

TITLE

Control of invasive meningococcal disease: is it achievable?

AUTHORS**Associate Professor Helen Marshall, MBBS MD MPH DCH**

Senior Medical Practitioner and Director, Vaccinology and Immunology Research Trials Unit,
Women's and Children's Hospital

NHMRC Career Development Fellow and Associate Professor in Vaccinology

Discipline of Paediatrics, School of Paediatrics and Reproductive Health

Research Leader, Robinson Research Institute, The University of Adelaide

Principal Research Fellow, SAHMRI

Address: Women's and Children's Hospital, North Adelaide, 5006, SA

T: 08 8161 8115

E: helen.marshall@adelaide.edu.au

Ms Bing Wang, MBBS MPhil (Public Health)

Vaccinology and Immunology Research Trials Unit (VIRTU), Women's and Children's Hospital,
South Australia, AUSTRALIA

The Robinson Research Institute and School of Paediatrics and Reproductive Health/Population
Health, University of Adelaide, South Australia, AUSTRALIA

E: bing.wang@adelaide.edu.au

Professor Steve Wesselingh, BMBS, PhD, FRACP

Executive Director

South Australian Health and Medical Research Institute (SAHMRI)

T: 08 8128 4010

E: steve.wesselingh@sahmri.com

Dr Matthew Snape, MBBS, MD, FRACP

Oxford Vaccine Group

T: +44 (0)1865 857420

E: matthew.snape@paediatrics.ox.ac.uk

Andrew J Pollard, BSc, MBBS, PhD, DIC, MRCP(UK), FRCPCH, FHEA, FIDSA

Professor of Paediatric Infection and Immunity

Department of Paediatrics

University of Oxford

T: +44 (0)1865 234226/226909

E: andrew.pollard@paediatrics.ox.ac.uk

ABSTRACT (303 WORDS)

Neisseria meningitidis still leads to deaths and severe disability in children, adolescents and adults. Six different capsular groups of *N. meningitidis* cause invasive meningococcal disease in the form of meningitis and septicaemia in humans. Although conjugate meningococcal vaccines have been developed to provide protection against four of the capsular groups causing most disease in humans, vaccines against capsular group B, which causes 85% of cases in Australia and the United Kingdom, have only recently been developed. A capsular group B meningococcal vaccine, 4CMenB (Bexsero®), has recently been licensed in the European Union, Canada and Australia. In Australia, a submission for inclusion of 4CMenB in the funded national immunisation programme has recently been rejected. A decision to include the vaccine in the national immunisation programme in the United Kingdom is mandated if a cost-effective price can be obtained. With the current low incidence of invasive meningococcal disease in many regions, cost – effectiveness of a new capsular group B meningococcal vaccine is borderline in both the United Kingdom and Australia. Cost-effectiveness of an infant programme is determined largely by the direct protection of those vaccinated and is driven by the higher rate of disease in this age group. However, for an adolescent programme to be cost-effective it must provide both long term protection against both disease and carriage. The potential of vaccination to reduce the rate of severe invasive disease is a real possibility. A dual approach using both an infant and adolescent immunisation programme to provide direct protection to those age groups at highest risk of meningococcal disease and to optimise the potential herd immunity effects is likely to be the most effective means of reducing IMD. This commentary aims to describe the known disease burden and consequences of meningococcal disease and the development and potential effectiveness of new capsular group B meningococcal vaccines.

KEY WORDS

carriage, herd immunity, immunisation policy, invasive meningococcal disease, meningococcal

B vaccines

INTRODUCTION (5168 WORDS)

Although uncommon, invasive meningococcal disease (IMD) causes death in young healthy children and adolescents in up to 10% of cases.¹⁻³ Debilitating consequences frequently follow resolution of the infection, with 21-57% of cases developing long term complications including amputation, cerebral infarction and severe skin scarring.⁴⁻⁷ The World Health Organisation estimates that there were approximately 171,000 deaths in 2000 caused by IMD.⁸ A high proportion of these deaths occur in developing countries such as Africa where traditionally the Sub-Saharan “meningitis belt” has been associated with high mortality rates from IMD caused by seasonal outbreaks due to capsular group A.

The highest incidence of IMD occurs in children < 5 years of age (particularly those under 12 months of age) with a second peak in adolescents and young adults, 15-24 years of age.⁹⁻¹² The average annual incidence of IMD in Australia is 1:100,000,¹³ and in the United Kingdom (UK) 2:100,000,¹⁴ and is higher in young infants (1.1-8.4:100,000-age specific rate).¹² The meningococcus is carried in the nasopharynx and IMD results following invasion of the blood or meninges by a hypervirulent strain. Adolescents have the highest prevalence of naso-pharyngeal carriage of both benign and hypervirulent meningococcal subtypes.¹⁵

IMD causes high anxiety in both the medical community and the general public due to its rapid onset with the potential for a fatal outcome within 24 hours of onset of infection, in previously healthy children and adolescents. Despite advances in early diagnosis and treatment with antibiotics children remain vulnerable to IMD due to the relative immaturity of their immune system.¹⁶

This commentary aims to present the best available evidence for use of meningococcal vaccines in the control of IMD in children, adolescents and adults. Our literature review was confined to publications most relevant to the evaluation of IMD immunisation programmes in relation to

disease burden and epidemiology, meningococcal vaccine safety and efficacy, and potential programme barriers and facilitators. We identified relevant articles with searches of PubMed and Embase and references from identified papers on these topics. Only papers published in English were included.

EPIDEMIOLOGY

There are 13 known capsular groups of *Neisseria meningitidis* identified by their different capsular polysaccharide structure, however almost all invasive disease is caused by six meningococcal capsular groups (A, B, C, W, Y and X).^{17, 18} There is a seasonal variation in disease incidence with most cases in temperate climates occurring in winter and early spring, while those in sub-Saharan Africa occur during the dry season.^{8, 19} Viral infections, in particular influenza, have been shown to predispose to secondary infection with meningococci.²⁰

Prior to the Second World War, capsular group A meningococcal disease (MenA) was a common cause of meningococcal infection in the UK and caused a high proportion of disease in the Australian Indigenous population in the early 1970s, but is now rarely found in either country.²¹⁻

²³ The reason for this decline is unknown but it remains the most common capsular group worldwide due to the high incidence of group A disease in Sub-Saharan Africa, though this is falling rapidly as a result of a targeted vaccine programme.²⁴ Capsular group Y is more common in some settings and causes 30% of cases in the USA¹⁰ Group Y is more often associated with disease in the elder²⁵ particularly in adolescents. This increase has been seen globally, including a slight increase in Australia and the UK in 2011/2012.^{19, 26} Capsular group W is a more common cause of IMD in Asia and Africa than the UK and Australia, and an increasing cause of IMD in Latin America. However recent surveillance in the UK has identified an increase in group W disease in all age groups in England and Wales which does not appear to be related to travel or an association with pilgrimage to Hajj (historically associated with increase in cases). Capsular group X is rare and tends to cause sporadic outbreaks, the majority of which occur in Africa.²⁷

Prior to the implementation of the national capsular group C meningococcal (MenC) immunisation programme in the UK (November 1999) and in Australia (January 2003), one third of cases in both countries were due to group C meningococci. A large decline in group C disease

occurred following MenC vaccine introduction in both countries, however there has been no impact on disease caused by other capsular groups including capsular group B disease.

Capsular group B disease is endemic in high and middle income countries, including North America, Australia, South America and the European Union (EU). In Australia, 85% of cases of IMD are now due to group B, a significant change in the serogroup epidemiology, with 65% of cases occurring in children and adolescents.^{12, 19} In England and Wales, 764 cases were notified in 2011-2012 with the majority due to group B.²⁶ In the USA, around 30% of cases are due to group B and in the EU, 70% of cases are due to group B since introduction of MenC vaccines.^{9, 28}

THE BURDEN OF INVASIVE MENINGOCOCCAL DISEASE: OUTCOMES AND CONSEQUENCES

The true global burden of disease is unknown due to varying quality of surveillance systems in different regions of the world, leading to under reporting in many countries. A study conducted in the UK prior to the introduction of a MenC vaccine, identified that 57% of 58 cases had major physical sequelae, with greater cognitive deficits associated with younger age at diagnosis.⁴ The study also found that medical follow-up was poor with only 53 of 101 (52%) cases reporting any follow-up after IMD, with significant unrecognised and untreated morbidity. Another recent UK study, MOSAIC (meningococcal outcome study in adolescents and children) using a case-control approach, identified major sequelae in 36% of meningococcal survivors with a lower quality of life, greater risk of depression and poor mental health function in child and adolescent survivors of IMD compared with age and sex matched controls.²⁹ Although this study provided a detailed assessment of the outcomes of IMD in the UK in children and adolescents, the burden of disease is likely to be different in different countries where different meningococcal genotypes circulate, and in the UK during different periods. In comparison a Canadian study of IMD cases found 21% of survivors developed major sequelae.³⁰ The outcomes and impact from IMD in Australian children are poorly documented.^{19,31-34}

In a recent audit of 10 years of IMD cases in children in South Australia, 37.6% (41/109) developed sequelae including limb amputation, hearing loss, skin scarring and chronic headaches and lethargy.⁷ A long term follow-up of survivors who had experienced bacterial meningitis in childhood was reported in the year 2000.³¹ The study prospectively followed a cohort of 166 children admitted to the Royal Children's Hospital, Melbourne between the ages of 3 months to 14 years between 1983 and 1986. This case-control study indicated 8.5% of bacterial meningitis survivors had major neurological, auditory or intellectual impairment. A further 18% of survivors had an attributable risk of minor impairment. A retrospective five year case review study of IMD

cases in Western Australia between 1990 and 1995 found a morbidity rate of 8.6% with sequelae including hearing loss, limb amputation and skin scarring and a case fatality rate of 8.6%.³⁴ As it is difficult to predict which children are at risk of IMD, apart from those with immunodeficiency conditions, studies have attempted to predict children that develop severe disease or sequelae.^{7,35} In the recent review examining outcomes of IMD in South Australian children, those admitted with a diagnosis of meningitis and septicaemia compared to meningitis or septicaemia alone were more likely to develop sequelae (OR=7.8; P=0.002, OR=15.5; P<0.001, respectively), with high fever on presentation to hospital a predictor of development of sequelae (OR=4.5;p=0.012).⁷ This study also highlighted the controversial finding that antibiotics given early prior to hospital admission may be associated with a more severe outcome, although children who receive antibiotics are likely to have more severe disease on presentation and be more easily diagnosed as a possible IMD case. A systematic review delineated the contradictory results from studies of the effects of early antibiotic treatment, suggesting confounding factors and the proportions of cases receiving antibiotics could explain the heterogeneity in results between studies.³⁶

In addition to the devastating direct consequences of the disease, affected children and their families may also be compromised by the neuropsychological consequences of this infection including depression, post-traumatic stress disorder, reduced educational attainment and inability to lead a successful and productive life.^{29, 37}

MENINGOCOCCAL VACCINE DEVELOPMENT

Polysaccharide meningococcal vaccines (MenACWY)

Pure polysaccharide meningococcal vaccines against disease caused by capsular groups A, C, W, and Y were initially developed and derived from capsular polysaccharides of the bacteria. The capsular polysaccharide is a virulence factor for the bacteria and helps prevent immune mediated bacterial killing. These vaccines are relatively ineffective in young children < 2 years of age, because they are unresponsive to these T-cell independent antigens.³⁸ The effectiveness of these vaccines is therefore limited as the burden of disease is concentrated in the age group amongst whom these vaccines are least effective.³⁹ In addition, these vaccines have mostly shown no effect on nasopharyngeal carriage and therefore do not contribute to herd immunity, an important community benefit of childhood immunisation programmes.⁴⁰

Conjugate meningococcal vaccines to provide broad protection (MenC, MenA, MenACWY vaccines)

Conjugate polysaccharide vaccines have been developed in which the polysaccharide capsules are conjugated to a carrier protein to induce a T cell dependent response, making these vaccines immunogenic from early infancy. In the USA a quadrivalent conjugate vaccine is recommended routinely for adolescents from 11 years of age in a 2 dose schedule.⁴¹ In Australia, the UK and other EU countries monovalent MenC vaccines have been introduced in response to the large proportion of cases due to capsular group C in the past few decades. These MenC vaccines have been associated with a decrease in group C disease in other, unvaccinated, age groups providing evidence of the effect of conjugate vaccines on carriage and the additional benefits to the community of herd immunity. In Australia the MenC vaccine is given as 1 dose at 12 months of age, and at the time of introduction in 2003 a catch-up programme to 20 years of age was implemented. In the past few years group C disease has rarely been reported in those aged

under 20 years old in Australia and there have been only a handful of cases in older adults. In the UK, where the MenC vaccine was initially provided as a 3 dose then 2 dose infant schedule, again accompanied by a catch-up campaign incorporating adolescents and young adults, the incidence of MenC disease has decreased by 94% in immunised populations and 67% in unimmunised populations.^{24, 42, 43} Concerns about waning of MenC antibodies in populations immunised in early childhood resulted in a booster dose being added to the infant schedule in the UK which now consists of one dose at 3 months, a second dose at 12 months and a further dose in adolescence at 13-15 years of age.⁴⁴

A conjugate group A vaccine was recently developed in response to the enormous disease burden from capsular group A disease in the Sub-Saharan meningitis belt. A large reduction in group A disease has been observed in Sub-Saharan countries that have already implemented the programme.^{45,46}

Capsular group B meningococcal vaccines

i. Difficulties developing a MenB vaccine to provide protection against endemic strains

The development of an effective and safe capsular group B meningococcal (MenB) vaccine has been a priority in combating meningococcal disease, since this capsular group is now the predominant cause of infection in the UK, Australia and other countries. MenB vaccine development has been impeded because the group B capsular polysaccharide, a homopolymer of alpha(2-8)-linked polysialic acid, is identical to sugars decorating human foetal neural cell adhesion molecule, and therefore a human self-antigen. A capsular polysaccharide vaccine is unsuitable for vaccine development due to lack of immunogenicity (presumably as a result of tolerance to a self antigen) and the theoretical risk of autoimmunity. When purified capsular group B polysaccharide was used to vaccinate adult volunteers, no measurable increase in anti-capsular antibody was demonstrated.⁴⁷ The use of capsular group B polysaccharide non-

covalently complexed to outer membrane proteins as a human vaccine generates only short-lived IgM responses.⁴⁸ Even when conjugated to a carrier protein, it was noted to have poor immunogenicity.^{49, 50} Therefore, development of a conjugate MenB vaccine was not possible and other ways to develop MenB vaccines were considered.

ii. Development of MenB vaccines against specific MenB serosubtypes causing epidemics (e.g. MeNZB vaccine; OMV based serotype specific vaccines)

In response to the meningococcal epidemics in countries such as New Zealand and Cuba, serosubtype specific or “tailor-made” MenB outer membrane vesicle (OMV) vaccines were developed. The meningococcus continuously releases “blebs” or outer membrane vesicles during development containing hundreds of different antigens.⁵¹ These outer membrane blebs contain lipopolysaccharide (LPS) and outer membrane proteins (OMPs). In these OMVs, the OMP Porin A is an immunodominant protein which has been shown to be immunogenic and has over 600 different variants.⁵² These variants induce limited cross protection in young children and in this age group any vaccine developed from OMVs tends to provide protection limited to the specific serosubtype causing the epidemic. Such vaccines were developed and implemented during long epidemics in New Zealand (MeNZB), Norway (MenBVac) and Cuba (VA-MENGOCC-BC) caused by specific serosubtypes but cannot protect against endemic group B disease. The MeNZB[®] vaccine which was based on a typical isolate from the outbreak, was used in New Zealand with success⁵³ but this does not provide sufficient coverage of other circulating subtypes in Australia and globally.⁵⁴ It was established early in clinical trials that immunogenicity waned and that a booster dose was important in maintaining protective antibody levels. Post-licensure surveillance of 200,000 children who received MeNZB[®] vaccine, found no increase in serious adverse event rates of pre-selected conditions (e.g. acute flaccid paralysis, encephalopathy, seizures), in excess of the background rates to be expected in the general population for these conditions.⁵⁵ Injection site reactions (redness and/or swelling) occurred

more frequently in infants than control vaccines (Men C vaccine) but were of short duration and short term fevers were common but comparable to those receiving the control vaccine and did not require medical intervention.⁵³ With more than 3 million doses of MeNZB[®] administered to individuals under 20 years of age no new or unexpected safety concerns were identified. More specifically systemic events including fever were not associated with any increased risk of febrile convulsion in young children following vaccination.⁵⁶ Although the MeNZB[®] vaccine was considered protective only against the epidemic MenB strain, there was some evidence of protection (VE=54%) against non-epidemic MenB strains.⁵⁷ The effectiveness of the New Zealand immunisation programme was estimated to be 80% for children < 5 years of age⁵⁸ and 77% overall.⁵⁷

iii. New capsular group B meningococcal vaccines with the potential for protection against endemic disease (OMV and outer membrane protein-derived vaccines)

In view of the difficulties with polysaccharide vaccines against capsular group B meningococcal disease, researchers have focused on non-capsular targets in search of candidate vaccine antigens. This, however, has been problematic due to the high level of antigenic diversity of the meningococcus.⁵⁹

Two newly developed vaccines designed to protect against capsular group B disease (although lacking the capsular polysaccharide that defines this Group) have been developed with the potential to offer protection against endemic and epidemic disease; one licensed in several countries including Australia, Canada and the European Union, 4CMenB (Bexsero[®], Novartis) and one recently licensed in the USA, rLP2086 (Trumenba[®], Pfizer) ⁶⁰ The rLP2086 vaccine received the Food and Drug Administration's Breakthrough Therapy designation (to expedite the development and review of potential new medicines for serious and life-threatening

diseases)⁶¹ which includes more intensive FDA guidance on an efficient drug development programme.⁶²

a) 4CMenB vaccine

A new approach to vaccine development known as “reverse vaccinology” identified new OMPs as potential vaccine candidates. In contrast to the traditional approaches that have been used to develop vaccines, reverse vaccinology uses the genome sequence of the bacteria to identify likely surface-exposed candidate antigens and then, after expression of the protein and preclinical immunisation experiments, selects those proteins that meet set criteria as potential vaccine candidates. In the case of 4CMenB, these antigens include factor H binding protein (fHbp), neisserial adhesion A (NadA), and neisserial heparin-binding antigen (NHBA), which were formulated with the New Zealand outbreak vaccine to produce 4CMenB. In December 2010, a file on 4CMenB was submitted to the European Medicines Agency for a marketing authorisation and was assigned the trade name, Bexsero®.⁶³

b) Safety and predicted effectiveness of 4CMenB

The safety and reactogenicity profile of 4CMenB was evaluated in early phase studies, the majority of which were conducted in the UK, with a large Phase 3 trial conducted in five European countries.^{64, 65} Studies involving over 8000 participants have shown that 4CMenB has an acceptable safety profile. Overall, reactogenicity rates amongst participants receiving 4CMenB with routine vaccines were increased compared with the rates amongst those receiving routine vaccines only or those receiving MenC and routine vaccines. Use of paracetamol to reduce the proportion and level of fever in infants and children < 2 years of age at the time of vaccination has been studied and shown to be effective and therefore recommended in Australia, the UK and Quebec, Canada. In contrast to a previous study that showed a reduction in immunogenicity when concomitant paracetamol was received with routine infant

immunisations,⁶⁶ a Phase II study of children receiving 4CMenB and routine vaccines with or without prophylactic paracetamol showed no important effect on immune response to the concomitant vaccine antigens,^{67, 68}

Safety data from the first population implementation of 4CMenB, in Quebec has shown an acceptable safety profile “in the field”. Of 12,332 completed telephone surveys of a total of 43,740 persons aged 2 months – 20 years receiving their first dose of 4CMenB, 14-15% of children < 2 years were reported as having a fever with one febrile convulsion reported in a one year old child.⁶⁹ Predicting efficacy of MenB vaccines is complicated, not only due to the low incidence of disease but also due to the number of vaccine antigens and the number of naturally occurring protein variants. When clinical efficacy trials are not feasible, appropriate surrogate markers of protection that allow interpretation of immunogenicity are therefore essential. Use of the serum bactericidal antibody (SBA) assay as a correlate of protection has been used in the case of 4CMenB, and is the licensure criterion for the vaccine. The SBA measures functional activity of antibody through complement-mediated lysis of the bacteria. This is the accepted correlate because complement-mediated bacterial killing by bactericidal antibodies is believed to be the primary mechanism of protection against meningococcal disease. The role of antibodies in natural immunity to meningococcal disease was established by Goldschneider *et al.* where an inverse correlation between the incidence of disease and the prevalence of SBA against MenA, MenB and MenC were reported.⁷⁰ The presence of anti-meningococcal antibodies, measured by bactericidal activity (hSBA titer \geq 1:4) using an intrinsic human complement source in the assay, was indicative of protection against systemic meningococcal infection. Thus, an hSBA titre of \geq 4 was used as the established end point measurement for MenB vaccines efficacy. This approach was affirmed in 2005 at a World Health Organization (WHO) sponsored meningococcal serology standardisation workshop⁷¹ and from several efficacy studies of OMV vaccines.^{72, 73} However, a hSBA \geq 1:5 was used in a number of Phase 2 and 3

studies of 4CMenB, to be conservative and due to regulatory requirement.⁷⁴ Despite variation of assays between laboratories, the proportion of participants with a fourfold rise in antibodies remained relatively constant.⁷⁵ Data on SBA activity of pooled serum obtained at approximately 13 months of age from infants immunised with 3 dose priming and 1 dose booster course of 4CMenB indicated 88% of a panel of 40 invasive strains in England and Wales were susceptible to killing by post-immunisation sera.⁷⁶ Nevertheless, whether titres of anti-group B meningococcal bactericidal antibody correlate with true protection from meningococcal disease is unknown without a longitudinal vaccine efficacy trial. Indeed, some studies have suggested that protection against group B infection may also be due to opsonic antibodies and to innate immune responses, which are not demonstrated in the SBA.⁷⁷⁻⁸⁰

4CMenB is immunogenic against a set of four reference strains by testing hSBA responses to vaccine antigens, NadA, fHbp, NHBA and NZ PorA P1.4 in infants (from 2 months of age), toddlers, adolescents and adults up to 50 years of age.^{64, 65, 81-85} A booster dose at one year of age is licensed in the approved vaccination schedule for infants in Australia⁸⁶ and any child immunized under 2 years of age in the EU to support waning immunity.^{74, 87}

Although immunogenicity studies have demonstrated a robust immune response to 4CMenB, efficacy or effectiveness have not yet been proven as efficacy studies are unachievable due to the large number of participants required to show an effect (reduction in meningococcal disease) in view of the rarity of the disease. Strain coverage as determined by Meningococcal Antigen Testing (MATS) suggests that this vaccine could protect against 76% of circulating genotypes causing invasive meningococcal disease in Australia and 73% in England and Wales.^{88, 89} Predicted coverage was shown to vary between states in Australia with coverage potentially as high as 90% in South Australia, 71% in New South Wales and 84% in Queensland with other state coverage estimates less likely to be accurate due to the small number of samples analysed

(Tasmania 45%).⁹⁰ The true effectiveness will not be known until the vaccine is used at a population level, however the PorA component in 4CMenB is common to the MeNZB[®] vaccine which showed 73% effectiveness when implemented in a national immunisation programme in New Zealand. In addition, the potential effect of MenB vaccines on carriage of the meningococcus in the nasopharynx is limited.^{1, 67, 91, 92} Very little is known about the effects of a MenB vaccine on carriage, but there is the potential that introduction of new MenB vaccines may disrupt the usual carriage ecosystem with non-vaccine type replacement genotypes. Provisional results from a Phase III study show 4CMenB had a modest impact on *N. meningitidis* carriage with a decrease of 16.5% in existing carriage.⁹³ Therefore monitoring of clinical severity of disease and sequelae and causative genotypes will be essential prior to, during and after vaccine introduction.¹⁹

c) rLP2086 MenB vaccine

The new MenB vaccine developed by Pfizer includes a MenB outer membrane protein, designated as LP2086 which has been shown to be a bacterial virulence factor and a target for functional bactericidal antibodies. LP2086 was subsequently determined to be fHbp which the bacterium uses to evade complement-mediated bacteriolysis and which is also contained in 4CMenB. The LP2086 amino acid sequences from MenB isolates can be divided into 2 subfamilies, A and B, and 1 member from each family has been included in this investigational vaccine candidate to provide broad coverage against all MenB isolates. Although 4CMenB also contains this important OMP, it only contains fHbp from one sub family, not both.

Clinical trials have been conducted in adolescents, children and toddlers using an initial formulation of the rLP2086 vaccine which then underwent optimisation to improve the stability of the vaccine and increase the immunogenicity.⁹⁴ The initial formulation showed robust immune responses against strains matched to the vaccine antigens but reduced immunogenicity

against divergent strains. Overall, the vaccine has been well-tolerated in clinical trials in adults, adolescents, children and toddlers.⁹⁵⁻⁹⁷ An improved formulation of the rLP2086 has been produced and tested in adults and adolescents with robust immune responses elicited against divergent strains.⁹⁸ Results of a small pilot study of the safety and immunogenicity of rLP2086 in 46 infants, showed high fever rates with 64% and 90% of infants developing fever after receiving one 20- or 60- μ g rLP2086 dose, respectively. Only two infants in the 20- μ g group and one infant in the 60- μ g group experienced fevers $>39.0^{\circ}\text{C}$. Due to these high fever rates, the study was terminated early with the potential use of this vaccine for infants still undetermined.⁹⁹ The majority of clinical trials of the Pfizer candidate rLP2086 MenB vaccine have been conducted in Australia through a network of vaccine trials units; the National Vaccine Research Network.⁹⁴⁻⁹⁸

This vaccine has been developed primarily to provide protection for adolescents. Several recent MenB outbreaks in universities in the USA have confirmed the importance of having available MenB vaccines to control disease transmitted by hyper virulent strains where young people live in close proximity.¹⁰⁰

iv. Potential additional benefits of MenB vaccines

One potential advantage of these OMP containing MenB vaccines is the possibility that they may provide cross protection against disease caused by other capsular groups. As all capsular groups contain OMPs such as fHpb, an incidental benefit may be even broader protection than intended. In vitro studies support this potential benefit.^{101, 102}

As suggested above the impact of the MenB vaccine on carriage remains uncertain but even a modest reduction in colonisation rates, or colonisation density, could potentially contribute to reduction in disease in unvaccinated populations.^{93, 103}

DISCUSSION

Vaccines are now available for the first time with the potential to provide protection against a high proportion of strains causing endemic and epidemic IMD in humans. Until recently, vaccines to provide protection against the Men A, C, W, Y have been available and funded in many countries. A vaccine to provide protection against the commonest strain (MenB) in high income countries is now licensed and available but not yet federally supported in a national immunisation programme. Although group B disease accounts for 85% of IMD cases in Australia, the Pharmaceutical Benefits Advisory Committee (PBAC), Australia has rejected the inclusion of 4CMenB on the National Immunisation Programme Schedule for the prevention of MenB disease in infants and adolescents due to unsatisfactory cost-effective estimates.¹⁰⁴ The PBAC concluded the rarity of the disease does not justify the cost of a mass vaccination programme, with uncertainties around effectiveness and duration of immunity contributing to this decision. However medical professionals and meningococcal research organisations in Australia and the UK have argued that the burden of the disease and long-term impact is not fully understood with effectiveness unlikely to be established until the vaccine is introduced into a national programme.^{105, 106}

In the UK, the vaccine has borderline cost-effectiveness, with an initial analysis finding the vaccine to be just cost-effective at a very modest price¹⁰⁷ a further analysis (published in an interim JCVI statement) finding it unlikely to be cost-effective,⁶⁷ and a final analysis, conducted using updated data, concluding that the vaccine could be cost-effective at a low vaccine price.¹⁰³ The UK process uses published guidance to determine cost-effectiveness and included a period of stakeholder consultation to ensure the best evidence was used to inform the cost-effectiveness model.¹⁰⁸

In the recently released final position statement from the JCVI, a recommendation has been made to the UK Departments of Health that the MenB vaccine should be included in the funded national immunisation programme, if a cost-effective price can be negotiated.¹⁰³ Acknowledged uncertainties about herd immunity, strain coverage, projected disease rates, duration of protection, costs to the health service and efficacy of 4CMenB have resulted in difficulty in evaluating cost-effectiveness of the vaccine, essential to any funding decision.¹⁰⁷ Paradoxically, many of these data will only be available through use of the vaccine in large populations.⁷² The success of a mass immunisation campaign against group C disease in the UK has demonstrated strong evidence of high vaccine efficacy and herd immunity with an 80% reduction in serogroup C disease within 18 months of programme implementation.¹⁰⁹

Cost-effectiveness considerations of funding a MenB vaccine.

Despite the difficulties with cost-effectiveness estimates it is expected that a programme will be implemented in the UK. The final position statement from JCVI acknowledged the importance of contributions from meningitis charities and commented that “the rapid and severe nature of IMD, the burden of disease in infants and young children and the value society places on preventing diseases in its youngest members were considered throughout the committee’s deliberations”.¹⁰³ Reducing the number of vaccinations for MenB immunisation as suggested by the JCVI (2 primary + 1 booster compared to the 3 primary + 1 booster dose recommended by the manufacturer) will contribute to a more cost-effective national programme, however there are limited data on the immunogenicity of this reduced regime. A Phase 2 study comparing 4 doses to a single dose of 4CMenB vaccine, reported good immunogenicity after 2 doses at 2 and 4 months of age.⁶⁴ Reduced dose schedules have been introduced with other vaccine programmes (3 doses rather than the recommended 4 doses of Prevenar7/13 in the UK and Australian immunisation programmes).

The availability of two licensed MenB vaccines in Australia is a much closer reality with the second MenB vaccine being licensed in the USA very recently for use in adolescents and young adults 10-25 years of age.

There are other likely societal benefits from introduction of MenB vaccines including reduction in public anxiety and fear about IMD.

Education of parents and immunisation providers about the use of MenB vaccines is important prior to introduction of a funded programme. The increased incidence of fever seen with 4CMenB could result in increased medical attention or lead to lower uptake of subsequent vaccinations and therefore, parental and healthcare professional education about the potential reactogenicity of 4CMenB when administered with other concomitant immunisations will be important, in addition to the use of paracetamol/acetaminophen. A recent study identified that despite the potential for 4CMenB to cause fever in infants, parents and the community as a whole considered the benefits of this vaccine outweighed the risks.¹¹⁰ Only 10.8% (95% CI; 8.5–13.2) of parents reported they would be less likely to have their child immunised with a MenB vaccine due to potential associated mild-moderate fever. A further study has indicated that family physicians regard the MenB vaccine for children the highest priority for a funded programme compared to currently unfunded but recommended pertussis, influenza and human papillomavirus vaccine programmes.¹¹¹

CONCLUSION

Although eradication of the meningococcus bacteria is not achievable through vaccination and not necessarily desirable, the potential to reduce severe invasive meningococcal disease is a real possibility. There is a strong theoretical basis and early emerging evidence to suggest that these OMP based vaccines such as the new MenB vaccines may provide not only protection against group B strains but potentially could provide cross protection against other capsular groups. However significant reduction in meningococcal disease is likely to require the dual approach of both an infant and adolescent immunisation programme to provide protection to age groups where the highest rates of IMD occur and to optimise the potential herd immunity effects which have been so important in the success of conjugate meningococcal vaccines. Such an impact depends critically on the extent and duration of protection against carriage (and therefore herd immunity), which remains an unknown parameter. Furthermore, while an infant or adolescent programme could be cost-effective depending on the different modeling scenarios applied, for an adolescent programme this would be dependent on the vaccine providing long term protection against both disease and carriage.¹¹²

Surveillance of IMD following introduction of a MenB vaccine in the UK, Australia and other countries will be essential to determine how effective the vaccine is, and identify problems with increased reactogenicity including additional health care utilisation, any herd immune effects and any replacement disease with new virulent or non-virulent meningococcal strains emerging.

The opportunity to reduce rates of meningococcal disease is within reach and is an important consideration when prioritising vaccines for national immunisation programmes.

REFERENCES

1. Bilukha OO, Rosenstein N, National Center for Infectious Diseases (CDC), Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recommendations and reports : Morbidity and mortality weekly report Recommendations and reports / Centers for Disease Control. 2005;54(RR-7):1-21.
2. Peltola H. Meningococcal disease: still with us. Rev Infect Dis. 1983;5(1):71-91.
3. Trotter CL, Chandra M, Cano R, et al. A surveillance network for meningococcal disease in Europe. FEMS Microbiol Rev. 2007;31(1):27-36.
4. Borg J, Christie D, Coen PG, Booy R, Viner RM. Outcomes of meningococcal disease in adolescence: prospective, matched-cohort study. Pediatrics. 2009;123(3):e502-9.
5. Davis KL, Misurski D, Miller J, Karve S. Cost impact of complications in meningococcal disease: evidence from a United States managed care population. Hum Vaccin. 2011;7(4):458-65.
6. Karve S, Misurski D, Miller J, Davis KL. Costs of Sequelae Associated with Invasive Meningococcal Disease: Findings from a US Managed Care Population. Health Outcomes Research in Medicine. 2011;2(4):e215-e26.
7. Wang B, Clarke M, Thomas N, Howell S, Afzali HH, Marshall H. The clinical burden and predictors of sequelae following invasive meningococcal disease in Australian children. Pediatr Infect Dis J. 2014;33(3):316-8.

8. Atkinson W. Epidemiology and prevention of vaccine-preventable diseases: Dept. of Health & Human Services, Public Health Service, Centers for Disease Control and Prevention; 2000.
9. Surveillance of invasive bacterial diseases in Europe 2008/2009. European Centre for Disease Prevention and Control, 2011, Stockholm: ECDC, viewed 21 April 2014, <http://www.ecdc.europa.eu/en/publications/Publications/1107_SUR_IBD_2008-09.pdf>.
10. Hershey JH, Hitchcock W. Epidemiology and meningococcal serogroup distribution in the United States. *Clinical Pediatrics*. 2010;49(6):519-24.
11. Safadi MA, Cintra OA. Epidemiology of meningococcal disease in Latin America: current situation and opportunities for prevention. *Neurol Res*. 2010;32(3):263-71.
12. Chiu C, Dey A, Wang H, et al. Vaccine preventable diseases and vaccination coverage in Australia, 2005 to 2007. *Commun Dis Intell Q Rep*. 2010;34(Supplement):S50-6.
13. Notification Rate of Meningococcal disease (invasive)*, received from State and Territory health authorities in the period of 1991 to 2012 and year-to-date notifications for 2013 [database on the Internet], Department of Health and Ageing, viewed 8 November 2013, <http://www9.health.gov.au/cda/source/rpt_4.cfm>.
14. Ladhani SN, Flood JS, Ramsay ME, et al. Invasive meningococcal disease in England and Wales: implications for the introduction of new vaccines. *Vaccine*. 2012;30(24):3710-6.
15. Stephens DS, Greenwood B, Brandtzaeg P. Epidemic meningitis, meningococcaemia, and *Neisseria meningitidis*. *Lancet*. 2007;369(9580):2196-210.
16. Davies EG. The immunology of neonates and children and its relation to susceptibility to infection. *Infectious Diseases in the Pediatric Intensive Care Unit*. Berlin: Springer; 2008:1-58.

17. Harrison LH, Trotter CL, Ramsay ME. Global epidemiology of meningococcal disease. *Vaccine*. 2009;27 Suppl 2:B51-63.
18. Kliegman R. *Nelson Textbook of Pediatrics*: Elsevier/Saunders; 2011.
19. Lahra MM, Enriquez RP. Annual report of the Australian Meningococcal Surveillance Programme, 2012. *Commun Dis Intell Q Rep*. 2013;37(3):E224-32.
20. Cartwright KA, Jones DM, Smith AJ, Stuart JM, Kaczmarski EB, Palmer SR. Influenza A and meningococcal disease. *Lancet*. 1991;338(8766):554-7.
21. Creasey SA. Epidemic meningococcal meningitis in central Australia in the 1970s. *Med J Aust*. 1991;155(10):725-6.
22. Jones D. *Epidemiology of Meningococcal Disease in Europe and the USA*. Meningococcal disease. Chichester, UK: Wiley; 1995.
23. Patel MS, Merianos A, Hanna JN, et al. Epidemic meningococcal meningitis in central Australia, 1987-1991. *Med J Aust*. 1993;158(5):336-40.
24. Nadel S. Prospects for eradication of meningococcal disease. *Arch Dis Child*. 2012;97(11):993-8.
25. Broker M, Jacobsson S, Kuusi M, et al. Meningococcal serogroup Y emergence in Europe: update 2011. *Hum Vaccin Immunother*. 2012;8(12):1907-11.
26. Public Health England. *Invasive meningococcal infections (England and Wales), annual report for 2011/12*. Health Protection Report.2013;7(18-22).
27. Boisier P, Nicolas P, Djibo S, et al. Meningococcal meningitis: unprecedented incidence of serogroup X-related cases in 2006 in Niger. *Clin Infect Dis*. 2007;44(5):657-63.

28. Active Bacterial Core Surveillance Report: Emerging Infections Program Network, *Neisseria meningitidis*, Centers for Disease Control and Prevention, 2012, viewed 21 April 2014, <<http://www.cdc.gov/abcs/reports-findings/survreports/mening12.html>>.
29. Viner RM, Booy R, Johnson H, et al. Outcomes of invasive meningococcal serogroup B disease in children and adolescents (MOSAIC): a case-control study. *Lancet Neurol*. 2012;11(9):774-83.
30. Bettinger JA, Scheifele DW, Le Saux N, Halperin SA, Vaudry W, Tsang R; Members of Canadian Immunization Monitoring Program, Active (IMPACT). The disease burden of invasive meningococcal serogroup B disease in Canada. *Pediatr Infect Dis J*. 2013 Jan;32(1):e20-5
31. Grimwood K, Anderson VA, Bond L, et al. Adverse outcomes of bacterial meningitis in school-age survivors. *Pediatrics*. 1995;95(5):646-56.
32. Guimont C, Hullick C, Durrheim D, Ryan N, Ferguson J, Massey P. Invasive meningococcal disease--improving management through structured review of cases in the Hunter New England area, Australia. *J Public Health (Oxf)*. 2010;32(1):38-43.
33. Hansman D. Meningococcal disease in South Australia: incidence and serogroup distribution 1971-1980. *J Hyg (Lond)*. 1983;90(1):49-54.
34. Olesch CA, Knight GJ. Invasive meningococcal infection in Western Australia. *J Paediatr Child Health*. 1999;35(1):42-8.
35. de Jonge RC, van Furth AM, Wassenaar M, Gemke RJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infect Dis*. 2010;10:232.

36. Hahne SJ, Charlett A, Purcell B, et al. Effectiveness of antibiotics given before admission in reducing mortality from meningococcal disease: systematic review. *BMJ (Clinical research ed)*. 2006;332(7553):1299-303.
37. Garralda ME, Gledhill J, Nadel S, Neasham D, O'Connor M, Shears D. Longer-term psychiatric adjustment of children and parents after meningococcal disease. *Pediatr Crit Care Med*. 2009;10(6):675-80.
38. Borrow R, Goldblatt D, Andrews N, Richmond P, Southern J, Miller E. Influence of prior meningococcal C polysaccharide vaccination on the response and generation of memory after meningococcal C conjugate vaccination in young children. *J Infect Dis*. 2001;184(3):377-80.
39. Gold R, Lepow ML, Goldschneider I, Draper TL, Gotschlich EC. Clinical evaluation of group A and group C meningococcal polysaccharide vaccines in infants. *J Clin Invest*. 1975;56(6):1536-47.
40. Dellicour S, Greenwood B. Systematic review: Impact of meningococcal vaccination on pharyngeal carriage of meningococci. *Trop Med Int Health*. 2007;12(12):1409–1421.
41. Centers for Disease Control and Prevention. Recommendations of the Advisory Committee on Immunization Practices (ACIP): Prevention and control of meningococcal disease. *MMWR* 2013;62(RR-2):14.
42. Ramsay ME, Andrews NJ, Trotter CL, Kaczmarski EB, Miller E. Herd immunity from meningococcal serogroup C conjugate vaccination in England: database analysis. *BMJ (Clinical research ed)*. 2003;326(7385):365-6.
43. Campbell H, Andrews N, Borrow R, Trotter C, Miller E. Updated postlicensure surveillance of the meningococcal C conjugate vaccine in England and Wales: effectiveness,

validation of serological correlates of protection, and modeling predictions of the duration of herd immunity. *Clin Vaccine Immunol.* 2010;17(5):840-7.

44. Changes to the meningococcal C conjugate (MenC) vaccine schedule 2013 to 2014: advice for healthcare professionals. London: Department of Health; 2014 [cited 21 April 2014].

45. Collard JM, Issaka B, Zaneidou M, et al. Epidemiological changes in meningococcal meningitis in Niger from 2008 to 2011 and the impact of vaccination. *BMC Infect Dis.* 2013;13(1):576.

46. Daugla DM, Gami JP, Gamougam K, et al. Effect of a serogroup A meningococcal conjugate vaccine (PsA–TT) on serogroup A meningococcal meningitis and carriage in Chad: a community study. *Lancet.* 2014;383(9911):40-7.

47. Wyle FA, Artenstein MS, Brandt BL, et al. Immunologic response of man to group B meningococcal polysaccharide vaccines. *J Infect Dis.* 1972;126(5):514-21.

48. Zollinger WD, Mandrell RE, Griffiss JM, Altieri P, Berman S. Complex of meningococcal group B polysaccharide and type 2 outer membrane protein immunogenic in man. *J Clin Invest.* 1979;63(5):836-48.

49. Finne J, Leinonen M, Makela PH. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. *Lancet.* 1983;2(8346):355-7.

50. Zollinger WD, Moran EE, Devi SJ, Frasch CE. Bactericidal antibody responses of juvenile rhesus monkeys immunized with group B *Neisseria meningitidis* capsular polysaccharide-protein conjugate vaccines. *Infect Immun.* 1997;65(3):1053-60.

51. Williams JN, Skipp PJ, Humphries HE, Christodoulides M, O'Connor CD, Heckels JE. Proteomic analysis of outer membranes and vesicles from wild-type serogroup B *Neisseria meningitidis* and a lipopolysaccharide-deficient mutant. *Infect Immun*. 2007;75(3):1364-72.
52. Devoe IW, Gilchrist JE. Release of endotoxin in the form of cell wall blebs during in vitro growth of *Neisseria meningitidis*. *J Exp Med*. 1973;138(5):1156-67.
53. Oster P, Lennon D, O'Hallahan J, Mulholland K, Reid S, Martin D. MeNZB: a safe and highly immunogenic tailor-made vaccine against the New Zealand *Neisseria meningitidis* serogroup B disease epidemic strain. *Vaccine*. 2005;23(17-18):2191-6.
54. Tapsall J. Annual report of the Australian Meningococcal Surveillance Programme, 2007-
-Amended. *Commun Dis Intell Q Rep*. 2009;33(1):1-9.
55. 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 Vaccin Immunother*. 2013;9(6):1241-53.
56. McNicholas A, Galloway Y, Stehr-Green P, et al. Post-marketing safety monitoring of a new group B meningococcal vaccine in New Zealand, 2004-2006. *Hum Vaccin*. 2007;3(5):196-204.
57. Arnold R, Galloway Y, McNicholas A, O'Hallahan J. Effectiveness of a vaccination programme for an epidemic of meningococcal B in New Zealand. *Vaccine*. 2011;29(40):7100-6.
58. Galloway Y, Stehr-Green P, McNicholas A, O'Hallahan J. Use of an observational cohort study to estimate the effectiveness of the New Zealand group B meningococcal vaccine in children aged under 5 years. *Int J Epidemiol*. 2009;38(2):413-8.

59. Bai X, Borrow R. Genetic shifts of *Neisseria meningitidis* serogroup B antigens and the quest for a broadly cross-protective vaccine. *Expert Rev Vaccines*. 2010;9(10):1203-17.
60. Food and Drug administration, Vaccines, bloods and biologics; Trumenba. Viewed 03 November 2014, <<http://www.fda.gov/biologicsbloodvaccines/vaccines/approvedproducts/ucm421020.htm>>.
61. Food and Drug Administration Safety and Innovation Act. U. S. Food Drug Administration, 2012, viewed 15 April 2014, <<http://www.gpo.gov/fdsys/pkg/PLAW-112publ144/pdf/PLAW-112publ144.pdf>>.
62. Frequently asked questions: breakthrough therapies. U. S. Food Drug Administration, 2014, viewed 15 April 2014, <<http://www.fda.gov/regulatoryinformation/legislation/federalfooddrugandcosmeticactfdcaact/significantamendmentstotheact/fdasia/ucm341027.htm>>.
63. Bai X, Findlow J, Borrow R. Recombinant protein meningococcal serogroup B vaccine combined with outer membrane vesicles. *Expert Opin Biol Ther*. 2011;11(7):969-85.
64. 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):1127-37.
65. 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):825-35.

66. 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;374(9698):1339-
67. Joint Committee on Vaccination and Immunisation (JCVI) interim position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health, 24 July 2013, viewed 2 September 2013, <<https://www.gov.uk/government/publications/jcvi-interim-position-statement-on-the-use-of-bexsero-meningococcal-b-vaccine-in-the-uk>>.
68. 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 Vaccin Immunother*. 2014;10(7).
69. Rapport interimaire de surveillance de la securite de la premiere dose du vaccine contre le meningocoque de serogroup B au Saguenay-Lac-Saint-Jean. Institut national de sante publique du Quebec. Viewed 09 November 2014, <http://www.inspq.qc.ca/pdf/publications/1885_Vaccin_Menincogoque_SerogroupeB.pdf>.
70. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus. I. The role of humoral antibodies. *J Exp Med*. 1969;129(6):1307-26.
71. Borrow R, Carlone GM, Rosenstein N, et al. Neisseria meningitidis group B correlates of protection and assay standardization--international meeting report Emory University, Atlanta, Georgia, United States, 16-17 March 2005. *Vaccine*. 2006;24(24):5093-107.
72. Bjune G, Gronnesby JK, Hoiby EA, Closs O, Nokleby H. Results of an efficacy trial with an outer membrane vesicle vaccine against systemic serogroup B meningococcal disease in Norway. *NIPH Ann*. 1991;14(2):125-30; discussion 30-2.

73. Holst J, Feiring B, Fuglesang JE, et al. Serum bactericidal activity correlates with the vaccine efficacy of outer membrane vesicle vaccines against *Neisseria meningitidis* serogroup B disease. *Vaccine*. 2003;21(7-8):734-7.
74. Martin NG, Snape MD. A multicomponent serogroup B meningococcal vaccine is licensed for use in Europe: what do we know, and what are we yet to learn? *Expert Rev Vaccines*. 2013;12(8):837-58.
75. Borrow R, Balmer P, Miller E. Meningococcal surrogates of protection--serum bactericidal antibody activity. *Vaccine*. 2005;23(17-18):2222-7.
76. Frosi G, Biolchi A, Lo Sapio M, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. *Vaccine*. 2013;31(43):4968-74.
77. Lehmann AK, Halstensen A, Naess A, Vollset SE, Sjursen H, Bjune G. Immunization against serogroup B meningococci. Opsonin response in vaccinees as measured by chemiluminescence. *APMIS*. 1991;99(8):769-72.
78. Lehmann AK, Halstensen A, Aaberge IS, et al. Human opsonins induced during meningococcal disease recognize outer membrane proteins PorA and PorB. *Infect Immun*. 1999;67(5):2552-60.
79. Lehmann AK, Gorringer AR, Reddin KM, West K, Smith I, Halstensen A. Human opsonins induced during meningococcal disease recognize transferrin binding protein complexes. *Infect Immun*. 1999;67(12):6526-32.

80. Ison CA, Anwar N, Cole MJ, et al. Assessment of immune response to meningococcal disease: comparison of a whole-blood assay and the serum bactericidal assay. *Microb Pathog.* 1999;27(4):207-14.
81. 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.* 2012;307(6):573-82.
82. Snape MD, Dawson T, Oster P, et al. Immunogenicity of two investigational serogroup B meningococcal vaccines in the first year of life: a randomized comparative trial. *Pediatr Infect Dis J.* 2010;29(11):e71-9.
83. Santolaya ME, O'Ryan ML, Valenzuela MT, et al. Immunogenicity and tolerability of a multicomponent meningococcal serogroup B (4CMenB) vaccine in healthy adolescents in Chile: a phase 2b/3 randomised, observer-blind, placebo-controlled study. *Lancet.* 2012;379(9816):617-24.
84. Kimura A, Toneatto D, Kleinschmidt A, Wang H, Dull P. Immunogenicity and safety of a multicomponent meningococcal serogroup B vaccine and a quadrivalent meningococcal CRM197 conjugate vaccine against serogroups A, C, W-135, and Y in adults who are at increased risk for occupational exposure to meningococcal isolates. *Clin Vaccine Immunol.* 2011;18(3):483-6.
85. 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 Vaccines.* 2011;7(6):646-53.

86. Australian Technical Advisory Group on Immunisation, Advice for immunisation providers regarding the use of Bexsero®—a recombinant multicomponent meningococcal B vaccine (4CMenB). Australian Government Department of Health, 2014, viewed 21 April 2014, <[http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/85A6879534C02B4DCA257B640002F38E/\\$File/ATAGI-advice-bexsero.pdf](http://www.immunise.health.gov.au/internet/immunise/publishing.nsf/Content/85A6879534C02B4DCA257B640002F38E/$File/ATAGI-advice-bexsero.pdf)>.
87. Summary of Product Characteristics: Bexsero Meningococcal Group B vaccine for injection in pre-filled syringe. eMC, 02 December 2013, viewed 21 April 2014, <<http://www.medicines.org.uk/emc/medicine/28407/SPC/Bexsero+Meningococcal+Group+B+vaccine+for+injection+in+pre-filled+syringe/>>.
88. Tozer SJ, Whiley DM, Smith HV, et al. Use of the meningococcal antigen typing system (MATS) to assess the Australian meningococcal strain coverage with 4CMenB serogroup b vaccine. 27th Congress of the International Pediatric Association; 28 August 2013; Melbourne, Australia.
89. Vogel U, Taha MK, Vazquez JA, et al. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. *Lancet Infect Dis.* 2013;13(5):416-25.
90. Serruto D, Bambini S, Tomita T, Hogg G, Sloots TP, Nissen MD. Use of the Meningococcal Antigen Typing System (MATS) to Assess Australian Epidemiology and Meningococcal Strain Coverage With a Multicomponent Serogroup B Vaccine. International Congress of Paediatrics, Melbourne, Australia 2013.
91. Bjune G. "Herd immunity" and the meningococcal vaccine trial in Norway. *Lancet.* 1992;340(8814):315.

92. Perkins BA, Jonsdottir K, Briem H, et al. Immunogenicity of two efficacious outer membrane protein-based serogroup B meningococcal vaccines among young adults in Iceland. *J Infect Dis.* 1998;177(3):683-91.
93. Read RC, Baxter D, Chadwick DR, Faust S, Finn A, Gordon S. Impact of a quadrivalent conjugate (MenACWY-CRM) or a serogroup B (4CMenB) meningococcal vaccine on meningococcal carriage in English university students. 31st Annual Meeting of the European Society of Paediatric Infectious Diseases 2013; Milan, Italia.
94. Marshall HS, Richmond PC, Nissen MD, et al. Safety and immunogenicity of a meningococcal B bivalent rLP2086 vaccine in healthy toddlers aged 18-36 months: a phase 1 randomized-controlled clinical trial. *Pediatr Infect Dis J.* 2012;31(10):1061-8.
95. Marshall HS, Richmond PC, Nissen MD, et al. A phase 2 open-label safety and immunogenicity study of a meningococcal B bivalent rLP2086 vaccine in healthy adults. *Vaccine.* 2013;31(12):1569-75.
96. Richmond PC, Nissen MD, Marshall HS, et al. A bivalent *Neisseria meningitidis* recombinant lipidated factor H binding protein vaccine in young adults: results of a randomised, controlled, dose-escalation phase 1 trial. *Vaccine.* 2012;30(43):6163-74.
97. Nissen MD, Marshall HS, Richmond PC, et al. A randomized, controlled, phase 1/2 trial of a *Neisseria meningitidis* serogroup B bivalent rLP2086 vaccine in healthy children and adolescents. *Pediatr Infect Dis J.* 2013;32(4):364-71.
98. Richmond PC, Marshall HS, Nissen MD, et al. Safety, immunogenicity, and tolerability of meningococcal serogroup B bivalent recombinant lipoprotein 2086 vaccine in healthy adolescents: a randomised, single-blind, placebo-controlled, phase 2 trial. *Lancet Infect Dis.* 2012;12(8):597-607.

99. Martinon-Torres F, Gimenez-Sanchez F, Bernaola-Iturbe E, Diez-Domingo J, Jiang Q, Perez JL. A randomized, phase ½ trial of the safety, tolerability, and immunogenicity of bivalent rLP2086 meningococcal B vaccine in healthy infants. *Vaccine*. 2014;32(40):5206-11.
100. Serogroup B Meningococcal Vaccine and Outbreaks. Centers for Disease Control and Prevention, viewed 04 April 2014, <<http://www.cdc.gov/meningococcal/outbreaks/vaccine-serogroupB.html>>.
101. Hong E, Giuliani MM, Deghmane AE, et al. Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control *Neisseria meningitidis* capsular group X outbreaks in Africa? *Vaccine*. 2013;31(7):1113-6.
102. Claus H, Borrow R, Taha M-K, et al. Potential coverage of the 4CMenB vaccine in non-B meningococci. 18th International Pathogenic *Neisseria* Conference 2012; Wurzburg, Germany.
103. JCVI position statement on use of Bexsero® meningococcal B vaccine in the UK. London: Department of Health, 21 March 2014, viewed 04 April 2014, <<https://www.gov.uk/government/publications/meningococcal-b-vaccine-jcvi-position-statement>>.
104. November 2013 PBAC Meeting Outcomes - "1st time" decisions not to recommend. Canberra: Department of Health, 2013, viewed 20 January 2014, <<http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes>>.
105. Patients want "compassion" on meningococcal vaccine. *PharmaDispatch*; 15 January 2014, viewed 20 January 2014, <<http://www.pharmadispatch.com/patients-want-compassion-on-meningococcal-vaccine/>>.
106. Head C. Immunisation against meningococcus B. *The Lancet*. 2013;382(9896):935.

107. Christensen H, Hickman M, Edmunds WJ, Trotter CL. Introducing vaccination against serogroup B meningococcal disease: an economic and mathematical modelling study of potential impact. *Vaccine*. 2013;31(23):2638-46.
108. Minute of the meeting on 11th/12th February 2014. London: Department of Health, 2014, viewed 16 April 2014, <<https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation>>.
109. Miller E, Salisbury D, Ramsay M. Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story. *Vaccine*. 2001;20 Suppl 1:S58-67.
110. Marshall H, Clarke M, Sullivan T. Parental and community acceptance of the benefits and risks associated with meningococcal B vaccines. *Vaccine*. 2014;32(3):338-44.
111. Taylor K, Stocks N, Marshall H. The missing link: family physician perspectives on barriers and enablers to prescribing non-funded vaccines. *Vaccine*. 2014 Jul 16;32(33):4214-9.
112. Pollard AJ, Riordan A, Ramsay M. Group B meningococcal vaccine: recommendations for UK use. *Lancet*. 2014;383(9923):1103-4.