CHU Saint-Pierre
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Pneumococcal diseases in children

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No conflict of interest

Steptococcus pneumoniae: a leading cause of bacterial infections

- Invasive bacterial infections (germs invade parts of the body that are normally free from germs)
  - Meningitis
  - Bacteremia without a known site of infection is the most common invasive clinical presentation of pneumococcal infection among children 2 years old or younger, accounting for approximately 70% of invasive disease in this age group.
  - Bacteremic pneumonia accounts for about 12–16% of invasive pneumococcal disease among children 2 years old or younger.
- Non invasive bacterial infections
  - Pneumonia, acute otitis media, sinusitis, periorbital cellulitis, mastoiditis, conjunctivitis
  - Osteomyelitis, arthritis, soft tissue infections, pericarditis, endocarditis

Detected aetiologies for the study population according to age.

De Schutter I, et al. (2014) Pneumococcal Aetiology and Serotype Distribution in Paediatric Community-Acquired Pneumonia. PLOS ONE 9(2): e89013.

	Total	Age <2 yrs	Age ≥2 yrs	p-value
Aerobic bacteria	159/539 (29.5)	19/110 (17.3)	140/429 (32.6)	0.002
Streptococcus pneumoniae	332/539 (61.7) [a]			
Conventional methods alone	66/539 (12.2)	10 (9.1)	56 (13.1)	NS
All methods combined	156/211 (73.9) [b]	17/28 (60.7)	139/183 (76.0)	NS
Streptococcus pyogenes	3/539 (0.6)	2/110 (1.8)	1/429 (0.2)	NS
Non-typeable *Haemophilus influenzae*	1/539 (0.2) [c]	0	1/429 (0.2)	NS
Pseudomonas aeruginosae	1/539 (0.2) [d]	1/110 (0.9)	0	NS
Viruses, n tested	193	59	134	
Virus detected	61 (31.6)	23 (39.0)	38(28.4)	NS
Respiratory syncytial virus	12 (6.2)	3 (5.1)	9 (6.7)	NS
Influenza A	24 (12.4)	8 (13.6)	16 (11.9)	NS
Influenza B	27 (14.0)	15 (25.4)	12 (8.9)	0.01
Other	2 (1.0)	1 (1.7)	1 (0.7)	-
***Mycoplasma pneumoniae*, n tested**	160	52	108	
Yes	4 (2.5)	0	4 (3.7)	NS

Values are numbers (%) of subjects. NS, not significant.

Pneumonia is the leading KILLER of children !!!

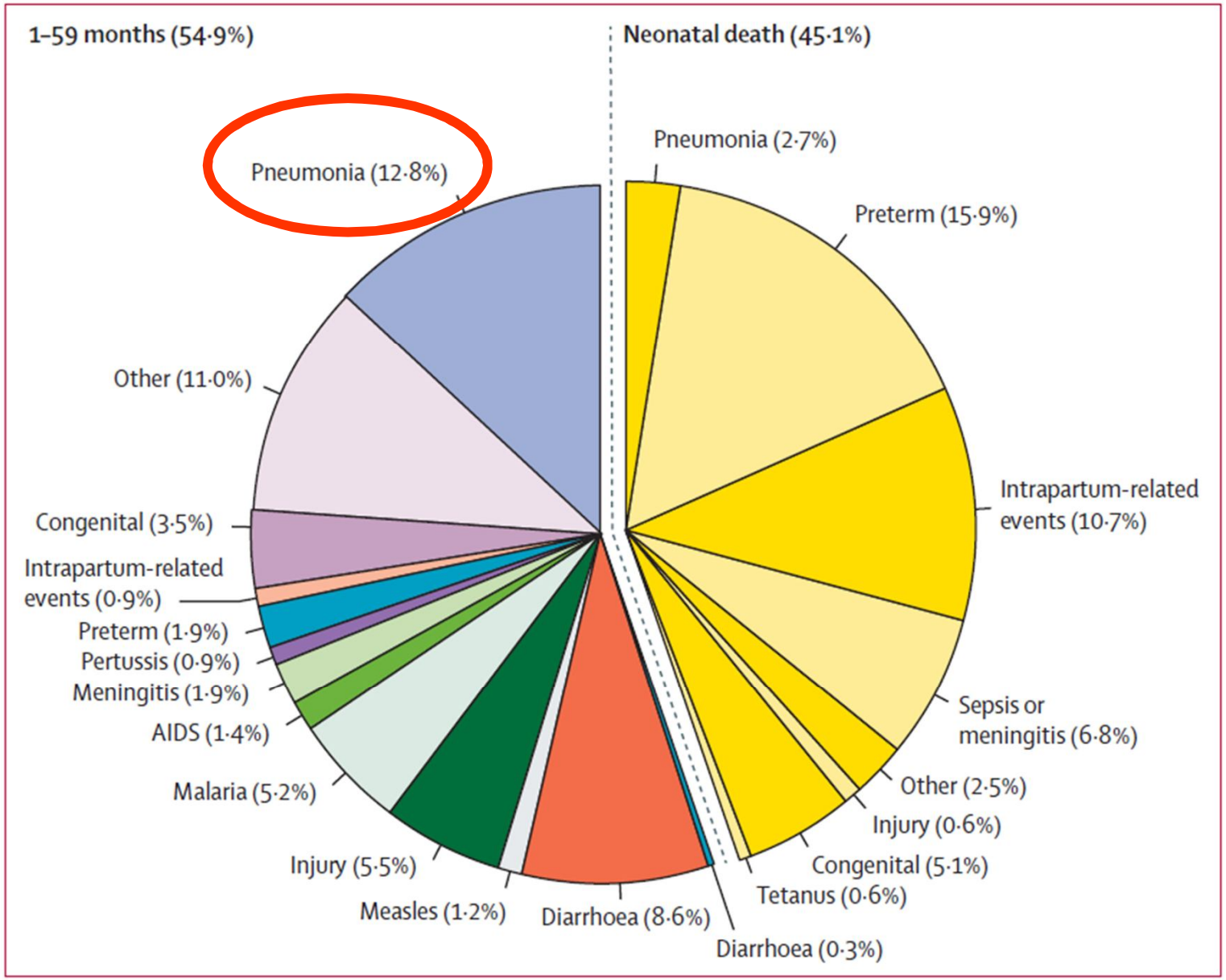
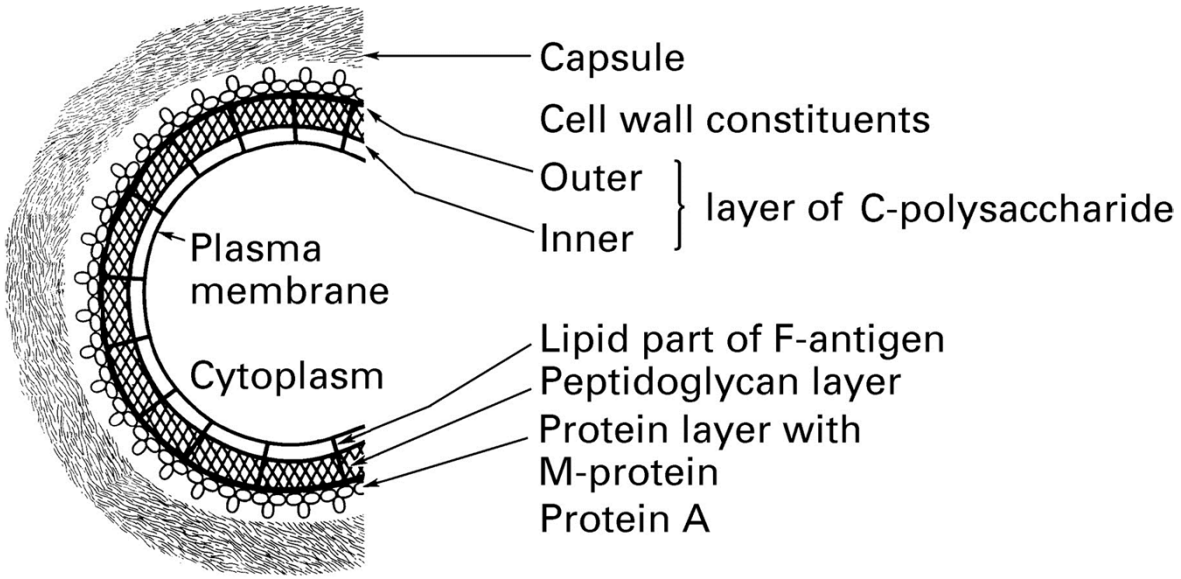


Figure 1: Global causes of under-5 deaths in 2015

Lancet 2016

Steptococcus pneumoniae

- Is transmitted mostly by respiratory droplets
- Frequently colonizes the human nasopharynx
- Infants and young children are the main reservoir
- Its virulence is largely due to its polysaccharide capsule

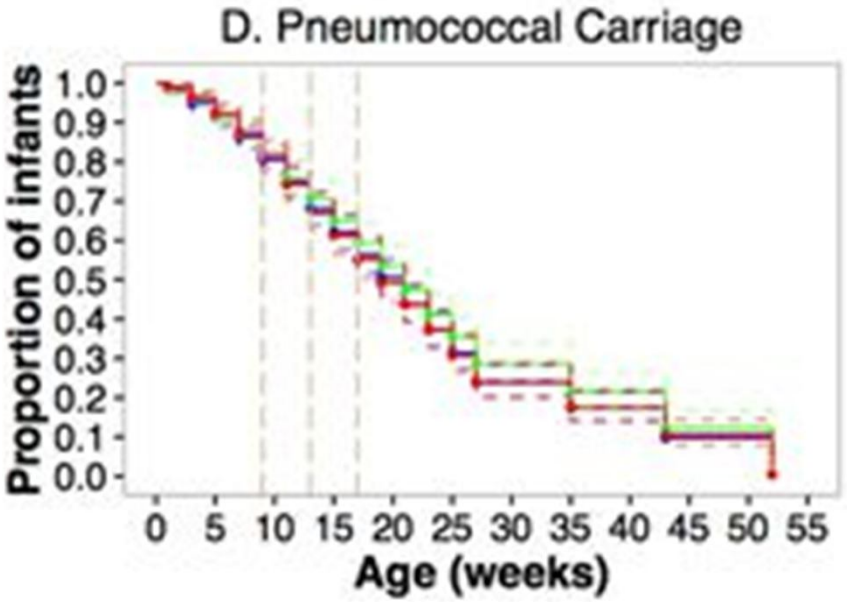


Picture from: Mats Kalin. Thorax 1998;53:159-162

Pneumococcus serotypes

- >90 pneumococcal serotypes classified within 46 serogroups identified on the basis of differences in the antigenic characteristics of the capsular polysaccharide
- Epidemiologic studies have found associations between capsular type and disease type
- Some serotypes have more invasive potential than others and only a limited number of serotypes cause most invasive pneumococcal disease worldwide
- Some serotypes are more likely than others to be resistant to antimicrobials

Nasopharyngeal carriage dynamics of pneumococcus in the first year of life



Kaplan Meier Survival Curve for time to first acquisition of pneumococcus in a study on Gambian infants followed since birth

Scientific Reports, volume 7, Article number: 8127 (2017)

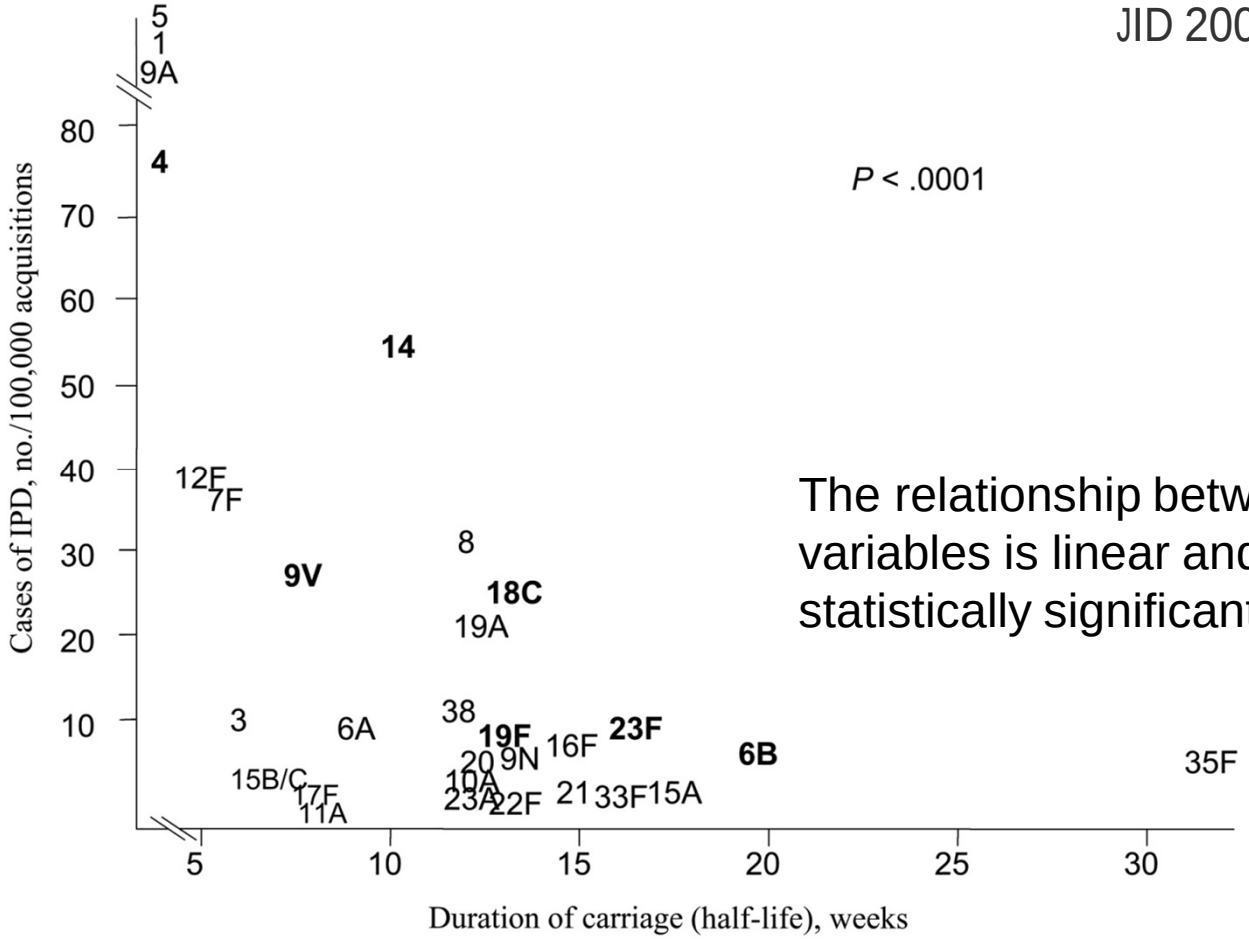
- Nasopharyngeal colonization can occur as early as the first week of life
- Rates and duration of colonization are influenced by age, race and day care attendance
- The average length of carriage is 3-4 months but young infants may harbor pneumococci for over a year
- At any given time, around 75% of young children are colonized

Pneumococcus serotypes

- Nasopharyngeal colonization is a prerequisite for IPD
- Infection occurs most often within the month after acquisition of a new pneumococcal strain
- The capsular serotype is a major determinant of both pneumococcal duration of carriage and attack rate
- There is an inverse correlation between attack rate and duration of carriage
- Attack rate varies by capsular serotype, from >80 cases/100,000 acquisitions to <10 cases/100,000 acquisitions

Inverse relationship between the attack rate of a capsular serotype and its duration of carriage.

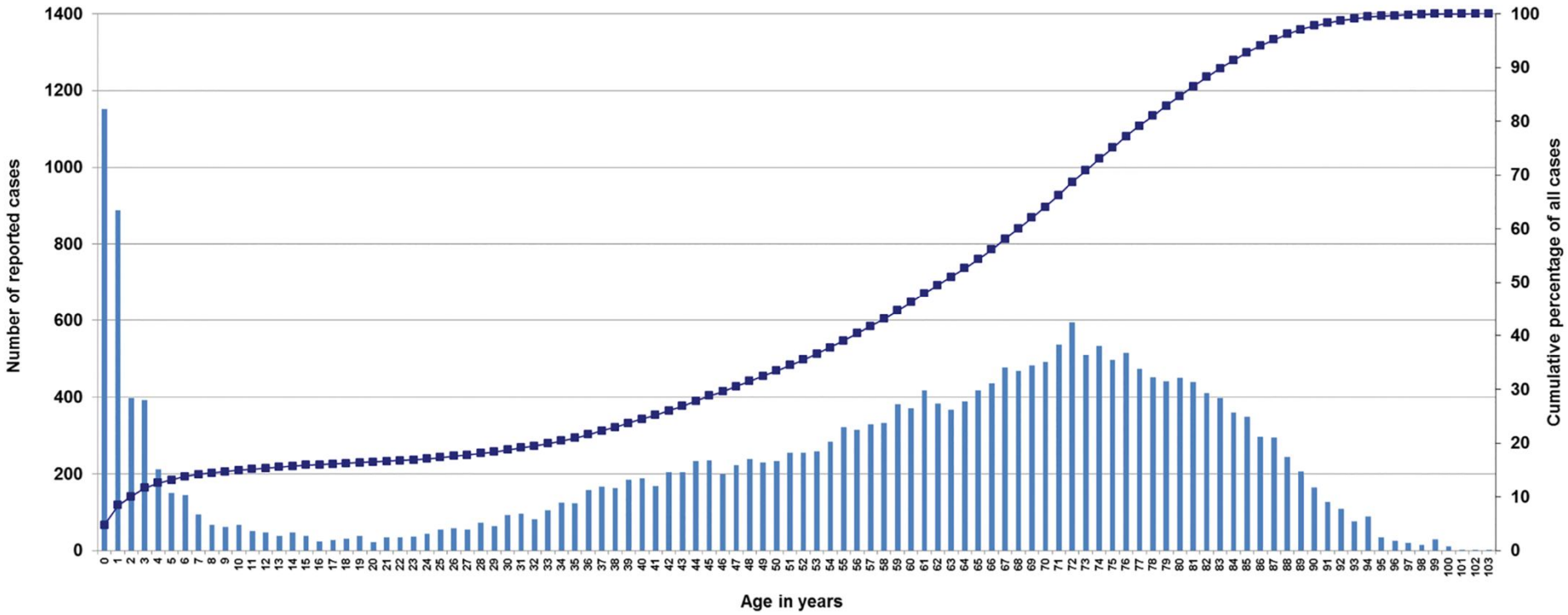
JID 2006;194:682–688



The relationship between the 2 variables is linear and statistically significant (P<.0001)

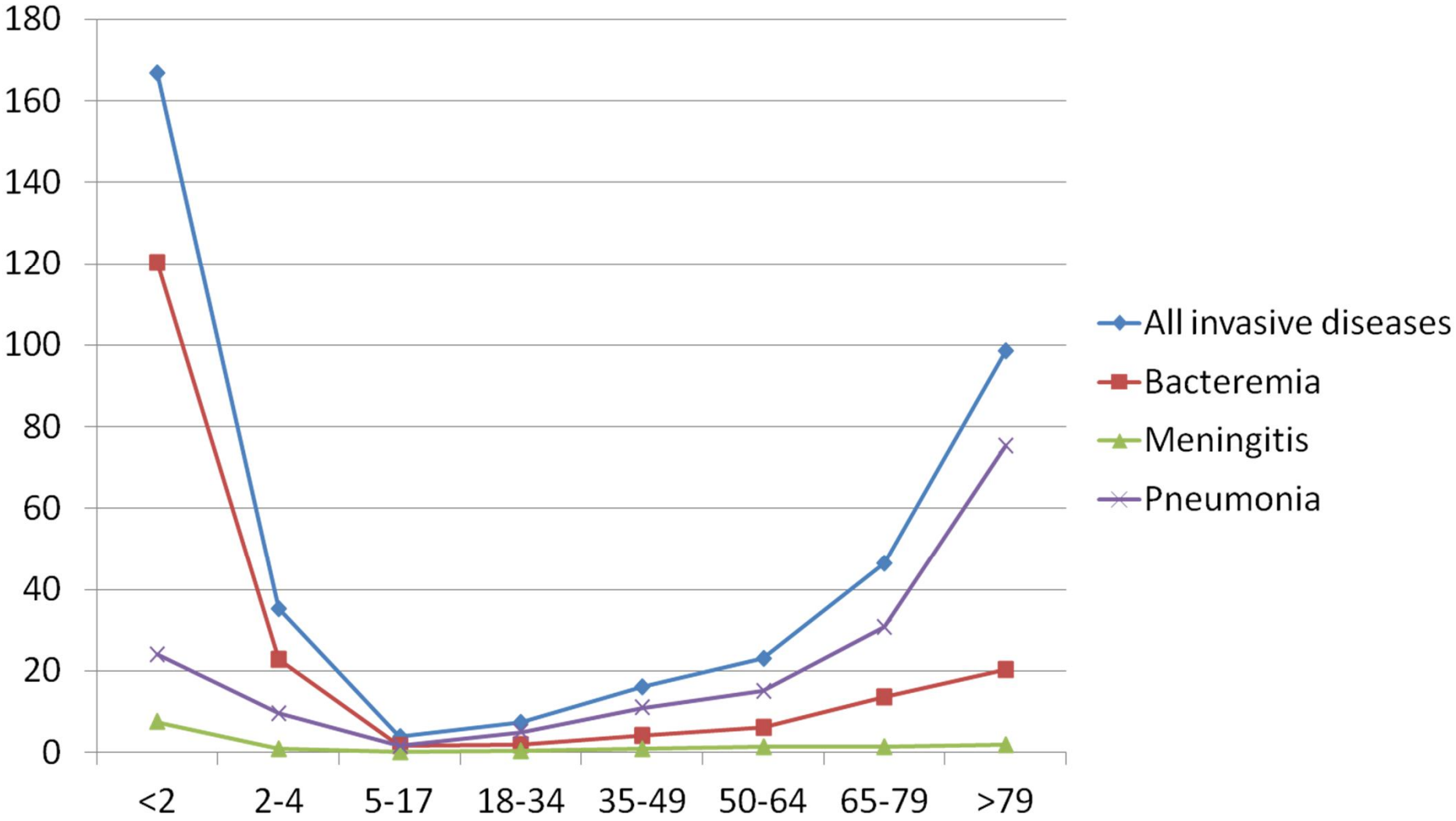
The relative attack rates were measured using national UK surveillance data on IPD incidence and data on incidence of pneumococcal acquisition from longitudinal studies of nasopharyngeal pneumococcal carriage in children <2 years.

Age distribution of reported IPD isolates (1992–2014) in Germany (n = 24,235)



van der Linden M, et al. Effects of Infant Pneumococcal Conjugate Vaccination on Serotype Distribution in Invasive Pneumococcal Disease among Children and Adults in Germany. PLoS One 2015;10(7): e0131494.

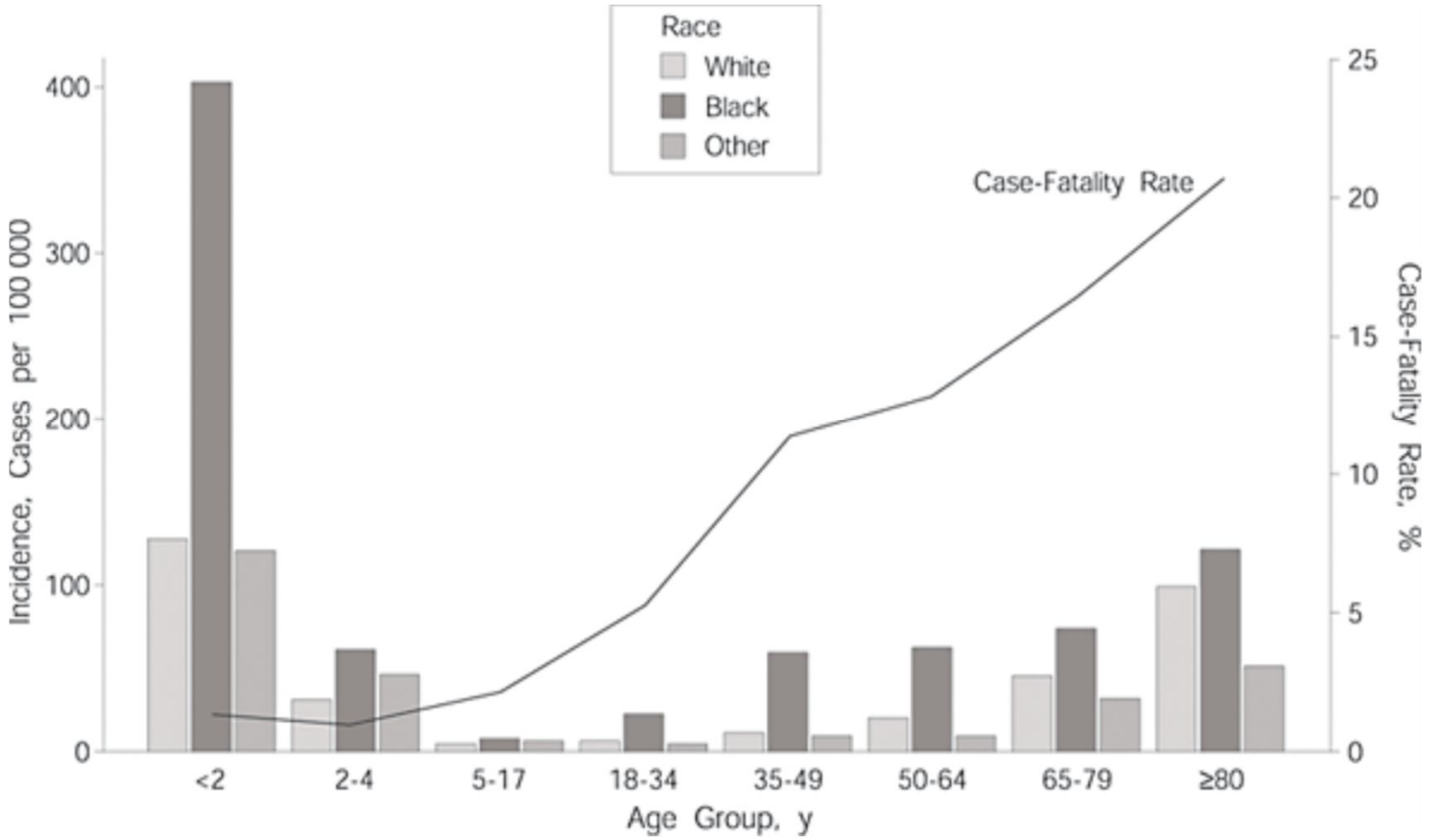
Incidence of IPD in the USA (/100,000), 1998



JAMA. 2001;285(13):1729-1735

From: **Epidemiology of Invasive Streptococcus pneumoniae Infections in the United States, 1995-1998: Opportunities for Prevention in the Conjugate Vaccine Era**

JAMA. 2001;285(13):1729-1735. doi:10.1001/jama.285.13.1729



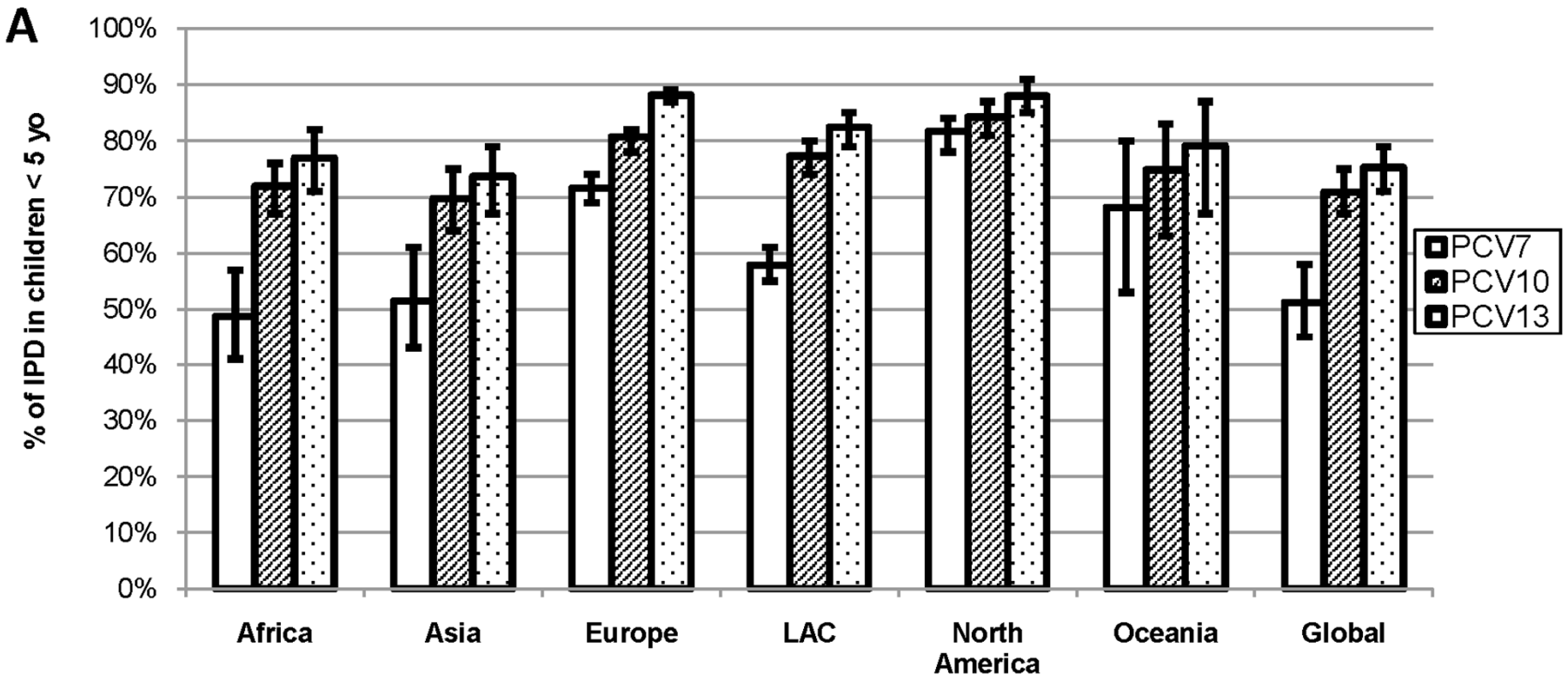
Pneumococcal vaccines

- **23-valent polysaccharide vaccine**, licensed in the US in 1983.
  - Poorly immunogenic before 2 years of age
  - It may not prevent nasopharyngeal colonization or mucosal infections
- **Pneumococcal conjugate vaccines (PCVs)** made by conjugating PSs to proteins. Their immunogenicity may be determined by:
  - The protein carrier
  - The method of conjugation
  - The ratio of PS to carrier
  - The length of the saccharide chains (PS vs oligosaccharide)
  - The quantity of PS
- PCV10 differs in terms of the carrier protein and conjugation methods from PCV7 and PCV13
- Variability of the conjugation process may influence the response and limit extrapolation of the results of one PCV formulation to another

Serotype composition of pneumococcal conjugate vaccines

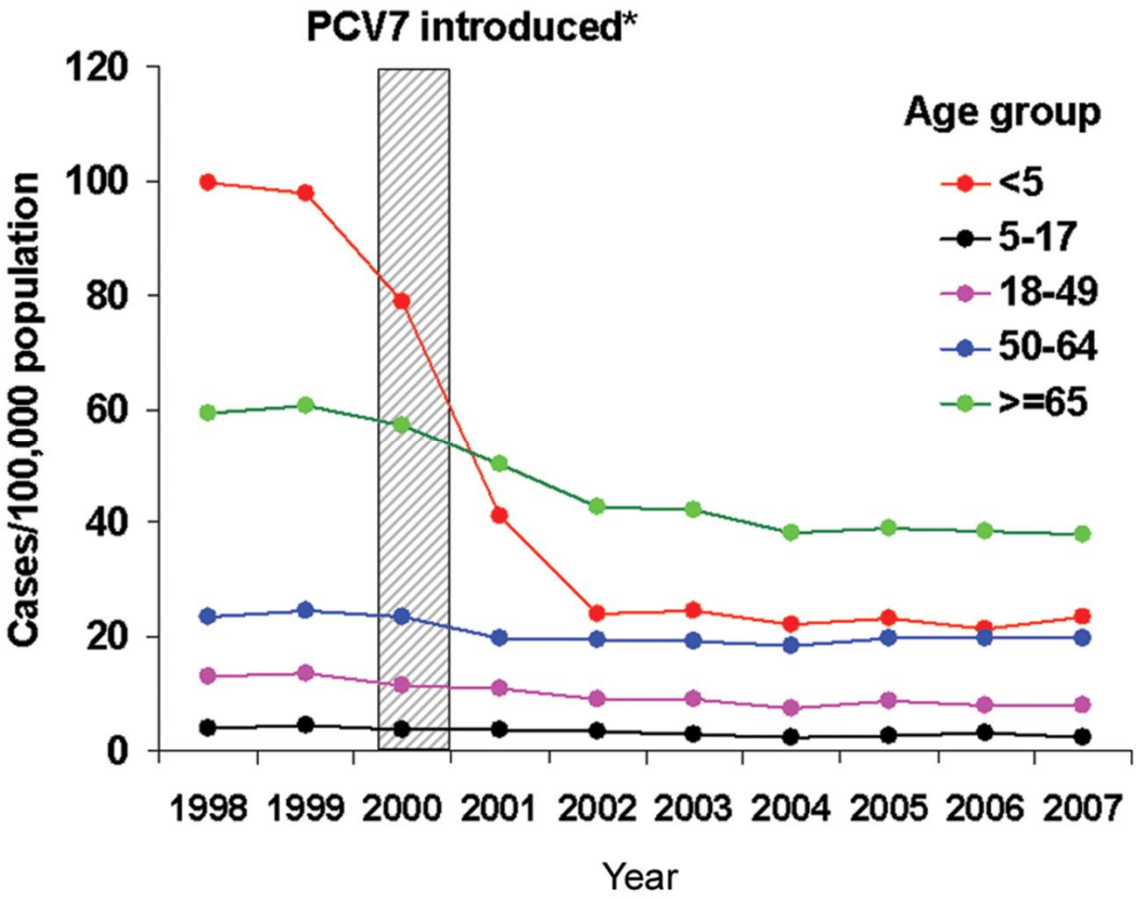
7-valent	10-valent	13-valent
4	4	4
6B	6B	6B
9V	9V	9V
14	14	14
18C	18C	18C
19F	19F	19F
23F	23F	23F
	1	1
	5	5
	7F	7F
		3
		6A
		19A

Proportion of IPD in children <5 years of age due to serotypes in existing PCV formulations.



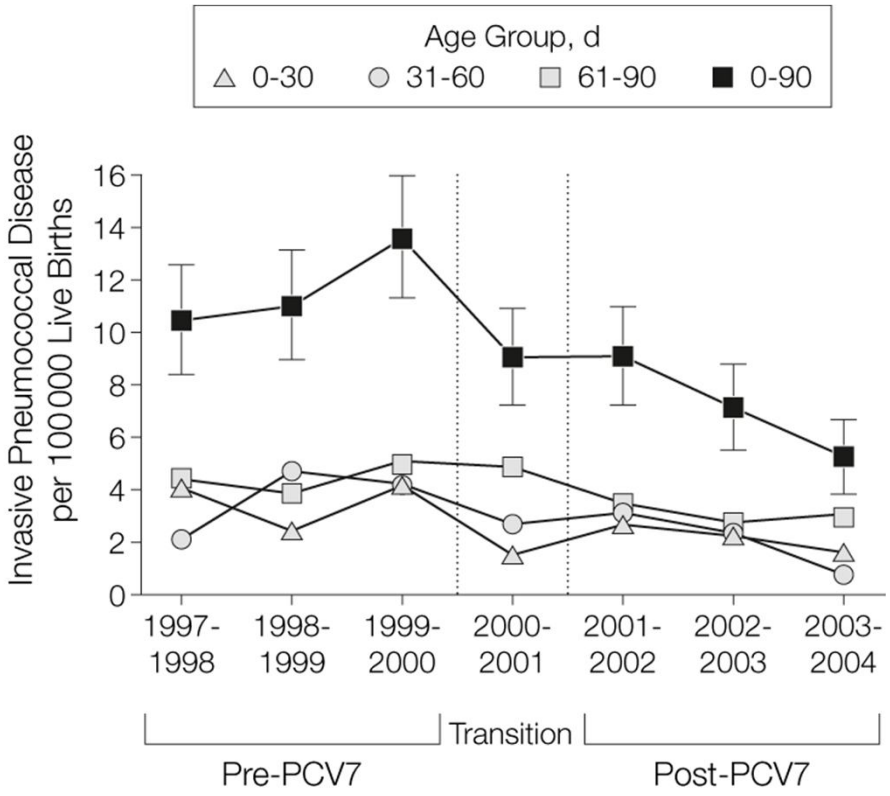
Johnson HL, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: The Pneumococcal Global Serotype Project. PLOS Medicine 2010;7(10): e1000348.

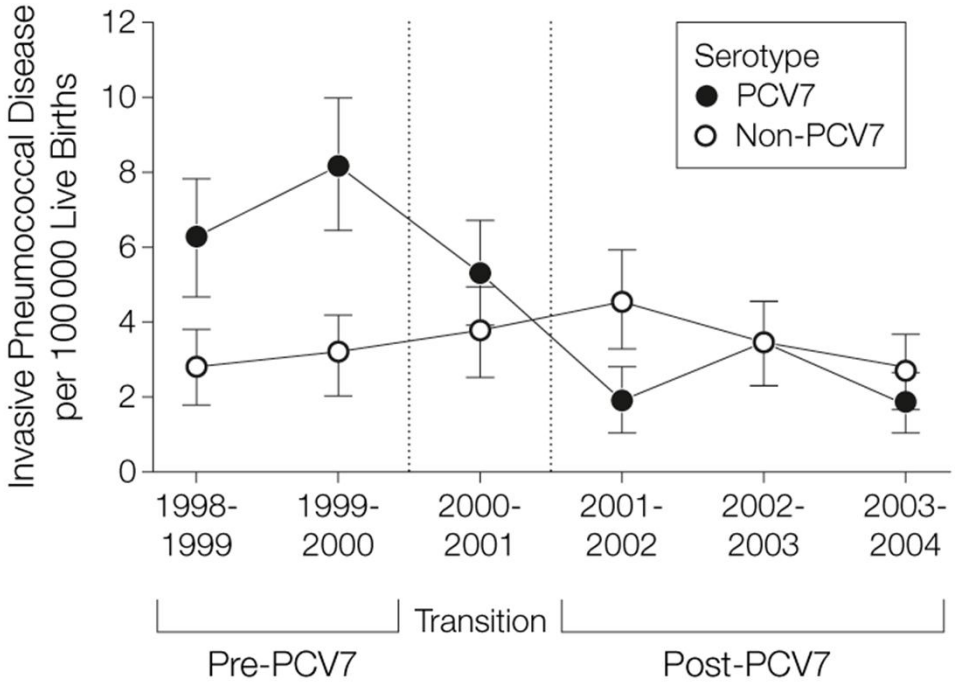
Changes in overall IPD incidence rates by age group, 1998–2007, USA.



JID 2010;201:32–41

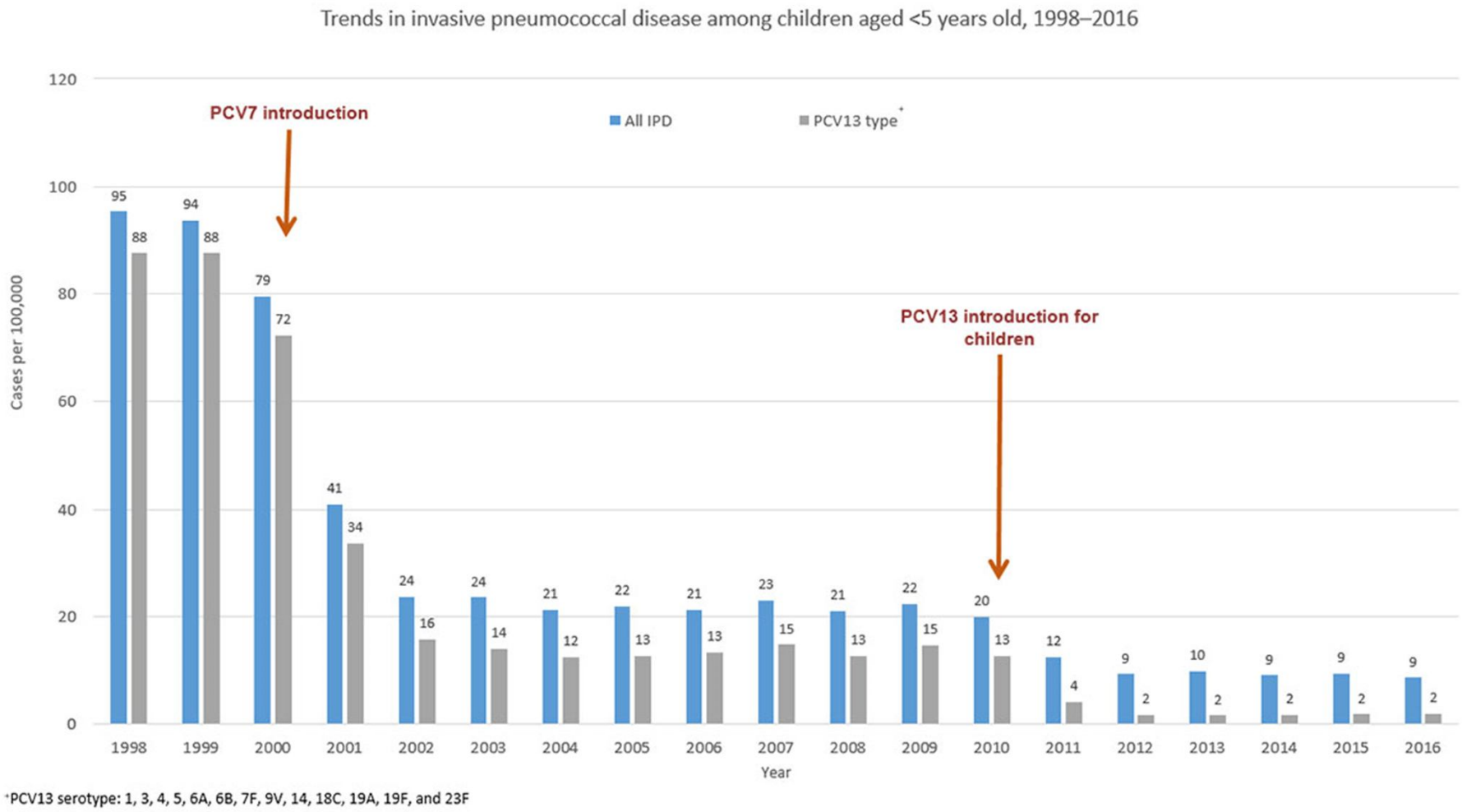
Evidence for herd effects in children.
Rates of IPD in infants aged 0-90 days.





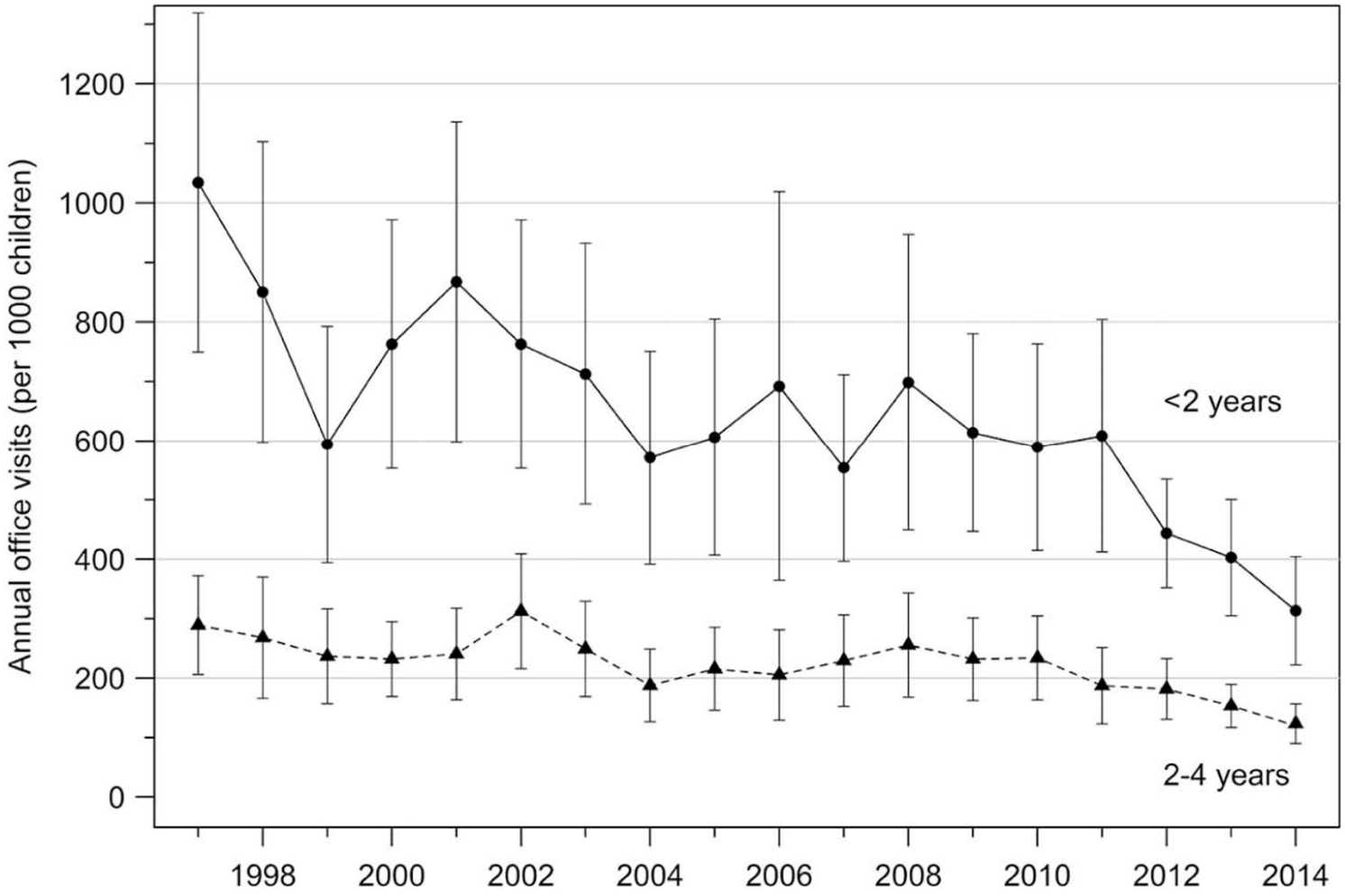
KA Poehling, et al. JAMA 2006;295:1668-74

Incidence of IPD among children <5 years old from 1998 through 2015 in the US



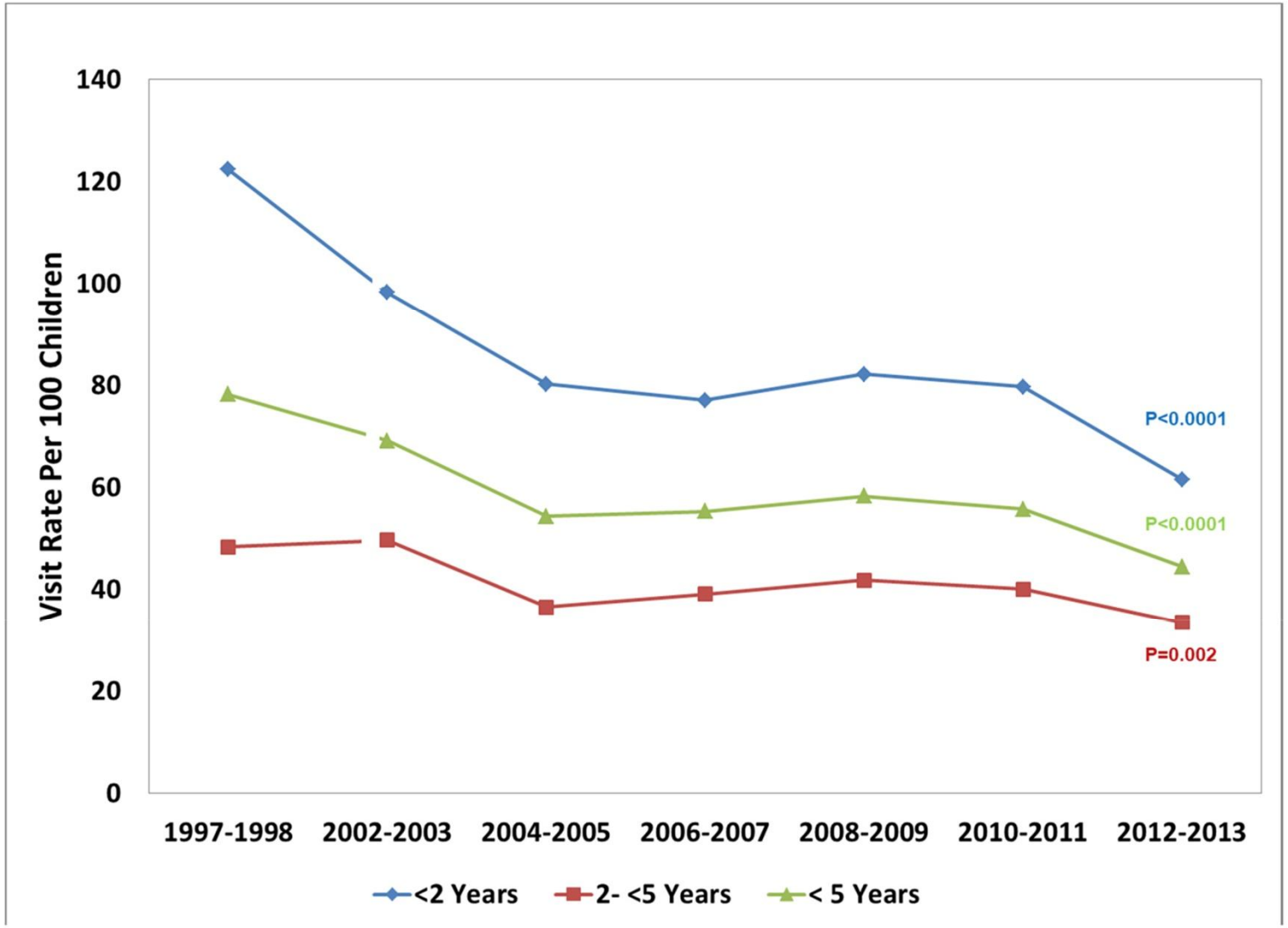
From: https://www.cdc.gov/abcs/reports-findings/survreports/spneu-types.html . Acceded 20 Feb 2019

Annual office visit for OM among children <5 years of age between 1997 to 2004 in the US



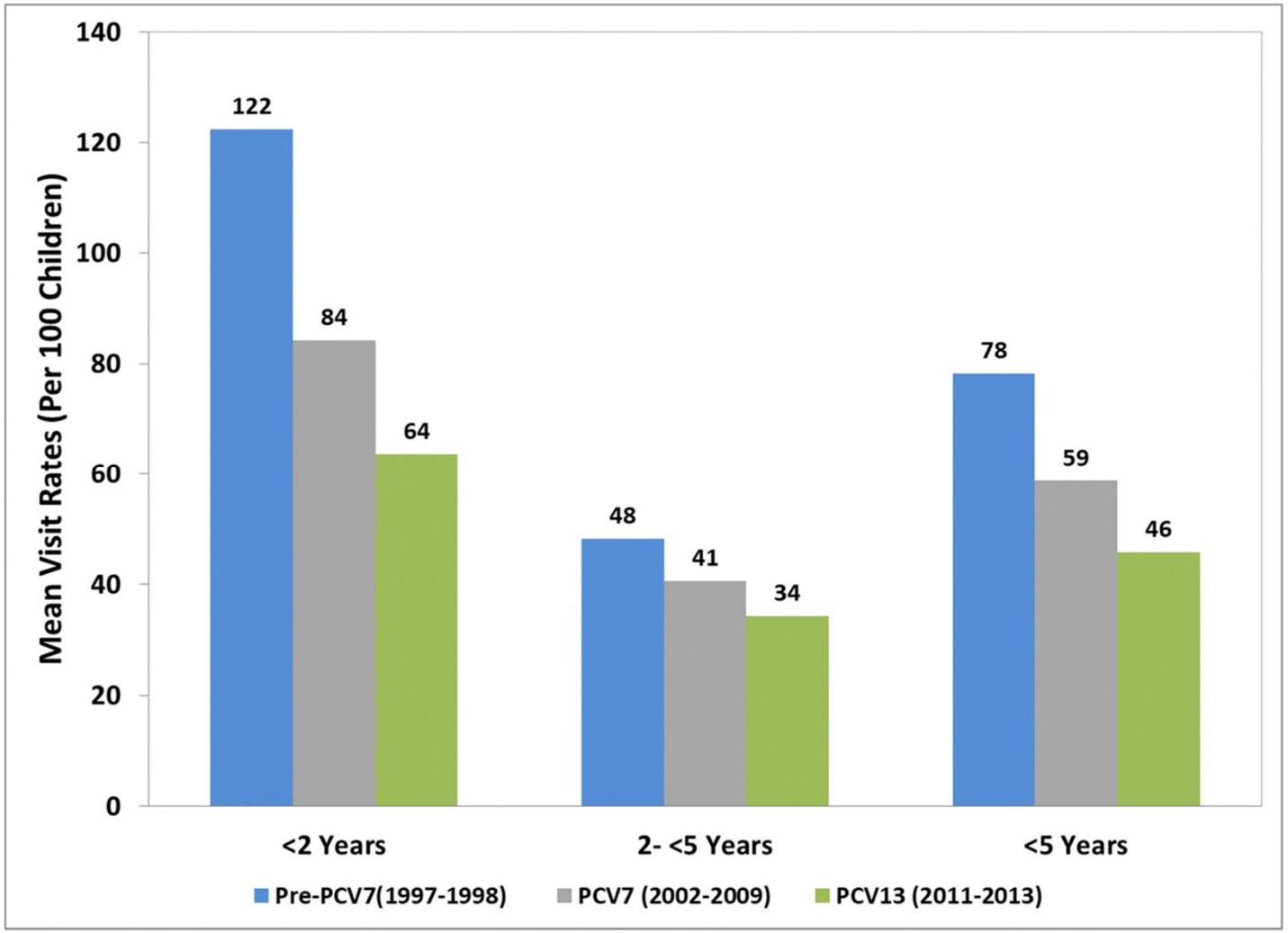
J Ped 2018;201:122-127

Average annual visit rates (per 100 children) of otitis media in the US



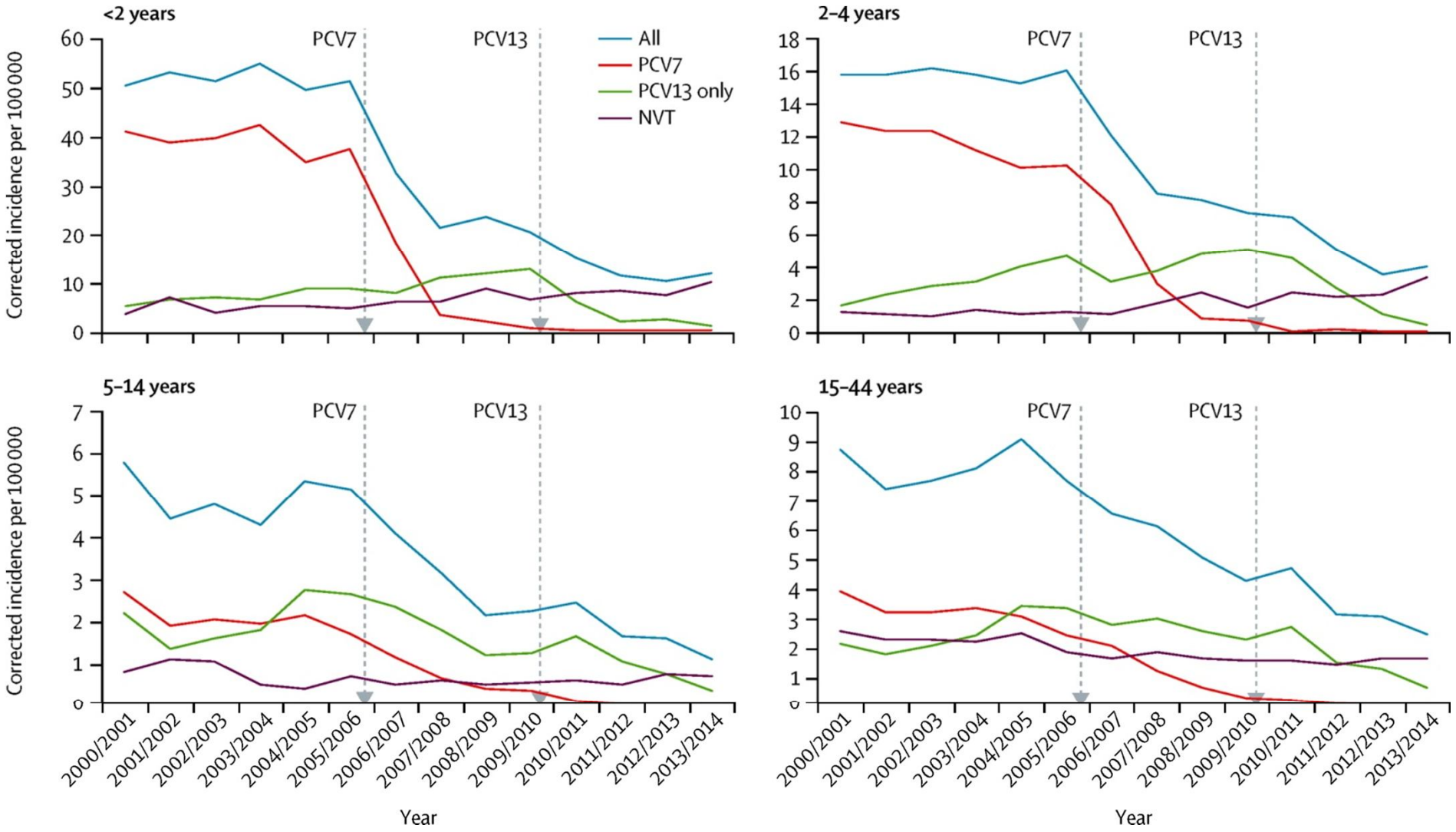
Int J Pediatr Otorhinolaryngol 2019;119:96-102

Mean OM visit rates (per 100 children) during the Pre-PCV7, PCV7, and PCV13 periods in the US



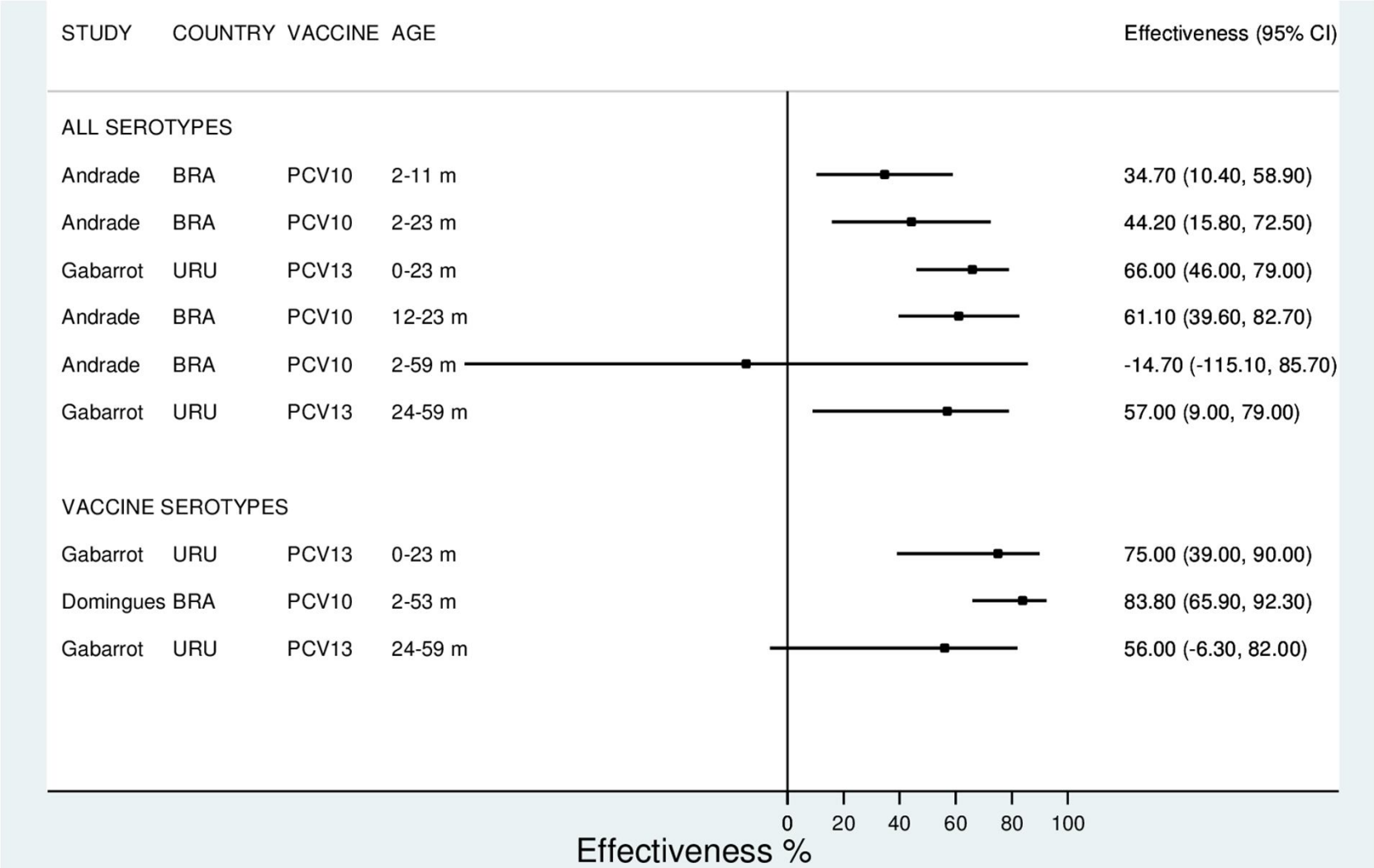
Int J Pediatr Otorhinolaryngol 2019;119:96-102

IPD incidence from epidemiological year 2000/01 to 2013/14, by serotype grouping and age in England and Wales



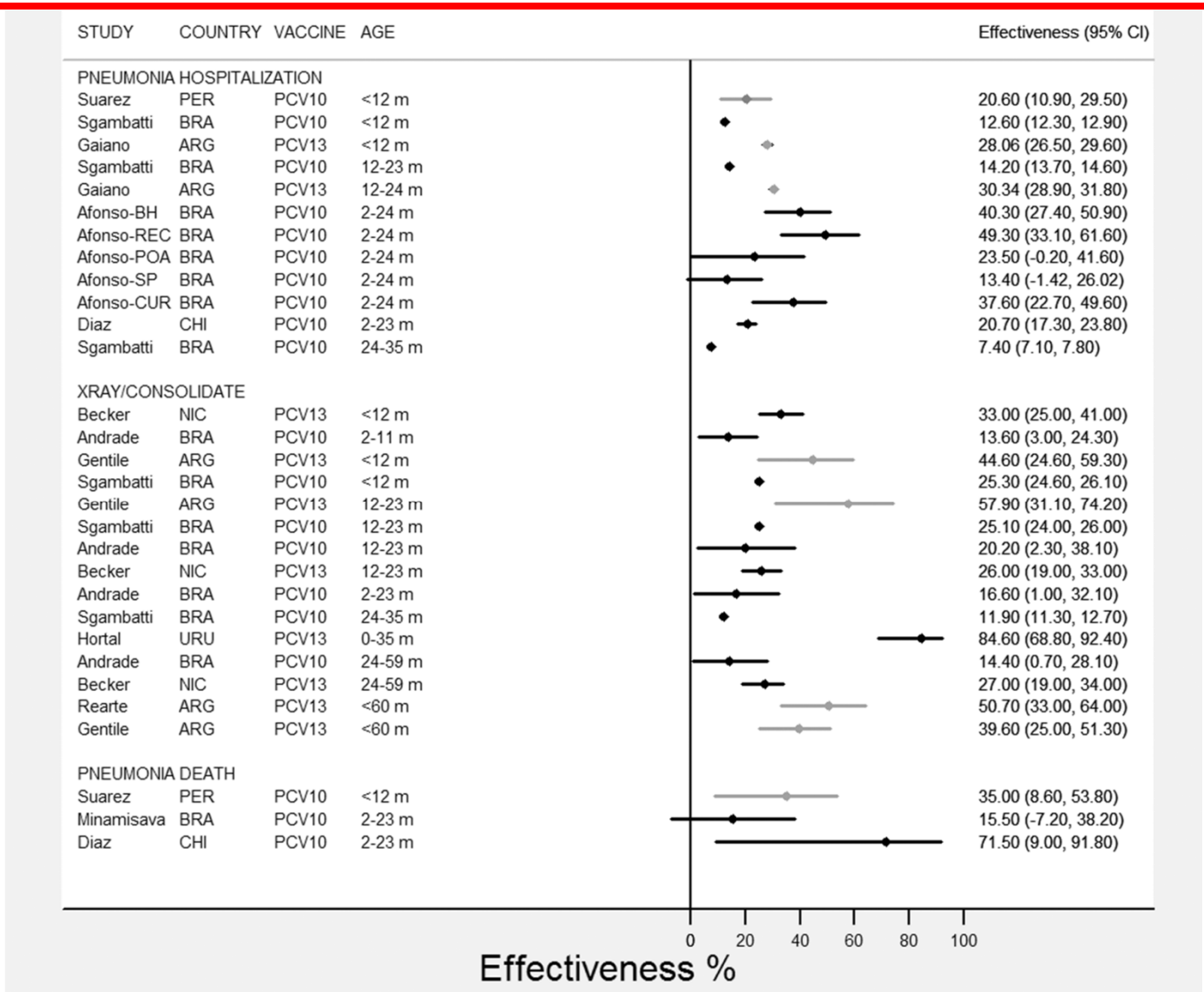
Waight PA, et al. Lancet Infect Dis 2015

Vaccine effectiveness against invasive bacterial disease, by vaccine, group of age, vaccine serotypes and all serotypes, and hospitalization or death.



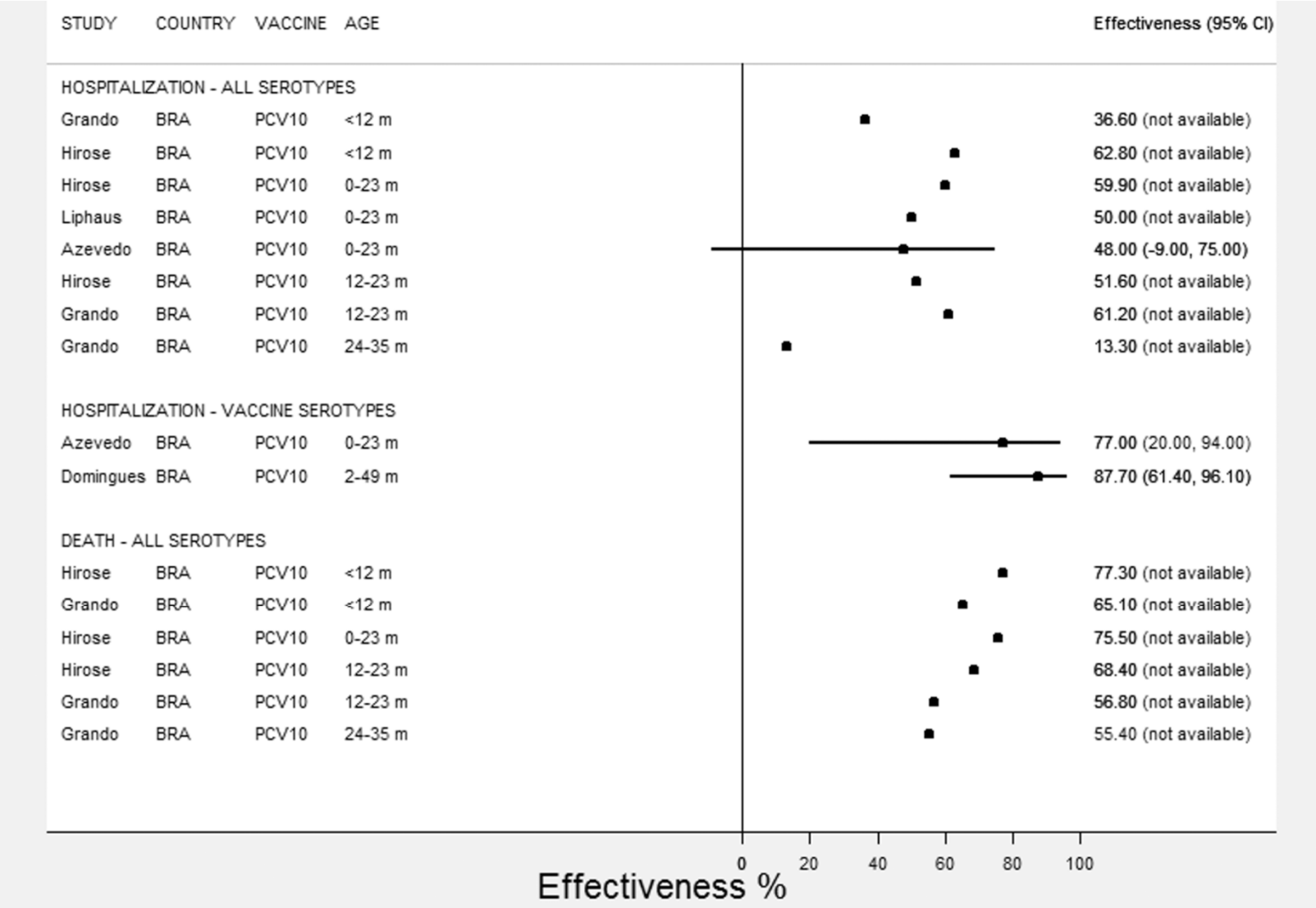
de Oliveira LH, et al. Impact and effectiveness of 10 and 13-valent pneumococcal conjugate vaccines on hospitalization and mortality in children <5 years in Latin American countries: A systematic review. PLoS One 2016;11(12):e0166736.

Vaccine effectiveness against pneumonias clinical and X-Ray/consolidated, by vaccine, group of age, and hospitalization or death.



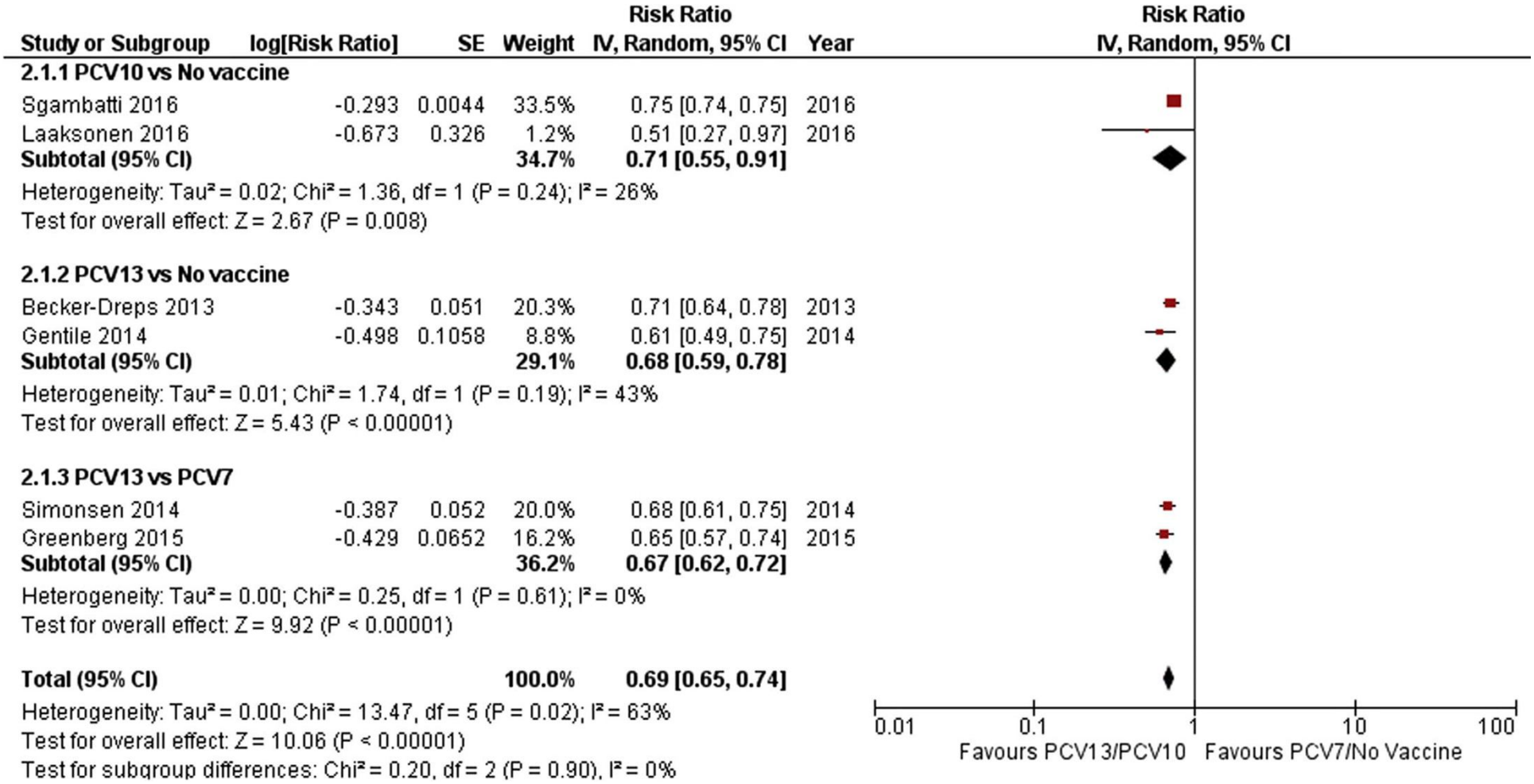
de Oliveira LH, et al. Impact and effectiveness of 10 and 13-valent pneumococcal conjugate vaccines on hospitalization and mortality in children <5 years in Latin American countries: A systematic review. PLoS One 2016;11(12):e0166736.

Vaccine effectiveness against meningitis, by vaccine, group of age, vaccine serotypes and all serotypes, and hospitalization or death.



de Oliveira LH, et al. Impact and effectiveness of 10 and 13-valent pneumococcal conjugate vaccines on hospitalization and mortality in children <5 years in Latin American countries: A systematic review. PLoS One 2016;11(12):e0166736.

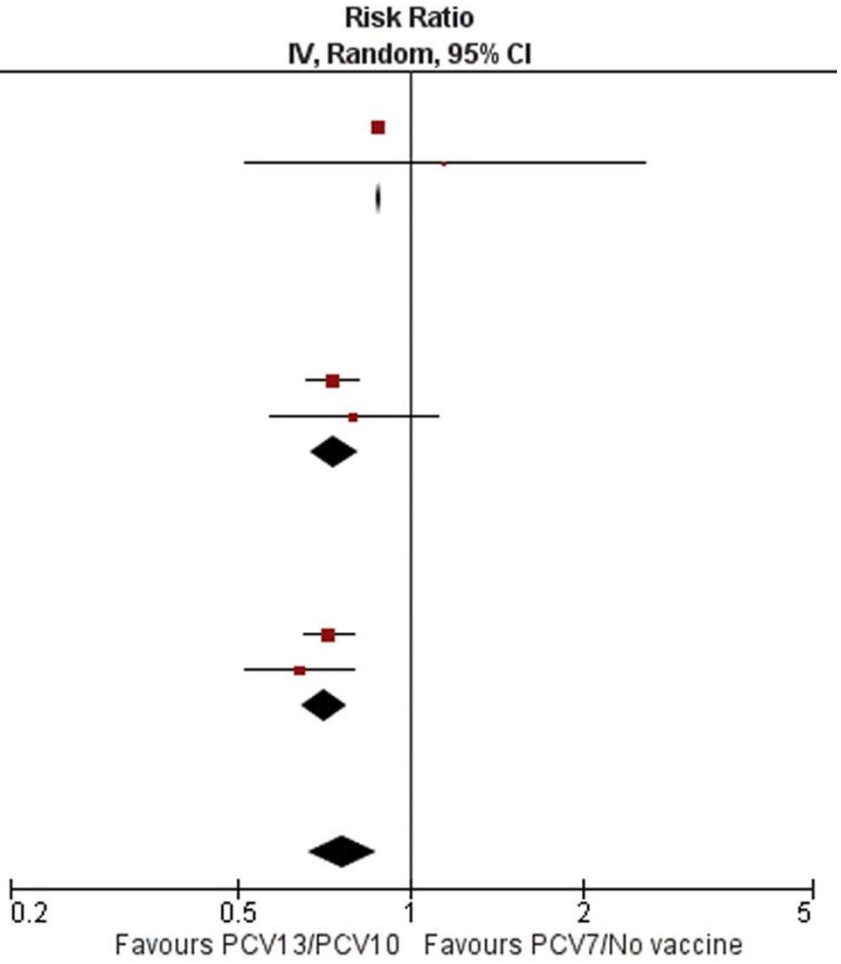
Meta-analysis of studies reporting hospitalization rates for X-ray confirmed pneumonia among children <24 months



Vaccine 2017;35;5776-85

Meta-analysis of studies reporting hospitalization rates for X-ray confirmed pneumonia among children aged 24–59 months.

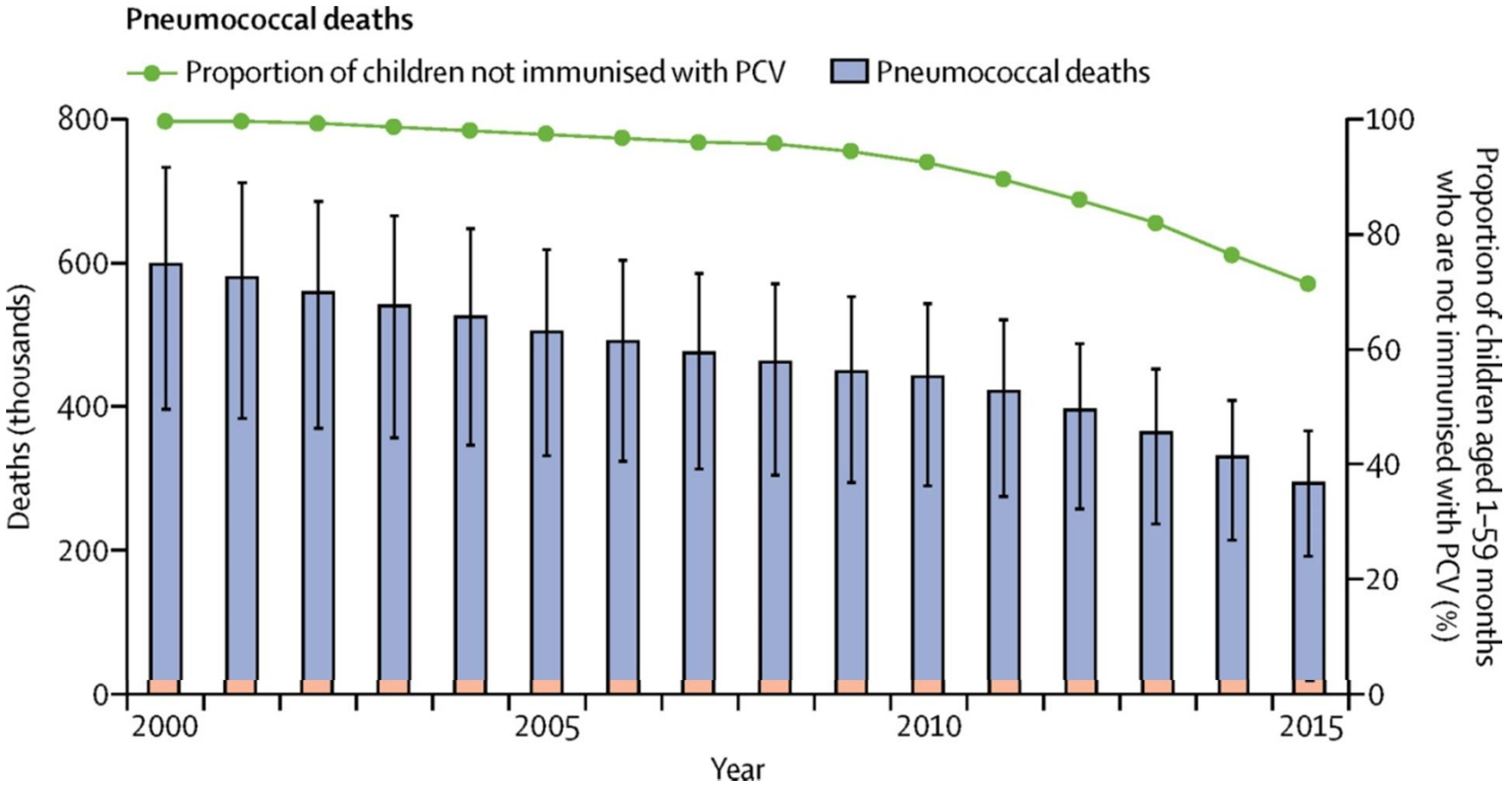
Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Random, 95% CI	Year
2.2.1 PCV10 vs No vaccine					
Sgambatti 2016	-0.1267	0.0041	26.0%	0.88 [0.87, 0.89]	2016
Laaksonen 2016	0.135	0.4095	2.6%	1.14 [0.51, 2.55]	2016
Subtotal (95% CI)			**28.6%**	**0.88 [0.87, 0.89]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%					
Test for overall effect: Z = 30.90 (P < 0.00001)					
2.2.2 PCV13 vs No vaccine					
Becker-Dreps 2013	-0.315	0.052	22.7%	0.73 [0.66, 0.81]	2013
Gentile 2014	-0.229	0.171	10.2%	0.80 [0.57, 1.11]	2014
Subtotal (95% CI)			**32.9%**	**0.74 [0.67, 0.81]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 1 (P = 0.63); I² = 0%					
Test for overall effect: Z = 6.19 (P < 0.00001)					
2.2.3 PCV13 vs PCV7					
Simonsen 2014	-0.331	0.051	22.9%	0.72 [0.65, 0.79]	2014
Greenberg 2015	-0.446	0.112	15.6%	0.64 [0.51, 0.80]	2015
Subtotal (95% CI)			**38.5%**	**0.70 [0.64, 0.77]**	
Heterogeneity: Tau² = 0.00; Chi² = 0.87, df = 1 (P = 0.35); I² = 0%					
Test for overall effect: Z = 7.56 (P < 0.00001)					
Total (95% CI)			**100.0%**	**0.76 [0.67, 0.88]**	
Heterogeneity: Tau² = 0.02; Chi² = 37.54, df = 5 (P < 0.00001); I² = 87%					
Test for overall effect: Z = 3.85 (P = 0.0001)					
Test for subgroup differences: Chi² = 36.03, df = 2 (P < 0.00001), I² = 94.4%					



Vaccine 2017;35;5776-85

Deaths due to pneumococcus in HIV-negative children aged 1–59 months.

The Lancet Global Health 2018;6(7):e744-e757



WHO/UNICEF vaccine coverage estimates have been adjusted to represent the proportion of children aged 1–59 months that received PCV.

Impact of vaccination on the nasopharyngeal microbial ecology

- As the carriage of vaccine serotypes decreases, the colonization with previously rare serotypes become more prevalent, altering the epidemiology of pneumococcal prevalence.
- Colonizations and infections with non vaccine serotypes increase in vaccinated population by
  - **Capsular switching**: occurs when the genes encoding one capsular serotype are exchanged, via transformation and recombination, with the genes encoding a different capsular serotype
  - **Serotype replacement**: is defined as a decrease in the prevalence of vaccine serotype pneumococci accompanied by a corresponding increase in non vaccine serotype pneumococci, which fill the ecological niche formerly occupied by the vaccine serotypes

Serotype replacement

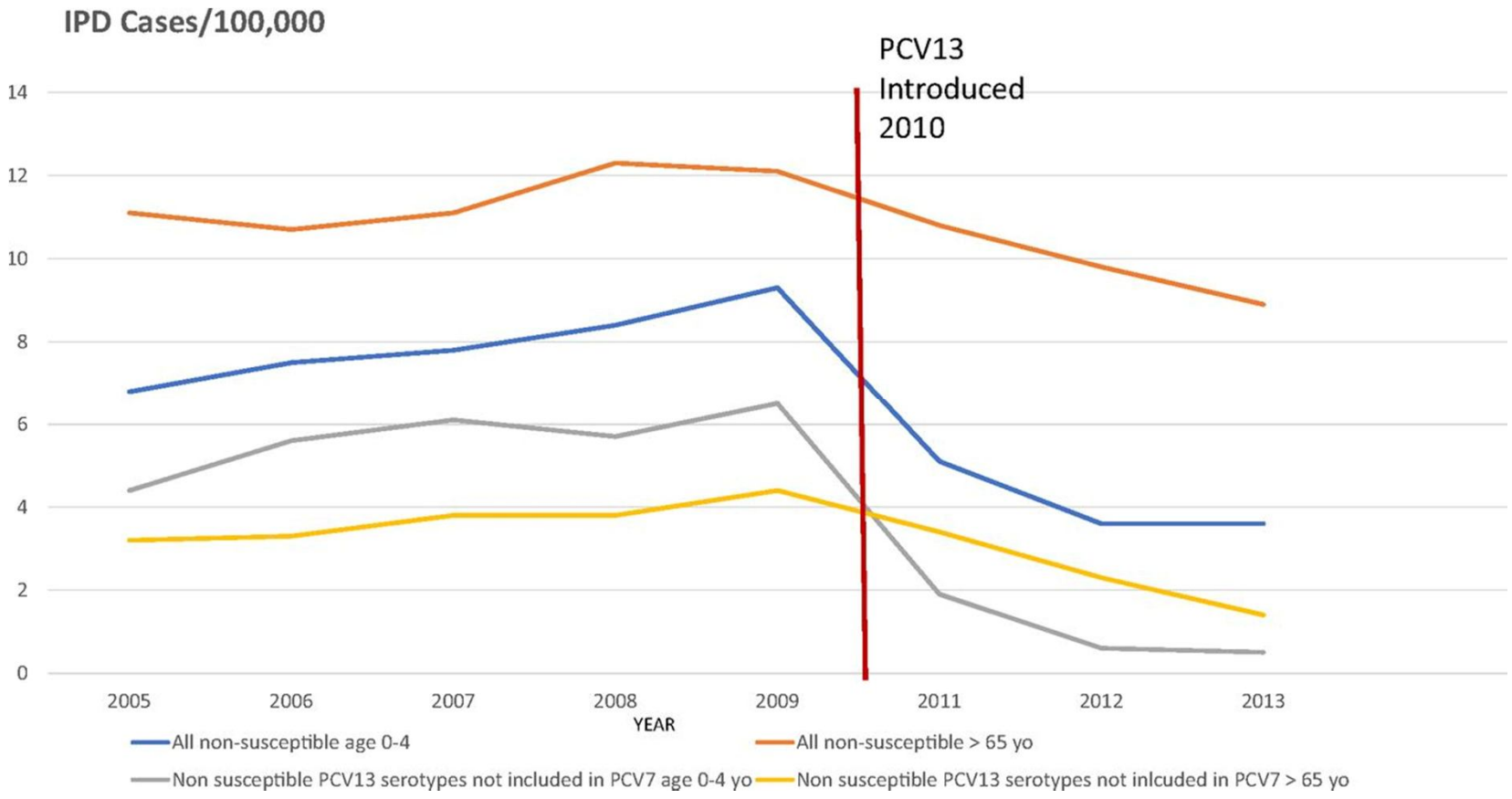
- Serotype replacement occurs wherever the conjugate vaccines have been used
- Serotype replacement has not affected the number of IPD cases prevented by the vaccine in the US
- However, serotype replacement has decreased the protective coverage of PCVs in other regions
- In the extreme, serotype replacement nullified the benefits of PCV7 as in parts of Alaska (PIDJ 2008) or in White Mountain Apaches population (CID 2008)

Effect of PCV on ATB-resistant strains

- PCV could impact antibiotic-resistant infections in two ways:
  - Through a direct reduction in the organisms and strains carrying resistant genes that are specifically targeted by the vaccine
  - Through a reduction in febrile illnesses that often lead to the use of antibiotics.

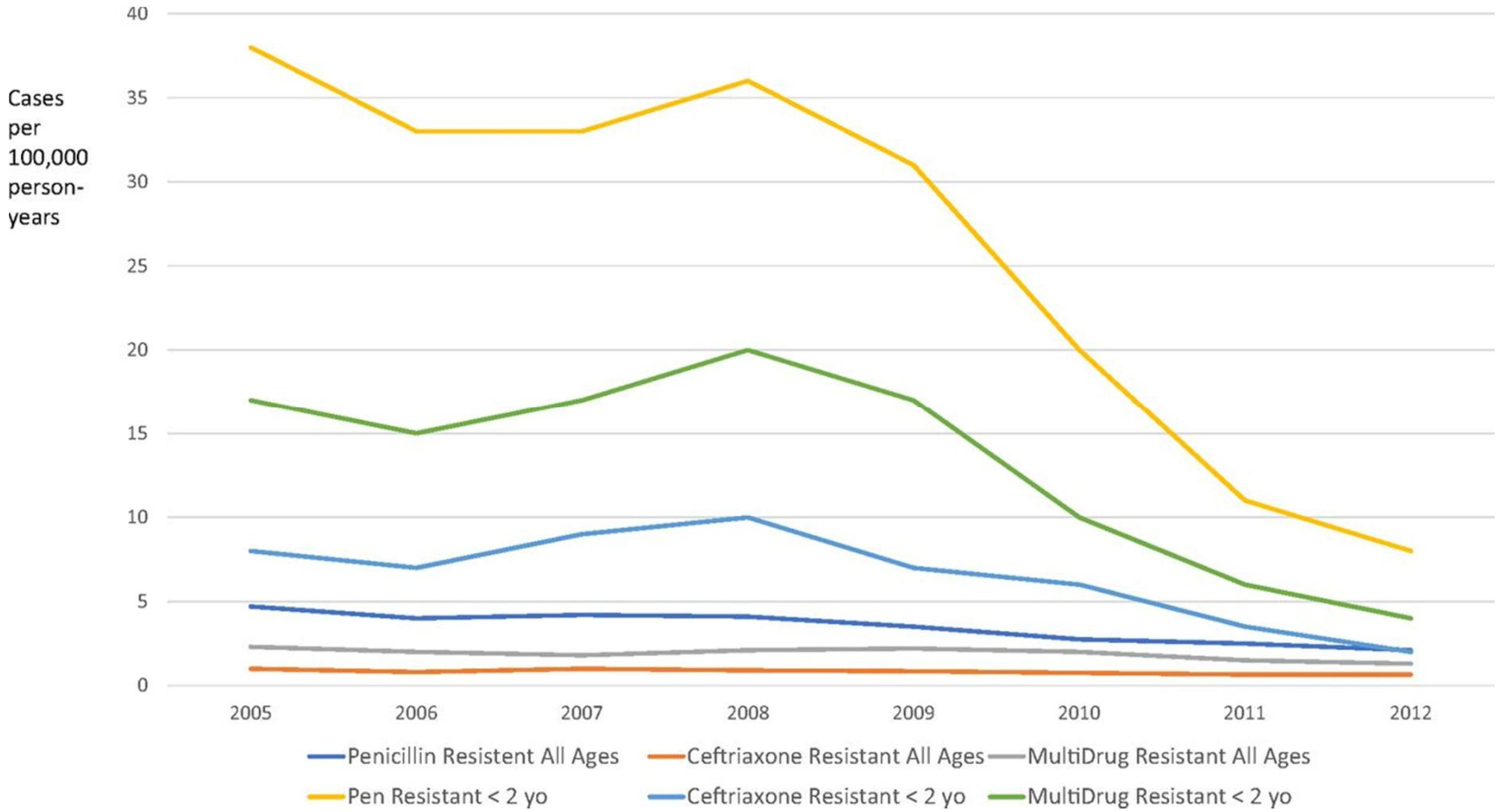
- Colonization with non vaccine serotypes increases in vaccinated population and some of these serotypes are also associated with resistance to antimicrobials

US trends in invasive non–penicillin-susceptible pneumococcal disease 2005–2013.



Keith P. Klugman, and Steven Black PNAS 2018;115:51:12896-12901

Trends in invasive pneumococcal disease in South Africa pre- and post-PCV introduction.



Keith P. Klugman, and Steven Black PNAS 2018;115:51:12896-12901

Impact of PCV

- Declines in disease rates in young children
- Herd benefit in unvaccinated children
- Fewer resistant infections

But….

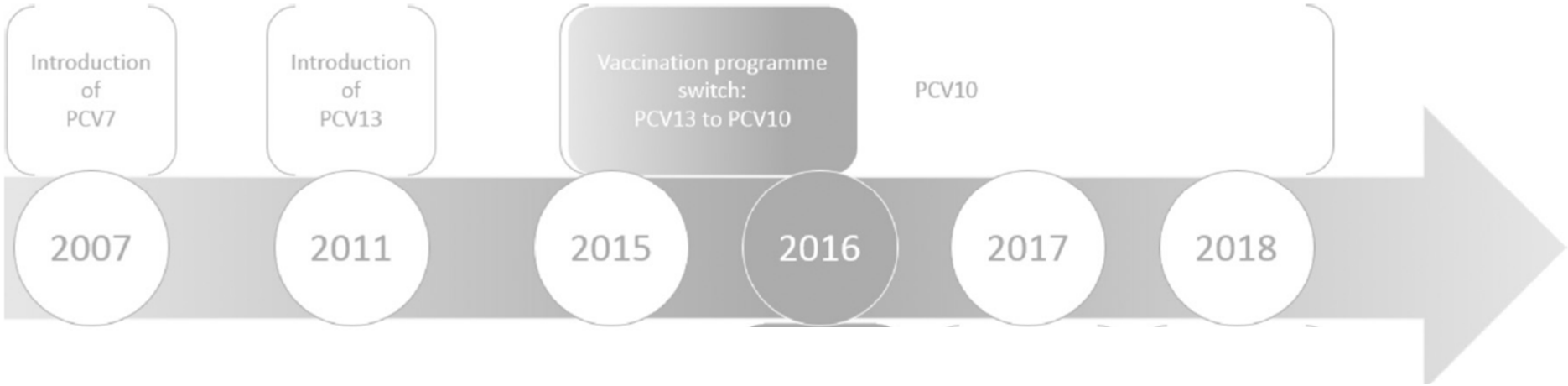
- Replacement disease by serotypes not in the vaccine reduces the overall impact of PCV

Conjugated anti-pneumococcal vaccines programme in Belgium

- Implemented in all infants since 2007 (2+1 schedule)
- 2007: PCV7
- 2011: PCV 13
- June 2015 (Flanders): PCV 10
- April 2016 (Wallonia): PCV 10
- High coverage (≈90%)

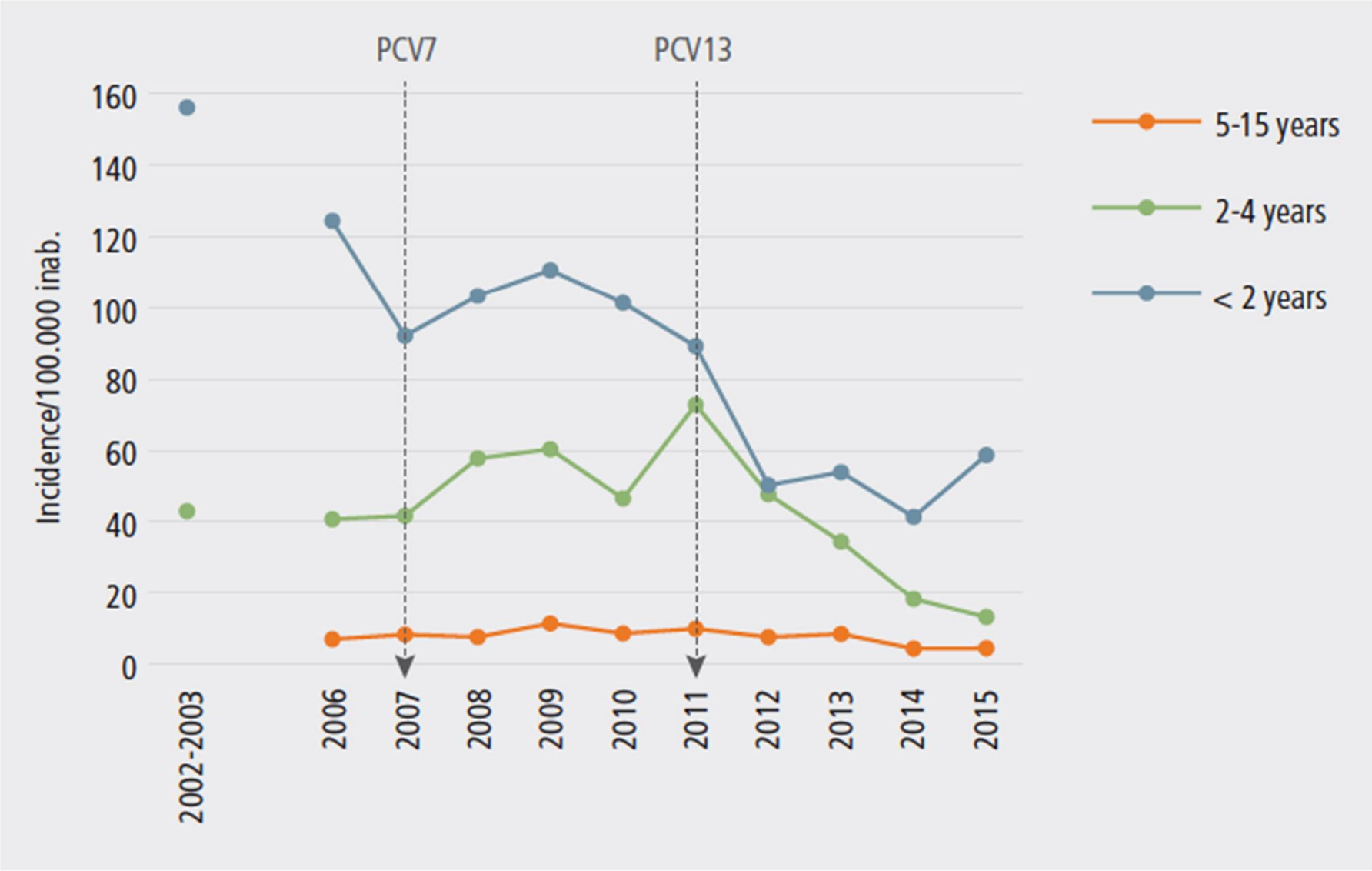
Conjugated anti-pneumococcal vaccines programme in Belgium

Implemented in all infants since 2007



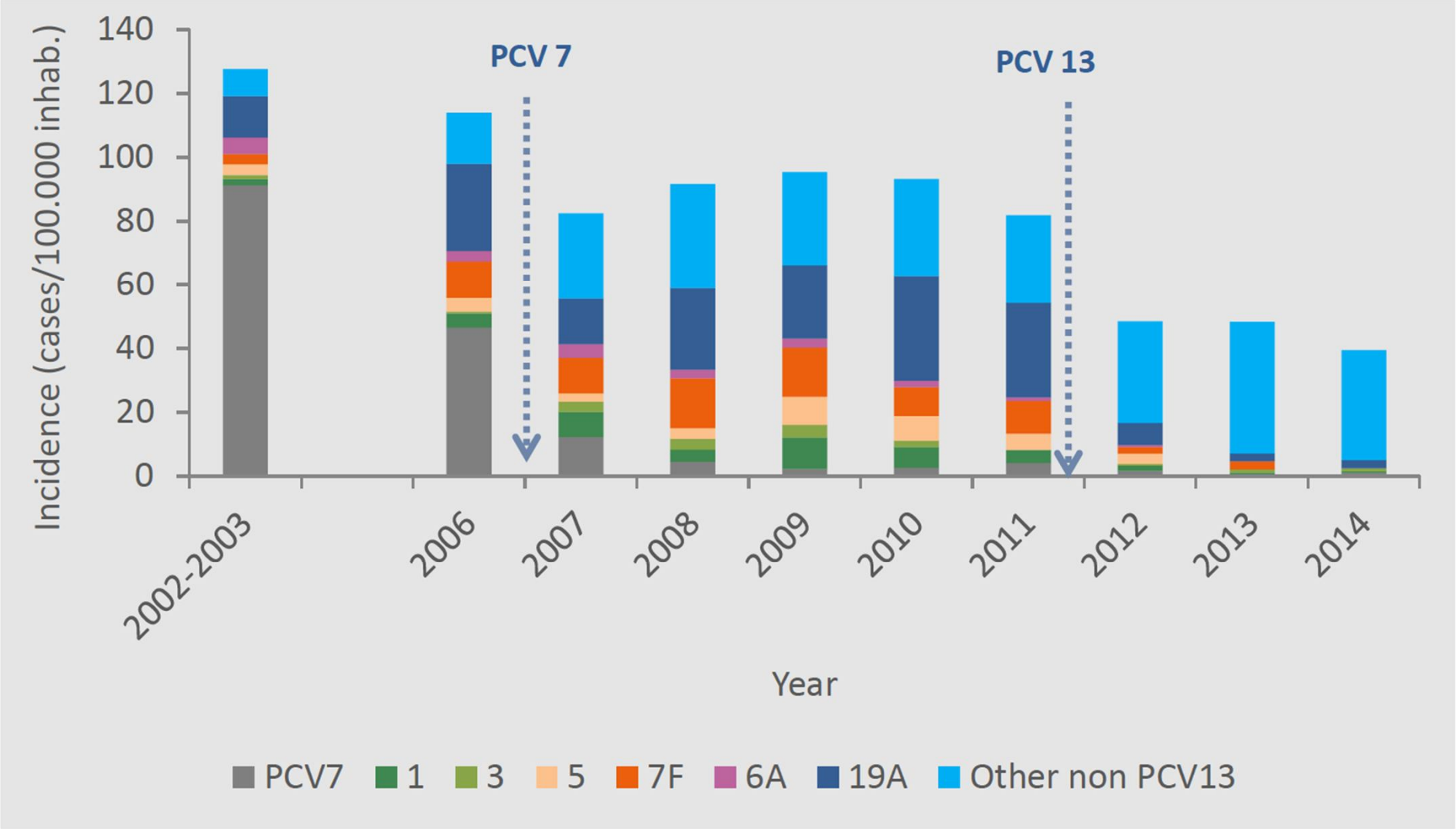
From: Nasopharyngeal *S. pneumoniae* carriage and density in Belgian infants after 9 years of pneumococcal conjugate vaccine programme.
Ine Wouters et al. Vaccine 2018;36:15-22.

Incidence of IPD in children <16 years in Belgium by age group (Sources PediSurv (WIV-ISP))



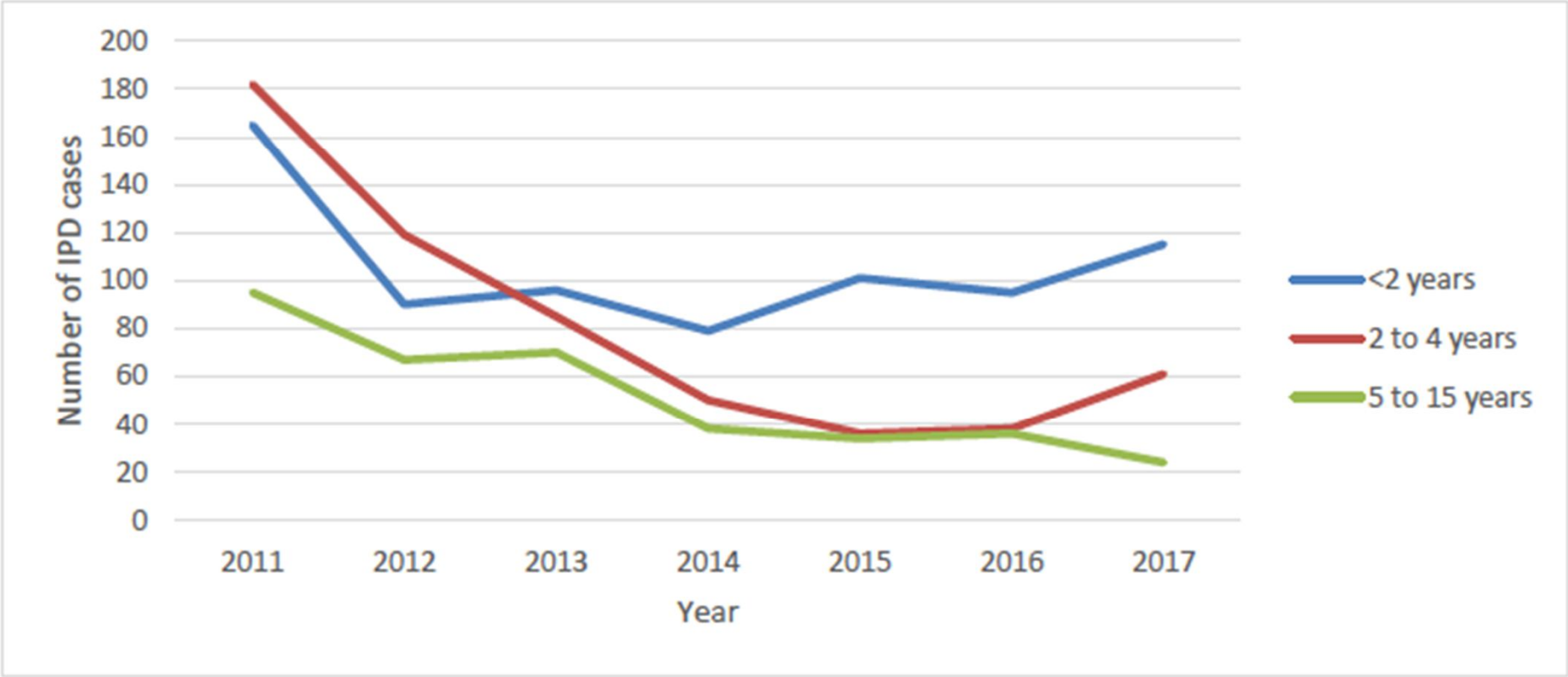
Incidence of IPD by serotype group among children <2 years in Belgium

(CNR *S. pneumoniae*, UZ Leuven, PediSurv, WIV-ISP)



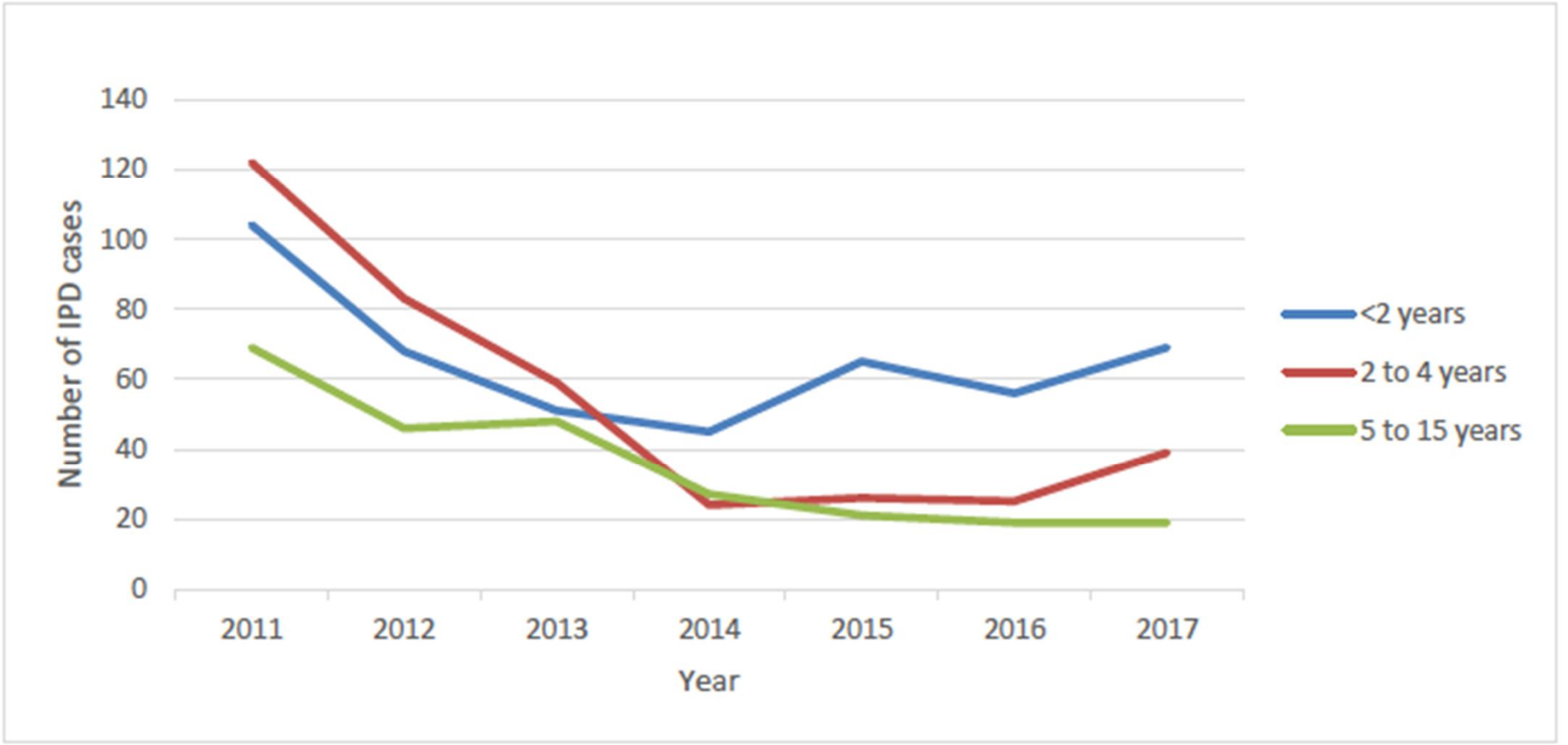
Cases of IPD in children <16 years in Belgium by age, 2011-2017

(Source des données: CNR *S. pneumoniae*, UZ Leuven)



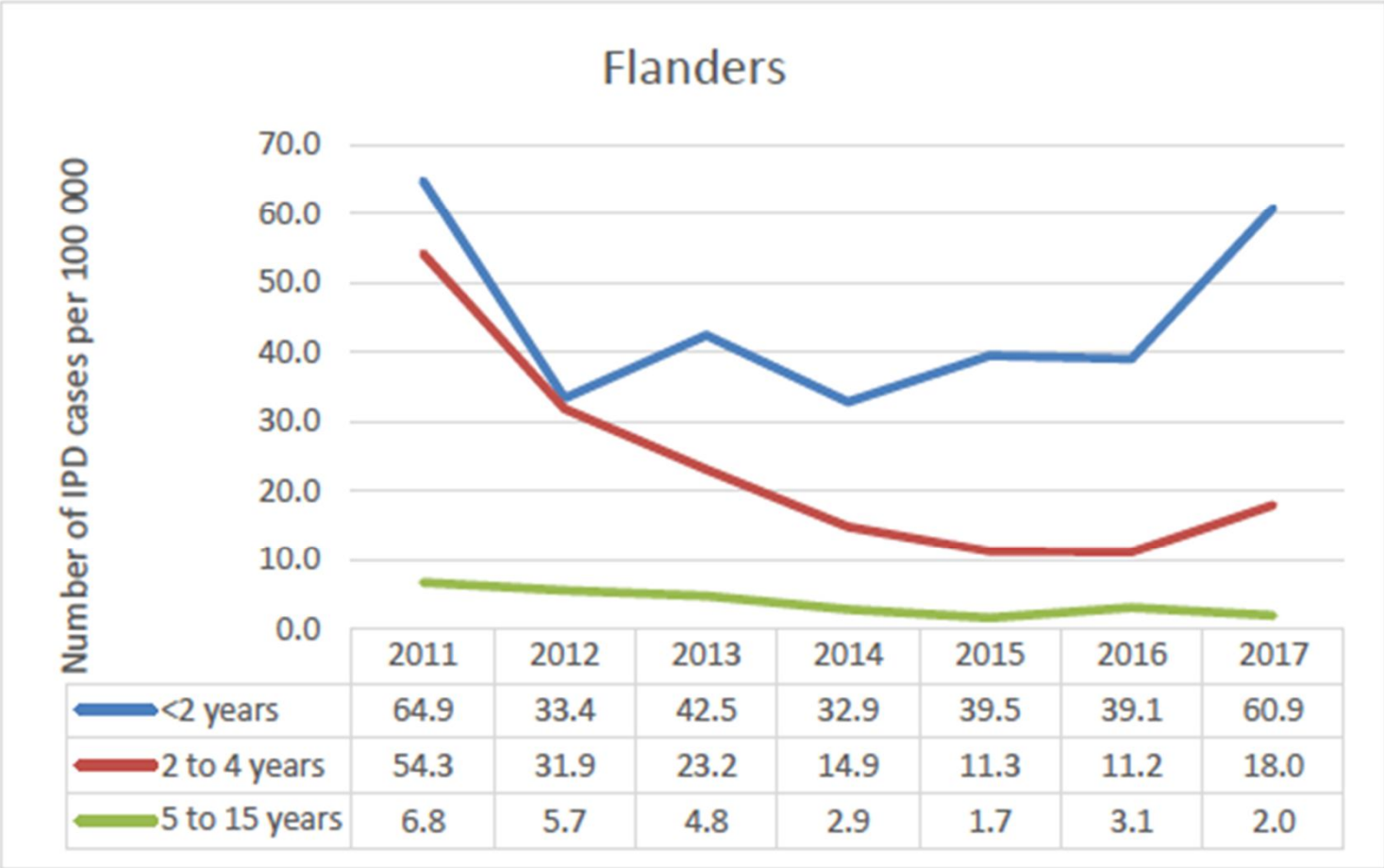
Cases of IPD in children <16 years in Belgium by age, 2011-2017

(Source des données: Laboratoires vigies, Sciensano)



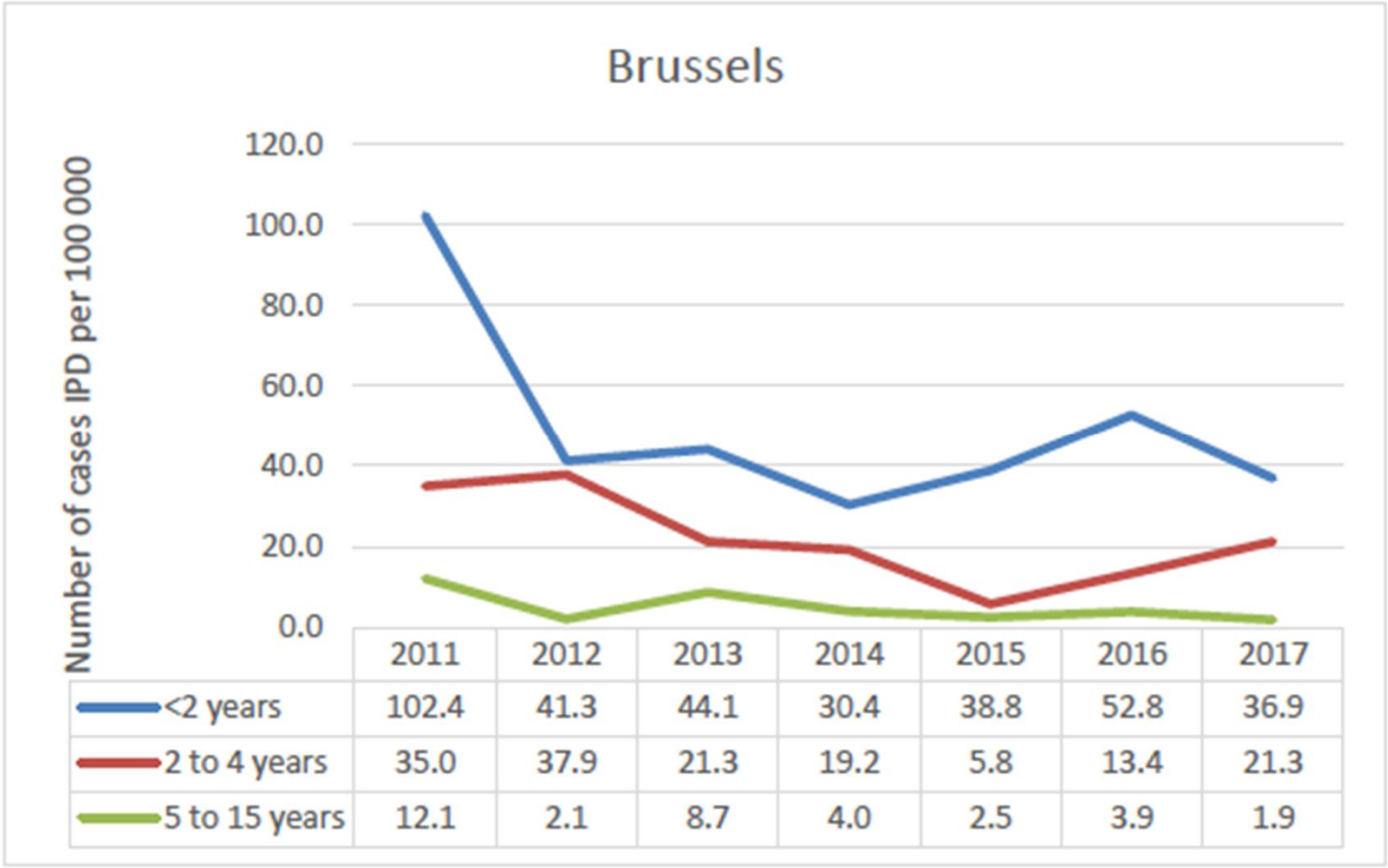
Cases of IPD in children <16 years in Flanders per 100,000 children of the same age category, 2011-2017

(Source: CNR *S. pneumoniae*, UZ Leuven)



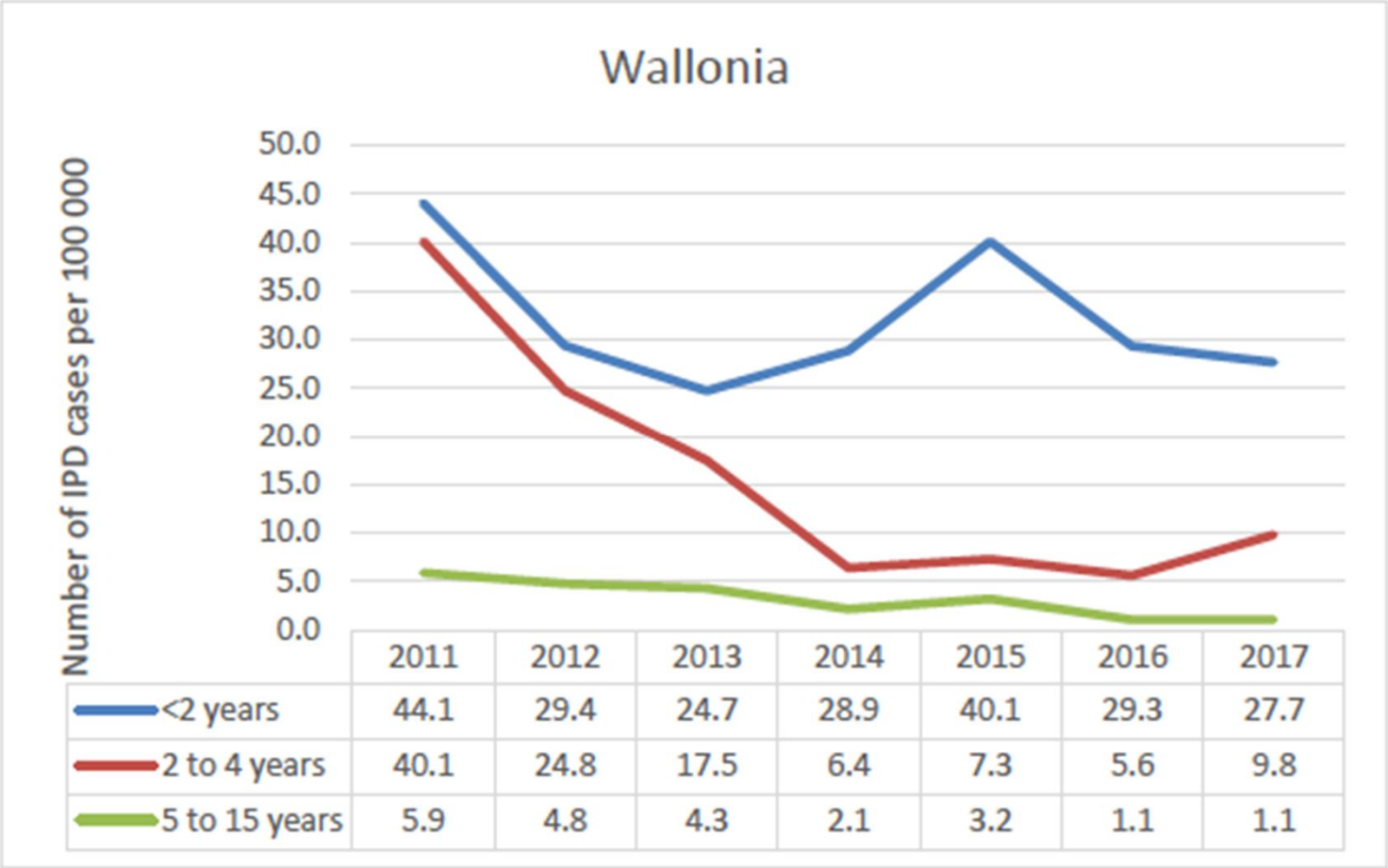
	2011	2012	2013	2014	2015	2016	2017
<2 years	64.9	33.4	42.5	32.9	39.5	39.1	60.9
2 to 4 years	54.3	31.9	23.2	14.9	11.3	11.2	18.0
5 to 15 years	6.8	5.7	4.8	2.9	1.7	3.1	2.0

Cases of IPD in children <16 years in Brussels per 100,000 children of the same age category, 2011-2017



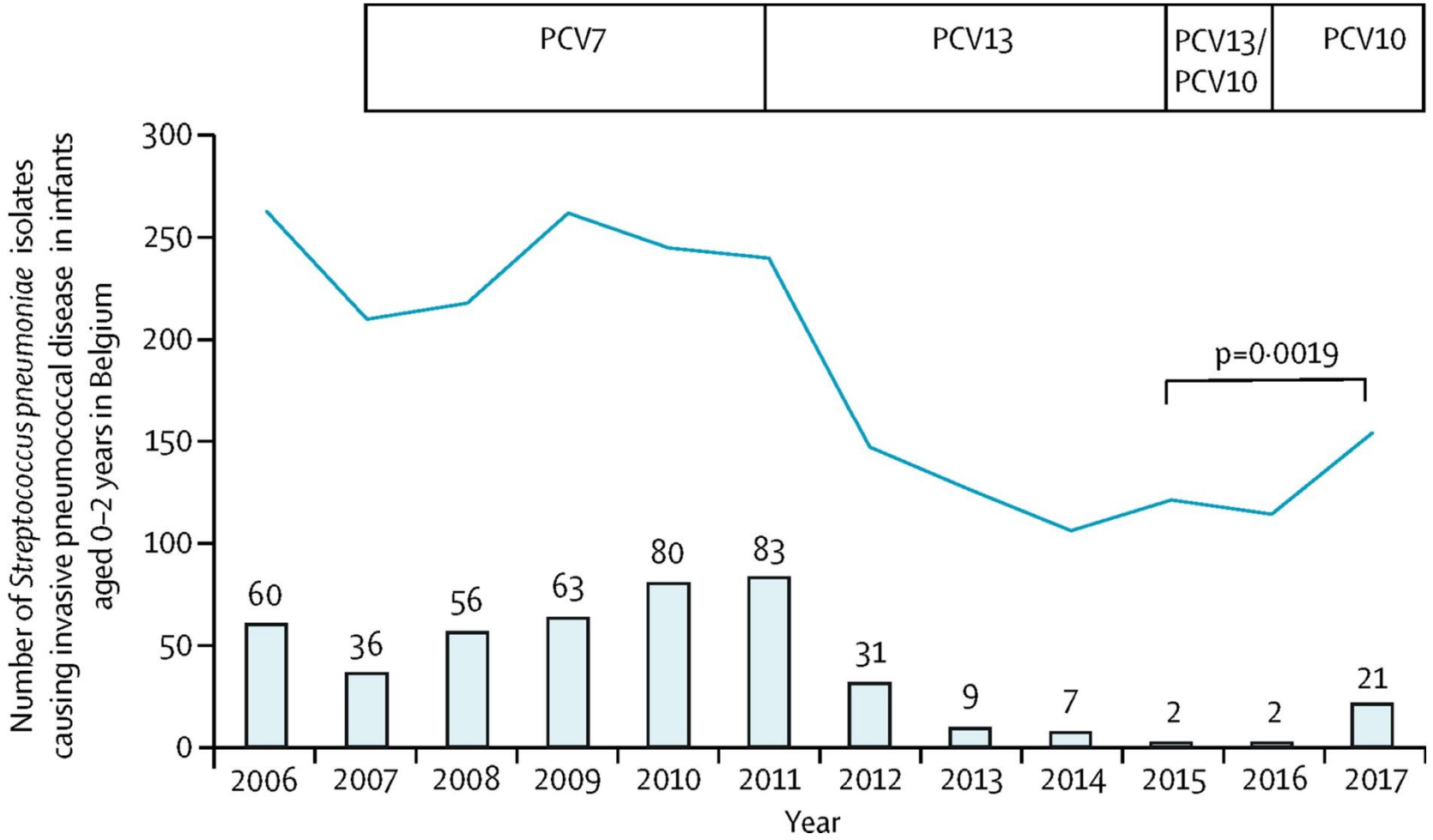
	2011	2012	2013	2014	2015	2016	2017
<2 years	102.4	41.3	44.1	30.4	38.8	52.8	36.9
2 to 4 years	35.0	37.9	21.3	19.2	5.8	13.4	21.3
5 to 15 years	12.1	2.1	8.7	4.0	2.5	3.9	1.9

Cases of IPD in children <16 years in Wallonia per 100,000 children of the same age category, 2011-2017



	2011	2012	2013	2014	2015	2016	2017
<2 years	44.1	29.4	24.7	28.9	40.1	29.3	27.7
2 to 4 years	40.1	24.8	17.5	6.4	7.3	5.6	9.8
5 to 15 years	5.9	4.8	4.3	2.1	3.2	1.1	1.1

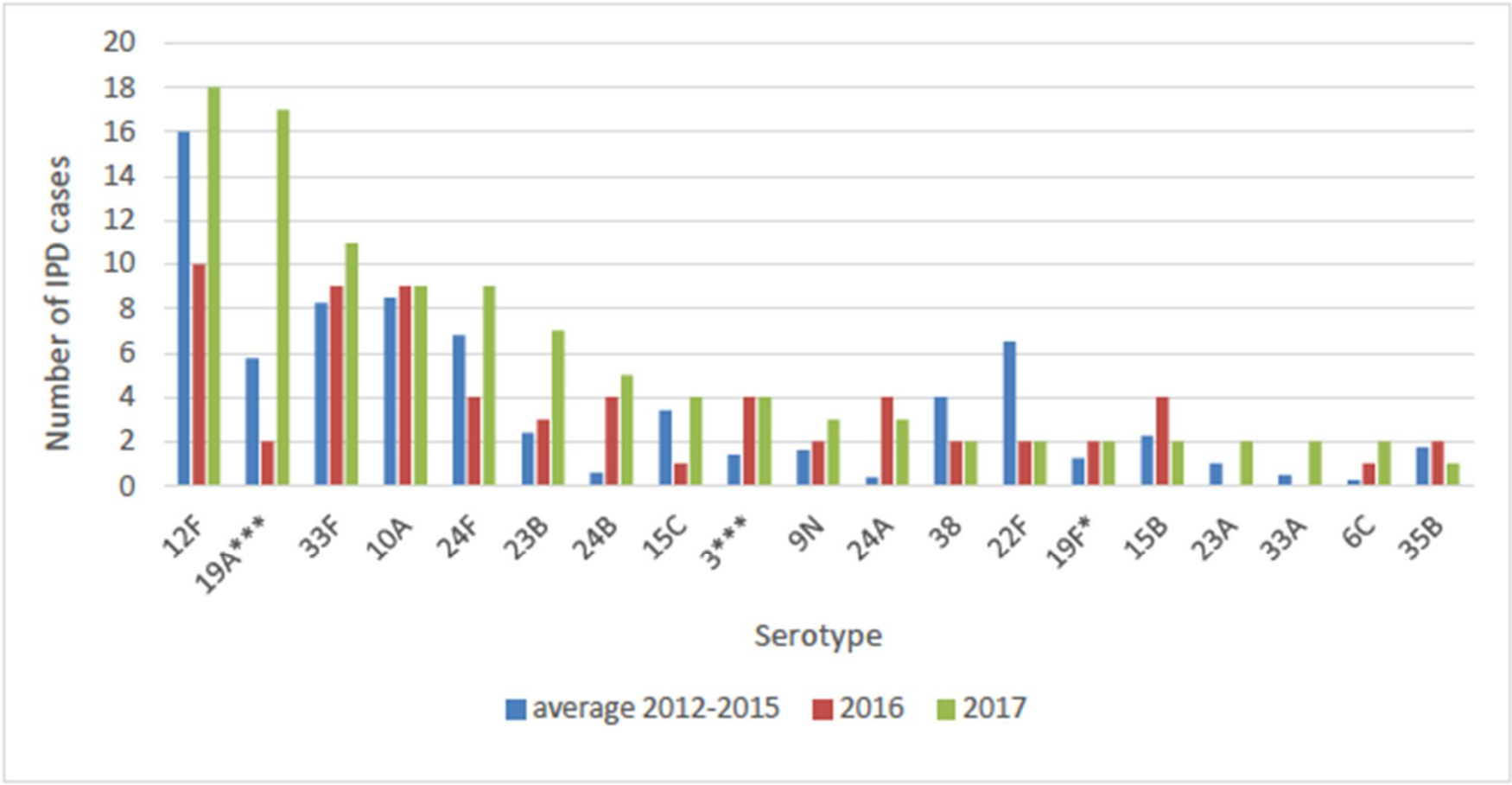
Numbers of pneumococcal isolates (line) and serotype 19A isolates (columns) in Belgium causing IPD in children <2 years, 2006-17



Desmet S, et al. Lancet Infect Dis 2018;18:830-31

Serotypes isolated among the cases of IPD in children <2 years in Belgium: mean 2011 to 2015, 2016 and 2017

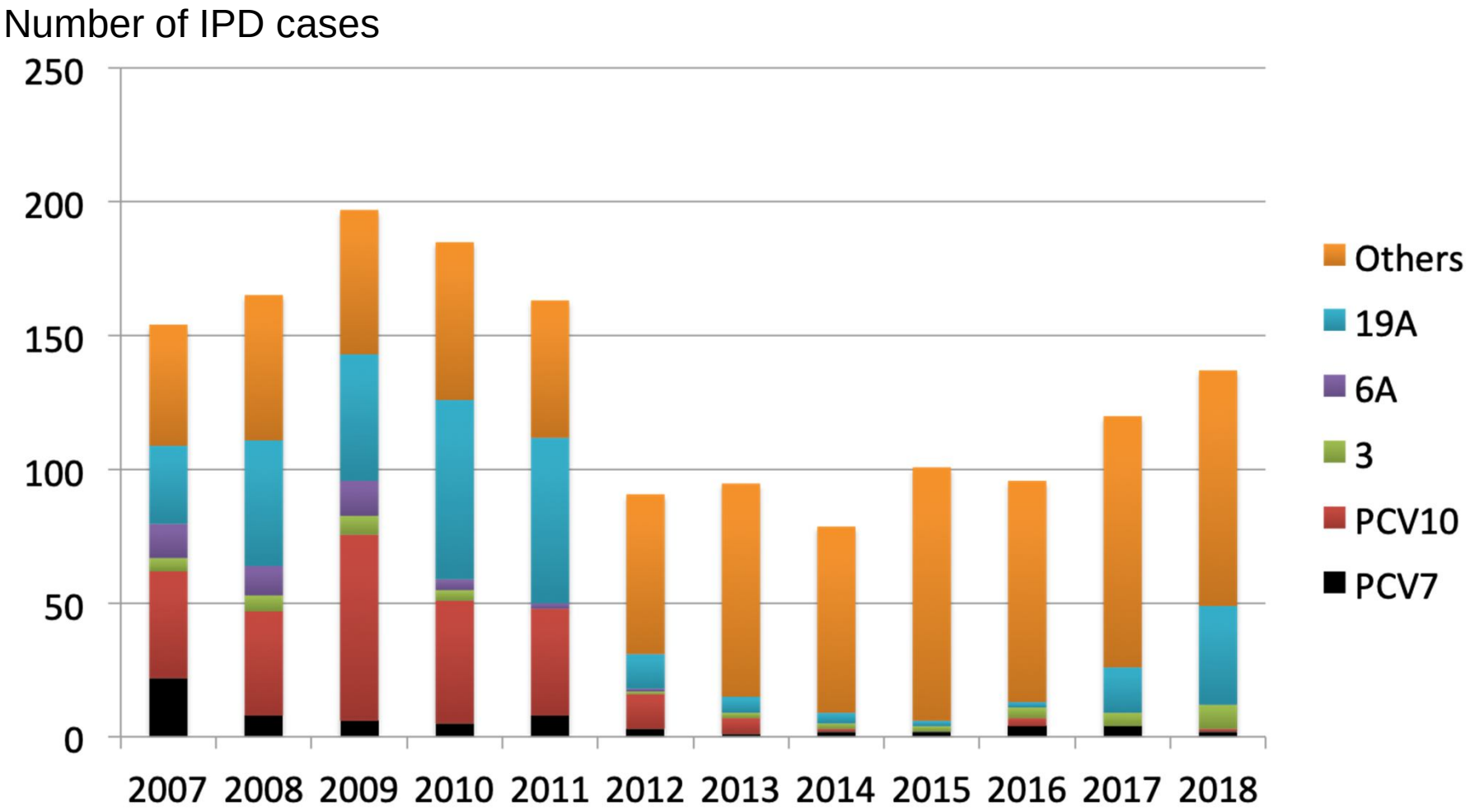
(Source des données : CNR *Streptococcus pneumoniae* invasifs)

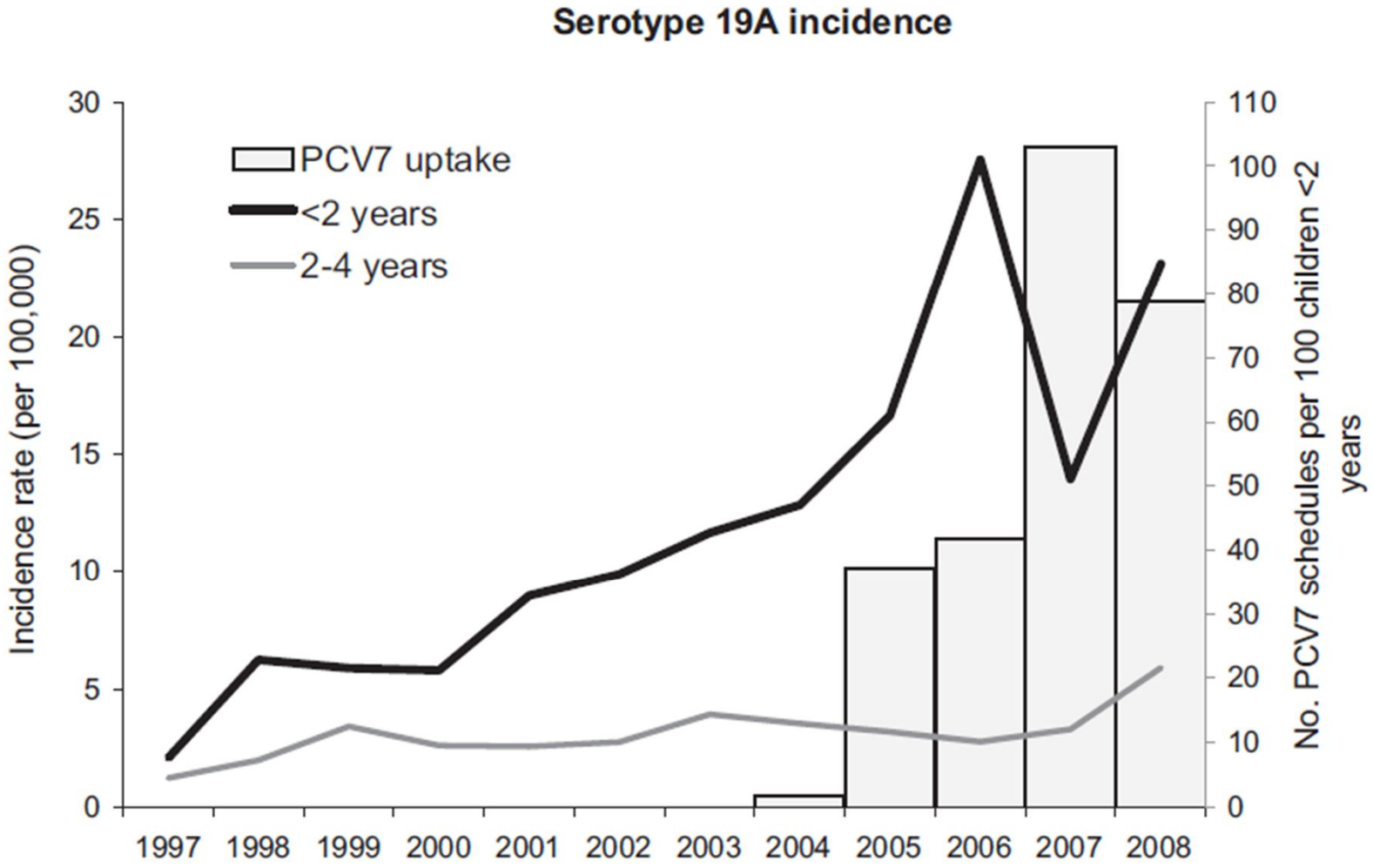


sérotypes dans le PCV7, * sérotypes dans le PCV13 ; les autres sérotypes ne pas couverts par les vaccins conjugués disponibles*

Serotypes causing IPD in children <2 years old for period 2007-2018 (based on isolates sent to the NRC).

National Reference Centre *S. pneumoniae*, UZ Leuven





G. Hanquet et al. / Vaccine 29 (2011) 2856–2864

Why Serotype 19A?

- Not all increases in NVT invasive disease are vaccine-related, because confounding secular trends in serotype prevalence can actually be rapid and sizeable.
- Relatively common cause of disease and commonly carried before vaccine use.
- PCV7 provides no cross-protection but PCV10 may offer some cross-protection against 19A.
- 19A is frequently antibiotic resistant. Antibiotic selection pressure might thus be additive or synergistic to the vaccine.
- Clonal expansion and possible capsular switching (Pai R et al J Infect Dis 2005).

Conclusions

- Use of conjugated vaccines in Belgium led to a decline in the incidence of IPD in children under 16 years with the largest decline in children under 2 years of age.
- The incidence of IPD caused by PCV7 serotypes declined to almost zero in children younger than 2 years.
- IPD caused by non vaccine serotypes tend to increase.
- The full effects of the conjugate vaccines on the pneumococcal population will be observed only some years after full vaccine implementation and need a continuous monitoring.

Conclusions

- As PCVs are extensively used, pneumococci will continue to adapt to the vaccine pressures.
- As PCVs removes the primary disease-causing serotypes, the replacement serotypes may be less invasive and the most desirable goal may be not eradication but replacement with less virulent serotypes.
- Vaccines are in development that do not rely on capsule-specific responses but widely expressed non-capsular antigens instead and might provide a permanent solution.