Meningococcal conjugate vaccines

Mary Ramsay
Consultant Epidemiologist
Immunisation, Hepatitis and Blood Safety Department
HPA Centre for Infections
Meningococcal serogroup C (MCC) conjugate vaccination in the UK

- The first conjugate vaccine for meningococcal disease was introduced into the UK in 1999
  - Based on successful approach used for Hib vaccines
- Incidence too low to undertake efficacy trials
  - Licensed on the basis of immune responses
- Vaccine produced protective levels of serum bactericidal antibodies
  - Superior to plain polysaccharide vaccine
- Evidence of immunological memory
  - Response to challenge dose of plain polysaccharide vaccine
  - Increase in antibody avidity with time

MCC vaccine implementation in the UK

- Vaccine given with the routine schedule at 2, 3 and 4 months of age
  - Coverage of >90% rapidly achieved
- Based on pre-vaccine epidemiology, catch-up for all children <18 years of age completed in 2000
  - Coverage exceeded 85% in all cohorts up to 16 years
- Immediate dramatic impact on disease rates
  - Impact now sustained for over 10 years
- Vaccine introduced in several European countries between 2000 and 2002
Incidence of invasive meningococcal disease and number of serogroup C infections England and Wales
Post marketing studies of MCC vaccines in UK

- Short term protection high in all age groups (>=90%)
  - correlated well with immunological correlate (rSBA >=1:8)
- Protection declines over time in younger vaccinees
  - Remains high if vaccinated as older child / adolescent

<table>
<thead>
<tr>
<th>Age at vaccination</th>
<th>Within 1 year</th>
<th>More than 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants (routine)</td>
<td>97 %</td>
<td>68 %</td>
</tr>
<tr>
<td>Toddlers (catch-up)</td>
<td>89 %</td>
<td>71 %</td>
</tr>
<tr>
<td>3 to 18 years</td>
<td>96 %</td>
<td>93 %</td>
</tr>
</tbody>
</table>

Further studies in Europe

• Antibody levels and individual protection decline with time
  – Particularly in young infants
  – Persistence of antibody strongly related to age at vaccination

• Despite this declining protection, major reduction in MenC incidence in all age groups in all countries
  – Different vaccines used
    NeisVac-C (Baxter)   Tetanus toxoid
    Meningitec (Pfizer)  CRM$_{197}$
    Menjugate (Novartis) CRM$_{197}$
  – Different schedules used
## Schedules used for routine introduction of meningococcal serogroup C conjugate vaccine (MenC)

<table>
<thead>
<tr>
<th>Country</th>
<th>Routine schedule</th>
<th>Year introduced</th>
<th>Catch-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belgium</td>
<td>12 months</td>
<td>2002</td>
<td>To 17 years</td>
</tr>
<tr>
<td>Ireland</td>
<td>2, 4 and 6 months</td>
<td>2000</td>
<td>To 23 years</td>
</tr>
<tr>
<td>Netherlands</td>
<td>14 months</td>
<td>2002</td>
<td>To 18 years</td>
</tr>
<tr>
<td>Spain</td>
<td>2, 4 and 6 months</td>
<td>2000</td>
<td>To 19 years (15 regions) To 6 years (4 regions)</td>
</tr>
<tr>
<td>UK</td>
<td>2, 3, 4 months</td>
<td>1999</td>
<td>To 18 years</td>
</tr>
</tbody>
</table>
Percentage reduction in MenC incidence in European countries over time

- Belgium (2001)
- Ireland (2000)
- Netherlands (2001)
- Spain (2000)
- UK (1999)
Summary of impact in Europe

- All countries achieved very high coverage (>90%) for routine and catch-up vaccination
  - Rapid and dramatic decline in disease rates
- Impact of programme less rapid and dramatic in Spain
  - Probably due to less extensive initial catch up campaign in some autonomous regions (to six years of age)
- Main reason for dramatic impact was indirect (herd) protection
  - Reduced acquisition of nasopharyngeal carriage
  - Required vaccination of in older children and teenagers
Nasopharyngeal carriage rates of serogroup C *Neisseria meningitidis*, UK adolescents

Quadrivalent (MCV4) meningococcal vaccines

- In 2005, the first conjugate against serogroups A, C, W135 and Y was licensed in USA
  - Menactra – diphtheria conjugate (Sanofi)
- Used as adolescent vaccine (>11yrs) in USA
  - Impact of vaccine modest in comparison to MCC experience

- USA preliminary effectiveness for Menactra from case control study

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Within one year</th>
<th>One to two years</th>
<th>Two to five years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness (%)</td>
<td>74%</td>
<td>99%</td>
<td>80%</td>
<td>46%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(35-90%)</td>
<td>(0-100%)</td>
<td>(-3, 96%)</td>
<td>(-66%-83%)</td>
</tr>
</tbody>
</table>

Reason for modest impact observed in the USA

- No indirect protection (herd immunity) as coverage low and took some years to accumulate
- Evidence of rapid decline in protection
  - GMTs slightly lower with this conjugate
- Other quadrivalent vaccines now available / close to licensure
  - Different conjugate proteins (CRM197 and tetanus)
  - May have better immunogenicity than product used in USA
The Meningitis Vaccine Project (MVP)

*MenAfrivac™,* a new group A meningococcal conjugate vaccine

- **PsA-TT**, MenA polysaccharide (Ps) conjugated to tetanus toxoid (TT)
  

- Comprehensive product development according to GMP/GLP/GCP
  - 2005- 2010: 7 trials conducted in 8 sites / 5 countries
  - India, Mali, The Gambia, Senegal, Ghana

- Regulatory pathway, indication 1 to 29 year olds
  
  - Marketing authorization in country of manufacture, Drugs Controller General of India – 2009
  - WHO prequalification certificate – 2010
  - Non-inferiority to the reference licensed meningococcal polysaccharide vaccine (percentage of vaccinees having a 4-fold or greater increase in SBA titer)
**Immune Response**

*MenAfrivac™ 1 to 29 year-olds indication*

**Group A rSBA Geometric Mean Titers (GMT) with 95%CI**

*Pre-vaccination and 28 days after immunization ITT*

*PsA-TT-001, PsA-TT-002, PsA-TT-003, PsA-TT-003a and PsA-TT-005*
Immune Persistence
*MenAfrivac™ 1 to 29 year-olds indication*

Group A rSBA Titers Reverse Cumulative Distribution Curves in 12-23 month-olds
*Pre-vaccination, 1 month and 10 months after immunization - ITT*
*PsA-TT-002*
Summary of Results from studies so far

MenA conjugate vaccine safety and immunogenicity

- **Safety**
  - 9943 subjects in trials, 6920 subjects received the PsA-TT vaccine
  - safe and well tolerated, no safety concern in any age group

- **Immunogenicity after a single dose of MenAfriVac™**
  - superior immune response vs. licensed polysaccharide vaccines in all age groups (1 to 29 year-olds indication)
  - bactericidal antibody sustained to 2 years and evidence of immune memory
  - Response consistent between vaccine lots

MenAfriVac™ Introduction

Strategy

• Mass vaccinations of 1-29 year olds with a single dose of Men A conjugate vaccine to induce strong herd immunity

• Protection of new birth cohorts
  ➢ Follow-up campaigns every 5 years of 1-4 year olds or
  ➢ Routine immunization in infants
  ➢ Infant indication, development ongoing
    ▪ Preliminary data in < 1 year-olds are promising and analyses are currently ongoing to confirm the most appropriate dosage and schedule
    ▪ Detailed results will be available to present at the next SAGE session
Impact evaluation

- Disease and Group A disease rates
  - Case-based surveillance (Burkina Faso and Niger)
  - Weekly reporting from 13 countries WHO/IST
  - SOPs and laboratory support from WHO and CDC

- CSF Bacteriologic data

- Case control studies (Burkina Faso, Mali)

- Linked carriage studies (pre- and post vaccinations studies in Burkina Faso, Mali & Niger)
Conclusions

• Conjugate vaccines produce high short term protection (superior to polysaccharide vaccines)
  – Particularly in infants and toddlers
  – Age dependent decline in protection over time

• For major impact need high coverage in age group where carriage occurs
  – Important to vaccinate adolescents and young adults

• Circulating antibody is important for individual protection
  – High initial levels correlate with longer protection
  – Advantage in picking most immunogenic vaccines

• Role of boosting (natural and vaccine) not yet clear
  – Booster doses have been added in many countries
Acknowledgements

• WHO - Marie-Pierre Preziosi, Carole Tevi-Benissan
• CDC - Nancy Messonnier, Amanda Cohn
• HPA - Ray Borrow, Helen Campbell

• EU-IBIS collaborators in Europe
  – Sabine de Greef, Rosa de Cano Portero, Germaine Hanquet, Margaret Fitzgerald