

SAFETY AND IMMUNOGENICITY OF BACILLUS CALMETTE-GUERIN VACCINE IN CHILDREN BORN TO HIV-1 INFECTED WOMEN

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Abstract. This prospective cohort study was conducted to determine the complication of Bacillus Calmette-Guerin (BCG) vaccination given to newborn infants born to HIV-1 seropositive mothers and to compare the tuberculin reaction 9 months after BCG vaccination between HIV-1 infected and non infected children. Two hundred and twenty-three infants with BCG immunization at birth were examined. No BCG complication was noted. Tuberculin skin tests were performed on 126 children (56.5%). Eleven of them were excluded because of failure to have skin tests read at 48 hours. Of the 115 infants enrolled to this study, 15 (13%) had no BCG scar and 50 (43.5%) had no tuberculin reaction. Twenty-six children were classified as group 1 or HIV-1 infected children and 89 children were group 2 or HIV-1 non infected. Group 1 children had a smaller tuberculin skin response (X±SD) than group 2 (1.15 ± 2.82 vs 4.64 ± 4.29 mm; p < 0.0001). Mean weight + SD of group 1 children was also significantly less than those in group 2 (8,013 ± 741 vs 8,540 ± 984 g; p < 0.05). The proportion of children with non reactivity to the tuberculin test, a negative tuberculin test and no BCG scar in group 1 was significantly higher than that in group 2 (76.9% vs 33.7%, 92.3% vs 52.8% and 36.4% vs 6.7% respectively; p < 0.0001 for all). But, the proportion of non reactivity to the tuberculin test in children with or without BCG scar of each group was not different (p > 0.05). Positive tuberculin tests were 7.7% and 47.2% in group 1 and 2 respectively. None of the children with positive tuberculin tests had clinical evidence of tuberculosis. The findings of this study indicate that BCG vaccine given to newborn infants of HIV-1 seropositive mothers is safe. Although tuberculin skin responses of HIV-1 infected children are less than those of HIV-1 non infected children, it is possible that BCG vaccine might protect these children from developing severe tuberculosis.

INTRODUCTION

According to the World Health Organization recommendation, in areas with high tuberculosis risk, BCG vaccine should be given to every newborn infants including those born to HIV-1 seropositive mothers (WHO, 1987). Several case reports of regional lymphadenitis and disseminated BCG infection in HIV-1 seropositive infants and the suggestion that BCG immunization might accelerate the course of HIV-infection have raised concern about the safety of this vaccine (Besnard *et al*, 1993; Gouzales *et al*, 1989). Population based retrospective studies about the adverse effect of BCG vaccination and the response of tuberculin test in Congo (Lallemant-Le Coeur *et al*, 1991) and Rawanda (Msellati *et al*, 1991) did not demonstrate serious BCG complications in infants of HIV-1 seropositive mothers. The safety and ef-

ficacy of BCG vaccination in HIV-1 infected infants has not yet been prospectively studied.

Conversion to a positive tuberculin skin test is less common among HIV infected infants. Lallemant-Le Coeur *et al* (1991) and Msellati *et al* (1991) reported a conversion rate of 33% and 27.3% respectively, but it is unclear if the tuberculin reactivity is also suppressed by other host-related factors, such as poor nutrition, other viral infections and severe disseminated tuberculosis. These factors were not investigated in these studies. We therefore conducted a prospective cohort study on infants born to HIV-1 seropositive mothers in order to determine complications of BCG vaccination and to compare the tuberculin reaction after BCG vaccination between HIV-1 infected and non infected children.

PATIENTS AND METHODS

All full term infants born to asymptomatic HIV-1 seropositive mothers who belonged to a

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research projects on prevention of HIV-1 vertical transmission conducted at King Chulalongkorn Memorial Hospital were included in this study. The infants were given BCG vaccine within 24 hours of birth by experienced nurses. Reconstituted freeze - dried BCG vaccine 0.1 ml corresponding to 0.05 mg of organisms was injected intradermally at the deltoid area of the left arm. Infants were actively followed by the authors as outpatients at 3,6,9,12,15,18 and 24 months of age. They received a complete physical examination and appropriate blood tests according to the protocol of the main project. They were also examined for a BCG scar and BCG complications such as chronic ulceration, deep abscess, regional lymphadenopathies and disseminated BCG. Enlarged left axillary and/or supraclavicular lymph nodes ≥ 1 cm in diameter were defined as regional lymphadenopathies.

Tuberculin skin tests by Mantoux technique were performed on these children at age 9 months by an experienced nurse. Purified protein derivative (Thai Red Cross, Liquid Tuberculin) 0.1 ml containing 10 tuberculin units was injected intradermally at the volar surface of the forearm. Tuberculin reactivities were read by the authors (PT, PP and SP) 48 hours after injection. The diameter of induration was measured transversely to the long axis of the forearm by ballpoint-pen technique and the greatest diameter in millimeters was recorded (Pouchot *et al*, 1997). Children with tuberculin reaction 10 mm or larger were investigated for possible mycobacterial infection and treated accordingly. Children with tuberculin reaction less than 10 mm would not receive a chest X-ray unless it was indicated by clinical findings. Non-reactivity to the tuberculin test was defined as 0 mm of induration. Induration 0-4 mm was considered as a negative tuberculin test and a positive tuberculin test was defined as induration of ≥ 5 mm (American Thoracic Society, 1990; American Academy of Pediatrics, 1996).

According to their HIV-1 infected status, children were classified into 2 groups. Children with positive results of HIV polymerase chain reaction on two separate determinations at 6 months of age and/or HIV-antibody after 18 months of age. These were defined as the HIV-1 infected group (Group 1). Group 2 or HIV-1 non-infected children were those with negative results of the above serology tests, and without any AIDS-defining clinical condition (Anonymous, 1994). During the study, the authors were not aware of any of the

test results.

The nutritional status was evaluated by measurement of body weight and this was compared with the normal weight curve for Thai children from the Ministry of Public Health of Thailand. At 9 months of age any child with body weight less than 7,000 g would be designated as a poorly nourished child.

Statistical analyses were performed using SPSS FW software. Comparison of proportion was determined by chi-square or Fisher exact test. Unpaired *t*-test was used to determine statistical significance for comparison of measurements. Statistical significance was designated at $p < 0.05$. Ninety-five percent CI_s were given when appropriate.

RESULTS

Two hundred and twenty-three infants were enrolled. One hundred and ninety-eight (88.8%) and 164 (73.5%) infants were followed at 3 and 9 months of age respectively. Two infants died, one at age 4 months due to pneumonia of undetermined origin. Another infant had multiple congenital anomalies and died at the age of 1 year of congestive heart failure secondary to congenital heart disease. Neither had regional lymphadenopathy or other BCG complications. Tuberculin skin tests were performed on 126 of these children (56.5%). Eleven were excluded from the study because they did not return for tuberculin reaction reading. Only 115 children were fully evaluated.

There were 54 males and 61 females. Fifteen (13%) had no BCG scar and 50 (43.5%) had non-reactivity to the tuberculin test. Tuberculin reactions of 0 - 4 mm, 5 - 9 mm and ≥ 10 mm were noted in 61.8, 21.7 and 16.5 respectively. A positive tuberculin test was found in 44 children (38.3%); 7.7% in group 1 and 47.2% in group 2 (Table 1).

There were 26 children in group 1 and 89 children in group 2. Group 1 children had significantly smaller tuberculin reactions than group 2 ($X \pm SD$), (1.52 ± 2.82 vs 4.64 ± 4.29 mm; $p < 0.001$). The proportion of children with non-reactivity to the tuberculin test, negative tuberculin test and no BCG scar in group 1 were higher than those in group 2. This was significant (Table 2). But the proportion of non-reactivity to the tuberculin test among children with and without BCG scars in each group were not statistically different ($p > 0.05$),

(Table 3). Mean weight \pm SD of group 1 children at 9 months of age was significantly less than that of group 2, ($8,013 \pm 741$ vs $8,504 \pm 984$ g; $p < 0.05$). Mean weight \pm SD of children with a positive tuberculin tests was also higher than that of children with a negative tests ($8,667 \pm 1,089$ vs $8,269 \pm 839$ g; $p < 0.05$). Six children were defined as poorly nourished. All of them had negative tuberculin tests except one child in group 2 who had a positive test. Common concurrent illnesses were rhinitis and diarrhea which were not different

in terms of frequency in both groups of children. Twelve children in group 1 had symptoms of HIV related infection classified as mildly symptomatic or clinical category A according to the 1994 CDC revised classification system for HIV infection in children (Anonymous, 1994). All of these symptomatic HIV-1 infected children except one child, had non reactivity to the tuberculin test. None of group 2 children had HIV-1 related symptoms.

Children with tuberculin reaction ≥ 10 mm had no clinical and chest x-ray findings compatible with tuberculosis, although 2 of them, one in each group, had parents that were suffering from active pulmonary tuberculosis. INH prophylaxis was given to these children.

Table 1
Tuberculin reactivity in children at
9 months old.

Tuberculin reactivity (mm)	Group 1 N=26	Group 2 N=89	Total N=115 (%)
0	20	30	50 (43.5)
1-4	4	17	21 (18.3)
5-9	1	24	25 (21.7)
≥ 10	1	18	19 (16.5)

DISCUSSION

In this study, no case of BCG complication was identified. Our results support those of other studies (Lallemant-Le Coeur *et al*, 1991; Msellati *et al*, 1991). Although local complication and dis-

Table 2
Reaction to tuberculin skin test (TT) among HIV-1 infected (group 1) and
non-infected children (group 2).

Category	Group 1 N=26	Group 2 N=89	p-value
Mean diameter of reaction (mm) $\bar{X} \pm SD$	1.15 \pm 2.82	4.65 \pm 4.29	<0.0001
Median diameter of reaction (mm) (Range)	0 (0-12)	4 (0-13)	
Proportion of children with non reactivity TT (95% CI)	76.9% (81.8-102.8%)	33.7% (42.2-63.4%)	<0.0001
Proportion of children with positive TT (95% CI)	7.7% (0-18%)	47.2% (36.6-57.8%)	<0.0001

Table 3
Proportion of non-reactivity to tuberculin test and positive tuberculin test in
children with and without BCG scars.

Tuberculin reaction	Group 1		Group 2	
	BCG scar	No BCG scar	BCG scar	No BCG scar
Non reactivity (PPD = 0)	12/17 ^a	8/9 ^c	28/83 ^c	2/6 ^a
Positive tuberculin test (PPD ≥ 5)	2/17 ^b	0/9 ^a	39/83 ^a	3/6 ^a

^{a,b,c} and all are not statistical significant.

seminated disease have been reported in almost all of HIV-1 infected children after clinical symptoms of HIV infection have developed, 12 HIV-1 infected children with clinical symptoms of HIV-1 infection have not shown adverse effect. However, due to the small sample size we can not conclude that BCG vaccination in these infants is absolutely safe. However, the risk of disseminated BCG infection is very rare, approximately 3.4/million vaccinated newborn (Gouzales *et al*, 1989).

No BCG scar was found in 15 infants (13%) which had been seen more commonly among the HIV infected infants. Our prevalence of BCG scar was lower than that reported by Msellati *et al* (1991) but it is quite similar to the prevalence in normal Thai children (Payanandana *et al*, 1993). Dark-skinned individuals are more susceptible to hypertrophic scar or keloid formation (Alhedy and Sivanantharajak, 1969). This might be the reason why there was such a high prevalence of BCG scar among African children in the study by Msellati *et al* (1991). Other factors can influence BCG scar formation such as the potency of BCG vaccine and technique of vaccination. But these factors should not be major causes. The Thai Red Cross BCG vaccine used in our study is a standardized vaccine and nurses who administered it, are experienced in this work.

Prevalence of the tuberculin conversion rate was only 7.7% in group 1 while it was 47.2% in group 2 in our study which is less than previous reports (Lallemant-Le Coeur *et al*, 1991; Msellati *et al*, 1991). These older retrospective reports did not state data regarding tuberculosis exposure which might have an impact on their prevalence of the tuberculin conversion rate and several of their children died due to HIV-1 related diseases before they were skin tested, their prevalence of the tuberculin conversion rate might be overestimated.

The proportion of children with non reactivity to tuberculin test in HIV-1 infected group is very high (76.9%). This is perhaps a result of both the immunosuppression related to HIV-1 infection and poor nutritional status. The Mantoux test may be used as diagnostic aid to detect tuberculous infection and to determine the prevalence of conversion rate in groups of people. However, a small or no reaction to a tuberculin skin test alone does not exclude the diagnosis of tuberculosis from further consideration. The Mantoux test positivity does not reliably predict the degree of protection against tuberculosis either (CDC, 1988). Therefore

the use of this test in HIV-1 infected children is limited. Persons exposed to tuberculosis may be more likely to develop overt tuberculosis if they are infected with HIV (Quinn, 1989). None of our HIV-1 infected children has tuberculosis even though they are in the environment of increased exposure to this disease. Whether or not BCG is less effective in HIV-1 infected children is not known, and it is unclear if the BCG induced tuberculin response bears any relationship to protection. A trial among British school children (D'Arcy Harf *et al*, 1967) showed that the protection conferred by BCG vaccination was as good among those who showed little or no response to tuberculin after vaccination as among those who showed a strong response. We believe that HIV-1 infected children might develop some protective immunity to tuberculosis after BCG vaccination during neonatal period.

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