

IMMUNE RESPONSES TO MEASLES IMMUNIZATION AND THE IMPACTS ON HIV-INFECTED CHILDREN

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Abstract. This prospective cohort study was conducted to determine the seroconversion rate and the pattern of antibody response to measles vaccine administered at age 9 months in HIV infected and non-infected children born to HIV-1 seropositive mothers. Thirty children born to HIV-1 seropositive mothers and 3 born to HIV-1 seronegative mothers were recruited. One single dose of Schwarz strain of measles virus vaccine (Rouvax®) was given to every child at 9 months of age. Clinical status and measles antibody levels were evaluated at the time just before vaccination, 2 and 12 weeks post-vaccination. Antibody was measured by an enzyme immunoassay commercial kit (Enzygnost, Dade Behring Manufacturer, Germany). Children were classified into 3 groups, groups 1 and 2 were children with and without HIV infection respectively. Group 3 children were those born to HIV-1 seronegative mothers. Of the 33 enrolled children, 16, 14 and 3 were classified as groups 1, 2 and 3 respectively. Four children, 2 of each, in groups 1 and 3 did not complete the study. Group 3 was excluded due to the small number of children recruited. There was no short term complication and no measles infection noted during the course of study. None of the children had pre-existing antibodies. The median (range) of CD4 count and CD4/CD8 ratio measured at the time of vaccination were statistically different between groups 1 and 2 children. Group 2 children had better antibody response than group 1 in terms of seroconversion rate and median of antibody levels at 12 weeks post-vaccination. Only 7 of 29 children (24.1%) had detectable measles antibodies at 2 weeks post-vaccination. A decrease in antibody was noted in 2 symptomatic HIV infected children as their disease had progressed. Various potential predictors of measles vaccine responses in HIV infected children including CD4 count and CD4/CD8 ratio were not statistically different between the responders and non-responders. All 4 asymptomatic HIV infected children were responders.

This study demonstrated that all of the children had already lost their maternal acquired antibodies at age 9 months. HIV infected children had a poorer antibody response to measles vaccine than the non-infected children.

INTRODUCTION

Measles is one of the most contagious childhood diseases. HIV infected children are at increased risk of complications and death following this infection (Markowitz *et al*, 1988). The Immunization Practices Advisory Committee, Centers for Disease Control and Prevention (ACIP, 1988) and the World Health Organization (WHO, 1987) have recommended measles vaccination for all children regardless of their HIV infectivity. Humoral immune responses to this vaccine have been studied in HIV infected children at different ages. Seroconversion rates have been reported between 25-85% (Krasinski and Borkowsky, 1989; Palumbo *et al*, 1992; Lepage *et al*, 1992; Brena *et al*, 1993; Cutts *et al*, 1993; Frenkel *et al*, 1994; Rudy *et al*,

1994; Arpadi *et al*, 1996). Brena *et al* (1993) reported a significantly lower response rate of HIV infected children older than 1 year of age (51%) in comparison with those of non-infected controls (92%). Two studies by Lepage *et al* (1992) and Rudy *et al* (1994) did not find any difference in response to measles vaccine in children with and without HIV infection when immunization was given before 1 year of age. However most of the studies were performed retrospectively in various age groups and measles antibodies were tested at different times after vaccine administration. Since measles vaccination as early as 9 months of age is commonly practiced in Thailand and there is no previous study examining the conversion rate and the titer of antibody response among HIV infected children in this country, we conducted a prospective study to determine the rate of measles antibody response in children born to HIV-1 seropositive mothers. The pattern of antibody response of HIV infected and non-infected children was also evaluated.

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MATERIALS AND METHODS

A cohort of 33 children were recruited. Three were born to HIV-1 seronegative mothers and 30 were born to HIV-1 seropositive mothers. The Schwarz strain of measles virus vaccine (Rouvax® Pasteur Merieux) 0.5 ml was administered subcutaneously to all children at age 9 months. Each immunization dose contains at least 1,000 TCID₅₀ of live hyper-attenuated measles virus. None of them received intravenous gamma globulin or had a history of measles infection. Measles antibody tests were performed just before vaccination and 2 and 12 weeks post-vaccination. Specimens were stored in a deep freezer at -70°C. Measles IgG antibody was measured by an enzyme immunoassay commercially available from Dade Behring, Germany (Enzygnost® Anti-masern-Virus/IgG), according to the manufacturer's instructions. The antibody activity expressed in "miu/ml" is based on the WHO International Standard for anti-measles serum. Test samples yielding a result of less than 150 miu/ml were defined as negative. The CD4 and CD8 counts and hemoglobin were determined at the time of assessment of measles antibody. Children born to HIV-1 seropositive mothers were classified into 2 groups according to the Centers for Disease Control and Prevention revised classification system for HIV infection in children (CDC, 1994). Groups 1 and 2 were children with and without HIV infection born to HIV positive mothers; group 3 were children born to HIV-1 seronegative mothers.

The study was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University. Written informed consent was obtained

from the mothers or guardians.

Statistical analysis was done by Mann - Whitney non-parametric test, Fisher's exact test, and chi-square test.

RESULTS

Of the 33 children enrolled in the study, 16, 14 and 3 were classified as groups 1, 2 and 3, respectively. Twelve children of group 1 had HIV associated symptoms, category A. Four children in group 1 and group 3, two of each group, did not complete the study. One child in group 1 who was in terminal stage of HIV infection died just before 12 weeks post-vaccination. The male to female ratio was 7:9 in group 1 and 8:6 in group 2. Median weight (range) of children in both groups were similar. Median (range) of CD4 count (percent and absolute number) and CD4/CD8 ratio measured at the time of measles vaccination were statistically different between group 1 and group 2 children, (Mann-Whitney, $p < 0.01$) (Table 1). None of the children had maternally acquired measles antibodies prior to vaccination. There were no short term complications and no measles infection noted during the course of study. Since the number of children in group 3 was too small, their data were not used for comparison.

At week 2 post-vaccination, only 7 children, 2/14 of group 1 and 5/13 of group 2 had detectable antibody levels. All 3 children of group 3 had no antibody response. At age 1 year or 12 weeks post-vaccination, 8 out of 14 (57.1%) HIV infected children and all 14 (100%) non-infected children were seroconverters. Among these seroconverters,

Table 1
Clinical characteristics of children at 9 months of age prior to measles vaccination.

	Median (range)		(Mann Whitney) p-value
	HIV infected (Group 1)	HIV non infected (Group 2)	
Number of children enrolled	16	14	
Sex M:F	7:9	8:6	
Body weight, g	7,700 (6,400-9,100)	8,125 (5,100-10,050)	>0.05
CD ₄ count, -total cell/mm ³	1,677 (485-2,876)	2,627 (1,299-3,946)	<0.0001
- %	26.5 (10-36)	35 (20-44)	0.002
CD ₄ /CD ₈ ratio	0.85 (0.3-1.67)	1.72 (0.71-2.35)	0.001
Hemoglobin, g/dl	10.5 (7.2-12.4)	11.8 (10.6-14)	0.008

Table 2
Antibody responses at 2 and 12 weeks after measles vaccination in HIV – 1 infected (group 1) and non infected children (group 2).

	Group 1	Group 2
No. (%) of seroconverters		
at 2 weeks ^a	2/13 (14.3)	5/13 (38.5)
at 12 weeks ^b	8/14 (57.1)	14/14 (100)
Median levels (range) of antibody responses (miu/ml)		
At 2 weeks ^c	1,785 (270-3,300)	460 (360-4,700)
At 12 weeks ^d	610 (180-2,700)	2,800 (360-19,000)

^a = $p > 0.05$ (Fisher's exact); ^b = $p < 0.05$ (chi-square)

^c = $p > 0.05$ (Mann-Whitney); ^d = $p < 0.01$

Table 3
Predictor for response to measles vaccine in HIV-1 infected children.

	Median (range)	
	Responders	Non-responders
CD4 count, - total, cells/mm ³	1,506 (485-2,876)	1,677 (543-2,389)
- %	30 (14-36)	16.5 (10-32)
CD ₄ /CD ₈ ratio	1.09 (0.35-1.67)	0.42 (0.3-1.28)
Hemoglobin level, g/dl	11.1 (7.9-12.4)	10.3 (7.2-11.0)
Body weight (g)	8,425 (7,000-9,100)	7,350 (6,400-8,900)

All $p > 0.05$ (Mann Whitney non parametrics test)

group 1 children had antibody levels significantly lower than group 2 ($p < 0.01$). The median levels (range) were 610 (180-2,700) and 2,800 (360-19,000) miu/ml. respectively (Table 2). Antibody levels of these children rose distinctively from 2 to 12 weeks post-vaccination, except those of 2 symptomatic HIV infected children. Antibodies of these 2 children had declined. The level of one child declined from 3,300 to 440 miu/ml. Another child with antibody level of 270 miu/ml became a seroreverter later. CD4/CD8 ratio of both children changed to a reverse ratio (< 1) when they lost their antibody response, but their CD4 count remained in the normal range.

Various clinical parameters, including CD4 count, CD4/CD8 ratio, hemoglobin level and body weight at the time of vaccination were evaluated as potential predictors of measles vaccine response in HIV infected children. None of them was found to be statistically different between the responders and non responders. All 4 asymptomatic children were the responders whereas only 4 out of 10 symptomatic children (40%) were responders (Table 3).

DISCUSSION

In this study, all 33 children born to both HIV-1 seropositive or HIV-1 negative mothers had no pre-existing measles antibody at age 9 months. It suggests that children at this age have already lost their maternal acquired antibodies. This finding reinforces the recommendation of the Immunization Practices Advisory Committee (Markowitz *et al*, 1988) to vaccinate the children as young as 6 months of age with monovalent measles vaccine when exposure to natural measles is considered likely. No short term complications of measles vaccine were noted, which is similar to previous studies (Krasinski and Borkowsky, 1989; Palumbo *et al*, 1992; Lepage *et al*, 1992; Brena *et al*, 1993; Cutts *et al*, 1993; Frenkel *et al*, 1994; Rudy *et al*, 1994; Arpadi *et al*, 1996). Although one HIV-infected child died after immunization, the cause of death was not related to the vaccine. Live attenuated virus vaccine is generally contraindicated in immunodeficient patients because of the possibility of clinically severe infection due to vaccine virus. In HIV-infected children there is the

additional theoretical risk of antigenic stimulant triggering of T-lymphocyte proliferation which may potentiate the replication of HIV virus (Dagan *et al*, 1987; Roilides *et al*, 1991). But Borkowsky *et al* (1992) have demonstrated that most HIV-infected children have primary cellular and humoral immune responses during the first 2 years of life. Thus, measles vaccine should be safe for these children at an early age.

The response rate to measles vaccine of our study was comparable to many studies (Krasinski and Borkowsky, 1989; Palumbo *et al*, 1992; Brena *et al*, 1993; Cutts *et al*, 1993; Frenkel *et al*, 1994). The rate was low in HIV infected children (57.1%) which is differed from those reported by Lepage *et al* (1992) and Rudy *et al* (1994). Their response rates were 85% and 69%, respectively. This is probably due to the vaccination being performed at different ages and the use of different types of vaccine. Some of their children received vaccine at 6 months of age which was earlier than the time of vaccination in our children. Better antibody responses might be achieved in HIV-infected children at younger age while their humoral immunity is still well preserved (Borkowsky *et al*, 1992). A high dose Edmanston-Zagreb measles vaccine was used in study reported by Lepage *et al* (1992). Antibody responses in HIV-infected and non-infected children in their study were not different which were similar to that shown by Whittle *et al* (1988). The latter authors suggested that both dose and strain of virus were important in achieving a good serological response to measles vaccine and Edmanston Zagreb vaccine produced higher levels of measles antibody than Schwarz vaccine did. A decline of antibody response was also noted in our study. Al-Attar *et al* (1995) reported that almost all HIV infected children in their study with initially detectable measles antibodies had a significant decline in titer over time, and 10 of 17 lost antibody during the course of the study. They believed loss of antibody was probably the cause of such a low response rate in their study. Several potential explanations for a failure to respond to this vaccine in HIV infected children have been suggested (Roilides *et al*, 1991). It may be due to a concomitant infection at the time of vaccination or a depletion of T-helper cells to the point that a specific immune response can no longer be developed. None of our children had opportunistic infection or low CD4 counts. CD4/CD8 ratio seemed to be a better predictor for response to measles vaccine in HIV infected children in our study. The median ratio of the HIV-

infected group was significantly lower than that of the non-infected group. At 12 weeks post-vaccination when the antibody level of 2 children declined, their CD4/CD8 ratios were also decreased to the value of <1. However, the median ratio (range) of the responders and non-responders among HIV infected children were not statistically different, [1.09 (0.35-1.67) vs 0.42 (0.3-1.28), $p > 0.05$]. The process of antibody response is rather slow as demonstrated in this study, only 7 out of 29 children (24.1%) had detectable antibody at 2 weeks post-vaccination.

The findings in the present study indicated that every HIV infected children should be tested for antibody response after measles immunization, since non-responders might get benefit from revaccination. Further study to evaluate the response to booster immunization should be performed in order to determine the appropriate time for administration of the booster vaccine. Due to the slow antibody response and the low seroconversion rate, post-exposure prophylaxis with immunoglobulin G should also be given to HIV infected children regardless of their immune status.

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REFERENCES

- ACIP. Immunization of children infected with human immunodeficiency virus- supplementary ACIP statement. *MMWR* 1988; 37: 181-3.
- Al-Attar I, Reisman J, Muehlmann M, *et al*. Decline of measles antibody titers after immunization in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 1995; 14: 149-51.
- Arpadi SM, Markowitz LE, Baughman AL, *et al*. Measles antibody in vaccinated human immunodeficiency virus type 1-infected children. *Pediatrics* 1996; 97: 653-7.
- Borkowsky W, Rigaud M, Krasinski K, *et al*. Cell mediated and humoral immune responses in children infected with human immunodeficiency virus during the first four years of life. *J Pediatr* 1992; 120: 371-5.
- Brena AE, Cooper ER, Cabral HJ, *et al*. Antibody response to measles and rubella vaccine by children with HIV

- infection. *J AIDS* 1993; 6: 1125-9.
- CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994; 43: 1-10.
- Cutts FT, Mandala K, St. Louis M, *et al.* Immunogenicity of high-titer Edmonston - Zagerb measles vaccine in human immunodeficiency virus-infected children in Kinshasa, Zaire *J Infect Dis* 1993; 167: 1418-21.
- Dagan R, Phillip M, Sarov I, *et al.* Cellular immunity a T-lymphocytes subsets in young children with acute measles. *J Med Virol* 1987; 22: 175-82.
- Frenkel LM, Nielsen K, Garakian A, *et al.* A search for persistent measles, mumps, and rubella vaccine virus in children with human immunodeficiency virus type 1 infection. *Arch Pediatr Adolesc Med* 1994; 148: 57-60.
- Krasinski K, Borkowsky W. Measles and measles immunity in children infected with HIV. *JAMA* 1989; 261: 2512-6.
- Lepage P, Dabis F, Msellati P, *et al.* Safety and immunogenicity of high-dose Edmonston-Zagreb measles vaccine in children with HIV-1 infection. *Am J Dis Child* 1992; 146: 550-1.
- Markowitz LE, Chandler FW, Roldan EO, *et al.* Fatal measles pneumonia without rash in a child with AIDS. *J Infect Dis* 1988; 158: 480-3.
- Palumbo P, Hoyt L, Demasio K, *et al.* Population-based study of measles and measles immunization in human immunodeficiency virus infected children. *Pediatr Infect Dis J* 1992; 11: 1008-14.
- Roilides E, Clerici M, Depalma L, *et al.* Helper T-cell responses in children infected with human immunodeficiency virus type 1. *J Pediatr* 1991; 118: 724-30.
- Rudy BJ, Rutstein RM, Pinto-Martin J. Responses to measles immunization in children infected with human immunodeficiency virus. *J Pediatr* 1994; 125: 72-4.
- Whittle HC, Mann G, Eccles M, *et al.* Effects of dose and strain of vaccine on success of measles vaccination of infants aged 4-5 month. *Lancet* 1988; 2: 963-6.
- World Health Organization. Expanded Programme on Immunization, Global Advisory Group. *Weekly Epidemiol Rec* 1987; 62: 5-9.