



# 2018 Status of PCV Use and Impact

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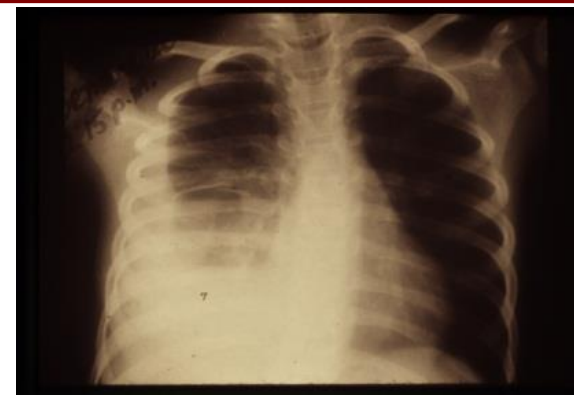


EVIDENCE > POLICY > ACCESS

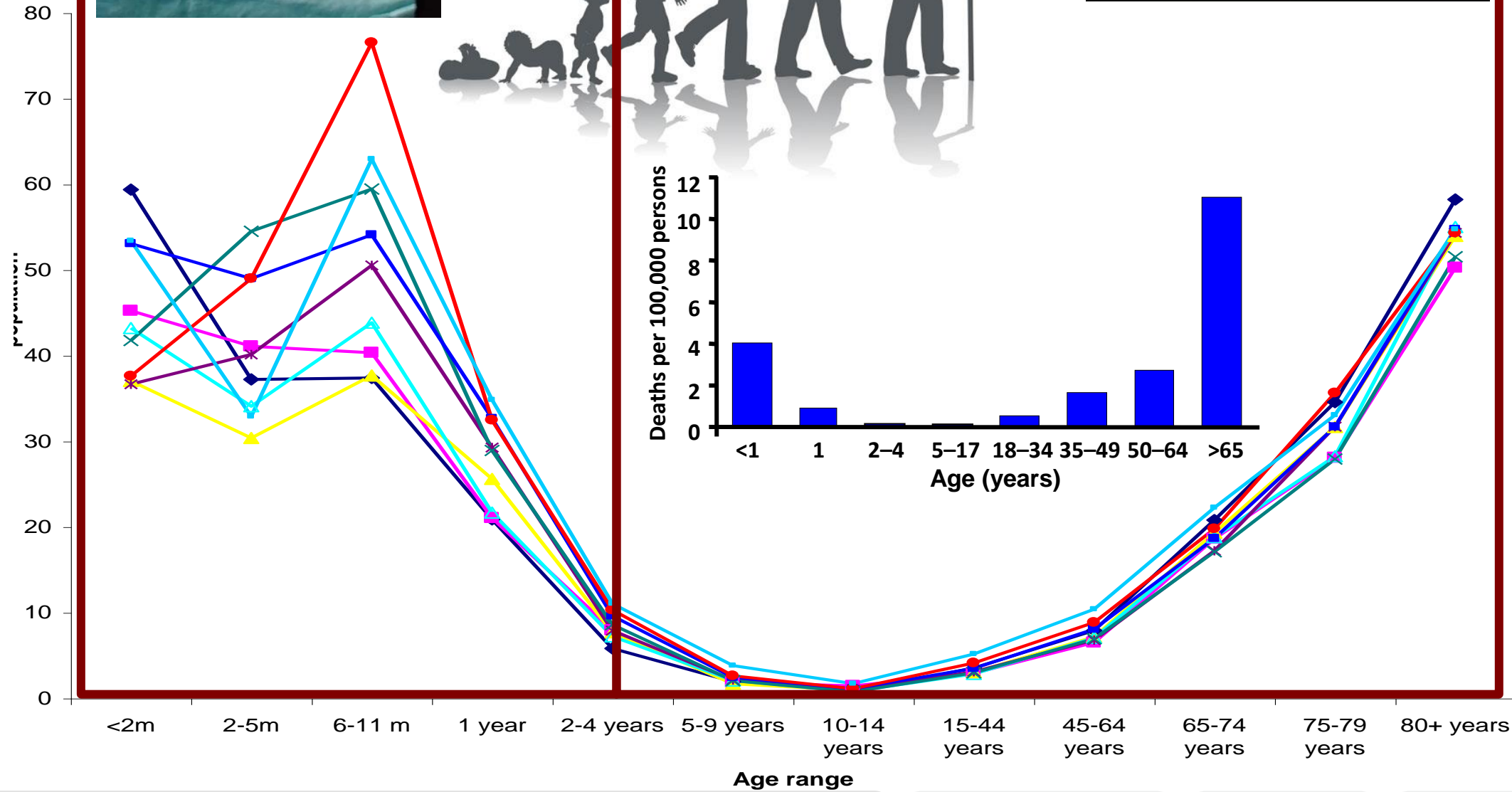
# Overview

1. Epidemiology, burden of disease
2. Current status of global introduction
3. Impact of PCVs
  - Products
  - Interchangeability
  - Serotype replacement
4. Gaps in understanding impact

**.....in 15 minutes**



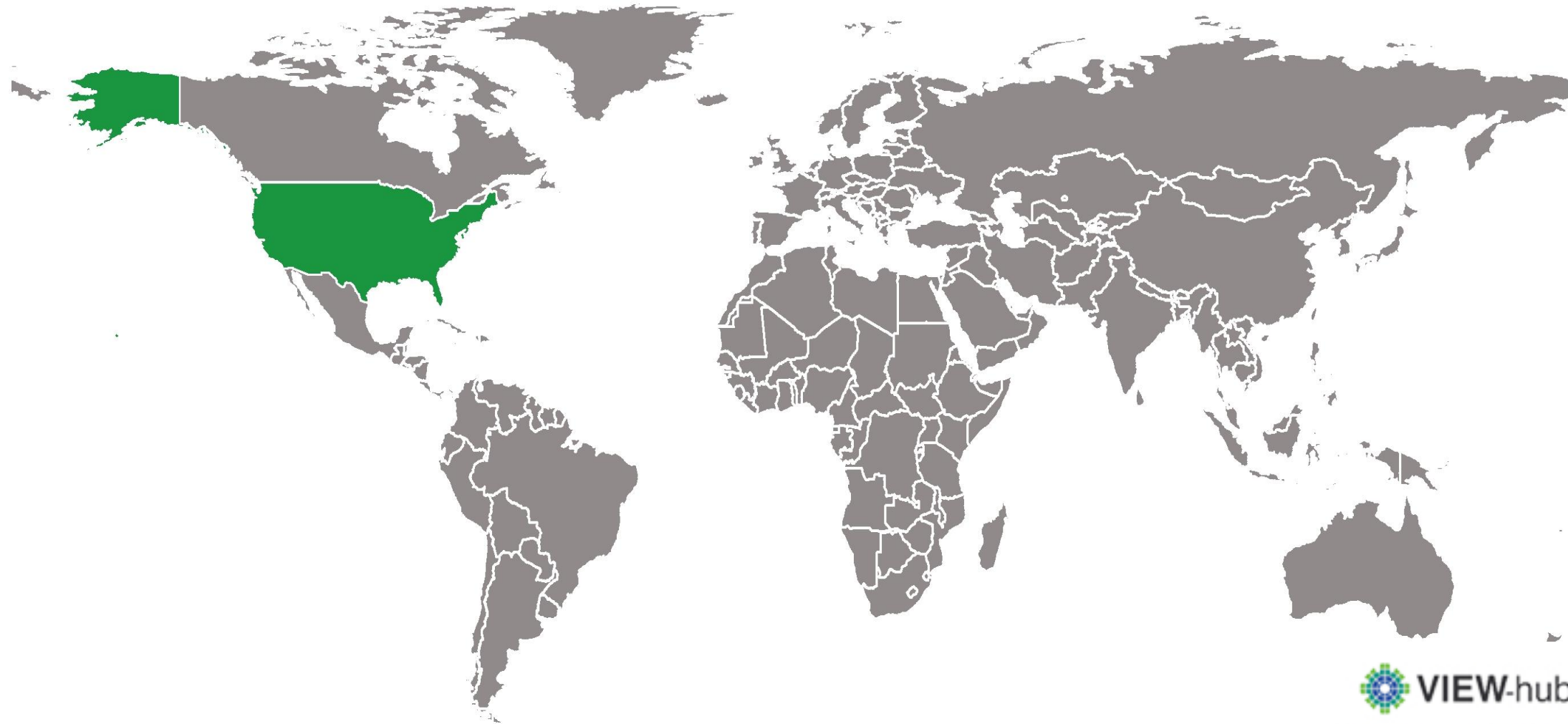
Rate per 100,000





# PCV in 2000

## 1 Country

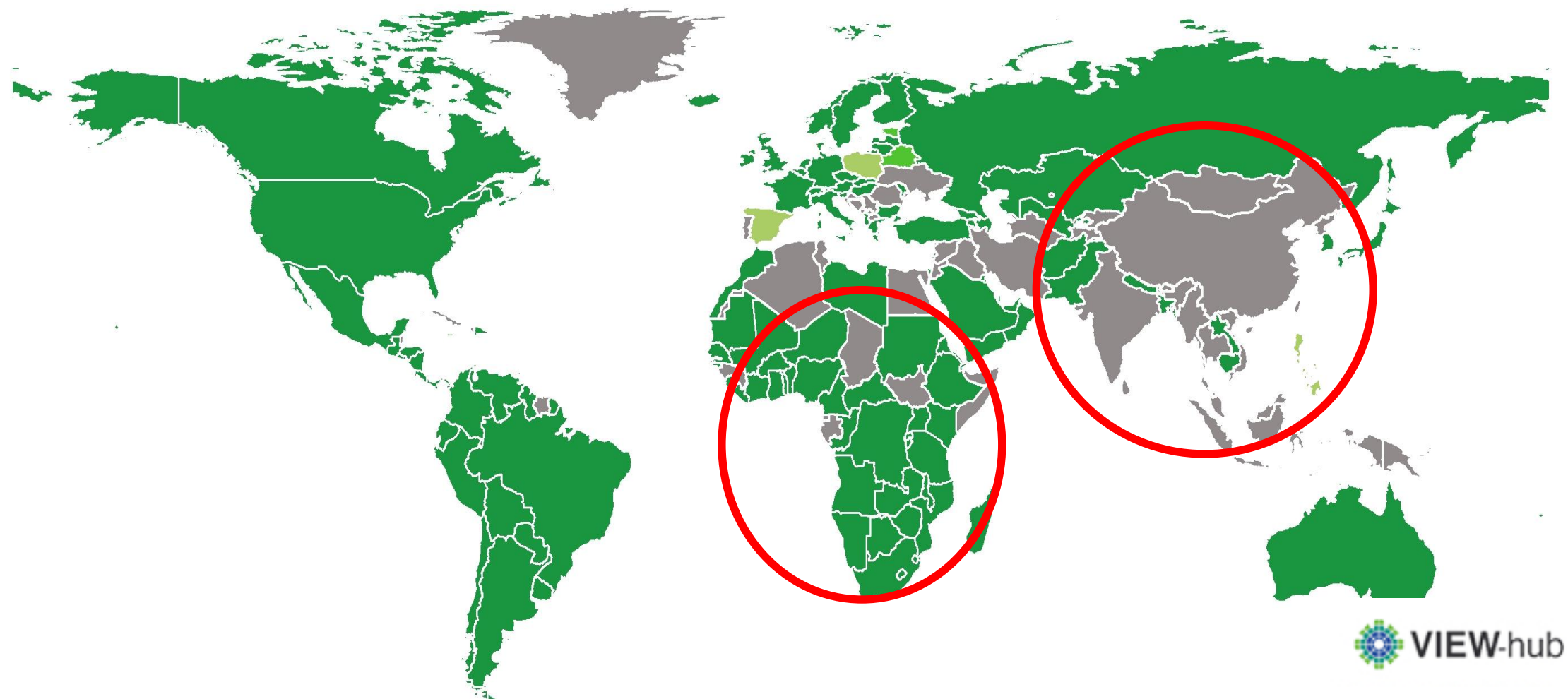


# Pneumococcal conjugate vaccine (PCV) 2000 (PCV7)----- 2009 (PCV10/13)



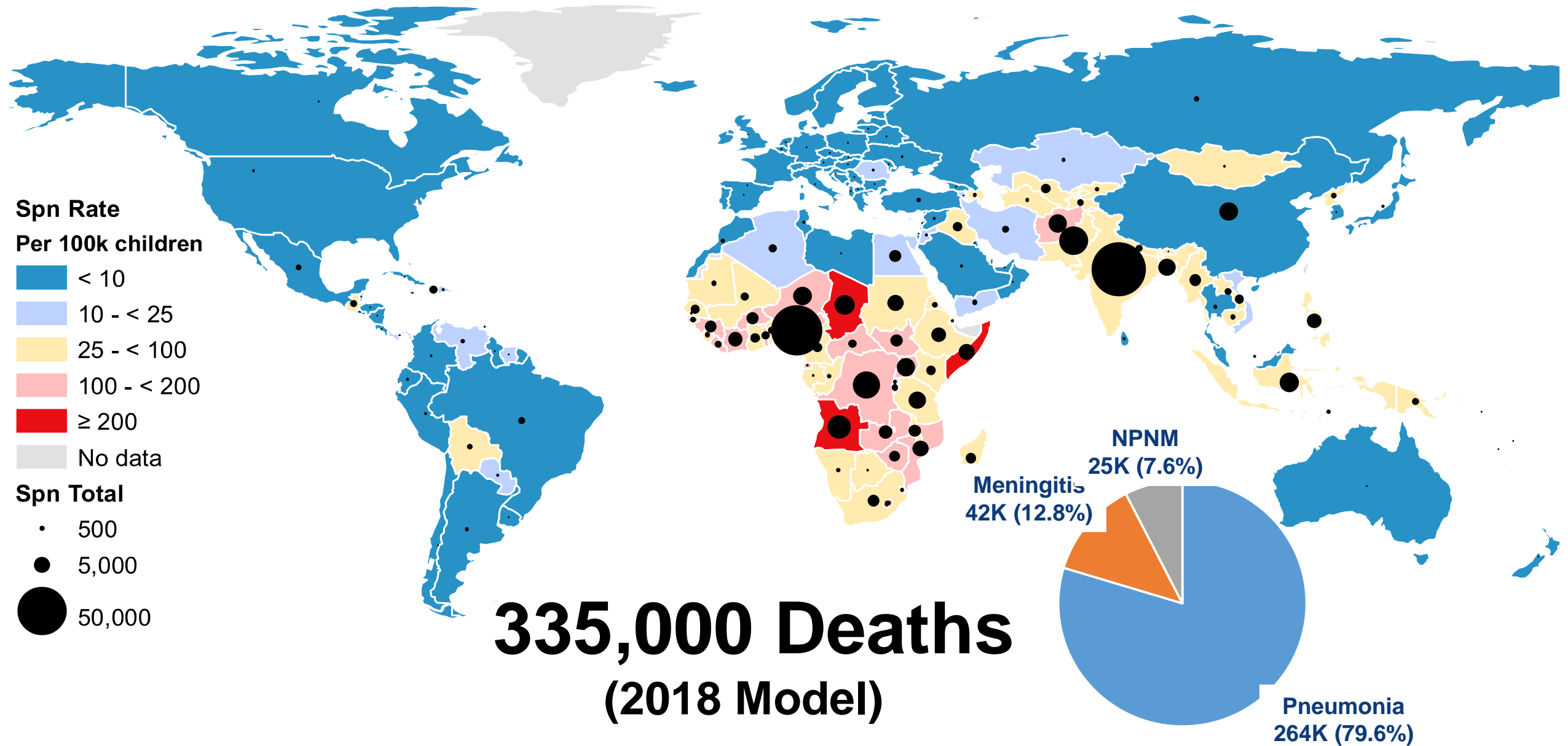
# PCV in 2015

## 134 Countries



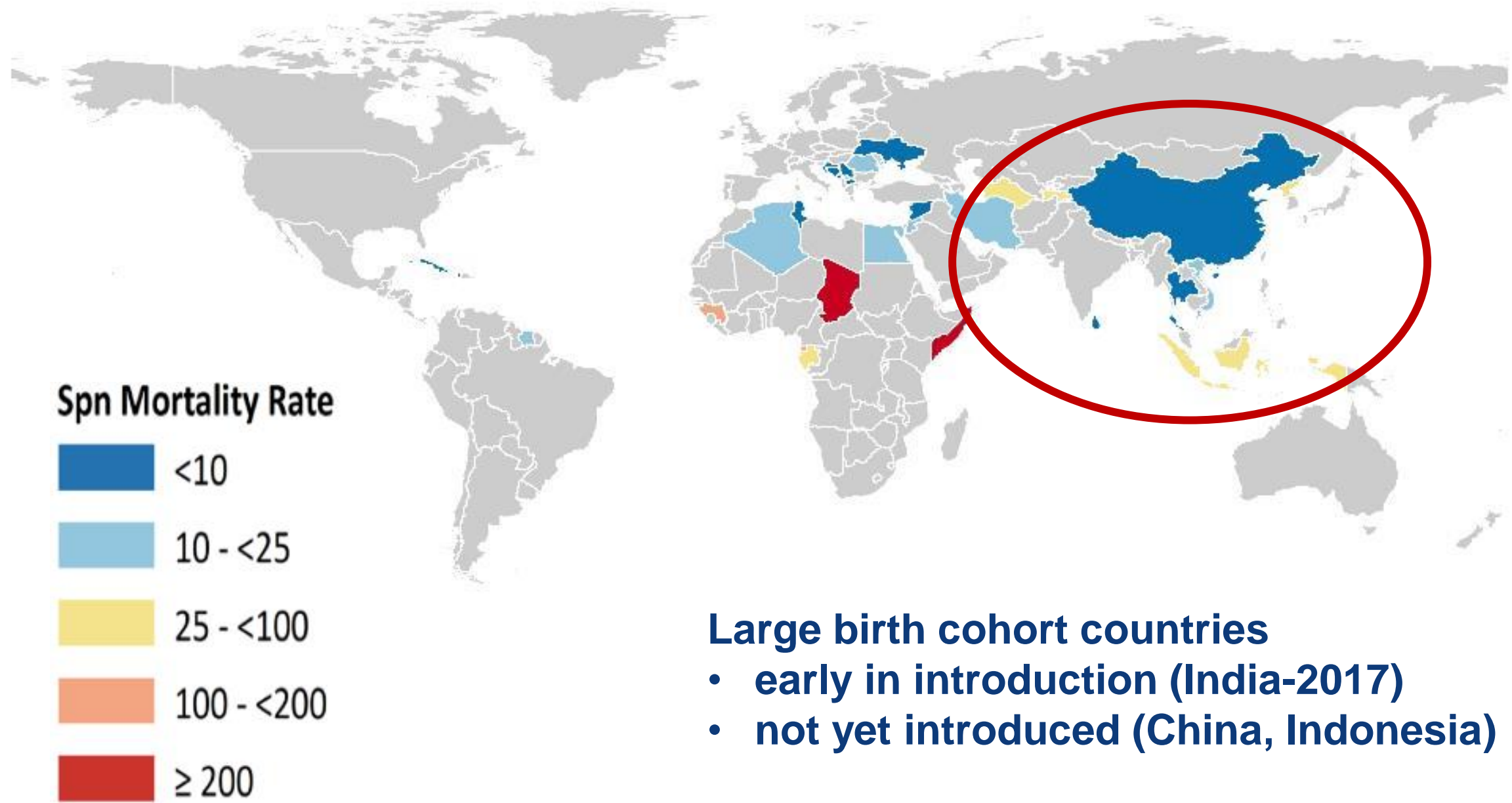
# Pneumococcal mortality rate and absolute deaths

## Children 1-59 mo, 2015



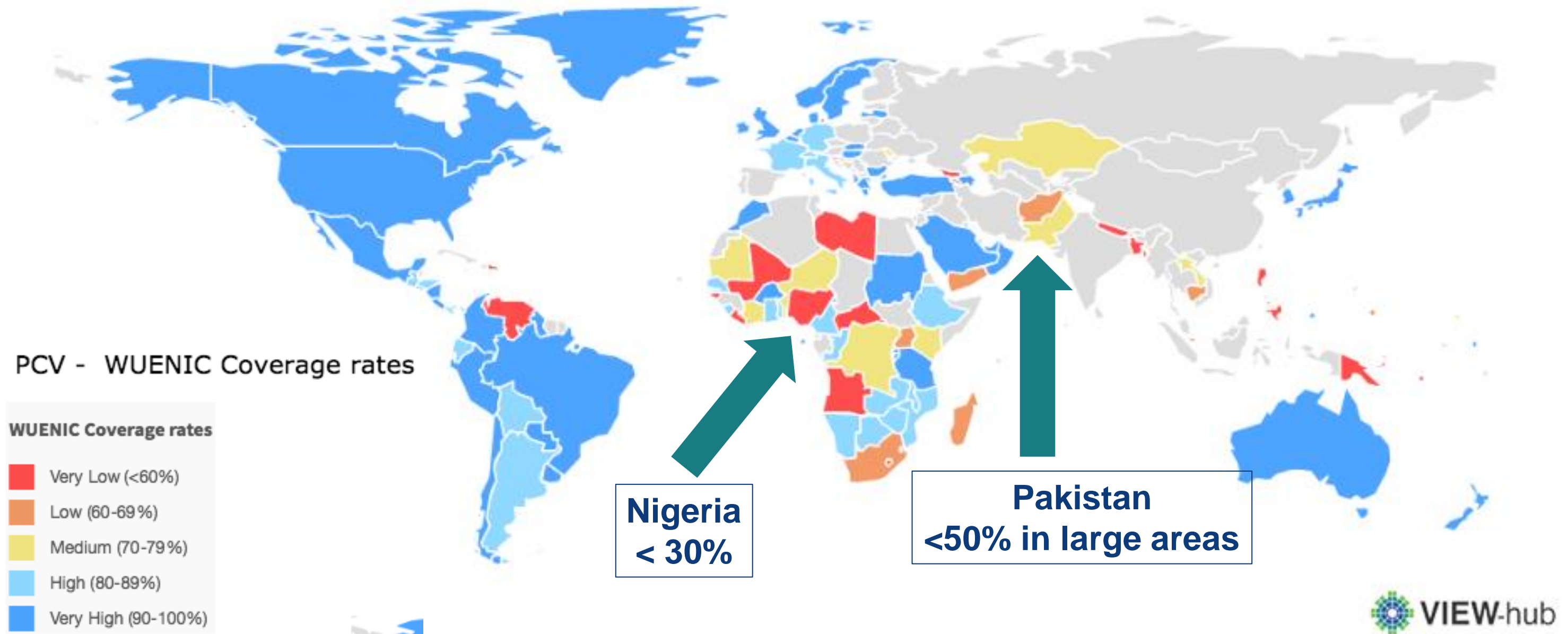


# Few countries without PCV by 2018





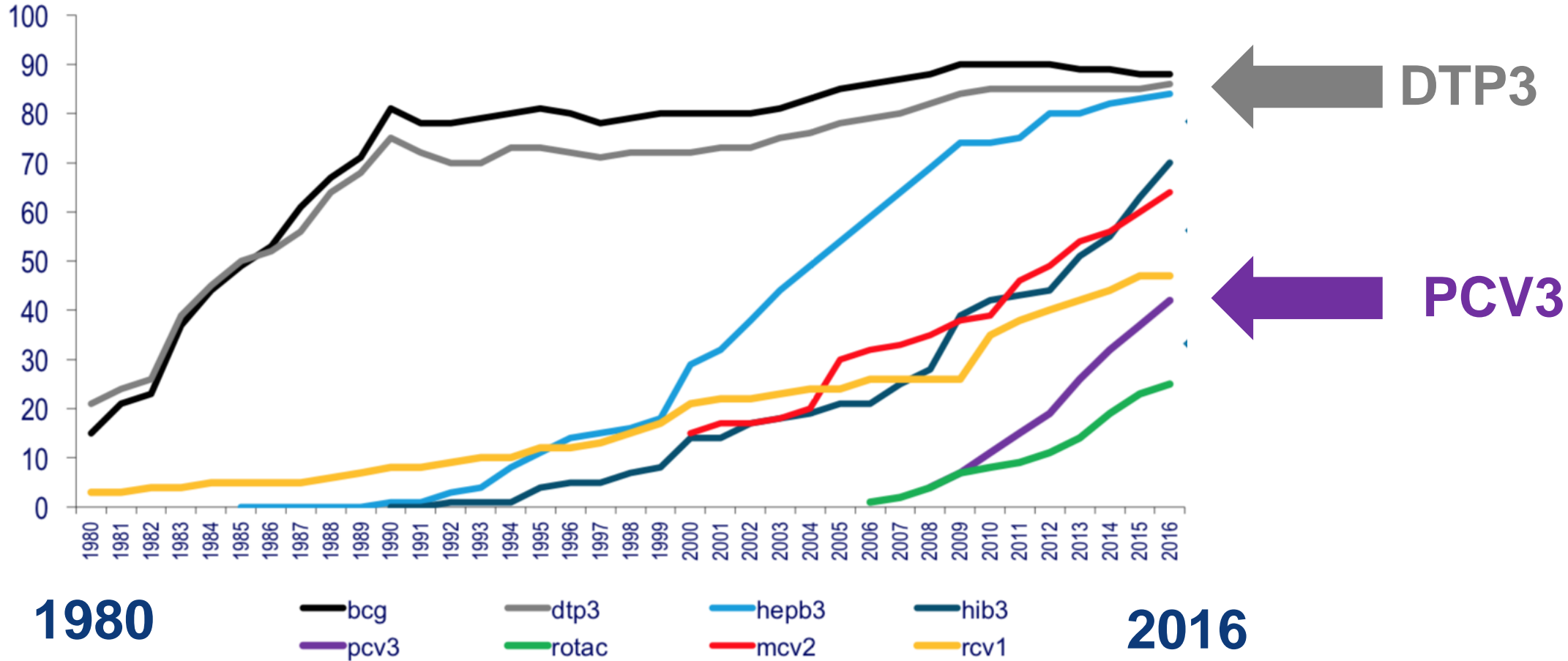
# Even in countries using PCV, coverage is incomplete (2015)



Source: IVAC, accessed June 11, 2017. Exported from [www.VIEW-hub.org](http://www.VIEW-hub.org).

# 2016 Global PCV3 Coverage Well Below DTP3

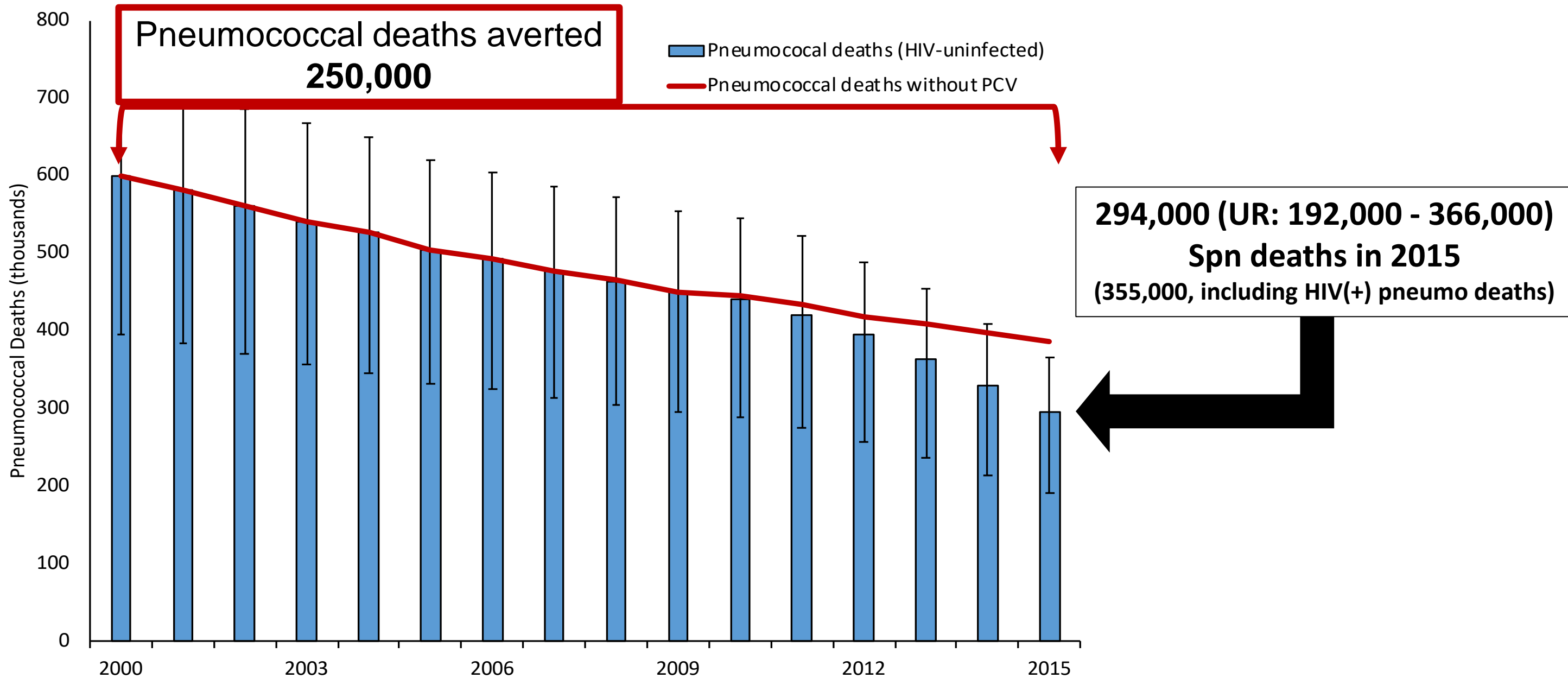
% Coverage



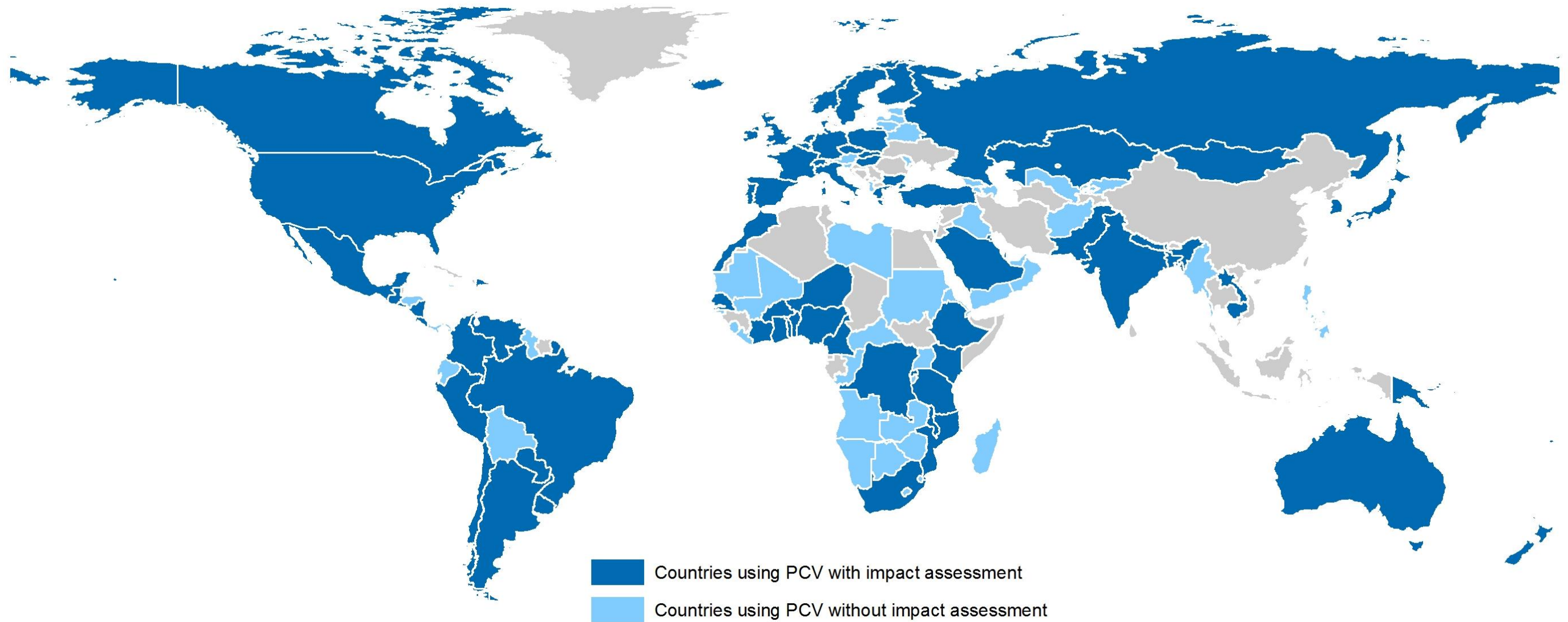
1980

2016

# Pneumococcal deaths have been falling PCV has accelerated that pace 2000 - 2015



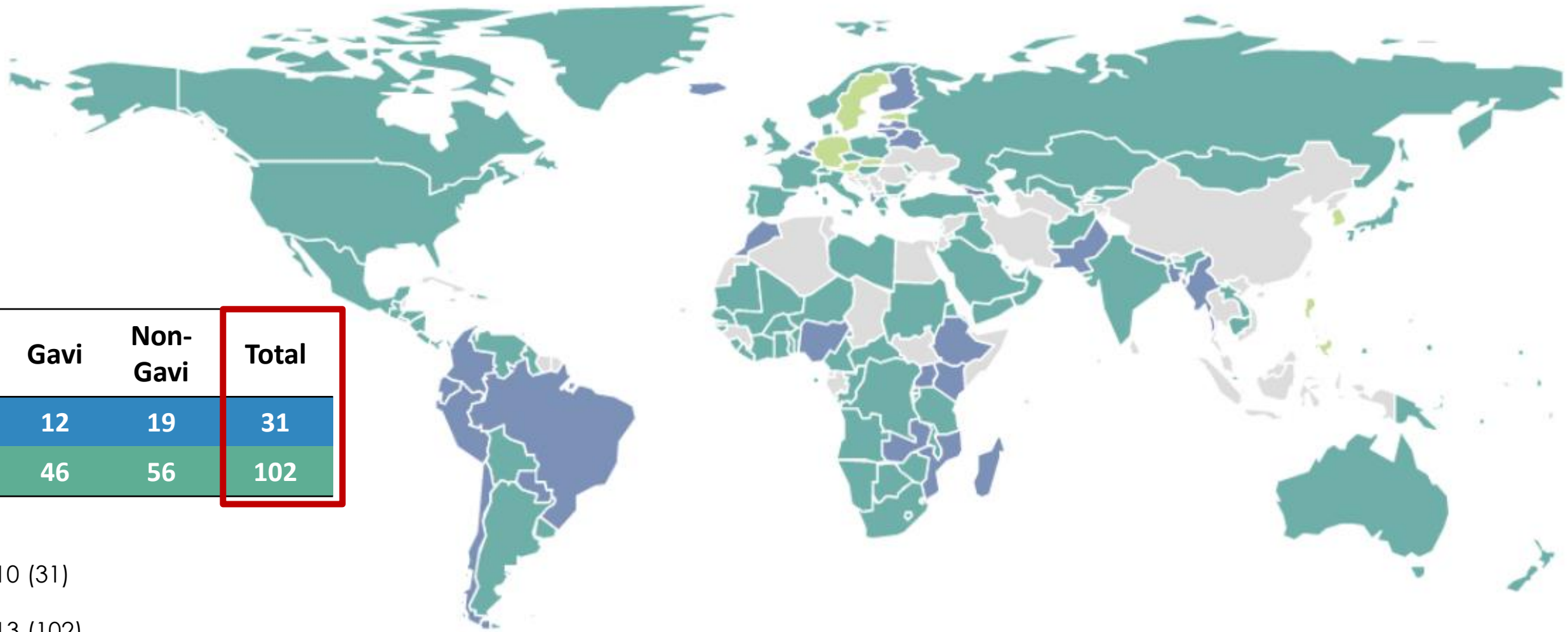
# PCV Countries with Impact Studies (March 2018)





# PCV Product Use, Globally

(March 2018)

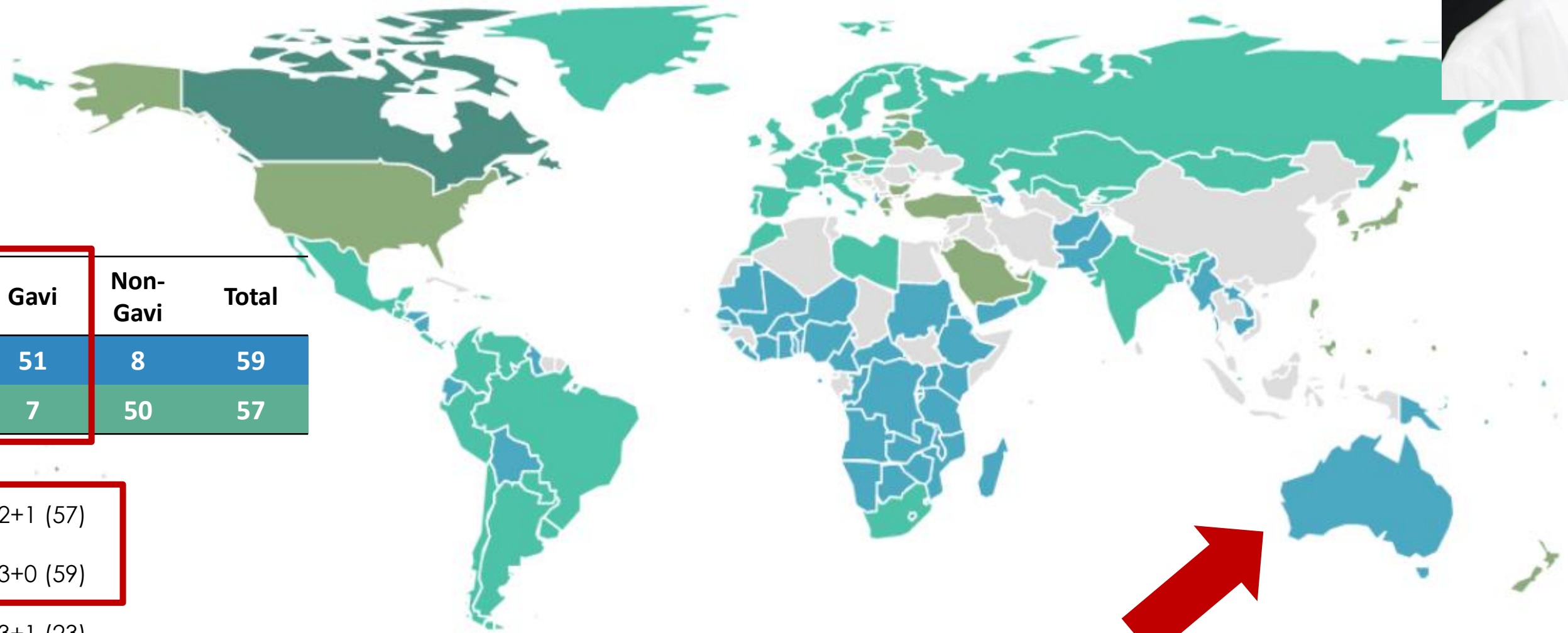


Product	Gavi	Non-Gavi	Total
PCV10	12	19	31
PCV13	46	56	102

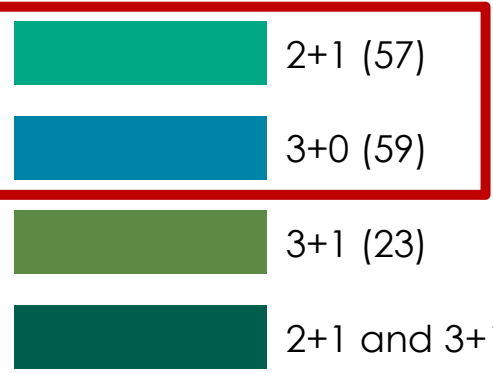
- PCV10 (31)
- PCV13 (102)
- PCV10 and PCV13 (8)

# PCV Dosing Schedule, Globally

(March 2018)



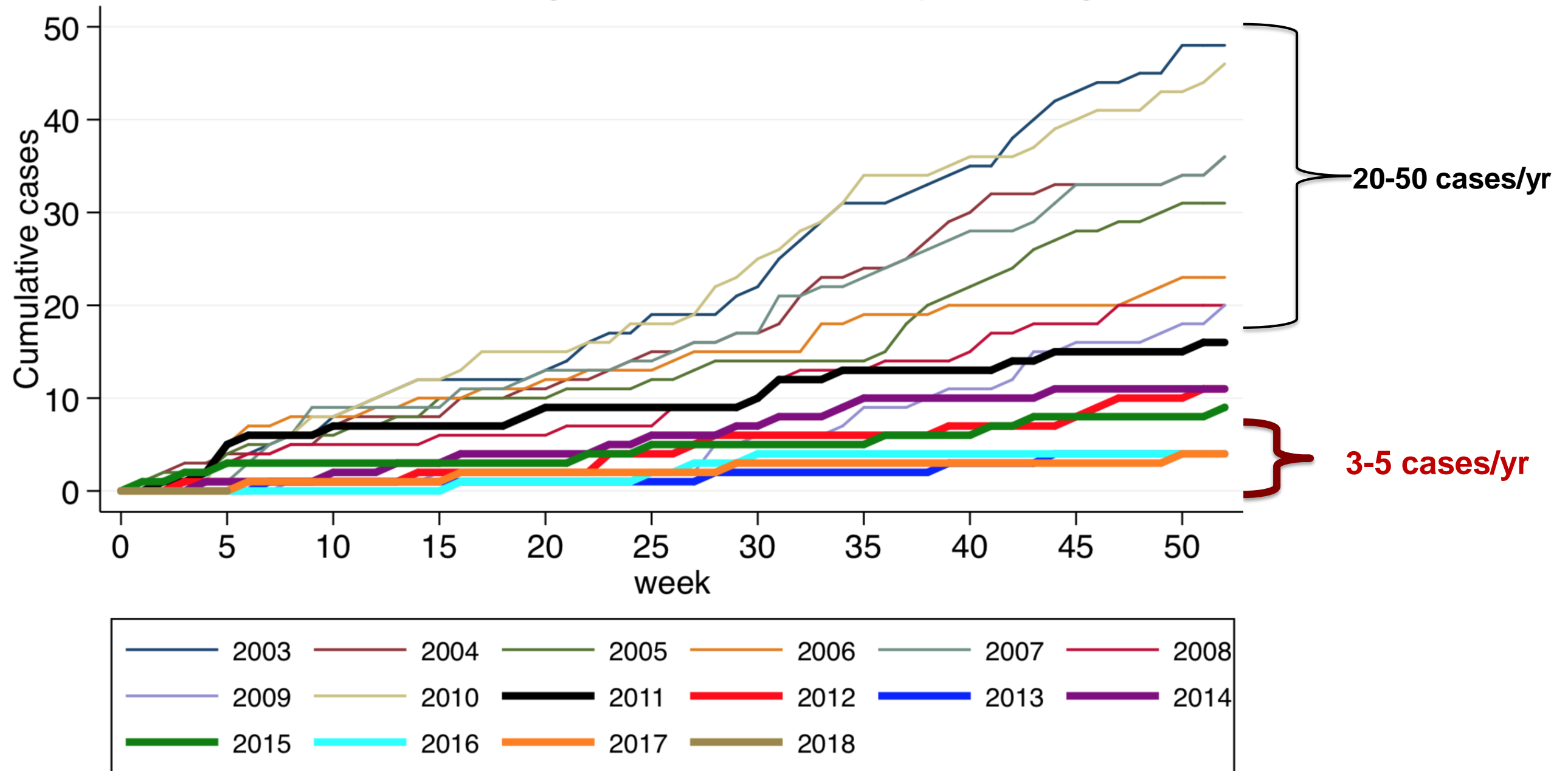
Dosing Schedule	Gavi	Non-Gavi	Total
3+0	51	8	59
2+1	7	50	57



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- 3. Impact of PCVs**
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# Pneumococcal Vaccine Serotype IPD Impact Kenya PCV10/3+0, < 5 yo

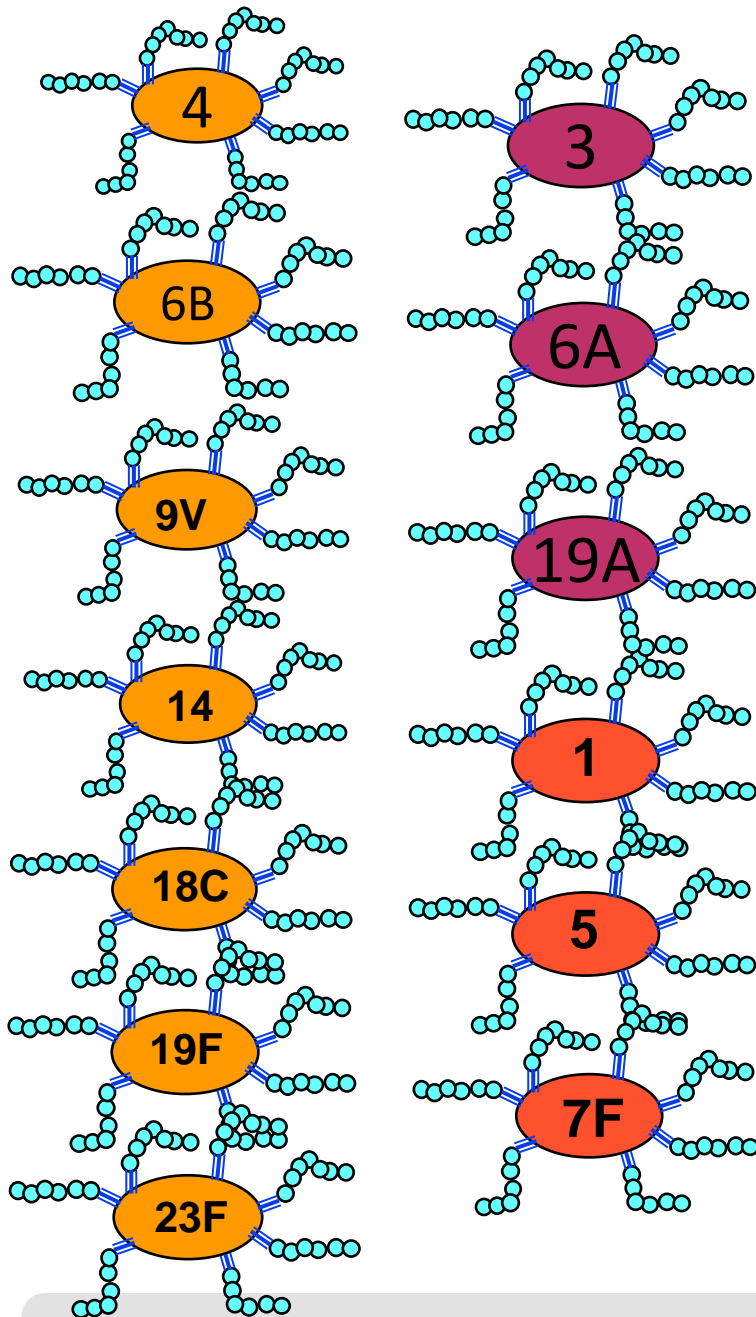




# South Africa Effectiveness, PCV13/2+1

## Nutrition and HIV

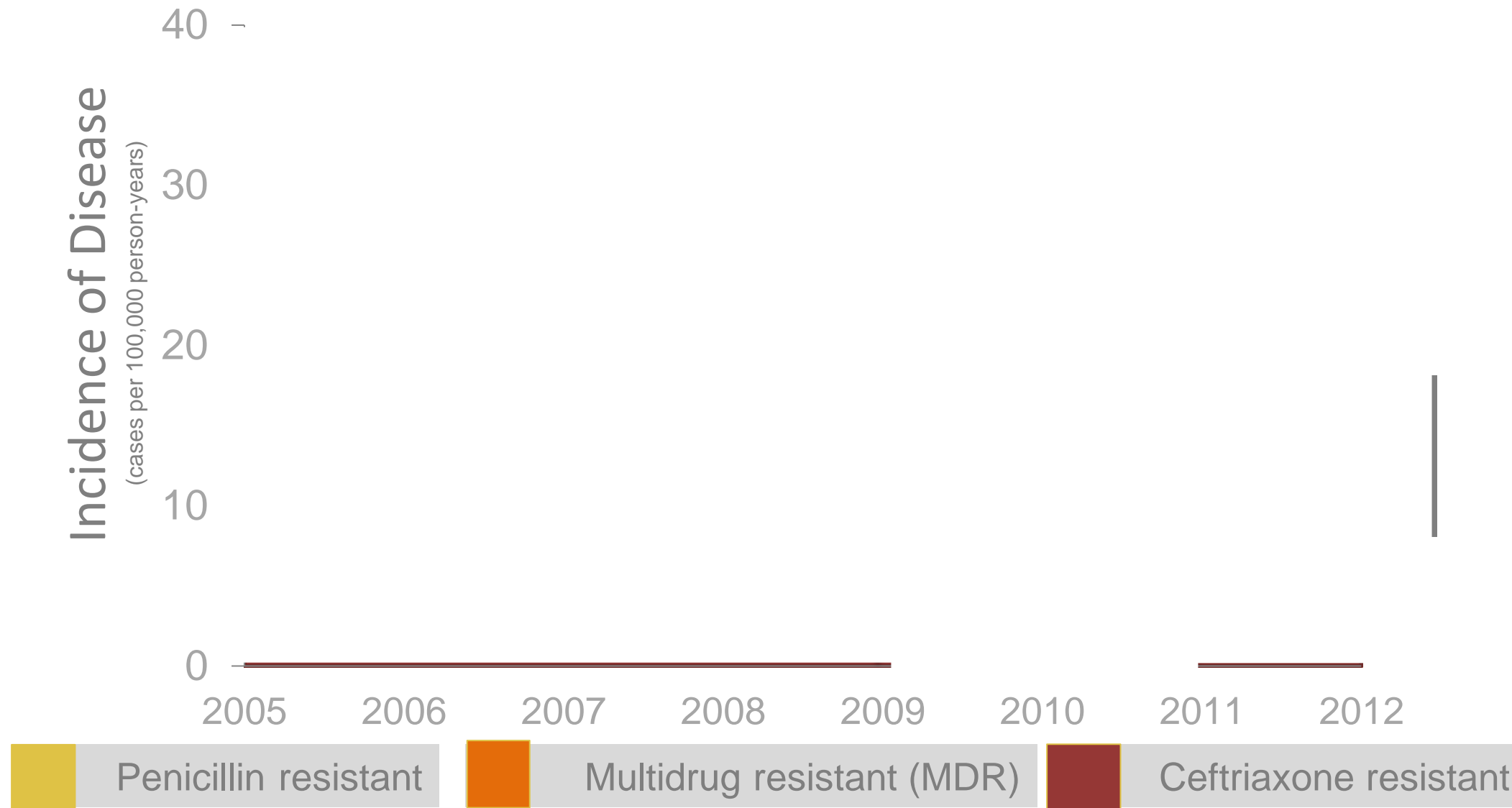
Lancet Glob Health 2017;  
5: e359-69



	Unadjusted vaccine effectiveness (95% CI)	Adjusted vaccine effectiveness (95% CI)*
<b>Children aged ≥16 weeks not infected with HIV</b>		
Overall	83% (61 to 92)	78% (46 to 91)
Exposed to HIV	91% (60 to 98)	87% (38 to 97)
Not exposed to HIV	81% (51 to 93)	82% (44 to 94)
Malnourished	85% (44 to 96)	90% (53 to 98)
Not malnourished	81% (40 to 94)	77% (17 to 94)
<b>Children aged ≥16 weeks with HIV infection</b>		
Overall	26% (-98 to 72)	17% (-304 to 80)
Severe immunosuppression†	-42% (-723 to 76)	-104% (-1433 to 73)
No severe immunosuppression	75% (-31 to 95)	66% (-94 to 94)
Malnourished	-40% (-390 to 60)	-23% (-454 to 73)
Not malnourished	70% (-140 to 96)	-7% (-3420 to 97)

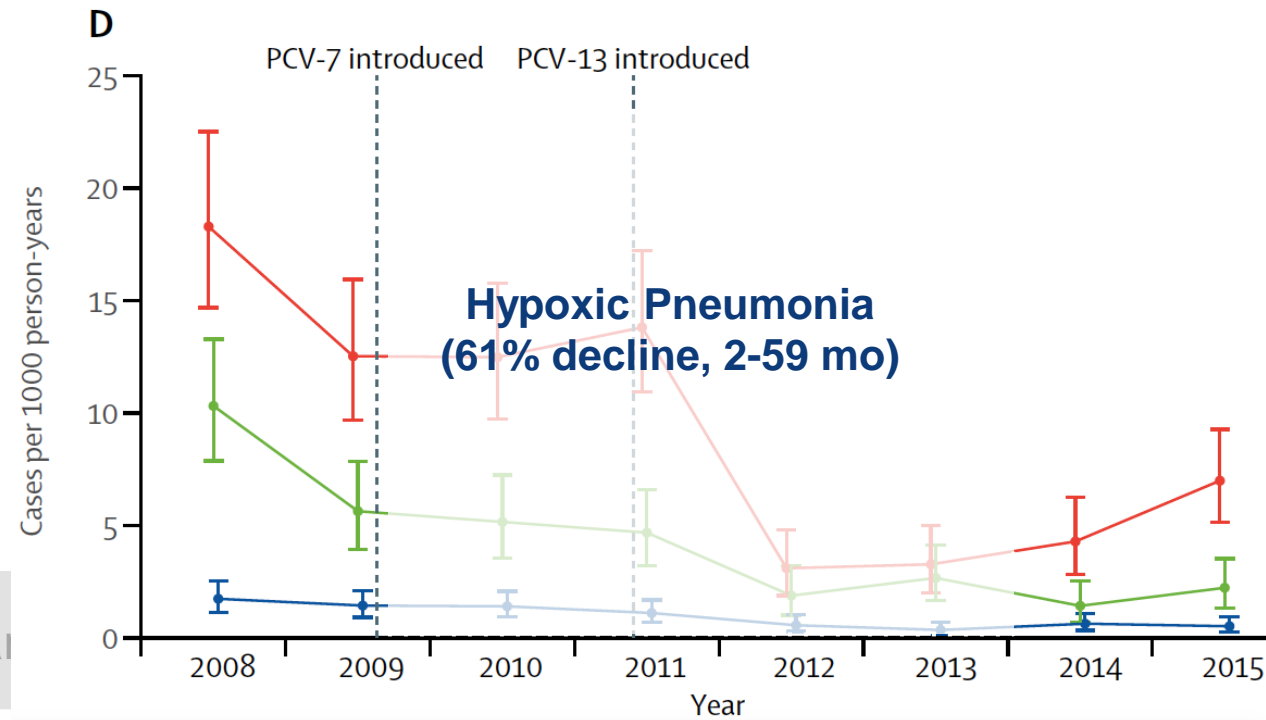
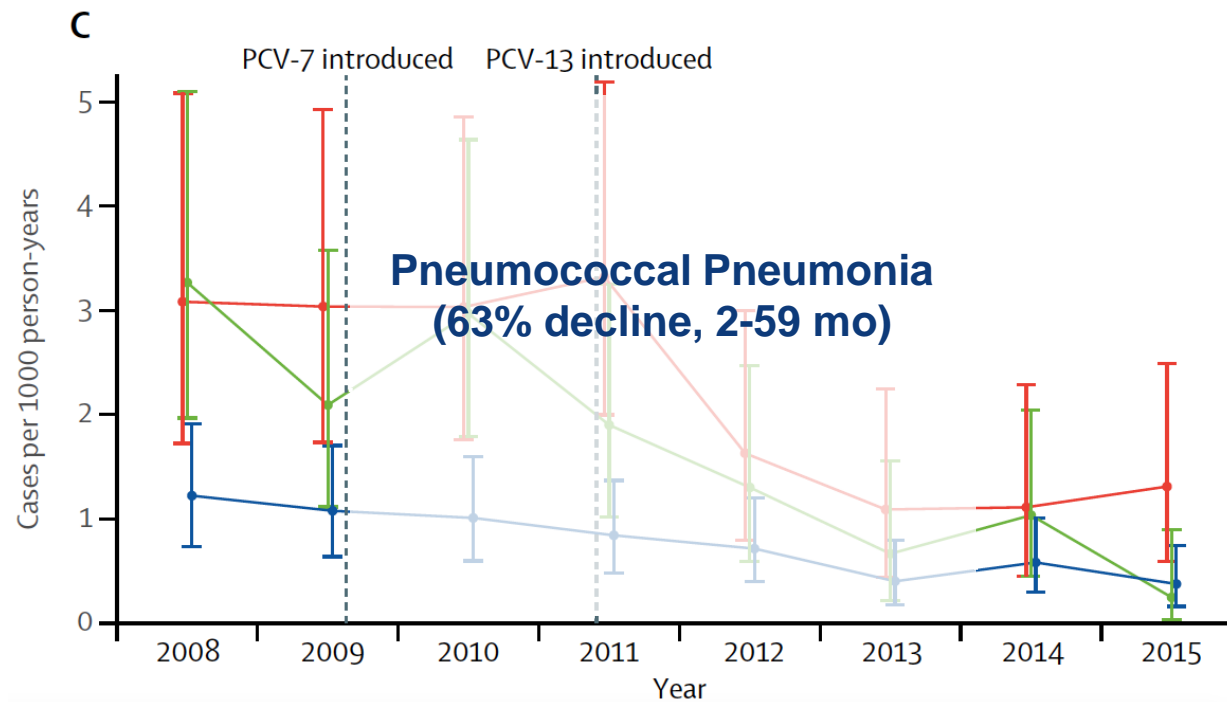
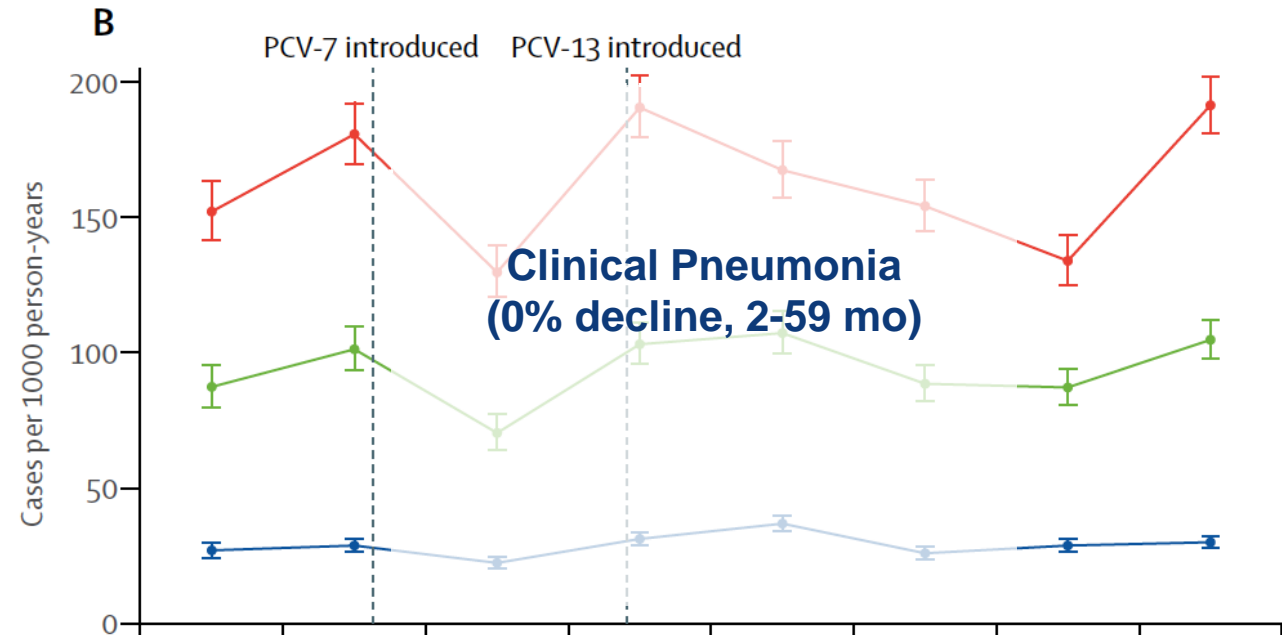
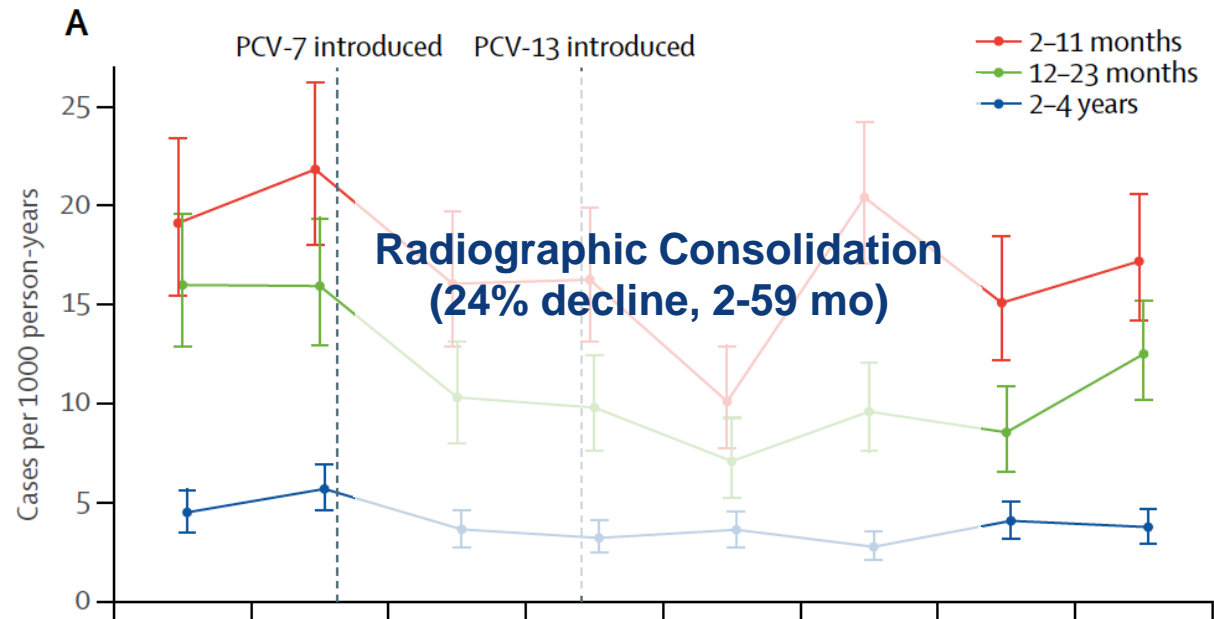
# Declining Pneumococcal Antibiotic Resistance South Africa

*Incidence of Antibiotic Resistant Invasive Pneumococcal Disease (IPD) in Children <2 years of age (von Gottberg et al. N Engl J Med 2014; 371:1889-1899)*



# Gambia PCV13/3+0 impact on pneumonia

MacKenzie G et al Lancet ID 2017



22 May

Full text > ACCESS

# Fully quantifying PCV value (PCV10/2+1 or 3+1)

Vaccine-preventable disease incidence of pneumococcal conjugate vaccine in the Finnish invasive pneumococcal disease vaccine trial

Arto A. Palmu<sup>a,\*</sup>, Jukka Jokinen<sup>b</sup>, Heta Nieminen<sup>a</sup>, Hanna Rinta-Kokko<sup>b</sup>, Esa Ruokokoski<sup>b</sup>, Taneli Puumalainen<sup>b</sup>, Marta Moreira<sup>c</sup>, Lode Schuerman<sup>c</sup>, Dorota Borys<sup>c</sup>, Terhi M. Kilpi<sup>b</sup>

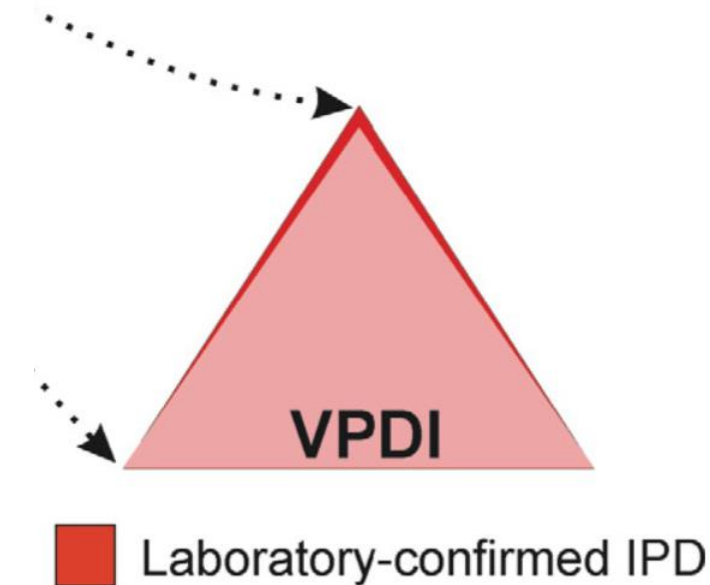
Vaccine 36 (2018) 1816–1822

**VPDI:**  
Per 10<sup>5</sup>

**1143**  
**11,381**

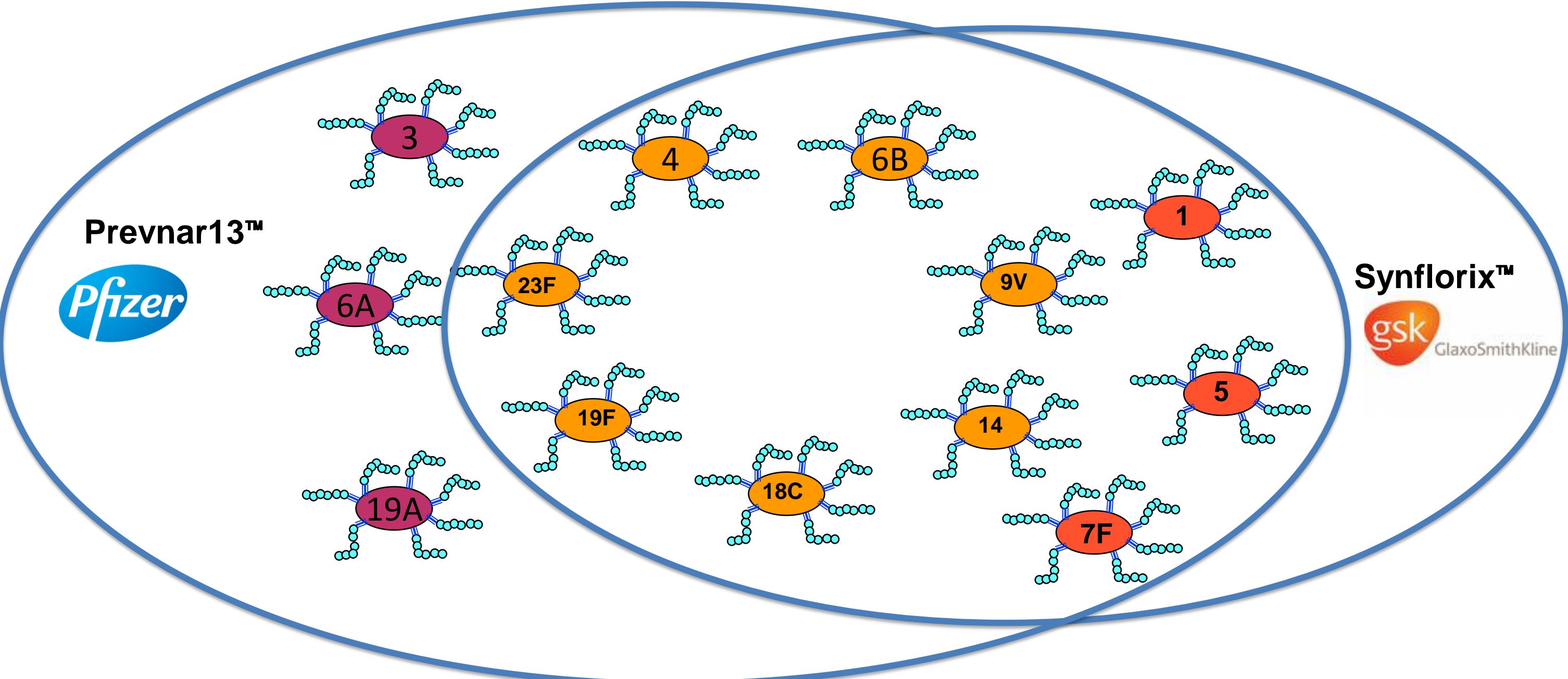
**210**  
**271**

**75**

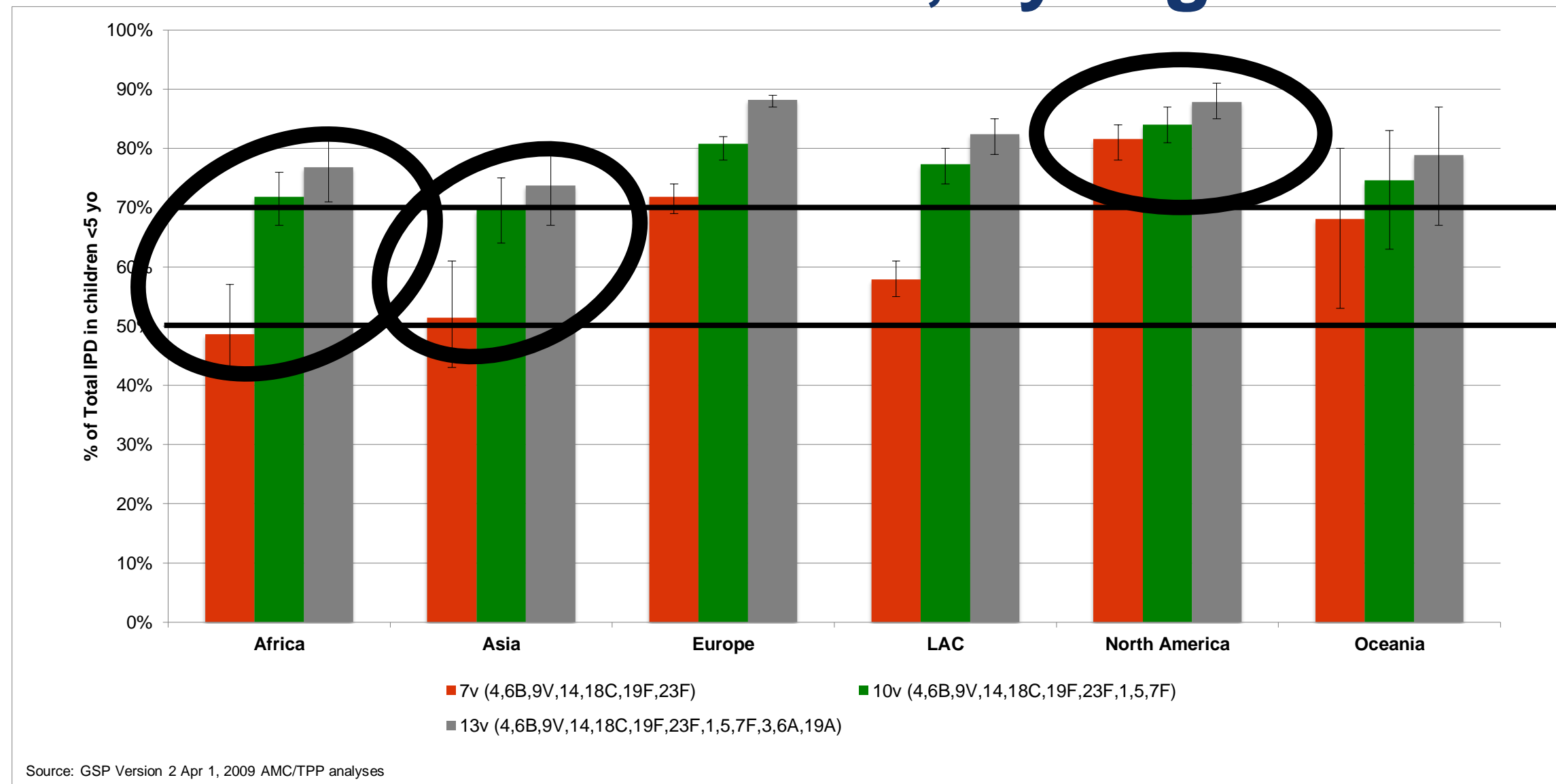




# Pneumococcal Conjugate Vaccines: 10 & 13 Valent came 10 years after 7-valent



# Proportion of IPD represented by serotypes in vaccine formulations, by region



Johnson HL, et al. (2010) Systematic Evaluation of Serotypes Causing Invasive Pneumococcal Disease among Children Under Five: The Pneumococcal Global Serotype Project. PLoS Med 7(10): e1000348. doi:10.1371/journal.pmed.1000348

# Product Comparison Results: Vaccine Type IPD

Vaccine Impact on PCV10/13-Type Disease by Product and Previous PCV7 Use:

## Results:

- Both products similarly reduced (directly and indirectly) IPD caused by the serotypes within each vaccine

PCV10: (n=6)

Prior PCV7 Use	Number of Studies:	Range of Point Estimates
No	N=4	87 to 93%
Yes	N=2	77 to 96%

PCV13: (n=10)

Prior PCV7 Use	Number of Studies	Range of Point Estimates
No	N=1	82%
Yes	N=9	65 to 100%

# Product Comparison Results: ST3 IPD

## Vaccine Impact on ST3 Disease by Product and Previous PCV7 Use:

### Results:

- PCV10 showed no impact on ST3 (not included in the vaccine), but limited data
- PCV13 had inconclusive results

### PCV10:

Number of Studies:	Range of Point Estimates
N=3	-354 to 29%
<ul style="list-style-type: none"> <li>• No or low Impact (n=1)</li> <li>• Increase (n=2)*</li> </ul>	29% (NS) -194 to -354%
N=1 Case Control**	8% (NS)

\*Both Finland

\*\*Ineligible 4-dose study that was reviewed by SAGE WG (Brazil, Domingues 2014)

### PCV13:

Number of Studies	Range of Point Estimates
N=7	-35 to 85%
<ul style="list-style-type: none"> <li>• Impact (n=2)</li> <li>• No or low Impact (n=5)</li> </ul>	68 to 85% -35 to 41% (NS)
N=2 Case Control*	0 to 26% (NS)

\*Includes n=1 ineligible 4-dose study that was reviewed by SAGE WG (Germany, Weinberger 2016)

# Product Comparison Results: ST19A IPD

## Vaccine Impact on ST19A-Type Disease by Product:

### Results:

- PCV10: only effectiveness (i.e., case-control) studies indicate some protective direct effects
  - Indirect effects studies suggest no change or increase in 19A disease
- PCV13: all studies showed protective effects (both direct and indirect)

### PCV10:

Number of Studies:	Range of Point Estimates
N=2	-54% to no change
<ul style="list-style-type: none"> <li>• No or low impact (n=2)</li> </ul>	-54% to no change
N=5 Case Control*	29 to 82%

\*n=1 ≥2 doses, n=4 ≥1 dose; Includes indirect cohort studies

### PCV13:

Number of Studies	Range of Point Estimates
N=8	68 to 100%
<ul style="list-style-type: none"> <li>• Impact (n=8)</li> </ul>	68 to 100%
N=6 Case Control*	67 to 94%

\*n=3 ≥2 doses, n=3 ≥1 dose; includes indirect cohort studies



# Product Comparison: Overall Conclusions

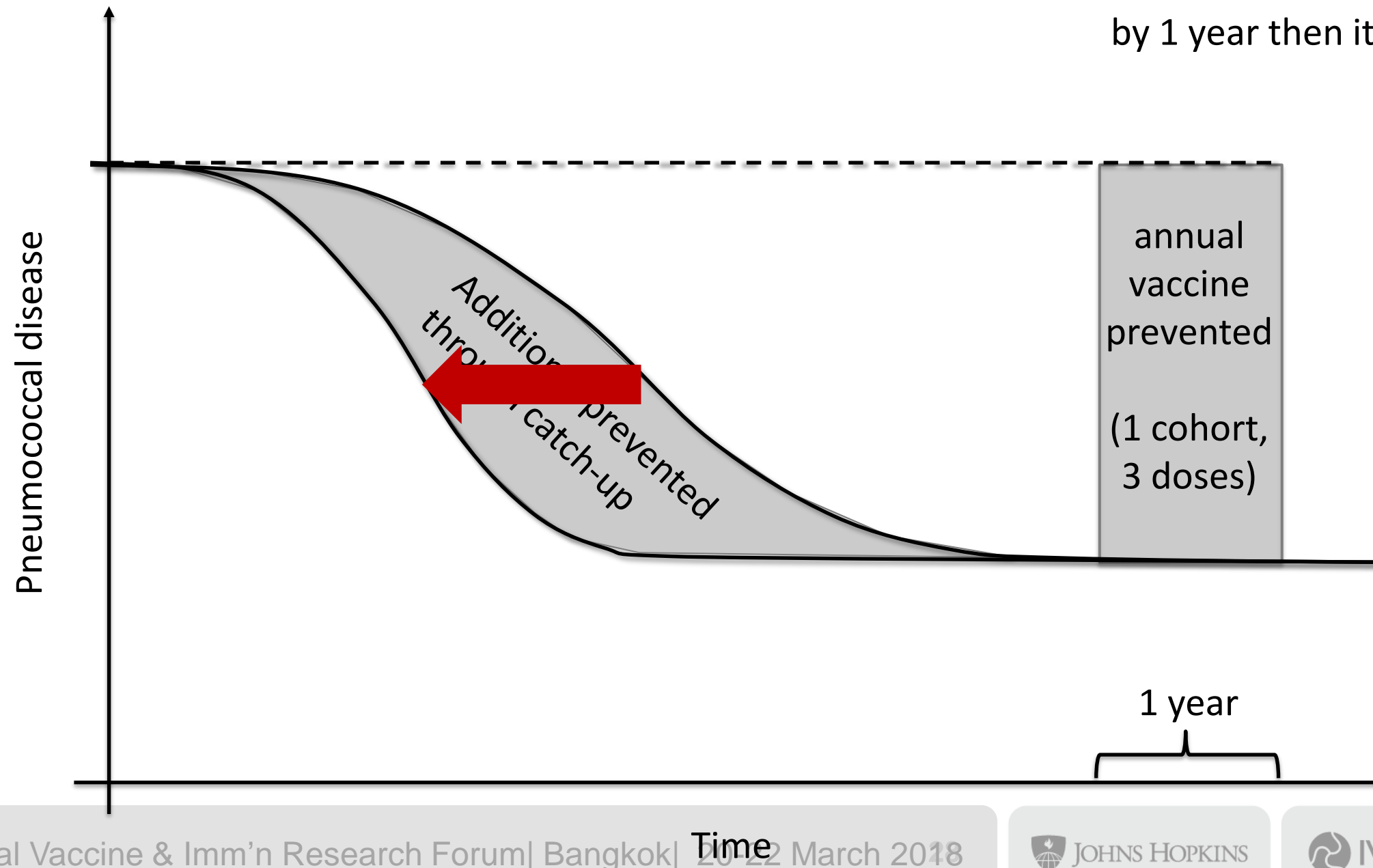
Outcome	Vaccine Serotypes in Common	Serotypes in PCV13 and not in PCV10			ST6C
		ST3	ST6A	ST19A	
Immunogenicity	Impact with both products	Favors PCV13	Impact with both products but Favors PCV13	Impact with both products but Favors PCV13	Evidence not available
NPC	Impact with both products	No Impact with either product	Impact with both products; Declines more pronounced with PCV13	PCV10 Impact not demonstrated. Favors PCV13	Limited data for both products
IPD	Similar impact with both products	Impact not demonstrated for either product	Impact with both products; data limited	Limited data but Favors PCV13	Some impact with PCV13 but data limited; No data for PCV10
Overall	Impact with both products	Impact not demonstrated for either product	Impact with both products	Limited data but Favors PCV13	Insufficient evidence to compare products

# What about Catch-up Schedules?

# Catch-up concept

## RULE OF THUMB:

If a 1 dose catch-up across 3 age groups can accelerate the impact of a 3 dose programme by 1 year then its similarly efficient



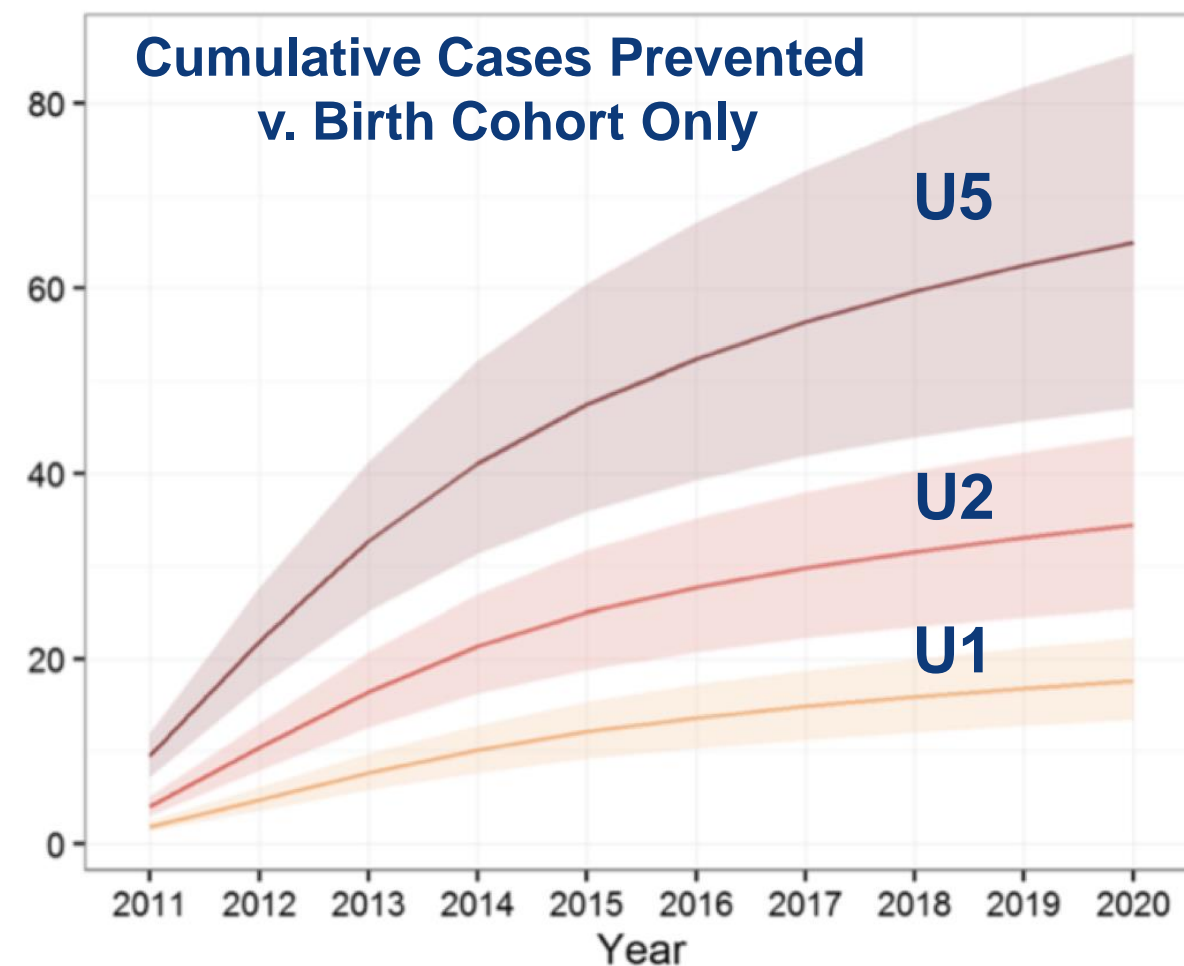
# Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya



Stefan Flasche<sup>1\*</sup>, John Ojal<sup>1,2</sup>, Olivier Le Polain de Waroux<sup>1</sup>, Mark Otiende<sup>2</sup>, Katherine L. O'Brien<sup>3</sup>, Moses Kiti<sup>2</sup>, D. James Nokes<sup>2,4</sup>, W John Edmunds<sup>1</sup> and J. Anthony G. Scott<sup>1,2</sup>

Flasche *et al. BMC Medicine* (2017) 15:113  
DOI 10.1186/s12916-017-0882-9

## Impact magnitude and efficiency varies by pneumococcal (NP) prevalence



**Table 2** The impact and efficiency of alternative introduction strategies

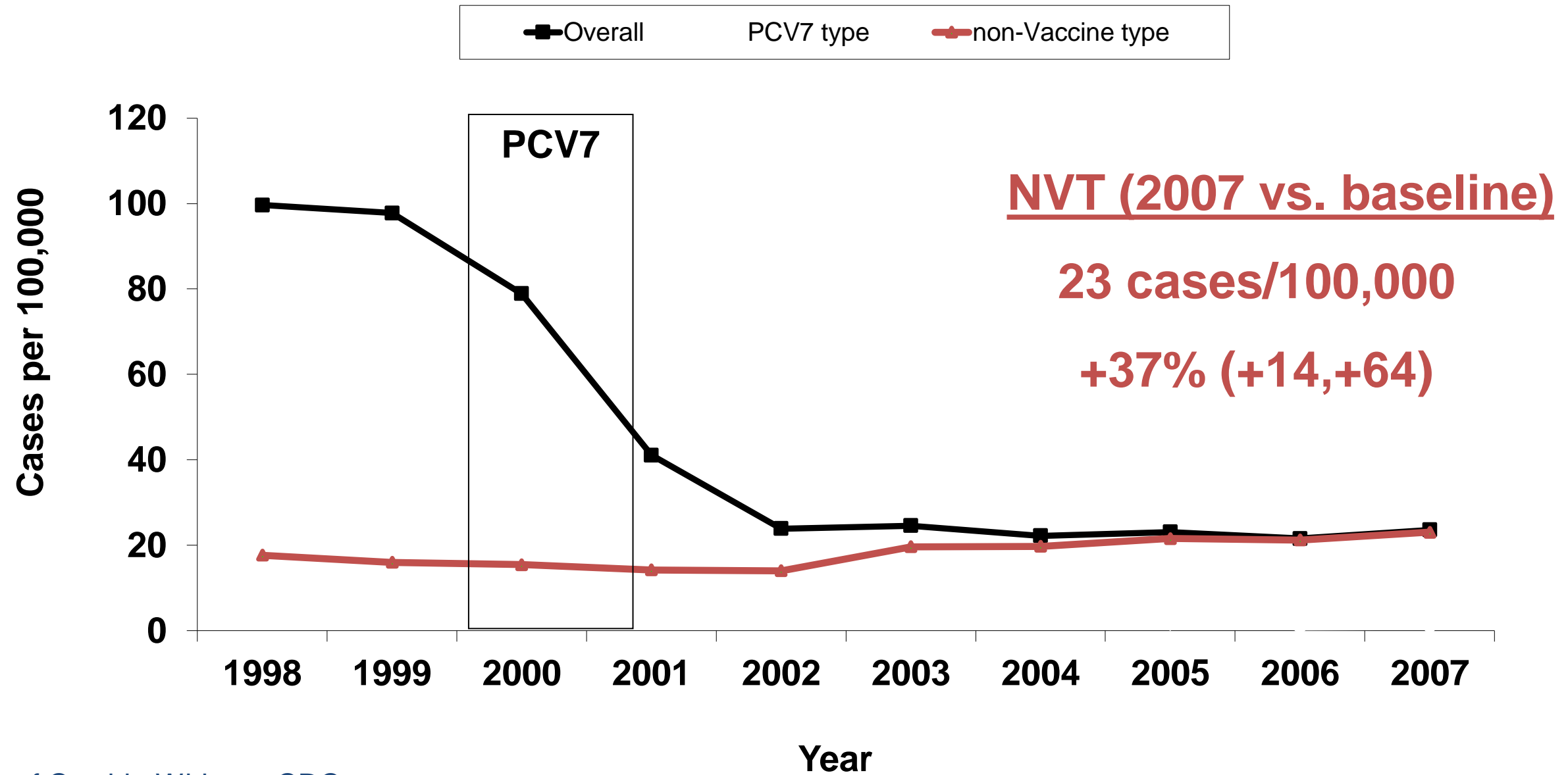
Introduction of PCV via	IPD averted after 10 years	Doses administered	Incremental NVN	NVN
Cohort only	155 (121–193)	204,671	1321 (1058–1698)	1321 (1058–1698)
+ U1 catch-up	173 (134–216)	218,089	757 (618–973)	1263 (1012–1623)
+ U2 catch-up	189 (147–235)	224,952	412 (296–606)	1188 (958–1527)
+ U5 catch-up	220 (172–270)	241,546	543 (403–763)	1098 (894–1405)

The number of vaccine doses needed to prevent a case of IPD (NVN) is used as a measure of efficiency. Incremental NVN refers to the additional number of doses needed to prevent one additional cases of IPD in respect to cohort introduction with the next smaller catch-up

# Should we be concerned about serotype replacement?

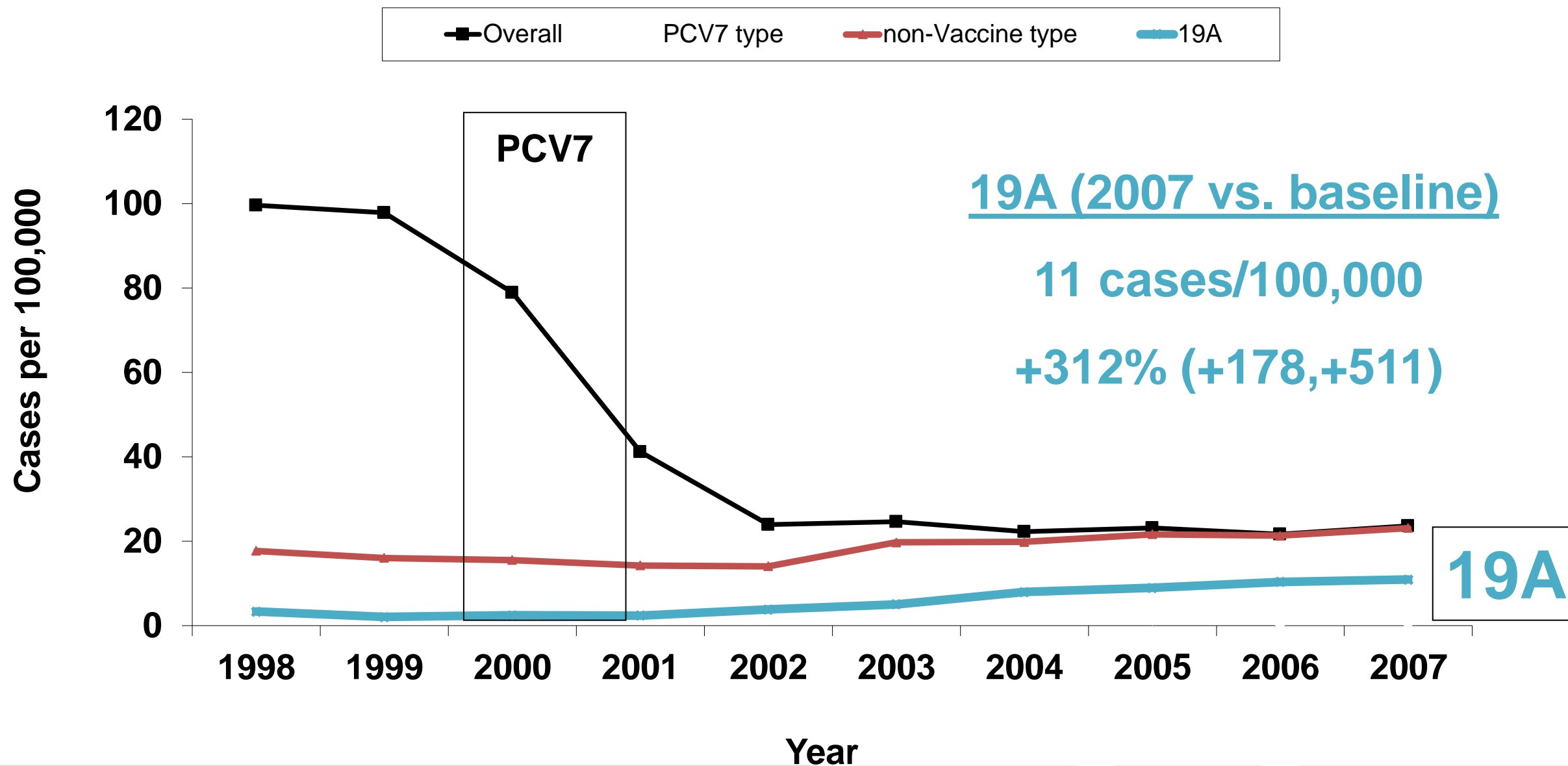


# Rates of invasive pneumococcal disease among children <5 years, PCV7 era, ABCs 1998-2007



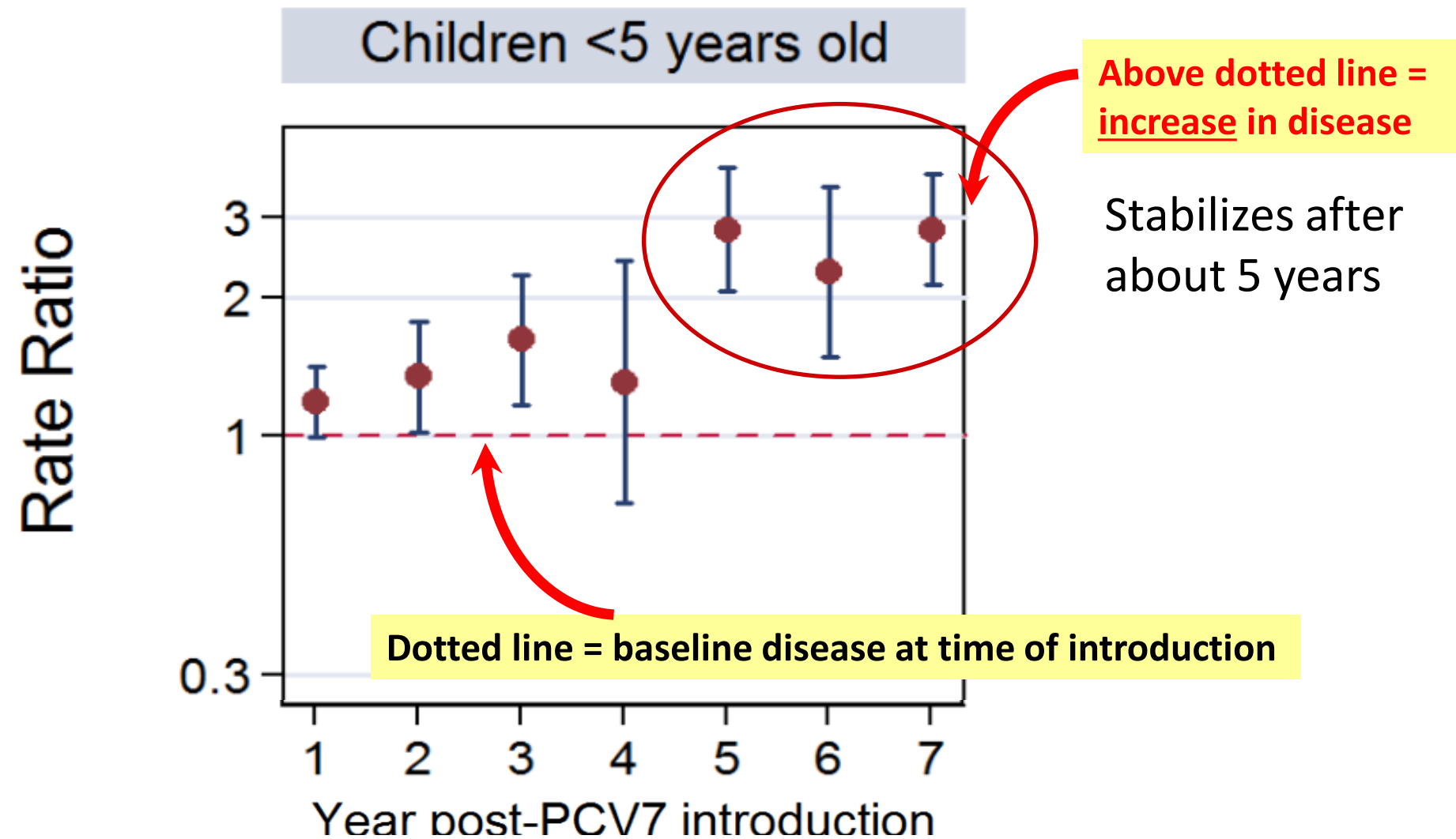
Slide courtesy of Cynthia Whitney, CDC

# Rates of invasive pneumococcal disease among children <5 years, PCV7 era, ABCs 1998-2007



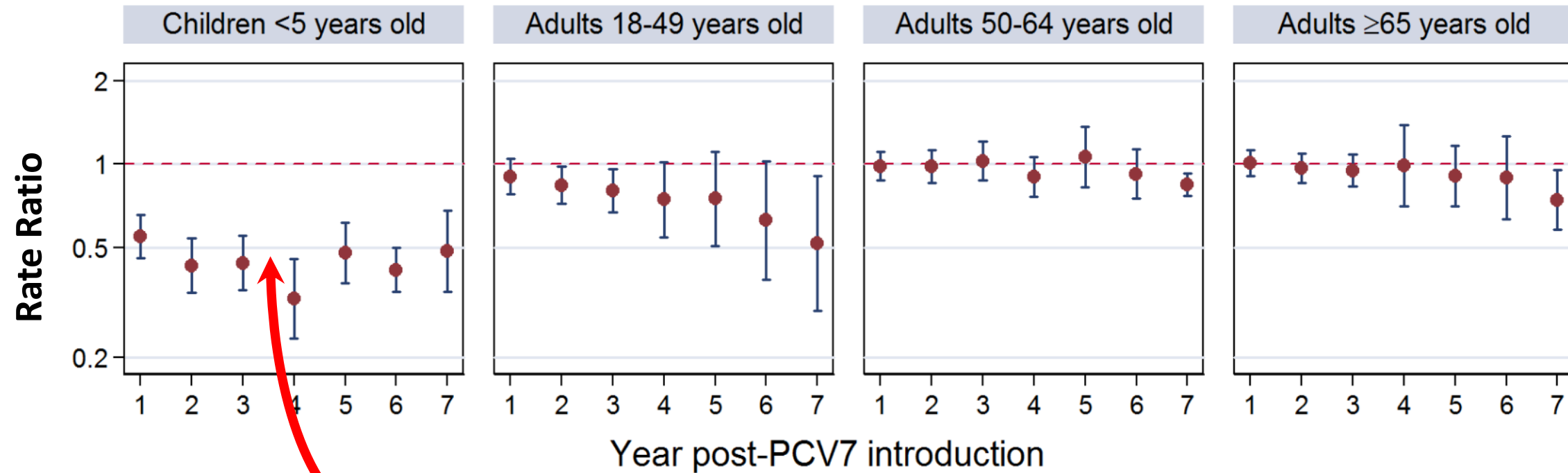
# Non-Vaccine Type IPD Increased after PCV-7 Introduction

## Pooled Global Analysis



# What is the net effect?

## 50% Decline in total IPD after PCV-7 Introduction



**Net effect:** despite replacement disease, there is substantial overall decline in pneumococcal disease

# Serotypes in PCV10/13 Era

Table 3. Serotype-specific contributions (%) to paediatric IPD cases in settings that have introduced PCV10 or PCV13.

	OVERALL (N = 20)	LATIN AMERICA (N = 1†)	NORTH AMERICA (N = 4)	EUROPE (N = 8)	WESTERN PACIFIC (N = 4)	AFRICA (N = 1)	EASTERN MEDITERRANEAN (N = 2)
PCV7	12.5 (8.8–17.7)	32.5 (25.5–41.3)	3.4 (2.5–4.5)	4.4 (3.3–5.7)	5.8 (1.6–21.1)	* 25.5 (22.3–29.2)	** 62.6 (46.3–84.7)
PCV10-7	9.2 (6.9–12.2)	10.1 (5–20.4)	7.9 (4.5–13.9)	10.1 (6.6–15.4)	4.6 (1.5–14)	* 9.8 (7.9–12.2)	** 8.9 (1–81.8)
PCV13	49.1 (42.3–56.9)	71.2 (65.9–77)	37.3 (25.4–54.7)	27.9 (19.9–39.1)		* 57.3 (52.4–62.6)	** 91 (78.2–100)
19A	14.2 (11.1–18.3)	12.5 (7.7–20.2)	20.8 (13.3–32.6)	11.3 (7.6–17)		* 11.4 (9.3–13.9)	** 6.2 (3.4–11.2)
3	5.3 (4.2–6.7)	6.7 (4.7–9.7)	6.1 (3.9–9.3)	4.7 (3.6–6.1)		* 2 (1.3–3.2)	* 2.2 (0.8–5.8)
6A	3.2 (2.1–4.9)	5.5 (4.2–7.1)	** 1 (0.6–1.8)	1 (0.5–2)		* 8.5 (6.8–10.8)	** 4.9 (2.2–11.3)
NON-PCV13	42.2 (36.1–49.5)	28.5 (23.4–34.7)	57.8 (41.6–80.4)	71.9 (63.1–82)		* 42.7 (38.5–47.4)	* 9.2 (3.7–22.9)
22F	5.3 (4.2–6.7)	2.3 (1.4–3.7)	6.9 (4.9–9.7)	5.2 (3.6–7.5)		–	–
12F	4.3 (3.5–5.3)	4 (2.8–5.7)	** 3.3 (1.3–8.3)	5.6 (4.4–7)		* 4 (2.9–5.6)	* 1.3 (0.2–9.1)
33F	4.5 (3.4–5.9)	** 2 (0.8–4.8)	4.9 (2.2–10.8)	4.9 (3.3–7.4)		–	–
24F	4.2 (2.6–6.8)	2.4 (1.6–3.8)	–	6.7 (3.8–11.9)		–	–
15C	4 (3.1–5)	1.5 (0.2–2.7)	4.2 (2.3–7.8)	3.9 (4.1–7.8)		–	–
15B	3.7 (3.1–4.4)	2.5 (1.5–4.3)	4.2 (2.3–7.8)	3.7 (2.6–5.2)		* 4.3 (3.1–5.9)	–
23B	3.4 (2.6–4.3)	4 (2.8–5.7)	4.2 (2.3–7.8)	3.7 (2.6–5.2)		–	* 1.3 (0.2–9.1)
10A	3.4 (2.2–5.4)	1.3 (0.8–2.3)	** 2.6 (1.7–3.8)	6.7 (3.7–12.4)		–	–
38	3.4 (2.4–4.8)	1.8 (0.6–5.5)	** 5 (1.7–14.3)	3.2 (1.8–5.6)		–	–
15A	2.9 (1.9–4.4)	1.4 (0.8–2.5)	3.3 (1.5–7.4)	3.9 (1.9–7.9)		–	–
35B	2.6 (1.8–3.8)	1.2 (0.2–6.4)	4.5 (1.7–11.4)	1.4 (0.9–2.3)		–	–
6C	2.4 (1.8–3)	2.4 (1.6–3.7)	2.3 (1.6–3.3)	1.6 (0.7–3.6)		–	–
8	2.2 (1.3–3.8)	1.2 (0.6–2.3)	** 1.5 (0.9–2.5)	2.9 (1.3–6.2)		* 8.3 (6.6–10.5)	* 1.3 (0.2–9.1)
11A	2 (1.6–2.6)	2.2 (1.5–3.3)	** 2.5 (1.6–3.7)	1.7 (1.1–2.6)		–	–
23A	2 (1.6–2.6)	2 (1.2–3.6)	2.2 (1.5–3.2)	1.6 (1–2.5)		–	* 2.6 (0.6–10.2)
9N	1.3 (1–1.8)	1.3 (0.6–2.8)	** 1.3 (0.7–2.4)	1.3 (0.7–2.4)	** 1.5 (0.5–4.7)	* 1.8 (1.1–3)	–

+60 types

- Early PCV10/13 Use
- Global Update Starting

22F  
12F  
33F  
24F  
15B/C  
23B  
10A  
38



# Programmatic Considerations



Product	Serotype & Carrier Protein													Preservative	Shelf life	Size	Gavi Price
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F				
PCV10	1µg PD		3µg PD	1µg PD		1µg PD	1µg PD	1µg PD	1µg PD	3µg TT		3µg DT	1µg PD	2-phenoxyethanol	36	2.4	\$3.05
PCV13	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	4.4µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2.2µg CRM	2-phenoxyethanol	24	3	\$2.95

## PCV13 – Prevenar-13:

- Carrier Protein: CRM197 a non-toxic mutant of diphtheria toxin (CRM)

## PCV10 – Synflorix:

- Carrier Proteins: protein D from non-typeable Haemophilus influenzae (PD) (NTHi), Tetanus Toxoid (TT), Diphtheria Toxoid (DT)

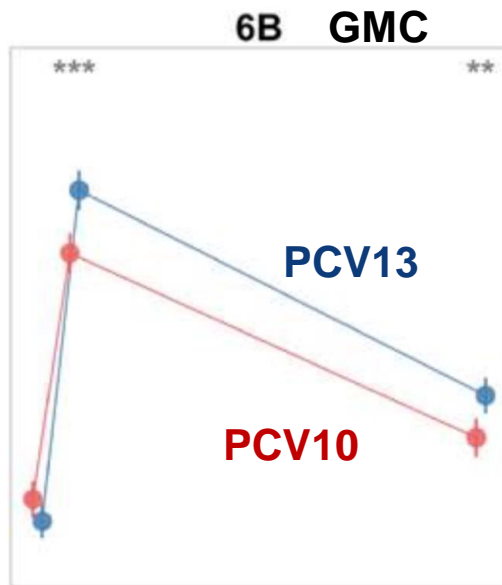
# PCV interchangeability/mixed PCV regimens

- Impact Could Go Either Way
  - (+) Carrier suppression avoided
  - (+) Differences in amount of antigen
  - (-) B-cells not primed by same carrier
- Few Studies (n=4)

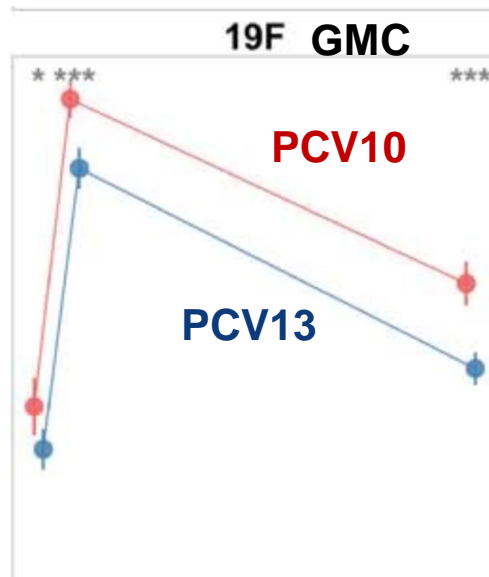
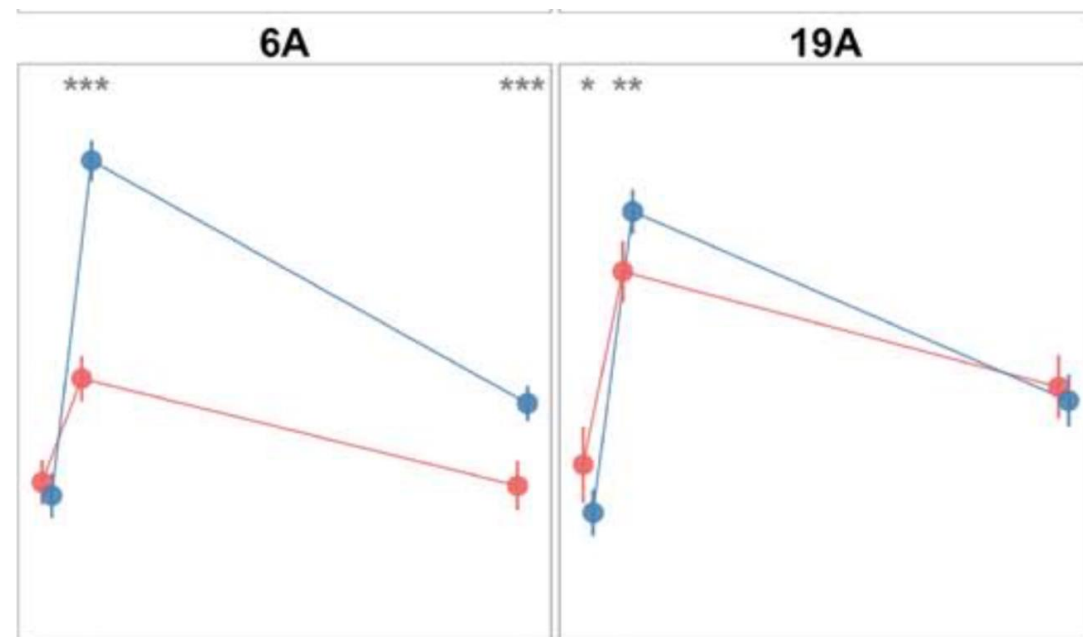
	PCV7-Primed	PCV10-Primed	PCV13-Primed
PCV10-Boosted	Immuno (Finland)	N/A	Immuno (UK)
PCV13-Boosted	N/A	IPD (Canada/Quebec) Immuno (Czech Rep)	N/A

# PCV Interchangeability Acceptable

## UK Example: PCV13 + PCV10 v. PCV13



Both products boosted for types not in PCV10



- PCV13 somewhat more immunogenic (GMC, OPA, %>0.35)
- Clinical impact likely not observable
- ? Relevance as new products licensed
  - Switching will be time limited
  - One birth cohort
  - In setting of high PCV use
- ? Strategic applications

Truck et al PIDJ 2016

# 10- year horizon

- **Introduction continues at pace**
- **Coverage enhanced, especially in high need areas**
- **Additional products on market reduce prices**
- **Serotype replacement is limited**



- **Countries continue investment in PCV**
- **Maximum health benefit is accrued**




# Alternative Scenario for 10- year horizon

- **Failure to Achieve Optimized Impact**
- **Serotype Replacement Substantial**
- **Subnational Inequity Persists**
- **Supply Challenges**



- **Weakened country commitment**
- **Withdrawal of PCV**





# Gaps and Way Forward

- ❖ Quantify the full impact of PCV
- ❖ Next Generation Vaccines
  - ❖ Serotype Replacement Magnitude
  - ❖ Serotype Distribution in New Era
- ❖ Optimizing Dosing
- ❖ Reservoirs of Colonization and Disease
- ❖ Product Preferences
- ❖ Coverage, coverage, coverage