

# Epidemiologic Characteristics of Pediatric Active Tuberculosis Among Immigrants from High to Low Tuberculosis-Endemic Countries: the Israeli Experience\*

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**Key words:** childhood tuberculosis, epidemiology, Israel, migration, outcome assessment, process assessment

## Abstract

**Background:** During the last decade, Israel, a country with low tuberculosis rates, absorbed some 900,000 new immigrants from TB-endemic countries.

**Objectives:** To analyze the specific impact of our screening procedures on active TB among children in Israel.

**Methods:** We conducted a retrospective analysis of epidemiologic and clinical data of all children (aged 0–17) with TB notified to the Ministry of Health between 1990 and 1999.

**Results:** There were 479 children with TB (male/female ratio 1.36). Most cases (81.8%) were foreign born, predominantly (88.2%) immigrants from Ethiopia and, therefore, huge differences existed in TB incidence rates according to countries of origin. Some 80% were diagnosed within 3 years of arrival, mainly due to active case-finding. Pulmonary TB, with infiltrates on chest X-ray, was found in 49.5%. Extra-pulmonary TB sites were: intra-thoracic lymphadenitis (31.1%), extra-thoracic lymphadenitis (12.5%), bones (3.6%), pleura (1.3%), meninges (1%), and others (1%). Seventy percent had a tuberculin skin test reaction  $\geq 10$  mm in size. Two (non-immigrant) children died of TB meningitis.

**Conclusions:** Most of the pediatric TB cases occurred in recent immigrants and were diagnosed within 3 years of immigration. These data support our policy of active case-finding among new immigrants from Ethiopia and extensive contact evaluation for all TB cases.

*IMAJ 2006;8:21–26*

Compared with low prevalence countries, the risk of being infected by *Mycobacterium tuberculosis* early in life in endemic countries is high, leading to a greater percentage of cases in the younger population [1]. During the last decade, some 900,000 new documented immigrants [2] – mainly from countries with a high level of tuberculosis endemicity, namely Ethiopia and the Former Soviet Union [3] – were absorbed in Israel, a country of six million inhabitants and low TB rates (3–4/100,000)

in the established population. From 1989 onwards we actively screened Ethiopian immigrants for TB on arrival [4] and recommended investigations of close contact for all active TB cases, regardless of the country of origin. This recommendation was only fully implemented with the inauguration of a new national TB control program in 1997 [5]. Although a report of pediatric tuberculosis in Israel for the district of Ashkelon was previously published [6], the present article analyzes, for the first time at a national level, the epidemiologic and clinical characteristics of pediatric active tuberculosis in Israel, and the specific impact of our screening procedures on active TB among children.

## Patients and Methods

### Case studies

Notification of TB by both physicians and laboratories is mandatory in Israel [5]. All active pediatric cases (aged 0–17 at notification) registered for the period 1990–1999 at the Ministry of Health's Department of TB and AIDS were analyzed retrospectively according to epidemiologic characteristics. A pediatric pulmonologist (H.B.) retrospectively reviewed all medical charts with an emphasis on clinical and radiologic data. These children were either native Israeli or immigrants (all Israeli or naturalized citizens), almost all from Ethiopia or the former Soviet Union where high rates of TB exist. This article does not cover any children from the Palestinian Authority.

At the end of 1999 the number of Israeli children aged 0–14 was 1.78 million (468,700 of them Arab Israelis – 26%) [2]. During the years 1990–99, some 149,000 children aged 0–14 immigrated from the former Soviet Union and some 35,000 children immigrated from Ethiopia or were born in Israel to Ethiopian parents [2,7]. The time interval between the date of immigration and notification of the TB was also evaluated.

### Classification of TB

The classification was based on the following criteria adapted from the World Health Organization/International Union against TB and Lung Disease definitions [8] and from the U.S. Centers for Disease Control and Prevention [9]: Patients with a positive *Mycobacterium tuberculosis* culture of sputum, broncho-alveolar lavage or gastric aspirate were classified as having a “definite TB” [8]. Patients with negative cultures were classified as having

\* Part of this paper was presented at the World Congress of the International Union Against Tuberculosis and Lung Disease (IUATLD), Paris, 2001.

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TB = tuberculosis

an "other than definite TB" when they met both of the following conditions: a) a clinician's judgment that the patient's clinical and/or radiologic signs and/or symptoms were compatible with tuberculosis; and b) a clinician's decision to treat the patient with a full course of anti-tuberculosis therapy [8]. In addition, (clinical) diagnosis was based on two or more of the following criteria [9]: a) a positive tuberculin skin test; b) other signs and symptoms compatible with tuberculosis, such as an abnormal, unstable (worsening or improving) chest X-ray, or clinical evidence of current disease; c) treatment with two or more anti-tuberculosis medications; and d) completed diagnostic evaluation.

### Screening procedures

In Israel, all children and some new immigrants are routinely screened for TB [3,4]. All Israeli new immigrants from hyper-endemic countries such as Ethiopia and their children born in Israel are actively screened with a two-step tuberculin skin test and a chest X-ray upon arrival in Israel (active case-finding). Children younger than 6 years old whose skin tests are negative are vaccinated with BCG.

Passive case-finding is used for all other new immigrants (including those from the former Soviet Union). Close contacts of an active TB case are also investigated and those with findings indicating recent or previous infection are treated for latent TB [4,5,10,11]. Since 1959 [4], all schoolchildren aged 12–13 years have been screened by using a single-step TST by the Mantoux method. Those who test positive are referred to a physician for further examination and treatment of their latent TB infection [4,5].

### Data completeness and statistical analysis

We assessed the completeness of the National TB register and found it to be 97% for the patients notified in 1990–92 [12]. From 1997 onwards, notification rates probably improved since a new TB control program was launched in that year, in which full notification to Ministry of Health District Health Offices is a condition for reimbursement for treatment [5]. In order to calculate the rates we used published and other demographic data from the Central Bureau of Statistics [2] and from the Ministry of Absorption [7]. When calculating rates among different immigrant groups, we took into account the difference in our screening procedures for Ethiopian children considered at particular high risk for TB (see below) and immigrant children from other countries. Regarding the risk of exposure to TB, immigrant children born in Israel were considered to be at the same risk as native Israelis, except for children of parents from Ethiopia. We did not calculate TB rates for children aged 15–17 (48 cases, 10%) since general statistical data were available only for the group aged 15–19 [2]. We performed few statistical analyses due to the fact that we did not study a sample but the overall population and all TB cases included in the study period. Statistical significance was set at  $P < 0.05$  when chi-square was used.

TST = tuberculin skin test

## Results

Between the years 1990 and 1999, 479 children with TB (276 boys and 203 girls) were registered (11.7% of the 4,093 cases reported in Israel during this period). The age and gender distribution, by country of origin, is shown in Table 1. Most of the cases (346 cases, 72.2%) were from Ethiopia, 40 (8.4%) were among immigrants from the former Soviet Union, 7 (1.5%) were immigrants from other countries, and 86 (17.9%) were Israeli born (63 Jewish Israelis, 13.1%; and 23 Arab Israelis, 4.8%). The male to female ratio in these five different groups was 1.37, 1.5, 1.3, 1.25 and 1.3, respectively. TB was more frequently diagnosed among young children (aged 0–4 years) of Ethiopian origin (39.9%) compared to those from the former Soviet Union (17.5%) ( $P = 0.067$ ). Among adolescents (15–17 years old) it was the opposite (5.8% vs. 22.5%, respectively,  $P < 0.002$ ). While calculating 10 years cumulative TB incidences, we noted huge differences in the order of magnitude of the rates, heavily dependent on the countries of origin of the different population groups [Table 1].

Regarding the time interval between arrival and diagnosis [Table 2], TB was diagnosed in the year of arrival in 60% of the children from Ethiopia and in 37.5% of those from the former Soviet Union. Within 3 years of arrival most (83.6%) of the Ethiopian children and 52.5% of children from the former Soviet Union had their TB diagnosed. The few new immigrants from

**Table 1.** Tuberculosis among children, by age, gender and country of origin, Israel 1990–99: absolute number (percentage in parenthesis), and 10 years cumulative incidences (rates per 100,000)

Age (yrs)	Ethiopia		Former Soviet Union		Other foreign-born		Jewish Israeli born		Arab Israelis		Total
	M	F	M	F	M	F	M	F	M	F	
0–4	86	52	4	3	0	0	11	11	6	5	178 (37.2)
5–9	54	46	8	4	0	0	6	6	2	3	129 (26.9)
10–14	48	40	6	6	4	2	7	6	4	1	124 (25.9)
15–17	12	8	6	3	0	1	11	5	1	1	48 (10)
<b>Subtotal</b>	<b>200</b>	<b>146</b>	<b>24</b>	<b>16</b>	<b>4</b>	<b>3</b>	<b>35</b>	<b>28</b>	<b>13</b>	<b>10</b>	<b>479 (100)</b>
<b>Total</b>	<b>346 (72.2)</b>		<b>40 (8.4)</b>		<b>7 (1.5)</b>		<b>63 (13.1)</b>		<b>23 (4.8)</b>		<b>479 (100)</b>
<b>M/F</b>	<b>1.37</b>		<b>1.5</b>		<b>1.3</b>		<b>1.25</b>		<b>1.3</b>		<b>1.36</b>
<b>Rates per 100,000</b>											
0–4	984.8		14.4		NC		5.7		6.0		
5–14	733.0		22.9		NC		3.4		3.5		

NC = Not calculated

**Table 2.** Tuberculosis among children, Israel 1990–99: time interval between the year of immigration and the year of TB notification

Origin	Ethiopia	Former Soviet Union	Other foreign-born	Total
<b>Time interval (yrs)</b>	<b>No. (%)</b>	<b>No. (%)</b>	<b>No. (%)</b>	<b>No. (%)</b>
Same year	208 (60.1)	14 (37.5)	6 (85.7)	229 (58.3)
1–2	81 (23.5)	6 (15.0)	–	87 (22.1)
3–4	24 (6.9)	9 (22.5)	–	33 (8.4)
5+	33 (9.5)	10 (25.0)	1 (14.3)	44 (11.2)
<b>Total</b>	<b>345 (100)</b>	<b>40 (100)</b>	<b>7 (100)</b>	<b>392 (100)</b>

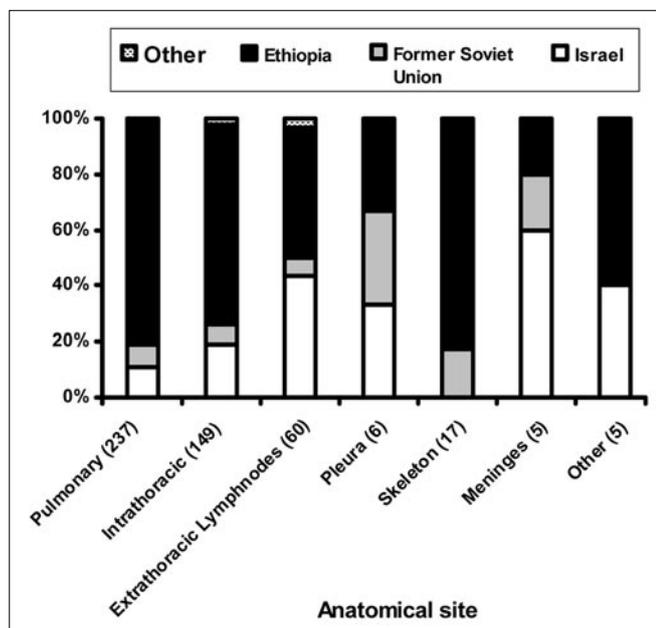


Figure 1. Site of tuberculosis by country of origin, Israel 1990-99

other countries were almost all (85.7%) diagnosed in the same year of their immigration.

#### Localization of disease

The distributions of the different sites are shown in Figures 1 and 2. Pulmonary TB (documented by chest X-ray) was found in 237 children (49.5% of all pediatric TB cases). The different extra-pulmonary TB sites included 242 cases (50.5%). In 22 cases, TB was found in both pulmonary and extra-pulmonary sites. According to the WHO/IUATLD recommendation [8], we registered and analyzed them as pulmonary TB cases. Intra-thoracic (mediastinal) lymphadenitis was the most frequent extra-pulmonary site (61.6% of extra-pulmonary cases and 31.1% of all cases). Intra-thoracic lymphadenitis occurred most often in the youngest age group of children, 0-4 years (40.3%). The next most frequent extra-pulmonary TB site was extra-thoracic lymph nodes (24.8% of extra-pulmonary and 12.5% of all cases), followed by skeletal involvement (7.0% of extra-pulmonary, 3.5% of all cases). Extra-pulmonary TB was diagnosed in 44.9% of cases of TB in children from Ethiopia, in 52.5% of TB children from the former Soviet Union and in 71.4% of TB in children from other countries. Pleural effusions were found in only six children.

#### Skin tests and bacteriology

Of 437 of 479 children with active TB for whom we have the results of their tuberculin skin tests, only 36 (8.2%) had a TST reaction of less than 5 mm. It was  $\geq 10$  mm in 307 children (70.25%). Thus, almost all children suffering from tuberculosis had a TST reaction of 5 mm or more. However, in the young-

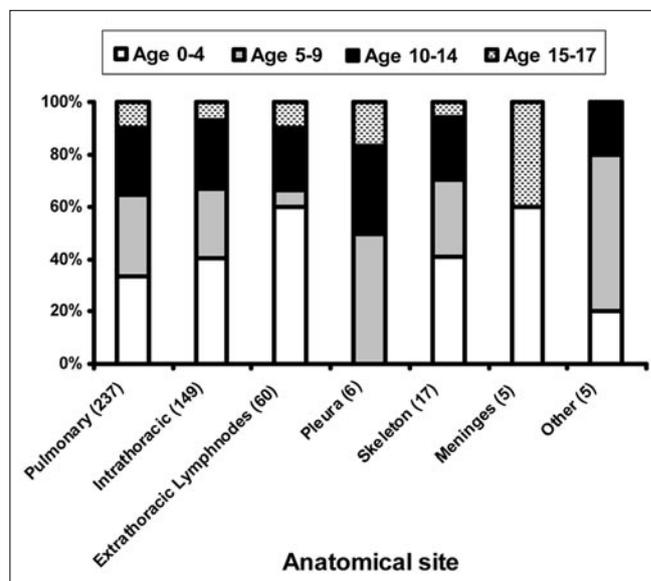


Figure 2. Site of tuberculosis, by age group, Israel 1990-99

est children suffering from active TB (0-4 years old), a sizeable proportion, 28 children (17%), had a TST of less than 5 mm. The TST was < 5 mm in 4.9%, 0% and 5.4% of the age groups 5-9, 10-14, 15-17 years respectively. Ethiopian children had larger reactions to tuberculin than their counterparts from the former Soviet Union. A TST of less than 10 mm was found in only 24.8% of Ethiopian children, compared to 47% of children born in the former Soviet Union or in Israel.

The response to tuberculin was influenced by organ involvement. There was a marked difference in the rate of skin tests < 5 mm according to the site of disease: 3.6% among children with pulmonary TB, 4.6% among children with intra-thoracic lymphadenopathy, and 25.3% of children with other extra-pulmonary TB.

Data on cultures were available in 93 children (39.2%) with pulmonary TB and in 110 (45.4%) with extra-pulmonary TB. Cultures were positive for *M. tuberculosis* in 68 children (28.7%) with pulmonary TB and in 53 (21.9%) with extra-pulmonary TB. Sixteen percent of pulmonary TB and 19% of extra-pulmonary TB cases were smear-positive. Most (74%) of the children with culture-positive extra-thoracic TB had TB of the lymph nodes or skeleton.

#### TB and AIDS

Only four children in this series had AIDS, and all of them came from Ethiopia and had pulmonary TB.

#### Deaths

In this 10 year period, two children (under the age of 1 year) died with TB meningitis. Both were born in Israel.

#### Discussion

In western developed countries, there has been an increase in morbidity and mortality from TB in the 1990s after years of declining rates. Since the 1960s, the TB incidence in Israel decreased

WHO/IUATLD = World Health Organization/International Union against TB and Lung Disease

steadily until 1983 (to 5.4 cases/100,000), but rose again between 1984 and 1991, mainly due to immigration from Ethiopia [3,4], and since 1990, due to immigration from the former Soviet Union [3]. Israel now has by far the highest proportion in the WHO-European Region of foreign-born TB cases (some 86%) [3]. As a result, most of the pediatric TB cases were found in recent immigrants, and were diagnosed within 3 years of immigration, due to the Israeli policy of active case-finding among new immigrants from Ethiopia and extensive contact evaluation for all TB cases.

While comparison with other western countries should be done with caution, our experience on a national scale (in a small country) and the approach we have used may be of interest to larger countries on a district, regional or state level especially when dealing with screening policies for immigrants from high and moderate TB prevalence countries.

### Screening policy and its application

In this article we analyzed the impact of our differential screening policy on the diagnosis of active TB cases among children (and not on the prevalence of latent tuberculosis infection). The 10 years cumulative incidence of pediatric TB in Israel is much higher among children who immigrated from Ethiopia (and those born in Israel to Ethiopian parents), compared to those from the former Soviet Union (TB rates > 700/100,000 vs. 14–22/100,000, respectively) [Table 1] and other Israeli children. This justifies the policy of active case-finding in Ethiopian children even though this policy carried a risk of stigmatization.

Regarding TB rates among immigrants from the former Soviet Union, although these are still higher than those observed among Israeli born children (14–22/100,000 vs. 3–6/100,000, respectively), the present data indicate that our policy of passive case-finding among immigrants from the former Soviet Union was probably adequate for early identification of active TB cases since more than half the cases were diagnosed within 3 years of their arrival to Israel [Table 2], and no foreign-born children died of TB during the whole decade. The main reasons for not performing active case-finding among former Soviet Union immigrants were: a) TB rates differed a great deal among each of the 15 states from the former Soviet Union [13], complicating an evidence-based policy for targeting only one of these states; b) Israel offered free and full access to healthcare for every one of these documented immigrants who are naturalized Israeli citizens, and the policy is to prefer relying on good access to healthcare rather than engage in active case-finding for all the immigrants [3]; and c) we wished to avoid stigmatizing such a large number of immigrants for a probably very low yield of active TB cases. Lastly, from our Israeli perspective, immigration from the former Soviet Union was a mass immigration of almost 100,000 new immigrants annually [2], causing tremendous logistic issues. This phenomenon had occurred in a period of fragmented TB infrastructures [3,5]. Moreover, our screening policy has to take into consideration the socio-cultural characteristics of the immigrants' country of origin (Ethiopia vs. the former Soviet Union) and the host country.

In 1996, the American Academy of Pediatrics issued recommendations for the TB screening of children, moving from a policy of universal screening to one based on high risk groups only [10], including school testing. In a previous article [14], we addressed the issue of targeted testing in schoolchildren in Israel and showed that the high risk groups were primarily new immigrants from Ethiopia, and secondly those from the former Soviet Union.

Other studies considered a good contact investigation an important aspect of the screening policy [15,16]. Kimerling et al. [15] argued that half of their cases classified as preventable were due to failure of the contact investigation interview. Reichler et al. [16] reviewed all contacts of 349 patients with culture-positive pulmonary TB, aged 15 and older. They concluded that improvement is needed in the process of contact investigations in order to ensure that contacts will be identified and appropriately screened.

In populations that have emigrated from high risk areas, re-infection may contribute significantly to the rate of recurrent tuberculosis. Timely, adequate medical evaluation and follow-up care of immigrants and refugees have a relatively high yield and should be a high priority for TB prevention and control programs [11]. Screening for active disease on arrival from countries with high endemicity (i.e., Ethiopia) in combination with adequate treatment facilities for all newcomers [3] and contact investigation of each index case [5] should have a higher priority for TB control programs [3,11,14] than general population-based screening and treatment of latent infection.

### Clear screening policy: difficulties in diagnosing TB among children

Diagnosing TB in children is difficult [17]. Over one-half of young TB patients have few or no symptoms, despite the presence of significant abnormality on chest X-ray [17]. Many cases are identified by contact screening and population-based skin testing rather than by evaluation of children with symptomatic disease [18]. In endemic countries, the diagnosis is based mainly on clinical grounds, while in western countries most of the cases are diagnosed during contact investigation [17].

Radiographic evidence of pulmonary disease is often observed in pediatric patients, but such findings are neither sensitive nor specific [17]. In this study there were pulmonary infiltrates in 60% of children with active tuberculosis, followed by mediastinal lymphadenitis in 38%. Pleural effusion was extremely rare, appearing in less than 2%. However, it was not uncommon (almost 40%) to find a normal chest X-ray in many cases of definite TB [17]. The positive chest X-rays showed patterns highly characteristic of pulmonary TB, lymphadenopathy, miliary disease, upper lobe cavities, and primary complex disease [18]. Other pediatric TB studies have reported much higher rates of positive radiographic changes in their patients, perhaps because non-specific findings such as consolidation and atelectasis were considered positive [17]. Leung and associates [18] found lymphadenopathy in 92% of chest X-rays of 191 children with pediatric primary tuberculosis. This finding was more com-

mon in younger children (0–3 years), whereas older children had a higher prevalence of parenchymal abnormalities.

In our study we found less intra-thoracic lymphadenopathy than the studies mentioned above and the finding decreased with age, being common (71.8%) in children from Ethiopia, similar to Leung's finding that white children had less lymphadenopathy than non-white children [18].

#### Site of disease: pulmonary vs. extra-pulmonary disease

According to WHO/IUATLD definitions that we used for extra-pulmonary TB [8], intra-thoracic lymph node involvement is considered extra-pulmonary TB, as is pleural TB [8]. Of 242 cases of extra-pulmonary disease, extra-thoracic involvement was found in 93 children (38.4% of extra-pulmonary cases, but 19.4% of all cases). Most of them – 60 (64.5%) – had TB of lymph nodes, in keeping with the literature as the most common form of extra-thoracic TB in children [6,17]. As of 1990, lymph node involvement was the most common site of extra-pulmonary disease in the United States, occurring in approximately 30% of cases [19], which is similar to our figures. Lymphadenitis was also the most common manifestation in immigrants to the USA from Somalia, affecting 58% of extra-pulmonary cases [19]. In recent years, extra-pulmonary TB has been commonly associated with human immunodeficiency virus infection [19]. Although some 45.4% of HIV/AIDS cases in the last decade in Israel came from Ethiopia [20], and 93% of children diagnosed with HIV infection in Israel were born either abroad or in Israel to parents who emigrated from areas hyper-endemic for AIDS [21], AIDS related to TB among children aged 0–17 was found in only 4 cases (of the 21, 19%) notified during our period of study. The most feared complication of TB in children is tuberculous meningitis, which develops in 5–10% of children infected before 2 years of age, with the frequency dropping to 1% or less later in life [19]. In our study three of the five children who developed TB meningitis (1% of the total) were found among the 179 in the age group 0–4 years. Two of the five children with TB meningitis (40%) succumbed to this often lethal complication, one with polyresistant TB. Low rates of TB meningitis are considered a marker of efficient TB control [1].

#### Bacteriology

Adequate diagnostic specimens are often difficult to obtain from children under the age of 8 because of a lack of sputum production [18]. The yield from sputum, nasogastric aspirate cultures and smears in children is very low and varies greatly depending on frequency of sampling, techniques used, and stringency of criteria used to define true positive cases [22]. Thus, bacteriologic diagnosis of pulmonary TB in the pediatric population presents a challenge. Symptoms of *M. tuberculosis* infection are often non-specific or absent in affected children [18]. Furthermore, currently available diagnostic tests are costly, slow, and lacking in sensitivity, and even under the best circumstances *M. tuberculosis* is isolated in fewer than 50% of pediatric

cases [22]. In the majority of cases, the diagnosis is established using a combination of factors, including history of exposure to an adult with active tuberculosis, a positive tuberculin skin test, a negative evaluation of other etiologies, a chest radiograph and physical examination consistent with tuberculosis, as well as a response to anti-TB chemotherapy [23].

In our study, a positive culture for *M. tuberculosis* was found in 28.7% of children with pulmonary TB and in 21.9% of children with extra-pulmonary TB. These data are similar to another study [17], where bacteriologic confirmation was achieved in only 22.2% of the children. In a prior study done in Israel [6] it was found that only 11% of the children had positive cultures. Toppet et al. [24] found *M. tuberculosis* by gastric lavage among 15% of the children with TB. In another study [25], a positive smear or culture result for *M. tuberculosis* was obtained in 9 of 54 patients (16.6%) and 25 of 50 patients (50%), respectively.

#### Tuberculin skin tests

In this study, almost all children suffering from tuberculosis had a TST reaction of  $\geq 5$  mm. A reaction of less than 5 mm never excluded an active TB. A variable associated with skin test reactions of  $<5$  mm in our study is the site of TB: 12.8% in extra-pulmonary TB compared to 3.6% in pulmonary TB. In other series, approximately 10% of immunocompetent children with culture-documented TB did not react initially to TST [4]. We do not have data on the eventual response to TST in our patients. This is of interest since negative tests in active TB often converts to positive during treatment.

#### Conclusions

Our finding that the majority (83.6%) of the children from Ethiopia in our study were diagnosed within 3 years of arrival reflects favorably on our screening and control policies. In addition, no immigrant child died from TB even though the policy is not to screen all immigrants on arrival. Our study shows that in order to prevent pediatric TB, the target population for TST should be recent immigrants from highly endemic countries. Screening for active disease on arrival among Ethiopian immigrants, adequate treatment facilities for all new immigrants [3], and contact investigation of each index case [5] should be the policy of choice for TB control programs [3,11,14] rather than a general population-based screening and treatment of latent TB infection.

**Acknowledgments.** We gratefully acknowledge the healthcare professionals who notify TB cases and care for TB patients and their families with so much energy and devotion. We are grateful to the Israel Lung Association, Tel Aviv, for its support. Special thanks are due to Prof. G.L. Baum for his valuable comments on the present manuscript. We acknowledge Dr. D. Shoseyov at the Pediatric Department in Bikur Cholim Hospital, Jerusalem, for his contribution to the investigation and care of children with TB, and to Dr. Z. Mor and Ms. A. Zaken, from the Department of Tuberculosis and AIDS for their help in data management.

HIV = human immunodeficiency virus

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