

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 United States, 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 2-dose vaccination series was achieved in the target population. From the initiation of MenB vaccination through February 1, 2015, no additional cases of serogroup B meningococcal disease occurred in University A students. However, the ninth 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 ninth case demonstrates that carriage of serogroup B *Neisseria meningitidis* among vaccinated persons was not eliminated.

FREE

WHAT'S KNOWN ON THIS SUBJECT: Outbreaks of serogroup B meningococcal disease occur at universities and other organizations. 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 United States.

WHAT THIS STUDY ADDS: We describe 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 United States.

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Dr 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, and drafted the initial manuscript; Dr Shumate 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 of vaccination coverage and safety data, and critically reviewed the manuscript;

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 United States. However, in 2013, 2 recombinant MenB vaccines were under prelicensure review in the United States: the 3-dose vaccine rLP2086 (Trumenba; Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer, Inc., Philadelphia, PA) and the 2-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 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 2-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.

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 >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 United States, 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 3 weeks before 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 8 cases, *Neisseria meningitidis* serogroup was determined by slide agglutination at the state public health laboratory and confirmed by real-time polymerase chain reaction at CDC.²⁻⁴ Serogroup determination and Porin A (PorA) typing for 1 case was performed in Greece by using polymerase chain reaction.

At CDC, isolates were characterized by using pulsed-field gel electrophoresis, multilocus sequence typing, and molecular typing of factor H binding protein (fHbp), Neisserial heparin binding antigen (Nhba), *Neisseria meningitidis* adhesin A (NadA), and PorA, as previously described.⁵⁻⁸ Novartis assessed whether 4CMenB vaccine was expected to protect against the outbreak strain by using human serum bactericidal assay (hSBA) and

meningococcal antigen typing system (MATS).^{9,10}

Epidemiologic Investigation

After the sixth 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 risk¹ 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 the Food and Drug Administration 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 United States. 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 <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 after vaccination.

Potential vaccine recipients were notified of the clinic through multiple mechanisms, including e-mail, 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 nonstudents, by collecting copies of the informed consent paperwork. Reports of adverse events after 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, 7 cases occurred in University A undergraduates and 1 additional case occurred in a high school student who became ill after staying in an undergraduate dormitory at University A. Excluding the 1 case that occurred during the university's summer break, case-patients lived or stayed in 6 of the 50 undergraduate dormitories at University A immediately before 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, whereas 1 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 3 case-patients had long-term sequelae (unilateral hearing loss [$n = 1$], neurocognitive deficits [$n = 1$], and chronic headaches [$n = 1$]).

The ninth case occurred in March 2014, after the 4CMenB vaccination campaigns and 109 days after the eighth 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 before disease onset. The ninth 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 male (56%) and female individuals and across 4 undergraduate classes (Fig 1). No case-patients had a previous diagnosis of a medical condition that increases risk of meningococcal disease (ie, 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 on 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 8 cases identified in the United States were characterized further; all were sequence type 409 (ST-409) of clonal complex 41/44/Lineage 3 and had the same pulsed-field gel electrophoresis 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 2 academic years. Only 1 person was identified as a close contact of more than 1 case (cases 4 and 7); however, these cases occurred nearly 6 months apart and the contact in question received chemoprophylaxis immediately after 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, 5241 undergraduate and 2666 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,

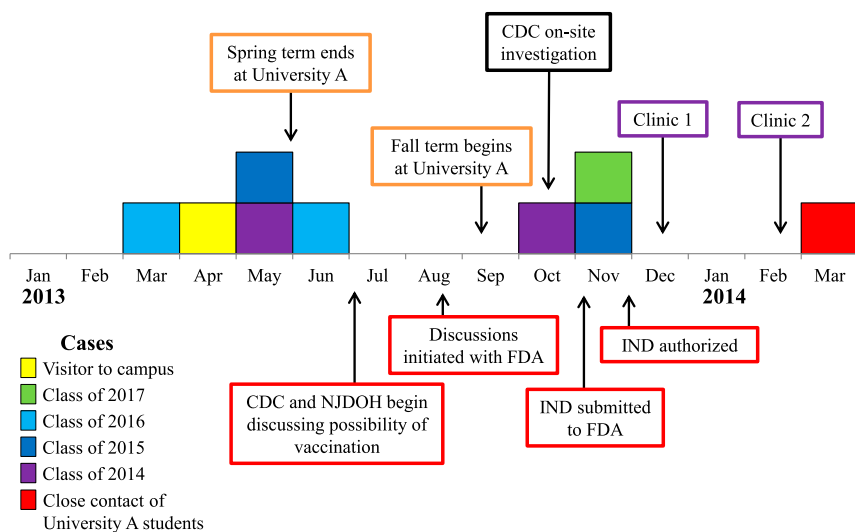


FIGURE 1
Timeline of outbreak cases and response activities.

$t = 13, P < .0001$). 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 ($n = 5241$); 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 caregivers 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 to 12, 2013, and the second-dose clinic was held February 17 to 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, 1 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 after 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 previously, the ninth case did occur after the vaccination campaigns. The ninth 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, before 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 United States. The attack rate among undergraduate students at University A, 134 per 100 000, was

more than 1400 times greater than the national incidence in this age group (1, CDC, unpublished data). Before 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 United States. Aside from the samples received from this outbreak, CDC has received only 9 (0.25%) serogroup B ST-409 isolates of 3595 unique case isolates that have been characterized by multilocus sequence typing (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 United States 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 United States.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 4 undergraduate class years, and

TABLE 1 Coverage of 4CMenB Vaccine in Targeted Populations at University A, December 9, 2013–May 14, 2014

Constituency	No. in Target Population	No. First Doses Given	Coverage with First Dose, %	No. Second Doses Given	Coverage with 2-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 ^a	17	16	94.1	13	76.5
Total	5799	5502	94.9	5165	89.1

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

therefore the entire undergraduate population was targeted for vaccination. Although 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 United States occur in persons aged <25 years and the mean age of the graduate students living in dormitories was <25 years.¹¹ Although 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.

More than 5000 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 e-mails, 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. Although 2 doses of the vaccine are critical for a sustained immune response,²⁰ 1 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 2 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, was licensed for use in individuals 10 to 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>. Although 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 United States.

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 ninth case demonstrates that carriage of serogroup B *N 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.

ACKNOWLEDGMENTS

We thank Evangeline Reynolds and Wendy Chung of Dallas County Health and Human Services, Dallas; Tamara Baldwin and Grace Kubin, Texas

Department of State Health Services, Austin; Johanna Vostok, Massachusetts Department of Public Health, Boston; Ami Patel, Office of Public Health Preparedness and Response, CDC, Atlanta, and Philadelphia Department of Public Health; Lauren Finn, Philadelphia Department of Public Health; Lisa Dettinger and Christina Russell, Pennsylvania Department of Health, Exton; Maria Orsini and Howard Sarubin, NJDOH, Trenton; and the staff of the Princeton Health Department, Princeton, the Mercer

County Division of Public Health, Trenton, Papageorgiou General Hospital, Thessaloniki, the American Hospital of Paris, Neuilly-sur-Seine, Drexel University, and the Presbyterian University Hospital for assistance with case investigations, contact tracing, and meningococcal testing. We are grateful to the staff of Novartis Vaccines and Diagnostics, Siena, Italy, for coordinating MATS and hSBA testing of patient isolates and vaccine procurement as well as for providing information about the

4CMenB vaccine. We thank Chad Myers and the New Jersey staff of Maxim Healthcare Services, Columbia, MD; Sarah Meyer and Tejpratap Tiwari, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, CDC, Atlanta; Natalie Kratz, CDC/Council of State and Territorial Epidemiologists Applied Epidemiology Fellow assigned to the NJDOH, Trenton; and the staff and students of University A for their work implementing and supporting the vaccination campaigns.

Dr Johnsen participated in collection of epidemiologic data on the cases and population at risk, contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, contributed to collection of vaccination coverage and safety data, and critically reviewed the manuscript; Ms MacNeil 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, and critically reviewed the manuscript; Dr Patel 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, and critically reviewed the manuscript; Dr Bhavsar and Ms Finnie contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, and critically reviewed the manuscript; Dr Cohn contributed to the conception and design of the epidemiologic investigation and analysis, and critically reviewed the manuscript; Ms Dinitz-Sklar and Dr Neglia participated in collection of epidemiologic data on the cases and population at risk, and critically reviewed the manuscript; Dr Duffy contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, contributed to collection and analysis of vaccination safety data, and critically reviewed the manuscript; Ms Garon and Mr Hary participated in collection of epidemiologic data on the cases and population at risk, and critically reviewed the manuscript; Drs Hu and Wang collected and analyzed laboratory data, and critically reviewed the manuscript; Dr Kamiya participated in collection and analysis of epidemiologic data on the cases and population at risk, contributed to collection of vaccination safety data, and critically reviewed the manuscript; Drs Kim, Kolligian, and Yu contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, and critically reviewed the manuscript; Ms Oakley contributed to collection and analysis of vaccination coverage data, and critically reviewed the manuscript; Ms J. Wagner and Ms K Wagner contributed to the conception and design of the vaccination campaign and vaccination coverage and safety data collection, contributed to collection of vaccination coverage data, and critically reviewed the manuscript; Drs Montana, Tan, and Clark and Ms Izzo contributed to the conception and design of the epidemiologic investigation and analysis, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-4015

DOI: 10.1542/peds.2014-4015

Accepted for publication Feb 19, 2015

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

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FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported in part by an appointment to the Applied Epidemiology Fellowship Program administered by the Council of State and Territorial Epidemiologists (CSTE) and funded by the Centers for Disease Control and Prevention Cooperative Agreement 5U38HM000414-5.

POTENTIAL CONFLICT OF INTEREST: Dr Johnsen was invited by Pfizer (manufacturer of rLP2086, Trumenba) to speak to their vaccine group and at 3 national conferences. Pfizer paid for Dr Johnsen's airfare and lodging to attend these events; he did not receive an honorarium or other reimbursements. Dr Johnsen was also invited by the National Meningitis Association to participate in a round table at another conference. The National Meningitis Association paid for Dr Johnsen's lodging but did not provide any honorarium or other reimbursements. The other authors have indicated they have no potential conflicts of interest to disclose.

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Pediatrics 2015;135;798

DOI: 10.1542/peds.2014-4015 originally published online April 27, 2015;

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Pediatrics 2015;135:798

DOI: 10.1542/peds.2014-4015 originally published online April 27, 2015;

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