Update
Le point

Articles in the Update series give a concise, authoritative, and up-to-date survey of the present position in the selected fields, and, over a period of years, will cover many different aspects of the biomedical sciences and public health. Most of the articles will be written, by invitation, by acknowledged experts on the subject.

Les articles de la rubrique Le point fournissent un bilan concis et fiable de la situation actuelle dans le domaine considéré. Des experts couvriront ainsi successivement de nombreux aspects des sciences biomédicales et de la santé publique. La plupart de ces articles auront donc été rédigés sur demande par les spécialistes les plus autorisés.

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Meningococcal disease and its control with meningococcal polysaccharide vaccines*

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This article summarizes background information and specific evidence regarding the use of meningococcal polysaccharide vaccines. On the basis of currently available data, it seems premature to recommend that immunization against meningococcal disease be included within routine immunization programmes in developing countries. Factors contributing to this judgement include the irregularity of epidemics, the changing serogroups of meningococci, the different age distribution of cases in different areas, low efficacy of a single dose of meningococcal vaccine in children below 2 years of age, short duration of post-immunization immunity in infants and young children, and finally, the still high cost of current meningococcal vaccines.

The meningococcal vaccines can be effective, however, in controlling epidemics due to meningococci of serogroups A or C provided they are quickly administered to the age groups within the population who are most at risk.

Meningococcal disease is endemic throughout the world, the commonest forms being meningococcal cerebrospinal meningitis (the most commonly diagnosed and reported) and meningococcaemia. Epidemic waves of meningococcal disease occur at irregular intervals of several years and last from three to five years.

The "cerebrospinal meningitis belt of Africa", which consists of the semi-arid Sahelian zone south of the Sahara and north to the equator, experiences a high incidence of meningitis in endemic form and large epidemics occurring from time to time in the dry season. The most affected countries are: Chad, Mali, Niger, northern Nigeria, Sudan and Upper Volta. Recently, localized outbreaks of meningococcal disease have been reported in other regions, reflecting a generalized epidemic trend and suggesting the need to improve surveillance.

The incidence of meningococcal disease varies considerably in different areas and there is a variation in morbidity and mortality during epidemic and endemic cycles. In countries with a temperate climate the reported annual incidence ranges from less than 1 to 3 cases per

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100 000 population in non-epidemic conditions but may increase considerably during epidemics. In countries in the West African meningitis belt the reported annual incidence ranges from about 10 cases per 100 000 population in non-epidemic periods to more than 100 per 100 000 during epidemics. The case fatality rate (CFR) in meningococcal disease depends on how early the cases are detected and on the availability of medical care. With early diagnosis, modern therapy, and supportive measures, the CFR ranges from 5% to 10%. In untreated cases, however, it reaches 50% or more, and during epidemics may also rise dramatically.

THE INFECTIOUS AGENT

Serogroups of meningococci

Meningococci (*Neisseria meningitidis*) are serologically classifiable into several serogroups on the basis of their specific capsular polysaccharide (PS). Groups A, B, and C account for at least 90% of cases, although the proportions of groups Y and W 135 have increased in the last few years in several areas. Sporadic cases are more often caused by serogroups B, C, and Y, while serogroup A is mostly responsible for large epidemics. Although members of serogroup A are notorious for causing large outbreaks, such as those in Brazil and Finland in 1974 and 1975, some epidemics have been caused by group C organisms (Argentina 1972 – 75) or group B (Belgium 1970 – 73, Norway 1974 – 75).

In 1975, group C meningococci predominated over group A in the northern savannah areas of Nigeria. This was a striking change from the 1970 – 73 epidemics when all analysed cases were caused by group A meningococci. Some outbreaks were caused by a mixture of serogroups: epidemics started with serogroup C but serogroup A then became predominant and was responsible for the main epidemic peak.

Resistance of meningococci to sulfonamides

Increasing resistance of meningococci to sulfonamides has been noted since the early 1960s. It was first observed for serogroup B meningococci and then for serogroups A and C, and most major outbreaks of meningococcal disease during the past ten years have been caused by sulfonamide-resistant strains. Resistance of all meningococcal serogroups is now a major problem, especially in developing countries where both prophylaxis and treatment of meningococcal disease were traditionally based on cheap sulfonamides.

IMMUNITY TO MENINGOCOCCI

Immunity to meningococcal disease has been shown to be antibody-mediated. Circulating antibody confers resistance, and much of this antibody is directed against the group-specific polysaccharides of meningococci.

Natural immunity to meningococci may occur in persons carrying either group-specific or non-typable (i.e., nonagglutinable) meningococci, or presumably, other bacteria that possess polysaccharide capsules or other cell wall antigens that are immunologically similar to those of meningococci.

The antibodies against intact meningococci or their antigens may be detected by a number of tests:

— The antibody complement-dependent bactericidal reaction. This does not require purified antigen and measures antibodies that are known to be associated with protection against meningococcal disease.

— The haemagglutination assay. This is highly specific for group-specific meningococcal polysaccharides, if purified polysaccharide is used to sensitize the red blood cells. However, the technique measures mainly IgM antibodies and its results are only semi-quantitative.

— The quantitative precipitation reaction. This measures antibody independently of its immunoglobin class, but is insensitive and technically difficult.

— Radioimmunoassay. Radiolabelled polysaccharide – antibody complex is precipitated with ammonium sulfate to permit the measurement of all anti-polysaccharide antibodies without regard to their immunoglobulin class. The amount of antibody is expressed in micrograms (μg) of antibody protein per ml of serum. Although the amount of antibody to meningococcal polysaccharide required for protection against groups A and C meningococcal disease has not been determined directly, field trial data seem to indicate that a concentration of 1 – 2 μg per ml is necessary.

Age distribution of immunity and disease

Infants in the neonatal period have passive immunity acquired from their mothers. After birth, serum antibody content diminishes, reaching its lowest level at 5 – 7 months of age. Then, with exposure to meningococci and bacteria with similar antigens, the antibody level gradually increases, although its concentration may still be low up to 18 months of age. Between 2 and 12 years of age there is a further progressive increase, of approximately 5% per year, in the proportion of children with antibody against meningococci. Children aged 13 – 19 years may have antibody levels equal to those seen in adults. Sixty percent of unimmunized adults show antibody levels of 2 μg/ml or more, and 87% of them have more than 1 μg/ml. It has been observed that in areas where the incidence of disease due to group A meningococci has been very low (as in the USA), anti-A antibody is acquired naturally much earlier than anti-C antibody. This suggests that these natural antibodies may result from exposure to other antigens that cross-react with group A meningococci.

As the acquisition of natural immunity is a function of age, it can be expected that meningococcal disease will be most frequent in the age groups in which the proportion of individuals with antibody content above a given level is at a minimum.

Indeed, in the developed countries, from which most of the data on the acquisition of natural immunity come, meningococcal disease is most frequent in children less than 5 years old. The incidence of meningococcal disease per 100 000 was highest in the 0 – 4-year age group in non-epidemic conditions in Finland in 1969 – 72 and in the USA in 1969. Children in that age group accounted for 47 – 68% of cases in England and Wales in 1977 – 78, in France in 1970 – 72, in Belgium in 1975, and in the Netherlands in 1964 – 78. The proportion of the total number of cases of meningococcal disease occurring in children below 4 years of age may depend on the prevalent serogroup of meningococci; for example, in the USA in 1975, of the cases due to serogroups B, C, and Y, 69%, 59%, and 18%, respectively, occurred in children under 4 years old. During epidemics due to serogroups A or B in Romania in 1970, Finland in 1974, and Norway in 1976, relatively more cases were seen in older age groups, although cases in children under school age were still predominant.

The scanty data from Africa do not seem to confirm this pattern of age distribution, however. In Nigeria the proportion of cases among 0 – 4-year-old children in 1960 – 64 and

in 1970 – 73 ranged from 11% to 20%. In 1975, 14% of serogroup A cases and 32% of the serogroup C cases were in the 0 – 4-year age group. In one of the epidemic foci of serogroup A meningococcal meningitis in Rwanda in 1978 – 79, children below 4 years of age accounted for about 14% of all cases.

Children below 4 years of age accounted for 15 – 27% of cases reported in 1976 – 77 by Guinea Bissau, Madagascar, Senegal, and Sudan. Hospital data from Ghana showed that the highest incidence in 1972 – 73 was in persons above 5 years of age.

Further work is needed to clarify our understanding of the factors that account for the age distribution of meningococcal disease.

MENINGOCOCCAL POLYSACCHARIDE VACCINES

Types of vaccine and quality control

Three meningococcal vaccines are now available: monovalent vaccines composed of either group A or group C meningococcal purified capsular polysaccharide (PS), and a bivalent vaccine of groups A + C polysaccharides. The vaccines are available in the freeze-dried form and a single human dose usually contains 50 μg of the particular PS. So far it has not been possible to isolate an immunogenic capsular PS from group B meningococci. Attempts have recently been made to find a suitable protein or other cell envelope material for use in a group-B vaccine.

Much progress has been made in the isolation and characterization of specific polysaccharides from groups Y and W 135 organisms. Since the incidence of infection with these two strains is increasing in some countries, and since they are particularly virulent, it is important to make provision for their inclusion in meningococcal vaccines, particularly in situations where the meningococcal strain causing the disease has not been grouped.

So far there is no animal model for evaluation of the clinical potency of PS vaccines and therefore various *in vitro* physico-chemical and serological tests are used in the laboratory as indicators of the vaccines' *in vivo* specificity and immunogenicity. PS antigens readily depolymerize and their relative molecular mass (RMM) diminishes when they are exposed to ambient temperatures. It has been demonstrated that the immunogenicity of PS antigens in man is directly related to their relative molecular mass, and this can be determined in the laboratory by the partition coefficient, Kd, using column chromatography with Sephadex gel. The Kd value is inversely correlated with the RMM: the lower the Kd value, the more immunogenic the antigen. The partition coefficient determination may then be used as an indicator of the immunogenicity of PS vaccines and also to study the degree of depolymerization, and thus the thermal stability, of the vaccines as a function of time and storage temperature.

Stability of meningococcal vaccines

Purified polysaccharides, and especially group A polysaccharide, are unstable at ambient temperatures because of depolymerization. With early PS vaccines of group A storage at – 20 °C was therefore recommended. At that temperature the rate of depolymerization is negligible. The discovery that the replacement of sodium chloride by lactose as a menstruum for lyophilization stabilizes PS vaccines against thermal depolymerization represents a major step forward. The addition of a stabilizer and achievement of a low moisture content in freeze-dried vaccines has greatly improved their thermal stability.

Group A and C stabilized vaccines can now be stored at temperatures between 2 °C and

8 °C for two years. Group A + C vaccine from one manufacturer stored at 22 °C for 18 months showed very little depolymerization; at 45 °C the group A component reached a critical Kd value of 0.45 after 4 weeks, while the group C component was stable for 8 – 10 weeks at that temperature. Although reconstituted A + C vaccine was reported to be stable for 2 weeks at 25 °C and for 4 days at 37 °C, it is recommended that it be used during the day on which it is reconstituted. Data on the heat stability of vaccines produced by other manufacturers are not yet available.

Reactions following immunization

Adverse reactions to group A and C vaccines are generally mild and infrequent in school-age children and adults following primary and booster immunizations made by conventional subcutaneous injections or by jet injector. No serious local or systemic reactions have been reported, although transient local erythema at the injection site, and mild irritability or lethargy lasting for 1 – 2 days are infrequently noted.

In infants and young children in Finland, local reactions were also mild and included erythema, oedema, and tenderness at the injection site. However, fever reactions of 38.5 °C or more, as measured per rectum, occurred in less than 0.5% to 1.9% of children from 3 months to 5 years of age receiving group A vaccine. The reactions were age dependent; they occurred in 2.4% of infants less than 1 year old and in 0.6% of children aged 3 – 5 years. The difference in reaction rates observed following different lots of group A vaccine most probably reflected differences in the amount of endotoxin remaining in the vaccine. The rate of anaphylactic reactions among approximately 1.5 million immunizations was 0.8 per 100 000.

Efficacy of meningococcal vaccines

Immunity following immunization with group A and C vaccines is group specific and protection is achieved in one week. Group A and C meningococcal vaccines have been shown to be effective in preventing meningococcal disease during epidemics. Group A vaccine has been used in field trials in Egypt in children aged 6 – 15 years, in Sudan in persons aged under 21 years (children aged 1 – 5 years constituted only 21%), and in Finland in army recruits. The trials showed the clinical efficacy of the vaccine in adults and children over 6 years old to be about 90%.

Whereas the efficacy of the vaccine was proved among adults and older children there remain doubts about its efficacy among younger children and infants. Antibody response to the group A vaccines is clearly age dependent, and between 7 months and 21 years of age there is a linear relationship between peak anti-A antibody concentration and the logarithm of age. The concentration of antibody induced by immunization with a single dose of vaccine increases significantly with age: it is poor in infants below 1 year of age and reaches more than 5 μg/ml in children aged 2 years and older. The anti-A response in infants below 1 year of age did not reach the level of 2 μg/ml in 61 – 92% of infants immunized, and 38% to 88% of infants did not show a level of 1 μg/ml.

This problem could be overcome by administering a second dose 3 – 4 months later. The results of a field trial of a group A vaccine during a group A epidemic in Finland in 1973 – 75 indicated that the vaccine administered in two doses at an interval of 3 months provided complete protection for one year among infants initially aged 3 – 18 months. This primary series of two doses of vaccine appears to be necessary to achieve an adequate concentration of antibody to group A meningococci in infants under 24 months of age. However, even with two doses of group A vaccine, the percentage of infants with specific antibody levels exceeding 2 μg/ml three weeks following the second dose was 36% for infants 3 – 5 months

old and 61% for infants 6 – 11 months old. In children aged 12 – 17 months, the antibody level rose above 2 μg/ml following the second dose in 72%.

In older children, the antibody level had increased 8 – 11-fold three weeks after a single dose of vaccine and it reached 9 μg/ml in the 2-year-olds and 21 μg/ml in the 13 – 19-year-olds.

In army recruits in the USA the group C vaccine proved 90% effective. In children aged 24 – 35 months, during an epidemic caused by serogroup C sulfonamide-resistant *N. meningiditis* in São Paulo, Brazil, serogroup C vaccine was 75% effective in preventing disease. However, no protection was noted in infants aged 6 – 23 months.

It seems that currently available group C PS vaccines are not likely to induce a sufficiently high or persistent concentration of antibody in infants or younger children to warrant routine immunization.

The effectiveness of meningococcal vaccines against the carriage of meningococci is not known. In the field trial of a serogroup A vaccine in Egypt in 1973 – 75, the vaccine was found to reduce to less than half the rate of new infections with serogroup A meningococci (4.9 in immunized group and 12.0 in control group per 1000 student-months of follow-up) during the three months following immunization. The incidence of infection during the six-month period beginning nine months after immunization was 10.4 in the vaccinated persons and 13.6 in the controls per 1000 student-months of follow-up. No significant differences were observed during the six-month period beginning 21 months after immunization (10.4 and 10.0 per 1000 student-months for the vaccinees and the controls, respectively). However, a study carried out in Rwanda during a serogroup A epidemic did not seem to show any beneficial effect of immunization on the carrier rate in the 3 weeks following immunization.

Duration of immunity following immunization

The duration of post-immunization immunity is not known with certainty. The available data for group A vaccine suggest that a single dose of vaccine administered to persons over 2 years of age provides protection for 1 – 3 years. In the Finnish study the persistence of antibodies to the capsular polysaccharide of group A meningococci was found to be strongly dependent on age among vaccinees aged 3 months – 14 years followed for 3 years after immunization. In children below 12 months and between 12 and 17 months, and immunized with two doses of vaccine, significant antibody response was maintained for 1 and 2 years, respectively. After a single injection of the group A vaccine, statistically significant evidence of immunity was maintained for only 1 year if the vaccine was given at the age of 18 – 23 months, for 2 years if the vaccine was given at 2 – 3 years of age, and for 3 years if the child was 4 years or older when immunized.

It is likely that a primary series of two doses of vaccine at 3 – 6 months of age, followed by booster injections at 1.5 and 5 years of age, will provide long-lasting immunity against epidemic and endemic group A disease.

The patterns of persistence of antibody following immunization with group C vaccine are significantly different from those seen with group A vaccine. In both infants and older children, the rate of decline of concentration of antibody to group C meningococci is much more rapid than that of antibody to group A. The protective efficacy of group C PS vaccine seems to be of short duration, probably 1 year or less. The vaccine seems contraindicated in infants below 2 years of age, because of the immunological tolerance it may induce, i.e., reduced ability to respond to a second dose of group C vaccine given some months later.

The vaccine can be used, however, in persons over 2 years of age to combat a group C epidemic. It should be given in a single dose as soon as possible after the start of the epidemic. One should keep in mind that high relative molecular mass polysaccharides are

thymus independent antigens and as such do not elicit a true anamnestic ("booster") response unless memory B cells have first been formed as a result of cooperative interaction between T and B cells. Such T- and B- cell interaction usually occurs in response to thymus-dependent antigens.

The binding of the polysaccharide to a protein, such as tetanus toxoid, might therefore be expected to be the most active in providing lasting immunity. Much more work is needed to develop such an improved vaccine.

The use of meningococcal vaccine simultaneously with, or combined with, other vaccines

Group A and C meningococcal vaccines can be given simultaneously either at different sites or in the form of bivalent A + C vaccines without interference with the immune response to the individual antigens. Information on the immunogenicity and safety of simultaneous administration of meningococcal vaccines with other vaccines is scarce. A combination of meningococcal and *Haemophilus* type b polysaccharides seems to be safe and immunogenic in children over 2 years of age. A fourth dose of DPT vaccine given to 18-month-old children simultaneously with group A and C meningococcal vaccines had no adverse effect on the immunological response to meningococcal polysaccharides; however, the response to DPT vaccine was not reported. Although children over one year of age given meningococcal A or A + C vaccines mixed together with measles vaccine showed unimpaired immune response to group A and C polysaccharides, the measles response seemed to be depressed.

IMMUNIZATION POLICY

The justification for routine, mass immunization of infants and children with the currently available meningococcal vaccines remains to be established. The addition of any new vaccine to current schedules should be preceded by a careful analysis which includes its clinical efficacy, expected epidemiological impact, feasibility of administration, and expected cost in relation to expected benefits.

On the basis of currently available data, it seems premature to recommend that immunization against meningococcal disease be included within routine immunization programmes in developing countries. Factors contributing to this judgement include the irregularity of epidemics, the changing serogroups of meningococci, the variation in age distribution of cases in different areas, the need for a series of doses of group A vaccine in infants and young children to maintain long-lasting anti-A immunity, the low efficacy of group C vaccine in children below 2 years of age, the scarce information on the effect of simultaneous administration of meningococcal vaccines with other vaccines, and finally, the still high cost of the current meningococcal vaccines.

Nevertheless, group A and C vaccines can be recommended for use in the control of epidemics of cerebrospinal meningitis due to A and C serogroups of *N. meningitidis*. Effective use of specific vaccines to control outbreaks requires early, exact, etiological diagnosis. As soon as the serogroup is determined a specific immunization campaign tailored to the epidemiological circumstances existing within the affected communities should be carried out in order to prevent transmission of the infection.