The PCV 10 Vaccine: Updates on effectiveness and impact data.

Dr. William Mwiti MBChB, MSc Pharm Med, Vaccinology Country Medical Director
Outline

- Background- key facts about pneumococcal disease
- Synflorix™ - Efficacy and effectiveness data against:
  - Invasive Pneumococcal Disease
  - Pneumonia
  - Otitis Media
- Summary
## Bacterial infections

### Relative incidence (per 100,000 child years)

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Condition</th>
<th>Why vaccinate?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1x</td>
<td>Meningitis</td>
<td>Most serious form of bacterial meningitis</td>
</tr>
<tr>
<td>5-10x</td>
<td>Bacteraemia</td>
<td></td>
</tr>
<tr>
<td>100x</td>
<td>Pneumonia</td>
<td>#1 cause of infant death in the world, and a major cause of hospitalizations everywhere</td>
</tr>
<tr>
<td>2 - 5000x</td>
<td>Otitis media</td>
<td>Numbers of cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cost</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antibiotic Use and Resistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Possibility to lead to CSOM</td>
</tr>
</tbody>
</table>

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**Why vaccinate?**

- Numbers of cases
- Cost
- Antibiotic Use and Resistance
- Possibility to lead to CSOM

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**References:**
Pneumococcal mortality in children <5 years of age

Estimated 826,000 (582,000-926,000) deaths/year

PCVs recommendation

• WHO recommends PCVs childhood immunization worldwide particularly in countries with high childhood mortality.

• According to WHO, choice of PCV depends not only on vaccine serotypes but also on prevalent serotypes, vaccine supply, and cost-effectiveness considerations¹

• PCV’s of higher valencies (PCV-10 and PCV-13) were licensed on the basis of safety and immunogenicity data

• Clinical impact studies are required to confirm the effectiveness of new PCVs under routine use

¹Pneumococcal vaccines. WHO position paper. Weekly epidemiological record 2012; 87:129-144
Synflorix: Efficacy, Effectiveness & Impact Data
Synflorix™ efficacy and effectiveness: Evidence from randomized controlled trials

**FinIP**, Finland
47,000 subjects, primary objective: IPD

**Finland**
- **93%** (75,99)
- Vaccine serotypes: **100%**

**Latin America**
- **67%** (22,86)
- Vaccine serotypes: **100%**

**Compas**, Argentina, Colombia, Panama
24,000 subjects
primary objective: pneumonia

**Latin America**
- **26%** (8,40)

**Finland**
- **44%** (24, 59)

Efficacy and clinical impact data generated with Synflorix™

Quebec (Canada) IPD, Pneumonia, AOM

Kilifi (Kenya) IPD, carriage

COMPAS Panama, Colombia, Argentina
CAP, NP carriage, AOM

Brazil IPD, meningitis, CAP, carriage

Clinical trial Impact / effectiveness

FinIP (Finland) IPD, Antibiotics, CAP, Antibiotic use, NP carriage

The Netherlands IPD, AOM

New Zealand IPD, AOM

Iceland IPD, meningitis, CAP, AOM, antibiotic use

Bangladesh IPD, pneumonia

Otqro (Canada) IPD

Reduction of pneumonia cases by 1/3 one year after Synflorix introduction

Siggurðsson, et al. ISPPD 2014, 10-13 Mar, Hyderabad, India (abstract)

Reduction in all cause otitis media related visits children > 2 years

Goiania, Brazil

Pneumococcal vaccine introduction

Reduction of 44.5% of all-cause otitis in post vaccination period

Sartori, et al. ISPPD, Hyderabad, India, 10-14 March 2013 (poster)

Incidence of overall IPD children age 6–11 months

The Netherlands IPD, AOM

New Zealand IPD, AOM

Iceland IPD, meningitis, CAP, AOM, antibiotic use

Bangladesh IPD, pneumonia

Otqro (Canada) IPD

Invasive pneumococcal disease due to vaccine serotype children <5 years of age

Pneumococcal vaccine introduction

Antony Scott, KEMRI/Wellcome Trust Research Programme, Kilifi, Kenya, January 2014

http://www.who.int/pneumonia/asset-management/capsules/pneumonia_capsule_poster.pptx
Synflorix impact on vaccine type IPD in Kilifi, Kenya

Schedule: newborns: 6, 10, 14 weeks; 1–4 years: one time 2 dose catch-up

Synflorix impact on ALL IPD in Kilifi, Kenya
Schedule: newborns: 6, 10, 14 weeks; 1–4 years: one time 2 dose catch-up

PCV10-type carriage prevalence
Children <5 years, Kilifi, 2009 - 2012

Adjusted prevalence ratio = 0.36 (0.26 – 0.51)

Hammitt L et al Lancet Global Health 2014
PCV10-type carriage prevalence
People ≥5 years, Kilifi, 2009 - 2012

Adjusted prevalence ratio = 0.34 (0.18 – 0.62)

Hammit L et al Lancet Global Health 2014
Both PCVs have an impact on IPD in children < 2 years, irrespective of epidemiological setting and previous PCV use.

Efficacy/effectiveness estimates of various PCVs against radiologically confirmed pneumonia by the WHO case definition. Infant vaccination schedules in intention-to-treat (ITT) analysis.

Kilpi et al. ICAAC 2014
### AOM and pneumonia in Iceland: early reduction after Synflorix™ introduction

Comparison of cohorts of children 3 months to 2 years of age

Children born in 2011: vaccinated cohort (2+1 schedule)


<table>
<thead>
<tr>
<th></th>
<th>Mean Annual Incidence/10 000</th>
<th>Reduction (95%CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2008-10 (UnVacc)</td>
<td>2011 Vacc</td>
<td></td>
</tr>
<tr>
<td>OM</td>
<td>1198</td>
<td>915</td>
<td><strong>24%</strong> (13, 33)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>422</td>
<td>329</td>
<td><strong>23%</strong> (5, 36)</td>
</tr>
</tbody>
</table>

Siggurdson, et al. PIDJ 2015
Reduction in all cause otitis media related visits after Synflorix™ introduction children 2-23 moa in Brazil, Goiana

Reduction of 44.5% in rates of all-cause otitis in the postvaccination period

Sartori, et al. ISPPD, Hyderabad, India, 10-14 March 2013 (poster)
Cross protection against 19A

Is there any evidence of cross protection?
Synflorix™ Vaccine effectiveness:
Vaccine types and Serotype 19A

Quebec¹
(Unmatched case−control)
Vaccine-type (+6A)
VE=97% (95% CI: 84, 99)
19A
VE=71% (95% CI: 24, 89)

Brazil²
(Matched case−control)
Vaccine type
VE=84% (95% CI: 66, 92)
19A
VE=82% (95% CI: 11, 96)

Finland³
(Impact Study)
Rate Reductions
(pre vs post vaccine)
Vaccine type
RR=92% (95% CI: 86, 95)
19A
RR=62% (95% CI: 20, 85)

Conjugation Chemistry preserves 19F antigen
Cross reactive 19A functional antibodies
Protection vs 19A disease

Finland: PCV-10 reduces vaccine-related serotype IPD

IPD rates among children 3–38 months; post-Synflorix™ introduction (Sept 2010)

IPD rates (number of cases) in two reference cohorts compared with NVP cohort from June 2010 until September 2013 (N=334,087)

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Vaccine types</td>
<td>49.1 (162+157)</td>
<td>4.2 (14)</td>
<td>92 (86, 95)</td>
</tr>
<tr>
<td>Vaccine-related types</td>
<td>8.3 (31+23)</td>
<td>2.7 (9)</td>
<td>68 (38, 85)</td>
</tr>
<tr>
<td>19A</td>
<td>5.5 (23+13)</td>
<td>2.1 (7)</td>
<td>62 (20, 85)</td>
</tr>
<tr>
<td>6A</td>
<td>2.2 (5+9)</td>
<td>0.0 (0)</td>
<td>100 (41, 100)</td>
</tr>
<tr>
<td>Overall IPD</td>
<td>62.9 (216+193)</td>
<td>12.9 (43)</td>
<td>80 (72, 85)</td>
</tr>
</tbody>
</table>

IPD rates/100,000 person-years (number of cases) by cohort; data from National Infectious Disease Register

CI, confidence interval; IPD, invasive pneumococcal disease; NVP, National Vaccination Programme; Jokinen, et al. PLOS One 2015
### Effectiveness of PCV-10 against IPD in Brazil: a matched case control study

<table>
<thead>
<tr>
<th>IPD serotypes</th>
<th>Vaccine Effectiveness (95% CI) of age-appropriate PCV10 schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine serotypes</strong></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>83.8 (65.9-92.3)</td>
</tr>
<tr>
<td>6B</td>
<td>87.7 (60.8-96)</td>
</tr>
<tr>
<td>Vaccine related types</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>82.8 (23.8-96.1)</td>
</tr>
<tr>
<td><strong>19A</strong></td>
<td>77.9 (4-91.7)</td>
</tr>
<tr>
<td></td>
<td><strong>82.2</strong> (10.7-96.4)</td>
</tr>
</tbody>
</table>

Brazil schedule: 2,4,6 months plus booster at 12 months
4 age- and neighborhood-matched controls for each case (316 cases/1219 controls)

“Conclusion: In the context of the routine immunization program in Brazil, PCV10 prevents invasive disease caused by vaccine types and may provide cross protection against some vaccine-related types”

Domingues et al. 2014 Lancet Resp Med
**Effectiveness of PCVs to prevent IPD**

(Case control study study; VE ≥ 1 dose; schedule = 2+1)

- PCV7 introduced in UMV in Dec 2004, replaced by *Synflorix™* in June 2009, and PCV13 in Jan 2012
- 889 eligible IPD cases in children 2-59 months of age (2005-2013)
  - 58% returned written authorization to check immunization records (n=516)
- 1767 controls identified

<table>
<thead>
<tr>
<th></th>
<th>PCV7</th>
<th><em>Synflorix™</em></th>
<th>PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All serotypes</strong></td>
<td>50% (95%CI: 29-64)</td>
<td>72% (95%CI: 40-85)</td>
<td>66% (95%CI: 29-83)</td>
</tr>
<tr>
<td><strong>PCV-13 serotypes</strong></td>
<td>63% (95%CI: 45-74)</td>
<td>84% (95%CI: 65-93)</td>
<td>86% (95%CI: 62-95)</td>
</tr>
<tr>
<td><strong>Serotype 19 A</strong></td>
<td>42% (95%CI: -9-69)</td>
<td>71% (95%CI: 24-89)</td>
<td>74% (95%CI: 11-92)</td>
</tr>
</tbody>
</table>

VE computed by logistic regression model weighted for sampling fraction of controls and adjusted for age, year, season and underlying medical conditions including asthma and severe prematurity.

Deceuninck *et al*. Vaccines 2015
EMA’s positive opinion: Update of Synflorix effectiveness data against Vaccine type and vaccine related serotype 19A

Opinion of the committee for medicinal products for human use on a type II variation to the terms of the marketing authorisation for

<table>
<thead>
<tr>
<th>Medicinal product:</th>
<th>International non-proprietary name:</th>
<th>Presentations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synflorix</td>
<td>PNEUMOCOCCAL POLYSACCHARIDE CONJUGATE VACCINE ( ADSORBED)</td>
<td>See Annex A</td>
</tr>
</tbody>
</table>
Committee for Medicinal Products for Human use (CHMP)


- Approval of update of the SmPC with effectiveness data against pneumococcal vaccine serotypes and against vaccine related serotype 19A

- Update of the SmPC to include information on the immune response against serotype 19A observed in infants and children

- This opinion is forwarded to the European Commission, to the Member States, to Iceland and Norway

- With this variation approval, EMA recognizes that Synflorix can protect against pneumococcal disease, including: IPD, pneumonia and AOM caused by serotype 19A
Synflorix: Overview of Safety
Safety and reactogenicity of Synflorix™

- Most common adverse reactions
  - Following primary vaccination were redness at injection site (41%) and irritability (55%)\(^1\)
  - Following booster vaccination were pain at injection site (51%) and irritability (53%)\(^1\)

- Most reactions were of mild-to-moderate severity and were not long lasting\(^1\)

- In comparative clinical trials, incidence of local and general adverse events after each vaccine dose was within the same range as after vaccination with PCV7\(^2\)

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PCV7, 7-valent pneumococcal conjugate vaccine
Synflorix®: adverse events, contraindications and precautions

- **Adverse events**
  - Very common/common: appetite loss, local injection site reactions, drowsiness, irritability, fever
  - Rare/very rare: angioedema, anaphylaxis, hypotonic-hyporesponsive episode, apnoea in very premature infants (<28 weeks)

- **Contraindications and precautions**
  - Hypersensitivity to any component part
  - Postpone use in subjects with acute severe febrile illness
  - Use with caution in case of thrombocytopenia or coagulation disorder
  - Children with impaired immune responsiveness may have reduced antibody response, as may those using paracetamol prophylactically. Use antipyretic if simultaneously using whole cell pertussis and in children with seizure disorders or history of febrile seizures
  - Refer to SPC for details

SPC, Summary of Product Characteristics
Synflorix 4-dose vial with Preservative
Why did you add preservative in the 4 dose vial?

- The inclusion of a preservative (2-phenoxyethanol) is anticipated to allow opened vials to be kept up to 28 days instead of 6 hours for current (preservative-free) 2d vials in line with the WHO Multi-Dose Vial Policy.

- The Synflorix current 2-dose presentation is preservative-free, and must be used within 6 hours after first opening.
A Study to Compare the Immunogenicity of GSK Biologicals’ 10Pn-PD-DiT 4-dose Presentation to the Licensed 1-dose Synflorix™ (10Pn-PD-DiT) Vaccine When Co-administered With DTPw-combination Vaccine in Healthy Infants

Sponsor: GlaxoSmithKline  
ClinicalTrials.gov Identifier: NCT02447432  
Country - Bangladesh

<table>
<thead>
<tr>
<th>Tracking Information</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>First Received Date</td>
<td>May 7, 2015</td>
</tr>
<tr>
<td>Last Updated Date</td>
<td>September 3, 2015</td>
</tr>
<tr>
<td>Start Date</td>
<td>June 2015</td>
</tr>
<tr>
<td>Estimated Primary Completion Date</td>
<td>February 2016  (final data collection date for primary outcome measure)</td>
</tr>
<tr>
<td>Current Primary Outcome Measures (submitted: May 14, 2015)</td>
<td>Evaluation of the immune response to the investigational study vaccine in terms of antibody concentrations against vaccine pneumococcal serotypes. [ Time Frame: One month post-dose 3 (Month 3)] [ Designated as safety issue: No ]</td>
</tr>
</tbody>
</table>
Conclusions: What was the goal?
To develop a vaccine that shows:

1. High **OVERALL direct protection** of infants and young children against IPD

**OVERALL IPD protection =**
Impact on VT + impact on vaccine-related type – replacement with NVT

2. Significant **OVERALL herd protection** of older children and adults

3. Robust **protection against** mucosal disease

4. Acceptable **safety profile**

AOM, acute otitis media; VT, vaccine type; NVT, non-vaccine type
BACK-UP SLIDES
## COMPAS pneumonia results:
First episodes of CAP

<table>
<thead>
<tr>
<th>Clinical endpoint</th>
<th>Vaccine efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ATP</td>
</tr>
<tr>
<td>Likely bacterial pneumonia(^a)</td>
<td>22.0(^*) (7.7, 34.2)</td>
</tr>
<tr>
<td>X-ray-confirmed pneumonia(^b)</td>
<td>25.7 (8.4, 39.6)</td>
</tr>
<tr>
<td>Suspected clinical pneumonia(^c)</td>
<td>6.7 (0.7, 12.3)</td>
</tr>
</tbody>
</table>

\(^a\)Primary endpoint of the study: X-ray-confirmed pneumonia + pneumonia with CRP ≥40 µg/ml  
\(^b\)WHO definition 
\(^c\)Clinical suspicion of pneumonia with X-ray requested 
**ATP**, first occurrence of CAP from 2 weeks after administration of Dose 3 and part of the ATP cohort 
**ITT**, first occurrence of CAP from the administration of Dose 1 
*p=0.002; **p=0.0031

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### FinIP pneumonia results:
First episodes of hospitalised pneumonia

<table>
<thead>
<tr>
<th>Clinical endpoint</th>
<th>Synflorix® vaccine efficacy, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infant&lt;sup&gt;a&lt;/sup&gt; 3+1 schedule</td>
</tr>
<tr>
<td>Pneumonia diagnosed at the hospital</td>
<td>25.2 (2.6, 42.6)</td>
</tr>
<tr>
<td>Hospitalisation for pneumonia</td>
<td>24.6 (-2.2, 44.3)</td>
</tr>
<tr>
<td>Primary cause of hospitalisation</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Infants <7 months of age; <sup>b</sup>children 7–18 months of age. CI, confidence interval

Kilpi, et al. ESPID 2013, 28 May–1 June, Milan, Italy (abstract)
Iceland: PCV10 reduces pneumonia incidence

Children <2 years of age; post-Synflorix® UMV

- 2011 cohort (vaccinated) was compared with 2008–2010 cohorts (unvaccinated)
- Significantly lower incidence of pneumonia in the vaccinated cohort
  - OR: 0.74 (95% CI: 0.61, 0.88); p<0.001

Sigursson, et al. ESPID 2014, 6–10 May, Dublin, Ireland (poster)
Effectiveness of three PCVs to prevent invasive pneumococcal disease (IPD) in Quebec
(Case control study); VE (≥ 1 dose); Quebec schedule = 2+1

<table>
<thead>
<tr>
<th>IPD serotypes</th>
<th>PCV7</th>
<th>PCV10</th>
<th>PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV7+6A</td>
<td>90%*</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>PCV10+6A</td>
<td>79%*</td>
<td>99%*</td>
<td>100%</td>
</tr>
<tr>
<td>19A</td>
<td>42%</td>
<td>67%*</td>
<td>69%</td>
</tr>
<tr>
<td>PCV13</td>
<td>64%*</td>
<td>85%*</td>
<td>87%*</td>
</tr>
<tr>
<td>Non PCV13</td>
<td>-13%</td>
<td>10%</td>
<td>32%</td>
</tr>
<tr>
<td>All serotypes</td>
<td>53%*</td>
<td>75%*</td>
<td>79%</td>
</tr>
</tbody>
</table>

* = statistically significant p<.05

IPD cases in children 2–59 months and reported during the years 2005–2012 were eligible and controls randomly identified in the provincial health insurance registry. Parents interviewed by telephone and immunization records reviewed.

Results: Out of 830 IPD cases reported, full participation obtained for 480 cases (58%) and for 1,647 controls

Conclusion: “Results suggest that PCV10 and PCV13 are more effective than PCV7 thanks to the higher number of serotypes, and a high level of cross-protection against 19A for PCV10.”

Deceuninck et al. ISPPD 2014, P-271 (abstract)
Synflorix effect on serotype 19A colonization: RCT in Finland- Total vaccinated cohort analysis

![Graph showing the occurrence of 19A S. pneumoniae in NP Swabs (%)](image)

**VE (3+1: across all timepoints) = 47% (18–64)**

Note: A smaller study in the Netherlands that compared PHiD-CV to PCV7-CRM showed only marginal differences in 19A carriage. Van den Bergh CID 2012; Vesikari et al. ECCMID 2013, 27–30 April, Berlin, Germany (presentation); GlaxoSmithKline. Data on file.
Kenya Synflorix™ UMV vaccination programme

PCV10 introduced in 01/2011 Schedule: newborns: 6, 10, 14 weeks; 1–4 years: 2 doses

Data calculated manually by subtraction of IPD cases caused by any serotype minus IPD cases caused by PCV10 serotypes.

Effectiveness of three PCVs to prevent invasive pneumococcal disease (IPD) in Quebec (Case control study); VE (≥ 1 dose); Quebec schedule = 2+1

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<td>96%</td>
<td>ND</td>
</tr>
<tr>
<td>PCV10+6A</td>
<td>78%*</td>
<td>97%*</td>
<td>ND</td>
</tr>
<tr>
<td>19A</td>
<td>42%</td>
<td>71%*</td>
<td>74%</td>
</tr>
<tr>
<td>PCV13</td>
<td>63%*</td>
<td>84%*</td>
<td>86%*</td>
</tr>
<tr>
<td>Non PCV13</td>
<td>-83%</td>
<td>-78%</td>
<td>-151%</td>
</tr>
<tr>
<td>All serotypes</td>
<td>50%*</td>
<td>72%*</td>
<td>66%</td>
</tr>
</tbody>
</table>

* = statistically significant p<.05

IPD cases in children 2–59 months and reported during the years 2005–2012 were eligible and controls randomly identified in the provincial health insurance registry. Parents interviewed by telephone and immunization records reviewed.

Conclusion: “Results suggest that PCV10 and PCV13 are more effective than PCV7 thanks to the higher number of serotypes, and a high level of cross-protection against 19A for PCV10.”

Efficacy or effectiveness against 19A: studies with vaccines containing only 19F

Hausdorff BMC Pediatrics 2010
Comparative immunogenicity trials:
Higher functional activity (OPA) against serotype 19A for Synflorix™ vs PCV7

mo, month; OPA, opsonophagocytic activity; PCV7, 7-valent pneumococcal conjugate vaccine; wk, week

Comparative immunogenicity trials:
Higher functional activity (OPA) against serotype 19A for Synflorix™ vs PCV7

mo, month; OPA, opsonophagocytic activity; PCV7, 7-valent pneumococcal conjugate vaccine; wk, week

PHiD-CV consistently elicits higher anti-19A functional antibody activity (OPA) compared to PCV7<sub>CRM</sub>

How is that possible?

Both manufacturers start with same 19F polysaccharide, but differences in coupling chemistry and carrier proteins create antigenically distinct conjugates.

Native 19F structure

Oxidation + reductive amination (PCV7<sub>CRM</sub>)

Cyanylation (PHiD-CV)

Synflorix price reduction

From 2017 Synflorix price is 3.05 USD/dose

• New price of 3.05 USD/dose
• Approximately $1 USD saving per child for the course
• Applicable from 2017 for 2 doses & 4 doses (approval expected end 2017)
• Lowering the price is due to savings done in Manufacturing due to high volumes
• GSK Expanded volume commitments, pledging to deliver 720 million doses of the vaccine up to 2024.
• We continue to look at ways to reduce production costs and any savings we make we would pass on to Gavi.
• GSK commitment of prize freeze for graduated countries for 10 years