Prevention of Meningococcal Disease

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Neisseria meningitidis

- Polysaccharide capsule (12 serogroups) A, B, C, Y, X and W....
- Genetic characterization (DNA sequencing of 7 housekeeping genes - MLST)
- Whole genome phylogenetic analyses

Meningococcal Disease

Clinical syndromes

- Bacteriemia (37.5%) - Meningococcemia
- Meningitis (50%)
- Pneumonia (9%)
- Conjunctivitis arthritis, pericarditis, urethritis

IMD Can Result in Permanent, Long-term Sequelae

On average, 10%–20% of surviving patients have long-term sequelae

Typical Symptoms of IMD Appear Later in Older Children and Adolescents, Delaying Medical Care and Increasing the Risk of Long-term Effects of IMD

Timely GP/hospital admission is critical for successful treatment of IMD.

Meningococcal disease: risk factors\textsuperscript{1–3}

**Children and adults with HIV have increased (up to 26.5-fold) risk of meningococcal disease**


**MSM were several times more likely to contract invasive meningococcal disease than other males aged 18–64 years**


**There is a 1,000-fold increased risk of meningococcal disease (caused by unusual meningococcal strains) in patients with complement deficiency**


**Eculizumab use has been primarily associated with an increased risk (up to 10,000-fold higher) of meningococcal infections**


**Most cases (>90%) of meningococcal disease occur in previously healthy persons without identified risk factors\textsuperscript{2}**

Carriage and transmission

- Pharyngeal carriage is a prerequisite for invasive meningococcal disease.
- Asymptomatic carriage (may last a long time) - nasopharynx (< 1% - 30%)
- *N. meningitidis* is predominately carried by teenagers/young adults.

# Worldwide Available Polysaccharide Conjugate Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Polysaccharide Conjugate Vaccines</th>
<th>Carrier Protein&lt;sup&gt;46-53&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menjugate&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenC</td>
</tr>
<tr>
<td>Meningitec&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenC</td>
</tr>
<tr>
<td>NeisVac-C&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenC</td>
</tr>
<tr>
<td>Menitorix&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenC-Hib</td>
</tr>
<tr>
<td>MenAfriVac&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenA</td>
</tr>
<tr>
<td>Menactra&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenACYW</td>
</tr>
<tr>
<td>Menveo&lt;sup&gt;®&lt;/sup&gt;</td>
<td>MenACYW</td>
</tr>
<tr>
<td>Nimenrix™</td>
<td>MenACYW</td>
</tr>
</tbody>
</table>

New multivalent ACWY-TT and ACWYX vaccines are being developed
Meningococcal Conjugate Vaccines Represent a Significant Advance Compared With Existing Plain Polysaccharide Vaccines

Polysaccharide vaccine
- Antibody response of short duration
- No memory B-cell production

Conjugate vaccine
- Antibody response of long duration
- T cells stimulate B cells to produce antibodies
- Memory B cells produced

[Diagram showing the comparison between polysaccharide and conjugate vaccines]

Outbreaks caused by MenC.
High carriage rates of MenC in both refineries.

Ministry of Health replace the polysaccharide vaccine with the MenC conjugate vaccine for controlling MenC outbreaks.
Update on safety and immunogenicity (reduced schedule, concomitant administration and persistence data) of meningococcal conjugate vaccines
Antibody Persistence 6 years After Vaccination with MenC Conjugate

- Persistence of immunity is dependent on age at priming
- These data emphasizes the importance of the herd immunity effect and provide the first evidence supporting the introduction of a booster dose for cohorts of children immunized before school age.

Perrett K et al. CID, 2010
Antibody persistence 5 years after primary vaccination with MenACWY-CRM in infants, and booster response across all serogroups\textsuperscript{2,3}

**Time points assessed***:

- **1 month post-dose 4** (dose 4 at 12 months of age)\textsuperscript{1}  
  n=84–86
- **28 months post-dose 4** (at 40 months of age)\textsuperscript{2}  
- **48 months post-dose 4** (at 60 months of age)\textsuperscript{2,3}  
  n=103–115
- **Booster dose at 48 months post-dose 4** (at 60 months of age)\textsuperscript{3}  
  n=103–115

*Blood drawn at 13 months of age (1 month post–dose 4), 40 months of age (28 months post–dose 4), 60 months of age (48 months post–dose 4) and 61 months of age (1 month post–booster at 60 months of age).
Antibody persistence after MenACWY-CRM or MenACWY-DT up to 5 years after primary vaccination in adolescents aged 11–18 years

The majority of subjects maintained hSBA ≥1:8 against serogroups C, W and Y over 5 years

*Statistically significant higher response for MENVEO® vs Menactra®.

Adapted from Baxter R et al. Pediatr Infect Dis J 2014;33:1169–1176
Real-World Impact data on Meningococcal Vaccines Programmes implemented in Europe, Africa, North and Latin America
Direct and indirect protection with conjugated vaccines

Preventing the acquisition of carriage is crucial to optimize the impact of programs with conjugated vaccines

Vetter, Baxter, Sáfadi et al. ERV, 2016
MenC immunization programmes have reduced the burden of meningococcal C disease in Europe\textsuperscript{1–3}

Routine immunization programmes, including catch-up campaigns in children and adolescents, have been successful in reducing MenC disease incidence through direct and indirect protection

Meningococcal disease epidemiology in France, 2006-2015

Decreasing incidence of IMD cases in France from 2006 to 2015 (mainly related to the decrease in MenB cases).

Low MenC vaccination coverage in older age groups (32% in 10-14 y, 23% in 15-19 y and 7% in 20-24 y).
• Between 2011-2015 > 217 million (1 – 23 y) vaccinated in 19 countries from the “meningitis belt” with MenA-TT
• Incidence of suspected meningitis cases declined by 57% (95% CI 55–59) in vaccinated compared with unvaccinated populations.
• In fully vaccinated populations, the incidence of confirmed group A disease was reduced by more than 99%.
• The IRR for non-A serogroups was higher after completion of MenAfriVac campaigns (IRR 2·76, 95% CI 1·21–6·30).
Emergence of MenC and MenW disease in Africa.

- By June 2015, 8,500 suspected cases of MD in Niger, including 573 deaths. Most of the cases were MenC, belonging from a newly lineage ST-10217.
- **Nigeria**: Dec/2016 - May/2017: 14,473 cases. 80% of tested cases were serogroup C.
- The world’s largest reported serogroup C epidemic

- Outbreaks of MenW cc-11 in **Burkina Faso** from 2012 and **Togo** and **Ghana** in 2016
- Reactive vaccinations in 2016 with polysaccharide ACW, AC and ACW and MenC conjugate vaccines

http://www.ncdc.gov.ng/themes/common/files/sitreps/bf8ebe6d8a8187aa9ddf1b39aecd3ae.pdf
Mustapha M & Harrison L. HVI, 2018
Examples of Meningococcal conjugate vaccination programmes without catch-up campaigns:
Brazil and Chile
Brazil started vaccination with MenC Vaccine for all children < 2 years of age on late 2010.

- Infant immunization (3 and 5 months) with booster dose at 12 months.
- Children between 12 and 23 months: 1 dose
- No catch up campaign in older age groups
Incidence rates before and after Men C vaccination. Brazil, 2008-2015

Cases/100,000

Early impact on incidence rates of meningococcal disease observed only in the age groups targeted for vaccination.
Serogroup Distribution of MD, by age group. Brazil, 2017

< 5 anos

5-14 anos

15-29 anos

30-49 anos

50-59 anos

> 60 anos

B  C  W  Y
In Salvador, compared to the pre-vaccine period, a virtual disappearance of MenC disease was observed. However, in the state of Bahia (excluding the city of Salvador), no herd protection could be observed, with significant impact only among vaccine-eligible children within 5 years of introduction of the MCC vaccination program.
Decision for 2017 with MenC conjugate vaccine in Brazil:

- Booster doses in adolescents 9-13 years with MenC conjugate vaccine.
Increased incidence of MD in 2012 (from 0.4 to 0.8), associated with emergence of serogroup W (3 cases in 2010, 20 in 2011 and 60 in 2012).
Reactive MenW Immunization action in Chile

- An immunization campaign started in 2012 with the tetravalent conjugate vaccine (Men ACWY), initially targeting children aged 9 months to < 5 years.
- 9 m to < 2 y: 2 doses (MenACWY-DT) and > 2 y: 1 dose (MenACWY-CRM).
- Approximately 1 million children vaccinated (Coverage >95%).
- From 2014: 1 dose (MenACWY-TT) in toddlers at 12 months.

Impact of the MenACWY immunisation campaign in Chile, 2012-2017

- Reduction of 82% in the incidence rates of MD in children aged 1-5 years
- No significant impact on incidence rates of other unvaccinated age groups
Number of cases of serogroup W cases. Chile, 2010 - 2017

serogroup W cases

ACWY Vaccination

Meningococcal Disease in US.

- In 2016, 372 cases of MD reported (0.12/100,000). Declining incidence rates.
- 49 deaths (CFR 13%)

- Highest rates in infants, followed by a second peak in adolescence (16-23 y) and elderly.

- Serogroup B causes ~ 60% of cases in children < 5 years old. Serogroups C, Y, or W cause 73% of the cases among persons > 11 years old.
### Recommendation of meningococcal vaccination in USA (ACIP)

**Men ACWY conjugate vaccine is routinely recommended for all adolescents and high risk individuals.**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MenACWY-D</th>
<th>MenACWY-CRM</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals 11–21 years</td>
<td>✓</td>
<td>✓</td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>11–12 years</td>
<td>✓</td>
<td>✓</td>
<td>1 dose</td>
<td>Given if 1st dose before 16th birthday</td>
</tr>
<tr>
<td>13–18 years (not vaccinated)</td>
<td>✓</td>
<td>✓</td>
<td>1 dose</td>
<td>5 years post primary;</td>
</tr>
<tr>
<td>19–21 year (not vaccinated by 16)</td>
<td>✓</td>
<td>✓</td>
<td>1 dose as catch-up</td>
<td></td>
</tr>
<tr>
<td>High risk individuals</td>
<td>✓</td>
<td>✓</td>
<td>4 doses at 2, 4, 6, 12–15 months</td>
<td></td>
</tr>
<tr>
<td>2–18 months at high risk</td>
<td>✓</td>
<td>✓</td>
<td>2 doses 12 weeks apart</td>
<td>2 mos–6 years: 3 years post primary; Every 5 years thereafter</td>
</tr>
<tr>
<td>9–23 months at high risk</td>
<td>✓</td>
<td>✓</td>
<td>2 doses 12 weeks apart</td>
<td>≥7 years: 5 years post primary; Every 5 years thereafter</td>
</tr>
<tr>
<td>2–55 years at high risk</td>
<td>✓</td>
<td>✓</td>
<td>2 doses 12 weeks apart</td>
<td></td>
</tr>
<tr>
<td>2–55 years students, travelers, etc</td>
<td>✓</td>
<td>✓</td>
<td>1 dose</td>
<td></td>
</tr>
<tr>
<td>≥56 years</td>
<td>✓</td>
<td>✓</td>
<td>MPSV4 (primary recommendation)</td>
<td>Every 5 years with MenACWY if the person remains at risk</td>
</tr>
</tbody>
</table>
Vaccine effectiveness of MenACWY-D: Case-Control Study in Adolescents*

- Vaccine effectiveness was 77% and 51% for serogroups C and Y, respectively. Vaccine effectiveness against serogroup W could not be calculated due to the low incidence.
- Effectiveness waned 3 to <8 years post-vaccination.
- The estimates of VE from this evaluation informed the ACIP in its decision to add a booster dose of MenACWY 5 years after the first dose.

Vaccinated $\geq$ 3-8 years 61% (25%-79%)
The “South-American” serogroup W evolution.

An expanding South American/UK MenW strain was distinct from the ‘Hajj outbreak’ strain.
Jay Lucidarme et al. Journal of Infection 2015

These data also demonstrate the co-circulation of W ST-11 strains in South America, UK and other regions that are phylogenetically and antigenically distinct from the Hajj clone
Mustapha M et al. Ebio Medicine, 2015

The Jamboree-associated cluster formed part of a novel strain, the proposed ‘2013-strain’, which emerged in the UK in 2013.
Emergence of serogroup W in UK

• In the light of the rapidly increasing W (cc11) disease from 2009/10 to 2014/15, ACWY conjugate vaccine was introduced in late 2015 for 13-18 years teenagers and university freshers and is intended to induce herd protection.

• A quarter of cases occurred in children aged <5 years, and half the cases in adults aged ≥45 years.
• 49% of the cases presenting with septicemia¹
• CFR of 33% in a subgroup of adolescents 15-19 years, with higher CFR among patients with GI symptoms²

No cases in adolescents vaccinated with MenACWY. Early estimated vaccine effectiveness was 100% (−47% - 100%).

- MenACWY coverage of 36.6% among persons who left school.
- During the first 12 months of the MenACWY vaccination program for teenagers, a 69% decrease (18%–88%) was observed.

Campbell H et al. Emerg Infect Dis. 2017 Jul
There is currently an outbreak of Meningococcal W (MenW) in Central Australia.

In response, six states have started a meningococcal ACWY vaccination program for individuals in affected communities. The programs target adolescents aged 15-19 years, with NSW targeting 17-18 year olds.

In the Netherlands, the incidence of meningococcal serogroup W disease increased substantially in 2015–16 compared with 2014–15, with an incidence rate ratio of 5.2 (95% CI 2.0–13.5) and 11% case fatality.

The outbreak started mainly among people aged 65 years and older, with an increase among 10–19 year olds in 2016.

MenC was replaced by MenACWY in adolescents to prevent further serogroup W cases and deaths.

Emergence of MenW in Canada

- Increase of MenW in Canada, associated with emergence of ST-11 CC.
- The % of Men W isolates varied from 2.7% in 2012 to 18.8% in 2016\(^1\)
- WGS: evidence of presence “Hajj-related” and non-Hajj MenW ST-11 CC (related to “South American sub-lineage strains”)\(^2\)

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Despite 71% MenACWY vaccine coverage, carriage of group W increased substantially. Majority belongs to MenW:ST-11 clone.
Meningococcus B capsule is a self antigen, poorly immunogenic and cannot be used for vaccination

- Structurally identical polysialic acid units in fetal neural tissue
- Poorly immunogenic\(^1,2\)
- No functional activity of vaccine-induced AB\(^3\)

A Multicomponent Approach to MenB Vaccination

<table>
<thead>
<tr>
<th>The polysaccharide capsule?</th>
<th>single subcapsular protein component</th>
<th>Multiple subcapsular components?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poorly immunogenic(^1)</td>
<td>Susceptible to antigenic variability(^2,3)</td>
<td>Enables broad coverage across a number of strains(^4)</td>
</tr>
</tbody>
</table>

Factor H (fH) binding protein (fHBP) vaccine - Pfizer

- **Virulence factor**
- Binds fH → down regulates alternative complement pathway
- 3 variant groups:
  - Variant 1 (family B),
  - Variants 2 and 3 (family A).
- Two lipidated LP2086 variants in Pfizer vaccine were selected (one from each subfamily)
- 2 doses: 0 – 6 months or 3 doses: 0, 1-2 and 6 months (10 – 25 years of age)
Are any of the 4CMenB components in the circulating strains:
   (i) expressed to a sufficient degree, and
   (ii) similar enough to the antigens in the vaccine such that the antibodies generated by 4CMenB will kill the bacteria?

MATS can determine the minimum amount of recognizable antigen needed to result in bacterial killing, for each of the four components*.

1. fHbp, NHBA and NadA assessments use ELISA → PHENOTYPIC
2. PorA assessment uses PCR sequencing → GENOTYPIC

*individually
### 4CMenB Vaccine Licensed Immunization Schedules

#### European Union

**Age Group** | **Primary Immunization** | **Interval Between Primary Doses** | **Booster**
--- | --- | --- | ---
2–5 months | 3 Doses | ≥1 month | 1 Dose age 12–15 mo*
6–11 months | 2 Doses | ≥2 months | 1 Dose in the 2nd year of life ≥2 mo post–primary series
12–23 months | 2 Doses | ≥2 months | 1 Dose 12–23 mo post–primary series
2–10 years | 2 Doses | ≥1 month | Need not established
11+ years | 1 Dose | ≥1 month | 1 Dose age 12–15 mo*

*In case of delay, the booster should not be given later than 24 months.

BEXSERO [summary of product characteristics]
Estimated Potential MenB Strain Coverage for specific countries based on MATS

# Impact of 4CMenB on carriage.

## 4CMenB secondary

Carriage prevalence and calculated efficacy for carriage of combined capsular groups BCWY or all *N. meningitidis* strains across cumulative later timepoints (Visits 4–6)

<table>
<thead>
<tr>
<th>Capsular group</th>
<th>Vaccine Groups</th>
<th>Efficacy % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4CMenB</td>
<td>Control</td>
</tr>
<tr>
<td>B, C, W, Y</td>
<td>Number</td>
<td>449</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>18.0%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>2489</td>
</tr>
<tr>
<td>Any *N.</td>
<td>Number</td>
<td>797</td>
</tr>
<tr>
<td>meningitidis</td>
<td>%</td>
<td>32.0%</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>2489</td>
</tr>
</tbody>
</table>

**4CMenB reduces nasopharyngeal carriage of *N. meningitidis* capsular group BCWY strains**

Non-significant trends for virulent B strains (12.6%; p=0.350) and all ST B strains (15.6%; p=0.225)

Analyses adjusted for baseline carriage, treatment group, centre and significant risk factors as identified within the multivariate model.

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Read R et al. ESPID 2013
CONCLUSIONS: No serogroup B meningococcal disease cases occurred in persons who received 1 or more doses of 4CMenB vaccine, suggesting 4CMenB may have protected vaccinated individuals from disease. However, the ninth case demonstrates that carriage of serogroup B *Neisseria meningitidis* among vaccinated persons was not eliminated.
Outbreak of serogroup B disease in Saguenay-Lac-Saint-Jean, Canada.

- Serogroup B (ST-269) clone emerged in Quebec, Canada.
- Incidence rate of 3.4/100,000 from 2006 to 2013.
- After vaccination of population (2 m-20 years) with 4CMenB decreases were, respectively 92% and 67%, in age-group ≤20 years and in those > 20 years
Meningococcal disease on US college campuses, 2013–17

2. MMWR Morb Mortal Wkly Rep. 2015
## UK Immunization Recommendations for Meningococcal Vaccines

<table>
<thead>
<tr>
<th>AGE</th>
<th>Immunisation (Vaccine Given)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>• MenB</td>
</tr>
<tr>
<td>4 months</td>
<td>• MenB</td>
</tr>
</tbody>
</table>
| Between 12 - 13 months | • Hib/MenC (combined as one injection); plus:  
  • MenB |
| 13-18 years | • Men ACWY - given to 17-18 year olds and first time students up to 25 years. |

MenACWY – recommended for travelers to Mecca for religious festivals of *Hajj or Umrah*
Impact:
Comparing with the pre-vaccine period, a 50% reduction in MenB incidence rates was observed in the cohorts eligible for vaccination (p=0.0001).

Effectiveness:
- One dose of the vaccine: 22% (95% CI –105 to 67,1).
- Two doses of the vaccine: 82,9% (95% CI 24,1–95,2).
- At least one dose of the vaccine: 64% (95% CI 8,9–84).

UK introduced the MenB vaccination in September 2015 for infants at two and four months of age, with a booster dose at 12-13 months (high coverage)

Lancet, online 27 October 2016

Cases and incidence rates increased in every age group except persons 15–19 years of age (31% reduction) and infants <1 year (35% reduction).
Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent *Neisseria meningitidis* W Strain, England

<table>
<thead>
<tr>
<th>Table. Bactericidal antibody titers in pooled serum samples from infants vaccinated with Bexsero and adolescents immunized with Mencevo against 6 invasive clinical <em>Neisseria meningitidis</em> serogroup W isolates in England and Wales, UK, during 2011–2012*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adolescents receiving Mencevo</td>
</tr>
<tr>
<td>Isolate</td>
</tr>
<tr>
<td>M11–240417</td>
</tr>
<tr>
<td>M11–240427</td>
</tr>
<tr>
<td>M11–240802</td>
</tr>
<tr>
<td>M12–240016</td>
</tr>
<tr>
<td>M11–240798</td>
</tr>
<tr>
<td>M12–240754</td>
</tr>
</tbody>
</table>

- Samples of infants vaccinated with Bexsero presented hSBA > 1/32 against W cc11 meningococcal strains.
Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study

Helen Petousis-Harris, Janine Paynter, Jane Mangan, Peter Saxton, Barbara McArdle, Felicity Goodyear-Smith, Steven Black

Findings 11 of 24 clinics nationally provided records. There were 14,730 cases and controls for analyses: 1241 incidences of gonorrhoea, 12,487 incidences of chlamydia, and 1002 incidences of co-infection. Vaccinated individuals were significantly less likely to be cases than controls (511 [41%] vs 6424 [51%]; adjusted OR 0.69 [95% CI 0.61–0.79]; p<0.0001). Estimate vaccine effectiveness of MenZB against gonorrhoea after adjustment for ethnicity, deprivation, geographical area, and sex was 31% (95% CI 21–39).
Considerations for the future with meningococcal vaccines:

- Booster doses in adolescents with conjugate vaccines.
- Use of the protein-based Men B vaccines.