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ORIGINAL RESEARCH ARTICLE

Immunogenicity and Safety of a Quadrivalent Meningococcal Serogroups A, C, W-135 and Y Tetanus Toxoid Conjugate Vaccine (MenACWY-TT) Administered to Adults Aged 56 Years and Older: Results of an Open-Label, Randomized, Controlled Trial

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Abstract

Background The burden of invasive meningococcal disease is substantial in older adults in whom the case fatality rate is high. Travelers to regions with high rates of meningococcal disease, such as Hajj pilgrims, are at increased risk of meningococcal infection, and disease transmission from travelers to their close contacts has been documented. In younger individuals, meningococcal conjugate vaccines offer advantages over polysaccharide vaccines in terms of duration of protection and boostability, and induction of herd immune effects through reductions in nasopharyngeal carriage of meningococci. To date, few data are available evaluating meningococcal conjugate vaccine use in adults >55 years of age.

Objective To evaluate the immunogenicity and safety of quadrivalent meningococcal serogroups A, C, W-135 and Y vaccine with all serogroups conjugated to tetanus toxoid (MenACWY-TT, *Nimenrix*™, GlaxoSmithKline, Belgium) and a licensed quadrivalent polysaccharide vaccine (MenPS, *Mencevax*™ GlaxoSmithKline, Belgium) in adults >55 years of age.

Methods This was a phase IIIb, open-label, randomized (3:1), controlled study conducted at one study center in Lebanon. A total of 400 healthy adults between 56 and 103 years of age without previous MenPS or tetanus toxoid vaccination within the previous 5 years or meningococcal conjugate vaccination at any time previously were included. They received a single-dose vaccination with MenACWY-TT or MenPS with blood sampling before and 1 month after vaccination. The main outcome measures were serum bactericidal activity (rabbit complement source: rSBA) vaccine response (VR) rate [rSBA titer of ≥1:32 in initially seronegative subjects (rSBA titer <1:8); ≥4-fold increase in subjects with pre-vaccination rSBA titers between 1:8 and 1:128, and ≥2-fold increase in subjects with pre-vaccination rSBA titers ≥1:128]. The percentages of subjects with rSBA titers ≥1:8 and ≥1:128 and rSBA geometric mean titers (GMTs) were assessed. Solicited adverse events were recorded for 4 days following vaccination, and all other adverse events, including the incidence of new onset chronic diseases, were recorded for 31 days after vaccination.

Results One month after a single dose of MenACWY-TT, the rSBA VR rate in the MenACWY-TT group was 76.6 % for serogroup A, 80.3 % for serogroup C, 77.5 % for serogroup W-135 and 81.9 % for serogroup Y. VR rates in the MenPS group were 91.7, 84.8, 87.1 and 89.1 %, respectively. One month after vaccination, ≥93.2 % of subjects in the MenACWY-TT group and ≥93.9 % in the MenPS group had rSBA titers ≥1:128. In each group,

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GMTs increased by ≥13-fold for each serogroup. rSBA VR and GMTs tended to be lower in subjects who were over 65 years compared to 56–65 years of age. Only 6.3 % of MenACWY-TT recipients had anti-TT ≥0.1 IU/ml prior to vaccination, increasing to 28.1 % post-vaccination. The rSBA GMTs were 1.9- to 4-fold higher in anti-TT responders. Each local and general solicited symptom was reported by no more than 3.0 % of subjects in either group. No serious adverse events were considered vaccine related. *Conclusion* In adults 56 years of age and older, MenACWY-TT was immunogenic, with a vaccine response rate ≥76 % and with ≥93 % of subjects achieving rSBA titers ≥1:128 against all four serogroups after a single dose. MenACWY-TT induced low anti-TT concentrations in this population, which deserves further study.

1 Background

Invasive disease caused by *Neisseria meningitidis* is typically characterized by rapid onset with fulminant progression, resulting in death in around 10 % of individuals despite appropriate antibiotics and supportive care [1]. The incidence of invasive meningococcal disease is highest in infants, with a second peak that occurs during adolescence [2]. Notwithstanding, a substantial proportion of the disease burden lies with adults: in the US approximately 43 % of all invasive meningococcal disease cases were reported in adults aged 25 years and older (1998–2007 data) [2]. During the same observation period, 14 % of cases occurred in the age group 65 years and older, with a case fatality rate of 23.8 %, the highest in any age group [2]. Similar trends are observed in other countries: in Australia 6 % of all meningococcal cases in 2010 were in adults over 65 years of age, and 19 % were in adults 45 years of age and older [3]. In England and Wales, around 10 % of all meningococcal cases each year between 1993 and 2004 occurred in adults over 45 years of age [4]. These data point to a substantial disease burden in older adults, which is likely to become a greater public health concern as the global population ages.

Based on differences in the composition of the polysaccharide capsule, 12 meningococcal serogroups have been identified; however, 6 serogroups predominate as causes of invasive disease (serogroups A, B, C, W-135, X and Y) [5]. In the Middle East, available information suggests that serogroups A and W-135 are responsible for the majority of meningococcal invasive disease in the region. Serogroups A and W-135 are also responsible for major epidemics in Africa [1, 5], while serogroup X emerged more recently as a cause of local outbreaks in Africa [6–9]. By contrast, serogroups A, W-135 and X are infrequently identified in many Western countries, where serogroups B, C and to a lesser degree Y predominate [2, 5].

Adults are at increased risk of meningococcal infection when they travel to meningococcal endemic regions [10]. A serogroup W-135 outbreak that occurred during the 2000 Hajj spread intercontinentally from pilgrims to their contacts [11, 12], and more recently, cases of W-135 were identified in France among travellers who had returned from West Africa and their contacts [13]. These cases of intercontinental transmission highlight the relative ease by which meningococcal strains can be transmitted to immunologically naïve populations through global travel activity. Meningococcal vaccination against serogroups A, C, W-135 and Y is now required prior to Hajj attendance for all pilgrims over 2 years of age [14].

Vaccination is the best strategy to prevent meningococcal disease. Quadrivalent serogroups A, C, W-135 and Y (ACWY) meningococcal polysaccharide vaccines are available for use in adults and children from the age of 2 years [15]. However, polysaccharide vaccines do not stimulate T-cell-dependent immune responses and thus do not induce long-lasting protection or immune memory, but may induce immune hyporesponsiveness, particularly for serogroup C, on repeated administration [16, 17]. By contrast, meningococcal conjugate vaccines induce T-cell-mediated immune responses that appear to be long-lived, with evidence of immune memory upon re-exposure [15]. Long-term protection against invasive meningococcal disease appears to be dependent on the presence of circulating antibody rather than on memory responses [18]. Antibody levels decrease over time after both meningococcal polysaccharide and meningococcal conjugate vaccination, and the duration of protection afforded by meningococcal conjugate vaccination is not yet known.

Conjugate vaccines also induce herd protection by decreasing the carriage rate in vaccine recipients, which was demonstrated in the UK after a mass vaccination program with conjugate serogroup C vaccines [19]. Herd protection is important in interrupting the transmission of meningococci. Meningococcal conjugate vaccines therefore have advantages in terms of duration of protection and boostability in those who require sustained protection. In adults, meningococcal ACWY (MenACWY) conjugate vaccines show comparable or improved immunogenicity versus polysaccharide vaccines [20–22]. However, few studies have evaluated conjugate vaccine use in adults over 55 years of age [20].

GlaxoSmithKline has developed a MenACWY vaccine with all serogroups conjugated to tetanus toxoid (MenACWY-TT, *Nimenrix*™), which is licensed for use in Europe as a single dose in individuals as of 1 year of age [23]. MenACWY-TT was immunogenic and well tolerated in clinical trials conducted in children, adolescents and

adults up to age 55 years [21, 22, 24–30]. We conducted a phase IIIb, open-label, randomized, controlled study designed to evaluate the immunogenicity and safety of MenACWY-TT as compared to a licensed polysaccharide vaccine (*Mencevax*™ACWY, GlaxoSmithKline Vaccines: MenPS) when administered as one dose to healthy adults aged 56 years and older.

2 Methods

2.1 Study Design

The study (113807, www.clinicaltrials.gov NCT01235975) was conducted in a single center in Lebanon between 30 November 2010 and 3 August 2011. Adults were enrolled and randomized 3:1 into two parallel groups. Subjects in the MenACWY-TT group received a single dose of MenACWY-TT, while subjects in the MenPS group received a single dose of licensed MenPS. A randomization list was generated at GlaxoSmithKline Belgium and was used to number the vaccines. Treatment allocation at the investigator site was performed using a central, web-based randomization system. A blocking scheme ensured that balance between treatments was maintained. The randomization algorithm used a minimization procedure accounting for center and age strata. The enrollment ensured a 2:1 allocation of the population across two age strata: 56–65 years of age and >65 years of age.

This was an open study because the routes of administration of the study vaccine and the control vaccine were different.

The primary study objective was to evaluate the immunogenicity of MenACWY-TT as compared to MenPS in terms of serum bactericidal activity (rabbit complement source; rSBA) vaccine response (VR) rates 1 month after vaccination. A VR was defined as an rSBA titer of at least 1:32 in initially seronegative subjects (rSBA titer <1:8), at least a four-fold increase in subjects with rSBA titers between 1:8 and 1:128 before vaccination and at least a two-fold increase in subjects with rSBA titers ≥1:128 before vaccination.

2.2 Study Subjects

Adults were to be at least 56 years of age at enrollment, and females were to be of non-child bearing potential. Subjects were not enrolled if they had received prior vaccination with MenPS or tetanus toxoid (TT) within the previous 5 years or with any meningococcal conjugate vaccine at any time previously. Subjects were also excluded if they had previously suffered from meningococcal disease, if they were immunosuppressed for any reason including chronic (>14 days) immunosuppressant treatment, if they had a history of neurological disease, seizures or Guillain-Barre syndrome, or if they had active pulmonary, cardiovascular, hepatic or renal disease. Subjects who had received blood products within 3 months of vaccination or who had chronic alcohol consumption or drug abuse were also ineligible to participate.

2.3 Study Vaccines

One 0.5 ml dose of MenACWY-TT contained 5 μg each of meningococcal serogroup A, C, W-135 and Y polysaccharide conjugated to a total of approximately 44 μg TT. One 0.5-ml dose of MenPS contained 50 μg each of meningococcal serogroups A, C, W-135 and Y polysaccharide. MenACWY-TT was administered intramuscularly and MenPS given subcutaneously into the upper arm on the non-dominant side.

2.4 Immunogenicity Assessment

Blood samples were collected from all subjects before and 1 month after vaccination and were tested for rSBA for each meningococcal serogroup as previously described [31]. The cutoff of the rSBA assay was a 1:8 dilution and was considered indicative of seroprotection [32, 33]. Anti-TT antibodies were measured at each time point using an enzyme-linked immunosorbent assay (ELISA) [34], with an assay cutoff of 0.1 IU/ml.

2.5 Safety and Reactogenicity Assessment

Specific local and general symptoms were recorded on diary cards for 4 days after vaccination. Symptom intensity of redness, swelling and fever was graded by millimeter of reaction and degrees Celsius of fever, respectively, and all other symptoms were graded by the subject using a predefined scale. Grade 3 redness and swelling were defined as diameter >50 mm, grade 3 fever as oral temperature >39.5°C, and for other symptoms, grade 3 was defined as preventing normal activity. All other adverse events including serious adverse events and new onset of chronic illness were recorded for 31 days after vaccination.

2.6 Consent Procedures

The study protocol was approved by the institutional review board (IRB) prior to study start. Written informed consent was obtained from each subject prior to enrollment.

Enrollment was hampered by the distance between home communities and the study center in Beirut. In response, the principal investigator proposed setting up a mobile unit to perform study visits by study personnel in local villages, as per protocol. A mobile unit guidance

explaining the rationale for the mobile unit and the associated procedures was issued to the IRB for their information and the enrollment via the mobile unit started on the same day. Later, the IRB clarified that approval of the mobile unit was required. The IRB approved the mobile unit pending minor revisions a few days later. One hundred and two subjects were enrolled through the mobile unit prior to formal IRB mobile unit approval. All of these subjects were asked to re-consent. Twenty-nine subjects didn't re-consent (no subjects refused to re-consent because of an adverse event), and therefore these 29 subjects were eliminated from all statistical analyses.

2.7 Statistical Analyses

As this is the first study to investigate the immunogenicity of MenACWY-TT in a population of older adults, this exploratory study was designed as a descriptive analysis. The primary analysis of immunogenicity was done on the according-to-protocol (ATP) cohort for immunogenicity, which included subjects who had complied with all protocol-defined procedures and who had data available for at least one immunogenicity endpoint. Percentages of subjects with rSBA vaccine response and with titers/concentrations above threshold values, with exact 95 % CIs, were calculated. The effect of age at vaccination and of meningococcal vaccination history was investigated in exploratory analyses.

The target enrollment was set at 400 subjects randomized 3:1 to the MenACWY-TT group or MenPS group in order to have 360 evaluable subjects (270 subjects in MenACWY-TT group and 90 subjects in MenPS group), assuming a 10 % drop out of subjects throughout the study. With 270 evaluable subjects in the MenACWY-TT group and assuming a VR rate of 80 %, the exact 95 % CI around the estimate would be 74.7; 84.6. With 90 evaluable subjects in the MenPS group, the 95 % CI around the assumed VR rate of 80 % would be 70.2; 87.7.

Exploratory analyses were used to highlight potential differences between groups if the asymptotic standardized 95 % CI for the group difference in the percentage of subjects reaching specified immunological cutoffs did not contain the value '0' or if the 95 % CI for the geometric mean titer (GMT) ratio (ANCOVA model using the pre-vaccination logarithm_{10} transformation of the titers/concentrations, the vaccine group, age strata and meningococcal vaccination history as covariates) between groups did not contain the value '1'. Multiple comparisons were done without adjustment for multiplicity, and there is a risk that statistically significant differences may have occurred by chance alone. Thus, any statistically significant differences between groups should be interpreted cautiously. Exploratory analyses for statistical differences were performed on the cohort including all subjects; these analyses were not performed per age strata because of the limited available sample size per stratum.

The primary analysis of safety was done on the total vaccinated cohort, comprising all vaccinated subjects with safety data available.

Statistical analyses were performed using SAS® software version 9.2 (SAS Institute Inc., Cary, NC, USA) and ProcStatXact 8.1.

3 Results

3.1 Study Subjects

Four hundred adults whose age ranged between 56 and 103 years were enrolled in the study. Of these, 2 subjects were not vaccinated, and 29 were excluded from all statistical analyses (see Sect. 2). Thus, there were 369 subjects in the total vaccinated cohort, of which 260 (70 %) were eligible for inclusion in ATP analyses (Fig. 1). More females (68.3 %) than males (31.7 %) were enrolled. The two treatment groups were comparable in terms of demographic characteristics (Table 1).

One subject (an 84-year-old subject in the MenPS group) withdrew from the study because of a serious adverse event. This subject suffered a cerebrovascular accident and died 21 days after vaccination. The event was considered unrelated to vaccination by the investigator.

3.2 Immunogenicity

After a single dose of MenACWY-TT, the VR rate in the MenACWY-TT group was 76.6 % for serogroup A, 80.3 % for serogroup C, 77.5 % for serogroup W-135 and 81.9 % for serogroup Y (Table 2). VR rates in the MenPS group were 91.7, 84.8, 87.1 and 89.1 %, respectively.

One month after vaccination, at least 97.4 % in the MenACWY-TT group and at least 95.5 % in the MenPS group had rSBA titers $\geq$1:8 (Table 3). The percentage with rSBA $\geq$1:128 was at least 93.2 % in the MenACWY-TT group and at least 93.9 % in the MenPS group. In each group, GMTs increased by at least 13-fold for each serogroup (Table 3).

Exploratory analyses did not detect any statistically significant differences between groups in terms of the percentage of subjects who reached the 1:8 and 1:128 thresholds after vaccination. However, these analyses suggested that the magnitude of the response was statistically significantly lower in MenACWY-TT recipients than in MenPS recipients in terms of VR rate for serogroup A and rSBA GMTs for serogroups A and C. VR rates in individuals with pre-existing rSBA titers $\geq$1:128 tended to be lower for each serogroup in MenACWY-TT recipients

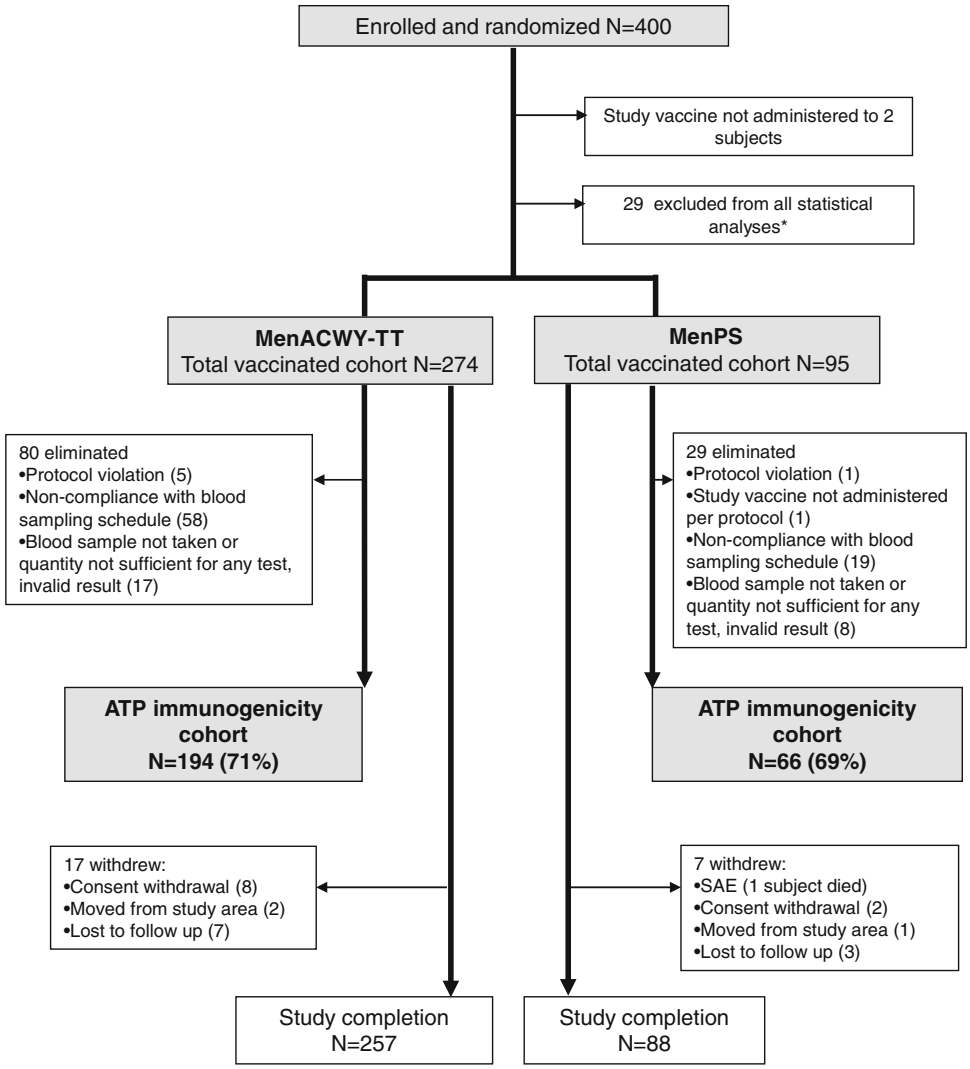

Fig. 1 Subject flow through the study. *ATP* according to protocol, *SAE* serious adverse event. *Twenty-nine subjects (randomized and vaccinated) who were enrolled via the mobile unit prior to approval and who did not re-consent after mobile unit approval by the institutional review board

(65.7–72.6 %) than in MenPS recipients (75.9–91.3 %), while the majority of initially seronegative subjects in both groups demonstrated VRs to each serogroup after vaccination (for serogroup A, 93.3 % in the MenACWY-TT group and 100 % in the MenPS group; for serogroup C, 96.3 and 90.9 %; for W-135, 88.7 and 86.4 %; and for Y, 100 % in both groups).

3.3 Effect of Age and Previous Meningococcal Polysaccharide Vaccination on the Immune Response

VR rates tended to be lower in subjects who were >65 years of age at the time of vaccination, compared to younger (56- to 65-year-old) subjects (Table 2). This trend was more pronounced in MenPS recipients for serogroups A, C and Y. Possible differences between groups were not statistically tested as these tests are not powered to do so, because of the low numbers of subjects in each subgroup.

The percentage of subjects with rSBA titers ≥1:128 and the rSBA GMT were within the same range in the 56–65 year and >65 year subgroups, although the small number of subjects in each group means that conclusions cannot be drawn (Supplementary table 1).

Approximately one-quarter of subjects had a history of having received a meningococcal polysaccharide vaccine more than 5 years previously (Table 1). Prior to vaccination, the percentage of subjects with rSBA ≥1:128 was between 57.5 and 60.7 % for serogroup A, 43.9 and 45.3 % for serogroup C, 48.4 and 52.1 % for serogroup W-135 and 62.4 and 71.9 % for serogroup Y (Table 3). The percentage of subjects with pre-vaccination titers ≥1:128 and rSBA GMTs for serogroups A and C, but not W-135 or Y, tended to be higher in subjects with a history of meningococcal vaccination than in unvaccinated subjects (Supplementary table 2). In the MenACWY-TT group, the post-vaccination rSBA GMTs in subjects who *had not* received a meningococcal dose previously were in the same range as in

Table 1 Summary of demographic characteristics (total vaccinated cohort)

Characteristic	MenACWY-TT $N = 274$	MenPS $N = 95$
Age (years)		
Mean (SD)	64.1 (7.22)	64.3 (7.39)
Range	56–103	56–86
Age stratum (years) *n* (%)		
56–65	184 (67.2)	63 (66.3)
>65	90 (32.8)	32 (33.7)
Gender *n* (%)		
Female	182 (66.4)	70 (73.7)
Male	92 (33.6)	25 (26.3)
Geographic ancestry *n* (%)		
Arabic/North African	274 (100)	95 (100)
Meningococcal vaccination history[a] *n* (%)		
Unknown	2 (0.7)	2 (2.1)
0	210 (76.6)	68 (71.6)
1	62 (22.6)	25 (26.3)
2	0 (0.0)	0 (0.0)

N total number of subjects, *n/%* number/percentage of subjects in a given category, *SD* standard deviation

[a] Number of previous meningococcal polysaccharide vaccinations. Note that previous meningococcal vaccines were received more than 5 years prior to enrollment

subjects who *had* received a prior meningococcal vaccination, although lower point values for rSBA-W-135 titers were observed in those previously vaccinated: for serogroup A, 1,372.0 [95 % CI 1,088.3; 1,729.6] versus 1,726.4 [1,067.5; 2,792.0]; for serogroup C, 2,584.3 [1,836.2; 3,637.2] versus 2,412.1 [1,504.7; 3,866.7]; for serogroup W-135, 1,791.7 [1,369.7; 2,343.7] versus 756.2 [406.2; 1,407.7]; and for serogroup Y, 2,664.0 [2,107.0; 3,368.3] versus 2,219.6 [1,324.1; 3,720.6]. In the MenPS group, the rSBA GMTs were: for serogroup A, 2,640.3 [1,768.5; 3,941.9] versus 3,968.1 [2,248.5; 7,003.0]; for serogroup C, 5,054.1 [2,661.9; 9,595.9] versus 4,712.0 [1,483.6; 14,965.4]; for serogroup W-135, 2,217.4 [1,363.6; 3,606.0] versus 1,325.9 [334.1; 5,261.7]; and for serogroup Y, 4,370.4 [2,756.7; 6,928.6] versus 3,710.3 [2,042.1; 6,741.0]. Due to the low numbers of subjects in each subgroup, comparisons between groups are not reliable (Supplementary table 2).

3.4 Response to Tetanus Toxoid

Few subjects had anti-TT antibodies ≥0.1 IU/ml prior to vaccination (12 subjects, 6.3 % in the MenACWY-TT group and 6 subjects, 9.1 % in the MenPS group). The anti-TT response after MenACWY-TT vaccination was low (Table 4).

A post-hoc analysis assessed rSBA GMTs in subjects according to pre- and post-vaccination anti-TT antibody status in the MenACWY-TT group. In adults with anti-TT antibodies ≥0.1 IU/ml prior to vaccine, post-vaccination rSBA GMTs after MenACWY-TT were as high or higher than those observed in the MenPS group for serogroups C, W-135 and Y, but not for serogroup A (rSBA GMT 2,479.8 [95 % CI 1,211.4; 5,076.2] for serogroup A, 7,492.7 [2,069.9; 27,121.6] for serogroup C, 3,250.5 [521.4; 20,263.8] for serogroup W-135, and 3,992.0 [1,028.7; 15,491.2] for serogroup Y, Supplementary table 3). Furthermore, the post-vaccination

Table 2 Percentage of subjects with a vaccine response 1 month after vaccination: all subjects and by age strata (ATP cohort for immunogenicity)

Serogroup	Group	All subjects			56- to 65-year-olds			>65-year-olds		
		N	*n*	% [95 % CI]	*N*	*n*	% [95 % CI]	*N*	*n*	% [95 % CI]
A	MenACWY-TT	175	134	76.6* [69.6; 82.6]	119	93	78.2 [69.6; 85.2]	56	41	73.2 [59.7; 84.2]
	MenPS	60	55	91.7 [81.6; 97.2]	37	37	100 [90.5; 100]	23	18	78.3 [56.3; 92.5]
C	MenACWY-TT	188	151	80.3 [73.9; 85.7]	128	106	82.8 [75.1; 88.9]	60	45	75.0 [62.1; 85.3]
	MenPS	66	56	84.8 [73.9; 92.5]	41	38	92.7 [80.1; 98.5]	25	18	72.0 [50.6; 87.9]
W-135	MenACWY-TT	187	145	77.5 [70.9; 83.3]	127	102	80.3 [72.3; 86.8]	60	43	71.7 [58.6; 82.5]
	MenPS	62	54	87.1 [76.1; 94.3]	38	33	86.8 [71.9; 95.6]	24	21	87.5 [67.6; 97.3]
Y	MenACWY-TT	188	154	81.9 [75.7; 87.1]	128	103	80.5 [72.5; 86.9]	60	51	85.0 [73.4; 92.9]
		64	57	89.1 [78.8; 95.5]	39	37	94.9 [82.7; 99.4]	25	20	80.0 [59.3; 93.2]

Vaccine response defined as: post-vaccination rSBA titer ≥1:32 in initially seronegative subjects; four-fold increase in initially seropositive subjects with rSBA titer 1:8 and <1:128; two-fold increase in initially seropositive subjects with rSBA titer ≥1:128

ATP according-to-protocol, *N* number of subjects with both pre- and post-vaccination results available, *n/%* number/percentage of responders; *95 % CI* 95 % confidence interval, *rSBA* rabbit complement source

* Statistically significant difference between the MenACWY-TT and MenPS groups (exploratory analysis)

Table 3 Percentage of subjects with rSBA titers ≥1:8 and ≥1:128 and GMTs (ATP cohort for immunogenicity)

Serogroup	Group	Time point	*N*	≥1:8		≥1:128		GMT [95 % CI]
				n	% [95 % CI]	*n*	% [95 % CI]	
A	MenACWY-TT	Pre	181	136	75.1 [68.2; 81.3]	104	57.5 [49.9; 64.8]	108.3 [77.9; 150.5]
		Post	186	185	99.5 [97.0;100]	177	95.2 [91.0; 97.8]	1,442.3* [1,174.4; 1,771.3]
	MenPS	Pre	61	43	70.5 [57.4; 81.5]	37	60.7 [47.3; 72.9]	102.1 [55.2; 188.7]
		Post	65	65	100 [94.5; 100]	63	96.9 [89.3; 99.6]	2,840.1 [2,062.3; 3,911.1]
C	MenACWY-TT	Pre	190	135	71.1 [64.0; 77.4]	86	45.3 [38.0; 52.6]	71.5 [51.1; 100.1]
		Post	192	192	100 [98.1; 100]	179	93.2 [88.7; 96.3]	2,498.6* [1,887.0; 3,308.2]
	MenPS	Pre	66	44	66.7 [54.0; 77.8]	29	43.9 [31.7; 56.7]	73.8 [38.0; 143.6]
		Post	66	65	98.5 [91.8; 100]	62	93.9 [85.2; 98.3]	4,815.1 [2,827.0; 8,201.2]
W-135	MenACWY-TT	Pre	188	135	71.8 [64.8; 78.1]	98	52.1 [44.7; 59.5]	84.7 [61.1; 117.3]
		Post	193	188	97.4 [94.1; 99.2]	183	94.8 [90.7; 97.5]	1,454.0 [1,130.5; 1,870.1]
	MenPS	Pre	62	40	64.5 [51.3; 76.3]	30	48.4 [35.5; 61.4]	68.5 [37.4; 125.3]
		Post	66	63	95.5 [87.3; 99.1]	62	93.9 [85.2; 98.3]	1,838.4 [1,134.6; 2,978.9]
Y	MenACWY-TT	Pre	189	148	78.3 [71.7; 84.0]	118	62.4 [55.1; 69.4]	137.6 [100.7; 187.9]
		Post	193	193	100 [98.1; 100]	187	96.9 [93.4; 98.9]	2,547.0 [2,059.6; 3,149.8]
	MenPS	Pre	64	55	85.9 [75.0; 93.4]	46	71.9 [59.2; 82.4]	217.4 [131.7; 358.9]
		Post	66	66	100 [94.6; 100]	65	98.5 [91.8; 100]	3,931.6 [2,726.1; 5,670.2]

ATP according-to-protocol, *GMT* geometric mean antibody titer calculated on all subjects, *N* number of subjects with available results, *n/%* number/percentage of subjects with titer within the specified range, *95 % CI* 95 % confidence interval, *Pre* Pre-vaccination, *Post* 1 month post-vaccination, *rSBA* rabbit complement source

* Statistically significant difference between the MenACWY-TT and MenPS groups (exploratory analysis)

Table 4 Percentage of subjects with anti-TT concentrations ≥0.1 and 1 IU/ml and GMCs (ATP cohort or immunogenicity)

Group	Timing	*N*	≥0.1 lU/ml		≥1 lU/ml		GMC [95 % CI]
			n	% [95 % CI]	*n*	% [95 % CI]	
MenACWY-TT	Pre	192	12	6.3 [3.3; 10.7]	3	1.6 [0.3; 4.5]	0.058 [0.053; 0.063]
	Post	192	54	28.1 [21.9; 35.1]	29	15.1 [10.4; 21.0]	0.137 [0.104; 0.180]
MenPS	Pre	66	6	9.1 [3.4; 18.7]	1	1.5 [0.0; 8.2]	0.060 [0.051; 0.070]
	Post	66	6	9.1 [3.4; 18.7]	1	1.5 [0.0; 8.2]	0.060 [0.051; 0.071]

ATP according-to-protocol, *GMC* geometric mean antibody concentration calculated on all subjects, *N* number of subjects with available results, *n/%* number/percentage of subjects with concentration within the specified range, *95 % CI* 95 % confidence interval, *Pre* Pre-vaccination, *Post* 1 month post-vaccination, *TT* tetanus toxoid

rSBA GMTs were between 1.9- and 4-fold higher in subjects who responded to TT: That is, the point values of the rSBA GMT for each serogroup was higher (no statistical test performed because of the low number of subjects) in subjects with post-vaccination anti-TT concentrations ≥1.0 IU/ml (3,581.8 [95 % CI 2,211.4; 5,801.4] for serogroup A, 3,891.4 [1,605.7; 9,430.6] for serogroup C, 3,750.9 [1,985.8; 7,084.8] for serogroup W-135 and 7,600.5 [4,588.7; 12,589.3] for serogroup Y) and was lower in subjects in whom the anti-TT concentration remained <0.1 IU/ml after vaccination (1,147.8 [891.5; 1,477.7] for serogroup A, 2,101.0 [1,510.1; 2,923.0] for serogroup C, 1,045.1 [788.0; 1,385.9] for serogroup W-135 and 1,831.1 [1,441.2; 2,326.6] for serogroup Y) (Supplementary table 3).

3.5 Reactogenicity and Safety

Incidences of local and general solicited symptoms were very low in both groups. In the MenACWY-TT group pain was reported by six subjects (2.3 % [95 % CI 0.8; 4.9]) and redness and swelling each by three subjects (1.1 % [0.2; 3.3]). No local symptoms were reported by subjects in the MenPS group. No local symptoms of grade 3 intensity were reported in either group.

Fatigue was reported by five subjects in the MenACWY-TT group (1.9 % [95 % CI 0.6; 4.3]) and no subjects in the MenPS group. Headache was reported by eight subjects (3.0 % [1.3; 5.9]) in the MenACWY-TT group and by two subjects (2.2 % [0.3; 7.9]) in the MenPS group.

Fever (defined as axilliary temperature ≥37.5°C) was reported by six subjects (2.3 % [0.8; 4.9]) in the MenACWY-TT group and by one subject (1.1 % [0.0; 6.1]) in the MenPS group. All fever episodes were ≤38.0°C except one, which was >38.0°C and one >38.5°C in the MenACWT-TT group. No subject in either group reported gastrointestinal symptoms during the solicited follow-up period.

No grade 3 local or general symptoms were reported by either group, and no solicited symptom led to a medically-attended visit. On observing the low incidences of adverse reactions after vaccination, the investigator re-questioned the subjects before the database was unblinded and the statistical analysis performed, and additional adverse events were not identified.

One serious adverse event was reported during the study (reported above). No cases of new onset of chronic disease were reported during the 31-day follow-up period.

4 Discussion

This is the first study to evaluate quadrivalent MenACWY-TT in an elderly population. MenACWY-TT was immunogenic in this age group, with at least 93.2 % of vaccinees achieving rSBA titers ≥1:128 after vaccination, at least a 13.3-fold increase in post-vaccination rSBA GMTs, and a VR observed in at least 76.6 % of subjects.

In contrast with previous studies conducted in children, adolescents and adults, we observed lower responses in the MenACWY-TT group compared to the MenPS group in terms of VR (serogroup A) and GMTs (serogroups A and C), mainly because of a lower response in subjects with high pre-existing rSBA titers (≥1:128), indicative of previous vaccination or exposure, who received MenACWY-TT. Immune hyporesponsiveness, in which the individual fails to mount an immune response after booster vaccination of at least the same, or of a greater magnitude, than that achieved after primary vaccination [16], has been well described in all age groups following repeated vaccination with serogroup C polysaccharide vaccine [17, 35]. Available data from studies in adolescents and young adults using MenACWY-TT or MenACWY-DT (diphtheria toxoid) show attenuated responses to all serogroups in subjects previously vaccinated with polysaccharide vaccines compared to vaccine-naïve subjects receiving their first conjugate vaccine dose [36–38]. This suggests that conjugate meningococcal vaccines only partially reverse immune hyporesponsiveness induced by prior meningococcal polysaccharide vaccination. Nevertheless, immune responses following meningococcal conjugate vaccination in previously vaccinated subjects were consistently high, with seroprotective rSBA levels achieved in the majority of subjects [36–38]. We observed comparable responses regardless of previous meningococcal vaccination in the MenACWY-TT group, except for the lower point values for serogroup W-135 rSBA titers. This study was not designed to evaluate booster responses in previously primed individuals, and we are unable to reach conclusions on the nature of the responses observed. Further studies are needed to define how meningococcal polysaccharide vaccination influences subsequent conjugate vaccination in adults.

Our study is one of the few that provide information on the immunogenicity of meningococcal conjugate vaccination in the elderly. ACWY-CRM_{197} was observed to be immunogenic in older individuals in a study that included a cohort of previously unvaccinated subjects between 55 and 65 years of age with SBA titers (human complement source) that were higher following conjugate vaccination than after meningococcal polysaccharide vaccination [20]. MenACWY-TT was also immunogenic in all four vaccine serogroups in subjects whose age ranged between 56 and 103 years. Our study comprised more females than males, which is typical of the gender distribution of this age group [39].

Conjugate vaccines using TT as carrier are typically highly immunogenic, in part related to T-cell help induced by the TT carrier [40]. We observed a very low percentage of subjects with anti-TT concentrations ≥0.1 IU/ml prior to vaccination and low anti-TT responses to a single dose of MenACWY-TT, consistent with vaccination practices in Lebanon where no tetanus booster is routinely recommended after childhood. Similarly low anti-TT seroprotection rates have been reported in other countries: In Turkey, only 15.4 % of nursing home residents (mean age 71 years) had anti-TT antibodies ≥0.1 IU/ml by ELISA [41]; in Egypt only 9.7 % of elderly individuals had anti-TT antibodies ≥0.15 IU/ml by ELISA [42], while in Spain, only 7.7 % of individuals over 70 years of age had protective titers by hemagglutination [43]. This is in contrast to studies done with MenACWY-TT in other adult populations where pre-vaccination anti-TT concentrations were higher (e.g., 51.5 % with anti-TT ≥0.1 IU/ml prior to vaccination in an Asian adult population aged 18–55 years, including adults from Lebanon [21]). The TT component of MenACWY-TT was highly immunogenic in that study (percentage of participants with anti-TT ≥0.1 IU/ml increased to 79.4 %) [21, 30]. Although vaccination records were not available, the low responses observed in our study may reflect a primary immune response, as observed following a single dose of TT in adults with an unknown or distant history of TT vaccination [44]. The absence of pre-existing immunity to TT or a vaccine response to the TT component of MenACWY-TT may have reduced the available T-cell help, resulting in lower rSBA responses than previously observed, appearing to particularly affect

serogroups A and C. This is supported by the observation that rSBA responses were 1.9- to 4-fold higher in individuals who mounted a booster response to TT (concentrations ≥1.0 IU/ml after vaccination) compared with those in whom the magnitude of the post-vaccination anti-TT concentration was lower. Immunogenicity of conjugate vaccines using DT and CRM_{197} carrier proteins is known to need prior DT priming to generate optimal responses [40]. Our results support the immunogenicity of MenACWY-TT in TT-unprimed individuals, but suggest that effective TT-priming may be critical to enhance the immune response to subsequent TT conjugate vaccines.

Studies of meningococcal conjugate vaccines specifically evaluating the effects of carrier priming and of prior polysaccharide exposure on subsequent responses to conjugate vaccination are not available. It is not clear whether the results of our study are predictive for individuals living in other countries where TT boosters may be more frequently administered and where fewer subjects may have received prior meningococcal polysaccharide vaccine. It is possible that in these settings higher immune responses to MenACWY-TT would be achieved in older adults. However, this needs to be confirmed in studies conducted outside of the Middle East. Antibody persistence and the response to subsequent MenACWY-TT doses in the elderly warrant further investigation. It would also be informative to study the immunogenicity of TT boosters in older Lebanese adults given the relatively poor response to the TT component of MenACWY-TT observed in this study.

Both of the meningococcal vaccines were associated with very low rates of local and general symptoms. This is consistent with other studies conducted in older individuals where substantially lower reactogenicity has been reported compared to administration of the same vaccines to younger age groups [45].

This study was potentially limited by its open design and because numerous exploratory statistical comparisons were performed without adjustment for multiplicity. Therefore, statistical findings should be interpreted with caution. Inclusion of adults who had previously received meningococcal vaccine was another potential limitation, although we performed sub-analyses to attempt to account for any effects of prior vaccination on the immune response.

5 Conclusion

This study provides the first information on MenACWY-TT immunogenicity and safety in the elderly. In adults 56 years of age and older with a varied meningococcal immunization history, MenACWY-TT was immunogenic, with 93 % of subjects achieving rSBA titers well above the seroprotective threshold (≥1:128) against all four serogroups after a single dose. MenACWY-TT was associated with few minor adverse events.

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Competing interests GD has received consulting fees and honoraria from GlaxoSmithKline within the last 3 years. NEA, SG and FH have no competing interests. VB, JM and NM are employees of GlaxoSmithKline Vaccines SA. JM and NM report ownership of GlaxoSmithKline stocks and stock options.

Authors contributions Ghassan Dbaibo, Nabil El-Ayoubi, Soha Ghanem and Farah Hajar contributed to the conception and design of the study, the identification of recruitment centers and the acquisition of data. Veronique Bianco was involved in the design and execution of statistical analyses. Jacqueline Miller and Narcisa Mesaros contributed to the conception and coordination of the study, in the analysis and interpretation of results. All authors were involved in the critical review of the manuscript and the approval of its final content.

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