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MEASLES IMMUNITY AND IMMUNIZATION IN DEVELOPING COUNTRIES OF AFRICA : A REVIEW

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Summary

Although an effective vaccine against measles has been available for several years, the disease is still prevelant in Africa. The disease is characterized by its occurrance in younger age groups and high morbidity and mortality. The African child is born with a high transplacentally acquired measles antibody level. However, the antibody declines rapidly, so that it is virtually absent after the age of 6 months. The measles vaccine with which the African child is immunized is of reduced potency because of poor storage and transportation facilities and the adverse effect of tropical climate on the vaccine. The pattern of measles immunity in Africa is different from that in developed countries. Measles immunization schedule in Africa, as in any other part of the world, must be based on sound epidemiological and serological data.

Résumé

Bien qu'on ait trouvé un vaccin contre la rougeole depuis des années, la maladie est toujours répandue en Afrique. La maladie est caractérisée par sa présence chez des enfants en bas âge et par sa haute morbidité et mortalité.

L'enfant africain est né avec un haut niveau d'anticorps de rougeole transplacentairement acquis. Cependant, le niveau d'anticorps baisse rapidement, si bien qu'il est presque absent a l'âge de 6 mois. Le vaccin contre la rougeole avec lequel on immunise l'enfant africain est d'une efficacité réduite à cause des pauvres facilités d'emmagasinage et de transportation et les influences adverses du climat tropical sur le vaccin. L'échantillon de l'immunité contre la rougeole en Afrique est different de celui des pays dévelopés. Le plan de l'immunisation contre la rougeole en Afrique, comme dans les autres régions du monde, doit se baser sur des données épidémiologiques et sérologiques valables.

Cette communication se donne comme tâche la revue des études faites sur l'immunité contre la maladie et l'immunisation en Afrique, et nous allons avancer quelques suggestions pour un programme efficace de l'immunisation contre la rougeole.

Introduction

The efficacy of measles vaccine in reducing the incidence of measles has been well documented in developed countries (Krugman, 1977; American Academy of Pediatrics, 1977; Dittman *et al.*, 1976). The number of reported cases of measles in the United States of America has dropped from 500 000 cases per year before the introduction of measles vaccine to about 35 000 cases per year with the introduction of the vaccine (Krugman, 1977). In several parts of Africa measles is still an endemic disease, associated with high morbidity and mortality in young children (Grigsby & Adetosoye, 1973; Kimati & Lyaruu, 1976; Abdurrahman, 1979). Hospital case – fatality rates of 6% to more than 12% are common (Anon., 1976). Moreover, the disease occurs frequently in younger age groups: in some reports 20 – 30% of cases of measles occur

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in children under one year of age (Grigsby & Adetosoye, 1973; Ministry of Health of Kenya and World Health Organization, 1977). Based on epidemiological and serological data, the recommended age of immunization against measles in United States of America was changed from 9 months to 12 months (U.S. Public Health Service Advisory Committee on Immunization Practice, 1965), and more recently to 15 months (Krugman, 1977). Since the disease occurs in younger age groups in Africa such a recommendation will not be applicable to most parts of Africa.

The aspects of measles immunity and immunization in Africa which this review proposes to discuss are: (1) efficacy of measles vaccine in Africa, (2) age groups susceptible to measles infection, and the optimal age of immunization, (3) factors that adversely affect the immune response of children in Africa, (4) trials carried out to overcome some of the problems associated with measles immunity and immunization in Africa, and (5) duration of immunity after active immunization against measles.

In discussing these topics, studies carried out in developed countries will be compared with similar studies done in Africa. Lastly, some recommendations will be made in the light of our present knowledge of measles immunity and immunization in Africa.

Efficacy of measles vaccine

Several studies have demonstrated the safety, immunogenicity and protective effect of measles vaccine (Feldman, 1964; Dittman *et al.*, 1976; Krugman, 1977). These studies were carried out under ideal, controlled conditions: relatively short distances from the point of vaccine manufacture to the consumer, good transport and refrigeration facilities, availability of manpower and facilities for virological and serological testing. Under such conditions the serological response of African children is similar to that of Caucasian children (Meyer *et al.*, 1964). In many parts of Africa the problems associated with measles vaccine include availability and cost of the vaccine, transportation, existence of chains of salesmen, lack of storage facilities, and adverse climatic conditions. All these factors result in uncertainty of the potency of the vaccine. Moreover, there are relatively few laboratories capable of measuring the potency of vaccines.

Measles vaccine is susceptible to both heat and light. Because of the long and often tortuous journey from the manufacturer to the consumer (factory→main distributor→minor distributors→Ministry of Health→Hospitals→Clinics) and inadequate storage and transport facilities, there may be great differences in potency of the vaccine at the factory and the potency at the time the vaccine is used. When the stability of measles vaccine in field conditions was investigated in England (Clarke, 1977), only one out of the forty-five samples tested had a serious loss of potency. In a tropical setting Hendrickse (1975) found that one out of twenty measles vaccine samples obtained from field workers in Nigeria contained an infectious virus, and the majority of the vaccines showed evidence of bacterial infection. Eghafona (1978) tested the efficacy of two different brands of measles vaccine collected from two states in Nigeria, using the following methods: cytopathic effect on tissue culture, haemagglutination inhibition (HAI) antibody levels in serum, and immmunocytoadherence. Both brands of vaccine were found not to be immunogenic, even though the vaccines had not expired. Anectodes exist of 'vaccine failures' in children immunized at the correct age with unexpired measles vaccines.

Children may thus be vaccinated but not immunized against measles.

One of the most serious effects of cases of 'vaccine failures' is the loss of confidence in the whole immunization programme by the consumer. Added to this is the high cost of the vaccine. In Nigeria, for example, one dose of measles vaccine costs as much as ₦2.73, equivalent to U.S. $4.75, in comparison with BCG and DPT which cost 24k and 0.04k per dose respectively (Medipharm, 1979). Several African countries cannot afford to spend large sums of money on measles vaccine alone, even though they have a large number of susceptible children.

Susceptible age groups and optimal age of immunization

In Africa, young infants are susceptible to measles, and infections occur under 6 months of age (Grigsby & Adetosoye, 1973; Ministry of Health of Kenya and World Health Organization, 1977; Abdurrahman *et al.*, 1980). It seems appropriate, therefore, to immunize children in Africa as early as possible. Experience in the

developed countries has shown that children immunized against measles before 1 year of age have lower seroconversion and poorer protection than children immunized after 1 year of age (Krugman, 1977; Shasby, 1977; Marks, Halpin & Orenstein, 1978; O'Neil, 1978). The probable mechanism for the lower seroconversion and poor protection is the persistence of transplacentally acquired maternal measles antibody (Albrecht *et al.*, 1977).

From these and other similar studies the recommended age for measles immunization in the United States of America is now 15 months.

In Africa, there are relatively few reports of serological studies done to determine the optimal age of measles immunization. Burrowes & Cruickshank (1976) carried out a trial in Bulawayo to ascertain the right age to immunize children against measles. Seventeen out of twenty-six (65%) of the 4-month-old infants in their study had pre-immunization measles antibody in their sera, and only two of the twenty-six (7.7%) children had significant seroconversion. Only fifteen out of forty-four (33%) 6-month-old infants had pre-immunization HAI level of 1:8 or greater. The seroconversion rate among the forty-four infants was 52%, compared with 97% among 9-month-old infants. In a study of 6–12-month-old infants in South Africa, Dick, Smith & Kipps (1975) found a seroconversion rate of 42% among the 6–8-month-old, compared with 80% among the 9–12-month-old children. In a rural part of Nigeria, Hendrickse & Montefiore (1968) found that only fourteen out of twenty-nine (48%) infants aged from 3 to 7 months had measles neutralizing antibody titre of 1:10. In a measles outbreak, Fabiyi & co-workers (1974) carried out a serological study in twenty-nine children who were hospitalized with measles, even though they had been immunized against measles about a year before the outbreak. Twenty-eight of these children were immunized between 6 and 9 months of age. Only eight out of the twenty-nine children had complement fixing measles antibody of 1:4 or greater: no antibody was detected in twenty-one children. More disturbing was the author's finding of significant seroconversion in only two out of the twenty-nine children following the infection. In our institution (Abdurrahman *et al.*, 1980), we found that thirty-four out of thirty-five (97%) newborn babies had HAI titre of $\geq$ 1:4, but the number of children with this level of antibody was only 6 out of 28 (21%) at 6 months of age. In a bigger and more elaborate collaborative study in Kenya (Ministry of Health of Kenya and World Health Organization, 1977), it was found that 90% of children no longer had maternal antibodies at 7–8 months, and that almost all the children seroconverted when vaccinated at 7½ months or older. Seroconversion occurred even if a lower level of maternal antibody still persisted when the vaccine was given.

Suppression of immune response

There are clinical conditions known to influence adversely the immunological response of the African child to an antigen. Protein calorie malnutrition (Smythe *et al.*, 1971) and infections such as measles, malaria and tuberculosis (Chandra & Newberne, 1977) have been shown to depress immunity. These adverse clinical conditions often co-exist in the same child. Because of the depressed immunity, and therefore fear of dissemination of live viruses, children with severe infections or malnutrition are not often immunized. However, McMurray and his colleagues (1979) have shown that moderately malnourished children produced as much antibody and had the same degree of post immunization morbidity as their well-nourished cohorts after measles immunization. From his study in Central Africa Glyn-Jones (1972) concluded that immunization of susceptible children against measles, even if these children are acutely ill and malnourished 'is not only justified but is mandatory'.

Trials to overcome problems of measles immunization in Africa

The various problems associated with measles immunization in Africa make it difficult to analyse satisfactorily the causes of apparent 'vaccine failure'. Are these failures due to vaccine deficiency at the time of manufacture, or due to transportation, storage, handling and distribution, or due to faulty technique by inexperienced field workers? These are not questions of theoretical interest only, judging by the study of McBean & co-workers (1976) who reported that 83% of the vaccines given to a measles campaign team was 'wasted'.

In an attempt to reduce the cost of measles

immunization, trials have been conducted with reduced vaccine dosage. The report by Burrowes & Cruickshank (1976) suggests that one third of the standard dose of measles vaccine is an effective immunogen. Hendrickse & Montefiore (1968) found that one fifth of the standard dose resulted in good seroconversion. In contrast, Wallace *et al.*, (1976) reported that reducing the vaccine virus dosage led to significant reduction in the seroconversion rate. In the light of the problems presented above in connection with measles immunization in Africa, it is not advisable to attempt to reduce the cost of measles immunization by giving reduced doses of the vaccine.

Another possible way of reducing the cost of measles immunization, and at the same time increasing the scope of an immunization programme, is by combining measles vaccine with other vaccines. That such combinations are feasible without loss of immunogenicity or increase in reaction has been demonstrated for measles, mumps and rubella (Weibel *et al.*, 1978), and measles and DPT (McBean *et al.*, 1978). Such vaccine combinations will be particularly useful in African Countries where attendance rates for immunization at health clinics are low and irregular. However, the most appropriate age to give these combined vaccines must be determined in each community.

Since measles occurs in Africa in young infants at an age when maternal antibody may still be present, it was thought that local immunization of the respiratory tract might produce immunity without the risk of vaccine inhibition by serum maternal antibody. A preliminary trial of intranasal administration of measles vaccine in 6-month-old African infants was reported by Zahradnik *et al.*, (1978). Eight out of twenty-eight (32%) infants seroconverted and six (21.4%) had HAI antibody in convalescent nasal washes; three of the latter six children had a fourfold titre rise of serum antibody. One child had a nasal antibody response without serum antibody response. The protection conferred on these infants can only be truly assessed when they are subsequently exposed to measles infection. It will be particularly useful to compare the infants with the three types of response to intranasal immunization: those who developed nasal and serum antibodies, those with serum antibody alone, and those with nasal antibody alone. An area of measles immunity and immunization that deserves priority attention in Africa is the production of heat-stable vaccines. Preliminary trials in the Cameroons with one such vaccine produced encouraging results (Anon., 1979).

Another area of measles immunity that deserves further study is the role of cell mediated immunity (CMI). CMI is important in immunity against viral diseases (Mackaness, 1971; Craddock, Longmire & McMillan, 1971), and measles is not likely to be an exception. Laboratory evidence has been produced for the involvement of CMI in measles infection (Labowskie *et al.*, 1974). The most convincing clinical evidence of the role of CMI in measles infection is the report that children with congenital agammaglobulinaemia recovered from measles without undue sequelae (Good & Zak, 1956). No measles antibody was detected in their serum following recovery from measles.

Duration of immunity

In the United States of America, the duration of immunity against measles following immunization has been estimated to be at least 15 years (Krugman, 1977). Little is known about the duration of immunity in African children immunized against measles. Our experience from a few children of middle income parents shows that measles antibody following immunization persists for at least 5 years (unpublished data). The number of children is small and the children are highly selected. Only long-term surveillance will give information on the duration and quality of vaccine-induced immunity.

Recommendations

There is a real need for cooperation between African countries in setting up regional reference laboratories for both the manufacture and the testing of potency of measles vaccines. In the manufacture of vaccines priority attention should be given to producing heat-stable vaccines which can withstand the tropical climate found in many parts of Africa. The laboratories should also be involved in trials to find the ideal dose of vaccine and the optimal age of immunization for different parts of the continent. We are convinced that the setting up of regional laboratories is a worthwhile investment if one considers the amount of money wasted (not spent) on imported measles vaccines of

uncertain potency.

Each country should carry out urban and rural field epidemiological and serological trials before formulating a policy of measles immunization for the country. Such trials should include evaluation of cost-benefit and cost-effectiveness of measles immunization programmes. While we are not against measles campaign *per se*, it should be stressed that they are bound to fail if provision is not made for an active continuing programme. Measles immunization should be part of an immunization programme of basic health services of any country.

There is a special need to protect 'high-risk' hospitalized patients: such patients include children suffering from malnutrition, malignancy and other debilitating diseases that suppress immunity. On admission into hospital children with kwashiorkor who have not had measles previously should be passively immunized with gamma globulin, followed by active immunization 8 to 10 weeks later. By this time their oedema would have subsided and the suppresive effect of the gamma globulin would have virtually disappeared. Children with moderate malnutrition can be safely immunized (McMurray *et al.*, 1979). Children with other immunosuppresive diseases or on immunosuppresive drugs should be given gamma globulin when exposed to cases of measles.

Until each country is able to determine the appropriate age to immunize its children against measles, we recommend that children in Africa be immunized between 7 and 8 months of age. This recommendation is based on the epidemiology of measles and the results of serological studies carried out in Africa.

In developed countries it has been suggested that children who were immunized before 1 year of age should receive a second dose of measles vaccine when they are older (Linneman *et al.*, 1972; Shasby *et al.*, 1977). Such a practice will be an expensive undertaking in most countries in Africa. Children in Africa rapidly lose their transplacentally acquired measles antibody, and they show good seroconversion when immunized at 7½ months of age or older (Burrowes & Cruickshank, 1976; Ministry of Health of Kenya and World Health Organization, 1977). Moreover, they are repeatedly exposed to measles. Children repeatedly exposed to measles have measles HAI titre greater than children who are relatively protected (Krugman, 1977). For these reasons, and in the absence of trials to show any benefits of reimmunization, we do not advocate a second dose of measles vaccine in African children.

After determining the right age to immunize children and obtaining the right vaccine under the ideal conditions, there is a greater need for consumer education, to make him accept immunization as a sensible health investment.

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