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Importance of circulating antibodies in protection against meningococcal disease

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Abbreviations: AAP, American Academy of Pediatrics; ACIP, Advisory Committee on Immunization Practices; CDC, Centers for Disease Control and Prevention; CI, confidence interval; Hib, *Haemophilus influenzae* type b; hSBA, serum bactericidal assay using human complement; MCC, meningococcal serogroup C conjugate; MCV4-DT, meningococcal diphtheria toxoid conjugate vaccine; MenC, meningococcal C conjugate; *N. meningitidis*, *Neisseria meningitidis*; rSBA, serum bactericidal assay using rabbit complement

Neisseria meningitidis infection results in life-threatening illnesses, including bacteremia, sepsis and meningitis. Early diagnosis and treatment are a challenge due to rapid disease progression, resulting in high mortality and morbidity in survivors. Disease can occur in healthy individuals, however, risk of infection is higher in patients with certain risk factors. *N. meningitidis* carriage and case-fatality rates are high in adolescents and young adults. The absolute incidence of meningococcal disease has decreased partially due to increasing meningococcal vaccination rates. Maintaining protective levels of circulating antibodies by vaccination is necessary for clinical protection against disease. The Centers for Disease Control and Prevention Advisory Committee on Immunization Practices guidelines recommend vaccination for all individuals aged 11 through 12 y, followed by a booster dose at age 16 y for maintenance of protective antibody levels throughout the high-risk years. Despite these guidelines, many adolescents remain unvaccinated and susceptible to infection and disease.

Introduction

Meningococcal infection, caused by the gram-negative aerobic bacteria *N. meningitidis*, can result in severe disease, including meningitis and sepsis, and death. The organism is spread through respiratory droplets and secretions. Transmission often results in nasopharyngeal colonization, but fortunately only a small percentage of colonized individuals develop invasive disease.[1] Colonized individuals serve as a reservoir for transmission, and eradication or prevention of the carrier state may be useful in reducing disease burden in a community. Prevalence of asymptomatic carriage in the general population varies depending on the region and/or group studied.[2] Results from a meta-analysis found that asymptomatic meningococcal carriage rates were highest in adolescents and young adults, occurring in approximately 24% of people in this group. In infants, this carriage rate was much lower, at an estimated 4.5%, and in adults aged ≥ 50 y, carriage rates were estimated to be around 8% (**Fig. 1**).[3] Carriage prevalence does not reliably predict disease risk. Virulence of meningococcal strain, host health and immune response, as well as environmental factors, all influence susceptibility to disease.[1]

Invasive meningococcal disease occurs when bacteria cross the mucosal surfaces (possibly due to irritated or damaged mucosal epithelium) and enter the bloodstream. Exposure to tobacco smoke or other irritants as well as concomitant viral respiratory infections or other similar processes may damage the mucosal epithelium and increase risk for invasive meningococcal disease.[4]

Adolescents appear to be at high risk for *N. meningitidis* colonization as well as invasive infection and death due to infection. This article discusses the importance of circulating antibodies to protect against invasive meningococcal disease.

Disease Burden and Clinical Features

Meningococcal disease is characterized by severe and rapidly progressing symptoms, often resulting in death or serious permanent sequelae, including limb amputations.[5] Case-fatality rates for meningococcal disease can be as high as 14%, even with prompt and appropriate medical treatment.[6,7] Because case-fatality rates increase with age, adolescents and young adults have higher rates than infants and toddlers, and the highest case-fatality rates occur in adults aged ≥ 65 y (**Fig. 2**).[7] In the United States (US) between 1998 and 2007, 337 of 1,525 total meningococcal cases and 41 of 189 meningococcal deaths were among adolescents and young adults (aged 14–24 y), resulting in a case fatality rate of 12%.

Infection due to *N. meningitidis* can cause a range of clinical presentations, most often as meningococcal meningitis and sepsis, but it can also present as pneumonia, conjunctivitis, arthritis or pericarditis.[8-10] Meningitis is an infection of the meninges

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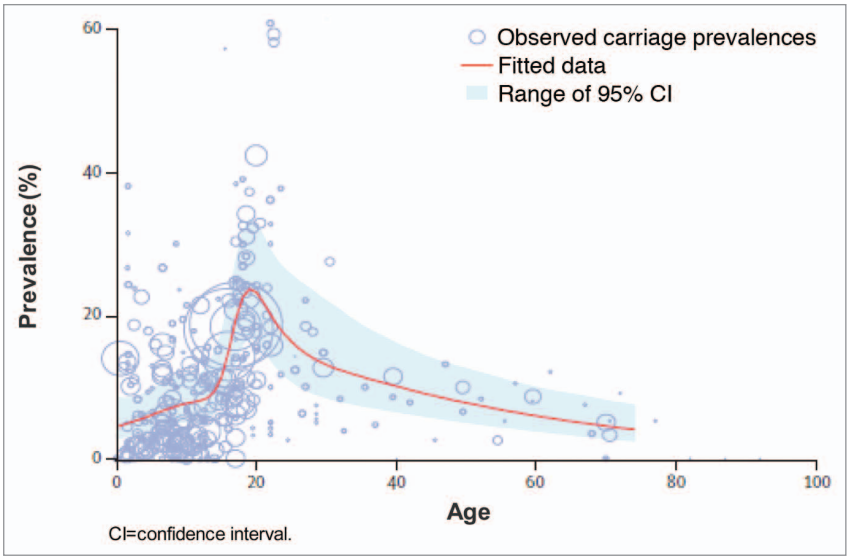

Figure 1. *Neisseria meningitidis* carriage rates by age group.[3] Reprinted from *Lancet Infect Dis.* 10(12), Christensen H, May M, Bowen L, Hickman M, Trotter C. Meningococcal carriage by age: a systemic review and meta-analysis. 853-861, Copyright (2010), with permission from Elsevier.

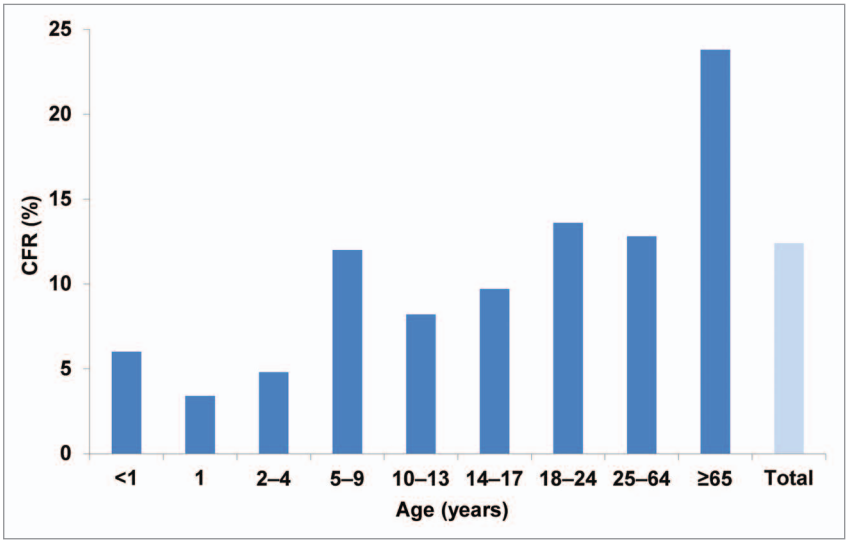

Figure 2. US case-fatality rates associated with meningococcal disease by age group, 1998–2007.[7]

surrounding the brain and spinal cord.[11] Meningococcal septicemia (meningococcemia) occurs when pathogenic organisms or their toxins accumulate in the bloodstream, and may be accompanied by disseminated intravascular coagulation, causing ischemic tissue damage and bleeding.[9,11,12] These conditions can be life-threatening and require immediate medical care, however, early diagnosis and treatment can be challenging, due to the nonspecific nature of the initial symptoms, which may appear similar to more common self-limiting viral infections.[13] Symptoms specific for meningococcal meningitis or septicemia, such as leg pain, abnormal skin color, photophobia and stiff neck, may not appear until 5 to 18 h after the onset of early-stage symptoms.[5] Nonspecific symptoms during the early stage of infection (4–8 h) include irritability, headache, fever and loss of appetite. Symptoms typically progress rapidly over the next several hours to include hemorrhagic rash, altered mental state, loss of consciousness and meningismus. Meningismus appears to be more common and to occur earlier in older adolescents (aged 15–16 y) as compared with younger patients.[5] Death can result within 24 to 48 h after the initial onset of symptoms.[5] Timely recognition of early symptoms of meningococcal disease is critical to insure early diagnosis and treatment of this life-threatening infection.

Survivors of meningococcal disease are often left with substantial morbidity and permanent sequelae, including neurologic damage, hearing loss, renal failure or limb amputation.[6,9,14] Long-term management of the disease and these sequelae result in substantial health care costs.[15]

Risk Factors

Adolescents and young adults often engage in many of the behaviors associated with increased risk for acquiring and transmitting meningococcal disease—including active or passive smoking, patronizing bars and nightclubs, drinking alcohol, intimate personal contact (e.g., kissing), and residing in crowded living conditions such as dormitories and barracks.[2,14,16]

The rate of meningococcal disease among US college freshmen living in dormitories during the 1998 to 1999 school year was 5.1 cases per 100,000 population, higher than that seen for any age group other than children aged < 2 y.[14,17] As noted above, meningococcal carriage is highest in adolescents and young adults (24%).[3] Military recruits, many of whom are in the adolescent/young adult age group, are also at increased risk for meningococcal disease due to crowded living conditions and exposure to new meningococcal strains.[2] Carriage rates in military recruits have been reported from 36% to 71%.[16]

Other risk factors for meningococcal disease that could apply to any age group include traveling to or residing in countries where *N. meningitidis* is hyperendemic or epidemic, having a terminal complement deficiency, and having anatomic or functional asplenia.[2,18-21]

Epidemiology

Considerable differences in disease incidence and serogroup distribution are observed across geographic regions, over time, and by individual age groups.[22] The reported incidence of meningococcal disease in the US from 1999 through 2009 ranged from 0.32 to 0.92 per 100,000, with the highest rate of disease

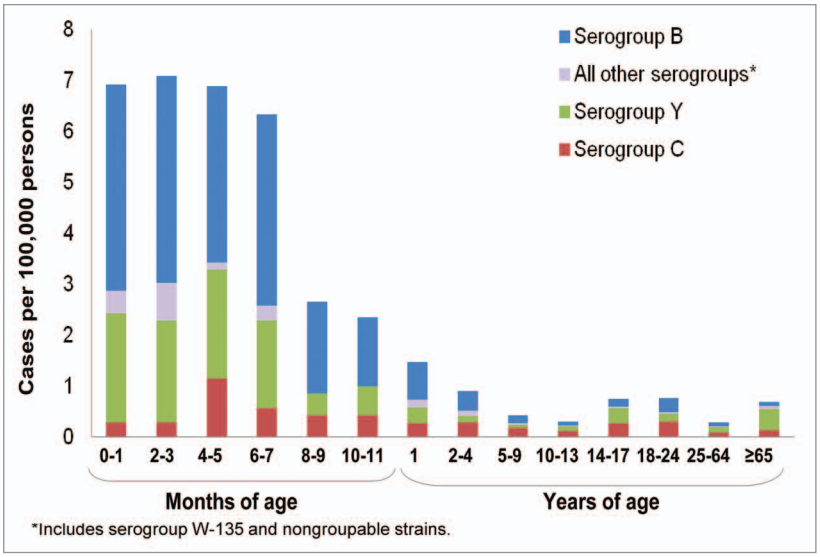

Figure 3. Incidence of meningococcal disease by age group in the US, 1998–2007.[7]

in 1999.[23] Approximately 1,000 to 2,700 cases of meningococcal disease per year were reported in the US during that time.[23] In the European Union, 4,637 cases were reported in 2009: the reported incidence of meningococcal disease ranged from 0.3 cases per 100,000 population in Italy to 3.37 cases per 100,000 population in Ireland.[24]

The burden of meningococcal disease is highest in infants, adolescents and elderly adults. In the US, the incidence of meningococcal disease was highest in children aged < 5 y, with additional peaks occurring in adolescents and young adults aged 14 through 24 y and those aged 65 y and older (**Fig. 3**).[7] Data from the European Union show that from 1999 to 2006 there were more than 14,000 cases of meningococcal disease in infants and children aged < 5 y and more than 5,000 cases in adolescents aged 15 to 19 y.[25]

Although 13 serogroups of *N. meningitidis* have been identified on the basis of the bacterial polysaccharide capsule, 5 serogroups, A, B, C, W-135 and Y, cause the vast majority of meningococcal disease globally.[22] In the US, serogroups B, C and Y currently cause most meningococcal disease, and serogroup A is uncommon (**Fig. 4**).[26] Serogroups B and C are also responsible for the majority of cases in Central and South America, as well as in Europe.[9] In Africa and Asia, serogroups A and C are predominant,[9] whereas serogroup X, which is uncommon in the rest of the world, has exhibited epidemic potential in sub-Saharan Africa.[22]

Changes in distribution of disease-causing serogroups within regions is unpredictable and can occur over relatively short periods of time.[7] Globally, serogroup W-135 was a rare cause of invasive disease until outbreaks during the Hajj pilgrimage in 2000. At that time, pilgrims returning to their home countries spread disease caused by serogroup W-135 to Africa, Europe, Asia, Saudi Arabia and North America.[22,27] Serogroup B was the most common serogroup in the US from 2000 through 2005,[26] however, by 2009, the most common serogroup was serogroup Y (**Fig. 4**).[26,28] Brazil has seen a dramatic increase in the proportion of disease caused by serogroup C; in 1993, serogroup C caused 31% of meningococcal cases, but by 2005 it was responsible for 71% of cases.[29,30] The opposite occurred in the UK between 1999 and 2001, when the proportion of disease caused by serogroup C declined 87%—from 38% to 16%.[31]

Serogroup distribution also varies among age groups. In the US, serogroup B currently causes the majority of cases in infants aged < 1 y, while serogroups C, Y and W-135 are responsible for 75% of cases in persons aged ≥ 11 y.[7,14] Similarly, in South Africa in 2001 and 2002, serogroup B caused the majority of meningococcal cases in infants aged < 1 y and serogroup A was predominant in adolescents and young adults aged 15 through 24 y.[32] Serogroup B causes the majority of meningococcal disease in Europe across all age groups, however, the proportion of disease due to serogroup B is lower in adolescents than in young children and infants.[24]

Dynamic serogroup changes may occur as a result of multiple factors, including exposure to other serogroup strains during international travel (subsequently introducing that strain to other areas), capsular switching, and other genetic modifications.[33] The use of multivalent vaccines such as conjugate vaccines against serogroups A, C, W-135 and Y has the potential to reduce the incidence of infection across a broad range of serogroups.

Prevention of Meningococcal Disease

People who are in close contact with individuals who have meningococcal disease are at risk of exposure and colonization by the organism, and are at higher than average risk of developing invasive meningococcal disease. Identifying close contacts of patients diagnosed with meningococcal disease and offering prompt and effective antimicrobial chemoprophylaxis has been a successful strategy in reducing secondary cases of disease, although this approach is labor intensive and costly. In the US, the agents recommended as prophylaxis for exposed individuals include rifampin, ceftriaxone and ciprofloxacin.[14] Antibiotic resistance has been observed, raising the possibility of antibiotic failure. Three cases of ciprofloxacin-resistant serogroup B *N. meningitidis* were identified in the US between 2007 and 2008.[34] Resistance was due to both point mutations and horizontal gene transfer from a resistant strain of *Neisseria lactamica* (a commensal of the human upper respiratory tract that is rarely pathogenic).[34] It is unknown whether ciprofloxacin resistance will increase over time.

Immunization of at-risk populations provides another line of defense, and is encouraged and supported by the CDC. In a recent CDC report, 63% of adolescents aged 13 through 17 y received quadrivalent meningococcal conjugate or meningococcal-unknown type vaccine in 2010, up from 54% in 2009, 42% in 2008 and 32% in 2007.[35-37] Increased vaccination rates

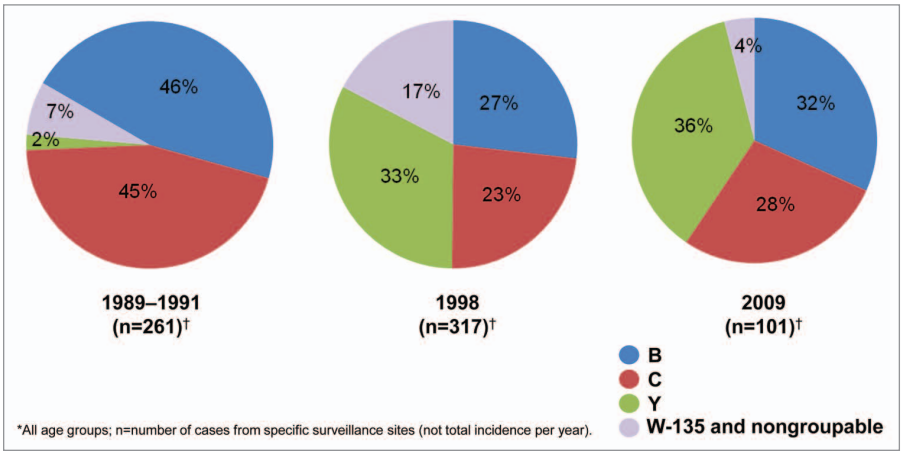

Figure 4. Changing serogroup distribution in the US, 1989–2009.[26,28]

in adolescents and young adults not only may protect the vaccine recipient against meningococcal disease, but may also reduce the carrier-state reservoir from which infection is transmitted to others.

Importance of Circulating Antibodies

After initial vaccination, circulating functional antibody levels naturally begin to decline; if further booster vaccination does not occur, there may be a waning of clinical protection over time.[33] Long-term protection after immunization depends on the maintenance of three mechanisms: memory response, the persistence of functional antibodies and herd protection.[38]

If immune memory is functioning properly, it will mount a defense against a recognized antigen with antibodies and T cells in 2 to 7 d.[39] In the interim, the host relies upon the innate immune response to combat the infection.

While some diseases, such as hepatitis B, do not require high circulating antibodies because of their slow pathogenesis (average incubation of 90 d),[40] innate immunity and high levels of protective circulating bactericidal antibodies are the primary immune defenses against rapidly progressing diseases such as those caused by *N. meningitidis*.[38] When the immune system encounters invasive meningococcal infection, the stimulated response from memory B cells may not occur quickly enough because protection resulting from antibodies raised by B-cell immune memory takes up to 5 d, and the incubation period of meningococcal disease is 3 to 4 d (**Fig. 5**).[18,39] Thus, maintaining the presence of circulating functional antibodies against *N. meningitidis* may be necessary for clinical protection against disease.[41]

A correlate of protection against meningococcal disease was established through seminal work conducted by Goldschneider and colleagues in the 1960s.[42] The ability of a meningococcal vaccine to induce antimeningococcal bactericidal antibodies is measured by an SBA using human (h) or rabbit (r) serum as the complement source in the assay. In general, an hSBA titer of ≥ 1:4 or ≥ 1:8 and an rSBA titer of ≥ 1:128 are accepted as protective thresholds.[43-45] The standard measure of meningococcal vaccine immunogenicity for regulatory authorities in the US is now hSBA; and both hSBA and rSBA have been used by regulatory bodies globally.

As host defenses driven by immunologic memory can lag behind the pace of infection, the best defense against rapidly progressing encapsulated bacteria, such as Hib and *N. meningitidis*, is to maintain clinically protective levels of circulating antibodies either directly by vaccination or through a booster dose after initial priming doses.[46,47] For example, despite the presence of demonstrated immune memory, MenC and Hib conjugate vaccine failures have occurred in infants in the UK and Canada.[48,49] Between January 2000 and December 2003, there were 465 confirmed cases of serogroup C meningococcal disease in the UK. Of these, 53 cases occurred in subjects who had received MCC vaccine primary immunization (2–4 mo) without a booster. Vaccine failure was defined as a laboratory confirmed case of meningococcal serogroup C disease occurring ≥ 10 d after the last vaccine dose in the primary series.[48] An anamnestic response was shown in subjects with vaccine failure, suggesting that serogroup C meningococcal disease occurred despite the MCC vaccine priming for immune memory.[48] The presence of circulating antibodies at the time of exposure may therefore be a more appropriate correlate of long-term protection for MCC vaccines than the ability to generate a memory response.[48]

Similarly, in the UK and Ireland from 1992 to 2001, 93 children were diagnosed with invasive Hib disease despite having received 3 doses of Hib conjugate vaccine.[49] During this time an accelerated vaccination schedule was in place, but it lacked requirement of a booster in the second year of life.[49] Higher antibody responses to invasive Hib disease were also observed in the vaccinated children with meningitis, reflecting priming for immunologic memory by the Hib vaccine. Although a majority of children were protected from Hib disease by immunization, the relative roles of immunologic memory and other immune mechanisms in conferring disease protection remain unclear.[49]

The researchers of these studies concluded that the vaccine failures may have resulted from rapid waning of immunity in early childhood after infant vaccinations and a lack or insufficiency in circulating functional antibodies that would have provided long-term protection against the disease. In light of these experiences, the UK began requiring booster doses of Hib and meningococcal vaccines to maintain circulating antibodies at protective levels. Similarly, Canada,[51] Greece, Ireland, Italy, Spain and Portugal[24,52] now recommend booster doses for toddlers in their meningococcal vaccine schedules.

In addition to the natural decay of antibody levels postvaccination, other factors may contribute to immunogenic variation among individuals, potentially leaving a vaccinated person susceptible to disease.[53] These include functional or anatomic asplenia (the spleen traps and disposes of bacteria; without it bacteremia

can result),[21,54] and deficiencies in the terminal common complement pathway.[18,54,55] Immune defects in T-cell responsiveness and immunoglobulin deficiencies may also lead to impaired production of bactericidal antibodies postvaccination.[53,56-58]

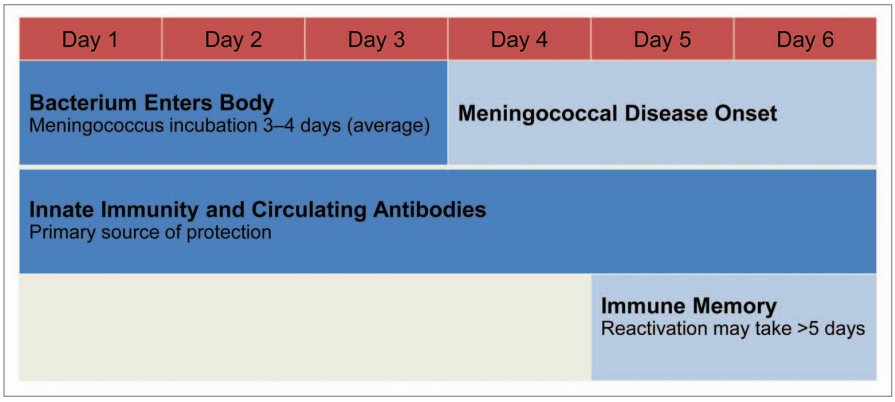

Figure 5. Meningococcal incubation and immune memory reactivation.[18,39,46,50]

Vaccine Strategies

A decrease in the absolute incidence of meningococcal serogroup C disease has occurred due to vaccination and prevention programs in the UK and Canada.[59,60] The MenC conjugate vaccination program introduced in the UK and Wales in 1999 initially provided routine vaccination to the infant population and a catch-up vaccination to everyone aged 1 through 18 y.[61] A year after the introduction of the MenC vaccine campaign in 1999, a survey conducted by the UK Meningococcal Carriage Group found an average 66% decrease in serogroup C carriage in students aged 15 through 17 y.[62] The catch-up MenC vaccine age group was extended in 2002 to include everyone aged ≤ 25 y.[61] By 2009, this approach led to a 99% reduction in the incidence of serogroup C meningococcal disease in individuals aged ≤ 20 y and to a 98.7% reduction for all age groups.[61] This finding shows that catch-up campaigns with conjugate vaccines in groups with high carriage rates, such as adolescents and young adults, can have a dramatic impact on the carriage of meningococci, the benefits of which can lead to herd immunity.[8,63]

Polysaccharide vaccines have shown effectiveness in adolescents and adults. In young children and infants, antibody levels decline swiftly, but detectible antibody levels in young adults have been reported 10 y after initial vaccination.[1,33,64] Unlike conjugate vaccines such as those used in the UK immunization campaign, polysaccharide vaccines do not induce immune memory or booster response (particularly in young children). Additionally, they produce only a short-term, transient effect on nasopharyngeal carriage rates and thus are not expected to reduce transmission or lead to herd immunity.[33,65,66] Repeated immunization with polysaccharide vaccines may lead to hyporesponsiveness, such that antibody levels following subsequent doses are lower than antibody levels following the initial dose.[33,65,67,68] Therefore, meningococcal conjugate vaccines are now being implemented in schedules globally, including in the US.[47]

ACIP and AAP Recommendations in Adolescents

In the US, significant numbers of cases and sporadic outbreaks due to all serogroups continue to cause substantial morbidity and mortality. In 2005, the ACIP recommended routine quadrivalent (serogroups A, C, W-135 and Y) conjugate meningococcal vaccination for youths aged 11 through 12 y.[14] Despite the routine implementation of a meningococcal conjugate vaccine in the adolescent group and an overall decline in the estimated number of meningococcal cases in the US since 2000, the meningococcal disease peak (due to serogroup C and Y infections) in older adolescents and young adults remains.[47]

The CDC's ACIP and the AAP now recommend meningococcal vaccination with a quadrivalent conjugate vaccine at age 11 through 12 y followed by a second dose at age 16.[47,69] This 2-dose vaccine series results in protective antibody levels throughout the period of time that adolescents remain at high risk for meningococcal disease. These recommendations were made based on data which suggested that many adolescents who receive a single dose of vaccine may lose protection after 5 y. A case-controlled study evaluating vaccine effectiveness of MCV4-DT showed that vaccine effectiveness dropped significantly 2 to 5 y after vaccination; the overall vaccine effectiveness in persons vaccinated 0 to 5 y earlier was 78% (95% CI: 29, 93). As length of time from primary vaccination increased, vaccine effectiveness decreased. The vaccine effectiveness for persons vaccinated < 1 y earlier, 1 y earlier and 2 through 5 y earlier was 95% (CI: 10, 100), 91% (CI: 10, 101) and 58% (CI: -72, 89), respectively.[47] In addition, clinical studies have shown waning of antibodies over time. Five years after vaccination with a quadrivalent conjugate vaccine, approximately 50% of adolescents had bactericidal antibody levels protective against meningococcal disease.[47,69] Therefore, persons immunized with a single vaccine dose at age 11 through 12 y become susceptible to infection and disease by age 16, when their risk for meningococcal disease is highest.[47]

The ACIP considered other vaccination strategies, such as delaying the initial single vaccination from age 11 or 12 to age 14 or 15, but concerns surrounding lack of coverage due to decreased likelihood of physician visits by this older age group led to the current recommendation of a booster dose with a quadrivalent meningococcal conjugate vaccine at age 16.[47] The impact of this strategy on the incidence of disease remains to be seen. However, in the same report, the ACIP presented results from an economic analysis that concluded that administering a booster dose is estimated to prevent twice the number of cases and deaths as administering a single dose at age 11 y or age 15 y, with equivalent cost per quality-adjusted life-year.[47]

The characteristics of conjugate vaccines which are believed to be critical in establishing long-term protection against a bacterial pathogen include production of protective circulating antibody,

memory T-cell response and herd immunity.[38,47] Although vaccination primes the immune system, the T-cell memory response which may occur after loss of protective antibody may not progress quickly enough to protect against the rapidly replicating bacteria. Thus, circulating antibodies are critical for protection against meningococcal disease.

Conclusion

In summary, adolescents and young adults are a population at increased risk for meningococcal disease. Waning immunity following a single dose of meningococcal vaccine may not offer sufficient protection and leaves adolescents and young adults at risk for meningococcal disease. Without the presence of circulating antibodies, the immune system's memory response may be too slow to offer protection against the rapid progression of meningococcal disease following infection. The CDC's updated recommendations for meningococcal conjugate vaccination recommends initial vaccination at age 11 through 12 y and a booster at age 16 y. This strategy aims to provide protective circulating antibody throughout the period of high risk.

Disclosure of Potential Conflicts of Interest

K.S.E. has received honoraria from Novartis Vaccines and Diagnostics for lectures and service on an advisory board. B.L.C. has received honoraria and consulting fees from Novartis Vaccines and Diagnostics.

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