PNEUMOCOCCAL VACCINE UPDATE

Gail L. Rodgers, MD
Bill & Melinda Gates Foundation
PNEUMONIA IS THE LEADING KILLER OF CHILDREN

- 5.6 million (5.4-6.0 million) under-5 deaths occurred in 2016; translating to 15,000 per day
- Pneumonia continues to be a leading cause of death in children; causing ~16% of all deaths in under-5 in 2016
- 2.6 million newborns died in 2016 – 7,000 per day, accounting for 46% of all under-5 deaths
- 11% of all <5 deaths are neonatal deaths due to infectious causes: pneumonia, tetanus, meningitis, and sepsis

UN Inter-agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality, Report 2017
GLOBAL BURDEN OF LRI MORTALITY IN CHILDREN < 5

- LRI are estimated to cause 2.74 million deaths per year
- Over 700,000 are in children < 5 years of age

NUMBER OF CHILDREN <5 YEARS OLD WHO DIE ANNUALLY FROM VACCINE-PREVENTABLE DISEASE

- Pneumococcal Disease: 393,000
- Rotavirus: 146,500
- Measles: 62,600
- Hib: 58,700
- Pertussis: 54,500
- Tetanus: 25,500
- Influenza: 10,200

55% of all LRI deaths in children < 5

*Streptococcus pneumoniae* is the leading cause of vaccine-preventable deaths globally

PREVENTION OF PNEUMOCOCCAL DISEASE

What are the areas of greatest need?

- Vaccine Delivery
- Evidence Generation for Sustainable Pneumococcal Immunization Programs
- Vaccine Development

Where can we have the greatest impact?

Where can we have the greatest impact?
The pneumococcal Advanced Market Commitment has allowed low income countries to introduce PCVs almost simultaneously to high income countries, thus avoiding the usual 15-20 year lag in new vaccine introductions.

<table>
<thead>
<tr>
<th></th>
<th>Gavi</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>National Introductions (as of Dec 2016)</td>
<td>57 (78%)</td>
<td>139 (72%)</td>
</tr>
<tr>
<td>Surviving Infants Have Access to PCV</td>
<td>41M (51%)</td>
<td>69M (52%)</td>
</tr>
<tr>
<td>Surviving Infants Immunized with PCV</td>
<td>29M (35%)</td>
<td>53M (37%)</td>
</tr>
</tbody>
</table>

Top 10 PCV Countries with Most Unimmunized/underimmunized Infants*

- Nigeria, Pakistan, Bangladesh, DRC, Uganda, Ethiopia, Angola, Nepal, Kenya, Afghanistan
- Philippines, Venezuela, Poland, South Africa, U.S., Dominican Republic, Brazil, Spain, Mexico, Argentina

*India not included because it introduced PCV in 2017

http://www.view-hub.org/viz/
http://www.gavi.org/
GLOBALLY, GAVI’S RATE OF PCV INTRODUCTIONS IS NEARLY 2X THAT OF THE MIDDLE INCOME COUNTRIES
What are the areas of greatest need?

Where can we have the greatest impact?

- Vaccine Delivery – expand coverage of existing vaccines
- Evidence Generation for Sustainable Pneumococcal Immunization Programs
- Vaccine Development
What are the areas of greatest need?

Where can we have the greatest impact?

- Vaccine Delivery
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- Vaccine Development
## EVIDENCE GENERATION FOR SUSTAINABILITY

### Assessment of Global PCV Impact

<table>
<thead>
<tr>
<th>Activities</th>
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<tbody>
<tr>
<td>Ensure that country relevant data is obtained</td>
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<tr>
<td>Evaluate both approved PCVs (PCV10 and PCV13)</td>
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<td>Assess endpoints: IPD, Pneumonia, NP Carriage</td>
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<td>Evaluate: Direct and Indirect Effects, Serotype Replacement</td>
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**EVIDENCE GENERATION FOR SUSTAINABILITY**

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<td>Assess other potential effects of PCV vaccination</td>
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THE BANGLADESH STORY: POTENTIAL UNACCOUNTED FOR BENEFITS OF VACCINATION

Emergency Room at Dhaka Shishu Children’s Hospital

Overcrowding Leads to Bed Sharing

Photographs courtesy of Dr. Samir Saha
THE BANGLADESH STORY: POTENTIAL UNACCOUNTED FOR BENEFITS OF VACCINATION

Admissions (A) and Refusals (B) at Dhaka Shishu Children’s Hospital 2015-2016

- Admissions – 23,064
- Refusals – 5,879

- Analysis of effect of rotavirus vaccination: in addition to preventing rotavirus associated diarrhea, it would result in release of 629 beds per year (11% of the refusals) with potential to impact mortality for other non-diarrheal diseases
- Analysis of effect of PCV could potentially be additive to rotavirus increasing bed availability and decreasing mortality further.

Saha S et al. Am J Trop Hyg 2018;98:360-3..
### Optimize 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 SCHEDULE – NEED FOR A BOOSTER DOSE

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>IPD</th>
<th>The Gambia (3+0)</th>
<th>South Africa (2+1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>No VT disease in last 21 mo</td>
<td>&lt;5 years</td>
</tr>
<tr>
<td>&lt;5 years</td>
<td>&gt;90% decrease</td>
<td>&gt;25 years</td>
</tr>
<tr>
<td>All ages</td>
<td>Effect on serotype 1 variable</td>
<td></td>
</tr>
<tr>
<td>VT Carriage</td>
<td>13%</td>
<td>4.2%</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 Mackensie G. data from OPP1020327
2 Von Gottberg A et al. Abstract submitted to ISPPD 2018, Melbourne Australia
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
- 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 Mackensie)**
- Cluster randomization
- 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
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>(2 m, 4 m; (N_{max} = 97)*)</td>
<td>(3 m; (N_{max} = 102)*)</td>
<td></td>
</tr>
<tr>
<td><strong>1</strong></td>
<td>1.25 (1.07-1.45)</td>
<td>0.57 (0.47-0.69)</td>
</tr>
<tr>
<td><strong>3</strong></td>
<td>0.28 (0.23-0.33)</td>
<td>0.27 (0.21-0.34)</td>
</tr>
<tr>
<td><strong>4</strong></td>
<td>1.08 (0.93-1.26)</td>
<td>0.43 (0.36-0.51)</td>
</tr>
<tr>
<td><strong>5</strong></td>
<td>0.90 (0.77-1.07)</td>
<td>0.29 (0.24-0.35)</td>
</tr>
<tr>
<td><strong>6A</strong></td>
<td>1.25 (1.00-1.56)</td>
<td>0.13 (0.11-0.15)</td>
</tr>
<tr>
<td><strong>6B</strong></td>
<td>0.26 (0.20-0.33)</td>
<td>0.09 (0.08-0.09)</td>
</tr>
<tr>
<td><strong>7F</strong></td>
<td>2.46 (2.11-2.88)</td>
<td>0.81 (0.69-0.95)</td>
</tr>
<tr>
<td><strong>9V</strong></td>
<td>0.73 (0.60-0.89)</td>
<td>0.18 (0.16-0.21)</td>
</tr>
<tr>
<td><strong>14</strong></td>
<td>4.19 (3.23-5.43)</td>
<td>1.13 (0.90-1.40)</td>
</tr>
<tr>
<td><strong>18C</strong></td>
<td>0.90 (0.73-1.11)</td>
<td>0.22 (0.19-0.27)</td>
</tr>
<tr>
<td><strong>19A</strong></td>
<td>1.56 (1.25-1.96)</td>
<td>0.33 (0.27-0.39)</td>
</tr>
<tr>
<td><strong>19F</strong></td>
<td>4.54 (3.80-5.42)</td>
<td>0.64 (0.54-0.76)</td>
</tr>
<tr>
<td><strong>23F</strong></td>
<td>0.43 (0.34-0.54)</td>
<td>0.09 (0.08-0.10)</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</th>
<th>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)</td>
<td>&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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>&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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>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)</td>
<td>&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

PREVENTION OF PNEUMOCOCCAL DISEASE

- Vaccine Delivery – expand coverage of existing vaccines
- Evidence Generation for Sustainable Pneumococcal Immunization Programs
- Vaccine Development - develop lower cost vaccines that provide equal or greater protection

What are the areas of greatest need?

Where can we have the greatest impact?
# NEXT GENERATION PCV VACCINES

## Investigational 10-13 Valant PCVs

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>Description</th>
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<tbody>
<tr>
<td>Walvax (China)</td>
<td>• Tetanus conjugated 13 valent PCV</td>
</tr>
<tr>
<td></td>
<td>• Current status: applied for licensure in China</td>
</tr>
<tr>
<td>Serum Institute of India PCV10 (PNEUMOSIL)</td>
<td>• Goal is equal protection to currently available vaccines at affordable prices</td>
</tr>
<tr>
<td></td>
<td>• Achieved POC in infants</td>
</tr>
<tr>
<td></td>
<td>• Current status: Phase III</td>
</tr>
<tr>
<td>Other manufacturers in earlier stages of development</td>
<td></td>
</tr>
</tbody>
</table>
**NEXT GENERATION PCV VACCINES**

**Most Common Non Vaccine Serotypes: 2010-2017***

**Non Gavi Countries**
13,126 isolates

Ten Most Common Non-PCV Types:
8, 12F, 22F, 24F, 10A, 35B, 15A, 23B, 6C & 15B/C

**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

University of Washington START Program, unpublished data – not for citation
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

- Current PCVs have had an enormous impact on disease and mortality.
- Most countries, including LICs, have introduced PCVs, but adequate coverage remains a challenge globally.
- Innovation in vaccine schedules may reduce cost and ensure sustainability of immunization programs.
- Vaccine development with higher valency PCVs and serotype independent vaccines is ongoing and have the potential to expand the reductions in disease and mortality.
The work is complicated. Why we do it is not.