TRIAL OF EDMONSTON-ZAGREB MEASLES VACCINE IN INFANTS AGED UNDER NINE MONTHS

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Abstract. Due to the recent finding that most infants in developing countries have lost maternal antibody for measles before nine months of age, immunization of infants younger than the recommended age of nine months would help reducing the incidence of measles in these endemic areas. We conducted a trial of Edmonston-Zagreb measles vaccine which is the strain that may be more immunogenic in young infants than the widely used Schwarz strain. Forty-five infants with mean age of 25 weeks received a dose of Edmonston-Zagreb vaccine. Antibody levels were measured, using plaque neutralization test, before and about 3 months after vaccination at which mean age was 38 weeks. The seroconversion rate was 89%. Only two infants (4.4%) had immunity before vaccination. Fifteen infants (33.33%) reported some adverse reactions including fever (13.33%), rhinorrhea (8.89%), rash (4.44%) and local reactions (22.22%). All of the reactions resolved spontaneously. We conclude that Edmonston-Zagreb measles vaccine is efficacious and safe in infants aged under nine months.

INTRODUCTION

Despite the availability of live attenuated measles vaccine since 1959 (Katz *et al,* 1958; Enders *et al,* 1960) measles remains an important cause of childhood morbidity and mortality in the developing world. Over 2 million children die of measles each year (Henderson *et al,* 1988) and the case-fatality rate is especially high among young infants (Hull *et al,* 1983; Loening and Coovadia, 1983). In the World Health Organization Expanded Programe on Immunization measles vaccine was recommended at 9 months of age in countries where measles frequently occurred in the first year of life (WHO, 1982). However, a substantial number of infants in endemic areas get measles before that age due to loss of maternal antibody (Loening and Coovadia, 1983; Taylor *et al,* 1988). In Thailand, two studies of seroepidemiology of measles antibody were conducted in 1982; one showed that maternal passive immunity disappeared at 6 months of age (Vanprapa *et al,* 1983), the other found only 25% of children aged 6-11 months had persistence of maternal antibody (Jayavasu *et al,* 1982). WHO now recommend that, in countries with a high incidence of measles in infancy, measles vaccine should be given at 6 months (Expanded Programme on Immunization, 1990). However, to overcome the possibility of vaccine failure which might occur in young infants due to residual maternal antibody, an alternative strain of vaccine has been sought. The Edmonston-Zagreb (EZ) strain of measles vaccine has been shown to be effective in immunizing children as early as 4 to 6 months of age since 1983 although many studies used vaccine of high rather than conventional dosage (Sabin *et al,* 1983; Whittle *et al,* 1984; Khanum *et al,* 1987; Whittle *et al,* 1988a; Aaby *et al,* 1988). To answer questions about the effect of standard dose of EZ vaccine on seroconversion rate and adverse reactions, we conducted a clinical trial of EZ vaccine administered to children aged under nine months.

MATERIALS AND METHODS

Study population

Forty-five healthy children were recruited for the trial including 13 orphans and 32 infants attending routine immunization clinic at Maharaj Nakhon Ratchasima Hospital, a regional hospital in Northeastern Thailand. All of the cases were less than 9 months old who had no history of measles or measles vaccination, no current illness,

no immunosuppressive therapy and no treatment with blood or blood components for the last 3 months. The children were excluded if weight-for-age were in the range of the second or third degree protein-energy-malnutrition according to the standard of the Ministry of Public Health. The purpose of the study was carefully explained to the mothers or guardians of the infants and the written informed consents were used.

Study design

A single 0.5 ml. Edmonston-Zagreb measles vaccine (Moraten Berna, Swiss Serum and Vaccine Institute, Berne) containing 1,000 $TCID_{50}$ live measles virus was injected subcutaneously in the deltoid muscle. The infants attending routine immunization clinic received the EZ vaccines on the same day when they were immunized with the third doses of diphtheria-tetanus-pertussis (DTP) and oral polio vaccines (OPV).

Before immunization 3 ml of venous blood were taken from each infant to determine pre-existing measles antibody. The second blood specimen was obtained about 3 months later to assess the seroconversion. Parents or guardians were asked to observe any symptoms probably related to the vaccine, record on a simplified form and bring back to the clinic on the day of second visit.

Serology

The measurement of measles antibody was done by using plaque neutralization test (PN). The tests were performed at Virology Laboratory of the Swiss Serum and Vaccine Institute, Berne, Switzerland. The starting serum dilution was 1:8 which detected 80 mIU/ml of PN antibody. The seroresponse was defined as a change from no detectable to detectable antibody in the postimmunization specimen. A PN antibody of less than 1:8 after vaccination was designated a failure. Only infants seropositive after vaccination have been taken into account for computation of geometric mean antibody titer.

RESULTS

Among 45 infants enrolled in the study, the age ranged from 17-33 weeks with the mean age of 25 weeks while the average age at assessment of seroresponse was 38 weeks (range 25-43 weeks). Twenty-five were males with M:F ratio of 1.25:1. Only two infants (4.4%) had immunity before vaccination.

Serologic response

Forty infants serconverted 3 months after vaccination resulting in the overall seroconversion rate of 89 percent (Table 1). Among seronegative infants, the seroconversion rate was 93% (40 out of 43) while both of the two infants with prevaccination immunity failed to seroconvert. Two out of three seronegative infants who failed to seroconvert were 4 months old. The geometric mean titer of PN antibody 3 months after vaccination was 251 (80-1720) mIU/ml.

Reactions to the vaccine

Fifteen infants (33.3%) reported some adverse reactions (Table 2). The most common were local signs and symptoms(10 out of 45, 22.2%)including pain and induration in equal proportions (15.5%) and erythema (8.9%). Fever was reported in 6 infants (13.3%) with a mean duration of 2.7 days. Onset of fever ranged from 5 to 14 days after vaccination. Rhinorrhea and skin rash occurred in 4 and 2 infants respectively (8.9% and 4.4%).

Table 1

Serologic response.

Infants	Total	No.(%) seroconverted
Seronegative	43	40 (93)
Seropositive	2	0 (0)
Overall	45	40 (89)

Table 2

Reactions to the vaccine.

Reaction	No.	%
Local	10	22.2
Erythema	4	8.9
Induration	7	15.5
Pain	7	15.5
Fever	6	13.3
Rhinorrhea	4	8.9
Rash	2	4.4
Total	15	33.3

None of the infants had conjunctivitis or convulsion associated with fever. Most of the reactions resolved spontaneously within 1 to 4 days.

DISCUSSION

Our study showed that 95.5% of infants have lost maternal antibody before 9 months of age, the age at which routine measles vaccination is recommended in developing countries. Thus measles immunization when a child reaches 9 months of age cannot provide effective measure against the risk of acquiring measles in endemic areas. Schwarz vaccine which is one of the most widely used measles vaccines in infants aged 9 months has been shown to produce significantly lower seroconversion rates than EZ vaccine among six-month-old infants (Sabin *et al,* 1983, 1984; Khanum *et al,* 1987; Whittle *et al,* 1988b; Fernandez *et al,* 1986). Sabin *et al* (1984) demonstrated 69, 89 and 100% seroconversion rates of 4-, 5- and 6-month-old infants, respectively given EZ vaccine by the subcutaneous route. Eighty-nine percent of children in our study seroconverted with EZ vaccine given before 9 months of age and the adverse reactions were minimal and self-limited. This finding coupled with other clinical studies of comparable results of vaccine efficacy and safety (Sabin *et al,* 1984; Fernandez *et al,* 1986; Tidjani *et al,* 1989; Markowitz *et al,* 1990), raised expectations that the EZ vaccine can help prevent measles in young infants, especially those in the countries where measles continues to be an important public health problem during the second half of the first year of life.

In Thailand, the national EPI was initiated on a nationwide basis in 1977 (Bhunbhu, 1989). Measles vaccine was introduced into the EPI in 1984, the year in which measles incidence was reported to be the highest (93.7 cases/100,000 population) in the past 10 years (Division of Epidemiology, 1984). Thereafter measles vaccination converage has been increasing in correlation with decreasing incidence of measles, except rising in 1987. However the percentage of achievement remains unsatisfactory (Division of Epidemiology, 1988). As shown in Table 3, only 55.5% of children aged nine months were vaccinated in 1988. This may be partly explained by the fact that parents or guardians are not familiar to bring their children to the immunization clinic at 9 months of age, the age not included in the previous schedule. It has already been established that measles vaccine can be given subcutaneously at the same time as OPV and DTP without interfering with the immune response to measles virus or to poliovirus (Krugman *et al,* 1977; Deforest *et al,* 1984). Therefore the improvement of measles vaccination coverage might be achieved if the EZ vaccine which is more effective for young infants could be given at the same time as the third dose of DTP and OPV.

Table 3

Measles vaccine coverage in Thailand.

Year	% Coverage
1984	5.9
1985	25.8
1986	44.9
1987	51.5
1988	55.5

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