

Global practices of meningococcal vaccine use and impact on invasive disease

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A number of countries now include meningococcal vaccines in their routine immunization programs. This review focuses on different approaches to including meningococcal vaccines in country programs across the world and their effect on the burden of invasive meningococcal disease (IMD) as reflected by pre and post-vaccine incidence rates in the last 20 years. Mass campaigns using conjugated meningococcal vaccines have led to control of serogroup C meningococcal disease in the UK, Canada, Australia, Spain, Belgium, Ireland, and Iceland. Serogroup B disease, predominant in New Zealand, has been dramatically decreased, partly due to the introduction of an outer membrane vesicle (OMV) vaccine. Polysaccharide vaccines were used in high risk people in Saudi Arabia and Syria and in routine immunization in China and Egypt. The highest incidence region of the meningitis belt initiated vaccination with the serogroup A conjugate vaccine in 2010 and catch-up vaccination is ongoing. Overall results of this vaccine introduction are encouraging especially in countries with a moderate to high level of endemic disease. Continued surveillance is required to monitor effectiveness in countries that recently implemented these programs.

Keywords: Invasive meningococcal disease, Epidemiology, Vaccines, Immunization schedule, Meningococemia, Serogroup, Global, Immunity, Meningococcus, Meningitis

Introduction

Neisseria meningitidis is one of the leading causes of bacterial meningitis globally. The annual number of cases related to invasive meningococcal disease (IMD) is estimated to be at least 1.2 million with 135 000 deaths.¹ To combat IMD, an increasing number of countries have included vaccines against *N. meningitidis* in their routine immunization programs. These include polysaccharide and conjugate, monovalent and polyvalent vaccine against serogroups A, C, W, and/or Y, and outer membrane vesicle (OMV) vaccines against serogroup B. The specific vaccine use in each country depends on the

predominant serogroups, cost, and availability. The impact of these vaccines has been documented in several countries with reliable surveillance systems, and includes a direct decrease in incidence rates as well as indirect benefits due to induction of herd protection. This review presents evidence of the impact that different vaccines have had globally and includes safety and efficacy data for recently introduced vaccines.

Methods

Search strategy and selection criteria

Our sources for the latest vaccine related data included the National Library of Medicine (PubMed), the WHO website of the Weekly Epidemiological Record, and the European Centre for Disease Prevention and Control. We searched PubMed with the following key

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terms: ('*Neisseria meningitidis*') OR ('meningococcal') OR ('meningococemia') OR ('meningococcus'). The search was limited to studies of people, studies published in English, and published from 1 Jan 1990 to 31 Dec 2010; the initial search yielded 5336 results. In addition, data were obtained from WHO's publications in the Weekly Epidemiological Record (WER) for the latest figures from 14 African meningitis belt countries. The European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS), which is now maintained by the European Centre for Disease Prevention and Control, was accessed for updated results from European countries. We searched references of identified articles for additional articles, and reviewed abstracts and titles and selected studies if we thought they were relevant to this review.

Types of Vaccines

Currently available meningococcal vaccines against serogroups A, C, W, and Y include both polysaccharide vaccines and polysaccharide-protein conjugate vaccines based on the meningococcal capsule. For serogroup B, vaccine development has included protein vaccines based on meningococcal OMV, while more recently a range of conserved proteins including Factor H Binding Protein (fHBP), *Neisseria* Adhesin A (*nadA*), and *Neisseria* Heparin Binding Antigen (NHba) have been used as vaccine components. One of the candidates serogroup B vaccines has three components, two of which are fusion proteins (Genome derived *Neisseria* Antigens – GNA 2091 fused with fHBP and NHba fused with GNA 1030). The third component is recombinant *nadA*. Different aspects of the immune response to polysaccharide and conjugate vaccines are compared in Table 1.

Polysaccharide Meningococcal Vaccines

There are several combinations of polysaccharide vaccines used globally, including bivalent (A, C), trivalent (A, C, W), and quadrivalent (A, C, Y, W) vaccines. The first polysaccharide vaccines containing high molecular weight polysaccharides suitable for vaccines were developed at Walter Reed Army Institute and used in military recruits to prevent recurrent outbreaks among newly recruited soldiers in 1960s.^{3,4} Polysaccharide meningococcal vaccines

are proven to be immunogenic and safe. They are highly effective in closed populations of adults at high risk for disease, including military recruits and household contacts of affected individuals⁵⁻⁷ and in outbreak control.⁸ Serogroup A polysaccharide vaccine has also been used effectively during outbreaks in Africa.⁹⁻¹¹

The major disadvantage of polysaccharide vaccines are their inability to produce memory cells leading to poor response to booster and short duration of protection. Hypo-responsiveness (as defined by impaired serum anticapsular antibody responses to subsequent vaccine doses) to serogroup C polysaccharide vaccine in infancy has been shown, especially if doses are repeated more than once. This hypo-responsiveness has not been shown by the use of meningococcal C conjugate (MCC).¹²

Although a few countries had a routine vaccination program with polysaccharide vaccines prior to the development of conjugate vaccines (Syria, Saudi Arabia), they have been used typically to protect persons at increased risk for disease, e.g. following splenectomy, travelers to the annual Muslim pilgrimage (Hajj), or in reactive vaccination campaigns in response to outbreaks. Polysaccharide meningococcal vaccines are still used for routine immunization in China and Egypt. In China, serogroup A polysaccharide vaccine was used in the routine immunization program since 1982, though the bivalent (A, C) polysaccharide vaccine was introduced in 2005 after the serogroup C outbreaks.¹³

Conjugate Meningococcal Vaccines

Meningococcal conjugate vaccines were introduced in 1999 with the initial introduction of MenC conjugate vaccines in the UK. Since then, conjugate quadrivalent (A, C, Y, W) and monovalent MenA vaccines have been licensed in various countries. Currently, 21 countries have introduced conjugate vaccines into their routine vaccination schedules (Table 3). Conjugate vaccines use a carrier protein to present the polysaccharide antigen to the immune system, in a manner that induces a T-cell immune response. Ten years of experience in countries with adequate surveillance systems have shown conjugate vaccines have a good safety profile and vaccine

Table 1 Overview of the broad immune response to polysaccharide and conjugate vaccines²

		Polysaccharide	Conjugate
Immunogenicity	Adults	High	High
Infants	Low	High	
Quality of antibodies	Avidity	Low	High
	Serum bactericidal antibody (SBA)	Low	High
Response to booster		Poor	High
Induction of immunologic memory		No	High
Reduction of colonization		No	Yes
Duration of protection		Short	Moderate

Table 2 Licensed Meningococcal Conjugate Vaccine Products

Vaccine	Manufacturer	Serogroups	Protein Conjugate	Licensed schedule	References
Menveo™	Novartis Vaccines	A, C, Y, W	Diphtheria cross Reactive material 197 (CRM197) Diphtheria toxoid	In US, one dose at the age of 2 years. 2nd dose 2 months after 1st dose in high-risk children aged 2–5 years In Europe, approved for use from 2 months of age	14,15
Menactra™	Sanofi Pasteur	A, C, Y, W	Diphtheria toxoid	1st dose in children aged 9–23 months. 2nd dose after 3 months in the age 2–55 years.	16–18
Meningitec™	Neuron Biotech	C	CRM197	4 doses for children <1 year at 2, 4, 6, and 12 months. One dose for children over 12 months, teenagers and adults	19
Menjugate®	Novartis Vaccines	C	CRM197	Age 2–4 months – 3 doses 8 weeks apart, 4–11 months – 2 doses 8 weeks apart, ≥12 months – 1 dose	20,21
NeisVac-C™	Baxter Bioscience	C	Tetanus toxoid	Age 2–12 months – 2 doses 2 months apart. ≥12 months – 1 dose	22
Menitorix™	GlaxoSmithKline	C	Tetanus toxoid	Age 2–12 months – 3 doses, 1 month apart. Booster from 12 months – 2 years	23,24
MenAfriVac™	Serum Institute of India	A	Tetanus toxoid	To be defined	24,25
MenHibrix™	GlaxoSmithKline	C & Y	Tetanus toxoid	Age 2–15 months – four doses	26

efficacy (VE). However, questions remain regarding long-term effectiveness of conjugate vaccines and how to optimize vaccination programs. Table 2 depicts different licensed conjugate vaccines with relevant references on effectiveness, immunogenicity, and safety, as well as most commonly used schedules.

Vaccine efficacy varies by the conjugate vaccine used and specific program implementation, but is higher in older children and adolescents compared to young children, with studies reporting short term VE as high as 97% for MenC vaccine in teenagers. Short term VE was high (83%) in infants and pre-school aged children who received immunization but declined with time. Estimates of VE over time in those vaccinated in infancy fell from 95% in the first year to 31% by the fourth year after vaccination.^{29–31} In the United States, initial VE estimates of 75% were found with MenACWY vaccine in adolescents with rapid waning even in teenagers who were expected to have higher efficacy.¹⁴

Another measure of the effectiveness of the meningococcal conjugate vaccination programs are their herd effects. Two years after introduction of MCC vaccine in the UK, the serogroup C carriage rate was reduced by 81%.³² Attack rates among unvaccinated children and adults in the UK declined by more than 67% in the 4 years following vaccine introduction. Between 1998 and 2009, the incidence of serogroup C disease in persons over 25 years dropped from 0.55/100 000 persons to 0.02/100 000 persons in the UK (96% decrease); and the number of cases in infants under 3 months of age dropped from 13 in 1998 to 1 in 2009 (92% decrease).^{26–28} These effects were seen despite a declining seroprevalence of protective antibodies among younger vaccinated cohorts as early as 18 months after the last scheduled dose of vaccine.³³

Recently, a vaccine, 4CMenB (Bexsero®), containing three recombinant proteins, and OMV derived from a serogroup B meningococcal strain (MenB) has been licensed in Europe and Australia and is indicated for persons aged 2 months or older. UK's Joint Committee on Vaccination and Immunisation (JCVI) has taken an interim position to not recommend Bexsero for routine vaccination at this time. Further information will be provided early next year. It has been shown to be safe in adolescents and infants. However, up to 80% of infants have experienced fever, particularly when 4cMenB was concomitantly given with routine vaccines.³⁴

MenC Conjugate Vaccines

Meningococcal C conjugate vaccine was first licensed in the UK based on antibody response studies, but without pre-licensure Phase III clinical trials. Several vaccine products are now licensed, conjugated to

tetanus toxoid, diphtheria toxoid or CRM-197. Multiple studies have since evaluated the safety and immunogenicity of MCC vaccination in several countries. Studies in healthy adults show a significant rise in GMT after vaccination.³⁵ Similar results have been seen in healthy adolescents.³⁶ At least five studies found MCC to be safe, with no major adverse reactions and only minor local reactions.³⁷⁻⁴¹ Immunogenicity studies have shown MCC to be immunogenic in infants as well. However, prior to moving the third dose to 12 months of age in the UK, Borrow, *et al.* found only 8–12% of children who had completed a three dose series in infancy to have rSBA titers $\geq 1:8$ by 4 years of age, with GMTs similar to pre-vaccination levels.⁴² In a phase four clinical trial of 250 children in the UK, rSBA titers were tested 6 years after the primary MCC series. Age at priming ranged from 2 months to 6 years. Only 25% (CI 20%–30%) of all children had protective titers $\geq 1:8$. A booster was highly effective in this cohort and resulted in titers of 1:8 in 99.6% of participants measured 1 year after the booster dose.⁴³

Recent data from the United Kingdom indicate that the memory response may not be rapid enough to protect against meningococcal disease following exposure through a close contact. After initial priming with monovalent MenC conjugate vaccine, a memory response after a booster dose is not measurable until 5–7 days. The incubation period of meningococcal disease is usually less than 3 days. Auckland, *et al.* have reported 53 cases of vaccine failure, largely in healthy children who had received a primary vaccination series in infancy. All cases mounted an anamnestic immune response.⁴⁴ Therefore, while a memory response may protect some individuals from disease or decrease disease severity, already present circulating antibody may be a more important indicator of direct long-term protection against meningococcal disease. Antibody responses were similar when MCC was co-administered simultaneously with other routine infant immunizations.⁴⁵⁻⁴⁷

Further studies have shown that a two dose series at 3 and 5 months yields equivalent immunity.^{46,48,49}

In summary, implementation of meningococcal conjugate vaccination programs, in countries across Europe, North America, and Australia, have all documented a reduction in serogroup C incidence. In the UK, incidence has decreased by 97% since 1998. The number of deaths from serogroup C disease declined from 78 in 1998 to 1 in 2009.⁴⁹ In Canada, incidence declined by 65%, 5 years after implementation. Ontario saw a 16% reduction per year in serogroup C disease among persons ≥ 20 years of age from 2000 to 2006 after introducing an MCC vaccination program in adolescents and infants.⁵⁰ No such reduction was seen in other serogroups that were

not included in the vaccine.⁵¹ Reductions in disease incidence have also been recorded in Australia, Netherlands, Spain, and Greece.⁵²⁻⁵⁵

Since the introduction of the meningococcal C (MenC) vaccination program in UK in November 1999, the vaccine schedule has undergone changes. Following the introduction of the vaccine, all children and adolescents under the age of 18 were offered immunization over the subsequent 2-year period. In 2002, the catch-up campaign was extended to include adults less than 25 years of age.⁵⁶ In 2006, the primary immunization course was changed to two doses at 3 and 4 months of age, and a booster dose at 12 months of age. This was based on studies that showed that protection waned in the second year of life.^{29,56,57} In July 2013, the UK implemented further changes to the schedule to maintain the success of the MenC vaccination program in the UK. This followed the recommendations from the UK Joint Committee on Vaccination and Immunisation (JCVI), based on a study that showed that a single dose in infancy was sufficient to provide protection in the first year of life, to remove the second dose given at 4 months of age from the schedule. JCVI also recommended the introduction of an adolescent booster to extend protection into early adulthood. Other countries that introduced the vaccine in later years have followed similar schedule changes based on the experience of the vaccine in UK. The MenC vaccine was introduced in Australia in 2003 as a single dose for all children less than 12 months of age. From 1 July 2013, the combined Haemophilus influenzae type b (Hib) and meningococcal serogroup C (MenC) vaccine, Menitorix®, was added to the National Immunisation Program (NIP) schedule at 12 months of age.

Quadrivalent Meningococcal Conjugate Vaccines

In 2005, the first quadrivalent meningococcal conjugate vaccine (A, C, W, Y) conjugated to diphtheria toxin (Menactra by Sanofi Pasteur) was licensed by the US Food and Drug Administration. A second MenACWY vaccine conjugated to CRM-197 (Menveo by Novartis) was licensed in 2010 and Nemenrix by GSK was licensed in 2012. In pre-licensure clinical studies, all these vaccines were found to be safe and immunogenic. In the United States these vaccines are licensed for the age 2–54 years, with studies evaluating a multiple dose series in infants and toddlers ongoing.

MenA Conjugate Vaccine

While meningococcal conjugate vaccines have the attributes needed to eliminate epidemic meningitis in Africa (including eliminating carriage of the organism), monovalent Men A conjugate C vaccines were not available earlier whereas quadrivalent meningococcal

Table 3 List of countries to have included meningococcal vaccines in routine immunization

Country	Ref.	Vaccine	Year introduced	Routine recommendations	Catch up program	Incidence rates
Africa (Burkina Faso, Niger, Mali) *	60	Serogroup A conjugate	2010	Still to be defined	Mass vaccination of 1–29 year old with a single dose	
Australia	67	Serogroup C conjugate	2003	Single dose at 12 months	All aged 1–19 years	3.5–7.9 pre-vaccine 1.4 post-vaccine
Belgium	68	Serogroup C conjugate	2002	Single dose at 12–14 months	Up to 19 years of age	3.69 pre-vaccine 0.8 post-vaccine
Canada	53,54,69	(1) Serogroup C conjugate (2) Quadrivalent conjugate including serogroups A, C, W, Y) approved in 2006.	2002	Most provinces use the MenC conjugate at 12 months while a few use the quadrivalent conjugate based on local epidemiology and/or children >2 years with primary antibody deficiencies		1.38 pre-vaccine 0.42 post-vaccine
China	68	(1) Serogroup A polysaccharide (2) Serogroups A/C polysaccharide	1982 2005	Vaccine at 6 and 18 months Vaccine at 3 and 6 years		
Cuba	69,70	Serogroup B OMV and Serogroup C polysaccharide	1991	Introduced into National Infant Immunization Program after epidemic incidence levels in 1980s		3.4–8.5 pre-vaccine <1 post-vaccine
Egypt	71	Serogroup A/C Polysaccharide	1992	School based vaccination program	Up to 24 years	
France	72	Serogroup C conjugate	2010	Age 12–24 months		
Germany	72,73	Serogroup C conjugate	2006	One dose in second year of life	Up to 19 years	7.58 pre-vaccine 14.8 pre-vaccine
Iceland	66,73	Serogroup C conjugate	2002	Part of routine immunization at 2, 4, and 6 months of age	Up to 23 years	
Ireland	74,75		2001	(now changed to 4, 6 months and booster in second year of life)		4.5 post-vaccine
Netherlands	55,65,76	Serogroup C conjugate	2002–3	Single dose at 12 or 14 months	Up to 18 years of age	4.51 pre-vaccine 17.4 pre-vaccine
New Zealand	77,78	Serogroup B OMV Serogroup C conjugate	2004	Mass immunization for everyone aged between 6 months and 20 years. MenZB routine use has now been terminated due to a marked decrease in the incidence of meningococcal B disease		2.6 post-vaccine
Portugal	79	Serogroup C conjugate	2001	3, 5, and 15 months of age	Up to 18 years	
Spain	66	Serogroup C conjugate	2001	Part of routine immunization at 2, 4, and 6 months of age (now changed to 2, 6, and booster at 15–18 months)	Up to 6 years in some regions, up to 19 in others. Later extended to 19 years in all Spanish regions)	3.74 pre-vaccine 1.3 post-vaccine
Switzerland	80,81	Serogroup C conjugate	2005	12–18 m	11–15 years	
UK		Serogroup C conjugate	1999	Part of primary immunization schedule at 2, 3, and 4 months of age. From 2006 at 3, 4, 12 months of age. From 2013 at 4, 12 months and 14 years of age.	Up to 18 years of age (1999–2000), up to 25 years (2001)	5.39 pre-vaccine 2.1 post-vaccine
USA	18,82	Serogroup A, C, Y, W conjugate (Serogroup A, C, Y, W polysaccharide alternative)	2005	Primary dose at age 11–12 years with a booster dose at age 16, people at increased risk as mentioned above	Adolescents aged 13–18 Booster dose at 5 years	0.8 pre-vaccine 0.28 post-vaccine

conjugate vaccines were costly and there was no development plan to license them in Africa. The Meningitis Vaccine Project was initiated in 2001 as collaboration with multiple partners, core partners being WHO and PATH, to bring an affordable conjugate vaccine targeting serogroup A to the African Meningitis Belt.

In 2010, a meningococcal A conjugate vaccine (MenAfriVac), manufactured by the Serum Institute of India, was licensed and subsequently prequalified by WHO. In September 2010, MenAfriVac was first introduced in mass vaccine campaigns in Burkina Faso, Mali, and Niger. All persons aged 1–29 years were vaccinated in the selected districts included in these initial campaigns, followed by nationwide campaigns in December 2010.

This vaccine has been shown to be highly immunogenic with a safety profile comparable to the safety profile of polysaccharide vaccine.⁵⁸ The conjugate vaccine-induced functional antibody response against meningococcal serogroup A was significantly higher and more persistent than that induced by a polysaccharide vaccine. In addition, the conjugate vaccine also induced immunologic memory. Recent studies have shown disappearance of serogroup A *Neisseria meningitidis* carriage among both vaccinated and unvaccinated populations which is consistent with a vaccine-induced herd protection effect.^{52,58} A study conducted in Burkina Faso has proved the effectiveness of the MenAfriVac vaccine as no serogroup A carriage was identified after vaccination compared to a baseline serogroup A carriage prevalence of 0.39%.⁵²

MenB OMV Vaccines

While progress toward reducing meningococcal disease globally has been made with meningococcal conjugate vaccines for serogroups A, C, Y, and W, vaccines to protect against various strains of serogroup B disease have presented a challenge because the B polysaccharide is not immunogenic and other potential antigen targets are highly diverse. Serogroup B vaccines have been developed for specific outbreak strains using the OMV specific to that strain, including vaccines to target disease in New Zealand and Cuba.^{59,60} These vaccines are immunogenic, but require multiple doses, especially in young infants, and efficacy appears to have a short duration of protection.⁶¹ Efforts to find novel vaccine antigens to protect against serogroup B disease have identified several protein surface antigens. Efficacy of a new vaccine using sub-capsular protein has been established in infants in several clinical trials.^{62,63} To predict regional strain coverage of this vaccine, a Meningococcal Antigen Typing System (MATS) has been employed in five European countries.^{64,65} This approach has been supplemented with studies using a

more accepted correlate or protection, SBAs, and pooled serum from vaccines. Another vaccine that targets conserved antigens is currently under investigation in clinical trials. These vaccines may have the potential to protect not only against serogroup B disease but against other serogroups as well. Preliminary data from these trials are promising, but the role these vaccines will play in controlling meningococcal disease remains to be determined. Research in Norway has suggested that although the MenB OMV vaccine conferred protection against group B meningococcal disease, the effect is not sufficient to justify the cost of a public vaccination program.⁶⁶ However, a recent study in Normandy showed that MenB vaccination was associated with a lower carriage rate among vaccinated children (0.31%) as compared to unvaccinated children (2.10%) indicating that meningococcal OMV-based vaccines reduce meningococcal carriage and may hence confer herd protection.⁶⁷ The population impact of these vaccines is likely to be key in determining the cost-effectiveness, and therefore in overcoming barriers to introduction.⁶⁷

Current Utilization of Meningococcal Vaccines in Routine Immunization Programs

Table 2 lists the countries that have included meningococcal vaccines in their routine immunization programs along with their year of introduction, vaccination schedule, and any special recommendations. Pre and post vaccination attack rates per 100 000 population, where available, have been included.

Economic Evaluations of Meningococcal Disease and Vaccines

Data on the cost of vaccine and financial burden of disease have been published from Africa and some industrialized countries where a vaccine has been introduced. Limited data on meningococcal carriage and incidence are available from other countries, especially in Asia, and thus cost effectiveness cannot currently be accurately determined for these countries.

One study in Burkina Faso found that the cost per household of a case of meningococcal disease in Sub-Saharan Africa is US\$ 90, with additional US\$154 expenditure if sequelae of the disease occur. The urban cost is more than 200% higher than the rural cost.⁸⁵ An idea of the overall burden of disease can be gaged from the total cost of the 2006–2007 outbreak, in Burkina Faso which was US\$ 9.4 million, 7.1M borne by the public health system and 2.3M borne by households which comprised 34% of the GDP capita.⁸³ The Meningitis Vaccine Project has the potential to:

- Prevent 123 000 deaths by 2018
- Prevent permanent disability in 287 000 children and adults

- Prevent 11 million DALYs lost
- Save approximately \$99.7 million in medical costs for diagnosis and treatment

Cost Effectiveness of Men C Conjugate Vaccine

Six countries reported economic evaluations before the introduction of MCC vaccines (Australia, Canada (Quebec), The Netherlands, UK, Portugal, and Switzerland). All of them recommended that one dose in the second year of life was more cost-effective than a three-dose infant schedule.⁸⁴ Further development of the dynamic model was undertaken after vaccine introduction to predict the impact of the meningococcal vaccination program and its cost effectiveness in the UK.⁸⁶ Various factors feed into this dynamic model, including the high transmissibility of the disease, the role of carriage/colonization and possibility of recurrent colonization with different serotypes, interaction between related bacteria, and the differing risks of colonization and disease at different ages. The model accurately reflected the trends of meningococcal disease in the UK when it was applied retrospectively to the actual experience in the UK from 1998 to 2004. It was also able to predict the significant herd protection that has been seen with the use of this vaccine. The UK model was also used to investigate the impact of vaccine schedules in the UK and Spain.⁸²

Fractional Doses

There has been concern that in the event of a large scale epidemic in the African meningitis belt, the supply of meningococcal vaccines may not be enough to match the demand. Thus, a trial was conducted to test the hypothesis that fractional doses of ACWY meningococcal polysaccharide vaccine confer for each serogroup in the vaccine an immunogenic response, which is non-inferior to the full dose licensed vaccine(s) in the population targeted during mass vaccination campaigns in Africa. The objective of the trial was to measure the immunogenicity of each component of a dose corresponding to 1/5th and 1/10th of the amount of the current licensed vaccine. This was a randomized, single-blind, non-inferiority trial, in which healthy subjects aged 2–20 years in Uganda were enrolled.⁸⁷

In the non-immune population, the immunogenicity of the 1/5th dose for serogroups A, W, and Y was non-inferior compared to full dose. In the ITT and PP analysis, the immunogenicity of 1/5th dose for serogroups W and Y was non-inferior compared to full dose. The immunogenicity of 1/5th dose was inferior to full dose for serogroup C. With the 1/10th dose, the antibody titers generated were lower compared to 1/5th dose, however, it was still non-inferior to full dose for serogroups W and Y.

In the event of an acute shortage of meningococcal vaccines during an epidemic, 1/5th or 1/10th of the

normal dose of ACWY polysaccharide vaccine can be considered depending on the serogroup causing the epidemic. However, since the absolute titers generated by the fractionated doses are lower compared to the full dose, the duration of protection provided by the fractionated doses is likely to be shorter than the full dose.

Conclusion

All countries considering the use of meningococcal vaccines should develop the surveillance infrastructure for monitoring IMD including clinical case definition, field investigation, and access to laboratory capacity for the diagnosis and characterization of *N. meningitidis*. The choice of vaccine for each country should depend on the serogroup(s) (or serosubtype in case of serogroup B for OMV vaccines) of *N. meningitidis* that are locally prevalent. In general, conjugate vaccines are preferred to polysaccharide vaccines due to their impact on decreasing nasopharyngeal carriage of *N. meningitidis* and their overall increased immunogenicity in children. However, in some countries the high cost of conjugated vaccines may be prohibitive, and polysaccharide vaccines are acceptable in those settings.

Countries with a high endemic rate of IMD (>10 cases/100 000 population per year in a country or large region), other than serogroup B, should use an appropriate meningococcal vaccine against serogroups A, C, W, and/or Y in their populations for prevention and/or outbreak response. In most high endemicity countries, the peak disease incidence is in young children and adolescents. Therefore, the recommended strategy is initial mass vaccination of young children through adolescents depending on the country-specific age distribution of disease, followed by a routine vaccination program with conjugate vaccination in previously unvaccinated young children. Continued surveillance of IMD should dictate the need and timing of repeat mass vaccination campaigns.

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