Clinical development of *Synflorix*™

(Pneumococcal non-typeable *Haemophilus influenzae* protein D-Conjugate Vaccine)

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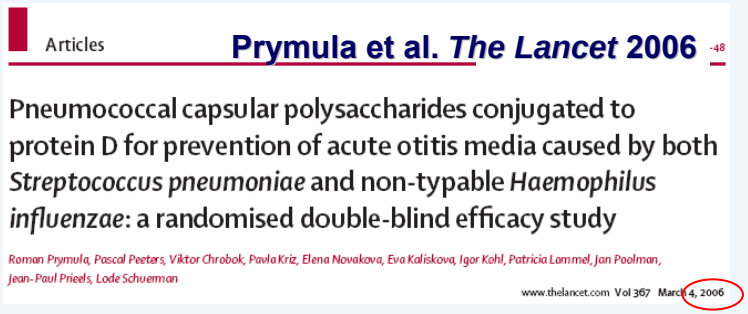
Clinical R&D and Medical Affairs
Latin America and the Caribbean

Simposio Regional de Nuevas Vacunas
Regional Symposium of New Vaccines
Lima, Perú
1–3 December, 2009

Synflorix™ innovative clinical development

1997 — **4 valent-PD** — 6B, 14, 19F, 23F

1999 — **11 valent-PD** — 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F



Articles

Prymula et al. *The Lancet* 2006 -48

Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study

Roman Prymula, Pascal Peeters, Viktor Chrobok, Pavla Kriz, Elena Novakova, Eva Kaliskova, Igor Kohl, Patricia Lommel, Jan Poolman, Jean-Paul Prieels, Lode Schuerman

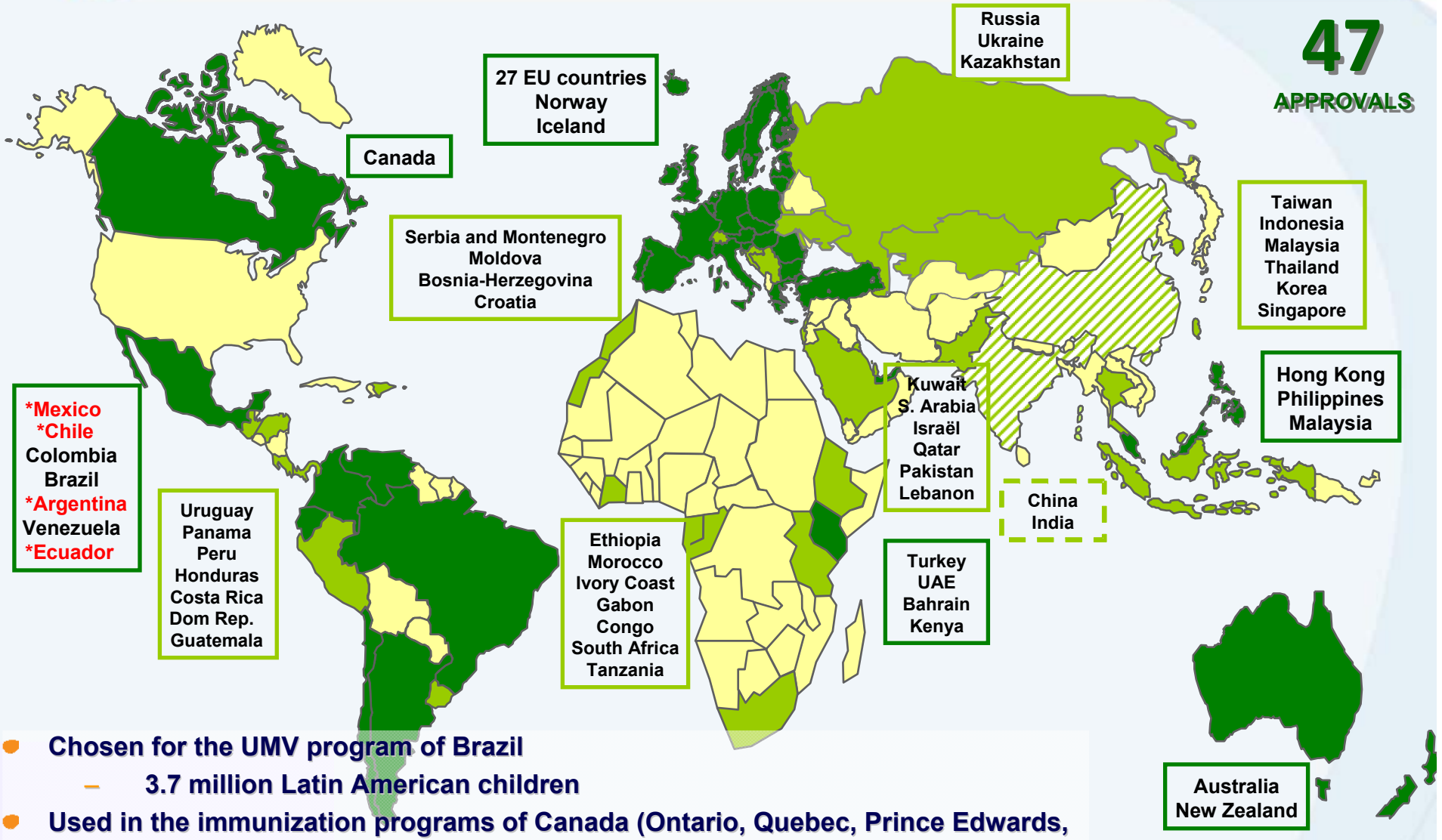
www.thelancet.com Vol 367 March 4, 2006

Pneumococcal Otitis Efficacy Trial

2006 — **10 valent-PD-Di-T** — 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F

2008 — **1st license in Canada**

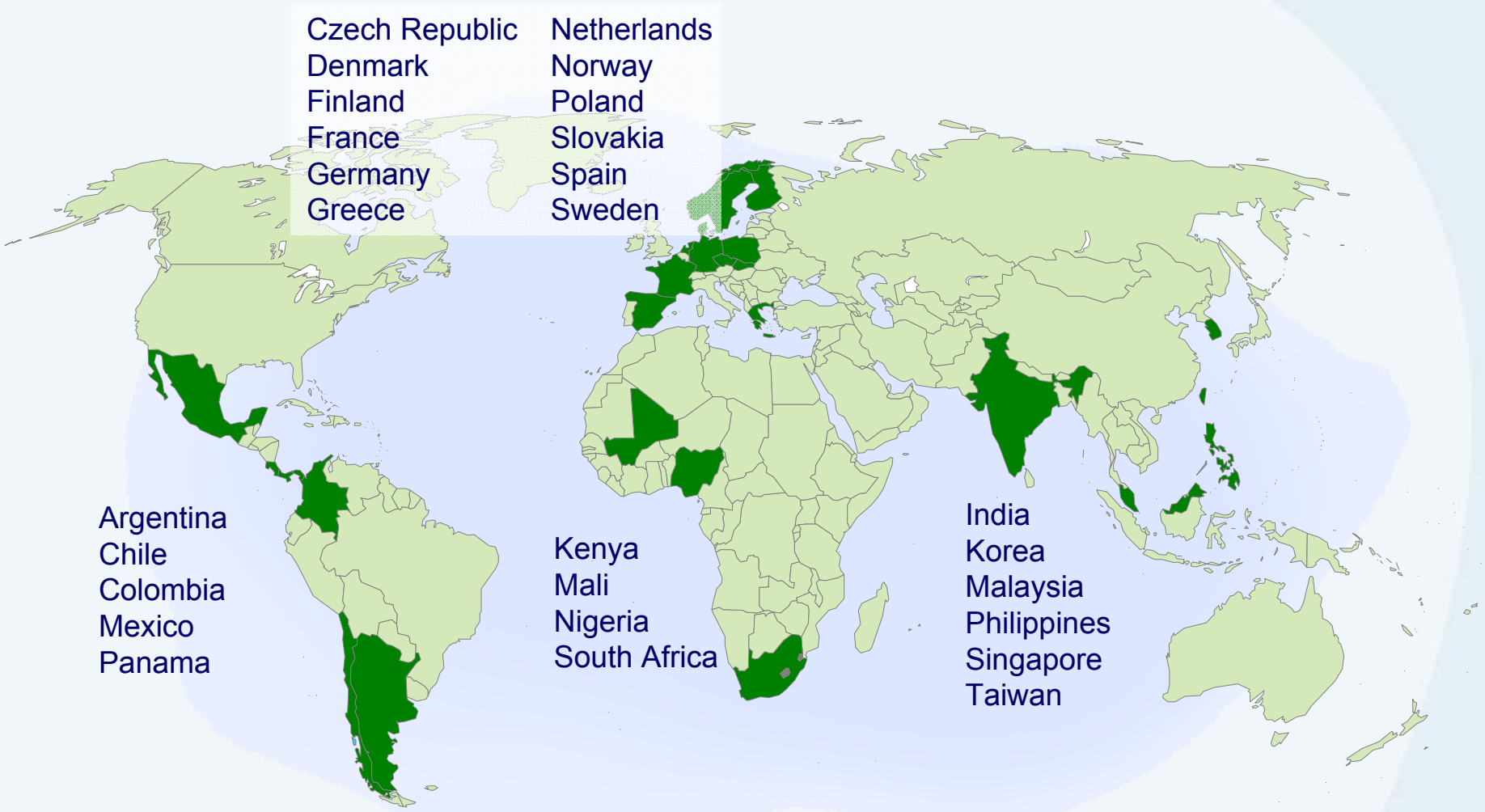
Synflorix™ regulatory status 18 November 09



- Chosen for the UMV program of Brazil
  - 3.7 million Latin American children
- Used in the immunization programs of Canada (Ontario, Quebec, Prince Edwards, territories) and selected Australian and Sweden provinces.
- First PCV with WHO pre-qualification

*Approved for the prevention of NTHi AOM

Synflorix™ clinical study sites distribution



- **4 continents, 27 countries**

Clinical Development Program in Latin America

About 25,000 subjects in clinical and epidemiological studies

AOM epidemiology studies

AOM Etiology

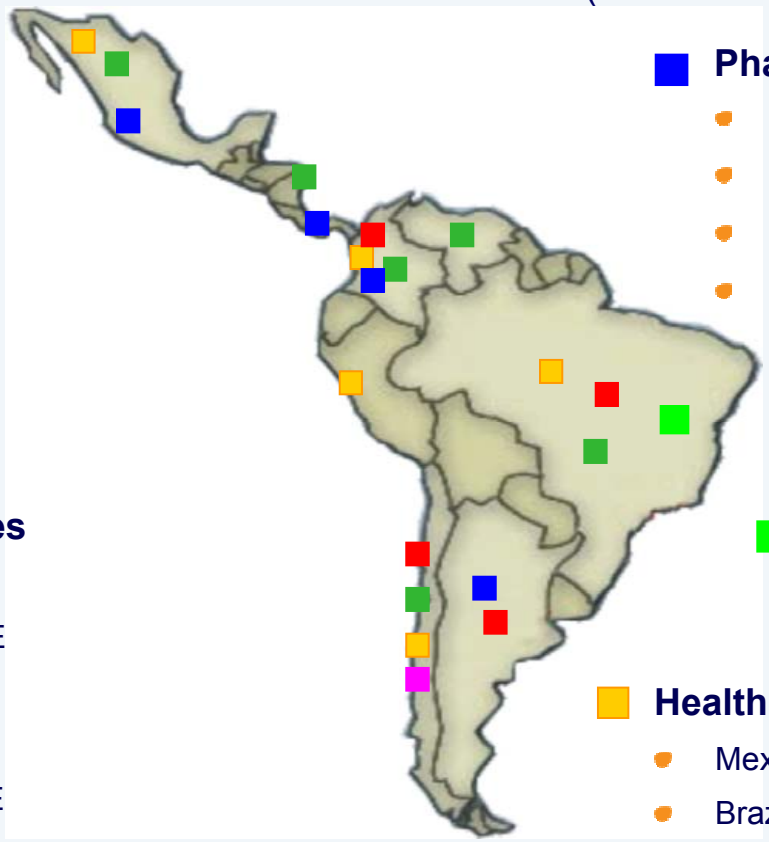
- Mexico - DONE
- Colombia - DONE
- Venezuela
- Costa Rica
- Chile

Incidence and Costs

- Mexico (Mar 2010)
- Brazil (Jan 2010)

IPD & CAP studies

- Chile - DONE
- Argentina - DONE
- Brazil - DONE
- Panama - DONE
- Colombia - DONE



Phase IIA clinical trials

- Chile (10-PN-PD-DIT005) - DONE
- Chile (10-PN-PD-DIT009-BST005) - DONE

Phase III clinical trials

- Mexico (10-PN-PD-DIT029) DONE
- Argentina (10-PN-PD-DIT028) COMPAS
- Colombia (10-PN-PD-DIT028) COMPAS
- Panama (10-PN-PD-DIT028) COMPAS

Phase IV clinical trial

- Brazil

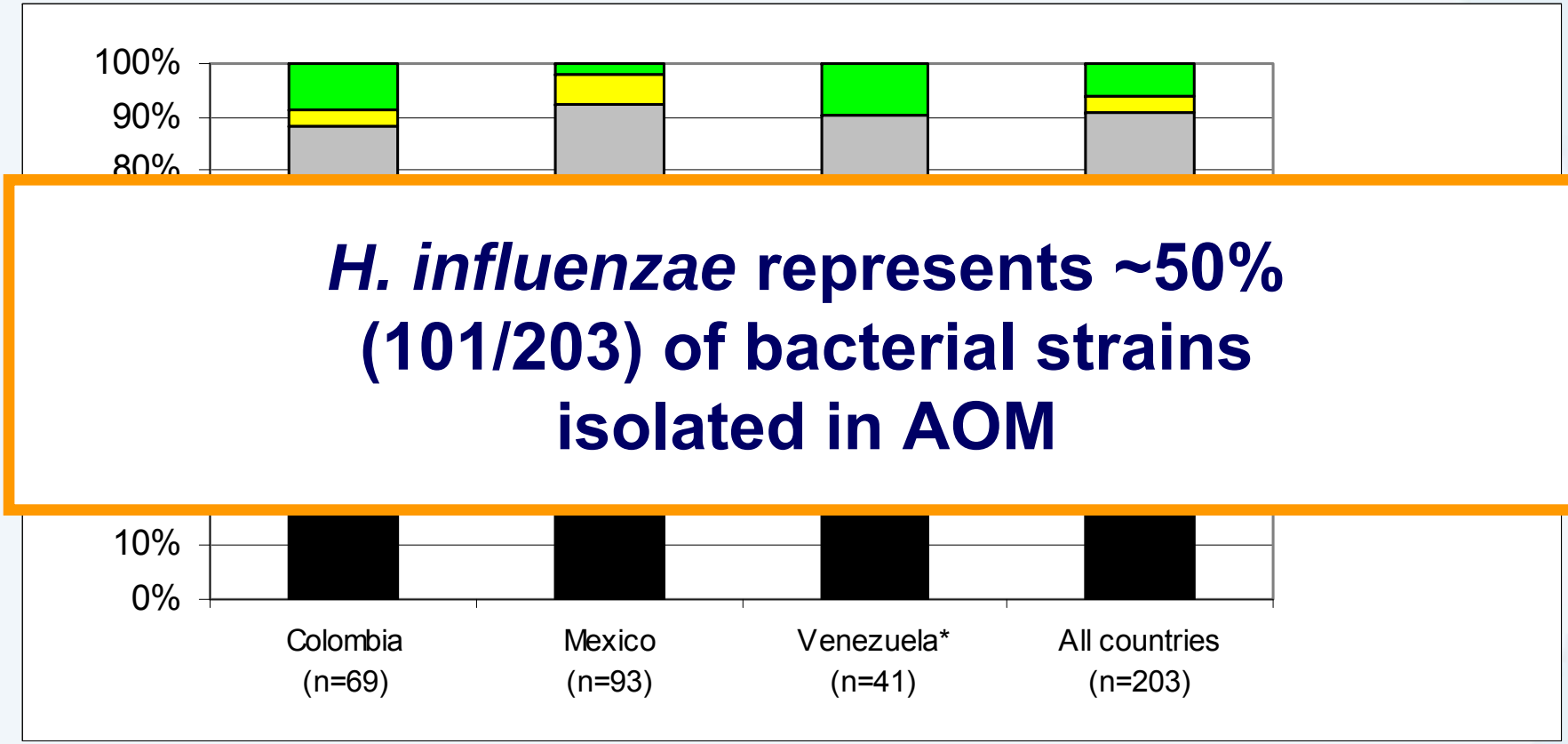
Health economics studies

- Mexico - DONE
- Brazil - DONE
- Chile
- Colombia
- Peru

AOM etiology studies in Latin America

Data on GSK file – in preparation for publication

Preliminary results



***H. influenzae* represents ~50% (101/203) of bacterial strains isolated in AOM**

Data on GSK file – in preparation for publication

* *Enrollment is ongoing **DATA FROM POSITIVE TESTS*

Burden of pneumococcal disease in children ≤5 years

From global to regional: The importance of pneumococcal disease in Latin America

Ciro A. de Quadros*

Albert B. Sabin Vaccine Institute (SVI), 2000 Pennsylvania Ave., N.W., Suite 7100 Washington, DC 20006, United States

Comparative estimates of the global burden of pneumococcal disease.

Region	Population (millions)	Annual number of cases			
		Meningitis	Bacteremia	Pneumonia (hospitalised)	Otitis media (children aged <5 years)
United States	281[a]	2,000	8,000	106,000–175,000	3,100,000
Asia	3634[b]	25,865	103,459	1,370,833–2,263,167	40,090,391
Africa	767[b]	5,459	21,836	289,331–477,669	8,461,566
Europe	729[b]	5,189	20,754	274,996–454,004	8,042,3490
Latin America	511[b]	3,637	14,548	192,761–318,238	5,637,367

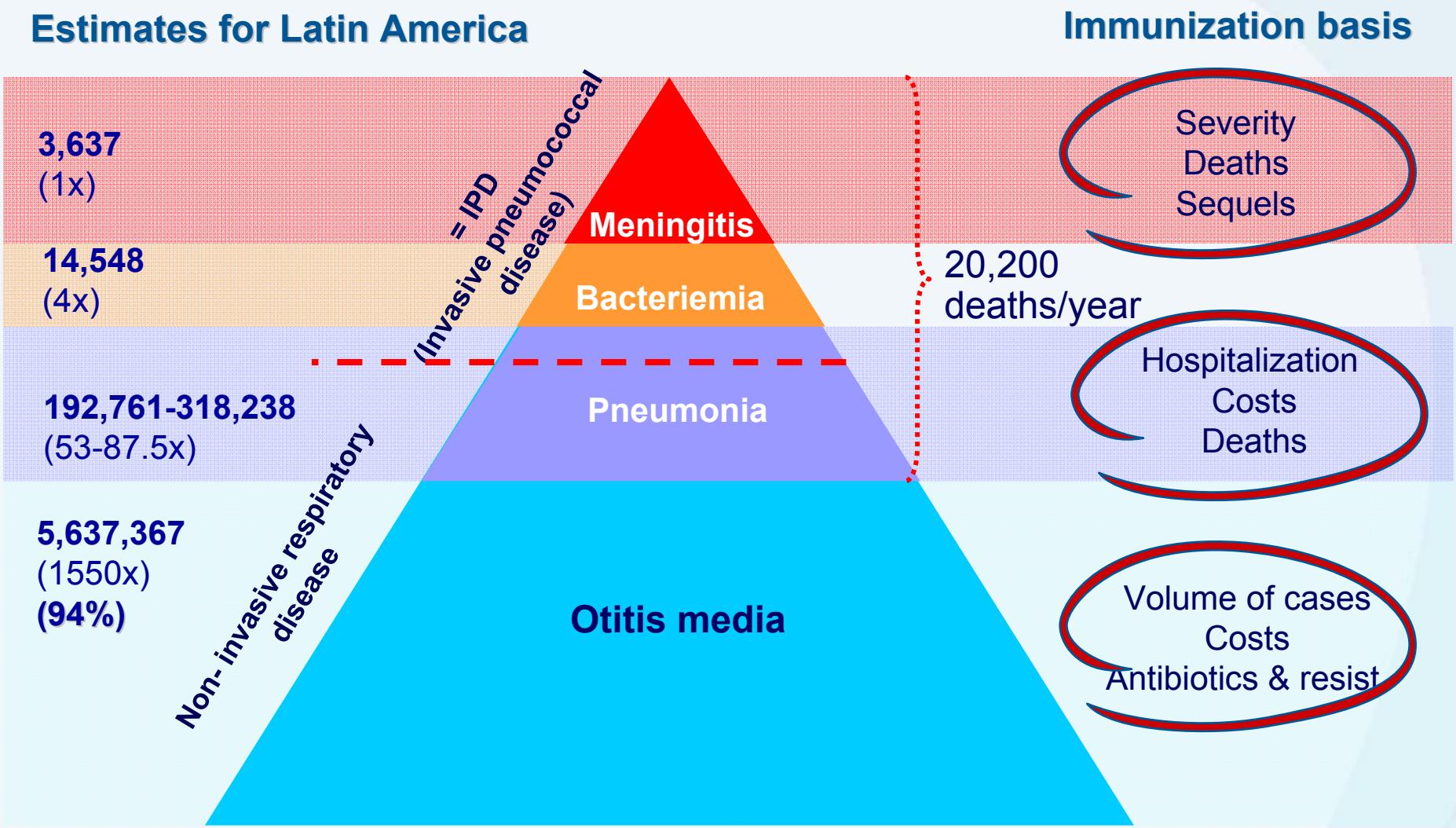
These data were extrapolated from the number of cases of invasive pneumococcal disease reported for the United States (Centers for Disease Control and Prevention. Manual for the surveillance of vaccine-preventable diseases. 4th ed. 2008 [4]) and extrapolated against populations for other geographic regions (United Nations. The world at six billion. Available at: http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf. [6]).

[a] US Census Bureau. US summary 2000 [5].

[b] United Nations. The world at six billion. Available at: http://www.un.org/esa/population/publications/sixbillion/sixbilpart1.pdf. [6].

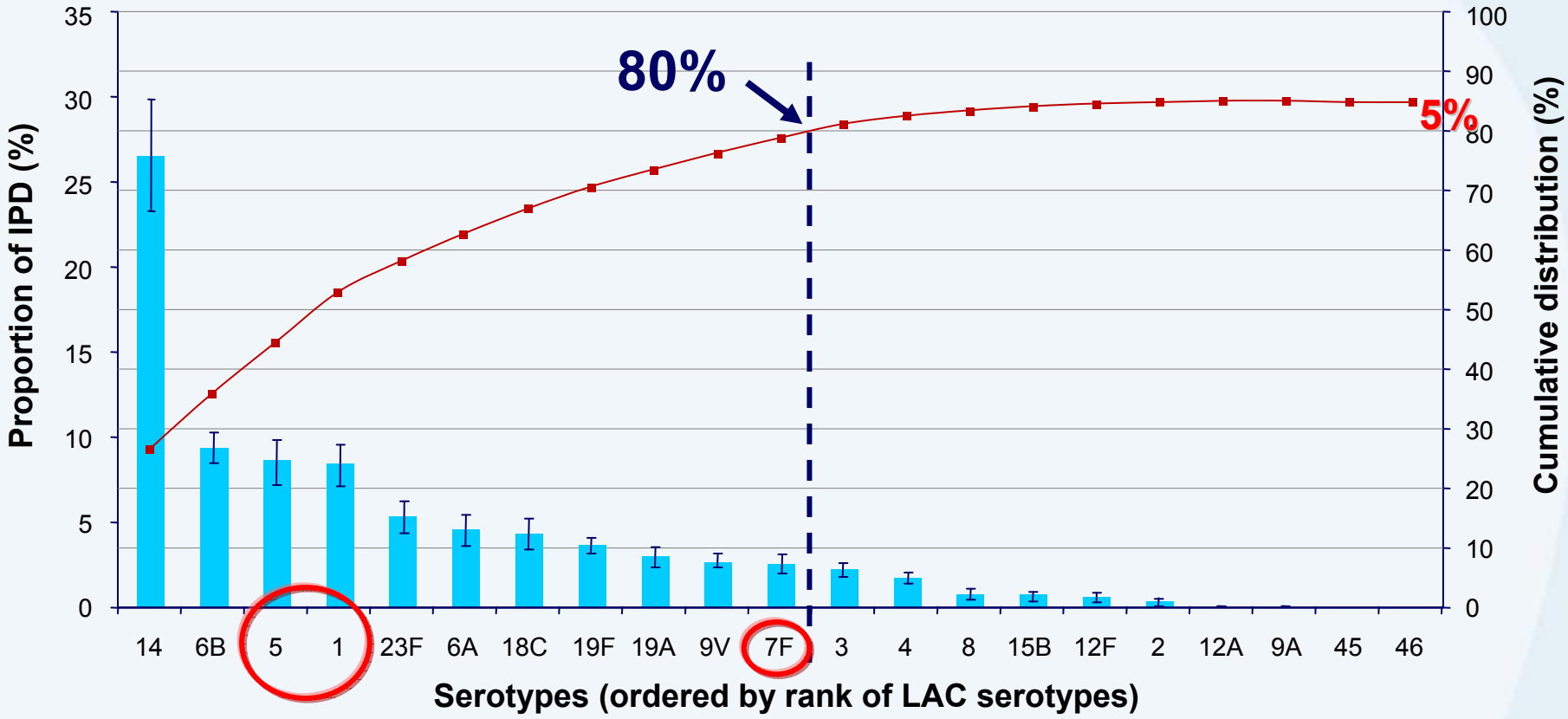
In press: de Quadros CA. From global to regional: The importance of pneumococcal disease in Latin America. Vaccine (2009), doi:10.1016/j.vaccine.2009.06.006

The value of immunization for *S. pneumoniae* includes invasive and non-invasive disease



In press: de Quadros CA. From global to regional: The importance of pneumococcal disease in Latin America. Vaccine (2009), doi:10.1016/j.vaccine.2009.06.006

Serotypes by rank and cumulative distribution: Latin America and Caribbean

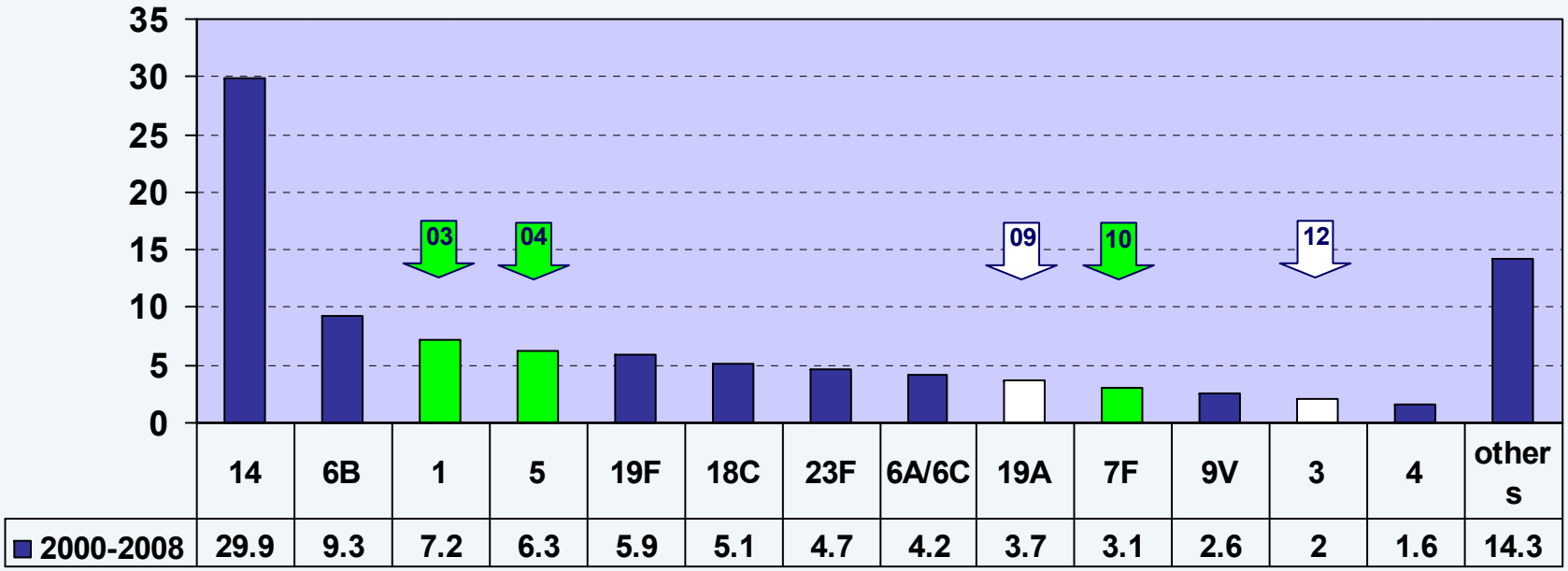


Synflorix™ contains 9 of 11 most frequent serotypes in Latin America and Caribbean, and is expected to confer cross-protection against ST 6A.

Global Serotype Project (Finalised Version 2.0 analyses) GSP2 report. Available from: http://www.vaccineamc.org/files/TTP_Codebook.pdf [Accessed March 2009].

SIREVA II (2000-2008)
Latin America and Caribbean (n=14,013)

Percentage of pneumococcal serotypes related to IPD in children less than 6 years old



	14	6B	1	5	19F	18C	23F	6A/6C	19A	7F	9V	3	4	others
2000-2008	29.9	9.3	7.2	6.3	5.9	5.1	4.7	4.2	3.7	3.1	2.6	2	1.6	14.3

Additional coverage of Synflorix™: 17%*

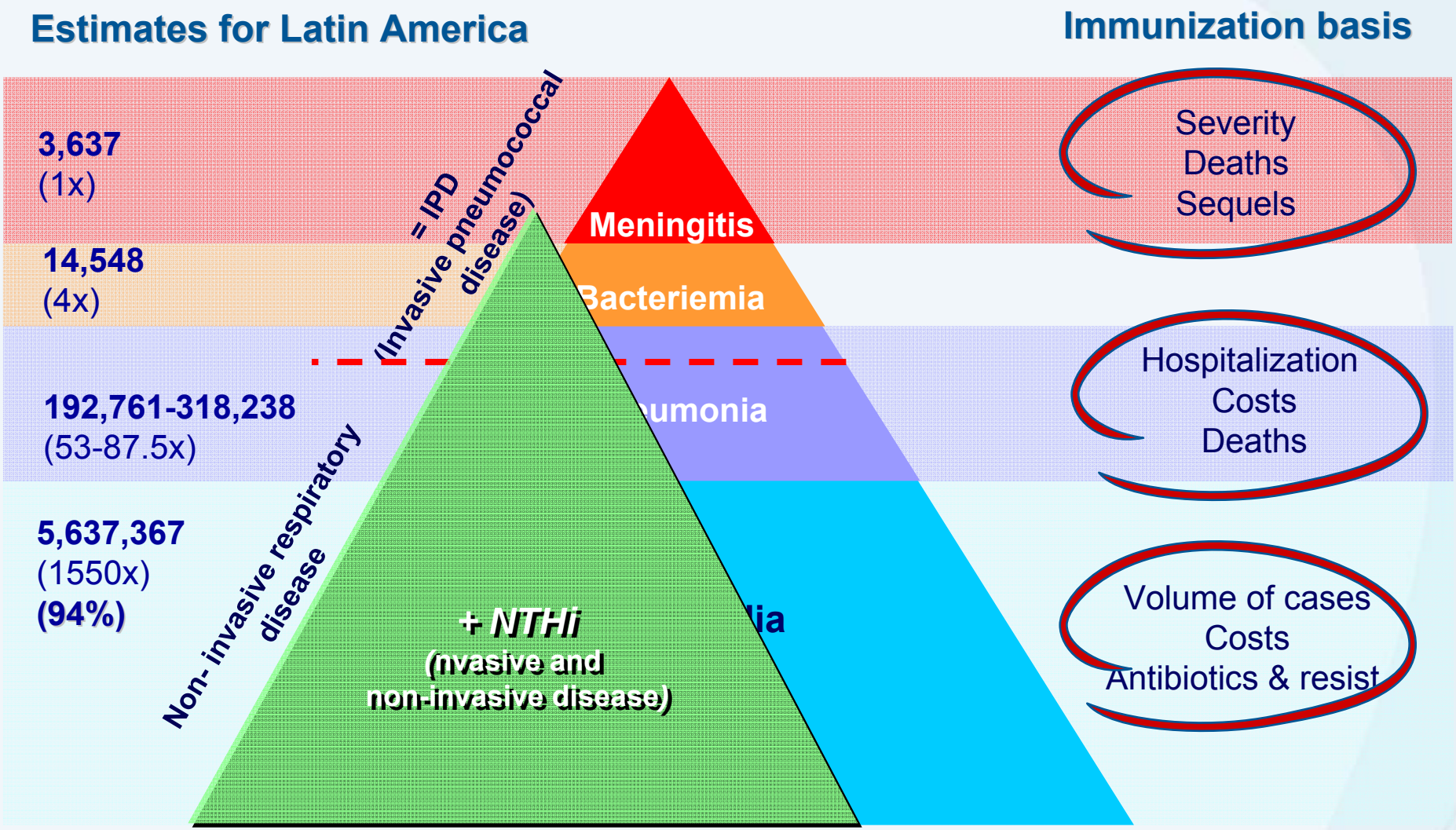
(*) ST6A included in coverage

Years 2000-2005 IPD in children less than 6 y.o.

Years 2006, 2007 and 2008 IPD in chlidren less than 5 y.o.

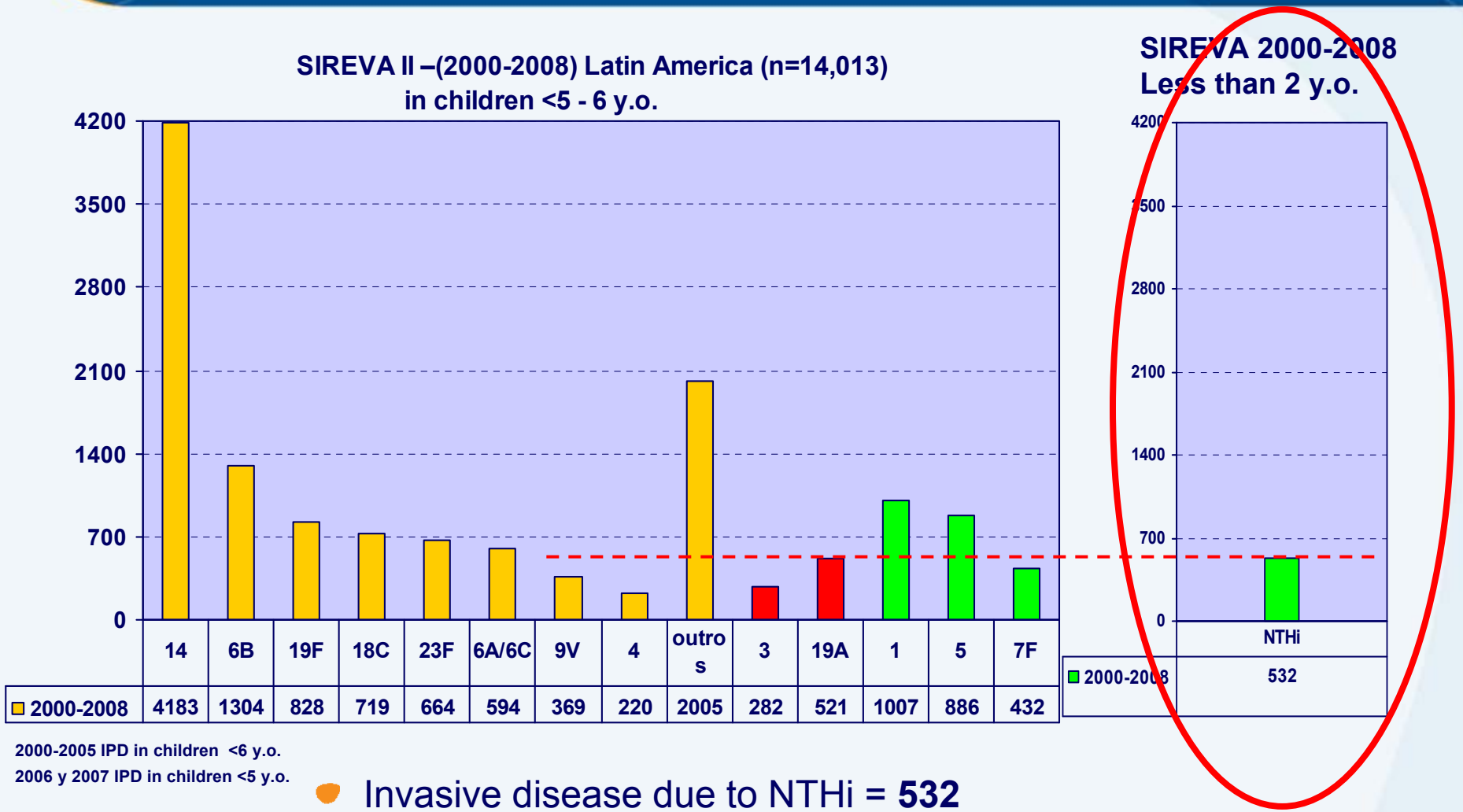
Adapted from: SIREVA II. Reporte 2007. THS/EV 2007/002 (datos 2000-2005); THR/EV-2008/001 (datos 2006), TRH/EV2008/003 (datos 2007) y THR/HT – 2009/002 (datos 2008)

The value of immunization for *NTHi* includes invasive and non-invasive disease



In press: de Quadros CA. From global to regional: The importance of pneumococcal disease in Latin America. Vaccine (2009), doi:10.1016/j.vaccine.2009.06.006

NTHi in Latin America. What is its significance? (SIREVA 2000-2008).

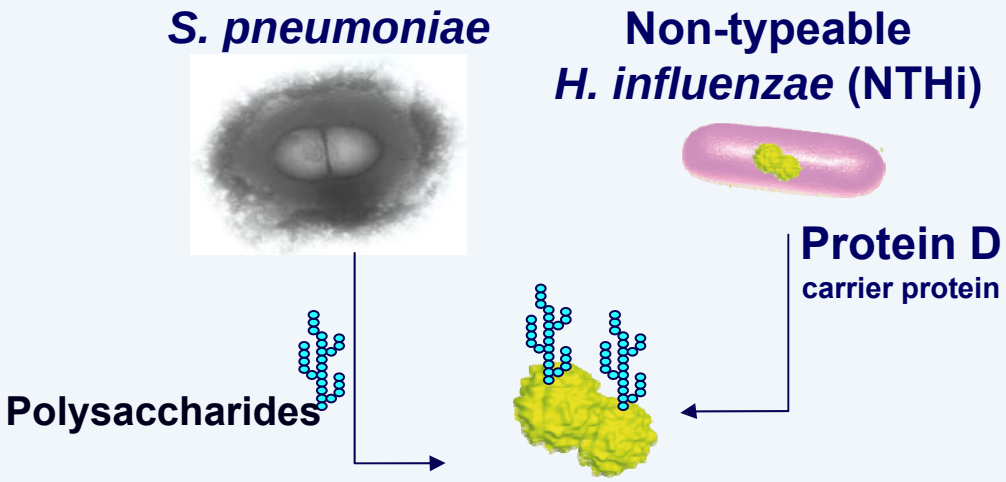


2000-2005 IPD in children <6 y.o.
2006 y 2007 IPD in children <5 y.o.

- Invasive disease due to NTHi = **532**
- **Diseases:** meningitis, bacteriemia/sepsis, pneumonía
- **Isolation site:** CSF, hemoculture

Adapted from: SIREVA II. Reporte 2007. THS/EV 2007/002 (datos 2000-2005); THR/EV-2008/001 (datos 2006), TRH/EV2008/003 (datos 2007) y THR/HT – 2009/002 (datos 2008)

A next generation PCV: *PHiD-CV*



NTHi Protein D	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F

- 8 serotypes conjugated to protein D;
- 18C to tetanus toxoid, 19F to diphtheria toxoid

Includes 10 pneumococcal serotypes (1, 5 and 7F + PCV7 serotypes)

Inclusion of the carrier protein NTHi-Protein D:

- to help minimize risk of interference with co-administered vaccines
- expected to offer protection against NTHi by virtue of Protein D carrier protein, based on clinical experience (POET)

European Medicines Agency (EMEA). Summary of product characteristics - Synflorix, 2009;
Prymula, *et al. Lancet* 2006;367:740–48

WHO licensure criteria for IPD

Immunological licensure criteria proposed by WHO and endorsed by European CHMP:

1. Non-inferiority of post-primary **EL** sponses compared to PCV7 (based ning pre-set thresholds)

2. Demo apacity of antibodies (tivity - **OPA**)

3. In of **immunological memory**

- **Approved in 47 countries**
- **Pre-qualified by the WHO**

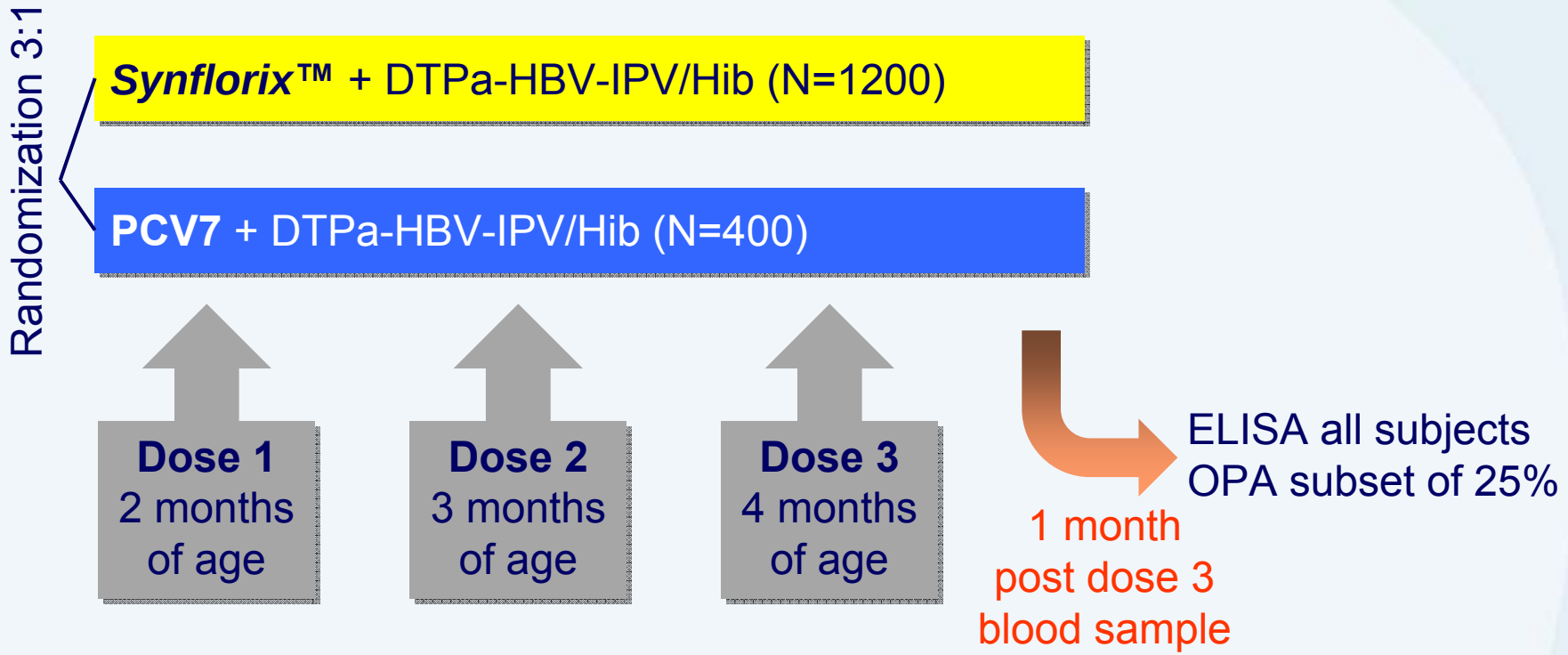
Jodar et al. Vaccine 2003; 21: 3265-72 - WHO Technical Report Series, No. 927, 2005, Annex 2
Concepcion et al. Clin Diagn Lab Immunol 2001; 8: 266-72

Clinical development of *Synflorix*™

- Immunogenicity compared with PCV7 [1–3,6–9]
- Functional responses (OPA) [1–3,6,8,9]
- Boostability of primary responses [1,2,8,9]
- Co-administration with routine vaccines [4]
  - DTPa-HBV-IPV/Hib, DTPa-HBV-IPV and DTPa-IPV/Hib [1–3,6,8,9]
  - MenC-CRM, MenC-TT and Hib-MenC [2]
  - DTPw-HepB/Hib and OPV [3]
  - MMRV (with booster dose) [7]
  - Rotavirus vaccine [8]
- Safety & tolerability profile similar to PCV7 [5]
- Interchangeability (*Synflorix*™ booster after PCV7 priming) [1]
- Immunisation schedules
  - 2-3-4 mo[1]; 3-4-5 mo[8]; 2-4-6 mo[2,3,6]; 3-5-11 mo[9]; 6-10-14 weeks[3]

1.Vesikari et al. PIDJ 2009; 28: S66-S76, 2.Wysocki et al. PIDJ 2009; 28: S77-S88, 3.Bermal et al. PIDJ 2009;28:S89-S96, 4.Knuf et al. PIDJ 2009; 28: S97-S108, 5.Chevaliler et al. PIDJ 2009;28:S109-S118, 6.Lagos et al. ISPPD6, Reykjavik, Iceland 2008, 7.Vesikari et al. ESPID, Graz, Austria, 8. Prymula et al. Lancet 2009;374:1339-50, 9. Silfverdal et al. PIDJ 2009;28:e276-82

Primary immunogenicity study



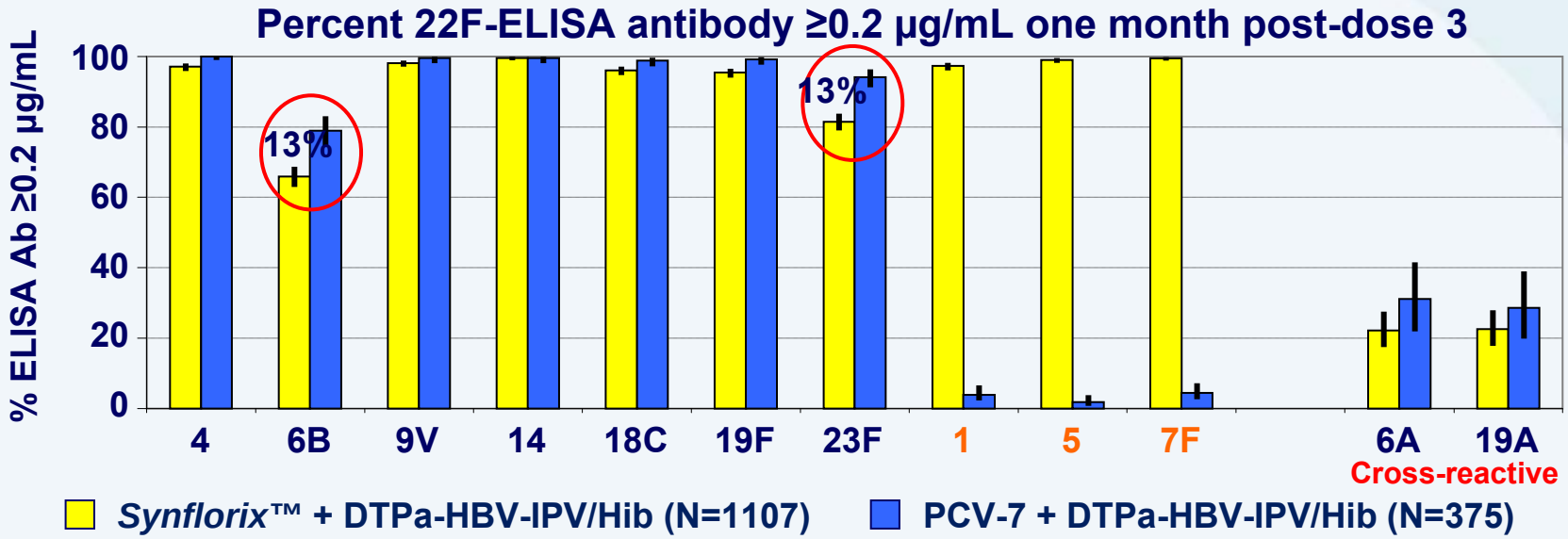
Single blind, controlled trial in Finland, France and Poland

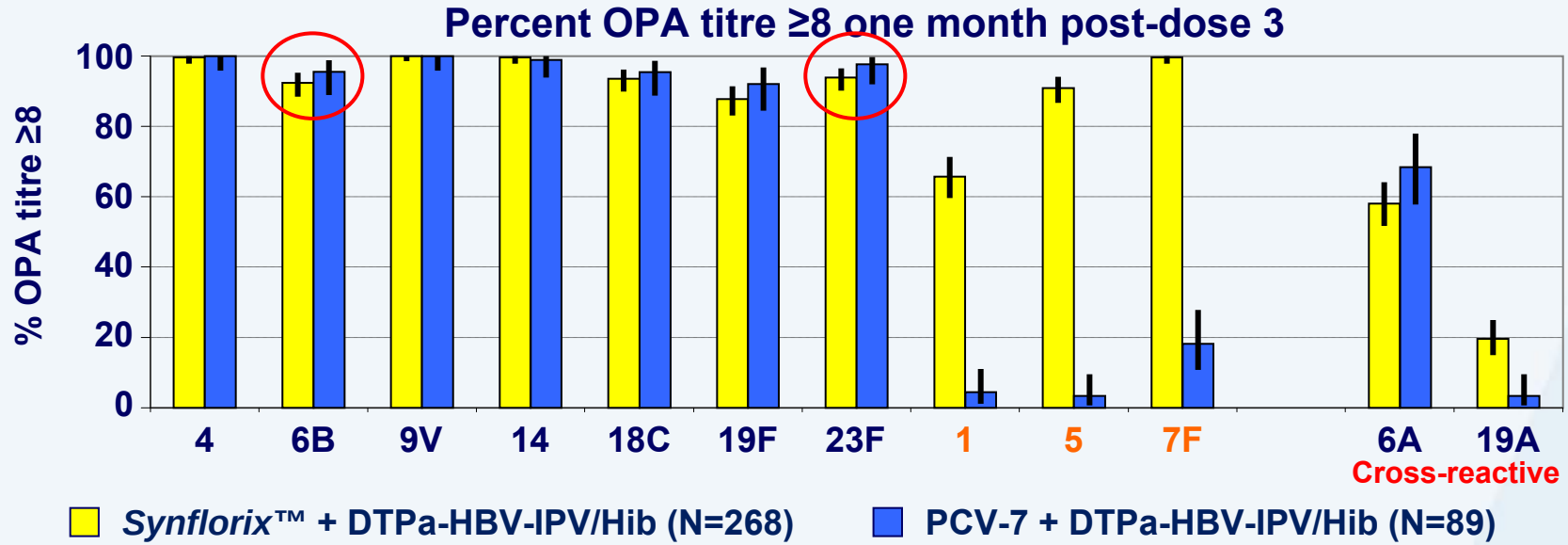
Study 10PN-PD-DIT-001 (NCT00307554)
Vesikari T. et al. Pediatr Infect Dis J 2009;28:S66–S76

DTPa-HBV-IPV/Hib = *Infanrix™ hexa* is a trademark of the GlaxoSmithKline group of companies

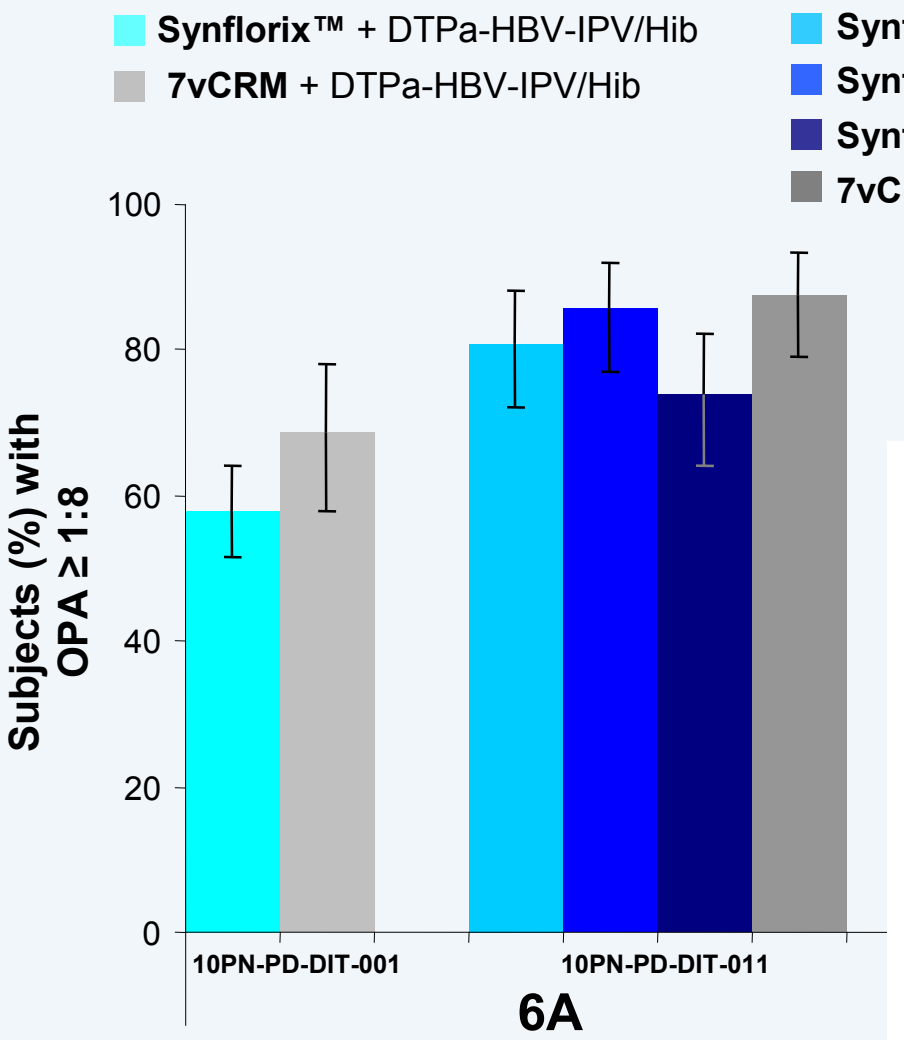
Antibody & OPA responses of *Synflorix*™ vs PCV7

Vesikari T *et al. Pediatr Infect Dis J* 2009:28;S66-76





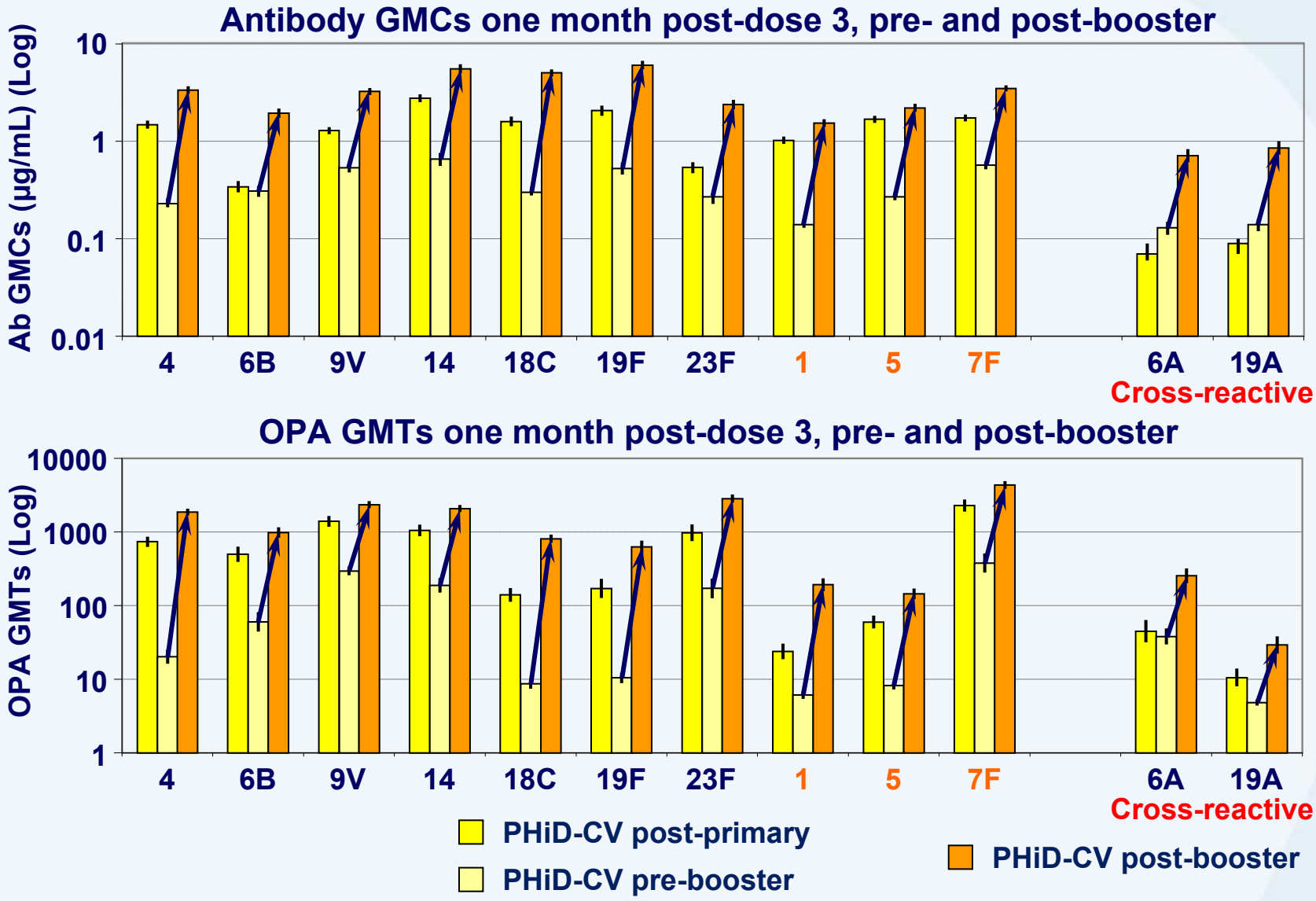
Cross-reactive Serotypes (6A & 19A) (Primary Immunisation)



NCT00307554/NCT00334334

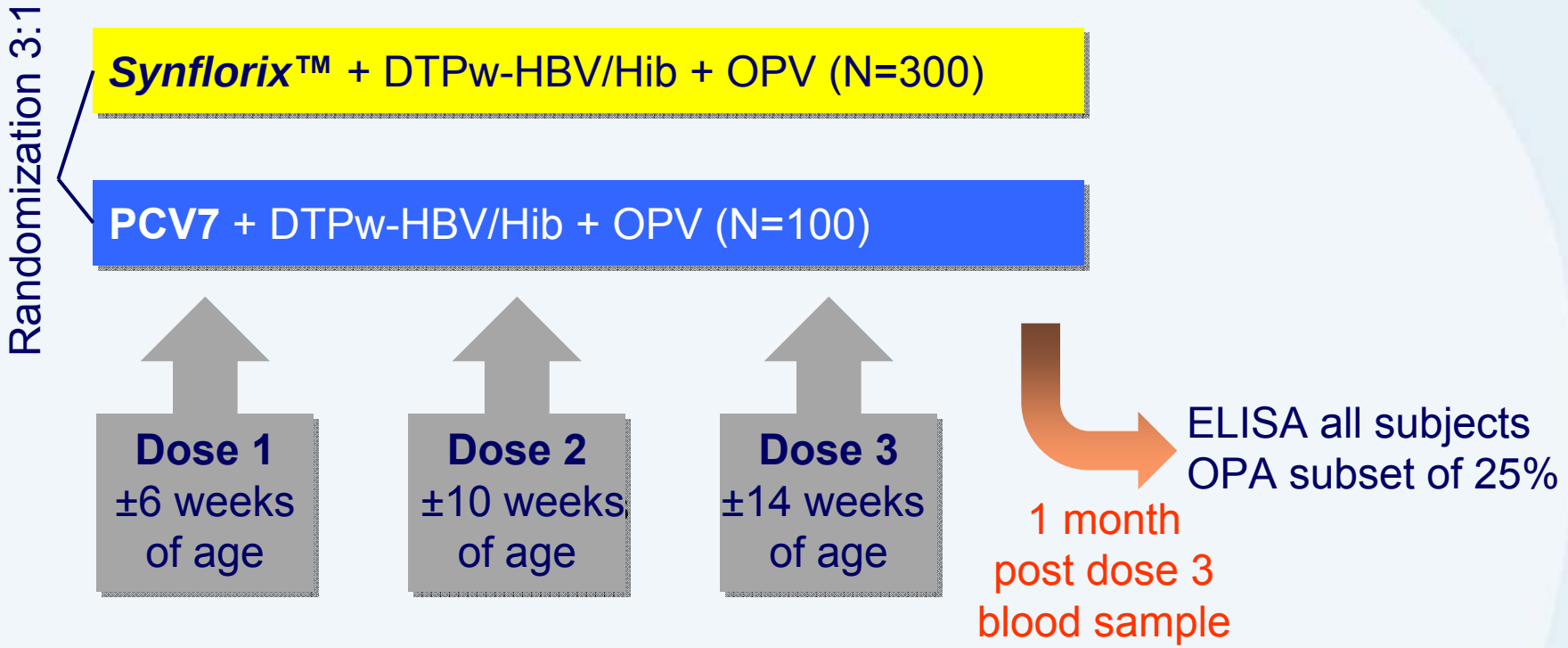
Vesikari T, *et al. Pediatr Infect Dis J* 2009;28:S66–S76.
Wysocki J, *et al. Pediatr Infect Dis J* 2009;28:S77–S88.

Synflorix™ booster responses



Vesikari *et al. PIDJ* 2009:28;S66-76

Synflorix™ co-administration with DTPw-HBV/Hib + OPV



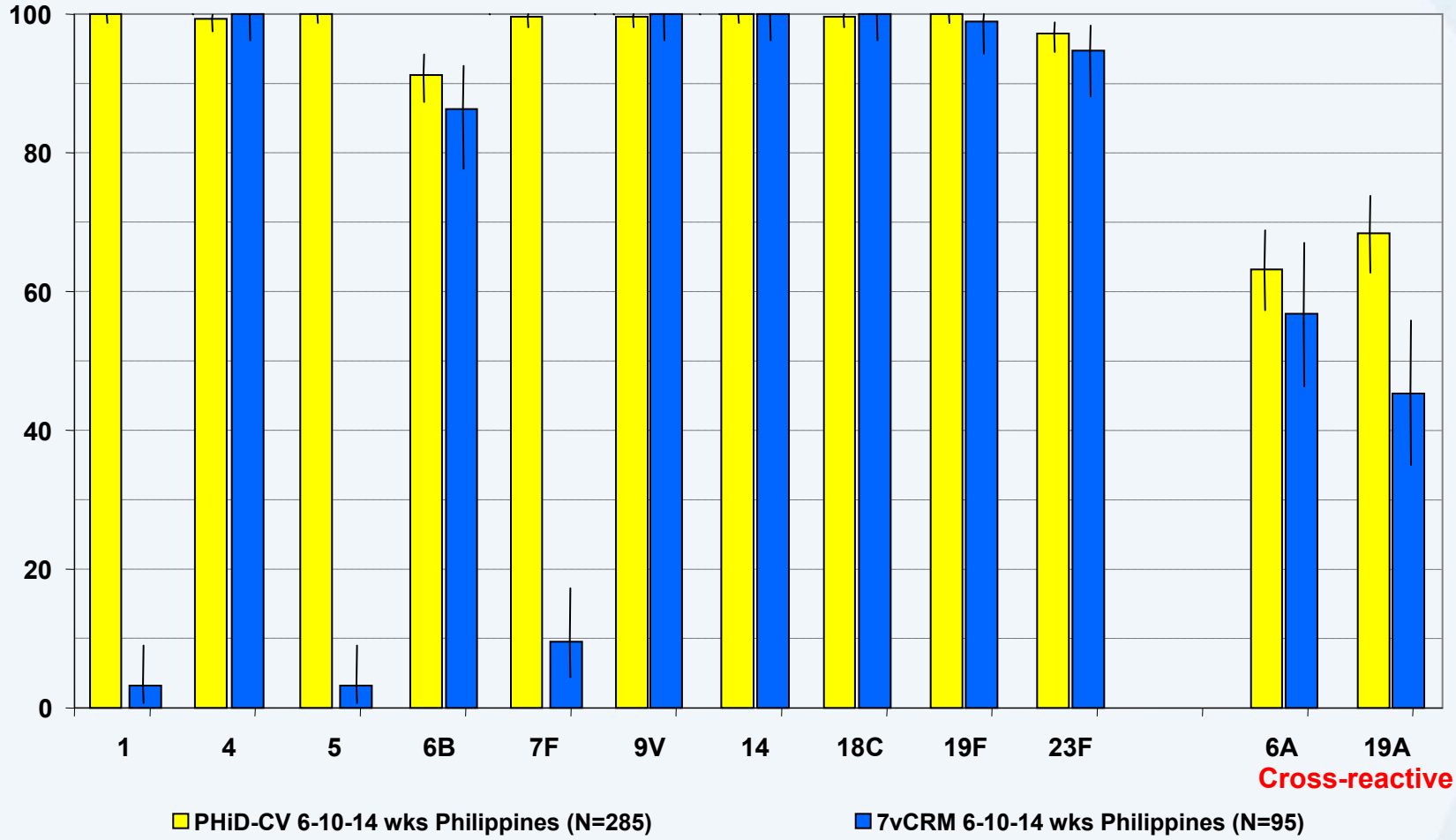
Double blind, controlled trial in Philippines

Study 10PN-PD-DIT-012 (NCT00344318)
Bermal et al. Ped Infect Dis J 2009;28: S89–S96

DTPw-HBV/Hib = *Tritanrix*™ is a trademark of the GlaxoSmithKline group of companies

Immunogenicity of PHiD-CV when co-administered with DTPw

Percentage of subjects with anti-pneumococcal antibody concentration ≥ 0.2 µg/ml one month post-dose 3 (22F-ELISA)

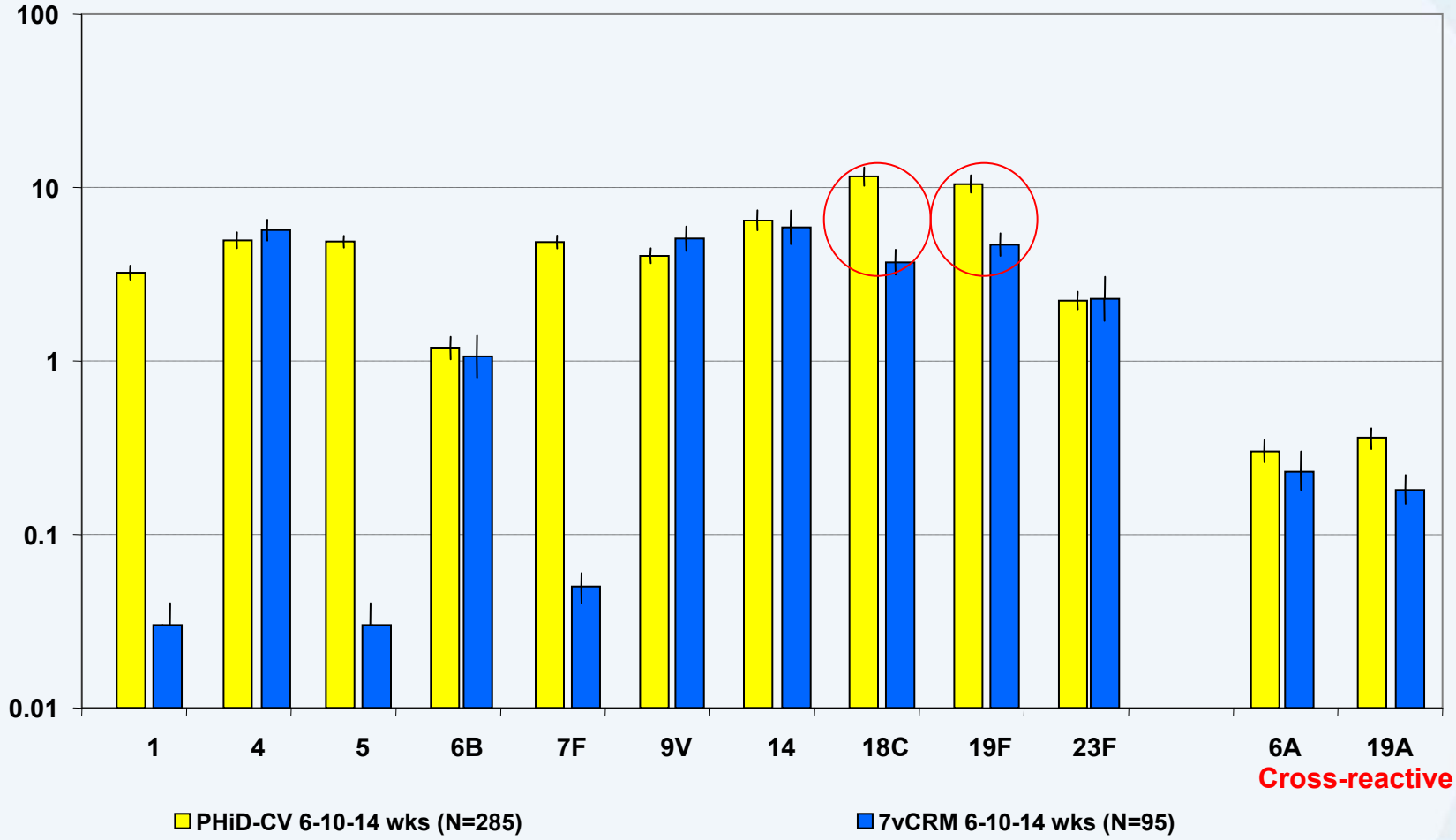


Bermal N *et al*. *PIDJ 2009;28:89-96*

PHiD-CV - Pneumococcal non-typeable *haemophilus influenzae* protein D conjugate vaccine; Synflorix™ ; DTPw-HBV/Hib: *Tritanrix*™-HepB/*Hiberix*™ ; IPV: *Poliorix*™ and OPV: *Polio Sabin*™ *are* trademarks of the GlaxoSmithKline group of companies; **PCV7-CRM:** *Prevenar*™/*Prevnar*™, Wyeth

Immunogenicity of PHiD-CV when co-administered with DTPw

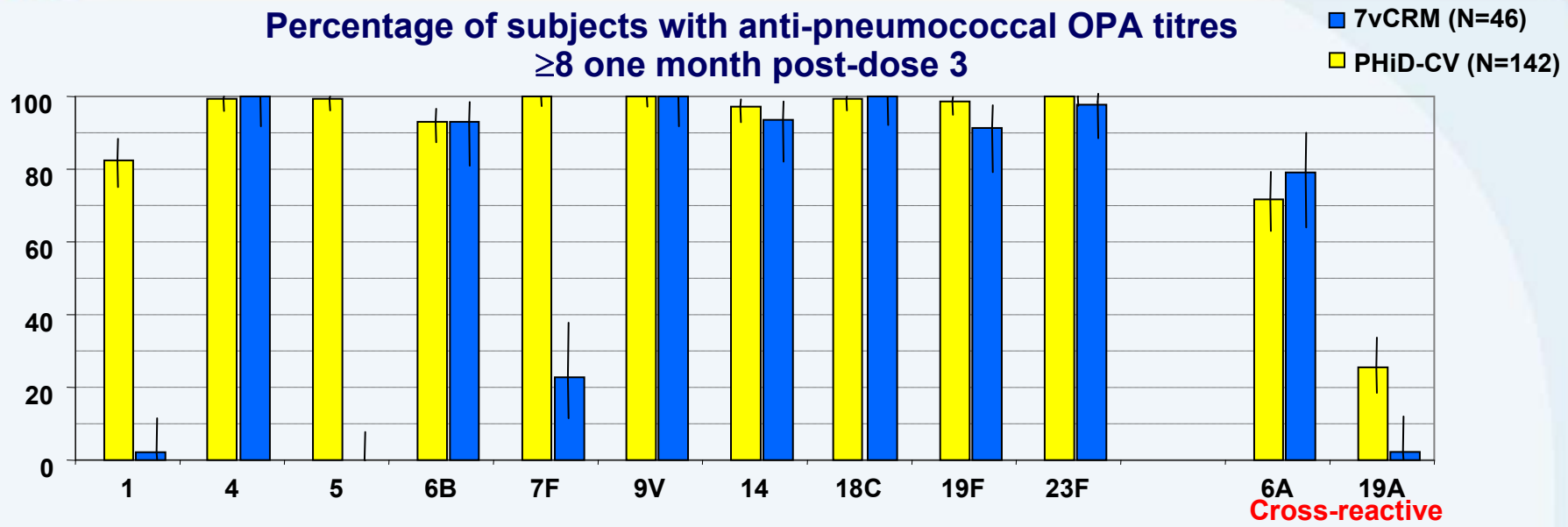
Anti-pneumococcal antibody concentration one month post-dose 3 (22F-ELISA µg/mL)

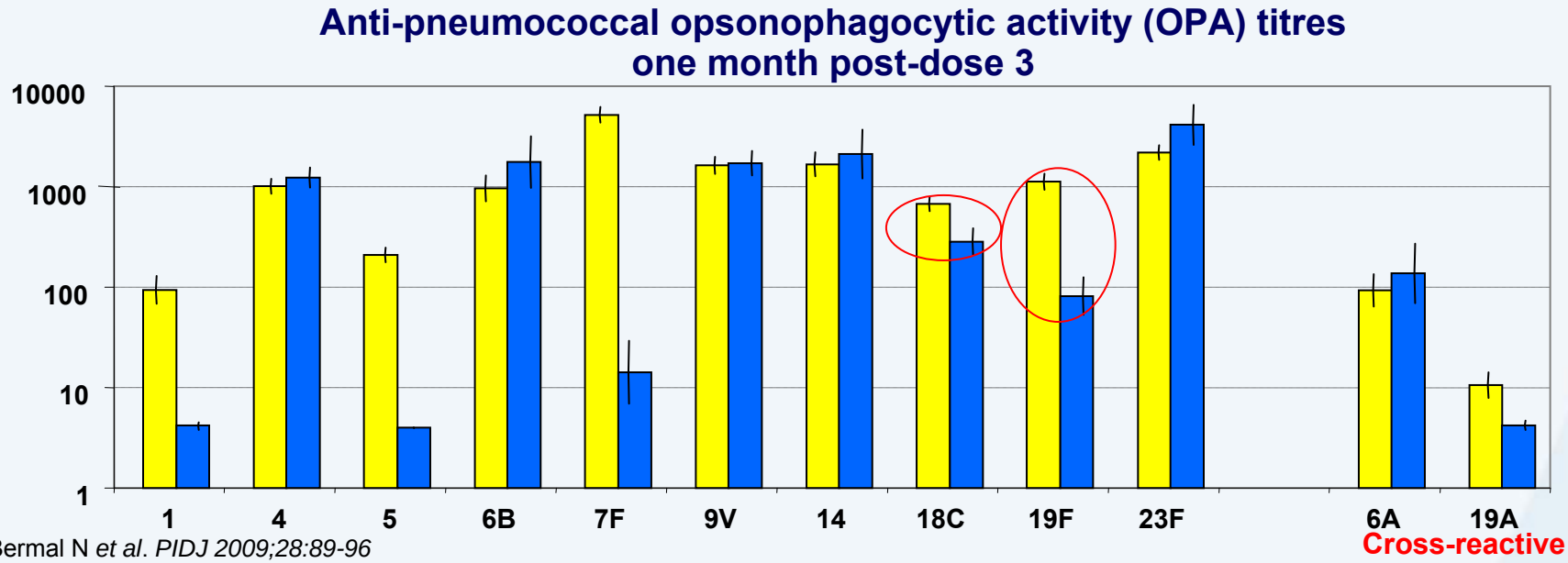


Bermal N *et al*. *PIDJ 2009;28:89-96*

PHiD-CV - Pneumococcal non-typeable *haemophilus influenzae* protein D conjugate vaccine; Synflorix™ ; DTPw-HBV/Hib: *Tritanrix*™-HepB/*Hiberix*™ ; IPV: *Poliorix*™ and OPV: *Polio Sabin*™ *are* trademarks of the GlaxoSmithKline group of companies; **PCV7-CRM:** *Prevenar*™/*Prevnar*™, Wyeth

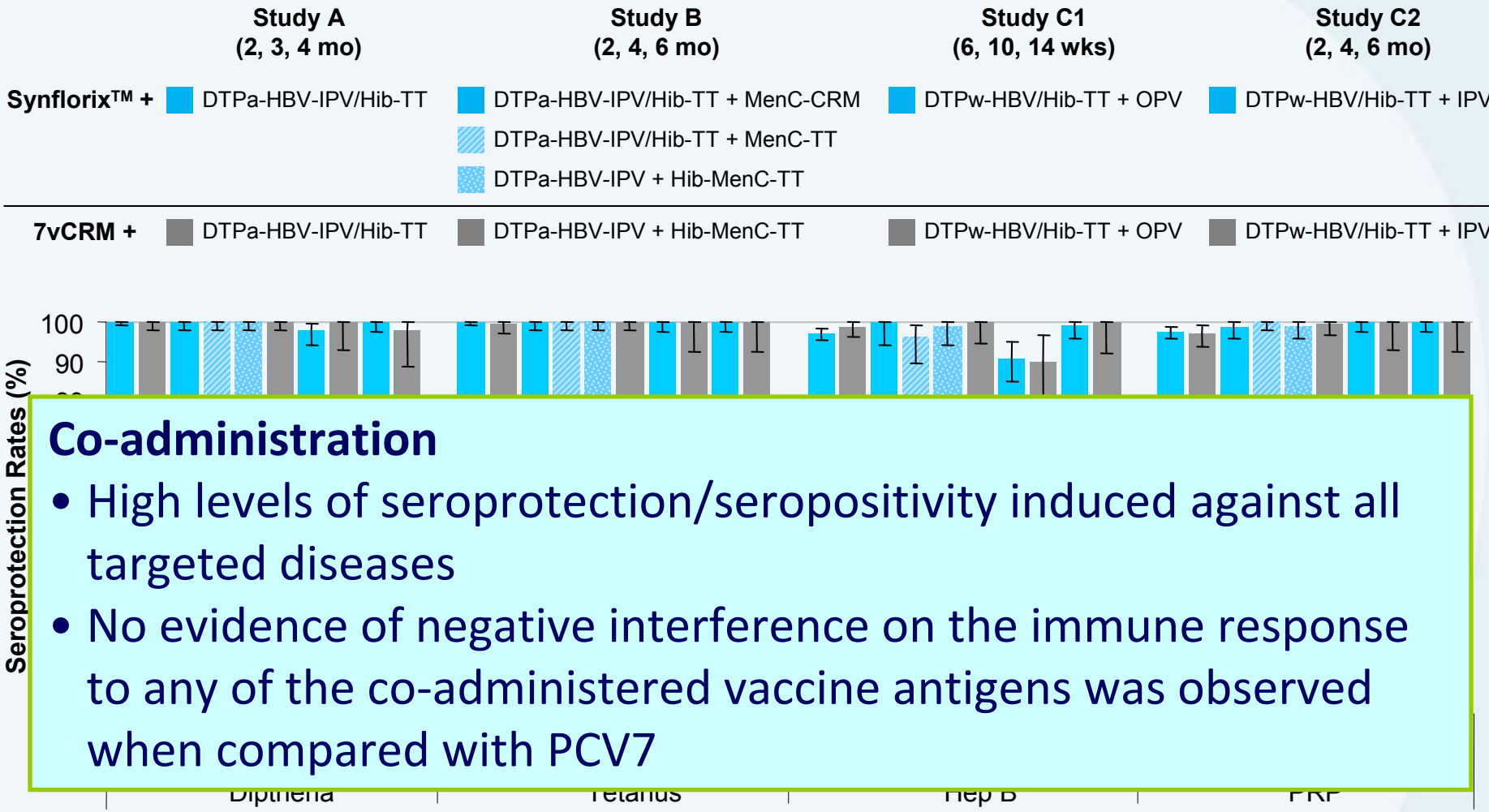
Immunogenicity of PHiD-CV when co-administered with DTPw





Bermal N *et al*. *PIDJ 2009;28:89-96*

Overall post-primary seroprotection rates for D,T, Hep B and Hib antigens



Co-administration

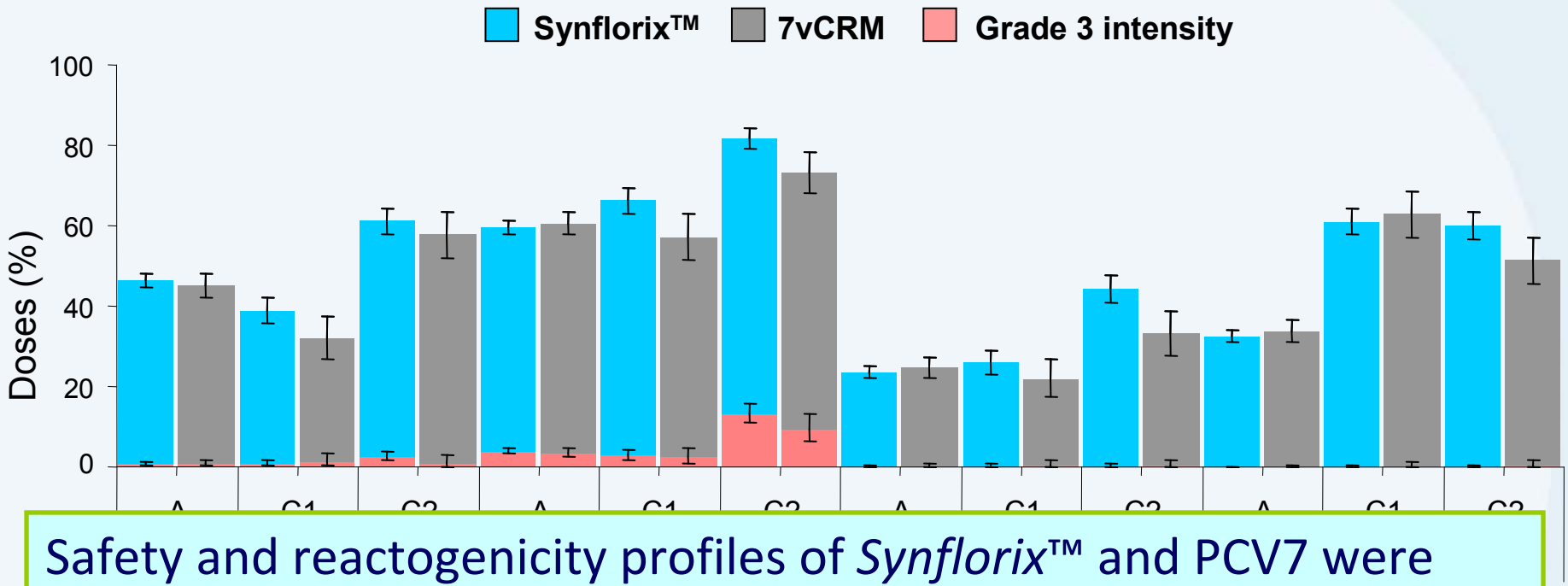
- High levels of seroprotection/seropositivity induced against all targeted diseases
- No evidence of negative interference on the immune response to any of the co-administered vaccine antigens was observed when compared with PCV7

Diphtheria: ELISA cut-off ≥0.1 IU/mL; Tetanus: ELISA cut-off ≥0.1 IU/mL;
Hepatitis B (Hep B): AUSAB cut-off ≥10 mIU/mL; Anti-PRP (Hib): ELISA cut-off ≥0.15 mg/mL

NCT00307554/NCT00334334/NCT00344318

Knuf, *et al. Pediatr Infect Dis J* 2009; 28: S97–S108

Overall per dose incidence (%) of general symptoms after primary dose



Safety and reactogenicity profiles of *Synflorix*™ and PCV7 were within the same range, when administered for primary and booster vaccination in co-administration with other routinely used pediatric vaccines

Synflorix™ is not licensed in China.
Synflorix™ is a trademark of the GlaxoSmithKline group of companies

NCT00307554/NCT00344318

Chevallier, *et al. Pediatr Infect Dis J* 2009; 28: S109–S118

Immunogenicity of *Synflorix*™ in Mexico and Chile

Synflorix™ reactogenicity and immunogenicity

Chile:

- **HAV** + DTPa-HBV-IPV/Hib (N =121)
- ***Synflorix***™ + DTPa-HBV-IPV/Hib (N =119)

Double blind, controlled, 1:1 randomized trial [1]

Mexico:

Synflorix™ + DTPa-HBV-IPV/Hib (N =230)

Open, single arm trial [2]

Dose 1 2 months of age

Dose 2 4 months of age

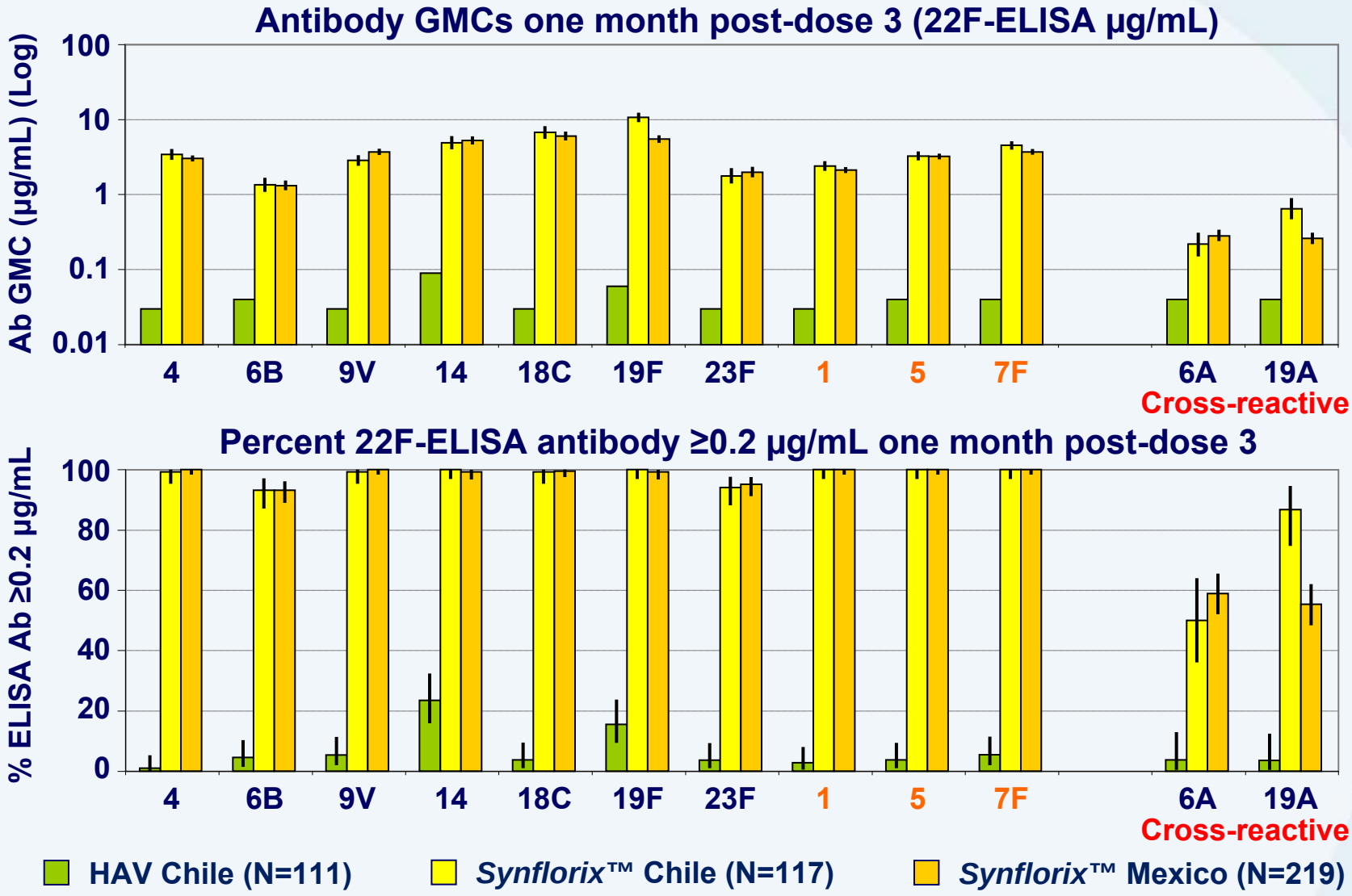
Dose 3 6 months of age

ELISA all subjects
OPA subset of 50%
1 month post dose 3

1. Lagos R. et al. ISPPD6, Reykjavik 2008
2. Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009

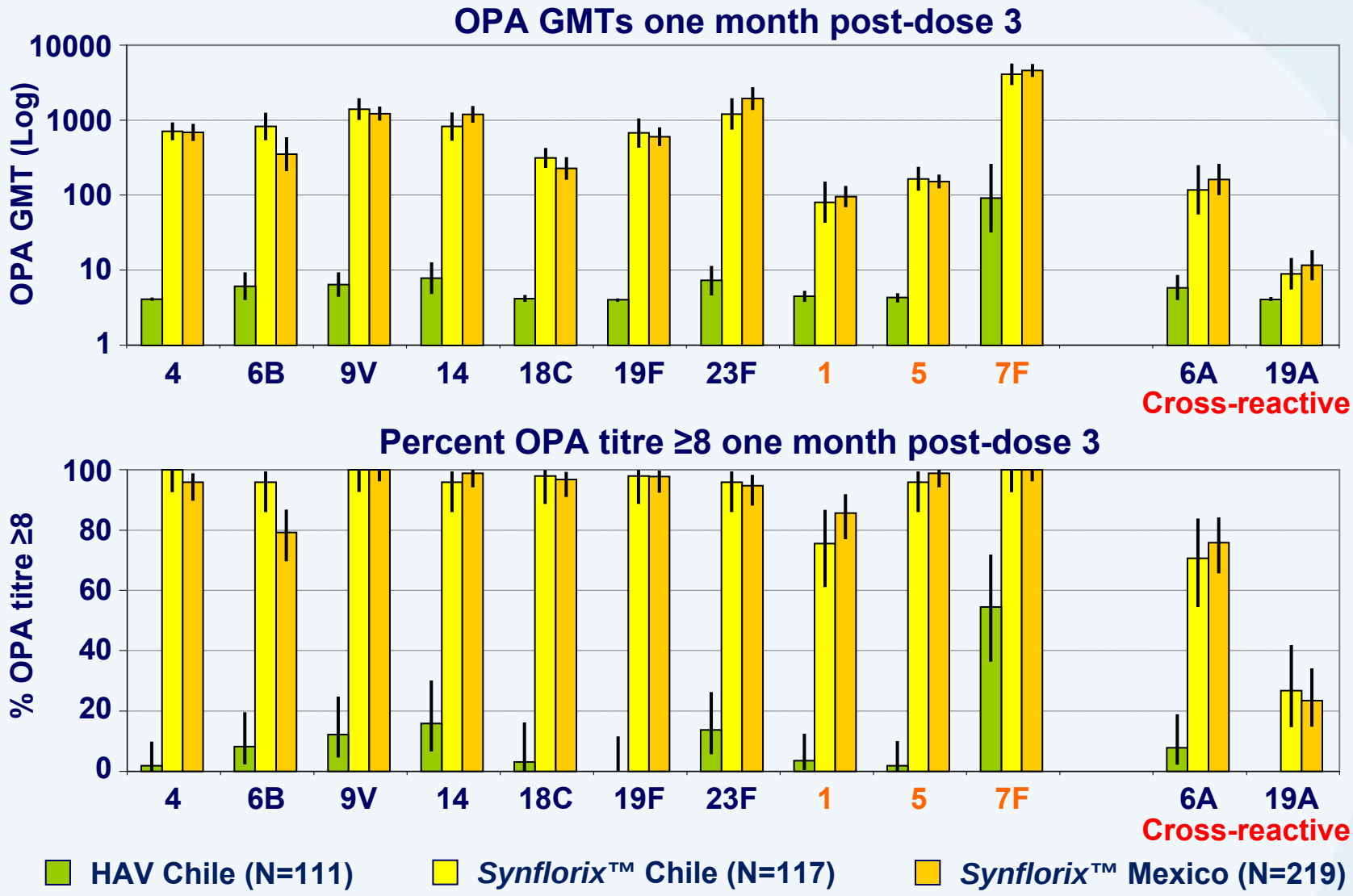
DTPa-HBV-IPV/Hib = *Infanrix*™ *hexa*, HAV = *Havrix*™
are trademarks of the GlaxoSmithKline group of companies

Post-primary immunogenicity of *Synflorix*™ in Mexico and Chile



Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009
GSK Clinical Data [Phase II Clinical Study 10PN-PD-DIT-005 (Chile) & 10PN-PD-DIT-029 (Mexico)] Data on file

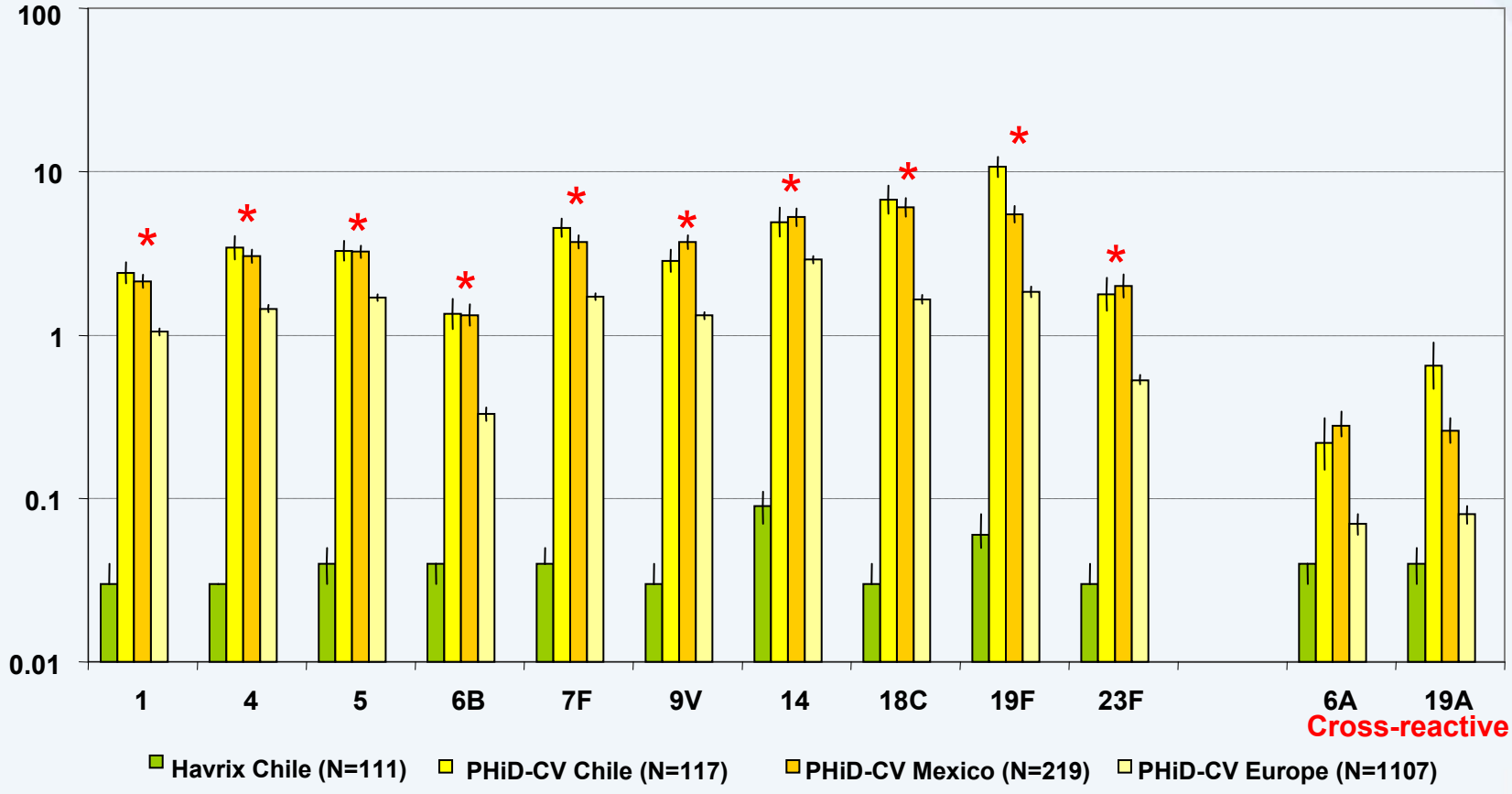
Post-primary immunogenicity of *Synflorix*™ in Mexico and Chile



Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009
GSK Clinical Data [Phase II Clinical Study 10PN-PD-DIT-005 (Chile) & 10PN-PD-DIT-029 (Mexico)] Data on file

Immunogenicity of Synflorix™ in Chile and Mexico vs Europe

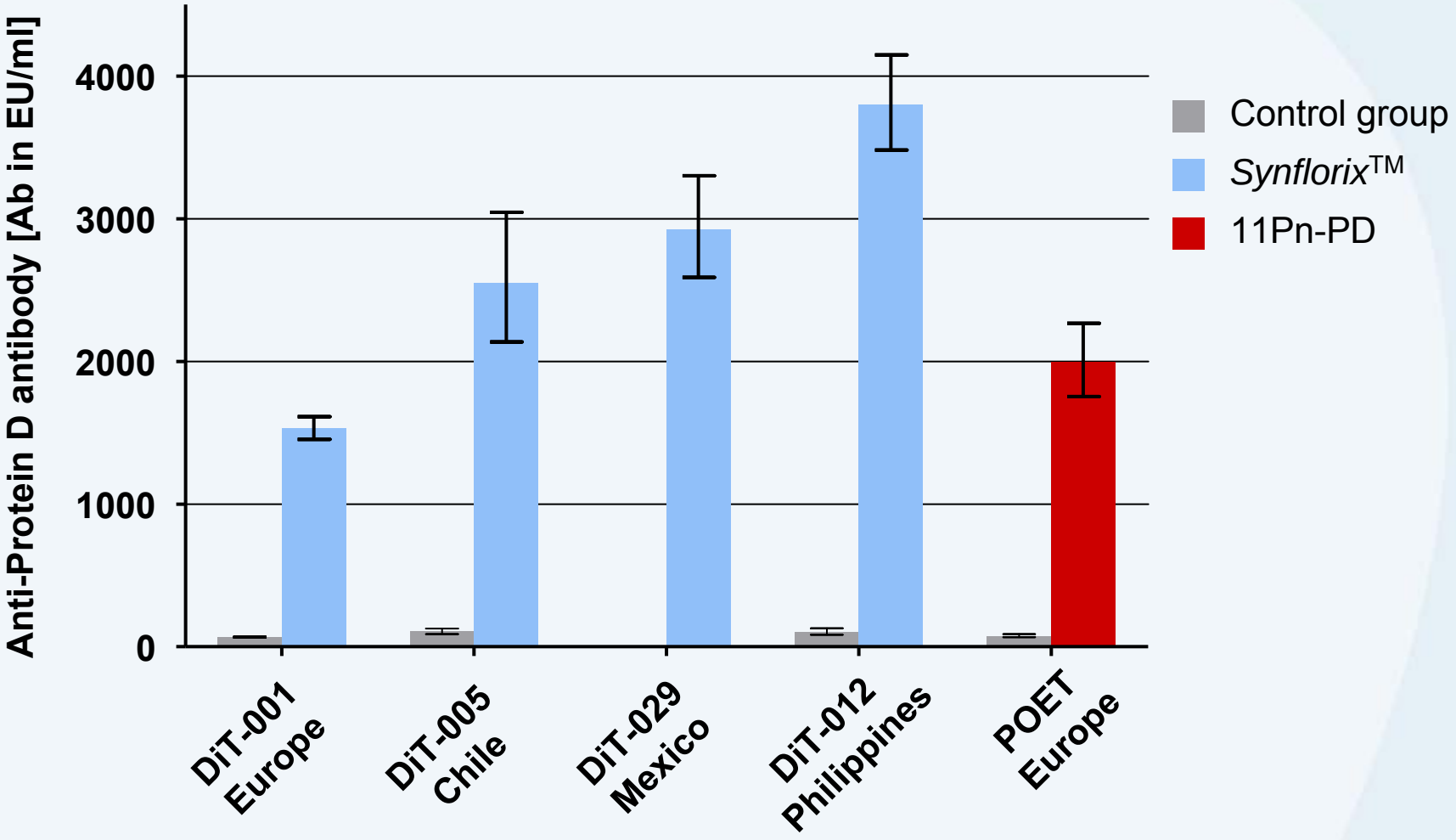
Anti-pneumococcal antibody concentration one month post-dose 3 (22F-ELISA µg/mL)



***statistical significant difference based on non-overlapping 95%CI**

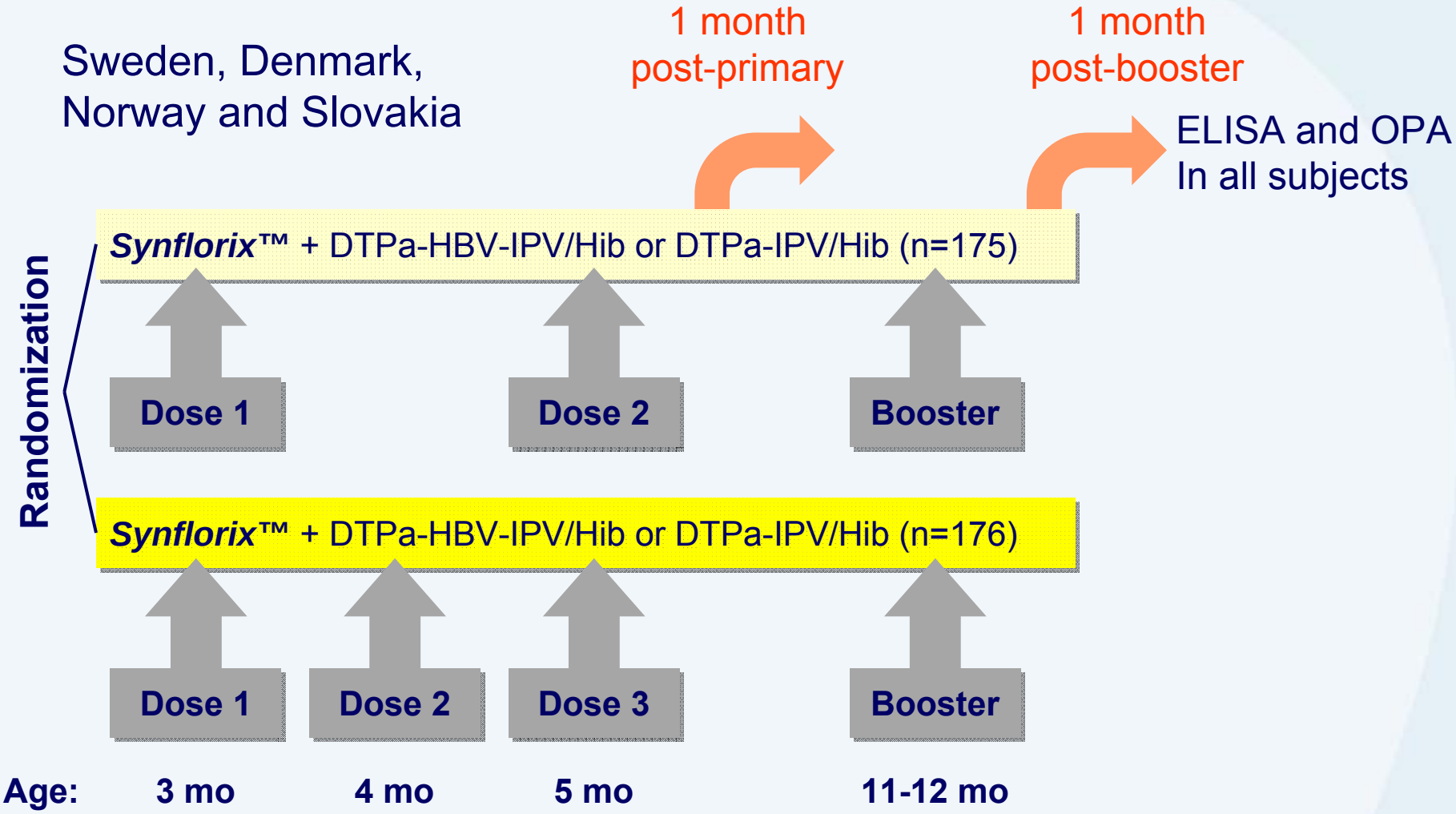
Lagos et al., ISPPD6, Reykjavik, Iceland 2008; Ruiz-Palacios G. et al. SLIPE, Guayaquil 2009; Vesikari et al. PIDJ 2009;28:S66–S76; GSK Clinical Data [Phase II Clinical Study (Chile) 10PN-PD-DIT-005] Data on file; GSK Clinical Data [Phase II Clinical Study (Mexico) 10PN-PD-DIT-029] Data on file

Synflorix™ anti-Protein D responses compared with POET



Adapted from Vesikari T, et al. *Ped Infect Dis J* 2009:28(4), S66-76 ; Lagos R, et al., ISPPD-6 2008, Reykjavk, Ruiz-Palacios G, et al. SLIPE 2009, Guayaquil; Bermal N, et al. *Ped Infect Dis J* 2009:28(4), S66-76 Prymula R, et al., Lancet 2006

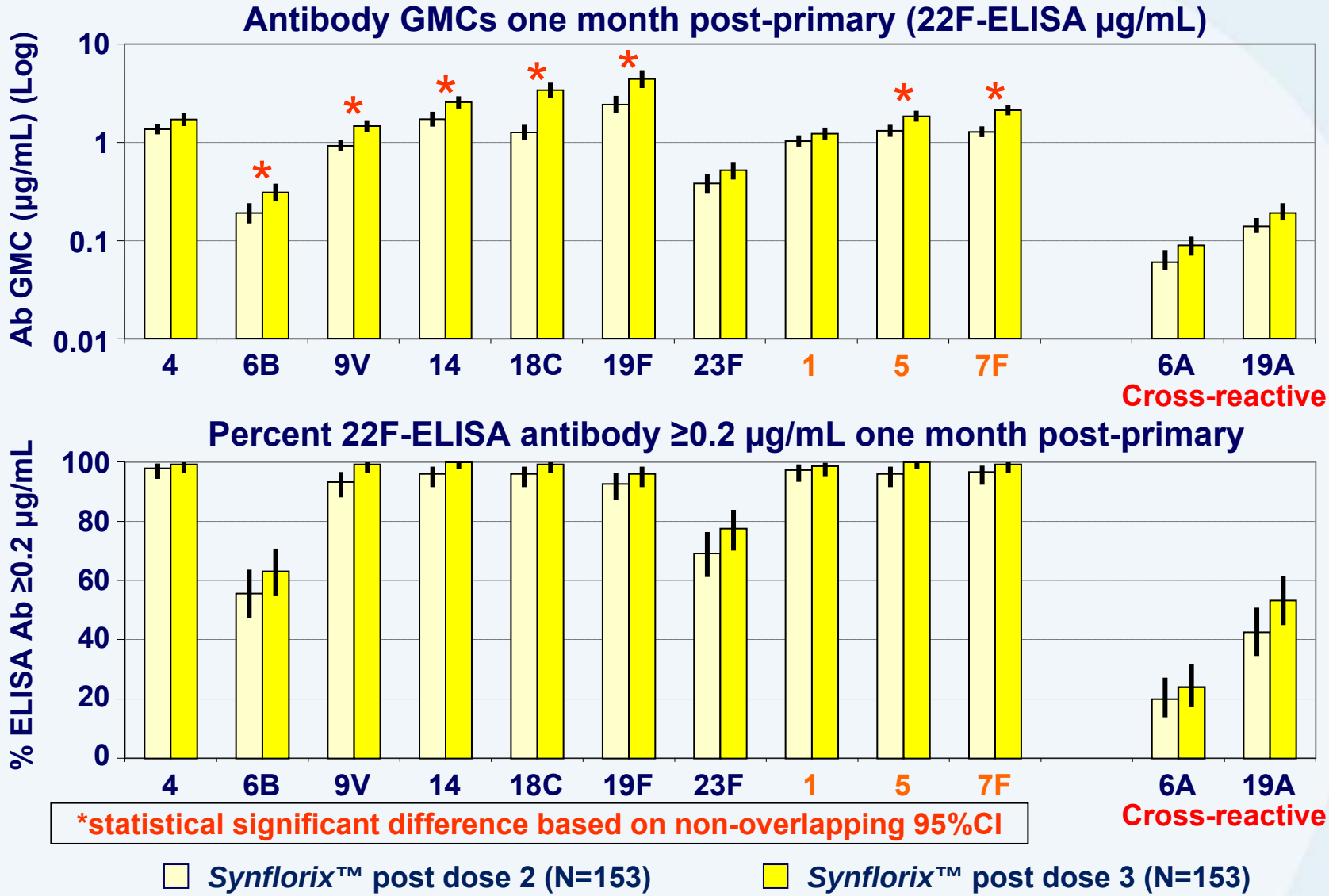
Synflorix™ immunogenicity following 2-dose priming



Study 10PN-PD-DIT-002 (NCT00307034)
Silfverdal S. et al., PedIatr Infect Dis J, 2009; 28: e276-82

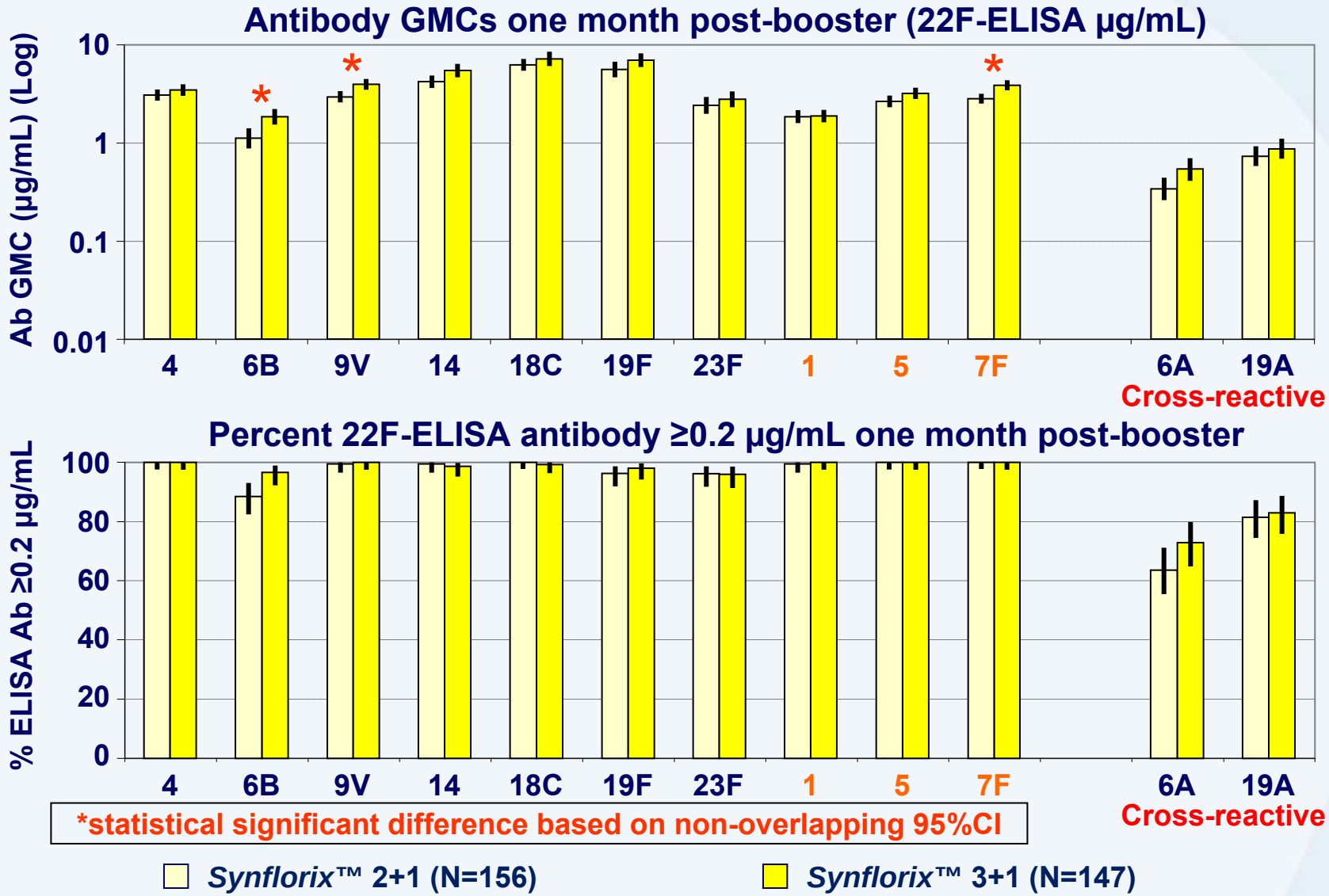
DTPa-HBV-IPV/Hib = Infanrix™ hexa (Sweden and Slovakia);
DTPa-IPV/Hib = Infanrix™ IPV-Hib (Denmark and Norway)
are trademarks of the GlaxoSmithKline group of companies

Synflorix™ 2+1 immunogenicity (Antibodies post dose 2 vs post dose 3)



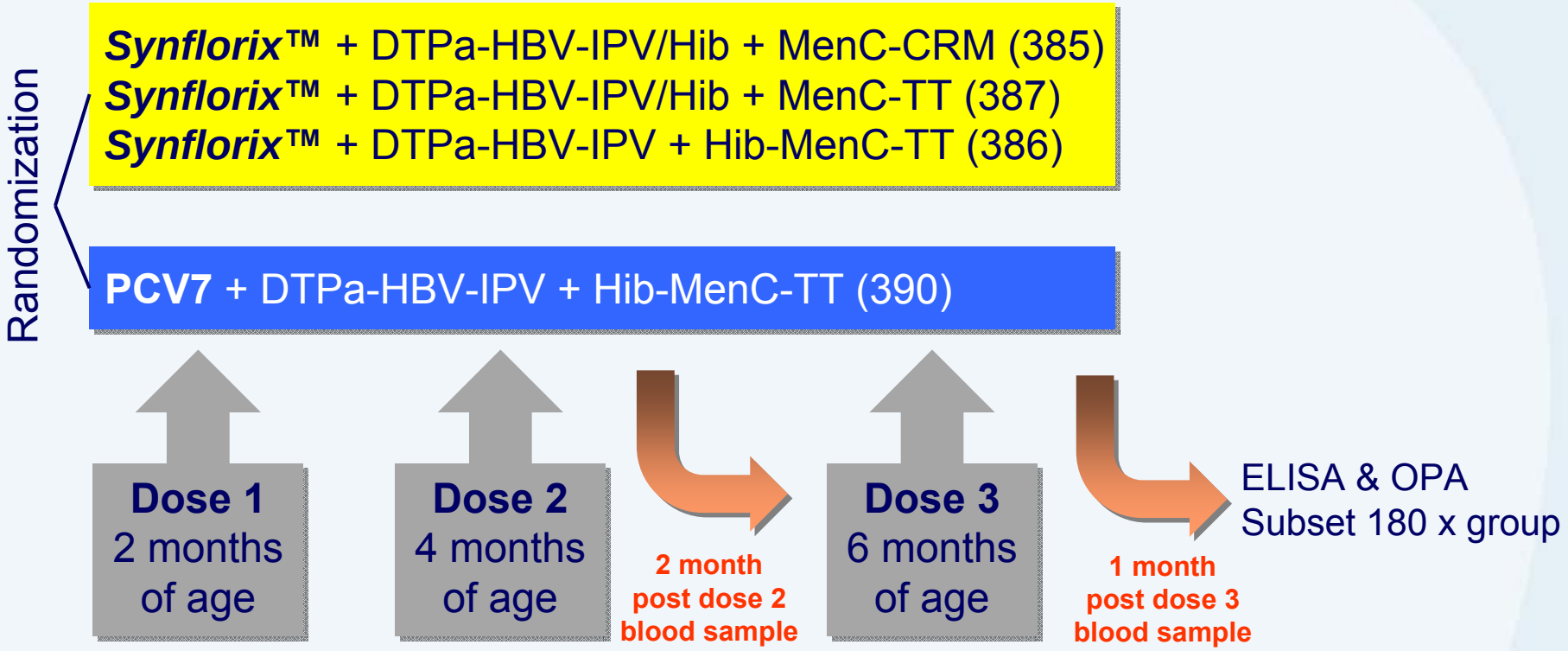
Silfverdal S. et al., Pedlatr Infect Dis J, 2009; 28: e276-82

Synflorix™ 2+1 immunogenicity (Antibodies post-booster 2+1 vs 3+1)



Silfverdal S. et al., Pedlatr Infect Dis J, 2009; 28: e276-82

Synflorix™ immunogenicity following 2-dose priming



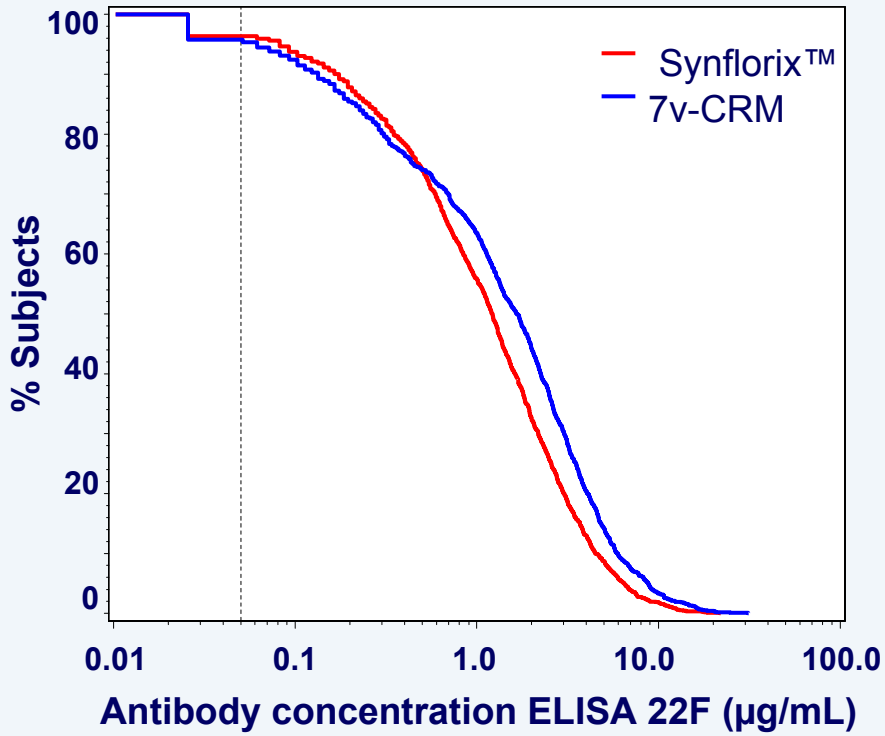
Open, controlled trial in Germany, Poland, and Spain

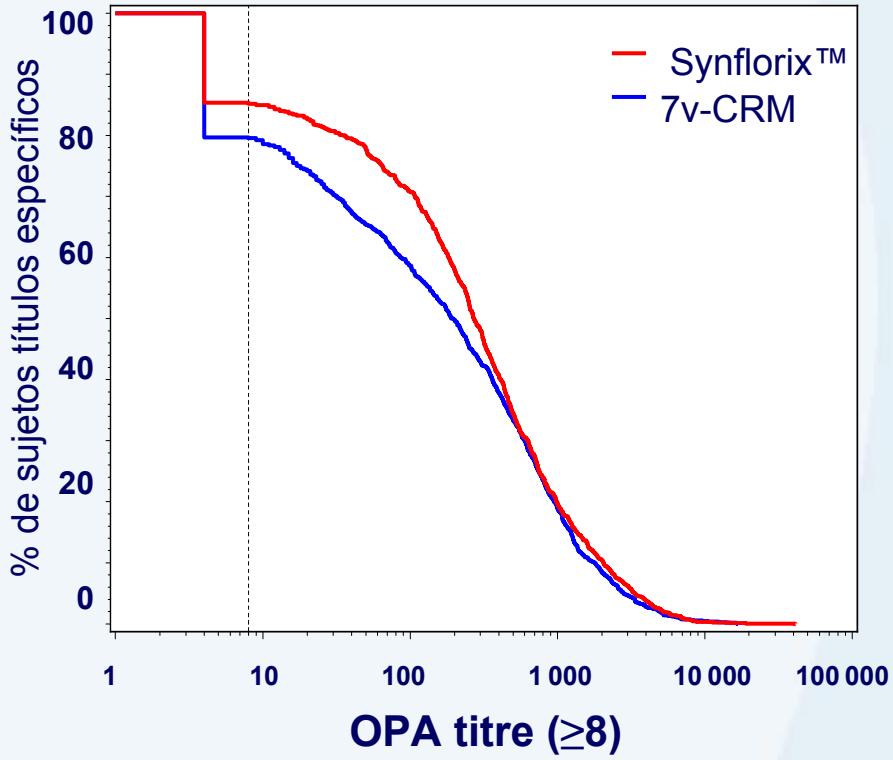
Study 10PN-PD-DIT-011 (NCT00334334)
Wysocki J. et al. Pediatr Infect Dis J 2009;28:S77–S88

DTPa-HBV-IPV/Hib = *Infanrix*™ *hexa* is a trademark of the GlaxoSmithKline group of companies

Antibody cumulative reverse curves post 2-dose

Aggregated response post 2-dose for the 7 common serotypes





Study 10PN-PD-DIT-011 (NCT00334334)
Wysocki J. et al. Pediatr Infect Dis J 2009;28:S77–S88

Conclusions

- *Synflorix*™ meets WHO immunological licensure criteria: ELISA - OPA - Immunological memory and has been licensed based on comparative immunogenicity data versus 7vCRM.
- Across the clinical development program, *Synflorix*™ was shown to be highly immunogenic, especially in Latin American children:
  - High antibody concentrations and functional OPA titers are induced against pneumococcal serotypes contained in the vaccine
  - Antibodies and OPA activity against **cross-reactive 6A and 19A serotypes** could also be measured
  - *Synflorix*™ can be co-administered with other routinely used pediatric vaccines according to a wide range of immunization schedules
  - High antibody concentrations are induced against the carrier protein D
- Clinical trial data from 11-valent prototype demonstrates **efficacy against NTHi** (35% reduction)[1]
- Synflorix™ has been selected for the UMV program of Brazil and selected regions of Canada, Australia, and Sweden.
- Synflorix™ is the first pneumococcal conjugated-vaccine **pre qualified by WHO.**

1. Prymula R *et al*. *Lancet* 2006;367:740–48