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ORIGINAL ARTICLE

Effect of number of BCG vaccination on tuberculin induration size

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Aim: The aim of this study is to interpret purified protein derivative (PPD) induration sizes with respect to the number of Bacillus Calmette–Guérin (BCG) scars.

Methods: We have considered 1879 school children between the ages of 7 and 14 years from seven primary schools in Kocaeli, Turkey. Children were injected with 5TU 0.1 mL PPD and induration sizes were measured at 72 h. Number of BCG scars, PPD application dates and induration sizes were recorded for each pupil. This study was also evaluated further for 312 households.

Results: The mean diameter of PPD induration size for 0, 1, 2 and 3 BCG vaccination scars were 1.43 mm (95% confidence interval (CI): 0.84–2.02), 6.39 mm (95% CI: 5.91–6.87), 10.46 mm (95% CI: 10.04–10.88) and 11.35 mm (95% CI: 9.36–13.34), respectively. Furthermore, 90% and 95% percentiles of PPD induration 0, 1, 2 and 3 vaccinations were 10 and 12 mm, 16 and 19 mm, 17 and 19 mm and 19.2 and 20 mm, respectively. There was evidence for a linear trend across from 0 to 3 BCG vaccinations, indicating that mean induration size increases with the number of vaccination scars. The size of indurations directly correlated with the number of vaccination scars, PPD induration size of children with no vaccination scar was quite small and it was generally less than 5 mm.

Conclusion: This study shows the importance of the number of BCG scars in the determination of PPD induration size limit when tuberculosis infection is evaluated.

Key words: Bacillus Calmette–Guérin; tuberculin skin test; tuberculosis.

Tuberculosis (TB) is still a major public health problem especially in developing countries. Although TB incidence has been in a decreasing trend in recent years owing to medication and improvement in life standards, the number of new cases has increased world-wide owing to poverty and poor health care.[1] World Health Organisation (WHO) estimates that more than one-third of world's population is infected with *Mycobacterium tuberculosis*.[1] In 2000, 751 individuals died from TB in the USA.[2]

Countries were categorised according to incidence as low (24 cases per 100 000 population per year), moderate (24–99 cases per 100 000 population per year), or high (100 cases per 100 000 population per year) incidence of TB, as reported by the 1997 report of the WHO.[3] Since 1995 the WHO has recommended a single dose of the Bacillus Calmette–Guérin (BCG) vaccine at or soon after birth in all countries with a high incidence of TB infection.[4] BCG vaccination is used primarily in young infants in more than 100 countries,[1] and multiple BCG vaccinations are still carried out in some countries as part of their TB control programme.[5]

A recent meta-analysis of published BCG vaccination trials suggested that BCG is 50% effective in preventing pulmonary TB in adults and children.[6] The protective effect for disseminated and meningeal TB appears to be slightly higher, with BCG preventing 50–80% of cases.[1] However, there is no evidence that BCG prevents infection with *M. tuberculosis*.[7]

BCG is compulsory for all infants in Turkey.[8] The first vaccine is applied in the third month and the second is at the age of 7 years. The policy of BCG vaccination at these ages has been adopted because of high risk of TB development among infants and children.[9] In addition, Health Ministry recommends the BCG vaccination if the tuberculin induration is found to be less than 5 mm at any time.[10] Previous vaccination with BCG can cause a reaction to a tuberculin skin test.[1] Revaccination with BCG can also alter the tuberculin skin test response and probably the diagnosis of TB infection.[10] This study was carried out in order to investigate the correlation of the size of tuberculin induration with the number of BCG vaccinations.

Key Points

1. Purified protein derivative (PPD) reaction shows high variability with the number of BCG vaccinations.
2. PPD induration size for patients with no vaccination scar was quite small and generally less than 5 mm.
3. Strongly positive skin tests are most probably due to tuberculosis infection rather than BCG.

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Methods

This study has been carried out during the 2000–2001 education year in seven primary schools in Kocaeli, Turkey. A total of 1879 school children between the ages of 7 and 14 years were considered. The total population of primary school students in Kocaeli was 193 984. Schools were selected on the basis of the socio-economic level determined by the financial status of parents, educational background, etc.

At the beginning of this study, name, date of birth, gender, school, number of BCG scars and purified protein derivative (PPD) application dates were recorded for each student. Parents were given a set of questionnaire about the health background and history of their children and were also asked to submit written documentations and statements. The school children who had varicella, measles, mumps, influenza and live-virus vaccines in the last 20 days were not considered in this study. Children with other viral illnesses and chronic diseases were not considered either. If there is a discrepancy between the number of scars and number of vaccinations stated in the document obtained from the parents, those children were also excluded. By doing so, we have made sure the number of vaccinations applied to children. Children who had any symptoms of any other diseases after the PPD injection were also excluded. One hundred and eighteen children out of a total of 1879 were excluded from the beginning owing to various reasons mentioned above.

PPD was applied to children between the ages of 7 and 14 years regardless of whether they have BCG scars or not. Single use, 26 gauge sterile injectors were used. 5TU 0.1 mL PPD solution was injected intradermally into top two-thirds of the volar face of the left forearm to create a 6–10 mm swelling. The PPD solution (JSC 'BIOLEC', Pomirky, Kharkiv 61070, Ukraine, RT23) used in this study was obtained from a filtrate of a thermally killed culture of the TB mycobacteria purified by ultra filtration or otherwise, precipitated by means of trichloroacetic acid, conditioned with ethanol and ether and dissolved in a stabilising solution (0.85% solution of sodium chloride with phosphate buffer, Tween-80 as a stabiliser and phenol as a preservative).

One of two experienced doctors measured the diameter of all PPD indurations along and transverse to the longitudinal axis of the arm at 72 h with ball point technique and transparent, plastic, millimetre scale rulers. The doctors, who carried out the measurements, had no prior knowledge regarding the number of BCG scars in students to prevent any prejudice during the reading of the reaction. They went through the same intensive training at the Tuberculosis Prevention and Treatment Center regarding the measurements and they did not carry out measurements of the same child.

Results

In this study, PPD was used in 1879 children. PPD indurations of 118 (6.3%) children could not be measured owing to various reasons stated before and only the readings of 1761 (93.7%) children were evaluated.

Children were classified as having received no BCG vaccination (0), one BCG vaccination, two BCG vaccinations and three BCG vaccinations. Correlation of mean transverse diameter of PPD indurations was compared with respect to these groups by using non-parametric test, Kruskall–Wallis test. Table 1 shows mean transverse values with 95% confidence intervals (CI) for these four groups and test statistic results (χ^2-values) with *P*-values. The mean diameter of PPD indurations for 0, 1, 2 and 3 BCG vaccinations were 1.43 (95% CI: 0.84–2.02), 6.39 (95% CI: 5.91–6.87), 10.46 (95% CI: 10.04–10.88), and 11.35 (95% CI: 9.36–13.34), respectively. The only statistically significant induration size was found for children with two BCG vaccination scars, but not for those children with three BCG vaccination scars. We should also note that sample size for three BCG vaccinations was too small to show any significant effect and CI is wider. The test for a linear trend was also performed and there was a significant linear trend, showing that induration size increases with increasing BCG vaccination scars ($P = 0.04$). Table 1 also shows 90 and 95 percentiles for four groups of BCG vaccinations.

The American Academy of Paediatrics suggests that 5, 10 and 15 mm values should be considered as cut-off values according to risk factors.[1] Out of 1761 children, 312 who had tuberculin indurations greater and equal to 15 mm were referred to a local TB treatment and control clinic along with all their household members for further evaluation and radiography. Table 2 shows the distribution of children with PPD induration diameter ≥15 mm according to the number of BCG scars. As the number of BCG scars increases, percentage of children who had PPD induration size greater and equal to 15 mm is increasing.

Table 2 Mean induration diameter ≥15 mm according to number of BCG scars

BCG scars (*n*)	Children (*n*)	Children with induration size ≥15 mm	
		n	%
0	171	4	2.3
1	752	95	12.6
2	801	202	25.2
3	37	11	29.7
Total	1761	312	17.7

Table 1 Mean induration transverse diameter, 95% CI, percentiles, *P*-value and χ^2-values with respect to BCG vaccination number groups

BCG	*n*	Mean transverse induration diameter (95% CI)	90 percentile	95 percentile	χ^2	*P*-value
0 (no BCG)	171	1.43 (0.84–2.02)	10	12	7.1	0.41
1	752	6.39 (5.91–6.87)	16	19	13.3	0.06
2	801	10.46 (10.04–10.88)	17	19	15.2	0.03
3	37	11.35 (9.36–13.34)	19.2	20	5.5	0.59

CI, confidence interval.

We assessed household contact of a child with a positive PPD reaction. It was found from the screening of household members that three of the children had household members with TB disease which they had no prior knowledge of. This information was not stated in the documents supplied by the parents either. It was discovered that one child's sister (23 years old at the time) had pulmonary TB, one child's father (47 years old) had pulmonary TB with cavity and another's brother (25 years old) had pulmonary TB. These three children with a positive tuberculin skin test who had shown no clinical or radiographic evidence of the disease were given isoniazid therapy. These three children had PPD indurations greater than their 90 percentile and their induration transverse diameters were 26 mm (2 scars), 27 mm (2 scars) and 25 mm (1 scar).

Discussion

Determining new cases of TB, treatment and vaccination programmes, screening of vaccinated or unvaccinated population and approaches in the treatment of this disease is still on the agenda of many countries and health organisations. BCG vaccination is considered as an important protective measure from the TB disease and is widely used around the world. There are still ongoing discussions about its protection capability and effectiveness against TB disease despite the fact that it has been used since 1921.[11]

PPD tests have been used for years to evaluate immunisation in the post-BCG vaccination period. It is an easy-to-apply technique and suitable for the screening of large numbers of population.[11]

It is generally considered acceptable for tuberculin reactions if induration size is less than 10 mm after the BCG vaccination, although larger reactions may occur in some individuals.[1] However, there is no clear indication whether high PPD values in children, who have had more than one BCG vaccination are due to BCG use or TB infection. It is also not clear as to how many millimetres should be considered positive or whether the same limits can be used for multiple vaccinations. These are still subject of further research.

Menzies *et al*. indicated that repeated BCG vaccination does not affect the tuberculin reaction clearly but a small group of people who had repeated vaccinations had longer tuberculin sensitivity.[12] Riley *et al*. in a study of 1100 people showed that BCG vaccination used during infancy does not affect the tuberculin reaction for 10–25 years later.[13] Sepulveda *et al*. in a study of 659 healthy children have shown that tuberculin reaction becomes negative approximately 3 years after the BCG vaccination.[14]

Repeated BCG vaccination increases PPD induration and one of the frequent reasons of the increase of tuberculin reaction is given as more than one BCG vaccination.[15] Bierrenbach *et al*. found that the presence of two BCG scars induced higher tuberculin reactivity than did the presence of only one scar.[16] In a study published by Saito *et al*. where they report that with an increasing number of BCG scars, the prevalence of positive PPD also increased among children.[17] The increase in the diameter of PPD indurations with the number of BCG scars was also put forward in a study carried out on 870 school children in Ankara by Gulnar and Bulut.[18] Our results are in good agreement with the studies reported in the literature where it is stated that PPD reaction shows high variability with the number of BCG vaccinations.[10,11,18,19]

There are studies which suggest that the limits of PPD indurations should be evaluated with respect to the number of BCG vaccinations. Our results show that 90th and 95th percentile values with zero scars are 10 and 12 mm, one scar 16 and 19 mm, two scars 17 and 19 mm and finally with three scars 19.2 and 20 mm. It is apparent that tuberculin reaction percentile values are higher in repeated BCG applications. PPD induration size of patients with no vaccination scar was quite small and it was generally less than 5 mm.

Our result indicated that PPD induration size may increase in BCG vaccinated children. Tuberculin skin test reaction is more related to repeated BCG applications. PPD responses greater than 90 and 95 percentiles of indurations are likely to be indicative of TB infection regardless of the number of BCG vaccinations previously given to an individual especially for the age group considered in this study. Larger PPD indurations in BCG vaccinated children may not be a sign of TB infection as the increase in TB reaction is more related to repeated BCG applications but strongly positive skin tests are most probably due to TB infection rather than BCG. These percentile values can be considered acceptable on children between the ages of 7 and 14 years in countries where multiple BCG vaccinations are used as part of their programme. Any policy based partly on PPD indurations must be planned by keeping in mind the existing TB prevalence rates in a community. The number of BCG vaccinations should be updated and decided by following the trend of TB prevalence in order to prevent unnecessary preventive treatment as well as possible future complications. These would also be affected by the speed and effectiveness of treatment.

It is our opinion that it is rather difficult to interpret PPD indurations clearly by simply looking at the scars. The absence of a scar does not imply that children did not receive BCG. Furthermore, repeated BCG application might be confusing in PPD interpretation. It is also our opinion that repeated BCG vaccinations can confound the interpretations of PPD skin testing for latent TB infection more than single BCG vaccinations. There appears to be no benefit in giving additional doses of BCG for TB prevention.[17] Although it is a health policy in Turkey to administer multiple BCG doses, there is no evidence that repeated doses increase protection against severe diseases.

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