ORIGINAL ARTICLE

Meningococcal B Vaccine to Prevent *Neisseria gonorrhoeae* Infection

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ABSTRACT

BACKGROUND

No vaccines are currently licensed for the prevention of *Neisseria gonorrhoeae* infection. Observational studies suggest that the four-component meningococcal serogroup B vaccine (4CMenB) may reduce the risk of gonorrhea.

METHODS

In this multicenter, double-blind, randomized, placebo-controlled trial, we assigned, in a 1:1 ratio, men who have sex with men (MSM) to receive two doses of 4CMenB or placebo. All the participants had recently received a diagnosis of *N. gonorrhoeae* infection or infectious syphilis and either tested negative for human immunodeficiency virus (HIV) and were receiving HIV preexposure prophylaxis or were living with HIV. Screening for sexually transmitted infections, including *N. gonorrhoeae* nucleic acid amplification testing of samples obtained from urogenital, anorectal, and oropharyngeal sites, was performed quarterly for 2 years. The primary outcome was a first *N. gonorrhoeae* infection after the receipt of vaccine or placebo in the per-protocol population (participants who received both 4CMenB or placebo doses, attended at least two scheduled follow-up visits after the second dose, and did not meet any exclusion criterion pertinent to the assessment of efficacy).

RESULTS

From July 2021 through May 2023, a total of 654 participants underwent randomization, of whom 587 were included in the primary analysis. The incidence of *N. gonorrhoeae* infection was 48.1 events per 100 person-years (160 events among 296 participants) in the 4CMenB group and 47.8 events per 100 person-years (155 events among 291 participants) in the placebo group (incidence rate ratio, 1.01; 95% confidence interval [CI], 0.80 to 1.26; P=0.97), for a vaccine efficacy of −0.5% (95% CI, −26.2 to 19.9). Vaccine efficacy was 5.5% (95% CI, −56.0 to 42.8) for symptomatic infection, −6.4% (95% CI, −47.5 to 23.2) for asymptomatic infection, and −20.0% (95% CI, −90.2 to 23.9), −1.2% (95% CI, −33.0 to 23.0), and 2.6% (95% CI, −27.7 to 25.7) for urogenital, anorectal, and oropharyngeal infection, respectively. Serious adverse events occurred in 4.7% of the participants in the 4CMenB group and in 2.8% of those in the placebo group.

CONCLUSIONS

4CMenB did not result in a lower incidence of *N. gonorrhoeae* infection than placebo among MSM who were at high risk for gonorrhea. (Funded by the Australian National Health and Medical Research Council and GSK; GoGoVax ClinicalTrials.gov number, NCT04415424.)

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*A complete list of the GoGoVax trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on July 8, 2026, at NEJM.org.

N Engl J Med 2026;395:349-61.
DOI: 10.1056/NEJMoa2516739

A Quick Take is available at NEJM.org

Neisseria gonorrhoeae infections (gonorrhea) pose a public health challenge worldwide, with an estimated incidence of 82.4 million cases in 2020.[1] The burden of gonorrhea is disproportionately high among men who have sex with men (MSM), young adults, and other key and vulnerable populations, including sex workers, transgender persons, persons living with human immunodeficiency virus (HIV), racial and ethnic minority populations, and Indigenous populations.[2] Untreated infection can lead to sexual and reproductive health complications, including infertility, pelvic inflammatory disease, ectopic pregnancy, and preterm birth, and to increased susceptibility to HIV infection.[3] The ongoing emergence of multidrug-resistant strains of *N. gonorrhoeae* has complicated treatment[4] and disease-control strategies, and no licensed gonorrhea vaccine currently exists.[5,6]

N. gonorrhoeae is closely related to *Neisseria meningitidis*. The four-component meningococcal serogroup B outer membrane vesicle (OMV) vaccine, 4CMenB, has been associated with a reduced incidence of gonorrhea in several observational studies,[7-15] with a recent meta-analysis showing an estimated risk reduction of 38% (95% confidence interval [CI], 28 to 48).[16] Given the presence of shared antigens between *N. gonorrhoeae* and *N. meningitidis*, cross-protection is biologically plausible and has been supported by laboratory data.[17-22] Programs for 4CMenB immunization have been implemented on the basis of observational data to prevent gonorrhea in adults 18 to 65 years of age in Galicia, Spain,[23] and in MSM at high risk for gonorrhea in the United Kingdom.[24] Recently, an open-label, randomized trial involving MSM in France, ANRS 174 DOXYVAC, did not show significant protection against the first episode of gonorrhea after vaccination, with wide confidence intervals (adjusted hazard ratio, 0.78; 95% CI, 0.60 to 1.01; P=0.06).[25] Here we report the efficacy and safety of 4CMenB for the prevention of *N. gonorrhoeae* infection in MSM.

METHODS

TRIAL DESIGN, PARTICIPANTS, AND OVERSIGHT

We conducted this double-blind, randomized, placebo-controlled trial to evaluate the efficacy of a two-dose schedule of 4CMenB for the prevention of urethral, oropharyngeal, and anorectal *N. gonorrhoeae* infection in men, transgender women, transgender men, and nonbinary persons who have sex with men. Eligible participants were 18 to 50 years of age and were negative for HIV and receiving HIV preexposure prophylaxis, receiving postexposure prophylaxis with plans to initiate preexposure prophylaxis after the cessation of postexposure prophylaxis, or living with HIV and had a CD4+ T-cell count of more than 350 cells per cubic millimeter and an undetectable HIV viral load (<200 copies per milliliter). Participants needed to have received a documented diagnosis of *N. gonorrhoeae* infection or infectious syphilis (primary, secondary, or early latent syphilis) within the preceding 18 months — a key enrollment criterion associated with an increased risk of gonorrhea.[27] The trial design and rationale are provided in the protocol (available with the full text of this article at NEJM.org) and have been described in detail previously.[28]

The trial was conducted at five publicly funded sexual health clinics (Sydney Sexual Health Centre, Western Sydney Sexual Health Centre, Melbourne Sexual Health Centre, Gold Coast Sexual Health Service, and RPA Sexual Health) and two private primary care clinics (Taylor Square Private Clinic and Prahran Market Clinic) in the eastern states of Australia. The protocol was approved by the Human Research Ethics Committee at St. Vincent's Hospital Sydney. All the participants provided written informed consent. The authors vouch for the accuracy and integrity of the data and for the fidelity of the trial to the protocol. The first three authors and the last author wrote the manuscript and made the decision to submit the manuscript for publication. Confidentiality agreements were implemented among coinvestigators, coordinators, and the Kirby Institute (which oversaw the trial). Funding was provided by the Australian National Health and Medical Research Council and GSK, which had no role in the design or conduct of the trial or in the analysis of the data.

TRIAL PROCEDURES

Participants were randomly assigned in a 1:1 ratio to receive two intramuscular injections, administered 3 months apart, of 4CMenB or saline placebo. Randomization was performed by means of a Web-based system and a permuted-block scheme stratified according to trial site. The treatment assignment was concealed from the participants, investigators, site clinicians and coordinators,

and trial personnel who were responsible for outcome assessment. The pharmacists and drug managers at the trial sites who prepared the trial interventions, along with the vaccinators who administered them, were aware of the trial-group assignments but had no role in outcome evaluation.

Follow-up visits were scheduled to occur every 3 months over a 24-month period. At each visit, participants underwent testing for sexually transmitted infections (STIs), including nucleic acid amplification testing (NAAT) for *N. gonorrhoeae*. Data on demographic characteristics, sexual behavior, and antibiotic use were collected. Unscheduled visits were permitted for participants seeking treatment of symptomatic or asymptomatic *N. gonorrhoeae* infection or for those attending a test-of-cure visit if such tests were routinely conducted at the clinic.

OUTCOMES

The primary efficacy outcome was a first *N. gonorrhoeae* infection at least 4 weeks after the second dose of vaccine or placebo. *N. gonorrhoeae* infection was defined by a urethral, anorectal, oropharyngeal, or vaginal swab specimen that was positive on NAAT. We also assessed all new *N. gonorrhoeae* infections that occurred at least 4 weeks after the second dose of vaccine or placebo.

For the analysis of all new infections, repeat positive NAATs of samples obtained from the same anatomical site within 30 days of a previous infection were reviewed to rule out data-entry errors and confirm whether the positive result reflected a new exposure. If a new exposure was confirmed, a repeat positive NAAT within 30 days, without an intervening negative test result, was considered to indicate a new infection; otherwise, the infection was classified as a treatment failure and not counted as a new infection.

Secondary efficacy outcomes included a first *N. gonorrhoeae* infection at least 4 weeks after dose two according to the presence or absence of symptoms and according to anatomical site, including the urethra, vagina, anorectal region, and oropharyngeal region, as determined with NAAT. Owing to the small number of transgender men and transgender women enrolled in the trial (<10 participants), urethral and vaginal *N. gonorrhoeae* infections are reported as urogenital infections. The safety of 4CMenB is established,[29,30] and the recording of adverse events in the current trial was limited to serious adverse events.

STATISTICAL ANALYSIS

We analyzed the primary efficacy outcome in a per-protocol population in order to examine the biologic effect of 4CMenB under ideal conditions. This population comprised participants who had received both doses of 4CMenB or placebo, had attended two or more scheduled follow-up visits after receipt of the second dose, and had not met any exclusion criterion pertinent to the assessment of efficacy. Follow-up for case ascertainment and person-years at risk in the analysis of the primary efficacy outcome started 4 weeks after receipt of the second dose. No measures were taken to determine whether infections identified during follow-up originated within the initial 4-week period after the second dose. Vaccine efficacy was calculated as (1 − incidence rate ratio) × 100, with the incidence rate ratio defined as the ratio of the incidence of *N. gonorrhoeae* infection in the 4CMenB group to that in the placebo group. The binomial exact method was used to calculate the 95% confidence interval for vaccine efficacy.

Using a fixed-event design, we estimated that a sample size of 730 participants (375 per group) and the occurrence at least 251 cases of a first *N. gonorrhoeae* infection at least 4 weeks after the second dose would provide the trial with a power of 80% to detect a vaccine efficacy of 30% (with a lower bound of >0% for the 95% confidence interval) at a two-sided significance level of 5%. These calculations were performed under the assumption that the incidence of a first *N. gonorrhoeae* infection at least 4 weeks after dose two would be 25 cases per 100 person-years in the placebo group, with a 24-month follow-up period and a 10% loss to follow-up. No interim efficacy analysis was planned or conducted.

The primary efficacy hypothesis was that the incidence of a first *N. gonorrhoeae* infection at least 4 weeks after the second dose would be at least 30% lower with 4CMenB than with placebo. We tested the primary efficacy hypothesis with an unadjusted analysis; adjusted analyses were performed for completeness and to confirm the results of the unadjusted analysis. The association between the incidence of a first *N. gonorrhoeae* infection at least 4 weeks after the

second dose and covariates was examined with Poisson regression. Covariates with a P value of 0.10 or less in the univariable analysis were considered in the multivariable regression analysis with backward elimination for estimation of the adjusted vaccine efficacy.

Subgroup analyses of the primary efficacy outcome were performed to test for evidence of effect modification in subgroups based on HIV status (positive or negative), sexual orientation, attained age at baseline (18 to 24, 25 to 34, 35 to 39, or ≥40 years), *N. gonorrhoeae* infection or an infectious syphilis diagnosis during the 18 months before baseline (yes or no), number of sex partners during the 6 months before baseline (2 to 5, 6 to 10, 11 to 50, or ≥50 partners), condom use with casual sex partners during the 6 months before baseline (never or either occasionally or often), group sex (defined as sex with ≥2 persons) during the 6 months before baseline (never, once a month or less, or more than once a month), and follow-up period after the receipt of the second dose (first year or second year). Subgroup analyses are not presented for sex at birth or current gender identity because only 4 participants had been assigned female sex at birth and only 10 had a current gender identity of female (4 participants), nonbinary (5), or other (1). No estimates of statistical power were performed for subgroup analyses.

Efficacy analyses were also performed in a modified intention-to-treat population, which comprised all the participants who had received at least one dose of 4CMenB or placebo and had completed at least 6 months of follow-up after the administration of the first dose. For the modified intention-to-treat analyses, *N. gonorrhoeae* infections that occurred 1 day after the baseline visit were counted. As an unplanned analysis, vaccine efficacy was also estimated in the full intention-to-treat cohort, which included all the participants who had undergone randomization; this analysis was performed with and without imputation of missing data. Analyses of vaccine efficacy were not adjusted for multiplicity, and the results should not be used to infer definitive treatment effects.

Serious adverse events were summarized according to trial group and relationship to the trial vaccine as judged by an independent medical monitor. The total number of events and the proportion of participants with at least one event were compared between the two groups. All statistical analyses were performed with Stata software, version 18.5 (StataCorp).

RESULTS

PARTICIPANTS

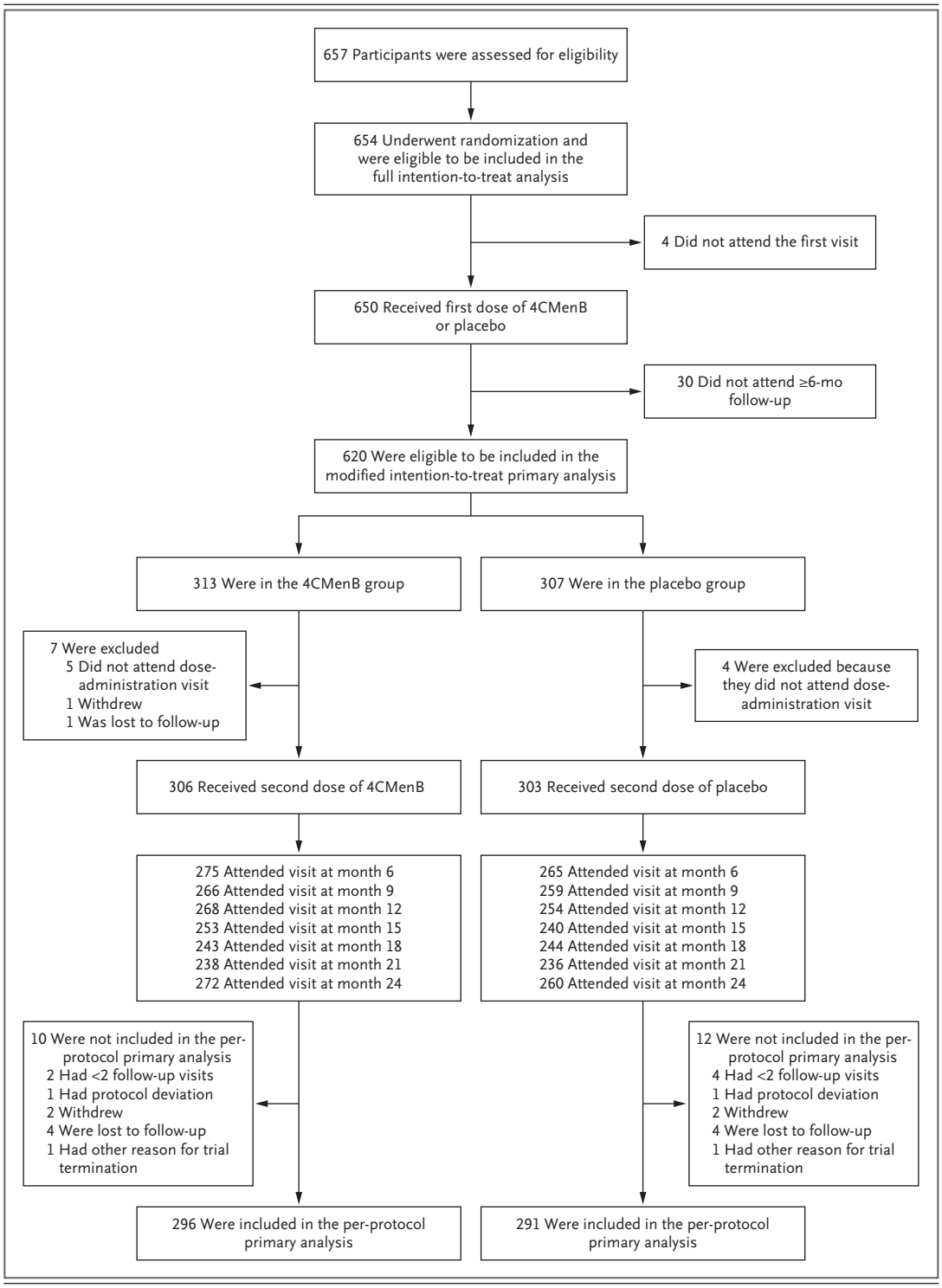
From July 2021 through May 2023, we screened 657 persons, of whom 654 met the eligibility criteria and were randomly assigned to receive 4CMenB or placebo (Fig. 1). The sample size was lower than the planned 730 participants because of decreased recruitment during the coronavirus disease 2019 pandemic. However, there was sufficient power for the primary outcome analysis because the incidence of a first *N. gonorrhoeae* infection in the placebo group was higher than the incidence assumed in the sample-size calculation (47.8 vs. 25.0 cases per 100 person-years).

Overall, 587 participants were included in the per-protocol primary efficacy analysis, with 296 in the 4CMenB group and 291 in the placebo group. The baseline characteristics of the two groups were balanced in the per-protocol, full intention-to-treat, and modified intention-to-treat populations (Table 1 and Table S1 in the Supplementary Appendix, available at NEJM.org). The mean age was 34.2 years; 98.3% of the participants identified as men, and 9.5% were living with HIV. At baseline, 89.6% had had *N. gonorrhoeae* infection during the previous 18 months, 61.4% (347 of 565 participants with available data) reported having had more than 10 sex partners

Figure 1 (facing page). Screening, Randomization, and Follow-up.

A total of 654 participants underwent randomization in a 1:1 ratio to receive the four-component meningococcal serogroup B vaccine (4CMenB) (327 participants) or placebo (327 participants). The full intention-to-treat population included all the participants who had undergone randomization. The modified intention-to-treat population included all the participants who had received at least one dose of 4CMenB or placebo and had been followed for 6 months or more after the first dose. The per-protocol population included all the participants who had received both doses of 4CMenB or placebo, had attended two or more scheduled follow-up visits after administration of the second dose, and had not met any exclusion criterion pertinent to the assessment of efficacy.

during the previous 6 months, 73.8% (416 of 564) reported having had group sex at least once in the previous 6 months, and 36.3% (205 of 564) reported having never used a condom with casual sex partners during the previous 6 months. In total, 26.2% of participants (154 of 587 with available data) tested positive for *N. gonorrhoeae* at screening or when the first or second doses



were administered (18.3% [107 of 586] at screening or when the first dose was given, and 10.3% [60 of 582] when the second dose was given). The percentage of patients with risk factors for gonorrhea during follow-up were similar in the two trial groups, with a similar prevalence of doxycycline use, number of recent sex partners, and incidence of *Chlamydia trachomatis* infection

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Per-Protocol Population		Modified Intention-to-Treat Population	
	4CMenB (N=296)	Placebo (N=291)	4CMenB (N=313)	Placebo (N=307)
Age — yr	34.0±6.3	34.5±6.7	33.9±6.2	34.3±6.7
HIV status — no. (%)				
Negative	266 (89.9)	265 (91.1)	279 (89.1)	280 (91.2)
Positive	30 (10.1)	26 (8.9)	34 (10.9)	27 (8.8)
Sex at birth — no. (%)				
Male	295 (99.7)	288 (99.0)	312 (99.7)	304 (99.0)
Female	1 (0.3)	3 (1.0)	1 (0.3)	3 (1.0)
Gender identity — no. (%)				
Male	288 (97.3)	289 (99.3)	305 (97.4)	305 (99.3)
Female	3 (1.0)	1 (0.3)	3 (1.0)	1 (0.3)
Nonbinary	4 (1.4)	1 (0.3)	4 (1.3)	1 (0.3)
Other	1 (0.3)	0 (0.0)	1 (0.3)	0 (0.0)
Sexual orientation — no. (%)				
Gay or homosexual	271 (91.6)	262 (90.0)	288 (92.0)	275 (89.6)
Other	25 (8.4)	29 (10.0)	25 (8.0)	32 (10.4)
Country of birth — no. (%)				
Australia	150 (50.7)	156 (53.6)	157 (50.2)	164 (53.4)
Other	146 (49.3)	135 (46.4)	156 (49.8)	143 (46.6)
N. gonorrhoeae infection in previous 18 mo — no. (%)				
No	25 (8.4)	34 (11.7)	26 (8.3)	37 (12.1)
Yes	270 (91.2)	256 (88.0)	286 (91.4)	269 (87.6)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Infectious syphilis in previous 18 mo — no. (%)†				
No	239 (80.7)	234 (80.4)	254 (81.2)	247 (80.5)
Yes	56 (18.9)	56 (19.2)	58 (18.5)	59 (19.2)
Missing data	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
No. of sex partners in previous 6 mo — no. (%)				
0–1	1 (0.3)	4 (1.4)	2 (0.6)	4 (1.3)
2–5	53 (17.9)	41 (14.1)	55 (17.6)	42 (13.7)
6–10	51 (17.2)	68 (23.4)	55 (17.6)	73 (23.8)
11–50	151 (51.0)	146 (50.2)	158 (50.5)	156 (50.8)
>50	29 (9.8)	21 (7.2)	32 (10.2)	21 (6.8)
Missing data	11 (3.7)	11 (3.8)	11 (3.5)	11 (3.6)

Table 1. (Continued.)

Characteristic	Per-Protocol Population		Modified Intention-to-Treat Population	
	4CMenB (N=296)	Placebo (N=291)	4CMenB (N=313)	Placebo (N=307)
Condom use with casual sex partners in previous 6 mo — no. (%)				
Never	102 (34.5)	103 (35.4)	108 (34.5)	112 (36.5)
Occasional or often	172 (58.1)	172 (59.1)	183 (58.5)	178 (58.0)
Always	5 (1.7)	2 (0.7)	5 (1.6)	2 (0.7)
No sex with casual sex partners	6 (2.0)	2 (0.7)	6 (1.9)	3 (1.0)
Missing data	11 (3.7)	12 (4.1)	11 (3.5)	12 (3.9)
Group sex in previous 6 mo — no. (%)‡				
Never	63 (21.3)	85 (29.2)	69 (22.0)	91 (29.6)
Once a month or less	208 (70.3)	178 (61.2)	217 (69.3)	187 (60.9)
More than once a month	14 (4.7)	16 (5.5)	16 (5.1)	17 (5.5)
Missing data	11 (3.7)	12 (4.1)	11 (3.5)	12 (3.9)

* Plus–minus values are means ±SD. The per-protocol population included all the participants who had received both doses of the four-component meningococcal serogroup B vaccine (4CMenB) or placebo, had attended at least two scheduled follow-up visits after administration of the second dose, and had not met any exclusion criterion pertinent to the assessment of efficacy. The modified intention-to-treat population included all the participants who had received at least one dose of 4CMenB or placebo and had completed at least 6 months of follow-up after administration of the first dose. HIV denotes human immunodeficiency virus, and *N. gonorrhoeae Neisseria gonorrhoeae*.
† Infectious syphilis included primary, secondary, and early latent syphilis.
‡ Group sex was defined as sex with at least 2 other persons.

(Tables S2 and S3). The representativeness of the trial population is shown in Table S4.

EFFICACY

The mean follow-up was 1.97 years among the 587 participants included in the per-protocol analysis. The incidence of a first *N. gonorrhoeae* infection at least 4 weeks after the second dose (primary outcome) was 48.1 cases per 100 person-years in the 4CMenB group and 47.8 cases per 100 person-years in the placebo group (Table 2). The cumulative probability of a first *N. gonorrhoeae* infection during the 24-month follow-up period was similar in the two groups (Fig. 2). The incidence rate ratio was 1.01 (95% confidence interval [CI], 0.80 to 1.26; P=0.97), for a vaccine efficacy of –0.5% (95% CI, –26.2 to 19.9). Vaccine efficacy was 1.6% (95% CI, –16.3 to 16.7) in the analysis of all episodes of *N. gonorrhoeae* infection and –9.7% (95% CI, –35.8 to 11.3) in the modified intention-to-treat analysis (Table 2). Vaccine efficacy in the full intention-to-treat analysis was similar to that in the modified intention-to-treat analysis (Table S5).

In the prespecified secondary efficacy analyses, the efficacy of 4CMenB was 5.5% (95% CI, –56.0 to 42.8) against incident symptomatic *N. gonorrhoeae* infection and –6.4% (95% CI, –47.5 to 23.2) against incident asymptomatic infection. Vaccine efficacy was –20.0% (95% CI, –90.2 to 23.9) against incident urogenital *N. gonorrhoeae* infection, –1.2% (95% CI, –33.0 to 23.0) against incident anorectal infection, and 2.6% (95% CI, –27.7 to 25.7) against incident oropharyngeal infection (Table 2).

Baseline characteristics that were significantly associated with a first *N. gonorrhoeae* infection at least 4 weeks after dose two were living with HIV, *N. gonorrhoeae* infection in the past 18 months, a higher number of sex partners in the past 6 months, and more frequent group sex in the past 6 months (Table S6). After adjustment for covariates, the incidence ratio of *N. gonorrhoeae* infection (vaccine vs. placebo) was 0.98 (95% CI, 0.77 to 1.24; P=0.84) (Table S7).

In prespecified subgroup analyses, the efficacy of 4CMenB against *N. gonorrhoeae* infection did not appear to vary substantially in relation to HIV

Table 2. Primary and Secondary Analyses.*

Analysis and Population	4CMenB			Placebo			Incidence Rate Ratio (95% CI)	Vaccine Efficacy (95% CI)
	No. of Events	No. of Person-Yr	Incidence	No. of Events	No. of Person-Yr	Incidence		
			events per 100 person-yr			*events per 100 person-yr*		*percent*
Primary analysis								
Per-protocol population†								
Primary outcome: first infection	160	330.0	48.1	155	324.2	47.8	1.01 (0.80 to 1.26)	−0.5 (−26.2 to 19.9)‡
All new infections§	291	486.5	59.8	285	468.7	60.8	0.98 (0.81 to 1.20)	1.6 (−16.3 to 16.7)
Modified intention-to-treat population¶								
First infection	184	388.5	47.4	173	400.7	43.2	1.10 (0.89 to 1.36)	−9.7 (−35.8 to 11.3)
Secondary analysis								
Per-protocol population†								
First symptomatic infection‖	34	379.8	9.0	35	369.5	9.5	0.95 (0.59 to 1.52)	5.5 (−56.0 to 42.8)
First asymptomatic infection‖	82	379.8	21.6	75	369.5	20.3	1.06 (0.78 to 1.46)	−6.4 (−47.5 to 23.2)
First urogenital infection	46	448.2	10.3	37	432.6	8.6	1.20 (0.78 to 1.86)	−20.0 (−90.2 to 23.9)
First anorectal infection	112	377.9	29.6	109	372.1	29.3	1.01 (0.77 to 1.32)	−1.2 (−33.0 to 23.0)
First oropharyngeal infection	113	392.1	28.8	112	378.6	29.6	0.97 (0.75 to 1.26)	2.6 (−27.7 to 25.7)

* Infection was defined by a positive nucleic acid amplification test (NAAT) for *N. gonorrhoeae* in a urine sample or on a swab sample obtained from the urethra, anorectal region, oropharyngeal region, or vagina. Vaccine efficacy was calculated as (1 − incidence rate ratio) × 100, with the incidence rate ratio defined as the ratio of the incidence of *N. gonorrhoeae* infection in the 4CMenB group to that in the placebo group. The binomial exact method was used to calculate the 95% confidence interval for vaccine efficacy. Confidence intervals were not adjusted for multiple testing and should not be used to infer definitive treatment effects.

† Data are for 587 participants — 296 in the 4CMenB group and 291 in the placebo group. Follow-up for case ascertainment started 4 weeks after the second dose.

‡ P=0.97 for the comparison of the 4CMenB group with the placebo group.

§ For the analysis of all new infections, repeat positive NAATs of samples obtained from the same anatomical site within 30 days after a previous infection were reviewed to rule out data-entry errors and confirm whether the positive result reflected a new exposure. If a new exposure was confirmed, a repeat positive NAAT within 30 days, without an intervening negative test result, was considered to indicate a new infection; otherwise, the infection was classified as a treatment failure and not counted as a new infection.

¶ Data are for 620 participants — 313 in the 4CMenB group and 307 in the placebo group. Follow-up for case ascertainment started 1 day after the baseline visit.

‖ The analysis includes data on symptoms that were reported only at scheduled or unscheduled visits at participating clinical trial sites. Data on symptoms that were reported at external visits are excluded.

status, age, *N. gonorrhoeae* infection in the past 18 months, and number of sex partners in the past 6 months (Fig. 3). For all the subgroups examined, the lower bound of the 95% confidence interval of the vaccine efficacy was less than 0.

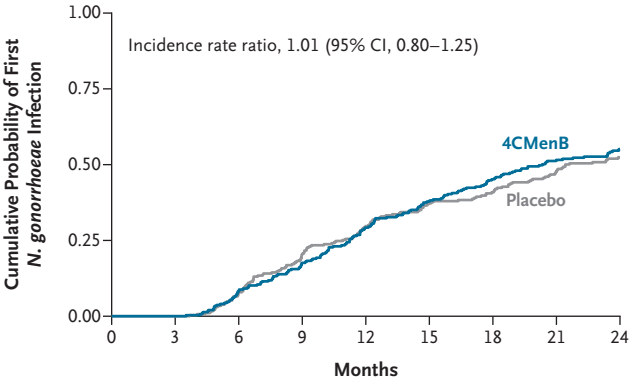
SAFETY

Sixteen serious adverse events were reported in the 4CMenB group and nine in the placebo group. One event was deemed by the investigators to be possibly related to the trial vaccine (Table S8). Serious adverse events occurred in 4.7% of the participants in the 4CMenB group and in 2.8% of those in the placebo group (P=0.20) (Table S9).

DISCUSSION

This double-blind, randomized, placebo-controlled trial provides evidence that 4CMenB did not differ from placebo regarding the incidence of a first *N. gonorrhoeae* infection and the incidence of any *N. gonorrhoeae* infection among MSM who were at high risk for infection. Our findings are consistent with those from ANRS 174 DOXYVAC and another smaller open-label randomized trial.[25,26] Taken together, the current trial and the two smaller trials provide strong evidence that the 4CMenB vaccine is not effective for gonorrhea prevention in MSM.

Our findings are in contrast to those from a number of case–control and retrospective cohort studies,[7-15] which, when combined, have reported a reduction of 38% (95% CI, 28 to 48) in the risk of gonorrhea among persons vaccinated with 4CMenB.[16] However, observational studies are susceptible to a range of potential known and unknown confounding factors, which could explain the difference between our findings and those from previous studies. Case–control studies of the association between 4CMenB and gonorrhea mainly included participants with chlamydia or other STIs as controls,[9,11,15] and one study also included persons from a population-based immunization register.[9] It is likely that 4CMenB vaccination history varied between the cases and controls in these studies for reasons other than a causal protective effect. The retrospective cohort studies assessed the incidence of gonorrhea among persons who had received 4CMenB as compared with those who had received meningitis vaccines that are not predicted to target



No. at Risk									
4CMenB	296	296	272	241	206	180	155	136	76
Placebo	291	291	268	231	199	172	162	142	86
No. of Cases									
4CMenB	0	24	28	34	25	21	18	9	1
Placebo	0	23	36	27	21	10	19	12	7

Figure 2. Time to a First *Neisseria gonorrhoeae* Infection.
Shown is a Kaplan–Meier analysis of the cumulative probability of a first *N. gonorrhoeae* infection in the per-protocol population. The analysis started at month 4 (i.e., 1 month after the second dose of the 4CMenB or placebo).

N. gonorrhoeae.[12,14] The fact that there are different clinical indications for the different vaccines may have led to confounding in these studies. Although the analyses in many of these studies were adjusted for potential confounders, residual confounding may still have been present. In one recently published case–control study, 4CMenB was associated with a decreased risk of gonorrhea in a statistical model with limited adjustment for confounders, but the association disappeared after adjustment for multiple confounders.[7] Ultimately, successful randomization is required to minimize confounding.

Our results cannot be generalized to genital infections in women. Differences in the mechanisms of *N. gonorrhoeae* infection between men and women have been described,[31] and two observational studies showed slightly higher vaccine effectiveness among women than among men with 4CMenB[8] and MeNZB (a serogroup B meningococcal OMV vaccine).[32] Women in different high-risk populations are being assessed in the following ongoing randomized, controlled trials: BIYELA (Bexsero Immunisation in Young Women in Africa), which includes women 18 to 45 years of age in Africa (ClinicalTrials.gov number, NCT06446752), and MAGI, which includes men and women 18 to 50 years of

Subgroup	4CMenB	Placebo	Incidence Rate Ratio (95% CI)
	no. of events/total person-yr (per 100 person-yr)		
Overall	160/330.0 (48.1)	155/324.2 (47.8)	1.05 (0.79–1.25)
HIV status			
Negative	142/298.0 (47.6)	135/301.3 (44.8)	1.06 (0.84–1.35)
Positive	18/34.9 (51.5)	20/22.9 (87.3)	0.59 (0.31–1.12)
Sexual orientation			
Gay or homosexual	147/307.1 (47.9)	143/286.3 (49.9)	0.96 (0.76–1.21)
Other	13/25.9 (50.2)	12/37.9 (31.7)	1.58 (0.69–3.66)
Age			
18–24 yr	5/9.3 (53.7)	6/7.3 (82.5)	0.65 (0.18–2.37)
25–34 yr	81/134.4 (60.3)	63/129.1 (48.8)	1.24 (0.88–1.73)
35–39 yr	46/105.1 (43.8)	45/106.2 (42.4)	1.03 (0.68–1.56)
≥40 yr	28/84.2 (33.3)	41/81.5 (50.3)	0.66 (0.41–1.07)
History of *N. gonorrhoeae* infection in previous 18 mo			
No	8/36.5 (21.9)	15/44.3 (33.9)	0.65 (0.28–1.52)
Yes	152/296.5 (51.3)	140/279.9 (50.0)	1.02 (0.81–1.30)
History of infectious syphilis in previous 18 mo			
No	132/262.0 (50.4)	125/261.7 (47.8)	1.05 (0.82–1.36)
Yes	28/70.9 (39.5)	30/62.4 (48.0)	0.82 (0.49–1.38)
No. of sex partners in previous 6 mo			
2–5	12/61.4 (19.5)	20/63.3 (31.6)	0.62 (0.30–1.28)
6–10	19/60.3 (31.5)	27/57.7 (46.8)	0.67 (0.37–1.22)
11–50	87/136.7 (63.6)	77/124.1 (62.0)	1.03 (0.76–1.38)
>50	23/27.3 (84.1)	12/16.3 (73.8)	1.14 (0.57–2.30)
Condom use with casual sex partners in previous 6 mo			
Never	59/141.4 (41.7)	69/135.6 (50.9)	0.82 (0.58–1.16)
Occasional or often	81/140.4 (57.7)	67/137.7 (48.7)	1.19 (0.86–1.64)
Group sex in previous 6 mo			
Never	24/101.8 (23.6)	22/120.2 (18.3)	1.29 (0.72–2.31)
Once a month or less	109/188.8 (57.7)	107/163.3 (65.5)	0.88 (0.67–1.15)
More than once a month	9/12.7 (70.7)	7/9.5 (73.6)	0.96 (0.40–2.33)
Follow-up period			
First year	117/231.2 (50.6)	112/221.9 (50.5)	1.00 (0.77–1.30)
Second year	43/101.7 (42.3)	43/102.3 (42.1)	1.01 (0.66–1.54)

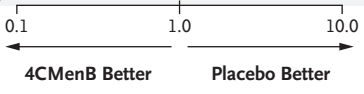


Figure 3. Subgroup Analysis of the Primary End Point.

Shown are the results of a subgroup analysis of a first *N. gonorrhoeae* infection at least 4 weeks after the second dose of 4CMenB or placebo in the per-protocol population. Infectious syphilis included primary, secondary, and early latent syphilis. Group sex was defined as sex with at least two other persons. Confidence intervals have not been adjusted for multiple testing and should not be used to infer definitive treatment effects.

age in the United States, Malawi, and Thailand (NCT04350138).

It is also possible that 4CMenB may be effective in populations with a lower incidence of gonorrhea and weaker preexisting immune responses, including MSM with lower previous exposure to gonorrhea. The effect of previous infection on vaccine efficacy remains uncertain but may be negative because *N. gonorrhoeae* uses immune evasion and modulation strategies that prevent lasting immunity.[33,34] For example, infection induces antibodies to the Rmp protein, which may block effective immune responses to subsequent infection or vaccination.[35,36] Consequently, it has been proposed that vaccination may need to occur before first exposure for efficacy. In our study, 89.6% of participants had tested positive for *N. gonorrhoeae* in the past 18 months, and 26.2% tested positive for *N. gonorrhoeae* at screening or when the first or second dose of 4CMenB or placebo was received. In the DOXYVAC trial, 68% of participants had had

N. gonorrhoeae infection in the past 12 months, and 13% had infection at enrollment.[25] In contrast, observational studies have primarily assessed the effects of 4CMenB in younger populations (persons 14 to 30 years of age) with a relatively low estimated incidence of gonorrhea (<1%); routine screening is uncommon in such populations, and most documented cases are symptomatic, urogenital infections.[7-10,12-14]

Key strengths of this trial include its double-blind, randomized, placebo-controlled design, with balanced groups at baseline with respect to typical confounders. During follow-up, sexual behaviors, chlamydia, and doxycycline use remained well balanced between the trial groups; these findings suggest that the participants remained unaware of their trial-group assignments. Retention of participants and adherence to the protocol were high, and 40% more primary events were captured in the current trial than the DOXYVAC trial.

Our trial had limitations. It was not powered to assess secondary outcomes such as vaccine efficacy against symptomatic infection, asymptomatic infection, or site-specific infection (urogenital, anorectal, or oropharyngeal) or vaccine efficacy according to subgroup. Larger trials would be needed to detect modest vaccine efficacy in such analyses. In addition, our outcomes were based on the results of NAAT for *N. gonorrhoeae*, which may not capture potential decreases in bacterial load or infection duration due to vaccination. Data on vaccine-induced immune responses are not yet available; however, these results will help identify heterogeneity in immunogenicity across subgroups. Quantitative data on the use of antibiotics other than doxycycline throughout the trial are not available. Finally, the exclusive focus on MSM with a high incidence of recent *N. gonorrhoeae* infection limits the generalizability of our findings to women or persons with minimal or no past exposure to *N. gonorrhoeae*. Ongoing and future studies are needed to address these gaps.

The World Health Organization (WHO) set a goal to reduce the global incidence of gonorrhea by 90% by 2030 and emphasized the need for new prevention strategies, including effective vaccines.[37] According to the WHO preferred product characteristics for gonorrhea vaccines, key populations for targeted gonorrhea vaccination include persons at higher risk for gonococcal infection, such as MSM, sex workers, transgender persons, and persons living with HIV, as well as adolescents and young adults, given that gonorrhea is most prevalent among persons 15 to 24 years of age.[2,5] Two 4CMenB immunization programs have already been implemented in populations at higher risk for gonorrhea — a program in the Galicia region of Spain is targeting high-risk adults 18 to 65 years of age,[23] and a program in the United Kingdom is targeting high-risk MSM.[24] However, our finding that 4CMenB is ineffective for gonorrhea prevention in MSM at high risk for infection is a setback for these programs.

No randomized trials are under way to evaluate the effects of 4CMenB in adolescents and young adults in the general population or in MSM at lower risk for gonorrhea than persons in the current trial — key groups for future implementation of the vaccine. Given the relatively low incidence of gonorrhea in these populations, conducting adequately powered trials may be impractical. In this context, observational studies may continue to provide insights to inform 4CMenB implementation strategies in lower-risk groups, but such studies will need to carefully control for confounding factors.

In the current trial, 4CMenB did not result in a lower incidence of *N. gonorrhoeae* infection than placebo among MSM who were at high risk for infection. This finding suggests that other vaccine targets, implementation strategies, or both may be needed.

Supported by a grant (GNT1182443) from the Australian National Health and Medical Research Council and by GSK.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

We thank the members of the GoGoVax Protocol Steering Committee not already listed as authors; the nonauthor coinvestigators and coordinators, pharmacists, drug managers, and clinical and laboratory staff at the trial sites; and the trial participants.

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