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

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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 (rSBA) titres than a licensed polysaccharide vaccine (PsACWY) [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 injection of either PsA-TT, 1/5 dose of Mencevax ACWY® or Hiberix® vaccine (Figures I and II):

- Study Vaccine: PsA-TT vaccine (MenAfriVac™), produced by Serum Institute of India Ltd. One dose of 0.5 mL contains 10 µg meningococcal A polysaccharide conjugated to 10-20 µg Tetanus Toxoid, with Al[PO]4 as adjuvant.
- Reference vaccine: licensed meningococcal tetravalent polysaccharide vaccine (GSK Mencevax ACWY®), one dose of 0.5 mL contains 50 µg of each meningococcal polysaccharide ACWY.
- Control vaccine: licensed Hib-TT vaccine (GSK Hiberix®), one dose contains 10 µg of purified PRP capsular polysaccharide of Haemophilus influenzae type b conjugated to 20-40 µg of tetanus protein.

Safety was assessed through active follow-up. Immunogenicity was evaluated in terms of functional activity measured by the SBA assay using complement preserved from baby rabbit serum (SBA titres are expressed as the reciprocal of the final serum dilution giving ≥ 50% killing after 60 minutes), and Group A-specific IgG measured by standardized ELISA.

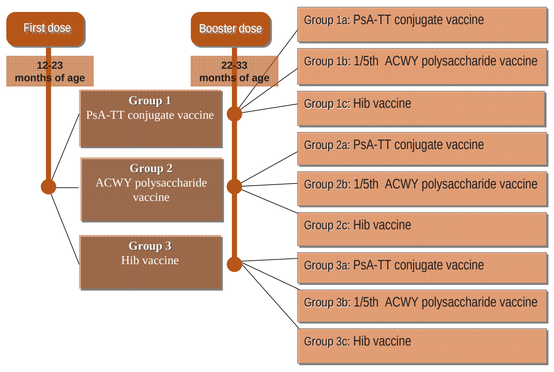


Figure 1. Vaccine administration overview

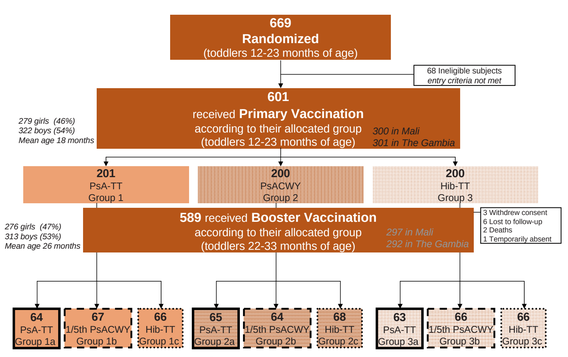


Figure 2. Study flow chart at booster vaccination (10 months post primary vaccination)

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% (5/292) of the subjects in site 2 (The Gambia).
- All systemic reactions resolved without sequelae within a maximum of 13 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 site 2 (The Gambia: 19%= 55/292 subjects with at least one systemic reaction) vs. site 1 (Mali: 4% = 12/297 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-TT group (Site 2 = The Gambia) which resolved within 5 days from onset. All resolved without sequelae. The most common reported AEs were malaria, lower respiratory tract infections, skin infections and gastroenteritis. 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 within the first 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 at age 12 to 23 months, as compared to the two other vaccine groups. Bactericidal antibodies and anti-MenA IgG persisted at a sustained level in the PsA-TT vaccine group and remained more than 20 times higher than those measured in the reference group, with virtually no MenA antibodies remaining 10 months after a single dose of the PsACWY polysaccharide vaccine received at age 12 to 23 months (Table 2, Figure IIIa).

Immunogenicity: PsA-TT was highly immunogenic at 7 and 28 days after the booster vaccination in both primed and naïve children aged 22 to 33 months. Responses in terms of rSBA 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 naïve children aged 22 to 33 months (Figure IIIb; Tables 2 and 3). The magnitude of the response at 7 days was greater in children primed with the PsA-TT as compared to those primed with the PsACWY vaccine. In all groups, rSBA titres were significantly higher at 7 days compared to 28 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 (1/5th) of polysaccharide vaccine were found in children primed with the PsA-TT vaccine than in children who received the PsACWY vaccine, in terms of rSBA GMTs (4-fold responders and percentages of subjects above the 1:128 threshold), and also ELISA Geometric Mean Concentrations (4-fold responders and percentages of subjects above the 2 mcg/ml threshold). Responses tended to be lower among children primed with the PsACWY vaccine than among naive children (Figure III; Tables 2, 3 and 4).

In all three groups who received a booster dose of Hib-TT vaccine, rSBA titres showed a slightly rising trend at 7 and 28 days, although not significantly so (Tables 2 and 3).

Table 1. Overall participant safety profile at 4 weeks after the booster vaccination

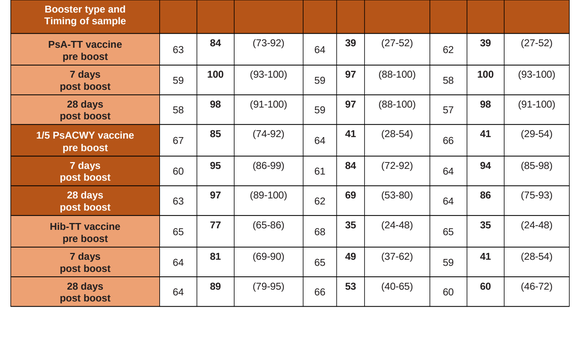
Primary vaccination	PsA-TT vaccine (N = 201)						PsACWY vaccine (N = 200)						Hib-TT vaccine (N = 200)					
Booster vaccination	PsA-TT (n= 64)		PsACWY (n= 67)		Hib-TT (n= 66)		PsA-TT (n= 65)		PsACWY (n= 64)		Hib-TT (n= 68)		PsA-TT (n= 63)		PsACWY (n= 66)		Hib-TT (n= 66)	
Type of Adverse Event Post-immunization	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)	n	% (95%CI)
Immediate Serious Reaction within 30 minutes	0	0 (0-6)	0	0 (0-5)	0	0 (0-5)	0	0 (0-6)	0	0 (0-6)	0	0 (0-5)	0	0 (0-6)	0	0 (0-5)	0	0 (0-5)
Local Reaction within 4 days	2	3 (0-11)	0	0 (0-5)	0	0 (0-5)	1	2 (0-8)	0	0 (0-6)	1	2 (0-8)	1	2 (0-9)	0	0 (0-5)	1	2 (0-8)
Systemic Reaction within 4 days	8	13 (6-23)	8	12 (5-22)	4	6 (2-15)	6	9 (4-19)	1 1	17 (9-29)	4	6 (2-14)	1 2	19 (10-31)	5	8 (3-17)	9	14 (6-24)
Adverse Event within 28 days	4	6 (1-13)	5	8 (3-17)	5	8 (3-17)	7	11 (4-21)	6	9 (4-19)	7	10 (4-20)	6	10 (4-20)	1 2	18 (10-30)	6	9 (3-19)
Serious Adverse Event within 28 days	0	0 (0-6)	1	2 (0-8)	0	0 (0-5)	0	0 (0-6)	0	0 (0-6)	1	2 (0-8)	0	0 (0-6)	0	0 (0-5)	1	2 (0-8)

Table 2. Group A serum bactericidal antibody titres (rSBA): ≥ 4-fold rise (percentage with 95% Confidence Interval) at pre-boost, 7 and 28 days post booster, and 10 months post primary vaccination (ITT).

Type of Primary Vaccination	PsA-TT vaccine (n = 201)			PsACWY vaccine (n = 200)			Hib-TT vaccine (n = 200)		
	N	%	(95%CI)	N	%	(95%CI)	N	%	(95%CI)
Booster type and Timing of sample									
PsA-TT vaccine pre boost	63	84	(73-92)	64	39	(27-52)	62	39	(27-52)
7 days post boost	59	100	(93-100)	59	97	(88-100)	58	100	(93-100)
28 days post boost	58	98	(91-100)	59	97	(88-100)	57	98	(91-100)
1/5 PsACWY vaccine pre boost	67	85	(74-92)	64	41	(28-54)	66	41	(29-54)
7 days post boost	60	95	(86-99)	61	84	(72-92)	64	94	(85-98)
28 days post boost	63	97	(89-100)	62	69	(53-80)	64	86	(75-93)
Hib-TT vaccine pre boost	65	77	(65-86)	68	35	(24-48)	65	35	(24-48)
7 days post boost	64	81	(69-90)	65	49	(37-62)	59	41	(28-54)
28 days post boost	64	89	(79-95)	66	53	(40-65)	60	60	(46-72)

Table 3. Group A serum bactericidal antibodies (rSBA): Geometric Mean Titres (GMT with 95% Confidence Interval) at pre-boost, 7 and 28 days post-booster, and 10 months post primary vaccination (ITT).

Type of Primary Vaccination	PsA-TT vaccine (n = 201)			PsACWY vaccine (n = 200)			Hib-TT vaccine (n = 200)		
	N	GMT	(95%CI)	N	GMT	(95%CI)	N	GMT	(95%CI)
Booster type and Timing of sample									
PsA-TT vaccine pre boost	63	1131	(666-1919)	64	43	(21-88)	63	43	(20-89)
7 days post boost	59	21721	(17706-26646)	59	12214	(9436-15811)	59	14063	(10940-18079)
28 days post boost	58	10037	(7885-12778)	59	6709	(5098-8830)	58	9343	(7044-12392)
1/5 PsACWY vaccine pre boost	67	1736	(1136-2651)	64	61	(28-133)	66	66	(31-142)
7 days post boost	60	8679	(7135-10557)	61	2295	(1800-2925)	64	4419	(3281-5951)
28 days post boost	63	5048	(4144-6150)	62	692	(380-1262)	64	1562	(958-2548)
Hib-TT vaccine pre boost	65	801	(458-1403)	68	41	(20-82)	66	51	(24-112)
7 days post boost	64	1448	(918-2284)	65	103	(51-209)	59	76	(35-165)
28 days post boost	64	1649	(1023-2659)	66	191	(91-399)	60	268	(128-562)



A. Pre boost MenA rSBA Titres RCD

B. 28 days Post boost MenA rSBA Titres RCD

Vaccine Groups: ***H*** *= Hib-TT (Hiberix®),* ***M*** *= PsACWY (Mencevax®),* ***P*** *= PsA-TT (MenAfriVac®)*

HH = Hib-TT/Hib-TT, **MH** = PsACWY /Hib-TT **PH** = PsA-TT/Hib-TT
HM = Hib-TT/PsACWY **MM** = PsACWY /PsACWY **PM** = PsA-TT/PsACWY
HP = Hib-TT/PsA-TT, **MP** = PsACWY /PsA-TT, **PP** = PsA-TT/PsA-TT

Figure 3. rSBA Reverse Cumulative Distribution Curves pre- and 28 days post booster

Table 4. Group A Serum IgG (ELISA): Geometric Mean Concentration (GMC with 95% Confidence Interval) at pre boost and 28 days post boost (ITT)

Type of Primary Vaccination	PsA-TT vaccine (n = 201)			PsACWY vaccine (n = 200)			Hib-TT vaccine (n = 200)		
Type of Booster Vaccination	N	GMC	(95%CI)	N	GMC	(95%CI)	N	GMC	(95%CI)
Timing of Sample									
PsA-TT vaccine pre boost	63	1.1	(0.8-1.4)	64	0.4	(0.3-0.5)	63	0.1	(0.1-0.2)
28 days post boost	58	38.2	(25.5-57.2)	59	38.1	(29.7-48.9)	58	15.4	(11.7-20.2)
1/5 PsACWY vaccine pre boost	67	1.1	(0.8-1.5)	64	0.5	(0.3-0.7)	65	0.1	(0.1-0.2)
28 days post boost	63	15.0	(11.6-19.4)	62	3.2	(2.0-5.1)	64	1.8	(1.2-2.6)
Hib-TT vaccine pre boost	65	1.0	(0.7-1.4)	68	0.5	(0.3-0.6)	65	0.2	(0.1-0.2)
28 days post boost	64	1.1	(0.7-1.6)	66	0.5	(0.3-0.6)	60	0.2	(0.1-0.2)

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

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