

# Potential of Pneumococcal Conjugate Vaccines in the Prevention of Pneumococcal Disease in African HIV-infected Children and Adults

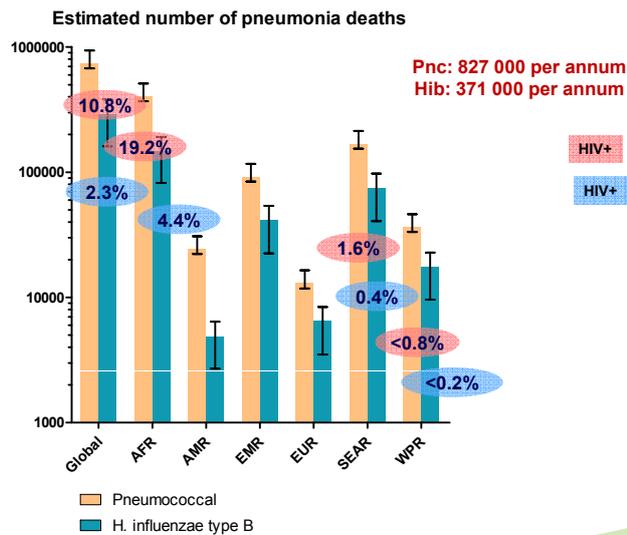
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University of Witwatersrand



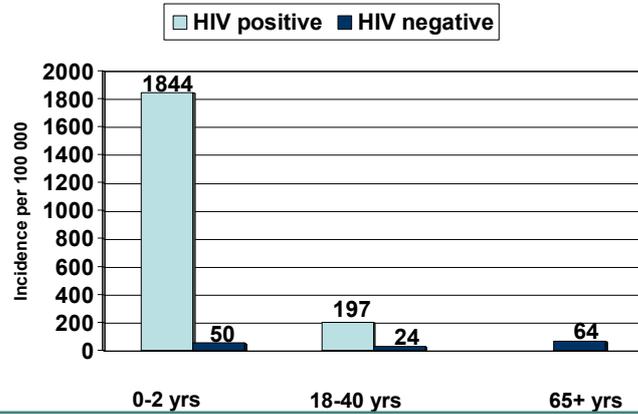
## Global pneumonia burden of death for Pneumococcus and *H. influenzae* type b.



1. O'Brien K et al., Lancet 2009;374:893-902 ; 2. Watt JP et al., Lancet. 2009;374:903-11 & supplementary web-appendix

## HIV: A major risk factor for pneumococcal disease in South Africa.

Annual incidence of pneumococcal bacteremia per 100,000 population (South Africa)<sup>1</sup>



•Rate of invasive pneumococcal disease is 37-42 fold greater in HIV+ children<sup>1,2</sup>

<sup>1</sup>Jones N, Huebner R, et al. AIDS 1998; 12(16): 2177-2184,  
<sup>2</sup>Madhi SA, Petersen K, et al. Peds Inf Dis J 2000; 19(12): 1141-1147.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### A Trial of a 9-Valent Pneumococcal Conjugate Vaccine in Children with and Those without HIV Infection

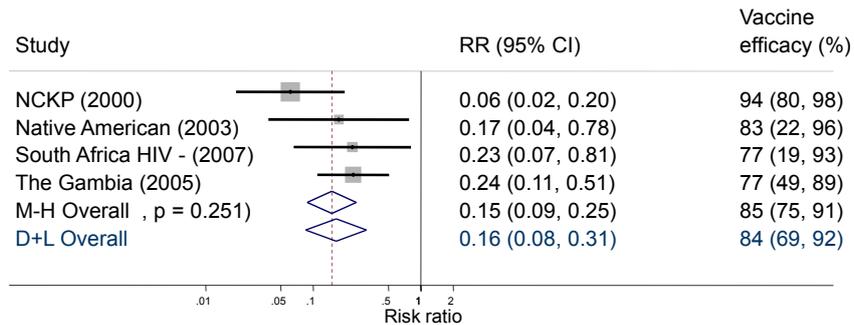
Keith P. Klugman, M.B., B.Ch., Ph.D., Shabir A. Madhi, M.B., B.Ch.,  
Robin E. Huebner, Ph.D., Robert Kohberger, Ph.D.,  
Nontombi Mbelle, M.B., B.Ch., M.Med., and Nathaniel Pierce, M.D.,  
for the Vaccine Trialists Group

N Engl J Med 2003;349:1341-8.

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## Meta-analysis: PCV Efficacious Against Vaccine-Serotype Specific Invasive Pneumococcal Disease in Randomized-Controlled Trials

7v vaccine type IPD HIV negative



Klugman KP et al. In *Pneumococcal Vaccines: The Impact of Conjugate Vaccine*; 2008; Chapter 21

## Vaccine Efficacy Against Vaccine-Serotype Specific IPD In HIV Infected (No HAART) and HIV Uninfected Children

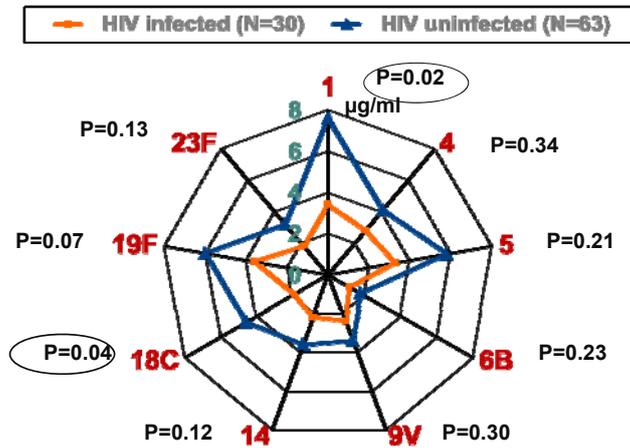
	Incidence* Vaccinees	Incidence* Controls	Efficacy (95%CI)	VAR*
<b>HIV Neg</b>	<b>7</b>	<b>39</b>	<b>83 (39, 97)</b>	<b>32</b>
<b>HIV Pos</b>	<b>300</b>	<b>870</b>	<b>65 (24, 86)</b>	<b>570</b>

•Per 100 000 child years \* VAR=Number of cases prevented per 100 000 child years

**Despite lower vaccine efficacy, absolute burden of IPD prevented by PCV was 18 fold greater in HIV-infected compared to HIV-uninfected children**

Klugman KP et al NEJM 2003; 349(14):1341-8.

### Geometric Mean Antibody Concentrations Following a Primary Series of PCV-9 (No HAART)



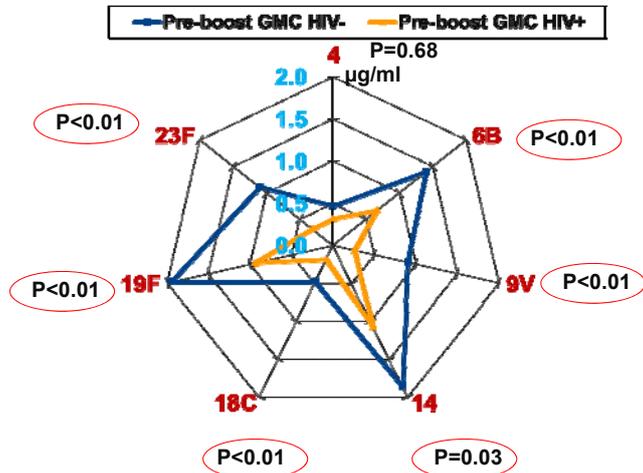
Madhi SA et al. Ped Infect Dis J 2005; 24: 410-416

### HIV Infected Children (No HAART) Less Likely to Have Functional Antibodies (OPA) Following A Primary Series of PCV-9

Serotype	HIV infected	HIV uninfected	P value
6B	N=27 (%)	N=56 (%)	
OPA >1:8	21 (78)	54 (96)	0.01
19F	N=28	N=57	
OPA >1:8	13 (46)	52 (91)	<0.001
23F	N=28	N=57	
OPA >1:8	16 (57)	53 (93)	0.002

Madhi SA et al. Ped Infect Dis J 2005; 24: 410-416

### Antibody Concentrations Less Sustainable in HIV Infected Children 5.3 Yrs Post-Vaccination and in The Absence of Booster Dose of PCV-9



HIV infected vaccinees have lower GMCs 5.3 years following vaccination

Madhi SA et al. *Vaccine* 2007; 25: 2451-7

### Reduced Long-Term Protection Against Invasive Pneumococcal Disease In HIV-Infected Children in the Absence of HAART and Booster Dose of PCV

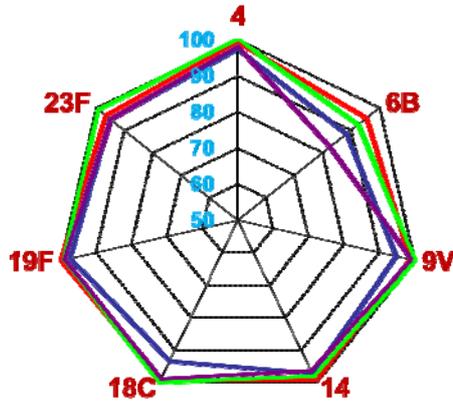
Outcome	PCV	Placebo	V.E. (95%C.I.)	VAR*
<b>HIV Uninfected</b>				
VT-IPD: Nov 01	3	17	83 (39 to 97)	32
VT-IPD: Oct 05	4	18	77 (34 to 93)	75
<b>HIV-infected</b>				
VT-IPD: Nov 01	9	26	65 (24 to 86)	570
VT-IPD: Oct 05	19	31	39 (-8 to 65)	940

\* Number of cases prevented per 100 000 children

Madhi SA et al. *Vaccine* 2007; 25: 2451-7

**Effect of HIV-exposure and timing of HAART on Immune Responses (% with serotype-specific antibody  $\geq 0.35\mu\text{g/ml}$ ) to Primary Series of PCV-7 in Infants.**

— HIV+/ART+ — HIV+/ART- — M+/I- — M-/I-

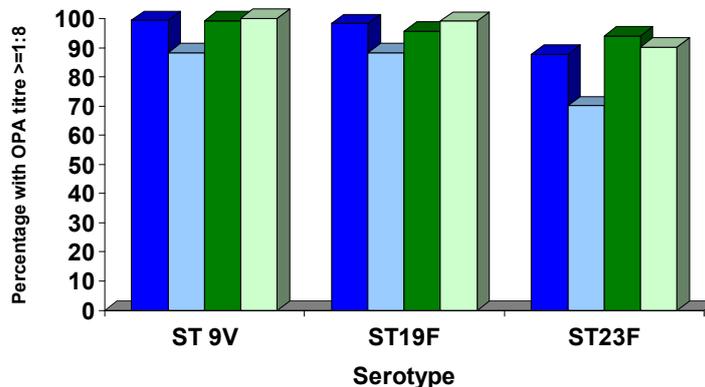


No differences in proportion of children with antibody concentration of  $\geq 0.35\mu\text{g/ml}$  based on timing of initiation of HAART or maternal HIV-infection status

Madhi SA, et al. J Infect Dis 2010; 202; 355: 61.

**Effect of HIV-exposure and timing of HAART on Qualitative Antibody Responses in Infants.**

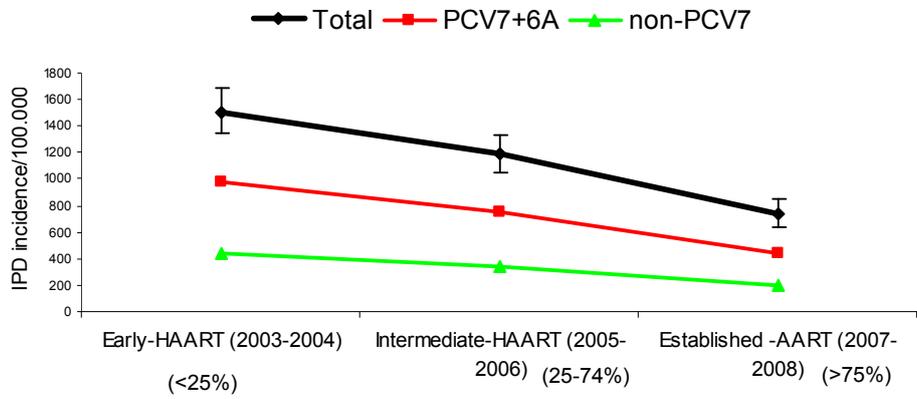
■ HIV+/ART+ ■ HIV+/ART- ■ M+/I- ■ M-/I-



Delaying HAART was associated with a lower proportion of HIV+ infants inducing functional antibody (i.e. OPA titres  $\geq 8$ ) for serotypes 9V (  $P=0.003$ ), 19F (  $P=0.003$ ) and 23F (  $P=0.09$ ).

Madhi SA, et al. J Infect Dis 2010; 202; 355: 61.

### Impact of HAART Access on Burden of Invasive Pneumococcal Disease in HIV infected children.



**HAART associated with 51% (95%CI 42-59) reduction in IPD in HIV+ children.**

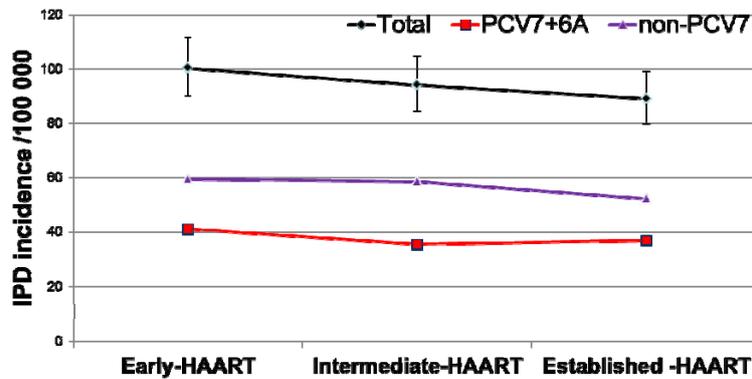
**Risk of IPD remains 21 fold (95%CI 16-28) greater in HIV+ than HIV- children**

Nunes M, et al. AIDS. 2011, 25: 453-62

### Preventing Severe Invasive Pneumococcal Disease in HIV-Infected African Adults.

## Lack of Impact of HAART Access on Reducing the Burden of IPD in HIV-infected Adults, Soweto, S. Africa

Nunes M et al. ISPPD, 2010



HAART associated with 57% reduction in IPD in HIV+ adults in the USA. However, burden of IPD remained 37 fold greater than general population.

Heffernan RT, J Infect Dis; 2005; 191: 2038-45

## Pneumococcal Polysaccharide Vaccine Increases Risk of Pneumonia In African HIV+ Adults

23-valent Pneumococcal polysaccharide vaccine (23vPPV):

Initial double-blind, randomized, placebo-controlled trial in Uganda: ↑ risk for

- IPD (HR: 1.47)
- Vaccine-related serogroups (HR: 2.10)
- All-cause pneumonia (HR: 1.89 [1.1-3.2])
- Detrimental effect especially in first 6 months

French et al. Lancet 2000;355:2106-11  
French et al. JID 2004;190:707-12

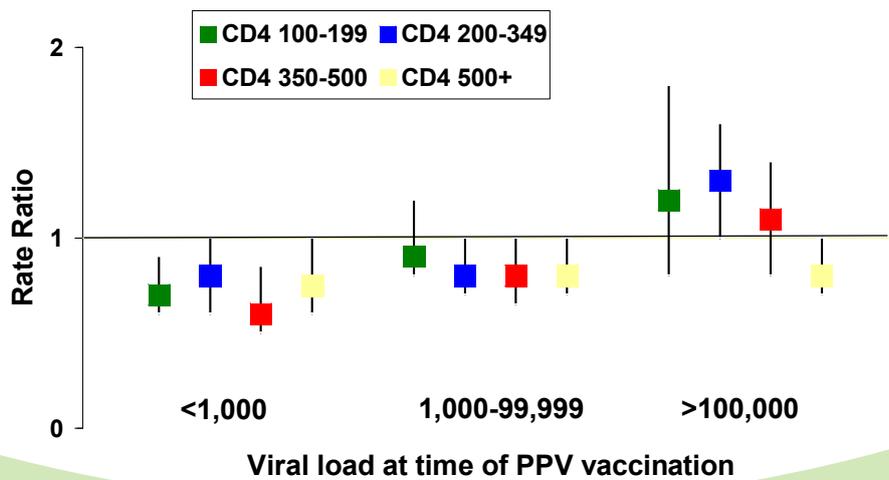
## Prevention of pneumonia in HIV+ patients

23vPPV – 6 year f/u results from Uganda trial:

- Persistent excess of rate of all-cause pneumonia in vaccinees (HR: 1.6 [1.0-2.4])
- Risk strengthened with higher CD<sub>4</sub> counts for
  - All cause pneumonia
  - Pneumococcal disease
- “Unexplained” survival benefit for vaccinees (HR: 0.84 [0.7-1.0]), especially for patients with CD<sub>4</sub> count 200-500/mm<sup>3</sup>

Watera et al. AIDS 2004;18:1210-3

## Pneumococcal polysaccharide vaccine And Pneumonia Incidence By Viral Load, CD4 At Time Of Vaccination

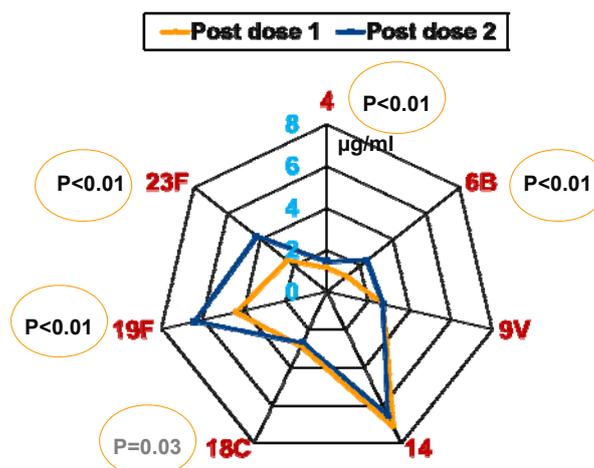


Teshale EH, et al. Vaccine, 2008; 26: 5830-4

### Effect of Past PPV on PCV Immunogenicity in HIV Infected Ugandan Adults Miiro G et al. J Infect Dis 2005; 192

- HAART naïve population
- No effect of past PPV on antibody concentration at baseline or following vaccination with one or two doses of PCV

### Comparison of Serotype Specific GMC 4 weeks following 1<sup>st</sup> and following 2<sup>nd</sup> Doses of PCV in HIV Infected ARV Naïve Adults

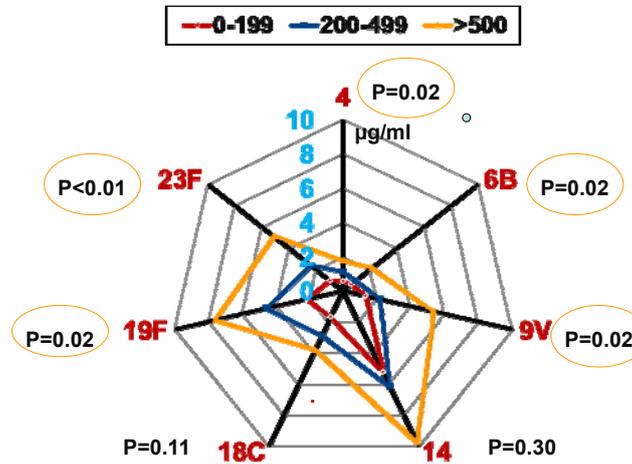


**Probable priming/induction of memory cells following 1<sup>st</sup> dose of PCV.**

Miiro G et al. J Infect Dis 2005; 192

### Serotype-specific GMCs Post-PCV-7 Immunization by CD4+ category in HIV Infected Adults.

Miuro G et al. J Infect Dis 2005; 192



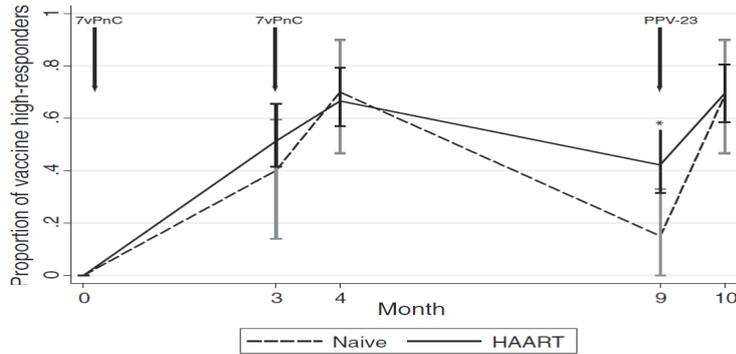
**Severely immunocompromised HIV+ adults had poorer quantitative antibody responses**

### Efficacy of two-doses of PCV against Vaccine-serotype IPD in HIV-infected adults with previous IPD

End point	Vaccine N=219	Placebo N=218	Adjusted Hazard Ratio (95%CI)
Vaccine serotype +6A (ITT)	5	19	0.31 (0.11-0.84)
CD4+ count			
<200 cells/mm	2	16	
200-500 cells/mm	1	1	
>500 cells/mm	0	1	
Vaccine serotype + 6A (PP)	4	18	0.26 (0.08-0.78)
Death: Any cause	73	63	1.24 (0.88-1.75)
Definite, probable or possible cause with pneumococcal disease	35	35	1.14 (0.71-1.85)

French N, et al. N Eng J Med 2010, 362; 812-22

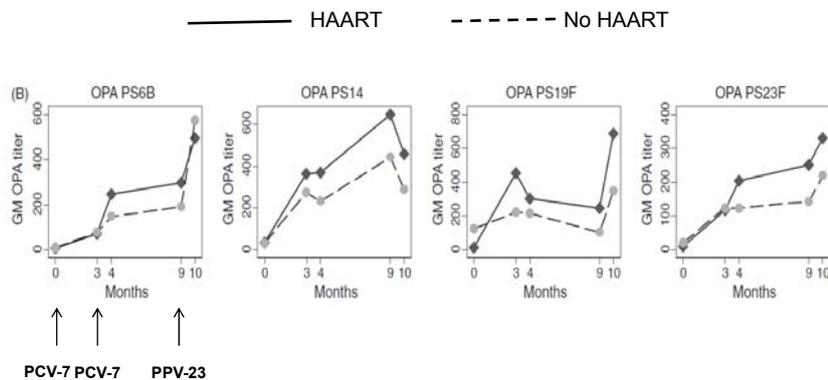
### Proportion of PCV-7 Responders Following PCV and Pnc Polysaccharide Vaccine In HIV-infected Adults, Stratified by Use of HAART.



Definition: "Responder" = protocol specified increase in antibody concentration to at least 5 of 7 serotypes.

Søgaard O et al. AIDS 2010; 24: 1315-13422

### Functional Antibody Responses (OPA) following 1 OR 2 Doses of PCV-7 In HIV-infected Adults, Stratified by Use of HAART.



**HAART associated with higher OPA GMTs following second dose of PCV, including 6 months later.**

Søgaard O et al. AIDS 2010; 24: 1315-13422

### Baseline Predictors of PCV-7 Responders at 6 months After Two Doses of PCV-7

	<i>n</i>	Persistent 7vPnC vaccine responders <sup>a</sup> [n (%)]	Crude OR	Adjusted <sup>b</sup> OR
On HAART				
No	20	3 (15.0)	1 (ref)	1 (ref)
Yes	71	30 (42.3)	4.15 (1.11–15.4)	4.65 (1.07–20.2)
Adjuvant				
Placebo	48	12 (25.0)	1 (ref)	1 (ref)
CPG 7909	43	21 (48.8)	2.86 (1.18–6.94)	3.26 (1.24–8.58)
Age				
≤50	52	20 (38.5)	1 (ref)	1 (ref)
>50	39	13 (33.3)	0.8 (0.34–1.91)	0.68 (0.26–1.83)
Baseline CD4 <sup>+</sup> cell count				
<500 cells/μl	29	11 (37.9)	1 (ref)	1 (ref)
>500 cells/μl	62	22 (35.5)	0.90 (0.36–2.24)	0.98 (0.33–2.92)
BMI				
≤25 kg/m <sup>2</sup>	61	23 (37.7)	1 (ref)	1 (ref)
>25 kg/m <sup>2</sup>	30	10 (33.3)	0.83 (0.33–2.07)	0.71 (0.25–2.07)
History of AIDS-defining event				
Yes	20	7 (35.0)	1 (ref)	1 (ref)
No	71	26 (36.6)	1.07 (0.38–3.03)	1.54 (0.47–5.07)
Current smoker				
Yes	30	6 (20.0)	1 (ref)	1 (ref)
No	61	27 (44.3)	3.18 (1.14–8.87)	2.97 (0.96–9.19)

7vPnC, seven-valent pneumococcal conjugate; CPG 7909, Toll-like receptor 9 agonist; OR, odds ratio; HAART, highly active antiretroviral therapy.

<sup>a</sup>Defined as a two-fold increase in IgG levels to 1 μg/ml or more for at least five of the 7vPnC serotypes.

<sup>b</sup>Adjusted for all the given variables.

Søgaard O et al. AIDS 2010; 24: 1315-13422

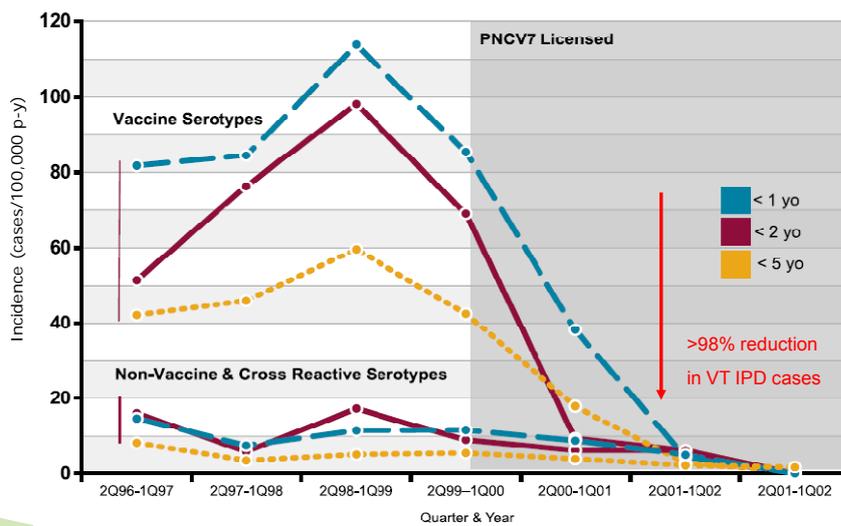
### Safety and Immunogenicity of PCV in HIV Infected Adults (USA)

- Higher antibody concentrations following PCV-PPV for 3 of 5 serotypes compared to PPV only group.
- Higher opsonophagocytic titers in PCV-PCV regimen or PCV-PPV compared to PPV alone for 2-3 of 5 serotypes.
- No effect of PCV-PCV or PCV-PPV combination on viral load 24 weeks post-vaccination
- Local adverse events slightly increased post PCV

Feikin DR et al. Vaccine 2002; Vol 20; AIDS Goetz et al. 2002; Vol 15

## Protecting Adults Against Invasive Pneumococcal Disease Through PCV Immunization of Children.

### PCV-7 Has Dramatically Reduced Vaccine-type IPD In US Children



Adapted from Black S, Shinefield H, et al. PIDJ 2004; 23(6): 485-9.

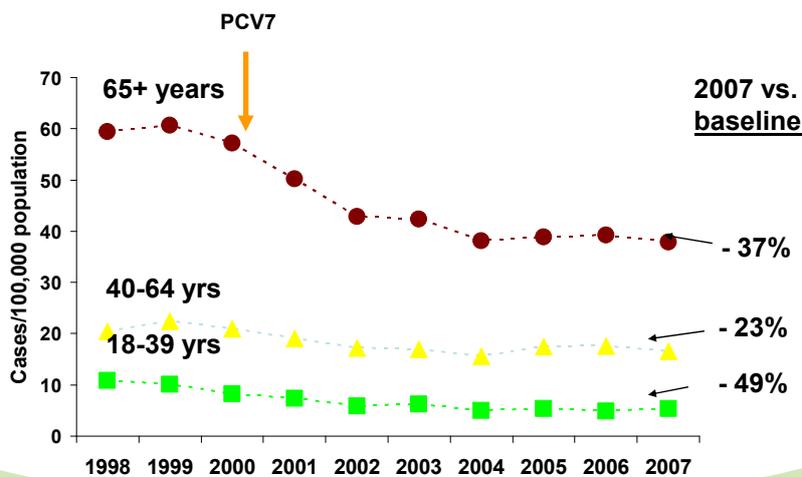
## VT and non-VT Carriage in Pneumococcal Vaccine Recipients

Author	Conjugate (valency)	Site	Age at vaccination (mo)	Carriage (mo) after vaccination	VT	Non VT
Dagan	D-4, T-4	Israel	2, 4, 6	1,6,7	↓	-
Dagan	OMP-7	Israel	12,15,18	12	↓	-
Yeh	OMP-7	US	2,4,6,12	1,6,7	↓	-
Obaro	CRM-5	Gambia	2, 3, 4	2, 3	↑	↑
Kristinsson	D-8, T-8	Iceland	3, 4, 6,12	>1	↓	N.S.
Mbelle	CRM-9	S. Africa	1.5, 2.5, 3	5.5	↓	↑
Dagan	D/T-11	Israel	2, 4, 6, 12	12	↓	-
Dagan	CRM-9	Israel	2, 3, 5	>1	↓	↑
O'Brien	CRM-7	USA (MMVA)	2,4,6,12	1,6,12	↓	↑
Kilpi	CRM-7	Finland	2, 4, 6,12	12	↓	↑
Lakshman	CRM-7	UK	2,3,4	20-44	-	-
Ghaffar	CRM-7	US	2,4,6,12	3-6	-	↑
Prymula	PCV10	Czech Republic	3,4,5	1,3,7,12	↓	↑
van Gils	CRM-7	Netherlands	2, 4,11	1, 7, 13	↓	↑
van Gils	CRM-7	Netherlands	2,4	8, 14, 20	↓	↑

Klugman, KP. *Lancet Infect Dis.* 2001;1:85-91; Yeh, *Vaccine.* 2003;21:2627-2631; Ghaffar F, et al. *Clin Infect Dis.* 2004;39:930-938; Prymula R, et al. *Lancet.* 2006;367:740-748; van Gils EJ, et al. *JAMA.* 2009; 302:159-67.

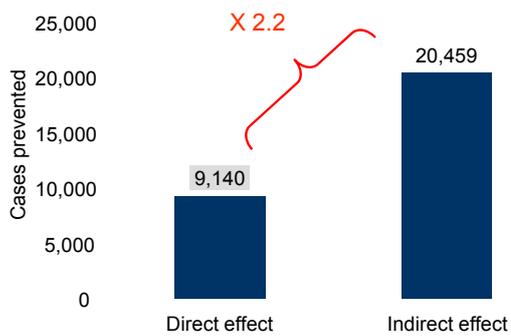
PCV reduces risk of acquisition of vaccine serotypes and subsequently been shown to interrupt transmission of VT to other household contacts.

## Indirect Effect in Adults Invasive Pneumococcal Disease Rates ABCs, 1998-2007



Lexau et al. *JAMA* 2004 and unpublished CDC data

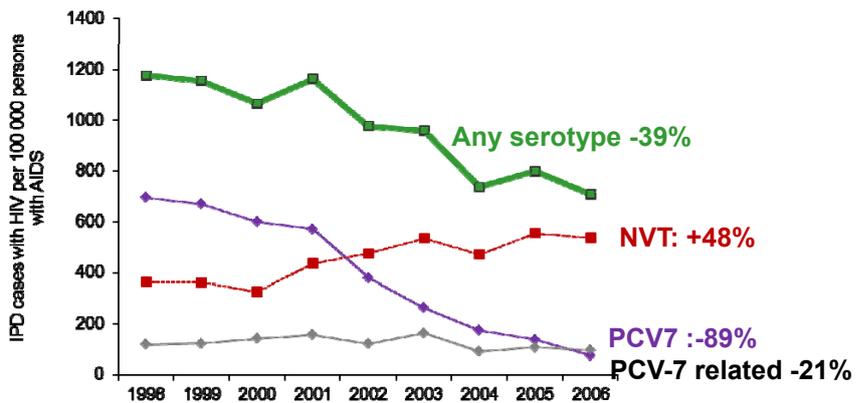
### Indirect Protection: Vaccine-type IPD Prevented by Direct and Indirect Effects of PnCRM: USA 2003



Estimated annual cases of vaccine-type IPD prevented in the US, 2003

CDC. MMWR 2005; 54: 893-7.

### Indirect Effect of PCV against IPD in Adults 18-64 years with HIV infection, USA



Cohen, A, et al AIDS, 2010: 24: 2252-62

### **Conclusions:**

- **Risk of serious pneumococcal disease remains approximately 21-37 fold greater in HIV+ individuals on HAART.**
- **In absence of HAART, PCV associated with modest efficacy against IPD, although suggestion of waning protection.**
- **Early initiation of HAART in infants associated with comparable quantitative and qualitative antibody responses to PCV in infants.**
- **Need for booster dose of PCV in children on and not on HAART remains to be resolved.**
- **PCV immunogenic in HIV-infected adults and enhanced by HAART.**
- **PCV associated with 69-74% efficacy against vaccine-serotype IPD in high-risk HIV-infected adults not on HAART.**
- **Potential for reduction of IPD in HIV+ adults in Africa through “indirect effect” of childhood PCV immunization needs to be evaluated.**