



Tuberculosis outbreak among students in a boarding school

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ABSTRACT: Tuberculosis (TB) outbreaks present a public health challenge. Six cases of active TB emerged in a boarding school in Israel during 1 yr. An epidemiological outbreak investigation was performed, followed by implementation of control measures.

The investigation included interviews, tuberculin skin test (TST) and chest radiographs of the students. Close contact (n=155) was defined as being in the same class or dormitory with a patient. Remote contact (n=246) was defined as being in the school.

An epidemiological association was detected among five of the cases and a distinct pattern was found in molecular analysis. TST was performed in 398 (99.2%) students. Repeated (two-step) TST was applied to the close contacts. The degree of contact, country of origin and previous bacille Calmette–Guérin vaccination were significantly associated with TST reactions. Preventive directly observed therapy was completed by 157 (91.3%) students. During 5 yrs follow-up, no additional cases emerged.

While investigating a tuberculosis outbreak, the definition of degree of contact is a significant predictor for detecting positive tuberculin test. Immigration from an endemic country, as well as previous bacille Calmette–Guérin vaccination have a major effect on tuberculin skin-test results. The directly observed therapy approach was found to be successful in preventing further morbidity.

KEYWORDS: Boarding school, outbreak, tuberculin skin test, tuberculosis

Tuberculosis (TB) had been declared by the World Health Organization as a global health emergency [1]. TB outbreaks emerge occasionally in long-term care facilities, including various educational establishments. Boarding schools are sites where adolescents are concentrated in conditions of relative overcrowding predisposing to TB outbreaks. These outbreaks present a public health challenge with respect to investigation and control [2–6].

Like many Western countries, the incidence of TB in Israel continuously declined from 200 cases per 100,000 population in 1950 to 4–5 per 100,000 in 1980. Since the 1990s, the incidence has increased to 8–10 cases per 100,000, mostly due to mass immigration from the former USSR and Ethiopia. Almost all TB cases are foreign-born and approximately two-thirds of them occur among recent (<5 yrs) immigrants. This significant increase led to the implementation of a national TB prevention and control programme [7–10].

During 1 yr, six cases of active TB were diagnosed among students in a boarding school. An epidemiological and laboratory outbreak investigation was performed and control measures were taken.

METHODS

Epidemiological investigation

Definitions

A case of TB was defined as a student with signs and symptoms compatible with TB. All the cases were culture confirmed. An epidemiological investigation was conducted for each case, including the immediate family members.

Laboratory investigation

The cases were diagnosed by isolation of *Mycobacterium tuberculosis* in culture from a clinical specimen (sputum or body fluid). Smears were stained by the Ziehl–Neelsen method. Susceptibility tests and biochemical assays were performed at the National Mycobacteria Reference Center (Tel Aviv, Israel). Molecular analysis included restriction fragment length polymorphism (RFLP)-standardised IS6110-based DNA fingerprinting and spoligotyping [11].

Tuberculosis screening of contacts

Tuberculin skin tests (TST) were performed by the Mantoux method using 5 TU of Tuberosol (CT-68, Connaught, ON, Canada). The reactions were assessed after 48–72 h. TST positivity was

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defined based on the American Thoracic Society criteria [12, 13]. Close contact was defined as being in the same class or dormitory with an active TB case. Remote contact was defined as being in the same school. Positivity for close contacts was defined as ≥ 5 mm of induration, and for remote contacts as ≥ 10 mm. Negative close contacts underwent a repeated test 2 weeks later (two step). A third test was performed 3 months later on those who were negative on the second test.

Previous bacille Calmette–Guérin vaccination

Previous bacille Calmette–Guérin (BCG) vaccination was defined based on medical history, evidence of vaccine scarring and country of birth.

Clinical evaluation and chest radiographs

The students were evaluated for symptoms and signs consistent with TB. Chest radiographs were performed in students whose TST reactions were defined as positive.

Preventive chemotherapy and follow-up

Preventive chemotherapy was provided in the boarding school and local TB clinics by the directly observed therapy (DOT) method. A follow-up period of 5 yrs was scheduled for the students who received preventive treatment.

Statistical analysis

Characteristics included age, country of birth, previous BCG vaccination and degree of contact (close/remote). TST results were processed at 5- and 10-mm cut-off values. Logistic regression model of TST reactions, according to these characteristics, used odds ratio (OR) and 95% confidence interval (CI). A p-value of <0.05 was considered significant.

RESULTS

Tuberculosis cases

The first case was diagnosed in April 1998 and the sixth in May 1999 (table 1). All were born in Ethiopia and had immigrated some years earlier. Cases 2, 4, 5 and 6 were hospitalised. Cases 1, 3 and 6 shared a dormitory (Nos 3 and 6 were roommates). Cases 4 and 5 shared another dormitory. Case 2 lived in another dormitory. Investigation of the first case included screening of roommates and close friends and led to the diagnosis of cases 2 and 3. When three cases emerged within 4 weeks (April–May 1999), the investigation was extended to the entire school.

Investigation of immediate family members of the cases did not reveal any active TB cases. The families were referred to local TB clinics for consultation, preventive therapy and follow-up.

Laboratory results

M. tuberculosis was isolated from five sputum specimens and one peritoneal fluid specimen. All isolates were susceptible to isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin. RFLP analysis illustrated a single-band pattern in five strains and a different 10-band pattern in one case (fig. 1a). The one-band profile was confirmed by spoligotyping (fig. 1b).

Epidemiological investigation

The boarding school was a technology education institute of seven grades (grades 9–15). Most of the students (62%) were recent immigrants from the former USSR and Ethiopia, and were of a low socio-economic level. There were seven dormitories and each bedroom was shared by four students from the same country of origin. The rooms were overcrowded with bunk-beds and poor ventilation. Intensive social interactions, including frequent switching of roommates inside a dormitory, were maintained among students from Ethiopia. The boarding school management, staff and the students' parents were very worried when informed about the investigation, and were concerned about the risk of additional cases.

Epidemiological investigation was performed during the months of May and June 1999, and included all 401 boarding school students, who were defined based on degree of contact with an active TB case. Thus, 155 (38.7%) were close contacts (grades 11 and 12) and 246 (61.3%) were remote contacts (grades 9, 10, and 13–15). All the students were male. The age range was 15–23 yrs (mean age 18.8 ± 1.6 , median 18.9 yrs). The country of birth was the former USSR in 158 (39.4%) students, Ethiopia in 88 (22%) and Israel in 155 (38.7%). The foreign-born students had immigrated between 1981 and 1999 (median 1993), and the mean period of time living in Israel was 6.1 ± 3.7 yrs.

BCG vaccination history was positive in 228 (56.9%), negative in 77 (19.2%) and missing in 96 (23.9%) students. Previous BCG vaccination was correlated with country of origin, being positive in 108 out of 109, 61 out of 69, and 59 out of 127 of students who were born in the former USSR, Ethiopia and Israel, respectively, and for whom information was available.

TABLE 1 General and clinical characteristics of the six tuberculosis (TB) cases

Case No.	Age yrs	Immigration yr [#]	Date of diagnosis month/yr	Clinical findings	Radiograph	Smear	Culture
1	21	1995	04/1998	Active pulmonary TB	Infiltrate	+	+
2	16	1997	08/1998	Active pulmonary TB	Effusion	-	+
3	20	1996	10/1998	Active pulmonary TB	Infiltrate	-	+
4	16	1991	04/1999	Peritoneal TB	Normal	-	+
5	19	1982	05/1999	Active pulmonary TB	Infiltrate	+	+
6	20	1992	05/1999	Active pulmonary TB	Infiltrate	-	+

[#]: All the cases were born in Ethiopia.

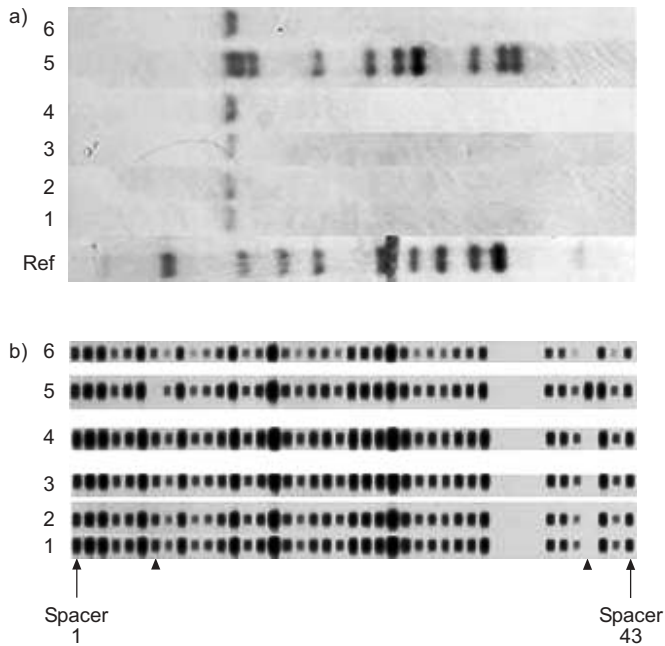


FIGURE 1. Molecular analysis of the six tuberculosis (TB) strains. a) Restriction fragment length polymorphism fingerprints of TB strains isolated from students throughout the investigation of the outbreak. Ref: reference (a TB strain of an isolate from a non-Ethiopian patient). b) Spoligotyping patterns of TB strains isolated from students throughout the investigation of the outbreak.

Routine newborn BCG vaccination was stopped in Israel in 1982.

Most (68.7%) of the foreign-born students had received BCG vaccination at least once as newborns, and sometimes also at age 6 yrs upon school entry.

Tuberculin skin tests

First TST

First TST screening was performed in 398 (99.2%) students, including 154 close contacts (two students left the country) and 244 remote contacts. Of the 154 close contacts, 67 (43%), 41 (27%) and 46 (30%) were from the former USSR, Ethiopia and Israel, respectively.

The association between TST reaction and degree of contact was significant at cut-off points of 5, 10 and 15 mm. At a cut-off of 5 mm, 76 out of 154 (49.4%) close contacts were positive compared with 89 out of 244 (36.5%) remote contacts (OR 1.70, 95% CI 1.1–2.61, $p=0.01$). At a cut-off point of 10 mm, 71 out of 154 (46.1%) close contacts were positive compared with 75 out of 244 (30.7%) remote contacts (OR 1.93, 95% CI 1.24–2.99, $p=0.001$). At a cut-off point of 15 mm, 41 out of 154 (26.6%) close contacts were positive compared with 35 out of 244 (14.3%) remote contacts (OR 2.17, 95% CI 1.27–3.71, $p=0.002$).

Reactions of ≥ 5 mm were found in 14.3, 39.8 and 69.2% of students born in Israel, Ethiopia and the former USSR, respectively ($p<0.01$). When the TST results were stratified according to birthplace and type of contact, a significant difference was noted between the three groups. TST results of ≥ 5 mm were observed in 13 and 14.8% of close *versus* remote contacts among Israeli-born students and in 71.6 *versus* 67.4% in those born in the former USSR. Among those born in Ethiopia, TST results of ≥ 5 mm were found in 53.7 *versus* 27.7% of close *versus* remote contacts, respectively. The association between TST reactions and degree of contact was significant only in students who were born in Ethiopia (table 2).

In a multiple logistic regression model, the variables 1) degree of contact, 2) country of birth and 3) BCG vaccination were found to be significantly and independently associated with the TST results, at a cut-off point of 5 mm (table 3).

Repeat TST

The 78 close contacts whose first TST reactions were negative were re-tested 2 weeks later. The results were 0–4 mm in 60 students (77%), 5–9 mm in eight students, 10–15 mm in eight students and ≥ 16 mm in two students. Two-step TST detected 18 out of 78 previously negative close contacts who were positive in the second test (23.1%, $SE=4.8$, 95% CI 14.3–34.0). When the first and second TST results were combined, 94 out of 154 (61%) close contacts were positive.

The 60 close contacts whose second test reactions were negative underwent a third TST 3 months later. The results were 0–4 mm in 51 students (85%), 5–9 mm in two students, 10–15 mm in four students and ≥ 16 mm in one student. Based on a definition of an increase in reaction to ≥ 10 mm, these five students were defined as converters.

TABLE 2 Results of first tuberculin skin test (TST) screening at a cut-off value of 5 mm according to place of birth stratified by degree of contact

Country of birth	Subjects n	TST				Odds ratio (95% CI)	p-value
		Positive ≥ 5 mm		Negative < 5 mm			
		Close contact	Remote contact	Close contact	Remote contact		
Ethiopia	88	22	13	19	34	3.03 (1.26–7.27)	0.01
Former USSR	156	48	60	19	29	1.2 (0.6–2.6)	0.571
Israel	154	6	16	40	92	0.9 (0.3–2.6)	0.774

CI: confidence interval.

TABLE 3 Multiple logistic analysis of first tuberculin skin test reaction results (at a cut-off point of 5 mm) of the students, according to the degree of contact, age group, country of birth and previous bacille Calmette–Guérin (BCG) vaccination

Variables	Odds ratio (95% CI)	p-value
Close contact	2.76 (1.6–4.6)	0.001
Country of birth		
Former USSR	9.1 (4.65–17.6)	0.001
Ethiopia	2.67 (1.27–5.7)	0.01
Previous BCG vaccination	3.8 (1.56–9.2)	0.003
Age group yrs		
17–19	1.77 (0.77–4.0)	0.1
19–21	1.05 (0.44–2.5)	0.9
21–23	1.24 (0.41–3.8)	0.7

CI: confidence interval.

Clinical evaluation and chest radiographs

Each student was interviewed and physically examined to detect symptoms and signs of active TB disease and none had evidence of the disease. Further evaluation with chest radiographs was performed in 172 students. These were 76 close contacts whose TST result was >5 mm, 75 remote contacts whose reaction was >10 mm and 21 students whose second or third reaction was >5 mm. All chest radiographs were normal.

Preventive chemotherapy and follow-up

Preventive chemotherapy with isoniazid for 6 months was prescribed to 172 students (after evaluation) and provided in the boarding school and local TB clinics by the DOT method and completed by 157 students (91.3%).

Liver function tests were performed in all students before isoniazid therapy. In one student (remote contact whose reaction was >10 mm), elevated liver enzymes were found after 3 months of therapy. He was found to be hepatitis B surface antigen positive, the therapy was discontinued and the liver enzymes normalised within 1 month. In all the other students, no major side-effects were reported.

During a follow-up period of 5 yrs, which was completed on June 2004, no additional TB cases emerged. The follow-up included data collection from the school, local TB clinics, TB hospital departments, the Israel Defense Force public health branch and the National Mycobacteria Reference Center.

DISCUSSION

TB outbreaks among school students have been reported previously in low-endemicity countries such as the UK, Italy, Ireland and several states in the USA [2–6]. The adolescent population in boarding schools might be susceptible to outbreaks due to overcrowding and close contact among the students for long periods of time, both conditions favouring transmission of TB. The environmental conditions and the level of infectiveness of a case are the primary risk factors for outbreaks. As opposed to young children, who are likely to develop systemic illness and are usually not infective, adolescents tend to develop infective pulmonary disease,

similar to the presentation of disease in adults [13, 14]. The level of infectiveness of a case affects the probability of further infection, based on degree of pulmonary involvement, presence of cavitations and positive sputum smears [1]. In the current outbreak, five out of six cases presented clinically with active pulmonary infection, none of them had cavitations and two had positive sputum smears.

An interesting observation is that all the sick students were born in Ethiopia and had immigrated several years earlier. Immigrants from Ethiopia are the population group with the highest TB infection rate in Israel [8]. In the present authors' opinion, a chain of infection probably occurred leading to clustering of cases, although it could not be determined whether all of them were infected inside the boarding school. The likelihood of a sequence of infection was supported by a history of tight interpersonal relationships among these students.

The molecular analysis demonstrated by RFLP and spoligotyping presented a distinctive similar single-band pattern in five cases. This pattern was noted sporadically in TB patients originating in Ethiopia and diagnosed in Israel. RAVINS *et al.* [15] studied 69 *M. tuberculosis* isolates from immigrants and local Israelis by RFLP. Immigrants from the former USSR and Ethiopia imported mycobacteria from their countries of origin, while clinical disease re-activated after immigration. No cross-infection was found between immigrants themselves or between immigrants and Israeli residents. Molecular methods are useful in epidemiological investigations, as comparing isolates of *M. tuberculosis* can complete conventional contact tracing. These techniques are clinically valuable for surveillance and public health objectives [16–19]. The impact of maintaining a longitudinal database was illustrated in an investigation of an isoniazid monoresistant TB outbreak in London (UK), in which earlier cases were identified by retrospective assessment [20].

The present epidemiological investigation in the boarding school included interviews, physical examinations, chest radiographs and TSTs. As no additional cases of active TB were detected, the preventive approach was based on the individual degree of contact with a sick student combined with the TST results. The association between TST results and degree of contact was significant only in students from Ethiopia, who had tight social inter-relations and were therefore more exposed to the likelihood of transmission. The role of an accurate definition of degree of contact, especially in a well-defined community, is essential. However, this definition is based on qualitative information regarding the length of exposure to the active TB patient and the environmental conditions in which this exposure occurred. In the presently studied boarding school, many hours were spent in classrooms and dormitories, hence the definition of 'close contact' as students sharing a class or a dormitory. The rest of the students were less likely to be exposed and were considered remote contacts, for whom a cut-off point of 10 mm was used, resulting in 30.7% positivity and the need for additional evaluation and follow-up.

The main limitation of the TST in terms of validity is the combination of a relatively high sensitivity together with a low

specificity. Overall, 41.5% of the school students had TST results of ≥ 5 mm; this included 49.4% of close and 36.5% of remote contacts. These rates are higher compared with those reported by PHILLIPS *et al.* [14], who investigated a TB outbreak in a USA high school with a 10% TST positivity in the school students and 19% in students sharing a school bus, presumably close contacts. BAILY *et al.* [21] presented a model aimed to improve TB contact investigation by including variables predicting a positive TST among contacts of an active TB case. They reported a high sensitivity of 87–92% and limited specificity of 34–38% of TST, and suggested the combination of determinants of the active TB patient, the contact and the environment of exposure (hours of contact).

The presently studied boarding school population included many (62%) immigrants from endemic countries, the former USSR and Ethiopia, and most of them (69%) had received BCG vaccination. The relatively high rate of positive results in the school's population can be attributed to previous BCG vaccination as well as exposure to environmental mycobacteria in the past. The overall rate of TST results of ≥ 5 mm was 14.3, 39.8 and 69.2% of students born in Israel, Ethiopia and former USSR, respectively ($p < 0.01$). The highest probability (OR 9.1) for positive TST results was found in students who were born in the former USSR. The effect of the degree of contact on TST results was studied, controlling for the country of birth and previous BCG vaccination. Previous BCG vaccination was significantly associated (OR 3.8) with a positive TST reaction, as would be expected [12, 13], and correlated with the country of origin. Screening results in immigrant children and adolescents are related to country of origin, time since immigration, age at immigration, BCG vaccination and socio-economic status [22]. Similar findings in Israel were noted by LEVITIN *et al.* [23], who reported TST screening of 10,133 seventh-grade children during 1991–1994. Of these, 655 were recent immigrants from former USSR and 9,478 from long-term resident families in Israel; 82.0% received BCG compared with 56% of Israeli children. TST results of ≥ 10 mm were found in 49.3% of vaccinated and 33.9% of nonvaccinated immigrant children, compared with 10.3 and 6.1% in Israeli children. Both BCG vaccination and prior place of residence were significant independent variables.

Recently, several whole-blood assays have been developed to quantitatively measure interferon- γ production by lymphocytes specific to the *M. tuberculosis* antigens. These tests are not affected by previous BCG vaccination or exposure to environmental mycobacteria. The Centers for Disease Control and Prevention (CDC) has recently recommended the use of the QuantiFERON®-TB Gold (QFT-G; Cellestis Limited, Carnegie, Victoria, Australia) in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants and surveillance programmes [24]. The higher specificity of the test and the option of a one-step contact evaluation are significant advantages. These assays were still unavailable at the time of the outbreak and, had they been used, it would probably have resulted in a considerable reduction in the number of students who needed further preventive chemotherapy and follow-up.

The repeated (two-step) TST considerably elevated the proportion of positive close contacts and, after repeated

testing, 61% of them were classified as latent TB infection. However, the use of two- and, later, three-step testing probably produced many nonspecific responses among these students. SNIDER *et al.* [25] stated that "there appears to be some confusion about the circumstances in which two-step tuberculin testing should be used". The current recommendations of the American Thoracic Society and the CDC on tuberculin screening include repeated tests in healthcare workers and in young children (aged < 5 yrs) [12]. Application of the two-step test in contacts of an active TB case is usually recommended to form a basis for decision whether to continue or end preventive therapy in latent TB. MENZIES [26] indicated that the predictive value of a positive second test varies according to the associated risk of disease, such as degree of contact.

WARD *et al.* [27] evaluated the results of school-based contact investigations and found 5.1% positivity in the first skin test and 3.5% in the second. They noted that more people are screened in school TB investigations than in other community-based investigations, primarily due to parental concerns and pressure on school and local public health officials. Parental concerns on the health of children and adolescents, such as those that had also been experienced during the present investigation, probably affected the decision to broaden the investigation to a maximum.

The high proportion of completion of treatment (91.3%) is noteworthy compared with other observations [14]. This high rate was achieved by the local public health and TB clinic teams working inside the school and providing DOT-based preventive therapy in the school with remarkable cooperation of the students, school administration and personnel, and the students' parents. Although the DOT approach is not routinely recommended for preventive therapy in contacts, the Israeli Ministry of Health TB guidelines stipulate directly observed preventative therapy in minors and immunosuppressed patients, and the present authors believe it is particularly appropriate for settings similar to boarding schools, particularly those with a population of adolescent students who have emigrated from endemic countries.

Guidelines on investigation and prevention of TB through contact investigations were recently published by the National Tuberculosis Controllers Association and the CDC in the USA [28]. These include recommended objectives for contact investigations by key indicators. The objectives of the proportion of contacts that are evaluated for TB disease and latent infection (90%), the proportion of contacts that begin (85%) and complete (75%) treatment for latent TB infection, were all successfully achieved in the specific setting described herein.

The follow-up period of 5 yrs covers the highest risk period for developing clinical TB disease and provides support for the effectiveness of prophylactic treatment. The present study illustrates the impact of DOT in achieving higher completion rates for prophylactic treatment than the limited adherence to therapy frequently observed in this age group.

In conclusion, boarding schools can be regarded as high-risk settings for the spread of TB infection. This is particularly true if the majority of students are immigrants from countries endemic for TB. When performing an investigation, it is possible to define the contacts according to degree of contact as

defined by sharing of classes and dormitories. During the investigation, not one case of secondary infection was detected in the classes where no previous cases were diagnosed. Investigations based on assessment of the individual risk of exposure can reduce the necessity to evaluate the whole school population.

The present authors also suggest that tuberculin skin test screening using the two-step approach upon entrance to boarding schools may be beneficial in providing data on the baseline reaction status of the students. Data on previous tuberculin skin test reactions can be used in investigations and enable better interpretation of test results. As a consequence, unnecessary screening, evaluation, follow-up and use of preventive therapy can be avoided.

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