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Meningococcal group B vaccines

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Meningococcal disease remains a devastating and feared infection with a significant morbidity and mortality profile. The successful impact of meningococcal capsular group C glyconconjugate vaccines introduced into the UK infant immunization schedule in 1999, has resulted in >80% of disease now being attributable to meningococcal capsular group B (MenB). MenB glyconconjugate vaccines are not immunogenic and hence, vaccine design has focused on sub-capsular antigens. Recently, a four component vaccine to combat MenB disease (4CMenB) has progressed through clinical development and was approved by the European Medicines Agency at the end of 2012. This vaccine has proven safe and immunogenic and has been predicted to provide protection against ~73% of the MenB disease from England and Wales. Recommendation/implementation of the vaccine into the UK infant schedule is currently being evaluated.

4CMenB has the potential to provide protection against a significant proportion of MenB disease in the UK which is currently unpreventable.

Introduction

Meningococcal disease caused by the encapsulated organism *Neisseria meningitidis* remains a feared and devastating illness due to its rapid onset and associated morbidity and mortality. Differences in the polysaccharide capsule surrounding the organism allow classification into 12 groups, of which A, B, C, W and Y are predominantly responsible for invasive disease. The introduction of monovalent group C glycoconjugate vaccines (MCC) into the UK schedule in 1999 has successfully achieved group C (MenC) disease control,[1] resulting in group B (MenB) now being responsible for > 80% of invasive disease. This disease burden disproportionately effects children <5 y with peak incidence in infants <1 y of age with a second smaller peak in adolescents.[2]

Meningococcal Vaccines

Effective vaccines based on purified meningococcal group A, C, W and Y polysaccharides have been developed, initially as plain polysaccharides and more recently as mono and multi-valent glycoconjugate formulations.[3] This approach has been unfeasible for MenB as its capsular polysaccharide is antigenically similar to the human fetal neural cell adhesion molecule resulting in poor immunogenicity and the potential to induce autoantibodies.[3] Consequently, attention has focused on alternative non-capsular vaccine candidates, which are accessible to the immune response, highly conserved and expressed among all meningococci.

Utilizing the natural ability of the meningococcus to shed outer membrane vesicles (OMV) during growth, monovalent OMV vaccines have been successfully developed from local outbreak strains in response to epidemics in Norway, Cuba, Chile and New Zealand. These vaccines have proven immunogenicity and efficacy against their respective outbreak strains although multiple doses are required and protection is generally of short duration, particularly in infants.[3] However, protection afforded by these vaccines is generally strain specific as the immune response is primarily directed against the immunodominant protein (PorA), which is variable between different meningococcal clones. Consequently, monovalent OMV vaccines are unable to provide protection in areas such as the UK with heterogeneous epidemiology leading to the development of bi-valent, hexavalent and nona-valent formulations.[3]

Reverse Vaccinology

Reverse vaccinology is the term given to vaccine design, based on the prediction of antigens in silico utilizing DNA sequence data. This approach was initially applied to MenB following the publishing of the whole genome sequence of a MenB strain MC58.[4] Preliminary screening identified 570 potential surface expressed proteins which were recombinantly expressed in *Escherichia coli*. Based on results from immunogenicity and conservation studies among MenB strains, the five most promising proteins were formulated as an investigational vaccine termed rMenB. These antigens include the three core immunogenic proteins, factor H binding protein (fHbp), *Neisseria* adhesion A (NadA) and *Neisseria* heparin binding antigen (NHBA). Two further proteins, genome derived neisserial antigen (GNA)2091 and GNA1030 were utilized as accessory fusion proteins with fHbp and NHBA, respectively to increase immunogenicity and antigen stability. The final formulation of the vaccine (4CMenB) incorporates OMVs from the New Zealand vaccine strain NZ 98/254 and has been assigned the trade name of Bexsero®.

The safety and immunogenicity of 4CMenB has been investigated in phase I to III clinical trials in infants, toddlers, adolescents and adults. The vaccine has been demonstrated to provide a robust immune response in all age groups against four laboratory MenB reference strains chosen to individually measure responses against each of the three recombinant proteins and the OMV (PorA).[3,5,6] Although trials are currently ongoing, there are yet no

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published data on the long-term persistence of protection or the effect on acquisition of carriage, both of which remain important questions. Infant recipients of 4CMenB are more likely to experience local reactions of induration, tenderness and erytherma, and systemic reactions of fever in comparison to those receiving comparator vaccines or placebos. The reactogenicity profile decreases with age and in adolescents and adults, injection site pain and systemic reactogenicity are the most commonly reported reactions which occur at a greater frequency when compared with those receiving comparator vaccines.[3,5,6]

Due to immune responses being directed against subcapsular proteins which are variable, genetically and in the amount expressed on the bacterial surface, calculating likely coverage of the vaccine has been difficult. The Meningococcal Antigen Typing System (MATS) has therefore been developed to predict if vaccine induced antibody responses would be able to kill individual disease isolates, i.e., be "covered by the vaccine."[7] MATS was used to predicted strain coverage of 4CMenB of 78% and 73% of MenB strains for Europe and England and Wales, respectively.[8]

Other Approaches

Multiple alternative candidate antigens and vaccines are in various stages of development utilizing various formulation approaches, diverging from individual recombinant antigens to genetic modification of OMVs. The most advanced of these is a bivalent vaccine also using fHbp but which was independently discovered by traditional vaccine discovery methods. This vaccine incorporates two diverse variants of fHbp in an attempt to broaden the strain coverage afforded by the vaccine and has been demonstrated to be immunogenic and well tolerated in phase I and II clinical trials in toddlers, adolescents and adults.[9]

Summary

4CMenB was approved by the European Medicines Agency at the end of 2012 as a two-dose schedule in adolescents and adults and a three-dose primary schedule in infants followed by a booster in the second year of life.[10] Recommendation decisions on potential implementation of the vaccine into national schedules remain outstanding. Numerous considerations will impact on such decisions which can be generally characterized into likely impact and cost effectiveness, which in turn are dependent upon different vaccination implementation strategies. Further data on antibody persistence, ability to impact on nasopharyngeal carriage and induction of herd protection are also required to enable a fully informed decision.

The availability of 4CMenB, could hopefully be used to prevent disease caused by the last of five major pathogenic meningococcal groups, which is currently unpreventable via vaccination. It is hoped that this could follow on from the success of the MCC vaccine and further reduce the burden of meningococcal disease.

Disclosure of Potential Conflicts of Interest

I have acted as a consultant, receiving travel support on behalf of the Health Protection Agency/Public Health England for Baxter Biosciences, GlaxoSmithKline, Novartis Vaccines and Diagnostics and Pfizer. I have also undertaken contract research on behalf of the HPA/PHE for Baxter Biosciences, GlaxoSmithKline, Novartis Vaccines and Diagnostics, Merck, Sanofi Pasteur and Pfizer.

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