

Impact of meningococcal C conjugate vaccine in the UK

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This review details the impact of the introduction of meningococcal serogroup C conjugate (MCC) vaccines in the UK. An overall reduction of 86.7% in the incidence of serogroup C infection in the targeted age groups has been observed from 1999 to 2001, with a concomitant decrease in deaths, from 67 in 1999 to 5 in 2001. The enhanced surveillance programme initiated to complement the introduction of MCC vaccines has been essential in generating data relating to vaccine coverage, vaccine failures and efficacy estimates. Vaccine coverage has exceeded 80% in all age groups targeted and up to the end of 2001, 25 confirmed and 1 probable vaccine failure have been observed in England and Wales. Efficacy estimates for England up to September 2001 were 91.5% in infants receiving three doses of MCC vaccine and 89.3% in toddlers receiving one dose of MCC vaccine (England). There is some evidence of herd immunity in unvaccinated cohorts of the target age groups, ranging from a reduction in disease incidence of 34% in 9–14 year olds to 61% in 15–17 year olds. Surveillance of the genotypic and phenotypic characteristics of invasive and carriage isolates has shown no evidence to date of capsular switching from serogroup C to serogroup B.

Introduction

In November 1999, the UK became the first country to introduce a national immunisation programme for meningococcal serogroup C conjugate (MCC) vaccines. Their introduction was the culmination of an intensive clinical trial research programme involving collaboration between the Department of Health (DH), public bodies, academia and vaccine manufacturers [1]. The objective of the research programme was to provide the necessary safety and immunogenicity data both to support licensure of the MCC vaccines and to underpin policy decisions about their use in the UK population.

As the MCC vaccines were licensed on the basis of serological correlates of protection without direct evidence of efficacy [2], a comprehensive post-licensure surveillance programme was initiated by the Public Health Laboratory Service to monitor the impact of the MCC vaccines on disease incidence and to derive age-specific efficacy estimates (<http://www.phls.co.uk/advice/>

[mensurvw.pdf](#)). The surveillance programme was also designed to monitor the effect of the immunological pressure exerted by MCC vaccination on the genotypic and phenotypic characteristics of invasive and carriage isolates, in particular to investigate the possibility of capsular switching between serogroup C and serogroup B organisms.

This paper reviews the impact of MCC vaccination on the incidence of meningococcal serogroup C disease in England, and provides age-specific vaccine efficacy estimates up to September 2001.

Epidemiology before the introduction of the MCC vaccine

The increase of meningococcal serogroup C (MenC) disease observed in the UK during the 1990s was due to the ET-15 clone of the ET-37 complex that also caused outbreaks in universities with associated high fatality rates [3]. In the 1990s, Spain [4] and Canada [5] suffered outbreaks of MenC disease. The ET-15 clone of the ET-37 complex arose in Canada [5, 6] before spreading world-wide [7]. ET-15 meningococci

tend to be more virulent than other members of the ET-37 complex and attack rates, case fatality rates and the proportion of survivors with sequelae have been reported to exceed the rates observed for other members of the ET-37 complex [7, 8]. The ET-15 clone of the ET-37 complex may be distinguished from other clones by a point mutation in the *fumC* gene used in multi-locus sequence typing [9]. In the UK the phenotypic marker serotype 2a has been shown to be an excellent subcapsular marker for the ET-37 complex [10].

Pre-licensure studies

The potential for an increase in MenC disease, and the opportunity to protect the population by the use of the new conjugate vaccines (then at an early stage of development), were recognised by the DH as early as 1994 when it funded the first MCC vaccine trials [1]. Following promising results in infants vaccinated under the UK 2/3/4 month schedule [11–13], the DH initiated further clinical trials to answer key policy-related questions. These trials determined the schedule to be used for catch-up immunisation of older age groups [14], the effect of prior vaccination with plain meningococcal C polysaccharide used for outbreak control on the response to MCC vaccines [15–17], and the compatibility of MCC vaccines when given at the same time as other vaccines used in the UK schedule, in particular diphtheria and tetanus vaccines which are similar to the carrier proteins in the MCC vaccines [1]. These DH-funded trials were complemented by manufacturer-sponsored trials designed to provide data required by the licensing authority, such as batch-to-batch variation [18] and the safety and immunogenicity of MCC vaccines compared with the licensed plain polysaccharide vaccine [19].

All three candidate MCC vaccines were found to induce bactericidal antibodies and immunological memory in UK toddlers after one dose [14], justifying the single dose catch-up schedule for children aged 1–18 years. The MCC vaccines were shown to be safe and immunogenic in infants following the 2/3/4 month schedule [11–13, 18] and in adolescents [19]. The hyporesponsiveness reported following meningococcal polysaccharide vaccines in young children and adults is overcome by administration of the MCC vaccine [15, 17, 20].

A key issue of the pre-licensure studies was the immunological assessment of MCC vaccines. Considerable efforts were made by the groups involved to develop and validate standardised assays to provide relevant correlates of protection. Previously, the serological correlate of protection against MenC disease had been established in military recruits in a serum bactericidal assay with human complement (hSBA) [21]. However, the standardisation of assays

undertaken in the pre-licensure studies used baby rabbit complement as the exogenous source of complement in the SBA (rSBA), which conforms to international recommendations regarding the standardisation of the SBA [22, 23]. A re-evaluation of the previously established correlate of protection was necessary because rSBA give generally higher titres than hSBA [24]. Data generated from the DH-funded clinical trials in which rSBA and hSBA titres were compared showed that rSBA titres <8 accurately predicted susceptibility and titres >64 predicted protection as defined by hSBA [2]. For vaccinees with rSBA titres in the equivocal range 8–64, it was proposed that additional evidence, namely a four-fold rise in rSBA titre supplemented by evidence of immunological memory, should be present to meet the serological criteria for protection [2].

Impact of MCC vaccines

The MCC vaccines were introduced in a phased programme because of initial restrictions on availability of the vaccine and targeted those age groups up to 18 years at higher risk of meningococcal disease. In general, vaccine coverage was high, exceeding 80%, in all age groups targeted [1].

The impact of MCC vaccines on the incidence of MenC disease within the targeted age groups has been significant. A comparison of laboratory-confirmed reports of MenC disease in 1999 and 2001 shows an overall reduction, for the targeted age groups indicated, of 86.7% (Fig. 1). The large reduction in MenC disease has been confined to the targeted age groups (Fig. 2a). There is some evidence of a reduction in MenC cases in those aged 20 years (24% fewer cases in 2001 compared with 2000), but this may be due to natural fluctuations in the yearly incidence of MenC disease, as there was only an 8% reduction in 2001 compared with 1999 (Fig. 2a). No systematic change in the incidence of serogroup B disease has been seen since the introduction of the MCC vaccination programme in those under 20 years of age or older (Fig. 2b).

A significant reduction in the number of deaths from MenC disease in those <20 years old has been observed (Fig. 3). Comparison of data from 1999 to 2001 shows a decrease from 67 deaths in 1999 to 5 deaths in 2001.

The introduction of the MCC vaccination programme has had a major impact on serogroup distribution of invasive meningococcal isolates in England and Wales (Fig. 4). Before its introduction, 634 (38%) of the 1683 meningococcal case isolates received by the Meningococcal Reference Unit (MRU) were serogroup C but this decreased to 16% (197 of 1237) in 2001 (Fig. 4). Although the percentage of serogroup B case isolates increased from 57% in 1999 to 73% in 2001, the actual numbers have remained relatively constant (951 in

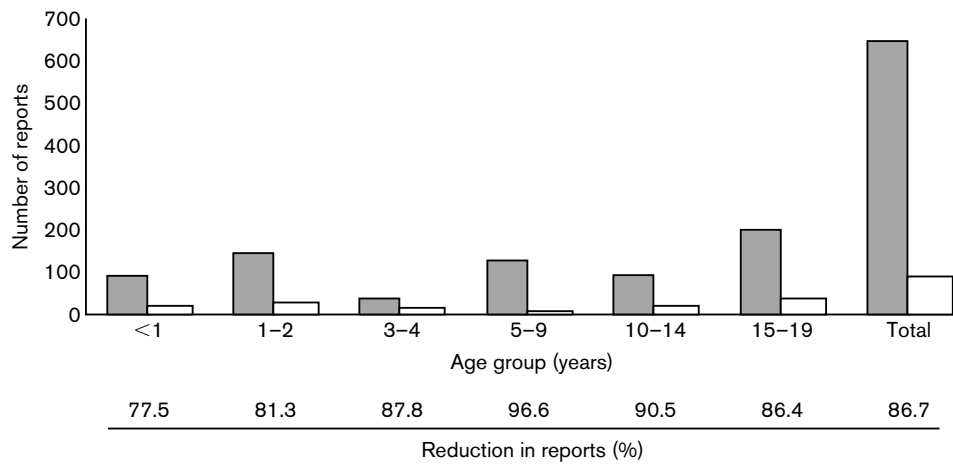


Fig. 1. Laboratory-confirmed reports of serogroup C meningococcal disease by age group in England for 1999 and 2001. ■, 1999; □, 2001.

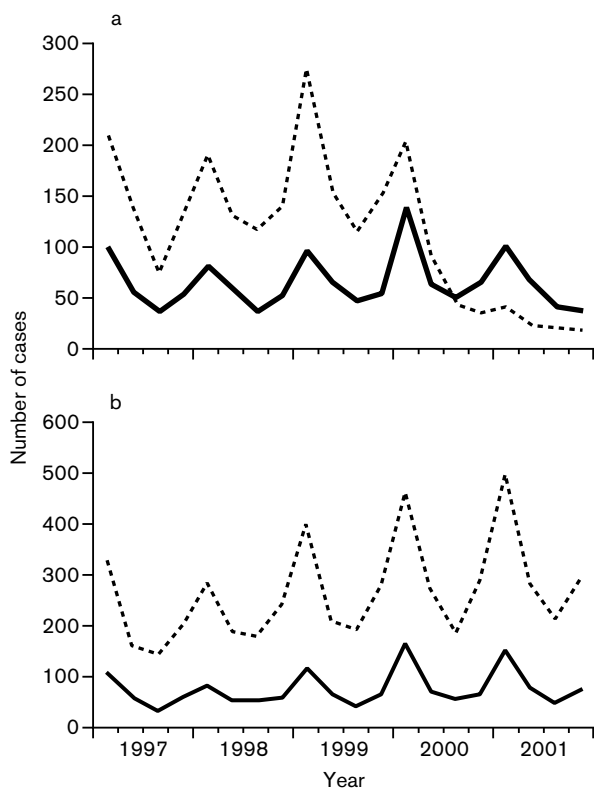


Fig. 2. Laboratory-confirmed cases of (a) meningococcal serogroup C disease and (b) meningococcal serogroup B disease, by quarter for England and Wales. ----, age <20 years; —, age ≥20 years.

1999 and 902 in 2001). An increase, both in the proportion and absolute number of serogroup W135 case isolates has been observed, from 3% (50 of 1683) in 1999 to 8% (97 of 1237) in 2001, associated with pilgrims returning from the Hajj [25].

The enhanced surveillance programme has allowed the continual monitoring of the number of vaccine failures. A vaccine failure is defined as a confirmed or probable case of MenC disease with onset >10 days after the last scheduled dose of MCC vaccine. Twenty-five confirmed vaccine failures and one probable vaccine

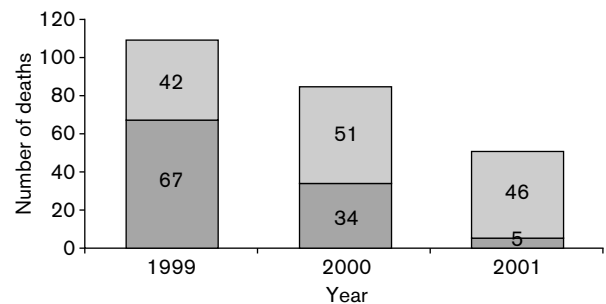


Fig. 3. Deaths from meningococcal serogroup C disease in England (1999–2001) reported to the Office of National Statistics or the Meningococcal Reference Unit. ■, age <20 years; □, age ≥20 years.

failure were observed in England and Wales by the end of 2001. An estimation of herd immunity could also be generated from the data obtained by the surveillance programme. The attack rates for MenC disease in unimmunised cohorts before and after the introduction of the MCC vaccine have been analysed (Table 1). The post-MCC period for each cohort chosen began after immunisation of that cohort had been completed and was compared with an equivalent period pre-MCC. The reduction in MenC disease in unvaccinated individuals ranged from 34% in 9–14 year olds to 61% in 15–17 year olds, providing some evidence of herd immunity. However, the confidence intervals are wide due to the small number of individuals included in this analysis.

Short-term vaccine efficacy estimates (up to September 2001), obtained by the screening method [26], are ≥90% for all the targeted age groups (Table 2).

Genotypic and phenotypic characteristics of invasive and carriage isolates

Surveillance of the genotypic and phenotypic characteristics of invasive and carriage isolates is essential to monitor the impact of the introduction of MCC vaccines on the population biology of the organism.

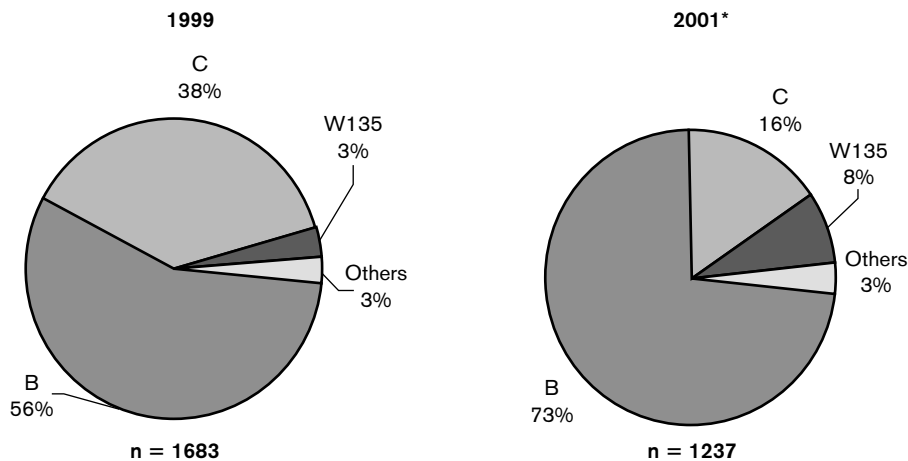


Fig. 4. Case isolates of *Neisseria meningitidis* reported to MRU in 1999 and 2001 by serogroup for England and Wales. Others: serogroups 29E, A, Y, Z and non-groupables.

Table 1. Percentage reduction in attack rate in unimmunised cohorts after the MCC campaign (England)

Age scheduled for MCC (years)	Rate per 10 ⁵ pre-MCC campaign	Rate per 10 ⁵ post-MCC campaign	Percentage reduction (95% CI)
15–17	9.28	3.62	61 (39–75)
9–14	4.49	2.95	34 (–11–61)
5–8	2.03	0.87	57 (–37–87)
1–4	4.67	2.34	50 (13–71)

Table 2. MCC vaccine efficacy estimates (England, September 2001) obtained by the screening method

Age groups	Number of doses	Vaccine efficacy (95% CI)
2–5 months	Exactly 3	91.5% (64.9–98.0)
2–5 months	2 or 3	88.6% (58.4–96.9)
2–5 months	Any	79.7% (38.2–93.3)
1–2 years	1	89.3% (72.7–95.8)
3–4 years	1	100% (84.9–100)
5–14 years	1	95.3% (88.3–98.6)
15–17 years	1	91.9% (73.3–98.4)

Studies in the UK have observed a 66% reduction in the carriage of serogroup C meningococci in 15–17 year olds 1 year after the introduction of MCC vaccine [27]. Concerns were raised that a change in the prevalence of serogroup C carriage due to the pressure exerted by the MCC vaccine might result in capsule switching from serogroup C to serogroup B. Meningococci can change serogroup while maintaining clonal features, thought to be a result of transformation and horizontal DNA exchange *in vivo* [28]. Capsule switching may be an important virulence mechanism of meningococci by which virulent strains evade natural or vaccine-induced immunity. To investigate if the immunological pressure exerted by the introduction of the MCC vaccines could lead to capsular switching, a subcapsular marker for the serogroup C ET-37 complex was selected. The expression of PorB serotype 2a, backed by multi-locus sequence typing data, has been used to monitor the numbers of serogroup B:2a cases. Since the introduction of the MCC vaccines, the

number of B:2a cases has not risen above historical levels observed (Fig. 5), illustrating that concerns over capsular switching between serogroup C and B driven by the introduction of the MCC vaccines remain speculative.

Serogroup C meningococci can express either O-acetylated (Oac⁺) or de-O-acetylated (Oac⁻) polysaccharide capsules. Two of the three MCC vaccines licensed in the UK are Oac⁺ and one is Oac⁻. In trials comparing responses to the three MCC vaccines, the Oac⁻ MCC vaccine induced significantly higher SBA titres than either of the two Oac⁺ MCC vaccines [14]. However, this may be due to other vaccine characteristics such as carrier proteins or conjugation methodologies. All three MCC vaccines were highly immunogenic and induced functionally protective antibodies against both Oac⁻ and Oac⁺ serogroup C strains [14]. A small study in the USA demonstrated that only 15% of serogroup C isolates from patients with meningococcal disease were Oac⁻ [29]. A larger study in the UK has been initiated, analysing the O-acetylation status of meningococcal serogroup C case isolates received by the MRU in January of each year. Before the introduction of the MCC vaccines in 1999, c. 12% of disease-causing serogroup C isolates from 1998 (14 of 111 isolates) and 1999 (20 of 164 isolates) were Oac⁻ [30]. In 2000, 21.95% (18 of 32) of serogroup C case isolates were Oac⁻, 27.9% (12 of 43) Oac⁻ isolates were observed in 2001 and 15.4% (2 of 13) in 2002. Therefore, allowing for natural fluctuations in the level of Oac⁻ isolates and the reduced numbers of serogroup C isolates post-MCC vaccines, the O-acetylation status of disease-causing serogroup C isolates in the UK does not appear to have been influenced by the introduction of MCC vaccines.

Conclusions

The impact of the MCC vaccines on MenC disease in the UK has been significant. Reductions in both the

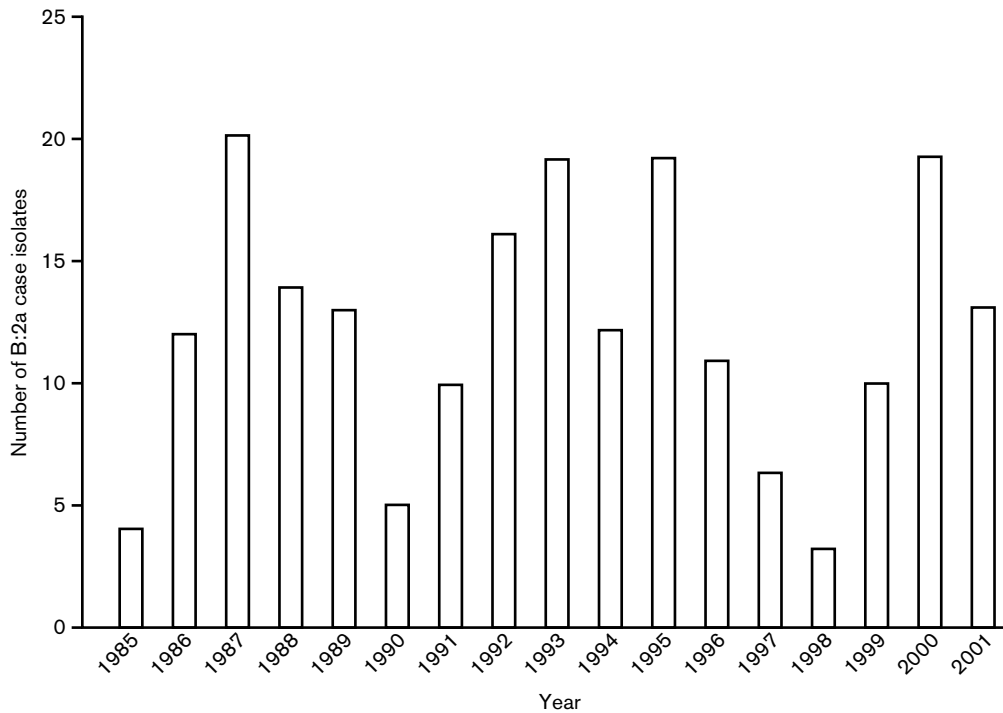


Fig. 5. Numbers of B:2a case isolates submitted to the PHLS Meningococcal Reference Unit from 1985 to 2001.

incidence of serogroup C infection and fatalities attributable to meningococcal serogroup C infection have been observed since the introduction of the MCC vaccines in 1999. Short-term vaccine efficacy estimates for the target age groups remain high and there is some evidence of herd immunity in unvaccinated cohorts of the target age groups. No evidence of capsular switching has been demonstrated to date.

The research undertaken in the UK was crucial in the licensure and subsequent use of MCC vaccines and illustrates the benefit of such focused research in the evaluation of bacterial polysaccharide-conjugate vaccines. Specific questions were addressed during the research and stimulated debate on such issues as the appropriate immunological correlates of protection for conjugate vaccines. The experience gained during the introduction of the MCC vaccines should provide a basis for the future evaluation of new meningococcal polysaccharide-conjugate vaccines.

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