CLINICAL RESEARCH STUDY

TB in a Low-Incidence Country: Differences Between New Immigrants, Foreign-Born Residents and Native Residents

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ABSTRACT

BACKGROUND: New immigrants and foreign-born residents add to the burden of pulmonary tuberculosis (TB) in low-incidence countries. The highest TB rates have been found among recent immigrants. Active screening programs are likely to change the clinical presentation of TB, but the extent of the difference between immigrant and resident populations has not been studied prospectively.

METHODS: Adult new immigrants were screened upon entry to 1 of 5 immigration centers in Switzerland. Immigrants with abnormal chest radiographs were enrolled and compared in a cohort study to consecutive admitted foreign-born residents from moderate-to-high incidence countries and native residents presenting with suspected TB.

RESULTS: Of 42,601 new immigrants screened, 112 had chest radiographs suspicious for TB. They were compared with foreign-born residents (n = 118) and native residents (n = 155) with suspected TB (n = 385 patients included). Active TB was confirmed in 40.5% of all patients (immigrants 38.4%, foreign-born residents 50%, native residents 34.8%). Clinical signs and symptoms of TB and laboratory markers of inflammation were significantly less common in immigrants than in the other groups with normal results in >70%. The proportion of positive results on rapid testing to detect *M. tuberculosis* (MTB) in 3 respiratory specimens was significantly lower in immigrants (34.9% for acid-fast staining; 55.8% for polymerase chain reaction) compared with foreign-born residents (76.2% and 89.1%, respectively) and native residents (83.3% and 90.9%, respectively). Isoniazid resistance and multi-drug resistance were more prevalent in immigrants.

CONCLUSION: New immigrants with TB detected in a screening program are often asymptomatic and have a low yield of rapid diagnostic tests but are at higher risk for resistant MTB strains. Postmigration follow-up of pulmonary infiltrates is essential in order to control TB among immigrants, even in the absence of clinical and laboratory signs of infection. © 2007 Elsevier Inc. All rights reserved.

KEYWORDS: Foreign-born; Clinical presentation; Immigrants; Residents; Screening; Tuberculosis

More than one-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis* complex (MTB). Eight million new cases of pulmonary tuberculosis (TB) and approximately 2 million deaths attributable to TB are reported each year.[1] In many developed countries, new immigrants and foreign-born residents are increasingly con-

tributing to the burden of TB in the host country. The proportion of TB cases in these 2 groups exceeds 50% in the US and parts of Europe.[2-4] In particular, new immigrants who are screened for TB as they enter a country show high TB prevalences (256-504/100,000 population per year).[3,5-8] Consistently high incidences (33-85/100,000 population per year) also have been reported for foreign-born residents in low-prevalence countries.[3,6,9,10] Among the native residents in these countries, the TB incidence is below 10/100,000 population per year.[3,10] The risk of disease for foreign-born

residents is highest in the first 5 years after arrival, with 50% of cases occurring in this period.[11]

Prompt identification, early effective treatment, and isolation of TB patients are important strategies in preventing an increase in the occurrence of TB in the general population of a low-incidence country. The most important criteria for establishing an early diagnosis are positive results in rapid diagnostic tests on respiratory specimens (acid-fast smear and polymerase chain reaction) and a case definition that is based on clinical and radiographic signs and risk factors. Although scoring systems and decision trees have been developed to more adequately predict patients at high risk for active TB,[12-15] they are difficult to apply in clinical practice.

The clinical presentation of TB depends largely on how far the disease has progressed in an individual. The diagnosis is particularly challenging in immigrants who are actively screened upon entry to their host country. We hypothesized that active screening changes the presentation of TB compared with passive case detection and that many actively screened immigrants presenting with TB are asymptomatic. The extent of this difference in comparison with the resident population has not been investigated in prospective studies before.

Active screening programs are currently under debate because of their costs and the limited evidence of a reduction in transmitting TB in the host country. If most immigrants with TB are asymptomatic, and thus cannot be diagnosed by passive case detection, active screening programs should be reinforced. This would aid in identification of large numbers of individuals who will benefit from therapeutic interventions and limit the transmission at least within the migrant community living under crowded conditions.

CLINICAL SIGNIFICANCE

- Immigrants add substantially to the burden of tuberculosis (TB) in low-incidence countries.

- Screening programs to detect TB in immigrants are recommended as a measure to support TB elimination efforts.

- Postmigration follow-up of pulmonary infiltrates is essential in order to control TB among immigrants, even in the absence of clinical signs of infection.

1 of the 5 State immigration centers (Basel) in Switzerland (active screening). Foreign-born residents (ie, persons with work permit in Switzerland and their families, students and tourists) are not actively screened for tuberculosis in Switzerland. Like the native residents, they were referred at the discretion of the general practitioners (passive case detection). Demographic data (age, sex, country of origin), duration of isolation, laboratory results, and microbiological data were collected prospectively and recorded in a database. Additional data (fever, weight loss, night sweats, cough, sputum production, dyspnea, and auscultatory findings) were extracted by chart review. Countries of origin were categorized into those with a low notification rate of TB ($<24/100,000$ population per year) and those with a moderate to high notification rate of TB ($\geq24/100,000$ population per year), as reported by the 1998 report of the World Health Organization (WHO). The study was reviewed and approved by the Ethics Committee of the University of Basel.

METHODS

Patient Population

From January 1997 through July 2004, all patients admitted to our hospital who were placed in respiratory isolation for suspected TB were included in this cohort study. The University Hospital Basel is a 780-bed primary and tertiary care center with approximately 23,000 admissions annually. The patients were categorized into new immigrants who were actively screened for TB upon entry into Switzerland, foreign-born residents who emigrated from countries with a moderate to high prevalence of TB, and native Swiss residents. Immigrants were referred to our hospital if the screening chest radiograph was suspect for TB upon entry to

Microbiology

Respiratory specimens were digested, decontaminated, concentrated, and stained with auramine-rhodamine and then examined with fluorescent microscopy. Ziehl-Neelsen acid-fast staining (AFS) was used to confirm the presence of acid-fast bacilli. Mycobacterial cultures were performed by sample-inoculation on to Loewenstein-Jensen media and into liquid media (radiometric Bactec 460 TB system, Becton Dickinson, Franklin Lakes, NJ, used from 1997 to 2000; BacT/ALERT 3D system, BioMérieux Inc., Durham, NC, used from 2001 through 2004) according to the manufacturers' instructions and incubated at 37°C for 8 weeks. Polymerase chain reaction (PCR) testing for MTB was performed by using the Roche Amplicor *Mycobacterium* test with a Cobas Amplicor analyzer (Roche Diagnostics Systems, Basel, Switzerland) according to the manufacturer's instructions on concentrated decontaminated specimens.

Study Definitions

Active TB was defined as one or more positive cultures of respiratory specimens for MTB (proven TB), or as culture-negative with a compatible abnormal chest radiograph and clinical and radiological improvement after therapy for 2-3 months with a standard combination therapy and without any alternative diagnosis (probable TB needing treatment). *Inactive TB* was defined as negative cultures and an abnormal chest radiograph, which was stable after a standard

therapy for 2-3 months in suspected TB cases without alternative diagnosis. An *alternative diagnosis* was defined as a diagnosis of an infection other than TB, cancer, or noninfectious diseases diagnosed by treating physicians and explaining the abnormal chest radiograph and the clinical presentations. *Multi-drug-resistance* (MDR) was defined as the resistance of MTB to both isoniazid and rifampin. *Excessive alcohol use* was defined as consumption of >14 standard drinks per week for men and >7 standard drinks per week for women, according to the criteria for "at risk" drinking established by the National Institute on Alcohol Abuse and Alcoholism.

Statistical Methods

The analyses were carried out by using SAS software (SAS Institute Inc., Cary, NC). All predefined associations that were considered to be important predictors were investigated. They consisted of using *t* tests between continuous data variables and chi-squared tests between categorical data variables. In situations where the cell counts fell below 5 in 20% or more of the cells, Fisher's exact test was performed. To overcome the problem inherent in multiple testing, *P*-values were adjusted by using the Bonferroni correction method.

RESULTS

Patient Characteristics

Between January 1997 and July 2004, 397 patients with suspected pulmonary TB were included in the study. Twelve patients (3.0%) were excluded because of incomplete data. The distribution of the patients and the diagnoses are shown in the Figure.

There were 42,601 new immigrants >16 years of age who were actively screened by chest radiograph upon entry to Switzerland at the Basel immigration center (median age 26 years; range 16-98 years). Of these, 112 (0.26%) were referred to the hospital with pulmonary infiltrates suspicious for TB. Table 1 shows the demographic characteristics and risk factors for TB.
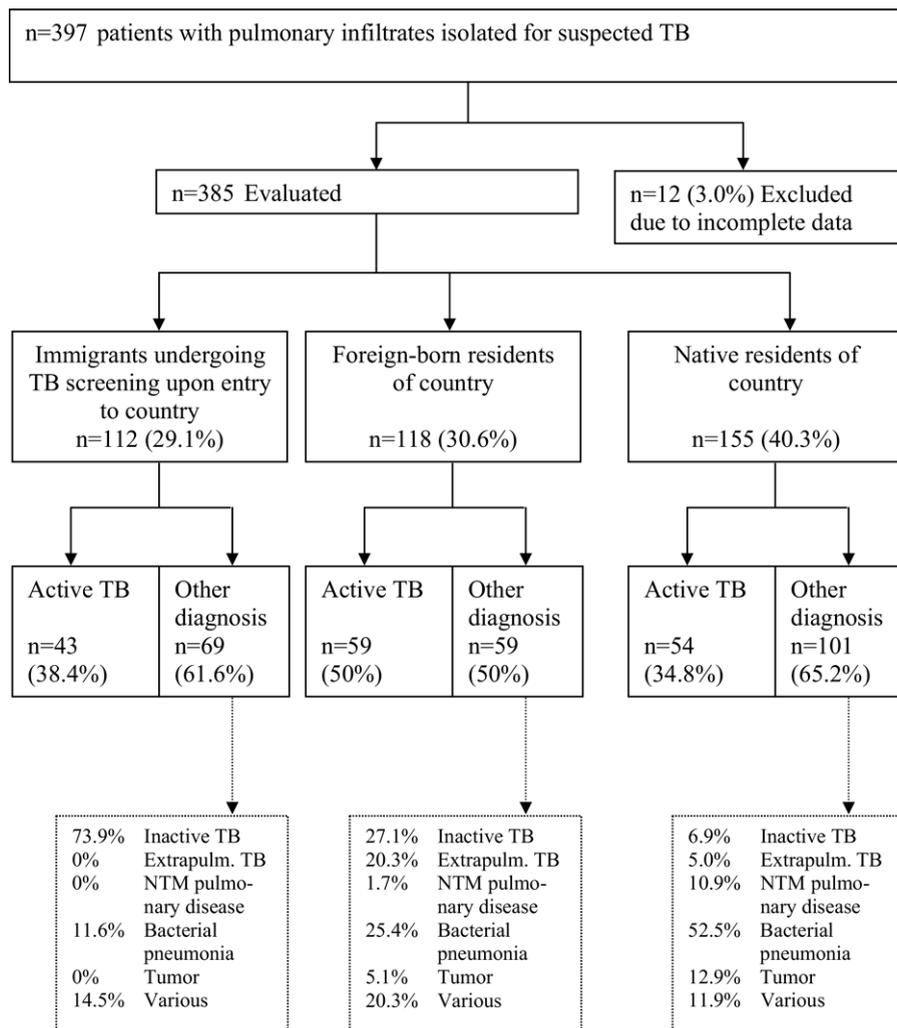
Figure　Diagnoses of patients in respiratory isolation with pulmonary infiltrates suspicious for pulmonary tuberculosis. TB = tuberculosis; NTM = nontuberculous mycobacteria.

Table 1 Demographic Characteristics of New Immigrants, Foreign-born Residents and Native Residents with Active Pulmonary Tuberculosis

Characteristic	Immigrant Group (n = 43)	Foreign-born Group (n = 59)	Native Group (n = 54)
Age (years)	30.6	35.1	50.2**
Mean range	16-49	16-86	23-88
Male sex (%)	90.7	61.0	72.2
Area of origin (%)			
Africa	18.6	15.3	—
Asia	9.3	16.9	—
Latin America	—	10.2	—
Eastern Europe	62.8	32.2	—
Southern Europe	9.3	25.4	—
Central Europe	—	—	100
TB risk factors (%)	0*	25.4	59.3**
HIV positive	0*	12.5	18.4**
Excess alcohol use	0	10.2	27.7**
Diabetes	0	5.1	7.4
Cancer	0	1.7	1.9
History of TB (%)	14.0*	1.7	3.7

TB = pulmonary tuberculosis; HIV = human immunodeficiency virus.

*P <.05 immigrants vs native and vs foreign-born.

**P <.05 native vs foreign-born and vs immigrants.

Active TB was confirmed in 40.5% of all patients isolated for suspected TB (38.4% in the screening group of new immigrants, 50.0% in foreign-born residents, and 34.8% in native residents). A prior history of tuberculosis was reported more often among new immigrants than among either foreign-born or native residents. Significantly more native residents with active TB had risk factors for TB, compared with new immigrants or foreign-born residents with active TB (Table 1). Excess alcohol use was the predominant risk factor.

Clinical, Radiological, and Laboratory Presentation

All clinical signs of infection (ie, fever, night sweats, weight loss, cough, sputum production, and dyspnea) were significantly less common in the screening group of new immigrants with active TB than they were in foreign-born and native residents with active TB (Table 2). The clinical presentation of TB in foreign-born and native residents did not differ with the exception of dyspnea, which was reported more often in foreign-born residents. Pulmonary auscultation was less likely to be abnormal in the screening group (new immigrants) compared with the foreign-born and native residents (Table 2). Radiological presentation was similar in the 3 groups with the exception of more multilobular involvement in native residents (Table 2), whereas foreign-born residents presented more often with cavitations (Table 2). Systemic signs of inflammation, as measured by C-reactive protein (CRP) and neutrophil counts, were significantly more elevated in native residents with active TB than they were in foreign-born residents with

Table 2 Disease Characteristics of New Immigrants, Foreign-born Residents, and Native Residents with Active Pulmonary Tuberculosis

Disease Characteristic	New Immigrant (n = 43)	Foreign-born (n = 59)	Native (n = 54)
Fever >38.3 n (%)	7/42 (16.7)*	40/56 (71.4)	40/52 (76.9)
Night sweats n (%)	7/40 (17.5)*	30/53 (56.6)	20/51 (39.2)
Weight loss n (%)	11/40 (27.5)*	32/52 (61.5)	30/52 (57.7)
Cough n (%)	19/42 (45.2)*	51/56 (91.1)	47/52 (90.4)
Sputum n (%)	10/42 (23.8)*	43/55 (78.2)	41/52 (78.8)
Dyspnea n (%)	3/39 (7.7)*	10/55 (18.2)†	24/52 (46.2)
Crackles n (%)	6/42 (14.3)*	20/56 (35.7)	21/52 (40.4)
Infiltrate			
Upper lobe n (%)	37/41 (90.2)	46/57 (80.7)	34/50 (68.0)
>1 Lobe n (%)	3/41 (7.3)	7/57 (12.3)	15/50 (30.0)‡
Bilateral n (%)	9/41 (22.0)	12/57 (21.1)	22/50 (44.0)
Cavitation n (%)	10/41 (24.4)	26/57 (45.6)§	17/50 (34.0)
Neutrophils Mean (10⁹/L)	5.83*	6.36†	9.18
Hemoglobin Mean (g/L)	14.2*	12.2	12.0
CRP Mean (mg/L)	17.0*	67.1†	90.7
Albumin Mean (g/L)	39.3*	32.0†	27.1
Case fatality rate (%)	0*	1/59 (1.7%)†	6/54 (11.1%)

CRP = C-reactive protein.

*P <.05 immigrants vs foreign-born and vs native.

†P <.05 foreign-born vs native.

‡P <.05 native vs immigrants.

§P <.05 foreign-born vs immigrants.

Table 3   Microbiological Data for Patients with Active Pulmonary Tuberculosis

| | Results According to Patient Category | | | | | |
| | Immigrant | | Foreign-born | | Native | |
Type of Data	Per specimen n = 134	≥1 Positive per patients n = 43	Per specimen n = 170	≥1 Positive per patients n = 59	Per specimen n = 128	≥1 Positive per patients n = 54
Proportion of positive acid-fast smear	23.1%*	34.9%*	57.3%	76.2%	75.6%	83.3%
Proportion of positive PCR	35.4%*	55.8%*	81.4%	89.1%	80.8%	90.9%
Proportion of positive culture	52.2%*	76.7%*	92.4%	100%	85.8%	98.1%

PCR = polymerase chain reaction.

*P <.05; immigrants vs foreign-born residents and vs native residents.

active TB (Table 2). Systemic signs of inflammation were low in the screening group of new immigrants (Table 2) and were absent in a substantial proportion of patients with active TB (normal CRP in 73.8%; normal neutrophil count in 71.4%) in this population. Furthermore, hemoglobin levels and albumin levels were lower in foreign-born and native residents with active TB than they were in new immigrants (Table 2). In-hospital mortality was increased among native residents with active TB (11.1% vs 0% in new immigrants and 1.7% in foreign-born residents; Table 2).

Microbiology

A total of 1158 respiratory specimens were collected for mycobacterial diagnostics (mean 3.0 specimens/patient). The proportion of positive rapid tests for MTB (AFS and PCR) was significantly lower in new immigrants in all specimens of patients with active TB (23.1% for AFS; 35.4% for PCR) compared with foreign-born residents (57.3% and 81.4%, respectively; Table 3) and native residents (75.6% and 80.8%, respectively; Table 3). Similar results were obtained from cultures for MTB (proportion of positive results in 52.2% of specimens of new immigrants vs. 92.4% in foreign-born residents and 85.8% in native residents; Table 3). Accordingly, the proportion of patients with active disease and at least one positive rapid test for MTB was lower in new immigrants (34.9% for AFS, 55.8% for PCR) compared with foreign-born residents (76.2% and 89.1%, respectively; Table 3) and native residents (83.3% and 90.9% respectively; Table 3). Specificity was 98% or higher throughout all 3 groups for rapid diagnostic tests, as well as for cultures. A significant proportion of new immigrants had culture-negative TB (23.3%), whereas only 1/113 patients in the other 2 groups had culture-negative TB.

Drug Resistance

Isoniazid resistance and multi-drug resistance were more prevalent in the new immigrant population (21.9% and 6.3%, respectively) than they were in foreign-born residents

(10.2% and 1.7%; P <.05) and native residents (5.8% and 1.9%; P <.05).

DISCUSSION

In our study, we demonstrated that immigrants in screening programs present with significantly fewer clinical signs compared with foreign-born residents and native residents living in a low-incidence country. This is not surprising because the latter 2 groups present with a disease, whereas the new immigrants were screened irrespective of clinical symptoms. The important result of this study is that the vast majority (>70%) of new immigrants screened upon entry show no clinical signs or symptoms of TB at all and present with normal laboratory markers of inflammation despite having active TB. The extent to which new immigrants are asymptomatic is a new finding. Previous retrospective studies report up to 50% of actively screened immigrants to be "symptom-free."[16] Moreover, the disappointing low yield of rapid tests for MTB underscores the diagnostic dilemma for this population and the need of a postmigration follow-up.

Prompt identification and effective isolation of patients with active TB is considered to have a high priority in TB control policies, especially in immigrants. Patients are less contagious while still smear-negative[17] and have a lower morbidity and mortality. In the US regulations require immigrants to undergo TB screening in their countries of origin, and travel to the US is permitted only if sputum smears are negative in individuals with pulmonary infiltrates. Almost 7% of immigrants who arrived in the US and were referred for further medical evaluation had active TB.[18] Furthermore, more than 80% of new immigrants in the US who are subsequently diagnosed with active TB were screened within 6 months before arrival in the US with negative results, and 50% were given a diagnosis within 30 days after arrival.[8] The ability of current overseas screening programs to detect TB based on chest radiographs and AFS is low[19] and will miss persons with AFS-negative active TB, who constitute the majority (65.1%) of new immigrants

in our study. Despite its superior accuracy compared with AFS[20] and its high negative predictive value in refugees with culture-positive TB,[5] PCR testing for MTB is not recommended in this setting. A strategy including chest radiographs upon arrival in the host country and a clinical work-up including repeated PCR testing in case of TB-suspicion may be superior, because the yield of AFS in the screening population in our study was disappointingly low and was even lower than previously reported in another screening population of immigrants in the Netherlands.[21] Despite posing a substantial financial burden to host countries with a low incidence of TB, similar strategies have been shown to be cost effective.[22,23]

Both the underdiagnosis and overdiagnosis of patients at risk for TB make actual isolation guidelines difficult to implement and not fully effective. Importantly, scoring systems and decision trees to identify patients at high risk for active TB[12-14] are not validated in screening populations and may not apply to this setting. In institutions that must deal with great numbers of TB patients, TB is confirmed in one of 7-10 patients isolated.[4,24,25] In our single-center study, active TB was confirmed in 40.5% of all isolated patients and initially missed in only 5%, which is in accordance with published data from the literature.[15]

The sensitivities of single cultures for MTB range from 50% to 81%[26] and are in line with the results obtained in our study. Low bacillary populations and temporal variations in the number of bacilli being expelled are possible explanations for a failure to isolate MTB.

About 17% of all TB cases among foreign-born persons in the US are culture-negative.[10] In our study, especially new immigrants in the screening group presented with a culture-negative TB, whereas the overall rate was only 7.1%, confirming the results of a retrospective study comparing active and passive screening for TB.[16]

The prevalence of drug-resistant MTB can reach up to 37% and is highest in Eastern Europe and parts of Asia.[27] In the US, the primary resistance rate to isoniazid in foreign-born residents was reported to be 11.6%, with multi-drug resistance being 1.7%.[10] Similar results were obtained in studies from the UK[7] and from Texas,[28] and these are in accordance with the rates obtained in our study. Importantly, especially in new immigrants the proportion of drug-resistant MTB-strains is high, as shown in our study.

Although the study was not designed to detect differences in mortality rates, native residents who died were older and had more risk factors for TB, including excess alcohol intake and HIV co-infection. Treating physicians possibly suspect TB less often in native residents in a low-incidence country, which may contribute to a delayed hospital admission, a more advanced disease at the time of presentation, and an increased case fatality rate. The higher proportion of HIV-infection in native residents with TB may explain the more frequent multilobular involvement on chest radiograph and is in concordance with previous reports from the literature.[10]

Our study shows several strengths. All 3 groups in the study consisted of a similar number of patients (more than 100 per group) with a high overall rate of confirmed TB (40.5%) and a similar TB rate in each group. The standard of care and the diagnostic approach of all patients in respiratory isolation were the same over a period of almost 8 years. There are 2 potential limitations to this study. First, this study is a single center study, which may not represent other settings in the Western world. Second, the communication with persons from foreign countries is often difficult, which may introduce a possible bias in taking an accurate patient's history.

In conclusion, foreign-born residents and native residents with active TB do not show significant differences in the clinical, radiological, and mycobacterial presentation in a low-incidence country. In contrast, new immigrants screened upon entry present without clinical signs and symptoms of TB in the majority of cases. Because the diagnostic yield of AFS in this population is low, a clinical work-up including better diagnostic tools like PCR testing and a postmigration follow-up is important in order to control TB among immigrants with pulmonary infiltrates, even in the absence of clinical and laboratory signs of infection.

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