**The success of 4CMenB in preventing meningococcal disease: evidence from real world experience**

Catherine Isitt1, Catherine A Cosgrove,2 Mary E Ramsay,3 Shamez N Ladhani.1, 3

1 Paediatric Infectious Diseases Research Group (PIDRG), St. George’s University of London, Cranmer Terrace, London SW17 0RE, UK

2 Clinical Infection Unit, St George's Hospital, Blackshaw Road, London SW17 0QT, UK

3 Immunisation and Countermeasures Division, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK

Corresponding author: Dr Shamez Ladhani, Immunisation and Countermeasures Division, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK. Email: shamez.ladhani@phe.gov.uk

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**Abstract**

Meningococcal disease remains one of the most feared infectious diseases because of its sudden onset, rapid progression and high case fatality rates, while survivors are often left with severe long-term sequelae. Young children have the highest incidence of invasive meningococcal disease (IMD) and nearly all cases in the UK, as in most of Europe and many other industrialised countries, are due to group B meningococci (MenB). The licensure of a broad-coverage, recombinant protein-based MenB vaccine (4CMenB) in 2013 was, therefore, heralded a major breakthrough in the fight against IMD. This vaccine was, however, licensed on immunogenicity and reactogenicity studies only, raising uncertainties about field effectiveness, long-term safety and antibody persistence. In 2015, the UK became the first country to implement 4CMenB into the national infant immunisation schedule and, since then, several countries have followed suit. Seven years after licensure, a wealth of real-world data has emerged to confirm 4CMenB effectiveness, along with large-scale safety data, duration of protection in different age groups, successful strategies to reduce vaccine reactogenicity, impact on carriage in adolescents and the potential for 4CMenB to protect against other meningococcal serogroups and against gonorrhoea. A number of questions, however, remain unanswered, including the investigation and management of vaccine-associated fever in infants, as well as disease severity and assessment of breakthrough cases in immunised children. Increasing use of 4CMenB will provide answers in due course. We now have vaccines against all the major serogroups causing IMD worldwide. Next-generation and combination vaccines against multiple serogroups look very promising.

**Introduction**

*Neisseria meningitidis* (the meningococcus) is a major cause of septicaemia and bacterial meningitis worldwide.1 Despite extensive awareness campaigns and improvements in healthcare and intensive care delivery, case fatality rates and severe neurodevelopmental sequelae among survivors of invasive meningococcal disease (IMD) remain unacceptably high.2 Twelve meningococcal serogroups are recognised, of which five (A, B, C, W and Y) are responsible for most IMD cases worldwide, although cases due to serogroup X have been increasing in the African meningitis belt.3 IMD incidence and serogroup distribution varies geographically and over time as new strains emerge and existing strains decline because of natural immunity or vaccination. In Europe and many industrialised countries, group B meningococci (MenB) are currently responsible for the majority of IMD cases, especially in young children and adolescents.4 Whilst capsular polysaccharide vaccines – and, more recently, polysaccharide-conjugate vaccines – against serogroups A, C, W and Y have been available for several decades,4 similar vaccines against MenB have been difficult to develop due to structural similarities of its capsular polysaccharide with human foetal neural cell adhesion molecules, rendering it poorly immunogenic.1

After more than 20 years in development, the licensure of the protein-based vaccine, 4CMenB (Bexsero®, GSK), in Europe in January 2013 was heralded a major breakthrough in the fight against IMD.1 This was the first broad-coverage MenB vaccine based on recombinant proteins, and is the only one approved for use in infants from 2 months of age.5 In January 2015, the United States also approved 4CMenB for use in 10-25 year-olds.6 7 4CMenB was licensed on immunogenicity and reactogenicity studies only, and as such there were initial concerns about its effectiveness and safety. Seven years on, a wealth of data has emerged following 4CMenB use in large populations. Here we summarise the real-world experience of 4CMenB use since its licensure.

**MenB Vaccines**

The first MenB vaccines were developed in the 1970s to tackle large outbreaks caused by single MenB strains.8 These vaccines use the wild-type Outer Membrane Vesicle (wtOMV) of the outbreak strain and are effective in controlling single-strain epidemics but offer little cross-protection against other MenB strains. One such vaccine (MeNZB) was developed and successfully used to control an IMD outbreak in New Zealand due to sequence type 41/44 [ST41/44] in the early 2000s.9

The problem with developing broad-coverage meningococcal vaccines is the significant antigen variability displayed by meningococci. A promising development for MenB vaccines came using reverse vaccinology whereby genome sequencing and complex bioinformatics were used to identify potential vaccine antigens which were then tested for their ability to produce bactericidal antibodies.10 The most immunogenic antigens were then combined to provide broad protection against invasive MenB strains.11 4CMenB is the first such vaccine to become licensed and includes the recombinant proteins Neisserial adhesin A (NadA), factor H binding protein (fHbp) and Neisseria Heparin Binding Antigen (NHBA) which are exposed on the meningococcal surface, as well as the OMV containing a major PorA antigen from the New Zealand outbreak ST41/44 strain (**Figure 1**).11

Another broad-coverage vaccine, MenB-FHbp (Trumenba®, Pfizer) received EMA approval in 2017. This vaccine contains two recombinant factor H binding proteins (fHbp) from separate subfamilies (A and B), antigens that are present in nearly all MenB strains. So far, the vaccine has not been implemented in any national or regional immunisation programme but has been successfully used to control MenB outbreaks in US universities.12 MenB-FHbp has been reviewed elsewhere recently.13

**Immunogenicity**

Given the low incidence of IMD, performing appropriately powered clinical trials to demonstrate protection against invasive disease prior to licensing is unfeasible due to the large number of participants required. Meningococcal vaccines are, therefore, licensed based on immunogenicity, reactogenicity and safety. The World Health Organization (WHO) accepts the serum bactericidal antibody assay with rabbit (rSBA) or human complement (hSBA) as a serocorrelate of protection against IMD and this had been used as the basis of licensing glycoconjugate vaccines against meningococcal serogroups A, C, W and Y.14

Determining the proportion of circulating MenB strains that would be killed by 4CMenB, however, would require hSBA assays against a wide panel of invasive strains and, therefore, large volumes of serum and complement, especially from infants, which is impractical. To circumvent this, the Meningococcal Antigen Typing System (MATS) was developed and standardised globally to predict whether an invasive MenB strain is potentially preventable by 4CMenB.15 MATS combines an enzyme-linked immunosorbent assay (ELISA) to measure the immunological cross-reactivity for three 4CMenB protein antigens (fHbp, NadA, and NHBA) with genetic typing of the PorA variable 2 (VR2) region, to predict susceptibility of MenB strains to killing in the hSBA assay. MATS is considered a conservative predictor for MenB strain coverage in different countries.15 16 17

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|  | Factor H binding protein (fHbp) – binds factor H, which enables bacterial survival in the blood  |
|  A picture containing indoor, sitting, table, cup  Description automatically generated | Neisserial adhesin A (NadA) – promotes adherence to and invasion of human epithelial cells, which may be important for colonisation |
|   | Neisseria heparin-binding antigen (NHBA) – present in virtually all strains and binds heparin, which may promote bacterial survival in the blood |
| A picture containing object  Description automatically generated | Outer Membrane Vesicle (OMV) incorporating the New Zealand PorA P.1.4 antigen – shown to induce strain-specific bactericidal antobody response when used in the New Zealand MenB outbreak |

**Figure. The 4 major antigens contained in 4CMenB (Bexsero®)**

In England and Wales, for example, a comparative analysis of MATS and hSBA using a representative panel of MenB strains causing IMD during 2007-08 reported a MATS-predicted coverage of 70% (95% CI, 55-85%) compared to 88% killing in the hSBA (95% CI, 72-95%).18 Global MATS positivity estimates range from 66% in Canada to 91% in the US.15 MATS, has, however, been shown to correlate with high rates of individual seroprotection,17 and, in one study, MATS-positive MenB isolates were associated with more severe disease and outcomes in children than MATS-negative isolates in the absence of vaccination.2 A notable limitation of MATS is that it can only predict coverage against cultured meningococci and cannot predict coverage for PCR-confirmed cases which account for around 50% of confirmed IMD cases in the UK.1,19 A new technique, the genetic Meningococcal Antigen Typing System (gMATS), bypasses this limitation by predicting vaccine coverage comparing the genetic sequences of the fHbp, NHBA and NadA antigens to reference strains in the PubMLST database, instead of using ELISA as in the standard MATS assay. Thus, gMATS could potentially be used to predict vaccine coverage directly from clinical samples without the need for culturing the meningococci. Similarly to MATS, however, gMATS also underestimates the vaccine coverage of strains.20

**4CMenB impact and effectiveness**

In September 2015, the UK became the first country to implement 4CMenB into its publicly funded national infant immunisation programme. Although initially not considered cost-effective, the Joint Committee on Vaccination and Immunisation (JCVI) subsequently recommended the introduction of 4CMenB at a reduced two-dose infant priming schedule (2+1) instead of the licensed three-dose (3+1) schedule.21 The decision was based on the results of a randomised controlled trial where infants received 4CMenB at 2, 4 and 6 months of age, but a blood sample taken one month after the second priming dose found that nearly all infants achieved seroprotective antibody thresholds against at least one vaccine antigen.22 As with all other infant vaccines in the national immunisation programme, uptake was very high and, within 10 months of the programme, MenB cases halved in vaccine-eligible infants, irrespective of vaccination status of the cases or strain coverage by 4CMenB.19 Vaccine effectiveness for two doses in infancy was estimated to be 82.9% in infants (aged <12 months). This was very reassuring given that a retrospective MATS analysis of MenB strains in England estimated only 66% MenB strain coverage by 4CMenB in infants during 2014-15, the year prior to 4CMenB implementation.17 After three years, 4CMenB continues to protect children against MenB disease at least until their third birthday; in England, there has been a 75% reduction in age-groups that were fully eligible for vaccination, irrespective of vaccine uptake, immunisation status of cases or strain coverage by 4CMenB.23 An estimated 277 cases were prevented compared to 169 cases confirmed (62% reduction) during the first three years of the programme. This trend has continued into the fourth year of the programme, with further reductions in MenB disease in children aged <5 years (**Figure 2**).



**Figure 2**. **Meningococcal B (MenB) cases in children under 5 years of age during 2014/15-2018/19 surveillance years (September to August following year) in England (solid line) compared to MenB cases predicted by trends among unvaccinated cases (dashed line) over the same period.** The arrowindicates the start of the MenB infant immunisation programme. Only half the birth cohorts in children under 5 years of age have been eligible for the 4CMenB immunisation programme. As the infant 4CMenB programme continues, more birth cohorts will be protected against MenB cases and cases should decline further in the coming years (SOURCE: Public Health England).

Subsequent studies have validated the UK decision to implement a reduced, two-dose infant priming schedule. Clinical trials have demonstrated similar immunogenicity in infants receiving two priming doses (at 3 and 5 months of age) compared to those receiving three doses (at 2.5, 3.5 and 5 months).24 Vaccine-induced antibodies from infants receiving these two schedules showed no differences in the percentage of strains killed in an hSBA assay against 40 MenB strains causing IMD in England.25

In addition to the UK, 4CMenB was also implemented in the Saguenay-Lac-Saint-Jean region of Quebec, Canada in 2014 in response to an increase in MenB disease incidence to 3.4/100,000, ten times higher than the national rate.26 Of the 59,373 individuals aged 2 months to 20 years who were eligible for the vaccine, 83% received it and MenB disease incidence in the target population fell from 11.4/100,000 in 2006-2014 to 0.4/100,000 in 2014-2018 (p < 0.0001). Five MenB cases occurred during a four year period from July 2014 to June 2018, including a six year-old child vaccinated with 2 doses at two years of age, one unvaccinated young adult and 3 unvaccinated older adults. Vaccine effectiveness was estimated to be 79% (95%CI, -231% to 99%) over this four-year period with an overall 86% (95%CI, -2% to 98%) reduction in MenB disease risk in the vaccine-eligible cohort, albeit with wide and non-significant confidence intervals because of small numbers of cases.26 More recently, Andorra, San Marino, Ireland, Italy, Lithuania and several regions in Spain including Castilla y Leon and the Canary Islands have also implemented 4CMenB into their publicly-funded national infant immunisation programmes,27–33 while in South Australia the vaccine is additionally being offered to toddlers and adolescents.34

Box 1: Summary of Implementation around the world in Children and Adolescents\*

Implementation into publicly funded National Immunisation Programme

* UK (September 2015) 2+1 infant schedule19
* Andorra (2016) 2+1 infant schedule31
* San Marino (2017) 3+1 infant schedule up to 2 years32
* Ireland (Oct 2016) 2+1 infant schedule27
* Italy (January 2017) 3+1 infant 27\*\*
* Lithuania (2018) 2+1 infant schedule28
* South Australia (2018)34

Recommended but not publicly funded

* Austria – 3 dose schedule ages 2 months to 2 years27
* Czech Republic- recommended for infants, toddlers and adolescents (2+1 for infants, 2 doses only for older children) 27
* Germany - Recommended only in Saxony region for infants and toddlers27
* USA – used in seven separate University outbreaks between 2013 and 2018 (California, New Jersey, Oregon, Pennsylvania, Wisconsin, Massachusetts)12 initially, currently also for adolescents with a category B recommendation (individual clinical decision based on risk-benefit)

Used in outbreak management only

* Canada- 2014 SLSJ region of Quebec- 59,373 individuals aged 2-20 years offered 4CMenB (2 doses)26

*\* Many other countries recommend 4CMenB for at-risk individuals of different ages*

*\*\* In Italy, the national recommendation is for a 3+1 schedule although individual regions are free to introduce different schedules and some regions have opted for a 2+1 schedule33*

**Vaccine Reactogenicity and Paracetamol Prophylaxis**

Pre-licensure clinical trials reported high rates of fever, especially in infants receiving 4CMenB concomitantly with other routine immunisations.35 36 Fever was reported in 26-41% of infants receiving 4CMenB alone and 23-36% with routine vaccines given alone compared to 51-61% when 4CMenB was co-administered with routine vaccines.36 A recent meta-analysis of published studies identified significantly higher rates of fever, local reactions and systemic reactions with 4CMenB compared to routine vaccinations, which were mainly mild-to-moderate, short-lasting and self-limiting.35 Rare cases of febrile convulsions and Kawasaki disease were also identified although numbers were too small to for comparison with background incidence.35

A randomised controlled trial subsequently reported significantly lower rates of 4CMenB-associated fever (especially fever ≥39.0oC) and adverse reactions in infants receiving prophylactic paracetamol (three doses at 4-6 hour intervals, with the first dose given around the time of vaccination) compared to those receiving the same vaccinations without paracetamol, without affecting the immunogenicity of any of the 4CMenB or routine vaccine antigens.37 This finding was in contrast to a previous trial that had reported lower antibody responses to routine vaccine antigens in infants receiving prophylactic paracetamol,38 but the evidence was sufficiently robust for the UK to recommend prophylactic paracetamol for infants receiving 4CMenB alongside their routine immunisations at 8 and 16 weeks of age with the first dose given around the time of vaccination and two further doses at 4 -6 hourly intervals.39 Similarly, following mass administration with 4CMenB in Quebec, Canada, significant reductions in fever rates were reported with paracetamol prophylaxis, although the magnitude of effect decreased with age. In children aged <2 years, for example, fever rates were 44% lower when paracetamol was co-administered with the first dose of 4CMenB compared to only a 22% reduction among 5-16 year-olds.40 An attitudinal survey of UK parents found that the overwhelming majority would accept 4CMenB immunisation despite the high rates of fever because the fear of their child developing IMD was far worse than self-limiting post-vaccination fever;41 most parents also had no concerns giving their infant prophylactic paracetamol to reduce the risk of vaccine-related adverse events.41 Prophylactic paracetamol is not recommended for the booster at one year because both parents and healthcare professionals expressed more confidence with managing fever and other vaccine-related reactions in the older infant.

In clinical trials, medical attention for fever was reported in up to 5% of infants receiving 4CMenB concomitantly with their routine immunisations (equating to potentially 40,000 infants in the UK) but these rates were substantially reduced with prophylactic paracetamol and providing parents with appropriate advice about the risk and management of fever after vaccination (5.3% to 1.4% in one study).37,42 In the UK, several post-vaccine implementation studies have reported a small increase in primary care consultations,43 Emergency Department attendance, short-care admissions and hospitalisations after 4CMenB vaccination,44 which together constitute <1% of vaccinated infants. For frontline clinicians, however, such infants present a diagnostic challenge because their presenting features (fever, vomiting, refusal to feed, lethargy) can be similar to serious bacterial infections and, since 4CMenB triggers a pro-inflammatory immune response, both the peripheral white cell count and C-reactive protein levels may also be raised. Consequently, a significant proportion of infants with vaccine-associated reactions post-4CMenB will be hospitalised and many will receive empiric intravenous antibiotics until investigations reliably exclude an underlying bacterial infection.44 Giving 4CMenB separately to routine immunisations, however, does not reduce the rate of adverse events. Using pooled data from multiple clinical trials, a recent study reported that, whilst vaccine-related adverse events (including fever) per episode were higher in infants receiving 4CMenB concomitantly with routine vaccines, the overall cumulative risk of adverse events was significantly lower than if the vaccines were given at separate immunisation visits.45

In premature infants, neonatologists were particularly concerned that the higher rates of adverse events (including fever) after 4CMenB might lead to clinical instability, leading many neonatal units to postpone vaccination and/or vaccinate without paracetamol prophylaxis. An exemplary, collaborative national audit involving neonatal units across England after 4CMenB implementation, however, found that although fever rates were higher in infants receiving 4CMenB concomitantly with routine vaccinations, the risk was reduced with prophylactic paracetamol and, importantly, there were no significant differences in the proportion of infants with reported apnoea, bradycardia, desaturation or increased respiratory support when compared to a historical cohort of premature infants that did not receive 4CMenB with their routine immunisations.46

**Safety**

Since 4CMenB was the first recombinant vaccine of its kind to be licensed, there were concerns about rare and/or long-term adverse events, which would only be identified after widespread use. After the first 3 million vaccines administered to nearly 1.3 million infants aged 2-18 months in the UK, no safety concerns were identified.47 There was no evidence of any increased risk of seizures, Kawasaki disease or sudden infant death syndrome among 4CMenB recipients. Ecological analyses identified no evidence of any increase in rates of febrile or afebrile seizures after the first, second and booster doses of 4CMenB.47 Post-implementation surveillance did identify 160 cases of local reactions described a persistent nodule at the site of injection, usually without other local symptoms, which is now included in the Summary of Product Characteristics.47 A potential concern following 4CMenB implementation was that adverse events after the first dose of vaccine may lead parents to avoid further vaccinations for their infants, thus potentially compromising the whole immunisation programme. Post-implementation surveillance, however, was reassuring with 95% of infants had receiving the second 4CMenB by 26 weeks of age.47

In Quebec, Canada, short-term safety surveillance following mass vaccination found high rates of injection site reactions and fever, in line with clinical trial data, but concluded that the overall short-term safety profile was acceptable for such an important vaccine.48 Active post-marketing surveillance did, however, identify several cases of nephrotic syndrome in the first year of the programme and further investigations revealed four cases in 2-5 year-olds with onset several months post-vaccination.49 Among 4CMenB-vaccinated children aged 1-9 years, nephrotic syndrome incidence was 3.6-fold higher (95%CI, 0.7-11.8; p=0.12) than the rest of the province for the same period, and 8.3-fold greater (95%CI, 1.1-62.0; p=0.039) than during the preceding eight years. The authors concluded that additional, larger studies are required to confirm or refute a potential link to vaccination. In Germany, post-marketing surveillance during 2013-2016, did not identify any safety concerns and, in particular, screening of patient records for immune-mediated and neurological diseases did not raise any safety signal.50

**Discussion**

4CMenB is currently approved in more than 40 countries worldwide, but only a few have implemented the vaccine into their national immunisation programme. In countries with a 4CMenB immunisation programme, all but South Australia have implemented an infant programme because they have the highest MenB disease incidence.4 34 The real-world data for the impact, effectiveness, reactogenicity and safety of 4CMenB, especially in infants and young children, is so far reassuring. There are, however, still a number of important questions that require answering.

Box 2: Questions surrounding 4CMenB that still need to be answered

* How to define breakthrough cases and vaccine failures in 4CMenB-immunised children?
* Do children who develop MenB disease after 4CMenB vaccination need additional investigations for underlying immune deficiency?
* The protection offered by the different antigens and antigen combinations in 4CMenB
* Does 4CMenB protect against other meningococcal serogroups?
* Timing of a booster in children immunised with 4CMenB during infancy?
* Considerations for an adolescent programme with 4CMenB
* Does 4CMenB protect against gonorrhoea?

*Vaccine failure*

4CMenB does not protect against all invasive MenB strains. MATS is helpful in estimating strain coverage at a population level, but can only be used for culture-confirmed cases making it impossible to assess which PCR-confirmed cases might be vaccine failures. Even among immunised children with culture-confirmed IMD, we have a poor understanding of which vaccine antigens are important for protection, whether some of the vaccine antigens offer more protection than others or whether some combinations of vaccine antigens might be more protective than others through synergy, for example. At the same time, in addition to harbouring the immunodominant PorA 1.4 antigen, the OMV component of 4CMenB has multiple minor antigens which also help protect against IMD but their contribution is difficult to measure.51 There are currently no data to suggest that breakthrough MenB cases in immunised children is associated with an underlying immune deficiency or risk of recurrent infections. It is also unclear whether immunised children develop less severe MenB disease than unimmunised children. More information should become available with increasing numbers of MATS-positive IMD cases in fully-immunised children over time.52 Gaining a better understanding of the protective effects of different vaccine antigens should also lead to more effective next-generation MenB vaccines.

*Protection against other serogroups*

There is emerging evidence that 4CMenB may protect against other meningococcal serogroups as the antigens in 4CMenB are potentially conserved for all meningococci. Vaccine-induced antibodies from children immunised with 4CMenB, for example, have potent serum bactericidal activity against the hyper-virulent MenW strain currently causing a national outbreak in the UK and elsewhere,53 while recent laboratory studies have also demonstrated broad protection provided by 4CMenB-induced antibodies against other meningococcal serogroups.54 Demonstrating real-world protection against non-MenB IMD, however, is a challenge because of small numbers of childhood cases in countries that routinely use 4CMenB.

*Expanding the use of 4CMenB*

Although MenB incidence is highest in infants, many countries have a smaller second peak in adolescence, where nasopharyngeal carriage is highest.55 If 4CMenB could prevent meningococcal carriage, then vaccinating adolescents would be an attractive option because of the potential for providing indirect (herd) protection across the population, as demonstrated with the MenC conjugate vaccine programme.56 One of the largest carriage studies conducted in South Australia, however, failed to show any impact of 4CMenB on meningococcal carriage. 57 This finding played an instrumental part in the South Australian 4CMenB programme to extend vaccination beyond infants to provide direct protection against MenB for toddlers and teenagers.

*Protection against gonorrhoea*

In addition to IMD, there is growing interest in the potential for 4CMenB to protect against gonorrhoea. A recent case-control analysis found that the OMV vaccine (MeNZB) given to 15-30 year olds as part of the national outbreak control programme in New Zealand was associated with a 31% reduction in gonococcal disease and a 24% reduction in hospitalisations caused by gonorrhoea.58,59 Additionally, 4CMenB-induced antibodies in laboratory workers have been shown to recognise gonococcal antigens.60 This is not surprising since *Neisseria gonorrhoeae* shares surface protein antigens with *N. meningitidis*.58 Because 4CMenB contains additional meningococcal antigens that are also present on gonococci (particularly NHBA which is conserved and surface-exposed on *N. gonorrhoea*),60 vaccine effectiveness against gonorrhoea may be even higher. In Quebec, for example, the 4CMenB campaign was associated with 59% fewer gonorrhoea notifications in vaccine-eligible adolescents, although this was not statistically significant (95% CI, −22% to 84; P=0.1).61 If confirmed in larger studies, 4CMenB – and potentially, next generation vaccines containing gonorrhoea-specific antigens – could be implemented for adolescents because of the rapidly rising incidence of gonorrhoea globally and growing concerns about multi-drug resistance.

*Antibody persistence*

The persistence of 4CMenB-induced antibodies and potential duration of protection remains to be determined. The antibodies are known to wane rapidly after completion of the infant schedule with the 12-month booster; after 24-36 months, antibody persistence against NadA and NHBA is greater than the OMV containing PorA or fHBp and an additional booster induces high antibody responses in children receiving either 2+1 or 3+1 schedules.62 24 Unlike conjugate vaccines, 4CMenB is a protein-based vaccine and, therefore, the immune mechanisms triggered by vaccination are likely to be different. Whether serum antibodies alone predicts protection remains to be established. In the UK, so far, 4CMenB effectively protects children against MenB disease until their third birthday.23 This is important because IMD incidence is very low after this age. In older children and adolescents, booster responses and antibody persistence are better.62 In order to protect against the small adolescent peak in MenB disease, those immunised with 4CMenB in infancy could be boosted with a single dose of 4CMenB, potentially at the same visit as the MenACWY vaccine offered to 13-14 year-olds.63 A more attractive option might be the availability of a next generation MenB vaccine with better strain coverage,64 ideally as a pentavalent MenABCWY combination vaccine, which are both currently under development.65

**Conclusions**

Despite initial concerns regarding the safety and effectiveness of this novel protein-based vaccine along with the high reactogenicity rates, especially fever and particularly in young infants, 4CMenB has been well-accepted by parents and healthcare professionals. There is now real-world evidence to support more widespread use for those who are most susceptible, with reductions of up to 75% reported in vaccine-eligible childhood cohorts. Ongoing surveillance in countries with established national immunisation programmes is critical for monitoring the long-term impact, breakthrough cases and protection against other serogroups. If confirmed, the additional protection against gonorrhoea could expand its use into the wider adolescent, young adult and high-risk populations.

**What is already known**

1. A novel, protein-based multi-component vaccine against group B meningococcal disease (4CMenB) was licensed in Europe in 2013
2. The vaccine was licensed at a 3+1 schedule based on immunogenicity and reactogenicity studies only
3. The UK was the first country to implement 4CMenB into the national infant immunisation schedule at a reduced 2+1 schedule in 2015

**What this study adds**

1. 4CMenB has been highly effective in preventing MenB disease in vaccine-eligible infants across England
2. After more than 3 million doses administered to infants, no safety concerns have been identified in the UK
3. A number of other countries worldwide have now implemented 4CMenB into their national immunisation programmes

**References**

1. Ladhani SN, Campbell H, Parikh SR, Saliba V, Borrow R, Ramsay M. The introduction of the meningococcal B (MenB) vaccine (Bexsero®) into the national infant immunisation programme – New challenges for public health. *J Infect*. 2015;71(6):611-614. doi:10.1016/J.JINF.2015.09.035

2. Parikh SR, Campbell H, Gray SJ, et al. Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010–2015. *Vaccine*. 2018;36(26):3876-3881. doi:10.1016/J.VACCINE.2018.02.038

3. Borrow R, Caugant DA, Ceyhan M, et al. Meningococcal disease in the Middle East and Africa: Findings and updates from the Global Meningococcal Initiative. *J Infect*. 2017;75(1):1-11. doi:10.1016/j.jinf.2017.04.007

4. Whittaker R, Dias JG, Ramliden M, et al. The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004–2014. *Vaccine*. 2017. doi:10.1016/j.vaccine.2017.03.007

5. Vernikos G, Medini D. Bexsero® chronicle. *Pathog Glob Health*. 2014;108(7):305-316. doi:10.1179/2047773214Y.0000000162

6. Folaranmi T, Rubin L, Martin SW, Patel M, MacNeil JR, Centers for Disease Control (CDC). Use of Serogroup B Meningococcal Vaccines in Persons Aged ≥10 Years at Increased Risk for Serogroup B Meningococcal Disease: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(22):608-612. http://www.ncbi.nlm.nih.gov/pubmed/26068564. Accessed October 14, 2019.

7. MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. Use of Serogroup B Meningococcal Vaccines in Adolescents and Young Adults: Recommendations of the Advisory Committee on Immunization Practices, 2015. *MMWR Morb Mortal Wkly Rep*. 2015;64(41):1171-1176. doi:10.15585/mmwr.mm6441a3

8. Holst J, Oster P, Arnold R, et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV) Lessons from past programs and implications for the future. *Hum Vaccines Immunother*. 2013;9(6):1241-1253. doi:10.4161/hv.24129

9. Oster P, Lennon D, O’Hallahan J, Mulholland K, Reid S, Martin D. MeNZBTM: A safe and highly immunogenic tailor-made vaccine against the New Zealand Neisseria meningitidis serogroup B disease epidemic strain. In: *Vaccine*. ; 2005. doi:10.1016/j.vaccine.2005.01.063

10. Tan LKK, Carlone GM, Borrow R. Advances in the development of vaccines against Neisseria meningitidis. *N Engl J Med*. 2010. doi:10.1056/NEJMra0906357

11. Toneatto D, Ismaili S, Ypma E, Vienken K, Oster P, Dull P. The first use of an investigational multicomponent meningococcal serogroup B vaccine (4CMenB) in humans. *Hum Vaccin*. 2011;7(6):646-653. doi:10.4161/hv.7.6.15482

12. Soeters HM, McNamara LA, Blain AE, et al. University-Based Outbreaks of Meningococcal Disease Caused by Serogroup B, United States, 2013-2018. *Emerg Infect Dis*. 2019;25(3):434-440. doi:10.3201/eid2503.181574

13. Findlow J, Nuttens C, Kriz P. Introduction of a second MenB vaccine into Europe – needs and opportunities for public health. *Expert Rev Vaccines*. 2019;18(3):225-239. doi:10.1080/14760584.2019.1578217

14. Villena R, Safadi MAP, Valenzuela MT, Torres JP, Finn A, O’Ryan M. Global epidemiology of serogroup B meningococcal disease and opportunities for prevention with novel recombinant protein vaccines. *Hum Vaccin Immunother*. 2018;14(5):1042-1057. doi:10.1080/21645515.2018.1458175

15. Medini D, Stella M, Wassil J. MATS: Global coverage estimates for 4CMenB, a novel multicomponent meningococcal B vaccine. *Vaccine*. 2015. doi:10.1016/j.vaccine.2015.04.015

16. Mulhall RM, Bennett D, Cunney R, et al. Potential Coverage of the 4CMenB Vaccine against Invasive Serogroup B Neisseria meningitidis Isolated from 2009 to 2013 in the Republic of Ireland. *mSphere*. 2018;3(4). doi:10.1128/mSphere.00196-18

17. Parikh SR, Newbold L, Slater S, et al. *Meningococcal Serogroup B Strain Coverage of the Multicomponent 4CMenB Vaccine with Corresponding Regional Distribution and Clinical Characteristics in England, Wales, and Northern Ireland, 2007–08 and 2014–15: A Qualitative and Quantitative Assessment*. Vol 17.; 2017. doi:10.1016/S1473-3099(17)30170-6

18. Frosi G, Biolchi A, Sapio M Lo, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine*. 2013;31(43):4968-4974. doi:10.1016/J.VACCINE.2013.08.006

19. Parikh SR, Andrews NJ, Beebeejaun K, et al. Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet*. 2016. doi:10.1016/S0140-6736(16)31921-3

20. Muzzi A, Brozzi A, Serino L, et al. Genetic Meningococcal Antigen Typing System (gMATS): A genotyping tool that predicts 4CMenB strain coverage worldwide. *Vaccine*. 2019. doi:10.1016/j.vaccine.2018.12.061

21. JCVI JC on V and I. *JCVI Position Statement on Use of Bexsero Meningococcal B Vaccination in the UK*.; 2014. https://www.gov.uk/government/uploads/system/uploads/attachment\_data/file/294245/JCVI\_Statement\_on\_MenB.pdf.

22. Findlow J, Borrow R, Snape MD, et al. Multicenter, Open‐Label, Randomized Phase II Controlled Trial of an Investigational Recombinant Meningococcal Serogroup B Vaccine With and Without Outer Membrane Vesicles, Administered in Infancy. *Clin Infect Dis*. 2010;51(10):1127-1137. doi:10.1086/656741

23. Ladhani SN, Andrews N, Parikh SR, et al. Impact and effectiveness of infant group B meningococcal vaccination (4CMenB), England. *N Engl J Med*. 2019;In Press.

24. Martinón-Torres F, Carmona Martinez A, Simkó R, et al. Antibody persistence and booster responses 24-36 months after different 4CMenB vaccination schedules in infants and children: A randomised trial. *J Infect*. 2017;76:258-269. doi:10.1016/j.jinf.2017.12.005

25. Biolchi A, Tomei S, Santini L, et al. Evaluation of strain coverage of the multicomponent meningococcal serogroup B vaccine (4CMenB) administered in infants according to different immunisation schedules. *Hum Vaccines Immunother*. 2019;15(3):725-731. doi:10.1080/21645515.2018.1537756

26. Deceuninck G, Lefebvre B, Tsang R, Betala-Belinga JF, De Serres G, De Wals P. Impact of a mass vaccination campaign against Serogroup B meningococcal disease in the Saguenay-Lac-Saint-Jean region of Quebec four years after its launch. *Vaccine*. 2019;37(31):4243-4245. doi:10.1016/j.vaccine.2019.06.021

27. European Centre for Disease Prevention and Control. *Expert Opinion on the Introduction of the Meningococcal B (4CMenB) Vaccine in the EU/EEA*.; 2017. doi:10.2900/18933

28. ECDC. Vaccine Scheduler: Lithuania Recommended Vaccines. Vaccine Scheduler: Lithuania Recommended Vaccines. https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByCountry?SelectedCountryId=120&IncludeChildAgeGroup=true&IncludeChildAgeGroup=false&IncludeAdultAgeGroup=true&IncludeAdultAgeGroup=false. Published 2018. Accessed October 21, 2019.

29. Gobierno de Canarias. Boletin Oficial de Canarias. http://www.gobiernodecanarias.org/boc/2019/126/001.html. Published 2019. Accessed October 31, 2019.

30. De castilla y Leon C. Boletín Oficial de Castilla y León. http://bocyl.jcyl.es/boletines/2019/04/25/pdf/BOCYL-D-25042019-41.pdf. Published 2019. Accessed October 31, 2019.

31. Govern d’Andorra. Prtoegeix els teus fills. https://www.salut.ad/images/stories/Salut/pdfs/temes\_salut/Targeto\_Vacunes.pdf. Published 2017. Accessed October 31, 2019.

32. Republica Di San Marino. Vaccinazioni raccomandate. Istituto per la Sicurezza Sociale. http://www.iss.sm/on-line/home/vaccini-e-vaccinazioni/vaccinazioni-raccomandate.html. Published 2017. Accessed October 31, 2019.

33. Signorelli C, Chiesa V, Odone A. Meningococcal serogroup B vaccine in Italy: state-of-art, organizational aspects and perspectives. *J Prev Med Hyg*. 2015;(56):E125-E132.

34. Government of South Australia; South Australian Meningococcal B expert working group. *A Meningococcal B Program for South Australia Public Report*.; 2018. https://www.sahealth.sa.gov.au/wps/wcm/connect/b82a9fb7-061a-48b9-be37-54e88a1907d1/2018-06+Optimal+Men+B+Program+for+SA+Public+Report+%282%29.pdf?MOD=AJPERES&CACHEID=ROOTWORKSPACE-b82a9fb7-061a-48b9-be37-54e88a1907d1-mMzmzGg.

35. Flacco ME, Manzoli L, Rosso A, et al. Immunogenicity and safety of the multicomponent meningococcal B vaccine (4CMenB) in children and adolescents: a systematic review and meta-analysis. *Lancet Infect Dis*. 2018. doi:10.1016/S1473-3099(18)30048-3

36. Gossger N, Snape MD, Yu LM, et al. Immunogenicity and tolerability of recombinant serogroup B meningococcal vaccine administered with or without routine infant vaccinations according to different immunization schedules: A randomized controlled trial. *JAMA - J Am Med Assoc*. 2012. doi:10.1001/jama.2012.85

37. Prymula R, Esposito S, Zuccotti GV, et al. A phase 2 randomized controlled trial of a multicomponent meningococcal serogroup B vaccine (I): Effects of prophylactic paracetamol on immunogenicity and reactogenicity of routine infant vaccines and 4CMenB. *Hum Vaccines Immunother*. 2014. doi:10.4161/hv.28666

38. Prymula R, Siegrist CA, Chlibek R, et al. Effect of prophylactic paracetamol administration at time of vaccination on febrile reactions and antibody responses in children: two open-label, randomised controlled trials. *Lancet*. 2009. doi:10.1016/S0140-6736(09)61208-3

39. Murdoch H, Wallace L, Bishop J, Robertson C, Claire Cameron J. Risk of hospitalisation with fever following MenB vaccination: self-controlled case series analysis. *Arch Dis Child*. 2017;102(10):894-898. doi:10.1136/archdischild-2017-313079

40. Insititut National de Sante Publique du Quebec. *Rapport Final de Surveillance de La Securite de La Vaccination Des Jeunes de 20 Ans et Moins Contre Le Meningococque de Serogroupe B Au Saguenay-Lac-Saint-Jean*.; 2016. https://www.inspq.qc.ca/sites/default/files/publications/2110\_surveillance\_securite\_vaccination\_jeunes\_meningocoque\_saguenay.pdf.

41. Jackson C, Yarwood J, Saliba V, Bedford H. UK parents’ attitudes towards meningococcal group B (MenB) vaccination: A qualitative analysis. *BMJ Open*. 2017. doi:10.1136/bmjopen-2016-012851

42. Vesikari T, Esposito S, Prymula R, et al. Immunogenicity and safety of an investigational multicomponent, recombinant, meningococcal serogroup B vaccine (4CMenB) administered concomitantly with routine infant and child vaccinations: results of two randomised trials. *Lancet*. 2013;381(9869):825-835. doi:10.1016/S0140-6736(12)61961-8

43. Harcourt S, Morbey RA, Bates C, et al. Estimating primary care attendance rates for fever in infants after meningococcal B vaccination in England using national syndromic surveillance data. *Vaccine*. 2018. doi:10.1016/j.vaccine.2017.11.076

44. Ladhani SN, Riordan A. The yin and yang of fever after meningococcal B vaccination. *Arch Dis Child*. 2017;102(10):881-882. doi:10.1136/archdischild-2017-313419

45. Zafack JG, Bureau A, Skowronski DM, De Serres G. Adverse events following immunisation with four-component meningococcal serogroup B vaccine (4CMenB): interaction with co-administration of routine infant vaccines and risk of recurrence in European randomised controlled trials. *BMJ Open*. 2019;9(5):e026953. doi:10.1136/bmjopen-2018-026953

46. Kent A, Beebeejaun K, Braccio S, et al. Safety of meningococcal group B vaccination in hospitalised premature infants. *Arch Dis Child Fetal Neonatal Ed*. 2019;104(2):F171-F175. doi:10.1136/archdischild-2017-314152

47. Bryan P, Seabroke S, Wong J, et al. Safety of multicomponent meningococcal group B vaccine (4CMenB) in routine infant immunisation in the UK: a prospective surveillance study. *Lancet Child Adolesc Heal*. 2018. doi:10.1016/S2352-4642(18)30103-2

48. De Serres G, Billard M-N, Gariépy M-C, et al. Short-term safety of 4CMenB vaccine during a mass meningococcal B vaccination campaign in Quebec, Canada. *Vaccine*. 2018;36(52):8039-8046. doi:10.1016/J.VACCINE.2018.10.095

49. De Serres G, Billard M-N, Gariépy M-C, et al. Nephrotic syndrome following four-component meningococcal B vaccination: Epidemiologic investigation of a surveillance signal. *Vaccine*. 2019;37(35):4996-5002. doi:10.1016/J.VACCINE.2019.07.017

50. Mentzer D, Oberle D, Keller-Stanislawski B. Adverse events following immunisation with a meningococcal serogroup B vaccine: report from post-marketing surveillance, Germany, 2013 to 2016. *Euro Surveill*. 2018;23(17). doi:10.2807/1560-7917.ES.2018.23.17.17-00468

51. Awanye AM, Chang CM, Wheeler JX, et al. Immunogenicity profiling of protein antigens from capsular group B Neisseria meningitidis. *Sci Rep*. 2019;9(1):1-14. doi:10.1038/s41598-019-43139-0

52. Lucidarme J, Lekshmi A, Willerton L, et al. Genotypic enhalnced surveillance after the introduction of 4CMenB in England, the first 29 months. In: *15th EMGM Congress*. Lisbon, Portugal; 2019:9. http://emgm2019.pt/en/content/programme/abstract-book/abstract-book.html.

53. Ladhani SN, Giuliani MM, Biolchi A, et al. Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England. *Emerg Infect Dis*. 2016;22(2):309-311. doi:10.3201/eid2202.150369

54. Biolchi A, De Angelis G, Moschioni M, et al. 4CMenB, A Multicomponent Meningococcal Vaccine Developed for Serogroup B Meningococcu Elicits Cross-Reactive Immunity Also Against Serogroups C, W and Y. In: *15th EMGM Congress*. Lisbon, Portugal; 2019:83. http://emgm2019.pt/en/content/programme/abstract-book/abstract-book.html.

55. Read RC, Baxter D, Chadwick DR, et al. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: An observer-blind, phase 3 randomised clinical trial. *Lancet*. 2014;384(9960):2123-2131. doi:10.1016/S0140-6736(14)60842-4

56. Read RC, Dull P, Bai X, et al. A phase III observer-blind randomized, controlled study to evaluate the immune response and the correlation with nasopharyngeal carriage after immunization of university students with a quadrivalent meningococcal ACWY glycoconjugate or serogroup B meningo. *Vaccine*. 2017;35(3):427-434. doi:10.1016/j.vaccine.2016.11.071

57. Marshall HS, McMillan M, Koehler A, et al. Impact of meningococcal B vaccine on meningococcal carriage in adolescents. *N Engl J Med*. 2019;In Press.

58. Petousis-Harris H, Paynter J, Morgan J, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. *Lancet (London, England)*. 2017;390(10102):1603-1610. doi:10.1016/S0140-6736(17)31449-6

59. Paynter J, Goodyear-Smith F, Morgan J, Saxton P, Black S, Petousis-Harris H. Effectiveness of a Group B Outer Membrane Vesicle Meningococcal Vaccine in Preventing Hospitalization from Gonorrhea in New Zealand: A Retrospective Cohort Study. *Vaccines*. 2019;7(1):5. doi:10.3390/vaccines7010005

60. Semchenko EA, Tan A, Borrow R, Seib KL. The Serogroup B Meningococcal Vaccine Bexsero Elicits Antibodies to Neisseria gonorrhoeae. *Clin Infect Dis*. 2019;69(7):1101-1111. doi:10.1093/cid/ciy1061

61. Longtin J, Dion R, Simard M, et al. Possible Impact of Wide-scale Vaccination Against Serogroup B Neisseria Meningitidis on Gonorrhea Incidence Rates in One Region of Quebec, Canada. *Open Forum Infect Dis*. 2017;4(suppl\_1):S734-S735. doi:10.1093/ofid/ofx180.002

62. Martinón-Torres F, Nolan T, Toneatto D, Banzhoff A. Persistence of the immune response after 4CMenB vaccination, and the response to an additional booster dose in infants, children, adolescents, and young adults. *Hum Vaccin Immunother*. 2019;0(0):1-12. doi:10.1080/21645515.2019.1627159

63. Davis K, Ford K, Craik R, Galal U, Rollier CS, Pollard AJ. The effect of a single 4CMenB vaccine booster in young people more than ten years after infant immunisation: protocol of an exploratory immunogenicity study. *Trials*. 2019;20(1):1-8. doi:10.1186/s13063-019-3494-1

64. Beernink PT, Vianzon V, Lewis LA, Moe GR, Granoff DM. A Meningococcal Outer Membrane Vesicle Vaccine with Overexpressed Mutant FHbp Elicits Higher Protective Antibody Responses in Infant Rhesus Macaques than a Licensed Serogroup B Vaccine. *MBio*. 2019;10(3). doi:10.1128/mBio.01231-19

65. Welsch JA, Senders S, Essink B, et al. Breadth of coverage against a panel of 110 invasive disease isolates, immunogenicity and safety for 2 and 3 doses of an investigational MenABCWY vaccine in US adolescents – Results from a randomized, controlled, observer-blind phase II study. *Vaccine*. 2018;36(35):5309-5317. doi:10.1016/J.VACCINE.2018.07.016