

The Impact of Pneumococcal Conjugate Vaccine on Children and Adults

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Direct and Indirect effects of PCV7:

A 7 valent pneumococcal conjugate vaccine was introduced in the US in 2000. Subsequently it has been introduced into more than 90 countries including the National Immunization Program in Over 30 countries.

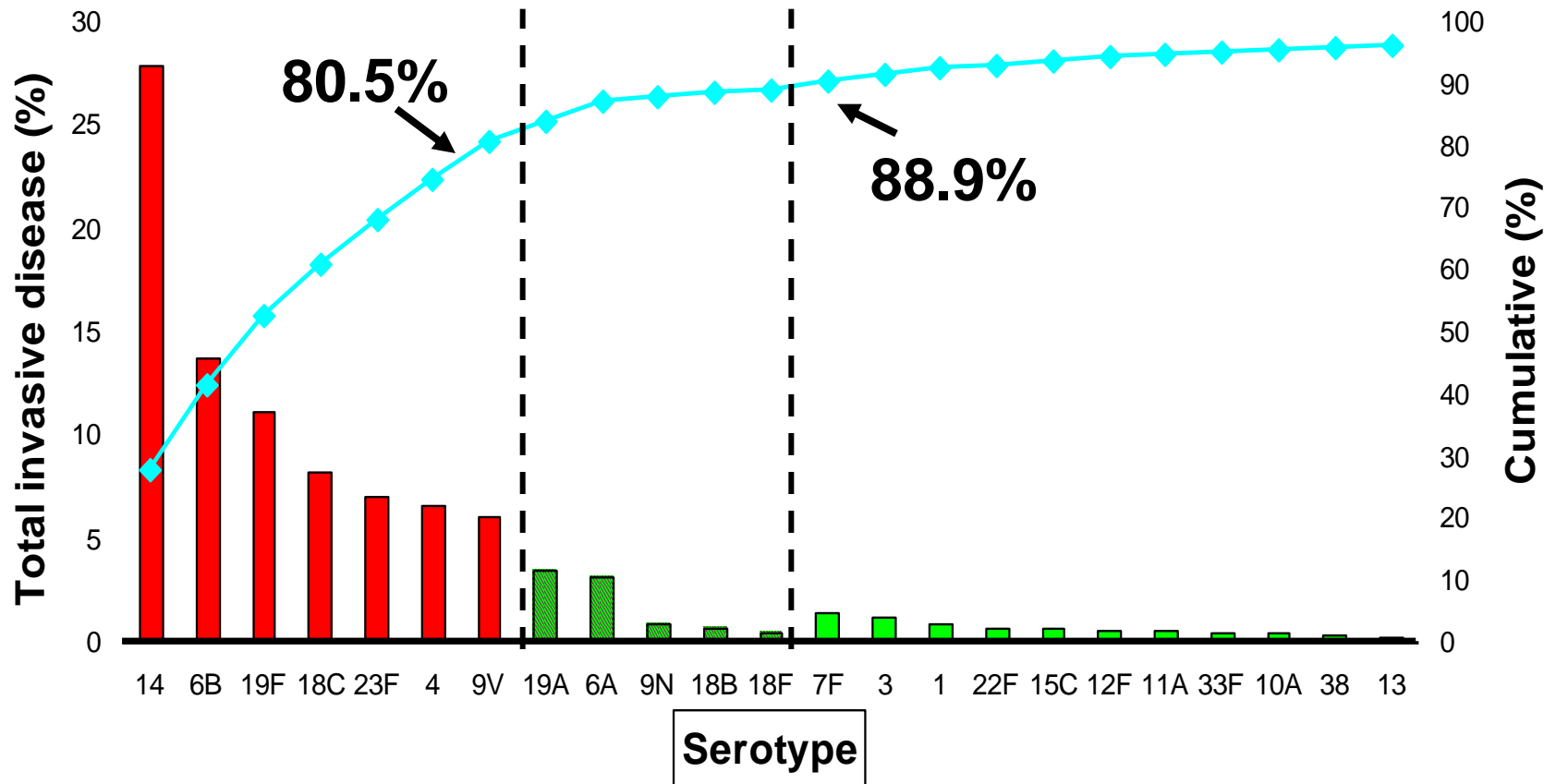
The **DIRECT** effect of PCV7 has been substantial.

The **INDIRECT** effect has been far greater than expected.

The **COMBINED EFFECT** has had a broad impact on Antimicrobial usage and the emergence of resistance as well as pneumococcal disease.

Impact on Invasive Pneumococcal Disease??

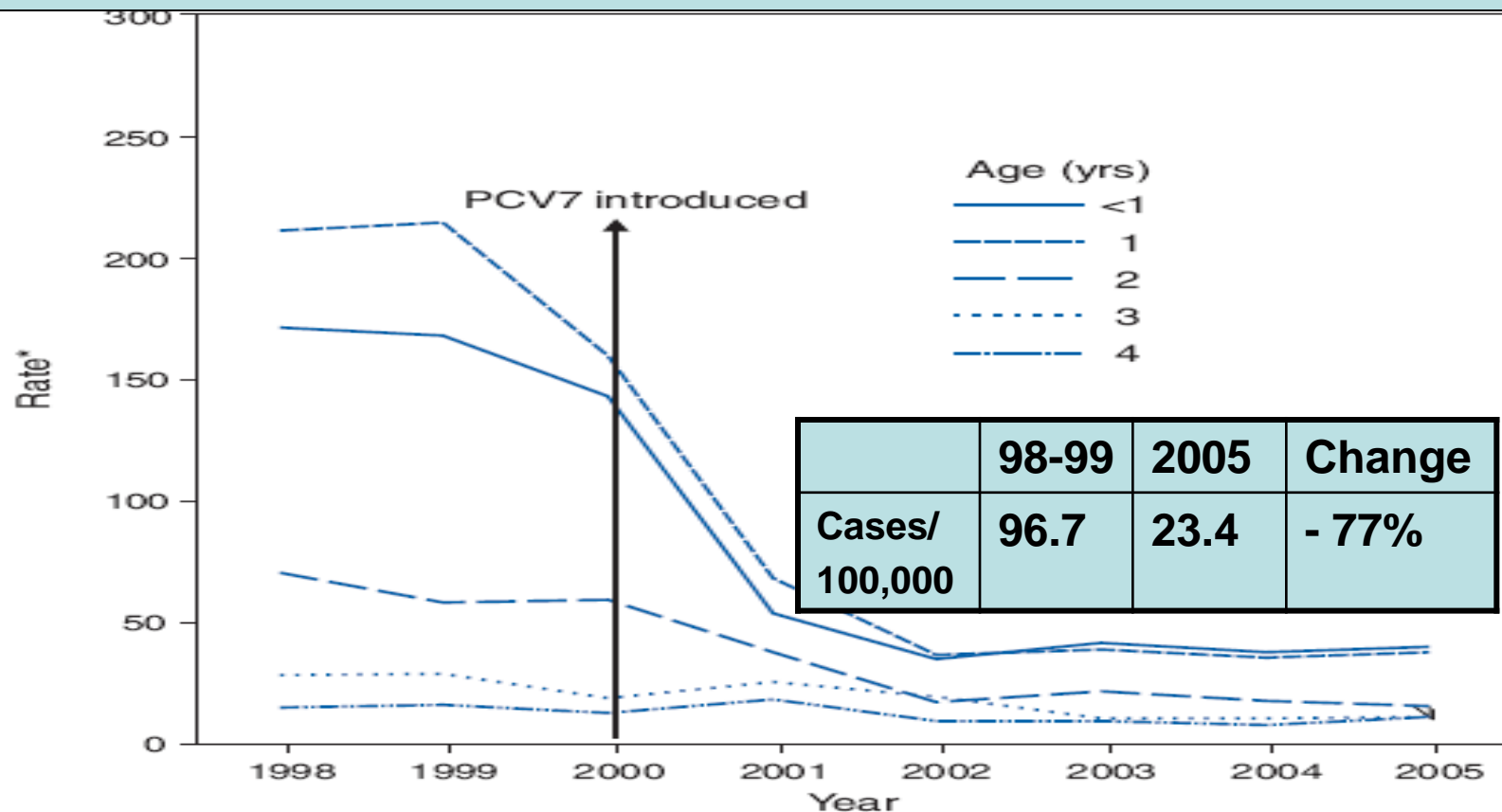
Pneumococcal Serotypes Causing Invasive Disease in North American Young Children prior to PCV7



Prevention of Pneumococcal Disease: Direct effects of PCV

Timing of Effect	Mechanism of Prevention	Protection
Following receipt of vaccine; while VST present in community	Antibody mediated clearance of VST	Against VST

Incidence rate of IPD in children less than 5 yrs. from ABC Data: 1998-2005



* Per 100,000 population.

† California (one county); the state of Connecticut; Georgia (20 counties); Maryland (six counties); Minnesota (seven counties); New York (seven counties); Oregon (three counties); and Tennessee (four counties).

Age Specific Rates of Admission for Pneumococcal Meningitis: 1994-2004

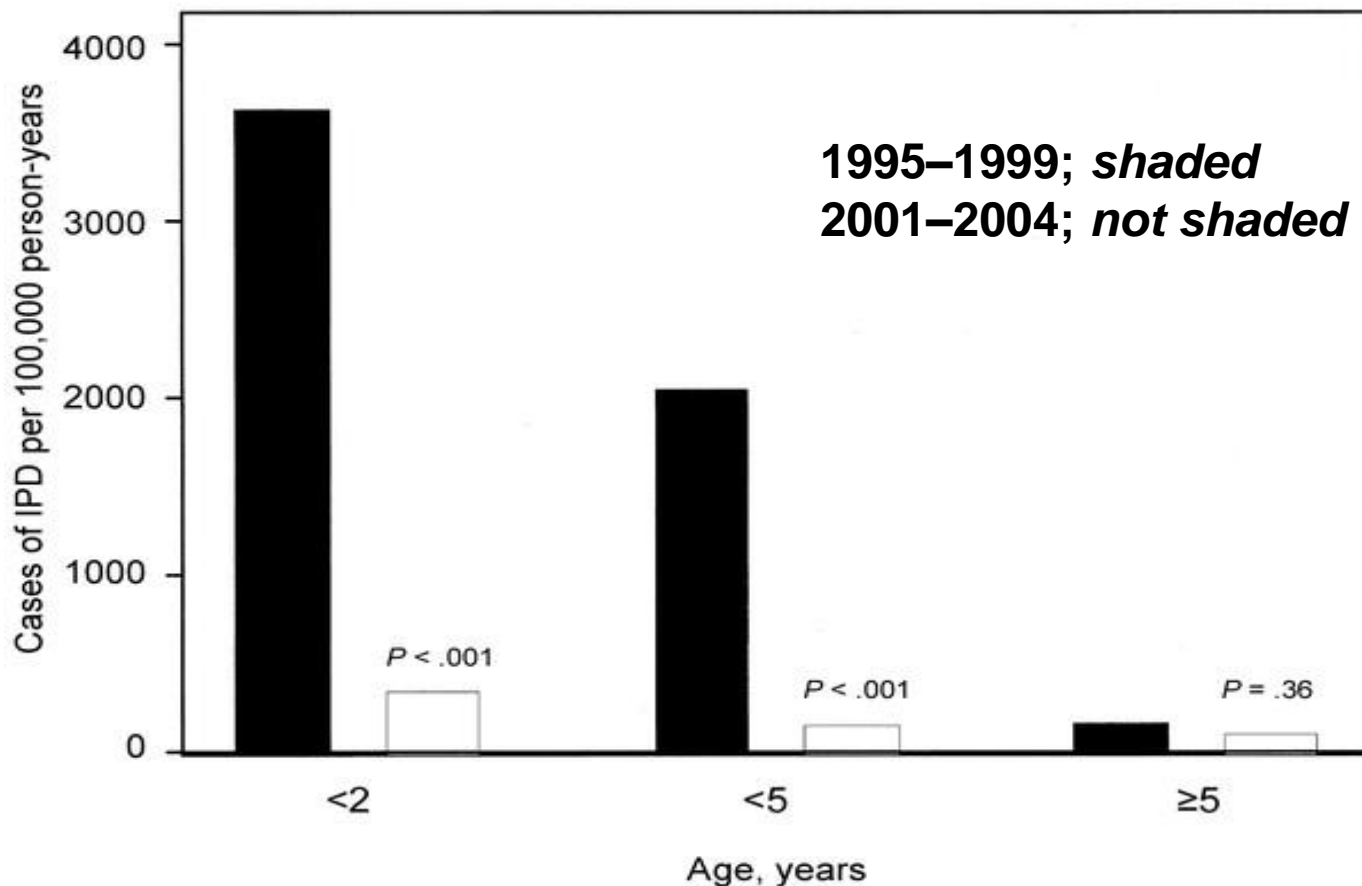
Reason for hospitalization and patient age	Hospitalization rate (95% CI)		Rate difference	Change (95% CI), %	P
	Baseline ^a	After PCV7 introduction ^a			
Pneumococcal meningitis					
<2 years	7.7 (6.6–8.9)	2.6 (2.1–3.2)	-5.1	-51.5 (-58.9 to -26.9)	<.001
2–4 years	0.9 (0.8–1.1)	0.5 (0.3–0.6)	-0.5	-51.5 (-58.9 to -26.9)	<.001
5–17 years	0.3 (0.2–0.3)	0.2 (0.2–0.3)	-0.0	-15.9 (-35.3 to 9.5)	.198
18–39 years	0.4 (0.3–0.4)	0.3 (0.2–0.3)	-0.1	-26.1 (-38.8 to -10.7)	.002
40–64 years	0.8 (0.7–0.9)	0.7 (0.6–0.8)	-0.1	-10.5 (-20.8 to 1.1)	.075
≥65 years	1.2 (1.1–1.4)	0.8 (0.7–1.0)	-0.4	-33.0 (-43.3 to -20.9)	<.001
Total	0.8 (0.8–0.9)	0.5 (0.5–0.6)	-0.3	-33.0 (-38.9 to -26.5)	<.001

400 fewer cases/yr in < 2 yr old

Baseline 1994-1999; post PCV7 2001-2004

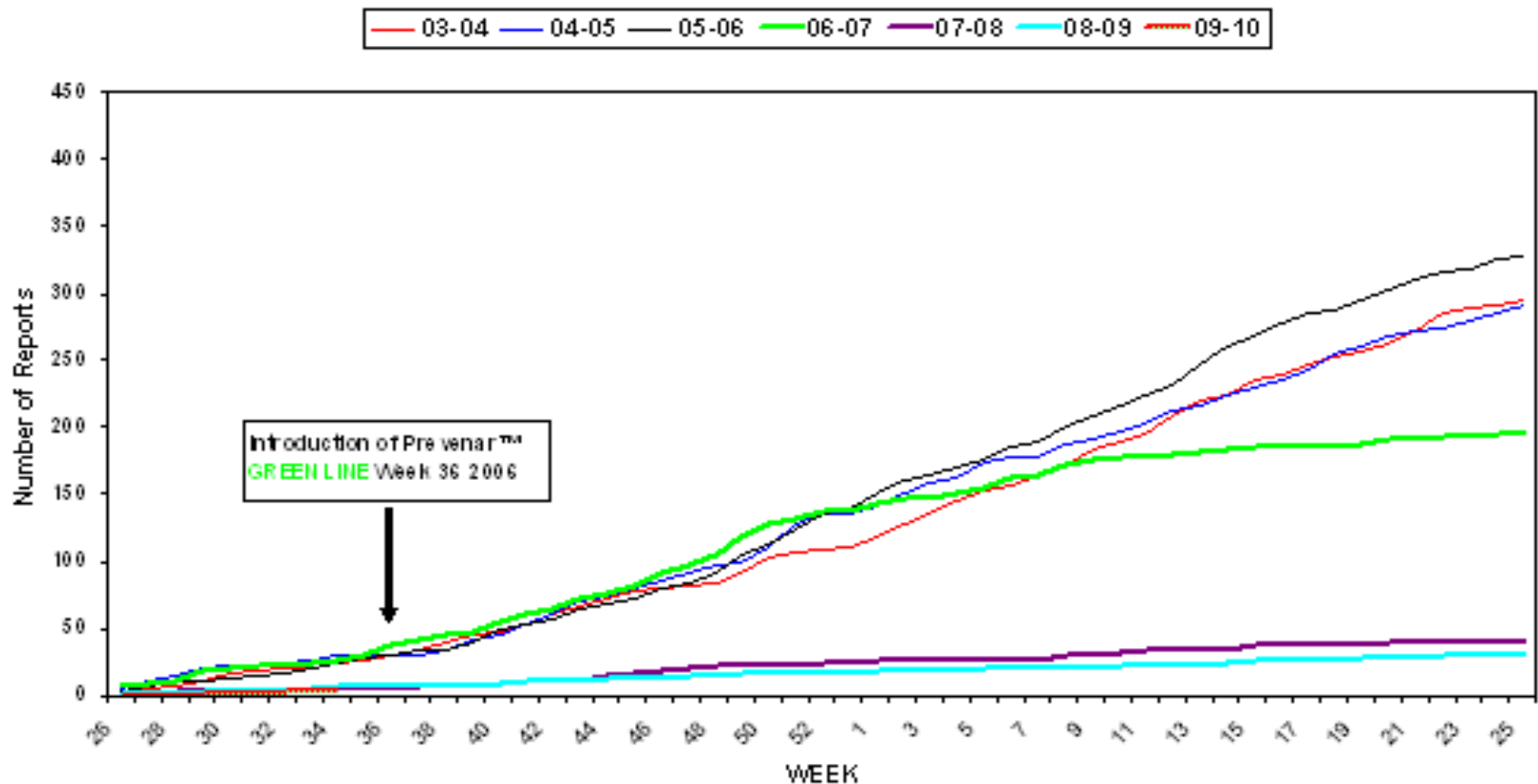
^a per 100,000

Invasive pneumococcal disease (IPD; cases per 100,000 person-years) among individuals with sickle cell disease



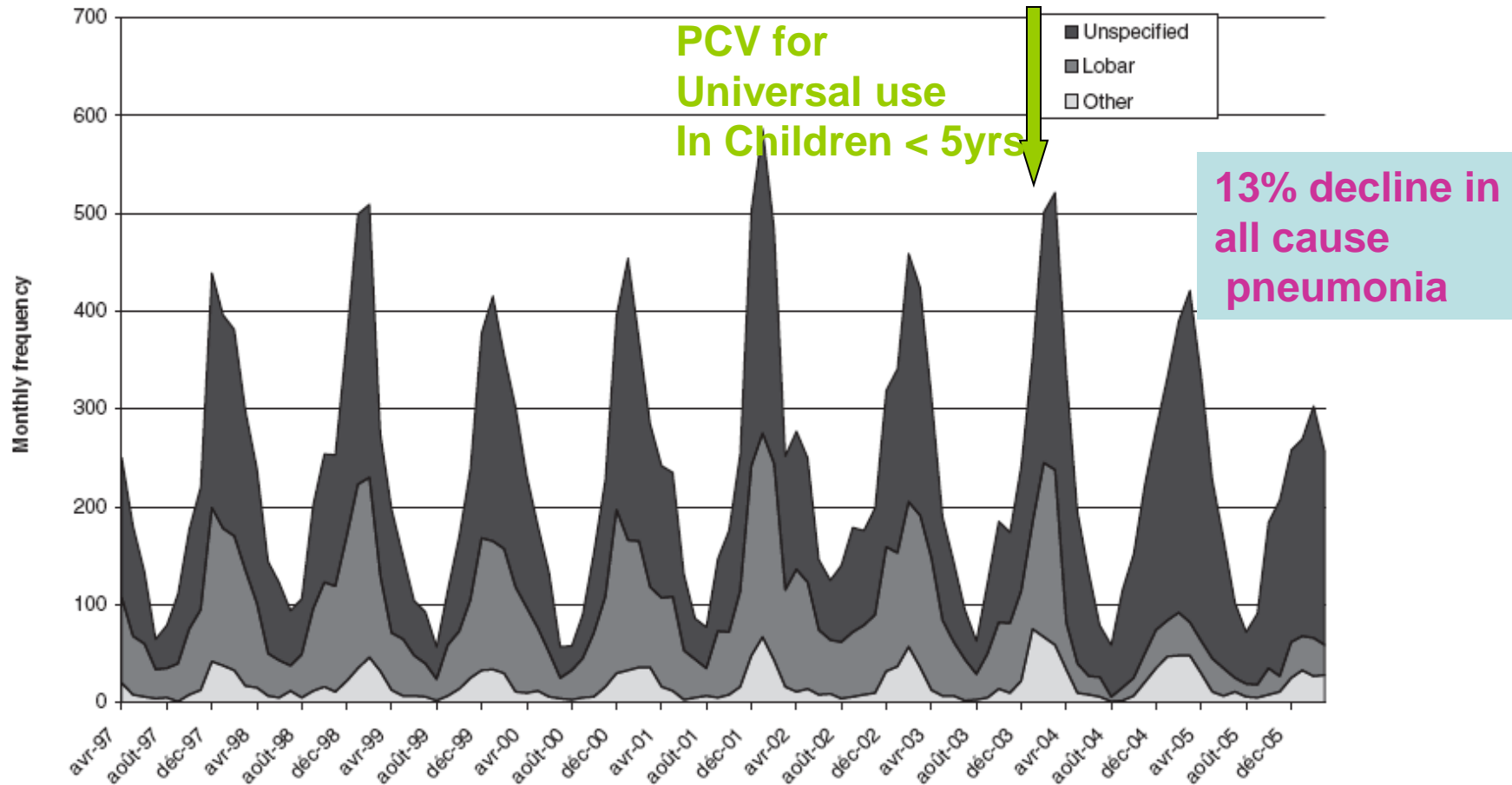
+ Halasa, N. Clinical Infectious Diseases 2007;44:1428-1433

Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the seven serotypes in PCV7 : Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- 9.11.2009)

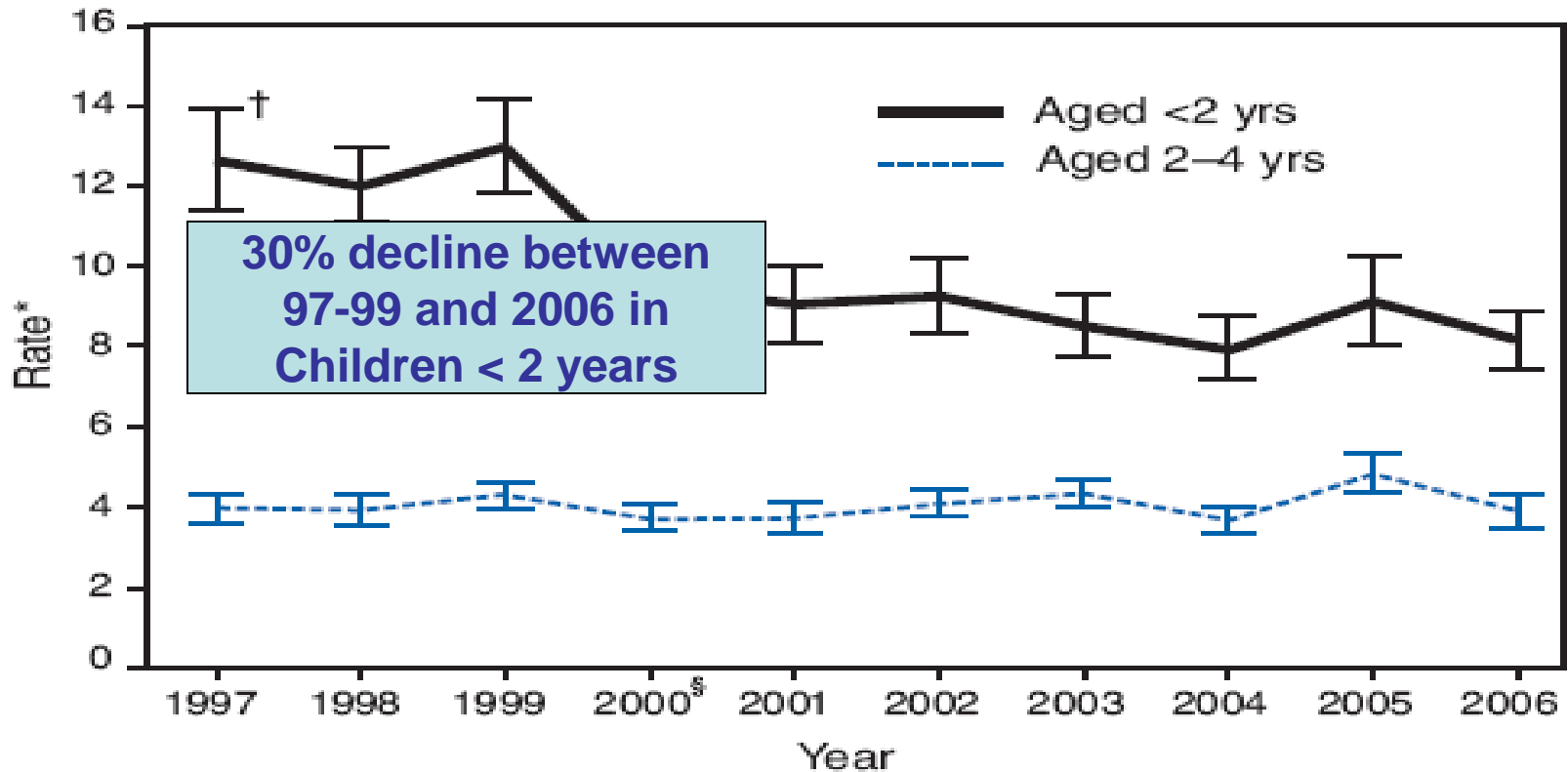


Reduction in Pneumonia

Monthly Admissions for Pneumonia in Children < 5 years of age in Quebec: April 1997-March 2006



Annual all-cause pneumonia hospitalizations among children < 2 and 2-4 years: US Nationwide Inpatient Sample



* Per 1,000 population.

† 95% confidence interval.

§ 7-valent pneumococcal conjugate vaccine licensed in February 2000.

**Why was the decline in all cause
pneumonia greater than expected based
on cases diagnosed as
Pneumococcal pneumonia?**

Etiology of Childhood Community Acquired Pneumonia+

Virus	Percent	Bacteria	Percent
Respiratory Syncytial	29	<i>S. pneumoniae</i>	37
Rhinovirus	24	<i>H. influenzae</i>	9
Parainfluenza 1,2,3	10	<i>M. pneumoniae</i>	7

Combined Viral and Bacterial Pneumonia is Most Common

Influenza	1	<i>S. pneumoniae</i>	5
Coronavirus	3	<i>S. pyogenes</i>	1
Human herpesvirus	3	<i>C. trachomatis</i>	1

(Modified from reference Juven, T., Mertsola, J., Waris, M. *et al.* (2000).

Etiology of community-acquired pneumonia in 254 hospitalized children. *Pediatric Infectious Disease Journal* **19**, 293–8.)

**Protection against Pneumococcal
AOM due to Vaccine Serotypes;
modest impact on clinical AOM**

EFFICACY OF PCV7 IN FINNISH CHILDREN WITH AOM†

<u>Endpoint</u>	<u>AOM Episodes</u>		<u>Vaccine Efficacy (%)</u>
	PCV7 (n = 831)	Control* (n = 831)	Point Estimate
Pneumococcal	271	414	34
-Vaccine serotypes	107	250	57
-Cross-reactive serotypes	41	84	51

*Hepatitis B vaccine

†Eskola J et al. *NEJM* 2001; 344:403-9.

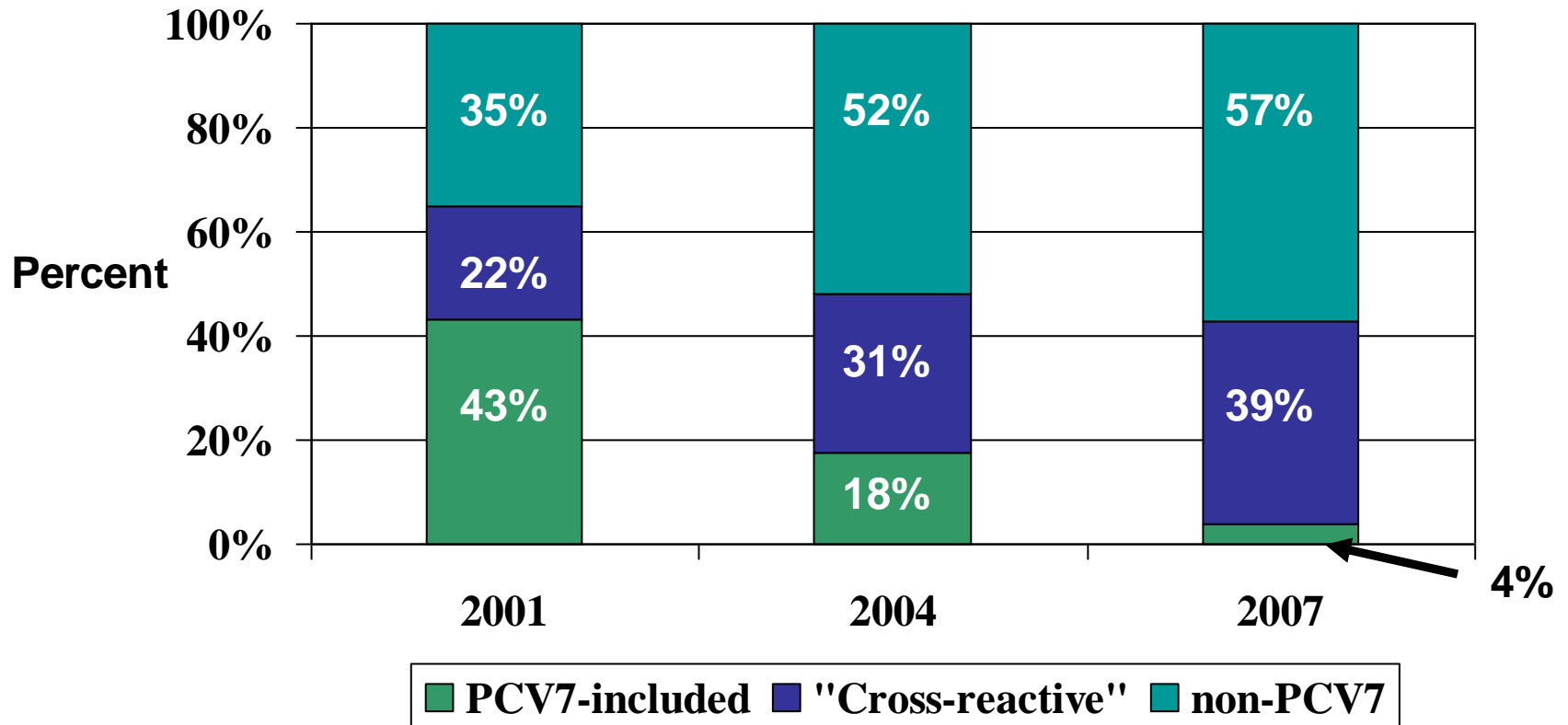
Impact of PCV7 on Clinical Episodes of AOM

Endpoint	No. of episodes		Efficacy (%)	
	PCV	Controls	Point estimate	(CI)
<u>FinOM</u>				
Culture Confirmed	1251	1345	6	-4, 16
<u>N. California Kaiser Permanente</u>				
Clinical Episodes/yr	1.69	1.81	7	4.7, 9.1

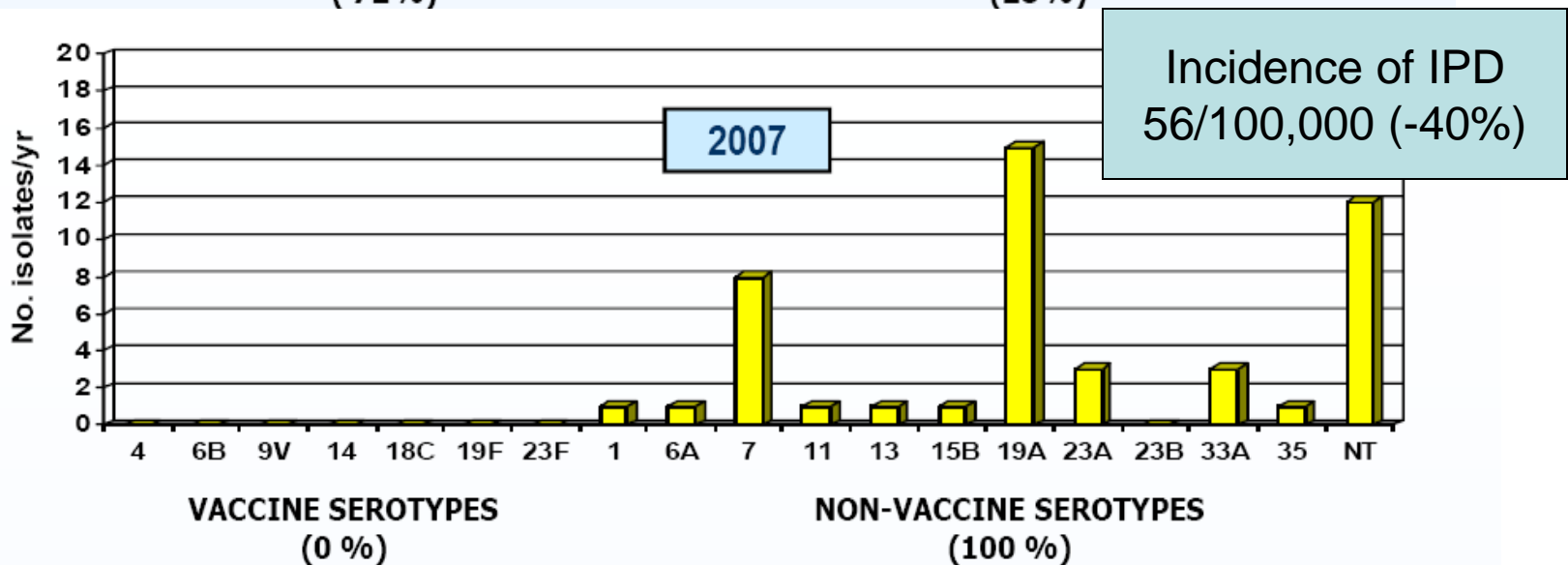
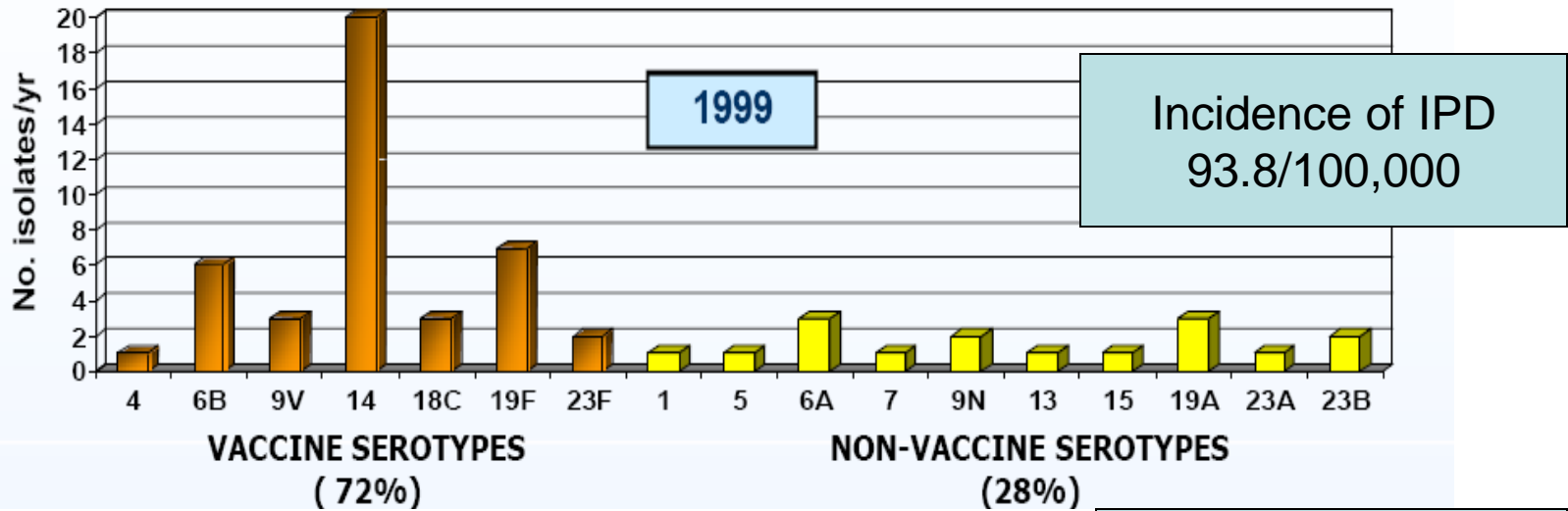
The Benefits of PCV7 Have Potential to extend beyond Direct Effect!

**Impact of PCV7 in nasopharynx and replacement disease –
An evolving story!**

Changing Ecology of NP Colonization: 2001-2004-2007



IPD at Children's Medical Center, Dallas: 1999 vs. 2007

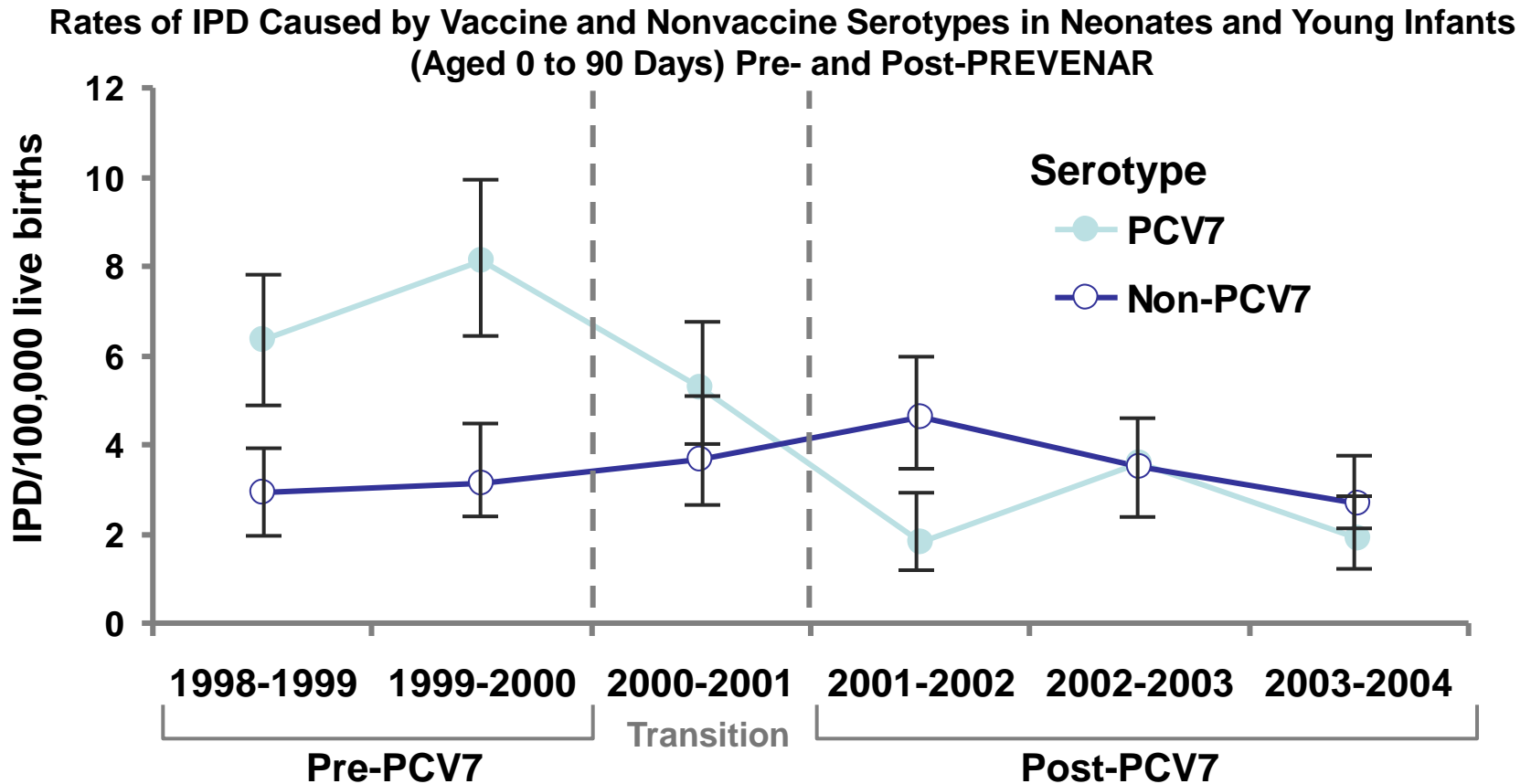


Pneumococcal Serotypes in AOM in Children with Initial Episode or ROM

Serotype	Prospective group	ROM and Treatment Failures
3	1 (8%)	0
6A	0	4 (19%)
7	0	1 (5%)
11/16	1 (8%)	2 (10%)
15	1 (8%)	2 (10%)
19A	4 (32%)	8 (38%)
19 not A	1 (8%)	0
23 A/B	2 (16%)	1 (8%)
Non typable	1 (8%)	3 (15%)
Other	1 (8%)	0
Total	12	21

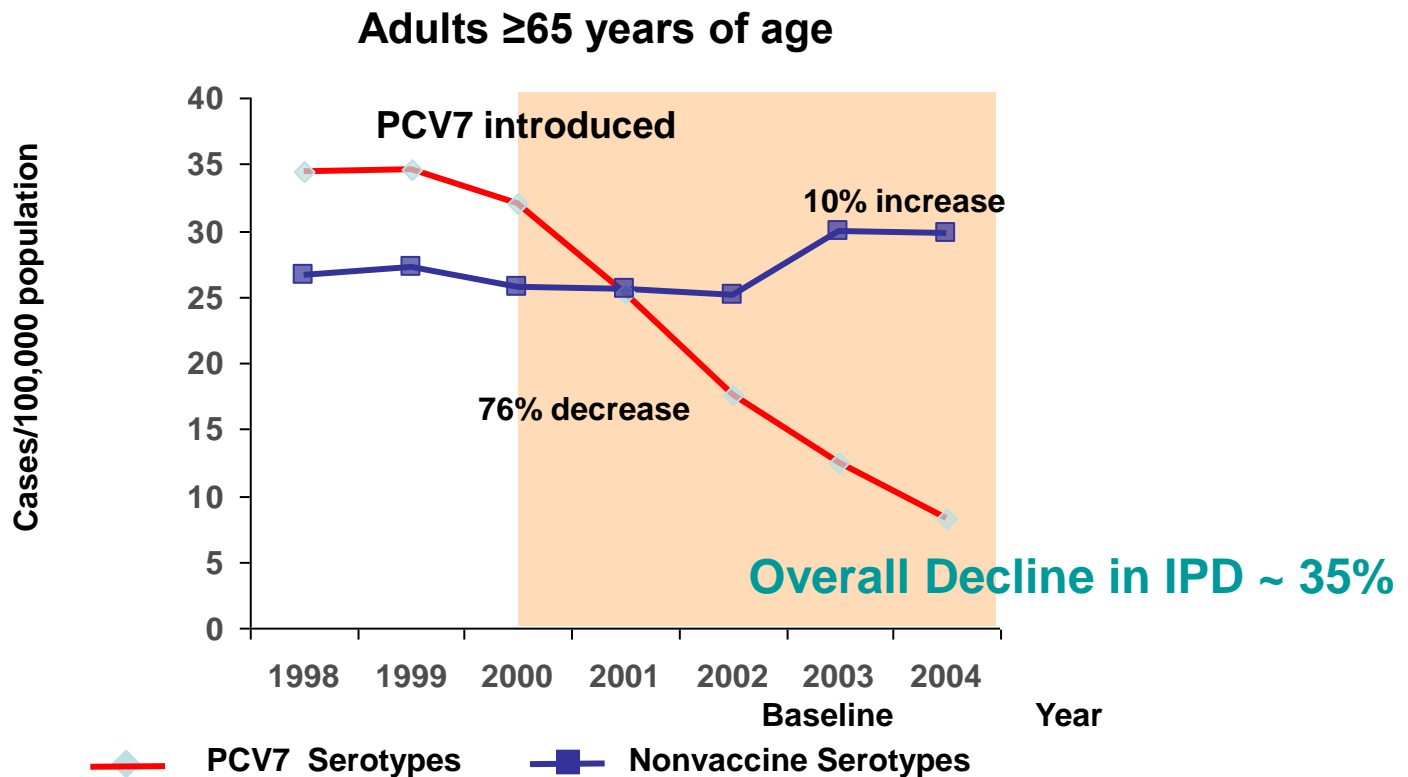
Indirect Effects of PCV7 Immunization in Children

Reduction in IPD in Children < 90 days of Age: Indirect Effect



- Rates of vaccine-type isolates decreased 67% without an increase in nonvaccine types
- Indirect effects of PCV7 include reduction of IPD incidence in infants from birth to 90 days (ie, prior to vaccination)

Indirect Effect of PC7 on IPD : Two Stories in One



Rates of IPD due to vaccine-type isolates significantly decreased in young and elderly, with a small increase in IPD due to nonvaccine serotypes

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≥65 years	1.2 (1.1–1.4)	0.8 (0.7–1.0)	-0.4	-33.3 (-40.8 to -25.8)	<.001
Total	0.8 (0.8–0.9)	0.5 (0.5–0.6)	-0.3	-37.5 (-40.8 to -34.2)	<.001

~160 fewer cases/yr in >65 yr old

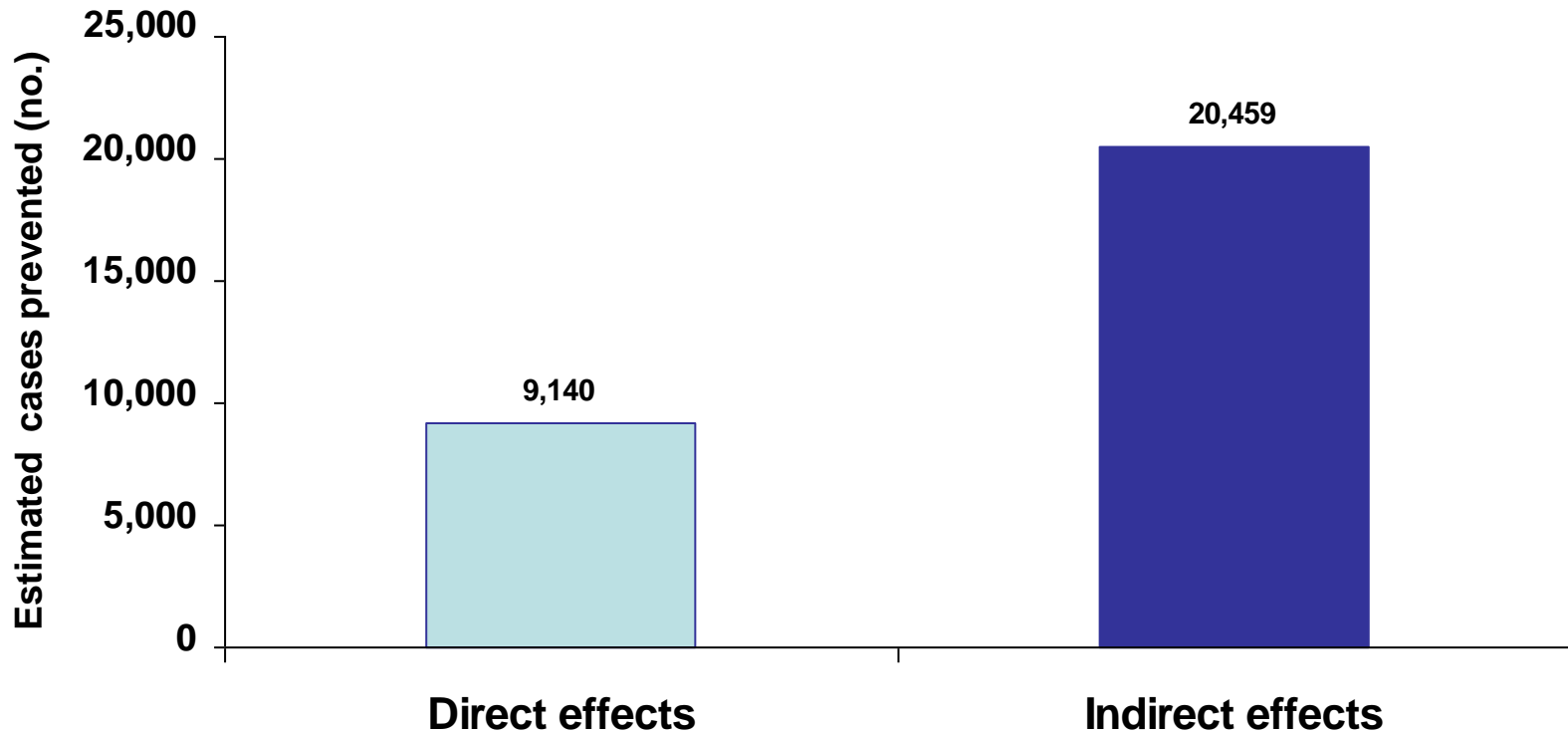
Baseline 1994-1999; post PCV7 2001-2004

^a per 100,000

Effectiveness of PCV7

Indirect and Direct Effect (U.S.)

Estimated Vaccine-type Cases Averted by Direct[†] and Indirect



The CDC Surveillance System has reported an increased incidence of IPD due to nonvaccine serotypes in children <5 and in adults ≥40 years of age. It is unknown whether these effects would be observed in other populations.

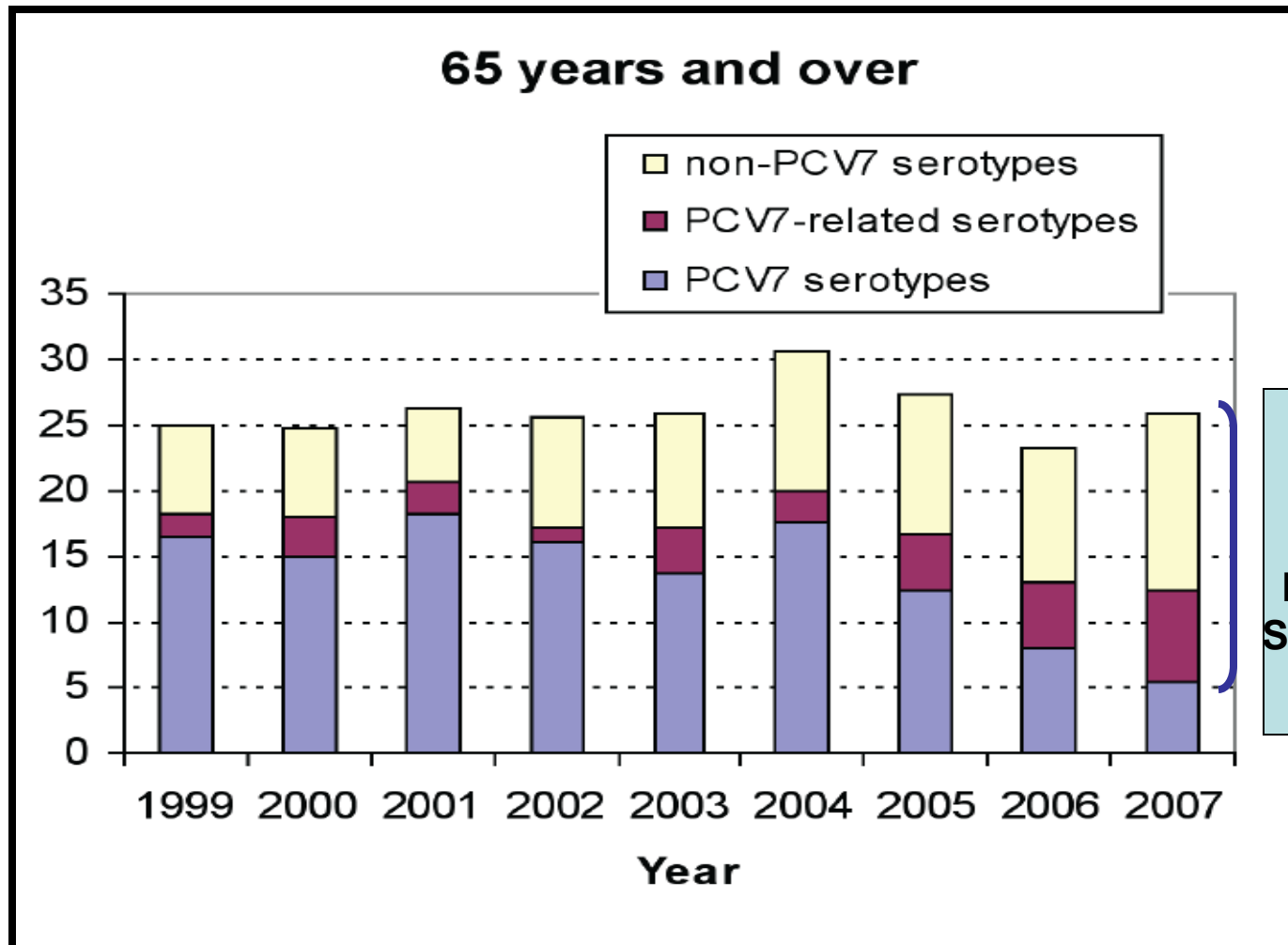
[†]Direct VT IPD cases prevented in 2003 = 1998/1999 average number of VT IPD cases in children <5 years of age x 2003 PREVENAR coverage with 3 doses (68.1%) x PREVENAR effectiveness for VT IPD (93.9%)

[‡]Indirect VT IPD cases prevented in 2003 = (1998/1999 average number of VT IPD cases across all ages – 2003 number of VT IPD cases across all ages) – 2003 direct VT IPD cases prevented

Note: Calculation of indirect cases prevented does not account for replacement disease

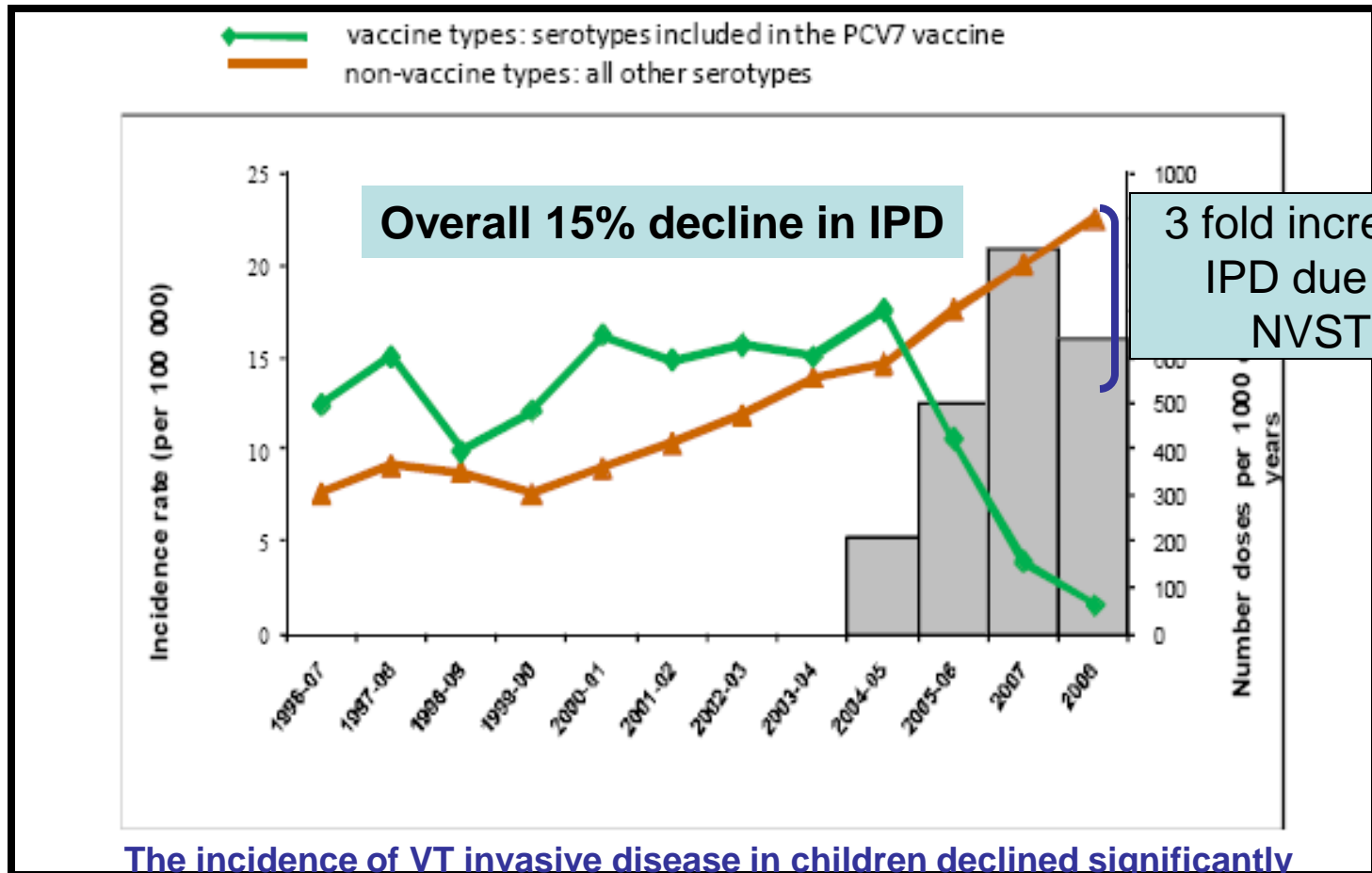
Adapted from CDC. *MMWR*. 2005;54:893-897.

IPD Incidence in Adults 65 and Over in Quebec: 1999-2007



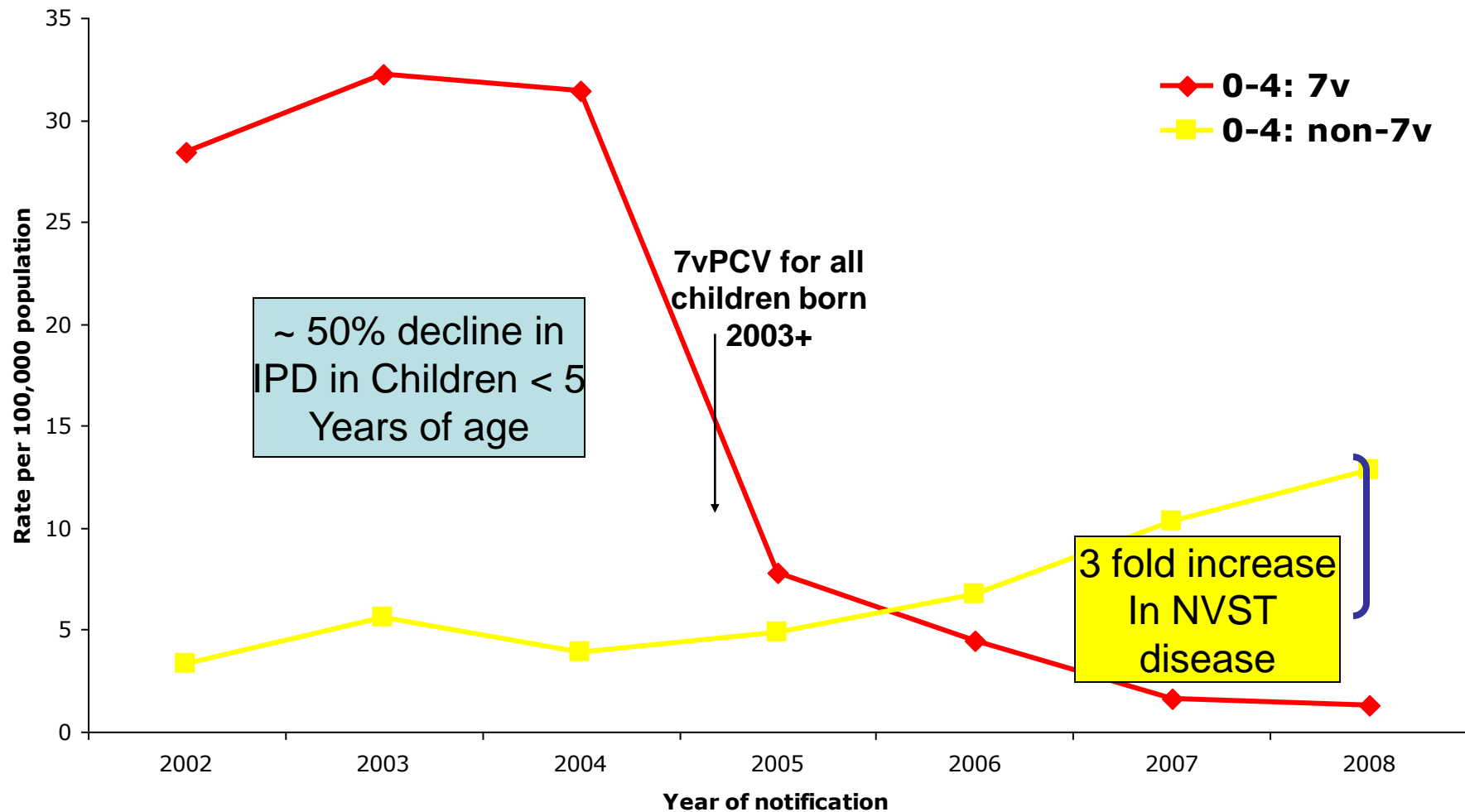
Increase in IPD due to NVST eroding Success of PCV

Incidence of IPD in Belgium in Children Less than 15 years



The incidence of VT invasive disease in children declined significantly after introduction of PCV7, while NVT increased significantly

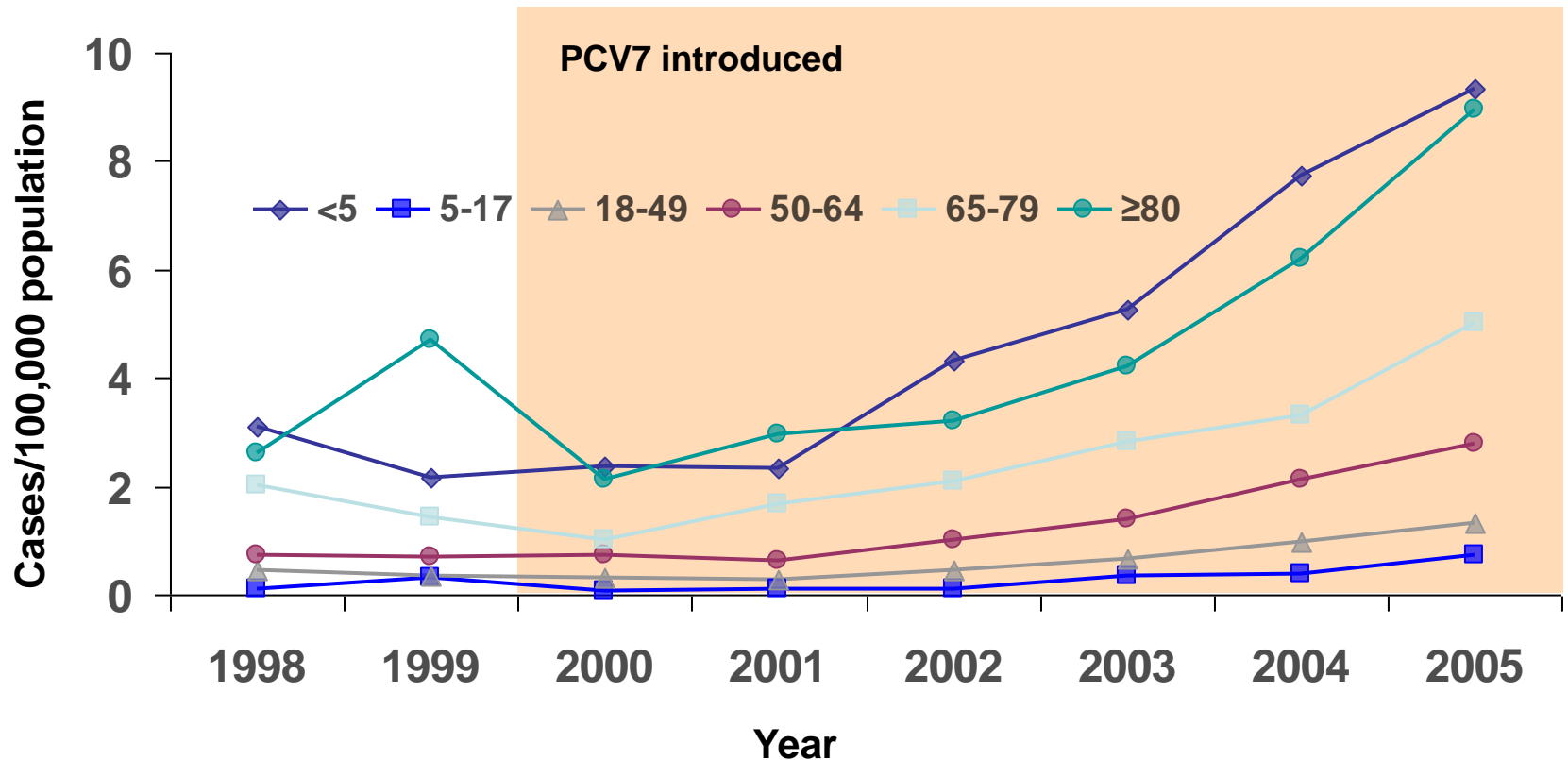
IPD notification rates for Victoria, Australia by Serotype Category: 2002 – 2008



Prevention of Pneumococcal Disease: direct and indirect effects of PCV

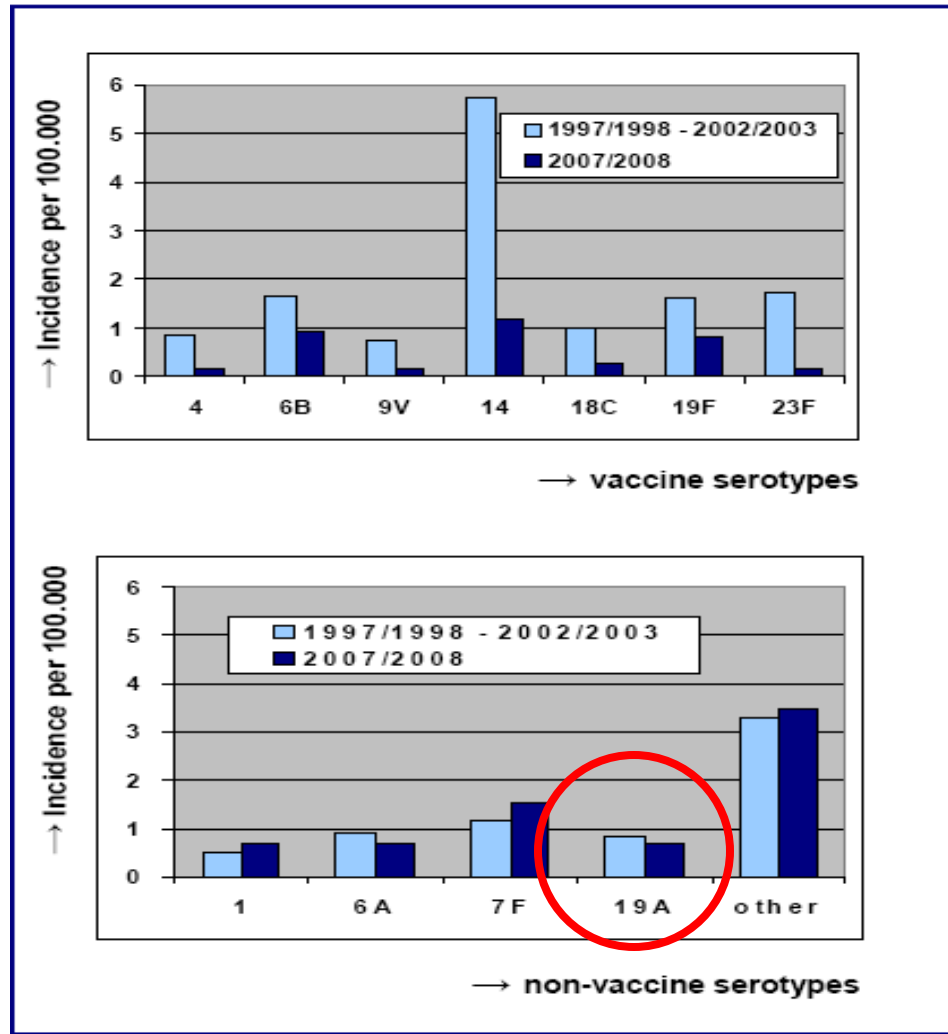
Timing of Effect	Mechanism of Prevention	Protection
Over time VST carriage is replaced with NVST	Reduced capacity of NVST to produce disease	Most NVST with reduced capacity to avoid host defenses

Age-specific Incidence of 19A IPD, 1998 to 2005 (U.S.)



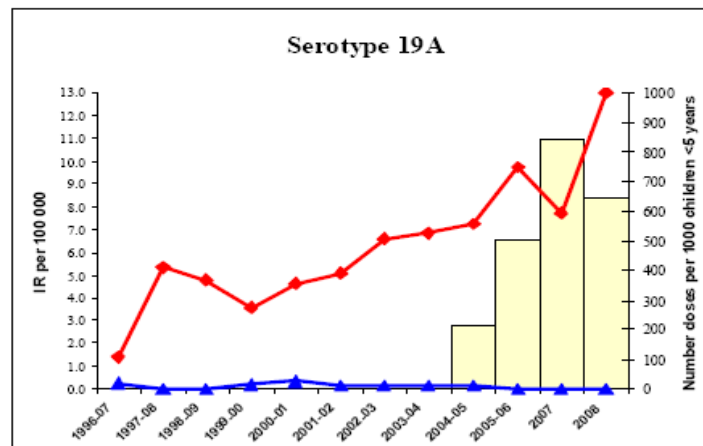
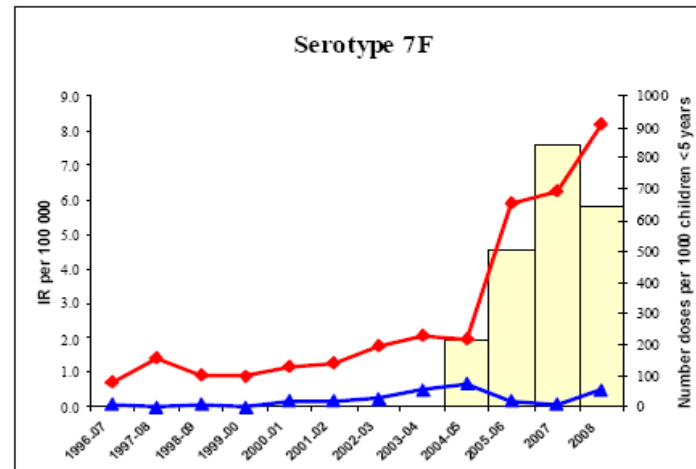
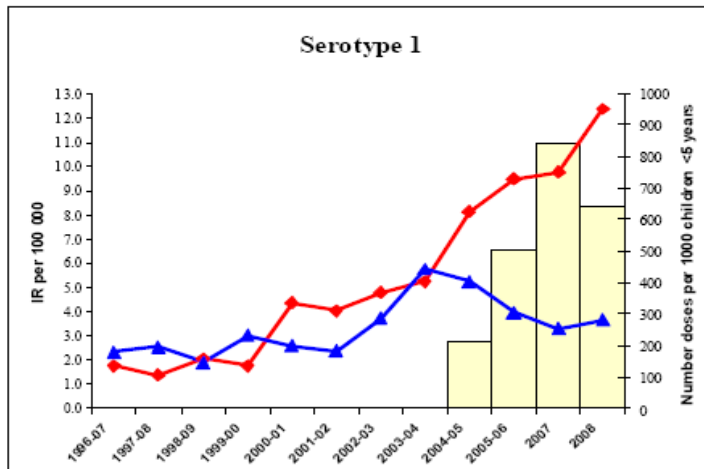
Overall IPD cases declined from ~ 57/100,000 to 17/100,000 following introduction of PCV7 in Massachusetts. Of the remaining cases 19A represented about 35-40%.

Serotype Specific Incidence of IPD in German Children < 2 yrs of Age

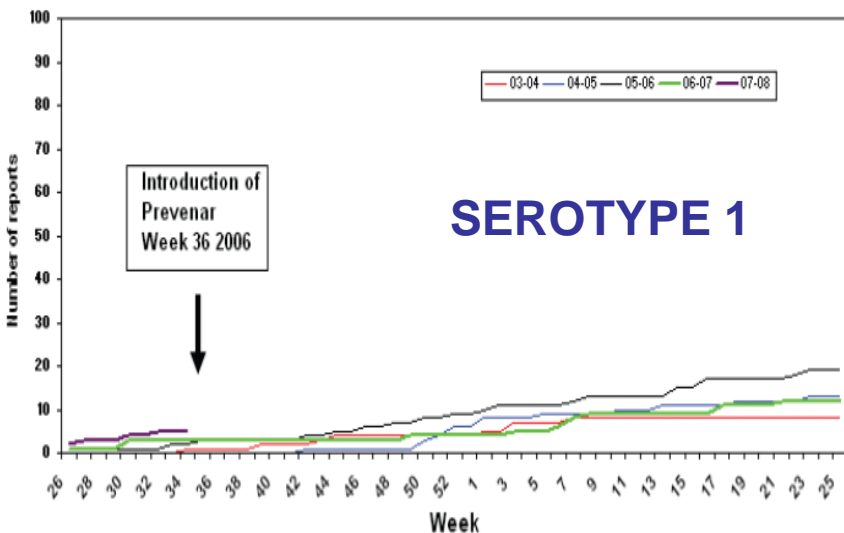


Incidence of IPD due to Serotypes 1, 7F and 19A in Belgium by Age Group

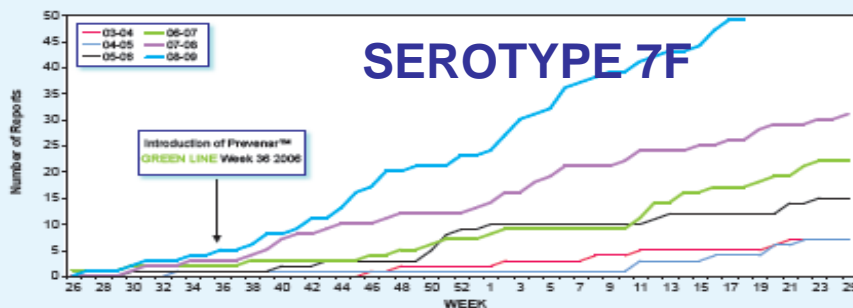
—●— incidence <5 years
—▲— incidence 5-14 years



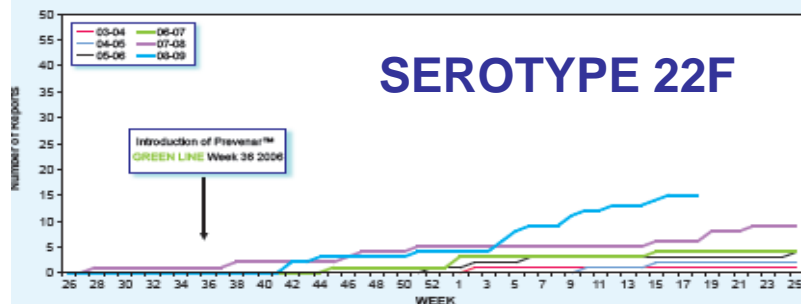
Changing Case Reports of Serotypes 1, 7F, 19A and 22F in UK after introduction of PCV7



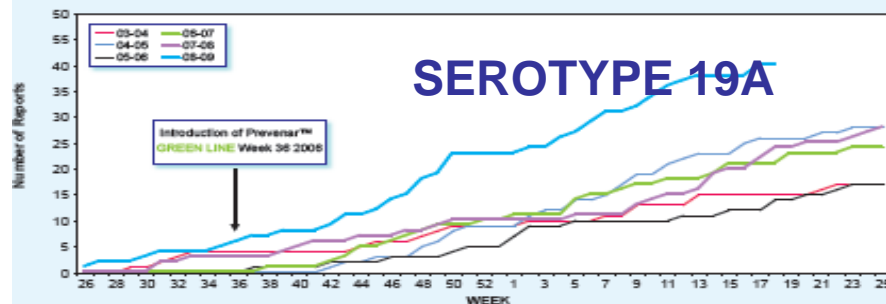
Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 7F Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 22F Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)



Cumulative weekly number of reports of Invasive Pneumococcal Disease due to serotype 19A Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- To Date)

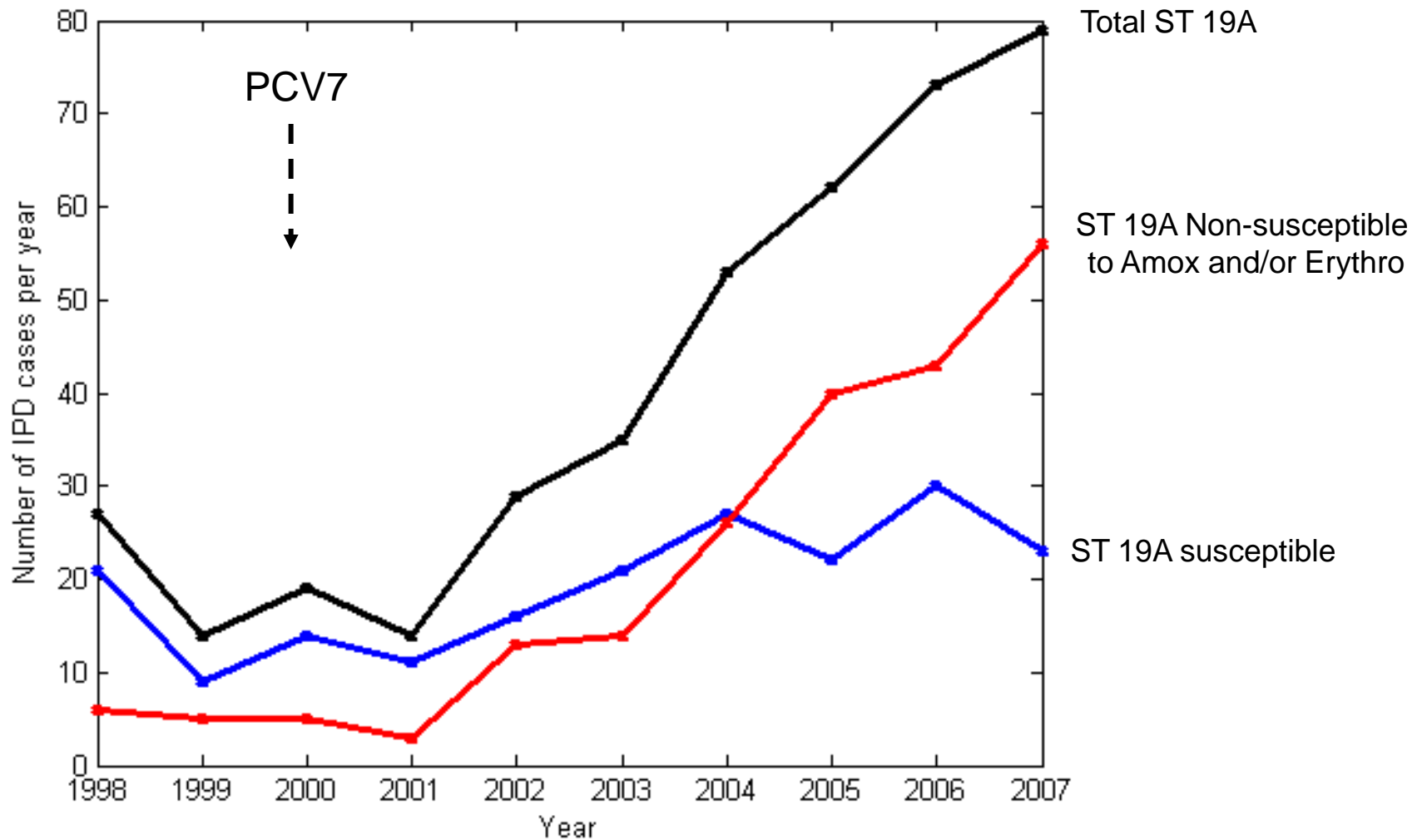


What Determines if Replacement Disease due to Nonvaccine serotypes is a large or a small problem

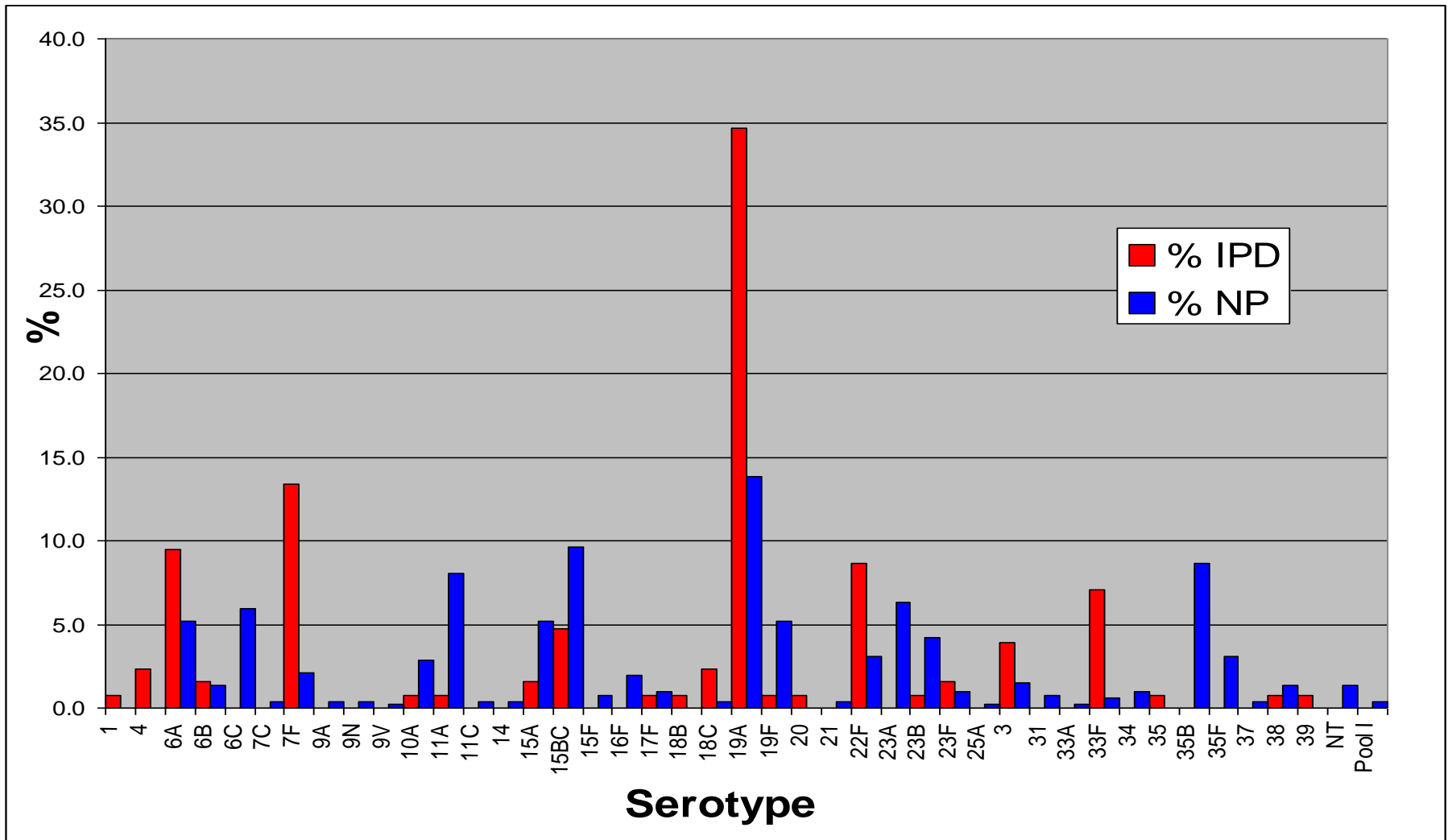
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1. Antibiotic Usage and Resistance among Serotypes
2. Ability to colonize the nasopharynx
3. Invasive potential of a specific serotype

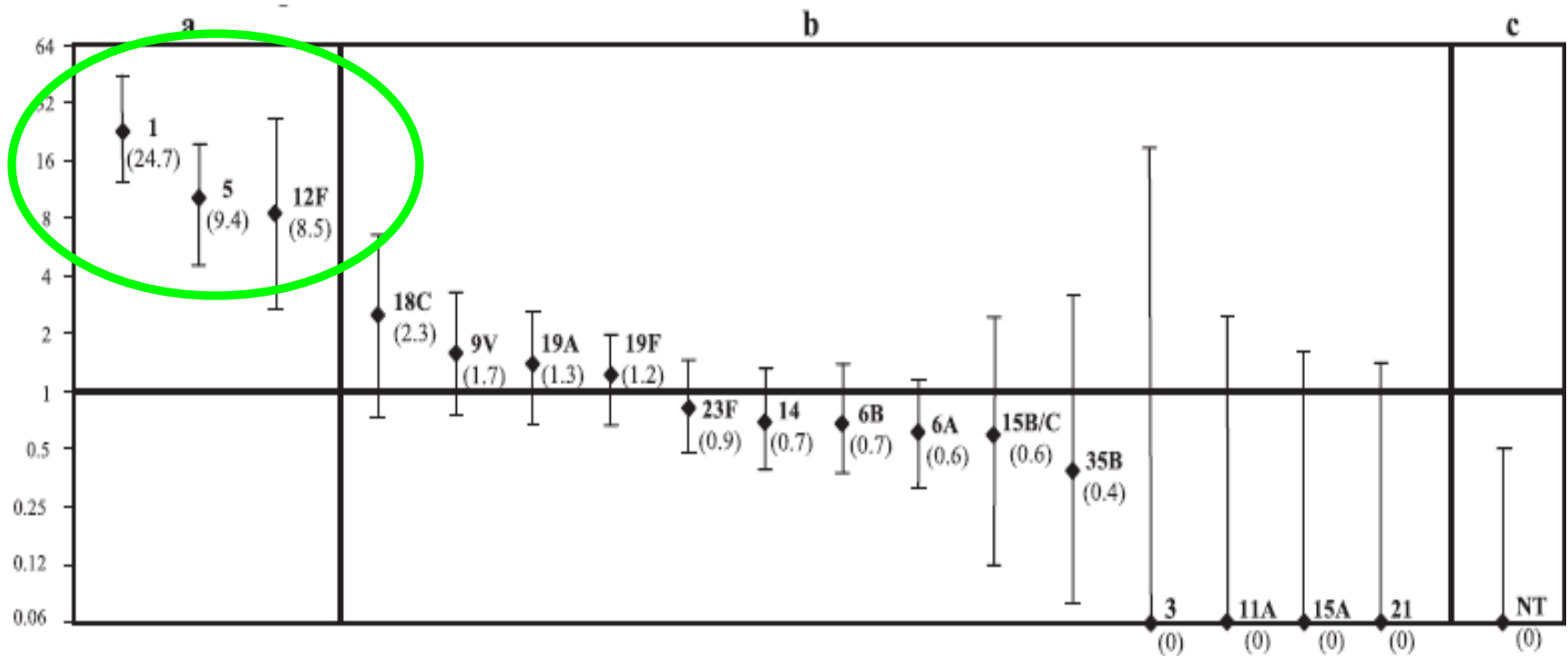
Emergence of 19A in US: Contribution of Antimicrobial Resistance



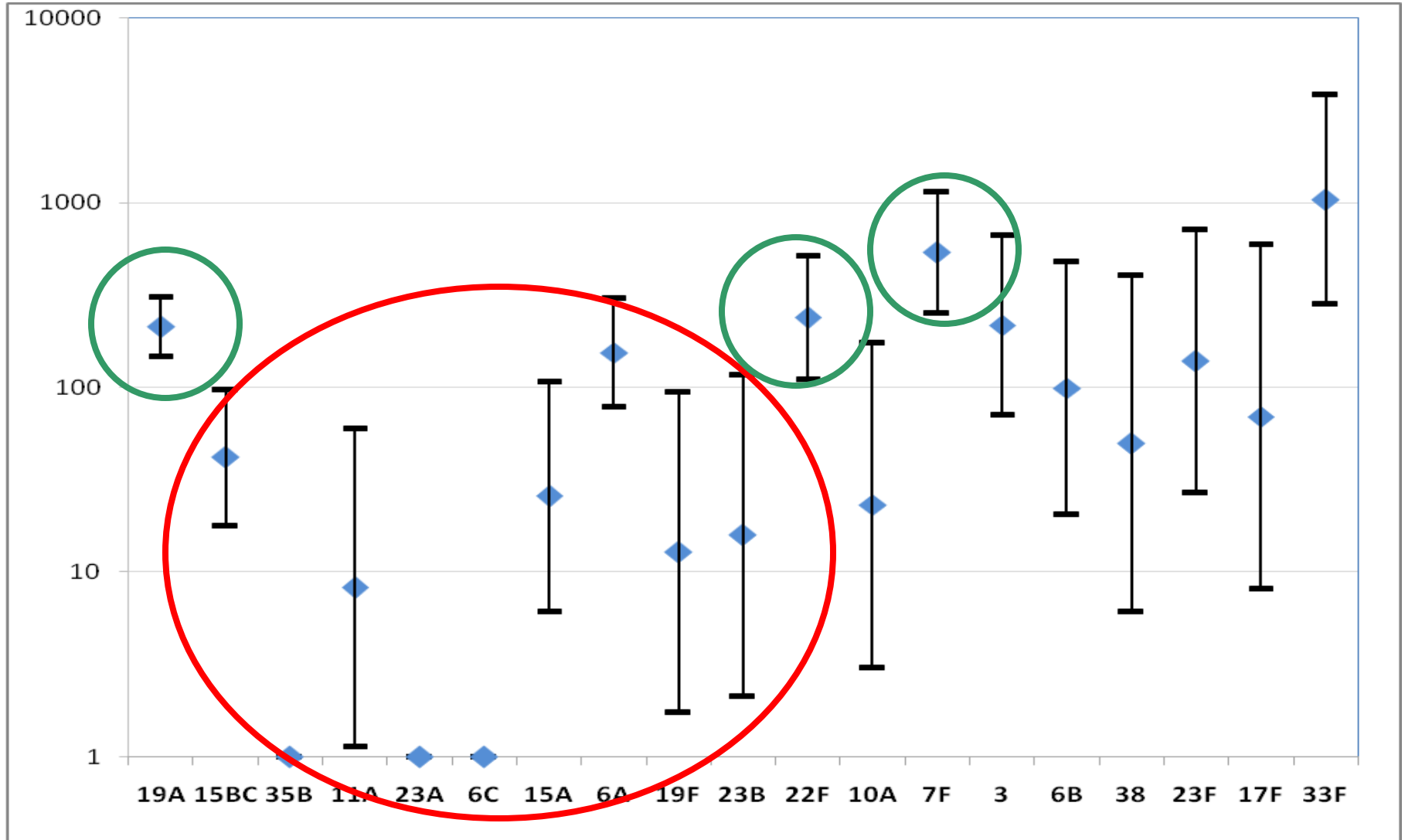
Distribution of Pneumococcal Serotypes in IPD and NP Carriage in Massachusetts Children < 7 years



Not all Serotypes are Equal: Analysis of Invasive Potential of Pneumococcal Serotypes



Invasive Potential of Pneumococcal Serotype in Massachusetts Children Less than 7 years of age (ordered by frequency of carriage)



Pneumococcal Conjugate Vaccine has had a substantial impact on child health wherever it has been introduced. We have observed the following:

a. Decline in invasive pneumococcal disease due to Vaccine Serotypes in children Including those too young to be protected through immunization and high risk children such as those with Sickle Cell Disease and HIV

b. Decline in pneumonia beyond the traditional Lobar pneumonia

c. Modest Decline in episodes of AOM

d. Decline in high level penicillin resistance

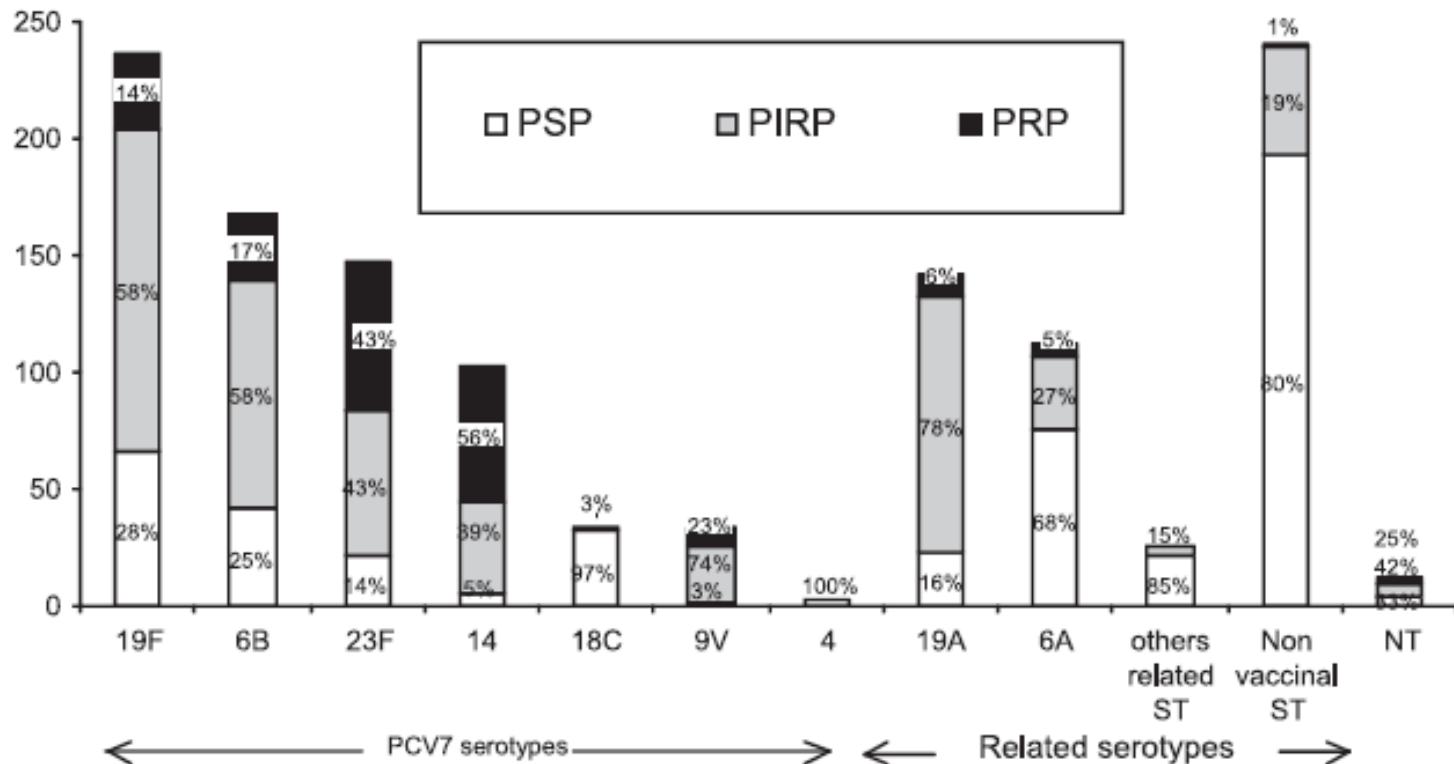
e. Decline in vaccine serotype disease in adults as a result of 'indirect' protection

f. Variable increases in diseases due to Non vaccine serotypes in all age groups

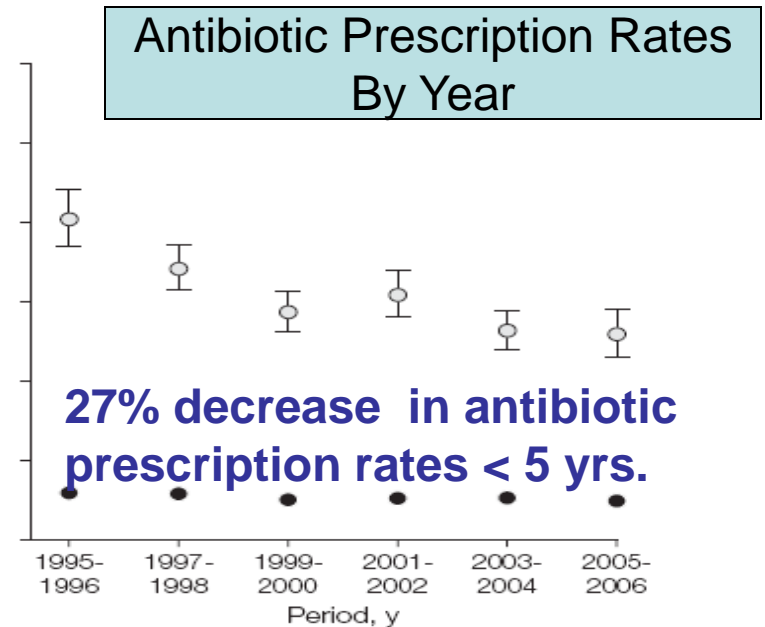
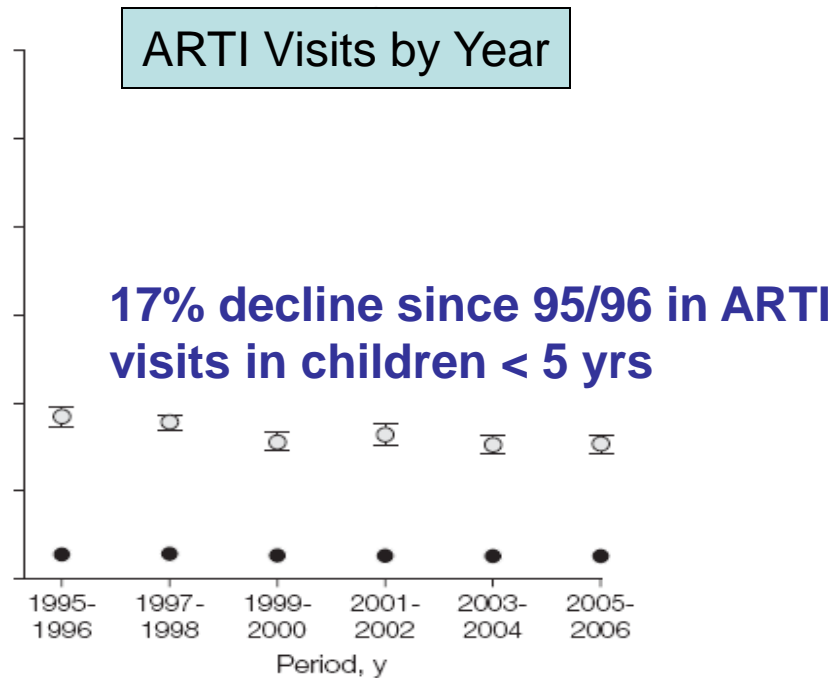
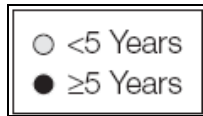
h. Decline in ambulatory visits and antimicrobial Prescriptions potentially related to introduction of PCV.

**Why did high level resistance
decline following the introduction of
PCV7?**

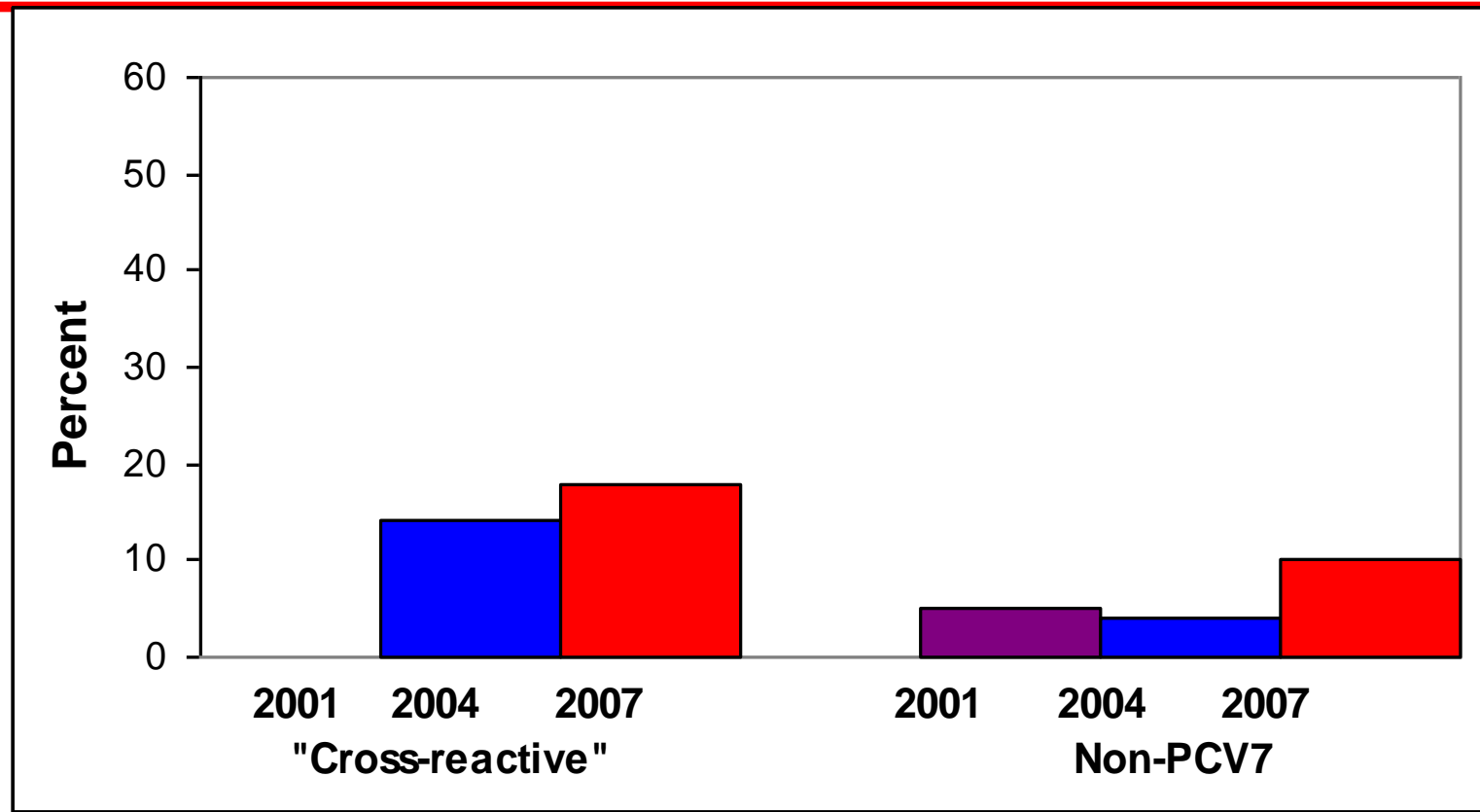
Distribution of Penicillin Resistance among Pneumococcal Isolates in France by Serotype



National US Rates of Ambulatory Visits and Antibiotic Prescribing



Multi-drug resistance (≥ 3 classes) among 'cross reactive' and nonvaccine serotypes of Nasopharyngeal isolates of *Streptococcus pneumoniae*



Impact of Prevenar™ on Resistance

Effect of Carriage on Resistant Strains (cont'd)

Decrease Carriage of PCN-resistant Pneumococci Was Offset by Increase in PCN-Intermediate Strains (1998-2004; Alaska)

Antimicrobial agent, susceptibility	No. (%) of isolates that were nonsusceptible to antimicrobial agents					p ^b	OR ^c (95% CI)
	At baseline ^a (n=275)	In 2001 (n=266)	In 2002 (n=266)	In 2003 (n=413)	In 2004 (n=377)		
Penicillin							
Resistant	36 (13)	19 (7)	20 (8)	27 (7)	24 (6)	0.002	0.45 (0.26-0.78)
Intermediate	32 (12)	26 (10)	24 (9)	57 (14)	72 ^d (19)	0.003	1.79 (1.14-2.80)
Cotrimoxazole							
Resistant	38 (14)	30 (11)	34 (13)	25 (6)	49 ^e (13)	0.17	0.93 (0.59-1.47)
Intermediate	22 (8)	15 (6)	17 (6)	45 (11)	27 (7)	0.51	0.89 (0.49-1.59)
Tetracycline, resistant ^f	32 (12)	21 (8)	20 (8)	30 (7)	21 (6)	0.004	0.43 (0.24-0.77)
Ceftriaxone							
Resistant	5 (2)	1 (0.4)	2 (0.8)	4 (1)	6 (1.6)	0.94	0.87 (0.26-2.89)
Intermediate	26 (9)	14 (5)	16 (6)	23 (6)	16 (4)	0.01	0.42 (0.22-0.81)
Erythromycin, intermediate ^g	36 (13)	28 (11)	34 (13)	43 (10)	30 (8)	0.05	0.56 (0.33-0.93)

NOTE. Isolates were classified according to the 2002 definitions of the NCCLS. Isolates that were classified as intermediate or resistant were considered to be nonsusceptible. CI, confidence interval, OR, odds ratio.

^a 1998-2000.

^b By χ^2 test of trend.

^c 2004 vs. baseline.

^d Of 72 isolates 26 were of serotype 19A.

^e Of 49 isolates, 16 were of serotype 19A; 15 of 49 isolates were of serotype 33F.

^f During the entire study, 2 isolates were intermediately resistant to tetracycline; these isolates were not included in trend analysis.

^g During the entire study, 4 isolates were fully resistant to erythromycin; these isolates were not included in trend analysis.

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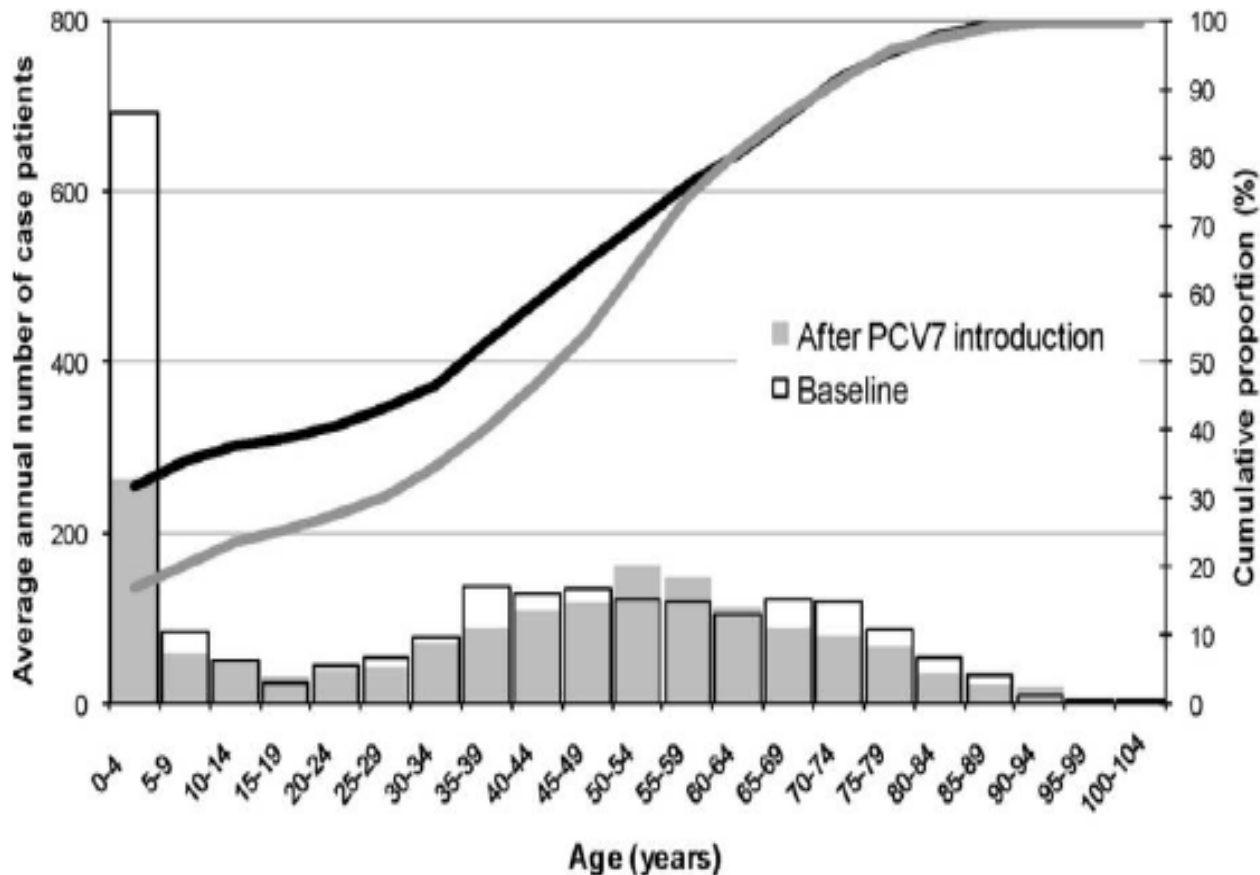
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e. Decline in vaccine serotype disease in adults as a result of 'indirect' protection

f. Variable increases in diseases due to Non vaccine serotypes in all age groups

h. Decline in ambulatory visits and antimicrobial Prescriptions potentially related to introduction of PCV.

Age Distribution for Hospitalization for Pneumococcal Meningitis



Efficacy Trials of PCV for X-Ray Confirmed Pneumonia

Study/Population	Efficacy (95% CI) [CXR-positive Pneumonia] (Alveolar infiltrate)
US—NCKP ¹ reanalysis (WHO criteria for pneumonia)	26% (7-41)
South Africa ² [HIV-uninfected Children]	20% (2-35)
The Gambia ³	36% (27-43)

1. Hansen J, et al. *Pediatr Infect Dis J.* 2006;25:779-781.

2. Klugman KP, et al. *New Engl J Med.* 2003;349:1341-1348.

3. Cutts F, et al. *Lancet.* 2005;365:1139-1146.

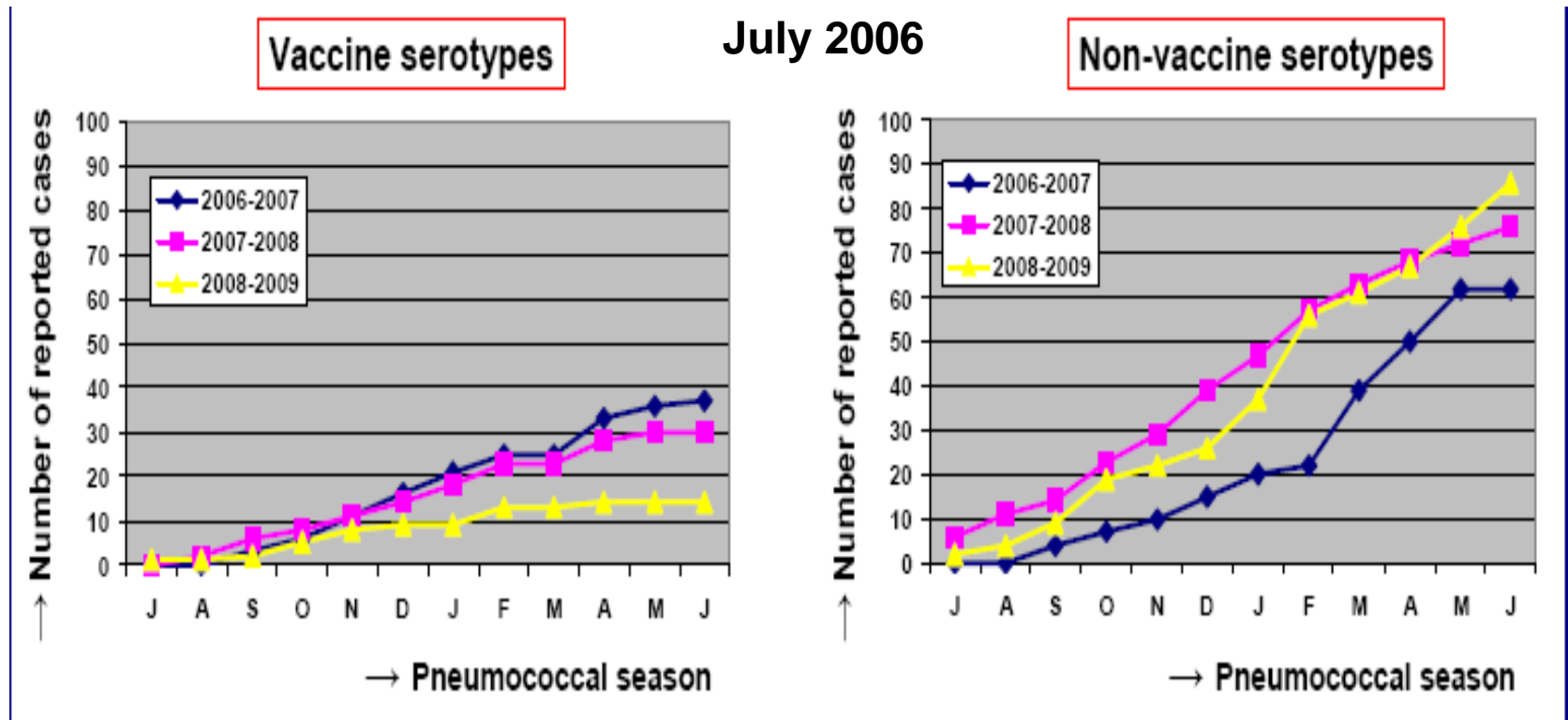
Efficacy of PCV in the prevention of human metapneumovirus (hMPV)–associated lower respiratory tract infections (LRTIs)

Hmpv Associated Outcome	Vaccine Recipients No.	Placebo Recipients No.	Efficacy (CI, 95%)
LRTI	41	74	45 (19,62)
Clinical Pneumonia	19	42	55 (22,74)
CXray	9 (36)	15 (68)	40 (-37,74)
Bronchiolitis	22	32	31 (-31,60)
WHO severe pneumonia	31	52	40 (7,62)
CRP_≥40 mg/dl	7 (23)	18 (46)	61 (7,84)

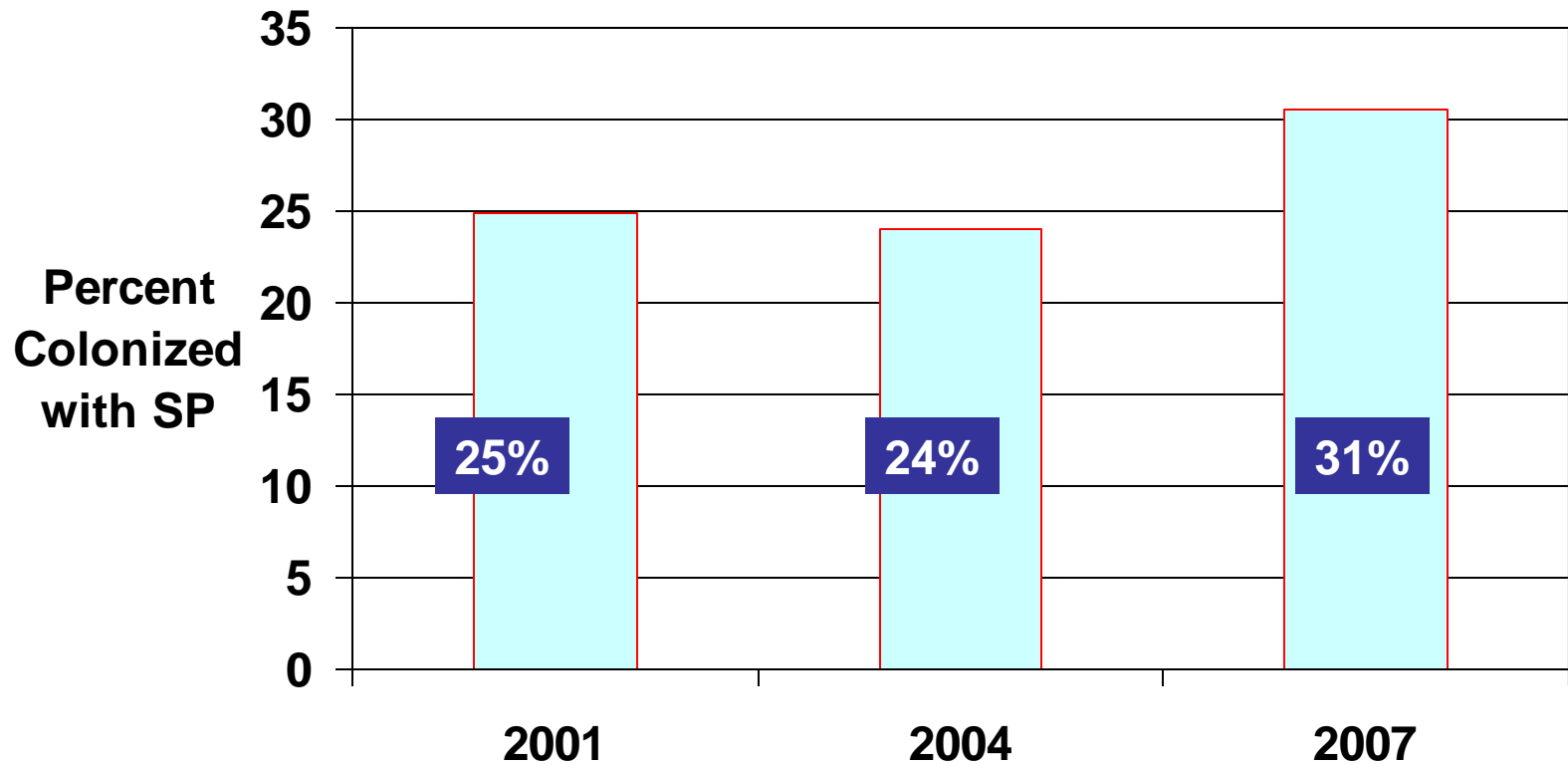
Data is for number of cases; numbers in parentheses indicate total No of LRTI cases for which test was performed.

Reported Cases of IPD in Adults in Saxony (Germany)

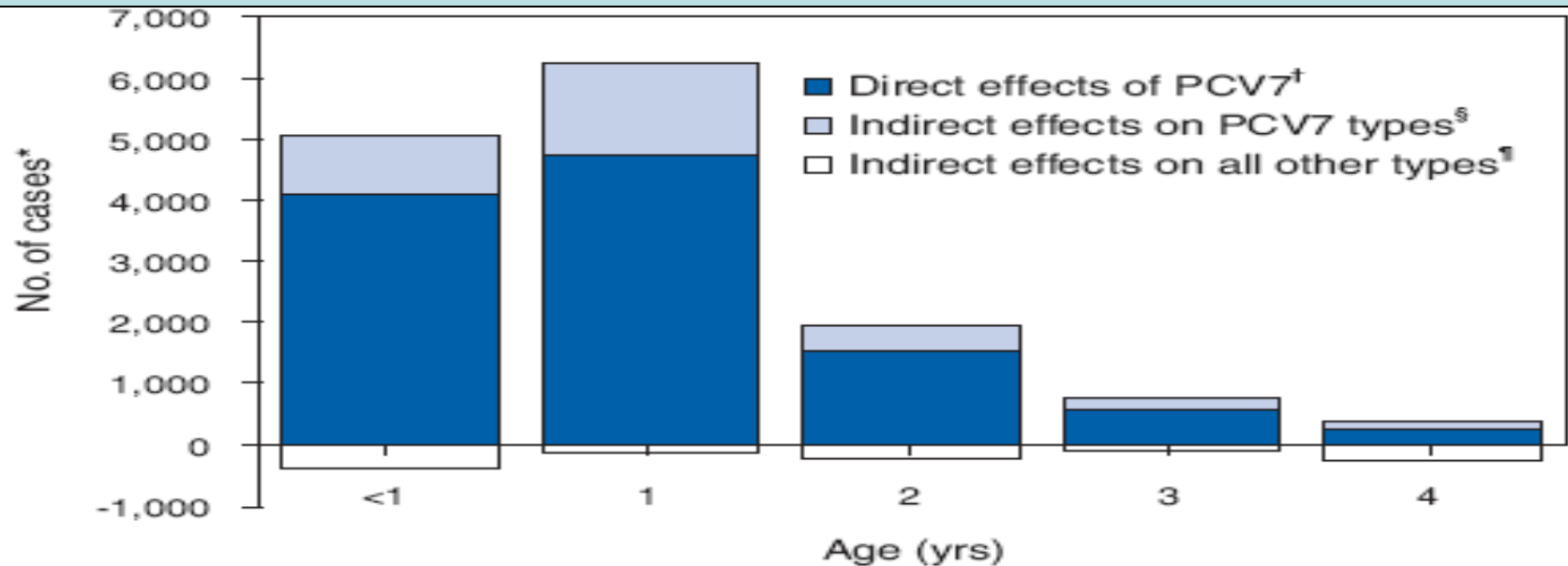
PCV7 introduced
July 2006



Carriage of *S. pneumoniae* in Massachusetts children 3 months to 7 years of age



Projected number of IPD cases prevented among children < 5 years: Indirect and direct effects in US in 2005



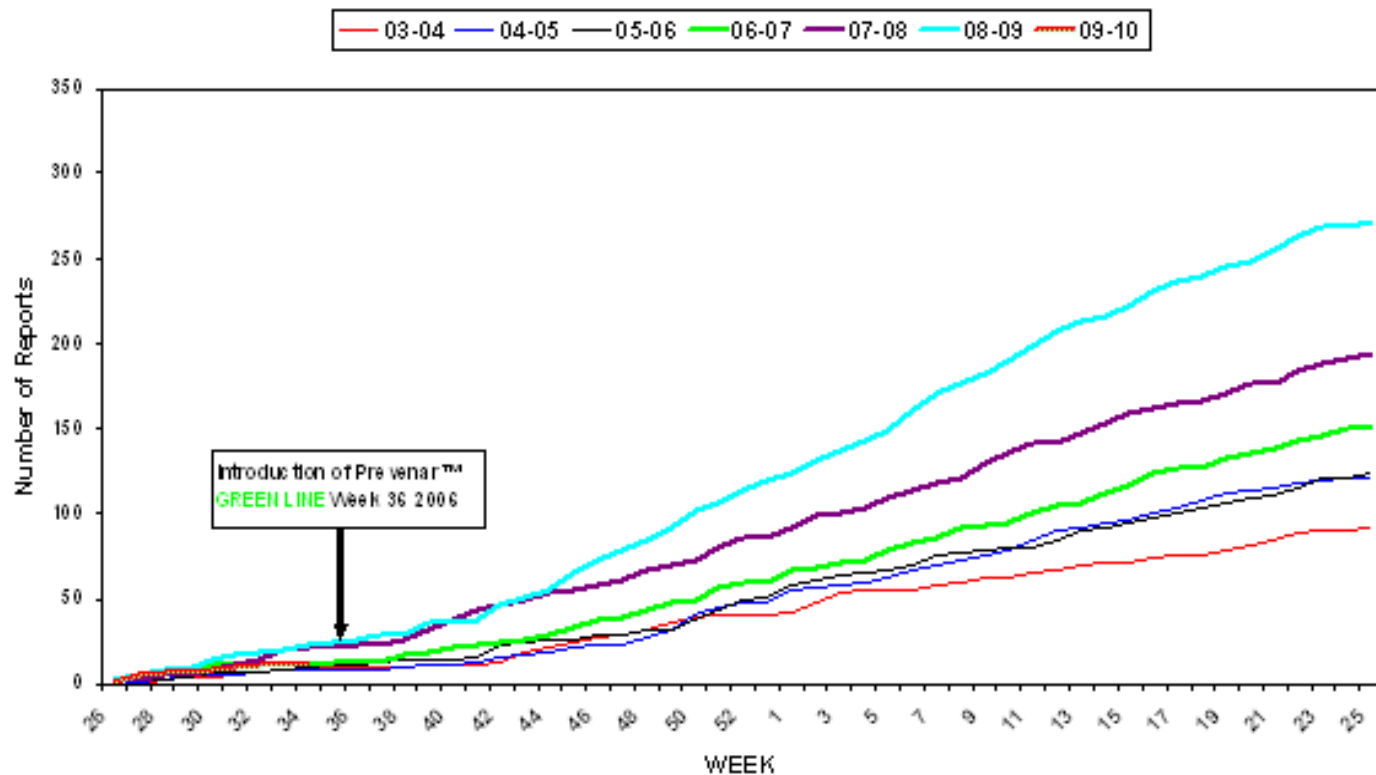
* National projections of IPD cases calculated applying ABCs age- and race-specific rates to the age and racial distribution of the U.S. population using U.S. Census 2000 data.

[†] Calculated as a product of national projections of PCV7-type IPD cases among children aged <5 years in 1998–1999, PCV7 coverage (≥ 3 doses) for each birth cohort in 2001–2005, and PCV7 efficacy against PCV7-type IPD.

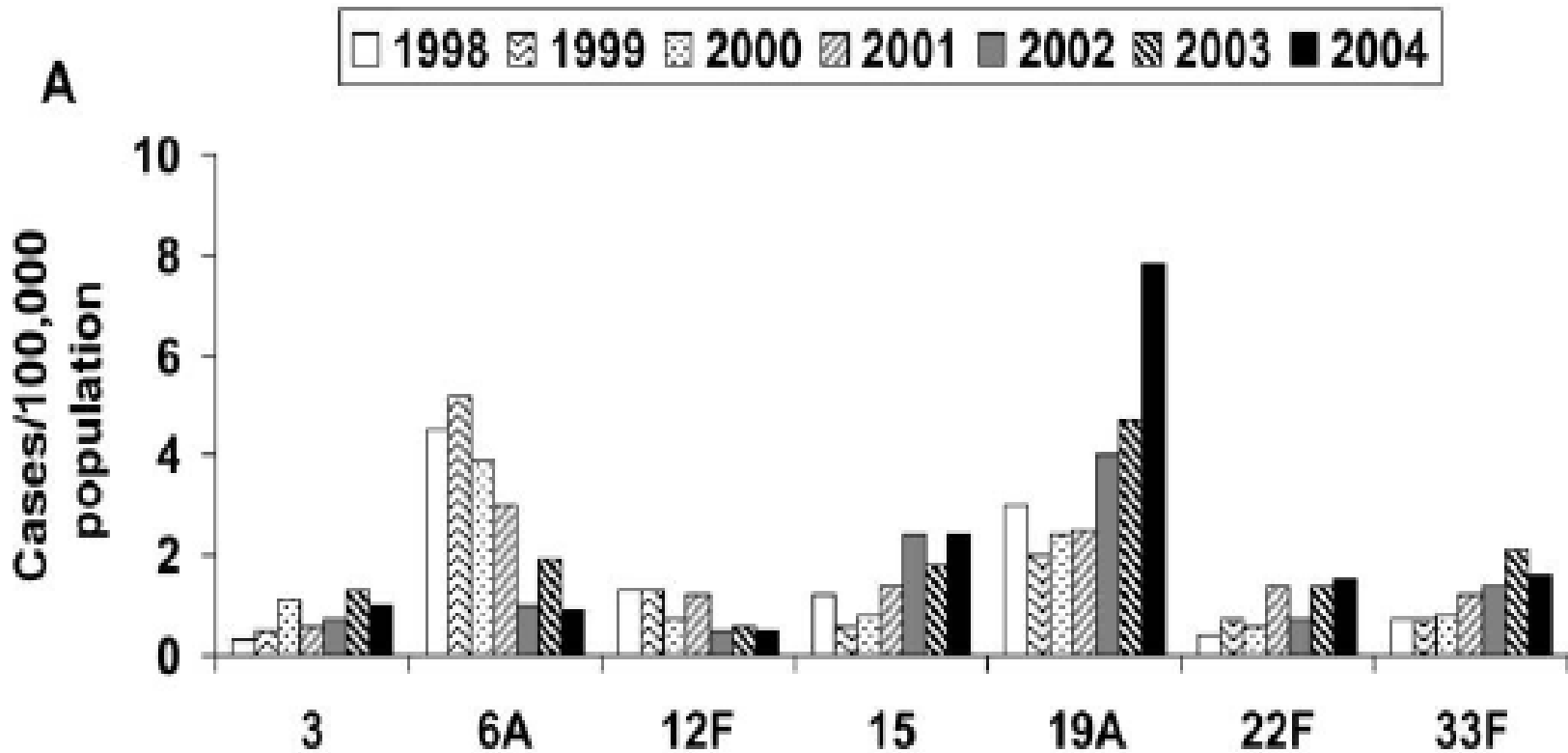
[§] Calculated by subtracting national projections of PCV7-type cases in 2005 from average national projections of PCV7-type IPD cases in 1998–1999 and then subtracting PCV7-type IPD cases prevented directly.

[¶] Calculated by subtracting national projections of non-PCV7-type cases in 2005 from average national projections of non-PCV7-type IPD cases in 1998–1999.

Cumulative weekly number of reports of Invasive Pneumococcal Disease due to any of the serotypes NOT IN PCV7 : Children aged < 2 Years in England and Wales by Epidemiological Year: July-June (2003- 9.11.09)



Change in Serotype Specific Incidence of IPD among Children Age less than 5 Years



Trends in the proportion of serotype 19A isolates demonstrating resistance to 3 classes of antimicrobial agents

Penicillin and ≥ 2 other antibiotic classes

