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Review

Effectiveness of meningococcal serogroup C vaccine programmes

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ABSTRACT

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® 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 ~12 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.

Contents

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

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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 *N. 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, serogroup 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) glyconjugate (MCC) vaccines. MCC vaccines were implemented to combat the increase in serogroup C disease due to the ST11 clonal 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 CRM_{197}, a mutated diphtheria toxoid (Menjugate® (MCC-CRM_{197}, Novartis), Meningitec® (MCC-CRM_{197}, 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], Menveo® (ACWY-CRM_{197}, 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® (MenCY-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 (*O*Ac+) form of polysaccharide, some MenC strains have de-*O*-acetylated (*O*Ac−) polysaccharide, which may affect antibody specificity and functional activity when used in a vaccine. NeisVac-C® contains a de-*O*-acetylated (*O*Ac−) 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.