Assessment of Bacille Calmette-Guérin Vaccine Reaction in HIV-Exposed Thai Infants

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We evaluated local reactions at 1, 2, and 4 months of age to bacille Calmette-Guérin vaccine given at birth to 1058 infants who were exposed to human immunodeficiency virus (HIV). No scar was discernible in 12 (12.4%) of 97 HIV-infected infants and 20 (2.1%) of 961 uninfected infants (relative risk, 5.9; 95% confidence interval, 3.0–11.8). This difference may reflect poorer immunogenicity in HIV-infected infants.

Bacille Calmette-Guérin (BCG) vaccine is recommended for all neonates in countries with a high prevalence of tuberculosis and has been shown to prevent severe forms of tuberculosis [1–4]. Cutaneous scarring due to BCG vaccination has been used as evidence, not only of having received BCG vaccination, but also of adequate immunogenic response. Studies have shown that local reactions to BCG vaccination correlate with postvaccination lymphoproliferative and IFN responses specific to mycobacteria (i.e., immunity against tuberculosis) [5, 6]. However, adverse events as a result of BCG vaccination have also been documented, particularly in immunocompromised hosts [7, 8]. Some studies suggest that HIV-infected children may be at risk of developing local complications [9–11], but other studies do not support this finding [12, 13]. We evaluated local reactions to BCG vaccination, scar formation, and the rate of short-term complications from BCG vaccination among HIV-infected and HIV-exposed, uninfected infants in Thailand.

Methods. We conducted a retrospective study by medical record review of 1202 infants born to HIV-infected mothers who were enrolled in 2 perinatal HIV transmission studies during 1996–2003. Both studies were conducted at 2 hospitals in Bangkok, Thailand, with similar populations [14–16]. All newborns received intradermal BCG vaccine (a 0.1-mL dose), provided by the Thai Ministry of Public Health (the product was from Queen Saovabha Memorial Institute, Thai Red Cross Society (Bangkok, Thailand), and contained a minimum of 200,000 colony-forming units per dose), shortly after birth, in accordance with Thailand’s Expanded Program of Immunization. Infants were seen at 1, 2, and 4 months of age for physical examination, vaccination, and examination of the BCG injection site, in accordance with the perinatal study protocols [14–16].

Typically, after intradermal inoculation with BCG vaccine, indurated papules develop, become ulcerated, and then drain for several weeks [5] before cutaneous scarring occurs. For this analysis, a scar was defined as a healed lesion from BCG inoculation, and a lesion was defined as any cutaneous evidence of BCG inoculation.

Two distinct analyses were performed, the first using patient data from all 3 possible follow-up study visits, regardless of missed appointments or recorded observations, and the second using patient data restricted to patients who had consistent findings of BCG reaction at all 3 study visits, thereby limiting the possibility of misclassification of results. PCR tests for HIV DNA were performed at birth and at 1 and 2 months of age, and serological testing for HIV was performed at 18 months of age. For the HIV-infected infants, viral load measurements were performed at 2 months of age, and CD4+ cell counts were performed at either 2 or 4 months of age. Antiretroviral therapy was provided to HIV-infected infants through the national treatment program. HIV infection was determined on the basis of at least 2 positive PCR test results and was confirmed by persistence of HIV antibody at ≥18 months of age.

Statistical analysis was performed with χ² tests for categorical variables, such as the presence of a BCG vaccination scar and HIV infection status, and relative risks (RRs) and confidence intervals were calculated. For continuous values, such as CD4+ cell count and viral load, the Wilcoxon rank-sum test was used.

Human subjects review was obtained from Mahidol University, the Thai Ministry of Public Health, and the Centers for Disease Control and Prevention for the 2 perinatal research...
studies, including the data used in this analysis [14–16]. Informed consent for mothers and infants was obtained from all women enrolled in the perinatal studies.

**Results.** All 1202 eligible infants had documented BCG vaccination; of these, 111 (9.2%) were infected with HIV. There were 4 HIV-infected infants who died before 4 months of age, 59 infants were lost to follow-up before the 4-month visit, and 61 infants missed some of the visits. Of the 1058 infants (88%) who returned for all 3 study visits (at 1, 2, and 4 months) and who had documented cutaneous reaction information recorded, 97 (9.2%) were HIV infected.

In the analysis of each visit for all infants, HIV infection was associated with the absence of BCG lesions or scars at all visits: 44 (39.6%) of 111 HIV-infected infants and 145 (14.3%) of 1014 HIV-uninfected infants did not have a scar or lesion at the 1-month visit (RR, 2.77; 95% CI, 2.1–3.6); 37 (34.6%) of 107 and 89 (8.8%) of 1013, respectively, did not have a scar or lesion at the 2-month visit (RR, 3.94; 95% CI, 2.8–5.5); and 29 (29.3%) of 99 and 94 (9.6%) of 982, respectively, did not have a scar or lesion at the 4-month visit (RR, 3.06; 95% CI, 2.1–4.4).

Of the 1058 infants who returned for all 3 visits, 32 infants (3%) never developed a scar or lesion, 802 (76%) had a BCG lesion or scar present at every visit, and 224 (21%) had a BCG lesion or scar present at some visits. Absence of a BCG lesion or scar was found more frequently in HIV-infected infants (12 [12.4%] of 97 vs. 20 [2.1%] of 961; RR, 5.9; 95% CI, 3.0–11.8). Twelve (12%) of 107 and 89 (8.8%) of 1013, respectively, did not have a scar or lesion at the 2-month visit (RR, 3.94; 95% CI, 2.8–5.5); and 29 (29.3%) of 99 and 94 (9.6%) of 982, respectively, did not have a scar or lesion at the 4-month visit (RR, 3.06; 95% CI, 2.1–4.4).

In analysis restricted to 834 infants with consistent reaction findings, HIV-infected infants were still more likely to never develop a scar or lesion (P < .001) (table 1). Those HIV-infected infants who never developed a BCG lesion or scar also had a higher median viral load at 2 months of age, compared with infants who always had a BCG lesion or scar (6.5 log_{10} copies/mL vs. 6.0 log_{10} copies/mL; P < .003). The 224 infants who had a BCG lesion or scar at some visits had a median viral load value that fell between the median viral load values for the other groups. However, there was no difference in the median absolute CD4+ cell count or median CD4+ cell percentage values measured at 2 and 4 months of age (table 1).

There were 16 infants with reported mild complications, all of whom were HIV uninfected. Infants with complications included 5 with a local abscess with drainage, 10 with axillary lymphadenopathy >0.5 cm, and 1 with a BCG cutaneous scar size >1 cm in diameter.

**Discussion.** Our study found that HIV-infected infants had less scar formation at BCG vaccination sites than did HIV-uninfected infants and that all infants had a low rate of complications. Moreover, we found that the lack of a local reaction correlated with a high viral load prior to receipt of antiretroviral treatment. Although absence of local reaction after BCG vaccination could be the result of poor vaccine quality (e.g., interruption of the cold chain), all infants received the vaccine from the same source; therefore, it is unlikely that poor vaccine quality explains our results.

Our study is, to our knowledge, the largest study to assess the development of BCG lesions, scars, or complications in a cohort of HIV-exposed infants, and our results support findings from 2 previous small studies. A Rwandan study found that 9% of 33 HIV-infected children, compared with only 1% of 136 HIV-uninfected children, never developed a scar after BCG vaccination [17]. Another study involving 23 HIV-infected Thai infants found that 19 (83%) of the infants did not develop a BCG scar, compared with 5 (23%) of 66 HIV-uninfected infants [18]. Of note, in the Thai study [18], there was a very low rate of scar development in both groups, even though this study and our study used BCG vaccine from the same source.

Lymphocytic infiltration with granuloma formation has been observed as early as 7 days after BCG vaccination in adult

**Table 1.** Factors affecting bacille Calmette-Guérin (BCG) scar or lesion formation in 834 Thai HIV-exposed infants who had consistent BCG reaction information recorded at each of 3 study visits at 1, 2, and 4 months of age.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of patients</th>
<th>BCG scar or lesion at every visit (n = 802)</th>
<th>BCG scar or lesion at some visits (n = 224)</th>
<th>BCG scar or lesion at no visits (n = 32)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-uninfected infants</td>
<td>961</td>
<td>756 (185)</td>
<td>20</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>HIV-infected infants</td>
<td>97</td>
<td>46 (39)</td>
<td>39</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Median HIV RNA level, median log_{10} copies/mL (IQR)</td>
<td>...</td>
<td>6.2 (5.7–6.4)</td>
<td>6.4 (5.9–6.8)</td>
<td>6.6 (6.4–6.6)</td>
<td>&lt;.003</td>
</tr>
<tr>
<td>CD4+ cell count, median cells/mL (IQR)</td>
<td>...</td>
<td>1649 (1274–2125)</td>
<td>2037 (1414–2757)</td>
<td>2082 (1335–2659)</td>
<td>.37</td>
</tr>
<tr>
<td>CD4+ cell percentage, median % (IQR)</td>
<td>...</td>
<td>29 (22–37)</td>
<td>25 (23–33)</td>
<td>24 (20–27)</td>
<td>.09</td>
</tr>
</tbody>
</table>

**NOTE.** IQR, interquartile range.

* P value compares the group with a BCG scar or lesion at every visit and the group with no BCG scar or lesion at any visit.

* Measured at 2 months of age.

* Measured at 2 or 4 months of age.
volunteers [5, 6]. Reactogenicity of BCG, as determined by duration of ulceration, correlated with in vitro cellular immune response [5, 6], suggesting that BCG reaction is a marker for induction of cell-mediated immunity. With this hypothesis, the lower reactogenicity in HIV-infected infants would account for a poor immunologic response. Unfortunately, we did not perform cell-mediated immunity response testing among these infants during these studies, and later testing for cell-mediated immunity response may reflect subsequent exposure to natural infection and not immune induction from BCG vaccination. From our current study, we conclude that BCG may be less immunogenic in HIV-infected infants, especially in those with poor virological control, and the absence of local response to BCG should prompt suspicion of HIV infection in countries with a high prevalence of HIV infection.

A mild reaction to BCG vaccine should cause fewer local complications. Our study found that none of the HIV-infected infants had complications from BCG vaccination. Although there have been reports of complications from neonatal BCG vaccination in HIV-infected children [9–11, 19], many studies have found minimal [20] or no increase in complications among HIV-infected infants [12, 13]. A report from South Africa described BCG-induced illness in HIV-infected children, many of whom were older, presenting with immune reconstitution reactions. Of 17 HIV-infected children with BCG-induced illness, only 2 had local disease at the BCG vaccination site, and 1 child had no BCG scar [9]. Therefore, absence of BCG complications or local reactions during infancy does not necessarily imply life-long absence of risk from BCG-associated illness in the long term. Because of a recent report of a relatively high risk of disseminated BCG-associated disease in HIV-infected infants in South Africa [19], the World Health Organization no longer routinely recommends neonatal BCG vaccination for HIV-exposed and asymptomatic HIV-infected infants in areas of endemicity [21].

Our study reflects the limited knowledge of the nature of immune induction by BCG vaccination and of how an immunocompromised host responds to BCG bacteria. Further studies are necessary to evaluate protective immunity against tuberculosis, especially in patients who do not experience local reactions to BCG vaccination.

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References