

## WANING OF POST VACCINIAL ALLERGY AFTER NEONATAL BCG VACCINATION

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### ABSTRACT

*Tuberculin sensitivity or post vaccinal allergy (PVA) is widely used as an indicator of successful BCG vaccination. The protection conferred by BCG vaccination, the duration of post-vaccinial allergy and the relationship between the two remain a subject of controversy. The present study was conducted with the aim of finding the duration of PVA and evaluate the need for revaccination. One thousand newborns were given BCG under controlled conditions and followed up for PVA by serial PPD (5TU) injection at 3, 6, 12, 24, 30 and 36 months. An induration of 5 mm or less was recorded as negative and no subsequent testing was done. At 3 month, all the infants were given PPD and 95.3% showed a positive response. The positivity rate declined significantly ( $p < 0.01$ ) to 19% by 3 years of age. A statistically significant ( $p < 0.01$ ) fall in the mean PPD induration size was also noted. At 3 months, the mean induration size was 10.68 mm but by 3 years it had decreased to 3.86 mm. The distribution of PPD size also showed that with the increase in age, there was a shift towards the smaller size. At 3 years of age, none of the children had an induration of more than 10 mm. The booster effect due to repeated PPD testing was seen in a small percentage and only at 6 and 12 months test. Subsequently no increase in PPD induration was noted. Sex of the child did not influence the PPD induration size significantly ( $p > 0.05$ ). At 3, 6 and 12 months of*

The vaccine against tuberculosis, BCG, was first used in 1921 by Weill-Halle' and from that time it has been in the midst of a number of controversial reports. One of the major problems in evaluating BCG induced immunity is that there are no definite means of quantifying the immune response. Tuberculin sensitivity also termed as post vaccinial allergy (PVA) is widely used as an indicator of successful BCG vaccination although it is recognized that it is a form of allergic reaction and not a direct measure of tuberculo-immunity. Attempts made at defining the duration of PVA have yielded varying results. Some authors have shown a decline of tuberculin response 2-5 years after vaccination while others have reported a persistence upto several years(1-5). It has also been felt that waning of BCG induced tuberculin hypersensitivity may be associated with a loss of protection against tuberculosis(6).

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*age, significant correlation between BCG lesion and PVA was noted, the co-efficient of correlation being 6. At later ages, all the children had a BCG scar while PVA had waned considerably.*

*It is concluded that PVA wanes significantly over 2-3 years following neonatal BCG vaccination and does not correlate well with the presence of a BCG scar at this age. It is recommended that a booster dose of BCG vaccination be given at 2-3 years of age.*

**Key words:** BCG vaccine, Tuberculin sensitivity.

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Considering the controversy it was felt pertinent to conduct the present study with the aim of finding the duration of PVA and evaluate the need for revaccination.

### Material and Methods

A total of one thousand newborns formed the study material. All of them were given BCG by the same person within one week of birth. The vaccine used was of Danish Strain 1331 prepared at Guindy laboratories, Madras. It was stored at 2-4°C and was taken out of the fridge just before vaccination. A dose of 0.1 ml was injected intradermally in the upper part of left arm of the baby after cleaning with ether.

Tuberculin testing was done using the purified protein derivative (PPD) supplied by Span Diagnostics Pvt Limited, Udhana, Surat. Manufacturers claim that the source material is calibrated against Batch RT 23 manufactured by Statens Serum Institute, Denmark. It was diluted with a special buffer containing Tween 80 as a stabilizer. The strength of PPD used was 5 tuberculin units (TU) per 0.1 ml. The PPD solution was drawn in a sterile tuberculin syringe. The skin of volar aspect of forearm was cleaned and then stretched with one hand. The solution was injected intradermally raising a bleb of 6-8 mm diameter. Serial Mantoux testing was done at 3,6,12,24, 30 and 36 months of age. The injections were given alternately on right or left forearm.

The reading was taken 48-72 hours after the injection. Induration was measured by the Pen method and recorded in millimeters using non-stretchable measuring tape. An induration of 5 mm or less was taken as negative. The age at which PPD was negative was noted and no further testing was done. The presence of BCG scar was noted and correlated with tuberculin sensitivity.

The data was statistically analyzed using Students 't' test and correlation of coefficient.

### Results

All the thousand newborns vaccinated at birth with BCG, were given PPD at 3 months of age. The number of cases tested at different ages is shown in *Table I*. At 3 months of age, 95.3% of cases showed a positive tuberculin test. Positivity rate declined progressively to 81.8% at the end of first year of life. At 2 years of age it fell to less than 50% and by 3 years only 19% showed a positive response. This significant decay in post vaccinal allergy can be seen in *Fig. 1*.

*Table II* shows the mean PPD induration size at different ages. A statistically significant ( $p < 0.01$ ) decrease in the mean PPD induration size was noted from 3 months to 3 years of age. On evaluating the distribution of PPD sizes at different ages an induration greater than 10mm was noted more among infants upto 1 year of age. At age 2 years and beyond only 20.8% of the children showed a reaction of more than 10 mm. All the children tested at 3 years of age had an induration of 10 mm or less. An attempt was

**TABLE I-Positive PPD at Different Ages**

Age	Total cases	PPD positive	Percentage
3 mo	1000	956	95.3*
6 mo	982	899	91.5*
12 mo	507	415	81.8*
2yrs	272	116	42.6*
2.5 yrs	207	69	33.3*
3yrs	21	4	19.0*

\*  $p < 0.01$ ; statistically significant.

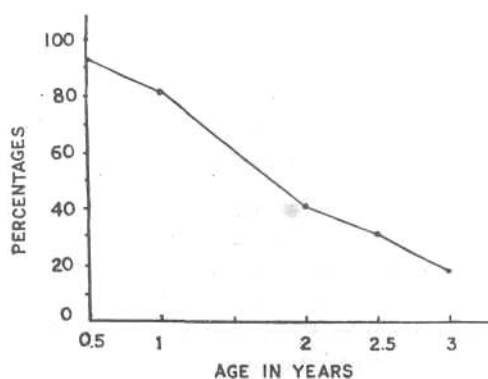


Fig. 1. Decay curve of tuberculin sensitivity.

TABLE II—Mean PPD Induration Size at Different Ages

Age	Mean PPD induration size (mm)
3 mo	10.68 ± 3.1*
6 mo	9.90 ± 3.4*
12 mo	8.47 ± 3.9*
2 yrs	6.23 ± 4.89*
2.5 yrs	5.16 ± 3.8*
3 yrs	3.86 ± 2.54*

\*  $p < 0.01$ ; statistically significant.

made to evaluate the booster effect of repeated PPD injections. From 3 months test to 6 months, 12.7% of the infants showed a mean increase of 2.2 mm. From 6 months to 12 months, the increase was of 3.0 mm and seen in only 3.7% of the cases. From 12 months to subsequent PPD testing at 2, 2.5 and 3 years age, no increase in the PPD induration size was noted.

There was no significant difference in the PPD induration size of boys or girls. On correlating the size of BCG scar with the PPD induration, at 3, 6 and 12 months of

age a significant relationship was observed with the coefficient of correlation being greater than 6 (PE). At 2, 2.5 and 3 year of age, all the children had a BCG scar while the corresponding post vaccinal allergy had dropped significantly.

## Discussion

The duration of post vaccinal allergy has been the subject of many studies but still remains controversial. The problems inherent in such studies are the effect of acquired tuberculous infection as well as the enhancement of tuberculin allergy by previous testing. In the present study, tuberculin positivity attained after neonatal BCG vaccination dropped steeply from 95.3% at 3 months to 19% by 3 years of age. A similar waning of PVA by 2 years of age has been observed by others also(1,2,7). In an earlier cross-sectional study from this institution, Punnachalil noted the tuberculin conversion rate at 1 to 1.5 years to be 62%; 55% at 1.5 to 2 years and 23% at 2 to 3 years(8). Ungthavorn has also reported waning in older age groups(9). Grindulis *et al.* tested the tuberculin response at 2 years in Asian children and found half the children with a BCG scar to be Mantoux negative(10). Elliot *et al.* observed that following BCG at birth, there was a fall in tuberculin positivity of about 10 to 20% during the first year, a finding similar to the present study(11). Ungthavorn and Lohsoonthorn showed that tuberculin conversion rates fell from 54.8% during infancy to 31.5% for children aged 1-5 years(12). Kulkarni and Rao reported only 14.2% of children tested between 1 to 2 years were Mantoux positive(13). Al Kassimi *et al.* observed that 71% of children aged 5 to 14 years who had received BCG at birth reacted negatively to 5TU PPD supporting the finding of waning of PVA(14). In another study, Al Kassimi *et al.* found

that by 5 years only 7.8% children vaccinated at birth had a Mantoux of 10 mm or more(15).

With increasing age, not only the tuberculin positivity rate declines but also the size of the reaction becomes progressively smaller. In the present study, a statistically significant fall in the mean PPD induration size from 10.68 mm at 3 month to 3.86 mm at 3 years of age was noted and also the distribution of induration size showed a shift to lower values. Similar decrease in mean PPD induration size has been observed by others also(7). Karalliede reported a decrease from 3.5 mm at 8 months to 1.5 mm by 5 to 7 years of age(16). The results of Ungthavorn and Elliott *et al.* were equivocal(9,11).

In contrast to the above reports, a persistence of tuberculin allergy upto several years after BCG has been demonstrated by several authors(4). It has also been suggested that tuberculin sensitivity can be maintained by repeated tuberculin testing(17). With repeated tuberculin testing an increase in the size of tuberculin skin reaction may occur and this has been termed the booster effect. It is analogous to the anamnestic response and is seen more frequently with increasing age and is rare in children(18,19). In this study, some boosting of the PPD induration was noted during the infancy but at later ages no increase in size was seen.

In the present study, a significant correlation between BCG lesion and PVA was noted during infancy while later on the PVA declined, although the BCG scar could be seen in all the cases. Other studies which have assessed this correlation in the early post vaccinal period, upto 12 to 16 weeks, have found a positive correlation(1,20). Punnachalil's results were similar to the

present study showing a linear relationship between BCG scar size and PVA till 1 to 1.5 years and then declining(9). Lack of convincing correlation between the two has been reported by others also(10,21).

The results of this study indicate that PVA following neonatal BCG vaccination wanes by 2 to 3 years of age and does not correlate with the presence of a BCG scar. As the waning of PVA may reflect some degree of loss of protection against tuberculosis, it is recommended that a booster dose of BCG be given at 2 to 3 years of age.

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