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REVIEW

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Routinely vaccinating adolescents against meningococcus: targeting transmission & disease

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ABSTRACT

Adolescents have the highest rates of meningococcal carriage and transmission. Interrupting the adolescent habitat in order to reduce carriage and transmission within adolescents and to other age groups could help to control meningococcal disease at a population level. Compared to immunization strategies restricted to young children, a strategy focused on adolescents may have more profound and long-lasting indirect impacts, and may be more cost effective. Despite challenges in reaching this age-group, experience with other vaccines show that high vaccine coverage of adolescents is attainable.

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Introduction

Neisseria meningitidis is a commensal of the human nasopharynx. Rarely, it invades the mucosae and enters the bloodstream to cause invasive meningococcal disease (IMD), characterized by meningitis and/or septicemia. IMD case fatality is between 10% and 12% despite antibiotics, and is highest when septicemia is present (up to 18%), and in older adults (14–24%) [1,2]. Long-term sequelae such as limb loss and neurological impairment can affect up to 19% of IMD survivors [3,4]. Meningococci are serogrouped on the basis of their polysaccharide capsule, and further characterized into serotypes, serosubtypes, immunotypes, or clonal complexes using molecular methods [5]. Outbreaks of IMD occur when a virulent strain is transmitted within a population with low underlying immunity to that strain [6]. Although cases of IMD are generally rare, the severity of the disease and potential for outbreaks support a role for prevention through vaccination.

The six serogroups (A, B, C, W, Y, and X) that cause the majority of endemic and epidemic IMD worldwide vary in their regional distribution, and their distribution also changes over time. Serogroup B (MenB) dominates in Europe, followed by serogroup C (MenC) in countries without MenC vaccination programs [2]. Few cases of IMD are caused by serogroup W in Europe. However, serogroup W disease has been rising steeply in England and Wales since 2010, and accounts for 25% for all IMD cases in 2014–2015 [2,7,8]. Serogroup Y IMD remains important in several countries in Europe, mainly in Scandinavia [2,9]. In the United States (U.S.), MenB, MenC, and MenY predominate among IMD cases [3]. South American countries have experienced IMD outbreaks in recent years caused by MenC (Brazil) and MenW (Chile and Argentina) [10,11]. Serogroup A was the major cause of epidemic IMD in sub-Saharan Africa for many years, but has been in decline since the introduction of MenA-conjugate vaccination: in 2015 the majority of confirmed cases in Niger and Nigeria were due to MenC [12].

In industrialized countries the incidence of IMD peaks in infancy, with a secondary peak in adolescence [1,3,13,14]. Some studies have also observed a small increase in incidence among adults over 65 years of age [3,13,14]. Over the last two decades, the overall incidence of IMD in the U.S. has decreased; it was estimated to be 0.14 per 100,000 population (all ages) in 2014 [3,15]. The incidence of IMD in Europe in 2012 was 0.68 per 100,000 population (range between individual countries of 0.11 to 1.76 per 100,000 population) with decreases in MenB and MenC disease [2]. There were two cases of IMD in 11- to 17-year-olds reported to the Active Bacterial Core Surveillance in the U.S. in 2014, which may be a reflection of vaccination in place in this age group;

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the highest incidence was children under 1 year of age, and between 1 and 2 years of age (1.65 and 0.62 per 100,000 population, respectively) [15]. In Europe, the 2012 incidence of IMD was 0.7 and 1.1 per 100,000 population in 5- to 14-year-olds and 15- to 24-year-olds, respectively [2].

MenC vaccines were developed during the 1990s in response to an increase in the number of MenC IMD cases, with rising public awareness. At that time, technical challenges prevented the successful development of a MenB vaccine, and total cases of A, W, and Y remained very few in number in industrialized countries. Since licensure of the first monovalent MenC conjugate (MCC) vaccines in 1999, most countries with MCC immunization programs have observed significant declines in MenC IMD [2,16–19]. These countries employ a range of vaccination strategies that target different age groups (either individually or in various combinations) that include infants, toddlers, and adolescents. Because of the rarity of IMD, the meningococcal conjugate vaccines were licensed without classical Phase III efficacy studies, but with safety and immunogenicity data derived from experience with meningococcal polysaccharide vaccines. Lessons learnt after their licensure and widespread use include knowledge about meningococcal epidemiology, nasopharyngeal carriage, effectiveness, and the duration of protection induced by vaccination. Increasing knowledge has led to refinement of immunization strategies in many countries; with several introducing, or considering, adolescent vaccination.

In this review, we highlight the pivotal role of adolescents in meningococcal epidemiology and argue why routine vaccination of this age group is needed to optimize control of IMD in the longer term. We also discuss the challenges involved in achieving this goal.

The importance of carriage in IMD

In contrast to the rarity of IMD, asymptomatic carriage of meningococci is common. Humans are the only hosts for *N. meningitidis* and transmission occurs from host to host via oral contact or respiratory secretions. Meningococci colonize the nasopharynx, attaching to the mucosal surface where they reside for weeks or months until cleared by the host. The carriage state is the natural habitat of the meningococcus, and IMD is a rare outcome that does not favor survival of the bacterium. Carriage induces a strain-specific immune response that is thought to convey protection against disease and further carriage of the same strain [20,21]. The nasopharynx may harbor many pathogenic and non-pathogenic bacteria including different meningococcal strains. This environment fosters horizontal exchange of genetic material which may be associated with switching of capsule or other antigenic structures, potentially leading to increased virulence or antibiotic resistance [22,23]. Horizontal gene transfer, as well as spontaneous chromosomal mutations which are also common among meningococci, results in wide genetic and antigenic diversity among strains [24]. Strains that invade the mucosa and cause disease are thought to differ from carriage strains in terms of the expression of capsule and other virulence factors [25–27]. Those strains that undergo genetic changes linked to adaptations that improve survival, such as the ST11 clonal complex which emerged during the 1990s [6], can be widely transmitted, potentially resulting in local outbreaks and global spread.

Available data indicate that in industrialized countries age is the most important factor related to meningococcal carriage prevalence, with the highest prevalence observed in adolescents and young adults [28,29]. In a meta-analysis of carriage data from European countries and other countries where MenB and MenC disease predominated, meningococcal carriage prevalence peaked at 23.7% in 19-year-olds, versus 4.5% in infants, 7.7% in 10-year-olds, and 7.8% in 50-year–olds [28]. Carriage prevalence may be much higher (up to 70%) in closed communities such as military barracks and university halls where the potential for person-to-person transmission is high [29].

Patterns of meningococcal carriage appear to be different in sub-Saharan Africa, potentially reflecting different social factors and behaviors across the region [30]. A study in seven sub-Saharan African countries reported the highest overall carriage prevalence in 5- to 14-year-olds (4.9%) followed by 15- to 29-year-olds (3.6%) [31]. However, there was marked variability between countries (overall carriage prevalence 0.20% in Nigeria versus 8.76% in Niger) and between seasons (up to 20% in Senegal during the dry season, possibly reflecting preferential carriage of encapsulated strains that resist desiccation during the dry season) [31].

Vaccines with an ability to reduce carriage can interrupt transmission and enable indirect protection to be induced that benefits both vaccinated and unvaccinated populations. This indirect protective effect of vaccination is achieved by high coverage of the segment of the population in which carriage and transmission are greatest, and is referred to as ‘herd protection’. Herd protection can bring substantial added value to vaccination programs in terms of cost–effectiveness and long-term disease control across the population. The likely mechanism leading to reduced carriage and herd protection is a reduction in the acquisition of new

strains (no carriage/no transmission). Herd protection effects have been demonstrated for polysaccharide-protein conjugate vaccines used to prevent disease due to *Streptococcus pneumoniae, Haemophilus influenzae* type b (Hib), and *N. meningitidis*; all of which are encapsulated bacteria that colonize the nasopharynx, and which are transmitted via respiratory secretions [32].

Nasopharyngeal carriage studies are difficult to perform, requiring large numbers of subjects with repeated sampling conducted over long periods. Microbiological culture of nasopharyngeal swabs may be unreliable, and costly methods such as polymerase chain reaction are needed to increase rates of meningococcal detection [33]. Molecular detection methods are yet to become fully standardized, making comparison of results between studies difficult. Furthermore, density of carriage may also play a role in transmission, but is rarely investigated. While there is consensus that in industrialized countries meningococcal carriage prevalence peaks in those aged 16–24 years, age and serogroup-stratified carriage data remain limited, with much remaining to be understood regarding the epidemiology and dynamics of meningococcal carriage and transmission. Most recent information on carriage in the general population derives from studies conducted in Europe, with less information available from North America, Africa, the Middle East, and Asia [34,35]. It is challenging to study the impact of vaccination on carriage, because reliable and detailed baseline data collected prior to vaccine introduction are often lacking.

The pivotal role of adolescents and young adults in the epidemiology of meningococcal disease

In industrialized countries, adolescents and young adults play a crucial role in the epidemiology of IMD. Not only have carriage studies established that these age groups are at highest risk for carriage acquisition and transmission, but they frequently have the highest incidence of IMD after infants and young children. The increased risk of carriage and disease in adolescents and young adults is a result of social behaviors that result in close physical contact, which facilitates meningococcal transmission; such as frequent kissing, nightclub attendance, living in a residential college, smoking, and participation in fraternities and sororities [36,37]. High rates of asymptomatic meningococcal carriage create a habitat which both promotes exchange of genetic material between strains and fosters the reservoir for transmission within that age group and to other age groups (Figure 1). In this way the separation of peak disease incidence and carriage reservoir is different from other vaccine-preventable invasive diseases caused by encapsulated pathogens where disease

Figure 1. Simplified illustration of the pivotal role of adolescents in the epidemiology of meningococcal disease compared to other pathogens that also cause invasive disease [25,28,31,32,42,43].

The frequency of interactions between adolescents and other specific age groups may depend on factors including culture and social norms. This figure illustrates the potential of adolescents to transmit to all contacts, regardless of age. Grey arrows indicate transmission of pathogens.

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and carriage peak in similar age groups. Unlike *N. meningitidis*, both carriage and invasive disease caused by *S. pneumoniae* and Hib peak during early childhood. As a result, childhood vaccination strategies (that include a toddler booster dose) using pneumococcal conjugate vaccines (PCVs) and Hib conjugate vaccines have been accompanied by significant herd protection effects [32]. This is in contrast to polysaccharide vaccines for which an impact on carriage is not observed in the same range [38]. For example, the introduction of Hib vaccination was followed by a 79% reduction in invasive Hib disease in infants too young to be vaccinated in the United Kingdom (U.K.) [39]. In the years after PCV introduction in the U.S., there was a 30% reduction in invasive pneumococcal disease in adults over 65 years of age [40]. Reductions in hospital admissions for pneumonia (all-cause) have also been observed in unvaccinated cohorts [41]. For PCVs, the number of infections prevented through herd effects exceeds those directly prevented through vaccination, making infant vaccination programs highly cost-effective [40].

While these successful childhood PCV and Hib conjugate vaccine programs produce marked herd protection effects, isolated childhood programs without catch-up campaigns using meningococcal conjugate vaccines do not; this disparity reflects the dissociation between peak susceptibility to IMD among infants and peak carriage among adolescents. Toddler immunization using MCC was recommended in the Netherlands in 2002, with catch-up until 18 years of age, and in Germany in 2006 without a concerted catch-up campaign. In the Netherlands, herd protection in unvaccinated age groups was observed (Figure 2) [44], while

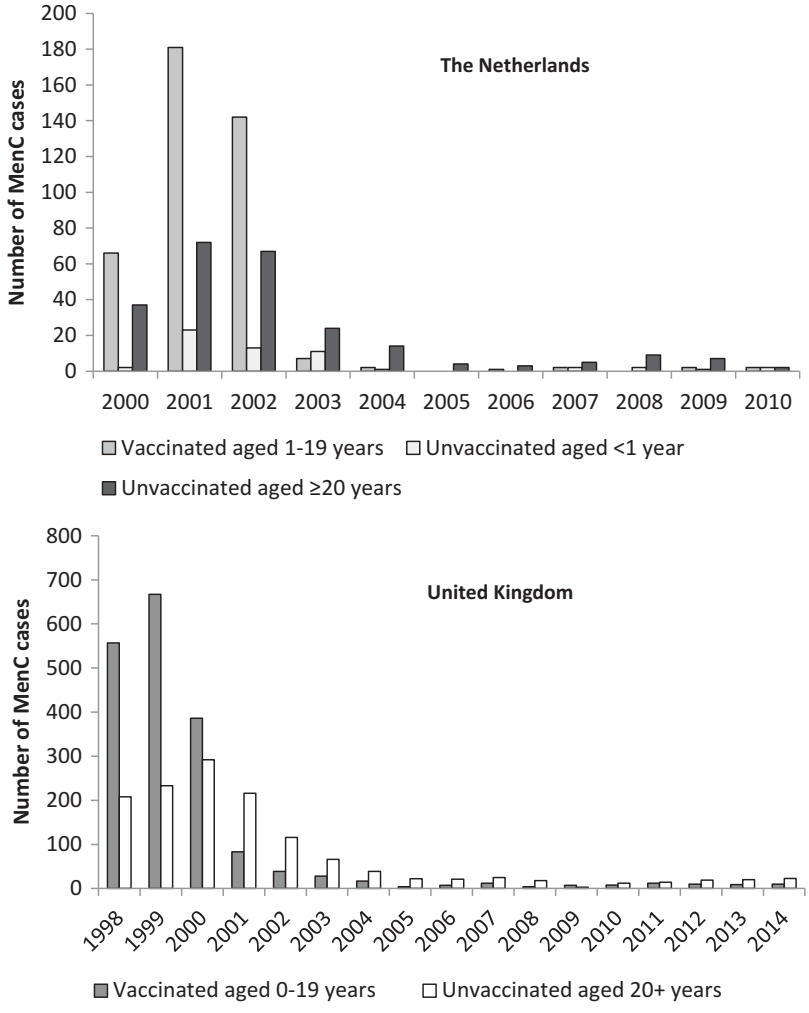

Figure 2. Evidence of herd protection in countries which implemented a large catch-up campaign (the Netherlands [44] and the United Kingdom [46]) after the onset of meningococcal serogroup C conjugate vaccination programs.

Vaccination commenced in the Netherlands in 2002: one dose administered at 14 months of age with catch-up to age 18 years, inclusive. Vaccination commenced in the U.K. in 1999: administered at 2, 3, and 4 months of age with catch-up to age 18 years, inclusive. For the U.K. 2014 data are provisional.

in Germany, MenC IMD decreased in the targeted age, with little impact observed in other age groups [45]. In Brazil, vaccination of infants with MCC with catch-up only in toddlers reduced IMD in the targeted population, but did not induce early herd protection [11]. Similarly, introduction of MenACWY vaccination in 9-month to 5-year-olds in Chile in response to an outbreak of MenW disease in 2012 did not prevent increases in disease incidence in unvaccinated age groups, despite almost complete vaccine coverage of the target population [11]. By contrast, the U.K. MenC program that began in 1999 included vaccination at 2, 3, and 4 months of age with catch-up to age 18 years. High coverage (at least 85% in most age groups) and herd protection effects were rapidly achieved (Figure 2) [17].

Conjugate vaccines

The first licensed MCC vaccines were used from 1999 to successfully end a protracted MenC outbreak in the U.K. [17]. Since then, the spectrum of available meningococcal conjugate vaccines has expanded to include vaccines with up to four serogroups, as well as vaccines combined with Hib conjugate vaccines: monovalent MenC (*Meningitec*™ Nuron Biotech, *Menjugate*™ GSK Vaccines, *NeisVac*-C™ Pfizer) and MenA (*MenAfriVac*® Serum Institute of India Ltd., used in Africa) vaccines, Hib-MenC (*Menitorix*™ GSK Vaccines), Hib-MenCY (*MenHibrix*™ GSK Vaccines, only licensed in the U.S.), and three quadrivalent MenACWY conjugates that use different protein carriers; tetanus toxoid (TT: *Nimenrix*™ GSK Vaccines*), diphtheria toxoid (DT: *Menactra*™ Sanofi Pasteur), and non-toxic mutant diphtheria toxoid (CRM: *Menveo*™ GSK Vaccines).

Vaccine effectiveness of MCC against IMD due to MenC is approximately 90% or more in all age groups within the first year after vaccination [16,17,47,48]. Evidence supporting effectiveness of MenACWY in preventing IMD due to non-MenC serogroups is more limited. One study in the U.S. indicated that the effectiveness of MenACWY-DT within 3 to 4 years after vaccination was approximately 80–85% against MenC and MenY disease in adolescents, which was lower than initially anticipated and comparable to the effectiveness reported for meningococcal polysaccharide vaccines [49]. A study in Chad using monovalent MenA conjugate vaccine noted a 94% decrease in IMD cases in a vaccinated compared to a non-vaccinated region during an epidemic season [50]. Information on the effectiveness of the MenW conjugate component is currently lacking.

Licensure of meningococcal conjugate vaccines is based on achieving accepted antibody thresholds for serum bactericidal activity (SBA) after vaccination. SBA is measured in assays that use either baby rabbit (rSBA) or human (hSBA) complement. An hSBA titer ≥4 was identified in the 1960s as the surrogate of natural protection for meningococcal disease: although a titer below 4 did not necessarily indicate susceptibility [21]. Human complement is difficult to source, the assay to measure hSBA is difficult to standardize, and no reference laboratory for hSBA currently exists. Because of these limitations, baby rabbit complement was also recommended for use in SBA assays [51]. rSBA gives higher titers than hSBA, and experience with MCC in the U.K. established an rSBA cutoff ≥8 as indicative of protection, although subsequent investigations suggested that this cutoff underestimated efficacy [52]. The World Health Organization indicates that hSBA ≥ 4 and rSBA ≥ 8 are accepted correlates of protection against serogroups A, C, W, and Y, even though correlations between efficacy and serum SBA titers for A, W, and Y have not been specifically evaluated [53].

All three licensed quadrivalent MenACWY conjugate vaccines have been evaluated in adolescents, with demonstration of adequate tolerability, and with the majority reaching accepted antibody thresholds for SBA using rabbit or human complement source (Table 1). Vaccination in adolescents induces durable immune responses, with persistence data currently available up to 5 years after vaccination [54–57]. The duration of antibody persistence may increase with older age at the time of vaccination [58].

The ability of meningococcal conjugate vaccines to impact carriage is considered a class effect: this is based on evidence relating to MCCs and MenA conjugate vaccine (Table 2), and on experience with Hib and PCVs. Compelling evidence came from the U.K. using observations facilitated by their extensive catch-up campaign that included adolescents and young adults (i.e. the key transmission group) following introduction of MCC (Table 2) [69]. More recently, large carriage studies conducted before and after implementation of MenA immunization campaigns in Africa confirm the effect of conjugate vaccines in reducing serogroup-specific carriage (Table 2). Strong evidence supporting an impact of quadrivalent MenACWY vaccines on carriage is currently lacking. However, two smaller studies in different populations (university students in the U.K. and Polish military personnel) have shown reductions in carriage after MenACWY-TT, lending support to the notion that quadrivalent vaccines may have impacts on carriage, as observed with monovalent vaccines (Table 2) [70,71]. In the English study in university students, carriage of MenY decreased by

Table 1. Phase II and III studies of MenACWY conjugate vaccines and MenB vaccines in adolescents.

Author	Country	Age (years)	NCT	N	Serogroup A	C	W	Y
ACWY-TT (*Nimenrix*, GSK Vaccines[a])						**rSBA % ≥8**		
Phase II								
Ostergaard [59]		15–19	NCT00126945	23–25	100 (83.9; 100)	100 (85.2; 100)	100 (85.2; 100)	100 (85.2; 100)
Bermal [60]	Philippines, India, Taiwan	11–17	NCT00464815	760	100 (99.5; 100)	100 (99.0; 100)	99.7 (99.1; 100)	99.9 (99.3; 100)
Phase III								
Ostergaard [61]	Sweden, Denmark	11–17	NCT00465816	113	100 (96.8;100)	99.1 (95.3; 100)	100 (96.8; 100)	100 (96.8; 100)
				335[b]	99.7 (98.4; 100)	99.7 (98.5; 99.9)	100 (99.0; 100)	99.7 (98.5; 100)
Lupisan [62]	Philippines, Thailand, Panama	18–25	NCT01154088	359–375 (lotA)	100 (99.0; 100)	100 (99.0; 100)	100 (99.0; 100)	100 (99.0; 100)
Bermal [60]	Philippines, India, Taiwan	11–17	NCT00464815	760	100 (99.5; 100)	99.7 (99.0; 100)	99.7 (99.1; 100)	99.9 (99.3; 100)
						hSBA % ≥8		
Baxter [63]	U.S.	10–25	NCT00454909	479–517	81.9 (78.2; 85.1)	96.1 (94.0; 97.6)	91.4 (88.6; 93.8)	95.2 (92.9; 96.8)
ACWY-DT (*Menactra*, Sanofi Pasteur)								
Jackson [64]	U.S.	11–18	NCT00450437	288–501	67 (62; 72)	84 (80; 87)	88 (84; 92)	69 (63; 74)
Baxter [63]	U.S.	10–25	NCT00454909	149–173	70.7 (63.1; 77.4)	98.8 (95.9; 99.9)	76.5 (68.9; 83.1)	81.8 (75.1; 87.3)
						hSBA % ≥4		
Halperin [65]	U.S., Canada	10–25	NCT01165242	286–306	73.1	98.3	83.2	94.1
ACWY-CRM (*Menveo*, GSK Vaccines)						**hSBA % ≥8**		
Phase II								
Jackson [66]	U.S.	11–17	Not provided	148	81 (74; 87)	84 (77; 90)	91 (84; 95)	95 (90; 98)
Phase III								
Jackson [64]	U.S.	11–18	NCT00450437	1024–1483	75 (73; 78)	84 (82; 86)	96 (95; 97)	88 (85; 90)
Phase II or II/III						**hSBA≥ 4**		
4CMenB (*Bexsero*, GSK Vaccines)					**44/76-SL**[c]	**5/99**[c]	**NZ98/254**[c]	
Santolaya [67]	Chile	11–17	NCT00661713	98–126[d]	100 (97–100)	100 (96–100)	100 (95–100)	
				179–211[e]	100 (97–100)	100 (97–100)	100 (97–100)	
rLP2086 (*Trumenba*, Pfizer)					**PMB1745**[f]	**PMB17**[f]	**PMB1321**[f]	**PMB2948**[f]
Richmond [68]	Australia, Spain, Poland	11–19	NCT00808028	–	92.8	86.6	88.0	83.9
					PMB1256[f]	**PMB3302**[f]		
					~75	100		

N = number in the according-to-protocol cohort.
[a]Nimenrix is a trademark of GSK group of companies, licensed to Pfizer.
[b]Subjects received ACWY-TT co-administered with *Twinrix* (combined hepatitis A and B vaccine, GSK Vaccines).
[c]Indicator strains: i.e. strains selected because they express one of the MenB vaccines proteins.
Results after subjects received two doses at a 1-month[d] or 2-month[e] interval.
[f]Test strains randomly selected from groups encompassing 1263 invasive MenB strains from several countries.

39.0% (95% confidence intervals [CI]: 17.3–55.0) and combined serogroups CWY by 36.2% (95% CI: 15.6–51.7), two months after vaccination with MenACWY-CRM [70]. In professional soldiers, meningococcal carriage was 9.6% in unvaccinated individuals and 1.2% in individuals vaccinated 1–3 years previously with a MenACWY conjugate vaccine (Table 2) [71].

Serogroup B meningococcal protein vaccines

Two protein vaccines targeting MenB were licensed in 2014: 4CMenB (*Bexsero*® GSK Vaccines) is licensed in the U.S. as a 2-dose schedule in 10- to 25-year-olds, and in Europe, Australia, Canada, and some countries in South America as a 3-dose schedule from 2 months of age, with a booster in the second year of life. rLP2086 (*Trumenba*, Pfizer) is licensed in the U.S. as a 3-dose schedule in 10- to 25-year-olds. To date, few countries have introduced a MenB vaccine into routine immunization schedules (Table 3). Immunization of infants with 4CMenB at 2, 4, and 12 months of age has been implemented in the U.K. recently [73].

The determination of SBA against MenB is only done using hSBA. This is because the use of rSBA has been associated with elevated SBA titers due to the presence of low-avidity anti-MenB capsular polysaccharide antibody in test sera [78]. Both MenB vaccines induce SBA above the accepted threshold for seroprotection against selected MenB strains in adolescent populations (Table 1). No effectiveness data for either vaccine are currently available. Compared to conjugate vaccines, where the impact of PCV, Hib, and meningococcal conjugates on carriage and herd protection has been demonstrated, the capacity for 4CMenB and rLP2086 to influence MenB carriage is less clear. One study conducted in university students showed no effect of 4CMenB on MenB carriage, although small but significant reductions in other serogroups were observed (CWY 28.5% reduction, 95% CI: 2.8–47.5) [70].

Table 2. Studies of nasopharyngeal carriage of meningococcus after meningococcal conjugate vaccination.

Country	Campaign/study	Age group	Population	Serogroup	Carriage prevalence (%)	
					Study year 1999 (N = 14,056)	Study year 2001 (N = 17,770)
U.K. [69]	1999 MenC campaign	2, 3, 4 months with catch-up to 18 years	Students (vaccinated)	All	16.7	18.7
				C	2.51	0.48 ($p < 0.001$)
Burkina Faso [72]	2010 MenA campaign	1–29 years	1–29 years (vaccinated)		2009 (N = 20,326)	2011 (N = 22,093)
				All	3.98	6.95
				A	0.39	0 ($p < 0.05$)
Chad [50]	2011 MenA campaign	1–29 years			2011 (N = 4278)	2012 (N = 5001)
			<1 (unvaccinated)	All[a]	1	0
				A	1	0
			1–29 (vaccinated)	All[a]	45	39
				A	25	1
			>30 (unvaccinated)	All[a]	10	2
				A	6	0
					Group MenACWY-CRM (N = 983)	Group Control[b] (N = 984)
England [70]	Study in university students	18–24 years				
			2 months post-dose 1	CWY	6[c]	7
				Y	5[c]	7
Poland [71]	Study in professional soldiers	21–52 years	1–3 years post-MenACWY vaccine		MenACWY (N = 257)	Unvaccinated (N = 302)
				All	1.2	9.6
				B	0.8	2.3
				C	0	2.3
				Y	0	2.6
				Other	0.4	2.3

N = number studied.
[a]All = serogroups A, W, Y, and other.
[b]Received Japanese encephalitis vaccine.
[c]Statistically significant difference compared with controls who received placebo.

The potential impact of a meningococcal vaccine on carriage, and the extent and duration of any herd protection induced, is crucial for the strategy under which the vaccine should be used. In order to have an impact that is similar to conjugate vaccines, MenB protein vaccines need to have a similar impact on carriage and transmission. However, carriage and transmission studies are challenging to conduct, requiring baseline age- and serogroup-stratified insights into carriage prevalence to power studies appropriately to detect carriage reduction in the vaccinated group; and may not be possible until after licensure, when large cohorts of vaccinated individuals are available. Along with effectiveness data, critical carriage data obtained using MenC and MenA vaccines was only possible after their widespread use, and well after licensure. While observational data following vaccine introduction may be a practical alternative to large pre-licensure clinical trials, this is not ideal given the importance of this information in predicting the vaccine impact.

Meningococcal vaccination schedules: advantages and disadvantages of different approaches

There was little information to support informed decision-making regarding the ideal/optimal schedule when MCCs were first licensed. Different countries employed a diverse range of vaccination schedules in their efforts to maximize effectiveness in the context of local epidemiology while maintaining cost–effectiveness (Table 3). In the beginning, and in the absence of data suggesting the potential impact of herd protection, most countries chose a strategy aiming to provide direct protection of the age group most affected by IMD. As experience with MenC vaccines has grown, and as the potential of herd protection effects has been demonstrated, many countries have modified their schedules to adapt to new knowledge. Nevertheless, there is currently no agreed consensus on a single optimal strategy.

Infant and toddler immunization

Infant immunization prevents disease in the age group with the highest incidence of IMD and was the first schedule (along with a catch-up campaign) in which MCCs were used [17]. Although controlling disease in this age group, infant immunization requires multiple doses, is thus costly to implement, does not protect very young infants prior to the first dose, and has since been shown to induce relatively short-lived immunity, requiring booster doses [79]

Table 3. Routine meningococcal immunization strategies in use globally [74–77].

	Vaccines in use in routine immunization schedules			Age groups targeted for immunization		
Country	MenC vaccines	MenACWY conjugate vaccines	MenB (protein/ OMV) vaccines	Infant	Toddler/child	Adolescent
Austria	Y	Y			12–14 months	12 years MenACWY
Belgium	Y				15 months	
Cyprus	Y				12–13 months	At risk from 2 years MenACWY-PS
Czech Rep.		Y	Y (protein)	2, 3, 4 months MenB (+catch-up[a])	1–2 and 5–6 years MenACWY	13–15 years MenACWY
France	Y				12–23 months	2–24 years MenC
Germany	Y				11–23 months	2–17 years MenC
Greece	Y	Y		2, 4 months	6 months – 5 years	11 years MenACWY
Iceland	Y			6, 8 months		
Ireland	Y			2, 4 months	13 months	
Italy	Y		Y (protein: some regions)		13–15 months	11–18 years MenC
Liechtenstein	Y				12–15 months	11–15 years MenC
Luxembourg	Y				13 months	
Netherlands	Y				14 months	
Poland	Y			2–6 months	From 6 months	
Portugal	Y				12 months	
Spain	Y			2 months	12 months	12 years MenC
U.K.	Y	Y	Y	3 months (MenC) 2, 4 months (MenB from Sept 2015)	12–13 months (MenB & C)	14–15 years MenC (MenACWY from Aug 2015)
U.S.		Y				11–12 and 16 years
Canada	Y	Y			12 months	12 years
Australia	Y	Y			12 months	
Argentina		Y		2, 4 months	12 months	
Brazil	Y			3, 5 months	12–15 months	
Cuba			Y (OMV)	3, 5 months		
Chile		Y			12 months (MenACWY)	

OMV: outer membrane vesicle vaccine. The Cuban vaccine (VA-MENGOC-BC) is a serogroup B OMV plus a serogroup C polysaccharide vaccine. MenACWY-PS: quadrivalent polysaccharide vaccine.
Targeted strategies of at-risk groups are not presented here.
[a]Czech Republic, MenB 3 priming + booster doses in infancy, 2 doses in 6-month to 2-year-olds, 2 doses in 2- to 10-year-olds, 2 doses in 13- to 15-year-olds.

(Table 4). A single dose administered to toddlers is less costly and induces a somewhat longer lasting immune response, but has little or no impact on the burden of IMD in infants. Infant and toddler immunization without catch-up vaccination of older age groups does not by itself induce herd protection: this outcome is expected given that carriage and transmission are not sufficiently impacted.

Catch-up campaigns

Catch-up campaigns are 'one-time' activities where wider age ranges (including adolescents and young adults) are offered the vaccine, generally at the time of introduction of a new vaccine. Catch-up campaigns using MCC vaccines were originally conducted to provide rapid protection to age groups at risk of IMD during periods of high incidence; for example, during outbreaks in the U.K. and in the Netherlands [17,44]. An unexpected and early benefit of the U.K. catch-up campaign which targeted children and adolescents to age 18 years was marked decreases in overall IMD rates, consistent with the onset of herd protection very soon after commencement of the program (Figure 2). Similar results were observed in the Netherlands where a single MCC dose was administered to toddlers at age 14 months, with catch-up to age 18 years (Figure 2), and subsequently in countries/regions where high coverage of the catch-up population (adolescents and young adults) was achieved [16,18]. The success of catch-up campaigns is dependent on achieving high enough coverage in adolescents and young adults to interrupt carriage and transmission. This is illustrated by the experience in Spain, where a catch-up program into adolescence was not universally implemented, and resulted in lower herd protection than observed in the U.K. or the Netherlands [11]. The initial dramatic reductions in cases achieved by catch-up campaigns may not be long-lasting, particularly as any indirect benefits initially induced will wane over time as new cohorts of adolescents are left unvaccinated in the absence of a routine schedule. In addition, catch-up campaigns have an immediate and significant budgetary impact (Table 4).

Routine adolescent immunization

To date, adolescents have been immunized in the context of wider-ranging catch-up campaigns, where their specific contribution to herd protection is difficult to

Table 4. Vaccination strategies targeting meningococcal disease.

Strategy	Advantages	Disadvantages
Infant vaccination	• Early, direct protection of high incidence age group • High coverage achievable if linked to other routine immunizations	• Low immunogenicity and multiple doses needed • Rapid waning of immunity • Very young (unvaccinated/partially vaccinated) infants not covered • High costs (2 + 1 schedule) • Low impact on herd protection without catch-up
Toddler vaccination	• Less doses needed • Better immune response compared to infants • Relatively early protection • Lower costs • High coverage achievable if linked to other routine immunizations	• No direct protection of infants • Low impact on herd protection without catch-up • Rapid waning of immunity
Catch-up vaccination	• Immediate and substantial achievement of herd protection • Direct protection of vaccinated cohorts • Protection of unvaccinated age groups	• High cost in the beginning (budget impact) • High coverage necessary for success (organizational challenge)
Adolescent vaccination	• Direct protection of at-risk group • Addressing age group with highest carriage • High impact on herd protection • Lower costs (less doses)	• High coverage difficult to achieve

determine. Several countries have added a dose of meningococcal vaccine during adolescence to existing infant/toddler primary vaccination schedules in response to data showing that vaccine effectiveness wanes rapidly after immunization during early childhood, and that circulating antibodies are necessary for protection against IMD (Table 3) [79,80]. It is too early to determine the impact of these changes on the overall disease burden (Table 4).

Finally, adolescents may be immunized as a standalone strategy, as currently recommended in the U.S. Recommendations for vaccination with MenACWY in the U.S. were extended to include all adolescents from 2007 [3]. MenACWY vaccine uptake was slow, reaching only 40% by 2008 and approximately 50% by 2009, with no herd protection demonstrated [3,81]. A booster adolescent dose was recommended in 2010 due to evidence of waning immunity and concerns about ongoing protection [1,82]. By 2013 coverage of at least one dose of MenACWY in adolescents was approximately 75% without evidence of herd protection to date [3,81]. The potential contribution of the type of vaccine used in the U.S. on effectiveness is not known, and effectiveness data now that coverage has increased have yet to be generated. The incidence of IMD in the U.S. is currently very low, and evidence to demonstrate herd protection based on a reduction in IMD cases in unvaccinated groups is therefore much more challenging.

In response to evidence of waning immunity to MenC in adolescents [83], in 2013 the U.K. moved one dose of MCC from infants to adolescents 14–15 years of age [84]. In a more recent development in response to an increase in severe disease due to an epidemic serogroup W clone in England and Wales, the U.K. Joint Committee on Vaccination and Immunisation recommends adolescent vaccination with MenACWY-TT to commence in August 2015 [8]. This program will target all 13- to 18-year-olds over the next 2 years. One of the stated objectives of the program is the induction of herd protection with benefits expected to be extended to other age groups [8]. This is the first time a nationwide adolescent-only immunization campaign has been implemented to control meningococcal disease. It is possible that infant immunization with 4CMenB, implemented in 2015, may also impact carriage and disease caused by serogroup W. However, given current knowledge this remains theoretical. The impact of the MenACWY campaign on serogroup W epidemiology in the U.K. will provide important information on the outcomes possible using an adolescent-only vaccination strategy.

Targeted strategies

Targeted vaccination strategies include vaccination of individuals with underlying medical conditions that place them at increased risk of IMD, or vaccination of specific populations during an outbreak, for example college students. Both of these strategies are currently in use in several countries, such as the U.S. [85,86]. While possibly successful in containing a local outbreak, targeted strategies have limited impact outside of the vaccinated individual, and are unlikely to be cost-effective in areas where incidence is low (Table 4) [87,88].

Hajj pilgrims

There is strong evidence that the Hajj is an important transmission opportunity for the meningococcus.

Pilgrims are more likely to return as carriers and disseminate the meningococcus in their local communities. There is evidence that this was the basis for wider global spread of MenW in 2000–2001 [89]. Hajj pilgrims reflect a large annual group requiring vaccination with a MenACWY vaccine, and while MenACWY polysaccharide vaccines provide a cheaper option, use of MenACWY conjugate vaccines for Hajjis merits consideration in view of the inability of polysaccharide vaccines to prevent carriage acquisition.

The case for vaccinating adolescents

While it was expected that like PCVs and Hib vaccines, meningococcal conjugate vaccines might induce herd protection, studies supporting this only became available after licensure, and were a result of catch-up campaigns that included adolescents and young adults. Sixteen years of experience using meningococcal conjugate vaccines have led to greater understanding about the importance of interrupting carriage and transmission in achieving herd protection. Based on this information, arguments can be made for routine immunization of all adolescents in countries wishing to maximize control of IMD.

The case for vaccinating adolescents rests on three principles: (1) in countries with existing infant or toddler vaccination programs there is a need for a booster dose to counter waning immunity after vaccination in early childhood, (2) the observation that herd protection may be best achieved with high vaccine coverage in adolescents/young adults, the age groups with the highest carriage rates, and (3) health economic considerations.

In regions where substantial herd protection effects were achieved (U.K., the Netherlands, Quebec, parts of Spain, Australia), catch-up strategies were implemented that included all individuals until 18–20 years of age. These countries and others, such as Austria [90], have since adopted a dual strategy of infant and/or toddler vaccination with a booster dose administered during adolescence. These decisions have been based on evidence suggesting that infant vaccination, or a single toddler dose, is not sufficient for long-term protection, as well as the expectation that adolescent vaccination will maintain herd immunity induced by catch-up campaigns [91,92]. It is not yet known whether herd protection can be achieved by adolescent vaccination alone, since in the only country to implement this strategy (U.S.), herd protection has not been observed to date; possibly due to low coverage or the low incidence of the disease in the U.S. [1].

Modeling studies conducted in the context of evaluating cost–effectiveness show the greatest number of cases prevented when an infant or toddler dose is combined with an adolescent dose (Table 5) [93–96]. While these studies differ in their underlying assumptions, reductions in IMD cases are predicted to be highest when herd protection is included in the model, and when the dose administered in adolescence offers broader protection (i.e. MenACWY rather than MCC).

Unanswered questions

Information about the duration of protection induced by meningococcal vaccination during adolescence, the impact on serogroup-specific carriage and on mechanisms of carriage and genetic exchange, the need for additional booster dose, and the optimal choice of vaccine remains incomplete. Vaccine choice should reflect local epidemiology, but increased protection and broader impacts on carriage using vaccines addressing A, B, C, W, Y serogroups may offset the increased costs associated with a multivalent vaccine. Modeling studies suggest that the effect of vaccination on carriage may persist for at least several years [97]. However, questions still remain as to the need for booster doses to provide a long-term impact on carriage.

The new MenB vaccines are faced with the same questions that confronted MCC vaccines when they were first licensed in 1999; data are currently lacking about efficacy, cross-protection, impact on carriage, and long-term protection at different ages, all of which influence schedule choice. As the concept of meningococcal protein vaccines is different from that of the established conjugate vaccines, it is not yet known whether learning from conjugates will be able to be directly transferred to protein vaccines. Preliminary evidence suggests that protein vaccines may show some advantages in terms of cross-protection for other serogroups, but may be inferior with regard to their impact on carriage. However, these initial findings have yet to be confirmed. Models to assess potential benefits and cost–effectiveness of 4CMenB have used data from experience with conjugate vaccines (Table 5), but it is too soon to know if these assumptions are valid.

Challenges to vaccinating adolescents

Compared with infants and young children, adolescents infrequently access health-care services and present fewer opportunities for preventative health

Table 5. Modeling results of meningococcal vaccine effectiveness under different schedules.

	U.S. [94]	U.S. [95]			Canada [96]			U.K. [93]		
Model	Monte Carlo	Cohort simulation			Markov-like			Dynamic transmission		
Incidence data	ABC, 1991–2002	ABC, 1993–2002			Canadian surveillance data for 1995–2001			Hospital episode statistics 2005–2012		
Time frame	10 years	(1) years			–			100 years		
Reference	No vaccination	No vaccination			No vaccination			No vaccination		
Vaccine efficacy (VE)	93% (78–98)	91.5% (65–98)	92% (65–98)	93% (78–98)	98.3% (96.5–100) at 1 year dose, 97.6 % (93.0–99.7) at 12 year dose			95%		
Herd protection	Age-specific U.K. data	None	None	None	67% (52–77)			30% efficacy against carriage		
Duration of protection	10 years	22 years (25% decrease in VE after 10 years)			Decrease in VE of 9.6% per year after toddler dose and 3.3%/1.7% per year after adolescent dose/booster			18 months after priming, 36 months after booster, 120 months in adolescents		
Population	11- to17-year-olds	Birth cohort	Birth cohort	11-year-old cohort	Continuous population			Birth cohort		
Schedule	11 years	2, 4, 6 months	12 months	11-year-olds	1 year	1 year + 12 years	1 year + 12 years	2, 3, 4, 12 months	2, 3, 4, 12 months + 13 years	13 years (+catch-up)
Catch-up	11–17 years	None	None	None	None	None	None	None	None	14–17 years
Vaccine	MenACWY	MenACWY	MenACWY	MenACWY	MCC	MCC/MCC	MCC/MenACWY	4CMenB	4CMenB	4CMenB
Coverage	70% (66–95)	77 % (34–90)	91% (54–98)	71% (16–95%)	90%	90%/70%	90%/70%	88% strain coverage. Age specific uptake		
N (%) cases prevented										
With herd protection	825 (48%) annually				1.6 (28%)	3.9 (68%)	4.8 (85%)	52,152 (26.3% in 5 years)	91,304 (48.8% in 10 years, 59.7% in 20 years)	64,667
Without herd protection	156 (9%) annually	447 (41%) over 22 years	385 (35%) over 22 years	270 (45%) over 22 years	1	1.7	2.0	–	–	–

ABC: Active Bacterial Core Surveillance; MCC: meningococcal serogroup C conjugate vaccine.

interventions such as vaccination [98]. Vaccination of adolescents also presents challenges in communication, providing information, and achieving consent from the subject, as well as their parents/guardians who may not be present at the time of the vaccination contact [98,99].

On top of these issues are those related to health-care providers who need to be kept abreast of updated immunization strategies, and with whom adolescent vaccination may receive less priority than vaccination of younger pediatric age groups [99]. Thus, while adolescent vaccination has been recognized as a significant opportunity for prevention of important diseases such as human papillomavirus (HPV) infection, pertussis, and meningococcal disease [100], levels of vaccine coverage in the adolescent population are often suboptimal compared to younger age groups [81,101]. Experience with adolescent vaccination programs is growing, with progress being made in addressing many of the attendant hurdles. Strategies that have been shown to improve coverage include immunization recall notices in schools with existing health-care provision services, and mandated (legislated) vaccination for school attendance [102,103]. Coverage of the pertussis booster dose among adolescents 13–17 years of age in the U.S. was 86% in 2013 [81]. School-based immunization programs have proved highly successful in the U.K., where sustained high coverage of HPV vaccine has been achieved (91.1%, 89.8%, and 86.7% for the first, second, and third doses, respectively in 2013–2014) [104].

While a secondary IMD peak occurs during adolescence, IMD is rare and most of the benefit from vaccinating adolescents comes from herd effects conferred on other age groups. Adolescents and their parents might need to be better educated about the benefits of vaccination, although the arguments used may need to be different for both groups. However, since there are strong emotions around IMD, this may be less difficult than for other adolescent vaccines such as HPV, where the perceived benefits are more distant. Experience during catch-up programs, for example in the U.K. and the Netherlands, that achieve high coverage (>85% and 94%, respectively), suggests that acceptance of meningococcal vaccines for adolescents is very high [17,44].

Serogroup replacement is an important public health concern associated with conjugate vaccines, with clear evidence of vaccine-driven replacement events associated with PCVs. A strong impact on carriage by conjugate vaccines leading to replacement by virulent strains can put the short-term benefit of a vaccination program into question. Currently available meningococcal conjugate vaccines are directed against only a selected number of the range of capsular serogroups that exist. The potential for vaccine-induced serogroup replacement to occur, whereby other serogroups subsequently fill the ecological niche vacated by vaccine targeted serogroups, is not known. Since asymptomatic carriage in the nasopharynx is the natural state of the meningococcus, this becomes particularly relevant for vaccination strategies that target adolescents where carriage is highest. To date, there is no evidence that selective vaccination against certain meningococcal serogroups has led to a clinically significant increase in disease caused by non-vaccine serogroups, although the evidence is limited [105–107]. Better knowledge of the dynamics of carriage and the adolescent habitat is needed to understand the potential impact of widespread use of meningococcal vaccines in adolescents on serogroup replacement.

The extent to which MenB vaccines may impact MenB carriage will determine their potential to provide herd protection and to allow serogroup replacement. This is particularly relevant as there is evidence that MenB may be carried at a higher prevalence than other serogroups [29,69]. Furthermore, protein-based vaccines targeting MenB also contain antigens common to other capsular serogroups, so may additionally reduce carriage of non-B strains, which could potentially widen their overall impact on disease control [70].

Expert commentary

Most meningococcal conjugate vaccine policies try to directly target the age group in which IMD is most frequent. However, meningococcal transmission/carriage occurs in a different age group to that in which the majority of the disease burden occurs. This is unlike patterns of transmission and disease observed for other childhood pathogens such as Hib and pneumococcus. Thus, while vaccinating the age group with the highest disease burden (infants and young children) is a valid approach, interruption of carriage and transmission by vaccinating the population that acts as the reservoir for infection (adolescents and young adults) may have a more profound and long-lasting impact.

Evidence and consensus opinion supporting reduction of carriage/transmission of the meningococcus in adolescents is only now becoming available. Nevertheless, compelling evidence may be needed by policy makers to show that meningococcal vaccines will induce herd protection before going ahead and investing in routinely vaccinating adolescents. Vaccination programs need to weigh up the objectives of individual protection versus benefits to the wider community. Vaccine policies directed at extending protection

beyond the vaccinated individual are not novel and are currently used in other contexts: prevention of infant pertussis by maternal vaccination, 'cocooning' (vaccinating parents and close contacts), or prevention of influenza transmission by vaccinating children against influenza. In order to identify such indirect, effective and strategic vaccination programs, the pattern of carriage and transmission of a pathogen has to be well investigated and understood within a population. Studies are still necessary to improve this understanding for many diseases and populations.

Vaccinating adolescents against IMD potentially achieves the dual goals of direct protection of an age group at relatively high risk for IMD and potentially maximizing herd protection. This occurs through a reduction in carriage acquisition, resulting in protection to all age groups through interruption of transmission. The extent of the disruption of the natural habitat of the meningococcus by vaccination and the potential effects on cycles of carriage, transmission, and genetic exchange are not exactly known, but assumptions can be made for modeling purposes.

Adolescent vaccination programs are not without challenges, but high coverage has been achieved in some settings for HPV vaccination, and lessons learnt from experience with HPV vaccine programs can be applied to meningococcal vaccines. These might include mandated vaccination for school attendance, targeted school-based immunization programs, and improved documentation of vaccination in this age group, with use of recall systems.

Countries need to determine which vaccine is most appropriate to address the IMD burden in their local setting. Quadrivalent vaccines afford broader protection than MCC vaccines, and have been shown to extend the effectiveness of the adolescent dose (Table 5). Current knowledge suggests that an adolescent dose following infant or toddler vaccination may provide good disease control. MenB vaccines are an important new development but their effectiveness (both direct and indirect) and their impact on MenB carriage and carriage of other serogroups is not clear. A MenB vaccine with very little or no effect on carriage and no indirect effects would impact cost considerations and be used differently than conjugate vaccines. Under such a scenario, differential use in terms of direct or herd protection of conjugate vaccines and protein vaccines may be a valid option to achieve meningococcal disease control.

Five-year view

Vaccination schedules for meningococcal vaccines have evolved considerably since the introduction of the first conjugate vaccines in 1999. This is likely to continue as individual countries see changes in the epidemiology of IMD in response to vaccination or shifts in prevailing serogroups, and in response to availability of new vaccines. The next five years will see the first experience with use of protein-based MenB vaccines, and importantly, studies to document their effects on carriage are likely to provide conclusive information that will have a major impact on how these vaccines will be used. Further development of meningococcal combination vaccines targeting all relevant serogroups may facilitate meningococcal prevention programs in the future. The importance of the adolescent dose is anticipated to be increasingly appreciated, with a growing number of countries adopting this schedule as immunity achieved in infant/toddler programs wanes, and as direct and herd protection effects decrease. Demonstration of continuing herd protection effects in countries with an adolescent booster schedule is likely to occur, giving confidence in the pivotal role of the adolescent in IMD epidemiology. Results of the adolescent MenACWY program in the U.K. in controlling serogroup W IMD will provide important information. Experience with achieving high adolescent vaccination coverage will increase, with improved resources to meet this challenge.

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Key issues

- Adolescents are the major platform in the epidemiology of meningococcal disease, having high carriage rates, high rates of transmission, and an important disease burden.
- A substantial proportion of the impact of meningococcal conjugate vaccines arises because of herd effects, whereby disease is also reduced in unvaccinated age groups.
- Herd effects are the result of reduced transmission of the bacteria, and are greatest when vaccination protects against acquisition of new carriage in populations that usually harbor the bacterium, and that are key in terms of transmission.
- Herd effects have been observed most obviously after catch-up campaigns, when high meningococcal vaccine coverage is achieved within a short time frame and among adolescents in whom carriage is most common.
- Successful vaccination programs have to be based on the understanding of carriage, mechanisms of transmission, and infection of a disease within a population.
- Targeted vaccination of age groups with a high burden of clinical disease is traditionally the primary strategy used to control meningococcal disease. However, targeted vaccination of adolescents could have wider and longer lasting effects by reducing meningococcal transmission and increasing herd protection.
- Economic analyses estimate adolescent vaccination to be a more cost-effective option than other strategies such as direct protection of infants.
- The impact of new MenB protein vaccines on carriage and transmission, duration of protection, and efficacy to prevent disease is not clear, but this information is crucial for the strategy under which these vaccines should be used in the future.
- Adolescent vaccination programs are not without challenges, but important lessons have been learned during implementation of other vaccine programs in this age group.

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•• of considerable interest

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