Clinical development of Synflorix™

(PHiD-CV - Pneumococcal non-typeable *Haemophilus influenzae* protein D - Conjugate Vaccine)

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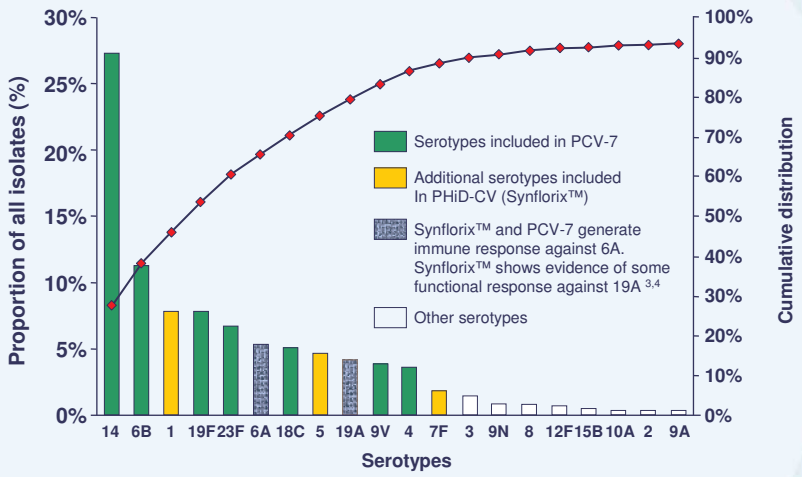
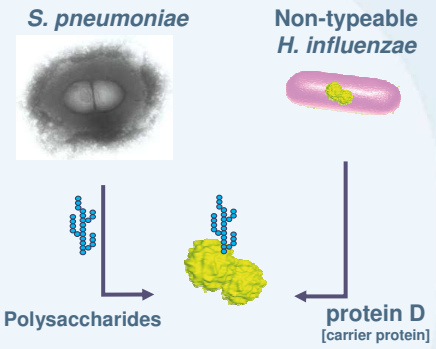
Global serotype distribution for Invasive Pneumococcal Disease in children <5



GAVI PneumoADIP Report, 2007
Available at: http://www.preventpneumo.org/pdf/GSP%20Summary%20for%20SAGE%20Nov6-8%202007_Oct%2019-07.pdf

Design of PHiD-CV *(Synflorix™)*

- **10 pneumococcal serotypes**
  1, 4, **5**, 6B, **7F**, 9V, 14, 18C, 19F, 23F
- **8 serotypes conjugated to protein D**
  (*H. influenzae* outer membrane protein)
- **Serotype 18C conjugated to TT and serotype 19F conjugated to DT**



Novel carrier protein D chosen to
- minimize risk of carrier interference with other EPI vaccines
- potentially provide protection against non-typeable *H. influenzae* (NTHi)

Wysocki et al. Pediatr Infect Dis J 2009;28: S77–S88; Dagan et al. Expert Rev Vaccine 2008; 7: 97-115

PHiD-CV meets the WHO licensure criteria for IPD

Immunological licensure criteria proposed by WHO and endorsed by European CHMP:

1. Non-inferiority of post-primary **ELISA** antibody responses compared to PCV-7 (based on % of subjects reaching pre-set thresholds)
   - Threshold initially defined as 0.35 µg/ml for ELISA assay used during PCV-7 efficacy trials
   - ELISA assay with 22F-adsorption currently recommended to increase specificity. Immunological bridging needed with initial non-22F assay
   - WHO and CHMP: non-inferiority <u>should not be seen</u> as an absolute prerequisite for each serotype
2. Demonstration of functional capacity of antibodies (OpsonoPhagocytic Activity - **OPA**)
3. Induction of **immunological memory**

Jodar et al. Vaccine 2003; 21: 3265-72 - WHO Technical Report Series, No. 927, 2005, Annex 2
Concepcion et al. Clin Diagn Lab Immunol 2001; 8: 266-72.

Immunogenicity measurements

- **ELISA (Enzyme-Linked ImmunoSorbent Assay)** [1]
  - **Measures the amount of antibodies**
  - Standardized **assay**
  - WHO recommended **assay for evaluation of new pneumococcal vaccines**
  - Ab concentration of 0.35 µg/ml with non-22F WHO reference lab ELISA demonstrated to be = **0.20 µg/ml with GSK 22F-ELISA** [3]
- **OPA (OpsonoPhagocytic Assay)** [2]
  - **Measures the quality of antibodies (their capacity to kill pneumoccocci)**
  - More variable, complex and labour intensive **assay**
  - WHO recommended assay**, in addition to ELISA, for demonstration of the** functionality of induced antibodies
  - May correlate better with vaccine efficacy

1. Henckaerts et al. Clin. Vaccine Immunol. 2006; 13: 356-60 – 2. Henckaerts et al. Vaccine 2007; 25: 2518-27
3. Poolman et al. Clin. Vaccine Immunol. 2009; doi:10.1128/CVI.00289-09

Post-primary % OPA ≥1:8 correlates with IPD VE

	ELISA ≥ 0.2 µg/ml (N ~790)*	CDC Case Control vaccine effectiveness**	OPA ≥ 1:8 (N ~380)*
Pneumococcal vaccine serotypes			
4	**100%** (99.5; 100)	**93%** (65, 99)	**100%** (99.0; 100)
6B	**84.8%** (82.1; 87.2)	**94%** (77, 98)	**95.5%** (93.0; 97.4)
9V	**99.4%** (98.5; 99.8)	**100%** (88, 100)	**99.7%** (98.5; 100)
14	**99.6%** (98.9; 99.9)	**94%** (81, 98)	**97.9%** (96.0; 99.1)
18C	**99.0%** (98.0; 99.6)	**97%** (85, 99)	**98.4%** (96.6; 99.4)
19F	**99.2%** (98.4; 99.7)	**87%** (65, 95)	**92.1%** (89.0; 94.6)
23F	**94.9%** (93.2; 96.4)	**98%** (80, 100)	**98.9%** (97.3; 99.7)
Vaccine related serotypes			
6A	**51.8%** (47.1; 56.5)	**76%** (39, 90)	**77.8%** (72.4; 82.6)
19A	**32.2%** (27.9; 36.7)	**26%** (-45, 62)	**1.8%** (0.6; 4.1)

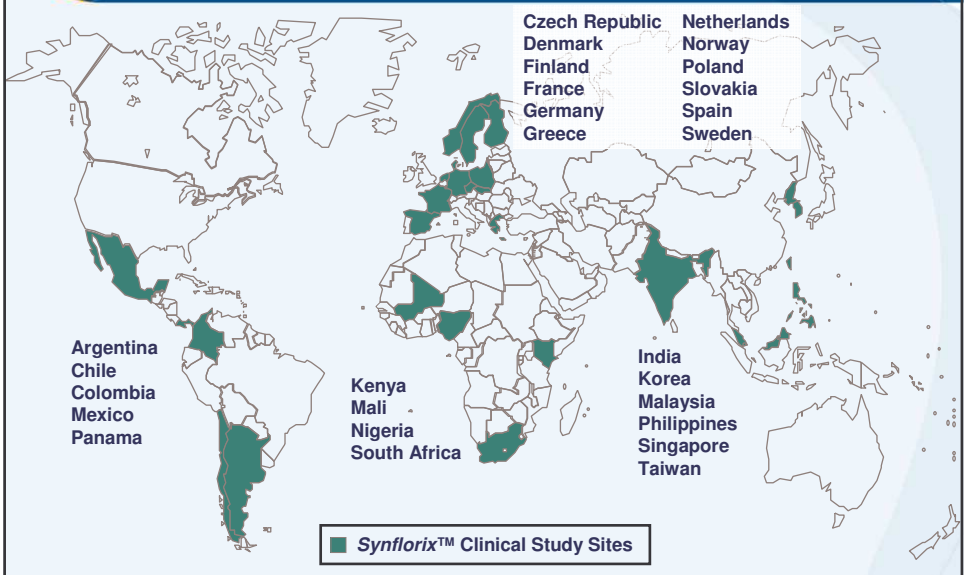
*Pooled PCV-7 data from studies -001, -003, -011 and -012
(Vesikari *et al.* PIDJ 2009, Wysocki *et al.* PIDJ 2009, Bermal *et al.* PIDJ 2009)
**Whitney *et al.* Lancet 2006
Prymula et al. Expert Rev Vaccines 2009; 8: 1479-1500

Clinical development of PHiD-CV

- Immunogenicity compared to PCV-7 [1,2,3,6,7,8,9]
- Functional responses (OPA) [1,2,3,6,8,9]
- Boostability of primary responses [1,2,8,9]
- Co-administration with routine vaccines [4]
  - DTPa-HBV-IPV/Hib, DTPa-HBV-IPV and DTPa-IPV/Hib [1,2,3,6,8,9]
  - MenC-CRM, MenC-TT and Hib-MenC [2]
  - DTPw-HepB/Hib and OPV [3]
  - MMRV (with booster dose) [7]
  - Rotavirus vaccine [8]
- Safety & tolerability [5]
- Impact of prophylactic paracetamol [8]
- Immunization schedules
  - 2-3-4 mo [1]; 3-4-5 mo [8]; 2-4-6 mo [2,3,6]; 3-5-11 mo [9]; 6-10-14 weeks [3]

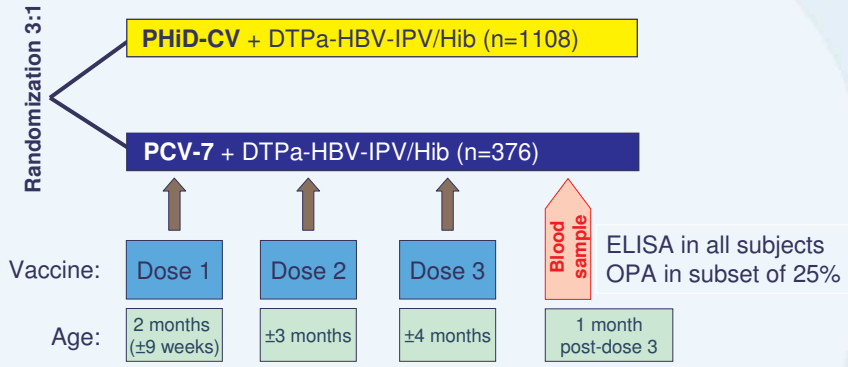
1) Vesikari et al. PIDJ 2009;28:S66–S76
2) Wysocki et al. PIDJ 2009;28:S77–S88
3) Bermal et al. PIDJ 2009;28:S89–S96
4) Knuf et al. PIDJ 2009;28:S97–S108
5) Chevaliler et PIDJ 2009;28:S109–S118
6) Lagos et al., ISPPD6, Reykjavik, Iceland 2008;
7) Vesikari, ESPID, Graz, Austria
8) Prymula et al. Lancet 2009; 374 1339-50
9) Silfverdal PIDJ 2009 28 e276-82

Synflorix™ clinical study sites distribution



Pivotal non-inferiority study in Europe

Single blind, controlled, randomized trial in Finland, Poland and France

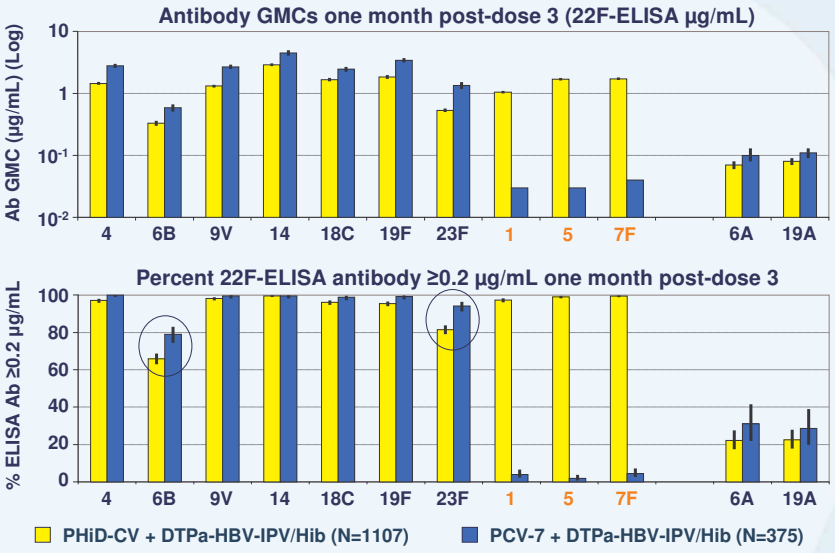


PHiD-CV - Pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; Synflorix™;
DTPa-HBV-IPV/Hib: *Infanrix™ hexa; are* trademarks of the GlaxoSmithKline group of companies;
PCV7-CRM: *Prevenar™/Prevnar™* is a trademark of Wyeth

Vesikari et al. PIDJ 2009;28:S66–S76

Immunogenicity of PHiD-CV in Europe

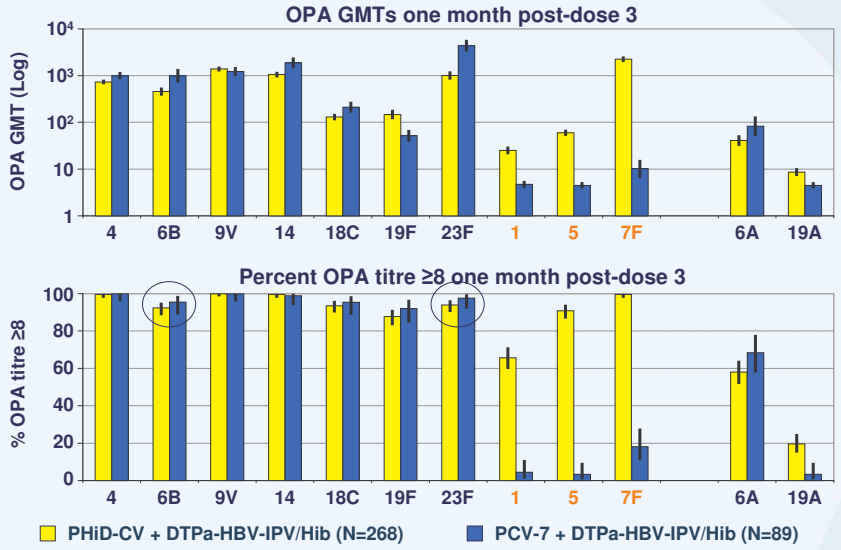
Antibody responses compared to PCV-7



Adapted from Vesikari T *et al. Pediatr Infect Dis J* 2009:28;S66-76

Immunogenicity of PHiD-CV in Europe

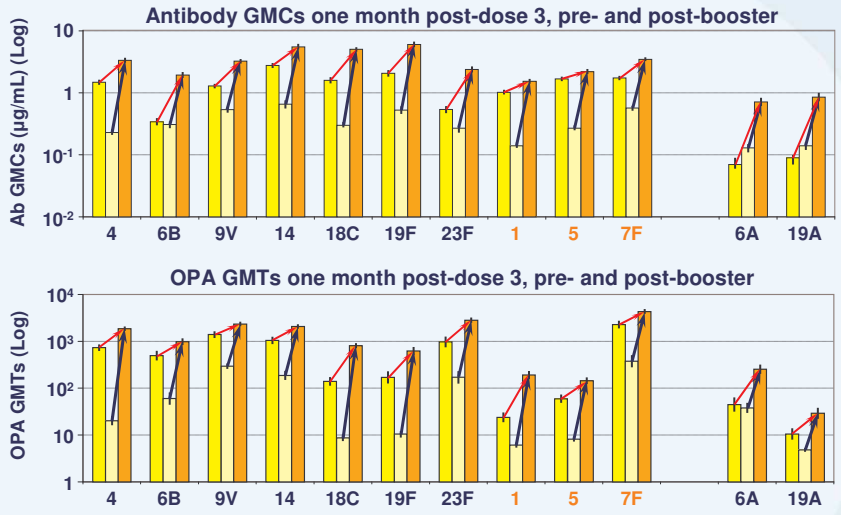
OPA responses compared to PCV-7



Adapted from Vesikari T *et al. Pediatr Infect Dis J* 2009:28;S66-76

PHiD-CV booster responses

ELISA antibody concentrations & OPA titres



Adapted from Vesikari *et al. PIDJ* 2009:28;S66-76

PHiD-CV immunogenicity conclusion

- **PHiD-CV was licensed for IPD protection based on:**
  - Immunogenicity for the 10 pneumococcal serotypes contained in the vaccine.
  - Non-inferiority of the percentage of vaccinees reaching the reference antibody concentration of 0.2 µg/mL, following 3-dose PHiD-CV primary vaccination compared to 7vCRM, complemented with high OPA seropositivity (titre ≥1:8) within the same range for both vaccines.
  - Robust antibody and OPA responses following a PHiD-CV booster dose, indicative of induction of immunological memory following primary vaccination.

Licensure criteria for Pneumococcal Conjugate Vaccines

Pneumococcal Conjugate Vaccines (PCVs) target prevention of a wide range of pneumococcal infections:

1. **Invasive Pneumococcal Disease (IPD):**
   Licensure for protection against IPD can be based on immunological criteria defined by an independent group of experts and published by WHO

2. **Acute Otitis Media (AOM):**
   No licensure criteria exist for mucosal infections such as AOM. Licensure for protection against AOM should therefore be based on evidence of efficacy

Jodar et al. Vaccine 2003; 21: 3265-72 - WHO Technical Report Series, No. 927, 2005, Annex 2

POET study

Pneumococcal capsular polysaccharides conjugated to protein D for prevention of acute otitis media caused by both *Streptococcus pneumoniae* and non-typable *Haemophilus influenzae*: a randomised double-blind efficacy study

Roman Prymula, Pascal Peeters, Viktor Chrobok, Pavla Kriz, Elena Novakova, Eva Kaliskova, Igor Kohl, Patricia Lommel, Jan Poolman, Jean-Paul Prieels, Lode Schuerman

- **Double blind**, randomized (1:1) study in Czech and Slovak Republics
- 11Pn-PD vaccine versus Havrix™
- **11Pn-PD: 11-valent pneumococcal conjugate prototype vaccine** with *H. influenzae* Protein D as carrier
  - 1, 3, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F (1 µg each)
  - each conjugated to protein D
- **Schedule**: 3 doses (at 3, 4 and 5 mo) + booster (at 12-15 mo)
- **Study population:** ~ 5000 infants, with 24 mo follow-up
- **Co-administration:** with acellular pertussis hexavalent vaccine (Infanrix hexa™)

° Hexavalent diphtheria-tetanus-3-component acellular pertussis-hepatitis B-inactivated poliovirus types 1, 2, and 3-*Haemophilus influenzae* type b; *Havrix* and *Infanrix hexa* are trade marks of the GlaxoSmithKline Group of Companies

Prymula R, et al. *Lancet* 2006;367:740-748.

POET overall AOM efficacy

	Control (N=2452)	11Pn-PD (N=2455)	VE (%)	95%CI	
Clinical AOM	499	333	**33.6**	20.8	44.3
Bacterial	178	306	**42.1**	27.7	53.7
Pneumococcal	92	189	**51.5**	36.8	62.9
- Vaccine types	141	60	**57.6**	41.4	69.3
- Related types	8	23	**65.5**	22.4	84.7
NTHi	63	41	**35.3**	1.8	57.4

Protective efficacy for 11Pn-PD vaccine for any AOM episode during the per-protocol follow-up

Prymula R, et al. Lancet 2006;367:740-748.

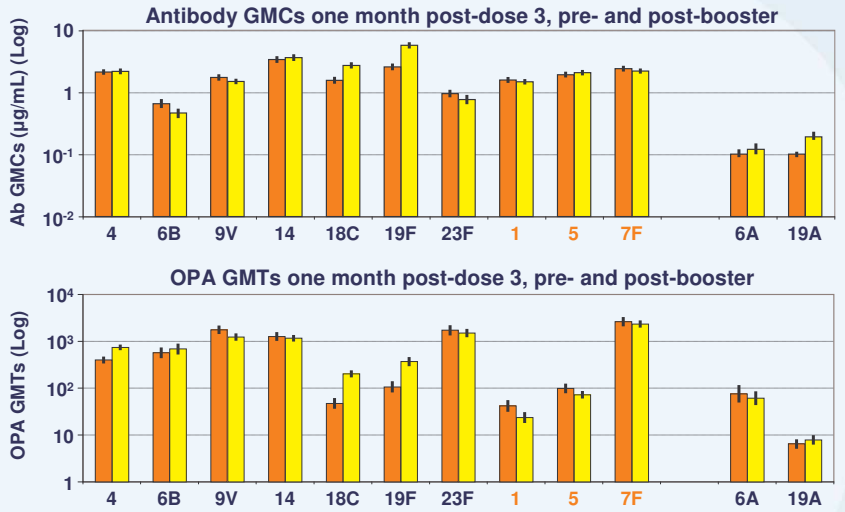
POET pneumococcal AOM efficacy

Serotype	Control (N=2452)	11Pn-PD (N=2455)	VE (%)	95%CI	
1	1	1	0.2	-1495.0	93.8
3	17	20	-17.1	-126.5	39.5
4	3	0	100.0	-27.8	100.0
5	0	0			
6B	24	3	87.6	58.4	96.3
7F	1	0	100.0	-283.6	100.0
9V	8	3	62.6	-40.8	90.1
14	22	1	95.5	66.0	99.4
18C	5	3	40.1	-176.6	87.0
19F	43	24	44.4	8.3	66.3
23F	18	5	72.3	24.8	89.8

Prymula et al. Lancet 2006;367:740-8

PHiD-CV and 11Pn-PD immunogenicity

ELISA antibody concentrations & OPA titres



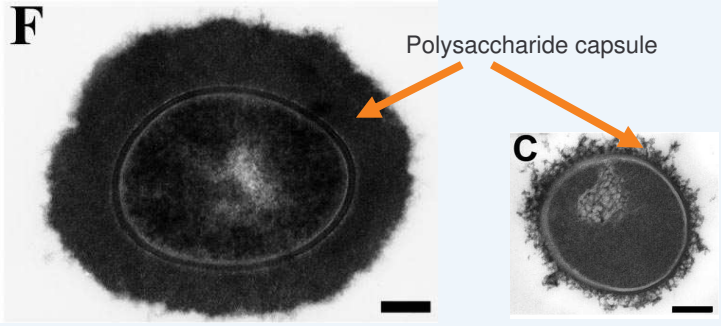
11Pn-PD POET

PHiD-CV Czech Rep (without antipyretics)

Prymula et al. Lancet 2006; 367: 740-8 – Schuerman et al. Vaccine 2007; 25: 1962-8
Prymula et al. Lancet 2009; 374: 1339-50 – Schuerman et al. Vaccine 2009; 27: 5748-54

No protection against serotype 3 AOM

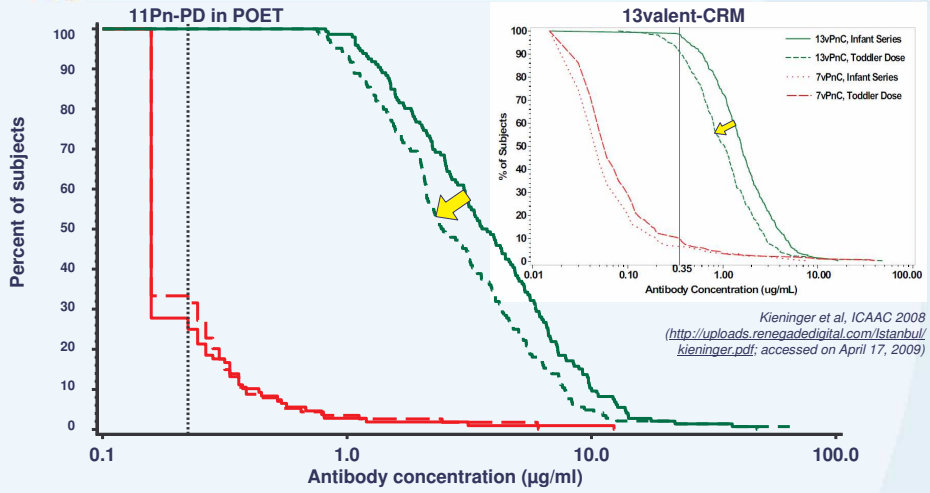
- Serotype 3 pneumococci have a dense polysaccharide capsule, making them possibly less vulnerable to antibody mediated opsonophagocytosis



Serotype 3 Serotype 19F

Hammerschmidt et al. IAI 2005; 73:4653

Serotype 3 immunogenicity



Kieninger et al, ICAAC 2008 (http://uploads.renegadedigital.com/Istanbul/kieninger.pdf; accessed on April 17, 2009)

➡ Lower antibody concentrations post-booster compared to post-primary are observed against serotype 3 for both PHiD-CV and 13-valent CRM-conjugate

Adapted from Prymula R. et al. Lancet 2006; 367: 740-8.

Summary of AOM indication

- The AOM indication for PHiD-CV is based on efficacy data generated with the related 11Pn-PD vaccine (POET) [1] and a comparison of the antibody and functional OPA responses between 11Pn-PD and PHiD-CV [2,3,5]
- Serotype 3 was removed from the PHiD-CV formulation due to the lack of AOM efficacy and the poor boostability observed for serotype 3 polysaccharide [3]
- Functional OPA responses for serotypes 18C and 19F in PHiD-CV were improved compared to 11Pn-PD by changing the carrier protein used for these serotypes [5]
- With these changes to the vaccine formulation, PHiD-CV can be considered to have at least the same impact on pneumococcal AOM as the 11Pn-PD formulation [5,6]

1. Prymula et al. Lancet 2006; 367: 740-8 – 2. Schuerman et al. Vaccine 2007; 25: 1962-8 – 3. Poolman et al. Vaccine 2009; 27: 3213-22
4. Prymula et al. Lancet 2009; 374: 1339-50 – 5. Schuerman et al. Vaccine 2009; 27: 5748-54 – 6. Synflorix SPC

PHiD-CV: Safety and tolerability profile

- Safety and tolerability profile comparable to PCV-7 [1,2]
- Broad clinical development program of the PHiD-CV vaccine includes trials in Europe as well Asia, Africa and Latin America
- Over 55,000 doses of GSK's pneumococcal conjugate vaccines have been administered so far **over 40 clinical trials worldwide**
- No safety concerns were identified during this clinical development program

1. Knuf et al. Pediatr Infect Dis J 2009;28: S97–S108
2. Lagos et al., ISPPD6, Reykjavik, Iceland 2008