

# Interpretation of the PPD skin test in BCG-vaccinated children

J.H. JONCAS, MD, PH D; R. ROBITAILLE, RN; T. GAUTHIER, RN

**Summary:** Skin testing with 5 tuberculin units (TU) of purified protein derivative (PPD) of tuberculin stabilized with polysorbate (Tween) 80 was done 3 months and 1 year after immunization with bacille Calmette-Guérin (BCG) vaccine in two groups of children: one group vaccinated at birth and another group at age 6 years.

Interpretation of the PPD skin test with 5 TU is possible in children 1 year and older vaccinated with BCG at birth: if the diameter of induration is more than 10 to 12 mm the reaction cannot be ascribed to BCG vaccination and is highly suggestive of supervening infection with *Mycobacterium tuberculosis* or occasionally atypical mycobacteria. In contrast, the interpretation of a PPD test in children vaccinated at age 6 years is extremely difficult.

**Résumé:** Interprétation de l'épreuve cutanée au PPD chez des enfants vaccinés au BCG

Dans le but de faciliter l'interprétation de l'épreuve cutanée à la tuberculine nous avons entrepris l'étude de deux groupes d'enfants. Le premier groupe reçut le vaccin du bacille Calmette-Guérin (BCG) à la naissance, l'autre groupe à l'âge de 6 ans. L'épreuve cutanée avec 5 unités de dérivé protéique purifié de tuberculine (5 TU de PPD) stabilisé à l'aide du polysorbate (Tween) 80 fut faite 3 mois et 1 an après la vaccination.

Les résultats de cette étude démontrent clairement que l'épreuve PPD avec 5 TU faite à l'âge de 1 an ou plus chez les enfants vaccinés à la naissance par le BCG peut être interprétée. Lorsque le diamètre de l'induration est supérieur à 10 à 12 mm, cette réaction n'est pas due au BCG et suggère fortement une surinfection par *Mycobacterium tuberculosis* ou par des mycobactéries atypiques. Par contre, l'interprétation d'une épreuve PPD chez l'enfant vacciné à l'âge de 6 ans est beaucoup plus difficile.

Interpretation of the tuberculin test in a child immunized with bacille Calmette-Guérin (BCG) vaccine is often difficult. Aside from the individual biologic variations in reactivity, the diameter of the reaction is dependent on the source of the vaccine, viable counts in the vaccine, the method of inoculation,<sup>1,2</sup> the age at the time of vaccination,<sup>3,4</sup> the time elapsed since vaccination<sup>5</sup> and the effect of supervening infection by atypical mycobacteria or virulent *Mycobacterium tuberculosis*.<sup>6</sup> We have observed that, when tested with purified protein derivative (PPD) of tuberculin after the age of 1 year, many children vaccinated with BCG at birth react only to 100 tuberculin units (TU) or to 5 TU with an induration diameter of less than 10 mm. To facilitate the interpretation of the tuberculin test we studied two groups of children vaccinated with BCG at different ages.

## Material and methods

The vaccine used was the liquid BCG from the Institute of Microbiology and Hygiene of Montréal (concentration, 60 mg of BCG per ml; approximately 10<sup>7</sup> viable units/ml). It was given in six 1-cm long scarifications in the lumbar area except in neonates, in whom it was given in four scarifications of the same length, two on each shoulder.

Skin testing was done with 5 TU of PPD stabilized with polysorbate (Tween) 80 at 3 months and 1 year after vaccination. Reactions were read by two nurses who had compared their method of reading the reaction immediately before this study.

Two groups of children were vaccinated: 68 infants at birth and 165 children at age 6 years, 86 of whom had been previously vaccinated at birth and 79 of whom had never previously been vaccinated.

## Results

The results of this study are summarized in Table I. The percentage of conversion after vaccination varied from 83.7 in those vaccinated at birth, to 90 in those vaccinated at age 6 years. When tested 1 year after vaccination 58.1% of the infants vaccin-

ated at birth had negative reactions, but of those vaccinated at age 6, only 22.2 to 33.3% had negative reactions. Furthermore, the individual maximum diameter of the reaction 1 year after vaccination did not exceed 11 mm in those vaccinated at birth, whereas it reached 20 mm in some children vaccinated at age 6. The relative frequency of reversion to negative in infancy is highly significant ( $P < 0.005$ ).

In contrast, the tuberculin skin reaction exceeded 12 mm of induration in children aged 1 year or more vaccinated with BCG at birth, in whom a proved or presumed diagnosis of pulmonary tuberculosis was made at Sainte-Justine Hospital, Montréal in the past 3 years. This is illustrated by the case reports of patients 1 and 2. Patient 3 is representative of BCG-vaccinated children of the same age referred for investigation at Sainte-Justine Hospital after contact with pulmonary tuberculosis in a family member.

## Case reports

### Patient 1

An Indian boy aged 18 months, vaccinated with BCG at birth, was admitted to Sainte-Justine Hospital with pulmonary infiltrates in both lower lobes, atelectasis of the right middle lobe and right hilar adenopathy suggestive of pulmonary tuberculosis. He nevertheless appeared to be in good health and his height and weight were in the 90th percentile. Skin testing with 5 TU of PPD resulted, after 48 hours, in induration of 30 mm in diameter. Gastric washings cultured on Löwenstein-Jensen medium did not yield *M. tuberculosis*. The patient was treated with isoniazid, 250 mg/d and rifampin, 150 mg/d. The pulmonary infiltrates resolved over 3 to 4 months.

### Patient 2

A 13-month-old girl, vaccinated with BCG at birth, was referred to Sainte-Justine Hospital because her mother had active pulmonary tuberculosis. The child appeared to be in good health and there were no abnormal physical findings. The chest radiograph was normal. In view of a strongly positive tine test, a PPD test using 1 TU instead of 5 TU was done. The diameter of induration after 48 hours exceeded 10 mm. Gastric washings cultured on Löwenstein-Jensen medium yielded 5 weeks later *M. tuberculosis*. A year's therapy with isoniazid was begun

From the Institute of Microbiology and Hygiene of Montréal

Reprint requests to: Dr. J.H. Joncas, l'Institut de microbiologie et d'hygiène de Montréal, 531, boul. des Prairies, CP 100, Ville de Laval, Qué. H7N 4Z3

and rifampin was added after the results of the culture were known.

### Patient 3

A 2-year-old boy, vaccinated with BCG at birth, was referred to Sainte-Justine Hospital after active pulmonary tuberculosis was diagnosed in the grandfather, who lived with the family. The child was apparently healthy. Results of the physical examination and chest radiograph were normal. The tine test was negative, but testing with 5 TU of PPD resulted in induration of 5 mm in diameter after 48 hours. Cultures of three gastric washings remained negative for *M. tuberculosis*. Chemoprophylaxis with isoniazid for 1 year was instituted. Four follow-up radiographs showed no abnormalities.

### Discussion and conclusion

The results of this study and that of Lifschitz<sup>4</sup> clearly show that when children vaccinated with BCG at birth are skin tested with 5 TU of PPD at age 1 year or older the reaction can be interpreted. If the diameter of induration is more than 10 to 12 mm the reaction cannot be ascribed to BCG vaccination and is highly suggestive of supervening infection with *M. tuberculosis* or occasionally atypical mycobacteria. Our experience to date at Sainte-Justine Hospital further supports the findings of this study: children over age 1 year, vaccinated with BCG at birth, in whom a proved or presumed diagnosis of pulmonary tuberculosis was made, have had reactions to PPD skin testing exceeding 12 mm of induration. A waning of the skin test reaction to tuber-

culin in the absence of supervening tuberculous infection was also noted by Lifschitz<sup>4</sup> in children 1 year or more after BCG vaccination at birth. Likewise, in these children supervening tuberculous infection was associated with tuberculin reactions to 5 TU of PPD of more than 12 mm in diameter.

In contrast, the interpretation of a PPD test in children vaccinated at age 6 years is extremely difficult. The greater skin reactivity of these children is probably due to a booster effect of the vaccine at that age because of previous infection with antigenically related atypical or other mycobacteria. In fact, in children revaccinated at age 6 years there seems to be an influence of prior vaccination at birth on the persistence of skin test reactivity. A booster effect is probably responsible for the mean diameter of the tuberculin reaction being 11.7 mm 3 months after vaccination and for the percentage of positives being 77.8% after 1 year in those revaccinated at age 6 years, compared with 9.7 mm and 66.7% in those vaccinated at age 6 for the first time. There is some evidence, however, from the literature<sup>1,2</sup> that using BCG from other sources or vaccine containing fewer viable units and given intradermally could facilitate the interpretation of the tuberculin test in children vaccinated at an older age. The disappearance of a positive tuberculin skin reaction to 5 TU of PPD in most children aged 1 year and over after BCG vaccination at birth is probably due to a relative immunologic immaturity or a different technique of vaccination or

both. It does not, however, mean loss of immunity: as shown by Lifschitz<sup>4</sup> in his series of children, and from results in a few children we have tested (not described), skin testing with 100 TU gives positive reactions. It has been clearly shown<sup>7</sup> that the incidence of tuberculosis after exposure is lowest in groups of individuals negative to 5 TU but positive to 100 TU of PPD.

The interpretation, therefore, of a PPD test with 5 TU, as performed in most hospitals in Canada, in children vaccinated at birth and tested after the age of 1 year, is clearly feasible. The interpretation, however, of the same test done in children vaccinated at a later age is extremely difficult but could possibly be made easier if BCG was given by the intradermal route with a smaller number of viable units.

### References

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Table 1—Reactions to skin testing with 5 TU of PPD\* after BCG† vaccination in children of two age groups

Group and timing of PPD test	Reactions no. (%)‡	Diameter (mm)			
		Maximum	Minimum	Mean	Median
Infants 3½ to 16 months old vaccinated at birth (n = 68)					
PPD test:					
Less than 1 year after vaccination (n = 37)	Positive 31 (83.7) Negative 6 (16.3) <sup>a</sup>	20 4	5 3	11.5 3.2	10 3
More than 1 year after vaccination (n = 31)	Positive 13 (41.9) <sup>b</sup> Negative 18 (58.1)	11 4	5 0	7.4 0.8	6.5 0
6-year-old children revaccination at 6 years (n = 86)					
PPD test:					
3 months after vaccination (n = 41)	Positive 36 (87.8) Negative 5 (12.2) <sup>c</sup>	20 4	5 3	11.7 3.8	11-12 4
1 year after vaccination (n = 45)	Positive 35 (77.8) <sup>d</sup> Negative 10 (22.2)	20 4	5 0	10.2 1.8	10 0
6-year-old children with primary vaccination at 6 years (n = 79)					
PPD test:					
3 months after vaccination (n = 40)	Positive 36 (90) Negative 4 (10) <sup>e</sup>	20 4	5 0	9.7 2.5	10 3
1 year after vaccination (n = 39)	Positive 26 (66.7) <sup>f</sup> Negative 13 (33.3)	20 4	5 0	10.0 1.1	8-9 0

\*5 tuberculin units of purified protein derivative of tuberculin

†bacille Calmette-Guérin

‡Significance of differences: between a and b, P < 0.005; between b and d, P < 0.005; between b and f, P < 0.1; and between e and f, P < 0.1.