

Infections invasives à Pneumocoque, épidémiologie et effets de la vaccination



ACTIV



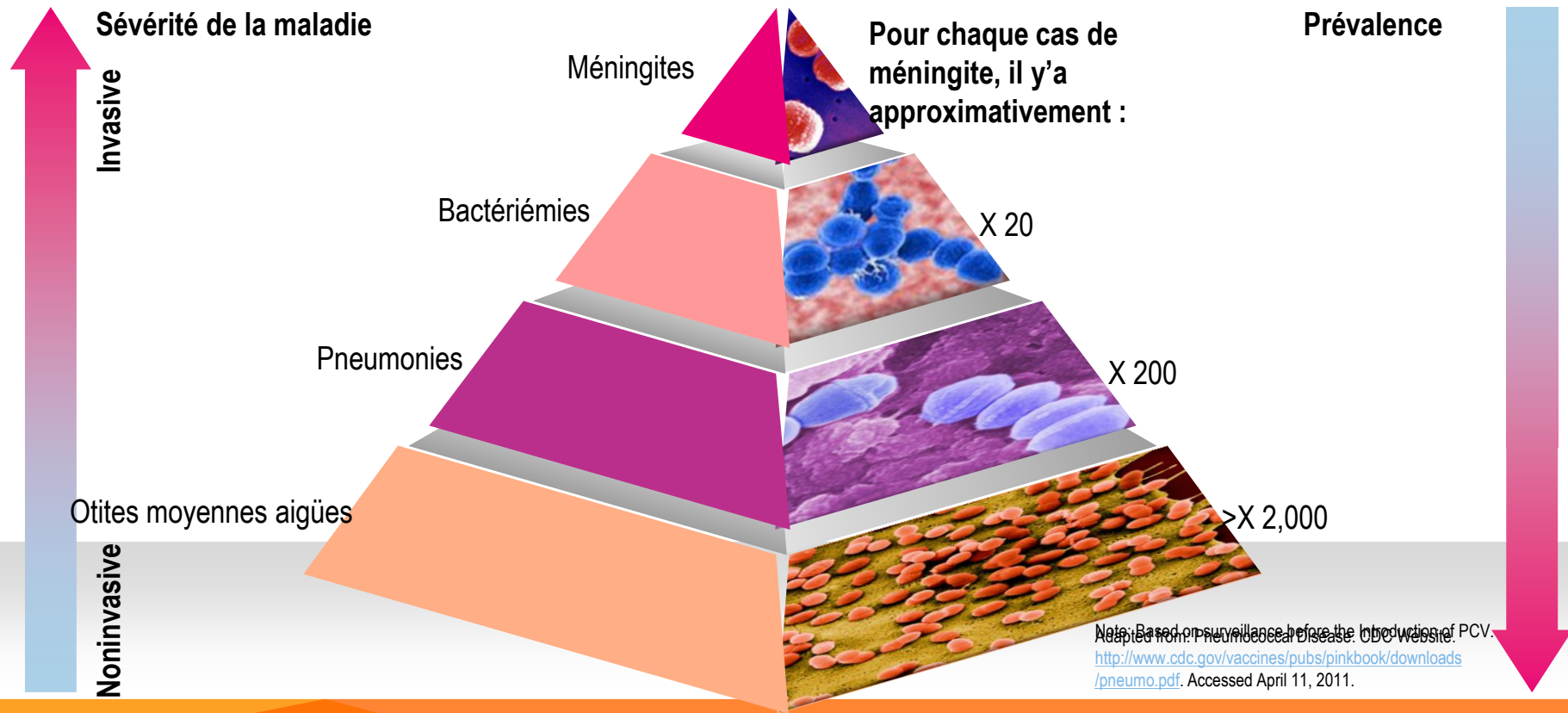
Robert Cohen

Coordonateur InfoVac
Unité Court-Séjour Petit Nourrisson
CHI Créteil

AVANT LA VACCINATION

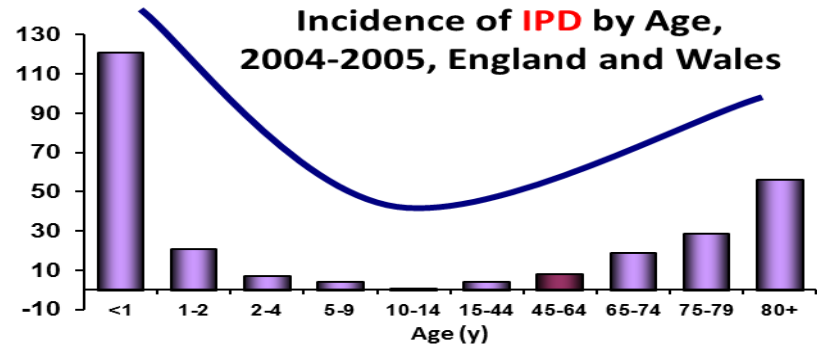
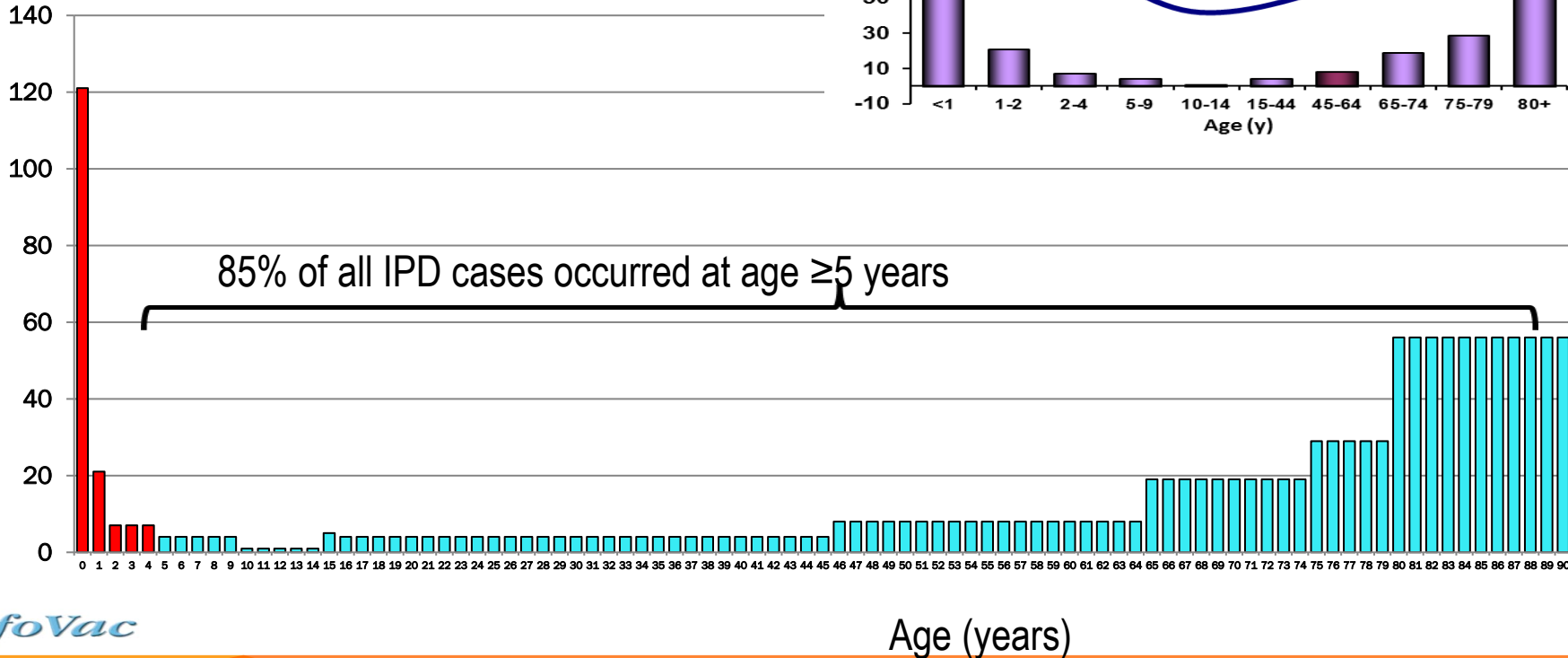
- Incidence des infections pneumococciques
- Spectre des infections pneumococciques
- Sérotypes du pneumocoque
- La résistance aux antibiotiques

Spectre des infections à pneumocoque de l'enfant



Ron Dagan slide

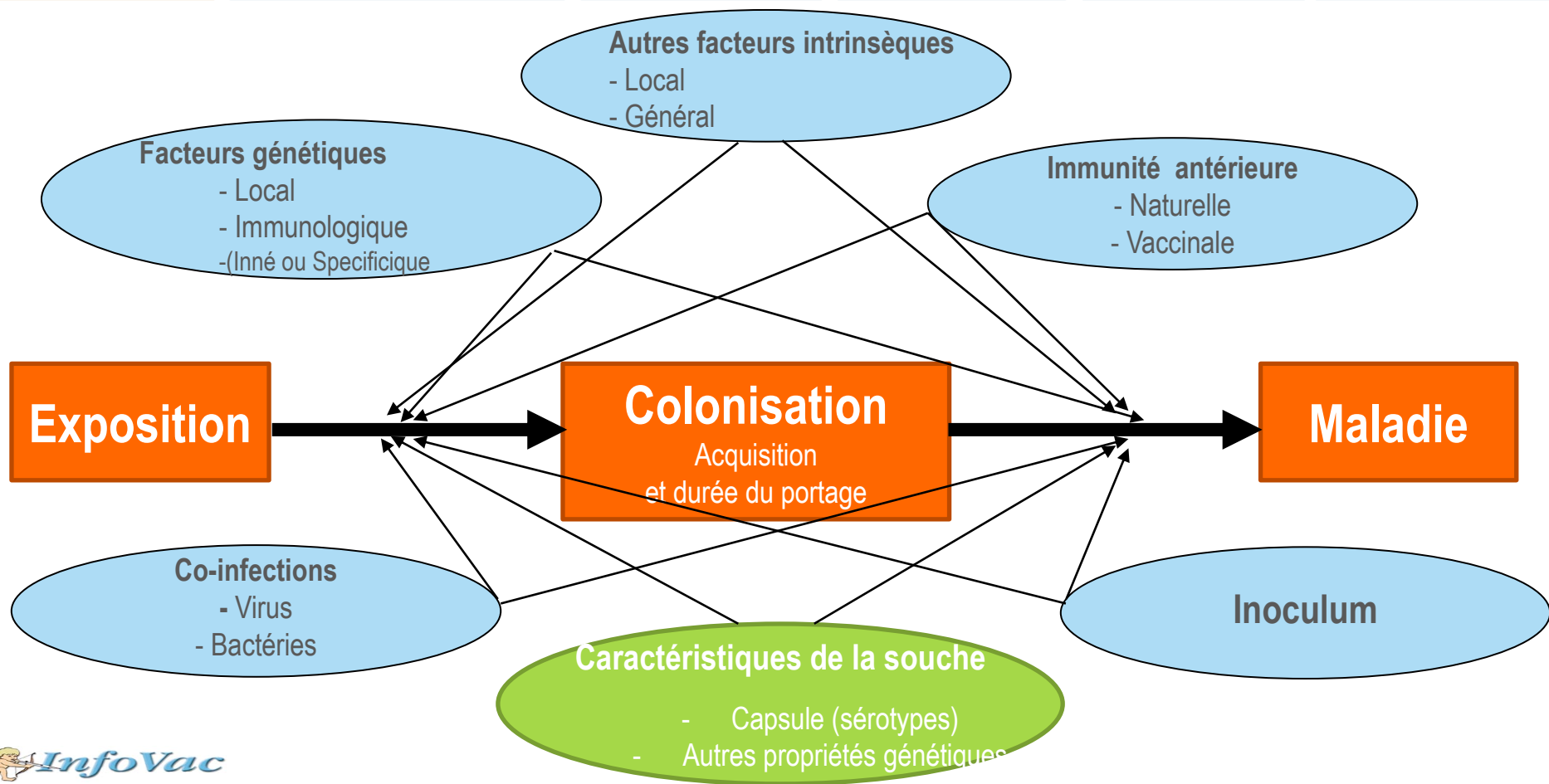
Incidence IPD per 100,000



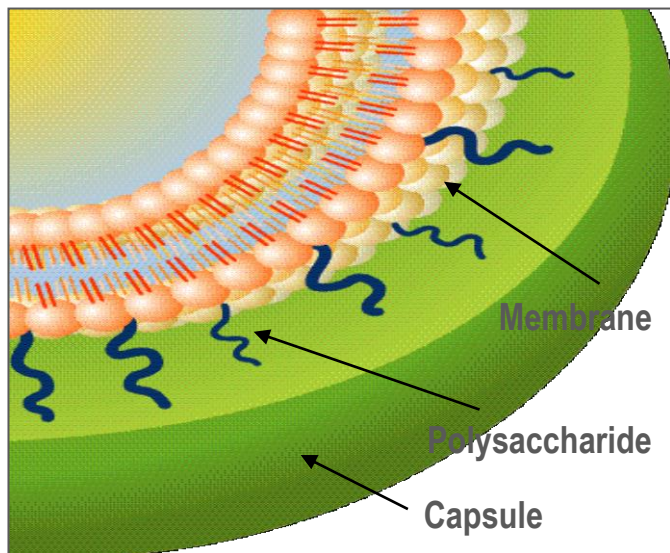
La niche écologique du pneumocoque : le microbiome rhino-pharyngé

- > 700 espèces
- Très peu sont impliquées dans les infections
- La plus importante...le pneumocoque





Sérotypes



Coupe schématique d'un pneumocoque

◆ Capsule polysaccharidique

- Protège de la phagocytose
- Activité anti-complémentaire
- Support en grande partie de la virulence → action pro-inflammatoire
- > 94 types capsulaires différents définissant les sérotypes, regroupés en 45 sérogroupes

◆ Le PCV7 « couvert » (4,6B,9V,14,18C,19F, 23F) :

- très bien les nourrissons et les jeunes enfants d'Amérique du nord (> 90 %)
- un peu moins bien les petits Européens
- Encore moins bien les enfants des pays « moins riches » ou « pauvres »

◆ Le PCV13 « couvert » (1,3,5,6B,7F,19A):

- les enfants plus grands
- les enfants des différents pays « riches », « moins riches » ou « pauvres »

Résistance : quelques sérotypes

Sérotypes	CMI péni			Macrolides		Total
	S	I	R	S	R	
1/3	100%	0%	0%	90%	10%	9
4*	100%			90%	10%	
9*	10%	40%	50%	50%	50%	10
18*	100%			90%	10%	15
14*	15%	40%	40%	40%	60%	35
23*	15%	20%	65%	20%	80%	62
19*	45%	50%	5%	40%	60%	67
6*	40%	40%	20%	40%	60%	89
15	30%	60%	10%			
NT	60%	30%	10%			
24	65%	30%	5%			
17/12/35/21/37	90%	10%	0%			

APRÈS LA VACCINATION

- Incidence a diminuée partout de façon plus ou moins importante
- **Spectre des infections pneumococciques : il a changé**
 - Répartition des différentes infections
 - Augmentation de la proportion des patients présentant une pathologie sous jacente
- **Sérotypes du pneumocoque**
 - Bouleversement
 - Plus grand chantier écologique depuis l'avènement de l'antibiothérapie
- **La résistance aux antibiotiques ↘ mais...**



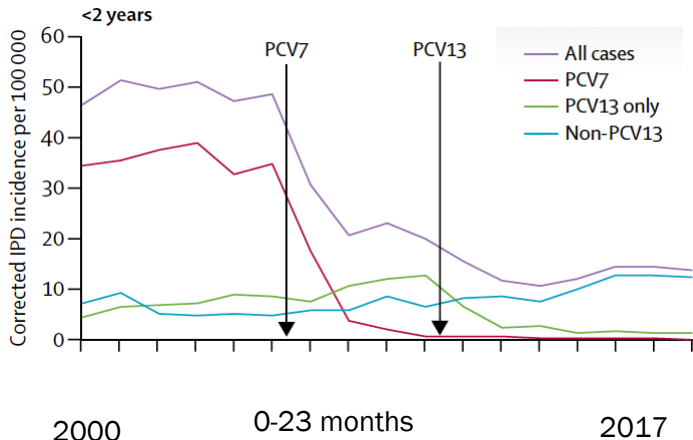
MAIS



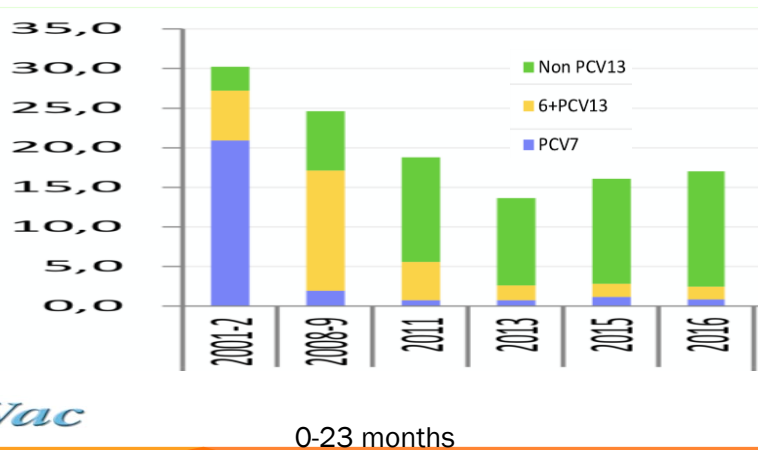
Impact of PCVs implementation on incidence of IPD (VT and NVT) in young children



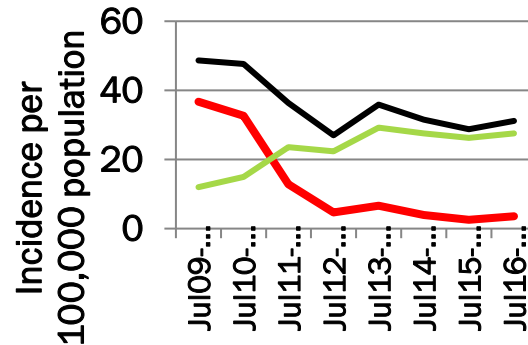
(1)



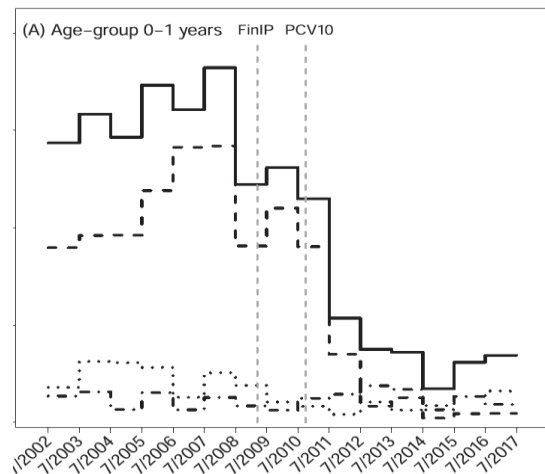
(2)



— VT13 — NVT — IPD



(3)



(4)



1) Ladhani LID Lancet Infect Dis. 2018 ;18:441

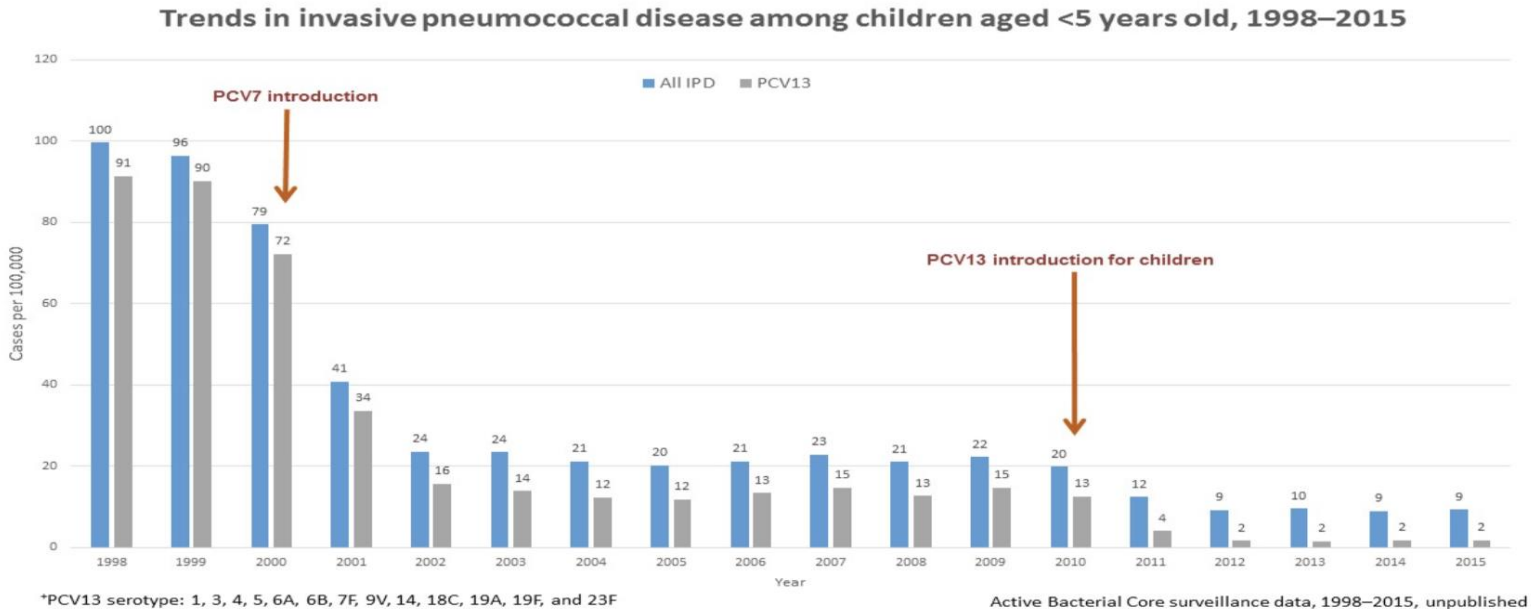
3) Benschmol Vaccine. 2014 Jun 5;32(27):3452-9; updated

2) French National Reference Center: <http://cnr-pneumo.com/docs/rapports/CNRP2017.pdf>

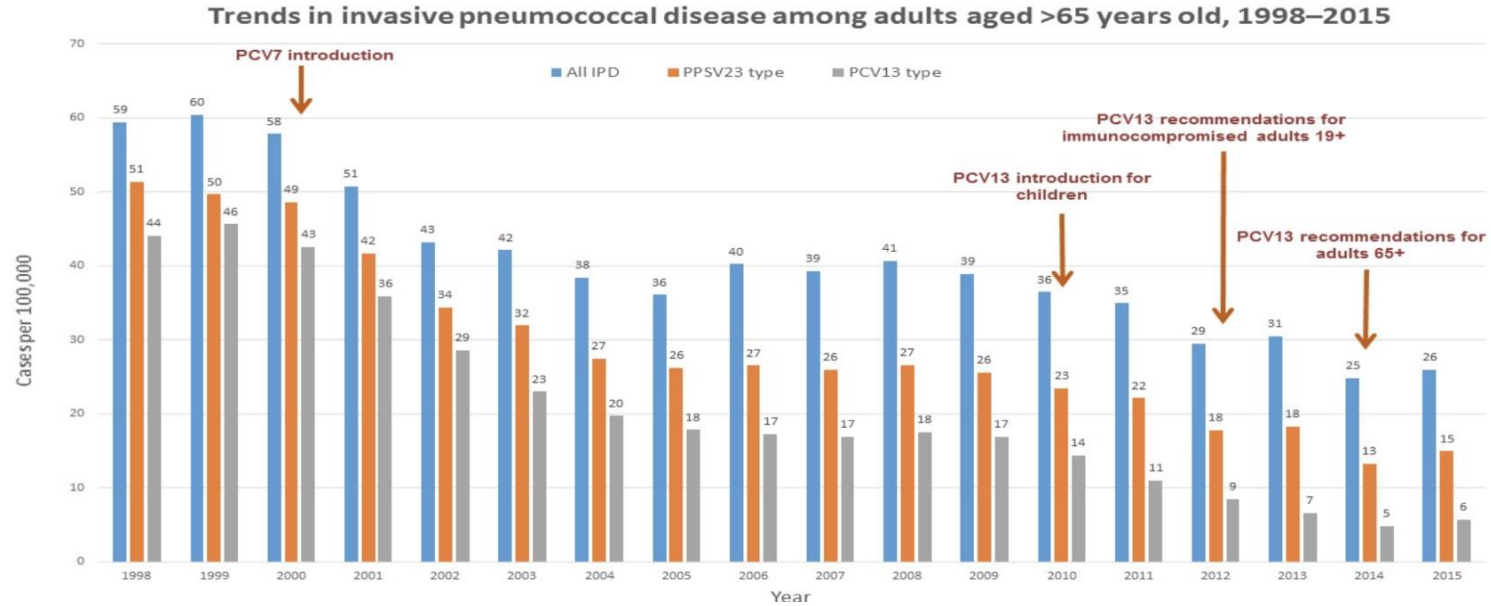
4) Rinta-Kokko Vaccine. 2018;36:1934

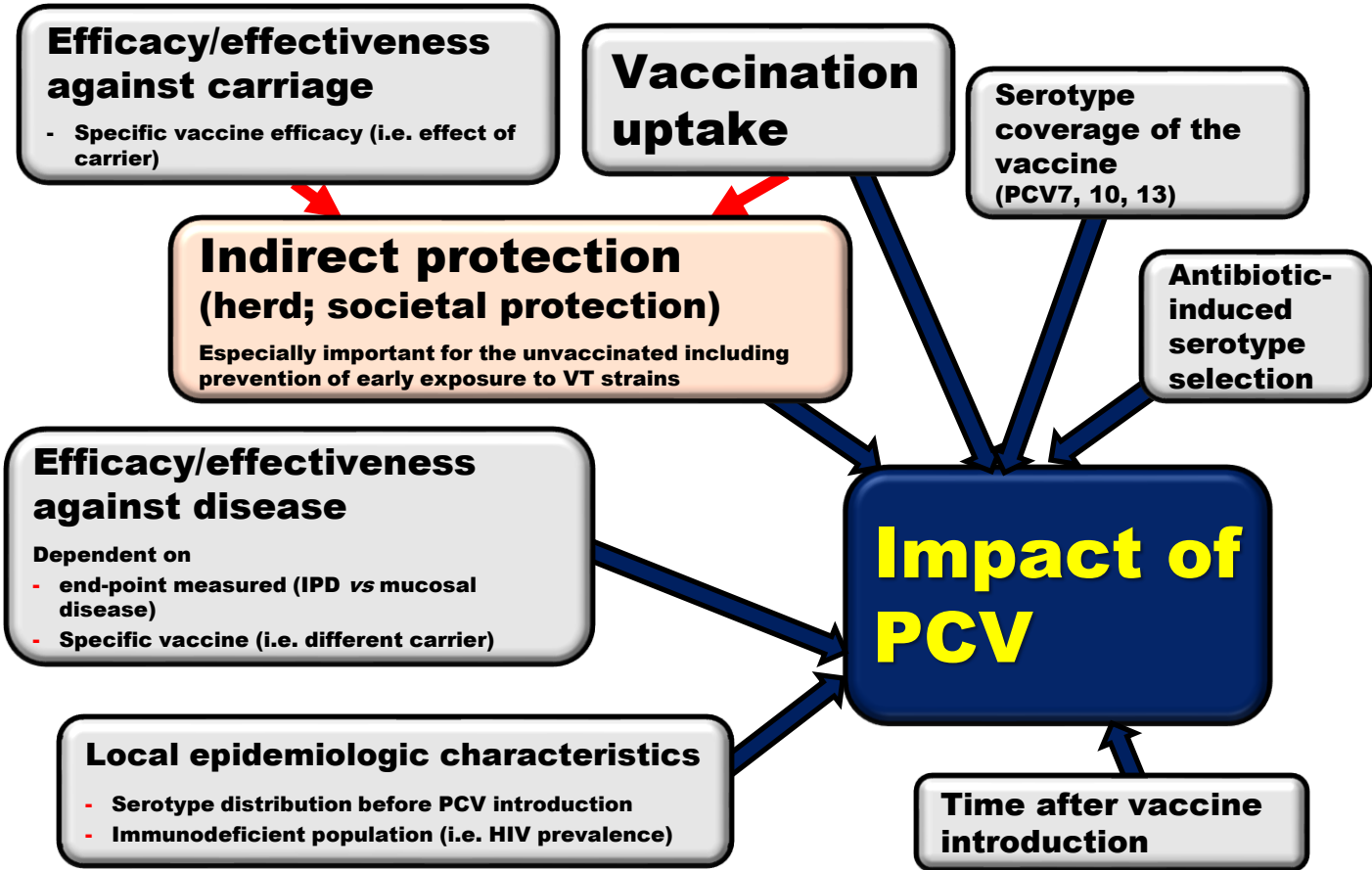
USA 1997 À 2015

Incidence des infections invasives pneumococques < 5 ans



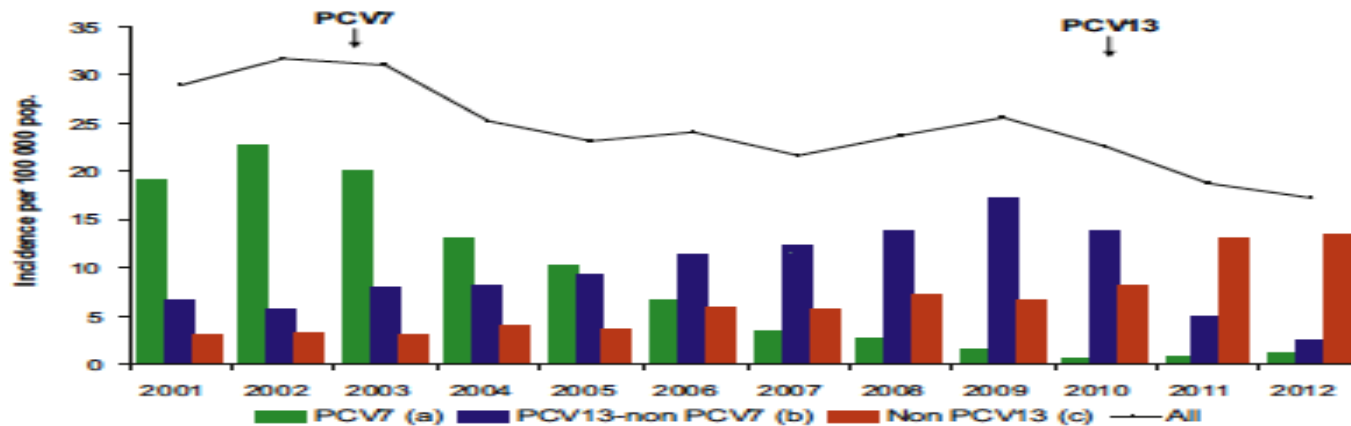
Incidence des infections pneumococciques chez l'adulte





FRANCE

Incidence des IPP



(a) PCV7 : PCV7 serotypes including serotypes , 6B, 9V, 14, 18C, 19F and 23F

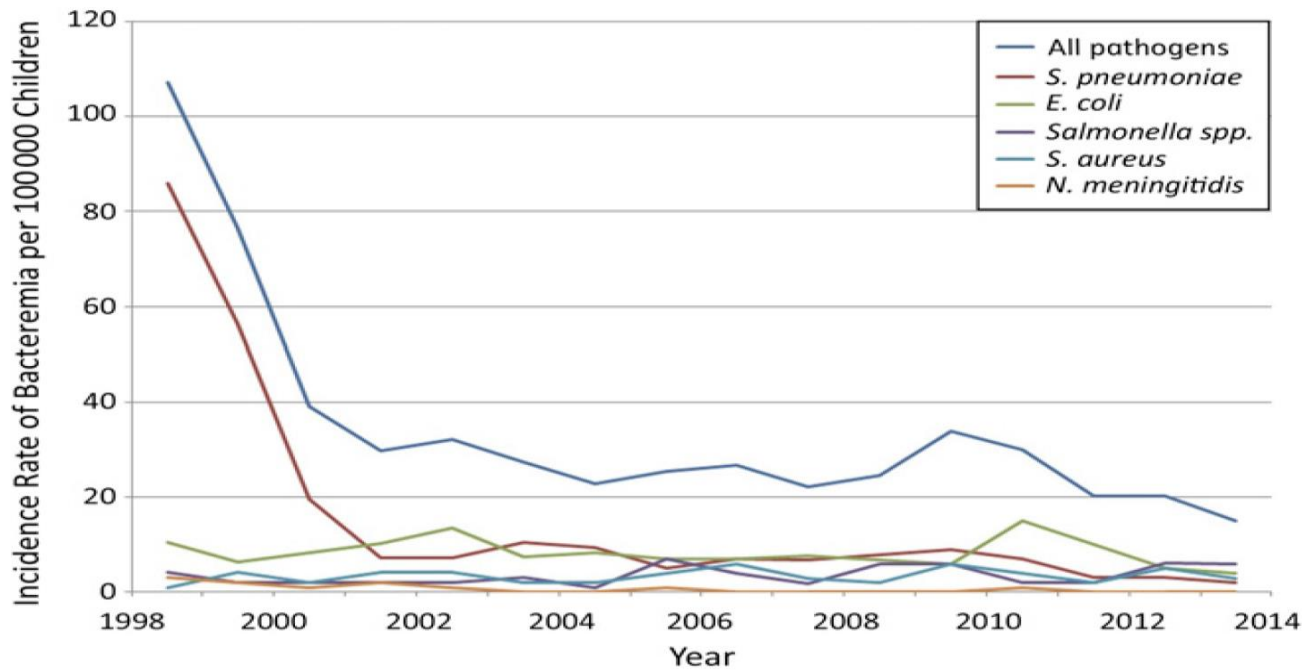
(b) PCV13-non PCV7 : PCV13-non PCV7 serotypes, including serotypes 1, 3, 5, 6A, 7F and 19A

(c) Non-PCV13 : other serotypes than PCV7 and PCV13-non PCV7

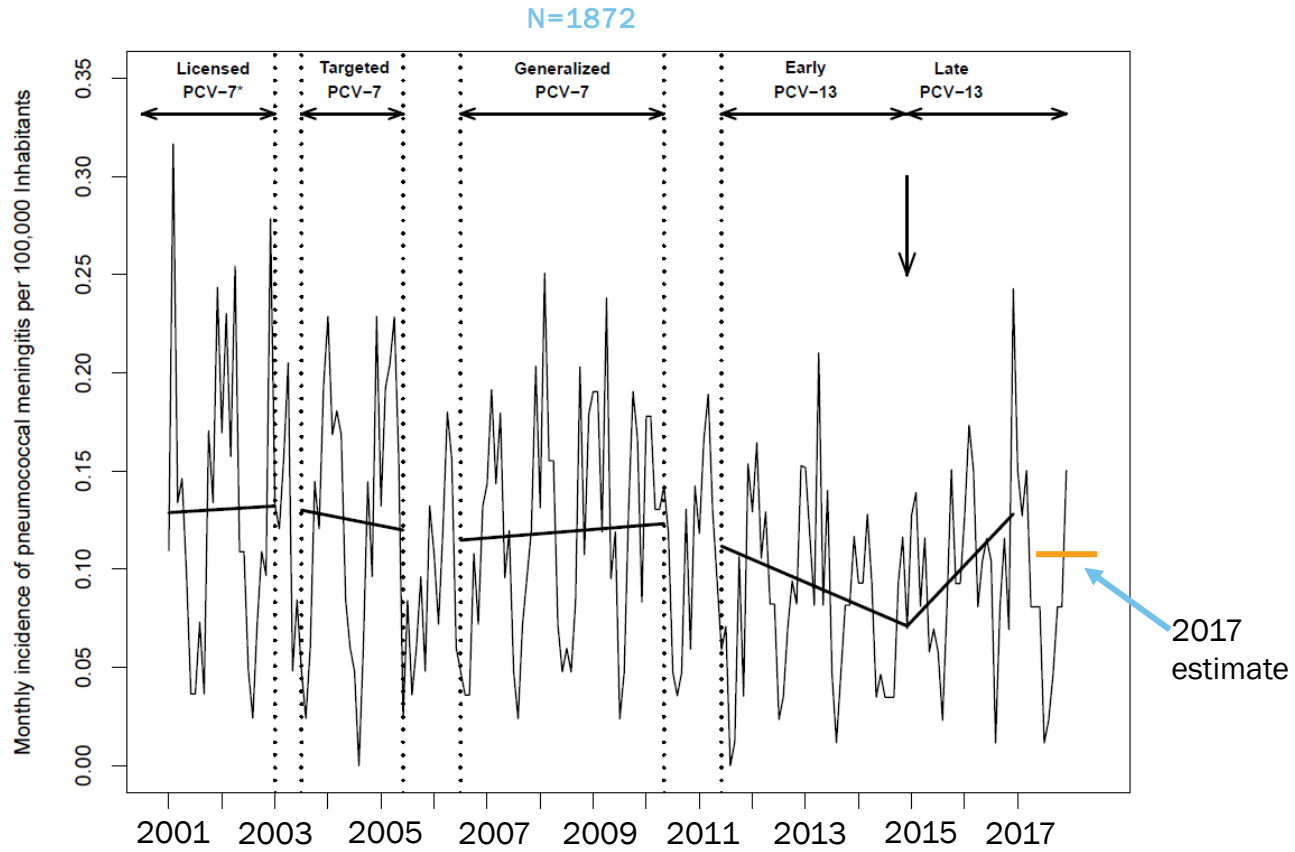
Bacteremia in Children 3 to 36 Months Old After Introduction of Conjugated Pneumococcal Vaccines

Tara L. Greenhow, MD,^a Yun-Yi Hung, PhD,^b Arnd Herz, MD^c

PEDIATRICS Volume 139, number 4, April 2017:

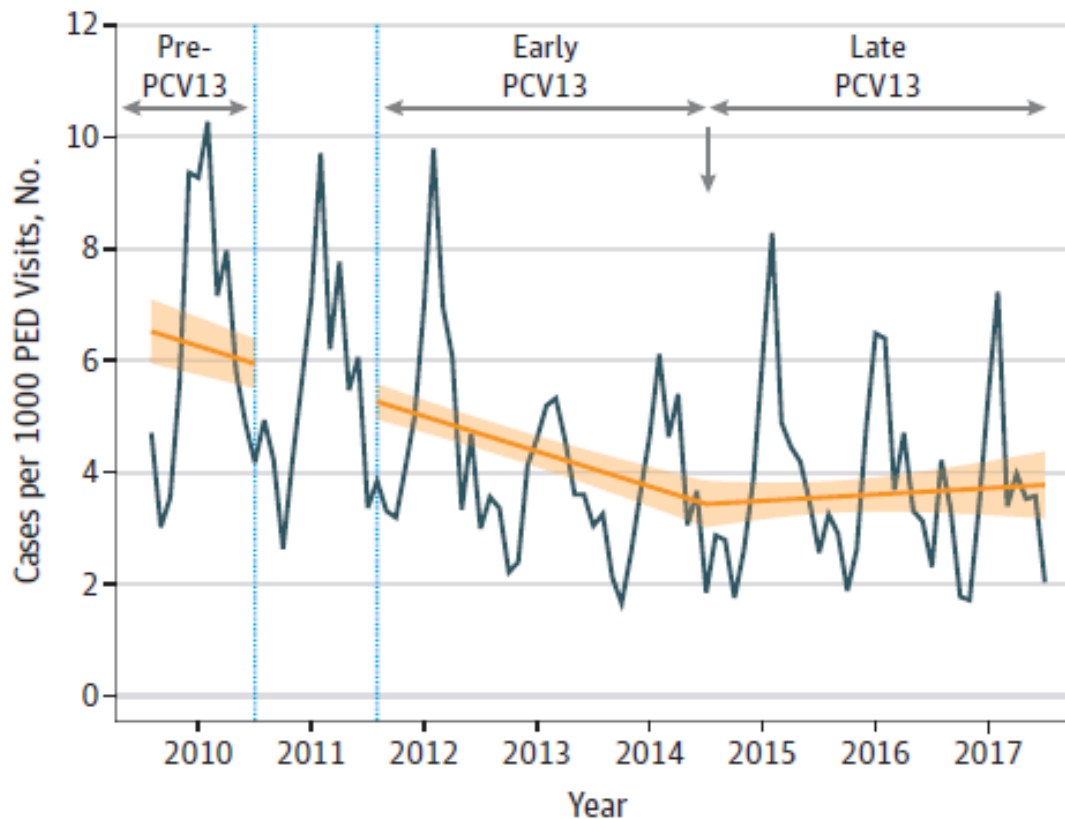


PNEUMOCOCCAL MENINGITIS IN CHILDREN <15 YEARS, FRANCE



ALL CAUSE PNEUMONIA IN CHILDREN <15 YEARS, FRANCE

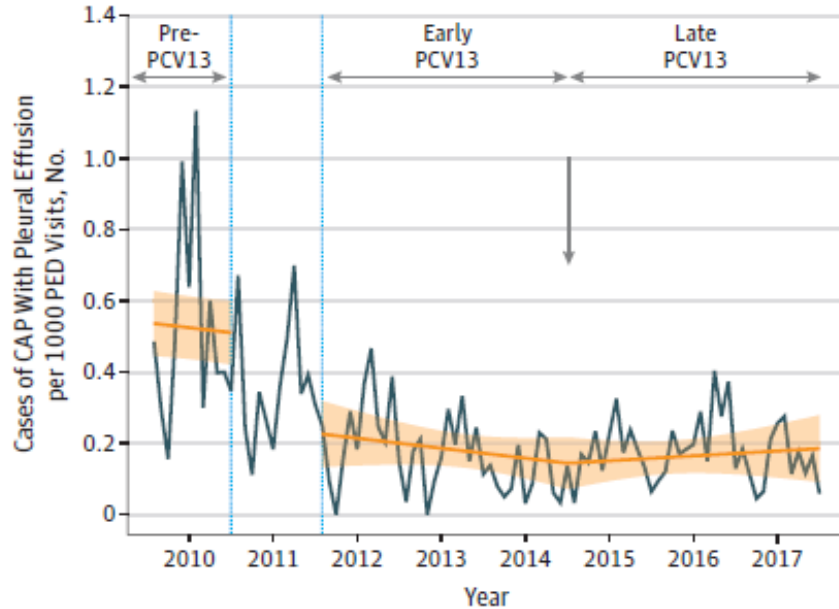
N=12,567



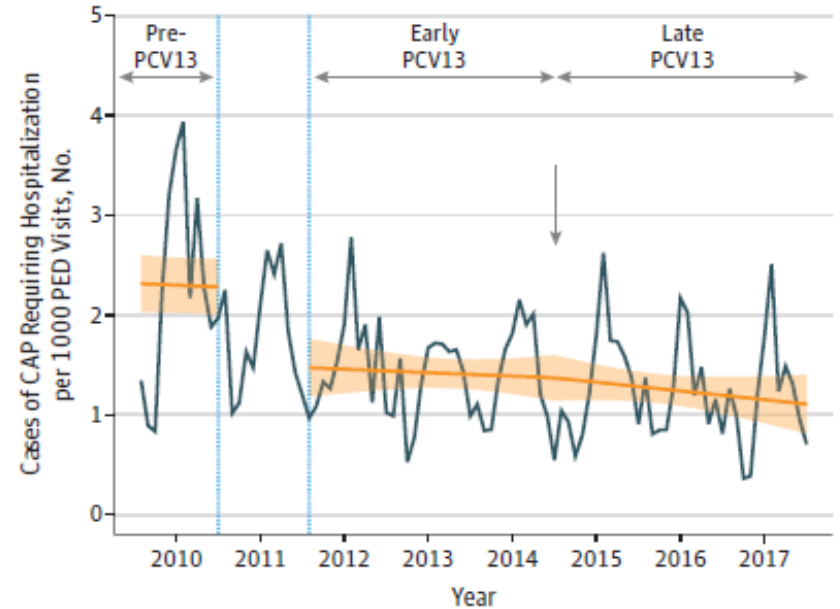
44% decrease until May 2014
7% increase since June 2014

SEVERE PNEUMONIA IN CHILDREN <15 YEARS, FRANCE

Pneumonia with pleural effusion, n=673



Hospitalized pneumonia, n=4273



Greenberg et al. JID 2016. Nasopharyngeal pneumococcal carriage during childhood community-acquired alveolar pneumonia: Relationship between specific serotypes and co-infecting viruses

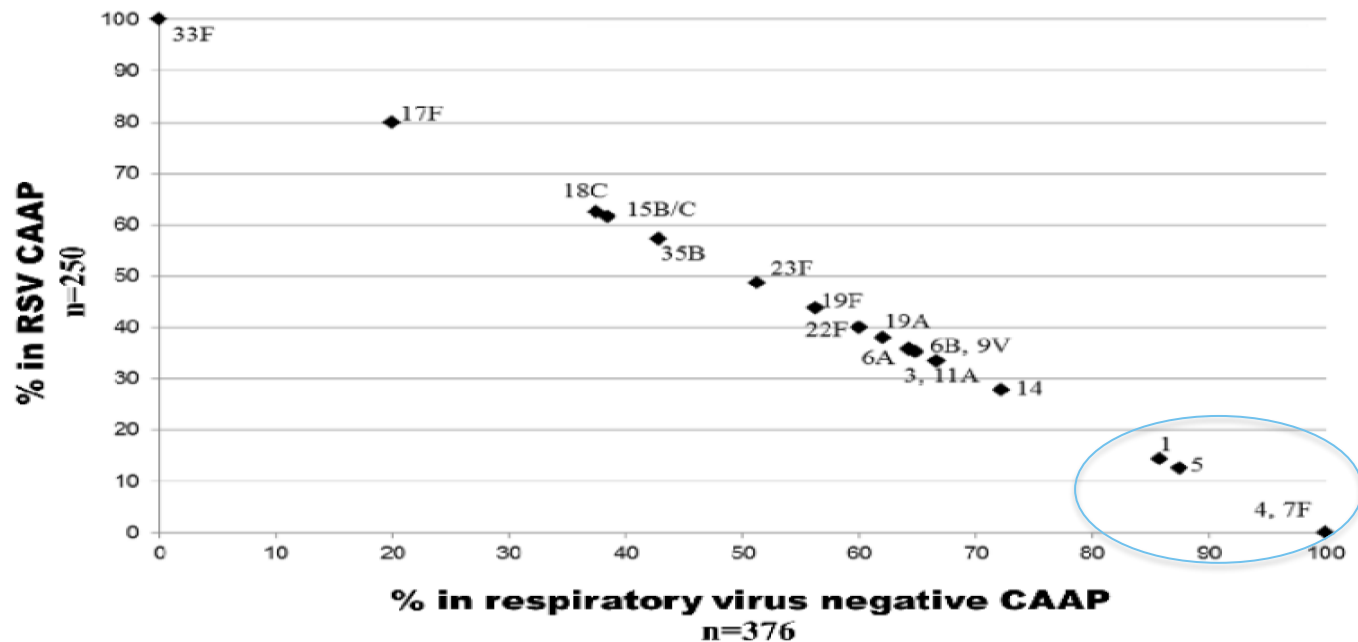


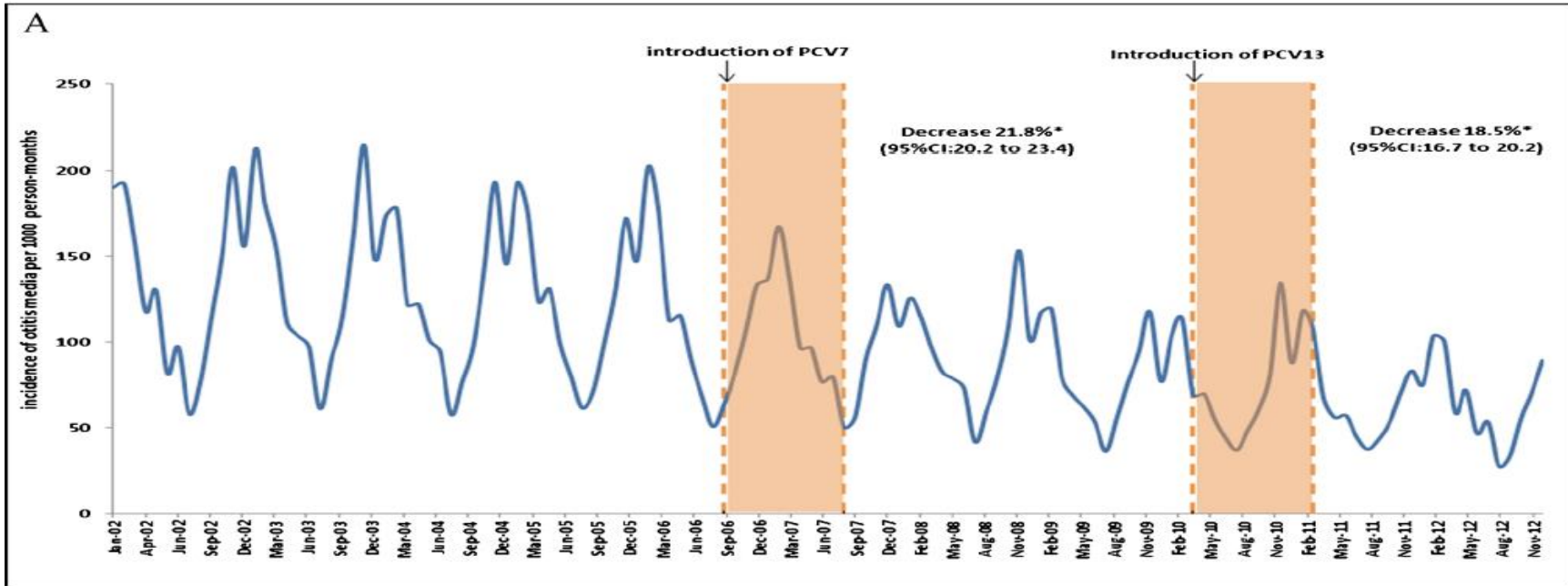
Table 1. Bacterial Causes Identified in Children Hospitalized for Parapneumonic Effusion and Pleural Empyema According to PCV13 Period

Bacterial Cause	Total (n = 220)	After PCV13				P
		Before PCV13 (June 2009–May 2011) (n = 110)	First Period (June 2011–May 2013) (n = 48)	Second Period (June 2013–May 2015) (n = 29)	Third Period (June 2015–May 2017) (n = 33)	
<i>Streptococcus pneumoniae</i> (n [%])	146 (66.4)	87 (79.1)	32 (66.7)	15 (51.7)	12 (36.4)	<.001
Positive pleural culture	33	25	4	2	2	
Positive blood culture	31	15	11	1	4	
Positive BinaxNOW/ag	72	40 ^a	16 ^b	11	5	
Positive PCR	10	7	1	1	1	
GAS (n [%])	38 (17.3)	7 (6.4)	10 (20.8)	6 (20.7)	15 (45.5)	<.001
Positive pleural culture	20	2	6	5	7	
Positive blood culture	2	0	1	0	1	
Positive PCR	16	5	3	1	7	
<i>Staphylococcus aureus</i> (n [%])	34 (15.5)	14 (12.7)	7 (14.6)	7 (24.1)	6 (18.2)	.472
Positive pleural culture	27	10	7	5	5	
Positive blood culture	7	4		2	1	
Others (n [%])	5	3 ^c	1 ^d	1 ^e	—	—



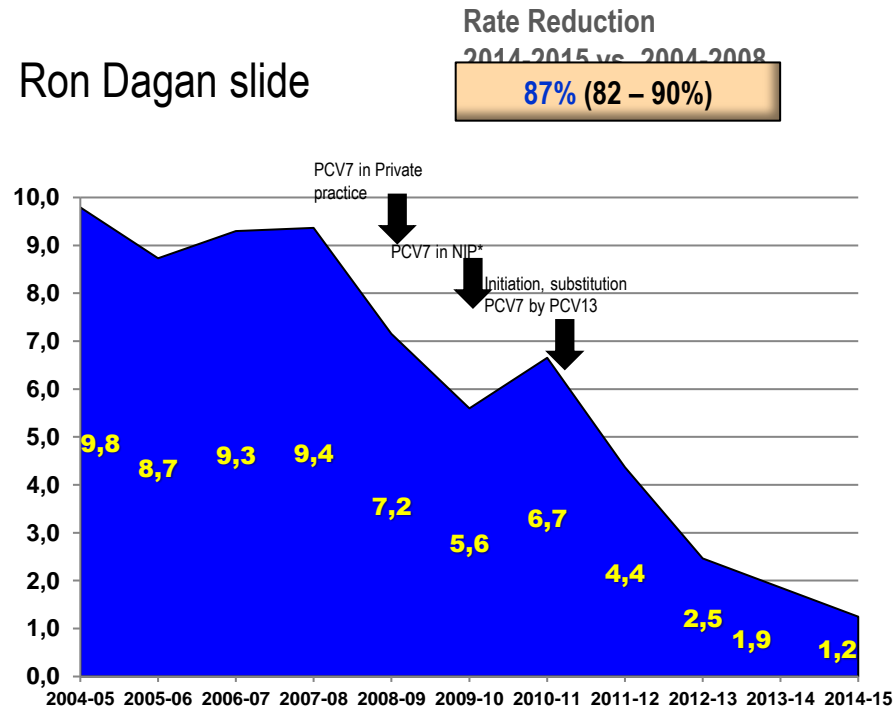
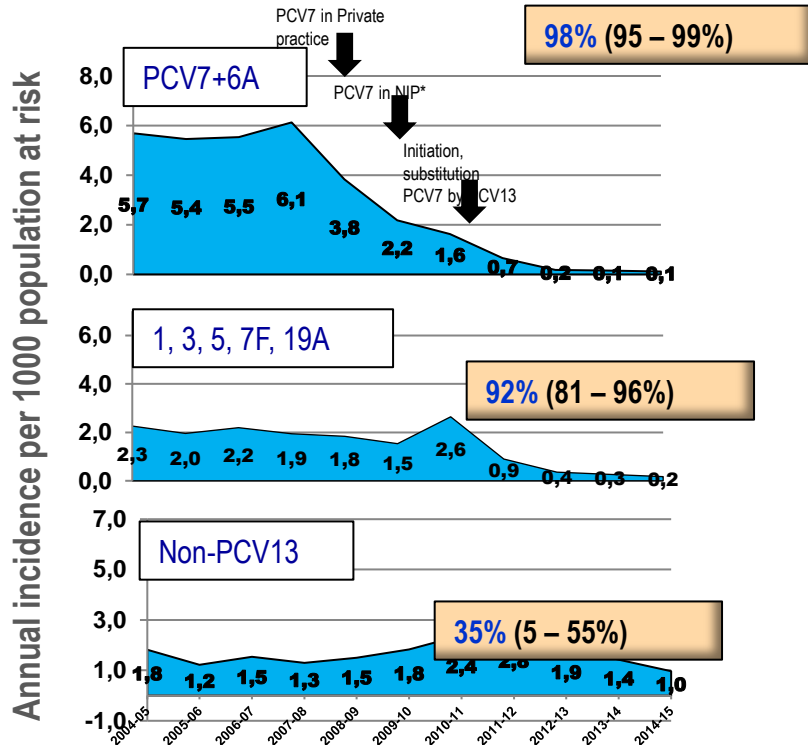
Impact of pneumococcal conjugate vaccines on childhood otitis media in the United Kingdom

Wallis C.Y. Lau^a, Macey Murray^b, Aisha El-Turki^{b,c}, Sonia Saxena^d, Shamez Ladhani^{e,g}, Paul Long^f, Mike Sharland^g, Ian C.K. Wong^{a,b}, Yingfen Hsia^{g,*}



Impact of the Sequential PCV7/PCV13

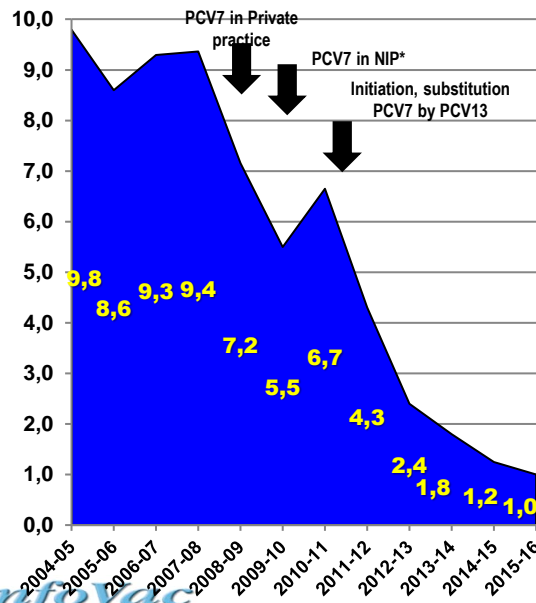
Introduction to the NIP on Pneumococcal OM, Children < 24m



Impact of the Sequential PCV7/PCV13 Introduction to the NIP on Pneumococcal OM, Children <24m

Ron Dagan slide

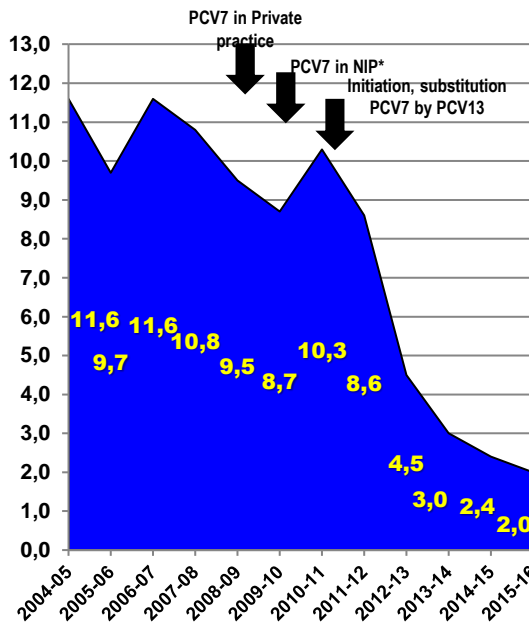
89% (85 – 92%)



All Pneumococcal OM

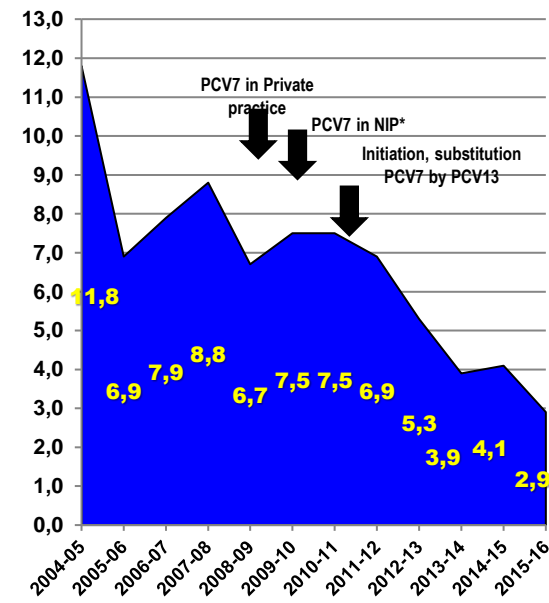
Rate Reduction
2014-2016 vs. 2004-2008

82% (77 – 84%)



NTHi

68% (61 – 74%)



Culture-negative

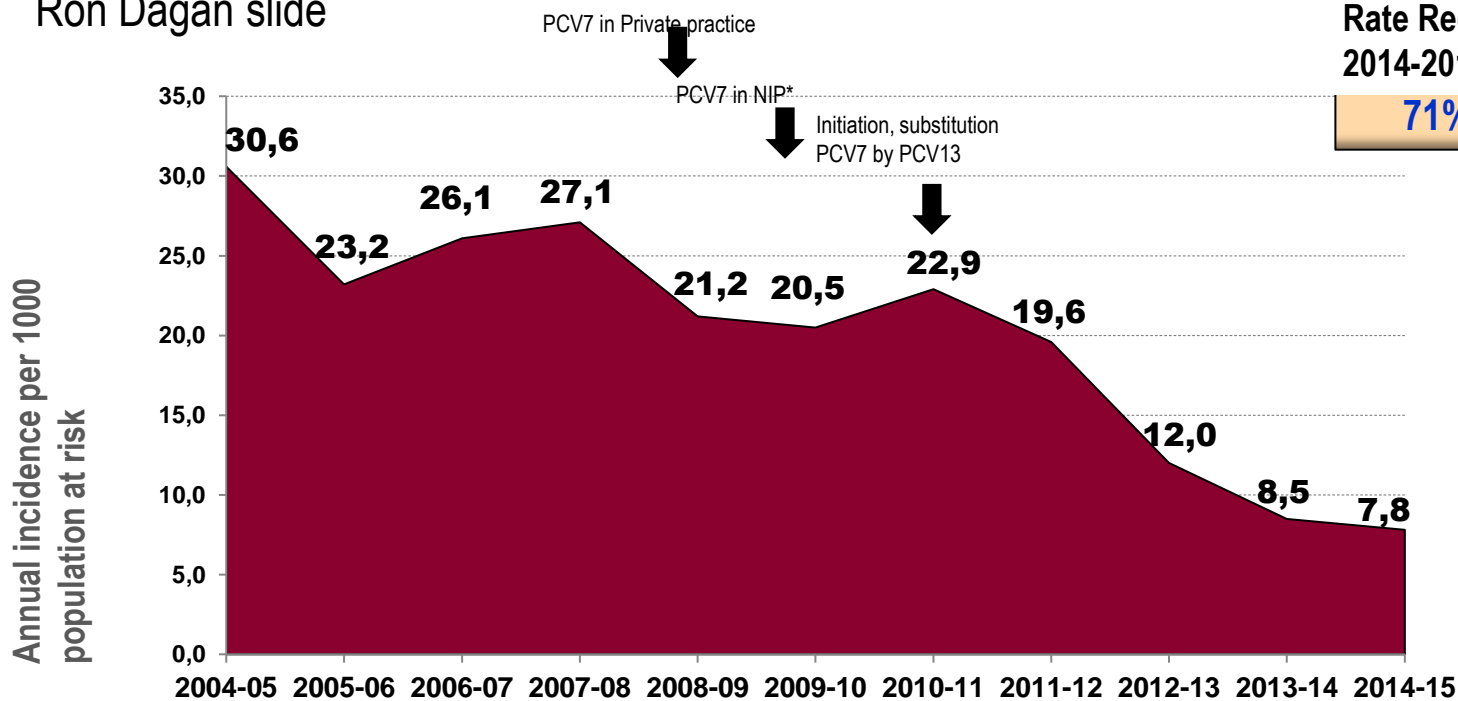
Annual incidence per 1000 population at risk

Infovac

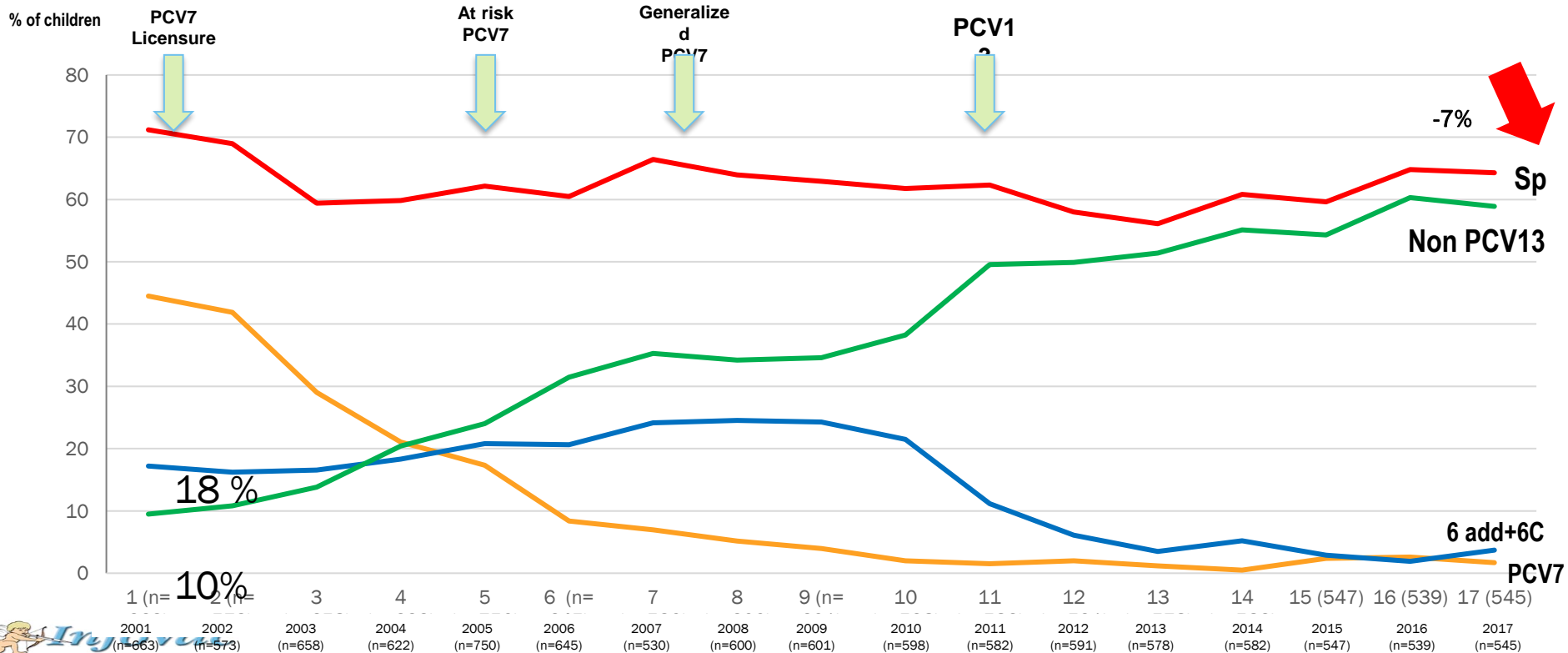
SOUTHERN ISRAEL, 2004-2015*

Overall OM (pneumococcal and non-pneumococcal) incidence in children < 24m with MEF culture

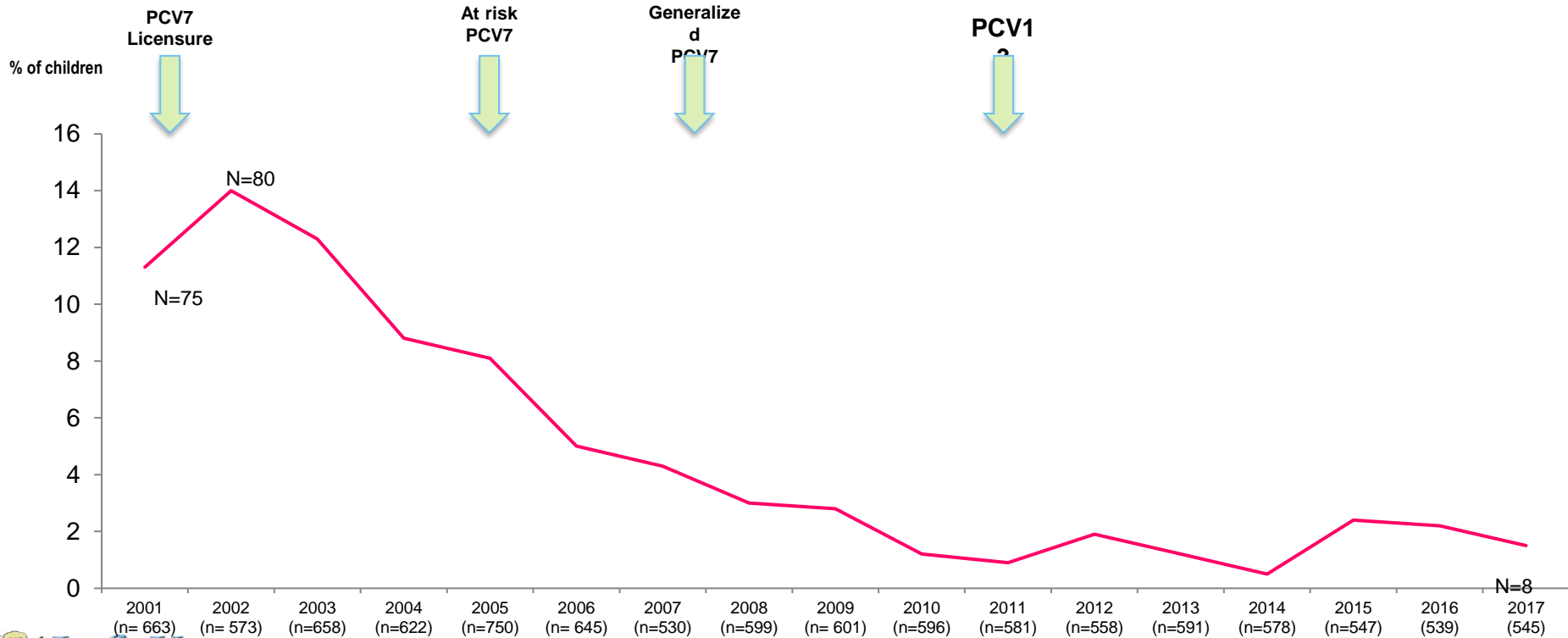
Ron Dagan slide



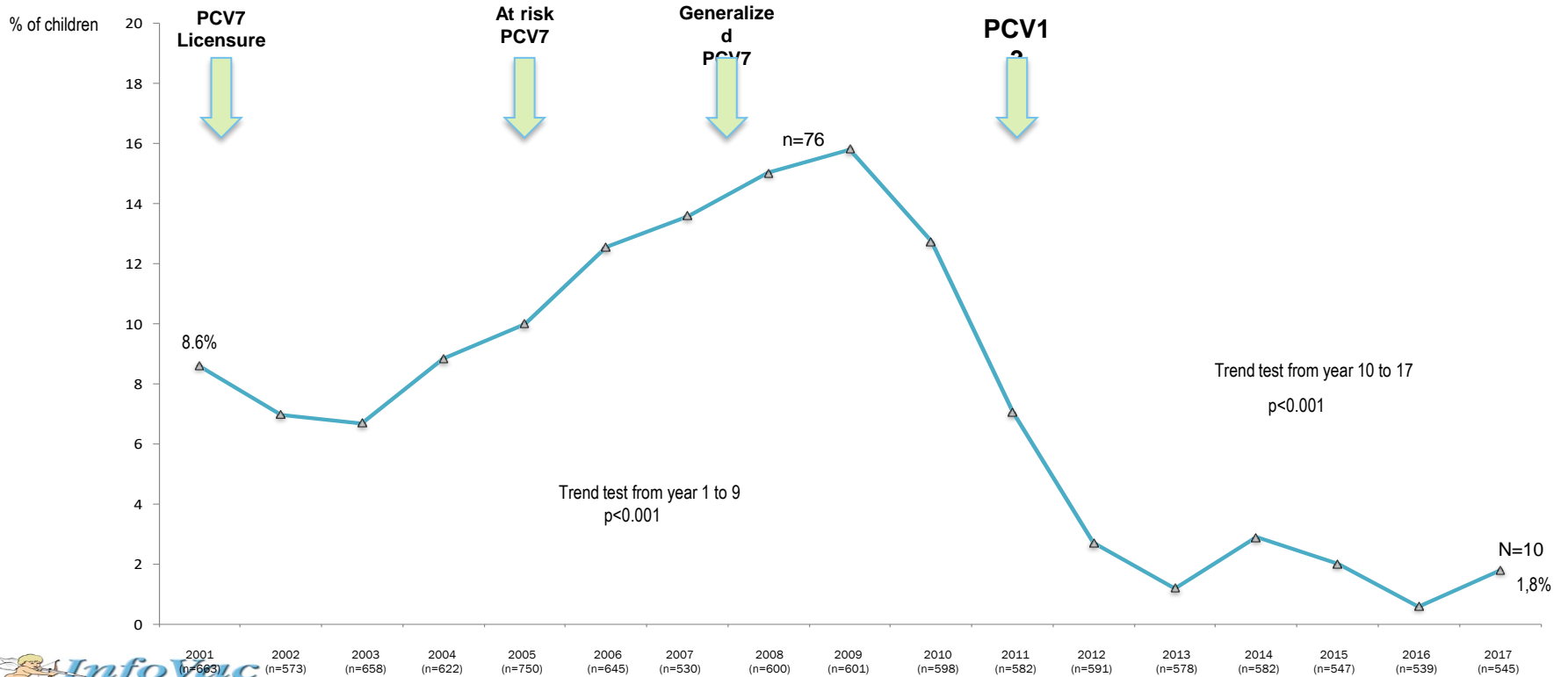
SP NASOPHARYNGEAL CARRIAGE DURING AOM : 10 204 CHILDREN, 17 YEARS



SEROTYPE 19F

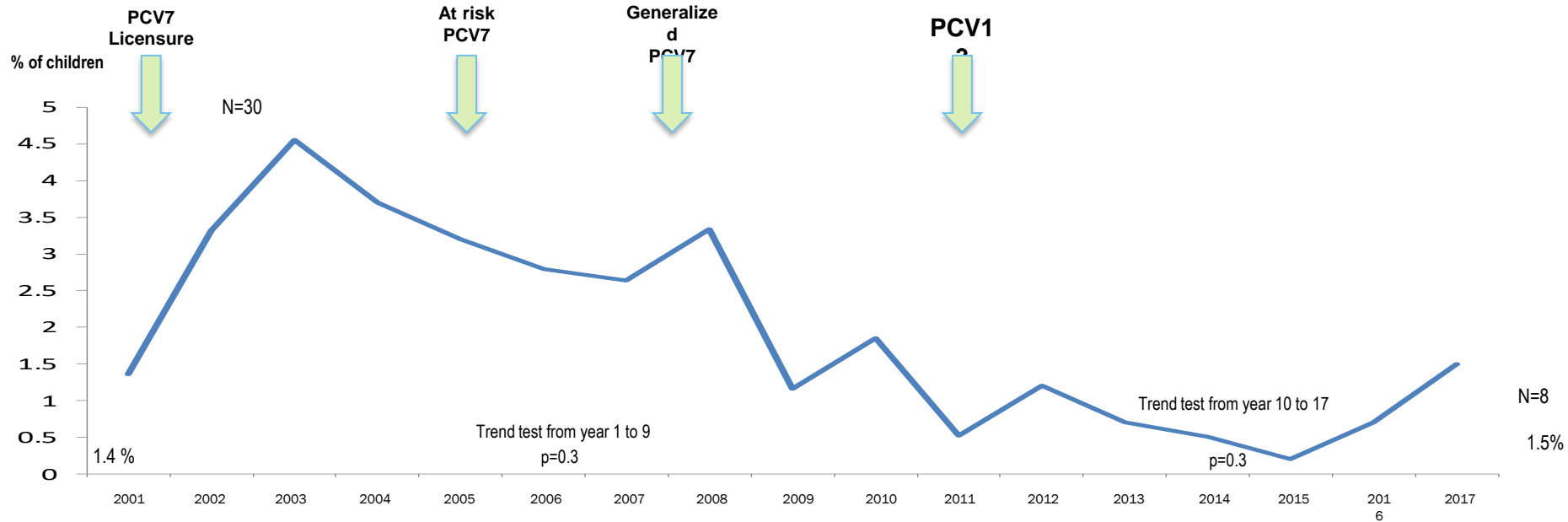


SEROTYPE 19A



Study Years (Year 1: Oct 2001/June 2002, Year 17: Oct 2017/ March 2018)

SEROTYPE 3



AOM 2006->2010 VS 2015->2018

CLINICAL CHARACTERISTICS

%	2006->2010		2015->2018	
	N=3498		N=2755	p
Sex M	52.8%		52.4%	0.7
Mean Age (months)	13.5 ± 5.0		13.6 ± 5.0	0.2
Day care center	41.1%	↗	57.3%	<0.001
History of AOM	56.1%	↘	52.4%	0.016
Otitis prone children	19.5%	↘	14.5%	<0.001
Antibiotics 3 months before	47.3%	↘	37.2%	<0.001
Fever ≥38.5	59.4%	↘	54.6%	<0.001
Otalgia	74.3%	↘	65.5%	<0.001
Otorrhea	8.4%	↘	6.8%	0.018
Conjunctivitis	25.3%	↗	28.2%	0.011



AOM WITH SPONTANEOUS OTORRHEA

	N = 470 %	
No Otopathogens	53.4	
Otopathogens	46,6	
NT <i>H. influenzae</i>	48,4	
	Alone (73)	Mixt (27)
<i>S. pyogenes</i>	34,7	
	Alone (83)	Mixt (17)
<i>S. pneumoniae</i>	27,9	
	Alone (60)	Mixt (40)

N (%)	Otorrhea n=48 Sp	Sp carriers n=1439 Sp
PCV13 +6C* serotypes	15 (31.3)*	115 (8)*
19F	3 (6.3)	48 (3.3)
19A	3 (6.3)	31 (2.2)
3	8 (16.7)	15 (1)
Non PCV13 serotypes	33 (68.7)**	1324 (92)**
15BC	2 (4.2)	188 (13.1)
23B	5 (10.4)	153 (10.6)
11A	4 (8.3)	144 (10)
35B	3 (6.3)	91 (6.3)
21	2 (4.2)	90 (6.3)
23A	2 (4.2)	78 (5.4)
10A	3 (6.3)	69 (4.8)
24F	3 (6.3)	42 (2.9)
16F	3 (6.3)	31 (2.2)
Other non PCV13 serotypes	5 (10.4)	255 (17.7)



*PCV 13 does not contain serotype 6C and is not indicated for the prevention of serotype 6C disease

Review



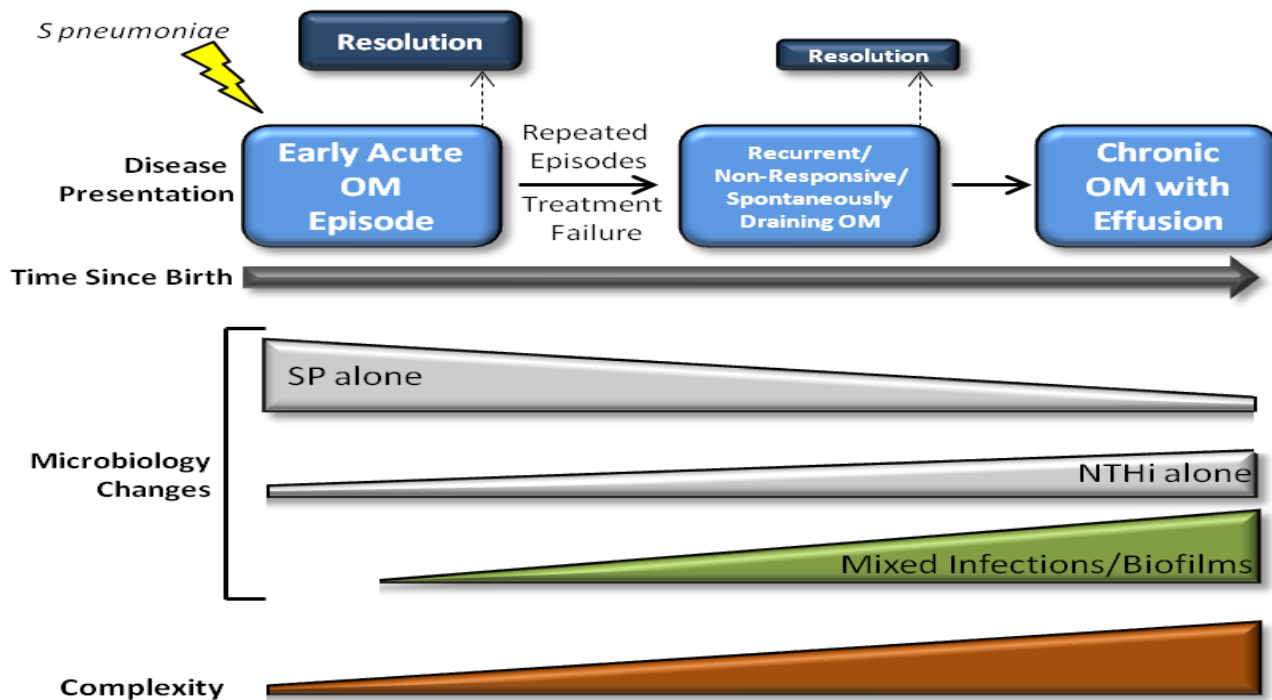
Prevention of early episodes of otitis media by pneumococcal vaccines might reduce progression to complex disease

Ron Dagan, Stephen Pelton, Lauren Bakaletz, Robert Cohen

Lancet Infect Dis 2016;
16: 480–92

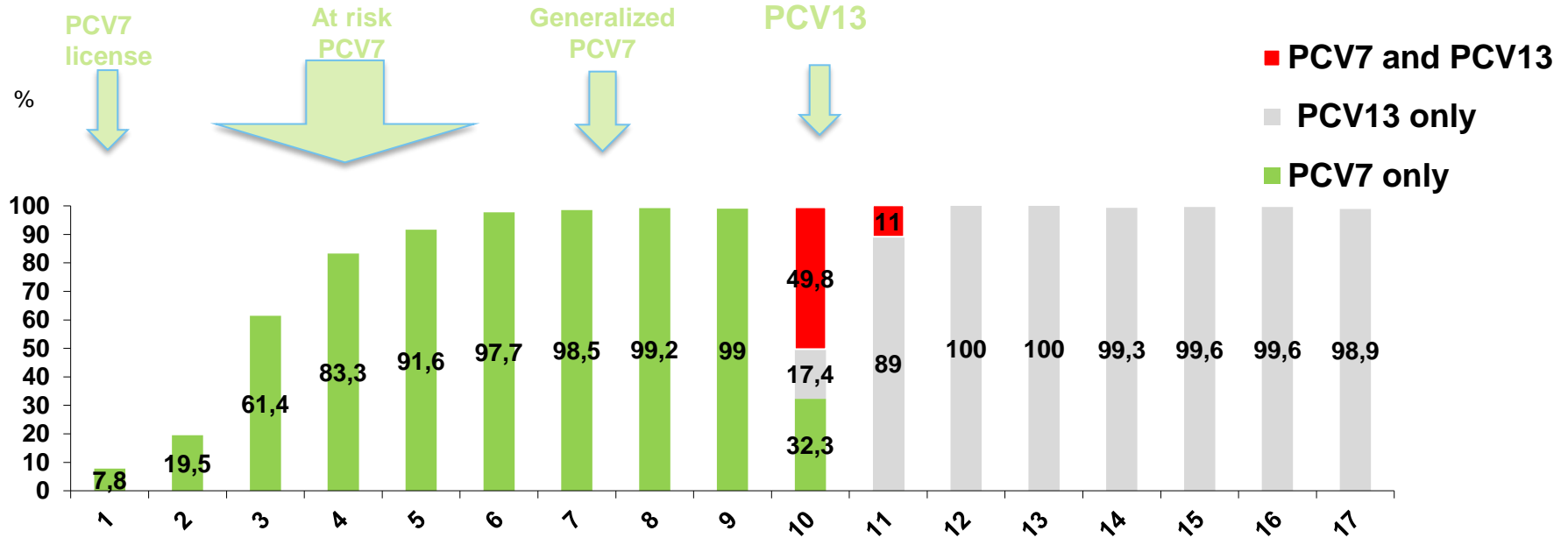
Otitis media is a common childhood infection of the middle ear and a major cause of morbidity. This multifactorial disease manifests as a spectrum of clinical syndromes from uncomplicated acute otitis media to more complex

Involvement of *S pneumoniae* in OM evolution: the disease continuum model of pathogenesis

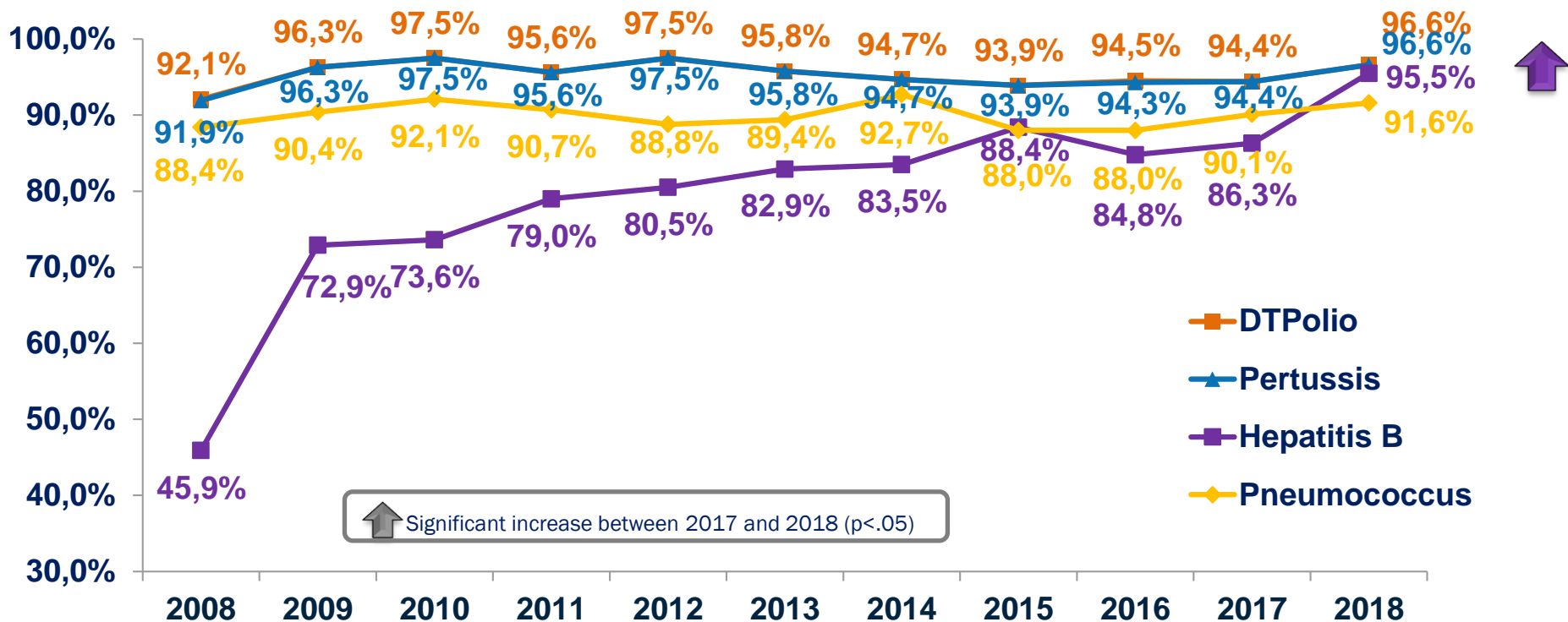


PCV vaccinated children

AOM fever ± otalgia, 10 204 children, 17 years

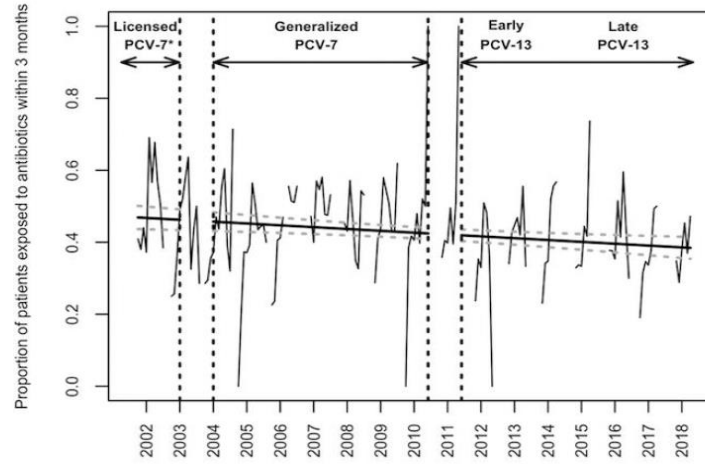


Vaccination coverage in general population

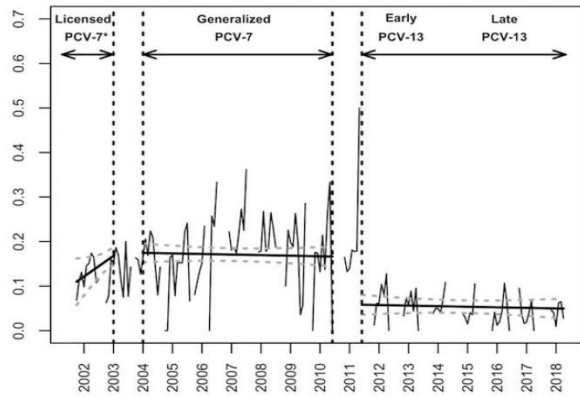


↑ Significant increase between 2017 and 2018 (p<.05)

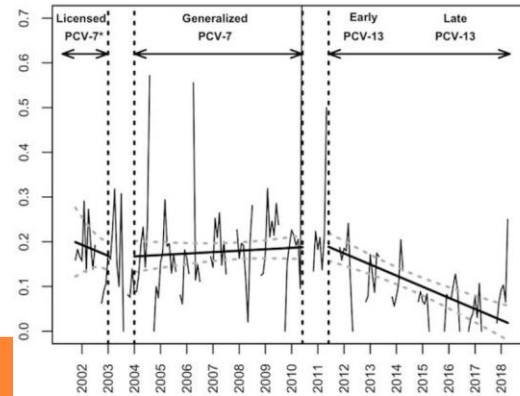
A Antibiotic use



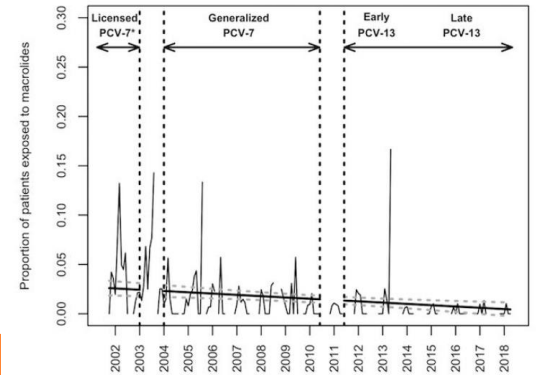
C Oral 3rd generation cephalosporin use



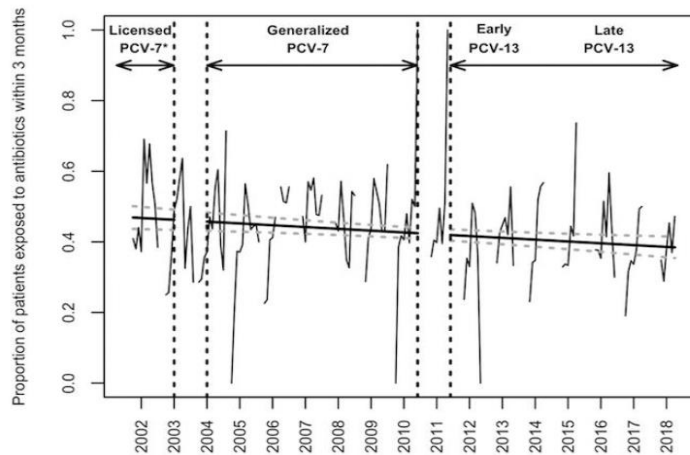
B Amoxicillin-clavulanate use



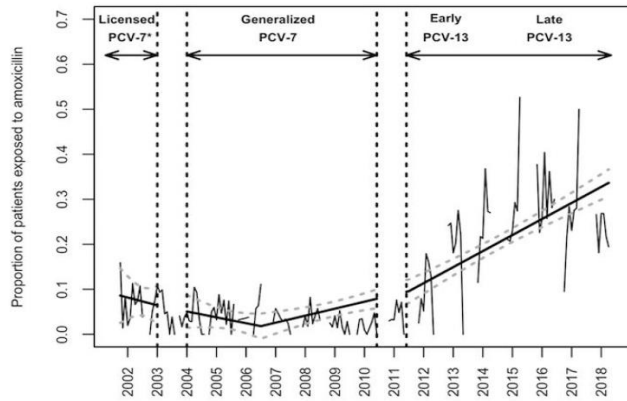
D Macrolides use



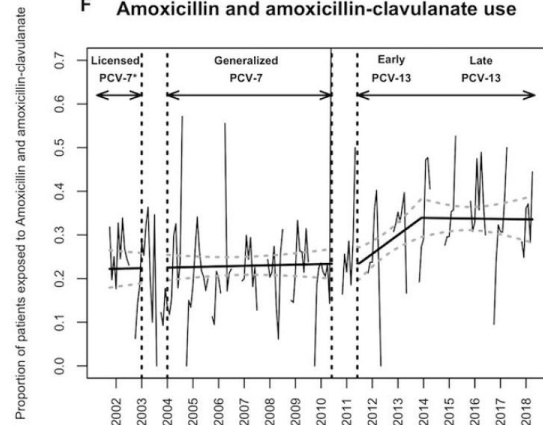
A Antibiotic use



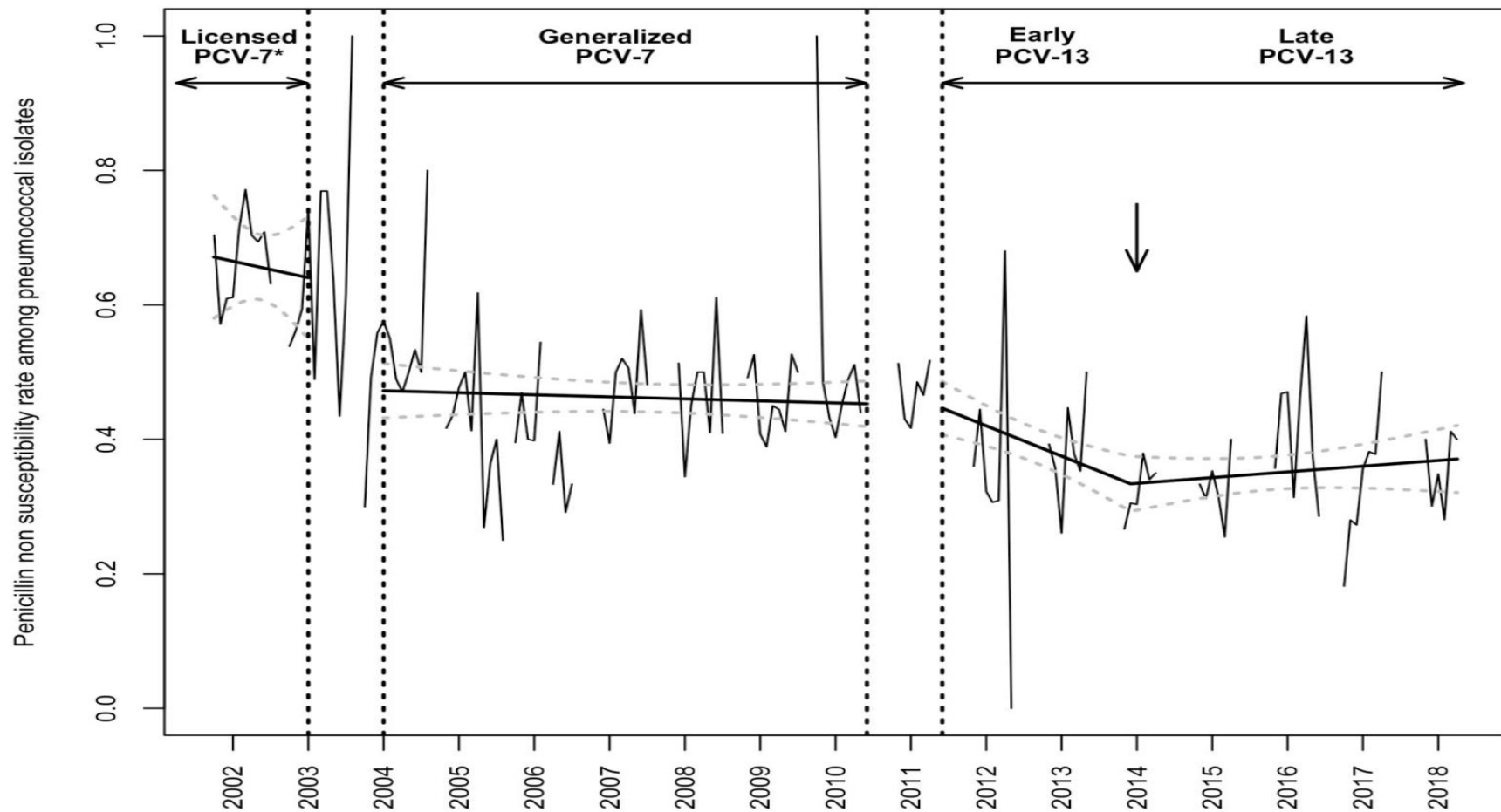
E Amoxicillin use



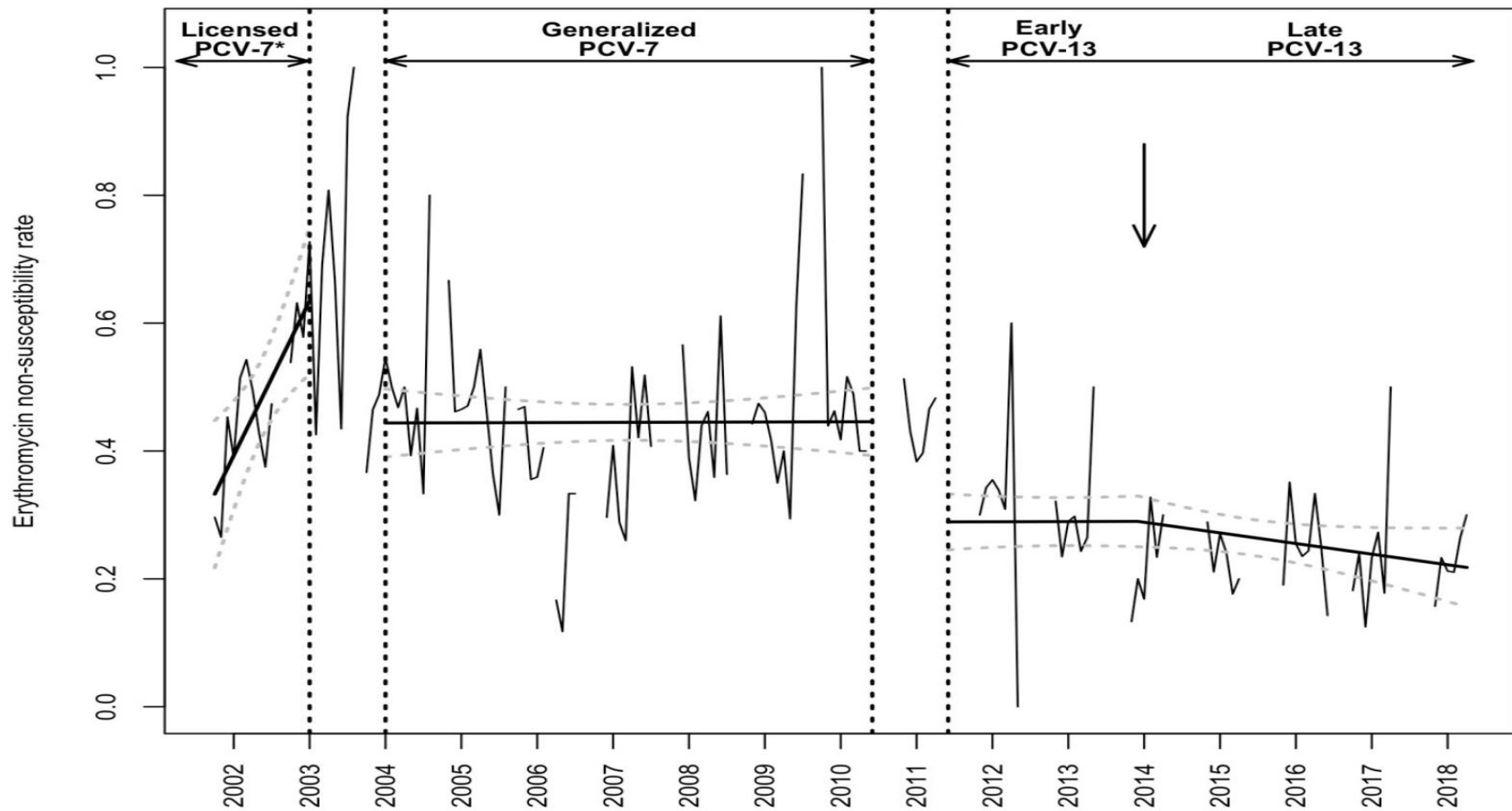
F Amoxicillin and amoxicillin-clavulanate use



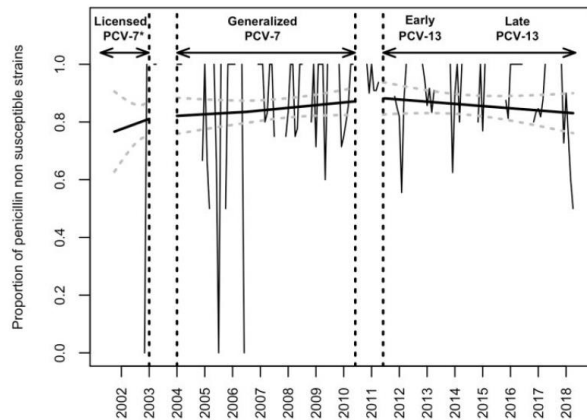
Impact of PCV7 and 13 on penicillin non susceptibility



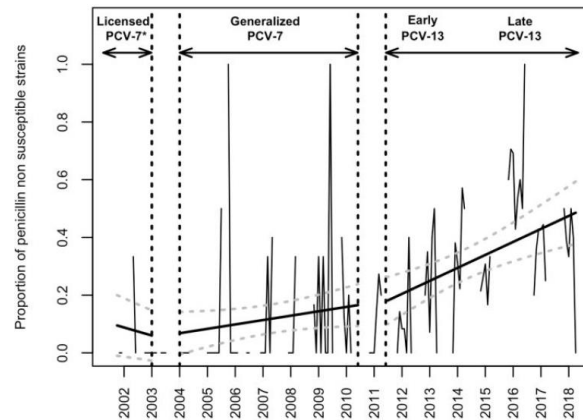
Impact of PCV7 and 13 on erythromycin non-susceptibility



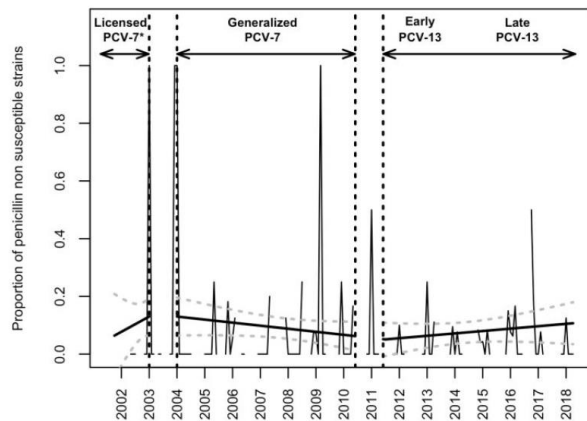
A Serotypes 35B and 15A



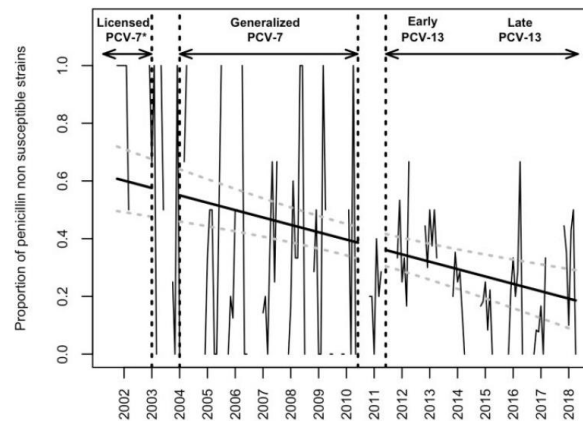
B Serotypes 11A and 23B



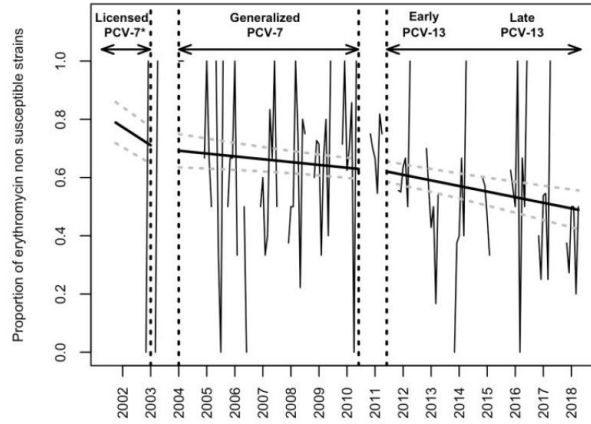
C Serotypes 10A, 21, 23A and 35F



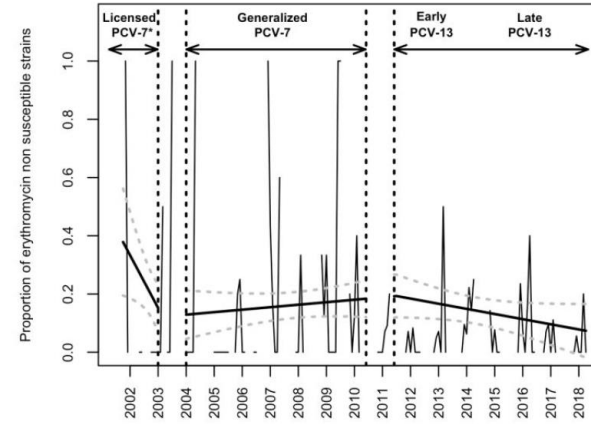
D Serotype 15BC



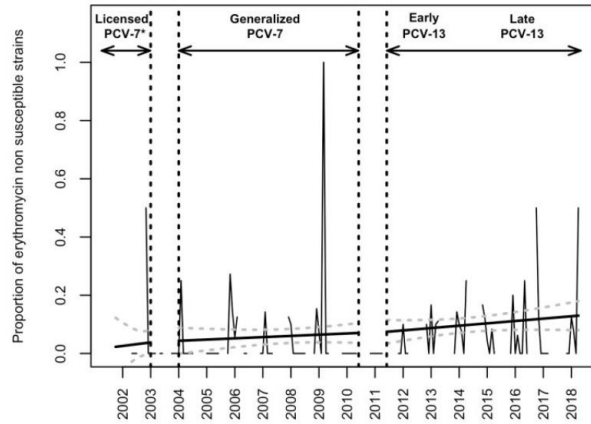
A Serotypes 35B and 15A



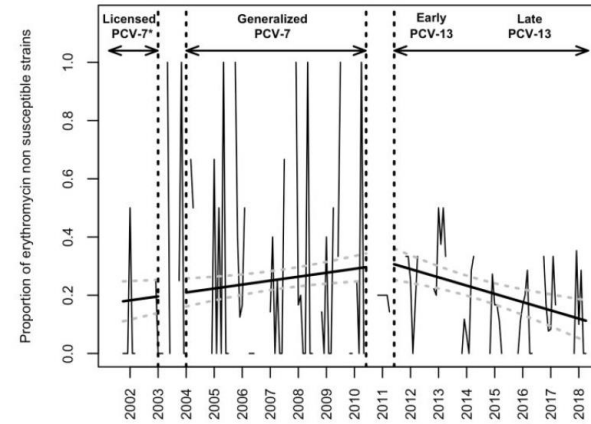
B Serotypes 11A and 23B



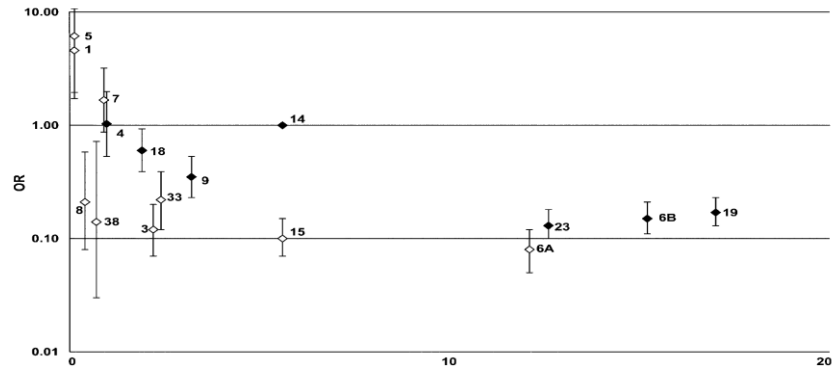
C Serotypes 10A, 21, 23A and 35F



D Serotype 15B/C



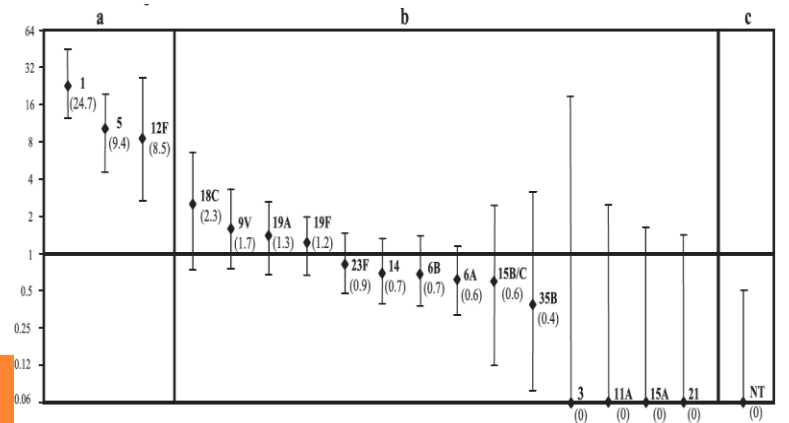
Serotype ^a	Total	Invasive	Carriage	OR (95% CI) ^b
4	6	5	1	12.1 (1.4–104.2)
1	5	4	1	9.6 (1.1–86.5)
14	75	54	21	8.8 (5.1–15.4)
18C	29	20	9	5.8 (2.6–13.2)
23F	48	7	41	0.4 (0.2–0.8)



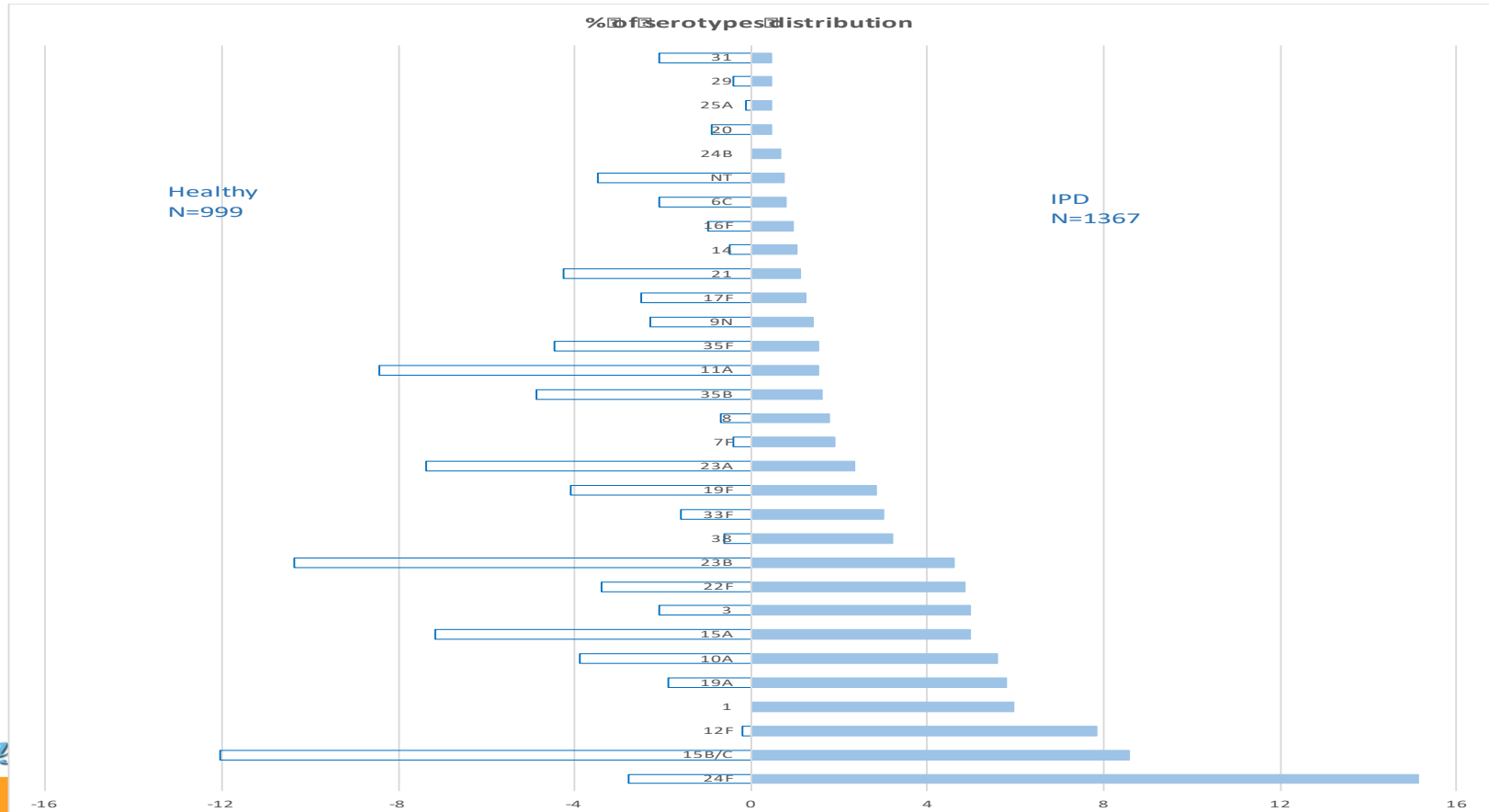
Hannage 2005;73:431...IPD 224

Serogroup or serotype	No. of invasive isolates (No. of carriage isolates)	OR	95% CI
38	6 (1)	5.94	0.71–49.79
14	40 (11)	4.07	2.03–8.17
18C	13 (4)	3.28	1.05–10.23
19A	17 (6)	2.89	1.12–7.47
7F	15 (6)	2.52	0.96–6.63
4	7 (4)	1.72	0.50–5.95
6B	51 (33)	1.643	1.01–2.67
9V	8 (5)	1.57	0.51–4.88
19F	22 (30)	0.68	0.38–1.22
23F	20 (29)	0.64	0.35–1.16
3	1 (2)	0.48	0.04–5.36
10	1 (2)	0.48	0.04–5.36
6A	14 (28)	0.45	0.23–0.88
15	2 (5)	0.38	0.07–1.99
22	1 (4)	0.23	0.03–2.15
35F	2 (9)	0.21	0.04–0.98

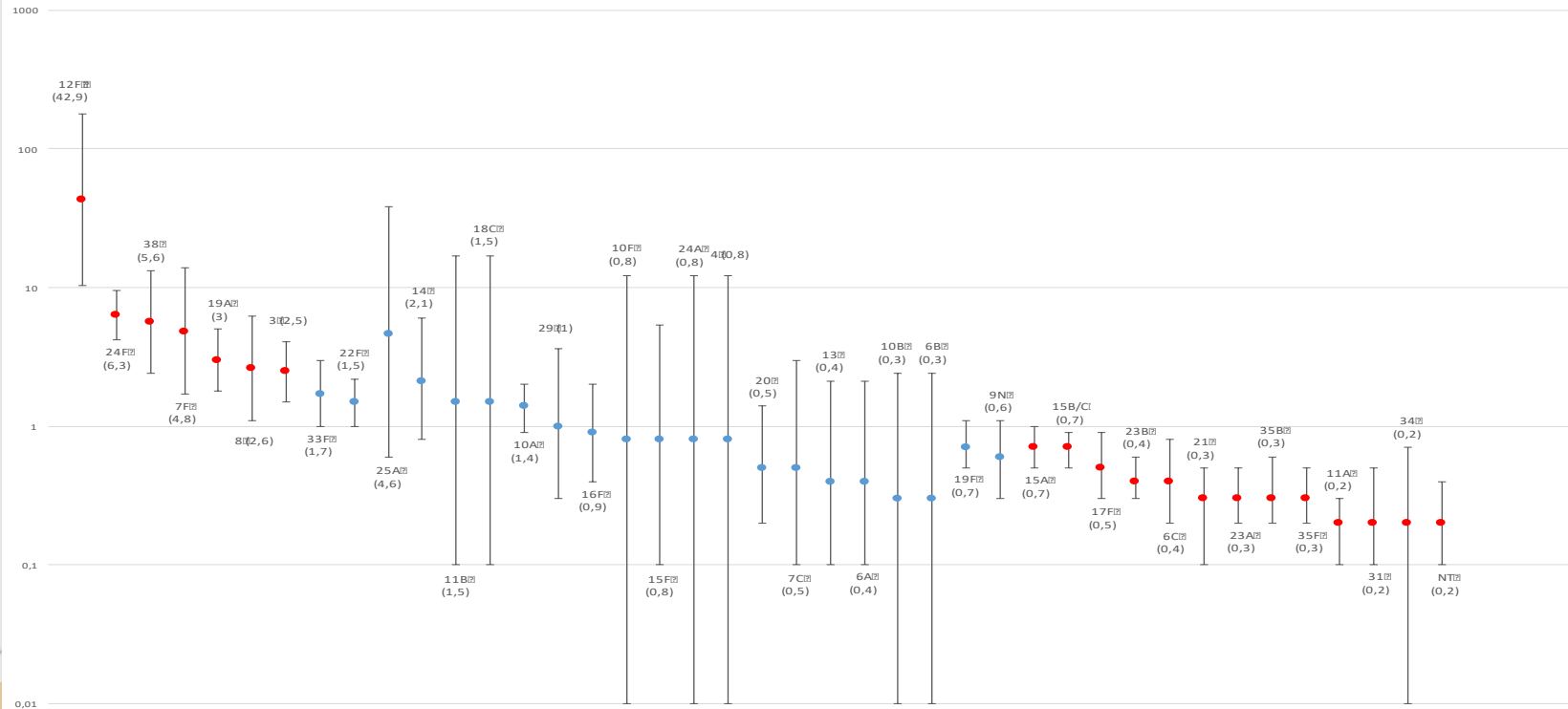
Shouval PIDJ 2006;25:603... IPD189/ Ca176



SEROTYPE DISTRIBUTION

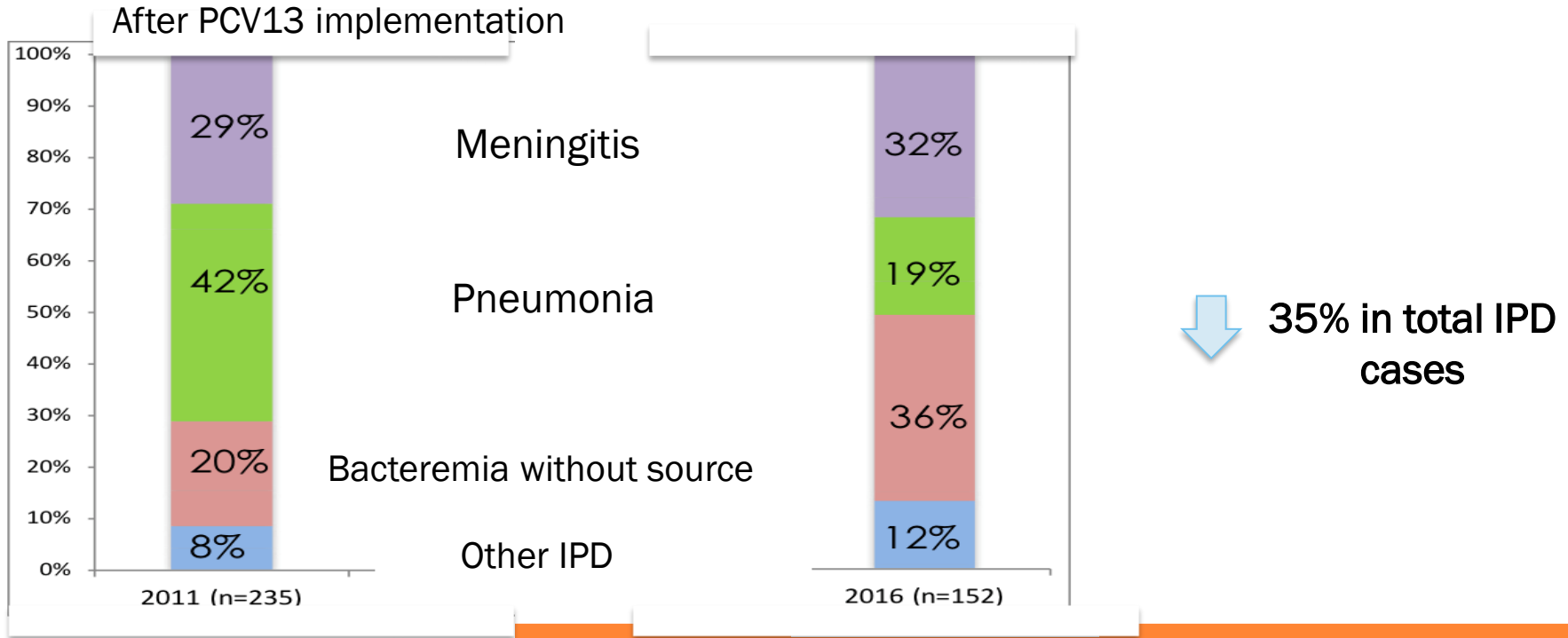


Titre bibliographique



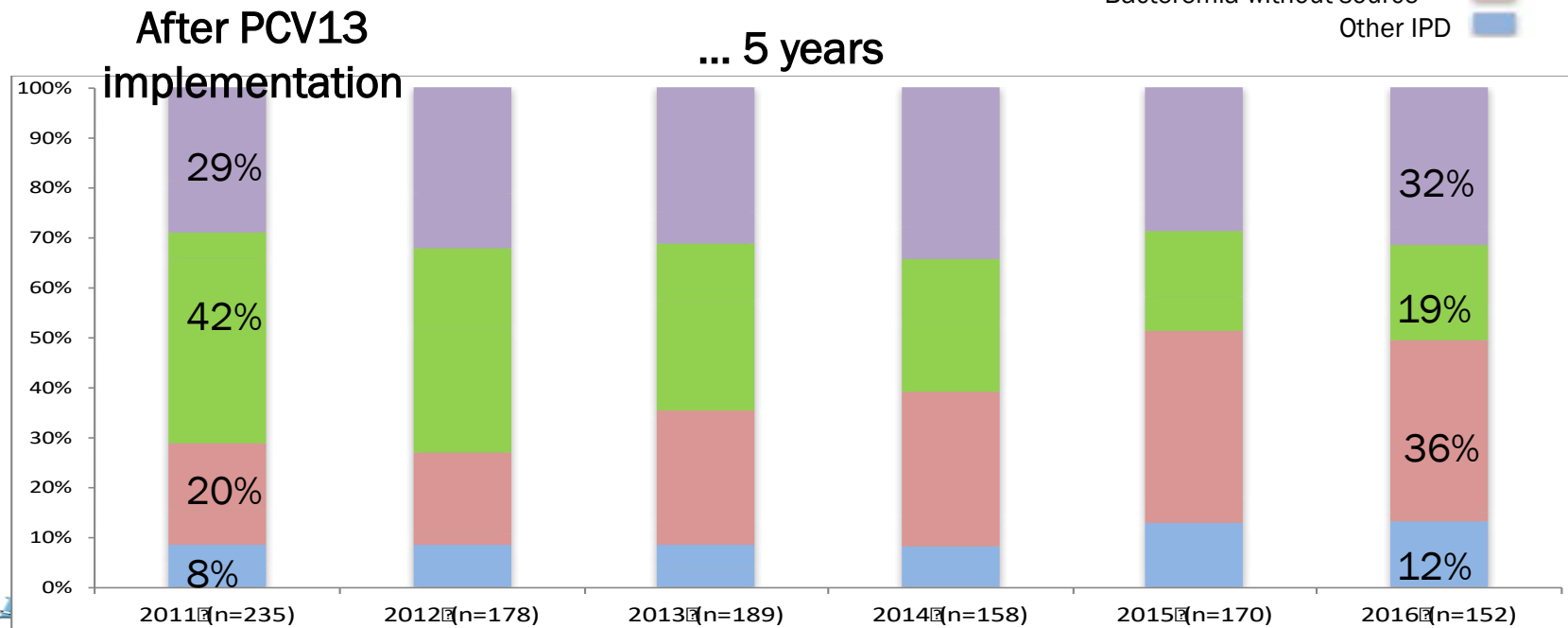
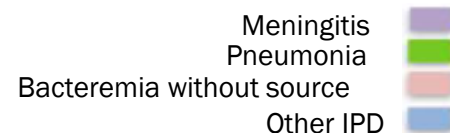
DISTRIBUTION OF IPD BY CLINICAL ENTITIES

1082 IPD from 2011 to 2016



DISTRIBUTION OF IPD BY CLINICAL ENTITIES

1082 IPD from 2011 to 2016



ALL SEROTYPES WERE ABLE TO INDUCE ALL CLINICAL PRESENTATIONS, HOWEVER...

PCV type and serotypes	Pneumonia N=340 % [95% CI]	Meningitis N=335 % [95% CI]	Bacteremia without an identified source N=301 % [95% CI]	Other IPD N=106 % [95% CI]
PCV13+6C (n=372)	58.1 [52.9;63.1]	21.5 [17.4;26.0]	13.2 [9.9;17.0]	7.3 [4.8;10.4]
Non-PCV13 (n=710)	17.5 [14.7;20.5]	35.9 [32.4;39.6]	35.5 [32.0;39.1]	11.1 [8.9;13.7]

ALL SEROTYPES WERE ABLE TO INDUCE ALL CLINICAL PRESENTATIONS, HOWEVER... FOR PCV13 SEROTYPES

PCV type and serotypes	Pneumonia N=340 % [95% CI]	Meningitis N=335 % [95% CI]	Bacteremia without an identified source N=301 % [95% CI]	Other IPD N=106 % [95% CI]
PCV13+6C (n=372)	58.1 [52.9;63.1]	21.5 [17.4;26.0]	13.2 [9.9;17.0]	7.3 [4.8;10.4]
1 (n=111)	91.9 [85.2;96.2]	3.6 [0.1;9.0]	0.9 [0.02;4.9]	3.6 [0.1;9.0]
19A (n=91)	45.1 [34.6;55.8]	25.3 [16.7;35.5]	16.5 [9.5;25.7]	13.2 [7.0;21.9]
7F (n=47)	57.4 [42.2;71.7]	25.5 [13.9;40.3]	14.9 [6.2;28.3]	2.1 [0.5;11.3]
3 (n=42)	54.8 [38.7; 70.2]	16.7 [7.0;31.4]	21.4 [10.3;36.8]	7.1 [1.5;19.5]
19F (n=39)	23.1 [11.1;39.3]	48.7 [32.4;65.2]	25.6 [13.0;42.1]	2.6 [0.06;13.5]

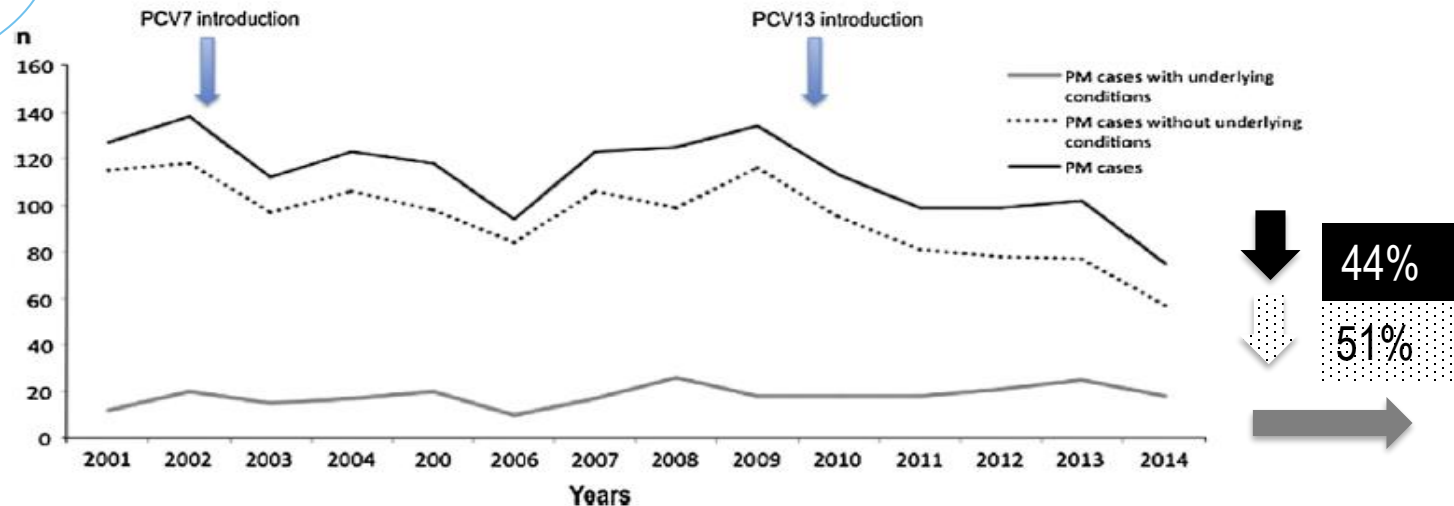
ALL SEROTYPES WERE ABLE TO INDUCE ALL CLINICAL PRESENTATIONS, HOWEVER... FOR NVT WITH HIGH AND LOW DP

PCV type and serotypes	Pneumonia N=340 % [95% CI]	Meningitis N=335 % [95% CI]	Bacteremia without an identified source N=301 % [95% CI]	Other IPD N=106 % [95% CI]
Non-PCV13 (n=710)	17.5 [14.7;20.5]	35.9 [32.4;39.6]	35.5 [32.0;39.1]	11.1 [8.9;13.7]
High disease potential* (including serotypes 8, 12F, 24F, 33F, n=252)	27.8 [22.3;33.7]	31.3 [25.7;37.5]	32.1 [26.4;38.3]	8.7 [5.6;12.9]
Low disease potential* (including serotypes 15A, 15BC, 23B, 16F, n=173)	9.8 [5.8;15.3]	38.7 [31.4;46.4]	39.9 [32.5;47.6]	11.6 [7.2;17.3]

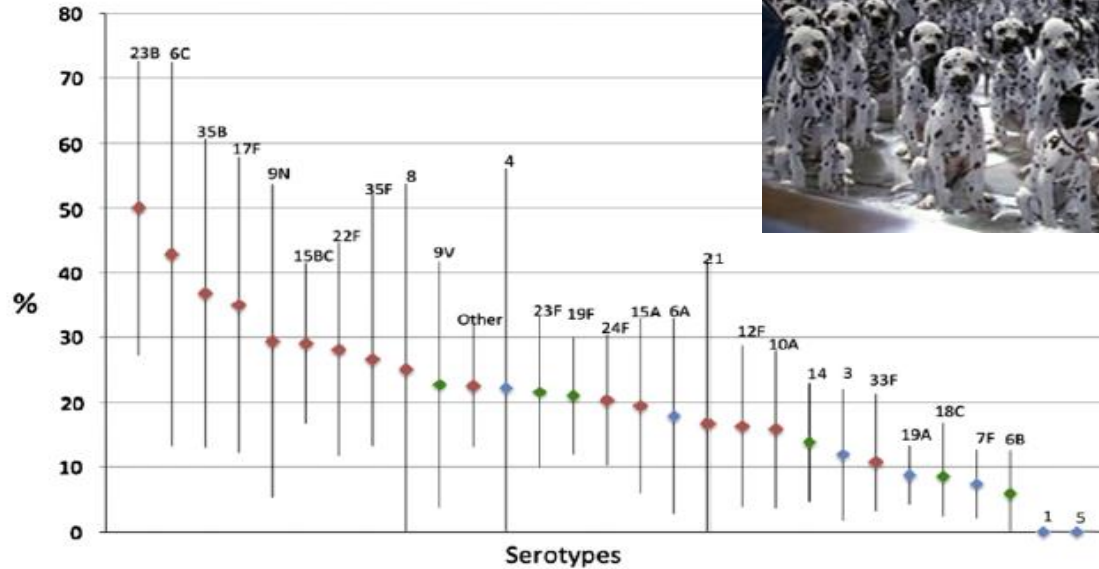
* Using the classification of Balsells et al. Plos One 2017

Distribution des méningites à pneumocoque en fonction de la présence de facteurs de risque

Le nombre de patients ayant un FDR et une méningite à pneumocoque est resté stable après l'introduction des PCVs.



Prévalence de méningites à pneumocoque avec facteur de risque par sérotype



Data are percentage (95% CI).

Other = all non vaccine serotypes < 12 cases

Les sérotypes vaccinaux (PCV13) ont diminué de 68% dans cette population

Worldwide, the implementation of PCV — with adequate coverage — has been followed by a decrease in PD

	Efficacy against IPD	Efficacy against carriage	Remarks
4	↓↓↓↓	↓↓↓↓	
6B	↓↓↓↓	↓↓↓↓	Cross protection against 6A
9V	↓↓↓↓	↓↓↓↓	
14	↓↓↓↓	↓↓↓↓	
18C	↓↓↓↓	↓↓↓↓	
19F	↓↓↓↓	↓↓	Cross protection against 19A IPD for PCV10
23F	↓↓↓↓	↓↓↓↓	
1	↓↓↓↓	↓↓↓↓	
5	↓↓↓↓	↓↓↓↓	
7F	↓↓↓↓	↓↓↓↓	
3	↓↓	↓↓	
6A	↓↓↓↓	↓↓↓↓	With 6B, cross protection against 6C
19A	↓↓↓↓	↓↓	



Vaccine	Serotype	Country, schedule, study design and vaccine effectiveness estimates			
		Australia (3+0) Case-control*	UK (2+1) Indirect cohort ^{#6,36}	US (3+1) Case-control ^{12,16}	Germany (3+1) Indirect cohort ^{†19}
7vPCV	All VTs	93% (28 to 99%)	93% (70 to 98%)	100% (94 to 100%)	95% (57 to 100%)
	4	na	99% (72 to 100%)	93% (65 to 99%)	70% (-636 to 100%)
	6B	75% (1.2 to 94%)	49% (-14 to 77%)	94% (77 to 98%)	90% (66 to 98%)
	9V	na	79% (-2 to 90%)	100% (88 to 100%)	89% (-13 to 100%)
	14	82% (-76 to 98%)	93% (80 to 98%)	94% (81 to 98%)	90% (66 to 98%)
	18C	81% (32 to 94%)	94% (64 to 99%)	97% (85 to 99%)	8% (-239 to 76%)
	19F	7% (-214 to 72%)	70% (29 to 87%)	87% (65 to 95%)	55% (-34 to 87%)
	23F	76% (-3 to 95%)	76% (20 to 94%)	98% (80 to 100%)	61% (-62 to 94%)
13vPCV	All VTs	86% (12 to 98%)	79% (25 to 94%)	86% (76 to 92%)	91% (61 to 99%)
	7vPCV types	75% (-10 to 97%)	90% (34 to 98%)	Na	83% (-240 to 100%)
	13v-non7v	72% (45 to 85%)	73% (57 to 83%)	87% (77 to 93%)	82% (66 to 91%)
	1	na	84% (54 to 95%)	na	83% (15 to 97%)
	3	31% (-275 to 89%)	26% (-69 to 68%)	80% (30 to 95%)	74% (2 to 93%)
	6A	na	98% (64 to 99.8%)	na	96% (56 to 100%)
	7F	100% (<-1000 to 100%)	97% (70 to 98%)	97% (83 to 100%)	84% (18-98%)
	19A	73% (40 to 87%)	67% (33 to 84%)	86% (71 to 94%)	77% (47 to 90%)

CONCLUSIONS

- **Incidence des infections pneumococciques** ↘↘ à ↘↘↘
 - La surveillance doit se poursuivre
- **Spectre des infections pneumococciques : il a changé**
 - Répartition des différentes infections
 - Augmentation de la proportion des patients présentant une pathologie sous jacente
- **Sérotypes du pneumocoque**
 - Bouleversement
 - Plus grand chantier écologique depuis l'avènement de l'antibiothérapie
- **La résistance aux antibiotiques** ↘

MAIS

