Meningococcal vaccines and Herd protection. Potential Role, Coverage and Impact on carriage of the New Serogroup B protein vaccines in the Region

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FUNCEI Buenos Aires - FIDEC Miami
Vaccines Board, Argentine Infectious Diseases Society (SADI)

Meningococcal Surveillance Effectiveness Workshop
Sao Paulo, August 11, 2015
FIDEC-FUNCEI

• FIDEC (Fighting Infectious Diseases in Emerging Countries)
  – Non profit organization, based in Miami, President Dr Daniel Stamboulian associated with University of Miami

• FUNCEI (Fundación Centro de Estudios Infectológicos)
  – Argentine Foundation based in Buenos Aires, President Dr Daniel Stamboulian, associated with several Argentine Universities

• Both organizations received grants from public and private institutions including pharmaceutical industry

• Speaker for GSK, Novartis & Pfizer
What have we learnt after the introduction of Men C conjugate vaccines?

- Immediate and long term impact of vaccination
- Reduction of carriage
- No evidence of replacement
- Evidence of herd protection
Impact on *N meningitidis* C carriage and Herd protection after Large Vaccination Program in UK

**Reduction in Carriage**

*(Immunized adolescents 15–19 years of age)*

<table>
<thead>
<tr>
<th>Year</th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meningococci (% of isolates)</td>
<td>3.0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

- **Serogroup C**
  - 71% reduction in 2000
  - 81% reduction in 2001

**Direct and Herd Protective Effect**

<table>
<thead>
<tr>
<th>Age groups</th>
<th>0–19 years</th>
<th>≥20 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Protection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herd Protection</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Herd protection was quantified as 67% and 75% after 1 & 2 years respectively.

Dynamic models of Meningococcal Carriage, Disease and the Impact of Serogroup C conjugate Vaccination

Years after vaccination

Number of cases

Infant
Toddler
Toddler + 12y
Infant + catch-up <18y

What do we expect from MenB proteins vaccines?

- Are proteins vaccines equally efficacy-effective as conjugated polysacharides vaccines?
- Does hSBA predict efficacy?
- How do we evaluate vaccine coverage?
MenB FHbp Vaccine Use 2 Conserved Antigens

FHbp: factor H binding protein
- Binds factor H, which enables bacterial survival in the blood

Two subfamilies of fHbp A and B
3 dose series 0-2-6 months
Approved by FDA from 10-25 years

Men B outbreak and Carriage evaluation in Rhode Island. Inc 44/10^5

- 3,525 students received first dose of MenB FHbp
- 717 participated in carriage evaluation 2 weeks after the first dose
  - Prevalence of Nm carriage 25%
  - None carried the outbreak strain

Possible explanations: lower propensity for carriage stage, chemoprophylaxis, and vaccine coverage.
4CMenB Vaccine Use 4 Conserved Antigens

**FHbp: factor H binding protein**
- Binds factor H, which enables bacterial survival in the blood

**NadA: neisserial adhesin A**
- Promotes adherence to and invasion of human epithelial cells
- May be important for colonisation

**NHBA: neisseria heparin-binding antigen**
- Binds heparin, which may promote bacterial survival in the blood
- Present in virtually all strains

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

<table>
<thead>
<tr>
<th>Dose</th>
<th>fHbp fusion protein</th>
<th>NadA protein</th>
<th>NHBA fusion protein</th>
<th>OMV</th>
<th>Al^{3+}</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5ml</td>
<td>50 mcg</td>
<td>50 mcg</td>
<td>50 mcg</td>
<td>25 mcg</td>
<td>0.5 mg</td>
</tr>
</tbody>
</table>
Effect of 4CMenB or Conjugated Men ACWY on Meningococcal Carriage in England

Consort

RCT. Observer Blind
10 centers in England
University students

2968 subjects enrolled

2954 randomised

14 not randomised*
   - 11 inappropriately enrolled
   - 2 withdrew consent
   - 1 protocol deviation/violation

979 assigned to 4CMenB
988 assigned to MenACWY-CRM
987 assigned to control

<table>
<thead>
<tr>
<th></th>
<th>4CMenB (N=979)</th>
<th>MenACWY-CRM (N=988)</th>
<th>Control (N=987)</th>
<th>Total (N=2968)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>19.9 (1.6; n=977)</td>
<td>19.9 (1.6)</td>
<td>19.8 (1.6)</td>
<td>19.9 (1.6; n=2966)</td>
</tr>
<tr>
<td>Men</td>
<td>463 (47%)</td>
<td>455 (46%)</td>
<td>440 (45%)</td>
<td>1369 (46%)</td>
</tr>
<tr>
<td>White</td>
<td>860 (88%)</td>
<td>876 (89%)</td>
<td>866 (88%)</td>
<td>2610 (88%)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>69.7 (13.2; n=973)</td>
<td>68.8 (13.4; n=985)</td>
<td>69.2 (13.5; n=986)</td>
<td>69.2 (13.4; n=2950)</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>172.6 (9.4; n=974)</td>
<td>172.5 (9.4; n=987)</td>
<td>172.0 (9.4; n=986)</td>
<td>172.4 (9.4; n=2953)</td>
</tr>
<tr>
<td>Smokers, n/N (%)†</td>
<td>159/974 (16%)</td>
<td>161/983 (16%)</td>
<td>143/984 (15%)</td>
<td>463/2941 (16%)</td>
</tr>
</tbody>
</table>

**Effect of 4CMenB or Conjugated Men ACWY on Meningococcal Carriage in England**

<table>
<thead>
<tr>
<th>Participants with carriage n/N (%; 95% CI)</th>
<th>Group difference (95% CI)*</th>
<th>Odds ratio (OR) (95% CI)</th>
<th>Carriage reduction, † % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4CMenB (N=974) Control (N=984) MenACWY-CRM (N=981) Control (N=984)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1 (baseline)</td>
<td>78/974 (8%; 6-10)</td>
<td>72/984 (7%; 6-9)</td>
<td>0.6% (-1.6 to 2.7)</td>
</tr>
<tr>
<td>1 month after second vaccination</td>
<td>87/916 (9%; 8-12)</td>
<td>75/928 (8%; 6-10)</td>
<td>1% (-1.5 to 3.5)</td>
</tr>
</tbody>
</table>

| Day 1 (baseline)                         | 58/981 (6%; 5-8)           | 49/984 (5%; 4-7)         | 0% (-0.4 to 0.4)              | NA | NA |
| 1 month after second vaccination         | 57/956 (6%; 5-8)           | 58/947 (6%; 5-8)         | -1% (-2.8 to 0.8)             | 0.9% (0.6-1.3) | 10.5% (-34.2 to 40.3) |

No significant impact on carriage at 1 month after full vaccination (co-primary endpoints)

### MenACWY-CRM Impacted Carriage Prevalence of CWY Combined

#### Ten study centers in England. University Students

<table>
<thead>
<tr>
<th>Serogroups</th>
<th>Vaccine Groups</th>
<th>Efficacy % (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C, W, Y</td>
<td>MenACWY-CRM</td>
<td>36.2% (15.6–51.7)</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>193</td>
<td>260</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3520</td>
<td>3504</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Serogroups</th>
<th>Vaccine Groups</th>
<th>Efficacy % (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
<td>MenACWY-CRM</td>
<td>39.0% (17.3–55.0)</td>
<td>0.6 (0.5–0.8)</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number</td>
<td>157</td>
<td>227</td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>5%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>3520</td>
<td>3504</td>
<td></td>
</tr>
</tbody>
</table>

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

N=number of swabs

Ten study centers in England. University Students

<table>
<thead>
<tr>
<th>B, C, W, Y Serogroups</th>
<th>Vaccine Groups</th>
<th>Efficacy % (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>4CMenB</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>N 2489 539</td>
<td>449</td>
<td>539</td>
<td>26.6%</td>
</tr>
<tr>
<td>% 18.0%</td>
<td>18.0%</td>
<td>20.9%</td>
<td>(10.5–39.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All N meningitidis</th>
<th>Number</th>
<th>Efficacy % (95% CI)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>4CMenB</td>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>N 2489 2576</td>
<td>797</td>
<td>885</td>
<td>18.2%</td>
</tr>
<tr>
<td>% 32.0%</td>
<td>32.0%</td>
<td>34.4%</td>
<td>(3.4–30.8)</td>
</tr>
</tbody>
</table>

Analyses adjusted for baseline carriage, treatment group and significant risk factors as identified within the multivariate model.
N=number of swabs

Summary of Clinical Findings from Carriage Study in England

• During the 1 year follow up both vaccines significantly reduced carriage of *N. meningitidis* but neither vaccine showed an immediate effect.

• Glyconjugated MenACWY demonstrated impact on carriage of vaccine serogroups and the effect is mainly by decreasing new acquisitions.

• 4CMenB has a broad effect, demonstrated impact on carriage of BCWY combined and all *N. meningitidis*, but no effect on B strains.
  - Effect enhanced among groups at high risk for transmission.
  - Trends observed in carriage impact and new acquisition of MenB strains but cases were small for conclusions.

• Overall results support a potential herd impact by both vaccines.

• Thus, for greatest effect, a vaccine programme might be initiated among early teens rather than university students.

• Both vaccines were well tolerated, with increased rates of transient local injection pain and myalgia in the 4CMenB group. No unexpected safety concerns were identified.

Antigens used in 4CMenB can be found in circulating strains.

For bacterial killing by antibodies induced by this vaccine, antigens have to be:

(i) Expressed to a sufficient degree

(ii) Similar enough to the antigens in the vaccine such that the antibodies generated by the vaccine will kill the bacteria

Sufficient expression of at least 1 antigen is enough for a strain to be killed.

PBT = Positive Bactericidal Threshold is defined for each antigen.

Meningococcal Antigen Typing System (MATS) can estimate the percentage of MenB strains in a region that are potentially covered by the Vaccine.
Predicted Coverage of 4CMenB in Brazil

Predicted coverage of Meningococcal B strains by number of 4CMenB antigens above Positive Bactericidal Threshold

Percent (%)

- 46.4% >2Ag
- 19.3% >1Ag
- 29.2% 0Ag
- 5.1% >3Ag

Vaccine Strain Coverage Estimates

Brazil: 81%
95% CI (71, 95)

Coverage based on MATS from pooled sera from 13-month-old infants, vaccinated at 2, 4, 6 and 12 months of age, tested on 99 strains isolated from year 2010, representing about 53% of serogroup B cases.

Predicted Coverage of 4CMB for Invasive Meningococcal Disease

Vaccine serogroup B coverage

Conclusions

• Standardized surveillance systems and carriage studies are mandatory

• Better understanding of the incidence, case fatality rates and prevalent serogroups in Latin America is needed

• The use of PCR for diagnosis and surveillance of IMD

• Vaccines with broader coverage and more immunogenicity are desirable in young infants

• Prevention strategies should include immunization of young infants and catch-up children and adolescents

• Combined meningococcal vaccines and coadministration is needed

(Pediatr Infect Dis J 2014;33:284–290)
Estudios de portación de *N meningitidis* en América Latina

- **México DF, N: 800**
  - Universitarios
  - 15 a 21 años
  - Tasa: 2,9 %

- **Bogotá, N: 1450**
  - 15 a 21 años
  - Tasa: 8,5 %

- **RM-Valparaíso-Bíobio, N: 4217**
  - 10 a 19 años
  - Tasa: 6,5 %

- **La Habana, N: 163**
  - Est universitarios (1999)
  - Tasa: 32%

- **San Pablo, N: 1231**
  - 11 a 19 años
  - Tasa: 9,9%

- **La Plata, N: 700**
  - 18 a 21 años
  - Tasa: 16 %

**Presentación ISP, Chile - Julio 2013 - Fuente: Proyecto PAHEF e Instituto Adolfo Lutz, San Pablo, Brasil**
Final Comments and Conclusions

• Prevention of Meningococcal Diseases is based on direct immunity and herd protection
• New proteins vaccines have proved to be safe and effective, at least for preventing carriage
• Effectiveness needs to be assessed after vaccine introduction in a systematic immunization program
• It is important to spread MATS methodology for a better understanding of strains vaccine coverage
• Our region should standardized surveillance systems in order to ensure best tools for decision making
Muchas Gracias!

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