Review

Effectiveness of meningococcal serogroup C vaccine programmes

Ray Borrow\textsuperscript{a,}b, Raquel Abad\textsuperscript{b}, Caroline Trotter\textsuperscript{c}, Fiona R.M. van der Klis\textsuperscript{d}, Julio A. Vazquez\textsuperscript{b}

\textsuperscript{a} Vaccine Evaluation Unit, Public Health England, Clinical Sciences Building, Manchester Royal Infirmary, Manchester, UK
\textsuperscript{b} Laboratorio de Referencia de Meningococos, Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid, Spain
\textsuperscript{c} University of Cambridge, Department of Veterinary Medicine, Madingley Road, Cambridge, UK
\textsuperscript{d} National Institute of Public Health and the Environment, Bilthoven, The Netherlands

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A B S T R A C T

Since the introduction of monovalent meningococcal serogroup C (MenC) glycoconjugate (MCC) vaccines and the implementation of national vaccination programmes, the incidence of MenC disease has declined markedly as a result of effective short-term vaccination and reduction in acquisition of MenC carriage leading to herd protection. Monovalent and quadrivalent conjugate vaccines are commonly used vaccines to provide protection against MenC disease worldwide. Studies have demonstrated that MCC vaccination confers protection in infancy (0–12 months) from the first dose but this is only short-term. NeisVac-C\textsuperscript{c} has the greatest longevity of the currently licensed MCC vaccines in terms of antibody persistence, however antibody levels have been found to fall rapidly after early infant vaccination with two doses of all MCC vaccines – necessitating a booster at \textasciitilde12 months. In toddlers, only one dose of the MCC vaccine is required for routine immunization. If herd protection wanes following catch-up campaigns, many children may become vulnerable to infection. This has led many to question whether an adolescent booster is also required.

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1. Introduction

1.1. Incidence and epidemiology

Bacterial meningitis is a life-threatening disease that is caused by bacterial infection of the meninges. Neisseria meningitidis is the most common cause of bacterial meningitis and a major cause of
septicaemia [1–3]. In Europe, the US and other developed countries, meningococcal disease incidence is typically between 1 and 10 per 100,000 population, with occasional ‘hyperendemic’ periods of persistent disease caused by particular strains. The incidence of meningococcal disease is highest among infants; the rates drop after infancy but increase during adolescence and early adulthood.

There are 12 serogroups of Neisseria meningitidis, defined on the basis of different immunochemical variants of the polysaccharide capsule that surrounds the bacteria but only six (A, B, C, W, X, Y) cause life-threatening disease [4]. While large meningococcal serogroup A outbreaks have been prevalent in Africa, serogroups B and C meningococci cause most disease in Europe, where most cases are sporadic, with small case clusters periodically occurring [5]. In 2008 (n = 4978) and in 2009 (n = 4637), a total number of 9615 cases of invasive meningococcal disease were reported in Europe with an overall notification rate of 0.99 per 100,000 population in 2008 and 0.92 in 2009 [6].

A major advance in meningococcal disease prevention has been the development of meningococcal glycoconjugate vaccines including meningococcal serogroup C (MenC) glycoconjugate (MCC) vaccines. MCC vaccines were implemented to combat the increase in serogroup C disease due to the ST11 clone complex which, before reaching the UK, had spread through Canada, Spain and the Czech Republic [7]. The UK was the first country to introduce MCC vaccination in 1999, incorporating MCC vaccines into the routine infant schedule at 2, 3 and 4 months of age. An extensive single-dose catch-up campaign was implemented for 1- to 18-year olds [7]. Other European countries, Australia and Canada followed suit and have all subsequently observed substantial reduction in MenC disease [8–12]. In addition to MCC vaccines, quadrivalent conjugate vaccines against serogroups A, C, Y, and W are available and recently, a four-component recombinant serogroup B vaccine has been licensed in Europe.

2. Concepts of vaccination

Several underlying concepts of vaccination (summarized in Table 1) are important for fully understanding the impact of MCC vaccination programmes. Within medical communities in some territories there is a danger that the current low incidence of MCC disease may lead to a misconception that scheduled vaccination programmes can be halted or scaled back. This view is erroneous and there is a need to increase awareness of MCC vaccination and emphasize the importance of continued vaccination. Vaccination programmes have been associated with a significant reduction in disease incidence but continued vaccination is essential to sustain this (Fig. 1).

A widely accepted correlate of protection for MenC disease is the outcome of a serum bactericidal antibody (SBA) [13] assay because complement mediated bacterial killing by serum antibodies is the primary mechanism of protection against meningococcal disease. The original assay used complement preserved human serum but, due to ease of availability, it is now accepted that 3- to 4-week old baby rabbit serum may be used as an alternative complement source for the SBA assay [14]. Serum bactericidal antibody titres of ≥4 with human complement (hSBA) and ≥8 with baby rabbit complement (rSBA) are indicative of protective efficacy [15]. High circulating levels of SBA are important because the onset of the disease is so rapid that the production of antibodies in response to infection is too slow a process to be protective [16].

Catch-up campaigns have been employed by many countries implementing national vaccination programmes. These are one-time programmes targeting the age groups at highest risk of disease.

The primary outcome measures of vaccination trials relate to the individual protection of immunized individuals, however, this focus may underestimate the impact of a vaccine programme on a population. While vaccines provide direct protection for the immunized population, they can also benefit unvaccinated individuals. Disease transmission can be interrupted when a large proportion of the population is immune. The more individuals in a given population there are with immunity, the lower the likelihood for a susceptible person coming into contact with an individual carrying the bacterium. This concept is known as herd protection [17,18]. Herd protection is of great importance in vaccination campaigns as it provides indirect protection, with reductions in disease rates in unimmunized individuals, however, herd protection can only usually occur if vaccination programmes achieve a large-scale coverage of a population.

3. MCC vaccines: the clinical evidence

Commercially available vaccines that contain serogroup C comprise monovalent conjugate vaccines, quadrivalent conjugate vaccines, polysaccharide vaccines and a combination MenC-Haemophilus influenzae type b (Hib) conjugate vaccine. Their formulation, adjuvants used and antigenic content are summarized in Table 2.

Polysaccharide vaccines are effective in the short term but are not used in routine vaccination campaigns because they do not induce a T-cell-dependent immune response, and are therefore poorly immunogenic in young children and only confer short-term protection [4]. Conjugate vaccines elicit B- and T-cell responses and induce immunity and immune memory in infants <2 years of age [18,19]. Three MCC vaccines were first licensed in the UK in 1999/2000, two conjugated to CRM197, a mutated diphtheria toxoid (Menjugate® (MCC-CRM197, Novartis), Meningitec® (MCC-CRM197, Pfizer), and one to tetanus toxoid (NeisVac-C® (MCC-TT, Baxter). Quadrivalent meningococcal conjugates are Menactra® (ACWY-DT, Sanofi Pasteur) licensed in the US for 2–55 years and given to 11–18 year olds [20], Menevo® (ACWY–CRM197, Novartis Vaccines), which is licensed in Europe and the US for ≥2 years (until 55 years in US) and Nimenrix® (ACWY-TT, Glaxo SmithKline) licensed in Europe for individuals 12 months of age and older.

Meningococcal–Haemophilus influenzae type b (Hib) combination vaccines are available in form of Menitorix® (MCC-TT/Hib-TT, GlaxoSmithKline), which is routinely given as a booster vaccines in toddlers in the UK, and MenHibrix® (MenC-TT/Hib-TT, GlaxoSmithKline), licensed in the US.

Different MCC vaccines produce different immune responses, which may have an impact on vaccination programmes [21,22]. Different conjugates have been found to induce different antibody avidity and with varying capabilities to prime for immunologic memory [23,24]. Formulations using different carrier proteins have similarly been shown to demonstrate varying avidity [25].

The polysaccharide capsule of MenC has been integral to vaccine development. While Menjugate® and Meningitec® vaccines contain the O-acetylated (OAc+) form of polysaccharide, some MenC strains have de-O-acetylated (OAc−) polysaccharides, which may affect antibody specificity and functional activity when used in a vaccine. NeisVac-C® contains a de-O-acetylated (OAc−) oligosaccharide and has been shown in clinical studies to demonstrate greater immunogenicity than Menjugate and Meningitec [26]. The reason for the improved immunogenicity is not clear, it may arise from several factors including the O-acetylation, the TT conjugate, the conjugate chemistry, the length of polysaccharide constituents or adjuvants. It should be noted, however, that there is a general waning of protection in all age groups independent of the vaccine used.
Table 1
Vaccination definitions and concepts.

<table>
<thead>
<tr>
<th>Definition</th>
<th>Description</th>
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<tbody>
<tr>
<td>Vaccine immunogenicity</td>
<td>The ability of the vaccine to elicit an immune response. Greater vaccine antigenicity leads to an enhanced host response. For MenC vaccines the accepted correlate of protection is serum bactericidal antibody [3] which measures functional antibodies against the MenC bacterium.</td>
</tr>
<tr>
<td>Vaccine effectiveness</td>
<td>The capability of MCC vaccines to provide protection from disease in an immunized individual.</td>
</tr>
<tr>
<td>Antibody persistence</td>
<td>SBA persistence in the host following vaccination.</td>
</tr>
<tr>
<td>Immune memory</td>
<td>The capacity of the host to raise an enhanced immune response at short or long time intervals after initial priming. Memory B cells persist and can be reactivated to generate functional antibodies against the MenC bacterium. In previous clinical studies the immune memory was assessed by either challenging with plain polysaccharide vaccines or the use of avidity indices.</td>
</tr>
<tr>
<td>Herd protection</td>
<td>The concept that even susceptible (unimmunized) individuals can be indirectly protected against infection if the proportion of immune (vaccinated) individuals is high enough. This is an important benefit of the MCC vaccine where catch-up campaigns were performed.</td>
</tr>
<tr>
<td>Catch-up immunization</td>
<td>A process that involves immunizing large cohorts of the population – in addition to routine use of the vaccine in infants or toddlers. Provision of catch-up vaccination programmes has resulted in the induction of herd protection by preventing the acquisition of carriage and hence increased and prolonged the preventive effect of immunization.</td>
</tr>
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Fig. 1. Introduction of vaccination programmes in 1999 has resulted in a significant and sustained decrease in meningococcal serogroup C disease. (Source: Meningococcal Reference Unit, Health Protection Agency, UK).

3.1. Maternal immunity

Maternal-derived antibodies may influence the vaccine antibody responses in infants. The presence of maternal antibodies can inhibit the development of an infant humoral response to vaccines. In a recent study, anti-MenC antibody concentrations were found to be equal in maternal and cord blood samples [27]. However, despite placental transfer, cord blood anti-MenC antibody concentrations were low, possibly placing neonates at risk before they receive their primary vaccinations [27]. As MCC-vaccinated women reach childbearing age the protection of their neonates against MenC is likely to improve. However, the estimated half-life of maternal IgG in infants is just 5–6 weeks and consequently antibody levels at birth are not sufficient to provide protection if the first vaccination is given in the second year of life. However, most infants are currently indirectly protected through herd protection [28,29].

3.2. Priming of infants (0–12 months)

Because infants (i.e., those under 12 months of age) are the age group most often affected by meningococcal disease, clinical studies have focused on this age group. The implementation of MCC programmes in infancy has significantly reduced the incidence of MenC disease [16,30] (Fig. 2). Following initial licensure of MCC vaccines, the infant posology consisted of three vaccine doses.

Fig. 2. Incidence of meningococcal serogroup C disease by age group (England and Wales) Source of plotted data: Ref. [54].
Table 2

Polysaccharide and conjugate vaccines for the prevention of meningococcal serogroup C disease.

<table>
<thead>
<tr>
<th>Vaccine composition</th>
<th>Adjuvants/Amount of oligosaccharide</th>
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<tbody>
<tr>
<td>Meningitec® (MCC-CRM197, Wyeth/Pfizer)</td>
<td>10 µg MenC oligosaccharide conjugated to 15 µg CRM197 aluminium phosphate adjuvant</td>
</tr>
<tr>
<td>NeisVac-C® (MCC-TT, Baxter)</td>
<td>10 µg MenC polysaccharide conjugated to TT aluminium hydroxide adjuvant</td>
</tr>
<tr>
<td>Quadrivalent conjugated MenC vaccines</td>
<td></td>
</tr>
<tr>
<td>Menjugate® (quadrivalent, MCV4, Sanofi Pasteur)</td>
<td>4 µg each of MenA, C, Y and W135 oligosaccharides conjugated to approximately 48 µg of CRM197 No adjuvant</td>
</tr>
<tr>
<td>Menveo® (quadrivalent vaccine, MenACWY-CRM197, Novartis)</td>
<td>10 µg of MenA, and 5 µg each of Men C, Y and W oligosaccharides conjugated to approximately 48 µg of CRM197 No adjuvant</td>
</tr>
<tr>
<td>Nimenrix® (quadrivalent, MenACWY, GlaxoSmithKline)</td>
<td>5 µg of MenA, and 5 µg each of Men C, Y and W oligosaccharides conjugated to 44 µg of tetanus toxoid carrier protein</td>
</tr>
<tr>
<td>Other conjugate and polysaccharide vaccines</td>
<td></td>
</tr>
<tr>
<td>Menitorix® (MCC-TT/Hib-TT, GlaxoSmithKline)</td>
<td>5 µg Hib PRP + 12.5 µg TT + 5 µg MenC PSC + 5 µg TT powder No adjuvant</td>
</tr>
<tr>
<td>Polysaccharide vaccines</td>
<td></td>
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During the pre-licensure studies of NeisVac-C, the seroprotection rate was 100% after the first of three doses, a proportion that was maintained after the second and third doses. By 12–14 months of age, SBA titres had dropped significantly, being protective in only 47% of infants. All infants given booster doses of NeisVac-C had significant antibody responses, providing strong evidence that NeisVac-C adequately primes for immunologic memory [31]. A high seroprotection rate observed after the first dose in infants was observed in further studies, suggesting that the number of primary doses of NeisVac-C could be reduced [32–34].

A study of NeisVac-C delivered concomitantly with the diphtheria, tetanus, three component acellular pertussis and Hib conjugate vaccine delivered to infants (n = 106) at 2, 3 and 4 months confirmed that a reduced vaccination schedule of NeisVac-C could be used [35].

A comparison of three MCC vaccines has been performed with vaccination occurring at 2 and 3 or 2 and 4 months of age [35]. Following the first dose of NeisVac-C, 97% of infants acquired an rSBA titre of ≥8, compared with 80% and 53%, respectively, for Menjugate and Meningitec. Following the two doses of NeisVac-C, Menjugate or Meningitec, 98–100% of infants achieved protective antibody levels. Two years after the booster dose, a follow-up of the same trial showed that the proportions of subjects with putatively protective rSBA titres of ≥8 for children who previously received NeisVac-C, Menjugate and Meningitec were 43%, 22% and 23%, respectively. The proportion of subjects in each of these groups who achieved rSBA titres ≥8 at the prebooster visit and 1, 2, 12 and 24 months after receiving a booster dose of Menitorix at 12–14 months of age, are given in Fig. 3. Further boosting was not deemed necessary during adolescence in 2010 owing to the effects of herd protection [21]. The study concluded that NeisVac-C and Menjugate showed good immunogenicity after a single dose at 2 months of age and should be investigated further in single-dose priming strategies.

Another study consolidated the view that there is a difference in antibody persistence depending on the priming vaccine used. This was a randomized, multicentre, open-label clinical trial infants (n = 389) aged 14–18 months who had been previously primed with either three doses of MCC-CRM197 conjugate or two doses of NeisVac-C were randomized to receive a booster with either vaccine and dosed with the DTaP-IPV-Hib vaccine at the same time.

![Fig. 3](https://example.com/image.png)

Fig. 3. Percentages of subjects with SBA titres ≥8 before and 1, 2, 12, and 24 months following administration of Menitorix at 12–14 months of age, by priming MCC vaccine. Source of plotted data: Ref. [21].
Children primed with NeisVac-C had higher SBA geometric mean titres (GMT) than those primed with MCC-CRM197 (SBA GMT 6520 [95% CI, 5359–7932] vs. 1903 [95% CI, 1600–2260]) irrespective of which vaccine was used as the booster [36]. A 12-month follow-up study revealed that seroprotection in the group primed and boosted with NeisVac-C was 92.8% compared with 61.5% for those primed and boosted with MCC-CRM197 conjugate. This indicated longer antibody persistence in those primed with NeisVac-C [22], a factor that can be considered important for future changes in vaccination schedules involving priming vaccines (Fig. 4).

Infant vaccination with NeisVac-C or Meningitec (in combination Infanrix® hexa, GlaxoSmithKline) followed by a booster dose of Menitorix demonstrated robust and persistent responses [37,38].

The conclusions from infant studies are that a high level of protection is acquired from first dose and that priming with the correct vaccine is important. Priming with NeisVac-C gives the greatest longevity in terms of maintaining antibody titres of the currently licensed vaccines.

3.3. Booster in the 2nd year of life

A booster dose is an extra administration of a vaccine after an earlier dose, resulting in re-exposure to the immunizing antigen. This boosting aims to restore immunity back to protective levels after it has decreased over a specified period of time. This topic is discussed in greater detail later in this article.

Following the implementation of MCC vaccination in the UK in 1999, the long-term effectiveness of MCC vaccines was studied. In a report of the effectiveness of MCC vaccination in the UK 4 years after its introduction into the routine immunization schedule at 2, 3 and 4 months, it was found that vaccine effectiveness in infants following routine vaccination appeared to wane rapidly, and cohorts vaccinated at older ages in a catch-up campaign seemed to have better and longer-lasting protection than those vaccinated in infancy. It was concluded that a dose later in infancy or in the second year of life may improve long-term protection [11,12]. A Spanish study also showed that vaccine effectiveness decreases over time when given in infancy in a 2, 4, 6 month schedule. High short-term vaccine effectiveness values were found in the 4 years following its introduction, but there was loss of effectiveness with time among children vaccinated in infancy [9].

MenC antibody persistence data are important in indicating the duration of protection in otherwise vulnerable groups and the point at which booster doses become necessary. For example, in one study in the UK, 1 year after a course of 3 doses of MCC vaccine at 2, 3, and 4 months of age, 54% of children had an SBA titre of ≥ 8 but this had decreased to 12% after 4 years. This indicates that MenC SBA titres in infants rapidly wane, eventually to a level that is not considered protective [39–41].

Based on these observations, the official recommendation included in the Summary of Product Characteristics of all MCC vaccines has been that a booster dose should be given in the second year of life after completion of the primary infant immunization series.

4. Toddler priming

In a study of toddlers (n = 226) aged 12–18 months, a single dose of the three licensed MCC conjugate vaccines resulted in a high SBA GMT and rates of SBA ≥ 8. NeisVac-C induced higher SBA GMTs and higher seroprotection rates, 1 month and 6 months after vaccination. Challenge with a plain AC polysaccharide vaccine demonstrated the induction of immunologic memory of all three vaccines. Again the NeisVac-C group reached a significantly higher SBA GMT [26].

In 2002, a single MCC (NeisVac-C) vaccination at the age of 14 months was implemented for all newborns in the Dutch national immunization programme (NIP). The reason to include MCC vaccination in the NIP was the rapidly progressive increase in the incidence of MenC disease in 2000–2001. This programme also included a catch-up group of individuals aged 14 months to 18 years. After introduction of vaccination, a sharp rise in MenC-specific IgG and functional antibodies was observed in the age-cohort 15–23 months. However, after this peak in antibody levels, a steep decline in IgG antibodies was observed, and IgG concentrations had decreased to pre-MCC introduction era levels in children between 23 and 72 months of age. In older children, who were vaccinated in the catch-up programme between 9 and 18 years of age, MenC-specific IgG and SBA titres increased gradually with age and were significantly higher than in the pre-MCC introduction era (Fig. 5) [28]. It can be concluded from these studies that only one dose of vaccine is required in toddlers, together with a suitable catch-up campaign, for successful routine immunization.

4.1. Clinical experience of using a quadrivalent vaccine in infants and toddlers

Infants and toddlers are the two age groups that are immunized under the current vaccination programmes and where the primary immune response is understood. A recent randomized controlled multicentre trial investigated the use of Menevo (ACWY-CRM197) in infants. After immunization with ACWY-CRM197 at 2, 3, and 4 months of age, the percentage of participants with hSBA titres ≥ 4 after three doses were: serogroup A, 93%; C, 96%; W-135, 97%; and Y, 94% [42]. A recently approved conjugated vaccine, ACWY-TT (Nimenrix™; GlaxoSmithKline), has been shown to have good effectiveness and to have a clinically acceptable safety profile in toddlers over 1 year of age and older children [43]. This was shown in a study that included 240 toddlers who were 12–14
months of age. 1 month after vaccination with differing formulations of ACWY-TT, 88.1–92.7% had rSBA-Men C titres of ≥128 compared with 87.0% of controls and 97.6–100% of ACWY-TT-vaccinated toddlers had rSBA titres of ≥128 against serogroups A, W and Y compared with no more than 35.9% of controls [43]. More recently, a variety of other studies have also shown the good efficacy, safety and tolerability of quadrivalent meningococcal conjugate vaccines in infants and toddlers [44–47]. Whilst these studies show promising results, some investigators comment that persistence of antibodies may be a more appropriate correlate of long-term protection for meningococcal conjugate vaccines than the ability to generate a booster response after exposure to the pathogen [48].

A study in 382 infants in the UK and Canada investigated the persistence of immunity following different priming- and booster schedules with ACWY- or MCC vaccines. At 5 years of age, a decrease in SBA activity against all serogroups was observed. Substantially better persistence was observed in children primed with MCC vaccine, as compared to the quadrivalent vaccine [49].

4.2. Studies in adolescents (11–18 years) and adults (18 years onwards)

All licensed MCC vaccines have a good response in adolescents. They are currently routinely administered to this age group only in the USA (quadrivalent) and Canada (MCC), but adolescent boosters should be considered elsewhere. In a recent study assessing SBA responses in adolescents 22 months after vaccination with a single dose of Menveo or Menactra, the immune response was found to be sustained [48]. In a study in which a booster dose of either a polysaccharide vaccine or MCC-CRM197 was administered to adolescents previously immunized with the conjugate vaccine, the booster dose produced significantly raised \( P < 0.0001 \) SBA titres that remained elevated 1 year later. Introduction of an adolescent booster dose of MCC vaccine might provide enhanced long-term population control of the disease [48,50]. The immunogenicity of a single dose of NeisVac-C has been investigated in vaccine-naive adults \( (n = 73) \) compared with adults previously vaccinated with a meningococcal serogroup A–C polysaccharide MACP vaccine \( (n = 40) \). Before vaccination, seroprotection was significantly higher in previously vaccinated adults \( (P < 0.001) \). Both at one week and 1 month after vaccination, seroprotection was still slightly higher in those previously vaccinated but, 6 months after vaccination, seroprotection was higher in adults who had originally been vaccine-naïve [51]. This study showed that NeisVac-C is safe and immunogenic in naive and adults previously vaccinated with bivalent AC polysaccharide vaccine, although the magnitude and persistence of post-vaccination SBA responses in the latter group were lower.

4.3. Impact of national vaccination programmes

The UK implemented a national MCC vaccination programme at the end of 1999. 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 those aged up to 18 years was launched. The vaccine was well accepted and routine coverage has been consistently above 90%. Uptake in the catch-up campaign varied by age group, with over 75% of preschool children and over 85% of school children aged 5–16 immunized. The catch-up campaign was carried out over 12 months, with older teenagers and young children, i.e., those assessed to be at highest risk of disease, targeted first. The winter of 2000/2001 was therefore the first opportunity to observe the full effect of the vaccine campaign. Cases of MenC disease declined rapidly: by 2007/2008, fewer than 30 cases occurred, a decrease of over 97% compared with 1998/1999. In an assessment of surveillance data 4 years after the introduction of the vaccination programme, MCC vaccine effectiveness remained high in children vaccinated in the catch-up campaign (aged 5 months to 18 years). However, for children vaccinated in the routine infant immunization programme, the effectiveness of the MCC vaccine fell to low levels after only 1 year [11]. As a result, the vaccination scheduling was changed; two doses of MCC conjugate vaccine are now given at 3 and 4 months with a booster at 12 months [7,12].

Further seroprevalence analysis found that the proportion with SBA titres ≥8 was higher in cohorts receiving MCC immunization at 5–17 years \( (n = 1009) \) as part of a catch-up campaign than it was in children offered the vaccine at 1–4 years \( (n = 610) [52] \). Protective titres in children offered routine immunization were initially high (75%), however, these titres fall to much lower levels (36%) beyond 18 months post immunization [53]. Antibody persistence has also been found to be poor in individuals less than 2 years of age in the catch-up campaign [53].

Despite these findings, the impact on MenC disease has been sustained, with the lowest recorded incidence \( (0.02 \text{ cases per 100,000 population in the } 2008/2009 \text{ epidemiological year}) [54] \). The population impact on MenC disease has been maintained as a result of herd protection resulting from the catch-up vaccination programme [54,55].

The scale of the herd protection effect on MenC disease in England and Wales is illustrated in Fig. 6, which compares the observed number of cases of MenC disease with the predicted number of cases for models that do and do not include a parameter that reduces the risk of MenC acquisition in vaccinated individuals. Clearly, the model that does not include this herd protection greatly overestimates the number of cases of disease [Fig. 6] [16,56]. The high coverage during the catch-up campaign has led to a low incidence of MenC for over a decade.

In The Netherlands routine vaccination has been administered at 14 months as a single dose with no observed reduction in vaccine effectiveness over time. In the same year as routine immunization was introduced, a catch-up campaign was implemented for all children and adolescents between 1 and 18 years of age, who were given a single dose of NeisVac-C (overall vaccine coverage 94%). Soon after implementation of The Netherlands’ programme, MenC disease significantly decreased in vaccinated persons, and a sharp decline was observed in non-immunized cohorts. These reductions were most likely a consequence of herd protection [57]. No primary vaccine failures have been reported but clinical data up to
2011 show that there have been three secondary vaccine failures of which two were in immunodeficient patients [58]. Only sporadic cases of MenC disease in non-immunized age-cohorts have occurred, indicating low transmission due to the herd effect. However, monitoring the persistence of vaccine-induced protection in various age categories after a single immunization remains relevant since widespread introduction of the conjugate vaccine has led to reduced circulation, leading to a lack in natural boosting, eventually resulting in possible waning immunity in vaccinated and non-vaccinated age-cohorts. After introduction of vaccination, the prevalence of SBA titres >8 in infants between 15 and 23 months of age was 92.6%. However, this peak was followed by a decline in SBA levels although they remained well above the SBA levels observed in the pre-introduction era (P < 0.0001). Individuals who had been vaccinated during the catch-up campaign in 2002 were 5–22 years of age during the post-MCC introduction study in 2006/2007. The prevalence of functional SBA titres was higher in the age-cohort 6–9 years compared with the pre-introduction era (P < 0.05). SBA titres increased gradually with age for children vaccinated between 5 and 18 years of age and were significantly higher than in the pre-MCC introduction era (P < 0.0001). SBA titre >8 prevalence had increased from 45.2% to 95.5% in the age-cohorts 9–10 and 19–21 years, respectively. The prevalence of SBA titres >8 in the post-MCC introduction era in cohorts over 25 years of age was comparable to the pre-MCC introduction era: 21% and 23%, respectively. In all age categories combined, the overall seroprevalence of SBA titres >8 was higher after wide-spread introduction of MCC vaccination than before, 43.0% vs. 19.7%, respectively [28]. The vaccination campaign has been highly successful; by 2006 there were only four reported cases of MenC disease. However, administration of a booster dose early in adolescence is being investigated to provide protection during this period of increased risk of meningococcal disease and to maintain antibody levels in sufficient numbers of individuals to sustain herd protection [59].

Spain implemented a nationwide MCC vaccination campaign (including 16 out of the 19 autonomous Spanish regions) in autumn 1997 using a plain polysaccharide vaccine in a target population aged 18 months to 19 years [59,60] with an overall estimated vaccine coverage of 76.3%. This reduced the overall incidence of MenC by 45%. A reduction was seen in all age groups; the number of MenC cases in the target group fell by 76% in comparison with the year before vaccination was used for that specific intervention. However, the incidence of MenC disease continued to increase in the years following vaccination, a foreseeable circumstance given the limitations in the immunogenicity of polysaccharide vaccine [61,62]. Conjugate vaccines became available in Spain in 2000, and were included in the infant vaccination schedule involving a 3 dose primary series at 2, 4 and 6 months of age. A catch-up campaign was then implemented among children and young adults in Spain but the coverage and duration varied by region. Four regions did not implement additional catch-up campaigns, 10 autonomous communities implemented the catch-up campaign for those under 19 years old and three regions included children under 15–16 years of age as the target population. Additional catch-up campaigns were implemented in different years and using different strategies; some were completed in 1 year, others were undertaken over 2–3 or 4 years. [60]. The risk of suffering from MenC disease during 2002/2003 was 25% less than the previous year and 58% less compared with the year before vaccination. The risk of MenC disease was lower compared with that observed during each of the previous years except for 2000/2001 [60].

A decrease in the number of MenC cases in children under ten years was observed during the last three seasons in this study. These children were either born after the conjugate vaccine was included in the routine vaccination schedule or were part of the target group for the catch-up campaign. In the epidemiologic year 2002/2003, 38 cases due to MenC (1.0/100,000) were reported in children under 10 years, compared with 254 cases (6.6/100,000) during the season before MCC vaccine was introduced, which represents an 85% reduction in the incidence at this age. There was increased incidence in the 10–14 year age group, although not statistically significant. At the time of the study, only about 35% of the population in this group had been vaccinated [60]. Spain had therefore not experienced the same level of herd protection as the UK and The Netherlands; the result being that the campaign did not immunize all adolescents, in whom carriage prevalence is highest [9]. In fact, the number of MenC cases is still higher than in most other countries with national programmes [6]. There is therefore a need to revise current vaccination guidelines in Spain.

In Canada, a MCC vaccination campaign designed to control an emerging epidemic, vaccinations were given to 82.1% of those aged 2 months to 20 years. After the campaign, the number of cases of MenC disease decreased from 58 in 2001 to 27 in 2002, and the incidence fell from 7.8 per million to 3.6 per million. Vaccine effectiveness was found to be 96.8% (95% confidence interval, 75.0–99.9%)[63]. An adolescent booster has now been introduced [64]. In Australia the MCC vaccination campaign offered a single dose at 12 months of age and catch-up vaccination for those aged under 20 years. This initiative achieved a 75% reduction in MenC cases between 2002 and 2005 and a booster dose in adolescents has now been implemented.

Mathematical models have enhanced our understanding of herd protection [65]. However, it is not clear how long herd protection will persist and whether changes in the current immunization programmes will be necessary to maintain these effects in the longer term. Long-term strategies to include a booster dose in adolescents to maintain antibody levels therefore need to be considered [10,16,56].

4.4. Guidelines and recommended immunization practices

Many countries are now considering the need for a MCC booster in adolescents to counter the decline in titre after initial and subsequent vaccine doses. It has been reported that if herd protection starts to decline many children will be vulnerable. Falling levels of immunity against MenC have been reported in Greece, The Netherlands, UK and Spain. Several countries, including Austria, Canada and Switzerland, have already introduced booster vaccinations for teenagers [66].

In the US, the latest recommendations from the Advisory Committee on Immunization Practices [67] state that adolescents should be vaccinated at 11 or 12 years, with a booster dose at 16 years of age. They also recommend a 2-dose primary series administered 2 months apart for persons aged 2–5 years having persistent complement component deficiency and functional or anatomic asplenia, and for all adolescents with human immunodeficiency virus (HIV) infection [67].

Brazil has recently introduced routine vaccination with MCC vaccine, the first time it has been used in a country in which most of the MenC isolates do not belong to the ST11 clonal complex. It will be important to follow the evolution in this country to determine whether current knowledge of the ST11 and MCC vaccine can be extrapolated to other strains. This is of importance due to the high rates of capsule expression of the ST11 clonal complex [55].

In England, a recent Joint Committee on Vaccination and Immunization advised that for MenC vaccination, an adolescent booster should be given and the course decreased to a single dose in infancy. It is expected that Spain and The Netherlands may adapt their routine meningococcal vaccine recommendations; however, each region has its own advisory committee and all proposed changes are likely to depend on epidemiology as well as other reasons.
5. Concluding remarks

A considerable body of evidence exists for the clinical effectiveness of MCC vaccines and the success of routine vaccination programmes. All of the available MCC vaccines, however, show significantly greater long-term effectiveness when administered to toddlers than to infants. Of the currently licensed MCC vaccines, NeisVac-C shows the greatest longevity of immune response. However, the protective antibody titre of all MCC vaccines has been found to drop within 18 months of vaccination, raising the question as to whether a booster dose is needed in teenagers to maintain protection into adolescence. To address this, several factors need to be considered such as herd protection (including the likely persistence of herd protection), age of vaccination, epidemiology, monovalent or quadrivalent booster, and cost (since most governments now have cost-effectiveness criteria).

A question mark remains over how to maintain low levels of MenC disease in Europe. Many European countries are now using MCC vaccines but using different schedules and targeting different age groups. Because of this, there are many ‘islands’ of susceptible populations within Europe, where MenC circulation may be able to (re-)establish. Because the incidence rate in general is low, there are few possibilities that one MenC strain will arrive at the susceptible islands but, when one strain does arrive, there are no immunologic barriers against colonization and transmission, which is likely to produce invasive cases [68]. If elevated protective antibody levels can be maintained in teenagers, Europe will probably uphold low levels of MenC disease.

Conjugate vaccines have proven effective, but even quadrivalent preparations can only cover the minority of disease-causing strains. Whether or not protection of adolescents should be extended to serogroups A, W and Y in addition to C depends on the epidemiology of the country in question. For example, in the UK there are high levels of meningococcal serogroup Y carriage in adolescents [69] but relatively low levels of disease, therefore introducing a meningococcal serogroup Y-containing vaccine may, theoretically, be detrimental and should only be considered when there is further evidence explaining how this may affect carriage and disease. Decisions to introduce conjugate vaccinations should be informed by disease surveillance data. There is, however, a continuing need for a comprehensive childhood MCC vaccination programme even when the incidence of disease is low.

Future developments in meningococcal vaccination will include the use of a recently licensed vaccine against serogroup B disease [70], development of new vaccines (including those with the potential to protect against serogroups B and X), worldwide vaccination programmes to improve global coverage and revised vaccination programmes to improve adolescent and adult protection.

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booster dose of meningococcal C conjugate vaccine in the second year of life.


