Combination Vaccine within Sanofi Pasteur
Brief History and focus on Pentaxim experience

Calmet J. September 2011

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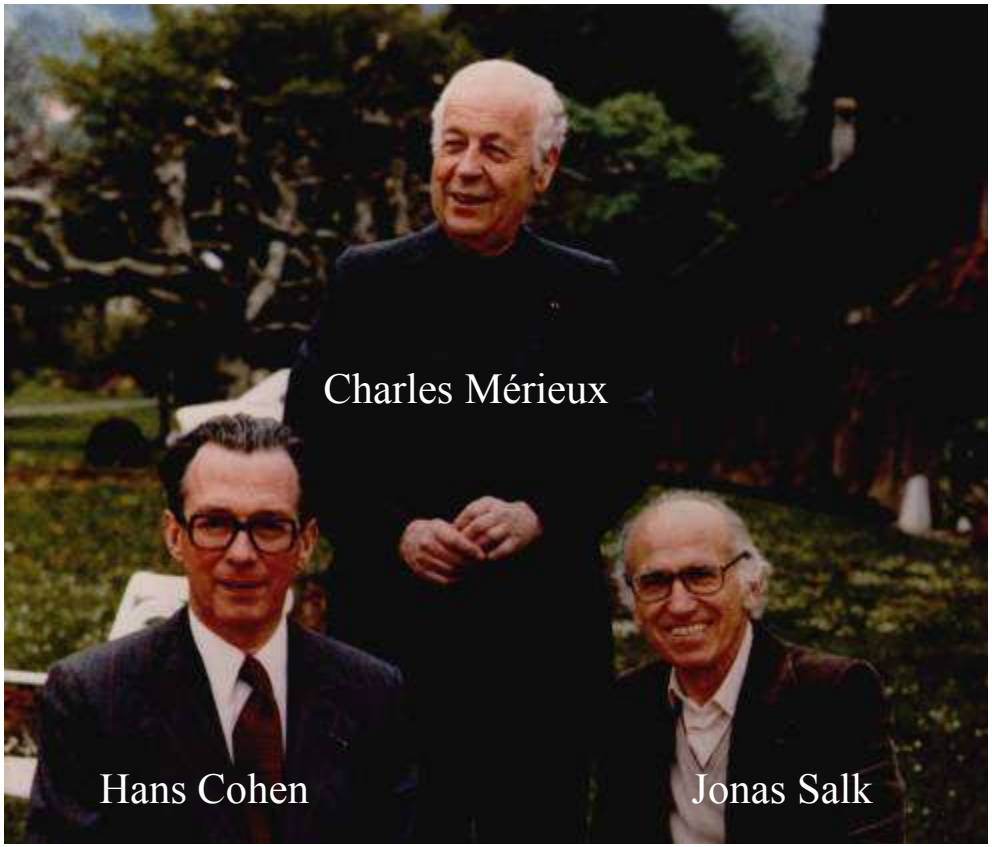
The Sanofi Pasteur combination approach is enrooted in Polio, through Injectable Polio

- **The problem in 1975**
  1. **Safety of OPV in question**
  2. **Efficacy in routine immunization with 3 OPV sub-optimal in the tropics**

- **The challenge for IPV**
  1. **Industrialize IPV production**
  2. **Standardize antigenicity (test in vitro)**
  3. **Demonstrate immunogenicity and efficacy both in developed and developing countries**
  4. **License new product in all countries**

The trio that made it possible
Veyrier-du-Lac, 1978



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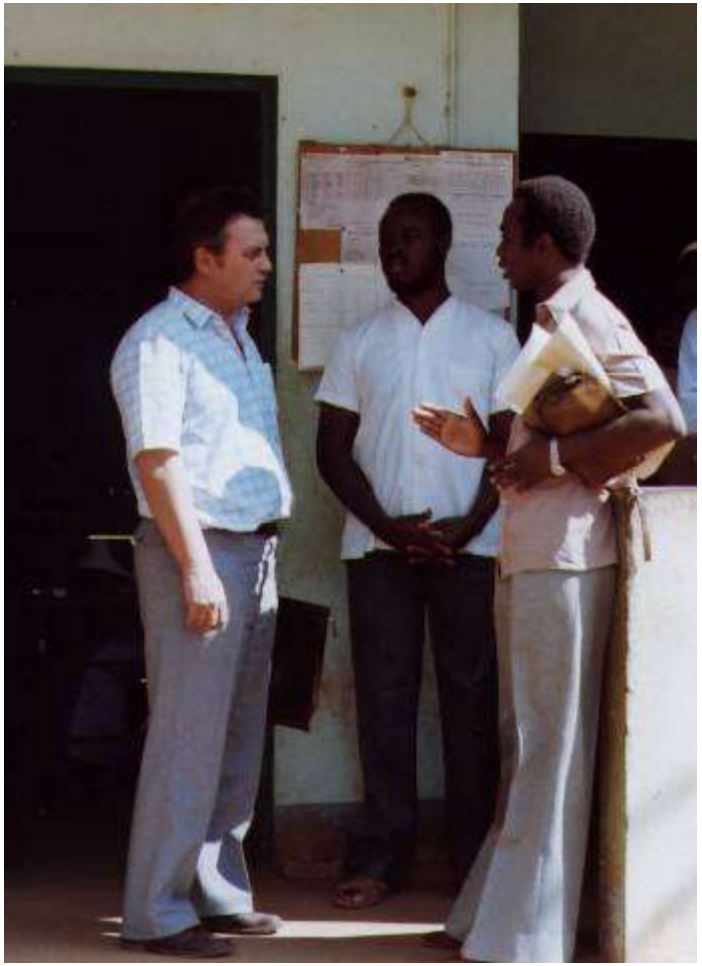
Clinical Studies were conducted in West Africa

1 – Studies of immunogenicity of IPV of different potency, adsorbed and non-adsorbed

Poliovirus Vaccines	Type 1	Type 2	Type 3
Adsorbed & Non-adsorbed Control : TT	320	32	64
	80	8	16
	20	2	4
	5	0,5	1

2 – Studies of immunogenicity of 40-4-16 followed by 40-8-32 D-Ag units for type 1, 2 and 3 respectively

3 – Studies of immunogenicity, effectiveness and efficacy in Kolda, Sénégal



Dr. AL. Van Wezel and Dr. A. Kaboré in Burkina Faso on an AMP mission for FAIR

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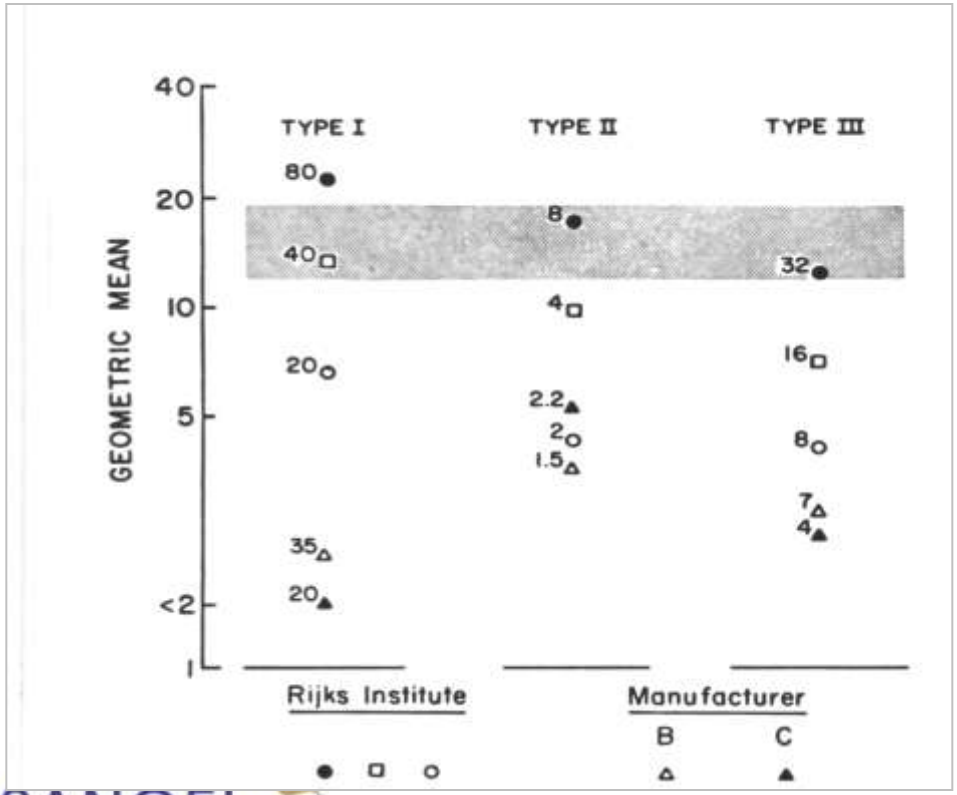
Studies were conducted in humans to determine the best antigen dosage

- Killed Poliovirus antigen titration in humans, J. Salk, H. Cohen, A.L.van Wezel, P. Stœckel & al. in 15th IABS Congress, Dev. Biol. Stan., vol 41, pp.119-132 (S. Karger, Basel, 1978)
- Antigen content of Inactivated Poliovirus Vaccine for use in One- or Two-dose Regimen J. Salk, P. Stœckel, AL van Wezel, K. Lapinleimu, G van Steenis In Annals of Clinical Research 14: 204-212, 1982



40, 8, 32 D-antigen unit/dose for type 1, 2 and 3 respectively

Finland inactivated poliovirus study

Geometric mean antibody titers induced by a first dose of vaccines of different D-Ag U content: comparison of vaccines prepared by RIVM and manufacturers B & C

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Clinical efficacy of a new, enhanced-potency, inactivated poliovirus vaccine was demonstrated during an outbreak of paralytic poliomyelitis in Senegal in 1986-87

- Enhanced-potency vaccine (eIPV): 40, 8, 32 D-antigen unit/dose for type 1, 2 and 3 respectively
- The outbreak provided an opportunity to conduct a vaccine efficacy study of e-IPV in the Kolda region where it had been used since 1980. 89 cases, confirmed to have Poliomyelitis, were enrolled in a case control study, 5 matched controls being obtained for each case

Estimates of efficacy of e-IPV* in Kolda (Sénégal)	
1 dose *vs* 0 doses	36% (0% - 67%)
2 doses *vs* 0 doses	89% (62% - 97%)

The Lancet, April 23, 1988

*AMP began a pilot vaccine delivery program in the Kolda region of Senegal in 1980. AMP used the quadruple DTwP-eIPV vaccine prepared by Institut Mérieux. The formulation for Polio type 1,2 and 3 was respectively 40-4-16 D-antigen units per dose in 1980 & 1981, and 40-8-32 thereafter. The vaccine was delivered by mobile team using jet injectors.

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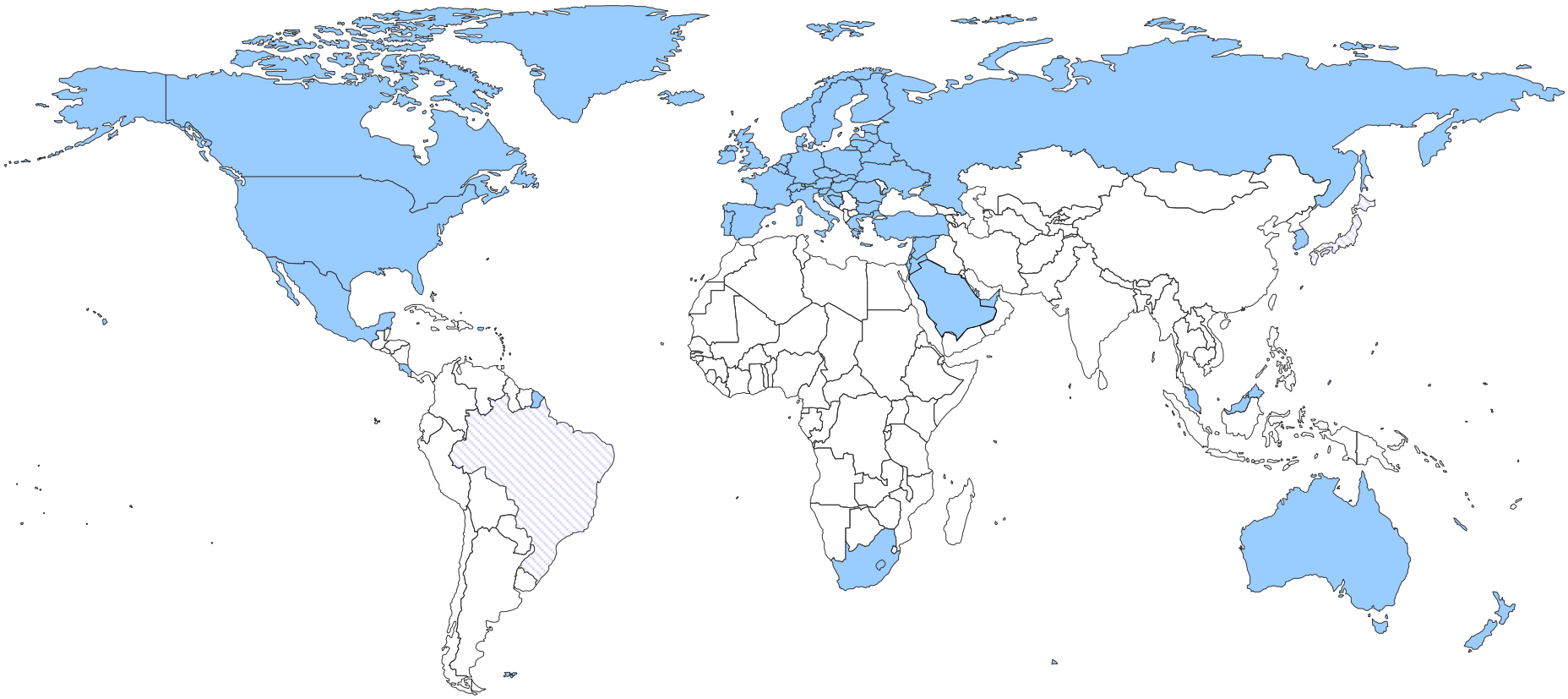
56 countries have already introduced IPV in their routine pediatric public vaccination schedule



Countries that have introduced IPV as of January 2011

Countries that plan to introduce IPV

Sources: WHO data + sanofi pasteur internal analysis

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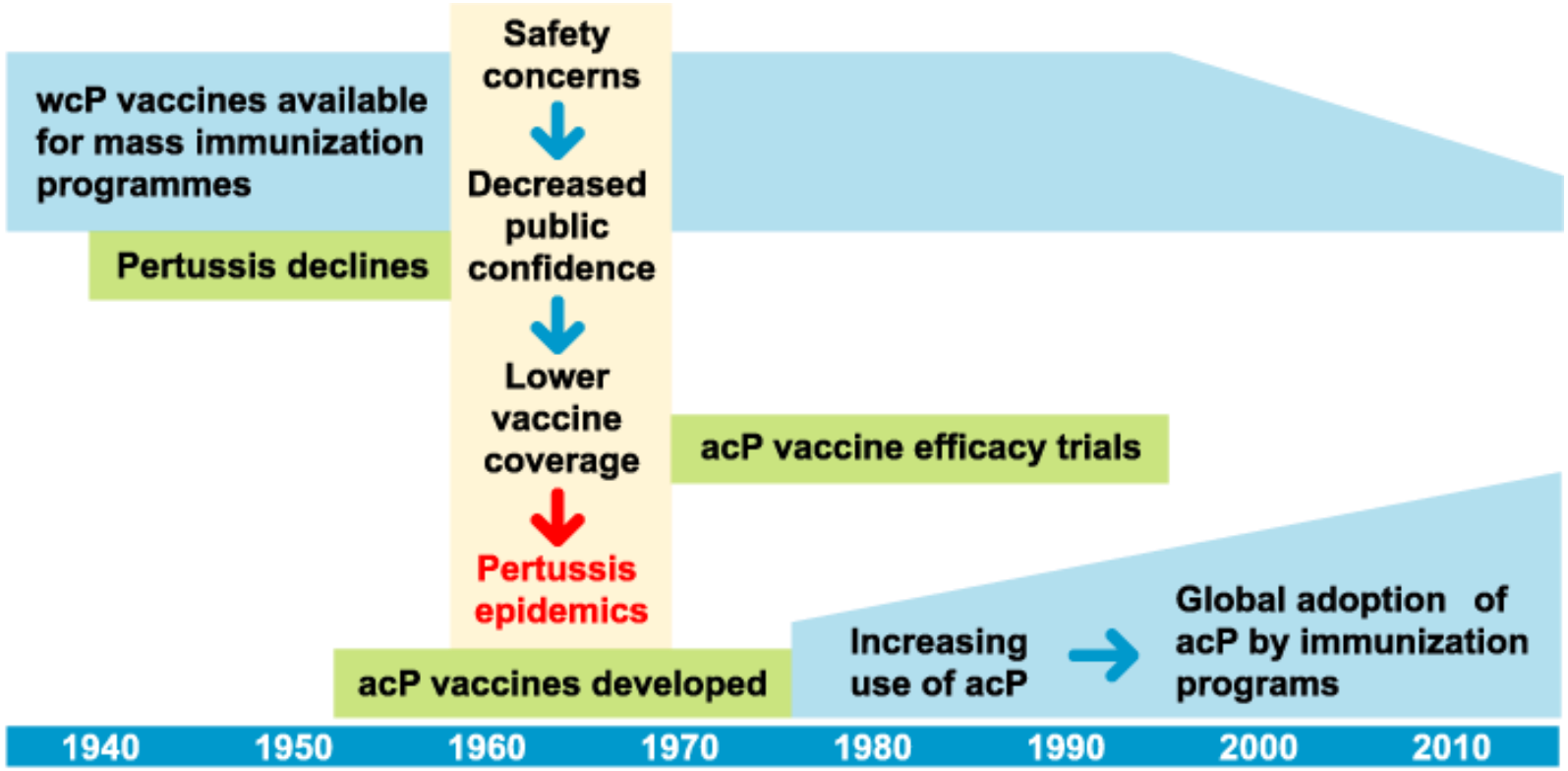
The base of combination vaccines (DTP) is affected by a technological shift: From whole cell to Acellular Pertussis

Advantages of acP Vaccines Led to Increased Use and Increased Compliance



[1] Adapted from Orenstein WA. In: Brown et al. *Dev Biol Stand*. Basel 1997

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Since nearly 30 years, sanofi pasteur has developed a wide range of IPV-containing vaccines

Sanofi pasteur marketed IPV containing vaccines as of May 2011

Vaccine	Product name	1st license	Volume distributed since 1st licensure	Countries were registered
IPV	Imovax Polio	France, 1982	Over 272 M doses	Over 90 countries
DTacP-IPV	Tetraxim	Sweden, 1998	Over 15M doses	Over 80 countries
	Quadracel*	Canada, 1997	Over 6,5M doses	Australia, Canada, Mexico, New Zealand
DTacP-IPV//Hib	Pentaxim	Sweden, 1997	Over 100M doses	Over 100 countries
	Pentacel*	Canada, 1997	Over 55M doses	North America
DTacP-IPV-Hib	Pediacel	Canada, 2000	Over 30M doses	Over 45 countries
TdacP-IPV	Adacel Polio	Germany, 2001	Over 18M doses	25 countries
Td-IPV	Revaxis	Germany, 1999	Over 65M doses	54 countries

*mrc5-IPV containing vaccines

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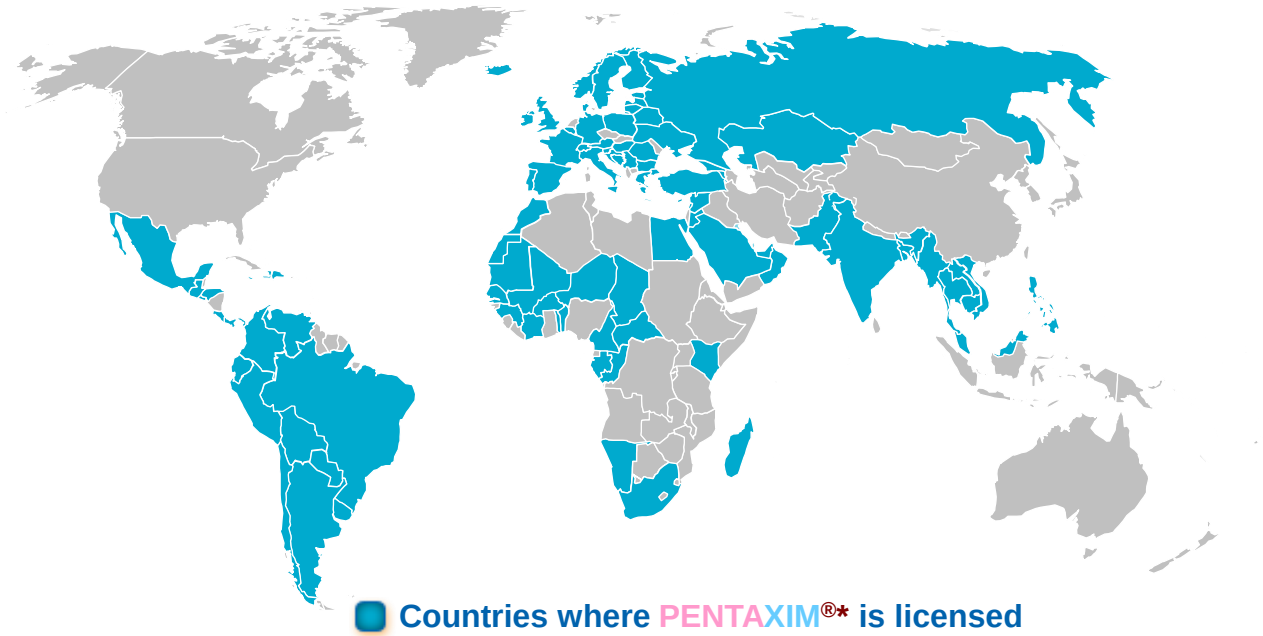
PENTAXIM® Experience

- 1st licensed in Sweden in 1997
- Licensed in >100 countries
- >110 Million doses distributed to date



*** Licensed under the trade name PENTAVAC® in the European Union**

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PENTAXIM® : Increasing use in National Immunization Programs

- Pentaxim® is used Private markets of 80 countries around the world.
- Past / current National Immunization Program (NIP) / Public market use includes:
  - Austria, Belgium, France, Germany Iceland, Italy, Ireland, Spain, Portugal, Nordic countries
  - Estonia, Latvia, Lithuania, Romania, Slovenia, Ukraine
  - Dutch Antilles, French Polynesia, French Guiana, Guadeloupe, Martinique, Mayotte, New Caledonia
- Recent Pentaxim® Public Markets introductions has enabled the switch from wcP/OPV to acP/IPV:
  - Mexico
  - Turkey
  - Malaysia
  - South Africa
- Planned expanded use of Pentaxim® in NIP in various regions of the world

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PENTAXIM® has been Extensively Studied in Numerous Immunogenicity and Safety Trials around the Globe

- PENTAXIM®: administered in primary series during the first year of life has been investigated under numerous schedules:
  - **2-3-4 months** in **5 studies** in France, Turkey and China
  - **2-4-6 months** in **4 studies** in France, Sweden, Chile and Thailand
  - **3-4-5 months** in the study in China
  - **3-5 months** in the study in Sweden
  - **EPI schedule (6-10-14 weeks)** in India, the Philippines and S. Africa

- In addition, PENTAXIM®
  - Assessed in comparison to administration of separate vaccines in 3 studies
  - Co-administration of Pentaxim with Hep B vaccines was assessed in 6 studies
  - Booster administered in the second year of life investigated in most studies

() Langue et al. *ESPID*, 1997 () Mallet et al. *ESPID*, 1997 () Reinert. *ESPID*, 1997 () Kanra et al. *Vaccine*, 2000 () Li et al. 13th *APCP*, 2009 () Carlsson et al. *PIDJ*, 1998 () Lagos et al. PIDJ, 1998 () Thisyakorn et al. *SA J TMPH*, 2010 () Dutta et al. 3rd *APCP*, 2009
() Madhi et al. 13th *ICID*, 2008 () Capeding et al. *Bull WHO*, 2008;86(6) () SP. Study A181 IVBI/A3R08396 ()

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Immunogenicity of PENTAXIM®

Primary vaccination

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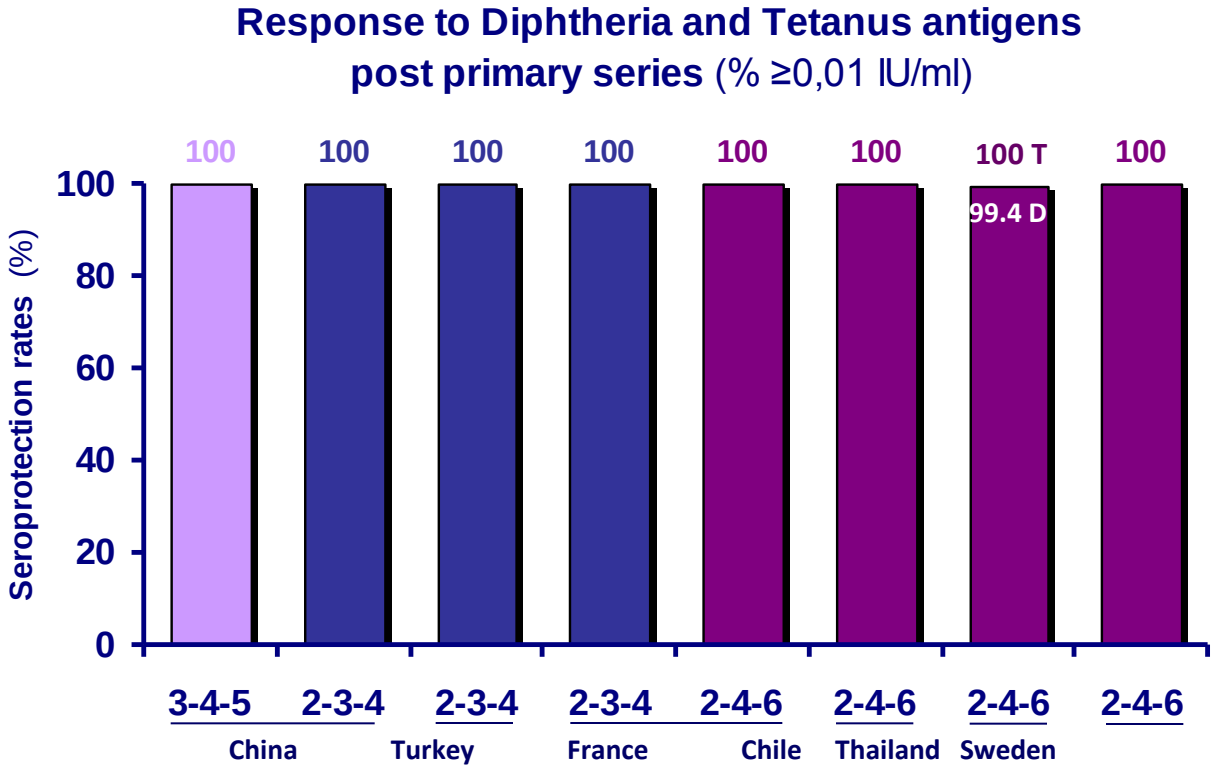
PENTAXIM® Provides High D & T Immune Responses Across Countries and with All Routine Vaccination Schedules

- All infants achieved seroprotection to diphtheria and tetanus antigens ≥0.01 IU/ml regardless of vaccination schedule



() Li et al. 13th Asian Pacific congress of Pediatrics, 2009 () Reinert. *ESPID*, 1997 () Mallet et al. *ESPID*, 1997
() Carlsson et al. *PIDJ*, 1998;17(11) () Lagos et al. PIDJ, 1998;17(4) () Thisyakorn et al. *SA J Trop Med Public Health*, 2010

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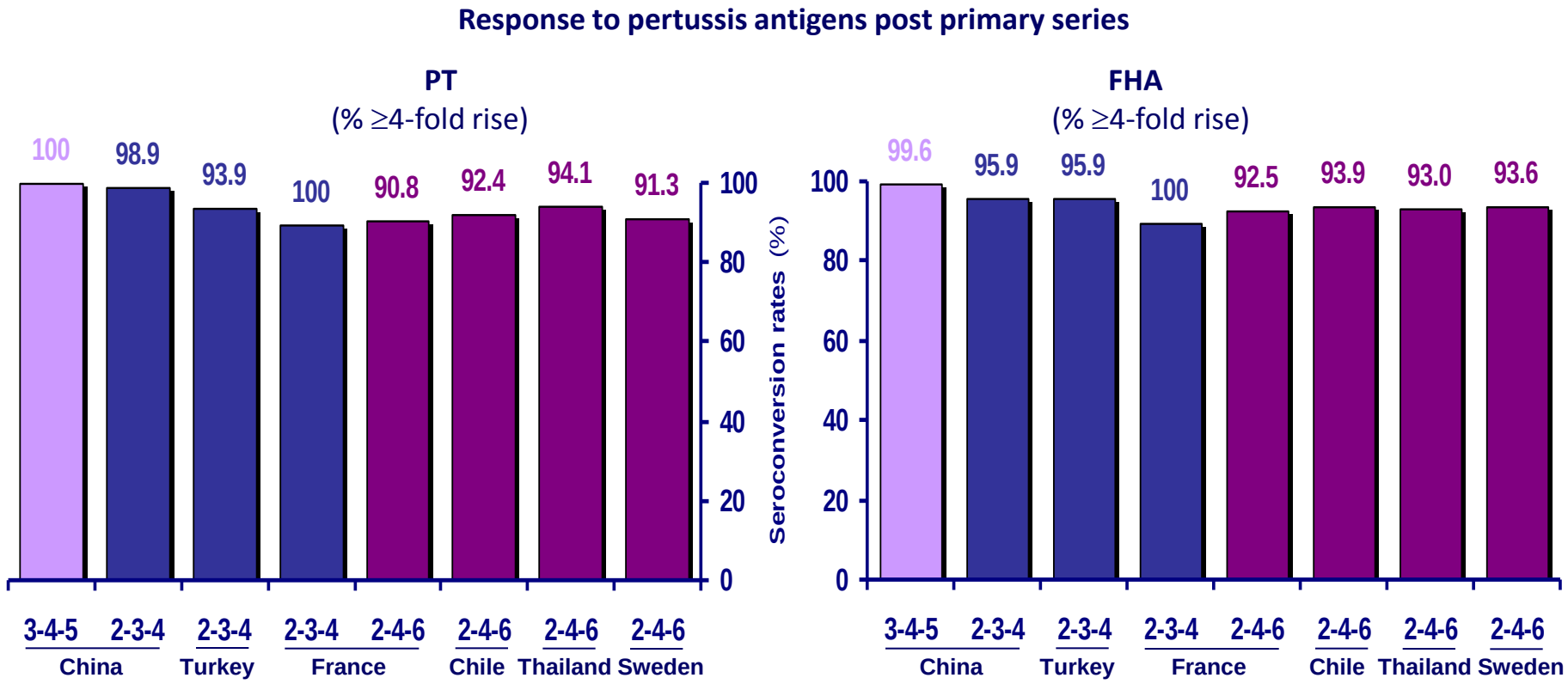
PENTAXIM® Provides High Immune Responses to PT and FHA across Countries and with All Routine Vaccination Schedules

- Seroconversion rates to PT & FHA antigens are similarly high **(≥90.8% and ≥92.5% respectively)** under all primary vaccination schedules



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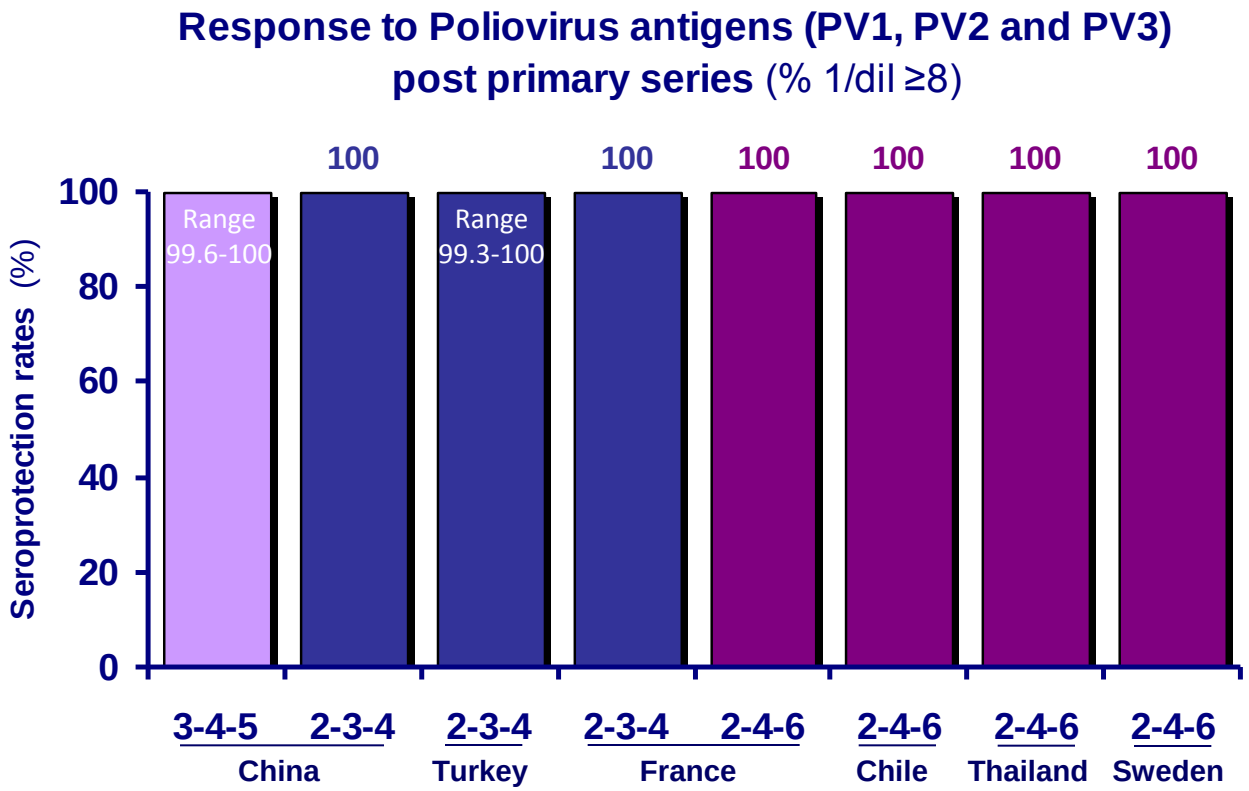
PENTAXIM® Provides High Immune Responses to All Polio-viruses across Countries with All Routine Vaccination Schedules

- Seroprotection rates to all poliovirus antigens post primary vaccination are similarly high **(>99%)** under all vaccination schedules



() Li et al. 13th Asian Pacific congress of Pediatrics, 2009 () Reinert. *ESPID*, 1997 () Mallet et al. *ESPID*, 1997
() Carlsson et al. *PIDJ*, 1998;17(11) () Lagos et al. PIDJ, 1998;17(4) () Thisyakorn et al. *SA J Trop Med Public Health*, 2010

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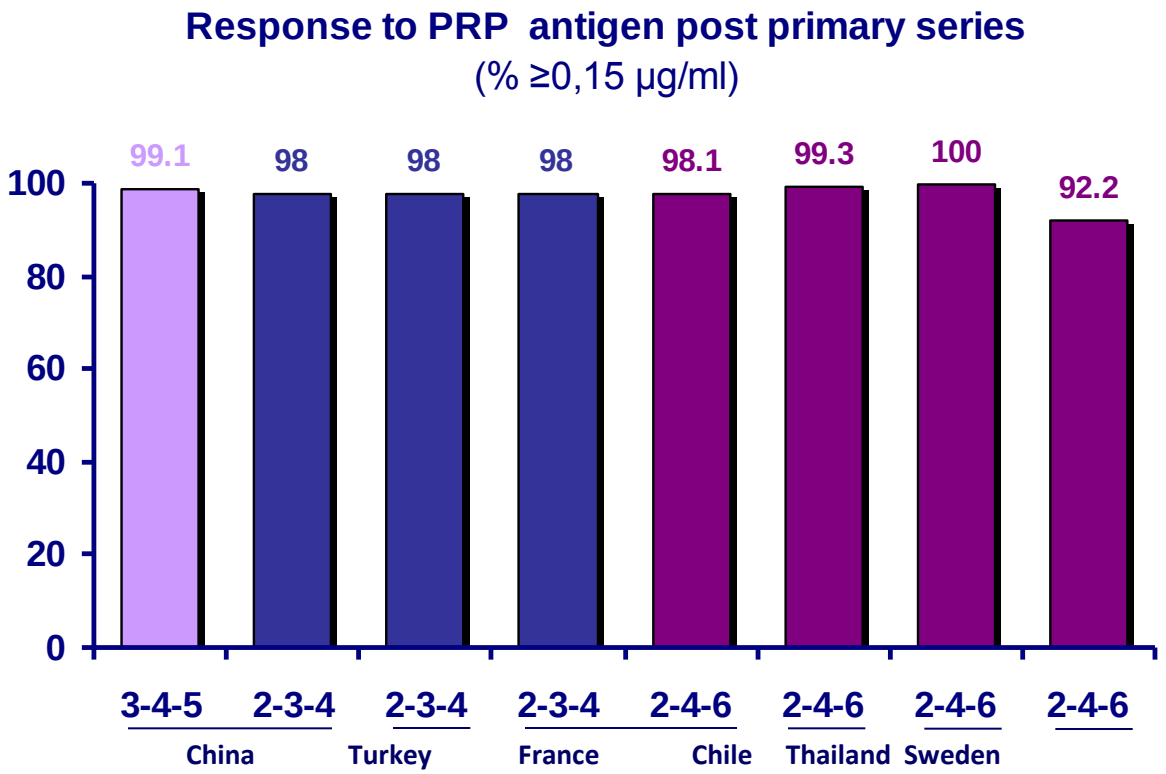
PENTAXIM® Provides High Immune Response to PRP-T across Countries and with All Routine Vaccination Schedules

- Seroprotection rates to PRP-T antigen are similarly high **(>92.2%)** under all vaccination schedules



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() Carlsson et al. *PIDJ*, 1998;17(11) () Lagos et al. PIDJ, 1998;17(4) () Thisyakorn et al. *SA J Trop Med Public Health*, 2010

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Safety of PENTAXIM®

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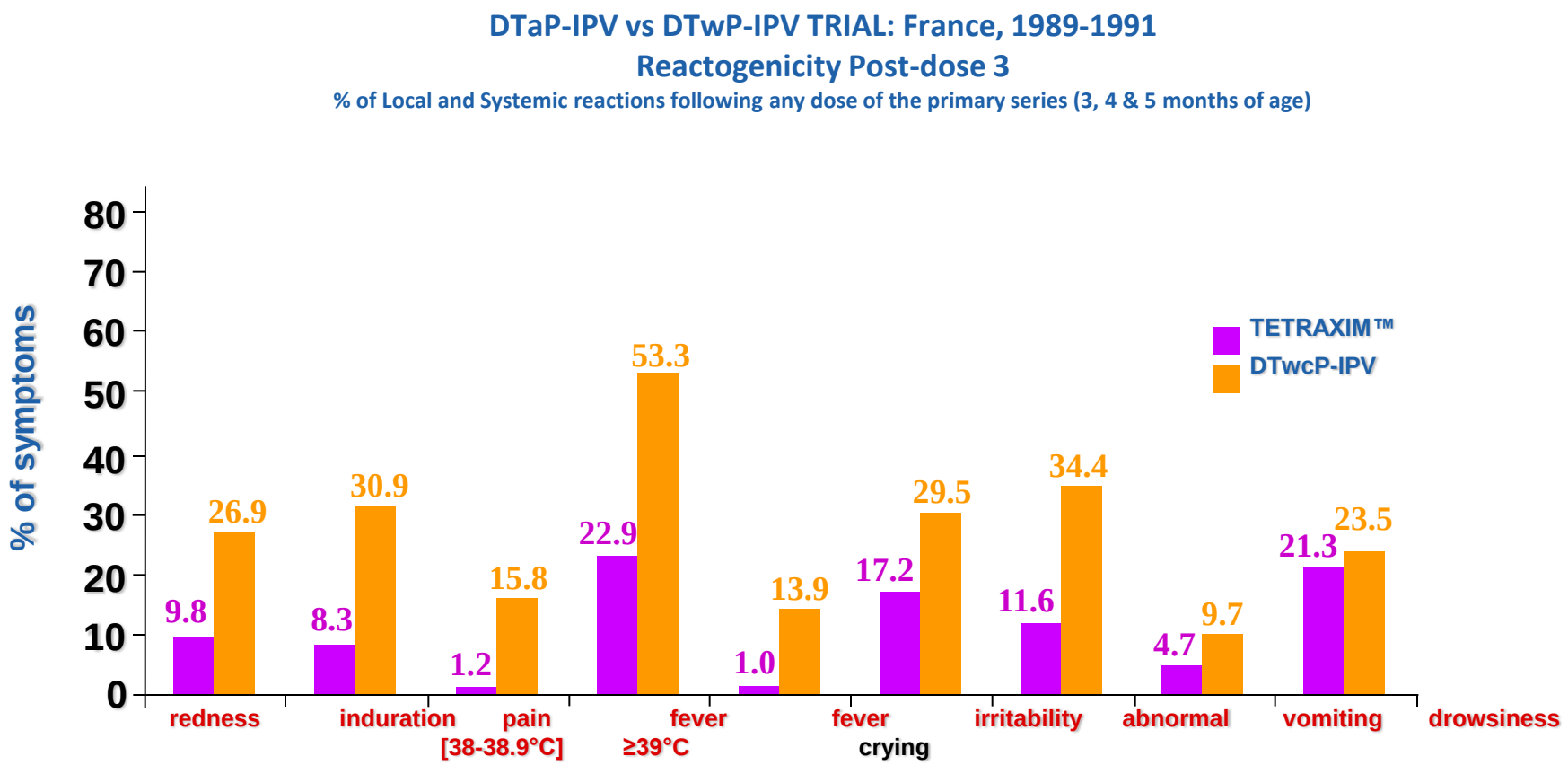
DTacP-IPV Vaccine is less Reactogenic DTwP-IPV Vaccine



Sanofi Pasteur. *Data in File*

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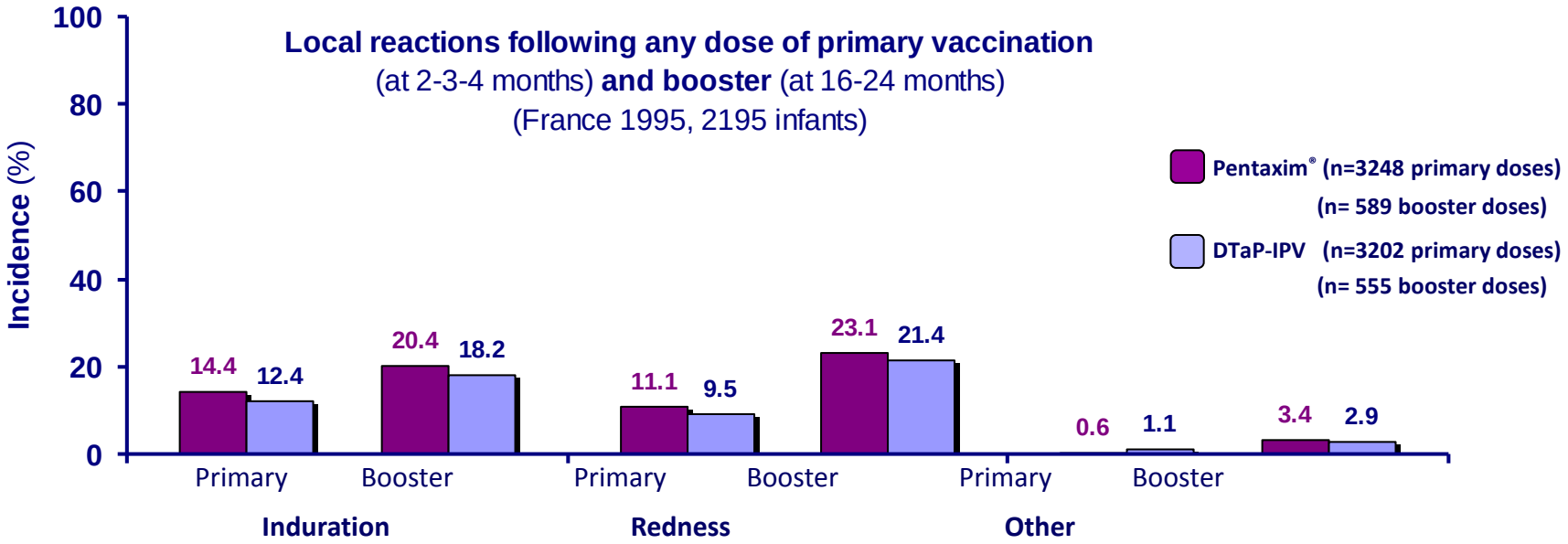
PENTAXIM®: As Well Tolerated As Separate Injections of DTaP-IPV and Hib

- The safety of Pentaxim vs Tetraxim + Hib was assessed in 2195 French infants primed at 2-3-4 and boosted at 16-24 months of age **(Reinert; Clin rep)**
  - **Incidences of local reactions were similarly low in both vaccine groups**



() Reinert et al. *ESPID*, 1997; Ab. 75

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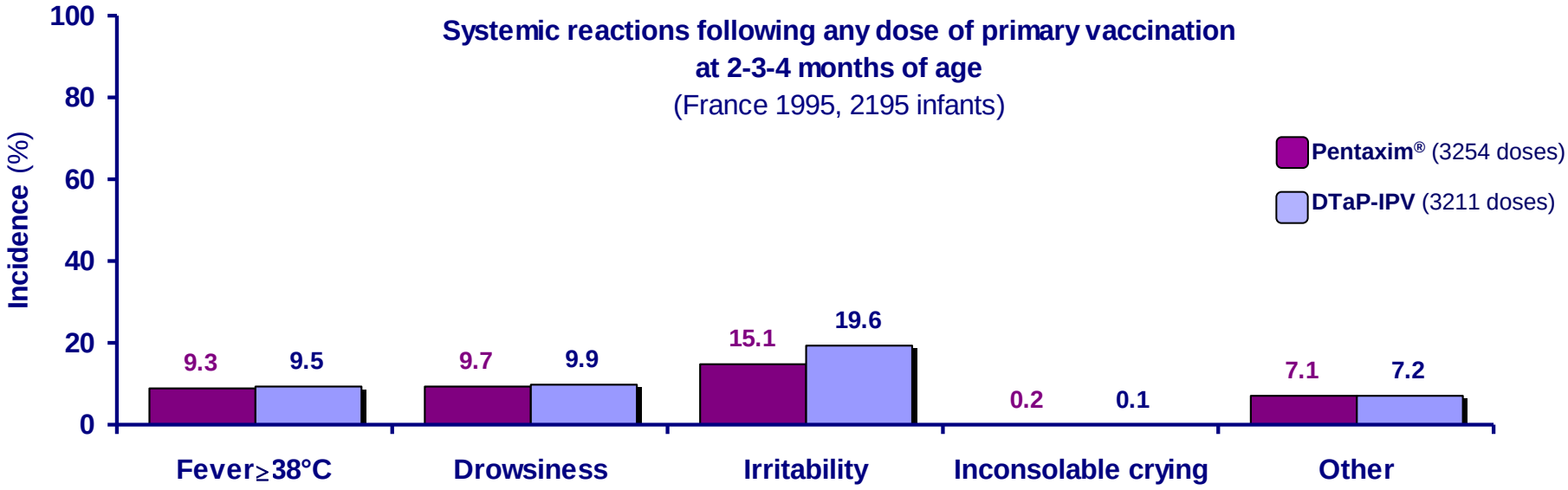
PENTAXIM®: As Well Tolerated As Separate Injections of DTaP-IPV and Hib

- **Incidences of systemic reactions were similar in both vaccine groups**
- **Most fever episodes were below 39° C** (fever ≥39° C <1.0% in both groups after primary series)
  Incidence of fever increased after the booster (22.1 and 23.8% respectively)
- **No HHE, seizure, nor SAE related to vaccination were detected reported after primary or booster vaccination in either group**



() Reinert et al. *ESPID*, 1997; Ab. 75

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Long-term impact of PENTAXIM® in the reduction and control of pertussis in Sweden (1997-2007)

Data from the 10-year Report

(1 Oct 1997 – 31 Dec 2007)

Swedish National Surveillance System
Swedish Institute for Infectious Disease Control

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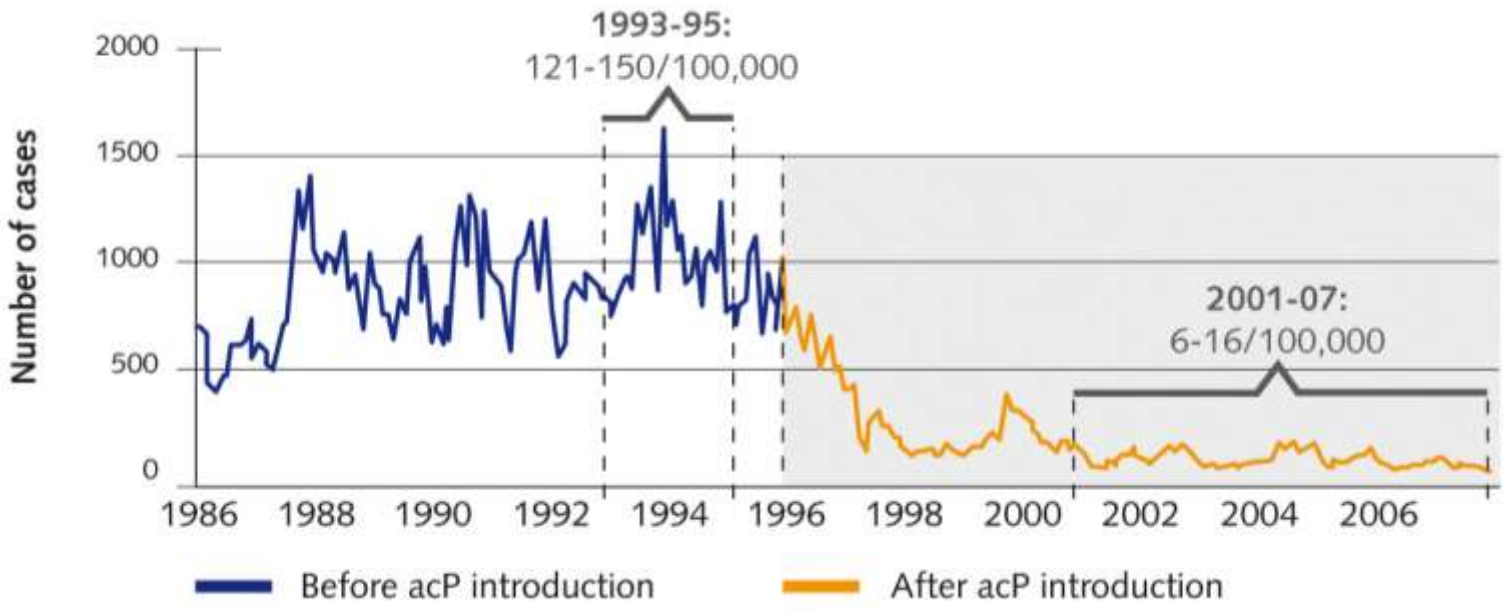
Without pertussis vaccination (1979-96), pertussis remained highly endemic in Sweden until introduction of acP vaccines

- **1979 – withdrawal of wcP vaccine in Sweden due to safety concerns [1]**
- **1996 – introduction of acP vaccines, switching from DT to DTacP at 3-5-12m; 3-dose coverage reached 98-99% within a year. [1]**

Cases of pertussis per year in Sweden [adapted from (1)]



[1] Gustafsson L, Carlsson RM. TEN YEAR REPORT – Pertussis surveillance in Sweden progress report October 1, 1997 – December 31, 2007.

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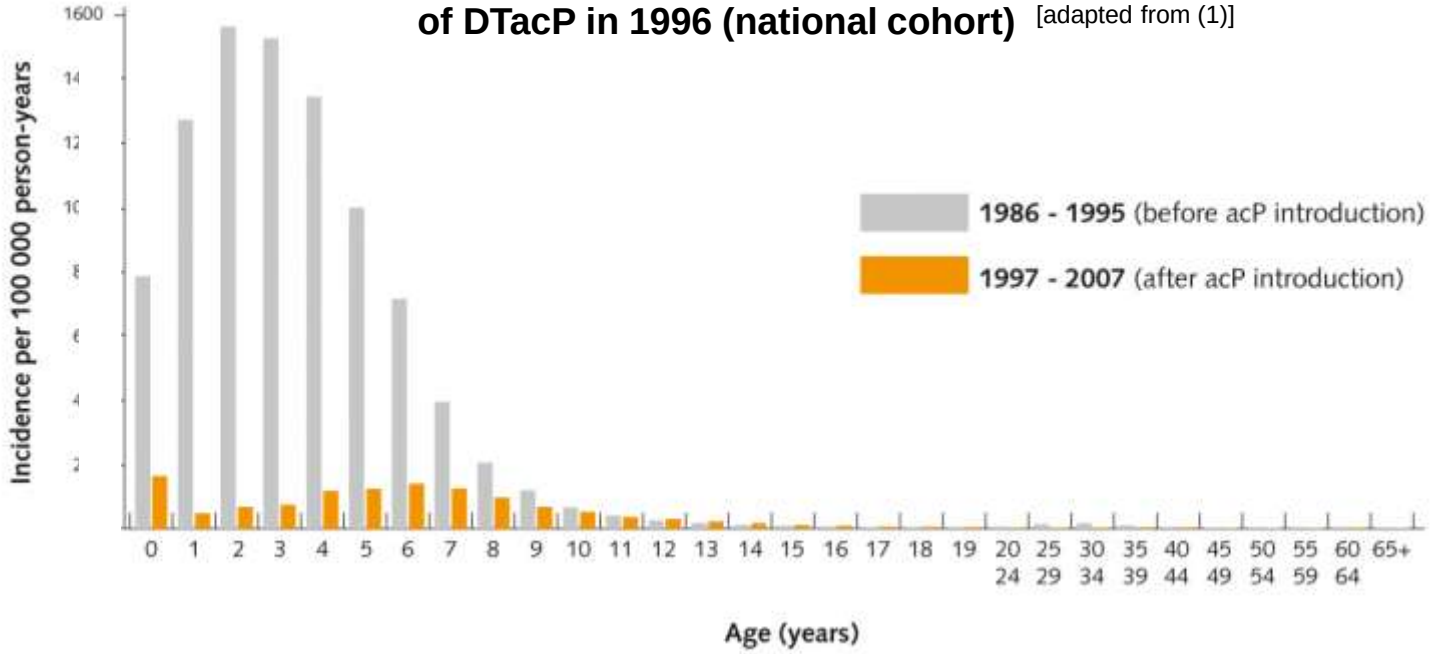
Introduction of acellular pertussis vaccines reduced the incidence of pertussis in Sweden

- Birth cohorts after introduction of acP had a much lower age-specific incidence of pertussis than had the corresponding age-groups before introduction of acP

- The modest increase in pertussis incidence approximately 5 years after the acP doses were administered could suggest waning of protection.

Age-specific incidence of pertussis before and after introduction of DTacP in 1996 (national cohort) [adapted from (1)]



[1] Gustafsson L, Carlsson RM. TEN YEAR REPORT – Pertussis surveillance in Sweden progress report October 1, 1997 – December 31, 2007.

Conclusions

- Acellular/IPV combination vaccines are well documented in terms of
  - Safety
  - Effectiveness
  - Programmatic suitability

- With more than 30 years of experience, Sanofi Pasteur can:
  - Provide a wide range of different combination vaccines, adapted to various scheme, including for booster dose.
  - Provide a documented effectiveness of its Pentavalent vaccine when used in national programs

- Considering the changes both in terms of epidemiology (disappearance of polio, shift in age of pertussis) and technology (switch to acellular pertussis), all parameters are in line with a safe introduction of a combination vaccine in most region of the globe as long as the region is non polio endemic and the program can be sustainably funded by the public sector.

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