Rogaška Slatina
15 June 2013

A 6-in-1 fully liquid vaccine for infant immunisation

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The challenge of combination vaccines

- Major area of vaccine research
- Development of a new vaccine
- Clinical data
  - Immunogenicity
  - Safety

- Development of Hexacima®
  - 11 years from start of the project to license
- Production of Hexacima®
  - Up to 33 months to produce a high-quality batch
    - 18 to 24 months: production and control
    - 9 months: filling, formulation, packaging, quality control

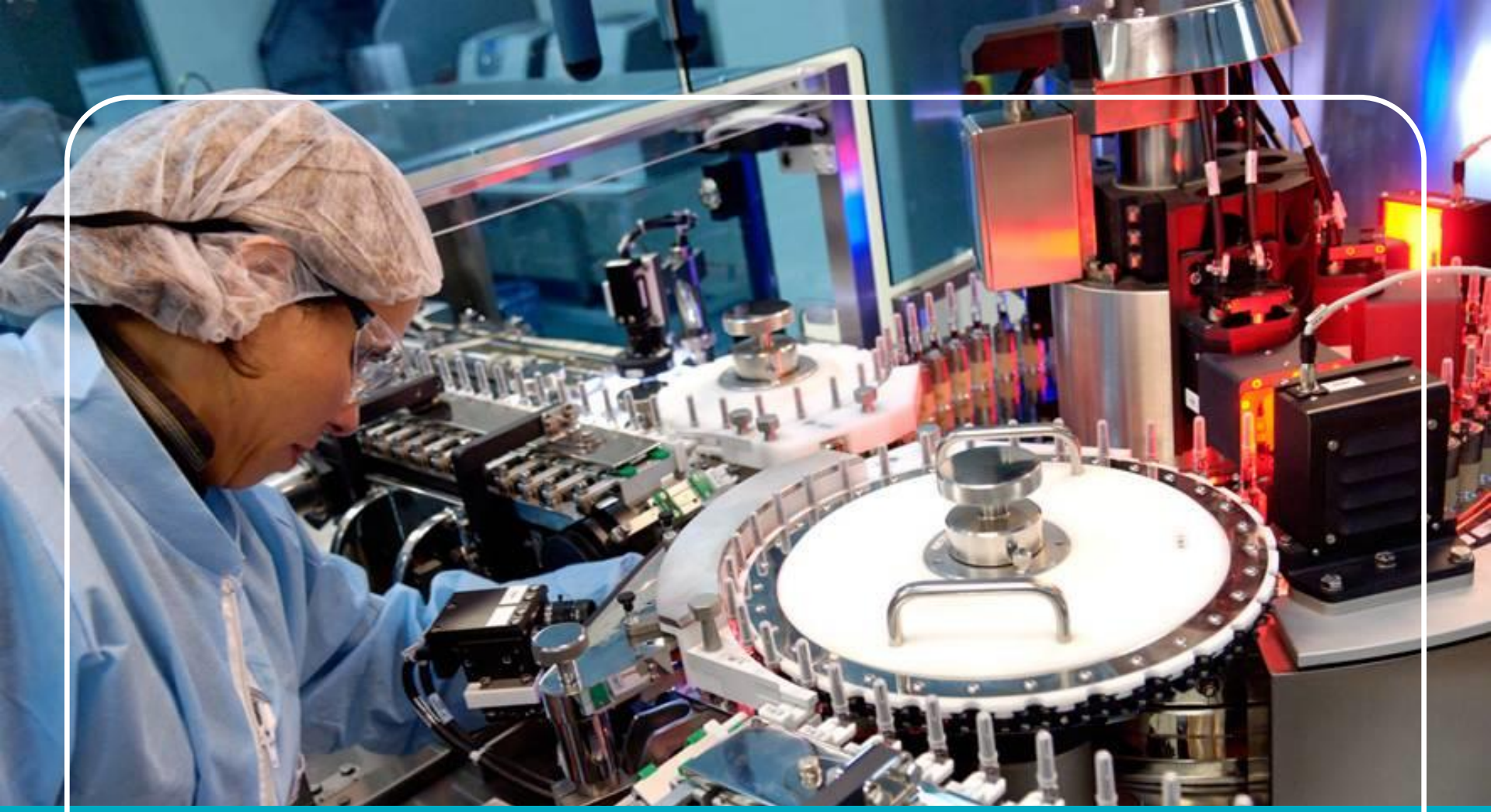
VACCINE ANTIGENS

HEXACIMA®

Combination of Sanofi Pasteur's heritage and innovation

- **HEXACIMA®, fully liquid, ready-to-use formulation, contains**
  - Established Sanofi Pasteur's antigens (D,T, aP, IPV, Hib (PRP-T)) used worldwide as either a standalone or combination vaccine
  - Sanofi Pasteur's new hepatitis B antigen

Hexacima



MANUFACTURING PROCESS

HEXACIMA®

Sanofi Pasteur's 100% in-house 6-in-1 vaccine

Diphtheria toxoid extracted from *C. diphtheriae* culture	Tetanus toxoid extracted from *C. tetani* culture	PT & FHA extracted from *B. pertussis* culture	Poliovirus types 1 (Mahoney), 2 (MEF-1) & 3 (Saukett) propagated on Vero cells	PRP capsular polysaccharide extracted from *H. influenzae* type b culture	HBsAg extracted from recombinant yeast *H. polymorpha* culture
Detoxification & Purification	Detoxification & Purification	Purification & Detoxification of PT	Purification & Inactivation	Purification, Activation & Conjugation with concentrated tetanus protein	Purification
Purified diphtheria toxoid	Purified tetanus toxoid	Adsorbed, purified PTxd & FHA	Concentrated trivalent polioviruses	PRP conjugated to tetanus protein	Adsorbed concentrated HBsAg

Blending

Water + Amino acids

pH adjustment

Aluminium hydroxide

Buffers

ling of sterile vials

Filling of sterile syringes

Secondary packaging

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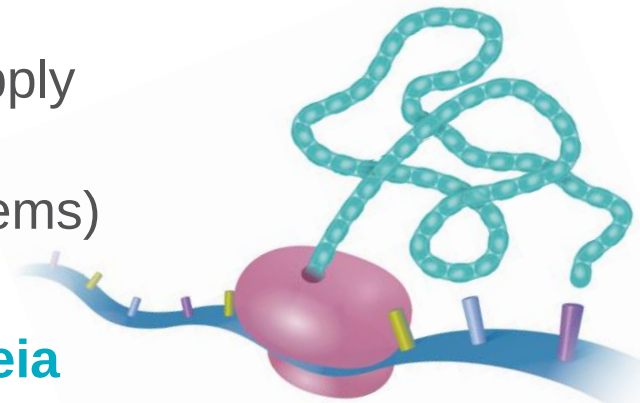
HEXACIMA® - Hepatitis B antigen

- **Produced using the patented *Hansenula polymorpha* yeast expression system**
  - Consistent high quality and reliable supply
  - No need for methanol as solvent (used with other yeast expression systems)



- **Compliant with European Pharmacopoeia Monograph 1056 & WHO TRS 786**

- **Produced exclusively for use in HEXACIMA®**

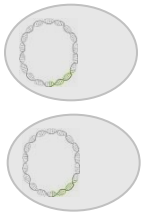
Production of Sanofi Pasteur's new *H. polymorpha*-derived HBsAg

surface protein S-encoding gene (DNA)

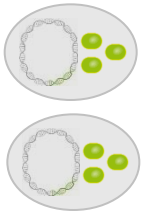
H. Polymorpha yeast technology

State of the art expression system

Fermentation of the modified yeast cells



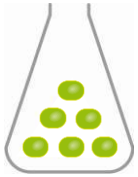
Modified yeast cells product HBsAg



4 months, 11 QCs tests to release one batch of HBs

Purification

Recombinant HBs for exclusive use in Hexaxim



Inclusion in

Hexacima

10µg/0,5 ml

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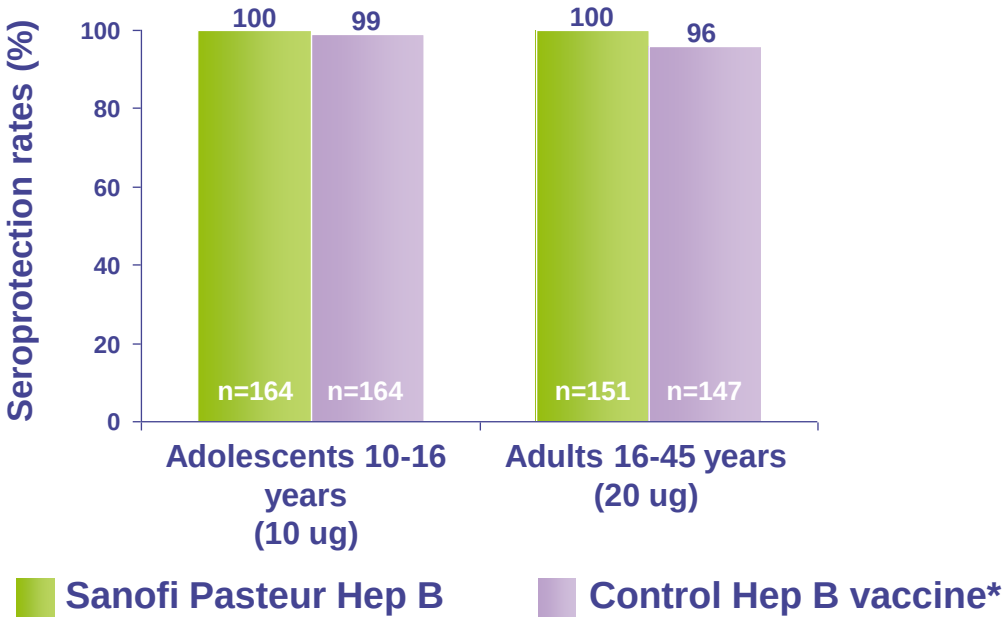
Sanofi Pasteur's new hepatitis B antigen induces high immune response against hepatitis B

Seroprotection rates (Anti-HBsAg ≥ 10mIU/mL)
Post-vaccination at 0,1,6 months[7]



Based on high and consistent immune response, Sanofi Pasteur's hepatitis B antigen (10 µg) was included in HEXACIMA®

*Engerix B

Tregnaghi. *Vaccine*, 2010;28(20)

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Composition of HEXACIMA®

Active substances[0]

- Each unit dose **(0,5 ml)** contains antigens against all diseases in the following concentrations:
- All antigens included in HEXACIMA® are manufactured by Sanofi Pasteur

Adjuvants

- Each unit dose (0,5 ml) is adsorbed on aluminum hydroxide, hydrated (0.6mg Al3+)[30]
- HEXACIMA® is **preservative free**

Purified diphtheria toxoid	≥20 IU
Purified tetanus toxoid	≥40 IU
Acellular pertussis antigens Pertussis Toxoid (PT)	25 µg
Filamentous Haemagglutinin (FHA)	25 µg
Polioviruses inactivated: Type 1 poliovirus (Mahoney)	40 units
Type 2 poliovirus (MEF-1)	8 units
Type 3 poliovirus (Saukett)	32 units
Haemophilus influenzae type b polysaccharide	12 µg
Purified recombinant hepatitis B surface antigen	10 µg

[30] Sanofi Pasteur. HEXACIIMA®. Summary of Product Characteristics

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HEXACIMA® – Clinical Development

Comprehensive clinical development plan

- 13 large scale studies
- >5.000 subjects included
- Immunogenicity and safety evaluations
- Primo & booster schedules
- Large-scale safety study
- Lot-to-lot consistency
- Co-administration studies
- Long-term antibody persistence

HEXACIMA® - Clinical Development Overview

Different vaccination schedules

- 6-10-14 weeks
- 2-3-4 months
- 2-4-6 months

With or without HB at birth

- Booster dose (15-24 months)

Different control caccines (standard of care)

- Acellular pertussis combination vaccines
  - Infanrix hexa
  - Pentaxim
- Whole cell Pertussis combination vaccines
  - CombAct-Hib + Engerix B + OPV
  - Tritanrix-HepB/Hib + OPV

Different Concomitant Vaccines

Primary series

- PCV7 (Prevenar), Rotavirus (Rotarix)

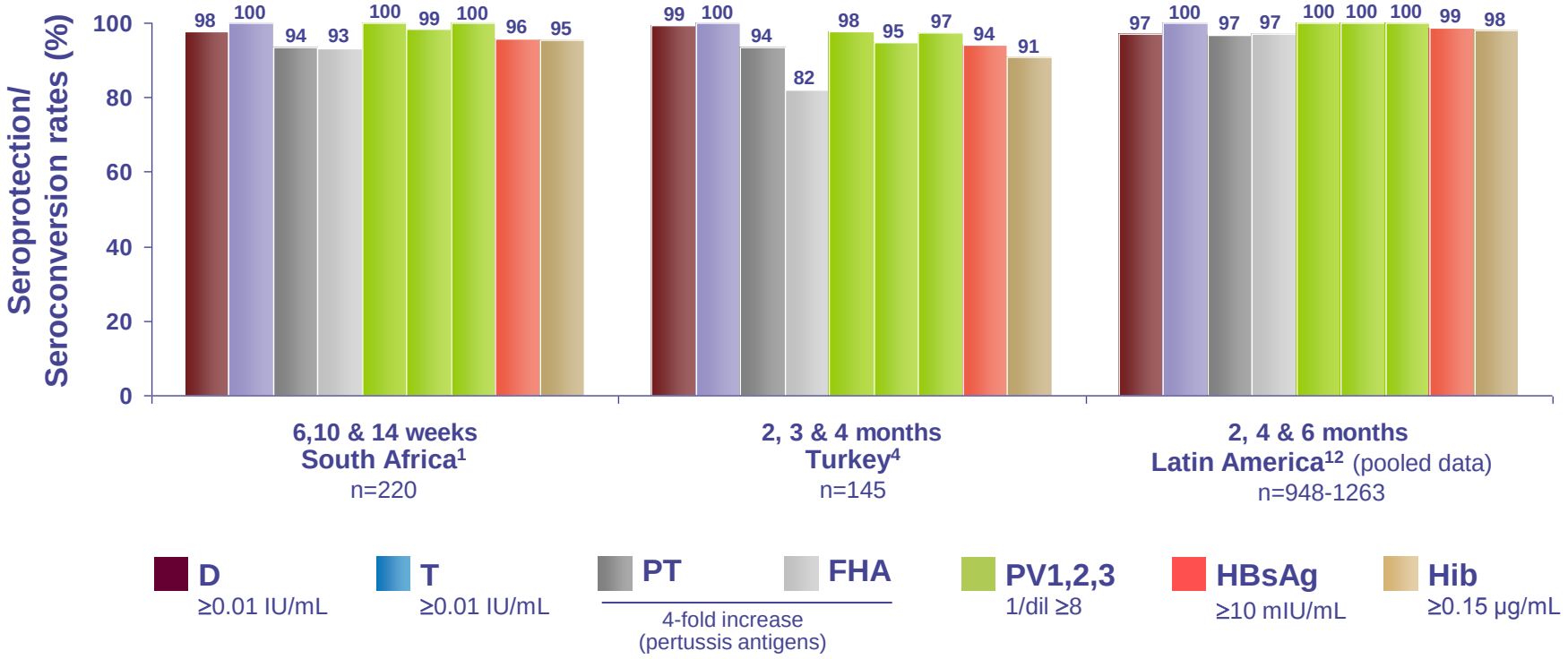
Booster series

- MMR (Trimovax), Varicella (Varilrix)

HEXACIMA®
Immunogenicity after primary vaccination

Seroprotection/seroconversion rates after the 3rd dose of HEXACIMA® under various primary schedules

(No Hep B vaccine at birth, no concomitant vaccine)

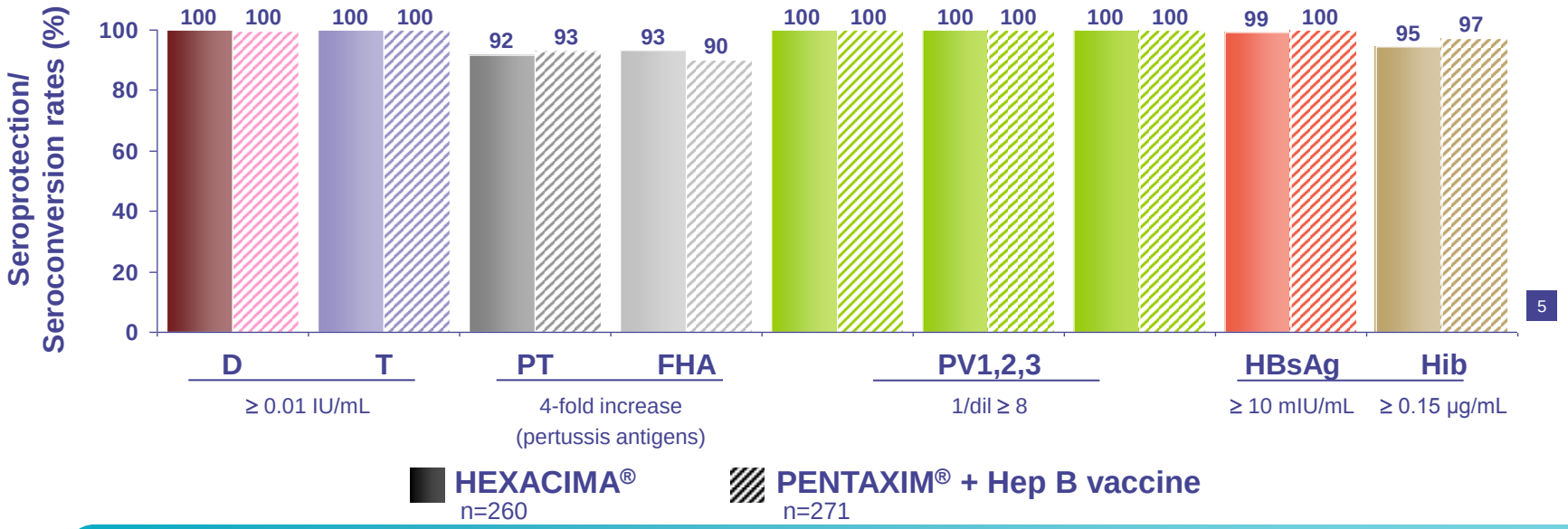


[1] Madhi et al. *PIDJ*, 2011;30(4) **[4]** Ceyhan et al. *5th ACPID* Congress, 2010 **[12]** Tregnaghi et al. *30th ESPID Congress*, 2012

HEXACIMA®
Immunogenicity compared to PENTAXIM®

Seroprotection/Seroconversion rates after the 3rd dose of HEXACIMA® or PENTAXIM® in infants vaccinated at 2, 4 & 6 months of age

(No Hep B vaccine at birth, no concomitant vaccine)



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The immune response to all HEXACIMA® antigens is high and similar to that of PENTAXIM® co-administered with standalone hepatitis B vaccine

Tregnaghi et al. *PIDJ*, 2011;30(6)

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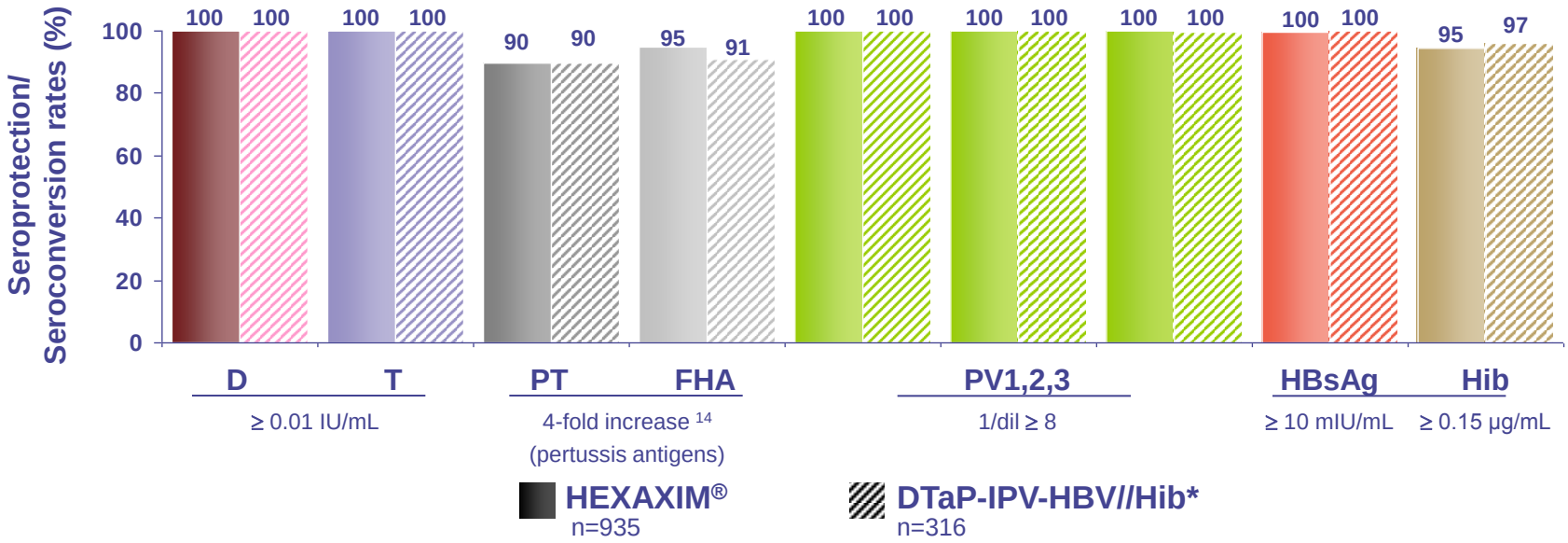
HEXACIMA®

Immunogenicity compared to another licensed hexavalent vaccine

Seroprotection/seroconversion rates after the 3rd dose of HEXACIMA®
or DTaP-IPV-HBV//Hib*in infants vaccinated at 2, 4 & 6 months of age
(Hep B vaccine at birth, concomitant PCV7 & rotavirus vaccine)



The immune response to all HEXACIMA® antigens is high and similar to that of another licensed hexavalent vaccine

* Infanrix Hexa® Lopez et al. *15th ICID Congress*, 2012 Sanofi Pasteur. Data on file

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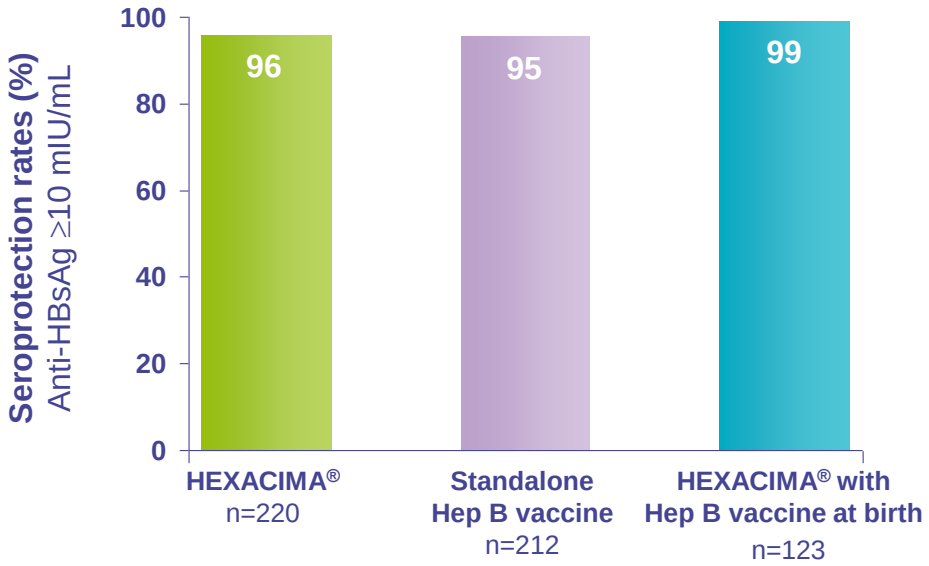
HEXACIMA®

Highly immunogenic against hepatitis B

Anti-HBsAg seroprotection after the 3rd dose of HEXACIMA®
in infants vaccinated at 6,10 &14 weeks of age
(No concomitant vaccine)



HEXACIMA® is the only hexavalent vaccine licensed for use with the EPI schedule in the absence of hepatitis B vaccination at birth

Madhi et al. *PIDJ*, 2011;30(4)

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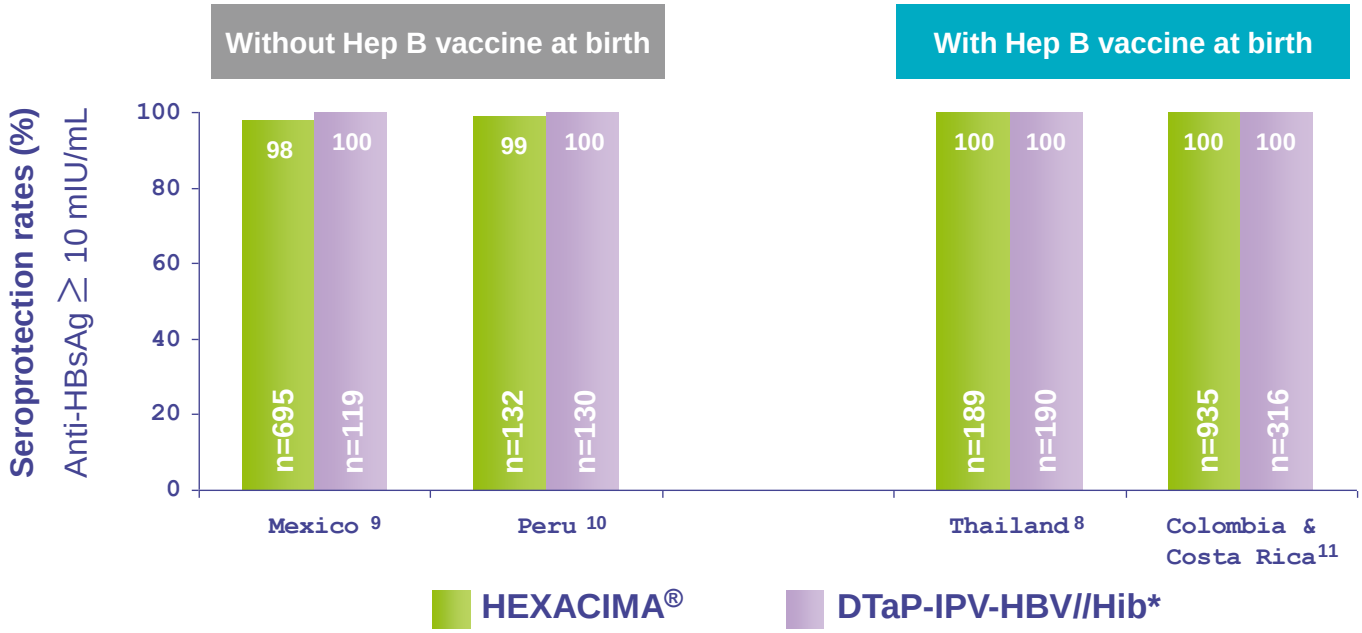
HEXACIMA®

Highly immunogenic against hepatitis B

Anti-HBsAg seroprotection rates after the 3rd dose of HEXACIMA® or DTaP-IPV-HBV//Hib* in infants vaccinated at 2, 4 & 6 months of age



HEXACIMA® induces consistently high immune responses to hepatitis B antigen

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* Infanrix® Hexa **[8]** Kosalaraska et al. *IntJInfectDis*, 2011;15(4) **[9]** Aquino et al. *Vaccine,* 2012;30(45) **[10]** Lanata et al. *Vaccines Vaccin*, 2012;3(1)**[11]** Lopez et al. *15th ICID Congress*, 2012

HEXACIMA®
Highly immunogenic against hepatitis B

- Under various vaccination schedules
- Similar to that of another licensed hexavalent vaccine
- In the absence of hepatitis B vaccination at birth
- Even under the challenging EPI schedule (6,10,14 weeks)
  - HEXACIMA® is the only hexavalent vaccine indicated for the EPI schedule in the absence of hepatitis B vaccination at birth

HEXACIMA® induces strong booster responses regardless of primary series vaccine

- **HEXACIMA® has been given as a booster in children primed with**
  - **HEXACIMA®** at 6-10-14 weeks; 2-3-4 months; 2-4-6 months of age
  - **PENTAXIM® + standalone Hep B vaccine** at 2-3-4 months of age
  - **DTaP-IPV-HBV//Hib*** at 2-4-6 months of age

- **Regardless of the primary series vaccine,**
  a HEXACIMA® booster results
  in strong anamnestic responses to all antigens

* Infanrix Hexa®

Aquino et al. *Vaccine*, 2012;30(45)

Sanofi Pasteur. Data on file

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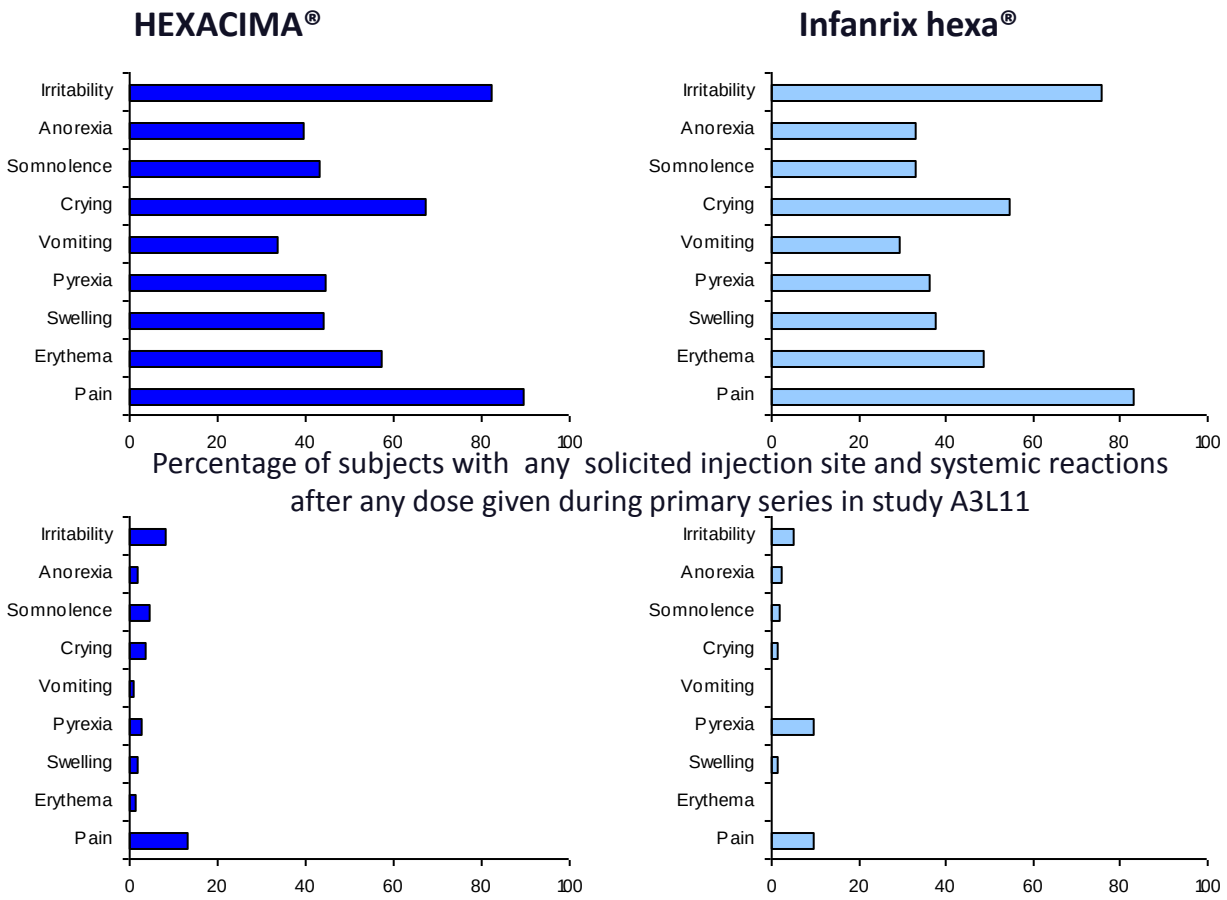
HEXACIMA®
Safety & Tolerability

Grade 3

Pain = cries when injected limb is moved or the movement of the injected limb is reduced
Erythema/Swelling = ≥5 cm in diameter
Pyrexia = ≥39.5°C
Vomiting = ≥6 episodes per 24 hours
Crying = >3 hours
Somnolence = sleeping most of the time
Anorexia = refuses ≥3 feeds/meals
Irritability = inconsolable



Percentage of subjects with any solicited injection site and systemic reactions after any dose given during primary series in study A3L11

Adverse Events (Any – Grade 3) during primary series

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Becerra A, et al. Vaccine 2012;30:6492-6500

HEXACIMA® – Safety

- Safe and well tolerated
  - **Under various primary schedules (6-10-14 weeks, 2-3-4 and 2-4-6 months)**
  - **When given as a booster in the 2nd year of life**
    - **Regardless of primary schedule**
    - **Regardless of primary vaccine (HEXACIMA®, PENTAXIM®, DTaP-IPV-HBV//Hib)**
- Better tolerated than wP-based combination vaccines
- Comparable safety profile to other licensed aP-based combination vaccines (PENTAXIM®, DTaP-IPV-HBV//Hib)
- Can be safely administered concomitantly with other routine pediatric vaccines

HEXACIMA®

Summary of clinical trials

- 13 large scale studies enrolling >5.000 infants:
  Similar and high immune response to all antigens
  post-primary and post-booster vaccination, as compared to
  - **DTwP combined vaccines**
  - **PENTAXIM®**
  - **and another licensed hexavalent vaccine**
- HEXACIMA® induces high booster immune-response regardless of primary series vaccine (HEXACIMA®, PENTAXIM® or another licensed hexavalent vaccine)
- Can be co-administered with pneumococcal conjugate, rotavirus and MMR vaccines

HEXACIMA®

An innovative hexavalent vaccine

- High quality production process for all antigens fully manufactured by Sanofi Pasteur
- A recombinant hepatitis B surface antigen specifically developed and manufactured for inclusion in HEXACIMA®
- Improved convenience and compliance via the 6-in-1 vaccine
  - **Reducing the number of injections / medical visits**
- **A fully liquid, ready-to-use vaccine**
  - **No reconstitution required**
  - **Reducing administration time and thus stress for the baby and parental anxiety[1]**
  - **Ensuring the right dose of each antigen every time**
- **Registered in Europe** via the centralised procedure
  - **Positive opinion: 21 February 2013**
  - **Approval: 17 April 2013**

[1] Wiedenmayer. *Vaccine*, 2009;27(5)

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Hvala za vašo pozornost

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