Group B Meningococcal (MenB) vaccines explained

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Key points

• Meningococci
• Why group B are harder
• Epidemiology:
  – When/who most need protection
• Meningococcal immunity understanding
• 4cMenB: Bexsero
  – What we know
  – Known unknowns
  – When will we know?
Background

- Severe disease
- Uncommon disease
- Common carriage
- Group B
  - Covered in non-immunogenic sugar
- All other groups ACWY
  - Sugar immunogenic
  - Successful vaccines
How serious a disease is *N. meningitidis*?

Meningococcal disease has a case fatality rate of approximately 10%, however more deaths are caused by septicaemia than by meningitis.

4CMenB

Capsular polysaccharide (self antigen)

GpB PS - polymer of sialic acid:
- chemically identical to polysaccharides found in human tissues during development
- (2→8)-α-Neu5Ac as a self antigen of humans
- potential cause of immunopathology
Nasopharyngeal colonisation

Scanning electron micrograph: attachment of *N. meningitidis* by pili to the microvilli of nonciliated cells in the nasopharynx

Colonisation
- Common
- Transient
- Increased in adolescence
- Majority- totally asymptomatic
Invasive Meningococcal Disease

## Risk factors: meningococcal disease

<table>
<thead>
<tr>
<th>Immature Immune System(^1)</th>
<th>Impaired Immune System(^2,3)</th>
<th>Nasopharyngeal Irritation(^3)</th>
<th>Social Factors(^3,4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Infants</td>
<td>- Asplenia</td>
<td>- Smoking</td>
<td>- Close contact - case</td>
</tr>
<tr>
<td>- Waning Ab</td>
<td>- Complement deficiency</td>
<td>- Respiratory-tract infection</td>
<td>- Crowding</td>
</tr>
<tr>
<td>- PS response</td>
<td>- Humoral deficiency</td>
<td></td>
<td>- Mult kissing contacts</td>
</tr>
<tr>
<td>- Prematurity</td>
<td>- HIV/AIDS</td>
<td></td>
<td>- Pubs/Discos</td>
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</table>

Most cases of meningococcal disease occur in previously healthy persons without identified risk factors.

Meningococcal Epidemiology Victoria
Meningococcal notifications

Meningococcal infections notified in Victoria, 1936-2012

Year


Number of notified cases

0 500000 1000000 1500000 2000000 2500000 3000000 3500000 4000000 4500000

Cases

VIC Population


0 50000 100000 150000 200000 250000 300000 350000 400000 450000

Courtesy Lucinda Franklin/Kath Taylor, DH Victoria
Invasive meningococcal disease

Notified cases of invasive meningococcal disease by type, 1 Jan 2002 to 31 Mar 2013

MenC vaccine introduced
Meningococcal immunity
Bactericidal activity in an Army recruit population & susceptibility to group C meningococcal disease

**BOOT CAMP ENTRY**

492 recruits at Fort Dix, NJ – 1968

- **438** had bactericidal antibody - **No disease**
- **54** were initially lacked bactericidal antibody
  - SBA: SERUM BACTERICIDAL ACTIVITY

**OUTCOME: 54 WITH NO SBA**

- **24** became exposed to the group C epidemic strain
- **11** developed SBA
  - **No disease**
- **13** failed to develop SBA
  - **5/13** – group C IMD (38.5 % attack rate)

Highest incidence of meningococcal meningitis occurs at lowest bactericidal antibody prevalence.

Group B immunity

• SBA other serogroups directed against capsular PS
• ELISA developed to correlate with SBA
  – All other vaccines developed using these
  – NEVER LICENSED ON EFFICACY
• Can’t use PS for Gp B
• SBA against other bits...
Reverse Vaccinology Allowed the Identification of Novel MenB Antigens

*Genomic-based approach to vaccine development*

4CMenB: Bexsero™

Capsular PS: shared by all
Proteins: more variable between strains of Group B
Aust strains will share 0-4 of vaccine peptides
Summary of Antigenic Components of BEXSERO

*Important for meningococcal survival, function, or virulence*

- **NadA: Neisserial adhesin A Protein**
  - Promotes adherence to and invasion of human epithelial cells\(^1\)-\(^3\)

- **fHBP: factor H Binding Protein**
  - Binds factor H, which enables bacterial survival\(^4\),\(^5\) in the blood

- **NHBA: Neisseria Heparin-Binding Antigen Fusion Protein**
  - Binds heparin, which may increase the serum resistance of bacteria\(^6\)-\(^8\)

- **NZ PorA P1.4: porin A**
  - Major outer membrane vesicle protein—induces strain-specific bactericidal response

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BEXSERO® studies: RCT

Approximately 7800 subjects (from 2 months of age) received at least 1 dose of the vaccine*

Infants and children 2 months to <2 years of age
- 5850 received at least 1 dose of BEXSERO
- 3285 received booster dose in second year of life

250 children 2 to 10 years of age

1703 adolescents and adults ≥11 years of age

*BEXSERO was evaluated in 13 studies, including 9 randomized controlled clinical trials.

Data on file, Novartis Vaccines and Diagnostics.
MATS: infant immuno & persistence

Immunogenicity varies between proteins
Immune response wanes: amount also varies
BEXSERO® Can Be Co-Administered With Other Vaccines

<table>
<thead>
<tr>
<th>Vaccine Antigens</th>
<th>Measles</th>
<th>Mumps</th>
<th>Rubella</th>
<th>Varicella</th>
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<tbody>
<tr>
<td>Diphtheria</td>
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<tr>
<td>Tetanus</td>
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<tr>
<td>Acellular pertussis</td>
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<tr>
<td>Inactivated poliomyelitis</td>
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<tr>
<td>Hepatitis B</td>
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<tr>
<td><em>Haemophilus influenzae</em> type b</td>
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<tr>
<td>Heptavalent (7-valent) pneumococcal conjugate</td>
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</tbody>
</table>

Inconsistent results were seen across studies for responses to inactivated poliovirus type 2 and pneumococcal conjugate serotype 6B and lower antibody titers to the pertussis pertactin antigen were also noted, but these data do not suggest clinically significant interference.

Note: Bexsero has not been studied in concomitant administration with Prevenar13, Rotavirus vaccine or MenC conjugate vaccine
*No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series.

†Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; BEXSERO+Routine: N=2478; MenC+Routine: N=490; Routine: N=659.

‡Fever was categorized as severe if temperature was ≥40°C. All other reactions were categorized as severe if subject was unable to perform normal daily activities.

BEXSERO® Tolerability in Infants

Solicited local reactions when BEXSERO is given separately from routine vaccines—post–dose 1

*No increase in the incidence or severity of the adverse reactions was seen with subsequent doses of the vaccination series; Hatched lines represent severe (erythema, swelling and induration were categorized as severe if local reaction was >50 mm). Tenderness was categorized as severe if subject cried when injected limb was moved).

†Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; BEXSERO: N=626; Routine: N=613.

When Fever Occurred, it Generally Followed a Predictable Pattern, With the Majority Resolving the Day After Vaccination

*BEXSERO® given with routine vaccines—post–dose 1*

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Inform your patients about the likelihood of fever lasting one to two days

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*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib; BEXSERO+Routine: N=2433–2478; MenC+Routine: N=486–490; Routine only: N=643–659. Fever was defined as rectal temperature ≥38.5°C.

Prophylactic Paracetamol at the Time of and Closely After Vaccination Reduced Fever

*When BEXSERO® is given concomitantly with routine infant vaccines*

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Advising your patients about prophylactic paracetamol administraion at the time and closely after vaccination can reduce the incidence and intensity of post-vaccination febrile reactions.

**NPP:** no prophylactic paracetamol (N=182); **PP:** with prophylactic paracetamol (N=178-179).

Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.

Predicted Coverage of MenB Strains Indicates BEXSERO® Has the Potential to Impact MenB Disease

In March 2014, the Department of Health’s Technical Advisory Group on Immunisation issued ‘Advice for immunisation providers regarding the use of Bexsero®’

Recommendations

Based on their higher disease risk, 4CMenB is recommended for:

- Infants and young children, particularly those aged <24 months
- Adolescents aged 15 to 19 years
- Children and adults with medical conditions that place them at a high risk of IMD, such as functional or anatomical asplenia or complement component disorders (see Chapter 4.10 of *The Australian Immunisation Handbook*, 10th edition)
- Laboratory personnel who frequently handle *Neisseria meningitidis*.

4CMenB is also recommended for all children and young adults who wish to reduce their risk of MenB IMD.
### Table 1. Recommended schedule of 4CMenB by age group

<table>
<thead>
<tr>
<th>Age at commencement of vaccine course</th>
<th>Primary immunisation</th>
<th>Interval between primary doses</th>
<th>Age for booster dose</th>
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<tbody>
<tr>
<td>2 months*</td>
<td>3 doses, delivered at ~2*, 4 and 6 months of age; (intervals ~2 months, at least 1 month)</td>
<td></td>
<td>12 months</td>
</tr>
<tr>
<td>3 to 5 months</td>
<td>3 doses</td>
<td>1–2 months</td>
<td>12 months</td>
</tr>
<tr>
<td>6 to 11 months</td>
<td>2 doses</td>
<td>2 months</td>
<td>12 months, or 2 months after previous dose, whichever is later</td>
</tr>
<tr>
<td>12 months to 10 years</td>
<td>2 doses</td>
<td>2 months</td>
<td>No booster required†</td>
</tr>
<tr>
<td>11 years and above‡</td>
<td>2 doses</td>
<td>1–2 months</td>
<td>No booster required‡</td>
</tr>
</tbody>
</table>

* 4CMenB is registered for use in persons ≥2 months of age; however, the 1st dose of 4CMenB may be administered as early as 6 weeks of age to align with the NIP infant schedule.
† The need for a booster dose for this age group is as yet uncertain.
‡ There are currently no data on the use of 4CMenB in individuals aged over 50 years, however, based on first principles, ATAGI recommends that 4CMenB can be used in older persons who are at high risk of IMD.

MATS: adolescent immuno & persistence
Known unknowns

• Will it work?
  – Modified serology says yes
  – But untested given not directed against PS

• Will it provide herd immunity?
  – 12.6% (−15.9%, 34.1%) reduction in NP carriage

• Will protection last?

• Will there be “escape strains”?  

• Will it increase fever/febrile convulsions?

• Will Australians follow paracetamol advice
  – Will that change febrile seizure risk anyway?

• How will we register adolescent doses?
BEXSERO Approvals and Recommendations

Approved for use in >30 countries

35 APPROVALS
12 RECOMMENDATIONS

Approved for use in >30 countries
Saguenay – Lac St. Jean region

• Programme:
  – all persons aged 2 months to <20 years of age
  – Between May 5 and June 17, **43,740** persons received their first dose of Bexsero

• Safety study:
  – Online safety survey of 12,332 vaccinees
  – Diary cards to assess fever, paracetamol use, school absenteeism, etc.
  – Within 8 days and 6 months after vaccination
  – Antipyretic use high (93% in persons 2 years age and under)
  – No signal of concern to date

• Effectiveness study, incl. vaccine registry:
  – Routine surveillance monitors for potential vaccine
Antipyretic prophylaxis significantly reduced the risk of fever in infants and children aged under 5 years.

Proportion of vaccinees who reported fever on days 1 and 2 by age and number of antipyretic prophylaxis doses.

- In children under the age of 2 years, administration of 2 or more doses of antipyretic reduced the likelihood of fever by approximately 50% within the first 48 hours.
- There was a greater reduction in the risk of fever with a higher number of doses of antipyretic prophylaxis.
- Antipyretic prophylaxis significantly reduced the risk of fever in the children aged 2-4 years, and to a lesser extent in the children aged 5-11 years.
- The prophylactic effect was more pronounced in those who had co-administration of other vaccines than in those who received 4CMenB alone.

Thank you

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