

The Capsular group B Meningococcal Vaccine, 4CMenB: Clinical Experience and Potential Efficacy

Christine S. Rollier, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE, UK

PhD, Post-doctoral research associate, Meningococcal projects, Oxford Martin fellow and Jenner Institute Investigator

Christina Dold, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE, UK

PhD, Post-doctoral fellow, Meningococcal projects

Leanne Marsay, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE, UK

PhD, Post-doctoral fellow, Meningococcal projects

Manish Sadarangani, Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE, UK

BM BCh MRCPCH DPhil, Clinical Lecturer in Paediatric Infectious Diseases and Immunology

Andrew J Pollard* Oxford Vaccine Group, Department of Paediatrics, University of Oxford, and the NIHR Biomedical Research Centre, Churchill Hospital, Oxford, OX3 7LE, UK

MRCP FRCPCH PhD, Professor of Paediatric Infection and Immunity, director Oxford Vaccine Group

***Corresponding author:** Tel +44 (0)1865 234226

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Abstract

Introduction. Capsular group B meningococcal disease is a leading cause of childhood meningitis and septicaemia. Up to 10% of sufferers die, and sequelae remain in more than 30% of survivors. A vaccine, 4CMenB, designed with the aim to induce broad coverage against this highly variable bacterium, has been licensed in countries including in the European Union, Canada and Australia.

Areas covered. Immunogenicity and safety data, published in peer-reviewed literature between 2004 and 2014, are presented in the context of the recent recommendation for the use of the vaccine in infants in the UK.

Expert opinion. 4CMenB induces significant reactogenicity when administered with routine infant vaccines, in particular with respect to fever rates. Fevers can be somewhat reduced using paracetamol. The efficacy of the vaccine is unknown but has been extrapolated from effectiveness data obtained from use of one of its components in New Zealand, immunogenicity data from clinical trials and estimation of coverage from *in vitro* studies. These data suggest that the vaccine will prevent a proportion of invasive meningococcal disease cases in infants and young children. Implementation and well-planned post-marketing surveillance will address uncertainties over field effectiveness.

Keywords: Four component meningococcal group B vaccine (4CMenB), Meningococcal disease, Outer membrane vesicles, Recombinant proteins, capsular group B meningococcus, Vaccine

1. Introduction

Neisseria meningitidis causes approximately 500,000 cases of meningococcal meningitis and septicaemia globally every year, with a peak incidence in children under 2 years^{1, 2}. Adverse outcomes are common, with a case-fatality rate of 10% in resource-rich settings, and 30% of survivors suffer severe long-term disability including deafness, amputation and cognitive impairment¹. The case-fatality rate has not decreased significantly since the 1950s³, despite advances in medical care and increased education of the public and healthcare professionals. Vaccination is the optimal way to reduce the mortality and morbidity from this disease. The organism is categorised into groups on the basis of its polysaccharide capsule, with most disease caused by groups A, B, C, W, X and Y⁴. There are currently effective polysaccharide-protein conjugate vaccines available against capsular groups A, C, W and Y organisms, which are used in Europe (group C vaccine), North America (group C and groups ACWY vaccines) and Australia⁵. The majority of disease in Europe, Australia and Canada is now therefore caused by capsular group B strains (MenB, 85-90% of cases in the UK)⁵. The capsular group B polysaccharide consists of a polysialic acid, which is poorly immunogenic because it is identical to polysialic acid found on foetal brain tissue⁶. Effective vaccines based on outer membrane vesicles (OMVs) have been used to tackle strain-specific epidemics in Cuba, New Zealand and a hyper-endemic outbreak in France⁷. OMVs are produced naturally by *N. meningitidis*, and contain the outer membrane components, including the protective but strain-specific and highly variable antigen porin A (PorA)⁷. The efficacy of these vaccines was largely restricted to the vaccine strain and provided only a limited degree of cross-protection against strains containing heterologous PorA variants in older individuals but not in infants⁷. Such vaccines would be unlikely to provide broad protection in countries with endemic disease and a wide range of circulating group B strains, such as the UK, but are more suited to the outbreak situations in which they have been used⁷. There is therefore a need for a MenB vaccine with a potential for broad-spectrum coverage, i.e. the ability to protect against a wide range of circulating strains. 4CMenB has been developed with this aim, and has the

additional advantage that inclusion of multiple antigens not only increases breadth of coverage but reduces the likelihood that an organism can escape from vaccine-induced immunity by variation of a single antigen. It has now been licensed in several countries including in the European Union, Australia and Canada⁴. A regional campaign has started in 2014 in Québec's Saguenay-Lac-Saint-Jean region, where 4CMenB is being offered to individuals from 2 months to 20 years of age⁸. In March 2014 the UK Joint Committee on Vaccination and Immunisation (JCVI), which reports to the UK Department of Health, made a recommendation based on cost-effectiveness that the vaccine should be included as part of the UK routine immunisation schedule, given to children at 2, 4 and 12 months of age⁹.

2. Overview of the market

Invasive meningococcal disease is rare, and the average incidence in the UK has been decreasing in the past decade (on average 1.8/100,000 per year in the period 2006-2012⁴). In the US, there is currently an even lower rate of disease, with 0.15 cases per 100,000 reported in the year 2012¹⁰. However, recent outbreaks at Universities in Ohio, New Jersey and California underline the potential use of a MenB vaccine in the USA¹¹, and 4CMenB is currently being used in two of these universities under a treatment Investigational New Drug designation in an effort to control these outbreaks. The highest MenB incidence is observed in infants, peaking around 5 months of age, and a second smaller peak is observed at around 18 years¹². Therefore, young children and adolescents, being at most risk, are the primary target for vaccination in the countries where prevalence of MenB is 1-2 cases per 100,000 (Europe, Canada and the South-American countries)^{13, 14}.

In some countries, cost-effectiveness is not a major part of the process for adoption of a new vaccine programme but in others, such as the UK, cost-effectiveness analysis is a key issue⁴. Calculating the cost-effectiveness is hampered by the limited or absent data on costs to the health service, vaccine efficacy and duration of protection¹⁵. Several models were used to estimate the cost-effectiveness of 4CMenB (evaluating scenarios for both adolescent and/or infant programmes); A scenario involving

an infant 3-dose immunization program, assuming 95% efficacy, 88% strain coverage and 36 month duration of protection was predicted to be cost-effective in the UK^{16, 17}. Conversely, in The Netherlands, where the rate of disease is lower than in the UK, 4CMenB was deemed not cost-effective¹⁸.

Another vaccine with a potential for broad protection is in clinical development: a MenABCWY meningococcal vaccine combining 4CMenB with the MenACWY conjugate vaccine, is currently in phase II clinical trials¹⁹. This vaccine is thus designed to induce protection against the majority of invasive disease-causing strains worldwide. Several countries are only using monovalent MenC or MenA vaccines as a result of local epidemiological data (e.g. MenA is the predominant cause of disease in subSaharan Africa), while others already have established routine programmes containing MenACWY⁵. The United States Food and Drug Administration (FDA) has granted “Breakthrough Therapy” designation to both this vaccine candidate and to 4CMenB, thus allowing fast track development program features and intensive FDA guidance. Another MenB vaccine designed to induce broad protection has been developed for adolescents²⁰. It contains two variants of the outer membrane lipoprotein factor H binding protein (FHbp, also referred as rLP2086 in this vaccine) and has been approved by the FDA in October 2014 to prevent invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B in individuals 10 through 25 years of age.

3. Composition of 4CMenB.

4CMenB contains 4 components, three of which are recombinant outer membrane proteins: *Neisseria* adhesin A (NadA) group I, FHbp variant 1.1 and *Neisseria* heparin binding antigen (NHBA) variant 24. NHBA and FHbp are fused to two other outer membrane proteins GNA1030 and GNA2091 respectively. The fourth component is OMVs derived from the New Zealand epidemic strain NZ98/254, chemically detoxified (MeNZB), ²¹. Every dose contains 50µg each of NadA, FHbp-

GNA2091 and NHBA-GNA1030 in addition to 25µg of OMVs. The vaccine is formulated with 1.5mg Al(OH)₃ in 10 mM histidine buffer containing 110–120 mM saline.

4. Safety and tolerability.

4.1 Fever rates in infants

4CMenB has been administered to over 7500 infants, children, adolescents and adults (Table 1). Fever rates ($\geq 38^{\circ}\text{C}$) of 26-41% are reported when 4CMenB is administered alone to 2 months old infants, which is not significantly higher than MeNZB (16-37% in infants 6 to 10 weeks of age and 9-11% in 16 to 24 month old toddlers) ²¹⁻²⁴. However, most use of the vaccine will be in the context of concomitant administration with routine vaccines, which increases the risk of systemic reactions substantially^{22, 25}: incidence rates of fever were 51-61% ($\geq 38^{\circ}\text{C}$) in phase IIb, and 65.3% ($\geq 38.5^{\circ}\text{C}$) in phase III, compared to 23-36% and 32.2% respectively for routine vaccines alone, though the fevers generally resolved within 2 days (Table 2)^{22, 25}. This effect was less pronounced in earlier phase II trials ^{26, 27}. Prophylactic paracetamol is recommended by the JCVI for infants receiving the combination of 4CMenB and routine infant vaccines (upon vaccination and a further 2 doses 4 to 6 hours apart): a Phase II trial showed no clinically significant effects of the paracetamol on the immune responses to the vaccines²⁸. Incidence of fever $\geq 38.5^{\circ}\text{C}$ after the primary dose of 4CMenB with routine vaccines decreased to 39% from 70% when paracetamol was used as compared to 27% in infants receiving routine vaccines with MenC without paracetamol²⁸.

4.2 Systemic effects in adolescents/adults

Headaches were reported by 42% of adolescents following 4CMenB immunisation compared with 27% in those receiving a placebo ²⁹. These rates are high in comparison to those reported for human papilloma virus (HPV) vaccine in adolescent, 9.2% and 10.6% in the vaccine and placebo groups respectively³⁰. However, the most common adverse event (AE) was transient malaise, with 51% of

immunised participants affected compared to 30% of those receiving the placebo³⁰. In a study of 53 adults, 4 to 5 participants remained at home after each dose and 5 to 10 required antipyretic/analgesic medication³¹.

4.3 Local reactions

4CMenB induces severe local tenderness in all age groups, with higher rates (9 to 15%) than have been reported for the OMV vaccines MeNZB and MenBvac, compared with rates of 1-3% with routine vaccines^{28, 32}. Previously, fear of pain and adverse events with other vaccines has been identified as an important barrier limiting vaccination compliance in children³³. Reactogenicity is increased when 4CMenB is co-administered with routine vaccines, incidence rates of severe pain were reported as 12-16% in phase IIb (infants), 24-29% in phase III (infants), 14-15% in phase III (toddlers) and 17% in adolescents ^{25-27, 29}. In preschool children receiving two doses of 4CMenB, 91 and 92% reported pain after 1 or 2 doses respectively, severe in 10-13% of the children for up to 3 days. Pain was still reported at day 7 in 19% of participants³⁴. These results are similar to induration reactions reported in adults³¹.

4.4 Unsolicited adverse events

During Phase III studies, four possibly vaccine-related febrile seizures and one case of Kawasaki disease were reported as possibly related to the study vaccine in one trial ²². In another Phase III trial, two cases of febrile seizures were defined as probably related to the vaccine and four cases of Kawasaki disease possibly related to 4CMenB²⁵. All AEs deemed to be related to 4CMenB resolved by the end of the studies. The febrile convulsions are likely to be directly related to the vaccines but the relationship with Kawasaki disease still remains uncertain at this stage.

5. Clinical immunogenicity and expected coverage

Efficacy can only be adequately measured in a phase III controlled clinical trial, but the low incidence of disease makes it unlikely that such a study could ever be undertaken⁴. Only the effectiveness of the OMV component of the vaccine has thus far been evaluated (73% observed in New Zealand for MeNZB)³⁵. For this reason, the potential efficacy must be estimated from immunogenicity data and accepted correlates of protection. The latter is estimated by using a serum bactericidal activity against selected target strains, with an exogenous human complement source (hSBA), titres $\geq 1:4$ being the assumed correlate of protection used for vaccine licensure⁴. However, titres can differ among laboratories³⁶. Use of this assay is hampered by the small volumes of serum available from infant studies, and difficulties in sourcing a suitable exogenous human complement for each strain tested. Therefore the assay is routinely performed only against a small selection of strains, and it is difficult to derive firm conclusions about activity against the population of disparate bacterial strains that cause disease, complicated by different expression levels of the target antigens between strains.

5.1 Immunogenicity

The results of the Phase II clinical trials demonstrated that 4CMenB is immunogenic in children, with the proportion of vaccinees achieving protective SBA titres varying from 85 to 95% depending on the target strain used, 1 month after the third dose²⁶. Furthermore, a fourth booster dose elicited anamnestic responses, with the proportion of subjects with protective titres reaching 93 to 100% depending on the strain used²⁶. In the analysis used by JCVI a short-term vaccine efficacy of 95% was considered a plausible estimate⁹.

5.2 Expected coverage

Infants immunised with 4CMenB at 2 and 4 months had hSBA titres $\geq 1:4$ against strains expressing homologous PorA, NadA and FHbp as well as related antigenic variants of NadA and FHbp²⁶. Due to serum volume limitations in infant studies, a reductionist approach was adopted in which four MenB

indicator strains were selected for SBA testing to measure the contribution of each antigen: 44/76-SL for FHbp, 5/99 for NadA, NZ98/254 for PorA, M10713 for NHBA, each primarily expressing one 4CMenB-specific antigen variant but mismatched for the remaining three³⁷, except for NZ98/254 which also contains an homologous NHBA. However immunization with NHBA does not elicit bactericidal activity against this strain, which therefore measures the contribution of PorA-specific antibodies³⁷. Strain M10713 has only relatively recently been incorporated into the immunogenicity analysis plans and thus not all trials have results for this strain. In addition, the meningococcal antigen typing system (MATS) was developed with the aim of measuring both the quantity of target expressed on the surface of the bacterial strains and the binding activity of the antibody raised by the vaccine. For PorA, which is constitutively expressed, the variable loops are sequenced. For the other antigens, a sandwich ELISA is performed^{38 39}: In one study I was shown that MATS may underestimate the potential activity against meningococcal strains measured using hSBA⁴⁰. Using MATS, estimates of 66-91.2% for coverage of the vaccine for disease-causing strains in various countries were predicted (Table 3). The largest study to assess strain coverage using MATS estimated that 78% of European strains (n=1052) might be covered by 4CMenB³⁹. While highly dependent on a given country's circulating strains, studies predict that cross-protective bactericidal activity will be elicited by NHBA (21.2-82.6% of expected coverage), FHbp (7-69%), PorA (1-21%) and NadA (0.7-4%)^{39, 41, 42}. A study using hSBA rather than MATS predicted an overall vaccine strain coverage of 88%⁴⁰, and while these predictions, whether from MATS or hSBA, cannot be directly linked to effectiveness data until after an implementation, the latter has been used in the most recent modelling scenarios¹⁷. Of note, both SBA and MATS were performed using pooled sera, which may increase the activity detected through synergistic capacity of antibodies from individuals responding to different epitopes.

5.3 Duration of bactericidal activity

Because invasion is so rapid following acquisition, persistence of circulatory antibody is important for vaccine efficacy, and immunological memory may have a lesser role. A limited number of studies have assessed the bactericidal antibody persistence conferred by the 4CMenB vaccine (Table 4). Findlow and colleagues²⁶ described waning of hSBA geometric mean titres (GMTs) six months after the last dose of immunisation delivered in a schedule at 2, 4 and 6 months of age: at this time-point, bactericidal activity against all four reference strains had decreased as compared with those measured five months earlier (Table 4, top row). A booster administered at 12 months of age elicited greater bactericidal antibody levels than those observed one month after the third (6 month) dose²⁶. Waning of immunity among those under 2 years of age can therefore be somewhat mitigated by the 12 month toddler dose. However, at 3-4 years of age, SBA GMTs were found to have declined significantly, with the exception of those against NadA₄₃, suggesting that the infant schedule is unlikely to provide sustained bactericidal activity into later childhood and adolescence, and further booster doses would be required to maintain immunity. These results suggest that the estimation of 36 months duration of protection used by recent modeling studies of vaccine impact^{15, 17}, which were based on clinical trials with 4CMenB and observations from other meningococcal vaccines, may actually be optimistic.

Data on persistence of immunity in teenagers indicate waning of bactericidal antibody titres 18-24 months after the last immunisation, regardless of whether two or three doses were used ⁴⁴. However, greater duration of bactericidal activity was observed in these older age groups in comparison to the younger cohorts, with hSBA GMTs remaining above pre-immunisation levels⁴⁴ (Table 4). Currently, there are no data available to indicate how long the hSBA GMTs observed 18-24 months post second immunisation (above the protective threshold) will be maintained. While there is a much lower disease incidence in teenagers than infants limiting the impact of direct protection in this age group, antibody persistence would have considerable importance in population protection if 4CMenB was able to induce herd protection, *i.e.* the capacity to decrease carriage rates in adolescents which effectively

decreases transmission and disease in non-vaccinated individuals, as observed with capsular group C meningococcal vaccine ⁴⁵.

The antigen-specific waning of bactericidal antibodies in both infants^{34, 43, 46} and teenagers⁴⁴ is of importance in determining the persistence of expected coverage. However, rates of waning are not the same for antibodies directed against each of the 4 vaccine antigens: in vaccinated infants, 20 or 28 months post booster (Table 4, top and second rows), SBA GMTs decreased sharply against PorA and FHbp, while the decrease was less pronounced or absent against NadA and NHBA, as compared with one month post boost^{34, 43}. Bactericidal antibodies titers against strain NZ98/254 (PorA) were below the putative protection threshold 20 months post booster (Table 4)^{34, 43}. Bactericidal activity induced by immunisation with FHbp is variable and dependent upon FHbp expression levels in the target strains, and strain 44/76-SL is considered a high expresser of FHbp variant 1.^{147, 48}. Therefore, given hSBA GMTs in children aged five years old who have received a 3+1 schedule have not remained at high levels (4.69 [95% CI: 1.98-11]) against strain 44/76-SL³⁴, it is unlikely that bactericidal activity against circulating strains will remain against low variant 1 expressors or distantly related variants. SBA titers against 5/99 (NadA) are maintained at high levels in children ³⁴ and teenagers⁴⁴, but it is unlikely that this will provide much persistent cross-reacting bactericidal activity given the *NadA* gene is present in only 20-50% of MenB strains ^{49, 50}. NHBA-specific bactericidal titers are low after vaccination and do not decrease rapidly^{26, 43} (Table 4). However, contribution of persistence to coverage can only be made with the introduction of routine immunisation.

5.4 Impact on carriage acquisition

Post-implementation analyses demonstrated that a major effect of capsular group C meningococcal vaccines was to interrupt transmission⁵¹. This effect dramatically enhanced the efficacy and the cost-effectiveness of the vaccine⁵¹. Whether 4CMenB induces similar effect is therefore of particular importance as such effect would dramatically increase the effectiveness of 4CMenB. Measuring this

potential effect is hampered by the need for large number of individuals and acquisition events to accurately power the studies. Currently, sufficient data are not available to determine whether 4CMenB will reduce carriage acquisition and thus curtail transmission. A single Phase III clinical trial (NCT01214850), evaluating the contribution of 4CMenB on *N. meningitidis* carriage in 18-24 year-olds has recently been completed. It indicated that, from 3 months after two doses, 4CMenB was associated with a modest decrease in carriage of any *N. meningitidis* strain (18.2% [95%CI: 3.4-30.8]), when the data for the time-points 3, 5 and 11 months post second vaccine dose were aggregated⁵². No impact of 4CMenB on capsular group B strains only was observed, and no impact was observed when each time point was analysed separately. This may be due to the low number of capsular group B carriage acquisitions during the study, in addition to the observation that most acquisition events occurred after the first vaccine dose and before the second. Based on these results, JCVI concluded that the impact of 4CMenB on prevention of carriage acquisition was likely comprised between 0 and 30%, and thus the potential effect at the population level is very difficult to predict at this stage⁹.

6. Conclusion.

Data from a series of clinical trials demonstrate that 4CMenB given with the current routine infant vaccines is associated with increased rates of fever, which can be partially reduced by the use of prophylactic paracetamol. The clinical efficacy of the vaccine has been estimated using two *in vitro* assays (SBA, required for vaccine licensure, and MATS). The immunogenicity data provide strong support for the use of the vaccine to prevent infection caused by strains expressing the vaccine antigens. However, the vaccine coverage remains uncertain for the wider population of meningococci that actually cause disease in each region, though current estimates, ranging from 66 to 88% in infants provide support for use of the vaccine. In infants, the vaccine should induce bactericidal antibodies through the period of greatest risk of disease, though the impact of differential waning of antibody directed against the four vaccine components remains uncertain. Waning of antibody after infant

vaccine indicates that protection may not persist through childhood without booster doses. Following introduction of an infant programme, 4CMenB is likely to prevent a proportion of invasive meningococcal disease in infants and young children: in the best case scenario, 26% of the cases would be prevented in the first five years following implementation of an infant program as recommended by the JCVI in the UK¹⁷. A 48.8% reduction of cases would be obtained at 10 years if the program included adolescent vaccination and the vaccine provided herd immunity, but the full impact of the vaccine will not be established until after implementation in routine infant vaccination schedules and following careful surveillance and identification of disease-causing strains.

7. Expert opinion.

The prospect of reducing the burden from this devastating disease after over 40 years of clinical trials of serogroup B meningococcal vaccines is an important milestone in public health. However, despite the wealth of data currently available about the vaccine, a number of questions remain unanswered. It is not clear if this vaccine will induce herd protection - if it does, population impact will be greater than estimates derived from direct protection. To provide this critical information, carriage studies should be conducted in all populations where the vaccine is introduced, either as part of the routine schedule or to control a specific outbreak. Strain coverage and vaccine efficacy have been estimated from *in vitro* data, but effectiveness in the field is unknown. The vaccine will protect against strains which express sufficient levels of the specific variants of the vaccine antigens on the surface, but protection against other strains is not known. The ability of MATS or SBA to predict efficacy for subcapsular meningococcal antigens is uncertain, and will only be clear from carefully conducted surveillance post-vaccine implementation. The relatively low rates of disease means it may be several years until this information is clear. Although this vaccine has been licensed as a group B vaccine, the polysaccharide capsule (which defines the group) is not a part of the vaccine. There is therefore the possibility the vaccine will be effective against other capsular groups, as suggested by hSBA titers

against several capsular group X strains detected in pooled sera from 4CMenB vaccinees⁵³. However, this vaccine will not eliminate all capsular group B meningococcal disease. It is therefore important that research into improved meningococcal vaccines continues, with the aim of inducing broad, long-lasting protection against all strains. The rapid evolution of *N. meningitidis* and its ability to evade the immune response makes this an ongoing challenge for vaccine developers. Finally, while the vaccine has proved to be safe in clinical trials, it has resulted in a higher rate of fever in infants when given with currently used vaccines in some studies. Public acceptance of a vaccine for meningitis is likely to be high, but in an era where there is significant vaccine hesitancy in some populations, accurate information about the vaccine will need to be disseminated to ensure that children are completely immunised, local and systemic reactions (especially fever) are minimised with paracetamol, and public confidence in vaccines is preserved.

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Drug summary box.

Drug name	Meningococcal group B (MenB) vaccine (Bexsero®)
Status	Licensed in European Union, Canada and Australia
Indication	Prevention of capsular group B meningococcal disease
Mechanism of action	Induction of specific bactericidal antibodies against four outer membrane antigens
Route of administration	Intramuscular injection
Pivotal trials	NCT00381615: phase 2 trial in healthy infants NCT00657709, NCT00847145: phase 3 trial

Tables

Table 1. Summary of the clinical trials involving 4CMenB

Country(s) Trial number	Age at first immunisation	Schedule and number of participants enrolled for 4CMenB (rMenB + OMV) intervention	phase	References
Switzerland V72P5	Healthy adults 18-40 Years n = 70	Randomized (I) 3 doses 4CMenB at 1 month intervals; n=28 (II) 3 doses rMenB + OMVNW (Norwegian strain) at 1 month intervals; n = 28 (III) 3 doses rMenB at 1 month intervals; n = 14	1	Toneatto et al., Human Vaccines 7:6, 646-653; June 2011
UK NCT00433914	Healthy infants 6-8 Months n = 60	Randomized 1:1 3 doses rMenB at Day 0, Day 60 and at age 12 months n = 30. 3 doses 4CMenB at Day 0, Day 60 and at age 12 months n = 30 Participants also received routine vaccines at 12 months in the opposite thigh to 4CMenB. 1	2	Snape et al., Pediatr Infect Dis J 2010;29: e71–e79)
UK NCT00381615	Healthy infants 2 or 12 Months n = 147	Randomly allocated 2:2:1:1 3 +1 doses rMenB at 2, 4 6 and 12 months of age n = 48 3 +1 doses 4CMenB at 2, 4 6 and 12 months of age n = 50 1 Dose rMenB at 12 months n = 25. 1 Dose 4CMenB at 12 months n = 24 Participants also received routine vaccinations 2	2	Findlow et al., Clinical Infectious Diseases 2010; 51(10):1127–1137
UK NCT01027351	Healthy infants 40-44 Months n = 113	Follow on study to trial NCT00381615 Previous rMenB at 2, 4 6 and 12 months; 1 booster n = 29 Previous 4CMenB at 2, 4 6 and 12 months; 1 booster n = 19	2	Snape et al., CMAJ 2013. DOI:10.1503 /cmaj.130257

Previous rMenB at 12 months; 2 boosters n = 14
 Previous 4CMenB at 12 months; 2 boosters n = 8
 Age matched naïve controls 2 doses at day 0 and 2 months n= 43

UK NCT01026974	Healthy infants 40-44 Months n = 71	Follow on study to trial NCT00433914 Previous rMenB at 6, 8 and 12 months; 1 booster rMenB n = 16 Previous 4CMenB at 6, 8 and 12 months; 1 booster 4CMenB n = 14 MenB vaccine naïve age matched controls; 2 doses 4CMenB 60 days apart n = 41	2	Snape et al., Pediatr Infect Dis J 2013;32:1116–1121
Italy and Germany NCT00560313	Healthy adults 18-50 Years n = 54	3 doses of 4CMenB at Day 0, 2 months and 6 months followed by 1 dose of MenACWY-CRM 1 month later n=54	2	Kimura et al., CVI, Mar. 2011
Belgium, UK, Czech Republic, Germany, Italy and Spain NCT00721396	Healthy Infants 2 Months n = 1885	Randomized 2:2:1:1 concomitant 3 doses of 4CMenB at 2, 4, and 6 months with routine vaccines ₃ n = 622 intercalated 3 doses of 4CMenB at 2, 4, and 6 months with routine vaccines at 3, 5, and 7 months n=632 Accelerated 4CMenB with routine vaccines at 2, 3, and 4 months n=317. Routine vaccines only at 2,3 and 4 months	2b	Gossger et al., JAMA. 2012;307(6):573-582
Chile NCT00661713.	Healthy adolescents 11-17 Years n = 1631	Randomized 3:3:3:3:1 1 dose of 4CMenB n = 375 with/without boost at month 6 n = 114/212 respectively 2 doses of 4CMenB 1 month apart n = 375 with/without boost at month 6 n = 112/225 respectively 2 doses of 4CMenB 2 months apart n = 380 with/without boost at month 6 n = 111/222 respectively 3 doses of 4CMenB 1 month apart n = 373	2b/3	Santolaya et al., Lancet 2012; 379: 617–24

3 doses placebo n = 128 with 1 dose of 4CMenB at month 6 n = 119

Austria, Czech Republic, Finland, Germany, Italy	Healthy infants 2 Months n = 3630	Priming phase open label immunogenicity subset randomized 1:1:1:1 received 3 doses of 1 of three lots of 4CMenB with routine vaccines ³ (n=1968, or routine vaccines alone n = 659 Safety subset (observer blinded) randomized 1:1:1:3 received 3 doses of 1 of three lots of 4CMenB with routine vaccines n=513 or routine vaccines with MenC n = 490. Booster phase for those completing priming phase randomized 1:1. Participants received 4CMenB with MMRV n=766 or with MMRV given 1 month after n=789.	3	Vesikari et al., Lancet 2013; 381: 825–35
NCT00657709 NCT00847145				

¹ a combined *Haemophilus influenzae* type B and meningococcal serogroup C glycoconjugate vaccine (Menitorix, GSK, Belgium)

² diphtheria-tetanus-acellular pertussis- *Haemophilus influenzae* type b (Hib) and inactivated poliovirus vaccine (Pediaceel: Sanofi Pasteur) at 2, 3, and 4 months of age, pneumococcal conjugate vaccine (Prevenar; Wyeth Pharmaceuticals) at 2, 4, and 13 months of age, meningococcal serogroup C (MenC) conjugate vaccine (Menjugate; Novartis) at 3 and 5 months of age, MenC-Hib conjugate vaccine (Menitorix; GSK Biologicals) at 12 months of age, and measles, mumps, rubella vaccine (Priorix; GSK Biologicals) at 13 months of age.

³ Routine vaccines: 7-valent pneumococcal and combined diphtheria, tetanus, acellular pertussis, inactivated polio, hepatitis B, *Haemophilus influenzae* type b vaccines.

Table 2. Summary of key safety and reactogenicity findings during phase 2b/3 trials in infants comparing regimens of co-administration of 4CMenB with routine vaccines vs. routine vaccines alone.

Trial	Regimens	Fever rates per group	Local pain per group	Other AEs
NCT00721396 Gossger et al., JAMA. 2012;307(6):573-582	Concomitant 4CMenB n = 622	≥ 38°C: 51% to 61%. ≥ 39°C :10 % to 15%,	Severe pain: 13% to 16%	Six infants observed in hospital with fever following 4CMenB vaccination
	Intercalated 4CMenB n = 632	≥ 38°C : 26% to 41% ≥ 39°C : 4% to 8%,	Severe pain : 8% to 10%	4 cases of seizures possibly related to the vaccine, one each following routine vaccination in the intercalated and accelerated groups and 2 after 4CMenB in the intercalated group.
	Accelerated n = 317	≥ 38°C: 44% to 59% ≥ 39 °C: 6% to 11%	Severe pain : 12% to 16%	2 episodes of hypotonic hyporesponsiveness, 1 within 12h of 4CMenB in the concomitant group and 1 within 6h of routine vaccines in the intercalated group
	Routine vaccines only n=314	≥ 38°C: 23% to 36% ≥ 39 °C: 3% to 4%	Severe pain : 1% to 3%	One case of Kawasaki disease possibly related to 4CMenB. One case each of aseptic meningitis, retinal dystrophy (believed to be congenital), transient synovitis of the hip, transient hearing loss and transient apnea all occurred after concomitant administration of vaccines and were deemed as possibly related to the vaccines.
NCT00657709	Priming phase:	≥ 38.5°C: 65%	79% to 87%	Two cases of febrile seizures in infants reported with 24h of concomitant vaccination were deemed to be probably related to the vaccines.
NCT00847145 Vesikari et al., Lancet 2013; 381: 825–35	Concomitant 4CMenB n = 2478	≥ 40°C: 1.2%	Across all sites	Four cases of Kawasaki disease (3 in concomitant and 1 in routine plus MenC).

Routine vaccine, n = 659	$\geq 38.5^{\circ}\text{C}$: 32% $\geq 40^{\circ}\text{C}$: 0%	53% to 59% Across all sites
routine vaccines with MenC n = 490.	$\geq 38.5^{\circ}\text{C}$: 34% $\geq 40^{\circ}\text{C}$: 0.2%	54% to 68% Across all sites
Booster phase : Concomitant with MMRV n = 766	$\geq 38.0^{\circ}\text{C}$: 30.6%	
MMRV given 1 month after n = 789.	$\geq 38.0^{\circ}\text{C}$: 31.6%	

One case of pyrexia during concomitant boost with MMRV were reported as possibly related to the vaccines

Argentina, Chile, Czech Republic, Hungary and Italy. NCT00937521 Prymula et al., Human Vaccines & Immunotherapeutics	Priming phase	$\geq 38^{\circ}\text{C}$: 57% to 77%	Severe pain: 9%	Medically attended fever rates ranged from 0% to 4%, 0% to 1% and 1% to 2% in groups I, II and III respectively across the primary course of vaccinations
	I concomitant 4CMenB n = 188	$\geq 39^{\circ}\text{C}$: 7% to 21%	to 15%	
	II concomitant 4CMenB + paracetamol n = 184	$\geq 38^{\circ}\text{C}$: 37% to 57% $\geq 39^{\circ}\text{C}$: 3% to 6%	Severe pain: 4%	No serious adverse events were deemed to be related to study vaccines.
	III concomitant MenC n = 186	$\geq 38^{\circ}\text{C}$: 24% to 39% $\geq 39^{\circ}\text{C}$: 1% to 5%	Severe pain: 1% to 3%	
	Booster phase n = 500 One dose of 4CMenB all groups	$\geq 38^{\circ}\text{C}$: 70%, 60% and 66% in groups I, II and III respectively	Severe pain: 20%, 14% and 20% in	

groups I, II and III respectively

For further details of the trials and the routine vaccinations see foot notes in Table 1.

Table 3. Predicted strain coverage by country using MATS

Country	Number of strains tested	Predicted strain coverage (95% CI)	Reference
England and Wales	1052	73% (57-87)	39
France		85% (69-83)	
Germany		82% (69-92)	
Italy		87% (70-93)	
Norway		85% (76-98)	
Czech Republic		74% (58-87)	
Spain		69% (48-85)	
Greece	148	89.2% (63.5-98.6%)	41
Spain	300	68.7% (48-85.3)	54
Australia	373	76% (63-87)	55
Brazil	99	80.8% (70.7-94.9)	56
Czech Republic	108	74% (59-87)	57
Germany	222	81% (71-93)	57
USA	442	91.2% (72.2-95.9)	58
Canada	157	66% (46-78)	42

Table 4. hSBA GMTs against four target strains observed following various infant and teenager immunisation schedules

Study cohort (Age at baseline)	No. of immunisation s administered	Time immunisation administered post baseline (months)	SBA Geometric Mean Titres (95% CI)				Ref.	
			44/76-SL	5/99	NZ98/254	M10713		
Infants (2 months)	5	0, 2, 4, 10, 38-42	Pre-immunisation	1.4 (1.2-1.7)	1.2 (1.0-1.3)	1.4 (1.1-1.8)	2.6 (1.8-3.7)	26, 43
			One month post 2 nd dose	28.0 (19-40)	6.6 (4.8-9.0)	104.0 (64.0-169.0)	2.1 (1.4-3.1)	
			One month post 3 rd dose	30 (19-46)	19 (11-33)	126.0 (77.0-205.0)	4.1 (2.6-6.3)	
			6 months post 3 rd dose	4.5 (2.9-7.0)	2.4 (1.5-3.9)	25.0 (13.0-47.0)	1.8 (1.2-2.7)	
			One month post booster	106.0 (71-159)	29.0 (15.0-56.0)	629.0 (324.0-1219.0)	4.9 (2.8-8.5)	
			28 months post-first booster	5.3 (3.3-8.8)	28 (9.4-83)	2.8 (1.4-5.6)	5.3 (2.3-12)	
			One month post-second booster	89 (68-116)	1708 (774-	47 (20-107)	39 (22-69)	
Infants (6 months)	4	0, 2, 6, 34-38	Pre-immunisation	1.70 (1.29-2.24)	1.05 (0.98-1.12)	1 (1-1)	27, 34, 43	
			One month post 2 nd dose	250 (173-361)	534 (395-721)	27 (21-36)		Not tested
			One month post 3 rd dose	189 (136-263)	906 (700-1172)	44 (32-62)		
			28 months post 3 rd dose	2.55 (1.15-5.66)	29 (18-47)	1.74 (0.91-3.33)		7.11 (3.61-14)
			One month post booster	114 (59-222)	926 (432-1988)	32 (14-71)		23 (13-41)
			20 months post booster	4.69 (1.98-11)	119 (56-252)	1.63 (0.86-3.08)		5.51 (2.19-14)
Teenagers (approximately 16 years)	1	0	Pre-immunisation	4.0 (3.1-5.1)	2.7 (2.2-3.3)	2.7 (2.1-3.4)	44	
			One month post immunisation	52 (42-63)	65 (53-79)	36 (29-45)		
			18-24 months post immunisation	29 (20-42)	8.0 (6.2-10)	8.9 (6.7-12)		
Teenagers (approximately 16 years)	2	0, 1	Pre-immunisation	3.0 (2.5-3.6)	2.3 (2.0-2.7)	2.4 (2.0-2.9)		
		0, 2	One month post second immunisation	211 (181-247)	610 (523-710)	104 (88-123)		Not tested
		0, 6	18-24 months post second immunisation	31 (24-39)	46 (38-55)	20 (16-24)		
Teenagers (approximately 16 years)	3	0, 1, 2	Pre-immunisation	3.5 (2.9-4.3)	2.4 (2.0-2.8)	2.8 (2.3-3.3)		
		0, 1, 6	One month post second immunisation	268 (230-312)	790 (679-920)	146 (124-172)		
		0, 2, 6	18-24 months post second immunisation	44 (35-55)	86 (72-104)	30 (24-37)		

