ESCMID: The impact of vaccines on public health
Prague 1-3 April 2011

Vaccines to prevent H. influenzae type b diseases

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A brief history of *Haemophilus influenzae* --

- The pretender: mistaken aetiology of influenza
- A serious pathogen, especially of children
- A naturally transformable bacterium
- Source of restriction enzymes (endonucleases)
- First conjugate vaccine
- First complete DNA sequence of genome of free-living organism
Spanish ‘Flu (1918-1919)
Spectrum of major diseases caused by Hib

- meningitis 70%
- epiglottitis 12%
- cellulitis 7%
- septic arthritis/osteomyelitis 5%
- bacteraemia 4%
- pneumonia 2%
Prior research crucial to Hib vaccine development

- 1931 Pittman identifies capsular antigens of Haemophilus influenzae

- 1933 Fothergill and Wright demonstrate importance of “killing power of blood” in human susceptibility to Hib infections

- Pioneering work on pneumococcal (1962 onwards) and meningococcal (1966 onwards) capsular polysaccharide vaccines
Serum antibodies to type b capsular polysaccharide are protective

Fothergill and Wright
J. Immunol. 1933

Anderson et al.
J. Infect. Dis. 1977
## Milestones in plain PRP Hib vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1965</td>
<td>Charles Janeway proposes Hib disease could be prevented by capsular p/s vaccine</td>
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<td>1968</td>
<td>Smith and Anderson in Boston USA and Robbins and Schneerson begin research to develop Hib vaccine</td>
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<tr>
<td>1973</td>
<td>Clinical trials show lack of immunogenicity of PRP in infants aged &gt; 2 years. NIH workshop explores future options. Kabat and Paul suggest “hapten-carrier” concept as possible solution</td>
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<td>1977</td>
<td>Finnish trial demonstrates efficacy of PRP in infants aged &gt;2y. PRP licensed for use (1987) in USA but unsatisfactory efficacy even in older children</td>
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Milestones in plain conjugate Hib conjugate vaccines

1982 Proof of concept of conjugate vaccines

1987 PRP-D efficacy trial in Finland followed by licensure of this and three other glycoconjugates by 1991

1996 Anderson, Robbins, Schneerson and Smith receive Lasker Award for Clinical Medical Research
Antibody Status of Children 1-5 Years after immunisation with purified plain polysaccharide (PRP)

<table>
<thead>
<tr>
<th>Age (mo) at Vaccination</th>
<th>Vaccine</th>
<th>Control</th>
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<tr>
<td>3-17</td>
<td>0.36</td>
<td>0.34</td>
</tr>
<tr>
<td>18-23</td>
<td>0.72</td>
<td>0.40</td>
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<tr>
<td>24-71</td>
<td>2.51</td>
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Conjugate vaccines

Polysaccharide

Ps Protein Conjugate

Protein

Ps
### Comparative immunogenicity (μg/ml) of 4 Hib conjugate vaccines

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<td>0.07</td>
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<td>PRP-omp</td>
<td>0.11</td>
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Decker et al. J. Ped. 1992
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Decker et al. J. Ped. 1992
Impact of Hib conjugate vaccines on incidence of Hib invasive diseases in four countries

Eskola and Kilpi unpublished 2011
Immunobiology of Hib conjugates

Comparatively:

- poor immunogenicity of PRP-D
- higher titers after just one dose of PRP-omp
- higher boosting by HbOC and PRP-T
Hib conjugate vaccines did not have the same efficacy in different epidemiological settings.

A new conjugate vaccine consisting of the capsular polysaccharide of H. influenzae type b covalently linked to a protein carrier (PRP-D), administered to infants beginning at the age of 3 months, is highly effective in protecting young Finnish children (7 to 24 months old) against invasive H. influenzae type b infections.

Eskola J et al. NEJM. 323. 1381 1990

“We found no evidence that the PRP-D vaccine provides significant protection, at least for Alaska Native infants, against invasive diseases caused by H. influenzae type b. The ineffectiveness of the vaccine paralleled its limited immunogenicity.”

Ward JI et al. NEJM. 323. 1393. 1990
Importance of age-related attack rates for Hib
PRP-T conjugate Hib vaccine prevented most cases of meningitis and pneumonia due to Hib in Gambian infants. The reduction in the overall incidence of radiologically defined pneumonia in PRP-T vaccinees suggests that about 20% of episodes of pneumonia in young Gambian children are due to Hib. The introduction of Hib vaccines into developing countries should substantially reduce childhood mortality due to pneumonia and meningitis.

Hib conjugate vaccines and herd immunity
Prospective evaluation of effect of Hib conjugate vaccine on colonisation

- 1188 pharyngeal cultures from 283 children
- 18-59 months
- Effectiveness in preventing subsequent carriage was 64% (95% CI 5.86)

Murphy et al. J.Pediat. 1993
Decline of *Haemophilus influenzae* meningitis in U.S. children under five years following introduction of *Haemophilus* b conjugate vaccines
Hib disease in England and Wales 1990-1998

- Under 5 years of age
- All ages (incl. under 5 years)
Lesson 1 from UK experience with Hib conjugate vaccines

Direct protection only accounted for 57-71%; therefore substantial immunity resulted from herd immunity (Trotter et. al. JID 2003)

*Attack rates for vaccinated and unvaccinated individuals for the same time period based on population vaccine coverage data and case vaccination histories.
Factors underlying the increase in true vaccine failures of Hib conjugates in UK

Accelerated infant immunisation schedule in UK 2,3,4 moonths

Herd immunity and lack of natural boosting

Priming and induction of memory not always sufficient to afford protection

Changes to immunisation schedule (DTaP/Hib); reduced serum antibodies to Hib component
Incidence of Hib cases and deaths per annum

- bacteremic disease: 486,000
- deaths: 114,225
- reduction through Hib CVs: 38,000 (about 8% of global disease burden)

Countries that have introduced Hib Vaccine  2011

Source: IVAC Vaccine Information Management System (VIMS)
Global Hib Introduction

- Introduced into National Program, 170 countries (88%)
- Planning Introduction, 17 countries (9%)
- Widespread Coverage through Private Market, 1 country (0.5%)
- No Decision, 5 countries (3%)
Summary

- Glycoconjugate vaccines have virtually eliminated invasive diseases caused by *H. Influenzae* type b in most countries in the world.

- No convincing evidence of vaccine escape through serotype replacement or serotype switching has emerged to date.

- The principles exemplified by Hib glycoconjugates have had a profound impact on vaccine development against other major pathogens e.g. pneumococcus, meningococcus, *Salmonella typhi* and Group B streptococcus.