Prevention of Meningococcal Disease

MARCO AURÉLIO PALAZZI SÁFADI

SABIN
VACCINE INSTITUTE

Prevention of Meningococcal Disease

Marco Aurélio Palazzi Sáfadi MD, PhD
Santa Casa de São Paulo School of Medical Sciences. São Paulo, Brazil

Introduction

Meningococcal disease (MD) is a major public health problem and remains a leading cause of meningitis and sepsis in several Latin American countries. Few diseases have as much power to cause panic among the population as MD, primarily because of its potential epidemic nature, the rapid onset of illness and its high case fatality rates (10% – 20%) and substantial morbidity. Up to 20% of survivors of meningococcal disease develop long-term sequelae, including deafness, neurological deficit, seizures, and/or limb amputation.[1,2]

Etiology and Pathogenesis

The causative agent of meningococcal disease (MD), *Neisseria meningitidis*, is a gram-negative, aerobic, encapsulated, non-mobile diplococcus, belonging to the *Neisseriaceae* family. The antigenic composition of the polysaccharide capsule enables the classification of *N. meningitidis* into 12 different serogroups: A, B, C, H, I, K, L, W, X, Y, Z and E.[3] Currently, serogroups A, B, C, Y, W and X are responsible for nearly all cases of disease reported worldwide, infecting only humans.[1-3] Meningococci are also classified into serotypes and serosubtypes according to the antigenic composition of the outer membrane proteins PorB and PorA, respectively. Meningococci have demonstrated the ability to exchange the genetic material that is responsible for producing the capsule, and thereby, to change the serogroup. Genetic multilocus sequence typing (MLST), polymerase chain reaction (PCR), and whole-genome sequencing (WGS) are currently the most specific methods to detect and characterize meningococcal strains.[4,5]

Meningococci are transmitted from person to person, by aerosolization of or contact with, respiratory secretions or saliva. Acquisition of meningococci can be transient, lead to colonization (carriage) or result in invasive disease. A majority of individuals will harbor *N. meningitidis* in the throat asymptomatically throughout their lives. Although meningococcal carriage is common in many or most human populations, invasive disease is a relatively rare outcome of meningococcal infection. For the majority of people, carriage is an immunizing process that results in protective antibodies.[6,7]

In non-epidemic settings, carriage studies performed around the world showed that approximately 5–10% of the population carries meningococci. Carriage rates were found to be very low in the first years of life, increasing in teenagers and young adults and then declining in adulthood.[6,7] Carriage rates of meningococci can

be considerably higher in outbreak situations, household contacts of people with the disease and in institutions, particularly in military personnel or other closed or semi-enclosed communities.[6,7]

When invasive disease develops, it usually occurs within 1–14 days of acquisition. In households where a case of meningococcal disease has occurred, the risk for invasive disease in family members is increased by a factor of 500–800.[8]

Epidemiology

MD affects individuals of all age groups, but the highest incidence is observed in children under 5 years and especially among infants. In some populations, incidence peaks can also be observed among two other age groups: adolescents and young adults, as well as adults aged 65 years of age and older. During outbreaks and epidemics, a shift in the age-distribution of MD is observed, with increased number of cases among adolescents and young adults. Most cases of meningococcal disease are sporadic with a larger number of cases during the winter.[2,3]

MD occurs all over the world, but there are marked geographical differences in incidence and the distribution of the different serogroups that cause disease. In North America, serogroups B, C and Y are the main serogroups causing MD, whereas in Africa, epidemic disease is most commonly associated with serogroup A, and more recently by serogroups C, W and X.[3,8-9] In European countries, serogroups B, W and Y are important causes of endemic invasive meningococcal disease (IMD), while serogroup C is still prevalent in countries without MenC vaccination programs.[3]

In Latin America, during the last decade, incidence rates of MD varied widely, from less than 0.1 cases per 100,000 in Mexico, Peru, Paraguay and Bolivia to 2 cases per 100,000 in Brazil, with the highest incidence generally observed in infants.[10] Regarding serogroup distribution, serogroups B and C are responsible for the majority of cases reported in the region. However, an increased number of serogroup W disease cases, associated with the ST-11 complex, was recently reported in Argentina and Chile.[10,11]

The availability and quality of published data for MD in Latin America are not uniform across the countries, with limited data available and exceedingly low rates of meningococcal disease reported by some countries. Brazil, Uruguay, Argentina and Chile are the countries with the highest burden of MD in Latin America, probably reflecting more robust surveillance systems and well-established laboratory infrastructure for MD.[10]

Clinical Manifestations

Invasive infections due to *N. meningitidis* result in a wide clinical spectrum characterized by one or more clinical syndromes, including: meningitis, bacteremia or sepsis, with meningitis being the most common clinical presentation. Pneumonia, pericarditis, myocarditis, conjunctivitis or arthritis are less common manifestations of *N. meningitidis* infection. Against this background, the term "meningococcal disease" is appropriate and has been adopted internationally. In less than 10% of the patients with MD, a self-limiting post-infectious inflammatory syndrome, most commonly characterized by fever, arthritis or vasculitis, can occur.[2]

Diagnosis

Diagnosis of invasive meningococcal disease is based on clinical presentation, as well as a variety of laboratory tests. The gold standard for the laboratory diagnosis of MD is the isolation of *N. meningitidis* by culture from a usually sterile body fluid, such as blood, cerebrospinal fluid (CSF), or, less commonly, synovial, pericardial or pleural fluid, and petechial or purpuric lesion scraping. A Gram stain of a petechial or purpuric scraping, CSF, and buffy coat smear of blood can be helpful. Latex agglutination tests utilize latex beads coated with antibodies to meningococcal capsular antigens in body fluids such as CSF, blood and urine. These kits can detect agglutination of five capsular groups: A, B, C, Y, and W.[2]

The polymerase chain reaction (PCR) is a rapid and sensitive test for diagnosing meningococcal infection. A major advantage of PCR over culture methods is that it allows for detection of *N. meningitidis* from clinical samples even when the organisms are nonviable after antimicrobial treatment.[2]

Treatment

Early diagnosis and initiation of antibiotic treatment, transfer to a hospital with an intensive care unit and aggressive management of shock are critical to reduce the case fatality rates associated with meningococcal disease. There are several acceptable antibiotic options for the treatment of MD, including penicillin G (250,000–400,000 U/kg/day divided q4–6 hours i.v.), or third generation cephalosporins like cefotaxime (200 mg/kg/day i.v.) or ceftriaxone (100 mg/kg/day i.v.). For patients with history of serious allergy to b-lactam antibiotics, chloramphenicol (75–100 mg/kg/day divided q6 hours i.v.) is the recommended antibiotic treatment.[2] Although isolates of *N. meningitidis* with relative resistance to penicillin (minimal inhibitory concentration of penicillin of 0.1– 1.0 mg/ml) have been reported in Latin American countries,[12] this degree of penicillin resistance (attributed to a genetic mutation that causes alteration in penicillin-binding protein 2) does not appear to impact response to therapy. Guidelines recommend 5–7 days of treatment. Optimal supportive care is critical. However, the use of steroids in children with shock caused by *N. meningitidis* is controversial since no pediatric studies have documented its benefit. Pediatric intensive care specialists may treat children with MD who have refractory shock and inadequate adrenal gland function with steroids.[13] There is available evidence to support the use of dexamethasone therapy given before antibiotics to reduce morbidity in children with Hib meningitis.[2] However, routine use of dexamethasone cannot be recommended for treatment of meningococcal meningitis based on current data. Adjuvant therapies have been used in children, but no beneficial effects on survival rates were observed.

Prevention

Chemoprophylaxis

Chemoprophylaxis should be offered to all household contacts of an index case of MD, people living and/or sleeping in the same household, childcare and nursery school contacts, and people who have been directly exposed to a patient's oral secretions through close contact, such as kissing or sharing of toothbrushes and others, during the 10 days before onset of symptoms of disease in the index case. Routine prophylaxis is not recommended for health care professionals, except in cases when mouth to mouth resuscitation, endotracheal intubation, or aspiration of secretions were made without respiratory precautions. To eradicate nasopharyngeal carriage of *N. meningitidis*, the index case should also receive chemoprophylaxis before hospital discharge, unless ceftriaxone or cefotaxime are the antimicrobial agents used for treatment of MD. Rifampin is the drug of choice for chemoprophylaxis of children and adults. Ceftriaxone given in a single intramuscular injection and ciprofloxacin in a single oral dose proved to be effective options to eradicate pharyngeal carriage of meningococci. Ciprofloxacin should only be used for people older than 18 years of age.[2]

Vaccines

Table 1. Meningococcal Vaccines Available Globally in 2016

Polysaccharide Vaccines	**Polysaccharide**	
Meningo A+C®	MenAC	
Mencevax®	MenACWY	
Menomune®	MenACWY	
Conjugate Vaccines		**Carrier Protein**
Menjugate®	MenC	CRM_{197}
Meningitec®	MenC	CRM_{197}
NeisVac-C®	MenC	TT
Menitorix®	MenC-Hib	TT
MenHibrix®	MenC-Y-Hib	TT
MenAfriVac®	MenA	TT
Menactra®	MenACYW	DT
Menveo®	MenACYW	CRM_{197}
Nimenrix®	MenACYW	TT
Protein Subunit Vaccines	**Antigenic Components**	
Bexsero®	fHbp, NadA, NHBA, and PorA Serosubtype P1.4	
Trumenba®	FHbp Subfamilies 1 and 2	

Source: Compiled by author.

Polysaccharide Vaccines

The polysaccharide vaccines currently available offer protection against serogroups A, C, W and Y. These vaccines, in common with other unconjugated polysaccharide vaccines, do not generate adequate immune response in children under 2 years of age, because of the lack of response to T-independent antigens at this age. Another characteristic of these vaccines is that, even in patients over 2 years of age, the protection offered is of limited duration; since they are unable to induce immune memory. Furthermore, they are capable of inducing hyporesponsiveness after subsequent doses. These features, combined with the fact that these vaccines have only transitory and incomplete effect in reducing the colonization and the transmission of the meningococci in the vaccinated population, have limited the use of polysaccharide vaccines.[14-17]

Polysaccharide Conjugate Vaccines

The conjugation of polysaccharides to protein carriers (non-toxic diphtheria mutant toxin [CRM_{197}] or tetanus toxoid) alters the nature of the antipolysaccharide response to include a T-dependent response. When B cells recognize the polysaccharide they process the conjugated carrier protein and present peptide epitopes to T-CD4+ cells. This antigenic complex induces the production of elevated antibody levels, including in young infants, higher antibody avidity and increases serum bactericidal activity. They also induce the formation of long-lasting memory B lymphocyte populations, providing an amnestic response (booster effect) on re-exposure. Furthermore, these vaccines have the capacity to prevent acquisition of nasopharyngeal colonization, reducing the number of carriers among those vaccinated and thus interrupting transmission of the pathogen within the population ("herd protection").[15-17]

Pharmaceutical companies initially developed, in the late 1990s, monovalent meningococcal conjugate vaccines against meningococcus C, containing one polysaccharide, conjugated to the mutant diphtheria toxin (MCC-CRM_{197}) or to the tetanus toxid (MCC-TT). These vaccines have proven to be immunogenic in infants, toddlers, older children, adolescents and adults. Later, it was also licensed as a combined *Haemophilus influenzae* type b (Hib)-MenC vaccine conjugated to the tetanus toxoid.[16-18] Randomized, controlled, Phase III trials, which assess the efficacy of a vaccine in a determined population, are not feasible due to low incidence of the serogroup C meningococcal disease. Thus, the serologic markers of immunity against infection by meningococcal C are used to infer the effectiveness of these vaccines and served as a basis for their licensing.[16] The correlate of protection accepted (i.e., the lowest antibody titer necessary to consider the vaccinated individual protected) is the presence of serum bactericidal antibody (SBA) $\geq$ 4 using human complement or SBA titers $\geq$ 8 when using complement obtained from baby rabbits.[16-17] During the pre- and post-licensure trials, good immunogenicity in the short-term and presence of immunologic memory associated with available conjugate vaccines were demonstrated, plus adequate tolerability and reactogenicity profiles.[14-17] In 1999, the vaccines were initially licensed in Europe with three doses for primary immunization of infants from 2 months of age. However, later immunogenicity trials showed that the scheme of primary immunization could be reduced to two or only one dose in this age group.[19]

Experience with Mass Immunization of the Population with Meningococcal Conjugate Vaccine

In 1999, the United Kingdom (U.K.) was first to introduce the MCC vaccine into routine childhood vaccination, vaccinating more than 15,000,000 individuals younger than 17 years in less than one year. The initial results were encouraging, with an 81% reduction of serogroup C incidence from the period of 1998–1999 compared to the period of 2000–2001. The one-dose effectiveness of the vaccine in reducing MD under routine field conditions was of up to 97% in adolescents and 92% in toddlers. Effectiveness was found to be 91% in infants who received three doses of the vaccine at ages 2, 3 and 4 months of age. The number of deaths attributed to serogroup C meningococcal disease dropped from 67 in 1999 to five in 2001.[18] There was a significant reduction in the incidence of meningococcal disease even in unvaccinated age groups, demonstrating that conjugate vaccines protect not only vaccinated individuals, but also the general population, most likely due to the reduction of the number of carriers of the bacteria in nasopharynx.[18-21] The success of the mass immunization program was attributed to both the high effectiveness of the vaccine (direct protection) and to the herd effect (indirect protection).

However, a few years after the introduction of the vaccine in the U.K., in 2004, a decline in effectiveness for all age groups was observed, especially in the group of infants vaccinated at 2, 3 and 4 months.[23] Between 2000 and 2003, 53 cases of MenC disease were registered in vaccinated children, and the investigation of these cases demonstrated no evidence of immunodeficiency. A similar phenomenon was observed in Spain, with a loss of protection in children that were vaccinated at 2, 4 and 6 months of age.[24-25]

Monitoring the incidence of disease caused by serogroup C, suggested waning efficacy of the vaccine after a few years, occurring mainly in children immunized in the first year of age, with two or three doses of the vaccine. As a result, the U.K. added a booster dose after 1 year of age, to ensure longer protection for infants immunized in the first year of life.[19]

In the U.K., a study on the effect of mass vaccination on rates of carriage, in 16,000 adolescents from 15 to 17 years, showed a 66% reduction in rates of meningococcal serogroup C nasopharyngeal carriage, compared to rates before the introduction of the meningococcal conjugate vaccines.[21] In this study, other serogroups' carriage rates among the vaccinated population remained relatively unchanged. One hypothetical concern is that after the dramatic reduction in the incidence of serogroup C MD in countries that adopted mass vaccination, other serogroups might "replace" the disease incidence gap left by serogroup C disease.[26] To date, surveillance data in the U.K. have not demonstrated a replacement effect.[26-27]

In 2002, the Netherlands started a routine immunization program with only one dose of the MCC vaccine conjugated to tetanus toxoid at 14 months of age. Additionally, a catchup campaign was introduced with the aim of immunizing all children and adolescents from 1 to 18 years with the same vaccine. The data from the Netherlands showed a rapid and dramatic reduction in the incidence of meningococcal disease both in vaccinated and unvaccinated age groups, with the greatest reduction (99%) verified in vaccinated age groups.[28] Other European countries obtained significant reductions in the incidence of serogroup C meningococcal disease after the introduction of the MCC vaccines in immunization programs.[29-32] These vaccines have also successfully controlled outbreaks of MenC disease. In Quebec, Canada, health authorities vaccinated all individuals from 2 months to 20 years of age with MCC vaccine. The vaccine effectiveness, verified more than one year after the outbreak, was greater than 96%, demonstrating again its potential use in controlling epidemics.[33]

Studies in the U.K. which assessed the persistence of protective antibody titers among children and adolescents vaccinated in different ages and schemes,[34] showed that only 25% of the children vaccinated between 2 months and 6 years old had protective antibody titers six to seven years after immunization. In contrast, children that had been vaccinated at older ages, between 6–15 years, maintained high rates of persistence of protective antibody titers. Four to five years after receiving the vaccine, 79% of the immunized children between 6–9 years and 88% of the immunized children between 10–15 years maintained rSBA $\geq$ 8.[35] These data confirm that the immune response provided by the MCC vaccines is age-dependent. Subjects vaccinated at older ages present more consistent and longer lasting responses. This recent evidence of rapid loss of protective antibody titers for children immunized in the first 6 years of life suggests that approximately 75% of these children are susceptible to the risk of carriage and to developing the disease when they enter adolescence.

The key to maintaining the success of the immunization program appears to be the prevention of carriage acquisition by maintaining high antibody levels in adolescents. Hence, several countries, including the U.K. and Canada, have introduced booster vaccinations in adolescents. The U.K. recently decided to replace their MenC adolescent booster with a MenACWY booster and to perform a catch-up campaign for students to prevent carriage and induce herd protection.[36]

In 2010, Brazil was the first Latin American country to introduce the MCC vaccine into the routine immunization schedule for infants, as a 2-dose schedule at 3 and 5 months of age, with a booster dose at 12 months of age. Toddlers between 12 and 23 months received one dose of the vaccine, with no catch-up campaign for older age groups. The introduction of MCC vaccine into the routine program in Brazil reduced incidence rates of disease in the age groups targeted for the vaccine. However, despite the dramatic decrease in the incidence rates of MD among the age groups that were vaccinated, no early impact was observed in other age groups, probably reflecting the lack of a catchup campaign in adolescents, usually the age group responsible for carriage and transmission.[11] Brazil is now considering the introduction of an adolescent dose of MCC to optimize the impact of the vaccination program. Currently, Brazil is the only country in Latin America that introduced the MCC vaccine routinely.

New Meningococcal Conjugate Vaccines

Currently, three quadrivalent (A, C, W and Y) meningococcal conjugate vaccines that use different protein carriers [tetanus toxoid (TT), diphtheria toxoid (DT) and non-toxic mutant diphtheria toxoid (CRM)] are licensed based on safety and immunogenicity data. In Latin America, the MenACWY-DT vaccine is licensed for children above 9 months of age, adolescents, and adults up to 55 years of age. The MenACWY-CRM_{197} vaccine is licensed for children above 2 months of age, adolescents and adults. The MenACWY-TT vaccine is licensed for children above 1 year of age, adolescents and adults.[37]

Effectiveness data regarding MenACWY vaccines are limited. In a study performed in the U.S., the effectiveness of MenACWY-DT against MenC and MenY disease in adolescents was approximately 80%–85% in the first year after immunization, with data suggesting decreasing effectiveness when evaluated after 3–5 years.[8]

In Chile, after the sustained increase in the number and proportion of serogroup W cases reported in 2012, the Ministry of Health decided to implement an immunization campaign in response, using two different quadrivalent conjugate vaccines (Men ACWY-DT and Men ACWY-CRM_{197}) aimed at children aged between 9 months and 5 years. In 2014, a vaccination program using the MenACWY-TT conjugate vaccine was included in the national immunization program for all children at 12 months of age.[11] The immunization campaign started

in October 2012 and rolled out nationwide during the first months of 2013. Coverage for the first dose of the vaccine was almost 100% for the targeted age group. A preliminary analysis of the data in Chile showed that after the Men ACWY immunization campaign, protection was observed only in the age groups targeted with the vaccine. There were no early indirect effects. The overall incidence rates of serogroup W MD in 2013, 2014 and 2015 were similar to 2012.[38] Consequently, new potential strategies, including immunization of young infants and a catch-up campaign targeting adolescents and young adults, are being discussed to optimize the impact of the vaccination program in Chile.

In the U.S., the Advisory Committee on Immunization Practices (ACIP) currently recommends the quadrivalent ACWY meningococcal conjugate vaccine to all adolescents from 11 to 12 years of age, with a booster dose after 5 years. Adolescents from 13 to 18 years, not previously vaccinated, should also be vaccinated.

In the U.S., vaccination with an age- and formulation-appropriate meningococcal conjugate vaccine is recommended for infants, children, adolescents and adults at increased risk of MD:[2]

- Individuals with persistent complement component deficiencies (C3, C5–C9, properdin, factor D, and factor H)
- Individuals with functional or anatomic asplenia (including sickle cell disease)
- Children above 2 years, adolescents and adults who have HIV, if another indication for immunization exists
- Individuals in communities with a meningococcal disease outbreak for which vaccination is recommended
- Individuals traveling to or residing in areas where meningococcal disease is hyperendemic or epidemic

Children who remain at risk should receive a booster dose of MenACWY conjugate vaccine three years after the primary series if they received their primary series before seven years of age, then every five years thereafter. If their primary series was given after seven years of age, then the booster dose should be given five years later and then every five years thereafter.[2] These vaccines are also recommended for use during epidemics or for controlling outbreaks.

In response to the continuing high levels of MenA disease in the meningitis belt in Africa, a MenA-TT conjugate vaccine was introduced through a mass immunization campaign targeting more than 150 million people of 1–29 years of age in African countries with the highest burden of disease. The incidence of MenA has dramatically decreased in the vaccinated countries and the vaccine has also had a profound impact in reducing carriage.[39-40]

Hib-MenCY-TT, a vaccine that contains meningococcal C and Y capsular polysaccharides conjugated to tetanus toxoid and *Haemophilus influenzae* type b capsular polysaccharide also conjugated to tetanus toxoid, was licensed by the U.S. Food and Drug Administration (FDA) in June 2012. Hib-MenCY-TT is approved by the FDA as a 4-dose series for children aged 6 weeks through 18 months and currently used only in U.S.

Vaccination with meningococcal conjugate vaccines is contraindicated among persons known to have a severe allergic reaction to any component of the vaccines, including diphtheria or tetanus toxoid. ACIP does not consider a history of Guillain-Barré syndrome (GBS) to be a contraindication or precaution for meningococcal vaccination. Pregnant women, if considered at risk of disease, can be vaccinated with meningococcal conjugate vaccines.[2,16] Premature infants may receive immunizations at the appropriate chronological age, according to the infant immunization schedule.

All meningococcal conjugate vaccines are inactivated vaccines, so they can be administered to persons who a re immunosuppressed as a result of disease or medications. However, response to the vaccine might be less than optimal.[2,16]

In general, the safety and reactogenicity profiles of meningococcal vaccines are adequate. The most commonly reported adverse events include pain, erythema and induration at the injection site, headache, fever and fatigue. In adolescents, syncope immediately after vaccination can occur. Anaphylactic reactions after vaccination are rare.[2,16]

Protein Subunit Vaccines

The capsular polysaccharide of meningococcus B has an antigenic structure (acetylneuraminic a-2-8-N acid) similar to that found in embryonic neural tissues. This peculiar characteristic, in addition to making it impossible for polysaccharide vaccines containing serogroup B to be immunogenic, also results in a risk of autoimmune reactions.[14,16] As a result, no polysaccharide conjugate vaccines developed for meningococcus B have been shown to be immunogenic and risk free. One attempt to overcome this problem was to develop vaccines that used non-capsular components of meningococcus B. Vaccines based on outer membrane proteins (OMV), developed in Cuba and Norway, were used successfully to control outbreaks. However, the immune response to these vaccines is specific to the serosubtypes of meningococcus B included in the vaccine. Protection was not provided to other meningococcus B serosubtypes not included in the vaccine.[14,16]

Recently, two protein subunit vaccines targeting MenB were licensed. The 4CMenB vaccine (*Bexsero*® by GSK) is composed of one variant of the factor H binding protein (FHbp), NadA, Neisseria heparin binding antigen (NHBA), and outer membrane vesicles that contain the New Zealand outbreak strain PorA serosubtype P1.4. The vaccine is licensed in the U.S. as a two dose schedule in adolescents and young adults, aged 10 to 25 years. This vaccine is also licensed in Europe, Australia, Canada, and some countries in South America beginning at two months of age.[41,42] For infants who start vaccination between two and five months of age, three doses are recommended, with the first dose administered at two months and with at least two months apart between doses. A booster dose may be administered at 12 months of age. For infants who start vaccination between six and 11 months, two doses of vaccine are recommended, with two months between them, with a booster after 12 months. For children who start vaccination between one and 10 years, two doses are recommended, with an interval of at least two months. Finally, for teenagers and adults up to 50 years of age, two doses are recommended, with at least a one month interval.

In adolescents and adults, the most common local and systemic adverse reactions observed after vaccination with 4CMenB were pain and erythema at the injection site, malaise and headache. In infants, injection site reactions, fever and irritability were frequently seen.[41]

The other protein subunit vaccine is rLP2086 (*Trumenba*® by Pfizer) which utilizes one variant of lipidated FHbp from each of the two FHbp subfamilies. The vaccine is currently licensed only in the U.S., either as a two (0 and 6 months) or three dose (0, 2 and 6 months) schedule in adolescents and young adults, aged 10 to 25 years.[41]

Both of these MenB vaccines induce SBA against selected MenB strains in adolescent populations. No robust effectiveness data for either vaccine are currently available. One study conducted in university students showed no effect of 4CMenB on MenB carriage, although 30% reductions in other groups of serogroups (CWY) were observed.[43] A Meningococcal Antigen Typing System (MATS) has been developed to predict the level of protection against a determined strain. Preliminary data for 4CMenB in Canada, US, several European countries and Brazil estimate coverage among MenB strains ranging from 66–91%.[44] For both vaccines, vaccine effectiveness against group B strains and non-B strains, as well as the duration of protection are still unknown.

In the U.S., persons aged ≥10 years who are at increased risk for meningococcal disease should receive MenB vaccine. Both MenB vaccines are approved for use in persons aged 10–25 years. However, ACIP supported routine use of MenB vaccines in persons aged ≥10 years who are at increased risk for serogroup B meningococcal disease, because there are no theoretical differences in safety for persons aged >25 years compared with those aged 10–25 years.[41] Persons at risk include those with persistent complement component deficiencies, persons with anatomic or functional asplenia, microbiologists routinely exposed to isolates of *N. meningitidis*, and persons identified as having an increased risk due to a serogroup B meningococcal disease outbreak.

The MenB vaccine series may also be administered to adolescents and young adults aged 16–23 years to provide short-term protection against most strains of serogroup B meningococcal disease. The preferred age for MenB vaccination is 16–18 years.

The U.K. was the first country to incorporate the MenB recombinant vaccine for routine immunization of infants, at a reduced schedule: two doses in the first year of life, at the age of two and four months with a booster dose at 12 months of age.[45]

Conclusions

Meningococcal disease is a major public health problem and remains a leading cause of meningitis and sepsis in countries around the world. Its high case fatality rate often causes public panic when outbreaks occur. MD affects persons of all ages, but the highest incidence is among children less than 5 years of age, especially among infants. In contrast to the rarity of MD, carriage of *N. meningitidis* in the human nasopharynx is frequent, especially among adolescents and young adults. These age groups proved to be crucial in the transmission of meningococci. Vaccination is considered the best strategy for disease prevention. The older polysaccharide unconjugated vaccines have several limitations, including the risk of hypo-responsiveness in repeated doses, the short duration of protection, and the lack of effect in preventing acquisition of carriage in vaccinated individuals. Therefore, these vaccines should be replaced with meningococcal conjugate vaccines when possible. Experience with Meningococcal C conjugate vaccines and more recently with Meningococcal A conjugate vaccine, has proven that these vaccines are safe, immunogenic and effective, inducing herd protection if used in immunization programs targeting those who are responsible for the highest rates of meningococci carriage. Experience with the use of quadrivalent conjugate vaccines is promising, yet there is limited evidence that they provide the same magnitude of indirect effects.

Available evidence suggests that the greatest impact of meningococcal conjugate vaccines occurs when introduced in the routine immunization program for infants, with a single expanded-age group vaccination campaign that includes adolescents and young adults, the age groups usually responsible for carriage and transmission. Booster doses in adolescence is crucial to maintaining protection among the population.

Finally, the recent licensure and availability of two multicomponent meningococcal B vaccines, containing surface exposed recombinant proteins, increases the possibility of broader protection against MD. Experiences with the implementation of these MenB vaccines in immunization programs in the coming years will be of paramount importance for a better understanding on the effectiveness against MenB as well as non-MenB disease, duration of protection and effect on carriage.

References

1. American Academy of Pediatrics. Meningococcal infections. In: Kimberlin DW, Brady M, Jackson MA, Long SS, editors. Red Book: Report of the 2015 Committee on Infectious Diseases. 30th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2015. p. 547–557

2. Halperin SA, Bettinger JA, Greenwood B, et al. The changing and dynamic epidemiology of meningococcal disease. *Vaccine* 2012;30(Suppl. 2):B26e36

3. Harrison OB, Claus H, Jiang Y, et al. Description and nomenclature of *Neisseria meningitidis* capsule locus. *Emerg Infect Dis* 2013; 19: 566–73.

4. Jeppesen CA, Snape MD, Robinson H et al. Meningococcal carriage in adolescents in the United Kingdom to inform timing of an adolescent vaccination strategy. *J Infect* 2015; 71(1):43–52

5. Lucidarme J, et al., Genomic resolution of an aggressive, widespread, diverse and expanding meningococcal serogroup B, C and W lineage, *J Infect* 2015 Nov;71(5):544–52

6. Trotter CL, Gay NJ, Edmunds WJ. The natural history of meningococcal carriage and disease. *Epidemiol Infect* 2006; 134:556–566

7. Christensen H, May M, Bowen L, et al. Meningococcal carriage by age: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; 10:853–861.

8. CDC. Meningococcal disease. In: Atkinson W HJ, Wolfe S, editor. Epidemiology and Prevention of Vaccine-Preventable Diseases. The Pink Book: Course Textbook. 12 ed. Washington DC: Public Health Foundation; 2012.

9. WHO. Africa risks large meningitis outbreak. [cited 2016 Aug 21]. Available from: http://www.who.int/mediacentre/news/releases/2015/meningitis-africa/en/

10. Safadi MA, O'Ryan M, Valenzuela Bravo MT *et al.* The current situation of meningococcal disease in Latin America and updated Global Meningococcal Initiative (GMI) recommendations. *Vaccine* 2015; 33(48):6529–36.

11. Safadi MAP, Berezin E & Arlant LHF. Meningococcal Disease: Epidemiology and Early Effects of Immunization Programs. *J Ped Infect Dis* 2014; 3:91–93.

12. Pan American Health Organization. Informe Regional SIREVA II 2013: Datos por país y por grupos de edad sobre las características de los aislamientos de *Streptococcus pneumoniae, Haemophilus influenzae y Neisseria meningitidis*, en procesos invasores. Washington, D.C.: OPS, 2015. (accessed August 7, 2016)

13. Stephens D, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia and *Neisseria meningitidis*. *Lancet* 2007; 369:2196–2210

14. Danzig l. Meningococcal Vaccines. *Pediatr Infect Dis J* 2004; 23: S285-92

15. Cohn A, MacNeil J, Clark T. Centers for Disease Control and Prevention (CDC). Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and Reports March 22, 2013/62 (RR02); 1–22.

16. Granoff DM, Harrison LH, Borrow R. Meningococcal vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines*. 5th ed. Philadelphia: Saunders/Elsevier; 2008; p. 399–434

17. Safadi MA, Barros AP. Meningococcal conjugate vaccines: Efficacy and new combinations. *J Pediatr* (*Rio J*) 2006; 82 (3 Suppl.): S35–S44.

18. Balmer P, Borrow R, Miller E. Impact of meningococcal C conjugate vaccine in the UK. *J Med Microbiol* 2002; 51:717–22.

19. Trotter CL, Maiden MC. Meningococcal vaccines and herd immunity: lessons learned from serogroup C conjugate vaccination programs. *Expert Rev Vaccines* 2009; 8:851–61.

20. Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. BMJ. 2003; 326:365–6.

21. Maiden MC, Stuart JM; UK Meningococcal Carriage Group. Carriage of serogroup C meningococci 1 year after meningococcal C conjugate polysaccharide vaccination. *Lancet* 2002; 359:1829-31.

22. Trotter CL, Andrews NJ, Kaczmarski EB, et al. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. *Lancet* 2004; 364: 365–367

23. Auckland C, Gray S, Borrow R, Andrews N, Goldblatt D, Ramsay M, et al. Clinical and immunologic risk factors for meningococcal C conjugate vaccine failure in the United Kingdom. *J Infect Dis* 2006; 194:1745–52.

24. Salleras L, Domínguez A, Cardeñosa N. Impact of mass vaccination with polysaccharide conjugate vaccine against serogroup C meningococcal disease in Spain. *Vaccine* 2003; 21:725–8.

25. Cano R, Larrauri A, Mateo S, Alcalá B, Salcedo C, Vázquez JA. Impact of the meningococcal C conjugate vaccine in Spain: an epidemiological and microbiological decision. *Euro Surveill* 2004; 9:11–5.

26. Trotter CL, Ramsay ME, Gray S, et al. No evidence for capsule replacement following mass immunisation with meningococcal serogroup C conjugate vaccines in England and Wales. *Lancet Infect Dis* 2006; 6:616–617

27. Fifteen Years of Protection by Meningococcal C Conjugate Vaccines: Lessons From Disease Surveillance Maiden M & MacLennan *J. Clin Infect Dis* 2014 Nov 1;59(9):1222–4

28. de Greeff SC, de Melker HE, Spanjaard L, Schouls LM, van Derende A. Protection from routine vaccination at the age of 14 months with meningococcal serogroup C conjugate vaccine in the Netherlands. *Pediatr Infect Dis J* 2006; 25:79–80.

29. de Voer RM, Mollema L, Schepp RM, de Greeff SC, van Gageldonk PG, de Melker HE, et al. Immunity against *Neisseria meningitidis* serogroup C in the Dutch population before and after introduction of the meningococcal c conjugate vaccine. *PLoS One* 2010; 5:e12144.

30. Kafetzis DA, Stamboulidis KN, Tzanakaki G, Kourea Kremastinou J, Skevaki CL, Konstantopoulos A, et al. Meningococcal group C disease in Greece during 1993–2006: the impact of an unofficial single-dose vaccination scheme adopted by most paediatricians. *Clin Microbiol Infect* 2007; 13:550–2.

31. Trotter CL, Ramsay ME. Vaccination against meningococcal disease in Europe: review and recommendations for the use of conjugate vaccines. FEMS *Microbiol Rev* 2007; 31:101–7.

32. Larrauri A, Cano R, García M, Mateo S. Impact and effectiveness of meningococcal C conjugate vaccine following its introduction in Spain. *Vaccine* 2005;23:4097–100.

33. De Wals P, Deceuninck G, Boulianne N, De Serres G. Effectiveness of a mass immunization campaign using serogroup C meningococcal conjugate vaccine. *JAMA* 2004; 292:2491–4.

34. Perrett KP, Winter AP, Kibwana E, Jin C, John TM, Yu LM, et al. Antibody persistence after serogroup C meningococcal conjugate immunization of United Kingdom primary-school children in 1999–2000 and response to a booster: a phase 4 clinical trial. *Clin Infect Dis* 2010; 50:1601–10.

35. Snape MD, Kelly DF, Lewis S, Banner C, Kibwana L, Moore CE, et al. Seroprotection against serogroup C meningococcal disease in adolescents in the United Kingdom: observational study. BMJ. 2008; 336:1487–91.

36. Campbell H, Saliba V, Borrow R, et al. Targeted vaccination of teenagers following continued rapid endemic expansion of a single meningococcal group W clone (sequence type 11 clonal complex), United Kingdom 2015. *Euro Surveill Bull* 2015; 20(28):pii=21188

37. Sáfadi MA, Bettinger JA, Maturana GM, Enwere G, Borrow R; Global Meningococcal Initiative. Evolving meningococcal immunization strategies. *Expert Rev Vaccine*. 2015 Apr;14(4):505–17.

38. Chile. Ministry of Health. Boletim de Vigilancia Epidemiológica. Enfermedad Invasora. *Neisseria meningitidis* 2011–2015. (Assessed on August 30, 2016). Available at: http://www.ispch.cl/sites/default/files/Boletin_NeisseriaMeningitidis.pdf

39. Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA-TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet* 2014; 383:40–7

40. Kristiansen PA, Diomande´ F, Ba AK, et al. Impact of the serogroup A meningococcal conjugate vaccine, MenAfriVac, on carriage and herd immunity. *Clin Infect Dis* 2013; 56:354–63

41. Centers for Disease Control and Prevention (CDC). Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep* 2015; 64(22);608–612.

42. Vetter V, Baxter R, Denizer G, Sáfadi MA, Silfverdal SA, Vyse A, Borrow R. Routinely vaccinating adolescents against meningococcus: targeting transmission & disease. *Expert Rev Vaccine* 2016 May;15(5):641–58

43. Read RC, Baxter D, Chadwick DR, Faust SN, Finn , Gordon SB, et al. Effect of the quadrivalent brassthectheccal theCWY glyctheconjugate or the serogroup B brassthectheccal vaccine on brassthectheccal carriage: an observer-blind, phase 3 randomised clinical trial. *The Lancet* 4201; 384 (9960): 2123–2131.

44. Medini D, Stella M, Wassil J. MATS: Global coverage estimates for 4CMenB, a novel multicomponent meningococcal B vaccine. *Vaccine* 33 (2015) 2629–2636

45. Joint Committee on Vaccination and Immunisation — Groups — GOV.UK. [Assessed 2016 July20]. Available from: https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation#minutes.