Impact of the pneumococcal conjugate vaccine in South Africa

Anne von Gottberg
Centre for Respiratory Diseases and Meningitis (CRDM)
Mortality due to pneumonia

- South Africa first African country to introduce pneumococcal vaccine into routine immunisation programmes
- National Strategic Plan: <5 mortality, infant mortality reductions
- Millennium Development Goals (MDG) 4: To reduce child mortality
- Sustainable Development Goal (SDG) 3: Ensure healthy lives and promote well-being for all at all ages
Pneumococcus (Streptococcus pneumoniae)

- Gram-positive cocci
- Carriage in nasopharynx (>50% of children <3 years of age) Bogaert et al, Lancet ID 2004
- Commonest bacterial cause of pneumonia
- Causes pneumonia, meningitis, sinusitis, otitis media
- Clinically significant bacteraemia in Kenya: 436/100,000 children <5 years Brent et al, Lancet 2006
- Associated with HIV
- High morbidity and mortality
Pneumococcal capsule

- Polysaccharide capsule
- >90 serotypes
- 23-valent polysaccharide vaccine
- Conjugate vaccine: effective in children
  - 7 serotypes in the 7-valent vaccine (PCV7): common paediatric serotypes, also most resistant
  - PCV10, PCV13
Description of the licensed PCV vaccines

**PCV7**
- **Serotypes:** 4, 6B, 9V, 14, 18C, 19F, 23F
- **Cross-protection:** 6A
- **CRM<sub>197</sub> Diphtheria carrier protein**

**PHiD-CV**
- **Serotypes:** 4, 6B, 9V, 14, 18C, 19F, 23F
- **1, 5, 7F**
- **Cross-reactivity:** 6A, 19A
- **T** D
- **NTHi protein D**

**POET formulation:** included serotype 3 + all polysaccharides conjugated to protein D

**PCV13**
- **Serotypes:** 4, 6B, 9V, 14, 18C, 19F, 23F
- **1, 5, 7F**
- **3, 6A, 19A**
- **CRM<sub>197</sub> Diphtheria carrier protein**
Randomised trials of efficacy of pneumococcal conjugate vaccine against vaccine-serotype specific disease

- NCKP²: 97.4%
- SA HIV (-)⁴: 84.6%
- Gambia⁵: 77.0%
- Am Ind³*: 76.8%
- SA HIV (+)⁴: 65.0%
Laboratory-based surveillance for IPD in South Africa

- GERMS-SA (Group for Enteric, Respiratory and Meningeal Disease Surveillance in South Africa)
  - surveillance for laboratory-confirmed cases
  - invasive disease
  - >270 clinical microbiology laboratories
  - enhanced surveillance at 25 hospital sites
Definitions and methods

- Active, national laboratory-based surveillance
- Case: identification of *Streptococcus pneumoniae*, from normally sterile site specimens
- Repeat isolates from the same patient are excluded; recurrent episodes were defined as repeated isolation >21 days
- Serotyping by Quellung
Number of cases of IPD reported by age and HIV, South Africa, 2005-2008 (enhanced sites only [7382/19233, 38% of all IPD], with known age and HIV status [5302/7382, 72%])
Percentage of invasive pneumococcal disease due to vaccine serotypes by age group in 2005-2008, South Africa (n=13723/19200 [71%] cases with serotyping results)
Pneumococcal Vaccine Introduction in South Africa

- PCV7 introduced in 2009, replaced by PCV13 in 2011
- Three-dose schedule
  - 6 weeks, 14 weeks and 9 months
- Estimated PCV7 coverage 2009 and 2010

(Expanded Programme on Immunisation administrative data)

<table>
<thead>
<tr>
<th>Year</th>
<th>PCV7 1st dose</th>
<th>PCV7 3rd dose</th>
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<tbody>
<tr>
<td>2009</td>
<td>41%</td>
<td>11%</td>
</tr>
<tr>
<td>2010</td>
<td>87%</td>
<td>63%</td>
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PCV7: 7-valent pneumococcal conjugate vaccine; PCV13: 13-valent pneumococcal conjugate vaccine
Changes in overall invasive pneumococcal disease (IPD) incidence rates by age group, 1998–2007. Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000.
Incidence of IPD by vaccine and non-vaccine serotypes, Soweto, 2003-2008

Nunes M et al, AIDS, 2011
Incidence of IPD Among All Ages
South Africa, 2005–2012

% change in IPD incidence: -40% (95% CI: -42% to -37%)

Pre-vaccine average 2005–2008

Post-vaccine year (2012)

- 35,192 IPD cases identified
- Isolates available for 70% (24,552)
- Age unknown for 5% (1648)
Incidence of IPD Among Those <15 Years of Age by Year and Age Group—South Africa, 2005–2012

Incidence of IPD Among HIV-Uninfected Children <2 Years of Age by Year and Serotype, South Africa, 2005-2012

VT: -85% (-89% to -79%)*

PCV13: -34% (-53% to -7%)*

Serotype 6A: -77% (-88% to -59%)*

NVT: +33% (+15% to +48%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of IPD Among HIV-Infected Children <2 Years of Age by Year and Serotype, South Africa, 2005-2012

VT: -86% (-91% to -78%)*

Vaccine serotypes (VT)

PCV13: -72% (-88% to -44%)*

Serotypes 1, 3, 5, 7F, 19A (PCV13)

NVT: -31% (-59% to +11)*

Serotype 6A: -85% (-95% to -62%)*

Non-vaccine serotypes (NVT)

Relative reduction=55%

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of IPD Among Those ≥15 Years of Age by Year and Age Group—South Africa, 2005–2012

INDIRECT EFFECT

Age group, years:
- 15–24
- 25–44
- 45–64
- >64

- 25-44 years of age: -34% (-39% to -29%)*
- 45-64 years of age: -14% (-23% to -3%)*
- >64 years of age: +1% (-26% to +22%)*
- 15-24 years of age: -29% (-42% to -16%)*

VACCINES REDUCE ANTIBIOTIC RESISTANCE

Incidence of antibiotic-resistant invasive pneumococcal disease in children < 2 years, South Africa (cases per 100,000 person-years)


#vaccineswork
GERMS-SA IPD surveillance featured in the journal *Nature* for the work being done on the impact of the pneumococcal vaccine in South Africa. *Nature*; Vol. 312, Aug., 2014; News in Focus, Vaccines column; Article entitled: “Hidden bonus from vaccination – Immunization against pneumococcus in Africa also reduces levels of antibiotic resistance.”
Effects of Vaccination on Invasive Pneumococcal Disease in South Africa


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Cumulative weekly number of IPD cases due to any of the seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) in PCV7: children <5 years of age, South Africa, from 2005 to date

PCV7 introduced in April 2009 and replaced with PCV13 in June/July 2011
Cumulative weekly numbers of IPD cases due to any of the serotypes not in PCV13: children <5 years of age, South Africa, from 2005 to date

PCV7 introduced in April 2009 and replaced with PCV13 in June/July 2011
Summary

• Using a novel, infant schedule aligned with developing country Expanded Programme on Immunization
  – Substantial reductions in IPD in HIV-infected and uninfected children
  – Indirect effects (adults and infants)
  – Some reductions due to HIV interventions, but bulk of impact due to PCV
• Antimicrobial resistance decreasing in all ages
• Non-vaccine serotype replacement
Thank you to all participating patients, laboratory, clinical and administrative staff for submitting case reports and isolates.

**GERMS-SA**: Carel Haumann, Patricia Hanise, Pieter Ekermans; Sandeep Vasaikar (EC); Anwar Hoosen, Dominique Goedhals, Madeleine Pieters (FS); Alan Karstaedt, Caroline Maluleka, Charl Verwey, Charles Feldman, Chris Lippincott, David Spencer, Gary Reubenson, Jeannette Wadula, Jeremy Nel, Kathy Lindeque, Maphoshane Nchabeleng, Mokotsi Molapisi, Norma Bosman, Rammini Kularatne, Ruth Lekalakala, Sharona Scetharam, Theunis Avenant, Trusha Nana, Vindana Chibabhai (GA); Adhil Mahajr, Asmeeta Burra, Fathima Naby, Halima Dawood, Koleka Misiana, Lisha Sookan, Praksha Ramjathan, Prasha Mahabeer, Sumayya Haffejee, Yacoob Coovadia (KZN); Ken Hamese, Ngoaka Sibya (LP); Greta Hoyland, Jacob Lebudi (MP); Eunice Weenink; Riezaah Abrahams, Sindiswa Makate (NC); Ebrahim Variava,。(NW); Andrew Whitelaw, Prerneshi Naicker, Shareef Abrahams (WC); Adrian Brink, Charlotte Sriturnat, Inge Zietsman, Maria Botha, Peter Smith, Suzy Budavari, Xoliswa Poswa (AMPATH); Chetna Govind, Keshree Pillay (LANCET); Catherine Samuel, Marthinus Senekal (PathCare); Anne Schuchat, Stephanie Schrag (CDC); Keith Klugman (Emory); Anne von Gottberg, Anthony Smith, Arvinda Sooka, Cecilia Miller, Charlotte Sriturnat, Cheryl Cohen, Chikwe Ihekweazu, Claire von Mollendorf, Genevie Ntshoe, Jack Manamela, Karen Keddy, Linda de Gouveia, Linda Erasmus, Marshagne Smith, Mnakgomo Rakhudu, Mokupi Manaka, Nazir Ismail, Nelesh Govender, Nevashan Govender, Nishi Sing, Olga Perovic, Oliver Murangandi, Penny Crowther-Gibson, Portia Mutvedzi, Riyadh Manesen, Ruth Mpembe, Sarona Lingana, Sibongile Walaza, Simbarashe Takuva, Sonwabo Lindani, Susan Meiring, Thejane Motladiile, Vanessa Quan, Verushka Chetty (NICD).

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Cumulative weekly numbers of IPD cases due to any of the six additional (1, 3, 5, 6A, 7F, 19A) serotypes in PCV 13 but not in PCV7: children <5 years of age, South Africa, from 2005 to date

PCV7 introduced in April 2009 and replaced with PCV13 in June/July 2011
Changes in invasive pneumococcal disease (IPD) incidence by serotype group among children aged <5 years (A) and adults aged ≥65 years (B), 1998–2007

*Seven-valent pneumococcal conjugate vaccine (PCV7) was introduced in the United States for routine use among young children and infants in the second half of 2000

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Pilishvili et al. JID 2010
Percentage of invasive pneumococcal disease due to vaccine serotypes by HIV infection in children ≤5 years, South Africa, 2003-2007 (2864/5865 [49%] from enhanced sites, 66% with HIV results)
Annual Incidence of Pneumococcal Bacteraemia by Age and HIV Status, Soweto, 1996

- Rate of pneumococcal bacteraemia is 37-fold increased in HIV-infected children and 8-fold increased in HIV-infected adults
- Rate of IPD is 42-fold increased in HIV-infected children

Incidence of IPD Among Those 25-44 Years of Age by Year and Serotype, South Africa, 2005-2012

Vaccine serotypes (VT):
-57% (-63% to -50%)*

PCV13:
-32% (-40% to -22%)*

Non-vaccine serotypes (NVT):
-11% (-21% to +4%)*

Serotype 6A:
-46% (-61% to -26%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of IPD Among HIV-Uninfected Adults 25-44 Years of Age by Year and Serotype, South Africa, 2005-2012

- **Vaccine serotypes (VT):**
  - Serotype 6A: -55% (-88% to +46%)*
  - Serotypes 1, 3, 5, 7F, 19A (PCV13): -11% (-42% to +36%)*

- **Non-vaccine serotypes (NVT):**
  - +28% (-7% to +51%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of IPD Among HIV-Infected Adults 25-44 Years of Age by Year and Serotype, South Africa, 2005-2012

Incidence (cases per 100,000 person years) by Year and Serotype, South Africa, 2005-2012

- Vaccine serotypes (VT): -59% (-65% to -52%)*
- Non-vaccine serotypes (NVT): -19% (-28% to -8%)*
- Serotypes 1, 3, 5, 7F, 19A (PCV13): -36% (-45% to -27%)*
- Serotype 6A: -47% (-62% to -27%)*

Relative reduction = 40%

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of Disease Caused by Non-Susceptible Pneumococcal Isolates, All Serotypes, Among All Ages by Year and Antimicrobial Agent, South Africa, 2005-2012

- Penicillin: -57% (-60% to -53%)*
- Ceftriaxone: -58% (-65% to -50%)*
- Multidrug resistance (MDR): -52% (-57% to -46%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Incidence of Disease Caused by Non-Susceptible Pneumococcal Isolates, All Serotypes, Among Children <2 Years of Age by Year and Antimicrobial Agent, South Africa, 2005-2012

Penicillin: -82% (-85% to -78%)*

MDR: -84% (-88% to -79%)*

Ceftriaxone: -85% (-91% to -77%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Age-specific incidence rates* for laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, South Africa, 2009 through 2013

(2009: N=4765; age unknown for n=163; 2010: N=4199; age unknown for n=142); 2011: N=3804; age unknown for n=219; 2012: N=3222, age unknown for n=253; 2013: N=2865, age unknown for n=141.)
Pneumococcal serotypes, in descending order, causing laboratory-confirmed, invasive pneumococcal disease, reported to GERMS-SA, in children <5 years, South Africa, 2009-2013

(2009: N=1337, n=1009 with viable isolates; 2010: N=909; n=649 with viable isolates; 2011: N=696, n=465 with viable isolates; 2012; N=509, n=353 with viable isolates; N=498, n=322 with viable isolates)
Cumulative weekly number of IPD cases due to any of the seven serotypes (4, 6B, 9V, 14, 18C, 19F and 23F) in PCV7: individuals ≥5 years of age, South Africa, from 2005 to date

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Cumulative weekly numbers of IPD cases due to any of the serotypes not in PCV13: individuals ≥5 years of age, South Africa, from 2005 to date

PCV7 introduced in April 2009 and replaced with PCV13 in June/July 2011
Number of laboratory-confirmed, invasive pneumococcal disease cases, reported to GERMS-SA, by age group and penicillin susceptibility, South Africa, 2013, n=2865 (n=1933 with viable isolates)

2013 CLSI breakpoints for penicillin (oral penicillin V) were used: susceptible, ≤0.06mg/L; intermediately resistant, 0.12-1mg/L; resistant, ≥2mg/L.
Clinical Infectious Diseases, 15 September 2014

≥2 PCV-7 doses effective in:
- HIV-uninfected – VE 74% (95% CI 25-91)
- HIV-exposed-uninfected – VE 92% (47-99)
- Effective against multidrug resistant IPD (VE 96%, 62-100)
- VE in HIV-infected -12% (-449-77)
Risk Factors for Invasive Pneumococcal Disease among Children less Than 5 Years of Age in a High HIV-Prevalence Setting, South Africa, 2010 to 2012.

von Mollendorf, Claire; Cohen, Cheryl; de Gouveia, Linda; Naidoo, Nireshni; Meiring, Susan; Quan, Vanessa; Lindani, Sonwabo; Moore, David P; Reubenson, Gary; Moshe, Mamokgethi; Eley, Brian; Hallbauer, Ute M; Finlayson, Heather; Madhi, Shabir A; Conklin, Laura; Zell, Elizabeth R; Klugman, Keith P; Whitney, Cynthia G; von Gottberg, Anne; for the South African IPD Case-Control Study Group

Pediatric Infectious Disease Journal, Post Acceptance: July 3, 2014
Risk Factors for Invasive Pneumococcal Disease among Children less Than 5 Years of Age in a High HIV-Prevalence Setting, South Africa, 2010 to von Gottberg, Anne von Mollendorf, Claire MBBCh, MSc +

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Summary

• Using a novel, infant schedule aligned with developing country Expanded Programme on Immunization
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Global Introduction Status of PCV

Incidence of IPD Among Those <2 Years of Age by Year and Serotype, South Africa, 2005-2012

VT: -89% (-92% to -86%)*
PCV13: -57% (-68% to -42%)*
Serotype 6A: -85% (-91% to -76%)*
NVT: +6% (-16% to +23%)*

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years
Number of Penicillin Non-Susceptible Isolates Causing IPD in Children <2 Years of Age by Year and Serotype South Africa, 2005-2012

*Random retrospective sampling of ~500 isolates/year for 2005-2008 using same microbroth dilution methodology used on all viable isolates from 2009 onwards