Evolving meningococcal immunization strategies

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Evolving meningococcal immunization strategies

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Meningococcal disease is a major public health problem and immunization is considered the best strategy for prevention. The introduction of meningococcal C conjugate immunization schedules that targeted adolescents, with catch-up programs in several European countries, Australia and Canada proved to be highly effective, with dramatic reduction in the incidence of serogroup C disease, not only in vaccinated, but also in unvaccinated individuals. Meningococcal quadrivalent (A, C, W, Y) conjugate vaccines are now licensed and are being used in adolescent programs in North America and to control serogroup W disease in South America. In the African meningitis belt, a mass immunization campaign against serogroup A disease using a meningococcal A conjugate vaccine is now controlling the devastating epidemics of meningococcal disease. After introducing new immunization programs, it is of importance to maintain enhanced surveillance for a better understanding of the changing nature of disease epidemiology. This information is crucial for identifying optimal immunization policies.

KEYWORDS: conjugate vaccine • immunization schedule • meningococcal • Neisseria meningitidis • serogroup A • serogroup C • serogroup W

Meningococci cause serious disease worldwide. In sub-Saharan Africa, large epidemics occur every 5–10 years. In the Americas and Europe, although the last major meningococcal epidemics were in the 1970s, the organism remains one of the leading causes of bacterial meningitis in children and young adults. The optimal way of preventing meningococcal disease (MD) is through immunization. Although in comparison with many other successful bacterial vaccines, meningococcal vaccines are a relatively recent development.

In the 1960s, Gotschlich *et al.* developed a methodology for purification of high molecular weight meningococcal polysaccharides that were safe and immunogenic in humans [1,2]. This formed the basis of the currently licensed bivalent (A and C) and quadrivalent (A, C, W and Y) polysaccharide vaccines. The principal limitations, however, of polysaccharide vaccines are that they do not induce T-cell-dependent immunity and are not immunogenic in infants. Furthermore, polysaccharide vaccines do not prevent the acquisition of carriage among vaccines, and are not able to interrupt transmission of the meningococci [3].

Subsequently, conjugate vaccines based on the meningococcal serogroup A and C polysaccharides were developed [4]. Monovalent meningococcal serogroup C conjugate (MCC) vaccines were tested extensively in clinical studies during the 1990s, and proved to be safe and capable of inducing highly bactericidal and boostable immune responses in infants and children [5–9]. Vaccine manufacturers developed quadrivalent meningococcal conjugate vaccines that contain serogroups A, C, Y and W; these now have widespread use [10–12].

To circumvent the poor immunogenicity of the serogroup B polysaccharide, outer membrane vesicle vaccines have been developed and used to curtail outbreaks of serogroup B disease in various Latin American countries, New Zealand, Norway and Normandy in France; these are critiqued elsewhere [13]. A broad coverage meningococcal vaccine, described as a recombinant protein meningococcal serogroup B vaccine, was recently licensed in Europe, Australia and Canada. To date, this new serogroup B vaccine has not been incorporated into routine immunization programs in any of these countries [14]. This review focuses on the experience with meningococcal conjugate vaccines and immunization programs.

A Global Meningococcal Initiative summit meeting was held in Cape Town, South Africa, in November 2013 with 13 Global Meningococcal Initiative members and experts

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from nine different countries. They presented on different meningococcal vaccines, vaccine schedules, impact on nasopharyngeal carriage and vaccine effectiveness. Following a discussion of this information, it was decided that a full review would be performed, summarizing the current epidemiology and the evidence on the experience resulting from different immunization policies used in countries with routine indications for meningococcal conjugate vaccines.

Europe

Epidemiology

In Europe, most cases of MD are sporadic and are currently caused by serogroups B and C with the highest incidence in infants and a secondary peak in adolescents. Epidemics due to serogroup B have occurred in Europe resulting in the establishment of the first meningitis charities, which have proven to be an important force in meningococcal research and advocacy, particularly in the UK. In the UK in the mid-1990s, there was an increase in serogroup C disease, due to a strain C:2a:P1.5 cc11, causing outbreaks in universities with associated high case fatality rates (CFR), leading to the call for the rapid development, evaluation and implementation of MCC vaccines [15,16]. Spain experienced two waves of serogroup C disease; in the mid-1990s due to strain C:2b:P1.5,2 cc8 and in the 2000s due to strain C:2a:P1.5 cc11 [17].

Immunization experience

In Europe, meningococcal immunization has to date centered around at-risk groups, travelers, outbreak control and finally broad population coverage with MCC immunization [18]. MCC vaccine schedules in Europe and elsewhere are constantly evolving as new knowledge on these and other conjugate vaccines is accrued. The introduction of MCC vaccines in the UK in November 1999 was the culmination of an intensive 5-year clinical trial research program. This program was instigated to accelerate the availability of MCC vaccines for the UK population and was a collaborative endeavor involving public bodies (e.g., meningitis charities), academia and vaccine manufacturers.

The infant studies of these vaccines involved looking at the UK accelerated schedule at 2, 3 and 4 months of age as was used for the *Haemophilus influenzae* type b conjugate vaccine before 2006. Trials were then completed in toddlers, pre-school children and adolescents, which showed that a single dose of MCC vaccine was safe and immunogenic in children and adolescents [8,9].

Due to the incidence of serogroup C disease being highest in infants with a secondary peak in adolescents coupled with the fact that the CFR was the highest in the adolescent population, a catch-up campaign was used in the UK, initially to 18 years of age and later extended to 24 years of age [16]. The huge importance of this catch-up, initially designed to give direct protection to those vaccinated, was the induction of indirect protection (i.e., herd protection) with significant declines in serogroup C disease in the unvaccinated cohorts [19]. Herd protection to serogroup C disease occurred by interrupting the acquisition of nasopharyngeal carriage of the organisms, mainly in the adolescent population [20,21].

In the UK, comprehensive, post-licensure surveillance highlighted a decline in vaccine effectiveness in infants more than 1 year after immunization [22,23]. Also learnt was the fact that while immune memory was induced and persisted in infants, this without circulating functional antibodies was insufficient to protect against the rapid onset of MD [24]. To extend protection in this age group, following the demonstration that a reduced schedule dose of MCC vaccine was immunogenic, the 2 months of age dose of MCC vaccine was moved to 12 months of age for a 3-, 4- and 12-month schedule [25]. The assumption was that a booster dose in the second year of life would give long-term protection. However, circulating functional antibodies following this 12-month booster dose also declined rapidly [26].

In order to monitor population immunity to serogroup C meningococci, a series of three age-stratified seroprevalence studies were performed [27–29]. These studies showed that seroprotective levels remained much higher in those who were eligible for immunization between 6 and 18 years of age compared with those who were immunized at 3–5 years of age. Protection was especially low in children who were immunized with 1 dose at approximately 1 year of age. In 2013, given the waning protection in those immunized early in life and to maintain the indirect and direct protection, the UK moved the infant MCC vaccine dose given at 4 months of age to children 14–15 years of age [30,31]. Thus, over the last 14 years, the MCC vaccine schedule has evolved from a 3 dose primary schedule in infancy with no adolescent booster but an initial catch-up campaign, to a 1 + 1 + 1 schedule at 3 months, 1 year and 14–15 years of age. Serogroup C disease remains under control with less than 40 cases per annum reported from 2005 to date (a decrease of over 97% compared with 1998/99).

In 1997, Spain implemented a nationwide meningococcal immunization campaign, including 16 of the 19 autonomous Spanish regions using a meningococcal bivalent A, C polysaccharide vaccine in those aged 18 months to 19 years [32]. The estimated vaccine coverage was 76.3% and the overall incidence of serogroup C was reduced by 45%. However, in the following years the incidence of serogroup C disease continued to increase. Spain introduced MCC vaccines in 2000 into the infant immunization schedule at 2, 4 and 6 months of age, with no booster. Catch-up campaigns among children and adolescents varied depending on the region. Ten regions immunized children and adolescents to 19 years of age with 1 dose, three regions immunized children and adolescents to 15–16 years of age with 1 dose and four regions did not offer a catch-up campaign [32]. Although large reductions in the number of serogroup C cases in the vaccinated cohorts were shown, carriage of serogroup C organisms was not uniformly interrupted and herd protection was not induced to the same level as in the UK due to lower coverage and the inconsistent mixture of

catch-up campaigns implemented in some regions. The net result was that in Spain, the number of serogroup C cases is still higher than in most other countries with national programs, indicating that there is a need to increase vaccine coverage, especially among adolescents, to optimize the impact of the immunization program [33].

In the Netherlands, a routine MCC immunization program was initiated in 2002 with 1 dose for children at 14 months of age along with a catch-up campaign for children and adolescents up to 18 years of age. Overall coverage was high at 94% and no observed reduction in vaccine effectiveness has been seen over time. Shortly after implementation, serogroup C disease significantly decreased in vaccinated and in unimmunized cohorts. Up to 2011, no primary vaccine failures were reported [32]. Only sporadic serogroup C cases in unimmunized age groups, including infants, have been reported, indicating low transmission of disease.

The antibody persistence following MCC immunization together with the booster response was studied in the Netherlands to determine the optimal age for an adolescent MCC booster [34]. Ten, 12- and 15-year olds were recruited who had been initially vaccinated with MCC 9 years earlier. Regardless of age group, rSBA geometric mean titers (GMTs) were low, although values were significantly lower among 10-year olds as compared with 12-year olds. One month after the MCC booster, GMTs indicated all participants mounted a memory response, regardless of age. One year after the MCC booster, GMTs had declined faster in the 10-year olds than in the 15-year olds but all participants still had GMTs above protective levels. Thus, the optimal age for boosting in adolescents is a trade-off between waning antibody levels with increasing age and the higher subsequent antibody levels induced by boosting at an older age.

Australia

Epidemiology

Australia reported in 1987 an outbreak of serogroup A MD in the Aboriginal population, which was followed by an increase in disease caused by serogroups B and C nationwide [35]. In the early 2000s, the age distribution of invasive MD showed a typical primary peak in young children predominantly caused by serogroup B and a secondary peak in adolescents and young adults associated with serogroup C disease.

Immunization experience

The increased number of serogroup C cases reported in the country motivated the implementation, in 2003, of a national MCC immunization program, with a single dose administered to all children aged 12 months, along with a catch-up targeting children and adolescents aged between 2 and 19 years [36]. This program resulted in a dramatic reduction in the number of laboratory-confirmed serogroup C cases, from 213 in 2002 to 11 cases in 2012. Serogroup B cases remained stable during this period, predominating now in all age groups [37].

North America

Epidemiology

As in Europe, serogroup C has been the predominant serogroup causing invasive disease in North America since the 1970s. In spite of this, regional differences in circulating serogroups and strains have been noted both within Canada and the USA. In the 1990s, serogroup Y emerged among older adolescents in the USA, whereas Canada did not experience a similar pattern of disease [38,39]. In the USA, Oregon has experienced hyperendemic serogroup B disease since the 1993 caused by strain ET-5 with an incidence of 2.2 per 100,000 [40]. In Canada, hyperendemic serogroup B disease caused by a clone of ST-269 with the antigenic formula B:17:P1.19 emerged in Quebec in 2004 [41–43] with some regions experiencing an eightfold increase in serogroup B incidence [44,45]. Finally, and perhaps most significantly in terms of the influence on immunization program implementation, the USA did not experience the outbreaks of serogroup C disease caused by serogroup C ET-15/ET-37 that occurred in Canada from 1999 to 2001 [46]. The different immunization programs implemented in Canada and the USA reflect each country's local epidemiology and overarching public health agendas.

United States

Immunization experience

Meningococcal quadrivalent conjugate vaccine was first recommended in the USA in 2005, but in 2006, due to limited supplies, was restricted to those entering high school or university. In 2007, the recommendation was extended to all those aged 11–18 years. In 2010, a booster was recommended at 16 years of age due to waning effectiveness and declining antibody levels. Three to five years following immunization with a quadrivalent vaccine, lower SBA titers to each of the four serogroups were observed [47,48]. For serogroup C, rSBA GMTs had declined by as much as 90% over 3 years. The proportion of adolescents vaccinated at age 11 years determined to have protective antibodies 3 years later was 71–95% [47]. Since 2006, vaccine coverage has been assessed annually among adolescents 13–17 years of age. For this age group, coverage with meningococcal quadrivalent conjugate vaccine increased from 10.2% in 2006 to 74.0% in 2012, however, coverage by state in 2011 ranged from 37.5% (Arkansas) to 94.3% (Rhode Island) [49,50]. From 2005 to 2009, the only meningococcal conjugate vaccine licensed in the USA was MenACWY-DT, therefore, post-licensure data primarily reflect the use of MenACYW-DT. During 2008–2009, the incidence of serogroups C, Y and W disease declined among adolescents aged 11 through 18 years [51]. However, incidence did not decline in those ≥20 years of age, suggesting a direct impact of immunization on adolescent disease, but no measurable evidence of indirect protection.

A carriage study was performed among US high school students in eight schools, randomized to receive meningococcal quadrivalent conjugate vaccine either at the start or conclusion of the study [52]. A total of 3314 students were enrolled,

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1636 in the vaccinated schools and 1442 in the control schools. Only 16 students were found to carry serogroup Y strains, 10 in the vaccinated and 6 in the control schools ($p = 0.44$). None were carrying serogroups A, C or W. Such low numbers made attempts to measure differences in carriage difficult, and hence insufficient to detect any indirect effect of immunization.

Canada

Clinical experience

Because immunization policy is a provincial level decision, a variety of immunization schedules have been implemented across Canada. Serogroup C outbreaks in 1999–2001 led to mass immunization campaigns in Quebec of individuals 2 months to 20 years of age with MCC vaccine and targeted immunization campaigns in Alberta and British Columbia with the polysaccharide vaccine [53]. The three provinces were the first to implement universal infant and/or toddler immunization programs with MCC vaccines starting in 2002–2003. British Columbia included a catch-up program for adolescents 14–18 years of age as part of its serogroup C immunization program. By 2007, all 13 provinces and territories had either an infant or toddler (12 months of age) MCC immunization program in place (Figure 1). Initially, some provinces initiated the school-based adolescent immunization as a catch-up program for adolescents 12–18 years of age designed to rapidly control the incidence of serogroup C disease and protect those age groups (adolescents) at high risk for infection. As evidence mounted from the UK [25,54,55] that a single dose in toddlers did not provide lasting protection, the catch-up programs became booster programs and provinces without adolescent immunization programs put one in place to ensure disease control objectives were met and protection remained during the second peak of age-related risk. Starting in 2006, Prince Edward Island implemented a quadrivalent meningococcal conjugate vaccine in its adolescent program to provide greater serogroup coverage. As of 2014, six provinces/territories provided the quadrivalent vaccine as part of their adolescent programs, six provided MCC vaccine and one (Northwest Territories) did not have a universal program for adolescents (Figure 1).

Clearly one dose of MCC vaccine given at 12 months of age with a booster dose in adolescence is the most common schedule utilized; however, two provinces/territories provide two doses in infancy (at 2 and 12 months) and one province provides 3 doses, initially on a 2-, 4- and 6-month schedule that was later modified to 2-, 4- and 12-month schedule with the evidence from effectiveness studies in England [21,22]. The heterogeneity in immunization schedules has allowed for comparison studies across provinces with results showing the 2- and 12-month schedule provides the same level of short-term protection as the 2-, 4- and 12-month schedule (100% 1 month after the 12-month dose) [56].

Regardless of the number of doses provided in early childhood, by targeting the groups at highest risk (young children and adolescents), serogroup C disease has been virtually eliminated in Canadian children, with incidence rates as low as 0.01 per 100,000 in 2011 [57]. Evidence suggests Canada's MCC immunization programs induced herd protection and likely reduced carriage with unvaccinated individuals enjoying a reduction in the incidence of disease of close to 50% [58–60].

The effects of immunization on carriage in the Canadian context have not been directly measured. The one study in 2001 was conducted in an outbreak setting and found an overall IMD carriage rate of 7.6% [61]. In 2010–2012, a study found serogroup B carriage in Quebec City of 2% in students 14–15 years of age and 7% in university students who lived in resident halls [62].

Latin America

Epidemiology

The overall incidence of MD in Latin America varied widely in the region and across the years, from less than 0.1 cases per 100,000 inhabitants in countries like Mexico, Paraguay, Peru and Bolivia to almost two cases per 100,000 inhabitants per year in Brazil, with a decreasing trend observed in almost all countries during the last decade [63]. Argentina, Brazil, Chile and Uruguay are the countries that report the higher incidence rates, probably reflecting a more robust surveillance system and a well-established laboratory infrastructure in place. According to the last published PAHO SIREVA report, in 2012 these four countries were responsible for 90% (809/901) of all meningococcal isolates characterized in the Latin American and Caribbean region [64].

The highest age-specific incidence of MD is consistently observed in infants. Most cases of MD are sporadic, with outbreaks occurring at irregular intervals. Outbreaks are more likely to involve older children and young adults, usually associated with increased CFR. Serogroups B and C have been responsible for the majority of cases reported in the region during the last 30 years with a virtual disappearance of serogroup A disease in the last decade.

Since the 1970s, Brazil has experienced three waves of serogroup C disease, caused by C:2a:P1.5,2 cc11, C:2b:P1.3 cc8 and most recently C:23:P1.14-6 cc103 [65]. During the 1980s and 1990s, serogroup B disease became more prevalent than C and practically no cases of serogroup A were reported. From 2002 onward, a significant rise in the number and proportion of cases due to serogroup C, associated with the ST-103 complex, was registered, with several outbreaks affecting different cities. Serogroup C is also the predominant cause of disease in Mexico, Central America and the Caribbean. In the Andean region, limited information is available, although serogroups B and Y appear to be predominant in Colombia and Venezuela [66].

The emergence of serogroup W disease cases, previously a rare cause of MD, was recently reported in South America. The increased number of serogroup W disease cases observed in Argentina and Chile has been linked to the hypervirulent clone W:P1.5,2:ST11 (ST11/ET37 clonal complex), which

emerged in 2000 among pilgrims returning from the annual Islamic pilgrimage to Saudi Arabia (the Hajj) and has since spread internationally [67,68]. In Argentina, the prevalence of this serogroup increased from 2% of cases with confirmed serogroup in 2000 to 58% in 2012 [69]. Similar to Argentina, an increased number of cases due to serogroup W was also reported in Chile. In 2012, 60 cases of serogroup W with 16 deaths (CFR of 26.6%, the highest CFR reported in Chile in the last 30 years) were confirmed throughout the country, compared with 22 cases reported in 2011 and 6 cases in 2010. Half of the cases reported during 2012 were in children younger than 5 years, but cases have been reported in all age groups [64].

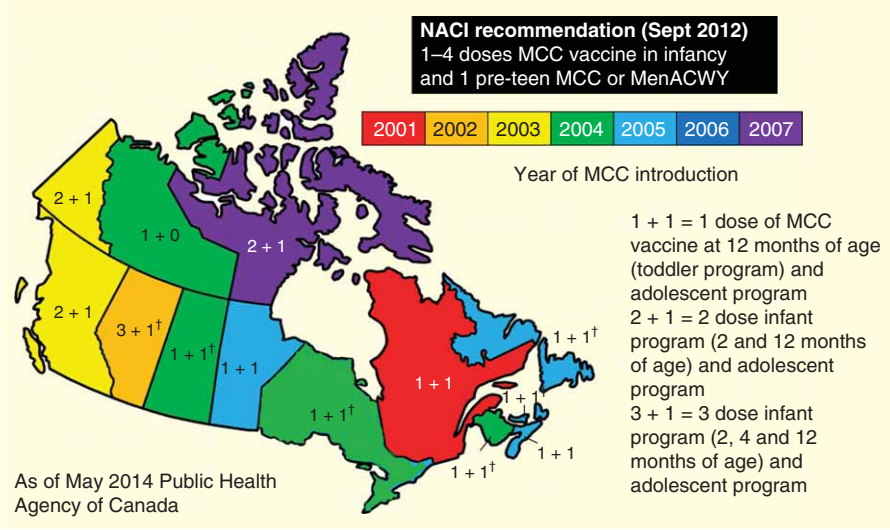

Figure 1. Meningococcal vaccination programs in Canada.
†Adolescent ACWY.
MCC: Meningococcal serogroup C conjugate.

Immunization experience

In late 2010, Brazil was the first country in Latin America to introduce MCC vaccine routinely into its Immunization Program, with two doses, at 3 and 5 months old, with a booster dose at 12 months of age. Toddlers between 12 and 23 months of age received one dose of the vaccine, with no catch-up campaign for older age groups. The decision was motivated by the epidemiological situation reported throughout the country at that period, showing 80% of the identified MD cases associated with serogroup C, incidence rates of 1.6 cases/100,000 habitants, with approximately 50% of all cases reported in children younger than 5 years of age, CFR as high as 20% and several serogroup C disease outbreaks, associated with clonal complex ST-103 [68].

Early trends, in the first 2 years after the introduction of the immunization program, derived from population-based data demonstrated a 50% reduction in the incidence rates of MD in children aged <2 years, the age group targeted for immunization. However, no impact was observed in unvaccinated age groups [68].

Very limited data describing meningococcal carriage in Latin America are currently available. The results of a recent study performed in Campinas, Brazil, evaluating the prevalence of meningococcal carriage in 1208 students 11–19 years showed that the overall meningococcal carriage was 9.9% (95% CI: 8.3–11.8%), with an unusually high prevalence of serogroup C carriage (1.32%) [70]. The results of this study, showing high rates of serogroup C carriage among Brazilian adolescents reinforce the importance of considering the inclusion of this age group in the immunization campaign to achieve herd effects and maximize the benefits of meningococcal immunization programs.

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 reactive campaign using two different quadrivalent conjugate vaccines (Men ACWY-DT and Men ACWY-CRM_{197}), targeting children aged 9 months to 5 years. The higher incidence rates observed in children younger than 5 years of age and also the minimum age that one of the quadrivalent meningococcal vaccines was licensed for use motivated the decision to include children 9 months to 5 years in the immunization campaign [71]. The immunization campaign started in October 2012, with a roll out to the whole country during the first months of 2013. Coverage for the first dose of the vaccine was almost 100% for the targeted age group.

Analysis of the epidemiologic situation in 2013 and in the first months of 2014, after the Men ACWY immunization campaign in Chile, showed that protection was observed only for the age groups targeted for the vaccine, without early indirect effects. In 2012, there were 60 laboratory-confirmed serogroup W cases, compared with 85 cases in 2013 and 60 cases by September 2014 [72].

Asia

Epidemiology

In China, reported incidence varies across the country from 0.01/100,000 to 0.70/100,000 with most disease currently due to serogroups A and C and a small proportion attributable to serogroup B [73,74]. Disease incidence is highest in infancy followed by a progressive decline in older age groups with no adolescent peak [74]. In India, the incidence of MD is higher in the temperate north than the tropical south, with recent outbreaks all attributable to serogroup A [75,76]. Since 2005, there has been an increase in the number of outbreaks in which adolescents and young adults were predominantly affected [75]. The Islamic Hajj pilgrimage to Mecca, Saudi Arabia has historically been associated with outbreaks of serogroup A and W MD but interventions including immunization have suppressed MD since 2002 [77].

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Immunization experience

In China, polysaccharide vaccine either monovalent serogroup A, bivalent AC or quadrivalent ACWY as well as a bivalent AC conjugate vaccine are used. Two doses of polysaccharide A vaccine are administered to children at 6 and 18 months of age and two doses of bivalent AC polysaccharide vaccine are administered to children at 3 and 6 years of age. In areas where children less than 2 years have been immunized, disease incidence has declined, whereas regions that have not implemented immunization campaigns continue to have outbreaks [74]. In India, only polysaccharide meningococcal vaccines are available in either a bivalent AC or quadrivalent ACWY formulation [75]. A monovalent conjugate vaccine against serogroup A (MAC) manufactured by the Serum Institute of India for countries in sub-Saharan Africa is licensed but as yet no policy on its use in India.

MD has been a serious public health issue in the Kingdom of Saudi Arabia (KSA), with epidemics occurring due to serogroup A and more recently serogroup W. One of the contributing causes is due to the unique yearly influx of international visitors to perform Hajj and Umra. Many pilgrims travel from areas where MD is endemic, increasing the risk of transmission and disease in the KSA. Prior to 2000, the KSA authorities required pilgrims attending either Hajj or Umra to be vaccinated with a bivalent meningococcal A/C polysaccharide vaccine [78]. However, this recommendation was changed to quadrivalent ACYW polysaccharide when serogroup W epidemics occurred between 2000 and 2002 [79,80]. In response, the Saudi Ministry of Health recommended the use of a quadrivalent meningococcal ACYW polysaccharide vaccine to provide coverage against serogroup W for school children in KSA and pilgrims [81,82]. The requirement of meningococcal quadrivalent ACYW immunization, whether conjugate or polysaccharide, is still a visa requirement for pilgrims, although disease incidence is low in the KSA.

Africa

Epidemiology

Although epidemic meningitis has been known to occur in South Saharan Africa (i.e., meningitis belt) for more than a century, identification of the causative organisms has only happened over the last 50 years and with exact specificity in the last decade or so [83]. The seasonality of epidemic meningitis has been documented, usually starting in the middle of the dry seasons and stops abruptly at the beginning of the rains, and recurring every 8–12 years [84]. Although epidemics generally occur in dry season, what makes a particular locality more vulnerable than the other in a particular season is not known making early prediction and prevention of meningitis outbreaks very challenging. There have been several postulations to explain the seasonality of epidemics with discussions centered on the role of absolute humidity, reduction in rainfall, type of land-cover, overcrowding, accumulation of a critical level nonimmune individuals and transient intense circulation of the organism [83,85–87].

All the six virulent meningococcal serogroups have been implicated in meningococcal infections in Africa at one time. Since the identification of causative organisms became possible, it has been shown that between 70 and 80% of the meningococcal epidemics in the African are due to serogroup A [88,89]. Perhaps one of the largest serogroup A epidemic in the belt was the 1996–1997 epidemic that affected the whole region, with as much as 250,000 cases, 25,000 of which died [90]. This epidemic awakened the conscience of the global community, culminating in the setting up of the Meningitis Vaccine Project for the development; licensure and introduction of the MAC vaccine [91].

In the past, serogroup C epidemics have been reported in places like Niger and Nigeria [92,93], but it appears that the occurrence of this particular serogroup has become increasingly infrequent. Although the carriage of serogroup W has been known to be present in the belt, it was only in 2002 that a large serogroup W epidemic occurred in Burkina Faso [94], mostly due to W:2a:P1.5,2 (cc11) [95]. Since then there have been smaller outbreaks of serogroup W infection in Burkina Faso, Sudan and Niger [96,97]. Sporadic cases of serogroup W have also been reported in Senegal and Gambia [98]. Historically, serogroup X has caused sporadic cases of meningitis in Togo between 2006 and 2009, and Kenya and Burkina Faso [99]. In 2006, a large outbreak of serogroup X was reported in Niger due to phenotype X:NT:P1,5 (cc181) with incidence rate as high as 74.6 cases per 100,000 population in children 5–9 years of age [100]. Other places where serogroup X has been reported include northern Ghana and Uganda [101,102].

Although serogroup B disease occurs mostly in Europe and America, sporadic cases have also been reported in Africa. Nakhla *et al.* reviewed data collected over a period of 42 years and showed that the introduction of school-based A/C polysaccharide immunization program in Egypt in the 1990s coincided with a shift from serogroup A to serogroup B predominance in MD [103]. Sporadic cases of serogroup B infection have also been reported in Angola and South Africa [104,105].

Put together there is ample evidence that whereas serogroup A organism has dominated the epidemic in the belt area, other serogroups have had important impact. To what extent this landscape of meningococcal infections is likely to change following the introduction of a MAC vaccine is unknown.

Immunization experience

Protection with meningococcal vaccines in Africa before fourth quarter of 2010 was mainly through reactive vaccination during outbreaks using polysaccharide vaccines: either A + C polysaccharide vaccines, trivalent vaccine A + C + W or tetravalent vaccine A + C + W + Y. The steps required for a reactive vaccination strategy such as determining when a community has reached the WHO-defined epidemic threshold, the numerous processes involved in requesting vaccine from WHO, transportation and the deployment of the vaccine in the midst of ongoing epidemic response, make it inefficient. In fact, a report

from northern Ghana estimated that while reactive vaccination prevented about 23% of cases and 18% of deaths [106], polysaccharide vaccines used in planning immunization programs in Nigeria and Egypt [103,107] resulted in as much as a 94% reduction in cases of meningitis following a school-based program over an 8-year period. However, there is limited experience with this, and coupled with the fact that these vaccines are not immunogenic in children less 2 years of age makes programs that use polysaccharide vaccine insufficient.

The safety and immunogenicity results from studies conducted in Africa and India led to the licensure of the MAC vaccine by Drug Control General of India and obtained WHO pre-qualification in 2010 [108–111].

Between 2010 and 2013, more than 150 million people 1–29 years of age, living in the meningitis belt were vaccinated with the MAC vaccine [90]. The initial decline in the incidence of serogroup A disease could have been due to natural trend [112], as the incidence of the disease was on the downward trend prior to the introduction. However, incontrovertible evidence is accumulating on the impact of the vaccine on both nasopharyngeal carriage of serogroup A and cases of meningitis in the communities who received the vaccine. Novak *et al.* collected data covering a 14-year period and showed that MAC reduced the risk of meningitis by 71%, risk of fatal meningitis by 64% and risk of probable meningitis in people who did not receive the vaccine by 55% [113], the latter being an important evidence of a herd effect. A recent publication from Chad which showed data over a 3-year period covering pre- and post-MAC vaccine from two districts one of which did not receive the vaccine due the decision of the home government showed a dramatic 94% reduction in the incidence of meningitis in the districts that received the vaccine [114]. This study also showed almost complete disappearance of nasopharyngeal carriage of serogroup A organisms in the communities that received the vaccine. This was similar to an earlier report by Kristiansen *et al.* that whereas pre-introduction of MAC vaccine the carriage of serogroup A was 0.39%, in post-vaccination period, no serogroup A was isolated from nasopharynx [115].

Currently, MAC vaccine is given only one time in a jurisdiction by mass vaccination to individuals 1–29 years of age. Since 2010 when the vaccine was first given in Burkina Faso, there has been accumulation of new unvaccinated birth cohorts. Meningitis Vaccine Project is trying to obtain licensure for the vaccine for use in infants, but introduction of the vaccine in routine infant immunization will not protect the older children, some of whom are in their sixth year now. Thus, catch-up programs are necessary.

Whether widespread introduction of MAC vaccine will lead to diseases by non-serogroup A organisms is not known. Results from elsewhere where MAC vaccine was introduced do not suggest this. However, considering the intensity of infection in the belt areas, coupled with other environmental factors, it will be surprising if there were no replacement serogroups in the future. Although very preliminary, a single study from Niger from 2008 and 2011 showed that serogroup A disease decreased and then disappeared completely, while serogroup W disease increased [112].

As highlighted earlier, there are other serogroups that cause outbreaks in the belt area. With the increasing importance of outbreaks caused by serogroup W and X, there is need for continued surveillance in order to monitor the trend. Besides, there is currently no vaccine for serogroup X infection. This should be a priority. The global community should think seriously of the possibility of a non-serogroup A epidemic and plan for an appropriate safe low price multivalent vaccine.

Also the sustainability of vaccination in the belt area, which is a resource-limited area, could be problematic. Not only will it be necessary to sustain the funding for MAC vaccine programs, but the issue of a single vaccine supplier will also exist and there is a need to diversify suppliers.

Disease control scenarios

Disease control remains the primary goal of invasive MD immunization programs and two types of control strategies have been used. The first relies on surveillance to identify an epidemic and then implement mass vaccination to control it, while the second, more measured approach, applies routine vaccination. Local epidemiology and cost have driven the choice of strategy in many places. In an endemic situation, routine immunization is usually applied by targeting those at greatest risk for the disease, usually children less than 5 years of age. In some endemic areas, adolescents have been included in routine immunization programs to offer protection to another group at increased risk and more importantly, to interrupt disease transmission. In settings with hyperendemic or epidemic disease, large segments of the population can be at risk and thus may be included in one-time mass immunization programs.

Studies have shown mass immunization to be the least effective method of control with estimates showing only a 45% reduction or less in disease incidence [30,106,116]. Moreover, unlike routine immunization, mass immunization does not prevent cases from occurring before or during the first year of an epidemic and does not protect individuals born after the mass campaign [117]. Modifications of this approach, such as Quebec's routine MCC vaccination program which provide 1 dose at 12 months of age for children born after the mass campaign, overcame some of the shortcomings of a mass vaccination campaign and extended the earlier established protection to unvaccinated cohorts. The control strategy adopted in the UK with a routine infant program and rapidly implemented catch-up program for children and adolescents had a similar effect [16,21,22].

De Wals *et al.* modeled the effectiveness of a variety of serogroup C immunization schedules to determine the 'optimal' approach and found a 5-dose schedule (2 months, 4 months, 12 months, 12 years and 18 years) to be the most effective, especially with a waning rate of protection estimated at 10% per year [118]. However, a 2-dose program with a dose at 12 months and 12 years was only marginally less effective

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Table 1. Estimated protection conferred by different immunization schedules using serogroup C meningococcal conjugate vaccine (emphasis on 2- and 5-dose program added).

Schedule	Number of doses	Age at vaccine administration	Protection†						
		2 months	*4 months*	*12 months*	*12 years*	*18 years*	*1% waning per year‡ (%)*	*3% waning per year‡ (%)*	*6% waning per year‡ (%)*	*10% waning per year‡ (%)*
A	1			X			72	51	35	25
B	1				X		54	40	30	22
C	1					X	39	29	21	17
D	2	X	X				74	51	35	24
E	2	X		X			74	53	37	26
F	2			X	X		78	62	50	40
G	3	X	X	X			74	53	37	27
H	3			X	X	X	80	67	56	48
I	4	X	X	X	X		80	64	52	42
J	5	X	X	X	X	X	82	69	58	50

†Expressed as the percentage reduction in disease risk over the entire lifespan.
‡Percentage of immune individuals becoming susceptible each year.
Reproduced from [118] with permission from Elsevier.

for one-third of the cost of the 5-dose program. Table 1 shows the estimated protection from a variety of different MCC immunization schedules and with different rates of waning protection [118]. Additional modeling found substituting quadrivalent vaccine for the adolescent dose would provide increased protection, primarily by preventing serogroup Y cases, but at a higher cost [119].

With any meningococcal conjugate vaccination program, the level of vaccine coverage in the population sufficient to provide indirect protection and the number of months or years required to reach this coverage level are important considerations for optimal control. The rapid and coordinated efforts in the UK and Quebec resulted in indirect protection and excellent long-term control of IMD at the population level, with a reduction in disease incidence of more than 80% in the first year and vaccine effectiveness of >90% [16,120,121]. This contrasts with results from more slowly implemented programs in other Canadian provinces and finding from initiatives with less-optimal coverage such as the adolescent program in the USA. In these instances, direct and indirect effects required more than 1 year to be detected and estimates of vaccines effectiveness were 80% [122–125].

Expert commentary

MCC vaccines were licensed and introduced on the basis of immunogenicity and safety data without Phase III effectiveness studies, thus knowledge learnt about these vaccines stems from national surveillance such as from the UK, The Netherlands and Canada. Surveillance data can be used to refine and improve vaccination schedules, even years after vaccine introduction. In the UK, the priority was to integrate MCC vaccines into the accelerated infant immunization schedule of 2, 3 and 4 months; however, due to the number of serogroup C cases and associated high CFR in colleges and universities, a catch-up campaign with MCC vaccine was completed for individuals up to 18 years of age [16]. As was subsequently learnt, the catch-up campaign proved essential to interrupt disease transmission and provided indirect protection, as effectiveness soon declined in those immunized with the 2-, 3- and 4-month schedule [22].

This knowledge then led the UK in 2006 to move the 2-month infant dose to 12 months of age and then in 2013 to move the 4-month infant dose to 14 years of age, the main driver for this being the maintenance of herd protection. The Netherlands, using the initial information from the earlier UK MCC, introduced a very different schedule, immunizing those aged over 14 months and relying on herd protection to protect infants [126]. In Canada, a number of different immunization schedules were adopted. These conjugate

vaccines have clearly demonstrated that their main attribute is in preventing the acquisition of carriage and interrupting transmission, thus inducing herd protection.

The whole basis of the introduction of MAC vaccine across the meningitis belt of sub-Saharan Africa, targeting those between 1 and 29 years of age was built on the MCC experience from Europe and North America. Surveillance is crucial to monitor the effects of MAC vaccine on serogroup A carriage and disease and this will inform future strategies to maintain disease control. Countries with existing MCC programs can provide an example of various immunization strategies for the increasing cohorts of unimmunized infants and children in Africa. The magnitude of the indirect effect provided by MCC vaccines was unanticipated. Understanding this effect has enabled the creation of more nuanced immunization programs to take advantage of this and measuring this effect with MAC vaccine has been important.

After the implementation of the routine infant MCC immunization program in Brazil, a dramatic decrease in the incidence rates of MD among the age groups that were vaccinated was observed. However, no early impact was observed in other unvaccinated age groups. In Chile, the reactive ACWY vaccination also provided a decrease in the incidence rates of serogroup W disease only in the age groups that received the vaccine, without early impact on unvaccinated age groups. Both scenarios in Brazil and in Chile, without early herd effects observed, probably reflect the lack of a catch-up program including adolescents, usually the age group responsible for carriage and transmission. The next step that is currently being discussed in these countries is to extend the vaccination to other age groups to achieve indirect protection, maximizing the effects of their meningococcal vaccination programs.

Whether meningococcal quadrivalent conjugate vaccines have similar effects as to the monovalent conjugates, data are limited and mixed. The low vaccine coverage and carriage rates in countries where the vaccine is used, such as in the USA, have made conclusions difficult but the evidence suggests an indirect effect. However, in the setting of a pathogen such as *Neisseria meningitidis*, with a relatively low estimated basic reproduction number (R0 about 1.36) [127], even a modest individual carriage effect might translate into a significant herd effect. After more than 15 years of experience with MCC vaccines, these vaccines have been proven to be safe, immunogenic and induce herd protection if used in immunization programs targeting those who are carriers of meningococci. The MCA vaccine, first introduced in Africa in 2010, is already showing the same positive attributes. Early data with regards to the interruption of transmission of meningococci for quadrivalent conjugate vaccines are promising, but need further study.

Five-year view

Epidemiological surveillance of cases and meningococcal carriage studies continue to provide vital information for evaluating meningococcal conjugate immunization schedules and to guide future design of programs. With the licensure of a broad coverage serogroup B vaccine and its potential implementation in public programs in the coming years, surveillance and carriage studies will be crucial for understanding how this novel vaccine can be optimally utilized.

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Key issues

- Meningococcal conjugate vaccines, whether monovalent serogroup A or C or quadrivalent for serogroups A, C, Y and W have proved safe and effective.
- Meningococci cause serious disease worldwide with immunization being the best means of prevention.
- Meningococcal serogroup A and C monovalent conjugate vaccines were licensed and introduced on the basis of immunogenicity and safety data without Phase III effectiveness studies, thus knowledge learnt about these vaccines stems from national surveillance programs.
- For serogroup C in Europe, Canada and Australia, immunizing teenagers, the most prevalent carriers of meningococci, was important in generating herd protection.
- The monovalent serogroup A conjugate vaccine, first introduced in Africa in 2010, has already proven to prevent both serogroup A disease and the acquisition of carriage.
- Meningococcal conjugate vaccines have clearly demonstrated that their main attribute is in prevention of the acquisition of carriage and interrupting transmission, thus inducing herd protection.
- The potential for herd protection should be taken into consideration by policy makers deciding vaccine strategies.
- A serogroup B vaccine is now licensed on the basis of safety and immunogenicity data, knowledge about this vaccine will only be learnt through introduction into immunization programs and surveillance.

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