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ORIGINAL RESEARCH

Immunogenicity and Safety of Quadrivalent Meningococcal Conjugate Vaccine (MenACYW-TT) in Potential Hajj/Umrah Pilgrims Aged ≥ 56 Years: A Phase III, Open-Label Study

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ABSTRACT

***Introduction*:** Invasive meningococcal disease poses a substantial disease burden worldwide, including older adults (aged ≥ 56 years) along with higher case fatality rates. MenACYW-TT, a quadrivalent meningococcal tetanus toxoid-conjugate vaccine, is indicated worldwide in individuals ≥ 56 years of age and is the only licensed vaccine in the USA for this age group. The annual Hajj pilgrimage is considered an epidemiologic event with approximately two million pilgrims per year; hence, immunization with a quadrivalent meningococcal vaccine is mandatory for visitors traveling to Saudi Arabia for Umrah and Hajj. We evaluated the immunogenicity and safety of a single dose of MenACYW-TT in prospective Hajj/Umrah pilgrims aged ≥ 56 years in Turkiye and Lebanon.

***Methods*:** In this open-label phase III study (NCT03869866), conducted in Turkiye and Lebanon, healthy adults aged ≥ 56 years received a single dose of the MenACYW-TT vaccine. Serum bactericidal assays were performed using human (hSBA) and rabbit (rSBA) complements to measure antibody titers against all four serogroups

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at baseline (D0) and 30 days post vaccination (D30). Safety data were collected up to 30 days (+14 days) post vaccination.

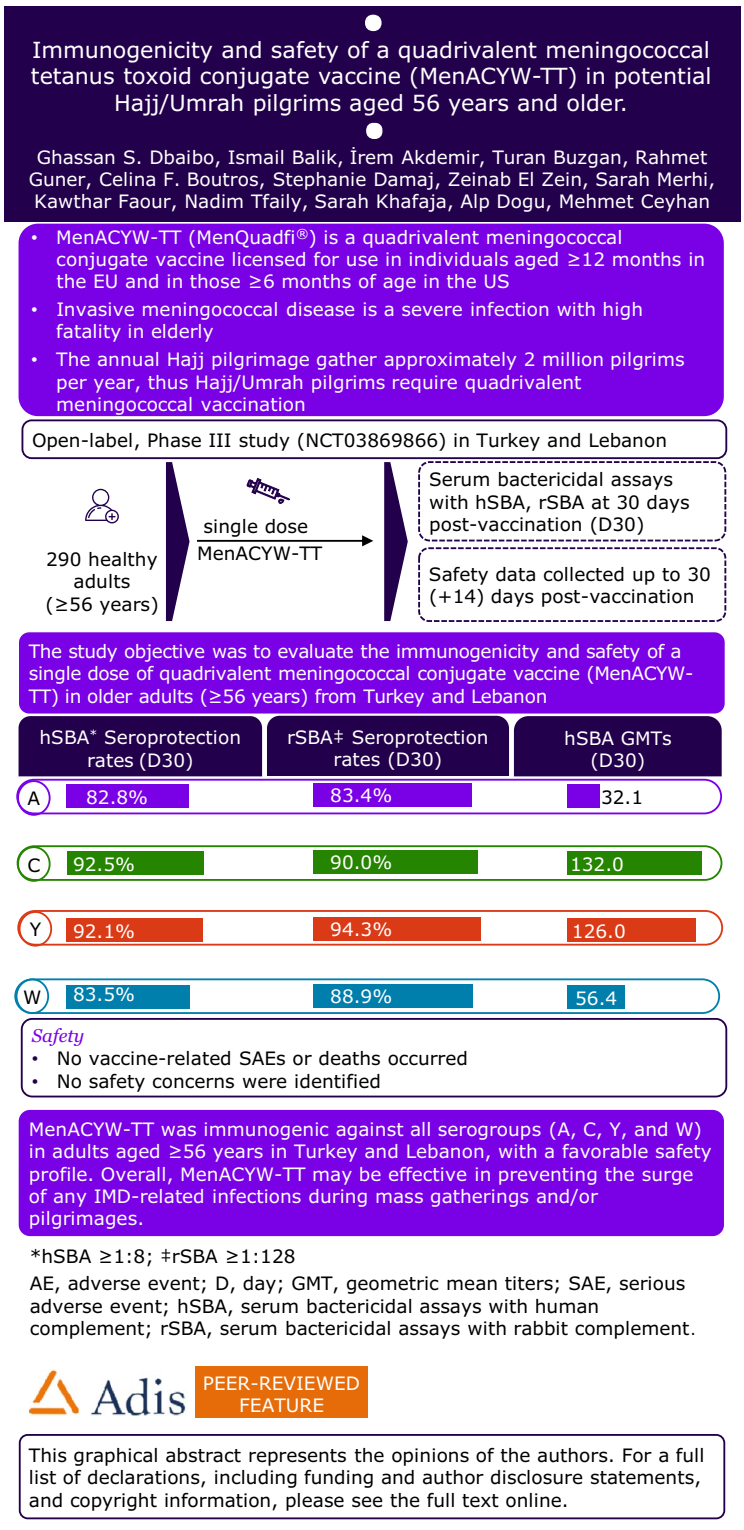
Results: A total of 290 individuals were enrolled in the study. On D30, vaccine seroprotection rates (hSBA titers ≥ 1:8) for serogroups A, C, Y, and W were 82.8%, 92.5%, 92.1%, and 83.5%, respectively, and rSBA titers (≥ 1:128) were 83.4%, 90.0%, 94.3%, and 88.9%, respectively. hSBA geometric mean titers (GMTs) were 32 [95% confidence interval (CI) 26.3–39.1], 132 (102–169), 126 (99.3–161), and 56.4 (43.8–72.6) for serogroups A, C, Y, and W, respectively. On D30, seroresponse rates in the per-protocol analysis set (PPAS) were 48–71.0%. Safety concerns and any serious adverse events related to the study vaccine were not observed.

Conclusions: MenACYW-TT vaccine induced a robust immune response against all serogroups (per seroprotection rates and GMTs). A single dose of the vaccine demonstrated acceptable safety profile in potential pilgrims aged ≥ 56 years.

Trial Registration: ClinicalTrials.gov, NCT03869866.

A Graphical Abstract is available for this article.

Graphical Abstract:



Keywords: MenACYW-TT; Invasive meningococcal disease; Older adults; Vaccine; Hajj/Umrah pilgrims; Immunogenicity; Safety

Key Summary Points

Why carry out this study?

Invasive meningococcal disease is a life-threatening infection across the globe with a higher incidence rate in older adults. The majority of international pilgrims are aged ≥ 56 years.

The quadrivalent meningococcal conjugate vaccine (MenACYW-TT) was found to be safe and immunogenic in previously conducted studies elsewhere; however, no studies have been conducted in pilgrim populations.

This study assessed the safety and immunogenicity of a single dose of quadrivalent meningococcal conjugate vaccine (MenACYW-TT) in prospective Hajj and Umrah pilgrims aged ≥ 56 years.

What was learned from the study?

A single dose of MenACYW-TT vaccine elicited immune responses, according to both hSBA and rSBA tests, against all serogroups contained in the vaccine (A, C, W, and Y).

This study confirmed that MenACYW-TT has a good safety profile in potential pilgrims and findings are consistent with previous studies.

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30919997

INTRODUCTION

Invasive meningococcal disease (IMD) is an acute and a potentially fatal infection that occurs worldwide. It is caused by *Neisseria meningitidis*, a Gram-negative diplococcus found exclusively in humans [1–3]. The annual global incidence of IMD is estimated to be 1.2 million cases, with case fatality rates ranging from 10% to 15%. Serious sequelae have also been reported, including loss of digits or limbs, neurological complications, and/or hearing loss, in survivors [3–6]. *N. meningitidis* has been classified into 12 different serogroups based on its capsular polysaccharides; however, the majority of IMD cases are attributed to only six serogroups, namely A, B, C, W, X, and Y [7]. Although the incidence of IMD is the highest in younger children (aged < 5 years), especially infants, the elderly population (aged ≥ 65 years) is the most impacted group in terms of case fatality rates [8–12].

Geographical variations also play an important role in serogroup distribution. For instance, serogroups B, C, and Y are frequently reported in North America, whereas serogroup A is more prevalent in parts of Asia and Africa [12]. Serogroup W has been associated with the majority of IMD cases during mass gatherings, especially during the Hajj or Umrah pilgrimage [9, 13, 14]. The Kingdom of Saudi Arabia (KSA) annually hosts over 10 million pilgrims from over 180 countries for Hajj or Umrah religious mass gatherings [15–17]. According to the Saudi Vision of 2030, the number of pilgrims visiting KSA is expected to surge to around 30 million by 2030 [18]. The Hajj is considered a public health challenge due to extended stay by pilgrims at Hajj sites, overcrowding, high humidity, and air pollution, which may increase the carriage rate of *N. meningitidis* to 80%, potentially causing an epidemic [19, 20]. Several instances of meningococcal disease outbreaks have been reported during Hajj and Umrah, including three major international instances: one serogroup A disease outbreak in 1987, and one serogroup W outbreak in 2000 and 2001 each. A few local disease outbreaks were also reported during the 1990s [20]. Following Umrah pilgrimages to KSA, a notable international outbreak was documented with 21 cases reported across multiple countries in 2024, including France, the UK, USA, Norway, Canada, and the Netherlands [21–24]. In 2025,

11 cases were reported by March, followed by six additional cases distributed between Eastern Mediterranean and European regions, ultimately reaching 51 cases by May 2025 [25, 26]. Additional cases were identified in Italy, India, and Qatar suggesting widespread international transmission associated with returning Umrah pilgrims [27–29].

As per the current recommendations from the Saudi Health authorities, all pilgrims are required to get vaccinated and submit a valid certificate indicating the receipt of a quadrivalent (ACWY) conjugate vaccine within the last 5 years [20]. Although strong disease surveillance will assist in understanding the ever-changing epidemiology of *N. meningitidis* and in predicting the possibility of future outbreaks, vaccination is considered the most effective solution for the prevention of meningococcal infection. According to the World Health Organization (WHO) recommendations, meningococcal vaccination is essential for high-risk age groups, including travelers to high-endemic regions [30]. A majority of pilgrims comprise of older adults (aged ≥ 56 years); hence, it is essential to provide a safe and immunogenic quadrivalent meningococcal vaccine for this susceptible population [31, 32]. A recent surge has been observed in IMD cases in the older population (aged ≥ 60 years) due to the absence of specific recommendations for prevention [33]. In older adults, IMD caused by the hypervirulent serogroups W and Y is more prevalent, and the infections are generally associated with atypical presentations, including pneumonia and septic arthritis [34–36]. Moreover, immune-related challenges in older adults (increased susceptibility to infections, waning of vaccine-related immunity) are some of the primary obstacles for the approval of effective vaccines in this age group [37, 38].

MenACYW-TT (MenQuadfi®, Sanofi) is a quadrivalent (serogroups A, C, W, and Y) meningococcal conjugate vaccine, licensed in more than 80 countries worldwide, including the European Union (EU), and is prequalified by the WHO. It was initially licensed for active immunization of individuals aged ≥ 12 months in the EU, Canada, and Australia (since 2020) and recently for those aged ≥ 6 weeks in the USA and Russia, since May 2025. Previously, a phase II (NCT01732627) and a phase III (NCT02842866) study reported that the safety profile of MenACYW-TT was tolerable, and it exhibited immunogenicity in older adults (≥ 56 years of age) that was comparable with the meningococcal polysaccharide (MPSV4) vaccine [32, 39]. The results from trial NCT02842866 demonstrated non-inferior seroresponse of MenACYW-TT compared with that of MPSV4 for all serogroups. Recently, a phase III study (NCT04142242) demonstrated sufficient immune response and favorable tolerability of a booster dose of MenACYW-TT in older adults (aged ≥ 59 years) primed with either MenACYW-TT or MPSV4 vaccine. Higher immune response was reported in participants primed with MenACYW-TT [40]. The immunogenicity and safety data for quadrivalent conjugate vaccines in the Middle Eastern population, especially older adults, are limited [41]. The aim of this phase III study was to evaluate the safety and immunogenicity of a single dose of quadrivalent meningococcal conjugate vaccine MenACYW-TT in older adults (aged ≥ 56 years) from Turkiye and Lebanon.

METHODS

Study Design and Participants

This was a phase III, open-label study to demonstrate the immunogenicity and safety of a single dose of MenACYW-TT vaccine in 290 healthy prospective pilgrims aged ≥ 56 years from Turkiye and Lebanon. Although the approximate recruitment target was 330 participants, the number of recruited participants was lower due to the coronavirus disease 2019 (COVID-19) pandemic, and the recruitment period was extended by 8 months. The study was performed from April 2019 (visit 1 for the first participant) to March 2022 (last visit for the last participant).

This study was registered on ClinicalTrials.gov (NCT03869866). The primary results of this study have been partially presented earlier [42]. The participants were excluded if they were involved in another study investigating a vaccine, drug, medical device, or procedure during

the study period; received any vaccine in the 4 weeks (28 days) preceding the study vaccination period; planned to get vaccinated prior to visit 2 except with influenza vaccine; or had previously been vaccinated against IMD with either the study vaccine or any other vaccine. Further exclusion criteria included known or suspected congenital or acquired immunodeficiency or receipt of immunosuppressive therapy within the preceding 6 months; a history of Guillain-Barré syndrome and/or meningococcal infection, confirmed either clinically, serologically, or microbiologically; high risk of meningococcal infection during the study (specifically, but not limited to, participants with persistent complement deficiency, with anatomic or functional asplenia); participants with bleeding disorder; or those who received anticoagulants in the 3 weeks preceding inclusion, contraindicating intramuscular vaccination. Participants with known systemic hypersensitivity to any of the vaccine components or history of a life-threatening reaction to the vaccine used in the study or to a vaccine containing any of the same substances were also excluded.

Key inclusion criteria were as follows: participants aged ≥ 56 years who were prospective Hajj or Umrah pilgrims (not within the next 10–12 months after vaccination). All eligible participants received a single dose (0.5 mL) of the MenACYW-TT vaccine, which contained 10 µg of each serogroup (A, C, W, and Y) and approximately 55 µg of tetanus toxoid protein carrier per dose formulated in 0.5 mL sodium acetate buffered saline solution. It was intramuscularly administered in the right or left deltoid region of the participants.

Ethical Approval

The protocol and any amendments were approved by applicable independent ethics committees or institutional review boards at each participating site and the appropriate regulatory agencies in each country (Supplementary methods). The study was consistent with the standard established by the Declaration of Helsinki and compliant with the International Council on Harmonisation guidelines for Good Clinical Practice, including all local and/or national regulations and directives. Signed and dated informed consent was received by all participants prior to the start of the study.

Immunogenicity

Pre-vaccination blood samples were collected from the participants for immunogenicity assessment at baseline (D0; visit 1) and on D30 (+ 14 days; visit 2).

Serum bactericidal assay (SBA) using human complement (hSBA; GI, Sanofi, Swiftwater, PA, USA) and baby rabbit complement (rSBA; UK Health Security Agency, Manchester, UK) was performed to measure the titers of antibodies against meningococcal serogroups A, C, W, and Y; both hSBA and rSBA were performed by qualified laboratory personnel as described previously [43]. The obtained bactericidal antibody titers were converted to geometric mean titers (GMTs) as described by Mak *et al*. [44]. The lower limit of quantification (LLOQ) of the hSBA assay was a titer of 1:4. Anti-tetanus antibodies were measured by electrochemiluminescence (ECL) assay performed at Global Clinical Immunology (GCI), Sanofi, Swiftwater, PA, USA according to a previous report by Varghese et al. [45].

The immunogenicity objectives were to describe the antibody response to meningococcal serogroups A, C, W, and Y measured by hSBA and rSBA before and 30 days (+ 14 days) after a single dose of MenACYW-TT vaccine. Endpoints for SBA testing were as follows:

- Seroprotection: For hSBA titer ≥ 1:8 and for rSBA titer ≥ 1:8 or 1:128 (conservative threshold).
- Seroresponse: For hSBA, participants with a pre-vaccination titer < 1:8 and a post-vaccination titer ≥ 1:16 or participants with a pre-vaccination titer ≥ 1:8 and ≥ fourfold increase.
- For rSBA, participants with a pre-vaccination titer < 1:8 and a post-vaccination titer ≥ 1:32 or participants with a pre-vaccination

titer ≥ 1:8 and ≥ fourfold increase hSBA and rSBA geometric mean titers (GMTs).

Antibody concentrations against tetanus toxoid at both pre- and post-vaccination time points, geometric mean concentrations (GMCs).

The proportion of participants achieving seroprotective levels of 0.01 international unit (IU)/mL and 0.1 IU/mL of antibody to tetanus toxoid protein at both pre- and post-vaccination time points.

Safety

Safety data were collected for up to 30 days following vaccination. Data regarding immediate unsolicited systemic adverse events (AEs) were collected within 30 min post vaccination. The participants were provided with diary cards, digital thermometers, and flexible rulers to monitor solicited injection-site reactions (pain, erythema, swelling, induration) and systemic reactions (fever, headache, malaise, myalgia) occurring up to 7 days after the vaccination. Any unsolicited AEs up to 30 days after the vaccination were recorded. Any serious adverse events (SAEs) were reported throughout the study period.

Statistical Analysis

Only descriptive analyses were performed in the study; therefore, no statistical hypothesis was tested. The 95% confidence interval (CI) of point estimates was calculated using the normal approximation for quantitative data and the exact binomial distribution (Clopper-Pearson method) for percentage. For GMTs or GMCs, 95% CI of point estimates were calculated using normal approximation assuming they were log-normally distributed. All immunogenicity analyses were performed for the per-protocol analyses set (PPAS), which comprised all participants who received at least one dose of the study vaccine, had a valid post-vaccination blood sample, and did not report any protocol deviation. The safety data were provided for the safety analysis set (SafAS), which comprised all participants who received at least one dose of the study vaccine and had safety data available.

RESULTS

Study Participants

A total of 290 participants were enrolled in this study (Turkiye, 31%; and Lebanon, 69%). At visit 1 (D0), 288 (99.3%) participants provided blood samples and received a dose of the MenACYW-TT vaccine. Participant flow through the study is shown in Fig. 1.

A total of 286 (98.6%) participants who were present on D30 provided a blood sample and completed the study. All (200/200) participants from Lebanon and 95.6% (86/90) of participants from Turkiye completed the study. Baseline demographic characteristics are summarized in Table 1.

Immunogenicity After Administration of MenACYW-TT

In the PPAS, the percentage of participants with meningococcal hSBA titer ≥ 1:8 for all serogroups was higher on D30 than that at baseline (D0) (serogroup A: 82.8% vs. 62.1%; serogroup C: 92.5% vs. 59.9%; serogroup W: 83.5% vs. 42.3%; serogroup Y: 92.1% vs. 54.1%) (Fig. 2a). A similar trend was observed for rSBA titers. On D30, the percentage of participants with meningococcal rSBA titers ≥ 1:128 for all serogroups was higher than that at baseline (D0) (serogroup A: 83.4% vs. 16.1%; serogroup C: 90.0% vs. 11.9%; serogroup W: 88.9% vs. 20.1%; serogroup Y: 94.3% vs. 22.5%) (Fig. 2b). In the PPAS, vaccine seroresponse rates on D30 were 48–71.0% (serogroup A: 48.0%; serogroup C: 71.0%; serogroup Y: 69.9%; and serogroup W: 63.4%) (Supplementary Table 1).

In the PPAS, baseline hSBA GMTs on D0 were lower than those on D30 across all serogroups (serogroup A: 9.50 vs. 32.1; serogroup C: 9.88 vs. 132; serogroup Y: 10.3 vs. 126; and serogroup W:

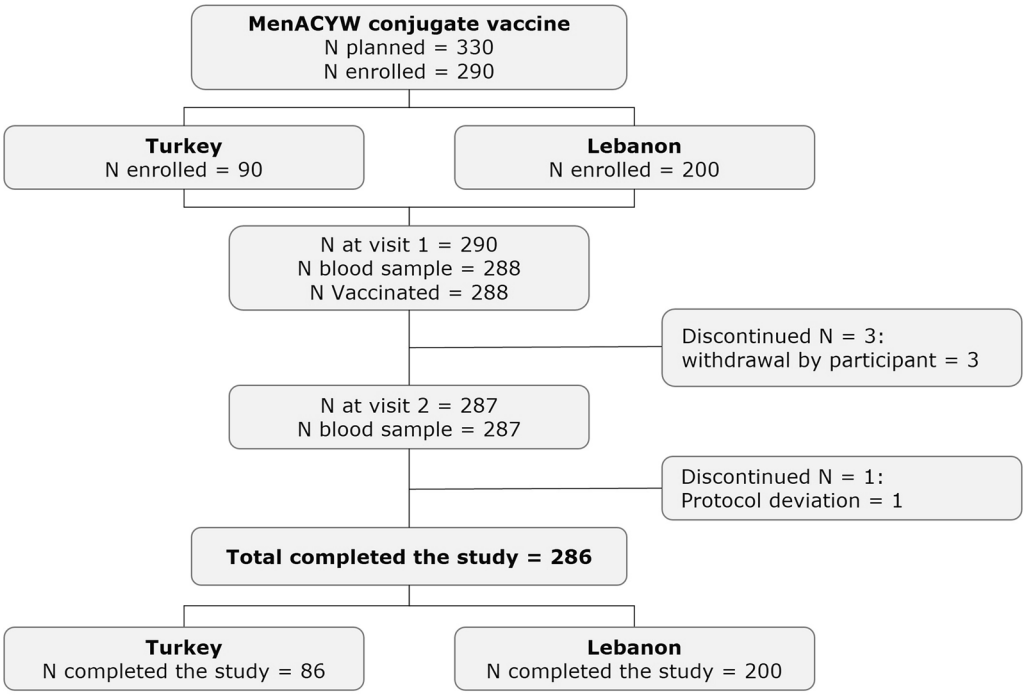


Fig. 1 Participant disposition flow chart. *N*, number of participants

Table 1 Baseline demographics of participants from SafAS

	SafAS (*N* = 288)
Sex, *n* (%)	
Male	187 (64.9)
Female	101 (35.1)
Sex ratio: male/female	1.85
Age, years	
Mean (SD)	64.7 (6.98)
Racial origin, *n* (%)	
White	288 (100)
Ethnicity, *n* (%)	
Not-Hispanic or Latino	288 (100)
Country, *n* (%)	
Turkiye	88 (30.6)
Lebanon	200 (69.4)

n, number of participants in the SafAS group; SafAS, safety analysis set

5.78 vs. 56.4) (Fig. 3a). Similarly, rSBA GMTs on D0 were lower than those on D30 for all serogroups (serogroup A: 8.75 vs. 658; serogroup C: 5.64 vs. 2038; serogroup Y: 8.16 vs. 2587; and serogroup W: 7.33 vs. 2725) (Fig. 3b). Furthermore, the percentage of participants with ≥ fourfold increase in hSBA titers from D0 to D30 was 50.9–73.8% (serogroup A: 50.9%; serogroup C: 72.0%; serogroup Y: 73.8%; and serogroup W: 69.2%) (Supplementary Table 1).

Anti-tetanus GMC (IU/mL) on D0 was 0.040 (95% CI 0.032; 0.049), and it increased to 0.425 (95% CI 0.287; 0.630) on D30. The percentage of participants achieving seroprotective levels ≥ 0.01 IU/mL and ≥ 0.1 IU/mL of antibody concentrations to tetanus toxoid was higher on D30 than at baseline (D0) (93.2% vs. 87.8% and 56.3% vs. 28.1%, respectively) (Table 2).

Safety

The safety profile of a single dose of MenACYW-TT for the SafAS is presented in Table 3. Overall, the MenACYW-TT vaccine was found to

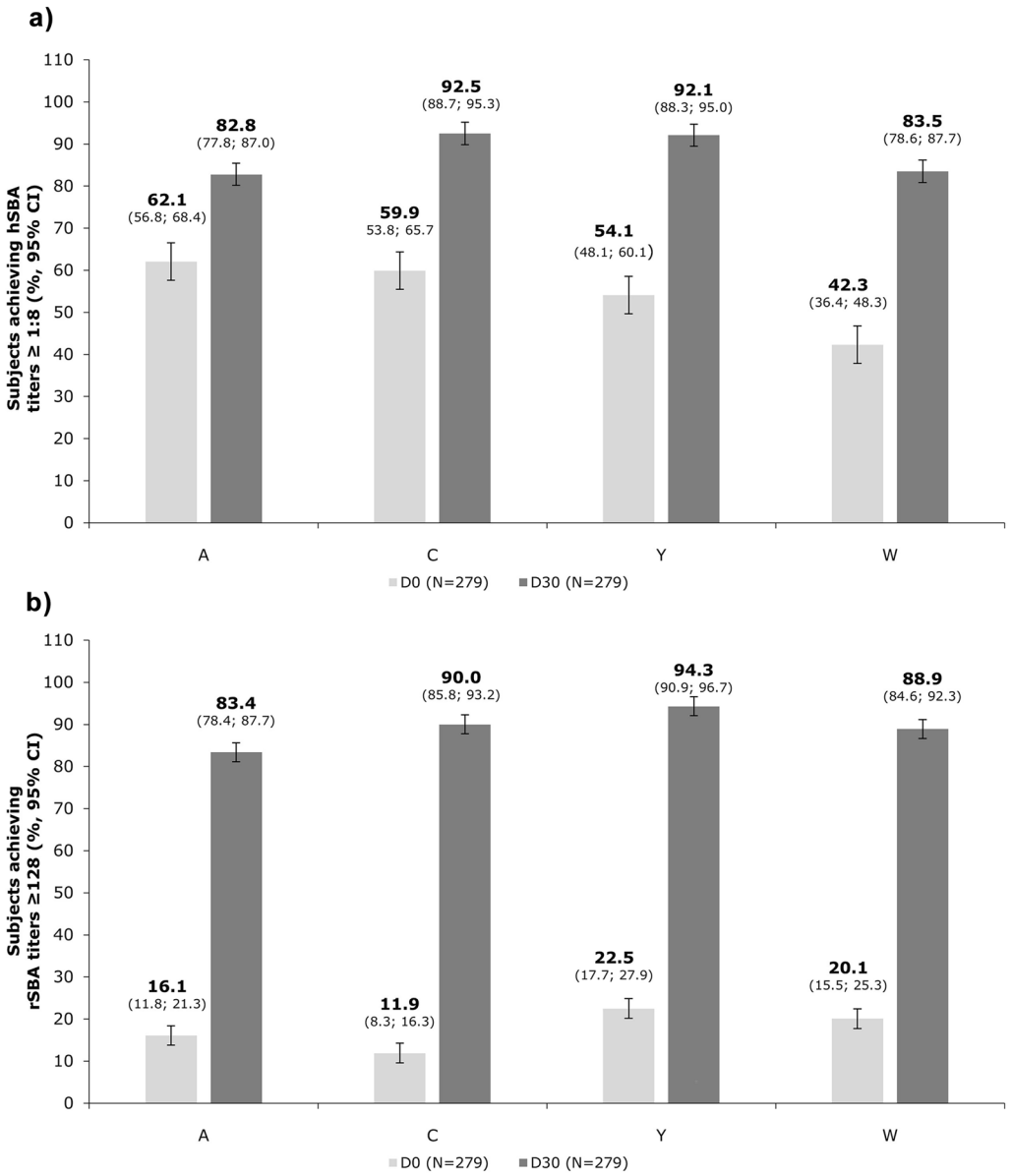


Fig. 2 **a** Percentage of participants achieving hSBA titers ≥ 1:8 at D30 (hSBA PPAS). **b** Percentage of participants achieving rSBA titers ≥ 1:128 at D30 (rSBA PPAS). CI, confidence interval; hSBA, serum bactericidal assay using human complement; PPAS, per-protocol analysis set; *N*, number of participants; rSBA, serum bactericidal assay using rabbit complement

be safe and well tolerated, with no identifiable safety concerns. Within 7 days post vaccination, 22.3% (64/287) of participants experienced at least one solicited reaction. The most frequently reported solicited injection-site reaction was injection-site pain in 13.6% (39/287) of participants, followed by injection-site swelling in 1.7% (5/287) of participants and injection-site erythema in 0.7% (2/287) of participants. Only 1 (0.3%) participant experienced at least one grade 3 solicited injection-site reaction. Overall, 20.6% (59/287) of participants experienced at least one solicited systemic reaction within 7 days after vaccination. The most frequently

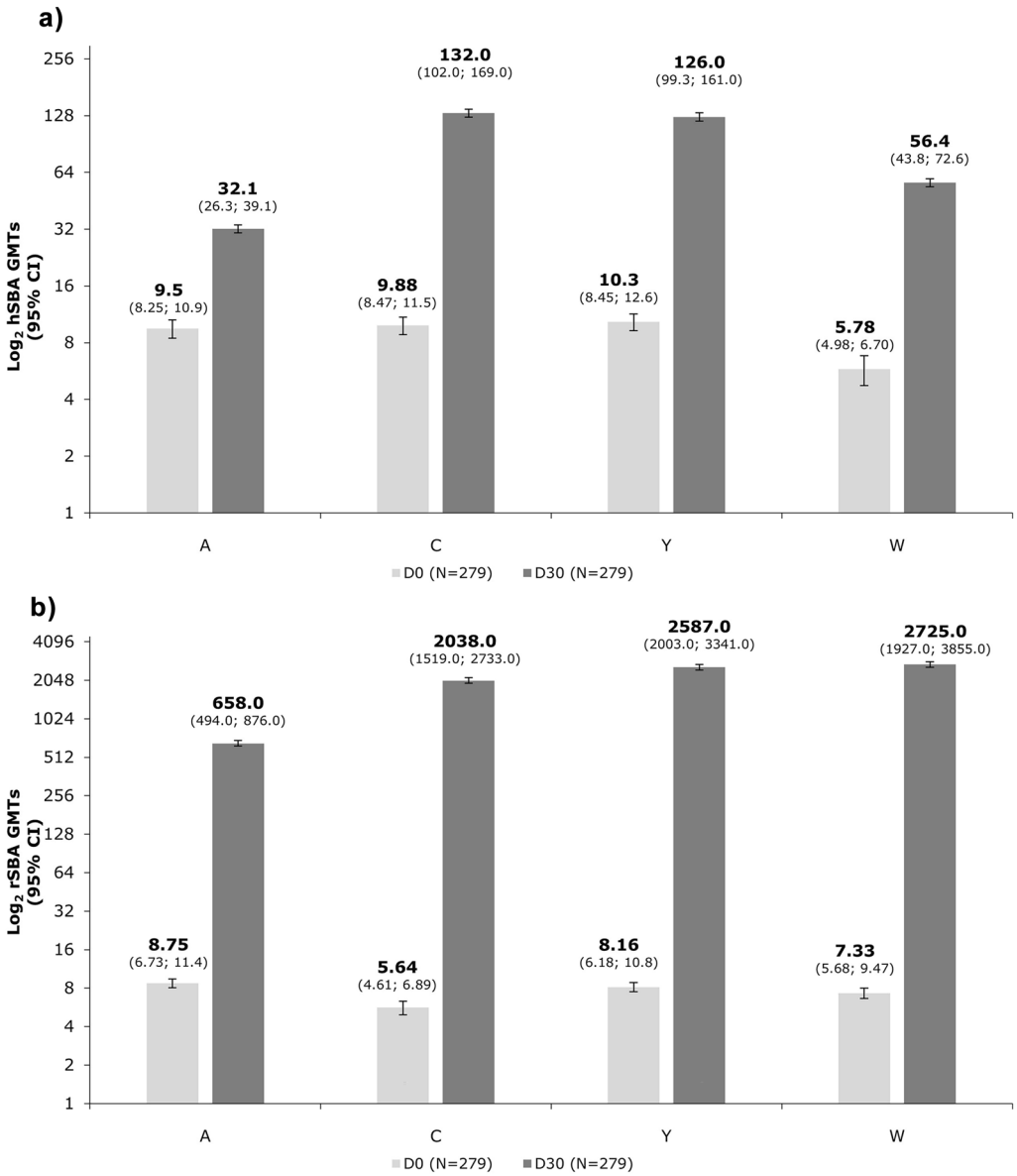


Fig. 3 **a** hSBA GMTS at D30 (hSBA PPAS) **b** rSBA GMTS at D30 (rSBA PPAS). CI, confidence interval; GMTs, geometric mean titers; hSBA, serum bactericidal assay using human complement; PPAS, per-protocol analysis set; *N*, number of participants; rSBA, serum bactericidal assay using rabbit complement

reported solicited systemic reaction was headache in 16.0% (46/287) of participants, followed by myalgia in 12.2% (35/287) of participants, malaise in 9.4% (27/287) of participants, and fever in 4.4% (12/271; a total of 16 participants were excluded from the denominator for solicited fever endpoints due to missing derived presence) of participants. Five (1.7%) participants reported at least one grade 3 solicited systemic reaction.

No immediate unsolicited AEs were reported within 30 min of vaccination. Within 30 days after vaccination, 14.2% (41/288) of participants experienced at least one unsolicited non-serious

Table 2 Anti-tetanus antibody concentration (ECL, IU/mL) (PPAS)

Seroprotection levels	PPAS ($N = 279$)
At D0	
≥ 0.01 IU/mL	
n (%)	244 (87.8)
95% CI	(83.3; 91.4)
≥ 0.1 IU/mL	
n (%)	78 (28.1)
95% CI	(22.9; 33.7)
GMC	0.040
(95% CI)	(0.032; 0.049)
At D30	
≥ 0.01 IU/mL	
n (%)	260 (93.2)
95% CI	(89.6; 95.9)
≥ 0.1 IU/mL	
n (%)	157 (56.3)
95% CI	(50.2; 62.2)
GMC	0.425
(95% CI)	(0.287; 0.630)

CI, confidence interval; D, day; ECL, electrochemiluminescence; GMC, geometric mean concentration; IU, international units; *N*, number of participants in hSBA PPAS; *n*, number of participants experiencing the endpoint listed in the first column; PPAS, per-protocol analysis set

AEs. Most participants experienced grade 1 or grade 2 unsolicited non-serious AEs, which were resolved within 7 days. Five grade 3 unsolicited non-serious AEs were reported in 4 (1.4%) participants. Overall, 1.7% (5/288) of participants experienced at least one unsolicited non-serious adverse reaction (AR) after 30 days of vaccination. Only 1 (0.3%) participant reported two grade 3 unsolicited non-serious ARs, including injection-site erythema and injection-site swelling. No AEs resulted in study discontinuation, and no adverse events of special interest (AESIs) were reported during the study. There were no related SAEs or deaths.

DISCUSSION

This phase III study demonstrated that a single dose of MenACYW-TT (MenQuadfi) was immunogenic and exhibited a favorable safety profile in healthy older adults (aged ≥ 56 years). This robust immune response of MenACYW-TT was based on the proportion of participants achieving hSBA and rSBA titers for serogroups A, C, W, and Y at D30 compared with that at baseline (D0). The overall immunogenicity data are consistent with previous phase II and III studies involving MenACYW-TT in older adults [32, 39]. Limited clinical evidence is available for the immune response of other meningococcal conjugate vaccines in older adults (aged ≥ 56 years). One study involving a conjugate vaccine (MCV4-TT; Nimenrix®, Pfizer) in comparison with a polysaccharide vaccine was immunogenic in this population. In this study, the GMTs elicited by MCV4-TT were lower compared to plain polysaccharide vaccine [41]. In previously mentioned studies MenACYW-TT provided higher GMTs compared to plain polysaccharide vaccine [32, 39]. The clinical relevance of this finding is unknown. MenACYW-TT provided more persistent immune responses compared with a plain polysaccharide vaccine. A small study involving MCV4-CRM (Menveo®, GSK) reported comparable or higher immune responses in older adult participants (56–65 years) than those of a polysaccharide vaccine [46]. Two other studies in this age group assessed the immunogenicity of booster doses of MenACYW-TT. Of these, one study demonstrated that a booster dose of MenACYW-TT was immunogenic and showed persistence in the immune response up to 7 years after primary vaccination; the second study confirmed the immunogenicity of a single booster dose of MenACYW-TT, with a higher immune response in participants primed with MenACYW-TT [40, 47]. Further, MenACYW-TT provided higher persistence compared to polysaccharide vaccine, and a booster dose of it was reported to be safe and immunogenic. These

Table 3 Safety overview post MenACYW-TT vaccination: SafAS

Period/participants experiencing ≥ 1	MenACYW-TT (*N* = 288)	
	n*/*M	**% (95% CI)**
Within 30 min after vaccination		
Immediate unsolicited AE	0/288	0 (0; 1.3)
Immediate unsolicited AR	0/288	0 (0: 1.3)
Solicited reaction within solicited period after vaccination	64/287	22.3 (17.6; 27.6)
Solicited injection-site reaction	39/287	13.6 (9.8; 18.1)
Solicited systemic reaction	59/287	20.6 (16.0; 25.7)
Within 30 days after vaccination		
Unsolicited AE	46/288	16.0 (11.9; 20.7)
Unsolicited AR	5/288	1.7 (0.6; 4.0)
Unsolicited non-serious AE	41/288	14.2 (10.4; 18.8)
Unsolicited non-serious AR	5/288	1.7 (0.6; 4.0)
Unsolicited non-serious injection-site AR	5/288	1.7 (0.6; 4.0)
Unsolicited non-serious systemic AE	36/288	12.5 (8.9; 16.9)
Unsolicited non-serious systemic AR	0/288	0 (0; 1.3)
AE leading to study discontinuation	0/288	0 (0; 1.3)
SAE	5/288	1.7 (0.6; 4.0)
Death	0/288	0 (0; 1.3)
AESI	0/288	0 (0; 1.3)

AE, adverse event; AR, adverse reaction related to study vaccine; CI, confidence interval; *n*, number of participants experiencing the endpoint listed in the first column; *N*, number of participants in the safety analysis set (SafAS); *M*, number of participants with available data for the relevant endpoint

findings are in line with the recommendations of the Ministry of Health of Kingdom of Saudi Arabia on primary and booster vaccination during Hajj and Umrah considering primary and booster vaccination [48]. Results from the current study, in addition to previously mentioned studies, suggest that MenACYW-TT can be used to protect the population aged ≥ 55 years against IMD.

We observed an increase in the GMC of tetanus toxoid antibodies in the participants receiving the study vaccine, due to the presence of the tetanus toxoid carrier protein. Although this observation is important, its clinical significance

is unclear. MenACYW-TT is not indicated for active immunization against tetanus infection, but similar observations were reported in other studies involving MenACYW-TT [49, 50] and other tetanus toxoid conjugate vaccines [51].

The MenACYW-TT vaccine was well tolerated, with no immediate hypersensitivity reactions, vaccine-related SAEs, and AEs leading to discontinuation, which was consistent with previous reports investigating MenACYW-TT in older adults aged ≥ 56 years [32, 40]. The country-stratified safety data revealed that the percentage of solicited reactions within 7 days after vaccination was higher in the participants from Lebanon (27.0% [54/200]) than in the participants from Turkiye (11.5% [10/87]). Similarly, the percentage of solicited reactions was higher in the participants from Lebanon (25.0% [50/200]) than in the participants from Turkiye (10.3% [9/87]). A similar trend was observed with solicited injection-site reactions. Although there is no specific explanation regarding the difference in the AEs between Turkiye and Lebanon, it may be attributed to the cultural/social differences between the countries. All participants experiencing unsolicited AEs belonged to Lebanon, except for one participant from Turkiye who experienced an unsolicited non-serious systemic AE. All SAEs were reported in the participants from Lebanon; however, the SAEs were unrelated to the vaccine. Moreover, the age-stratified safety data demonstrated that the percentage of solicited reactions within 7 days after vaccination was higher in the participants aged 56–64 years (30.5% [50/164]) than in the participants aged ≥ 65 years (11.4% [14/123]), and it was comparable between the participants aged 65–74 years (11.0% [10/91]) and those aged ≥ 75 years (12.5% [4/32]). Similarly, the percentage of solicited systemic reactions was higher in the participants aged 56–64 years (28.0% [46/164]) than in the participants aged ≥ 65 years (10.6% [13/123]), and it was comparable between the participants aged 65–74 years (9.9% [9/91]) and those aged ≥ 75 years (12.5% [4/32]).

This is the first study to report the immunogenicity and safety of MenACYW-TT (MenQuadfi®) in the Middle Eastern older adult population aged ≥ 56 years, who were prospective Hajj/Umrah pilgrims. Our study results are of primary importance for Middle-Eastern or North African regions because higher fatality rates have been reported for IMD in the older adult population than in the infants and children [11, 52, 53]; a majority of Hajj and Umrah pilgrims belong to this age group, and the immunogenic and safety responses of the study vaccine in this population are promising. These results are also important for pilgrims originating from the USA, as currently, MenACYW-TT is the only meningococcal vaccine licensed in the USA for older adults against IMD because the previously licensed vaccine (Menomune®, Sanofi) was discontinued a few years ago. Recent guidelines by the Centers for Disease Control and Prevention in the USA recommend the use of quadrivalent conjugate vaccines for pilgrims of all age groups, including older adults traveling to the African meningitis belt or for the Hajj pilgrimage [54]. Another strength of this study was that both hSBA and rSBA were performed in a similar environment (GCI Sanofi and UK Health Security Agency, Manchester, UK, respectively), which enhanced the credibility of our data. However, there were a few limitations. The statistical analyses were descriptive in nature, and the study was not powered to test any hypothesis. Another limitation that should be considered during the interpretation of the results is the open-label nature of the study, and the lack of randomization and a comparator. In the absence of a control group, our ability to attribute observed effects solely to the intervention is limited.

CONCLUSION

The MenACYW-TT vaccine exhibited immunogenicity against all four serogroups (A, C, W, and Y) in older adults (aged ≥ 56 years) from Turkiye and Lebanon. MenACYW-TT was associated with few minor AEs, but no vaccine-related SAEs or deaths were reported; hence, no safety concerns regarding the vaccine were observed. Overall, MenACYW-TT will be an effective asset in preventing the surge of any IMD-related infections during mass gatherings and/or pilgrimages.

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Data Availability. The dataset generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Qualified researchers may request access to patient-level data and related documents. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at https://www.vivli.org/.

Declarations

Conflict of Interest. The authors declare the following financial interests/personal relationships, which may be considered as potential competing interests: Alp Dogu is a Sanofi employee and may hold shares and/or stock options in the company. Ghassan Dbiabo received grants from Sanofi to his institution. Ismail Balik, Irem Akdemir, Turan Buzgan, Rahmet Guner, Celina Boutros, Stephanie Damaj, Zeinab El Zein, Sarah Merhi, Kawthar Faour, Nadim Tfaily, Sarah Khafaja, and Mehmet Ceyhan report no conflict of interest.

Ethical Approval. The protocol and any amendments were approved by applicable independent ethics committees or institutional review boards at each participating site and the appropriate regulatory agencies in each country (Supplementary methods). The study was consistent with the standard established by the Declaration of Helsinki and compliant with the International Council on Harmonisation guidelines for Good Clinical Practice, including all local and/or national regulations and directives. Signed and dated informed consent was received by all participants prior to the start of the study.

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