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STUDY REVIEW

4CMenB vaccine for group B meningococcal disease

Making Education Easy 2020

About the Expert

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This publication summarises and discusses use of the 4CMenB vaccine (BEXSERO®) against group B meningococcal disease in two recent studies published in the *New England Journal of Medicine*.[1,2] The first study evaluated the effect of 4CMenB on the incidence of invasive meningococcal group B disease in infants and children, 3 years after inclusion in the national vaccination programme in England.[1] The effectiveness of 4CMenB was also assessed.[1] The second study evaluated the effect of 4CMenB on carriage of meningococcal group B disease in adolescents, in a South Australian randomised controlled trial.[2] Take-home messages from these studies are:

- There was a 75% reduction in the number of cases of invasive meningococcal group B disease in infants and children eligible for 4CMenB during the first 3 years of the national vaccination programme in England.[1,5]
- Protection against meningococcal group B disease lasted for at least 2 years after receipt of two doses of 4CMenB plus a booster dose.[1]
- 4CMenB had no effect on the carriage of disease-causing meningococci (including group B) in adolescents with moderate-to-high vaccine coverage in South Australia, highlighting the importance of vaccinating individuals to achieve direct protection.[2]

Introduction

Group B strains of *Neisseria meningitidis* remain the most prevalent strain in New Zealand, accounting for 51% of cases of invasive meningococcal disease cases in 2019.[3]

4CMenB (BEXSERO®) is a multi-component meningococcal group B vaccine against invasive disease caused by *N. meningitidis* group B strains.[4] 4CMenB contains three surface-exposed recombinant proteins - factor H Binding Protein (fHBP), Neisseria adhesion A protein (NadA), Neisseria Heparin Binding Antigen fusion protein (NHBA) and outer membrane vesicles from the *N. meningitidis* group B strain NZ98/254 (NZ OMV) with PorA 1.4 antigenicity.[4]

4CMenB was approved in New Zealand in July 2018 for active immunisation in individuals at least 2 months of age,[4] following earlier approvals in Europe, the US and Australia. However, approvals were based on immunogenicity and safety rather than clinical endpoints.[1,2,5] Recently published studies in the *New England Journal of Medicine* provide important new data on the effects of 4CMenB on incidence and carriage of meningococcal group B disease.[1,2,5]

Effect and effectiveness of 4CMenB on invasive meningococcal group B disease in infants and children

Study background

In September 2015, 4CMenB was introduced into the UK national vaccination programme.[6] In this programme, 4CMenB is administered at 8 and 16 weeks of age, with a booster at 12 months.[6] Preliminary data from England showed a 50% reduction in the incidence rate ratio of meningococcal disease in the first 10 months of the vaccination programme, compared with pre-vaccine years.[6] 4CMenB effectiveness was estimated at 82.9% (95% CI 24.1-95.2%) after 2 doses by 6 months of age.[6]

The present study reported the effect and effectiveness of 4CMenB with regard to invasive meningococcal group B disease in infants and children at 1 and 2 years of age, after the first 3 years of the national vaccination programme in England.[1]

Study methods

Effect on incidence of invasive meningococcal group B disease[1]

The study used national surveillance data on cases of laboratory-confirmed meningococcal group B disease, to calculate the change in incidence of the disease from 4 pre-vaccine surveillance years (September 2011-August 2015) to the first 3 complete years after 4CMenB was introduced (September 2015- August 2018).

4CMenB vaccine for group B meningococcal disease

Age groups for analysis were as follows:

- 0-8 weeks (infants too young for vaccination)
- 9-17 weeks (some eligible for one 4CMenB dose in 2015-2016, all eligible in 2016-2017 & 2017-2018)
- 18-51 weeks (some eligible for two 4CMenB doses in 2015-2016, all eligible in 2016-2017 & 2017-2018)
- 1 year (some eligible for three 4CMenB doses in 2016-2017, all eligible in 2017-2018)
- 2 years (some eligible for three 4CMenB doses in 2017-2018)
- 3-4 years (children too old to receive 4CMenB throughout the study period).

Incidence rate ratios of meningococcal group B disease in each post-vaccination surveillance year were compared with those in the equivalent cohort during the 4 pre-vaccination years. Rate ratios were then adjusted for changes in the incidence of meningococcal group B disease in all children younger than 5 years who were not in the vaccine-eligible cohorts.

Effectiveness of 4CMenB[1]

Vaccine effectiveness was estimated in children eligible to receive 4CMenB through the routine vaccination programme (i.e., born on or after 1 July 2015), and who had onset of invasive meningococcal group B disease between 1 September 2015 and 31 August 2018.

Children were included if, at disease onset, they were aged:

- ≥77 days and <13 months (for estimates of the effectiveness of one dose)
- ≥133 days and <13 months (for estimates of the effectiveness of two doses)
- ≥365 days (for estimates of the effectiveness of three doses).

Vaccine doses received by children with confirmed disease were counted if onset of disease occurred ≥14 days after the dose was received. The comparator group included all children who were eligible to receive 4CMenB in England.

The effectiveness of 4CMenB vaccination was also estimated in vaccine-preventable strains of meningococcal group B disease, via Meningococcal Antigen Typing System (MATS) testing of isolates.

Study results

In the first 3 months of 2018, 92.5% of children in England (average annual birth cohort approximately 650,000) had completed the primary 4CMenB vaccinations by 1 year of age, and 87.9% had received all three doses by 2 years of age.[1]

Effect on incidence of invasive meningococcal group B disease[1]

Estimates of incidence rate ratios showed 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 (see **Table 1**). In children aged 18-51 weeks, there were fewer cases of meningococcal group B disease than expected for 3 consecutive years. In the second year of the programme, fewer than expected cases were also observed in children aged 1 year, who became eligible for the three-dose schedule after July 2016. This cohort continued to benefit from 4CMenB in the third year of the programme, with significantly fewer cases observed among children aged 2 years in 2017-2018.

When age groups in which all children eligible for 4CMenB vaccination were combined, the reduction in incidence of meningococcal group B disease was 75% compared with expected cases based on historical cohort data (incidence rate ratio 0.25; 95% CI 0.19-0.36) [see Figure 1]. When age groups in which only some children eligible for 4CMenB vaccination were combined, the reduction in incidence of meningococcal group B disease was 45% (incidence rate ratio 0.55; 95% CI 0.43-0.70). The overall risk reduction in the 4CMenB-eligible cohorts was 62% compared with expected cases.

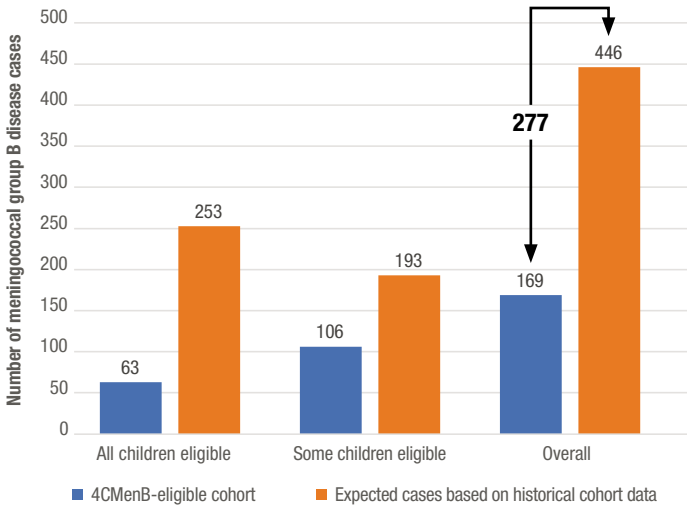

Figure 1. Cases of meningococcal group B disease after introduction of the 4CMenB national vaccination programme in England, compared with expected cases based on historical cohort data.[1]

Age group	Average annual no. of children with disease	No. of children with disease			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 vs 2015	2017-2018 vs 2010-2015
9-17 weeks	20.50	11	21	20	0.62 (0.32-1.20)	1.07 (0.63-1.81)	0.99 (0.56-1.74)
18-51 weeks	94.00	58	21	28	0.72 (0.52-0.99)	0.23 (0.14-0.38)	0.30 (0.19-0.49)
1 year	71.25	58	29	14		0.43 (0.28-0.66)	0.20 (0.11-0.36)
2 years	41.75	42	48	19			0.43 (0.25-0.74)

Table 1. Incidence of meningococcal group B disease before and after introduction of the 4CMenB vaccination programme in England.[1]

Data shown for each year are from September through August. Incidence ratio ratios were adjusted according to changes in the incidence of meningococcal group B disease in the age cohorts of children who were not eligible to receive 4CMenB.

Effectiveness of 4CMenB[1]

A total of 147 children were eligible for the analysis of 4CMenB effectiveness, including 74 children who were eligible for one dose of 4CMenB, 41 who were eligible for two doses and 29 who were eligible for three doses. A total of 26 children in the two-dose group and 12 in the three-dose group had disease confirmed by culture.

The adjusted vaccine effectiveness was 24.1% (95% CI -37.6%, 58.2%) for a single dose of 4CMenB. Adjusted effectiveness was 52.7% (95% CI -33.5%, 83.2%) for two doses of 4CMenB, and 59.1% (95% CI -31.1%, 87.2%) for three doses (see **Figure 2**). Confidence intervals were wide due to the small number of cases of meningococcal group B disease. When only MATS-positive strains of meningococcal group B disease were considered, vaccine effectiveness was 64.4% for two doses and 71.2% for three doses of 4CMenB.

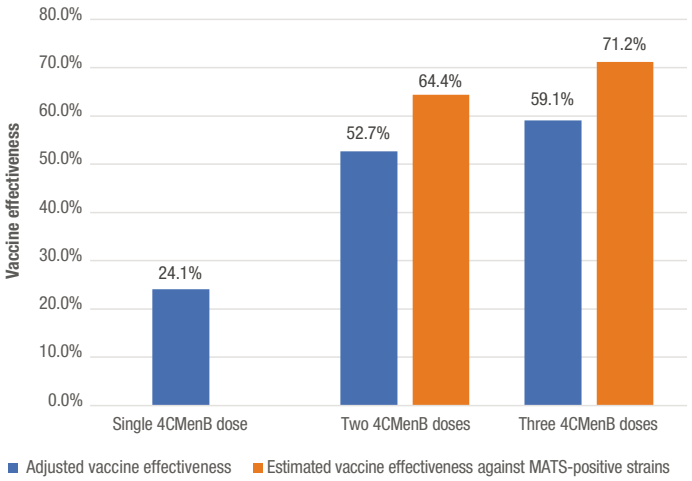

Figure 2. Effectiveness of 4CMenB in the national vaccination programme in England, according to number of doses and Meningococcal Antigen Typing System (MATS) positivity.[1]

Study interpretation

This study provides real-world evidence for the effectiveness of 4CMenB in preventing invasive meningococcal group B disease in infants and children.[1] Protection lasted for at least 2 years after receipt of two doses plus a booster dose.[1] Analysis included all children with meningococcal group B disease in the vaccine-eligible cohorts, regardless of vaccination status or strain coverage.[1]

The study is strengthened by the consistently high uptake of the 4CMenB vaccination programme across England.[1] However, the high uptake did mean there were very small case numbers to estimate vaccine effectiveness, and these results, while encouraging, did not reach statistical significance. The more meaningful finding of the study is the 75% reduction in incidence of meningococcal group B disease.[1]

The 4CMenB administration schedule used in this study of two priming doses plus a booster dose is now approved in New Zealand for infants aged ≥2 months.[4] This schedule has been validated in a randomised, controlled trial showing seroprotection in nearly all infants who received two priming doses.[7]

EXPERT COMMENT

The incidence rates of meningococcal group B disease in New Zealand have been trending upwards steadily since 2013. However, it is still a rare disease, only 26 cases of invasive disease were identified in children <4 years of age during 2019.[3] 4CMenB is approved for use in NZ but not currently funded.

The UK has been leading the world for decades with respect to meningococcal disease epidemiology and control. It was the first country to introduce a vaccine against group C disease into its infant immunisation schedule and now has very little meningococcal group C disease. The uptake of 4CMenB vaccine in this study population was remarkably high. This, combined with enhanced surveillance using a single central meningococcal reference unit, make the UK the ideal place to conduct this kind of observational study.

The estimated reduction in the number of cases of meningococcal group B disease, and the estimated vaccine effectiveness, are encouraging. The vaccine effectiveness was adjusted for what the expected incidence would have been were there no vaccination programme, and was estimated to be 59.1% (95% CI -31.1%, 87.2%) for a three-dose schedule.

4CMenB looks like it would be effective for preventing disease in young children if it were to be used in NZ. One caveat would be that we have limited information on how likely this vaccine is to protect against the specific strains that circulate in NZ. 4CMenB does not seem to provide any herd immunity, so an infant programme like the one used would still not protect adolescents who are also at higher risk of meningococcal disease.

The main barrier to the use of 4CMenB vaccine in New Zealand is the cost-effectiveness of introducing it into the national immunisation programme. Our current funding system means that to get it funded there would have to evidence that it would lead to a reduction in overall health costs. This is hard to demonstrate for such a rare disease. It may be that a more cost-effective targeted campaign for high risk groups is a better option for NZ.

Effect of 4CMenB on carriage of meningococcal group B disease in adolescents

Study background

Exposure to *N. meningitidis*, leading to oropharyngeal carriage, is common in the general population.[8] Carriage prevalence is age-related and peaks at approximately 19 years, likely as a result of increased numbers and closeness of social contacts and behaviour.[9,10] A reduction in carrier prevalence among adolescents could provide indirect protection to unvaccinated individuals, including infants.[10,11]

The South Australian meningococcal B vaccine carriage study, "B Part of It", investigated the effect of 4CMenB on the oropharyngeal carriage of disease-causing *N. meningitidis* in adolescent students.[2]

Study methods[2]

All 260 secondary schools in South Australia were invited to participate in the study, with oropharyngeal swabbing and vaccination of students provided through the school immunisation programme. Students eligible for the study were in school years 10-12 (aged approximately 15-18 years), and had provided written informed consent if aged ≥18 years, or assent with written informed consent from a parent/caregiver if aged <18 years. Swabs and cultures were analysed in a blinded central laboratory, using polymerase chain reaction-based assays for PorA and *N. meningitidis* genogroups.

Participating schools were randomised to the intervention group or the control group. Students in the intervention group received two doses of 4CMenB 2 months apart at baseline, while those in the control group received 4CMenB at 12 months. Stratification factors were school size (<60, 60-119, and ≥120 students per year level) and school socioeconomic status.

The primary study outcome was the prevalence of carriage of any disease-causing genogroup of *N. meningitidis* (A, B, C, W, X or Y) at 12 months. Secondary outcomes were the prevalence of carriage of each individual genogroup and of any *N. meningitidis*, and the acquisition of any disease-causing genogroup and of any *N. meningitidis* at 12 months. A further study objective was the identification of characteristics associated with baseline carriage of disease-causing genogroups and any *N. meningitidis*.

Study results[2]

A total of 34,489 students in years 10-12, from 237 participating schools, were enrolled between 1 April and 30 June 2017. The primary outcome analysis was conducted in 24,269 students in years 10 and 11 (12,746 in the intervention group and 11,523 in the control group). Analysis of risk factors for carriage was conducted in 10,220 students in year 12.

In the intervention group, 99.9% of students received the first dose of 4CMenB, and 97.7% received the second dose.

Prevalence and acquisition of carriage[2]

There was no significant difference in carriage prevalence of disease-causing *N. meningitidis* between the control group and the intervention group in the intention-to-treat analysis at 12 months (see **Table 2**). Genogroup A was not detected in any student. There were also no significant between-group differences in any of the prespecified secondary outcomes regarding carriage. However, in a post hoc analysis, the risk of non-groupable *N. meningitidis* was 29% lower in the intervention vs control group (1.65% vs 2.23%, respectively; adjusted odds ratio 0.71; 95% CI 0.54-0.91).

Post hoc analyses also revealed increased carriage (adjusted odds ratio 1.49; 95% CI 1.03-2.15) and acquisition (adjusted odds ratio 1.50; 95% CI 1.03-2.18) of disease-causing genogroups in rural schools, and decreased overall carriage in metropolitan schools (adjusted odds ratio 0.73; 95% CI 0.58-0.93) in the intervention group. However, the study authors noted that these results should be interpreted with caution due to the large numbers of interaction tests.

Risk factors for carriage[2]

The risk factors for carriage of disease-causing *N. meningitidis* in all students enrolled in years 10-12 included later year of schooling, current upper respiratory tract infection, cigarette smoking in the past week, water-pipe smoking in the past week, attending pubs or clubs in the past week, participation in intimate kissing in the past week, and being white (see **Table 3**).

The risk factors associated with carriage prevalence of any meningococci were similar, with the additional findings that students of Aboriginal or Torres Strait Islander ethnicity had almost double the carriage prevalence as white students (6.72% vs 3.66%, respectively; adjusted odds ratio 1.49; 95% CI 1.07-2.06), and boarding students were at higher risk than day students (adjusted odds ratio 2.10; 95% CI 1.16-3.80).

Vaccine coverage[2]

Overall vaccine coverage among South Australian students was 62% (students in years 10 and 11 enrolled in the trial divided by the total number of South Australian students in years 10 and 11). Among participating schools assigned to the intervention group, 82% had vaccine coverage of at least 50%. There was no association between vaccine coverage and outcomes of students in the intervention group regarding carriage of disease-causing *N. meningitidis* or any *N. meningitidis*.

Outcome at 12 months	Control group (n=11,523)	Intervention group (n=12,746)	Adjusted odds ratio (95% CI)
Carriage of disease-causing genogroup	2.52%	2.55%	1.02 (0.80-1.31)
Carriage of any *N. meningitidis*	4.87%	4.29%	0.85 (0.70-1.04)
Carriage of genogroup B	1.18%	1.29%	1.10 (0.81-1.47)
Carriage of genogroup Y	1.13%	0.92%	0.81 (0.56-1.18)
Carriage of genogroup W	0.18%	0.16%	0.89 (0.43-1.85)
Carriage of genogroup C	0.07%	0.11%	1.87 (0.63-5.55)
Carriage of genogroup X	0.01%	0.07%	7.59 (0.98-58.83)
Acquisition of any *N. meningitidis*	3.70%	3.38%	0.91 (0.73-1.13)
Acquisition of disease-causing genotype	2.07%	2.13%	1.03 (0.79-1.34)

Table 2. Prevalence and acquisition of *N. meningitidis* at 12 months in a randomised controlled study of 4CMenB vaccination in South Australian adolescents.[2]

Odds ratios were adjusted for randomisation strata and (excluding acquisition outcomes) corresponding baseline carriage result. The odds ratio for carriage of genogroup X was not adjusted owing to the small number of cases.

Study interpretation

This study highlights the need for direct protection of those at highest risk for meningococcal disease.[2] The study authors state that results have already been used to inform policies regarding meningococcal disease control, cost-effectiveness assessments of global 4CMenB immunisation programmes, and the design of next-generation meningococcal B vaccines.[2]

Findings from the current study differ from those of population-based studies of group A and C polysaccharide conjugate vaccines, which have shown an effect on carriage prevalence.[11-13] However, unlike capsular polysaccharides, the protein and outer membrane vesicle antigens in 4CMenB vary antigenically among the circulating strains that express them.[2,14]

The study authors noted they while they observed a lower-than-anticipated carriage prevalence of disease-causing *N. meningitidis*, the study was still powered to detect a clinically important effect of 4CMenB.[2]

Characteristic	Prevalence	Adjusted odds ratio (95% CI)
Sex		
Female	1.89%	1.00
Male	1.99%	1.09 (0.92-1.29)
Year of schooling		
10	1.02%	1.00
11	1.76%	1.64 (1.20-2.23)
12	3.29%	2.75 (2.03-3.73)
Current upper respiratory tract infection		
No	1.77%	1.00
Yes	2.58%	1.35 (1.12-1.63)
Smoked cigarettes in past week		
No	1.83%	1.00
Yes	7.80%	1.91 (1.29-2.83)
Smoked water pipe in past week		
No	1.81%	1.00
Yes	6.05%	1.82 (1.30-2.54)
Days out at pub or club in past week		
0	1.55%	1.00
≥1	3.48%	1.54 (1.28-1.86)
No. of persons kissed intimately in past week		
0	1.44%	1.00
≥1	3.59%	1.65 (1.33-2.05)
Boarding student		
No	1.92%	1.00
Yes	2.78%	1.33 (0.72-2.43)
Race or ethnic group		
White	2.05%	1.00
Aboriginal or Torres Strait Islander	3.36%	1.34 (0.90-2.01)
Asian	0.92%	0.50 (0.31-0.80)
Other	1.76%	0.98 (0.76-1.26)

Table 3. Risk factors for carriage of disease-causing *N. meningitidis* at baseline in a randomised controlled study of 4CMenB vaccination in South Australian adolescents.[2]

Odds ratios were adjusted for characteristics listed in the table as well as school socioeconomic status, school size, school location, antibiotic use, electronic cigarette use, and current relationship status.

EXPERT COMMENT

It seems that 4CMenB only offers individual protection and has no effect on the carriage of any meningococcus strains in adolescents.

The enormous success of polysaccharide conjugate vaccines (think meningococcal group C and haemophilus influenza type B vaccines) in preventing disease in children is partly due to their ability to reduce carriage in vaccine recipients. This not only prevents disease in the individual but reduces the chances of them spreading it. The 4CMenB vaccine has a different composition and does not have the same effect.

This finding is crucial for any planned vaccine programme in New Zealand. Meningococcal group B disease is most common in young infants, but there is a second peak in disease incidence among adolescents and young adults. Immunising one of these groups alone is unlikely to protect the others. Ideally a vaccination programme would need to vaccinate both groups, which then becomes very expensive.

This study had a fairly pragmatic design, which allowed it to include a very large number of schools. Participants did not have to provide many samples so it is possible that a short-term effect on carriage may have been missed. The overall carriage rates were pretty low in the end and this may reflect the age of participants being younger than the usual peak in carriage. I don't think either of these things have had a substantial impact on the overall study findings.

The study did show that if you want to reduce your teenager's risk of carriage you could ask them not to smoke, go to the pub or kiss anyone intimately. You may be doing this already.

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