A vaccine meets a strategy:

Eliminating epidemic meningitis from Sub-Saharan Africa

Dr. Bernard Guyer Lecture in Public Health
Center for Community Health and Prevention
University of Rochester Medical Center

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Disclosure

Dr. LaForce is employed by the Serum Institute of India where he serves as Director, Technical Services.
Meningitis belt in Sub-Saharan Africa

- Over 90 percent of global meningococcal disease occurs in the African meningitis belt.
- Until recently, one strain (Group A Nm) accounted for estimated 80% of all meningococcal cases.
- Focal epidemics occurred every year.
- Major epidemics occurred every 7-14 years.
Economic context in meningitis belt countries

- Poorest countries in the world
- Few natural resources
- Inhospitable arid climate
- Per capita income 1-2 dollars per day
- Families have little to no “disposable income”
Group A Nm meningitis in Bousse District (pop 134,000) - Burkina Faso Weeks 1-24, 2006

Total of 1003 cases of acute meningitis in 2006; incidence rate of 740 per 100,000
### Average district incidence rates per 100 000 in epidemic and non epidemic years (1994-2007)

<table>
<thead>
<tr>
<th>Country</th>
<th>Epidemic years</th>
<th>Non epidemic years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkina Faso</td>
<td>158 (54-353)</td>
<td>48 (18-115)</td>
</tr>
<tr>
<td>Mali</td>
<td>50 (1-141)</td>
<td>11 (0-29)</td>
</tr>
<tr>
<td>Niger</td>
<td>211 (10-834)</td>
<td>44 (2-118)</td>
</tr>
</tbody>
</table>

(In recent years US meningococcal incidence rates have ranged between 0.1 to 0.3 cases per 100,000 population)
Epidemic meningitis in Africa

Reported cases

Year

188,345
88,199
68,089
30,103
88,939
80,743
92,347
Flow of *Neisseria meningitidis* through a population

Transmission  
Release  
'Recovery'  
Colonisation  
Acquisition  
Invasion  
Disease

Courtesy Dr. Martin Maiden
Meningococcal structure: antigens for vaccines

Meningococcal capsular sugars are antigenic and were the basis for A/C polysaccharide (PS) vaccines developed in the 60s.

By 2005 a conjugate multivalent (A/C/Y/W) vaccine was developed for US and European markets.
# Properties of Meningococcal Vaccines

<table>
<thead>
<tr>
<th>Immunogenicity</th>
<th>Polysaccharide vaccines</th>
<th>Conjugate vaccines</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 year olds-adults</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Young children</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td><strong>Response to booster</strong></td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Quality of antibody in children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avidity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Bactericidal activity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Induction of memory</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Effect on colonization</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Availability of Meningococcal Vaccines for Sub-Saharan Africa in 2001

• Only A/C PS vaccines were available and were largely used in reactive campaigns.

• The reactive campaigns were expensive, largely ineffective, but politically necessary.

• There were no Pharma plans to develop a Group A Nm conjugate vaccine for Africa.
Creation of the Meningitis Vaccine Project

• The terrible 1996 meningitis epidemic in 1996 led African public health officials to ask WHO for help.

• Under WHO leadership international meetings were held in 2000 and 2001 that recommended that conjugate meningococcal vaccines be developed for Africa.

• In June 2001 MVP was created with Gates Foundation support as a 10 year partnership between WHO and PATH.

Goal: to eliminate epidemic meningitis in Africa as a public health problem through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines
Informing African partners while better understanding the problem – Fall 2001

• MVP discussions with African public health officials and WHO/AFRO (Harare, Niger, Burkina Faso, Nigeria) yielded consistent information

  • Cost of vaccine was the most important limiting factor to the introduction of new vaccines in Africa

  • Success of MVP (widespread use of a conjugate meningococcal vaccine in mass campaigns) would not be possible unless vaccines were priced less than $US 0.50 per dose
MVP negotiations with Pharma (01-02)

• Meetings with Chiron, Baxter and GSK (September 2001 – March 2002)

• Key issues in the negotiations included:
  • Vaccine price
  • Guaranteed purchase (effect of volume on price)
  • Investments to increase manufacturing capacity
  • Creating a “no risk” model
MVP becomes a virtual vaccine company in March 2002

• MVP could not reach an agreement with major vaccine manufacturers and negotiations ended in March 02

• Instead, MVP chose to become a virtual vaccine company to develop a Group A conjugate vaccine.

• Crucial elements in making this decision included
  • Inputs from African public health officials on the importance of a low vaccine price.
  • Availability of a business plan commissioned by WHO indicating that “cost of goods” for making 25-50 million doses of a Men A conjugate vaccine annually could be as low as $US 0.20 per dose.
Men A Vaccine development model

A PS produced by SynCo BioPartners, Amsterdam for initial development then transferred to Serum Institute of India

Serum Institute of India process development and manufacturing

Lyophilization and stabilization tech transfer from Aerial in France to Serum Institute

Target price US$ <0.50/dose

Conjugation method developed at CBER/FDA, Bethesda, USA, transferred and scaled-up at Serum Institute of India
Lee/Frasch (FDA) conjugation method

Derivatized TT (TTH)

Periodate activation of PsA

PsA-TT conjugate forms a “lattice” configuration
MVP Clinical Trials: A global effort
Geometric mean rSBA titers prior to and 28 days after a dose of Psa-TT or PsA vaccine (African trials in Mali, The Gambia and Senegal)

* Statistically significant
Potency and safety of vaccine

- Results from eight clinical trials showed that PsA-TT (10µg) when administered to African 1-29 year-olds
  - Was well tolerated and safe in any of the age groups evaluated (infants to 29-year-olds)
  - Was highly immunogenic
    - Superior immunogenicity vs. licensed PS vaccine
    - Induced immune memory
    - Bactericidal antibodies were sustained
  - Boosted anti-tetanus immunity
Licensure and Prequalification of PsA-TT

(*MenAfriVac™*)

- *MenAfriVac™* licensed by Drugs Controller General of India in December 2009.

- WHO prequalification awarded in June 2010.
Dec. 6, 2010 - Official launch day –
President of Burkina Faso
Official launch day – health workers
Burkina Faso campaign: 6-15 December

- **Target** population: 10,677,781 Burkinabes between 1 and 29 years of age

- **Duration** of the campaign: 10 days

- **Results**: 10.8 million persons immunized

*Very successful campaign with high acceptance!*
Meningitis cases by week – Burkina Faso
## 2011 bacteriologic data – Burkina Faso

<table>
<thead>
<tr>
<th>Category</th>
<th>No</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reported meningitis cases</td>
<td>3875</td>
<td></td>
</tr>
<tr>
<td>Number of CSF specimens</td>
<td>3412</td>
<td>88.1</td>
</tr>
<tr>
<td>Number of CSF sent for lab confirmation</td>
<td>3318</td>
<td>97.2</td>
</tr>
</tbody>
</table>

### Bacteriologic results (PCR, latex or culture)

<table>
<thead>
<tr>
<th>Status</th>
<th>No</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contaminated</td>
<td>609</td>
<td>18.3</td>
</tr>
<tr>
<td>Negative</td>
<td>1552</td>
<td>46.8</td>
</tr>
<tr>
<td>Positive</td>
<td>1157</td>
<td>34.9</td>
</tr>
<tr>
<td>Total</td>
<td>3318</td>
<td>100</td>
</tr>
</tbody>
</table>

### Distribution of pathogens (% based on positive samples)

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>No</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NmA</td>
<td>1</td>
<td>0.1%</td>
</tr>
<tr>
<td>NmX</td>
<td>161</td>
<td>13.9%</td>
</tr>
<tr>
<td>NmW135</td>
<td>110</td>
<td>9.5%</td>
</tr>
<tr>
<td>Nm indeterminant</td>
<td>2</td>
<td>0.2%</td>
</tr>
<tr>
<td>Pneumococcus</td>
<td>837</td>
<td>72.3%</td>
</tr>
<tr>
<td>Hib</td>
<td>43</td>
<td>3.7%</td>
</tr>
<tr>
<td>Other</td>
<td>3</td>
<td>0.3%</td>
</tr>
</tbody>
</table>
Reported meningitis cases with percent distribution of Group A meningococci
Burkina Faso, 2005-2012 (wk 26)

<table>
<thead>
<tr>
<th>Year</th>
<th>Cases</th>
<th>% Men A</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>3,626</td>
<td>11.6</td>
</tr>
<tr>
<td>2006</td>
<td>19,134</td>
<td>84.6</td>
</tr>
<tr>
<td>2007</td>
<td>26,878</td>
<td>91.1</td>
</tr>
<tr>
<td>2008</td>
<td>10,401</td>
<td>79.2</td>
</tr>
<tr>
<td>2009</td>
<td>4,723</td>
<td>30.1</td>
</tr>
<tr>
<td>2010</td>
<td>6,732</td>
<td>24.9</td>
</tr>
<tr>
<td><strong>Introduction of MenAfriVac in December 2010</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>3,875</td>
<td>0.4</td>
</tr>
<tr>
<td>2012 (wk 26)</td>
<td>5,987</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Carriage study results: Burkina Faso
Representative sampling of 1-29 year old Burkinabes

Dandé (rural)

Kaya (rural)

Bogodogo (urban)
Carriage of Group A *Neisseria meningitidis* before and after *MenAfriVac* campaign.
Observations on vaccine impact

**Consistent with vaccine derived herd immunity**

- Disappearance of Group A meningococcal meningitis
- Absence of Group A meningococci in carriage studies
Why such a powerful effect?

• The PsA-TT vaccine was a potent vaccine and very high coverage rates were attained.

• Background rates of Men A carriage in Burkina Faso were low at the time of introduction (about 0.4%).

• Immunity against Group A meningocococcus elevated in light of the 2006-2008 epidemic years that involved all districts.
Importance of Basic Reproductive Rate ($R_0$)

- The Basic Reproductive Rate ($R_0$) defines the transmission potential of an infectious agent. When $R_0$ falls to than 1 the agent in question disappears from a population

- $R_0 = c \cdot p \cdot d$
  - $c$ is no. of contacts per unit time (no vaccine effect)
  - $p$ is transmission rate per contact
  - $d$ is duration of infectiousness

- Study results
  - We know that PsA-TT blocks colonization; therefore $p$ falls
  - We think that PsA-TT shortens carriage (would also decrease $d$)

- Overall PsA-TT impact on $R_0 = c \cdot p \downarrow d \downarrow$
What happened? Impact of a conjugate vaccine on circulation of Group A meningococci

Transmission

Acquisition

Invasion

Release

Colonisation

'D Recovery'

Disease
A report card for the MenA vaccine

<table>
<thead>
<tr>
<th>Costs</th>
<th>$US (mil)</th>
<th>Savings</th>
<th>$US (mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing and testing the vaccine</td>
<td>100</td>
<td>Family costs saved over 10 years (1 million cases at $110/case) plus $10/month for disabled</td>
<td>240</td>
</tr>
<tr>
<td>Mass vaccination programs for 280 million persons ($1.40 pp)</td>
<td>390</td>
<td>Savings from no longer doing reactive campaigns (5 mil/year at $3.00 per person)</td>
<td>150</td>
</tr>
<tr>
<td>EPI coverage over 10 years (birth cohort about 12 million/year with vaccine at 0.50 per dose)</td>
<td>60</td>
<td>Country savings: clinical and laboratory costs ($60 per case)</td>
<td>60</td>
</tr>
</tbody>
</table>

100 million $US to prevent 1,000,000 cases and 200,000 disabilities.

Total                      | 550       |                               | 450       |
Remaining problems

• Non-A *N. meningitidis* cause epidemics

  • 2002 Group W epidemic in Burkina Faso (>10,000 cases)
  • 2004-6 Group X epidemics in Niger (>4,000 cases)
  • 2015-2018 Group C epidemics in Nigeria, and Niger (>16,000 cases)

*Urgent need for an affordable polyvalent meningococcal conjugate vaccine active against Groups C, Y, W and X strains*
Development of an ACYWX conjugate vaccine

- A new ACYWX meningococcal conjugate vaccine has been developed through a PATH/Serum Institute collaboration with funding from the UK’s Department for International Development (DFID).

- IND filed with US/FDA in 2016;
  - Phase 1 study in Baltimore completed in 2017.
  - Phase 2 study in Malian toddlers completed in 2018.

- ACYWX conjugate vaccine very immunogenic; no safety issues.
African challenges over the next 10 years

• Ensure that Men A conjugate vaccine is included as an EPI vaccine in meningitis belt countries.

• Maintain strong case based surveillance in selected countries and continue to improve epidemiologic and laboratory capabilities for all countries.

• Support WHO regional and country epidemic response activities.

• Assess introduction strategies for new Nm polyvalent vaccines.
In collaboration with Health Authorities of 26 countries in Sub-Saharan Africa and of India
KICK MENINGITIS
OUT OF AFRICA
The Meningitis Vaccine Project