Brief Report

Two Doses of Measles Vaccine: Are Some States in India Ready for It?

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Summary

We present the results of two surveys of measles outbreaks near Vellore, which perhaps supports the cause for introduction of a second dose of measles vaccine. Survey one had 590 under 10-year olds. The attack rate was 15.1, 11.7 and 5.7% in the unimmunized, among those vaccinated at 6 months and at 9 months, respectively. The overall vaccine efficacy (VE) was 28% if vaccinated at 6 months and 66% if at 9 months. Second survey had 1702 children and adolescents. There were 59 cases of measles of which 49 were over 5 years of age, the mean age being 8.8 years. The VE was 66% for children up to 6 years and 48.4% for those aged 7–15. The data suggests that measles vaccine is better given at 9 months. The low VE in school age children could be improved by introducing a second dose of measles vaccine.

Introduction

Measles can be severe and is most frequently complicated by diarrhoea, middle ear infection or bronchopneumonia and in one in 1000 cases, can cause encephalitis [1].

The goal of the World Health Organization’s global measles strategic plan was to reduce by half the estimated number of measles deaths by 2005 compared with 1999 estimates [2]. The target goal set by the Indian Ministry of Health and Family Welfare is to reduce measles mortality by 66% by 2010 compared with 2000 estimates [3].

Measles outbreaks continue to occur even in well-vaccinated populations when a single-dose measles vaccination strategy is employed. In December 2004, an outbreak of measles was reported in the Cuddalore district of Tamil Nadu where the estimated measles vaccination coverage was ~96% [4]. A substantial measles outbreak was also reported during 1999–2000 in Sri Lanka, where single-dose measles vaccination coverage since 1996 has been >90%. Of the cases, 54% in this outbreak were over 15 years of age [5]. The state of Tamil Nadu has set three objectives for its measles control programme: (i) measles vaccination coverage of ≥95% through routine vaccination of children aged 9–12 months, (ii) ring vaccination after occurrence of measles cases and (iii) treatment of ill persons to prevent complications.

Various methods of measles control have been utilized in different areas with varying degrees of success. Some countries used high titre vaccines, and some areas used measles vaccine after 6 months of age followed by second dose after 12 months of age [6]. For most developing countries, it has been thought that it is premature to adopt a routine two-dose schedule as universally high coverage of the first dose should be a higher priority [6].

When measles vaccine was introduced under the Expanded Programme on Immunization (EPI), in countries in which measles mortality was high, the aim was to reduce infant mortality, the incidence and case fatality being highest in the second 6 months of life. In nations where the mortality due to measles was low, a two dose policy was adopted, with the first...
dose given between 12 and 19 months and the second dose given at school entry around 5 years of age [7].

The Department of Community Health at Christian Medical College (CMC), Vellore, India, had been offering the standard titre measles vaccine from 6 months of age from 1986. A study by Job et al. [7] in 1984 had shown that by 6 months of age about 90% of children in the area did not have detectable maternal antibody. The study also showed that seroconversion was good with a single dose of measles vaccine, with seroconversion being 87% in those aged 6–8 months, 97% in those aged 9–11 months and 100% between 12 and 15 months [8]. There was no significant difference in risk of death between infants vaccinated between 6 and 8 months and those vaccinated between 9 and 11 months [9].

However, later studies done by the group have shown that 13% of children among those vaccinated between 9 and 11 months and 67% of children vaccinated before 9 months did not show optimum levels of measles antibodies at 5 years of age [10].

Clinical measles might result among school going children consequent to primary vaccine failure, the presence of cohorts of unvaccinated children or because of the immunity waning with time. These cases could generate secondary cases among susceptible younger siblings with consequent morbidity and mortality in this vulnerable group [11]. Two doses of measles vaccine by improving individual protection and herd immunity may prevent the cases in younger siblings, as well as the later vaccine failures [7]. A two—dose measles vaccination programme is therefore an essential component of preventive health care in developing, as well as developed countries.

Questions remain. Are parts of India ready for the second dose of measles schedule? Would a second dose of measles vaccine successfully protect the children who do not currently have protective levels of IgG after one dose? At what age would the administration of the second dose of measles vaccine be appropriate? Should it be given as part of the MMR vaccine?

We report the results of two surveys of outbreaks that occurred in the area served by Christian Medical College, Vellore, which we believe supports the cause for introduction of a second dose of measles vaccine in the routine immunization programme.

### Setting and Methods

The Community Health Department of the Christian Medical College, Vellore, India has established an integrated Community Health and Development (CHAD) programme in Kaniyambadi block, details reported elsewhere [12]. The measles vaccine coverage among under five children in this block was 68% in 1985, 79% in 1988 and over 90% since 1990.

There have been two outbreaks that have been investigated over time. Cross-sectional surveys were conducted in areas in which measles cases were occurring (Table 1).

The methodology adopted in both outbreaks was the same. Notification of outbreaks, either by the CHAD team or by medical officers at the Primary Health Centres prompted the surveys. Experienced field staff conducted the initial survey, identifying households, which had a child with history of fever and non-vesicular exanthematous rash. These were screened by one of four physicians (P.C., S.J., S.P. and S.S.), under the supervision of a paediatrician (A.B.). Subjects were considered as being immunized if they had completed 3 weeks after receiving the dose of measles vaccine. Blood was drawn on five randomly chosen cases of exanthematous fever and tested for measles IgM antibody using the Serion IgM Elisa kit. All cases were followed up for 1 month to identify complications. Data entry and analysis was done using Epiinfo Version 6.03 and SPSS Version 9.

### Table 1

**Outbreaks of measles in Kaniyambadi block**

<table>
<thead>
<tr>
<th>Year of outbreak</th>
<th>Timing of vaccination</th>
<th>Number of cases</th>
<th>Mean attack rate (%)</th>
<th>Maximum attack rate</th>
<th>Case fatality rate (%)</th>
<th>VE rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>a) No vaccine</td>
<td>70/590 under 10 years</td>
<td>a) 15.1</td>
<td>24% at 7 years</td>
<td>2.9 Overall: 6–8 months = 21% &gt;8 months = 62%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b) 6–8 months = 395/575</td>
<td></td>
<td>b) 11.7</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>c) At or after 9 months = 69/575</td>
<td></td>
<td>c) 5.7</td>
<td></td>
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</tr>
<tr>
<td>2006</td>
<td>After 9 months</td>
<td>59/1702 under 19 years</td>
<td>3.4</td>
<td>9.1% at 9–11 years</td>
<td>0 Overall: 43.2% 1–6 years = 66% 7–15 years = 48.8%</td>
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254 Journal of Tropical Pediatrics Vol. 55, No. 4
Vaccine efficacy (VE) of the measles vaccine was calculated using the formula:

\[
VE = \frac{\text{Attack rate among unvaccinated} - \text{attack rate among vaccinated}}{\text{Attack rate among unvaccinated}}
\]

An outbreak in 1979, prior to the introduction of the measles vaccine showed a mean attack rate of 44% with the highest attack rate of 73.5% in the age-group 2–3 years. There was a case fatality rate due to measles of 7.2% [13].

Results

1999: Outbreak I
In this survey, 590 children under 10 years were included. Fifteen children, who were under 6 months of age, were excluded as they had no cases of fever with rash. Of the 575 children, 111 were unvaccinated, 395 vaccinated at 6 and 69 at 9 months. Total vaccine coverage was 79%. All the five blood specimens sent for serology were positive for measles IgM antibody. Of the 70 cases, 13 (18.6%) had diarrhea, 6 (8.6%) pneumonia and 3 (4.3%) otitis media. Two children, aged 6 and 7 years, respectively, died; both were vaccinated at 6–8 months of age and died of pneumonia for which health care was not accessed.

The attack rate was 15.1% among the unimmunized and 11.7% among those vaccinated at 6–8 months. Those who were vaccinated at or after 9 months had an attack rate of 5.7%. Among those vaccinated at or after 9 months the attack rate was 0% in the first 2 years, 10% by 5–6 years of age and 7% among the children over 7 years. The VE was 28% for those vaccinated at 6 months and 66% for those vaccinated at 9 months. In children under the age of 5 years the VE was 69% in those vaccinated at 6–8 months and 82% in those vaccinated at 9 months. Among the children aged 5 years or more, the VE in those vaccinated at 6–8 months was 0% compared with 52% in those vaccinated after 8 months (Table 1).

2006: Outbreak II
A total of 1702 children and adolescents were included in the survey. Fifty-nine children developed measles of which 49 children were over the age of 5 years. Of the 1231 under 15-year-old children, 81% were immunized at or beyond 9 months of age. The mean and median age of the cases was 8.8 and 9 years, respectively. The highest attack rate of 9.1% was among the children between 9 and 11 years. The overall vaccine efficiency for 15- to 19-year olds was 43.2%. The VE was 66% for children up to 6 years and 48.4% for 7- to 15-year old children. There were no deaths attributed to measles in this outbreak.

Discussion
In 1979, prior to the introduction of measles vaccine, the morbidity and mortality due to measles was considerable, with an attack rate of 43% and a case fatality rate of 7.2% [13]. The success of the measles vaccine was subsequently apparent as the number of cases dropped and the mortality due to the disease dropped [14].

Based on the findings of Job et al. [7], the Department of Community Health adopted the younger age of 6 months for the timing of the measles vaccine. The age at immunization was changed to 9 months later.

There was a ‘honey-moon period’ which is recognized with measles, when the outbreaks of measles declined [15]. In 1999 was the first documented outbreak in the community, which showed that the VE was higher in those who had received the vaccine at a relatively older age, at or after 9 months of life. The protection was nil for those vaccinated between 6 and 8 months, and 50% protection in those vaccinated after 9 months. Regardless of the timing of the vaccination, the VE for those children who were over 5 years of age at the time of the outbreak was very low. This shows that the immunity of a single dose of vaccine wanes with time.

In both the outbreaks, the attack rate was higher in those over 5 years of age, regardless of the immunization status of the individual, in an area where the vaccine coverage was 81%. The attack rate was lower in those who were immunized. The reasons for the outbreak could be the presence of cohorts of unvaccinated children, primary vaccine failure and also waning vaccine immunity with time; the VE being higher in those who were immunized at or after 9 months. The first dose should, therefore, be given at or after 9 months of age.

It has been considered premature to adopt a routine two-dose schedule for measles vaccine in the National schedule in India. Priority in resource allocation should be given to achieving universally high coverage rates with the first dose and this has been achieved in states like Tamil Nadu where the coverage is 98%, sufficient for herd immunity to be apparent.

We believe that our data suggests that a single dose of measles vaccine could result in outbreaks involving schooling age children. High measles transmission in children of school going age could result in secondary cases among susceptible younger siblings with consequent morbidity and mortality in this vulnerable group [11]. We, therefore, feel that a second dose of measles vaccine is required to be included in the National schedule in India.

At what age should the second dose of the vaccine be given? Typically, the first dose of a late two-dose schedule is given at 9–15 months of age, and the second dose at school entry. There are other
considerations that would come into play in the timing of the second dose in India.

For India, any changes in the immunization schedule should ideally be done with minimal change in the logistics of the existing programme. This could be effected by giving the second dose of measles vaccine as part of the MMR vaccine. This would result in a net reduction of costs of the measles vaccine and would provide protection against the considerable burden of disease due to congenital rubella syndrome, the incidence of which is high. The MMR vaccine could be timed to coincide with the first DPT booster at 18 months and not cause any change in the logistics of the existing immunization programme.

What is Already Known

- A second dose of measles vaccine is used in several countries.
- A second dose was considered premature for India as initial measles vaccine coverage should be high before the introduction of a second dose.

What This Paper Adds

- Documentation of better vaccine efficacy if measles vaccine given at or after 9 months.
- Occurrence of outbreaks even in populations with high vaccine coverage, as in Tamil Nadu.
- Documented lower vaccine efficacy after 5 years of age, resulting in outbreaks in school age children.
- Vaccine efficacy over 5 years of age is low with one dose of measles vaccine.
- Outbreaks can occur in school age children, increasing the risk for younger infants.

References