

Can we control all-cause meningococcal disease in Europe?

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Abstract

Invasive disease caused by *Neisseria meningitidis* is potentially devastating, with a case-fatality rate of 5-15% and high rates of significant sequelae among survivors following septicaemia or meningitis. Capsular group C (MenC) conjugate vaccines have been highly successful in achieving control of MenC disease across Europe, and some countries have also introduced quadrivalent MenACWY conjugate vaccines to reduce disease caused by groups A, W and Y in addition. These vaccines elicit putatively protective levels of bactericidal antibodies in all age groups, induce immunological memory and reduce nasopharyngeal carriage, thereby leading to herd protection. Protein-based meningococcal vaccines based on subcapsular components, and designed primarily to target MenB disease, have recently been licensed. These vaccines are highly immunogenic in infants and adolescents, inducing bactericidal antibodies against strains expressing high levels of vaccine antigens which are identical to the variants present in the vaccines. Effectiveness of these vaccines at a population level will be determined by whether vaccine-induced antibodies provide cross-protection against variants of the vaccine antigens present on the surface of the diverse collection of circulating invasive strains. The level of serum bactericidal activity induced against strains seems also to depend on the level of expression of the vaccine antigens. The duration of protection and impact on carriage of meningococci will have a major bearing on the overall effectiveness of the programme. In September 2015 the UK became the first country to introduce 4CMenB into a national routine immunisation schedule and data on the effectiveness of this program are anticipated in the next few years.

Introduction

Neisseria meningitidis (the meningococcus) is a Gram-negative diplococcus, categorised into capsular groups on the basis of the polysaccharide capsule. Six of the 12 groups (A, B, C, W, X and Y) are responsible for almost all cases of invasive disease worldwide [1]. It is a common nasopharyngeal commensal, found in approximately 10% of the population, but bacteria occasionally enter the bloodstream to cause devastating invasive diseases such as meningitis and septicaemia [2]. In Europe it is a rare endemic disease, although hyperendemic and epidemic disease patterns also occur. Onset of disease in susceptible individuals may be very rapid and the case-fatality rate (CFR) is high, especially in those with septic shock [3, 4]. There are high rates of long-term neurological and non-neurological sequelae among survivors [5-12]. Individual susceptibility involves a complex relationship between environmental, host and bacterial factors, and prevention of disease through vaccination offers the only realistic prospect for disease control. The recent license of vaccines designed to control endemic disease caused by capsular group B (MenB) organisms has made the possibility of control of all-cause disease (i.e. disease caused by all groups) a step closer.

Why should we want to control meningococcal disease?

The spectrum of meningococcal infection ranges from asymptomatic nasopharyngeal carriage to fulminant septic shock, which can result in death within a few hours. Septicaemia and acute meningitis are the commonest manifestations of invasive disease. Classical meningococcal septicemia is one of the most recognisable clinical syndromes, with fever and widespread purpura, with or without shock. Occult bacteremia and chronic meningococcemia can also occur. A small number of individuals develop focal infections such as pneumonia,

septic arthritis, osteomyelitis, myocarditis, pericarditis, peritonitis, conjunctivitis, endophthalmitis, sinusitis and otitis media.

A major reason for the poor outcomes from invasive disease, and hence the importance of achieving disease control through prevention, is the rapid progression from a non-specific febrile illness indistinguishable from minor viral infections to fulminant septicaemia and/or severe meningitis. In children who ultimately develop septicaemia, the most frequent early symptoms are fever, nausea and vomiting and lethargy. A blanching, salmon-coloured, maculopapular rash, similar to viral exanthema, may also be present [13]. As disease progresses, signs of shock start to become apparent. A rash is present in 70-80% of meningococcal bacteraemia cases at hospital presentation and is usually non-blanching (i.e. petechial or purpuric). A study of prehospital symptoms showed that most affected patients have only non-specific symptoms in the first 4 to 6 hours, with the typical features of petechial/haemorrhagic rash, meningism and impaired consciousness developing later at a median of 13 to 22 hours [14]. In those with meningitis, the classical manifestations observed in older children are rarely present in infants and young children, when disease is most common. The illness usually begins with fever, nausea and vomiting, photophobia and severe headache. Occasionally the first sign is a seizure, but this can also occur later in disease. Irritability, delirium and altered level of consciousness develop as central nervous system (CNS) inflammation progresses. The most specific signs are neck stiffness, associated with Kernig and Brudzinski signs, but these are often absent in children. Focal neurological abnormalities may also occur [13]. In some cases of meningitis signs of raised intracranial pressure occur. Where septicaemia and meningitis co-exist, neurological symptoms and signs are due to a combination of cerebral ischaemia and meningeal inflammation.

Despite advances in critical care and specific therapy with β -lactam antibiotics, the CFR in resource-rich countries has remained around 5-15% since the 1950s. This varies depending on disease presentation – meningitis has a CFR of approximately 1% in Europe [3, 15] and 4% in the meningitis belt of sub-Saharan Africa [16], while septic shock in the absence of meningitis has a CFR of 16-52% [3, 4]. Some specialist centres have recently published improved survival data (CFR of 5%) following early aggressive circulatory support [17, 18]. Complications of disease occur during both the early, acute phase and also later, resulting in long-term sequelae (Table 1). Long-term, survivors have very high rates of significant sequelae (up to 20 to 30% in most studies), leading to long-term disability [5]. Studies with long-term follow-up of up to 15 years have found rates of sequelae up to 50-60%, including physical and neuropsychiatric problems [6-12]. Significant emotional problems in close family members have also been found in these studies, highlighting the societal impact of this disease.

The rapid onset, difficulty in early diagnosis, severity of disease, and high CFR are features of meningococcal disease which support the use of vaccines as the appropriate public health strategy for control of disease. The recent license of vaccines targeting MenB have now made control of disease caused by all capsular groups a possibility.

Epidemiology of meningococcal disease in Europe

Invasive disease is rare in Europe, with rates of 0.11-1.77 cases per 100,000 population, depending on the country (Figure 1). Between 2008 and 2012 there was a slight decrease in the overall incidence rate from 0.95 per 100,000 per year to 0.68 per 100,000 per year, with

highest rates in the UK, Ireland and Lithuania. Highest disease incidence rates occur in infants under 1 year of age (>10 per 100,000 per year), followed by 1-4 year-olds and adolescents/young adults aged 15-24 years (Figure 2). The majority of cases in 2012 were caused by group B organisms (68%), followed by group C (17%), Y (8%) and W (4%). Between 2008 and 2012 there was a decrease in the number of cases caused by group B and C organisms. In part this can be attributed to introduction of capsular group C (MenC) conjugate vaccines in a number of countries (Figure 3); however until 2015 there have been no licensed vaccines targeting MenB and this decrease is probably part of the natural fluctuations in disease incidence [19]. Other factors which could have contributed to this decrease include changes in other known risk factors, such as reduction in the prevalence of smoking in many countries [20] and more widespread use of influenza vaccines. Disease rates also fluctuate due to changes in population immunity relating to the arrival and disappearance of new clones, some of which have much higher virulence. Almost all European countries include 1-3 doses of the monovalent MenC conjugate vaccine in the routine childhood immunisation schedule [21]. In Austria and Greece, an adolescent booster of the quadrivalent MenACWY conjugate vaccine is used, and in the Czech Republic the quadrivalent vaccine is used for all 3 doses. In the UK there has been an increase in capsular group W (MenW) disease due to expansion of a hypervirulent strain, from 22 cases in 2009 to almost 180 in 2014-15 [22, 23]. In 2013-14, MenW was responsible for 15% of all cases of invasive disease, compared to historical levels of 1-2% [24]. In response to this increase, the adolescent booster dose in the UK was changed from the monovalent MenC vaccine to quadrivalent MenACWY vaccine in September 2015 [25]. The dynamic nature of meningococcal disease epidemiology highlighted here emphasises the need for continued high quality surveillance systems across Europe and National Immunisation Technical

Advisory Groups who are able to rapidly respond to epidemiological changes, utilising all available vaccines to achieve optimal disease control, irrespective of capsular group.

Meningococcal vaccines for capsular groups A, C, W and Y

The first meningococcal vaccines in regular use were plain polysaccharide vaccines, and these are based on the capsule which surrounds the organism and is used for grouping. These purified polysaccharide group-specific vaccines were produced to target disease caused by groups A, C, W and Y. They are effective in protecting older children and adults against disease, but the resulting immune response does not involve recruitment of helper T cells, and therefore these vaccines do not induce immunological memory, induce short-term protection only, are associated with immunological hyporesponsiveness (reduced responses after administration of booster doses), and do not elicit a response in children under 2 years of age [26-31]. In the 1990s conjugate vaccines, which are able to overcome these problems, were successfully developed whereby the polysaccharides were conjugated to protein carriers, such as tetanus toxoid and CRM₁₉₇ (a non-toxic genetic variant of diphtheria toxin) [32]. The first monovalent MenC conjugate vaccines were licensed in the UK in 1999 and subsequently in the rest of Europe. These conjugate vaccines were introduced into the UK routine immunisation programme from November 1999, and between 1999 and 2001 there was a reduction in MenC cases of 87% among the vaccinated groups [33].

Following the success of monovalent MenC conjugate vaccines, the same technology was used to develop conjugate vaccines targeting other capsular groups. In 2005, the first quadrivalent ACWY conjugate vaccine was licensed in the USA, and multiple quadrivalent conjugate vaccines are now available with different protein carriers (diphtheria toxoid,

CRM₁₉₇ and tetanus toxoid). These multivalent formulations elicit antibody responses that are at least as good as their plain polysaccharide counterparts but have the inherent advantages of conjugate vaccines. In the USA there are high rates of disease caused by groups B, C and Y so the Advisory Committee on Immunization Practices (ACIP) recommends the routine immunisation of adolescents with the MenACWY conjugate vaccine at 11-12 years of age, with a booster dose at age 16 years [34]. The rate of disease caused by groups C, W and Y in the USA has decreased in 11-19 year olds from 1.13 per 100,000 per year in 1998-99 to 0.05 per 100,000 per year in 2010-11, although this rate was already decreasing prior to vaccine introduction in 2005. An affordable monovalent MenA-tetanus toxoid conjugate vaccine has been produced for use in the meningitis belt of sub-Saharan Africa, following collaboration between the World Health Organisation (WHO), Food and Drug Administration (FDA), PATH, National Institute of Health, the Serum Institute of India (who manufacture the vaccine) and the Bill & Melinda Gates Foundation [35]. It was rolled out from 2010 and has resulted in a 94% reduction in disease incidence in Chad [36, 37], with no reports of group A meningococcal meningitis among vaccinated individuals. However, other capsular groups have since caused significant outbreaks in the meningitis belt, demonstrating the need for multivalent meningococcal conjugate vaccines for this population.

Conjugate vaccines have been the mainstay of meningococcal disease control globally over the last 15 years with the incredible success of conjugate vaccines to dramatically reduce disease caused by capsular group A, C, W and Y. Based on the capsular group distribution of disease in Europe in 2012, only 17% of current disease is preventable with monovalent MenC vaccines and 29% with MenACWY vaccines [38]. The majority of disease in endemic countries is therefore now caused by capsular group B *N. meningitidis*.

Meningococcal vaccines for capsular group B

The group B polysaccharide capsule is not a suitable vaccine candidate

The polysaccharide capsule of group B meningococci is not immunogenic in humans due to structural homology between the polysaccharide and human tissue, leading to immunological tolerance. The key component of the serogroup B capsule is an $\alpha(2-8)$ linked sialic acid homopolymer, which contains epitopes that are cross-reactive with the polysialylated form of the neural cell adhesion molecule [39]. Alternative strategies for the development of MenB vaccines have therefore been required, and these have focussed on subcapsular components, particularly outer membrane proteins (OMPs). OMPs, however, are antigenically diverse so a successful vaccine must contain either different OMPs and/or multiple variants of the same OMP to ensure broad coverage of protection against the diverse range of strains observed in countries with endemic disease. The majority of vaccine development programmes have utilised outer membrane vesicles (OMVs). These vesicles are similar to outer membrane blebs naturally released by *N. meningitidis* during culture and infection, and contain lipopolysaccharide (LPS), OMPs, periplasmic proteins and phospholipid [40]. Although OMVs contain a number of different potential antigens, the resulting SBA response is predominantly against the PorA protein [41-43]. This results in restricted protection against PorA homologous strains and limited protection against strains which express a different PorA variant. This is appropriate to control outbreaks due to expansion of a single clone, and has been successfully used in this context in Cuba, New Zealand and France [44-46], but is unsuitable for broad protection against the range of strains occurring in Europe. In addition there is limited persistence of immunity necessitating multiple dose regimens, and lower efficacy in younger children [43, 47-51].

Protein-based vaccines for capsular group B disease

Two new vaccines designed to induce protection against a number of different MenB strains have recently been licensed in Europe and North America.

rLP2086 is a bivalent vaccine containing two variants of the immunogenic outer membrane lipoprotein factor H binding protein (fHBP), and has been licensed in the USA for individuals aged 10-25 years [52]. In a phase 3 clinical trial in Australia, Poland and Spain, three doses of rLP2086 in 11-18 year olds resulted in seroconversion (≥ 4 fold rise in serum bactericidal antibody (SBA) titre) in 87-93% of participants (<https://clinicaltrials.gov>, identifier NCT00808028, accessed 7 September, 2015). The gene encoding fHBP is present in all meningococci, and the lipoprotein is expressed on the surface of almost all organisms, making it a good vaccine antigen [53]. It appears to be needed for survival of bacteria in the bloodstream, helping them to evade complement-mediated lysis. The difficulty with designing a vaccine based on fHBP is its variability - there are over 1,000 different fHBP alleles (<http://pubmlst.org/neisseria/fHbp>, accessed 7 September, 2015) divided into two to three families. rLP2086 includes variants from two different families, aiming to achieve broad protection by inducing sufficiently cross-protective bactericidal antibodies to prevent disease by the majority of circulating invasive strains. In one study, sera from 75-100% of adolescents and young adults immunised with rLP2086 had bactericidal activity against a panel of representative strains [54]. There is also evidence of this cross-protection from animal studies - in mice immunised with fHBP, those more central in a phylogenetic network elicited bactericidal antibodies with broader activity and thus with the potential to confer protection against strains with divergent fHBP sequences if replicated in humans [55].

A 4-component vaccine, 4CMenB, was recently licensed in Europe, the USA, Canada and a number of other countries and contains three recombinant OMPs (neisserial heparin binding antigen (NHBA), neisserial adhesin A (NadA) and fHBP) formulated with the OMV derived from the New Zealand outbreak strain [56]. NHBA binds to heparin and is also thought to have a role in evading complement-mediated killing [57, 58]. NadA is involved in adhesion of bacteria to the nasopharyngeal epithelium during infection [59]. Like fHBP, these proteins are highly variable, with >600 NHBA alleles and approximately 150 NadA alleles currently identified (<http://pubmlst.org/neisseria>, accessed 8 September, 2015). Following 3 doses of 4CMenB given at 2, 4 and 6 months of age 85-95% of infants had an SBA titre of $\geq 1:4$ (the presumed protective threshold when using human complement in the assay) against target strains which expressed the same antigen variants as those present in the vaccine. This increased to 93-100% after a booster dose at 12 months [60]. However, SBA titres against vaccine mismatched strains (expressing different variants of the vaccine antigens) were lower (4-78%) in the same study. In more recent studies, 84-100% of infants vaccinated with the same schedule had an SBA titre of $\geq 1:5$ against strains expressing identical variants of the vaccine antigens [61]. (A more conservative 1:5 threshold was used in these studies in an attempt to ensure with 95% confidence that subjects with a titre $\geq 1:5$ will have achieved a titre of $\geq 1:4$.) At 40-44 months of age, 41-76% of children had SBA titres $\geq 1:4$ following 4 doses of vaccine at 2, 4, 6 and 12 months, compared with 0-68% of unvaccinated children when strains matched for vaccine antigen variants were used in the SBA assay. The unvaccinated children presumably gained some immunity from carriage of *N. meningitidis* or related bacteria, such as *N. lactamica* during early life [62]. The magnitude, duration, and breadth of the antibody response was greater among adolescents and adults than in infants [63]. There are no directly comparable studies of persistence after monovalent OMV

vaccines, but in New Zealand 28% of 17 month old children had an SBA titre $\geq 1:4$ after 3 doses of an OMV vaccine received at 6-8 months of age [64]. 4CMenB has recently been used to control outbreaks of meningococcal disease at two US universities [65] and in 2014 was used in a vaccination campaign for hyperendemic disease in the Saguenay-Lac-Saint-Jean region of Quebec, Canada [66]. No cases of MenB disease have been identified in vaccinated individuals in this region up to September 2015 (P. de Wals, personal communication). In September 2015, 4CMenB was introduced into the routine infant immunisation schedule in the UK with a schedule of 3 doses at 2, 4 and 12 months of age. It is expected that that this vaccine will have an impact on disease caused by some MenB strains and also against MenW disease since the current MenW outbreak strain contains the *nadA* gene [67].

Data on the impact of these population interventions are eagerly awaited. While these vaccines are highly effective in inducing bactericidal antibodies against strains with high expression of antigens which are identical to those contained in the vaccines, their effectiveness at a population level will depend on the variants and surface expression levels of vaccine antigens present in circulating strains and the degree of cross-protection induced. Although a large number of variants of the vaccine antigens have been identified, only a relatively small number contribute to the majority of disease-causing isolates. One study using a collection of strains across 7 European countries suggested that the coverage of 4CMenB would be 78% overall, varying from 69% to 87%, depending on the country [68].

Both 4CMenB and rLP2086 are reactogenic in young children. In clinical trials, 4CMenB caused fever in 51-65% of infants when administered concomitantly with other routine

vaccines, compared with 23-34% in those given other routine vaccines alone, thought to be primarily due to LPS within the OMV component [61, 69]. This has led to recommendations in the UK and in Quebec that prophylactic paracetamol (acetaminophen) is given with the vaccine in infants since this reduces the occurrence of fever without having a clinically significant impact on immunogenicity of any of the vaccines [70]. Infant studies of rLP2086 were discontinued following high rates of fever (64-90%) [71]. In adolescents (the age group in which the vaccine is licensed), fever occurs in 1-6% with the most common adverse events being fatigue and headache - 16-57% and 11-62% compared with 52-71% and 39-46%, respectively, in control groups [72].

Predicting effectiveness of capsular group B vaccines

Capsular group B meningococcal disease has a relatively low incidence in countries where it is endemic, so the large sample size required for vaccine efficacy studies prohibits such trials. It has therefore been necessary to identify a correlate of protection which can be measured in clinical trials. The importance of “bactericidal substances” in human blood in determining protection was first proposed in the early 1900s [73, 74]. In 1969 an inverse correlation between the incidence of disease and the prevalence of complement-dependent SBA provided evidence that circulating antibody was this critical “substance” [75]. In the modern SBA assay, *N. meningitidis* target strains are killed in the presence of meningococcal-specific antibody (from post-vaccination serum) and exogenous complement [76]. The SBA assay is therefore accepted as an adequate correlate of protection for use in research studies and is also a requirement for vaccine licensure. For the MenC conjugate vaccine, an SBA titre of $\geq 1:8$ (with rabbit complement) correlated strongly with post-licensure vaccine effectiveness [76]. For MenB disease the data are less secure - the proportions of group B vaccine

recipients with ≥ 4 -fold rises in SBA following vaccination or SBA titres $\geq 1:4$, using human complement, have been correlated with clinical efficacy in trials of OMV vaccines [44, 48, 77]. These cut-offs are therefore currently considered the protective threshold in evaluation of vaccines, but post-implementation data will be required to confirm if they are also appropriate for the recombinant protein vaccines.

New assays have been developed, to be used in conjunction with *N. meningitidis* epidemiological typing data, in an attempt to predict the population-level effectiveness of rLP2086 and 4CMenB. In the meningococcal antigen typing system (MATS) assay, expression levels of vaccine antigens are combined with a measure of estimated cross-protection to predict whether a given strain will be killed in the SBA assay [78]. This assay has been used to predict that coverage of 4CMenB would be 66-91% in various countries, using representative disease-causing isolates [79]. This can only be confirmed with effectiveness data following implementation. For rLP2086, a flow cytometric surface expression assay has been developed using a monoclonal antibody that recognises a functional epitope common to all surface-expressed fHBP lipoproteins, and is designed to measure the amount of fHBP which is accessible to antibody. A value of greater than approximately 1,100 mean fluorescent intensity units in this assay predicted susceptibility to killing by bactericidal antibodies [80]. If this assay is accurate, effectiveness of this vaccine would ultimately be determined by the expression levels fHBP in invasive isolates.

The importance of herd immunity in maintaining vaccine-induced protection against meningococcal disease

The reduction in nasopharyngeal meningococcal carriage by conjugate vaccines has been an important contribution to their extraordinary success at the population level. The MenC conjugate vaccine in the UK reduced transmission of group C *N. meningitidis*, thereby providing herd protection - indirectly protecting susceptible unvaccinated individuals [81]. Following the introduction of the vaccine the number of cases among unvaccinated age groups fell by 67%, corresponding to a similar reduction in MenC carriage rates seen in vaccinated young adults [82]. Given that the highest rates of meningococcal carriage occur in adolescents and young adults [83] many countries include an adolescent booster dose of MenC or MenACWY conjugate vaccine to maintain herd protection, which provides a highly effective way of maintaining protection of the population [84], as long as high vaccine uptake rates can be maintained. Data from the mass vaccination campaigns in the meningitis belt of sub-Saharan Africa suggest that the MenA conjugate vaccine is also able to successfully protect against carriage and generate herd protection [36]. In the US programme with the MenACWY vaccines, there has thus far been no evidence of herd protection, which is likely related to the slow introduction of the programme and low vaccine uptake observed (28-92%, depending on the state) [34].

The importance of herd protection in the success of MenC conjugate vaccines has focussed attention on whether or not a similar phenomenon will be observed with the recombinant protein vaccines. In a randomised clinical trial of almost 3,000 university students in the UK, 2 doses of 4CMenB vaccination resulted in a 27% reduction in carriage rates of group B, C, W or Y *N. meningitidis* during the period 3-12 months following the 2nd dose of vaccine in a

modified intention-to-treat analysis [85]. Although this reduction was modest it highlights that this vaccine is not a true 'MenB' vaccine but, being based on subcapsular components, has the ability to impact on non-B capsular groups. No significant effect was observed in the first month following vaccination in this study. In comparison, one dose of MenACWY-CRM₁₉₇ conjugate vaccine led to a 36% reduction in carriage of C, W or Y group organisms during 2-12 months post vaccination. Data on the effect on carriage of rLP2086 are not available. Since carriage rates peak among adolescents and young adults, it is likely that a vaccine that reduced carriage in this age group would have greatly enhanced effectiveness in a vaccine programme. Duration of protection in adolescents would also influence the effect of these vaccines on carriage. In one study, 100% of adolescents had SBA titres $\geq 1:4$ after 2 or 3 doses of 4CMenB, which dropped to 77-94% (2 doses) or 86-97% (3 doses) at 18-24 months after the final dose [86]. The longer protection is sustained, the greater the direct protection and the potential effect is likely to be on carriage. Although these studies suggest that these vaccines may have some impact on carriage, the key question is the reduction in hyperinvasive lineages, i.e. those strains responsible for invasive disease, which are only a small proportion of all meningococcal strains found in the nasopharynx. Studies to address this question will likely need to be even larger than the one described above.

Cost effectiveness of capsular group B vaccines

The relatively low incidence rates of invasive meningococcal disease and high cost of current vaccines (the UK National Health Service (NHS) list price for 4CMenB is £75 per dose) has resulted in intense debate on vaccine cost-effectiveness prior to implementation. Though the approach to cost-effectiveness analysis and the weight placed on it varies in different countries, the method takes account of a range of factors, including the cost of the vaccine

and its administration, the number of doses required, disease incidence, estimated strain coverage, vaccine efficacy against disease, duration of protection, effect on carriage and therefore ability to induce herd immunity, calculation of quality of life losses and discounting. The majority of published data for 4CMenB describe immunogenicity in infants after 3 doses, but based on data from other vaccines and additional unpublished data from the vaccine manufacturer the Joint Committee on Vaccination and Immunisation (JCVI) in the UK opted for a schedule of 2 doses in infants at 2 and 4 months, with an additional booster at 12 months of age, in an attempt to reduce vaccine cost without impacting on effectiveness (Table 2) [87]. Disease incidence naturally fluctuates and currently is at relatively low levels when considered in the context of rates over the last 100 years (Figure 4). While an early cost-effectiveness analysis included a relatively narrow recent timeframe (2008-10) for disease incidence estimates, the subsequent analysis used a longer term average, based on data during 2005-12, which was thought to be more appropriate to inform a policy decision [19, 88]. Duration of protection is less critical among infants, where most disease is in the first 12-18 months of life and more so among adolescents where the individual risk of disease remains relatively low and a longer duration is required to have sufficient impact on disease. If these vaccines are able to reduce carriage acquisition in adolescents this would lead to a substantial long term reduction in disease incidence, which would also be the most favourable scenario economically [19]. A number of cost-effectiveness models have been published (Table 3) highlighting the uncertainty associated with some of these parameters.

Concluding remarks

The recent exciting development of new meningococcal vaccines have led to the prospect of protection against all disease-causing capsular groups of *N. meningitidis* which are

predominant across Europe, including group B for the first time. However, despite data demonstrating that these new vaccines are highly immunogenic, a number of questions remain unanswered and the impact these vaccines will have is difficult to predict. Strain coverage and vaccine efficacy have been estimated from *in vitro* assays, but only post-implementation surveillance which includes detailed typing of strains causing disease will be able to determine vaccine effectiveness, and this may take several years given the low current disease incidence rates. The meningococcus has a remarkable capacity to evade the human immune system through variation of antigens decorating the surface of the organism. While current vaccines have attempted to circumvent this by including multiple components of the same or different antigens, it is possible that there will be sufficient variation in the future to evade vaccine-induced protection directed at specific protein variants, highlighting the importance of ongoing typing of circulating strains. The vaccines have been shown to induce anamnestic responses in clinical trials, and 4CMenB had a modest effect on carriage, suggesting that it may be possible to induce a degree of herd protection, though no direct evidence yet exists. Further studies are needed to identify any impact on carriage of disease-causing isolates, which would have a significant influence on clinical and cost-effectiveness of vaccine programmes. In the majority of current cost-effectiveness analyses, the cost effective price has been estimated at <£10 per dose, but further data on immunogenicity of reduced dose schedules, duration of protection and effect on carriage could result in significant changes to these estimates. In September 2015, the UK became the first country to introduce 4CMenB routinely into a national immunisation schedule. If MenB vaccines are used, especially in the context of use of MenACYW conjugate vaccines, an impact on all meningococcal disease is finally a reality, though the extent of the impact will only be known in the years ahead.

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Tables

Table 1. Complications of invasive meningococcal disease [5, 89]

Early neurological complications*	Early complications secondary to severe shock & tissue hypoperfusion	Long term neuropsychological complications	Long-term complications secondary to severe shock & tissue hypoperfusion
Seizures	Skin necrosis	Sensorineural hearing loss	Severe skin scarring – may need skin grafting
Syndrome of inappropriate anti-diuretic hormone (SIADH) secretion	Grangrene of parts or entire limbs, possibly requiring amputation	Epilepsy	Growth plate damage – may require multiple surgical procedures until growth is complete
Subdural effusions and empyema		Learning difficulties	Arthritis +/- permanent joint damage
Hydrocephalus		Motor/cognitive impairment	
Raised intra-cranial pressure			
Focal neurological abnormalities			
Cerebral venous sinus thrombosis			
Cerebral infarction			

*caused by meningitis and cerebral hypoxic-ischemic damage secondary to shock

Table 2. Published studies comparing 2 vs 3 doses of 4CMenB in clinical trials.

Study population	Target strain in SBA assay	Primary target vaccine antigen in SBA assay	Vaccine schedule (months)	% with SBA $\geq 1:4$ one month after 2 doses	% with SBA $\geq 1:4$ one month after 3 doses	SBA GMT (95% CI) one month after 2 doses	SBA GMT (95% CI) one month after 3 doses	Ref
Infants, first dose at 2 months of age	44/76-SL	fHBP	0,2,4	95	87	28.0 (19.0-40.0)	30.0 (19.0-46.0)	[60]
	NZ98/254	PorA (OMV)	0,2,4	74	85	6.6 (4.8-9.0)	19.0 (11.0-33.0)	
	5/99	NadA	0,2,4	100	95	104.0 (64.0-169.0)	126.0 (77.0-205.0)	
	M01 240101	None	0,2,4	28	47	2.1 (1.4-3.1)	4.1 (2.6-6.3)	
	M00 242922	None	0,2,4	64	63	4.7 (3.2-6.9)	8.2 (4.7-14.0)	
	M01 240364	None	0,2,4	3	12	1.2 (1.0-1.5)	1.6 (1.1-2.2)	
	M01 240355	None	0,2,4	0	0	1.0 (1.0-1.1)	1.1 (1.0-1.2)	
Adolescents	44/76-SL	fHBP	0,1,2	100	99	193 (164-228)	240 (205-280)	[90]
	NZ98/254	PorA (OMV)	0,1,2	100	99	92 (77-110)	122 (102-145)	
	5/99	NadA	0,1,2	100	100	481 (415-556)	584 (510-668)	

Similar responses occurred in these studies after 2 or 3 doses of 4CMenB with regards to proportion of participants with SBA titres $\geq 1:4$ (the presumed protective titre) and modest increases in the SBA GMT associated with the 3rd dose.

SBA = serum bactericidal antibody; GMT = geometric mean titre

Table 3. Cost-effectiveness models for introduction of 4CMenB into vaccine programmes, including model parameters

Country	Proposed schedule	Estimated strain coverage	Estimated efficacy against disease ‡	Cost effective price (per dose) †	Ref
Canada (Ontario)	4 doses (2, 3, 4, 12 months)	66%	90%	<Can\$0	[91]
UK	4 doses (2, 3, 4, 12 months)	73%	95%	<£0	[19, 87]
UK	4 doses (2, 3, 4, 12 months)	88%	95%	£3 / €3.8 / US\$4.9	[19]
Netherlands	4 doses (2, 3, 4, 11 months)	Combined coverage & efficacy: 75%		€4.7	[92]
Italy	4 doses (2, 3, 4, 12 months)	100%	75%	€7.9	[93]
UK	4 doses (2, 3, 4, 12 months)	100%	75%	£9	[88]
Chile*	<12 months: 3 doses (2, 4, 6 months) 12 mths - 25 yrs: 1 dose	100%	80% (infants) 92% (adolescents)	≤US\$18	[94]

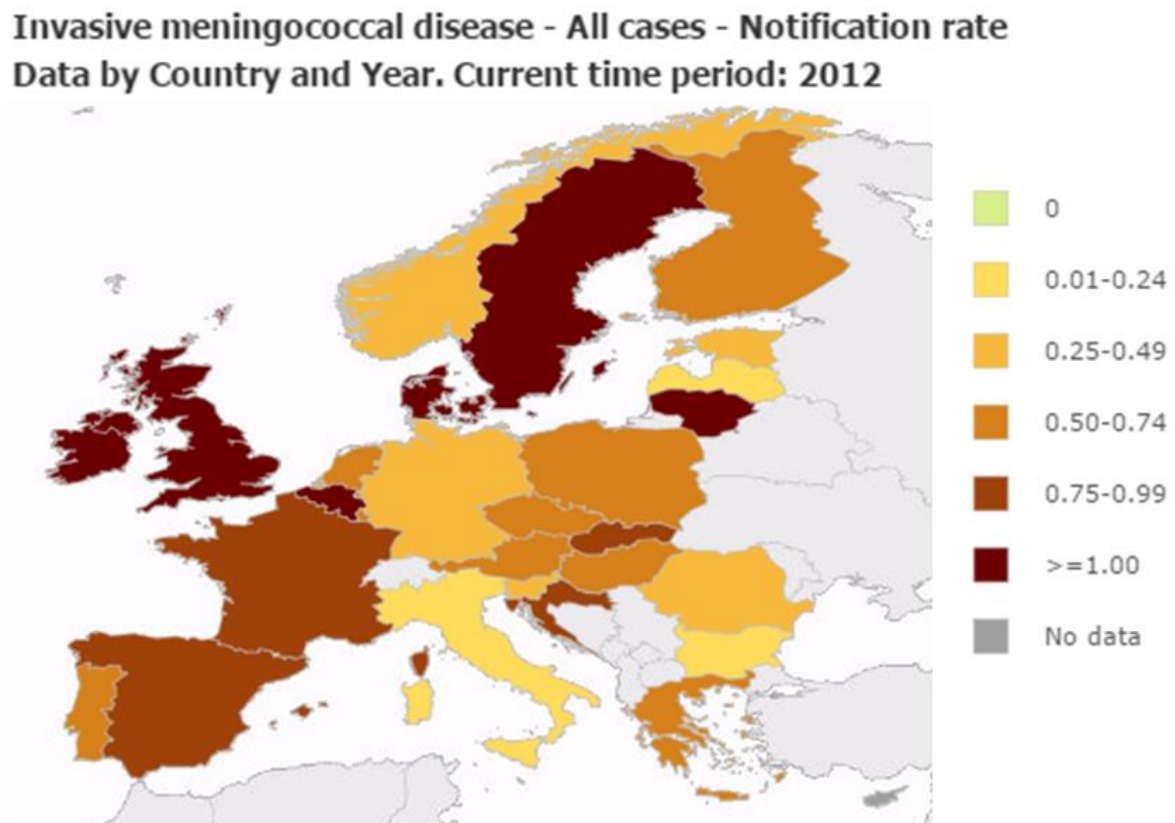
*Analysis for hypothetical scenario of a mass vaccination campaign for an outbreak, not routine implementation into the immunisation schedule.

‡ The majority of models assumed no efficacy against carriage acquisition. This was considered in some of the sensitivity analyses, but would be unlikely to have a significant impact with the proposed schedules because herd protection depends on reduction of carriages in adolescents.

† Costs included in this column are for the base case model. Confidence intervals around each figure vary according to different sensitivity analyses done in each model.

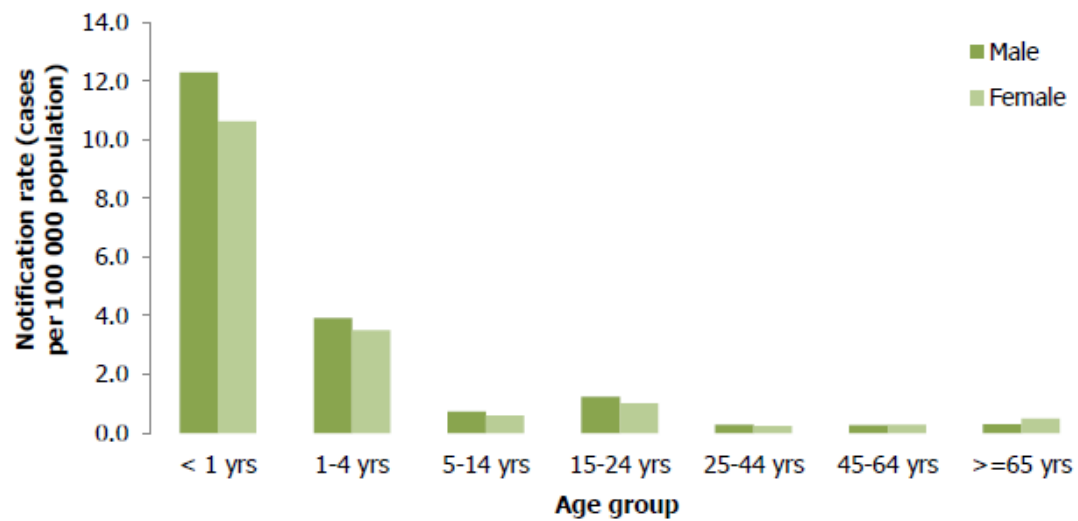
Figures

Figure 1. Map of notification rates per 100,000 population of invasive meningococcal disease in Europe in 2012



Source: ECDC surveillance atlas of infectious diseases, accessed 3 September 2015 (<http://ecdc.europa.eu/en/data-tools/atlas/Pages/atlas.aspx>).

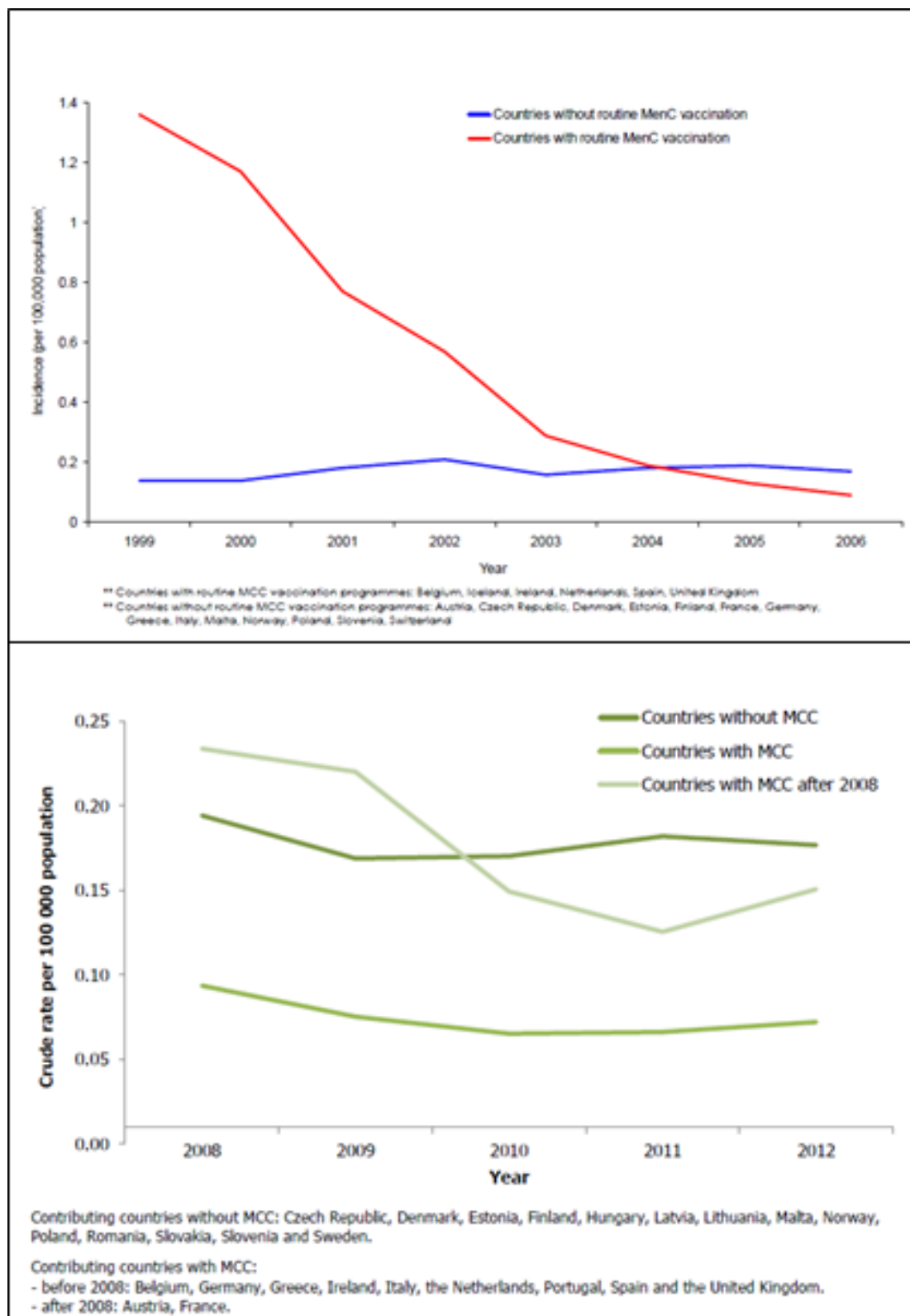
Figure 2. Notification rate of confirmed cases of invasive meningococcal disease by age group and gender in Europe in 2012



Contributing countries: all reporting countries except for Cyprus (population coverage unknown)

Source: European Centre for Disease Prevention and Control Surveillance Report 2012. Total number of cases included: 3,439 [38].

Figure 3. Impact of meningococcal capsular group C (MenC) conjugate vaccines on MenC disease in Europe [95, 96]



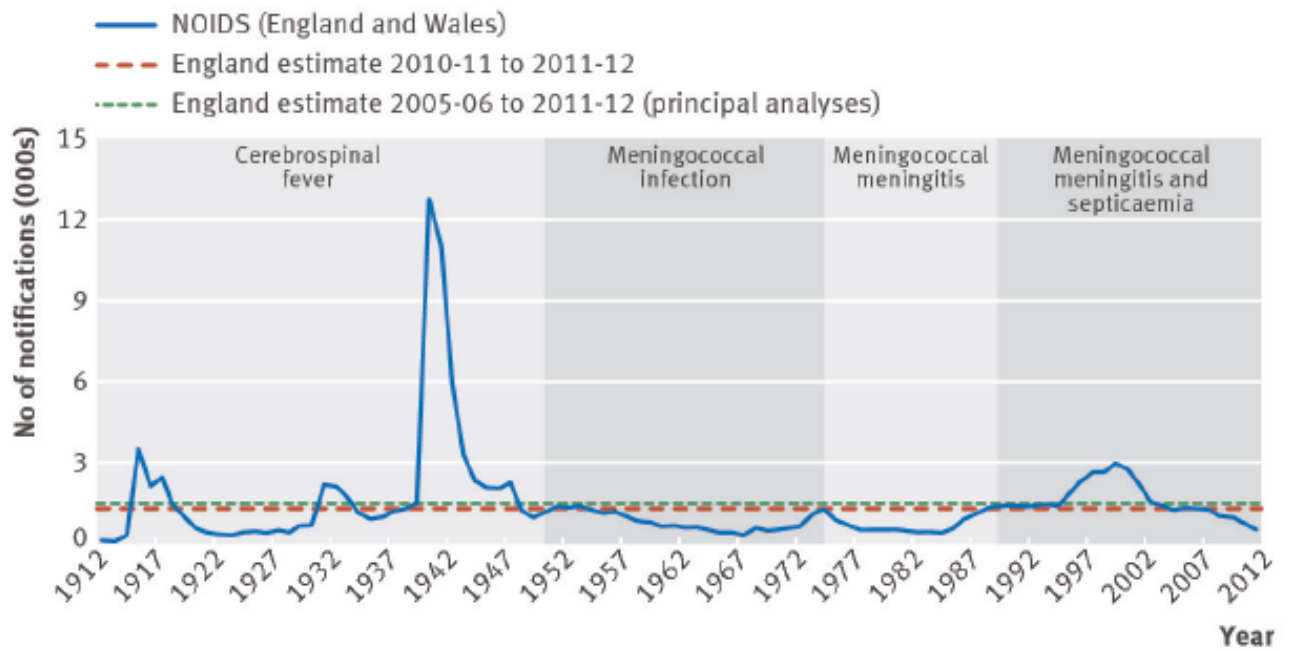
MCC = meningococcal capsular group C conjugate vaccine

Top panel: Reduction in incidence rate of confirmed and probable capsular group C meningococcal disease (1999-2006) in countries which did include MCC in their routine vaccination schedule, but not in those countries without MCC.

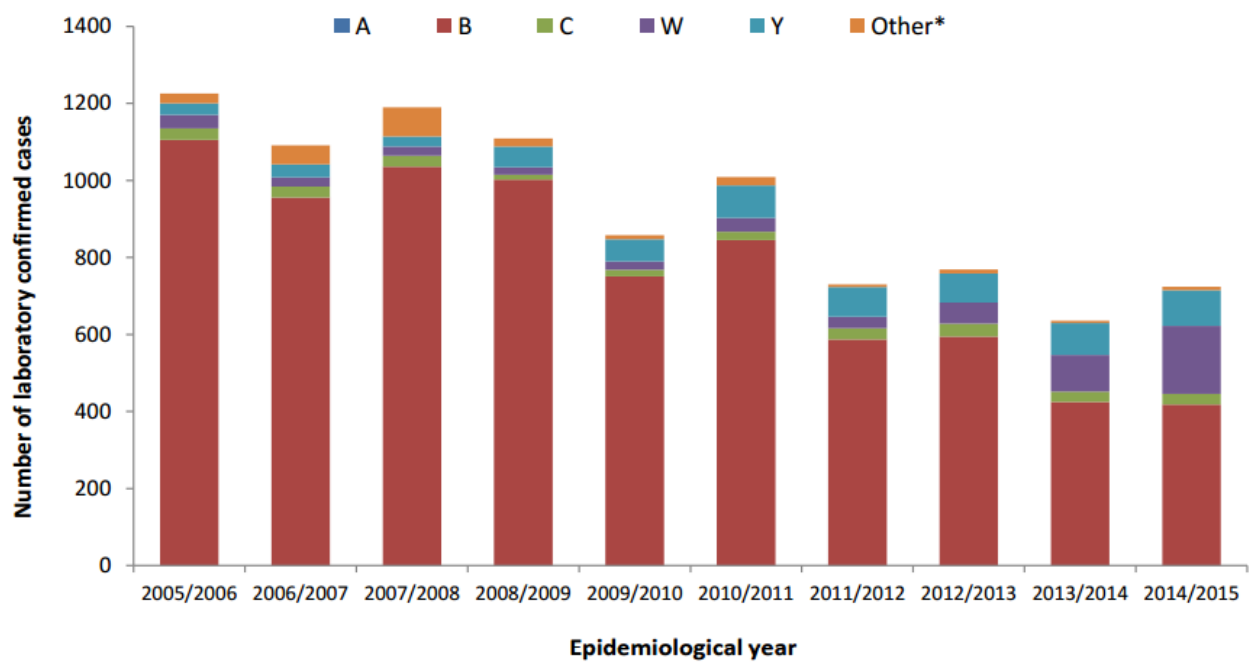
Bottom panel: Incidence rates of capsular group C meningococcal disease by vaccination policy in countries within Europe.

Figure 4. Number of cases of meningococcal disease over time in England and Wales, 1912-2012 [19] (A) and 2005-2015 [22] (B).

A.



B.



Source of original data for (A): Notifications of Infectious Diseases (NOIDS) for England and Wales, with sections indicating diseases reported during different time periods.

Reference lines for England estimates based on hospital episode statistics data.