Persistence of specific bactericidal antibodies against serogroup B meningococcus at 5 years of age after immunisation with 4CMenB in infancy and at 40 months

Dr Fiona McQuaid
Paediatric clinical research fellow
Oxford Vaccine Group, University of Oxford
FIS conference: 12th November 2013
MenB incidence (England and Wales) 2006/7-20010/11

(Ladhani et al 2012)
4CMenB

• Contains multiple antigenic proteins:
  – fHbp variant 1.1
  – Outer membrane vesicle (New Zealand strain)
  – NadA allele 3
  – NHBA1.2

• Capable of inducing antibodies against MenB reference strains under a variety of infant schedules (Snape et al 2010, Findlow et al 2010, Vesikari et 2013, Gossger et al 2012)
### 4CMenB

Licensed in Europe early 2013

<table>
<thead>
<tr>
<th>Licensed indications</th>
<th>Population</th>
<th>Age</th>
<th>Dose series</th>
<th>Interval</th>
<th>Booster recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infants</td>
<td>2 to 5 months</td>
<td>3</td>
<td>1 to 2 months</td>
<td>At 12 to 23 months</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated infants</td>
<td>6 to 11 months</td>
<td>2</td>
<td>2 months</td>
<td>At 12 to 23 months; ≥2 months from primary series</td>
</tr>
<tr>
<td></td>
<td>Unvaccinated toddlers and children</td>
<td>12 months to 10 years</td>
<td>2</td>
<td>≥2 months</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adolescents and adults</td>
<td>11 years and older*</td>
<td>2</td>
<td>1 to 2 months</td>
<td></td>
</tr>
</tbody>
</table>
Current issues

- Interim statement from JCVI (July 2013):

  “On the basis of the available evidence, routine infant or toddler immunisation using Bexsero® is highly unlikely to be cost effective at any vaccine price based on the accepted threshold for cost effectiveness used in the UK and could not be recommended.”

Dept of Health, JCVI interim position statement on use of Bexsero meningococcal B vaccine in the UK. Pub 24th July 2013.
However...

• Questions remain regarding:
  – Effect on carriage (esp. adolescents)
  – Herd immunity
  – Persistence of antibody response

• Separate recommendations for “at-risk groups”
However...

• Questions remain regarding:
  – Effect on carriage (esp. adolescents)
  – Herd immunity
  – Persistence of antibody response

• Separate recommendations for “at-risk groups”
This study

- Follow on study
- Antibody Persistence compared to Naive Children
- Safety, Tolerability, and Immunogenicity of booster doses of 4CMenB
- Healthy UK children
Months of age of immunisation with 4CMenB

2  4  6  12  40  42  60  62

= Parent study (Findlow et al 2010)
= Part 1 at 40m (Snape et al 2013)
= Part 2 at 60m
### 4CMenB

<table>
<thead>
<tr>
<th>Population</th>
<th>Age</th>
<th>Dose series</th>
<th>Interval</th>
<th>Booster recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>2 to 5 months</td>
<td>3</td>
<td>1 to 2 months</td>
<td>At 12 to 23 months</td>
</tr>
<tr>
<td>Unvaccinated infants</td>
<td>6 to 11 months</td>
<td>2</td>
<td>2 months</td>
<td>At 12 to 23 months; ≥2 months from primary series</td>
</tr>
<tr>
<td>Unvaccinated toddlers and children</td>
<td>12 months to 10 years</td>
<td>2</td>
<td>≥2 months</td>
<td></td>
</tr>
<tr>
<td>Adolescents and adults</td>
<td>11 years and older*</td>
<td>2</td>
<td>1 to 2 months</td>
<td></td>
</tr>
</tbody>
</table>

1. +40m booster

2. Not according to licensed dosing
Objectives

• Antibody persistence in children at 60 months of age who previously received 4CMenB

• Antibody response of a two-dose catch-up regimen of 4CMenB at 60 and 62 months of age.

• (Assess safety and tolerability of catch up doses at 60 +62m)
## Study procedures

<table>
<thead>
<tr>
<th>Group</th>
<th>Previously</th>
<th>60m</th>
<th>62m</th>
<th>63m</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (N= 50→18)</td>
<td>4CMenB at 2, 4, 6, 12, 40m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 (N= 24→6)</td>
<td>4CMenB at 12, 40, 42m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 (N= 43→32)</td>
<td>4CMenB at 40 +42m</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 (N= 50)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Blood draw

- [Heart]

### Immunisation

- [Cake]

---

[www.ovg.ox.ac.uk](http://www.ovg.ox.ac.uk)

Oxford Biomedical Research Centre
Enabling translational research through partnership

National Institute for Health Research
Immunogenicity methods

- Samples analysed for serum bactericidal antibodies against reference strains

- hSBA titre $\geq 1:4$ considered protective

<table>
<thead>
<tr>
<th>Strain</th>
<th>fHbp</th>
<th>Por A (OMV)</th>
<th>NadA</th>
<th>NHBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HA 44/76</td>
<td>1.1</td>
<td>P1.16</td>
<td>-</td>
<td>(3)</td>
</tr>
<tr>
<td>5/99</td>
<td>2.8</td>
<td>P1.2</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>M10714</td>
<td>2.9</td>
<td>P1.3</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>NZ98/254</td>
<td>1.14</td>
<td>P1.4</td>
<td>-</td>
<td>2</td>
</tr>
</tbody>
</table>
Results
Reference strains

HA44/76
(fHbp)

5/99
(NadA)

Timing of 4CMenB
- 2,4,6,12,40 months
- 12,40,42 months
- 40+42 months
- 60+62 months
Reference stains

NZ 98/254
(OMV)

M10713
(NHBA)

% with hSBA ≥1:4

Timing of 4CMenB
- 2,4,6,12,40 months
- 12,40,42 months
- 40+42 months
- 60+62 months
Additional strains

**UK P1.7-2,4**

- **GB101**

- **GB355**

- **GB364**

Timing of 4CMenB:

- **2,4,6,12,40 months**
- **12,40,42 months**
- **40+42 months**
- **60+62 months**
Infant schedule + 40m booster

% with hSBA \( \geq 1:4 \)

Age in months

4CMenB

44/76-SL
5/99
NZ98/254
M10713
Conclusions

• Antibody waning depends on strain and schedule

• Estimating duration, breadth of protection and cost effectiveness is complicated

• Role of a pre-school booster is uncertain

• Remaining questions
  – Effect on nasopharyngeal carriage and herd immunity
  – Department of Health decision on use of 4CMenB in UK
Thank you

Acknowledgments:
MD Snape, T John, S Kelly, H Robinson, M Voysey, N Gossger, A Kimura, D Toneatto, C Kittel, P Dull, A Pollard

Funding:
Novartis Vaccines and Diagnostics

Fiona McQuaid does not receive personal payments in any form from any vaccine manufacturer
References

- Gossger N, Snape MD, Yu LM, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: a randomized control trial. JAMA. 2012. 307 (6):573-582
Local reactogenicity

% Children reporting reaction

- Pain Imm1
- Pain Imm2
- Erythema Imm1
- Erythema Imm2
- Induration Imm1
- Induration Imm2
- Swelling Imm1
- Swelling Imm2

Severe (>100mm)
Systemic reactogenicity

%Children reporting reaction

- Change in appetite
- Sleepiness
- Vomiting
- Diarrhoea
- Irritability
- Headache
- Arthalgia
- Rash
- Fever >38

Post Imm 1
Post Imm 2
SAES

• 1x UTI with haematuria
  – 2m after last vaccine. Fully recovered and not related. Observed in hospital.

• 1x somatitis herpetica
  – 2m after last vaccine, became dehydrated as not drinking, fully recovered. IV Aciclovir and fluids.

www.ovg.ox.ac.uk
Enrolled
N=50

Received first dose
N=50

Received second dose
N=46

Withdrawal of consent
N=4

Withdrawal of consent
N=1

Pre and Post imm blood sample available
N=42

Included in immunogenicity analyses
N=42

Included in safety analyses
N=50

Flow chart
Group 4