ORIGINAL ARTICLE

Effectiveness of a Meningococcal Group B Vaccine (4CMenB) in Children

J. Castilla, M. García Cenoz, R. Abad, L. Sánchez-Cambronero, N. Lorusso, C. Izquierdo, S. Cañellas Llabrés, J. Roig, A. Malvar, F. González Carril, A.L.D. Boone, J. Pérez Martín, M.J. Rodríguez Recio, A. Galmés, A. Caballero, A. García Rojas, F. Juanas, M. Nieto, L.J. Viloria Raymundo, E. Martínez Ochoa, A.I. Rivas, D. Castrillejo, D. Moreno Pérez, A. Martínez, E. Borràs, A. Sánchez Gómez, E. Pastor, V. Nartallo, J.M. Arteagoitia, B. Álvarez-Fernández, R. García Pina, S. Fernández Arribas, J. Vanrell, S. García Hernández, R.M. Mendoza, M. Méndez, M.M. López-Tercero, Á. Fernández-Rodríguez, Á. Blanco, F.J. Carrillo de Albornoz,* J. Ruiz Olivares, R. Ruiz-Montero, A. Limia, J.A. Navarro-Alonso, J.A. Vázquez, and A. Barricarte

ABSTRACT

BACKGROUND

In September 2015, the four-component, protein-based meningococcal serogroup B vaccine (4CMenB; Bexsero) became available for private purchase in Spain.

METHODS

We conducted a nationwide matched case–control study to assess the effectiveness of 4CMenB in preventing invasive meningococcal disease in children. The study included all laboratory-confirmed cases of invasive meningococcal disease in children younger than 60 months of age between October 5, 2015, and October 6, 2019, in Spain. Each case patient was matched with four controls according to date of birth and province. 4CMenB vaccination status of the case patients and controls was compared with the use of multivariate conditional logistic regression.

RESULTS

We compared 306 case patients (243 [79.4%] with serogroup B disease) with 1224 controls. A total of 35 case patients (11.4%) and 298 controls (24.3%) had received at least one dose of 4CMenB. The effectiveness of complete vaccination with 4CMenB (defined as receipt of at least 2 doses, administered in accordance with the manufacturer's recommendations) was 76% (95% confidence interval [CI], 57 to 87) against invasive meningococcal disease caused by any serogroup, and partial vaccination was 54% (95% CI, 18 to 74) effective. Complete vaccination resulted in an effectiveness of 71% (95% CI, 45 to 85) against meningococcal serogroup B disease. Vaccine effectiveness with at least one dose of 4CMenB was 64% (95% CI, 41 to 78) against serogroup B disease and 82% (95% CI, 21 to 96) against non–serogroup B disease. With the use of the genetic Meningococcal Antigen Typing System, serogroup B strains that were expected to be covered by 4CMenB were detected in 44 case patients, none of whom had been vaccinated.

CONCLUSIONS

Complete vaccination with 4CMenB was found to be effective in preventing invasive disease by serogroup B and non–serogroup B meningococci in children younger than 5 years of age.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Castilla can be contacted at jcastilc@navarra.es or at Instituto de Salud Pública de Navarra, Leyre 15, 31003 Pamplona, Spain.

*Deceased.

N Engl J Med 2023;388:427-38.
DOI: 10.1056/NEJMoa2206433

Neisseria meningitidis is a major cause of severe disease in infants and children.[1] After the introduction of serogroup C vaccines, serogroup B meningococcus has become the main cause of invasive meningococcal disease in Europe.[1,2]

The four-component protein-based meningococcal B vaccine (4CMenB; Bexsero, GSK) was licensed in the European Union in 2013.[3] This vaccine is composed of three recombinant antigens (factor H–binding protein, neisseria heparin–binding antigen, and neisseria adhesin A), as well as outer-membrane vesicles containing Porin A subtype P1.4 from the strain NZ98/254.[4] Authorization of 4CMenB was based on the results of immunogenicity studies.[5] An observational study showed that the percentage of persons who were vaccinated was lower among those with serogroup B meningococcal disease than among those in the general population and that the incidence of serogroup B disease was lower among vaccine-eligible infants than among vaccine-ineligible infants.[6] Further immunogenicity studies confirmed these preliminary results.[7,8]

Although some countries have introduced 4CMenB into publicly funded infant immunization programs,[9] the low incidence of the disease has limited the conduct of postcommercialization studies of effectiveness. The few published evaluations have yielded effectiveness estimates from 59.1% (with a two-dose priming schedule plus a 1-year booster in the United Kingdom) to 93.6% (with a four-dose schedule in Tuscany, Italy).[10-12] Because 4CMenB vaccine antigens are not unique to serogroup B meningococcus, the vaccine might also be protective against disease caused by other serogroups.[13,14]

In Spain, the publicly funded immunization schedule included the meningococcal C conjugate vaccine for all children since 2000 and 4CMenB for persons with high-risk conditions for invasive meningococcal disease (i.e., history of meningococcal disease, complement deficiency, eculizumab treatment, anatomical or functional asplenia, and hematopoietic stem-cell transplantation) since 2015.[15] In addition, 4CMenB was available for private purchase, and vaccination of all children 2 months of age or older was recommended by the Spanish Pediatrics Association,[16,17] which resulted in a progressive increase in vaccination coverage. Temporary shortage of 4CMenB might have delayed the vaccination schedule in some children. In this study, we aimed to assess the effectiveness of 4CMenB in preventing invasive meningococcal disease in children younger than 60 months of age.

METHODS

STUDY DESIGN AND DATA SOURCES

In Spain, it is mandatory that clinicians and laboratory personnel report cases of invasive meningococcal disease, and all relevant data are actively completed by the regional epidemiologic surveillance units.[18] In this individually matched case–control study, the case patients were all the children younger than 60 months of age who were born and residing in Spain and had received a laboratory-confirmed diagnosis of invasive meningococcal disease between October 5, 2015, and October 6, 2019. Invasive meningococcal disease was defined as a positive culture or polymerase-chain-reaction (PCR) test for *N. meningitidis* in a normally sterile body site. Diagnostic samples from the patients with confirmed cases were tested by means of agglutination or PCR to determine the serogroup. With the use of electronic databases, each case patient was matched with four controls from the same province of birth and residence who were born on the same day as the case patient or on the days immediately preceding or following the case patient's date of birth — two controls had identification numbers in the regional health care service that immediately preceded and two had numbers that immediately followed the number for the case patient. Each region provided data from all matched sets that included each case patient and the four eligible controls.

High-risk conditions for meningococcal disease were identified with the use of electronic health records of the case patients and controls. Information about the first case date (the date of symptom onset, the first positive test, or hospital admission, whichever came first), clinical presentation (meningitis, sepsis, both, or other), admission to an intensive care unit, and clinical outcome that included recovery, sequelae (neurologic damage, amputation, or hearing loss), or death was obtained from the epidemiologic surveillance system. Full details of the study conduct are provided in the protocol, available with the full text of the article at NEJM.org.

The authors had sole responsibility for the

study design, data analysis, writing of the manuscript, and decision to submit the manuscript for publication. The study protocol specified that anonymized data were to be collected from the electronic medical records of the case patients and controls. The protocol was approved by the institutional review board of Navarre, which waived the need for obtaining informed consent. This study was carried out by public health professionals and institutions in Spain without specific funding. The 4CMenB vaccine was publicly funded for children with a high-risk condition, and for the other children who were vaccinated, the vaccine was paid for by their families.

VACCINATION STATUS

Data on meningococcal immunization (with 4CMenB, serogroup C conjugate, or ACWY [serogroups A, C, W-135, and Y] vaccines) were sourced from the electronic regional vaccination registries. 4CMenB vaccination status was classified according to the manufacturer's recommendations (Table S1 in the Supplementary Appendix, available at NEJM.org),[3] which included that the infant vaccination schedule starts at 2 months of age and a second dose should be given 60 or more days later for complete primary vaccination. In children who were vaccinated before 6 months of age, a booster dose at 12 to 15 months of age was needed in order for the child to be considered fully immunized. In children who started the vaccination series during the sixth month of age or after, the booster dose was required during the second year of age. Children who started the vaccination series at the age of 24 months or older were deemed to be fully immunized after receipt of the second dose.[2,17] To allow time for the immune response, vaccine doses that were administered within the 14 days preceding the first case date were considered separately. Vaccination status on the first case date was determined for the case patients; for the matched controls, vaccination status on the same calendar day as the first case date of their respective case patient was used.

GENETIC CHARACTERIZATION

Group B meningococcal isolates were analyzed with the use of the genetic Meningococcal Antigen Typing System (gMATS) at the National Center for Microbiology (Instituto de Salud Carlos III).[19-21] A strain was considered to be vaccine-preventable if a gMATS test was positive for any of the four components included in 4CMenB, not vaccine-preventable if a gMATS test was negative for all four vaccine antigens, and unpredictable if a gMATS test result could not be related to currently available MATS data. Cases in which the isolate was completely genotyped by gMATS were classified as having been caused by strains covered by 4CMenB, by strains not covered by this vaccine, or by strains for which coverage by the vaccine could not be predicted.

STATISTICAL ANALYSIS

Each case patient and the matched controls for the patient were compared with respect to 4CMenB vaccination status by means of conditional logistic regression to obtain crude and adjusted (according to sex and high-risk conditions) matched odds ratios with 95% confidence intervals. The analysis of non–serogroup B cases was also adjusted for meningococcal C vaccination. Vaccine effectiveness was estimated as a percentage according to the following formula: (1 − adjusted matched odds ratio) × 100.

Four categories were used for 4CMenB vaccination status: unvaccinated (reference), receipt of the first dose within 14 days before the first case date, partial vaccination, and complete vaccination. Estimates were also obtained for vaccination with at least one dose of 4CMenB, including partial and complete vaccination. Further analyses were conducted according to invasive disease caused by meningococcus serogroup (B or non–serogroup B), age group (<24 or ≥24 months), and study period (October 5, 2015, to October 8, 2017 [period 2015–2017] or October 9, 2017, to October 6, 2019 [period 2017–2019]). A sensitivity analysis was performed after the exclusion of children younger than 134 days of age, those unvaccinated against serogroup C meningococcus, and those with a high-risk factor. These restrictions ensured a minimum age at which one could be fully vaccinated, excluded certain children with an increased risk of disease, and improved the comparability of the use of health care services.

We also assessed the effect of 4CMenB in preventing severe disease, including cases leading to death, admission to an intensive care unit, or sequelae. Vaccination status was compared between the case patients with meningococcal

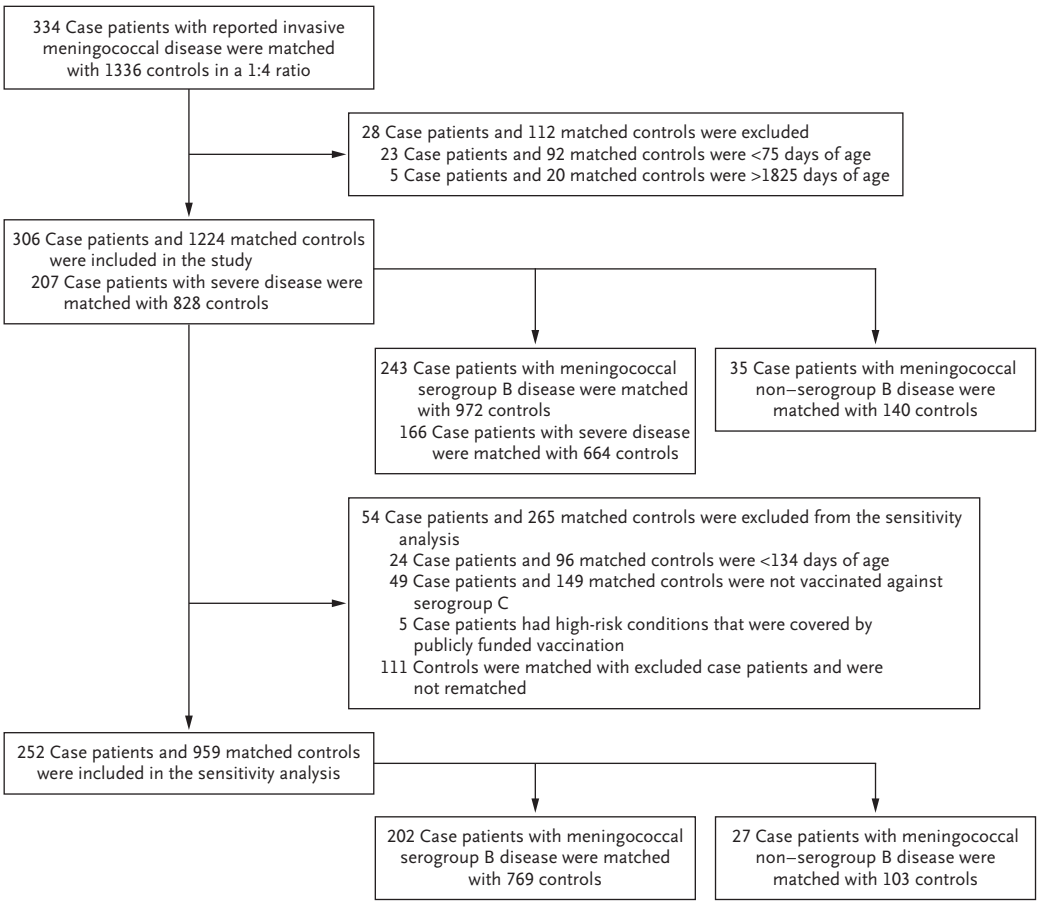

Figure 1. Eligible Case Patients and Matched Controls.

Shown is the flow of eligible case patients and controls through the study analyses. Each case patient was matched with four controls. A case patient or a control could have more than one reason for exclusion. Among the 306 case patients, the serogroup could not be tested in 28, and among the 252 case patients included in the sensitivity analysis, the serogroup could not be identified in 23. The main and sensitivity analyses of meningococcal non–serogroup B disease were estimated to be possibly underpowered according to the study protocol.

serogroup B disease and their matched controls according to the gMATS classification. In post hoc analyses, the vaccine effectiveness in fully vaccinated children was assessed according to number of 4CMenB doses (2 or >2 doses), age at receipt of the first dose (<24 or ≥24 months), and time elapsed since receipt of the last dose (<12 or ≥12 months).

RESULTS

CHARACTERISTICS OF CASE PATIENTS AND CONTROLS

Invasive meningococcal disease had been reported in 334 patients; 23 were excluded because the disease had developed before 75 days of age, and 5 were excluded because the disease had developed after 1825 days of age. Thus, 306 case patients were included in the study (Fig. 1), of whom 243 (79.4%) had serogroup B disease, 5 (1.6%) had serogroup C disease, 20 (6.6%) had serogroup W disease, 7 (2.3%) had serogroup Y disease, 3 (1.0%) had disease caused by nongroupable meningococcal strains (i.e., case patients who tested negative for serogroups A, B, C, W, and Y), and 28 (9.2%) had cases in which the serogroup could not be tested. Clinical presentation included meningitis in 102 case patients (33.3%), sepsis in 118 (38.6%), both meningitis and sepsis in 76 (24.8%), and other conditions in 10 (3.3%). A total of 204 case

Table 1. Characteristics of the Cases and Controls Included in the Analysis of Invasive Meningococcal Disease According to Meningococcal Serogroup.*

Characteristic	Serogroup B		Non–Serogroup B†		Any Serogroup‡	
	Cases (N=243)	Controls (N=972)	Cases (N=35)	Controls (N=140)	Cases (N=306)	Controls (N=1224)
	number (percent)					
Sex						
Male	130 (53.5)	486 (50.0)	16 (45.7)	77 (55.0)	163 (53.3)	621 (50.7)
Female	113 (46.5)	486 (50.0)	19 (54.3)	63 (45.0)	143 (46.7)	603 (49.3)
Age						
<6 mo	41 (16.9)	164 (16.9)	6 (17.1)	24 (17.1)	55 (18.0)	220 (18.0)
6 to <12 mo	54 (22.2)	216 (22.2)	8 (22.9)	32 (22.9)	65 (21.2)	260 (21.2)
12 to <24 mo	44 (18.1)	176 (18.1)	11 (31.4)	44 (31.4)	63 (20.6)	252 (20.6)
24 to <36 mo	51 (21.0)	204 (21.0)	3 (8.6)	12 (8.6)	57 (18.6)	228 (18.6)
36 to <60 mo	53 (21.8)	212 (21.8)	7 (20.0)	28 (20.0)	66 (21.6)	264 (21.6)
Epidemiologic season						
2015–2016	73 (30.0)	292 (30.0)	5 (14.3)	20 (14.3)	84 (27.5)	336 (27.5)
2016–2017	61 (25.1)	244 (25.1)	7 (20.0)	28 (20.0)	75 (24.5)	300 (24.5)
2017–2018	55 (22.6)	220 (22.6)	13 (37.1)	52 (37.1)	75 (24.5)	300 (24.5)
2018–2019	54 (22.2)	216 (22.2)	10 (28.6)	40 (28.6)	72 (23.5)	288 (23.5)
High-risk condition§	3 (1.2)	0	2 (5.7)	0	5 (1.6)	0
Serogroup C vaccination						
Yes	204 (84.0)	854 (87.9)	29 (82.9)	123 (87.9)	257 (84.0)	1075 (87.8)
No	39 (16.0)	118 (12.1)	6 (17.1)	17 (12.1)	49 (16.0)	149 (12.2)
ACWY vaccination	0	0	0	0	0	0
4CMenB vaccination						
Unvaccinated	218 (89.7)	763 (78.5)	30 (85.7)	93 (66.4)	271 (88.6)	926 (75.7)
Vaccinated <14 days¶	1 (0.4)	15 (1.5)	0	0	1 (0.3)	18 (1.5)
Partially vaccinated	12 (4.9)	72 (7.4)	4 (11.4)	19 (13.6)	18 (5.9)	106 (8.7)
Fully vaccinated	12 (4.9)	122 (12.6)	1 (2.9)	28 (20.0)	16 (5.2)	174 (14.2)
No. of 4CMenB doses						
0	219 (90.1)	778 (80.0)	30 (85.7)	93 (66.4)	272 (88.9)	944 (77.1)
1	8 (3.3)	55 (5.7)	4 (11.4)	17 (12.1)	14 (4.6)	83 (6.8)
2	10 (4.1)	93 (9.6)	1 (2.9)	21 (15.0)	13 (4.2)	128 (10.5)
≥3	6 (2.5)	46 (4.7)	0	9 (6.4)	7 (2.3)	69 (5.6)

* Percentages may not total 100 because of rounding. ACWY refers to the tetravalent ACWY (serogroups A, C, W-135, and Y) meningococcal conjugate vaccine, and 4CMenB the four-component, protein-based meningococcal serogroup B vaccine.
† Non–serogroup B included 5 case patients with serogroup C disease, 20 with serogroup W disease, 7 with serogroup Y disease, and 3 with disease caused by nongroupable meningococcal strains, together with their respective controls.
‡ Any serogroup included the 243 case patients with serogroup B disease, 35 with non–serogroup B disease, and 28 in whom the serogroup could not be tested, along with their respective controls.
§ The five children with high-risk conditions had complement deficiency or were receiving eculizumab treatment at presentation.
¶ "Vaccinated <14 days" denotes the children who had received the first dose of 4CMenB in the previous 14 days.

patients (67.7%) had been admitted to a intensive care unit, 16 (5.2%) had died, and 27 (8.8%) had survived with sequelae (Table S2).

Among the 306 case patients, 35 (11.4%) had received at least one dose of 4CMenB — 16 (5.2%) were fully vaccinated, 18 (5.9%) were

partially vaccinated, and 1 (0.3%) had received the first dose within the previous 14 days; the corresponding vaccination statuses among 298 (24.3%) of the 1224 matched controls who had received at least one dose were recorded in 14.2%, 8.7%, and 1.5% (Table 1). Among the 243 case patients with a serogroup B disease, 138 (56.8%) had isolates that were completely genotyped with the use of the gMATS. Of these 138 case patients, 44 (31.9%) had strains expected to be covered by 4CMenB, 62 (44.9%) had strains that were not expected to be covered, and 32 (23.2%) had strains for which coverage by the vaccine could not be predicted. The percentage of controls who had received at least one dose of 4CMenB increased from 4.5% in the 2015–2016 season to 44.1% in the 2018–2019 season (Fig. S1).

4CMenB in Prevention of Meningococcal Disease

We compared the 4CMenB vaccination status of 306 case patients with that of the 1224 matched controls. The effectiveness of complete vaccination with 4CMenB was 76% (95% confidence interval [CI], 57 to 87) against invasive meningococcal disease caused by any serogroup, and partial vaccination was 54% (95% CI, 18 to 74) effective. In the sensitivity analysis that excluded children younger than 134 days of age, those who were unvaccinated against serogroup C meningococcus, and those with high-risk conditions, the estimates of effectiveness were similar to those in the overall analysis — 78% (95% CI, 59 to 88) for complete vaccination and 54% (95% CI, 17 to 74) for partial vaccination. Complete vaccination resulted in an effectiveness of 71% (95% CI, 43 to 86) against severe meningococcal disease (Table 2).

The effectiveness of complete vaccination remained high in both period 2015–2017 and period 2017–2019, but it appeared to be higher among children younger than 24 months of age (88%; 95% CI, 68 to 95) than among those 24 to 59 months of age (53%; 95% CI, 1 to 78) (Table 3). Post hoc analyses showed no relevant differences in effectiveness among fully vaccinated children according to the number of vaccine doses (2 vs. >2) or the time elapsed since receipt of the last dose (<12 months vs. ≥12 months); however, among children who had received the first dose of 4CMenB before 24 months of age, the effectiveness was 84% (95% CI, 67 to 93), and among those who started the vaccination series at 24 to 59 months of age, the effectiveness was 35% (95% CI, −65 to 74) (Table S3).

4CMenB in Prevention of Serogroup B Disease

We estimated the effectiveness of 4CMenB against meningococcal serogroup B disease among 243 case patients as compared with 972 individually matched controls. The effectiveness was 64% (95% CI, 41% to 78%) for vaccination with at least one dose of 4CMenB, 71% (95% CI, 45 to 85) for complete vaccination, and 50% (95% CI, 3 to 75) for partial vaccination (Table 4). Serogroup B strains that were expected to be covered by 4CMenB according to the gMATS result were detected in 44 case patients, none of whom had been vaccinated; among the 176 matched controls for these case patients, 26 (14.8%) had been vaccinated. Vaccination with at least one dose of 4CMenB was also protective against serogroup B strains that were not expected to be covered by the vaccine according to the gMATS result (64%; 95% CI, 10 to 85) (Table S4).

4CMenB in Prevention of Non–Serogroup B Disease

The estimate of the effectiveness of 4CMenB in preventing non–serogroup B disease was 82% (95% CI, 21 to 96) for vaccination with at least one dose of 4CMenB and 92% (95% CI, 28 to 99) for complete vaccination. The result of the sensitivity analysis was similar to that of the main analysis (Table 4).

DISCUSSION

We found that complete vaccination with 4CMenB was 76% effective in preventing meningococcal disease caused by any serogroup, 71% effective in preventing disease caused by serogroup B, and 92% effective in preventing disease caused by non–serogroup B meningococci. Furthermore, vaccination with at least one dose of 4CMenB showed a moderately preventive effect (54%) when the vaccination scheme had not been completed because of young age or vaccine shortage issues. In the analysis of the most severe cases, the estimates of effectiveness were similar to those in the main analysis, findings that are particularly relevant given that prevention of severe disease is the primary objective of vaccination programs.

Table 2. Effectiveness of 4CMenB in Preventing Invasive Meningococcal Disease Cases Caused by Any Serogroup.

Vaccination Status	Case Patients		Controls		Matched Odds Ratio (95% CI)*		Vaccine Effectiveness (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Crude	Adjusted†	
	number						*percent*
Main analysis							
≥1 Vaccine dose	34	271	280	926	0.32 (0.21 to 0.50)	0.32 (0.21 to 0.50)	68 (50 to 79)
Partially vaccinated	18	271	106	926	0.47 (0.27 to 0.82)	0.46 (0.26 to 0.82)	54 (18 to 74)
Fully vaccinated	16	271	174	926	0.24 (0.13 to 0.43)	0.24 (0.13 to 0.43)	76 (57 to 87)
Sensitivity analysis‡							
≥1 Vaccine dose	31	221	244	705	0.31 (0.19 to 0.49)	0.31 (0.19 to 0.49)	69 (51 to 81)
Partially vaccinated	16	221	87	705	0.46 (0.25 to 0.83)	0.46 (0.26 to 0.83)	54 (17 to 74)
Fully vaccinated	15	221	157	705	0.22 (0.12 to 0.41)	0.22 (0.12 to 0.41)	78 (59 to 88)
Severe cases§							
≥1 Vaccine dose	27	180	186	635	0.43 (0.26 to 0.70)	0.41 (0.25 to 0.68)	59 (32 to 75)
Partially vaccinated	16	180	77	635	0.63 (0.34 to 1.17)	0.61 (0.32 to 1.14)	39 (–14 to 68)
Fully vaccinated	11	180	109	635	0.29 (0.15 to 0.58)	0.29 (0.14 to 0.57)	71 (43 to 86)

* Matched odds ratios were obtained by means of a conditional regression analysis. Children who had received the first dose of 4CMenB in the previous 14 days were also included in the model in a separate vaccination category. The results obtained from fitting the models are provided in the Supplementary Appendix.
† Matched odds ratio were adjusted for sex and high-risk conditions.
‡ The sensitivity analysis was limited to children 134 to 1825 days of age and those who were unvaccinated against serogroup C meningococcus or had high-risk conditions.
§ Severe cases included those causing death, admission to an intensive care unit, or sequelae.

Table 3. Effectiveness of 4CMenB in Preventing Invasive Meningococcal Disease Cases Caused by Any Serogroup According to Age at the Date of Case Diagnosis and Period.

Vaccination Status	Case Patients		Controls		Matched Odds Ratio (95% CI)*		Vaccine Effectiveness (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Crude	Adjusted†	
	number						*percent*
Children <24 mo of age							
≥1 Vaccine dose	19	163	183	534	0.23 (0.13 to 0.42)	0.22 (0.12 to 0.42)	78 (58 to 88)
Partially vaccinated	13	163	81	534	0.37 (0.18 to 0.73)	0.35 (0.17 to 0.72)	54 (18 to 74)
Fully vaccinated	6	163	102	534	0.12 (0.05 to 0.31)	0.12 (0.05 to 0.32)	88 (68 to 95)
Children ≥24 mo of age							
≥1 Vaccine dose	15	108	186	635	0.51 (0.27 to 0.96)	0.54 (0.29 to 1.00)	59 (32 to 75)
Partially vaccinated	5	108	77	635	0.69 (0.26 to 1.86)	0.72 (0.27 to 1.92)	28 (–92 to 73)
Fully vaccinated	10	108	109	635	0.45 (0.21 to 0.95)	0.47 (0.22 to 0.99)	53 (1 to 78)
Period 2015–2017‡							
≥1 Vaccine dose	7	152	64	566	0.35 (0.15 to 0.83)	0.36 (0.15 to 0.83)	64 (17 to 85)
Partially vaccinated	7	152	25	566	0.81 (0.32 to 2.02)	0.81 (0.32 to 2.04)	19 (–104 to 68)
Fully vaccinated	7	152	39	566	0.08 (0.01 to 0.57)	0.08 (0.01 to 0.57)	92 (43 to 99)
Period 2017–2019‡							
≥1 Vaccine dose	27	119	216	360	0.32 (0.19 to 0.52)	0.31 (0.19 to 0.52)	71 (48 to 81)
Partially vaccinated	12	119	81	360	0.37 (0.19 to 0.75)	0.36 (0.18 to 0.74)	64 (26 to 82)
Fully vaccinated	15	119	135	360	0.28 (0.15 to 0.53)	0.28 (0.15 to 0.53)	72 (47 to 85)

* Matched odds ratios were obtained by means of conditional regression analysis. Children who had received the first dose of 4CMenB in the previous 14 days were also included in the model in a separate vaccination category. The results obtained from fitting the models are provided in the Supplementary Appendix.
† Matched odds ratios were adjusted for sex and high-risk conditions, when possible.
‡ Two 2-year periods were considered with respect to epidemiologic seasons: October 5, 2015, to October 8, 2017 (period 2015–2017) and from October 9, 2017, to October 6, 2019 (period 2017–2019).

Table 4. Effectiveness of 4CMenB in Preventing Invasive Meningococcal Disease Cases Caused by Serogroup B and by Non–Group B *Neisseria meningitidis*.

Vaccination Status	Case Patients		Controls		Matched Odds Ratio (95% CI)*		Vaccine Effectiveness (95% CI)
	Vaccinated	Unvaccinated	Vaccinated	Unvaccinated	Crude	Adjusted†	
	number						*percent*
Serogroup B cases							
Main analysis							
≥1 Vaccine dose	24	218	194	763	0.36 (0.22 to 0.59)	0.36 (0.22 to 0.59)	64 (41 to 78)
Partially vaccinated	12	218	72	763	0.49 (0.25 to 0.96)	0.50 (0.25 to 0.97)	50 (3 to 75)
Fully vaccinated	12	218	122	763	0.28 (0.15 to 0.54)	0.29 (0.15 to 0.55)	71 (45 to 85)
Sensitivity analysis‡							
≥1 Vaccine dose	23	179	170	591	0.37 (0.22 to 0.61)	0.36 (0.22 to 0.61)	64 (39 to 78)
Partially vaccinated	12	179	62	591	0.53 (0.27 to 1.05)	0.53 (0.27 to 1.05)	47 (–5 to 73)
Fully vaccinated	11	179	108	591	0.27 (0.14 to 0.53)	0.27 (0.14 to 0.53)	73 (47 to 86)
Severe cases§							
≥1 Vaccine dose	19	147	131	528	0.45 (0.26 to 0.79)	0.45 (0.25 to 0.79)	55 (21 to 75)
Partially vaccinated	11	147	51	528	0.69 (0.33 to 1.42)	0.69 (0.33 to 1.42)	31 (–42 to 67)
Fully vaccinated	8	147	80	528	0.30 (0.14 to 0.67)	0.30 (0.13 to 0.66)	70 (34 to 87)
Non–serogroup B cases							
Main analysis							
≥1 Vaccine dose	5	30	47	93	0.23 (0.07 to 0.81)	0.18 (0.04 to 0.79)	82 (21 to 96)
Partially vaccinated	4	30	19	93	0.50 (0.13 to 1.96)	0.42 (0.08 to 2.30)	58 (–130 to 92)
Fully vaccinated	1	30	28	93	0.08 (0.01 to 0.68)	0.08 (0.01 to 0.72)	92 (28 to 99)
Sensitivity analysis‡							
≥1 Vaccine dose	3	24	37	66	0.17 (0.04 to 0.77)	0.17 (0.04 to 0.74)	83 (26 to 96)
Partially vaccinated	2	24	11	66	0.38 (0.07 to 1.98)	0.36 (0.07 to 1.99)	64 (–99 to 93)
Fully vaccinated	1	24	26	66	0.07 (0.01 to 0.71)	0.08 (0.01 to 0.70)	92 (30 to 99)

* Matched odds ratios were obtained by means of conditional regression analysis. Children who had received the first dose of 4CMenB in the previous 14 days were also included in the model in a separate vaccination category. The results obtained from fitting the models are provided in the Supplementary Appendix.
† Matched odds ratios were adjusted for sex and high-risk conditions. The analysis of non–group B cases was also adjusted for meningococcal C vaccination.
‡ Sensitivity analysis were limited to children 134 to 1825 days of age and excluded those who were unvaccinated against serogroup C meningococcus or had high-risk conditions.
§ Severe cases included those causing death, admission to an intensive care unit, or sequelae.

The estimate of vaccine effectiveness against serogroup B disease (71%) was consistent with the percentage of cases caused by strains covered by 4CMenB in Spain (68.7%).[21] None of the cases that were caused by strains that were expected to be neutralized by 4CMenB-induced antibodies were detected among the vaccinated children, which suggests a high vaccine effectiveness against strains that were shown by the gMATS results to be covered by 4CMenB.[22] The analysis of cases not covered by the vaccine also suggested a possible vaccine effect. Because the gMATS assay provides a conservative estimate of the strains covered by 4CMenB, it is not surprising to find some vaccine protection against gMATS-negative cases, especially among fully vaccinated children.[23]

The effectiveness of complete 4CMenB vaccination seemed to be lower after 2 years of age and with vaccination schemes starting at the age of 2 years or older. In catch-up strategies for this vaccination scheme, the two priming doses may be separated by less than 2 months, and a booster dose is usually not required.[3]

The high correlation between the age of the child and the vaccination schedule prevented us from reaching a conclusion about the separate role of each variable. Changes in the percentage of meningococcal strains covered by the vaccine and a possible waning immunity are also factors to be considered.[24] However, we did not find evidence of waning immunity among fully vaccinated children. Sensitivity analyses supported the study findings and decreased biases that were due to the inclusion of children who were not old enough to be fully vaccinated or of those who had not received publicly funded vaccines.

The effectiveness estimates obtained in the present study against serogroup B meningococcal disease are in the range of the results from other countries. Parikh et al. evaluated a reduced 4CMenB vaccination schedule in infants in England using the screening method and observed an effectiveness of 82.9% for two doses.[6] Ladhani et al. updated this analysis and found that the effectiveness decreased to 52.7% with a two-dose priming schedule and to 59.1% with two doses followed by a booster dose during the second year of age.[10] A hospital-based, matched case–control study in Portugal showed an effectiveness of 79% among children and adolescents.[11] In two Italian regions, the screening method showed an effectiveness of 93.6% with a four-dose schedule and 91.0% with a three-dose schedule.[12] Differences in the percentage of strains covered by 4CMenB[20] and in the vaccination schedule may explain these differences in estimates. In addition, 4CMenB has been used to control outbreaks of serogroup B disease, with no cases being detected among vaccinees.[25-29]

The effectiveness of 4CMenB against invasive diseases caused by meningococcal serogroups other than serogroup B has been suggested[13,14] and can be explained by the fact that the vaccine components are not unique to serogroup B. The results of our study showed that effectiveness against disease caused by other serogroups was similar to that against serogroup B disease. Most cases caused by serogroup W in Spain during the study period involved the same strain that had been detected in England, which was shown to be covered by 4CMenB according to the MATS result.[13] Nevertheless, 4CMenB has not been shown to have an effect on the carriage of disease-causing meningococci.[30]

The percentage of children with invasive meningococcal disease who were admitted to intensive care unit was high. However, such patients are frequently admitted to an intensive care unit for a short period of observation in anticipation of possible worsening.

This study has some limitations. The study size was small for analyses other than the vaccine effectiveness in the prevention of disease caused by any serogroup and by disease caused by serogroup B; therefore, other results should be viewed with caution. Because 4CMenB was available for private purchase, higher socioeconomic status might have been associated with higher vaccine coverage; in addition, higher socioeconomic status has been considered to be related with a lower incidence of meningococcal diseases.[31,32] This potential confounding factor was only partially controlled by matching according to province of birth and residence and could have resulted in an overestimation of the effectiveness. However, the following circumstances might dilute the effect of this bias: vaccination with 4CMenB was publicly funded for high-risk children, the vaccine shortage affected all children regardless of their household income level, the decision to vaccinate was based

on the recommendation of each child's individual pediatrician, the vaccine effectiveness did not change substantially during the study period despite the fact that vaccine coverage increased markedly, and the high effectiveness that was observed could not be fully explained by this bias. The results of the gMATS were not available for all children with cases caused by serogroup B, a number of cases yielded unpredictable results, and the possibility of differences in gMATS results between tested and untested patients cannot be excluded. This study was mainly retrospective; however, we think that the sources of information are reliable.

The strengths of this study are the individual matched case–control design with comparability by the matching variables, the relatively large number of cases, the use of immunization registries, and the nationwide representativeness. Because vaccination with 4CMenB was not publicly funded during the study period, the vaccination coverage reached a medium level, and the vaccine shortage increased the diversity in vaccination patterns.

Complete vaccination with 4CMenB was shown to be effective in preventing invasive disease due to serogroup B and non–serogroup B meningococci in Spanish children younger than 5 years of age. This evidence may be useful in making decisions about the inclusion of this vaccine in the immunization program of countries where invasive meningococcal disease in children is problematic and its prevention a priority.

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

APPENDIX

The authors' full names and academic degrees are as follows: Jesús Castilla, M.D., Ph.D., Manuel García Cenoz, M.D., Ph.D., Raquel Abad, Ph.D., Laura Sánchez-Cambronero, M.D., Nicola Lorusso, M.D., Conchita Izquierdo, Ph.D., Soledad Cañellas Llabrés, M.D., Javier Roig, M.D., Alberto Malvar, M.D., Fernando González Carril, M.Sc., An L.D. Boone, M.D., Jaime Pérez Martín, M.D., M. Jesús Rodríguez Recio, M.D., Antònia Galmés, M.D., Arturo Caballero, M.D., Amós García Rojas, M.D., Felipe Juanas, M.D., Mercedes Nieto, M.D., Luis J. Viloria Raymundo, M.D., Eva Martínez Ochoa, M.D., Ana I. Rivas, M.D., Daniel Castrillejo, Ph.D., David Moreno Pérez, M.D., Ana Martínez, Ph.D., Eva Borràs, Ph.D., Amaya Sánchez Gómez, Ph.D., Eliseo Pastor, M.D., Victoria Nartallo, M.D., José M. Arteagoitia, M.D., Blanca Álvarez-Fernández, R.N., Rocío García Pina, M.D., Socorro Fernández Arribas, M.D., Joana Vanrell, M.D., Sara García Hernández, R.N., Rita M. Mendoza, M.D., Manuel Méndez, M.D., M. Mar López-Tercero, M.D., Ángela Fernández-Rodríguez, Ph.D., Ángela Blanco, M.D., F. Javier Carrillo de Albornoz, M.D., José Ruiz Olivares, M.D., Rafael Ruiz-Montero, M.P.H., Aurora Limia, M.D., Ph.D., José A. Navarro-Alonso, M.D., Julio A. Vázquez, Ph.D., and Aurelio Barricarte, M.D., Ph.D.

The authors' affiliations are as follows: Instituto de Salud Pública de Navarra, Instituto de Investigación Sanitaria de Navarra, Pamplona (J.C., M.G.C., A.B.), Consorcio de Investigación Biomédica en Red de Epidemiología y Salud Pública (J.C., M.G.C., C.I., A.M., R.G.P., E.B., A.B.), Ministerio de Sanidad (L.S.-C., A.L., J.A.N.-A.), and Dirección General de Salud Pública, Comunidad de Madrid (S.C.L., A.S.-G.), Madrid, National Center for Microbiology, Instituto de Salud Carlos III, Majadahonda (R.A., J.A.V.), Dirección General de Salud Pública y Ordenación Farmacéutica de Andalucía, Sevilla (N.L., D.M.P.), Agència de Salut Pública de Catalunya, Barcelona (C.I., A.M., E.B.), Dirección General de Salud Pública y Adicciones de la Comunidad Valenciana, Valencia (J.R., E.P.), Dirección Xeral da Saúde Pública da Galícia, Santiago de Compostela (A.M., V.N.), Dirección de Salud Pública y Adicciones del Gobierno Vasco, Vitoria (F.G.C., J.M.A.), Servicio de Vigilancia Epidemiológica de Asturias, Oviedo (A.L.D.B., B.A.-F.), Dirección General de Salud Pública y Adicciones, Instituto Murciano de Investigación Biosanitaria–Arrixaca, Murcia (J.P.M., R.G.P.), Servicio de Epidemiología de Castilla y León, Valladolid (M.J.R.R., S.F.A.), Direcció General de Salut Pública i Participació, Illes Balears, Palma de Mallorca (A.G., J.V.), Servicio Epidemiología de Castilla–La Mancha, Toledo (A.C., S.G.H.), Dirección General de Salud Pública de Canarias, Santa Cruz de Tenerife (A.G.R., R.M.M.), Dirección General de Salud Pública de Aragón, Zaragoza (F.J., M.M.), Dirección General de Salud Pública de Extremadura, Mérida (M.N., M.M.L.-T.), Dirección General de Salud Pública de Cantabria, Santander (L.J.V.R., A.F.-R.), Dirección General de Salud Pública, Consumo y Cuidados de La Rioja, Logroño (E.M.O., A.B.), Consejería de Sanidad, Consumo y Gobernación, Ceuta (A.I.R., F.J.C.A.), Dirección General de Salud Pública y Consumo, Melilla (D.C., J.R.O.), and Instituto Maimónides de Investigación Biomédica de Córdoba, Reina Sofia University Hospital, University of Cordoba, Cordoba (R.R.-M.) — all in Spain.

REFERENCES

1. Whittaker R, Dias JG, Ramliden M, et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004-2014. Vaccine 2017;35:2034-41.
2. Ladhani SN, Flood JS, Ramsay ME, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. Vaccine 2012;30:3710-6.
3. European Medicines Agency. Bexsero: summary of product characteristics. September 18, 2017 (https://www.ema.europa.eu/en/documents/product-information/bexsero-epar-product-information_en.pdf).
4. Giuliani MM, Adu-Bobie J, Comanducci M, et al. A universal vaccine for serogroup B meningococcus. Proc Natl Acad Sci U S A 2006;103:10834-9.
5. Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. Lancet 2013;381:825-35.
6. Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in

England: a national observational cohort study. Lancet 2016;388:2775-82.
7. Martinón-Torres F, Safadi MAP, Martinez AC, et al. Reduced schedules of 4CMenB vaccine in infants and catch-up series in children: immunogenicity and safety results from a randomised open-label phase 3b trial. Vaccine 2017;35:3548-57.
8. Flacco ME, Manzoli L, Rosso A, et al. Immunogenicity and safety of the multicomponent meningococcal B vaccine (4CMenB) in children and adolescents: a systematic review and meta-analysis. Lancet Infect Dis 2018;18:461-72.
9. European Centre for Disease Prevention and Control. Vaccine scheduler: vaccine schedules in all countries in the EU/EEA (https://vaccine-schedule.ecdc.europa.eu).
10. Ladhani SN, Andrews N, Parikh SR, et al. Vaccination of infants with meningococcal group B vaccine (4CMenB) in England. N Engl J Med 2020;382:309-17.
11. Rodrigues FMP, Marlow R, Simões MJ, Danon L, Ladhani S, Finn A. Association of use of a meningococcus group B vaccine with group B invasive meningococcal disease among children in Portugal. JAMA 2020;324:2187-94.
12. Azzari C, Moriondo M, Nieddu F, et al. Effectiveness and impact of the 4CMenB vaccine against group B meningococcal disease in two Italian regions using different vaccination schedules: a five-year retrospective observational study (2014–2018). Vaccines (Basel) 2020;8:469.
13. Ladhani SN, Giuliani MM, Biolchi A, et al. Effectiveness of meningococcal B vaccine against endemic hypervirulent Neisseria meningitidis W strain, England. Emerg Infect Dis 2016;22:309-11.
14. Biolchi A, De Angelis G, Moschioni M, et al. Multicomponent meningococcal serogroup B vaccination elicits cross-reactive immunity in infants against genetically diverse serogroup C, W and Y invasive disease isolates. Vaccine 2020;38:7542-50.
15. Ministerio de Sanidad. Recomendaciones de utilización de la vacuna frente a enfermedad meningocócica por serogrupo B. 2015 (https://www.mscbs.gob.es/profesionales/saludPublica/prevPromocion/vacunaciones/comoTrabajamos/docs/MenB_situacEspeciales.pdf).
16. Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). Modificación de las condiciones de prescripción y dispensación de la vacuna Bexsero: eliminación de la clasificación como de uso hospitalario. September 23, 2015 (http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/vacunas/2015/NI-MUH_23-2015-vacuna-bexsero.htm).
17. Moreno-Pérez D, Álvarez García FJ, Arístegui Fernández J, et al. Immunisation schedule of the Spanish Association of Paediatrics: 2016 recommendations. An Pediatr (Barc) 2016;84(1):60.e1-60.e13.
18. Instituto de Salud Carlos III. Protocolos de la Red Nacional de Vigilancia Epidemiológica. April 9, 2013 (https://www.isciii.es/QueHacemos/Servicios/VigilanciaSaludPublicaRENAVE/EnfermedadesTransmisibles/Documents/PROTOCOLOS/PROTOCOLOS%20EN%20BLOQUE/PROTOCOLOS_RENAVE-ciber.pdf).
19. Muzzi A, Brozzi A, Serino L, et al. Genetic Meningococcal Antigen Typing System (gMATS): a genotyping tool that predicts 4CMenB strain coverage worldwide. Vaccine 2019;37:991-1000.
20. Vogel U, Taha MK, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis 2013;13:416-25.
21. Abad R, Medina V, Stella M, et al. Predicted strain coverage of a new meningococcal multicomponent vaccine (4CMenB) in Spain: analysis of the differences with other European countries. PLoS One 2016;11(3):e0150721.
22. Lucidarme J, Bai X, Lekshmi A, et al. Invasive serogroup B meningococci in England following three years of 4CMenB vaccination — first real-world data. J Infect 2022;84:136-44.
23. Brunelli B, Del Tordello E, Palumbo E, et al. Influence of sequence variability on bactericidal activity sera induced by Factor H binding protein variant 1.1. Vaccine 2011;29:1072-81.
24. Snape MD, Saroey P, John TM, et al. Persistence of bactericidal antibodies following early infant vaccination with a serogroup B meningococcal vaccine and immunogenicity of a preschool booster dose. CMAJ 2013;185(15):E715-E724.
25. Basta NE, Mahmoud AAF, Wolfson J, et al. Immunogenicity of a meningococcal B vaccine during a university outbreak. N Engl J Med 2016;375:220-8.
26. De Wals P, Deceuninck G, Lefebvre B, et al. Impact of an immunization campaign to control an increased incidence of serogroup B meningococcal disease in one region of Quebec, Canada. Clin Infect Dis 2017;64:1263-7.
27. 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;135:798-804.
28. Biswas HH, Han GS, Wendorf K, et al. Notes from the field: outbreak of serogroup B meningococcal disease at a university — California, 2016. MMWR Morb Mortal Wkly Rep 2016;65:520-1.
29. Thabuis A, Tararbit K, Taha M-K, et al. Community outbreak of serogroup B invasive meningococcal disease in Beaujolais, France, February to June 2016: from alert to targeted vaccination. Euro Surveill 2018;23:1700590.
30. Marshall HS, McMillan M, Koehler AP, et al. Meningococcal B vaccine and meningococcal carriage in adolescents in Australia. N Engl J Med 2020;382:318-27.
31. MacNeil JR, Bennett N, Farley MM, et al. Epidemiology of infant meningococcal disease in the United States, 2006-2012. Pediatrics 2015;135(2):e305-e311.
32. Stanton MC, Taylor-Robinson D, Harris D, et al. Meningococcal disease in children in Merseyside, England: a 31 year descriptive study. PLoS One 2011;6(10):e25957.