Annex 3

Part C. Clinical evaluation of group C meningococcal conjugate vaccines (Revised 2007)

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Recommendations published by WHO are intended to be scientific and advisory in nature. The parts of each section printed in type of normal size have been written in such a form that, should a national regulatory authority desire, they may be adopted as they stand as definitive national requirements or used as the basis of such requirements. Those parts of each section printed in small type are comments and recommendations for guidance for those manufacturers and national regulatory authorities who may benefit from additional information.

It is recommended that modifications be made only on condition that the modifications ensure that the vaccine is at least as safe and efficacious as that prepared in accordance with the recommendations set out below.

The terms “national regulatory authority” and “national control laboratory” as used in these recommendations, always refer to the country in which the vaccine is manufactured.
C.1 Introduction
C.1.1 Background

Recommendations for the production and control of meningococcal group C conjugate vaccines (1) were adopted by the Expert Committee on Biological Standardization at its fifty-second meeting in 2001. On that occasion, the Committee recommended the development of guidance on evaluation of immune responses to these vaccines. In response to this, an addendum devoted to the evaluation of the immunogenicity of group C meningococcal conjugate vaccines was prepared and adopted by the Committee at its fifty-third meeting in 2003 (2).

Following adoption of the Recommendations to assure the quality, safety and efficacy of group A meningococcal conjugate vaccines in October 2006, a need to update the Recommendations provided in the Annex 3 of the report of the fifty-third meeting (2), was identified.

The aim of this document is to provide more detailed recommendations, updated according to the new data on immunogenicity and effectiveness of group C meningococcal (MenC) conjugate vaccines that have become available since 2003. This document should be read in conjunction with the Annex 2 of the TRS 924. The establishment of this document will lead to discontinuation of Addendum 2003 to Annex 3 of the TRS 926.

C.1.2 General considerations for clinical studies

In general, clinical trials should adhere to the principles described in the WHO guidelines on good clinical practice (3).

General principles described in the WHO guidelines on clinical evaluation of vaccines: regulatory expectations apply to MenC conjugate vaccines and should be followed (4). Some of the issues that are specific to MenC conjugate vaccines and/or particularly to the clinical development programme for MenC conjugate vaccines are discussed in the following sections and should be read in conjunction with the general guidance mentioned above.

These recommendations should be viewed in the light of further data on the safety, immunogenicity and effectiveness of MenC conjugate vaccines and any relevant data on other types of meningococcal conjugate vaccines that may become available in the future.

C.1.3 Scope of the studies

The focus of the clinical development programme for a new MenC conjugate vaccine will be studies of immune responses to the new vaccine and not studies that estimate the protection afforded by the vaccine against MenC disease. This is because:
As described in section C.2.1, assay of functional anti-MenC antibody elicited in response to vaccination is well established and widely accepted as a marker for protection against invasive MenC disease.

It is therefore not necessary and in addition it is not ethical to perform studies to estimate the absolute protective efficacy (i.e. in comparison with an unvaccinated group) of a new MenC conjugate vaccine.

Similarly, studies of relative protective efficacy (i.e. in comparison with a licensed MenC vaccine) are not necessary and are very unlikely to be feasible since large studies of long duration would be required to accumulate sufficient cases of MenC disease.

The first MenC conjugate vaccines to be licensed and widely used employed 10 µg of conjugated polysaccharide per dose. Initially these were administered as a three-dose primary series to infants and as a single priming dose to older children and adults. However, it has since become apparent that lower doses of MenC conjugated polysaccharide and/or fewer than three doses in the infant primary series may achieve satisfactory post-primary immune responses (5). Also, several studies have reported better post-boosting immune responses when lower doses and/or fewer doses have been administered in infancy than when using regimens of three doses of 10 µg (5).

Therefore it is important that the early development programme for new MenC conjugate vaccines, especially if included in a combination vaccine in which the other antigens may affect the anti-MenC response, should provide data to support the choice of appropriate primary regimens for children under 1 year old, children aged approximately 1–4 years and older subjects.

The general approach to confirmatory clinical study design should be based on a comparison of immune responses between the MenC conjugate in the new vaccine and at least one licensed vaccine that contains a MenC conjugate. It is clear that the immunogenicity of licensed MenC conjugate vaccines varies according to the nature of the conjugate, the age of the recipient and the antigens that are co-administered (5, 6). Therefore, the selection of the comparative vaccine(s) in any one study requires careful consideration and justification that takes into account the age group concerned and the antigens that will be co-administered.

In addition, it is recognized that some national regulatory authorities may expect that at least one confirmatory study that includes a comparison with a licensed unconjugated MenC polysaccharide vaccine should be conducted in the age groups in which these vaccines have been shown to be immunogenic and protective (e.g. in adolescents and young adults).
C.2 Assessment of the immune responses
C.2.1 Antibody assays
The assays used should be fully validated.

Assay of serum bactericidal antibody
The serum bactericidal antibody (SBA) assay measures functional antibody and should be regarded as the primary means of assessing the immune response because SBA titres are considered to be the most important criteria for evaluation of the likely protective efficacy of a MenC conjugate vaccine.

The source of complement used may be either baby rabbit or human. The source of complement affects the results of SBA assays since higher SBA titres are obtained with the majority of sera when baby rabbit complement is used rather than human complement (7, 8).

In a prospective study in US army recruits, Goldschneider et al. (9) observed a strong correlation between development of MenC disease, which was the only group circulating at that time in the population studied, and anti-MenC SBA titres < 1:4 (measured using human complement; hSBA) at the time of entry into basic training. In addition, hSBA titres ≥ 1:4 seemed to correlate approximately with clinical protection against group A, B or C meningococcal disease based on studies with sera from unvaccinated subjects aged from 0–26 years and data on disease epidemiology (10).

Further information on the correlation between SBA titres and protection against invasive meningococcal disease has emerged following the introduction of MenC conjugate vaccines in the United Kingdom in 1999. Serial evaluations of the correlates of protection for MenC disease have been performed as data have emerged since 1999 on vaccine effectiveness and the results of SBA testing in which baby rabbit complement (rSBA) was employed (11–15). From the estimates of effectiveness by age group in the UK and the immunogenicity data obtained from clinical trials with three MenC conjugate vaccines it was proposed that rSBA titres of 1:8 using the method originally described by Maslanka et al. (16) and the UK reference laboratory methodology correlated with short-term protection (17, 18).

Currently there is no consensus regarding the choice of human or baby rabbit complement for SBA assays and opinion is divided regarding the possible advantages and disadvantages of each (7, 8, 19–22).
**Assay of MenC-specific antibody**

MenC-specific antibody concentrations (total or only IgG, IgG subclasses) may be used as secondary parameters in the assessment of the immune response. The most common methodology used is an enzyme-linked immunosorbent assay (ELISA) (23). However, only a proportion of the capsule-specific antibody may be functional and functionality would be affected by antibody isotype and avidity. The concentration of anti-capsular antibody required for protection against MenC disease is not known with any degree of certainty.

Additional investigations of antibody quality may include measurement of antibody avidity. These assays may assist in assessment of maturation of the immune responses (e.g. in response to booster doses of the conjugate).

**C.2.2 Criteria for assessment of immune responses**

In comparative studies of post-primary immune responses against licensed MenC conjugate vaccines the primary analysis will most likely be based on demonstrating that the proportion of previously seronegative subjects (i.e. pre-vaccination hSBA < 1:4 or rSBA < 1:8) that achieves hSBA titres ≥ 1:4 or rSBA titres ≥ 1:8 post-vaccination is non-inferior to that in the comparative vaccine group(s). The predefined margin of non-inferiority should be carefully justified (24).

However, it is very important that the overall comparison of immune responses between vaccine groups should examine other potentially important parameters. For example, if baby rabbit complement is used in the assay then a plan should be in place to make the comparisons of geometric mean titres (GMTs), proportions with rSBA titres ≥ 1:128 and proportions with 4-fold increases in titre from pre-immunization to 1 month post-immunization.

In comparisons between a new vaccine that contains a MenC conjugate and a licensed unconjugated vaccine, which would be possible only in age groups in which the licensed unconjugated vaccine have been shown to be immunogenic and protective, the primary analysis might have to be based on increments in titres if a large proportion of vaccinees have pre-vaccination hSBA titres ≥ 1:4 or rSBA titres ≥ 1:8. In these age groups post-priming immune responses and/or persistence of antibody might be expected to be better with the conjugated vaccine. Therefore, the pre-planned analyses of early post-vaccination immune responses and of antibody persistence might include progression to an evaluation of superiority for the MenC conjugate vaccine once it has been established that the pre-defined non-inferiority criteria have been met.

If data on MenC-specific antibody concentrations are also generated (e.g. using ELISA), a similar approach should be taken for the analyses. Any
deviations in the pattern of immune responses compared to those seen with SBA should be explored and discussed.

C.2.3 Antibody persistence, immune memory and booster doses

In recent years it has become clear that maintaining circulating functional antibody (i.e. as demonstrated by SBA) is necessary for continued protection against MenC invasive disease (25, 26). Documentation of antibody persistence after administration of MenC conjugate vaccines by following SBA titres over time is therefore considered to be extremely important (see section 3). Furthermore, MenC conjugate vaccines have been shown to prime the immune system and this priming probably accounts for, or at least contributes to, the maintenance of protective SBA titres. Therefore, the characterization of the immune response to the priming dose(s) should include demonstration of an anamnestic response to a booster dose of a MenC conjugate vaccine when administered at least 6 months to 1 year after completion of the primary series.

The use of unconjugated MenC polysaccharide vaccine is not recommended for the assessment of prior induction of immune memory. In addition, the administration of second or further doses of unconjugated MenC polysaccharide vaccine should be avoided. Therefore, in any studies that initially compare the immune response to priming with conjugated and unconjugated MenC vaccines any plan for assessing responses to booster doses should be confined to administration of MenC conjugate vaccine.

The investigation of the induction of immune memory during the primary series has often been assessed in the past by administration of a small amount (e.g. 1/5 adult dose) of a licensed unconjugated MenC vaccine at least 6 months later.

However, newer data suggest that individuals vaccinated with unconjugated MenC polysaccharide vaccine develop MenC antibody hyporesponsiveness. That is, lower antibody titres are elicited after subsequent injections of unconjugated MenC polysaccharide or of MenC conjugate vaccines than are seen in subjects who have not previously received unconjugated MenC polysaccharide (27–30). The magnitude of the impaired antibody response is inversely correlated with age (i.e. greater in infants than adults) and greater after two or more previous doses of unconjugated MenC polysaccharide, whether full or fractional, than after one dose.
Immunologic priming may also be inferred from an increase in (i.e. maturation of) anti-capsular avidity as measured in sera obtained 1 month and 6 months or longer after the primary series (27). Therefore, it is recommended that changes in the avidity of MenC-specific IgG from pre- to post-primary series and before and after a booster dose of MenC conjugate vaccine should be evaluated in a subset of vaccinees.

C.2.4 Immune responses to carrier protein

To date, proteins such as a non-toxic diphtheria toxin molecule (CRM197), diphtheria toxoid and tetanus toxoid have been used in the production of various meningococcal conjugate vaccines. Administration of these conjugated saccharides alone has been found to result in measurable amounts of antibody to the carrier proteins but not to a sufficient extent that routine immunization schedules for diphtheria or tetanus could be amended. Co-administration of these conjugates with routine vaccines containing diphtheria and tetanus toxoids has generally enhanced the total antibody levels against these antigens (depending on the carrier). These issues should be investigated for any new conjugate vaccine and should take into account the functionality of the antibody to the carrier. If notable increases in anti-diphtheria or anti-tetanus toxin antibody titres are observed under these circumstances then consideration should be given to the potential for adverse events to occur (e.g. as a result of hyperimmunization).

For any novel proteins that may be used to manufacture conjugate vaccines (i.e. those not already components of existing licensed conjugate vaccines), the immune response to the carrier protein should be explored. Any foreseeable potential clinical significance of the findings should be discussed and further studies conducted as necessary.

C.2.5 Combined vaccines and concomitant administration with other vaccines

C.2.5.1 Combined vaccines

It is already well documented that immune responses to certain types of conjugated antigens are lower when they are combined with some other antigens in pre-formulated products compared to separate but concomitant and/or separate and non-concomitant administration (e.g. lower responses to Hib conjugates when they are combined with acellular pertussis components). In some instances the immune response to a conjugated antigen has been shown to be lower when it is mixed with other antigens only immediately before injection. More recently it has become apparent that there may be particular problems of immune interference when more than one conjugated antigen is included in a combined vaccine. Therefore, if a candidate MenC conjugate vaccine is
to be included in a combination product, with or without other conjugated saccharide(s), there should be an adequate exploration of the potential for immune interference to occur.

Although the ideal would be to demonstrate that incorporation of a MenC conjugate into a combined vaccine has no adverse consequences for safety or immunogenicity with respect to any antigen, the design of studies that evaluate the effects of adding antigens could be very complex depending on the novelty of the total combination. Since several MenC conjugate vaccines have been approved for use in a wide age range a comparison of anti-MenC SBA titres between the test vaccine and at least one licensed MenC conjugate-containing vaccine may be used to establish that there is no important adverse effect on immune responses to the candidate MenC conjugate when it is included in the combined product.

The immune responses to the other antigens in the final combined formulation should also be satisfactory. If there is any immune interference observed with respect to any of the combined antigens, the possible clinical implications should be carefully considered before proceeding with clinical development.

C.2.5.2 Concomitant administration with other vaccines

In recent years, it has also become apparent that concomitant administration of some types of conjugates with other vaccines in routine use, including other conjugated vaccines, may give rise to detectable immune interference although the clinical significance of the observed phenomena is not always clear (31). Examples include depression of anti-MenC SBA GMTs on co-administration with acellular pertussis vaccines and higher anti-Hib responses when Hib-tetanus toxoid (PRP-T) conjugates are co-administered with MenC-T conjugates than after co-administration with MenC-CRM197 conjugates.

Therefore it is important that immune responses to candidate MenC conjugate vaccines (whether monovalent or in a combined vaccine) should be evaluated on co-administration with other vaccines that are representative of types that, for convenience and compliance reasons, are very likely to be given at the same clinic visits. Responses to other co-administered antigens should also be evaluated. The approach to these studies is based primarily on demonstrating non-inferiority of responses to antigens when vaccines are co-administered compared to each vaccine given alone, with careful justification of pre-defined non-inferiority margins.

C.3 Post-marketing studies and surveillance

For the post-licensure period, there should be plans in place to further assess vaccine safety and effectiveness.
Based on experience it is expected that a booster dose of MenC conjugate vaccine will be needed after priming of infants with any novel vaccine containing a MenC conjugate. The optimal timing of this booster dose may be influenced by the magnitude of the post-primary immune response and so potentially may vary depending on the vaccine used for priming. It is not yet known if additional boosters will be needed after the second year of life or if routine boosters will be needed to maintain protection in older people who received a single priming dose.

Thus it is essential that data on longer-term antibody persistence should be gathered in order to assess the need for and optimal timing of booster doses (see C.2.3). Whenever possible these data should be supplemented by information on the long-term effectiveness of the vaccine during routine use.

In reality, sound and comprehensive safety and effectiveness data cannot be collected by the manufacturers alone. Therefore, there should be discussions between the vaccine manufacturers responsible for placing the product on the market and national and international public health bodies regarding the feasibility of estimating effectiveness in the postmarketing period. Reliable estimates of effectiveness can only be obtained in geographical locations in which appropriate vaccine campaigns are initiated and where there is already a suitable infrastructure in place to identify cases of MenC disease.

All data collected should be submitted to the responsible national regulatory authorities at regular intervals so that any implications for the marketing authorization can be assessed.

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