VHPB ASIA Meeting
Hanoi, Vietnam
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Immunogenicity and safety of combined hepatitis B vaccines
European experience

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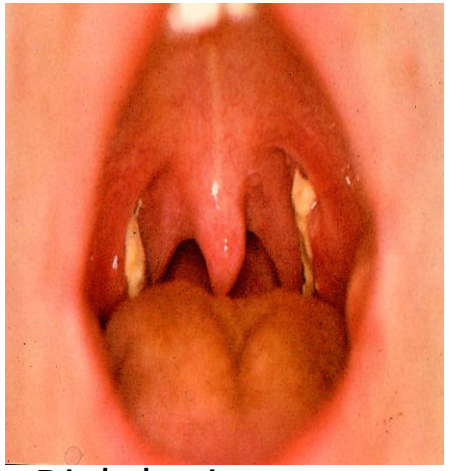
NO CONFLICTS OF INTEREST TO DECLARE

Presentation outline

- Why hexavalent vaccines?
- Safety of hexavalent vaccines
- Immunogenicity of hexavalent vaccines
- Data on long term protection
- Remaining challenges
- Conclusions

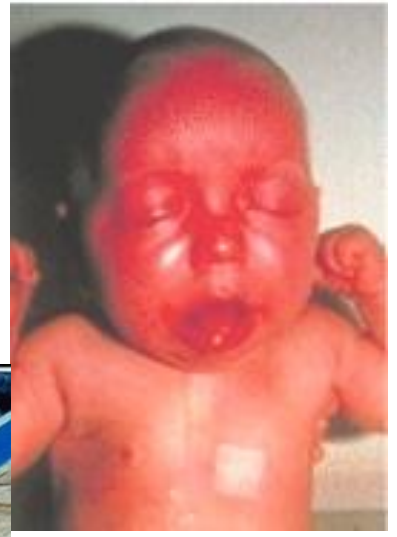
Why hexavalent vaccine ?

Provides protection against six diseases with one vaccination given at/after the age of 6 weeks of age



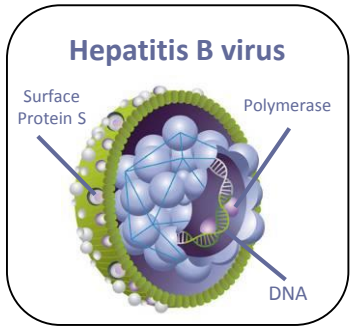
Diphtheria

Tetanus



Pertussis

Hib



Hepatitis B

Poliomyelitis

History of hexavalent vaccines available in Europe

- Hexavac (Sanofi Pasteur MSD, Lyon, France)
  - licensed in 2000 – suspension of authorization in 2005
- Infanrix-hexa (GSK, Riixensart, Belgium)
  - Licensed in 2000
  - Powder and suspension for injection.
- Hexaxim (Hexyon or Hexacima) (Sanofi Pasteur MSD, Lyon, France)
  - Licensed in 2013
  - suspension for injection in pre-filled syringe.
- Vaxelis (Sanofi Pasteur & MSD)
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Esposito S et al CMI 2014
Obando-Pachero P et al Vaccine 2017
www.ecdc

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- More than 20 countries routinely use hexavalent
- Only few use hepatitis B birth dose

Esposito S et al CMI 2014
Obando-Pachero P et al Vaccine 2017
www.ecdc

	Infanrix hexa (GSK)	Hexyon (Sanofi Pasteur)	Vaxelis (MSD)
Diphtheria Toxoid	not less than 30 IU	not less than 20 IU	not less than 20 IU
Tetanus Toxoid	not less than 40 IU	not less than 40 IU	not less than 40 IU
Bordetella pertussis antigens Pertussis Toxoid (PT) Filamentous Haemagglutinin (FHA) Pertactin (PRN) Fimbriae Types 2 and 3 (FIM)	 25 µg 25 µg 8 µg -	 25 µg 25 µg - -	 20 µg 20 µg 30 µg 50 µg
Hepatitis B surface antigen	10 µg	10 µg	10 µg
Poliovirus (Inactivated) Type 1 (Mahoney) Type 2 (MEF-1) Type 3 (Saukett)	 40 D antigen units 8 D antigen units 32 D antigen units	 40 D antigen units 8 D antigen units 32 D antigen units	 40 D antigen units 8 D antigen units 32 D antigen units
Haemophilus influenzae type b polysaccharide (RPR)	10 µg - conjugated to TT 25 µg	12 µg - conjugated to TT 22-36 µg	3 µg – conjugated to OMPC 50 µg
Adjuvants	aluminium hydroxide, hydrated, aluminium phosphate	aluminium hydroxide, hydrated	aluminium phosphate, amorphous aluminium hydroxyphosphate sulfate
Administration age	6 weeks – 36 months	6 weeks – 24 months	6 weeks – 15 months
Co-administration	PCV7, PCV10, PCV13, MenC, MenACWY, Rota, MMRV	PCV, MMR, Rota, MenC, MenACWY	PCV13, MMRV, Rota, MenC

Vaccines SPC's

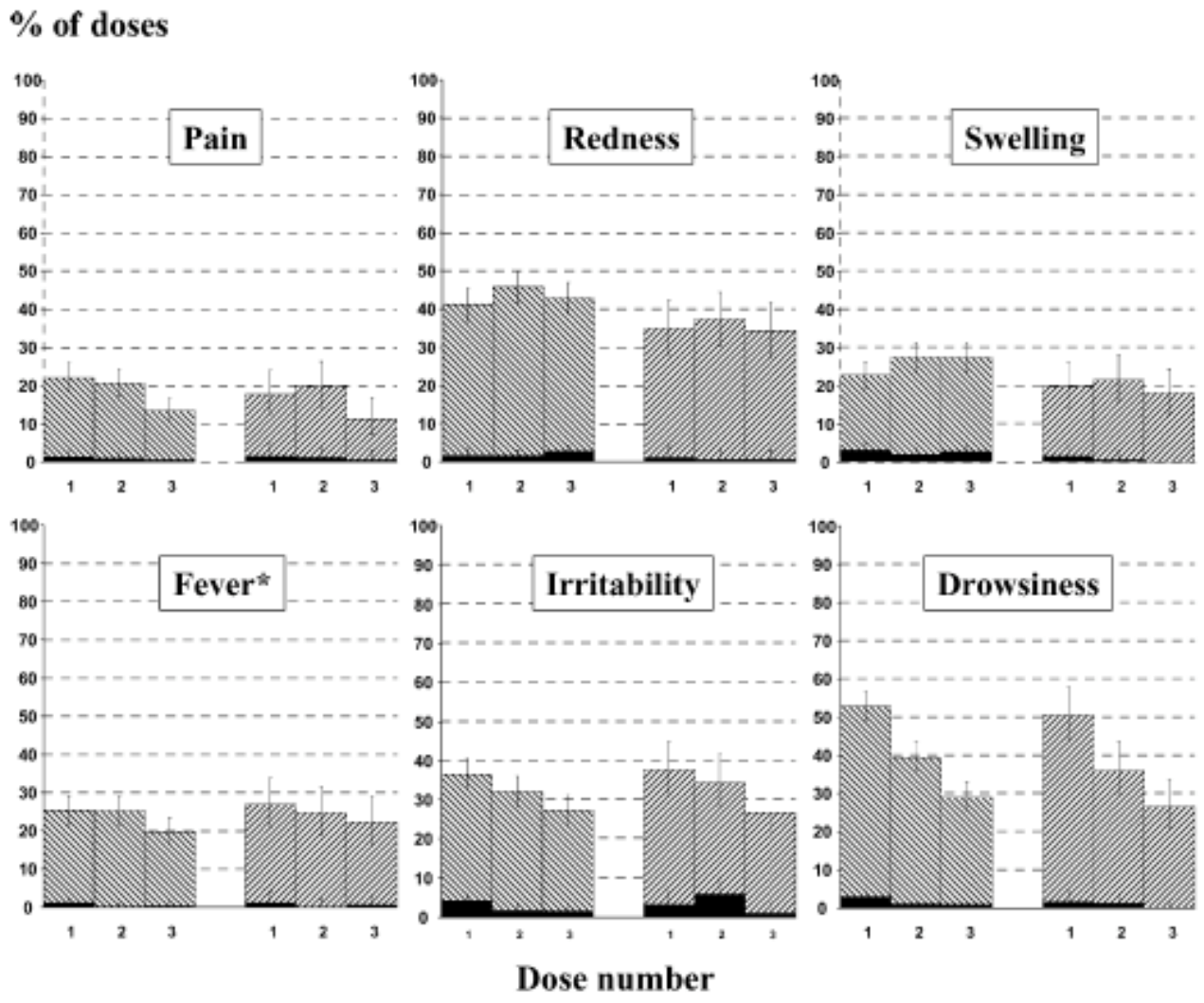
Safety of hexavalent vaccines

Safety of hexavalent vaccines

- May be administered in infants ≥ **6 weeks of age**
- Overall well tolerated and safe even when co-administered with other pediatric routine vaccines (PCVs, MCCs, MenB, rotavirus, MMR, VZV).
- Most common AE:
  - local redness at injection site most common
  - fever >38 ^{0}C in a third of infants but >39.5 ^{o}C in only 3.5%
- SAE reported in <3% of vaccine recipients.
- Sudden unexpected death (SUD) not associated with hexavalent vaccines.

Esposito S et al CMI 2014
Von Kries R et al Eur J Pediatr 2005
Saenger R et al Vaccine 2005
Traversa G et al PLoS One 2011

Safety profile of Infanrix Hexa vs penta +HBV



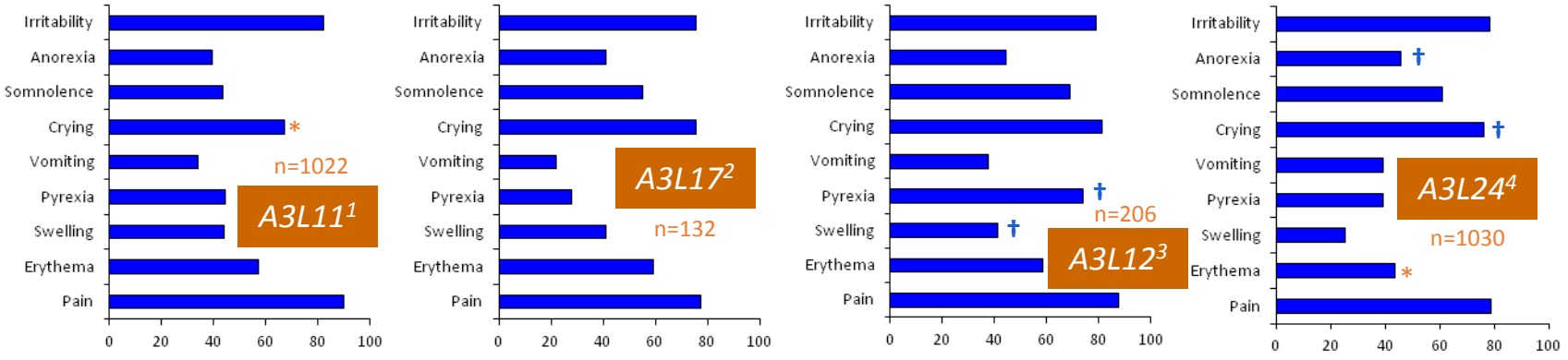
Zepp et al Vaccine 2004

Comparable incidence of solicited reactions reported during primary series Infanrix Hexa versus Hexyon

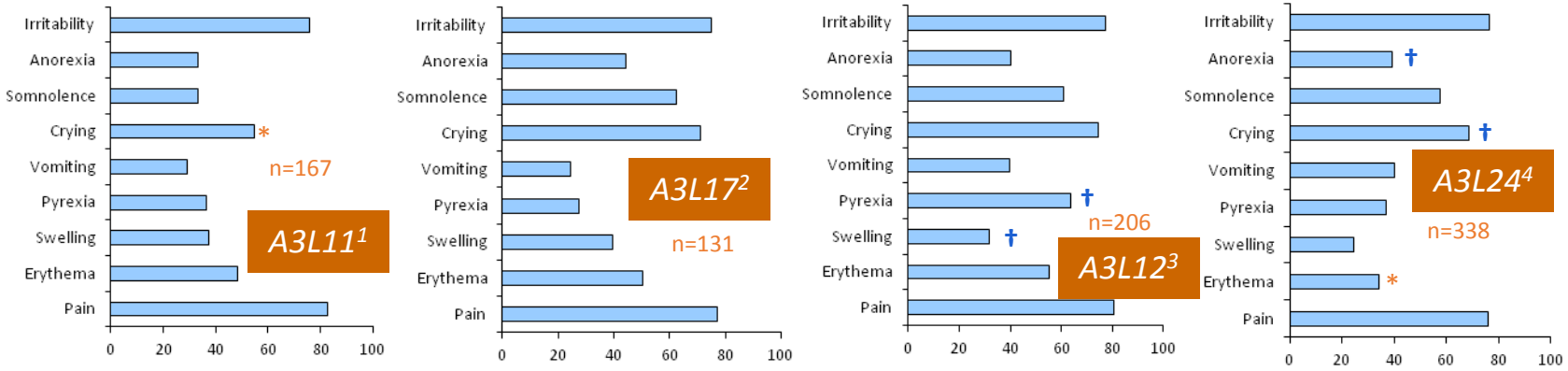
A3L11[1]
A3L17[2]
A3L12[3]
A3L24[4]

Schedule 2/4/6 ± 15/18 months

Hexyon

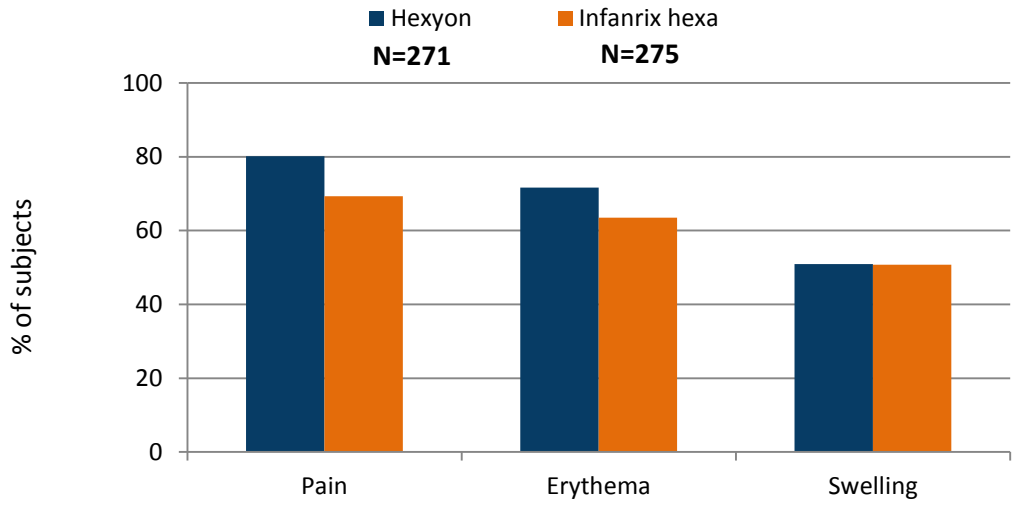


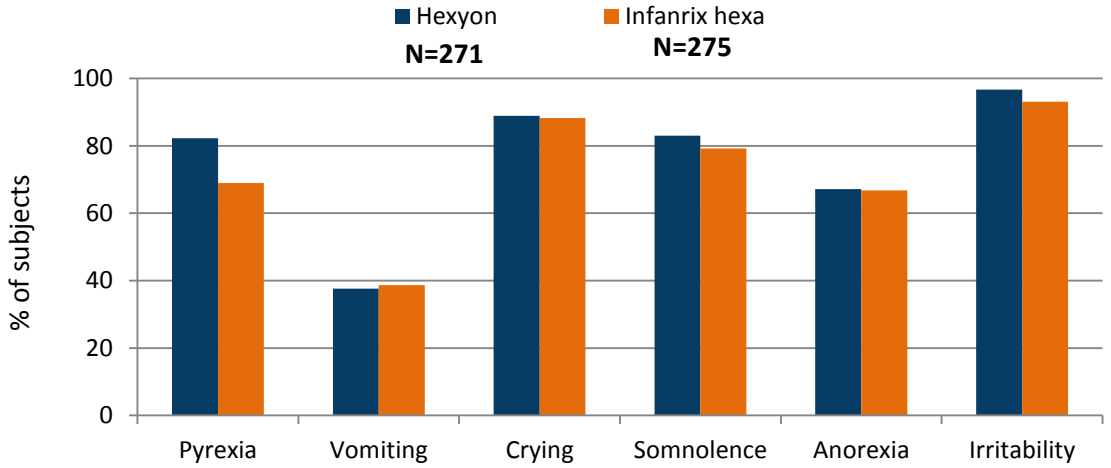
Infanrix Hexa



1. Becerra A et al. Vaccine 2012;30:6492–6500 ;
2. Lanata C et al. Vaccine and Vaccination 2012;3(1):1-5
3. Kosalaraska P et al. Int J Infect Dis. 2011;15(4):e249–256
4. López P et al. Congress ICID: 13-16 June 2012

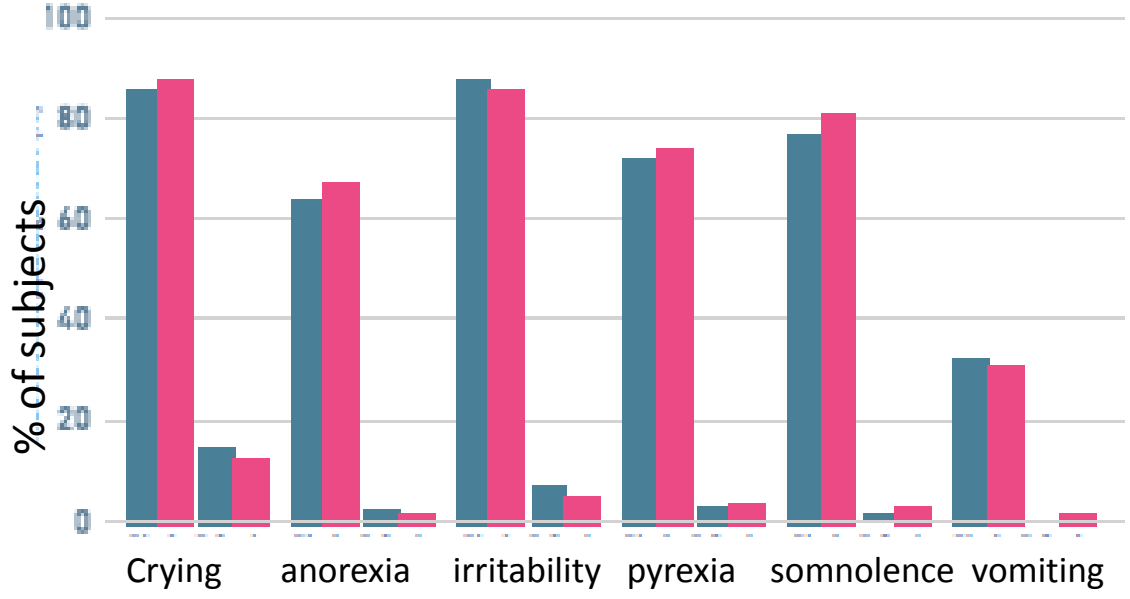
Safety profile of Infanrix hexa and Hexyon co-administered with PCV13 in a 2+1 schedule (3, 5, 11/12 mos)

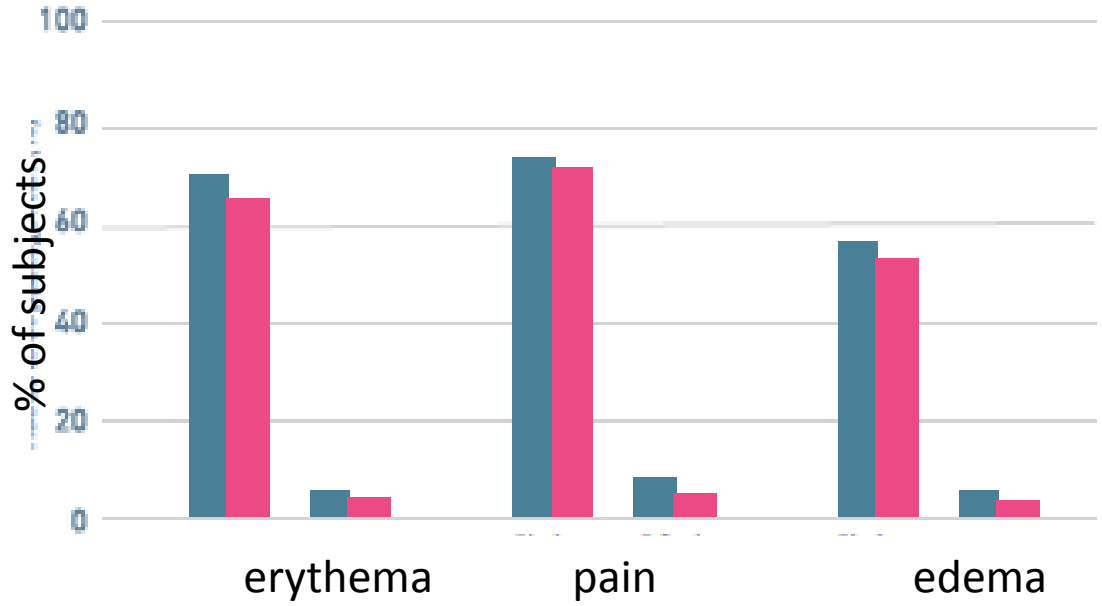




Vesikari T et al Vaccine 2017

Safety profile of Vaxelis and Infanrix hexa co-administered with PCV13/RotaTeq in a 3+1 schedule (2,3,4, 12 mos)





Vesikari T et al PIDJ 2017

Safety of hexavalent vaccines

- Hypotonic-hyporesponsive episode (**HHE**) is defined as the sudden onset of hypotonia, hyporesponsiveness, and pallor or cyanosis that occurs within 48 hours after vaccination.
- HHE is benign self-resolving, continuation of vaccination is recommended

Vigo A et al. HVI 2017

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- Paracetamol administered **prophylactically** post immunization decreases reactogenicity but also reduces immunogenicity to several antigens

Vigo A et al. HVI 2017
Primula et al Lancet 2009
Das RR et al PLoS One 2014

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- Infanrix Hexa may be used for the timely immunization of premies >24 wks GA, limited data on Vaxelis

- Experience >15 years, million doses administered

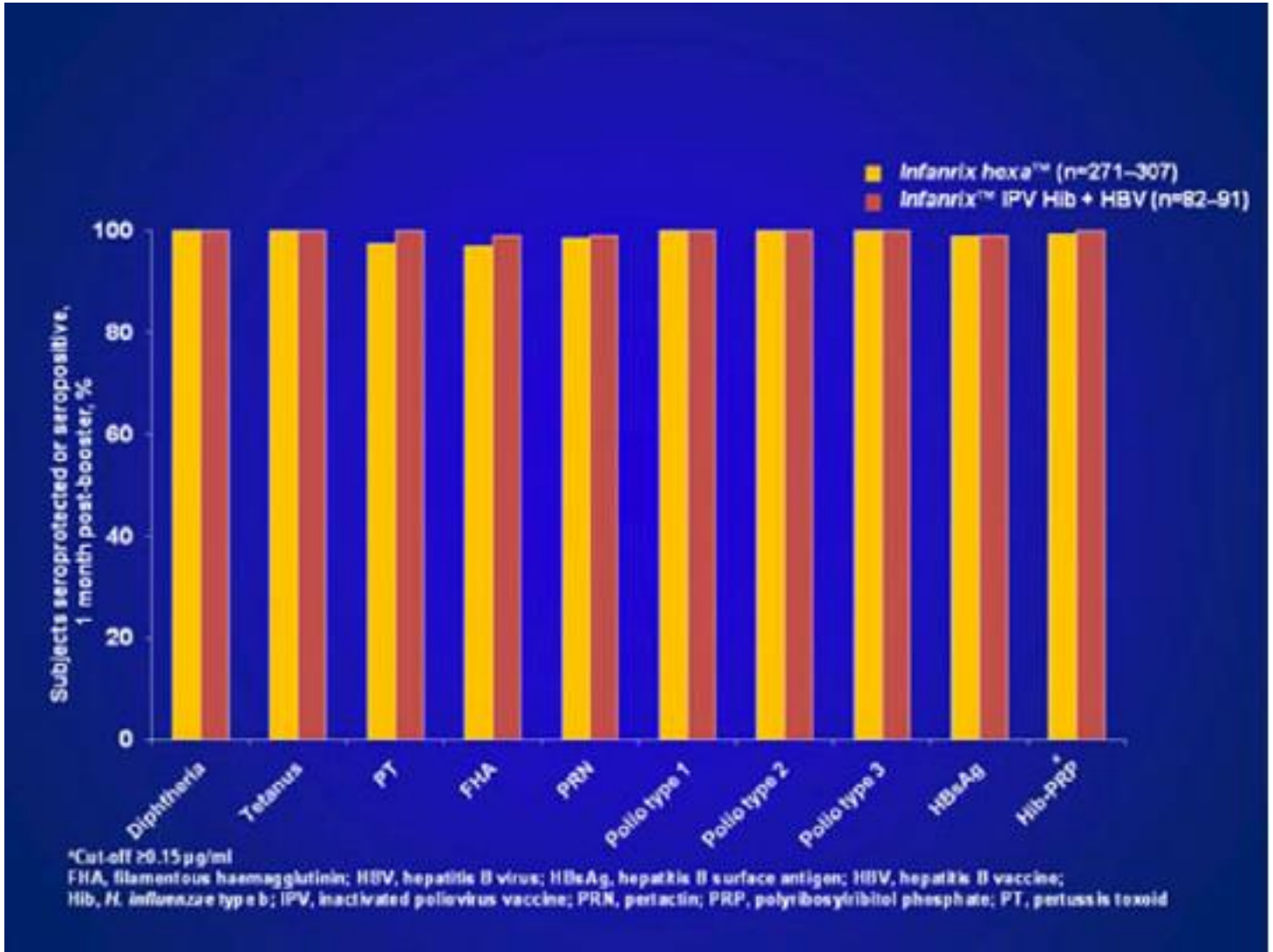
Vigo A et al. HVI 2017
Primula et al Lancet 2009
Das RR et al PLoS One 2014

Immunogenicity of hexavalent vaccines

Immunogenicity of hexavalent vaccines

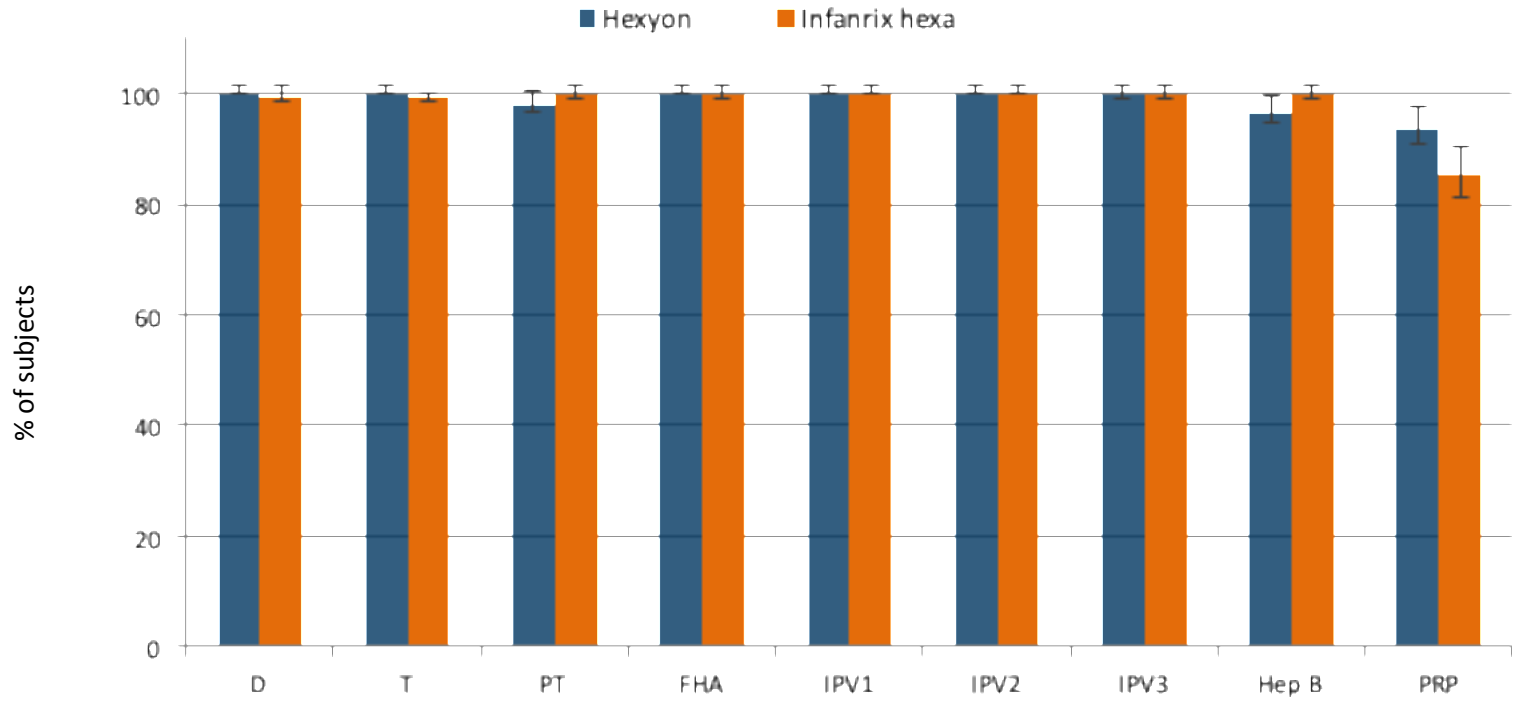
All three available formulations have shown non-inferiority of immunogenicity

Immunogenicity
Infanrix Hexa vs Infanrix-IPV-Hib + HBV



Heininger U et al Vaccine 2007

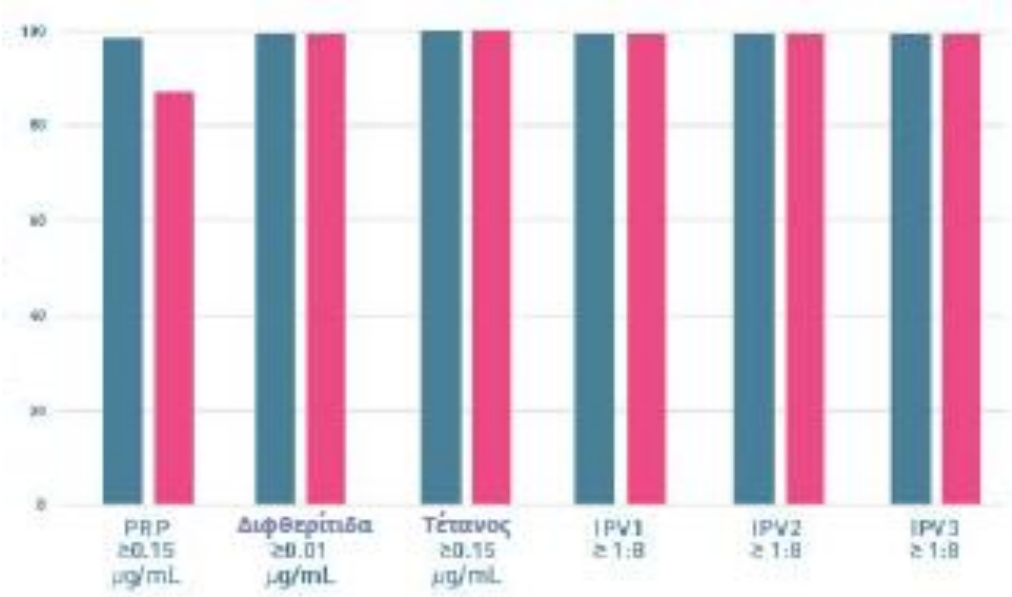
Immunogenicity: Infanrix Hexa vs Hexyon co-administered with PCV13 at 3, 5 –11/12 months (2+1)



Non-inferiority in seroconversion rates 1 month post dose 3

Vesikari T et al PIDJ 2017

Immunogenicity
Vaxelis versus Infanrix Hexa



VAXELIS® Infanrix hexa

Vesikari T et al PIDJ 2017

Long term protection

Long term protection post Infanarix-Hexa

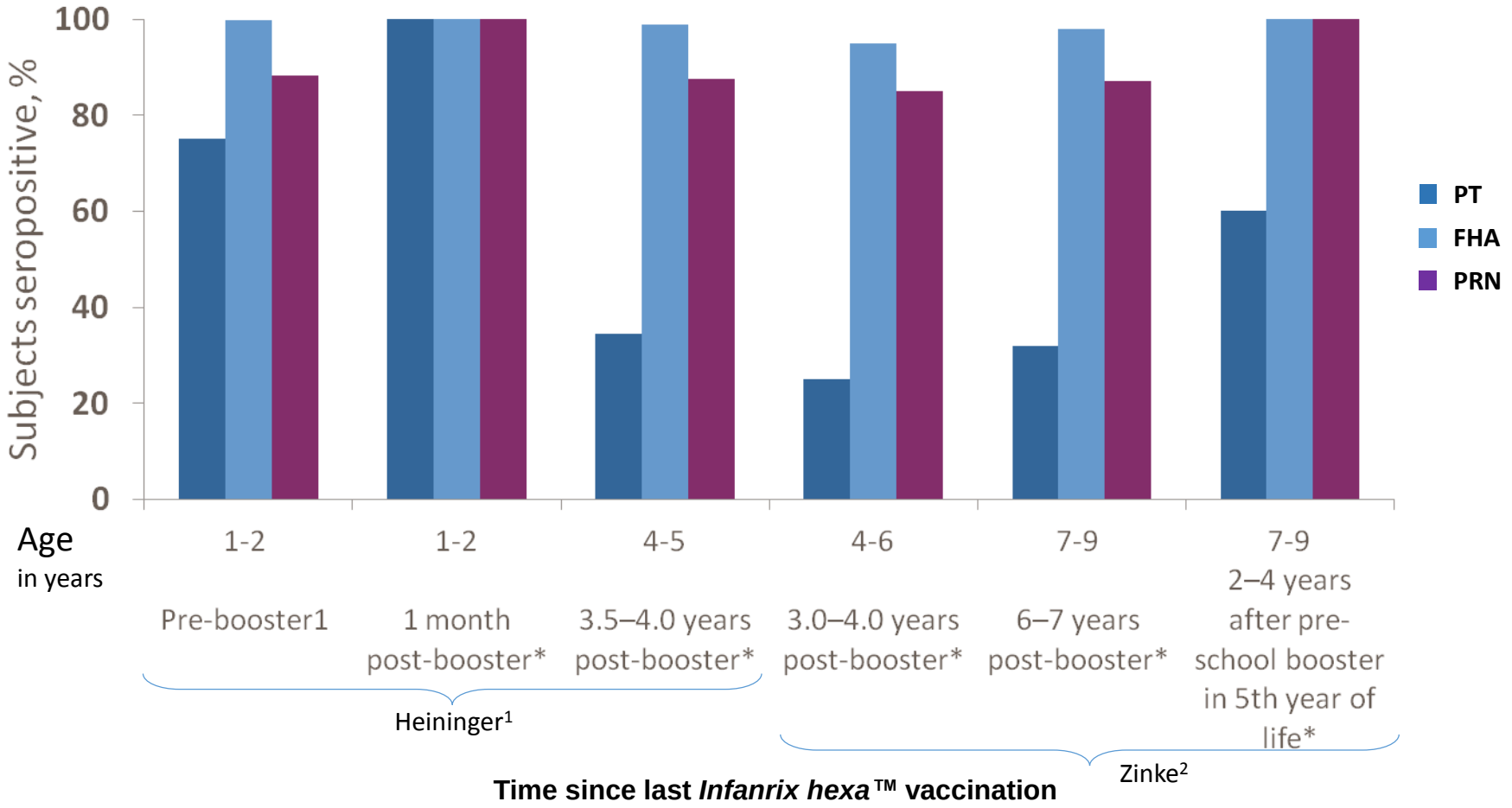
Antigen	Subjects seroprotected/seropositive, %		
	Children 4–6 years of age	Children 7–9 years of age (not boosted)	Children 7–9 years of age (boosted)
Diphtheria	96	86	>98[a]
Tetanus	74	64	100[a]
PT	25	32	>60[a]
FHA	>95[a]	98	100[a]
PRN	>85[a]	87	100[a]
Polio type 1	>95	91	100[a]
Polio type 2	>95	91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

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

Zinke et al Human Vacc 2010
Esposito S et al CMI 2014

Long-lasting Immunogenicity Efficacy

High seropositivity rates were documented to persist for FHA and PRN pertussis antigens up to 7 years



*Toddlers 3-dose primed with *Infanrix hexa*™ or *Infanrix*™ IPV Hib and HBV, having received an *Infanrix hexa*™ booster in the 2nd year of life
FHA, filamentous haemagglutinin; PRN, pertactin; PT, pertussis toxoid

1. Heininger *et al. Vaccine* 2007;25(6):1055–1063; 2. Zinke *et al. Hum Vaccine* 2010;6(2):189–193

Immunological persistence in 5yo (Hexa @ 3,5,11 months)

Table 1 Number* with antibody levels above assay cut-offs and geometric mean concentrations (GMC) in children 5 y of age after vaccination in infancy at 3, 5 and 11–12 months of age

		DTPa-HBV-IPV/Hib			DTPa-IPV/Hib		
		Post II	Post III	Persistence at 5 y of age	Post II	Post III	Persistence at 5 y of age
Diphtheria	≥0.1 IU/ml	11/11	11/11	7/12	37/38	39/39	28/45
	GMC (95% CI)	2.8 (1.4; 5.6)	8.8 (5.3; 14.9)	0.130 (0.1; 0.2)	0.9 (0.6; 1.4)	4.9 (3.8; 6.4)	0.2 (0.1; 0.3)
Tetanus	≥0.1 IU/ml	11/11	11/11	10/12	38/38	39/39	34/44
	GMC (95% CI)	4.2 (2.6; 6.7)	8.9 (6.3; 12.6)	0.3 (0.1; 0.6)	3.0 (2.2; 4.0)	9.9 (8.3; 11.9)	0.4 (0.2; 0.6)
PT	≥5 EU/ml	9/9	10/10	0/12	37/37	38/38	9/45
	GMC (95% CI)	32.3 (19.8; 52.7)	76.8 (50.5; 116.9)	2.5 (2.5; 2.5)	41.1 (32.6; 51.7)	89.9 (72.2; 112.0)	4.2 (2.9; 6.0)
FHA	≥5 EU/ml	9/9	10/10	12/12	37/37	38/38	41/45
	GMC (95% CI)	124.5 (62.5; 247.7)	325.8 (217.5; 488.1)	32.6 (11.5; 92.5)	208.9 (160.6; 271.8)	443.1 (345.4; 568.5)	50.7 (30.6; 84.1)
PRN	≥5 EU/ml	9/9	11/11	8/12	37/37	38/38	34/45
	GMC (95% CI)	105.3 (41.4; 268.0)	354.2 (193.6; 648.0)	6.2 (3.9; 9.9)	87.4 (58.9; 129.9)	265.5 (182.0; 387.2)	11.9 (8.4; 16.8)
HBV**	≥10 mIU/ml	6/6	7/7	5/12	NA	NA	NA
	GMC (95% CI)	249.8 (110.2; 566.2)	1436.6 (535.9; 3851.1)	9.0 (3.9; 20.9)	NA	NA	NA
Hib	≥0.15 µg/ml	9/10	11/11	10/12	35/38	39/39	40/45
	GMC (95% CI)	0.7 (0.2; 2.4)	16.5 (9.5; 28.5)	0.4 (0.2; 0.7)	1.5 (0.8; 2.7)	26.4 (17.3; 40.3)	0.9 (0.6; 1.4)

Silfverdal SA et al HVI 2014

Overview of recommended schedules for the hexavalent vaccines

Table 4
Posology specified in the summary of product characteristics of the different hexavalent vaccines available.

	Full-term infants		Preterm infants >24 weeks		HepB
	Primary Vaccination (minimum 6 weeks old)	Booster Vaccination	Primary Vaccination	Booster Vaccination	In the absence of hepatitis B vaccination at birth, it is necessary to give a hepatitis B vaccine booster dose. Hexavalent vaccines can be considered for HepB booster dose. When a hepatitis B vaccine is given at birth, hexavalent vaccines can be used as replacement for supplementary HepB doses after week 6.
Infanrix® Hexa	3-dose (at least 1 month intervals between doses)	At least 6 months after priming and preferably before 18 months*	3-dose (at least 1 month intervals between doses)	At least 6 months after priming and preferably before 18 months.	
	2-dose (at least 2 month intervals between doses)	At least 6 months after priming and preferably before 11–13 months*			
Hexyon®	3-dose (at least 1 month intervals between doses)	At least 6 months after priming**	No data available		
	2-dose (at least 2 month intervals between doses)	At least 6 months after priming**			
Vaxelis®	3-dose (at least 1 month intervals between doses)	At least 6 months after priming***	Can be given	Can be given	
	2-dose (at least 1 month intervals between doses)	At least 6 months after priming***	Can be given	Can be given	

* Not later than 36 months.
** Not later than 24 months.
*** Not later than 15 months.

Obando-Pachero P et al. Vaccine 2017

Challenges

- Long term data on newer formulations
- Immunogenicity against Hib
- Pertussis (PT post hexa)
- Interchangeability – vaccine shortage
- Too many hepatitis B vaccine doses ???
  - Studies Latin America & Asia post birth dose
  - Flexibility to combine with pentavalent vaccines shown in a recent review and clinical practice

Wang S et al Exp Rev Vacc 2017
Capeding M et al Vaccine 2014
Kwak G et al. Vaccine 2012
Dolhain J et al Exp Rev Vacc 2018

Hexavalent vaccines and alternative schedules take home message

	Birth dose (HBV monovalent)	Primary vaccination			Booster dose (11 mos – 24 mos)
		1st dose	2nd dose	3rd dose	
1	+/-	2mos	4mos	6mos	√
2	+/-	2mos	3mos	4mos	√
3	+/-	2mos	4mos	-	√
4	+/-	3mos	5mos	-	√
6	+/-	6wks	10wks	14wks	√

Hexavalent vaccines and alternative schedules take home message

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*** Pentavalent vaccines used**

Hexavalent vaccines and alternative schedules take home message

	Birth dose (HBV monovalent)	Primary vaccination 1st dose	2nd dose	3rd dose	Booster dose (11 mos – 24 mos)
1	+	2mos	**4mos**	6mos	√
2	+	2mos	**3mos**	4mos	√
3	+	2mos	**4mos**	-	√
4	+	3mos	**5mos**	-	√
6	+	6wks	**10wks**	14wks	√

*** Pentavalent vaccines used**

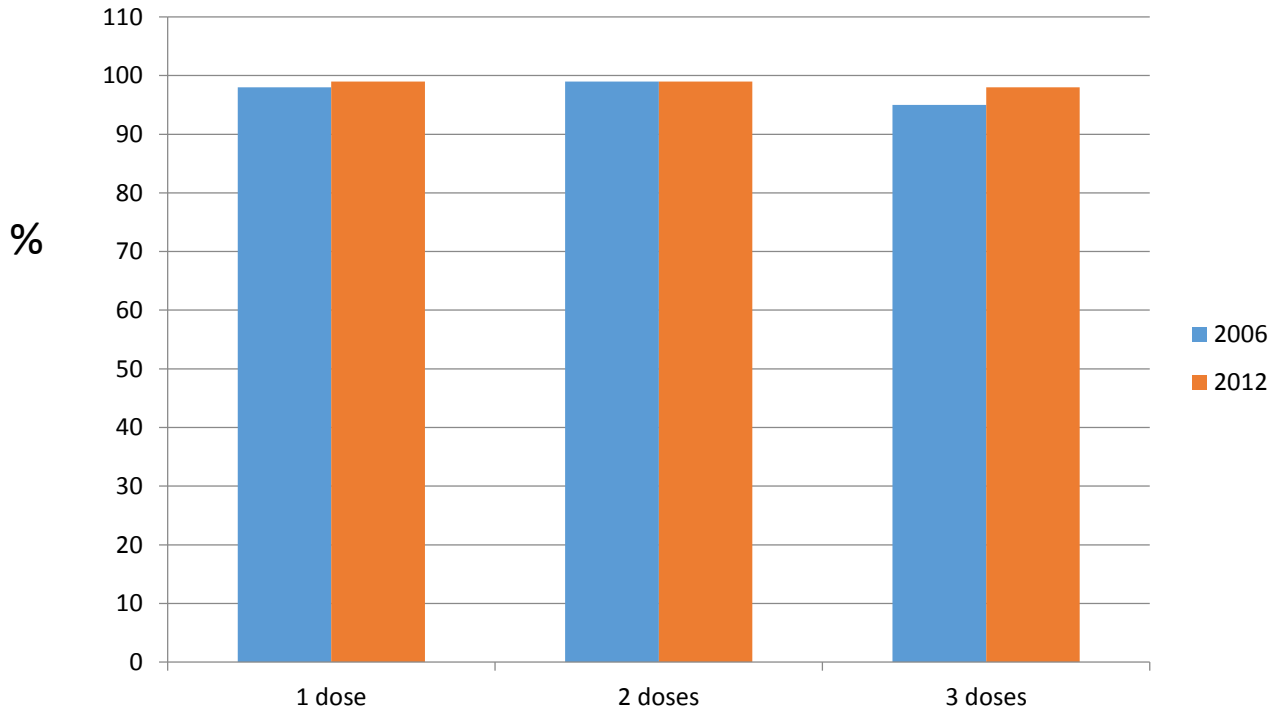
Use of hexavalent vaccines

to increase vaccination coverage against hepatitis B

The example of Greece

Example of Greece

- HBV vaccine was introduced in NIP in 1998
- Hep B vaccination coverage among 6 year old children

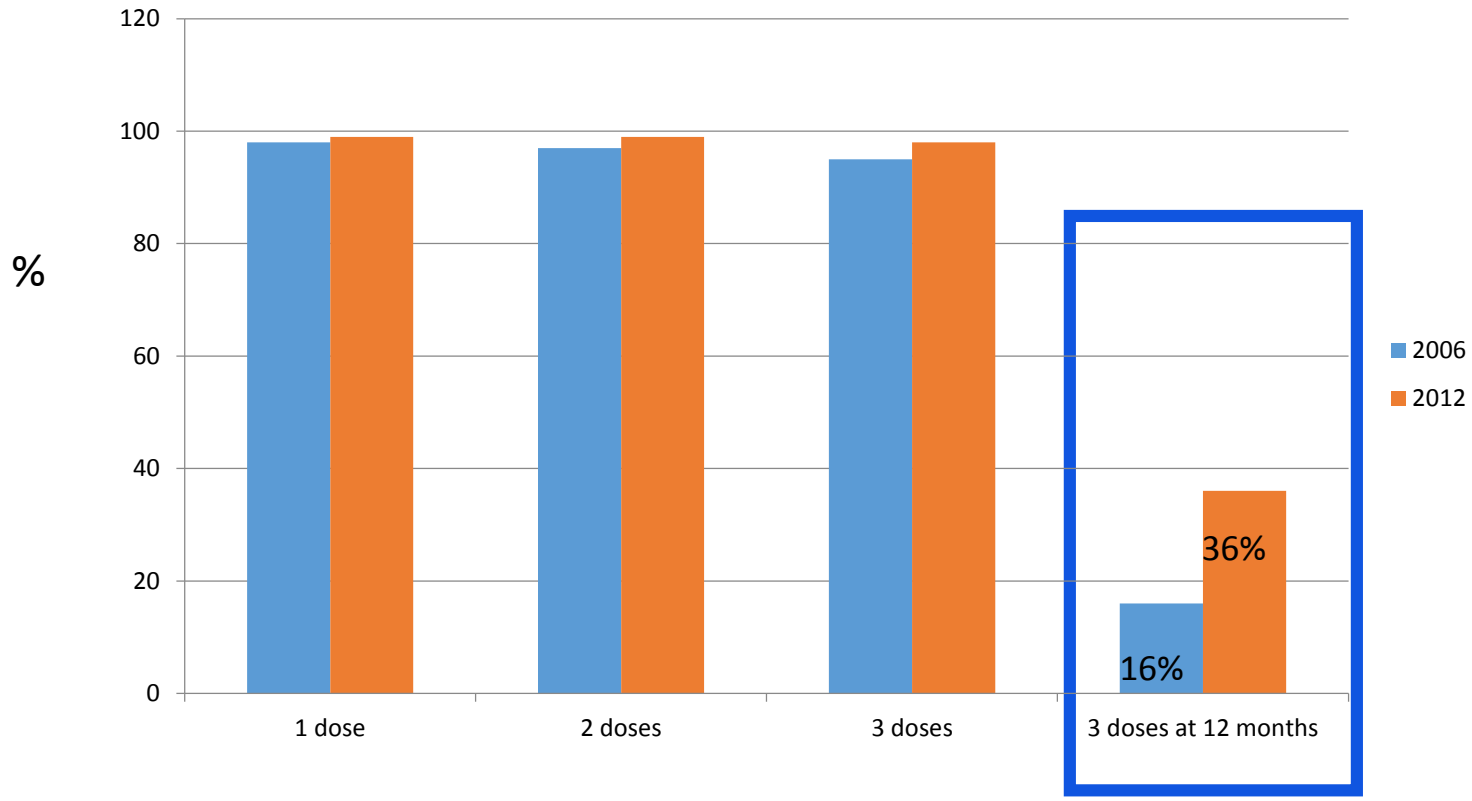


Source: Panagiotopoulos T,et al.
National Vaccination Coverage study 2006 & 2012.

Example of Greece

VHPB

However, timeliness of HBV vaccine administration suboptimal



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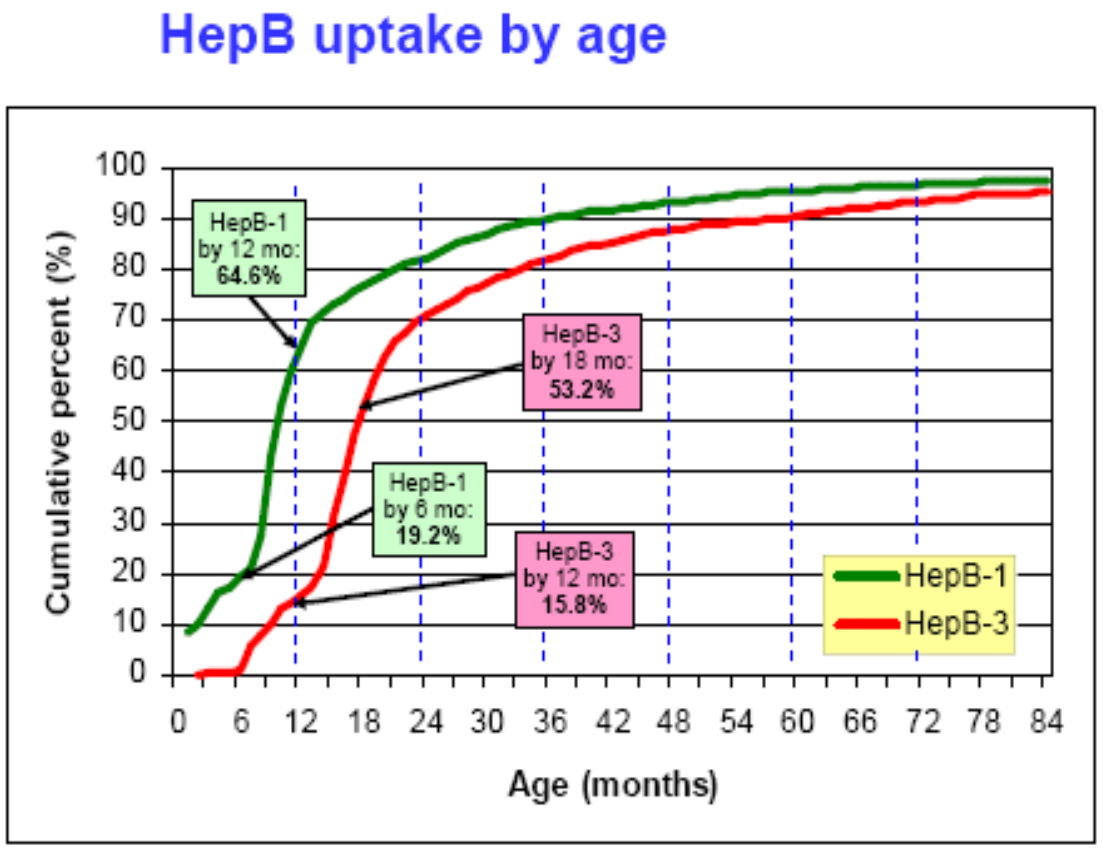
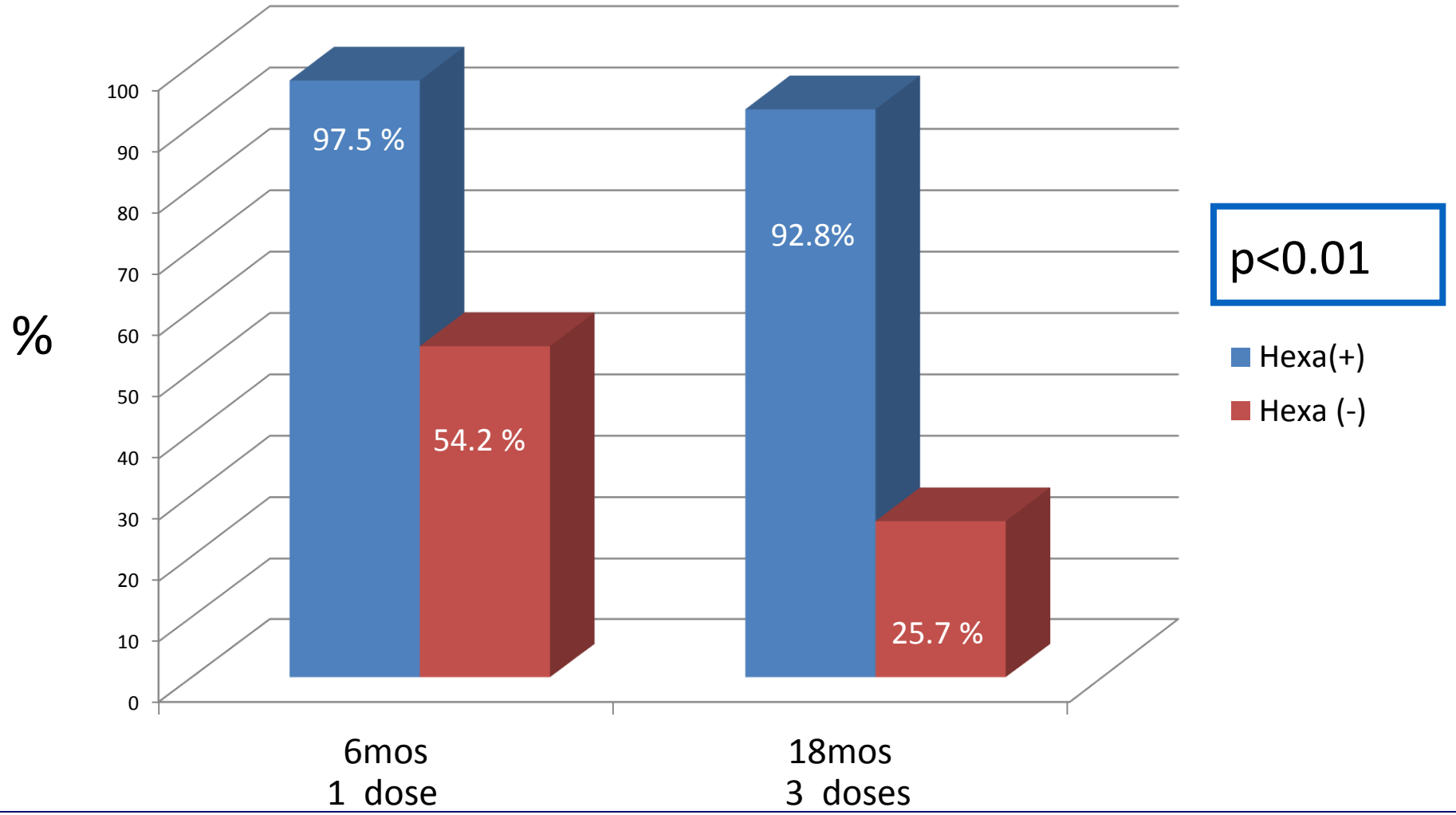
Example of Greece

VHPB



Source: Panagiotopoulos T,et al.
National Vaccination Coverage study 2006 .

HBV vaccination and use of hexavalent vaccine



Papaevangelou V et al. BMC Public Health. 2014

Conclusions

SOS
1. Either table with studies on birth dose
2. Overview of studies from old talks

- Hexavalent vaccines are immunogenic
- Can be administered in infants ≥ 6 weeks of age
- Have been used in Europe for more than 15 years and have shown excellent safety and tolerability profile
- Provide long term protection against all infections including hepatitis B – more data is needed for the new formulations
- Can be co-administered with other pediatric routine vaccines
- Use of hexavalent vaccines increases protection against VPDs

Thank you for your attention