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Association of Use of a Meningococcus Group B Vaccine With Group B Invasive Meningococcal Disease Among Children in Portugal

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IMPORTANCE A 4-component meningococcus group B vaccine (4CMenB) is the only vaccine in use to prevent group B invasive meningococcal disease in young children, but no matched controlled studies have evaluated it.

OBJECTIVE To determine the association between receipt of 4CMenB and invasive group B meningococcal disease.

DESIGN, SETTING, AND PARTICIPANTS Matched incidence density case-control study. Patients presenting from October 2014 to March 2019 were ascertained, with follow-up until death or discharge (last follow-up in June 2019) in 31 pediatric services in Portugal. Children and adolescent residents in Portugal with laboratory-confirmed invasive meningococcal disease were included. Controls, usually 2 per case, with unrelated conditions who were at the same hospital at the same time were matched for sex, age, and residence.

EXPOSURES Immunization with 4CMenB, ascertained from the national database (2-4 doses are recommended, depending on age).

MAIN OUTCOMES AND MEASURES The primary outcome was group B invasive meningococcal disease in fully vaccinated cases compared with controls. The secondary outcomes were all serogroup invasive meningococcal disease in fully vaccinated cases compared with controls and group B and all serogroup invasive meningococcal disease in cases compared with controls who received at least 1 vaccine dose.

RESULTS Of 117 patients with invasive meningococcal disease, 98 were eligible for inclusion and 82 had group B invasive meningococcal disease; 69 were old enough to have been fully vaccinated and considered protected. Among these 69 cases, the median (interquartile range) age was 24 (4.5-196) months, 42 were male, and the median (interquartile range) duration of hospitalization was 8 (0-86) days. Five of 69 cases (7.2%) and 33 of 142 controls (23.1%) were fully vaccinated (difference, −16.0% [95% CI, −26.3% to −5.7%]; odds ratio [OR], 0.21 [95% CI, 0.08-0.55]). For all serogroup invasive meningococcal disease, 6 of 85 cases (7.1%) and 39 of 175 controls (22.3%) were fully vaccinated (difference, −15.2% [95% CI, −24.3% to −6.1%]; OR, 0.22 [95% CI, 0.09-0.53]). For group B disease, 8 of 82 cases (9.8%) and 50 of 168 controls (29.8%) received at least 1 vaccine dose (difference, −20.0% [95% CI, −30.3% to −9.7%]; OR, 0.18 [95% CI, 0.08-0.44]) and for all serogroup invasive meningococcal disease, 11 of 98 cases (11.2%) and 61 of 201 controls (30.3%) received at least 1 vaccine dose (difference, −19.1% [95% CI, −28.8% to −9.5%]; OR, 0.23 [95% CI, 0.11-0.49]).

CONCLUSIONS AND RELEVANCE During the first 5 years of vaccine availability in Portugal, vaccination with 4CMenB was less likely among children who developed invasive meningococcal disease compared with matched controls without invasive meningococcal disease. These findings may help inform the use of the 4CMenB vaccine in clinical practice.

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Supplemental content

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Neisseria meningitidis serogroup B (MenB) is the leading cause of invasive meningococcal disease in European countries, including Portugal. A protein-antigen vaccine, 4CMenB (Bexsero; GSK Biologicals), was licensed in Europe in 2013 and is the only available vaccine for the prevention of MenB disease in infants and young children. Containing 3 recombinant antigens and an outer membrane vesicle complex derived from the New Zealand outbreak strain[1] that are not restricted to MenB, it has the potential to protect against other serogroups as well.[2,3] Before licensure, the efficacy of 4CMenB was never demonstrated in randomized clinical trials, and the only evidence supporting its use comes from immunogenicity studies, observational studies comparing vaccine rates in individuals with MenB disease with those in the whole population, and ecological studies comparing disease incidence trends in age groups offered the vaccine with those predicted from trends in other age groups. 4CMenB has been implemented in the national immunization programs of only a few European countries.[4] In the US,[5] MenB vaccines are only recommended for individuals at high risk and for outbreak control. In the UK, a 50% reduction in MenB disease was initially observed in vaccine-eligible infants.[6] Using the screening method, by which immunization rates among cases are compared with whole-population coverage rates,[7] vaccine effectiveness against MenB for 2 infant doses in the first 10 months of use was 82.9% (95% CI, 24.1%-95.2%),[6] but was lower over the first 3 years of use (to August 2018) at 52.7% (95% CI, −33.5% to 83.2%) following 2 infant doses and 59.1% (95% CI, −31.1% to 87.2%) following the booster.[8] The current study was done to determine the association between receipt of 4CMenB and invasive group B meningococcal disease using concurrent cases and controls.

Key Points

Question Among children in Portugal, was there an association between receipt of a 4-component meningococcus group B vaccine (4CMenB) and group B invasive meningococcal disease?

Findings In this matched case-control study that included 299 children, the likelihood of full vaccination with 4CMenB among children old enough to be fully immunized was significantly lower among cases with group B invasive meningococcal disease compared with controls without invasive meningococcal disease (odds ratio, 0.21).

Meaning During the first 5 years of vaccine availability in Portugal, full vaccination with 4CMenB was less likely among children who developed group B invasive meningococcal disease compared with matched controls.

Methods

The study was approved by the ethics committee of Centro Hospitalar e Universitário de Coimbra including anonymized data collection from medical records without informed consent.

Study Design and Setting

We conducted a matched case-control study, using an incidence density design,[9] with close matching for time of presentation because vaccination coverage rates changed during the period covered by the study. Children and adolescents presenting to 31 pediatric hospitals (including all 5 tertiary pediatric units) throughout Portugal with laboratory-confirmed invasive meningococcal disease from October 2014, after the time 4CMenB became available, until March 2019 were included. Data were collected at the contributing hospitals through June 2019. Vaccination records were obtained from the central immunization records database (Aplicação VACINAS), implemented in 2014 before 4CMenB became available, which is linked to electronic patient records for all children in Portugal. It contains details of all vaccines children have received, including those that are not included in the national immunization program and only available through private clinics, such as 4CMenB.

Case Inclusion Criteria

Sites provided data on all children and adolescents younger than 18 years with laboratory-confirmed invasive meningococcal disease. Invasive meningococcal disease was defined as a positive culture and/or polymerase chain reaction result for *Neisseria meningitidis* in a normally sterile biological sample (eg, blood, cerebrospinal fluid, pleural fluid, joint fluid).

Cases were excluded if they did not reside in Portugal at the time of presentation; were known to belong to a risk group for invasive meningococcal disease at the time of diagnosis, including asplenia, hyposplenia, splenic dysfunction, and immunodeficiency (including but not restricted to complement deficiency); were receiving eculizumab (a monoclonal antibody against complement C5); had a history of invasive meningococcal disease or were a recent contact of a case; or had no available information about meningococcal vaccines from the central immunization records database.

For each case, sites sought up to 3 controls attending the same hospital with an illness that was clearly not invasive meningococcal disease (ie, not meningitis, sepsis, or pyrexia of unknown origin). To minimize bias, controls were matched to cases by sex, area of residence (same or adjacent regional postcode), date of birth (for cases aged <2 years, the date of birth of the controls had to be within 14 days of the cases; for cases aged 2-5 years, within 60 days; and for cases aged >5 years, within 90 days), and date of attendance (within 14 days of the case's attendance). Exclusion criteria for controls were the same as for cases. For each case, emergency service records were screened for eligible matching controls on the day of presentation of the case, followed by each successive day earlier and then later until the controls (usually 2 but occasionally 1 or 3) had been identified. When cases were identified in a tertiary hospital who had been transferred from secondary care facilities, controls were identified in the latter, on or around the day of initial presentation, using the same approach.

Case and Control Ascertainment and Data Collection

At each site, a named clinician identified eligible cases from local clinical and laboratory records. Because vaccination

uptake rates varied during the study period, we used an incidence density case-control design. For each case, age-matched controls were identified who attended the same hospital within a 2-week period of the case's attendance. Thus, controls were drawn from the same population at risk as the cases, rather than the population at the beginning or end of the study.[9] Microbiological data, final diagnosis, underlying risk factors, outcomes, and sequelae were extracted and recorded on a standard anonymized case report form. Data collection methods were identical for cases and controls. After controls were selected and clinical information was extracted from medical records of cases and controls, information on vaccination status was obtained only from the linked national central database by the same clinicians. We based vaccine status definitions on the Portuguese Society of Pediatrics recommendations that the infant schedule should commence at 2 months, with a second dose given by 4 to 5 months. After 2 doses of vaccine, infants were considered fully immunized, but only until 16 months unless they received a booster dose after 12 months of age. Children who were not vaccinated in infancy had to have received 2 doses after their first birthday, but required no further boosting thereafter, to be considered fully immunized. To allow time for an immune response, vaccine doses within 14 days prior to attendance were discounted. Thus, the youngest valid age for partial vaccination was 74 days and for full vaccination was 134 days. The vaccine status of each case was assessed at the date of presentation, and that of the matched controls was then determined at the same chronological age in days as the corresponding case.

Outcomes

The predefined primary outcome measure was group B invasive meningococcal disease in cases compared with controls who received the full recommended schedule of 4CMenB for their age. Predefined secondary outcome measures were all serogroup invasive meningococcal disease in fully vaccinated cases compared with controls and group B and all serogroup invasive meningococcal disease in cases compared with controls who received at least 1 vaccine dose. Clinical outcomes (death and sequelae) among cases and bacterial strain coverage by 4CMenB among fully and partially vaccinated cases were post hoc outcomes.

Molecular Characterization

Isolates were characterized genetically using methods as previously described.[10] This methodology uses the sequences of the neisserial genes in cultured invasive strains for the proteins included in 4CMenB to allocate peptide identification numbers to the variants that exist and, by comparison with results obtained by the Meningococcal Antigen Typing System,[11] analysis is used to predict whether isolates expressing particular protein variants will be recognized by antisera from fully immunized individuals.

Statistical Methods

Prior to study initiation, we completed a sample size calculation to ensure that the study was feasible,[12] which determined that a minimum of 36 cases with 2 matched controls per case would be required to have 80% power (using a 2-sided α of .05) to demonstrate an odds ratio (OR) of vaccination of 0.2,[6] assuming 30% vaccine uptake in controls. The OR was used as an estimate of vaccine effectiveness between cases and controls. This was calculated using both simple whole-cohort comparison and matched conditional logistic regression with no additional covariates in the primary analysis. Proportions were compared using Fisher exact tests and nonparametric assessment was done using Wilcox signed rank test. Statistical analyses were performed with R, version 4.0.2. Missing data were minimal, so no imputation was performed. Statistical significance was defined using a 2-sided significance level of α = .05. Because of the potential for type I error due to multiple comparisons, findings for analyses of secondary end points should be interpreted as exploratory.

Sensitivity and Adjusted Analyses

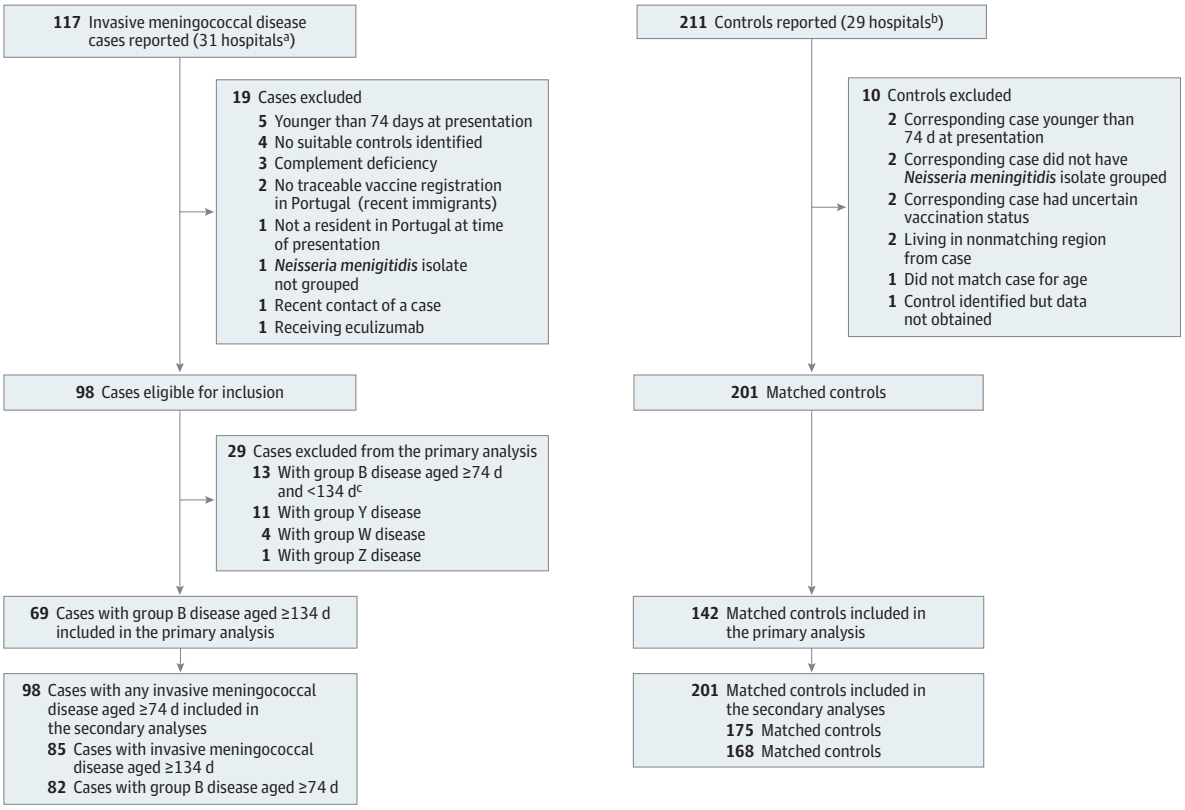
Although cases and controls were comprehensively matched, to evaluate whether any differences existed between cases and controls or between vaccinated and unvaccinated children in the study with regard to wealth and social class, which could potentially bias results, we performed an adjusted analysis that included the purchasing power indicator (a metric used to compare relative wealth between areas of Portugal with the country as a whole averaged to 100, ranging from 55.83 in the poorest municipality to 214.54 in Lisbon) for the first half of the postcode (municipality) of residence[13]; this was included as an additional covariate in the regression model.

Additional sensitivity analyses included estimation of ORs using the screening method, comparing 2-dose 4CMenB coverage in cases presenting by their first birthday with national vaccine coverage data.[7] The screening method is an alternative way of assessing vaccine programs, comparing the proportion of vaccinated cases with the proportion of population targeted for vaccination, in which the OR of vaccination = (proportion of vaccinated cases/1 − proportion of vaccinated cases) × (1 − proportion of population targeted for vaccination/proportion of population targeted for vaccination). A binomial regression stratified by year was performed against the corresponding vaccination rates of cases in the study. Also, an analysis of association without allowing 14 days for vaccine immune responses to take effect was done.

Results

National statistics show 2-dose coverage of 4CMenB in Portugal by the first birthday, delivered entirely through private clinics, increasing from 32.8% in the 2015 birth cohort to 44.2% in 2016, 53.5% in 2017, and 56.7% in 2018 (written personal communication, Ana Leça, MD, Directorate-General of Health, Lisbon, Portugal, August 21, 2020). The overall national coverage during the study period was 47%, and the percentage of controls in this study who received at least 2 doses of 4CMenB by the time they reached their first birthday was 50%. Among 33 controls aged 5 years and older, only 1 was fully immunized.

Figure. Flow of Eligible Cases and Controls in a Study of the Association of a Meningococcus Group B Vaccine With Group B Invasive Meningococcal Disease Among Children in Portugal



[a] Controls all came from the hospitals of origin of cases. One hospital only reported cases who had been transferred in. One hospital reported a single case of a child with complement deficiency and did not provide controls for that case, who was excluded from further analysis per protocol.

[b] Matching occurred at each site at the time of data extraction for the cases by sex, date of birth, date of presentation, and region of residence. For each case, investigators were asked to identify at least 2 matched controls if possible. On occasion, only 1 eligible control could be found or 3 were identified, in which cases they were included in the analyses. Children who presented as close in time as possible and up to a maximum of 14 days either side of the case, were eligible as controls.

[c] The youngest valid age for partial vaccination was 74 days and for full vaccination was 134 days.

The designation and exclusion of cases and controls is shown in the **Figure**. Of 117 cases with invasive meningococcal disease, 98 were eligible for inclusion. The closeness of match of baseline demographics of the 98 included cases and 201 controls are shown in **Table 1**. Three eligible matched controls were identified for 7 cases, 2 for 89 cases, and 1 for 2 cases. MenB was responsible for invasive meningococcal disease in 82 cases and, of these, 69 were aged at least 134 days at presentation and thus were old enough to have potentially achieved full immunization status and formed the cohort for primary analysis. Of these 69 cases, the median (interquartile range [IQR]) age was 24 (4.5-196) months, 42 were male, and the duration of hospitalization was a median (IQR) of 8 (0-86) days. The characteristics of the invasive meningococcal disease cases used in the primary and secondary analyses are summarized in **Table 2**.

The primary and secondary outcomes are shown in **Table 3**. Five of 69 cases (7.2%) with group B disease and 33 of 142 controls (23.1%) aged at least 134 days (eligible for full immunization) were fully vaccinated (difference, −16.0% [95% CI, −26.3% to −5.7%]; OR, 0.21 [95% CI, 0.08-0.55]). Among those who were eligible for full immunization, 6 of 85 cases (7.1%) with any serogroup invasive meningococcal disease and 39 of 175 controls (22.3%) were fully vaccinated (difference, −15.2% [95% CI, −24.3% to −6.1%]; OR, 0.22 [95% CI, 0.09-0.53]). Among those aged at least 74 days, 8 of 82 cases with group B disease (9.8%) and 50 of 168 controls (29.8%) received at least 1 vaccine dose (difference, −20.0% [95% CI, −30.3% to −9.7%]; OR, 0.18 [95% CI, 0.08-0.44]) and 11 of 98 cases (11.2%) with any serogroup invasive meningococcal disease and 61 of 201 controls (30.3%) received at least 1 vaccine dose (difference, −19.1% [95% CI −28.8% to −9.5%]; OR, 0.23 [95% CI, 0.11-0.49]).

In post hoc analyses, outcomes were available for all 11 cases (median [IQR] age, 22 [14-33] months) who developed invasive meningococcal disease after 74 days of age and received at least 1 dose of 4CMenB at least 14 days prior to developing the disease (**Table 4**). None died or had sequelae (0% [95% CI, 0% to 28%]) (Table 2). In contrast, among the remaining 87 cases aged at least 74 days who were 4CMenB unimmunized (median [IQR] age, 14 [6.2-49.3] months), 7 (8%) died

Table 1. Baseline Characteristics of Cases and Controls in a Study of the Association of a Meningococcus Group B Vaccine With Group B Invasive Meningococcal Disease Among Children in Portugal

Characteristic	Median (interquartile range)		
	Cases (n = 98)	Controls (n = 201)	Difference between matched groups[a]
Age	17.5 mo (7.1-48.5)	15.9 mo (7.1-49.2)	<2 y: 6 (3-10) d; 2-5 y: 23 (10-40) d; >5-17 y: 28 (12-57) d
Sex, No. (%)			All cases and controls were matched by gender
Male	61 (62.2)	127 (63.2)	
Female	37 (37.8)	74 (36.8)	
Cases/controls per site	3 (2-4)	6 (4-8)	All cases and controls were matched by site of origin
Date of attendance, days			1 (0-3)
Socioeconomic purchasing power[b]	95.4 (78.4-109.7)	96.0 (84.0-113.2)	7.1 (0-36.4)
Reason for hospitalization, No. (%)	39 (39.8) for septicemia and meningitis; 27 (27.6), meningitis; 21 (21.4), septicemia; 9 (9.2), bacteremia; 2 (2.0), arthritis	57 (28.4) for upper respiratory tract infection; 19 (9.5), acute gastroenteritis; 17 (8.5), acute otitis media; 14 (7.0), acute bronchiolitis; 10 (5.0), asthma; 7 (3.5), pneumonia; 7 (3.5), urinary tract infection; 6 (3), trauma; 6 (3), rash; 4 (2), viral infection; 54 (26.6), other	

[a] The absolute differences in age at presentation to hospital are shown for 3 age ranges. However, the immunization status of the controls was ascertained at the same chronological age as the matched cases on the day of presentation of the latter in each instance.

[b] Socioeconomic purchasing power is a metric used to compare relative wealth between municipalities in Portugal with the country as a whole averaged to 100, with values ranging from 55.83 in the poorest location to 214.54 in Lisbon.[13]

Table 2. Demographics, Microbiology, and Clinical Outcomes of Patients With Invasive Meningococcal Disease Included in the Analysis in a Study of the Association of a Meningococcus Group B Vaccine With Group B Invasive Meningococcal Disease Among Children in Portugal

Characteristic	No. (%)			
	Cases with group B disease aged ≥134 d (primary analysis; n = 69)[a]	Cases with any invasive meningococcal disease aged ≥134 d (n = 85)[a]	Cases with group B disease aged ≥74 d (n = 82)[a]	Cases with any invasive meningococcal disease aged ≥74 d (n = 98)[a]
Age, median (IQR), mo	24.1 (10.1-50.1)	24.1 (9.6-51.3)	17.5 (6.2-43.6)	17.5 (7.1-48.5)
Sex				
Male	42 (60.9)	54 (63.5)	49 (59.8)	61 (62.2)
Female	27 (39.1)	31 (36.5)	33 (40.2)	37 (37.8)
Diagnosis[b]				
Septicemia and meningitis	32 (46.4)	33 (38.8)	38 (46.3)	39 (39.8)
Meningitis	16 (23.2)	23 (27.1)	20 (24.4)	27 (27.6)
Septicemia	14 (20.3)	19 (22.4)	16 (19.5)	21 (21.4)
Bacteremia	6 (8.7)	8 (9.4)	7 (8.5)	9 (9.2)
Arthritis	1 (1.4)	2 (2.4)	1 (1.2)	2 (2.0)
Duration of admission, median (IQR), d	8 (7-10)	7 (6-10)	8 (7-10)	7 (7-10)
Outcome[c]				
Alive with no sequelae	49 (71.0)	64 (75.3)	60 (73.2)	75 (76.5)
Alive with sequelae	15 (21.7)	15 (17.6)	16 (19.5)	16 (16.3)
Developmental delay	9 (13.0)	9 (10.6)	10 (12.2)	10 (10.2)
Death	5 (7.2)	6 (7.1)	6 (7.3)	7 (7.1)
Amputation	4 (5.8)	4 (4.7)	4 (4.9)	4 (4.1)
Deafness	1 (1.4)	1 (1.2)	1 (1.2)	1 (1.0)
Other	1 (1.4)	1 (1.2)	1 (1.2)	1 (1.0)
Meningococcal capsular group[d]				
B	69 (100)	69 (81.2)	82 (100)	82 (83.7)
Y	0	11 (12.9)	0	11 (11.2)
W	0	4 (4.7)	0	4 (4.1)
Z	0	1 (1.2)	0	1 (1)

Abbreviation: IQR, interquartile range.

[a] The youngest valid age for partial vaccination was 74 days and for full vaccination was 134 days.

[b] Diagnoses at hospital discharge were options provided on the case report forms to reporting clinicians without strict definition. Twelve children and adolescents were transferred from secondary to tertiary care facilities.

[c] Outcomes were extracted from the medical records accessed at the time of data collection, so they reflect information obtained both during admission and follow-up.

[d] Meningococcal capsular grouping was done by polymerase chain reaction, as recommended by the World Health Organization.[14]

Table 3. Results of Primary and Secondary Outcome Analyses in a Study of the Association of a Meningococcus Group B Vaccine With Group B Invasive Meningococcal Disease Among Children in Portugal

Analysis	No. of participants/total No. (%)		Absolute difference (95% CI), %	Odds ratio (95% CI)	
	Cases	Controls		Crude[a]	Matched
Primary					
Cases with group B disease and controls aged ≥134 d fully immunized for age[b]	5/69 (7.2)	33/142 (23.2)	−16.0 (−26.3 to −5.7)	0.26 (0.10 to 0.69)	0.21 (0.08 to 0.55)[c]
Secondary					
Cases with any invasive meningococcal disease and controls aged ≥134 d and fully immunized for age[b]	6/85 (7.1)	39/175 (22.3)	−15.2 (−24.3 to −6.1)	0.26 (0.11 to 0.65)	0.22 (0.09 to 0.53)[c]
Cases with group B disease and controls aged ≥74 d who received ≥1 vaccine dose	8/82 (9.8)	50/168 (29.8)	−20.0 (−30.3 to −9.7)	0.26 (0.11 to 0.57)	0.18 (0.08 to 0.44)[c]
Cases with any invasive meningococcal disease and controls aged ≥74 d who received ≥1 vaccine dose	11/98 (11.2)	61/201 (30.3)	−19.1 (−28.8 to −9.5)	0.29 (0.14 to 0.58)	0.23 (0.11 to 0.49)[c]
Sensitivity (including purchasing power)[d]					
Cases with group B disease and controls aged ≥134 d fully immunized for age[b]	5/69 (7.2)	33/142 (23.2)	−16.0 (−26.3 to −5.7)	0.26 (0.10 to 0.69)	0.21 (0.07 to 0.65)

[a] Unmatched analysis of entire case cohort against the control cohort.

[b] Fully immunized is considered 2 or more doses 14 or more days prior to presentation for those aged 2 to 15 months and either 2 or more doses in infancy plus 1 dose after the first birthday or 2 or more doses after the first birthday with completion at least 14 days prior to presentation for those aged 16 months and older.

[c] Matched conditional logistic regression analysis with no additional covariates.

[d] Adjusted for purchasing power linked to the first half of the postcode (municipality) of residence.

Table 4. Details of Cases With Invasive Meningococcal Disease Aged 74 Days or Older Who Received 1 or More Vaccine Doses

Age at presentation, mo	Sex	Clinical diagnosis[a]	Duration of admission, d[b]	Meningococcal capsular group	No. of vaccine doses	Age at vaccination, mo	Vaccination status[c]	Clonal complex[d]	Porin A variable region 1[e]	Porin A variable region 2[e]	Factor H binding protein[f]	Neisserial heparin binding antigen[f]	Neisserial adhesin A[f]
9	Male	Septicemia	10	B	1	7	Partial	461	19-2	13-2	47	118	0
12	Male	Septicemia and meningitis	6	B	2	3, 5	Full	Not done	Not done	Not done	Not done	Not done	Not done
16	Female	Meningitis	9	B	1	15	Partial	103	5-1	10-46	25	24	0
20	Male	Septicemia and meningitis	7	B	4	5, 7, 9, 15	Full	213	22	14	0	18	0
22	Male	Bacteremia	4	B	3	5, 7, 18	Full	865	19	15-1	25	6	0
23	Male	Septicemia and meningitis	7	B	2	13, 17	Full	32	7-2	16-26	21	47	100
35	Male	Septicemia and meningitis	9	B	3	4, 6, 10	Partial	213	22	14	29	18	0
59	Female	Septicemia and meningitis	9	B	2	28, 30	Full	ST1768 UA	21	4[g]			
7	Male	Bacteremia	7	W	1	2	Partial	11	5	2	22	29	0
32	Female	Septicemia	4	Y	3	5, 8, 18	Full	23	5-2	10-1	25	7	0
119	Male	Septicemia and meningitis	8	Z	1	118	Partial	865	7-1	1	19	130	0

Abbreviations: ST, sequence type, UA, unassigned to any clonal complex.

[a] Clinical diagnoses shown were options provided on the case report forms to reporting clinicians without strict definitions.

[b] All these cases survived with no sequelae.

[c] Partial vaccination indicates at least 1 dose but fewer than needed for full vaccination (≥2 doses if aged 2-16 months and ≥2 infant doses and a second-year booster or ≥2 doses after the first birthday if aged >16 months).

[d] Clonal complex is used to designate lineages and define genetic epidemiology of *N meningitidis* and is used in predictions of vaccine coverage and effect.

[e] Porin A, which has 2 variable regions, is the predominant antigen in the outer membrane vesicle component of the vaccine.

[f] Factor H binding protein, neisserial heparin binding antigen, and neisserial adhesin A are the 3 recombinant antigens in the vaccine. The numbers in the respective columns below these protein names are types allocated to distinct genetic variants. They indicate that these isolates, with only 1 exception,[g] were not matched to the vaccine.

[g] Antigen variant predicted to be recognized by immune responses to 4CMenB.

(95% CI, 3%-16%) and 16 (18%) had sequelae (95% CI, 11%-28%); therefore, 23 children (26%) died or had sequelae (95% CI, 18%-37%), a difference of 26% (95% CI, 2%-37%).

Among the 11 cases who developed invasive meningococcal disease after 74 days of age and had received at least 1 dose of 4CMenB at least 14 days prior to developing the disease, 5 were fully immunized cases with MenB disease. In addition, a fully immunized 2-year-old child developed *N meningitidis* serogroup Y (MenY) disease. The remaining 5 cases were partially immunized (Table 4). Of the 5 fully immunized cases with MenB (Table 4), 1 had no isolate nor bacterial DNA available for genomic analysis. Among the other 4 cases, 1 had a true vaccine failure because the infecting strain had a vaccine-matched Porin A antigen. In the other 3 cases, the 1 case with MenY, and the 5 partially immunized cases, genome sequencing of the isolates failed to identify any antigen that matched those in 4CMenB.

Results of the sensitivity analysis that included mean purchasing power by postcode/municipality of residence showed similar results to the primary analysis (Table 3). The median (IQR) family purchasing power of vaccinated children (94 [82-108]) and unvaccinated children (96 [81-115]) and between controls (96 [84-113]) and cases (95 [78-110]) were not significantly different (eFigure in the Supplement).

The calculation using the screening method and national coverage rates produced an OR of 0.21 (95% CI, 0.07-0.50).[7] In the third sensitivity analysis, in which immediate protection against invasive meningococcal disease was assumed following vaccination without allowing for a 14-day delay in developing a protective vaccine response, the OR of the association between full immunization with 4CMenB and disease was 0.18 (95% CI, 0.07-0.48).

Discussion

This study demonstrated that vaccination with 4CMenB was significantly less likely among children and adolescents who developed invasive meningococcal disease compared with matched controls. Purchase of this vaccine in pharmacies by parents or guardians following the advice of private pediatricians, a phenomenon frequently seen in Portugal for licensed pediatric vaccines not yet adopted in the national schedule, combined with the available medical and vaccination records, permitted this study to be performed. The OR for the primary outcome of 0.21 corresponds to an estimate of vaccine effectiveness (1 − OR) of 0.79. This estimate is similar to the 82.9% initially reported for UK infants using the screening method,[6] although more recent UK estimates have been lower.[8] The current study included a wider age group and a longer follow-up period after vaccination than previous reports. MenB strain coverage by 4CMenB may also differ between Portugal and the UK at the times studied.

During the study period, most invasive meningococcal disease cases reported in children and adolescents across Portugal (84%) and 84% of eligible cases in this cohort were caused by MenB. When cases caused by other capsular groups were included, the observed associations were similar. Larger studies are needed to evaluate whether 4CMenB reliably protects against non-group B meningococci, but 4CMenB protein antigens can also be found in such organisms and 4CMenB-induced antibodies have bactericidal activity against some *N meningitidis* serogroup C strains, *N meningitidis* serogroup W strains, and MenY strains.[2,15] Eleven of 16 cases with non-MenB disease in this study had MenY disease, and available molecular genetic data on recent invasive Portuguese MenY strains obtained between 2016 and 2019 do not suggest that the vaccine is likely to protect against them (written communication, Maria João Simões, PhD, Instituto Nacional de Saúde Doutor Ricardo Jorge, August 9, 2020). Invasive meningococcal disease in fully and partially immunized children caused by strains expected to be neutralized by vaccine-induced antibodies was rare in this study (occurred in only 1 child).[16]

Among children with invasive meningococcal disease, none of the 11 children who received any 4CMenB vaccine died or were left with reported sequelae, compared with 26% of unimmunized children. The numbers of cases with MenY disease and partially immunized cases in this study are too small to draw firm conclusions. The most recent UK estimate of single-dose effectiveness was only 24.1% (95% CI, −37.6% to 58.2%),[8] and invasive meningococcal disease in immunized children is more likely to be caused by non-vaccine-preventable meningococcal strains.

Limitations

The study had several limitations. First, matching by age, sex, time of presentation, and location of residency reduced the risk of biases that may have confounded the results. Nevertheless, a potential weakness of this study is that bias associated with wealth and social class could influence the results. 4CMenB is only available privately at a cost, so vaccinated children may come from wealthier families compared with unvaccinated children. Studies from other countries have reported lower invasive meningococcal disease incidence in high socioeconomic classes compared with low socioeconomic classes.[17,18] Also, children attending emergency departments, often for minor ailments (controls), might be from relatively poorer families less able to afford 4CMenB vaccination or to access private care and information about the vaccine. Data on mean purchasing power by municipality of residence were included[13] as an additional covariate in a sensitivity analysis, and no change in the association was found. Second, selecting controls from those receiving medical care could potentially lead to higher rates of vaccination among controls than the general population. However, immunization rates with 2 doses of 4CMenB by the time of first birthday were similar in the included controls and the general population (50% vs 47%).

Conclusions

During the first 5 years of vaccine availability in Portugal, vaccination with 4CMenB was less likely among children who developed invasive meningococcal disease compared with matched controls without invasive meningococcal disease. The findings may help inform the use of the 4CMenB vaccine in clinical practice.

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