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Tuberculosis outbreak among students in a boarding school

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ABSTRACT

Background: Tuberculosis (TB) outbreaks present a public health challenge. Six cases of active tuberculosis emerged in a boarding school during one year. An epidemiological outbreak investigation was performed followed by implementation of control measures.

Methods: The investigation included interviews, tuberculin skin test (TST) and chest x-rays 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.

Results: An epidemiologic 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 BCG vaccination were significantly ($p<0.01$) associated with TST reactions. Preventive directly observed therapy (DOT) was completed by 157 (91.3%) students. During five years follow up, no additional cases emerged.

Conclusions: While investigating a TB 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 BCG vaccination have a major effect on TST results. The DOT approach was found successful in preventing further morbidity.

INTRODUCTION

Tuberculosis (TB) had been declared by the World Health Organization as a global health emergency (1). Tuberculosis 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 as to investigation and control (2, 3, 4,5,6).

Like many western countries, the incidence of tuberculosis in Israel continuously declined from 200/100,000 population in1950 to 4-5/100,000 in 1980. Since the 1990's, the incidence increased to 8-10/100,000, 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 (less than five years) immigrants. This significant increase led to implementation of a national TB prevention and control program (7, 8,9,10).

During one year, six cases of active tuberculosis were diagnosed among students in a boarding school. An epidemiologic and laboratory outbreak investigation was performed and control measures were taken.

METHODS

Epidemiologic Investigation

Definitions

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

Laboratory Investigation

The cases were diagnosed by isolation of *M. tuberculosis* in culture from a clinical specimen (sputum or body fluid). Smears were stained by Ziehl – Neelsen method. Susceptibility tests and biochemical assays were performed at the National Mycobacteria Reference Center. Molecular analysis included Restriction Fragment Length Polymorphism (RFLP) standardized IS*6110* 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, Canada). The reactions were assessed after 48 to 72 hours. TST positivity was 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 school. Positivity for close contacts was defined as 5 and above millimeters of induration and for remote contacts as 10 and above. Negative close contacts underwent a repeated test two weeks later (two step). A third test was performed three months later on those who were negative on the second test.

Previous BCG vaccination

Previous BCG vaccination was defined based on medical history, evidence of vaccine scarring and country of birth.

Clinical evaluation and chest x-rays

The students were evaluated for symptoms and signs consistent with Tuberculosis Chest x- rays were performed in students whose TST reactions were defined positive.

Preventive chemotherapy and follow up

Preventive chemotherapy was provided in the boarding school and local TB clinics by DOT (Directly Observed Therapy) method. A follow-up period of five years 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 mm and 10 mm cut off values. Logistic regression model of TST reactions, according to these characteristics, used odds ratio and 95% confidence interval. A p value of less than .05 was considered significant.

RESULTS

Tuberculosis cases

The first case was diagnosed on April 1998 and the 6th on May 1999 (table1). All were born in Ethiopia and immigrated some years earlier. Cases 2, 4, 5 and 6 were hospitalized. Cases 1, 3 and 6 shared a dormitory (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 diagnosis of cases 2 and 3. When three cases emerged within four 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 and one peritoneal fluid specimens. All isolates were susceptible to isoniazid, rifampicin, ethambutol, pirazinamid and streptomycin. Restriction Fragment Length Polymorphism analysis illustrated a single band pattern in five strains and a different ten band pattern in one case (Figure 1A). The one-band profile was confirmed by spoligotyping (Figure 1B).

Epidemiologic investigation

The boarding school was a technology education institute of seven grades (9-15th). Most of the students (62%) were recent immigrants from the former USSR and Ethiopia, of a low socio-economic level. There were 7 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 on the investigation and concerned about the risk of additional cases.

Epidemiologic investigation was performed during the months of May and June 1999 including all 401 boarding school students, which were defined based on degree of contact with an active TB case. Thus, 155 (38.7%) were close contacts (grades 11^{th} and 12^{th}) and 246 (61.3%) remote contacts (grades 9^{th}, 10th, 13^{th}, 14^{th} and 15^{th}). All the students were male. The age range was 15 to 23 years (mean 18.8±1.6, median 18.9 years). The country of birth was former USSR in 158 (39.4%) students, Ethiopia in 88 (22%) and Israel in 155 (38.7%). The foreign-born students, immigrated from 1981 until 1999 (median 1993) and the mean number of years in Israel was 6.1±3.7. BCG vaccination history was positive in 228 (57%), negative in 77 (19.2%) and missing in 95 (23.8%) students. Previous BCG vaccination was correlated with country of origin, being positive in 108/109, 61/69 and 59/127 of students who were born in the former USSR, Ethiopia and Israel, respectively, for whom information was available. Routine newborn BCG vaccination was stopped in Israel in 1982. Most (68.7%) of the foreign-born students received BCG at least once as newborns and sometimes also at age 6 years upon school entry.

Tuberculin skin tests (TST)

First TST

First TST screening was performed in 398 (99.2%) students, including 154 close contacts (1 student left the country) and 244 remote contacts. Of the 154 close

contacts 67 (43%), 41 (27%) and 46 (30%) were from former USSR, Ethiopia and Israel, respectively.

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

Reactions of 5 mm and more were found in 14.3%, 40.2% and 69.2% of students born in Israel, Ethiopia and former USSR, respectively ($p< 0.01$). When the TST results were stratified according to birth place and type of contact a significant difference was noted between the 3 groups. TST results of 5mm or more were observed in 13% and 14.8% of close vs. remote contacts among Israeli born students and in 71.6% vs. 67.4% in those born in former USSR. Among those born in Ethiopia TST results of 5mm or more were found in 56% vs. 27.7% of close vs. remote contacts, respectively. The association between TST reactions and degree of contact was significant only in students who were born in Ethiopia (table 2).

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

Repeat TST

The 78 close contacts whose first TST reactions were negative were re-tested two weeks later. The results were 0-4 mm in 60 students (77%), 5-9 mm in 8 students, 10-

15 mm in 8 students and 16 + in 2 students. Two step TST detected 18 / 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, 94/154 (61%) of the close contacts were positive.

The 60 close contacts whose second test reactions were negative underwent a third TST three months later. The results were 0-4 mm in 51 students (85%), 5-9 mm in 2 students, 10-15 mm in 4 students and 16 + in 1 student. Based on a definition of an increase in reaction to 10 mm and above, these 5 students were defined as converters.

Clinical evaluation and chest x-rays

Each student was interviewed and physically examined to detect symptoms and signs of active TB disease and none had evidence of disease. Further evaluation with chest x- rays was performed in 172 students. These were 76 close contacts whose TST was above 5 mm, 75 remote contacts whose reaction was above 10mm and 21 students whose second or third reaction was above 5 mm. All chest x- rays 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 DOT (Directly Observed Therapy) 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 above 10mm) elevated liver enzymes were found after 3 months of therapy. He was found to be HBsAg positive, the therapy was discontinued and the liver enzymes normalized within one month. In all the other students no major side effects were reported.

During a follow-up period of five years 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, Israel Defense Force public health branch and National Mycobacteria Reference Center.

DISCUSSION

Tuberculosis outbreaks among school students had been reported previously in low endemicity countries such as the United Kingdom, Italy, Ireland and several states in the United States (2,3,4,5,6). 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, conditions favoring transmission of tuberculosis. 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 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 immigrated several years earlier. Immigrants from Ethiopia are the population group with the highest TB infection rate in Israel (8). In our opinion, a chain of infection probably occurred leading to clustering of cases, although it could not be determined whether all of them were indeed infected inside the boarding school. The likelihood of a sequence of infection was supported by a history of tight inter-personal relationships among these students.

The molecular analysis demonstrated by RFLP and spoligotyping 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 studied by RFLP 69 *Mycobacterium tuberculosis* isolates from immigrants and local Israelis. Immigrants from 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 (15). Molecular methods are useful in epidemiologic investigations, as comparing isolates of *Mycobacterium tuberculosis* can complete conventional contact-tracing. These techniques are valuable clinically, for surveillance and public health objectives (16,17,18,19). The impact of maintaining a longitudinal database was illustrated in an investigation of an isoniazid mono-resistant TB outbreak in London, in which earlier cases were identified by retrospective assessment (20). The epidemiologic investigation in the boarding school included interviews, physical examinations, chest x-rays and tuberculin skin tests. 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 this boarding school many hours were spent in classrooms and dormitories, hence the definition of close contacts as students sharing a class or a dormitory. The rest of the students were less likely to be exposed and considered remote contacts, for whom a cutoff of 10mm was used resulting in 30.7% positivity and 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 5mm or more, 49.5% of close and 36.5% of remote contacts. These rates are higher compared to those reported by Phillips et al who investigated a TB outbreak in a US high school with a 10% TST positivity in the school students and 19% in students sharing a school bus, presumably close contacts (14).

Baily at el presented a model aimed to improve TB contact investigation by including variables predicting a positive tuberculin skin test among contacts of an active TB case (21). 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 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 or more was 14.3%, 40.2% 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 former USSR. We studied the effect of the degree of contact on TST results 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 could 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 7th grade children in 1991-1994. Of these, 655 were recent immigrants from former USSR; 537(82.0%) received BCG compared to 56% of Israeli children. Results of 10 mm or more were found in 49.3% of vaccinated and 33.9% of non-vaccinated immigrant children, compared to 10.3% and 6.1% in Israeli children. Both BCG vaccination and prior residence place were significant independent variables.

Recently, several whole blood assays have been developed to quantitatively measure interferon gamma (IFN-gamma) production by lymphocytes specific to the Mycobacterium tuberculosis antigens. These tests are not affected by previous BCG vaccination or exposure to environmental mycobacteria. The CDC has recently recommended the use of the QuantiFERON-TB Gold test in all circumstances in which the TST is currently used, including contact investigations, evaluation of recent immigrants, and surveillance programs (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 step and later three step testing probably produced many nonspecific responses among these students. Snider et al stated that "there appears to be some confusion about the circumstances in which two-step tuberculin testing should be used" (25). The current recommendations on tuberculin screening of the American Thoracic Society and the Centers for Disease Control and Prevention (12) include repeated tests in health care workers and in young children (less than 5 years

old). Applying the two step test in contacts of an active tuberculosis case is usually recommended to form a base for decision whether to continue or end preventive therapy in latent TB. Menzies indicated that the predictive value of a positive second test varies according to the associated risk of disease, such as degree of contact (26). 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 health of children and adolescents, as those we had also experienced during the investigation, probably affected the decision to broaden the investigation to a maximum.

The high proportion of completion of treatment (91.3%) is noteworthy compared to 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, we believe it should be adopted for settings similar to boarding schools, particularly those with a population of adolescent students who 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 centers for disease control and prevention in the US (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 we described.

The follow up period of five years covers the highest risk period for developing clinical tuberculous disease and provides support for the effectiveness of prophylactic treatment. Our study illustrates the impact of Directly Observed Treatment 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 we did not detect a single case of secondary infection 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.

We also suggest that TST screening using the two-step approach upon entrance to boarding schools may be beneficial in providing data on baseline reaction status of the students. Data on previous TST 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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Table1. General and clinical characteristics of the six TB cases

Case no.	Age (years)	Immigration year*	Date of diagnosis	Clinical findings	X-ray	Smear	Culture
1	21	1995	04/ 98	Active pulmonary TB	Infiltrate	+	+
2	16	1997	08/ 98	Active pulmonary TB	Effusion	-	+
3	20	1996	10/ 98	Active pulmonary TB	Infiltrate	-	+
4	16	1991	04/ 99	Peritoneal TB	Normal	-	+
5	19	1982	05/ 99	Active pulmonary TB	Infiltrate	+	+
6	20	1992	05/ 99	Active pulmonary TB	Infiltrate	-	+

* All the cases were born in Ethiopia

Table 2.

Results of 1st Tuberculin Skin Test screening at a cut off value of 5 mm - according to place of birth stratified by degree of contact.

Country of birth	Tuberculin Skin Test				Odds Ratio (95% C I)	*P* value
	Positive ≥ 5 mm		Negative < 5 mm			
	Close contact	Remote contact	Close contact	Remote contact		
Ethiopia (n = 88)	23	13	18	34	3.2 (1.2-8.6)	0.01
Former USSR (n = 156)	48	60	19	29	1.2 (0.6-2.6)	0.571
Israel (n = 154)	6	16	40	92	0.9 (0.3-2.6)	0.774

Table 3.

Multiple Logistic Analysis of 1st TST reaction results (at a cut off 5mm) of the students, according to the variables: degree of contact, age group, country of birth and previous BCG vaccination.

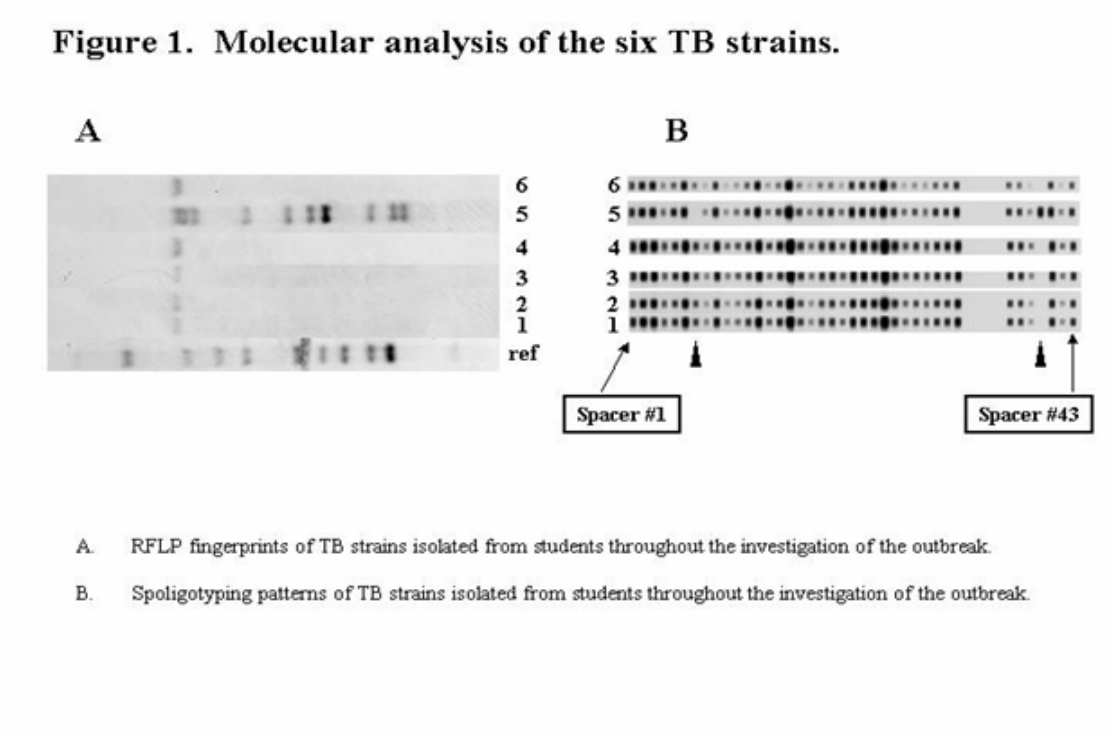
Variables	Odds Ratio	95% C I	*p* value
Close contact	2.76	1.6-4.6	0.001
Country of birth former USSR	9.1	4.65-17.6	0.001
Country of birth Ethiopia	2.67	1.27-5.7	0.01
Previous BCG vaccination	3.8	1.56-9.2	0.003
Age groups			
17-19 years	1.77	0.77-4.0	0.1
19-21 years	1.05	0.44-2.5	0.9
21-23 years	1.24	0.41-3.8	0.7

Figure 1. Legend

Molecular Analysis of the six Tuberculosis strains

A. RFLP fingerprints of TB strains isolated from students throughout the investigation of the outbreak.

B. Spoligotyping patterns of TB strains isolated from students throughout the investigation of the outbreak.



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