SIGNIFICANCE OF THE TUBERCULIN TEST IN SINGAPORE

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ABSTRACT

The standard tuberculin test used by all Singapore government hospitals and institutions is the intradermal Mantoux test using 1 TU of PPD RT23 with Tween 80, and read 72 hours later.

There is almost 100% BCG coverage in Singapore children for many years, and therefore the tuberculin skin reaction must be interpreted with special consideration.

Taking 8 mm and above as positive, six month old infants vaccinated at birth gave a positive rate of 42% and a mean reaction size of 5.89 mm. The reaction appeared to wane rapidly and among 6 year old school children the positive rate dropped to 12% and the mean size to 2.38 mm. By the age of 11 years, the children showed a positive rate of 36% and a mean size of 6.27 mm. A further increase is observed in 15 year old children, the positive rate being 88% and mean size 13.28 mm.

Among tuberculosis contacts, the positive rate and mean size of the tuberculin reaction are generally higher, especially in the younger age groups.

Tuberculosis patients above 15 years old were observed to be practically all positive reactors with a mean size of at least 16 mm.

Key Words: Tuberculin, Mantoux, tuberculosis, contacts, school children

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INTRODUCTION

Eight years after Robert Koch discovered the tubercle bacilli, he was able to prepare a broth culture filtrate of the bacilli which he called tuberculin. He first used it to treat tuberculous patients on the premise that the tuberculin would promote healing through its specific action, not on the tubercle bacilli, but on the "living tuberculous tissue" in which the bacilli were enmeshed. Unhappily, his claims for the curative properties of tuberculin were soon to be challenged and discredited. However, his observation that tuberculin, when injected into tuberculous patients, produced a sharp rise in temperature, but had little or no effect on non-tuberculous subjects, led to the use of tuberculin as a diagnostic tool to detect tuberculous infection (1).

The best use of the tuberculin skin test for the diagnosis of tuberculous infection is in a low prevalence country where a non-BCG-vaccinated person known to be previously non-reactive to tuberculin, becomes positive, i.e. a recent converter. In a relatively high prevalence country like Singapore where the BCG vaccination coverage in infants is almost 100% and practically all adults are positive reactors through natural infection, the tuberculin skin reaction must be interpreted with special consideration.

This paper presents the tuberculin reaction in certain sections of our local population under different conditions. It is hoped that this will give clinicians and epidemiologists a better understanding of the significance of the tuberculin reaction in our local context.

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METHOD

A standard method of doing the tuberculin test, namely the intradermal Mantoux test recommended by WHO (2) is adopted by all Government institutions in Singapore. One unit (0.1 ml) of PPD RT23 with Tween 80 (a detergent which prevents the adsorption of the tuberculin on to the glass container) is injected intradermally on the volar aspect of the left forearm with a special tuberculin syringe and needle. Reading of the transverse diameter of the induration is done 72 hours later using a ruler calibrated in millimeters. Both the tests and the readings were done by specially trained and experienced staff of the Department of Tuberculosis Control.

The Department of Tuberculosis Control in its surveillance, preventive and case-finding work, has accumulated a large amount of data on the tuberculin reaction of various groups of people. Some of these data have been analysed and the results presented below include the following groups:

1. **Six month old babies BCG vaccinated at birth –**
Post-vaccination Mantoux Test for this group of babies was done periodically since 1979 as part of our surveillance on the potency of the vaccine used. Babies born in our government hospitals are vaccinated one or two days after birth. A group of 500 to 600 of these babies was called up for the tuberculin test when they were 6 months old.

2. **Six year old Primary 1 school entrants –**
The Mantoux Test was done routinely for all primary school entrants without BCG scar until 1981 when it was discontinued. The test was also done for those with BCG scar in 1970.

3. **Eleven year old Primary 6 school children –**
All children in this group receive the Mantoux test routinely to screen out negative reactors for booster BCG vaccination. The staff of the Department of Tuberculosis Control have been doing this until 1981 when it was integrated into the School Health Services' immunisation programme.

4. **Fifteen year old Secondary 4 school children —**
The Mantoux Test is done routinely for all in this group of children as for Primary 6 students.

5. **Age 0 to 19 years who are contacts of tuberculosis patients —**
The Mantoux test is done as a routine procedure in this age group as part of our contact examination.

6. **All tuberculosis patients treated in our department —**
A routine Mantoux test was done for all tuberculosis patients registered for treatment in our department between 1983 and 1985. Only those bacteriologically confirmed patients are included in the analysis. The number of confirmed cases below 15 years of age was too small for analysis.

Although a tuberculin reaction of 10 mm is usually considered as a positive reaction, our studies have shown that we have an intermediate group of reactors of 5 mm to 10 mm where the curves for the negative and positive reactors overlap. A reaction size of 8 mm and above was therefore taken as positive.

RESULTS

Tuberculin Reaction among Normal Subjects —
Figure 1 shows the post-vaccination tuberculin reaction in 6-month old babies born in 1979. 42% of the babies were positive reactors of 8 mm and above, and the overall mean reaction size was 5.89 mm. A few other studies done in subsequent years gave very similar results.

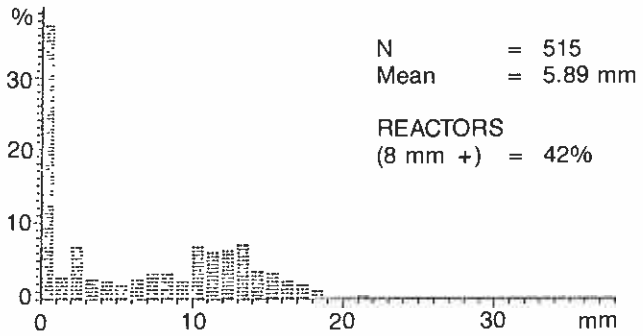

FIGURE 1 — 6 month old babies vaccinated at birth (1979)

Compared to the 6-month old babies, 6-year old children, all of them vaccinated at birth, seem to exhibit very low levels of tuberculin allergy (Figure 2). Only 12% were positive with reactions of 8 mm and above, and the mean size was 2.38 mm. In Sweden where BCG was given extensively at birth, a study using 2 TU of RT23 showed that only 8.4% — 13.7% of 7 year old children had positive reactions of 10 mm and above (3). Karalliedde et al also found significant waning of the tuberculin reaction at age

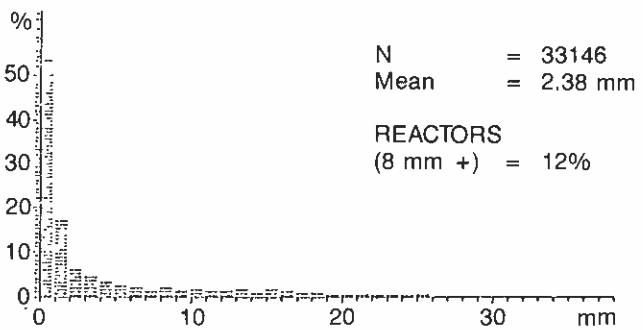

FIGURE 2 — 6 year old school children with BCG scar (1970)

5 — 7 years in Sri Lanka children who were vaccinated at birth (4).

For 11-year old children, 36% were positive reactors and the mean size was 6.27 mm (Figure 3). Several factors could account for this marked difference of the positive rate compared to that in 6-year old children in Primary 1. Firstly, the "booster effect" could be responsible because a proportion of these children examined when they were in Primary 1 and found to have no BCG scar were Mantoux tested. Most of these would have been negative reactors and therefore BCG vaccinated, adding further to the positive pool. Secondly, infection with non-tuberculous mycobacteria which is known to be prevalent in this region is a possibility as the children leave home and become exposed to a wider environment. It is unlikely that much of this high positive rate is due to natural infection with virulent human mycobacteria because the incidence of tuberculosis in the age group 10 — 14 years is very low (below 10 per 100,000) (5).

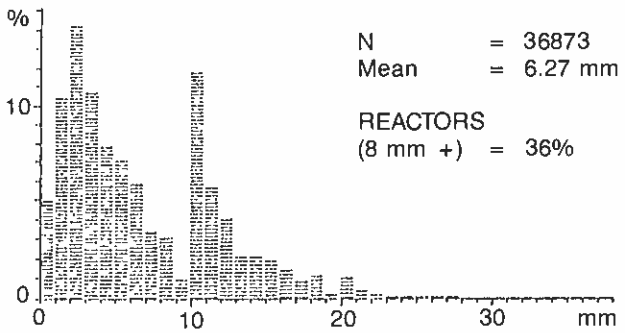

FIGURE 3 — 11 year old school children with BCG scar (1980)

In 15-year old children in Secondary 4 (Figure 4) the positive rate increased to 88% and the mean size to 13.28 mm. This sudden surge of positive rate is mainly due to the accumulation of positive reactors from previous years. Those children who were negative at age 11 years were all re-vaccinated with BCG.

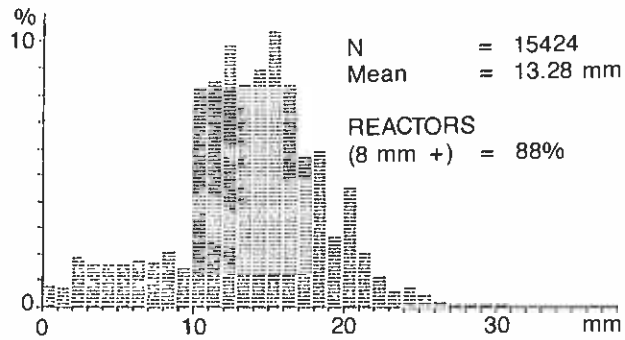

FIGURE 4 — 15 year old school children with BCG scar (1980)

Tuberculin Reaction among Contacts —
The data here have been analysed by age group for comparison with pre-schoolers, primary school and secondary school children.

For the age groups 4 — 8 years (Fig 5), and 9 — 13 years (Fig 6), the positive rate and overall mean reaction size were both higher than those in the corresponding age groups of normal school children, i.e. Pr. 1 and Pr. 6. This is to be expected since contacts are exposed to tuberculosis. The older children 14 — 18 years (Fig 7), gave similar figures as those of Sec. 4 students.

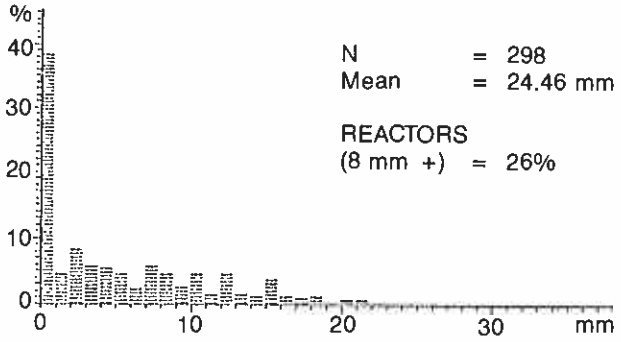

FIGURE 5 — TB contacts aged 4 — 8 years (1988)

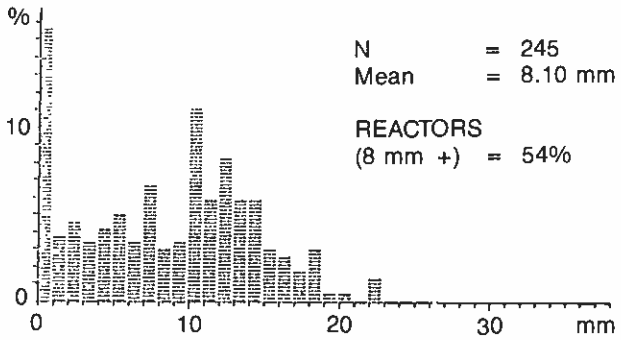

FIGURE 6 — TB contacts aged 9 — 13 years (1988)

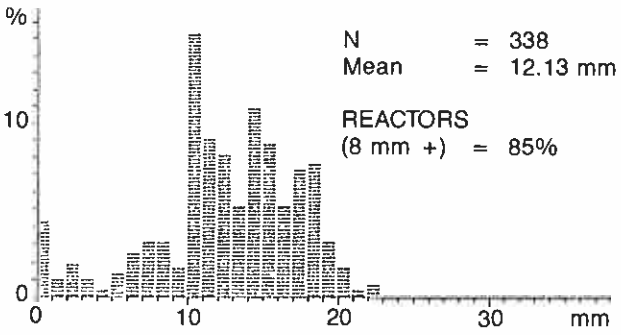

FIGURE 7 — TB contacts aged 14 — 18 years (1988)

Tuberculin Reaction among Tuberculosis Patients —

From Figures 8 to 11, it is noted that above 95% of all tuberculosis patients aged 15 years and above were positive reactors. The mean size ranged progressively from 16.82 mm in those above 60 years of age to 18.45 mm in the 15 — 19 age group. The decrease in reaction size with increasing age is statistically significant. ($z = 2.01$, $0.05 < p < 0.02$). This phenomenon has been well documented (6).

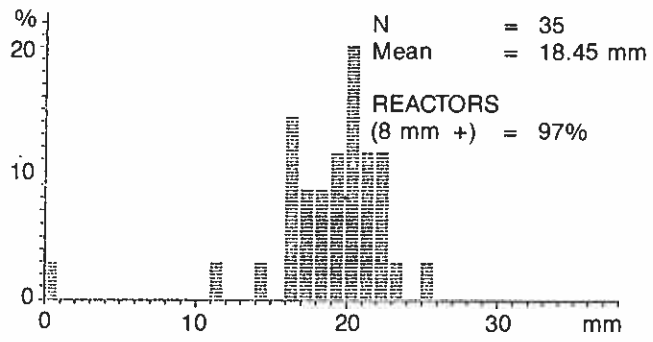

FIGURE 8 — TB Patients aged 15 — 19 years (1983 — 85)

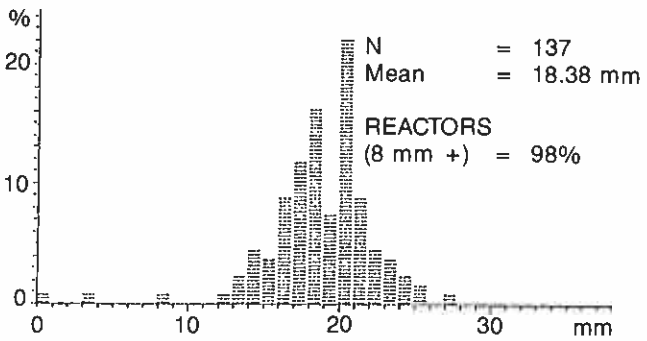

FIGURE 9 — TB Patients aged 20 — 39 years (1983 — 85)

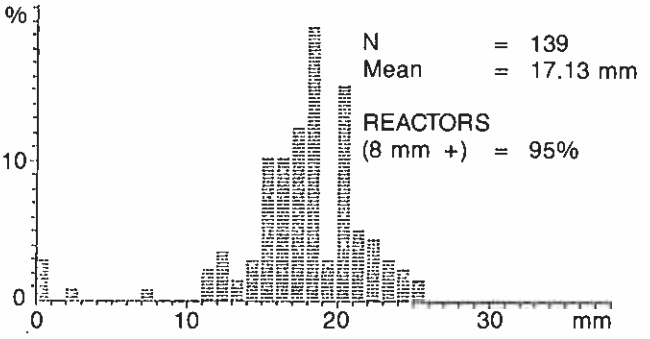

FIGURE 10 — TB Patients aged 40 — 59 years (1983 — 85)

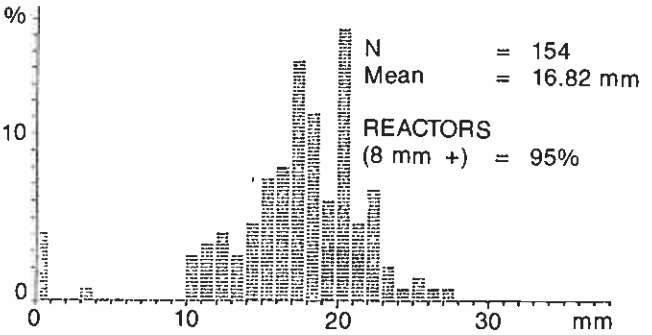

FIGURE 11 — TB Patients aged 60 and above (1983 — 85)

The mean size of 18.45 mm in tuberculous patients in the 15 — 19 age group (Figure 8) when compared to the 12.13 mm mean size in tuberculosis contacts in the similar age group (Figure 7) gives a difference which is highly significant statistically ($z = 8.36$, $p < 0.001$).

There is no question that a high percentage of tuberculosis patients have a positive tuberculin reaction. A review of the literature shows that most studies from other countries used 5 to 10 TU of PPD for the tuberculin test, but Aziz and Haq (7) of Pakistan using 1 TU of RT23 for the Mantoux test found that over 93% of confirmed Tuberculosis patients gave a reaction of 10 mm and above.

DISCUSSION

The validity of the tuberculin test depends on a number of factors which may be classified as host, environmental and technical factors.

Host factors —

The presence or absence of previous BCG vaccination obviously will give different significance to the tuberculin reaction. Different types of BCG vaccines will also give an appreciable difference in the mean size of the tuberculin reaction (8). The "booster effect" (9) must also be kept in mind if repeated tuberculin testing is done.

Immunocompromised subjects are known to have a suppressed tuberculin reaction. Schick and Dolgin (10)

have shown this in their study of 30 tuberculous children who were given oral prednisolone. In the local context, K H Tan (11) also found that all the children who had received adrenal-cortical steroid therapy prior to the test gave a negative reaction. Other diseases like sarcoidosis, amyloidosis, lymphomas, Hodgkins disease, leukemias, hypothyroidism and viral infections like measles (12, 13, 14), acquired immune deficiency syndrome, diabetes, and conditions like gastrectomy, jejuno-ileal bypass (15) are known to suppress the tuberculin reaction. Severe forms of tuberculosis like meningeal and miliary tuberculosis may give a negative tuberculin reaction due probably to the physiological release of corticosteroids during the period of stress. Edwards and Kirkpatrick refer to the immunosuppressive effect of an antigen excess state in tuberculosis (16). Therefore, the tuberculin reaction in ill patients should be interpreted with caution.

Reversion of a positive to a negative reaction is known to occur quite frequently in subjects who have received INH chemoprophylaxis (17). This variability of the tuberculin response in patients receiving INH was recently confirmed by Tager and his co-workers although they conceded that the reversions were not stable in all cases and the variability could be due to technical errors (18).

Perinatal malnutrition is implicated as a cause of poor response to tuberculin (19), but Seth et al (20) showed that a mild to moderate degree of malnutrition does not interfere with the elicitation of response in BCG vaccinated children.

Environmental factors –

In countries where the prevalence of tuberculosis is very low and BCG vaccination is not extensively practised, a positive tuberculin reaction can be taken to be diagnostic of the presence of infection. In high prevalence countries where mass BCG vaccination is the practice, the usefulness of the tuberculin test is limited. Another confounding environmental factor is the presence of non-tuberculous mycobacteria. This group of mycobacteria gives a non-specific sensitivity (21, 22) which may be strong enough to cause a problem in certain countries especially in South and South-east Asia (23, 24).

Technical factors –

Several methods of doing the tuberculin test like the Tine and Heaf multiple puncture and the Moro patch test are easy to apply but, because of the uncertain dosage released, are difficult to standardise and interpret. The intra-dermal Mantoux test recommended by WHO requires trained staff to carry out the test as well as read the reaction. Variability in reaction size due to differences in technique and reading by different testers and readers is well documented (25, 26). Chaparas et al (27) estimated a consistency of 67.2% to 69.7% in the reading of the skin reaction. In our Department, an assessment of our readers was made in 1982 with Primary 6 students as subjects. Our "standard reader" showed a 83.5% consistency in dual readings. The consistency of our other readers compared to our "standard reader" ranged from 63.1% to 78.3%.

The type and dosage of the tuberculin used must also be taken into consideration in the interpretation of the tuberculin reaction.

CONCLUSION

For local comparison to be useful, the standard intradermal Mantoux test must be done with 1 TU of RT23 and the induration read 72 hours later.

The tuberculin reaction profile of the groups of subjects shown in Figures 1 to 11 are summarised and tabulated in Table 1. It shows that in infancy the mean reaction size is about 6 mm with 42% positive rate.

The level of allergy appears to wane gradually till age 6 years when the mean reaction size dropped to 2.38 mm and the positve rate to 12%.

At age 11 years, without any intervening booster BCG, the mean reaction size increased to 6.27 mm and the positive rate to 36%.

Mainly because of the booster BCG at age 11 years for all negative reactors, by age 15 years about 90% were positive with a mean reaction size of 13.28 mm.

If there was a history of contact with tuberculosis, the mean reaction size and positive rate were generally higher than in normal school children. However, from 15 years old and above, contact with tuberculosis seems to make very little difference to the tuberculin reaction.

Patients 15 years old and above with tuberculosis have a positive rate of over 95% and a significantly bigger tuberculin reaction size ranging from 16.82 mm to 18.45 mm. Though no valid figures of tuberculin reactions are available for younger children with tuberculosis, it is reasonable to assume that their values will also be proportionately higher compared to normal children.

In order to help the clinicians who often use the tuberculin skin test as one of the diagnostic tools for tuberculosis, we have attempted to provide a rough guideline relating tuberculous lung lesion to the Mantoux test. Normal distribution was assumed for Mantoux reaction sizes of 8 mm and above in confirmed tuberculous patients treated in our department between 1983 and 1985, and the mean and standard deviation of these reaction sizes were calculated (Table 2). With the aid of a computer programme based on Simpson's rule, the areas under the normal curve were estimated for readings 8 – 15 mm in the different age groups. Mathematically, this is equivalent to the estimated proportions of reactors with these Mantoux reaction sizes. The proportions of non-reactors below 8 mm were calculated as simple percentage of the number of non-reactors in the respective sample. The estimated values tabulated in Table 2 show that the chances of a tuberculous patient having a reaction of 0 – 7 mm (i.e. a non-reactor) are about 2% if the patient is 15 – 39 years of age, and 4% if he is 40 years or older. For readings between 8 and 15 mm, the chances increase to 7% and 22% respectively.

TABLE 1
PROFILE OF MANTOUX REACTION IN SELECTED GROUPS

	Number	Positive rate %	Mean size in mm
Normal subjects:			
6 months old	515	42	5.89
6 years old	33146	12	2.38
11 years old	36873	36	6.27
15 years old	15424	88	13.28
TB Contacts:			
4 – 8 years old	298	26	4.46
9 – 13 years old	245	54	8.10
14 – 18 years old	338	85	12.13
TB Patients:			
15 – 19 years old	35	97	18.45
20 – 39 years old	137	98	18.38
40 – 59 years old	139	95	17.13
60+ years old	154	95	16.82

It must be emphasised that the tuberculin test has one important problem: its variability. Assuming that all other factors are equal, there is still a whole spectrum of reactions in different individuals ranging from fully active cell-mediated response to complete anergy (28). So the message is clear in regard to the interpretation of tuberculin skin reactions – "clinical judgement, not a fallible finger, should be the basis for a diagnosis of tuberculous infection" (29).

TABLE 2
ESTIMATED RATES AMONG TUBERCULOUS PATIENTS WITH DIFFERENT MANTOUX REACTION SIZES

Age Groups (years)	Reactors ⩾ 8 mm Normal Distribution Curve				Proportion of non-reactors (< 8 mm) %
	Number	Mean (mm)	SD_{n-1}	Proportion under curve (8 – 15 mm) %	
15 – 19	34	19.00	2.807	4.1	2.8
20 – 39	135	18.64	2.875	10.3	1.5
15 – 39	(average to whole number)			7	2
40 – 59	133	17.84	3.002	20.4	4.3
60+	147	17.61	3.473	22.6	4.5
40+	(average to whole number)			22	4

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