The Future of Meningococcal Vaccination in LATAM

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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)

Ex.: C:P1.22,14-6 (ST-103)
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.

### Carriage rates of *N. meningitidis* by age groups in Campinas, Brazil, 2012

<table>
<thead>
<tr>
<th>Variable</th>
<th>Prevalence of carriage %</th>
<th>Chi-square test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9,8</td>
<td>0,028</td>
<td>0,866</td>
</tr>
<tr>
<td>Female</td>
<td>10,1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>School Nature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Public</td>
<td>11,3</td>
<td>7,834</td>
<td>0,005*</td>
</tr>
<tr>
<td>Private</td>
<td>5,8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Level of education</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>13,2</td>
<td>8,787</td>
<td>0,032*</td>
</tr>
<tr>
<td>Fundamental</td>
<td>10,3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basic</td>
<td>10,4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>5,6</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Agglomeration</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13,1</td>
<td>3,774</td>
<td>0,052</td>
</tr>
<tr>
<td>No</td>
<td>9,1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Previous vaccination</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5,2</td>
<td>5,165</td>
<td>0,023*</td>
</tr>
<tr>
<td>No</td>
<td>10,5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Passive smoking</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13,2</td>
<td>6,67</td>
<td>0,010*</td>
</tr>
<tr>
<td>No</td>
<td>8,4</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Disco/night clubs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>13,8</td>
<td>15,768</td>
<td>0,000*</td>
</tr>
<tr>
<td>No</td>
<td>5,8</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Influenza-like illness</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12,7</td>
<td>5,090</td>
<td>0,024*</td>
</tr>
<tr>
<td>No</td>
<td>8,5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Moraes JC; Safadi M; Bricks L et al. ESPID 2013
Meningococcal disease.

L.M., 15 months. Previously healthy. All vaccines updated. Started with fever 12 h ago, irritability and a rash. Evaluated in a ER that diagnosed allergy. After 1 h in observation she deteriorated with increased number of lesions. Reffered to Santa Casa. CSF normal, white blood cells -15.700. Shock, received volume in bolus, intubated, and admitted in the ICU
Meningococcemia.

Santa Casa SP
Sequelae (amputation) associated with Invasive Meningococcal Disease

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
</tr>
<tr>
<td>Neurological impairment</td>
<td>7</td>
</tr>
<tr>
<td>Hearing impairment</td>
<td>4</td>
</tr>
<tr>
<td><strong>Meningitis</strong></td>
<td></td>
</tr>
<tr>
<td>Hearing loss</td>
<td>2.6</td>
</tr>
<tr>
<td>Profound hearing loss</td>
<td>2.1</td>
</tr>
<tr>
<td>Seizures</td>
<td>0.5</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>1.6</td>
</tr>
<tr>
<td>Motor deficits</td>
<td>0.6</td>
</tr>
<tr>
<td>Behavioural difficulties</td>
<td>0.6</td>
</tr>
<tr>
<td><strong>Septicaemia</strong></td>
<td></td>
</tr>
<tr>
<td>Chronic pain</td>
<td>21</td>
</tr>
<tr>
<td>Skin scarring</td>
<td>13</td>
</tr>
<tr>
<td>Amputations</td>
<td>3</td>
</tr>
</tbody>
</table>

D. Pace, A.J. Pollard / Vaccine 30S (2012) B3–B9
Proportion of meningococcal disease by serogroup and region

Fig. 1. Proportion of meningococcal disease by serogroup by geographic region.
Incidence rates of Meningococcal Disease.

US

- During 2005–2011: ~ 800–1,200 annual cases of MD in US.
- 0.3 cases/100,000 pop.
- CFR: 10-15%
- Sequelae in 11-19% of survivors

Peaks in infants, adolescents and older adults

Cohn et al. CID, 2010; 50:184

MMWR, 2013
Serogroup distribution of meningococcal disease cases by country in Latin America, 2012.

Serogroup Distribution in Latin America - 2012

- B: 44
- C: 29
- W: 20
- Y: 5
Incidence rates of meningococcal disease by age groups – Latin America

Inc. rate
(per 100,000 hab.)

Argentina

Brazil

Colombia

Chile

CVE, 2010 Brazil
### Case fatality rates of meningococcal disease

CFR in selected countries:

- **Argentina**: 10 – 15% (2000-2010)
- **Brazil**: 18 - 21% (2000-2012)
- **Chile**: 26% (2012)
- **Panama**: 12.5% (2010)

[SINAN](http://epi.minsal.cl/epi/html/boletis/reporte/Meningitis/meningitis.pdf)
Saladi M et al. Epidemiol Infection 2013
The epidemiology of meningococcal disease in Latin America 1945–2010: an unpredictable and changing landscape

Chronological overview of epidemics and outbreaks in Latin America by serogroup.

- Central America
  - Mexico 1945 – ?
  - Costa Rica 1971 – C
  - Panama 1989/90 – ?

- Caribbean
  - Cuba 1983 – B
  - Trinidad 1993 – B

- South America
  - Brazil 1971 – C
  - Brazil 1987 – B
  - Uruguay 1993 – C
  - Bulgaria 2001 – B
  - Brazil 1995 – B/C
  - Brazil 1995 – B
  - Uruguay 2001 – B
  - Brazil 2009 – C
  - Brazil 2005 – W135
  - Argentina 2008 – W135
  - Chile 2006 – W135
Passive surveillance systems may underestimate the real burden of meningococcal disease.
Number of annual cases of Meningococcal Disease reported in Mexico. 2000-2010.
Active hospital-based surveillance of bacterial meningitis in < 16 years in Mexico.

*N. meningitidis* was the leading cause of BM.

High IR in < 1y (49/100,000) - Tijuana.

This study suggests that rates of IMD in Mexico may be substantially higher than reported.
Incorporation of Real-Time PCR into Routine Public Health Surveillance of Culture Negative Bacterial Meningitis in São Paulo, Brazil

N=499 patients whose CSF had >100 leukocytes/mm³ and > 60% neutrophils or blood or cerebrospinal fluid (CSF) culture positive for one of the three study organisms

Additional yield of 85%, 52% and 20% for detection of *N. meningitidis, S. pneumoniae and H. influenzae* with RT-PCR over culture-based results.

Lessons learned with Meningococcal Vaccines
Limitations of Polysaccharide Vaccines

Characteristics:¹

• Low immunogenicity in children <2 years (MenC)
• Induce short duration immune response, T-independent (IgM) without anamnestic response
• Partial and transient effect on carriage
• Diminished antibody responses after repeated vaccinations against serogroup C (hyporesponsiveness)

¹Safadi M, Pimentel A. J Ped, 2006;
What did we know at the time Meningococcal C conjugate vaccines were licensed?

Men C Conjugate Vaccines

- Protein carriers - CRM$_{197}$, TT – convert Polysaccharide in T-dependent antigen
- Immunogenic in all age groups, including infants
- Induce immunologic memory - avidity
- Adequate safety profile
Reduction in Carriage After Vaccination with MenC Conjugate – UK

Meningococcus (% of isolates)

Group C

-71%  -81%

Group W135

Group B

Group Y

Effectiveness of the MenC conjugate vaccine after 4 years according to age group when vaccinated

Effectiveness of the vaccine wanes rapidly in children vaccinated early in life, especially in infants.

# New Immunization Schedule – UK

**March 2006**

<table>
<thead>
<tr>
<th>Age (months)</th>
<th>Vaccine Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>DTaP/IPV/Hib + pneumococcal vaccine</td>
</tr>
<tr>
<td>3</td>
<td>DTaP/IPV/Hib + MenC vaccine</td>
</tr>
<tr>
<td>4</td>
<td>DTaP/IPV/Hib + MenC + pneumococcal vaccine</td>
</tr>
<tr>
<td>12</td>
<td>Hib/Men C</td>
</tr>
<tr>
<td>13</td>
<td>MMR + pneumococcal vaccine</td>
</tr>
</tbody>
</table>
...What about long term protection?

The role of immunologic memory, persistence of antibodies and herd immunity
Comparison of cases of serogroup C disease categorized as vaccine failures and unvaccinated cases

<table>
<thead>
<tr>
<th>Vaccine status</th>
<th>N</th>
<th>SBA GMT (95% CI)</th>
<th>Fold difference</th>
<th>Adjusted* fold difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure</td>
<td>31</td>
<td>3580 (1316 – 9734)</td>
<td>2.6</td>
<td>5.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Control</td>
<td>35</td>
<td>1378 (498 – 3812)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Auckland et al. JID, 2006
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.

Age (in months) at priming vaccination:

- < 6 m: 12%
- 5-11 m: 16%
- 12-23 m: 26%
- 24-35 m: 23%
- 36-47 m: 33%
- 48-59 m: 26%
- 60-83 m: 48%
## UK Decision for 2013:

<table>
<thead>
<tr>
<th>Vaccine/Age</th>
<th>2 months</th>
<th>3 months</th>
<th>4 months</th>
<th>12 m</th>
<th>13m</th>
<th>3-5 years</th>
<th>13-18 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria, Tetanus, Pertussis, Polio, Hib</td>
<td>DTaP-IPV-Hib</td>
<td>DTaP-IPV-Hib</td>
<td>DTaP-IPV-Hib</td>
<td></td>
<td></td>
<td>dTaP-IPV</td>
<td>dT-IPV</td>
</tr>
<tr>
<td>Meningococcal C vaccine</td>
<td>MenC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HIV-MenC</td>
<td></td>
</tr>
<tr>
<td>Measles, Mumps, Rubella</td>
<td></td>
<td></td>
<td></td>
<td>MMR</td>
<td>MMR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccine</td>
<td>PCV13</td>
<td>PCV13</td>
<td>PCV13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer (HPV)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HPVx3</td>
</tr>
</tbody>
</table>
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 MCC for all children < 2 years of age in 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 is planned at this moment
The rates of MD in children aged < 2 years declined from an average of 25.9/100,000 persons in the pre-vaccination baseline period to 18.8/100,000 in 2011 and 10.9 in 2012.

- Reduction of 27% and 55%, respectively, (p<0.01) in incidence rates of children < 2 y
Incidence rates before and after Men C vaccination. Brazil, 2008-1012

Impact in incidence rates of meningococcal disease observed only in the age groups targeted for vaccination.
New meningococcal vaccines
• Men A conjugate vaccine administered to more than 20 million individuals 1 to 29 years in 2010 and 35 million in 2011 (African meningitis belt)!!!

• A dramatic drop from 25% in 2010 to 0.4% of the meningitis cases in 2011, after vaccine introduction

## Recommendation of meningococcal vaccination in USA (ACIP)

### Routinely recommended for adolescents 11–18 years and high risk individuals.

<table>
<thead>
<tr>
<th>Age Group</th>
<th>MenACWY-D</th>
<th>MenACWY-CRM</th>
<th>Hib-MenCY-TT</th>
<th>Primary</th>
<th>Booster</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Individuals 11–21 years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11–12 years</td>
<td>✓</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></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></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>
<td></td>
</tr>
<tr>
<td>2–18 months at high risk</td>
<td>✓</td>
<td></td>
<td></td>
<td>4 doses at 2, 4, 6, 12–15 months</td>
<td></td>
</tr>
<tr>
<td>9–23 months at high risk</td>
<td>✓</td>
<td></td>
<td></td>
<td>2 doses 12 weeks apart</td>
<td></td>
</tr>
<tr>
<td>2–55 years at high risk</td>
<td>✓</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></td>
<td>1 dose</td>
<td>2 mes–6 years: 3 years post primary; Every 5 years thereafter</td>
</tr>
<tr>
<td>≥56 years</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>MPSV4 (primary recommendation)</td>
<td></td>
</tr>
</tbody>
</table>

MMWR, 2013
# Vaccine Effectiveness of MenACWY-D: Case-Control Study in Adolescents*

<table>
<thead>
<tr>
<th>Cases (N=157)*</th>
<th>Controls (N=180)</th>
<th>VE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccinated &lt;1 year</td>
<td></td>
<td>82% (54%-93%)</td>
</tr>
<tr>
<td>Vaccinated 1-2 years</td>
<td></td>
<td>80% (52%-92%)</td>
</tr>
<tr>
<td>Vaccinated ≥3-6 years</td>
<td></td>
<td>59% (5%-83%)</td>
</tr>
</tbody>
</table>

Incidence rates by age group of Meningococcal Disease in Chile. 1990-2012

Incidence (2011): 0.4 /100,000 hab.
(2012): Santiago – 1.1/100,000

Number of cases of W135 in 2012: 60
CFR: 26% (23% of the cases in infants)

Meningococcal Disease: Distribution by Serogroup. Chile, 1997 - 2012

Serogroup B
Serogroup C
Others (Y, W135)

## Case fatality rates of meningococcal disease. Chile, 2010 - 2013

### Tabla 1B. Letalidad por grupo etario

<table>
<thead>
<tr>
<th>Edad</th>
<th>n de fallecidos</th>
<th>n casos</th>
<th>Letalidad (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Menores de 5 años</td>
<td>5</td>
<td>28</td>
<td>17,9</td>
</tr>
<tr>
<td>5 a 19 años</td>
<td>2</td>
<td>7</td>
<td>28,6</td>
</tr>
<tr>
<td>20 a 60 años</td>
<td>8</td>
<td>17</td>
<td>47,1</td>
</tr>
<tr>
<td>Mayores de 60 años</td>
<td>4</td>
<td>8</td>
<td>50,0</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>60</td>
<td>31,7</td>
</tr>
</tbody>
</table>

![Graph showing case fatality rates by age group](image)

---

Gobierno de Chile / Ministerio de Salud

Moreno G. Rev Chilena Infect 2013
An immunization campaign with the tetravalent conjugate vaccine (Men ACWY), targeting children aged 9 months to < 5 years (approximately 1 million children), started in 2012. Coverage for the first dose of the vaccine was almost 100% for the targeted age group.

- CFR of serogroup W disease: 25%.
- 69% from metropolitan area
- 59% with meningococcemia
Vaccines against meningocococcus B
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 \(^3\)

Lack of immunogenicity of serogroup B OMV meningococcal vaccines against heterologous strains

Three doses of OMV vaccine made using the New Zealand strain; administered at 0, 6, and 12 weeks.

Reverse Vaccinology Allowed the Identification of Novel MenB Antigens

Based on the genome sequence of MC58, 600 ORFs that potentially encoded novel surface exposed or exported proteins were identified. Approximately 350 proteins successfully expressed in *E. coli*, purified, and used to immunize mice.

IHT-A

IHT-B

IHT-C

expression and purification

purified proteins

91 novel surface-exposed proteins identified

28 novel protein antigens with bactericidal activity were identified

immunizations
MATS Concept

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*

*individually

1. fHbp, NHBA and NadA assessments use ELISA → PHENOTYPIC
2. PorA assessment uses PCR sequencing → GENOTYPIC
MATS Allows for Systematic Estimation of 4CMenB Coverage for Any Given Region

Percent of strains predicted covered by number of 4CMenB antigens above PBT†

†Coverage based on MATS from pooled sera from 13-mo-old infants vaccinated at 2, 4, 6, and 12 mo of age tested.
**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)
Immunogenicity of three doses of rLP2086 vaccine in Adolescents against LP2086 variants
Tolerability of LP2086 Pfizer vaccine in adolescents

<table>
<thead>
<tr>
<th></th>
<th>60 µg</th>
<th>120 µg</th>
<th>200 µg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 (N=22)</td>
<td>2 (N=22)</td>
<td>3 (N=21)</td>
<td>1 (N=192)</td>
</tr>
<tr>
<td>38-0-38.4°C</td>
<td>0</td>
<td>1 (4.5%)</td>
<td>0</td>
<td>9 (4.6%)</td>
</tr>
<tr>
<td>38.5-38.9°C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>39.0-40.0°C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
</tbody>
</table>

Data are n (%).

Table 4: Frequency of fevers according to electronic diary within 7 days of vaccination, by dose (safety population)

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
Gracias!!!

Thanks!!!

Obrigado!!!