HHS Public Access

Author manuscript

*J Am Coll Health*. Author manuscript; available in PMC 2019 June 17.

Published in final edited form as:

*J Am Coll Health*. 2017 ; 65(6): 380–388. doi:10.1080/07448481.2017.1312418.

# Safety of a meningococcal group B vaccine used in response to two university outbreaks

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## Abstract

**Objective:** To assess the safety of meningococcal group B (MenB)-4C vaccine.

**Participants:** Undergraduates, dormitory residents, and persons with high-risk medical conditions received the MenB-4C vaccine two-dose series during mass vaccination clinics from 12/2013 through 11/2014.

**Methods:** Adverse events (AEs) were identified by 15 minutes of observation postvaccination, spontaneous reports, surveys, and hospital surveillance. Causality was assessed for serious adverse events (SAEs).

**Results:** 16,974 persons received 31,313 MenB-4C doses. The incidence of syncope during the 15-minutes post-dose 1 was 0.88/1000 persons. 2% of participants spontaneously reported an AE (most common were arm pain and fever). 3 SAEs were suspected of being caused by the vaccine, including one case of anaphylaxis.

**Conclusions:** Most AEs reported were nonserious and consistent with previous clinical trial findings. Measures to prevent injury from syncope and to treat anaphylaxis should be available wherever vaccines are administered. Our safety evaluation supports the use of MenB-4C in response to outbreaks.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

**Keywords**

Latex hypersensitivity; meningococcal vaccines; *Neisseria meningitidis*; serogroup B; pharmacovigilance; postvaccination syncope; student health services

## Introduction

*Neisseria meningitidis* can cause meningitis or sepsis, either of which can be fatal or result in long-term disability.[1] *N. meningitidis* serogroups A, B, C, W, and Y are the most common causes of meningococcal disease. Vaccines to prevent infections by serogroups A, C, W, and Y have been recommended for adolescents in the United States since 2005.[2] The first meningococcal serogroup B (MenB) vaccine was approved in the United States in October 2014.

Meningococcal infections occur sporadically or as outbreaks. There were MenB outbreaks at seven US universities between 2008 and 2015.[3] Two US universities experienced unrelated MenB outbreaks in 2013. Between March 2013 and March 2014, there were nine cases among persons linked to University A in New Jersey.[4] At University B in California, there were five cases among students between March and November 2013. Each university worked with their state and local public health authorities to provide antibiotic prophylaxis to close contacts of the MenB case-patients and launched health education campaigns in an attempt to prevent further cases. When these two outbreaks were identified, a MenB vaccine was not yet licensed in the US, but had already been studied in phase 3 clinical trials. The Centers for Disease Control and Prevention (CDC) received permission from the Food and Drug Administration (FDA) to sponsor mass vaccination campaigns using the four-component MenB vaccine (MenB-4C; Bexsero, Novartis Vaccines) at each university under an expanded access investigational new drug (IND) protocol. The purpose of the IND was to provide access to the vaccine to persons at increased risk of meningococcal disease because of these outbreaks, not to establish the efficacy or safety of the vaccine. However, vaccine safety monitoring was required under the IND, and we describe the results of the safety monitoring here.

## Methods

### Vaccination

Persons associated with each university who were determined to be at increased risk of MenB disease due to the outbreaks were eligible to receive vaccine, which included: all undergraduate students; anyone residing in a dormitory; and students, faculty, and staff with a medical condition that increases the risk of meningococcal disease (eg functional or anatomic asplenia, complement pathway deficiencies). The protocol was approved by the CDC institutional review board. Written informed consent was obtained from all participants ≥18 years old, and parental consent and written assent were obtained for participants <18 years. Vaccination costs were covered by each university; vaccine was offered free of charge to eligible individuals.

MenB-4C vaccine is a two-dose series with the doses administered at least 1 month apart via intramuscular injection into the deltoid muscle. MenB-4C was supplied in a prefilled syringe, the tip cap of which may contain natural rubber latex. The vaccine may contain less than 0.01 micrograms of kanamycin, which is an aminoglycoside antibiotic used in the manufacturing process.

Each university held mass vaccination clinics in a multipurpose room over 4- to 10-day periods. Up to 25 nurses administered as many as 2,000 doses per 8 hour day. A screened-off area with cots and limited medical supplies was set up for the use of a physician and nurse who were present to evaluate and treat any participant who might experience an adverse event (AE). Additional catch-up vaccination dates were offered for smaller numbers of individuals. Vaccines were administered at University A from December 2013 through November 2014 and at University B from February 2014 through June 2014.

Each participant completed a written questionnaire prior to vaccination to screen for potential contraindications or precautions to receiving MenB-4C, including hypersensitivity to vaccine components or latex, and also for conditions in which this vaccine had not been previously studied (those with chronic medical conditions or who were pregnant, breastfeeding, or aged >50 years). Persons who screened positive were interviewed by medical staff to determine whether vaccination could proceed or should be deferred pending additional information. In an effort to prevent postinjection syncope, participants were asked if they had a history of fainting with injections and were offered the opportunity to receive the injection lying down instead of seated. At University A, fainting history was assessed verbally by staff performing the injection; at University B, a written question was added to the screening questionnaire.

## Vaccine safety monitoring

An AE was defined as any untoward medical occurrence associated with the use of the vaccine, whether or not it was considered to be caused by the vaccine. A serious adverse event (SAE) was any AE that resulted in death, a life-threatening event, hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect.[5] To determine whether each SAE was suspected of being caused by the vaccine, we performed individual-level causality assessment.[6]

We identified AEs using active and passive methods. Clinic staff observed vaccinees in a seating area for 15 minutes post vaccination. We instructed participants to report anything that they considered to be a serious side effect to a dedicated phone number, which was answered 24 hours a day. Both universities had on-campus student health clinics where providers documented any visit by a participant in which either the patient or provider suspected an AE might be related to MenB-4C. When participants came to receive dose 2, they were required to complete a written questionnaire intended to solicit potential SAEs. We sent emails to participants 30 days following dose 2 (and to those who only received dose 1) requesting that they complete an online version of the same questionnaire regarding events that had occurred since the last dose. The health service at each university

communicated with local hospitals to document emergency department visits and inpatient admissions following vaccination among students.

### Analysis

We coded AEs and categorized SAEs using the medical dictionary for regulatory activities (MedDRA) version18. Each diagnosis or symptom was assigned to one MedDRA "Preferred Term." If a diagnosis was reported, then associated symptoms were not coded. Rates were calculated by dividing the number of AEs by the number of persons vaccinated or the person-time under surveillance as appropriate. Statistics were calculated using SAS9.3 and OpenEpi.[7]

## Results

University A had 6,556 undergraduates eligible for vaccination (representing 5 class years) of whom 98% received the first dose and 93% the second dose, for a series completion rate of 93%. There were 835 eligible graduate students. University B had 19,257 undergraduates (representing 4 class years) of whom 51% received the first dose and 40% the second dose, for a series completion rate of 78%. Very few graduate students were eligible for vaccination. For the two universities combined, there were 16,974 participants vaccinated with at least one dose and 31,313 total MenB-4C doses administered (Table 1).

### Screening

Prior to dose one, 7% screened positive for potential contraindications or precautions at University A and 8.4% at University B (excluding the additional question about fainting history) (Table 2). History of latex sensitivity was reported by 116 participants, but upon interview, only 9 (0.05% of participants screened) described a history consistent with a true hypersensitivity reaction. All 9 were asked to either provide medical documentation or consult with an allergist prior to vaccination, but 8 were lost to follow-up despite attempts to contact them. A possible aminoglycoside allergy led to deferral in only 1 participant. Two participants thought they might be pregnant, but both subsequently had a negative pregnancy test prior to vaccination. Overall, after interview by medical staff, only 20 (0.1% of all participants) were not allowed to be vaccinated immediately, and ultimately only 1 participant was determined after receipt of medical history documentation to have a true contraindication to receiving the vaccine (a severe latex allergy).

### All adverse events

At University A, we collected 754 AE reports regarding 640 unique individuals, and at University B, we collected 964 AE reports regarding 784 unique individuals (Table 3). For both universities combined an AE was recorded for 8.4% of vaccinated individuals. The AEs corresponded to 292 different MedDRA Preferred Terms (ie distinct types of events). Overall, the most commonly reported AEs were pain in the injected arm (10%), fever (9%), headache (5%), nausea (4%), and fatigue (4%).

There were 114 AEs during the 15-minute observation period; the most common were presyncope (56%), syncope (15%), dizziness (6%), nausea (4%), and anxiety (3%). Two

participants were treated for pruritus with oral antihistamines. One had localized pruritus of the anterior neck. The other developed generalized pruritus 4 hours after the first dose and began having itching on the back within 15 minutes of the second dose. There were no SAEs during the 15 minutes.

Only 2% of vaccinated individuals spontaneously reported a concern or sought medical care or advice for an AE by calling the phone line or making a clinic visit. Phone calls most commonly concerned fever (14%), pain in the injected arm (10%), chills (8%), headache (7%), nausea (6%), fatigue (5%), dizziness (5%), and myalgia (5%). 17% of all phone calls were regarding injection site reactions alone. At University A, half of the phone calls occurred on postvaccination days 0 and 1, and 90% by day 9 (range 0–130); at University B, half of the phone calls occurred on postvaccination days 0 and 1, and 90% by day 6 (range 0–27). The most common AEs recorded during clinic visits were pain in the injected arm (13%), fever (8%), headache (8%), sore throat (6%), fatigue (5%), nausea (5%), myalgia (4%), dizziness (3%), and neck pain (3%). Among all clinic visit AEs, 21% were injection site reactions alone. At University A, half of the clinic visits occurred on postvaccination days 0 and 1, and 90% by day 8 (range 0–59); at University B, half of the clinic visits occurred by postvaccination day 4, and 90% by day 17 (range 0–59). The types of AEs reported by phone and clinic visits were similar following both doses.

The AE questionnaire administered in person prior to dose 2 and online following dose 2 (or following dose 1 for those who received only one dose) asked participants to report AEs regardless of whether or not they believed the AE was caused by the vaccine. The two most common AEs identified by this method were pain in the injected arm (10%) and fever (8%), but the third most common was emergency room visits for alcohol poisoning (3%). Injuries from accidents and sports accounted for 10% of AEs reported on the questionnaires. There were no AEs associated with pregnancy. Eight participants became pregnant following vaccination, but all had elective abortions for reasons unrelated to vaccination.

### Serious adverse events

Among all persons vaccinated, 54 (0.3%) experienced an SAE (University A, n = 27; University B, n = 27). These included 52 hospitalizations, 1 death, and 1 potentially life-threatening event. The death was an accidental drowning that occurred 27 days post dose 1 and was not related to vaccination. The most common category of SAE was “infections and infestations” (n = 16), which includes appendicitis, the single most common diagnosis among SAEs (n = 8) (Table 4). Seven appendicitis cases occurred following dose 1 (symptom onset ranged from 0 to 54 days postvaccination). The eighth case had onset 14 days after dose 2. The incidence of appendicitis during the safety monitoring period among persons vaccinated was 1.14 per 1000 person-years. This is similar to the baseline incidence rate in the United States of 1.53/1000 person-years for ages 10–19 years and 1.30/1000 for ages 20–29 years.[8]

The second most common category of SAE was “psychiatric disorders” (n = 13). 11 of these cases were identified at University B, which routinely tracked mental health hospital admissions among its undergraduate students. The incidence of mental health hospitalizations at University B among vaccinated persons was 2.75 per 1000 person-years,

which was lower than the baseline rate of 4.48 per 1000 person-years during the calendar year prior to the start of the MenB-4C vaccination program. The distribution of the diagnoses for these cases was also similar to base-line (data not shown).

Only three SAEs were suspected of being caused by MenB-4C vaccine. First was a case of rhabdomyolysis requiring hospitalization in a 20-year-old male following dose 2. He lifted weights soon after vaccination and developed myalgia and fever later that day. The myalgia was in the shoulders and back and increased over the next 2 days after which his serum creatine phosphokinase was found to be elevated. Vaccination is unlikely to be a sufficient cause of rhabdomyolysis, but based on the timing it may have been a contributory factor, so the AE was considered to be possibly related to vaccination. Second was a case of anaphylaxis in a 22-year-old female. She developed swelling in her throat and face 30 minutes following dose 1. She was treated in the clinic and emergency room with quick resolution of symptoms. Of note, she had hives on her trunk during the 2 days prior to vaccination, which may have been related to a topical medication for skin infection. This AE was classified as serious because it may have progressed to a life-threatening condition if the participant had not been evaluated and treated promptly. Third was an 18-year-old male participant who developed fever, myalgia, malaise, and neck stiffness approximately 7 hours following dose 1. Tests for infectious diseases, including lumbar puncture, were negative, but he was hospitalized for 1 day and treated empirically with antibiotics. His symptoms resolved within 24 hours. This event was determined to be possibly related to vaccination based on the timing of symptom onset and the absence of an identified alternative cause.

### Urticaria and rash

Few participants reported events that could potentially represent hypersensitivity reactions. Urticaria was reported by 61 (0.4%) participants, but only 6 made a clinic visit and 7 a phone call regarding the urticaria. Three participants reported injection site urticaria after dose 1, but all received dose 2 without any additional AEs reported. Urticaria that began on postvaccination days 0 or 1 was reported by 18 (0.1%) participants. These events are not necessarily vaccine related, but are more likely to be so than urticaria with later onset.[9] Nonurticarial rashes were reported by 86 (0.5%) participants (22 injection site rash and 64 at other body sites); 16 involved a clinic visit and 26 made phone calls. No one reported a rash after both doses. Most (77%) injection site rash reports were not medically attended and the descriptions given did not always clearly differentiate from injection site erythema. Only one dermatologic condition was considered clinically significant: a 19-year-old female developed a persistent papular rash on her extremities 1 day following dose 2. She had multiple medical visits and a skin biopsy diagnosed leukocytoclastic vasculitis, which resolved with oral corticosteroids. The causality assessment was indeterminate.

### Syncope and presyncope

Syncope and presyncope occurred most commonly during the 15-minute observation period, though in some cases it occurred later (Table 5). Syncope cases occurred throughout the 15-minute observation period, not all were at the time of injection. The incidence of syncope during the 15-minute observation period following dose 1 was higher for women (1.45 per 1,000) than for men (0.38 per 1,000), $p = 0.02$. Presyncope also occurred more frequently in

women (4.69 versus 3.20 per 1,000), $p = 0.08$. Two participants sustained minor lacerations after falling, and another participant fell from a standing position and hit his head resulting in an emergency room evaluation but no injuries. Persons who had syncope or pre-syncope following dose 1 were no less likely to receive dose 2 than those who did not ($p = 0.30$). Only one person had syncope after both doses.

At University B, 5% of participants reported a history of fainting on the pre-dose 1 screening. During the 15-minute observation period, the occurrence of syncope among those who reported a history of fainting [n = 1 (0.20%)] was not significantly greater than those without such a history [n = 7 (0.07%)], $p = 0.67$, whereas the occurrence of presyncope was significantly greater for those with a fainting history [n = 13 (2.61%)] compared to those without [n = 32 (0.34%)], $p < 0.0001$. Screening did not identify everyone who would experience postvaccination syncope or presyncope. Among cases that occurred during the 15-minute observation period, 74% had not reported a history of fainting. Specifically among those with syncope, 87% had not reported a history of fainting. The relative risk of syncope at University B compared to University A controlling for sex was 0.65 (95%CI: 0.23, 1.78) and of presyncope was 1.51 (95%CI:0.89, 2.54).

## Comment

During large vaccination campaigns with MenB-4C at two US universities in which vaccinated persons were given multiple opportunities and methods to report AEs following vaccination, 8% reported an AE, of which 96% were not serious. The most common AEs reported were fever and pain in the injected arm, which were expected based on the clinical trials of this vaccine.[10–13] Anecdotally, many more vaccinees experienced pain in the injected arm than who reported it. Participants were not required to report every nonserious symptom, and not all felt the need to seek care or advice for these milder types of reactions. The anticipatory guidance provided about the expected types and severity of adverse reactions may have reduced the number of individuals who sought medical care or advice. Our results indicate the amount of health care utilization to expect for a mass vaccination campaign using MenB-4C; 2% of vaccine recipients called or visited the clinic for an AE, mostly within the first week postvaccination.

It should be kept in mind that not all AEs that occur after vaccination are caused by the vaccine. For some events, the timing is coincidental. We did not perform individual level causality assessment for all the nonserious AEs reported, however some clinic visits were for events such as pharyngitis and upper respiratory tract infection, which were most likely not related to vaccination. Individual-level causality assessment was done for all SAEs, and only 3 were even suspected of being caused by the vaccine. All three of these participants recovered with no long-term sequelae. One participant had an anaphylactic reaction, which quickly resolved with outpatient treatment. Anaphylaxis is possible with any type of vaccine, but is rare, occurring in about 1 per million vaccine doses.[14] This is the only known case of anaphylaxis following MenB-4C reported to date. Too few doses have been given to date to know whether MenB-4C might be associated with a different rate of anaphylaxis than other vaccines.

Causality assessment can also be evaluated at the population level by looking at the observed incidence rate of an AE and comparing it to the background rate in the population expected to occur by chance alone. Appendicitis was the most common diagnosis among SAEs. While these cases were not suspected of being caused by vaccine at the individual level, the lack of association with vaccine is supported by the population level assessment, which found the observed rate to be similar to the expected rate. The vast majority of vaccine recipients were aged 18–22, and appendicitis is a relatively common condition in this age group. There were only single cases of most other types of SAEs, so comparison to background rates was not performed for those.

AE monitoring was required because these vaccination programs were conducted under an IND. Now that MenB vaccines are licensed in the United States, colleges or other organizations conducting MenB vaccination campaigns would not be required to conduct this type of extensive safety monitoring. However, observing patients for 15 minutes after vaccination in a seated or lying position is advised for all vaccines given by injection, regard-less of the setting of vaccination.[15] This is because of concern for syncope. Syncope can result in injuries from falling, which can be serious.[16] There are few publications reporting postvaccination syncope rates, and estimates vary by the age group studied and/or the method of ascertainment. The syncope rate we observed in this population of mostly 18–22 year olds was lower than the rate in adolescent girls who received HPV vaccine in several US health care organizations but higher than in US military personnel.[17,18] We observed a higher rate with the first dose in the series, suggesting that those who had syncope/presyncope after dose 1 may have been more likely to take preventive measures for dose 2. Also of note is that the fainting history screening approach with a written questionnaire and medical consultation used at University B did not result in a lower rate of syncope following dose 1 compared to verbal screening by vaccine administrators used at University A. The screening did not identify most of the people who would go on to experience syncope or presyncope following dose 1, which reinforces the need for all persons being vaccinated to follow the Advisory Committee on Immunization Practices (ACIP) guidelines about postvaccination observation to prevent injuries.

### Limitations

We did not require participants to report nonserious AEs, therefore the incidence of expected AEs such as pain in the injected arm or myalgia is likely underestimated. The online AE questionnaire sent following the last dose had a low response rate at both universities (≤51%). Other methods of reporting were available following both doses, so it is unlikely that any SAE a participant believed to possibly be vaccine-related went unreported. It was not possible to evaluate vaccine effectiveness in these vaccination programs, but no cases of MenB disease occurred in participants who received one or more doses of MenB-4C vaccine.

## Conclusion

The ACIP currently recommends use of MenB vaccine during outbreaks and also for persons who are at increased risk for serogroup B meningococcal disease because of certain

risk factors.[19] The ACIP also states that a MenB vaccine series may be administered to adolescents and young adults aged 16–23 years based on individual clinical decision making.[20] Our vaccine safety evaluation identified no adverse reactions with lasting sequelae and supports the use of MenB-4C in response to outbreaks. A second MenB vaccine (Trumenba, Pfizer), which was not evaluated in this safety assessment, was also licensed in the United States after these two outbreaks. As with all vaccines, CDC and FDA will continue to monitor the safety of MenB vaccines now that they are licensed. Providers and patients in the United States are encouraged to report clinically significant AEs to the Vaccine Adverse Event Reporting System, even if unsure of whether the vaccine caused the AE.[21]

## Acknowledgments

The authors would like to thank the following individuals for their contribution to data collection: Anna Acosta, Maria Cano, Hema Datwani, Temitope Folaranmi, Hajime Kamiya, Sarah Meyer, Heidi Soeters, Lakshmi Sukumaran, and Tejpratap Tiwari (CDC); Natalie Kratz, Prathit Kulkarni, and Alice Shumate (New Jersey Department of Health); Tanesha Barnwell, Janet Neglia, Judith Oakley, and Peter Suttile (Princeton University); and Stephanie Coghlan, Thomas Dixon, Elizabeth Downing, Kim Finegold, Leticia Gonzalez, Nancy Gustafson, Mark Hansen, Dana Huffman, Betsy Reynolds-Malear, and Holly Smith (University of California Santa Barbara). The authors would also like to thank the CDC's Clinical Immunization Safety Assessment project staff and consultants for their assistance with clinical review of selected AEs, especially the following individuals: Steven Black, Karen Broder, C. Buddy Creech, Kathryn M. Edwards, Michael Gronostaj, Lee Hampton, Theresa Harrington, and Devindra Sharma.

Conflict of interest disclosure

The authors confirm that the research presented in this article met the ethical guidelines, including adherence to the legal requirements, of the United States and received approval from the Institutional Review Board of the Centers for Disease Control and Prevention. Dr. Johnsen received travel support from Pfizer and Dr. Ferris received travel support from Pfizer, Novartis, and the National Meningitis Association to attend meetings to share their experiences responding to these out-breaks. The other authors have no conflicts of interest to report.

Funding

The information reported in this paper was generated as part of public health outbreak response activities paid for by Princeton University, the University of California Santa Barbara, and the Centers for Disease Control and Prevention. There was no external funding.

## References

1. CDC. Meningococcal Disease. 2016 Available at: http://www.cdc.gov/meningococcal/index.html. Accessed May 11, 2016.
2. Cohn AC, MacNeil JR, Clark TA, et al. Prevention and control of meningococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2013;62(RR-2):1–28.
3. MacNeil J Considerations for Use of Serogroup B Meningococcal (MenB) Vaccines in Adolescents Advisory Committee on Immunization Practices; 6 24, 2015; Atlanta, GA.
4. McNamara LA, Shumate AM, Johnsen P, et al. First Use of a Serogroup B Meningococcal Vaccine in the US in Response to a University Outbreak. Pediatrics. 2015;135 (5):798–804. [PubMed: 25917990]
5. IND safety reporting. 21 CFR § 312.32 (2010).
6. Halsey NA, Edwards KM, Dekker CL, et al. Algorithm to assess causality after individual adverse events following immunizations. Vaccine. 2012;30(39):5791–5798. [PubMed: 22507656]
7. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health. Available at: www.OpenEpi.com. Published 2013.

8. Buckius MT, McGrath B, Monk J, Grim R, Bell T, Ahuja V. Changing epidemiology of acute appendicitis in the United States: study period 1993–2008. J Surg Res. 2012;175(2):185–190. [PubMed: 22099604]

9. Wood RA, Berger M, Dreskin SC, et al. An algorithm for treatment of patients with hypersensitivity reactions after vaccines. Pediatrics. 2008;122(3):e771–777. [PubMed: 18762513]

10. Block SL, Szenborn L, Daly W, et al. A comparative evaluation of two investigational meningococcal ABCWY vaccine formulations: Results of a phase 2 randomized, controlled trial. Vaccine. 2015;33(21):2500–2510. [PubMed: 25795256]

11. Perrett KP, McVernon J, Richmond PC, et al. Immune responses to a recombinant, four-component, meningococcal serogroup B vaccine (4CMenB) in adolescents: a phase III, randomized, multicentre, lot-to-lot consistency study. Vaccine. 2015;33(39):5217–5224. [PubMed: 26232542]

12. Read RC, Baxter D, Chadwick DR, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. Lancet. 2014;384(9960):2123–2131. [PubMed: 25145775]

13. Santolaya ME, O'Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. Lancet. 2012;379(9816):617–624. [PubMed: 22260988]

14. McNeil MM, Weintraub ES, Duffy J, et al. Risk of anaphylaxis after vaccination in children and adults. J Allergy Clin Immunol. 2016;137(3):868–878. [PubMed: 26452420]

15. CDC. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2011;60(2):1–64.

16. Woo EJ, Ball R, Braun MM. Fatal syncope-related fall after immunization. Arch Pediatr Adolesc Med. 2005;159(11): 1083.

17. Gee J, Naleway A, Shui I, et al. Monitoring the safety of quadrivalent human papillomavirus vaccine: findings from the Vaccine Safety Datalink. Vaccine. 2011;29(46): 8279–8284. [PubMed: 21907257]

18. Oh G Syncope after immunization by injection, US armed forces 1998–2007. Med Surveillance Mon Rep. 2008;15(7): 2–5.

19. Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR. Use of serogroup B meningococcal vaccines in persons aged ≥10 years at increased risk for serogroup B meningococcal disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR. 2015;64(22):608–612. [PubMed: 26068564]

20. MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. Use of serogroup B meningococcal vaccines in adolescents and young adults: Recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR. 2015;64(41):1171–1176. [PubMed: 26492381]

21. Vaccine Adverse Event Reporting System (VAERS). Available at: https://vaers.hhs.gov/index. Accessed May 11, 2016.

**Table 1.**

Demographic characteristics and number of persons vaccinated with MenB-4C vaccine.

| | University A | University B | Combined |
|---|---|---|---|
| Doses administered | | | |
| Dose 1 | 7,143 | 9,831 | 16,974 |
| Dose 2 | 6,632 | 7,707 | 14,339 |
| Total doses | 13,775 | 17,538 | 31,313 |
| University affiliation | | | |
| Undergraduate students | 6,437 | 9,800 | 16,237 |
| Graduate students | 671 | 6 | 677 |
| Faculty/staff/other | 35 | 25 | 60 |
| Age in years, median (range) | 20(16–65) | 20(18–64) | 20 (16–65) |
| Sex | | | |
| Male | 3,713 | 4,247 | 7,960 |
| Female | 3,400 | 5,553 | 8,953 |
| Unknown | 30 | 31 | 61 |

**Table 2.**

Number of persons answering “yes” on questionnaire administered prior to dose 1 to screen participants for potential contraindications or precautions to receiving MenB-4C vaccine.

| Question | University A n (%) | University B n (%) | Combined n (%) |
|---|---|---|---|
| Are you aware of any severe reaction to any vaccine you have previously received that required medical attention? | 36 (0.50%) | 36 (0.37%) | 72 (0.42%) |
| Do you have a known sensitivity to latex? | 39 (0.55%) | 77 (0.78%) | 116 (0.68%) |
| Do you have a known allergy to kanamycin? (Kanamycin is an antibiotic similar to neomycin and streptomycin.) | 4 (0.06%) | 4 (0.04%) | 8 (0.05%) |
| Do you have any known serious or chronic medical problems that we should be aware of? | 420 (5.9%) | 726 (7.38%) | 1,146 (6.75%) |
| Are you older than 50 years? | 6 (0.08%) | 2 (0.02%) | 8 (0.05%) |
| Are you pregnant or think you could be pregnant? | 0 (0%) | 2 (0.02%) | 2(0.01%) |
| Are you breastfeeding? | 0 (0%) | 0 (0%) | (0%) |
| Have you ever fainted or passed out after getting a vaccine, receiving an injection, or having your blood drawn?[A] | n/a | 500 (5.08%) | n/a |

*Note*.

[A]This question was not included on the written questionnaire at University A and no data was collected for the verbal fainting history screening conducted there.

**Table 3.**

Number of adverse event reports following each MenB-4C vaccine dose in the two-dose series by method of report.

| | University A | | University B | |
|---|---|---|---|---|
| **Method of report** | **Dose 1 n (%)[A]** | **Dose 2 n (%)[B]** | **Dose 1 n (%)[A]** | **Dose 2 n (%)[B]** |
| 15-minute observation | 35 (0.49%) | 7(0.11%) | 67 (0.68%) | 5 (0.06%) |
| Phone call | 53 (0.74%) | 36 (0.54%) | 126(1.28%) | 104(1.35%) |
| Email | 5 (0.07%) | 2 (0.03%) | 0 | 0 |
| Clinic visit | 63 (0.88%) | 51 (0.77%) | 115 (1.17%) | 78(1.01%) |
| Pre-dose 2 questionnaire[A] | 328 (4.95%) | n/a | 333 (4.32%) | n/a |
| Online questionnaire[C] | 11 (0.15%) | 156 (2.35%) | 11 (0.11%) | 80 (1.04%) |
| Local hospital surveillance | 2 (0.03%) | 5 (0.08%) | 30 (0.31%) | 15(0.19%) |
| Total | 497 (6.96%) | 257 (3.88%) | 682 (6.94%) | 282 (3.66%) |

*Note*.

[A]The percentage is among participants who received dose 1, except for the “pre-dose 2 questionnaire” row, which is among participants who received dose 2.

[B]The percentage is among participants who received dose 2.

[C]The online questionnaire was completed by 51% of participants at University A and 11% at University B.

**Table 4.**

Serious adverse events following MenB-4C vaccine identified at Universities A and B (n = 54) categorized by MedDRA "System Organ Class" categories.[A]

| MedDRA "system organ class" category | n | Primary MedDRA preferred term for each participant with an SAE (n)[B] |
|---|---|---|
| Infections and infestations | 16 | Appendicitis (8), gastroenteritis (4), cellulitis[C] (1), infective pulmonary exacerbation of cystic fibrosis (1), meningitis viral (1), pneumonia (1) |
| Psychiatric disorders | 13 | Suicidal ideation (6), depression (2), substance-induced psychotic disorder (2), bipolar disorder (1), panic attack (1), suicide attempt (1) |
| Injury, poisoning, and procedural complications | 6 | Limb fracture[D] (4), alcohol poisoning (1), stab wound (1) |
| Gastrointestinal disorders | 5 | Abdominal pain (2), gastritis (1), gastrointestinal hemorrhage (1), small intestinal obstruction (1) |
| General disorders and administration site conditions | 5 | Pyrexia (4), drowning (1) |
| Musculoskeletal and connective tissue disorders | 3 | Rhabdomyolysis (2), hip deformity (1) |
| Immune system disorders | 1 | Anaphylactic reaction (1) |
| Nervous system disorders | 1 | Seizure[E] (1) |
| Renal and urinary disorders | 1 | Renal failure[F] (1) |
| Reproductive system and breast disorders | 1 | Ovarian cyst (1) |
| Respiratory, thoracic, and mediastinal disorders | 1 | Pulmonary embolism[G] (1) |
| Surgical and medical procedures | 1 | Jaw operation[H] (1) |

*Note.*

[A] These serious adverse events (SAEs) occurred following vaccination, but were not necessarily caused by the vaccine. See the text for details on causality assessment of SAEs.

[B] Additional clarifying details about certain cases are provided in the footnotes.

[C] The cellulitis was on the knee.

[D] All 4 cases of bone fracture were due to accidental injuries.

[E] This was the participant's first-ever known seizure, which occurred following dose 1 on postvaccination day 22.

[F] Due to congenital renal hypoplasia.

[G] Diagnosed following onset of dyspnea on postvaccination day 8 in a female participant taking oral contraceptive pills.

[H] This surgery was performed for a condition that was known to exist prior to vaccination.

**Table 5.**

Number of persons vaccinated with MenB-4C vaccine who experienced postvaccination syncope or presyncope by timing of onset and dose number in the two-dose series.

| | University A | | University B | |
|---|---|---|---|---|
| **Onset** | **Dose 1 n (%)** | **Dose 2 n (%)** | **Dose 1 n (%)** | **Dose 2 n (%)** |
| During 15-minute observation | | | | |
| Syncope[A] | 7 (0.10%) | 1 (0.02%) | 8 (0.08%) | 2 (0.03%) |
| Presyncope[A] | 21 (0.29%) | 3 (0.05%) | 45 (0.46%) | 2 (0.03%) |
| Postvaccination days 0 and 1, excluding 15-minute observation | | | | |
| Syncope | 1 (0.01%) | 1 (0.02%) | 5 (0.05%) | 1 (0.01%) |
| Presyncope | 0 | 4 (0.06%) | 5 (0.05%) | 1 (0.01%) |
| Postvaccination day ≥2[B] | | | | |
| Syncope | 6 (0.08%) | 1 (0.02%) | 5 (0.05%) | 0 |
| Presyncope | 0 | 0 | 0 | 0 |

*Note.*

[A] A case of syncope was defined as a brief loss of consciousness as evidenced by a loss of postural tone. A case of presyncope was defined as a person reporting that they felt like they were about to faint but who did not lose consciousness or postural tone. Symptoms such as dizziness that occurred in a person who did not report that they felt like they were about to faint were not counted as presyncope.

[B] These syncope and presyncope events occurred from 2 to 53 days postvaccination.