OPTIMUM AGE FOR MEASLES IMMUNIZATION IN MALAYSIA

S.T. CHEN and S.K. LAM*

Departments of Paediatrics and *Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia.

INTRODUCTION

Measles is a serious communicable disease of childhood causing high morbidity and mortality in developing countries (Chen, 1979; John *et al.*, 1980; Hull *et al.*, 1983; Lo *et al.*, 1983). Although effective and safe vaccines have been available for more than twenty years and measles have been controlled and in the process of being eliminated in developed countries, there is still controversy regarding the optimum age for immunization. In developed countries, such as USA, the optimum age for immunization is 15 months (Krugman, 1977), but in developing countries children develop measles early in life, much of it during the later part of the first year when immunization with measles vaccine may not be effective due to the presence of maternal antibodies. The optimum age for measles immunization varies with different countries. In developing countries some studies have indicated that the optimum age for immunization is about 9 months of age (WHO, 1979; Bhatnagar *et al.*, 1981; John *et al.*, 1982; Mohan *et al.*, 1981; Ogunmekan *et al.*, 1981; Heymann *et al.*, 1983; Lee *et al.*, 1983; Vanprapar *et al.*, 1983). The objective of this study is to determine the age when children begin to acquire natural infection and the optimum age when immunization with measles vaccine is most effective.

MATERIALS AND METHODS

The study was carried out at the University Hospital, Kuala Lumpur, Malaysia from June 1980 to June 1983. The University Hospital serves a predominantly urban population of different socioeconomic background, living in and around Kuala Lumpur and Petaling Jaya. Two samples of population were selectted, one for the study of age-specific prevalence of measles infection and the other for age-specific seroconversion rates following measles immunization.

Age-specific prevalence: Blood samples were drawn into capillary tubes by means of heel pricks from 331 newborns and by finger pricks from their mothers. Samples were also obtained from 1,811 children, aged from a few days to 12 years, who were admitted to the University Hospital for various illnesses, together with 290 mothers of these children. Of the 1,811 children only 12 were admitted for measles disease. Previous history of measles immunization and infection were obtained from their parents or guardians. Thirteen children with history of previous measles immunization were not included in the study.

Study of seroconversion: All children, aged 9 months to 6 years, who attended the University Hospital Child Health or Immunization clinic and who had no definite history of measles immunization or infection were offered measles immunization. A dose of 0.5 ml of reconstituted vaccine, which contains not less than 1,000 tissue culture infectious doses 50% (1,000 $TCID_{50}$) of the Schwarz strain measles virus, was given subcutaneously. One capillary tube of blood was drawn by means of a finger prick before and six to eight weeks after immunization. Altogether 1,495 children had their pre-immunization blood samples taken. Of these only

971 provided post-immunization blood samples. Parents were advised to keep a record of side effects or complications if any and such history was obtained when children returned for post-immunization bleeding.

The haemagglutination-inhibition (HI) test described by Severs (1962) was used with some modifications. Measles haemagglutinins (HA) were obtained from several commercial sources. Titration of the antigens was accomplished by mixing 25 µl of diluted antigen with 25 µl of a 0.5% of cynomolgus monkey *(Macaca fascicularis)* red blood cells. The mixture was incubated at 37°C for 60 minutes before reading. It was found that the antigen from Beringwerke gave consistently high HA titres and this was used for the rest of the study.

In order to remove non-specific haemagglutinins, 15 µl of sera were diluted with 60 µl of phosphate-buffered saline and absorbed with 75 µl of a 20% suspension of RBC. This was then incubated for 60 minutes at 4°C, centrifuged at 1500 rpm for 3 minutes, and the supernatant (considered as 1:10 dilution of sera) titrated for HI antibody.

Doubling dilutions of 25 µl of sera from 1:10 to 1:160 were mixed with equal volumes of 4 HA units of antigen. The plates were incubated at room temperature for 60 minutes. 50 µl of a 0.5% RBC suspension were then added and further incubated at 37°C for 60 minutes. Positive and negative control sera were included in each run. The highest dilution of sera which gave complete inhibition of haemagglutination was considered the HI titre of the sera.

RESULTS

Table 1 shows that 54% of the newborns had passively acquired measles antibodies. The percentage of children, with positive measles antibodies of 1:10 or greater, decreased with increasing age, being 44% below 3 months and 26% at 3 to 5 months of age. The percentage remained at about the same level being 25% at 6 to 8 months and 26% at 9 to 11 months of age. From 12 months of age, however, the percentage increased sharply reaching 33% at 12 to 17 months and 44% at 18 to 23 months. Thereafter, it increased progressively being 51% at 3 years, 79% at 5 years and 94% at 10 years.

Table 1

Measles antibody titres according to age distribution in children.

Age	Sample size	Titres ≤1:10 No. (%)	Geometric mean titre (those with titres ≥ 1:10)
Newborn	331	180 (54.4)	24.1
< 3 mo	211	93 (44.1)	19.7
3-5 mo	188	49 (26.1)	20.0
6-8 mo	187	46 (25.0)	32.2
9-11 mo	164	42 (25.6)	36.7
12-17 mo	129	42 (32.6)	68.3
18-23 mo	69	30 (43.5)	72.2
2-yr	121	57 (47.1)	60.1
3-yr	127	65 (51.2)	64.7
4-yr	116	75 (64.7)	71.5
5-yr	100	79 (79.0)	66.8
6-yr	78	65 (83.3)	59.4
7-yr	60	53 (88.3)	68.3
8-yr	68	59 (86.8)	62.3
9-yr	55	50 (90.9)	65.9
10-yr	54	51 (94.4)	50.9
11-12 yr	84	74 (88.1)	53.9
Adults (mothers of newborn babies)	331	265 (80.1)	34.6
Adults (mothers of children	290	211 (72.8)	27.6

Table 2

Correlation between measles antibody titres in baby's and mother's blood.

Antibody titres* in mother's blood	Antibody titres in baby's blood*						Total no. examined
	< 10	10	20	40	80	≤ 160	
< 10	66**	0	0	0	0	0	66
10	21	11**	1	0	0	0	33
20	35	8	44**	0	0	0	87
40	17	4	27	21**	2	0	71
80	11	3	16	8	12**	0	50
≤ 160	1	1	7	6	5	4**	24
Total no. examined	151	27	95	35	19	4	331

*Reciprocal of dilutions of titres.
**The figures indicate the number of titres when the B/M ratio = 1 — a total of 158 pairs (48%).

The geometric mean titre of measles antibodies was 24 at birth and 20 thereafter till 5 months of age. From 6 months onwards there was an increase in the level; 32 at 6 to 8 months and 37 at 9 to 11 months. From 12 months onwards there was a sharp increase in the level; 68 at 12 to 17 months and 72 at 18 to 23 months of age, thereafter if remained at about the same level ranging from 59 to 71 till 9 years of age when the level began to fall to 51 at 10 years of age and 28 to 35 during adulthood.

The results (Table 1) indicate that measles is common in Malaysia and a small number of children began to acquire natural measles infection from 6 to 8 months of age onwards. However, the peak age for the acquisition of measles infection was from 12 months to 5 years of age with the sharpest rise during the second year of life.

Correlation between measles antibody titres in baby's and mother's blood is shown in Table 2. There was a lineal correlation between measles antibody titres in the baby's and mother's blood ($r = 0.6$). Of the 331 paired baby/maternal sera, the ratio of 1 occurred in 158 pairs (48%) and a ratio of 2 occurred only in 3 pairs of subjects indicating that in general, babies' antibody titres were at a lower level compared with their mothers. 85 newborns (26%) of mothers with positive measles antibody titres of 1:10 or greater had no detectable measles antibody in their blood.

Seroconversion following measles immunization with live attenuated measles vaccine is shown in Table 3. Of the 971 children, 86

Table 3

Seroconversion following measles immunization among those who were initially seronegative.

Age at immunization (months)	No. immunized	Children with titre ≥ 10 No.	%	Geometric mean titre (all cases)
9-	107	102	95.3	25.2
10-	158	148	93.7	28.9
11-	92	90	97.8	47.3
12-	89	88	98.9	40.5
13-17	240	237	98.8	47.0
18-23	112	108	96.4	40.4
24-72	87	83	95.4	39.6

(9%) had positive pre-immunization measles antibody titres of 1:10 or greater. In the 885 seronegative children, 94 to 99% seroconverted following immunization. However, the rates were higher when vaccination was given at 11 months of age or older compared with those when vaccination was given at the age of 9 or 10 months. This difference is statistically significant ($0.02 > p > 0.01$). Further, the geometric mean antibody titre was also higher when vaccination was given at 11 months of age or older being 40-47 compared with 25-29 when vaccination was given at 9 or 10 months of age. This difference is also statistically significant ($p = 0.01$). It should be noted that the geometric mean titre is an underestimation since the highest dilution of serum tested was at 1:160.

Vaccination reactions to measles immunization were recorded. Of the 971 children vaccinated 398 (41%) developed some side reactions. Of these 280 (70%) had one reaction and 118 (30%) had 2 reactions. Fever was the most common type of reaction, occurring in all the children who had reactions. The median onset of fever was 4.6 days from the time of vaccination while the median duration of fever was 1.3 days. Fever was reported to be mild in 286 children (72% of those with fever). Two of the children with high fever developed febrile fits. The second common reaction was rash which occurred in 116 (12%) of the children. The median onset of rash was 6.7 days from the time of vaccination and the median duration of rash was 2.3 days. The rash was generalised in 76 children (66% of those with rash).

DISCUSSION

This study shows that in Malaysia 94% of the children had acquired natural measles infection by 10 years of age. However, only 73-80% of adults had detectable antibody titres. This may not imply that these adults had lost their natural immunity as their antibody levels could be less than 1:10. Krugman (1977) had indicated the importance of testing for low levels (1:2 or 1:4) when evaluating persistence of antibody or immunity following natural infection or immunization and he had demonstrated a difference in results when the cut off point was a titre of 1:2 compared with that of 1:8.

Only 54% of the newborns had detectable measles antibody titres compared with 80% of their mothers. Although there is a good correlation between maternal and baby antibody titres, the level in babies was generally lower than their mothers. Hence, some of the babies with titres of less than 1:10 were not detected by the method used in this study. Clinical impression would support this view because very few children developed measles below 6 months of age (Chen, 1979).

The age at which 50% of children showed serological evidence of natural measles infection was 3 years. This is intermediate between that reported for some developing countries and developed countries. For example, it was below one year in Nigeria and Kenya (WHO, 1977; Harry *et al.*, 1981; Abdurrahman *et al.*, 1982), 1-2 years in India (Steinhoff and John, 1982) and 2.9 to 5.5 years in Italy (Santoro *et al.*, 1984).

The present study also shows that children began to acquire infection as early as 6-8 months of age, increasing steadily from one year of age.

The seroconversion rate after measles vaccination with one dose of live attenuated measles vaccine, given at 9 months of age or older, was good (more than 90%) but better (more than 95%) when given at 11 months of age or older. This confirms the studies of others in developing countries. The study in Kenya (WHO, 1977) shows good seroconversion even when vaccination was given at 6 and 8 months of age. However, in the

Kenyan study, the sample size was rather small. Studies in USA (Krugman, 1977) indicate that the antibody response was poorer when measles vaccination was given at the age of 12 months than when it was given after the age of 13 or 14 months, being 80%-85% and more than 95% respectively. The present study, however, shows that there was no difference in antibody response whether the vaccine was given at 11 months of age or older. The geometric mean titre was lower when vaccination was given at 9 or 10 months of age compared with that when given at 11 months of age or older.

Epidemiologic data have confirmed the results of serologic studies that the efficacy of measles vaccine improves with increasing age at the time of vaccination during the first year of life. Hull *et al.*, (1983) found that in West Africa, the vaccine efficacy was 37% for children vaccinated at 6 to 8 months of age, 85% at 9 to 14 months and 90% after 15 months of age. In USA, Faich *et al.*, (1981) found that the measles attack rates were 9% among those vaccinated before the age of 12 months and 3% among those vaccinated at 12 months of age or older while Faust and Thompson (1983) showed similar results. Shelton *et al.*, (1978) also found an increase risk of vaccine failure among those vaccinated at 12 to 14 months compared with those vaccinated at 15 months of age or older. In Zambia, Rolfe (1982) found a very high rate of vaccine failure among children vaccinated at 6 to 9 months of age.

In Malaysia the number of children acquiring natural measles infection from 6 to 8 months of age was small. From 12 months of age there was a sharp increase in the prevalence of measles infection. Children therefore need to be protected before they reach one year of age. Since measles seroconversion rate was better and the geometric mean higher from 11 months of age, the optimum age for measles immunization in Malaysia should be 11 months.

With the launching of National measles immunization programme in Malaysia in 1982, the vaccine can reduce the rate of virus circulation and thus will raise the age at which children become infected. This fact has been demonstrated by Sejda (1983) in Czechoslovakia and Heymann *et al.*, (1983) in Cameroon. Once this has occurred, the age at vaccination can be raised to 12 months of age or older.

SUMMARY

A study was carried out at the University Hospital, Kuala Lumpur, Malaysia to determine the age-specific prevalence of measles infection by serology and the age specific-seroconversion rates following measles vaccination.

The results show that the percentage of children with passively acquired measles antibodies decreased with increasing age till 3 to 5 months of age. From 12 months of age, the percentage of positivity increased sharply due probably to natural infection. The geometric mean antibody titre was low at birth, but from 6 months it started to increase. These results indicate that measles infection is common in Malaysia and a small number of children began to acquire natural measles infection from 6 to 8 months of age; however the peak age for the acquisition of measles infection was from 12 months to 5 years of age.

Seroconversion rates following vaccination from 9 months of age, ranged from 94% to 99%. However, the rates and the geometric mean titre were higher among those vaccinated at 11 months of age or older compared with those vaccinated at 9 or 10 months of age. Basing on the above results, it was concluded that the optimum age for measles

immunization in Malaysia should be 11 months.

REFERENCES

ABDURRAHMAN, M.B. *et al.*, (1982). Measles antibody levels from birth to 9 months of age in Nigerian infants. *Afr. J. Med. Sci., 11* : 113.

BHATNAGAR, S.K. *et al.*, (1981). Optimum age for measles immunization: Study of pre-and post-immunization level of HI antibody titres. *Ind. Pediatr., 18* : 625.

CHEN, S.T., (1979). Measles in Peninsular Malaysia. *Med. J. Malaysia, 34* : 18.

FAICH, G.A. *et al.*, (1981). Measles outbreak in Rhode Island. *Public Hlth., Rep., 96* : 264.

FAUST, H.S. and THOMPSON, F.E., (1983). Age at and time since vaccination during a measles outbreak in a rural community. *Amer. J. Dis. Child., 137* : 977.

HARRY, T.O. and OGUNMEKAN, D.A., (1981). Optimal age for vaccinating Nigerian children against measles. I. Neonatal antibody profile and subsequent susceptibility to measles. *Trop. Geogr. Med., 33* : 375.

HEYMANN, D.L. *et al.*, (1983). Measles Control in Yaounde : justification of a one dose, nine month minimum age vaccination policy in tropical Africa. *Lancet, 2* : 1470.

HULL, H.F. *et al.*, (1983). Measles mortality and vaccine efficacy in rural West Africa. *Lancet, 1* : 972.

JOHN, T.J., (1982). Optimum age for measles immunization. *Ind. Pediatr., 19* : 455.

JOHN, T.J. *et al.*, (1980). Epidemiology and prevention of measles in rural South India. *Indian J. Med. Res., 72* : 153.

KRUGMAN, S., (1977). Medical progress : Present status of measles and rubella immunization in the United States : A medical progress report. *J. Pediatr., 90* : 1.

LEE, Y.L. *et al.*, (1983). The optimal age for vaccination against measles in an Asiatic City, Taipei, Taiwan : Reduction of vaccine induced titre by residual transplacental antibody. *Int. J. Epidemiol., 12* : 340.

LO, E.K.O. and NAFISAH, A., (1983). Measles in Malaysia : A brief report of the 1981 anti-measles pilot study. *Rev. Infect. Dis., 5* : 405.

MOHAN, M. *et al.*, (1981). Optimum age of measles immunization - Maternal and transplacentally transmitted measles antibodies in infancy. *Ind. Pediatr., 18* : 631.

OGUNMEKAN, D.A. and HARRY, T.O., (1981). Optimal age for vaccinating Nigerian children against measles. II. Seroconversion to measles vaccine in different age groups. *Trop. Geogr. Med., 33* : 379.

ROLFE, M., (1982). Measles immunization in the Zambian Copperbelt : cause for concern. *Trans. Roy. Soc. Trop. Med. Hyg., 6* : 529.

SANTORO, R. *et al.*, (1984). Measles epidemiology in Italy. *Int. Epidemiol., Assoc., 13* : 201.

SEJDA, J., (1983). Control of measles in Czechoslovakia (CSSR). *Rev. Infect. Dis., 5* : 564.

SEVER, J.L., (1962). Application of a microtechnique to viral serological investigations. *J. Immunol., 88* : 320.

SHAOYUAN, W. *et al.*, (1982). An investigation of the causes of failures in measles vaccination in early infancy. *J. Biol. Stand., 10* : 197.

SHELTON, J.D. *et al.*, (1978). Measles vaccine efficacy : influence of age at vaccination

vs duration of time since vaccination. *Pediatrics, 62* : 961.

STEINHOFF, M.C. and JOHN, T.J., (1982). Appropriate strategy for immunization of children in India. IV: Measles and its control, priority number one. *Indian J. Pediat., 49* : 303.

VANPRAPAR, N. *et al.*, (1983). Disappearance of measles antibody in Thai infants after birth. *Southeast Asian J. Trop. Med. Pub. Hlth., 14* : 488.

WHO, (1977). Collaborative study by the Ministry of Health of Kenya and the World Health Organization. Measles immunity in the first year after birth and the optimum age for vaccination in Kenya children. *Bull. W.H.O., 55* : 21.

WHO, (1979). Expanded programme of immunization : Measles immunization. *Wkly. Epidem. Rec., 54* : 337.