Pneumococcal conjugate vaccine effects on severe disease in South Africa – the first 5 years

Anne von Gottberg
Centre for Respiratory Disease and Meningitis
National Institute for Communicable Diseases
South Africa
annev@nicd.ac.za
Overview

• PCV introduction in South Africa
• Methods
  – GERMS-SA surveillance
  – IPD CC study
• Published data on impact
• More recent data
• Outstanding questions and way forward
Majority of pneumonia deaths in low- and middle-income countries

South Africa

- South African population 50 million
- In 2012
  - 6.4 million living with HIV
  - HIV prevalence:
    - Children 0-14 years - 2%
    - Adults 15-49 years - 19%
    - Pregnant women - 30%
- Rapid increase in access to antiretroviral drugs and prevention of mother-to-child HIV transmission
- Infant mortality rate in 2013: 33/1,000 live births
- Pneumonia commonest cause of death in children <5 years in 2012

SA National HIV Prevalence, Incidence and Behaviour survey 2012
Pneumococcus (*Streptococcus pneumoniae*)

- Commonest bacterial cause of pneumonia
- Associated with HIV
- High morbidity and mortality
- Carriage in nasopharynx (>50% of children <3 years of age)  
  Bogaert et al, Lancet ID 2004

- Polysaccharide capsule
  - >90 serotypes
  - 23-valent polysaccharide vaccine
  - Conjugate vaccine: effective in children
Description of the licensed pneumococcal conjugate vaccines (PCVs)

PCV7
- Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F
- CRM$_{197}$ Diphtheria carrier protein
- Cross-protection: 6A

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

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

- NCKP$^2$
- SA HIV (-)$^4$
- Gambia$^5$
- Am Ind$^3*$
- SA HIV (+)$^4$

Vaccine efficacy (%)}

O’Brien and Levin, Lancet, 2006
GERMS-SA Surveillance for IPD in South Africa

• National laboratory-based surveillance since 1999
• Active surveillance nationally and enhanced surveillance at 25 hospital sites since 2003
• Case: identification of *Streptococcus pneumoniae*, from normally sterile site specimens
• >270 clinical microbiology laboratories
Case-control study

- Nested within GERMS-SA
- Matched case-control study design with 4-6:1 age-, hospital- and HIV status-matched controls
- 24 sentinel enhanced surveillance hospitals in all nine provinces + additional sites
- Children aged ≥8 weeks in South Africa who are part of the birth cohort eligible to receive PCV through the Expanded Programme on Immunisation (EPI)
Number of Cases of IPD Reported by Age and HIV Status
South Africa, 2005–2008*

HIV-infected individuals approximately 40x increased incidence of IPD

PCV7 introduced in April 2009.

*Enhanced sites only (n=7382/19,233 [38%] of all IPD), with known age and HIV status (n=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)

<table>
<thead>
<tr>
<th>Age group (in years)</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>0–4</td>
<td>398</td>
</tr>
<tr>
<td>5–9</td>
<td>63</td>
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<tr>
<td>10–14</td>
<td>18</td>
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<td>15–19</td>
<td>282</td>
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<td>20–24</td>
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<td>25–29</td>
<td>112</td>
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<td>30–34</td>
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<td>35–39</td>
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<td>40–44</td>
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<td>60–64</td>
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<td>&gt;64</td>
<td>57</td>
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<tr>
<td>Age unknown</td>
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<table>
<thead>
<tr>
<th>Percentage</th>
<th>other</th>
<th>pcv13</th>
<th>pcv10</th>
<th>6A</th>
<th>pcv7</th>
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PCV introduction in South Africa

- PCV7 introduced in 2009, replaced by PCV13 in 2011
- Three-dose schedule
  - 6 weeks, 14 weeks & 9 months
  - No PCV7 catch-up vaccination campaign
  - PCV13 limited catch-up at 18 months
- PCV coverage *
  - 2009: PCV 1\textsuperscript{st} dose – 41%; 3\textsuperscript{rd} dose – 11%
  - 2012: PCV 1\textsuperscript{st} dose – 100%; 3\textsuperscript{rd} dose – 99%
- Important questions:
  - Effectiveness of novel 2+1 schedule aligned with EPI
  - Effectiveness and indirect effect in high HIV-prevalence middle-income setting

*Expanded Programme on Immunisation administrative data
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

Pilishvili et al. JID 2010
Incidence of IPD by vaccine and non-vaccine serotypes, Soweto, 2003-2008

Nunes M et al, AIDS, 2011
HIV-exposed but uninfected infants:
• 2-4 times increased incidence of IPD
• 2 times increased in-hospital mortality
Incidence of IPD Among All Ages South Africa, 2005–2012

- Pre-vaccine average 2005–2008
- % change in IPD incidence: -40% (95% CI: -42% to -37%)

- 35,192 IPD cases identified
- Isolates available for 70% (24,552)
- Age unknown for 5% (1648)

von Gottberg et al NEJM 2014
Incidence of IPD Among Those <15 Years of Age by Year and Age Group—South Africa, 2005–2012


- <2 years old: -69% (-72% to -65%)*
- 2–4 years old: -59% (-67% to -50%)*
- 5–9 years old: -44% (-54% to -33%)*
- 10–14 years old: -6% (-28% to +23%)*

von Gottberg et al NEJM 2014
Incidence of IPD Among HIV-Uninfected Children <2 Years of Age by Year and Serotype, South Africa, 2005-2012

Incidence (cases per 100,000 person-years) vs. Time (years)

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

PCV7: -34% (-53% to -7%)*

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

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

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

*% change in IPD incidence: post-vaccine (2012) vs. pre-vaccine (2005-2008) years

von Gottberg et al NEJM 2014
Incidence of IPD Among HIV-Infected Children <2 Years of Age by Year and Serotype, South Africa, 2005-2012

Vaccine serotypes (VT)
- PCV7: -86% (-91% to -78%)*
- Serotypes 1, 3, 5, 7F, 19A (PCV13): -72% (-88% to -44%)*

Non-vaccine serotypes (NVT)
- Serotype 6A: -85% (-95% to -62%)*
- NVT: -31% (-59% to +11%)*

Relative reduction = 55%

PCV7:
- VT: -86% (-91% to -78%)*
- PCV13: -72% (-88% to -44%)*

von Gottberg et al NEJM 2014

*% 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%)*

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


von Gottberg et al NEJM 2014
Vaccines reduce antibiotic resistance

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


#vaccineswork
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
Effectiveness of 7-Valent Pneumococcal Conjugate Vaccine Against Invasive Pneumococcal Disease in HIV-Infected and -Uninfected Children in South Africa: A Matched Case-Control Study

Cheryl Cohen,1,2 Claire von Mollendorf,1,2 Linda de Gouveia,1 Nireshni Naidoo,1,2 Susan Meiring,1 Vanessa Quan,1 Vusi Nokeri,1 Melony Fortuin-de Smit,1 Babatyi Malope-Kgokong,1 David Moore,4 Gary Reuben,5 Mamokgethi Moshe,6 Shabir A. Madhi,1,4,7 Brian Eley,8 Ute Hallbauer,9 Raamini Kularatne,10 Laura Conklin,11 Katherine L. O’Brien,12 Elizabeth R. Zell,11 Keith Klugman,7,13 Cynthia G. Whitney,11 and Anne von Gottberg1,7; for the South African Invasive Pneumococcal Disease Case-Control Study Group

≥2 PCV7 doses effectiveness against PCV7 serotypes in:

- HIV-uninfected: 74% (95% CI 25-91)
- HIV-exposed-uninfected: 92% (47-99)
- HIV-infected: 12% (-449-77)

≥2 PCV7 doses effectiveness against all serotypes:

- Multidrug resistant IPD: 96%, 62-100
Vaccine effectiveness (VE) estimates ≥2 PCV13 doses in individuals aged ≥16 weeks eligible to receive PCV13 HIV uninfected, 2011-2014

<table>
<thead>
<tr>
<th>Endpoint (Number of cases, number of controls)</th>
<th>Percent VE (95% CI) unadjusted</th>
<th>Percent VE (95% CI) adjusted^</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV-13 additional serotypes (28, 135)</td>
<td>95 (66,99)*</td>
<td>92 (40,99)*</td>
</tr>
<tr>
<td>PCV-13 serotypes (all) (52,240)</td>
<td>93 (71,98)*</td>
<td>85 (37,96)*</td>
</tr>
<tr>
<td>All IPD (237, 1053)</td>
<td>67 (29,82)*</td>
<td>52 (-12,79)</td>
</tr>
<tr>
<td>Non-PCV-13 types (185,813)</td>
<td>30 (-114,78)</td>
<td>15 (-189,75)</td>
</tr>
</tbody>
</table>

^Adjusted for maternal education level, DTP coverage and malnutrition
*Statistically significant
• IPD – invasive pneumococcal disease
Vaccine effectiveness (VE) estimates ≥2 PCV13 doses in individuals aged ≥16 weeks eligible to receive PCV13 HIV infected

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Percent VE (95% CI) unadjusted</th>
<th>Percent VE (95% CI) adjusted^</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCV13 additional serotypes (13,41)</td>
<td>97 (55,100)*</td>
<td>82 (-155,100)</td>
</tr>
<tr>
<td>PCV13 serotypes (all) (21,70)</td>
<td>94 (20,100)*</td>
<td>91 (-35,100)</td>
</tr>
<tr>
<td>All IPD (69,277)</td>
<td>43 (-138,87)</td>
<td>3 (-163, 93)</td>
</tr>
<tr>
<td>Non-PCV-13 types (50,210)</td>
<td>-107 (-1679,76)</td>
<td>-558 (undefined,51)</td>
</tr>
</tbody>
</table>

*Statistically significant
^Adjusted for receipt of antiretroviral therapy, CD4 count & trimethoprim sulfamethoxazole receipt
Vaccine effectiveness (VE) estimates ≥2 PCV13 doses in HIV uninfected individuals eligible aged ≥16 weeks eligible to receive PCV13

<table>
<thead>
<tr>
<th>Serotype (Number cases, number controls)</th>
<th>Vaccine product</th>
<th>Percent VE (95% CI) unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>4* (5,26)</td>
<td>PCV7 &amp; PCV13</td>
<td>85 (-126,100)</td>
</tr>
<tr>
<td>6B *(26,109)</td>
<td>PCV7 &amp; PCV13</td>
<td>66 (-54,92)</td>
</tr>
<tr>
<td>14* (8,40)</td>
<td>PCV7 &amp; PCV13</td>
<td>97 (31,100)</td>
</tr>
<tr>
<td>19F* (24,122)</td>
<td>PCV7 &amp; PCV13</td>
<td>12 (-1044,89)</td>
</tr>
<tr>
<td>23F* (20,106)</td>
<td>PCV7 &amp; PCV13</td>
<td>97 (71, 100)</td>
</tr>
<tr>
<td>1** (3,13)</td>
<td>PCV13</td>
<td>70 (-4162,100)</td>
</tr>
<tr>
<td>5** (3,17)</td>
<td>PCV13</td>
<td>94 (-789,100)</td>
</tr>
<tr>
<td>19A ** (12,59)</td>
<td>PCV13</td>
<td>94 (32,100)</td>
</tr>
<tr>
<td>6A (8,38)</td>
<td>PCV13</td>
<td>93 (21,100)</td>
</tr>
</tbody>
</table>

Not estimated for 9V, 18C, 3, 7F because of insufficient numbers
*Pooled analysis PCV7 and PCV13 period
**PCV13 period only
Vaccine effectiveness (VE) estimates ≥2 doses of PCV13 or PCV7 in individuals eligible aged ≥16 weeks eligible to receive PCV13 or PCV13 against PCV7 serotype IPD or 6A HIV infected by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percent VE (95% CI) unadjusted</th>
<th>Percent VE (95% CI) adjusted^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnourished (84, 271)</td>
<td>-34 (-303,56)</td>
<td>-23 (-454,73)</td>
</tr>
<tr>
<td>Not malnourished</td>
<td>70 (-140,96)</td>
<td>-7 (-3420,97)</td>
</tr>
<tr>
<td>Severe immunosuppression (64, 217)</td>
<td>-42 (-723,76)</td>
<td>-104 (-1433,73)</td>
</tr>
<tr>
<td>Not severe immunosuppression</td>
<td>75 (-31,95)</td>
<td>66 (-94,94)</td>
</tr>
</tbody>
</table>

Possibly less effective in severely immunosuppressed infants

^Adjusted for receipt of antiretroviral therapy, CD4 count & trimethoprim sulfamethoxazole receipt
Vaccine effectiveness (VE) estimates ≥2 doses of PCV13 or PCV7 in individuals eligible aged ≥16 weeks eligible to receive PCV13 or PCV13 against PCV7 serotype IPD or 6A HIV uninfected by subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Percent VE (95% CI) unadjusted</th>
<th>Percent VE (95% CI) adjusted^</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnourished (84, 362)</td>
<td>85 (44,96)</td>
<td>90 (53,98)</td>
</tr>
<tr>
<td>Not malnourished</td>
<td>81 (40,94)</td>
<td>77 (17,94)</td>
</tr>
<tr>
<td>HIV-exposed (64, 217)</td>
<td>91 (60,98)</td>
<td>87 (38,97)</td>
</tr>
<tr>
<td>HIV-unexposed</td>
<td>81 (51,93)</td>
<td>82 (44,94)</td>
</tr>
</tbody>
</table>

Vaccine is effective in HIV-exposed and malnourished children

^Adjusted for whether the patient had received 3 doses of diphtheria, tetanus and pertussis vaccine at 16 weeks of age and presence of crowding in the home
The NICD is an expert advisory body providing specialist advice in outbreak situations as well as offering laboratory support when required. NICD specialists liaise with provincial and local health authorities in the management and follow-up of outbreaks and offer expertise to co-ordinate the management of interventions and the monitoring of the effectiveness of such interventions. The NICD utilizes a 24/7 emergency number: 082 883 9930, which is operated by senior medical specialists for consultation and guidance in the management of outbreaks.

Outbreaks and Surveillance

Ebola Virus Disease Updates
- Ebola Laboratory Investigation Guidelines
- Clinical Management of patients with Ebola
- Ebola Virus Disease Investigation Protocol
- Suspected Ebola Virus Disease case definition
- Updated 24 November
- Ebola Frequently Asked Questions
- Testing for Ebola for the SADC Region

Resources

- Invasive Pneumococcal Disease Surveillance: 2005 to Date

What’s New

- Influenza vaccine availability for the 2015 Influenza season
  Alerts | April 14, 2015
- Ebola Virus Disease Outbreak Situation Update - 9 April 2015
  Alerts | April 9, 2015
- Clinical Management Of Patients With Ebola Virus Disease
  Alerts | April 7, 2015
- Key Facts on TB in South Africa
  Alerts | March 24, 2015
- Hand, Foot & Mouth Disease Fact Sheet
  Alerts | March 18, 2015

For travel health advice, link to SANITHNET - South African Travel Health Network - a collaboration between the NICD, South National Dept of Health (Communicable Disease Directorate) and the South African Society of Travel Medicine (SASTM)

www.sanithnet.co.za
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 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
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.
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.

PCV7 introduced in April 2009 and replaced with PCV13 in June/July 2011.
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: individuals ≥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**: 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 invasive pneumococcal disease cases due to non-PCV13 serotypes among children <2 years, 2008 and 2014, South Africa
Number of invasive pneumococcal disease cases due to non-PCV13 serotypes in adults 25—44 years, 2008 and 2014, South Africa
Summary

• Using data from a large stable, national active surveillance programme
• A novel, infant schedule aligned with developing country EPI schedule →
  – 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
  – Vaccine effective in HIV uninfected and HEU infants
  – Effectiveness unclear in HIV-infected group
• 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.

**Surveillance Officers:** Sandisiwe Joyi, Siyabonga Mboxwana, Badikazi Mtiwana (EC); Khasiane Mawasha, Thandeka Kosana (FS); Anna Motsi, Dikeledi Leshaba, Fiona Timber, Hazel Mzolo, Molly Morapeli, Nthatise Mokotani, Ophita Kaoho, Phindile Ngema, Rachel Nare, Thandi Mdima, Venesa Kok, Vusi Ndlovu, Zodwa Kgaphele (GA); Indran Naidoo, Nkosinathi Mbhele, Nokuthula Nzuza, Thobeka Simelani (KZN); Tebogo Modiba (LP); Sunnieboy Njikho, Ennica Ntllemao (MP); Matsheko Siyak (NC); Bekiwe Newana, Joyce Tsototsoto, Louisa Phalatse, Sibongile Rasmeni-Quariva (NW); Cheryl Mentor, Elizabeth Jerome, Nazila Shalabi, Priscilla Mouton, Catherine Bishop

**CED:** Elias Khomane, Florah Mnyameni, Husna Ismail, Jack Kekana, Mimmy Ngomane, Mzikazi Dickmolo, Rosah Mabokachaba, Thshegofatso Tshabalala, Mandile Thobela, Munyadzi Muvhali, Nomsa Tau, Portia Mogale, Emily Dlobo.

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**CTB:** Tiisetso Lebaka, Lebogang Matlou.

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**DPHSR:** Emily Sikanyika, Tsakane Nkuna.

**GERMS-SA:** Carol Haumann, Patricia Hanise, Pieter Ekermans, Sandeep Vasaikar, John Black, Vanessa Pearce (EC); Anwar Hoosen, Madeleine Pieters (FS); Alan Karstaedt, Caroline Maluleka, Charl Verwey, Charles Feldman, David Moore, David Spencer, Gary Reubenson, Khile Siswane, Jeanette Wadula, Jeremy Nel, Kathy Lindeque, Maphoshe Nchabeleng, Mokotsi Molapisi, Norma Bosman, Rammini Kularatne, Ruth Lekalakala, Sharona Secharam, Theunis Avenant, Trusha Nana, Vindana Chibabhai (GA); Adhil Maharaj, Asmeeta Burra, Fathima Naby, Halima Dawood, Koleka Mlisana, Lisha Sookan, Praksha Ramjathan, Prasha Mahabeer, Sumayya Haefjee, Yacoob Coovadia (KZN); Ken Hamese, Ngoaka Sibiya (LP); Greta Hoyland, Jacob Lebudi (MP); Riezaah Abrahams, Pieter Jooste, Sindiswa Makate (NC); Ebrahim Varia (NW); Andrew Whitelaw, Prashini Naicker, Shareef Abrahams (WC); Adrian Brink, Elizabeth Prentice, Inge Zietsman, Maria Botha, Peter Smith, Xoliswa Poswa (AMPATH); Chetna Govind, Keshree Pillay, Suzy Budavari (LANCET); Catherine Samuel, Marthinus Senekal (PathCare); Cynthia Whitney (CDC); Keith Klugman (Emory); Ananta Nanoo, Anne von Gottberg, Anthony Smith, Arvinda Sooka, Cecilia Miller, Charlotte Sitruttan, Cheryl Cohen, Chikwe Ihekweazu, Claire von Mollendorf, Frans Radebe, Genevieve Ntshe, Gillian Hunt, Karen Keddy, Linda de Gouveia, Linda Erasmus, Marthiaghe Smith, Martha Bodiba, Mbhekiseni Khumalo, Motshabi Modise, Nazir Imaan, Nelesh Govender, Nicole Page, Olga Perovic, Oliver Murangandi, Penny Crowther-Gibson, Portia Mutevedzi, Riyadh Manesen, Ruth Mpembe, Samantha Iyaloo, Sarona Lengana, Shabir Madhi, Sibongile Walaza, Sonwabo Lindani, Susan Meiring, Thejane Motlati, Vanessa Quan, Verushka Chetty (NICD).

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EXTRA SLIDES
Vaccine effectiveness (VE) estimates ≥2 PCV13 doses in **HIV uninfected** individuals eligible aged ≥16 weeks eligible to receive PCV13

<table>
<thead>
<tr>
<th>Serotype (Number cases, number controls)</th>
<th>Vaccine product</th>
<th>Percent VE (95% CI) unadjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>4* (5,26)</td>
<td>PCV7 &amp; PCV13</td>
<td>85 (-126,100)</td>
</tr>
<tr>
<td>6B *(26,109)</td>
<td>PCV7 &amp; PCV13</td>
<td>66 (-54,92)</td>
</tr>
<tr>
<td>14* (8,40)</td>
<td>PCV7 &amp; PCV13</td>
<td>97 (31,100)</td>
</tr>
<tr>
<td>19F* (24,122)</td>
<td>PCV7 &amp; PCV13</td>
<td>12 (-1044,89)</td>
</tr>
<tr>
<td>1** (3,13)</td>
<td>PCV13</td>
<td>70 (-4162,100)</td>
</tr>
<tr>
<td>19A ** (12,59)</td>
<td>PCV13</td>
<td>94 (32,100)</td>
</tr>
</tbody>
</table>

Not estimated for 9V, 18C, 3, 7F because of insufficient numbers

*Pooled analysis PCV7 and PCV13 period

**PCV13 period only
Vaccine effectiveness (VE) estimates ≥2 doses of PCV13 or PCV7 in individuals eligible aged ≥16 weeks eligible to receive PCV13 or PCV13 against PCV7 serotype IPD or 6A

**HIV infected by subgroup**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>(Number of cases, number of controls)</th>
<th>Percent VE (95% CI) unadjusted</th>
<th>Percent VE (95% CI) adjusted(^)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnourished</td>
<td>(84, 271)</td>
<td>-34 (-303,56)</td>
<td>-27 (-398,68)</td>
</tr>
<tr>
<td>Not malnourished</td>
<td></td>
<td>84 (33,96)</td>
<td>75 (-76,96)</td>
</tr>
<tr>
<td>Severe immunosuppression</td>
<td>(64, 217)</td>
<td>55 (-62, 87)</td>
<td>53 (-71,88)</td>
</tr>
<tr>
<td>Not severe immunosuppression</td>
<td></td>
<td>64 (-70,92)</td>
<td>67 (-85,95)</td>
</tr>
</tbody>
</table>

*Statistically significant
\(^\)Adjusted for receipt of antiretroviral therapy, CD4 count & trimethoprim sulfamethoxazole receipt
Total numbers enrolled

**CASES**
- 719 eligible cases aged ≥16 weeks included
  - 309 PCV13 period
    - 236 HIV-uninfected cases
    - 73 HIV-infected cases
  - 410 pre-PCV13 period
    - 251 HIV-uninfected cases
    - 159 HIV-infected cases

**CONTROLS**
- 3141 eligible controls aged ≥16 weeks included
  - 1785 pre-PCV13 period
    - 1216 HIV-uninfected controls
    - 568 HIV-infected controls
  - 1356 PCV13 period
    - 1093 HIV-uninfected controls
    - 260 HIV-infected controls
Serotype distribution in enrolled cases PCV13 period

HIV uninfected n=236

HIV infected n=73