Planning, registration, and implementation of an immunisation campaign against meningococcal serogroup C disease in the UK: a success story

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Abstract

The introduction of meningococcal C conjugate (MCC) vaccine in the UK in November 1999 as a routine 3 dose infant immunisation course, with a single catch-up dose for all children aged between 12 months and 17 years, was the result of an intensive 5 year collaborative research programme funded by the Department of Health for England and involving public bodies, academia and vaccine manufacturers. The research programme established the safety and immunogenicity of MCC vaccines in infants, toddlers, pre-school and school-aged children. The nature and frequency of common adverse events in school-aged children was similar to that after a booster dose of diphtheria and tetanus vaccine given to the same age groups. The recommendation that a single dose was adequate for children aged 12 months and above was based on antibody levels measured by serum bactericidal assay and evidence of induction of immunological memory as shown by maturation of antibody avidity. Licensure by the Medicines Control Agency was based on serological criteria alone without direct evidence of efficacy and has set a precedent for other meningococcal conjugate polysaccharide vaccines. Vaccine coverage of around 85% was achieved in the targeted age groups and has resulted in a drop in the incidence of serogroup C disease in these groups of over 80% within 18 months of the start of the vaccination programme. Early post-licensure efficacy estimates for toddlers and teenagers (88 and 96%, respectively, in the first 16 months after vaccination) validate the serological criteria used for licensure. Surveillance of the prevalent serogroups and serosubtypes among invasive case isolates has shown no evidence of any capsular switching to serogroup B during the first 18 months of the MCC vaccination programme. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Meningococcal serogroup C disease; Meningococcal conjugate vaccine

1. Introduction

In November 1999, the UK became the first country to implement an immunisation programme against meningococcal serogroup C disease using a conjugate vaccine. Its introduction was the culmination of an intensive 5 year clinical trial research programme sponsored by the Department of Health (DH) for England. The objective was to accelerate the availability of such new vaccines for the UK population. The DH-funded research programme was a collaborative effort involving public bodies, academia and vaccine manufacturers and was primarily designed to provide the scientific information needed for policy decisions about the use of meningococcal serogroup C conjugate (MCC) vaccines in the UK. However, the research was conducted in such a way that it also provided data to support the licensure of MCC vaccines by the UK Medicines Control Agency (MCA).

This paper describes the rationale for the DH-funded clinical trial programme, the pivotal safety and immunogenicity studies, the criteria used to license MCC vaccines, the implementation arrangements and the epidemiological impact of the first 18 months of the MCC vaccination programme.

2. Epidemiology of meningococcal disease in the UK before the introduction of MCC vaccines

Meningococcal serogroup C disease has been endemic in England and Wales for many years although at a lower incidence than serogroup B disease (Fig. 1). In 1994, serogroup C infections comprised 292 (25.8%) of the 1132 cases confirmed in England and Wales by the Meningococcal Reference Unit (MRU) of the Public Health Laboratory Service (PHLS). In 1998, the last year before the introduction of MCC vaccines, serogroup C infections comprised 823 (34%) of the 2418 meningococcal infections confirmed by the MRU.
The apparent increase in the incidence of confirmed meningococcal infection was due in part to the introduction of more sensitive polymerase chain reaction (PCR) methods for the identification and serogrouping of meningococci [1,2]. However, serogroup C disease increased proportionately more than other serogroups, confirming a true rise in the level of endemic serogroup C infection. Rates of serogroup C disease were particularly high in adolescents (Fig. 2a) in whom school-based outbreaks attracted considerable public concern and media interest. Case fatality rates increase with age and are higher in cases of serogroup C than B infection, particularly serogroup C2a which is the predominant serosubtype in the UK [3]. Because of this, the number of deaths from meningococcal serogroup C infection in children aged 10–19 years in England and Wales exceeded those due to meningococcal B disease prior to the introduction of the MCC vaccination programme (Fig. 2b).
Table 1

Invasive meningococcal disease by serogroup: number and rate per 10,000 persons in England and Wales

<table>
<thead>
<tr>
<th>Serogroup</th>
<th>Age group (years)</th>
<th>No.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;1</td>
<td>1–4</td>
<td>5–14</td>
</tr>
<tr>
<td>B</td>
<td>315</td>
<td>435</td>
<td>1.7</td>
</tr>
<tr>
<td>C</td>
<td>108</td>
<td>235</td>
<td>0.9</td>
</tr>
<tr>
<td>Otherb</td>
<td>51</td>
<td>97</td>
<td>0.4</td>
</tr>
<tr>
<td>Not confirmed</td>
<td>585</td>
<td>540</td>
<td>2.1</td>
</tr>
<tr>
<td>Total</td>
<td>1059</td>
<td>1307</td>
<td>5.1</td>
</tr>
</tbody>
</table>

* Cases identified through the enhanced national surveillance system between 1 January 1999 and 31 December 1999.

3. Rationale of the DH-funded clinical trial programme

Early in 1994, it was apparent to DH and PHLS that there was a real possibility that the UK would face increases of group C meningococcal disease caused by the ET37 complex C2a, as had been seen in Canada, Spain, and the Czech Republic. A decision was therefore taken to change the focus of the DH-funded Vaccine Evaluation Consortium (VEC) away from combination vaccines based on acellular pertussis to conjugate group C meningococcal vaccines. This approach was considered promising in view of the

3 The clinical and pre-clinical components of the DH-funded clinical trials programme are undertaken by the UK Vaccine Evaluation Consortium (VEC), a collaborative group involving three public funded bodies, the PHLS, the National Institute for Biological Standards and Control (NIBSC) and the Centre for Applied Microbiology and Research (CAMR) Porton Down, together with an academic immunobiology unit at the Institute of Child Health (ICH), London. The field work involved in the trials is carried out in the two PHLS vaccine evaluation units by trained study nurses based in general practices in Gloucester and Hertfordshire.
outstanding success of conjugate *Haemophillus influenzae* type b (Hib) vaccines wherever they had been introduced. Unlike the existing plain serogroup C polysaccharide vaccines, the development of a conjugate vaccine would offer the prospect of protection in young children and induction of long term immunity.

All manufacturers were approached and three responded with interest in collaborating on a MCC vaccination development programme. Funding was obtained by the PHLS from the DH to evaluate each of these candidate vaccines under the UK 2/3/4 month infant schedule. Two of the three candidates, MCC vaccines were CRM197-based conjugates and the third was a tetanus-based conjugate. All proved highly immunogenic under the UK schedule with evidence of induction of immunological memory and putative protective antibody levels after only one or two doses [6–9].

Given the wide age range of cases of serogroup C disease in the UK, it was planned to achieve an immediate impact by accompanying the introduction of MCC vaccine into the primary infant schedule with a mass catch-up programme for all children aged >4 months to <18 years, the ages and timing dictated by the availability of vaccine. Implementation of such a programme required answers to the following policy-related questions:

- What is the effect of prior vaccination with plain meningo-
  coccal C polysaccharide vaccine on the magnitude and
  kinetics of the response to MCC vaccine?

A parallel component of the DH-funded research pro-
gramme was the development of pre-clinical tests for con-
trolling the quality of the batches of MCC vaccines once licensed. The National Institute for Biological Standards and Control (NIBSC) carried out this work, and the experience gained was invaluable in facilitating the rapid batch release of MCC vaccines once licensure of the first vaccine was granted in October 1999 and subsequently [10–12].

4. Immunological assessment of MCC vaccines

Early discussions between manufacturers and the MCA indicated that licensure of MCC vaccines on the basis of immunogenicity data alone, without direct evidence of protective efficacy, would be considered. The basis of this decision was the existing licensure of plain serogroup C polysaccharide vaccines for children aged 2 years and above for whom there was direct evidence of efficacy and accepted serological correlates of protection. Extrapolation of these correlates to infants, in whom the plain C polysaccharide is neither immunogenic nor efficacious, was the basis for licensure of the MCC vaccines in the UK and has established an important precedent for other meningococcal conjugate polysaccharide vaccines.

Because of this precedent, considerable attention was given by the VEC to the development and validation of the assays which provided the serological correlates of protection. The "gold standard" correlate of protection against meningococcal serogroup C disease was established in military recruits using a serum bactericidal assay (SBA) with the exogenous complement derived from human sera (hSBA) [13]. However, because of the lack of a standardised commercial source of human complement, international standardisation of the SBA is now based on a method in which baby rabbit serum is used for the complement source (rSBA). Since the rSBA gives generally higher titres than the hSBA, a re-evaluation of serological correlates of protection for MCC vaccines was undertaken [14]. This included comparison of rSBA and hSBA titres in naturally immune and vaccinated individuals, and measurement of four-fold rises in rSBA titre following vaccination and maturation of IgG antibody avidity to evaluate the induction of immunological memory. Antibody avidity is a measure of effective antigen bind-
ing, with high avidity characteristic of a T cell-dependent response and indicative of immunological memory [15].

Based on a detailed analysis of the responses in infants, toddlers and adolescents using the above measures, it was proposed that a rSBA titre ≥8 using rabbit complement was likely to be indicative of protection, even though the hSBA titre may be <4 [14]. Since the organism used in the standardised SBA (C11 strain) is not the same as that currently circulating in the UK, additional SBA were carried out on a subset of sera using organisms which were representative of prevalent UK strains, including those in which the capsular polysaccharide is de-O-acetylated (Oac−). Such strains comprised 12% of the prevalent meningococcal serogroup C organ-
isms causing invasive infection in 1999 [16]. Interestingly, both CRM197-based MCC vaccines were derived from O-acetylated strains whereas the tetanus toxoid-based conjugate from Baxter was derived from an Oac− strain.

5. Key results of the research programme

The clinical trial research programme established the follow-
ing:

- In toddlers, a single dose of each of the three MCC vac-
  cines was safe and immunogenic and primed for memory [17].

- In young children, prior plain C polysaccharide did not interfere with the induction of immunological memory to MCC vaccines, although SBA levels may be lower than those in naive MCC-vaccinated children [18].
Fig. 3. Percentage of teenagers reporting symptoms within 3 days of vaccination with meningococcal C conjugate (MCC) or a booster dose of low dose diphtheria/tetanus (Td) vaccine. Data derived from follow-up diaries completed by school children aged 13–17 years of age randomised to receive either a dose of MCC (n = 280) or Td (n = 275) vaccine.

- In pre-school children and school leavers, there was no adverse effect on immunogenicity or reactogenicity of either the MCC or the diphtheria/tetanus booster vaccines if administered at the same time or within a month of each other (CDSC, unpublished).
- In primary and secondary school children, the MCC vaccines had a good safety profile, the nature and frequency of common adverse events being similar to that of the diphtheria and tetanus vaccines given to these age groups (Fig. 3).
- In young adults, vaccination with plain C polysaccharide-induced hyporesponsiveness to a subsequent dose of plain vaccine but did not compromise the response to MCC vaccine [19]. In those with pre-existing antibody to C polysaccharide, there was no decline in antibody levels immediately following MCC vaccination. Protective SBA levels were reliably present 10 days after MCC vaccination irrespective of prior vaccination with C polysaccharide [20].

The DH-funded clinical trial programme, together with complementary manufacturer-sponsored studies [21–24], culminated in the licensure of the first MCC vaccine, the Wyeth Lederle product (Meningitec™) in October 1999. Licensure of the Chiron (Menjugate™) and the Baxter (Neisvac™) vaccines followed in March and July 2000, respectively.

6. Implementation of the MCC programme

In the DH’s 1998 Comprehensive Spending Review, the introduction of MCC vaccine was anticipated for October 2000, and plans were in development for resources to become available to support this. However, the winter meningococcal season of 1998/1999 showed continuing increases in the proportion and number of meningococcal C infections, especially in adolescents. It was also apparent that the results from the clinical trials were strongly reassuring, and because of rapid recruitment into the trials, the research programme could be completed early. The manufacturers were asked in January 1999 to consider bringing forward the introduction of MCC vaccine by a year, and the three companies responded positively.

In February 1999, Frank Dobson, Secretary of State for Health, agreed that the programme should go forward in the autumn of 1999, subject to demonstration of cost-effectiveness, availability of resources, and adequate supplies of vaccine [25]. In May 1999, the Joint Committee on Vaccination and Immunisation, the independent expert advisory group to DH, reviewed the epidemiology, the results of the vaccine studies, and the outline implementation options. The committee recommended the introduction of vaccination as soon as possible, subject to granting of product licenses and supplies, the programme to be targeted according to age risk groups and vaccine availability. The forthcoming introduction of the MCC vaccine programme was announced to Parliament in July 1999 and immediately thereafter tenders for supply were invited, in line with European Directives on Government procurement. Manufacturers were pressed to make their forecasts of number of doses and expected dates of completion of manufacturing available to the DH as early as possible.

It was decided to vaccinate 5–17 year olds through schools and the under 5 through general practice. Steps were therefore urgently taken to alert the education system to the probability of a school-based immunisation campaign starting in the late autumn. Local immunisation co-ordinators were briefed on the campaign and asked to provide the
DH with estimates of the numbers of children in each age group in order to plan vaccine allocation to schools. Since data had been collected on the number of doses of diphtheria/tetanus/pertussis/Hib (DTP/Hib) vaccine that had been ordered by each general practitioner (GP) over the preceding 2 years, it was possible to estimate the number of children under 5 years cared for by each GP. Vaccine was then issued to each GP either weekly or fortnightly, and no ordering was necessary. The suppliers of software for the national childhood immunisation computing systems were given the projected dates for immunisation of children under 5 years of age who were invited for immunisation through the computerised call-up programmes, exactly in line with supplies to GPs. The target population was over 15 million children to be immunised in 12 months: there were no shortages of vaccine and the full requirement of vaccine was issued according to the schedule.

Following market testing amongst parents and young people, advertising materials were issued. Leaflets were available in primary care, pharmacists and supermarkets, and sufficient were provided to every school to allow each child to take a leaflet home. The leaflets included a consent form that was returned to the school and used to complete the information on the school lists that were used by the local immunisation co-ordinators. A television advertisement was developed whose main message was that parents should not make appointments since every child would be invited for the new immunisation in turn.

In line with the available supplies, MCC vaccine was initially introduced from the beginning of November 1999 for 15–17 year olds, the age groups in whom mortality rates (Fig. 2b) and the risk of outbreaks were highest. Infants due to receive their three dose primary immunisation course with combined DTP/Hib vaccine at 2/3/4 months of age were scheduled to receive MCC vaccine at the same time from late November 1999 onwards. Toddlers aged 12–23 months and infants aged 5–11 months were scheduled to receive one and two doses of MCC vaccine, respectively, from mid January 2000 onwards. Vaccination of 2–4 year olds was targeted to be completed by late 2000. The remaining school-aged children between 5 and 15 years were scheduled to receive MCC vaccine by Autumn 2000 with the order of priority as determined by the age-specific morbidity and mortality data (Fig. 2a and b), beginning with 10–14 years old and followed by 5–9 year olds.

As expected, immunisation provided by GPs proved to be less timely than delivery through schools as the number of children who could be vaccinated at a school session was considerably greater than the number who could be vaccinated at a GP session.

7. National surveillance strategy

Since the UK was the first country to introduce MCC vaccines, furthermore without direct evidence of efficacy, the PHLS put in place a comprehensive surveillance strategy to monitor the impact of the new MCC vaccination programme. Its objectives are as follows:

- to measure the impact on the age-specific and serogroup-specific incidence of meningococcal disease;
- to measure age-specific vaccine coverage;
- to obtain formal estimates of age-specific MCC vaccine efficacy;
- to document the risk factors for vaccine failure;
- to develop an active system for monitoring vaccine safety;
- to monitor any changes in the genotypic characteristics of invasive and carriage strains of meningococci.

All cases of confirmed and probable serogroup C disease in individuals under 20 years of age are being followed up to obtain vaccination history (including manufacturer and batch number). Multi locus sequence typing of invasive and carriage isolates is being undertaken to monitor the impact of the programme on the population genetics of Neisseria meningitidis. The full protocol for the surveillance programme and for the investigation of vaccine failures can be found on the PHLS website (http://www.phls.co.uk/advice/mensurvw.pdf).

A case of confirmed serogroup C disease is defined as clinical meningococcal disease plus one or more of the following:

- Phenotypically serogroup C positive from samples taken from a normally sterile site.
- PCR serogroup (sidD) C positive sample taken from a normally sterile site or rash aspirate.
- Meningococcal C antigen detected by latex in blood, CSF or urine.
- Four-fold rise in IgG antibody to C polysaccharide between acute and convalescent sera, and a convalescent sample with a concentration of specific IgG antibody greater than 3 μg/ml.

Cases with compatible clinical symptoms in whom serogroup C meningococcus is only isolated from a nasopharyngeal or conjunctival swab are classified as probable cases.

A confirmed MCC vaccine failure is defined as: confirmed invasive meningococcal serogroup C disease with onset of more than 10 days after the last dose of MCC vaccine scheduled for that age group, namely three doses for children vaccinated by 4 months of age; two doses for children aged 5 years and up; and one dose for children aged 12 months and up. A probable vaccine failure is defined as a case of probable serogroup C infection with the above vaccination history.

8. MCC vaccine coverage

8.1. Routine vaccination coverage

Coverage data was collected from 91/100 (91%) of health authorities for the first cohort of infants (born between 1
October 2000 and 31 December 2000) to be offered three doses of MCC vaccine at 2/3/4 months of age [26]. Coverage in this cohort was 87.0%.

8.2. Catch-up vaccination coverage

Five one-off request forms were devised in order to capture the coverage in the English population from 5 months to 17 years. By May 2001, provisional data had been returned from 87/100 (87%) health authorities and reflects vaccination status on 28 February 2001.

Coverage in infants between 5 and 12 months of age at the start of the campaign (born between 11 January 1999 and 28 July 1999) was 82.2% (167,187/203,440). This is likely to be an underestimate due to difficulties in recording immunisations given as part of the two-dose infant catch-up course.

In toddlers aged 12 months to 2 years, (born between 11 January 1998 and 10 January 1999) coverage was 85.5% (327,779/383,189). In children aged 2–4 years (born between 1 September 1994 and 10 January 1998) coverage was only 77.4% (1,026,931/1,326,448). This latter group has experienced delays in scheduling due to pressure on sessions in primary care.

Data was also collected for children who started school years 1–10 in September 1999 (children born between 1 September 1993 and 1 August 1985) by school year. A separate collection was made for school years 11–13 (1 September 1983 to 31 August 1982) and any persons in this age group who were at sixth form colleges, further education colleges or not in school. Coverage was 86.7% overall (4,612,987/5,316,421) and varied from 89.8 to 67.6% by school year and was generally lower in the senior years. Coverage in other formal education settings was similar to that in sixth form colleges, further education colleges or not in school. Coverage was 86.7% overall (4,612,987/5,316,421) and varied from 89.8 to 67.6% by school year and was generally lower in the senior years.

Coverage of MCC vaccine suggests that the vaccine was broadly acceptable to parents and children with coverage in most cohorts exceeding 85%. Coverage in some groups (e.g. children aged 2–4 years and senior school years) was lower, but this mainly reflects difficulty with scheduling vaccine rather than acceptability.

9. Impact of MCC programme on meningococcal disease

The programme had an immediate and profound effect on the incidence of meningococcal serogroup C disease in the targeted age groups [28]. Comparison of the numbers of cases of confirmed serogroup C disease between July 2000 and April 2001 with those in the comparable period in 1998/1999 showed an overall reduction of 81% (Table 2). The smaller reduction in the 5–9 year age group (64%) reflects the fact that immunisation of this cohort was not completed until the end of 2000.

No impact has yet been seen on the incidence of serogroup C disease in age groups too old to have been vaccinated (Fig. 4), suggesting that little herd immunity has been generated in these age groups by vaccination of younger school age children. This is not surprising given the high rates of meningococcal carriage in young adults aged 20–24 years [29].

Surveillance of the prevalent serogroups and serosubtypes among invasive case isolates has shown no evidence of any...
change in the 18 months since the MCC vaccination pro-
gramme was introduced (Kaczmarek, personal communica-
tion). Concerns that the prevention of serogroup C disease
by vaccination might result in a capsular switch to serogroup
B remain entirely speculative.

10. Cases in vaccinated children

Information on vaccination status was obtained for 415
of the 421 (98%) confirmed or probable serogroup C in-
fecteds identified by April 2001 in age groups eligible for
MCC vaccination (Table 3). Of the 29 cases with a history
of vaccine prior to onset, 14 developed disease before ad-
equate immunity could be established (defined as less than
10 days after the completing dose of a schedule appropriate
for their age at the time of vaccination). This included nine
children who developed disease after completing only a sin-
gle dose of a three dose course, one child who developed
disease 14 days after the second dose of a three dose course
and four children who developed disease between 3 and 5
days after a single dose course. The remaining 14 confirmed
cases and 1 probable case therefore fulfil the case definition
of confirmed or probable vaccine failures. Fourteen of these
cases developed disease after a single dose course, one de-
veloped disease after completing a two-dose schedule be-
tween the age of 5 and 12 months. Clinical data on these
cases is still being collected but the majority have no indi-
cation of pre-existing risk factors for vaccine failure.

11. Vaccine efficacy

Efficacy estimates for toddlers and 15–17 year olds dur-
ing the first 9 months of the MCC vaccination programme
were high, 92% (95% CI, 65–98) and 97% (77–99), respec-
tively [28]. Updated efficacy estimates after 16 months of
follow-up for the toddlers and 15–17 year olds in England
calculated as previously [28] are 88% (95% CI, 67–95) and
96% (95% CI, 85–99.1), respectively. These short-term effi-
cacy estimates support the proposed serological correlate of
protection based on a rSBA titre \( \geq 8 \) [14] and suggest that
the higher cut-off of \( \geq 128 \) proposed by Santos et al. [30] is
unnecessarily stringent (Table 4) [14]. Formal efficacy es-
timates for infants under 1 year of age have not yet been
calculated but the paucity of cases in vaccinated infants in
this age group who had received two or more doses \( \geq 10 \)
days after onset is consistent with high efficacy after only
two doses. Surveillance is continuing in order to monitor
long-term efficacy which will depend on the ability to mount
rapidly a booster response on exposure to the organism.

12. Adverse events

Post-licensure surveillance of adverse vaccine events
through passive reports from health professionals to the
MCA/Committee on Safety of Medicines was enhanced
for MCC vaccines by requesting reports of any suspected
reaction, whatever the severity. By September 2000 a total
4764 reports had been received, a reporting rate of 1 per
2875 MCC doses distributed [31]. The vast majority were
non-serious reactions such as headache, local reaction,
pyrexia and dizziness, reflecting the pattern of common
symptoms seen in the clinical trials (Fig. 3). Anaphylactoid
reactions were reported at a rate of 1 per 500,000 doses
distributed.

Other rare adverse events such as purpura, erythema
multiforme, arthritis and arthropathy have been reported.
Investigation of the potential causal relationship with

<table>
<thead>
<tr>
<th>Age</th>
<th>Vaccine efficacy (%)</th>
<th>rSBA ( \geq 1/8 ) (%)</th>
<th>rSBA ( \geq 1/128 ) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12–30 months</td>
<td>88 (69–95)</td>
<td>92–96</td>
<td>68–81</td>
</tr>
<tr>
<td>15–17 years</td>
<td>96 (85–99)</td>
<td>96</td>
<td>100</td>
</tr>
</tbody>
</table>

\*rSBA data from [17,18].
MCC vaccination is being studied using record linkage methods [32].

13. Conclusion

The UK experience with the planning, registration and implementation of MCC vaccines illustrates what can be achieved if a pro-active approach is taken by those responsible for national immunisation policy. A key factor in the success of the UK MCC development strategy was the independent funding from the DH which ensured that the collaboration between public sector, academia and industry provided both the evidence for national immunisation policy as well as data to support licensure. Early dialogue between manufacturers and the licensing authority greatly facilitated this process. The UK experience should serve as a model for the development, licensure and implementation of polysaccharide conjugate vaccines currently under development to combat serogroup A, Y and W135 meningococcal disease.

Acknowledgements

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References

seregroup C conjugate vaccine administered at 2–4 months of age.


