Conclusions from the PSERENADE Project: Implications for Pneumococcal Vaccine Policy and What is Happening Next

Presented by Maria Deloria Knoll, PhD on behalf of the PSERENADE Team

Meningitis Research Foundation
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Conflicts of Interest

Dr. Maria Knoll reports grants from Merck, personal fees from Merck, and grants from Pfizer, outside the submitted work.

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**Background**

- Pneumococcal conjugate vaccines (PCVs) have been widely introduced into infant immunization programs over the last 20 years
  - 10 years of PCV10 (GSK) and PCV13 (Pfizer) use
- Invasive pneumococcal disease (IPD) caused by serotypes targeted by the vaccines has been reduced
- But questions remain regarding the net overall impact after long term use on pneumococcal disease, in both children and adults
- Countries want to understand differences between PCV10 and PCV13 in the overall impact on all pneumococcal disease
- The amount of disease prevented in older children and adults through indirect herd protection has varied by country
The PSERENADE Project was conducted to use all available data globally to answer these questions.

**Aim:** to assess the impact of PCVs introduced into infant immunization programs on invasive pneumococcal disease (IPD), including meningitis.

The following questions will be addressed in this presentation:

1. What were the direct effects of PCV10/13 vaccination in children <5 years old on all IPD?
2. Were there differences between countries that used PCV10 vs PCV13?
3. Was impact the same for meningitis?
4. What were the indirect effects on older children and adults?
5. What were the effects on Serotype 1 outbreaks?
6. Did vaccine schedule affect vaccine impact? Is a booster dose needed?
7. What pneumococcal serotypes remain?
8. What proportion of remaining disease is caused by serotypes covered by higher valency products?
Overview of Sites with invasive pneumococcal disease (IPD) data

Eligibility Criteria

- PCV universally recommended in the infant immunization schedule
- At least 50% uptake of PCV
- ≥1 complete post PCV year of invasive pneumococcal disease (IPD)*
- At least 50% of cases serotyped
- Stable surveillance system

Number of eligible sites included in analyses:

- Incidence: 47 sites in 33 countries
- Serotype Distribution: 54 sites in 41 countries

*IPD = predominantly pneumonia, meningitis and sepsis cases with pneumococcus detected in blood or cerebral spinal fluid (CSF)

Methods: estimating change in incidence over time relative to pre-PCV period (incidence rate ratios)

Step 1: estimate IPD Incidence over time for each site

- PCV7 Intro
- PCV13 Intro

Pre-PCV rate

Pre-PCV period

Post-PCV period

Incidence rate per 100,000

Time relative to PCV10/13 introduction

-10 -8 -6 -4 -2 0 2 4 6 8 10

*Time 0 = year of PCV7 introduction and year +4 = 5th year of PCV use

Observed IR (data from site)
Site-specific modeled IR & surrounding 95% CIs

INTERNATIONAL VACCINE ACCESS CENTER
Methods: estimating change in incidence over time relative to pre-PCV period (incidence rate ratios)

Step 1: estimate IPD Incidence over time for each site

Step 2: Calculate Incidence Rate Ratio relative to pre-PCV period

- Observed IR (data from site)
- Site-specific modeled IR & surrounding 95% CIs

*Time 0 = year of PCV7 introduction and year +4 = 5th year of PCV use
Methods: estimating change in incidence over time relative to pre-PCV period (incidence rate ratios)

Step 2: Calculate Incidence Rate Ratio relative to pre-PCV period

*Time 0 = year of PCV7 introduction and year +4 = 5th year of PCV use
Methods: meta-averaged change in incidence across sites

Step 2: Calculate Incidence Rate Ratio relative to pre-PCV period

IRRs from example site

Year Relative to PCV10/13 Introduction

Inception Date

PCV10/13 introduction

Incidence Rate Ratio

PCV7 Intro

PCV13 Intro

Time relative to PCV10/13 introduction

0 1 2 3 4 5 6 7 8 9 10

PCV7 Intro

PCV13 Intro

0 0.5 1.0 1.5

Incidence Rate Ratio
Methods: meta-averaged change in incidence across sites

Annual IRRs calculated for each site

Year Relative to PCV10/13 Introduction

Incidence Rate Ratio

PCV10/13 introduction

IRRs from all sites
Methods: meta-averaged change in incidence across sites

Annual IRRs calculated for each site

Meta-average across sites
Why do IRRs at year 0 vary across the sites?

Annual IRRs calculated for each site

Change in IRR due to prior PCV7 use
Why do IRRs at year 0 vary across the sites?

Stratification by prior PCV7 use:

- No PCV7 use
- Moderate PCV7 impact
- Substantial PCV7 impact

Year Relative to PCV10/13 Introduction

Incidence Rate Ratio

PCV10/13 introduction
Methods: meta-averaged change in incidence across sites

Stratification by prior PCV7 use:
- No PCV7 use
- Moderate PCV7 impact
- Substantial PCV7 impact
Results:
Number of cases of pneumococcal meningitis and IPD

33 countries with eligible data

Over 500,000 IPD cases
  <5 years: ~76,000 cases
  18+ years ~450,000 cases
  65+ years ~210,000 cases

Proportion of IPD that was meningitis:
  <5 years: ~15%
  18+ years: ~7%

Larger IPD sample size enables more sub-analyses
1. What were the **direct effects** of PCV10/13 vaccination in children <5 years old on all IPD?

2. Were there differences between countries that used PCV10 vs PCV13?
Change in IPD in children <5 years: PCV10 Types

Key messages
• Prior PCV7 use greatly impacted PCV7 type IPD
• The new serotypes covered by PCV10/13 declined substantially and are expected to continue declining.

Incidence Rate Ratio
86-99% declines
70-94%

PCV7 Serotype IPD
Serotypes 1, 5, and 7F IPD

Date, 2021

INTERNATIONAL VACCINE ACCESS CENTER
Change in IPD in children <5 years: PCV13 (non-PCV10) Types

**Key messages**

- Evidence of cross protection against 6A for PCV10
- 19A was reduced at PCV13 sites, but not eliminated; it increased at PCV10 sites
- No clear trends in Serotype 3 for either product

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**PCV10/13 Intro**

Serotype 6A

Incidence Rate Ratio

- PCV10/13 Intro

Serotype 19A

1.5-2.2 fold increase

Serotype 3

67-87% decrease

Year since PCV10/13 introduction

PCV7 Impact

- Substantial
- Moderate
- No use

DATE, 2021
Change in IPD in children <5 years: Non-PCV13 Types

Key messages
Non-vaccine serotypes increased 2-2.8 fold by year 5
Has not stabilized
Similar for both PCV10 & PCV13

*High HIV prevalence site that had other concurrent interventions besides PCV13, including ART therapy
Change in all IPD in children <5 years

Incidence Rate Ratio

Pre-PCV Rate

PCV10/13 Intro

60-79% decline

Year since PCV10/13 introduction

PCV10/13

PCV10

PCV13

PCV7 Impact

- Substantial
- Moderate
- No use

Key messages

• Overall, all IPD declined 60-79% (IRRs 0.21-0.40) by 5 years after PCV10/13 introduction across strata

• No meaningful differences between PCV10 and PCV13
3. Was impact the same for meningitis?
Key messages: children <5y

- Reduction in pneumococcal meningitis was >50% in all strata for both products
- PCV impact on pneumococcal meningitis was ~5% less than for all IPD

See poster: Changes in Pneumococcal Meningitis Incidence Following Introduction of PCV10 and PCV13: Results from the Global PSERENADE Project (J. Yang)
4. What were the indirect effects in adults?
Herd Effects of Infant PCV program on IPD in Adults >65 years

Key messages:
- **Vaccine type** IPD decreased substantially (>75%) in adults >65y
  - Took 2-3 years longer for the full effect than for children <5y
- **Non-vaccine type** increased ~>2 fold

- **PCV10 serotypes**
  - >75% declines

- **Non-PCV13 serotypes**
  - 1.7 to 2.5 fold increase

Years Relative to PCV10/13 Introduction

DATE, 2021
Herd Effects of Infant PCV program on all IPD in Adults ≥65 years

Key messages:

Net effect of VT declines and non-VT increases: Heterogenous

Total IPD incidence had sustained declines in some sites but others returned to baseline
3. Was impact the same for meningitis? (Adults)
Impact of PCV on Pneumococcal Meningitis vs all IPD: Adults ≥18y

by PCV10/13 product and years of prior PCV7 impact

Key messages: Adults ≥18y

- Results for meningitis were generally similar to all IPD
- Heterogeneous by site, ranging from no net change to ~50% decline

See poster: Changes in Pneumococcal Meningitis Incidence Following Introduction of PCV10 and PCV13: Results from the Global PSERENADE Project (J. Yang)
5. What were effects of PCV10/13 on Serotype 1 outbreaks?
**Key messages:**

ST1 IPD substantially declined in all sites among all ages & in all regions

- Including Sub-Saharan Africa, but...
- Did not have data from countries with largest outbreaks (e.g., Burkina Faso, Niger)

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**ST1 IPD IRRs, by region and age group**

<table>
<thead>
<tr>
<th>Region</th>
<th>&lt;5 years</th>
<th>5-17 y</th>
<th>18-49 y</th>
<th>50-64 y</th>
<th>65+ y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td></td>
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<tr>
<td>North America</td>
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<td>Oceania</td>
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<td>Sub-Saharan Africa</td>
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<td>North Africa &amp; Western Asia</td>
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<td>Asia</td>
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<tr>
<td>Latin America &amp; Caribbean</td>
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</tbody>
</table>

Incidence Rate Ratio

Ref: Bennett JC et al. *Microorganisms*. 2021
ST1 IPD IRRs, by region and age group

Ref: Bennett JC et al. Microorganisms. 2021

- Little to no data in adults in Northern Africa, Asia or Latin America & Caribbean
- Also do not have adult data in all regions
ST1 IPD IRRs, by region and age group

Key messages:
- ST 1 outbreaks occurred in all age groups
- Outbreaks continued for 3-4 years after PCV10 and 13 introduction, but eventually stopped

Ref: Bennett JC et al. Microorganisms. 2021
Key messages:

- ST1 nearly eliminated in all ages after 6 years
- Older children and adults similar to children <5y (small lag)

Bennett JC et al. *Microorganisms*. 2021

November 2020
6. Did dosing schedule affect vaccine impact? Is a booster dose needed?
Impact of Vaccine Schedule on Serotype 1 IRR

Key messages:
ST1 IRR decreased in all age groups similarly by vaccination schedule

Reference: Bennett JC et al. Microorganisms. 2021
7. What pneumococcal **serotypes** remain?

8. What proportion of remaining disease is caused by serotypes covered by future higher-valency PCV products?
Serotype distribution after extensive PCV10/13 use

When did serotype distribution stabilize:
- **Children <5 years**: after ~5 years of PCV10/13 use
- **Adults**: after ~7 years of use
Serotype distribution after extensive PCV10/13 use (after 5-7 years use)

**Key messages:**
- ST 3 was dominant and at both PCV10 and PCV13 sites, and in both children and adults.
- STs 19A was the leading serotypes at PCV10 sites and still observed at PCV13 sites.
Percent of remaining IPD due to serotypes included in future vaccines

**PCV13 Sites**

**Children <5 years**

**Adults >50 years**

**Key messages:**
- Future PCVs (PCV20 & PCV24) cover 50-60% of remaining cases (after excluding ST3)
- Polysaccharide 23-valent (PPV23) covers ~60% of IPD in adults (after excluding ST3)

**Additional Serotypes Covered by:**
- **PCV15**: 22F, 33F
- **PCV20**: 22F, 33F, 8, 10A, 11A, 12F, 15BC
- **PCV24**: 22F, 33F, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20
**Percent of remaining IPD due to serotypes included in future vaccines**

### PCV10 Sites

<table>
<thead>
<tr>
<th>Vaccine Serotypes</th>
<th>Children &lt;5 years</th>
<th>Adults &gt;50 years</th>
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<tbody>
<tr>
<td>PCV10</td>
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<td>PCV13</td>
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<td>PCV24</td>
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<tr>
<td>PPV23</td>
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</tbody>
</table>

**Key messages:**

Results were similar for PCV10 sites.

**Future Products**

- **PCV10 Sites**
  - Children <5 years
  - Adults >50 years

- **Additional Serotypes Covered by**:
  - **PCV15**: 22F, 33F
  - **PCV20**: 22F, 33F, 8, 10A, 11A, 12F, 15BC
  - **PCV24**: 22F, 33F, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20
Summary of PCV10 & PCV13 Impact

- All IPD in children <5 years declined 60-79%
  - Similar for PCV10 & PCV13
- All IPD declined on average ~20% in adults but was heterogeneous among sites
- Vaccine serotypes declined substantially in all age groups
- Non-vaccine serotypes increased in all age groups
- Impact on meningitis generally similar to all IPD
- Serotype 1 outbreaks declined substantially – across all age groups, vaccination schedules and regions
- Over half of remaining IPD in children is due to serotypes covered by possible future PCV20 & PCV24
- 75% of remaining adult IPD is due to serotypes covered by PPV23
What is Happening Next

For PSERENADE:
1. Heterogeneity among sites in herd effects in adults
2. Pneumonia cases
3. Determine if some non-VT serotypes emerging faster than others
4. Does a booster schedule matter for some serotypes?
   Ex. Breakthrough 19F cases seen with 3+0 schedule

Globally:
1. Results from Burkina Faso & Ghana anticipated (impact on ST1 in adults)
2. Higher valency PCV products (PCV15, PCV20, PCV24) anticipated
3. Policy/guidance about switching products must be determined
4. Push for data support and well characterized surveillance of older age groups in LMICs (especially in meningitis belt)
PSERENADE Team

PSERENADE Core Team:

IVAC / JHU:
- Maria Deloria Knoll (PI)
- Kyla Hayford (previously PI)
- Julia Bennett
- Maria Garcia Quesada
- Scott Zeger
- Yangyupei (Jade) Yang
- Marissa Hetrich
- Carly Herbert

WHO:
- Daniel Feikin
- Adam Cohen
- Katherine O’Brien

Technical Advisory Group:

- William Hausdorff
- Thomas Cherian
- Catherine Satzke
- Cynthia Whitney
- Elizabeth Miller
- Shabir Madhi

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PSERENADE Site Investigators

Active Bacterial Core Surveillance (ABCs): R. Gierke, T. Piliščivili
Arctic Investigations Program (AIP): D. Bruden, M. G. Bruce
Casper (Calgary Streplococcus pneunumiae Epidemiology Research): J. D. Kellner, L. J. Ricketson
Administración Nacional de Laboratorios e Institutos de Salud “Dr. Carlos G. Malbrán”: C. S. Lara, D. Napoli, J. Zintgraff, N. M. Sánchez Eluchans
CDC Global Disease Detection (GDD) Regional Center (collaborated with the Kenya Medical Research Institute (KEMRI) in Nairobi): G. M. Bigogo, J. R. Verani
Dhaka Shishu Hospital (DSH), Shishu Shasthya Foundation Hospital, & Kumudini Women’s Medical College Hospital (WHO-IBD Sites) BGD-1: CMOSH; BGD-2: DSH; BGD-3: Kumuduni; BGD-4: SSF: H. Hasanuzzaman, H. Rahman, S. K. Saha
National Reference Center of Streptococcus Pneumoniae - Belgium: S. Desmet
Brazilian National Reference Laboratory for Pneumococcal Infections: M. C. Brandileone, S. C. Almeida
Department of Medical Microbiology, Faculty of Medicine, Medical University of Sofia, Sofia, Bulgaria: L. P. Setchanova
Navajo Nation and White Mountain Apache Tribal Lands: C. G. Sutcliffe, L. L. Hammitt
Public Health Department of Catalonia: C. Izquierdo, M. Cuñó-Almagro, P. Ciruela, S. Broner
SIREVA Site/ ISP – Chile: J. C. Hormazabal, D. Iglesias, M. T. Valenzuela, P. Alarcon, R. Puente
SIREVA/ Centro Nacional de Referencia de Bacteriología (National Reference Lab); Instituto Costarricense de Investigación y Enseñanza en Nutrición y Salud – Costa Rica: G. Chanto Chacón
National Reference Lab for streptococcal infections, NIPH - Czech Republic: J. Kozakova, P. Krizova
IPD Surveillance Statsen Serum Institut, S - Denmark: P. Valentin-Branth, T. Dalby
ECDC: E. Colzani, L. P. Celentano, S. Bacci
Fiji IB-VPD- New Vaccine Evaluation Project: A. Sahu Khan, E. Rafai, F. M. Russell, R. Reyburn
National Institute for Health and Welfare (THL) - Finland: H. Rinta-Kokko, J. P. Nuorti, M. Toropainen
IPD surveillance /EPIBC/CNRP, the French national public health agency: F. Lefebvre, G. Deceuninck, P. De Wals
SIRGA Basse - The Gambia: G. A. Mackenzie, I. Hossain
German National Reference Center for Streptococci (GNRCS): M. van der Linden
National Surveillance of Invasive Pneumococcal Disease (IPD): F. Riccardo, M. Del Manzo, R. Camilli
National Epidemiological Surveillance of Infectious Diseases: NESID (Adult IPD data) National Hospital Organization Mie (Pediatric IPD data) - Japan: K. Oishi, S. Suga
KEMRI-Wellcome Trust Research Programme (KWTRP); Kilifi Health and Demographic Surveillance System (KHDSS): E. W. Kagucia, J. A. Scott
The Centre for Disease Prevention and Control (CDPC) - Latvia: E. Dimina, L. Savrasova
Notifiable Disease Surveillance System: EDO (SISPAL) - Madrid: J. C. Sanz, L. García Comas, M. Ordoñoz Gavín, S. de Miguel
Massachusetts pop. based surveillance/ Maxwell Finland Laboratory (Boston): I. Yildirim, S. I. Pelton
CHRC or NHCMCH; Sukhothaar District Hospital; Combined site (6 Hospitals as 1 Site) (WHO-IBD Sites) - Mongolia: T. Mungun, U. Chuluunbat
Surveillance of IPD in Casablanca - Morocco: I. Diawara, K. Zerouali, N. Nzyokkorika
Navarra Institute of Public Health: J. Castilla, M. Guevara
Netherlands Reference Laboratory for bacterial meningitis: A. Steens, M. J. Knol, N. M. van Sorge
Institute of Environmental Science and Research (ESR) - New Zealand: C. Gilmson, Y. M. Galloway
Kaiser Permanente Northern California (KPCN) Vaccine Study Center: L. Aukes, N. P. Klein
Norwegian surveillance system for communicable diseases: B. A. Winje, D. F. Vestreheim
Laboratorio Central de Salud Publica (LCSP) - Paraguay: A. Kawabata, G. Chamorro, M. E. León
Poland National Reference Centre for Bacterial Meningitis: A. Kuch, A. Skoczylska
Public Health England: S. N. Ladhani, Z. Amin-Chowdhury
Province of Quebec: B. Lefebvre, G. Deceuninck, P. De Wals
NHS Scotland: A. Smith, C. Cameron, K. Scott, L. Macdonald
MoH/ National Public Health Laboratory/ KK Women’s and Children’s Hospital - Singapore: G. Tran, K. Choon, M. Ang
Slovak National Surveillance - National Reference Center for Pneumococcal and Haemophilus Diseases: L. Mad'arová, M. Avdičová
Nacionalni inštitut za javno zdravje (NIJZ) (National Institute of Public Health) Nacionalni laboratoriji za zdravje, okolje in hrano; National Laboratory for Health, Environment and Food - Slovenia: M. Gric-Titek, M. Paragi, N. Sinkovec-Zorko
Group for Enteric Respiratory and Meningeal Disease Surveillance sites (GERMS-SA) - South Africa: A. von Gottberg, C. Cohen, J. Kleyhnans, L. de Gouveia, M. du Plessis
SpIDNet/ Epicentre: C. Savulescu, G. Hanquet
Public Health Agency - Sweden: E. Morfeldt, T. Lepp
Mandatory notification of invasive pneumococcal disease - Switzerland: M. Hilty, R. Born
Toronto Invasive Bacterial Diseases Network (TIBDN): A. McGeer
Primary Children’s Medical Center (PCMC); Salt Lake City, UT; Intermountain Healthcare): C. L. Byington, K. Ampofo
WHO IB-VPD: F. Serhan, S. Antoni, T. Nakamura
WHO IB-VPD AfrO: J. M. Mwenda
WHO IB-VPD PAHO: G. Rey-Benito, H. O. Oliveira

Thank you!
**Publications & Presentations**

**Meningitis Research Foundation Oral Poster Presentation:**
Changes in Pneumococcal Meningitis Incidence Following Introduction of PCV10 and PCV13: Results from the Global PSERENADE Project (J. Yang)

**Microorganisms 2021: Special Issue on Epidemiology and Vaccination of Bacterial Meningitis**
Changes in Invasive Pneumococcal Disease Caused by Streptococcus pneumoniae Serotype 1 following Introduction of PCV10 and PCV13: Findings from the PSERENADE Project (Bennett, et al.)
Serotype Distribution of Remaining Pneumococcal Meningitis in the Mature PCV10/13 Period: Findings from the PSERENADE Project (Garcia Quesada, et al.)

**WHO SAGE yellow book 2020**
Changes in serotype-specific incidence and serotype distribution in older adults following the use of PCV in childhood immunization schedules, Session 9, page 13-16 (Hayford, et al.)

**IDWeek 2021 Poster Presentations**
Changes in Invasive Pneumococcal Disease Incidence Following Introduction of PCV10 and PCV13 Among Children <5 Years: The PSERENADE Project (J. Bennett)
Serotype Distribution by Age of Remaining Invasive Pneumococcal Disease After Long-Term PCV10/13 Use: The PSERENADE Project (M. Garcia Quesada)
Comparing Changes in Pneumococcal Meningitis Incidence to all Invasive Pneumococcal Disease Following Introduction of PCV10 and PCV13: The PSERENADE Project (Y. Yang)