Closing the Gaps in Hib and Pneumococcal Vaccination for the Developing World

5th ESCMID Conference on Vaccines, Bilbao, Spain, Sep. 6-8, 2019

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Public Health in the time of War – The EMR

• **62 million** people in need of health care as a result of emergencies – 50% of all people in need globally

• **30 million** people displaced (internally and in neighboring countries): 9 million refugees from EMR, 21 million internally displaced in EMR

• **3 Level 3** emergencies in Syria, Iraq, Yemen

• Greatest number of **longstanding** emergencies

• Of **health security threats** currently of global concern, 3 are present in the Region:
  – H5N1, MERS CoV, Polio
  – Largest cholera outbreak in the world
Vaccines - Significant demand and Platform for Health Services
Overview

1. Update on global uptake

2. Perspectives on accelerated uptake

3. Impact

4. PCV issues:
   - Products
   - Interchangeability
   - Serotype replacement

5. Where do we go from here?
Historically 15-20 years passed before new vaccines reached poorest children.
The Hib Initiative – A Consortium of Academic and Public Health Institutions

“To expedite and sustain evidence-informed decisions at the global, regional and country levels regarding the use of Hib vaccination to prevent childhood meningitis and pneumonia”
GAVI’s PneumoADIP

Mission: To improve child health by accelerating the evaluation of and access to new, life-saving pneumococcal vaccines for the world’s children.
Why are developing countries not adopting new vaccines?

- **Vaccine value**: disease burden, vaccine efficacy/impact, CE, safety

- **Health systems**: EPI programs, vaccine cost/financing, supply

- **Policy**: at global (strong & clear recommendations, donor commitment), Competing priorities/ focus on broader context (e.g. child health), political will/factors, a “policy” window

- Lack of awareness, communication and focus
Health Systems factors
Competition: other vaccines in strained systems

Vaccine launches in 2013

- 1 million people

- Pentavalent
- Pneumococcal
- Rotavirus
- Measles 2nd dose
- Measles-rubella campaign
- Measles SIA
- HPV demonstration project
- Meningitis A campaign
- Yellow fever campaign

Courtesy Orin Levine, IVAC.BMGF

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World Health Organization

Regional Office for the Eastern Mediterranean

GAVI Alliance
Routine Hib immunization programs 2005

101 countries, including 19 (25%) GAVI countries
Hib Global Introduction (Sept. 2019)

Hib Global Product
PCV in 2000
1 Country
PCV Global Introduction
PCV Uptake Fastest ever in Low Income Countries

- **Hib High-income country**
- **Hib Low-income country**
- **PCV High-income country**
- **PCV Low-income country**

Introduction of PCV according to income category*

Proportion of countries

HICs, GAVI supported, MICs not GAVI supported, All countries

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* GNII per capita, WB Atlas method
So is there a standard process for decision making?
Hib Initiative - Strategic Approach

Communication

Evidence-informed decisions

Research and Surveillance

Coordination

Hib Meningitis Studies in Asia
(Children <5 years of age)

Hong Kong (’86)
Thailand (’00)
Vietnam (’03)
Sri Lanka (’03)
Mongolia (’03)
Indonesia* (’02)

Hib meningitis incidence: cases/100,000

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PCV - Collaborative Action

*Saving lives requires country, donor, and industry efforts to coincide*

- $ Billions in GAVI financing
- Countries co-financing their share
- More doses for GAVI countries than high & middle income combined
- Vaccines <$3.50 per dose to countries; includes ST 1&5 in all doses
- WHO recommendation for all countries to introduce
- Country estimates of disease burden and cost-effectiveness; regional estimates of ST distribution

Prevention occurs when all 3 overlap
Global Immunization 1990-2018,
3rd dose of Hib coverage in infants
Global coverage at 72% in 2018

Immunization Vaccines and Biologicals (IVB), World Health Organization (WHO).
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Immunization coverage with 3rd dose of Hib containing vaccines in infants, 2018

- <50% (10 countries or 5%)
- 50%-79% (21 countries or 12%)
- 80%-99% (32 countries or 16%)
- >=90% (128 countries or 84%)
- Not available or Hib not in schedule (3 countries or 2%)
- Not applicable

Disclaimer:
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Determined lines on maps represent approximate geographic delineation only and do not imply any claim of sovereignty.
The Group of Gavi countries that were supported during the current strategic period - "Gavi 68", reached 81% coverage in 2018, compared to 92% for the rest of the world.

They are home to almost 80% of the un and under vaccinated children (15.1m out of 19.4m)
Pneumococcal Conjugate Vaccine (PCV) 3rd dose coverage by WHO region, 2008-2018 global coverage at 47% in 2018

Almost 80 million infants require vaccinations in Gavi 68 countries every year, far exceeding all other countries combined, and growing much faster.

By 2030, UNPD expects there will be 85 million infants in Gavi 68 countries, with African Gavi countries accounting for most of that growth.
Pneumococcal Deaths: Where are the remaining deaths in 2015?

335,000 Deaths
(2018 Model)

India 23%
Nigeria 17%
DRC 5%
Pakistan 5%
Angola 3%
Indonesia 3%
Chad 3%
China 2%
Ethiopia 2%
Other 37%

Pneumococcal deaths have been falling;
PCV has accelerated that pace.
2000 - 2015

Pneumococcal deaths averted
250,000

294,000 (UR: 192,000 - 366,000)
Spn deaths in 2015
(355,000, including HIV(+) pneumo deaths)
Impact???
Elimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study

Richard A Adegbola, Ousman Secka, George Lahai, Nellie Lloyd-Evans, Alpha Njie, Stanley Usen, Claire Oluwalana, Stephen Obaro, Martin Weber, Tumani Corrah, Kim Mulholland, Keith McAdam, Brian Greenwood, Paul J M Milligan

Incidence of Hib in children <5 (cases per 100,000)
PCV Countries with Impact Studies
PCV impact: Any comparisons of PCV impact by product, schedule, serotypes … are going to be confounded by epidemiologic setting.

Age and Setting Major Determinants of Pneumococcal Colonization Prevalence

Substantially Higher in LIC than HIC Settings

PCV Impact LIC Doesn’t Mirror HIC
PCV Review of Impact Evidence (PRIME)

Provide up-to-date summary of evidence on PCV immune response, effectiveness and impact

**METHODS:**
- Systematic review published 1994-2017
- Clinical trials and observational studies of routine use
- 3-dose schedule (2+1 and 3+0)
- PCV10 and PCV13

**OUTCOMES:**
PCV effectiveness and impact on:
- Immunogenicity
- Nasopharyngeal carriage
- Invasive disease (IPD)
- Pneumonia
- Mortality

**ANALYSES:**
- Meta-analyses for immunogenicity
- Descriptive summary for other outcomes due to differences in methods and epidemiologic settings
- Considered:
  - previous PCV7 use,
  - age (<5 years and >5),
  - dosing schedule,
  - time since introduction,
  - catch-up program
PRIME Inclusion/Exclusion Criteria:

**Included:**
- **Product**: PCV10 or PCV13
- **Dosing Schedule**: 3+0 or 2+1
  - 2+0 and 3+1 included where technically relevant
- **Outcomes**:
  - Vaccine-type immunogenicity (IgG GMC, % Responders),
  - Vaccine-type nasopharyngeal carriage,
  - Vaccine-type invasive pneumococcal disease (IPD)
- **Study types**: clinical trials, observational studies reporting pre- and post-vaccine introduction incidence rates for disease outcomes or prevalence for carriage

**Excluded:**
- **Outcomes**: otitis media, immunogenicity measured by opsonophagocytic activity or avidity
- **Study types**: Post-only disease incidence data; case-series data for disease outcomes (i.e., no denominator)
- **Indirect effects**: studies with less than 3 years of PCV10/13 use
# Schedule Comparison: Overall Conclusions

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine Type (VT) Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunogenicity</td>
<td>- Antibody concentration (GMC):</td>
</tr>
<tr>
<td></td>
<td>- 3 primary doses more immunogenic than 2 primary doses</td>
</tr>
<tr>
<td></td>
<td>- 2+1 more immunogenic after 3rd dose</td>
</tr>
<tr>
<td></td>
<td>- % Responders: Schedules showed similar impact except for 6A, 6B and 23F</td>
</tr>
<tr>
<td>NP Carriage</td>
<td>Schedules showed similar impact</td>
</tr>
<tr>
<td>IPD</td>
<td>- VT: Both schedules showed similar impact; limited 3+0 data</td>
</tr>
<tr>
<td></td>
<td>- ST1: Clear evidence of 2+1 impact; evidence of 3+0 impact but limited data</td>
</tr>
<tr>
<td>Overall</td>
<td><strong>Both schedules are effective</strong> in reducing VT Carriage and Disease</td>
</tr>
</tbody>
</table>
# Product Comparison: Overall Conclusions (PRIME, 2017)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vaccine Serotypes in Common</th>
<th>Serotypes in PCV13 and not in PCV10</th>
<th>ST6C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ST3</td>
<td>ST6A</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Impact with both products</td>
<td>Favors PCV13</td>
<td>Impact with both products but Favors PCV13</td>
</tr>
<tr>
<td>NPC</td>
<td>Impact with both products</td>
<td>No Impact with either product</td>
<td>Impact with both products; Declines more pronounced with PCV13</td>
</tr>
<tr>
<td>IPD</td>
<td>Similar impact with both products</td>
<td>Impact not demonstrated for either product</td>
<td>Impact with both products; data limited</td>
</tr>
<tr>
<td>Overall</td>
<td>Impact with both products</td>
<td>Impact not demonstrated for either product</td>
<td>Impact with both products</td>
</tr>
</tbody>
</table>
Pneumococcal Vaccine Serotype IPD Impact
Kenya PCV10/3+0, < 5 yo (PCV introduced 2011)

http://kemri-wellcome.org/programme/pcvis-2/ Accessed March 20, 2018
Gambia PCV13/3+0 impact on pneumonia

MacKenzie G et al Lancet ID 2017

Radiographic Consolidation: 24% decline, 2-59 mo

Pneumococcal Pneumonia: 63% decline, 2-59 mo

Hypoxic Pneumonia: 61% decline, 2-59 mo

Clinical Pneumonia: 0% decline, 2-59 mo
South Africa Effectiveness, PCV13/2+1
Nutrition and HIV

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted vaccine effectiveness (95% CI)</th>
<th>Adjusted vaccine effectiveness (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children aged ≥16 weeks not infected with HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>83% (61 to 92)</td>
<td>78% (46 to 91)</td>
</tr>
<tr>
<td>Exposed to HIV</td>
<td>91% (60 to 98)</td>
<td>87% (38 to 97)</td>
</tr>
<tr>
<td>Not exposed to HIV</td>
<td>81% (51 to 93)</td>
<td>82% (44 to 94)</td>
</tr>
<tr>
<td>Malnourished</td>
<td>85% (44 to 96)</td>
<td>90% (53 to 98)</td>
</tr>
<tr>
<td>Not malnourished</td>
<td>81% (40 to 94)</td>
<td>77% (17 to 94)</td>
</tr>
<tr>
<td>Children aged ≥16 weeks with HIV infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>26% (-88 to 72)</td>
<td>17% (-304 to 80)</td>
</tr>
<tr>
<td>Severe immunosuppression†</td>
<td>-42% (-723 to 76)</td>
<td>-104% (-1433 to 73)</td>
</tr>
<tr>
<td>No severe immunosuppression</td>
<td>75% (-31 to 95)</td>
<td>66% (-94 to 94)</td>
</tr>
<tr>
<td>Malnourished</td>
<td>-40% (-390 to 60)</td>
<td>-23% (-454 to 73)</td>
</tr>
<tr>
<td>Not malnourished</td>
<td>70% (-140 to 96)</td>
<td>-7% (-3420 to 97)</td>
</tr>
</tbody>
</table>
Declining Pneumococcal Antibiotic Resistance South Africa


<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence of Disease (cases per 100,000 person-years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>10</td>
</tr>
<tr>
<td>2007</td>
<td>20</td>
</tr>
<tr>
<td>2009</td>
<td>30</td>
</tr>
<tr>
<td>2011</td>
<td>40</td>
</tr>
</tbody>
</table>

- Penicillin resistant
- Multidrug resistant (MDR)
- Ceftriaxone resistant
What about Catch-up Schedules?

Assessing the efficiency of catch-up campaigns for the introduction of pneumococcal conjugate vaccine: a modelling study based on data from PCV10 introduction in Kilifi, Kenya

Stefan Flasche1, John Opal2, Olivier Le Pelletier de Waroux1, Mark Ottende1, Katherine L. O’Brien2, Moses Kiti2, D. James Nkac1, W John Edmunds1 and J. Anthony G. Scott1,2
Flasche et al. BMC Medicine (2017) 15:113
DOI 10.1186/s12916-017-0882-9

Impact magnitude and efficiency varies by pneumococcal (NP) prevalence

Table 2 The impact and efficiency of alternative introduction strategies

<table>
<thead>
<tr>
<th>Introduction of PCV via</th>
<th>IPD averted after 10 years</th>
<th>Doses administered</th>
<th>Incremental NVN</th>
<th>NVN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort only</td>
<td>155 (121–193)</td>
<td>204,671</td>
<td>1321 (1058–1698)</td>
<td>1321 (1058–1698)</td>
</tr>
<tr>
<td>+ U1 catch-up</td>
<td>173 (134–216)</td>
<td>218,089</td>
<td>757 (618–973)</td>
<td>1263 (1012–1623)</td>
</tr>
<tr>
<td>+ U2 catch-up</td>
<td>189 (147–235)</td>
<td>224,952</td>
<td>412 (296–606)</td>
<td>1188 (958–1527)</td>
</tr>
<tr>
<td>+ U5 catch-up</td>
<td>220 (172–270)</td>
<td>241,546</td>
<td>543 (403–763)</td>
<td>1098 (694–1405)</td>
</tr>
</tbody>
</table>

The number of vaccine doses needed to prevent a case of IPD (NVN) is used as a measure of efficiency. Incremental NVN refers to the additional number of doses needed to prevent one additional cases of IPD in respect to cohort introduction with the next smaller catch-up
Should we be concerned about serotype replacement?
ABCs: Changing Hi epidemiology post vaccine, all ages, 1993-2008

- Most disease now caused by non-typeable Hi
- Shifts in clinical presentation;
  - pneumonia: 52%
  - bacteremia: 35%
  - meningitis: 8%
Is there replacement disease for H. flu post Hib vaccination?


MacNeil JR et al. CID 2011:1230-6

- Data from Alaska and N. Canada shows significant burden of *Hi a* in indigenous children <2 years old: 21 and 102/100,000 resp. (Bruce M et al. *Emerg Infect Dis*. 2008:48-55)

- No evidence of increase incidence of disease due to *Hia*, other non-b serotypes, or NT *Hi* among indigenous children in Australia (Menzies RI et al; *Int J Circumpolar Health*. 2013)
Rates of invasive pneumococcal disease among children <5 years, PCV7 era, ABCs 1998-2007

19A (2007 vs. baseline)
11 cases/100,000
+312% (+178,+511)

Slide courtesy of Cynthia Whitney, CDC
Countries with HPV vaccine in the national immunization programme
In Conclusion…. and Way Forward

• Tremendous progress in past decade as result of coordinated efforts
  • Pricing, supply, data, policy better than ever

• Opportunities and Challenges remain
  o Competition: Multiple vaccines in systems of varying strength
  o Coverage: From introduction to high vaccination
  o Big countries: India & Indonesia
  o Financing: Multiple vaccines, graduation, LMICs outside GAVI

• Quantify the full impact of PCV

• Next Generation Vaccines
  o Serotype Replacement Magnitude
  o Serotype Distribution in New Era

• Optimizing Dosing
  Coverage, Coverage, Coverage....
Way Forward- Taking advantage of current policy context, push towards more impact, UHC, SDGs, ....

The 13th GPW 2019-2023

Mission
Promote health – keep the world safe – serve the vulnerable

Strategic Priorities (and goals)
Ensuring healthy lives and promoting well-being for all at all ages by:
Achieving universal health coverage – 1 billion more people benefitting from universal health coverage
Addressing health emergencies – 1 billion more people better protected from health emergencies
Promoting healthier populations – 1 billion more people enjoying better health and well-being

Strategic shifts
Stepping up leadership – diplomacy and advocacy; gender equality, health equity and human rights; multisectoral action; finance

Driving public health impact in every country-differentiated approach based on capacity and vulnerability
Policy dialogue – to develop systems of the future
Strategic support – to build high performing systems
Technical assistance – to build national institutions
Service delivery – to fill critical gaps in emergencies
Mature health system
Fragile health system

Organizational shifts
- Measure impact to be accountable and manage for results
- Reshape operating model to drive country, regional and global impacts
- Transform partnerships, communications and financing to resource the strategic priorities
- Strengthen critical systems and processes to optimize organizational performance
- Foster culture change to ensure a seamless, high-performing WHO

Regional Office for the Eastern Mediterranean
Give Vaccines, PCV and Hib - a “Hiba” (Gift) of life

No child should die from a vaccine preventable disease.....

Thank you
Coverage of a third dose of vaccine protecting against diphtheria, tetanus, and pertussis (DTPcv-3) remains at 86% in 2018, leaving 19.4 million children vulnerable to vaccine preventable diseases.

The key goal of the Immunization Agenda 2030 is to make vaccination available to everyone, everywhere, by 2030.

While immunization is probably the most successful public health intervention, reaching 86% of infants is not enough. The upward trend in coverage has increased by only 5% in the past decade and has plateaued.
FIGURE 1
Vaccine-type pneumococcal carriage prevalence among all children swabbed, before and after the introduction of PVC10. Patan Hosp, Nepal

Post-vaccine is defined as 2016 and 2017 together, except in community-based rural children, where data from only 2017 was included.
There are more people living inside this circle than outside of it.
HPV Vaccine introduction in EMR countries
Few countries without PCV by 2018

Large birth cohort countries
- early in introduction (India-2017)
- not yet introduced (China, Indonesia)
PCV impact on radiographic pneumonia

23%-29%
Proportion of IPD represented by serotypes in vaccine formulations, by region

Source: GSP Version 2 Apr 1, 2009, AMC/TPP analyses

Pneumococcal Carriage and Transmission: What do we really understand?

Context
1. Adult challenge and animal studies---may not fully apply to infant/PCV
2. Epidemiologic variability strongly influences clinical findings

Findings
1. Carriage determined by capsule
2. IgG against capsule reduces shedding, transmission, acquisition
3. Other immune effectors likely involved; elusive
4. Pre-existing antibody reduces PCV immunogenicity---carriage impact
5. PCV high impact on carriage --- but incomplete especially in high transmission settings
### Pneumococcal mortality rate and absolute deaths

**Children 1-59 mo, 2015**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Deaths</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>264K</td>
<td>79.6%</td>
</tr>
<tr>
<td>Meningitis</td>
<td>42K</td>
<td>12.8%</td>
</tr>
<tr>
<td>NPNM</td>
<td>25K</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

**Total Deaths**: 335,000 (2018 Model)

**World Map**: Showing the global distribution of pneumococcal deaths by region.

- **Spn Rate**: Rate per 100k children
  - < 10
  - 10 - < 25
  - 25 - < 100
  - 100 - < 200
  - ≥ 200
  - No data

- **Spn Total**: Number of cases
  - 500
  - 5,000
  - 50,000

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Even in countries using PCV, coverage is incomplete (2015)

Nepal PCV10 study (Patan Hosp) - above protective threshold is similar for the 2 schedules, no difference after the booster

Courtesy of Andrew Pollard
Nepal PCV10 study (Patan Hosp)- Using 2+1 gives better protection after 9 months of age for the leading serotypes (measured at 2-4 years of age)

2+1 = 6, 14 weeks and 9 months
3+0 = 6,10, 14 weeks

Courtesy of Andrew Pollard