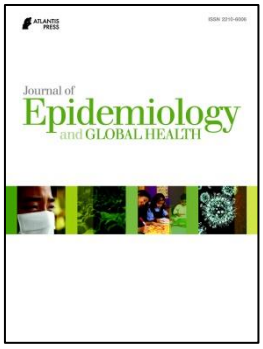

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# Consensus recommendation for meningococcal disease prevention in children and adolescents in the Middle East region

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**Abstract** Facing the availability of the new generation of quadrivalent meningococcal conjugate vaccines (Menveo®, Menactra® and others pending for license) and their recent implementation in Saudi Arabia, experts from 11 countries of the Middle East region met at a ''Meningococcal Leadership Forum'' (MLF), which took place in May 2010 in Dubai. The participants of the conference discussed the importance of introducing the concept of conjugate vaccines — especially for children and adolescents — and elaborated a consensus recommendation to support healthcare professionals and decision makers with their expertise. In experts' opinion, conjugate vaccines are the best choice for the prevention of meningococcal disease caused by serogroups A, C, W-135 and Y. As quadrivalent meningococcal conjugate vaccines are registered and available in the Middle East region, they should replace plain polysaccharide vaccines and be integrated in pediatric and adolescent vaccination schedules, including infant vaccination concomitantly with basic EPI vaccines when licensed.


## 1. Scientific background meningococci

### 1.1. Pathogen and transmission

Worldwide, most cases of meningococcal diseases are caused by 5 of 12 known serogroups (A, B, C, W-135, Y) of *Neisseria meningitidis*, which is transmitted from human to human by respiratory

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secretion or direct contact and colonizing the nasopharynx. Asymptomatic carriage is common in the general population and can be as high as 35% [1], during Hajj it can reach up to 86% [2]. Rather few carriers become symptomatic, when the bacteria penetrate the barrier of nasopharyngeal mucosa and get into blood circulation and/or the brain, causing septicemia and/or meningitis. There are several risk factors associated with bacterial carriage, including: (i) crowded conditions (e.g. military barracks, dormitories, pubs, events); (ii) travels to endemic areas; and (iii) personal behaviors (e.g. kissing, coughing, smoking), all of which increase exposure to the bacteria [1]. Most if not all these risk factors apply to adolescents, who are the biggest global reservoir for *N. meningitidis* of all age groups and thus the key for transmission [3].

*N. meningitidis* is a very diverse, genetically unstable bacterial pathogen that changes genomic information and can change in itself through various mechanisms (e.g. mutation, horizontal gene transfer, recombination) to survive selective pressures like immune responses or antibiotics [4]. Capsular switch is a well-known example for the biodiversity of meningococci and was the cause of the emergence of serogroup W-135, which is regarded to have originated from a virulent serogroup C strain [5]. The capsular polysaccharides on the bacteria's cell surface are the prerequisite for its pathogenicity and escape mechanism against the body's defenses and thus the target of vaccines (except for serogroup B vaccines).

## 1.2. Burden of disease

*N. meningitidis* remains the primary cause of bacterial meningitis and septicemia that have not yet been fully controlled by conjugate vaccines, as it was achieved for *Haemophilus influenzae* type b (Hib) [6] and pneumococcal disease [7]. While some countries (e.g. the United Kingdom) have made significant progress by introducing meningococcal serogroup C conjugate vaccines, this only covered disease caused by serogroup C and did not affect other serogroups. The potentially life-threatening meningococcal disease occurs suddenly in otherwise healthy persons and the progression can be very rapid and unpredictable [8]. Due to the nonspecific, flu-like symptoms in the early stage, meningococcal disease is difficult to diagnose and accurate treatment may be delayed [9]. Signs may be subtle even in far-advanced stage and can be misdiagnosed. Therefore the time frame for appropriate treatment is very tight: The mean hospital admission time is 19 h after the onset of first symptoms, but a critical situation or death can already occur within 24 h [9]. Even with appropriate treatment and intensive care, the case-fatality rate (CFR) is high: 10—30% depending on manifestation, age (CFR increases with age) and serogroup (W-135 and Y are associated with higher CFR than B and C) [10—12]. Up to 20% of survivors suffer from permanent severe sequelae such as hearing loss, skin necrosis, seizures or limb amputation [10]. In most countries meningococcal disease shows a bimodal age distribution with the highest burden in infants and toddlers (0—4 years of age) followed by a second peak in adolescents and young adults (15—24 years of age). Compared to infants, meningococcal disease is more severe and CFR is higher in adolescents [8]. Besides the individual burden of the patients and their families, also the societal impact and the healthcare costs are substantial. For all these reasons, prevention of meningococcal disease plays an important role — currently four serogroups can be covered by the vaccination: A, C, W-135 and Y (with the exception of New Zealand and Cuba, where specific OMV-vaccines are used to cover specific endemic B-strains).

## 1.3. Changing epidemiology

Both incidences of disease and distribution of serogroups are continually changing. Long-term data show various incidences of meningococcal disease with a cyclic change over time that is also observed in Saudi Arabia and in the countries of the African meningitis belt, where the peaks are almost equal in the neighboring countries (''synchrony'') [13]. All five major serogroups exist everywhere at the same time, but the relative proportions highly vary from country to country and are changing unpredictably. There are numerous examples for the dynamic change in serogroup distribution, e.g. in the United States [14] and Colombia [15], serogroup Y increased significantly in the last decade, whereas Canada [16], Brazil [17] and the Czech Republic [18] reported a shift to serogroup C in that period. In Saudi Arabia [19] W-135 gained dominance within only 2 years followed by other countries also observing much higher proportions of W-135 (e.g. Turkey, South Africa, Nigeria, and Argentina) [20].

Besides the genetic variability of bacteria, travel is one of the major drivers influencing the change of epidemiology. International travel can promote and accelerate the spread of different serogroups all over the world (especially after mass gatherings like the Hajj), which can lead to global outbreaks as well as to the unexpected establishment of a prior non-endemic serogroup, as documented e.g. for A and W-135. The global spread

of serogroup A was the effect of three great pandemics in Asia during the last century; recent outbreaks are reported from India and the Philippines [21]. In 2000 and 2001, serogroup W-135 was transferred from Hajj to other countries all over the world and caused secondary infections in the home countries of pilgrims [19]. A comparison of the two outbreaks in Saudi Arabia in 2000 and 2001 shows a large spread of disease outside the holy cities and an increase of cases in young children (<5 years of age) [22]. This clearly proves that the use of polysaccharide vaccines after the first outbreak could not significantly reduce carriage and therefore could not prevent transmission and infection in the unvaccinated-unlike the experiences with conjugate vaccines in general have shown.

The changing epidemiology is an important public health challenge and requires networking and surveillance at the global, national and district levels for decision-making of comprehensive intervention methods. The cyclic nature of meningococcal disease, the unpredictable change of serogroup distribution and increasing travel underscore the need for a prevention strategy that incorporates all major serogroups. Long-term protection with conjugate vaccines against as many serogroups as possible and among as many age groups as possible would be the optimal solution.

## 1.4. Polysaccharide vs. conjugate vaccines

Nowadays, plain meningococcal polysaccharide vaccines are considered to be outdated because of important limitations (Table 1): they are not immunogenic in young children (<2 years of age), who have the greatest burden of disease; they do not elicit an immune memory and provide only limited duration of protection (~3 years); they have no significant impact on carriage and transmission (no herd immunity); and they cannot be boosted. Repeated polysaccharide vaccinations result in reduced immune responses (hyporesponsiveness) [5]. Most of these disadvantages are based on the lack of T-cell activation by plain polysaccharides.

The technology of meningococcal conjugate vaccines may overcome these limitations. As a result of a carrier protein to which the capsular polysaccharides are chemically linked (conjugated), a T-cell mediated immune response with all its benefits is induced: Much more and, above all, functional antibodies are produced (high immunogenicity even in infants aged >2 months) and an immune memory is induced (prolonged duration of protection), effective boosting (no hyporesponsiveness) and prevention/clearance of carriage can be achieved [5]. The latter is of fundamental importance to prevent further transmission of bacteria for contributing to the herd immunity, as demonstrated over the years by the widespread use of Hib and pneumococcal conjugate vaccines, as well as in some countries with meningococcal C conjugate vaccines.

## 1.5. Success of meningococcal C conjugate vaccines

The development of conjugate vaccines has brought considerable immunologic improvements over plain polysaccharide vaccines [5]. During the 1990s a dramatic and rapid increase of severe meningococcal C cases and a serogroup shift to hypervirulent C strains was observed in European countries, as well as in Canada, where the incidence of C cases was tripling at that time. When the new generation of meningococcal C conjugate vaccines became available, immunization programs were implemented in several countries. In the United Kingdom a national vaccination program started in 1999 with two parallel approaches: meningococcal C conjugate vaccination was included in the routine immunization schedule for infants (three doses at 2, 3, and 4 months of age) and in a catch-up campaign for all children aged 1–18 years (one single dose). With this strategy high coverage rates among the age groups most at risk were achieved within a short period of time. The data are very well analyzed and show a significant continuous reduction in serogroup C disease (up to −97%) as well as an overall reduction in the

**Table 1** Comparison of plain polysaccharide versus conjugate vaccines.

| Vaccine characteristics | Polysaccharide vaccines | Conjugate vaccines |
|---|---|---|
| Effective in infants | No | Yes |
| Immune memory | No | Yes |
| Prolonged duration of protection | No | Yes |
| Booster effect | No | Yes |
| Reduction of carriage | No | Yes |
| Contribution to herd effect | No | Yes |
| Hyporesponsiveness with repeated doses | yes | No |

Harrison LH, Prospects for vaccine prevention of meningococcal infection. *Clin Microbiol Rev* 2006; 9(1):142–164.

incidence of meningococcal disease, even in the unvaccinated population [23].

Thus, conjugate vaccines not only had a substantial direct impact on vaccinees, but also generated an impressive indirect effect in unvaccinated individuals. This herd immunity is created at high vaccination coverage by the significant reduction of serogroup C carriage (−81%) that ceases transmission [24]. The impact of conjugate vaccination on the carriage is also reflected in the serogroup distribution, as in the UK for which the percentage of serogroup C decreased significantly [24]. As expected, there was no impact on other serogroups (neither on carriage nor on actual cases of invasive meningococcal disease), because no cross-protection between the immunologically different meningococcal serogroups exists. Importantly, until today, no replacement is observed, i.e. the ecological niche in the throat is not replaced by other serogroups of meningococci. Similar success documenting that meningococcal C conjugate vaccines are very effective tools for a dramatic reduction of meningococcal disease and death was achieved in the Netherlands, Belgium, Iceland, Ireland, Spain, Portugal and Canada.

## 1.6. Conjugate technology and carrier proteins

The capsular polysaccharides (sugar chains) of meningococcal serogroups differ biochemically and thus immunologically. Therefore a specific immune response against A, C, W-135 and Y is required, respectively, and no cross-reaction between antibodies directed to one serogroup against another is possible. The biochemistry (formulation) of a vaccine helps to identify its essence and is the prerequisite for good clinical efficacy. Many factors of the complex technology of a conjugate vaccine can have an impact on immunogenicity (and tolerability), in particular the length and homogenicity of the sugar chains, the nature of the carrier protein and the method of linkage in between (direct or indirect conjugation via a linker).

The following carrier proteins are used for the conjugation of polysaccharides by different manufacturers:

- Hib vaccines: $CRM_{197}$ (*Corynebacterium diphtheriae* cross-reactive material), diphtheria toxoid (D), tetanus toxoid (T), OMPC (outer membrane protein complex).
- Pneumococcal vaccines: $CRM_{197}$, Protein D from *H. influenzae*, T (in development).
- Meningococcal C vaccines: $CRM_{197}$, T (also Hib/MenC combination).
- Meningococcal ACWY vaccines: $CRM_{197}$, D, T (in development).

For the first quadrivalent meningococcal conjugate vaccine (Menactra®) D is used as carrier protein, the other recently developed ACWY conjugate vaccine (Menveo®) contains $CRM_{197}$. One further quadrivalent conjugate vaccine using T as carrier protein is currently under clinical investigation. D, T and $CRM_{197}$ have a long history in human use and are well known to induce a robust immune response in a broad range of age groups (including infants) as well as for their proven safety profile. Whereas D and T have to be detoxified with formaldehyde, $CRM_{197}$ is a natural non-toxic mutant of D and therefore needs no chemical inactivation. (For details of conjugation technology see Bröker et al. [25] and Ravenscoft [26].)

*N. meningitidis* is the only bacterium that can generate widespread outbreaks and epidemics of meningitis [27]. Most cases of invasive meningococcal disease occur in infants and young children. Due to the high morbidity and mortality and the changing epidemiology, vaccination as broad as possible in the serogroup coverage and in the age group coverage is recommended for the prevention of meningococcal infections. Until now meningococcal polysaccharide vaccines are widely used in the Middle East, present day quadrivalent conjugate vaccines are available that provide superior advantages (see Table 1).

## 1.7. Waning immunity

Experience with the large scale immunization program in the UK using monovalent meningococcal C conjugate vaccine showed that infants primed with MenC conjugate vaccines needed a booster dose to provide persistently protective antibody levels later in life [28]. Since meningococcal disease can progress more rapidly than the time for reactivation of immune memory to take place, the persistence of circulating bactericidal antibodies at a protective level is necessary for clinical protection [29]. Consequently the schedule of 2, 3, 4 months of age was changed to 2, 4, 12 months to induce longer persistence of circulating antibodies by the booster dose. However, the great success of the campaign achieving the herd immunity was mainly accomplished by the catch-up campaign in adolescents. Due to waning immunity and in the absence of an adolescent booster, the herd immunity is likely to diminish over the coming years. Based on the UK experience, the introduction of a routine adolescent booster dose is being discussed in several countries. Some countries have started to introduce an adolescent booster, (e.g. Canada, Switzerland), Austria is the first country to

recommend an adolescent booster explicitly with quadrivalent Men ACWY conjugate vaccine following primary immunization with monovalent Men C vaccine.

## 2. Pediatric consensus-recommendation for meningococcal ACWY conjugate vaccination

### 2.1. Prevention in adolescents

As described in part 1 of this paper, adolescents have the highest carriage rate and are the largest global reservoir for *N. meningitidis* of all age groups (key for transmission). Consequently, they are at high risk for contracting meningococcal disease (2nd peak of incidence after infants/toddlers), mainly because of their social behavior and individual lifestyle [30]. Compared with infants, meningococcal disease is more severe in adolescents and case fatality rate is higher [31,32]. In addition, it has been observed, that hypervirulent strains tend to circulate preferably in adolescents, and especially during epidemics, the peak in adolescence is very high [33].

It is very important to reduce the carrier rate in the teenage group, as targeting the adolescents will also indirectly protect infants and potentially boost the waning immunity. Vaccinating this age group will both enhance the immune response and will have optimal effect on carriage. The need for high vaccine coverage rates remains the most important challenge: Health issues in general, and vaccinations in particular, are not considered a priority of teenagers, and vaccination campaigns in this age group may need new approaches. The most successful approach to catch adolescents and young adults would be with school campaigns and within the military establishment.

Also from a societal perspective, the ability to prevent morbidity and mortality in a segment of population that is critical for a nation's future (because adolescent health is critical to social productivity) creates an imperative to have adolescent vaccination as a cornerstone of the public health policy. Notably, because vaccinating adolescents leads to a higher persistence of seroprotective antibodies, the public health investment will be more durable [34,35].

### 2.2. Vaccination practices in the Middle East region

In many countries of the Middle East region meningococcal polysaccharide vaccines are given routinely to children above 2 years of age or to schoolchildren or selectively to risk groups like pilgrims, soldiers, healthcare workers and travelers. Many of these vaccinees get immunized every 3 years or even more frequently. Thus hyporesponsiveness is an important issue in this region.

An unmet medical need is the protection of infants and toddlers below 2 years of age, because polysaccharide vaccines are not efficacious in this most vulnerable age group with the highest incidence of meningococcal disease. Conjugate meningococcal ACWY vaccines can overcome these limitations and will be the optimal protection strategy for all age groups. Saudi Arabia decided to convert to ACWY conjugate vaccines in 2010 [36], starting to target all people involved in pilgrimage, and is working on an adolescent immunization program with meningococcal vaccination as an integral part of it.

### 2.3. Consensual recommendation for meningococcal ACWY conjugate vaccination

The experts of the Middle East region agree on the concept of using conjugate vaccines replacing polysaccharide vaccines. Conjugate vaccines are regarded as the best choice for the prevention of meningococcal disease caused by serogroups A, C, W135 and Y. The potential benefits of meningococcal conjugate vaccines include longer duration of protection, reduction of carriage, contribution to the herd immunity without hyporesponsiveness upon repeated doses, and giving a good sero-response in subjects previously vaccinated with repeated doses of the polysaccharide vaccines (i.e. overcoming the hyporesponsiveness induced by polysaccharide vaccines) [37]. Their potential to reduce transmission by prevention/clearance of carriage offers the possibility to prevent dissemination of the bacteria. Many countries have experienced the occurrence of meningococcal infections despite high coverage of polysaccharide vaccinations. Therefore, the impact of conjugate vaccines on carriage is of major interest from an epidemiologic, economic and also from a public health perspective. Each single case of meningococcal disease, no matter if imported or indigenous, requires a public health response (i.e. identification of close contacts for chemoprophylaxis). Another important advantage is the chance of reducing the ''overuse'' of antibiotics: upon large scale and widespread use of conjugate vaccines, there will be no more — or at least much less — need for chemoprophylaxis. A remaining concern, however, is that conjugate ACWY vaccines do not cover all serogroups (B, X).

### 2.4. How to integrate tetravalent conjugate vaccines in pediatric and adolescent settings?

- Step1: Adolescents and young adults (the major age cohort of carriage) should be vaccinated as soon as possible — ideally together with other important vaccinations at this age (for example TdaP booster, Rubella, HPV; depending on each country's adolescent vaccination program, which is not uniform in the countries of the region). With implementation in schools/at military, this target group can be reached more easily.
- Step 2: For infants and toddlers (above 2 months to below 2 years of age) ACWY conjugate vaccination should be part of the national immunization program and be integrated into the routine schedules upon licensure in the respective age. As the majority of invasive meningococcal disease occurs in early infancy, the ideal timeframe would be concomitant administration with basic EPI vaccines, depending on national immunization schedules of individual countries, for instance at the 2,4,and 6 months-schedule.

### 2.5. Which implementation strategy is recommended?

- The optimal strategy is to carry out a mass immunization campaign of all adolescents (11 years and above) at the same time, followed by regular adolescent cohort vaccinations (at the age of 11 years or above, potentially when Td booster doses are scheduled, according to national policies).
- Infant and toddler vaccinations should be implemented when licensed. Preferred age would be early infancy.

As early as available, quadrivalent meningococcal conjugate vaccines should be preferred over polysaccharide vaccines. At present, the use of ACWY conjugate vaccines is limited to the registered age (2 years without upper age limit for Menveo®, 9 months to 55 years for Menactra®. Both vaccines are registered and are available in the Middle East region, including Saudi Arabia. For some countries, the costs of conjugate vaccines may be a financial burden at introduction, but costs will be recovered within some years through long-term protection and the added value of the herd immunity. The concept of conjugate vaccines is convincing and offers the opportunity to significantly reduce the burden of meningococcal disease in all age groups.

## Conflict of Interest

None.

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