Background
Recurrent severe epidemics of meningococcal disease strike the meningitis belt extending from Senegal to Ethiopia where annual incidences can reach 1/100. A vaccine that induces long-lasting protection and herd immunity is needed (1). The Meningitis Vaccine Project (MVP) was created in 2001 by a grant from the Bill & Melinda Gates Foundation as a partnership between WHO and PATH to eliminate meningococcal epidemics in Sub-Saharan Africa through accelerated development and introduction of an affordable meningococcal group A (MenA) conjugate vaccine (2).

A new MenA conjugate vaccine (PsA-TT), manufactured by the Serum Institute of India Ltd, was found to be safe and immunogenic with durable immunity when tested in a Phase I study in Indian adults (3). In a phase II study among Gambian and Malian toddlers (12 to 23 months of age), the MenA conjugate vaccine elicited 20-fold higher serum bactericidal antibody (sBMA) titres than a licensed polysaccharide vaccine (PACWY) (4).

Here we report the results of the booster study performed 10 months later in Mali and The Gambia in the same toddlers between 22 and 33 months of age.

Methods
The study was conducted according to ICH-GCP and all applicable regulatory guidelines. Community permission and parents’ individual consent was obtained before vaccination. A total of 589 subjects aged 22 to 33 months received one dose of either the study, the reference or the control vaccine 10 months prior to booster. They were randomized in a 1:1:1 ratio to receive a single booster of iM of injection of either PsA-TT, 1/5 dose of Mencevax ACWY® or Hiberix® vaccine

Safety Results
After booster vaccination: rates of local and systemic reactions, Adverse Events (AEs), and Serious Adverse Events (SAEs) were similar in all nine groups that received the three vaccines. All SAEs were unrelated to the study vaccines (Table 1).

- There were no immediate serious reactions within the 30 minutes following booster vaccination. All local reactions were mild and transient (i.e. they resolved without sequelae within 2 days from their onset). Similar rates of local reactions were reported in both sites: 0.3% (1/297) of the subjects with at least one local reaction in site 1 (Mali) vs. 2% (2/92) of the subjects in site 2 (The Gambia).

- All systemic reactions resolved without sequelae within a maximum of 11 days from their onset. All fevers were <40°C. A total of 93 systemic reactions was reported for 67 subjects. More systemic reactions were reported in The Gambia (19% = 55/292 subjects with at least one systemic reaction) vs. site 1 (Mali) 8% = 12/159 subjects with at least one systemic reaction), p<0.05.

- All AEs were of mild or moderate intensity, except for one case of severe diarrhoea in the Hib-TT/Hib-ACWY group (Site 2 = The Gambia) which resolved within 5 days from onset. All children with these events had febrile seizures. The most common reported AEs were malaria, lower respiratory tract infections, skin infections and gastroenteritides. A total of 61 AEs were reported for 58 subjects. More AEs were reported in site 2 (The Gambia 17% = 50/292 subjects with at least one AE) vs. site 1 (Mali 3% = 8/297 subjects with at least one AE), p<0.05.

- Three SAEs, including one death, were reported between 10 and 90 days after the administration of the booster vaccination. They were unrelated to vaccination: one child died of complication of marasmus at 42 days; one child had a femur fracture at 75 days and recovered completely; and one child had a case of cerebral malaria at 87 days and fully recovered.

Immunogenicity Results
Antibody persistence at age 22 to 33 months was excellent in the group who received a single dose of the MenA conjugate vaccine a year earlier, as compared to the two other vaccine groups: Bacterial antibodies and anti-MenA IgG persisted at a sustained level in the PsA-TT vaccine group and remained above 20 times higher than those measured in the reference group, with virtually no MenA antibodies remaining 10 months after a single dose of PACWY polysaccharide vaccine received at age 12 to 23 months (Table 2, Figure 1).

The geometric mean titre (GMT) of PsA-TT was highly immunogenic at 7 and 28 days after the booster vaccination in both primed and naive children aged 22 to 33 months. Responses in terms of SBA Geometric Mean Titers (GMTs), 4-fold responders, and percentages of subjects above the 1:128 threshold were impressive in all PsA-TT vaccine groups including naive children aged 22 to 33 months (Figure 1B, Tables 3 and 4). The magnitude of the response at 7 days was greater in children primed with the PsA-TT as compared to those primed with the PACWY vaccine. In all groups, sBMA titres were significantly higher at 7 days compared to 0 days. This has been previously reported and attributed to the role of IgM in the early-vaccine-induced response, given that IgM are strong activators of the complement system but have a shorter half-life than IgG.

Immune memory: Significantly higher responses to a reduced dose (1/10th) of polysaccharide vaccine were found in children primed with the PsA-TT vaccine than in children who received the PACWY vaccine. geometric means of sBMA GMTs (4-fold responders and percentages of subjects above the 1:128 threshold), and also ELISA concentrations (4-fold responders and percentages of subjects above the 2 mcg/ml threshold).

Response tended to be lower among children primed with the PsA-TT vaccine than among naive children (Figure 2, Tables 3, 2 and 4). In all the three groups who received a booster dose of HbTT vaccine, sBMA titres showed a slight rising trend at 7 and 28 days, although not significantly so (Tables 2 and 3).

Conclusions
- Antibody persistence and boost responses elicited by the new vaccine are in accordance with the characteristic features of a conjugate vaccine.
- One dose of the new MenA conjugate vaccine administered in the second year of life is safe and effectively primes for immunological memory.
- It is expected that the widespread use of this vaccine in 1 to 29 year-olds will eliminate Group A meningitis epidemics from sub-Saharan Africa.

References

A Phase II, Observer-blind, Randomized, Controlled Study to Evaluate the Safety, Immunogenicity, and Memory of a Booster Dose of a Meningococcal A Conjugate Vaccine (MenAfriVac™) in Healthy African Children

Brown J Okolo, Samba Sow, Milagritos Tapia, Richard Adedjoli, Marie-Pierre Pratson, Elisa Marchetti, Fatima Chicack Haridar, Olubukola Iyako, Awa Traoré Dibembi, Julie Chalbumont, Yasha Parloka, Brian Pikayts, Hellen Fintion, Cheryl Ellis, Ray Bonrow, George Carlone, Jean-Mario Pratson, Prasad Kokumb, Saban Kapile, Soare Jathav, Massa Hassan King, Marc LaLonde, Simonaetta Viviani


Table 3: Group A sero-bacterial antibody titres (sBMA) Geometric Mean Titres (GMT) with 95% Confidence Interval at pre boost, 7 and 28 days post-booster, and 10 months post-primary vaccination (ITT).

Table 4: Group A sero-bacterial antibody titres (sBMA) GMT with 95% Confidence Interval at pre boost and 28 days post-booster (ITT)