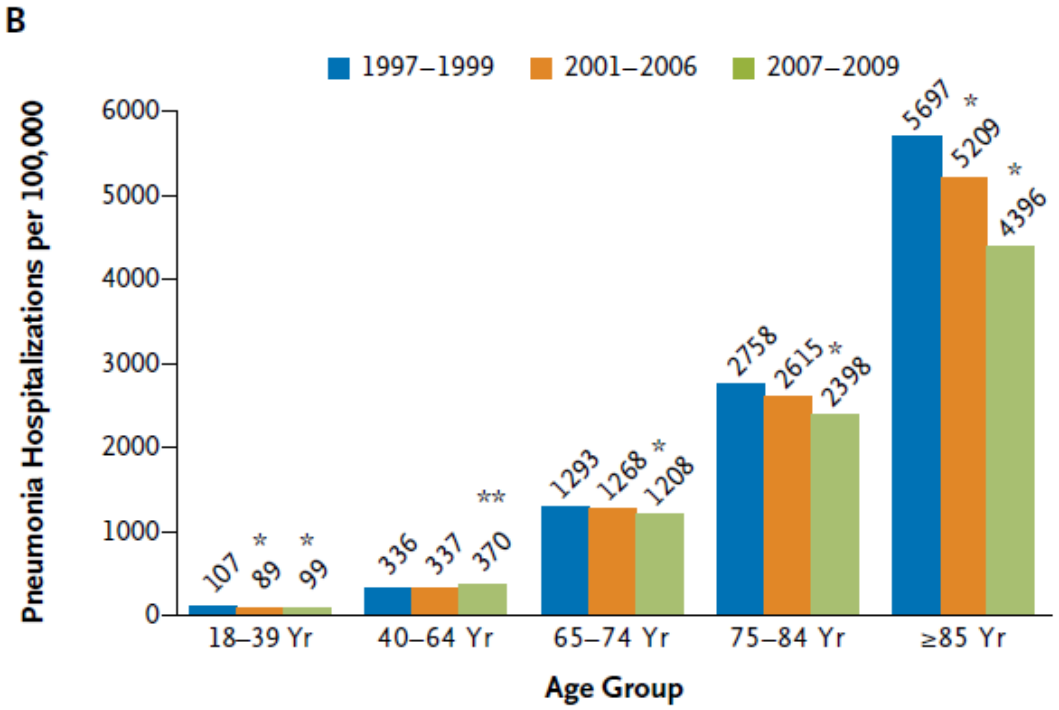


Figure 1. Average Annual Rates of U.S. Hospitalizations for Pneumonia before and after the Introduction of PCV7, According to Age Group.

PCV7 denotes 7-valent pneumococcal conjugate vaccine.



Griffin et al. (2013). *NEJM*, 369,155-163

Herd Protection Through Interruption of Carriage

Table 2. Differences in Rates of Hospitalization for Pneumonia from Any Cause 3 Years before and 7 to 9 Years after the Introduction of PCV7.*

Age	U.S. Population, 2009	Difference in Hospitalization Rates per 100,000 Population, Pre-PCV7 vs. Late PCV7	Reduction in Hospitalizations, Pre-PCV7 to Late PCV7	Estimated Absolute Reduction in Hospitalizations, 2009
	millions	*no. (95% CI)*	*% (95% CI)*	*no. (95% CI)*
<2 yr	8.6	551.1 (445.1 to 657.1)	43.2 (34.9 to 51.6)	47,000 (38,000 to 56,000)
2–4 yr	12.7	51.3 (9.8 to 92.8)	12.5 (2.4 to 22.6)	7,000 (1,000 to 12,000)
5–17 yr	53.2	4.4 (–5.9 to 14.7)	4.5 (–6.1 to 15.1)	2,000 (–3,000 to 8,000)
18–39 yr	92.5	8.4 (0.6 to 16.2)	7.8 (0.6 to 15.1)	8,000 (<1,000 to 15,000)
40–64 yr	100.4	–33.8 (–57.4 to –10.2)	–10.1 (–17.1 to –3.0)	–34,000 (–58,000 to –10,000)
65–74 yr	20.8	85.3 (7.0 to 163.6)	6.6 (0.5 to 12.7)	18,000 (1,000 to 34,000)
75–84 yr	13.1	359.8 (199.6 to 520.0)	13.0 (7.2 to 18.9)	47,000 (26,000 to 68,000)
≥85 yr	5.6	1300.8 (984.0 to 1617.6)	22.8 (17.3 to 28.4)	73,000 (55,000 to 91,000)
All age groups†	307.0	54.8 (41.0 to 68.5)	10.5 (7.9 to 13.1)	168,000 (126,000 to 210,000)

Griffin et al. (2013). *NEJM*, 369:155-163

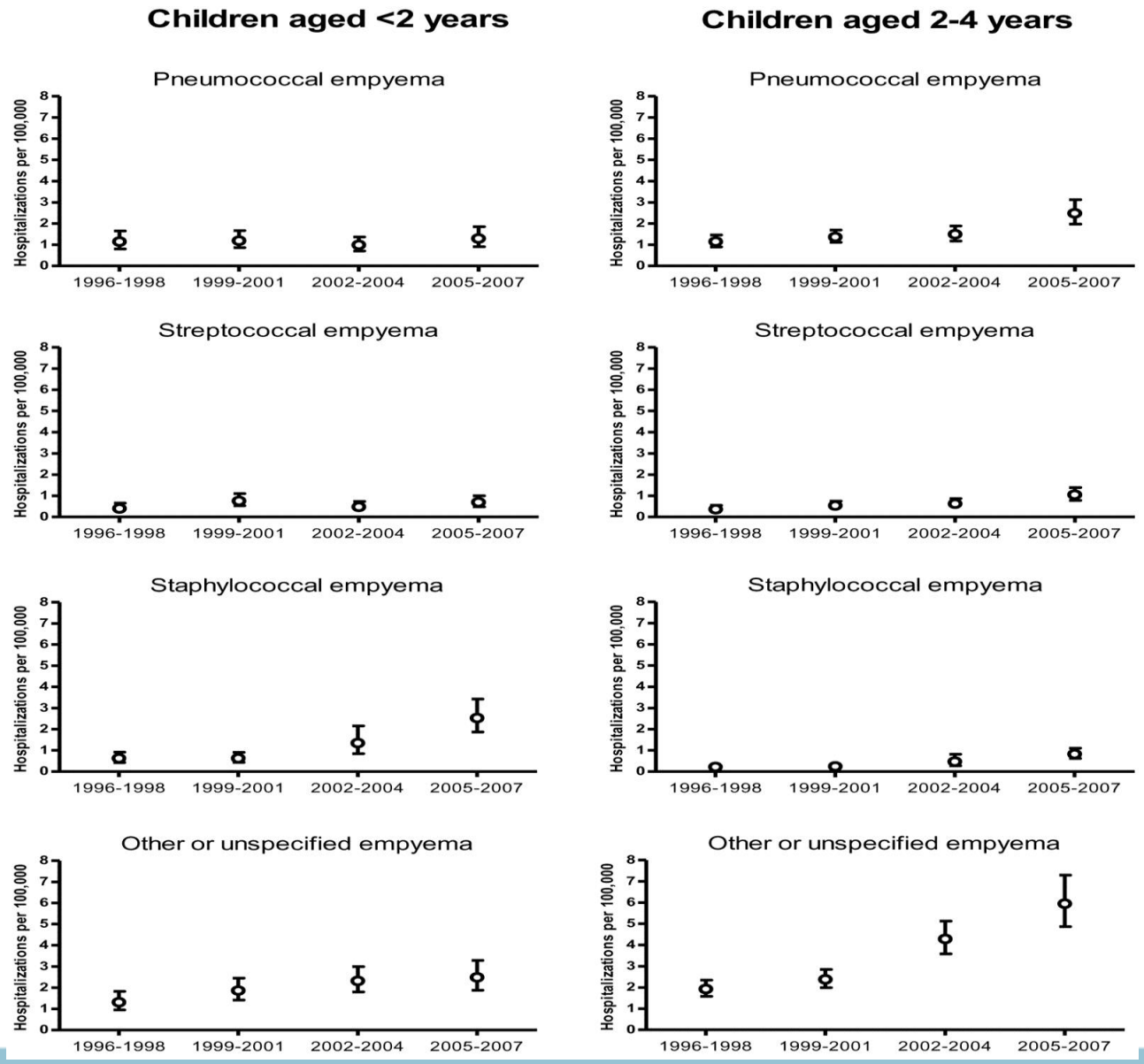


Figure 3. Rates of pneumonia hospitalizations complicated by empyema by associated pathogens, United States children aged <5 years (1996–2007). Error bars indicate 95% confidence intervals.

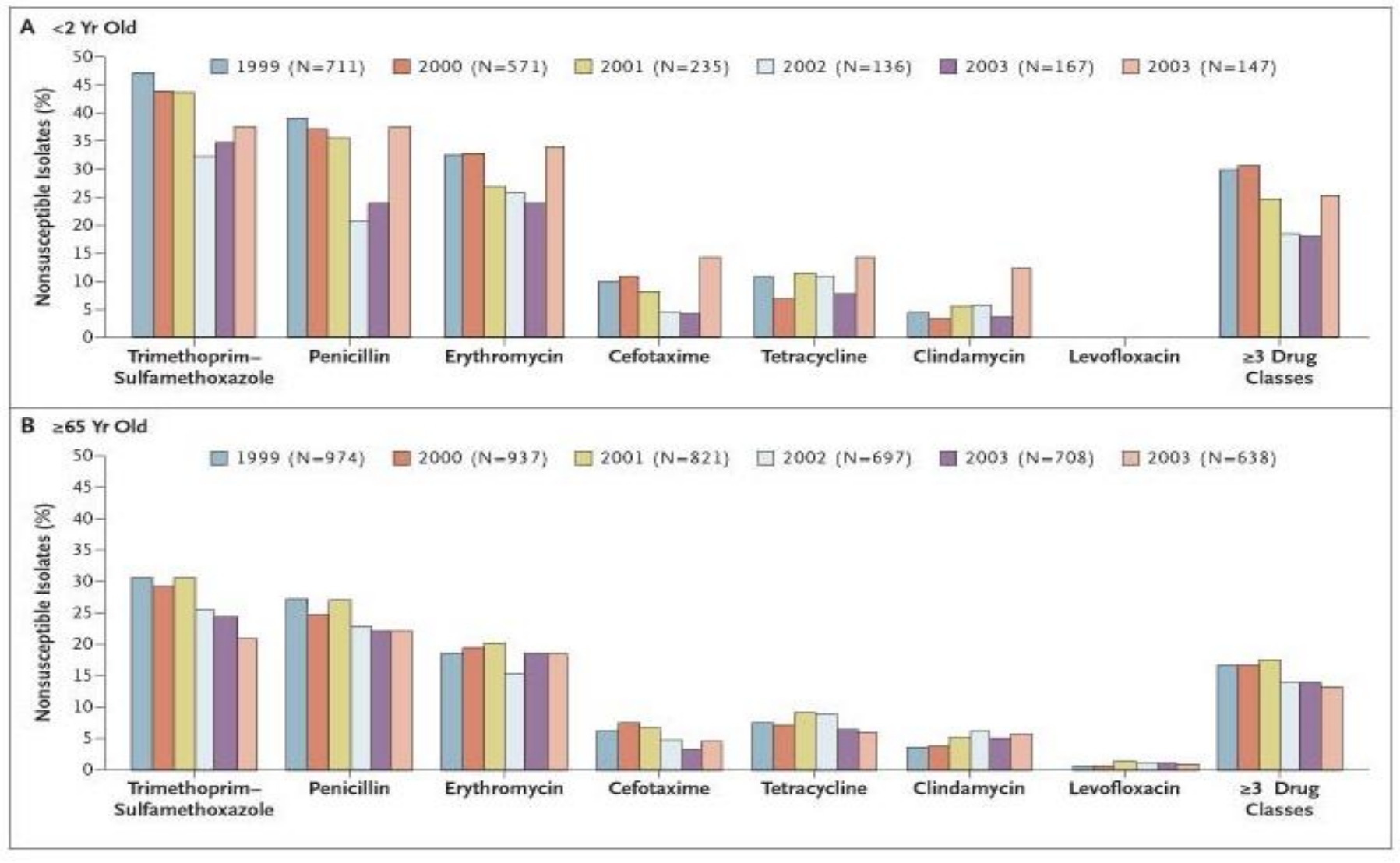
Impact of PCV13 on Hospital Admissions in USA

	All-cause pneumonia	Invasive pneumococcal disease	Non-invasive pneumococcal or lobar pneumonia	Empyema
<2 years	21% (14 to 28)*	64% (47 to 75)*	40% (14 to 59)*	50% (22 to 68)*
2–4 years	17% (7 to 27)*	55% (16 to 75)*	33% (–3 to 56)	46% (21 to 64)*
5–17 years	–3% (–20 to 11)	25% (–24 to 54)	51% (29 to 66)*	37% (13 to 54)*
18–39 years	12% (6 to 17)*	37% (20 to 51)*	32% (17 to 44)*	–8% (–25 to 6)
40–64 years	2% (–2 to 6)	13% (–1 to 26)	25% (16 to 33)*	–4% (–13 to 3)
≥65 years	3% (–1 to 6)	29% (16 to 40)*	34% (27 to 41)*	–1% (–10 to 7)

Data are percentage change (95% CI) according to our model. Assumes vaccine coverage at March, 2012 level.
*Significant reduction ($p<0.05$).

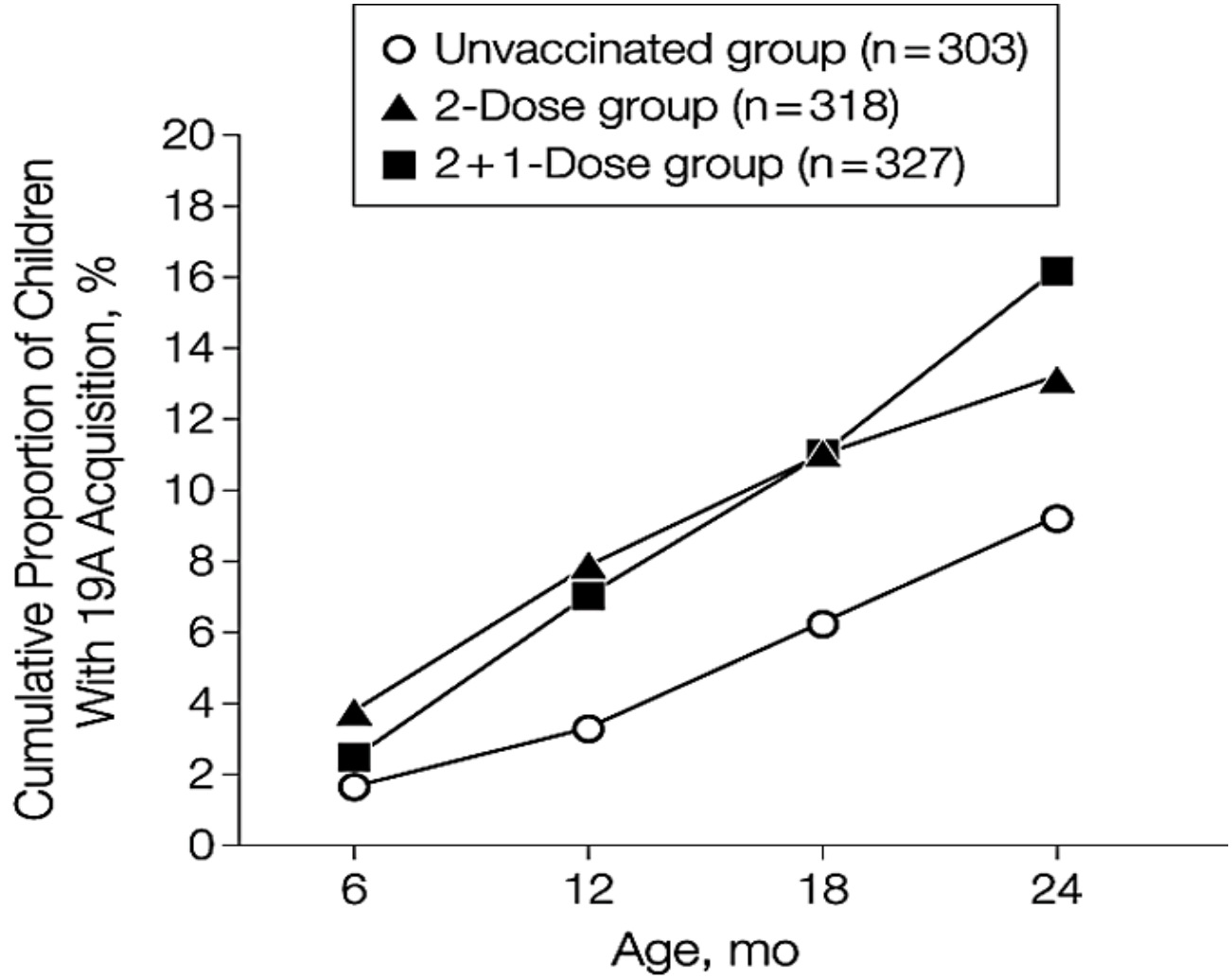
Simonsen et al, Lancet Resp Med, Mar 5 2014 epub ahead of print

Effect of introduction of PCV-7 on drug-resistant *S. pneumoniae*



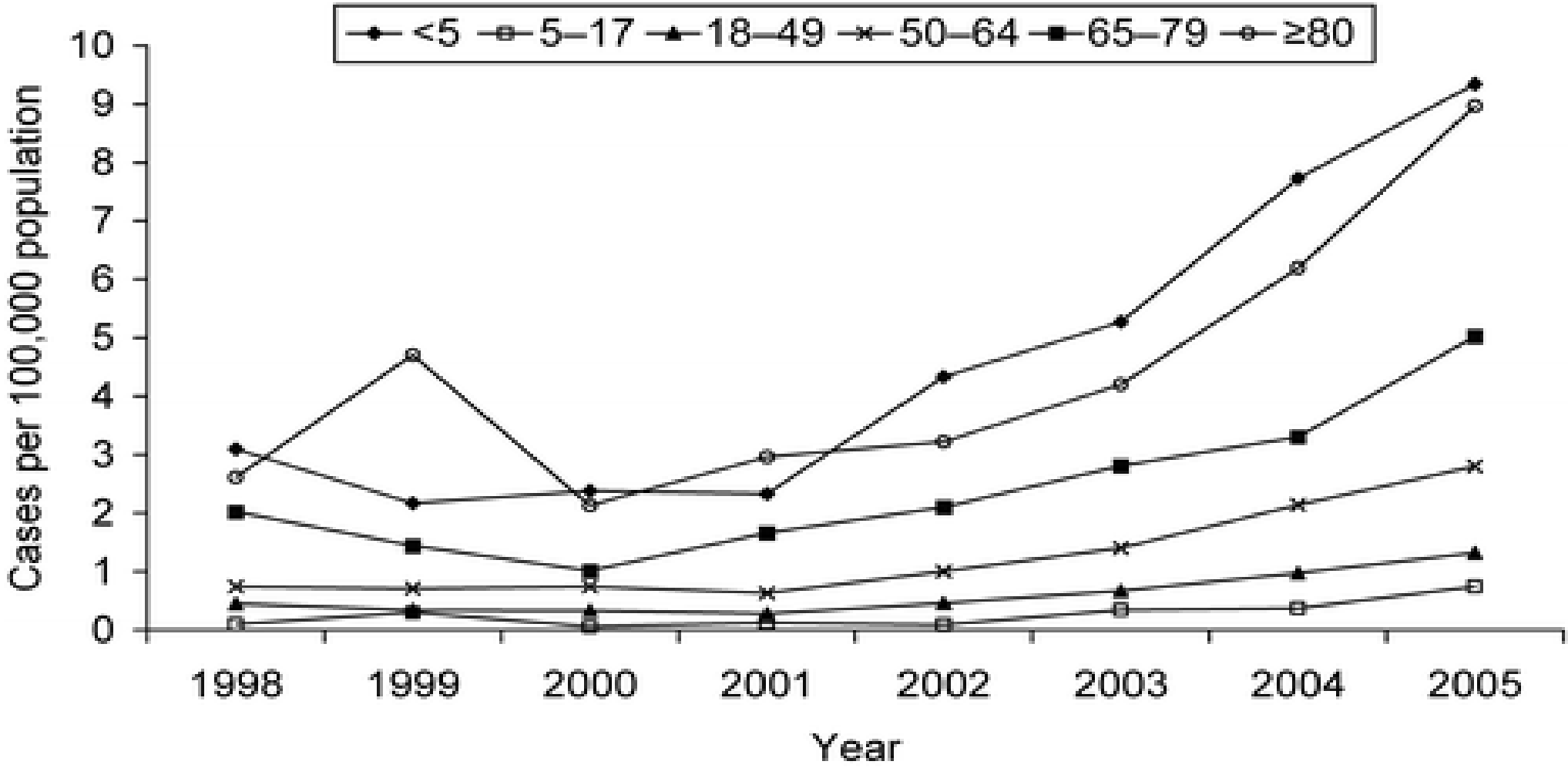
Kyaw *et al*. *N Engl J Med*. 2006; **354**:1455–63

Figure 2. Cumulative Proportions of Children With New Acquisition of Serotype 19A After Finishing Primary Series of 7-Valent Pneumococcal Conjugate Vaccine vs Unvaccinated Children



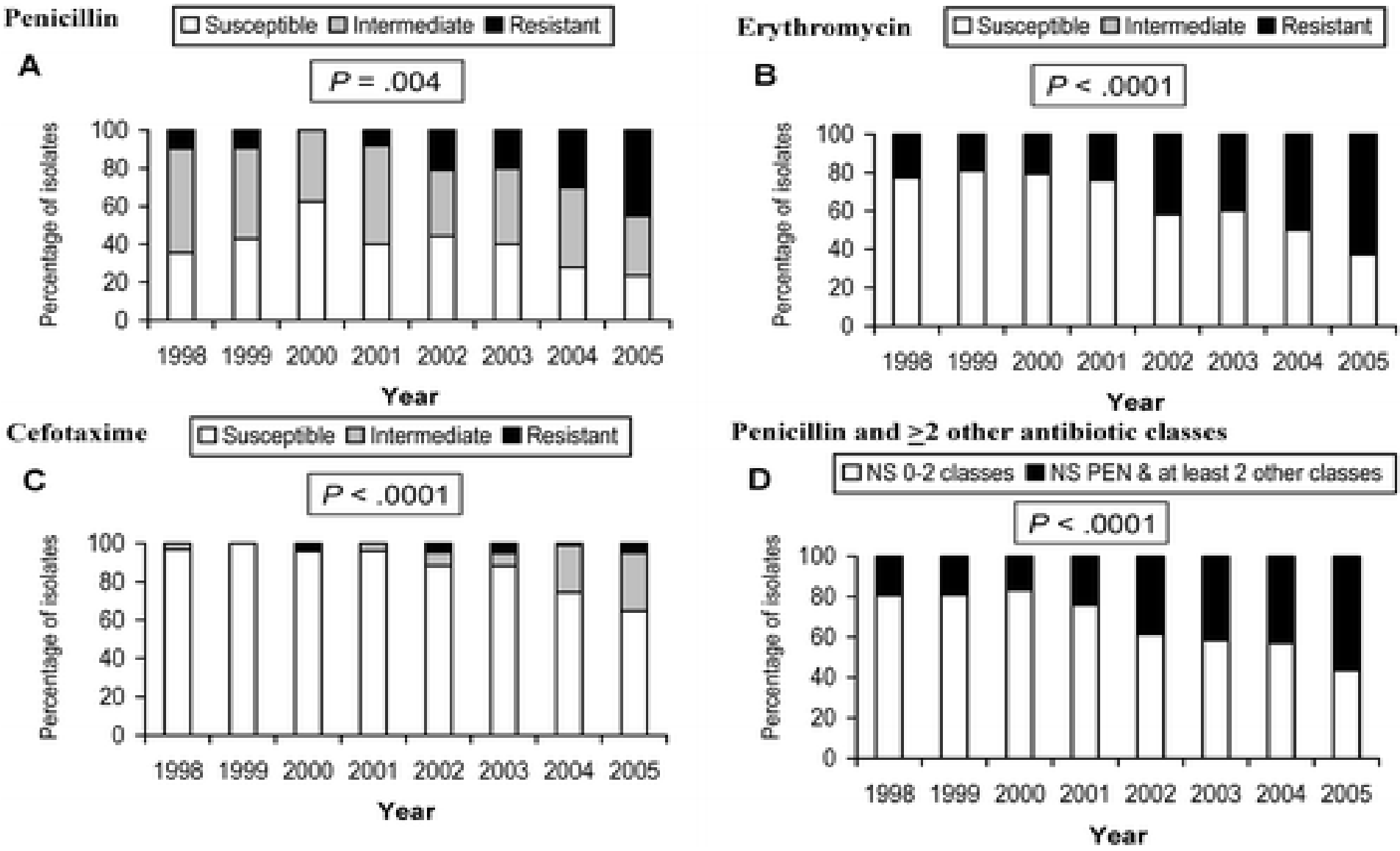
van Gils, E. J. M. et al. JAMA 2010;304:1099-1106

Serotype 19A



Moore et al, JID, 2008, 197(7):1016–1027

Serotype 19A

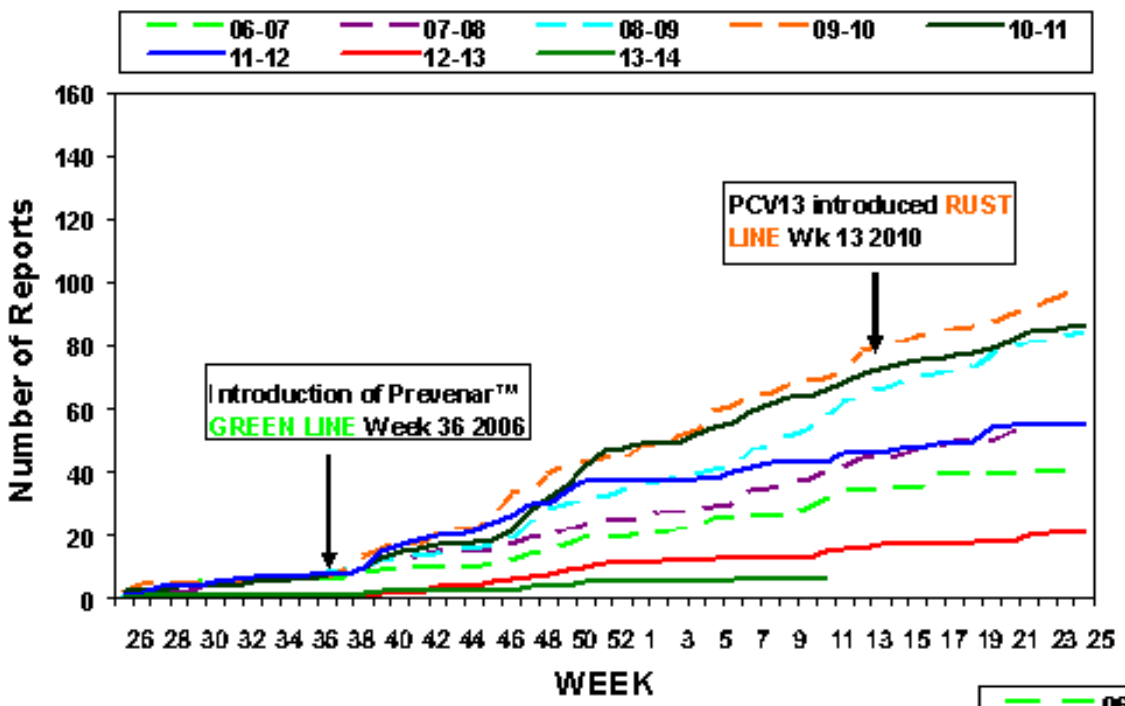


Moore et al, JID, 2008, 197(7):1016–1027

Emergence of Antibiotic – Resistant Serotype 15A - USA

Serotype, characteristic	No. (%) of isolates per year								
	1999	2000[a]	2001[b]	2002[a]	2003	2004[a]	2005	2006	2007
15A									
Patient age, years									
0–4	0	0	0	0	2	1	1	6	12
⩾5	8	7	5	22	12	34	62	78	105
Susceptibility to penicillin									
Susceptible	6 (75.0)	3 (42.9)	2 (40.0)	9 (40.9)	4 (28.6)	5 (14.3)	8 (12.7)	11 (13.1)	18 (15.4)
Intermediate resistance	2 (25.0)	4 (57.1)	3 (60.0)	13 (59.1)	10 (71.4)	30 (85.7)	55 (87.3)	72 (85.7)	98 (83.8)
Resistance	0	0	0	0	0	0	0	1 (1.2)	1 (0.8)

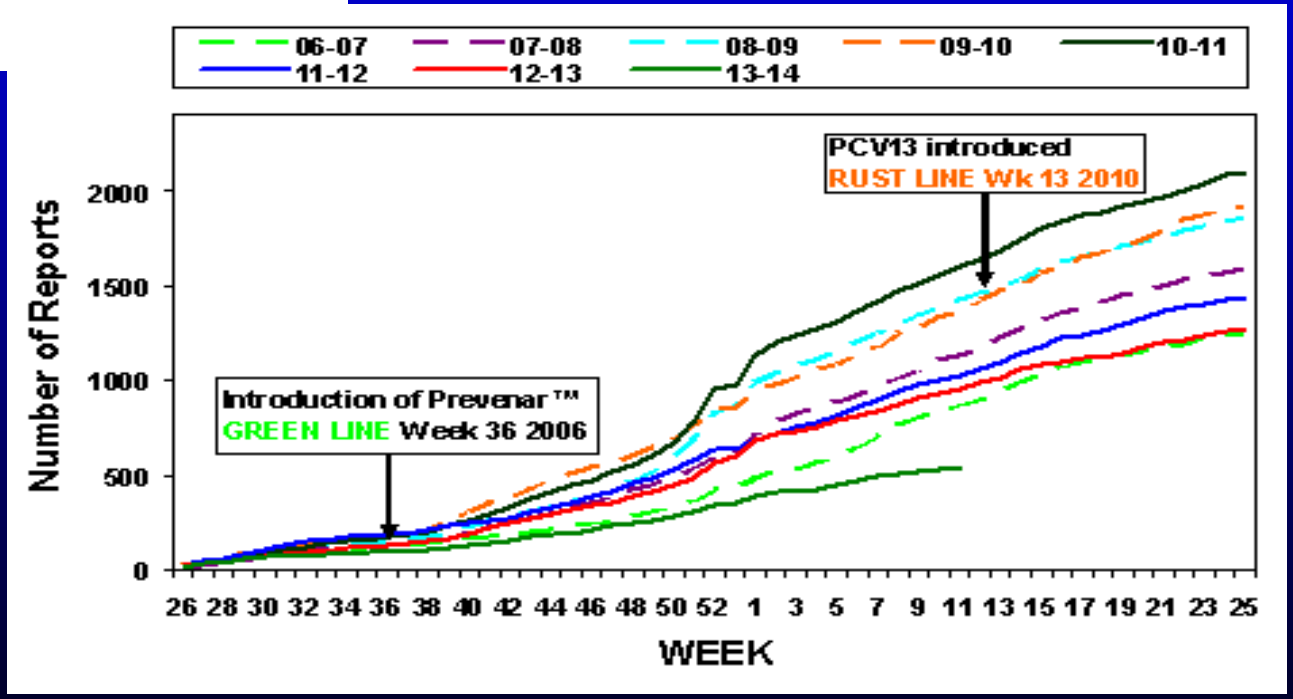
Gertz R E et al. J Infect Dis. 2010;201:770-775



England and Wales
Serotypes in PCV13 not in PCV7

Ages 2-4 updated 25 Apr 2014

Ages >5



http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1207821645727?p=1203409671876

Minimal Estimates of the Pneumococcal Role in Pneumonia in Patients Hospitalized with Seasonal Respiratory Viral Infections Including Influenza

Virus	PCV9 vaccinees	Controls	Vaccine efficacy	95% CI	P
Influenza A/B	31	56	45	14 - 64	0.01
PIV1-3	24	43	44	8 - 66	0.02
hMPV	26	62	58	34 - 73	0.001
RSV	90	115	22	-3 - 41	0.08

VT pneumococcal bacteremia 0 vs 1

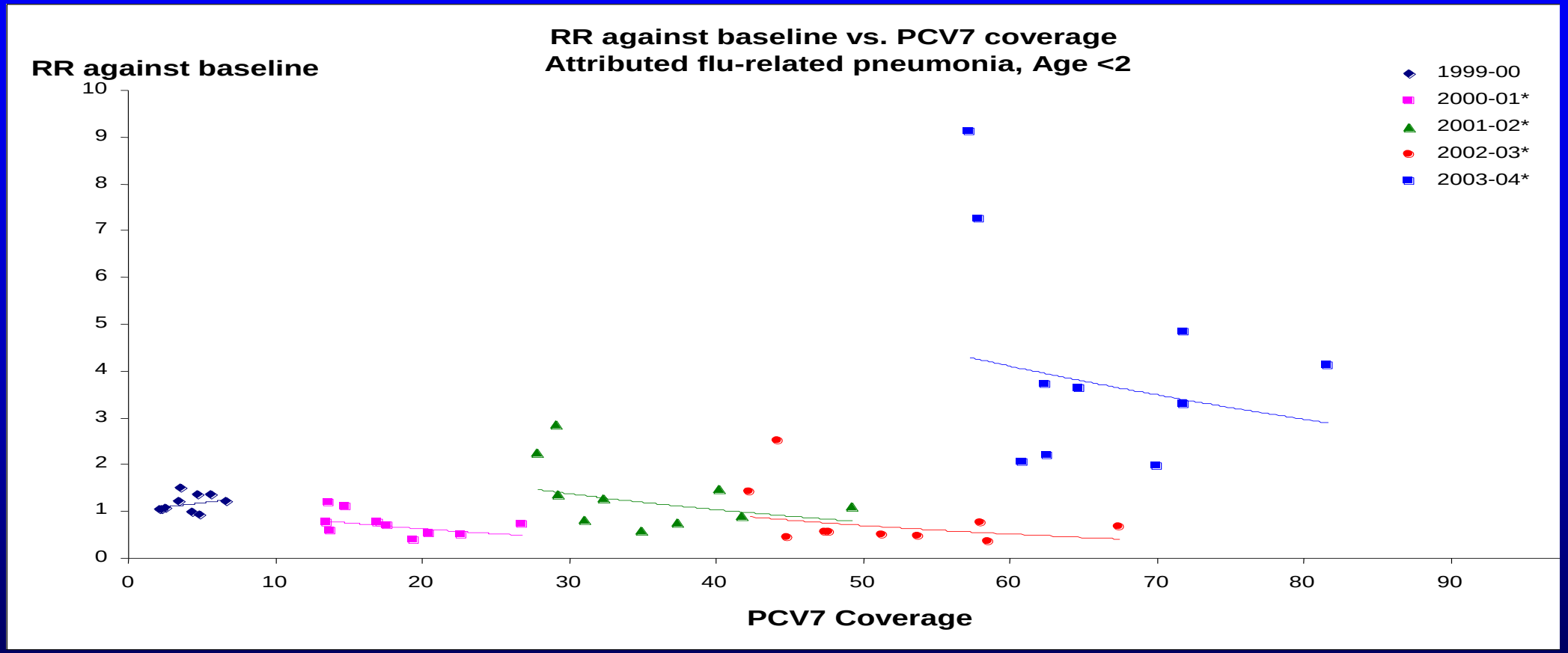
Madhi, Klugman et al. Nature Medicine 2004;10:811–13
Madhi et al, J Infect Dis, 193:1236-43, 2006

PCV Reduces Hospitalization for Pandemic Flu

- Spanish case control study
- Receipt of PCV was associated with 48% reduction (95% CI 1% - 76%) in H1N1 2009 pandemic influenza admission
- No reduction in following year seasonal flu but PCV7 serotype coverage was less than 5% by end 2009 in Madrid and most kids got PCV7

Dominguez et al, PIDJ, 2013, 32, 330-4

PCV7 Coverage Versus RR of Influenza Hospitalization By State



Simonsen, …., Klugman, mBio, 2011, e00309-10

PCV Reduces Viral Associated Hospitalization for RSV

- In a population of 566 children with URTI or LRTI in whom microarray detection of viruses was performed, viruses were detected in 70% (RSV 57% >Paraflu 30% >rhino 18% >flu 14% >adeno 8% > Boca 6%).
- Receipt of PCV reduced hospitalization by 48% (95% CI 19% - 67%); P= 0.004
- Viruses detected in 397 children – PCV reduced hospitalization by 49%; P=0.006
- RSV hospitalization reduced 57%; P = 0.01

Kuoni et al, ICAAC 2012, Late Breaker Poster G3-1563a, p329 and pers. comm.

Arguments For / Against PCV In Adults

- Pro: Equivalent or better immunogenicity; impact on non – bacteremic pneumonia (CAPITA); possibility of better boostability; possibility of more prolonged efficacy; direct protection from IPD in immunocompromized groups
- Con: Lack of disease burden to prevent if children receive the same vaccine and transmission is interrupted in the community; herd protection gives higher coverage and is cheaper than adult immunization; dose may be too low

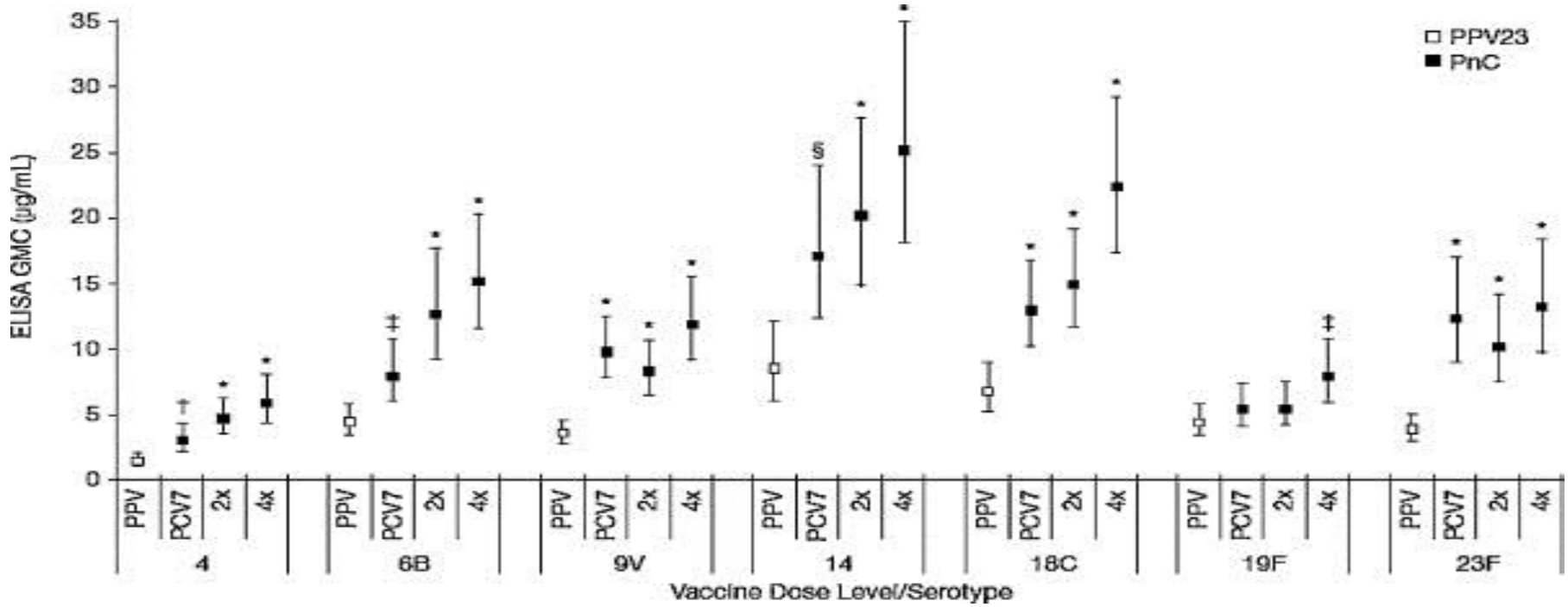


Fig. 1 Antipneumococcal polysaccharide binding antibody concentrations 1 month after a single vaccine dose in the all-available subject population. Bars represent the 95% confidence intervals (CIs). PCV7 and PPV data have been reported previously...

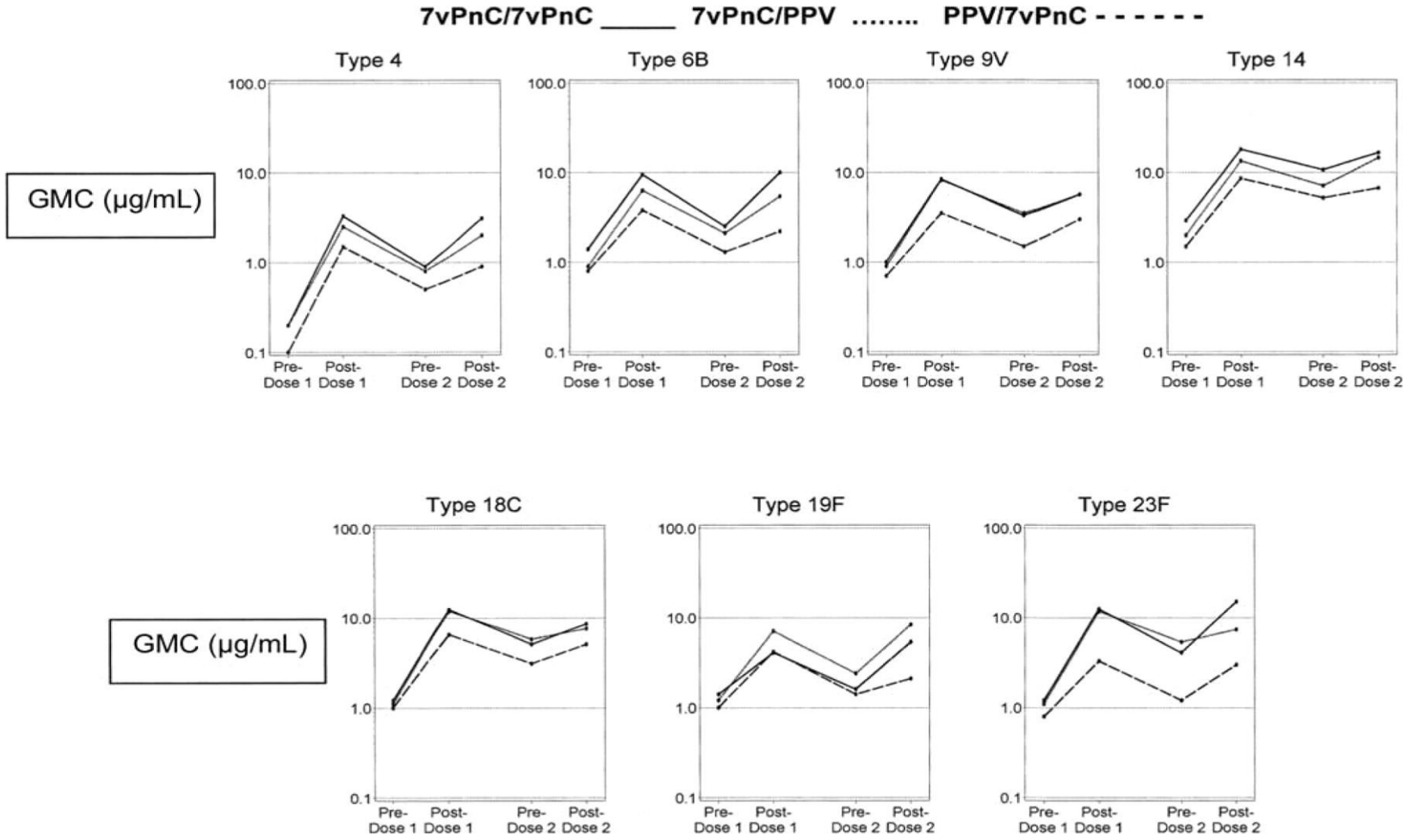
H. Lode , B. Schmoele-Thoma , W. Gruber , N. Ahlers , P. Fernsten , S. Baker , A. Razmpour , G. Siber , J. Hack...

Dose-ranging study of a single injection of pneumococcal conjugate vaccine (1?, 2?, or 4?) in healthy subjects aged 70 years or older

Vaccine Volume 29, Issue 31 2011 4940 - 4946

http://dx.doi.org/10.1016/j.vaccine.2011.04.132

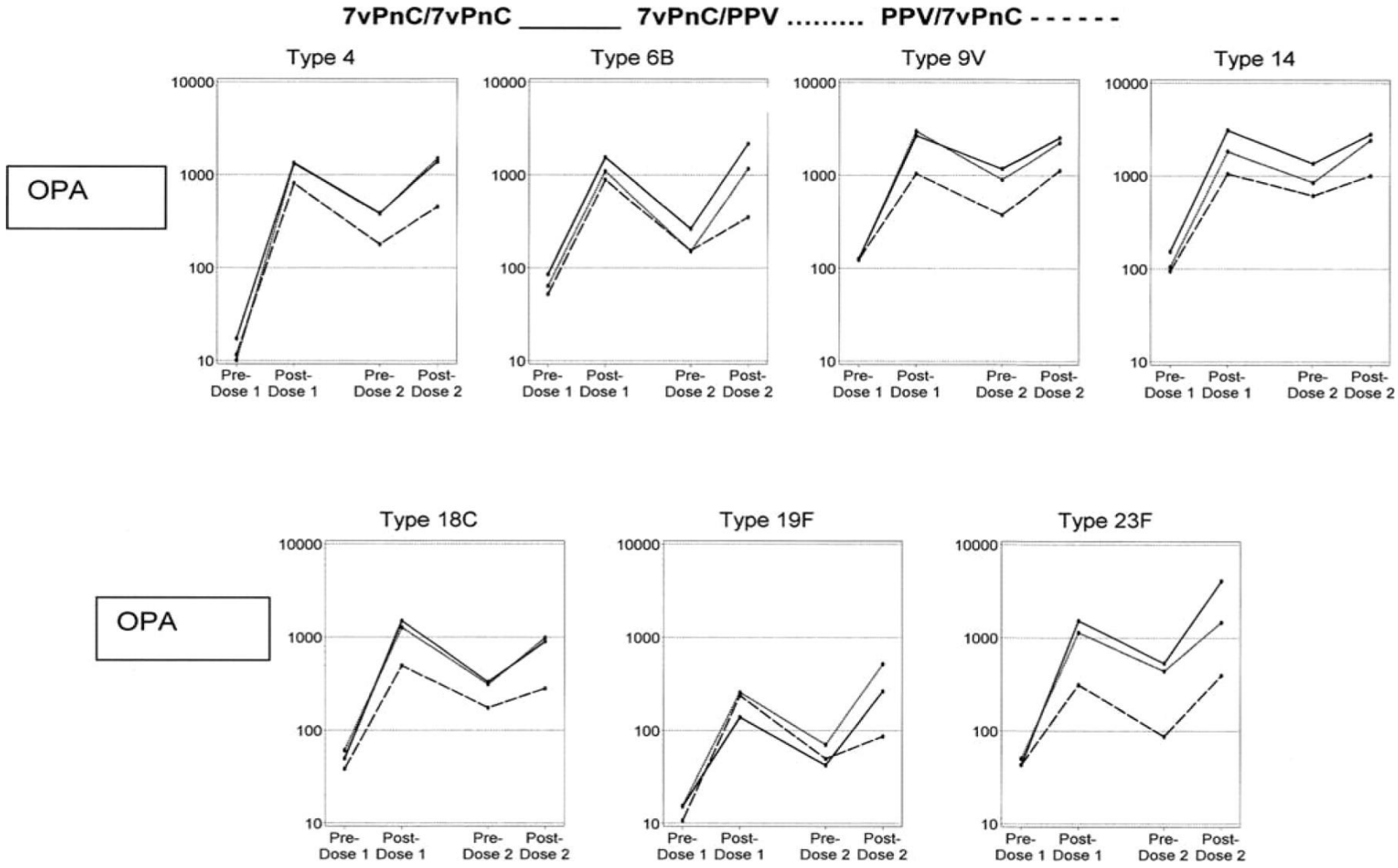
Antipneumococcal polysaccharide binding antibody responses elicited during the immunization series.



de Roux A et al. Clin Infect Dis. 2008;46:1015-1023

Clinical Infectious Diseases

Antipneumococcal opsonophagocytic assay (OPA) responses elicited during the immunization series.



de Roux A et al. Clin Infect Dis. 2008;46:1015-1023

Clinical Infectious Diseases

Changing Spectrum of IPD in the Post PCV7 Era in US

	1998-1999 (n=5,699)	2009 (n=3,338)
Median age (range), years	56 (18-101)	58 (18-104)
Race		
White	62%	70%
Black	35%	24%
Other	2%	5%
Gender		
Male	54%	51%
Case Fatality Ratio†¶	13%	11%
Meningitis	5%	5%
Bacteremia without focus†	25%	15%
Bacteremic Pneumonia†	68%	75%
ACIP Indication for PPV23†§	51%	61%

†p-value <0.05
¶Excludes cases with unknown outcome; 60 in 1998-1999 and 25 in 2009.
§Includes all ACIP indications except age ≥65 years.

Muhammad et al, Clin Infect Dis. 2013;56:e59-67.

Pneumococcal Vaccine Indications in Adults with IPD in USA, 2009

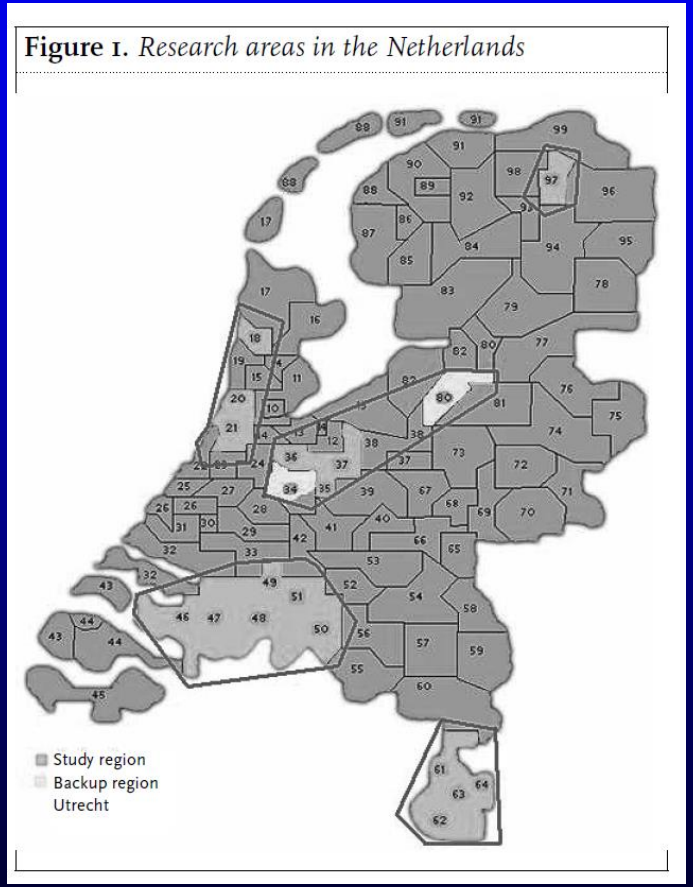
- Any PPV indication 61%
- Diabetes 20% (10% in 1998/9)
- Chronic Lung Disease 19%
- Cardiac Disease 18%
- Cancer 13%
- Alcoholism 10%
- HIV AIDS 8%

Muhammad et al, Clin Infect Dis. 2013;56:e59-67.

Table 1. *Definitions of community-acquired pneumonia (CAP) and invasive pneumococcal disease (IPD)*

CAP diagnosis category[1]	Episode of CAP plus ...
VT pneumococcal CAP	Culture of VT S. *pneumoniae* from blood and/or pleural fluid[2] or: positive urinary VT antigen[3] or: positive VT blood PCR[3]

CAPITA Trial



Hak et al, Neth J Med. 2008 Oct;66(9):378-83.

CAPITA Trial Results

- PCV13 prevented both IPD and non – bacteremic pneumococcal pneumonia
- VT IPD – Efficacy 75% (95% CI 41% - 91%)
- VT Pneumococcal CAP 46% (CI 22% - 62%)
- All Pneumococcal CAP 31% (CI 10% - 47%)
- No impact on all cause mortality (non – signif impact on CAP mortality)
- VT CAP defined by UAD – most cases (78%) non PCV7 – serotypes 1, 3, 5, 6A, 7F, 19A

Presentation at ISPPD, Hyderabad, India, March, 2014

http://www.pfizer.com/news/press-release/press-release-detail/pfizer_presents_detailed_results_from_landmark_community_acquired_pneumonia_immunization_trial_in_adults_capita_evaluating_efficacy_of_prevenar_13

CAPITA Trial Results

- Discussion points:
- 46% protection against VT CAP is significant but less than anticipated – suggests protection similar to VT otitis media and has implications for disease burden estimates in children
- Protection in adults > 85 Years of age
- Protection in immunocompromised (ACIP recommended group)
- Preventable disease burden (Infants received PCV7 throughout, then late in trial PCV10)

Presentation at ISPPD, Hyderabad, India, March, 2014

Efficacy of Two Doses of PCV7 on VT IPD + 6A in HIV^{+} Adults in Malawi

Table 3. Primary and Secondary End Points, Adverse Events, and Loss to Follow-up in 437 Patients with HIV Infection.*

End Point	Vaccine		Placebo		Hazard Ratio for First Event (95% CI)†	
					Unadjusted	Adjusted
	no. of patients	*no. of events*	*no. of patients*	*no. of events*		
Primary end point						
Vaccine serotype or serotype 6A (intention-to-treat analysis)	5	5	19	19	0.26 (0.10–0.70)	0.31 (0.11–0.84)‡

French et al, NEJM, 2010, 362, 812 - 22

Next Generation Vaccines

- 15 valent conjugate from Merck in Phase I / II
- SII making 10 valent PCV (about to enter Phase I)
- Numerous developing world preclinical projects
- Protein candidates incl PhtD, pneumolysoid, PspC, PsaA and others in Phase II with carriage endpoints expected 2014 (GSK). No impact on carriage in Phase I (Sanofi, 2014)
- Whole cell Phase I complete; in dose escalation and age de-escalation studies in Kenya
- Tcell activating proteins (Genocea) in Phase I
- Novel conjugation (Multiple Antigen Presentation System, Avidin Biotin, Affinyvax); nanoparticles (Liquidia)

Conclusions

- PCV reduces carriage by 50% in randomized trials but PCV 7 or 10 or 13 have been shown in both developed and developing countries to interrupt transmission of vaccine types
- This leads to herd protection of all ages from IPD and pneumonia
- As herd protection from VT reaches 99 -100% it is more effective than direct protection from VT pneumonia (46%)
- Replacement types cause less disease in most communities but may do so in highly susceptible populations
- PCV prevents a large proportion (> ½) of hospitalization associated with respiratory viruses
- PCV efficacy in adults is proven – disease burden preventable depends on herd protection induced by immunizing infants