HUMAN VACCINES & IMMUNOTHERAPEUTICS
2016, VOL. 12, NO. 7, 1825–1837
http://dx.doi.org/10.1080/21645515.2016.1143157

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PRODUCT REVIEW

Meningococcal quadrivalent tetanus toxoid conjugate vaccine (MenACWY-TT, Nimenrix™): A review of its immunogenicity, safety, co-administration, and antibody persistence

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ABSTRACT

Introduction: Meningococcal disease is a major cause of morbidity and mortality worldwide with reported epidemics and outbreaks in different parts of the world. Despite the availability of antimicrobial therapy, challenges remain in early recognition and prevention of disease. Several vaccines have been developed to date aiming at preventing disease spread. Discussion: MenACWY-TT (Nimenrix™) has been extensively studied for use in different age groups. Phase II and III randomized trials have demonstrated its immunogenicity when administered in children aged 1 year and older, adolescents and adults. It has an acceptable safety profile with minor adverse events comparable to other vaccines. Follow up studies have shown persistence of protective antibodies up to three years. MenACWY-TT was safely and effectively co-administered with different recommended vaccines. Conclusion: MenACWY-TT is a safe and immunogenic vaccine that can be used to protect against these four serogroups in individuals older than 1 year of age.

ARTICLE HISTORY
Received 25 November 2015
Revised 27 December 2015
Accepted 12 January 2016

KEYWORDS
conjugate vaccine; immunogenicity; MenACWY-TT; meningococcal disease; nimenrix; randomized trials

Introduction

Neisseria meningitidis was first isolated in 1887 but illnesses resembling meningococcal disease have been reported since the 16th century. To date, meningococcal disease remains a major cause of meningitis worldwide with major epidemics in the sub-Saharan Africa and outbreaks of various sizes all over the world.[1] There are an estimated 1.2 million cases of meningococcal infection per year, with a death toll of ~135,000 worldwide.[2] Between 2006 and 2011, an estimated 113 cases of culture proven meningococcal disease occurred annually among infants <1 year in the United States. Of these cases, 23% could have been prevented with a serogroup C and Y vaccine if protection was achieved by age 4 months.[3]

Meningococcal disease poses a challenge in early diagnosis due to common clinical manifestations with other less serious diseases.[1] The most common presentation is meningitis, which manifests in 50%–60% of children with sudden onset of headache, fever, vomiting and neck stiffness, but may have a more insidious onset in younger infants.[1,3] Meningococcemia, meningococcal sepsis, is due to very high concentrations of the pathogen and endotoxin in the blood. It occurs in only 5–20% of patients and has a more severe course with abrupt onset of fever and petechial rash progressing at times to purpurafulminans and multi-organ failure.[1,3,4] Both meningitis and meningococcemia generally have a rapidly progressive course with death occurring within 24–48 hours without appropriate therapy. Pneumonia occurs in around 5–15% of patients with invasive meningococcal disease.[1] Other less common presentations include septic arthritis and otitis media.[4] In about 30% of patients, hypotension may be the only initial presentation and if left untreated might progress to meningitis or shock.[3] These clinical features underscore the importance of prevention by vaccination.

With the exception of patients with complement deficiency, who are predisposed to meningococcal infections, immunocompetent individuals are unlikely to develop the disease more than once.[5]

Microbiology

Neisseria meningitides is a gram-negative diplococcus and an obligate human pathogen.[1,6] It is a fastidious bacterium, dying within hours on inanimate surfaces.[2] It colonizes the nasopharynx and is carried mostly asymptomatically in 10% of the population.[5,6] Transmission of *N. meningitides* requires direct close contact or spread of respiratory droplets by an infected or colonized person.[5]

There are 13 serogroups of *N meningitides* based on their capsular PS. The capsule protects the pathogen during the invasion process and is a major virulence factor. Only 6 serogroups (A, B, C, W, X and Y) however account for the vast majority of invasive disease in the world.[5,7,8]

Epidemiology

Age-specific attack rate

The age distribution of meningococcal disease exhibits 3 peaks.[9] The first and highest peak occurs among infants less

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than 1 year of age in whom protective antibodies have not yet developed. The second peak occurs during adolescence and early adulthood.[1,9,10] Waning of maternal bactericidal antibodies explains the peak in infants, while adolescents have a higher rate of nasopharyngeal acquisition and colonization and thus a higher rate of infection.[10] Another peak is also seen in elderly people aged above 65 years whose immune system weakens due to senescence.[11]

Serogroup distribution

Different meningococcal serotypes predominate in different geographical locations. Serogroups A, B, and C account for most cases of meningococcal disease worldwide.[1] The highest incidence of meningococcal disease occurs in the sub-Saharan Africa,[5,12-14] known as the "meningitis belt," where during epidemics disease can affect as much as 1% of the population.[14] The most common serogroup in this area prior to the introduction of the specific conjugate vaccine was serogroup A. More recently other serogroups started circulating including serogroups C, X and W.[5,12-14] Serogroup X has recently shown epidemic potential in the sub-Saharan region.[5,12] In the Americas, the incidence of meningococcal disease is 0.3–4/100,000. However, it is much lower in the United States where serogroups B and C are most commonly isolated.[14] Another recently emerging serogroup is W in areas of South America.[2,14,15] In the United States and Canada the most prevalent serogroup currently is Y.[13,14,16] In Europe, the main serogroups are B and C, although serogroup C has been relatively controlled by vaccination. More recently serogroup Y has caused outbreaks in some European countries,[14] however no country qualifies as highly endemic for any of these serogroups.[9] The same serogroups as in Europe also circulate in Australia and New Zealand.[14] In Asia, there is limited data on the circulating serogroups, but serogroups A and C have been mainly reported.[9,14] However, Saudi Arabia has experienced some outbreaks with W serogroup during pilgrimage seasons.[9,17]

Most cases are sporadic and less likely occur as part of outbreaks. During epidemics, a single serogroup usually predominates and a shift toward older ages is noted. Epidemics occur mostly during winter and spring in temperate areas and during the dry season in tropical areas.[18]

Prevention of disease

Meningococcal disease can be controlled by implementation of the appropriate vaccination strategies and most importantly early vaccination when possible. The most remarkable testament for the unparalleled role of vaccination in protection against infection is the successful implementation of the new conjugate MenA vaccine in Africa (MenAfriVac™, India Serum Institute). Following the 1996–1997 dreadful sub-Saharan meningitis epidemic, the Meningitis Vaccine Project was created as a partnership between WHO and PATH with a generous grant from the Bill and Melinda Gates Foundation with a sole goal of developing a new conjugate A vaccine for Africa.[19,20] The new developed vaccine (MenAfriVac™, India Serum Institute) proved to be safe and immunogenic in infants and older population with antibody persistence lasting for up to 5 years.[21-24] The vaccine was first introduced in 2010 and by 2014, more than 217 million Africans were vaccinated.[19] Following this mass vaccination, a dramatic drop of more than 90% of meningitis cases due to serogroup A was reported in a period of three years.[25] In the USA, the Advisory Committee on Immunization Practices has set guidelines for routine immunization of healthy individuals and for those at increased risk for meningococcal disease.[11]

As previously stated, *N. meningitidis* strains are classified into serogroups based on the type of polysaccharide capsule expressed, which is the target of most of the currently available vaccines. The development of a universal polysaccharide vaccine including serogroup B was hampered by the striking molecular mimicry in the serogroup B capsule with a component of the human neural cell adhesion molecule (NCAM).[26-28] This made a group B polysaccharide poorly immunogenic with risks of autoimmunity and thus efforts focused on developing protein based vaccines, which became recently available.[28] Not until recently has serogroup X emerged as a cause of a number of outbreaks in the meningitis belt threatening with its epidemic potential especially following the introduction of the MenA conjugate vaccine.[26,29] Thus, the development of a vaccine against serogroup X has only recently become a public health need and will likely be included in future combination vaccines as serogroup X spreads. Currently there are three types of vaccines; the PS and PS-protein conjugated vaccines for serogroups A, C, W, and Y and vaccines based on the bacterium outer membrane proteins[15,30] developed for the control of serogroup B disease.

PS vaccines have been available for several decades and were first used in the 1970s for control of military outbreaks of *N. meningitides* in the US.[31] There are currently five licensed PS vaccines against four of the invasive serogroups (A, C, W, and Y). Although they are safe vaccines and elicit acceptable bactericidal antibodies in adults and older children,[32] they are poorly immunogenic in children under 2 years of age and do not provide long lasting immunity or immunological memory. Another drawback of these vaccines is that they induce hypo responsiveness on repeated dosing and have little or no effect on nasopharyngeal carriage and consequently on herd immunity.[7,13,16,33,34]

Several conjugate vaccines have been licensed in the past decade to overcome the limitations posed by the PS vaccines.[16] In these vaccines, the capsular PS is coupled to a carrier protein with a T-cell epitope that would induce T-cell dependent response. Thus, the result would be an improved immune response in infants, induction of immune memory and higher bactericidal antibody titers and consequently longer antibody persistence.[11,16,34,35] To date, the available and licensed conjugate meningococcal vaccines include: a serogroup A vaccine (MenAfriVac™, India Serum Institute), three serogroup C vaccines (Meningitec™, Pfizer; Menjugate™, GSK Vaccines; NeisVac-C™, Pfizer), and three quadrivalent (A, C, W, and Y) vaccines (Menactra™, Sanofi-Pasteur; Menveo™, GSK; and Nimenrix™ initially developed by GlaxoSmithKline and acquired by Pfizer in 2015).

Table 1. Neisseria meningitidis serogroup distribution in different regions and the estimated vaccine preventable meningococcal disease.

Region	Representative Countries	Serogroup Distribution (% of total)[§]						ACWY Vaccine-Preventable	B-Vaccine Preventable
		A	C	W	Y	B	X[**]		
North America	USA[73]		36		9	26		≥ 45%	26%
	Canada[74]		20		13	54		≥ 33%	54%
South America	Brazil[75]		55	5	2	38		≥ 62%	38%
	Argentina[75]		11	13	7	69		≥ 31%	69%
Europe			13		4	71		≥ 17%	71%
Middle East	Saudi Arabia[76]			36				≥ 36%	
Africa	African Meningitis Belt[*74]	91		8				≥ 99%	
	South Africa[77]		10	43	4	18		≥ 57%	18%
South East Asia	China[78]	16.4	61.2			4.5		≥ 77%	4.5%
	Japan[79]			1	39	57		≥ 40%	57%
Australia			6			85		≥ 6%	85%

Notes. [§]Data are from most recently available references for the different regions.

[*] Countries include: Gambia, Senegal, Guinea-Bissau, Guinea, Mali Burkina Faso, Ghana, Niger, Nigeria, Cameroon, Chad, Central African Republic, Sudan, South Sudan, Uganda, Kenya, Ethiopia, Eritrea, Togo, Benin, Cote D'Ivoire, Mauritania, Tanzania, Burundi, Rwanda, Democratic Republic of Congo.

[**]Serogroup X has only recently emerged as an important cause of outbreaks in the African meningitis belt mostly following the introduction of MenA conjugate vaccine. In Burkina Faso during 2011, 59% of confirmed meningococcal cases were due to MenX.[29] In southwestern Niger, incidence reached 90% for MenX during the 2006 outbreak.[12]

Licensed conjugate vaccines

MenACWY-DT (Menactra™), manufactured by Sanofi Pasteur was licensed in January 2005 by the US Food and Drug Administration (FDA) for persons aged 11–55 years. The FDA extended the age of vaccination in 2007 to include 2 to 10-year-old children, and in 2011, infants 9–23 months of age were also included in the immunization schedule. MenACWY-DT is approved for use as a two-dose series for children aged 9–23 months (8 weeks apart) and as a single dose in people 2 to 55 years.[11,13,18]

MenACWY-CRM (Menveo™), developed by Novartis Vaccines and recently acquired by GSK, was approved in February 2010 by the FDA for use in subjects 11 to 55 years of age. The next year, the covered age group extended to include individuals aged 2 to 55 years. In August 2013, the ACIP extended its recommendations to infants aged 2 to 23 months who are considered at high risk for meningococcal disease.[11,13,18,36]

However, both conjugate vaccines have not been licensed for use in children below 2 years in Europe, and both are not approved for single dosing in this age group. Table 1 illustrates the global distribution of the different meningococcal serogroups and their possible prevention by available vaccines.

Introduction to MenACWY-TT (Nimenrix™)

Nimenrix™ is a quadrivalent meningococcal conjugate vaccine comprising *N. meningitidis* capsular PS for serogroups A, C, W, and Y using tetanus toxoid (TT) as a carrier protein developed by GlaxoSmithKline (GSK) Biologicals and recently acquired by Pfizer.[13,37] It was approved in April 2012 by the European Medicines Agency as the first quadrivalent vaccine against invasive meningococcal disease to be administered as a single dose in individuals 12 months of age or older. It was also approved in Canada as a single dose for the immunization of individuals aged 12 months to 55 years.[11,13,34]

In MenACWY-TT, the serogroups A and C polysaccharides are coupled with an adipicdihydrazide (AH) spacer and indirectly conjugated to TT whereas W and Y polysaccharides are conjugated directly to TT.[37] The final approved MenACWY-TT formulation contains 0.5 μg of each of the four polysaccharides conjugated to 44 μg of TT in sucrose and trometamol excipients. The vaccine is reconstituted in 0.5 ml sterile saline and administered intramuscularly.[37,38] Nimenrix™ is supplied as a sterile lyophilized white powder in a single dose vial. The diluent (sodium chloride and water for injections-0.5 ml) is a sterile clear and colorless liquid supplied separately in a prefilled syringe or ampoule.[37] The vaccine should be stored in a refrigerator (2°C–8°C). After reconstitution, the vaccine should be given directly, but stability has been demonstrated for 8 hours at 30°C after reconstitution though delay is not recommended.[37]

Immunogenicity of MenACWY-TT

The very low incidence of meningococcal disease is a major obstacle for the feasibility of vaccine efficacy studies. Therefore, licensure of meningococcal vaccines is based on serologic correlates of protection. Conjugate vaccines produce bactericidal antibodies against capsular polysaccharides of the different serogroups. These antibodies are measured using serum bactericidal activity as a marker of efficacy.[39] Serum bactericidal assay using human complement (hSBA) or rabbit complement (rSBA) with titers ≥ 1:4 and ≥ 1:8, respectively, has been validated for use as correlate of protection for serogroup C and has been extended to the other serogroups, and thus is used for evaluation of quadrivalent meningococcal vaccines.[39-41] In addition, serogroup-specific antibody titers are also measured using a threshold of 1:128, which is the more conservative correlate of protection. In MenACWY-TT vaccine studies, vaccine response was defined as a post vaccination rSBA titer of ≥1:32 in initially seronegative subjects and a ≥4-fold increase in rSBA titer from pre- to post vaccination in initially seropositive subjects. All immunological assays were performed at GlaxoSmithKline laboratories (Rixensart, Belgium).

Immunogenicity in infants and toddlers

Immunogenicity in this age group was studied in several phase II and III clinical trials. MenACWY-TT was initially assessed using four formulations of the experimental vaccine in 240 healthy 12 to 14 months toddlers from multiple clinics in Germany and Austria.[42] Subjects received either monovalent meningococcal C conjugate vaccine (MenC-CRM197, Meningitec™) or one of the four MenACWY-TT formulations. All formulations were found to be immunogenic with a vaccine response against the four serogroups in 91.1% of subjects. At least 97.7% achieved a post vaccination rSBA titers ≥ 1:8 against all serogroups after a single dose of MenACWY-TT.[42] Following this study, the formulation containing 5 μg of each of the four meningococcal PS antigens with spacer technology for PS A and C, which had the best immune response, was selected for further development.[42] In another study, Vesikari et al. demonstrated in 304 healthy toddlers aged 12 to 23 months that MenACWY-TT was non-inferior to MenC-CRM197 in terms of immunogenicity to serogroup C and the prespecified immunogenicity criteria for the other serogroups were met.[43] Percentage of toddlers with rSBA ≥ 1:8 post vaccination were 100% in the MenACWY-TT, and at one month a higher percentage of toddlers had rSBA titers ≥ 1:128 against serogroup C in the MenACWY-TT when compared to MenC-CRM197 group (99.1% vs. 82.4%).[43] In another phase II randomized study including 385 healthy infants 9 to 12 months old, Klein et al. studied the immunogenicity of a single dose of MenACWY-TT at 12 months compared to 2 doses given at 9 and 12 months.[44] A single dose at 12 months was found immunogenic in 50.8% to 94.6% for different serogroups; however higher hSBA titers for all serogroups were observed when MenACWY-TT was administered according to a 2-dose schedule reaching 88.4% to 100%.[44] A further study by Vesikari et al. also showed that MenACWY-TT was non-inferior to MenC-CRM197 and was immunogenic in terms of serogroups A, W and Y when administered one thousand toddlers aged 12 to 23 months.[45] In a more recent phase III study conducted in Finland where 1303 healthy toddlers aged 12 to 18 months-out of the 1554 enrolled - were included in the analysis, MenACWY-TT was found immunogenic in 100% of the subjects with hSBA titers > 1:8 and non-inferior to HibMenCY-TT for the serogroups C and Y.[46]

Immunogenicity in children

Knuf et al. established in his study the immunogenicity of four experimental formulations of MenACWY-TT in 268 children aged 3 to 5 years and demonstrated that it was non-inferior to the tetravalent PS vaccine (Mencevax™, GSK Biologicals).[42] Another phase III study was conducted in 7 centers in Philippines, India, Lebanon and Saudi Arabia studying the efficacy of a single dose of this vaccine among 1504 healthy children aged 2 to 10 years.[47] Almost 100% of the MenACWY-TT recipients achieved an rSBA titer ≥ 1:8 for all serogroups. Vaccine response was statistically significantly higher with MenACWY-TT compared to the PS vaccine.[47] In another study, Dbaibo et al. demonstrated the immunogenicity of MenACWY-TT in 271 individuals aged 4.5–34 years either naïve or vaccinated 2.5–3 years earlier with a tetravalent PS vaccine. Those who had been previously vaccinated with a PS vaccine showed lower rSBA titers although more than 97% of all subjects achieved protective rSBA titers ≥ 1:128 at one month post vaccination.[48] In an open randomized phase II study performed in Finland, MenACWY-TT was non–inferior to PS vaccine in 309 children aged 2 to 10 years in terms of rSBA vaccine response for all serogroups. Actually, exploratory analysis detected higher rSBA geometric mean titers at one month post vaccination for all serogroups in the MenACWY-TT group.[49] Again the immunogenicity of this vaccine in this same age group was evaluated in a phase III randomized study enrolling 415 subjects in Germany and France.[50] A single dose of MenACWY-TT was non-inferior to MenC-CRM197 in terms of immunogenicity and vaccine response rates.[50] Moreover, MenACWY-TT was compared to another tetravalent conjugate vaccine MenACWY-DT in 1011 healthy 10 to 25 years old in a multi-centered phase II clinical trial in Canada and the United States. Vaccine response was found non-inferior in the MenACWY-TT group. Furthermore, the percentage of participants with antibody titers > 1:4 was significantly higher in the MenACWY-TT group for serogroup C and comparable to MenACWY-DT for serogroups A, Y, and W at one month.[51]

Immunogenicity in adolescents and young adults

Several phase II and III trials were published studying the immunogenicity of MenACWY-TT in this age group. A paper published in 2009 using five formulations demonstrated the immunogenicity of the vaccine.[52] MenACWY-TT was compared to a meningococcal PS in 2 separate studies including 125 adolescents aged 15 to 19 years and 50 young adults aged 18 to 25 years.[52] A single dose of any of the five formulations of MenACWY-TT induced a vigorous bactericidal immune response and 100% of subjects had rSBA titers ≥ 1:8 after one month.[52] Another phase II randomized controlled study was conducted on 872 subjects aged 10–25 years to assess the immunogenicity of MenACWY-TT using the quadrivalent MenACWY-DT as a comparator.[53] Results confirmed that MenACWY-TT was immunogenic in healthy subjects aged 11 to 25 years. When results in 10 year old children for each serogroup were compared, ≥ 83% of the MenACWY-TT group and ≥ 70.7% the MenACWY-DT group had hSBA titers ≥ 1:4.[53] In a different trial, the immunogenicity of MenACWY-TT was compared to MenACWY PS vaccine in a phase III randomized trial involving 1025 adolescents aged 11 to 17 years from the Philippines, India, and Taiwan. Vaccine response was non-inferior to MenACWY PS and the post-vaccination rSBA GMT against all serogroups were statistically significantly higher following MenACWY-TT versus MenACWY-PS vaccine after one month.[54] Another study including 225 adolescents from Philippines and Saudi Arabia also showed non-inferiority in the immunologic response to MenACWY-TT compared to the PS vaccine.[55]

Berry et al. studied the role of O-acetylation of serogroup APS antigenic epitopes in humans and mice and demonstrated that serum bactericidal titers following immunization with de-O-acetylated (de-O-Ac) conjugate vaccine were at least 32-fold lower than those following immunization with O-Ac PS-conjugate vaccine.[56] Subsequently, in a phase III randomized controlled study conducted at 3 centers in Panama, the Philippines, and Thailand, 1170 healthy subjects aged 18 to

25 years were randomized to receive one dose from either of two lots of MenACWY-TT vaccine with different acetylation levels of serogroup A (68% vs. 92% O-acetylation) compared to PS vaccine (82% O-acetylation). There was no impact on the O-acetylation level and the vaccines were found to be immunogenic with all subjects achieving an rSBA titer >1:8 for all serogroups.[57] Similarly, Halperin et al. showed that MenACWY-TT with different O-acetylation levels was immunogenic in 1016 subjects aged between 10 and 25 years and was non-inferior to MenACWY-DT for all serogroups.[51]

Immunogenicity in adults

In a phase III randomized study conducted at one center in Lebanon and three centers in the Philippines, MenACWY-TT achieved adequate vaccine responses in healthy adults aged 18 to 25 years. Around 99.3% of the 1179 evaluated subjects had an rSBA titer ≥ 1:8 for both MenACWY-TT and Men-PS. In addition, it was noted that vaccine response rates and rSBA GMTs at one month were statistically significantly higher in the MenACWY-TT group than in the Men-PS group suggesting potential benefit of this conjugate vaccine in this age group.[58] Previous administration of a meningococcal PS vaccine in adults up to 34 years old induced lower rSBA titers than those who were vaccine-naïve as demonstrated by Dbaibo et al, but still MenACWY-TT proved to induce a robust immune response in all subjects studied regardless of their previous vaccination status.[48] Additionally, a phase II randomized study enrolling 149 subjects in Philippines and Saudi Arabia demonstrated the non-inferiority of the studied vaccine in 11 to 55 years old subjects compared to Men-PS for the four serogroups.[55] Immunogenicity of MenACWY-TT was also studied in an older age group where risk of meningococcal disease shows another relatively smaller peak. Adults 56 years of age and older who hadn't received any meningococcal PS vaccine or tetanus toxoid vaccine in the past 5 years or conjugate meningococcal vaccine at any time were randomized to either receive a single dose of Men-PS or a single dose of MenACWY-TT. A total of 400 healthy subjects as old as 103 years were enrolled in this phase III open-label randomized study conducted in Lebanon. MenACWY-TT was found to be immunogenic in this age group with 93.2% of all subjects achieving rSBA titers ≥ 1:128 post vaccination, a 13.3-fold increase in rSBA GMTs and a vaccine response (VR) observed in at least 76.6%. However, following MenACWY-TT vaccine, VRs and GMTs tended to be lower in this age group and even lower in those above 65 years when compared to studies conducted on younger age groups. This was mainly due to hypo-responsiveness because of high pre-existing rSBA titers secondary to previous vaccination or exposure.[59]

Antibody persistence studies

In addition to the immunogenicity of this conjugate vaccine, several clinical trials have assessed the persistence of antibodies to the four serogroups in different age groups following vaccination. In the phase II study conducted in Germany and Austria as an extension to the study evaluating four formulations of the vaccine, persistent antibody responses (rSBA ≥ 1:8) were documented at 15 months post vaccination in > 92% of the 85 toddlers who received the vaccine at the age of 12 to 14 months and in all 100 children who received it at the age of 3–5 years.[60] In this same study, the investigators were able to prove that MenACWY-TT was able to induce immune memory for the four serogroups. This was demonstrated by challenging toddlers who had been primed with MenACWY-TT earlier with a licensed PS vaccine and showing higher rSBA GMTs after one month for serogroups A, W and Y compared to the group that had received MenC-CRM197 in the primary study.[60] In a five-year persistence follow up in the study conducted by Vesikari et al,[43] data up to 3 years post vaccination showed that 93.9% and 90.8% of 229 of the 304 original toddlers who received MenACWY-TT at the age of 12 to 23 months had rSBA titers ≥ 1:8 at 2 and 3 years, respectively.[43] The persistence of rSBA (93.9% vs. 73.1%) and hSBA (93.7% vs. 53.9%) antibodies against serogroup C was observed to be higher after vaccination with MenACWY-TT compared with MenC-CRM197 up to two years post-vaccination.[43] Moreover, Klein et al. demonstrated in his study comparing single dosing (at 12 months) to a 2-dose schedule (at 9 and 12 months) that protective rSBA titers at one year post vaccination were retained for all serogroups except for serogroup A in both groups.[44] In another phase II clinical trial published by Vesikari et al. in the same year, persistence was evaluated in 309 children 2 to 10 years old.[49] Subjects were randomized to either receive MenACWY-TT vaccine or a licensed meningococcal PS vaccine and serum bactericidal activity was measured up to three years post vaccination. Greater antibody persistence was observed in the children who received MenACWY-TT vaccine with rSBA titers ≥ 1:8 in at least 98.4% of these children.[49] In another study, Ostergaard et al. demonstrated that MenACWY-TT conjugate vaccine showed consistently high bactericidal antibodies (rSBA ≥ 1:8) three years following vaccination in young adults aged 18 to 25 years.[52] An additional study involving adolescents and adults aged 11 years to 55 years from the Philippines and Saudi Arabia, antibody persistence at 5 years post vaccination was investigated, but only results up to three years are published so far.[55] A total of 500 participants were enrolled and randomized to receive either MenACWY-TT or Men-PS. In the MenACWY-TT group, more than 99.2% and 92.9% retained rSBA titers ≥ 1:8 and ≥ 1:128 respectively for the four serogroups at 3 years, which was statistically higher than titers retained in the Men-PS group.[55] In another smaller study including 36 adolescents 15 to 19 years old, a single dose of MenACWY-TT vaccine was compared to Men-PS at 42 months following vaccination.[61] All subjects in each group had serum bactericidal activity titers ≥1:8 against all serogroups at 42 months post-vaccination with higher GMTs than pre-vaccination titers, except for two subjects in the Men-PS group against serogroup C.[61]

Safety profile

All trials evaluating the immunogenicity of MenACWY-TT vaccine have assessed the safety and reactogenicity of this vaccine in different age groups.

Local (pain, redness, and swelling) and general symptoms (fatigue, fever, gastrointestinal symptoms, and headache) were recorded daily on diary cards given to participants for 4 days up to 31 days after each vaccination. Symptom intensity was graded by subjects or parents on a scale of 0–3. Serious adverse

events (SAEs) and new onset of chronic illness were reported for 6 months after the first vaccination during the extended safety follow-up phase. All symptoms occurring at the injection site were considered to be related to vaccination. The relationship of all other symptoms to vaccination was assessed by the investigator.

Infants, toddlers, and children

Knuf et al. demonstrated that MenACWY-TT (in four investigational formulations), MenC-CRM197 (Meningitec™, Wyeth), and the PS vaccine (Mencevax™) were, in general, tolerated well. Grade 3 symptoms were rarely reported among both toddlers (12–14 months) and children (3–5 years) and there were no statistically significant differences between the MenACWY-TT group and the age appropriate licensed control.[42] In toddlers from both groups and in children 3 to 5 years from the MenACWY-TT group, erythema at the injection site was the most commonly solicited local reported adverse event (AE). However, pain at site of injection was the most commonly reported in the Men-PS group. Drowsiness and irritability were the most commonly reported general solicited AEs in both toddlers and children from any group.[42] In a single study where infants 9 months old were enrolled, MenACWY-TT was found well tolerated in this age group with pain and irritability being the most common reported AE.[44] Though fever was reported in 3.3% of the vaccinated 9 months old infants, none had a fever $> 40^{\circ}C$.[44] In the five-year persistence study by Vesikari et al, toddlers 12 to 24 months old received MenACWY-TT and reactogenicity was assessed and compared to that of MenC-CRM.[43] Both had comparable safety profile and were, in general, tolerated well. Redness at the injection site (36% in the MenACWY-TT group vs. 33% in the MenC-CRM group) and irritability (38.6% vs. 39.7%) were the most commonly reported solicited local and general AEs, respectively. Fever was reported in around 15% of MenACWY-TT recipients within four days after vaccination. Grade 3 solicited symptoms were rarely reported.[43] In the phase III randomized study by Memish et al., including children 2 to 10 years old from the Philippines, India, Lebanon, and Saudi Arabia, MenACWY-TT vaccine was found to have an acceptable safety profile that was similar to licensed PS vaccine in all vaccinated cohorts.[47] Grade 3 AEs were infrequently reported in both treatment groups and no SAEs occurred that were considered related to vaccination. Local and general solicited AEs in the 2–5 years strata were statistically similar in both groups. The most common AEs were pain (around 20%) followed by redness and swelling. In the 6–10 years strata, using exploratory analysis, pain was reported more in the group receiving Men-PS (30%) compared to MenACWY-TT (20%) (P-value < 0.05). Moreover, in another phase III trial, involving children aged 2–10 years from Germany and France, solicited local AEs seemed to be more frequently reported than in the previously mentioned study[50] but similar to those reported by Knuf et al.[42] Redness was the most common grade 3 solicited AE in both age strata. No statistically significant difference in local and general AEs was observed between those who received MenACWY-TT and those who received MenC-CRM with redness (35%) being the most common solicited AE in the 2–5 years strata and pain (44%) in the 6–10 years strata. Irritability was the most common general solicited AE among 2–5 years age group, while fatigue followed by headache was the most common among 6–10 years age group. None of the SAEs reported were considered related to vaccination.[50] In another randomized trial by Vesikari et al, 309 Finnish children aged 2 to 10 years were randomized to either receive MenACWY-TT or MenACWY PS vaccine.[49] Pain was the most common local solicited AE but the incidence was lower in those who received MenACWY-TT. In the 2–5 years age group, drowsiness was the most common solicited general AE in the MenACWY-TT cohort (26.5%) and irritability in the MenACWY PS cohort (28.2%). Fatigue was the most common solicited general AE in children aged 2–10 years occurring in 38.5% and 20.5% in the ACWY-TT and Men-PS cohorts, respectively. None of the SAEs reported were considered related to the vaccination. In conclusion MenACWY-TT was found to have a clinically acceptable safety profile in this age group.[49]

Adolescents and adults

The safety and reactogenicity of MenACWY-TT vaccine was evaluated in its five initial investigational formulations among adolescents 15 to 25 years old compared to a licensed PS vaccine.[52] Among the 175 enrolled subjects, fever was reported in 6 (3 in each group). Pain was the most frequently reported local AE while fatigue and headache were the most frequently reported general AEs. Both MenACWY-TT and PS vaccine had similar safety profiles except for one of the formulations of MenACWY-TT (C), which had significantly higher incidences of pain and swelling at site of injection. Grade 3 AEs were rarely reported and included pain, redness, headache, fatigue and gastrointestinal symptoms. Only one patient receiving a MenACWY-TT formulation (5B) had urticaria after 8 days of the vaccine that was considered as a SAE. Neither formulations (5B or C) were later developed to the currently reviewed Nimenrix™.[52]

In the study by Halperin et al, reactogenicity of MenACWY-TT was compared to MenACWY-DT in adolescents and young adults aged 10 to 25 years.[51] The most common local AE reported was pain at site of injection observed in 57.5% of the subjects in the MenACWY-TT group compared to 59.5% in the MenACWY-DT group. Systemic AEs, most frequently headache and fatigue, were reported in almost 42% of subjects in the MenACWY-TT group compared to 42.3% in the MenACWY-DT group. Serious AEs at 6 months follow-up were reported in 8 subjects from the MenACWY-TT group but none were attributable to the vaccine.[51]

In another cohort of 784 adolescents and young adults aged 11 to 25 years, safety of MenACWY-TT was compared to MenACWY-DT vaccine.[53] Both had similar safety profiles with pain being the most commonly reported AE (54.1% with MenACWY-DT vs. 54.9% with MenACWY-TT). Other AEs included redness (10.8% vs. 13.3%), swelling (6.7% vs. 10.9%), fatigue (32% vs. 29%), fever (8.2% vs. 7.1%), gastrointestinal symptoms (16.5% vs. 18.8%) and headache (37.1% vs. 33%). AEs of grade 3 severity were equally reported in all groups and didn't exceed 3.3%. Over the 6 month follow up, only 0.9% in the MenACWY-TT group, 2.3% in the subgroup including 10 year olds, and 1% in the MenACWY-DT group reported SAEs, but all improved and none of these were considered related to

vaccination.[53] Among 500 healthy adolescents and adults from the Philippines and Saudi Arabia, pain was the most common solicited local AE following vaccination with either MenACWY-TT (38.6%) or Men-PS (32.3%).[55] Injection site redness and swelling were more frequently reported in the MenACWY-TT group.[55] However, both vaccines had acceptable safety profile at day 4, day 31, and at 6 months extended safety follow up. None of the SAEs reported were related to the vaccine up to 3 years post vaccination.[55] In another randomized trial in a single center in Lebanon, safety was assessed in 400 healthy adults from 56 to 103 years of age.[59] In this age group, vaccine had lower reactogenicity as compared to younger age groups and was very well tolerated. Less than 3% of subjects from both MenACWY-TT group and Men-PS group reported any local or general AEs. The most common reported AEs in the MenACWY-TT group were pain (2.3%), redness and swelling at the injection site (1.1%), fatigue (1.9%), and headache (3%). No grade 3 AEs were reported by either group and only one SAE was recorded but was not considered vaccine-related.[59] In addition, in the 42-month persistence study by Ostergaard et al, no SAEs among the 50 vaccinated adolescents were reported during this period.[61] In another randomized trial by Dbaibo et al, conducted at a center in Lebanon and three centers in the Philippines, MenACWY-TT had an adequate safety profile with pain (19.4%) and headache (16.3%) being the most commonly reported AEs in recruited adults 18 to 55 years old.[58] Grade 3 AEs were rarely reported in the MenACWY-TT and Men-PS groups. Unsolicited and grade 3 unsolicited AEs were equally infrequently reported in both groups and only two AEs (abdominal pain and gastritis), reported by one subject, were considered related to vaccination but resolved without sequelae.[58] In summary, MenACWY-TT has an excellent safety profile. The slightly higher frequency of local AEs compared to the PS comparator is probably related to the protein content.

Co-administration

When an individual is eligible for more than one vaccine, co-administering these vaccines on the same visit increases the probability of this individual to be fully immunized as appropriate for age.[62] Co-administration is also important when planning for travel if more than one vaccine is needed within a short time prior to takeoff. Based on extensive clinical trials, most of the live and inactivated vaccines available can be administered simultaneously with MenACWY-TT during the same visit with similar vaccine responses and rate of adverse events as observed when these vaccines are administered separately.[62]

Several phase III clinical trials have been conducted to demonstrate the safety and immunogenicity of co-administering MenACWY-TT (Nimenrix™) with influenza virus vaccine (Flaurix™, GlaxoSmithKline) in adults, hepatitis A and hepatitis B vaccine (Twinrix™, GlaxoSmithKline) in children and adolescents, a 10-valent pneumococcal conjugate vaccine (Synflorix™, GlaxoSmithKline) in toddlers, diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated poliomyelitis, and *Haemophilus influenzae* type b (Hib)conjugate vaccine (DTaP-HepB-IPV/Hib; Infanrix-hexa™, GlaxoSmithKline) and DTaP (Infanrix™,GlaxoSmithKline) in toddlers, and finally with measles, mumps, rubella and varicella vaccine (Priorix-tetra™, GlaxoSmithKline) in toddlers.

Co-administration with seasonal influenza vaccine (Flaurix™, GlaxoSmithKline)

This was evaluated in a phase III randomized trial at one center in Lebanon and three centers in the Philippines enrolling 517 adults aged 18 to 55 years who received MenACWY-TT alone, with seasonal influenza, or Men-PS alone.[63] No statistically significant differences were seen in terms of vaccine response in either group. However, exploratory analysis showed lower GMTs in the co-administration group as compared to MenACWY-TT for serogroups A and C, but higher GMTs to serogroups A, W and Y as compared to Men-PS. This suggested the possibility of some immune interference when influenza vaccine was administered at the same time. Yet, almost 99% and 97% of subjects in all groups achieved rSBA titers $\geq$1:8 and $\geq$1:128 respectively for each of the four serogroups. At the same time, the co-administration group showed antibody responses to the three influenza strains as per the predefined criteria for acceptable immune responses set by the European Medicines Agency Committee for Proprietary Medicinal Products.[63]

MenACWY-TT proved to have an acceptable safety profile in adults when co-administered with the influenza vaccine. Pain and headache were the most common solicited local and general AEs respectively in all groups and grade 3 AEs were only rarely reported. Only seven patients reported SAEs and all were in the MenACWY-TT group, but none were considered vaccine related except for an episode of abdominal pain and gastritis noted above. Otherwise, at the extended 6 month follow up period, there were no reported events.[63]

Co-administration with hepatitis A and B vaccine (Twinrix™, GlaxoSmithKline)

Hepatitis A and B cause vaccine preventable liver disease and are a major cause of morbidity and mortality worldwide.[64,65] Their combination in one vaccine was shown to be immunogenic and with a good safety profile in children and adolescents in addition to adults.[65] Since hepatitis A and B (HepA/B), and meningococcal disease are usually endemic in the same areas, the ability to co-administer these vaccines would promote adherence to vaccination schedules especially among those traveling to endemic areas.[66] In his clinical trial, Ostergaard et al. demonstrated that co-administration of MenACWY-TT with HepA/B vaccine (Twinrix™, GSK) didn't interfere with the immunogenicity or safety profile of either vaccine.[66] A total of 609 adolescents aged 11 to 17 years completed the study and were randomized to either receive HepA/B vaccine alone, MenACWY-TT alone or simultaneously in the same visit. It was demonstrated that a single dose of MenACWY-TT induced rSBA titers $\geq$ 1:128 for each of the four serogroups in up to 100% of subjects at 1 month and 7 months post vaccination whether the vaccine was given alone or co-administered with HepA/B vaccine. At the same time, all subjects were seropositive for hepatitis A and achieved seroprotection against hepatitis B at one month after the third dose of HepA/B vaccine whether they had received HepA/B vaccine alone or co-administered with MenACWY-TT. Both vaccines were tolerated well,

in general, and pain at the injection site was the most reported local AE. General solicited AEs, mainly headache and fatigue, and grade 3 AEs were infrequently reported and were comparable among all groups. There were two SAEs reported in the co-administration group by one subject (syncope and concussion) that resolved within two days but were considered to be possibly related to the vaccine.

Co-administration with a ten-valent conjugate pneumococcal vaccine (Synflorix™, GlaxoSmithKline)

This phase III clinical trial included 363 toddlers 12 to 23 months from 2 centers in Mexico and 3 centers in Taiwan who had received their primary vaccination series with PHiD-CV (10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine; Synflorix™,GSK) in a previous study.[67] Healthy toddlers were randomized to either receive PHiD-CV alone followed by MenACWY-TT in a second visit, MenACWY-TT at one visit followed by PHiD-CV in a second visit, or both vaccines together at the same visit. In the three groups, 97.5% to 100% of toddlers had rSBA titers $\geq$1:128 for each serogroup and thus demonstrating the non-inferiority of co-administration to giving MenACWY-TT alone. Concerning the immunogenicity of PHiD-CV in the co-administration group, immune response to all serotypes except for serotype 18C, met the pre-specified criteria for non-inferiority of co-administration over PHiD-CV alone. However, this had no clinical applicability since for all serotypes including serotype 18C, there was a robust increase in the antibody concentration following the booster dose of PHiD-CV. Most importantly, in the three groups, 96% of the toddlers reached antibody concentrations $\geq$ 0.2 μg/ml for each serogroup and a robust increase in the mean geometric antibody concentrations. Safety was also evaluated in this randomized trial.[67] Pain at the site of injection was found to be the most common reported solicited AE in all studied groups. Grade 3 intensity pain was reported in 2.4% to 7.8% of toddlers at the MenACWY-TT injection site. General solicited AEs reported were less than 1.2% with irritability being the most reported. SAEs and grade 3 unsolicited AEs were rarely reported and none of the SAEs were considered related to vaccination. Co-administration was therefore considered clinically acceptable and didn't modify the safety profile of either vaccine.[67]

Co-administration with DTaP-HepB-IPV/Hib(Infanrix-hexa™, GlaxoSmithKline)

In a phase III randomized trial that enrolled healthy toddlers in their second year of life from 72 centers in Germany, Austria and Greece.[68] Subjects were randomized into four groups to either receive both MenACWY-TT and DTaP-HepB-IPV/Hib on the same day, or MenACWY-TT followed by DTaP-HepB-IPV/Hib (ACWY/Hexa) one month later, or DTaP-HepB-IPV/Hib initially followed by MenACWY-TT (Hexa/ACWY) a month later, or a single dose of MenC-CRM197 (Meningitec™, Pfizer). Co-administration of both vaccines was shown to be non-inferior to administering either alone, with the number of subjects with rSBA titers $\geq$1:8 reached above the predefined limit for all serogroups, and there was no difference in terms of hepatitis B, Hib, diphtheria, tetanus, and polio immunogenicity. In fact, exploratory analysis revealed that significantly higher percentages had rSBA titers $\geq$ 1:8 for serogroups C and Y, and higher rSBA titers $\geq$ 1:128 for all serogroups in the co-administration group. When compared to the MenC control group, the co-administration group showed significantly more subjects with rSBA-MenC $\geq$1:128.

Moreover, almost all subjects developed seroprotective antibodies against diphtheria, tetanus, hepatitis B, Hib, and the three poliovirus types. All subjects were seropositive for antibodies against pertussis toxin, filamentous hemagglutinin, and pertactin. However, exploratory analysis showed significantly lower rSBA GMTs for serogroups A, C, and W-135 and lower anti-tetanus antibodies in the Hexa/ACWY group than in the ACWY/Hexa group.

All groups had similar reactogenicity and co-administration of these vaccines didn't alter the safety profile of either vaccines. Redness was the most common local solicited AE equally reported in all groups, but pain at the injection site was more frequently reported at the MenACWY-TT injection site in the co-administration group. Drowsiness and irritability were the most common reported general AEs in all groups. Grade 3 AEs were infrequently reported and none of the SAEs were considered related to the vaccination.[68]

Co-administration with DTaP (Infanrix™, GlaxoSmithKline)

In another trial by Leonardi et al, 1303 healthy infants who had been primed with HibMenCY-TT (MenHibrix™) and DTaP-HBV-IPV (Pediarix™) at 2, 4, and 6 months were analyzed for immunogenicity and safety of co-administration of DTaP (Infanrix™) and MenACWY-TT (Nimenrix™).[69] The control group received Pediarix and Hib-TT (ActHIB™) at 2, 4, and 6 months then Infanrix between 15 and 18 months old. The remaining subjects were randomized to either receive Nimenrix at 12–15 months then Infanrix at 15–18 months, or MenHibrix at 12–14 months then Infanrix at 15–18 months, or were brought at 15–18 months for both Nimenrix and Infanrix vaccine co-administration. Blood samples were withdrawn from all groups after the 15–18 months visit, and 99% were found to have anti-tetanus and anti-diphtheria antibodies $\geq$ 0.1 IU/ml and all but one subject were seropositive for antibodies against pertussis antigens. However, exploratory analysis revealed lower post vaccination geometric mean antibody concentrations for pertussis antigens in the 3 groups compared to the control group. Immunogenicity and vaccine response to MenACWY-TT when co-administered with DTaP were not evaluated in this clinical trial.

In general, co-administration had an acceptable safety profile that was comparable to all other study groups. All groups showed similar local and general solicited symptoms. Yet, three SAEs were reported and were attributed to vaccination, one of which was sudden infant death syndrome at 89 days post dose 1 in the MenHibrix group.

Co-administration with measles, mumps, rubella and varicella (Priorix -tetra™, GlaxoSmithKline)

A thousand healthy toddlers aged 12 to 23 months from 14 different centers in Finland were enrolled in this phase III clinical trial.[45] Group 1 (MMRV+ACWY-TT group) received both MenACWY-TT and MMRV at visit one then a second dose of MMRV after 12 weeks, group 2 (ACWY-TT group) received

Table 2. Summary of the main results of phase III clinical trials on co-administration of MenACWY-TT with other vaccines.

Author	Country	Age	Co-administration group	Immunogenicity	Safety	Notes
Knuf et al.[68] 2011	Austria, Germany, Greece	12 to 23 months	MenACWY-TT +*Infanrix*^{TM} *Hexa*, GSK	97.3% had rSBA titres ≥1:8 and at least 88.2% had titres ≥1:128 for all four serogroups. 99.4% had anti-D and anti-T concentrations ≥0.1 IU/ml. All subjects were seropositive for antibodies against pertussis; all subjects had seroprotective antibodies against Hib. At least 98.2% had seroprotective antibodies against hepatitis B and each of the three poliovirus types.	AEs were within the same range for all groups. Pain, redness and swelling at site of injection were more frequent in the Coad groups.	Higher percentages with rSBA ≥1:8 for serogroups C & Y in the Coad group. Lower anti-tetanus and anti-Hepatitis B antibodies in the Hexa/ACWY than in the ACWY/Hexa group.
Vesikari et al.[45] 2011	Finland	12 to 23 months	MenACWY-TT +*Priorix*^{TM} *Tetra*, GSK	Co-administration was non-inferior to administering vaccines at separate visits. 99.7% of subjects had rSBA titers ≥1:8 against each vaccine serogroup. All seroconverted against measles and rubella, 83.3%–87% 97.9% (Coad) against varicella	Comparable safety profile for all groups. Fever and rash due to the measles component was similar in all groups.	Lower anti-rubella GMCs in the Coad group. Higher rSBA titers against serogroup C in the ACWY-TT groups than in the MenC group
Ostergaard et al. [66] 2012	Sweden, Denmark	11 to 17 years	MenACWY-TT +*Twinrix*^{TM}, GSK	All subjects achieved rSBA titers ≥ 1:128 after 1st dose of ACWY-TT for each serogroup in both groups. All subjects were seropositive for hepatitis A and achieved seroprotection against hepatitis B after 3rd dose of HepA/B in both groups.	Safety profile was similar for both groups.	Significantly lower rSBA GMTs to serogroup C noted in the Coad group
Aplasca-De Los Reyes et al.[63] 2012	Lebanon, Philippines	18 to 55 years	MenACWY-TT + *Fluarix*^{TM}, GSK	99.0% and 97.1% of subjects in all vaccine groups achieved rSBA titers ≥ 1:8 and ≥1:128 respectively, for each of the four serogroups. The Coad group met all pre-defined statistical criteria for antibody responses against influenza antigens A/H1N1, A/H3N2 and B.	Safety profile was similar for all groups. Pain at injection site and headache were the two most frequently reported symptoms.	
Ruiz-Palacios et al.[67] 2013	Mexico, Taiwan	12 to 23 months	MenACWY-TT + *Synflorix*^{TM}, GSK	96% of the toddlers reached antibody concentrations ≥ 0.2 μg/ml for each pneumococcal serogroup in all studied groups. At least 97.5% achieved r SBA titers ≥1:128 to each meningococcal serogroup in all studied groups.	Safety profile was similar for both groups.	Non-inferiority criteria of co-administration over PHiD-CV alone was not met for serotype 18C
Leonardi et al.[69] 2015	USA	2 months	MenACWY-TT +*Infanrix*^{TM}, GSK	99% had anti-tetanus and anti-diphtheria protective titers. All but one were seropositive for antibodies against pertussis antigens.		Lower post vaccination antibody GMCs for pertussis antigens in the 3 groups compared to the control group. Immunogenicity and vaccine response to MenACWY-TT when co-administered with DTaP were not evaluated

Note. Infanrix Hexa, DTaP-HepB-Hib/IPV; Priorix Tetra, MMRV; Twinrix, HepA/B; Fluarix, influenza vaccine; Synflorix, ten-valent pneumococcal vaccine; Infanrix, DTaP.

MenACWY-TT at visit one followed with 2 doses of MMRV separated by 6 weeks each, group 3 (MMRV group)received MMRV at visit one then MenC-CRM197 in 6 weeks and a second dose of MMRV 6 weeks later, and group 4 (MenC group) received MenC-CRM197 followed in 6 weeks by 2 doses of MMRV separated by 6 weeks each. The primary objective was to assess the immunogenicity and safety of MenACWY-TT.

Co-administration of MenACWY-TT vaccine and MMRV was non-inferior to administering either of the vaccines on separate visits. After 42 days of vaccination, 99.7% of subject had rSBA titers ≥ 1:8 for all serogroups after administration of MenACWY-TT in both groups 1 and 2. In fact, significantly higher percentages of subjects achieved rSBA titers ≥ 1:128 against serogroup C in the ACWY+MMRV and in the MenACWY-TT groups than those in the MenC group. All subjects became seropositive for all vaccine components in both the MMRV and MenACWY+MMRV groups following the first dose of MMRV. There were no statistically significant differences in geometric mean antibody concentrations (GMC) at 42 weeks post vaccination in both groups except for anti-

rubella GMCs, which were significantly lower in the co-administration group.

Both had comparable safety profiles and were tolerated well among toddlers aged 12–23 months, with redness and irritability being the most common solicited AEs within 4 days of vaccination. The incidence of the transient rash and fever due to the measles component in the MMRV vaccine was similar in the co-administration group and MMRV group. Fever incidence peaked between 4 and 10 days after receiving MMRV in all groups.

In summary, MenACWY-TT can be co-administered with most commonly used vaccines. Table 2 summarizes the findings from these co-administration studies.

Licensure and recommendations for the use of MenACWY-TT

Nimenrix™ is currently registered and approved for sale in 61 countries across the European Economic Area, Canada, Australia and Emerging Markets, with registrations under review in another 18 countries across Africa, Asia, Eastern Europe and the Middle East.

Recommendations for meningococcal vaccine use in countries where MenACWY-TT is licensed: United Kingdom and the European Union.

In the UK, MenC conjugate vaccine was first introduced into the vaccination schedule in November 1999 in conjunction with a catch up campaign to persons up to 18 years then extended to include adults aged up to 25 years. The schedule included initially 3 doses at age 2, 3 and 4 months in addition to the catch-up dose.

In 2006, the 2 months vaccine dose was replaced by a booster dose at 12 months of age that was combined with Hib as Hib/MenC vaccine. Then in 2013, the Joint Committee on Vaccination and Immunization (JCVI) recommended adding an adolescent booster dose at age 13–14 years to the schedule and the second dose of MenC at 4 months was therefore removed.

While rates of serogroup C meningococcal infections in the UK have decreased, the rates of infections attributed to serogroup W have rapidly increased since 2009 with the number of cases escalating from 22 in 2009 to 117 in 2014. So, in October 2014 JCVI recommended replacement of the adolescent MenC dose with quadrivalent ACWY conjugate vaccine. In February 2015, JCVI further recommended an emergency catch-up program with the ACWY conjugate vaccine for all adolescents aged.

14–18 years. As a result, a MenACWY campaign was announced in June 2015 by Public Health Ministry that started in August 2015 to vaccinate all adolescents born between 1 September 1996 and 31 August 1997.[70] Available approved conjugate quadrivalent meningococcal vaccines in the UK includeMenACWY-CRM197 and MenACWY-TT.[70]

Other European countries licensed and introduced MenC conjugate vaccine as of 2000 (Ireland and Spain). By 2009, 12 European countries included MenC conjugate vaccine in their routine vaccination program.[71] Moreover, MenACWY-CRM197 was licensed by the European Agency of Medicine in 2010 for persons aged 11 years and up while MenACWY-TT was licensed in 2012 for use in all individuals older than 1 year of age.[72] An ongoing clinical trial is evaluating this vaccine's immunogenicity and safety in infants below one year of age. Future studies are required to determine the timing and need for any booster doses in individuals older than 1 year of age.

Conclusion

Invasive meningococcal disease is a serious and important cause of morbidity and mortality worldwide. MenA, MenC, and MenB vaccines are included on the vaccination schedules of all infants in some countries whereas MenACWY is used in others but limited to high risk groups. Vaccination against a single serogroup might lead to replacement by other serogroups. The most effectivevaccination strategy would be to vaccinate against all serogroups that are known to cause human diseasein order to halt outbreaks and decrease morbidity and mortality rates. However, financial and logistical barriers exist that prevent such strategy from being implemented in most countries. MenACWY-TT is one of the available quadrivalent conjugate vaccines that has been shown through many clinical trials to be immunogenic and safe from as young as 1 year of age.Clinical trials are ongoing to determine its immunogenicity and safety in infants younger than 12 months. Additionally, it is the only conjugated meningococcal vaccine that has been studied in individuals older than 56 years, a particularly vulnerable population. It can also be administered simultaneously with other vaccines without altering the immunogenicity and safety of either vaccine.

Abbreviations

MenACWY-TT	quadrivalent serogroups A, C, W and Y vaccine with all serogroups conjugated to the tetanus toxoid carrier protein
PS	polysaccharide
AE	adverse events
rSBA	meningococcal bactericidal titers using rabbit complement as exogenous complement source
hSBA	meningococcal bactericidal titers using human complement as exogenous complement source
GMC	geometric mean antibody concentration
GMT	geometric mean antibody titer
GSK	GlaxoSmithKline Biologicals

Disclosure of potential conflicts of interest

GD has received honoraria for speaking engagements and Advisory Board memberships from GSK, Pfizer, Sanofi-Aventis, Merck Sharpe and Dohme (MSD), and Hikma and also received research grants through his institution from GSK, Pfizer, and MSD.

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