Danish Bacille Calmette-Guérin Vaccine–Induced Disease in Human Immunodeficiency Virus–Infected Children

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An analysis of isolates of Mycobacterium tuberculosis complex was performed to determine the prevalence of bacille Calmette-Guérin (BCG) disease among human immunodeficiency virus (HIV)–infected children. Speciation was done with polymerase chain reaction; 183 isolates from mycobacterial cultures for 49 HIV-infected patients were analyzed. The Danish Mycobacterium bovis BCG strain was isolated from 5 patients. No cases of Tokyo M. bovis BCG strain disease were detected. All patients were asymptomatic at birth, <12 months of age, and severely immunodeficient at presentation. Four patients had regional axillary adenitis ipsilateral to the vaccination site, and 2 had pulmonary BCG disease. Two patients with regional BCG disease had simultaneous pulmonary M. tuberculosis infection. Although chest radiographic features were similar to those seen in patients with tuberculosis, BCG disease should be considered in HIV-infected infants with right axillary adenitis ipsilateral to the vaccination site. Young, symptomatic, HIV-infected infants are at risk for BCG-related complications. Controlled, population-based studies are needed to assess the risk of BCG in HIV-infected children.

Bacille Calmette-Guérin (BCG) vaccine, which uses a live, attenuated strain of Mycobacterium bovis, was introduced into South Africa in 1973 [1] and incorporated into the World Health Organization (WHO) Expanded Programme on Immunization infant vaccination schedule in 1974 [2]. In South Africa, vaccine policy was changed from percutaneous administration of the Tokyo M. bovis BCG strain to intradermal administration of the Danish M. bovis BCG strain in July 2000.

Although relatively safe, BCG immunization may be associated with adverse events, such as injection-site lesions, adenitis, and, in rare cases, systemic disease [2]. Adverse events vary with strain type, physical-chemical properties, and bacillary load [2]. Reported rates of adenitis among BCG recipients vary widely, ranging from 0% to 17.6% [3]. The incidence of disseminated BCG disease has previously been reported to be 0.19–1.56 cases per 1 million vaccinated infants [4], and such disease has been mainly associated with severe immunodeficiency, frequently with fatal outcome [5].

The implications of HIV infection and the associated immunocompromise are of particular concern with regard to the safety of BCG. The WHO recommends that
all HIV-infected children, except those with symptomatic HIV disease, receive BCG vaccination at birth [6, 7]. In the absence of antenatal screening for HIV and neonatal symptoms of HIV disease, the early diagnosis of vertically transmitted HIV infection is difficult. Various reports describe local complications of BCG vaccination, both in symptomatic and in asymptomatic HIV-infected patients [8–12], but the risk of developing BCG-related adverse events among HIV-infected patients remains poorly characterized. One case of apparent reactivation of BCG with disseminated disease has been documented in a patient with AIDS 30 years after vaccination [13]. The limited number of cases of disseminated BCG disease that have been reported, as reviewed by Lotte et al. [4] and Talbot et al. [5], may reflect underreporting.

Another concern is that BCG disease may be misdiagnosed as tuberculosis, especially in areas where the prevalence of tuberculosis and HIV infection is high and where BCG vaccine is routinely administered [5]. Routine identification of mycobacterial isolates in clinical laboratories involves culture of Mycobacterium tuberculosis complex, which consists of a number of species, including M. tuberculosis, M. bovis, and the vaccine strain, M. bovis BCG [14]. Traditional laboratory biochemical and growth characteristics are not definitive for BCG. PCR-based methods now allow rapid and accurate differentiation of M. tuberculosis complex species, including M. bovis BCG [15, 16].

Tuberculosis is endemic in the Western Cape Province of South Africa, where the incidence of tuberculosis infection is 700 cases per 100,000 individuals [17]. The reported prevalence of HIV infection was 8.6% (95% CI, 5.6%–11.6%) among women attending antenatal clinics in the region in 2001 [18]. Antiretroviral therapy for HIV-infected children is not routinely available in the public health sector. We postulated that, against this background, M. bovis BCG could be an important cause of mycobacterial disease in infants with vertically transmitted HIV infection. The aims of the present study were to determine whether culture-confirmed mycobacterial disease in HIV-infected children had been caused by BCG vaccination and/or M. bovis infection and to describe the clinical features of M. bovis BCG and M. bovis–related disease.

METHODS

Subjects and setting. Participants in this retrospective hospital-based study were children routinely investigated for suspected tuberculosis at the Tygerberg Children’s Hospital, a referral hospital in the Western Cape Province, South Africa. Routine sample collection and culture for bacteriological confirmation of tuberculosis through testing for M. tuberculosis complex was performed. Mycobacterial isolates from these children were stored in a sample bank as part of ongoing tuberculosis research. For the present study, all isolates from children 0–13 years of age with known HIV infection obtained during the 10-year period from January 1992 through August 2002 were reviewed. HIV infection was diagnosed by positive results of ELISA and was confirmed by PCR in children <15 months of age or by a second ELISA test in older children. Isolates from children with unknown or negative HIV status, those from children >13 years of age, and those identified as environmental mycobacteria were excluded from this study.

Mycobacterial isolates and M. tuberculosis complex speciation by PCR analysis. Mycobacterial isolates were identified using PCR analysis (figure 1). Subcultures of M. tuberculosis complex were initially prepared on Bactec 12B medium (Becton Dickinson) and then subcultured onto Lowenstein-Jensen medium. Standard protocol for prevention of cross-contamination was followed. Specimens were heat-inactivated and lyed at 100°C for 15 min and stored at −20°C before PCR analysis. M. tuberculosis complex species were initially differentiated into M. tuberculosis and M. tuberculosis complex by PCR amplification of the TBD1 region [19]. Subsequently, the M. tuberculosis complex subgroups were identified as M. bovis or M. bovis BCG by PCR amplification of the RD10 region and the RD1 region, as described by Talbot et al. [15] and Parsons et al. [16]. The PCR diagnostic approach and primer sequences used for PCR are indicated in figure 1. Positive and negative controls were used according to routine practice. Dual infection was defined by 202- and 308-bp DNA fragments on amplification of the RD10 region and 150- and 200-bp DNA fragments on amplification of the RD1 region. BCG was further confirmed by spoligotyping, using the internationally standardized method [20].

Clinical data. Clinical information about symptoms and signs at presentation, chest radiographic findings, tuberculin skin test results, and clinical progression of disease was obtained by a retrospective medical record review. Chest radiographs were reviewed by 2 independent pediatric tuberculosis specialists and read in a standardized way. The Talbot classification of BCG complications and working definition of disseminated BCG disease were used to classify cases (table 1) [5]. Disease categories included “regional disease,” “extraregional localized disease,” and “disseminated disease.” The Centers for Disease Control and Prevention classification for HIV in children <13 years of age was used to classify HIV disease [21].

Ethical considerations. The collection of gastric aspirates and other body fluids for culture of M. tuberculosis complex forms part of routine clinical practice for children in whom tuberculosis is suspected. The collection of mycobacterial isolates in a sample bank was approved by the institutional review board of Stellenbosch University (Cape Town, South Africa). HIV testing for these patients was done in the course of routine clinical management; informed consent was obtained, and pre-
Perform PCR amplification of the TBD1 region [19]

TBD1 region absent: Probable *M. tuberculosis*

TBD1 region present: *M. bovis*, *M. bovis BCG*, *M. africanum*, *M. microti*, *M. canetti*, *M. tuberculosis*

PCR amplification of the RD10 region [16]

RD10 region present (308 bp)

* M. tuberculosis
  * M. africanum, *M. canetti*

RD10 region absent (202 bp)

* M. bovis, *M. bovis BCG, M. africanum*

PCR amplification of the RD1 region [15]

RD1 region present (150 bp)

* M. bovis BCG*

RD1 region absent (200 bp)

* M. bovis, M. africanum*

**PRIMER SEQUENCES**

<table>
<thead>
<tr>
<th>Region</th>
<th>Primer Sequences</th>
</tr>
</thead>
</table>
| RD10 (Region Present, 308 bp; Region Absent, 202 bp) | RD10 FF 5'-CTG-CAA-CCA-TCC-GGT-ACA-C-3'  
RD10 INT 5'-GAA-GTC-GTA-CTC-GGC-GA-5'  
RD10 FR 5'-AAG-CGC-TAC-ATC-GCC-AAG-3' |
| RD1 (Region Present, 150 bp; Region Absent, 200 bp) | (RD1) ET1 5'-AAG-CGG-TTG-CCG-CCG-ACC-GAC-C-3'  
(RD1) ET2 5'-CTG-GCT-ATA-TTC-CTG-GCG-CCG-G-3'  
(RD1) ET3 5'-GAG-GCG-ATC-TTG-GCG-TTG-GG-G-3' |
| TBD1 Deletion (Region Present, 351 bp; Region Absent, No Product) | TBD1F 5'-AAG-GCG-AGG-CGG-TGT-CAA-TC-3'  
TBD1R 5'-CCG-CCG-CCG-TTA-CCA-ATA-G-3' |

**Figure 1.** Diagnostic flow chart for PCR analysis of mycobacterial isolates from HIV-infected children in South Africa. Nos. in brackets are reference citations. BCG, bacille Calmette-Guérin.
Table 1. Classification of complications following bacille Calmette-Guérin (BCG) vaccination.

<table>
<thead>
<tr>
<th>Disease category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regional disease</td>
<td>Persistent ulcer, abscess, fistula, or lymphadenopathy limited to inoculation area</td>
</tr>
<tr>
<td>Extraregional localized disease</td>
<td>Infection at single anatomical site (e.g., osteitis or cutaneous abscess outside inoculation region)</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>Cases in which all 3 of the following conditions are met: (1) isolation of BCG on culture and identification at least by biochemical methods; (2) dissemination, evidenced by either positive results of blood or bone marrow culture or evidence of infection at ≥2 anatomical sites beyond the region of vaccination; and (3) a systemic syndrome compatible with mycobacterial disease.</td>
</tr>
<tr>
<td>Other BCG syndromes</td>
<td>Syndromes following vaccination in which bacteria are identified (e.g., keloid formation and uveitis; these syndromes may have an immune-system basis)</td>
</tr>
</tbody>
</table>

NOTE. Adapted from Talbot et al. [5], with permission.

* Evidence of infection includes culture positive for or histopathological demonstration of acid-fast bacilli. Examples of acceptable sources are lymph node or nodes beyond the ipsilateral lymph node; ≥1 cutaneous abscess beyond the region of vaccination; osteomyelitis at ≥1 site; brain or CSF; lung biopsy specimen; liver; spleen; intestine and/or stool; sputum; pleura and/or pleural fluid or gastric aspirate; and kidney and/or urine. Multiple isolates from the same organ system are counted only once (e.g., infection of multiple distant lymph nodes constitutes 1 source).

and posttest counseling were available. HIV-infected children were identified from a confidential database maintained by the pediatric infectious diseases unit at Stellenbosch University, which is accessible to attending physicians only (M.F.C. and A.C.H.). Standard procedure to maintain patient confidentiality was maintained through coding of mycobacterial cultures and patients’ personal information and through blinding of laboratory staff to isolate and patient information. After PCR speciation of *M. tuberculosis* complex was performed, the results were linked to patients’ personal information. Maximum effort was made to trace these patients through repeat telephone calls and home visits. Informed consent was obtained before clinical information was studied. This study proposal was approved by the institutional review board of Stellenbosch University.

### RESULTS

The sample bank for the study period included 602 mycobacterial isolates from 342 children. Of these, 183 isolates from 49 HIV-infected children were analyzed. Fifteen isolates from 5 patients were identified as *M. bovis* BCG (10% of all HIV-infected patients). No isolates of *M. bovis* were identified. Furthermore, no

Table 2. Results of a PCR-based diagnostic algorithm for speciation of mycobacterial isolates from 49 HIV-infected children in South Africa.

<table>
<thead>
<tr>
<th>Isolate</th>
<th>PCR result, by genetic region</th>
<th>Mycobacterium species</th>
<th>Source of isolate(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>A2</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>A3</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>FNA from axillary lymph node</td>
</tr>
<tr>
<td>A4</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>A5</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>A6</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Axillary lymph node biopsy specimen</td>
</tr>
<tr>
<td>B1</td>
<td>Absent 308 150</td>
<td><em>M. tuberculosis</em></td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>B2</td>
<td>Present 202/308 150/200</td>
<td><em>M. bovis</em> BCG and <em>M. tuberculosis</em></td>
<td>FNA from axillary lymph node (yielded 2 species)</td>
</tr>
<tr>
<td>B3</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Pus swab from axillary lymph node</td>
</tr>
<tr>
<td>B4</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Axillary lymph node biopsy specimen</td>
</tr>
<tr>
<td>B5</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Axillary lymph node biopsy specimen</td>
</tr>
<tr>
<td>B6</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Pus swab from axillary lymph node</td>
</tr>
<tr>
<td>C1</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Pus swab from axillary lymph node</td>
</tr>
<tr>
<td>D1</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Gastric aspirate</td>
</tr>
<tr>
<td>E1</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Pus swab from axillary lymph node</td>
</tr>
<tr>
<td>E2</td>
<td>Present 202 200</td>
<td><em>M. bovis</em> BCG</td>
<td>Pus swab from axillary lymph node</td>
</tr>
<tr>
<td>E3</td>
<td>Absent 308 150</td>
<td><em>M. tuberculosis</em></td>
<td>Gastric aspirate</td>
</tr>
</tbody>
</table>

NOTE. BCG, bacille Calmette-Guérin; FNA, fine-needle aspirate.
cases of BCG disease were identified in the group of HIV-infected children who had been vaccinated with the Tokyo M. bovis BCG strain before July 2000 (78 isolates and 21 patients). Two of the M. bovis BCG–infected patients (patients B and E) were co-infected with M. tuberculosis. The results of PCR speciation of isolates from these patients are summarized in table 2.

The clinical characteristics of the 5 patients with BCG disease are described in table 3. All were infants who had severe symptomatic HIV disease at presentation. They were all healthy at birth and received routine BCG vaccination with the Danish BCG strain. In only 1 case (patient A) was the mother known to be infected with HIV. This infant and his mother had received antiretroviral prophylaxis with zidovudine, but HIV infection was diagnosed in the infant at 5 weeks of age. Antiretroviral therapy was only available in 1 case (patient B). Treatment for BCG disease was not standardized.

Although drug susceptibility testing is not routinely done, susceptibility testing was done for patients A, B, and E, using the Bactec method (Becton Dickinson). Isoniazid resistance was detected in the BCG isolates (from fine-needle aspirate from an axillary gland) from patients A, B, and E. Furthermore, subsequent isolates from patient A demonstrated acquired rifampin resistance. Tests for susceptibility to pyrazinamide were not done. Response to therapy was poor; only 2 patients were alive at the end of the follow-up period.

After the study period ended, 2 more cases of BCG disease in HIV-infected infants were prospectively diagnosed by PCR methods. One patient had dual infection, with pulmonary M. tuberculosis disease and BCG adenitis. The other had BCG adenitis only. Both were infants who had severe symptomatic HIV disease at presentation. By August 2003, 1 patient had died.

**DISCUSSION**

All patients with BCG-related disease were infants who were vaccinated after the change in vaccine policy in July 2000, when South Africa’s Department of Health changed its recommendations from a percutaneous vaccine with the Tokyo M. bovis BCG strain to an intradermal vaccine with the Danish M. bovis BCG strain. This suggests that the method of administration and/or properties of the vaccine strain itself may have been partially responsible for the complications. The change to the intradermal route has brought South Africa’s practice in line with that of most other countries that use BCG vaccine. Data on the reactogenicity of the Danish BCG strain and the Tokyo BCG strain in similar settings are limited. In a report from Durban, South Africa, the rate of overall adverse events was 3.1% among 9763 neonates vaccinated with the intradermal Danish strain, with a decrease in local adverse events from 3.8% to 2.2% after 6 months [22]. The authors of that study con-

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**Table 3. Clinical characteristics of 5 HIV-infected children with bacille Calmette-Guérin (BCG) disease.**

<table>
<thead>
<tr>
<th>Patient</th>
<th>HIV</th>
<th>MBD</th>
<th>Sex</th>
<th>Age at diagnosis, months</th>
<th>Age at BCG disease confirmation, months</th>
<th>HIV disease characteristics</th>
<th>BCG disease characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.5</td>
<td>6</td>
<td>M</td>
<td>14</td>
<td></td>
<td>FTT, HSM, oral candidiasis, general lymphadenopathy</td>
<td>Right axillary adenitis ipsilateral to BCG vaccination site</td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>4</td>
<td>F</td>
<td>9</td>
<td></td>
<td>FTT, HSM, oral candidiasis, general lymphadenopathy, P. jiroveci pneumonia, pancytopenia</td>
<td>Right axillary adenitis ipsilateral to BCG vaccination site</td>
</tr>
<tr>
<td>C</td>
<td>3</td>
<td>3</td>
<td>M</td>
<td>10</td>
<td></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>D</td>
<td>3</td>
<td>3</td>
<td>M</td>
<td>Postmortem</td>
<td></td>
<td>Septicemia, FTT, HSM, oral candidiasis, general peripheral lymphadenopathy</td>
<td>None</td>
</tr>
<tr>
<td>E</td>
<td>9</td>
<td>10</td>
<td>M</td>
<td>13</td>
<td></td>
<td>FTT, HSM, general peripheral lymphadenopathy, disseminated (miliary) TB</td>
<td>Right axillary adenitis ipsilateral to BCG vaccination site</td>
</tr>
</tbody>
</table>

**NOTE.** All patients were asymptomatic at birth and received BCG vaccination at birth. Amik, amikacin; DOT, directly observed therapy; Eth, ethambutol; Ethi, ethionamide; FTT, failure to thrive; HSM, hepatosplenomegaly; INH, isoniazid; MBD, mycobacterial disease; Ofx, ofloxacin; PZA, pyrazinamide; Rif, rifampin; TB, tuberculosis; TST, tuberculin skin test; U, unknown; VL, virus load.

* The Centers for Disease Control and Prevention classification for HIV in children <13 years of age was used to classify HIV disease [21].
* At 3 weeks after HAART and anti-TB therapy were initiated (immune reconstitution syndrome).
* Resolved after initiation of anti-TB therapy.
Chest radiographic findings | MBD type | BCG disease classification | BCG disease treatment | HIV treatment | Follow-up period | Outcome
--- | --- | --- | --- | --- | --- | ---
Mediastinal adenopathy, persistent lobar consolidation | BCG | Extraregional localized and possible disseminated BCG disease | INH+Rif+Eth; 2 months treatment interruption; then Rif+Eth+Eth+Ofx+Amik (14 months DOT total) | No antiretroviral therapy available | 18 months | Died at 2 years of age
Bronchopneumonic opacification, pneumatocele, bronchiectasis | BCG with pulmonary TB | Regional BCG disease | INH+Rif+Eth+Ethi (8 months DOT) | HAART started at 3 months of age | 10 months | Disease free with good weight gain during HAART
U | BCG | Regional BCG disease | U | U | U | U
Diffuse alveolar opacification | BCG | Extraregional localized BCG disease | None; BCG disease was diagnosed postmortem | None | Died at 3 months of age, 4 days after admission
Miliary opacification | BCG with pulmonary TB | Regional localized BCG disease | INH+Rif+PZA; then INH+Rif+Eth+Ethi+Ofx (9 months therapy total; initially community based, then DOT) | No antiretroviral therapy available | 5 months | Miliary TB resolved; progressed to advanced HIV disease

cluded that the occurrence of complications may have been operator dependent and, thus, decreased as operator skills improved.

All patients in the present study were infants who had advanced HIV disease at the time of presentation, which supports the theory that young, symptomatic, HIV-infected children are at risk of developing BCG-related disease. However, our subjects were all asymptomatic and had no clear clinical indication of HIV disease at birth, when they were vaccinated. This suggests that children who have acquired HIV infection through vertical transmission and progress rapidly to symptomatic HIV disease may have a high risk of BCG-related disease, although this group cannot be identified at birth.

The typical clinical presentation of BCG disease in the present study included axillary adenitis ipsilateral to the vaccination site. Radiographic features, when present, were similar to those associated with tuberculosis, such as the mediastinal adenopathy seen on chest radiography of patient A. Discrimination between BCG disease and tuberculosis on the basis of clinical features, in the absence of ipsilateral axillary adenitis, may be difficult. This correlates with previous descriptions of BCG disease in immunocompromised children [5]. The clinical presentation of 2 patients was further complicated by dual infection with *M. tuberculosis* and *M. bovis* BCG. This is highly relevant in settings in which the prevalence of tuberculosis and HIV is high and routine BCG immunization programs are in place. The possibility of laboratory contamination must be considered in 1 case (patient B), in which both *M. bovis* BCG and *M. tuberculosis* were identified from the same source (fine-needle aspirate from an axillary lymph node), because a confirming culture was not available. Contamination rates for this research laboratory are <4%; cross-contamination is unlikely [23]. In patients B and E, dual infection was established by identification of isolates from different sources: *M. bovis* BCG from an axillary node and *M. tuberculosis* from gastric aspirate.

Although disease in patients A and C did not fit the Talbot criteria for disseminated BCG disease [5], patient A may have had disseminated BCG disease, and patient C may have had pulmonary involvement resulting from dissemination. However, the clinical findings of general peripheral and/or intra-abdominal lymphadenopathy with hepatosplenomegaly in these patients were not specific for disseminated BCG disease. In these immunocompromised patients, definitive diagnosis of dissemination cannot be made in the absence of examination of deep-tissue biopsy specimens or mycobacterial blood cultures. However, disseminated BCG disease may be present even when standard diagnostic criteria are not fulfilled. Patient B presented with a more benign manifestation of BCG disease, namely, acute suppurative axillary adenitis. In this patient, the onset of disease coincided with the initiation of HAART and...
antimycobacterial therapy and may reflect restoration of immune function. The restoration of cellular immunity to mycobacterial antigens has been reported after initiation of HAART in HIV-infected, immunocompromised patients and may be associated with the onset of clinical syndromes [24].

In HIV-infected infants, BCG disease can be suspected in the presence of axillary adenitis ipsilateral to the site of vaccination. Clinicians should be aware of regional BCG-related complications and the possibility of BCG dissemination. This is especially relevant when HAART is not available. In settings in which the prevalence of tuberculosis and HIV is high, speciation using molecular methods becomes necessary for the rapid and definitive diagnosis of BCG disease. The PCR-based diagnostic algorithm described adequately differentiates between mycobacterial species. It is an essential tool for research and may be affordable for routine clinical management.

In keeping with previous reports, the response to antituberculous therapy was poor. This may be the result of a number of host factors, such as HIV-related gastrointestinal disease with inadequate absorption (patients A, B, and D) [25, 26], poor compliance, delayed diagnosis, or a severe degree of HIV-related immunosuppression. Furthermore, M. bovis species are inherently resistant to pyrazinamide [14], and the possibility of resistance to other drugs exists [27]. Limited data exist on the treatment of BCG disease. Surgical excision of large axillary lymph nodes may be necessary for local containment of regional disease, as was needed for patient B [28]. Treatment similar to that for disease caused by non-BCG M. bovis strains (e.g., regimens containing rifampin, isoniazid, and ethambutol, at minimum) may be useful, but prolonged treatment may be required [5, 29]. Increases in the doses of isoniazid and rifampin may be necessary; the MICs of these drugs for the Danish BCG strain are higher than those for M. tuberculosis and other BCG strains (data not shown).

This study has a number of limitations. Selection bias existed as a result of the hospital-based entry point. Because children with known HIV status were selected, the proportion of BCG disease among HIV-infected children, compared with an HIV-uninfected control group, could not be calculated. The HIV status was unknown for the majority of children who had mycobacterial isolates stored in the sample bank, and, thus, it was not possible to calculate a true incidence or to extrapolate these results to the general HIV-infected pediatric population. However, it is possible that disseminated BCG disease in this group was rare, compared with some reports of up to 30% [30], but higher than the rates of 0.19–1.56 cases per 1 million vaccinated infants reported elsewhere [4].

In conclusion, the Danish BCG strain poses a risk for localized and disseminated disease in infants who are infected with HIV through vertical transmission, even if these infants are asymptomatic at birth. The limitations of this study prevent a true estimation of the risk of BCG disease in this cohort of HIV-infected children. However, because HIV infection greatly increases the incidence of tuberculosis, even a small degree of protection against tuberculosis may have an important impact [31]. The studies now available do not provide sufficient evidence to support a change in current BCG vaccine policy [32–35]. More-severe and rare BCG complications can only be examined in a case-control study design that incorporates community-wide surveillance in a population that includes at least 10,000 vaccinees annually [36]. A further complication is that several substrains of BCG exist that differ in virulence and reactogenicity. The safety of use of live, attenuated vaccines in HIV-infected children should be considered in the development of new vaccines.

Acknowledgments

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References

In an article in the 1 November 2003 issue of the journal (Hesseling AC, Schaaf HS, Hanekom WA, Beyers N, Cotton MF, Gie RP, Marais BJ, van Helden P, Warren RM. Danish bacille Calmette-Guérin vaccine–induced disease in human immunodeficiency virus–infected children. Clin Infect Dis 2003; 37:1226–33), 2 errors appeared in figure 1. The classification of “M. bovis BCG” should be directed from the box labelled “RD1 region absent (200 bp),” and the classification of “M. bovis, M. africanum” should be directed from the box labelled “RD1 region present 150 bp” [not vice versa]. The corrected figure is below. The authors regret this error.

Figure 1. Diagnostic flow chart for PCR analysis of mycobacterial isolates from HIV-infected children in South Africa. Nos. in brackets are reference citations. BCG, bacille Calmette-Guérin.