The booster effect with repeat tuberculin testing in children and its relationship to BCG vaccination

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Summary

One hundred and twenty-seven children, aged 6 months - 14 years, attending a day-care centre in Pretoria had two Mantoux tuberculin tests performed 8 weeks apart. On initial testing 19.7% of the children had reactions ≥ 10 mm and positive tests were commoner in the older children — who had received BCG vaccination twice. On repeat testing a significant increase in the mean tuberculin reaction size was noted and 13% of the children converted to tuberculin positivity. Since an extensive search revealed no evidence of active tuberculosis in either children or adults at the day-care centre, it was concluded that the observed enhancement of the tuberculin reactions was due to the booster effect. This phenomenon was most marked in preschoolers with a BCG scar. It is important to recognise that boosting can occur in children and may be confused with true conversion to tuberculin positivity caused by infection with Mycobacterium tuberculosis.

With repeated tuberculin testing in the same individual, an increase in the size of the tuberculin skin reaction that is not due to tuberculous infection may occur. This booster effect is analogous to the anamnestic response in serology and is thought to be due to recall of tuberculin sensitivity induced by bacille Calmette-Guérin (BCG) or various Mycobacteria that have waned with time.

Because tuberculosis is common in South Africa, children with unexplained prolonged respiratory complaints often undergo tuberculin testing and this may well be repeated at a later clinic visit. It is therefore important to know how commonly changes in tuberculin reaction size are due to the booster phenomenon.

This phenomenon has been studied extensively in adults but has received little attention in children. The booster effect in relation to BCG vaccination in children has only recently been reported. A study was undertaken to assess the booster phenomenon in healthy children and its relationship to BCG vaccination at birth and on school entry. It was decided to repeat the tuberculin tests after 8 weeks, since this is commonly practised to detect conversion to purified protein derivative (PPD) positivity after exposure to an infective source.

Subjects and methods

The study population consisted of preschoolers and schoolchildren from middle-class families attending a day and afternoon-care centre in Pretoria. The parents of each child were requested to fill in a questionnaire detailing their child's vaccination history and whether the child had ever been investigated or treated for tuberculosis. Children in whom BCG vaccination at birth could not be confirmed by hospital or clinic records or by the parents were excluded from this study. Records of revaccination on school entry were available at the day-care centre.

After informed consent was obtained, Mantoux skin testing was performed (on 127 children aged 6 months - 14 years) by the intradermal injection of 0.1 ml of Japan freeze-dried tuberculin PPD (containing 5 TU) using a tuberculin syringe and a 26-gauge needle. Injections were given into the volar surface of the right forearm. The reaction size was read after 48 hours by measuring the transverse width of palpable induration with a ruler. All the injections and readings were performed by two sisters experienced in the administration of Mantoux tests. The technique of measuring the size of skin reactions was supervised by a sister from the Tuberculosis Research Institute of the South African Medical Research Council. Note was made of the presence or absence of a visible BCG scar.

Eight weeks after the initial readings, the tuberculin tests were repeated by the same sisters, who did not have access to the initial test results. Children with reactions ≥ 10 mm on either occasion underwent physical and radiological examination and were observed for at least 9 months to exclude the development of any abnormal signs or symptoms.

Data were analysed using Student's t-test for paired samples and the chi-square test (with Yates' correction) for proportions.

Results

The day-care centre caters for preschoolers and scholars from the ages of 6 months to 14 years and, at the time of this study, employed 35 adults.

A total of 127 children (mean age 5.5 years) were entered into the study. Eighty-five were preschoolers aged 6 months - 6 years (mean 3.7 years) and 42 were scholars aged 6 - 14 years (mean 9 years). All the children had received BCG vaccination soon after birth and none had any history of, or had received treatment for, tuberculosis. All the scholars had been revaccinated on school entry. The distribution of the sizes of the children's initial and repeat tuberculin reactions is shown in Fig. 1. On initial testing, 25 of the 127 children (19.7%) had skin reactions ≥ 10 mm, of which 11 were at least 15 mm (8.7% of the total tested). Seventy-three children (57.4%) had skin reactions < 4 mm.

The differences between the results of the initial and repeat tests are shown in Table I. Eighty-seven of the repeat tests were within 3 mm of the initial test, 13 (10.2%) decreased in size by < 3 mm and 27 (21.2%) showed a > 3 mm increase in size. Conversion to tuberculin sensitivity is considered to have occurred if the size of the Mantoux skin test reaction — on repeat testing — increases by at least 6 mm from < 10 mm to ≥ 10 mm and this was recorded in 16 cases (12.6%). There were an additional 4 cases in which repeat skin test reactions increased by < 6 mm but vesiculation or ulceration occurred. None of the initial tests showed vesiculation or ulceration.
A BCG scar was detected in 32 of the 127 children (25%). The differences in BCG scarring of scholars and preschoolers is shown in Table II. Significantly more scholars had BCG scars. The relationship between the presence or absence of BCG scars, the number of BCG vaccinations received and the change in tuberculin skin reaction size is shown in Table III. The preschoolers with a BCG scar were the only group of children to show a statistical increase in the size of the skin reaction to repeat PPD administration. The scholars, whether they exhibited a BCG scar or not, had only a small increase in skin reaction size with repeat testing.

Table IV shows the number of initial tuberculin tests that were positive in the preschoolers v. the scholars. The scholars — who had received two BCG vaccinations — were more likely to have a positive PPD skin reaction than the preschoolers ($P < 0.05$).

### TABLE IV. NUMBERS OF POSITIVE INITIAL TUBERCULIN TESTS (SKIN REACTION $\geq 10$ mm) IN CHILDREN VACCINATED ONCE OR TWICE

<table>
<thead>
<tr>
<th></th>
<th>No. of positive PPDs</th>
<th>No. of negative PPDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preschoolers</td>
<td>11</td>
<td>64</td>
</tr>
<tr>
<td>Scholars</td>
<td>14</td>
<td>28*</td>
</tr>
</tbody>
</table>

* $P < 0.05$ (chi-square test with Yates' correction).

Children with positive skin reactions ($\geq 10$ mm) were examined and had chest radiographs taken. Calcified axillary glands were detected in 1 child and biopsy of one of these revealed evidence of healed tuberculosis. Since this child had recently immigrated from France, this infection was not acquired in this country. Three other children had radiological evidence of hilar gland enlargement, but at the time had clinical evidence of an upper respiratory tract infection and the radiological changes were thought to be due to a viral infection. Follow-up radiography of these children showed resolution of the hilar adenopathy. Only 1 child had parenchymal lung changes and this resolved on treatment with antibiotics.

The condition of the children in whom initial tuberculin skin reactions were $\geq 15$ mm was discussed with their parents and most of the children were given isoniazid for 6 months. No further children were placed on isoniazid therapy after the repeat tuberculin tests even if these became positive. During the 9-month follow-up period none of the children developed any suspicious clinical features. Thus, with the exception of 1 child who acquired tuberculosis overseas, none of the children had or developed any definite evidence of tuberculous disease.

Because of the unexpectedly large number of positive tuberculin reactions, an infective source at the day-care centre had to be excluded. For this reason all the adults working there underwent radiography; all the radiographs were clear.

### Discussion

The booster effect, which can occur when skin testing is repeated 1 week - 1 year (or even longer) after the initial test, manifests most often in people older than 50 years. This enhancing effect is considered to be rare in children and one study found no booster effect in kindergarten children. However, unexpected high rates of positive reactions with repeated tuberculin tests have been found in children and recently a study conducted on preschoolers found significant boosting when tuberculin testing was repeated after 2 weeks. It is not usual, however, to repeat tuberculin testing after only 2 weeks: more commonly testing is repeated after 6 - 8 weeks to detect conversion after exposure to an infective person. For this reason, this study looked at the changes in tuberculin skin reaction size in tests repeated after 8 weeks in healthy children with no apparent exposure to an infective source.

There was a significant increase in the mean size of skin reaction to PPD with repeated testing. Of the 127 children, 27 (21%) showed a $> 3$ mm increase and 16 (13%) converted to PPD sensitivity, i.e. an increase of at least 6 mm in skin reaction size from $< 10$ mm to $\geq 10$. A further 4 children
developed vesiculation on repeat testing. Conversion rates due to the booster effect vary according to the ages of the subjects tested and the prevalence of tuberculosis and non-tuberculous Mycobacteria in the population; rates varying from 0% to 25% have been reported in adults.\(^4,9,10\)

Excluding technical inaccuracies, conversion to PPD sensitivity may be due to recent infection with \(M.\) tuberculosis or to the booster phenomenon. Because of the former possibility, an extensive search for evidence of tuberculous infection was conducted at the day-care centre. All the children with a tuberculin skin reaction size \(\geq 10\, \text{mm}\) were examined, had chest radiography and were followed-up clinically for at least 9 months. All the adults working at the day-care centre were also radiographed and no evidence of tuberculous disease was detected in any of the children or adults — with the exception of 1 child with healed tuberculous adenitis (see ‘Results’).

It is therefore highly unlikely that the children who converted to PPD sensitivity all became infected at the same time without any apparent exposure to an infective source; the more likely explanation for the increase in the size of PPD skin reactions is that of the booster phenomenon. To overcome the problem of distinguishing between the booster effect and true conversion it has been recommended that 3 consecutive skin tests be performed.\(^11\) The second test is performed 1 week after the first, which is too early for true conversion to have taken place but at which time boosting will already be apparent. Since it has been shown that further repeated skin testing does not result in further boosting,\(^7\) an increase in reaction between the second and third tests performed more than 6 weeks apart indicates true conversion.

The boosting effect was especially marked in the preschoolers and, in fact, when the scholars were analysed separately, a significant increase in the mean size of the PPD skin reaction with repeated testing could not be demonstrated. A possible explanation for this is that boosting will only occur in individuals in whom previous tuberculin sensitivity has waned and the scholars — who have received two vaccinations — are more likely to still be tuberculin-sensitive than the preschoolers. This is borne out by the finding that more scholars had positive initial PPD skin reaction readings (\(\geq 10\, \text{mm}\)) than preschoolers \((P < 0.05)\).

Sepulveda et al.\(^2\) demonstrated a strong association between the size of BCG scarring in preschoolers and the degree of boosting. In this study, a relationship between the presence of a BCG scar and the booster phenomenon was only demonstrated in the preschoolers. The scholars did not show this association, possibly because of the much lesser booster effect noted in these children.

The results of this study indicate that conversion to tuberculin sensitivity in children may be due to the booster effect. This is most probably related to BCG vaccination, which induces tuberculin sensitivity that wanes with time but can be recalled by repeat PPD administration. The presence of a BCG scar in preschoolers may help to identify those children most likely to exhibit boosting. It is important to be aware of this phenomenon when interpreting repeat tuberculin reactions in vaccinated children.

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REFERENCES


