EFFECT OF VACCINATION ON ANTIMICROBIAL RESISTANCE : THE EXAMPLE OF THE IMPACT OF PCVS ON ANTIBIOTIC RESISTANCE

Pr Robert Cohen

CHI Créteil

France

DISCLOSURES

- **I have received during the las 3 years honorarium for symposium and board from**
  - Astra-Zenzca
  - GSK
  - Merck
  - Pfizer
  - Sanofi-Pasteur
- My institution has received research grants from
  - Astra-Zenzca
  - GSK
  - Merck
  - Pfizer
  - Sanofi-Pasteur

- There is a growing interest for the role of vaccines in confronting the problem of antimicrobial resistance (AMR)
- Vaccines can reduce the prevalence of AMR by reducing :
  - colonization and IPD due to resistant strains
  - need for antimicrobial use by ↘ the incidence of diseases
  - the number of pathogens that may be responsible for some clinical syndromes, leading to
    - decreasing the severity of the diseases
    - decreasing the need of broad spectrum antibiotics

- *These effects may be amplified by herd immunity*
- *Vaccination can reduce pressure for resistance even in pathogens not included in the vaccine and present in microbiota*
  - *H. influenzae*
  - *E. coli*

SYNERGISTIC EFFECTS BETWEEN ANTIBIOTICS AND PCVS

CARRIAGE AND PENICILLIN SUSCEPTIBILITY ACCORDING TO VACCINATION STATUS AND ANTIBIOTIC USE WITHIN THE LAST 3 MONTHS

%	Vaccinated - Antibiotics - N=782	Vaccinated - Antibiotics + N=650	Vaccinated + Antibiotics - N=603	Vaccinated + Antibiotics - N=491
PSP IC95%	33 [29%;36%]	21 [18%;24%]	31 [27%;35%]	24 [20%;27%]
PIP IC95%	27 [24%;30%]	34 [30%;38%]	24 [20%;27%]	23 [20%;27%]
PRP IC95%	10 [8%;12%]	15 [13%; 18%]	4 [3%;6%]	8 [6%;11%]
Non Carriers IC95%	30 [27%;33%]	30 [26%;33%]	41 [37%;45%]	45 [41%;50%]

Impact of Pneumococcal Conjugate Vaccine and of Reduction of Antibiotic Use on Nasopharyngeal Carriage of Nonsusceptible Pneumococci in Children With Acute Otitis Media

Robert Cohen, MD,* Corinne Levy, MD,† France de La Rocque, MD,† Nathalie Gelbert, MD,‡ Alain Wollner, MD,† Bernard Fritzell, MD,§ Eric Bonnet, MD,§ Robert Telelboum, MD,§ and Emmanuelle Varon, MD‖

The Pediatric Infectious Disease Journal • Volume 25, Number 11, November 2006

↘ OF PNEUMOCOCCAL RESISTANCE

- In pneumococcal diseases

- In pneumococcal carriage

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 6, 2006 VOL. 354 NO. 14

Effect of Introduction of the Pneumococcal Conjugate Vaccine on Drug-Resistant *Streptococcus pneumoniae*

Moe H. Kyaw, Ph.D., M.P.H., Ruth Lynfield, M.D., William Schaffner, M.D., Allen S. Craig, M.D., James Hadler, M.D., M.P.H., Arthur Reingold, M.D., Ann R. Thomas, M.D., M.P.H., Lee H. Harrison, M.D., Nancy M. Bennett, M.D., Monica M. Farley, M.D., Richard R. Facklam, Ph.D., James H. Jorgensen, Ph.D., John Besser, M.S., Elizabeth R. Zell, M.Stat., Anne Schuchat, M.D., and Cynthia G. Whitney, M.D., M.P.H., for Active Bacterial Core Surveillance of the Emerging Infections Program Network

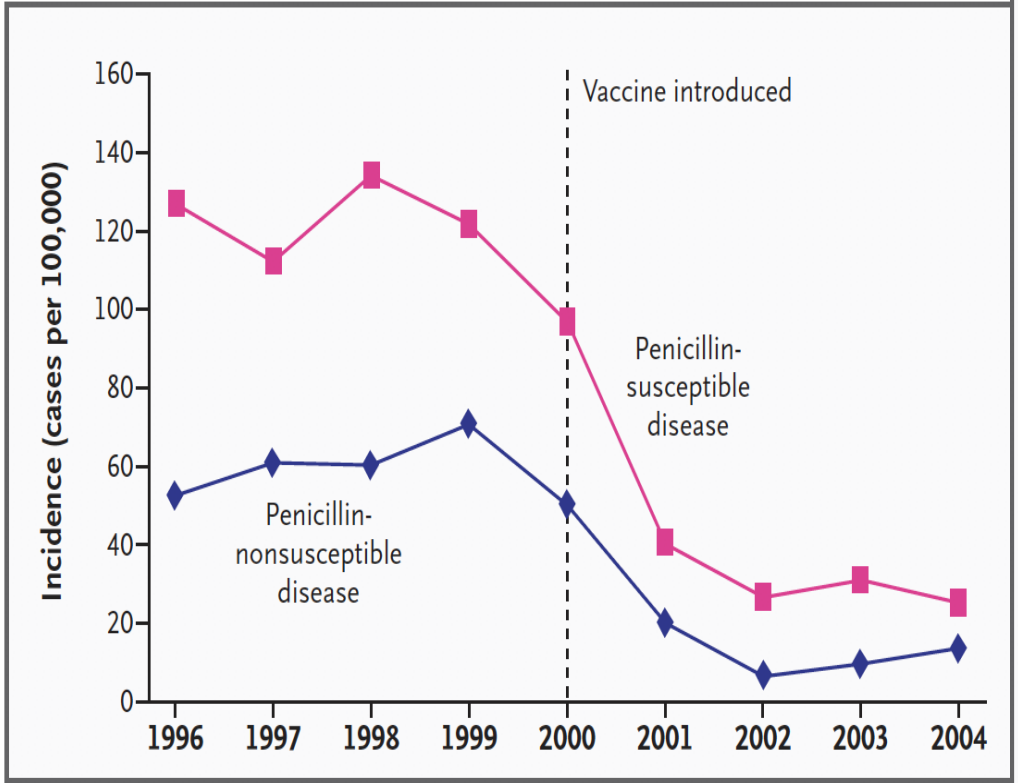


Figure 1. Annual Incidence of Invasive Disease Caused by Penicillin-Susceptible and Penicillin-Nonsusceptible Pneumococci among Children under Two Years of Age, 1996 to 2004.

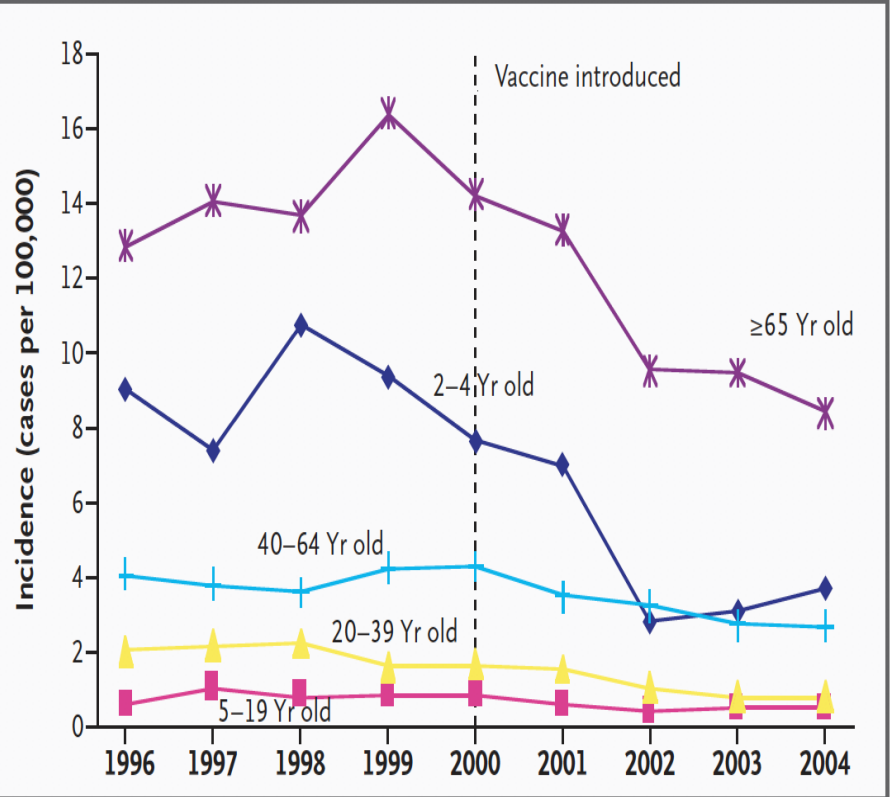


Figure 2. Annual Incidence of Invasive Disease Caused by Penicillin-Nonsusceptible Pneumococci in Persons Two Years of Age or Older, 1996 to 2004.

PATIENTS AND METHODS

- September 2001 – May 2017
- 90 pediatricians took part in this study
- Children 6-24 m with AOM
- NP specimens
- were taken with cotton-tipped wire swabs
- placed in transport medium
- and sent within 48 hours to
  - National Reference Center for Pneumococci (HEGP)
  - Robert Debré Hospital
- Isolates identification
- Serotyping
- Antibiotic susceptibility

} performed using standard microbiological methods

Vaccine 33 (2015) 5118–5126

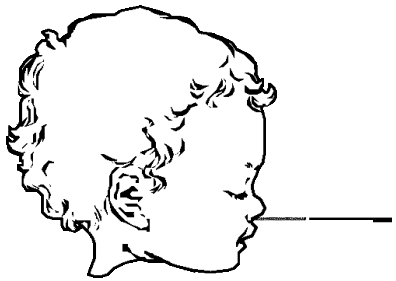
Contents lists available at ScienceDirect

Vaccine

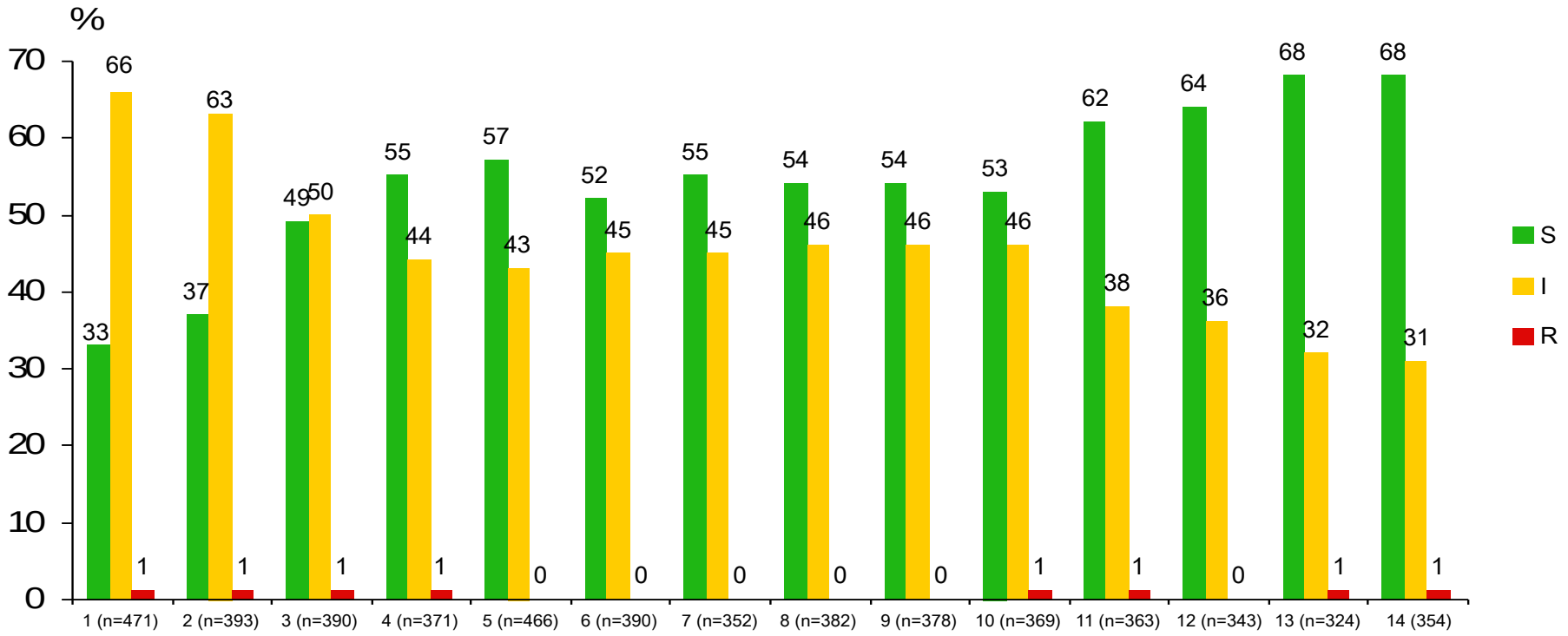
journal homepage: www.elsevier.com/locate/vaccine

A 13-year survey of pneumococcal nasopharyngeal carriage in children with acute otitis media following PCV7 and PCV13 implementation

Robert Cohen[a,b,c,d,e], Emmanuelle Varon[f], Catherine Doit[g,h], Catherine Schlemmer[b], Olivier Romain[b], Franck Thollot[b,d], Stéphane Béchet[b], Stéphane Bonacorsi[g,h], Corinne Levy[a,b,c,d,*]



PENICILLIN RESISTANCE OF *S. PNEUMONIAE* ISOLATED FROM NP FLORA OF YOUNG CHILDREN WITH AOM



Study Years (Year 1: Oct 2001/June 2002, Year 14: Oct 2014/ March 2015)

Cohen R et al. Vaccine 2015

PNEUMOCOCCAL RESISTANCE DOES NOT INVOLVE ALL PNEUMOCOCCAL SEROTYPES

- > 94 ≠ serotypes
- Among them ≈ 20 are +/-resistant to antibiotics
- Strong correlation between the duration of carriage and the risk of occurrence of resistance

Evolution of antibiotic resistance is linked to any genetic mechanism affecting bacterial duration of carriage

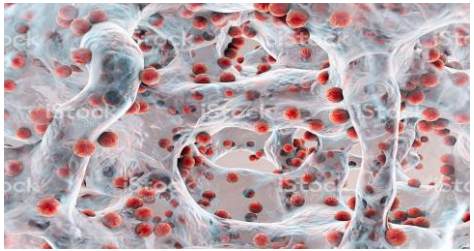
Sonja Lehtinen[a,b,1], François Blanquart[b], Nicholas J. Croucher[b], Paul Turner[c,d,2], Marc Lipsitch[e,f,g,3], and Christophe Fraser[a,3]

[a]Oxford Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford OX3 7LF United Kingdom; [b]Department of Infectious Disease Epidemiology, Imperial College London, London W2 1PG United Kingdom; [c]Shoklo Malaria Research Unit, Mahidol–Oxford Tropical Medicine Research

PNAS | January 31, 2017 | vol. 114 | no. 5 | 1075–1080

- According notably to the properties of the capsule, some serotypes are more adapted to persist in the NP microbiota

PNEUMOCOCCAL RESISTANCE DOES NOT INVOLVE ALL PNEUMOCOCCAL SEROTYPES



- *S. pneumoniae* strains are buried in biofilms that make it easier for them to resist immune defenses and antibiotics
- the long duration of carriage explains that these strains are more frequently
  - challenged by antibiotics
  - have more opportunity to exchange DNA materials
    - with other streptococci from NP microbiome
    - frequently resistant to antibiotics

BEFORE PCVS IMPLEMENTATION

- The serotypes implicated in pneumococcal infections (IPD and mucosal)
  - in high income countries
  - in young children
- The serotypes more frequently carried (generally for long periods…)
- The serotypes frequently resistant

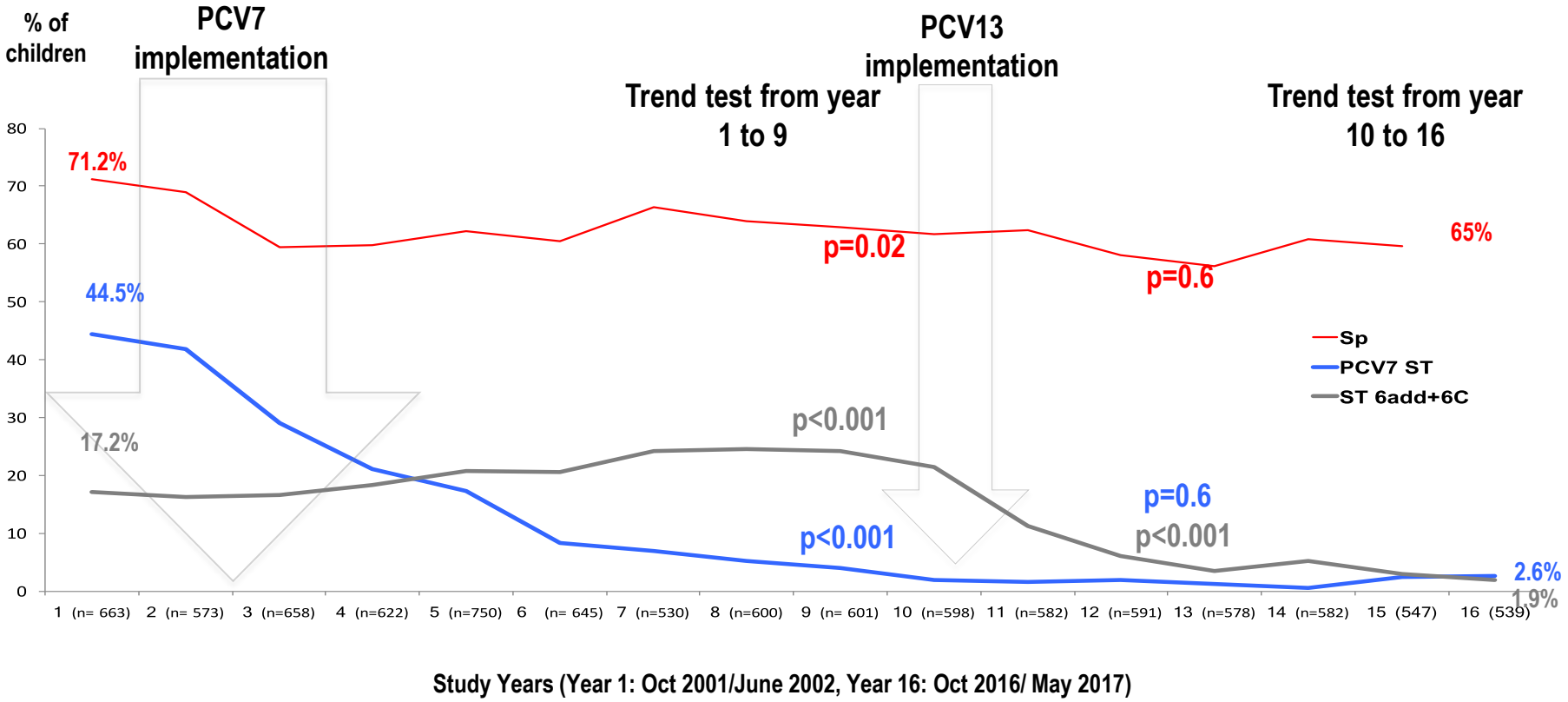
were the same
[6,9,14,19,23]

> 70 %

THE MAIN DRIVER OF PCVS IMPLEMENTATION FOR ANTIBIOTIC RESISTANCE WAS THE DISEAPPARENCE OF VT

SP NP CARRIAGE

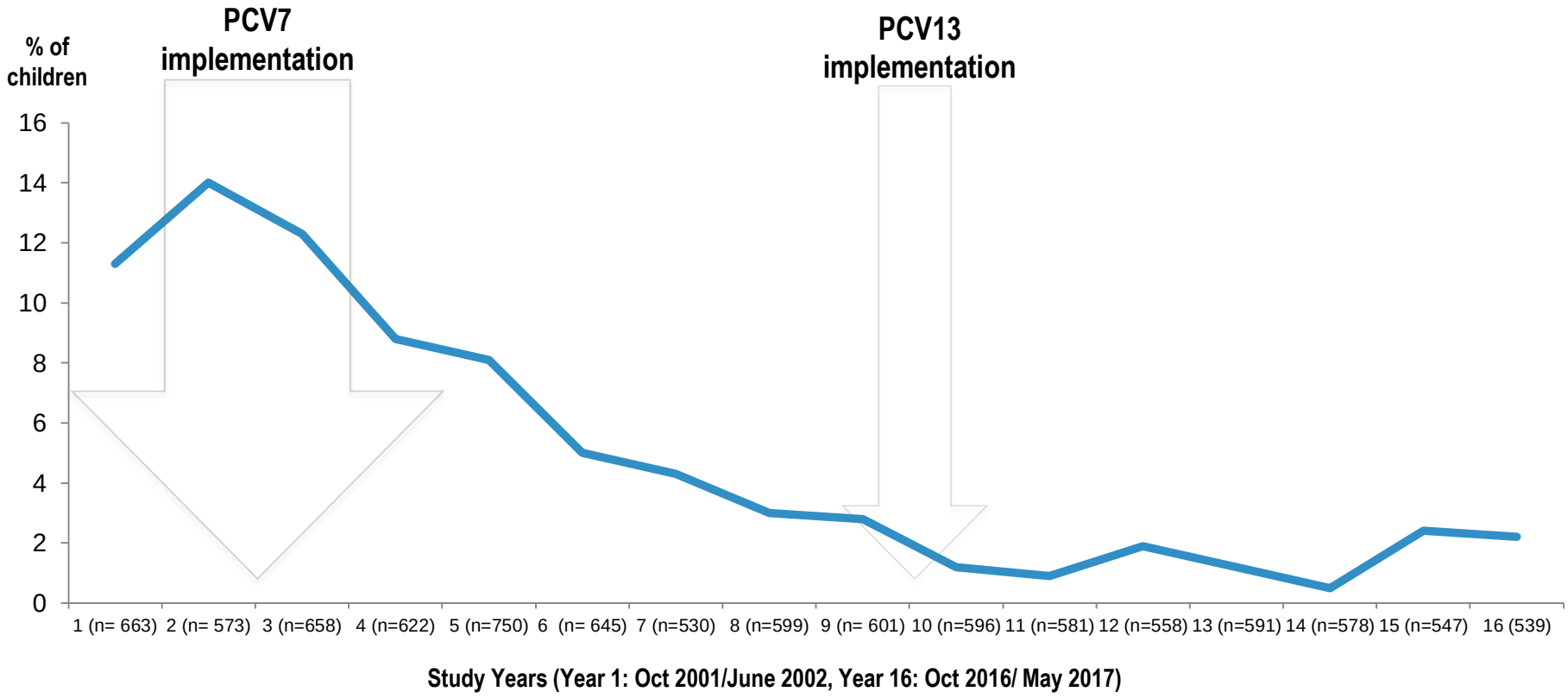
AOM FEVER± OTALGIA, 9659 CHILDREN, 16 YEARS



Cohen R et al. Vaccine 2015

SEROTYPE 19F

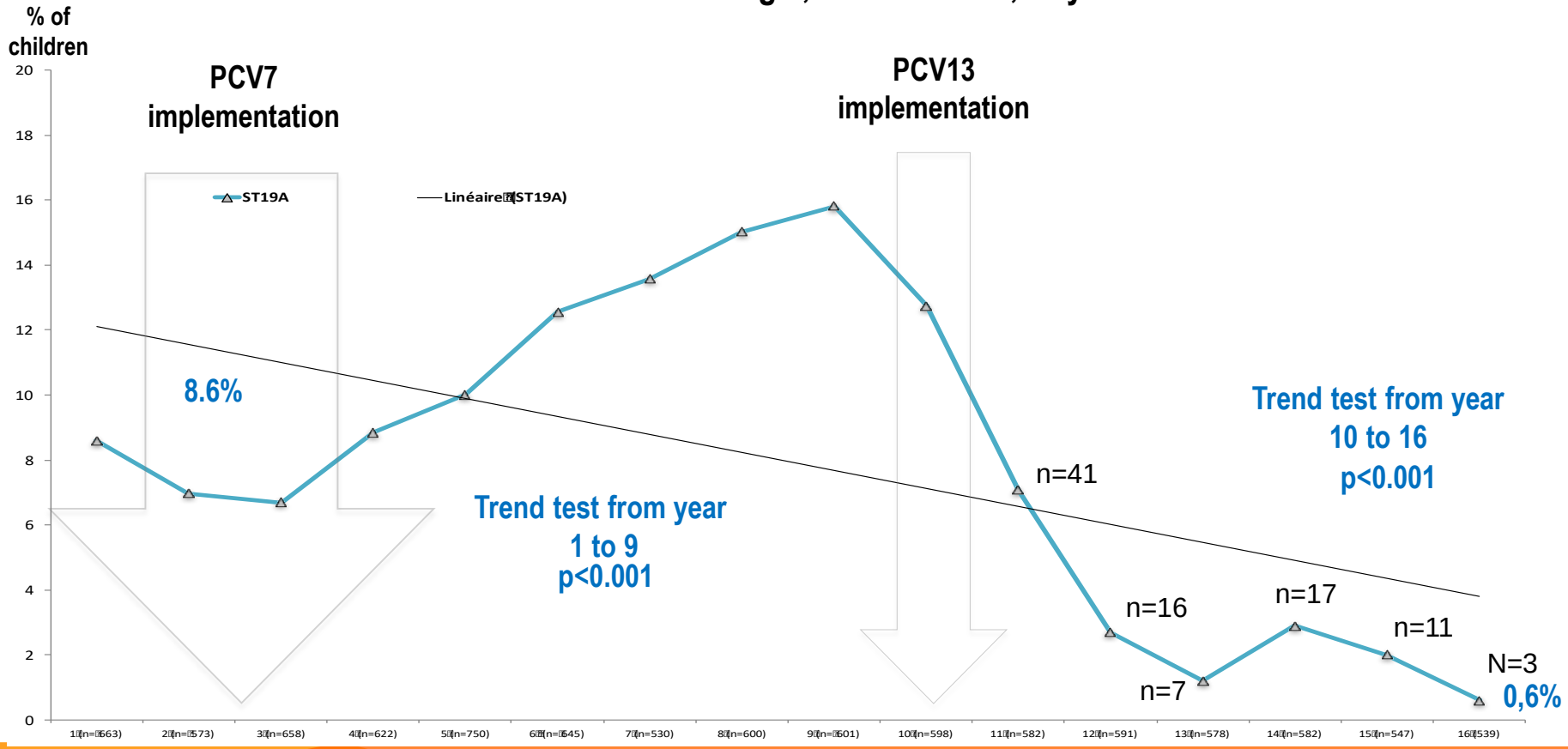
AOM FEVER± OTALGIA, 9659 CHILDREN, 16 YEARS



Cohen R et al. Vaccine 2015

SEROTYPE 19A

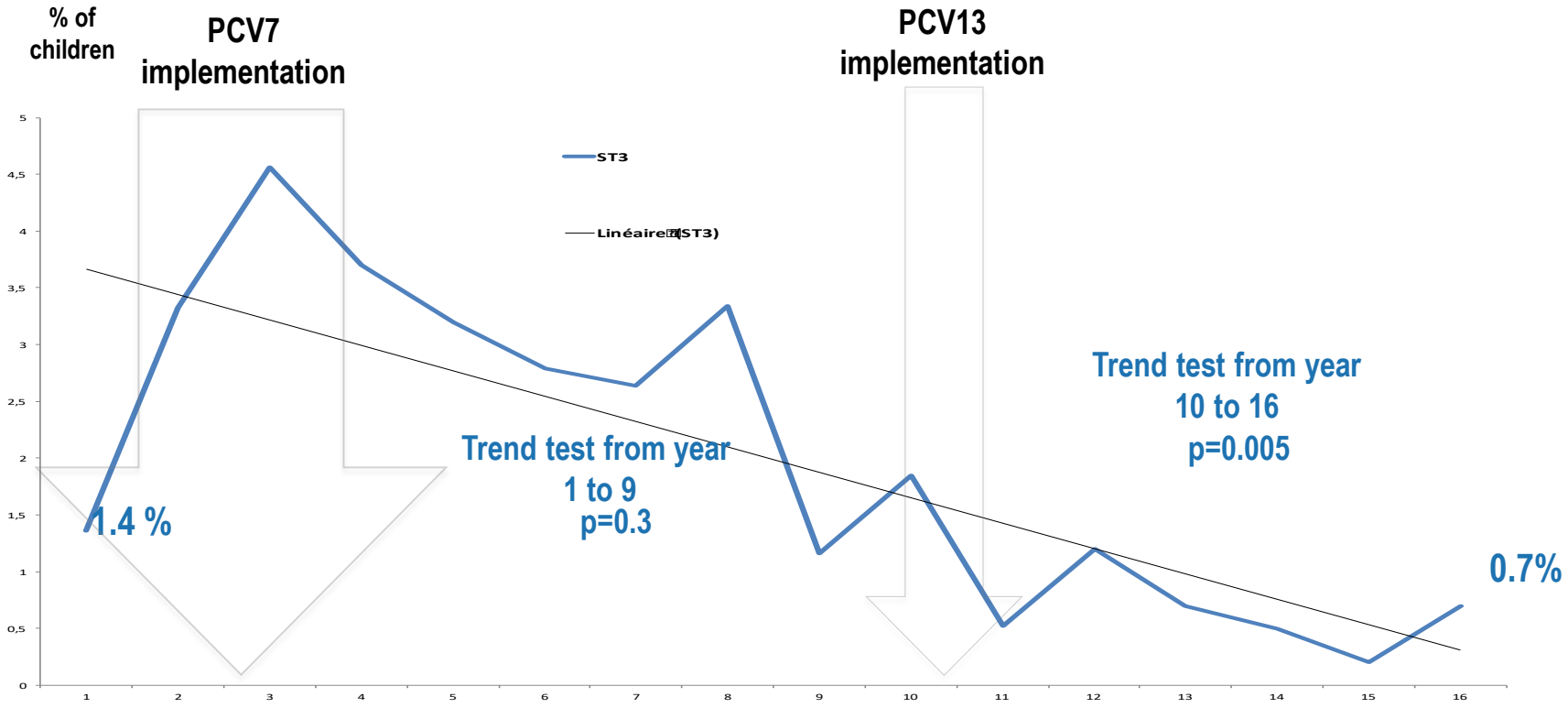
AOM fever± otalgia, 9659 children, 16 years



Cohen R et al. Vaccine 2015

SEROTYPE 3

AOM fever± otalgia, 9659 children, 16 years

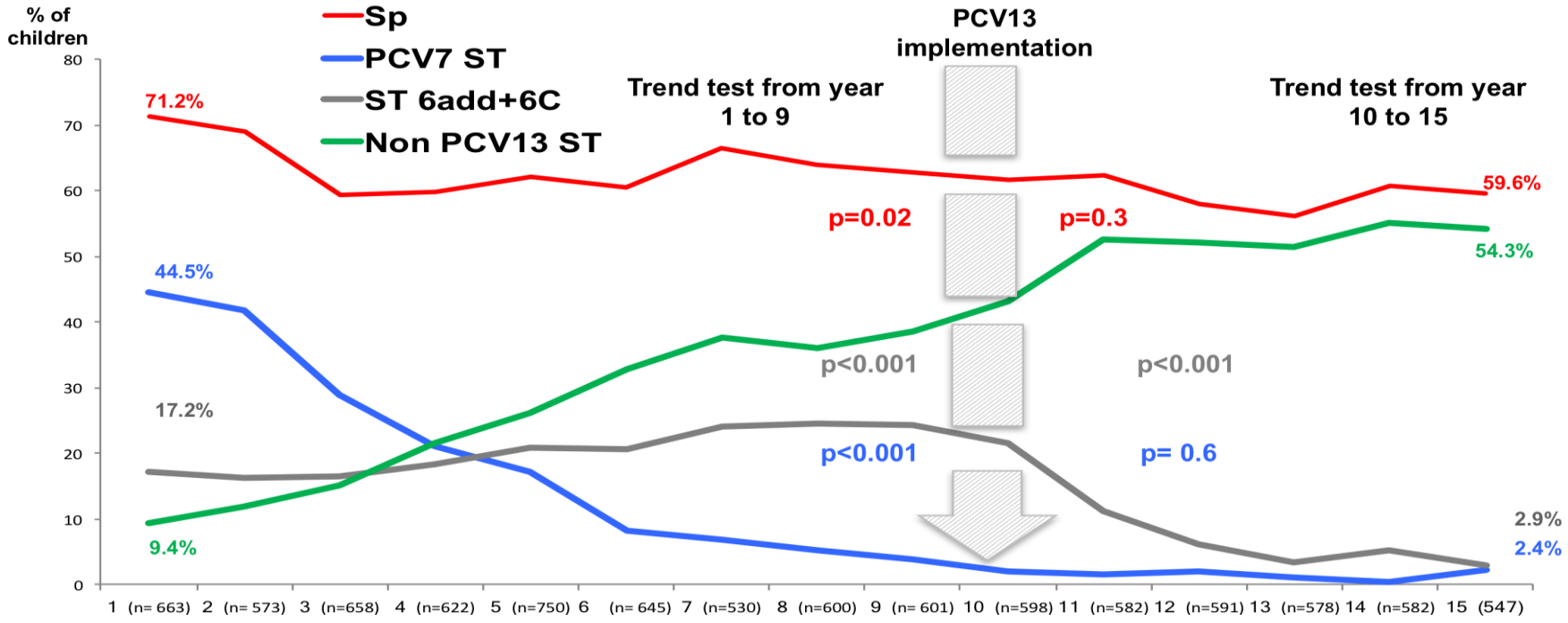


Cohen R et al. Vaccine 2015

- However, the situation is evolving, according to the emergence in NP flora of NVT
- Among them, the great majority
  - were present in NP flora before PCVs implementation (at low level : previously minor clones)
  - have long duration of carriage
  - have become resistant to antibiotics
  - **but** have low disease potential

Pneumococcal carriage

Expansion of previously minor clones

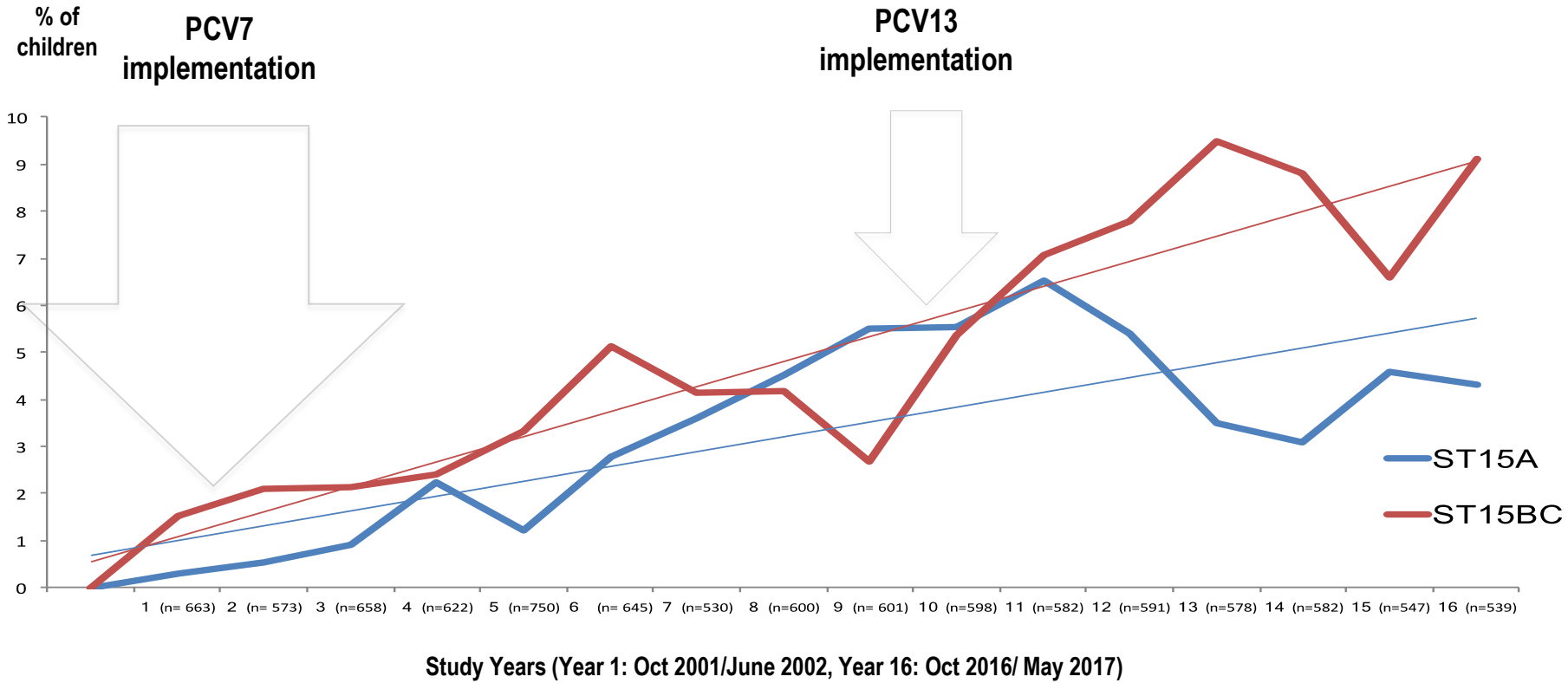


Study Years (Year 1: Oct 2001/June 2002, Year 15: Oct 2015/ May 2016)

Cohen R et al. Vaccine 2015

Emerging serotypes: ST 15A, 15B/C

AOM fever± otalgia, 9659 children, 16 years

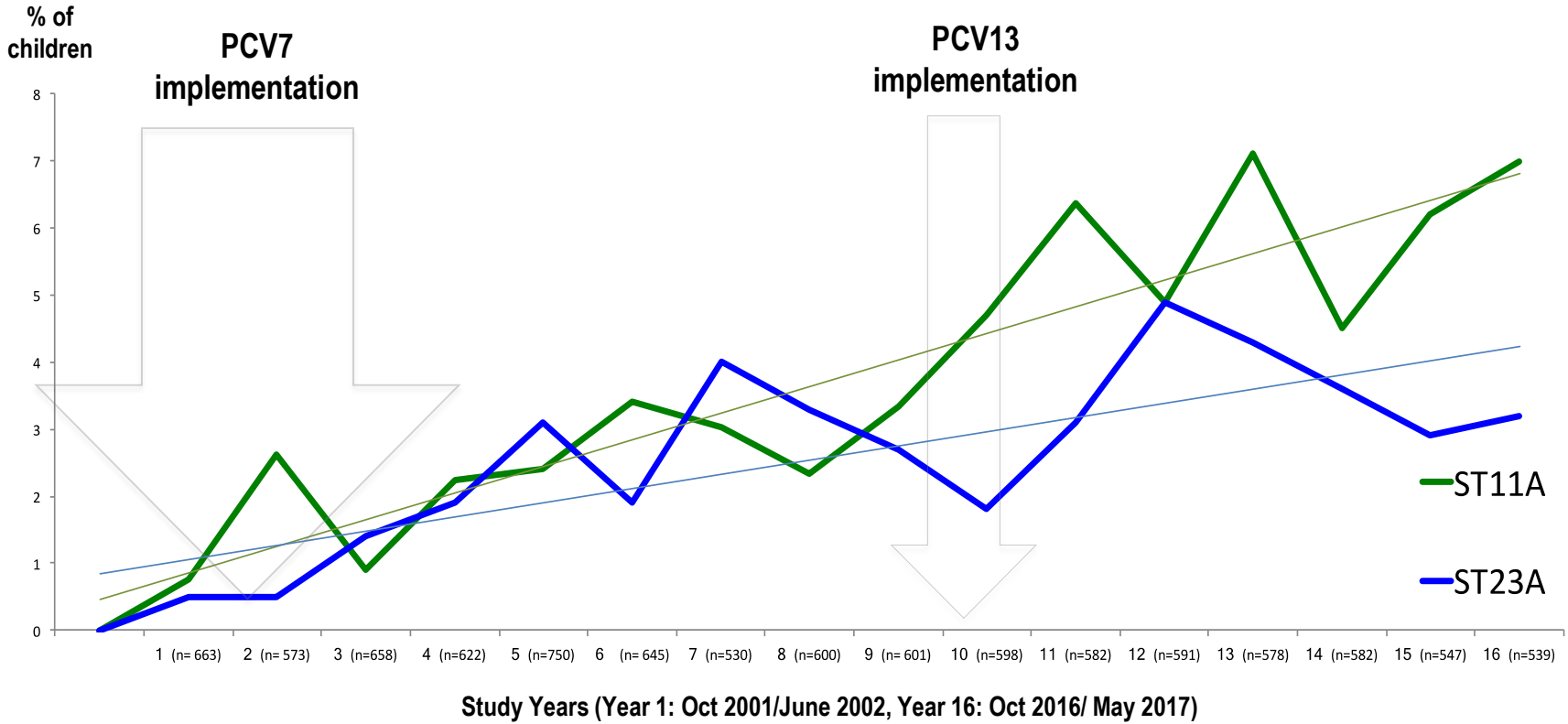


Study Years (Year 1: Oct 2001/June 2002, Year 16: Oct 2016/ May 2017)

Cohen R et al. Vaccine 2015

Emerging serotypes: ST 11A, 23A

AOM fever± otalgia, 9659 children, 16 years

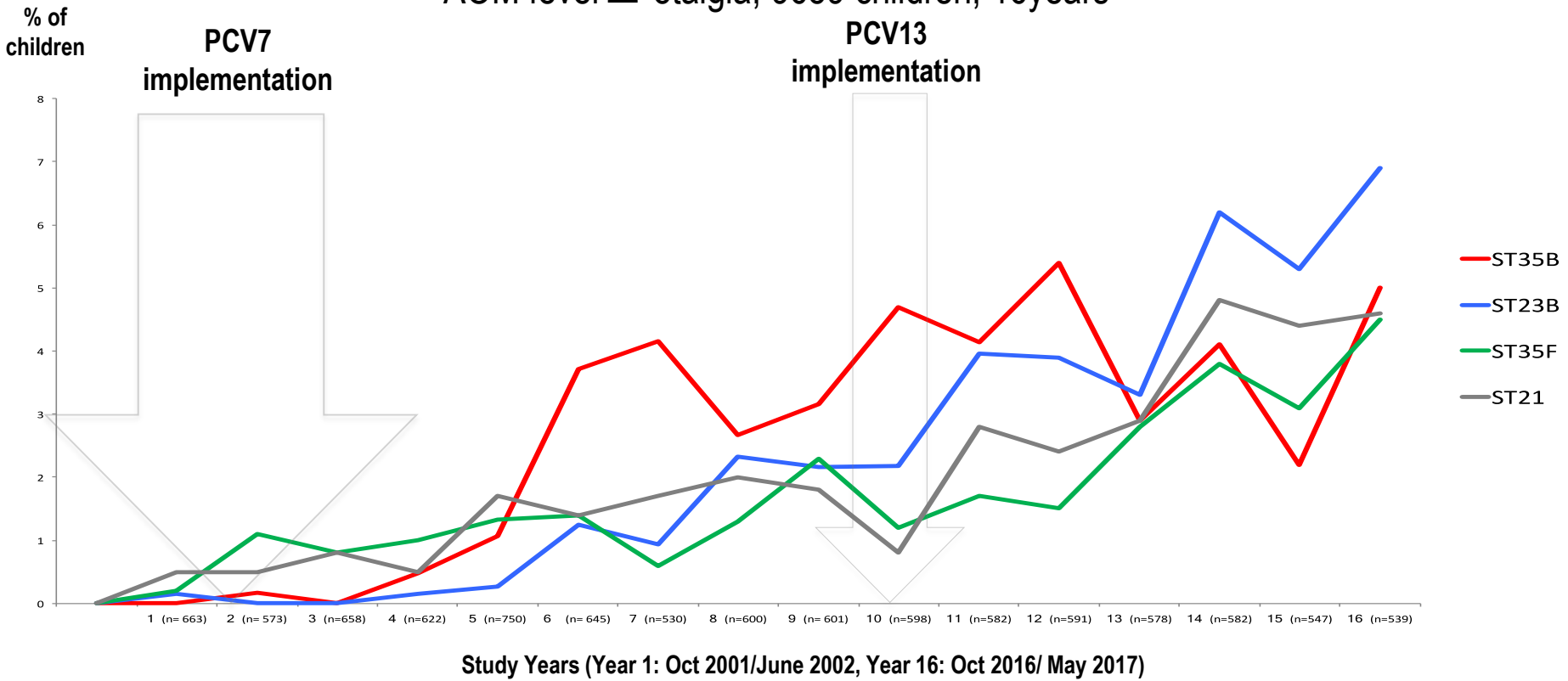


Study Years (Year 1: Oct 2001/June 2002, Year 16: Oct 2016/ May 2017)

Cohen R et al. Vaccine 2015

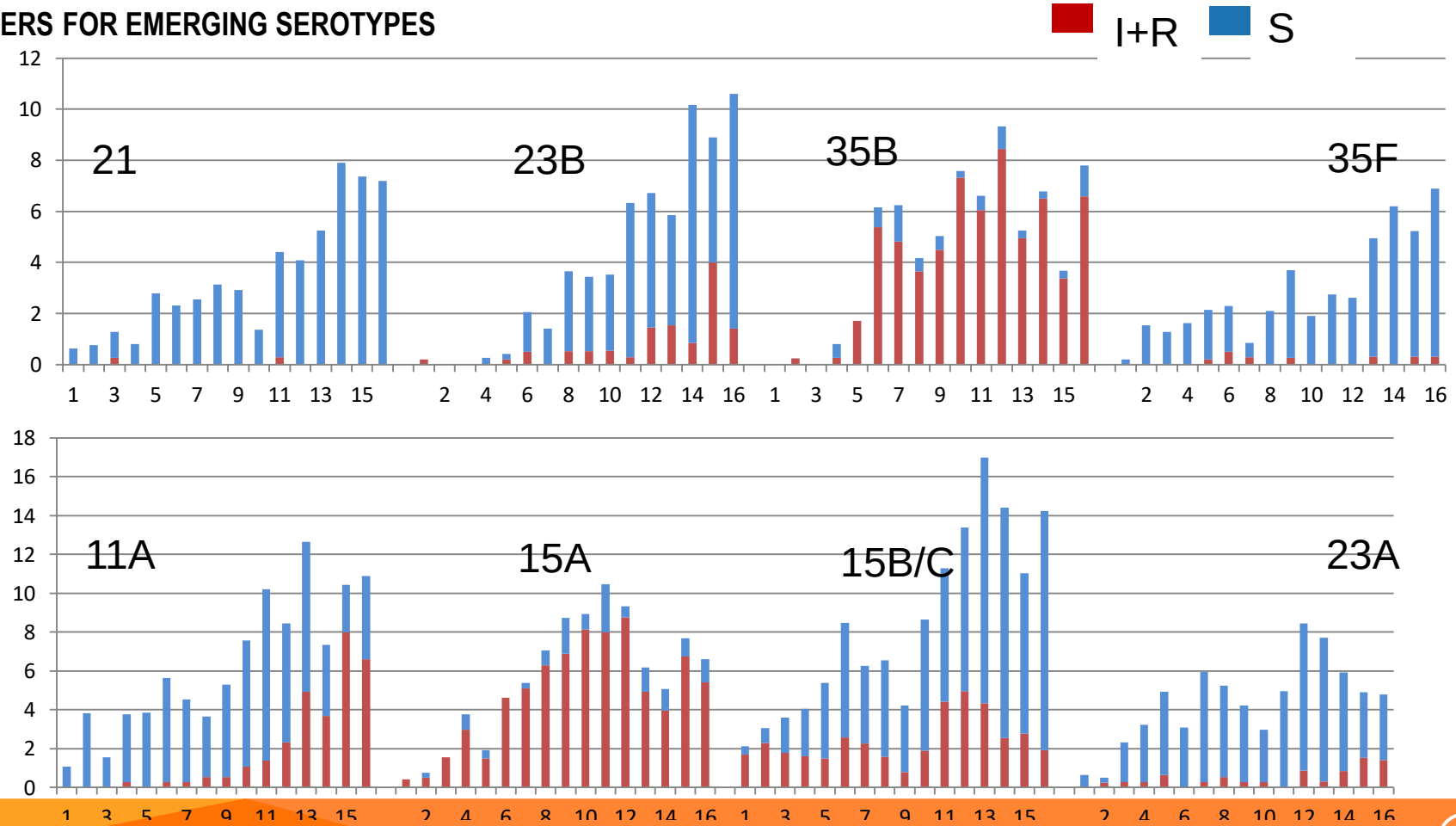
Emerging serotypes: ST 35B, 35F, 23B, 21

AOM fever± otalgia, 9659 children, 16years



Cohen R et al. Vaccine 2015

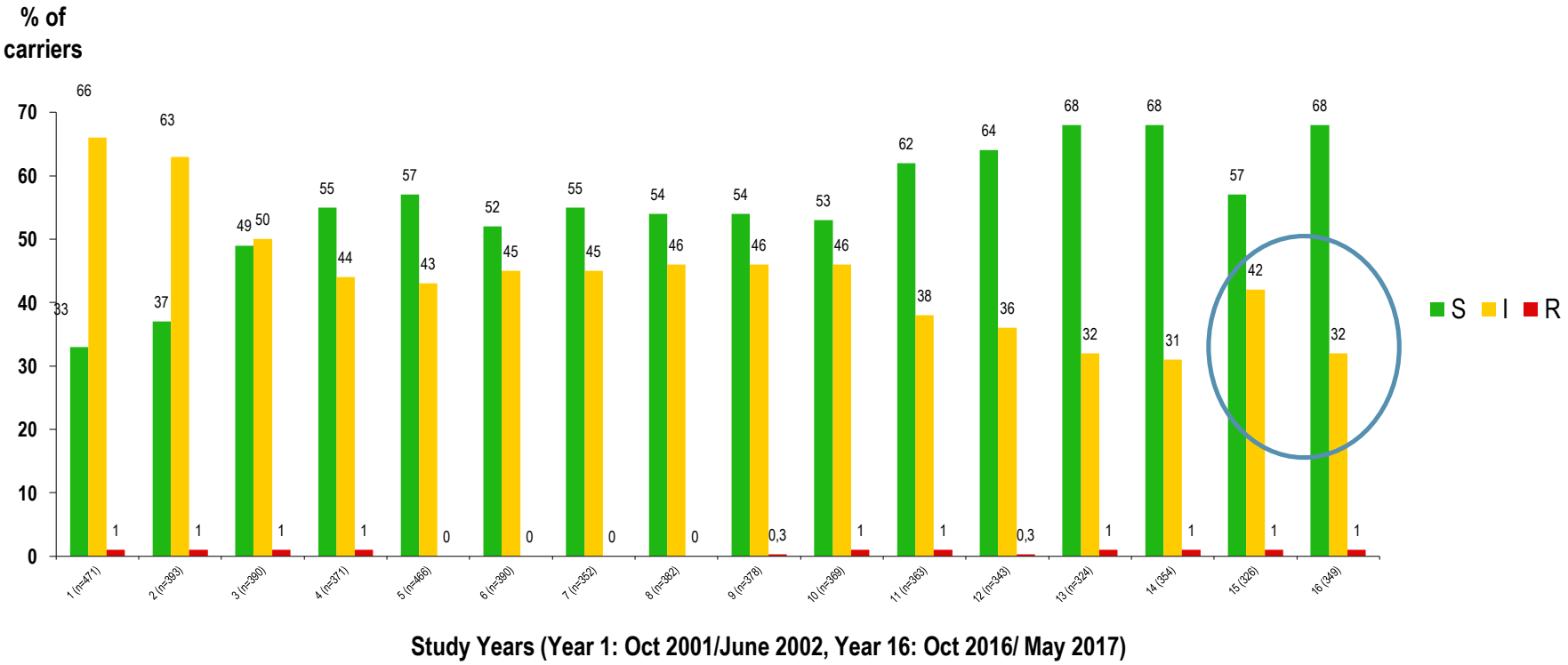
DYNAMICS OF PENICILLIN NON-SUSCEPTIBLE STRAINS AMONG PNEUMOCOCCAL CARRIERS FOR EMERGING SEROTYPES



Cohen R et al. Vaccine 2015

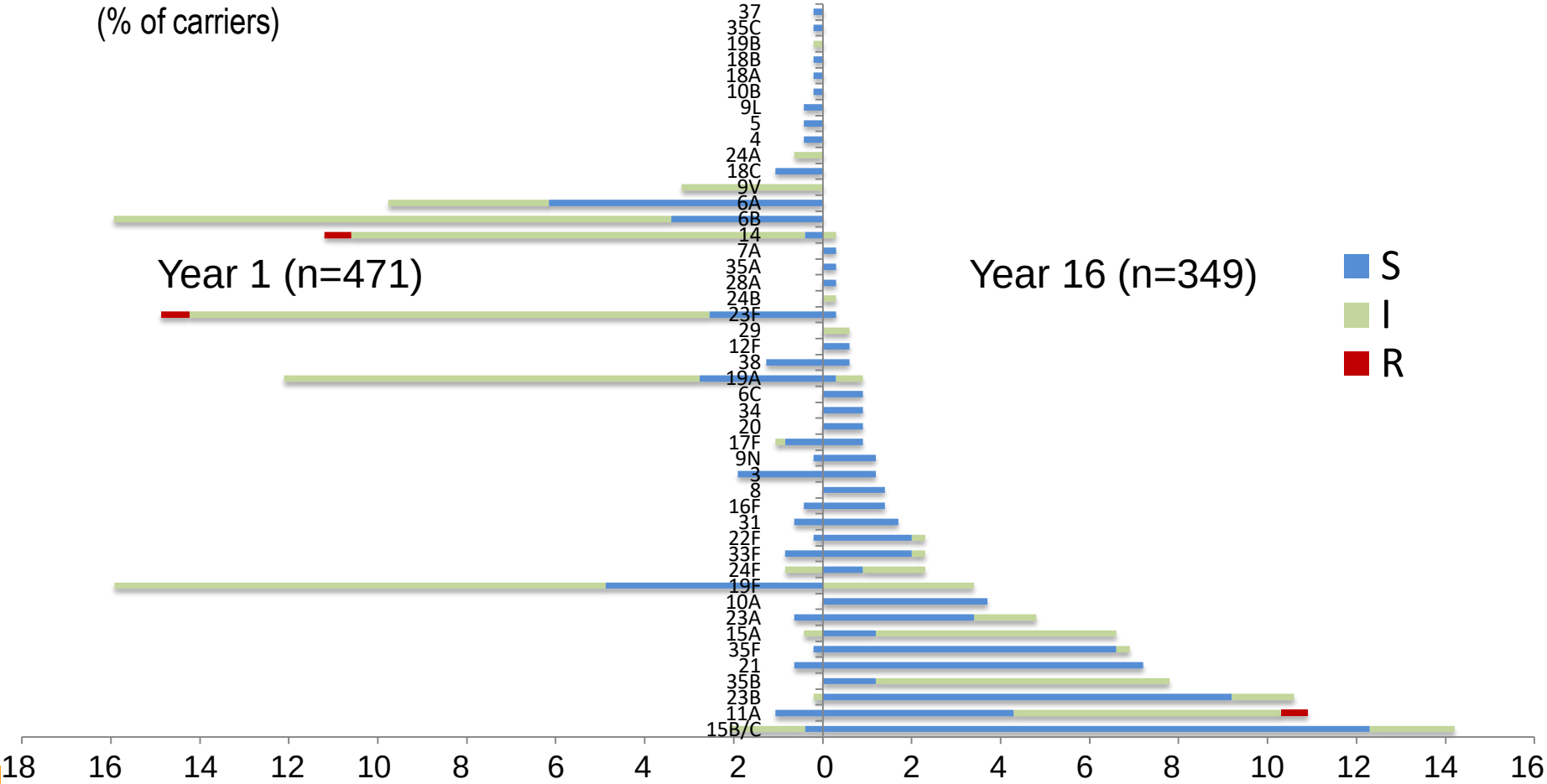
PENICILLIN SUSCEPTIBILITY

AOM FEVER± OTALGIA, 9659 CHILDREN, 16YEARS



Cohen R et al. Vaccine 2015

DISTRIBUTION OF SEROTYPES (AOM FEVER ±OTALGIA)



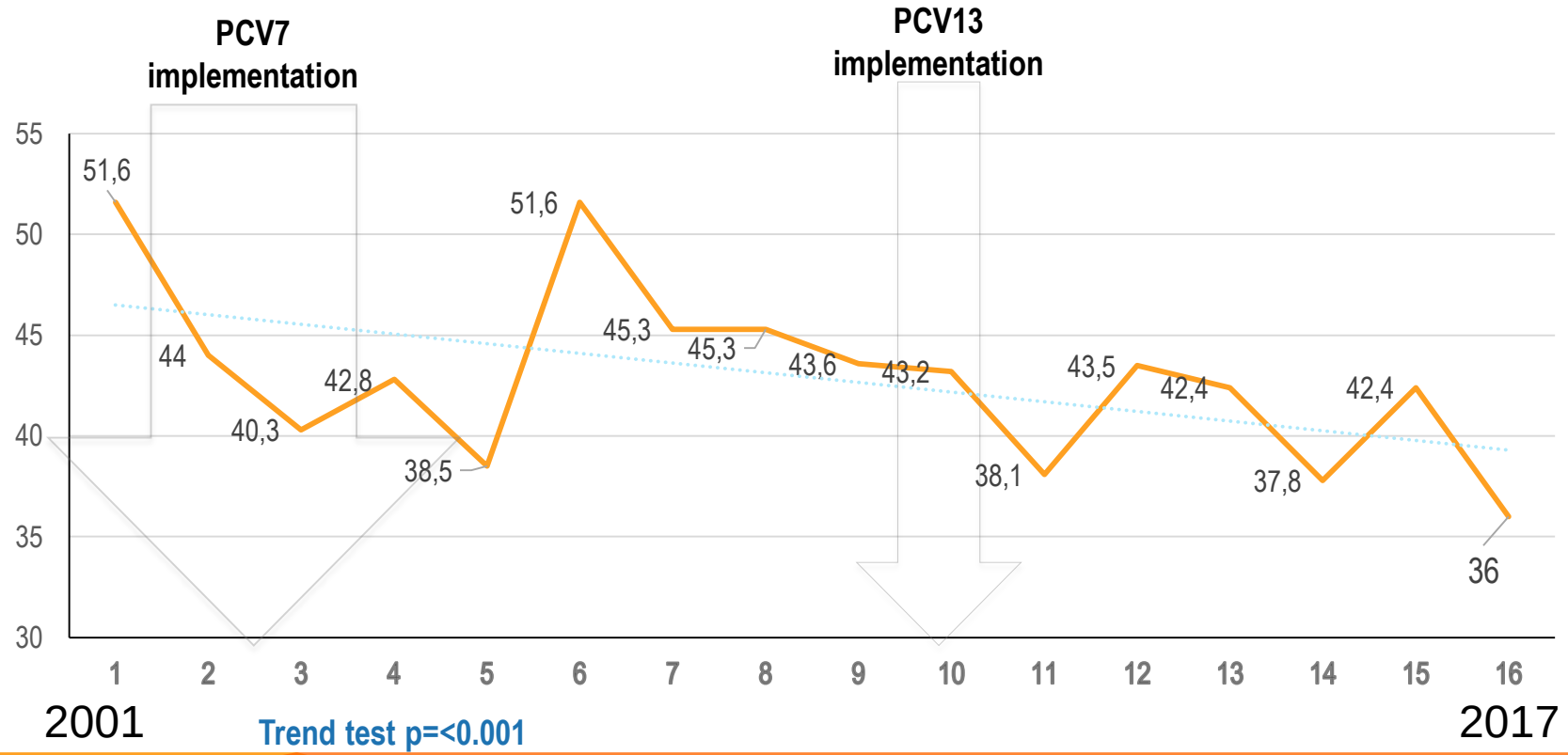
AOM FEVER± OTALGIA: CHARACTERISTICS OF PATIENTS

	2001/2005 N=3266	2006/2008 N=2376	2009/2010 N=1180	2012/2017 N=2837	P
Age (months) Mean±SD	13.6±5	13.5±5	13.7±5	13.9±5.1	0.02
Median	13	12.8	13	13.4	
Day care attendance					<0.001
Home	33	28	22	19	
Childminder	34	33	33	30	
Day care center	33	40	45	52	
Temp≥38.5°C	84	71	68	68	<0.01
Otalgia	85	83	84	82	0.03

Cohen R et al. Vaccine 2015

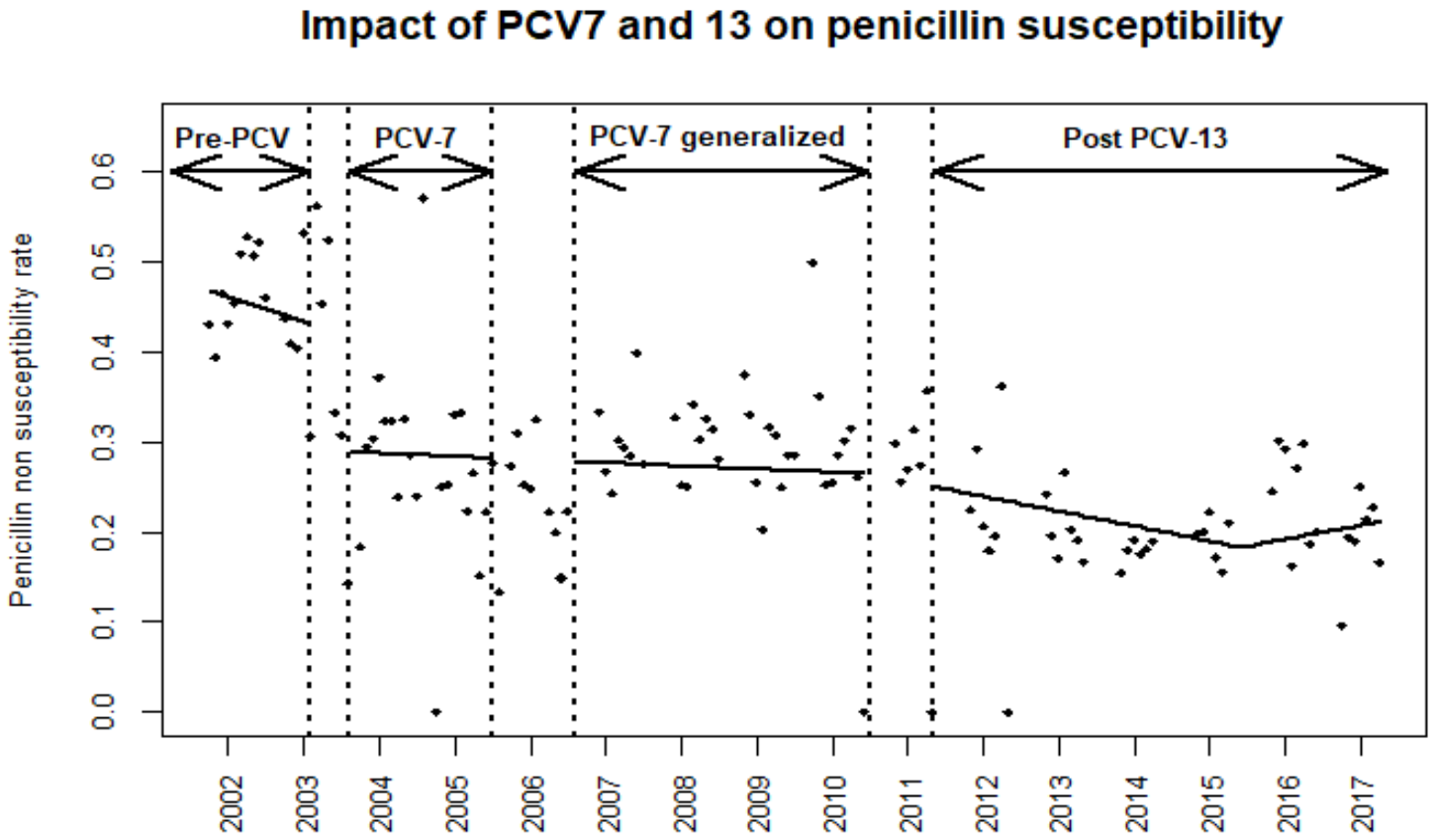
ATB 3 MONTHS BEFORE

AOM FEVER± OTALGIA, 9659 CHILDREN, 16 YEARS



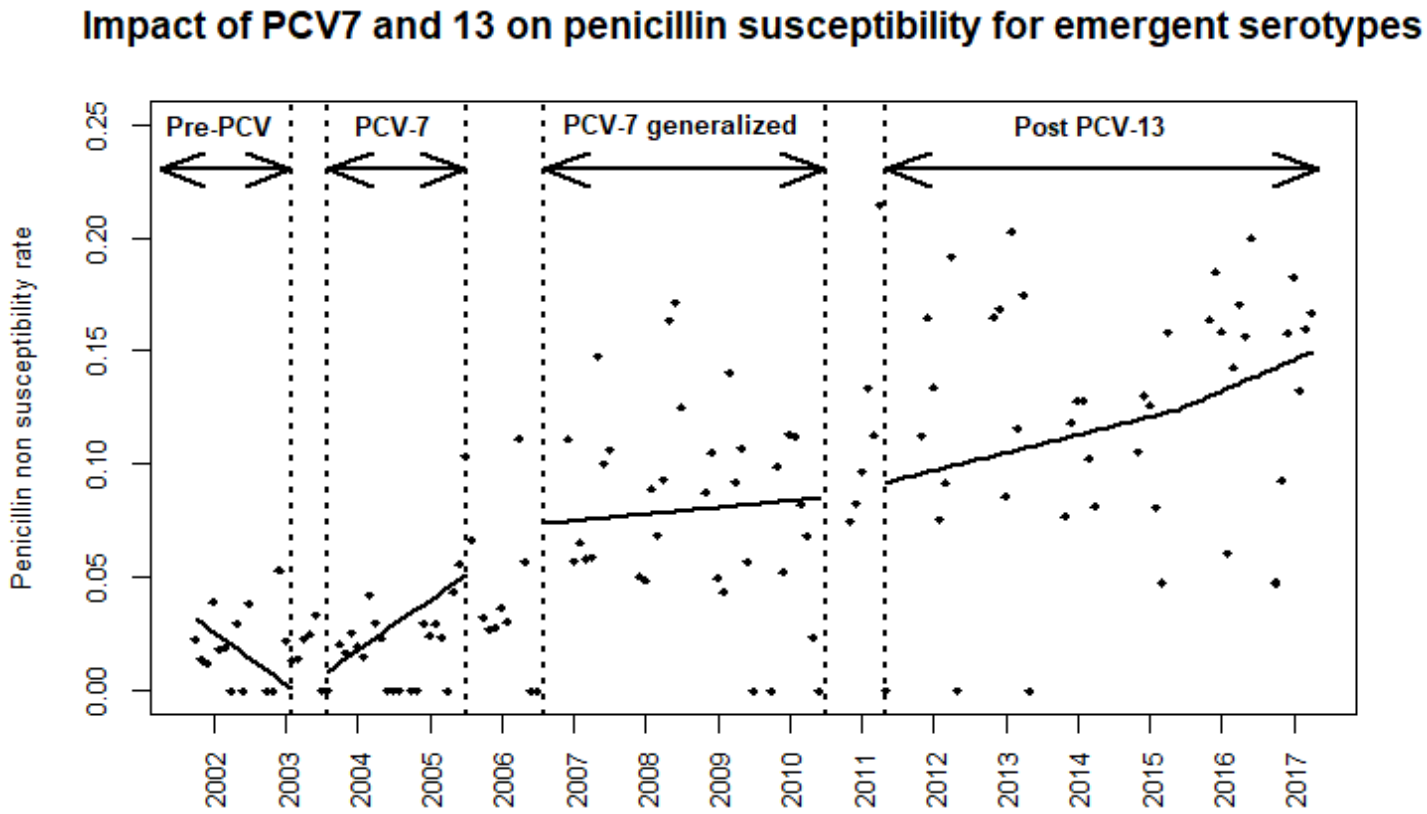
Cohen R et al. Vaccine 2015

TIME SERIE ANALYSIS : PNEUMOCOCCAL RESISTANCE TRENDS



Cohen R et al. Unpublished data

TIME SERIE ANALYSIS : EMERGING SEROTYPES: RESISTANCE TRENDS

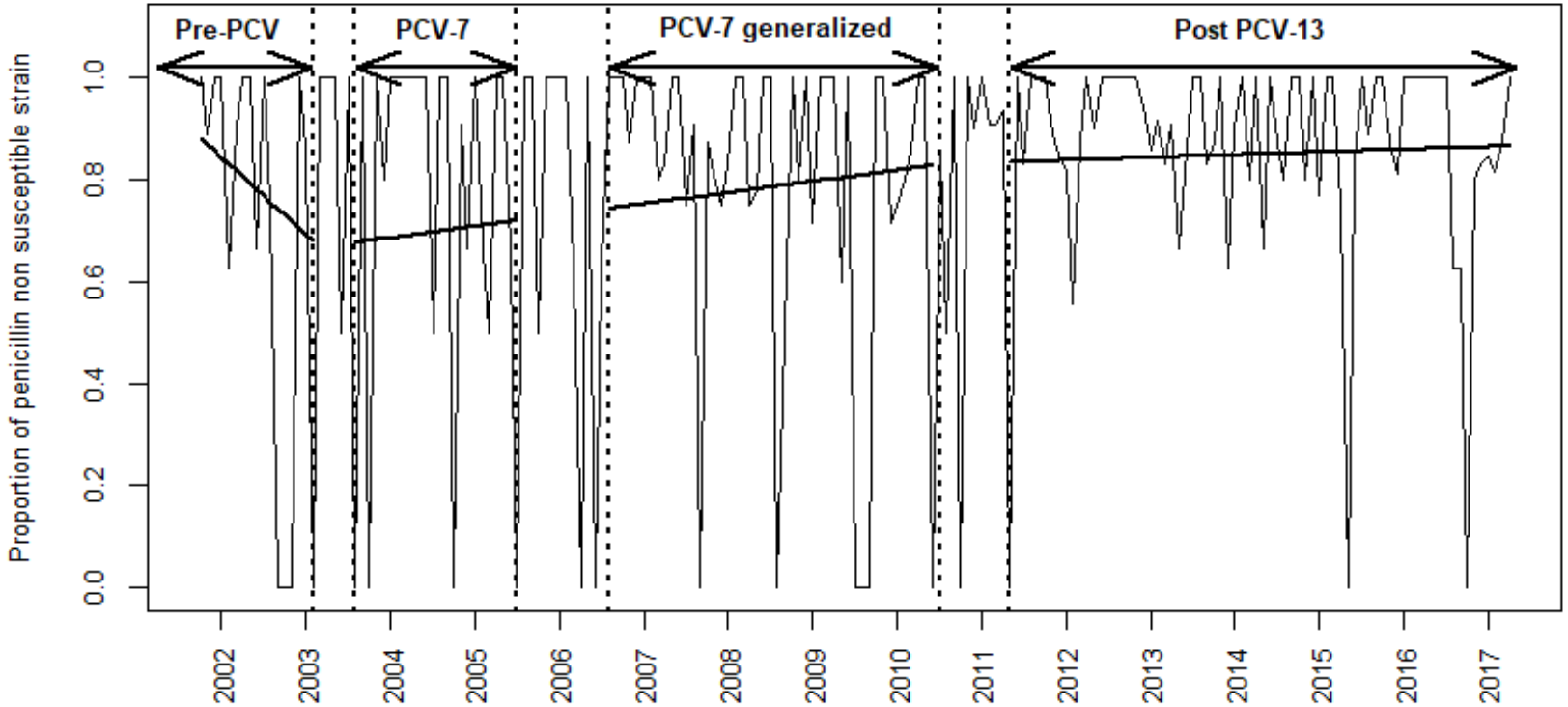


Cohen R et al. Unpublished data

AMONG THE EMERGING SEROTYPES

3 DIFFERENT PROFILS

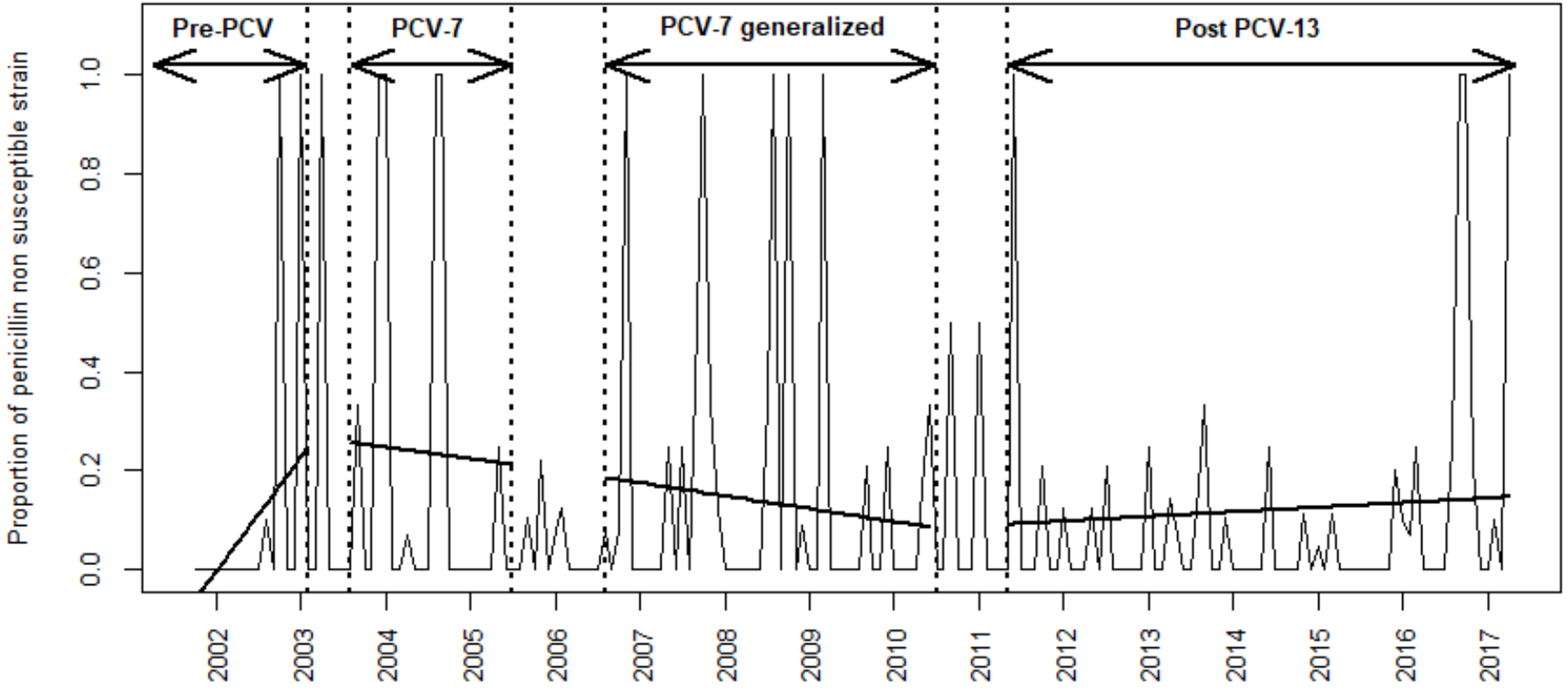
1) HIGHLY RESISTANT, SLIGHTLY CHANGE AFTER PCVS: 35B AND 15A



Cohen R et al. Unpublished data

No significant change after the PCVs

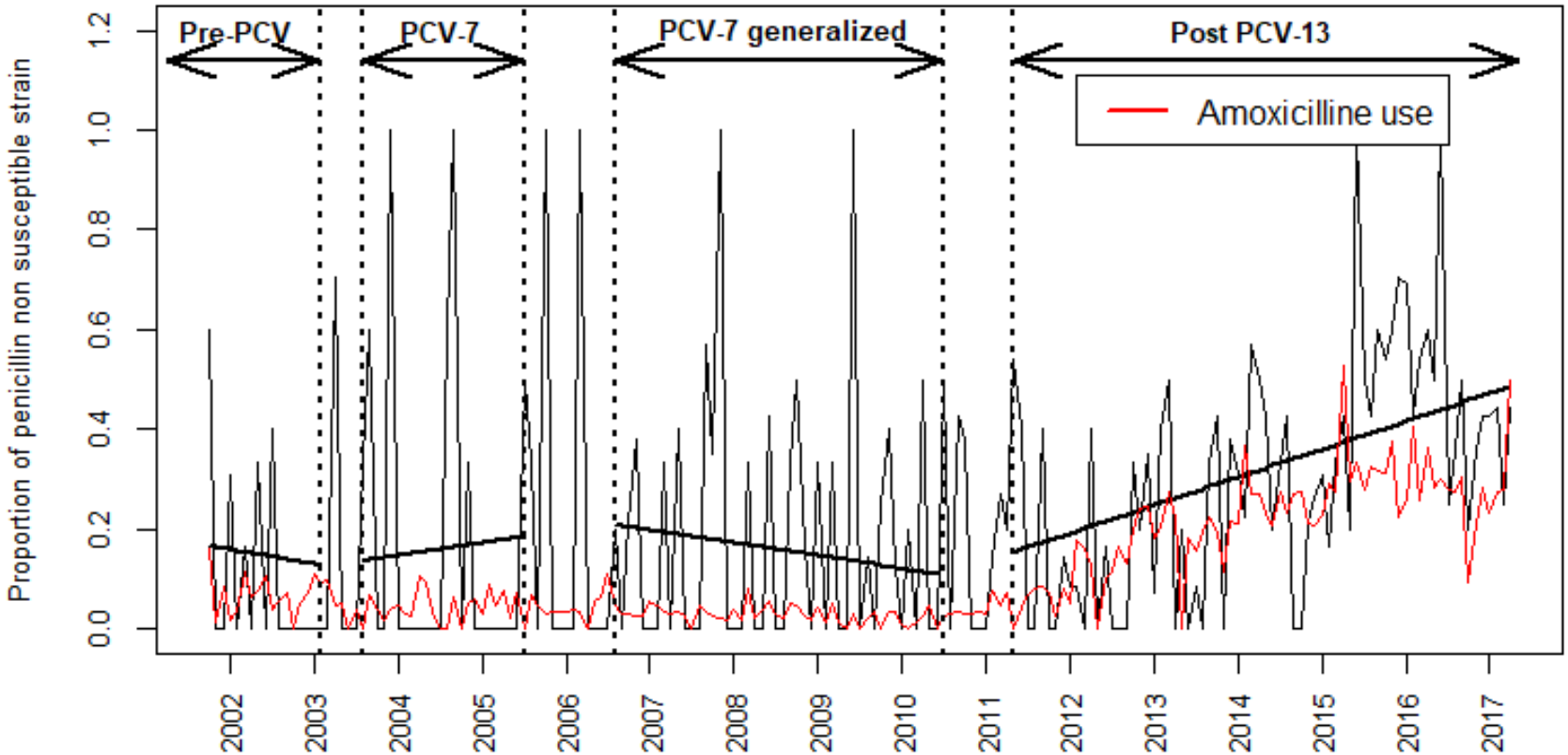
2) LOW LEVEL OF RESISTANCE, SLIGHTLY CHANGE AFTER PCVS 21, 23A AND 35F



Cohen R et al. Unpublished data

No significant change after the PCVs

3) EVOLUTION OF THE RESISTANCE AFTER PCVS 11A AND 23B



Cohen R et al. Unpublished data

PLOS ONE | https://doi.org/10.1371/journal.pone.0177113 May 9, 2017

RESEARCH ARTICLE

Serotype distribution of *Streptococcus pneumoniae* causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis

Evelyn Balsells[1]*, Laurence Guillot[1], Harish Nair[1], Moe H. Kyaw[2]

Predominant non-PCV13 serotypes overall were:

22F, 12F, 33F, 24F, 38

15C, 15B, 23B, 10A

Rank order varied by region

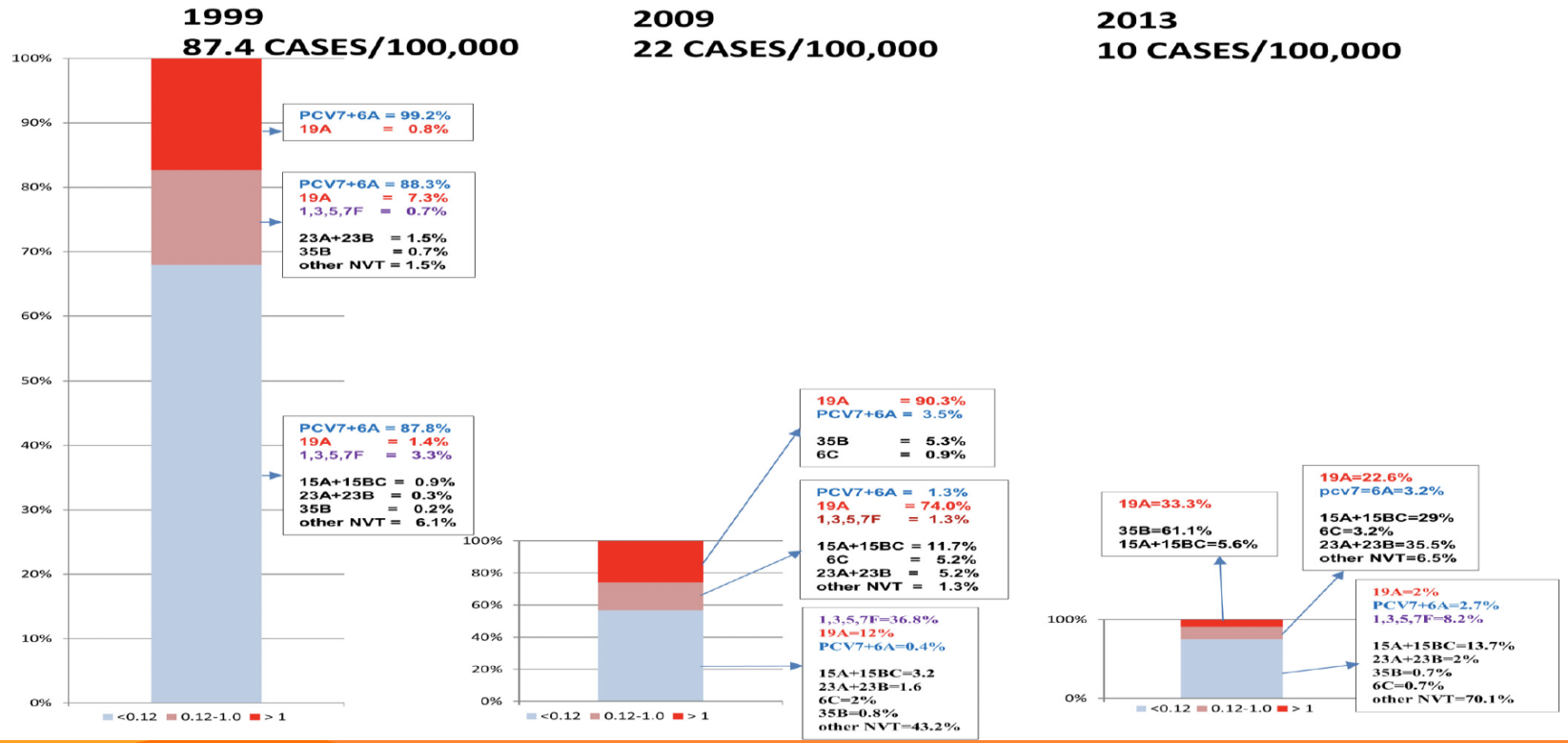
AMERICAN SOCIETY FOR MICROBIOLOGY | Clinical Microbiology Reviews

July 2016 Volume 29 Number 3

Biological and Epidemiological Features of Antibiotic-Resistant *Streptococcus pneumoniae* in Pre- and Post-Conjugate Vaccine Eras: a United States Perspective

Lindsay Kim,[a] Lesley McGee,[b] Sara Tomczyk,[a] Bernard Beall[b]

Epidemiology Section[a] and Streptococcus Laboratory,[b] Respiratory Diseases Branch, Centers for Disease Control and Prevention, Atlanta, Georgia, USA



DISEASE POTENTIAL

Vaccine 33 (2015) 6178–6185

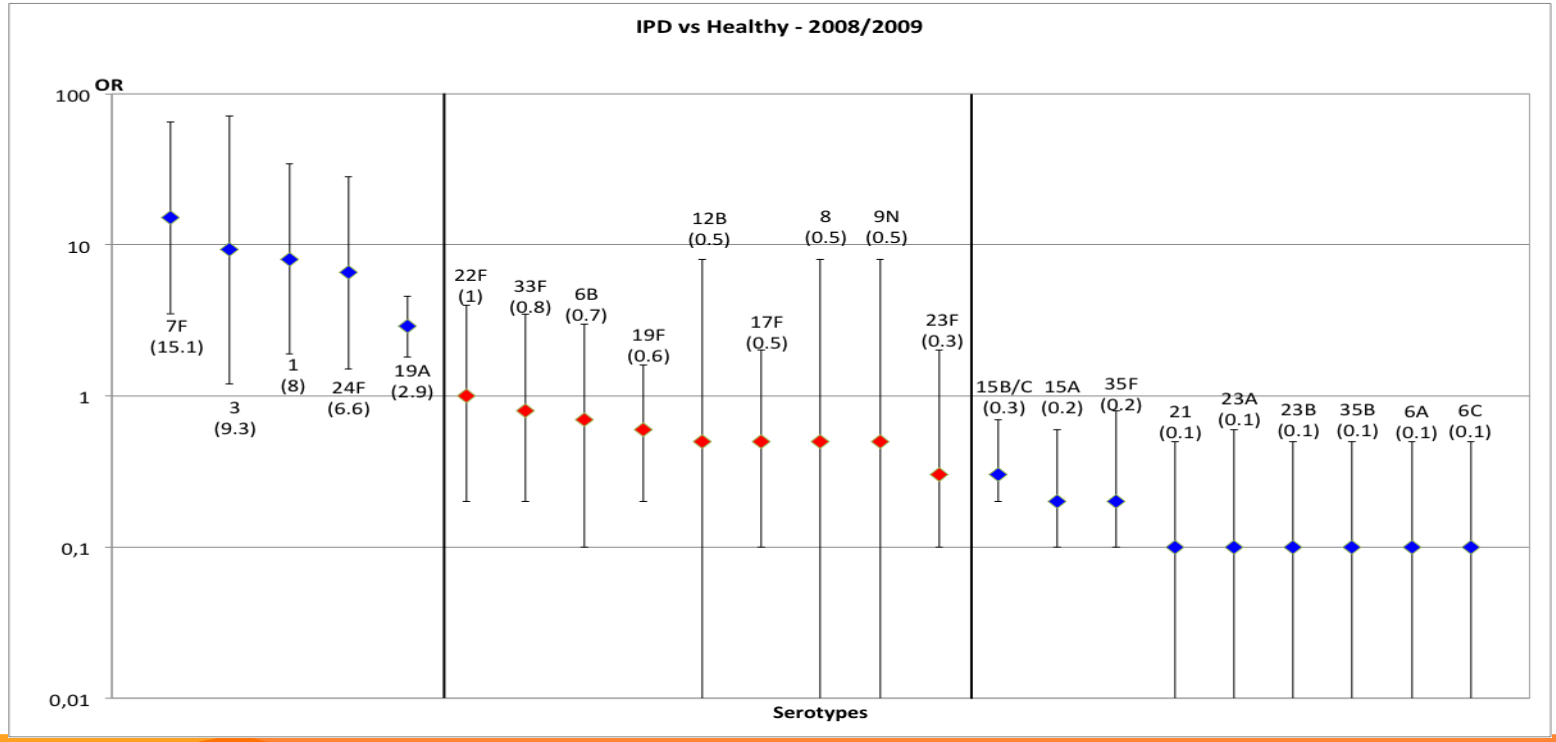
Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Invasive disease potential of pneumococci before and after the 13-valent pneumococcal conjugate vaccine implementation in children

Emmanuelle Varon[a], Robert Cohen[b,c,d,e,f], Stéphane Béchet[d,e], Catherine Doit[g,h], Corinne Levy[b,c,d,e,*]



DISEASE POTENTIAL

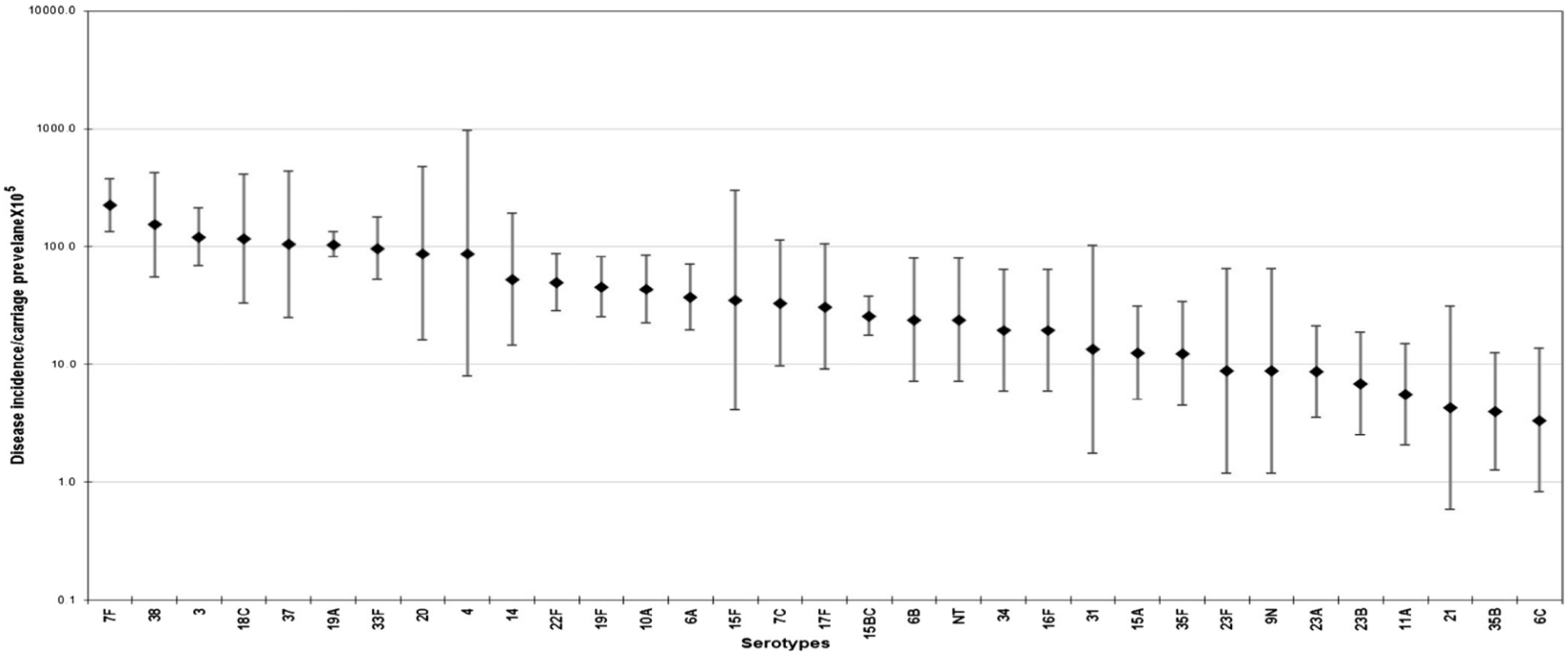


Fig. 3. Serotype specific invasive capacity in children <7 years, Massachusetts, 2001–2015* (Y-axis is displayed on log-scale).

I. Yildirim et al. / Vaccine 35 (2017) 4002–4009

IMPACT OF PCVS ON ANTIBIOTIC PRESCRIPTIONS

- Dagan : -17% (CI% = 13-21%)
  - Day care center, efficacy PCV7
  - *Pediatr Infect Dis J 2001;20:951*
- Fireman : - 6% (CI95%= 4-7%)
  - General population, efficacy PCV7
  - *Pediatr Infect Dis J 2003;22:10*
- Palmu : - 7% (CI95% = 1-13)
  - General population, efficacy PCV10
  - *Lancet Infect Dis 2014;14:205*
- Palmu : - 17% (CI95% = 17-18)
  - General population, effectiveness PCV10
  - *Pediatr Infect Dis J 2017*

Lee et al. BMC Medicine 2014, 12:96
http://www.biomedcentral.com/1741-7015/12/96

BMC Medicine

RESEARCH ARTICLE Open Access

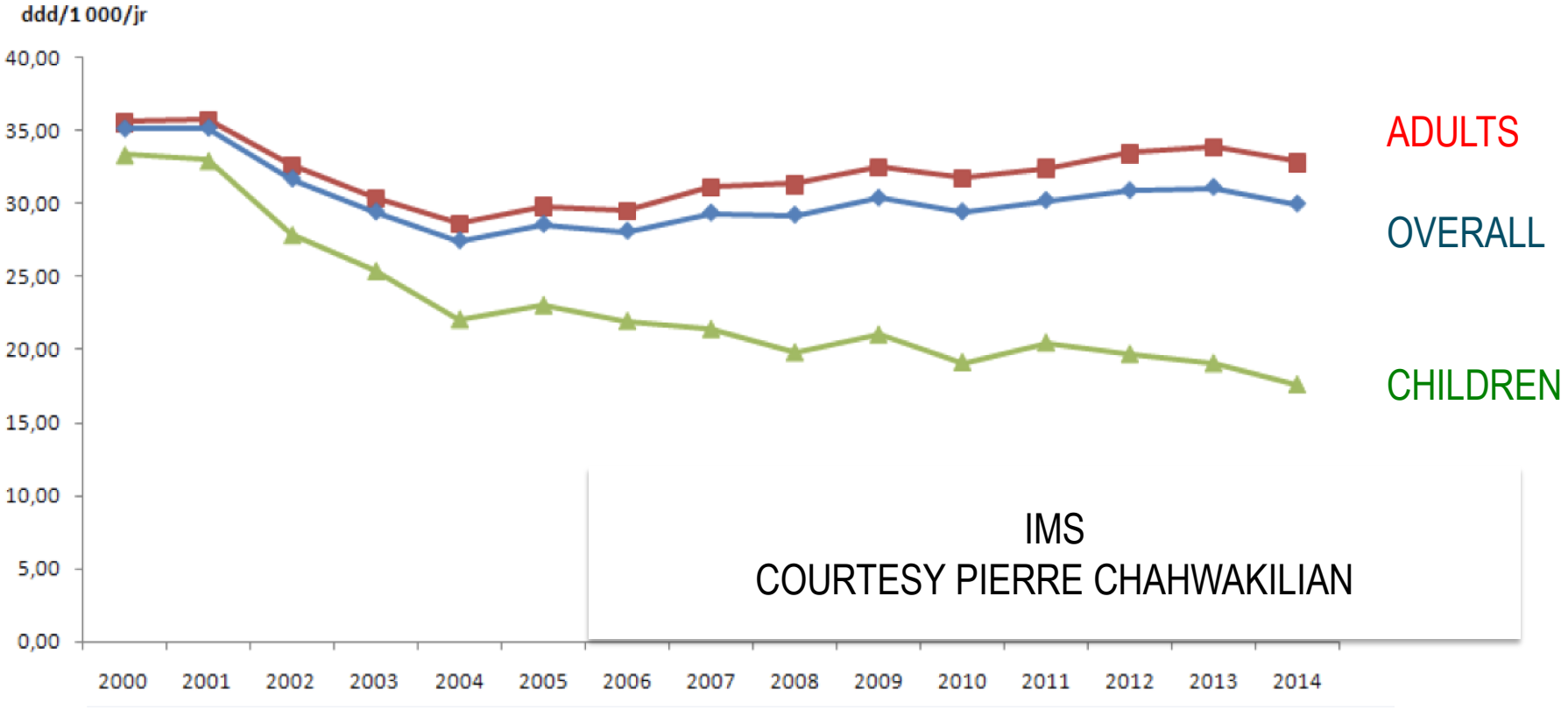
Outpatient antibiotic prescribing in the United States: 2000 to 2010

Grace C Lee[1,2], Kelly R Reveles[1,2], Russell T Attridge[2,3], Kenneth A Lawson[1], Ishak A Mansi[4], James S Lewis II[1,2] and Christopher R Frei[1,2*]

Overall antibiotic prescribing

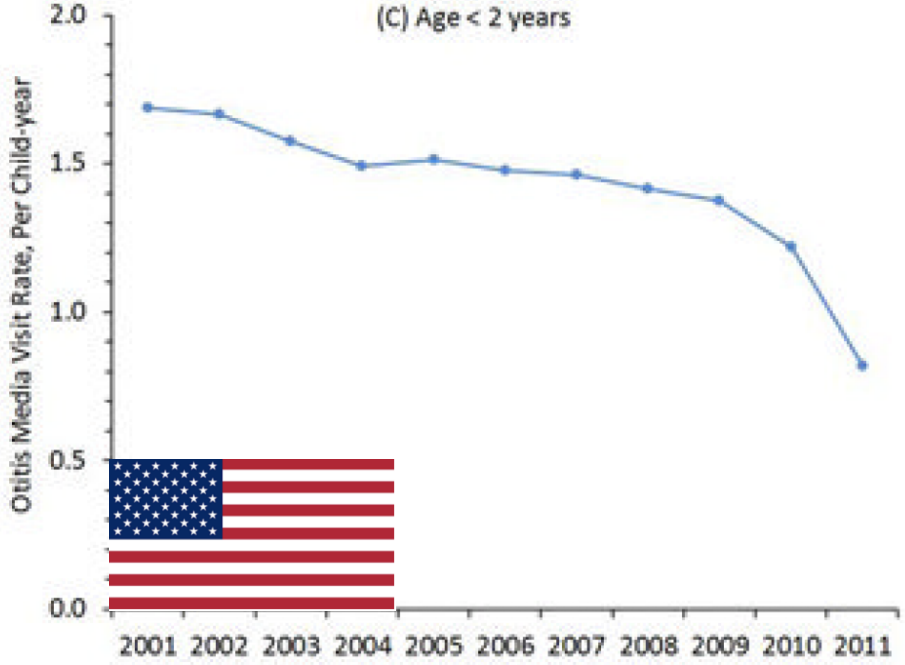
- decreased 18% (risk ratio (RR) 0.82, 95% confidence interval (95% CI) 0.72 to 0.94) among children and adolescents,
- remained unchanged for adults
- increased 30% (1.30, 1.14 to 1.49) among older adults

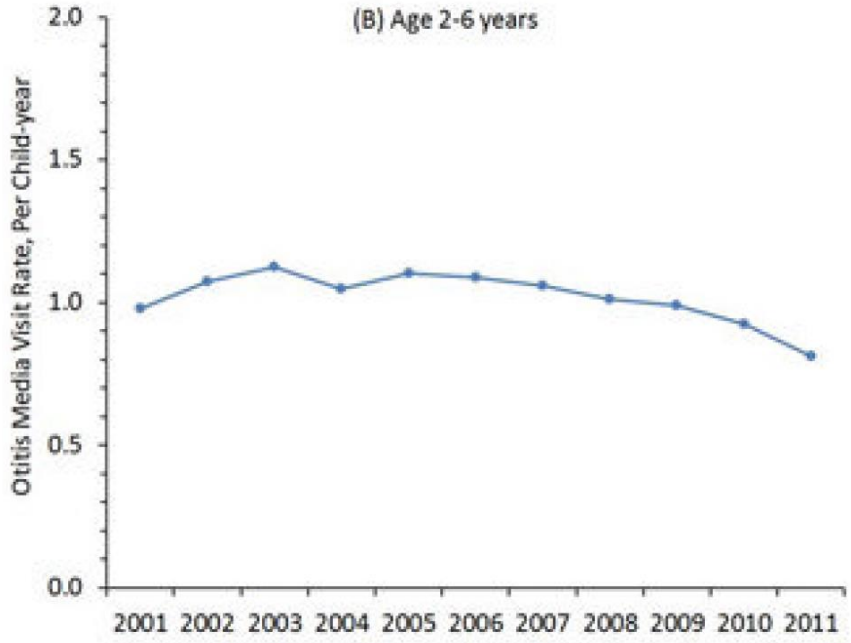
TRENDS IN ANTIBIOTIC PRESCRIPTIONS



Trends in Otitis Media-related Health Care Utilization in the United States, 2001-2011

Tal Marom, MD[1], Alai Tan, MD, PhD[2], Gregg S. Wilkinson, PhD[2], Karen S. Pierson, MA[2],





JAMA Pediatr. 2014 January ; 168(1): 68–75.

Vaccine 33 (2015) 5072–5079

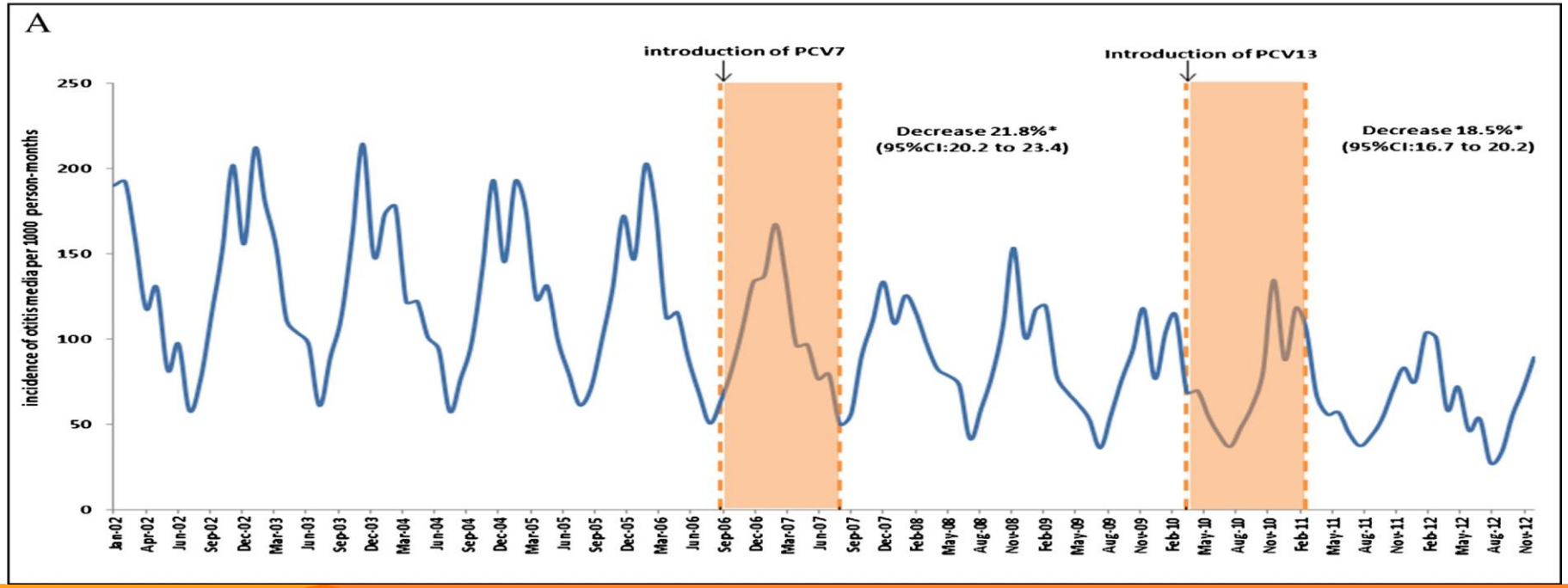
Contents lists available at ScienceDirect

Vaccine

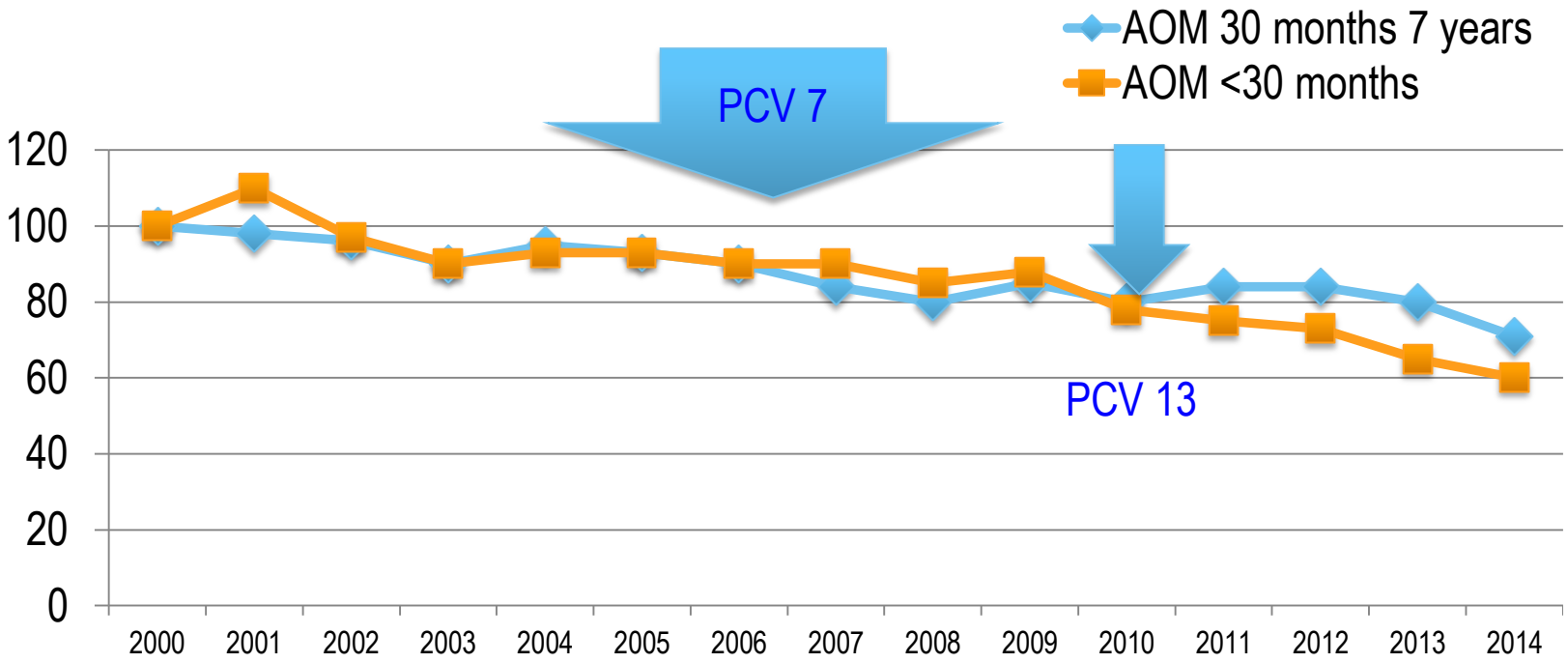
journal homepage: www.elsevier.com/locate/vaccine

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,*]



TRENDS OF PEDIATRIC VISITS FOR AOM (IMS DATA)

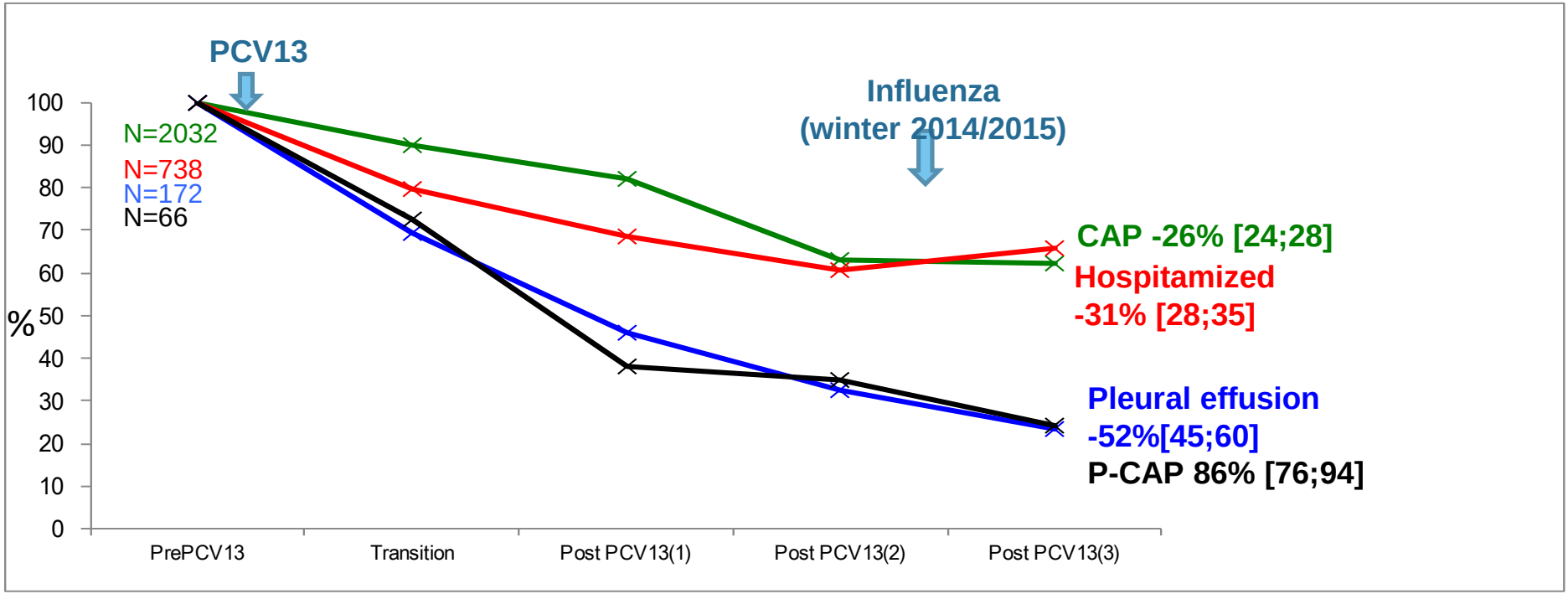


Courtesy of Pierre Chahwakilian

ANTIBIOTIC PARADIGM CHANGES ARE NEEDED

- **Reduction of the the risk of severe disease in front of some clinical syndromes have to redefine :**
  - Diagnosis methods
  - The role and the type of antibiotics
- **Clinical syndromes**
  - AOM
  - Pneumonia
  - Fever without source

Trend of pneumonia (2009/2015)



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Impact of PCV13 on community-acquired pneumonia by C-reactive protein and procalcitonin levels in children

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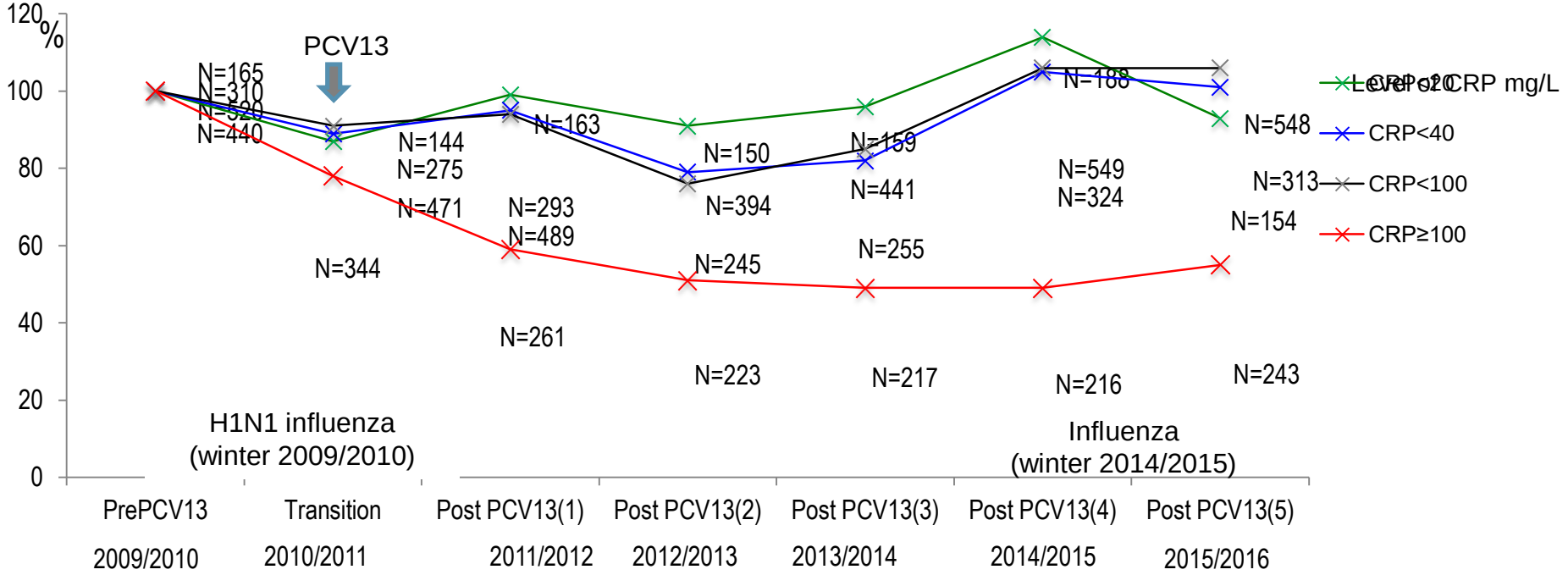
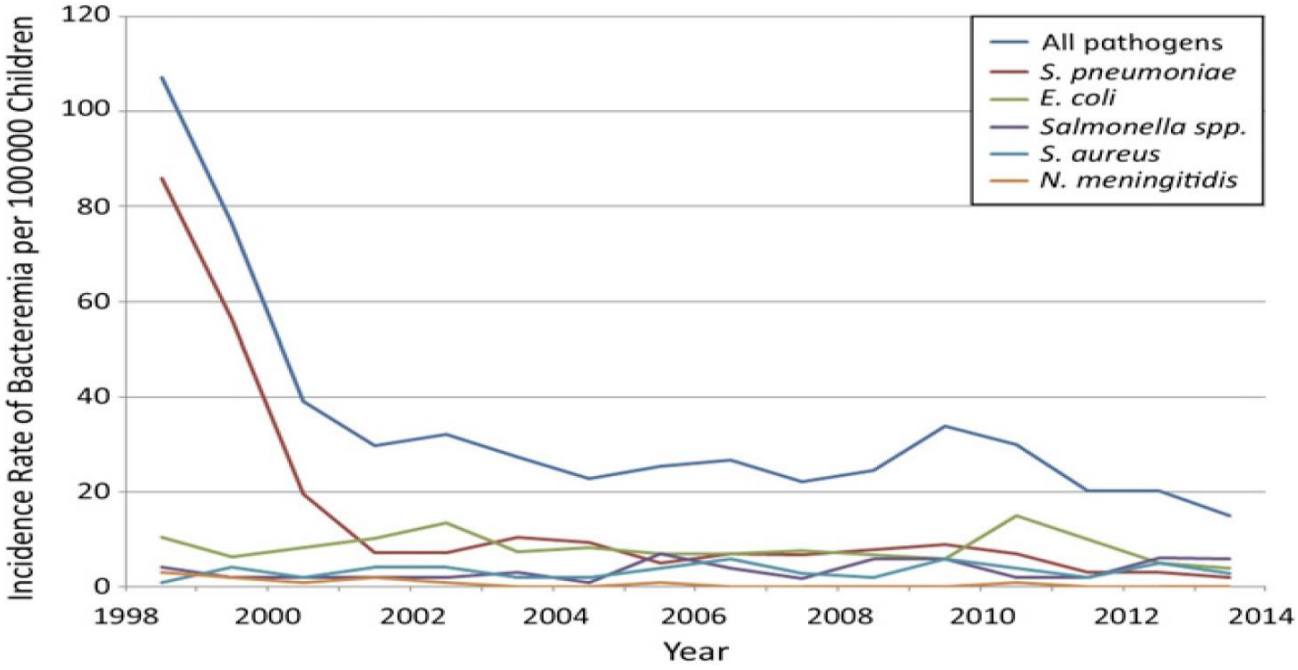


Bacteremia in Children 3 to 36 Months Old After Introduction of Conjugated Pneumococcal Vaccines

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

PEDIATRICS Volume 139, number 4, April 2017:



OTHER EXISTING VACCINES WITH POTENTIAL EFFECT TO REDUCE ANTIBIOTIC USE AND ANTIBIOTIC RESISTANCE

BACTERIAL

- Diphteria
- Pertussis
- Hib
- Meningococal

VIRAL

- Influenza
- Measle
- Varicella

IN CONCLUSION

- Implementation of PCVs in vaccination programs has reduced pneumococcal antibiotic resistance particularly in countries where the level of resistance was high
- The decreases of resistance were mainly due to the disappearance of VT pneumococci
- The reduction of antibiotic prescriptions secondary to the pneumococcal diseases decrease play certainly also a role
- Finally, an indirect effect due to the dramatic decrease of the risk of severe diseases was not sufficiently taking into account