THE FUTURE OF PCV’S

GVIRF, Bangkok, Mar 2018

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LOWER RESPIRATORY DISEASES ARE THE LEADING INFECTIOUS CAUSE OF DEATH IN ALL AGES

LRI: 2.38 million deaths in 2016 (95% UI: 2.15-2.51)
23.0% decrease from 1990
REGIONAL UNDER 5 LRI MORTALITY AND INCIDENCE PLOTTED AGAINST SDI

Figure 2: Under-5 LRI mortality rate per 100 000 (A) and incidence per child-year (B) is shown. Data points show 5-year increments from 1990 to 2015. The black line is a least-squares cubic spline regression, with knots at 0·4, 0·6, and 0·8, using the under-5 LRI mortality rate or incidence for each geographic location, and represents the expected rate based on SDI alone (estimates above the black line are higher than expected and those below are lower than expected). More information on the formulation and theory of the SDI can be found in the Cause of Death GBD 2015 capstone paper.5 LRI=lower respiratory tract infection. SDI=Sociodemographic Index.
### EFFICACY OF PCV AGAINST PNEUMOCOCCAL DISEASE

#### VT IPD vs VT Pneumonia

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Efficacy, % (95% CI), PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>VT IPD vs VT Pneumonia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutts FT, et al. Lancet. 2005;365:1139-1146.</td>
<td>PCV9a 3 + 0</td>
<td>71% (76-86)</td>
</tr>
</tbody>
</table>

#### Pneumonia (CXR+) (1st episode)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Vaccine</th>
<th>Efficacy, % (95% CI), PP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonten MJM et al. N Engl J Med. 2015; 372: 1114-25 (Adults)</td>
<td>PCV13</td>
<td>5% (-5-14)</td>
</tr>
</tbody>
</table>

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1 VT = Vaccine type; PP = Per-protocol analysis; CI = confidence interval.
2 PCV9, investigational CRM197-conjugated pneumococcal conjugate vaccine
3 PCV11, investigational tetanus-diptheria toxoid-conjugated pneumococcal conjugate vaccine
4 PCV10, investigational  and PCV10 licensed nontypeable Haemophilus influenzae protein D-conjugated pneumococcal conjugate vaccine
5 PncOMPC, investigational pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine

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GLOBALLY, GAVI’S RATE OF PCV INTRODUCTIONS IS NEARLY 2X THAT OF THE MIDDLE INCOME COUNTRIES
EVIDENCE GENERATION FOR SUSTAINABILITY OF IMMUNIZATION PROGRAMS

Optimize PCV Dosing Regimens

Move from individual protection to maintenance of herd protection

Evaluate alternate dosing regimens:
• Booster containing regimens vs. primary schedule only
• Alternate schedules: 1+1, 0+1

Develop guidelines/policy for changing if studies yield positive results
PCV 7 AND 13 IMPACT ON IPD IN SOUTH AFRICA: 2 + 1 SCHEDULE

A TALE OF SEROTYPE 1 IN TWO COUNTRIES IN AFRICA – THE GAMBIA AND SOUTH AFRICA

PCV9 Trials 3+0 Without A Booster

Timeline of Cases of Invasive Pneumococcal Disease
Due to Serotypes 1 and 5 in Gambia and South Africa

Serotype 5

South Africa Study Imm. Timing

Gambia Study Imm. Timing

Serotype 1

Age (m) of IPD case

Red = Not PCV-Vaccinated
Black = PCV-Vaccinated
= South Africa
= Gambia

Klugman et al, Vaccine, 2011, 29, 3372 - 3
LACK OF HERD IMPACT ON SEROTYPE 1 USING PCV 13 IN GHANA USING 3 + 0 (NO BOOSTER)
A booster dose provides better reduction in vaccine serotype (VT) carriage and improved impact on serotype 1 disease in children and adults

• Comparison of countries with similar times since introduction (5-6 years) and coverage rates (>90%) show similar reduction in IPD (>90%) but almost 3X greater VT carriage reduction when a booster is given

<table>
<thead>
<tr>
<th>The Gambia (3+0)¹</th>
<th>South Africa (2+1)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPD</td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>No VT disease in last 24 mo</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>VT disease &gt;90% decrease</td>
</tr>
<tr>
<td>All ages</td>
<td>Zero cases serotype 1 in 2017</td>
</tr>
<tr>
<td>VT Carriage</td>
<td>47% (pre-PCV) reduced to 15% in 2015</td>
</tr>
</tbody>
</table>

• Despite PCV coverage of 85%, using a 3+0 schedule, after 3 years of introduction, Ghana experienced a serotype 1 meningitis outbreak (incidence increased from <5 to 300/100,000). Majority of cases were in those >5 and thus unimmunized; median age of 20.

Data suggest that a 2+1 or potentially a 1+1 schedule could provide better herd impact than a 3+0 schedule

¹ Mackenzie G. unpublished data
² Von Gottberg A et al. Abstract submitted to ISPPD 2018, Melbourne Australia
WANING IMMUNITY OF 3 + 0 DIRECT PROTECTION WITH AGE IN AUSTRALIA

Jayasinghe et al, Clin Infect Dis, Mar 8 2018, epub ahead of print
WANING IMMUNITY LEADS AUSTRALIA TO ADD A BOOSTER DOSE

Review of experience in countries with similar longevity of pneumococcal conjugate vaccine use and high quality surveillance but using alternate schedules for 13vPCV (3+1 in the USA and 2+1 in the UK): Published and unpublished data (provided in confidence by Public Health England [UK] and Centers for Disease Control and Prevention [USA]) were reviewed. The comparison across all three schedules showed better protection in children aged 1 year and older following schedules that included a booster dose in the second year of life. This is because immunity wanes following completion of the primary series; administration of a booster dose results in vigorous antibody responses that enhance the degree and duration of protection. This higher level of immunity achieved by second year of life boosting has also been associated with improved herd protection of older age groups.

REDUCED HERD PROTECTION IN ADDITION TO WANING IMMUNITY LEADS AUSTRALIA TO ADD A BOOSTER DOSE

In the 2–4 years age group, the reduction in IPD due to 13v-non7v serotypes in Australia was statistically significantly less than that observed in the UK, after 5 years of 13vPCV use. The decline in 13v-non7v serotypes was also less in all adult age groups, especially in the 15–44 years age group. Among individual serotypes, only 19A IPD had significant reductions across all age groups in Australia, while in the UK, significant reductions were also seen in serotypes 7F and 3.

When age-specific reductions in IPD incidence rates in the UK (using a 2+1 schedule) were used to impute incidence rates in Australia, it was estimated that, had the 2+1 schedule been used in Australia over the same time period, a total of approximately 270 fewer cases of 13vPCV serotype IPD would have been observed in the fifth year after 13vPCV introduction.

### BMGF SPONSORED ALTERNATE PCV DOSING STUDIES

**South Africa (PI: Shabir Madhi)**
- Individual randomization
- PCV10 and PCV13
- 2+1 vs. 1+1 (6 or 14 wks +9mo)
- Endpoints: Immunogenicity, NPC
- Results: 2Q2019

**United Kingdom (PI: David Goldblatt)**
- Individual randomization
- PCV10 and PCV13
- 2+1 vs. 1+1 (2mo + 12 mo)
- Endpoints: immunogenicity, NPC
- Results: Sept 2017

**India (PI: Ashish Bavdekar)**
- Individual randomization
- PCV10 and PCV13
- 3+0 and 2+1 vs. 1+1 (6 +9mo)
- Endpoints: Immunogenicity, NPC
- Results: May 2019

**The Gambia (PI: Grant Mackenzie)**
- Cluster randomized
- PCV13
- 3+0 vs. 1+1 (6wks + 9mo)
- Endpoints: NPC in pneumonia patients
- Results: 2Q2022

**Vietnam (PI: Kim Mulholland)**
- Individual randomization
- PCV10 and PCV13
- 3+1, 3+0, 2+1,1+1, 0+1
- Endpoints: Immunogenicity, NPC
- Results: 4Q2019

**Vietnam (PI: Lay-Myint Yoshida)**
- Cluster randomized
- PCV10: 3+0, 2+1,1+1, 0+1
- Endpoints: NPC, pneumonia
- Results: 1Q2021

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Last updated: May 25, 2018

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UK 2+1 VS. 1+1 STUDY

• PCV13 given at 2+1 (2, 4 and 12 mo) or 1+1 (3 and 12 mo)

Post Primary GMCs obtained at 5 mo of age

<table>
<thead>
<tr>
<th>Post-primary group 1</th>
<th>Post-primary group 2</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>(2m, 4m; N_{case} = 97)</td>
<td>(3m; N_{case} = 102)</td>
<td></td>
</tr>
<tr>
<td>1 1.25 (1.07-1.45)</td>
<td>0.57 (0.47-0.69)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3 0.28 (0.23-0.33)</td>
<td>0.27 (0.21-0.34)</td>
<td>0.66</td>
</tr>
<tr>
<td>4 1.08 (0.93-1.26)</td>
<td>0.43 (0.36-0.51)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>5 0.90 (0.77-1.07)</td>
<td>0.29 (0.24-0.35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6A 1.25 (1.00-1.56)</td>
<td>0.13 (0.11-0.15)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>6B 0.26 (0.20-0.33)</td>
<td>0.09 (0.08-0.09)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>7F 2.46 (2.11-2.88)</td>
<td>0.81 (0.69-0.95)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>9V 0.73 (0.60-0.89)</td>
<td>0.18 (0.16-0.21)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>14 4.19 (3.23-5.43)</td>
<td>1.13 (0.90-1.40)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>18C 0.90 (0.73-1.11)</td>
<td>0.22 (0.19-0.27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>19A 1.56 (1.25-1.96)</td>
<td>0.33 (0.27-0.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>19F 4.54 (3.80-5.42)</td>
<td>0.64 (0.54-0.76)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>23F 0.43 (0.34-0.54)</td>
<td>0.09 (0.08-0.10)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

UK ALTERNATE PCV DOSE STUDY (1+1 VS. 2+1)

Post-booster GMCs obtained at 13 mo of age

<table>
<thead>
<tr>
<th>Post-boost group 1 (2 m, 4 m, 12 m; N_max=91)</th>
<th>Post-boost group 2 (3 m, 12 m; N_max=86)</th>
<th>Group 2 to group 1 ratio† Adjusted‡ p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1  3:07 (2.58–3.64)</td>
<td>8:92 (7.42–10.73)</td>
<td>2.73 (2.13–3.51) &lt;0.0001</td>
</tr>
<tr>
<td>3  0.61 (0.51–0.74)</td>
<td>0.62 (0.52–0.74)</td>
<td>0.93 (0.72–1.19) 0.57</td>
</tr>
<tr>
<td>4  2.55 (2.15–3.04)</td>
<td>3.43 (2.86–4.12)</td>
<td>1.29 (1.01–1.64) 0.047</td>
</tr>
<tr>
<td>5  1.74 (1.49–2.03)</td>
<td>2.11 (1.81–2.45)</td>
<td>1.15 (0.93–1.42) 0.20</td>
</tr>
<tr>
<td>6A  8.62 (7.29–10.21)</td>
<td>6.36 (5.34–7.58)</td>
<td>0.69 (0.54–0.87) 0.002</td>
</tr>
<tr>
<td>6B  6.19 (5.10–7.50)</td>
<td>2.39 (1.94–2.94)</td>
<td>0.36 (0.27–0.47) &lt;0.0001</td>
</tr>
<tr>
<td>7F  3.98 (3.42–4.62)</td>
<td>3.36 (2.93–3.86)</td>
<td>0.82 (0.67–1.01) 0.059</td>
</tr>
<tr>
<td>9V  2.34 (2.00–2.73)</td>
<td>2.50 (2.16–2.88)</td>
<td>1.02 (0.83–1.26) 0.85</td>
</tr>
<tr>
<td>14  10.49 (8.84–12.44)</td>
<td>16.9 (13.54–21.08)</td>
<td>1.57 (1.19–2.08) 0.002</td>
</tr>
<tr>
<td>18C  1.98 (1.70–2.30)</td>
<td>1.63 (1.42–1.87)</td>
<td>0.78 (0.64–0.95) 0.017</td>
</tr>
<tr>
<td>19A  8.38 (7.17–9.80)</td>
<td>8.83 (7.4-10.52)</td>
<td>1.00 (0.79–1.26) 0.98</td>
</tr>
<tr>
<td>19F  11.12 (9.46–13.07)</td>
<td>14.76 (12.54–17.37)</td>
<td>1.28 (1.02–1.61) 0.035</td>
</tr>
<tr>
<td>23F  2.87 (2.38–3.46)</td>
<td>1.72 (1.44–2.05)</td>
<td>0.56 (0.44–0.73) &lt;0.0001</td>
</tr>
</tbody>
</table>

Post-booster dose:
- all GMCs high (>1ug/mL) except serotype 3
- GMCs not significantly different for 5 serotypes: 3, 5, 7F, 9V, 19A
- GMCs lower in the 1+1 group for 4 serotypes: 6A, 6B, 18C, 23F
- GMCs higher in the 1+1 group for 4 serotypes: 1, 4, 14, 19F

## NEXT GENERATION PCV VACCINES

### Investigational 10-13 Valent PCVs

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Details</th>
</tr>
</thead>
</table>
| Walvax (China)              | • Tetanus conjugated 13 valent PCV  
                             | • Current status: applied for licensure in China                        |
| Serum Institute of India PCV10 (PNEUMOSIL) | • Goal is equal protection to currently available vaccines at affordable prices  
                             | • Achieved POC in infants  
                             | • Current status: Phase III                                           |

Other manufacturers in earlier stages of development: SK Chemicals, South Korea; PnuVax, Montreal; BioE, Hyderabad; Finlay Institute, Havana.
NEXT GENERATION PCV VACCINES

Most Common Non Vaccine Serotypes: 2010-2017

**Non Gavi Countries**
13,126 isolates


**Gavi Countries**
1,468 Isolates

- Ten Most Common Non-PCV Types: 12F, 2, 35B, 18, 10A, 15A, 6, 23B, 46, & 10F

**Higher valency Conjugate Vaccines**

- Several in clinical development extending to 20+ valencies: Pfizer, Affinivax
- ? Immunogenicity threshold
- Large number of serotypes make up the remaining pneumococcal disease, thus increasing valencies adds limited incremental protection
- Potential for serotype replacement continues to be present
- Additional serotypes most often represent those prevalent in HIC, not LIC, where burden is greatest
• Serotypes that are poorly invasive in children may still be highly invasive in older adults.

• Therefore nasopharyngeal replacement of VT with NVT in adults may NOT necessarily lead to less disease in adults.

• E.g., if you replace VT 18C with 23A, in children that would be 1/1000 less invasive. In adults the difference is < 10-fold.

Weinberger et al. Amer J Epidemiol, 2016; 183, Web Appendix – blue arrows contributed by Bill Hausdorff!
FUTURE PNEUMOCOCCAL VACCINES

• **Non-conjugate vaccines (protein vaccines, whole cell vaccine)**
  • Potential to have broad coverage for all serotypes
  • PCV have set a high bar- will these need to affect disease endpoints as well as carriage and transmission?
  • Regulatory pathway potentially requires an efficacy study
  • Currently, no protein vaccine has been successful in advanced clinical development; WCV in Phase I/II
  • Replacement with potentially more pathogenic organisms a concern?
SUMMARY

- Deaths are declining in children, but pneumonia remains a major killer of both children and adults

- Pneumococcal conjugate vaccine has rolled out in many developing countries – optimizing the number of doses and their schedule for herd protection rather than individual protection may make future PCV schedules more sustainable

- Vaccines of 20+ valency may be needed but replacement may further erode future gains

- A whole cell vaccine remains a possibility if it can impact transmission as well as protect against pneumonia
THE WORK IS COMPLICATED.
WHY WE DO IT IS NOT.