

# **The Global Situation on Pneumococcal Disease and its Prevention**

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# Agenda

- **Pneumococcal Disease Burden**
- **Serotype epidemiology**
- **Efficacy & Effectiveness**
  - ▶ **IPD, Pneumonia and AOM**
  - ▶ **Indirect effects**
  - ▶ **Antibiotic resistance**
- **Safety**
- **Immunogenicity**

# Agenda

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- Safety
- Immunogenicity

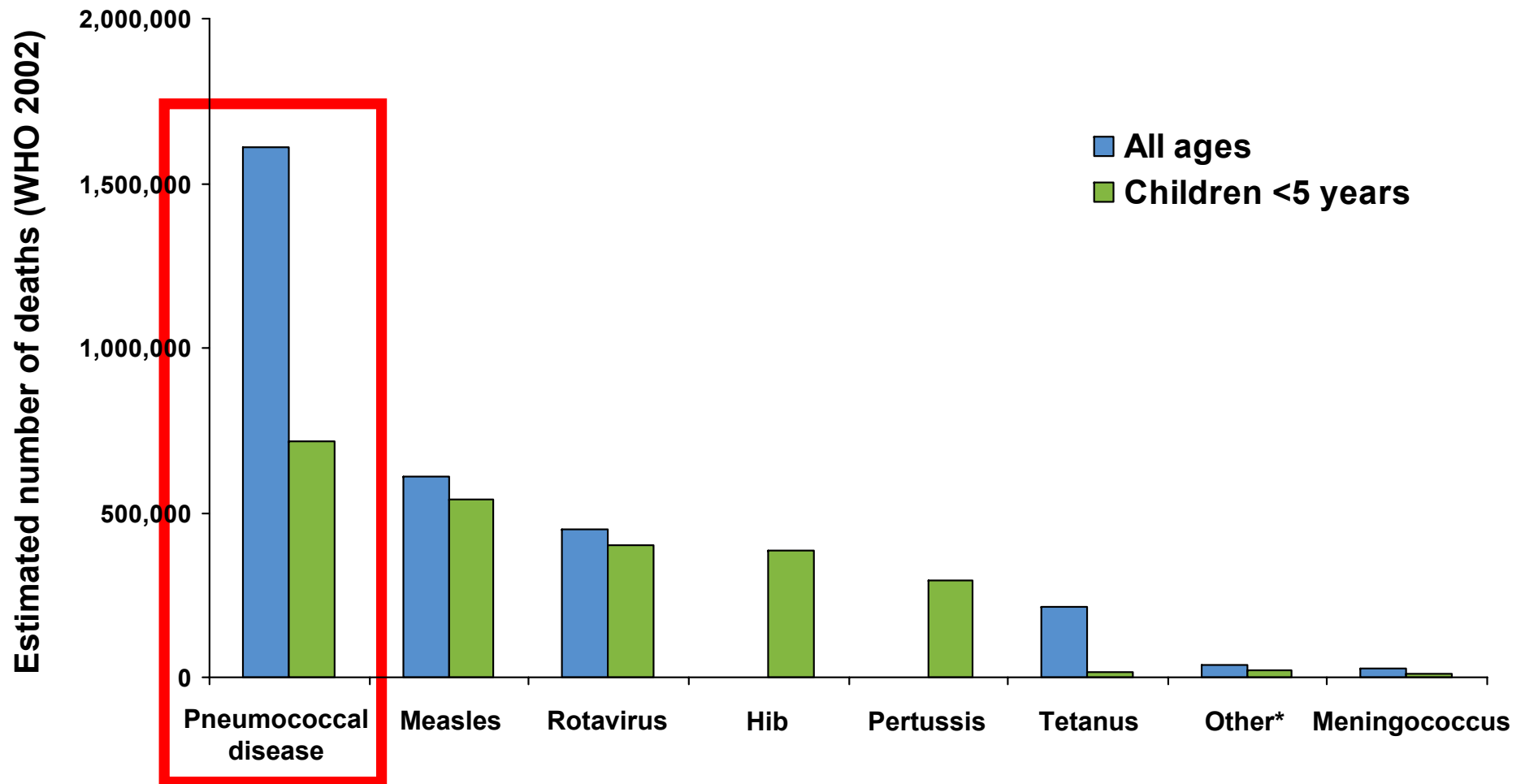
# Pneumococcal Disease

# QUESTION 1

**1. Every year the number of deaths from pneumococcal disease worldwide in children less than 5 years is reported to be :**

- A. 500,000**
- B. 600,000**
- C. 800,000**
- D. 900,000**
- E. 1,000,000**

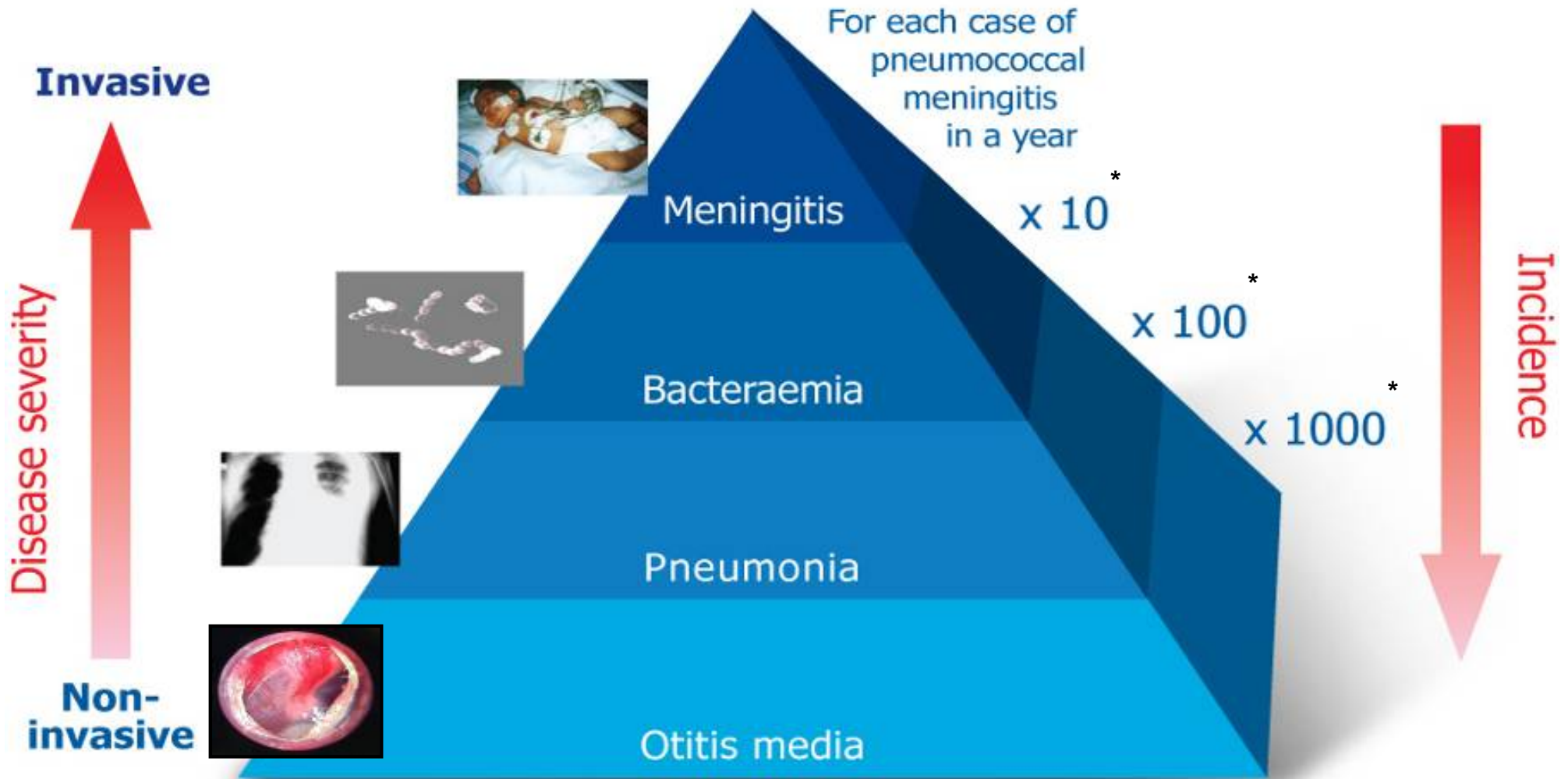
# Global Perspective Vaccine-Preventable Deaths (WHO)



***Streptococcus pneumoniae* is the leading cause of vaccine-preventable deaths globally**

\*Polio, diphtheria, yellow fever

# *S. pneumoniae* Disease Burden in Children



Adapted from: American Academy of Pediatrics. *Pediatrics*. 2000;106:367-376 & *MMWR*. 1997;46:1-24

\* Provisional estimates

# Pneumonia



# QUESTION 2

**2. How many countries in Asia belong in the top ten countries with the most number of pneumonia cases in the world today?**

**A. 3**

**B. 4**

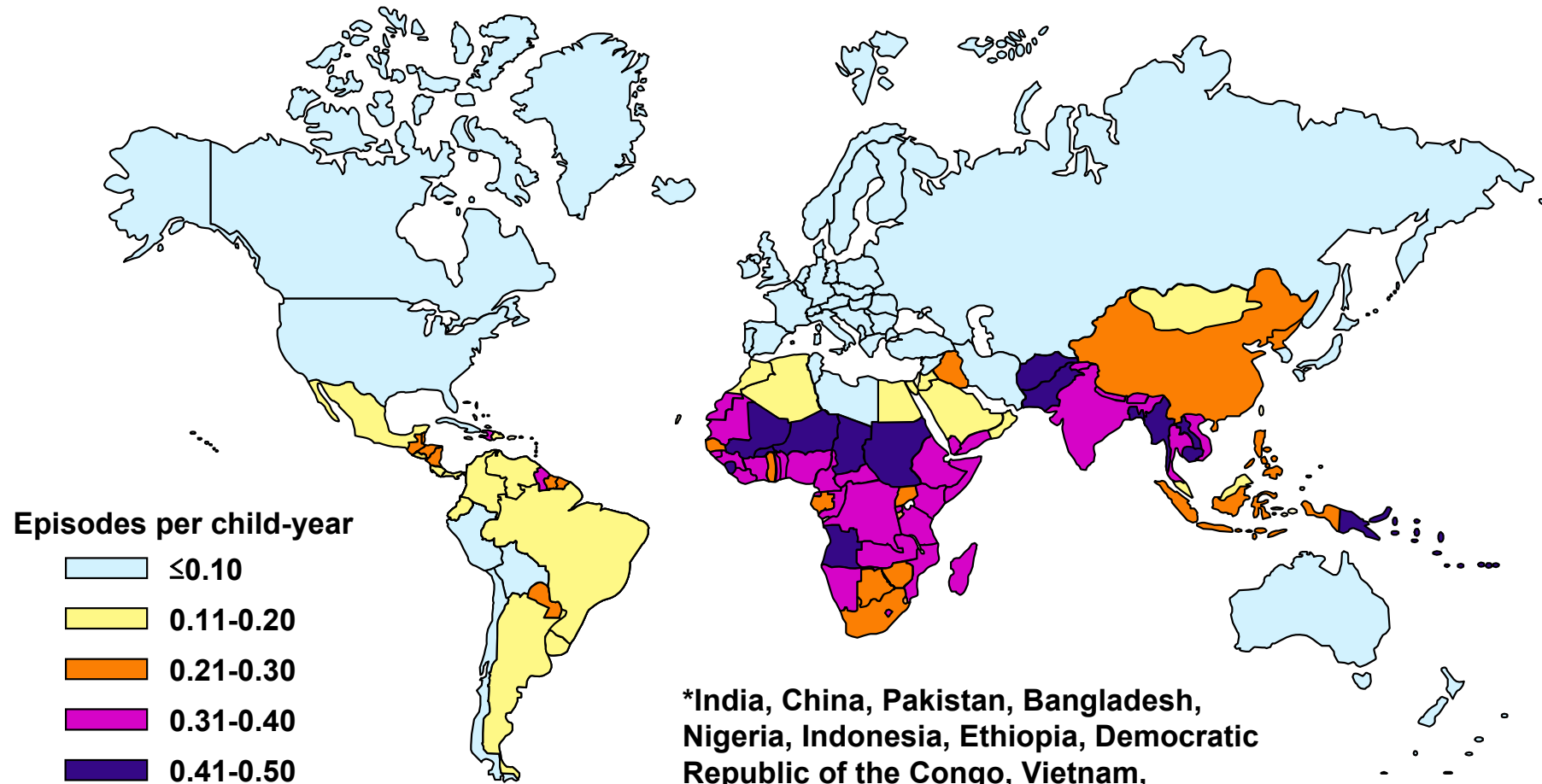
**C. 5**

**D. 6**

**E. 7**

# Pneumonia Episodes per Child-year Worldwide (WHO Estimate)

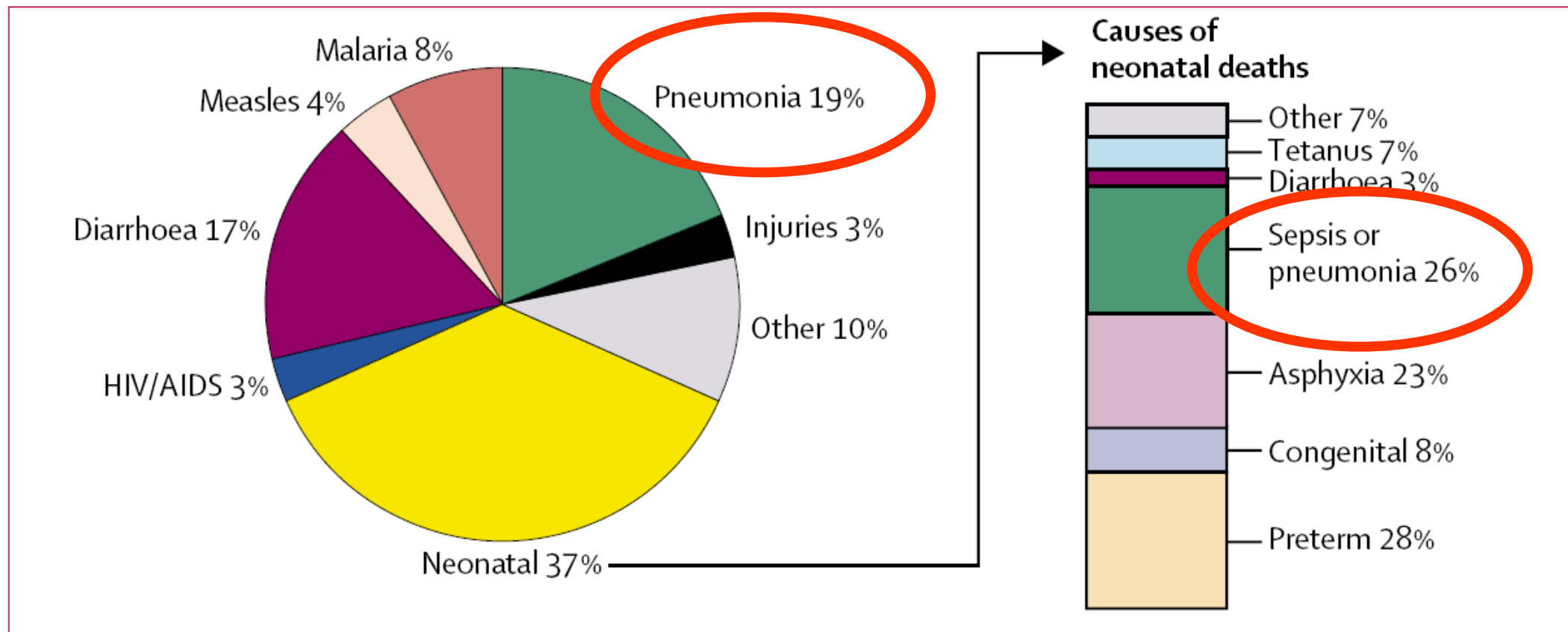
Nearly three-quarters of all pneumonia episodes worldwide in children <5 years of age occur in just 15 countries\*



\*India, China, Pakistan, Bangladesh, Nigeria, Indonesia, Ethiopia, Democratic Republic of the Congo, Vietnam, Philippines, Sudan, Afghanistan, United Republic of Tanzania, Myanmar, Brazil

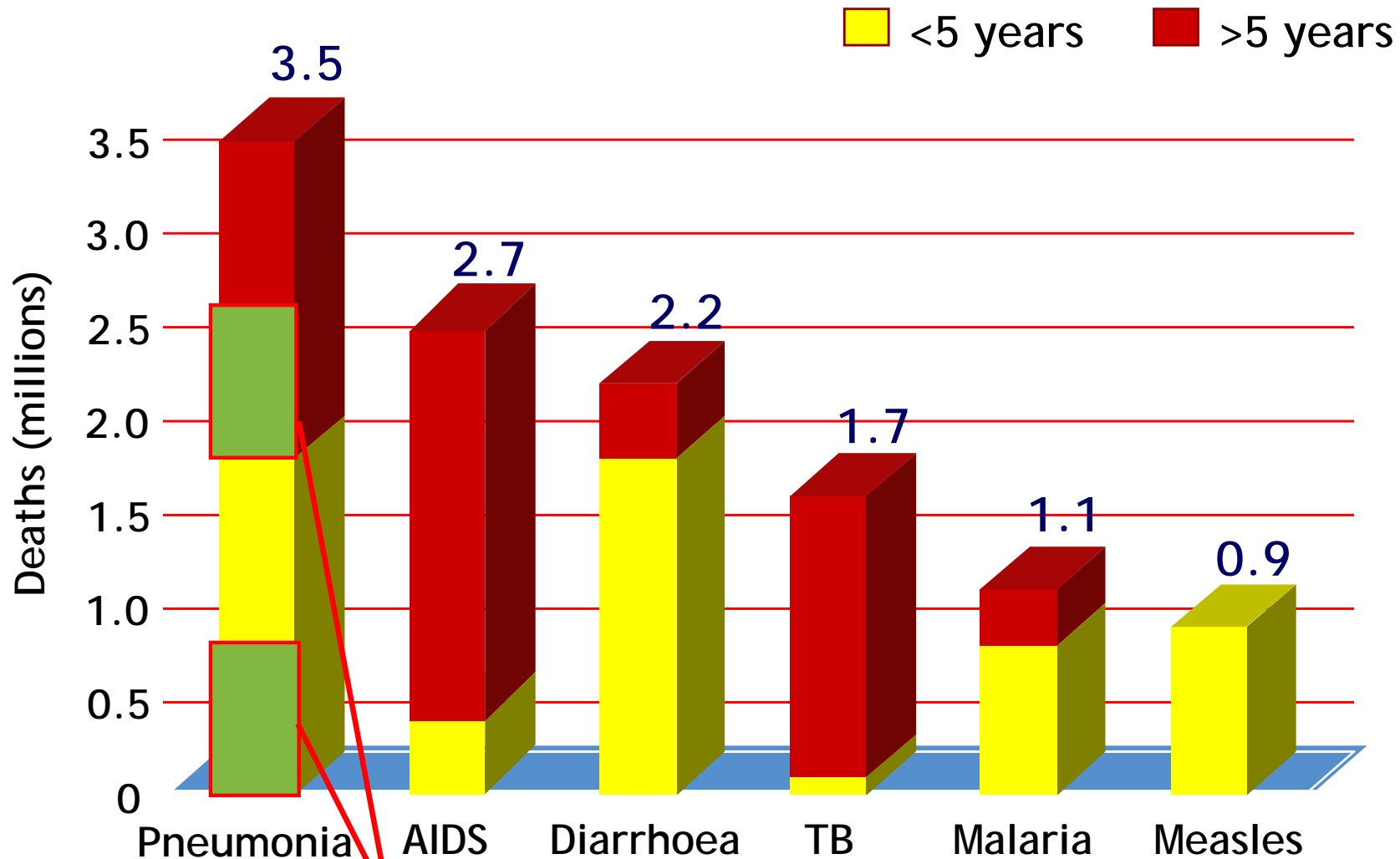
WHO=World Health Organization

# WHO: Major causes of death in children younger than age 5 years and in neonates



**Pneumonia is the leading KILLER of children !!!**

# Leading Infectious Causes of Global Mortality



*S. pneumoniae*:  
~1.6 million deaths, including  
~800,000 child deaths



# PNEUMONIA

THE FORGOTTEN  
KILLER OF  
CHILDREN

*S. pneumoniae*  
IS THE MAJOR  
CAUSE IN 40-  
50% OF CASES

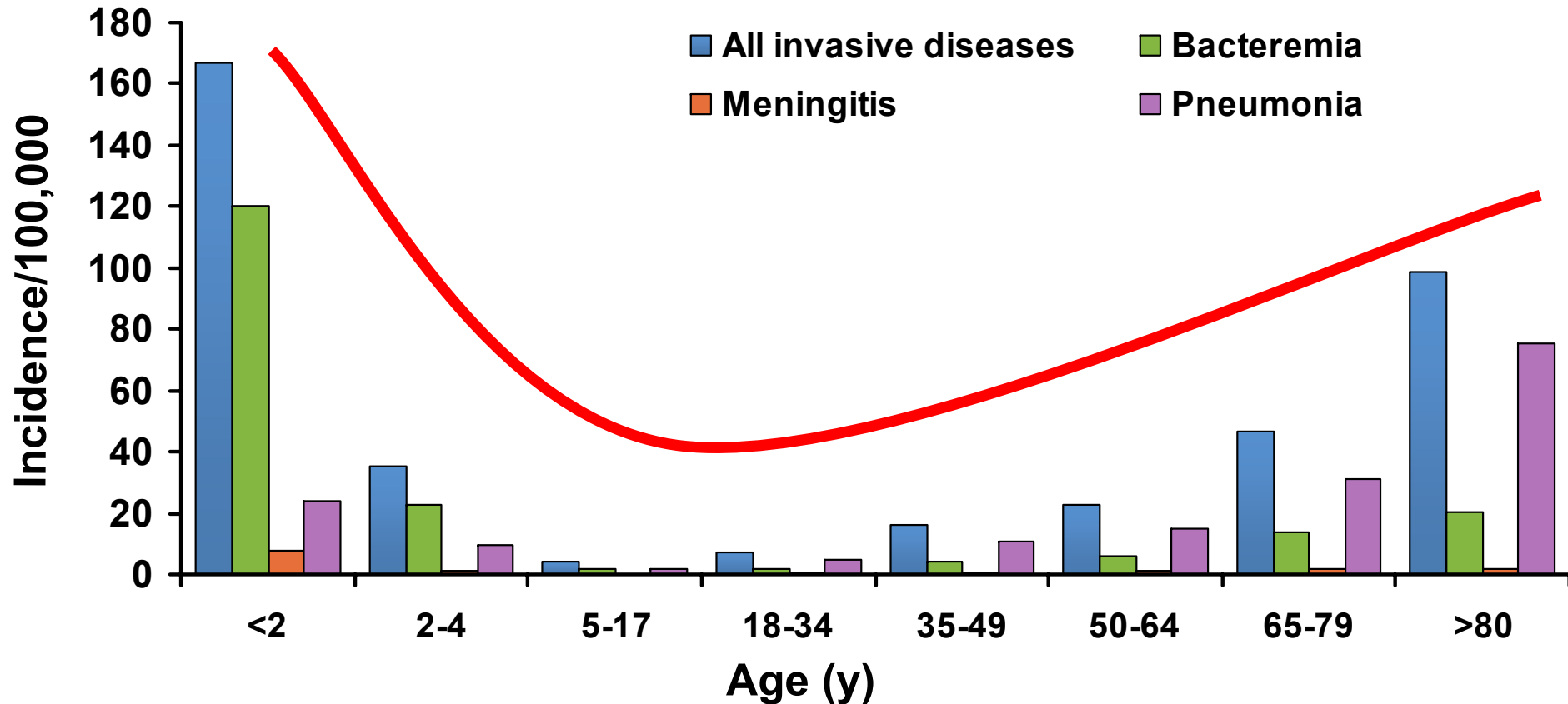
# IPD

( Invasive Pneumococcal Disease )

# Background

## Incidence of IPD by Age and Type (U.S.)

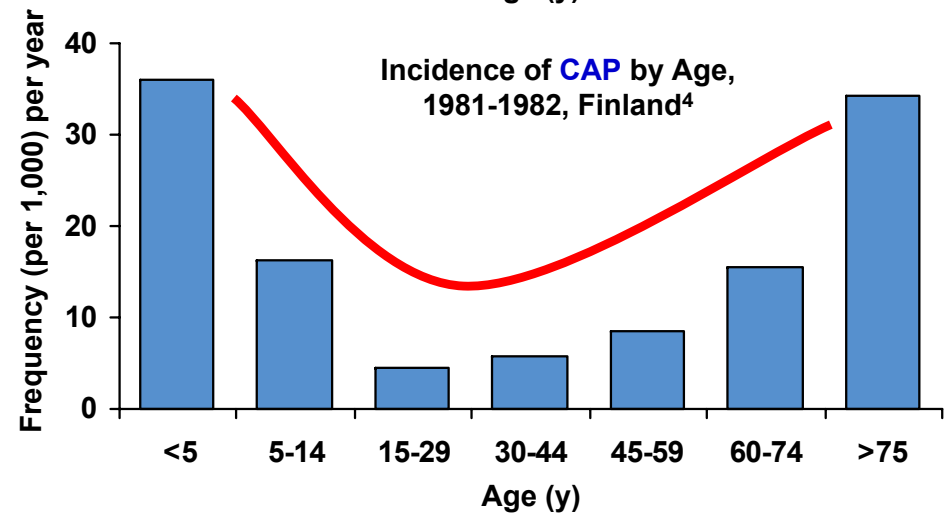
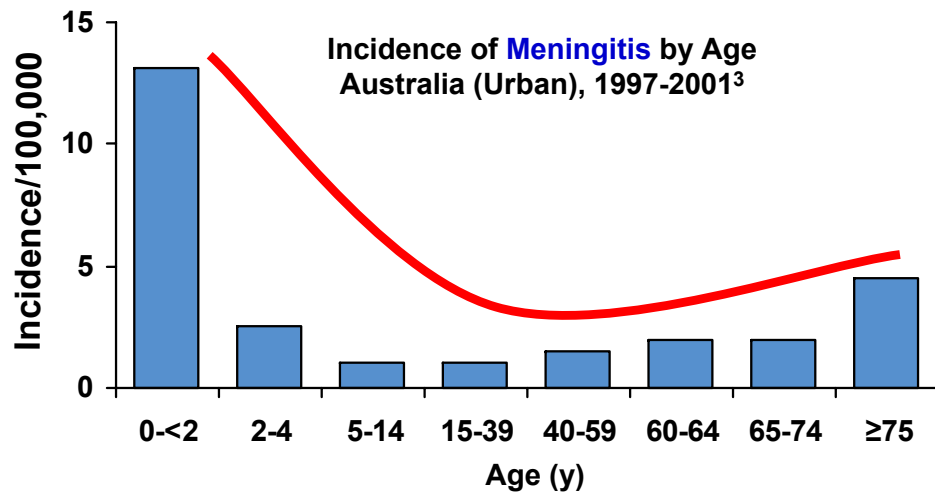
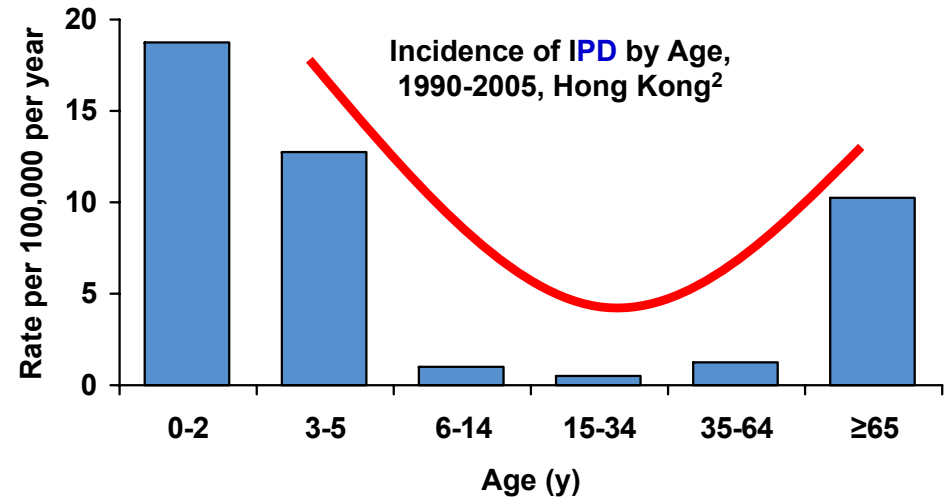
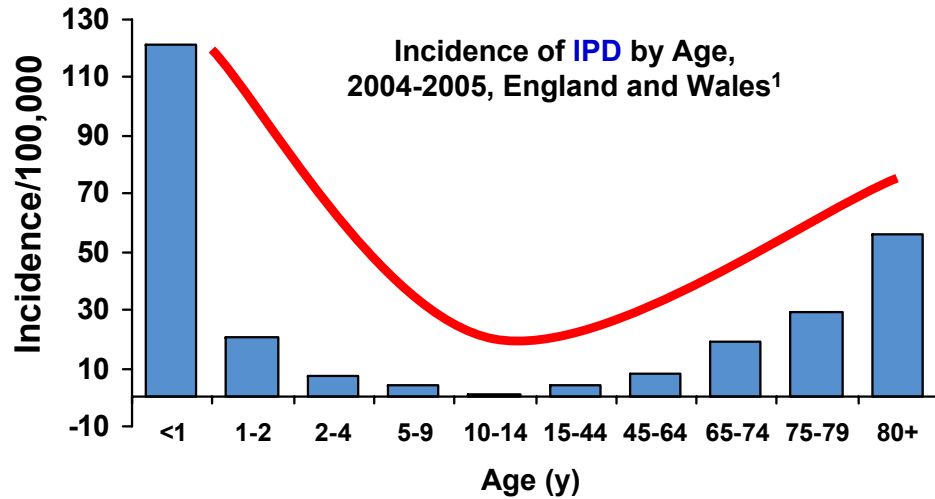
“U-shaped” Curve With Peaks at Extremes of Age



Incidence of IPD is highest at extremes of age

# Background

## Incidence of IPD, CAP, and Meningitis by Age—Worldwide



**Incidence of IPD, pneumonia, and meningitis is highest at extremes of age**

1. Health Protection Agency. [http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb\\_C/1195733823380?p=1203409671876](http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1195733823380?p=1203409671876). Accessed June 30, 2008.

2. Ho PL, et al. *Pediatr Infect Dis J*. 2006;25:454-455.

3. McIntyre P, et al. *NSW Public Health Bulletin*. 2003;14:85-89.

4. Jokinen C, et al. *Am J Epidemiol*. 1993;137:977-988.



# Agenda

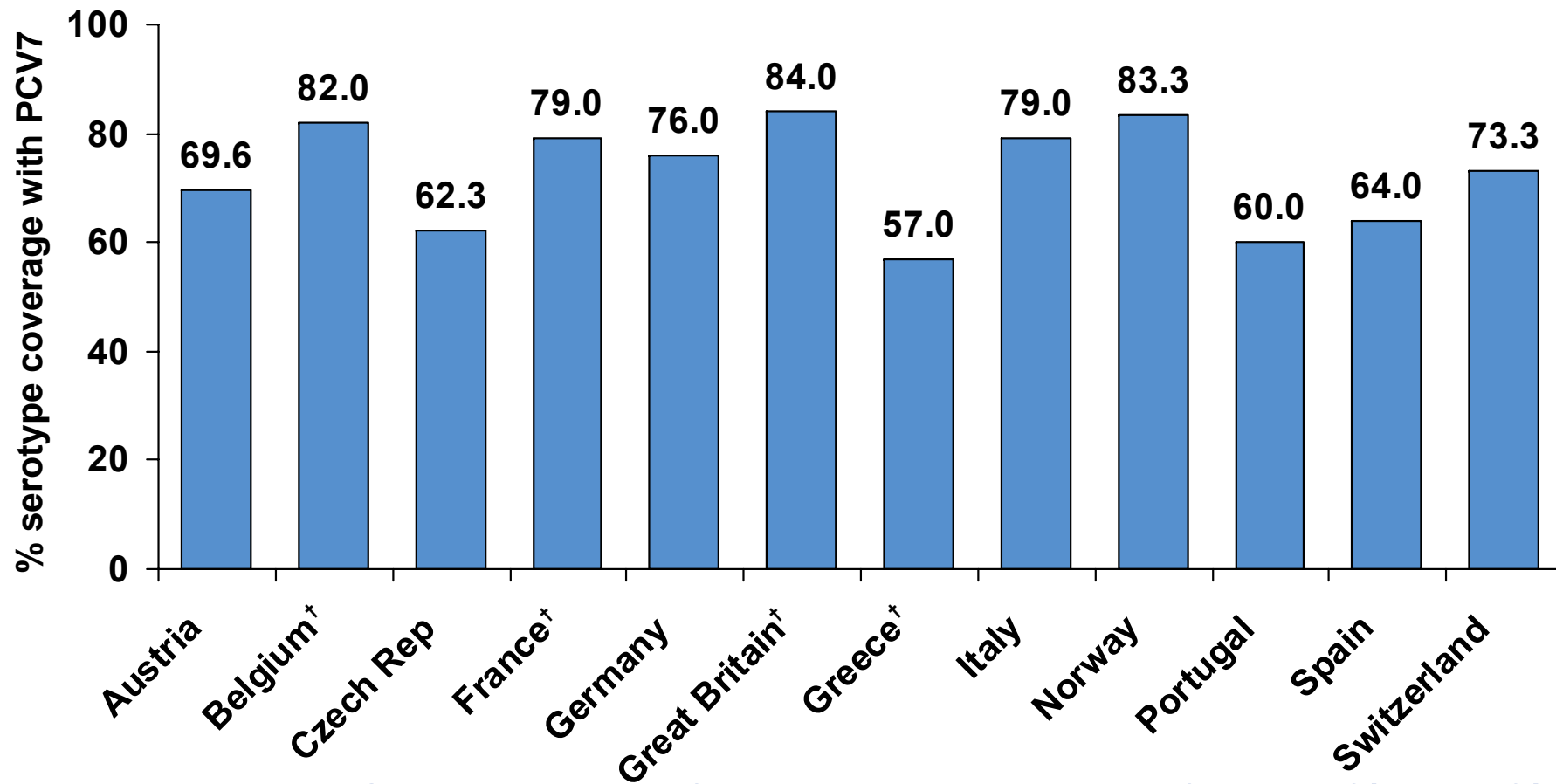
- Pneumococcal Disease back ground
- **Serotype epidemiology**
- Efficacy & Effectiveness
  - ▶ IPD, Pneumonia and AOM
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- Safety
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# Serotype coverage by PCV7

# European Union

## Serotype Coverage by Country

**Estimated Serotype Coverage Data for Total IPD by Country for Children <5 Years of Age**



**Estimated PCV 7 coverage for EU nations ranges from 57% to 84%**

\*Trademark

†Includes serogroup coverage

McIntosh EDG, et al. *Epidemiol Infect.* 2007;135:644-656.

# QUESTION 3

**3. The vaccine serotype coverage of the PCV7 for IPD in Thailand in 2000-2005 is:**

**A. 70.3%**

**B. 73.9%**

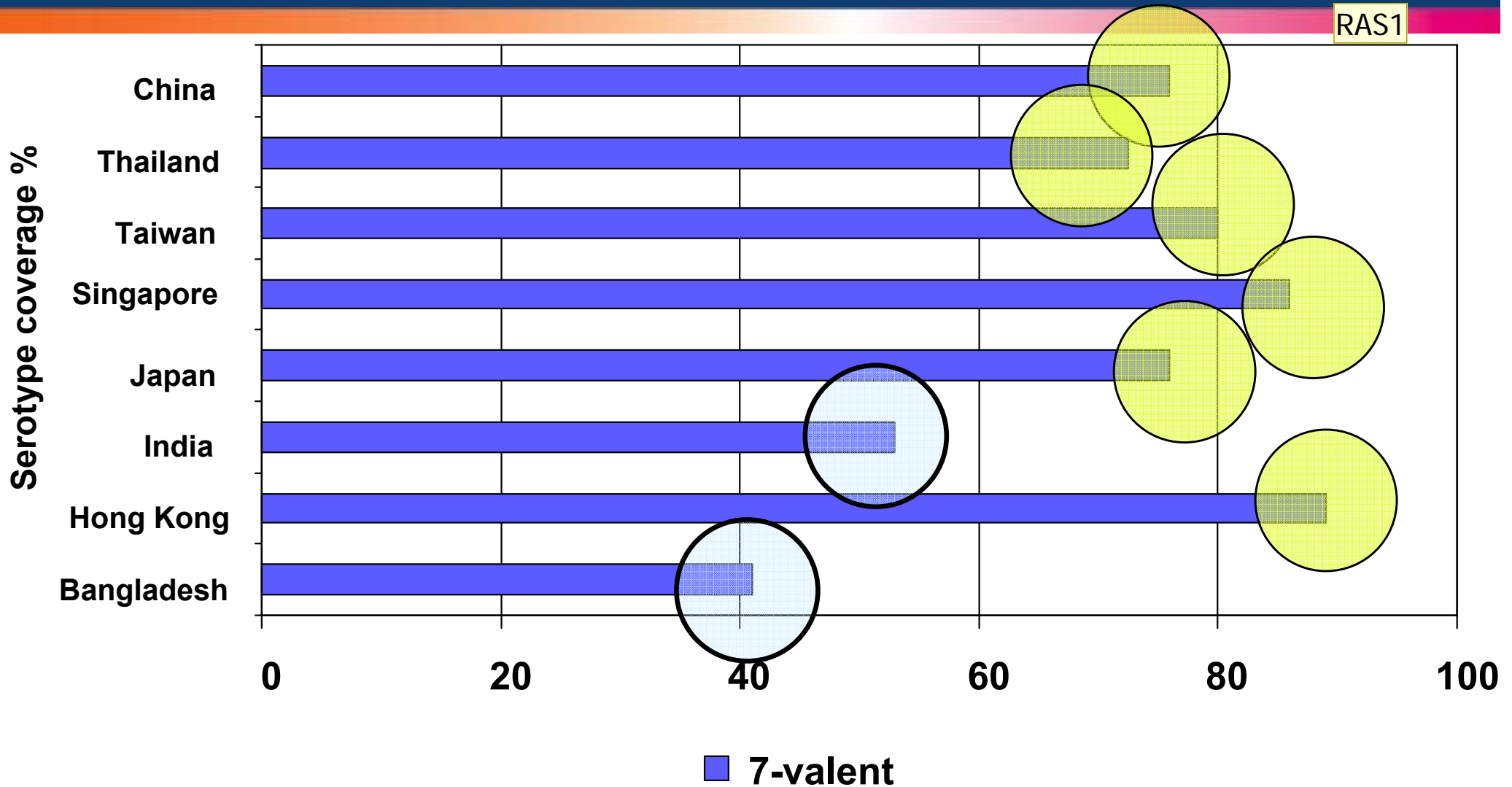
**C. 75.8%**

**D. 77.4%**

**E. 87.8%**

# Asia Pacific

## serotype coverage by countries



Various published sources

Slide 21

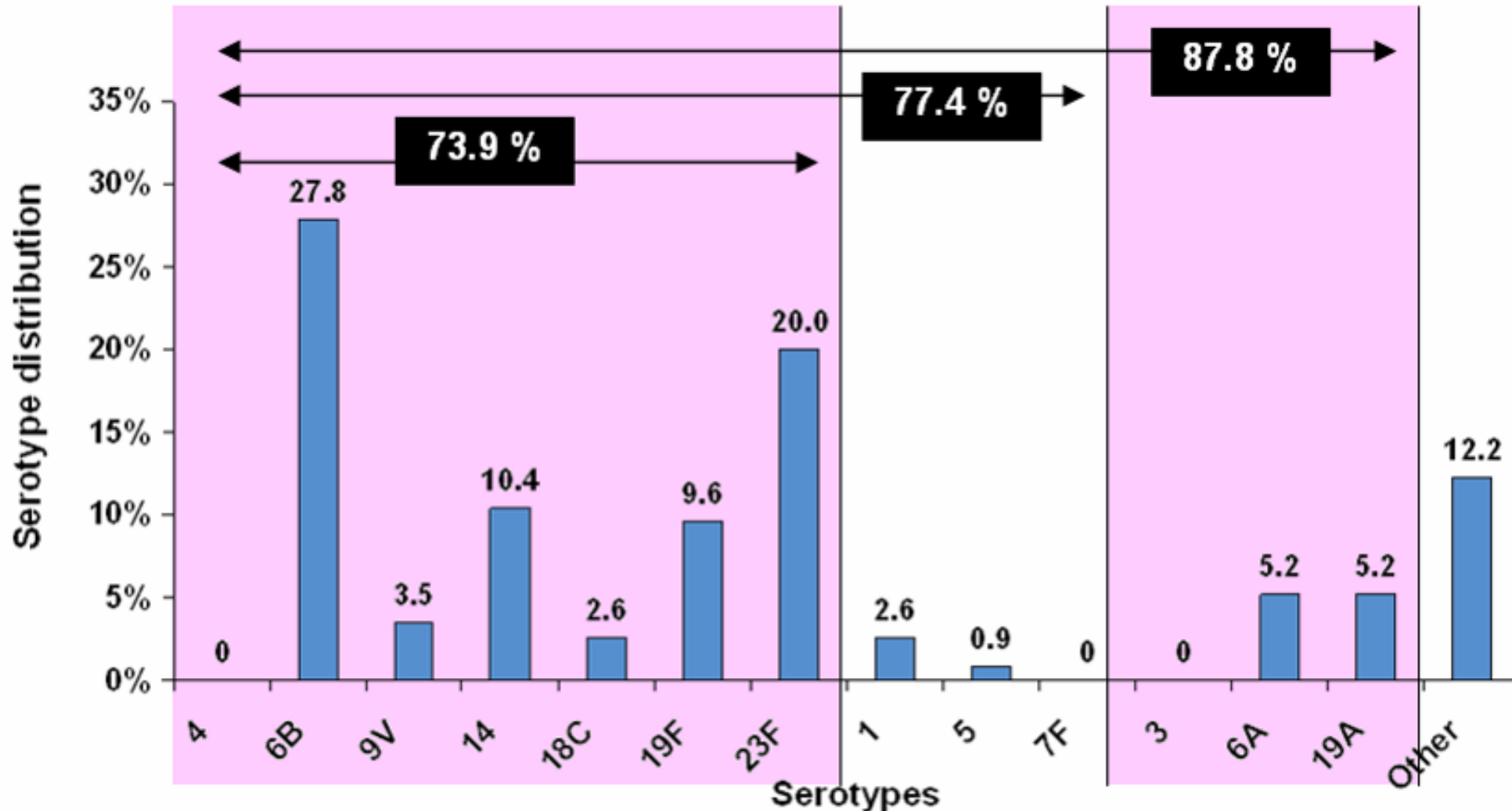
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RAS1

What does this colored circle mean versus the light blue

Ronald A. Salerno, Ph.D., 11/13/2008

# Serotype distribution of invasive pneumococcal disease in Thai children under 5 years old (2000-2005, N=115)



Serotype emergence



# QUESTION 4

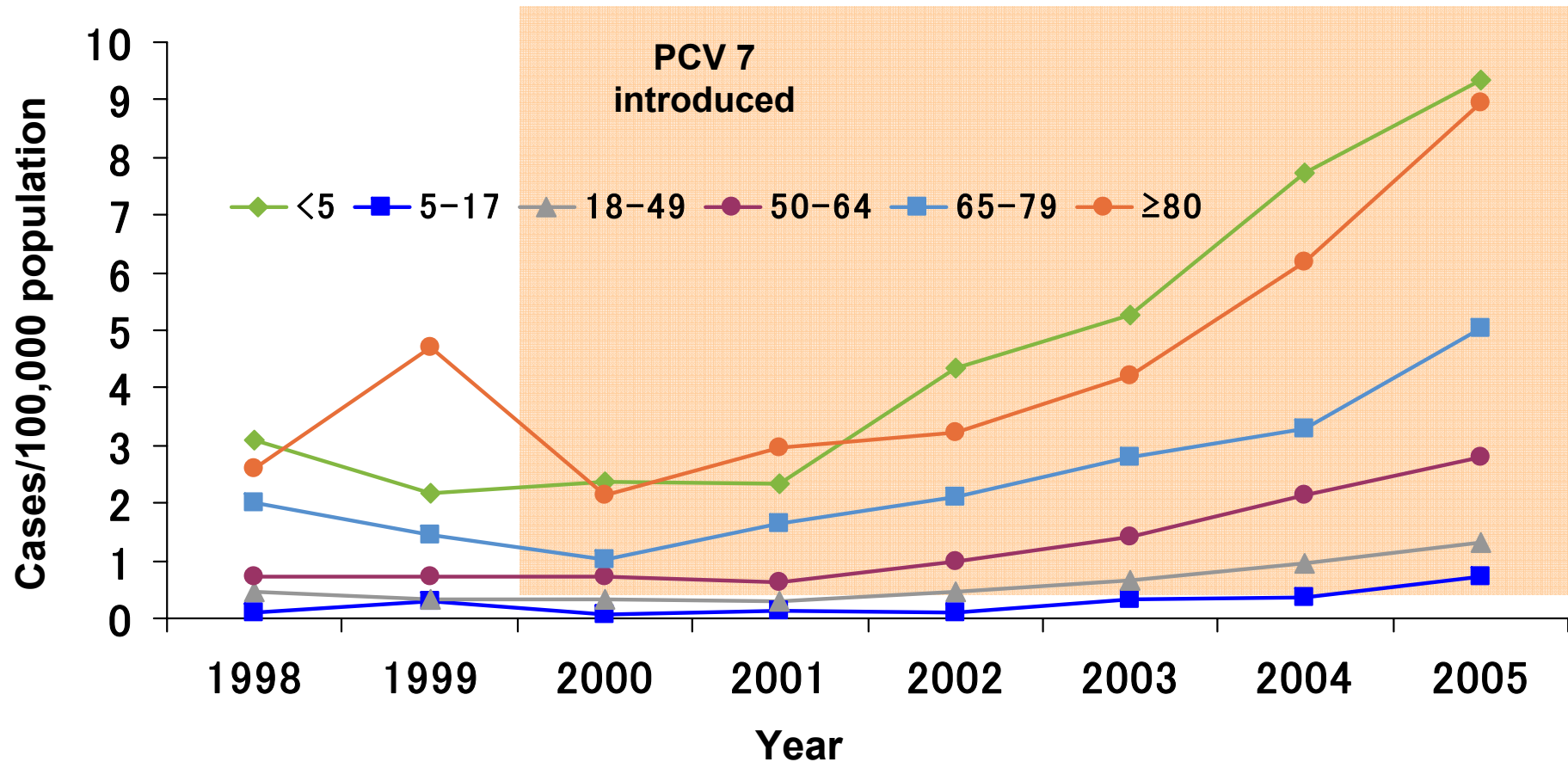
- 4 . Serotype 1 is a common serotype in**
- A. Children less than 2 years**
  - B. Children more than 2 years**
  - C. Children with Otitis Media**
  - D. Children with meningitis**
  - E. Elderly > 65 years**

# Importance of Serotypes in Investigational Pneumococcal Conjugate Vaccines

<b>Serotype 1</b>	<ul style="list-style-type: none"><li>● Important cause of PD in many regions, especially in older children (greater than 2 years)</li></ul>
<b>Serotype 5</b>	<ul style="list-style-type: none"><li>● Cause epidemic disease</li><li>● Rarely cause AOM</li></ul>
<b>Serotype 7F</b>	<ul style="list-style-type: none"><li>● Important cause of PD globally</li><li>● Rarely causes AOM</li></ul>
<b>Serotype 3</b>	<ul style="list-style-type: none"><li>● 3, 6A, 19A important cause of PD including pneumonia and AOM</li></ul>
<b>Serotype 6A</b>	<ul style="list-style-type: none"><li>● Common serotypes in many regions of the world including Thailand</li></ul>
<b>Serotype 19A</b>	<ul style="list-style-type: none"><li>● 6A and 19A are frequently antibiotic resistant</li><li>● Some decrease in 6A IPD (not NP carriage or herd effect) has been noted following use of PCV7</li><li>● 19F in Prevnar does not cross-protect for 19A</li></ul>

# Serotype Epidemiology

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

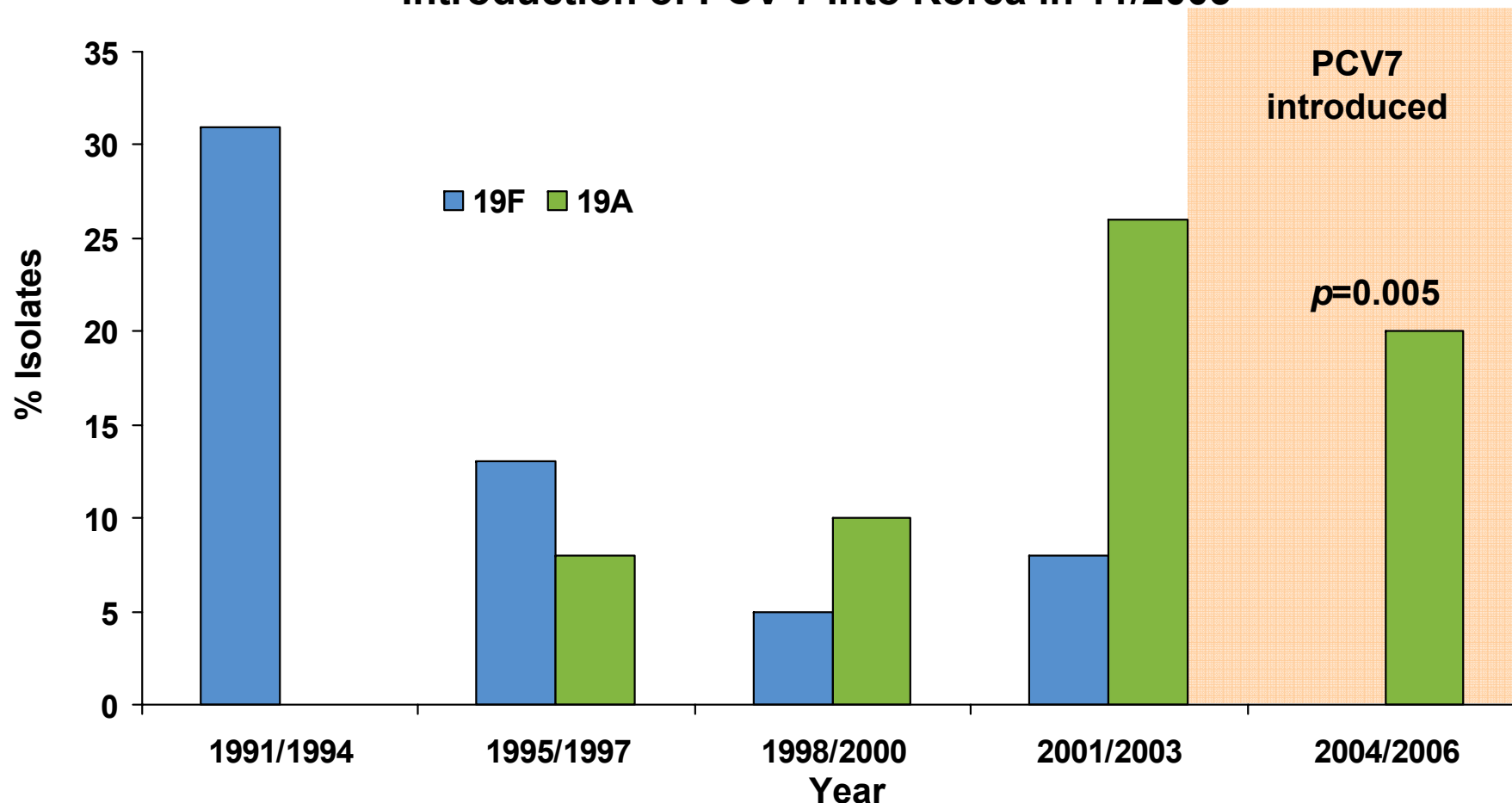


Lack of PCV 7 coverage against serotype 19A, antibiotic resistance, clonal expansion and emergence, and capsular switching have contributed to the emergence of 19A in the U.S.

# Serotype Epidemiology

## Replacement With 19A (Korea)

Increasing Proportion of 19A Isolates in Children <5 Years of Age Prior to Introduction of PCV 7 Into Korea in 11/2003



**A cause-and-effect relationship between PCV 7 and increasing 19A cannot be determined, as evidenced by increased 19A prior to the introduction of PCV 7 in S. Korea**

Choi EH, et al. *Emerg Infect Dis.* 2008;14:275-281.

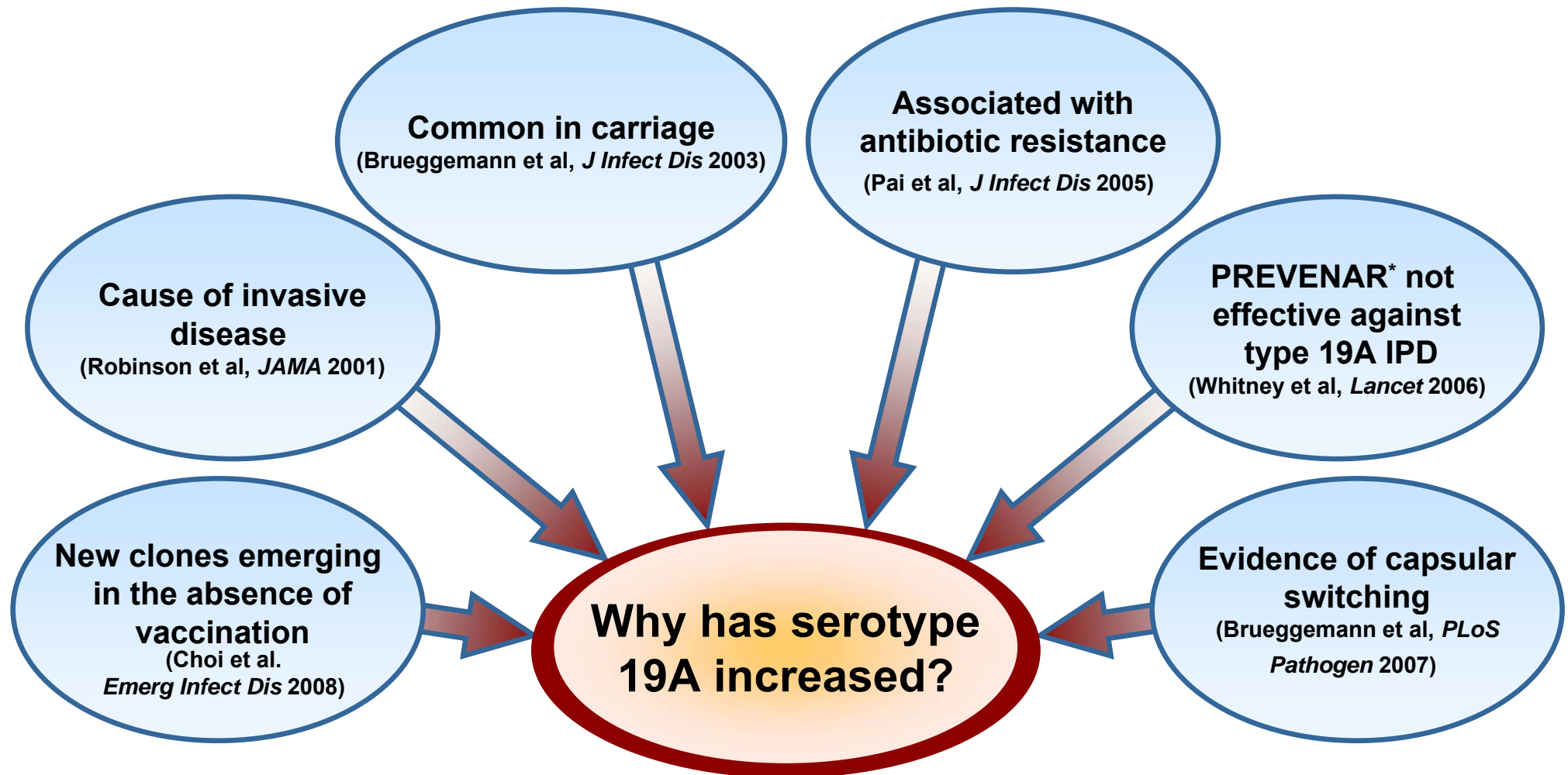
Slide courtesy of Professor Ron Dagan.

\*Trademark

# Serotype Epidemiology

## Factors Contributing to 19A Emergence

Multiple factors contribute to observed increases in serotype 19A disease



# Pneumococcal Conjugate Vaccines

<b>PCV 7</b>	<b>Protein Carrier: CRM<sub>197</sub></b>	<b>4</b>	<b>6B</b>	<b>9V</b>	<b>14</b>	<b>18C</b>	<b>19F</b>	<b>23F</b>				
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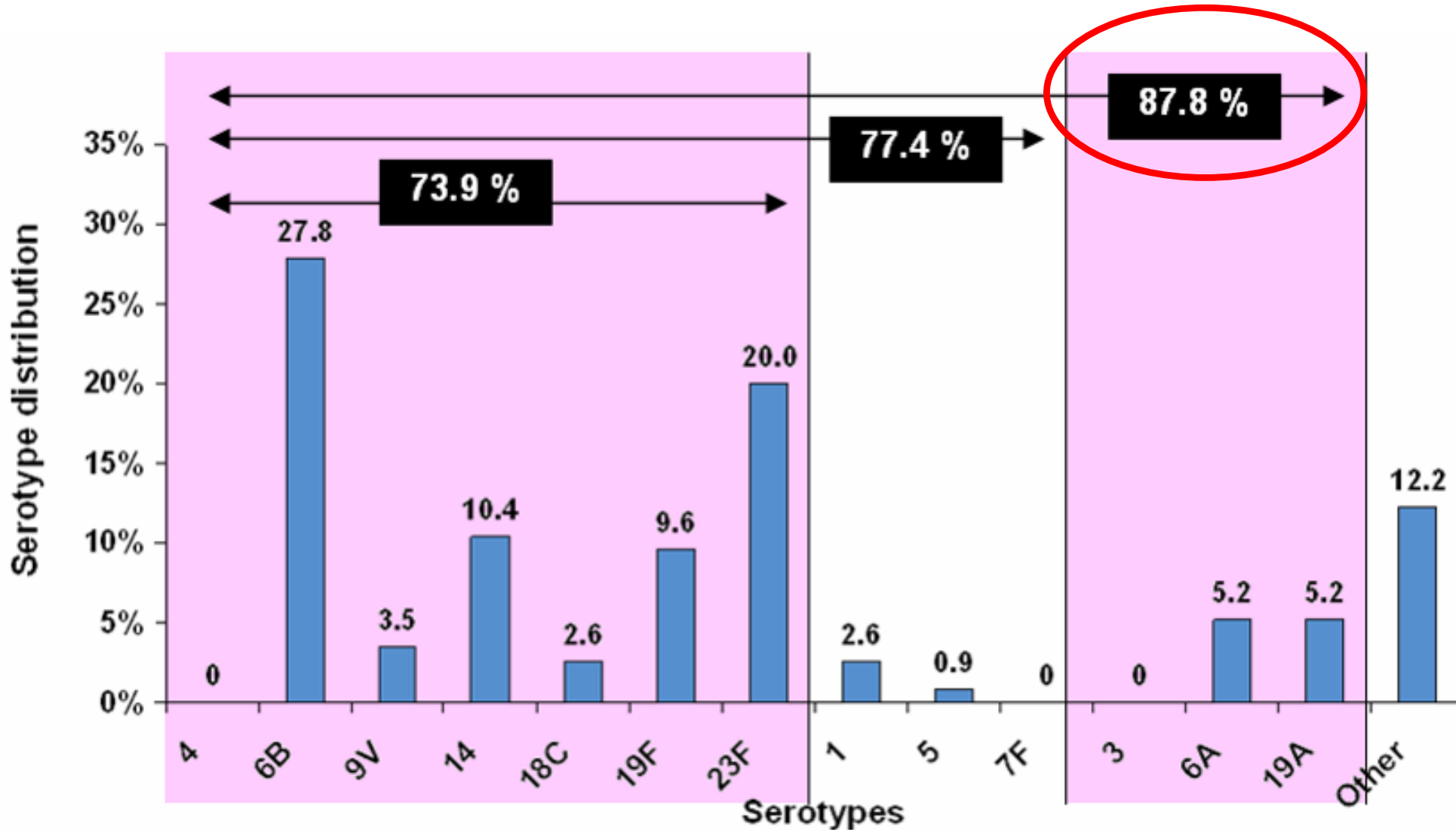
<b>PV10</b>	<b>Protein Carriers:</b> <ul style="list-style-type: none"> <li>• <b>Protein D</b></li> <li>• <b>†Diphtheria toxoid</b></li> <li>• <b>‡Tetanus toxoid</b></li> </ul>	<b>4</b>	<b>6B</b>	<b>9V</b>	<b>14</b>	<b>18C‡</b>	<b>19F†</b>	<b>23F</b>	<b>1</b>	<b>5</b>	<b>7F</b>	
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<b>Investigational PCV 13*</b>	<b>Protein Carrier: CRM<sub>197</sub></b>	<b>4</b>	<b>6B</b>	<b>9V</b>	<b>14</b>	<b>18C</b>	<b>19F</b>	<b>23F</b>	<b>1</b>	<b>5</b>	<b>7F</b>	<b>3</b>	<b>6A</b>	<b>19A</b>
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\*Trademark

1. Pneumococcal 7-valent Conjugate Vaccine (Diphtheria CRM197 Protein) Prevnar® Package Insert. Wyeth Pharmaceuticals Inc.
2. SYNFLORIX Canada Monograph
3. Kieninger D.M. 48th ICAAC/46th IDSA 2008, Abstr # 2638

# Serotype distribution of invasive pneumococcal disease in Thai children under 5 years old (2000-2005, N=115)



# Agenda

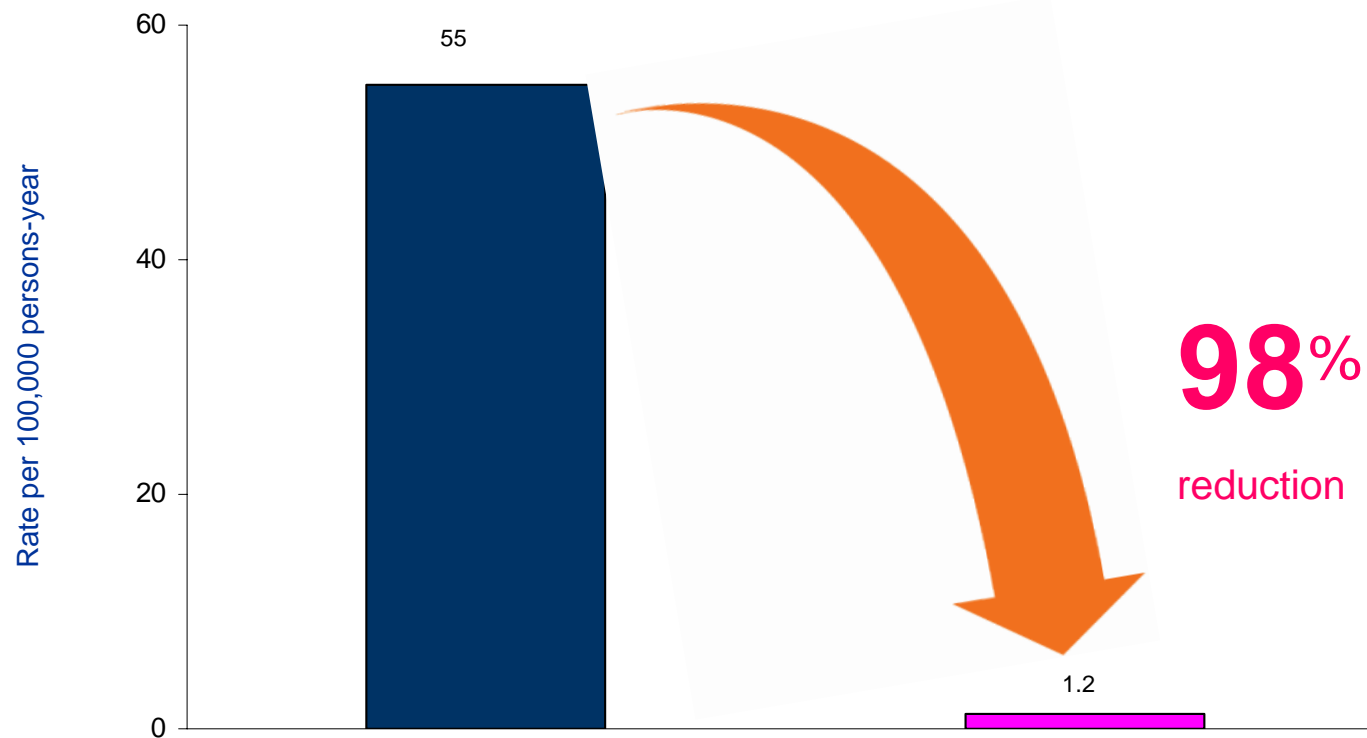
- Pneumococcal Disease back ground
- Serotype epidemiology
- **Efficacy & Effectiveness**
  - ▶ IPD, Pneumonia and AOM
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  - ▶ Antibiotic resistance
- Safety
- Immunogenicity



# Efficacy & Effectiveness

# Effectiveness of PCV7 IPD (U.S.)

Incidence of IPD due to vaccine serotypes in children younger than 2 years of age before and after a routine childhood immunization program with PCV7 <sup>1,16,27</sup>



<sup>1</sup>United States: 2005 vs. prelicensure baseline (1998 to 1999). Prelicensure figure is an average of the annual incidence of IPD in 1998 and 1999.

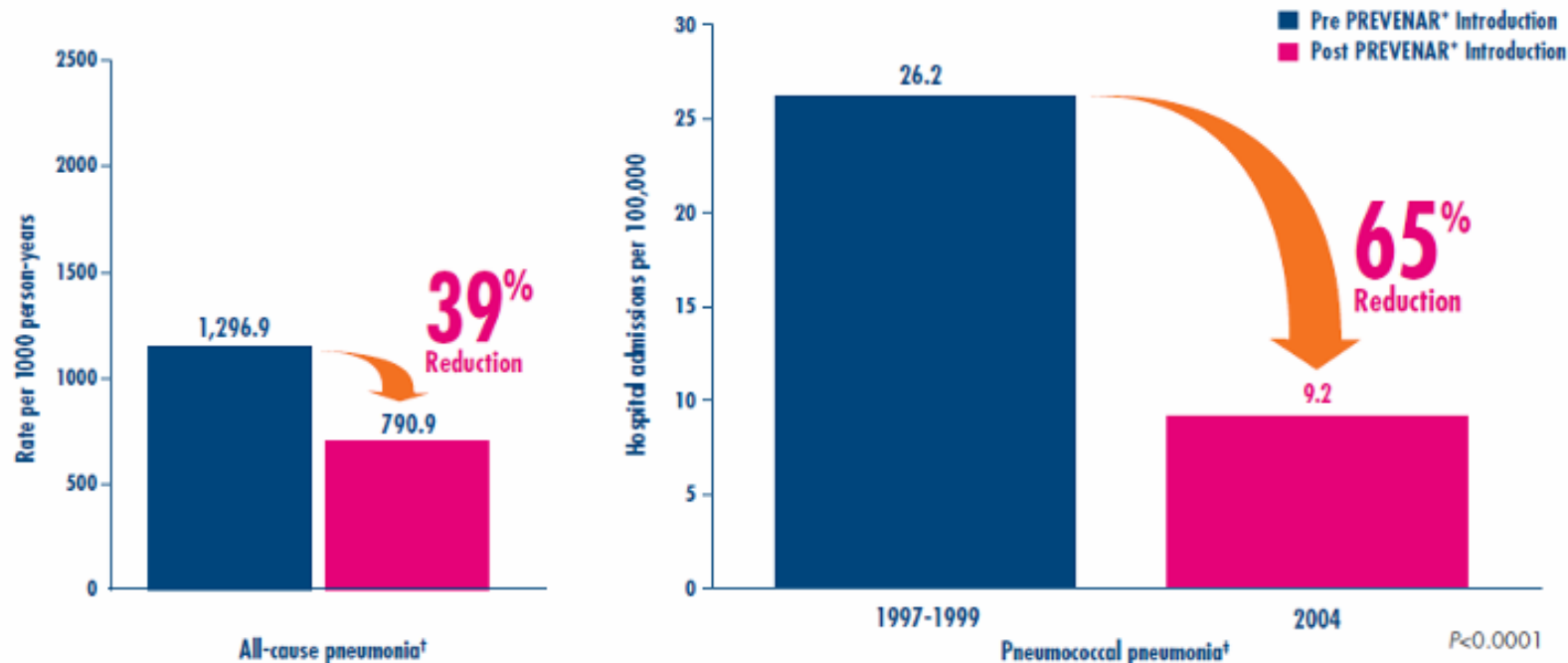
# QUESTION 5

**5. How much annual % reduction in ALL CAUSE PNEUMONIA was observed in the USA after the introduction of PCV 7?**

- A. 25%**
- B. 30%**
- C. 39%**
- D. 45%**
- E. 49%**

# Effectiveness of PCV 7 All Pneumonia & Pneumococcal Pneumonia (U.S.)

Rates of hospital admissions due to pneumonia in children <2 years of age in the United States<sup>23</sup>

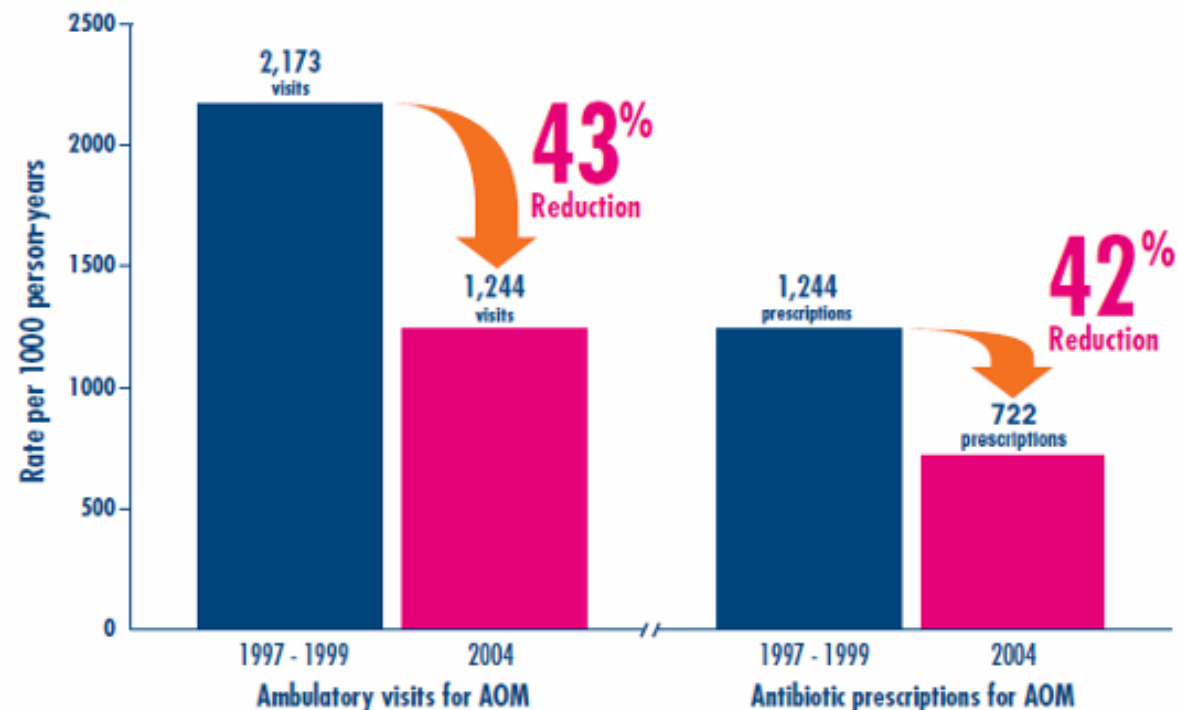


†Based on ICD-9 data.

After the introduction of PREVENAR, there was a 39% annual decline in all-cause pneumonia admissions—representing ~41,000 fewer pneumonia admissions in 2004 in children <2 years of age

# Effectiveness of PCV 7 Acute Otitis Media (USA)

Rates of ambulatory visits and antibiotic prescriptions for AOM in U.S. children <2 years of age<sup>26</sup>



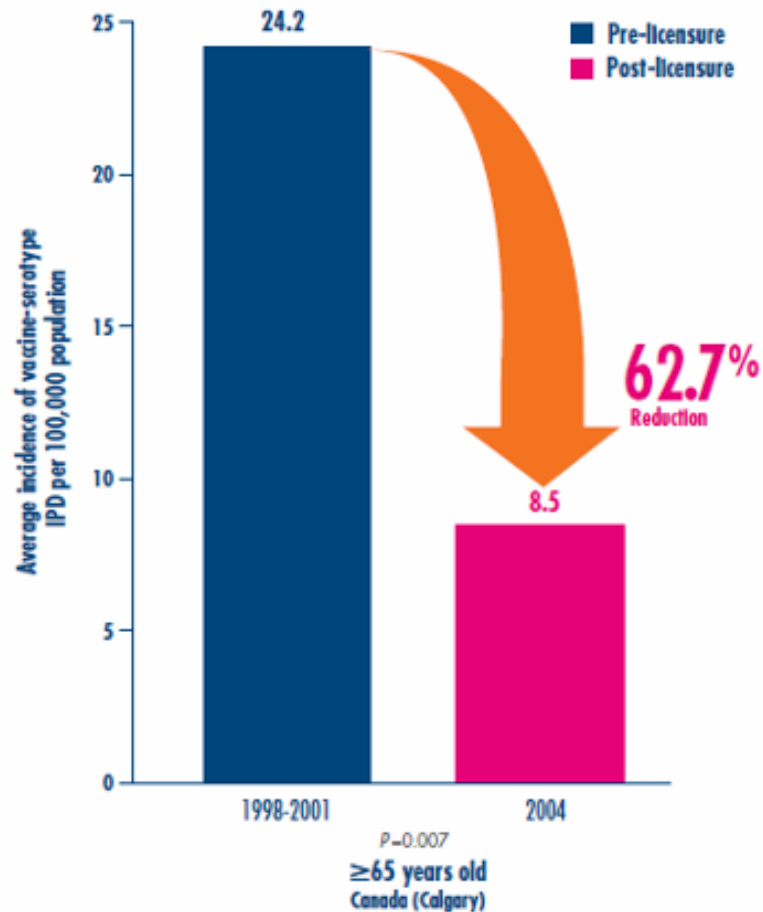
Data from 1997-2004 Market Scan databases, defined by ICD-9 codes.

# Indirect effect

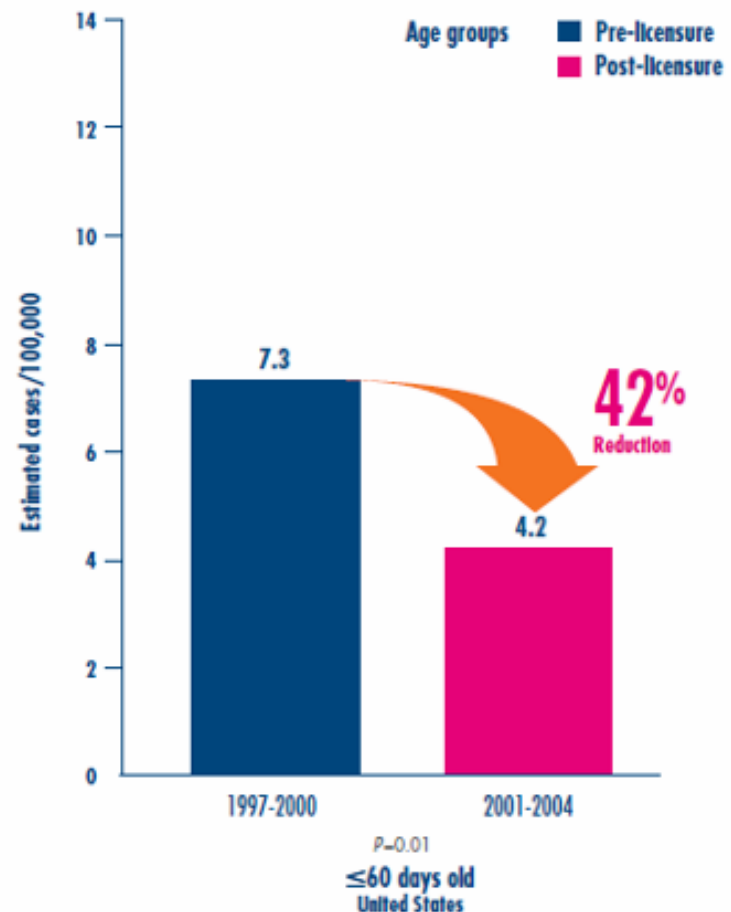
( herd effect )

# Effectiveness of PCV 7 Indirect Effect—IPD (U.S.)

## ADULTS—Reductions in IPD due to vaccine serotypes<sup>20</sup>



## INFANTS—Reductions in IPD due to vaccine serotypes among infants ≤60 days of age<sup>20</sup>



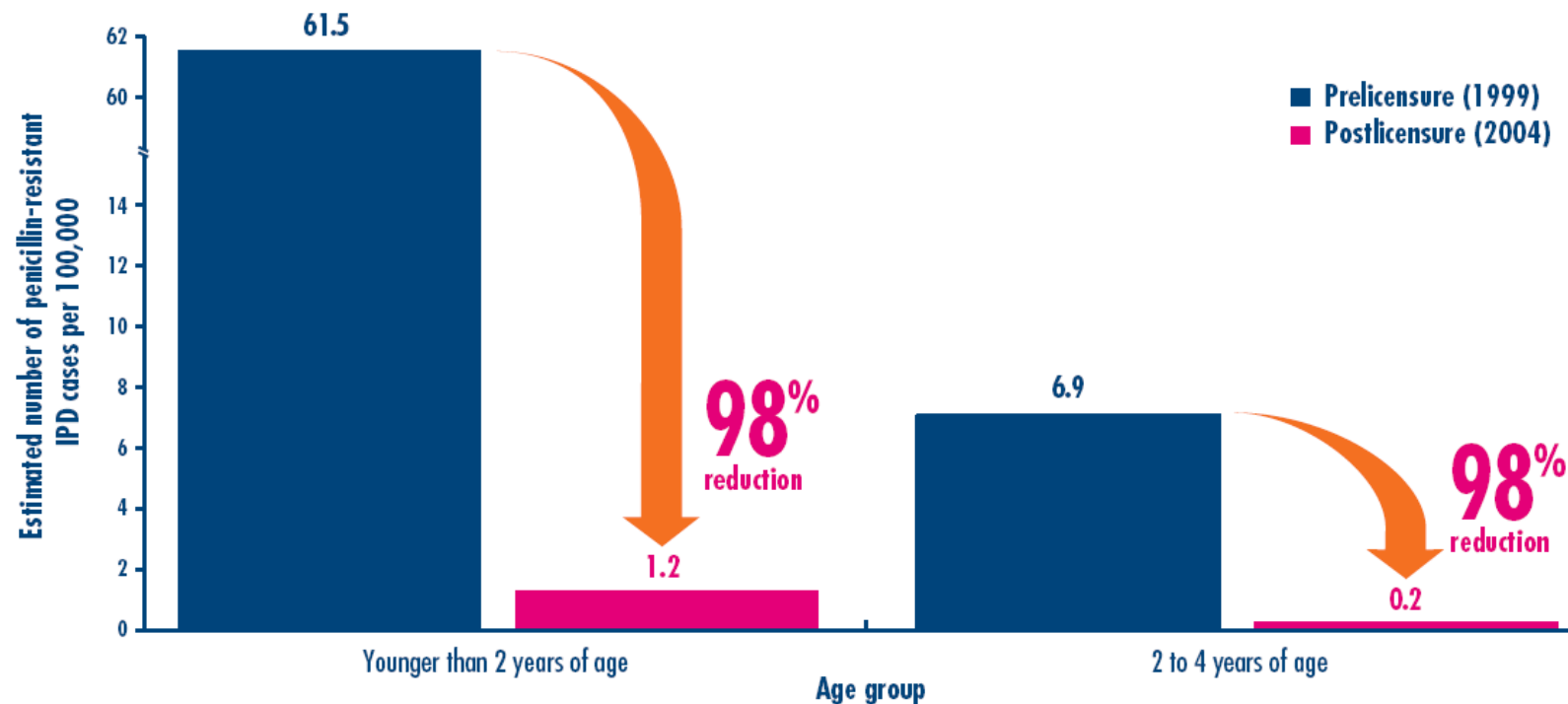
1. Kellner JD, et al. *CMAJ*. 2005;173:1149-1151.
2. Poehling KA, et al. *JAMA*. 2006;295:1668-1674.

# Antibiotic Resistant Reduction



# Effectiveness of PCV 7 antibiotic-resistant IPD

## Significant reductions in penicillin-resistant IPD caused by vaccine serotypes<sup>1†</sup>



<sup>†</sup>Data extrapolated from the Active Bacterial Core surveillance, Emerging Infections Program Network. Results from vaccinated and nonvaccinated populations following the inclusion of PREVENAR into the routine U.S. pediatric immunization schedule.

# Effectiveness of PCV7

## Summary

- **Effectiveness studies have shown that routine use of PCV7 is associated with **significant declines** in:**
  - **IPD rates in all age groups, including neonates, vaccinated children, healthy adults, and the elderly**
  - **All-cause pneumonia admissions in children younger than 2 years of age**
  - **Pneumonia-related health care utilization in children younger than 2 years of age**
  - **Rates and adverse outcomes of AOM**
  - **Rate of antibiotic-resistant pneumococcal infections in young children and older adults**

# Agenda

- Pneumococcal Disease back ground
- Serotype epidemiology
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- Immunogenicity

# Safety of PCV7

Children in Clinical Studies <sup>1</sup>	Children in Post-licensure Safety Studies <sup>1</sup>
N=18,168	N=162,305

- **PCV7 has a well-documented safety profile<sup>2</sup>**
  - ▶ **Post-licensure safety studies with more than 160,000 children<sup>2</sup>**
- **In clinical studies, the most frequently reported adverse events included**
  - ▶ **Injection site reactions**
  - ▶ **Fever ( $\geq 38^{\circ}$  C/ $100.4^{\circ}$  F)**
  - ▶ **Irritability, drowsiness, restless sleep,**
  - ▶ **Decreased appetite, vomiting, diarrhea**
  - ▶ **Rash**
- **Contraindications to vaccine:**
  - ▶ **Hypersensitivity to any vaccine component, including diphtheria toxoid**

1. Wyeth Pharmaceuticals, data on file.

2. Wyeth, SMPC.

# Safety of PCV7

**Long-term safety over 200 million doses distributed worldwide**

# Agenda

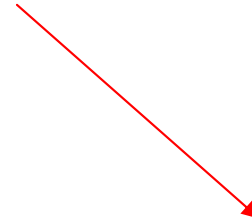
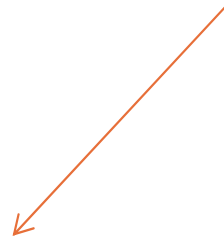
- Disease Background
- Pneumococcal Conjugate Vaccine
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# Immunogenicity

# Immunogenicity

## ELISA

(Enzyme-linked immunosorbent assay)



**GMC**  
(Geometric Mean Concentration)

**% Achieving IgG Antibody Concentration**

**> 0.35 µg/ml**

**> 0.2 µg/ml**

WHO recommends that the licensure and the efficacy of future PCVs be assessed on their ability to achieve noninferiority to the licensed pneumococcal vaccine, based on the 0.35 µg/mL reference standard



# Immunogenicity

## OPA

( Opsonophagocytic activity )

**GMT**  
( Geometric Mean Titer )

**OPA reciprocal of serum  
dilution to  $\geq 50\%$  killing ( $\geq 8$ )**

# OPA Post Primary Series (2, 3, 4 months)

	% Achieving $\geq 8$		GMTs		
	PCV10	PCV 7	PCV10	PCV7	% Difference**
1					
4	99.6	100	734.9	1,010.4*	73
5					
6B	92.4	95.5	457.4	999.4*	46
7F					
9V	100	100	1,399.7	1,233.3	88
14	99.6	98.9	1,061.0	1,890.6*	56
18C	93.6	95.5	130.1	212.3*	61
19F	87.7	92.1	148.6^	52.0	35
23F	93.9	97.7	1,010.0	4,412.9*	23

\*\*example: for serotype 4 the PCV10's OPA GMTs are 73% of those elicited by Prevenar

**Discussion states that despite not meeting non-inferiority for serotypes 6B and 23F, OPA responses >92%, fails to mention that OPA responses (% > 8 and GMTS) were lower in the PCV10 group and GMTs were significantly lower**

**\*Prevnar elicited significantly higher OPA GMTs for 5 of the 7 common serotypes**

**^PCV10 elicited significantly higher OPA GMTs for serotype 19F**

# OPA Post Booster (2, 3, 4 & 12-18 months)

	% Achieving $\geq 8$	
	PCV10	PCV7
1	91.0	3.6
4	100	100
5	96.3	1.2
6B	96.6	98.7
7F	99.7	31.1
9V	100	100
14	100	100
18C	99.7	100
19F	94.9	92.5
23F	99.7	98.8

GMTs		
PCV10	PCV7	% Difference*
192.2	4.3	-
1,856.3	2,812.6*	65
144.1	4.1	-
981.2	3,459.6*	28
330.3	25.2	-
2,343.5	5,357.4*	44
2,085.9	2134.2	98
810.3	968.7*	84
624.3^	287.8	46
2,830.1	13,900.7*	20

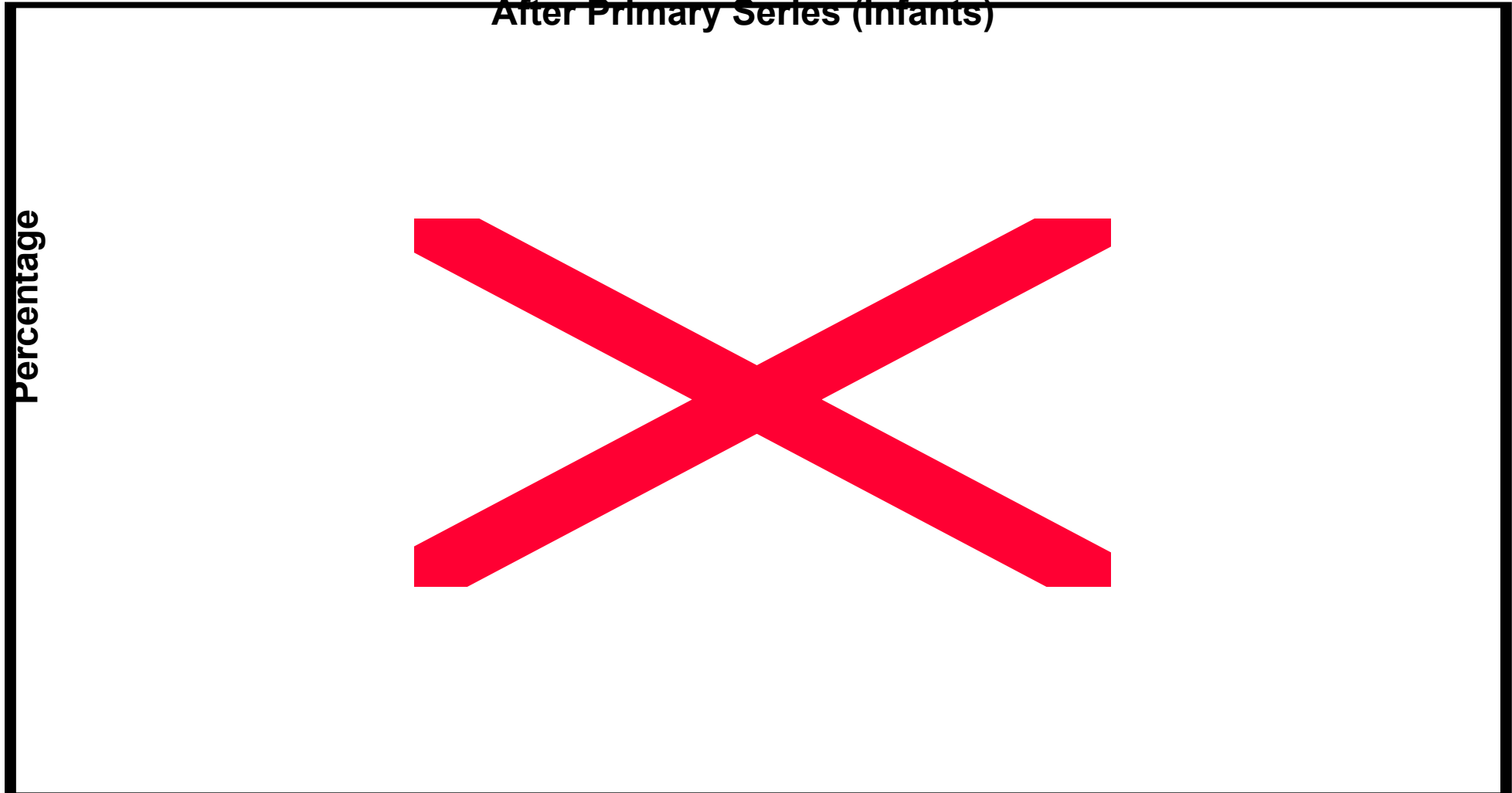
\*PCV 7 elicited significantly higher OPA GMTs for 5 of the 7 common serotypes

^PCV10 elicited significantly higher OPA GMT for serotype 19F

# Transition Recommendations

# Post-Infant Series Immunogenicity Data, Pivotal Non-inferiority German Trial

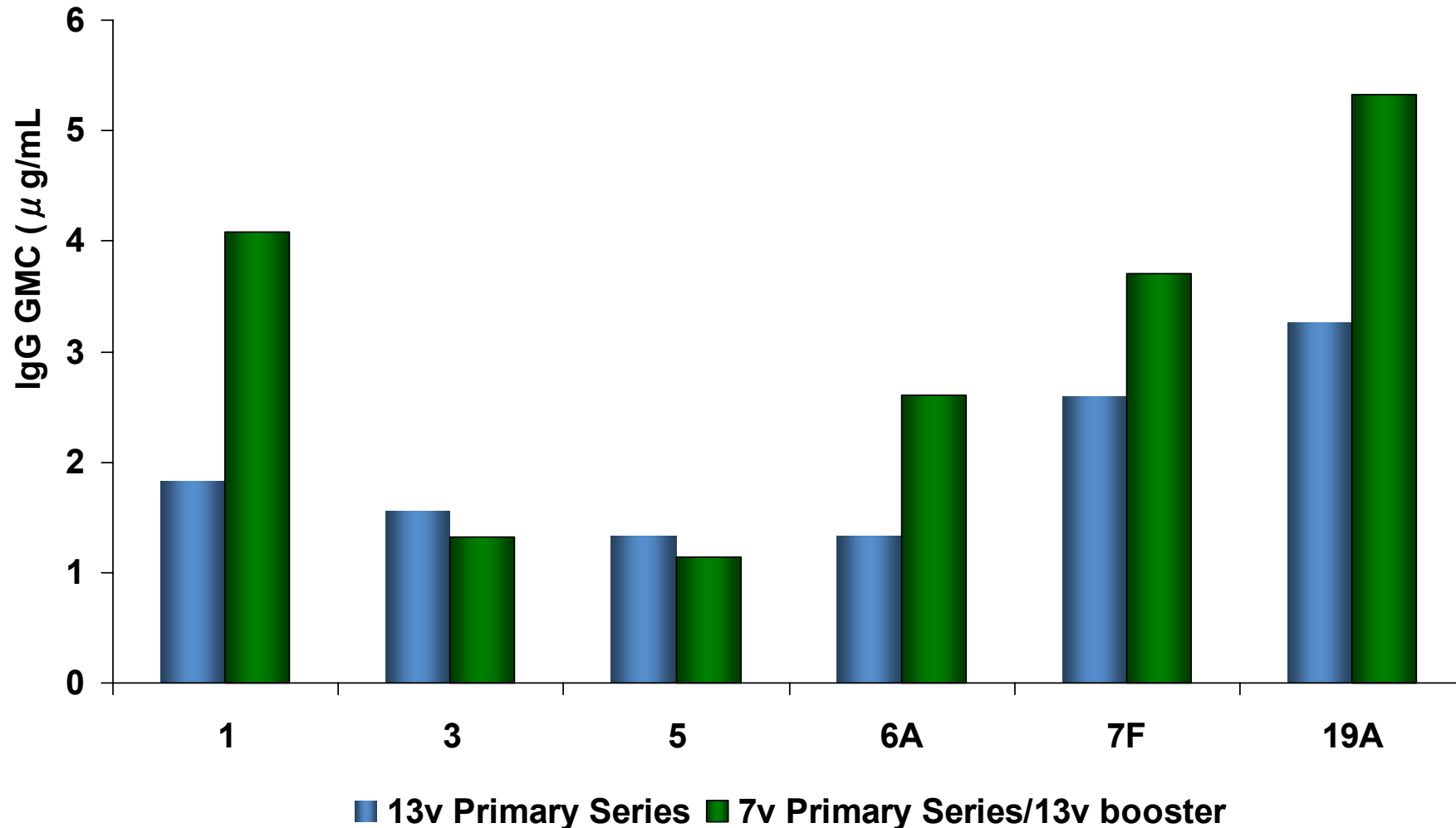
Subjects Achieving a Pneumococcal IgG Antibody Concentration  $\geq 0.35 \mu\text{g/mL}$   
After Primary Series (Infants)



\*Study 6096A1- 006 (Germany)

# Transition: 3 Doses of PCV13 in Infants vs. 1 Dose of PCV13 in Toddlers for the Six New Serotypes

## Pneumococcal Anti-capsular Polysaccharide IgG Antibody GMC



# Transition from PCV7 to PCV13

**PCV13 provides broader serotype coverage and is built on the proven efficacy and well documented effectiveness and safety profile of PCV7**

## Proposed Recommendations:

- Children who have begun immunization with PCV7 may complete immunization by switching to PCV13
- Children who have completed the primary series with PCV7 should receive a single dose of PCV13 in the second year of life
- Children who have received the primary/booster with PCV7 should receive a single dose of PCV13 for new serotype catch-up
  - ▶ **Safety data on receipt of more than 4 doses of CRM-based PCV is being collected**

Regional	PCV Available	NIP	Regional	PCV Available	NIP	Regional	PCV Available	NIP	
North America	Canada	x	Europe	Austria		Asia	Bahrain	x	
	Mexico	x		Belgium	x		Brunei		
	United States	x		Bulgaria			China		
Central America	Aruba			Croatia			Sep 09	Hong Kong	x
	Bahamas			Cyprus	x		India		
	Barbados	x		Czech Republic	x		Indonesia		
	Cayman Islands			Denmark	x		Israel	x	
	Costa Rica	x		Estonia			Jordan		
	Curacao			Finland			Korea		
	Dominican Republic			France	x		Kuwait	x	
	El Salvador			Germany	x		Lebanon		
				Greece	x		Mexico	x	
								x	
							x		
South America	Argentina			Luxembourg	x			Syria	
	Brazil			Malta				Taiwan	
	Bermuda	x		Netherlands	x			Thailand	
	Botswana		Norway	x		United Arab Emirates	x		
	Chile		Poland		Australia	Australia	x		
	Colombia		Portugal			New Zealand	x		
	Ecuador		Romania		Africa	Kenya			
	Peru	x	Slovenia			Mauritius			
	Uruguay	x	Slovak Republic	x		Morocco			
	Venezuela	x	Spain	x		Namibia			
			Sweden	x		South Africa	x		
			Switzerland	x		Tunisia			
			Turkey	x					
		United Kingdom	x						

**Now Available in 97 countries**  
**Established NIP 41 countries**



# KEY MESSAGES

- 1. Pneumococcal Disease is the top killer of infants and children below 5 years in the world today.**
- 2. Prevention of Pneumococcal Disease both in vaccinated and unvaccinated (herd immunity) can be achieved and supported by evidences of safety, immunogenicity and efficacy studies.**
- 3. Surveillance for serotype distribution in each country will help monitor efficacy and effectiveness of vaccination with PCVs.**
- 4. There is a need for global efforts to raise awareness on pneumococcal disease to improve child survival**

**Thank you**