

Prevenar 13: A 13-valent Pneumococcal Conjugate Vaccine

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October 1, 2009

Wyeth
Vaccines

Prevenar (PCV7): Seven-valent Pneumococcal Conjugate Vaccine

PREVENAR*	Carrier: CRM₁₉₇	4	6B	9V	14	18C	19F	23F	
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*Trademark

Prevenar

- **Indications: Prevention of pneumococcal disease caused by the serotypes included in the vaccine:**
 - ▶ **Invasive Disease** (meningitis, sepsis, bacteremia, bacteremic pneumonia)
 - ▶ **Pneumonia**
 - ▶ **Otitis media**
- **Approved for children 6 weeks to 5-9 years of age**
- **Dosing Schedules:**
 - ▶ **3 primary doses and a booster (3+1)**
 - ▶ **2 primary doses and a booster (2+1)**

Prevenar Effectiveness

- **Effectiveness data has mirrored the impact predicted by controlled clinical efficacy trials for IPD**
- **Effectiveness data for pneumonia and otitis media has surpassed that predicted by efficacy trials**
- **Impact on nasopharyngeal carriage has resulted in significant herd effect**
 - ▶ Documented decreases in IPD and pneumonia in unvaccinated populations (adults and children too young to be immunized)
- **Effectiveness is the basis of the cost-effectiveness of Prevenar**

Prevenar – Routine Pediatric Immunization Programs

Routine Pediatric Programs

Australia	Germany	Mexico	Spain
Bahrain	Greece	Netherlands	Sweden
Barbados	Hong Kong	New Zealand	Switzerland
Belgium	Hungary	Norway	TURKEY
Bermuda	Ireland	Oman	United Kingdom
Canada	Israel	Peru	United States
Costa Rica	Italy	Qatar	United Arab Emirates
Cyprus	Kuwait	Rwanda	Uruguay
Denmark	Liechtenstein	Saudi Arabia	
France	Luxembourg	Slovak Republic	
Gambia	Macau	South Africa	

Regional or High Risk Programs

Brazil	Panama
Colombia	Poland
Czech Republic	Taiwan

Current Situation: New PCVs

- **Need for expanded serotype coverage with a minimal impact on the effectiveness of the original seven (7) serotypes**
 - ▶ Experience with CRM197-based pneumococcal conjugate¹
 - ▶ 2v → 5v → 7v → 9v → 13v
- **Inability to perform efficacy trials**
 - ▶ The need for a reference value associated with clinical efficacy² (correlate of protection)
- **Two new pneumococcal conjugate vaccines:**
 - ▶ Synflorix: 10v conjugate from GSK
 - ▶ Prevnar 13: Wyeth
- **Each will be judged in the context of the efficacy and effectiveness of Prevnar**

¹Nurkka A, et al. *Pediatr Infect Dis J.* 2004;23:1008-1014.

²WHO. Technical Report Series No. 927. 2005.

Immunologic Criteria for Evaluation of New Pneumococcal Conjugate Vaccines

- **New PCVs are to be compared directly to PCV7 (or conjugate with proven efficacy)**
- **Consideration given to all elements of the immune response:**
 - ▶ Anti-polysaccharide IgG: % ≥ 0.35 ug/ml and GMC
 - ▶ Functional Activity: opsonophagocytic activity
 - ▶ Immunological memory: booster response in second year of life

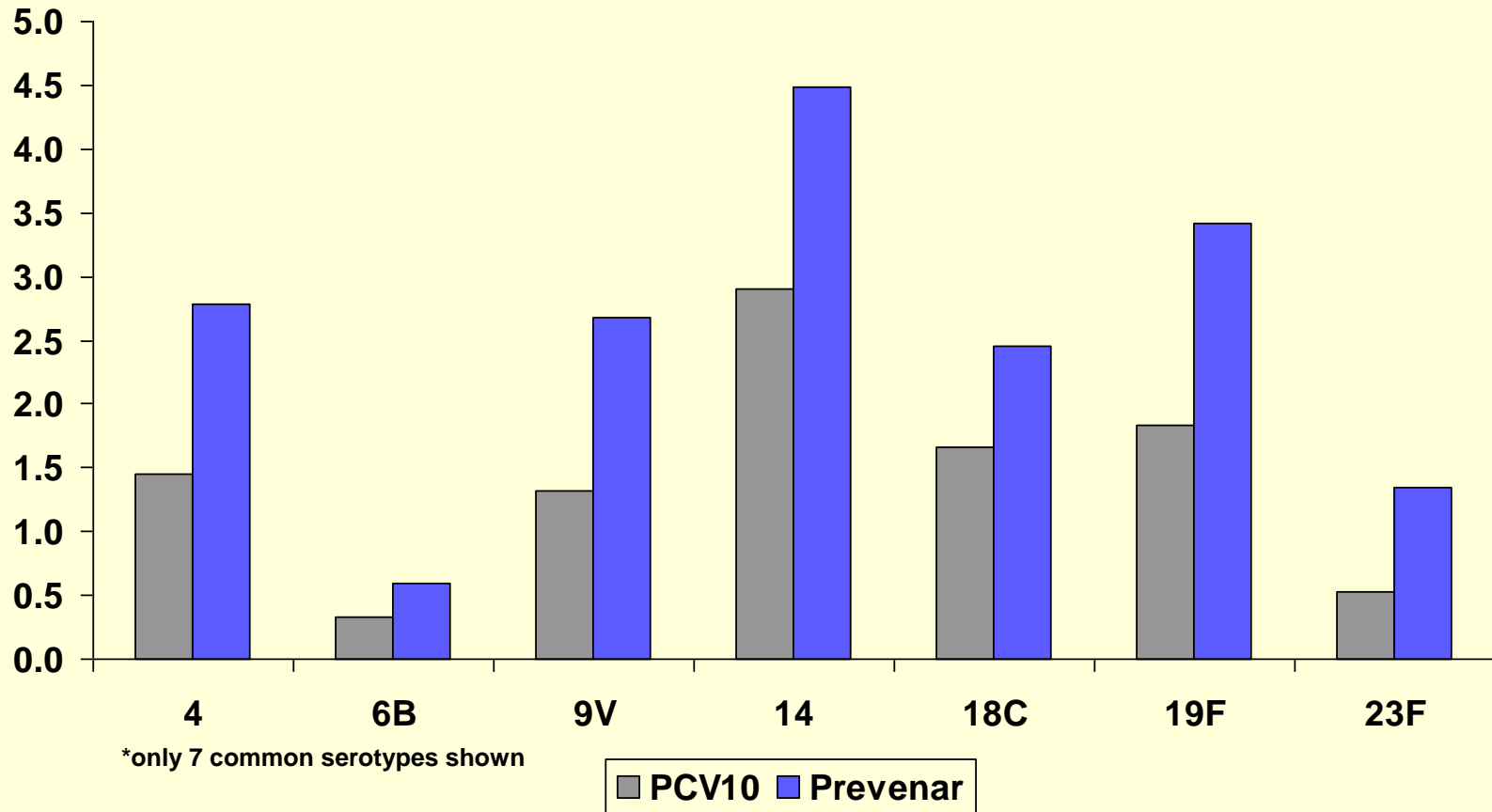
WHO Expert Committee on Biological Standardization. WHO Technical Report Series No. 927. Geneva, Switzerland

Conjugate Pneumococcal Vaccines

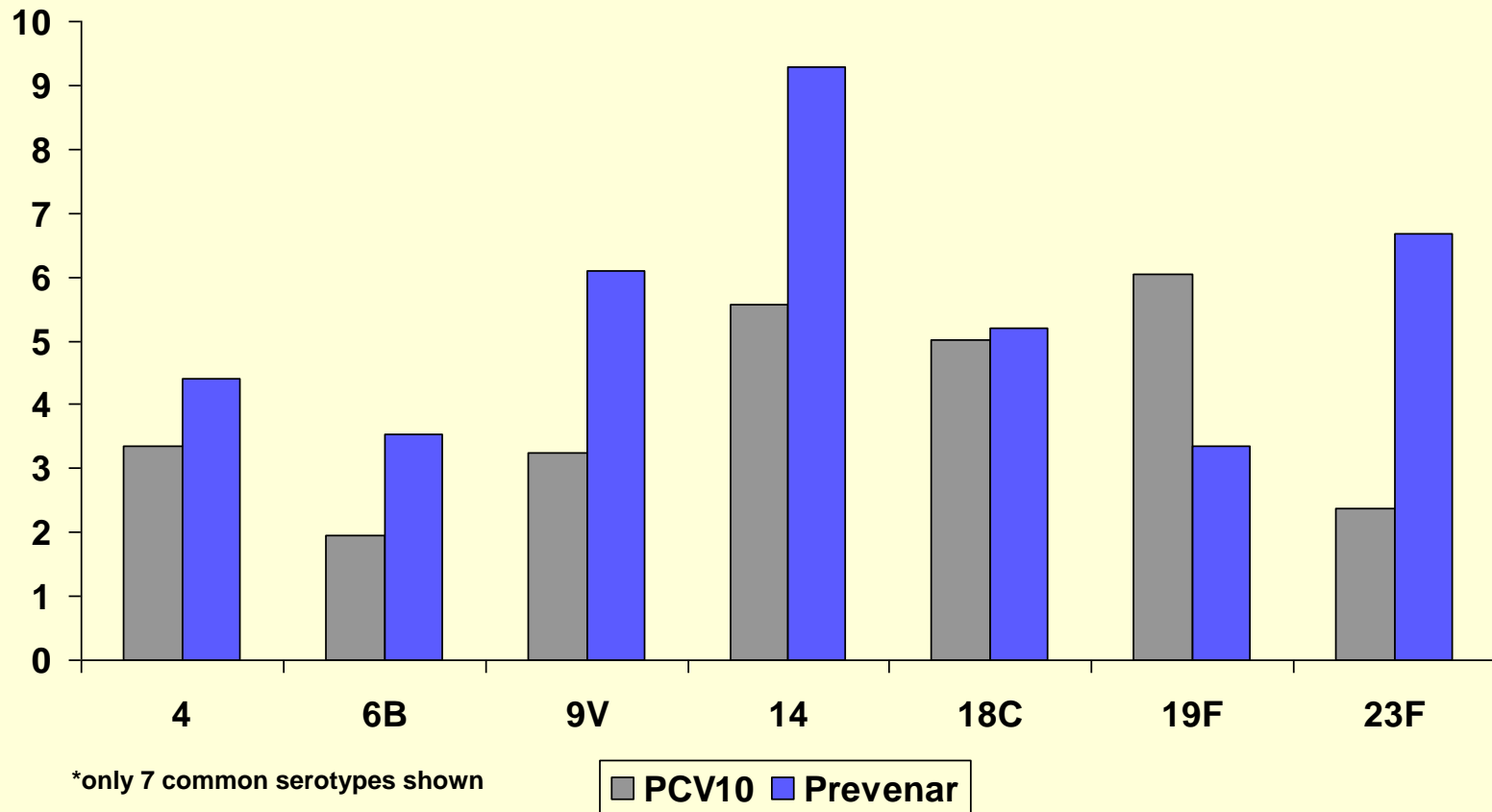
Pevnar	Protein Carrier: CRM₁₉₇	4	6B	9V	14	18C	19F	23F	
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10v	Protein Carriers: · Protein D · Diphtheria toxoid · Tetanus toxoid	4	6B	9V	14	18C	19F	23F	1	5	7F	
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PCV10: GMC Levels Post Primary Series* (2, 3, 4 mos)



PCV10: GMC Levels Post Booster* (2, 3, 4 & 12-18 mos)



Comparison of PCV7 and PCV10

- PCV7 has demonstrated efficacy and effectiveness against IPD, otitis media and pneumonia
- In Europe, PCV7 indicated for invasive disease, otitis media and **pneumonia**
- Antibody response to the seven common serotypes higher for PCV7 by ELISA and OPA
- PCV7 can be given at 3+1 or **2+1** schedule
- PCV7 can be given to children to children up to **5 years of age**

EMA: CHMP issued its positive opinion for PCV13



European Medicines Agency
Pre-Authorisation Evaluation of Medicines for Human Use

London, 24 September 2009

Doc.Ref. EMEA/CHMP/546417/2009

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
SUMMARY OF POSITIVE OPINION*
for
PREVENAR 13

Common Name:

13-valent pneumococcal polysaccharide conjugate vaccine (13-valent, adsorbed)

Same
diseases and
age limit of
Prevenar

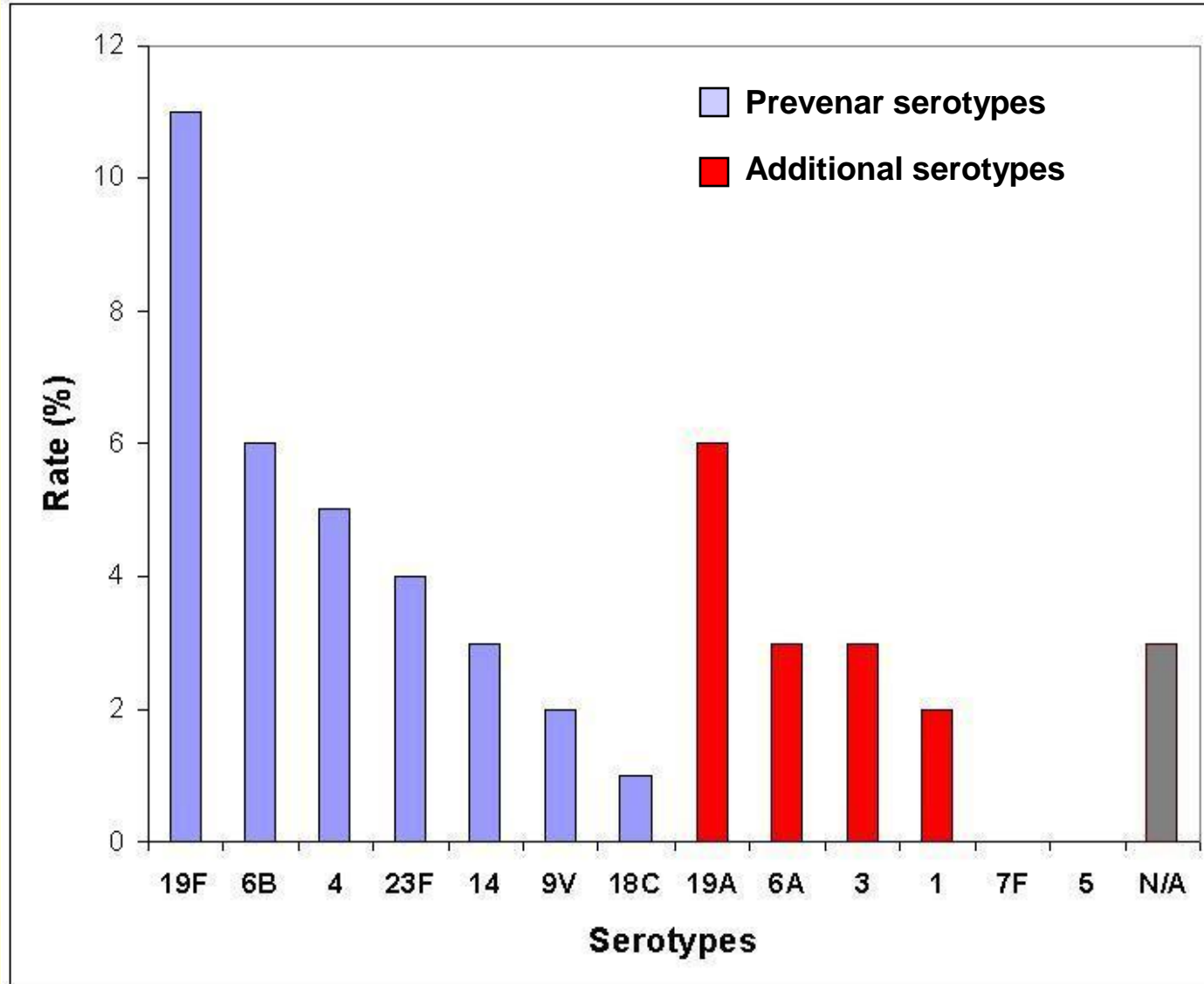
On 24 September 2009 the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Prevenar 13, 13-valent pneumococcal conjugate vaccine adsorbed intended for "Active immunisation for the prevention of invasive disease, pneumonia and acute otitis media caused by *Streptococcus pneumoniae* in infants and children from 6 weeks to 5 years of age".

PCV13 Serotype Composition

Pevnar	4	6B	9V	14	18C	19F	23F						
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A

PCV13 contains the same carrier protein – CRM₁₉₇

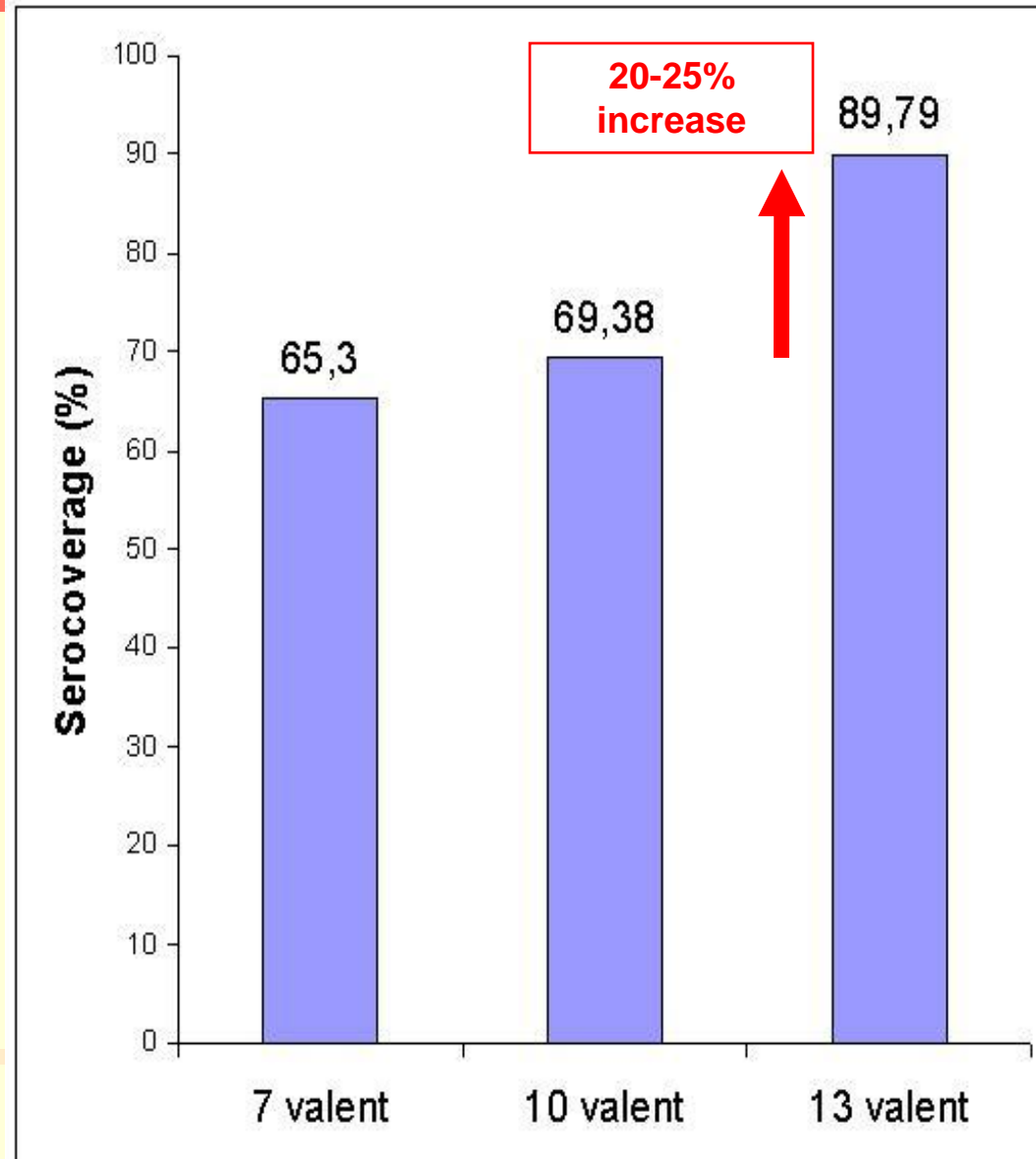
Serotype distribution of IPD isolates from children 0-2 yrs in Turkey, 2008–2009



Serotype coverage of IPD isolates from children 0-2 yrs in Turkey, 2008–2009

13 centers
nationwide
(0-16 yrs)

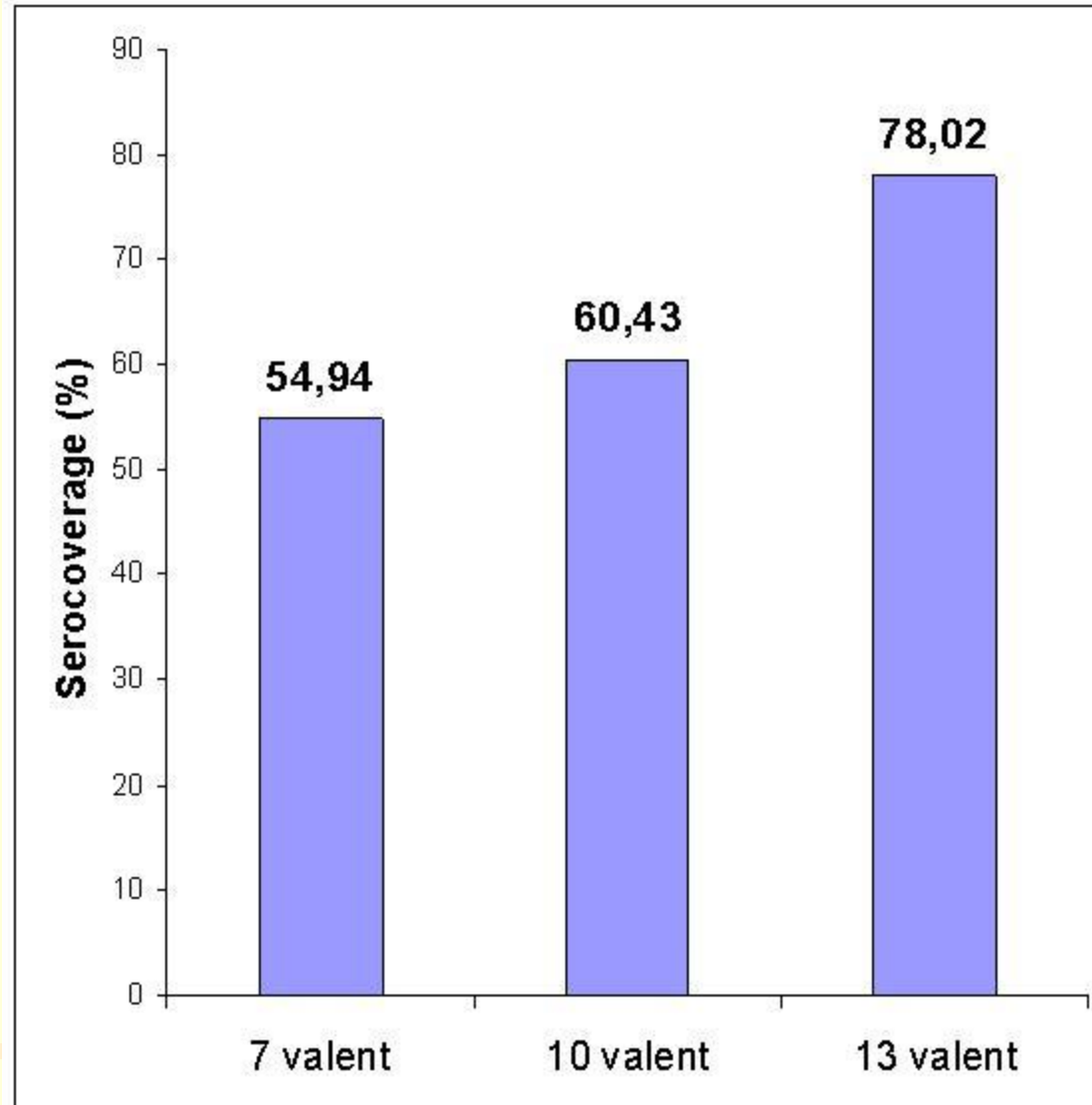
n= 49/135



Serotype coverage of IPD isolates from children 0-5 yrs in Turkey, 2008–2009

**13 centers
nationwide
(0-16 yrs)**

n= 91/135

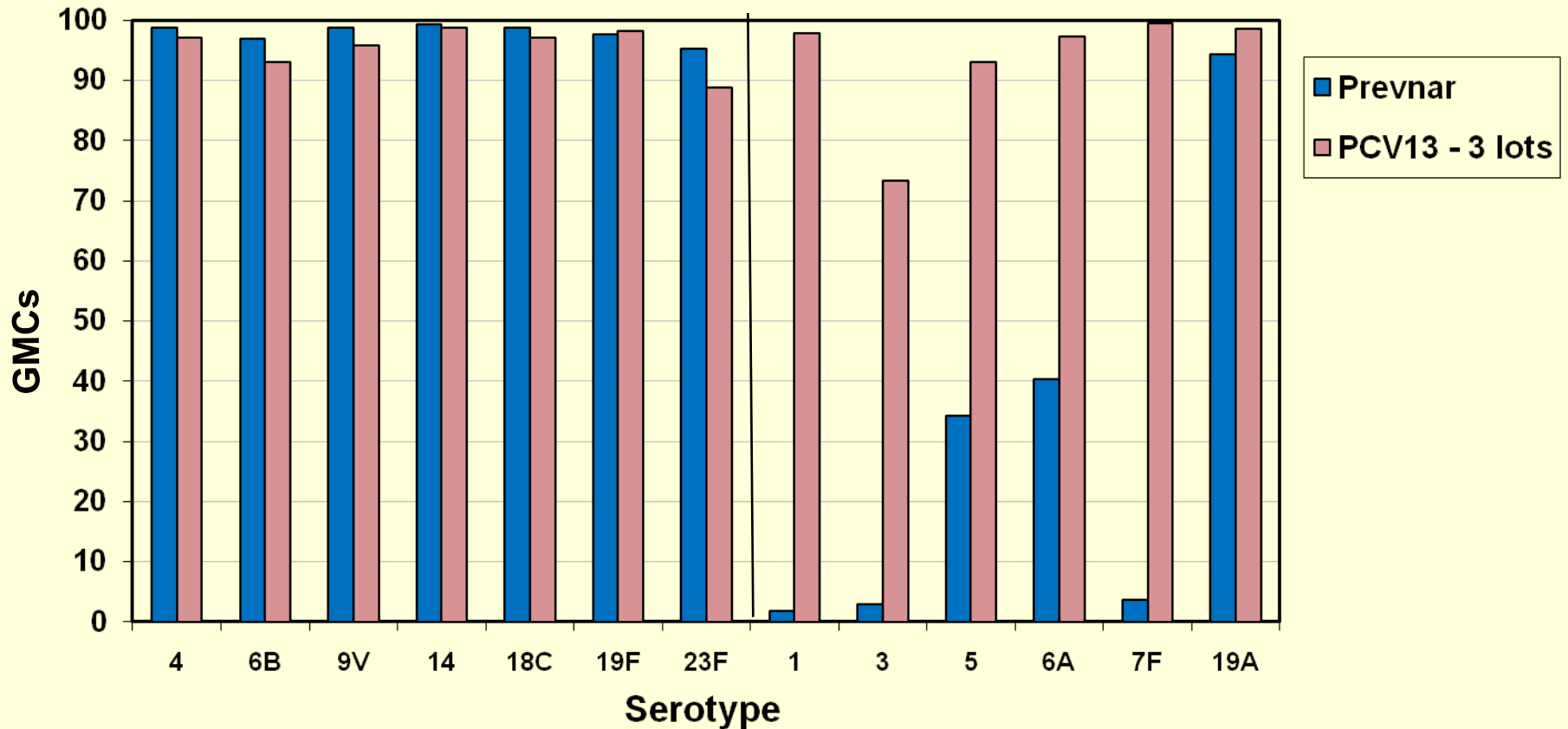


PCV13 Phase 3 Clinical Plan Overview

Clinical trials	Schedule (Months)	Vaccines	Immunologic assessments
Pivotal noninferiority –US (004)	2, 4, 6, 12-15	PCV13 vs PCV7 Pediatrix, ActHIB, ProQuad	Pneumo noninferiority Concomitant noninferiority
Pivotal noninferiority – Germany (006)	2, 3, 4, 11-12	PCV13 vs PCV7 Infanrix hexa	Pneumo noninferiority Concomitant noninferiority
Safety, immuno & concomitant – Canada (3008)	2, 4, 6, 12	PCV13 vs PCV7 Pentacel, NeisVac C	PCV13 immunogenicity Concomitant noninferiority
Safety, immuno & concomitant – Spain (501)	2, 4, 6, 15	PCV13 vs PCV7 Infanrix hexa, Meningitec	PCV13 immunogenicity Concomitant noninferiority
Safety, immuno & concomitant – France (008)	2, 3, 4, 12	PCV13 vs PCV7 Pentavac	PCV13 immunogenicity Concomitant noninferiority
Safety, immuno & concomitant – Italy (500)	3, 5, 11	PCV13 vs PCV7 Infanrix hexa	PCV13 immunogenicity Concomitant noninferiority
Safety, immuno & concomitant – Spain (3007)	2, 4, 6, 15	PCV13 vs PCV7 Infanrix hexa , NeisVacC	PCV13 immunogenicity Concomitant noninferiority
Safety, immuno & concomitant – UK (007)	2, 4, 12	PCV13 vs PCV7 Pediaceel NeisVacC/Menintorix	PCV13 immunogenicity Pertussis, Hib responses
Safety, immuno & concomitant – India (011)	6, 10, 14 weeks	PCV13 C vs PCV7 Easy5, Biopolio	Pneumo immunogenicity Whole cell pertussis
Polysorbate 80 noninferiority – Poland (009)	2, 3, 4, 12	PCV13 +/- P80	PCV13 noninferiority
Clinical consistency – US (3005)	2, 4, 6, 12	PCV13 x 3 vs PCV7	PCV13 immunogenicity
Manufacturing scale trial – Poland (3000)	2, 3, 4, 12	PCV13 x 2	PCV13 immunogenicity
Naïve subjects trial – Poland (3002)	1, 2 or 3 doses	PCV13	PCV13 immunogenicity

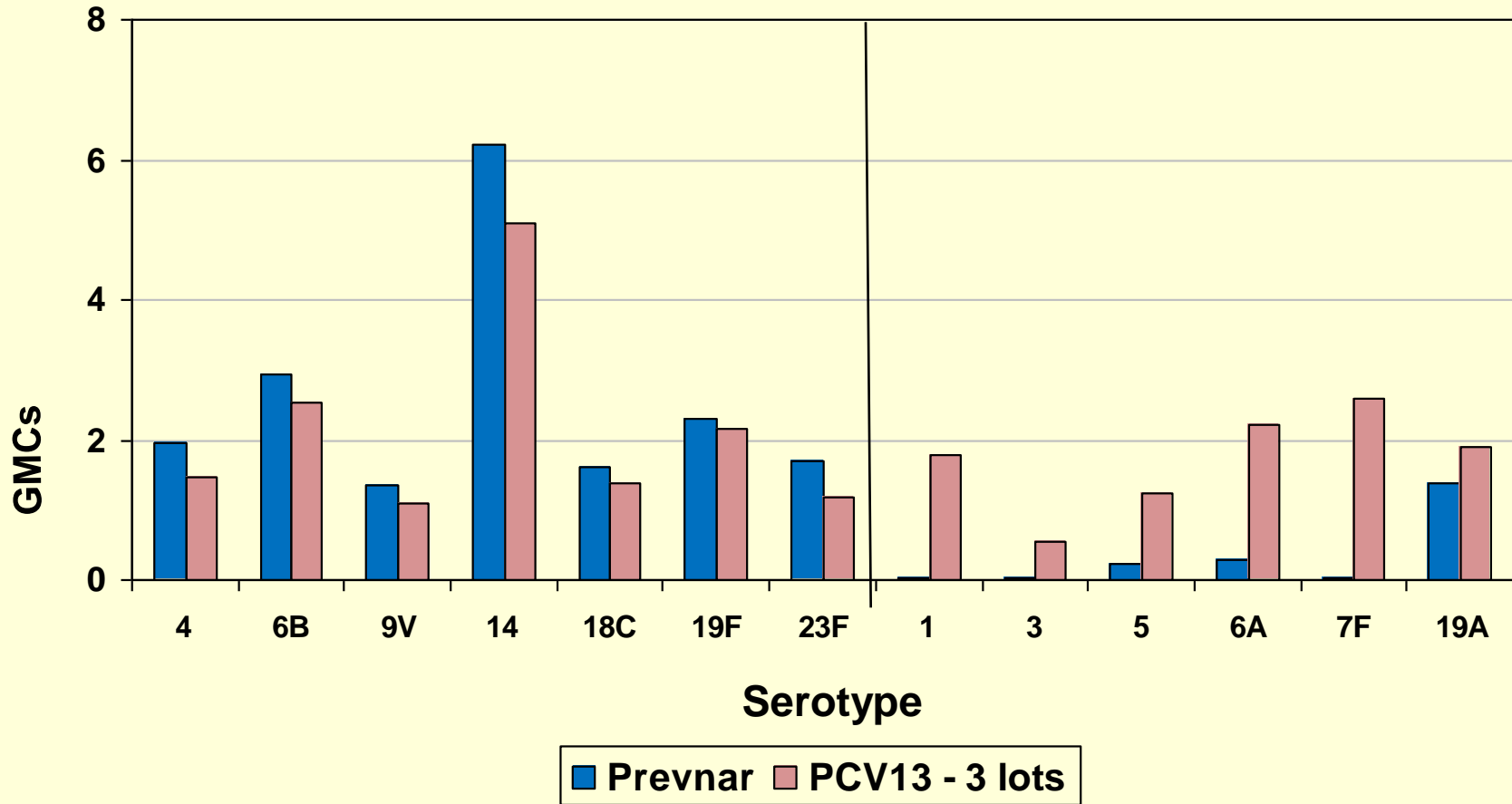
Comparison of Prevnar vs PCV13 (3005)

Subjects Achieving a Pneumococcal IgG Antibody Concentration $\geq 0.35 \mu\text{g/mL}$ After the Infant Series

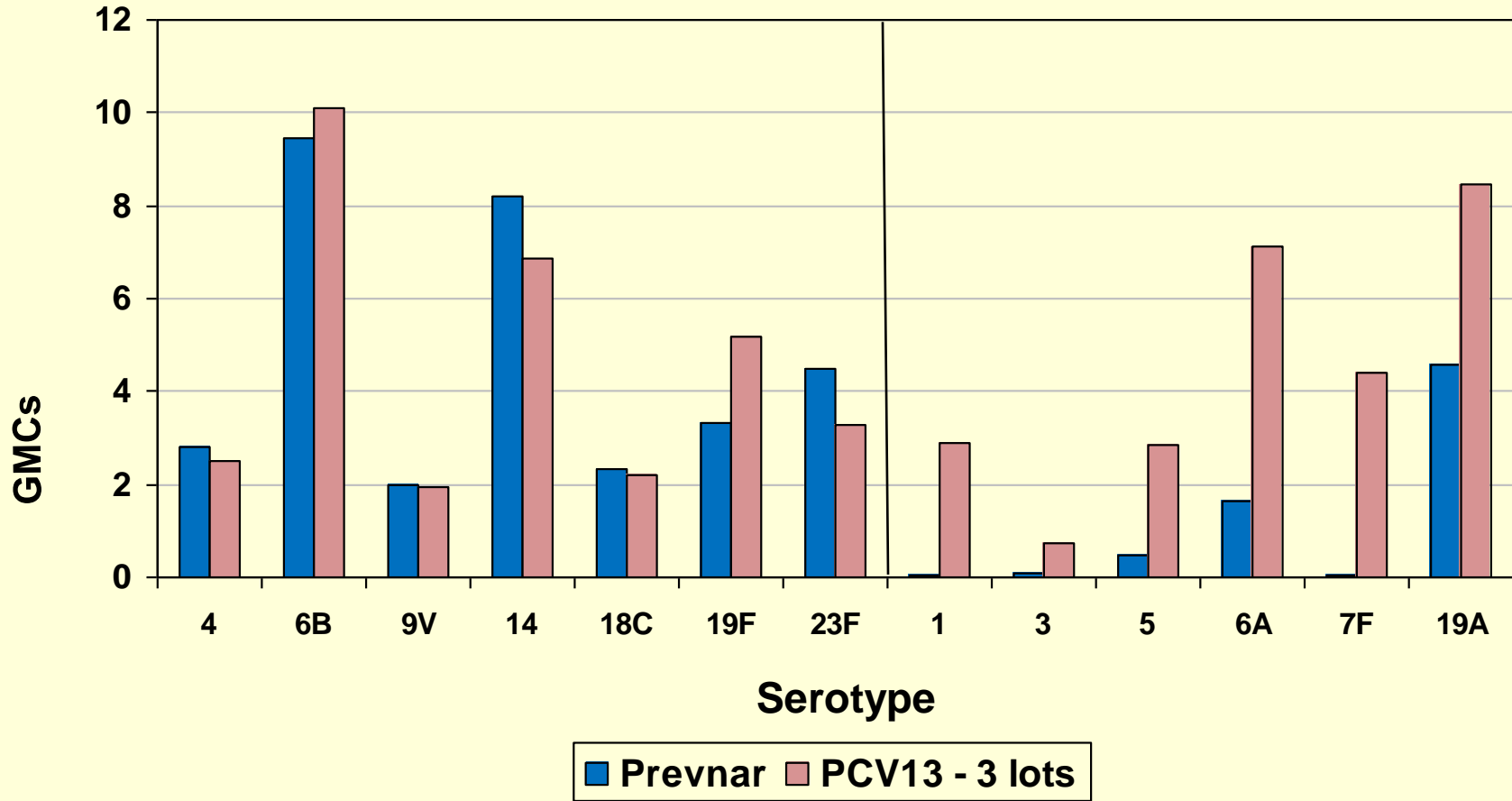


Non-inferiority criteria met for the 7 common serotypes

GMCs Post Primary Series Prennar vs PCV13 (3005)



GMCs Post Toddler Series Prennar vs PCV13 (3005)

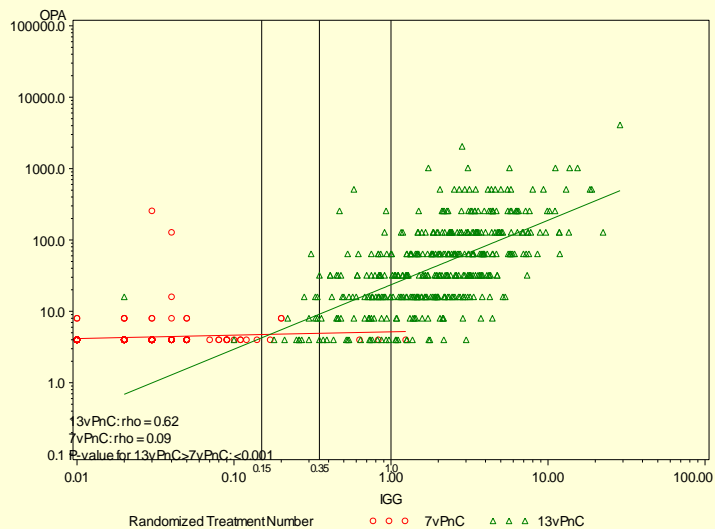


Functionality of Antibody Response to PCV13: Opsonophagocytic Activity

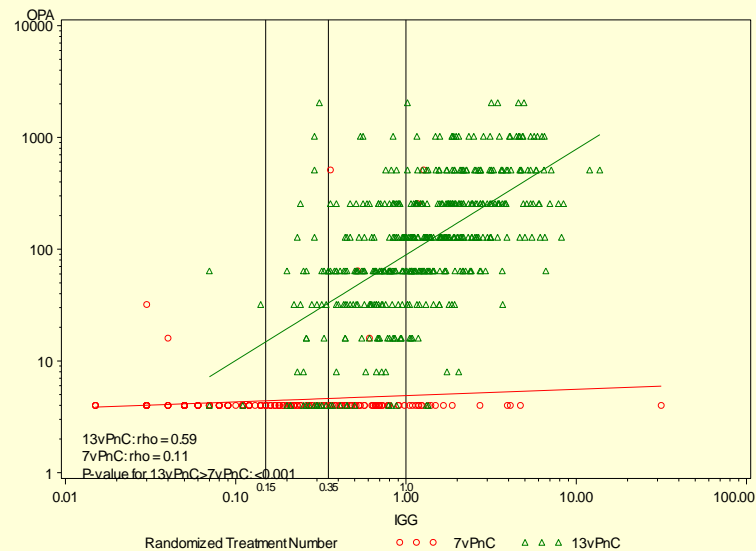
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Additional Serotypes 1, 5 and 7F: Concordance of ELISA and OPA Responses

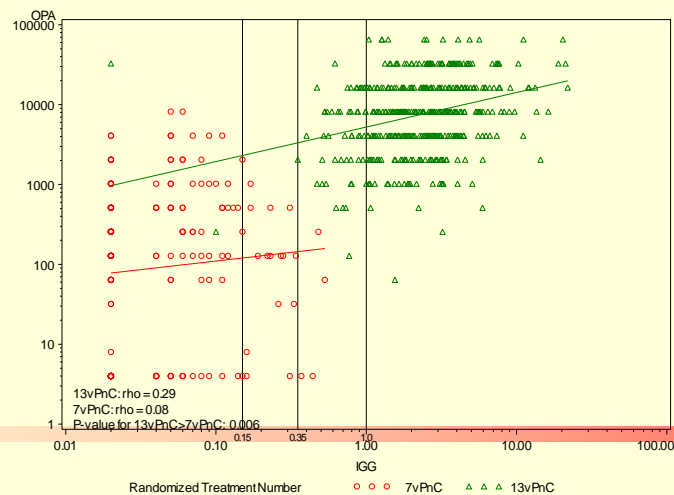
ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 1 - After Infant Series



ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 5 - After Infant Series



ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 7F - After Infant Series



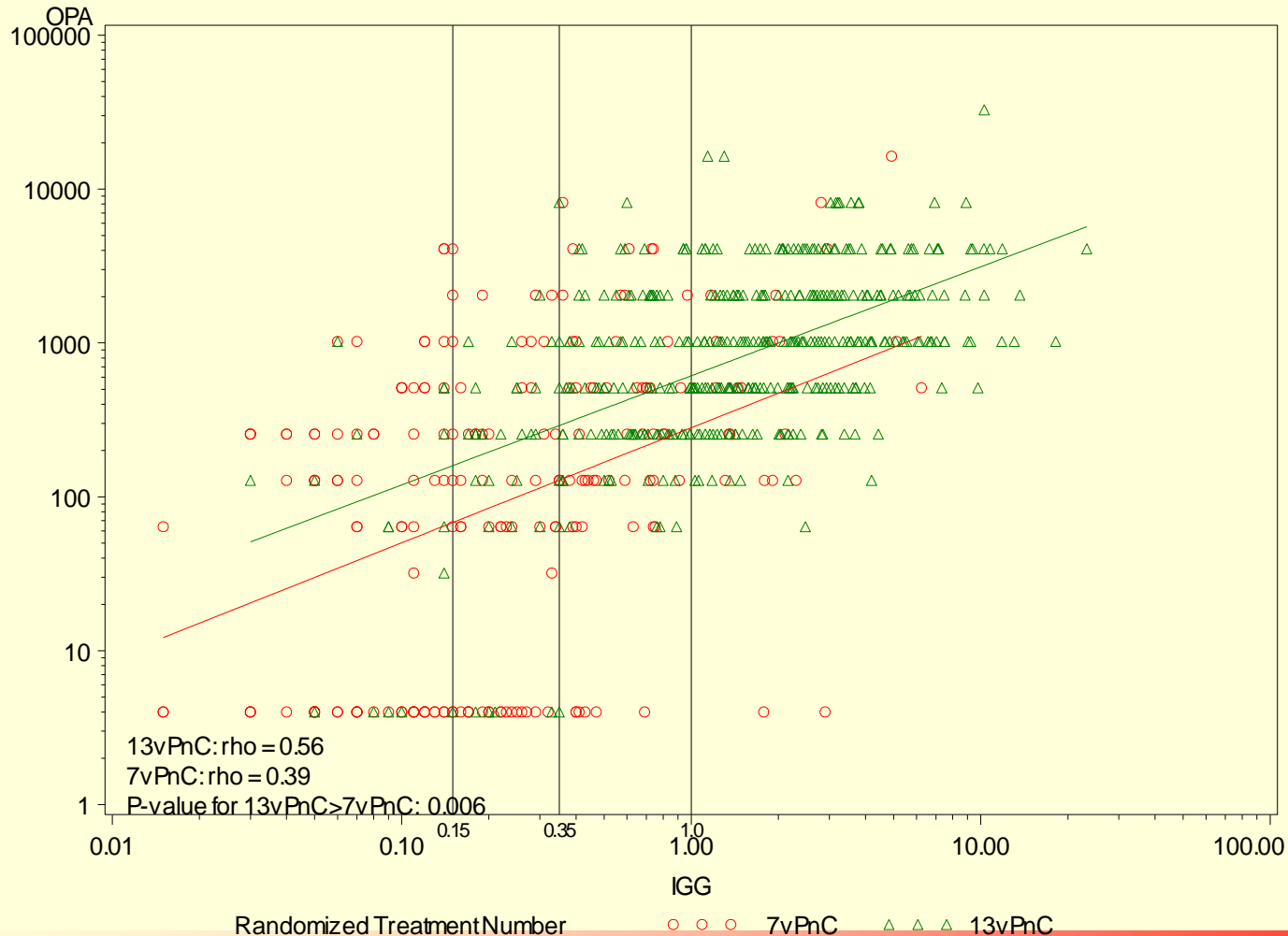
Protection Against Serotype 6A

- **Antibody to serotype 6B (in PCV7) induces cross-protection against 6A**
 - ▶ Magnitude is less than direct and indirect effects on 6B
- **Cross-protective effect is reflected in cross-reactive function immune response**
- **Conjugate 6A (in PCV13) induces 10-fold greater response than the cross-reaction from 6B (PCV7)**
- **Antibody to 6A conjugate induces function response to 6C**
 - ▶ 6C is a new and emerging serotype (the 91st)¹

¹ M. Nahm, ICAAC (2009)

Serotype 6A: Concordance of ELISA and OPA Responses

ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 6A - After Infant Series



Functional Antibody Response to Serotype 6A

	<u>OPA titer</u>		<u>6A/6B (PCV7)</u>
	<u>6B</u>	<u>6A</u>	
<u>PCV7 vs. PCV13</u> ¹			
PCV7	1160	122	0.10
PCV13	744	1228	1.10
<u>PCV7 vs. PCV10</u> ²			
PCV7	999	83	0.08
PCV10	457	41	0.04
Serotype 6A Conjugate Should Be Included To Insure Robust Response			

¹Kieninger DM et al. 2008 ICAAC: abstract 2638.

²Vesikari et al (2009) PIDJ 28: S66.

Functional Antibody Response to Serotype 6A

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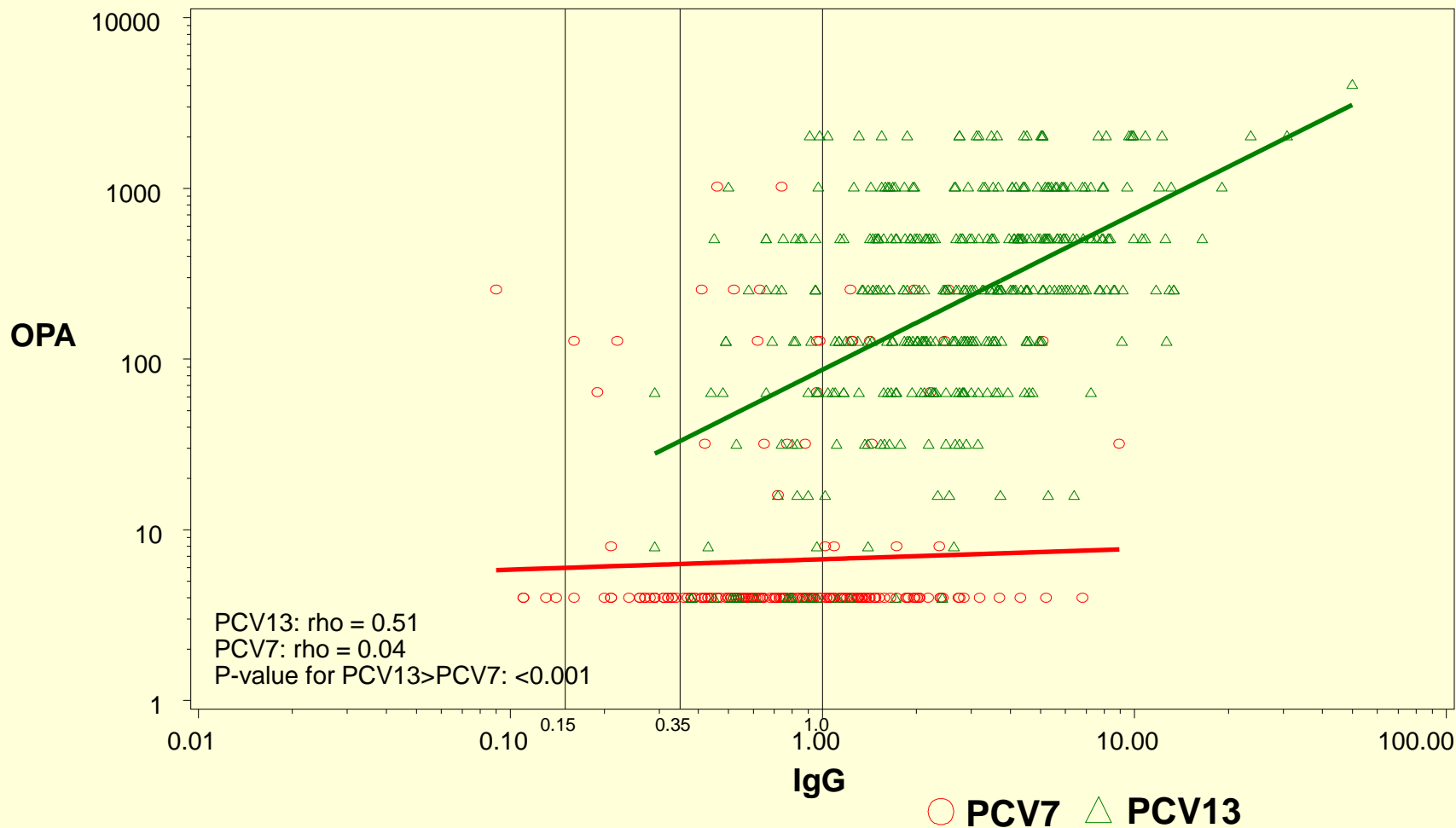
²Vesikari et al (2009) PIDJ 28: S66.

Protection Against Serotype 19A

- Antibody to 19F (in PCV7) induces no cross-protection against serotype 19A
- Lack of efficacy reflected in poor immune response to serotype 19A

Serotype 19A: Concordance of ELISA and OPA Responses

Plot of polysaccharide-binding IgG vs OPA assay data



Function Antibody Response to Serotype 19A

<u>Trial</u>	<u>OPA titer</u>	
	<u>19F</u>	<u>19A</u>
<u>PCV7 vs. PCV13</u>		
PCV7	165	6.7
PCV13	150	442
<u>PCV7 vs. PCV10</u>		
PCV7	52	4.5
PCV10	149	8.6

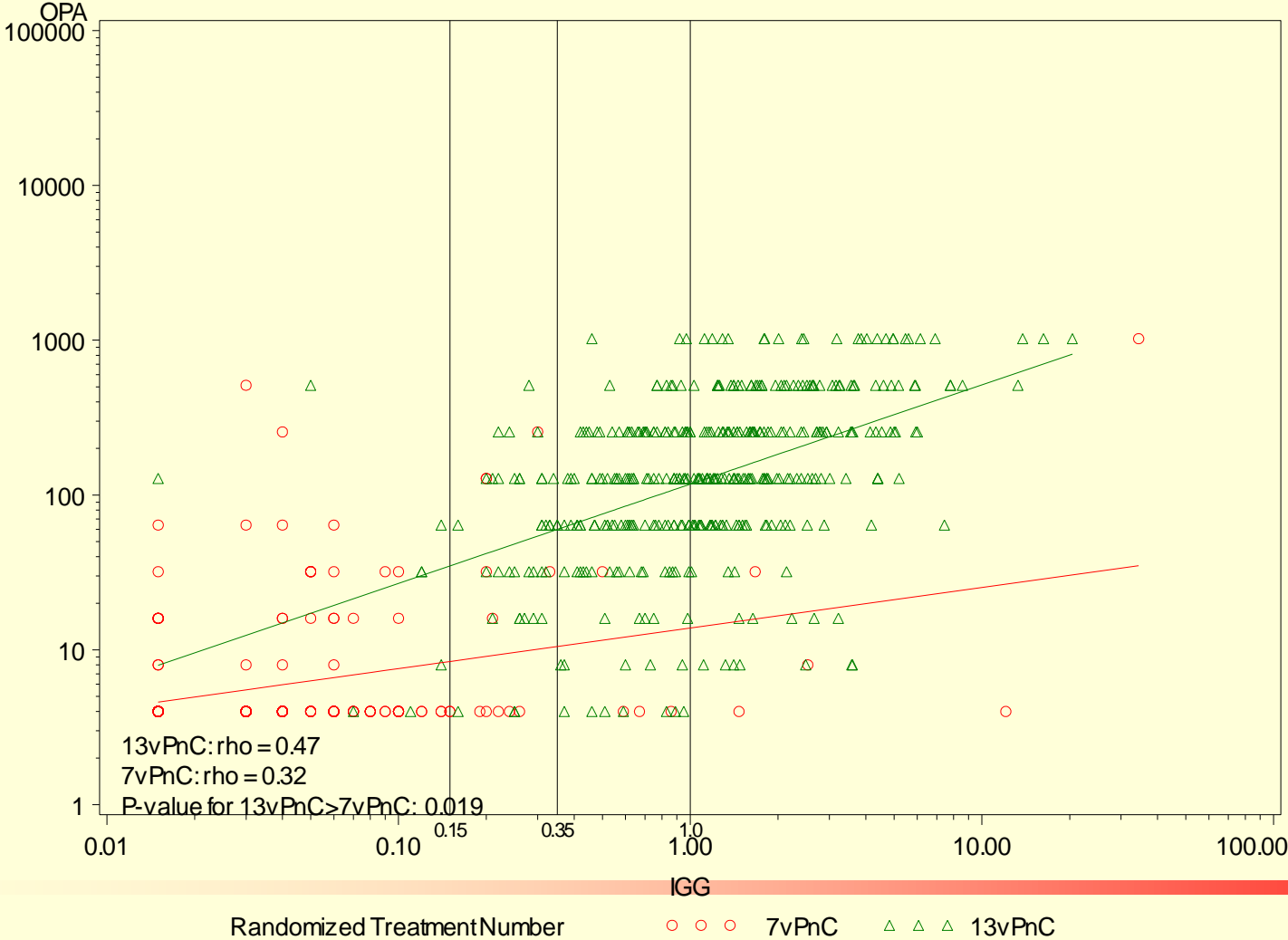
**Serotype 19A Conjugate Should Be Included
To Insure Robust Response**

1Kieninger DM et al. 2008 ICAAC: abstract 2638.

2Vesikari et al (2009) PIDJ 28: S66.

Serotype 3: Concordance of ELISA and OPA Responses

ISI - Plot of IgG vs OPA Assay Data by Treatment - Serotype 3 - After Infant Series



Serotype 3 OPA Responses Across Trials

Study	Country	Vaccination Schedule (months)	Post-Infant		Post-Toddler	
			% $\geq 1:8$	GMT	% $\geq 1:8$	GMT
004	USA	2, 4, 6 & 12-15	96.8	121	97.8	380
006	GER	2, 3, 4 & 11-12	99	251	98	188
500	ITA	3, 5 & 11	99	176	100	505
007	UK	2, 4, 12	100	109	100	307

Transition from PCV7 to PCV13

- **PCV13 is designed to be interchangeable with PCV7 at any point in the immunization schedule**
 - ▶ 7 serotypes are common
 - ▶ CRM₁₉₇ is the carrier protein
- **A single dose of PCV13 in those over 12 months of age will induce a response to the 7 common serotypes and the 6 new serotypes in over 90% of the children**

Grimprel E, Laudat F, Baker SA et al. Presented at the 27th Annual Meeting of the European Society for Paediatric Infectious Disease (ESPID), June 9-13, 2009, Brussels, Belgium.

Safety Conclusions

Integrated Safety Database

- **Safety database of >5000 patients with >16,000 doses of PCV13 administered**
- **Safety parameters, solicited and unsolicited, for systemic and local reactions, were assessed in a uniform fashion in all studies**
- **Adverse events and serious adverse events incidence comparable between PCV7 and PCV13 groups**

Safety profile of PCV13 comparable to that of PCV7

Concomitant Vaccine Conclusions

- **PCV13 can be given with any of the following vaccine antigens, either as monovalent or combination vaccines:**
 - ▶ Diphtheria
 - ▶ Tetanus
 - ▶ Acellular or whole cell pertussis
 - ▶ *Haemophilus influenzae* type b
 - ▶ Inactivated poliomyelitis
 - ▶ Hepatitis B
 - ▶ Meningococcal serogroup C
 - ▶ Measles, mumps, rubella and varicella
 - ▶ Rotavirus vaccine (safety evaluation)
 - ▶ Hepatitis A (safety evaluation)

Conclusions

- **PCV 13 is built on the scientific foundation of PCV7, using the same protein carrier, CRM₁₉₇**
- **PCV 13 meets all the WHO recommended licensing criteria of immunologic non-inferiority, safety and use with concomitant vaccines**
- **PCV 13 will provide the broadest coverage of any conjugate vaccine with an excellent immune response and flexibility of schedules**
- **PCV13 is designed to be interchangeable with PCV7 at any point in the vaccination schedule**