

Emerging clinical experience with vaccines against group B meningococcal disease

A. L. Wilkins, M. D. Snape*

Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine, Churchill
Hospital, University of Oxford, United Kingdom

*Corresponding author:

Oxford Vaccine Group, Centre for Clinical Vaccinology and Tropical Medicine, Churchill
Hospital, Old Road, Headington, Oxford OX3 7LJ;

tel: +44 1865 611 400;

fax: +44 1865 289 695;

Email address: matthew.snape@paediatrics.ox.ac.uk

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1 **Introduction**

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3 *Neisseria meningitidis* is responsible for severe and often fatal cases of invasive bacterial
4 disease. Of the 6 capsular groups (A, B, C, W, X, Y) responsible for severe meningitis and
5 septicaemia, capsular group B meningococcus (MenB) is now the leading cause of invasive
6 meningococcal disease (IMD) in many high-income settings. Although there is a trend for a
7 reduction in annual cases of MenB per 100,000 population in some countries, the case fatality
8 ratios are significant, with an average of 3 - 10% globally [1].

9
10 The immunological cross-reactivity between the MenB polysaccharide capsule and human
11 polysialylated neuronal cell adhesion molecule (PSA-NCAM) gives rise to a poorly
12 immunogenic capsule that risks inducing autoimmune disease if used as a vaccine antigen;
13 both leading to significant challenges in the development of an effective vaccine. To
14 overcome this limitation, vaccines using outer membrane proteins as target antigens have
15 been developed, presented either in outer membrane vesicles or as recombinant proteins. One
16 of the latter vaccines (Bexsero®, 4CMenB; GSK) is now used in the routine immunisation
17 schedules for infants in the United Kingdom (UK) and Ireland, while another (Trumenba®,
18 Bivalent rLP2086; Pfizer) has been licensed in the United States (US) for adolescents. This
19 article will review the development of these MenB vaccines, their current use and highlight
20 areas requiring further research.

21 22 **Outer Membrane Vesicle Vaccines**

23
24 Outer membrane vesicle (OMV) vaccines against MenB disease have been developed for use
25 in humans since the 1970s [2,3]. Following the removal of the toxic lipooligosaccharide from

the OMV of the meningococcal bacteria, the soluble proteins from the OMV are utilised in the vaccine to induce an immune response [4]. The immunodominant protein in these OMVs is Porin A (PorA), resulting in induction of antibodies which are most effective in targeting MenB strains bearing homologous PorA variants. Due to this specificity, these vaccines are most suitable for use in clonal outbreaks, where a vaccine can be developed to target a specific strain.

OMV MenB vaccines have been used across Cuba, New Zealand, Brazil, Chile and France to combat epidemic MenB outbreaks. Efficacy results of the first OMV vaccines used - in Cuba, Norway and France – were promising, at over 80% for 2 dose schedules [5–7]. However, when longer follow up periods were assessed including an OMV vaccine studied over 20 months in Chile, the efficacy decreased to close to 50%, indicating poor longevity of response [6,8,9]. The OMV vaccines developed in Cuba and Chile demonstrated reduced efficacy and effectiveness (respectively) in younger children aged < 4 years old when compared to older children and adolescents [8,10,11]. There was particularly poor protection against MenB vaccine strains bearing heterologous PorA in this age group. [5,12].

A national roll-out of an OMV MenB vaccine (MenNZB®) occurred in New Zealand in 2004 – 2008 for the outbreak due to meningococcal clonal complex (cc) 41/44, harbouring PorA variable region (VR) P1.4. Effectiveness of a 3 dose schedule was estimated at as high as 77% for those aged 0-19 years old over a 3 year period [13]. An observational evaluation of New Zealand residents less than 20 years of age between 2001 and 2008 found the protection provided by MenNZB (comparing fully vaccinated individuals to unvaccinated individuals) against non-epidemic strain MenB disease and non-group B strains were statistically significant and both over 50% [13]. However, there were wide confidence intervals for these

estimates and the possibility of confounding factors contributing to these results is highlighted by the authors.

4CMenB (Bexsero®)

The need for a MenB vaccine with the potential to protect against multiple endemic strains led to the development of a multicomponent MenB vaccine (4CMenB), incorporating novel proteins identified from the genome of a representative MenB strain through a process of ‘reverse vaccinology’. 4CMenB combines the OMV component of the New Zealand vaccine (derived from strain NZ 98/254), in which PorA is the immunodominant protein, with the recombinant sub-capsular proteins factor H binding protein (fHbp), Neisserial adhesin A (NadA) and Neisserial Heparin Binding Antigen (NHBA).

Immunogenicity

4CMenB was licensed in Europe in 2013 for children ≥ 2 months of age, followed by other parts of the world including Canada and Australia for children ≥ 2 months of age, and in the US for individuals aged 10 – 25 years (see table 1 for the current licensed dosing schedules) [14–17]. In the absence of efficacy data, licensure was based on immunogenicity as determined in clinical trials, measured using serum bactericidal antibody (SBA) assays with human complement, the known correlate of protection. When tested against MenB strains expressing closely matched antigens to those included in the vaccine, these licensed schedules of 4CMenB are able to induce levels of bactericidal antibodies above the correlate of protection in the vast majority of recipients [14].

Vaccine induced SBA titres are known to wane following immunisation in infancy, such that by 12 months of age fewer than 20% of children had SBA titres $\geq 1:5$ titres for two out of the four strains [18], with further waning by 24 months of age [19]. In both Phase 2 and 3 infant studies, following a booster dose at 12 months, the proportion of children reaching these titres against all strains increased to 93-100% [18,20], supporting the licensed recommendation for a booster dose in the second year of life. Despite this booster dose, by four years of age, SBA titres were consistently higher than controls only for 1 out of 4 reference MenB strains, regardless of whether the booster dose was administered at 12, 18 or 24 months of age [21]. A further booster dose at 4 years of age increased SBA titres to levels similar to, but no higher than, those observed after the toddler dose.

Recent immunogenicity data from a Phase IIIb multi-centre international study has demonstrated comparable immunogenicity between infants receiving a 2 dose (3.5 and 5 month) and 3 dose (2.5, 3.5 and 5 month) priming immunisation schedule [22], providing support for the reduced dose infant immunisation schedule adopted by the UK.

Predicted Coverage

It is not expected that 4CMenB, given it is based on variable outer-membrane proteins, would cover 100% of MenB bacteria. Due to antigenic variability and differing levels of protein expression on a given MenB strain, in addition to uncertainty surrounding the degree of cross reactivity of antibodies against heterologous MenB strain antigens, the predicted coverage offered by 4CMenB vaccine is difficult to estimate. Coverage of 4CMenB has been assessed using several methods including the meningococcal antigen typing system (MATS), Bexsero

Antigen Sequence Types (BAST) and using pooled sera from immunised children for testing against representative panels of hSBA strains.

MATS uses genotyping of PorA and a modified enzyme-linked immunosorbent assay (ELISA) to provide a strain-specific assessment of both the level of expression of target antigens (fHBP, NadA and NHBA), and their likely cross reactivity with antibodies induced by immunisation with 4CMenB. This ascertains whether the strain is 'covered' by 4CMenB [23]. Over 1000 meningococcal strains isolated across Europe were tested using MATS, which predicted that 78% of all meningococcal strains would be killed by sera from fully vaccinated children [24]. Data from England and Wales from 2014/15, just prior to the introduction of 4CMenB to the routine schedule, showed MATS predicted coverage of 66% [25], which had decreased from the 2007-2008 estimate of 73%. However, comparison of this result with bactericidal antibodies against a panel of representative MenB strains - where 88% of isolates were killed by hSBA, suggests MATS may underestimate coverage [26].

Both this hSBA panel and MATS rely on the assumption that pooled sera will reflect the average vaccination response from any chosen individual whose sera is within the pool. Support for this assumption was recently provided by Budroni et al, who suggested pooled-serum hSBA from vaccinated children in England and Wales accurately predicts individual hSBA titres [27].

An alternative approach, based on analysis of DNA sequences to determine the presence (or absence) of genes encoding the antigens found in 4CMenB has been used to generate a Bexsero antigen sequence type (BAST) for meningococcal isolates, potentially predictive of coverage of any individual isolate by 4CMenB. One of the advantages of BAST is that it is

more reproducible than MATS, however it does not provide information on antigen expression. Great Britain and Ireland isolates have shown a small number of BASTs which account for over a third of all invasive isolates, and with 4CMenB having a predicted a coverage of 66.1% of capsular group B isolates in 2010 – 2014, similar to predicted coverage estimated by MATS [28].

Use of 4CMenB in outbreaks and routine immunisation schedules

4CMenB has been used during MenB disease outbreaks pre- and post-licensure. Prior to its licensure in the US, the Food and Drug Administration (FDA) approved the use of 4CMenB under the expanded access Investigational New Drug (IND) regulation for students at Princeton University [29,30] and University of California at Santa Barbara [31] in 2013 during outbreaks. Following its approval in Canada, 4CMenB was also used in the Saguinay-Lac-Saint-Jean region of Quebec in 2014 for individuals aged 2 months to 20 years [32,33]. At Princeton University, with a two-dose vaccination series and 89.1% coverage, no cases of MenB disease occurred in those who received at least 1 dose of 4CMenB. However, there was relatively poor immunogenicity against the outbreak strain, with 33.9% of recipients of 2 doses having a hSBA titre of <4 to this strain [30].

Subsequent to its licensure, 4CMenB has been introduced for routine use in infants in the United Kingdom from September 2015 [34], in Ireland from December 2016 [35], and in certain regions of Italy since 2014 [36]. Other countries, including the Czech Republic [37] and Australia [38], have recommended routine immunisation in infants but not provided funding for this as part of the routine immunisation programme. In Australia, the most recent submission to the Australian Pharmaceutical Benefits Advisory Committee (PBAC) in July

2015 saw the vaccine rejected, for a third time, for inclusion for routine use as part of the national immunisation programme [39].

Beyond routine immunisation of infants, 4CMenB has received recommendations from vaccine advisory committees in the Czech Republic [37], France [40], Germany [41], the UK [34], the US [42] and Australia [38] for use in certain at risk populations (e.g. immunocompromised individuals, microbiologists) or in the event of an outbreak. 4CMenB has also been recommended for use in adolescents and young adults in the US [42] and Australia [38].

The UK was the first country to introduce 4CMenB to the infant routine immunisation schedule, with MenB (compared with other capsular groups) being responsible for the majority of IMD cases in infants and young children in the preceding years (see Figure 1) [43]. Following the licensure of 4CMenB by the European Medicines Agency (EMA) in early 2013, prolonged deliberations regarding cost-effectiveness eventually led to the UK Department of Health's Joint Committee on Vaccination and Immunisation (JCVI) recommending the introduction of the vaccine using a reduced dose schedule (vaccine administration at 2, 4 and 12 months of age) [44]. This campaign began on 1st September 2015 for all children born from 1st July 2015 onwards, combined with a limited catch up campaign for children born between this date and the 1st May 2015. Analysis of the effectiveness of the UK 4CMenB infant vaccination programme 10 months following its introduction is promising, with cases in vaccine-eligible infants halving in this period compared with previous years. There was a mean of 73.5 cases per year in the same time period in the years prior to the vaccine programme (2011 – 2015) and just 37 cases in the 10 month vaccination period studied [45]. The data shows a vaccine uptake of 88.6% for eligible

infants receiving at least 2 doses of the vaccine by 6 months of age. Vaccine effectiveness evaluated by the screening method (using Public Health England (PHE) surveillance data for confirmed MenB cases) is estimated at 82.9% (95% CI 24.1% to 95.2%), and assuming 88% of MenB strains are covered by 4CMenB, a vaccine effectiveness against vaccine-preventable strains of 94.2% [45].

Further modelling studies have investigated the cost-effectiveness of catch-up vaccine programmes for older children in the UK [46]. Offering a catch-up vaccination programme for children in their second year of life could be cost effective if a vaccine price of \leq £8 were used, however a campaign including 3 to 4 years olds would not be cost effective at any vaccine price.

Reactogenicity

4CMenB has been found to have an acceptable reactogenicity profile in regard to local and systemic reactions, with most attention focused on fever rates following 4CMenB when given concomitantly with routine vaccines. Pre-licensure studies have also highlighted irritability in young children (experienced by 70 - 80% of infants and pre-schoolers), and headache and malaise in adolescents [14]. Rare events have been reported that have been considered possibly related to 4CMenB immunisation, including seizures and Kawasaki disease; the relationship of these conditions with 4CMenB immunisation will be further delineated in post-licensure surveillance.

With regard to post-immunisation fever, 51-61% of infants in the Phase IIB study reported fever of \geq 38°C following administration of both 4CMenB and routine immunisations

together, compared with 23 – 36% of infants given the routine immunisations alone [47]. The impact of increased fever rates on acceptability of the vaccine and frequency of medical service attendances led to exploration of the effect of prophylactic paracetamol use to prevent fever post-vaccination. Results demonstrated a reduction in fever rates without any clinically relevant effect on immunogenicity when paracetamol was given routinely at the time of vaccination, and 2 further doses in the 24 hours following vaccination [48]. Based on these results, PHE recommend 3 doses of paracetamol within 24 hours following the 2 and 4 month immunisations when 4CMenB is administered to infants in the UK.

Surveillance data following the introduction of 4CMenB to the routine schedule in the UK however has since shown an increase in accident and emergency department attendances for fever post-immunisation [49]. Syndromic surveillance data has also been utilised to assess GP fever consultation rates in children eligible for 4CMenB doses in the first three months of vaccination programme compared with the previous 5 years [50]. The average daily fever consultation rate was 2.52 times higher (95% CI 1.32 – 4.71) in children 7-10 weeks of age and 1.16 times higher (95% CI 0.46 – 2.6) in children 15 – 18 weeks of age. Other age groups also demonstrated an increase in number (although to a lesser degree) of consultations for fever during this period, and analysis is underway to explore these findings further over an extended period.

Impact on carriage

It remains uncertain as to whether routine use of 4CMenB will affect nasopharyngeal meningococcal carriage and therefore potentially induce herd immunity. This is particularly relevant in adolescents where carriage rates are highest [51] and immunisation campaigns

targeting only infants (such as in the UK) are unlikely to generate herd protection given low rates of carriage in this population. Given the impact of herd immunity on cost effectiveness evaluations, JCVI have advised that a targeted study should be undertaken to evaluate the potential impact of 4CMenB on the acquisition of meningococcal carriage in adolescents [44]. One such study is underway in South Australia [52], while another is planned for the United Kingdom [53], and the results of these will be crucial to informing a possible adolescent 4CMenB programme in the UK.

In the absence of such data, knowledge about the impact on carriage comes from a randomised study on the effect of 4CMenB on meningococci carriage when administered to 18-24 year old university students in the UK [54]. This study demonstrated an 18.2% reduction in the rates of carriage of any meningococcal strain compared to control vaccine from 3 months after the vaccination course, however no significant effect on the carriage of MenB strains alone. The relationship between pre- and post-vaccination hSBA titres and carriage was explored in a subset of this same cohort of university students and differences between those who had or had not received prior MenC vaccination as young children [55]. This study reported higher rates of carriage of capsular group B, C and Y meningococci in subjects with protective hSBA titres at baseline, and no correlation between post-vaccination hSBA titres and carriage of disease-associated capsular meningococcal groups.

Of relevance to the effect of 4CMenB on carriage is the final case of MenB disease in the outbreak affecting Princeton University, which occurred in an unvaccinated student from another college in social contact with vaccinated students from Princeton. [29]. This apparent onward transmission by students immunised with 4CMenB does not in itself suggest that immunisation with 4CMenB would not impact on meningococcal carriage at a population

level, as such effects generally occur through the prevention of new acquisitions of meningococci, rather than the elimination of strains already being carried at the time of immunisation.

Protection against non-B capsular groups

The immunogenic components used in 4CMenB are based on proteins commonly expressed on MenB strains, however they are also expressed by strains from non-B capsular groups, allowing the possibility that 4CMenB could induce antibodies protective against multiple capsular groups. This is particularly important given the increasing rates of non-B meningococci responsible for invasive disease in certain parts of the world, including meningococcal capsular groups W and X.

Capsular group W meningococcal (MenW) disease accounts for an increasing number of invasive meningococcal disease (IMD) globally, secondary to the emergence of the hyperinvasive ST-11 clonal complex (cc11), associated with high case fatality rates [56,57]. A recent study has shown that post-immunisation sera from 4CMenB vaccinated infants is able to kill this hyperinvasive strain, most likely due to cross-reactive antibodies induced by 4CMenB. This is consistent with the reduction in the number of MenW cases in infants vaccinated with 4CMenB in 2015-2016 in England [58]. Antibodies induced by the 4CMenB NadA variant are highly cross-reactive with the NadA alleles possessed by the hypervirulent MenW cc11 circulating in the UK. The NHBA peptide allele possessed by this strain, differing by a single nucleotide, may also have the potential to be targeted by cross-protective antibodies induced by 4CMenB [59]. Hence, there is particular importance in surveillance

studies in countries with routine 4CMenB use focusing on the impact of the vaccine on
invasive disease caused by MenW.

Similar work has been performed concentrating on cross-protection from antibodies induced
by 4CMenB against capsular group X meningococcus (MenX), a meningococcal isolate
emerging in countries of the meningitis belt in Africa. Bactericidal assays against nine MenX
isolates using pooled-sera from individuals vaccinated with 4CMenB suggested that the
isolates would be covered by 4CMenB vaccination [60].

Bivalent rLP2086 (Trumenba®)

In the pursuit to develop a vaccine against multiple meningococcal B strains, a bivalent
vaccine (Bivalent rLP2086) was developed and licensed in the US in 2014 for individuals 10-
25 years old, similar ages to those for 4CMenB in this country. This vaccine comprises of 2
fHbp variants, one from each of fHbp subfamilies A and B. These proteins contain a lipid tail
(differing from the structure of fHbp included in 4CMenB), which aids in inducing a robust
immune response [61].

Phase II and III studies demonstrate an immunogenic profile for Bivalent rLP2086. Through
testing hSBA titres against 4 meningococcal B strains (each expressing heterologous fHbp
variants) which are prevalent in the US, phase II studies showed > 80% of adolescent
participants reached hSBA titres of $\geq 1:8$ for both A and B subfamily strains [61]. More
recent data demonstrates over 50% of participants in one trial sustaining hSBA titres for at
least 4 years following 3 doses of Bivalent rLP2086, in 3 out of 4 strains tested [62].

To investigate the breadth of MenB strain coverage elicited by bivalent rLP2086, individual sera from adolescents and young adults was tested against 27 MenB strains prevalent across the US and Europe (including 14 different fHbp variants, estimated to account for 80% of MenB invasive isolates) [63]. After three doses of bivalent rLP2086 more than 75% of individuals had hSBA titres $\geq 1:8$ for all MenB strains tested, reflecting induction of a robust immune response and broad strain coverage.

Reactogenicity and tolerability of Bivalent rLP2086 has been evaluated in children, adolescents and young adults. Most recently, a large, randomised controlled study enrolling over 5000 participants aged 10 to 26 years old demonstrated Bivalent rLP2086 to have an acceptable adverse event profile, consistent with phase I and II studies. Of note is that an infant clinical trial of a precursor to Bivalent rLP2086 was terminated early due to the rates of fever following vaccination, with 64% of infants developing fever who received the lower dose of 20ug of this vaccine, and 90% of infants receiving the increased 60ug dose, compared to 29% of controls [64].

Bivalent rLP2086 was accepted for accelerated approval from the FDA in the US, and following this, the American Academy of Pediatrics, in agreement with the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, recommends the vaccine be administered to individuals aged 16 to 23 years of age to provide ‘short-term protection against most strains of serogroup B meningococcal disease (category B recommendation)’ [65]. Bivalent rLP2086 can be given as either a three dose or two dose course (see Table 2 for current licensed schedule)[66]. In the US, Bivalent rLP2086 is also recommended for children at increased risk for meningococcal disease, including certain immunocompromised individuals and microbiologists. In May 2017 Bivalent rLP2086

received marketing authorisation from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP), for its use in individuals 10 years and older as either a two or three dose course [67].

Bivalent rLP2086 was used during a meningococcal B disease college outbreak in Rhode Island, US, in 2015, in which three doses of Bivalent rLP2086 were given to college students. Alongside this a study conducting four cross sectional surveys of meningococcal carriage was conducted. While this reported no impact of vaccination on carriage of either all meningococcal capsular groups or MenB alone, only 615 students were sampled on multiple occasions and the rates of completion of a full immunisation course were low (27%), making it difficult to draw any firm conclusions from these data [68].

Conclusion

The significant morbidity and mortality associated with invasive meningococcal disease has provided the impetus to license the novel MenB vaccines without direct evidence of their effectiveness, instead inferring this from clinical trial immunogenicity data. The promising preliminary results for effectiveness of 4CMenB routine use in infants in the UK support this approach and offer the hope that these vaccines will successfully reduce the global burden of invasive meningococcal disease. Ongoing enhanced surveillance to better understand the impact of these MenB vaccines at an individual and population level is crucial to informing how they can best be used to reduce the incidence of this devastating illness.

Conflicts of interest

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350 Dr Snape has been an Investigator on clinical trials of capsular group B vaccines sponsored
351 and funded by Glaxosmithkline and Pfizer, as well as vaccine clinical trials funded and
352 sponsored by Medimmune and Janssen. These activities are conducted on behalf of the
353 University of Oxford and Dr Snape receives no personal financial benefit. Dr Snape has had
354 travel and accommodation expenses paid for attendance at Internaional paediatric infectious
355 diseases conferences paid for by vaccine manufacturers including Glaxosmithkline and
356 Pfizer.

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Figure 1. Laboratory confirmed cases of invasive meningococcal disease in England by quarter a) < 1 year olds; b) 1-4 year olds. Adapted from Public Health England Invasive Meningococcal Disease reports [43]

