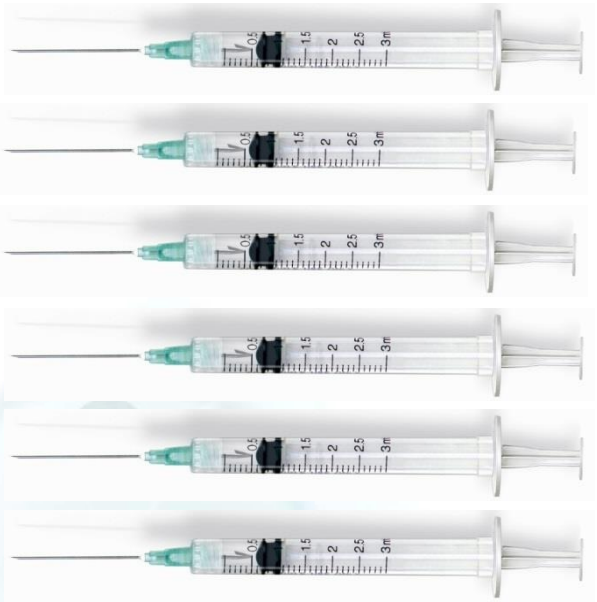
Viral Hepatitis Prevention Board
Hanoi, 25–26 July 2018



Hexavalent Vaccines: Hepatitis B antibody response and co-administration with other vaccines

Prof. Timo Vesikari
Vaccine Research Center
University of Tampere
Tampere, Finland

Academic Expertise in Vaccine Research

Vaccine Research Center
UNIVERSITY OF TAMPERE
Finland

Timo Vesikari
Conflicts of Interest

PI in several study protocols on

- Infanrix Hexa (GSK)
- Hexaxim/Hexyon (SP-MSD)
- Vaxelis or PR5I (Merck)

Consultant to GSK 2016

Member (Chair) of SP-MSD Advisory Board for Pediatric Vaccines until 2017

Consultant to Merck on PR5I until 2017

Landscape

Infanrix hexa (GSK)

- gold standard
- requires reconstitution of lyophilized Hib component

Hexyon / Hexacim (Sanofi Pasteur)

- fully liquid

Vaxelis (Merck)

- gully liquid

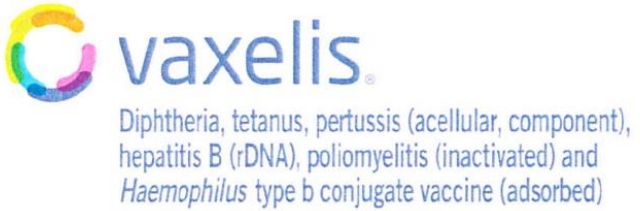
Real differences in immunogenicity between the vaccines are minor or non-existent

Infanrix hexa™ (GSK)

Clever trade name implying that this is the basic vaccine for infants

Hexaxim / Hexyon® (Sanofi Pasteur)

Vaxelis® (Merck)



Runner-ups for trade name and substance

Comparison of pertussis components in hexavalent vaccines

Vaxelis	5	PT, FHA, PRN, FIM2,3
Infanrix hexa	3	PT, FHA, PRN
Hexyon	2	PT, FHA

No known difference in clinical protection against pertussis

Aluminum adjuvant in hexavalent vaccines

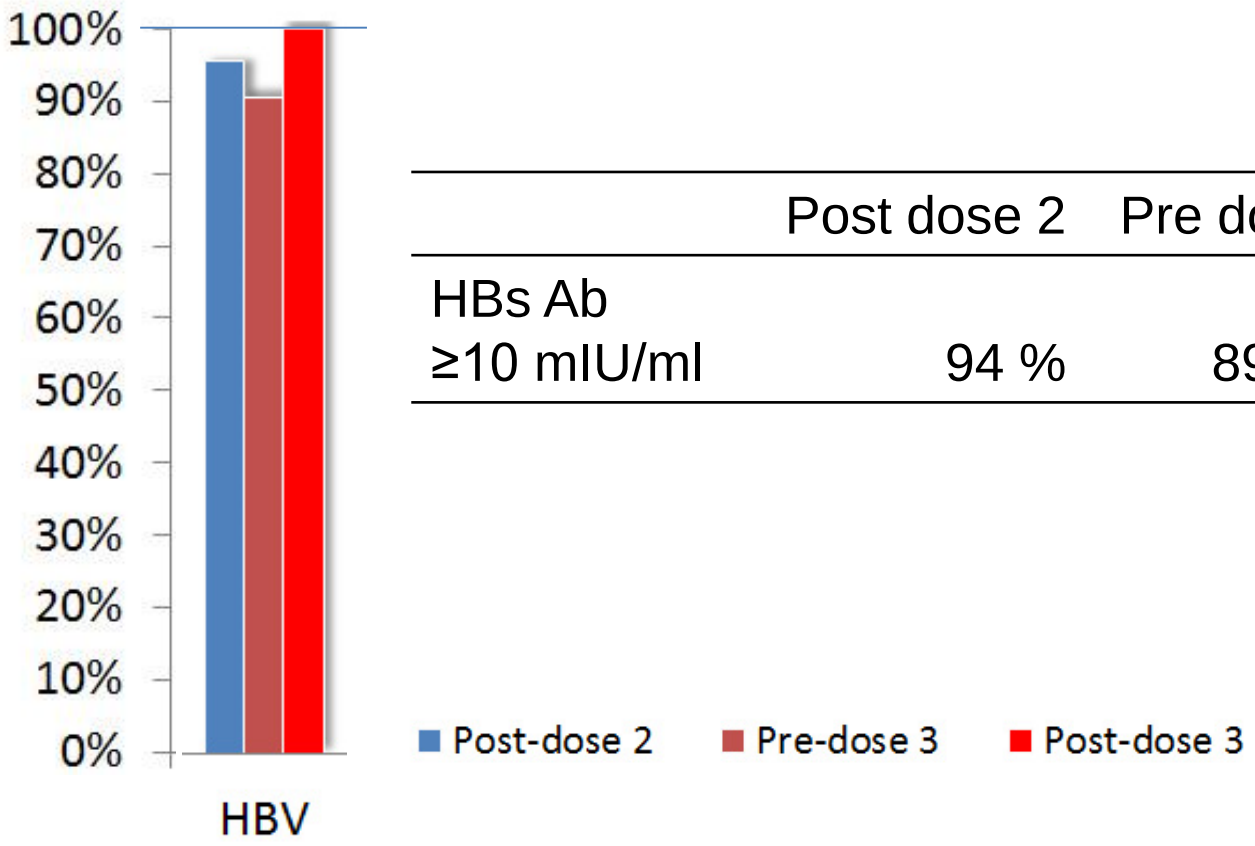
	Al^{+++} per dose
Vaxelis	0.3 mg
Hexyon	0.6 mg
Infanrix hexa	0.8 mg

Clinical experience with *Infanrix hexa*

Antibody	SP cut-off	% SP subjects
Anti-D	0.1 IU/ml	≥ 98.0
Anti-T	0.1 IU/ml	≥ 99.6
Anti-HBs	10 mIU/ml	≥ 96.8
Anti-polio 1	1:8	≥ 99.4
Anti-polio 2	1:8	≥ 95.7
Anti-polio 3	1:8	≥ 98.8
Anti-PRP	0.15 µg/ml	≥ 91.7 (2 doses)
		≥ 96.4 (3 doses)

All schedules combined. Data from *Infanrix™ hexa* European SPC

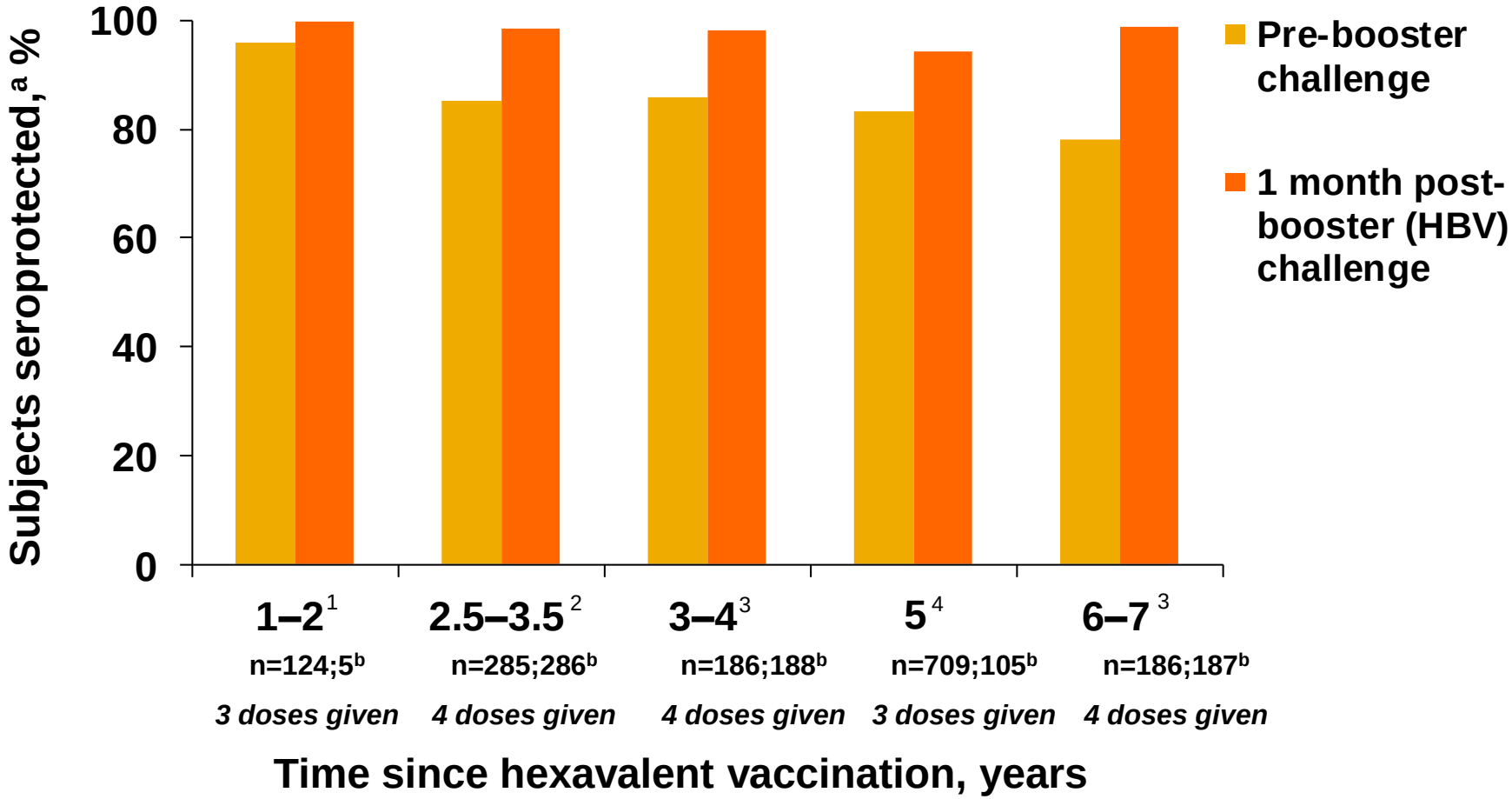
Experience in Finland:
(2+1 schedule 3-5-12 months of age)



	Post dose 2	Pre dose 3	Post dose 3
HBs Ab ≥10 mIU/ml	94 %	89.7 %	99.1 %

Kilpi TM et al. Hum Vaccine 2009;5:18–25.

Infanrix hexa™ induced long-lasting immune memory against HBV



[a]Defined as subjects with an anti-HBsAg titre ≥10 mIU/ml; [b]Number of subjects with available results (pre-booster;post-challenge)
HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus

1. Giambi *et al. BMC Infect Dis* 2008;8:100; 2. Steiner *et al. BMC Infect Dis* 2010;10:9; 3. Zinke *et al. Hum Vaccin* 2009;5(9):592–598;
4. Zanetti *et al. Lancet Infect Dis* 2010;10(11):755–761

Infanrix hexa™: Established use

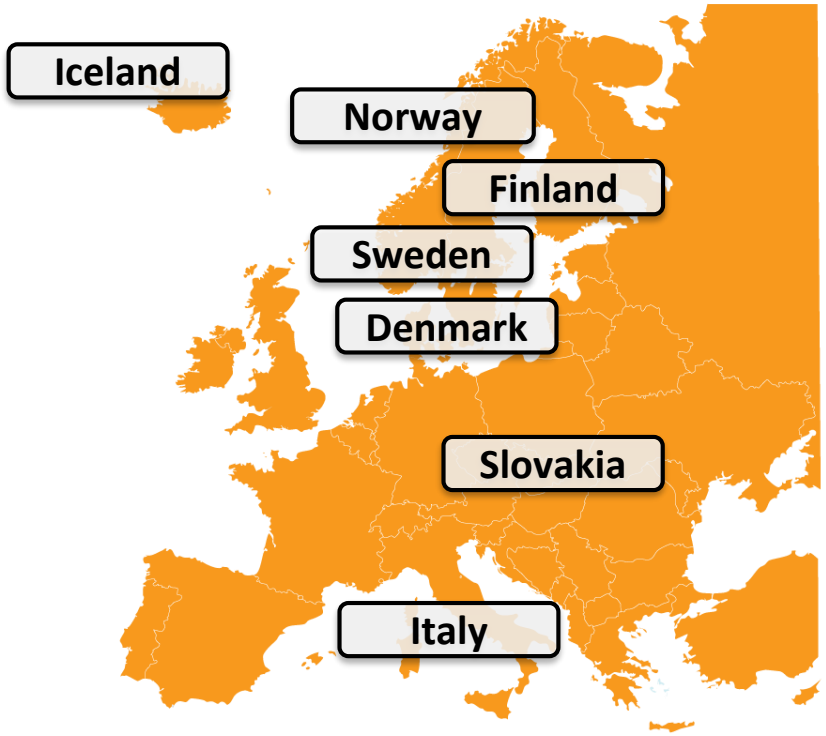
Infanrix hexa™ has extensive evidence supporting its use, encompassing >10 years of clinical practice and >15 years in clinical studies[1–3]

– In the decade following licensure, *Infanrix hexa*™ was administered in over 100 GSK-sponsored interventional studies with 27 500 infants receiving *Infanrix hexa*™ as a primary vaccine, and over 21 000 children receiving a booster dose

As of the end of December 2012, over 90 million doses of *Infanrix hexa*™ have been distributed worldwide, helping to protect children in 95 countries against six serious childhood diseases[4,5]

Infanrix hexa™ can be used in a two-dose primary and booster vaccination schedule[1]

A number of countries recommend the use of a 2-dose primary and booster vaccination schedule, including:[2]



Please check individual country recommendations for the full schedules

Infanrix hexa™ can be given with other vaccines

Infanrix hexa™ can be co-administered with the following vaccines:[1–12]

Pneumococcal vaccines

- ***Prevenar***®
- ***Prevenar 13***®
- ***Synflorix***™

Meningococcal vaccines

- ***Bexsero***™
- ***Nimenrix***™
- ***NeisVac-C***™
- ***Meningitec***™

Rotavirus vaccines

- ***Rotarix***™
- ***RotaTeq***®

MMRV vaccine

- ***Priorix-Tetra***™
- ***ProQuad***®

In general, co-administration does not meaningfully impact on the immunogenicity of any of the vaccine components[13–18]

MMRV, measles-mumps-rubella-varicella

Hexyon

- Unique hexavalent vaccine in a fully liquid, ready-to-use formulation
- Indicated for primary and booster vaccination of infants and toddlers from 6 weeks to 24 months of age combining:
  - Well-established antigens (D,T, aP, IPV, Hib) used in combined Sanofi Pasteur MSD vaccines as Pentavac
  - New hepatitis B antigen

Hexyon

Abbreviations: D: diphtheria, T: tetanus, aP: acellular pertussis, IPV: Inactivated poliovirus, Hib: *Haemophilus influenzae* type b, Hep B: Hepatitis B antigen

Sanofi Pasteur MSD Hexyon® Summary of Product Characteristics, 2013

A new hepatitis B antigen specifically developed for Hexyon

Produced using the patented *Hansenula polymorpha* yeast expression system:

- Consistent high quality and reliable supply[1,2]

Compliant with European Pharmacopoeia Monograph 2067[3]

Manufactured and controlled in Sanofi Pasteur's state-of-the-art facility in Argentina[4]

- Completely dedicated to this new hepatitis B antigen[4]

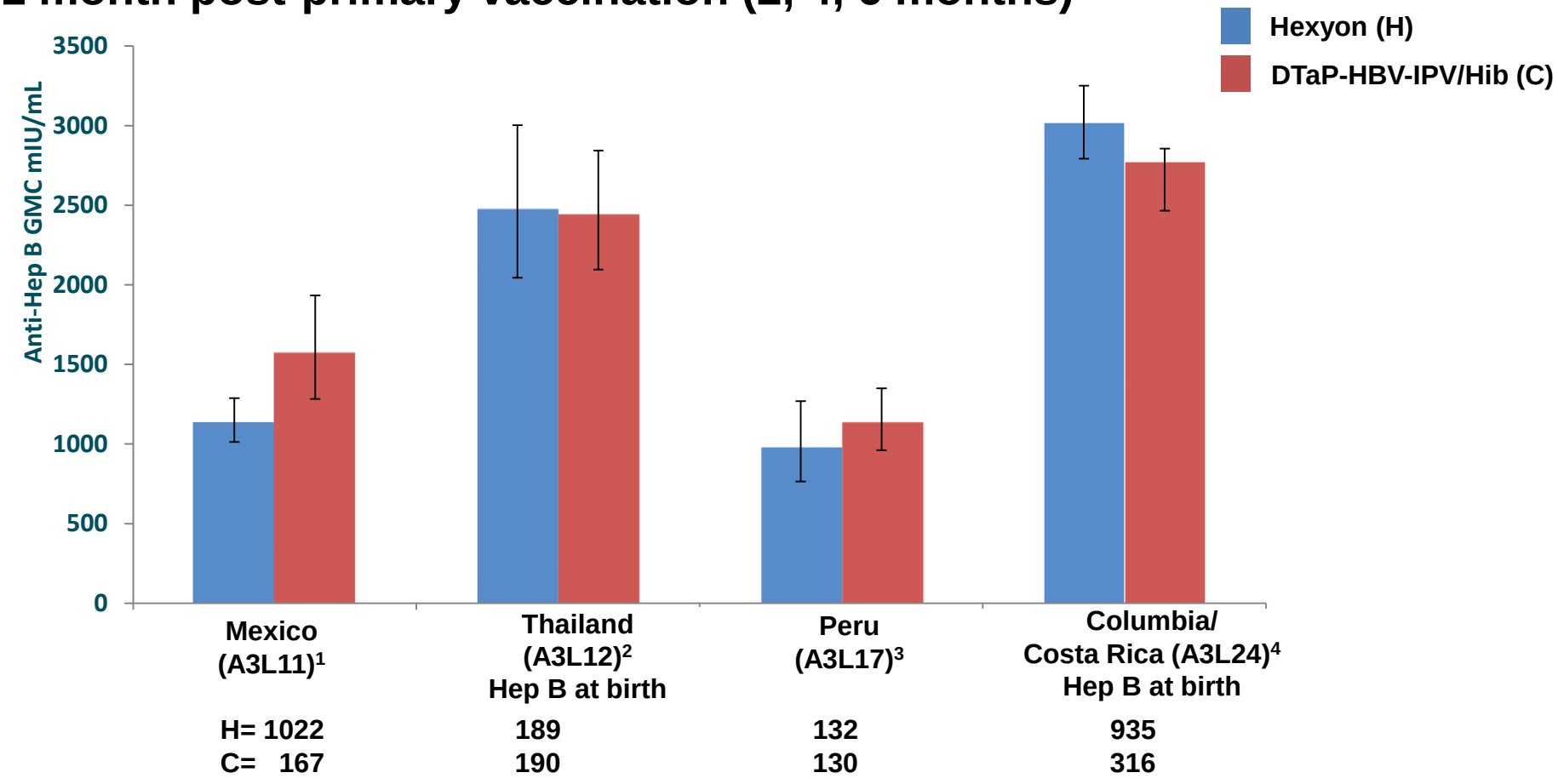
Produced exclusively for use in Hexyon[4]

*This facility passed a GMP inspection by the French Agency (on behalf of the EMA and the WHO) in February 2012.

1. Celik E et al. Biotechnol Adv, 2012;30(5):1108–1118; 2. Shouval D et al. J Hepatol, 2003;39(Suppl1):S70–S76. 3. European Public Assessment Report for Hexyon: EMA/137344; EMEA/H/C/002796. Last accessed October 2013. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002796/WC500145760.pdf. Last accessed October 2013; 4. Sanofi Pasteur MSD, data on file, 2013.

Hexyon vs DTaP-HBV-IPV/Hib (Infanrix Hexa™): Hepatitis B immune responses

1 month post-primary vaccination (2, 4, 6 months)*†



*** Primary vaccination at 2, 4 and 6 months. Measurements made 1 month post-primary vaccination series.**

† A3L11 and A3L17 participants did not receive hepatitis B vaccination at birth, whereas all A3L12 and A3L24 participants received hepatitis B vaccination at birth.

1. Becerra A et al. Vaccine 2012;30:6492–6500. 2. Kosalaraska P et al. Int J Infect Dis. 2011;15(4):e249–e256. 3. Lanata C et al. Vaccine and Vaccination 2012;3:1. 4. López P et al. Poster presented at the Congress ICID: 13–16 June 2012.

Co-administration of Hexyon/Hexaxim™ or Infanrix Hexa™ with Prevnar13

Schedule 3, 5, 11–12 months

Finland and Sweden

Protocol A3L38 Sanofi Pasteur

Vesikari T, et al. PIDJ 2017;36:87–93.

Hepatitis B responses

	Hexyon N=248	Infanrix hexa N=249
Seroconversion after 3 doses		
≥10 mIU/mL	96.4 %	99.6%
≥100 mIU/mL	91.2 %	98.0%
GMT		
Pre-dose 3	76.5 (62.0,94.4)	260 (218,311)
Post-dose 3	1370 (1069,1757)	5015 (4178,6020)

Vesikari T, et al. PIDJ 2017;36:87–93.

Protocol A3L38
Responses to Prevnar13 after 3 doses

	Hexyon N=249	Infanrix hexa N=248
Serotype 3	86.3 %	88.0 %
Serotype 5	95.1 %	98.1 %
All other serotypes	98.2–100 %	98.1–100 %

Vesikari T, et al. PIDJ 2017;36:87–93.

Hexyon/Hexacim co-administration with RV vaccine (Rotarix) at 2 and 4 months of age

Rotavirus IgA antibody responses		
	Hexyon	**Infanrix hexa**
Seroconversion	77.9 % (71.1,83.7)	86.9 % (75.8,94.2)
GMC	110 (85.4,142)	155 (96.6,250)

”Similar”

Lopez P, et al. PIDJ 2017;36:e272–e282.

Hexyon co-administration with MenC at 2 and 4 months of age

Men C responses ≥8 SBA

After dose 1	99.4%
After dose 2	100%

GMC

After dose 1	885 (737,1063)
After dose 2	580 (505,664)

MenC vaccine can be given together with Hexyon

One dose is as good as two (or better)

Vesikari T, et al. Vaccine 2017;35(3):452-458.

Hexyon / Hexacima / Hexaxim is registered in 98 countries

- A fully liquid ready-to-use, preservative free hexavalent paediatric vaccine
- Indicated for primary (3 doses) and booster vaccination of infants and toddlers from six weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae* type b
- Should be in accordance with official recommendations

- Marketing authorisation granted by the European Commission [30 countries] on 17 April 2013 [http://ec.europa.eu/health/documents/community-register/html/h829.htm]
- Marketing authorisation granted in Latin America [Peru, Chile, Guatemala, Mexico, Paraguay, Argentina, El Salvador, Uruguay], Asia [Malaysia, Philippines], Africa [South Africa], Greater Europe [Georgia, Kazakhstan]

sanofi pasteur MSD
vaccines for life

Marketing Autorisation granted

EC Decision 15-FEB-2016

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003982/human_med_001962.jsp&mid=WC0b01ac058001d124

http://ec.europa.eu/health/documents/community-register/html/h1079.htm

vaxelis

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and *Haemophilus* type b conjugate vaccine (adsorbed)

C Confidential

Property of MCM Partnership (VAXELIS)

Vaxelis (PR5I) is a unique combination of well-established antigens from vaccines licensed in EU or US

		Antigen(s)	Amounts	Licensed vaccine containing the same antigen(s)
P	Merck	**PRP-OMPC** Polyribosylribitol phosphate polysaccharide coupled to the outer membrane complex of *Neisseria meningitidis*	3 µg	PedvaxHIB (US)
R		**HBsAg[2]** Recombinant hepatitis B surface antigen	10 µg	HBVaxPro RECOMBIVAX HB (US)
5	Sanofi Pasteur	**5 component acellular pertussis[1]**		PENTACEL (US) PEDIACEL
		PT: Pertussis Toxoid	20 µg	
		FHA: Filamentous Haemagglutinin	20 µg	
		PRN: Pertactin	3 µg	
		FIM: Fimbriae Types 2 and 3	5 µg	
		Diphtheria Toxoid[1]	≥20 IU	
		Tetanus Toxoid[1]	≥40 IU	
I		**IPV Inactivated Poliovirus**		IMOVAX POLIO PENTAVAC, HEXYON PEDIACEL
		Type 1	40-D	
		Type 2	8-D	
		Type 3	32-D	

Aluminium used as adjuvant

([1] adsorbed on aluminium phosphate (0.17 mg Al^{3+}), [2] adsorbed on amorphous aluminium hydroxyphosphate sulfate (0.15 mg Al^{3+}))

Protocol V419-007 (Vaxelis)
3+1 schedule at 2, 3, 4 and 12 months

PR5I (Vaxelis) *vs.* Infanrix hexa

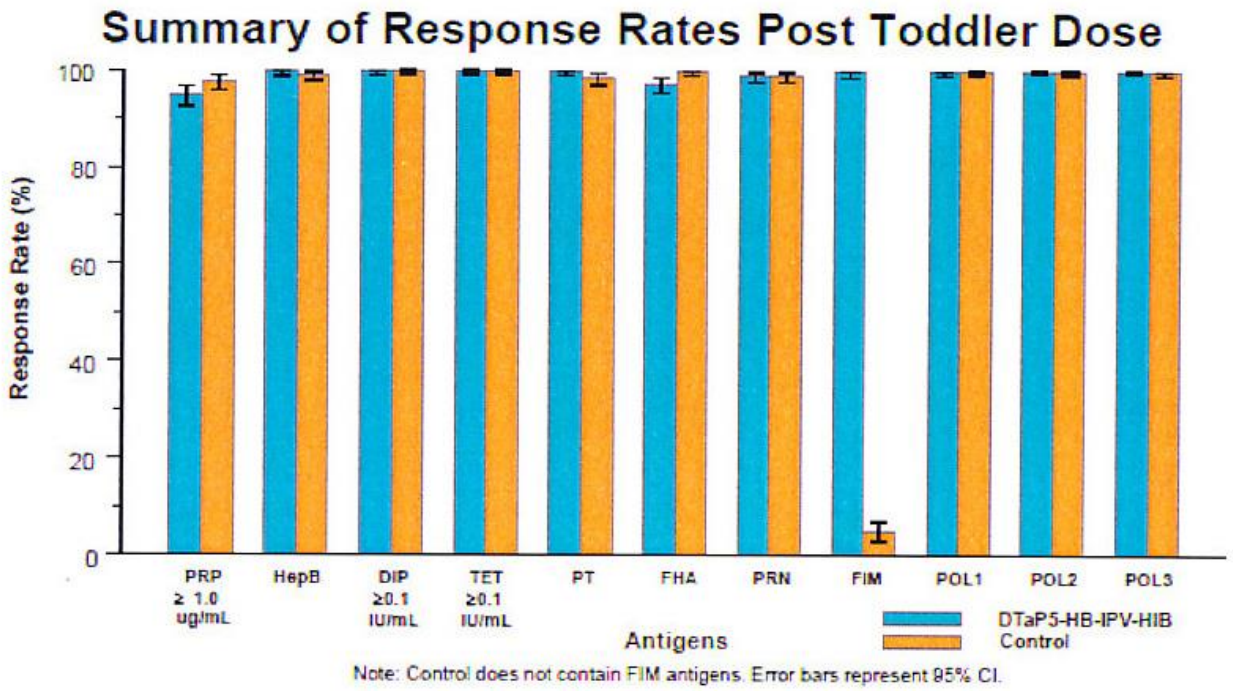
PR5I was non-inferior for all immunogenicity comparisons

PRP responses 1 month after infant series

	% with titer ≥0.15µg/ml
PR5I	98%
Infanrix hexa	87%
	Group difference 11.4% (8.4, 14.7)
	”Significant”

Vesikari T, et al. PIDJ 2017;36:209–215.

Non-inferiority of Vaxelis versus Infanrix hexa demonstrated for the 3+1 schedule (007)



Note: Control does not contain FIM antigens. Error bars represent 95% CI.

Pertussis response:

If pre-vaccination antibody concentration was < 4x lower limit of quantification (LLOQ), then the post-vaccination antibody concentration was ≥ 4x LLOQ;

if pre-vaccination antibody concentration was ≥ 4xLLOQ,

then the post-vaccination antibody concentration was ≥ pre-vaccination levels

HepB: ≥ 10mIU/mL

Polio: ≥ 1:8 dil

Post Toddler dose:

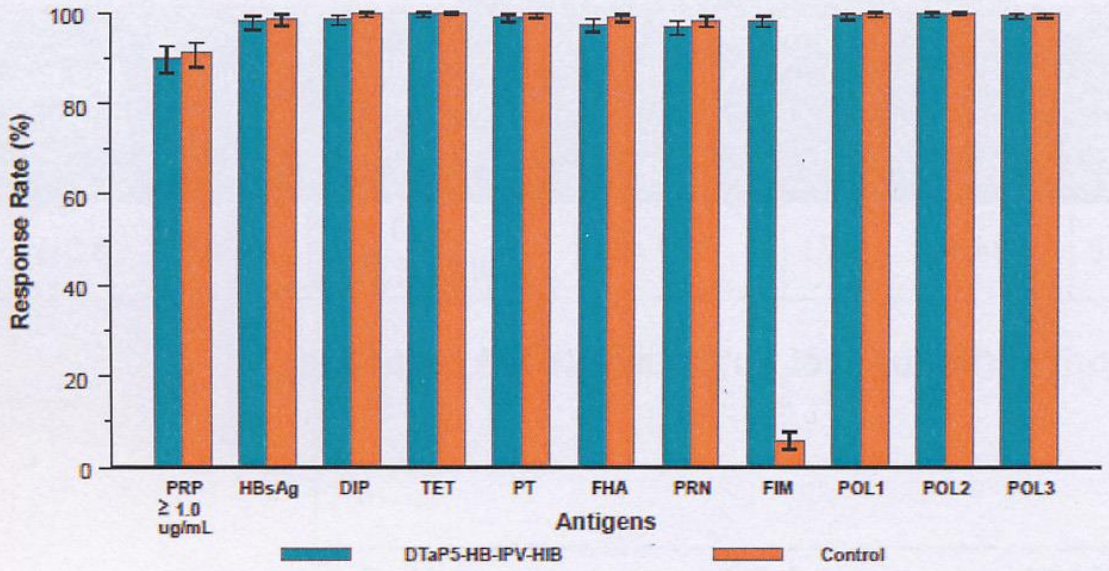
- High response rates for all PR5I antigens (≥95%)
- non-inferiority to Infanrix hexa regarding the response rates to HepB and pertussis antigens

Vesikari T et al, 33rd ESPID, May12-16,2015, Leipzig, Germany
V419-007 CSR

Vesikari T, et al. PIDJ 2017;36:209–215.

Non-inferiority of Vaxelis versus Infanrix hexa demonstrated for the 2+1 schedule (008)

Summary of Response Rates Post Toddler Dose



Note: Control (INFANRIX™hexa) does not contain FIM antigens. Error bars represent 95% CI.

*If pre-vaccination antibody concentration was <LLOQ, then the post-vaccination antibody concentration was ≥LLOQ; If pre-vaccination antibody concentration was ≥LLOQ, then the post-vaccination antibody concentration was ≥pre-vaccination levels (the pre-vaccination level was defined as the antibody titer at pre-Dose 1)

Post Toddler dose:

- High response rates for all PR5I antigens
- non-inferiority to Infanrix hexa demonstrated regarding the response rates to all PR5I antigens

sanofi pasteur MSD
vaccines for life

Silfverdal SA, et al. Vaccine 2016;34:3810–6.

Vaxelis vs. Infanrix hexa Coadministration with routine pediatric vaccines in the US (2, 4, 6 months)

	Vaxelis N=522	Infanrix hexa N=274
RV IgA GMC	282	277

GMC ratio 1.02 (0.83 to 1.24)

Marshall GS, et al. Pediatrics 2015;136:e323–e332.

Booster dose at 12 months of Vaxelis *vs.* Infanrix hexa given concomitantly with MMRV

	Vaxelis N=467	Infanrix hexa N=474
Measles	96.2%	96.4%
Mumps	94.9%	91.8%
Rubella	98.3%	97.9%
Varicella	97.6%	97.7%

Conclusion: Vaxelis can be given concurrently with MMRV

Vesikari T, et al. PIDJ 2017;36:209–215.

Conclusions for HepB in hexavalent vaccines

- AntiHBs responses to various hexavalent vaccines are not equal (highest after Infanrix hexa)
- High primary responses are associated with better persistence
- AntiHBs responses may be (simply) correlated with the quantity of Al^{+++} adjuvant in hexavalent vaccine

Vesikari T, et al. PIDJ 2017;36:209–215.

Conclusions on coadministration of other childhood vaccines with hexavalent vaccines

- No interference with pneumococcal conjugate vaccine one way or the other
- No significant suppression of RV IgA response after vaccination
- No suppression of MenC response
- No interference with MMRV

Vesikari T, et al. PIDJ 2017;36:209–215.

Vaccine Research Center

UNIVERSITY OF TAMPERE
Finland

Thank you!