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Vaccination of Infants with Meningococcal Group B Vaccine (4CMenB) in England

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ABSTRACT

BACKGROUND

In September 2015, the United Kingdom introduced the multicomponent meningococcal group B vaccine (4CMenB, Bexsero) into its publicly funded national immunization program at a reduced two-dose priming schedule for infants, with a 12-month booster.

METHODS

Using data from enhanced national surveillance of invasive meningococcal disease in England, we evaluated the effect of vaccination on the incidence of meningococcal group B disease during the first 3 years of the program. The effect of vaccination was assessed by comparing the observed incidence of disease with the expected incidence based on the incidence during the 4-year prevaccination period in equivalent cohorts and with the use of disease trends in cohorts of children younger than 5 years of age who were not eligible to receive the vaccine. Vaccine effectiveness was estimated with the use of the indirect screening method.

RESULTS

4CMenB uptake in England remained consistently high; data from the first 3 months of 2018 showed that 92.5% of children had completed the primary immunizations by their first birthday and 87.9% had received all three doses by 2 years. From September 2015 through August 2018, the incidence of meningococcal group B disease in England (average annual birth cohort, approximately 650,000 infants) was significantly lower in vaccine-eligible cohorts than the expected incidence (63 observed cases as compared with 253 expected cases; incidence rate ratio, 0.25; 95% confidence interval [CI], 0.19 to 0.36), with a 75% reduction in age groups that were fully eligible for vaccination. The adjusted vaccine effectiveness against meningococcal group B disease was 52.7% (95% CI, −33.5 to 83.2) with a two-dose priming schedule for infants and 59.1% (95% CI, −31.1 to 87.2) with a two-dose priming schedule plus a booster at 1 year). Over the 3-year period, there were 169 cases of meningococcal group B disease in the vaccine-eligible cohorts, and an estimated 277 cases (95% CI, 236 to 323) were prevented.

CONCLUSIONS

The 4CMenB program was associated with continued positive effect against meningococcal group B disease in children in England, and protection after three doses of the vaccine was sustained for at least 2 years. (Funded by Public Health England.)

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Neisseria meningitidis, a major cause of meningitis and septicemia throughout the world, is associated with considerable morbidity and mortality. Twelve different meningococcal capsular groups are recognized, of which six (A, B, C, W, X, and Y) are responsible for most cases of invasive meningococcal disease. In Europe, meningococcal group B is responsible for most cases of childhood meningococcal disease, although the incidence of this disease has declined over the past decade.[1] Polysaccharide–protein conjugate vaccines have been effective in preventing meningococcal disease caused by capsular groups A, C, W, and Y because of the direct protection and indirect (herd) protection through prevention of carriage acquisition among vaccinated adolescents.[2] The development of such a vaccine against meningococcal group B has been challenging because of the structural similarity of the meningococcal group B polysaccharide capsule with polysialic acid structures on human neuronal cells, which results in poor immunogenicity.[3]

In January 2013, a protein-based, multicomponent vaccine against meningococcal group B (4CMenB, Bexsero, GlaxoSmithKline Biologicals) was licensed in Europe at a three-dose priming schedule for infants, followed by a booster in the second year of life. The vaccine includes three recombinant proteins (factor H–binding protein [FHbp] peptide 1 [variant 1], neisserial heparin-binding antigen [NHBA] peptide 2, and neisseria adhesin A [NadA] peptide 8 [variant NadA-2/3]), along with PorA P1.4–containing outer-membrane vesicles from the New Zealand outbreak strain. This vaccine was licensed on the basis of safety and immunogenicity studies only, without real-world evidence of protection against invasive disease.

The Meningococcal Antigen Typing System (MATS) was developed to predict strain coverage by 4CMenB. It comprises genotypic characterization of PorA in conjunction with a qualitative and quantitative enzyme-linked immunosorbent assay to quantify FHbp, NHBA, and NadA expression in combination with their recognition by 4CMenB-induced antibodies on individual meningococcal isolates. This assay can be performed only on culture isolates and not on specimens obtained from patients with disease confirmed by nonculture methods such as the polymerase-chain-reaction (PCR) test only.[4] The MATS estimated 73% strain coverage in England and Wales before the introduction of 4CMenB.[5]

In September 2015, the United Kingdom became the first country to offer 4CMenB to all infants free of charge. The vaccine is offered at 8 and 16 weeks of age, with a booster at 12 months. At the start of the program, an opportunistic catch-up vaccination was also offered to children at 12 and 16 weeks of age at their routine immunization visits. Within 10 months after the program began, cases of meningococcal group B disease in infants who were eligible to receive the vaccine had nearly halved, and the effectiveness of two doses of vaccine was 82.9% (95% confidence interval [CI], 24.1 to 95.2) against all cases of laboratory-confirmed invasive meningococcal group B disease in infants.[6] In 2016, the first infants who received the primary immunizations became eligible for the 12-month booster. Here, we report the effect and effectiveness of 4CMenB with regard to invasive meningococcal group B disease in infants and children at 1 year of age and 2 years of age after the first 3 years of the national immunization program in England.

Methods

Disease Surveillance and Vaccine Uptake

Public Health England conducts enhanced national surveillance for invasive meningococcal disease in England.[6] Briefly, hospital laboratories routinely submit isolates obtained from patients with invasive meningococcal disease to the Meningococcal Reference Unit of Public Health England for confirmation and serogrouping. Since 2014, all isolates of invasive meningococcal group B have undergone testing with the MATS.[6] The Meningococcal Reference Unit also provides a free meningococcal PCR testing service for patients with suspected meningococcal disease across England, and the Immunisation and Countermeasures Division at Public Health England provides public health and vaccination advice for individual patients and supports the investigation and management of suspected clusters and outbreaks. As a result of the multiple data sources used for surveillance, case ascertainment has remained consistently high across all age groups.[7,8] Public Health England routinely collects data on the vaccination history, risk factors, clinical presentations, and outcomes of all

patients with invasive meningococcal disease. Full details of the meningococcal surveillance plan in England are available at www.gov.uk/government/publications/meningococcal-disease-enhanced-surveillance-plan.

Data on vaccine uptake in England are routinely collected through primary care and child health information systems. In addition to reporting the percentage of eligible children who received two doses by 12 months and three doses by 18 months, the timing of vaccination in days of age was calculated with the use of individual-level data from local child health information systems (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

STUDY DESIGN AND SUPPORT

The authors had sole responsibility for the study design; the data collection, analysis, and interpretation; and the writing of the manuscript. All the authors are employed by Public Health England, the study funder, which is a public body and an executive agency of the U.K. Department of Health. The first author had full access to all the data and final responsibility for the decision to submit the manuscript for publication.

STATISTICAL ANALYSIS

The population effect was estimated with the use of national surveillance data on cases of laboratory-confirmed meningococcal group B disease. We calculated the change in the incidence of the disease from 4 prevaccine surveillance years (September through the following August) to the first 3 complete years after 4CMenB was introduced. The age groups for the analysis were the following: 0 to 8 weeks (infants who were too young for vaccination), 9 to 17 weeks (part of this group was eligible for one 4CMenB dose in the 2015–2016 surveillance year, and the whole group was eligible for one 4CMenB dose in 2016–2017 and 2017–2018), 18 to 51 weeks (part of this group was eligible to receive two 4CMenB doses in 2015–2016, and the whole group was eligible in 2016–2017 and 2017–2018), 1 year (part of this group was eligible to receive three doses in 2016–2017, and the whole group was eligible to receive three doses in 2017–2018), 2 years (part of this group was eligible to receive three doses in 2017–2018), and 3 to 4 years (children who were too old to receive 4CMenB throughout the study period).

To estimate effect in each vaccine-eligible group, we initially estimated incidence rate ratios by comparing the numbers of cases of disease in each postvaccination surveillance year with those in the equivalent cohort during the 4 prevaccination years. To account for any changes over time that were unrelated to meningococcal group B vaccination, the incidence rate ratios were then adjusted for changes in the incidence of meningococcal group B disease in all children younger than 5 years of age who were not in the vaccine-eligible cohorts. This was possible because the meningococcal group B immunization program for infants does not provide any indirect protection to unvaccinated children. Full details regarding the Poisson models used for estimation of the incidence rate ratios and the predicted incidence in the absence of vaccination are provided in the Supplementary Appendix. Estimates of incidence rate ratios and 95% confidence intervals have not been adjusted for multiple comparisons, so inferences based on these intervals may not all be reproducible.

Vaccine effectiveness was estimated in children who were eligible to receive the vaccine through the routine program (i.e., those born on or after July 1, 2015) and who had laboratory-confirmed invasive meningococcal group B disease with an onset between September 1, 2015, and August 31, 2018. Children who were eligible for opportunistic vaccination (i.e., those who were born in May or June 2015) were excluded because their priming schedules were different and their vaccine uptake was not as well documented. Children were included if they were at least 77 days of age and younger than 13 months at the onset of disease (for estimates of the effectiveness of one dose), at least 133 days of age and younger than 13 months (for estimates of the effectiveness of two doses), and at least 365 days of age (for estimates of the effectiveness of three doses). Vaccine doses received by children with confirmed disease were counted if the onset occurred at least 14 days after the dose was received. The comparator group included all children who were eligible to receive 4CMenB in England.

If 4CMenB was protecting infants from meningococcal group B disease, then the percentage of vaccinated children with confirmed disease would be lower than the percentage of children who were vaccinated in the whole popu-

lation. The formula for vaccine effectiveness (VE) based on this screening method[9] is

$$VE = 1 - [PCV/(1 - PCV)]/[PPV/(1 - PPV)],$$

where PCV is the percentage of vaccinated children with meningococcal group B disease and PPV is the vaccine coverage in infants across England who were born in the same year and month and at an age in days exactly 14 days younger than the age of the child at disease onset (the comparator cohort for each individual child with the disease) (see the Supplementary Appendix). This 14-day period allows for an immune response to develop after vaccination. In order to use this age-matched and period-matched coverage for each child with disease, logistic regression was used with the vaccination status of the child as the binary outcome variable, only a constant fitted, and an offset for the log odds of the matched coverage. Vaccine effectiveness was calculated as 1 minus the odds ratio in the model. Vaccine effectiveness was assessed this way according to the number of doses: one primary dose with meningococcal group B disease diagnosed before 13 months of age; two primary doses with meningococcal group B disease diagnosed before 13 months of age; and the complete three-dose schedule with meningococcal group B disease diagnosed before 36 months of age. To estimate vaccine effectiveness according to the number of doses, the coverage for the equivalent number of doses in the population was used. Data were analyzed with the use of Stata software, version 14 (StataCorp).

Since 4CMenB does not protect against all meningococcal group B strains, the results of the MATS testing of isolates of invasive meningococcal group B obtained from vaccinated children were used to estimate the vaccine strain coverage of meningococci causing invasive disease in the different vaccinated cohorts. To estimate vaccine effectiveness against vaccine-preventable meningococcal group B strains only, the vaccine effectiveness against all meningococcal group B disease (vaccine effectiveness$_{all}$) was adjusted by applying the proportion (p) of culture-confirmed cases in vaccinated children that were MATS-positive to the total number of confirmed cases of meningococcal group B disease with MATS results in that cohort. The adjusted vaccine effectiveness (VE_{mats}) assumed no protection against MATS-negative strains. The following formula was used:

$$VE_{mats} = 1 - 1/\{1 + [1/p] \times [VE_{all}/(1 - VE_{all})]\}.$$

The derivation is provided in the Supplementary Appendix.

RESULTS

VACCINE UPTAKE

In England, 4CMenB uptake has remained consistently high since the vaccine was introduced into the national program in September 2015 (Fig. 1A). Data from the first 3 months of 2018 showed that 92.5% of children in England (average annual birth cohort, approximately 650,000 infants) had completed the primary immunizations by their first birthday and 87.9% had received all three doses by 2 years. In a representative sample of approximately 60,000 infants receiving the first dose, approximately 60,000 receiving the second dose, and approximately 30,000 receiving the booster in different geographic areas across England (see the Supplementary Appendix), the median age at 4CMenB vaccination was 61 days (interquartile range, 58 to 67) for the first dose, 128 days (interquartile range, 120 to 144) for the second dose, and 387 days (interquartile range, 377 to 407) for the booster (Fig. 1B).

EFFECT OF VACCINATION

The fitted model showed a 29% increase in the number of cases between 2013–2014 and 2017–2018, based on the observed number of cases of meningococcal group B disease in unvaccinated cohorts (P=0.11) (Fig. 2). The model for estimating effect showed no evidence of lack of fit (P=0.57), indicating that it was reasonable to assume that changes in cohorts of children who were not eligible to receive the vaccine because of age would have also occurred in the vaccine-eligible cohorts.

The estimates of adjusted incidence rate ratios show significant decreases in the incidence of meningococcal group B disease in all vaccine-eligible cohorts of children who received at least two doses of 4CMenB, including those in which only some of the group were eligible for vaccination (Table 1). In children who were 18 to 51 weeks of age, there were fewer cases of meningo-

coccal group B disease than expected for 3 consecutive years. In the second year of the program, fewer than expected cases were also observed in children who were 1 year of age and who became eligible for a three-dose schedule after July 2016. This cohort continued to benefit from vaccination in the third year of the program, with significantly fewer cases observed among children who were 2 years of age during 2017–2018 (Fig. 2).

When the age groups in which all children were eligible for vaccination were combined, the reduction in the incidence of meningococcal group B disease was 75% (63 observed cases as compared with 253 expected cases; incidence rate ratio, 0.25; 95% CI, 0.19 to 0.36), as compared with a reduction of 45% in the cohorts in which only some children were eligible (106 observed cases as compared with 193 expected cases; incidence rate ratio, 0.55; 95% CI, 0.43 to 0.70). The difference between the number of observed cases (169 cases) and expected cases (446 cases) of meningococcal group B disease in the vaccine-eligible cohorts was 277 (95% CI, 236 to 323) in the first 3 years of the program (i.e., 62% fewer cases than expected).

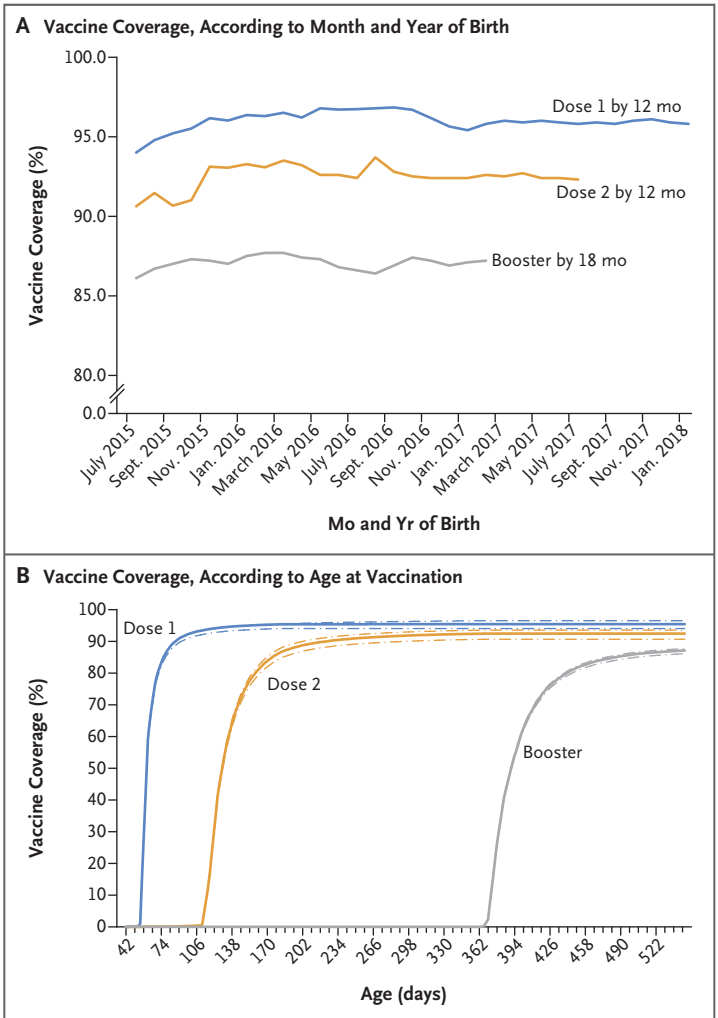

Figure 1. 4CMenB Vaccine Coverage, According to Recipients' Month and Year of Birth and Age at Vaccination.

Panel A shows vaccine coverage by 12 months for the first and second doses of the meningococcal group B vaccine (4CMenB), as well as uptake of the 12-month booster by 18 months of age. Panel B shows vaccination coverage according to age in days at the time of the first dose of the vaccine, the second dose, and the booster dose among infants born in the months with the lowest (July 2015, lower dashed line), median (January 2017, solid line), and highest (March 2016, upper dashed line) final vaccine coverage. The first dose was offered at 8 weeks of age, the second dose was offered at 16 weeks of age, and the booster dose was offered at 12 months.

VACCINE EFFECTIVENESS

Of the 187 children with meningococcal group B disease who were born after July 1, 2015, a total of 147 who were at least 77 days of age were eligible for the vaccine effectiveness analysis. The adjusted vaccine effectiveness for a single dose of 4CMenB was 24.1% (95% CI, −37.6 to 58.2) according to data on 74 children with disease (16 children who had not received the vaccine and 58 who had received one dose). Of the children with an onset of meningococcal group B disease between 133 days and 13 months of age, 4 were unvaccinated and 37 had received two doses of 4CMenB. Thus, the adjusted vaccine effectiveness was 52.7% (95% CI, −33.5 to 83.2). In this group, 26 children had disease that was confirmed by culture and, of these, 16 (62%) had MATS-positive disease. Assuming that only the MATS-positive strains were preventable by 4CMenB, the estimated vaccine effectiveness against vaccine-preventable meningococcal group B strains among children who received two doses was 64.4%.

Meningococcal group B disease developed in 29 infants who were eligible for the three-dose schedule, including 25 who had received the three recommended doses. The adjusted vaccine effectiveness among children who received three doses was 59.1% (95% CI, −31.1 to 87.2). Of the 12 isolates obtained from children with culture-confirmed disease, 7 (58%) were MATS-positive. The estimated vaccine effectiveness against vaccine-

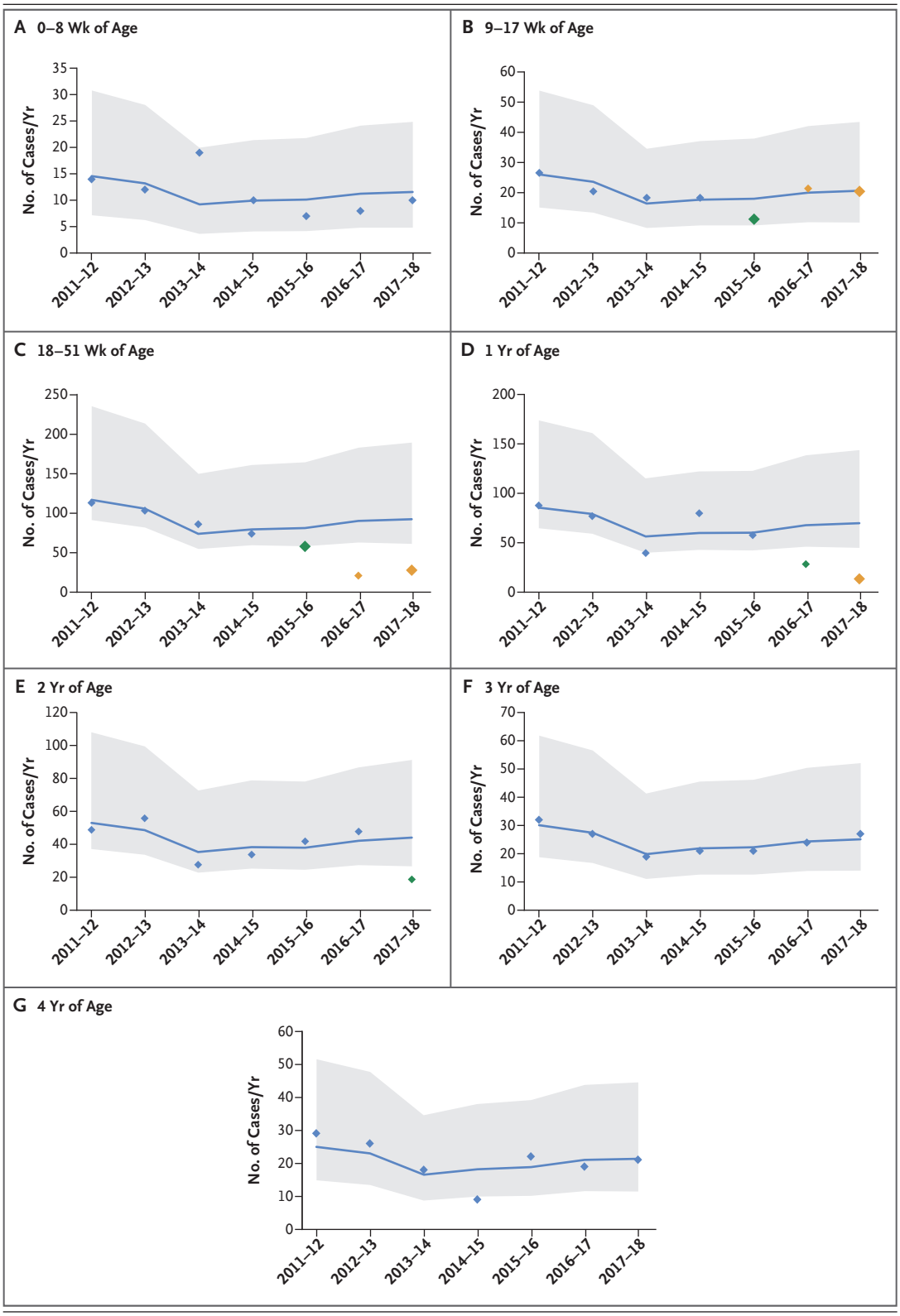

Figure 2 (facing page). Number of Children with Meningococcal Group B Disease in Each Surveillance Year.

The orange diamonds indicate children who were fully eligible to receive the vaccine, the green diamonds those who were partially eligible to receive the vaccine, and the blue diamonds those in the comparator cohorts. The fitted prediction in the absence of vaccination (blue line) and its 95% prediction interval (gray region) are also shown. Data shown for each year are from September through August. Infants who were 8 weeks of age or younger (Panel A) were not eligible to receive the vaccine. Among infants who were 9 to 17 weeks of age (Panel B), some infants in 2015–2016 (green diamond) and all the infants in the 2016–2017 and 2017–2018 periods (orange diamonds) were eligible to receive one dose. Among infants who were 18 to 51 weeks of age (Panel C), some infants in 2015–2016 (green diamond) and all the infants in the 2016–2017 and 2017–2018 periods (orange diamonds) were eligible to receive two doses. Among children who were 1 year of age (Panel D), some children in 2016–2017 (green diamond) and all the children in 2017–2018 (orange diamond) were eligible to receive two priming doses plus a 12-month booster. Among children who were 2 years of age (Panel E), some children in 2017–2018 (green diamond) were eligible to receive two priming doses plus a 12-month booster. Children who were 3 and 4 years of age (Panels F and G) were not eligible to receive the vaccine.

preventable meningococcal group B strains among children who received three doses was 71.2%.

DISCUSSION

This study provides real-world evidence of the effectiveness of 4CMenB in preventing invasive meningococcal group B disease 3 years after its introduction into the U.K. national infant immunization program. Our analysis included all children with meningococcal group B disease in the vaccine-eligible cohorts, irrespective of vaccination status or strain coverage. We found that the 12-month booster protected against meningococcal group B disease for at least 2 years, which is reassuring given the initial concerns about rapidly waning levels of antibodies.[10] This is particularly important because the highest burden of meningococcal group B disease in England occurs during the first 3 years of life.[11] Our point estimates of vaccine effectiveness are consistent with the reduction in cases of meningococcal group B disease in each of the vaccine-eligible cohorts; the estimates of vaccine effectiveness have wide confidence intervals because of the small numbers of cases.

Table 1. Incidence of Meningococcal Group B Disease before and after the Vaccine Introduction Period.*

Age Group	Average Annual No. of Children with Disease, Prevaccination Period	No. of Children with Disease, Postvaccination Period			Incidence Rate Ratio (95% CI)†			Adjusted Incidence Rate Ratio (95% CI)‡		
	2010–2011 to 2014–2015	2015–2016	2016–2017	2017–2018	2015–2016 vs. 2010–2015	2016–2017 vs. 2010–2015	2017–2018 vs. 2010–2015	2015–2016 vs. 2010–2015	2016–2017 vs. 2010–2015	2017–2018 vs. 2010–2015
0–8 wk	13.75	7	8	10	0.52 (0.24–1.14)	0.60 (0.28–1.25)	0.75 (0.38–1.48)			
9–17 wk	20.50	11	21	20	0.55 (0.29–1.02)	1.05 (0.65–1.69)	1.01 (0.62–1.65)	0.62 (0.32–1.20)	1.07 (0.63–1.81)	0.99 (0.56–1.74)
18–51 wk	94.00	58	21	28	0.63 (0.48–0.83)	0.23 (0.15–0.35)	0.31 (0.21–0.45)	0.72 (0.52–0.99)	0.23 (0.14–0.38)	0.30 (0.19–0.49)
1 yr	71.25	58	29	14	0.83 (0.63–1.11)	0.42 (0.28–0.61)	0.20 (0.12–0.35)		0.43 (0.28–0.66)	0.20 (0.11–0.36)
2 yr	41.75	42	48	19	1.02 (0.73–1.43)	1.18 (0.85–1.62)	0.46 (0.29–0.75)			0.43 (0.25–0.74)
3 yr	24.75	21	24	27	0.83 (0.52–1.33)	0.97 (0.62–1.52)	1.11 (0.72–1.7)			
4 yr	20.50	22	19	21	1.04 (0.65–1.66)	0.90 (0.55–1.48)	1.02 (0.63–1.64)			

* Data shown for each year are from September through August, and the data are aggregated according to the surveillance year in which the specimen was obtained.
† These incidence rate ratios were adjusted only to account for changes in the population denominators.
‡ These incidence rate ratios were adjusted according to changes in the incidence of meningococcal B disease in the age cohorts of children who were not eligible to receive the vaccine.

The strength of this study lies in the consistently high vaccine uptake nationally and the near real-time enhanced national surveillance for all laboratory-confirmed cases, which is facilitated by the provision of a single national meningococcal reference unit. This surveillance allows for rapid assessment of vaccine effect and effectiveness at a national level. Our previous model, which used common trend lines for the expected cases,[6] did not fit the data after 2013–2014 because of an increase in cases of meningococcal group B disease in the cohorts of children who were not eligible to receive the vaccine (P=0.002 for testing for goodness of fit). Inclusion of the year as a factor improved the model (P=0.57 for testing for goodness of fit); this indicates that it was reasonable to assume that the secular changes observed in the nonvaccinated cohorts could be used to predict what would have happened without vaccination. The use of cases of disease from cohorts of children who were not eligible to receive the vaccine in order to predict disease trends in vaccine-eligible age groups can be justified because the program for infants is not expected to have any indirect (herd) effect.

The estimate of vaccine effectiveness is based on protection against all meningococcal group B strains. This is likely to be an underestimate of the true vaccine effectiveness because 4CMenB should not protect against all meningococcal group B strains. We attempted to estimate vaccine effectiveness against vaccine-preventable meningococcal group B strains by adjusting for the proportion of MATS-positive strains among the smaller number of culture-confirmed cases in the vaccine-eligible cohort. Our estimates also assumed that the proportion of strains that were MATS-positive would be similar in culture-confirmed and PCR-confirmed cases. In addition, we assumed no protection against MATS-negative strains, although there is likely to be some cross-protection, particularly in toddlers who will have received all three doses in the complete 4CMenB immunization schedule in the United Kingdom.[12] Finally, if 4CMenB protects only against these vaccine-preventable, MATS-positive meningococcal group B strains (although meningococcal group B disease would be less likely to develop in fully-immunized infants overall), then the smaller number of cases that do occur in immunized children would be more likely to be unpreventable by the vaccine (i.e., MATS-negative), although some cases of genuine vaccine failure will also occur. More accurate vaccine effectiveness against the vaccine-preventable strains may be possible with larger numbers of cases over time and improved nonculture methods of characterization of meningococci causing invasive disease.

In keeping with our previous report,[6] vaccine effectiveness among children who received a single priming dose in infancy was only 24.1% against all meningococcal group B strains, which is consistent with the lack of effect seen in infants who were 9 to 17 weeks of age. Vaccine effectiveness among infants who received two priming doses of 4CMenB was 52.7% — lower than previously reported.[6] This may be due to small numbers of cases in the earlier analysis and exclusion of the catch-up cohort from the current analysis. It could also be due to waning of protection within the first year of life, which may not have manifested in the previous analysis because of a shorter follow-up period.

The effectiveness of 4CMenB is also supported by data from a recent clinical trial,[13] a recent systematic review,[14] and other observational studies.[15-20] Although 4CMenB was licensed with a schedule of three priming doses in infants plus one booster dose, on the basis of limited data on immunogenicity, the United Kingdom implemented a reduced schedule for infants of two doses plus one booster dose.[21] This schedule has now been validated in a randomized, controlled trial that showed seroprotection in nearly all infants who received two priming doses.[13] In 2014, a mass immunization program was initiated in a region in Quebec, Canada, in response to a local outbreak of meningococcal group B disease; in that program, 82% of 59,000 persons who were 2 months to 20 years of age were immunized.[15] No cases of meningococcal group B disease occurred among vaccinees, and a multivariate analysis showed an estimated 78% reduction in meningococcal disease after the campaign. 4CMenB has also been administered to several thousand students during outbreaks in universities, and no additional cases have been identified.[16,18-20,22] As of December 2019, no major safety concerns had been identified after more than 3 million doses had been administered to infants,[23] older children and adolescents,[24,25] and premature infants.[26] Unlike the polysaccharide–protein conjugate vaccines, however, 4CMenB does not have any effect on menin-

gococcal group B carriage in immunized adolescents; therefore, immunization strategies with 4CMenB will need to focus on direct (individual) protection against meningococcal group B disease.[27]

In conclusion, 3 years after its implementation, 4CMenB continued to protect infants and toddlers against invasive meningococcal group B disease. This protection lasted for at least 2 years after receipt of two doses plus a booster dose.

Public Health England has legal permission, provided by Regulation 3 of the National Health Service ("Control of Patient Information") Regulations 2002, to process patient confidential information for national surveillance of communicable diseases. This includes responsibility of Public Health England to monitor the safety and effectiveness of vaccines, and individual patient consent is not required.

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

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