Understanding invasive meningococcal disease

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Aims

• Explain what *Neisseria meningitidis*
  – What it is
  – Why it is a serious infection
  – How it causes disease

• Meningococcal vaccines
  – Who the disease affects
  – Polysaccharide vaccines
  – Protein based vaccines

• The Future: Other uses for broad spectrum meningococcal vaccines
“A devastating disease”

Source: meningitisnow.org
What is *N. meningitidis*?
Serogroups

- Gram negative diplococcus

- The polysaccharide capsule is used to identify the different serogroups.

- There are 12 capsular groups

- Five main serogroups cause the majority (95%) of all meningococcal disease around the world – A, B, C, W (formerly W135) and Y.

Courtesy of Prof Ray Borrow
Neisseria meningitidis – the meningococcus

- Bacterium
- Leading global cause of meningitis and septicaemia
- ‘Accidental pathogen’
- Asymptomatic nasopharyngeal carriage in ~10% of individuals.

Courtesy of Dr Jay Lucidarme
Host interactions

Why do some people get invasive meningococcal disease while others do not?

~10% of Population (6.4 million)

Nasopharyngeal carriage

661 (2014) to 2801 (1999) cases per year England and Wales

Harmless commensal to invasive pathogen

Cleared (transient bacteraemia)

Systemic infection - Sepsis (blood poisoning)

Localized infections - joints - meninges

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Combination of factors

Environment

Host

Meningococcus

Courtesy of Dr Jay Lucidarme
• Slimy outer capsule
• Used to determine different serogroups
  - e.g. A, B, C, W, Y
  - NG (non-groupable)
• Most important virulence factor*

Lack genes
Switched off

No capsule = killed *

*in healthy immunocompetent individuals

Courtesy of Dr Jay Lucidarme
Capsule = may survive

- Slimy outer capsule
- Serogroup determinant
  - e.g. A, B, C, W, Y
  - NG (non-groupable)
- Essential for disease*

Lack genes → Switched off

Polysaccharide

*Essential for disease means that the capsule is necessary for the development or progression of the disease. It is likely to be a key component of the pathogenicity of the organism.
Who does it affect and what can we do about it?
Laboratory confirmed IMD by age group (2012-2017)
# Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Vaccine type</th>
<th>Capsular group</th>
<th>Target</th>
<th>Cross-protection</th>
<th>Carriage reduction</th>
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<tr>
<td>Conjugate</td>
<td>MenC, MenA/C/W/Y</td>
<td>Polysaccharide capsule</td>
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- Highly immunogenic including infants*
- Long lasting immunogenicity in older children/adults*
- Impact on carriage → herd protection*

*when conjugated to protein carrier
Epidemiological years

Number of laboratory confirmed cases

- **MCC vaccine introduced**
- **cc11**: MenW begins to increase rapidly

Hyperinvasive ST-11 clonal complex (cc11)

Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage.


- **Propensity to cause large outbreaks**

- Caused serogroup C (MenC) outbreaks in the US military in the 1960s and UK universities in the 1990s,
- a global Hajj-associated serogroup W (MenW) outbreak in 2000-2001
- subsequent MenW epidemics in sub-Saharan Africa. More recently, endemic MenW disease has expanded in South Africa
- South America and the UK, and MenC cases have been reported among European and North American men who have sex with men (MSM).
Although MenW outbreak is caused by the same clonal complex MCC would not work against this group due to the difference in their polysaccharide capsule.
"N. meningitidis" - characterisation & typing targets

Serogroup capsule

C:2a:P1.5,2

Serotype PorB

Serosubtype PorA

eg. B:NT: NT/P1.4/NT

Serotype

Courtesy of Dr Steve Gray
Cases of MenW disease by age group 2012/13 to
Meningococcal vaccines

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BUT….
The polysaccharide capsule of MenB is UNSUITABLE a polysialic acid and **identical to human foetal neuronal cells:**
- Poorly immunogenic
- Potential to induce autoimmune response

*when conjugated to protein carrier
• Polysaccharide
• Subcapsular proteins
• Detergent extraction
• 4CMenB (Bexsero)
  • 20 years to develop using
  • Reverse vaccinology
Meningococcal B vaccines

- Poly saccharide
- Subcapsular protein
- Detergent extraction

Outer membrane vesicles - Highly effective BUT PorA dominant antigen → PorA diverse/poorly cross-protective → Strain specific response

✓ Clonal outbreaks
× Diverse endemic disease

Our biggest weapon against IMD

Courtesy of Dr Jay Lucidarme
4CMenB introduced in the infant immunisation programme in the UK from September 2015
rLP2086

- Licensed in the US in 2014
- Ages 10-25 years
- Licensed in the UK 2017
- fHbp is vital for the bacteria’s survival in the human host and interacts with human factor H to invade the innate immunity
- Although FHbp is antigenically diverse, it can broadly be divided into two genetically distinct subvariant families
- Trumenba contains two antigenic variants of fHbp from both subfamilies
- Rationale: subfamilies are immunogenically distinct, while within a subfamily, there is evidence of cross-reactivity

Feavers and Maiden 2017, Clinical and Vaccine Immunology
The future of meningococcal vaccines
Vaccination with MeNZB resulted 31% reduction in incidence of gonorrhoea in vaccinated populations up to 10 years after the vaccine was introduced.
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