ORIGINAL ARTICLE

Meningococcal B Vaccine and Meningococcal Carriage in Adolescents in Australia

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ABSTRACT

BACKGROUND

The meningococcal group B vaccine 4CMenB is a new, recombinant protein-based vaccine that is licensed to protect against invasive group B meningococcal disease. However, its role in preventing transmission and, therefore, inducing population (herd) protection is uncertain.

METHODS

We used cluster randomization to assign, according to school, students in years 10 to 12 (age, 15 to 18 years) in South Australia to receive 4CMenB vaccination either at baseline (intervention) or at 12 months (control). The primary outcome was oropharyngeal carriage of disease-causing *Neisseria meningitidis* (group A, B, C, W, X, or Y) in students in years 10 and 11, as identified by polymerase-chain-reaction assays for *PorA* (encoding porin protein A) and *N. meningitidis* genogroups. Secondary outcomes included carriage prevalence and acquisition of all *N. meningitidis* and individual disease-causing genogroups. Risk factors for carriage were assessed at baseline.

RESULTS

A total of 237 schools participated. During April through June 2017, a total of 24,269 students in years 10 and 11 and 10,220 students in year 12 were enrolled. At 12 months, there was no difference in the prevalence of carriage of disease-causing *N. meningitidis* between the vaccination group (2.55%; 326 of 12,746) and the control group (2.52%; 291 of 11,523) (adjusted odds ratio, 1.02; 95% confidence interval [CI], 0.80 to 1.31; P=0.85). There were no significant differences in the secondary carriage outcomes. At baseline, the risk factors for carriage of disease-causing *N. meningitidis* included later year of schooling (adjusted odds ratio for year 12 vs. year 10, 2.75; 95% CI, 2.03 to 3.73), current upper respiratory tract infection (adjusted odds ratio, 1.35; 95% CI, 1.12 to 1.63), cigarette smoking (adjusted odds ratio, 1.91; 95% CI, 1.29 to 2.83), water-pipe smoking (adjusted odds ratio, 1.82; 95% CI, 1.30 to 2.54), attending pubs or clubs (adjusted odds ratio, 1.54; 95% CI, 1.28 to 1.86), and intimate kissing (adjusted odds ratio, 1.65; 95% CI, 1.33 to 2.05). No vaccine safety concerns were identified.

CONCLUSIONS

Among Australian adolescents, the 4CMenB vaccine had no discernible effect on the carriage of disease-causing meningococci, including group B. (Funded by GlaxoSmithKline; ClinicalTrials.gov number, NCT03089086.)

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Invasive meningococcal disease, caused by *Neisseria meningitidis*, is an important cause of disease and death worldwide, owing to difficulties in early diagnosis, a rapid clinical progression, and a high case fatality rate.[1,2] The most important meningococcal disease–associated capsular groups are A, B, C, W, X, and Y, with group B disease predominating in many high-income countries, including Australia.[1] Infants and adolescents are especially affected by meningococcal disease, and many countries are considering the implementation of meningococcal B vaccine programs.[1] A program involving administration of the meningococcal B vaccine 4CMenB (Bexsero, GlaxoSmithKline) in infants that was introduced in the United Kingdom in 2015 has been shown to protect of infants and toddlers for at least 2 years, following a two-dose priming schedule plus a booster at 1 year.[3]

Exposure to *N. meningitidis* is common in the general population, leading to asymptomatic pharyngeal carriage, which may be transient or long term.[4] Age influences carriage, with an increase in carriage prevalence from 15 years of age to a peak at approximately 19 years, probably owing to increases in the numbers and closeness of social contacts and behavior.[5-7] Meningococcal disease is a rare outcome of infection, and the relationship between carriage and risk of disease is incompletely understood.[8] Given that carriage and transmission rates are higher among adolescents than in other age groups, a reduction in carriage prevalence among adolescents could provide indirect protection to unvaccinated persons, including infants.[6]

Conjugate polysaccharide vaccines can induce mucosal respiratory responses that interfere with acquisition of carriage of several meningococcal capsular groups (e.g., group C and group W).[9,10] However, the same cannot be assumed for the protein and outer membrane vesicle antigens in meningococcal B vaccines, which, unlike capsular polysaccharides, vary antigenically among the circulating strains that express them. The South Australian meningococcal B vaccine carriage study "B Part of It" examined the effect of 4CMenB, a multiantigen vaccine designed to control group B meningococcal disease, on the carriage of disease-causing meningococci in adolescent students in order to inform the design of meningococcal vaccine programs and the assessment of cost-effectiveness globally.[11,12]

METHODS

TRIAL DESIGN AND OVERSIGHT

This investigator-initiated and -led, parallel, cluster-randomized, controlled trial was conducted in the Australian state of South Australia from 2017 through 2018 in accordance with a previously published protocol,[12] available with the full text of this article at NEJM.org. The trial was designed and overseen by an independent scientific advisory committee and was managed by the University of Adelaide. GlaxoSmithKline provided a research grant to fund the trial and provided 4CMenB vaccine free of charge. Employees of GlaxoSmithKline contributed to the trial conception, the protocol, and the interpretation of results but played no role in the data collection or analysis.

The protocol was approved by the Women's and Children's Health Network Human Research Ethics Committee.[12] The trial was performed in accordance with the Declaration of Helsinki and with the Good Clinical Practice guidelines of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. The authors assume responsibility for the accuracy and completeness of the data and vouch for the fidelity of the trial to the protocol.

PARTICIPANTS

All 260 secondary schools in South Australia were invited to participate, with oropharyngeal swabbing and vaccination of students provided through the school immunization program, which was managed by the Immunisation Section of SA Health. Each school year level in South Australia comprises 19,000 to 20,000 students. All secondary school students in years 10, 11, and 12 (approximately 15 to 18 years of age) in 2017 were eligible to participate if they provided written informed consent (for those ≥18 years of age or older; those <18 years of age provided assent, with written informed consent obtained from a parent or guardian), were available at school to undergo at least the first oropharyngeal swabbing, and were willing to adhere to the trial procedures. Students were ineligible if they had received 4CMenB previously, had previously had an anaphylactic reaction to any component of the vaccine, or were known to be pregnant.

Because year 12 is the final year of schooling

in Australia, the trial was designed to include the 12-month results of oropharyngeal swabbing only in students who were in years 10 and 11 in the first year of the study in order to provide data for the primary-outcome analysis. Students in year 12 contributed to the baseline analysis of risk factors for carriage because they were likely to have the highest carriage rates and also in an effort to reduce any possible effect of the vaccine on carriage due to the mixing of unimmunized year 12 students with immunized year 10 and 11 students at schools assigned to the vaccination group.

OUTCOMES

The primary outcome was the prevalence of carriage of any disease-causing genogroup of *N. meningitidis* (A, B, C, W, X, or Y) at 12 months. Secondary outcomes were the prevalence of carriage at 12 months of each individual genogroup (A, B, C, W, X, and Y) and of any *N. meningitidis* and the acquisition of carriage (i.e., negative status at baseline and positive status at 12 months) of disease-causing genogroups and of any *N. meningitidis*. In addition to comparisons of the randomized groups, a further objective of the trial was to identify the characteristics associated with baseline carriage of disease-causing genogroups and any *N. meningitidis*.

RANDOMIZATION AND BLINDING

Schools were randomly assigned to the intervention group (in which students received two doses of 4CMenB 2 months apart) or the control group (in which students received 4CMenB vaccination after the 12-month oropharyngeal swab). Stratification factors were school size (<60, 60 to 119, and ≥120 students per year level) and school socioeconomic status, as measured by the Index of Community Socio-Educational Advantage (ICSEA; scores range from approximately 500 to 1300, with higher scores indicating more educational advantage; the categories for this study were as follows: <970 [low], 970 to 1020 [medium], and >1020 [high]).[13] The randomization schedule was generated by an independent statistician using Stata software, version 14. School staff and students were unaware of their group assignments until the day of the first trial visit (Fig. S1 in the Supplementary Appendix, available at NEJM.org). Laboratory personnel and investigators were unaware of the group assignments for the duration of the trial.

TRIAL PROCESSES

Written informed consent was obtained from a parent or guardian with assent obtained from the student (for those <18 years of age), or written informed consent was obtained from the student (for those ≥18 years of age). Participants completed a questionnaire to obtain information on characteristics relevant to meningococcal carriage (e.g., smoking history, household size, and recent antibiotic use) at each swab visit at school and were provided with an A$20 iTunes gift card on questionnaire completion. All the collected data were securely stored in a database held by Adelaide Health Technology Assessment at the University of Adelaide.

Oropharyngeal swabs were obtained by nurses using a standardized technique of wiping a flocculated swab across the posterior oropharynx from one tonsillar area to the other. Swabs were placed immediately in a transport medium (skim milk, tryptone, glucose, and glycerine; Thermo Fisher Scientific), placed in a portable cooler, and delivered to a central laboratory (SA Pathology). On receipt of the samples, DNA was extracted with the use of Roche MagNA Pure analyzers, followed by polymerase-chain-reaction (PCR) screening for the presence of specific meningococcal DNA. An assay specific for the detection of *PorA* (encoding porin protein A) was used because of its high sensitivity to and specificity for all pharyngeal carriage of *N. meningitidis*.[14,15] Samples with a positive result for *PorA* on PCR were genogrouped according to group-specific PCR results (genogroups A, B, C, W, X, and Y) and subsequently cultured for neisseria species on selective agar with incubation in 5% carbon dioxide at 35°C. Plates were examined daily up to 72 hours for the presence of *N. meningitidis*. All isolates were identified by means of standard diagnostic laboratory methods, including oxidase reaction, matrix-assisted laser desorption–ionization with time-of-flight mass spectrometry, and a further genogrouping PCR assay.[12] Samples and isolates were classified as not able to be grouped if the capsule biosynthesis genes for these genogroups were not detected.

STATISTICAL ANALYSIS

Assuming a carriage prevalence of 8% in the unvaccinated cohort,[16] we calculated that a sample of 12,160 participants in each group would provide the trial with 90% power to detect a 20% relative lower risk of carriage (6.4% vs. 8%) among vaccinated participants (at a two-tailed alpha of 0.05). If enrollment or trial completion were lower than expected, the trial would still have 80% power, provided that swab results at 12 months were obtained for at least 8970 participants per group. These calculations incorporated a design effect of 2.19, on the basis of an average of 120 students per school and an intraclass correlation coefficient estimate of 0.01.[17]

Analyses were undertaken according to a prespecified statistical analysis plan. Data were analyzed according to the randomized group of the student's school (intention-to-treat principle). A sensitivity per-protocol analysis of the primary outcome was also conducted; this analysis included students in the vaccination group who received two doses of 4CMenB and students in the control group who did not receive 4CMenB before the 12-month follow-up.

The primary outcome of carriage of disease-causing *N. meningitidis* genogroups detected by PCR at 12 months was compared between groups with the use of logistic regression, with generalized estimating equations used to account for clustering at the school level. The difference in carriage between groups was expressed as an odds ratio with a 95% confidence interval. Adjustment was made for the student's baseline carriage and randomization strata (school size and ICSEA category). Secondary carriage outcomes were also compared between groups with the use of logistic generalized estimating equations. Missing data on the carriage outcomes were addressed with the use of multiple imputation, with imputation performed separately for the two randomized groups with the use of chained equations.[18] In planned subgroup analyses of the primary and secondary outcomes, the effect of the 4CMenB vaccine was examined separately in metropolitan and rural schools and in students in year 10 and year 11; on the basis of the number of interaction tests, one significant test ($P<0.05$) would be expected by chance alone. No adjustment was made for multiple hypothesis testing, so P values are provided only for the primary outcome and for interaction tests in subgroup analyses. All the analyses were performed with the use of SAS software, version 9.4, and Stata software, version 15.

RESULTS

CHARACTERISTICS OF THE PARTICIPANTS

A total of 34,489 students in year 10, 11, or 12 were enrolled between April 1 and June 30, 2017, from 237 participating schools. A total of 24,269 students in years 10 and 11 (12,746 students in the vaccination group and 11,523 in the control group) contributed data for the primary-outcome analysis (Fig. 1). A total of 10,220 students in year 12 contributed to the analysis of risk factors for carriage. Primary-outcome data were available for 21,126 students (87.0%) after the withdrawal of 43 students and loss to follow-up of 3100 students (Fig. 1).

The characteristics of the participants at baseline were similar in the two groups (Table 1). In the vaccination group, 99.9% of the students received the first dose of 4CMenB, and 97.7% received the second dose.

PRIMARY OUTCOME

There was no significant difference in carriage prevalence of disease-causing *N. meningitidis* between the vaccination group (326 of 12,746 students [2.55%]) and the control group (291 of 11,523 students [2.52%]) in the intention-to-treat analysis at 12 months (difference, 0.03 percentage points; adjusted odds ratio, 1.02; 95% confidence interval [CI], 0.80 to 1.31; $P=0.85$) (Table 2). The adjusted intraclass correlation coefficient for the primary outcome was 0.005. There was little evidence of an effect of treatment when the analysis was restricted to complete cases, under a per-protocol or post hoc Bayesian analysis, or in sensitivity analyses that used the missing-data mechanism (see the Supplementary Appendix).

SECONDARY OUTCOMES

There were no significant between-group differences in any of the prespecified secondary outcomes regarding carriage (Table 2). In a post hoc analysis, the risk of nongroupable *N. menin-*

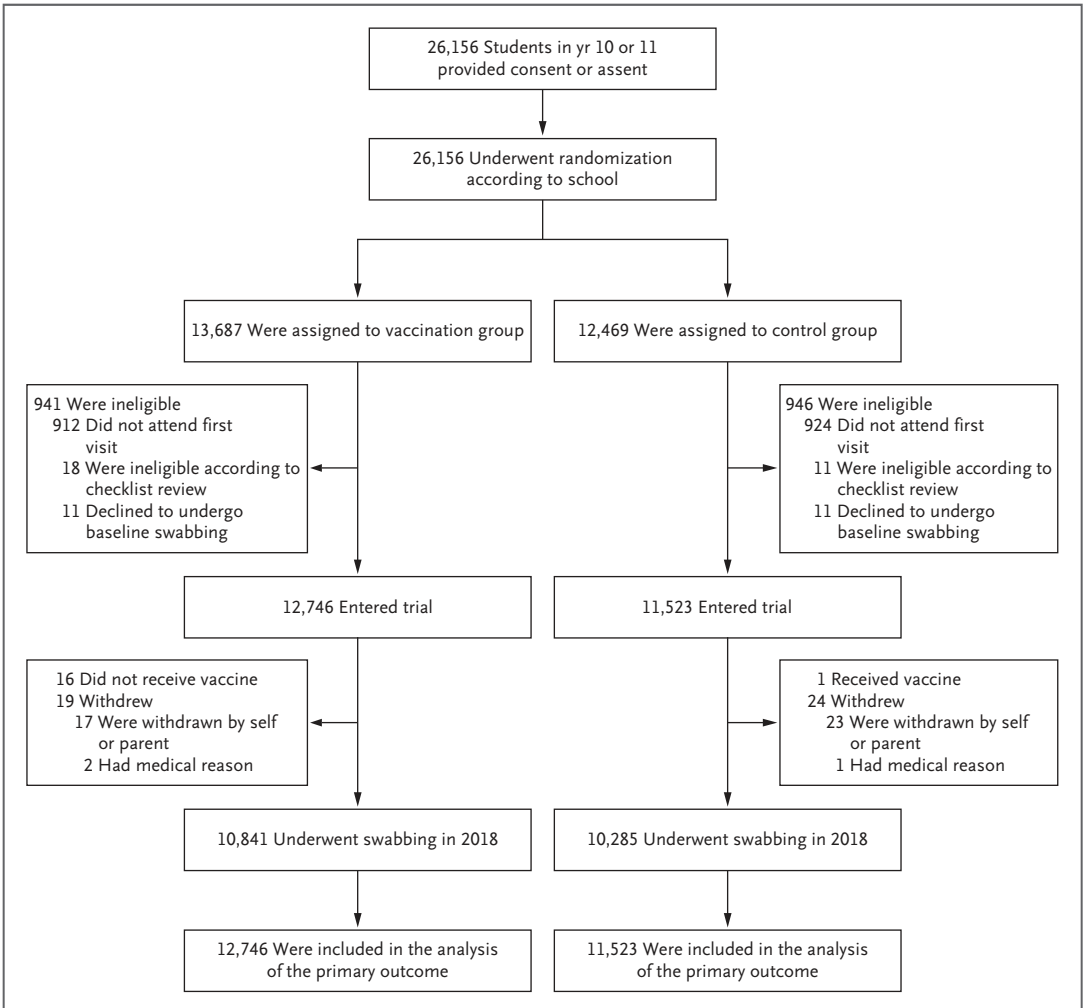

Figure 1. Consent, Randomization, and Follow-up of the Participants.

Written informed consent was obtained from a parent or guardian with assent obtained from the student (for those <18 years of age), or written informed consent was obtained from the student (for those ≥18 years of age).

gitidis was 29% lower in the vaccination group than in the control group (1.65% vs. 2.23%; adjusted odds ratio, 0.71; 95% CI, 0.54 to 0.91). Unimputed results were similar for all outcomes (Table S4).

RISK FACTORS FOR CARRIAGE

The risk factors for carriage of disease-causing *N. meningitidis* for all students enrolled in year 10, 11, or 12 included the following: later year of schooling (adjusted odds ratio for year 12 vs. year 10, 2.75; 95% CI, 2.03 to 3.73), current upper respiratory tract infection (adjusted odds ratio, 1.35; 95% CI, 1.12 to 1.63), cigarette smoking in the past week (adjusted odds ratio, 1.91; 95% CI, 1.29 to 2.83), water-pipe smoking in the past week (adjusted odds ratio, 1.82; 95% CI, 1.30 to 2.54), attending pubs or clubs in the past week (adjusted odds ratio, 1.54; 95% CI, 1.28 to 1.86), participation in intimate kissing in the past week (adjusted odds ratio, 1.65; 95% CI, 1.33 to 2.05), and being white (adjusted odds ratio for Asian vs. white race, 0.50; 95% CI, 0.31 to 0.80) (Table 3). The risk factors associated with carriage prevalence of any meningococci were similar, with the additional results that students of Aboriginal or Torres Strait Islander ethnicity had almost double the carriage prevalence as that among white students (6.72% vs. 3.66%; adjusted odds ratio, 1.49; 95% CI, 1.07 to

Table 1. Baseline Characteristics of the Students in Years 10 and 11, According to Trial Group.*

Characteristic	Vaccination Group (N=12,746)	Control Group (N=11,523)
School ICSEA category — no. (%)†		
<970	2175 (17.06)	2471 (21.44)
970 to 1020	3763 (29.52)	3601 (31.25)
>1020	6808 (53.41)	5451 (47.31)
School size — no. (%)‡		
<60 students/year level	2112 (16.57)	1536 (13.33)
60 to 119 students/year level	4181 (32.80)	3903 (33.87)
>119 students/year level	6453 (50.63)	6084 (52.80)
School location — no. (%)		
Metropolitan	9829 (77.11)	8147 (70.70)
Rural	2917 (22.89)	3376 (29.30)
Year of schooling — no. (%)		
10	6576 (51.59)	6188 (53.70)
11	6170 (48.41)	5335 (46.30)
Age — yr	15.6±0.7	15.6±1.2
Female sex — no. (%)	6670 (52.33)	5795 (50.29)
Boarding student — no./total no. (%)	340/12,686 (2.68)	190/11,469 (1.66)
Smoking in previous week — no./total no. (%)		
Cigarettes	209/12,666 (1.65)	181/11,454 (1.58)
Electronic cigarette	127/12,626 (1.01)	127/11,408 (1.11)
Water pipe	369/12,626 (2.92)	281/11,406 (2.46)
N. meningitidis carriage — no./total no. (%)		
Disease-causing genogroup§	169/12,735 (1.33)	163/11,519 (1.42)
Any *N. meningitidis*	356/12,735 (2.80)	302/11,519 (2.62)
Genogroup B	106/12,735 (0.83)	83/11,519 (0.72)
Genogroup C	3/12,735 (0.02)	7/11,519 (0.06)
Genogroup W	9/12,735 (0.07)	11/11,519 (0.10)
Genogroup X	2/12,735 (0.02)	2/11,519 (0.02)
Genogroup Y	52/12,735 (0.41)	63/11,519 (0.55)

* Plus–minus values are means ±SD. There was no significant difference in the baseline characteristics between the groups after clustering at the school level was accounted for. Percentages may not total 100 because of rounding.
† Scores on the Index of Community Socio-Educational Advantage (ICSEA) range from approximately 500 to 1300, with higher scores indicating more educational advantage. A score between 970 and 1020 indicates average status and is considered a benchmark.[13] The categories for this study were as follows: less than 970 (low), 970 to 1020 (medium), and greater than 1020 (high). The scores for all schools involved in the study ranged from 515 to 1177, with a median score of 1000.
‡ School size was assessed as follows: fewer than 60 students per year level indicated small size, 60 to 119 students per year level indicated medium size, and more than 119 students per year level indicated large size.
§ Disease-causing genogroup refers to all capsular genogroups identified (B, C, W, X, and Y).

2.06) and boarding students were at higher risk than day students (adjusted odds ratio, 2.10; 95% CI, 1.16 to 3.80) (Table S3).

Overall vaccine coverage (percentage of students who received the vaccine) among South Australian students was 62% (students in years 10 and 11 enrolled in the trial, divided by the total number of students in years 10 and 11). Vaccine coverage was at least 50% in 82% of the participating schools (89 of 109 schools) that

Table 2. Analysis of Primary and Secondary Outcomes for *N. meningitidis* Carriage and Acquisition at 12 Months with the Use of Multiple Imputation.*

Outcome	Vaccination Group (N=12,746)	Control Group (N=11,523)	Odds Ratio (95% CI)†
	no. (%)		
Carriage of disease-causing genogroup	326 (2.55)	291 (2.52)	1.02 (0.80–1.31)‡
Carriage of any *N. meningitidis*	547 (4.29)	561 (4.87)	0.85 (0.70–1.04)
Carriage of genogroup B	164 (1.29)	135 (1.18)	1.10 (0.81–1.47)
Carriage of genogroup Y	117 (0.92)	131 (1.13)	0.81 (0.56–1.18)
Carriage of genogroup W§	17 (0.16)	18 (0.18)	0.89 (0.43–1.85)
Carriage of genogroup C§	12 (0.11)	7 (0.07)	1.87 (0.63–5.55)
Carriage of genogroup X§	8 (0.07)	1 (0.01)	7.59 (0.98–58.83)¶
Acquisition of any *N. meningitidis*	430 (3.38)	427 (3.70)	0.91 (0.73–1.13)
Acquisition of disease-causing genogroup	272 (2.13)	238 (2.07)	1.03 (0.79–1.34)

* A P value is provided for the primary outcome only. The 95% confidence intervals for secondary outcomes have not been adjusted for multiple comparisons and hence should not be used to imply treatment effects. Missing data were multiply imputed. Average numerators across the 100 imputed data sets were rounded to the nearest integer value and hence may not correspond exactly with reported percentages. Genogroup A was not detected in any student.
† Analysis was adjusted for randomization strata and (excluding acquisition outcomes) corresponding baseline carriage result.
‡ P=0.85.
§ Multiple imputation was not applied owing to the small numbers of cases. Complete data were available for 10,841 students in the vaccination group and for 10,285 in the control group.
¶ We did not perform an adjusted analysis owing to the small number of cases.

had been randomly assigned to the vaccination group. There was no association between vaccine coverage and outcomes in schools in the vaccination group regarding carriage of disease-causing *N. meningitidis* (odds ratio per 1-percentage-point increase in coverage, 1.01; 95% CI, 0.995 to 1.02) or any *N. meningitidis* (odds ratio, 1.00; 95% CI, 0.99 to 1.01).

SUBGROUP ANALYSES ACCORDING TO RANDOMIZATION STRATA

Primary and secondary outcomes stratified according to school location (metropolitan or rural) and school year level (year 10 or 11) provided evidence of effect modification according to school location for the carriage of disease-causing meningococcal disease genogroups and all genogroups and for the acquisition of disease-causing genogroups (Tables S4 and S5). Post hoc tests revealed increased carriage (adjusted odds ratio, 1.49; 95% CI, 1.03 to 2.15) and acquisition (adjusted odds ratio, 1.50; 95% CI, 1.03 to 2.18) of disease-causing genogroups in rural schools and decreased overall carriage in metropolitan schools (adjusted odds ratio, 0.73; 95% CI, 0.58 to 0.93) in the vaccination group. However, these results should be interpreted with caution given the large numbers of interaction tests. There was no evidence of effect modification according to year level.

DISEASE EFFECT AND SAFETY

There were no cases of meningococcal B disease in this trial population during the trial period (2017–2018) and no cases to date (as of December 27, 2019), as compared with 12 cases among students 15 to 18 years of age from the period 2015–2016.[19] After the administration of 58,639 doses, 193 adverse events were reported in 187 students (187 of 58,639 [0.32%]), of which 9 were serious adverse events (Table S7). The most common adverse events reported were injection-site reactions (126 events), headache (99), and nausea (61).

DISCUSSION

This cluster-randomized, controlled trial provided evidence that 4CMenB had no effect on the carriage of disease-causing meningococci (including group B) in adolescents. These results have

Table 3. Risk Factors for Carriage of Disease-Causing Genogroup at Baseline in Students in Year 10, 11, or 12.

Characteristic	Participants	Odds Ratio (95% CI)*
	no./total no. (%)	
Sex		
Female	338/17,909 (1.89)	1.00
Male	330/16,550 (1.99)	1.09 (0.92–1.29)
Year of schooling		
10	130/12,757 (1.02)	1.00
11	202/11,497 (1.76)	1.64 (1.20–2.23)
12	336/10,205 (3.29)	2.75 (2.03–3.73)
Current upper respiratory tract infection		
No	478/26,959 (1.77)	1.00
Yes	186/7213 (2.58)	1.35 (1.12–1.63)
Smoked cigarettes in past week		
No	615/33,630 (1.83)	1.00
Yes	49/628 (7.80)	1.91 (1.29–2.83)
Smoked water pipe in previous week		
No	600/33,085 (1.81)	1.00
Yes	63/1042 (6.05)	1.82 (1.30–2.54)
Days out at pub or club in past week		
0	421/27,226 (1.55)	1.00
≥1	246/7064 (3.48)	1.54 (1.28–1.86)
No. of persons kissed intimately in past week		
0	372/25,865 (1.44)	1.00
≥1	278/7749 (3.59)	1.65 (1.33–2.05)
Boarding student		
No	644/33,546 (1.92)	1.00
Yes	21/756 (2.78)	1.33 (0.72–2.43)
Race or ethnic group†		
White	506/24,686 (2.05)	1.00
Aboriginal or Torres Strait Islander	32/953 (3.36)	1.34 (0.90–2.01)
Asian	31/3383 (0.92)	0.50 (0.31–0.80)
Other	87/4936 (1.76)	0.98 (0.76–1.26)

* Analyses were adjusted for the characteristics listed in the table as well as for school ICSEA category, school size, school location, antibiotic use, electronic cigarette use, and current relationship status.
† Race and ethnic group were reported by participating students.

informed policies regarding control of meningococcal disease, assessments of cost-effectiveness of 4CMenB immunization programs globally, and the design of the next generation of meningococcal B vaccines. Our findings differ from those regarding group A and C polysaccharide conjugate vaccines, in which an effect on carriage rates has been seen in observational studies assessing the effect of population-based vaccination programs.[9,20-22] Conjugate vaccine programs that achieve high coverage in adolescents have provided evidence of indirect protection to other age groups, thus reducing the need for vaccination of infants.[23,24]

The lack of effect of 4CMenB on carriage of disease-causing meningococci emphasizes the

need for direct protection of those at highest risk for meningococcal disease. Because the incidence of meningococcal disease peaks among preschool children and adolescents, it is important to consider vaccination for direct protection in these age groups. In South Australia, where 4CMenB is estimated to cover 90% of disease-causing isolates,[25] a program was implemented as of October 1, 2018, to vaccinate those at highest risk, including infants, toddlers (1 to 3 years of age), and adolescents and young adults (15 to 20 years of age).[26] It will be important to monitor the effect of the vaccine in this population-based program.

Our findings are consistent with those of a previous study, in which a small reduction in carriage of strains expressing groups C, W, or Y was attributed mostly to a reduction in group Y carriage with no effect on group B carriage.[27] The observed reduction in non–disease-causing meningococci in our trial may reflect an effect on unencapsulated meningococci, in which vaccine-type outer membrane proteins are potentially more exposed. Whole-genome sequencing and Bexsero Antigen Sequence Typing analysis of all isolates may assist in determining predictive coverage.

Smaller observational studies assessing the effect of 4CMenB and MenB-FHbp (Trumenba, Pfizer) in university outbreaks in the United States have also shown no significant effect on carriage.[28,29] Combined with our findings, these observations have implications for outbreak-control protocols. Although 4CMenB may reduce the risk of late cases in such outbreaks, it is unlikely to reduce transmission; therefore, antibiotics remain necessary to offer rapid elimination of carriage. Preexposure vaccination for those entering settings where the risk of outbreaks is high is likely to be a more effective use of the vaccine.

Important aspects of the trial design include randomization at the school level; a real-world setting, because students were enrolled at an age at which meningococcal vaccine programs are introduced to prevent invasive disease; a short enrollment period; the high retention of students in the trial; and high adherence to the trial protocol.

A limitation of the trial was the lower-than-anticipated prevalence of carriage of disease-causing *N. meningitidis* among adolescents at 12 months. Despite this, the 95% confidence interval for the primary outcome in the intention-to-treat analysis did not contain odds ratios less than 0.80, the value approximating our smallest clinically important difference. Similarly, per-protocol and post hoc Bayesian sensitivity analyses of the primary outcome provided little support for a clinically important effect of 4CMenB on carriage (Table S6), although the lower boundary of the 95% confidence interval in the per-protocol analysis was marginally less than 0.80. These results, along with the negative findings on secondary outcomes regarding carriage, suggest that 4CMenB was ineffective in reducing carriage of disease-causing *N. meningitidis*.

The trial was also limited by the fact that we used a single outcome measure of carriage after vaccination at 12 months, but this was chosen to reduce seasonal variation and to ensure that any reduction in carriage was sustained at least until 1 year after vaccination. Underestimation of the effect of vaccine on disease-causing or all meningococci due to moderate coverage rates is possible, and unvaccinated students may serve as a source of ongoing transmission. However, vaccine coverage of approximately 65% is realistic for vaccine programs involving students in high schools, and there was no association between school-level coverage and carriage.

In conclusion, our results did not show an effect of 4CMenB on carriage of disease-causing meningococci in a program involving adolescents that had moderate-to-high vaccine coverage.

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