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Review article

Meningococcal Group A, C, W, and Y Tetanus Toxoid Conjugate Vaccine: A Review of Clinical Data in Adolescents

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A B S T R A C T

MenACWY-TT (Nimenrix) is a quadrivalent meningococcal vaccine containing polysaccharides from serogroups A, C, W, and Y conjugated to a tetanus toxoid carrier protein. MenACWY-TT is licensed in some countries as a three-dose primary series in individuals as young as 6 weeks of age and as a single dose in individuals ≥12 months of age. MenACWY-TT use is supported by long-term immunogenicity and safety across age groups, including data from several phase 2, 3, and 4 clinical studies in adolescents and young adults. Adolescents are an important population in the epidemiology, transmission, and prevention of invasive meningococcal disease, with this age-based population having the highest risk for carriage and transmission as well as one of the highest risks of disease. This age group is emerging as a target population in meningococcal vaccination programs globally, as vaccinating adolescents and young adults could potentially not only decrease disease rates directly for those vaccinated but also indirectly for unvaccinated individuals by decreasing carriage and eliciting herd protection. This review will consider available data for MenACWY-TT in adolescents, including safety and immunogenicity, booster and memory responses, persistence, and coadministration with other vaccines, with an emphasis on the rationale for use of MenACWY-TT and other quadrivalent meningococcal vaccines in adolescents to address the changing epidemiology of meningococcal disease.

IMPLICATIONS AND CONTRIBUTION

This review emphasizes the importance of adolescents as a target for meningococcal vaccination, owing to the high risk of carriage and disease in this age-based population. Clinical data for a meningococcal serogroup A, C, W, and Y tetanus toxoid conjugate vaccine in adolescents are reviewed.

Neisseria meningitidis is the causative agent of invasive meningococcal disease (IMD) [1], presenting most commonly as meningitis and septicemia [2]. *N meningitidis* infection can occur in previously healthy individuals and has a high mortality rate [3,4]. Survivors may experience long-term morbidities including amputation, loss of hearing, brain damage, and neurologic impairments [1,3].

Meningococcal disease is a global concern [5] due to the ability of the pathogen to cause rapid, severe, and epidemic disease [3,6]. In industrialized countries, IMD cases are typically sporadic although outbreaks can also occur [2,5,7]. The major endemic disease burden is in developing regions, which are characterized by frequent epidemics and poor outcomes [6,8].

Adolescents and young adults are an important population in IMD epidemiology, transmission, and prevention. In many regions, this population is at highest risk for carriage and transmission [2,9,10] and has the highest disease risk after infants and young children [7,11]. Adolescents are also at increased disease risk during meningococcal outbreaks [12] and adolescent survivors of IMD are at risk of long-term debilitating sequelae [13]. Increased carriage and disease risk in adolescents are thought to be

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attributed to social behaviors that result in close physical contact that promotes transmission [2,10,14], including living and interacting in crowded communities and engaging in increased social mixing [11,14]. Carriage can lead to transmission, a prerequisite for IMD [10], making adolescents an important target for disease control through vaccination.

Of the 12 meningococcal serogroups, most IMD is caused by serogroups A, B, C, W, X, and Y [15]. However, the prevalence of these disease-causing serogroups can vary over time, geographically, and by age [16]. For example, in adolescents and young adults, meningococcal serogroups B, C, and Y are most commonly associated with meningococcal disease in the United States [17], and serogroups B and C are most commonly associated with IMD in this population in Europe [18]. However, an increase in meningococcal serogroup W disease has been observed across age groups in Europe since 2011, including in individuals aged 15–24 years, with the greatest burden of serogroup W disease reported in the United Kingdom (.33 cases/100,000 persons in the United Kingdom vs. .06 cases/100,000 persons in Europe in 2015) [18]. This increase in serogroup W disease in the United Kingdom is attributed to endemic expansion of a single and highly virulent type 11 clonal complex (cc11) [19], which has resulted in an increased number of cases among individuals aged 5–19 years (three cases in 2008–2009 vs. 16 cases in 2013–2014) [20]. Mass gathering events have also been associated with recent meningococcal serogroup W outbreaks in adolescents. For instance, at the 2015 World Scout Jamboree in Japan, meningococcal serogroup W cc11 cases were reported among five attendees and one close contact from the United Kingdom and Sweden [21]. Notably, none of the individuals had received meningococcal vaccination prior to attending the jamboree.

Vaccination is currently the best means to prevent IMD [22,23]. A number of vaccines are available to prevent infection with disease-causing serogroups, either targeting single serogroups or a combination of multiple serogroups [24]. Multivalent meningococcal vaccines provide broad coverage and have the potential to protect individuals in countries with several predominant disease-causing serogroups and may also reduce disease risk from newly emergent serogroups [25,26]. For instance, although quadrivalent vaccines protecting against serogroups A, C, W, and Y were available, a meningococcal serogroup C booster dose for adolescents previously vaccinated with a monovalent serogroup C vaccine was introduced in the United Kingdom to maintain herd protection in those vaccinated in infancy and early childhood [19]. However, the endemic increase in serogroup W cc11 disease has led to revisions to the recommendations whereby quadrivalent meningococcal vaccines are being offered to adolescents. This approach addressing the changing epidemiology of meningococcal disease is supported by data indicating that a booster dose of quadrivalent meningococcal vaccines is immunogenic and protective in adolescents who had previously received a meningococcal serogroup C vaccine in childhood [27,28].

MenACWY-TT (Nimenrix; Pfizer Ltd, Sandwich, Kent, United Kingdom), a meningococcal serogroup A, C, W, and Y tetanus toxoid conjugate vaccine, is one of the available quadrivalent meningococcal vaccines. This review considers clinical data for MenACWY-TT in adolescents, including safety and immunogenicity, booster and memory responses, persistence, and coadministration with other vaccines. The rationale for use of MenACWY-TT and other quadrivalent meningococcal vaccines in adolescents to address the changing epidemiology of meningococcal disease will be described.

History of Quadrivalent Meningococcal Vaccination in Adolescents

Meningococcal polysaccharide vaccine development began with monovalent vaccines against serogroup C and has since progressed to quadrivalent polysaccharide and conjugate vaccines against serogroups A, C, W, and Y (Table 1) [2,29–31].

Meningococcal polysaccharide vaccines have been available for >40 years [31]. These vaccines have a well characterized safety and effectiveness profile and a long history of use [32,33], including successful implementation in outbreaks and for mass and routine vaccination [31]. However, widespread use has been restricted by limitations that include poor immunogenicity in children aged <2 years, lack of immunologic memory and booster response, short duration of protection, minimal effect on carriage, and immunologic hyporesponsiveness with repeated vaccination [31,32].

These limitations have spurred development of meningococcal conjugate vaccines [32], which covalently link the capsular polysaccharide to a carrier protein, resulting in increased immunogenicity in infants, immunologic memory at re-exposure, possible carriage reductions, herd protection [22,31,33–36], booster response, and ability to overcome immune hyporesponsiveness [32]. Meningococcal conjugate polysaccharide vaccines have been available since 1999 with the introduction of the meningococcal serogroup C conjugate vaccine in the United Kingdom [33,37]. For the reasons listed above, these vaccines have since replaced unconjugated polysaccharide vaccines. Although surveillance data have shown the acceptable safety profile and effectiveness of these vaccines [33], continued monitoring is important to identify the emergence of newly prevalent serogroups.

The first licensed quadrivalent meningococcal conjugate vaccine was MenACWY-D (Menactra; Sanofi Pasteur Inc., Swiftwater, PA), which is conjugated to diphtheria toxin [2,38]. MenACWY-D was licensed in 2005 in the United States for individuals aged 11–55 years [2]. Licensure in the same age group of a MenACWY vaccine conjugated to CRM_{197} (MenACWY-CRM; Menveo; Novartis Vaccines and Diagnostics S.r.l., Sovicille, Italy) followed in 2010. MenACWY-D and MenACWY-CRM are now licensed in the United States for individuals aged 9 months through 55 years and 2 months through 55 years, respectively [38,39]. Both vaccines have been reported to be safe and immunogenic [33,38,39]. MenACWY-D is not licensed in Europe [40], while MenACWY-CRM is licensed in Europe in individuals from 2 years of age as a single dose [41].

MenACWY-TT, a quadrivalent meningococcal vaccine conjugated to a tetanus toxoid carrier protein, was licensed in Europe in

Table 1
Currently Available Quadrivalent Meningococcal Vaccines [2,29]

Formulation	Trade name (manufacturer)	Type	Serogroups	Licensed age range
MenACWY-TT	Nimenrix (Pfizer Ltd; Sandwich, Kent, United Kingdom)	Conjugate	A, C, W, Y	≥6 weeks
MenACWY-D	Menactra (Sanofi Pasteur Inc; Swiftwater, PA)	Conjugate	A, C, W, Y	9 months–55 years
MenACWY-CRM	Menveo (Novartis Vaccines and Diagnostics S.r.l; Sovicille, Italy)	Conjugate	A, C, W, Y	2–55 years

2012 for children >12 months of age [29]. The indication was extended to infants aged ≥6 weeks in 2016 [42]. The MenACWY-TT clinical data in adolescents are discussed in more detail below.

Recommendations for Quadrivalent Meningococcal Vaccines for Adolescents in Response to the Changing Epidemiology of Meningococcal Disease

The World Health Organization recommends that meningococcal vaccination programs be introduced in countries with intermediate to high endemic rates of disease or with frequent epidemics [43]. Initial mass vaccination of young children and adolescents is a recommended strategy, depending on the specific age distribution of disease of a given country, followed by routine vaccination as part of childhood vaccination programs [43]. An alternative strategy is mass meningococcal conjugate vaccine use followed every 3–5 years by supplementary vaccination activities (e.g., for outbreaks or through private vaccination services) for at-risk age-based populations.

The variable prevalence of meningococcal serogroups among adolescents, coupled with the potential breadth of coverage afforded by multivalent vaccines, has led to the modification of several national and regional recommendations for meningococcal vaccination in adolescents (Table 2) [44–59]. For instance, although the Australian vaccination guidelines recommend meningococcal serogroup B vaccination of individuals aged 15–19 years [60], five states in Australia are currently providing conjugate MenACWY vaccination to adolescents (Queensland, New South Wales, Victoria, Western Australia) or to individuals ≥2 months of age (Ceduna Region, South Australia) beginning in the 2017 school year and continuing in some states until 2018/2019 in response to increased prevalence of serogroup W disease [44–48].

In Canada, the national vaccination guide recommends either a conjugated meningococcal C or MenACWY vaccine be administered to healthy adolescents and young adults aged 12–24 years [61]. However, eight Canadian provinces have also elected to provide conjugate MenACWY vaccines without charge to children and adolescents in grades 4 (9–10 years of age; Newfoundland and

Table 2
Recommendations for Quadrivalent Meningococcal Vaccines for Adolescents in Response to the Changing Epidemiology of Meningococcal Disease

Country	Recommendation					
Australia						
Queensland [44]	MenACWY available without charge to: • Year 10 students (~14–15 years) in 2017 • Individuals 15–19 years from June 2017 to May 2018 who can access the vaccine via their doctor or immunization provider					
New South Wales [45]	MenACWY available without charge to: • Year 11 and 12 students in 2017 through the New South Wales School-based Vaccination Program • Adolescents in 2017 who have left school through their GP					
Victoria [46]	MenACWY-D available without charge to: • Individuals 15–19 years from April 18 to December 2017 through the secondary school immunization program or a clinical setting					
South Australia (Ceduna Region) [47]	MenACWY available without charge to: • Individuals ≥2 months from March to June 2017 living in the Ceduna region • MenACWY-CRM to be used for infants (2–11 months) and MenACWY-TT or MenACWY-CRM for individuals ≥12 months					
Western Australia [48]	MenACWY-TT available without charge to: • Individuals 15–19 years through the current meningococcal immunization program and to be administered through schools or through healthcare providers • All aboriginal and/or Torres Strait Islander individuals 15–19 years can receive the vaccine throughout 2017; the vaccine will be available to incoming Year 10 students (~14–15 years) only in 2018 and 2019					
Canada	MenACWY conjugate vaccine available without charge to children by school grade[a]					
	Grade 4	Grade 5	Grade 6	Grade 7	Grade 8	Grade 9
British Columbia[b] [49]						✓
Alberta[b] [50]						✓
Saskatchewan[b] [51]			✓			
Ontario[c] [52]				✓		
New Brunswick [53]						✓
Prince Edward Island[c] [54]						✓
Nova Scotia [55]				✓		
Newfoundland and Labrador [56]	✓					
Italy [57]	• MenACWY conjugate vaccine for individuals aged 12–18 years					
The Netherlands [59]	• Beginning in 2018, MenACWY conjugate vaccine[d] to be offered to adolescents aged 12–14 years					
United Kingdom [58]	• Beginning August 2015, MenACWY conjugate vaccine[d] for individuals aged 13–14 years and new university entrants ≤25 years • From 2015 to 2017, catch-up MenACWY conjugate vaccine for individuals aged 14–18 years in 2015					

Data are current as of October 2017.
[a] Grade 4, 6, 7, and 9 corresponds to children approximately 9–10, 11–12, 12–13, and 14–15 years of age, respectively.
[b] Includes MenACWY-CRM, MenACWY-D, and MenACWY-TT [51,86,87].
[c] Includes MenACWY-D [52,54].
[d] Includes MenACWY-D and MenACWY-TT [58,59].

Labrador), 6 (11–12 years of age; Saskatchewan), 7 (12–13 years of age; Ontario, Nova Scotia), and 9 (14–15 years of age; British Columbia, Alberta, New Brunswick, Prince Edward Island) in response to the increase in cases covered by the quadrivalent vaccine [49–56].

The increase in meningococcal serogroup W cases in some European countries has also resulted in modified vaccine recommendations among adolescents. For instance, in 2015 the United Kingdom included conjugate MenACWY vaccines (i.e., MenACWY-TT and MenACWY-D) in the national immunization program for adolescents aged 13–14 and for new university entrants up to 25 years of age in response to a national serogroup W outbreak [58]. Catch-up vaccination for adolescents aged 14–18 years at the beginning of the program was also offered from 2015 to 2017. Similarly, the Ministry of Health, Welfare, and Sport in the Netherlands began offering MenACWY conjugate vaccines in 2018 to adolescents aged 12–14 years in response to the increase in serogroup W cases [59]. In Italy, conjugate MenACWY vaccination is provided for adolescents aged 12–18 years [57].

The success of such programs requires adapting to the variable nature of meningococcal disease so that vaccines targeting currently prevalent disease-causing serogroups are recommended. As multiple MenACWY vaccine options are often available, the choice of which quadrivalent meningococcal vaccine to use requires consideration of the properties, licensure, dosing and administration, immunogenicity, antibody persistence, and safety and tolerability profile of the particular vaccine in a specific population. These characteristics of MenACWY-TT are described in more detail in the following sections.

MenACWY-TT Development

MenACWY-TT is an intramuscular, quadrivalent meningococcal vaccine conjugated to a tetanus toxoid carrier protein [29]. One .5-mL reconstituted dose of MenACWY-TT contains 5 μg each of serogroup A, C, W, and Y polysaccharides conjugated to 44 μg of tetanus toxoid carrier protein [22]. Serogroups A and C polysaccharides are conjugated with a spacer molecule and indirectly conjugated to the tetanus toxoid carrier protein; serogroups W and Y polysaccharides are conjugated directly to the carrier protein.

MenACWY-TT is licensed in the European Union and has been launched in 43 additional countries (as of October 2017) including those in Africa (18 countries), Asia (seven countries), Eastern Europe (three countries), the Middle East (eight countries), North America (two countries), Oceania (two countries), and South America (three countries). MenACWY-TT is not currently licensed in the United States. In Europe and other countries, MenACWY-TT is indicated as a three-dose series for infants beginning between the ages of 6 and 12 weeks, with the second dose administered 2 months later and the third dose given at 12 months of age [29]. MenACWY-TT is administered as a single dose for previously unvaccinated children older than 12 months, adolescents, and adults. A booster dose can be given to individuals who have previously received conjugated or polysaccharide meningococcal vaccines and continue to be at risk of meningococcal disease. Of note, booster dosing of adolescents with meningococcal conjugate vaccines, including MenACWY-TT, is currently included in the United Kingdom national immunization program [62]. In some countries, including Canada and Australia, MenACWY-TT is indicated for individuals aged 12 months to 55 years [63,64]. MenACWY-TT is the first conjugated meningococcal vaccine that has been investigated in individuals aged >56 years [65].

MenACWY-TT safety and immunogenicity were established or continue to be investigated in several phase 2 and 3 clinical studies in infants, toddlers, children, adolescents, and adults. Similar to development programs for other meningococcal vaccines, the low incidence of meningococcal disease has precluded conduct of large vaccine efficacy studies for MenACWY-TT [6,66]. Serum bactericidal assays (SBAs), which measure vaccine-elicited serum bactericidal antibody responses, are used as a surrogate of efficacy using either human (hSBA) or rabbit complement (rSBA) [67]. An hSBA titer ≥1:4 is the accepted correlate of protection [66–69], whereas rSBA titers ≥1:8 to 1:64 are considered protective [31,69–71].

The MenACWY-TT safety profile includes pooled data from >10,000 subjects, including infants (6–12 weeks at first dose), toddlers (12–23 months), children (2–10 years), adolescents (11–17 years), and adults (18–55 and >55 years) [29]. The most common local reactions reported after MenACWY-TT vaccination across age groups (>12 months) are pain, redness, and swelling (Table S1 [29]). In toddlers and young children (12 months–5 years), irritability, drowsiness, appetite loss, and fever are most commonly reported. In older age groups, headache, fatigue, gastrointestinal symptoms, and fever are most common.

The MenACWY-TT clinical study program has demonstrated the immunogenicity, safety, and persistence of immune responses of a primary dose of the vaccine across various age groups and of MenACWY-TT given as a booster dose in individuals previously vaccinated with a conjugate or polysaccharide meningococcal vaccine [65,72]. MenACWY-TT is also the only meningococcal conjugate vaccine licensed in infants from 6 weeks of age and the first to be investigated in older individuals aged 56 years and older. Thus, MenACWY-TT is a vaccine that can be used across all age groups and is an important option for the prevention of IMD in individuals who are at high risk of infection or carriage. Because adolescents and young adults are often at highest risk for meningococcal carriage, have one of the highest IMD rates of any age group [2,7,9,11], and are emerging as a target population in meningococcal vaccination programs globally, a summary of MenACWY-TT clinical studies in this age group is described in detail in the following section.

MenACWY-TT Clinical Data in Adolescents

The MenACWY-TT clinical trial program includes several phase 2, 3, and 4 studies in adolescents and young adults (Table 3) [25,27,28,73–82]. Antibody persistence after primary MenACWY-TT vaccination and coadministration of MenACWY-TT with vaccines commonly administered in this population have also been assessed or are ongoing.

Immunogenicity

MenACWY-TT use in adolescents and young adults was first evaluated in two phase 2 studies comparing different formulations of MenACWY-TT (varying by polysaccharide concentration and conjugation method) to MenACWY-PS (Mencevax; Pfizer Australia Pty Ltd, Ryde, New South Wales, Australia) in 125 participants aged 15–19 years and 50 participants aged 18–25 years (Table 4) [25,27,28,73–81,83]. In this study by Ostergaard and colleagues, all participants receiving MenACWY-TT demonstrated rSBA titers ≥1:8 across all serogroups 1 month after vaccination.

Another phase 2 study, which included 872 participants aged 10–25 years, compared MenACWY-TT with MenACWY-D [79]. In this study by Baxter and colleagues, MenACWY-TT was immunogenic in those aged 11–25 years (n = 784), and immunogenicity in

Table 3
Overview of MenACWY-TT Clinical Trial Program in Adolescents and Young Adults Including Study Phase, Design, Population, Country of Investigation, and Status

Study	ClinicalTrials.gov identifier	Design	Participants	Location	Duration/Status
003 (phase 2) [73]	NCT00196950	Comparison of MenACWY-TT to MenACWY-PS	50 participants aged 18–25 years	Belgium	September 2003–September 2006/Completed
009 (phase 2) [82]	NCT00196963	Comparison of four formulations of MenACWY-TT to MenACWY-PS	125 participants aged 15–19 years	Belgium	March–July 2005/Completed
012 (phase 2) [73]	NCT00126945	Comparison of five formulations of MenACWY-TT to MenACWY-PS	125 participants aged 15–19 years	Denmark	August 2005–October 2005/Completed
015 (phase 2b) [74]	NCT00356369	Comparison of MenACWY-TT to MenACWY-PS	500 participants aged 11–55 years	Saudi Arabia, Philippines	December 2006–August 2010/Completed
020 (phase 2b) [83]	NCT00356369	Extension of study 015 to evaluate long-term antibody persistence of response of MenACWY-TT 5 years after primary vaccination	404[a] participants aged 11–55 years	Saudi Arabia, Philippines	December 2006–February 2013/Completed
021 (phase 2) [82]	NCT00661557	Comparison of MenACWY-TT in those who received prior MenACWY-PS versus those who are meningococcal vaccine naive	272 participants aged 4.5–34 years	Lebanon	May–June 2009/Completed
024, 025, 026 (phase 2) [75]	NCT00390143	Extension of study 012 to evaluate persistence of response of MenACWY-TT	46[a] participants aged 15–19 years	Denmark	February 2007–May 2009/Completed
036 (phase 3) [25]	NCT00464815	Comparison of MenACWY-TT and MenACWY-PS	1,025 participants aged 11–17 years	India, Philippines, Taiwan	May 2007–September 2008/Completed
037 (phase 3) [76]	NCT00465816	Comparison of MenACWY-TT given with and without HepA/B vaccine	611 participants aged 11–17 years	Denmark, Sweden	April 2007–April 2008/Completed
043 (phase 3) [77]	NCT00974363	Extension of study 036 to evaluate long-term antibody persistence of MenACWY-TT	478[a] participants aged 11–17 years	India, Philippines	August 2010–April 2013/Completed
052 (phase 2) [78]	NCT01165242	Comparison of MenACWY-TT to MenACWY-D	1,011 participants aged 10–25 years	United States, Canada	August 2010–March 2011/Completed
Baxter et al. (phase 2) [79]	NCT00454909	Comparison of MenACWY-TT to MenACWY-D	872 participants aged 10–25 years	United States	April 2007–April 2008/Completed
054 (phase 3) [82]	NCT01755689	Assessment of MenACWY-TT given with and without HPV and DTP vaccine	1,300 female participants aged 9–25 years	Dominican Republic, Estonia, Thailand	January 2013–April 2014/Completed
059 (phase 2) [80]	NCT00715910	Extension of study 052 to evaluate long-term antibody persistence of MenACWY-TT 1, 3, and 5 years after vaccination	312[a] participants aged 10–31 years	United States	August 2008–September 2013/Completed
084 (phase 3) [82]	NCT01641042	Assessment of MenACWY-TT in at-risk participants	86 participants aged 1–17 years	Czech Republic, United States	September 2012–March 2015/Completed
093 (phase 3) [81]	NCT01154088	Comparison of MenACWY-TT and MenACWY-PS	1,170 participants aged 18–25 years	Panama, Philippines, Thailand	August–December 2010/Completed
098 (phase 3) [82]	NCT01767376	Assessment of MenACWY-TT coadministered with DTP	692 participants aged 11–25 years	Republic of Korea, Germany, Dominican Republic	January 2013–January 2014/Completed
099 (phase 3) [82]	NCT01934140	Comparison of the long-term antibody persistence of MenACWY-TT to MenACWY-PS from 6 to 10 years after primary vaccination	336 participants aged 17–66 years	Philippines	April 2014–September 2018/Ongoing
Ishola et al. (phase 2/3) [28]	NCT01192997	Comparison of MenACWY-TT and MenACWY-CRM booster in adolescents previously vaccinated with MenC at 3.5 to 5.9 years	93 participants aged 16–19 years	United Kingdom	June 2012–March 2014/Completed
van Ravenhorst et al. (phase 4) [27]	EudraCT number: 2013-001823-38	Comparison of MenA, MenW, and MenY antibody levels of MenACWY-TT and MenC-TT booster doses in adolescents previously vaccinated with MenC-TT at 14 months to 3 years	246 participants aged 10 (n = 83), 12 (n = 82), and 15 (n = 81) years	The Netherlands	–

DTP = diphtheria, pertussis, and tetanus; HepA/B = hepatitis A/B; HPV = human papilloma virus.
[a] The number of participants at the longest follow-up period is shown.

Table 4
Overview of Published MenACWY-TT Clinical Studies in Adolescents and Young Adults

Study	Design	Immunogenicity	Safety
Phase 2 studies			
Ostergaard et al. (study 012 and 003; 024, 025, and 026 [extension]) [73,75]	MenACWY-TT versus MenACWY-PS (study 012: aged 15–19 years [n = 125]; study 003: aged 18–25 years [n = 50])	*Vaccine response*[a] *(aged 15–19 years)* 1 month: 72.0%–100% versus 78.3%–96.0% 42 months[b]: 100% versus 88.2% *rSBA ≥1:8 (aged 18–25 years)* 1 month: 100% versus 100% 36 months: 100% versus 91.7%–100%	*Most common local event*: pain *Most common systemic event*: fatigue, headache *SAEs*[c]: 1 (urticaria) versus 0; considered related and completely resolved
Baxter et al. [79,80]	MenACWY-TT (aged 11–25 years, n = 587) versus MenACWY-D (aged 11–25 years, n = 197) versus MenACWY-TT (aged 10 years, n = 88) Booster dose administered at 5 years	*hSBA ≥1:4* 1 month: ≥83.0% versus ≥70.7% versus ≥89.9% 1 year: 30.3%–98.5% versus 31.5%–86.6% versus 29.8%–100% 3 years: 39.2%–95.9% versus 47.4%–88.6% versus 45.1%–98.1% 5 years[d]: 52.5%–95.7% versus 44.4%–90.9% versus 37.5%–92.3%	*Primary dose* *Most common local event*: pain (54.9% versus 54.1% versus 55.8%) *Most common systemic event*: headache (33.0% versus 37.1% versus 34.9%) *SAEs*: .9% versus 1.0% versus 2.3%; no SAEs related to vaccination reported ≤5 years after vaccination *Booster dose* *Most common local event*: pain (58.8% vs. 54.1% vs. 60.4%) *Most common systemic event*: headache (35.9% vs. 27.0% vs. 24.2%)
Halperin et al. (study 052) [78]	MenACWY-TT (n = 673) versus MenACWY-D (n = 338) (aged 10–25 years)	*hSBA ≥1:8* 1 month: 51.0%–82.5% versus 39.0%–76.3%	*Most common local event*: pain (51.1% vs. 55.4%) *Most common systemic event*: fatigue (28.9% vs. 27.3%) *SAEs*: 8 (asthma [n = 2 events], tooth infection, appendicitis, influenza, pneumonia [n = 2 events], hypoxia) versus 2 (jaw fracture, post-procedural hematoma); none considered related
Borja-Tabora et al. (study 015 and 020 [extension]) [74,83]	MenACWY-TT (n = 225) versus MenACWY-PS (n = 76) (aged 11–17 years)	*rSBA ≥1:8* 1 month: 99.7%–100% versus 100% 1 year: 99.7%–100% versus 99.1%–100% 2 years: 99.4%–99.7% versus 90.1%–99.1% 3 years: 99.1%–100% versus 86.7%–100% 4 years: 76.5%–88.7% versus 20.0%–82.7% 5 years: 74.0%–92.8% versus 23.7%–80.3%	*Most common local event*: pain (38.6% vs. 32.3%) *Most common general event*: headache (17.5% vs. 12.0%) *SAEs*: 2 (costochondritis, mental disorder) versus 0; none considered related; 0 vaccine-related events reported ≤5 years after vaccination
Phase 3 and 4 studies			
Bermal et al. and Quiambo et al. (study 036 and 043 [extension]) [25,77]	MenACWY-TT (n = 768) versus MenACWY-PS (n = 257) (aged 11–17 years)	*rSBA ≥1:8* 1 month: 99.7%–100% versus 99.6%–100% 3 years (n = 643): 82.0%–93.1% versus 30.0%–86.0% 4 years (n = 541): 77.2%–94.1% versus 26.9%–86.9% 5 years (n = 478): 86.0%–97.5% versus 34.9%–93.0%	*Any general symptoms 4 days postvaccination (10–18 years)*: 25.4% (195/768) versus 24.5% (63/257) *Grade 3 general symptoms 4 days postvaccination (10–18 years)*: 1.6% (12/768) versus .4% (1/257)
Lupisan et al. [81]	MenACWY-TT (n = 780) versus MenACWY-PS (n = 390) (18–25 years)	*Vaccine response*[e] 1 month: 79.1%–97.0% versus 73.7%–94.1%	*Most common local event*: pain (53.9%–54.7% vs. 36.8%) *Most common general event*: fatigue (28.6%–30.3%), headache (26.9%–31.0%) *SAEs*: 1 (blighted ovum; potentially related) versus 1 (appendicitis; not related); all resolved

(*continued on next page*)

Table 4 (*Continued*)

Study	Design	Immunogenicity	Safety
Ostergaard et al. (study 037) [76]	MenACWY + HepA/B (n = 367) versus MenACWY alone (n = 122) versus HepA/B alone (n = 122) (aged 11–17 years)	*rSBA ≥1:8* 1 month: 99.7%–100% versus 99.1%–100% versus NA 7 months: 99.4%–100% versus 98.2%–100% versus NA *Seroconversion rates for hepatitis A* 1 month after third HepA/B dose: 100%[f] versus NA versus 100% *Seroconversion rates for hepatitis B* 1 month after third HepA/B dose: 99.1%[f] versus NA versus 100%	*Most common local event*: pain (49.6% vs. 48.7% vs. NA[g]; 39.2% vs. NA vs. 43.0%[h]) *Most common general event*: fatigue and headache *SAEs*: 1.1% versus 0 versus .8%
Ishola et al.[i] [28]	MenACWY-TT booster versus MenACWY-CRM booster (aged 16–19 years; previously vaccinated with MenC at 3.5–5.9 years)	*rSBA ≥1:8* Prebooster: 11%–49% versus 7%–30% 1 month: 98%–100% versus 100% 6 months: 91%–100% versus 95%–100% 9 months: 100% versus 96%–100%	*Local or general events*: similar between groups; severe redness and muscle pain more common with MenACWY-CRM and severe tiredness more common with MenACWY-TT *SAEs*: 1 (appendicitis) versus 3 (ulcerative colitis, hospitalization for transient disorientation likely from spiked social drinks, hospitalization for tonsillitis)
van Ravenhorst et al.[j] [27]	MenACWY-TT booster versus MenC-TT booster (aged 10, 12, and 15 years; previously vaccinated with MenC-TT at 14 months–3 years)	*rSBA ≥1:8*[k] Baseline: 15.1%–32.0% versus NR 1 month: 94.5%–100% versus NR 1 year: 94.5%–100% versus NR	NR

HepA/B = hepatitis A/B; hSBA = serum bactericidal assay using human complement; NA = not applicable; NR = not reported; rSBA = serum bactericidal assay using rabbit complement; SAE = serious adverse event.

[a] For initially seronegative subjects, postvaccination antibody titer ≥1:32; for initially seropositive subjects, antibody titer ≥4-fold the prevaccination antibody titer.

[b] Included 50 participants who were vaccinated in study 012; values are rSBA titers ≥1:8.

[c] As reported 8 days after vaccination.

[d] At 5 years, a booster dose was administered to 218, 56, and 38 participants in the MenACWY-TT (aged 11–25 years), MenACWY-D (aged 11–25 years), and MenACWY (aged 10 years) groups, respectively.

[e] For initially seronegative subjects (rSBA titer <1:8), postvaccination titer ≥1:32; for initially seropositive subjects (rSBA titer ≥1:8), postvaccination titer ≥4 times the prevaccination antibody titer.

[f] Percentage of subjects with concentration above the specified cutoff (HepA: 15.0 mIU/mL; HepB: 10.0 mIU/mL).

[g] Occurring after MenACWY-TT administration.

[h] Occurring after the first HepA/B administration.

[i] Phase 2/3 study.

[j] Phase 4 study.

[k] Does not include meningococcal serogroup C.

those aged 10 years was comparable with that in older adolescents (Table 4). For both vaccines, a high proportion of participants had hSBA titers ≥1:4 for all serogroups 1 month postvaccination. An exploratory assessment found that the proportion of participants with hSBA titers ≥1:8 for serogroups A, W, and Y was higher after MenACWY-TT vaccination compared with MenACWY-D.

MenACWY-TT has also been evaluated in adolescent and young adult populations from Asia. In a phase 3 study by Bermal and colleagues in 1,025 participants aged 11–17 years conducted in India, the Philippines, and Taiwan, the noninferiority of MenACWY-TT immunogenicity to MenACWY-PS was assessed [25]. MenACWY-TT induced a vaccine response against each serogroup in ≥85% of participants (Table 4). Significantly higher rSBA vaccine response rates were observed in MenACWY-TT recipients for serogroups A, W, and Y as compared with MenACWY-PS recipients. Consistent findings were also reported in a phase 3 study by Lupisan and colleagues conducted in Panama, the Philippines, and Thailand in 1,170 participants aged 18–25 years, which compared two lots of MenACWY-TT with MenACWY-PS [81].

A phase 2 study in 500 adolescents and adults aged 11–55 years conducted in the Philippines and Saudi Arabia compared MenACWY-TT with MenACWY-PS [74]. In this study by Borja-Tabora and colleagues, noninferiority of the immune response induced by MenACWY-TT compared with MenACWY-PS was met for all serogroups (Table 4). Significantly higher rSBA vaccine response rates for serogroups A and Y after administration of MenACWY-TT compared with administration of MenACWY-PS were observed in exploratory analyses.

Safety following primary vaccination

A pooled analysis of the safety and reactogenicity profile of MenACWY-TT in adolescents following primary vaccination is not available, and assessment is reliant on data from the clinical studies conducted in this population.

In the two phase 2 studies comparing different MenACWY-TT formulations with MenACWY-PS, MenACWY-TT was well tolerated, with reactogenicity profiles consistent with MenACWY-PS (Table 4) [73]. Pain was the most common local event and fatigue and headache the most common systemic events with both vaccines. A serious adverse event (SAE) of urticaria was reported in a recipient who received MenACWY-TT. The event occurred eight days after vaccination, was considered causally related to vaccination, and completely resolved. Similar findings were reported in a phase 2 study in adolescents and adults aged 11–55 years comparing MenACWY-TT with MenACWY-PS, with both vaccines found to be well tolerated and showing generally comparable safety and reactogenicity profiles [74].

In the phase 2 study comparing MenACWY-TT with MenACWY-D, MenACWY-TT was found to have an acceptable and generally comparable reactogenicity and safety profile to MenACWY-D, with pain and headache the most frequently reported reactogenicity events with both vaccines [79]. Most reactogenicity events were mild to moderate in intensity, of short duration, and resolved spontaneously. Consistent findings were observed in another phase 2 study comparing two lots of MenACWY-TT with MenACWY-D in adolescents and young adults [78].

Booster and memory responses and persistence

A 3.5-year follow-up of 46 adolescents from a study by Ostergaard and colleagues, which compared MenACWY-TT with MenACWY-PS in participants aged 15–19 years, found that all adolescents vaccinated with MenACWY-TT had rSBA titers ≥1:8 against all serogroups up to 42 months postvaccination (Table 4) [75]. In those vaccinated with MenACWY-PS, all participants had rSBA titers ≥1:8 for serogroups A, W, and Y, and only 88% had titers ≥1:8 for serogroup C. No vaccine-related SAEs or IMD cases were reported ≤42 months postvaccination. For young adults (aged 18–25 years) from the companion phase 2 study, all participants who received MenACWY-TT and 91.7%–100% of participants who received MenACWY-PS achieved rSBA titers ≥1:8 across serogroups A, C, W, and Y at 36 months [73].

Five-year antibody persistence has been reported from the phase 2 study by Baxter and colleagues that included 872 participants aged 10–25 years and compared MenACWY-TT with MenACWY-D [80]. The extension study also evaluated safety and immunogenicity of a MenACWY-TT booster dose given 5 years after primary vaccination. Overall, 312 participants were assessed for persistence of antibody response, and a booster dose of MenACWY-TT was administered to 322 participants at 5 years. Most participants vaccinated with MenACWY-TT or MenACWY-D retained hSBA antibody titers ≥1:8 up to year 5 for serogroups C, W, and Y (Table 4). Rapid waning in the proportion of participants retaining hSBA titers ≥1:8 for serogroup A was observed with both vaccines. Exploratory analyses of a MenACWY-TT booster dose to participants who had received primary vaccination with MenACWY-TT or MenACWY-D suggested that vaccine responses for all four serogroups were higher than in those who had not received the primary vaccine. Vaccine responses to serogroups A and W induced by the booster dose were also potentially higher in participants who received primary MenACWY-TT vaccination compared with those who received primary MenACWY-D vaccination, although statistical significance was not examined. Reactogenicity events were similar after administration of booster and primary MenACWY-TT doses. These findings support induction of immunologic memory with MenACWY-TT and boosting of primary vaccination responses by MenACWY-TT or Men-ACWY-D and suggest that MenACWY-TT can be used interchangeably with MenACWY-D as a booster dose when primary vaccination with MenACWY-D was used.

A phase 3 study by Bermal and colleagues of 1,025 participants aged 11–17 years conducted in India, the Philippines, and Taiwan that compared MenACWY-TT with MenACWY-PS [25] included an extension phase assessing antibody persistence of MenACWY-TT up to 5 years after primary vaccination [77]. Of note, participants from Taiwan were excluded from the extension phase of the study owing to the small sample size recruited from the two corresponding centers in the primary study. Among participants 16–23 years of age 5 years after primary vaccination, antibody persistence was sustained up to 5 years postvaccination with at least 86% of recipients maintaining rSBA titers ≥1:8 for each serogroup (Table 4). Antibody titers against serogroup A were higher among those receiving MenACWY-TT compared with MenACWY-PS, and a small increase in antibody titers was observed in both groups between years 4 and 5 for serogroups A, W, and Y.

Persistence of antibody responses 5 years after vaccination was assessed in a phase 2 study by Borja-Tabora and colleagues in 500 adolescents and adults aged 11–55 years conducted in the Philippines and Saudi Arabia that compared immunogenicity and safety of MenACWY-TT with MenACWY-PS [83]. Overall, 404 participants were included in the year 5 assessment; of these, 284 were aged 11–17 years. Five years after primary vaccination, the percentage of adolescents with rSBA titers ≥1:8 was 74%–93% in the

MenACWY-TT group and 24%–80% in the MenACWY-PS group (Table 4). Immunogenicity findings for adolescents were consistent with data for the total population. No vaccine-related SAEs were reported ≤5 years after vaccination.

Two studies reported the effect of a booster dose of quadrivalent meningococcal vaccines in adolescents who had been primed with a meningococcal C vaccine at preschool age [27,28]. In the first study, conducted in the United Kingdom, 93 participants aged 16–19 years previously randomized to receive a meningococcal C vaccine at the ages of 3–6 years were randomized to receive a booster dose of MenACWY-TT or MenACWY-CRM (Table 4 [28]). Both MenACWY-TT and MenACWY-CRM yielded protective functional antibody titers against all serogroups in adolescents who were primed >10 years prior with a meningococcal C vaccine irrespective of the primary vaccine received. In the second study, a phase 4 study conducted in the Netherlands, children and adolescents aged 10, 12, and 15 years previously primed with a meningococcal C conjugate vaccine at 14 months–3 years of age were randomized to receive a booster dose of MenACWY-TT or a meningococcal C vaccine [27]. MenACWY-TT elicited robust antibody responses against serogroups A, W, and Y and 95% maintained protective titers 1 year after vaccination; data for serogroup C were not reported. The findings from these studies suggest that a booster dose of MenACWY-TT is a viable option for adolescents who previously received a meningococcal C vaccine in childhood.

Coadministration with other vaccines

Coadministration of MenACWY-TT with other vaccines in adolescents has been reported. In a phase 3 study that included 611 adolescents aged 11–17 years, coadministration of MenACWY-TT with the hepatitis A/B (HepA/B) vaccine was assessed [76]. Participants received either a single MenACWY-TT dose administered with HepA/B vaccine (0-, 1-, 6-month administration), MenACWY alone, or HepA/B vaccine alone. Noninferiority of the immunogenicity of coadministration to the single administration of each vaccine was assessed 1 and 7 months after vaccination. MenACWY-TT coadministered with HepA/B vaccine was noninferior to the administration of MenACWY-TT alone (Table 4). HepA/B vaccine coadministered with MenACWY-TT was also shown to be noninferior to the administration of HepA/B vaccine alone. The authors suggested that the ability to administer MenACWY-TT with the HepA/B vaccine could simplify immunization schedules of adolescent travelers to endemic regions and national immunization programs in countries in which these diseases are endemic. Studies assessing coadministration of MenACWY-TT with other vaccines given in adolescence are also being completed, including coadministration of MenACWY-TT with the tetanus, diphtheria, and pertussis vaccine and with the human papilloma virus vaccine (Table 3).

Discussion and Summary

Meningococcal disease is a serious global health concern and a priority for prevention owing to the rapid onset of symptoms and the high mortality rate, even after treatment [3,5,6]. Vaccines are available to effectively prevent infection by most disease-causing meningococcal serogroups. However, the epidemiology and cyclic nature of IMD require continuous surveillance to identify populations most at risk of disease and carriage and the causative serogroups in a region at a particular time [2,6,23,84,85]. Therefore, successful vaccination programs should adapt to the variable nature of meningococcal disease. Such programs focus on recommending effective and safe vaccines that target currently prevalent disease-causing serogroups and strive to achieve high coverage potential in the target population.

Adolescents and young adults in many countries are at highest risk for meningococcal carriage and have one of the highest IMD rates of any age group [2,7,9,11]. Thus, adolescents and young adults are emerging as a target of meningococcal vaccination programs globally. The goal of this initiative is to directly decrease disease rates for those vaccinated and indirectly reduce disease by decreasing carriage and creating herd protection in unvaccinated individuals [10].

MenACWY-TT is a single-dose quadrivalent meningococcal vaccine supported by long-term immunogenicity and safety data across age groups [29,41,72]. In adolescents and young adults, MenACWY-TT has been investigated in several completed and ongoing clinical studies. Based on available data in adolescents and young adults comparing MenACWY-TT with other available polysaccharide and conjugate quadrivalent meningococcal vaccines, MenACWY-TT has shown robust and sustained immunogenic responses [25,73–81,83]. An acceptable tolerability profile was also demonstrated when MenACWY-TT was administered alone or in combination with vaccines that might also be administered in this age group.

To address the changing epidemiology of meningococcal disease in which serogroup W cases have recently emerged, data are also available supporting the use of a booster dose of MenACWY-TT in adolescents previously vaccinated with a meningococcal serogroup C vaccine in childhood [27,28]. These and forthcoming data in this population at high risk of carriage and/or meningococcal disease, coupled with its increased use and inclusion in vaccination programs, suggest that MenACWY-TT will contribute significantly to meningococcal disease prevention.

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Supplementary Data

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