

ORIGINAL ARTICLE

Early Protection Against Measles Infection in Children Immunized with DPT-measles Vaccine at the Age of 4 Months

by

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Abstract

A study on early immunization with DPT-measles vaccine at the age of 4 months, was carried out during 1990 - 1991 on 348 babies at the Health Centre of Surabaya regency. Three hundred and fourty eight babies were served as control.

The results of the study reported here were : (a) By giving a mixture of DPT and measles at an early age (4 months of age) the coverage of measles immunization could be increased to 24% - 27% . (b) Twenty two percents of measles cases could be prevented. (c) The geometric mean titer using hemagglutination inhibition test of the babies who got a mixture DPT-measles vaccination at an early age was significantly higher than that of the GMT HI test of babies who got measles vaccination at the age of 9 months (z test, $p < 0,05$).

The result of analysis of data showed that an early immunization program using a mixture of DPT-measles could protect babies under 9 months and thus prevent them from measles infection.

Introduction

In many developing countries, general resistance of infants living in the overcrowded area is very poor. Exposure to infections due to early loss of maternal antibody will hazard infants of 4-12 months old.

Measles which commonly occurs during that age contributes to the important cause of death among them.

In Indonesia measles is one of the ten leading causes of child mortality and morbidity [1], where the majority of infants become susceptible shortly after the age of 4 months as reported by Yusak [2]. Moreover the case fatality rate of measles is the highest at young age, especially between 4-12 months.

In Indonesia immunization against measles has been launched since 1981; however until now the coverage is still very low subsequently offering a low protection to the high risk children.

Outbreaks not infrequently occurred

in the isolated areas of East Timor, Jambi, West and South Sumatra, and Bengkulu, leading to a high mortality rate [3].

The WHO has recommended that in Indonesia one dose of measles vaccine should be given to infants at the age of 9 months.

This strategy leaves open a window for a high risk of measles death between the age of 4 and 9 months [4]. Report of the proportion of measles cases under 9 months in Surabaya area, Indonesia was 22%.

Studies on Edmonston-Zagreb measles vaccine to immunize children earlier in South Afrika, and also biochemical development of adjuvant, informed us that adjuvant could enhance the immunogenic vaccine. Owing to the factors mentioned, during 1990 - 1991 the authors carried out a study on a DPT-measles vaccine to immunize 348 babies at the age 4 months at the regency of Surabaya-Indonesia.

Materials and Methods

Study population and procedure outlined

The study was conducted in Surabaya, East Java, Indonesia from March 1, 1990, to September 30, 1991; all of the 696 children who were randomly found at the 45 Health Centers of the regency at Surabaya, were divided into two groups: first, for the study, a mixture of measles DPT vaccine were given to 4-month old babies; and second, the control group received vaccination in accordance to the national program (measles vaccine given at age 9 months).

During one year they were under continuous follow up study for the immune response of the sequence of vaccination effects, beside the measles morbidity.

The diagnosis of measles was based largely on recognition of the typical rash, the "atypical" desquamating violaceous rash which was not in common was excluded.

Serologic support for the presumptive

diagnosis of measles was obtained by taking a 1.5 ml of venous blood sample of the suspected cases, stored at -20°C - -25°C until assayed by the hemagglutination inhibition (HI) method.

Vaccines

The study used: (1) measles vaccine, type live further attenuated (Schwarz strain) containing not less than 10^5 TCID₅₀ per dose of 0.5 ml for subcutaneous injection, formed as a freeze dried vial of 10 doses and a 5 ml dilution liquid. (2) DPT vaccine containing diphtheria toxoid 40 Lf, tetanus toxoid 15 Lf, pertussis bacilli 24 million, aluminum phosphate 3 mg and merthiolate 0.1 mg, formed as a colloid solution, in a 5 ml vial for 10 doses.

All vaccines were produced by the Pasteur Institute in Bandung. A mixture of measles and DPT vaccines were obtained by mixing a solution of 5 ml DPT 10

solve a vial of 10 doses freeze dried measles vaccine, and immediately injected by a deep subcutaneous route at site 1/3 antero lateral of the thigh. This mixture of measles-DPT vaccine should not be used after more than one hour.

Serology

After an informed consent was signed by the mother, a pre vaccination venous blood specimen was obtained and a 0.5 ml mixture of measles-DPT was administered to the study group by a nurse who did not know the status of the patient. A post vaccination venous blood specimen was obtained sequently after 1,5,6 and 11 months. Paired serum samples were stored and simultaneously examined for measles antibody by the standard hemagglutination inhibition test (HI).

Technically to measure measles level

HI antibody we employed a method using a serial of two fold serum dilution starting at 1 : 4 for measles and the results were expressed as the reciprocal of the highest serum dilution.

Complete inhibition of hemagglutination antibody titer were measured at the laboratory of the Ministry of Health Republic Indonesia, Jakarta.

In the control group, blood specimens were obtained at the ages of 4, 5, 9, 10, and 15 months. Blood specimens taken from the control group of 9 months old were done prior to measles vaccination.

Statistical method

The data of morbidity and coverage of immunization were analysed using the chi-square test. The data of serological findings were analysed using z test.

Results

Among 696 babies enrolled in this study, only 307 babies as study group and 301 babies as control group met criteria for efficacy analysis.

Along with the study (by September 30, 1991), there were 95 new measles cases, 15 were included in the study group and 80 in the control group (Table I).

In the morbidity table analysis, the babies who received a mixture of measles-DPT vaccine at 4 months, had a significant lower morbidity compared to the control group. This means, that the young baby could be protected by early immunization with a mixture of DPT-measles vaccine.

Midterm evaluation showed that the control group had a higher morbidity than study group; with a significant difference between the two groups (Table II).

Serology

The result of serologic tests as listed in Table III showed that :

- There is no significant difference in measles antibody detected by hemagglutination inhibition test in cases of 4 months old in both groups, meaning that before the experimental study was done, the HI antibody titer to measles of both groups were the same.
- The titer of HI measles antibody at the ages of 5 and 9 months in both groups showed a significant difference; a higher level of antibody titer was noted in the study group, leaving a message that immune response to a mixture of measles-DPT vaccine is higher than that the maternal antibody of the latter. Thus early immunization would give a protective level of HI antibody titer in babies since 5 month old.
- The hemagglutination inhibition antibody titer to measles at 10 and 15 months old showed a higher level in the study group with a significant difference meaning that the serologic response of the study group is better than that of the control group.

Table I. Distribution measles cases of study group and control group evaluated during March 1, 1990-September 30, 1991

Measles infection	Study group	Control group
(+)	15	80
(-)	292	221
Chi square 52,61 p = 000		

Table II. Distribution of measles cases of study group and control group in mid-term evaluation - during March 1, 1990 - September 20, 1992

Measles infection	Study group	Control group
(+)	12	65
(-)	294	236
Chi square 41,44 p = 000		

Immunization coverage

Based on this experience the coverage is higher in the early immunized infants of 4 month old compared to that of the 9

months or older who had immunization (Figure 1) meaning that young babies get more attents from the mother than older one.

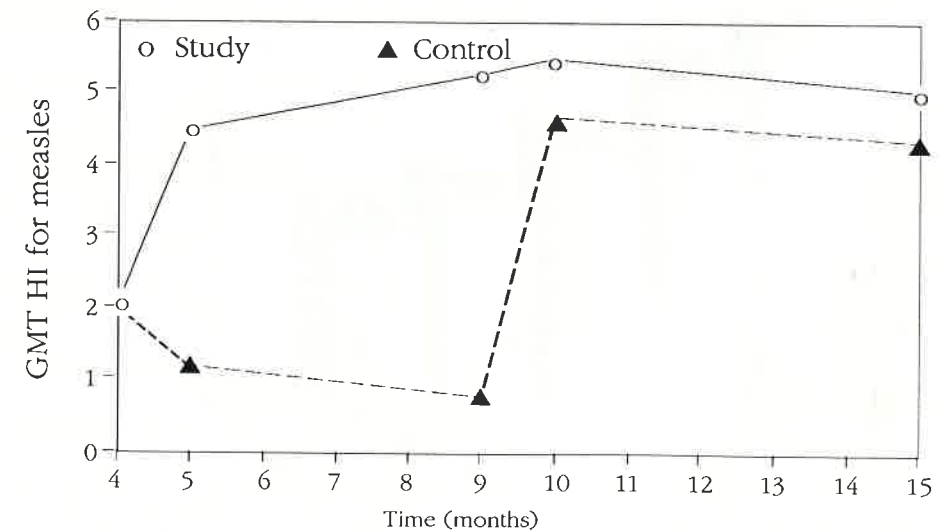


Figure 1. Hemagglutination inhibition antibody to measles at 4,5,9,10 and 15 months old (study and control groups)

Table III. Hemagglutination inhibition antibody to measles at 4, 5, 9, 10 and 15 months old (study and control groups)

Age (months)	Study group	Control group	
4	n ₁ = 192 x ₁ = 1.938 s ₁ = 1.432	n ₂ = 149 x ₂ = 1.966 s ₂ = 1.94	z = 0.153, p > 0.05
5	n ₁ = 192 x ₁ = 4.750 s ₁ = 1.018	n ₂ = 149 x ₂ = 1.333 s ₂ = 1.638	z = 23.61, p < 0.05
9	n ₁ = 192 x ₁ = 5.109 s ₁ = 0.727	n ₂ = 149 x ₂ = 0.953 s ₂ = 0.436	z = 58.483, p < 0.05
10	n ₁ = 192 x ₁ = 5.109 s ₁ = 0.754	n ₂ = 149 x ₂ = 4.953 s ₂ = 0.007	z = 2.212, p < 0.05
15	n ₁ = 192 x ₁ = 4.917 s ₁ = 0.069	n ₂ = 149 x ₂ = 4.652 s ₂ = 0.391	z = 9.212, p < 0.05

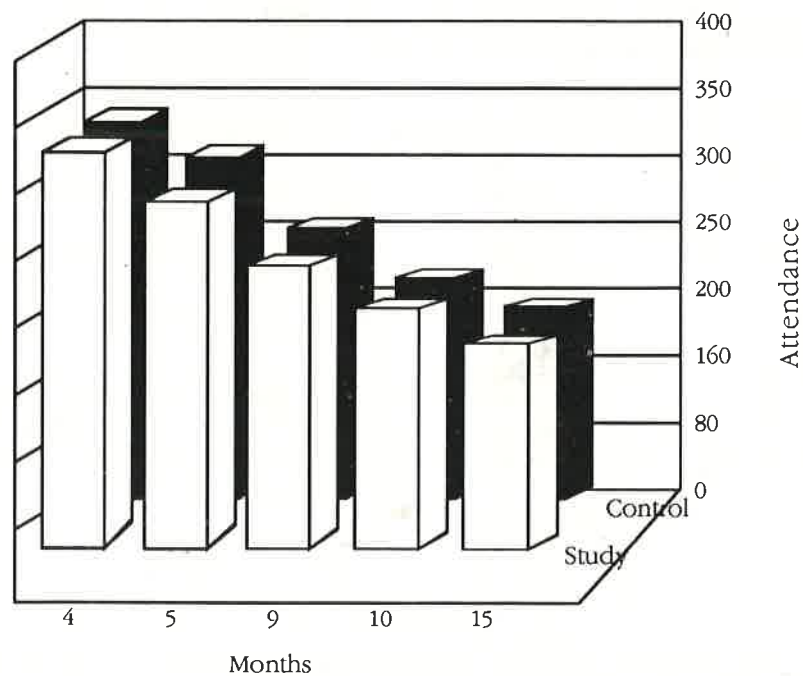


Figure 2. Study and control group attendance at ages 4, 5, 9, 10 and 15 months

Discussion

In recent years, in the clinical laboratory, to detect measles antibodies generally employs one of four methods: hemagglutination inhibition (HI), enzyme immuno assay (EIA), complement fixation (CF) and ELISA.

To determine the immune status of children observed, HI test (which was done in the Ministry of Health, Jakarta) was chosen for its efficacy, efficiency and specificity.

The result of this study suggested that measles-DPT mixture vaccine is of importance in achieving a good serological response to measles vaccine in children of 4 months of age (Table III and Figure 1).

In our experience 346 babies of four months old were taking part in the study and followed up for one year. The result showed that in babies who were immunized with a mixture of measles-DPT vaccine at 4 months old, the levels of antibody titer measured after one month, five months, six months and 11 months were good.

These good results of immune response might be due to an immunogenic character of the vaccine derived by mixing measles and DPT vaccines in a bottle or a vial. Immunization response could be explained by three kinds of mechanism of the adjuvant, by means of DPT vaccine and its solvent.

According to the literature, there are three kinds of mechanism of adjuvant known in the process of immunization: first a slow release of antigen adjuvant mimicking multiple injections of antigen and stimulating a secondary type of antibody [5].

Second, adjuvant causes an accumulation of mononuclear cells, especially macrophages at the site of injection as a granulomatous response. The macrophage releases a monokine interleukin 1 (Il-1) which stimulates the T helper cell to secrete the lymphokine interleukine 2 (Il-2), and T cell growth factor. The consequence of the serial action of Il-1 or Il-

2 is the clonal expansion of T helper cell.

Third, adjuvant effect on B lymphocytes, will induce the clonal expansion of T helper cells followed by their interaction with B cells which in turn secrete antibody. Result of both T and B cells stronger potential action are of the adjuvant influence. Beside the effect of the adjuvant, the higher level of antibody titer which had been found in the study, could be stimulated by killed virus where the immune response is as if the babies got immunization with killed vaccine.

A preliminary study using tissue culture showed that less than 10^2 viruses are still alive one hour after mixing measles and DPT vaccines, so these viruses could maintain a higher level of titer of HI antibody.

As mentioned above, all mechanisms work together to make it successful. Supported by the epidemiologic surveillance of measles cases in the study and control group this trial showed that, measles antibody in the study group was a significantly lower than in the control group; it means that babies under 15 months especially below 9 months (22%) could be protected by immunization with measles-DPT vaccine at the early age (4 months).

In our early program study (4 months old baby) along with mother giving more attention to their babies the coverage were higher than the later program (9 months), therefore this program might be an effective and efficient method of immunization in developing countries.

Some factors which could influence the immunization response is the tending to decrease nutritional state of the babies, as a warning that the children should be revaccinated.

In this study the authors did not found any serious side effect; the side effect found was similar to that of post DPT vaccination.

Summary

By measles-DPT mixture vaccine using to immunize babies at the age of four months, compared with immunization according to the National EPI Program scheme as control, the result showed that :

1. The immunization coverage increases significantly by 95-96 %
2. Prevention against measles occurred in

22% of babies before the age of nine months.

3. GMT HI for measles in the study group is significantly higher compared to the control group.
4. GMT HI in malnourished children had not reach the protected level and this needs further study.

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