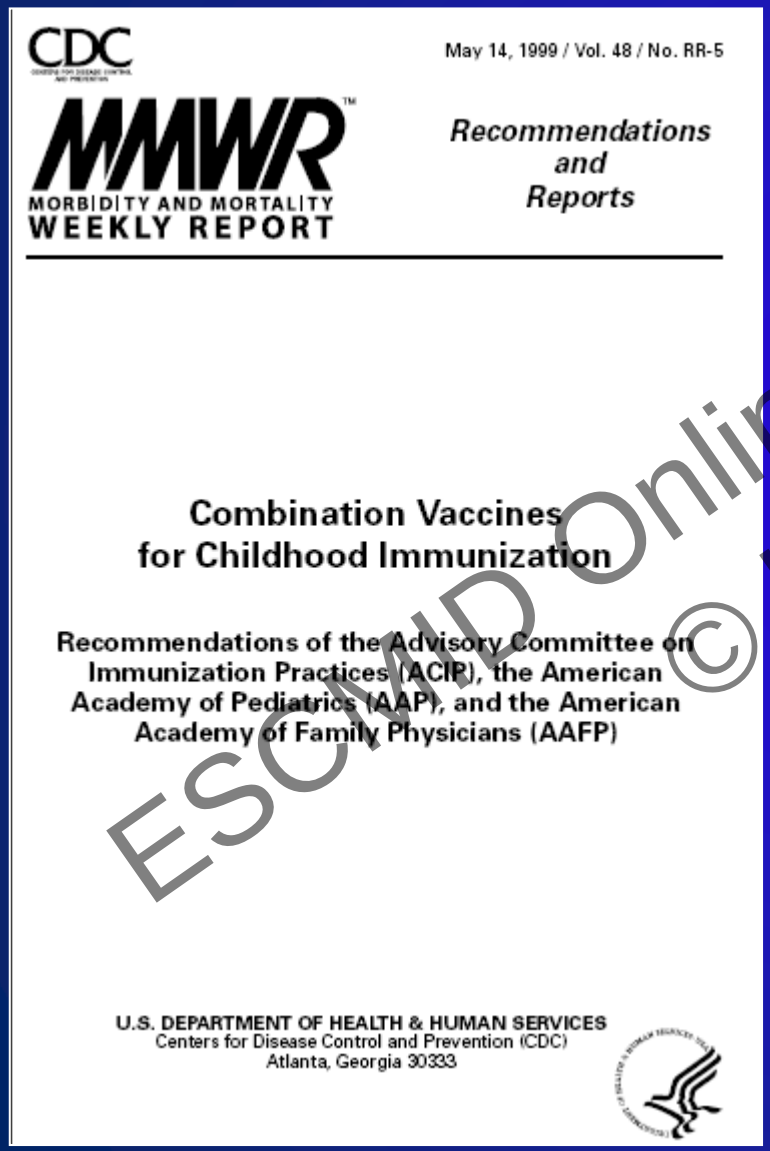
MULTIVALENT PEDIATRIC VACCINES: THE EXPERIENCE WITH DTP-HBV-IPV-HIB VACCINE INFANRIX-HEXA

Susanna Esposito
Pediatric Clinic 1, University of Milan
Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico
Milan, Italy

ACIP, AAP and AAFP opinion



CDC

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MMWR™
MORBIDITY AND MORTALITY
WEEKLY REPORT

Recommendations and Reports

Combination Vaccines for Childhood Immunization

Recommendations of the Advisory Committee on Immunization Practices (ACIP), the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP)

U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
Centers for Disease Control and Prevention (CDC)
Atlanta, Georgia 30333

- *"…Combination vaccines may be used whenever any components of the combination are indicated and its other components are not contraindicated…"*
- *"…Administration of extra-dose of many live-virus vaccines and Hib or HepB vaccines has not been found to be harmful…"*

CDC MMWR 1999; 48; RR-5

Infanrix hexa^{TM} vaccination schedule

- **Primary vaccination: 0.5 mL**
  - 3 doses series:
    - Months 2, 3, 4
    - Months 3, 4, 5
    - Months 2, 4, 6
    - Week 6, 10, 14 if HBV given at birth
  - 2 doses: at months 3, 5*
    - Space between doses: min 1 months
- **Booster vaccination**:
  - At least 6 months after the last dose of primary series
  - With 3-dose schedule: booster before 18 months olds
  - With 2-does schedule; booster given between 11-13 months
- Deep Intramuscular administrations

Primary vaccination

DTPa-HBV-IPV/Hib (*Infanrix hexa*™): Primary vaccination trials

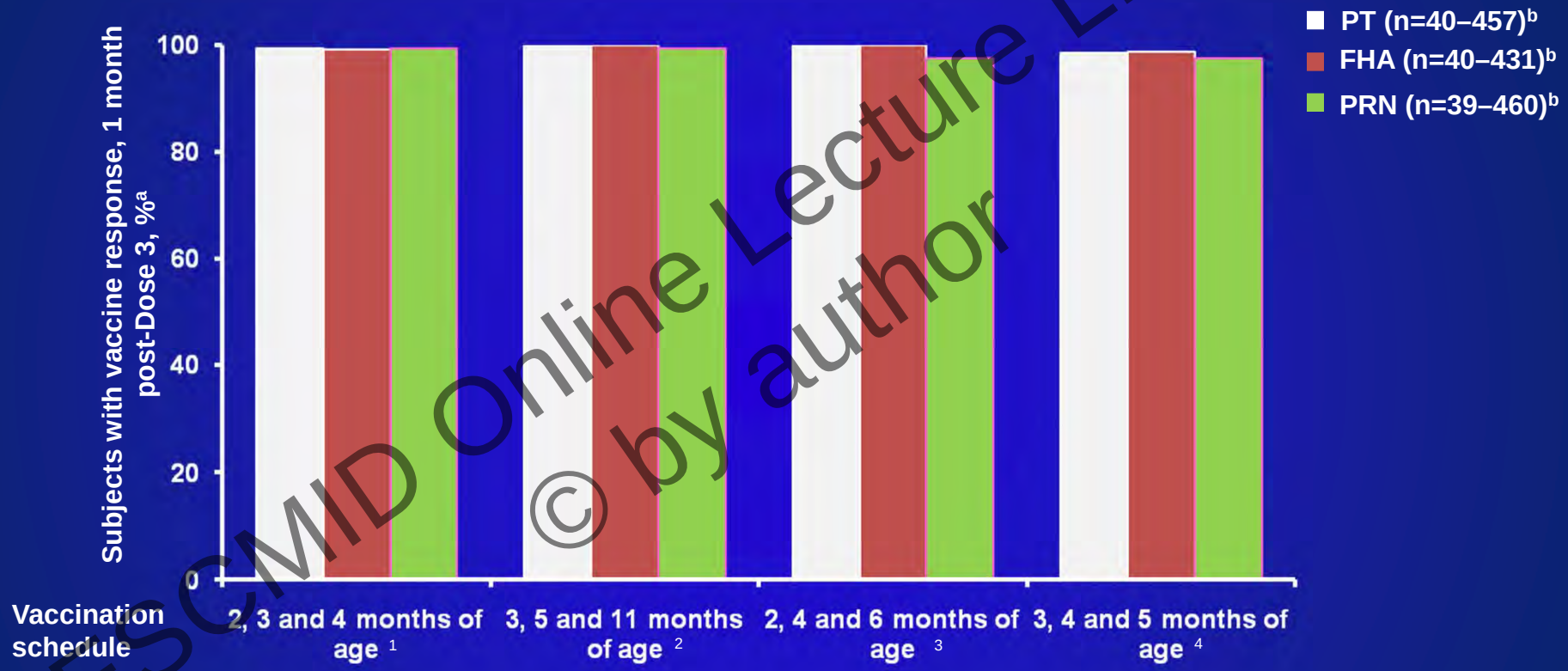
Author (country)	Schedule (months)	n[a]	Study arms
Schmitt (Germany)[1]	2, 3, 4	180	*Infanrix hexa*™ *Infanrix Penta*™ + Hib
Avdicová (Slovakia)[2]	3, 5, 11	141	*Infanrix hexa*™ *Infanrix*™ IPV Hib + HBV
Arístegui (Spain)[3]	2, 4, 6	120	*Infanrix hexa*™ *Infanrix*™ IPV Hib + HBV
Zepp (Germany)[4]	3, 4, 5	2163[c]	*Infanrix hexa*™ *Infanrix*™ IPV Hib + HBV
Heininger (Germany)[5,b]	3, 4, 5	341	*Infanrix hexa*™ *Infanrix*™ IPV Hib + HBV

[a]Number receiving *Infanrix hexa*™ with immunogenicity or reactogenicity results available; [b]Antibody persistence evaluated before booster vaccination at 9 months in infants who had completed the Zepp *et al*. 2004 study; [c]Immunogenicity evaluated in 474 infants

HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine

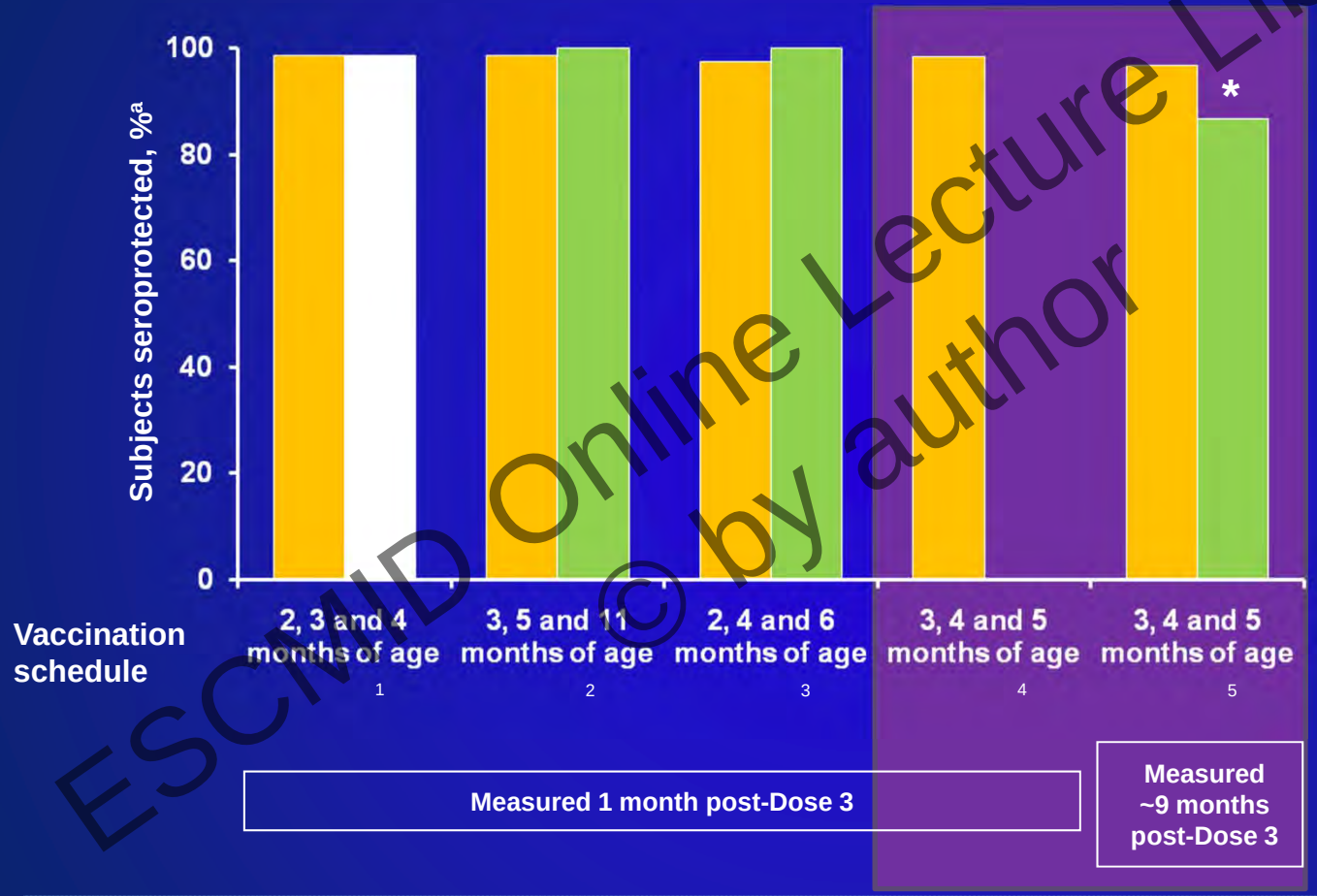
1. Schmitt *et al.* 2000; 2. Avdicová *et al.* 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Infanrix hexa™ induces a high pertussis vaccine response



[a]Defined as ≥5 EU/ml if initially seronegative or at least maintenance of pre-vaccination antibody titres for initially seropositive subjects
[b]Subjects with available results
FHA, filamentous haemagglutinin; PRN, pertactin; PT, pertussis toxoid
1. Schmitt *et al.* 2000; 2. Avdicová *et al*. 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004

Infanrix hexa™ achieves high seroprotection rates against hepatitis B



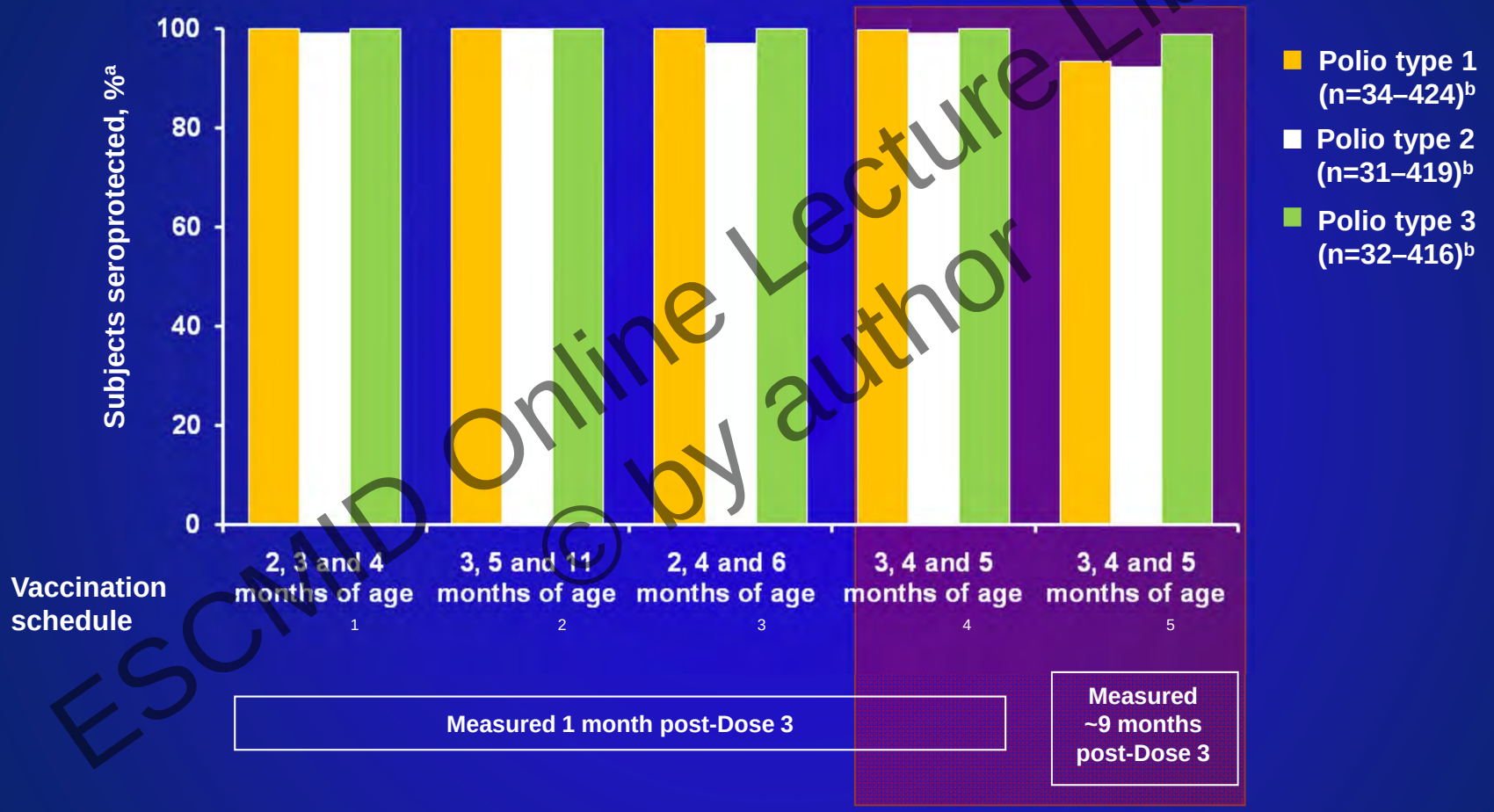
- *Infanrix hexa*™ (n=39–472)[b]
- *Infanrix Penta*™ + HBV (n=141)[b]
- *Infanrix*™ IPV Hib + HBV (n=31–138)[b]

Shaded purple area highlights that the Heininger *et al.* 2007 study was a continuation of the Zepp *et al.* 2004 study in the same subjects

*No overlap of 95% confidence intervals

[a]Subjects with titres ≥10 mIU/ml; [b]Subjects with available results
HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine
1. Schmitt *et al.* 2000; 2. Avdicová *et al*. 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Infanrix hexa™ induces protection against polio

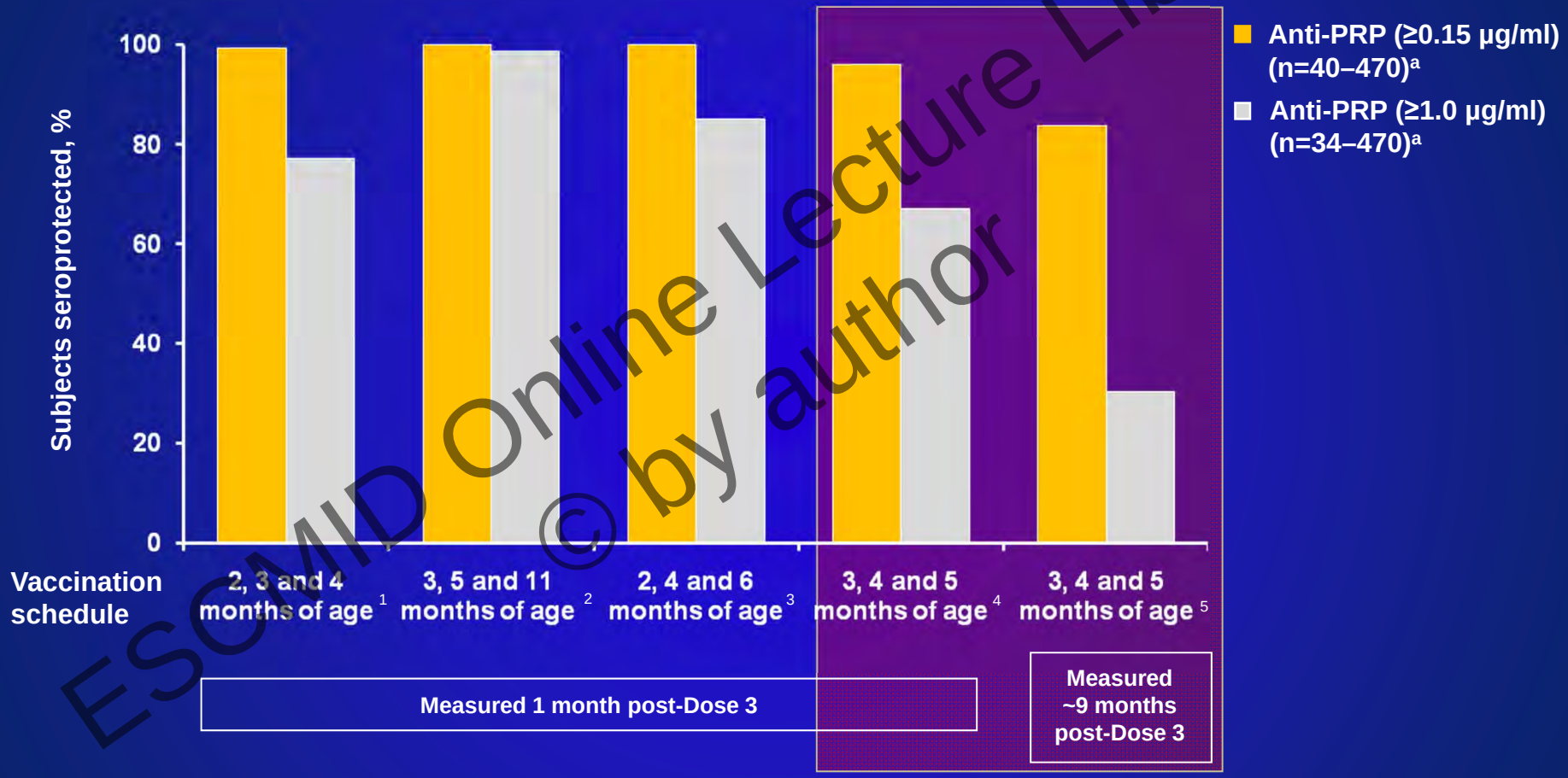


Shaded purple area highlights that the Heininger *et al.* 2007 study was a continuation of the Zepp *et al.* 2004 study in the same subjects

[a]Subjects with ≥1:8 dilution; [b]Subjects with available results

1. Schmitt *et al.* 2000; 2. Avdicová *et al*. 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Infanrix hexa™ induces high seroprotection levels against Hib



Shaded purple area highlights that the Heininger *et al.* 2007 study was a continuation of the Zepp *et al.* 2004 study in the same subjects

[a]Subjects with available results

Hib, *H. influenzae* type b; PRP, polyribosylribitol phosphate

1. Schmitt *et al.* 2000; 2. Avdicová *et al.* 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Infanrix hexa™ protects against diphtheria

Shaded purple area highlights that the Heininger *et al.* 2007 study was a continuation of the Zepp *et al.* 2004 study in the same subjects

[a]Subjects with ≥0.1 IU/ml; [b]Subjects with available results
HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine

1. Schmitt *et al.* 2000; 2. Avdicová *et al*. 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Infanrix hexa™ protects against tetanus

Shaded purple area highlights that the Heininger *et al.* 2007 study was a continuation of the Zepp *et al.* 2004 study in the same subjects

[a]Subjects with ≥0.1 IU/ml; [b]Subjects with available results
HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine

1. Schmitt *et al.* 2000; 2. Avdicová *et al*. 2002; 3. Arístegui *et al.* 2003; 4. Zepp *et al.* 2004; 5. Heininger *et al.* 2007

Booster vaccination

Infanrix hexa™ is effective as a booster vaccine and can induce immune memory

- Heininger *et al*. 2007[1]
  - 341 infants received *Infanrix hexa™* and 102 infants received *Infanrix™* IPV Hib + HBV at 3, 4 and 5 months of age
  - All received an *Infanrix hexa™* booster at 12–18 months of age

HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine; PRP, polyribosylribitol phosphate

1. Heininger *et al.* 2007

Infanrix hexa™ is effective as a booster vaccine at 12–18 months of age

[a]Cut-off ≥0.15 µg/ml

FHA, filamentous haemagglutinin; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B vaccine; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxoid

Heininger *et al.* 2007

Use in preterm infants

Infanrix hexa™ use in preterm infants: Study designs (1)

- Omeňaca *et al*. 2005[1] (primary study)
  - 94 preterm infants and 92 full-term infants received 3 doses of *Infanrix hexa*™ at 2, 4 and 6 months of age
  - Immunogenicity was assessed 4 weeks post-vaccination
- Omeňaca *et al*. 2007,[2,3] 2010[4]
  - Infants from the primary study received a booster dose of *Infanrix hexa*™ at 18–20 months of age and a booster dose of *Infanrix*™ at 4 years of age[3]
  - Anti-PRP antibodies were evaluated before and after the primary and booster doses[2]
  - Anti-HBsAg antibodies were evaluated before and after the primary and booster doses[4]

HBsAg, hepatitis B surface antigen; PRP, polyribosylribitol phosphate

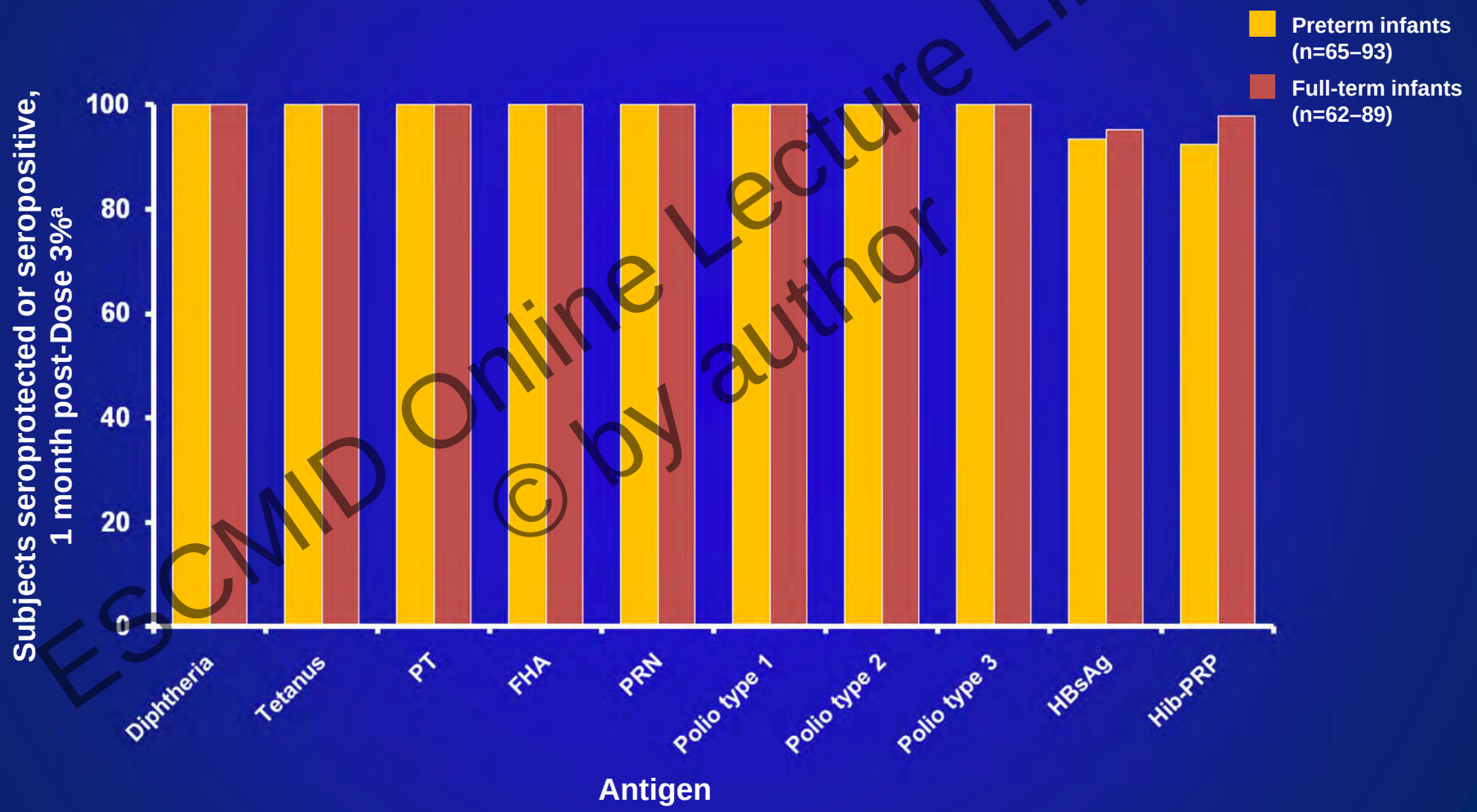
1. Omeñaca *et al*. 2005; 2. Omeñaca *et al*. 2007a; 3. Omeñaca *et al*. 2007b; 4. Omeñaca *et al*. 2010

Infanrix hexa™ use in preterm infants: Study designs (2)

- Vázquez *et al*. 2008[1]
  - 170 preterm infants received *Infanrix hexa*™ at 2, 4 and 6 months of age and a booster vaccination at 18–24 months of age
  - Immunogenicity was assessed before and 1 month after receiving the primary vaccination course, and before and 1 month after the booster dose
  - Analysis was stratified into two groups: infants with birth weight 1.5–2.0 kg and those with birth weight <1.5 kg

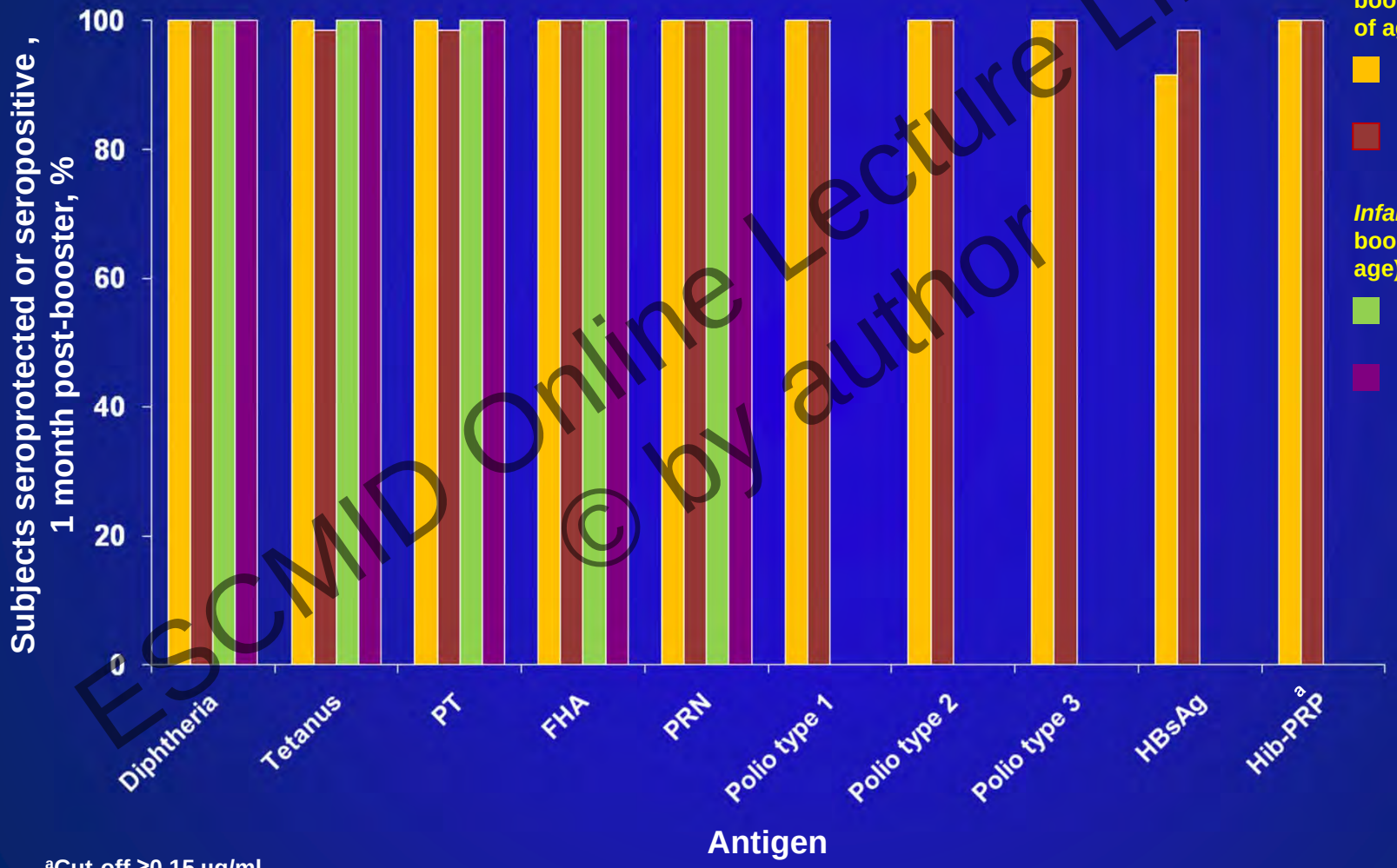
1. Vázquez *et al*. 2008

Infanrix hexa™ is immunogenic in preterm infants



[a]Subjects with antibodies ≥0.1 IU/ml for diphtheria and tetanus, ≥10 mIU/ml for HBsAg, ≥1:8 for poliovirus types 1–3, ≥0.15 µg/ml for PRP
FHA, filamentous haemagglutinin; HBsAg, hepatitis B surface antigen; Hib, *H. influenzae* type b; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxoid
Omeñaca *et al*. 2005

Infanrix hexa™ induced immune memory in preterm infants

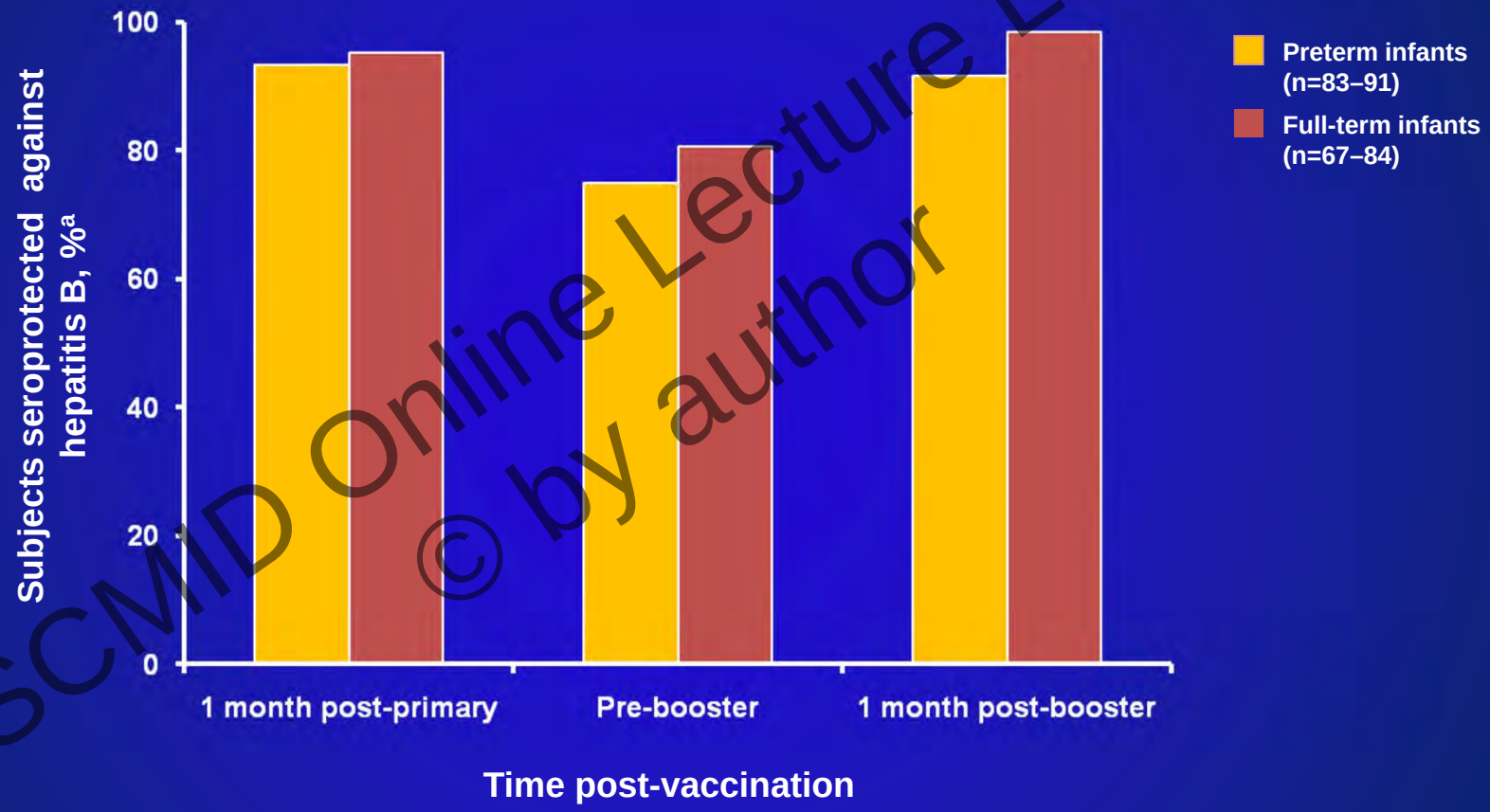


[a]Cut-off ≥0.15 µg/ml

FHA, filamentous haemagglutinin; HBsAg, hepatitis B surface antigen; Hib, *H. influenzae* type b; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxoid

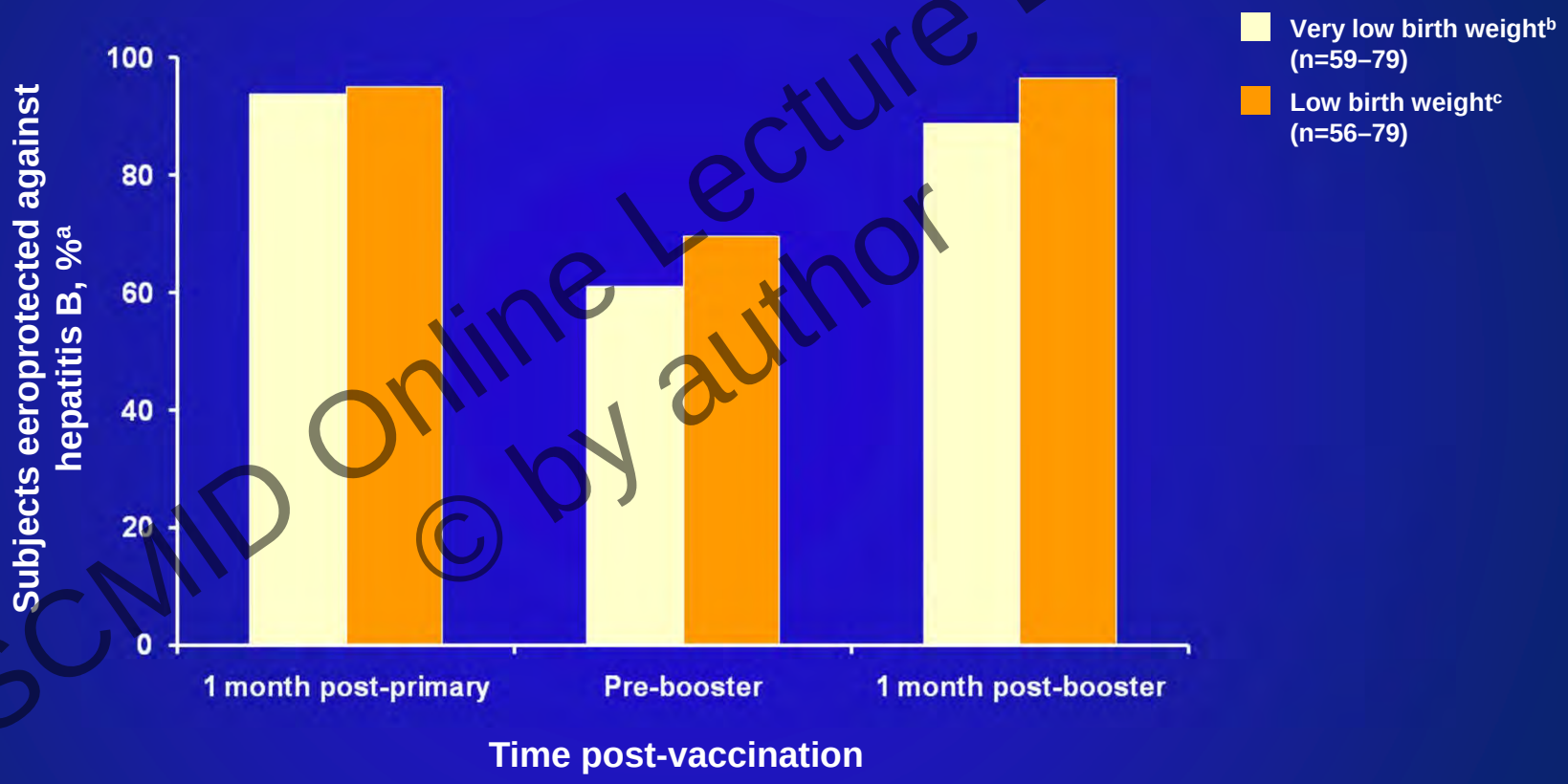
Omeñaca *et al.* 2007

Infanrix hexa™ achieves satisfactory hepatitis B response after primary and booster vaccination



[a]Subjects with anti-HBsAg ≥10 mIU/ml
HBsAg, hepatitis B surface antigen
Omeñaca *et al*. 2010

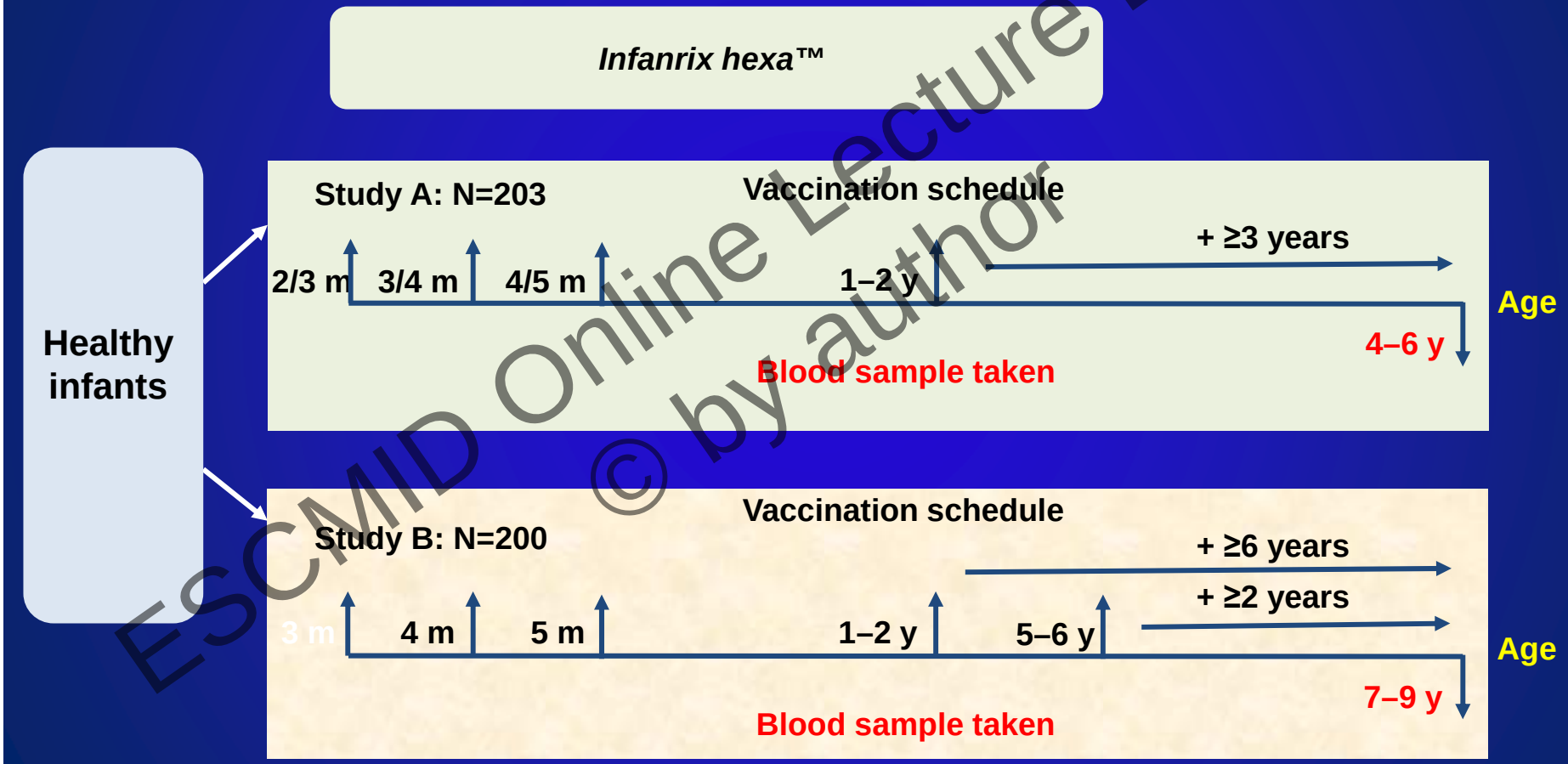
Infanrix hexa™ is effective in protecting preterm infants of very low birth weight against hepatitis B



[a]Subjects with anti-HBsAg ≥10 mIU/ml; [b]<1.5 kg; [c]≥1.5 kg and <2.0 kg
HBsAg, hepatitis B surface antigen
Vázquez *et al*. 2008

Infanrix hexa™
(DTPa-HBV-IPV/Hib)
Persistence data

Persistence of *Infanrix hexa*™: Study design



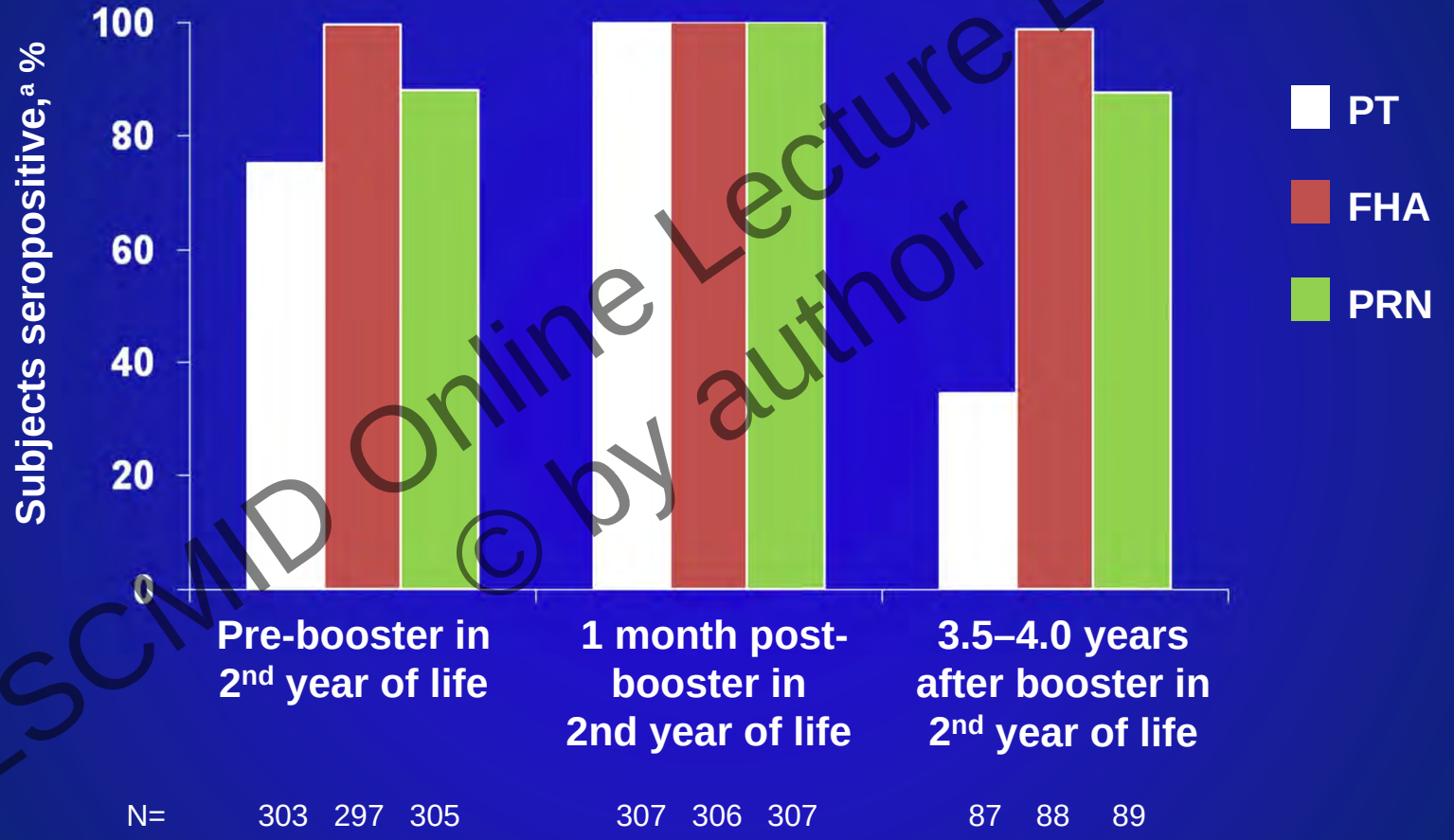
Zinke *et al.* 2011

Infanrix hexa™ induces long-lasting immune responses against all vaccine antigens

	Subjects seroprotected/seropositive, %		
Antigen	Children 4–6 years of age (Study A)	Children 7–9 years of age (not boosted) (Study B)	Children 7–9 years of age (boosted) (Study B)
Diphtheria	96	86	>98[a]
Tetanus	74	64	100[a]
PT	25	32	>60[a]
FHA	>95[a]	98	100[a]
PRN	>85[a]	87	100[a]
Polio type 1	>95	91	100[a]
Polio type 2	>95	91	100[a]
Polio type 3	>95	97	100[a]
HBsAg	86	77	Not tested
Hib-PRP	>95	99	Not tested

[a]Exact numbers not quoted
FHA, filamentous haemagglutinin; HBsAg, hepatitis B surface antigen; Hib, *H. influenzae* type b; PRN, pertactin; PRP, polyribosylribitol phosphate; PT, pertussis toxoid
Zinke *et al.* 2011

Seropositivity rates persist for most pertussis antigens 4 years after *Infanrix hexa*™ primary vaccination



[a]Defined as ≥5 EU/ml if initially seronegative or if seropositive ≥ initial titre
FHA, filamentous haemagglutinin; PRN, pertactin; PT, pertussis toxoid
Heininger *et al.* 2007

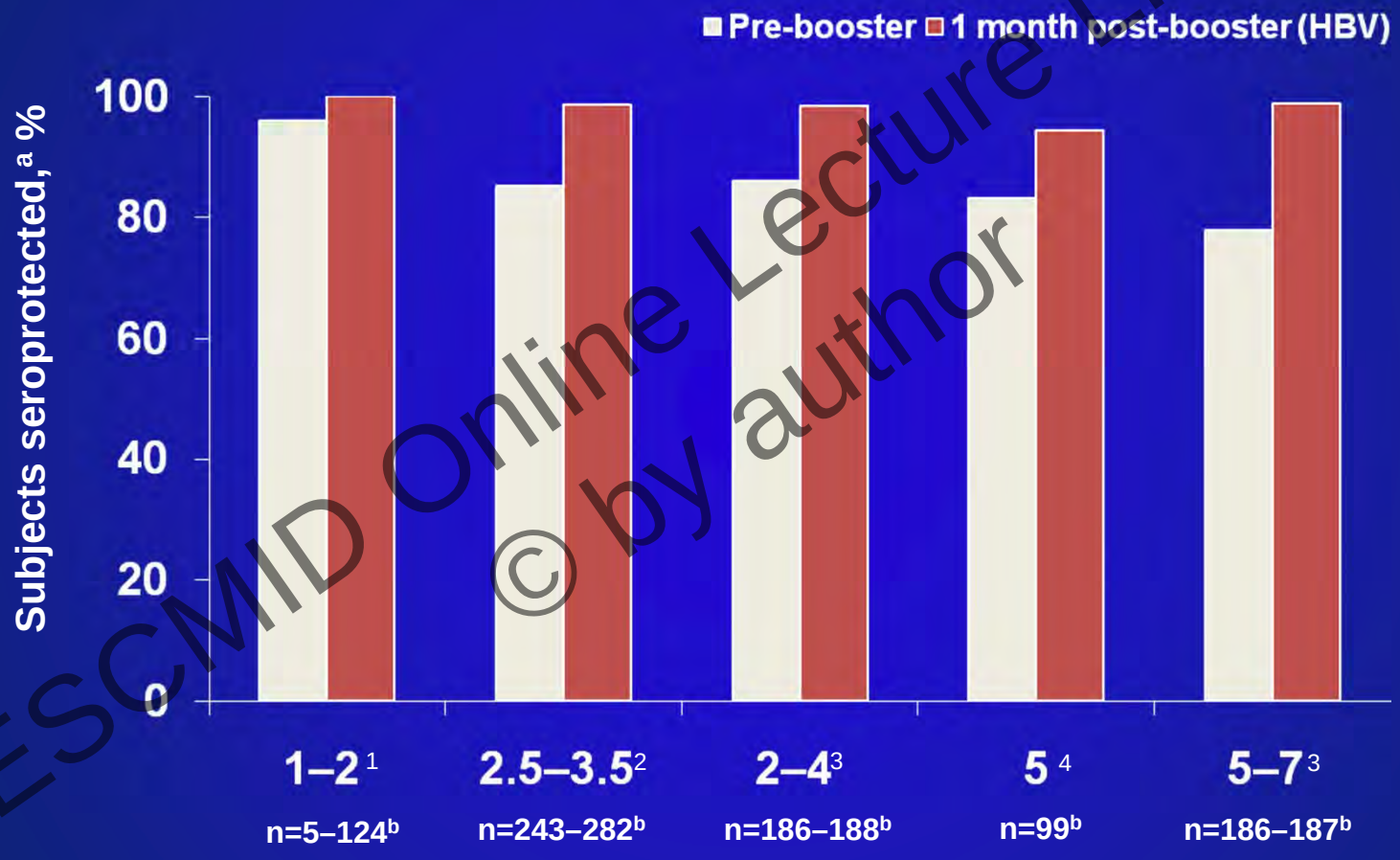
Long-term immunogenicity of HBV vaccine following *Infanrix hexa™* primary vaccination: Study design

Trial	n	Age at which persistence of immunity assessed	Vaccination history	Challenge
Giambi *et al.* 2008[1]	124 113	3 years of age (1–2 years post-vaccination)	3 doses *Infanrix hexa*™ 3 doses Hexavac®	Monovalent HBV (*Engerix-B*™ or HBVaxPro 5®)
Zinke *et al.* 2009[2]	203 200	4–6 years of age (Study A) (2–4 years post-vaccination) 7–9 years of age (Study B) (5–7 years post-vaccination)	4 doses *Infanrix hexa*™	Monovalent HBV (*Engerix-B*™)
Steiner *et al.* 2010[3]	301	4–5 years of age (2.5–3.5 years post-vaccination)	4 doses *Infanrix hexa*™	Monovalent HBV (*Engerix-B*™)
Zanetti *et al.* 2010[4]	710 833	5–6 years of age (5 years post-vaccination)	3 doses *Infanrix hexa*™ 3 doses Hexavac®	Randomised: Monovalent HBV (*Engerix-B*™ or HBVaxPro 5®)

HBV, hepatitis B virus

1. Giambi *et al.* 2008; 2. Zanetti *et al.* 2010; 3. Steiner *et al.* 2010; 4. Zinke *et al.* 2009

Infanrix hexa™ induces long-lasting immune memory against HBV



Time since hexavalent booster vaccination, years

[a]Defined as subjects with an anti-HBsAg titre ≥10 mIU/ml; [b]Number of subjects with available results
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus
1. Giambi *et al.* 2008; 2. Steiner *et al.* 2010; 3. Zinke *et al.* 2010; 4. Zanetti *et al.* 2010

Hexavalent vaccines are highly effective against Hib disease in Germany

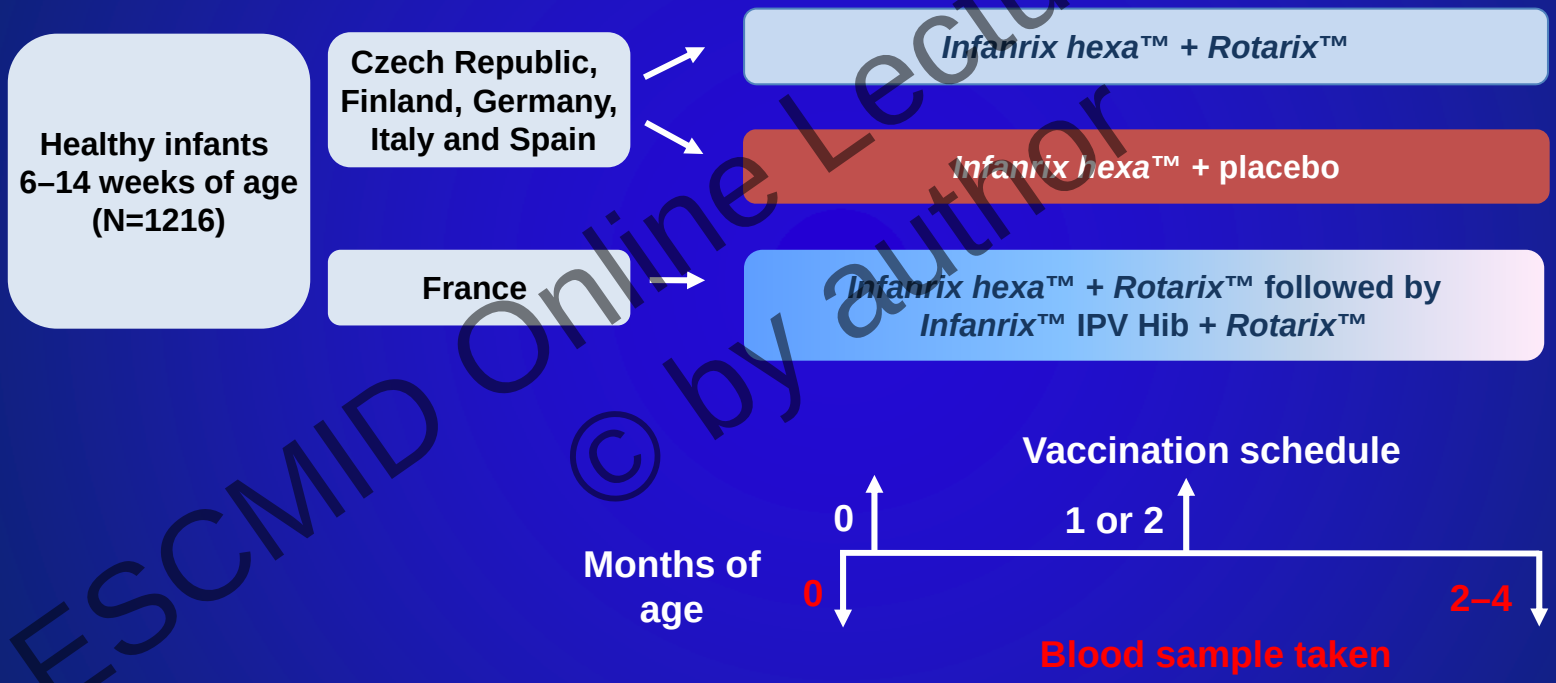
- Case-cohort study
- Invasive Hib disease cases reported during the 5-year study period

	Infanrix hexa™ vaccine effectiveness, % (95% CI)
1–2 dose(s)	68.4 (19.0–87.6)
3 doses	90.4 (70.6–96.8)
3 doses plus booster	100.0 (52.7–100.0)

CI, confidence interval; Hib, *H. Influenzae* type b
Kalies *et al.* 2008

Infanrix hexa™
Co-administration with other vaccine

Co-administration of *Infanrix hexa*™ with *Rotarix*™: Study design



Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine
Vesikari *et al.* 2006

Co-administration of *Infanrix hexa*™ and *Rotarix*™ does not impair the immune response to either vaccine

- The immune response to *Rotarix*™ was high: the anti-rotavirus immunoglobulin A seroconversion rate 1–2 months post-Dose 2 was 86% in both groups
- Co-administration of *Infanrix hexa*™ and *Rotarix*™ did not impair the immune response to *Infanrix hexa*™ antigens
- Seropositivity/seroconversion rates for all vaccine antigens were:
  - 92–99% for *Infanrix hexa*™ + *Rotarix*™
  - 90%–100% for *Infanrix hexa*™ + placebo

Hib, *H. influenzae* type b; IPV, inactivated polio vaccine
Vesikari *et al.* 2006

Co-administration with other pediatric vaccines

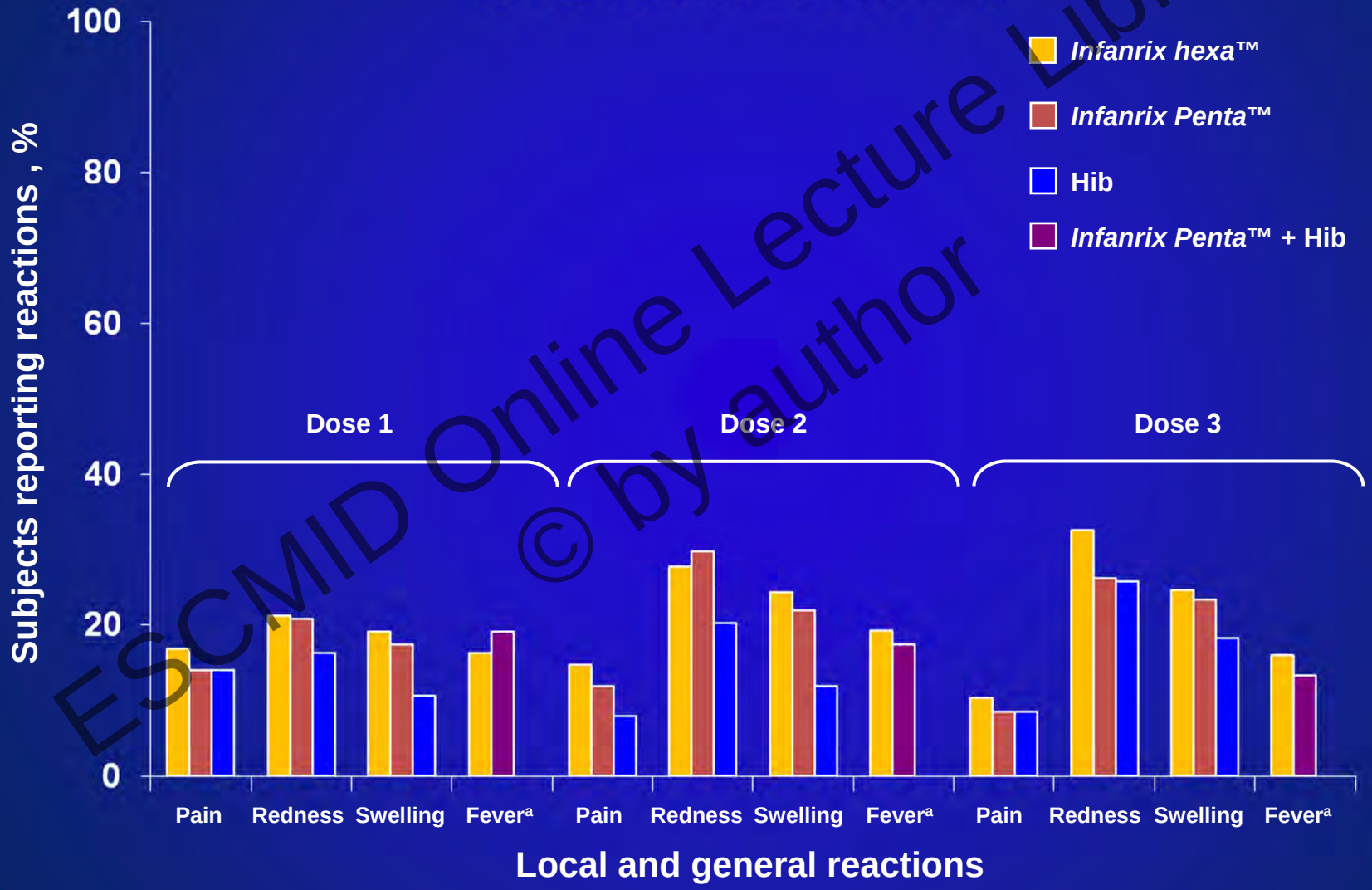
- *"There are sufficient data with regard to the efficacy and safety of simultaneous administration of Infanrix hexa™ and Measles-Mumps-Rubella vaccine".*

- *"Data on concomitant administration of Infanrix hexa™ with Prevnar have shown no clinically relevant interference in the antibody response to each of the individual antigens when given as a 3 dose primary vaccination".*

Infanrix Hexa Prescription information version 7

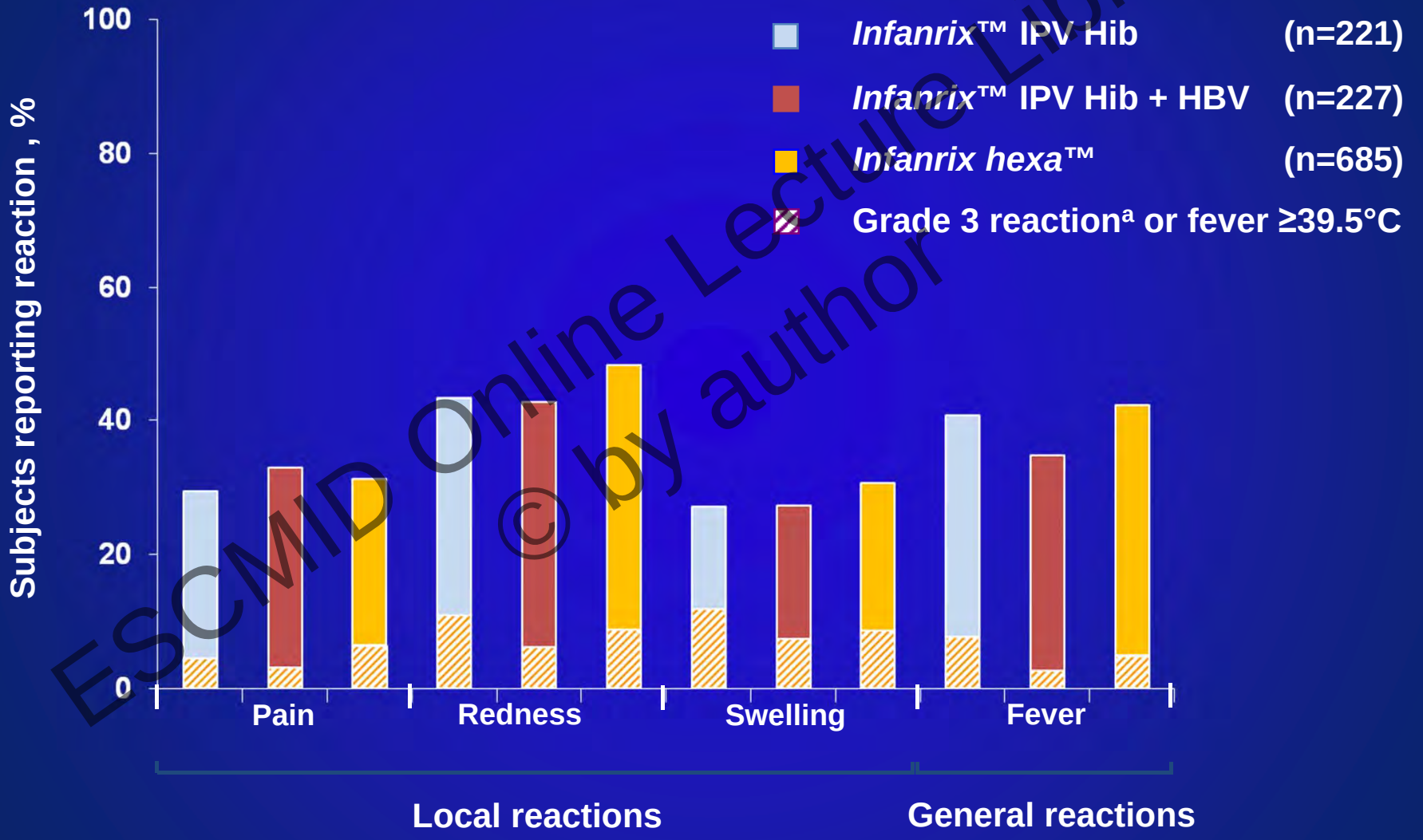
Safety profile of *Infanrix hexa*™

Primary vaccination with *Infanrix hexa*™ is well tolerated



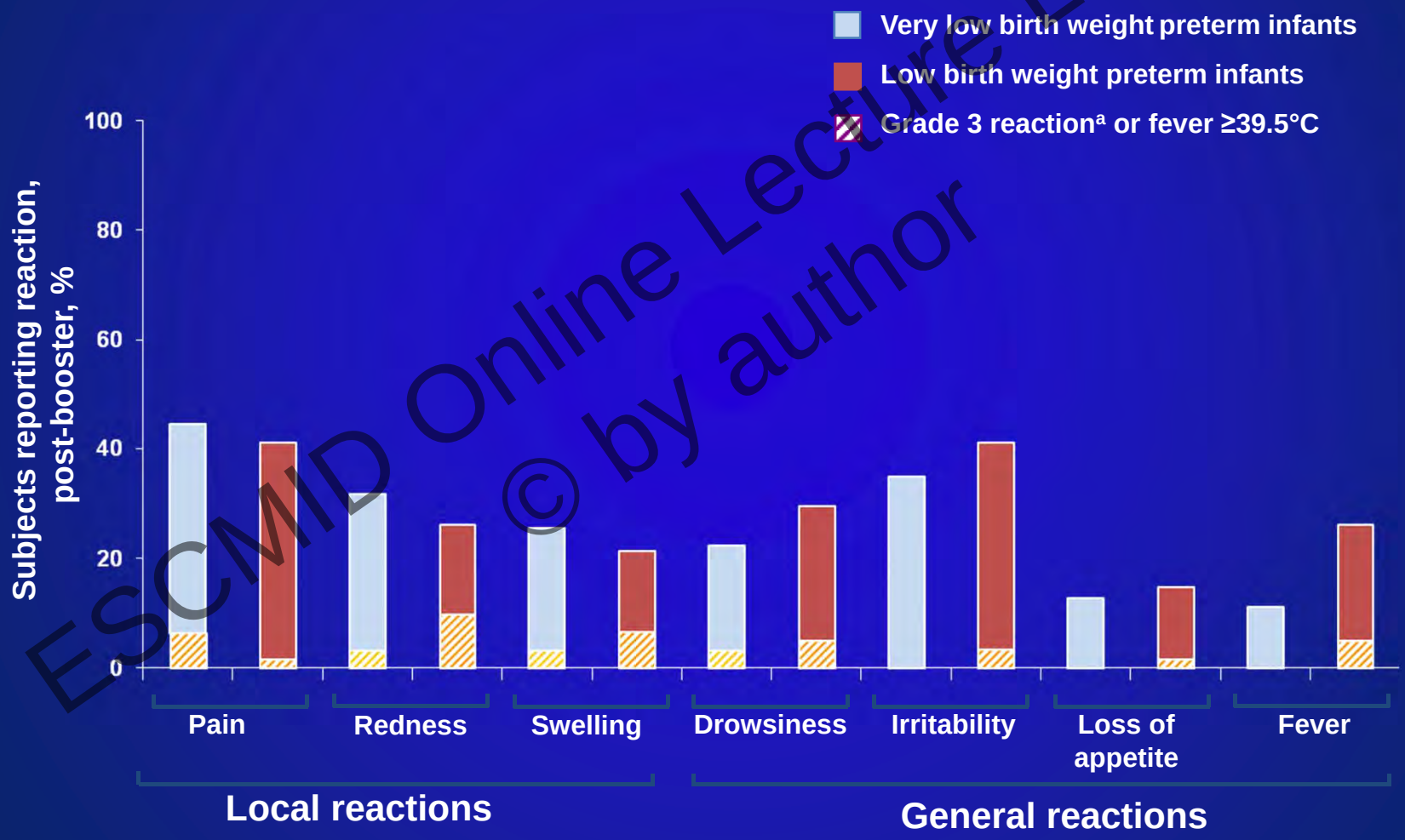
[a]Orange bars represent the incidence of fever after *Infanrix Penta*™ and Hib administration
Hib, *H. influenzae* type b
Schmitt *et al*. 2000

Tolerability of a booster dose of *Infanrix hexa*™ is comparable to that of other booster vaccines



[a]Defined as crying when the limb was moved/spontaneously painful (pain) and diameter >20mm (redness and swelling)
HBV, hepatitis B virus; Hib, *H. influenzae* type b; IPV, inactivated poliovirus vaccine
Saenger *et al*. 2005

Infanrix hexa™ is well tolerated when given to preterm infants



[a]Defined as crying when the limb was moved (pain), diameter >20mm (redness and swelling), inconsolable or persistent crying (irritability) and preventing normal daily activities (all other symptoms)

Vázquez *et al*. 2008

Infanrix hexa™ summary: Reactogenicity

- *Infanrix hexa*™ is well tolerated when used for either primary vaccination or booster vaccination of German infants[1,2]
- The most common reactions reported for *Infanrix hexa*™ are pain, redness and swelling (local), and fever (general)[1–3]
- *Infanrix hexa*™ has been demonstrated to have a favourable tolerability profile when given to preterm infants of low birth weight[4]
- Studies have also demonstrated *Infanrix hexa*™ to be well tolerated when co-administered with other paediatric vaccines, including PCV7, PCV13 and meningococcal vaccines[5–7]

PCV7, 7-valent pneumococcal conjugate vaccine

1. Schmitt *et al.* 2000; 2. Tichmann *et al.* 2006; 3. Saenger *et al.* 2005; 4. Vázquez *et al*. 2008; 5. Tichmann-Schumann *et al.* 2005; 6. Knuf *et al.* 2006; 7. Tejedor *et al.* 2004

Conclusion

- DTPa-HBV-IPV/Hib vaccine as primary and booster vaccination for all its component toxoids/antigens in infants aged <2 years regardless of vaccination schedules:
  - Highly immunogenic
  - Generally safe and well tolerated.
- DTPa-HBV-IPV/Hib (Infanrix *hexa*™) induces long-lasting immune responses against all vaccine antigens.
- Combination vaccines offer advantage of better compliance and coverage and extra doses of antigen/s (e.g HBV) associated with the use of combination vaccine have not found to be harmful.

Thank you
very much for your attention