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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