

# OPTIMUM AGE FOR MEASLES IMMUNIZATION IN MALAYSIA

S. T. CHEN  
S. K. LAM

## 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 three to five 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 six 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 six to eight months of age; however the peak age for the acquisition of measles infection was from 12 months to five years of age.*

*Seroconversion rates following vaccination from nine months of age, ranged from 94 – 99%.*

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S. T. Chen, MBBS, MPH, MD

S. K. Lam, MSc, PhD  
Departments of Paediatrics and Medical Microbiology  
Faculty of Medicine  
University of Malaya  
59100 Kuala Lumpur, Malaysia

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*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 nine or ten months of age.*

*Based on the above results, it is concluded that the optimum age for measles immunization in Malaysia should be 11 months.*

## INTRODUCTION

Measles is a serious communicable disease of childhood causing high morbidity and mortality in developing countries.<sup>1-4</sup> 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,<sup>5</sup> 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 nine months of age.<sup>6-13</sup>

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 socio-economic background, living in and around Kuala Lumpur and Petaling Jaya. Two samples of population were selected, 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 of measles infection

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. 13 children with history of previous measles immunization were not included in the study.

### Study of seroconversion following measles immunization

All children, aged nine months to six 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<sub>50</sub>) 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.

### Method of Blood Titration: Haemagglutination-Inhibition (HI) Test

The HI test described by Sever<sup>14</sup> was used with some modifications.

Measles haemagglutinins (HA) were obtained from several commercial sources. Titration of the antigens was accomplished by mixing 25  $\mu$ l of diluted antigen with 25  $\mu$ l of a 0.5% of cynomolgous 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  $\mu$ l of sera were diluted with 60  $\mu$ l of phosphate-buffered saline and absorbed with 75  $\mu$ l 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  $\mu$ l 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  $\mu$ l 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

### Age-specific prevalence of measles infection

Table I shows that 54% of the newborns had passively acquired measles antibodies. The per-

**TABLE I**  
**FREQUENCY DISTRIBUTION OF CHILDREN BY MEASLES ANTIBODY TITRES AND AGE**

| Age                                   | Sample size | Subjects with titres $\geq 1:10$ |      | Geometric mean titre<br>(those with titres<br>$\geq 1:10$ ) |
|---------------------------------------|-------------|----------------------------------|------|-------------------------------------------------------------|
|                                       |             | Number                           | %    |                                                             |
| Newborn                               | 331         | 180                              | 54.4 | 24.1                                                        |
| < 3 months                            | 211         | 93                               | 44.1 | 19.7                                                        |
| 3 – 5 months                          | 188         | 49                               | 26.1 | 20.0                                                        |
| 6 – 8 months                          | 187         | 46                               | 25.0 | 32.2                                                        |
| 9 – 11 months                         | 164         | 42                               | 25.6 | 36.7                                                        |
| 12 – 17 months                        | 129         | 42                               | 32.6 | 68.3                                                        |
| 18 – 23 months                        | 69          | 30                               | 43.5 | 72.2                                                        |
| 2 years                               | 121         | 57                               | 47.1 | 60.1                                                        |
| 3 years                               | 127         | 65                               | 51.2 | 64.7                                                        |
| 4 years                               | 116         | 75                               | 64.7 | 71.5                                                        |
| 5 years                               | 100         | 79                               | 79.0 | 66.8                                                        |
| 6 years                               | 78          | 65                               | 83.3 | 59.4                                                        |
| 7 years                               | 60          | 53                               | 88.3 | 68.3                                                        |
| 8 years                               | 68          | 59                               | 86.8 | 62.3                                                        |
| 9 years                               | 55          | 50                               | 90.9 | 65.9                                                        |
| 10 years                              | 54          | 51                               | 94.4 | 50.9                                                        |
| 11 – 12 years                         | 84          | 74                               | 88.1 | 53.9                                                        |
| Adults (mothers<br>of newborn babies) | 331         | 265                              | 80.1 | 34.6                                                        |
| Adults (mothers<br>of children)       | 290         | 211                              | 72.8 | 27.6                                                        |

centage of children, with positive measles antibodies of 1:10 or greater, decreased with increasing age, being 44% below three months and 26% at three to five months of age. The percentage remained at about the same level being 25% at six to eight months and 26% at nine 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 three years, 79% at five years and 94% at ten years.

The geometric mean titre of measles antibodies was 24 at birth and 20 thereafter till five months

of age. From six months onwards there was an increase in the level, being 32 at six to eight months and 37 at nine to 11 months. From 12 months onwards there was a sharp increase in the level, being 68 at 12 to 17 months and 72 at 18 to 23 months of age, thereafter it remained at about the same level ranging from 59 to 71 till nine years of age when the level began to fall to 51 at ten years of age and 28 to 35 during childhood.

The results indicate that measles is common in Malaysia and a small number of children began to acquire natural measles infection from six to eight months of age. However, the peak age for

the acquisition of measles infection was from 12 months to five 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

Table II shows that there is 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 three 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

Of the 971 children, 86 (9%) had positive pre-immunization measles antibody titres of 1:10 or greater. Table II shows that in the 885 seronegative children, 94 — 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 nine or ten 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 nine or ten 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

Of the 971 children vaccinated, 398 (41%) developed some side reactions. Of these, 280 (70%) had one reaction and 118 (30%) had two 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

TABLE II  
CORRELATION BETWEEN MEASLES ANTIBODY TITRES IN BABY'S AND MOTHER'S BLOOD\*

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

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

\*\*Reciprocal of dilutions of titres.

**TABLE III**  
**SEROCONVERSION FOLLOWING MEASLES IMMUNIZATION AMONG THOSE WHO WERE INITIALLY SERONEGATIVE**

| Age at immunization<br>(months) | Number immunised | Children with<br>titre $\geq 10$ |      | Geometric<br>mean titre<br>(all cases) |
|---------------------------------|------------------|----------------------------------|------|----------------------------------------|
|                                 |                  | No.                              | %    |                                        |
| 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                                   |

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

### Prevalence of measles infection

This study shows that in Malaysia 94% of the children had acquired natural measles infection by ten 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<sup>5</sup> 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 six months of age.<sup>1</sup>

The age at which 50% of children showed serological evidence of natural measles infection was three 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,<sup>15-17</sup> one to two years in India<sup>18</sup> and 2.9 to 5.5 years in Italy.<sup>19</sup>

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

### Measles seroconversion and efficacy

The seroconversion rate after measles vaccination with one dose of live attenuated measles vaccine, given at nine months of age or older, was good (more than 90%) but better (more than

95%) when given at eleven months of age or older. This confirms the studies of others in developing countries (Table IV). The study in Kenya<sup>17</sup> shows good seroconversion even when vaccination was given at six and ten months of age. However, in the Kenyan study, the sample size was rather small. Studies in USA<sup>5</sup> 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 nine months of age compared with that when given at eleven 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.*,<sup>2</sup> found that in West Africa, the vaccine efficacy was 37% for children vaccinated at six to eight months of age, 85% at nine to 14 months and 90% after 15 months of age. In USA, Faich *et. al.*,<sup>21</sup> 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; Faust and Thompson<sup>22</sup> showed similar results. Shelton *et. al.*,<sup>23</sup> also found an increased 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<sup>24</sup> found a very high rate of vaccine failure among children vaccinated at six to nine months of age.

### Optimum age for measles immunization in Malaysia

In Malaysia, the number of children acquiring

TABLE IV  
SEROCONVERSION RATES (%) AFTER MEASLES IMMUNIZATION  
BY AGE AND PLACE OF STUDY

| Age at immunization (months) | Malaysia | India <sup>8</sup> | China <sup>20</sup> | Kenya <sup>17</sup> | USA <sup>5</sup> |
|------------------------------|----------|--------------------|---------------------|---------------------|------------------|
| 4                            | —        | —                  | —                   | —                   | —                |
| 5                            | —        | —                  | 64                  | 60.0                | —                |
| 6                            | —        | —                  | —                   | 90.3                | —                |
| 7                            | —        | 86                 | 84                  | 66.6                | —                |
| 8                            | —        | —                  | —                   | 100.0               | —                |
| 9                            | 95.3     | —                  | —                   | 92.5                | —                |
| 10                           | 93.7     | 94                 | 94                  | —                   | —                |
| 11                           | 97.8     | —                  | —                   | —                   | —                |
| 12                           | 98.9     | —                  | 96                  | 100.0               | 80 – 85          |
| 13                           | —        | —                  | —                   | —                   | —                |
| 14                           | —        | 98                 | —                   | —                   | —                |
| 15                           | 98.8     | —                  | —                   | —                   | —                |
| 16                           | —        | —                  | —                   | —                   | —                |
| 17                           | —        | —                  | —                   | —                   | —                |

> 95 (after 13 or 14 months)

natural measles infection from six to eight 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 the 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<sup>25</sup> in Czechoslovakia and Heymann *et al.*,<sup>7</sup> in Cameroon. Once this has occurred, the age at vaccination can be raised to twelve months of age or older.

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