Meningococcal B vaccine. Is vaccine effectiveness confirmed?

Ray Borrow

ray.borrow@phe.gov.uk

Public Health England, Manchester, UK.
Meningococcal serogroups

- The polysaccharide capsule is used to classify into 12 distinct serogroups, 5 main serogroups cause the majority (95%) of all meningococcal disease around the world – A, B, C, W and Y.

- Polysaccharide vaccines were licensed for serogroups A, C, W and Y in the 1970s.

- Conjugate vaccines from 1999.

- Serogroup B vaccines licensed from 2013.

*N. meningitidis*, Gram-negative diplococci: magnification x20,000 at 35 mm size. Reproduced with permission from Science Photo Library [http://www.sciencephoto.com](http://www.sciencephoto.com)
Laboratory confirmed cases of meningococcal disease in England & Wales, 1995 to 2016
Laboratory confirmed cases of invasive meningococcal disease capsular group B (MenB) in England, calendar years 2009-2014
Why is there no MenB polysaccharide vaccine?

- MenB polysaccharide is polysialic acid, a compound identical to that found on the surface of human neuronal cells.

- Consequently;
  
  (i) Poorly immunogenic.
  (ii) Potential to induce an autoimmune response.

- Use subcapsular antigens, which are;
  
  (i) Surface exposed.
  (ii) Conserved.
  (iii) Induce bactericidal activity.
Subcapsular approaches

- Development of subcapsular antigen vaccines has broadly followed two pathways:

(i) Outer membrane vesicles (OMVs)
(ii) Individual proteins

- Used successfully to combat single clone epidemics of MenB disease.

- Immune response is primarily directed against the PorA protein, resulting in limited cross-protection.

Purified OMVs
OMV cross section showing multiple antigens
Reverse vaccinology uniquely allows rapid identification of promising vaccine candidates:

- Scan genome sequences
- Identify potential protein antigens
- Verify surface expression and bactericidal activity
- Vaccine candidates selected

**Bexsero (GSK) components**

Three recombinant proteins discovered by reverse vaccinology

- fHbp
- NadA
- NHBA

OMVs from the New Zealand strain (NZ 98/254)

+ PorA (P1.4) = 4CMenB

**Bexsero® formulation**

<table>
<thead>
<tr>
<th>Dose</th>
<th>fHbp fusion protein</th>
<th>NadA protein</th>
<th>NHBA fusion protein</th>
<th>OMV</th>
<th>AL&lt;sup&gt;3+&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mL</td>
<td>50 µg</td>
<td>50 µg</td>
<td>50 µg</td>
<td>25 µg</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>

2. BEXSERO [summary of product characteristics]. Siena, Italy: Novartis Vaccines and Diagnostics S.r.l.; 2014.
Bexsero, antigen diversity and cross-reactivity of induced antibody

- fHbp
- NadA
- NHBA
- PorA

Variant 1

Variants 1 & 2 & 3

Variants 4 & 5 & 6

785 VR2 variants

limited cross-reactivity to alternative variants


Variant contained within vaccine.

1Pubmlst.org- last updated 10/10/2016.
Strain coverage of Bexsero not universal - MATS predicted


*All invasive menB isolates tested. †Downweighted with respect to outbreak strains from Oregon. ‡Represents about 53% of capsular group B cases.
**Bexsero clinical program**

- Phase I to III studies in infant, toddlers and adolescents complete.
  - Over 5000 infants/toddlers & 19,000 adolescents/adults vaccinated.

- Induces serum bactericidal antibody (SBA) against a range of MenB strains.

- Acceptable safety and tolerability profile in all age groups.
  - Most reactions mild to moderate but increased systemic reactogenicity when combined with routine infant vaccination.

- Co-administered infant vaccines elicit expected immune responses when given with Bexsero.

- Licensed by European Medicines Agency in January 2013.
Solicited systemic reactions post-first dose of Bexsero* in infants when administered with routine vaccines

- No increase in the incidence or severity of the adverse reactions with subsequent doses.
- Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; Bexsero+Routine: N=2478; MenC+Routine: N=490; Routine: N=659.
- Fever categorised as severe if temperature ≥40°C. All other reactions categorised as severe if subject unable to perform normal daily activities.

*No increase in the incidence or severity of the adverse reactions with subsequent doses.

#Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; Bexsero+Routine: N=2478; MenC+Routine: N=490; Routine: N=659.
~Fever categorised as severe if temperature ≥40°C. All other reactions categorised as severe if subject unable to perform normal daily activities.
Proportions of infants, per vaccination group with temperatures ≥ 38.5 °C, following primary vaccination

Oral paracetamol at the time of vaccination, with two subsequent doses at 4 to 6 hours intervals

# Bexsero- UK immunisation schedule

## Licensed schedule (Summary of Product Characteristics)

<table>
<thead>
<tr>
<th>Population</th>
<th>Age</th>
<th>Primary dose series</th>
<th>Booster recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>2 to 5 months</td>
<td>3</td>
<td>Yes (12-23 months)</td>
</tr>
<tr>
<td>Unvaccinated infants</td>
<td>6 to 11 months</td>
<td>2</td>
<td>Yes (12-23 months)</td>
</tr>
<tr>
<td>Toddlers and above</td>
<td>≥12 months</td>
<td>2</td>
<td>-</td>
</tr>
</tbody>
</table>

## Proportions of infants with SBA titres ≥4 following second / third infant priming dose

<table>
<thead>
<tr>
<th>Antigen (SBA target strain)</th>
<th>Schedule</th>
<th>fHbp (44/76-SL)</th>
<th>NadA (5/99)</th>
<th>OMV (NZ 98/254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After three doses (at 2, 4 &amp; 6 months of age)</td>
<td></td>
<td>95%</td>
<td>95%</td>
<td>85%</td>
</tr>
<tr>
<td>After two doses (at 2 &amp; 4 months of age)</td>
<td></td>
<td>87%</td>
<td>100%</td>
<td>74%</td>
</tr>
</tbody>
</table>

Negotiations to procure at cost-effective price were concluded in late March 2015

**MenB vaccine given with routine immunisation appointments from 1\textsuperscript{st} September 2015**

**Routine cohort:** infants born on or after the **1 July 2015**

**Schedule:** 2, 4 and 12 months (2+1)

**Catch-up cohort:** infants born from **1 May to 30 June 2015**

**Schedule:** 3, 4 and 12 months (2+1)

**Schedule:** 4 and 12 months (1+1)
Bexsero implementation in the UK

Ministers accused of refusing life-saving vaccine as negotiations descend into acrimony

Dispute with drug company over meningitis jab

Wrangling over price for vaccine may cost "hundreds of thousands of babies"

Bexsero given with routine immunisation appointments from 1st September 2015
Cases: summary, first 10 months

- 01 September 2015 - 30 June 2016 (10 months)

- 55 lab-confirmed IMD cases in vaccine-eligible infants
  - born on or after 01 May 2015,
  - diagnosed on or after 01 September 2015
  - aged ≥10 weeks at diagnosis

- Capsular group distribution
  - 37 (67%) MenB,
  - 11 (20%) MenW,
  - 5 (9%) MenY
  - 2 (4%) ungrouped.
Comparison with previous years (September to June)

- **Vaccine ineligible cohort (<5 year-olds)**
- **Vaccinated cohort**
Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study

Sydol R, Parikh N, Abouzafar K, Baohejun H, Helen Campbell, Sonia Rabein, Charles Ward, Joanne M White, Roy Borou, Mary J Ramsay, Sumei N Latham

Summary

Background In September 2015, the UK became the first country to introduce the multicomponent group B meningococcal (MenB) vaccine (4CMenB, Bexsero) into a publicly funded national immunisation programme. A reduced two-dose priming schedule was offered to infants at 2 months and 4 months, alongside an opportunistic catch-up for 3 month and 4 month olds. 4CMenB was predicted to protect against 73–88% of MenB strains. We aimed to assess the effectiveness and impact of 4CMenB in vaccine-eligible infants in England.

Methods Public Health England (PHE) undertakes enhanced surveillance of meningococcal disease through a combination of clinical, public health, and laboratory reporting. Laboratory-confirmed cases of meningococcal disease are followed up with PHE local health protection teams, general practitioners, and hospital clinicians to collect demographic data, vaccination history, clinical presentation, and outcome. For cases diagnosed between Sept 1, 2015, and June 30, 2016, vaccine effectiveness was assessed using the screening method. Impact was assessed by comparing numbers of cases of MenB in vaccine-eligible children to equivalent cohorts in the previous 4 years and to cases in vaccine-ineligible children.

Findings Coverage of 4CMenB in infants eligible for routine vaccination was high, achieving 89–95% for one dose and 83–89% for two doses by 6 months of age. Two-dose vaccine effectiveness was 82–89% (5% CI 95% CI 0.24–1.39) against all MenB cases, equivalent to a vaccine effectiveness of 94–96% against the highest predicted MenB strain coverage of 88%. Compared with the pre vaccine period, there was a 50% incidence rate ratio (IRR) reduction in MenB cases in the vaccine-eligible cohort (73 cases vs average 74 cases; IRR 0.50 [95% CI 0.36–0.71]; p=0.001), irrespective of the infant’s vaccination status or predicted MenB strain coverage. Similar reductions were observed even after adjustment for disease trends in vaccine-eligible and vaccine-ineligible children.

Interpretation The two-dose 4CMenB priming schedule was highly effective in preventing MenB disease in infants. Cases in vaccine-eligible infants below the first 18 months of the programme. While ongoing national surveillance will continue to monitor the long-term impact of the programme, these findings represent a step forward in the battle against meningococcal disease and will help reassure that the vaccine protects against this deadly infection.

Funding Public Health England.
### Vaccine effectiveness of Bexsero against MenB disease, in England between 1\textsuperscript{st} Sept 2015 and 30\textsuperscript{th} June 2016 (10 months)

<table>
<thead>
<tr>
<th>Doses</th>
<th>Cases in vaccinated / total cases</th>
<th>Average matched vaccine coverage</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2+0</td>
<td>9/13 (69%)</td>
<td>92.9%</td>
<td>82.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(24.1% to 95.2%)</td>
</tr>
<tr>
<td>1+0</td>
<td>20/28 (71%)</td>
<td>76.2%</td>
<td>22.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(-105% to 67.1%)</td>
</tr>
<tr>
<td>At least one</td>
<td>29/37 (78%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Based on assumption that 100% MenB cases are preventable by Bexsero.
- If re-calculate on basis that 88% of MenB cases preventable; VE = ~94%

- VE calculated using the screening method.
- Cases in infants born on or after 1\textsuperscript{st} May 2015 with MenB disease diagnosed between 01/09/15 and 30/06/16.
- Dose discounted if disease diagnosed <14 days after vaccination.
Determined that there are no safety concerns so far…

On-going surveillance is essential to continue to monitor impact, including post-12 month booster.

Further work required into investigating the MenB breakthrough cases in terms of;

- Using MATS to determine if disease isolate was ‘vaccine preventable’.
- Underlying conditions in the patient.

Investigating the impact of Bexsero on non-MenB disease.

Bexsero – pharmacovigilance strategy

• UK first country to use Bexsero® in a national programme.

• Developed in advance of UK programme – endorsed by Commission on Human Medicines.

• Starting point:
  - Safety from clinical trial programme, post-marketing data outside of UK and the manufacturer’s risk management plan.

• Underpinned by Yellow card Scheme (passive surveillance) & supported by ad hoc analysis of data from Clinical Practice Research Datalink (active surveillance/epi studies).
Yellow Card (YCs) expectations

Planning assumptions:

• Expected ~120,000 routine doses/month, rising to 180,000 with boosters.

• Anticipated ~ 1 YCs per 1,000 doses (based on prior experience with major new vaccines eg MenC, HPV).

• Expected ~1.7m doses & 1,700 YCs by end Oct 2016

• What happened (as of Nov 2016)?

  Latest coverage ~1.5 to 1.8m doses given
  YCs 1,094
  ~1.6 per 1,000 doses - ~ half that expected
Number of events per System Organ Class

Mostly lethargy/sleepiness, faints, headache, hypotonic-hyporesponsiveness, some seizures

Mostly fever, malaise, crying, injection site reactions

Mostly irritability, restlessness, screaming

Mostly rashes

1,094 YCs include 2,845 event terms
Fever

- Fever (inc related event terms); n = 391
- Severity not always reported, and information in Yellow Cards not able to determine impact of Paracetamol.
- A small proportion with A&E attendance/admission for observation and some with precautionary antibiotic treatment septic screen due to severity of fever (ie to rule out underlying infections).
- Given number of children immunised and expected fever rates, no indication of anything unexpected or unusual.
Local reactions

• Wide range of event terms reported, n = ~ 600

• Isolated reports of extensive swelling, persistent local reactions and inability to use limb/bear weight
  - not unexpected

• ~ 100 reports refer to a nodule/mass (ie pea sized lump) under skin at injection site.
  - In several cases persisted for weeks/months.
  - In most cases, pain/redness/discomfort has not persisted, some report persistent itchiness.
Bexsero®, safety summary

• Yellow Card – not proof of causal associations
  - except injection site events

• No serious, unexpected safety issues identified to date
  - nature of Yellow Cards largely as anticipated
  - number of Yellow Cards low compared to expectations

• More robust analysis of seizures & Kawasaki Disease in progress

• In context of efficacy, safety profile is so far acceptable and reassuring

• Safety will remain under review
fHbp discovered by ‘traditional’ vaccinology.

Licensed in the US on 29th October 2014.

Licensed for 10-25 year olds

Either: Three dose 0, 1-2, 6 months or Two dose 0, 6 months
Summary

- Not been possible to produce a polysaccharide/conjugate MenB vaccine.
- Bexsero licensed in Europe in 2013.
- Bexsero implemented into the UK infant schedule from 1\textsuperscript{st} Sept 2015.
- Now have UK data for first 10 months of implementation;
  - Vaccine efficacy post-2\textsuperscript{nd} dose against MenB disease is 83%.
  - No safety concerns.
Acknowledgements

PHE Colindale:
Sydel R. Parikh, Nick J. Andrews, Kazim Beebejaun, Helen Campbell, Sonia Ribeiro, Mary E. Ramsay, Shamez N. Ladhani, Vanessa Saliba, Sema Mandal, Joanne Yarwood

PHE Manchester:
Stephen Clark, Stephen Gray, Jamie Findlow, Aiswarya Lekshmi, Jay Lucidarme, Lynne Newbold

MHRA:
Phil Bryan and team

MRF MENINGOCOCCUS GENOME LIBRARY
(http://www.meningitis.org/research/genome).