Optimal strategies for Pneumococcal prevention: the role of Pneumococcal Conjugate and Polysaccharide Vaccines

A/Prof Peter Richmond
UWA School of Paediatrics & Child health
Vaccine Trials Group, TICHR
Princess Margaret Hospital for Children, Perth, WA
Talk Outline

• Burden of pneumonia and pneumococcal disease in Asia Pacific

• Impact of Pneumococcal Conjugate Vaccines on Invasive Pneumococcal Disease
  - Different schedules
  - Evidence for herd immunity
  - Serotype replacement
  - High risk populations

• Alternative schedules and use of PPV

• Future Vaccines
High incidence of childhood clinical pneumonia in the Asia/Pacific region

Proportion of <5 mortality due to pneumonia
WPR - 13%
SEAR - 19%

Worldwide Incidence of Pneumococcal Disease

Incidence (per 100,000) of Pneumococcal Disease in Children 1-59 Months of Age

### Summary of PCV Efficacy Results

<table>
<thead>
<tr>
<th>Disease</th>
<th>NCKP PCV7 (3+1)</th>
<th>Navajo PCV7 (3+1)</th>
<th>RSA PCV9* (HIV-)</th>
<th>Gambia PCV9*</th>
<th>Latin America PCV10 (3+1)†</th>
<th>Finland PCV10†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2+1</td>
</tr>
<tr>
<td>IPD- VT</td>
<td>97#</td>
<td>77</td>
<td>83</td>
<td>77</td>
<td>100</td>
<td>92</td>
</tr>
<tr>
<td>IPD- all</td>
<td>90</td>
<td>n.a.</td>
<td>42</td>
<td>50</td>
<td>65</td>
<td>93</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>20</td>
<td>?</td>
<td>22</td>
<td>37</td>
<td>23</td>
<td>n.a.</td>
</tr>
<tr>
<td>Death</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>16</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>AOM- All</td>
<td>6-8</td>
<td>14</td>
<td></td>
<td>16</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>PE Tubes</td>
<td>24</td>
<td>31</td>
<td></td>
<td></td>
<td></td>
<td>n.a.</td>
</tr>
</tbody>
</table>

#: blue is statistically significant  
* 3 dose EPI schedule (6-10-14 wks; 3+0))

† Cluster randomised RCT: Palmu et al Lancet 2013; 381:214-22

‡ http://www.gsk-clinicalstudyregister.com

9V PCV include serotypes 1 and 5
Infant schedules for pneumococcal conjugate and polysaccharide vaccines

- **USA**: PCV at 2-4-6 months, booster at 12-15 months (3+1)
- **UK, Europe**: PCV at 2-4 mths of age, booster at 13 mths (2+1)
- **Australia**: PCV 2-4-6 months, no booster (3+0)
- **ATSI**: PCV at 2-4-6 months with PPV at 18 months to 2012 (3+PPV)
- **EPI**: 6-10-14 weeks, no booster (3+0)
- **South Africa**: 6-14 weeks booster at 9 mths (2+1)
- **PNG**: 1-2-3 months
  - Use of PPV at 9 months?
Impact of PCV7 with herd immunity in the USA (3 + 1 schedule)

**FIGURE 1.** Rate* of vaccine-type (VT) invasive pneumococcal disease (IPD) before and after introduction of pneumococcal conjugate vaccine (PCV7), by age group and year — Active Bacterial Core surveillance, United States, 1998–2003

*Per 100,000 population.
†For each age group, the decrease in VT IPD rate for 2003 compared with the 1998–1999 baseline is statistically significant (p<0.05).

**FIGURE 2.** Estimated number of cases of vaccine-type (VT) invasive pneumococcal disease (IPD) prevented by direct* and indirect† effects of pneumococcal conjugate vaccine (PCV7) — Active Bacterial Core surveillance, United States, 2003

*Direct VT IPD cases prevented in 2003 = 1998–1999 average number of VT IPD cases in children aged <5 years x 2003 PCV7 coverage with 3 doses (68.1%) x PCV7 effectiveness for VT IPD (93.9%).
†Indirect VT IPD cases prevented in 2003 = (1998–1999 average number of VT IPD cases across all age groups – 2003 number of VT IPD cases across all age groups) – 2003 direct VT IPD cases prevented. Calculation of indirect cases prevented does not account for replacement disease.
Herd Immunity after 2+1 PCV7 in UK

Miller E et al, The Lancet Infectious Diseases 2011; 11:760 - 768
Replacement disease for some serotypes after PCV7 by age group in England & Wales

Also significant rise in 22F
Introduction of new Pneumococcal conjugate vaccines in Australia

- 2001 - PCV7 funded for Aboriginal infants
  - given at 2-4-6 months of age with 23PPV at 18 months
- 2005 - PCV7 introduced for non-Aboriginal infants
  - Given at 2-4-6 months with no booster (3+0 schedule)
  - Catch up to 2 years of age
  - 23vPPV funded for all adults >65yrs
- Oct 2009 - NT introduces PCV10
  - 2-4-6-12 months schedule (3+1)
- July 2011 - PCV13 replaces PCV7 in remaining states
  - 3+0 with catch up to 3 years (single dose; limited coverage)
  - Early evidence of decrease in 19A
- 2012 - PCV13 replaces PPV as booster for indigenous children
Australian trends in IPD by age in 2002-2011 - Impact of 3+0 schedule

Source: National Notifiable Diseases Surveillance System

• Source Vicki Krause CDNA EIPDS WG

* Preliminary data
Herd Immunity in the Elderly in Australia

IPD notification rates in non-Indigenous adults aged ≥65 years, by serotype category and time periods, NNDSS Australia, 2002–2009

Source R. Menzies NCIRS, NNDSS
Reductions in pneumonia associated with PCV 3+0 schedule in Australia
Inverse relationship between vaccine efficacy and Vaccine Attributable Reduction in HIV-ve 5th African children

PCV= pneumococcal conjugate vaccine; WHO= World Health Organization; CXR= chest X-ray

Madhi et al. Vaccine 2012; 30, Supplement 3 C21 - C27
Pneumococcal infections in high risk populations
Replacement IPD in children <5 years: emergence of serotype 19A (non-indigenous) and serotype 1 (indigenous)

Serotype replacement may not be predictable after PCV in different populations

Source: National Notifiable Diseases Surveillance System
Early onset of nasopharyngeal carriage is associated with increased risk of pneumococcal diseases

Colonization of the upper respiratory tract:
- median age 17 days in PNG infants
- 100% by 3 months of age

Persistence of carriage into adulthood
- 43% in PNG compared to 1-13% in European countries
- ongoing risk of IPD in adults

Amanda Leach, Menzies School of Health Research
Why Neonatal Pneumococcal Vaccination?

- earlier protection against IPD
- improved immunisation coverage rates
- reduce pneumococcal carriage in first months of life

Why Pneumococcal polysaccharide vaccine?

- improve serotype coverage esp serotype 2
- provides booster for less immunogenic PCV serotypes
- documented to be immunogenic and reduce mortality in PNG infants
Serotype 2 responsible for 13.5% of all IPD and 20.4% (45/221) of Pnc meningitis

## Efficacy of pneumococcal polysaccharide vaccine against death Tari, Papua New Guinea (1981-85)

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>Person years at risk</th>
<th>Death due to Uncomplicated ALRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5 years</td>
<td>12909</td>
<td>Placebo/Vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21 / 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy 58% (p=0.02)</td>
</tr>
<tr>
<td>&lt;2 years</td>
<td>5488</td>
<td>Placebo/Vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>19 / 9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Efficacy 53% (p=0.06)</td>
</tr>
</tbody>
</table>

**All deaths**

<table>
<thead>
<tr>
<th>Placebo/Vaccine</th>
<th>71 / 51</th>
<th>59 / 39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>30% (p=0.05)</td>
<td>34% (p=0.04)</td>
</tr>
</tbody>
</table>

Riley et al, Lancet 1986
PCV7 responses are similar in neonatal & infant schedules in PNG infants and primes for PPV boost

Pomat et al PLoSOne 2013; 8:e56698
Salivary antibody responses to 6B in PNG infants after PCV priming and PPV booster

IgA

ST 6B

Age

0,1

1
2
3
4
9
10
18

T. Orami unpublished data

IgG

ST 6B

Age

0,1

1
2
3
4
9
10
18

T. Orami unpublished data
Antibody persistence in PNG Children at 4 yrs after PCV & PPV

- No evidence of hypo-responsiveness after PPV
  - Similar response to PPV 0.1mL challenge dose
  - Similar numbers memory B-cells
**Future Pneumococcal Protein Vaccines**

- **Bivalent protein vaccine (sanofi)**
  - Pneumococcal histidine triad d (Phtd) and Choline-binding protein A (CbpA)
  - Phase II trials planned in Bangladesh

- **PCV10 with proteins pneumolysin and PhtD (GSK)**
  - Currently in Phase II trial in Gambia
  - Planned trial for prevention of OM in American Indians

- **Pneumococcal whole-cell vaccine (Malley/PATH)**
  - Non-encapsulated & enriched for detoxified pneumolysin
  - Phase I completed, Phase II studies planned in Kenya

- **No correlate of protection for protein vaccines**
  - Will need endpoint studies
  - Need to consider alternative schedules
Conclusions

• PCV is highly effective for those strains in the vaccine with a variety of schedules
  - Invasive disease, pneumonia & ear disease
• Reductions in IPD due to vaccine types in adults due to herd immunity
  - Replacement disease with non-vaccine types is a problem
  - Important to monitor vaccine effectiveness and maintain surveillance for serious disease and carriage
• PPV may be useful as a booster for PCV particularly where PCV serotype coverage is low
  - Relevance of “hyporesponsiveness” needs to be clarified and may be setting specific
• Neonatal PCV schedules appear safe and immunogenic and may provide better coverage and earlier protection
• Pneumococcal protein-based vaccines offer hope of broader protection in high-risk populations
PCV in National Programs
June 2012

- PCV7 / PCV13
- PCV13 / PCV10 *
- PCV10

* Assumes 80% BC coverage for PCV13

Also Bangladesh, Nepal, Lao PDR, Japan, Fiji, PNG introducing vaccine
GAVI approved countries for support for PCV introduction

still work to do in Asia Pacific!
Questions
Acknowledgements

VTG/UWA
Chris Blyth
Selma Wiertsma
LeaAnn Kirkham
Andrew Currie
Ruth Thornton
Karli Corscadden
Jan Jones
Fiona McDonald
Jennifer Kent

PathWest
Tom Riley
Tony Keil
Jacinta Bowman
Jade Jones

International/national collaborators
Amanda Leach
Peter Morris
David Goldblatt
Kim Mulholland
Rob Menzies

TICHR
Deborah Lehmann
Anke Hoskins
Hannah Moore
Diedre Collins

Qld Pnc. Ref. Lab
Denise Murphy
Helen Smith

PNGIMR
Willie Pomat
Peter Siba
Jacinta Francis
Tilda Orami

WA CDCD
Carolien Giele
Paul Effler
Gary Dowse

All the children and parents who participated in the Studies

Funding
NHMRC
Wellcome
Allegra Scafidas Fund
Garnette Passe
UWA Project Grant
GlaxoSmithKline Australia

ENT
Harvey Coates
Shyan Vijayasekaran
Tim Cooney

CDNA
Vicky Krause
Heather Cook
Peter McIntyre
Enhanced IPD Surveillance Working group
Back Up Slides
WHO position on pneumococcal vaccines (C)

- For administration to infants, 3 primary doses (3p+0 schedule) or, as an alternative, 2 primary doses plus a booster (2p+1 schedule) are recommended.

- If the 3p+0 schedule is used, vaccination can be initiated as early as 6 weeks of age with a minimum interval between doses of 4 weeks, i.e. scheduled for administration at ages 6, 10, and 14 weeks or 2, 4, and 6 months, depending on programmatic convenience.

- If the 2p+1 schedule is selected, the 2 primary doses may be given as early as 6 weeks of age and at a minimum interval of 8 weeks or more for the youngest infants and 4-8 weeks or more for infants aged ≥7 months. One booster dose should be given between 9-15 months of age.
FIGURE 2. Countries that have introduced pneumococcal conjugate vaccines in their national Immunization programs, by income status* — worldwide, 2012

Pneumococcal ear discharge in NT ATSI children after PCV7 + PPV

67% VT; 24% Perforations

18% VT; 21% Perforations

Before PCV7

Post PCV7

PROMPT Study A. Leach et al
Total illness visits, acute lower respiratory infections, and invasive pneumococcal disease in vaccine and control groups

<table>
<thead>
<tr>
<th></th>
<th>Neonatal N=104</th>
<th>Infant N=105</th>
<th>Control N=109</th>
<th>Total N = 318</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total illness visits</td>
<td>355</td>
<td>423</td>
<td>441</td>
<td>1219</td>
</tr>
<tr>
<td>Mild ALRI</td>
<td>79</td>
<td>109</td>
<td>116</td>
<td>304</td>
</tr>
<tr>
<td>Moderate/Severe ALRI</td>
<td>73</td>
<td>73</td>
<td>78</td>
<td>224</td>
</tr>
<tr>
<td>IPD</td>
<td>1 (ST 8)</td>
<td>1 (ST19)</td>
<td>2 (2, 18C)</td>
<td>4</td>
</tr>
</tbody>
</table>
Similar non-PCV serotype-specific IgG responses to PPV in PCV-primed and unprimed children
Similar pneumococcal isolation rates from nasopharyngeal swabs by age in vaccinated and non-vaccinated children
PCV type carriage by age and vaccine schedule

- Age
  - 1w
  - 2w
  - 3w
  - 1m
  - 3m
  - 9m
  - 18m

- Serotype-specific IgG GMC pre-challenge dose
  - ST 2
  - ST 4
  - ST 5
  - ST 6B
  - ST 7F
  - ST 9V
  - ST 14
  - ST 18C
  - ST 19F
  - ST 23F

- PCV+PPV
- PPV
- Control
Increasing Invasive Pneumococcal Disease in Aboriginal population in WA

Carolien Giele, CDCD, DOH

Giele PHAA 2012
Emergence of serotype 1 in WA Aboriginal population

Number of IPD cases caused by 23PPV-non-7PCV serotypes by year in Aboriginal people.

- 2001-2002
- 2003-2004
- 2005-2006
- 2007-2008
- 2009-2010
- 2011

Serotype 1 in Aboriginal people by age group, 2010 and 2011.

- ST 1 cases
- Rate

Giele et al ISPPD 2012
Pneumococcal serotypes carried in young WA children (2009-10)

Children with Recurrent ear infections
Healthy Controls

Frequency (%)

Wiertsma Vaccine 2011 29:5163-7
Indigenous carriage in WA Vaccine types 2008-2011

Proportion of carriage serotypes included in PCVs and 23vPPV by age

Vaccine type

- 7v PCV
- 13v PCV
- 23v PPV
- Non-vaccine type

Proportion of serotype isolates

Legend:
- 0 to 1 (N=186)
- 2 to 4 (N=244)
- 5 to 14 (N=230)
- 15+ (N=71)
Serotypes 16F and 34 are not included in any vaccine

Overall, 18% carried more than one serotype

19A isolates: ~20% resistant to Cotrimoxazole and ~50% non susceptible to Penicillin

23F: 83% multi-resistant to tetracycline, cotrimoxazole and erythromycin
### Comparing IPD And Carriage in WA Indigenous Population

Most common serotypes causing IPD in WA compared with carriage serotypes (1 Aug 2008 - 30 June 2011)

<table>
<thead>
<tr>
<th>Serotype</th>
<th>&lt;15 years</th>
<th>≥ 15 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>proportion of clinical isolates IPD (N=54)</td>
<td>proportion of carriage isolates (N=601)</td>
</tr>
<tr>
<td>1</td>
<td>35%</td>
<td>1%</td>
</tr>
<tr>
<td>12F</td>
<td>20%</td>
<td>1%</td>
</tr>
<tr>
<td>8</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>22F</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>19A</td>
<td>7%</td>
<td>9%</td>
</tr>
<tr>
<td>16F</td>
<td>4%</td>
<td>8%</td>
</tr>
<tr>
<td>7F</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>10A</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>
Figure 2. NT IPD notification rates in aged <5yrs by vaccine serotypes

Source V Krause, H Cook NT Health ISPPD 2012
The effect of PCV7 vaccination on the prevalence of specific serotypes, by age group

Herd immunity and serotype replacement 4 years after seven-valent pneumococcal conjugate vaccination in England and Wales: an observational cohort study

Pneumonia is an important cause of < 5 year mortality in the Asia-Pacific.