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First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak

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Abstract

Background—In 2013–2014, an outbreak of serogroup B meningococcal disease occurred among persons linked to a New Jersey university (University A). In the absence of a licensed serogroup B meningococcal (MenB) vaccine in the US, the Food and Drug Administration authorized use of an investigational MenB vaccine to control the outbreak. An investigation of the outbreak and response was undertaken to determine the population at risk and assess vaccination coverage.

Methods—The epidemiologic investigation relied on compilation and review of case and population data, laboratory typing of meningococcal isolates, and unstructured interviews with university staff. Vaccination coverage data were collected during the vaccination campaign held under an expanded access Investigational New Drug protocol.

Results—Between March 25, 2013 and March 10, 2014, 9 cases of serogroup B meningococcal disease occurred in persons linked to University A. Laboratory typing results were identical for all 8 isolates available. Through May 14, 2014, 89.1% coverage with the two-dose vaccination series was achieved in the target population. From the initiation of MenB vaccination through February

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1, 2015, no additional cases of serogroup B meningococcal disease occurred in University A

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Contributor's Statements:

Lucy McNamara: participated in collection and analysis of epidemiologic data on the cases and population at risk, contributed to the conception and design of the epidemiologic investigation and analysis, contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, contributed to collection and analysis of vaccination coverage and safety data, drafted the initial manuscript, and approved the final manuscript as submitted.

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students. However, the 9th case occurred in March 2014 in an unvaccinated close contact of University A students.

Conclusions—No serogroup B meningococcal disease cases occurred in persons who received 1 or more doses of 4CMenB vaccine, suggesting 4CMenB may have protected vaccinated individuals from disease. However, the 9th case demonstrates that carriage of serogroup B *Neisseria meningitidis* among vaccinated persons was not eliminated.

Keywords

Meningococcal disease; vaccine; university; epidemiology

Introduction

Between March 25, 2013 and March 10, 2014, 9 cases of serogroup B meningococcal disease were reported in persons linked to a New Jersey university (University A). During this time, options for control of serogroup B meningococcal disease outbreaks were limited by the absence of a licensed serogroup B (MenB) vaccine in the US. However, in 2013 two recombinant MenB vaccines were under pre-licensure review in the US: the three-dose vaccine rLP2086 (Trumenba®, Pfizer) and the two-dose vaccine 4CMenB (Bexsero®, Novartis Vaccines and Diagnostics, Siena, Italy). Because 4CMenB had already been licensed in Europe and Australia in 2013 whereas rLP2086 was not yet licensed in any country, we thought 4CMenB would be more acceptable in the target population. The Centers for Disease Control and Prevention (CDC) therefore submitted an expanded access Investigational New Drug (IND) application to the Food and Drug Administration (FDA) to allow use of 4CMenB to control the outbreak at University A. The CDC, New Jersey Department of Health (NJDOH), Princeton Health Department, and University A collaborated to provide the two-dose vaccination series to the population at risk in the outbreak beginning in December 2013.

Here, we describe the epidemiologic investigation of the outbreak that led to the decision to vaccinate and the implementation of the vaccination campaign with investigational 4CMenB vaccine.

Patients and Methods

Case investigation

Meningococcal disease is nationally notifiable and suspected cases are reported directly to state or local public health authorities. The current Advisory Committee on Immunization Practices guidelines define an organization-based meningococcal disease outbreak as the occurrence of 3 or more cases in 3 months in persons with a common organizational affiliation but without direct close contact and a resulting attack rate of greater than 10 per 100,000 [1]. An outbreak case was defined as a case of serogroup B meningococcal disease with laboratory results consistent with the outbreak strain that occurred in a University A student or close contact of University A students. Cases were reported in New Jersey, Texas, Massachusetts, and Pennsylvania in the US as well as in Greece and were investigated by university and local and state health department staff to identify close contacts for antibiotic

chemoprophylaxis. The case-patient who became ill in Greece had been traveling with a group of University A students in Europe for three weeks prior to illness onset; no air travel contacts of this patient required chemoprophylaxis. NJDOH compiled data on all outbreak cases, including those initially reported elsewhere.

Molecular characterization

For eight cases, *N. meningitidis* serogroup was determined by slide agglutination at the state public health laboratory and confirmed by real-time polymerase chain reaction (rt-PCR) at CDC [2–4]. Serogroup determination and PorA typing for one case was performed in Greece using PCR.

At CDC, isolates were characterized using pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), and molecular typing of fHbp, NhbA, NadA, and PorA as previously described [5–8]. Novartis assessed whether 4CMenB vaccine was expected to protect against the outbreak strain using human serum bactericidal assay (hSBA) and meningococcal antigen typing system (MATS) [9,10].

Epidemiologic investigation

Following the 6th outbreak case in October 2013, NJDOH invited CDC to assist with an on-site investigation to determine the target population for potential vaccination. To understand whether cases shared epidemiologic links, case information gathered by NJDOH, the Princeton Health Department, and University A was compiled and reviewed. The population at risk [1] was characterized through interviews with University A staff and students and review of university data on student ages, living arrangements, and social interactions.

Vaccination clinic

In November 2013, use of 4CMenB vaccine was authorized per FDA under the expanded access IND regulations (21 CFR 312.320). The primary goal of the expanded access IND was to make vaccine available to the population at risk for serogroup B meningococcal disease during the outbreak given the lack of an adequate, approved alternative for prevention of this potentially life-threatening condition in the US. The primary purpose of an expanded access IND is to provide access to a vaccine or treatment; it is not intended to establish safety and efficacy of the product.

CDC's Institutional Review Board (IRB) served as the IRB for this IND protocol; the university's IRB deferred to CDC. Written informed consent was obtained from all vaccine recipients and parental consent and written assent were obtained for recipients under age 18 years.

University A and CDC collaborated to provide students, parents, faculty, and staff with accurate and timely information about the 4CMenB vaccination program; implement the vaccination campaign; and monitor adverse events following vaccination. Potential vaccine recipients were notified of the clinic through multiple mechanisms, including email, posters, and text messages. At the clinic, precautions and contraindications for vaccination were assessed through a screening questionnaire for each recipient; those with questions about the

vaccine or medical conditions received further evaluation from a clinical team composed of medical doctors from CDC and University A. Vaccination coverage was monitored through real-time entry of vaccination into recipients' electronic health records or, for non-students, by collecting copies of the informed consent paperwork. Reports of adverse events following vaccination are being collected passively via phone and student health clinic visits and actively via surveys administered at the time of second dose administration and 30 days after receipt of the second dose.

Results

Case ascertainment

Between March and November 2013, seven cases occurred in University A undergraduates and one additional case occurred in a high school student who became ill after staying in an undergraduate dormitory at University A. Excluding the one case that occurred during the university's summer break, case-patients lived or stayed in 6 out of the 50 undergraduate dormitories at University A immediately prior to disease onset. No cases occurred in graduate students, faculty, staff, local community members, or family members of case-patients. The median time between cases was 26 days (range 12–94).

All 8 of these case-patients experienced headache and fever and 7 of the 8 developed a rash. Seven case-patients had meningitis while one had bloodstream infection only. All case-patients were hospitalized; the median length of stay was 7 days (range 5–10 days). None of these 8 cases was fatal, but three case-patients had long-term sequelae (unilateral hearing loss (n=1), neurocognitive deficits (n=1), and chronic headaches (n=1)).

The 9th case occurred in March 2014, after the 4CMenB vaccination campaigns and 109 days after the 8th case. This case occurred in a student at a different university who had close contact with University A undergraduates at an off-campus social event 8 days prior to disease onset. The 9th case-patient exhibited a petechial rash but did not have evidence of meningitis. The ninth case was fatal, bringing the overall outbreak case-fatality ratio to 11%.

Outbreak case-patient ages ranged from 17 to 21 years (median 19); cases occurred in both males (56%) and females and across four undergraduate classes (Figure 1). No case-patients had a prior diagnosis of a medical condition that increases risk of meningococcal disease (i.e., functional or anatomic asplenia or persistent complement component deficiency) [1]. The annualized attack rate of serogroup B meningococcal disease among University A undergraduates was 134 per 100,000.

Immediately upon identification of each case, close contacts of case-patients were identified by University A, NJDOH, the Princeton Health Department, and other state and local health departments and were recommended antibiotic chemoprophylaxis. Close contacts include household contacts (including roommates), child care center contacts, and anyone else with a direct exposure to a case-patient's oral secretions [1]. No secondary cases occurred in close contacts of case-patients. In addition to chemoprophylaxis for close contacts, in May 2013 the university issued recommendations for students to reduce sharing of eating and drinking materials and other activities that could result in contact with oral secretions.

Molecular characterization

All cases were confirmed as serogroup B meningococcal disease and had the same PorA type (P1.5-1,2-2). Isolates from the eight cases identified in the US were characterized further; all were sequence type 409 (ST-409) of clonal complex 41/44/Lineage 3 and had the same PFGE pattern (429) and antigen types (fHbp 1.276, NhbA p0002, and NadA negative by Novartis nomenclature). The fHbp and NhbA antigens in the outbreak strain demonstrated cross-reactivity with 4CMenB vaccine antigens by MATS; hSBA testing showed that serum from people vaccinated with 4CMenB was able to kill the outbreak strain.

Epidemiologic investigation

The outbreak spanned two academic years. Only one person was identified as a close contact of more than one case (cases 4 and 7); however, these cases occurred nearly 6 months apart and the contact in question received chemoprophylaxis immediately following the identification of each case. No case-patients were found to share common extracurricular activities and no cases occurred in the same dormitory within an academic year.

In the 2013–2014 academic year, 5,241 undergraduate and 2,666 graduate students were enrolled at University A. More than 98% of undergraduates and 20% of graduate students lived in on-campus dormitories. For undergraduates, the mean age was 21 years (range 16–31) and vaccination coverage with quadrivalent meningococcal conjugate vaccine (MenACWY) was >99.9%. Graduate students living in the graduate student dormitory were significantly younger than graduate students living in university-owned apartments, with mean ages of 24.1 and 26.4 years, respectively (t-test, $t=13$, $p<0.0001$). Social mixing between undergraduate and graduate students was reported to be uncommon but extant; however, the degree of social mixing could not be quantified.

Based on this investigation, the target population for vaccination included: University A undergraduate students ($n = 5,241$), graduate students living in undergraduate and graduate student dormitories ($n = 541$), graduate students, faculty, and staff with a medical condition that increases risk of meningococcal disease ($n = 11$), and spouses and care-givers of undergraduate and graduate students living in a dormitory with the students ($n = 6$).

Vaccination Campaign

The first-dose vaccination clinic was held December 9–12, 2013 and the second-dose clinic was held February 17–20, 2014. Additional small clinics were held for persons unable to attend the larger clinics. Through May 14, 2014, 94.9% of the target population had received at least 1 dose of the vaccine and 89.1% had received both doses (Table 1). Within this target population, coverage was highest among undergraduate students, of whom 96.6% received the first dose and 91.4% received both doses (Table 1). As of February 1, 2015, one serious adverse event was deemed possibly related to the vaccine (a case of rhabdomyolysis with onset 1 day after the second dose), but no concerning patterns of adverse events following vaccination have been observed. Monitoring for adverse events is ongoing.

Through February 1, 2015, no cases of serogroup B meningococcal disease have been reported in individuals who received the 4CMenB vaccine. However, as noted above, the 9th case did occur after the vaccination campaigns. The 9th case-patient was a student at another university who had close contact with several University A students, most of whom had received 2 doses of 4CMenB, prior to disease onset. The student body of the second university was not considered to be at increased risk for meningococcal disease due to this incident.

Discussion

In this report, we describe the first time an expanded access IND program for an investigational vaccine has been implemented in response to a serogroup B meningococcal disease outbreak in the US. The attack rate among undergraduate students at University A, 134 per 100,000, was more than 1,400 times greater than the national incidence in this age group [1, CDC unpublished data]. Prior to routine MenACWY vaccination, most meningococcal disease outbreaks on college campuses were caused by serogroup C [11,12]. However, serogroup C outbreaks have declined with high MenACWY coverage in adolescents [13], leaving serogroup B as the cause of recent meningococcal outbreaks on college campuses.

The sequence type of the bacterial strain isolated in this outbreak, ST-409, is uncommon in the US. Aside from the samples received from this outbreak, CDC has received only 9 (0.25%) serogroup B ST-409 isolates out of 3,595 unique case isolates that have been characterized by MLST (isolates collected 1911–2014). None of these other ST-409 isolates had the same antigen profile as the University A outbreak strain. To our knowledge, no other outbreaks associated with ST-409 have been reported in the US or elsewhere. Little is known about the clinical presentation of meningococcal disease caused by ST-409, but in this outbreak the case-fatality ratio and proportion of case-patients with meningitis were consistent with those from meningococcal disease surveillance data for the US [14].

It is not clear why this strain caused an outbreak at University A. This strain might be more invasive than other *N. meningitidis* sequence types and indeed it is part of the ST-41/44 clonal complex, which is thought to be hypervirulent [15]. Alternatively, the undergraduate population may have had low baseline immunity to this novel bacterial strain, leading to a high attack rate once it was introduced into the student population.

Defining the population at risk in meningococcal disease outbreaks can be challenging. In this outbreak, cases occurred in students of four undergraduate class years, and therefore the entire undergraduate population was targeted for vaccination. While no cases occurred in graduate students, graduate students living in on-campus dormitories were targeted for vaccination because the increased risk of meningococcal disease for college freshmen living in dormitories [16–19] raised concerns that dormitory living might also increase risk for other populations. Furthermore, most outbreak-associated cases of meningococcal disease in the US occur in persons aged <25 years and the mean age of the graduate students living in dormitories was <25 years [11, CDC unpublished data]. While the population at risk must be determined separately for each outbreak of meningococcal disease, we hope the process

used to define the population at risk at University A can inform this determination in future outbreaks.

Over 5,000 students received 4CMenB vaccine during the 4-day first-dose vaccination campaign. Several factors likely contributed to the campaign's success. First, the university provided information about meningitis and the vaccination clinics to students and parents through multiple mechanisms, including emails, posters, text messages, a student-created video, and town hall meetings featuring University A and CDC staff. In addition, efficient clinic management and short wait times for participants resulted in high throughput. Finally, the high attack rate of meningococcal disease and the occurrence of cases shortly before the vaccination campaign likely motivated students to receive the vaccine. This highly successful vaccination campaign provides a model for future vaccination campaigns in response to outbreaks on college campuses.

As of February 1, 2015, no additional serogroup B meningococcal disease cases occurred at University A. While two doses of the vaccine are critical for a sustained immune response [20], one study demonstrated that adolescents also have a strong initial immune response after a single dose [21]. This fact might have contributed to the absence of cases between the first and second vaccination campaigns. However, a case did occur in a close contact of University A students in March 2014. Most of the students with whom the last case-patient had contact had received two doses of 4CMenB vaccine. The occurrence of this case demonstrates that the vaccination campaign had not eliminated carriage from the University A population by this time and that transmission of the outbreak strain was ongoing. This finding is consistent with a recent study demonstrating that 4CMenB has at most a modest impact on prevalence of meningococcal carriage in vaccinated people [22]. Ultimately, it is unknown whether additional cases would have occurred in University A students in the absence of the vaccination campaign, but the lack of cases in vaccinated persons combined with the evidence of ongoing transmission in the population suggests the campaign did succeed in providing primary protection to the student population.

The first vaccine for serogroup B meningococcal disease, rLP2086 (Trumenba®, Pfizer) was licensed for use in individuals 10–25 years old on October 29, 2014, and 4CMenB was approved for use in the same age group on January 23, 2015. Although the Advisory Committee on Immunization Practices has not yet developed recommendations for the use of either vaccine, CDC formed a meningitis outbreak working group to provide interim guidance for responding to outbreaks of serogroup B meningococcal disease. These guidelines are available online at <http://www.cdc.gov/meningococcal/outbreaks/vaccine-serogroupb.html>. While the number of sporadic cases of serogroup B meningococcal disease occurring in adolescents each year is at historic lows, the potential impact of MenB vaccines on both sporadic disease and outbreaks will be important to consider in the development of recommendations for use of licensed MenB vaccines in the US.

Conclusions

No serogroup B meningococcal disease cases occurred in students who had received 1 or more doses of 4CMenB vaccine, suggesting 4CMenB was effective in protecting vaccinated

individuals from disease. However, the 9th case demonstrates that carriage of serogroup B *Nesisseria meningitidis* among vaccinated persons was not eliminated. The outbreak investigation and highly successful vaccination campaign described here can serve as a model for how to approach similar outbreaks in the future.

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Abbreviations

CDC	US Centers for Disease Control and Prevention
hSBA	human serum bactericidal assay
FDA	US Food and Drug Administration
IND	Investigational New Drug
IRB	Institutional Review Board
MATS	Meningococcal Antigen Typing System
MenACWY	quadrivalent meningococcal conjugate vaccine
MenB	serogroup B meningococcal
NJDOH	New Jersey Department of Health
ST-409	Sequence type 409

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What's Known on This Subject

Outbreaks of serogroup B meningococcal disease occur at universities and other organizations. However, until October 2014 options for control of serogroup B outbreaks were limited by the absence of a licensed vaccine for serogroup B meningococcal disease in the US.

What This Study Adds

This report describes a serogroup B outbreak at a university in 2013 and the campaign with investigational serogroup B vaccine held in response. This was the first use of a serogroup B vaccine as an outbreak response in the US.

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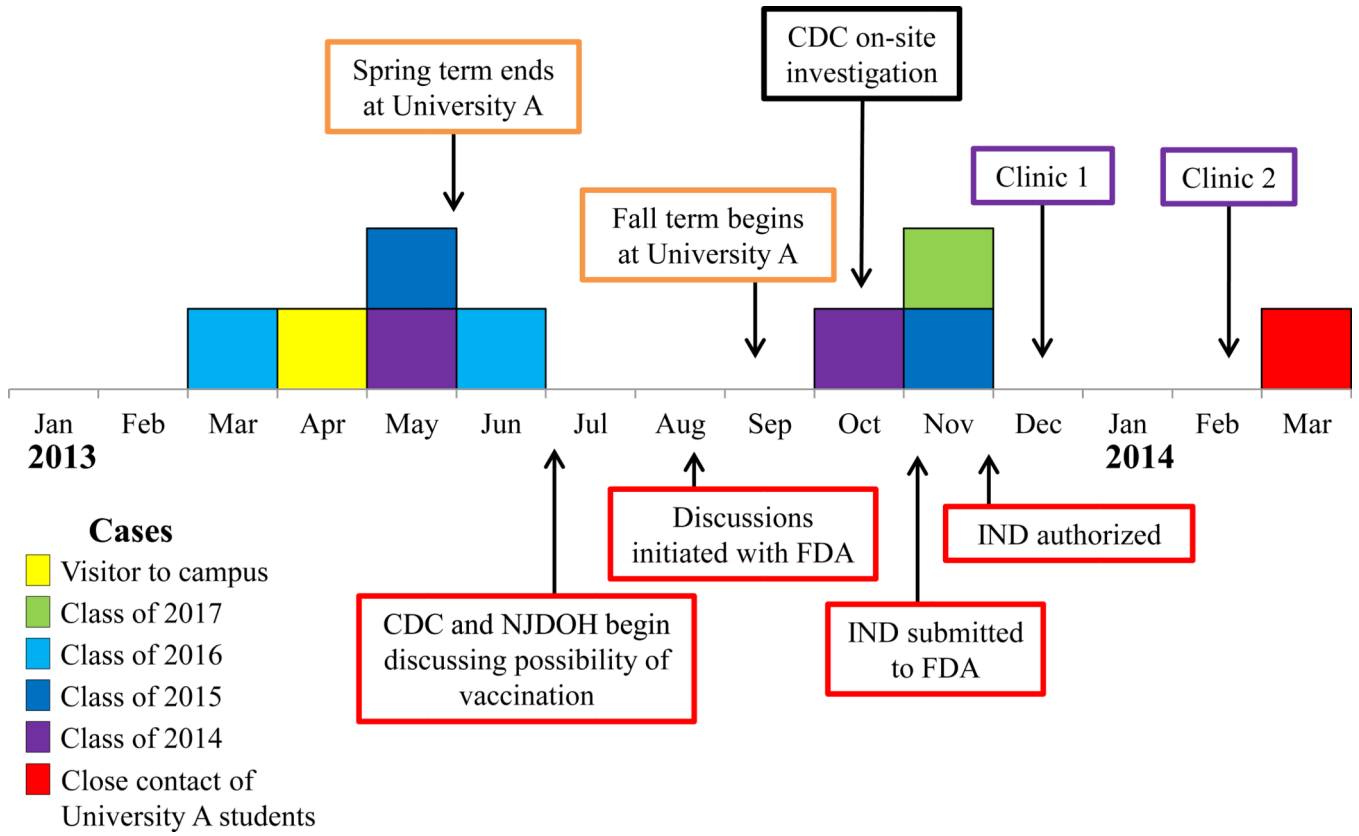


Figure 1. Timeline of outbreak cases and response activities.

4CMenB vaccine Vaccination Coverage in Targeted Populations at University A, December 9, 2013–May 14, 2014

Table 1

Constituency	# in Target Population	# First Doses Given	Coverage with First Dose (%)	# Second Doses Given	Coverage with Two-Dose Series (%)
Undergraduate students	5241	5062	96.6	4791	91.4
Class of 2017	1292	1260	97.5	1214	94.0
Class of 2016	1349	1296	96.1	1232	91.3
Class of 2015	1320	1274	96.5	1178	89.2
Class of 2014	1280	1232	96.3	1167	91.2
Graduate students	541	424	78.4	361	66.7
Other ¹	17	16	94.1	13	76.5
Total	5799	5502	94.9	5165	89.1

¹ Category includes faculty, staff, and graduate students with medical conditions that increase risk of meningococcal disease, and spouses and care-givers of graduate and undergraduate students living in a dormitory with the students.