PRIME Study:
PCV Review of Impact Evidence

SAGE
10/18/2017

Maria Deloria Knoll, PhD
on behalf of the PRIME Study Team
PCV Review of Impact Evidence (PRIME): Provide up-to-date summary of evidence on: PCV immune response, effectiveness and impact

**METHODS:**
- Systematic review published 1994-2017
- Clinical trials and observational studies of routine use
- 3-dose schedule (2+1 and 3+0)
- PCV10 and PCV13

**OUTCOMES:**
PCV effectiveness and impact on:
- Immunogenicity
- Nasopharyngeal carriage
- Invasive disease (IPD)
- Pneumonia
- Mortality

**ANALYSES:**
- Meta-analyses for immunogenicity
- Descriptive summary for other outcomes due to differences in methods and epidemiologic settings
- Considered:
  - previous PCV7 use,
  - age (<5 years and >5),
  - dosing schedule,
  - time since introduction,
  - catch-up program
PRIME Inclusion/Exclusion Criteria:

**Included:**
- **Product:** PCV10 or PCV13
- **Dosing Schedule:** 3+0 or 2+1
  - 2+0 and 3+1 included where technically relevant
- **Outcomes:**
  - Vaccine-type immunogenicity (IgG GMC, % Responders),
  - Vaccine-type nasopharyngeal carriage,
  - Vaccine-type invasive pneumococcal disease (IPD)
- **Study types:** Clinical trials, observational studies reporting pre- and post-vaccine introduction incidence rates for disease outcomes or prevalence for carriage

**Excluded:**
- **Outcomes:** Otitis media, immunogenicity measured by opsonophagocytic activity or avidity
- **Study types:** Post-only disease incidence data; case-series data for disease outcomes (i.e., no denominator)
- **Indirect effects:** Studies with less than 3 years of PCV10/13 use
PRISMA: Inclusion/Exclusion Report

Record Identification
- Records identified through Pubmed database search: Oct 9 2015, 20,852
- Additional records identified: ISPPD 2012 & 2014 abstracts (n=646)
- IVAC Literature Search Oct 9 2015 - May 13 2017 (n=162)
- Duplicates excluded: 8,945
- Records after duplicates removed: 11,907

Screening
- Records Title/Abstract screened: 12,715
- Records excluded: 8,997
- Records full text screened: 3,718
- Records excluded: 3,381

Abstraction
- Records fully abstracted: 337
- Records without sufficient detail to understand PCV impact: 130

Analysis
- Records included in analysis: 207
Data Hierarchy: Available Evidence

- Clinical Trials
- Observational Studies
- RCTs

Within Study Comparisons
Between Study Comparisons
# PICO Question 1: Schedule Comparison

<table>
<thead>
<tr>
<th>Intervention</th>
<th>2p+1 vs. 3p+0 schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
</tr>
<tr>
<td>• Vaccinated children (direct effects)</td>
<td></td>
</tr>
<tr>
<td>• Unvaccinated older children and adults (indirect effects)</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td></td>
</tr>
<tr>
<td>• Immunogenicity</td>
<td></td>
</tr>
<tr>
<td>• NP carriage</td>
<td></td>
</tr>
<tr>
<td>• IPD</td>
<td></td>
</tr>
</tbody>
</table>
Immunization

1

Immunogenic Response:
Vaccine Type specific antibody (IgG)

Immunogenicity
Schedule Comparison Results: Immunogenicity

Included Study Arms by Dosing Schedule, PCV Product and Region:

<table>
<thead>
<tr>
<th>Head to Head Trials</th>
<th>n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

- **2p Single Arm Trials**
  - PCV10
  - PCV13

- **3p Single Arm Trials**
  - PCV10
  - PCV13

Confounding potential: Uneven distribution by geography

2p = 2 Primary Doses; 3p = 3 Primary Doses
Schedule Comparison Results: Immunogenicity

Head to Head Comparison of Schedules: IgG geometric mean concentration (GMC)
Analysis: meta-analysis of 9 randomized clinical trials

<table>
<thead>
<tr>
<th>Post Primary (i.e. 2 vs 3 doses):</th>
<th>Results</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMC: Similar</td>
<td>3</td>
<td>19F</td>
</tr>
<tr>
<td>GMC: Favors 3p</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>7F</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>19A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6A</td>
<td>6B</td>
</tr>
<tr>
<td></td>
<td>23F</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-Dose 3 (i.e., at age 4m vs. 15m):</th>
<th>Results</th>
<th>Serotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>GMC: Similar</td>
<td>3</td>
<td>19A</td>
</tr>
<tr>
<td>GMC: Favors 2+1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>6A</td>
<td>7F</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>19F</td>
</tr>
<tr>
<td></td>
<td>23F</td>
<td>6B</td>
</tr>
</tbody>
</table>

- GMC reflects amount of antibody, not necessarily protection
- Higher GMC does not necessarily correlate to better protection if there is a threshold for protection
Schedule Comparison Results: Immunogenicity

Head to Head Comparison of Schedule: Percent Response (above correlate of protection)

**Post Primary (i.e. 2 vs 3 doses):**

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<tr>
<td>%Response: Similar</td>
<td>19F</td>
</tr>
<tr>
<td>GMC: Favors 3p</td>
<td>1</td>
</tr>
<tr>
<td>%Response: Similar</td>
<td>5</td>
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<td></td>
<td>7F</td>
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</tr>
<tr>
<td></td>
<td>19A</td>
</tr>
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<tr>
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<td>23F</td>
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**Post-Dose 3 (i.e., at age 4m vs. 15m):**

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<td>19A</td>
</tr>
<tr>
<td>GMC: Favors 2+1</td>
<td>1</td>
</tr>
<tr>
<td>%Response: Similar</td>
<td>5</td>
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<tr>
<td></td>
<td>6A</td>
</tr>
<tr>
<td></td>
<td>7F</td>
</tr>
<tr>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>19F</td>
</tr>
<tr>
<td></td>
<td>23F</td>
</tr>
</tbody>
</table>

**Results:** Similar % Response between schedules for most STs;  
-- Favors 3+0 in the primary series for 6A, 6B, 23F  
-- Favors 2+1 for 6B
PCV Modes of Action

1. Immunization

Immunogenic Response: Vaccine Type specific antibody (IgG)

2. Nasopharyngeal Carriage

Direct Protection Against Colonization
Schedule Comparison Results: NP Carriage

Included Studies in NPC Analysis by Product and Schedule:

By Region

- **2+1**
  - PCV10: 1 study
  - PCV13: 2 studies

- **3+0**
  - PCV10: 1 study
  - PCV13: 1 study

**Potential Confounding:** by geography

- North America
- Latin America
- Europe
- Australia/Oceania
- Asia
- Africa

By Previous PCV Use

- **2+1**
  - Prior PCV7 Use: 3 studies
  - No Prior PCV7 Use: 1 study

- **3+0**
  - Prior PCV7 Use: 7 studies
  - No Prior PCV7 Use: 2 studies

**Potential Confounding:** by prior PCV7 use

By Study Design

- **2+1 Single Arm**
  - Observational: 3 studies
  - RCT: 1 study
  - Potential Confounding: by product
    - PCV10
    - PCV13

- **3+0 Single Arm**
  - Observational: 4 studies
  - RCT: 1 study
  - Potential Confounding: by product
    - PCV10
    - PCV13
Schedule Comparison Results: NP Carriage

Vaccine Type Carriage: 2+1 (Red) vs 3+0 (Blue)

Analysis: Head to head trials, comparison of schedules between trials, and between-study comparisons of observational studies

Results: Head to head trials and single-schedule trials: directionally favoring 2+1 (red)

a) Head to Head RCTs:

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Finland PCV10 at 14.5m and 11.5m</th>
<th>Vietnam PCV10 at 12m</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+1</td>
<td>(Vesikari 2016)</td>
<td>(Muholland 2017)</td>
</tr>
<tr>
<td>3+0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b) H2H & Single-Schedule RCTs:

- *Finland, 2+1, PCV10, 3-5 yrs, (Jokinen 2016)
- Nepal, 3+0, PCV10, 9 mo, (Hamaluba 2015)
- COMPAS, 3+0, PCV10, 12-15 mo, (Borys 2012)
- *Finland, 3+0, PCV10, 11.5 mos, (Vesikari 2016)
- *Finland, 2+1, PCV10, 14.5 mos, (Vesikari 2016)
- *Finland, 3+0, PCV10, 6mos, (Vesikari 2016)
- Vietnam, 3+0, PCV10, 12 mos, (Muholland 2017)
Schedule Comparison Results: NP Carriage

Vaccine Type Carriage: 2+1 (Red) vs 3+0 (Blue)

Results: Between-study comparisons of observation studies suggest similar impact, but potential confounding

But confounding due to:
- Prior PCV7 use
- Current product
- Pneumococcal carriage prevalence

Results: Between-study comparisons suggest similar impact.

**Grey triangles represent prior use of PCV7, but no pre-PCV7 carriage data are available so the slope of the line is unknown. The triangle’s left edge extends to the year of PCV7 intro.**
PCV Modes of Action

1. Immunization

2. Immunogenic Response: Vaccine Type specific antibody (IgG)

Invasive Disease

Direct Protection Against Disease

Direct Protection Against Colonization

World Health Organization
Schedule Comparison Results: Invasive Disease

Included Studies in IPD Analysis by Product and Schedule:

Inclusion Criteria:
- VT IPD reported as a group or serotype-specific
- RCTs, case-control, and pre-post vaccination incidence
- Meningitis, bacteremic pneumonia

Exclusion Criteria:
- Immunocompromised or special populations
- Number of cases only (i.e., no incidence)

Confounding potential:
Most studies in the context of prior PCV7 use

Number of Study Arms

<table>
<thead>
<tr>
<th></th>
<th>Prior PCV7 Use</th>
<th>No Prior PCV7 Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+1</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>3+0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Confounding potential:
Differential distribution by region and product

Number of Studies

<table>
<thead>
<tr>
<th>Region</th>
<th>2+1</th>
<th>3+0</th>
</tr>
</thead>
<tbody>
<tr>
<td>North America</td>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>Latin America</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Europe</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Australia/Oceania</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Asia</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Africa</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Included Studies in IPD Analysis by Prior PCV7 Use:

<table>
<thead>
<tr>
<th>Prior PCV7 Use</th>
<th>Number of Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Prior PCV7 Use</td>
<td>2+1</td>
</tr>
<tr>
<td></td>
<td>16</td>
</tr>
</tbody>
</table>

World Health Organization

IVAC
### Schedule Comparison Results: Vaccine Type IPD

Vaccine Impact on PCV10/13-Type Disease by Schedule and Previous PCV7 Use:

**Results:** Both schedules reduce the burden of Vaccine-Type IPD; Similar impact seen between schedules

#### 2+1 Schedule: (n=14)

<table>
<thead>
<tr>
<th>Prior PCV7 Use</th>
<th>Number of Studies:</th>
<th>Range of Point Estimates (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>n=3</td>
<td>82 to 93%</td>
</tr>
<tr>
<td>Yes</td>
<td>n=11</td>
<td>70 to 100%</td>
</tr>
</tbody>
</table>

#### 3+0 Schedule: (n=4)

<table>
<thead>
<tr>
<th>Prior PCV7 Use</th>
<th>Number of Studies</th>
<th>Range of Point Estimates (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>n=2</td>
<td>92% to 92%</td>
</tr>
<tr>
<td>Yes</td>
<td>n=2</td>
<td>70 to 82%</td>
</tr>
</tbody>
</table>
Schedule Comparison Results: Invasive Disease

ST1 is a special vaccine type

Vaccine efficacy and impact

- Pre-licensure 3+0 trials in Africa show no impact on ST1 IPD (however, small N)
- Recent outbreaks in PCV-using countries raised concerns whether 3+0 produces long-lasting protection

Epidemiology

- Creates outbreaks
- Dominant IPD serotype in Africa and Asia
- Differentially occurs in older children
Schedule Comparison Results: Serotype 1 IPD

Vaccine Impact on ST 1 Disease by Schedule:

**Results:** Evidence that both schedules impact burden of ST1 IPD; substantial data paucity on 3+0

### 2+1 Schedule:

<table>
<thead>
<tr>
<th>2+1:</th>
<th>Range of Point Estimates (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=7  (all PCV13)</td>
<td>0 to 98%</td>
</tr>
<tr>
<td>• Impact (n=4)</td>
<td>88 to 98%</td>
</tr>
<tr>
<td>• No Impact (n=1)</td>
<td>0% (NS)</td>
</tr>
<tr>
<td>• Inconclusive (n=2)*</td>
<td>--</td>
</tr>
<tr>
<td>n=1 Case Control</td>
<td>84%</td>
</tr>
</tbody>
</table>

*Few ST1 IPD isolates pre-PCV13

NS = not statistically significant

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### 3+0 Schedule:

<table>
<thead>
<tr>
<th>3+0:</th>
<th>Range of Point Estimates (% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=4*</td>
<td>90%</td>
</tr>
<tr>
<td>• Impact (n=2)**</td>
<td>90%</td>
</tr>
<tr>
<td>• Inconclusive (n=2)***</td>
<td>--</td>
</tr>
</tbody>
</table>

*Includes two unpublished studies that were available to the SAGE working group after the PRIME analysis

**One unpublished study: no impact reported

**Few ST1 IPD isolates pre-PCV10/13
# Schedule Comparison: Overall Conclusions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine Type (VT) Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>Antibody concentration (GMC):</td>
</tr>
<tr>
<td></td>
<td>- 3 primary doses more immunogenic than 2 primary doses</td>
</tr>
<tr>
<td></td>
<td>- 2+1 more immunogenic after 3(^{rd}) dose</td>
</tr>
<tr>
<td></td>
<td>% Responders: Schedules showed similar impact except for 6A, 6B and 23F</td>
</tr>
<tr>
<td>NP Carriage</td>
<td>Schedules showed similar impact</td>
</tr>
<tr>
<td>IPD</td>
<td>VT: Both schedules showed similar impact; Limited 3+0 data</td>
</tr>
<tr>
<td></td>
<td>ST1: Clear evidence of 2+1 impact; evidence of 3+0 impact but limited data</td>
</tr>
<tr>
<td>Overall</td>
<td>Both schedules are effective in reducing VT Carriage and Disease</td>
</tr>
</tbody>
</table>
PICO Question 2: Product Comparison

<table>
<thead>
<tr>
<th>Intervention</th>
<th>PCV10 vs PCV13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population</td>
<td></td>
</tr>
<tr>
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<tr>
<td></td>
<td>• NP carriage</td>
</tr>
<tr>
<td></td>
<td>• IPD</td>
</tr>
</tbody>
</table>
PICO II Question: Product Comparison

Both products were licensed and pre-qualified on the basis of immunogenicity and non-inferiority to PCV7, which was licensed on the basis of demonstrated efficacy against invasive pneumococcal disease.

**PCV10 – Synflorix:**
- Carrier Proteins: protein D from non-typeable Haemophilus influenzae (PD) (NTHi), Tetanus Toxoid (TT), Diphtheria Toxoid (DT)

**PCV13 – Prevenar-13:**
- Carrier Protein: CRM197 a non-toxic mutant of diphtheria toxin (CRM)

<table>
<thead>
<tr>
<th>Product</th>
<th>Serotype &amp; Carrier Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>PCV10</td>
<td>1μg PD</td>
</tr>
<tr>
<td>PCV13</td>
<td>2.2 μg CRM</td>
</tr>
</tbody>
</table>
Product Comparison Results: Immunogenicity

**Analysis:** Between-study meta-analysis comparison at the post-dose 3 time point (all $n\geq14$)
- 7 representative serotypes of the 10 in common were analyzed

**Results:** For serotypes in common: GMC: more STs favored PCV13
%Responder: PCV10 and PCV13 were comparable
Product Comparison Results: Immunogenicity

Analysis: Between-study meta-analysis comparisons at the post-dose 3 time point (all n≥14 except ST3 PCV10 n=1))

Results: **For serotypes 3, 6A and 19A** in PCV13 but not in PCV10:

- PCV13 is more immunogenic than PCV10; limited evidence to evaluate ST3 in PCV10
- PCV10 is immunogenic against STs 6A and 19A, but only with 2+1 schedule
  - Fewer than 60% of PCV10-vaccinated infants reached correlate of protection with 3p+0
Product Comparison Results: NP Carriage VT

Vaccine Type Carriage: PCV10 (Orange) vs PCV13 (Blue)

**Analysis:** Head to head trials, between-trial comparisons of single product trials, and between-study comparison of observational studies of routine use

**Results:** Both products are effective against their respective serotypes; Similar impact seen between products
Product Comparison Results: NP Carriage VT

Vaccine Type Carriage: PCV10 (Orange) vs PCV13 (Blue)

Observational studies of NP Carriage before and after PCV introduction

Results:
• Similar declines for both PCV10 and PCV13 when adjusted for starting value
• Considerable confounding:
  • schedule (all PCV10 are 3+0)
  • previous use of PCV7 (~all PCV13 previously used PCV7)

**Grey triangles represent prior use of PCV7, but no pre-PCV7 carriage data are available so the slope of the line is unknown. The triangle’s left edge ends to the year of PCV7 intro.**

- Gambia 3+0 PCV13 <1yrs (Roca, 2015)
- Australia 3+0 PCV13 <3y Aboriginal (Wigger, 2014)
- Burkina Faso 3+0 PCV13 <5y (Moisi, 2016)
- Malawi 3+0 CU PCV13 3-5y (Swarthout, 2016)
- Cambodia 3+0 PCV13 0-11m (SuyKuong, 2016)
- France 2+1 PCV13 <2yrs (Dunais, 2015)
- Norway 2+1 PCV13 <2 yrs (Steens, 2016)
- Israel 2+1 CU PCV13 <5 yrs (Danino; Ben Shimol, 2016)
- UK 2+1 PCV13 <5 <4yrs (Devine; Jones, 2016)
- So.Af. 2+1 PCV13 <2yrs (Nzenze, 2016)
- UK 2+1 CU PCV13 <5yrs (Van Hoek)
- So.Af. 2+1 CU PCV13 <2yrs (Nzenze, 2015)
- Mozambique 3+0 PCV10 <2y (Sigaque, 2016)
- Kenya 3+0 CU PCV10 <2y (Hammitt, 2016)
- Kenya 3+0 PCV10 <5y (Kim, 2016)
- Kenya 3+0 CU PCV10 <5y (Kim, 2016)
- Fiji 3+0 PCV10 <2y (Dunne, 2016)
- Sweden 2+1 PCV13 <6 (Galanis, 2016)

*p<0.05
**Product Comparison Results: NP Carriage ST3**

**Serotype 3 Carriage: PCV10 (Orange) vs PCV13 (Blue)**

**Results:**
- Limited trial data available
- No evidence PCV10 impacted ST3 carriage

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**Head to Head RCTs**

![Graph showing head to head RCTs]

- Vietnam 2+1 at 12m (Temple 2016)

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**H2H And Single Product RCTs**

![Graph showing H2H and single product RCTs]

- Vietnam, 2+1, PCV13, 12mo (Temple 2016)
- Nepal, 3+0, PCV10, 9mo (Hamaluba 2015)
- Vietnam, 2+1, PCV10, 12 mo (Temple 2016, Smith-Vaughan 2016)
Product Comparison Results: NP Carriage ST3

Serotype 3 Carriage: PCV10 (Orange) vs PCV13 (Blue)

Observational studies of NP Carriage before and after PCV introduction

**Results:**
- No impact seen with either product
- Equal number of studies showed increases and decreases in carriage

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Gambia 3+0 PCV13 6-11 mo (Rocca, 2015)
- South Africa, Soweto 2+1 PCV13 <2yrs (Nzenze, 2015) CU
- *Norway 2+1 PCV13 <5 yr (Vestreheim, 2008; 2010)
- France 2+1 PCV13 <2yrs (Varon, 2015)
- *UK 2+1 PCV13 <4 <5 (Devine, 2016; Jones, 2016)
- Sweden 2+1 PCV13 <6 (Galanis, 2016)
- Netherlands 3+0 PCV10 11mo (Wyllie, 2016)
- Netherlands 3+0 PCV10 <2y (Vissers, 2016; Bosch, 2015;2014)
- Kenya, Kilifi 3+0 PCV10 <2 yr (Hammitt, 2014;2016) CU
- Kenya, Asembo 3+0 PCV10 <5 yr (Kim, 2016) CU
- Kenya, Kibera 3+0 PCV10 <5 yr (Kim, 2016)
- Malawi 3+0 PCV13 <5yr (Swarthout, 2016) CU
- Cambodia 3+0 PCV13 <5yr (Su & Kuo, 2016)
Product Comparison Results: NP Carriage ST6A

Serotype 6A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:
- Reductions seen for both products
- Some evidence favoring PCV13
  - Head to head trial favored PCV13 although non-significant; PCV10 trial (Finland) showed no reduction but had very low baseline carriage (<2.5%)
  - Declines in ST 6A more pronounced with PCV13 in routine use studies

Head to Head RCTs

Vietnam 2+1 at 12m (Mulholland 2017)

H2H And Single Product RCTs

- *Vietnam, 3+0, PCV10, 12mo (Mulholland 2017)
- Vietnam, 2+1, PCV10, 12mo (Mulholland 2017)
- Vietnam, 2+1, PCV13, 12mo (Mulholland 2017)
- Finland, 3+0, PCV10, 11.5mo (Vesikari 2016)
- Finland, 3+0, PCV10, 6mo (Vesikari 2016)
- Finland, 2+1, PCV10, 14.5mo (Vesikari 2016)
Product Comparison Results: NP Carriage ST6A

Serotype 6A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:
- Declines in ST 6A more pronounced with PCV13

Observational studies of NP Carriage before and after PCV introduction:
- Sweden 2+1 PCV13 <6 (Galanis, 2016)
- *Gambia 3+0 PCV13 6-11 mo (Rocca, 2015)
- *South Africa, Soweto 2+1 PCV13 <2yrs (Nzenze, 2015)
- *Norway 2+1 PCV13 <5 yr (Vestrheim 2008, 2010)
- *France 2+1 PCV13 <2yrs (Varon 2015)
- UK 2+1 PCV13 <5 <4 (Devine 2016, Jones, 2016)
- *Netherlands 3+0 PCV10 <2y (Vissers 2016, Bosch 2015;2014)
- Kenya, Kilifi 3+0
  PCV10 <2 yr (Hammitt, 2014;2016) CU
  Kenya, Asembo 3+0
  PCV10 <5 yr (Kim, 2016) CU
- Kenya, Kibera 3+0
  PCV10 <5 yr (Kim, 2016)
- Fiji 3+0
  PCV10 <2yr (Dunne; Russell, 2016)
- Malawi 3+0
  PCV13 <5yr (Swarthout, 2016) CU
- *Cambodia 3+0
  PCV13 <5yr (SuyKuong, 2016)
**Product Comparison Results: NP Carriage ST6C**

**Serotype 6C Carriage: PCV10 (Orange) vs PCV13 (Blue)**

**Analysis:** Between study comparisons of observational studies only
- No trial data available

**Results:**
- PCV13 shows reduction while PCV10 showed increase

---

**Analysis:**

**Results:**

- PCV13 shows reduction while PCV10 showed increase

---

* *p<.05*

---

**Graph:**
- NP Carriage before and after PCV introduction

---

**Legend:**
- Sweden 2+1 PCV13 <6 (Galalis, 2016)
- *UK 2+1 PCV13 <5 <4 (Devine, 2016; Jones, 2016)
- *Netherlands 2+1 PCV10 <2y (Vissers, 2016; Bosch 2015; 2014)
- Fiji 3+0 PCV10 <2yr (Dunne; Russell 2016)
- France 2+1 PCV13 6-24 mo (Varon, 2015)
- *Norway 2+1 PCV13 <7 (Steens, 2016)

---

* *p<.05*
Product Comparison Results: NP Carriage ST19A

Serotype 19A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:
- Evidence favors PCV13
  - Head to head trial showed greater impact with PCV13 though non-significant
  - Some increases seen in PCV10 single arm trials
  - Routine use of PCV13 showed reduction in carriage while PCV10 showed some increases

Head to Head RCTs

H2H And Single Product RCTs

*p<.05
Product Comparison Results: NP Carriage ST19A

Serotype 19A Carriage: PCV10 (Orange) vs PCV13 (Blue)

Results:
- PCV13 showed consistent reductions while PCV10 showed some increases

*Reduction attributed to natural variation, not PCV10 impact

*p<.05
### Product Comparison Results: NP Carriage

**In Summary:** products had similar results except ST19A and perhaps ST6A (favored PCV13)

<table>
<thead>
<tr>
<th>Vaccine Serotypes in Common</th>
<th>Serotypes in PCV13 and not in PCV10</th>
<th>ST6C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST3</td>
<td>ST6A</td>
</tr>
<tr>
<td>Similar impact with both products</td>
<td>No Impact with either product</td>
<td>Impact with both products; <strong>Declines more pronounced with PCV13</strong></td>
</tr>
</tbody>
</table>
Product Comparison Results: Vaccine Type IPD

Vaccine Impact on PCV10/13-Type Disease by Product and Previous PCV7 Use:

Results:
- Both products similarly reduced (directly and indirectly) IPD caused by the serotypes within each vaccine

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>No Prior PCV7 Use</th>
<th>Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV10:</td>
<td></td>
<td>N=4</td>
<td>87 to 93%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>N=2</td>
<td>77 to 96%</td>
</tr>
<tr>
<td>PCV13:</td>
<td></td>
<td>N=1</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>N=9</td>
<td>65 to 100%</td>
</tr>
</tbody>
</table>
Product Comparison Results: ST3 IPD

Vaccine Impact on ST3 Disease by Product and Previous PCV7 Use:

Results:
- PCV10 showed no impact on ST3 (not included in the vaccine), but limited data
- PCV13 had inconclusive results

**PCV10:**

<table>
<thead>
<tr>
<th>Number of Studies:</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=3</td>
<td>-354 to 29%</td>
</tr>
<tr>
<td>• No or low Impact (n=1)</td>
<td>29% (NS)</td>
</tr>
<tr>
<td>• Increase (n=2)*</td>
<td>-194 to -354%</td>
</tr>
</tbody>
</table>

N=1 Case Control**

8% (NS)

*Both Finland
**Ineligible 4-dose study that was reviewed by SAGE WG (Brazil, Domingues 2014)

**PCV13:**

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=7</td>
<td>-35 to 85%</td>
</tr>
<tr>
<td>• Impact (n=2)</td>
<td>68 to 85%</td>
</tr>
<tr>
<td>• No or low Impact (n=5)</td>
<td>-35 to 41% (NS)</td>
</tr>
</tbody>
</table>

N=2 Case Control*

0 to 26% (NS)

*Includes n=1 ineligible 4-dose study that was reviewed by SAGE WG (Germany, Weinnberger 2016)
Product Comparison Results: ST6A IPD

Vaccine Impact on ST6A Disease by Product:

**Results:**
- Data for both products limited, but supportive of direct effect
- PCV13 studies were in context of prior PCV7 use with low burden of ST6A remaining; reductions seen in both vaccinated and unvaccinated cohorts

**PCV10:**

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2</td>
<td>56 to 89%</td>
</tr>
<tr>
<td>• Impact (n=1)</td>
<td>89%</td>
</tr>
<tr>
<td>• Non-Significant Impact (n=1)</td>
<td>56% (NS)</td>
</tr>
<tr>
<td>N=2 Case Control*</td>
<td>15 to 62% (NS)</td>
</tr>
</tbody>
</table>

*Impact of ≥1 dose

**PCV13:**

<table>
<thead>
<tr>
<th>Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=6</td>
<td>36(NS) to 100%</td>
</tr>
<tr>
<td>• Impact (n=2)</td>
<td>100%</td>
</tr>
<tr>
<td>• Inconclusive (n=4)*</td>
<td>--</td>
</tr>
<tr>
<td>N=1 Case Control**</td>
<td>98%</td>
</tr>
</tbody>
</table>

*Few ST6A IPD isolates remaining post PCV7
**Impact of ≥2 doses
Product Comparison Results: ST6C IPD

Vaccine Impact on ST6C Disease by Product:

Results:
- PCV10: no data available
- PCV13: non-significant impact in vaccinated cohorts
  - Indirect Effects: Impact seen in >65y cohort (n=1)

<table>
<thead>
<tr>
<th>PCV10:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Studies:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of Point Estimates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Available Evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCV13:</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Studies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range of Point Estimates</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Significant Impact (n=3)</td>
<td>36 to 63% (NS)</td>
<td></td>
</tr>
<tr>
<td>3+1 schedule (n=1)*</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

*Ineligible 4-dose study that was reviewed by SAGE WG; 69% (95%CI 55 – 78) among unvaccinated cohorts (Pilishvili et al. IDWeek 2017)
Product Comparison Results: ST19A IPD

Vaccine Impact on ST19A-Type Disease by Product:

Results:
- PCV10: only effectiveness (i.e., case-control) studies indicate some protective direct effects
  - Indirect effects studies suggest no change or increase in 19A disease
- PCV13: all studies showed protective effects (both direct and indirect)

<table>
<thead>
<tr>
<th>PCV10: Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=2</td>
<td>-54% to no change</td>
</tr>
<tr>
<td>• No or low impact (n=2)</td>
<td>-54% to no change</td>
</tr>
<tr>
<td>N=5 Case Control*</td>
<td>29 to 82%</td>
</tr>
</tbody>
</table>

* n=1 ≥2 doses, n=4 ≥1 dose; Includes indirect cohort studies

<table>
<thead>
<tr>
<th>PCV13: Number of Studies</th>
<th>Range of Point Estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=8</td>
<td>68 to 100%</td>
</tr>
<tr>
<td>• Impact (n=8)</td>
<td>68 to 100%</td>
</tr>
<tr>
<td>N=6 Case Control*</td>
<td>67 to 94%</td>
</tr>
</tbody>
</table>

* n=3 ≥2 doses, n=3 ≥1 dose; includes indirect cohort studies
**Product Comparison Results: IPD**

**In Summary:** products had similar results except ST19A favors PCV13; unknown for ST6C

<table>
<thead>
<tr>
<th>Vaccine Serotypes in Common</th>
<th>Serotypes in PCV13 and not in PCV10</th>
<th>ST6C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ST3</td>
<td>ST6A</td>
</tr>
<tr>
<td>Similar impact with both products</td>
<td>Impact not demonstrated for either product</td>
<td>Impact with both products; data limited</td>
</tr>
<tr>
<td>Outcome</td>
<td>Vaccine Serotypes in Common</td>
<td>Serotypes in PCV13 and not in PCV10</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ST3</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Impact with both products</td>
<td>Favors PCV13</td>
</tr>
<tr>
<td>NPC</td>
<td>Impact with both products</td>
<td>No Impact with either product</td>
</tr>
<tr>
<td>IPD</td>
<td>Similar impact with both products</td>
<td>Impact not demonstrated for either product</td>
</tr>
<tr>
<td>Overall</td>
<td>Impact with both products</td>
<td>Impact not demonstrated for either product</td>
</tr>
</tbody>
</table>
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