Development update on a new African pentavalent ACYWX conjugate vaccine

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F Marc LaForce
Serum Institute of India
Impact of *MenAfriVac*

- More than 250 million Africans vaccinated from 2010-2015
- Dramatic fall in cases of Group A meningococcal meningitis in every country after introduction
- No case of NmA reported in a vaccinated individual
- Herd protection achieved with carriage studies showing elimination of Group A Nm after immunization
- Birth cohort strategy to be started in 2016
Despite the success of MenAfriVac Sub-Saharan Africa remains a high-risk area for meningitis

- Baseline meningitis rates (outside epidemic years) are 10 to 100 times higher than US rates

- There is no pathophysiologic explanation why meningococci cause epidemics under dry and dusty conditions in Africa and not elsewhere

- As long as pathogenic Neisseria freely circulate in unprotected Sub-Saharan Africans the potential for major meningitis epidemics is always present
Non Group A strains cause epidemics

• Major W epidemic in Burkina Faso in 2002
  – Over 12,000 cases; incidence about 100/100,000

• Smaller W epidemics when analyzed, show local attack rates greater than 1 percent

• Moderate and geographically dispersed Men X epidemics
  – Over 4,000 cases in Niger in 2006

• Major Men C epidemics in Nigeria and Niger in 2014 and 2015
Developing an affordable polyvalent meningococcal conjugate vaccine for Africa

• The effort began in 2008 with a DFID funding opportunity

• Partnership between PATH and Serum Institute

Goal:

Develop and license a thermostable, affordable polyvalent meningococcal conjugate vaccine (ACYWX) for Africa
Early development issues

• SIIL faced major intellectual property issues since polyvalent meningococcal conjugate vaccines are heavily “patented”

• No published guidelines for Group X meningococcal vaccines
Process development and immunogenicity studies on a serogroup ‘X’ Meningococcal polysaccharide conjugate vaccine

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ABSTRACT

Meningococcal group X (MenX) is responsible for recent outbreaks of meningitis reported in sub-Saharan region of Africa. Although protective vaccines are available for meningitis, they are not effective against MenX. An efficacious, monovalent conjugate vaccine was designed against MenX and a fed-batch fermentation process was developed. The MenX polysaccharide (PS) was purified and yield estimated to be 15-fold higher than the reported elsewhere. Structure of MenX polysaccharide was confirmed by $^{1}H$, $^{13}C$ NMR spectroscopy analysis. Molecular weight of PS was found to be 310 kDa using HPLC-SEC coupled to refractive index (RI) detector. The MenX–Tetanus toxoid (TT) monovalent conjugate proved to be highly immunogenic in mice, and the bactericidal titers of MenX–TT conjugate were 10-fold higher than native PS. Increasing the dose of MenX–TT conjugate from 0.5 μg to 1.0 μg induced an 8-fold higher antibody titer as well as serum bactericidal titer. The current work suggests that the MenX–TT conjugate is a candidate vaccine against meningitis caused by Meningococcal group X strains.

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Product optimization

Fermentation/purification
• Yields of crude PS range from 600 mg/L (X) to 900 mg/L (Y and W).
• Purified PS yields 350 – 650 mg/L.

Conjugation
• New conjugation technology with conjugation yields between 20-35%.

Formulation/configuration
• Lyophilization – with stabilizers and adjuvated (aluminium phosphate, 125 µg Al$^{3+}$).
• Detailed stability studies on Men A and Men C.
Conjugation Scheme

CPPT Conjugation IP (PCT/US2010/061133) Exclusively Licensed to SIIL

Meningococcal Polysaccharide A / X

- Polysaccharide Sizing
- Activation of Ps with CPPT
  - Linker Addition
    - Linker Attached Polysaccharide
    - TT(Purified), EDC Addition
    - Reaction Monitoring - Quenching
  - Conjugate Purification

Meningococcal Polysaccharide C / Y / W

- Polysaccharide Sizing
- Activation of Ps with CPPT
  - Activated CRM Addition
    - Reaction Monitoring
  - Quenching
  - Conjugate Purification
## Target Product Profile

<table>
<thead>
<tr>
<th>Active (Lyophilized) Composition/Dose</th>
<th>Men/Poly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men A -TT</td>
<td>5 μg</td>
</tr>
<tr>
<td>Men C-CRM</td>
<td>5 μg</td>
</tr>
<tr>
<td>Men Y-CRM</td>
<td>5 μg</td>
</tr>
<tr>
<td>Men W-CRM</td>
<td>5 μg</td>
</tr>
<tr>
<td>Men X -TT</td>
<td>5 μg</td>
</tr>
<tr>
<td>Presentation</td>
<td>Lyophilized, 1 &amp; 5 Dose</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diluent / Dose</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Alum phosphate</td>
<td>125 μg / Dose (0.5 ml)</td>
</tr>
<tr>
<td>Vehicle</td>
<td>Sodium chloride in WFI</td>
</tr>
<tr>
<td>Preservative</td>
<td>No</td>
</tr>
</tbody>
</table>
## Immunogenicity Study

<table>
<thead>
<tr>
<th>Animal Model</th>
<th>New Zealand White Rabbits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>2-3 months, 800-1200 gm body weight</td>
</tr>
<tr>
<td>Rabbits per formulations</td>
<td>Six rabbits (3 males, 3 females)</td>
</tr>
<tr>
<td>Formulations</td>
<td>Licensed Comparator SIIL-F2, SIIL-F3, SIIL-F4</td>
</tr>
<tr>
<td>Injection volume</td>
<td>0.5 ml / dose</td>
</tr>
<tr>
<td>Route of immunization</td>
<td>IM</td>
</tr>
<tr>
<td>Immunization Schedule</td>
<td>Day 0, 14,28</td>
</tr>
<tr>
<td>Bleeding Schedule</td>
<td>Day 0, 28, 35</td>
</tr>
<tr>
<td>Immune response</td>
<td>IgG &amp; SBA</td>
</tr>
</tbody>
</table>
Immunogenicity in Rabbits – Men A and Men C SBA data
Immunogenicity in Rabbits – Men Y and Men W SBA data

[Graph showing GMT over time for Men Y serology and Men W serology]
Immunogenicity in Rabbits – Men X

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Summary

- A, C, Y, W polysaccharides comply to WHO specifications.
- The lyophilized Men A-TT and Men C-CRM conjugates showed excellent stability even when stored at 40 degrees C for six months.
- Rabbit SBA results show that the lead pentavalent candidate vaccine is equivalent or better than the licensed comparator for serogroups A, C, Y and W. The Men X Ps -TT conjugate generated high SBA titers.
- One and five dose presentations are being proposed for the pentavalent without preservative. All conjugates vaccine components are at 5 μg with 125 μg of alum per human dose.
Next steps

• First in Man Phase 1 study to begin in May 2016 at CVD/Maryland

• All other clinical studies to be done in Africa (9 months-29 years) and India (9 months-55 years)

• Expected licensure 2019-2020
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