

Safety and Immunogenicity of a Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-DT): A Multicenter, Open-label, Non-randomized, Phase III Clinical Trial

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Objective: To assess the safety and immunogenicity of a quadrivalent meningococcal (groups A,C,Y,W) polysaccharide diphtheria toxoid conjugate vaccine (MenACYW-DT) in India.

Design: Open-label, descriptive, non-randomized study.

Setting: Three medical college hospitals, one each in New Delhi, Bengaluru and Mumbai, India.

Participants: 300 healthy, vaccine-naïve participants (100 children aged 2-11 years, 100 adolescents aged 12-17 years, and 100 adults aged 18-55 years).

Intervention: One dose (0.5 mL) of MenACYW-DT administered intramuscularly.

Main outcome measures: Serum bactericidal antibody titers against A, C, Y, and W were measured before and after MenACYW-DT vaccination. Safety data were also collected

Results: Thirty days post-vaccination, geometric mean titers rose across all serogroups. Most participants had protective titers ≥ 8 (1/dil) across the four serogroups. The percentage (95% CI) achieving ≥ 8 (1/dil) in the Adolescent Group was typical – A: 96.9% (91.2%; 99.4%); C: 96.9% (91.2%; 99.4%); Y: 100% (96.3%; 100%); W: 100% (96.3%; 100%). In general, solicited reactions were mild and short-lived. Unsolicited events were uncommon and unrelated to vaccination.

Conclusions: MenACYW-DT was well tolerated and elicited a robust and protective immune response 30 days post-vaccination against meningococcal serogroups A, C, Y, and W-135 in the Indian study participants aged 2-55 years.

(Trial registration No. ClinicalTrials.gov NCT01086969).

Keywords: Efficacy, Immunization, *Neisseria meningitidis*, Protection, Vaccine.

Meningococcal disease is responsible for considerable morbidity and mortality worldwide. The case-fatality rate is above 10%, and up to 20% of survivors suffer substantial neurological sequelae [1-3]. In India, endemic disease is relatively low, but pyogenic meningitis is associated with up to 3% of acute admissions to pediatric hospitals [4]. This is probably an underestimate given the difficulty verifying *Neisseria meningitidis* disease involvement. Sinclair, *et al.* [4] reviewed the reports of meningococcal disease in India and showed that four meningococcal disease epidemics have occurred since 1930; the bulk of the disease in these epidemics and in other cases reported during non-epidemic periods was caused by serogroup A strains [4].

Vaccination offers effective protection against meningococcal illness targeting the key polysaccharide antigens in clinically relevant meningococcal serogroups:

A, C, Y, and W-135; however, PS vaccines are poorly immunogenic in those below 2 years of age and elicit a T-cell-independent immune response that provides neither a memory response nor antibody affinity maturation. Repeated PS vaccine dosing may lead to reduced immunogenicity known as hypo-responsiveness [1].

Accompanying Editorial: Pages 445-8.

MenACYW-DT, a vaccine composed of polysaccharide antigens A, C, Y and W-135, separately conjugated to diphtheria toxoid (Menactra, Sanofi Pasteur Inc., Swiftwater PA, USA) was licensed in the US in 2005 for those aged 9 months to 5 years. MenACYW-DT confers direct protection as good as polysaccharide vaccines but can also promote an anamnestic response and reduce acquisition of *N. meningitidis* virulent strains and transmission [3]. Circulating antibody levels were shown to be higher among adolescents 3 years after

receiving a conjugate vaccine than among those given polysaccharide vaccines [1,5]. Results indicate that MenACYW-DT produces serogroup-specific protective titers in 86%-100% of 9- to 12-month-old children [6] and nearly universal protection among adolescents [5]. Serious adverse events are uncommon and rarely linked to vaccination [6,7]. A second conjugated quadrivalent meningococcal vaccine, MenACYW-CRM (Menveo; Novartis Vaccines and Diagnostics), was also recently licensed in the US.

We report on an open-label study conducted in India to assess the safety and immunogenicity of a single dose of MenACYW-DT in participants 2 to 55 years of age.

METHODS

The trial followed the Declaration of Helsinki (Edinburgh revision) and Good Clinical Practice defined by the International Conference on Harmonization. The final protocol was approved prior to the start of the trial by the relevant committees at the three study sites: Institutional Ethics Committee of Maulana Azad Medical College (New Delhi), Kempegowda Institute of Medical Sciences (Bangalore), and Lokmanya Tilak Municipal Medical College and Lokmanya Tilak Municipal General Hospital (Mumbai). Participants or their parents were approached during a routine visit at the investigational site by a site employee (unaffiliated with the investigator or investigation team) and their relatives were solicited to participate. All potential, eligible, participants or their parents were invited to visit the sites where the study was explained in detail. At this point, informed consent was explained, and forms signed prior to participation.

This multicenter, open-label, non-randomized, phase III clinical trial assigned participants to one of three cohort groups: children aged 2-11 years (Child Group), adolescents aged 12-17 years (Adolescent Group), and adults aged 18-55 years (Adult Group). One objective was to describe titers of the Serum bactericidal assay in the presence of baby rabbit complement (SBA-BR) prior to and 30 days after a single dose of MenACYW-DT. Another objective was to describe the safety profile of participants after receiving 1 dose of MenACYW-DT. Participants received in the deltoid a single 0.5 mL dose of MenACYW-DT (Lot U3091AA) containing 4 µg of each of the polysaccharides (A, C, Y, and W-135) conjugated to ~48 µg diphtheria toxoid protein carrier in phospho-buffered saline.

Healthy participants were eligible if they could attend all scheduled visits and comply with procedures. Key exclusion criteria were known or suspected pregnancy, participation in another clinical trial in the within 4 weeks

preceding or after MenACYW-DT immunization, receipt or planned receipt of any vaccine within 4 weeks of trial vaccination (other than influenza vaccine given ≥ 2 weeks before trial vaccination), and documented history of invasive meningococcal diseases [9]. Febrile illness or moderate/severe acute illness/infection on the day of vaccination or antibiotic therapy received ≤ 72 hours prior to any blood draw were contraindications delaying vaccination until resolution.

Sera were collected before immunization and ~30-35 days post-vaccination. SBA-BR were performed by Sanofi Pasteur Global Clinical Immunology laboratories (Swiftwater, PA, USA) as per standard methodology [6,10].

Participants were observed for 30 minutes post-vaccination for reactions and to treat immediate adverse events. On Day 1 and the next 7 days, participants graded and recorded solicited adverse reactions. For injection site swelling and erythema for those aged 2-11 years, the grading criteria were Grade 1 < 2.5 cm, Grade 2 ≥ 2.5 cm and < 5 cm, and Grade 3 ≥ 5 cm. For injection-site swelling and erythema for those aged ≥ 12 years, criteria were Grade 1 ≥ 2.5 cm to ≤ 5 cm, Grade 2 ≥ 5.1 cm to ≤ 10 cm, Grade 3 > 10 cm. Injection-site pain was recorded as Grade 1, easily tolerated; Grade 2, discomfort interfering with usual activities; and Grade 3, unable to perform usual activities. Fever was graded as Grade 1 ($\geq 38.0^\circ\text{C}$ and $\leq 38.4^\circ\text{C}$), Grade 2 ($\geq 38.5^\circ\text{C}$ and $\leq 38.9^\circ\text{C}$), and Grade 3 ($\geq 39.0^\circ\text{C}$). Headache, malaise, and myalgia intensity was graded as Grade 1, noticeable discomfort without interference with daily activities; Grade 2, interferes with daily activities; Grade 3, prevents daily activities.

For three consecutive days post-vaccination, participant/guardians were contacted by telephone to report all collected safety information. Information on solicited or unsolicited adverse events occurring over the first 7 days was collected during a house visit 8-10 days post-vaccination. Participants/guardians were asked to record information on other medical events 30 days post-vaccination. Data were collected and collated by electronic data capture system, and Medical Dictionary for Regulatory Activities (MedRA) preferred nomenclature described all adverse events. These were "serious" if life threatening, required hospitalization or disability, or constituted an important medical condition. Solicited systemic and injection-site adverse events were considered vaccination-related. The opinion of the investigator established other instances of vaccination-related events.

Data analysis: The sample size was sufficiently large to identify common adverse events (270 evaluable

participants at 95%CI can detect an adverse event occurring with a frequency of $\geq 1.1\%$).

Statistical parameters included geometric mean titer (GMT), the % participants with a ≥ 4 -fold increase in titer, and the % participants with SBA-BR titers ≥ 8 (1/dil) or ≥ 128 (1/dil). GMTs and their 95% confidence intervals (CIs) were calculated by normal approximation. Safety-related 95% CIs were calculated by exact binomial distribution for percentages (Clopper-Pearson).

RESULTS

The study enrolled 100 participants per group from June to November 2010. Participants in the Child and Adolescent Groups were evenly distributed between the LTM Medical College & General Hospital, Mumbai, India and Maulana Azad Medical College, New Delhi, India; participants in the Adult Group came from Kempegowda Institute of Medical Sciences, Bangalore, India. There were three voluntary withdrawals: one in the Child Group and two in the Adolescent Group. In the Child Group, the mean age was 7.2 years with 47% boys; in the Adolescent Group, the mean age was 14.2 years with 52% boys; in the Adult Group, the mean age was 34.8 years with 62% men.

All participants received a single MenACYW-DT dose and blood was drawn twice but three participants (1 Child Group; 2 Adolescent Group) were prematurely withdrawn due to family relocation before the second blood samples were drawn. For the second blood sampling, most were taken per-protocol, but two participants (1 Child Group; 1 Adolescent Group) were sampled at Day 29, and 8 participants (5 Child Group; 1 Adolescent Group; 2 Adult Group) were sampled between Days 36 and 52.

Temperature variations of some samples resulted in a freezer temperature excursions (TE) to $+8.6^\circ\text{C}$ (all samples were to remain $\leq -10^\circ\text{C}$). The affected sera included both prevaccination (49 Child Group; 34 Adolescent Group) and post-vaccination (48 Child Group and 20 Adolescent Group) samples. TEs are technically protocol violations, but the SBA-BR includes a heat inactivation step of 56°C for 30 min prior to testing (a temperature increase \geq than any sample experienced in a TE). The most likely consequence was a negligible or slightly negative change to the bactericidal activity in the sera; TE-affected samples yielded similar results compared to per-protocol results. Therefore, we pooled the immunogenicity results of all samples.

Immunogenicity: GMTs and % participants achieving a ≥ 4 -fold increase in GMT for all age groups are presented in **Table I**. In general, titers rose to 1000-4000 (1/dil) 30 days post-vaccination. Exceptions were observed in serogroup C, where Child Group GMTs rose to approximately 600 (1/dil). Across serogroups, 68% to 97% of participants achieved a 4-fold titer increase.

The MenACYW-DT induced high levels of protection, with 92%-100% of participants achieving serogroup-specific titers ≥ 8 (1/dil) at 30 days post-vaccination (**Table II**). With few exceptions, similar percentages of participants achieved titers ≥ 128 (1/dil).

Safety: Solicited reactions were experienced by approximately one-third of children or adolescents, and approximately one-half of adults. Most injection site reactions were reported as Grade 1. Solicited systemic reactions were generally Grade 1, although none lasted longer than 8 days and most resolved by Day 4. There were few unsolicited adverse events (**Table III**); none

TABLE I PRE-VACCINATION AND POST-VACCINATION GEOMETRIC MEAN TITERS (GMT) MEASURED BY SBA-BR

Serogroup		Child Group [#] (n=100)		Adolescent Group (n=100)		Adult Group (n=100)	
		GMT (95% CI) 1/dil	% ≥ 4 -fold rise (95% CI)	GMT (95% CI) 1/dil	% ≥ 4 -fold rise (95% CI)	GMT (95% CI) 1/dil	% ≥ 4 -fold rise (95% CI)
A	Pre	9.51 (6.43,14.1)		15.0 (9.65,23.4)		9.78 (6.90, 13.9)	
	Post	1145 (854,1536)	84.8 (76.2, 91.3)	1324 (1002,1750)	84.5 (75.8,91.1)	2261 (1749,2924)	95.9 (89.9,98.9)
C	Pre	9.92 (7.01,14.0)		17.9 (12.2,26.2)		56.9 (36.6,88.3)	
	Post	610 (392,949)	87.9 (79.8, 93.6)	2343 (1563,3512)	90.8 (83.3,95.7)	7486 (5380,10417)	96.0 (90.1,98.9)
Y	Pre	355 (256,491)		309 (222,430)		156 (110,222)	
	Post	1964 (1607,2399)	67.7 (57.5, 76.7)	3190 (2502,4067)	75.3 (65.5,83.5)	3926 (2855,5398)	88.8 (80.8,94.3)
W-135	Pre	31.3 (20.6,47.7)		47.8 (32.3,70.9)		28.6 (18.6,44.1)	
	Post	1756 (1240,2486)	92.9 (86.0, 97.1)	2538 (1947,3307)	95.9 (89.8,98.9)	3183 (2360,4293)	97.0 (91.4,99.4)

pre = pre-vaccination; post = post-vaccination; SBA-BR: * 98 and [#]99 participant for post-vaccination studies.

TABLE II *PARTICIPANTS WITH PROTECTIVE (≥ 8) MENINGOCOCCAL TITERS PRE-AND POST- MENACWY VACCINATION AS MEASURED BY SBA-BR

Sero-Group	Child Group		Adolescent Group		Adult	
	Pre	Post	Pre	Post	Pre	Post
A	17.0 (10.2, 25.8)	96.0 (90.0, 98.9)	27.0 (18.6, 36.8)	96.9 (91.2, 99.4)	23.0 (15.2, 32.5)	99.0 (94.4, 100)
C	24.0 (16.0, 33.6)	91.9 (84.7, 96.4)	43.0 (33.1, 53.3)	96.9 (91.3, 99.4)	66.0 (55.8, 75.2)	99.0 (94.6, 100)
Y	92.0 (84.8, 96.5)	100 (96.3, 100)	92.0 (84.8, 96.5)	100 (96.3, 100)	89.0 (81.2, 94.4)	100 (96.3, 100)
W-135	54.0 (43.7, 64.0)	97.0 (91.4, 99.4)	68.0 (57.9, 77.0)	100 (96.3, 100)	52.0 (41.8, 62.1)	100 (96.3, 100)

CI = confidence interval; pre = pre-vaccination; post = post-vaccination; 100 participants in each of the three groups for pre titers and 99, 98 and 100 participants in Child, Adolescent and Adult group for post titers, respectively. *All values in % (95% CI).

were serious or led to study withdrawal. The sole unsolicited, vaccination-related adverse event was a case of injection-site induration that spontaneously resolved after 8 days. There were no deaths.

DISCUSSION

This study showed that a protective response against meningococcal serogroups A, C, Y, and W-135 was achieved 30 days post-vaccination by MenACYW-DT vaccination along with an excellent safety profile. These data confirm the previous results of Keyserling, *et al.* [11].

Until recently, only bivalent (serogroups A and C) and quadrivalent (serogroups A, C, Y, and W-135) polysaccharide meningococcal vaccines were licensed in India. While providing short-term protection in high-risk individuals and outbreak control, these vaccines may induce hyporesponsiveness after repeat doses in pediatric and adolescent populations and do not elicit strong immune responses in children [2,12]. Studies have demonstrated reduced carriage of invasive meningococcal serogroup A and C strains after immunization with conjugate vaccines [13,14]. Although such data are not yet available for other serogroups, conjugate vaccines of serogroup Y and W probably have a similar effect on *N. meningitidis* nasopharyngeal carriage.

A monovalent serogroup A conjugate vaccine licensed in 2009 has not yet been commercialized for use in India [15]. Quadrivalent conjugate vaccine data are now available, showing robust disease protection against clinically important serogroups combined with an excellent safety profile [6, 16, 17]. All three age groups in the present study had high percentages of serogroup Y protective titer possibly as a consequence of relatively high carriage rates of the serogroup Y strain in the Indian population. Although no detectable serogroup Y disease was found in the literature of Sinclair, *et al.* [4], the implication of latent serogroup Y meningococci might argue that a broadly protective meningococcal vaccine may be of more utility than is currently realized in the Indian population.

Recent studies in children and adolescents [16,17] have shown that MenACYW-DT induces a robust booster response in naïve participants. These studies also showed MenACYW-DT could partially overcome hyporesponsiveness in those previously vaccinated with PS vaccines. The clinical data presented here makes MenACYW-DT a candidate vaccine for primary prevention of meningococcal disease in India. The World Health Organization recommends [18] meningococcal vaccines be used to prevent invasive disease by prevalent regional serogroup(s) for risk groups. MenACYW-DT has recently been shown to elicit protective antibodies in HIV-affected children and adolescents [19-21].

The study results show that MenACYW-DT elicited a robust and protective response against meningococcal serogroups A, C, W-135, and Y, 30 days post-vaccination. The results also showed that the vaccine was well tolerated. These results further confirm previous results obtained in different populations.

Contributors: SY, MVM, DHAN, SS, HSR, RA, SA, and PO designed and conducted the study; VBC developed the statistical analysis plan. All authors supervised the writing of the manuscript and subsequent revisions. All authors approved the final draft.

TABLE III ADVERSE EVENTS AMONG PARTICIPANTS RECEIVING MENACWY-D VACCINE

Adverse Event	Child Group (n=100) %(95% CI)	Adolescent Group (n=100) %(95% CI)	Adult Group (n=100) %(95% CI)
Any solicited	38 (28.5, 48.3)	29 (20.4,38.9)	52 (41.8,62.1)
Injection-site	31 (22.1, 41.0)	23 (15.2,32.5)	38 (28.5,48.3)
Systemic	23 (15.2, 32.5)	22 (14.3,31.4)	29 (20.4,38.9)
Unsolicited	06 (2.2, 12.6)	01 (0.0,5.4)	04 (1.1,9.9)

WHAT IS ALREADY KNOWN?

- The safety and immunogenicity of MenACYW-DT against four serogroups known to cause meningococcal disease have been demonstrated in pre- and post-licensure studies, mostly conducted in the US.

WHAT THIS STUDY ADDS?

- MenACWY-DT demonstrated protective immunogenicity at 1 month post-vaccination with a good safety profile in Indian participants aged 2-55 years.

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Competing interests: RA is an employee of Sanofi Pasteur India Pvt Ltd. PO and VBC are employees of Sanofi Pasteur. Serum bactericidal assays in the presence of baby rabbit complement (SBA-BR) were performed by Sanofi Pasteur Global Clinical Immunology laboratories (Swiftwater, PA, USA).

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