Adverse Reactions to Accidental Forearm Injection of Bacille Calmette-Guérin Vaccine in Schoolchildren: 12-Month Cohort Follow-up

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This study examined the natural history of reaction after accidental intradermal administration of bacille Calmette-Guérin (BCG) vaccine instead of purified protein derivative (PPD) in 226 schoolchildren. At 18 days after vaccination, a local reaction with a diameter of 4.5–14 mm was found in 62% of the students, and ulceration with discharge was found in 26.6%; corresponding rates at 120 days were 72.3% and 38% and at 281 days were 73% and 6%. At 345 days, 85% of the students had a dry scar measuring 5–14 mm in diameter, and none had ulceration or discharge.

Bacille Calmette-Guérin (BCG) was developed from an original strain of Mycobacterium bovis [1]. It was first used in France in 1921 and, despite modest efficacy [2–4], has since been used for routine vaccination against tuberculosis in >80% of the world’s population [5]. The most-utilized vaccination techniques consist of administering either 18–20 needle punctures over 1 drop of vaccine placed in the deltoid region, or a subcutaneous injection of a dose of 0.05 mL or 0.1 mL, depending on the strain [6,7]. Serious adverse reactions to BCG vaccine are rare, with an incidence of <1 in 1 million [8].

In Israel, BCG vaccination of children was discontinued in 1982. At present, it is recommended only for those at high risk of exposure to tuberculosis—mainly newborns of new immigrants from Ethiopia, which has a high incidence of tuberculosis. To measure the prevalence of tuberculosis, current national health policy stipulates that all seventh-grade students be tested by intracutaneous injection of 0.1 mL of tuberculin (i.e., PPD) [9] on the volar forearm. However, because it is a common practice to administer BCG vaccine to tuberculin-negative children [1], the accidental use of BCG vaccine instead of PPD is not uncommon. In 1998, the Communicable Disease Report Weekly [10] reported on the inadvertent inoculation with BCG vaccine of schoolchildren undergoing health testing. In such cases, the BCG vaccine dose is usually high, because the technique for administering PPD is followed. One group described an accidental BCG vaccine overdose in infants, which occurred when a technique recommended for the PPD test was used [11]. The aim of the present study was to examine the natural history of reaction after accidental BCG vaccination in schoolchildren.

Patients and methods. The study group included 226 seventh-grade students (aged 11–12 years) from a single school in Israel. The children were accidentally injected intracutaneously on the volar forearm with 0.1 mL of BCG vaccine, instead of PPD, during a routine, 1-day inoculation program supervised by the Ministry of Health. In Israel, the PPD CT-68 used for the Mantoux test is supplied by Tubersol (Pasteur Merieux Connaught) in the form of a clear solution in 10-cc bottles. The bottles are refrigerated at a temperature of 2°C–8°C. The material is injected intracutaneously (dose, 0.1 mL) on the volar forearm. BCG vaccine is supplied by the same company in 2 bottles: dry powder in one and a clear solution for dissolution in another. The bottles are refrigerated under the same conditions as PPD. The error in our case was apparently caused by the school nurses, who removed the wrong bottles from the refrigerator, and it was first discovered 10 days after inoculation, when several children complained of itching and pain at the injection site. Examination of the 226 students 72 h after inoculation revealed that only 7 children had a positive skin reaction 10–18 mm in diameter. On notification of the error, the Ministry of Health asked all 226 children to attend follow-up, with parental consent, every 2 weeks for the first 2 months and every 2 months thereafter for up to 1 year.

Results. Table 1 summarizes the findings regarding local adverse reactions to the BCG inoculation. At 18 days after vaccination, 62% of the students had a local reaction 5–14 mm in diameter, and 26.6% had ulceration with discharge. At 120 days, 72.3% of the students had a local reaction 5–14 mm in diameter, and 38% had ulceration with discharge. At 281 days, 73% of the students had a local reaction 5–14 mm in diameter, and only 6% had ulceration with discharge. By 345 days, 85% of the students had a dry scar measuring 5–14 mm in diameter,
Table 1. Characteristics of skin lesions in 226 schoolchildren after accidental bacille Calmette-Guérin vaccine injection.

<table>
<thead>
<tr>
<th>Lesion characteristics</th>
<th>Percentage of subjects, by day after injection</th>
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<tbody>
<tr>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Diameter</td>
<td></td>
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<tr>
<td>0–4 mm²</td>
<td>21.0</td>
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<tr>
<td>5–9 mm</td>
<td>31.5</td>
</tr>
<tr>
<td>10–14 mm</td>
<td>30.5</td>
</tr>
<tr>
<td>15–19 mm</td>
<td>1.9</td>
</tr>
<tr>
<td>20–29 mm</td>
<td>10.9</td>
</tr>
<tr>
<td>30–39 mm</td>
<td>3.3</td>
</tr>
<tr>
<td>≥40 mm</td>
<td>1.0</td>
</tr>
<tr>
<td>Ulceration with discharge</td>
<td>26.6</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
</tr>
</tbody>
</table>

* Negative skin reaction.

and none of the children had ulceration or discharge. In 4 children, suppurative lymphadenitis of the arm and axilla, in addition to the local lesion on the forearm, was detected. All 4 received isoniazid treatment, and 2 underwent surgical drainage.

Discussion. The expected reaction to the percutaneous injection of BCG vaccine is a cold abscess at the site of injection that turns into a bluish-red papule after 3 weeks. The lesion reaches maximum size (∼5 mm in diameter) at about 6 weeks, when the overlying skin becomes thin and shiny and frequently ulcerates, and it usually heals by the 13th week [12].

In neonates and young infants, errors in the dose administered may increase the frequency of BCG-associated adenitis [13]. Such errors tend to occur when administering institutions change from the Pasteur vaccine, which is administered in 0.1 mL doses, to the Tokyo strain vaccine, which is administered in 0.05 mL doses [6, 7].

Puliyel et al. [11] studied 556 infants in the United Kingdom who were inadvertently injected with 5 times the recommended intradermal dose of a percutaneous BCG preparation. Adverse local reactions occurred in 11% of the infants. A large, national study in Australia documented a 5% rate of adverse reactions to BCG vaccine; one-half of the reactions were abscesses [19]. The authors noted that the development of adverse reactions to BCG vaccine was not significantly associated with previous administration of BCG or other vaccines, or with patient sex, birth weight, or age. Both of these studies reported much lower reaction rates than the 50% found in our study. This might be attributable to the age of the study participants. All participants in the British study and 80% of those in the Australian study were infants; the rest were adults.

In our study, at 17 weeks after BCG vaccine administration, 72.3% of the children still had a lesion 5–14 mm in diameter, 14% had a lesion 20–29 mm in diameter, and 38% had ulceration with discharge. At 40 weeks after inoculation, 73% of the children had a lesion 5–14 mm in diameter, 3.6% had a lesion of 20–29 mm in diameter, and 6% had ulceration with discharge. We speculate that these high rates of local reaction were due to the vaccine being injected into the volar forearm instead of the deltoid.

Vaccinations are most often given on the outer region of the upper arm for reasons of safety and easy access. However, the skin on the deltoid, sternum, and upper back has a tendency to form hypertrophic or keloid scars [15]. Some of the scars are sufficiently unsightly to necessitate surgery. The reported incidence of hypertrophic or keloid scars from vaccination is 33%–38%; the incidence of keloid scars is 2%–4% [16–18].

Pigmented skin also has a tendency for hypertrophic scarring [19]. Accordingly, in our study, scar formation, ulceration, and discharge were much more intense in children of North African and Ethiopian origin than in those of European or North American origin.

In addition to the lesion on the forearm, 4 children in our group had suppurative lymphadenitis of the arm and axilla. All 4 were treated with isoniazid, and 2 also underwent surgical drainage. Neither method yielded an improvement. Data supporting the use of isoniazid and erythromycin for the resolution of abscess formation remain inconclusive [20, 21]. Although medical therapy for lymphadenopathy is not routinely indicated in the management of adverse reactions to BCG vaccine [22], therapy for suppurative lymphadenitis and abscess formation at the injection site is often recommended. However, surgical drainage of suppurative lymphadenitis is controversial, and there are no data unequivocally supporting the use of routine incision, drainage, removal, or simple aspiration. Although osteitis was reported as a relatively frequent, late complication of BCG vaccine [23, 24], we did not find cases of adverse bone and joint involvement in our 1-year follow-up study.

When the error was discovered in the case we describe here, the district health office opened a crisis intervention center at the school. In addition to facing the children’s complaints of pain and itching, we had to face the questions of anxious and worried parents as to the gravity and prognosis of the suppurative papule and its possible effect on their children’s future health. Unfortunately, the available literature held few answers. As a consequence of the event, the health authority mandated that before the initiation of any BCG vaccination to groups, a double control (i.e., 2 staff members) must check the vaccine material.

We agree with Turnbull et al. [14] from Australia, who commented that vaccination by health-care providers with lack of experience might have contributed to the development of the majority of adverse effects. In order to prevent accidental vaccination with BCG, we recommend not only adhering to na-
tional guidelines for trained providers and double controls [14], but also storing BCG vaccine and PPD in separate places, in bottles labeled with large letters in 2 languages: the local language and the language of the manufacturer.

In conclusion, the majority of children accidentally injected with BCG vaccine will have an itchy, painful skin reaction at the injection site. The course is benign but prolonged (40 weeks), suggesting that, in accidental events, such as the one reported here, a prolonged and appropriate follow-up should be implemented. After 1 year, there should be dry scarring of the lesion.

References