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**EDITORIAL REVIEW**

# Vaccination against meningococcus in complement-deficient individuals

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Inherited deficiency syndromes have been described for each of the component proteins and for many of the regulators of the complement system [1–3]. Although each of these syndromes is rare, increasing awareness has led to recent identification of many individual cases, as well as areas where one particular genetic defect is segregating in the population [4–6]. A useful subdivision of complement deficiencies is based upon the part of the pathway involved and the clinical syndrome produced [7]. The first group consists of individuals deficient in components of the classical activation pathway (C1, C4, C2) who most commonly present with immune complex disease which often resembles systemic lupus erythematosus. These individuals also have an increased susceptibility to bacterial infection, most commonly with encapsulated organisms such as *Streptococcus pneumoniae, Neisseria meningitidis* and *Haemophilus influenzae*. The second group comprises those deficient in C3, including those in whom the deficiency is secondary to absence of a regulator such as factor H or factor I; they rarely develop immune complex disease but have a marked propensity to develop severe, recurrent bacterial infections, usually with the encapsulated organisms listed above. The third group, individuals deficient in components of the alternative pathway (factor D, factor B, properdin), show a particular susceptibility to infection with *N. meningitidis*. With the exception of properdin deficiency, all are very rare. The fourth group consists of individuals deficient in components of the terminal pathway (C5, C6, C7, C8, C9); these have a propensity to develop infections, frequently recurrent, with *N. meningitidis* and other organisms of the genus *Neisseria.*

In each of the four groups there is an increased susceptibility to infection with *N. meningitidis*, but there are several distinguishing features. In deficiencies of classical pathway components or C3, meningococcal infection is usually just one feature on a background of immune complex disease and/or frequent infection with other organisms. In deficiencies of the alternative and terminal pathways meningococcal infections are usually the only clinical problem. Properdin deficiency, by far the most common alternative pathway deficiency, is inherited in an X-linked manner and is thus found almost exclusively in males [8,9]. These individuals usually present with meningococcal infections, often with septicaemia, in childhood or early adult life. The infection is often fulminant and may be rapidly fatal, but recurrence of infection in this group is rare and always due to a different serogroup of the organism [10]. Individuals deficient in one of the terminal components usually present with recurrent meningococcal infections, often with septicaemia. There are reports that the disease is frequently less severe than in normal individuals [4,6]. If this is so it is not yet possible to attribute this clinical difference to (i) absence of a complete pathway, (ii) development of ameliorating antibodies, or (iii) the development of clinical disease due to infections with less virulent strains. Clinical strains isolated from South African complement-deficient patients were found to have genetic differences when compared with strains isolated from the population at large [11]. These differences suggest the development of disease following infection by organisms which would be non-pathogenic in normal individuals. It is still not unusual for complement-deficient individuals to escape diagnosis until well into adulthood, because increased susceptibility to infection is frequently not manifest until late childhood or even later [4,5,12]. Suspicion should be high in any individual with recurrent infections, or disease with rare serogroups presenting late in childhood or early adulthood [11,12].

The increased risk of meningococcal disease in patients with complement deficiencies varies with areas but it is considerable. In North America, deficiency of either a terminal complement component or properdin has been estimated to increase the risk of meningococcal infection 7000-fold compared with normal individuals, making complement deficiency a major risk factor [4]. These patients require supportive care and measures to reduce the risks of further infection. The management of patients with terminal component deficiency rests first of all on education and support, so that patients and their families can live normal lives but are also aware of the susceptibility so they can take steps for early diagnosis and treatment should infections occur, and secondly on prophylaxis. In patients with properdin deficiency the risk of recurrences is much less, but fatality associated with infection is very much higher [9], so that the emphasis in these families should be on identification of affected family members, and prophylaxis for all those affected.

For patients with complement deficiency, two prophylactic strategies are available, although neither is entirely satisfactory. Long-term antibiotic therapy (chemoprophylaxis), although widely practised and of proven benefit [13,14], frequently has poor patient acceptance and carries the risk of generating antibiotic-resistant strains. Immunization with relevant meningococcal polysaccharide vaccines has been shown in several large studies to be extremely effective at reducing the risk of infection in the population at large [15,16]. However, the problem with meningococcal polysaccharide vaccines is that serogroup B polysaccharide is a poor immunogen, particularly when given as a vaccine [16], and its structure

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appears identical to polysialic acid present in many mammalian tissues [17,18], so that it can be considered a self antigen. Although in Europe and the USA infections in complement-deficient individuals are frequently with the rare serogroup W135 or Y strains [4,11], serogroup B strains were nevertheless found responsible for about 20% of all infections in deficient patients [4]; moreover, in South Africa serogroup B infections represented almost 50% of infections in complement-deficient individuals [10].

For serogroups A, C, Y and W135 polysaccharides the efficacy of vaccination in individuals with complement deficiencies depends on (i) the host ability to produce a good antibody response despite the complement deficiency, and (ii) in terminal component-deficient individuals the ability of those antibodies to promote opsonophagocytic killing as serum bactericidal activity is absent. Following natural infection, complement-deficient individuals generate antibodies against outer membrane proteins and capsular polysaccharide [19,20]. Antibodies to capsular polysaccharide have been found to be effective in both bactericidal and opsonophagocytic assays [21] and opsonophagocytic activity is all important for terminal complement-deficient subjects. Several small studies have reported a normal or near-normal antibody response to meningococcal polysaccharide vaccination in individuals with deficiencies of the terminal pathway [21,22], although one did suggest that the maintenance of the anti-polysaccharide response is reduced in deficient compared with normal individuals [21]. Also, immunization failed to generate a bacteriolytic activity against meningococcus in a small group of C7-deficient individuals but induced respectable opsonophagocytic activity [23]. Properdin-deficient individuals have been observed to have normal antibody response to the meningococcal tetravalent vaccine [24]; this is reassuring, as a recent work suggested that alternative pathway complement activity may be an important mechanism whereby the innate immune response aids specific antibody production [25,26]. Moreover, properdin-deficient individuals, once successfully immunized, will efficiently opsonize and lyse meningococci, and thus rarely suffer recurrences [4].

A paper in this issue by Fijen *et al*. describes a study of the response to immunization with the tetravalent (A,C,Y,W135) capsular polysaccharide vaccine in a cohort of 53 complement-deficient individuals (7, C3; 19, properdin; 27, terminal component) [27]. All generated a respectable antibody response to immunization, and bactericidal (using heterologous serum) and opsonizing activities against meningococcus were increased to a similar extent in deficient and control groups. The majority of patients were followed for 6 years post-immunization and in this time, six new episodes of meningococcal disease occurred. Four of these were with serogroup B and were thus not unexpected. The remaining two were with organisms of serogroup Y, present in the vaccine and provoking a good antibody response in all immunized individuals. These latter infections both occurred in individuals deficient in the terminal pathway component C8, 3·5 years and 5 years after immunization. While no comparison of the frequency of recurrence in unimmunized complement-deficient individuals was made in this study, the fact that only two cases of re-infection occurred involving serogroups contained within the vaccine, and then only after a lengthy disease-free interval, is very promising. However, as meningococcal disease occurs infrequently even in terminal component-deficient individuals, it is very difficult to gather sufficient data to prove the efficacy of the vaccine. Examination of the data available on the 20 complement-deficient patients who were followed up after vaccination shows that the rate of infection with the relevant organism (A, C, Y, W135) was almost the same pre- and post-vaccination. In normal individuals the polysaccharide antigens do not give more than about 3 years protection [27], and what is important in the study by Fijen *et al*. is that there were no relevant infections in the 3 years post-vaccination. Therefore it is very much to be hoped that the cohort of patients reported by Fijen *et al*. will be re-vaccinated, so that the study can continue and that eventually there will be sufficient data for definitive conclusions to be drawn. Another study failed to show benefit of the vaccine; Platonov and co-workers immunized 18 patients with terminal component deficiency with the same vaccine and obtained a good antibody response [22]. Two individuals developed recurrences in the first year; however, as the serogroups of these recurrent strains are unknown, these infections may have been serogroup B and would not represent vaccine failure. Indeed, all these studies confirm that the possibility of group B infections means that this vaccine cannot provide complete disease protection.

Fijen *et al*. make the recommendations that all complement-deficient individuals, and particularly those deficient in terminal components, should be immunized with a capsular polysaccharide meningococcal vaccine and that booster injections should be given at regular intervals to maintain immunity [27]. To this we would add that steps should be taken to ensure that tetravalent vaccine, including serogroups Y and W135, is used. The polysaccharide vaccine on the drugs register, and normally available in the UK and Ireland, is the bivalent A and C vaccine. This does not provide protection against Y and W135 infections, which are particular problems in complement-deficient individuals. The manufacturers will provide tetravalent vaccine for complement-deficient individuals on a named patient basis, but this is difficult to organize and most clinicians do not realize it is available. In Ireland vaccination is also an additional considerable expense for patients. Properdin-deficient individuals, though less prone to recurrence, should nevertheless be immunized to ensure immunity against as many serogroups as possible. Chemoprophylaxis remains an important adjunct to immunization and in areas where serogroup B infections are prevalent may be the method of prophylaxis of choice [13]. Unfortunately development of outer-membrane protein vaccines, which will hopefully eventually protect against relevant serogroup B infections in normal individuals and probably properdin-deficient subjects, may not help terminal component deficiency as the antibodies they induce have been shown to be ineffective in opsonophagocytic assays [21]. Therefore, the use of the tetravalent vaccine may be the best vaccine protection that will be available for these complement-deficient patients for the foreseeable future.

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