

RECOMMENDATION

Vaccination against meningococcal disease in Europe: review and recommendations for the use of conjugate vaccines

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Abstract

At the end of 2005, six European countries had implemented public immunization campaigns with serogroup C conjugate vaccines, and all had experienced substantial declines in the incidence of serogroup C disease. A quadrivalent ACWY meningococcal vaccine is in use in the USA, but serogroup A is extremely rare in Europe and serogroups Y and W135 are infrequent causes of disease. This paper outlines recommendations on the use of conjugate vaccines in Europe based on the experience with meningococcal C conjugate (MCC) vaccines so far.

Introduction

Primary prevention is seen as the key to controlling meningococcal disease through the implementation of effective vaccination programmes. However, there is currently no broadly effective vaccine against serogroup B, the most common serogroup, and there is no consensus on the use of new and existing vaccines against serogroup C and quadrivalent vaccines against serogroups A, C, W135 and Y (ACWY). Here, we discuss the epidemiology of meningococcal disease in Europe and the observed and potential impact of serogroup C and ACWY conjugate vaccines. On the basis of this evidence, we make recommendations on the information requirements and vaccination strategies that should be considered. Future opportunities for the control of meningococcal disease in Europe are discussed.

Meningococcal conjugate vaccines

Conjugate vaccines, in which the capsular polysaccharide is attached (conjugated) to an immunogenic protein, were first developed for *Haemophilus influenzae* type b (Hib). By contrast with polysaccharide-only vaccines, conjugate vaccines are immunogenic in children aged under 2 years and induce immune memory. The success of Hib conjugate vaccination programmes (Peltola, 2000) encouraged researchers to use the same approach for meningococcal vaccines. In the UK, clinical trials and the licensure of meningococcal C conjugate (MCC) vaccines were accelerated in response to increasing morbidity and mortality from serogroup C disease, and the first MCC vaccines were licensed in 1999 on the basis of safety and immunogenicity studies (Miller *et al.*, 2001). Three different single MCC

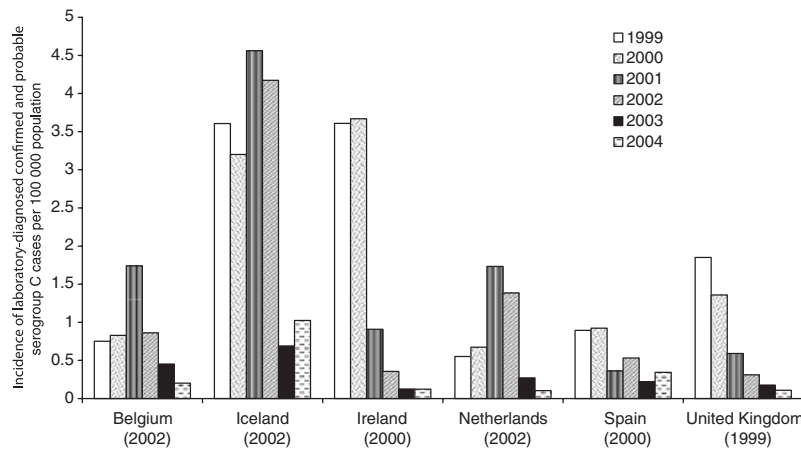


Fig. 1. Incidence of serogroup C disease in countries that have introduced public meningococcal C conjugate (MCC) vaccination programmes (1999–2004) by country (year of vaccine introduction).

vaccines are currently available, two of which are conjugated to diphtheria (CRM-197) and one to tetanus toxoid. A combination MCC–Hib vaccine (conjugated to tetanus toxoid) has also been licensed recently in the UK, and will be used as a booster at 12 months of age from September 2006 onwards (Chief Medical Officer, 2006).

Quadrivalent conjugate vaccines offering protection against serogroups A, C, W135 and Y have recently been licensed. Serogroup A has caused remarkably few cases of disease in Europe over the past few decades, despite being common in Europe in the early half of the 20th century. The last large serogroup A outbreak in Europe occurred in Finland in the 1970s (Peltola *et al.*, 1976) and, although endemic and epidemic serogroup A disease is still common in other parts of the world, particularly sub-Saharan Africa, disease has not re-established in Europe. The reasons for the disappearance of serogroup A in Europe are not clear. Serogroup W135 has emerged as an important cause of disease in Africa (Mueller *et al.*, 2006), and serogroup Y is an important contributor (25%) to meningococcal disease in the USA (Rosenstein *et al.*, 1999). Because of this latter finding, quadrivalent conjugate vaccine (MCV-4) has recently been recommended for use in adolescents in the USA (Centers for Disease Control and Prevention (CDC), 2005).

Experience with MCC vaccination in Europe

The countries that have introduced MCC vaccines to date are those that have experienced the highest burden of serogroup C disease, particularly those that have experienced increases in incidence since the late 1990s. Most of these increases have been a result of the introduction and spread of a hyperinvasive, hypervirulent clone, serologically typed as C:2a:P1.2,5 and identified by multi-locus sequence typing as ST-11 clonal complex. This clone had earlier caused increases in disease in Canada (Whalen *et al.*, 1995)

and the Czech Republic (Krizova & Musilek, 1995), and was then identified in the UK, the Netherlands and Ireland. Spain experienced a hyperendemic period of serogroup C disease in the mid-1990s, which was caused by a C2b clone (Berron *et al.*, 1998) and, as a result, implemented a polysaccharide vaccine campaign. In the late 1990s, serogroup C ST-11 clones emerged in Spain, leading to the introduction of MCC vaccines in 2000 (Cano *et al.*, 2004). The incidence of serogroup C disease in the year before implementation in the countries now using MCC vaccines is shown in Fig. 1.

In the UK, the concern about the seriousness of meningococcal infection amongst parents (Yarwood *et al.*, 2005) contributed to the decision to fast-track prelicensure evaluation of MCC vaccination. The UK was also the first country to introduce MCC vaccines, in 1999. The MCC vaccines were incorporated into the routine infant immunization schedule at 2, 3 and 4 months of age, and a catch-up campaign targeting all children under the age of 18 years was launched. Subsequently, Ireland, Spain, the Netherlands, Belgium, Iceland and Portugal introduced national mass MCC vaccination programmes, although the schedules/strategies used varied (Table 1).

Because of the relatively low incidence of serogroup C disease, it was not feasible to conduct phase three clinical trials for MCC vaccines, and postlicensure surveillance was required to determine the effectiveness of the vaccine. The early indications from England, both in terms of short-term vaccine effectiveness (Ramsay *et al.*, 2001) and safety (Anon, 2000), were very encouraging. The experience of the UK was thus essential in informing policy makers in other countries. All European countries that have introduced routine MCC vaccination have now experienced a substantial decline in the incidence of serogroup C disease (Fig. 1). A striking feature of the MCC vaccination programme in both England and the Netherlands has been the additional decrease in disease incidence as a result of herd immunity (Ramsay *et al.*, 2003; de Greeff *et al.*, 2006).

Table 1. Meningococcal C conjugate (MCC) vaccination schedules used in Europe

Country	Routine (months)	Catch-up	Year started
UK*	2, 3, 4	Under 18 years (to 24 years in 2001)	1999
Ireland	2, 4, 6	Under 23 years	2000
Spain†	2, 4, 6	Under 6 years (regional variation)	2000
Netherlands	14	1–19 years	2002
Belgium	12	1–5/1–18 years (regional variation)	2002
Iceland	6, 8	Up to 20 years	2002
Portugal	3, 5, 15	Up to 18 years	2006

*The UK routine infant immunization schedule changed in September 2006, whereby two doses of MCC vaccine are administered at 3 and 5 months of age, and a booster dose is given at 12 months of age (Chief Medical Officer, 2006).

†After 2001, all regions in Spain adopted a catch-up to age 18 years.

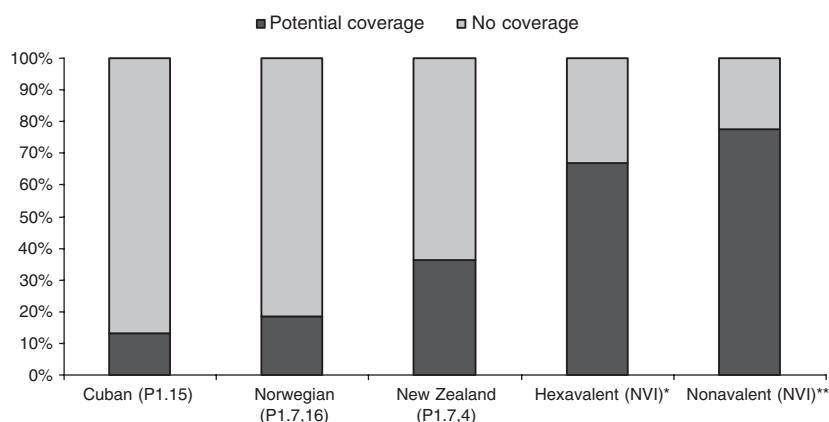


Fig. 2. Potential coverage of candidate outer membrane vesicle vaccines, 1999–2004 combined.

* P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4

** P1.7,16; P1.5-1,2-2; P1.19,15-1; P1.5-2,10; P1.12-1,13; P1.7-2,4; P1.22,14; P1.7-1,1; P1.18-1,3,6

Serogroup B vaccines

Unlike the other major pathogenic serogroups, a vaccine based on the serogroup B polysaccharide has not been developed. The serogroup B polysaccharide is poorly immunogenic, probably because of a structural similarity to a human glycoprotein found in neural tissues. There have been no reported severe adverse effects to natural or vaccine-induced anti-B capsular polysaccharide antibody (Stein *et al.*, 2006), but conjugate serogroup B vaccines have not been trialled because overcoming the apparent immune tolerance to this self-antigen carries the theoretical risk of inducing autoimmunity (Finne *et al.*, 1983). Noncapsular antigens have therefore become the focus for vaccine targets, and vaccines based on outer membrane vesicles (OMVs) from single strains of serogroup B meningococci have been developed for use in Norway, Cuba and, most recently, New Zealand (Oster *et al.*, 2005). The main difficulty with targeting noncapsular antigens, such as PorA, is that they are antigenically diverse, and display considerable temporal and geographical variability. Multivalent OMV vaccines are being developed (Borrow *et al.*, 2006), targeting the most

common outer membrane proteins (OMPs) associated with serogroup B, although, of course, as subcapsular antigens are targeted, efficacy will not be restricted to serogroup B strains. There may also be some cross-protection against nonvaccine OMPs, which would improve the strain coverage of these multivalent vaccines. It seems unlikely, however, that OMV vaccines will offer any protection against the carriage of homologous strains, and so the vaccines will only offer direct protection to vaccinated individuals.

The potential benefit from OMP vaccines will depend on the main strains causing disease in a particular country. Using subtyping data from cases in the European Union Invasive Bacterial Infections Surveillance (EU-IBIS) Network between 1999 and 2004 ($n = 16\,143$), we have estimated the potential coverage of the major OMV vaccines described (Jodar *et al.*, 2002; Oster *et al.*, 2005; Borrow *et al.*, 2006), assuming that protection against all variants of each PorA subtype is provided. This indicates that the multivalent preparations produced by the Netherlands Vaccine Institute have the potential to prevent the majority of serogroup B infection in Europe (Fig. 2), although differences may occur in PorA distribution

between individual countries. The potential cost-effectiveness of a vaccine containing nine OMVs plus pneumococcal conjugate has been assessed in the Netherlands (Bos *et al.*, 2006). The authors concluded that this combined vaccine was likely to be cost-effective in that setting and could prevent 201 cases of meningococcal B meningitis per year.

Recommendations

(1) Each country should collect accurate information on meningococcal serogroup C infection to inform cost-effectiveness analyses for MCC vaccine.

In order to justify the use of scarce health resources, a vaccine must be shown to be effective and, increasingly, it must also be shown to be cost-effective. To estimate the cost-effectiveness of MCC vaccination, the benefits of the vaccination programme (e.g. cases prevented, life years saved and the savings from reduced treatment costs) must be compared with the costs of the vaccination programme. For this, data on the epidemiology (incidence, age distribution, trends) and burden (disease complications and mortality) of disease are required.

Many European countries have conducted economic analyses of MCC vaccines and, in most, this has played some part in the decision to introduce (or not) the vaccine (Welte *et al.*, 2005). A key factor influencing the cost-effectiveness of MCC vaccines is the burden of serogroup C disease. MCC vaccines were judged unlikely to be cost-effective in countries such as Switzerland (Ruedin *et al.*, 2003), with a very low incidence of serogroup C disease. By comparing disease rates with those in other countries in which cost-effectiveness has been assessed, countries may gain an initial idea of the likely cost-effectiveness in their own state. The thresholds for determining 'cost-effectiveness' will, however, vary by country, as different states have different health budgets and priorities for public health.

Cost-effectiveness will be improved if the impact of herd immunity is included, but the transmission dynamic models needed to estimate the indirect effects of vaccination are more complex than the standard decision models used in economic analysis (Trotter & Edmunds, 2006).

(2) The schedule for routine MCC vaccination in Europe should include a dose of vaccine after the age of 1 year.

The first countries to introduce MCC vaccination (UK, Ireland and Spain) added the vaccine to their routine infant schedule. This was based mainly on pragmatic decisions to deliver the new programme alongside other routine infant vaccinations.

Vaccine effectiveness studies in England (the country with the longest follow-up) have shown that high levels of direct protection are maintained 4 years after vaccination in

children immunized between the ages of 5 months and 18 years, but the effectiveness wanes to low levels after only 1 year in children immunized at 2, 3 and 4 months of age (Trotter *et al.*, 2004). Spain has reported a similar decline in effectiveness in children immunized routinely at 2, 4 and 6 months of age (Larrauri *et al.*, 2005). The evidence of decline in protection in the UK and Spain has raised questions about the consequences of this approach, without a booster in the second year of life.

In contrast, the Netherlands and Belgium decided to offer only a single dose of vaccine at 12–14 months of age. This approach has been predicted to be more cost-effective for the UK (Trotter & Edmunds, 2002) but, because of the desire to protect young infants, for whom the incidence of disease is high, the infant schedule was chosen. In retrospect, data from both the UK and the Netherlands have demonstrated that infants can be successfully protected by indirect protection (herd immunity). Vaccination in the second year of life is therefore likely to provide longer term protection and to prove more cost-effective than infant vaccination, not least because fewer doses are given. Countries with a high burden of infant disease should consider adding a booster dose to an existing infant schedule.

(3) The catch-up programme for MCC vaccination should include the vaccination of teenagers.

Because of the secondary peak in serogroup C incidence in adolescence, all countries other than Spain have conducted a catch-up campaign including adolescents, with the upper age ranging from 17 to 25 years. In some autonomous regions of Spain, as older children had been vaccinated with polysaccharide vaccine in 1997, only children up to 6 years of age were targeted in the initial MCC catch-up programme.

The impact of the catch-up campaigns in older children appears to have been crucial in providing higher levels of herd immunity, probably by reducing high carriage rates in older teenagers. MCC vaccines have been shown to reduce the prevalence of carriage (Maiden *et al.*, 2002), which means that the risk of disease, even in unvaccinated individuals, is lower, as they are less likely to be exposed to and acquire serogroup C meningococci. Spain, in which many areas initially only targeted children up to the age of 6 years, has not experienced the same level of herd immunity as the UK and the Netherlands.

Based on the likely carriage rates in Europe (Dominguez *et al.*, 2001; Pavlopoulou *et al.*, 2004; Bogaert *et al.*, 2005), countries considering a catch-up campaign will maximize the indirect effects of the programme by including adolescents. These observations are also supported by the findings of mathematical modelling studies (Trotter *et al.*, 2005).

Alternative approaches may include vaccinating only in adolescence or vaccinating both preschool children and adolescents. The effectiveness of these approaches have not

been assessed with MCC vaccine in Europe. The experience with quadrivalent conjugate vaccine, now being recommended for 11–12 year olds in the USA (CDC, 2005), will therefore be of interest.

(4) Countries should evaluate the impact of MCC vaccine on other vaccines in the childhood programme.

Even if MCC vaccination is shown to be cost-effective, it needs to be considered alongside other new priorities for infant vaccination, such as pneumococcal conjugate vaccination. The administration of MCC vaccination may be facilitated by giving it alongside other childhood vaccines, but practical concerns about too many vaccinations administered on the same day may be raised. Combination vaccines, for which compatibility between components has been assured, may be helpful. The availability of a combined MCC – Hib vaccine, for example, could facilitate the introduction of routine vaccination in countries in which Hib is given as a routine booster in the second year of life. Evidence must be available to show that the schedule likely to be used for MCC vaccines in each country will produce no adverse interactions with other vaccines given simultaneously or at the same injection site.

(5) Countries introducing MCC vaccine should monitor potential adverse events at an individual or population level.

Although no serious adverse events have been associated with MCC vaccine, reports of seventeen cases of Guillain–Barré syndrome, temporally related to MCV-4 vaccination in the USA, could cause public concern about the use of this vaccine. The introduction of new vaccines should be accompanied by postmarketing surveillance for adverse events, and public health authorities need to be prepared to investigate and respond to safety signals at short notice. At present, the CDC continues to recommend the use of MCV-4 for persons for whom vaccination is indicated (Anon, 2006).

Meningococci have the ability to switch capsule (Swartley *et al.*, 1997) and, theoretically, MCC vaccines could create a strong selective pressure against meningococci expressing the serogroup C capsule, causing them to switch to a serogroup B or other capsule. Concerns regarding capsular replacement were strongly voiced before MCC vaccines were introduced in the UK (Maiden & Spratt, 1999). Although a report from Spain suggested that capsule replacement occurred in the Basque region (Perez-Trallero *et al.*, 2002), there is no evidence that (clinically significant) capsule replacement has occurred in England and Wales (Trotter *et al.*, 2006), the countries with the longest experience of MCC vaccines. The detection of emergent hypervirulent strains may be possible using standard typing techniques and close monitoring of incidence and case fatality (Trotter *et al.*, 2006). This should be supplemented by multi-locus sequence typing to determine the genetic lineage of novel strains causing concern.

(6) Each country should collect accurate information on the proportion of meningococcal infections caused by serogroups A, Y and W135.

The decision about whether or not to introduce mass vaccination using quadrivalent vaccine against serogroups A, C, W135 and Y meningococcal disease will depend on the contribution of these serogroups to burden in each country. As discussed earlier, serogroup A disease is now rare in Europe, and serogroups W135 and Y are not currently a major cause of disease in Europe, although the potential for them to become more widespread remains. Given the present epidemiological situation, it is difficult to envisage the extensive use of ACWY vaccines in Europe, but continued surveillance is vital to detect any increases in the burden of disease attributable to these serogroups and to inform vaccine policy decisions.

(7) Each country should contribute to surveillance of meningococcal subtypes and PorA variants in Europe.

Although some countries do not have the facilities for the subtyping of strains from all invasive cases, through European collaboration all countries should be able to access subtyping (either using monoclonal antibodies or by PorA sequencing) for a representative collection of strains. An increase in cases caused by a hypervirulent serogroup B clone has the potential to be tackled by a designer vaccine, in the same manner as has been introduced recently in New Zealand (Oster *et al.*, 2005). Subtyping information should therefore be obtained for large outbreaks or if an increase in incidence or in fatal disease is observed. The ongoing collection of representative information on PorA subtypes from Europe will inform the production of appropriate vaccines for the future. Increasingly, this information will be based on molecular rather than immunological methods (Brehony *et al.*, 2006). Further studies are required to determine whether vaccines made from certain PorA variants are able to offer cross-protection against other variants of that subtype.

Concluding remarks

Meningococcal vaccination has the potential to prevent cases and deaths from meningococcal infection in Europe. Conjugate vaccines have proven effectiveness, but even quadrivalent preparations can only cover the minority of disease-causing strains. Decisions to introduce conjugate vaccinations should be informed by accurate disease surveillance data.

Multivalent vaccines based on targets other than the capsular polysaccharide have the potential for broad coverage against serogroup B infection, the major cause of endemic disease in Europe. European surveillance has therefore provided an important baseline for informing vaccine

development, and can be used to evaluate vaccination programmes both now and in the future.

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