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

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ABSTRACT

Background

In September 2015, the protein-based meningococcal group B vaccine (4CMenB, Bexsero) became available for private purchase in Spain. This study aimed to assess the effectiveness of the 4CMenB vaccine in preventing invasive meningococcal disease in children.

Methods

A nationwide matched case-control study included the laboratory-confirmed cases of invasive meningococcal disease in children aged less than 60 months from 2015 to 2019 in Spain. Each case was individually matched by date of birth and province to 4 controls. 4CMenB vaccination status of the cases and controls was compared using multivariate conditional logistic regression.

Results

We compared 306 cases (79.4% of serogroup B) with 1224 controls. Thirty-five cases (11.4%) and 298 controls (24.3%) had received any dose of the 4CMenB vaccine. The effectiveness of complete vaccination with 4CMenB was 76% (95% confidence interval [CI], 57% to 87%) against invasive meningococcal diseases caused by all serogroups and partial vaccination was 54% (95% CI, 18% to 74%) effective. Complete vaccination yielded an effectiveness of 71% (95% CI, 45% to 85%) against meningococcal group B disease. Any 4CMenB dose was 64% (95%CI, 41% to 78%) effective against group B disease and 82% (95%CI, 21% to 96%) effective against non-group B disease. None of the 44 group B strains covered by the 4CMenB vaccine according to the result of the genetic Meningococcal Antigen Typing System was detected in vaccinated children.

Conclusions

Complete 4CMenB vaccination was notably effective in preventing invasive disease by group B and non-group B meningococci in children younger than 5 years.

INTRODUCTION

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 multicomponent protein-based meningococcal B vaccine (4CMenB, Bexsero, GSK) was licensed in the European Union in 2013.[3] This vaccine is composed of 3 recombinant antigens: factor H-binding protein, Neisseria heparin-binding antigen, and Neisseria adhesin A, as well as outer-membrane vesicles containing Porin A P1.4 from the strain NZ98/254.[4] As the efficacy of the 4CMenB vaccine was not demonstrated in randomized clinical trials, its authorization was based on immunogenicity studies.[5] An observational study found a lower percentage of vaccination in patients with group B meningococcal disease than in the general population and a reduction in the incidence of group B disease in vaccine-eligible infants.[6] Further immunogenicity studies confirmed these preliminary results.[7,8]

Although some countries have introduced the 4CMenB vaccine into the publicly-funded infant immunization programs,[9] the low incidence of the disease has limited the conduct of post-commercialization studies of effectiveness. The few published evaluations have yielded estimates from 59.1% with a two-dose priming schedule plus a one-year booster in the United Kingdom, to 93.6% with a four-dose schedule in Tuscany, Italy.[10-12]

As 4CMenB vaccine antigens are not unique to group B meningococcus, the 4CMenB 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 since 2000 for all children and 4CMenB vaccine since 2015 for subjects 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.[18] In addition, the 4CMenB vaccine was available for

private purchase and vaccination of all children aged 2 months or older was recommended by the Spanish Pediatrics Association,[15,16] thus resulting in a progressive increase in vaccination coverage. Temporary shortage of the 4CMenB vaccine might have delayed the vaccination schedule in some children.

In this study, we aimed to assess the effectiveness of the 4CMenB vaccine in preventing invasive meningococcal disease among children aged less than 60 months.

METHODS

Study design, setting and data sources

An individually matched case-control study was carried out in Spain. Invasive meningococcal disease reporting by clinicians and laboratories is mandatory, and all relevant data are actively completed by the regional epidemiological surveillance units.[17] Invasive meningococcal disease was defined as a positive culture or polymerase chain reaction (PCR) test result for *N. meningitidis* in a normally sterile body site. Confirmed cases were tested by agglutination or PCR to determine the serogroup.

Cases were all children aged less than 60 months, born and residing in Spain, and with a laboratory-confirmed diagnosis of invasive meningococcal disease between October 2015 and September 2019. Using electronic databases, each case was individually matched to controls of the same province of birth and residence, and born on the same day or days immediately before and after. Each region provided data from all matched sets that included each case and the four eligible controls that had the two immediately preceding and the two immediately following identification numbers in the regional healthcare service.

High-risk conditions were obtained from electronic health records for cases and controls. From the epidemiological surveillance system, we obtained the first case date (symptom onset, testing or hospitalization), clinical presentation (meningitis, sepsis, both, or other),

intensive care unit admission, and clinical outcome that included recovery, sequelae (neurological damage, amputation, or hearing loss), and death.

The authors had sole responsibility for the study design, data analysis, writing of the manuscript, and decision to submit the manuscript for publication.

Vaccination status

Data on meningococcal immunization (4CMenB, serogroup C conjugate, and ACWY vaccines) were sourced from the electronic regional vaccination registries. 4CMenB vaccination status was classified following the manufacturer recommendations (Table S1),[3] according to which the infant vaccination schedule starts at 2 months of age and a second dose should be given 60 or more days later to achieve complete primary immunization. In children who were vaccinated before 6 months of age, a booster dose at 12-15 months of age was needed to be considered fully immunized. In those who started the vaccination during the sixth month of age or after, the booster dose was required during the second year of age. Children who started the vaccination at the age of 24 months or older were deemed fully immunized after receiving the second dose.[2,16] To allow time for the immune response, vaccine doses administered within the 14 days preceding the first case date were discounted. The vaccination status of each case was assessed on the first case date, and that of their controls was determined at the same calendar day.

Genetic characterization

Group B meningococcal isolates were analyzed by genetic Meningococcal Antigen Typing System (gMATS).[19-21] A strain was considered to be vaccine preventable if gMATS tested positive for any of the 4 components included in the 4CMenB vaccine, not vaccine preventable if gMATS tested negative for all 4 vaccine antigens, and unpredictable when gMATS results could not be related to currently available MATS data. Cases completely

typed by gMATS were classified as caused by strains covered by the 4CMenB vaccine, strains not covered by this vaccine, and unpredictable strains.

Statistical analysis

4CMenB vaccination status was compared between each case and their matched controls using conditional logistic regression to obtain matched odds ratios (OR), with their 95% confidence intervals (CI), crude and adjusted by sex and high-risk conditions. The analysis of non-group B cases was also adjusted for meningococcal C vaccination. Vaccine effectiveness was estimated as a percentage: (1−adjusted matched OR)×100.

Four categories were considered according to the 4CMenB vaccination status: unvaccinated (reference), first dose within the previous 14 days, partial vaccination, and complete vaccination. Estimates were also obtained for any dose of vaccine, including partial and complete vaccination. Further analyses addressed separately invasive disease caused by meningococcus serogroup (B and non-group B), age group, and period. A sensitivity analysis was performed after excluding children aged less than 134 days, those unvaccinated against group C meningococcus, and those with high risk factor. These restrictions ensured a minimum age to be fully vaccinated, excluded certain children with an increased risk of disease, and improved the comparability in the use of health care services.

We also assessed the 4CMenB vaccine effect in preventing severe disease, including cases causing death, intensive care unit admission, or sequelae. Vaccination status was compared between the group B cases and their matched controls by gMATS categories.

Post hoc analyses separated fully vaccinated children into varying categories to explore the vaccine effectiveness by number of 4CMenB doses, age at first dosing, and time elapsed since the last dose.

RESULTS

Characteristics of cases and controls

Of the 334 cases of invasive meningococcal disease reported, 23 and 5 were excluded because they had developed the disease before 75 days or after 1825 days of age, respectively. Finally, 306 cases were included in the study (Fig. 1): 243 (79.4%) of group B, 5 of group C, 20 of group W, 7 of group Y, 3 non-groupable cases, and 28 cases could not be grouped.

Meningitis was the clinical presentation in 33.3% cases, sepsis in 38.6%, both in 24.8%, and others in 3.3%. Two hundred and four cases (67.7%) were admitted to the intensive care unit, 16 (5.2%) died, and 27 (8.8%) survived with sequelae (Table S2).

Among the 306 cases, 35 (11.4%) had received any dose of 4CMenB vaccine, 16 (5.2%) were fully vaccinated, 18 (5.9%) were partially vaccinated, and one (0.3%) had received the first dose within the previous 14 days. These vaccination statuses were recorded in 24.3%, 14.2%, 8.7% and 1.5% of the 1224 matched controls, respectively (Table 1).

Among the 243 cases with a group B disease, 138 isolates (56.8%) were completely typed using the gMATS. Of these isolates, 44 (31.9%) had strains covered by the 4CMenB vaccine, 62 (44.9%) had strains not covered, and 32 (23.2%) yielded unpredictable results.

The percentage of controls who had received any dose of the 4CMenB vaccine increased from 4.5% in the 2015-2016 season to 44.1% in the 2018-2019 season (Fig. S1).

4CMenB vaccine in preventing meningococcal disease

We compared the 4CMenB vaccination status of the 306 cases and 1224 controls. The effectiveness was 76% (95%CI, 57 to 87) for complete vaccination and 54% (95%CI, 18 to 74) for partial vaccination. Estimates from the analysis excluding children aged less than 134 days, those unvaccinated against group C meningococcus, and those with high-risk conditions were similar, 78% (95%CI, 59 to 88) for complete 4CMenB vaccination and 54% (95%CI, 17

to 74) for partial vaccination. Complete vaccination prevented 71% (95%CI, 43 to 86) of severe cases of meningococcal disease (Table 2).

Complete vaccination effectiveness remained high in both study periods, 2015-2017 and 2017-2019, but it seems to be higher among children under the age of 24 months (88%; 95% CI, 68 to 95) than among those aged 24-59 months (53%; 95%CI, 1 to 78)(Table 3). Post hoc analyses showed no relevant differences in effectiveness in fully vaccinated children by number of vaccine doses (2 versus >2) or by time since last dosing (<12 months versus ≥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 at the age of 24-59 months was 35% (95%CI, –65 to 74)(Table S3).

4CMenB vaccine in preventing group B disease

The effectiveness of the 4CMenB vaccine against meningococcal group B disease was evaluated in a comparison between 243 cases and 972 individually matched controls. The effectiveness was 64% (95%CI 41% to 78%) for any dose, 71% (95%CI, 45 to 85) for complete vaccination and 50% (95%CI, 3 to 75) for partial vaccination (Table 4).

None of the 44 cases with a gMATS covered by the 4CMenB vaccine were detected in vaccinated children versus 26 (15%) of their 176 matched controls. Any dose of the 4CMenB vaccine also was protective against cases with a gMATS result not covered by the vaccine (64%; 95%CI, 10 to 85) (Table S4).

4CMenB vaccine in preventing non-group B disease

The effectiveness estimate of any dose of the 4CMenB vaccine in preventing non-group B cases was 82% (95%CI, 21 to 96) overall and was similar in the sensitivity analysis (Table 4).

DISCUSSION

We found that complete vaccination with the 4CMenB was notably effective in preventing invasive diseases by all meningococci (76%), by group B, and by non-group B meningococci. Furthermore, any doses of the 4CMenB vaccine demonstrated a moderately preventive effect (54%) when the vaccination scheme had not been completed because of the child excessive young age or owing to vaccine shortage issues. The effectiveness estimates were similar against the most severe cases, which is particularly relevant considering that its prevention is the primary objective of vaccination programs.

The vaccine effectiveness estimate against group B cases was consistent with the proportion of cases caused by strains covered by the 4CMenB vaccine in Spain (68.7%).[21] None of the cases caused by strains expected to be neutralized by 4CMenB-induced antibodies were detected in vaccinated children, which suggests a very high vaccine effectiveness against strains covered by the 4CMenB vaccine according to the gMATS results.[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 the 4CMenB vaccine, it is not surprising to find some vaccine protection against gMATS-negative cases, especially among fully vaccinated children.[23]

According to our results, 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 more. In this vaccination scheme used in catch-up strategies, 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 children age and the vaccination schedule prevented us from reaching a conclusion about the separate role of each variable. Changes in the proportion of meningococcal disease cases 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 in fully vaccinated children.

Sensitivity analyses supported the study findings and ruled out biases 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 group B meningococcal disease are in the range of the results from other countries. Parikh *et al.* evaluated a reduced infant 4CMenB vaccination schedule in England using the screening method, observing an effectiveness of 82.9% for two doses.[6] Ladhani *et al.* updated this analysis and found that the effectiveness declined to 52.7% with a two-doses 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 reported a effectiveness of 79% in children and adolescents.[11] In two Italian regions the screening method showed an effectiveness of 93.6% and 91.0%, for schedules with four and three doses, respectively.[12] Differences in the proportion of strains covered by the 4CMenB vaccine,[20] and in the vaccination schedule may explain these differences in estimates. Additionally, the 4CMenB vaccine has been used to control outbreaks of group B disease, with no cases being detected among vaccinees.[25-29]

The effectiveness of the 4CMenB vaccine against invasive diseases caused by meningococcal groups other than group B has been suggested,[13,14] and can be explained because the vaccine components are not unique to group B. The results of our study show a similar effectiveness against cases caused by other groups compared with group B cases. Most cases caused by serogroup W in Spain during the study period belonged to the same strain that had been detected in England, which was covered by the 4CMenB vaccine.[13] Nevertheless, the 4CMenB vaccine has not demonstrated effect on the carriage of disease-causing meningocicci.[30]

The proportion of cases admitted to intensive care unit was high because short-term admission was frequent to anticipate a possible worsening.

This study has some limitations. The study size was small for analyses other than the vaccine effectiveness in preventing all cases and group B cases; therefore, other results should be viewed with caution. Because the 4CMenB vaccine was available for private purchase, a higher socioeconomic status might have been associated with higher vaccine coverage, in addition to having been related to a lower incidence of meningococcal diseases.[31,32] This potential confounding factor was only partially controlled by the matching by 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: the 4CMenB vaccine was publicly funded for high-risk children, the vaccine shortage affected all children regardless of their household income level, the vaccination was based on the recommendation of each individual paediatrician, the vaccine effectiveness remained during the study period despite the fact that the vaccine coverage increased markedly, and the high effectiveness found that could hardly be fully explained by this bias. The results of the gMATS were not available for all group B cases, a number of cases yielded unpredictable results, and gMATS differences between tested and untested patients cannot be excluded. This study was mainly retrospective; however, it was based on high-quality sources of information.

The strengths of this study are the individual matched case-control design with perfect comparability by the matching variables, the relatively large number of cases, the use of immunization registries, and the nationwide representativeness. As the 4CMenB vaccine 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.

In conclusion, complete vaccination with the 4CMenB vaccine demonstrated a notable effectiveness in preventing invasive disease due to group B and non-group B meningococci in

Spanish children younger than 5 years. 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 a concerning problem and its prevention is a priority.

This study was conducted by the regional epidemiological surveillance units without specific funding. The study protocol proposed an anonymized data collection from the patient electronic medical records and was approved by the institutional review board of Navarra, which waived the need for obtaining the informed consent.

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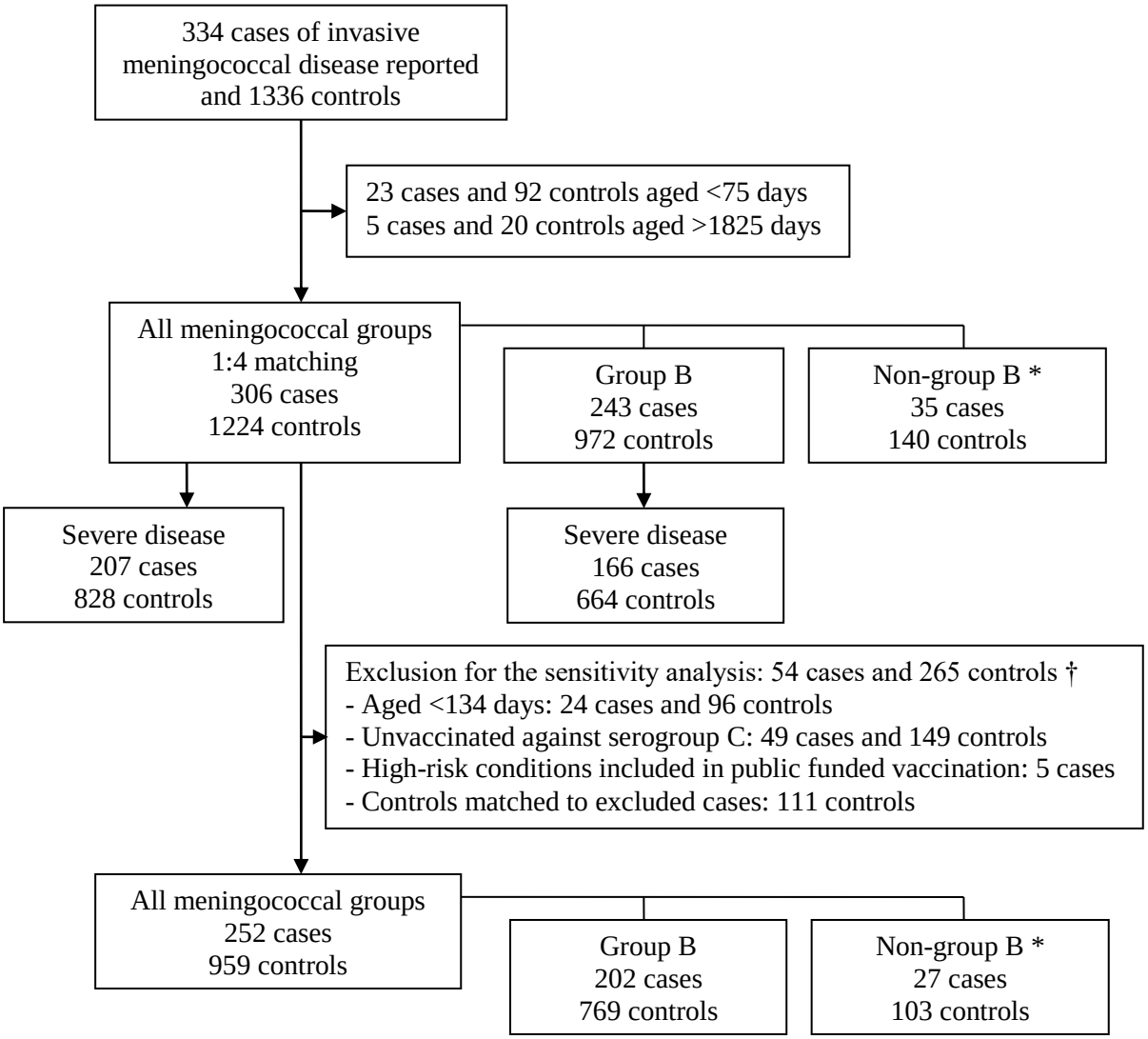
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Figure 1. Flow of eligible cases and individually matched controls.



*Comparison with possibly insufficient power.

†Some individuals had more than one cause of exclusion.

Table 1. Characteristics of the cases and controls included in the analysis of invasive meningococcal disease according to the meningococcal group.

	Group B		Non-group B*		All meningococci †	
	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)	Cases n (%)	Controls n (%)
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, months						
<6	41 (16.9)	164 (16.9)	6 (17.1)	24 (17.1)	55 (18.0)	220 (18.0)
6 to <12	54 (22.2)	216 (22.2)	8 (22.9)	32 (22.9)	65 (21.2)	260 (21.2)
12 to <24	44 (18.1)	176 (18.1)	11 (31.4)	44 (31.4)	63 (20.6)	252 (20.6)
24 to <36	51 (21.0)	204 (21.0)	3 (8.6)	12 (8.6)	57 (18.6)	228 (18.6)
36 to <60	53 (21.8)	212 (21.8)	7 (20.0)	28 (20.0)	66 (21.6)	264 (21.6)
Epidemiological 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 conditions ¶	3 (1.2)	0	2 (5.7)	0	5 (1.6)	0
Group 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)
<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 (0)	9 (6.4)	7 (2.3)	69 (5.7)
Total	243 (100)	972 (100)	35 (100)	140 (100)	306 (100)	1224 (100)

* Include 5 cases of group C, 20 of group W, 7 of group Y, and 3 non-groupable cases, together with their respective controls.

† Including 28 not grouped cases together with their respective controls.

‡ Children who had received the first dose of the 4CMenB vaccine in the previous 14 days.

¶ The 5 children with high-risk conditions presented complement deficiency or eculizumab treatment.

Table 2. Effectiveness of the 4CMenB vaccine in preventing invasive meningococcal disease cases caused by all serogroups.

4CMenB vaccination status	Nº vaccinated / nº unvaccinated		Matched odds ratio (95% CI)*		Vaccine effectiveness (95% CI)
	Cases	Controls	Crude	Adjusted †	
Main analysis					
≥1 vaccine dose	34/271	280/926	0.32 (0.21-0.50)	0.32 (0.21-0.50)	68% (50 to 79)
Partially vaccinated	18/271	106/926	0.47 (0.27-0.82)	0.46 (0.26-0.82)	54% (18 to 74)
Fully vaccinated	16/271	174/926	0.24 (0.13-0.43)	0.24 (0.13-0.43)	76% (57 to 87)
Sensitivity analysis ‡					
≥1 vaccine dose	31/221	244/705	0.31 (0.19-0.49)	0.31 (0.19-0.49)	69% (51 to 81)
Partially vaccinated	16/221	87/705	0.46 (0.25-0.83)	0.46 (0.26-0.83)	54% (17 to 74)
Fully vaccinated	15/221	157/705	0.22 (0.12-0.41)	0.22 (0.12-0.41)	78% (59 to 88)
Severe cases ¶					
≥1 vaccine dose	27/180	186/635	0.43 (0.26-0.70)	0.41 (0.25-0.68)	59% (32 to 75)
Partially vaccinated	16/180	77/635	0.63 (0.34-1.17)	0.61 (0.32-1.14)	39% (–14 to 68)
Fully vaccinated	11/180	109/635	0.29 (0.15-0.58)	0.29 (0.14-0.57)	71% (43 to 86)

CI, confidence interval.

* Matched odds ratio obtained through 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 output from fitting the models is included in the Supplementary Appendix.

† Matched odds ratio adjusted for sex and high-risk conditions.

‡ Sensitivity analysis limited to children aged 134-1825 days and excluding those unvaccinated against group C meningococcus or with high-risk conditions.

¶ Severe cases included those causing death, intensive care unit admission, or sequelae.

Table 3. Effectiveness of the 4CMenB vaccine in preventing invasive meningococcal disease cases caused by all serogroups by age at the date of case diagnosis and period.

4CMenB vaccination status	Nº vaccinated / nº unvaccinated		Matched odds ratio (95% CI)*		Vaccine effectiveness (95% CI)
	Cases	Controls	Crude	Adjusted †	
Children <24 months					
≥1 vaccine dose	19/163	183/534	0.23 (0.13-0.42)	0.22 (0.12-0.42)	78% (58 to 88)
Partially vaccinated	13/163	81/534	0.37 (0.18-0.73)	0.35 (0.17-0.72)	54% (18 to 74)
Fully vaccinated	6/163	102/534	0.12 (0.05-0.31)	0.12 (0.05-0.32)	88% (68 to 95)
Children ≥24 months					
≥1 vaccine dose	15/108	186/635	0.51 (0.27-0.96)	0.54 (0.29-1.00)	59% (32 to 75)
Partially vaccinated	5/108	77/635	0.69 (0.26-1.86)	0.72 (0.27-1.92)	28% (–92 to 73)
Fully vaccinated	10/108	109/635	0.45 (0.21-0.95)	0.47 (0.22-0.99)	53% (1 to 78)
Period 2015-2017 ‡					
≥1 vaccine dose	7/152	64/566	0.35 (0.15-0.83)	0.36 (0.15-0.83)	64% (17 to 85)
Partially vaccinated	7/152	25/566	0.81 (0.32-2.02)	0.81 (0.32-2.04)	19% (–104 to 68)
Fully vaccinated	7/152	39/566	0.08 (0.01-0.57)	0.08 (0.01-0.57)	92% (43 to 99)
Period 2017-2019 ‡					
≥1 vaccine dose	27/119	216/360	0.32 (0.19-0.52)	0.31 (0.19-0.52)	71% (48 to 81)
Partially vaccinated	12/119	81/360	0.37 (0.19-0.75)	0.36 (0.18-0.74)	64% (26 to 82)
Fully vaccinated	15/119	135/360	0.28 (0.15-0.53)	0.28 (0.15-0.53)	72% (47 to 85)

CI, confidence interval.

* Matched odds ratio obtained through 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 output from fitting the models is included in the Supplementary Appendix.

† Matched odds ratio adjusted for sex and by high-risk conditions when it was possible.

‡ Using epidemiological seasons, two biannual periods were considered, from 5 October 2015 to 8 October 2017 (Period 2015-2017) and from 9 October 2017 to 6 October 2019 (Period 2017-2019).

Table 4. Effectiveness of the 4CMenB vaccine in preventing invasive meningococcal disease cases caused by serogroup B and by non-group B *Neisseria meningitidis.*

4CMenB vaccination status	Nº vaccinated / nº unvaccinated		Matched odds ratio (95% CI)*		Vaccine effectiveness (95% CI)
	Cases	Controls	Crude	Adjusted †	
Serogroup B cases					
Main analysis					
≥1 vaccine dose	24/218	194/763	0.36 (0.22-0.59)	0.36 (0.22-0.59)	64% (41 to 78)
Partially vaccinated	12/218	72/763	0.49 (0.25-0.96)	0.50 (0.25-0.97)	50% (3 to 75)
Fully vaccinated	12/218	122/763	0.28 (0.15-0.54)	0.29 (0.15-0.55)	71% (45 to 85)
Sensitivity analysis ‡					
≥1 vaccine dose	23/179	170/591	0.37 (0.22-0.61)	0.36 (0.22-0.61)	64% (39 to 78)
Partially vaccinated	12/179	62/591	0.53 (0.27-1.05)	0.53 (0.27-1.05)	47% (–5 to 73)
Fully vaccinated	11/179	108/591	0.27 (0.14-0.53)	0.27 (0.14-0.53)	73% (47 to 86)
Severe cases ¶					
≥1 vaccine dose	19/147	131/528	0.45 (0.26-0.79)	0.45 (0.25-0.79)	55% (21 to 75)
Partially vaccinated	11/147	51/528	0.69 (0.33-1.42)	0.69 (0.33-1.42)	31% (–42 to 67)
Fully vaccinated	8/147	80/528	0.30 (0.14-0.67)	0.30 (0.13-0.66)	70% (34 to 87)
Non-group B cases					
Main analysis					
≥1 vaccine dose	5/30	47/93	0.23 (0.07-0.81)	0.18 (0.04-0.79)	82 (21 to 96)
Partially vaccinated	4/30	19/93	0.50 (0.13-1.96)	0.42 (0.08-2.30)	58% (–130 to 92)
Fully vaccinated	1/30	28/93	0.08 (0.01-0.68)	0.08 (0.01-0.72)	92% (28 to 99)
Sensitivity analysis ‡					
≥1 vaccine dose	3/24	37/66	0.17 (0.04-0.77)	0.17 (0.04-0.74)	83% (26 to 96)
Partially vaccinated	2/24	11/66	0.38 (0.07-1.98)	0.36 (0.07-1.99)	64% (–99 to 93)
Fully vaccinated	1/24	26/66	0.07 (0.01-0.71)	0.08 (0.01-0.70)	92% (30 to 99)

CI, confidence interval.

* Matched odds ratio obtained through 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 output from fitting the models is included in the Supplementary Appendix.

† Matched odds ratio adjusted for sex and high-risk conditions. The analysis of non-group B cases was also adjusted for meningococcal C vaccination.

‡ Sensitivity analysis limited to children aged 134-1825 days and excluding those unvaccinated against group C meningococcus or with high-risk conditions.

¶ Severe cases included those causing death, intensive care unit admission, or sequelae.