# Compliance to Treatment of Latent Tuberculosis Infection in a Region of Israel

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**Key words:** *Mycobacterium tuberculosis*, tuberculin skin test, latent tuberculosis infection

## Abstract

**Background:** One of the measures adopted in Israel since 1959 as part of the tuberculosis control program was screening children aged 12–13 years old. The screening comprised single-step tuberculin skin testing using the Mantoux method.

**Objectives:** To assess the efficacy of tuberculin skin screening for TB in schoolchildren in southwestern Israel as well as the compliance to treatment for latent tuberculosis infection.

**Methods:** We retrospectively reviewed the records of children in the Ashkelon region who underwent a tuberculin skin test during the period 1995–99.

**Results:** Of the 28,016 eligible children, 27,232 were tested. In 923 children, mostly from the former USSR and Ethiopia, an induration of 10 mm or more was found. Only 52 Israeli-born children tested positive. Tuberculosis was found in seven children with a positive test, five of whom were from Ethiopia. All children who tested positive were referred to the local TB clinic; only 266 children (28.8%) presented. Only 151 completed the recommended treatment of isoniazid for 6 months. Thus, although screening included most of the targeted children aged 13, only a third of them presented to a TB clinic, and of these only about half completed treatment for latent infection.

**Conclusions:** Our results indicate that the current policy of screening for latent TB in our region is ineffective in terms of implementation of the recommended treatment. We suggest that only high risk groups be screened, and that a concerted effort be made to implement treatment.

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The incidence of tuberculosis in Israel in the early 1950s was over 200 per 100,000 population, and an intensive campaign was waged to control the disease [1]. Among the control measures adopted since 1959 was the screening of children aged 12–13 years old by single-step tuberculin skin testing using the Mantoux method. The TB control program was effective in reducing rates to below 15/100,000 [2] in 1974. At that time the annual tuberculin skin testing of schoolchildren, performed by school nurses and followed by immunization with bacille Calmette-Guérin [1], was the only ambulatory TB service that remained active. Although BCG immunization was suspended in Israel in 1982, the screening program continued because of the rising incidence of TB [2], mostly due to immigration from the former Soviet Union and Ethiopia [3,4]. Many schoolchildren from these countries have positive skin tests [3] – indicating latent infection with TB and risk of reactivation tuberculous disease – and, as such, are candidates for treatment of the latent infection [5,6]. The TB control strategy, isoniazid preventive therapy, or treatment of latent TB infection, is sometimes recommended in industrialized countries, especially in the United States and Canada [7].

The aim of our study was to evaluate the results of the tuberculin test screening program in the Ashkelon region and, particularly, its efficacy in terms of treatment completion for latent TB infection.

## Patients and Methods

The study population included all (28,016) children in grade 7 in the Ashkelon district (southwestern Israel) between 1995 and 1999. The Ashkelon District Health Office is responsible for public health issues in the study region. Clinical evaluation of the subjects was performed in one of the two regional TB clinics in the cities of Ashkelon and Rehovot.

Tuberculin tests using 0.1 ml 5 TU PPD (Tubersol, Connaught Laboratories, Canada) [8,9] were performed and read between 48 and 72 hours after injection, by school nurses and public health nurses, under the supervision of the Ashkelon District Health Office according to the guidelines of the American Thoracic Society [7]. Trained nurses registered and filed the results. These data was used in the study. According to ATS

TB = tuberculosis

BCG = bacille Calmette-Guérin
ATS = American Thoracic Society

recommendations [7], an induration of 15 mm was considered a positive result in children with previous BCG immunization. In non-BCG immunized children, 10 mm or more was considered a positive result. Previous BCG vaccination was verified by the nurses according to the vaccination scar and/or vaccination card.

The school nurses referred the children with positive tuberculin results to the two TB centers located in the region (mostly to the Ashkelon but also to the Rehovot TB center). Each child had a chest X-ray and was examined by a physician.

Using the data of the children on file in the schools and the TB clinics, we checked how many children had positive tuberculin tests, how many of them were sent to the TB centers; and among those who reached the centers, how many completed the recommended treatment.

The country of birth and/or the ethnic origin of the child were defined according to data registered in the school lists. Four groups were defined: children born in the "former USSR," children of "Ethiopian origin," children born "in Israel," and "other children." The definition "Ethiopian origin" included all children born in Ethiopia or children whose mother and father were born in Ethiopia.

### Statistical analysis

The difference between the groups was evaluated using ANOVA and chi-square analysis of contingency groups.

## Results

Of the 28,016 children registered in the seventh grade in the Ashkelon region during the years 1995–99, tuberculin tests were performed in 27,232 (97%) and read in 26,772. The results of the screening procedure are presented in Table 1.

A positive tuberculin test was found among 3.4% (923 children) of the tested and read children. The number of children with positive tests was greatly influenced by the country of origin [Table 2]. For example, only 0.26% of children born in Israel (52 of 20,158) had a positive tuberculin test, compared to 11.3% in children from the former USSR (622 of 5,515) and 23% of children of Ethiopian origin (213 of 925). More than 20% of the "other children" (36 of 174) had a positive tuberculin test. The "other children" included 72 from South America, 36 from India, 28 from Yemen, 26 from France, and 12 from other European countries or the USA.

A total of 871 children had been previously vaccinated with BCG; and for them 15 mm or above was used to define a positive test. Only 52 children were not previously vaccinated with BCG and in them a positive tuberculin test was defined as 10 mm or above. According to these criteria the total number of positive tests was 923.

Active TB was diagnosed in seven children who had a positive tuberculin test (five children from Ethiopia and two from the former USSR).

With regard to completion of treatment, 460 children did not return to have their tests read (1.7% of all tests). Of these, 368 (1.8%) were born in Israel, 69 (1.25%) were born in the former USSR, and 23 (2.4%) were born in Ethiopia (*P*=NS).

Table 3 presents the distribution of children examined in one of the two regional TB centers and their completion of

**Table 1.** Tuberculin school screening (grade 7) in the Ashkelon region in Israel, 1995–99

| Year | No. of children in grade 7 | Children tested and read (%) | Positive tuberculin tests (%) | Active TB diagnosed through systematic screening |
|---|---|---|---|---|
| 1995 | 4,266 | 3,914 (91.7) | 140 (3.6) | 0 |
| 1996 | 5,531 | 5,246 (94.8) | 174 (3.3) | 4 |
| 1997 | 5,005 | 4,773 (95.3) | 104 (2.2) | 0 |
| 1998 | 8,368 | 8,077 (96.5) | 291 (3.6) | 2 |
| 1999 | 4,846 | 4,762 (98.2) | 214 (4.5) | 1 |
| Total | 28,016 | 26,772 (95.5) | 923 (3.4) | 7 |

**Table 2.** Ratios (positive results over total tested) of children with positive tuberculin tests in the Ashkelon region in Israel, 1995–99, by country of origin

| Year | Former USSR (%) | Ethiopia (%) | Israel (%) | "Other" (%) | Total (%) |
|---|---|---|---|---|---|
| 1995 | 102/536 (19) | 21/128 (16.4) | 10/3,218 (0.3) | 7/32 (21.8) | 140/3,914 (3.6) |
| 1996 | 120/951 (12.6) | 41/ 106 (38.6) | 9/4,163 (0.2) | 4/26 (15.4) | 174/5,246 (3.3) |
| 1997 | 76/994 (7.6) | 22/183 (12) | 3/3,575 (0.1) | 3/21 (14.3) | 104/4,773 (2.2) |
| 1998 | 151/1,803 (8.3) | 103/281 (36.6) | 24/5,942 (0.4) | 13/51 (25.5) | 291/8,077 (3.6) |
| 1999 | 173/1,231 (14) | 26/227 (11.5) | 6/3,260 (0.2) | 9/44 (20.5) | 214/4,762 (4.5) |
| Total | 622/5,515 (11.3) | 213/925 (23) | 52/20,158 (0.3) | 36/174 (20.7) | 923/26,772 (3.4) |

**Table 3.** Proportion of children with positive tuberculin tests examined at the TB clinic and their completion of recommended therapy, according to country of origin

| Country of origin | No. of children examined at TB clinic (% of total tuberculin tests) | No. that completed recommended therapy (% of total children examined) |
|---|---|---|
| Former USSR | 190 (30.5) | 106 (55.8) |
| Ethiopia | 57 (26.8) | 37 (64.9) |
| Israel | 17 (32.7) | 6 (35.3) |
| Other | 2 (6) | 2 (100) |
| Total | 266 (28.8) | 151 (56.8) |

treatment for latent TB, according to their country of origin. Of the 923 children with a positive tuberculin test referred for examination, only 266 (28.8%) were examined and recommended treatment (213 in Ashkelon and 53 in Rehovot). Of these, only 151 children (56.7%) completed the recommended 6 months treatment – 127 in Ashkelon (59.6%) and 24 in Rehovot (45.3%). There was no significant difference in compliance with clinic visits and treatment between the groups according to country of origin.

## Discussion

Tuberculin skin testing is the only routinely available and comparatively inexpensive method for detecting individuals infected with *Mycobacterium tuberculosis* [6,7]. According to several comprehensive studies, there is a positive association between tuberculin test reactivity and the risk of subsequently developing active TB [8]. This is the rationale for the treatment of persons with latent *Mycobacterium tuberculosis* infection and has been an essential component of TB control in the USA for many years [10].

In Israel, screening for TB is performed in new immigrants from high prevalence countries [1], healthcare workers [11] and schoolchildren [1]. A study evaluating the status of latent TB infection in schoolchildren found that less than 2% of children related to low risk groups had a positive tuberculin test, while children related to high risk groups had a 6–24 times higher rate of positive test results [8]. Considering the association between tuberculin test reactivity and latent TB infection and the low efficacy of mass screening, it was recommended that screening programs target individuals in high prevalence populations with a high risk of prior infection and hence a significant risk of developing active TB [8]. Those testing positive should receive treatment to eradicate their latent infection.

The present evaluation of a tuberculin screening program in the Ashkelon region of southwestern Israel between 1995 and 1999 showed that 97% of eligible children were screened. Our study further revealed that all 923 children with a positive test were referred to a local TB clinic but only 30% presented for further evaluation. All were recommended treatment for latent TB infection with isoniazid for 6 months. Only 151 (56.7%) completed the recommended therapy. This rate of therapy completion is twice the rate of presentation for evaluation, as noted above. This may reflect the fact that the parents of a child who came to the clinic were more ready to comply with treatment and follow-up than those who ignored the initial recommendation for evaluation.

Seven children were found to have active TB (0.026% of the study population and 0.8% of the positive tuberculin test group). Five of them were from Ethiopia and two from the former USSR. None of them had open TB; five had pulmonary lymphadenopathy and two had pleural TB. It is likely that additional cases of active TB would have been discovered among the children with positive tuberculin screening tests who did not present for evaluation.

The poor results of universal screening of schoolchildren in our district, as shown in this study, are not entirely unexpected as other authors have also demonstrated poor adherence to "preventive" or "prophylactic" therapy for latent TB infection [10]. The policy in itself is only justifiable in programs aiming at eradication or elimination of TB, as indeed is the current policy in Israel [12,13].

The unfortunate results raise several issues that need to be addressed. Non-targeted screening is unwarranted on both epidemiologic and cost-effective grounds [14]. The cost-benefit analysis of such mass tuberculin test screening was evaluated by Mohle-Boetani et al. [14], who found that targeted tuberculin screening of schoolchildren is considerably less costly than mass screening and was more efficient in prevention of TB. Historically, when TB rates in Israel were above 200/100,000, universal screening was probably appropriate. Later, even though rates no longer justified mass screening, the deterioration of TB facilities in the late 1980s and early 1990s led us to continue with this policy in order to maintain basic TB public health skills [12]. Mass skin testing demanded involvement by all district health offices and public health nurses, ensuring that the proficiency to place and read skin tests, which is not a trivial matter, would not be lost. With the institution of a new TB control program [12,13], this need no longer exists.

However, although targeted testing is rational and probably cost-effective, in an immigrant society such as ours and in the situation we are faced with, these advantages are confounded by the adverse effect of feelings of discrimination against minority groups that targeted screening might raise. Our study shows clearly that the high risk groups for targeting are new immigrants. These groups may perceive justifiable public health measures as a form of discrimination. In schoolchildren in particular, such measures could cause stigmatization [3]. In 1996, the discarding of blood donations by Ethiopian immigrants due to the risk of transmitting human immunodeficiency virus caused major repercussions and was an issue in the country's general elections at that time [15]. This consideration negates, in our opinion, the advantages of targeted screening in schoolchildren today. Thus, we will continue with the current policy and reevaluate the situation as more data are accumulated. Nonetheless, we have to address the significant problem of false positive results incurred with inappropriate screening of low risk groups [9]. One way of countering this negative effect would be to raise the threshold for a positive result, perhaps even above the 15 mm recommended by other researchers [16].

In evaluating this program we did not investigate the reasons for presenting at testing and for not completing therapy. Measures for increasing compliance such as community outreach programs have been described elsewhere [8] and are probably applicable here. For instance, a lengthy referral process may discourage patients from starting treatment for latent TB infection [17]. Compliance may be improved by simple measures, such as providing flexible clinic hours, reducing waiting time in the clinic, and adjusting the treatment regimen to suit the patient's needs [17]. Other strategies to promote

adherence with treatment for latent TB infection are patient education (explaining in simple clear language what latent infection is, the health threat it presents, and how it can be eradicated) [18,19], the use of health workers from the patient's social and/or cultural group [3,20], incentives (e.g., cash payments) [21], and directly observed therapy [22]. Despite the fact that we are implementing some of these strategies [3], our results show that there is room for improvement. At the time of this study we did not have the resources to perform an active epidemiologic investigation for each child with a positive skin test. These investigations were limited to the cases of active TB only.

## Conclusion

Our local program – apart from the actual placing and reading of the tuberculin screening tests, and implementation of treatment, which is the goal of screening – appears to be extremely inefficient. There is a need for similar evaluation in other regions in Israel to ascertain whether the Ashkelon picture reflects the whole of Israel, in which case there is a need to reevaluate the national screening policy of schoolchildren for tuberculosis.

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*I shall let the little I have learnt go forth into the day in order that someone better than I may guess the truth, and in his work may prove and rebuke my error. At this I shall rejoice that I was yet a means whereby this truth has come to light.*

*Albrecht Dürer, 1513. Quoted by Neil McIntyre and Karl Popper in "The Critical Attitude in Medicine: The Need for a New Ethics."* ***Lancet*** *1983.*