Prevention of Meningococcal Disease

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Outline of the presentation

- Brief overview on the burden of MD
- Lessons learned with plain polysaccharide and conjugate vaccines
- New recombinant protein vaccines
- Global recommendations
**Neisseria meningitidis**

- Polysaccharide capsule (12 serogroups) A, B, C, Y, X and W...

**Clinical Syndromes associated with Meningococcal Disease**

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

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>7</td>
</tr>
<tr>
<td>Neurological impairment</td>
<td>4</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>2.6</td>
</tr>
<tr>
<td>Meningitis</td>
<td>2.1</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>0.5</td>
</tr>
<tr>
<td>Profound hearing loss</td>
<td>0.5</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.2</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1.0</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>0.6</td>
</tr>
<tr>
<td>Behavioral difficulties</td>
<td>0.6</td>
</tr>
<tr>
<td>Septicemia</td>
<td>21</td>
</tr>
<tr>
<td>Chronic pain</td>
<td>13</td>
</tr>
<tr>
<td>Skin scarring</td>
<td>13</td>
</tr>
<tr>
<td>Amputations</td>
<td>3</td>
</tr>
</tbody>
</table>
The low availability of data from low-income and middle-income countries suggests the need for improved surveillance before vaccination strategies are designed.
Annual number of cases and Incidence of Invasive Meningococcal Disease: Latin America.

Notified incidence rates/100,000 persons

- > 1
- 0.3 to 1
- <0.3
- Not reported

Lessons learned with Meningococcal Vaccines
<table>
<thead>
<tr>
<th>Property</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective in infants</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Immune memory</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Booster effect</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Reduction of carriage</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Contributes to herd effect</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Hyporesponsiveness with repeated dosing</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Carriage Rate and Effects of Vaccination after Outbreaks of Serogroup C Meningococcal Disease, Brazil, 2010

Marco Aurelio Palazzi Sáfadi, Telma Regina Marques Pinto Carvalharas, Ana Paula de Lemos,
Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 20, No. 5, May 2014

Overall meningococcal carriage

<table>
<thead>
<tr>
<th>Variable</th>
<th>% Workers exposed</th>
<th>% Workers not exposed</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antimicrobial drug use†</td>
<td>12.9</td>
<td>22.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Crowded living conditions</td>
<td>17.4</td>
<td>22.9</td>
<td>0.14</td>
</tr>
<tr>
<td>Active smoking</td>
<td>23.2</td>
<td>21.2</td>
<td>0.41</td>
</tr>
<tr>
<td>Respiratory symptoms†</td>
<td>24.2</td>
<td>20.9</td>
<td>0.28</td>
</tr>
<tr>
<td>Low level of education‡</td>
<td>32.9</td>
<td>19.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

*By Fisher exact test.
†in the 15 d before the collection of the nasopharyngeal sample.
‡Defined as not completing secondary education.
Impact of MenC Conjugate Vaccine on Disease Rates (UK)

Rapid, sustained and marked decline in the number of MenC cases, with evidence of herd immunity

Routine immunization of infants (2, 3 and 4 months) and “catch-up” of < 18 years

Age groups
- Red: 0 to 19 years
- Yellow: ≥20 years

Number of cases
- 0
- 50
- 100
- 150
- 200
- 250
- 300

Years
- 1995
- 1996
- 1997
- 1998
- 1999
- 2000
- 2001
- 2002
- 2003
- 2004

Trotter C. et al. Lancet, 2004
Impact of Men C vaccination - UK

Carriage rates
UK, 1999 a 2001

- Grupo C: 71% - Grupo W: 81%

Grupo B
Grupo Y

Confirmed cases
UK, 1999 - 2012

The campaign prevented ~13,000 cases and 1,300 deaths in UK

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
Importance of herd immunity on the impact of different strategies to prevent Men C disease.

Trotter CL et al. Am J Epidemiol 2005
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 routine Men C vaccination. Brazil, 2008-2014

Early impact on incidence rates of meningococcal disease observed only in the age groups targeted for vaccination.

Prevalence of carriage by serogroup

High carriage rates for serogroup C among adolescents of all age groups

Moraes JC; et al. Ped Infect Dis J, 2015
Increased incidence of MD in 2012 (from 0.4 to 0.8), associated to emergence of serogroup W (3 cases in 2010, 20 in 2011 and 60 in 2012).
Meningococcal Disease: Distribution by Serogroup. Chile, 1999 - 2014

Subtypes identified by sequencing variable regions of the gene encoding PorA in W135 isolates obtained during 2012 (n=60).

<table>
<thead>
<tr>
<th>Clonal complex</th>
<th>W135:P1.5,2</th>
<th>W135:P1.5,2-53</th>
<th>W135:P1.18-1,3</th>
</tr>
</thead>
<tbody>
<tr>
<td>ST-11</td>
<td>58</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>ST-22</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

W:2a: P1.5, 2 ST11 CC

Reactive MenW Immunisation action in Chile

• An immunisation 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).
• Coverage >95%.
• From 2014: 1 dose (MenACWY-TT) in toddlers at 12 months.

Impact of the MenACWY immunisation campaign in Chile, 2012-2014

- Reduction of 58% in the incidence rates of MD in children aged 1-5 years
- No impact on incidence rates of other age groups

Incidence rates (cases/1000)

Age (years)

Incidence rates (cases/1000)

- Pre-vaccine
- Post-vaccine

58% reduction
Number of cases of serogroup W MD. Chile, 2010 - 2014

Vaccination

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>5</td>
</tr>
<tr>
<td>2011</td>
<td>20</td>
</tr>
<tr>
<td>2012</td>
<td>40</td>
</tr>
<tr>
<td>2013</td>
<td>60</td>
</tr>
<tr>
<td>2014</td>
<td>80</td>
</tr>
</tbody>
</table>
The South-American/UK emergence of serogroup W

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

Mustapha M et al. Ebio Medicine, 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.
First implementation of MenA conjugate vaccination in Burkina Faso, Niger and Mali in December 2010
• 11 million people 1-29 years old vaccinated in 10 days. By Oct 2015 >217 millions vaccinated in 15 countries


Emergence of serogroup C and serogroup W disease in Africa.

- By June 2015, 8,500 suspected cases of MD in Niger, including 573 deaths. Most of the cases were serogroup C, ST-10217.

The predominant organism in Burkina Faso from 2012 was *N. meningitidis* serogroup W (62%), cc 11.
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\(^1,2\)

**N-propionylated polysaccharide conjugates**
- No functional activity of vaccine-induced antibodies \(^3\)
Antigenic Components of the 4CMenB Vaccine: Important for Meningococcal Survival, Function, or Virulence

- **NadA: neisserial adhesin A**
  - 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: neisserial heparin-binding antigen**
  - Binds heparin, which may increase the serum resistance of bacteria\(^6\)-\(^8\)

- **NZ PorA 1.4: porin A**
  - Major outer membrane vesicles protein – induces strain specific bactericidal response

<table>
<thead>
<tr>
<th>Dose</th>
<th>OMV</th>
<th>Al (^{3+})</th>
<th>287-953</th>
<th>936-741</th>
<th>961</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 ml</td>
<td>25 μg</td>
<td>0.5 mg</td>
<td>50 μg</td>
<td>50 μg</td>
<td>50 μg</td>
</tr>
</tbody>
</table>

Immunogenicity of 4CMenB in Infants

Percentage of infants with bactericidal titers (hSBA) ≥1:5

- 4CMenB was immunogenic in infants when given as a 3-dose primary series at 2, 4, and 6 months plus a booster at 12 months of age.

<table>
<thead>
<tr>
<th>Strain Antigen</th>
<th>44/76-SL fHbp</th>
<th>5/99 NadA</th>
<th>NZ98/254 PorA 1.4</th>
<th>M10713 NHBA†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>3 ± 1</td>
<td>4 ± 1</td>
<td>1 ± 1</td>
<td>33 ± 3</td>
</tr>
<tr>
<td>Post-primary*</td>
<td>82 ± 0</td>
<td>99 ± 0</td>
<td>84 ± 0</td>
<td>61 ± 0</td>
</tr>
<tr>
<td>Pre-booster</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>95 ± 0</td>
<td>84 ± 0</td>
</tr>
<tr>
<td>Post-booster†</td>
<td>100 ± 0</td>
<td>100 ± 0</td>
<td>98 ± 0</td>
<td>98 ± 0</td>
</tr>
</tbody>
</table>

*Blood drawn at 7 months, n=1,096–1,160; †Blood drawn at 13 months, n=209–211; ‡N=100.

Fever profile after three-dose primary immunization of 4CMenB in infants

- Rates of fever were comparable when 4CMenB and routine vaccines were given separately, but were increased when given concomitantly.

**Diagram:**

- **Group 1:** 4CMenB + Routine 2-4-6 mo (N = 605-624)
- **Group 2:** 4CMenB Alone 2-4-6 mo (N = 592-612)
- **Group 3:** Routine 3-5-7 mo (N = 602-627)
- **Group 4:** 4CMenB + Routine 2-3-4 mo (N = 310-317)

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

T ≥38.5° With or Without Prophylactic Paracetamol From Time of Each Vaccination

- Increase in T°C was reduced by prophylactic use of paracetamol.

Each vaccine group followed a 2-3-4 month accelerated dosing schedule.

*Routine vaccines: PCV7 and DTaP-HBV-IPV/Hib.
PP: prophylactic paracetamol; NPP: No PP.

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
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><strong>B, C, W, Y</strong></td>
<td>449</td>
<td>539</td>
</tr>
<tr>
<td><strong>Capsular group</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2489</td>
<td>2576</td>
</tr>
<tr>
<td><strong>Any N. meningitidis</strong></td>
<td>797</td>
<td>885</td>
</tr>
<tr>
<td><strong>Number</strong></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>2489</td>
<td>2576</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.

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.
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)
WHO Recommendations

• Countries with high (>10 cases per 100,000 population/year) or intermediate (2-10 cases per 100,000 population/year) endemic rates and/or frequent epidemics of invasive meningococcal disease:
  – conduct appropriate large scale meningococcal vaccination programmes.
  – The importance of conducting high quality surveillance and vaccination programme evaluation in these countries is also stressed.

• Countries where the disease occurs less frequently (<2 cases per 100,000 population/year):
  – meningococcal vaccination is recommended for defined risk groups.
  – Laboratory worker and travelers at risk of exposure should be vaccinated against the prevalent serogroup(s), and vaccination should be offered to all individuals suffering from immunodeficiency.

http://www.who.int/immunization/diseases/meningitis/en/
## Recommendation of meningococcal vaccination in USA (ACIP)

Men ACWY conjugate vaccine is routinely recommended for adolescents 11–21 years and high risk individuals.

### Age Group

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MenACWY-D</th>
<th>MenACWY-CK</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individuals 11–21 years</strong></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 1&lt;sup&gt;st&lt;/sup&gt; dose before 16&lt;sup&gt;th&lt;/sup&gt; 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><strong>High risk individuals</strong></td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–23 months at high risk</td>
<td>✓</td>
<td>✓</td>
<td>4 doses at</td>
<td>2 mos–6 years: 3 years post primary;</td>
</tr>
<tr>
<td>9–23 months at high risk</td>
<td>✓</td>
<td>✓</td>
<td>2 doses</td>
<td>Every 5 years thereafter;</td>
</tr>
<tr>
<td>2–55 years at high risk</td>
<td>✓</td>
<td>✓</td>
<td>2 doses</td>
<td>≥7 years: 5 years post primary;</td>
</tr>
<tr>
<td>2–55 years students, travelers, etc</td>
<td>✓</td>
<td>✓</td>
<td>1 dose</td>
<td>Every 5 years thereafter;</td>
</tr>
<tr>
<td>≥56 years</td>
<td>✓</td>
<td>✓</td>
<td>MPSV4</td>
<td>Every 5 years with MenACWY if the person remains at risk</td>
</tr>
</tbody>
</table>

MMWR, 2014
Persons considered at increased risk for Meningococcal Disease. US, ACIP

- Anatomical or functional asplenia or complement component deficiency.
- Persons receiving eculizumab for treatment of atypical hemolytic uremic syndrome or paroxysmal nocturnal hemoglobinuria
- First-year college students living in residence halls, military recruits, or microbiologists with occupational exposure
- Persons who travel to or reside in countries in which meningococcal disease is hyperendemic or epidemic, particularly if contact with the local population will be prolonged
- Vaccination of persons in at-risk groups to control outbreaks.

MMWR, June 12, 2015, Vol 64 #22 Use of Serogroup B Meningococcal (MenB) Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015 (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6422a3.htm)


MMWR, March 22, 2013, Vol 62, #RR02 Prevention and Control of Meningococcal Disease
# 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>3 months</td>
<td>• MenC</td>
</tr>
<tr>
<td>4 months</td>
<td>• MenB</td>
</tr>
<tr>
<td>Between 12 - 13 months</td>
<td>• Hib/MenC (combined as one injection); plus:</td>
</tr>
<tr>
<td></td>
<td>• MenB</td>
</tr>
<tr>
<td>13-18 years</td>
<td>• Men ACWY - given to 17-18 year olds and first time students up to 25 years.</td>
</tr>
</tbody>
</table>

**MenACWY** – recommended for travelers to Mecca for religious festivals of *Hajj* or *Umrah*
It is imperative that countries implement systems for epidemiological surveillance of MD in order to know its real magnitude and epidemiological profile.

Improve the quality of information and standardization of diagnostic laboratory techniques.

Countries with high burden of disease in young children that decide to introduce meningococcal conjugate vaccine as part of the routine immunization program targeting children aged <1 or <2 years should ideally include catch-up vaccination of children and adolescents, or at least of adolescents, given that this is the age-group with the highest carriage levels.
Key Learnings

• Dramatic reduction of disease incidence after immunization programs with Men C conjugate vaccines.

• Vaccine effectiveness wanes rapidly in young children and herd immunity is crucial for the success of Men C vaccination programs.

• New well tolerated and immunogenic multivalent conjugate vaccines are available, anticipating the possibility of a broaden protection against meningococcal disease.
Considerations for the future with meningococcal vaccines:

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