Antibiotic Resistance and Serotype Replacement of pneumococcus in Post-PCV era – What can we expect in South Asia?

Samir K Saha, Ph.D.
Child Health Research Foundation
&
Dhaka Shishu Hospital
PCV Introduction Status

Source: VIMS Report: Global Vaccine Introduction, IVAC; October, 2013
Estimated IPD cases prevented among all ages, United States 2001-2009

280,000 cases & 19,000 deaths prevented

Pilishvili JID 2010 & CDC unpublished
Some Limitations – Behavior of NVTs

IPD trends among Alaskan Native children <2 years in the era of PCV7

Figure 1. Rates of Invasive Pneumococcal Disease in Alaska Native Children Younger Than 2 Years, by Year and Serotype, 1995-2006

PCV7 Serotype

Non-PCV7 Serotype

PCV7 indicates 7-valent pneumococcal conjugate vaccine. Error bars indicate 95% confidence interval.
Rates of invasive pneumococcal disease among U.S. children <5 years, 1998-2009

Moore, IDSA, 2009
Who is Responsible for Erosion of Our Achievements?

Non-vaccine types – 19A?

Why 19A serotype is so special?

- Prevalent
- Clinically important
- Often highly and multiply resistant worldwide
- Not affected by PCV7
Are We Sure About 19A dynamics?

• Serotype 19A in Korea During Pre-PCV era
  – Dramatic Increase
    • All were Multi drug resistant
  – Not increased in Australian and some other population
We are possibly near to the end of 19A issues

- Further detail evidence from the countries with higher disease burden
- Availability of PCV-13
- Possibility of extended protection of 19F towards 19A
  - Domingues et al. ISPPD 9 – Abst 0288
Impact of PCV on Antibiotic Resistance

FURTHER REWARD FROM PCV
Impact of PCV on Resistance of Pneumococcus

Kyaw et al NEJM 2006;354:1455-83
Impact of PCV on Resistance of Pneumococcus

Proportion of penicillin non-susceptible *S. pneumoniae* among all strains studied by CNRP, France, 1984 to 2006 (n=50,300)

National plan for preserving the efficacy of antibiotics

PCV7 introduction

Note: no national figures from 1998 to 2000, as CNRP activities were interrupted.

CNRP: national reference centre for *S. pneumoniae*; PCV7: 7-valent pneumococcal protein conjugate vaccine.
Reduction in Antibiotic Use

- PCV contains most of the drug resistant strains
- Vaccination reduces these serotypes in vaccinated and unvaccinated population
- Leads to reduction in prevalence of resistant strains
- Finally, PCV is potentially contributing in reducing use of antibiotics and emergence of resistance

PCV impact in reducing resistance – has a caveat

<table>
<thead>
<tr>
<th>PCV</th>
<th>Antibiotic in last 3 months</th>
<th>Carriage with Pen&lt;sup&gt;R&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>No</td>
<td>4.8%</td>
</tr>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>8.6%</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>10.3%</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
<td>16.2%</td>
</tr>
</tbody>
</table>

Cohen R et al, PIDJ, 2006
MOVING TO SOUTH ASIA
# PCV Introduction Status South Asia

<table>
<thead>
<tr>
<th>Country</th>
<th>Program type</th>
<th>Year of Introduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bangladesh</td>
<td>GAVI approved</td>
<td>2014</td>
</tr>
<tr>
<td>Nepal</td>
<td>GAVI approved/approved with clarification</td>
<td>2014</td>
</tr>
<tr>
<td>Sri Lanka</td>
<td>Non-GAVI planning introduction</td>
<td>2016</td>
</tr>
<tr>
<td>Pakistan</td>
<td>Universal</td>
<td>2012</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>Universal</td>
<td>2013</td>
</tr>
<tr>
<td>Bhutan</td>
<td>Non-GAVI planning introduction</td>
<td>2016</td>
</tr>
</tbody>
</table>

SOUTH ASIA HAS ALL THE INGREDIENTS TO MAKE THE PCV OUTCOME COMPLEX
May have several 19As

DIVERSE SEROTYPES: >50
DIFFERENT SEROTYPES
Serotype causing IPD in Bangladesh 2000-2013

Total IPD N=1033 & detected serotype N=626

Total IPD 1033
Culture 421
Latex 211
ICT 380
PCR 21

Serotype Detected 626 (61%)
Serotypes causing IPD in India, Nepal & Sri Lanka
(n = 735)

Data for the period of 2005-2013
South Asia is Close to Tell More About NVTs - 19A and Beyond

• Bangladesh and Pakistan are introducing PCV-10

• With available multiyear Pre-PCV data and huge disease burden
  • These countries will be in a good position to shed light on PCV impacts
    • Looking forward to be advocate for the next introducers
    • Will be happy to volunteer for India – if ............
Possibly God is still kind (by and large)

ANTIBIOTIC RESISTANCE IN PNEUMOCOCCUS
Susceptibility of South Asian Pneumococcus

Penicillin

Cotrimoxazole

Chlormphenicol

Erythromycin
Are We Missing Something for Impact Studies?

SEROTYPE SPECIFIC SUSCEPTIBILITY
Cotrimoxazole Susceptibility Among Vaccine Types - Bangladesh

Cotrimoxazole Susceptibility:
- Susceptible
- Intermediate
- Resistant

Vaccine Types:
14, 18C, 19F, 23F, 4, 6B, 9V, 1, 5, 6A, 7F, 19A, 3

<table>
<thead>
<tr>
<th>Vaccine Type</th>
<th>Susceptible</th>
<th>Intermediate</th>
<th>Resistant</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>58%</td>
<td>46%</td>
<td>8%</td>
</tr>
<tr>
<td>18C</td>
<td>28%</td>
<td>36%</td>
<td>3%</td>
</tr>
<tr>
<td>19F</td>
<td>22%</td>
<td>36%</td>
<td>50%</td>
</tr>
<tr>
<td>23F</td>
<td>22%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>4</td>
<td>25%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>6B</td>
<td>11%</td>
<td>33%</td>
<td>56%</td>
</tr>
<tr>
<td>9V</td>
<td>4%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>1</td>
<td>11%</td>
<td>56%</td>
<td>45%</td>
</tr>
<tr>
<td>5</td>
<td>50%</td>
<td>55%</td>
<td>25%</td>
</tr>
<tr>
<td>6A</td>
<td>5%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>7F</td>
<td>25%</td>
<td>44%</td>
<td>34%</td>
</tr>
<tr>
<td>19A</td>
<td>5%</td>
<td>50%</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>100%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Susceptibility Penicillin Among Vaccine Types - Bangladesh

- 14: 29% Susceptible, 71% Resistant
- 18C: 8% Susceptible, 92% Resistant
- 19F: 11% Susceptible, 89% Resistant
- 23F: 10% Susceptible, 90% Resistant
- 4: 100% Susceptible
- 6B: 100% Susceptible
- 9V: 100% Susceptible
- 1: 100% Susceptible
- 5: 100% Susceptible
- 6A: 100% Susceptible
- 7F: 100% Susceptible
- 19A: 6% Susceptible, 94% Resistant
- 3: 100% Susceptible

Susceptible
Resistant

Child Health Research Foundation
Prevent Infections, Save Lives
For Optimal Control of IPD - Combined efforts of PCV and Antibiotic Use

- Is the model going to work in South Asia?
  - Introduction of PCV
  - Judicious use of Antibiotics
    - Remote possibility
  - Let’s take typhoid treatment as a model

Model of Ron and Keith
• MDR Reported from Bangladesh, India and UK
  – Physicians started using third generation Cephalosporin
  – It was proved to be wrong
  – The did not come back to the old practice
  – Good results.....

• Tried to help them more
  – Hand to hand delivery of report with minimal turn around time (24 hrs)

• Only 16% of Physicians switched to 1st line drug despite the evidence in hand

Typhoid MDR and Use of Antibiotic

- MDR Reported from Bangladesh, India and UK
  - Physicians started using third generation Cephalosporin
  - It was proved to be wrong
  - The did not come back to the old practice
  - Good results.....Thank you Doctor!!

- Tried to help them more
  - Hand to hand delivery of report with minimal turn around time (24 hrs)

- Only 16% of Physicians switched to 1st line drug despite the evidence in hand

Saha et al Antimicrobial Agents Chemother 1995,
Saha et al J Clin Microbiol 2001
Antibiotic Use in India
Molecule growth trajectory in Bangladesh

Source: Bangladesh Pharmaceutical Index (BPI) by IMS
Note: 2013 data estimated, based on YTD Q2 performance
Human Nasopharynx the Natural Habitat of Pneumococcus

CARRIAGE WITH INVASIVE POTENTIAL
**Invasiveness of Carriage**

**Invasive Strain (N=298, 2007-2012)**

**Carriage Strain (N=432, 2005-2007 & 2009-2011)**

<table>
<thead>
<tr>
<th>Invasive Potential</th>
<th>Carriage Serotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine Types</strong></td>
<td><strong>Non Vaccine Types</strong></td>
</tr>
<tr>
<td>&gt;90%</td>
<td>1, 5 &amp; 7F</td>
</tr>
<tr>
<td>80 - 90%</td>
<td>14, 18C, 23F, 6B, 19A</td>
</tr>
<tr>
<td>25 - 50%</td>
<td>3</td>
</tr>
<tr>
<td>&lt;25%</td>
<td></td>
</tr>
</tbody>
</table>
Carriage

• Pneumococcal carriage the greatest sources of resistance
  – Children carry the resistant strains more and for longer period of time
    • South Asian children have all the ingredients to harbor resistant strains
Carriage Rate of Pneumococcus – an ongoing longitudinal study
This is Only Superficial View

MULTIDIMENSIONAL CHALLENGE
Multiple Carriage - Colonization

Age in Months

- 6A
- 12F
- 14
- 23A
Dynamics of Multiple Carriage

![Graph showing visits and density](image-url)
Promiscuity – A trick of Pneumococcus to evade vaccine and antibiotic effect

- Naso-pharynx is an ideal place for Pneumococcus to transfer genetic material to its nearest one and make it smarter than us.
Conclusion

• South Asian countries will be saving more lives than the number of cases in US

• It will have challenges
  – Lack of pre-data
  – Diverse serotype
  – Low vaccine coverage

• It is important to have all modalities in place to ensure our clear understanding about the dynamics of Pneumococcus, during the post PCV era

• Considering the lack of data well designed carriage study should be considered seriously
Acknowledgement

I gratefully acknowledge
• Ron Dagan
• Thomas Cherian
• Cynthia Whitney
• Keith Klugman
• IVAC
• Last but not the least
  my team member