



DTaP_{2Fr}: an update on clinical experience

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Polio – Pertussis – Meninge – Hib Franchise

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The vaccines business of sanofi-aventis Group

Agenda

- **Historical background**
- **Performance against Pertussis disease**
- **Performance against Hib disease**
- **Performance against Polio**
- **Safety considerations**
- **Conclusions**

The *AcXim* Family

- ***AcXim*: DTaP_{2Fr} backbone**
 - Development started in the mid-eighties
 - ***DTaP (Triaxim). Not licensed***
 - **DTaP-IPV (Tetraxim)**
 - **DTaP-IPV / Hib (Pentaxim)**
 - **DTaP-IPV-HepB-Hib (Hexaxim; under development)**
 - Used in Europe and in some public markets of Asia, Middle East, Eastern Europe and Central America
 - In expansion

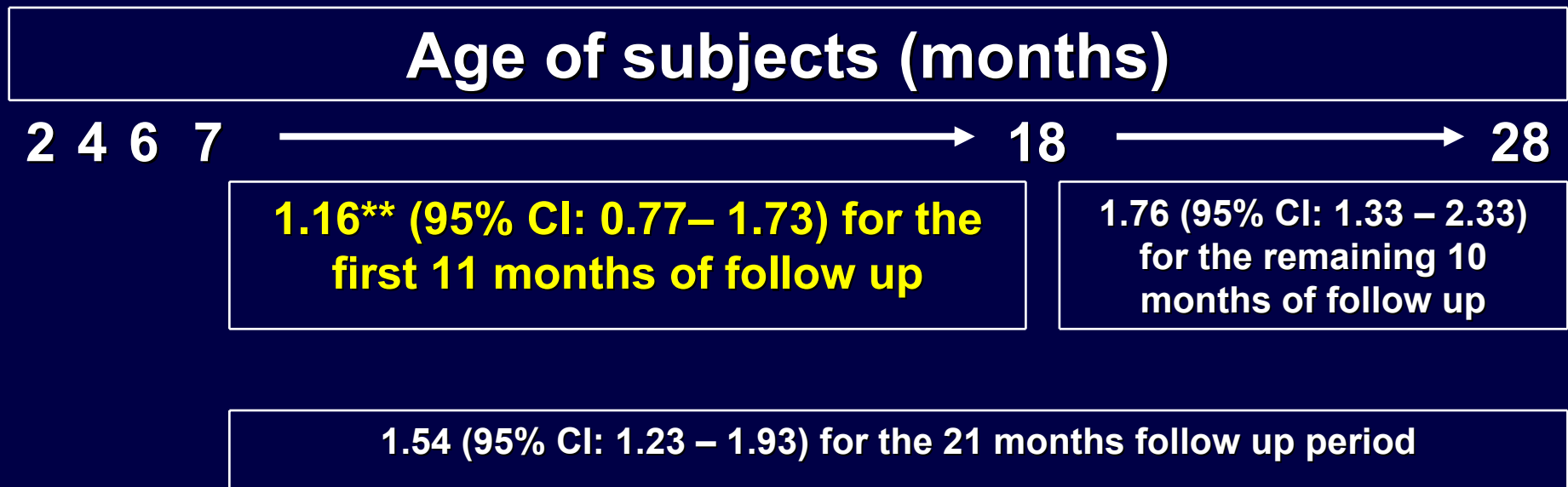
Efficacy Against Pertussis of DTaP_{2Fr}-containing vaccines

The Relative Efficacy Pertussis Senegal Trial

- Prospective, randomized, double-blinded, study of the relative efficacy of DTaP_{2Fr} versus DTwP_{Fr}
- Clinical outcome measured during a mean duration period of 21 months starting one month after the last pertussis vaccination (2 – 4 – 6 month of age)
 - 3193 aP-vaccinated infant-years at risk
 - 3165 wP-vaccinated infant-years at risk
- A prospective house-hold case-control study nested in the main study to evaluate absolute VE (secondary objective)
- An immunogenicity study nested in the main study for post-dose 3 immune response determination (secondary objective)
- Study done in a community followed for pertussis epidemiology since years, and for which pertussis surveillance continued long after end of trial follow up

The Relative Efficacy Pertussis Senegal Trial

Relative Risk (RR) to develop pertussis* between aP- and wP-subjects



* ≥ 21 days of cough + positive culture + positive serology or contact with a culture positive person

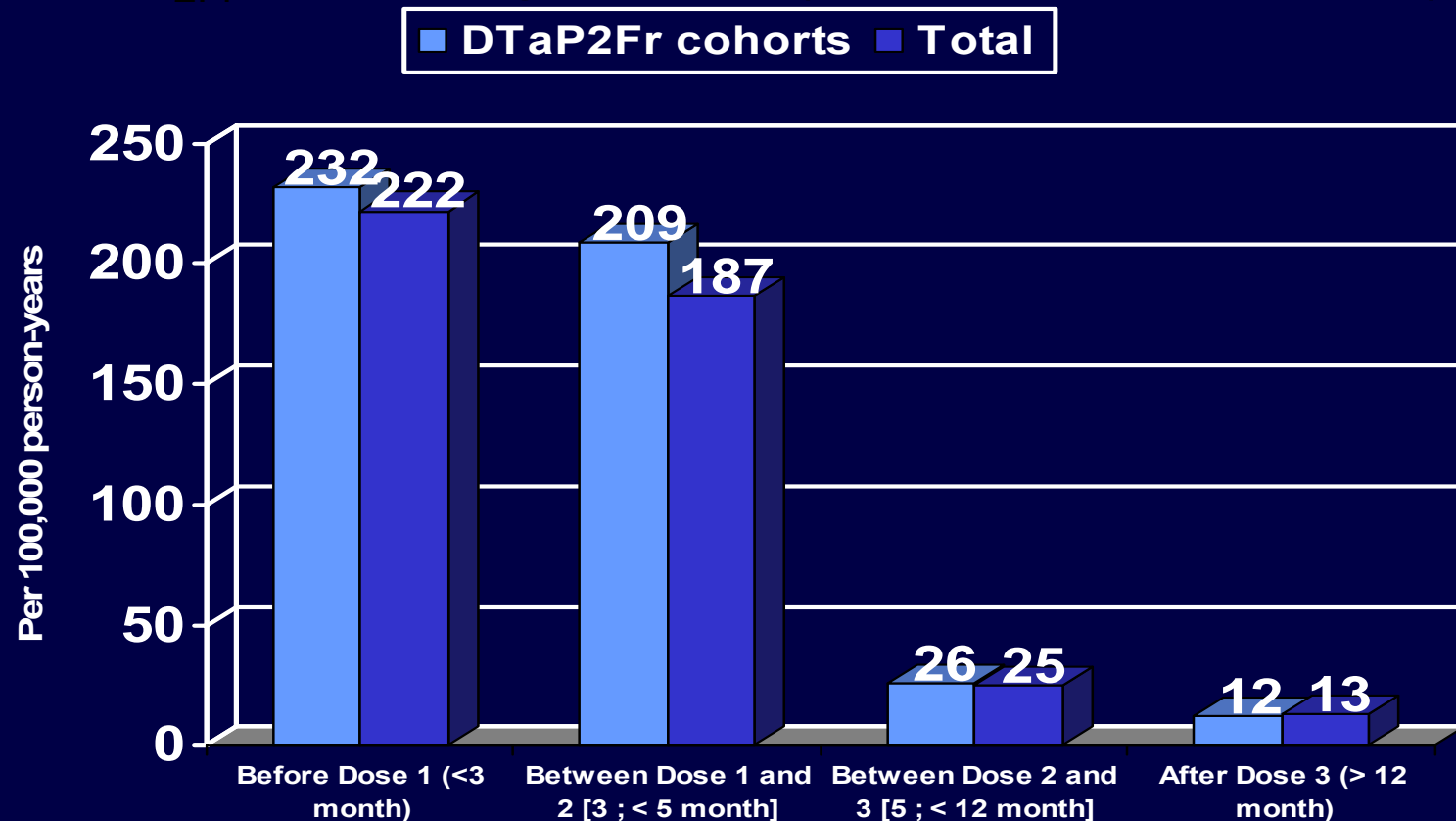
** higher RR when using WHO definition (≥ 21 days of paroxysmal cough)

The Relative Efficacy Pertussis Senegal Trial

- **Household case-contact study for absolute VE determination (full follow up period)**
 - WHO pertussis case definition + contact with a culture positive person
 - 96% for DTwP (95% CI: 86% - 99%)
 - 85% for DTaP (95% CI: 66% - 93%)
 - Using the WHO pertussis case definition
 - 92% for DTwP (95% CI: 81% - 97%)
 - 74% for DTaP (95% CI: 51% - 86%)
- **Pertussis surveillance before and after the trial follow up**
 - After the introduction of the vaccination program, overall incidence dropped by 27% after 3 yrs and by 46% after 6 yrs from a crude incidence of 183 per 1,000 child-years at risk under 5 years of age observed during the pre-trial era
 - Decrease of incidence involved all age groups and was most substantial in the group under 5 yrs and in particular in unvaccinated infants

The Swedish Pertussis Surveillance Program

Incidence of pertussis* in subjects who received exclusively DTaP_{2Fr}-containing vaccine (from Oct 97 to Dec 07)



* ≥ 21 days of paroxysmal cough + positive culture or positive PCR

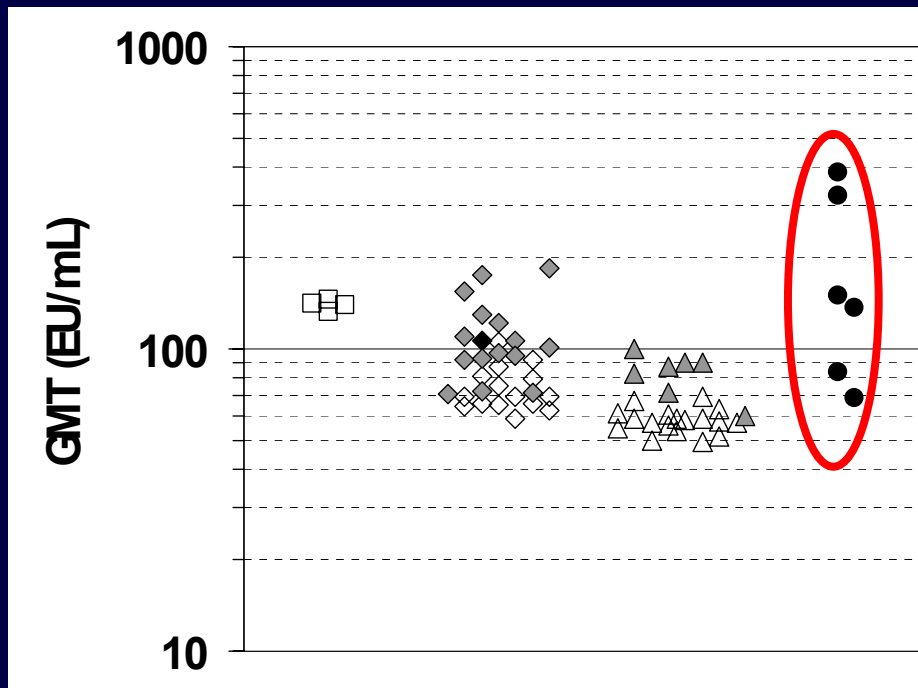
<http://www.smittskyddsinstitutet.se/upload/SMI-rapport%20nr%204-2008.pdf>

Immunogenicity of the Pertussis Antigens of DTaP_{2Fr}-containing vaccines

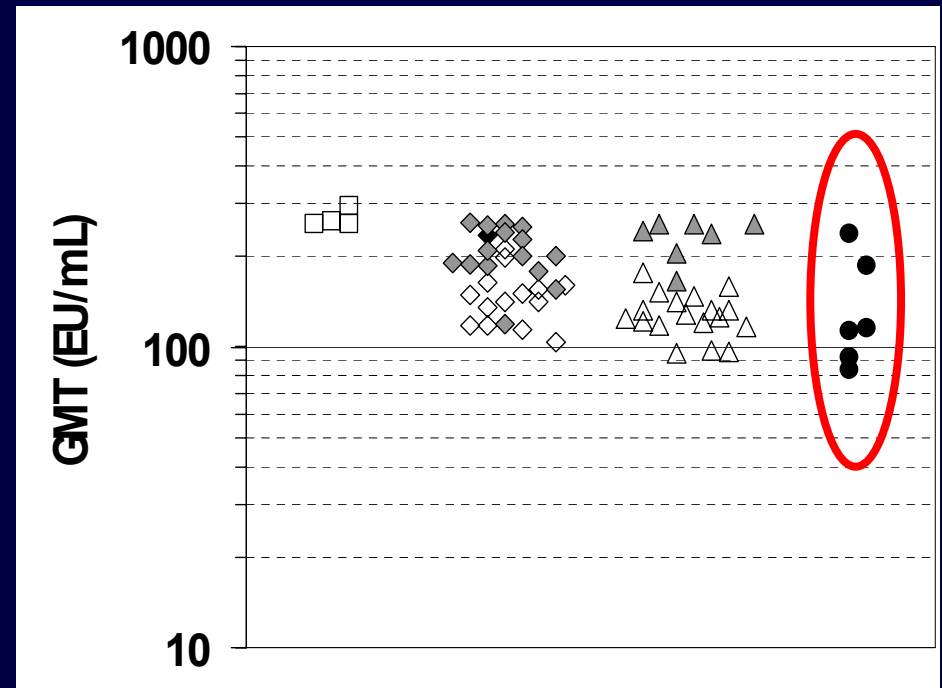
- **36 studies between 1987 and 2006 in 17 countries**
 - Europe (Western & Central)
 - The Americas
 - Africa
 - Asia
- **Eight different vaccines (licensed or backbones / ancestors of the licensed products)**
- **Data obtained from nearly 10,000 subjects with vaccines administered with the four existing Primary Series schedules**
 - Two shots during 1st year of life followed by a toddler booster
 - 3 – 5 – 12 months of age
 - Three shots during 1st year of life
 - 2 – 4 – 6 months of age
 - 2 – 3 – 4 or 3 – 4 – 5 months of age
 - 6 – 10 – 14 weeks of age (EPI schedule)

Immune Responses against PT and FHA in 62 study arms including the Sénégal Relative Efficacy Study arm (♦) in infants vaccinated with DTaP_{2Fr}-containing vaccines

Anti-PT GMTs



Anti-FHA GMTs



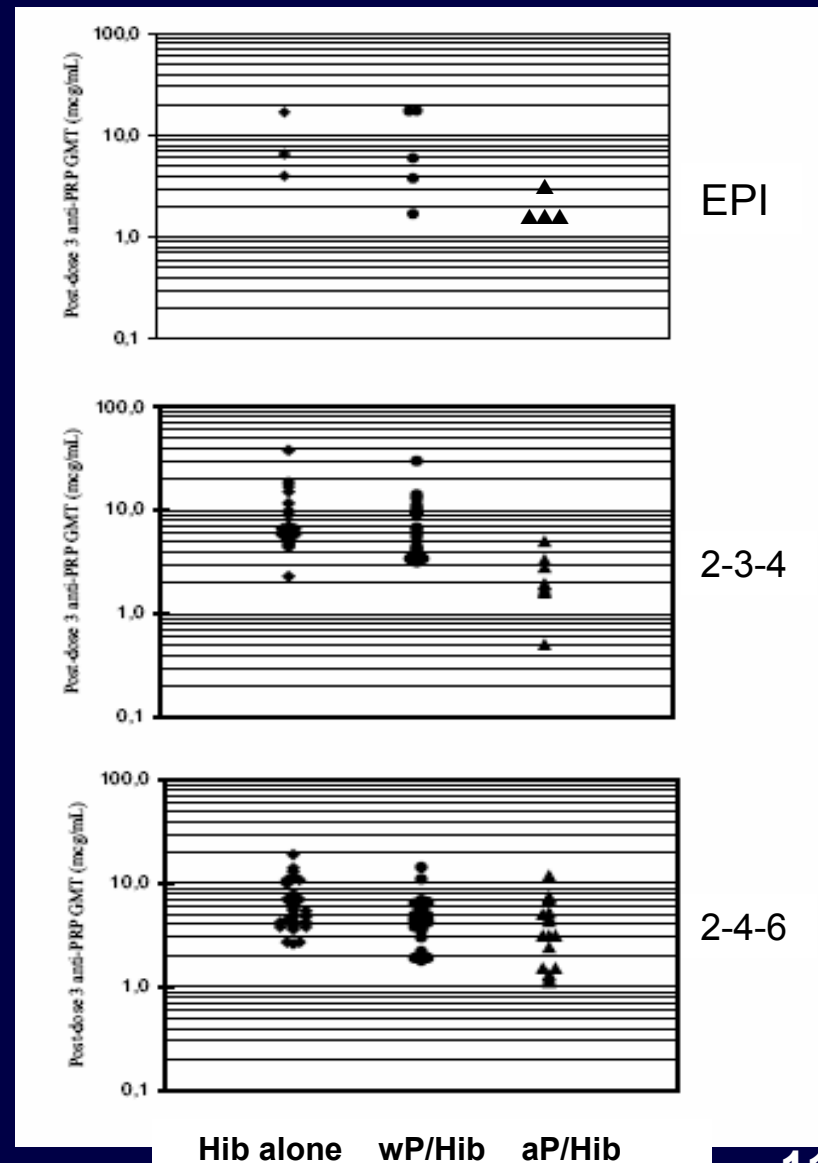
- 3 – 5 – 12 month schedule (Sweden, Italy)
- ◆ 2 – 4 – 6 month schedule (outside EU and NA) (bolded symbol for the Senegal efficacy trial)
- ◇ 2 – 4 – 6 month schedule (in EU and NA)
- ▲ 2 – 3 – 4 or 3 – 4 – 5 month schedule (outside EU and NA)
- △ 2 – 3 – 4 or 3 – 4 – 5 month schedule (in EU and NA)
- EPI schedule (outside EU and NA)

Immunogenicity of the Pertussis Antigens of DTaP_{2Fr}-containing vaccines

- The main source of variability is the Primary Series schedule
- % of subjects with a ≥ 4 -fold rise in their Ab titers from pre-dose 1 to post-dose 3 were less variable than GMTs
- The type of combination vaccine is not a source of variability
- Combining DTaP_{2Fr} with IPV, Hib and HepB antigens do not impair immune responses against pertussis Ags

Interference on Hib responses within aP-containing vaccines: Myth and Realities

- The only antigen impacted when combining DTaP with IPV, Hib and/or HepB is the Hib PS-tetanus conjugated vaccine with some aP-containing vaccines
- Even in the presence of an interfering effect on the post PS Hib response, the post-toddler booster vaccination antibody levels achieved with 2+1 or 3+1 schedules are clinically adequate
 - All epidemiological surveillance programs on Hib diseases ongoing in Ger., Can. and UK do confirm



Immunogenicity of IPV-containing vaccines in tropical countries: three decades of experience

- **53 trials (126 study arms) done with IPV-containing vaccines in 24 tropical countries since 1977**
 - 30 studies done in Low Income countries
- **Several types of study design**
 - Dose response for IPV or IPV cell substrate origin comparison
 - Comparative between IPV-containing vaccines and OPV
 - IPV schedules comparison
 - Mixed or sequential IPV / OPV schedule evaluations
 - Descriptive IPV-containing vaccines licensing studies
- **Several IPV-containing vaccines**
 - The historical IPVs
 - IPV standalone
 - wP-based IPV-combinations
 - aP-based IPV-combinations

GMT & % with SN titers $\geq 1:8$ induced by the 6-10-14 weeks schedule (polio type 1)

Country / Year	Product	Nb	Pre Dose 1	Pre Dose 3	Post Dose 3	Pre Booster	Post Booster
South Africa ¹ 1998	DTwP-IPV / Hib	119	20.3 (63.1%)		116 (99.2%)		
Philippines ² 2000	DTaP _{5Ca} -IPV-Hib	65	34.5 (81.5%)	285 (98.5%)	863 (100%)	1034 (100%)	3104 (100%)
South Africa ³ 2001	DTaP _{2Fr} -IPV-Hib-HepB	213 225	7.8 (51.3%) 7.8 (49.2%)		1226 (100%) 1302 (100%)	154 (100%) 159 (99.5%)	6383 (100%) 6455 (100%)
Philippines ⁴ 2003	DTaP _{2Fr} -IPV / Hib	192 174	10.2 (58.0%) 9.0 (53.6%)		533 (100%) 574 (100%)	78.4 (95.9%) 81.3 (97.2%)	10377 (100%) 9436 (100%)
South Africa ⁵ 2005	DTaP _{2Fr} -IPV / Hib	202			1453 (100%)	Ongoing	Ongoing
India ⁶ 2005	DTaP _{2Fr} -IPV / Hib	213	18.1 (74.6%)		440 (100%)		

Polio NID between post-dose 3 and pre-booster

1 Study HIT40, unpublished sanofi pasteur data in file; 2 Capeding & al. 3rd WCPID, 2002; 3 Study A3R25, unpublished sanofi pasteur data in file; 4 Capeding & al. Bull WHO 2008; 5 Madhi & al. 13rd ICID, 2008; 6 Dutta & al. 13rd ICID, 2008

GMT & % with SN titers $\geq 1:8$ induced by the 6-10-14 weeks schedule (polio type 2)

Country / Year	Product	Nb	Pre Dose 1	Pre Dose 3	Post Dose 3	Pre Booster	Post Booster
South Africa ¹ 1998	DTwP-IPV / Hib	119	23.1 (63.1%)		93 (99.2%)		
Philippines ² 2000	DTaP _{5Ca} -IPV-Hib	65	36.4 (81.5%)	256 (98.4%)	768 (100%)	1647 (100%)	6367 (100%)
South Africa ³ 2001	DTaP _{2Fr} -IPV-Hib-HepB	213 225	16.0 (72.6%) 14.1 (68.5%)		661 (100%) 694 (100%)	222 (99.5%) 220 (98.5%)	9671 (100%) 9537 (100%)
Philippines ⁴ 2003	DTaP _{2Fr} -IPV / Hib	192 174	14.7 (64.9%) 19.5 (74.9%)		789 (100%) 719 (100%)	139 (94.8%) 130 (97.2%)	12117 (100%) 10171 (100%)
South Africa ⁵ 2005	DTaP _{2Fr} -IPV / Hib	202			1699 (100%)	Ongoing	Ongoing
India ⁶ 2005	DTaP _{2Fr} -IPV / Hib	213	20.4 (74.2%)		458 (99.1%)		

Polio NID between post-dose 3 and pre-booster

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GMT & % with SN titers $\geq 1:8$ induced by the 6-10-14 weeks schedule (polio type 3)

Country / Year	Product	Nb	Pre Dose 1	Pre Dose 3	Post Dose 3	Pre Booster	Post Booster
South Africa ¹ 1998	DTwP-IPV / Hib	119	16.0 (46.7%)		166 (99.2%)		
Philippines ² 2000	DTaP _{5Ca} -IPV-Hib	65	13.5 (76.9%)	403 (96.9%)	901 (100%)	1873 (100%)	6158 (100%)
South Africa ³ 2001	DTaP _{2Fr} -IPV-Hib-HepB	213 225	4.8 (30.4%) 5.0 (49.2%)		1249 (100%) 1424 (100%)	202 (97.8%) 212 (97.0%)	11332 (100%) 10377 (100%)
Philippines ⁴ 2003	DTaP _{2Fr} -IPV / Hib	192 174	10.4 (58.3%) 10.1 (55.5%)		1968 (100%) 1571 (100%)	128 (99.5%) 112 (100%)	13303 (100%) 11514 (100%)
South Africa ⁵ 2005	DTaP _{2Fr} -IPV / Hib	202			2398 (100%)	Ongoing	Ongoing
India ⁶ 2005	DTaP _{2Fr} -IPV / Hib	213	9.9 (61.5%)		1510 (100%)		

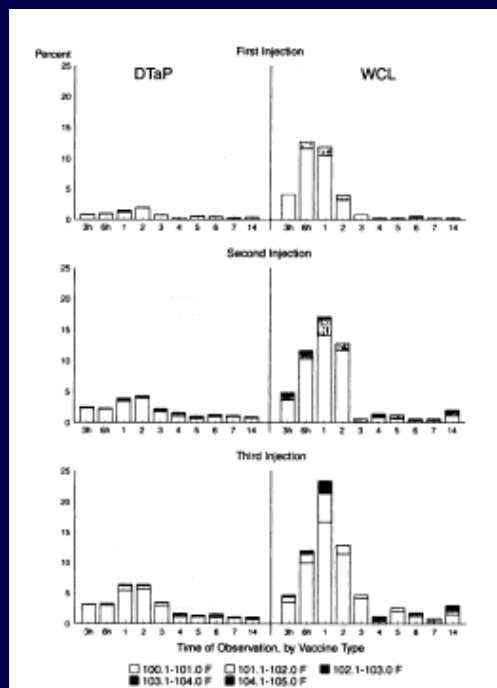
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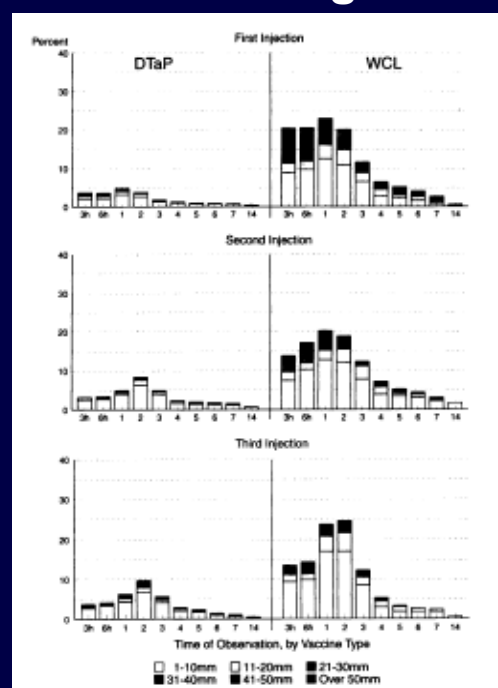
aP vaccines are always better tolerated than wP vaccines

- The NIH-Multi Acellular Pertussis Trial has evaluated 13 aP vaccines including the *AcXim* backbone

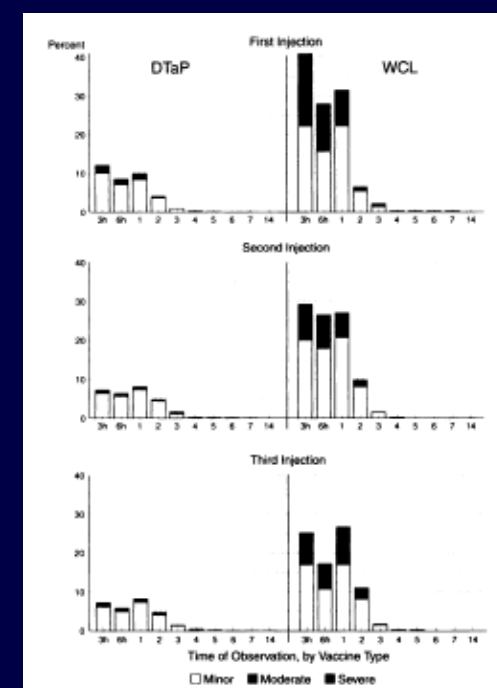
Fever



Swelling

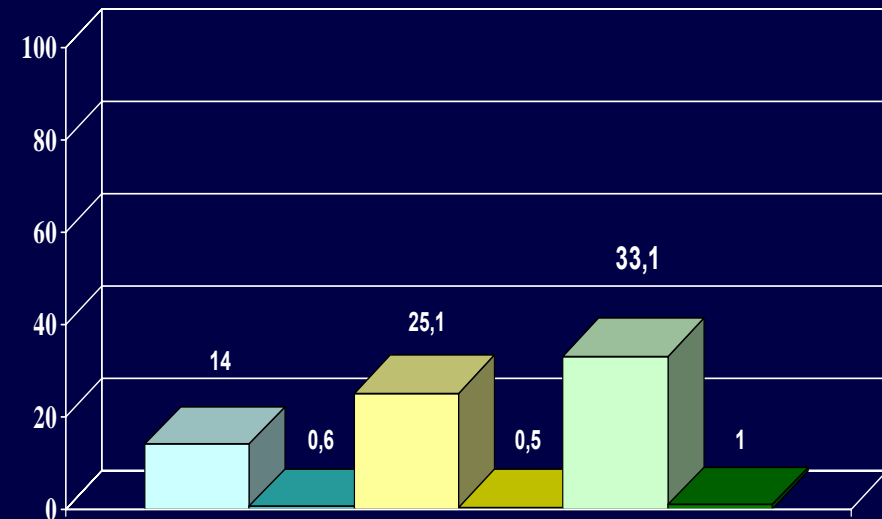
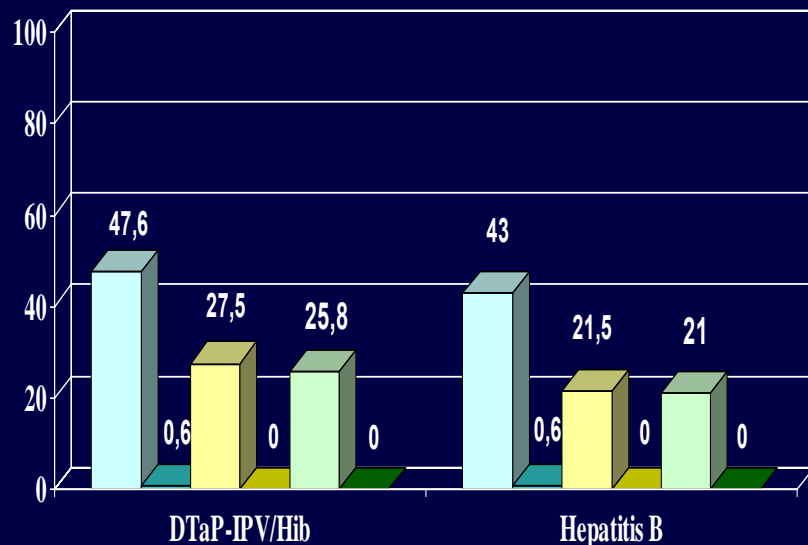


Pain



Subsequent trials have confirmed the excellent safety profile of Pentaxim

Incidence (%) of Solicited Local and Systemic Adverse Events (ITT subjects, 3 PS doses, 8 days)



- Pain (mild & moderate)
- Pain (severe)
- Redness (mild & moderate)
- Redness (severe)
- Swelling (mild & moderate)
- Swelling (severe)

- Fever (mild & moderate)
- Fever (severe)
- Drowsiness (mild & moderate)
- Drowsiness (severe)
- Irritability (mild & moderate)
- Irritability (severe)

Study E2143, unpublished sanofi pasteur data in file

Summary & Conclusions

- **The most complete vaccine of the *AcXim* family (DTaP-IPV / Hib; Pentaxim™) is under registration & launch in numerous countries**
- **Clinical experience demonstrates**
 - **High protective efficacy against pertussis, in line with that of other licensed DTaP vaccines, when used in an infant + toddler booster vaccination schedule**
 - **High immunogenicity of each antigen**
 - **Low reactogenicity, similar to all other acellular pertussis vaccines**
 - **Adapted to fit with several HepB vaccination schedules**

Thank you