Vaccination strategies for the prevention of meningococcal disease

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ABSTRACT
Routine prophylactic vaccination and mass vaccination strategies have been used to control both endemic and epidemic disease caused by Neisseria meningitidis globally. This review discusses real-world examples of these vaccination strategies, their implementation, and outcomes of these efforts, with the overall goal of providing insights on how to achieve optimal control of meningococcal disease through vaccination in varied settings. Tailoring immunization programs to fit the needs of the target population has the potential to optimally reduce disease incidence.

Epidemiology of Neisseria meningitidis

Neisseria meningitidis is a major cause of meningitis and septicaemia globally. Humans are the only known reservoir for the bacteria, which reside primarily in the nasopharynx. Meningococci are transmitted by droplets from the respiratory tract, and infected individuals can transmit the bacteria up to 24 hours after the initiation of antibiotic treatment. Although colonization occurs in ~10% of adults, rates as high as 42% have been observed among adolescents and young adults due to the social behavior of these populations (i.e., kissing, smoking, and alcohol consumption) that predispose them to transmission. Nasopharyngeal colonization usually does not cause disease; however, for reasons that are not completely understood, the bacteria can penetrate the mucosa, enter the bloodstream, and cause invasive meningococcal disease (IMD).

The incidence of IMD is generally low in industrialized countries (approximately ≤5 cases per 100,000 people), especially since the advent of national meningococcal vaccination programs. However, a much higher incidence (up to 1000 cases per 100,000 people) has been observed during epidemics, particularly in countries in the African meningitis belt. Overall, the highest incidence of infection occurs in children ≤4 years of age and adolescents and young adults aged 15 to 24 years. IMD typically carries a 10% to 15% mortality rate, even with appropriate antibiotic treatment. Death can occur within 24 to 48 hours after the onset of symptoms, and survivors often have permanent mental and physical impairments.

N meningitidis strains that cause IMD are encapsulated and categorized into 12 serogroups according to the biochemical composition of the capsular polysaccharide. Six serogroups (A, B, C, W, X, and Y) cause the majority of IMD, with serogroup prevalence varying by geographic location. Globally, serogroup A has been responsible for the greatest incidence of IMD and was the causative agent for epidemics in both industrialized and nonindustrialized countries. In the African meningitis belt, serogroup A has been responsible for a constant, low level of endemic disease interspersed with sporadic epidemics. During epidemics, the annual disease incidence can reach 100 cases per 100,000 population. Within smaller communities, IMD can increase by a factor of 10, peaking at 1000 cases per 100,000 population; historically, such epidemics occur almost every year in one of the meningitis belt countries. In 1996, an epidemic of serogroup A in Nigeria resulted in >100,000 infections and >11,000 deaths. Today, IMD due to serogroup A has virtually disappeared from countries within the meningitis belt due to the use of a monovalent meningococcal serogroup A conjugate vaccine licensed in 2014. With the waning of disease caused by serogroup A, epidemics of serogroup X are increasing in many African countries including Niger, Ghana, Kenya, Togo, and Burkina Faso. Serogroup C epidemics are also increasing in the region, as evidenced by the recent increase in IMD due to serogroup C in Niger in 2015 that resulted in 5855 cases and 406 deaths.

Serogroup W has also been implicated in large meningococcal epidemics in Africa. Specifically, during an epidemic in The Gambia in 2012, an incidence rate of 1470 cases of serogroup W per 100,000 population was observed in children <12 months of age. In Australia, the percentage of meningitis cases due to serogroup W increased from 4% to 30% during the 2-year interval between 2013 and 2015. Epidemics of serogroup W have been reported in Mecca among pilgrims attending the annual Hajj and in the native countries of pilgrims returning from the Hajj. Among serogroup W isolates, the hypervirulent sequence type 11 (ST11) clone, in particular,
has been increasing in prevalence since the 2000 Hajj, with disease incidence noted in many regions, including Latin America, Australia, and Canada. The emergence of serogroup W cases in South America, particularly in the southern cone, and in England and Wales was initially thought to be due to the virulent clone disseminating from strains associated with the Hajj. However, genomic analysis later revealed that these strains, although clonal, were genetically different. In the United Kingdom, the number of serogroup W cases began to increase in 2009 and almost doubled from 2013–2014 (95 cases) to 2014–2015 (176 cases). More recently, serogroup W has been responsible for several cases in teenagers that have been characterized by an atypical gastrointestinal presentation that includes nausea, vomiting, and diarrhea. Among 15 cases diagnosed in teenagers aged 15 to 19 years between July 2015 and January 2016, 7 had mainly gastrointestinal symptoms; of these, 5 died within 24 hours of hospitalization. Serogroup B is an important cause of endemic disease and is responsible for multiple prolonged epidemics in several industrialized countries, including Cuba, Norway, and New Zealand. Smaller outbreaks due to a single strain have also been reported in other countries such as France (from 2000–2003) and the United States (from 2013–2017), some of which have been associated with colleges and universities. In the United States, one lengthy outbreak over 3 academic years occurred at Ohio University beginning in 2008. Recent outbreaks have occurred at Princeton University and the University of California Santa Barbara in 2013, the University of Oregon and Providence College in 2015, Santa Clara University and Rutgers in 2016, and Oregon State University in 2017. Similar to serogroup B, serogroup C has been a major cause of IMD in adolescents and young adults, mostly in industrialized countries. In the United Kingdom, disease due to serogroup C declined dramatically after the introduction of a monovalent serogroup C conjugate vaccine into the routine immunization schedule, with a catch-up campaign at the start, in 1999. From 2014 to 2015, only 28 cases of serogroup C disease were identified, which was a substantial decrease from the 848 cases reported from 1999 to 2000. After multiple epidemics of a virulent serogroup C strain in 1990 in Canada, Quebec implemented a mass immunization program using an unconjugated polysaccharide vaccine that resulted in a significant decrease in disease during the following years. However, reemergence of the disease-causing clone in 2001 triggered national recommendations for the inclusion of meningococcal serogroup C conjugate vaccine into the childhood immunization schedule, targeting infants and young adults aged <20 years. By 2005, routine vaccination was in place in all provinces in Canada, with the exception of one. Following the initiation of routine vaccination in 2001, IMD due to serogroup C decreased 14% per year over the next 8 years, with reductions in IMD in both vaccinated (78% reduction) and unvaccinated populations (46% reduction). Serogroup Y was not a global concern before the 1990s; however, an increased incidence of disease was observed during routine active surveillance studies conducted by the Centers for Disease Control and Prevention. From 1992 to 1996, serogroup Y disease began to increase and accounted for approximately 26% of isolates collected in the United States. A steady, although smaller, increase in serogroup Y isolates was observed in Europe from 1995 to 2012. Different vaccination strategies have been used to control disease caused by various N meningitidis serogroups in varied settings globally. The following sections will review the vaccines currently available that target these disease-causing serogroups, real-world examples of strategies used to implement these vaccines into diverse populations, the outcomes of these efforts, and pertinent considerations for each approach (Table 1). Vaccination strategies for meningococcal disease Vaccination strategies used to manage meningococcal disease vary based on specific conditions within a region or country and the needs of the target population. For instance, routine, age-based prophylactic immunization is often used when typical, or endemic, disease rates prevail in specific age groups. In contrast, mass vaccination is often deployed under epidemic conditions, defined as an increase in cases compared with baseline endemic conditions. Examples of such vaccination strategies are discussed below. Routine prophylactic immunization in high-risk groups Meningococcal serogroup C vaccine in infants and adolescents in Europe From 1994 to 1998, serogroup C accounted for 26% to 34% of cases of confirmed IMD in England and Wales, with the majority of cases occurring in adolescents. From 1998 to 1999, the confirmed number of serogroup C disease cases reached 883 in England, and as a result of escalating disease incidence, 3 novel monovalent protein-conjugate serogroup C vaccines were fast-tracked for approval. The first vaccine approved used a cross-reacting material 197 (CRM197) carrier (MeningitecTM, Pfizer Ltd, Kent, UK and Wyeth Pharmaceuticals, Havant, UK); the other 2 vaccines used either a CRM197 (Menjugate®), GlaxoSmithKline Vaccines Srl, Siena, Italy) or a tetanus toxoid carrier (NeisVac-CTM, Pfizer Ltd., Kent, UK) (Table 2). In 1999, the United Kingdom became the first country to initiate a national immunization campaign focused on serogroup C. This vaccination strategy targeted infants, who received a 3-dose schedule, and children and adolescents 1 to 18 years old, who received a single dose as a catch-up regimen; infants <1 year old and adolescents 15 to 17 years old were vaccinated first in order to target the age groups at highest risk. Notably, children and adolescents received the vaccination in a school-based program, leading to vaccine uptake of >85% in these groups. Monovalent serogroup C conjugate vaccines proved to be immediately effective in controlling disease in the United Kingdom; decreases in IMD incidence were initially observed in vaccinated individuals and later in unvaccinated children and older adults who were not eligible for vaccination, suggesting herd protection. By 2000–2001, 1 year after the vaccination campaign was initiated, 389 cases of invasive meningococcal serogroup C disease were reported, a decrease of 56% compared
| Serogroup | Location | Year Implemented | Age Group | Vaccine   | Year: Cases † (Incidence Rate)‡ |
|-----------|----------|------------------|-----------|-----------|---------------------------------|
|           |          |                  |           |           | Prevaccination | Postvaccination |
| A         | Burkina Faso (epidemic) | 2010 | 1–29 y | MenAfriVac | 2009: 1994 | 2010: 430 |
|           | Chad (epidemic) | 2011 (N’Djamena regions) | 1–29 y | MenAfriVac | 2011: 111 | 2012: 49 |
|           |   | 2012 (Rest of Chad) |           |           | 2013: 4 | |
| B         | United Kingdom | 2014 | ≥ 2 mo | Bexsero | 2012–2013: 595 | 2014–2015: 418 |
|           | Cuba (epidemic) | 1989 | 3.5 mo to <20 y | VA–Mengoc–BC | 2013–2014: 424 | 2015–2016: 444 |
|           | Norway | 2004 | 1–19 y | MenBvac | 1999–2000: 83 (1.9) | NA |
|           | France | 2006 | 1–19 y | MenBvac | 2003–2006: 2B (8.6) | 2008–2010: 3 (1.5) |
|           | New Zealand | 2004 | <20 y | MeNZB | 2001: 265 (24.7) | 2004: 144 (12.1) |
|           | United States | 2013–2016 | 10–25 y | Trumenba | 2002: 211 (18.1) | 2005: 80 (6.7) |
|           | Princeton | 2013 | 10–25 y | Bexsero | 2003: 187 (15.8) | 2006: 37 (3.1) |
|           | Rutgers | 2016 | 10–25 y | Bexsero | 2008: 31 (2.6) | |
| C         | Quebec City, Canada (Epidemic) | 2001 | 2 mo to 20 y | Menjugate | 2001: 58 (7.84) | 2002: 27 (3.63) |
|           | United Kingdom (Epidemic) | 1999 | 2 mo to 17 y | MCCs (Meningitec, Menjugate, NeisVac-C) | 1998/1999: 537 | 2000–2001: 103 |
|           | Netherlands | 2002 | 14 mo (1-dose series) | MCC | 2001: 276 | 2003: 42 |
|           | Spain | 2000 | 2 mo to <6 y | MCCs (Meningitec, Menjugate, NeisVac-C) | 1999: 268 (7.04) | 2000–2001: 56 (1.46) |

(Continued on next page)
| Serogroup | Location          | Year Implemented | Age Group | Vaccine | Year: Cases (Incidence Rate) |
|-----------|-------------------|------------------|-----------|---------|-----------------------------|
|           |                   |                  |           |         | Prevaccination   | Postvaccination |
| ACWY      | United States     | 2005             | 11–12 y   | MCV4    | Serogroup C             |                |
|           |                   |                  | Increased risk: |         | 2004: 27 (0.07) | 2005: 25 (0.07) |
|           |                   |                  | 11–55 y   |         | 2006: 29 (0.08) |                |
|           |                   |                  | 2–10 y    | MCV4    | 2007: 31 (0.08) |                |
|           |                   |                  | >55 y     | MPSV4   | 2008: 39 (0.11) |                |
|           |                   | 2007             | 11–18 y   | MPSV4   | 2009: 42 (0.12) |                |
|           |                   |                  |           | MCV4    | 2010: 17 (0.05) |                |
|           |                   | 2010             | 11–12 + 16 y | MCV4   | 2011: 27 (0.07) |                |

NA = not available.

aTotal cases for all age groups.

bThe campaign was targeted at children <6 years, but in 3 of 19 regions, this age range was extended up to adolescence.

cCases collected during the primary vaccination phase.

dIncidence rate is per 100,000
with the previous year. By 2014–2015, the total number of cases of serogroup C disease decreased to 28 cases—a reduction of 97% compared with the prevaccination era. Nasopharyngeal carriage rates of serogroup C also declined dramatically in vaccinated individuals (ie, a 66% decrease in vaccinated adolescents). Although monovalent serogroup C conjugate vaccines were effective in reducing disease, the immune response of infants who received the 3-dose schedule waned beginning 1 year after vaccination, whereas protection persisted longer in older children immunized with the catch-up schedule. Thus, a booster dose of monovalent serogroup C vaccine was introduced into the routine immunization schedule at 12 months of age. This program continued to evolve based on the needs of the population, ultimately resulting in the removal of the second dose from the infant schedule and a booster dose in adolescents for those who received the vaccine during infancy.

In addition to the United Kingdom, monovalent serogroup C conjugate vaccines have been used to effectively control endemic meningococcal disease in several European countries as well as Australia and Canada. In the Netherlands in 2002, a single dose of the serogroup C vaccine was introduced as part of routine care in children 14 months old; a 1-dose catch-up campaign included children 1 to 18 years old. Epidemiology, logistics, and economics were driving factors for a 1-dose schedule at 14 months versus a 3-dose schedule in infancy. As a result of this campaign, IMD due to serogroup C in the Netherlands decreased rapidly in all age groups. Although herd protection against serogroup C was evident, vaccinated children and adolescents were afforded the greatest protection. In Spain, where children ≤6 years old were targeted in the initial catch-up campaign, substantial herd protection with monovalent conjugate serogroup C vaccines was not observed. It is likely that the failure to immunize teenagers—the population with the highest carriage rates—contributed to the lack of herd protection.

### Quadrivalent serogroup ACWY vaccine in adolescents in the United States

In the United States, the incidence of IMD caused by serogroups ACWY is low in children less than 12 months old compared with global statistics, and as a consequence, routine immunization of young children against these serogroups has not been recommended. The exceptions are infants who are at increased risk of IMD because of immune insufficiencies, those with certain conditions such as functional or anatomic asplenia, or those traveling to endemic areas or exposed to an epidemic. Two quadrivalent vaccines are available in the United States; one vaccine includes diphtheria toxin as the carrier protein (MenACWY-D, Menactra®, Sanofi Pasteur, Swiftwater, PA, USA) and the other includes CRM as the carrier protein (MenACWY-CRM, Menevo®, GlaxoSmithKline Vaccines, Srl, Sovicille, Italy). In the United States, adolescents and young adults are at increased risk of IMD compared with the general population. To protect against IMD during the peak susceptibility to infection, the Advisory Committee on Immunization Practices (ACIP) has recommended vaccination with a quadrivalent ACWY vaccine for children 11 to 12 years old since 2005. The rationale for vaccination during the preteen years included the decreased frequency of healthcare visits among older children and the supposition that immunity would be durable through adolescence. By 2007, the incidence of IMD caused by serogroups C, W, and Y decreased among those aged 11 to 17 years compared with prevaccination years. This same year, vaccination recommendations were expanded to include adolescents 11 to 18 years of age. With the availability of post-licensure immunogenicity data, the ACIP issued updated recommendations in 2010 to include routine vaccination of adolescents aged 11 or 12 years, with a booster dose at age 16 years, and a 2-dose primary series administered 2 months apart for persons aged 2 through 54 years with certain underlying comorbidities. The goal of this strategy was to strengthen protection during the period of highest risk. Since 2010, IMD caused by serogroups C, W, and Y has steadily decreased among individuals 18 to 22 years of age. Overall, ACWY vaccination in the United States has lead to a decrease in IMD caused by these serogroups; the exception was 2006 when there was a small spike in cases among those 11 to 17 years of age. For example, over a 2-year period from 2013 to 2014, the annual incidence of IMD was 1 case per 100,000 due to these vaccine serogroups among adolescents aged 11 to 17 years and 1 IMD case per 100,000 among adults aged 18 to 22 years compared with 7 IMD cases per 100,000 in each group in 2004, which was before any vaccine recommendations were implemented.

| Serogroup | Vaccine Formulation | Vaccine Type | Vaccine Name | Manufacturer |
|-----------|---------------------|--------------|--------------|--------------|
| A         | MenA-TT             | Conjugate    | MenAfri Vac63 | Serum Institute of India |
| B         | MenB-FHbp           | Recombinant (FHbp subfamily A and B) | Trumenba70 | Pfizer |
|           | MenB-4C             | Recombinant (FHbp subfamily B, NadA, NHBA, OMV) | Bexsero52 | GlaxoSmithKline |
| C         | MCC-TT              | Conjugate    | NeisVac-C53  | Pfizer |
|           | MCC-TT              | Conjugate    | Menitorix120  | GlaxoSmithKline |
|           | MCC-CRM             | Conjugate    | Menjugate52   | GlaxoSmithKline |
|           | MCC-CRM             | Conjugate    | MenHibrix211  | GlaxoSmithKline |
|           | Hib-MenCY-TT        | Conjugate    | Menactra122   | Sanofi Pasteur |
|           | Hib-MenCY-DT        | Conjugate    | Menevo123     | GlaxoSmithKline |
|           | MenACWY-CRM        | Conjugate    | Nimenrix123   | Pfizer |
|           | MenACWY-TT          | Conjugate    | Menveo        | GlaxoSmithKline |

CRM = cross-reactive material; DT = diphtheria toxoid; FHbp = factor H binding protein; Hib = Haemophilus influenzae type B; MCC = meningococcal serogroup C conjugate; NadA = neisserial adhesin A; NHBA = neisserial heparin-binding antigen; OMV = outer membrane vesicles; TT = tetanus toxoid.
A study reports the long-term effectiveness of the quadrivalent meningococcal vaccination program in the United States was recently completed by the Centers for Disease Control and Prevention. In adolescents aged ≥11 years who received 1 dose of MenACWY-D, vaccine effectiveness was 69% against serogroups C, W, and Y targeted by the vaccine (there were no cases of serogroup A). For individual serogroups, vaccine effectiveness was 77% and 51% for serogroups C and Y, respectively. Vaccine effectiveness against serogroup W could not be calculated due to the low disease incidence. Vaccine effectiveness against all serogroups was highest in the first year after vaccination (79%), decreasing to 69% and 61% during 1 to <3 and 3 to <8 years after vaccination, respectively. The waning in seroprotection over time supports the strategy of booster dosing in adolescents.

Serogroup B vaccines in the United Kingdom

Although a decrease in overall incidence of IMD was evident in the United Kingdom from 2002–2003 to 2011–2012, 80% of cases during this period were associated with serogroup B. Based on recommendations from the Joint Committee on Vaccination and Immunisation in 2014, the United Kingdom became the first country to include MenB-4C (Bexsero, GlaxoSmithKline Vaccines Ltd, Siena, Italy) in the national childhood immunisation schedule (Table 1). MenB-4C is directed against neisserial adhesin A, factor H binding protein (subfamily B), neisserial heparin binding antigen, and outer membrane vesicles containing the porin A (PorA) protein. MenB-4C was offered to infants born on or after July 1, 2015 using a modified 2-, 4-, and 12-month vaccination schedule rather than a 3-dose infant series with booster. A catch-up dose was offered to infants born between May 1 and June 30, 2015. Paracetamol use, particularly in those 2 and 4 months of age receiving Bexsero concomitantly with other routine vaccinations, was recommended to offset fever. This vaccination strategy is the first routine and prophylactic use of a meningococcal serogroup B vaccine to protect a target population in the absence of an epidemic. As a follow-up to the routine use of MenB-4C, a national surveillance study was conducted in the United Kingdom that examined vaccine effectiveness in infants for cases diagnosed between September 1, 2015, and June 30, 2016. During the 10-month period, a 50% reduction in MenB incidence was reported among vaccine-eligible infants compared with 4 years before vaccine implementation. This reduction was not dependent on the vaccination status of the infants assessed or strain coverage by the vaccine. Two doses of MenB-4C in infants resulted in an estimated vaccine effectiveness of 82.9% among those <1 year of age.

Mass vaccination and epidemic response

Serogroup A vaccine in the African meningitis belt

The African meningitis belt, which extends from Senegal to Ethiopia, includes more than 350 million people and accounts for the highest meningococcal disease burden worldwide. Traditionally, meningitis epidemics in Africa were not managed proactively; vaccination with unconjugated polysaccharide meningococcal vaccines would be initiated when the weekly incidence rate increased above 10 cases per 100,000 population. As a result, vaccination campaigns often began in the late stages of an epidemic or when the epidemic was declining. Although serogroup A polysaccharide vaccines have been shown to be effective in adults and children >2 years old, less than 30% of children aged <1 year develop immunity following vaccination. This overall failure to control disease was likely due to the intrinsic properties of the vaccine, including the relatively short-lived immunity to free polysaccharide antigens, corresponding lack of immunologic memory, and the absence of an effect on carriage.

Development of a monovalent meningococcal A conjugate vaccine was initiated by a partnership between the World Health Organization and the Program for Appropriate Technology in Health (PATH), a nonprofit organization funded by the Bill & Melinda Gates Foundation. The goal of this initiative was to develop an affordable meningococcal group A conjugate vaccine that induced a long-lasting immune response coupled with the potential to reduce carriage and establish herd immunity. The resulting vaccine, called MenAfriVac (PsA-TT, Serum Institute of India, Pune, India) (Table 2), was granted fast-track status by the World Health Organization in June 2010, and the vaccine was prequalified for use in children and adults aged 1 to 29 years.

In 2010, MenAfriVac was used prophylactically in Burkina Faso, Mali, and Niger. These countries were chosen for early introduction because of their potential for meningococcal epidemics and the presence of a supportive infrastructure, including surveillance capabilities and support from the Ministries of Health. Mali and Niger chose a regional vaccination campaign in which vaccination of individuals aged 1 to 29 years occurred in 2 phases in 2010 and 2011. Geography factored into the regional vaccination strategy because Mali and Niger both lie only partially within the meningitis belt and have sparsely populated desert regions in the north, where the incidence of disease is low; hence, a regional rather than national campaign was implemented. During the first round of vaccinations in 2010, the 10-day vaccination campaign in Niger and 2-week campaign in Mali resulted in the immunization of 3 million and 4.5 million residents, respectively. In Burkina Faso, which lies completely within the meningitis belt and has one of the highest incidences of IMD in the region, a national immunization campaign was initiated to immunize children and adults 1 to 29 years old over a 10-day period; approximately 11 million residents were vaccinated during this single campaign.

The effects of vaccination in Burkina Faso were evident immediately. By 2012, no cases caused by serogroup A were identified, and IMD caused by serogroup A has not been detected in Burkina Faso, Mali, or Niger through February 2015. Moreover, in a carriage study conducted in Burkina Faso over 4 sampling periods in 2008 and 2009, which was prior to the country-wide mass vaccination that occurred in 2010, the prevalence of serogroup A was 0.39% (80 positive cultures detected in 20,326 samples). In an assessment of carriage conducted 13 months after vaccination, no serogroup A was detected in over 20,000 samples, suggesting that MenAfriVac was effective in reducing carriage and could potentially...
eliminate the reservoir of serogroup A in the population. The impact of MenAfriVac was also notable in Chad, another country within the meningitis belt, where the vaccine was introduced in individuals aged 1 to 29 years during a serogroup A epidemic at the end of 2011. The following year, vaccinated regions experienced a 90% decrease in IMD due to serogroup A and a corresponding decrease in carriage.\(^8\) By 2014, >63 million individuals aged 1 to 29 years living within the meningitis belt received 1 dose of MenAfriVac, with more than 217 million doses administered since 2010; due to vaccination efforts, 1146 deaths due to serogroup A were reported in 2014, which is the lowest mortality rate reported since 2004.\(^3,9\) In January 2015, the World Health Organization recommended that MenAfriVac be included in routine infant immunization schedules in sub-Saharan African countries.\(^83\)

**Serogroup A disease and MenACWY vaccination during the Hajj**

The first epidemic of serogroup A reported internationally after the Hajj occurred in 1987 with 1841 cases confirmed in Saudi Arabia.\(^9\) The majority of cases were concentrated primarily in and around the cities most frequented during the Hajj.\(^9\) Demographically, pilgrims emigrated from a multitude of countries. As such, one notable consequence of the epidemic was the far-reaching dissemination of disease that occurred upon the re-entry of the pilgrims to their native countries. A second wave of disease was reported among the contacts of the infected pilgrims.\(^9\)

From 1995 to 1999, the annual incidence rate for meningococcal infections in Saudi Arabia was 0.2/100,000 persons, which equated to a median of 42 cases per year.\(^24\) In 1997, an epidemic of serogroup A disease occurred prior to the Hajj and 72 cases of serogroup A were identified. Three years later, during the 2000 Hajj, a large epidemic of serogroup A and W was identified; 253 cases were confirmed and of these approximately a quarter were due to serogroup A. Beginning in 2001, the government of Saudi Arabia required quadrivalent polysaccharide MenACWY vaccination for all Hajj pilgrims due to the increased prevalence of meningococcal disease.\(^9,12\) No meningococcal epidemic occurred during the 2002 Hajj. From 2002 to 2011, Saudi Arabia documented only 184 cases of meningococcal disease (all serogroups) and of these, only 9% occurred in Hajj pilgrims.\(^9\) Currently, both polysaccharide and quadrivalent vaccines are recommended for use by the Saudi Arabia Ministry of Health, with vaccination required not more than 3 and 5 years, respectively, prior to arrival.\(^93\)

**Mass vaccination in epidemics**

**Outer membrane vesicle vaccines**

In regions around the globe, epidemics caused by meningococcal serogroup B are continually emerging; epidemics occurring in Cuba,\(^31\) Norway,\(^32\) and New Zealand\(^94\) were noted for their longevity and number of confirmed cases. In each of these countries, an outer membrane vesicle (OMV) vaccine specifically targeted to the epidemic strain was developed in response to the epidemic. The immune response induced by these vaccines is highly specific for the immunizing strain, which is likely due to the specificity of the PorA response; as a result, the coverage afforded by OMV vaccines is limited to the epidemic strain.\(^95\)

In Cuba, the introduction of an OMV vaccine (VA-Mengoc-BC, Finlay Instituto, Havana, Cuba) in 1988 led to a substantial decline in IMD among vaccinated and unvaccinated individuals.\(^31\) In Norway, another OMV vaccine (MenBvac, Norwegian Institute of Public Health, Oslo, Norway) was developed in response to a 16-year epidemic that began in 1975.\(^32,96\) This same OMV vaccine was subsequently used to address an epidemic in France that was caused by a similar strain.\(^36\) In New Zealand, an epidemic in the early 1990s led to the development of an OMV vaccine to target the disease-causing strain.\(^95\) Details of this epidemic and vaccine are discussed below.

A prolonged epidemic of meningococcal B disease occurred in New Zealand starting in 1991, with the majority of cases caused by a single epidemic strain.\(^33,34\) At the peak of the epidemic in 2001, the annual IMD incidence was 17.4 cases per 100,000 population.\(^97\) The epidemic affected younger populations, with individuals <20 years old accounting for approximately 80% of all cases; among these, half were <5 years old.\(^98\) In response, a strain-specific OMV vaccine directed against the serogroup B epidemic strain (MeNZB\(^34\), Chiron/NZ Ministry of Health, Wellington, New Zealand) was developed through the cooperation of government, academic, and pharmaceutical partners.\(^95\) MeNZB was included in the national immunization program in New Zealand from 2004 to 2006. Vaccination was subsidized by the government and therefore offered free of charge to children and young adults <20 years old; infants and preschool children continued to be vaccinated until 2008; the last phase of the program, after which MeNZB was no longer available in New Zealand, was completed in 2011 and was limited to those with a high risk of disease.\(^99\) MeNZB was administered in a 3-dose schedule to children and young adults, with a booster dose added in 2006 for children who received their first dose before 6 months of age.\(^100-104\) In total, more than 1 million people in New Zealand were immunized during the vaccination campaign.\(^99\) By 2004, when the MeNZB vaccination campaign was initiated, the epidemic in New Zealand had begun to wane. Despite this, a prospective efficacy trial demonstrated that MeNZB significantly decreased the risk of infection by 4-fold in vaccinated individuals and had an effectiveness of 73%.\(^104\) By 2009, the incidence rate for IMD declined to 3.3 per 100,000 population compared with 17.4 per 100,000 population at the peak of the epidemic. By 2014, IMD due to serogroup B had an incidence rate of 1.0 case per 100,000 population,\(^8\) resulting in the lowest rate of disease in those ≥5 years old since 1997.\(^8\)

**Recombinant meningococcal serogroup B vaccines in the United States**

Although OMV vaccines have been effective in controlling epidemics dominated by a single disease-causing clone in several countries, including Cuba,\(^31\) Norway,\(^32\) France,\(^36\) and New Zealand,\(^33,34\) these vaccines have not been effective for the prevention of endemic disease caused by diverse serogroup B strains.
In 2013 when 2 serogroup B outbreaks occurred on college campuses in the United States (ie, Princeton University and University of California Santa Barbara), there were no licensed MenB vaccines available.\textsuperscript{37} In response to this acute unmet medical need, the US Food and Drug Administration granted breakthrough therapy designation to 2 MenB vaccines, MenB-FHbp (Trumenba\textsuperscript{8}, Bivalent rLP2086; Pfizer Inc, Collegeville, PA) and MenB-4C, which were subsequently licensed in 2014 and 2015, respectively, for the prevention of invasive serogroup B disease in individuals aged 10 to 25 years.\textsuperscript{70,72} MenB-4C had previously received approval in Europe for individuals \( \geq 2 \) months old.\textsuperscript{105} The different vaccination campaigns implemented using these licensed serogroup B vaccines in response to recent college outbreaks in the United States are discussed below.

Beginning in 2013, 9 cases of serogroup B have been associated with Princeton University (Princeton, NJ, USA), the ninth case occurring in a Drexel student after contact with Princeton students who traveled to Drexel for a social event.\textsuperscript{106} Also in 2013, 5 cases were identified at the University of California, Santa Barbara (UCSB; Santa Barbara, CA, USA).\textsuperscript{38} In response to these outbreaks, mass vaccination strategies were implemented with MenB-4C, which was not licensed in the United States at the time, administered in a 2-dose series at least 1 month apart for approximately 7500 and 20,000 undergraduates, faculty, and staff at Princeton and UCSB, respectively.\textsuperscript{38}

With the exception of the Drexel University student,\textsuperscript{106} additional cases have not been associated with the Princeton University or UCSB outbreaks after the initiation of the vaccination campaign.\textsuperscript{107} In response to the Drexel University case which occurred after the vaccination clinics, Princeton University decided to offer the vaccine to all incoming freshmen.\textsuperscript{106}

In 2015, additional serogroup B outbreaks occurred at Providence College (Providence, RI, USA)\textsuperscript{108} and the University of Oregon (Eugene, OR, USA).\textsuperscript{109} Providence College identified 2 cases of serogroup B disease, resulting in an attack rate of 44 cases per 100,000 students, which is approximately 500-fold higher than the national incidence of 0.15 cases per 100,000 among persons aged 17 to 22 years in the United States.\textsuperscript{108} At the University of Oregon, 6 students and 1 parent were diagnosed with IMD, resulting in 1 fatality. The vaccination campaign at Providence College used MenB-FHbp exclusively;\textsuperscript{108} the University of Oregon vaccinated primarily with MenB-FHbp, with MenB-4C available at off-campus pharmacies.\textsuperscript{38} Although MenB-FHbp was used in both outbreaks, there were a number of notable strategic differences.

Providence College provided vaccine to all eligible students and staff < 25 years of age using an opt-out strategy, whereby any individual declining vaccination was required to complete an opt-out form.\textsuperscript{108} The first vaccination clinic at Providence College occurred 6 days after 2 cases were confirmed to be due to serogroup B infections; a make-up day was scheduled 3 days later. The second and third doses were administered approximately 2 and 7 months after the first dose, with a single make-up day scheduled within 3 days of each dose. Vaccine uptake among eligible students ranged from 94% for dose 1 to 77% for dose 3.\textsuperscript{110} No additional serogroup B cases have been reported as of November 2016. A baseline carriage study at Providence College indicated that of the 25% of students who were carriers of \( N \) meningitidis, 4% were positive for serogroup B; however, no carriers were positive for the outbreak strain at baseline, making it difficult to assess vaccine effectiveness against carriage.\textsuperscript{108}

In contrast, the University of Oregon provided vaccine for all eligible students using an opt-in strategy.\textsuperscript{38} Students were required to provide their university identification card, medical insurance, and pharmacy card to receive the vaccine; uninsured students were provided with assistance in obtaining the vaccine. The first vaccination clinic was conducted approximately 45 days after the first case of serogroup B disease was identified and occurred over 4 consecutive days. A second clinic was conducted 2 months later and occurred over 2 days. No make-up vaccinations occurred outside of these periods. Among those eligible for vaccination, vaccine uptake was 46% for dose 1 and 29% for dose 2.\textsuperscript{38} After the vaccination campaign, 3 cases of serogroup B disease were reported. Two cases occurred after the first vaccination clinic. A third case occurred after the second vaccination clinic in a father who had visited the campus.

In 2016, 3 serogroup B cases were reported at Santa Clara University (Santa Clara, CA, USA).\textsuperscript{111} The university responded by organizing two 3-day vaccination clinics in which MenB-4C was administered to eligible students. In response to 2 serogroup B cases reported at Rutgers University (New Brunswick, NJ, USA), MenB-FHbp was offered to eligible students and faculty.\textsuperscript{41} All undergraduate students were required to submit a vaccination verification form or complete a declination form, confirming that the risks of meningococcal disease were understood. Studies are currently underway to examine any reduction in serogroup B carriage following these college-based vaccination campaigns.

At another university in Oregon, Oregon State University, 6 cases of MenB were reported in late 2016 to 2017\textsuperscript{42,112} which prompted the University to require that all students aged \( \leq 25 \) years be vaccinated against MenB; both MenB-FHbp and 4C-MenB were available to students at the student health center.\textsuperscript{42,43} The University had previously required vaccination for incoming students but amended the policy to include all students that were within the age requirement and issued a deadline for vaccination of February 15, 2018.\textsuperscript{42,43}

In 2014, a serogroup B vaccination campaign targeting individuals 2 months to 20 years was implemented in the Saguenay-Lac-Saint-Jean region of Quebec.\textsuperscript{113} This area had experienced a hyperendemic rate of serogroup B disease with an annual incidence rate \( > 10/100,000 \) from 2006 to 2013 compared with rates of 0.33/100,000 in Canada and 0.76/100,000 in Quebec.\textsuperscript{113} The highest incidence was reported in infants, followed by adolescents. In response, a vaccination campaign targeting approximately 60,000 individuals aged 2 months to 20 years, was implemented. Those aged 2 to 5 months received 4 doses, 6 to 11 months received 3 doses, and \( \geq 1 \) years received 2 doses. In the course of the vaccination campaign, approximately 45,000 individuals received at least 2 doses of MenB-4C. As a result of the vaccination efforts, serogroup B disease across
the region decreased dramatically and no cases have been reported in vaccinated individuals through January 2016; two cases have been reported among those who were not vaccinated.\(^\text{114}\)

### Conclusion

*Neisseria meningitidis* infection causes serious disease worldwide. The introduction of vaccines targeting disease-causing serogroups, such as vaccination against serogroup C in the United Kingdom and serogroup A in Africa, has led to dramatic decreases in IMD incidence.\(^{5,8,66}\)

Ongoing meningococcal vaccination campaigns should focus on implementing strategies that maximize the potential for disease prevention, which includes identifying groups most likely to carry and potentially be responsible for transmission across the population. Meningococcal conjugate vaccines clearly demonstrate a reduction in carriage, suggesting these vaccines have the ability to provide both direct protection to vaccinated individuals and herd protection to their close contacts by preventing transmission.\(^{115}\)

Routine prophylactic vaccination strategies targeting those at greatest risk aim to reduce IMD burden and prevent epidemic disease. The impact of recent infant and adolescent serogroup vaccination strategies should be revealed by ongoing surveillance in the coming years.

### Five-year view

Vaccination strategies against IMD include mass vaccination, routine vaccination, and a combination of the two approaches. Important considerations in determining the strategy to be used include understanding the disease epidemiology by age and serogroup and the vaccines available.

Currently, IMD is historically low in many regions of the world, with vaccination campaigns such as those in the African meningitis belt, Europe, and Canada successfully reducing IMD incidence by targeting relevant disease-causing serogroup (s) in at-risk populations.\(^{46,116}\) As IMD incidence is unpredictable, vaccination strategies will need to be updated to combat ongoing changes in meningococcal epidemiology and disease. A proactive strategy, which has been successful for vaccinating large numbers of students on University campuses in the United States,\(^{38}\) highlights the success that can be achieved through preemptive immunization. The United Kingdom also was responsive to changing needs and incorporated serogroup C booster dosing into the routine infant immunization program upon the realization that catch up vaccination schedules in older children afforded longer protection. The availability of licensed vaccines for the 5 serogroups responsible for the majority of IMD, coupled with the correct implementation and programmatic strategy, should aim to reduce the incidence and reservoirs of IMD through optimizing worldwide vaccination.

Over the next 5 years, more information on the potential effectiveness of recently licensed serogroup B vaccines will become available. The breadth of coverage that these vaccines will provide against disease in terms of clonal complexes and relevant protein antigens expressed by genetically-diverse strains will be determined. These data will potentially support more widespread use of serogroup B vaccines to control endemic disease and inform on the ability of these vaccines to interrupt transmission if vaccination programs are implemented in adolescents and young adults. Development of a serogroup ABCWY pentavalent vaccine over the next 5 to 10 years will potentially simplify vaccination schedules and ensure more comprehensive coverage against the serogroups responsible for the majority of disease. Vaccination strategies should also aim to reduce carriage and bacterial reservoirs, which should result in a reduction in disease transmission.

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All authors are employees of Pfizer Inc and may hold stock and/or stock options.

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