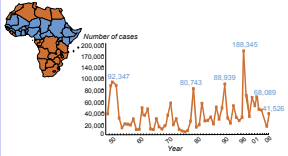
# Meningitis Vaccine Project

## Epidedemic Meningitis in Africa

- For over a century epidemic meningitis in Africa has caused death, disability, panic and major disruption to health and economic systems
- Annual outbreaks occur in hyperendemic countries; major epidemics every 10-12 years




## Immunization Strategies

- **Current recommended strategy based on detecting, confirming and vaccinating at-risk populations**
- **Based on intervention thresholds**
  - Alert threshold (5 cases/100,000/week) → confirmation of the serogroups
  - Epidemic threshold (15 cases/100,000/week) → mass immunization campaign

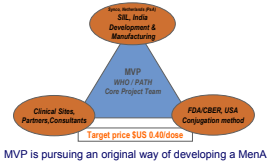
## The African request

- **The 1996 Men A meningitis epidemic was the largest outbreak of epidemic meningitis ever reported**
  - African ministers of health asked WHO for help
  - From 1998-2000 WHO sponsored scientific meetings to discuss the need to develop a preventive strategy using conjugate vaccines
  - 2001 proposal to the Gates Foundation

## Meningitis Vaccine Project

- The Meningitis Vaccine Project was created in June 2001 by a grant from the Bill & Melinda Gates Foundation as a 10-year *partnership* between WHO and PATH
- Goal of *eliminating epidemic meningitis as a public health problem* in sub-Saharan Africa through the development, testing, licensure, and widespread use of *conjugate* meningococcal vaccines

## MVP Vaccine Development Model




MVP is pursuing an original way of developing a MenA conjugate vaccine for Africa

- Attention to affordability and sustainability
- Partnership between WHO and PATH
- Local capacity building
- North → South technology transfer of new methods and skills
- South → South vaccine supply, capacity building & collaboration
- Commitment to developing country manufacturers as developers of new products

# A Phase II Safety and Immunogenicity Study of a New Meningococcal Group A Conjugate Vaccine in Healthy African Toddlers Residing in the Meningitis Belt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## PsA-TT Vaccine

### Men A Conjugate Vaccination Strategy

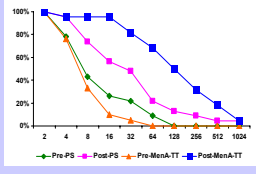
- **Mass vaccinations of 1-29 year olds with a single dose of Men A conjugate vaccine to induce strong herd immunity**
- **Protection of birth cohorts with Men A conjugate vaccine either**
  - **Follow-up campaigns every 5 years of 1-4 year olds or**
  - **Routine single dose at 15 months (12-18 months) or**
  - **Routine immunization in infancy**

➢**Technology transfer and scale up successful**

➢**Phase I study in Indian Adults**

**Safe and Immunogenic**

**Reverse Cumulative Distribution of hSBA Titers Pre and 4 weeks Post Immunization by Vaccine Group PsA-TT Phase I Study**



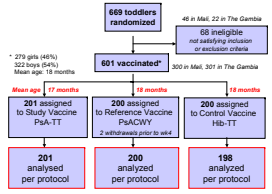

## PsA-TT-002 Phase II Clinical Trial Design:

### PsA-TT-002 Phase II, Ongoing

- Comparison of
  - Group A conjugate vaccine, PsA-TT
  - licensed PsA vaccine
  - Hib vaccine as control
- **Safety, Immunogenicity, Memory Induction and Antibody Persistence among toddlers12 to 23 months of age**
- Recruitment completed at two sites (Sept.-Nov. 2006)
  601 eligible toddlers received primary immunizations;
  *592 received booster immunizations (July-August 2007)*
  after parental consent
- No significant safety issue, high compliance for blood sampling
- As of 25 Sept 07: 11 SAEs - unrelated to the study vaccines

### Two Study Sites Located in Africa


### Study Profile for Week 4 Analysis




## PsA-TT-002 Safety in African Toddlers:

### Study Subjects Safety Profile at 4 Weeks after Immunization

| Type of Adverse Events | PsA-TT n/N | % | PsACWY n/N | % | Hib-TT n/N | % |
|---|---|---|---|---|---|---|
| Immediate Reactions (within 2 hours post-immunization) | 0/201 | 0 | 0/200 | 0 | 0/200 | 0 |
| Local Reactions (within 4 days post-immunization) | 27/201 | 13* | 10/200 | 5* | 19/200 | 10 |
| Systemic Reactions (within 4 days post-immunization) | 35/201 | 17 | 31/200 | 16 | 31/200 | 16 |
| Adverse Events (within 28 days post-immunization) | 77/201 | 38 | 66/200 | 33 | 59/200 | 30 |
| Serious Adverse Events** (up to 194 days + 7 months post-immunization) | 1/201 | 0.5 | 3/200 | 1.5 | 0/200 | 0.5 |

*P = 0.005 (more indurations reported in PsA-TT vs. PsACYW group in site 1-Mali)*
*** All SAEs were unrelated to the study vaccines*

### Local Reactions at Injection Site at 4 days Post-Immunization

| Local Reactions | | PsA-TT n/201 | % | PsACWY n/200 | % | Hib-TT n/200 | % |
|---|---|---|---|---|---|---|---|
| Tenderness | | 13 | 7 | 9 | 5 | 12 | 6 |
| Induration | All | 16 | 8* | 4 | 2* | 11 | 6 |
| (mm) | <5 | 12 | | 4 | | 8 | |
| | >5 | 2 | | 0 | | 1 | |
| | >20 | 2 | | 0 | | 1 | |
| | >50 | 0 | | 0 | | 1 | |
| At least one Reaction | | 35 | 17 | 31 | 16 | 31 | 16 |

** p = 0.01 more indurations in PsA-TT vs. PsACWY group. All were in site 1 (Mali), and were transient, mild (27/31 = 87%), and resolved without sequelae within 4 days from onset for 90% (28/31).*
*Tenderness was similar between vaccine groups, mild or moderate and resolved without sequelae within 3 days from onset.*

### Systemic Post-Immunization Reactions at 4 Days after Vaccination

| Systemic Reactions | PsA-TT n/201 | % | PsACWY n/200 | % | Hib-TT n/200 | % |
|---|---|---|---|---|---|---|
| Fever | 10 | 5 | 6 | 3 | 6 | 3 |
| Lethargy | 8 | 4 | 7 | 4 | 4 | 2 |
| Irritability | 5 | 3 | 5 | 3 | 3 | 2 |
| Vomiting | 3 | 2 | 7 | 4 | 4 | 2 |
| Diarrhoea | 20 | 10 | 21 | 11 | 20 | 10 |
| Loss of Appetite | 7 | 4 | 12 | 6 | 4 | 2 |
| At least one Reaction | 35 | 17 | 31 | 16 | 31 | 16 |

*All systemic reactions were similar between vaccine groups, resolved without sequelae within 5 days from onset (3 days from onset at maximum for some cases of diarrhoea). The most common systemic reactions were diarrhoea and fever. All fevers were < 39.5°C*

## PsA-TT-002 Immunogenicity in African Toddlers:

### rSBA

**Primary Endpoint:**

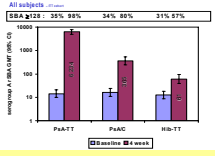
Non inferiority comparison of the proportion of subjects with ≥ four-fold rise in rSBA titer

**≥ 4-fold rise in serogroup A rSBA titre from week 0 to 4 – ITT cohort**

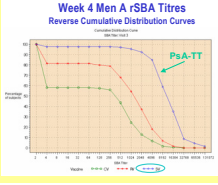
| Vaccine | N | 4-Fold Responders N | % | [95% Confidence Limit] |
|---|---|---|---|---|
| PsA-TT | 198 | 190 | 96 * | [ 92; 98 ] |
| PsACWY | 193 | 123 | 64 * | [ 57; 71 ] |
| Hib-TT | 194 | 69 | 36 | [ 29; 43 ] |

* Δ = p (PsACWY) – p (PsA-TT ) = -32% [ -40%; -26% ]
*Primary endpoint of non-inferiority achieved*

**Geometric Mean Men A rSBA Titres**
All subjects – ITT cohort




**Week 4 Men A rSBA Titres Reverse Cumulative Distribution Curves**

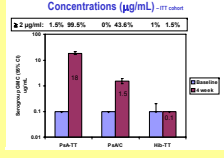



### Anti-PS IgG

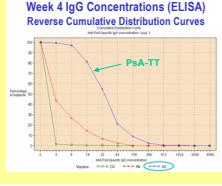
**≥ 4-fold rise in serogroup A-specific IgG concentrations from week 0 to 4 (ELISA) – ITT cohort**

| Vaccine | N | 4-Fold Responders N | % | [95% Confidence Limit] |
|---|---|---|---|---|
| PsA-TT | 198 | 197 | 99 | [ 97; 100 ] |
| PsACWY | 194 | 152 | 78 | [ 72; 84 ] |
| Hib-TT | 194 | 7 | 4 | [ 2; 7 ] |

**Serogroup A-specific IgG Geometric Mean Concentrations (µg/mL) – ITT cohort**




**Week 4 IgG Concentrations (ELISA) Reverse Cumulative Distribution Curves**




## Summary

➢**PsA-TT is highly immunogenic:** inducing rSBA titers more than 20 times higher than the currently available polysaccharide vaccine in young African children 12 to 23 months of age

➢**PsA-TT was safe:** local reactions were similar to the Hib-TT conjugate control, systemic symptoms were similar among all three vaccine groups and no serious adverse events were considered vaccine associated.

➢**PsA-002 initial phase results support continued development of this vaccine**

➢**The Meningitis Vaccine Project:** successfully supported and coordinated the development of a new meningococcal serogroup A conjugate vaccine

➢**Vaccination with PsA-TT vaccine will be affordable and sustainable**

➢**Infrastructure and expertise** development is incorporated into the MVP clinical development plan

➢**Goal:** successful elimination of epidemic meningococcal disease from the African Meningitis Belt. The strong immune responses shown here in the youngest target population suggest that the vaccination strategy planned will be successful