Impact and safety management in Meningococcal B vaccination

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“a pain you cannot describe”
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

No. of cases


Y W C B
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:
  1. Poorly immunogenic.
  2. Potential to induce an autoimmune response.

- Use subcapsular antigens, which are:
  1. Surface exposed.
  2. Conserved.
  3. 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.
Reverse vaccinology- a genomic based approach to vaccine development

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

Complete *N meningitidis* genome sequence → Bioinformatic analysis → Protein expression in *E coli* → 350 → 2158 → 570 → 3

Final candidates selected for vaccine development → Confirmation of bactericidal activity → Vaccine → Protein purification and immunisation → Bexsero® → 350 → 2158 → 570 → 3

Confirmation of surface exposure → 28 → 91

Bexsero (GSK) components

Three recombinant proteins discovered by reverse vaccinology

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

\[ \text{fHbp + NadA + NHBA} = 4CMenB \]

Bexsero, antigen diversity and cross-reactivity of induced antibody

Variant contained within vaccine.

836 VR2 variants\(^1\)
limited cross-reactivity to alternative variants

\(^1\)Pubmlst.org- last updated 29/03/2017.
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.

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.

- 4CMenB
- 4CMenB + paracetamol
- MenC
- 4CMenB + paracetamol
- MenC
- MenC

ESCMID eLibrary © by author
Negotiations to procure at cost-effective price were concluded in late March 2015

**MenB vaccine given with routine immunisation appointments from 1st 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

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.
CASES: before and after

Comparison with previous years (September to June)

Vaccine ineligible cohort (<5 year-olds)

Vaccinated cohort
### Vaccine effectiveness of Bexsero against MenB disease, in England between 1<sup>st</sup> Sept 2015 and 30<sup>th</sup> 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% (24.1% to 95.2%)</td>
</tr>
<tr>
<td>1+0</td>
<td>20/28 (71%)</td>
<td>76.2%</td>
<td>22.0% (-105% to 67.1%)</td>
</tr>
<tr>
<td>At least one</td>
<td>29/37 (78%)</td>
<td></td>
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</tbody>
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- 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<sup>st</sup> 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
  ~0.6 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 (i.e., 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
Trumenba® (Pfizer)

- fHbp discovered by ‘traditional’ vaccinology.

- Licensed in the US on 29th October 2014.
  - Licensed for 10-25 year olds
  - either: 3 dose 0, 1-2, 6 months or
    2 dose 0, 6 months

- 23 March 2017, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion.
Summary

- Not been possible to produce a polysaccharide/conjugate MenB vaccine.
- Bexsero licensed in Europe in 2013.

Bexsero:

- Bexsero implemented into the UK infant schedule from 1st Sept 2015.
- Now have UK data for first 10 months of implementation;
  - Vaccine efficacy post-2nd dose against MenB disease is 83%.
  - No safety concerns.
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(http://www.meningitis.org/research/genome).