Overview of PCVs

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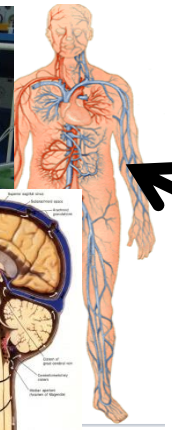
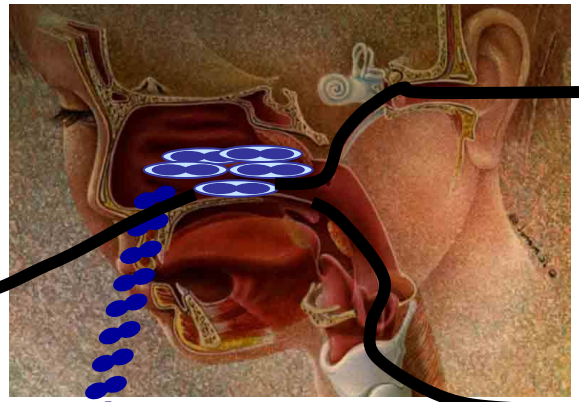
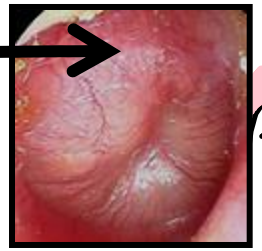
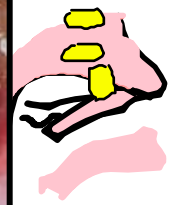
Pneumococcal Disease Endpoints

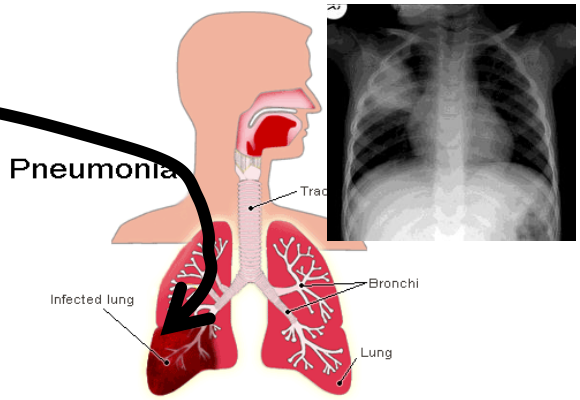








Otitis media
and its complications



Invasive infections

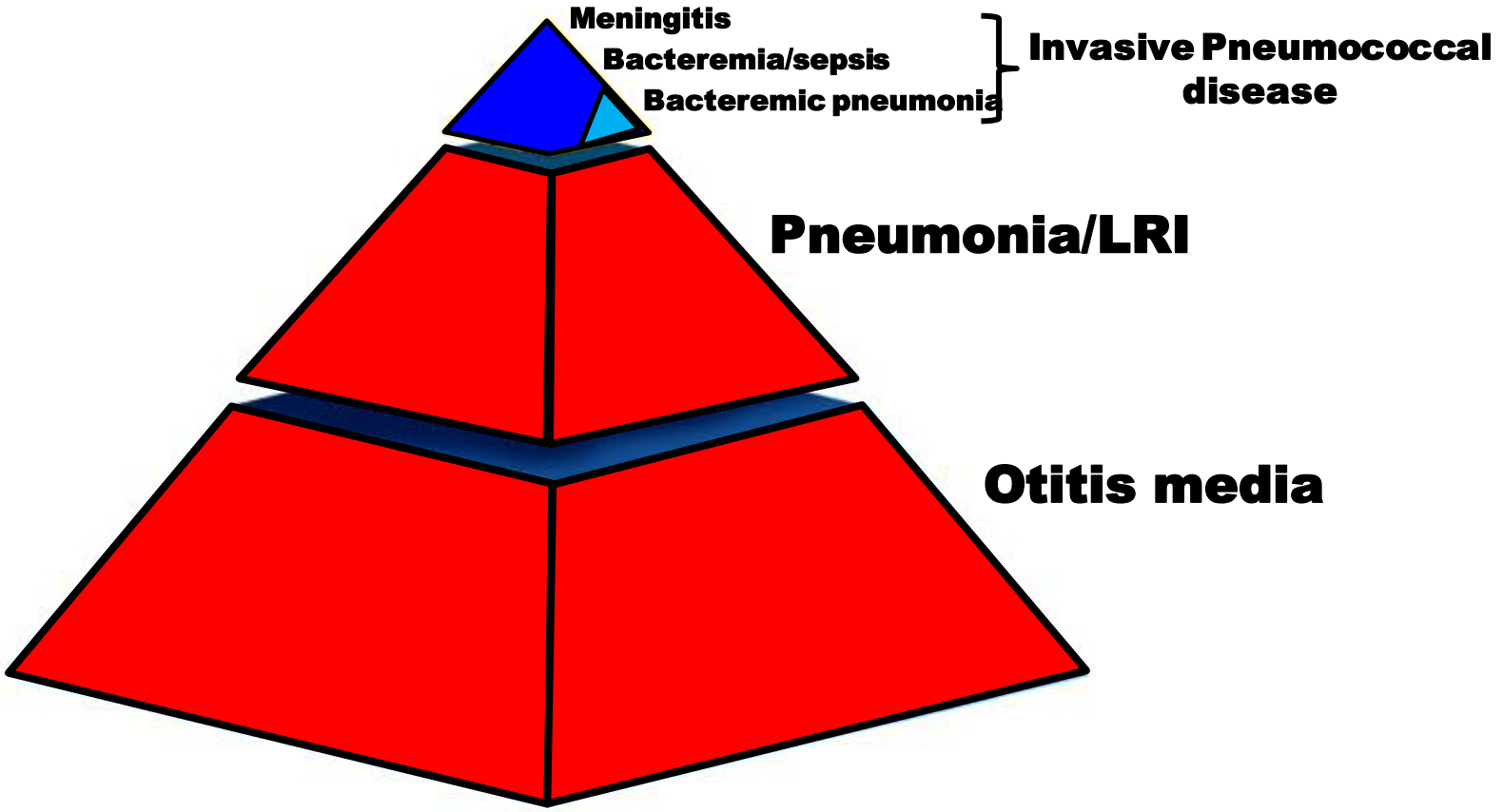
- sepsis
- meningitis
- Bacteremic pneumonia
- Osteomyelitis
- Septic arthritis
- Cellulitis
- Brain abscess
- Pericarditis, endocarditis

Carriage & spread to other individuals

Antibiotic resistance

Mucosal infections

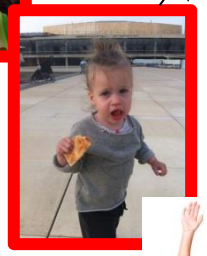
- otitis media
- sinusitis
- conjunctivitis
- pneumonia


Meningitis
Bacteremia/sepsis
Bacteremic pneumonia
Invasive Pneumococcal disease
Pneumonia/LRI
Otitis media

Neonate

Infant

Toddler



Children

Young adults

High risk

50+

80+

Licensed PCVs

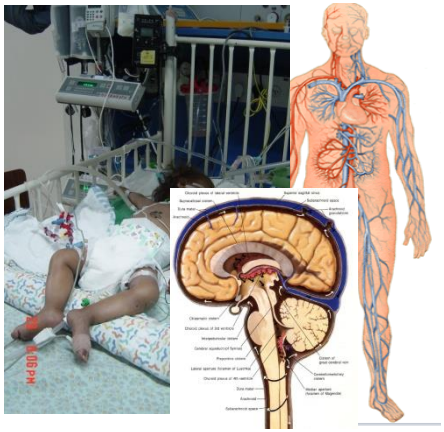
CRM_{197} conjugate

PCV7	4	6B	9V	14	18C	19F	23F						
PCV13	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A

***H. Influenzae* Protein D (4, 6B, 9V, 14, 23F, 1, 5, 7F); Tetanus toxoid (18C); Diphtheria toxoid (19F)**

PCV10	4	6B	9V	14	18C	19F	23F	1	5	7F

Pneumococcal Disease Endpoints

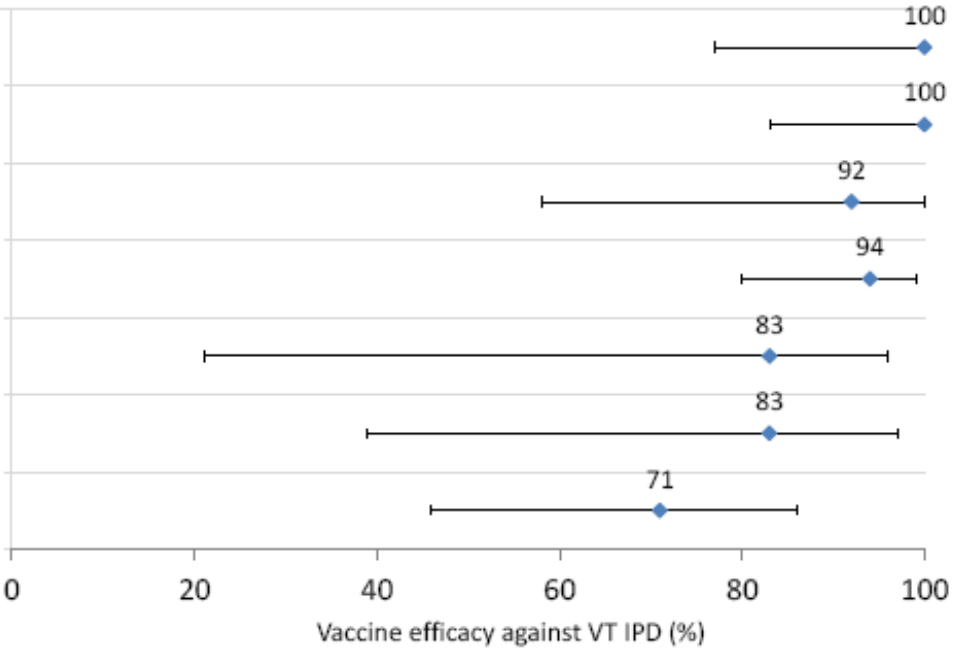


Invasive infections

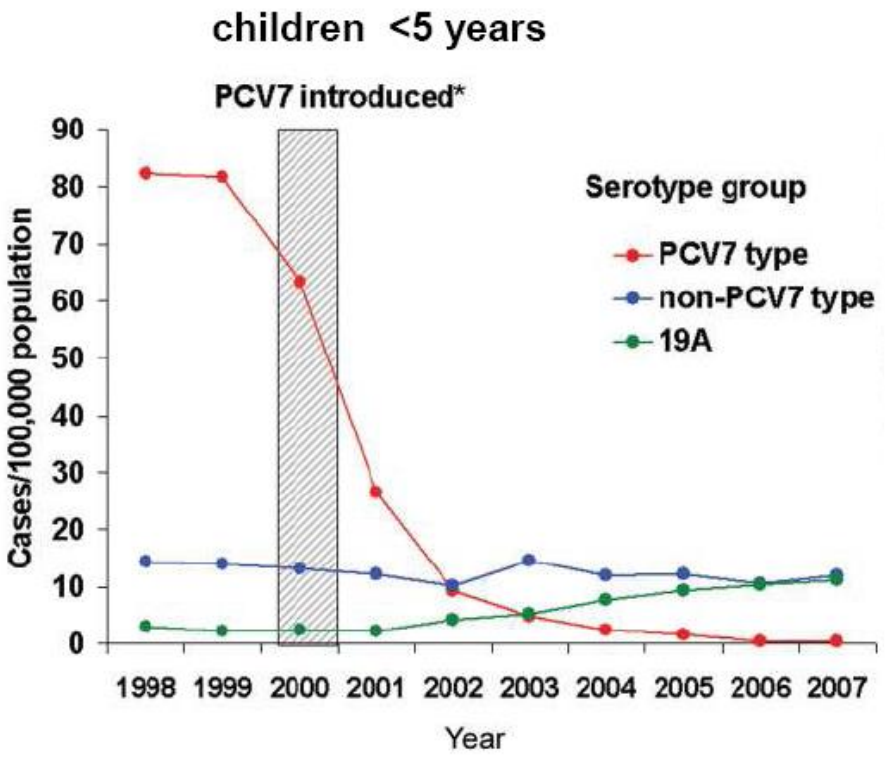
- sepsis
- meningitis
- Bacteremic pneumonia
- Osteomyelitis
- Septic arthritis
- Cellulitis
- Brain abscess
- Pericarditis, endocarditis

Vaccine Efficacy/Effectiveness Against Vaccine Serotype IPD in Double-blind Randomized Controlled Trials (Intent-to-treat Analyses)

Study	N	Vaccine (schedule)
COMPAS (Latin America)	23,597	PHiD-CV (3+1)
FinIP (Finland)[9]	20,474	PHiD-CV (3+1)
	20,255	PHiD-CV (2+1)
NCKP (USA)[10]	37,868	7vCRM (3+1)
Navajo (USA)[11]	5,792	7vCRM (3+1)
Soweto (South Africa)[12]	39,836	9vCRM (3+0)
The Gambia[7]	17,437	9vCRM (3+0)

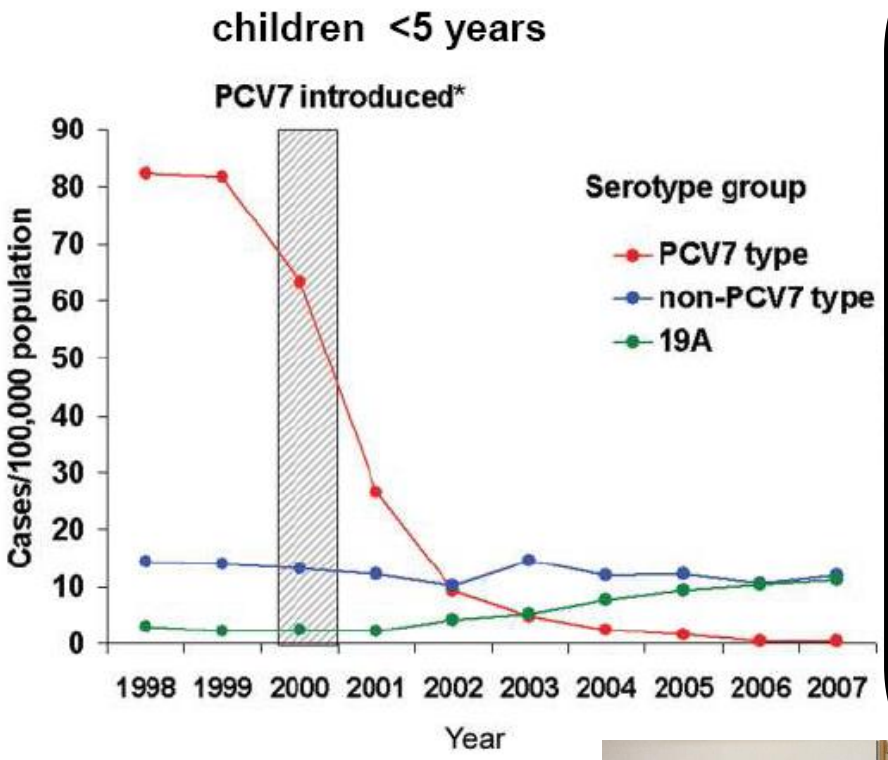


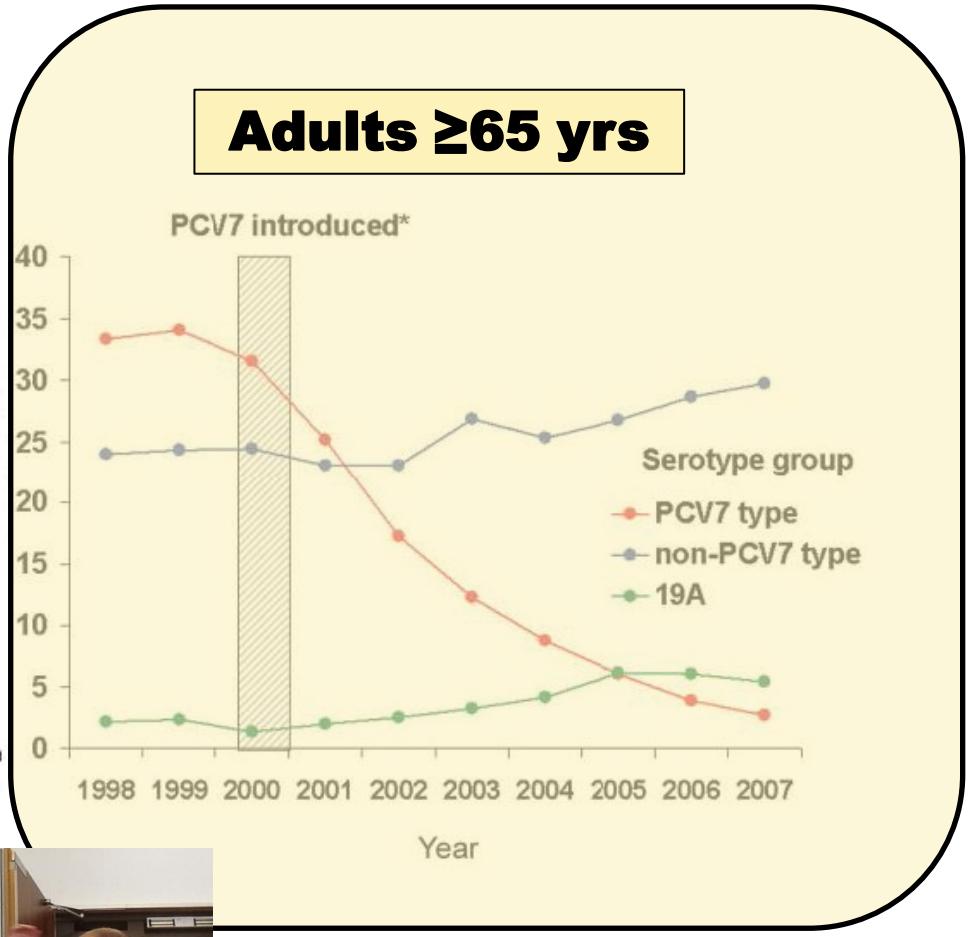
IPD Incidence After PCV7 Introduction in US Population



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

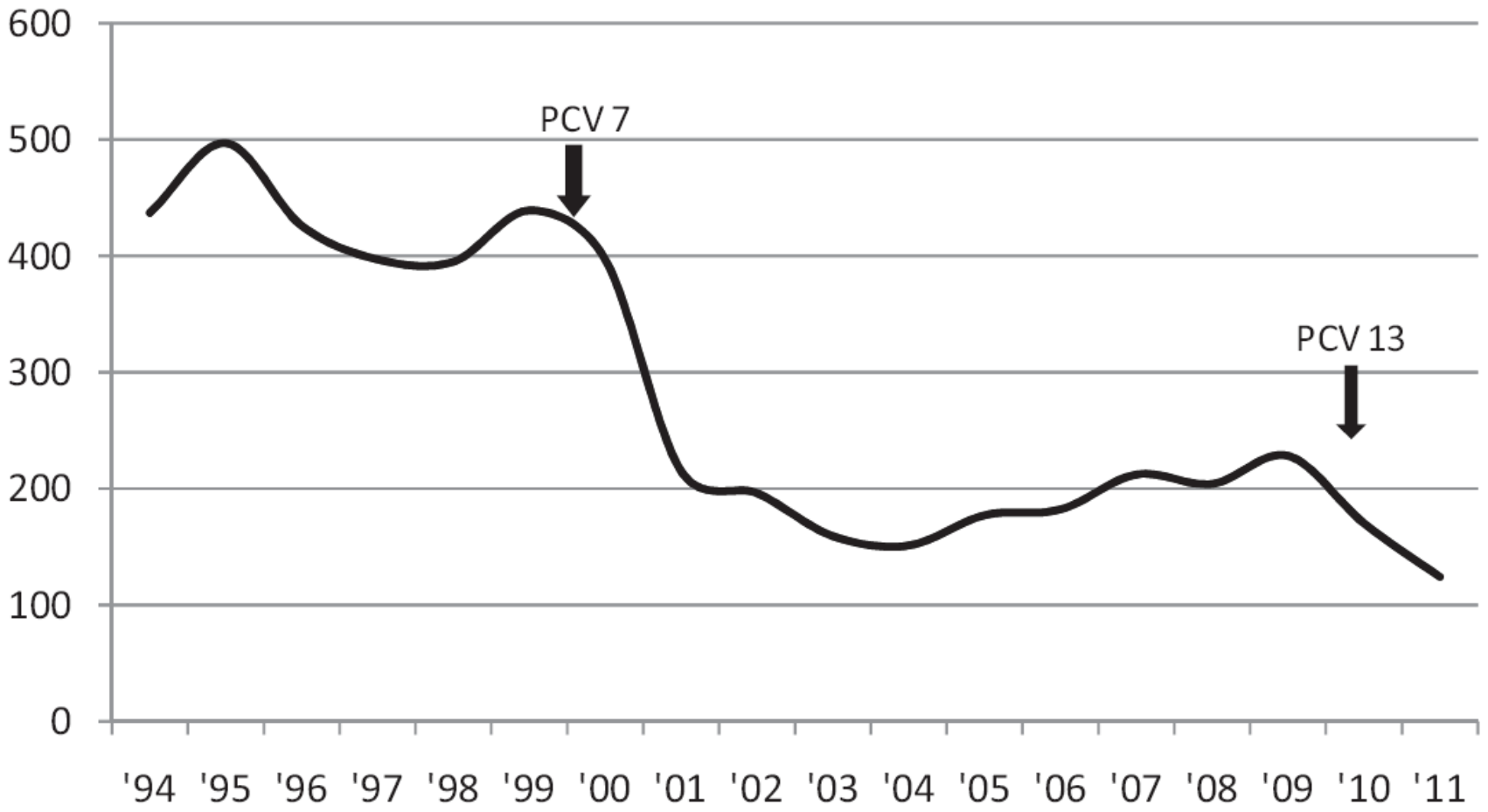
IPD Incidence After PCV7 Introduction in US Population





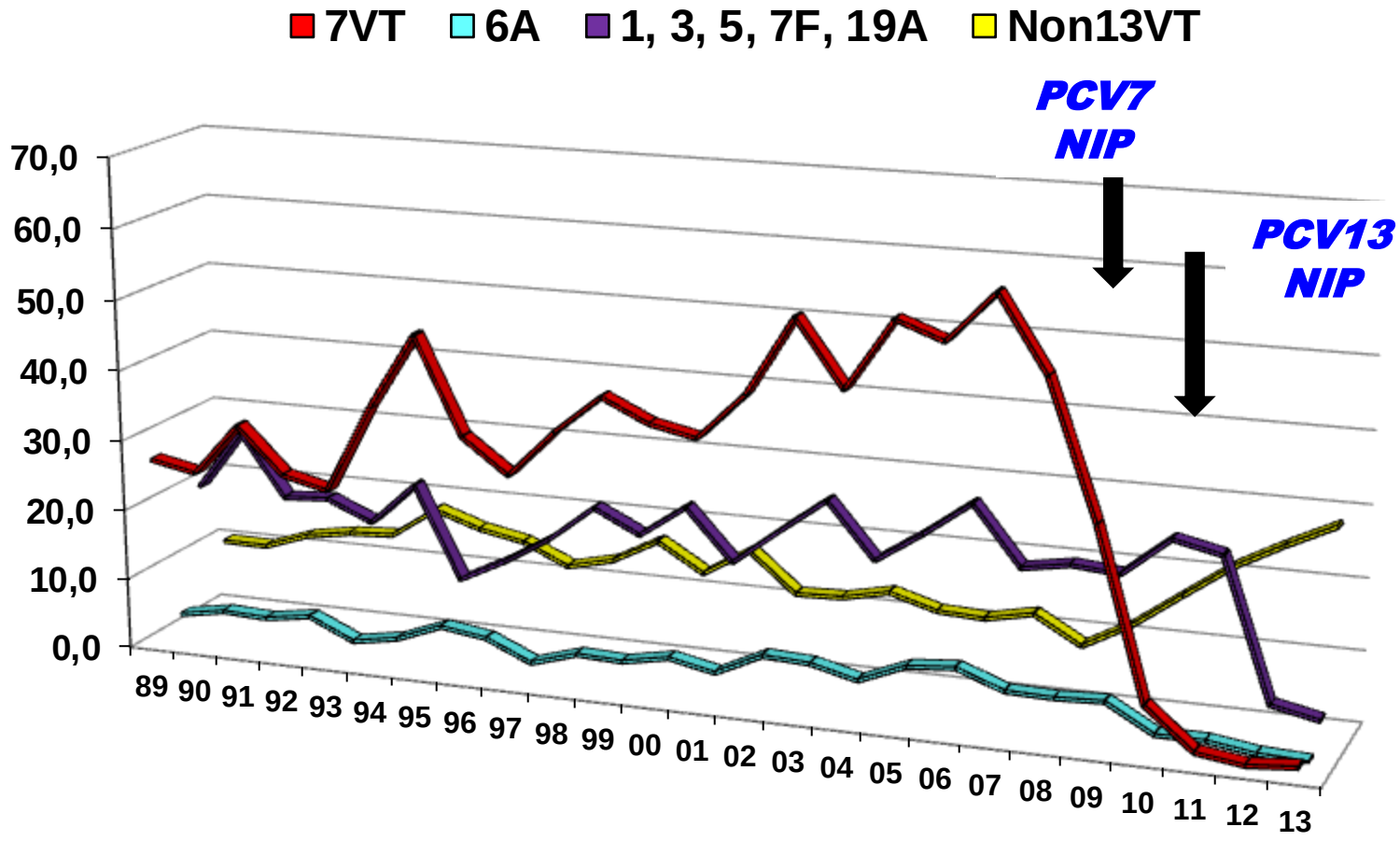
Pilishvili et al, *J Infect Dis*, 201:32-41, 2010

Number of Invasive Pneumococcal Isolates in Children Among 8 Children Hospitals by Study Years, 1994–2011



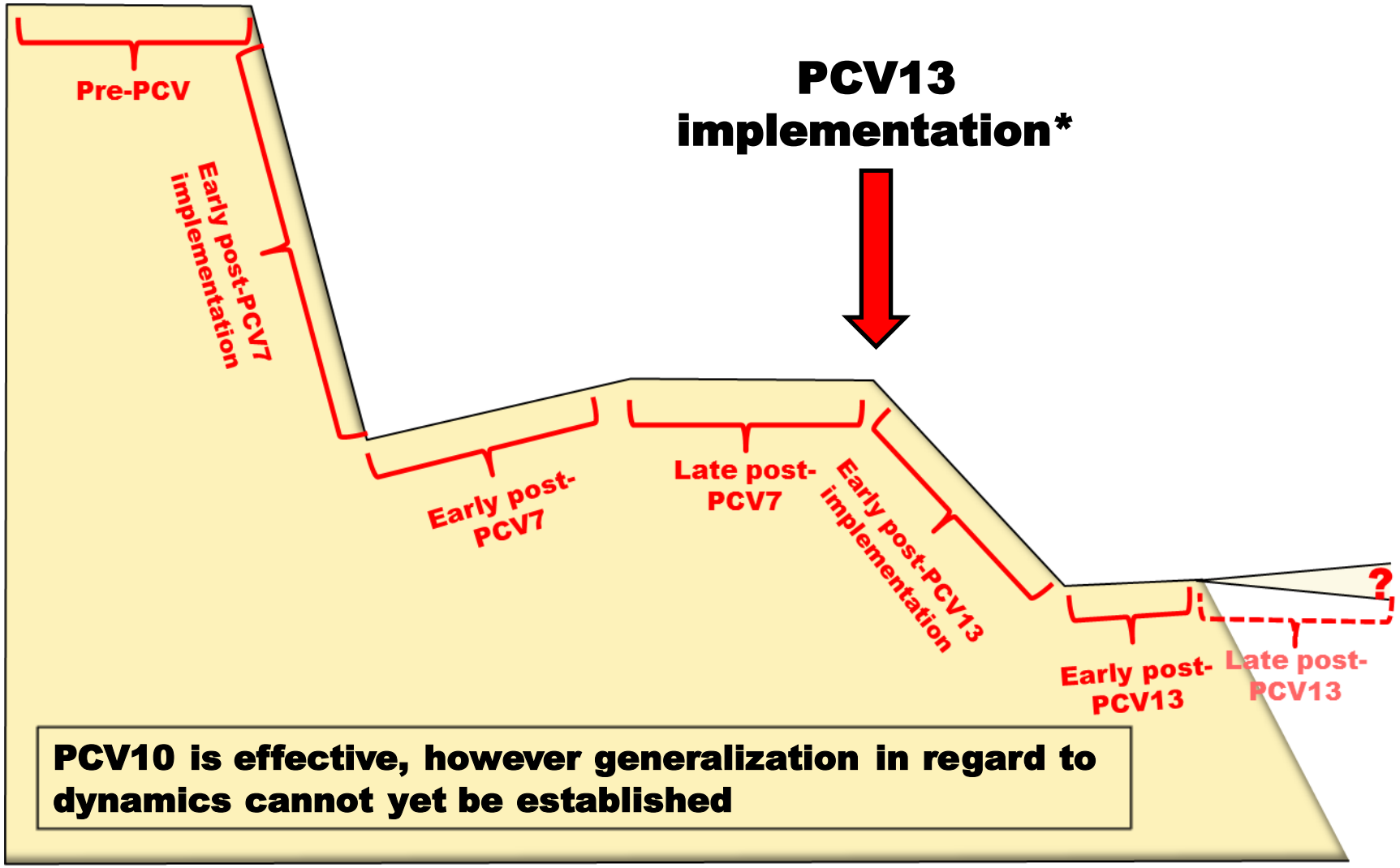
Kaplan et al, *PIDJ*; 32: 203–207, 20013

IPD Incidence in Children <24 Months, Israel, 1989-2013



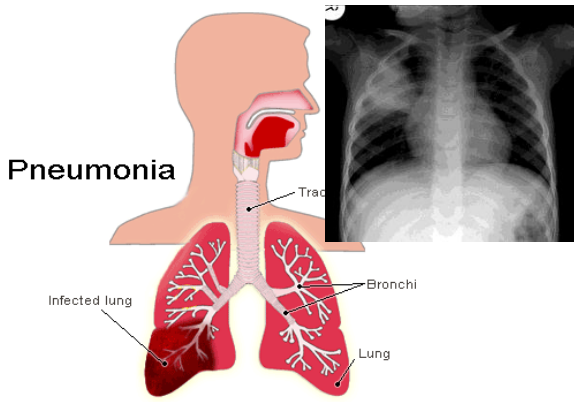
Dagan, unpublished data

IPD in Children <5 According to PCV Introduction



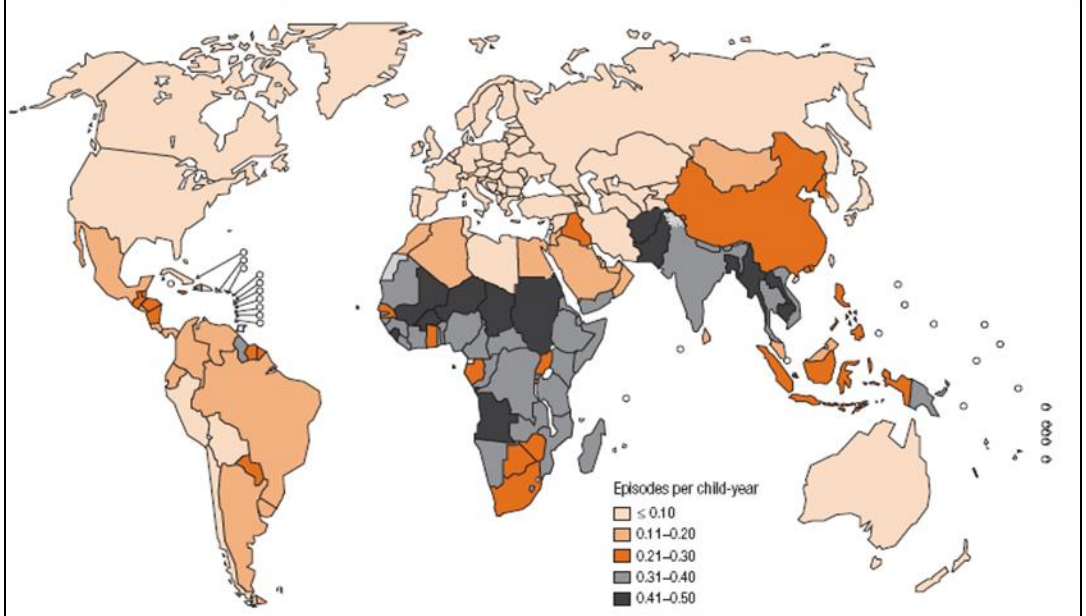
No data on further effect of PCV10 after PCV7 implementation are available

Pneumococcal Disease Endpoints

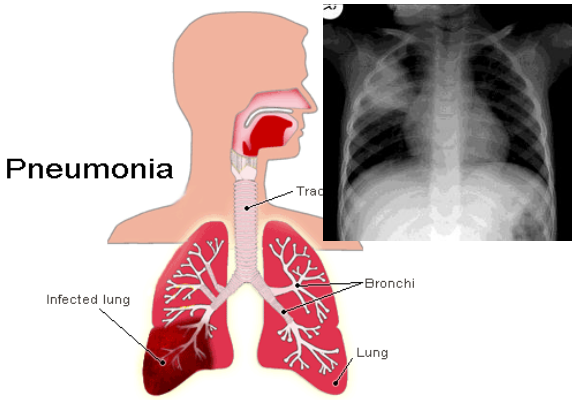


Pneumococcal Disease Endpoints

Incidence of Childhood Clinical Pneumonia



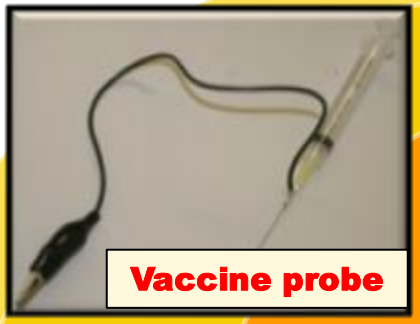
Rudan I, et al. *Bull WHO*, 86:408-416, 2008



95% of the ~800,000 deaths from pneumococcal cases in children <5 were attributable to pneumonia

O'Brien et al, *Lancet*, 374: 893–902, 2009

Defining Pneumococcal Pneumonia



Clinical diagnosis
(WHO fast breathing? Febrile? Other clinical signs?)

Any severe pneumonia

Any Chest X-ray abnormality

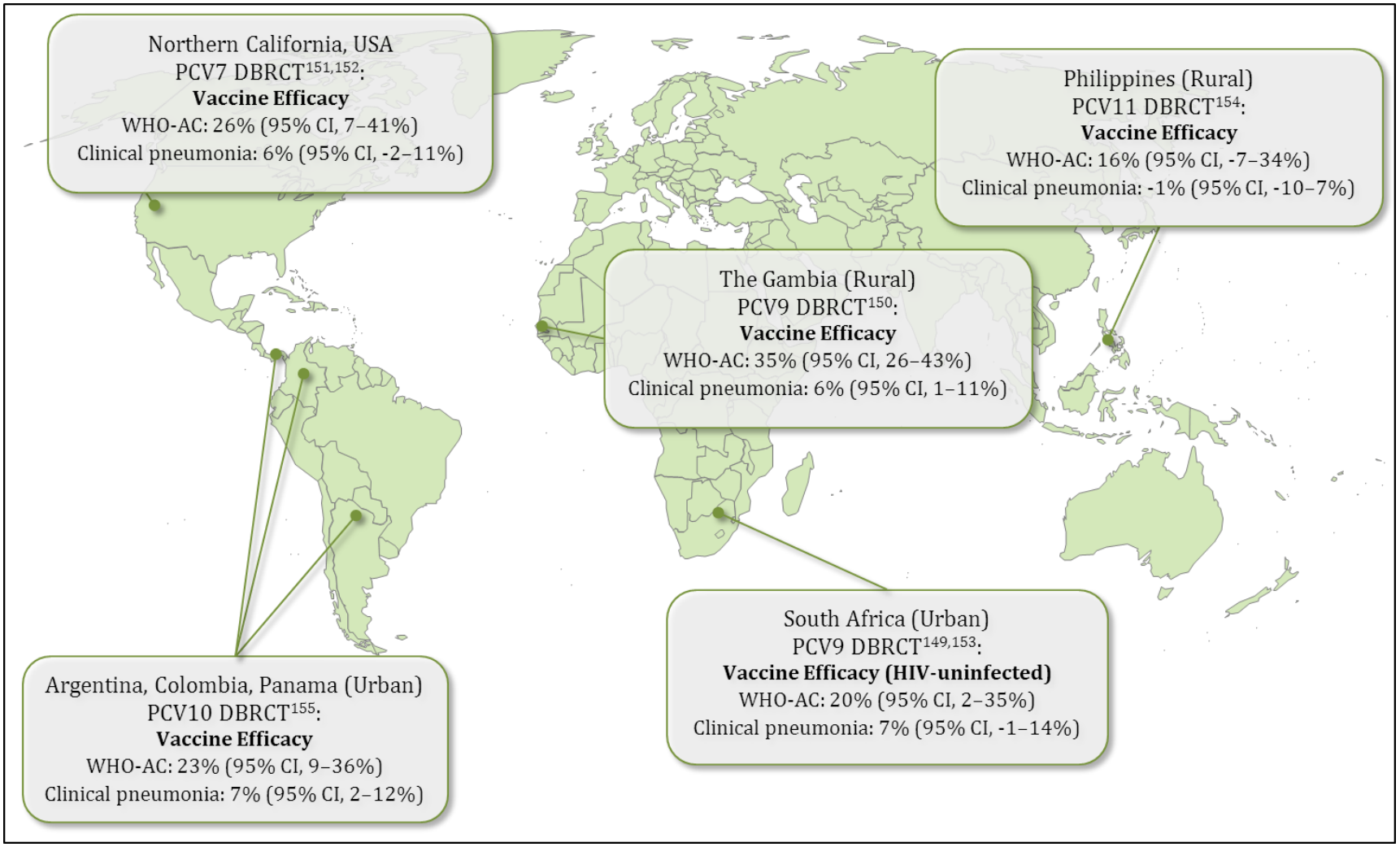
Lobar consolidation/pleural effusion or CRP >40 mg/L

Lobar consolidation/ pleural effusion

Culture-positive

Pneumococcal pneumonia

PCV Efficacy against the Syndrome of Radiological Confirmed and Clinical Pneumonia



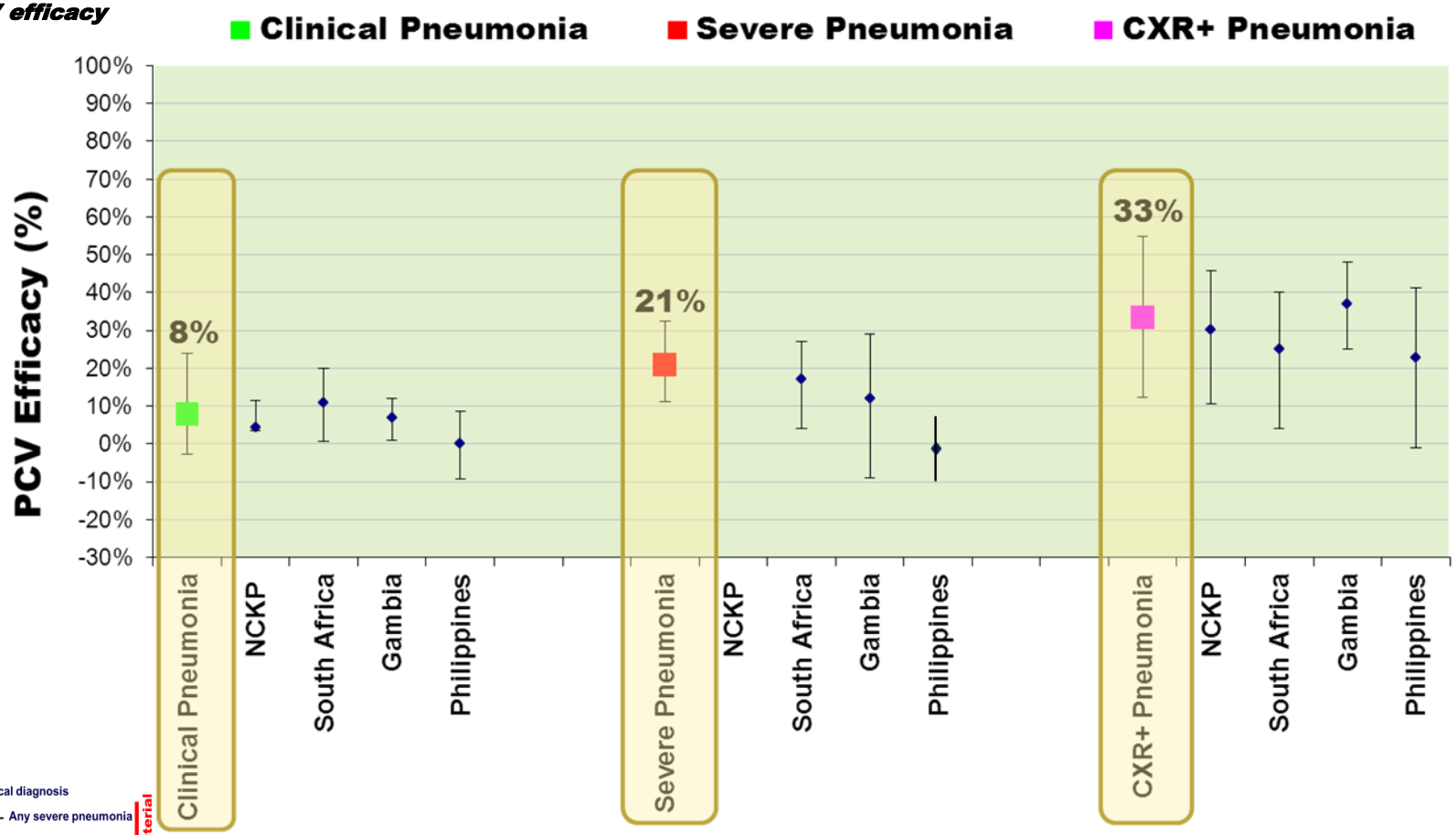
DBRCT = double-blind randomized controlled trial

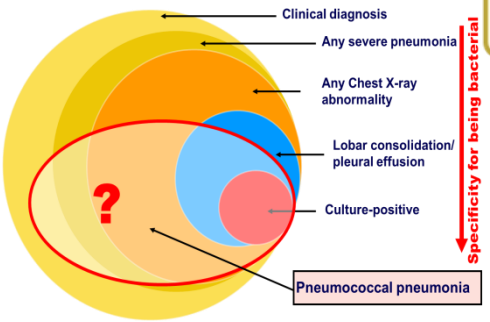
WHO-AC = World Health Organization-defined radiographic airways consolidation

Moore, Dagan & Madhi, *Expert Rev Resp Med,* In press

Meta-analysis of Efficacy of PCV7, PCV9 and PCV11 in Preventing Pneumonia

Meta-analysis of PCV efficacy

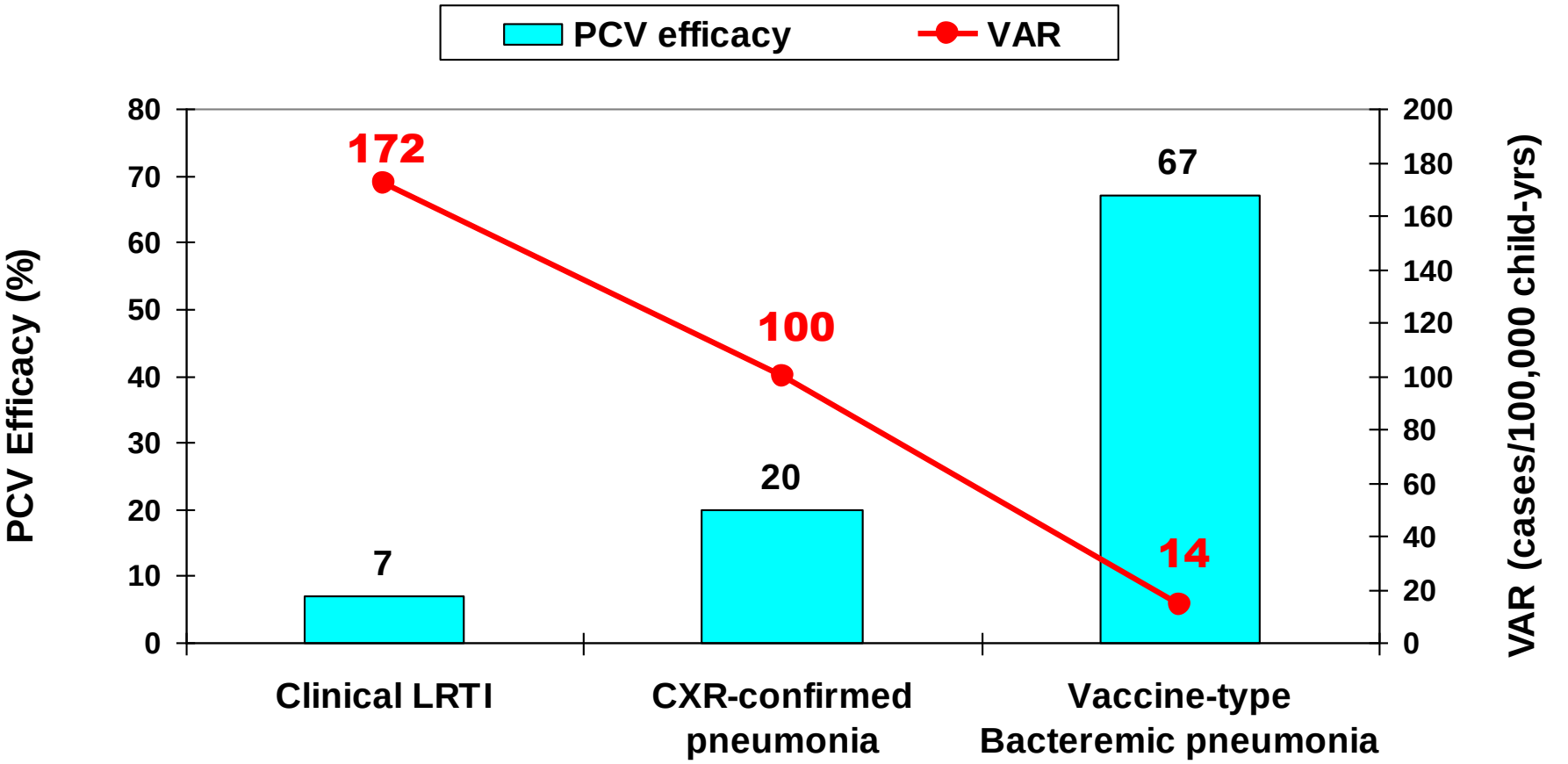




Vaccine Attributable Reduction (VAR)

7–95, 2000
41-8, 2003
–462, 2009
9–46, 2005
Madhi & Klugman, in pneumococcal vaccines: the impact of conjugate vaccine. Washington DC, ASM Press, 22: 327–46, 2008

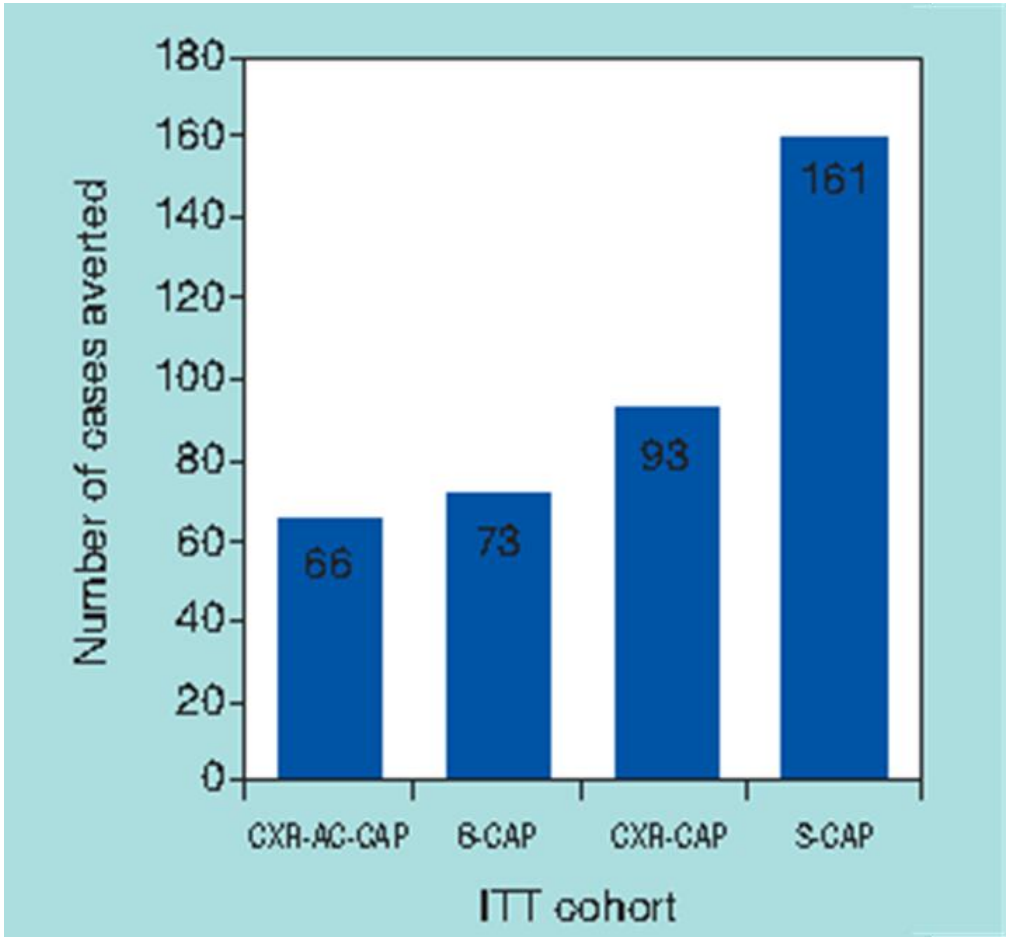
Inverse Relationship Between Vaccine Efficacy And Vaccine Attributable Reduction in HIV-Uninfected Children



12 cases of hospitalised "clinical LRTI" and 7 cases of CXR confirmed pneumonia prevented for every episode of bacteremic pneumonia prevented

Madhi, et al, *CID* 40: 1511-8, 2005

Number of cases averted by vaccine in ITT and Per Protocol cohorts



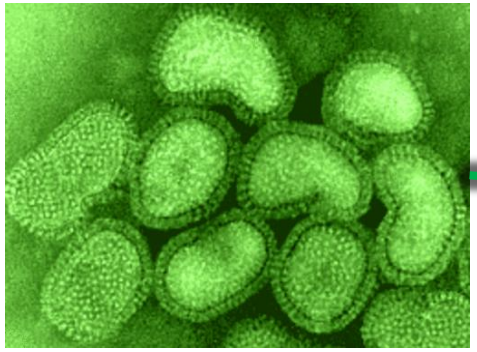
S-CAP: suspected pneumonia
CXR-AC-CAP: CXR+ (WHO) pneumonia
CXR-CAP: CXR+/- (any consolidation)
B-CAP: (CXR+ or any CXR +/- and CRP>40)

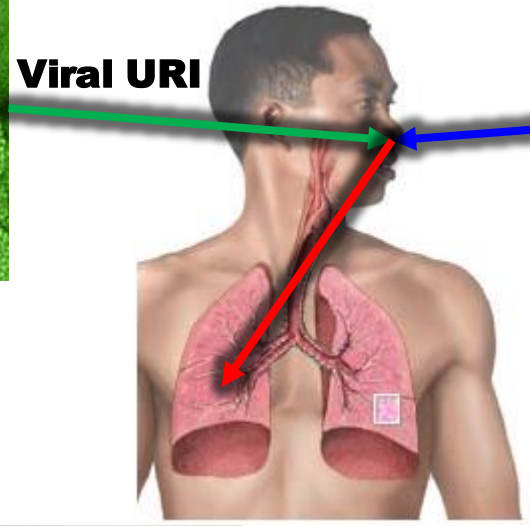
Tregnaghi et al, *XIV SLIPE*, Punta Cana, May 2011
Tregnaghi et al, *29th ESPID*, The Hague, June 2011
10PN-PD-DIT-028; NCT00466947

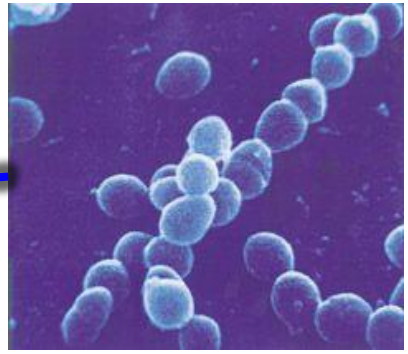
Average Annual Rates of U.S. Hospitalizations for Pneumonia Before and After the Introduction of PCV7, According to Age Group

Griffin et al, *NEJM*, 369:155-63, 2013

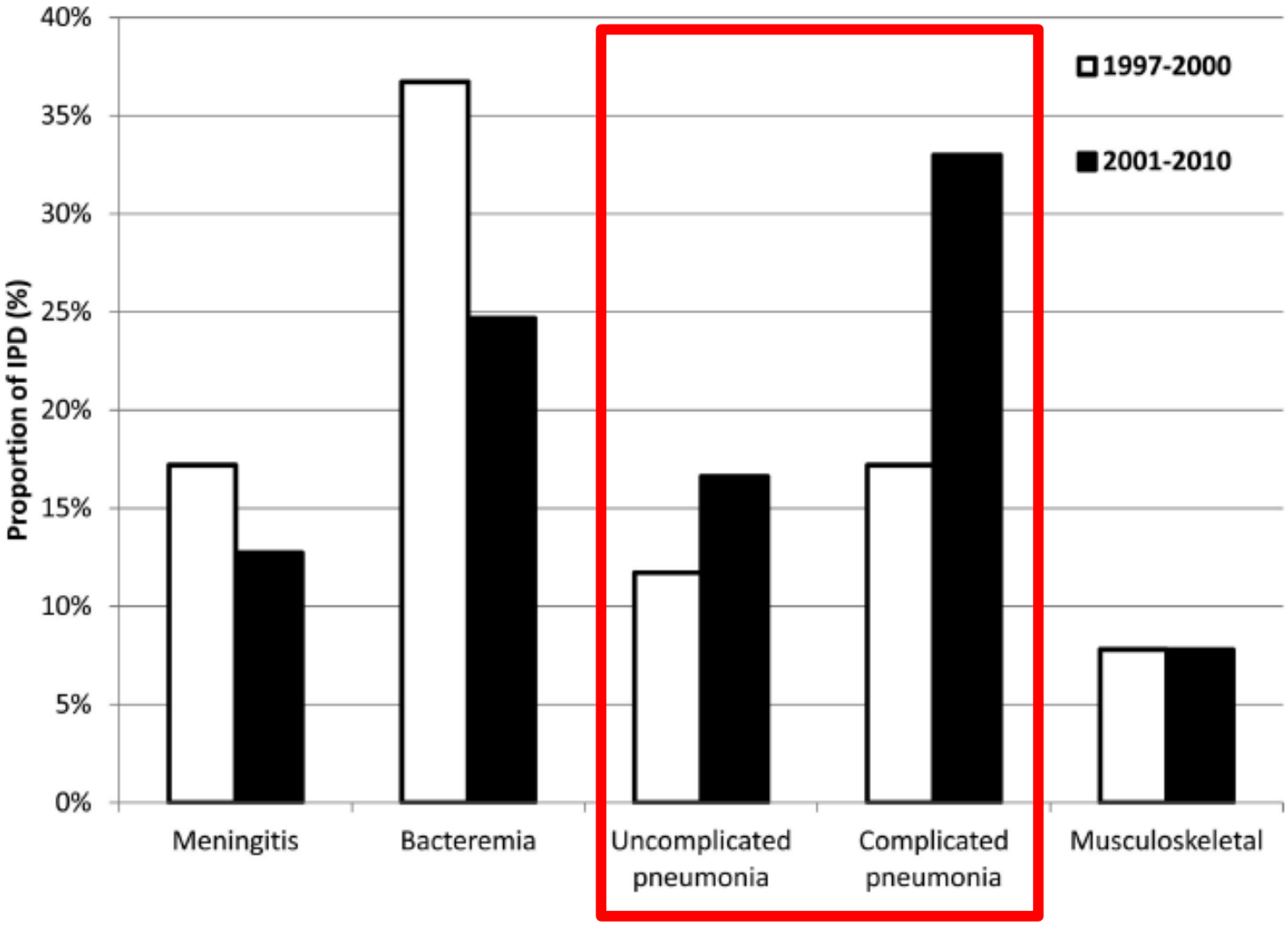
The Viral-Bacterial Interaction and Pneumonia







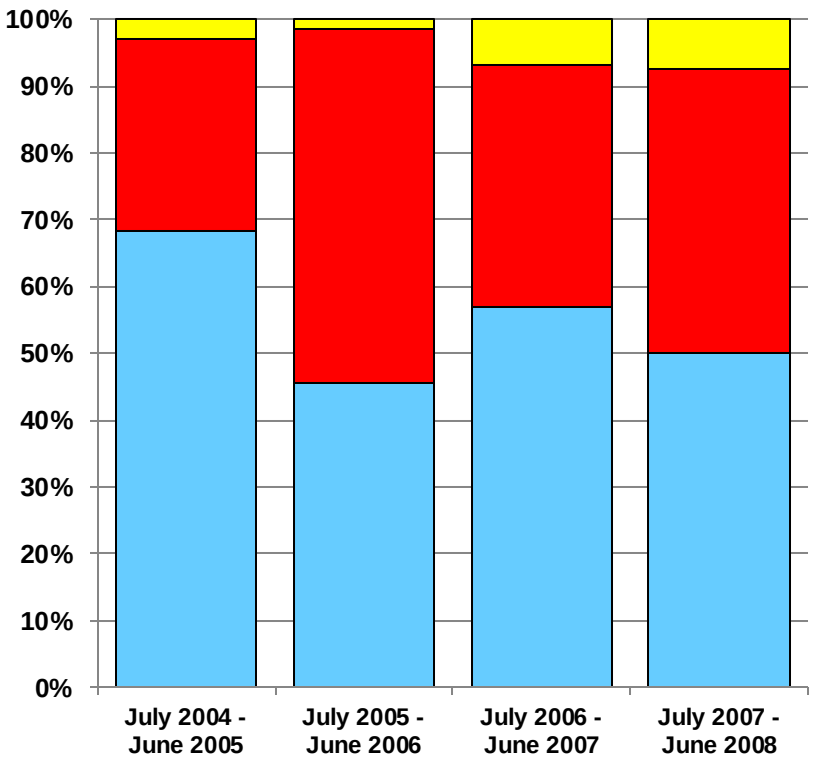
Proportion of IPD Attributed to Clinical Syndromes in Utah During the Pre-(1997–2000) and Post-vaccine (2001–2010) Periods



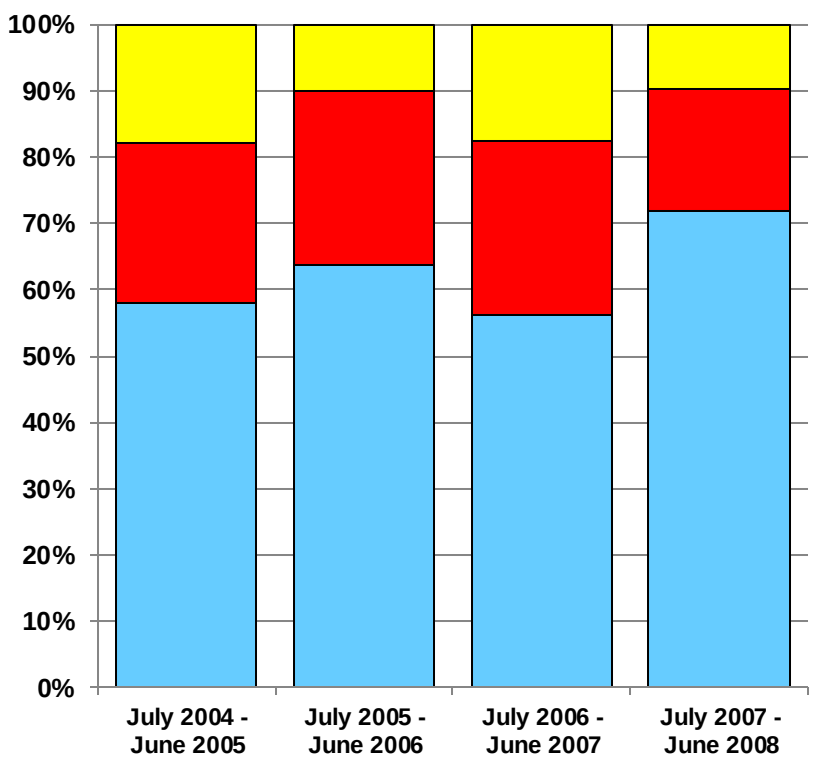
Ampofo et al, *PIDJ*; 31: 228–234, 20012

Pneumococcal Serotype Distribution: Bacteremic Pneumonia vs. Non-pneumonia IPD, Before PCV Implementation in Israel, Children <5 Yrs

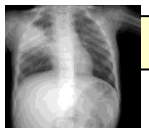
Bacteremic pneumonia



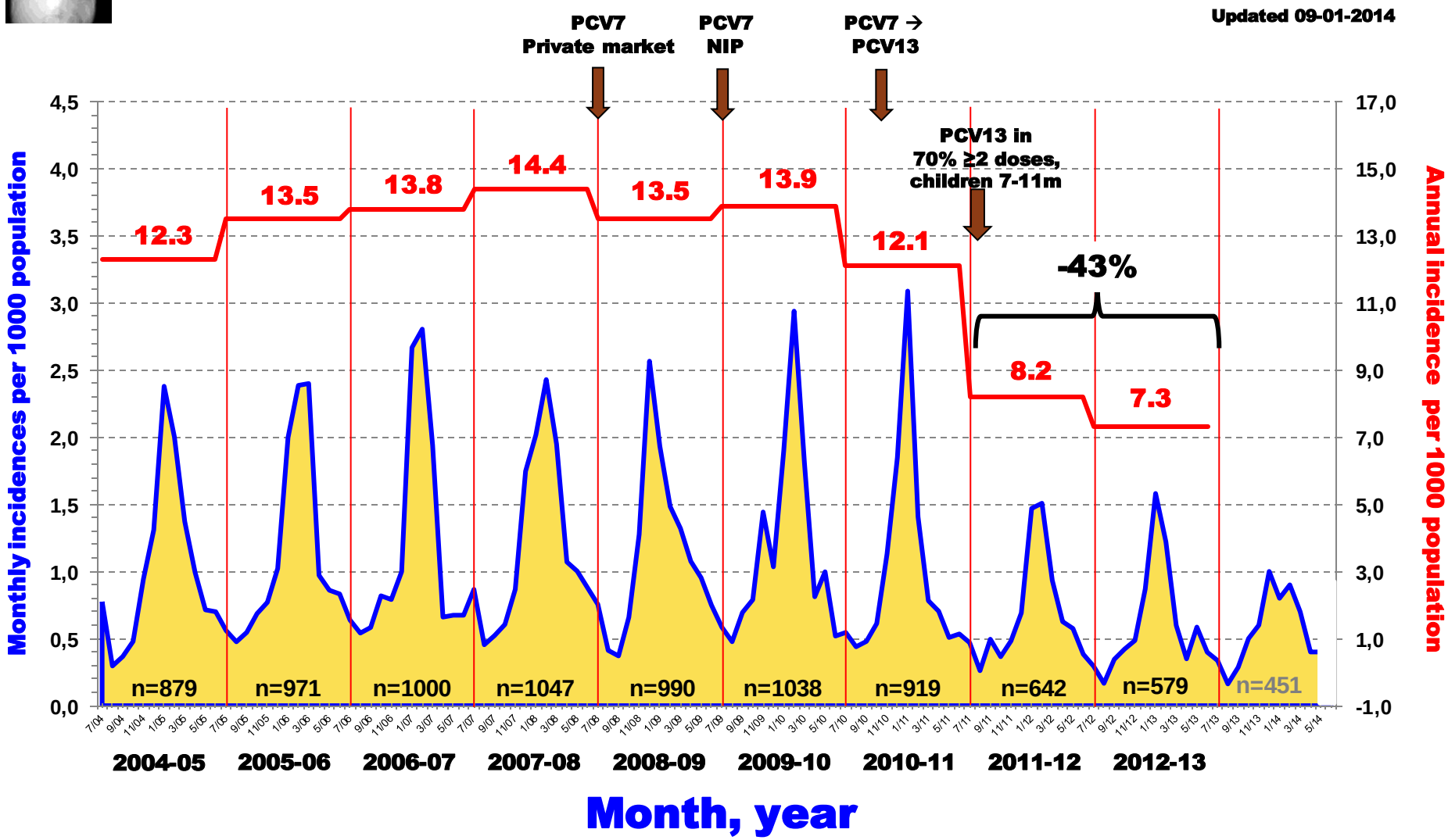
Non-pneumonia IPD



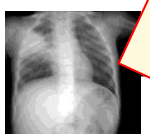
Monthly Hospital Visits for Alveolar Pneumonia in Children <5 Years, Southern Israel, Since July 2004



A prospective population-based study to document hospital use for alveolar pneumonia in young children



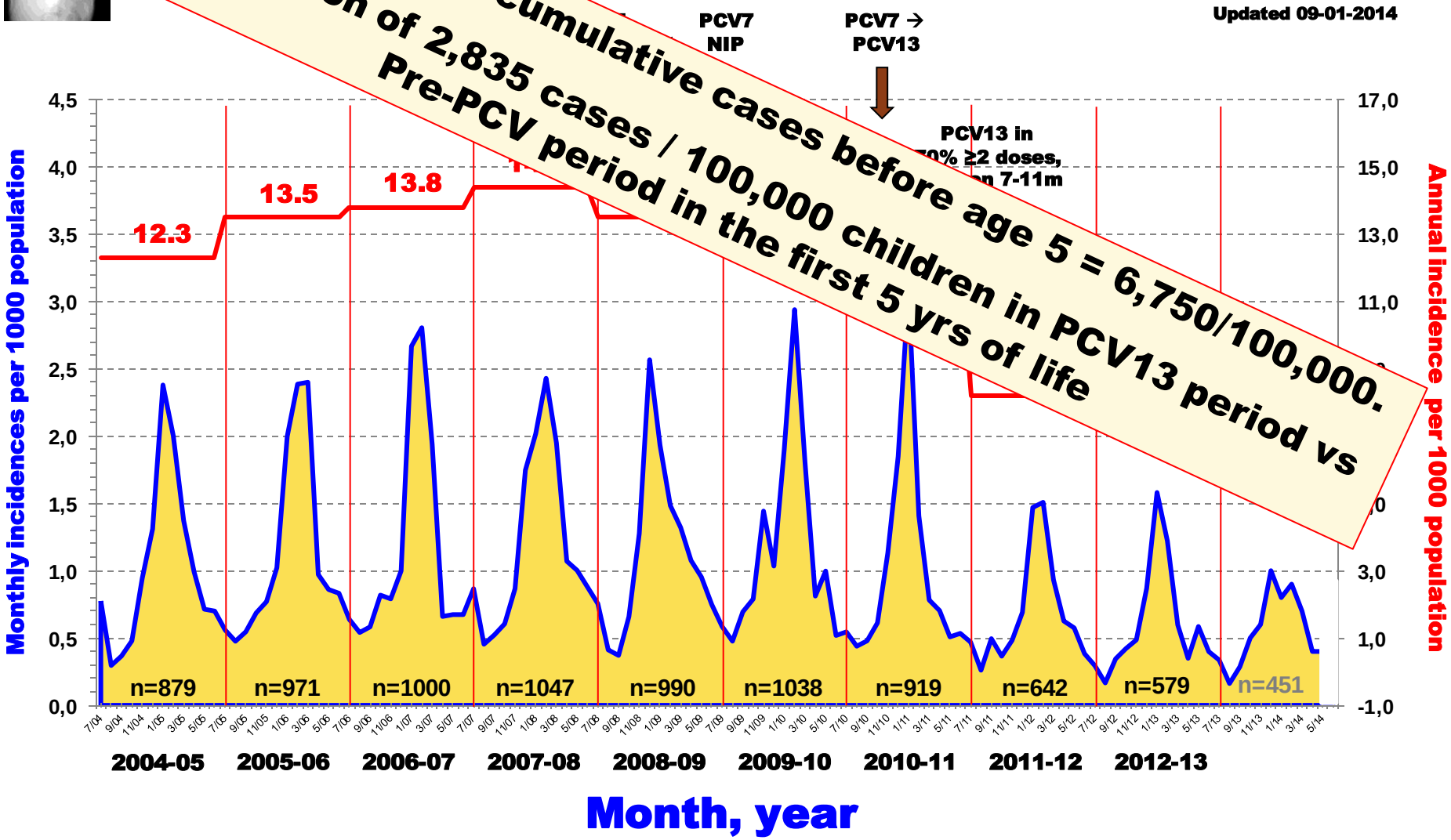
Monthly Hospital Visits for Alveolar Pneumonia in Children <5 Years, Southern Israel, Since July 2004



ed study to document hospital use for alveolar pneumonia in young children

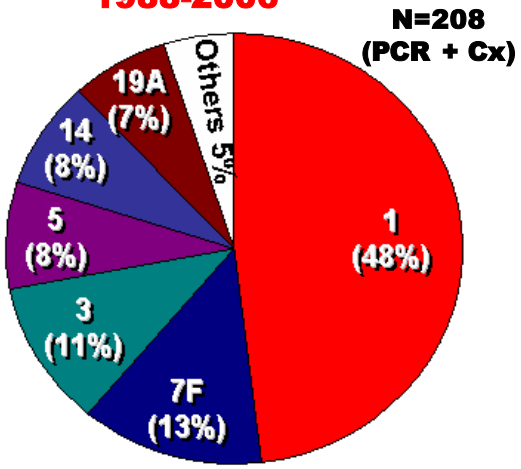
Pre PCV period - cumulative cases before age 5 = 6,750/100,000.

A reduction of 2,835 cases / 100,000 children in PCV13 period vs Pre-PCV period in the first 5 yrs of life



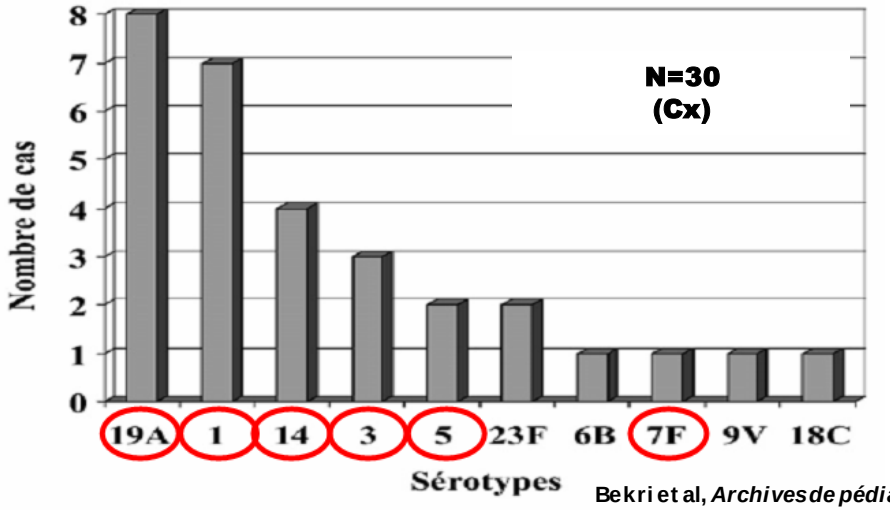
Serotypes Associated with Pleuropneumonia

Spain Children < 14 yrs 1988-2006



Obando et al, *Emerg Infect Dis* 14:1890-97, 2008

France Children < 16 yrs 2002-2004



Bekri et al, *Archives de pédiatrie*, 14: 239–243, 2007

Serotype	Age groups 0-23 mo	24-59 mo	5-14 y	Total	%	Cumulative %
14	82	31	5	118	30.5	30.5
1	14	27	36	77	19.9	50.6
[illegible]	19	31	19	69	17.8	68.3
[illegible]	[illegible]	11	0	25	6.5	74.0
[illegible]	[illegible]	[illegible]	3	23	5.9	80.7
[illegible]	[illegible]	[illegible]	[illegible]	21	5.4	86.1
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	4.9	91.0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	93.1
6A	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
19F	2	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
4	0	3	[illegible]	[illegible]	[illegible]	[illegible].7
18C	1	0	1	[illegible]	[illegible]	[illegible]7.2
8	1	0	1	2	[illegible]	[illegible]97.7
23F	1	1	0	2	0.5	98.2
Others	4*	2†	1‡	7	1.8	100
Total	191	123	73	387		

*9A, 9N, 19B, 33 F, n = 1; †23A, 23B, n = 1; ‡.22F, n = 1.

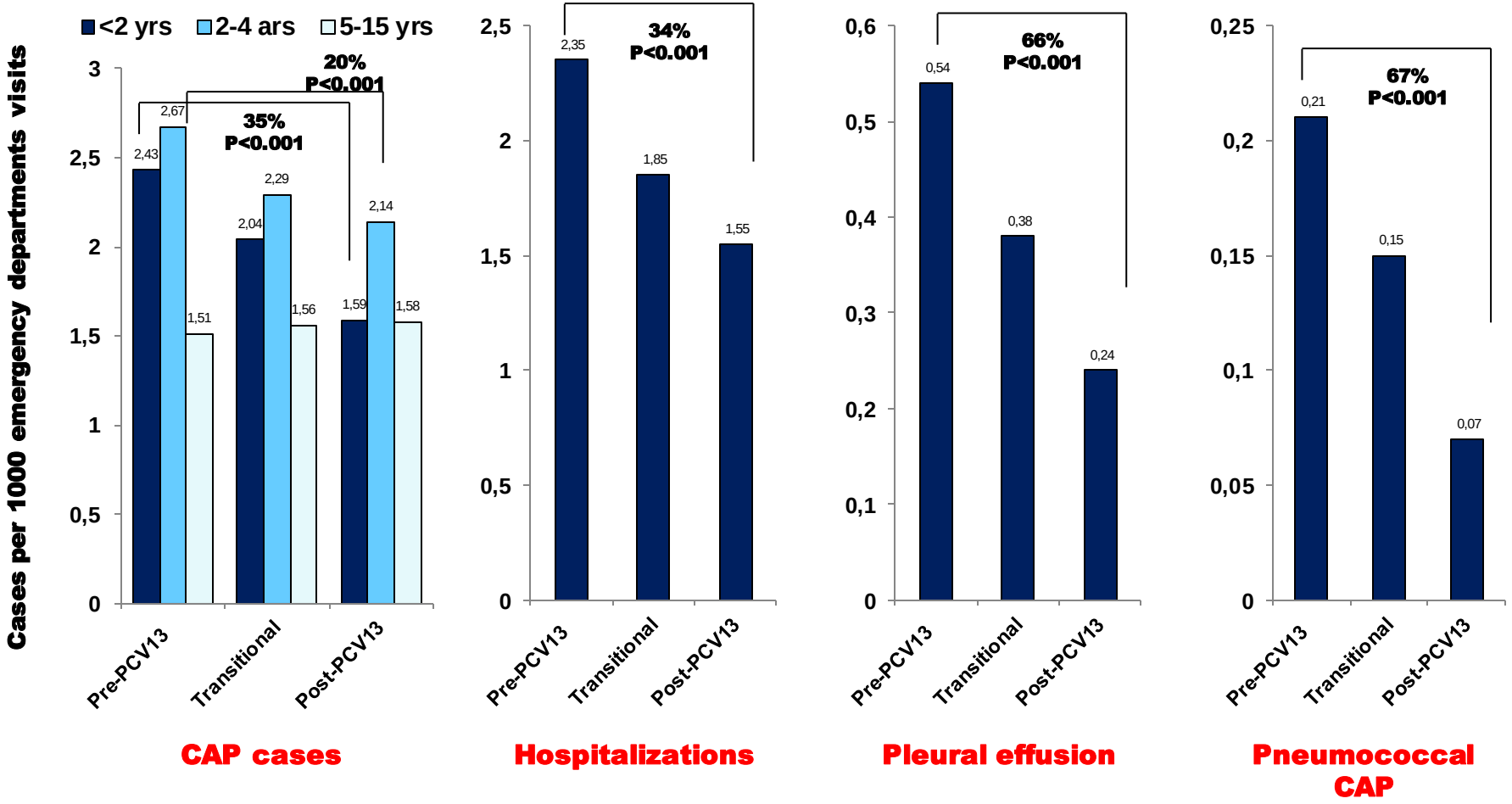
- 82% of all cases <2 yrs
- 85% of all cases 2-4 yrs
- 86% of all cases 5-14 yrs

Hortal et al, *J Pediatr*, 52:850-3, 2008

Pleuropneumonia
1, 3, 5, 7F, 14, 19A

PCV7	4	6B	9V	14	18C	19F	23F						
PCV10	4	6B	9V	14	18C	19F	23F	1	5	7F			
PCV13	4	6B	9V	14	18C	19F	23F	1	5	7F	3	6A	19A

Evolution of Community-acquired Pneumonia Cases: 8 Pediatric Pediatric Emergency Department Visit, France

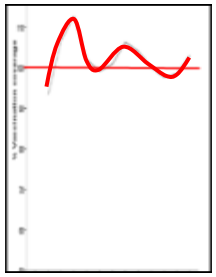


- Pre-PCV13 (June 2009 - May 2010)
- Transitional (June 2010 – May 2011)
- Post PCV13 (June 2011 – May 2012)

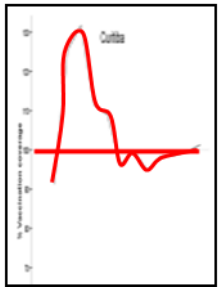
Angoulvant et al, *Clin Infect Dis*, in press

Annual % Change in Rates of Hospitalization among Children 2-23m, Brazil, Postvaccination Period (January 2005– August 2011)

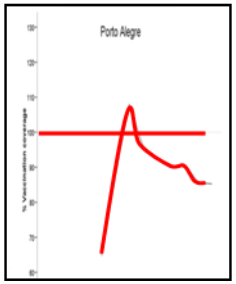
Belo Horizonte



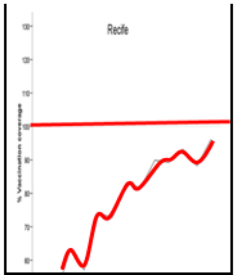
Cuitiba



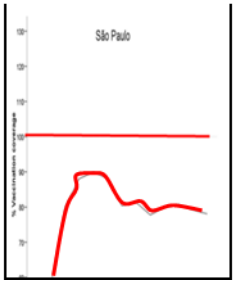
Recife



Sao Paolo



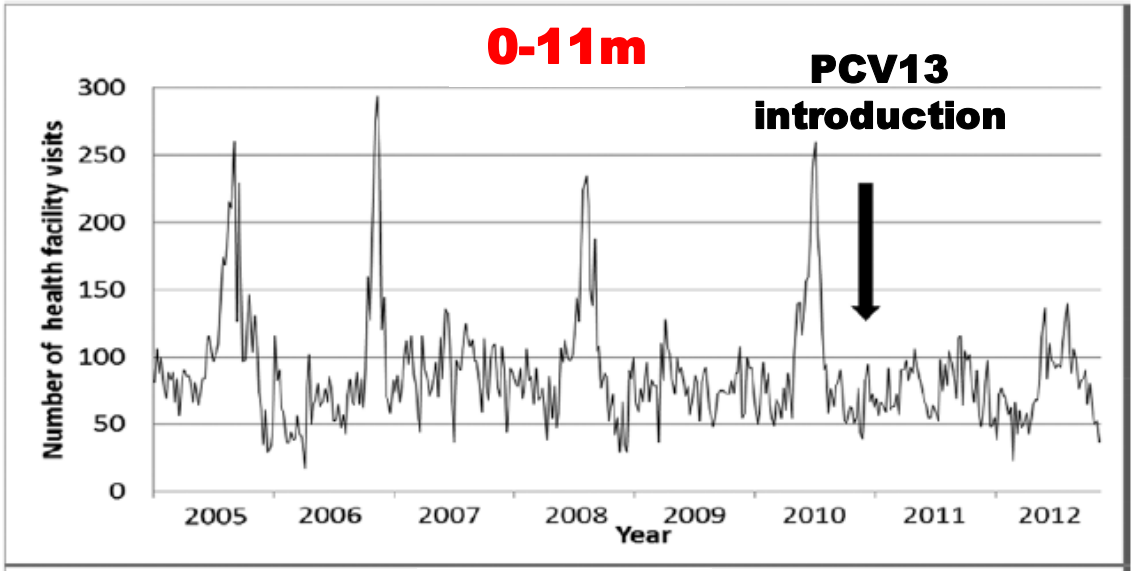
Porto Alegre



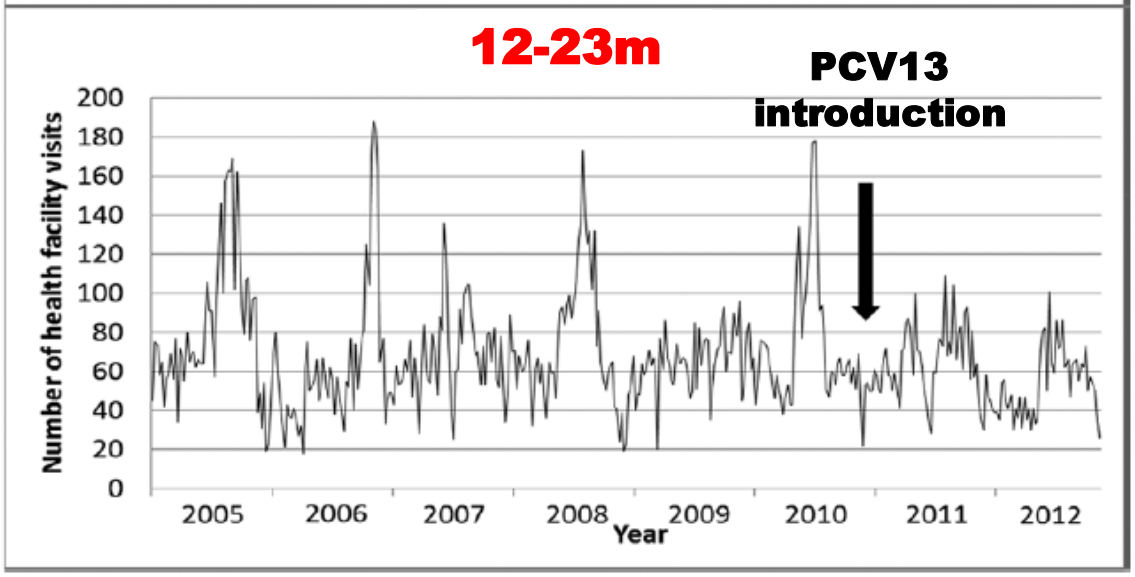
City	Hospitalizations for pneumonia		Hospitalizations for nonrespiratory causes		Difference in change	p value
	% Change (95% CI)	p value	% Change (95% CI)	p value		
Belo Horizonte	–40.30 (–50.88 to –27.44)	<0.001	–11.61 (–23.48 to 2.10)	0.093	–28.69	0.002
Curitiba	–37.59 (–49.63 to –22.68)	<0.001	–14.27 (–23.94 to –3.38)	0.012	–23.32	0.011
Recife	–49.32 (–61.63 to –33.05)	<0.001	–21.93 (–32.18 to –10.13)	0.001	–27.39	0.007
São Paulo	–13.38 (–26.02 to 1.42)	0.074	–11.60 (–19.31 to –3.15)	0.008	–1.78	0.827
Porto Alegre†	–23.51 (–41.60 to 0.18)	0.052	–21.18 (–31.08 to –9.86)	0.001	–2.33	0.845

Afonso et al, *EID*, 19:589-97, 2013

Number of Health Facility Visits for Pneumonia by Week for Infants and 1-year Olds, 2005–2012



Hospitalization pneumonia	Ambulatory pneumonia	All health visits for diarrhea
0.67 (0.59 – 0.75)	0.87 (0.75 – 1.01)	1.05 (0.81 – 1.36)

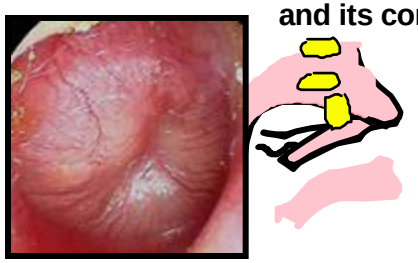


Hospitalization pneumonia	Ambulatory pneumonia	All health visits for diarrhea
0.74 (0.67 – 0.81)	0.84 (0.74 – 0.95)	1.16 (0.89– 1.51)

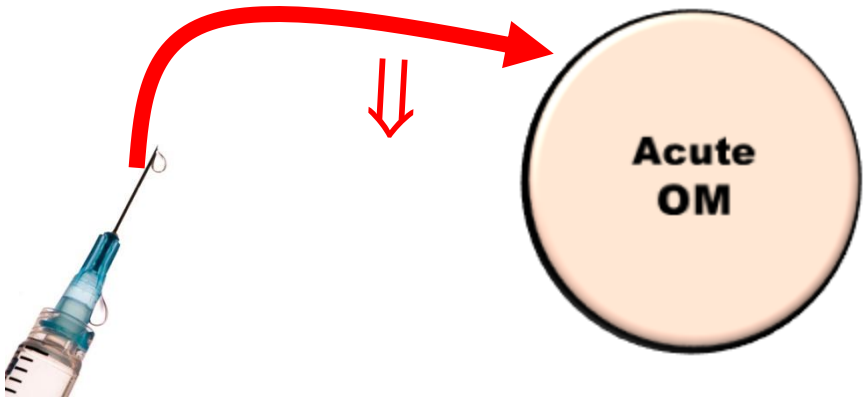
Becker-Dreps et al, *PIDJ*, 33:637–642, 2014

Pneumococcal Disease Endpoints

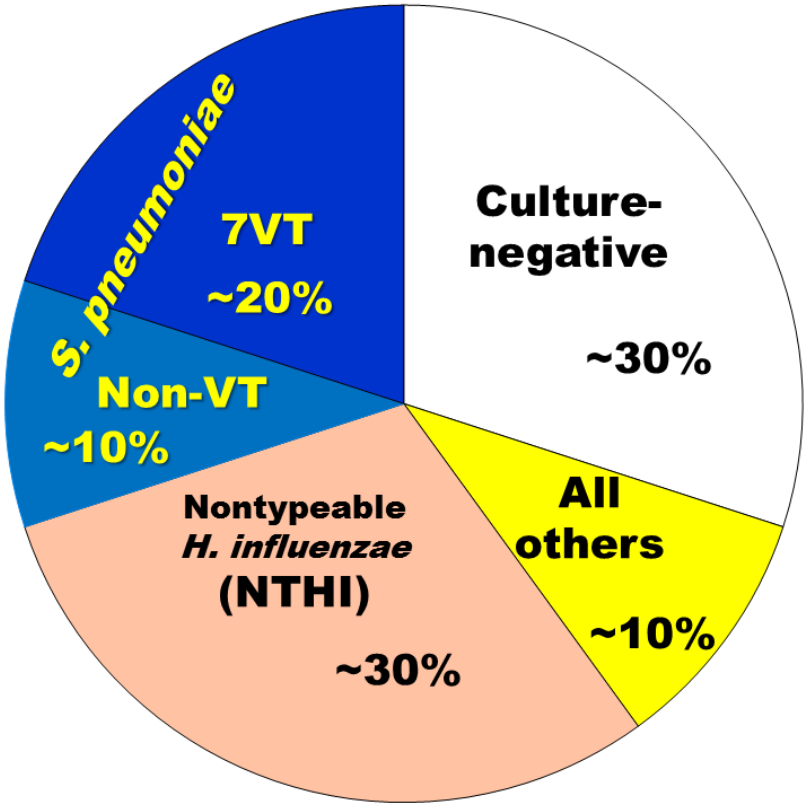
Otitis media
and its complications



Efficacy of PCVs on Otitis Media



PCV7



Before PCV7

Effect of $PCV_{CRM}7$ in Efficacy studies

Overall

<10%

Black et al, *Pediatr Infect Dis J* 19:187-95, 2000
Eskola et al, *N Engl J Med*, 344:406-9, 2001
Palmu et al, *PIDJ*, 23:732-8, 2004

Impact of PCV7/PCV13 Post Implementation on OM-Associated Burden

<24m
36.4%
(24.1–46.7)

Hospitalization with OM[1]

Recurrence/ Complexity/ Chronicity

<24m
42.7%
(42.4–43.1)

All OM-related ambulatory visits[3]

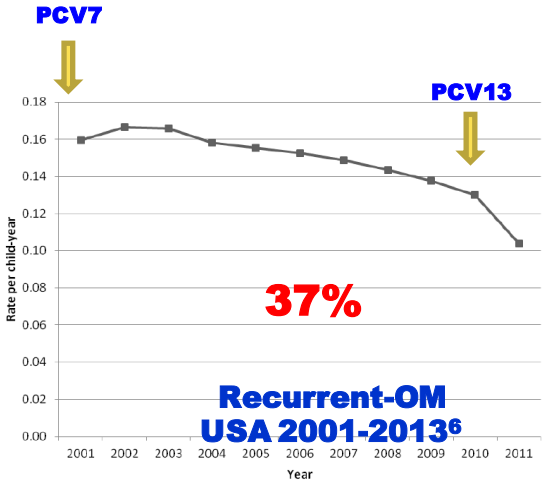
	Tennessee	New-York
2000-2001 birth cohort	<24m **17%** (14-19)	<24m **28%** (23-33)
2001-2002 birth cohort	<24m **8%** (6-11)	<24m **33%** (28-38)

Development of Frequent OM by age 2 yrs[4]

Chronicity→ Ventilation tube insertion

<12m	12-23m
23% (16–29)	**16%** (13–19)

Ventilation tube insertion[2]



Recurrent-OM USA 2001-2013[6]

* 75% <36m

<15yrs*
38%
P<0.001

Presenting to ER with OM complicated by otorrhea[5]

	Tennessee	New-York
2000-2001 birth cohort	<24m **16%** (11-21)	<24m **23%** (10-35)
2001-2002 birth cohort	<24m **3%** (-3-8)	<24m **21%** (6-33)

Ventilation tube insertion by age 2 yrs[4]

[1]Durando et al, *Vaccine* 27:3459–3462 2009

[2]Jardine et al, *Pediatr Infect Dis J*, 28:761–765, 2009

[3]Zhou et al, *Pediatr*. 121;253-260, 2008

[4]Poehling et al, Pediatrics, 119:707-15, 2007

[5]Stamboulidis et al, *Pediatr Infect Dis J,* 30: 551–555, 2011

[6]Marom et al, *JAMA Pediatr*, 168:68-75, 2014

Impact of PCVs on Otitis Media

PCV7

Acute OM

SP
NTHi
Mixed NTH+SP
NTHi in biofilms
Culture negative

Complex* OM

SP
NTHi
Mixed NTH+SP
NTHi in biofilms
Culture negative

Burden OM

Chronic OM

SP
NTHi
Mixed NTH+SP
NTHi in biofilms
Culture negative

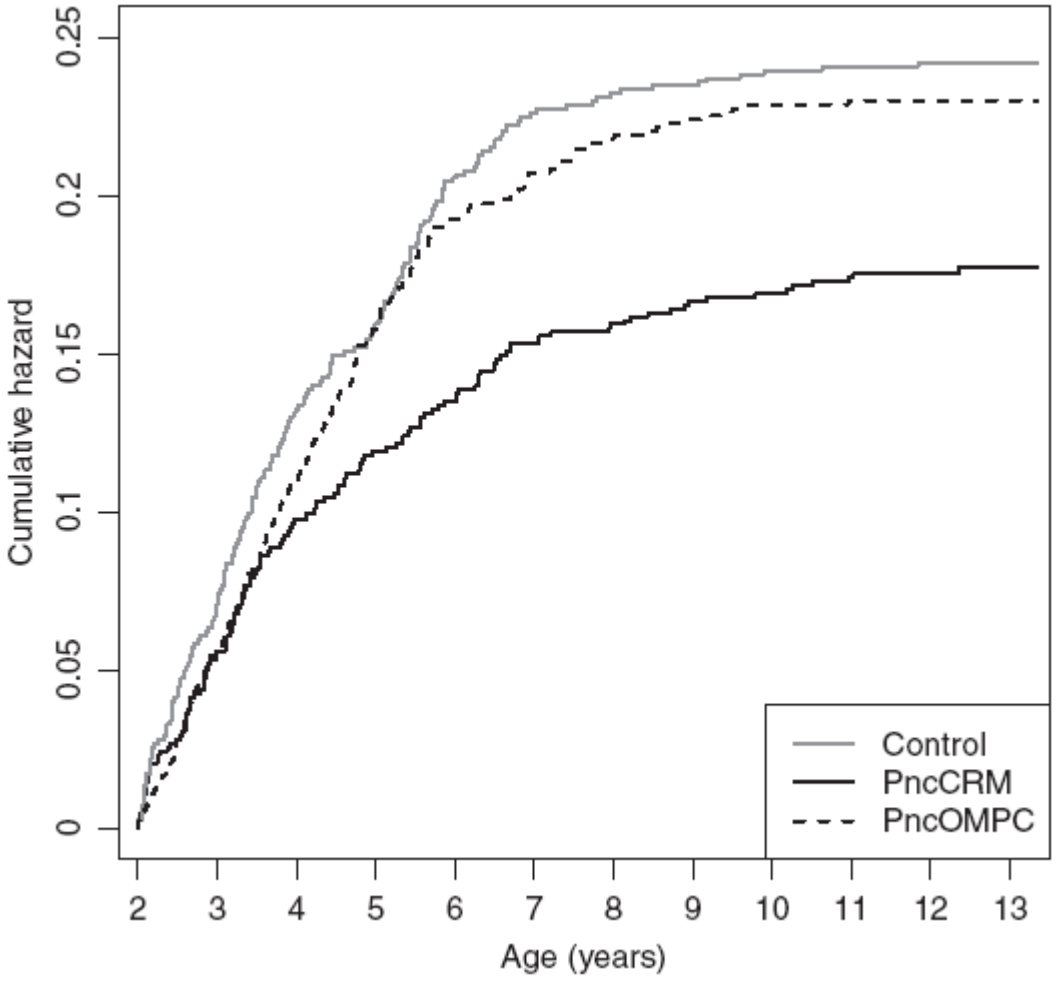
* Complex = Recurrent/non responsive/spontaneously draining/often bilateral

Effect of $PCV_{CRM}7$ in Efficacy studies

Overall	Recurrent	Chronic (SOM, Tube insertion)
<10%	~ 10-20%	~ 20-40%

Black et al, *Pediatr Infect Dis J* 19:187-95, 2000
Eskola et al, *N Engl J Med*, 344:406-9, 2001
Palmu et al, *PIDJ*, 23:732-8, 2004

Cumulative Hazard of Tympanostomy Tube Procedures in Different Vaccine Groups in the FinOM Register Follow-up



Control

PCV7-OMPC

PCV7-CRM$_{197}$

Sarasoja et al, *Pediatr Infect Dis J*, 32: 517–520, 2013

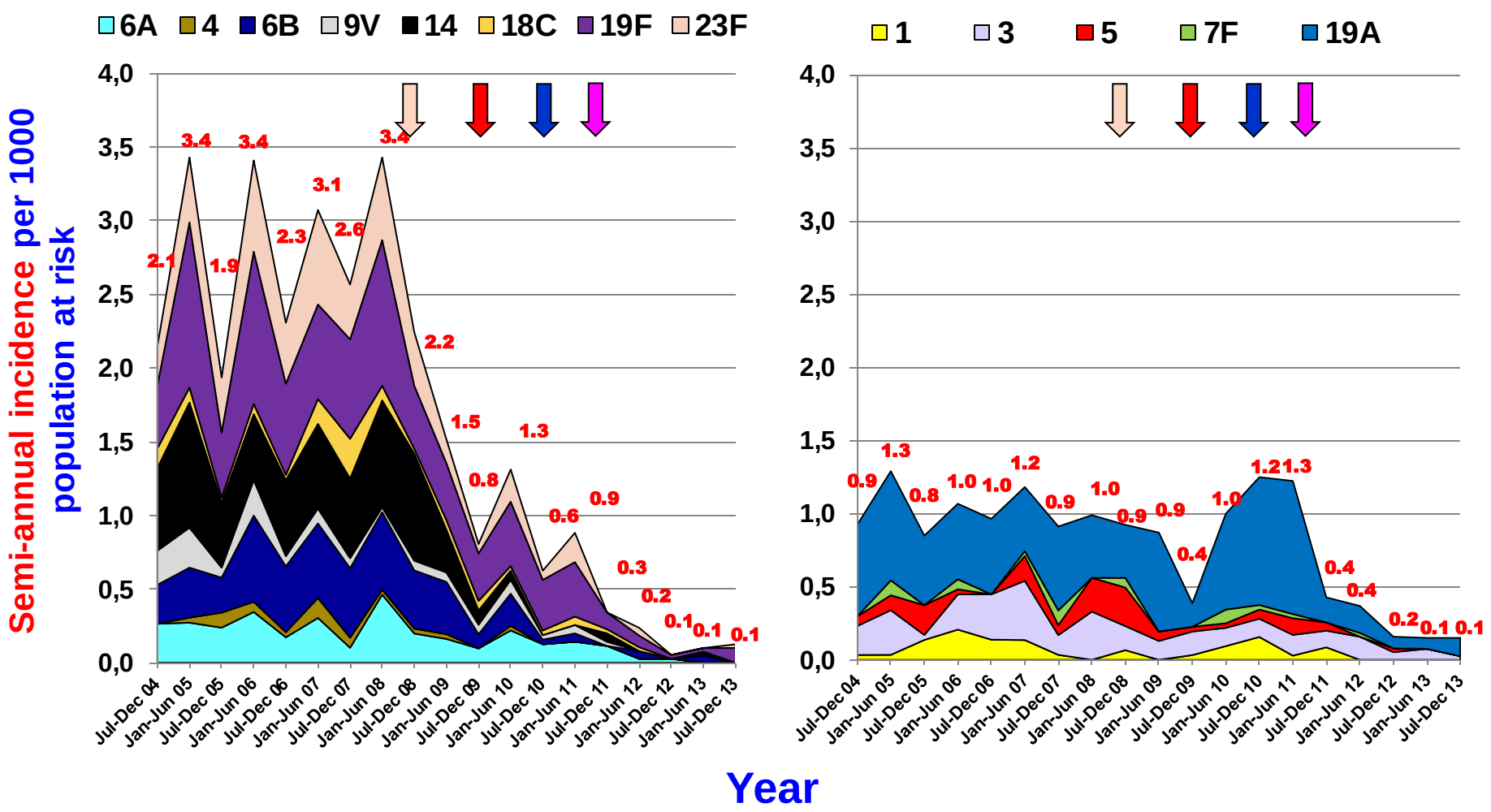
Serotype-specific Incidence (PCV7 and PCV13 Serotypes) in Children <24m with MEF Culture, Southern Israel, 2004-2013*

⇑ Vaccination Private + HMO

Initiation of PCV7 NIP + catch-up

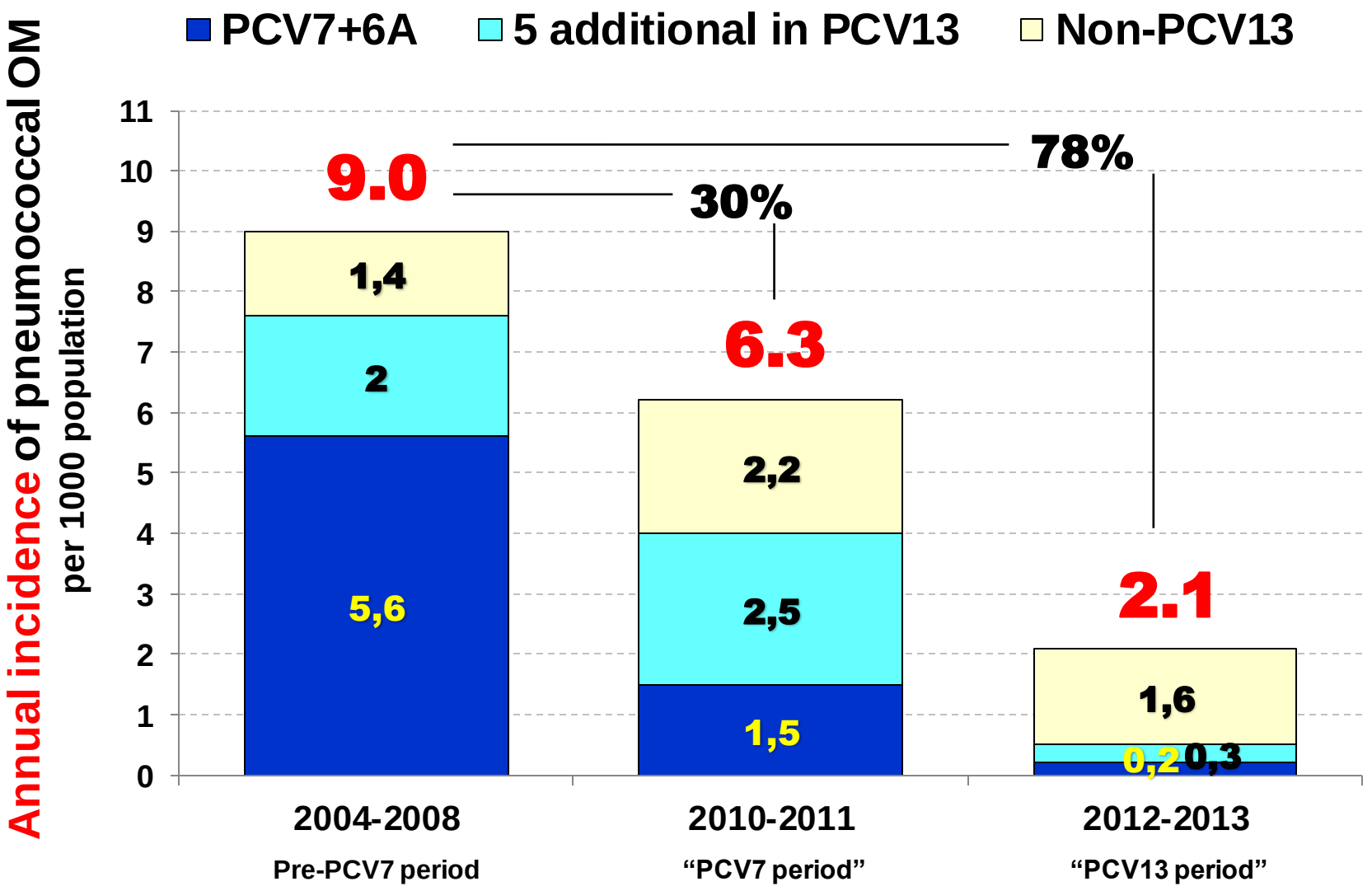
Gradual PCV7 → PCV13

>70% of children 7-11m with ≥2 PCV13 doses



* Each year is July 1st through June 30th

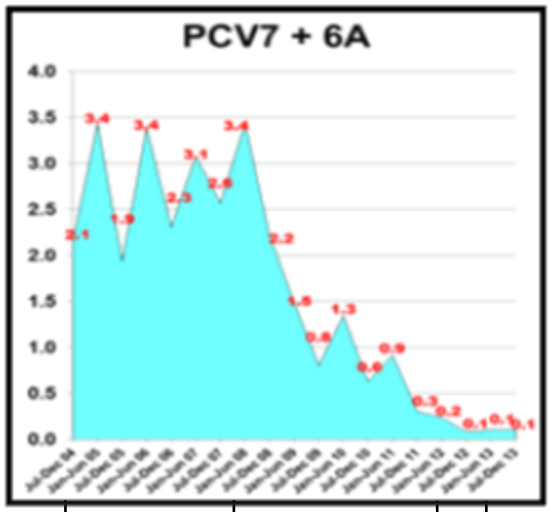
Reduction of Pneumococcal OM in Children <24 Months



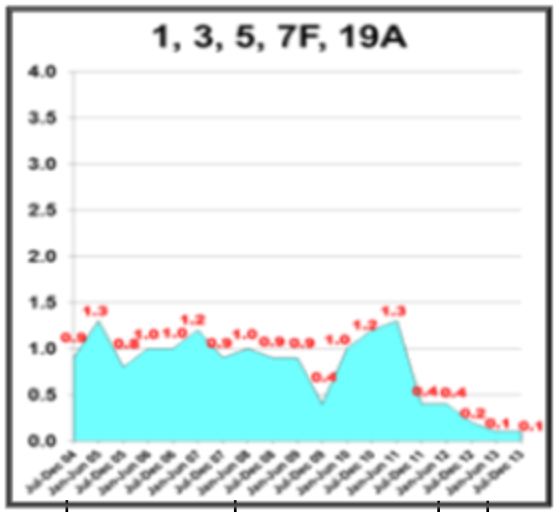
Dagan et al, ICAAC, Denver Co, Sept 2013

Pneumococcal Otitis Incidence in Children <24m with MEF Culture, Southern Israel, 2004-2013* and Rate Reduction, 2012-2013 vs. 2004-2008

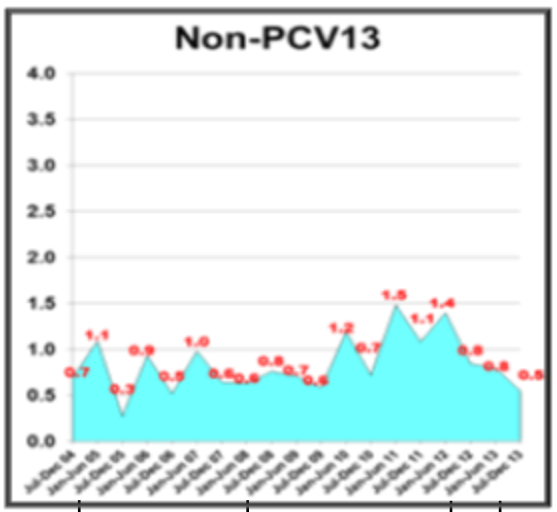
Semi-anneal incidence of pneumococcal OM per 1000 population



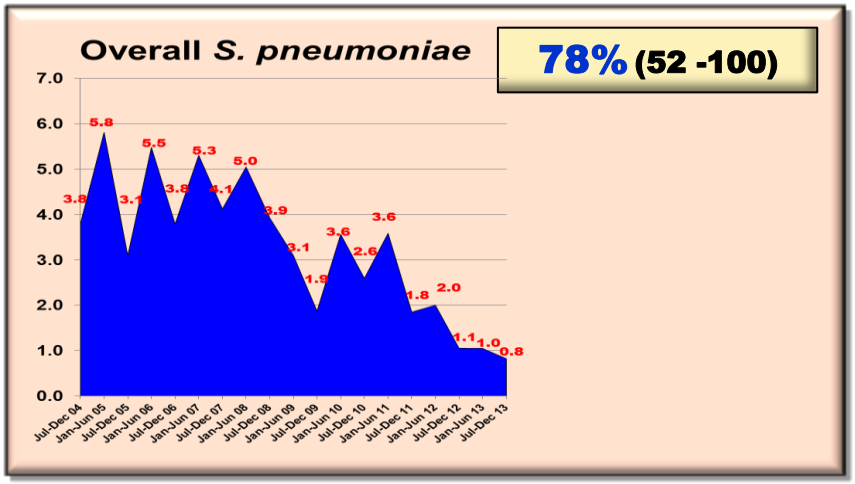
97% (72 - 100)



85% (53 - 100)



-14% (-39 - 11)



* Each study year is July 1st through June 30th

Dagan et al, ICAAC, Denver Co, Sept 2013 + updates

Impact of PCVs on Otitis Media

PCV7

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NTHi
Mixed NTH+SP
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Chronic OM

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* Complex = Recurrent/non responsive/spontaneously draining/often bilateral

Effect of $PCV_{CRM}7$ in Efficacy studies

Overall	Recurrent	Chronic (SOM, Tube insertion)
<10%	~ 10-20%	~ 20-40%

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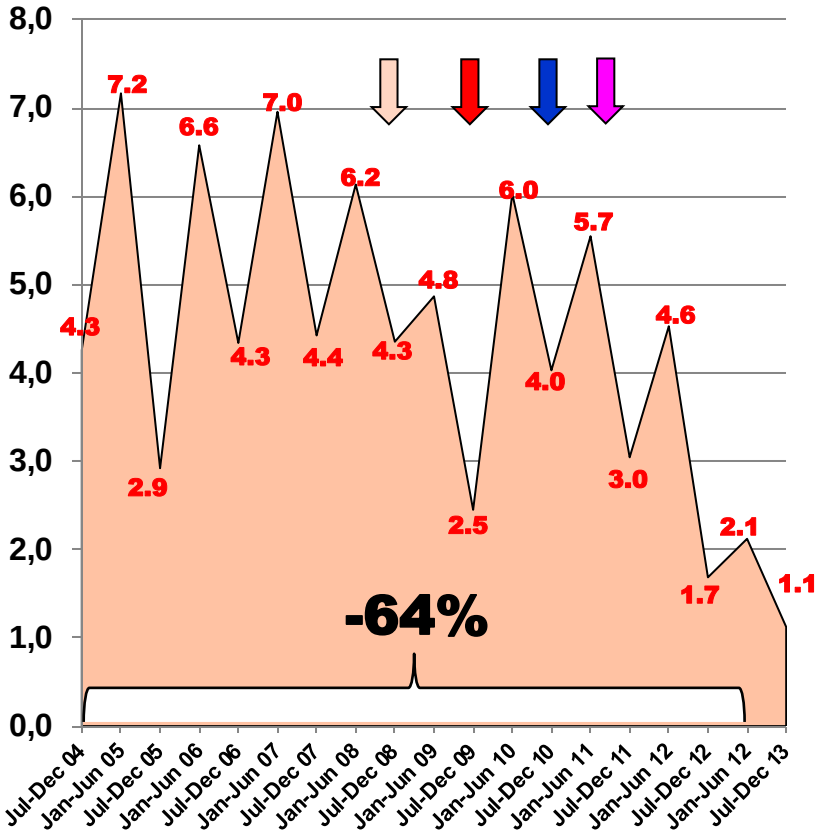
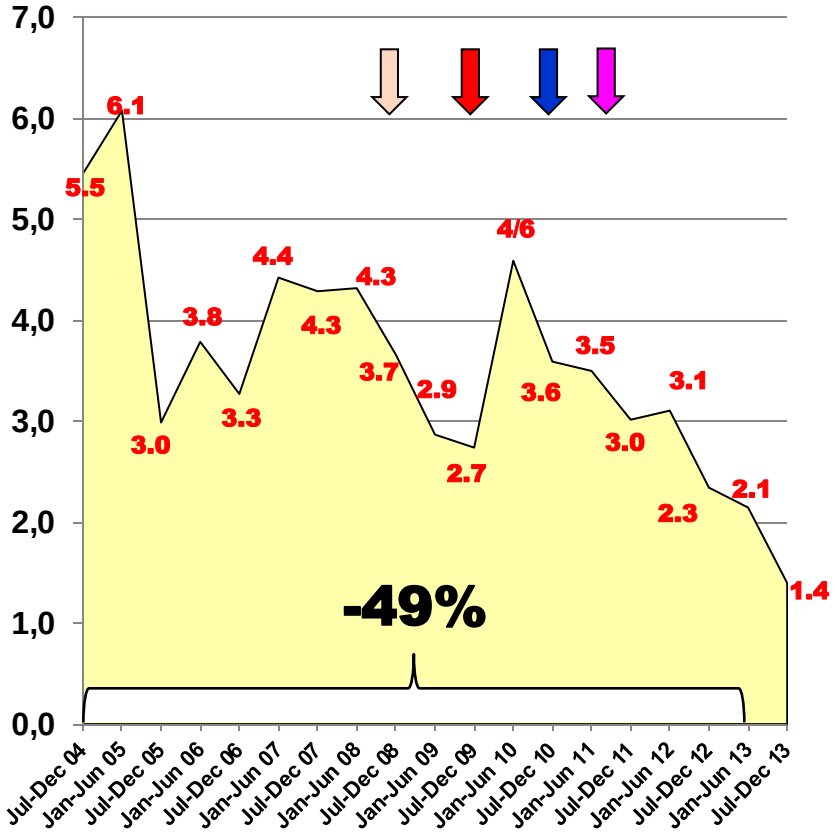
>70% of children 7-11m with ≥2 PCV13 doses

NTHi



Culture-negative



Semi-anneal incidence of pneumococcal OM per 1000 population

Year

* Each year is July 1st through June 30th

Overall OM (Pneumococcal and Non-pneumococcal) Incidence in Children <24m with MEF Culture, Southern Israel, 2004-2013* and the Rate Reduction in 2012-2013 vs. 2004-2008

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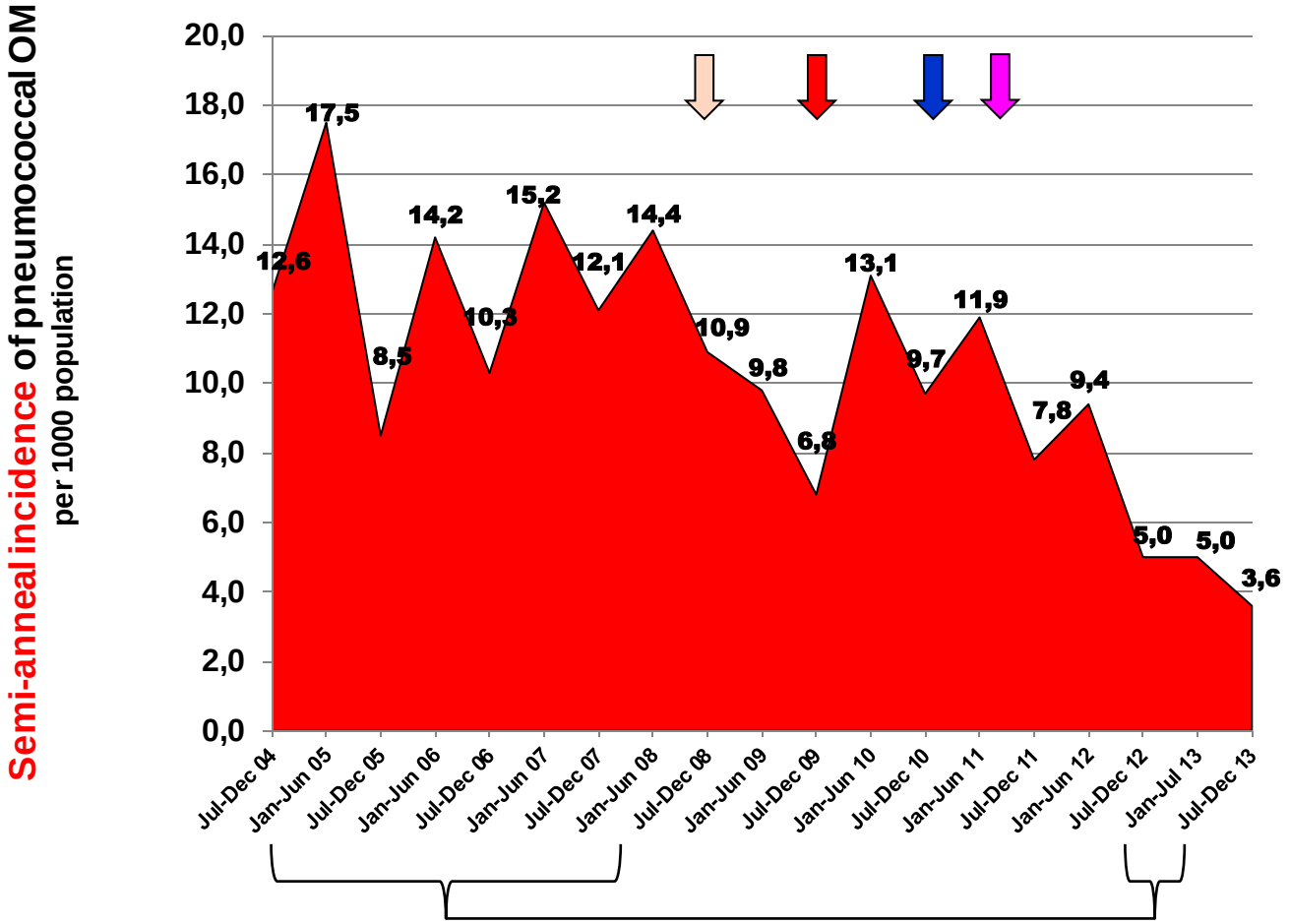
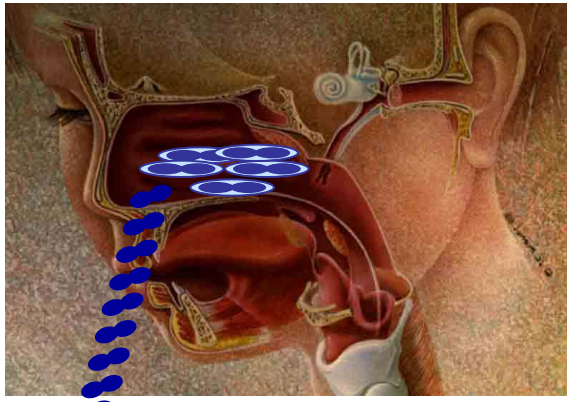
Overall *OM Cases*



61% (31 - 92)

Dagan et al, ICAAC, Denver Co, Sept 2013

Pneumococcal Disease Endpoints



Carriage & spread to other individuals

Antibiotic resistance

The Link between NP Carriage, Antibiotic Resistance and PCV

Most of antibiotic resistance globally is found in serotypes

6B, 9V, 14, 19F, 23F, 6A, 19A

PCV

NP

Antibiotic resistance

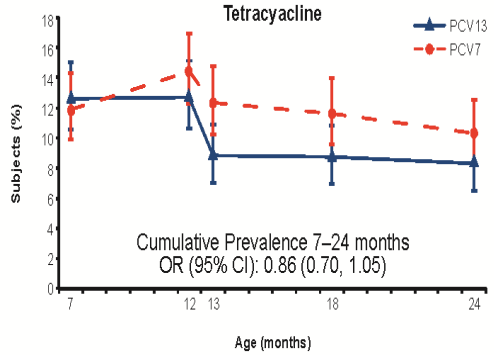
Antibio tic resista nce

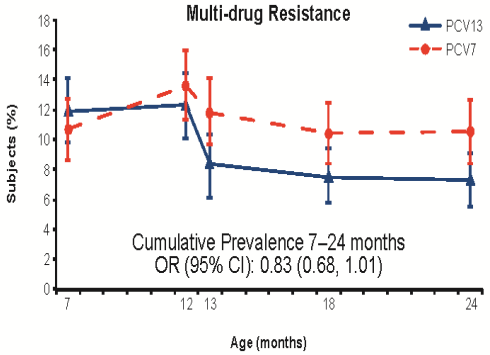
Antibio tic resista nce

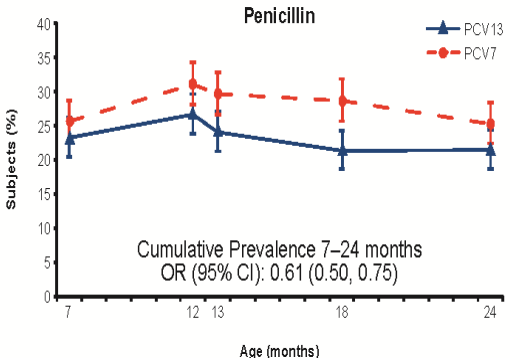
Antibio tic resista nce

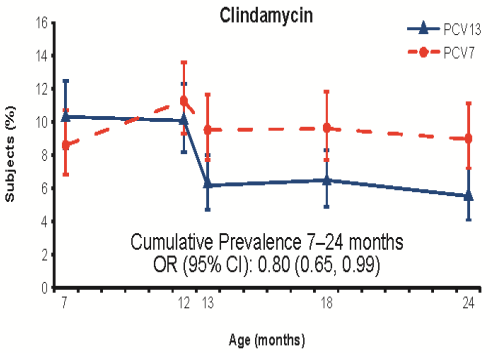
Antibiotics

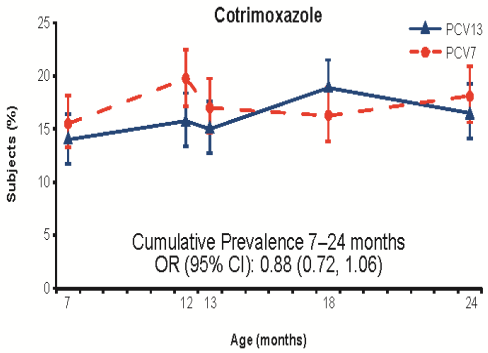
Prevalence of Antibiotic–nonsusceptibility for All Serotypes Combined at Pre-specified Time Points, by Vaccine Study Group

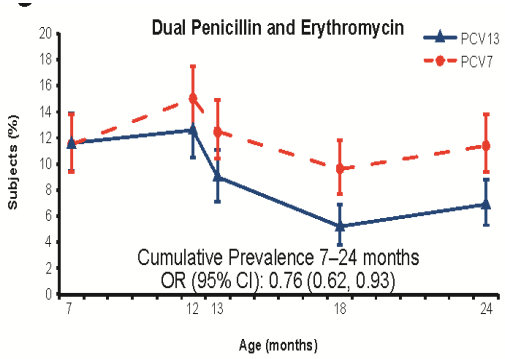


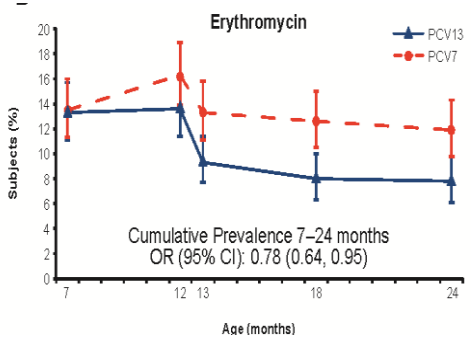












Dagan et al, submitted

Reduction of Nonsusceptible Pneumococcal AOM Children <24m and Incidence Rate reduction

Most of antibiotic resistance globally is found in serotypes

6B, 9V, 14, 19F, 23F, 6A, 19A

⇑ Vaccination Private + HMO

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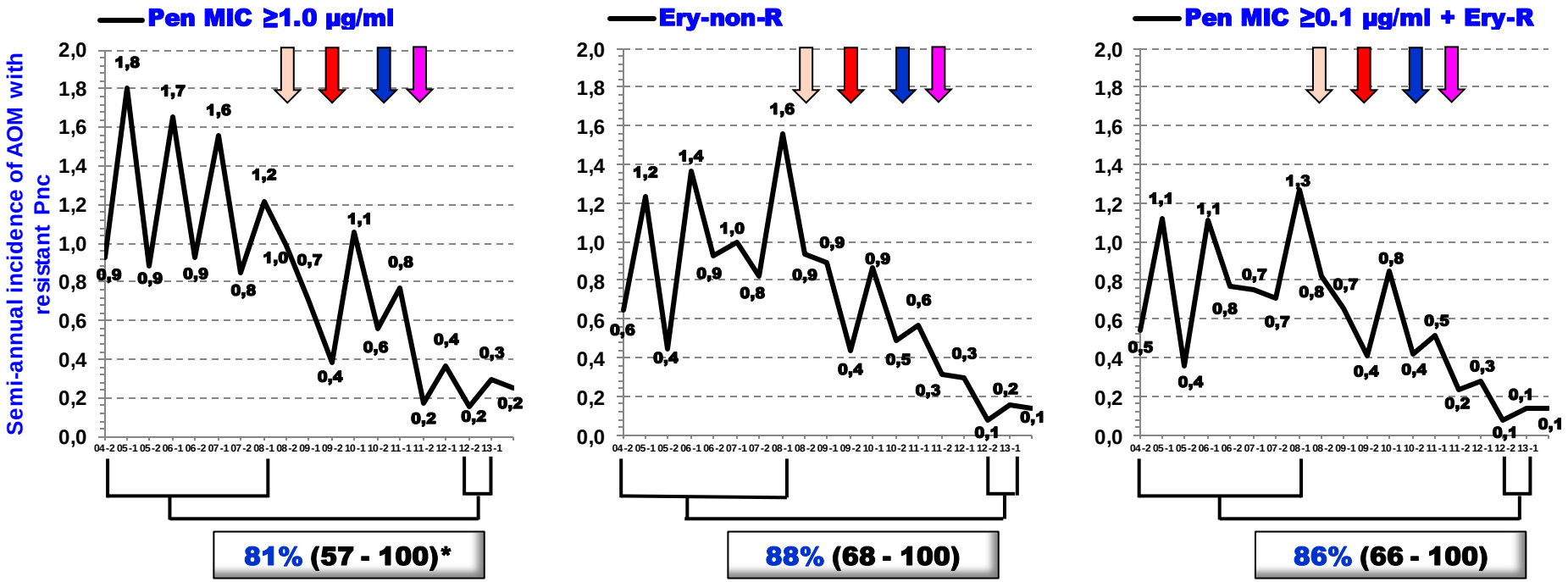
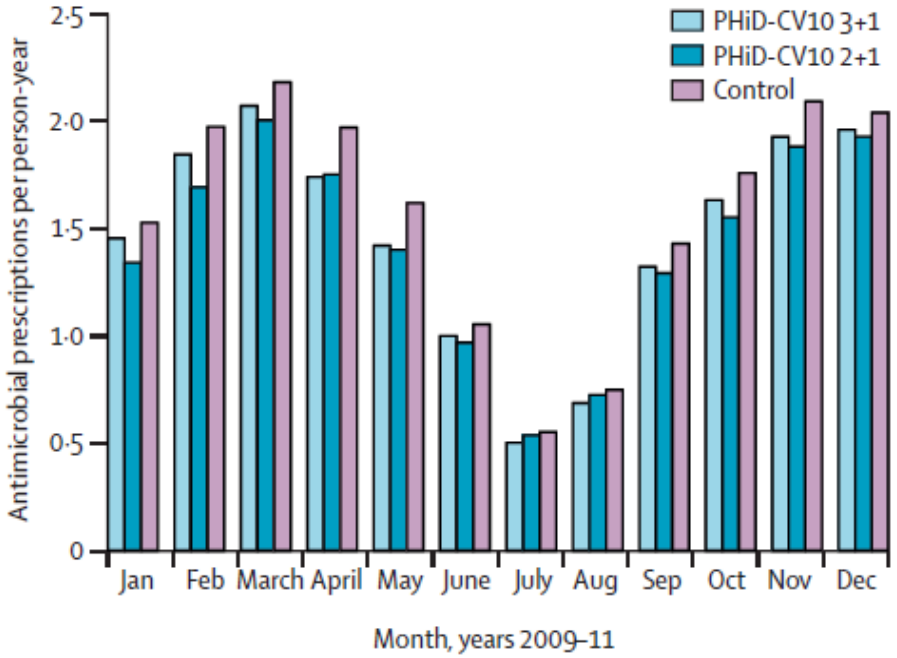


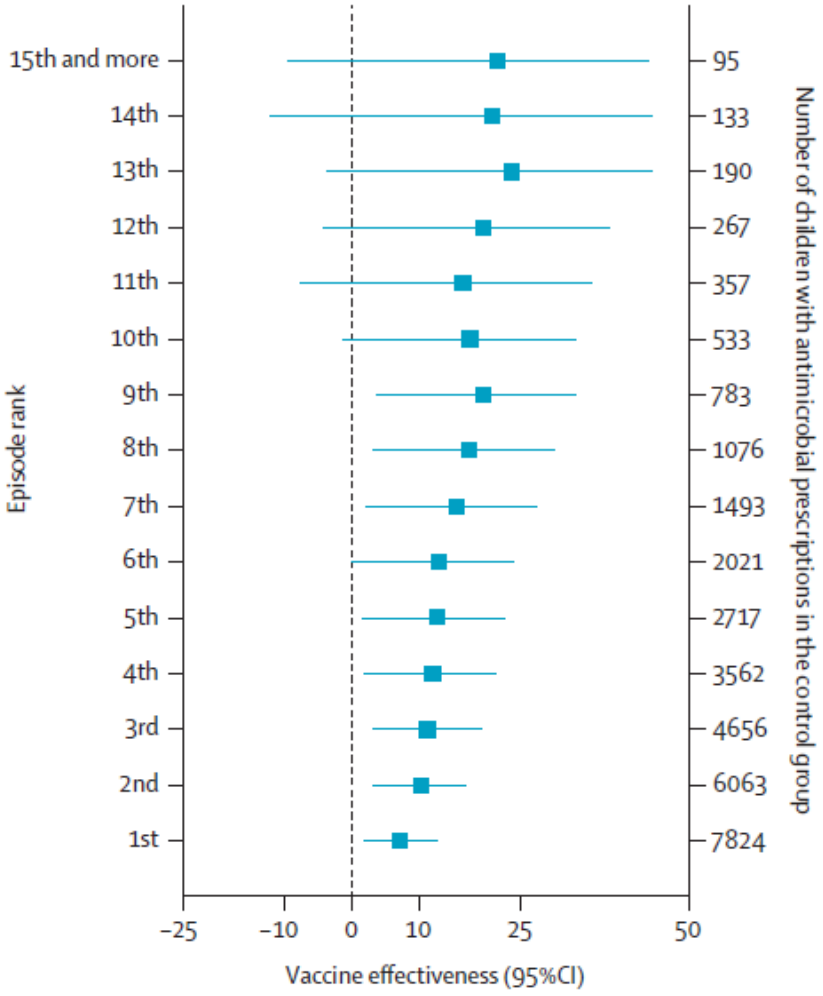
Each study year is July 1st through June 30th

Dagan et al, ICAAC, Denver Co, Sept 2013

Effectiveness of PCV10 against Outpatient Antimicrobial Prescriptions - FinIP Trial

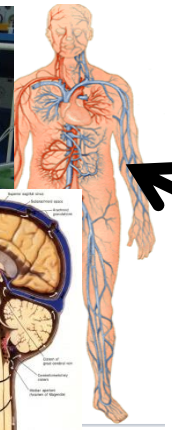
Vaccine effectiveness was 8% (95% CI 1–14) and the incidence rate difference 0·12 per person-year corresponding to the number needed to vaccinate of 5 (95% CI 3–67) to prevent one purchase during the 2 year follow-up

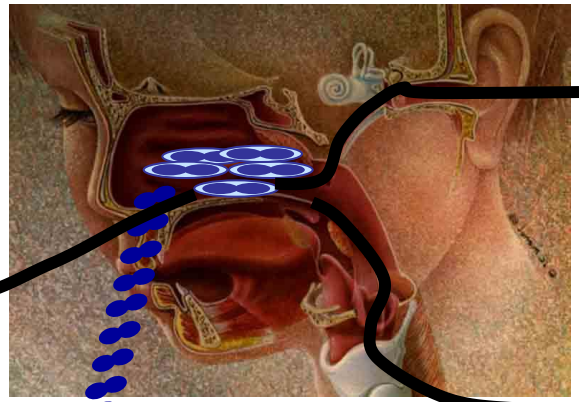


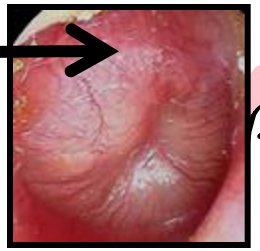


Palmu et al, *Lancet,* 14: 205–12, 2014

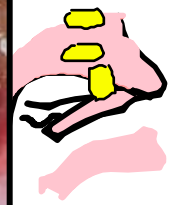
Pneumococcal Disease Endpoints

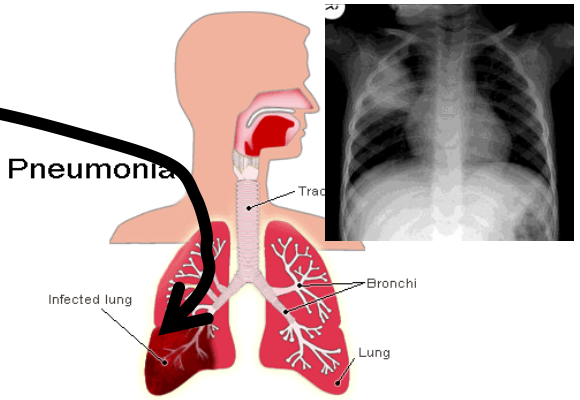






Otitis media
and its complications





Invasive infections

- sepsis
- meningitis
- Bacteremic pneumonia
- Osteomyelitis
- Septic arthritis
- Cellulitis
- Brain abscess
- Pericarditis, endocarditis

Carriage & spread to other individuals

Antibiotic resistance

Mucosal infections

- otitis media
- sinusitis
- conjunctivitis
- pneumonia