Recommendations for the production and control of group C meningococcal conjugate vaccines

Addendum 2003

The Expert Committee on Biological Standardization, at its fifty-second meeting, adopted "Recommendations for the production and control of group C meningococcal conjugate vaccines, which were published in its report (1). The Committee agreed with a proposal to draft an addendum on serological assays to evaluate the immune responses to these vaccines and to review the current recommendations in the light of data emerging from the United Kingdom following the introduction of the vaccine, especially data related to the demonstration of immunological memory.

Following a review of the accumulated immunological data, a first draft of this addendum was prepared by Dr R. Borrow, Public Health Laboratory Service, Manchester, United Kingdom, Dr Jodar, Scientist, Quality Assurance and Safety of Biologicals, WHO, and Dr Elwyn Griffiths, Coordinator, Quality Assurance and Safety of Biologicals, WHO. Acknowledgements are due to the following experts for their comments and advice: Dr I. Feavers, National Institute for Biological Standards an Control, England; Dr D. Granoff, Childrens Hospital Oakland Research Institute, California, USA; Dr C. Frasch, Center for Biologics Evaluation and Research, FDA, USA.

The addendum is intended to serve as an Appendix to the already adopted Recommendations.

Adopted by the 53rd meeting of the WHO Expert Committee on Biological Standardization, 17-21 February 2003. A definitive version of this document, which will differ from this version in editorial but not scientific detail, will be published in the WHO Technical Report Series.
APPENDIX 1

Evaluation of the immunogenicity of group C meningococcal conjugate vaccines

Different lots of single component or combined meningococcal C conjugate vaccines from each manufacturer should be evaluated for immunogenicity, including the induction of immunological memory, in the target age group before licensing. National control authorities should ensure that the data made available to them are relevant to individual national immunization programmes, so that appropriate recommendations may be made regarding vaccine co-administration. For combinations of group C meningococcal conjugate vaccine and other antigens, either pre-combined or to be given by mixing immediately before injection, the national control authority should ensure that there are adequate studies to demonstrate that there is no clinically significant interference with the immunogenicity or induction of immunological memory by the meningococcal C conjugate component.

Two assays are utilized to measure immunogenicity of meningococcal C conjugate vaccines, the serum bactericidal antibody assay that is regarded as the ‘gold standard’ and the serogroup C-specific IgG ELISA. Early studies by Goldschneider et al. with polysaccharide vaccines [2] demonstrated that serum bactericidal titre of 4 measured with human complement is an indicator of clinical protection against serogroup C meningococcal disease. The serum bactericidal antibody assay thus provides a good surrogate of protective immunity associated with natural disease. Following the introduction of meningococcal group C conjugate vaccines in the United Kingdom, a re-evaluation of the correlates of protection for group C was performed [3]
utilizing a large database of effectiveness data, the availability of sera for additional testing and practical serum bactericidal assays utilizing baby rabbit complement [4, 5]. Group C meningococci are more susceptible to the bactericidal activity of group C-specific antibodies when using baby rabbit complement rather than human complement, resulting in higher serum bactericidal assay titres for most specimens [6]. Nevertheless, there is a general consensus that when baby rabbit serum is used as the source of complement, serum bactericidal assay titres of <8 are predictive of susceptibility to invasive meningococcal disease. From efficacy estimates in the United Kingdom and the proportion of responders in various clinical trials of meningococcal C conjugate vaccines, it has been demonstrated that a serum bactericidal assay titre of 8 is the appropriate cut-off correlating with short-term protection [7]. This has now been supported by a UK group C seroprevalence study performed prior to the introduction of group C conjugate vaccines [8]. Other additional indicators may be used, which include a) evidence of a four fold or greater rise in serum bactericidal antibody titre between pre and 1 month post-primary immunization sera b) a serum bactericidal titre of ≥4 utilising human complement [3].

The ELISA is an antigen-binding assay and has less variability than the serum bactericidal assay, which is an assay for functional antibodies [9]. The ELISA can measure total or isotype-specific serum antibody responses. Thus ELISA is a useful adjunct to the serum bactericidal assay. It is however crucial that the ELISA correlates with the serum bactericidal assay. A number of serogroup C ELISA have been shown to do this [10,11,12]. Factors reported to increase the correlation include the use of highly purified polysaccharide, solid phase derivatized polysaccharide antigens, and incorporating chaotropic agents (thiocyanate) in the serum diluent.
Although correlates for long-term protection are not currently known, antibody levels decline with time and immunological memory may have to be relied upon. Immunization with meningococcal C conjugate vaccines primes for the ability to generate memory antibody responses upon subsequent exposure to plain meningococcal polysaccharide [13]. Although unproven, the ability of an immunized person to generate a memory antibody response upon exposure to the pathogen may be an important second mechanism of protection, particularly when serum antibody concentrations are below the protective threshold. Recent data (14) demonstrate immunological memory at 4 years of age in children who had been immunized with group C conjugate vaccine administered at 2, 3 and 4 months of age. At 4 years of age antibody levels had decreased to prevaccination levels.

Laboratory correlates for the induction of immunological memory include a) demonstration of immunological memory by a serum bactericidal titre ≥ that of the primary response 1 month following a 10 µg dose of plain polysaccharide administered at least 6 months following the primary series; or b) evidence of increase in avidity indices of serogroup C-specific IgG antibody 1 month to 6 months post primary series [3]. Long-term monitoring will be necessary to estimate whether induction of memory alone is enough to confer long-term protection against meningococcal disease.
The serum antibody response to the carrier protein should also be measured in recipients of the meningococcal C conjugate vaccine to ensure that the conjugate vaccine does not interfere with protective immunity that is relevant to that protein. To date, carrier proteins such as diphtheria (CRM₁₉₇) and tetanus toxoids have been used in the conjugation of meningococcal C conjugate vaccines. Since some of carriers are also components of other infant and childhood vaccines (e.g. DTP), antibody responses to those vaccines should be measured to ensure that there is no immune interference of clinical importance. The assay for these antibodies should be a bioassay or a validated equivalent.

The following reagents are available through the courtesy of manufacturers and national control agencies:

- Meningococcal group C polysaccharide, NIBSC code 98/730 available from the National Institute for Biological Standards and Control, Potters Bar, Herts, EN6 3QG, United Kingdom.

- Meningococcal serogroup anticapsular antibody human ref serum CDC1992, NIBSC code 99/706 available from the National Institute for Biological Standards and Control, Potters Bar, Herts, EN6 3QG, United Kingdom.

- Methylated human serum albumin, NIBSC code 99/592 available from the National Institute for Biological Standards and Control, Potters Bar, Herts, EN6 3QG, United Kingdom.
REFERENCES


12. Michon F, Huang C-H, Farley EK, Hronowski L, Di J, Fusco PC. Structure Activity Studies on Group C Meningococcal Polysaccharide-Protein Conjugate Vaccines:
