

## **Group B meningococcal vaccine science and policy**

Simon B Drysdale<sup>1</sup>, Andrew J Pollard<sup>1</sup>

<sup>1</sup>Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Oxford Biomedical Research Centre, Level 2, Children's Hospital, Oxford OX3 9DU, United Kingdom

Dr Simon B Drysdale

E mail: [simon.drysdale@paediatrics.ox.ac.uk](mailto:simon.drysdale@paediatrics.ox.ac.uk)

Tel: +44 (0)1865 226953

Corresponding author: Professor Andrew J Pollard

Email: [andrew.pollard@paediatrics.ox.ac.uk](mailto:andrew.pollard@paediatrics.ox.ac.uk)

Tel : +44 (0)1865 234226

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## **Abstract**

Capsular group B *Neisseria meningitidis* is one of the leading causes of death in developed countries. A new vaccine (4CMenB) has recently been developed which was found to have an acceptable safety profile in clinical studies and to be immunogenic. This review examines the evidence supporting the licensure of the 4CMenB vaccine and discusses recommendations for its use.

## Background

Invasive meningococcal disease causes much mortality and morbidity with an estimated 500,000 cases per year worldwide and 800 laboratory confirmed cases in the UK in the epidemiological year 2012/13 (1). Infection caused by *Neisseria meningitidis* is characterised by one of two clinical syndromes; the majority of children present with meningitis, which is rarely associated with life-threatening raised intracranial pressure and 7-10% present with the most severe septicaemic form of the disease with shock (2). The two syndromes occur together in about 40% (2). A meta-analysis of 45 paediatric studies investigating acute bacterial meningitis observed a mortality of 7.5% caused by *N. meningitidis* compared with 3.8% with *Haemophilus influenzae* and 15.3% with *Streptococcus pneumoniae* (3). The mean probabilities of other sequelae caused by *N. meningitis* were: deafness, 6.4%; “mental retardation”, 2.1%; spasticity and/or paresis, 2.1%; a seizure disorder, 1.4%; and no detectable sequelae, 90.0% (3).

*N. meningitidis* is a Gram-negative organism which is usually diplococcal in form. When isolated from blood and cerebrospinal fluid (CSF) it is encapsulated, rendering it resistant to antibody/complement-mediated killing and inhibiting phagocytosis. The capsule incorporates sialic acids and lipopolysaccharides which increase immune evasion as sialic acids are commonly found on host cell membranes (4). The capsular group B (MenB) meningococcal organism expresses an  $\alpha(2-8)$ -linked sialic acid homopolymer which is structurally identical to sugars decorating human foetal neural cell-adhesion molecule, which is essential for the functional plasticity of the central and peripheral nervous systems (4). This similarity between host and organism cell-

surface molecules partly explains the poor immune response generated against the MenB capsule by humans (5). Although vaccines against some meningococcal capsular groups (including A, C, Y, W) have been in widespread use for several years (6), vaccines against MenB have been difficult to develop, but this situation changed with the licensure of 4CMenB in the European Commission in January 2013. The potential impact of 4CMenB is difficult to estimate without widespread use (see later) but experience with the capsular group C meningococcal (MenC) vaccine, which has been part of the routine vaccine schedule in England and Wales since 1999, has provided some important insights into the variables that are likely to be important in evaluating 4CMenB vaccine effectiveness and cost-effectiveness.

### **Capsular group C meningococcal vaccine**

Since the MenC vaccine was introduced in England and Wales in 1999 there has been a sharp decline in the number of laboratory confirmed reports of invasive MenC disease in children; 815 cases reported in 1998 and only 29 in 2013 (7). Other countries have found a similar decline with no reported cases of MenC in vaccinated, immunocompetent individuals in The Netherlands since the introduction of the vaccination programme in 2001 (8). Various studies (9–18) have shown that direct protection through antibody and indirect protection through herd immunity are required for protection against invasive meningococcal disease. Matsunami and Kolmer (9–11) demonstrated that resistance to *N. meningitidis* was related to the bactericidal activity of whole blood and also that the bactericidal activity of serum from children against *N. meningitidis* was less than the activity of adult serum. Heist *et al* (12) found that isolates of *N. meningitidis* from pharyngeal carriers were “killed

by the whole blood of most men” whereas those isolates from the CSF of patients with invasive strains of *N. meningitidis* were not killed. In the 1960s Goldschneider and others (13) prospectively followed army recruits to investigate immune protection against *N. meningitidis*. Serum was taken at recruitment and again if they developed *N. meningitidis* infection. Of the 54 recruits with sera at baseline and at infection, only 5.6% of cases had baseline sera that had bactericidal activity against *N. meningitidis* in dilutions of 1:4 compared with 82% of controls. Further work indicated that the sera of the cases was deficient in antibodies to homologous and heterologous strains of pathogenic meningococci as determined by serum bactericidal activity and indirect immunofluorescence (13). More recent work has demonstrated that levels of bactericidal antibody correlate with vaccine effectiveness. The observed vaccine efficacy of the MenC vaccine in one study waned from around 95% within one to 11 months of vaccination to around 30% by 36 – 56 months after vaccination in young children (14) but waning was much less in those immunised later in childhood (19).

The MenC vaccine has also been shown to protect via herd immunity. Since the introduction of the MenC vaccine in England and Wales in 1999 there has been a significant drop in cases of invasive MenC in children and adolescents (from 695 cases in the epidemiological year 1998/9 to nine cases in 2012/13) but also in older adults ( $\geq 20$  years old) who have not been vaccinated (from 238 cases in the epidemiological year 1998/9 to 24 cases in 2012/13) (15,20), suggesting the MenC vaccine reduces carriage of MenC. A large systematic review and meta-analysis of studies undertaken before vaccine use, demonstrated that MenC carriage prevalence increased through childhood from 4.5% in infants to a peak of 23.7% in 19-year olds

and subsequently decreased in adulthood to 7·8% in 50-year olds (16). Therefore in countries with booster or catch up programmes for adolescents (e.g. the UK, the Netherlands and Canada) the effect of herd immunity is likely to be greatest (17,18).

Overall, the MenC vaccine has resulted in a significant drop in the number of cases of invasive MenC disease due to direct protection with high antibody levels and herd immunity. There is, however, a need for MenC vaccine boosters in adolescence to maintain protection, which have been introduced in many countries.

### **Capsular group B Meningococcal vaccine**

The serological classification of *N. meningitidis* is based on the capsule, outer membrane proteins PorA and PorB and lipopolysaccharides (21). Other surface expressed and immunogenic bacterial proteins have been identified from the bacterial genome and include factor H binding protein (fHbp), neisserial adhesion A (NadA) and neisserial heparin binding antigen (NHBA) which are targets of the 4CMenB vaccine (22). There are several hundred PorA genotypes among capsular group B meningococcal isolates (23) and thus it has not been possible to develop a vaccine that covers all of these, though most disease is caused by a handful of these PorA types. An outer membrane vesicle (OMV) strain-specific vaccine against MenB was developed for use in New Zealand following a meningococcal epidemic that started in 1991. Sixty one percent of isolates were capsular group B at the start of the epidemic and peaked at 94% of isolates in 2000. The dominant serotype accounted for 86% of serogroup B isolates from 1990 to 2003 (24). A vaccine (MeNZB™) (Chiron vaccines, Siena, Italy) was found to be safe and immunogenic with 75% of children

(16-24 months) who received three doses of the vaccine administered at 0, 6 and 12 weeks developing serum bactericidal antibody titres  $\geq 1:4$  compared with only 6% in the control MenB vaccine group (MenBvac<sup>TM</sup>, NIPH, Norway), which covered a different genotype (24). MenNZB<sup>TM</sup> elicited the strongest responses only against disease caused by bacteria sharing the same serosubtype (P1.4) as the New Zealand MenB strain and thus provides more limited coverage in other settings. The complete genome of *N. meningitidis* serogroup B was sequenced in 2000 and it contains over two thousand genes of which 53% have been assigned a biological role, suggesting several candidates for the development of a vaccine that could protect against more MenB strains (25).

The 4CMenB vaccine is composed of four components: the New Zealand vaccine (an outer membrane vesicle containing the PorA serosubtype P1.4) combined with NadA and the recombinant proteins NHBA-GNA1030 and fHbp-GNA2091 (22). The gene for fHbp is present in all invasive meningococci and appears to be essential for the survival of meningococci in blood. It allows the evasion of the human immune system by binding complement factor H and preventing the activation of the complement system. It consists of two or three families (26) and 4CMenB contains a variant from one of these families, which is the most prevalent. NadA helps adhesion of meningococcus to the nasopharyngeal epithelium. The genes coding for NadA are present in approx 50% of invasive meningococci and there are five variants (27,28). NHBA (GNA 2132) binds heparin and is also thought to have a role in helping meningococci evade complement-mediated killing. It is classified into 12 variants with genes coding for GNA 2132 found on almost all invasive meningococci as well

as non-pathogenic meningococci species. Peptide 2, the most common NHBA allele, is incorporated in the 4CMenB vaccine (22).

### **How effective will 4CMenB be?**

Because it is not possible to conduct large studies on the effectiveness of the vaccine in the UK prior to its implementation due to the small number of children that develop MenB disease, it is difficult to predict how effective 4CMenB will be. Effectiveness studies have been carried out for one component of the vaccine (the OMV) but there are no effectiveness data for the other components. Data from the New Zealand Ministry of Health (29) demonstrated the OMV vaccine had an overall effectiveness of 73% against the specific strain it was developed to prevent. In the absence of an efficacy trial, an alternative method to assess the predicted efficacy of a vaccine is the use of the serum bactericidal antibody (SBA) assay. Previous studies with the MenC vaccine and for OMV vaccines have demonstrated the validity of this method (18,30). 4CMenB was found to be immunogenic against MenB strains expressing homologous or related NadA and fHbp and strains expressing homologous PorA, with over 90% of infants having SBA titres  $\geq 1:4$  after four doses of the vaccine at 12 months of age (31). Although the SBA assay informs about the *in vitro* capacity of a vaccinee's blood to kill individual strains of meningococci it does not inform about the antibody response of individual components of the vaccine or, more importantly, against the wide range of bacteria causing disease in a population. The meningococcal antigen typing system (MATS) is an ELISA-based method which quantitates whether vaccine antigens on the surface of meningococci are detected by sera from vaccinees (32), therefore, combining these data with PCR sequencing of the PorA gene provides



insight into the potential coverage of strains by 4CMenB. Using this technique Vogel *et al* (33) predicted that 78% (95% CI 63-90%) of all MenB strains isolated in the 2007/08 epidemiological year in several countries in Europe would be killed by serum from recipients of the 4CMenB vaccine, thus potentially protecting against a significant proportion of invasive MenB strains isolated in Europe.

### **The safety of 4CMenB**

Vesikari *et al* (34) investigated the safety of the 4CMenB vaccine given to 2478 infants at 2, 4 and 6 months of age along with other routine vaccines compared to those who received only routine vaccines (diphtheria, tetanus and acellular pertussis, inactivated poliovirus, *Haemophilus influenzae* type b and hepatitis B). Some infants also received a booster dose of 4CMenB at 12 months of age. Overall there was increased reactogenicity in the recipients of the 4CMenB vaccine compared with those who received only routine vaccines. Local reactions were more common in the infants who received the 4CMenB vaccine at two, four and six months of age; 87% had tenderness (29% severe tenderness), 83% erythema, 77% induration and 47% swelling at the injection site compared with 59% (8% severe), 71%, 64% and 34% respectively in those who received only routine vaccines (34). Systemic reactions were also more frequently seen in those infants who received the 4CMenB vaccine. 77% of infants had a fever  $\geq 38.5^{\circ}\text{C}$  after any dose of the 4CMenB vaccine compared to 45% in those who received only routine vaccines (DTaP). As a consequence there was also an increase in the use of antipyretics in the 4CMenB group (93% versus 71%). There was, however, no increase in infants requiring medical attention for the fever in the 4CMenB group (2% for both groups). Other systemic reactions with an

increased rate in the 4CMenB group were change in eating habits (72% versus 50%), sleepiness (87% versus 72%), vomiting (27% versus 16%), diarrhoea (44% versus 33%), irritability (93% versus 83%), unusual crying (85% versus 64%) and rash (13% versus 12%) (34). The rates of both local and systemic reactions were lower for those infants receiving a booster dose of 4CMenB at 12 months of age compared to the primary schedule and at 12 months of age reaction rates were similar between those infants receiving 4CMenB and those receiving a routine vaccine (MenC vaccine) (34).

Another study (35) also showed increased reactogenicity in infants receiving the 4CMenB vaccine with routine vaccines (diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, *Haemophilus influenzae* type b and a 7-valent pneumococcal glycoconjugate vaccine) compared with infants receiving only routine vaccines. Increased reactogenicity was noted irrespective of whether the infants' received the 4CMenB vaccine at ages 2, 4, and 6 months together with routine infant vaccines; at 2, 4, and 6 months with routine vaccines given separately at 3, 5, and 7 months; or at 2, 3, and 4 months together with routine infant vaccines. Fever  $\geq 38.0^{\circ}\text{C}$  was described in 71-80% of the infants receiving 4CMenB in each schedule compared with 51% in the routine vaccine only group. Over the course of the whole study 166 serious adverse events were reported although only 20 were thought to be possibly related to the 4CMenB or routine vaccines (six infants required hospitalisation for observation for fever, four infants had seizures, two infants had a hypotonic hyporesponsive episode and there was one case of each of Kawasaki disease, aseptic meningitis, retinal dystrophy (likely congenital), transient synovitis of the hip, transient hearing loss and transient apnoea) (35).

## **The UK cost-effectiveness of 4CMenB**

Currently, the cost-effectiveness threshold in the UK is set at £20,000–30,000 per quality-adjusted life year. The cost-effectiveness of a vaccine is dependent on several variables including the price per dose of the vaccine and therefore number of doses given, disease incidence, strain coverage, quality of life losses, duration of protection from the vaccine, herd immunity and the discounting rate used. In England and Wales between 2003/4 and 2012/3 the incidence of invasive meningococcal disease reduced from approximately 55 cases per 100,000 infants (less than one year of age) to approximately 25 cases per 100,000 and to less than two cases per 100,000 people across all age groups (36). In the epidemiological year 2012/13 there were 621 laboratory confirmed cases of MenB infection (37). Data from the English National Health Service (NHS) Hospital Episode Statistics (HES) dataset demonstrated a similar recent reduction in invasive meningococcal disease (all serogroups) from a peak of 27 per 100,000 children (less than 16 years of age) in 1999 to nine per 100,000 in 2011 (38). There are few data on the duration of protection from the 4CMenB vaccine. Among children in one study (39) who received 4CMenB at 2, 4, 6 and 12 months of age, by 40 months of age the proportions with human complement serum bactericidal activity (hSBA) titres  $\geq 1:4$  were 65% for strain 44/76- SL (fHbp), 76% for strain 5/99 (NadA) and 41% for strain NZ98/254. These proportions represented a decline from 13 months of age (100%, 93% and 96%, respectively) (39). Another study (40) of adolescents (11-17 years old) demonstrated that one month after one 4CMenB dose, 93% of subjects had seroprotective hSBA titres ( $\geq 1:4$ ) against indicator serogroup B strains for individual vaccine antigens (fHbp, NadA and NZOMV) rising to 100% after two or three doses. After 18-24 months 62-73% of

subjects given one dose had titres  $\geq 1:4$  against the three antigens rising to 77-94% after two or 86-97% after three doses (40). Whether 4CMenB can protect against carriage of MenB is unknown and therefore there is no known target percentage of people that need to be vaccinated to achieve herd immunity. A study of almost 3000 English university students demonstrated that the 4CMenB vaccine resulted in a reduction in carriage of all capsular groups of *N. meningitidis* combined, although not specifically capsular group B, compared with students receiving a control vaccine (Japanese encephalitis), suggesting transmission of MenB could be affected somewhat by implementation of a national 4CMenB vaccination programme (41).

An economic modelling study by Christensen et al (42) demonstrated that a MenB vaccine could be cost effective. It was noted that introducing a MenB vaccine into the routine infant schedule which provides direct protection only could prevent 27% of meningococcal cases per birth cohort and this could be cost effective at £9 per vaccine dose. If the vaccine also reduced MenB carriage, including the MenB vaccine in routine infant vaccination with a catch-up programme, could reduce annual cases by 71% after ten years and would be cost effective at £17 per dose (42). Further refinement of these models was undertaken for policy development and will be published shortly.

The 4CMenB vaccine has been licensed for use in Europe, Australia and Canada and has been recommended for use in Australia (in private schemes), in some regions of Quebec, Canada, and in some regions of Germany, Ireland, Italy, Poland and the Czech Republic. It has already been used to control two MenB outbreaks at Princeton University and The University of California, Santa Barbara in the USA (43). In the

UK after much consideration the Joint Committee on Vaccination and Immunisation (JCVI) assessed the vaccine to be cost-effective for infants if a low price could be obtained and recommended it as part of the NHS immunisation schedule at 2, 4 and 12 months of age with an expected implementation date in the UK of late 2015.

## **Conclusion**

In summary, MenB is the leading paediatric cause of mortality in many developed countries. Initial studies have suggested 4CMenB is immunogenic and safe, though associated with fever and local reactions, but until its use is widely implemented there remains uncertainty about the breadth of protection and the scale of the impact it will have. It has, however, the potential to radically reduce the impact of one of parent's most feared illnesses.

Conflict of interest statement: AJP has previously conducted clinical trials of MenB vaccines on behalf of Oxford University which have been funded by Novartis, Pfizer, EC FP7 programme and the Wellcome Trust, but he does not receive any personal reimbursement from them. AJP is chair of the Department of Health's (DH) Joint Committee on Vaccination and Immunisation (JCVI) but the reviews expressed herein do not necessarily represent those of DH or JCVI.

SBD has no conflicts of interest to declare.

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