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M. Takechi, MD,PhD; M. Matsuo; D. Butao, BSc; I.L. Zungu; I. Chakanika and J. Michongwe, Community Health Sciences Unit, Ministry of Health and Population, Private Bag 65, Lilongwe, Malawi.

Request for reprints to: Dr. Miho Takechi, P.O. Box 30321, JICA, Lilongwe3, Malawi.

MEASLES SERO-SURVEILLANCE DURING MASS IMMUNISATION CAMPAIGN IN MALAWI

M. TAKECHI, M. MATSUO, D. BUTAO, I.L. ZUNGU, I. CHAKANIKA and J. MICHONGWE

ABSTRACT

Objective: **To determine age-specific measles antibody prevalence and serological response to vaccination during the first mass campaign against measles in Malawi.**
Design: **Cross-sectional study using a questionnaire and a serological particle agglutination (PA) test.**
Setting: **Two health centres in Salima district, central Malawi during the national measles immunisation week, 1998.**
Participants: **Two hundred forty six under-five year old children.**
Results: **Seventy four per cent of enrolled children (95% confidence interval, 69-80%) were measles PA antibody positive at the vaccination. The antibody positive rate was 17.4% in children aged 8-12 months and gradually increased up to 90% by four years-old, while the age-specific geometric mean titers (GMTs) in 48-59 months-old group were significantly lower than those in 24-35 months-old group, suggesting antibody waning after previous vaccination (p=0.0047). Two hundred and thirty follow up specimens were obtained eight weeks after the vaccination. The sero-conversion rate was 100% in 58 children sero-negative at the vaccination and the GMTs in 172 children seropositive at the vaccination were significantly increased (p<0.001).**
Conclusion: **These results indicated that the first national measles immunisation campaign successfully immunised the enrolled children or gave a booster response of antibody levels. It was also confirmed that the PA test was easy to perform and most suitable for the field condition in developing countries.**

INTRODUCTION

The effect of Expanded Programme on Immunisation (EPI) against measles started in 1981 in Malawi has made an impact on reduction of measles incidence. According to the report of Malawi Polio Immunisation Campaign 1997 and the Knowledge, Attitudes and Practices in Health Survey 1996, a high vaccine coverage of 68-98% in infants had been sustained between 1992 and 1996 in Malawi. In 1996, 4120 measles cases were reported, which represented only about ten per cent of those reported in 1990 (EPI Programme, Malawi). The resurgence of measles, however, showed 10845 cases in 1997 despite the routine immunisation coverage of 87%. In the Salima district of central Malawi, the previous data in 1995 revealed that 30% of the patients with measles had previous vaccine histories, and the incidence in older children as well as in infants was high (unpublished report, T. Akiba, 1996).

Vaccine efficacy can be influenced by its potency, the quality of the cold chain and vaccinated infants/children's immunity. Acquisition and sustainability of immunity are dependent on age, sex and health condition of children. In countries which have achieved high vaccination coverage, outbreaks in school-aged children have taken place due to antibody waning(1,2). The reasons why older children developed measles in Malawi are considered to be due to antibody waning over time after vaccination as well as missed immunisation opportunities in the beginning of EPI.

In order to improve measles vaccine coverage in children and interrupt measles transmission, mass immunisation campaigns have been conducted in other countries and their effectiveness have been reported(3-5).

In Malawi the Ministry of Health and Population carried out the National Measles Immunisation Week (NMIW) campaign from sixth to tenth October in 1998 with a view to eliminating measles by the year 2003. The NMIW targeted every child of nine months to 15 years of age irrespective of vaccination histories or past infections.

A seroepidemiological survey was conducted to determine the age-specific measles antibody prevalence in two sites with different incidence of measles and examined serological response (seroconversion) after measles vaccination during the NMIW, comparing antibody titers before and after vaccination. A measles PA test was used for this serological survey. Miyamura *et al*(6), had reported that the PA test had higher sensitivities than a haemagglutination inhibition (HI) test in the detection of measles antibody and could therefore be useful in the analysis of low maternal antibody levels in young infants as well as waning antibody due to previous immunisation in older children (6).

MATERIALS AND METHODS

Study sites: The survey was carried in two sites, Chipoka and Kaundu health centre in Salima District of central Malawi; the former was a site with measles outbreaks affecting 345 patients in 1997 and the latter was a site where outbreaks occurred in 1995 but with only one patient reported in 1997. This study was approved by the National Health Sciences Research Committee in Malawi, Ministry of Health and Population.

Study population: Target population comprised all the children under five years old attending the NMIW on 6th-9th October 1998 for vaccination. Every child aged nine months to 15 years was supposed to be involved regardless of the past vaccination or infection. Informed consent was obtained from the parents/guardians. Thereafter we filled out questionnaires which sought demographic data and past histories of measles and vaccination were filled out.

Serology: The staff pricked a finger of each enrolled child and collected 100 μ l blood into a capillary tube. The blood was put into a test tube and centrifuged to obtain the sera. The particle agglutination (PA) method using a Serodia®-Measles kit (Fujirebio, Japan) was performed. A two fold serial dilution (25μl) of each serum specimen was made in a U-bottomed, 96 well-microplate, after which 25μl of the antigen-coated gelatin particles was added. Agglutination was read after two hours at room temperature and interpreted to each antibody titer up to 1:8192.

Follow up: The parents/guardians were encouraged to bring their children at the same health spots eight weeks after vaccination. The survey team inquired about the second questionnaire. If the parent/guardian accepted, a follow up specimen was collected from the child at the second visit.

Statistical analysis: Differences in antibody positive rates by age between Chipoka and Kaundu were assessed by Chi-square test. Log_2 geometric mean titres (GMTs) of measles PA-antibodies were calculated for children with positive titres. Antibody >1:8192 was assumed to be 1:16384 in this calculation. Differences in GMTs between Chipoka and Kaundu at the vaccination and eight weeks after the vaccination, as well as in sero-conversion, and between two age groups at the vaccination were assessed by Student's t-test. Two titres obtained at vaccination and eight weeks after vaccination from the same children were compared by the paired t-test. Sero-conversion rate wa calculated for sero-negative children at the time of vaccination.

RESULTS

Profiles of the participants: A total of 246 children under five years old were enrolled from 6th to 9th of October 1998; 127 in Chipoka and 119 in Kaundu. There was no significant difference in sex or age distribution of children in each site. As shown in Table 1, the number of children with previous vaccine histories by caretaker's recall was; 106 (84%) (95% confidence interval [CI], 78-90%) in Chipoka, and 94 (79%) (95% CI, 72-86%) in Kaundu. The number of children with a history of clinical measles was; 9 (7%) (95% CI, 3-11%) in Chipoka, and six (5%) (95% CI, 1-9%) in Kaundu.

Age-specific prevalence and titres of measles PA-antibody in Chipoka and Kaundu: All the specimens were examined using the PA test and interpreted the results on the same day or on the following day. The age-specific positive rate of PA-antibody is shown in Table 1. The overall seroprevalence of measles PA-antibody in Chipoka and Kaundu was 80% (95% CI, 73-87%) and 69% (95% CI, 61-77%), respectively. The positive rates increased by age and reached more than 90% at three years of age in Chipoka and four years of age in Kaundu, indicating that most of the children had acquired measles immunity by four years of age. The antibody positive rate in Chipoka was significantly higher than in Kaundu in 24-35 months-old group (χ^2 test, p=0.0357). No other age groups showed statistically significant results. The GMTs by age in seropositive children at the vaccination are shown in Table 2. There were no significant difference of GMTs in each age group between Chipoka and Kaundu. The GMTs of both areas were highest in the 24-35 months-old group and significantly lower in the 48-59 months-old group than in that group (Student's t-test, p=0.0047).

Table 1

Prevalence of age-specific measles PA-antibody and proportion of measles vaccine history by age in two health centres

Age in months	%positive rate of PA-antibody (Positive/enrolled cases)						% proportion of measles vaccination history (Number/enrolled)					
	Chipoka		Kaundu		Total		Chipoka		Kaundu		Total	
8-11	21	(3/14)	11	(1/9)	17	(4/23)	29	(4/14)	22	(2/9)	26	(6/23)
12-23	74	(29/39)	60	(25/42)	67	(54/81)	85	(33/39)	76	(32/42)	80	(65/81)
24-35	89	(31/35)[a]	67	(18/27)[a]	79	(49/62)	94	(33/35)	82	(22/27)	89	(55/62)
36-47	100	(21/21)	87	(20/23)	93	(41/44)	95	(20/21)	91	(21/23)	93	(41/44)
48-59	94	(17/18)	100	(18/18)	97	(35/36)	89	(16/18)	94	(17/18)	92	(33/36)
Average	80	(101/127)	69	(82/119)	74	(183/246)	84	(106/127)	79	(94/119)	81	(22/246)

[a] p = 0.036 (χ^2 *test*)

Table 2

Geometric mean titres by age in children with positive antibody at the vaccination

Log2 geometric mean titer (SD) [number of children]				
8-11 months	12-23 months	24-35 months	36-47 months	48-59 months
9.8 (3.1) [4]	9.8 (2.2) [54]	10.8 (2.0) [49][a]	10.3 (2.5) [41]	9.4 (2.5) [35][a]

[a]p = 0.0047 (Student's *t* test)

Table 3

Measles PA-antibodies according to history of previous vaccination and clinical measles

	Ab-positive rate	No. of Ab-positives (past history of measles)	No. of Ab-negatives (past history of measles)
Chipoka			
Vaccination history (+)	91%	96 (9)	10 (0)
Vaccination history (-)	24%	5 (0)	16 (0)
Kaundu			
Vaccination history (+)	83%	76 (4)	16[a] (1)
Vaccination history (-)	24%	6 (1)	19 (0)
Total			
Vaccination history (+)	87%	172 (13)	26 (1)
Vaccination history (-)	24%	11 (1)	35 (0)

[a]Two children vaccinated just a week before this survey were omitted.
Ab; measles PA-antibody.

Measles PA-antibodies according to the history of measles vaccination and clinical measles: Measles PA-antibody positive rate in children with the vaccine history was 91% (95% CI, 86-96%) in Chipoka and 83% (95% CI, 75-91%) in Kaundu irrespective of measles attack history, (Table 3). Measles PA-antibody positive rate in children with vaccination history but without a history of measles attack was 90% (95%CI, 84-96%) in Chipoka and 83% (95% CI, 75-91%) in Kaundu.

Ten children showed positive antibody although they did not have a history of vaccination or clinical infection. There were two in the 0 year-old group, four in the 1 year-old group, one in the two-year old group, two in the three year old group and one in the four year-old group.

Table 4

Geometric mean antibody titres at vaccination and eight weeks after vaccination in two health centres

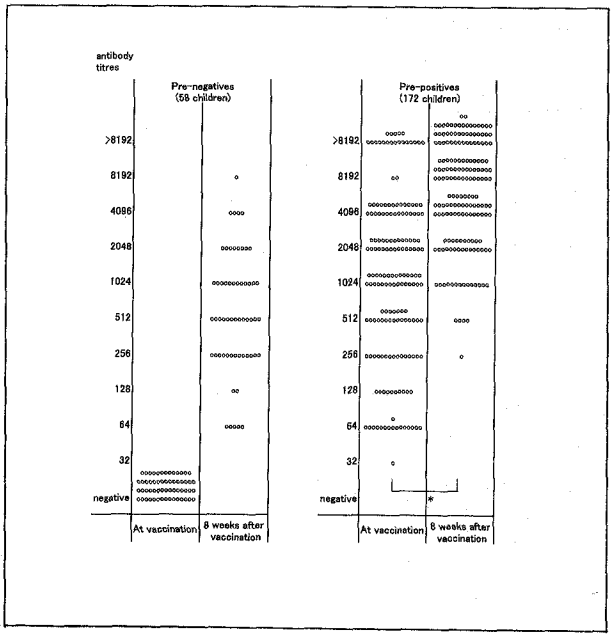
	Log2 geometric mean titre (SD) [number of children]	
	At vaccination	Eight weeks after vaccination
Chipoka	10.1 (2.4) [101][ab]	12.4 (1.3) [94][b]
Kaundu	10.2 (2.2) [82][a]	12.4 (1.5) [78]

[a]p=0.770 (Student's t test) [b]p<0.001 (Student's t test)

Figure 1

Scatter plot of measles PA-antibody titres for the enrolled children at vaccination and after eight weeks, Salima, 1998. Each dot indicates data of each child. 'Pre-negatives' is used to denote the children with negative antibody at vaccination and 'Pre-poitives' is used to denote the children with positive antibody at vaccination.

*Difference was statistically significant by the paired t test (p<0.001)



In Kaundu a sero-negative child was found but who had previouly been vaccinated and also had measles. Her caretaker did not have her health card and could not remember the exact date of her vaccination, hence confirmation of measles was difficult because of the uncertain information. In this survey we assured sero-conversion in her sera, indicating that she acquired immunity as a result of vaccination in the NMIW.

Results of follow up and sero-conversion rates eight weeks after vaccination: A follow up survey was conducted eight weeks after the NMIW. Out of 246 children enrolled, 230 (93.5%) had follow up specimens taken. The rest were lost to follow up. One died due to diarrhoea, fourteen moved to other villages or districts and one refused to have blood taken due to severe anaemia.

Post-vaccination measles sero-prevalence is shown in Figure 1. All of the 58 children sero-negative at the time of vaccination (pre-negatives) showed sero-conversion. The vaccination in sero-positive children at the time of vaccination (pre-positives) increased their antibody titres after eight weeks significantly (paired t-test, $p<0.001$). As shown in Table 4, GMTs were not statistically different between Chipoka and Kaundu both before and after the vaccination, but those were significantly increased after eight weeks in both areas (Student's t-test, $p<0.001$).

DISCUSSION

Age-specific measles antibody prevalence and titers were shown before and after vaccination using a PA test, carrying out the survey during the NMIW. The survey enrolled the children who were brought to the health centres and the NMIW sites during the mass vaccination campaign. Therefore, our study population may not include those who did not have access to the NMIW sites, or were too sick to go out, or whose parents were not well informed or motivated in terms of the NMIW, hence it may not be representative enough. This was a major limitation of the study and should be taken into account in assessing the results.

The antibody positive rate in enrolled children increased by age, while GMTs of the antibody diminished in 48-59 months age group after the peak in 24-35 months age, suggesting that immunity waned after measles vaccination. Several studies have indicated that older children with waning immunity could be involved in measles epidemics, especially in countries achieving high vaccination coverage(1,2). Our results showed that the vaccination during this mass campaign gave a booster response in sero-positive children at vaccination. However, little is known about how long the protective antibody level would last after the booster response following re-vaccination under the field conditions in Malawi. Further serological studies are necessary to examine the effect of primary vaccination and re-vaccination.

Measles antibody positive rates in children aged 8-12 months old and 12-23 months old were 17% and 67% respectively, while the rates of those with a history of measles vaccination were 26% and 80%. This discrepancy between antibody acquisition and vaccination history is thought to be due to immunisation failure caused by the less potent vaccines which were damaged in the cold chain and/or insufficient immune response in infants, who still had interfering maternal antibody at the vaccination(7,8). Malnutrition or HIV may also have affected these results. Thirty per cent of the patients with measles were reported to have had vaccination previously. This suggests that substantial vaccines were not potent enough, probably because of the breakdown of the cold chain. Our observation that 15 (23%) of 65 children aged 12-23 months who were given vaccine in infancy were sero-negative may coincide this speculation.

Comparing with previously reported vaccine coverage of 68-90% in <12-month old children, the rate of vaccine history of 26% in the same age group was shown in this study. It may be attributed to parents/guardians bringing children who had missed vaccination before the NMIW. Such an accurate level of the vaccine coverage is considered to relate directly to the incidence of measles(9). In order to interrupt transmission of measles, coverage >95% is recommended(10,11). Moreover, it is desirable to immunise as early as possible, since measles fatality and severe complications are highest in younger children(12).

The difference of PA-antibody positive rates in 24-35 months-old groups in the two areas was statistically significant (χ^2 test, $p=0.0357$). This may be due to measles outbreak in Chipoka in 1997. Wittle *et al*(13) studied the effect of measles epidemics on antibody titers in exposed children and showed that 45% of vaccinated children had a four-fold or greater rise in measles antibody titers without clinical symptoms and that its increase lasted for at least six months. In this study the booster effect of epidemics on antibody titers in Chipoka was not certain.

Our results showed that the sero-conversion rate following the NMIW was 100%. In addition, we found that antibody titers increased significantly in pre-antibody positive children after vaccination. Oliveira *et al*(4) showed a marked sero-positive rate, in a sero-epidemiological survey three months after a mass vaccination campaign in Brazil. It was 96.3% using HI and PRN with EIA in one to four years older children. This is in general agreement with our results. We confirmed that the sero-conversion rate in the first mass campaign of Malawi was satisfactory. It suggests that the cold chain, including vaccine storage and delivery was successfully maintained during the NMIW.

Mass campaign is effective to reach children not covered by the routine health services and to improve vaccine coverage nationwide. Most countries in the Americas have conducted measles vaccination mass campaigns, resulting in dramatically reduced measles incidence (6.5 per 100,000) among the six WHO regions, while the highest incidence (47.5 per 100.000) was reported in Africa(3). After the impact of mass campaign was shown in Brazil; and South Africa, however, measles outbreaks recurred within a few years(3,5,14,15). Measles

cases will be imported easily across the Malawian border. In order to sustain the impact of mass immunisation and prevent outbreaks, EPI activities for routine immunisation should be further strengthened.

Malawi Ministry of Health and Population aims to eliminate measles by 2003. Improving measles surveillance system accompanied with epidemiological laboratory investigations is essential to achieve this goal(11,16,17). Sero-epidemiological studies can help to determine the most effective immunisation strategy for measles control in Malawi. We confirmed that the PA test is useful in assessing a large number of specimens under field conditions. Miyamura *et al*(6) reported that the PA test is more sensitive than the HI test and is also as sensitive and specific as the neutralisation test, detecting not only anti-haemagglutinin antibody but also anti-fusion protein antibody, both of which are involved in neutralising measles virus. The PA test is considered to be suitable for quantitative sero-epidemiological studies in developing countries.

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