A school- and community-based outbreak of *Mycobacterium tuberculosis* in Northern Italy, 1992–3

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SUMMARY

In late 1992, three cases of smear-positive tuberculosis were diagnosed among secondary school students in Lodi, Italy. The three attended different schools but travelled on the same bus. Schoolmates, other bus riders, family members, and friends underwent tine testing and X-rays. Of the 3188 students tested, 277 (8·7%) were reactors. Independent risk factors for tine reactivity among students included living in the same town (odds ratio [OR] = 4·8; 95% confidence intervals [CI] = 3·8–6·0); having classroom contact (OR = 4·4; 95% CI = 3·4–5·7); or riding the same bus (OR = 5·4; 95% CI = 4·3–6·7) as a smear-positive case. Twenty-four cases of pulmonary tuberculosis were identified. The index case was a student whose father had had cavitary tuberculosis. Despite being tine test positive in 1989, he was not given prophylaxis and was lost to follow-up. This large outbreak emphasizes the need for identification and prompt chemoprophylaxis of reactors, especially in vulnerable adolescent populations.

INTRODUCTION

Historically, schools have been the setting for numerous outbreaks of tuberculosis (TB) [1]. The number of such outbreaks has declined, however, paralleling the overall decline of TB in recent years. With the recent resurgence of TB in the United States and Western Europe [2], such outbreaks are likely to become more common.

In this paper, we present a large school- and community-based outbreak that occurred recently in northern Italy in which a student attending a technical high school in Lodi infected at least 150 of his fellow-students and several of his friends. The outbreak resulted from failure to provide prophylaxis for family members of a person with cavitary disease and serves as a reminder of the apparent ease with which TB spread can occur in a vulnerable adolescent and young adult population.

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BACKGROUND

The outbreak took place in Lodi, a town of 43000 located near Milan in the region of Lombardy. Lodi, a relatively well-to-do community, contains 14 high schools, including a scientific high school, a classical high school, and several technical high schools which serve Lodi and several surrounding towns.

The index case was an 18-year-old male living with his parents in a small town outside of Lodi and attending school A who was diagnosed in October 1992 as having cavitary TB involving the upper lobe and apex of the left lung. He reportedly was a recreational drug user, but denied injecting drug use. His father was known to have tuberculosis, and the index case was discovered to be skin test positive in 1989. In 1990, an X-ray disclosed a calcified primary complex. He was never offered chemoprophylaxis and was lost to follow-up in February 1992, at which time he had a history of non-specific respiratory symptoms. His sputum smears in October showed acid-fast bacilli (AFB), and subsequent cultures grew *Mycobacterium tuberculosis* resistant to streptomycin. He was hospitalized and begun on treatment with isoniazid, ethambutol, and rifampicin, but developed a peripheral neuropathy and elevated liver function tests that were attributed to isoniazid. The isoniazid was then replaced with pyrazinamide. An HIV test performed during his hospitalization was negative.

The index case had a strong family history of tuberculosis. His father, who was a former injecting drug user, was skin test positive in 1987 and in 1990 developed cavitary disease. Smear-negative tuberculosis was also diagnosed in the index case's mother and a paternal uncle in 1990; both were successfully treated on an out-patient basis. His father was treated as an in-patient for a total of 4 months. and received an additional 6 months of out-patient therapy. Cultures prior to initiation of therapy yielded *Mycobacterium tuberculosis* sensitive to all antibiotics. He was initially treated with isoniazid, ethambutol, rifampicin and streptomycin. but the streptomycin was dropped when a sputum specimen performed 2 months after initiation of treatment demonstrated resistance. He continued on the remaining three drugs for 5 more months, followed by 3 months of isoniazid and rifampicin. Sputum cultures were negative at the time of his discharge from the hospital. After completing treatment, he was followed every 2 months and was reportedly stable until March 1993, when he suffered a relapse with a streptomycin-resistant organism. At that time, he was found to be HIV negative.

Two weeks after the diagnosis of the index case, two teenagers residing in the same school district developed symptoms compatible with TB and were found to have positive skin tests, X-rays, and sputum smears. The first, an 18-year-old male, was from a different town than the index case and attended school B. The second was a 17-year-old female who resided in the same town as the first case but attended school C, which is located on the same grounds as school B but shares no common facilities or staff with the other school. What the three students had in common, however, was that they had travelled on the same bus line to school.

In the previous 10 years, no cases of smear-positive TB had been observed among middle and secondary school students in the area. Furthermore, the rate of tine test reactivity among 8th-graders, who routinely undergo testing as part of a national screening programme, was relatively low (5·1 % in 1992 and 5·4 % in

1993). To find other cases and to determine the extent of the outbreak, public health authorities therefore undertook a widespread screening of students at the three schools attended by the three initial cases as well as other persons travelling on the same bus line as the cases.

METHODS

In November and December 1992, tine test screening using the PPD Sclavo Test was carried out on all students and staff at the three schools (A, B, and C) in Lodi attended by the three initially identified cases, as well as on all persons using the same bus line as the three. Screening was extended to a fourth school (D) when a bus passenger who attended that school was found to have cavitary disease. Eventually, students at the other 10 high schools in Lodi were screened as well, as were family members and non-student friends of those identified as active TB cases. All tests were read 48–72 h after application to the volar surface of the forearm by health assistants with many years of experience in performing and reading tine tests.

Chest X-rays were performed on all students from the four schools, on all bus passengers, and on any students in the other 10 schools who were found to be tine test positive. They were also carried out on skin test positive family members and non-student friends. Sputum smears were performed on all persons with X-ray evidence of tuberculosis. Cultures and sensitivity analysis were performed on some, but not all, of the cases.

Tine testing was repeated 3 months later among students from schools A, B, C, and D and bus passengers who were initially tine-negative, with chest X-rays performed on those with positive skin tests.

Tine testing rather than Mantoux testing was performed because of logistic difficulties of screening such a large number of subjects (> 7000) with the Mantoux test. For epidemiologic purposes, a reactor was defined as a person whose tine test showed confluent induration around the four tines ($3+$ on the IFF scale). A convertor was defined as a person who had been documented during the initial round of screening to have a negative tine test who subsequently had a positive test. A case of active TB was defined as a person with a positive tine test plus X-ray findings compatible with active TB; cases were further subdivided as having infectious or non-infectious TB based on the presence or absence of a positive AFB smear or, in one case, on the basis of X-ray findings compatible with cavitary disease.

Students who met the case definition of active TB were interviewed in depth about their contacts in and outside of school. In addition, all students were asked to complete a simple questionnaire at the time of tine testing containing information on age, sex, school, and grade, and class as well as on where they lived and means of transport used to get to and from school each day. (As is the case in most Italian schools, students remain cohorted through their high-school years and generally remain in the same classroom all day, with the teachers for different subjects rotating among the different classrooms.)

Data were entered in a DBase III file and analysed using Epi Info [3] and SPSS [4]. Based on available data from the student questionnaires, attack rates for skin

test reactivity were calculated by age, sex, area of residence, school attended, grade, classroom, floor on which the classroom was located, and by mode of transport. Relative risks and 95% confidence intervals (CI) were calculated to study risk factors for skin test positivity. Additionally, multivariate analysis was performed to examine the independent contributions of place of residence, bus contact, and classroom contact as risk factors.

RESULTS

Table 1 shows the numbers of persons tested and the rates of skin test positivity as well as the number of persons with active and infectious TB for students, teachers, and staff of schools A, B, C, and D, students in the remaining 10 high schools of Lodi, non-student users of bus line X, and non-student friends of TB cases. The highest rates of skin test positivity were seen among non-student bus passengers (38%), non-student friends (36%), and the non-teaching staff (25%) of the four implicated schools. Of the 3201 students attending the four high schools, 3188 (99·6%) were tested and 277 (8·7%) were found to be positive. This compares with a rate of 3·7% (123/3321) for students from the remaining 10 high schools in the area (Yates chi square = 69·2; $P < 10^{-7}$).

Tuberculosis cases

A total of 24 TB cases (including the initial 3 cases) were diagnosed, 14 of whom were students of schools A, B, C, and D (Table 1). One of the students was now attending school in another district, but during the 1991–2 school year she had attended school C and had taken the same bus line as the index case during the 1991–2 school year. In addition to the students, a teacher and a cleaning lady at school A were also diagnosed as having active tuberculosis. The teacher who taught the index case during the 1991–2 school year was diagnosed 3 months after the index case; her family was tine-negative. With the exception of the index's case's class, the other classes she taught during the 1991–2 and 1992–3 school years did not have excessively high rates of skin test positivity. The cleaning lady was diagnosed during routine screening and had a negative family history; although she was present during school hours, no direct contact with the other cases was documented.

Of the remaining eight cases of TB, two attended high schools not involved in the initial investigation, were not bus passengers or friends of other cases, and may not have been outbreak-related. A third was a middle school student who travelled on the same bus line as the index case. The other five were friends or acquaintances of the index case who had completed school, had dropped out, or who were attending night school. Three, including two who were brothers, were from the same area as the index case. A fourth friend who worked in a bar in Milan was diagnosed as having infectious TB in March 1993, and a fifth friend who was a resident of a complex for disadvantaged youth that house some former injecting drug users became ill in February and was diagnosed as having smear-negative pulmonary TB in April 1993. Of the four co-workers of the bar employee, two agreed to be tested; one was skin test positive but had negative chest X-ray. The room-mate of the friend living in the residential complex was negative.

Table 1. *Number of persons tested, rates of tine test positivity, number of cases of active and infectious tuberculosis by exposure category, Lodi, October 1992–January 1993*

Group	Number tested	Tine positive (%)	Number with TB	Number infectious
Students (schools A–D)	3188	8·7	14*	6
Students (other schools)	3321	3·7	2	1
Teachers (schools A–D)	274	15·0	1	1
Staff (schools A–D)	101	24·8	1	0
Non-student friends of active cases	22	36·4	5	3
Non-student bus users†	168	37·5	1	0
Total	7087	NA	24	11

* Includes students who attended school C during the 1991–2 school year and rode the bus with index case but subsequently transferred school district.
† Includes middle school students, bus drivers, other adult bus users.

Sensitivity results were available for the index case and 4 of the other 10 infectious cases. All had the same resistance pattern to streptomycin, which had also been observed in the father 2 months after the initiation of treatment in 1990 and again when he suffered a relapse in early 1993. Review of data from the main TB referral centre in Milan demonstrated that only 2·5 % of the 938 strains from the area that had undergone sensitivity testing in 1992 were streptomycin-resistant (unpublished data, Milanese State Institute for Chest and Lung Disease).

Risk factors for tuberculous infection

The remaining results concern only the results of the tine testing for students at schools A, B, C, and D. No significant differences were found in the rates of skin test positivity by age and sex (Table 2). However, major differences were observed in the rates among the four schools. The highest rate (17·3 %) was seen at school A, which was attended by the index case. Schools B and C, which each had one of the initially diagnosed students, had rates of 4·9 and 3·3 %, respectively. School D, which was screened when a bus passenger attending the school was found to have active TB, had a rate of 7·6 %.

In school A, students remain in the same classroom and with the same group of students from year to year thus enabling us to evaluate the distribution of skin test reactivity by location. We found that rates varied by floor, corridor, and classroom. The highest rates were seen on the ground and second floors (Fig. 1). On the ground floor, one of the classrooms on the left corridor had a rate of skin test positivity of 83 %; for the remaining classrooms on the corridor, values ranged from 18 to 25 %. On the second floor, one of the classrooms on the right corridor had a rate of 70 %. The areas with the highest rates correspond to the classroom location of the index case over the past two school years. In 1991–2, he was located in the second-floor classroom with the high rate of positivity. Because of poor performance, he had to repeat the grade, and in the fall of 1992, he was transferred to the ground-floor classroom that had a rate of 83 %. The school did not have central ventilation, although students had corridor contact with each other at the beginning and each of each school day and during a 15-min mid-morning break.

Table 2. *Number of persons tested, rates of tine test positivity, and relative risks and 95% confidence intervals associated with having a positive tine test for students at Schools A, B, C, and D, Lodi, October 1992–January 1993*

Characteristic	Number tested	Tine positive (%)	Relative risk	95% CI
Sex				
Male	2137	9·1	1·2	0·9–1·5
Female	1051	7·8	Referent	—
Age, years				
≤ 16	1921	7·6	Referent	—
> 16	1267	7·6	1·1	0·9–1·4
School				
A	861	17·3	5·1	3·5–7·6
B	486	4·9	1·5	0·9–2·5
C	860	3·3	Referent	—
D	981	7·6	2·2	1·5–3·5
Place of residence				
Tribiano/Paullo	111	55·0	8·6	6·7–10·9
Galgagnano/Montanaso	52	15·4	2·4	1·2–4·7
Zelo/Cervignano	99	14·1	2·2	1·3–3·7
Lodi	1047	7·1	1·1	0·8–1·5
All other	1879	6·4	Referent	—
User of bus line X				
Yes	262	31·7	4·8	3·8–6·0
No	2926	6·6	Referent	—

Infection rates within the catchment area of the school system were not uniform (Table 2). When we examined rates of skin test positivity by zone of residence for the students from the four schools, we found the highest rates in towns located to the northwest of Lodi. The highest rate of positivity (55%) was found in the area of Tribiano and Paullo, the area of residence of the three initial cases, with lower but nonetheless elevated rates (14–15%) seen in north-western towns closer to Lodi that were located on the same bus line as Tribiano and Paullo.

Travelling on the same bus line used by the index case was a risk factor for skin test positivity (Table 2). Overall, using bus line X was associated with a 4·8-fold increased risk of being skin test positive (95% confidence interval (CI) 3·8–6·0). When we examined attack rates for the bus passengers by area of residence, the highest rates were seen for students from Tribiano and Paullo (55·0%), which are located approximately 40 min from Lodi. Rates for Galgagnano/Montanaso. which are only 10–20 min from Lodi, were slightly higher than for Zelo/ Cervignano, which are located 25–35 min away (15·4 versus 14·1%, respectively, $P = 1·0$). According to anecdotal reports, the buses generally carried twice as many persons as there were seats, and those getting on at the stops closer to Lodi were crowded in the bus aisles.

Because it was possible for students to have multiple types of contact with an infectious case (e.g. classroom, bus, residence), we performed a multivariate analysis to look at the independent risk associated with each. Results are shown in Table 3. This analysis demonstrated that classroom, bus, and residence contact were all independent predictors of the risk of tuberculous infection.

To examine whether students who had two or more forms of contact with an
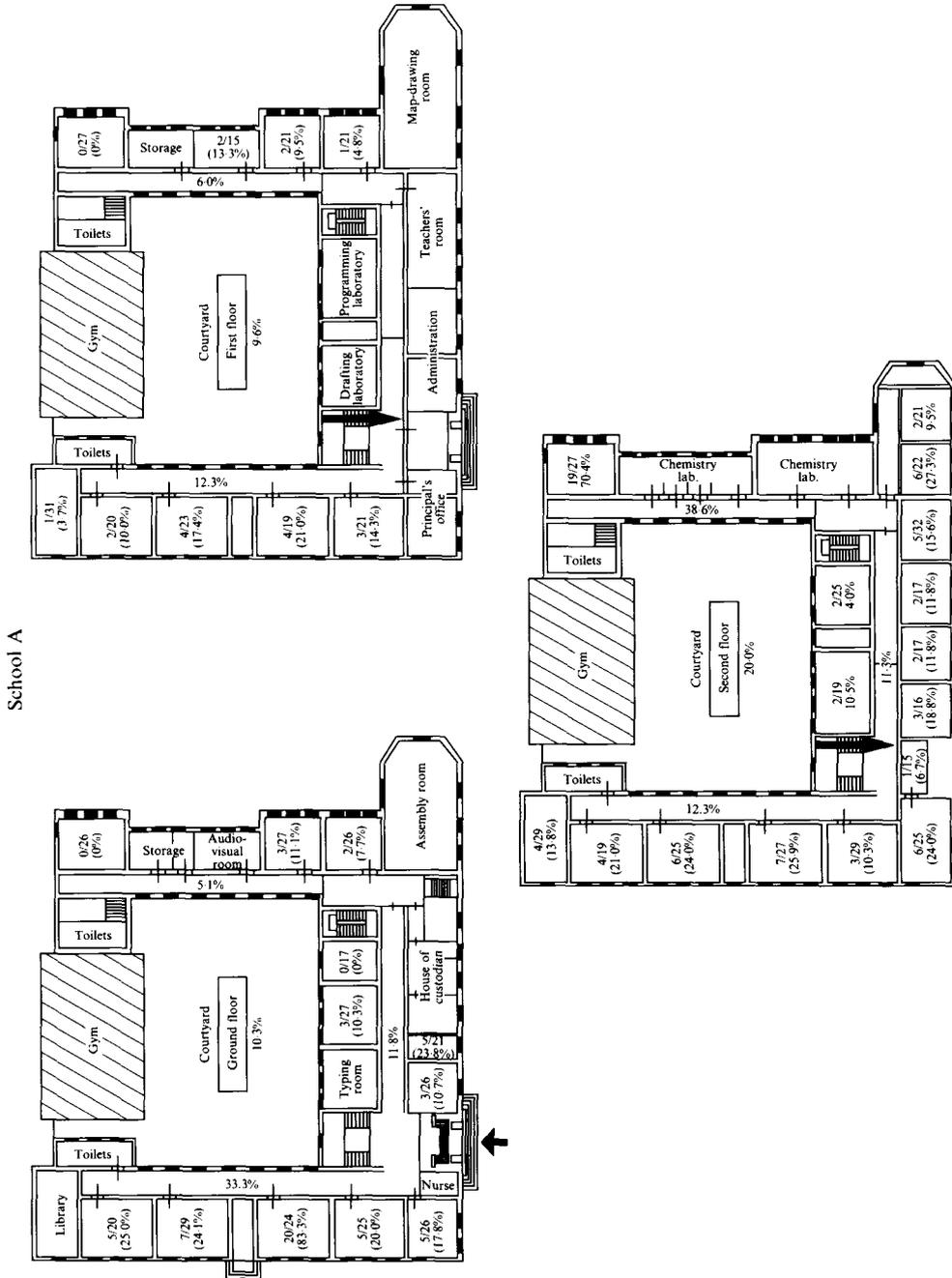
School A

Figure 1. Rates of skin test positivity by classroom and corridor, school A.

Table 3. *Independent effects of contact with infectious cases on the risk of skin test positivity among students attending Schools A, B, C, and D, as determined by logistic regression*

	Number tested	Tine positive (%)	Adjusted odds ratio	95% CI
Same area of residence	262	31·7	4·8	3·8–6·0
Bus contact	212	33·0	5·4	4·3–6·7
Classroom contact	163	32·5	4·4	3·4–5·7

infectious case were at higher risk than those with only one exposure, we examined infection rates for those with bus and classroom contact compared with those who had only one form of contact. Those with bus and classroom contact had a significantly higher rate (88·2%; 15/17) than those with only bus contact (33·0%; 70/212; $P = 0.00002$) or school contact (32·5%; 53/163; $P = 0.00002$). It was not possible to examine the combined effect of classroom and residential contact because virtually all the students living in Tribiano and Paullo travelled on the implicated bus line at least occasionally.

In order to determine if secondary transmission from cases presumably infected by the index case occurred, we compared rates of skin test positivity among classroom contacts of the index case, classroom contacts of the other five infectious cases, and those with no classroom contact. We found that the rate of positivity in those in classroom contact with the index case was 76%, nearly 11 times higher than for those with no classroom contact with any of the infectious cases (RR = 10·9; 95% CI = 8·7–13·4). Students in the same class with another of the infectious cases had a rate of 19%, almost three times higher than the no-contact group (RR = 2·8; 95% CI = 1·9–4·0). However, 10 of the 13 skin test positive classroom contacts of the other infectious cases were also bus passengers, suggesting that little secondary transmission occurred and that most of the cases resulted from contact with the index case.

A second round of screening was performed approximately 3 months after the initial screening to detect further conversions. One fifth (20·2%; 56/277) of the tine-test positive students in the four schools were detected during this second round of screening. Of the 56 conversions, 49 (87·5%) occurred among students attending school A. Twenty-two of the 49 (44%) occurred among students in classrooms on the same corridor as the index case's classroom, including 9 in the index case's 1992–3 class; an additional 4 conversions were observed in his 1991–2 class. Few bus passengers had converted. Of the 223 tested, only an additional 8 (3·6%) were positive where the second round of testing was performed, 3 of whom also attended school A.

DISCUSSION

This outbreak represents the largest reported outbreak of TB in Italy in recent years. Assuming a 3·7% baseline rate of skin test positivity in the school-age population in the area based on the results for the 10 unaffected schools, we estimate that 159 students were newly infected during the outbreak at the four schools alone. It also underlines the potential for spread of TB in an increasingly

mobile adolescent and young adult population. In this outbreak, the index case apparently infected a friend who worked in a bar, who in turn appears to have infected at least one of his four co-workers. He also infected a resident of a complex for disadvantaged youth that reportedly houses some former injecting drug-users.

The vast majority of infections can be attributed to contact with a single index case who would appear to have been highly infectious. It has been estimated that one third to a half of close household contacts of a smear-positive person will become infected [5]; in this case, three-quarters of his direct classroom contacts, a third of the students who used the same bus line, and a number of his friends became infected. In addition, he was most probably infectious for a period of several months, as evidenced by the high rate of infection in his class from last year and the discovery of a case in a student who had travelled on the bus with him last year and had transferred to another school district.

Transmission occurred in a variety of settings, including the classroom, the school bus, and among friends outside school. Most likely, it also occurred as a result of more casual but repeated contact, as evidenced by the higher rates of skin test positivity on the corridors of the school where the index case attended class. Students of school A who left or graduated in 1992 are currently being located and screened.

School and classroom transmission of TB had been well documented, and the rates of infection in our study are in keeping with those observed in other school outbreaks [1]. By contrast, transmission in public transport settings has been less well documented. In 1961, Mahady reported an outbreak in five rural schools served by a tuberculous bus driver in which the rate of tuberculin test reactivity was 20 times higher than in those who rode the bus than in those who did not [6]. In 1969, Darney and Clenny reported an outbreak in a middle and high school in which 78% of the students in the lower grades, whose contact with the presumed index case was largely limited to a poorly ventilated bus, were reactors [7]. In 1985, Sacks and colleagues reported an outbreak in a junior high school in the southern United States in which students who had only school bus contact with the index case were twice as likely as students with no known exposure [8]. More recently, transmission has been documented among factory workers using the same van to their worksite [9]. The risk of infection associated with travelling in the buswas even higher than that associated with classroom contact despite the relatively brief duration of the bus trip, suggesting that the high levels of crowding in the bus resulted in an efficient transmission of the organism.

In our investigation, we used the tine test rather than the Mantoux for logistic and practical reasons. This test, which is considered less sensitive and specific than the Mantoux [5, 10] also did not allow us to quantitate accurately the size of the reaction. Although the use of the tine test may have resulted in an over- or under-estimate of the number infected, it is unlikely to have influenced our findings on risk factors for disease transmission.

An interesting finding in our study was the 20% of students with tuberculous infection who were detected on the second round of screening. This contrasts with a yield of 3% on repeat testing in the school outbreak reported by Sacks and colleagues, although the students in their series were tested in the spring, several months after the beginning of the school year [8]. BCG vaccination was largely

discontinued in the area before the students in the cohort were born, and boosting as a result of previous testing is unlikely to explain most of these positive reactions. More likely, it is estimated that it takes 2–10 weeks following exposure to develop a positive skin test [11], and many of the newly positive students were in the classroom and on the corridor where the index case was moved during the 1992–3 school year and may not have had time to develop a positive response when the initial round of testing was performed.

In addition to the index case, 13 other student at schools A, B, C, and D developed pulmonary TB. If we assume that the number of new infections was approximately 160 among students at the three schools and that infection occurred over a 9-month period between February 1992 when the index case was lost to follow-up and November 1992, the rate of TB among those infected would be 11·7% per year. This value is similar to the rate that would be expected to occur in an untreated population in the first 2 years after infection [12]. Although caution is required in interpreting these results since the numbers are relatively small, the number of students recently infected is only an estimate and the duration of the index case's infectivity is not certain, it may also represent the increased vulnerability of adolescents to active infection [5, 12].

This outbreak could have been prevented. The father of the index case was known to have cavitary TB. In accordance with local policy, which recommended periodic medical evaluation rather than chemoprophylaxis, the index case had been followed over time but was not offered chemoprophylaxis when found to be skin test positive and to have a calcified primary complex. Medical follow-up of those who are skin test positive is problematic because of the frequent visits and repeated X-rays that are required. Even under optimal circumstances, TB may develop between visits.

This episode has had serious implications. First, it was costly in terms of both personnel and time. More than 10 health care personnel were diverted to work on the outbreak on a full-time basis during a 5-month period. Although costs are difficult to estimate directly, nearly 10000 tine tests and more than 3500 chest X-rays were performed. A second implication was that the outbreak caused considerable disruption for the schools involved and anxiety among the students, their families, and the staff; it also resulted in financial losses for the implicated bus line. In addition, the students who developed active TB, especially those who were considered infectious, missed several months of school. A third implication is that despite massive efforts, we are unlikely to have detected all of those infected, and not all of those detected are likely to complete the course of chemotherapy that has now been recommended by local health authorities. The region where the outbreak occurred has one of the highest rates of injecting drug use among young people in Italy and of HIV infection among injecting drug-users (approximately 44%) [13]. In fact, the index case admitted to being a recreational drug-user, and one of the friends he infected is currently residing in a community that includes former drug-users. The potential for spread to the local drug-using community, especially to street users who have little contact with the health care system, is worrisome.

In response to this outbreak, the regional policy on TB identification and treatment has been re-formulated and the importance of contact tracing and

chemoprophylaxis re-emphasized. Hopefully these guidelines will be useful in preventing such episodes in the future.

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