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REVIEW

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A new quadrivalent meningococcal tetanus toxoid conjugate vaccine: Menquadfi® (MENACWY-TT)

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ABSTRACT

Neisseria meningitidis (Nm) remains a major global health concern, causing invasive meningococcal disease (IMD) with significant morbidity and mortality. Despite vaccination efforts, Nm serogroup prevalence and antibiotic resistance continue to evolve, necessitating ongoing surveillance and novel immunization strategies. This review aims to assess the role of MenACWY-TT, a quadrivalent meningococcal conjugate vaccine, in IMD prevention by evaluating its immunogenicity, safety, and real-world effectiveness. The objectives include analyzing its advantages over existing vaccines, identifying gaps in long-term immunity data, and assessing its potential integration into National Immunization Programs (NIPs). MenACWY-TT has demonstrated strong immunogenicity, a favorable safety profile, and ease of administration with its liquid, non-adjuvanted formulation. Real-world studies show high vaccine effectiveness and herd protection benefits. However, further research is needed to evaluate long-term immunity and efficacy in high-risk populations.

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Introduction

Neisseria meningitidis (Nm) is a gram-negative diplococcus that commonly colonizes the upper respiratory tract and can lead to invasive meningococcal disease (IMD) after entering the bloodstream.[1,2] IMD primarily presents as meningitis and/or septicemia, but other forms of disease may also occur, such as septic arthritis, pericarditis, and pneumonia.[3] IMD can cause significant morbidity and mortality, as well as long-term sequelae among survivors, including neurologic complications, hearing loss, and skin scars and amputations.[4]

Twelve serogroups of *Nm* have been identified based on their capsular polysaccharide composition (A, B, C, E, H, I, K, L, X, W, Y, and Z), and serogroups A, B, C, W, X, and Y account for the majority of meningococcal cases worldwide.[5] The incidence and prevalence of *Nm* serogroups vary dynamically with time and geographical location.[6] Serogroup B is predominant in Europe, the United States (U.S.), and Australia, followed by C, W, and Y. Before the introduction of the Men A conjugated vaccine (MenAfriVac), serogroup A was the most predominant cause of meningococcal disease in sub-Saharan Africa and remained a significant serogroup in other parts of the world.[6] Serogroup W has emerged globally since the early 2000s, with particular relevance to travel-related outbreaks such as those associated with the Hajj. Serogroup W continues to be a significant serogroup affecting individuals of all age groups.[7] Men Y has been increasing in relative incidence over recent years in North America, South America, and South Africa, and most recently, Men X cases have been observed in sub-Saharan Africa.[8] Serogroup types and patient age are the most important key factors for mortality. A recent global meta-analysis and systematic review showed that serogroup W has the highest fatality rate, followed by serogroups Y and C, and serogroup B has the lowest case fatality number. The mortality rate was predicted to be 9.0% in infants, 7.0% in 7–10-year-old children, 10.4% in adolescents, and 15.0% in adults, with a gradual increase reaching 32.8% in 80-year-olds.[9] A retrospective epidemiological study from Spain revealed that 30% of the deaths occurred in children under 5 years of age, with a hospitalization rate of 46% in the same age group.[10]

IMD is still a considerable global health care problem with an eminently dynamic epidemiology due to extensive vaccine usage. The global incidence of IMD is generally < 1 case per 100,000 persons per year; the disease burden is disproportionately high in children <5 years old, particularly in those <1 year old.[11–14] Vaccination remains a pivotal element in IMD prevention and in achieving the WHO's 2030 goals for meningitis control.[15] The development of meningococcal vaccines began with polysaccharide vaccines and continued with conjugate vaccines.[16] Several advantages make conjugate vaccines favorable, including constant and stronger immunogenicity in all age groups, the ability to boost immunity, the potential to decrease nasopharyngeal carriage, and their contribution to herd protection.[6] The U.S. Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) recommends routine vaccination with

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a quadrivalent meningococcal conjugate vaccine (MenACWY) for adolescents aged 11 or 12 years, with a booster dose at age 16 years. In the United Kingdom (UK), MenACWY conjugate vaccines are routinely given to adolescents (ages 13–14) and are available up to age 25 for those who missed their dose, especially first-time university students.[17] In the Netherlands, MenACWY vaccination is administered as part of the National Immunization Program at 14 months, alongside the MMR vaccine, and again to adolescents aged 13–14 years to provide continued protection against meningococcal disease caused by serogroups A, C, W, and Y.[18] In Australia, MenACWY conjugate vaccines are given at 12 months and to adolescents aged 14–16 years through school-based programs. Catch-up doses are available for 15–19-year-olds and those at higher risk.[19] In Chile, MenACWY conjugate vaccines are given to toddlers as part of the national immunization program, typically at age 12 months.[20] In addition, high-risk groups include individuals with complement deficiencies, asplenia, HIV infection, laboratory exposure to *N. meningitidis*, or those who travele to endemic areas. The ACIP also recommends routine MenACWY vaccinations for individuals aged over 2 months within a risk group, as well as booster doses for previously vaccinated people who become or remain at increased risk.[21]

Several types of meningococcal vaccines are currently available: serogroup B or MenB vaccines (Bexsero® and Trumenba®) and various quadrivalent meningococcal conjugate or MenACWY vaccines (MenACWY-D (Menactra®), MenACWY-CRM (Menveo®), MCV4-TT (Nimenrix), and MenACWY-TT (MenQuadfi®)). PENBRAYA™ (MenACWY and MenB vaccine) has recently been approved by the U.S. Food and Drug Administration (FDA) as the first pentavalent vaccine that provides coverage against the five most common meningococcal serogroups in adolescents and young adults, from 10 to 25 years of age.[22]

MenACWY-TT is the latest approved MenACWY conjugate vaccine, which uses the tetanus toxoid (TT) as a protein carrier. The aim of this review is to provide an update on MenACWY-TT, highlight its role in IMD prevention, identify unmet needs, and explore its potential for broader integration into immunization strategies.

Materials and methods

We searched the medical literature in December 2024 using the electronic databases PubMed (MEDLINE), EMBASE, clinicaltrials.gov, and Cochrane Library databases. We restricted the search to peer-reviewed published articles in English, with no restrictions on publication years. We used keywords compliant with PubMed's Medical Subject Headings (MeSH) terms, including "invasive meningococcal disease," "invasive meningococcal disease prevention," "meningococcal vaccines," "meningococcal meningitis," "meningococcal vaccines," "conjugate meningococcal vaccine," "MenACWY," and "quadrivalent meningococcal vaccine." We employed the Boolean search technique during the literature search, combining the keywords "AND" and "OR." We then selected studies that met the following selection criteria: case reports, case series, clinical trials, original articles, and reviews. We excluded papers that were not written in English or were not relevant. The reviewers evaluated the full texts of eligible publications after screening the abstracts based on the inclusion and exclusion criteria.

Results

Meningococcal vaccines in historic evolution and current immunization perspective

There are three types of meningococcal vaccines: polysaccharide, conjugate, and protein. The first vaccines based on bacterial cell wall polysaccharides against serogroups A, C, W, and Y had several limitations, including a short duration of protection, poor immune responses in infants, and lack of immune memory.[23] Polysaccharides mostly trigger short-term B-cell responses by bonding the receptor, which leads to the differentiation of B cells into plasma cells to produce antibodies. Most polysaccharide vaccines do not produce new memory B cells; instead, the terminal differentiation of memory B cells to plasma cells reduces the memory B-cell pool and results in an inadequate response to booster doses.[24]

To boost cellular immune response and generate immune memory, researchers design conjugate vaccines by covalently binding an antigen to an immunogenic carrier protein (such as tetanus toxoid, diphtheria toxoid, or diphtheria toxoid variant CRM197).[24] Therefore, conjugated vaccines induce a T-cell-dependent response in association with MHC class II molecules, create a memory response to booster doses, and provide long-term immunity. Conjugate vaccines may also contribute to herd protection by reducing nasopharyngeal colonization and transmission.[25] Serogroup B has presented significant challenges in vaccine development, such as poor immunogenicity with conjugate vaccine strategies and triggering autoimmunity with polysaccharide vaccines.[23–26] Recently, there are two meningococcal protein-based serogroup B vaccines licensed, including the 4CMenB vaccine (Bexsero®) and the MenB-FHbp vaccine (Trumenba®).[26]

Targeting combinations of serogroups with the same vaccine has become a cost-effective way to stop meningococcal infections as more people travel around the world and the spread of these infections varies by location.[27] Therefore, researchers have developed four different quadrivalent meningococcal vaccines for serogroups A, C, W, and Y and implemented them in national immunization program schedules (NIPs) in various countries (Table 1).

MenACWY-DT (Menactra) is the first quadrivalent meningococcal conjugate vaccine, recommended as two doses for infants between 9 and 23 months of age, and as a single dose for individuals from 2 to 55 years old.[28] Waning immunity has been reported within 5 years of a primary dose; a booster dose 4 to 6 years after primary vaccination was shown to be safe and effective, and antibody persistence has been further documented 4 years after the booster dose.[29,30]

MenACWY-CRM (Menveo) was first licensed in 2010. It is currently available to people aged two months to 55 years old in the U.S. and other countries, including Argentina, Australia, and Saudi Arabia, as well as two years old in the European Union (EU).[31] It is recommended as a four-dose series in infants

Table 1. Four different quadrivalent meningococcal vaccines for serogroups A, C, W, and Y and NIPs.

Vaccine	Manufacturer	Trade Name	License (FDA/EMA)	Formulation	Posology
MenACWY-DT	Sanofi, USA	Menactra®	FDA (2005)- 9 months to 55 years	Solution for injection	Primary Vaccination: • Children 9 through 23 months of age: Two doses, three months apart. • Individuals 2 through 55 years of age: A single dose. Booster Vaccination: • A single booster dose may be given to individuals 15 through 55 years of age at continued risk for meningococcal disease, if at least 4 years have elapsed since the prior dose
MenACWY-CRM	GlaxoSmithKline Vaccines S.r.l.	Menveo®	FDA (2010)- 2 months–55 years/ EMA (2010)-≥2 years	Powder and solution for solution for injection	Primary Vaccination: • In children initiating vaccination at 2 months of age, administer as a 4-dose series at 2, 4, 6, and 12 months of age. • In children initiating vaccination at 7 months through 23 months of age, administer as a 2-dose series with the second dose administered in the second year of life and at least 3 months after the first dose. • In individuals aged 2 through 55 years, administer as a single dose. Booster Vaccination: • A single booster dose of MENVEO may be administered to individuals aged 15 through 55 years who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of a meningococcal (serogroups A, C, Y, W-135) conjugate vaccine.
MCV4-TT	Pfizer Europe MA EEIG	Nimenrix®	EMA (2012)- ≥2 years	Powder and solvent for solution for injection	Primary Vaccination: • Infants from 6 weeks to less than 6 months of age 2-dose series given 2 months apart at •Infants from 6 months of age, children, adolescents and adults single dose injection. Booster Vaccination: •Infants from 6 weeks to less than 12 months of age: A single booster dose at 12 months of age, at least 2 months after the last dose of Nimenrix.
MenACWY-TT	Sanofi, USA	MenQuadfi®	FDA (2020)- ≥2 years/ EMA (2020)- ≥12 months	Solution for injection	Primary Vaccination: • Individuals 12 months of age and older receive a single dose of MenQuadfi Booster Vaccination: • A single dose of MenQuadfi may be administered to individuals 15 years of age and older who are at continued risk for meningococcal disease if at least 4 years have elapsed since a prior dose of meningococcal (groups A, C, W, Y) conjugate vaccine

from two to six months of age with a considerable risk for meningococcal disease, a three-dose series in healthy infants from two to six months of age, a two-dose series between 7 and 23 months of age, and as a single dose from two years of age.[32] Recent reports showed that all age groups could maintain antibody levels for up to five years after the primary dose. Due to the effective memory response, booster doses dramatically triggered antibody titers for all four serogroups.[33,34] Two doses of MenACWY-CRM were found to be superior compared to a single dose in terms of antibody response and persistence in the first-year post-vaccination for serogroups C and Y in the 2- to 5-year-old age cohort and for serogroup Y in the 6- to 10-year -old age cohort.[35] However, this variability did not continue 5 years later, as the quantity of remaining antibodies was not different in both age groups. The decrease of antibody titers over the 5-year period was more prominent against serogroup A compared to the others.[36] The study demonstrated that MenACWY-CRM significantly reduced meningococcal carriage rates in the first 12 months post-vaccination among 18- to 24-year-old students in the UK.[37] Accordingly, administering a single dose of MenACWY-CRM to more than 1.5 million soldiers in the Korean Armed Forces significantly decreased meningococcal disease incidence and mortality in a 19- to 23-month follow-up period.[38]

MCV4-TT (Nimenrix) was first approved in 2012 and is now available for individuals over the age of six weeks in the EU. It is recommended to be used as a two-dose series in healthy infants from six weeks to six months of age, followed by a booster dose at 12 months of age, and as a single dose from six months of age. It is currently not approved by the U.S. FDA.[39]

There is remarkable variability in national immunization policies for meningococcal disease. The U.S. CDC recommends routine MenACWY vaccination for all adolescents at aged to 12 years old, with a booster dose at 16 years old, and for children and adults at increased risk for meningococcal disease.[40] In 2015, the UK replaced the adolescent MenC booster dose with a MenACWY dose. Spain, Andorra, and Greece kept the infant and/or toddler MenC dose but changed the adolescent MenC dose to MenACWY. in 2017, Spain introduced the MenACWY vaccination as a single dose for adolescents aged 12 to 14. Several other European countries, including Switzerland, Cyprus, and the Netherlands, fully replaced MenC vaccination with MenACWY in both children and adolescents.[41] Turkiye requires all Turkish pilgrims to the Hajj to have a quadrivalent meningococcal polysaccharide vaccine before traveling, despite not routinely recommending MenB and MenACWY conjugate vaccines for infants and adolescents.[42]

MenACWY-TT (MenQuadfi®): a new quadrivalent meningococcal conjugate vaccine

The latest available quadrivalent meningococcal conjugate vaccine is MenACWY-TT (MenQuadfi, Sanofi Pasteur). The U.S. FDA and the European Medicines Agency (EMA) approved MenACWY-TT in 2020, making it available for individuals 2 years and older in the USA and for those 12 months and older in Europe. MenACWY-TT comes in a ready-to-use liquid formulation, with a recommended single dose.[43,44]

MenQuadfi is the first and only quadrivalent conjugate meningococcal vaccine in the U.S. that utilizes tetanus toxoid as a protein carrier. It is the only MenACWY-TT conjugate vaccine available in Europe in a fully liquid formulation. MenACWY-TT was prepared with the conjugation of polysaccharides to TT at a high polysaccharide-to-protein ratio via reductive amination for serogroups C, W, and Y, and carbonyl diimidazole/adipic acid dihydrazide linker chemistry for serogroup A. As the addition of adjuvants did not generate any remarkable enhancement of the antibody response, it has been developed as a non-adjuvanted vaccine as well. Individual conjugate structures were evaluated for each serogroup (A, C, W, and Y). This novel formulation resulted in strong antibody responses in the preclinical studies.[45] Regulatory approvals are established based on the results of several randomized, multicentric clinical trials that evaluated safety and immune efficacy in vaccinated individuals (Table 2).[43,44]

The main element that protects against invasive meningococcal diseases is antibodies that kill bacteria by targeting capsular polysaccharides of serogroups A, C, W, and Y. There are two serum bactericidal activity (SBA) assays using either rabbit complement (rSBA) or human complement (hSBA). Antibody titers ≥ 1:4 are considered seroprotective, though often, a more conservative threshold of ≥ 1:8 is used in studies.

Immunogenicity and safety in toddlers and children

A Phase II study involving 188 toddlers aged 12–24 months was randomized 1:1 to MenACWY-TT or MCV4-TT in Finland (MET54; NCT03205358). Immunogenicity was assessed with two different assays: human complement (hSBA) and baby rabbit complement (rSBA) in this study. MenACWY-TT and MCV4-TT showed similar increases in serogroup-specific meningococcal hSBA GMTs, with over 90% of participants achieving seroprotection for all serogroups. The proportion of participants with an hSBA vaccine seroresponse was similar in both groups for serogroups A, W, and Y but was higher for serogroup C in the MenACWY-TT group (100%) than in the MCV4-TT group (86.0%). There were no immediate unsolicited adverse events or reactions after vaccination in either vaccine group.[46]

The participants in a different Phase III study were 918 12- to 23-month-old toddlers who had either never been vaccinated against meningococcal disease or had a primary monovalent meningococcal C (MenC) vaccination in their first year of life (MET 51; NCT02955797). The study administered either a single dose of MenACWY-TT or MCV4-TT. MenACWY-TT's vaccine response was non-inferior to MCV4-TT, regardless of their meningococcal vaccine background, and both vaccines were well tolerated. Seroprotection in vaccine-naïve participants was 90.8% vs. 89.5% against serogroup A; 99.3% vs. 81.4% against serogroup C, 83.6% vs. 83.4% against serogroup W, and 93.2 vs. 91.6% against serogroup Y for MenACWY-TT and MCV4-TT, respectively. In MCC-primed participants, seroprotection rates were 89.8% vs. 98.0% against serogroup A; 99.0% vs. 98.0% against serogroup C; 86.7% vs. 85.7% against serogroup W; and 95.9% vs. 91.9% against serogroup Y for MenACWY-TT and MCV4-TT, respectively.[47]

A Phase III, multicentric, modified double-blind study was performed to analyze the immune response for serogroup C with a single dose of the MenACWY-TT vaccine compared to a quadrivalent (MCV4-TT) or monovalent C tetanus toxoid conjugate meningococcal vaccine (menC-TT) in healthy meningococcal vaccine-naive 12–23 months old toddlers in 29 centers in Denmark, Germany, and Finland (MEQ00065; NCT03890367). This study demonstrated that MenACWY-TT had a superior serogroup C immune response compared to MCV4-TT in terms of hSBA titers (hSBA GMT ratio 16.3 [12.7–21.0] and seroprotection difference 10.43% [5.68–-16.20]). Also, rSBA levels for serogroup C showed that MenACWY-TT was not worse than MenC-TT (rSBA GMT ratio 1.32 [1.06–1.64] and seroprotection difference 0.0 (−2.30, 2.28)).[48]

A Phase III, double-blind, randomized, active-controlled study recruited 1000 healthy children aged 2–9 years to compare MenACWY-TT with MenACWY-CRM (MET35; NCT03077438). At day 30, researchers found MenACWY-TT to be noninferior to MenACWY-CRM in terms of seroresponsivity. Moreover, we found that MenACWY-TT had higher geometric antibody means for serogroups C, W, and Y than MenACWY-CRM. There were no safety problems reported.[49]

Immunogenicity and safety in adolescents and adults

3344 meningococcal vaccine-naive 10–55-year-olds were randomized to have either MenACWY-TT or the licensed quadrivalent meningococcal conjugate vaccine MCV4-DT in another phase III, randomized, modified double-blind, active controlled study across 90 centers in the U.S. (MET43; NCT02842853). Seroresponse was non-inferior in the MenACWY-TT group compared to MCV4-DT for all serogroups. The safety profiles were similar for both vaccines, without any concerns.[50]

A phase II, randomized, active-controlled, open-label, multicenter study involving 301 healthy adults aged ≥56 years (56.0–88.9 years) (MET44; NCT01732627) revealed that seroresponse rates were higher for serogroups W and Y compared with the ones achieved with the quadrivalent polysaccharide vaccine MPSV4. Both MenACWY-TT and MPSV4 had similar seroresponse rates for serogroups A and C were similar with both MenACWY-TT and MPSV4. There were no safety concerns with either vaccines.[51]

Another Phase III study was done with 906 healthy adults aged 56 and up (56.0–97.2 years) in 35 centers in the U.S. and Puerto Rico. The goal was to compare the safety and

Table 2. MenACWY-TT (MenQuadfi®) clinical trials.

Study Code	Study design	Age Group	Country	n (Total)	Comparator	Results
Immunogenicity and Safety Studies						
MET54	Phase II, open, randomized, controlled	12–23 Months	Finland	188	MCV4-TT	Seroresponse in MenACWY-TT was noninferior to that in MCV4-TT
MET51	Phase III, double blind, randomized, parallel, controlled	12–23 Months	Germany, Spain, Finland, Hungary	918	MCV4-TT	Seroresponse in MenACWY-TT was noninferior to that in MCV4-TT
MEQ00065	Phase III, randomized, double blind	12–23 Months	Denmark, Finland, Germany	707	MCV4-TT MenC-TT	Seroresponse in MenACWY-TT for serogroup C was superior to that in MCV4-TT Seroresponse in MenACWY-TT for serogroup C was noninferior to that in MenC-TT
MET35	Phase III, double blind, randomized, parallel, controlled	2–9 Years	USA	1000	MenACWY-CRM	Seroresponse in MenACWY-TT was noninferior to that in MenACWY-CRM
MEQ00071	Phase III, observer blind, randomized, controlled	10–17 Years	Spain, Hungary, Italy, Singapore	911	MCV4-TT	Seroprotection in MenACYW-TT was non-inferior to that MCV4-TT. The immune response by MenACYW-TT was comparable following sequential vs concomitant administration of MenACYW-TT with 9vHPV + Tdap-IPV
MET43	Phase III, double blind, randomized, controlled	10–55 Years	USA	3344	MenACWY-DT	Seroresponse in MenACWY-TT was noninferior to that in MenACWY-DT; Lot -to-lot consistency in immune response of three commercial lots.
MET44	Phase II, open, randomized, controlled	56+ Years	USA	301	MPSV4	Seroresponse in MenACWY-TT was comparable to that in MPSV4
MET49	Phase III, double blind, randomized, parallel, controlled	56+ Years	USA, Puerto Rico	906	MPSV4	Seroresponse in MenACWY-TT was noninferior to that in MPSV4
MEQ00063	Phase III, open	56+ Years	Turkiye, Lebanon	290	N/A	Increased GMTs and seroprotection for serogroups A, C, Y, and W after MenACWY-TT
Coadministration Studies						
MET57	Phase III, open, randomized, controlled	12–23 Months	Mexico, Russia, South Korea, Thailand	1183	MenACWY-TT + mmR + V MenACWY + DTaP + IPV + hepB + hib + PCV13	Seroresponse in MenACYW-TT when administered alone or concomitantly with routine pediatric vaccines (MMR, varicella, DTaP-IPVHepB-Hib, or PCV13)
MET50	Phase II, open, randomized, parallel	10–17 Years	USA	1715	MenACWY-CRM MenACWY+Tdap +HPV	Seroresponse in MenACWY-TT was noninferior to that in MenACWY-CRM Seroresponse in MenACWY-TT with Tdap and HPV4 was noninferior to that in MenACWY-TT alone
Booster Dose Studies						
MET62	Phase III, open	4–5 Years	Finland	91	MenACWY-TT; MCV4-TT	Persistence of immunogenicity for 3 years. Booster response against all four meningococcal serogroups (A, C, W, and Y) in children primed three years earlier as toddlers with MenACYWTT or MCV4-TT
MET56	Phase III, double blind, randomized, parallel, controlled	15+ Years	USA	810	MenACWY-DT	Seroresponse for the MenACYW-TT vaccine booster was non-inferior to the MCV4-DT booster in children primed 4–10 years before.
MET59	Phase III, open, randomized, parallel, controlled	13–26 Years	USA, Puerto Rico	570	MenACWY-CRM	Seroresponse of a booster dose of MenACYW-TT, administered 3–6 years after priming vaccination of participants with MenACYW – TT
MEQ00066	Phase III, open, randomized, controlled	59+ Years	USA, Puerto Rico	471	MPSV4	Seroresponse for the MenACYW-TT vaccine booster regardless of priming vaccine (MPSV4 or MenACYW-TT, 3 years prior)

immunogenicity of MenACWY-TT to MPSV4 (MET49; NCT02842866). The study not only showed that MenACWY-TT was not worse than MPSV4, but it also showed that more people had higher levels of bactericidal antibodies specific to their serogroup (hSBA ≥1:8) 30 days after being vaccinated with MenACWY-TT than with MPSV4 for all four serogroups. MenACWY-TT was well-tolerated in the study group.[52]

Immunogenicity and safety in special groups

A surveillance registry is recruiting to assess the safety of MenACWY-TT among pregnant women who were vaccinated during pregnancy or within 30 days prior to their last menstrual period and their babies (MEQ00070/NCT04843111).[53]

In a Phase III open-label, multicentric study that was done in Lebanon and Turkiye, older adults aged 56 and up who were planning to go on a Hajj or Umrah pilgrimage 10–12 months after getting vaccinated were asked about the safety and antibody response to meningococcal serogroups A, C, W, and Y (MEQ00063/NCT03869866).[54] Based on seroprotection rates and GMTs, the MenACWY conjugate vaccine produced a robust immune response against all serogroups, with an acceptable safety profile in potential pilgrims ≥56 years of age.[55]

Immunogenicity and safety in co-administration studies

Two different studies evaluated the co-administration of MenACWY-TT with several other vaccines. A study with 1715 teens (10–17 years old) from multiple centers (MET50-NCT02199691) showed that the MenACWY-TT vaccine was non-inferior to the MenACWY-CRM vaccine when given alone or with tetanus, diphtheria, acellular pertussis (Tdap), and human papillomavirus (HPV4) vaccines, which had already been approved. Immune response rates for each serogroup were higher with MenACWY-TT compared to the ones with MenACWY-CRM (Serogroup A: 75.6% vs. 66.4%; Serogroup C: 97.2% vs. 72.6%; Serogroup W: 86.2% vs. 66.6%; Serogroup Y: 97.0% vs. 80.8%). MenACWY-TT was well tolerated either alone or with Tdap and HPV4 vaccines in meningococcal vaccine-naive adolescents; no serious adverse events have been reported.[56]

A different co-administration study looked for healthy children aged 12 to 23 months to take part in a phase III, open-label, randomized, active-controlled, multicentric trial in South Korea, Thailand, Mexico, and the Russian Federation (MET57; NCT03205371). Co-administration of MenACWY-TT with routine pediatric vaccines (measles, mumps, and rubella [MMR]; varicella [V]; 6-in-1 combination vaccine against diphtheria, tetanus, pertussis, polio, hepatitis B, and Haemophilus influenzae type b [DTaP-IPV-HepB-Hib], and pneumococcal conjugate vaccine [PCV13]) was found to be effective and safe.[57]

A recently modified double-blind, Phase III study (NCT04490018) from Hungary, Italy, Spain, and Singapore randomly assigned 463 meningococcal vaccine-naive adolescents or MenC-primed (under the age of 2 years) to receive either MenACWY-TT or MCV4-TT and co-administered 9-valent HPV and Tdap-IPV vaccines. The study met primary endpoints; hSBA GMTs were higher for MenACWY-TT vs. MCV4-TT for serogroups C, Y and,W, and comparable for serogroup A 30 days after vaccination. Subjects receiving MenACWY-TT alone or co-administered with 9-valent HPV and Tdap-IPV vaccines showed comparable or higher immunogenicity results than the co-administration group, without any safety concerns.[58]

Further co-administration studies are still ongoing to exhibit immunogenicity and safety of Men ACWY-TT when given concomitantly with routine pediatric vaccines in different age groups starting at 6 weeks of age (MET33/NCT03630705; MET41/NCT03673462; MET61/NCT03691610; MET42/NCT03537508; MET58/NCT03547271; MET52/NCT03632720).[59]

Immunogenicity and safety of a booster dose

There were also several studies assessing the immune efficacy and safety of a booster MenACWY-TT dose. Another Phase III, open-label, multicentric study in Finland (MET62; NCT03476135) also investigated the immunogenicity and safety of a booster dose of MenACWY-TT in preschool-aged children who received their primary doses as toddlers (aged 12–23 months) with either MenACWY-TT or MCV4-TT. Antibody levels against all meningococcal serogroups remained higher at the pre-booster time point than at the pre-primary time point, highlighting the antibody response persistence up to 3 years after primary vaccination. In the MenACWY-TT-primed group, pre-booster meningococcal hSBA GMTs ranged from 12.1 (serogroup A) to 106 (serogroup C), and in the MCV4-TT-primed group, they ranged from 11.7 (serogroup C) to 21.9 (serogroup W). Children primed with MenACWY-TT or MCV4-TT achieved a vigorous response for all four meningococcal serogroups with a single booster dose of MenACWY-TT without any safety concerns. At day 30 after the post-booster dose, participants who showed a ≥ 4-fold increase were similar in both groups in terms of hSBA and rSBA titers (≥95.0% in the MenACWY-TT-primed group and ≥ 95.5% in the MCV4-TT-primed group for hSBA titers; and ≥ 92.3% and ≥ 81.8%, respectively, for rSBA titers).[60]

A phase III, modified double-blind, parallel-group, active-controlled, multicentric trial randomized 15-year-old and older individuals who had a primary MCV4 vaccine (MCV4-DT or MCV4-CRM) dose in the USA and Puerto Rico (MET 56; NCT02752906). Participants received either a booster dose of MenACWY-TT or MCV4-DT 4–10 years after the primary dose to compare the immunogenicity and safety. Almost all participants in both study groups had a sufficient immune response (hSBA titers ≥ 1:8) for all four meningococcal serogroups at day 30, regardless of the type of primary vaccine with an acceptable safety profile. To assess the rapidity of the booster response, samples from a subgroup of participants were examined on Day 6 post-booster vaccination. The rates of vaccine seroresponse and seroprotection were comparable between the MenACWY-TT and MCV4-DT groups. Additionally, the Day 6 hSBA GMTs for the four meningococcal serogroups were also similar across the vaccine groups.[61]

The MET59 study (NCT04084769), which was a phase IIIb study, looked at how long the immune response lasted 3–6 years after a priming vaccination with either MenACWY-TT or MCV4-CRM in teens and adults in the US and Puerto Rico, with or without a MenB vaccine. In terms of immune response persistence, GMTs decreased in the 3–6 years after the primary dose but remained higher than pre-vaccination levels for all serogroups. Participants then received a booster dose of MenACWY-TT either alone or with a single dose of a licensed MenB vaccine, MenB-T (Trumenba®) or 4CMenB (Bexsero). More than 93% of people across all serogroups showed a seroresponse 30 days after the booster dose of MenACWY-TT, no matter what kind of vaccine they had first (hSBA vaccine seroprotection against each serogroup in MenACWY-TT primed and MCV4-CRM primed participants). By Day 6, the seroresponse rate was greater than 75% for all serogroups in groups, suggesting a rapid onset of the immune response, regardless of the priming vaccine (MenACWY-TT or MCV4-CRM). The Day 6 GMTs were also comparable in groups for serogroups A and Y and were higher for serogroups C and W in MenACWY-TT primed. Co-administration with MenB vaccines did not affect MenACWY-TT immunogenicity. There were no reports of serious adverse events related to the vaccine.[62]

A two-stage Phase III study (MEQ00066; NCT04142242) of MenACWY-TT looked at the safety and effectiveness of a booster dose in older adults (≥59 years) who had already

been vaccinated with either MenACWY-TT or MPSV4. MenACWY-TT booster was immunogenic and well tolerated in older adults regardless of the type of the primer vaccine, whereas seroresponse rates for all serogroups varied from 49.2% to 60.8% in the MPSV4-primed group and 79.3–93.1% in the MenACWY-TT-primed group at day 30. In the group of people who were tested for immunogenicity on Day 6, the rates of hSBA seroresponse and seroprotection were much higher in the MenACWY-TT-primed booster group than in the MPSV4-primed booster group for all four serogroups. GMTs for serogroups C, W, and Y stayed or went up higher than pre-vaccination levels at both 3 and 6–7 years post-primary vaccination, highlighting the persistence of immunity.[63]

A recent review of randomized phase II and III clinical trials involving over 7,700 participants found that MenACWY-TT demonstrated non-inferiority in immunogenicity compared to other licensed quadrivalent meningococcal vaccines, showing similar safety and efficacy profiles for both initial vaccination and booster doses, supporting its role in preventing meningococcal disease caused by serogroups A, C, W, and Y.[64]

Immunogenicity and safety profiles of a booster MenACWY-TT dose are currently being evaluated in further studies covering a broad range of ages (MEQ00073/NCT04936685).[65]

Discussion

MenACWY-TT is made in a new way that uses a different serogroup conjugation strategy to connect capsular polysaccharides to TT, which acts as a carrier protein. In the preclinical studies, conjugation with TT led to the high level of total IgG and antibody responses that killed bacteria.[45] Various clinical studies have further confirmed a strong antibody response with this new formulation against all four serogroups in different age groups.[46–52,56] MenACWY-TT was shown to be immunogenically noninferior to MPSV4, MenACWY-CRM, MenACWY-D, and MCV4-TT, with a superior immune response against serogroup C in toddlers compared to MCV4-TT and the degree of immune response appears to vary by age group and population.[46–49,50–52,56] For instance, in toddlers aged 12–23 months, MenACWY-TT elicited significantly higher immune responses to serogroup C compared to MenACWY-CRM. In children aged 2 to 9 years, MenACWY-TT demonstrated higher geometric mean antibody titers for serogroups C, W, and Y compared to MenACWY-CRM, while maintaining noninferior seroresponse rates.[49] In adolescents aged 10–17 years, MenACWY-TT provided comparable or even higher seroresponse rates than MenACWY-D. However, it is important to note that the current clinical evidence is primarily based on healthy individuals. Data are still lacking on vaccine response and safety in individuals with chronic medical conditions and risk groups for meningitis, such as persistent complement component deficiencies, functional or anatomic asplenia, and HIV. Tailored immunization strategies may be necessary to ensure optimal protection in all demographic groups, especially those at higher risk of invasive meningococcal disease.

Coadministration studies with several different vaccines have been done to evaluate interference; hence, neither MenACWY-TT nor co-administered childhood vaccines affected each other's immunogenicity.[56,57] A robust immune response was achieved for all four meningococcal serogroups with a single booster dose of MenACWY-TT regardless of their primary vaccine.[60,61] Several other studies are ongoing in different target groups, such as infants, pregnant women, and Hajj and Umrah pilgrims.[53,54,59]

MenACWY-TT was approved in 2020 for use in individuals aged ≥2 years in the U.S. and ≥12 months in the EU and other countries, based on noninferior immunogenicity and comparable safety across age groups. Therefore, children can receive the MenACWY-TT vaccine from 12 months of age, providing protection from the severe disease and its consequences. Early vaccination can be beneficial because meningococcal meningitis is a significant burden for infants and young children, with high fatality rates and possible long-term psychosocial and neurological sequelae. A recent review evaluated the immunogenicity and safety of MenACWY-TT based on data from 10 studies across various age groups. It recommends updating Italy's vaccination schedule to include a booster dose for children aged 6–9 and extending the vaccine to young adults to combat waning immunity and high carrier rates.[66]

Many countries have not yet implemented these vaccines due to financial or logistical barriers. However, a single-dose vaccination schedule with MenACWY-TT could be more cost-effective and easier to implement. The U.S. Centers for Disease Control and Prevention (CDC) concluded that the cost of MenACWY-TT is within 5% of other licensed MenACWY conjugate vaccines, suggesting that its introduction would not significantly impact resource allocation within the immunization budget.[67] Additionally, a single-dose schedule may help alleviate the burden on health systems by simplifying vaccine delivery and addressing supply constraints. MenACWY-TT may thus offer a promising option to support global IMD prevention strategies; however, continued accumulation of long-term real-world and economic evidence will help guide its broader adoption into NIPs.

Although short-term studies are highlighting the immunogenicity and safety of MenACWY-TT, long-term follow-up is essential for monitoring its effectiveness and safety. However, there are several ongoing studies assessing the immunogenicity and safety profiles of both the primary and booster doses of MenACWY-TT in terms of long-term follow-up and coadministration combinations in different populations. For instance, in the MET62 study (NCT03476135), children aged 4–5 years showed sustained antibody levels three years after primary vaccination. Upon administration of a booster dose, seroprotection rates approached 100% across all serogroups.[60] Similarly, the MET59 study (NCT04084769), which included adolescents and young adults aged 13–26 years who were previously vaccinated with MenACWY-TT or MenACWY-CRM 3–6 years earlier, demonstrated elevated pre-booster hSBA GMTs and post-booster seroprotection rates nearing 100%, further supporting durable immunogenicity.[62] In older adults aged ≥59 years, the MEQ00066 study (NCT04142242) assessed the persistence of antibody responses up to 6–7 years following a single MenACWY-

TT or MenACWY-PS dose.[63] Results indicated that hSBA GMTs remained above pre-vaccination levels and that robust post-booster responses were maintained, particularly for serogroups C, W, and Y. Additionally, a recent longitudinal study in children confirmed seroprotection lasting up to five years post-primary MenACWY-TT vaccination, with ≥ 93% of participants achieving protective titers (≥1:8) within 30 days of a booster and no new safety concerns identified.[68] Collectively, these findings support the durability of primary immune responses and the efficacy of booster administration with MenACWY-TT across a broad age spectrum. Nonetheless, the optimal timing and necessity of additional boosters beyond these timeframes remain to be defined. Further studies are essential to determine long-term protection, especially in infants and high-risk populations, and to guide future immunization schedules.

In conclusion, MenACWY-TT has been shown to be safe and well-tolerated across different age groups, with immunogenicity noninferior to other licensed meningococcal vaccines across all serogroups and superior responses for serogroup C. Additionally, clinical trials support its safety and immunogenicity when coadministered with other routine vaccines, as well as its effectiveness in booster dose administration. Given its single-dose schedule and licensure for use in individuals aged 12 months and older, MenACWY-TT represents a promising candidate for inclusion in National Immunization Programs (NIPs), pending further evaluation. Its potential utility in group settings and for travelers may also support broader public health strategies aimed at preventing meningococcal outbreaks. Continued studies evaluating cost-effectiveness, long-term immunity, and use in high-risk or special populations will further inform its optimal role in immunization policies.

Study limitations

This review has several limitations that should be acknowledged. First, although a comprehensive literature search was conducted using MeSH terms and Boolean operators across major electronic databases, no formal systematic review protocol (e.g., PRISMA) was followed, as the study was designed as a narrative review. This may limit the reproducibility of the search strategy. Second, a formal risk-of-bias assessment tool was not applied to the included studies. Nevertheless, we attempted to mitigate this by including only peer-reviewed clinical trials and observational studies and by conducting a qualitative assessment of study quality during data interpretation. Additionally, a limited number of relevant poster presentations were also included to capture recent data not yet published as full-text articles; these should be interpreted with caution due to the preliminary nature. These limitations should be taken into account when evaluating the conclusions. Future studies may benefit from employing systematic review methodologies and validated bias assessment tools to enhance methodological rigor and comparability. Another significant limitation is that the current body of evidence is largely based on studies involving healthy individuals. There is a clear lack of data on individuals with chronic medical conditions particularly those at higher risk for invasive meningococcal disease, such as individuals with persistent complement deficiencies, functional or anatomic asplenia, or HIV. Further research is needed to evaluate the immunogenicity, safety, and durability of MenACWY-TT in these high-risk populations. These limitations should be taken into account when interpreting the conclusions of this review. Future studies may benefit from employing systematic review methodologies and validated bias assessment tools to enhance methodological rigor and comparability, as well as expanding the scope to include vulnerable patient groups.

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Ethical consideration

Ethical approval was not required as this study was based on publicly available data and did not involve human subjects.

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