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Molecular Epidemiology of Tuberculosis among Immigrants in Hamburg, Germany

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To study the characteristics of tuberculosis (TB) in foreign-born individuals living in Hamburg, Germany, and to discover in what way foreign-born individuals contribute to the incidence of TB in Hamburg, an in-depth epidemiological study was performed by a combination of classical and molecular methods. In total, 796 patients with TB were analyzed between 1997 and 2002 (88.7% of all patients with culture-positive TB in the study period). Of this total, 334 were foreign-born patients from 43 different countries. Of these, only 31 cases were identified as a consequence of the screening of 12,176 asylum seekers at entry. Of the foreign-born patients, 41.9% had been living in Germany for more than 5 years. On the basis of the IS*6110* typing results for isolates from all patients, 246 patients (31%) were classified into 68 clusters, with each cluster containing from 2 to 38 patients. Among foreign-born individuals, 86 (26%) were represented in 40 clusters. In multivariate analyses, a previous history as a TB contact had the highest predictive risk for clustering among foreign-born patients, followed by drug addiction, alcohol dependence, being an asylum seeker, and unemployment. Epidemiological links verifying recent transmission could be confirmed for 39 of the 86 foreign-born members (45.3%) who formed a cluster, comprising 16 source patients and 23 directly infected patients. Of 2,227 previously known contacts of foreign-born patients subjected to traditional contact investigation, 14 foreign-born individuals (0.6%) subsequently contracted culture-confirmed TB, but only 9 transmissions could be confirmed by IS*6110* typing (39.1% of the 23 confirmed fresh infections retrospectively confirmed by IS*6110* typing). In conclusion, only a minority of TB cases among foreign-born individuals are detected by screening of asylum seekers or conventional contact tracing. Recent transmission does not play an important role in TB among immigrants in Hamburg.

In Germany the incidence of tuberculosis (TB) is relatively low and is steadily decreasing, with a total of 7,866 new cases reported to the Robert Koch Institute in 2001 (9.6 per 100,000 inhabitants; cf. 11.0 per 100,000 inhabitants in 2000 and 12.1 per 100,000 inhabitants in 1999 [21]). However, the ratio between the respective incidences for foreign-born and German-born inhabitants is increasing (4.5 in 1999 and 5.0 in 2001 [22]), and, accordingly, the proportion of TB cases occurring among people born outside the country is also rising (from 41.5% in 2000 to 43.0% in 2001).

The city of Hamburg (one of the German federal states and, with 1.7 million residents, the second largest city in Germany) is particularly affected. There the incidence rate among Germans has declined to a relatively low level of 8.0 per 100,000 inhabitants (12), while the corresponding level for foreign-born inhabitants was 59.6 per 100,000, i.e., more than seven times greater than the level among native Germans. As a consequence, against the national downward trend described above, an overall TB incidence of 16.25 cases per 100,000 inhabitants was documented in Hamburg in 2001; this represents the highest TB incidence rate among all 16 German federal states (22).

Hamburg, further characterized by its international harbor and by being one of Germany's most popular tourist destinations, also has the highest proportion of foreign residents: 15.1%, compared with a national average of 8.9% reported for 31 December 2001 (24).

In order to identify the pathways of TB transmission and to determine the predictors of clustering of identical isolates in this metropolis, a long-term, prospective, population-based molecular-epidemiological study has been in progress since 1 January 1997. The study includes all patients with culture-confirmed TB reported to each of the seven district public health departments (7).

The analysis presented here was designed to discover in what way foreign-born individuals, including, in particular, refugees from countries with a high incidence of TB, contribute to the incidence of TB in Hamburg. Particular attention was paid to determination of the risk of recently transmitted disease in this population and whether the present public health surveillance efforts in Hamburg measure up to the task of detecting a sufficient number of cases to control the spread of TB from this source.

MATERIALS AND METHODS

Data collection. Data on patients diagnosed with TB from 1 January 1997 to 30 June 2002 were collected prospectively by trained public health staff using a standardized questionnaire. By interviewing each patient, the following information was obtained: the patient's sex, date and country of birth, nationality, immigration status (if applicable), number of years of residence in Hamburg (or Germany), present address (or whether the patient was homeless), whether the patient was living in a health care or any public institution, the nature of the patient's employment, socioeconomic status, any previous known exposure to other persons with TB (especially within the 6 months before the development of any symptoms), and the name of the patient's household contacts and/or any close contacts in occupational or crowded settings, if relevant.

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To obtain clinical variables, the following data were also included: date of first onset of illness (if possible, the time interval between the last possible exposure date and the time of onset of any symptoms and, if available, the time interval between the first contact tracing and the onset of any symptoms), presenting symptoms, date and cause of diagnosis, latency due to patient's delay, first date of case report to a public health office, associated medical problems (especially human immunodeficiency virus infection), tuberculin skin test results, chest radiographic findings and the results of microbiological analyses, and the presence of alcoholism (defined as a maladaptive pattern manifested by three or more criteria of the World Health Organization International Statistical Classification of Diseases and Related Health Problems, 10th revision, classification [26] occurring at any time in the same 12-month period). Extrapulmonary disease was defined as disease with no evidence of lung involvement.

Bacterial strains and drug susceptibility testing. Primary isolation and culture of mycobacterial isolates were performed as described elsewhere (14). All isolates were identified as members of the *Mycobacterium tuberculosis* complex by using gene probes, as instructed by the manufacturer (ACCUProbe; GenProbe, San Diego, Calif.), or the GenoType MTBC assay (Hain Lifescience GmbH, Nehren, Germany); differentiation among the species of the *M. tuberculosis* complex was performed as described previously (19). Drug susceptibility was determined by the proportion method on Löwenstein-Jensen medium and/or the modified proportion method with the BACTEC 460TB system (Becton Dickinson Microbiology Systems, Cockeysville, Md.).

IS*6110* DNA fingerprint analysis. Extraction of DNA from mycobacterial strains and DNA fingerprinting with IS*6110* as a probe were performed by standardized protocols, as described elsewhere (20). The IS*6110* fingerprint patterns of the mycobacterial strains were analyzed by using BioNumerics software (Windows NT, version 2.5; Applied Maths, Kortrijk, Belgium), as described previously (25). Clusters were defined as groups of patients infected with *M. tuberculosis* strains showing identical restriction fragment polymorphism (RFLP) patterns (the same number of IS*6110* bands at identical positions). Patients infected with isolates with less than five bands were not included in this study.

RESULTS

Study population. Up to 30 June 2002, 853 patients with pulmonary TB and 44 patients with extrapulmonary TB reported to public health offices were identified as culture positive for *M. tuberculosis* complex. Isolates cultured from 796 patients were available for RFLP fingerprinting (88.7%). Of these, 334 were foreign-born individuals from 43 different areas, including 65 patients from Africa (19.5%), 59 patients from Afghanistan (19.3%), 48 patients from Turkey (15.7%), 35 patients from countries of the Russian Federation (11.5%), and 27 patients from countries of the former Yugoslavia (8.9%).

Sociodemographic and clinical characteristics. Of the 334 foreign-born patients, 64.7% ($n = 216$) were male and 35.3% ($n = 118$) were female; the ratio of these individuals was thus about 2:1. The mean ± standard deviation (SD) age was 37.2 ± 16.1 years, with an age range from 9 months to 88 years. Twenty-nine cases were extrapulmonary. Of the 305 patients with pulmonary TB, 131 (43.0%) were sputum positive at the time of diagnosis and the other 174 (57.0%) were only culture positive. Of the 334 isolates, 299 (89.5%) were susceptible to all four drugs to which susceptibility was tested (isoniazid, rifampin, pyrazinamide, and ethambutol). Altogether, 10.5% were resistant to at least one of these drugs. Seven strains were multiresistant (these were obtained from one patient from Spain, one patient from Lithuania, one patient from Afghanistan, one patient from Russia, and three patients from Kazakhstan).

Asylum seekers and other immigrants. Among the 334 foreign-born patients included in this study, we distinguished between asylum seekers and other immigrants, with the latter group also including permanent residents. According to the German federal Asylbewerberleistungsgesetz (Asylum-Seekers Assistance Law), followed in July 2000 by the new Infektionsschutzgesetz (Infectious Diseases Law), all refugees and asylum seekers older than 15 years of age are required to undergo screening for TB on entry into the country. Because of the currently inadequate legal basis, there are no screening practices for immigrants other than asylum seekers.

TABLE 1. Asylum seekers entering Hamburg during the study period

Most frequent country of origin	No. of asylum seekers (% of total)	Incidence[a]	No. screened (% of country total)
Afghanistan	6,206 (48.6)	314.0	6,017 (97.0)
Turkey	899 (7.5)	34.9	833 (92.7)
Iran	825 (6.5)	17.9	801 (97.1)
Burkina Faso	620 (4.9)	18.3	601 (96.9)
Former Yugoslavia	547 (4.3)	28.5	514 (94.0)
Sierra Leone	522 (4.1)	71.6	499 (95.6)
Russian Federation	347 (2.7)	132.0	332 (95.7)
Guinea	223 (1.7)	65.2	216 (96.9)
Togo	194 (1.5)	27.6	188 (96.9)
Egypt	167 (1.3)	19.2	161 (96.4)
Other countries	2,201 (17.3)		2,014 (91.5)
Total	12,751 (100.0)		12,176 (95.4)

[a] Data from reference 27.

In all, 12,176 of 12,751 asylum seekers (Table 1) were screened in Hamburg from 1997 to mid-2002 (1997, 1,643; 1998, 1,862; 1999, 2,464; 2000, 3,252; 2001, 2,333; 1 January to 30 June 2002, 622). Most of these came from countries with a high incidence of TB (defined as those countries with a TB incidence of 20 or more cases per 100,000 inhabitants [10]), and more than half came from two countries with a high burden of TB, Afghanistan and the Russian Federation (27). They were given a general health examination and a chest X ray and at the same time were tested for tuberculin; 6,324 (51.9%) patients were females and 5,852 (48.1%) were males. As could be expected, of these patients, 7,549 (62.0%) gave positive results by tuberculin skin testing.

A total of 108 TB cases were identified among the asylum seekers (Table 2), and 31 (28.7%) of these cases were detected as a consequence of the screening at entry. Although only 31 (0.25%) of the 12,176 asylum seekers examined had disease without clinical symptoms at entry, this represents a prevalence of 255 per 100,000 population in this group. Thus, 9.3% (31 of 334) of all cases of TB detected among foreign-born inhabitants were diagnosed by screening.

The mean latent period of total foreign-born cases between the date of entry to Germany and the date of the first symptoms was 6.8 ± 8.3 years, with a range from 0 years (i.e., the first day of residence in Germany) to 46 years (2,392 weeks). The corresponding latent period for asylum seekers was 2.4 ± 3.8 years and, thus, was clearly shorter than the latent period of 8.9 ± 9.2 years for the other immigrants ($P < 0.001$) (Table 2). Furthermore, among the remaining 77 asylum seekers who had a negative result at screening but who later contracted TB (i.e., not counting those who were found to be positive at screening), the disease appeared with a mean latent period of 3.5 ± 4.2 years, a time significantly shorter ($P < 0.001$) than that found for the other immigrants, most of whom were guest workers or

TABLE 2. Sociodemographic and disease-related characteristics of foreign born-patients

Characteristic	Asylum seekers (n = 108)	Non-asylum seekers (n = 226)	P value
Age (yr [mean ± SD])	30.7 ± 15.4	40.2 ± 15.6	<0.001
Males (no. [%])	68 (63.0)	148 (65.5)	NS[a]
Females (no. [%])	40 (37.0)	78 (34.5)	
Latency (wk) from entry to disease (mean ± SD)	125.8 ± 197.4	460.5 ± 467.0	<0.001
Latency without cases found at entry (mean ± SD)	182.6 ± 218.9		
Clustered patients (no. [%] of patients)	40 (37.0)	46 (20.4)	0.001
Latency (wk) from entry to disease for clustered patients (mean ± SD)	219.1 ± 280.8	556.1 ± 449.9	<0.001
Patient delay (wk)[b]	6.5 ± 5.2	4.9 ± 3.1	0.009
Contacts (no. [mean ± SD])	8.0 ± 10.8	6.0 ± 7.9	NS
Prospectively known contacts with disease (no. of contacts with disease/total no.)	6/868	8/1,359	NS
No. (%) of patients with:			
AIDS	4 (3.7)	14 (6.2)	NS
Resistance to any drug	14 (13.0)	21 (9.3)	NS
Drug abuse	14 (13.0)	9 (4.0)	0.002
Ethanol dependence	7 (2.1)	42 (12.6)	0.003
Pulmonary TB	97 (89.8)	208 (92.0)	NS
Sputum smear positive	38 (35.2)	93 (41.1)	NS
Previous history of TB	15 (13.9)	33 (9.9)	NS
Background of diagnosis			
Screening at entry (no. [%] of patients)	31 (28.7)		
Symptomatic disease[c]	71/77 (92.2)	203 (89.8)	NS
Contact tracing[c]	3/77 (3.9)	4 (1.8)	NS
Others[c]	3/77 (3.9)	19 (8.4)	NS
Predisposition (no. [%] of patients)	5 (4.6)	22 (9.7)	NS

[a] NS, not significant.
[b] Latent period between the retrospectively determined onset of symptoms and the establishment of diagnostic procedures.
[c] Values represent number of patients with the indicated background/total number of patients (percent) for asylum seekers and number (percent) of patients for non-asylum seekers.

family members of those workers. While there was no clear difference between the latent periods of males and females among the asylum seekers (2.4 ± 3.9 and 2.5 ± 3.6 years, respectively), among the other immigrants the females had a conspicuously shorter latent period (6.0 ± 6.0 years) than their male counterparts (10.3 ± 9.9 years) ($P = 0.002$).

Up to the end of their second year of residence in Germany (Table 3), more than one-third (35.6%) of all cases of TB among foreigners had been diagnosed; for the subgroup of asylum seekers this value was more than one-half (50.7%). The annual incidence of TB was much smaller in the subsequent 3 years. For 41.9% of all foreign-born persons with TB, the individual concerned had been living in Germany for more than 5 years.

The distribution of the sexes among the asylum seekers who became infected did not differ from those for the other immigrants; however, the mean age of the asylum seekers who became infected, 30.7 years, was some 10 years lower ($P < 0.001$). The incidence rate of TB among asylum seekers who became ill after entering Germany was 77 per 12,145 (634 per 100,000) and was significantly higher ($P < 0.01$) among men [48/(5,852 − 24) = 48/5,828 = 0.82%] than among women [29/(6,324 − 7) = 0.46%].

The diagnosis of TB was based on symptoms for 82.0% (n = 274) of all cases diagnosed among foreign-born individuals. Although asylum seekers and other immigrants were represented with similar frequencies (71 of 77 [92.2%] and 203 of 226 [89.8%], respectively; $P = 0.36$), the asylum seekers showed a greater tendency to delay seeking medical help: the latent periods between a retrospectively established first manifestation and the establishment of diagnosis differed, being on average 6.5 ± 5.2 weeks for asylum seekers and 4.9 ± 3.1 weeks for other immigrants, a difference that was statistically significant ($P = 0.009$). This is attributed to the differences in the time delays in seeking medical help by the patients.

For 22 patients (6.6%), TB was first diagnosed in a different medical context (alcohol detoxification, $n = 8$; psychotic episodes, $n = 4$; bronchial carcinoma, $n = 3$; issue of a health certificate for employment in catering, $n = 3$; loss of control over diabetes mellitus, $n = 2$; first signs of AIDS, $n = 2$), and 7 (2.1%) cases were detected in a contact-tracing program (see below).

Of the asylum seekers, 37.0% (40 of 108) were members of a cluster (see below). This number is significantly higher than the corresponding number (46 of 226; 20.4%) of other immigrants ($P < 0.01$).

TABLE 3. Latent period between entry to the country and onset of disease for all foreigners and asylum seekers healthy at entry

Time (yr) in Germany	All foreigners			Asylum seekers[a]		
	No.	%	Cumulative %	No.	%	Cumulative %
<1	77	23.0	23.0	20	26.0	26.0
1–2	42	12.6	35.6	19	24.7	50.7
2–3	41	12.3	47.9	12	15.5	66.2
3–4	17	5.1	53.0	7	9.1	75.3
4–5	17	5.1	58.1	3	3.9	79.2
≥5	140	41.9	100.0	16	20.8	100.0
Total	334	100.0		77	100.0	

[a] With negative screening result at time of entry into Germany.

TABLE 4. Univariate analysis of characteristics of foreign born-patients associated with IS*6110* RFLP clusters[a]

Characteristic	No. of all patients (n = 334)	% of all patients	No. (%) of patients		P value
			Clustered group (n = 86)	Nonclustered group (n = 248)	
AIDS	17	5.1	8 (9.3)	9 (3.6)	0.04
Resistance to any drug	35	10.5	4 (4.7)	31 (12.5)	0.04
Multidrug resistance	7	2.1	4	3	NS[b]
Males	216	64.7	60 (69.8)	156 (62.9)	NS
Females	118	35.3	26 (30.2)	92 (37.1)	NS
Drug abusers	23	6.9	15 (17.4)	8 (3.2)	<0.001
Alcohol abusers	49	14.7	22 (25.6)	27 (10.9)	0.001
Unemployed	118	35.3	47 (54.7)	71 (28.6)	<0.001
Homeless	31	9.3	10 (11.6)	21 (8.5)	NS
Sputum smear positive	131	39.2	42 (48.8)	89 (35.9)	0.034
Chest film findings:					
Cavitary disease	92	27.5	24 (27.9)	68 (27.4)	NS
Other	213	63.8	54 (62.8)	159 (64.1)	NS
Extrapulmonary	29	8.7	8 (9.3)	21 (8.5)	NS
History of TB	48	14.4	13 (15.1)	35 (14.1)	NS
Previous contact tracing	32	9.6	16 (18.6)	16 (6.5)	0.001
Asylum seeker	108	32.3	40 (46.5)	68 (27.4)	0.001
Crowded living conditions	55	16.5	10 (11.6)	45 (18.1)	NS
Disease conveying risk of TB present	27	8.1	2 (2.3)	25 (10.1)	0.023
TB symptoms observed	283	84.7	75 (87.2)	208 (83.9)	NS

[a] The mean ± SD age for all patients was 37.2 ± 16.1 years (median, 35 years; range, 0.75 to 88 years). The mean ± SD age for clustered patients was 32.2 ± 13.1 years (median, 29.5 years; range, 3 to 67 years). The mean ± SD age for nonclustered patients was 38.9 ± 16.7 years (median, 36 years; range, 0.75 to 88 years). (P = 0.002).

[b] NS, not significant.

Clustering and recent transmission. IS*6110*-based RFLP typing of all TB cases revealed 68 clusters that together accounted for 246 patients. Among these, 86 foreign-born persons were represented in 40 clusters; of these individuals, 78 had at least culturally established pulmonary TB, 3 had pleuritis, 2 had osteoarticular TB, 2 had superficial lymph node TB, and 1 had TB of the esophagus.

By univariate analysis, it was found that the foreign-born cluster members (Table 4) were significantly younger than the nonmembers (P = 0.02), more frequently had AIDS (P = 0.04), were more frequently sputum positive (P = 0.34), and were less likely to have another disease that predisposed them to contract TB and harbored isolates that were less frequently resistant to antitubercular drugs (P = 0.04).

In the logistical regression, the most frequent independent variables (Table 5) found to represent the highest predictive risk for membership of the foreign-born patients in a cluster were previous history as a contact person (i.e., earlier participation in a contact investigation of an infected index person); this led to a fourfold increase in risk. It was followed by membership in the illicit drug scene (risk factor, 3.7) and alcohol dependence (risk factor, 2.8). The risk accompanying being an asylum seeker was 2.5 times greater, and that accompanying a state of unemployment was more than twice as high (risk factor, 2.3).

Of the 40 clusters that included foreign-born individuals, 20 consisted only of foreign-born individuals and the other 20 also contained German-born patients. The smallest cluster size was two patients (21 of 40 clusters, 52.5%), and the largest contained seven patients.

A detailed analysis of the epidemiological data on the probability of transmission within each cluster involving foreign-born patients (Table 6) showed that in 14 of the 20 clusters with only foreign-born individuals, a total of 30 patients had a coincidentally close timing of reactivation (of these, 12 clusters contained a total of 26 individuals with reactivation only) and 7 clusters contained members who all came from the same country. In 12 of the 20 clusters containing individuals of different origins, including a total of 17 foreign-born patients, no epidemiological connection could be found.

Within each of 11 clusters, at least one direct person-to-person infection from a foreign-born individual to a German-born individual could be established, i.e., 11 source patients with a total of 18 infected persons. A total of five foreign-born patients in three clusters (clusters 14, 33, and 51) were infected by German-born patients.

Conversely, for three clusters with individuals of different origins (clusters 26, 29, and 43), each cluster contained one foreign-born individual who had been infected by a German-born patient; and in another two clusters with individuals of different origins (clusters 4 and 5), seven and three German-born patients, respectively, had been infected by a foreign-born patient.

TABLE 5. Risk factors for recent transmission of *M. tuberculosis* in foreign-born individuals[a]

Risk factor	Odds ratio	95% CI	P
History of contact tracing	3.98	1.78–8.89	<0.001
Intravenous drug abuse	3.70	1.38–9.93	<0.01
Alcohol dependence (DSM-IV)	2.82	1.38–5.78	<0.005
Asylum	2.56	1.44–4.57	<0.002
Unemployment	2.31	1.32–4.04	<0.004

[a] Independent risk factors for recent transmission were calculated by multiple regression procedures for patients with clustered isolates. CI, confidence interval; DSM IV, Diagnostic and Statistical Manual of Disorders IV.

TABLE 6. Characteristics of foreign-born patients in clusters

Cluster	Patient no.	Sex	Country of origin	Age (yr)	Previously known to have TB	Total no. of patients in cluster	Epidemiological link(s)[a]
1	1	Male	Albania	52	No	4	Patient 2, family contact of patient 1 (source patient); patients 3 and 4, none established
	2	Female	Albania	21	No		
	3	Male	Portugal	46	No		
	4	Female	Ghana	38	No		
2	5	Male	Poland	48	No	38	Patient 5, none established; patient 7, intimate contact of patient 6 (source patient);
	6	Male	Poland	41	No		
	7	Female	Poland	37	No		
3	8	Male	Liberia	19	Yes	7	Patients 8 to 12, leisure partners of patient 8 (source patient); patients 13 and 14, none established
	9	Male	Burkina Faso	28	No		
	10	Male	Morocco	35	No		
	12	Male	Ghana	30	No		
	11	Male	Liberia	29	No		
	13	Male	Gambia	32	No		
	14	Male	Gambia	33	No		
4	15	Male	Portugal	33	No	8	Patient 15, caravan contact (source patient) of seven German-born individuals; patient 16, caravan contact (source patient) of three German-born individuals
5	16	Male	Switzerland	27	No	4	
7	17	Male	Macedonia	26	No	11	Patients 21 and 22, family contact of patient 19 (source patient); patients 17, 18, 20, and 23, none established
	18	Male	Macedonia	21	No		
	19	Female	Macedonia	20	No		
	20	Male	Turkey	45	No		
	21	Female	Macedonia	51	Yes		
	22	Male	Macedonia	18	No		
	23	Male	Macedonia	67	Yes		
8	24	Female	Romania	31	No	9	None established
	25	Male	Yugoslavia	62	No		
12	26	Female	Macedonia	23	No	4	Patients 27 to 29, family contacts of patient 26 (source patient)
	27	Male	Macedonia	3	No		
	28	Male	Macedonia	28	No		
	29	Female	Macedonia	26	No		
14	30	Male	Turkey	28	No	9	Patients 31 and 32, bar contacts of German-born individual (source patient)
	31	Male	Poland	44	No		
	32	Male	Yugoslavia	37	No		
15	33	Male	Kazakhstan	20	No	2	Patient 34, school contact of patient 33 (source patient)
	34	Female	Pakistan	14	No		
17	35	Male	Croatia	41	No	8	None established
18	36	Male	Poland	40	No	3	None established
19	37	Male	Turkey	48		2	None established
	38	Male	Turkey	66			
21	39	Male	Turkey	28	No	4	None established
23	40	Male	Turkey	23	No	2	None established
	41	Female	Turkey	39	No		
25	42	Male	Ghana	42	No	12	None established
26	43	Male	Morocco	36	No	2	Patient 43, drug contact (source patient) of German-born individual
27	44	Male	India	25	No	2	None established
	45	Male	Turkey	40	No		
29	46	Female	Ghana	34	No	2	Patient 46, intimate contact (source patient) of German-born client
33	47	Male	Malaysia	43	No	4	Patient 47, working contact of German-born colleagues
34	48	Male	Afghanistan	4	No	3	None established
	49	Female	Afghanistan	18	No		
	50	Female	Afghanistan	24	No		
35	51	Male	Afghanistan	40	No	3	None established
	52	Female	Afghanistan	59	No		
	53	Female	Afghanistan	12	No		

Continued on following page

TABLE 6—*Continued*

Cluster	Patient no.	Sex	Country of origin	Age (yr)	Previously known to have TB	Total no. of patients in cluster	Epidemiological link(s)[a]
37	54	Male	Morocco	31	No	2	Patient 55, student contact of patient 54 (source patient)
	55	Male	Morocco	26	No		
43	56	Male	Burkina Faso	18	No	5	Patient 57, hospital contact (source patient) of German-born male nurse
	57	Male	Nigeria	41	No		
	58	Male	Burkina Faso	18	No		Patients 56 and 58, none established
44	59	Male	Albania	51	No	2	None established
46	60	Male	Macedonia	23	No	2	None established
	61	Female	Macedonia	21	No		
48	62	Male	Ghana	23	Yes	2	None established
49	63	Male	Poland	44	No	2	Patient 64, family contact of patient 63 (source patient)
	64	Female	Poland	16	No		
51	65	Male	Poland	31	No	3	Patient 65, bar contact of two German-born individuals
52	66	Female	Afghanistan	24	No	2	Patient 67, household contact of patient 66 (source patient)
	67	Female	Afghanistan	24	No		
54	68	Male	Liberia	19	No	2	None established
	69	Male	Ghana	21	No		
55	70	Female	Yugoslavia	25	No	2	None established
	71	Female	Hong Kong	29	No		
56	72	Male	Afghanistan	29	No	2	None established
	73	Male	Lithuania	38	No		
59	74	Female	Poland	57	No	4	Patient 75, household contact of patient 74 (source patient); patient 76, bar contact of patient 75 (source patient)
	75	Male	Poland	35	No		
	76	Male	Poland	41	No		
61	77	Male	Turkey	35	No	2	None established
	78	Male	Turkey	52	No		
63	79	Female	Russia	25	No	2	None established
	80	Female	Portugal	38	No		
64	81	Female	Afghanistan	16	No	2	Patient 82, household contact of patient 81 (source patient)
	82	Female	Afghanistan	19	No		
66	83	Male	Nepal	24	No	2	Patient 83, patient contact (source patient) of German-born ear-nose-throat doctor
67	84	Female	Argentina	49	Yes	2	None established
68	85	Male	Kazakhstan	26	No	2	None established
	86	Male	Kazakhstan	22	Yes		

[a] All individuals mentioned in the epidemiological link column are patients with TB.

In summary, 39 of 86 foreign-born cluster members (45.3%), comprising 16 source patients and 23 directly infected patients, were involved in epidemiologically confirmed, fresh infections. This involved 19 of 40 (47.5%) of the clusters in which foreigners were present.

For the 10 foreign-born patients in nine clusters with individuals of different origins for which no epidemiological relationships could be established (clusters 8, 17, 18, 21, 25, 44, 48, 66, and 67), the mean latent period from the time of entry into Germany to the time of disease onset was 567 weeks, so that both an infection in Hamburg before the commencement of the study and a reactivation, followed by infection of German residents, is conceivable. Cluster 2, which comprised 38 members, of whom only 3 were non-Germans (Poles), included individuals involved in a long-term TB outbreak among the regular customers at a little bar close to the red-light district in Hamburg. That outbreak was due to a single strain that had been circulating on the scene for many years without a distinct source patient. Although within the period of the study only one fresh infection could be established among the foreign-born patients, it seems certain that the infection of the index patient and that of the other Pole took place in Hamburg and not in the country of origin.

Conventional contact tracing. During this study, a total of 2,227 contacts of foreign-born patients, of whom 1,601 (71.9%) were also foreign born, were subjected to contact investigations according to the guidelines of the Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose (German Central Committee for Combating Tuberculosis) by the ripple-in-the-pond principle; i.e., contact tracing is usually performed by screening close contacts first and moving in concentric circles from the infectious index patient. In the hope of improving the efficiency of the survey, we carried out X-ray examinations not only 3 and 9 months after contact with the presumed index

person, as required by the guidelines, but also 6 months after contact.

On average, each foreign-born patient had 6.7 ± 9.0 contact individuals (median, 4; range, 0 to 65). The number of contact persons investigated did not differ significantly between the asylum seekers (total, 868; mean ± SD, 8.0 ± 10.8) and the other immigrants (total, 1,359; mean ± SD, 6.0 ± 8.9) ($P = 0.13$). Of the known contact individuals, 14 foreign-born individuals (0.6%) subsequently contracted TB that was confirmed at least by culture; the frequencies among asylum seekers and others were comparable ($P > 0.05$). However, among these, only nine cases could be shown by RFLP analysis to have been due to direct infection through the cluster, so that in the other five cases the disease must be regarded as coincidental and due to infection by earlier exposure to a carrier other than the index person suspected in this study. In addition, only 7 of the 14 confirmed contacts were established within the period of contact tracing in this study (9 months): these included 3 of 77 (3.9%) asylum seekers (detected after periods of residence in Germany of 11, 26, and 27 months, respectively) and 4 of 226 (1.8%) other immigrants. The remaining seven patients became ill outside this period and sought medical help.

In relation to the 23 fresh infections within the study period established retrospectively by cluster analysis, the predictive value obtained for the detection of genuinely infected persons by traditional contact tracing was only 39.1%.

DISCUSSION

There is evidence to suggest that the risk of progression to disease from latent infection is greatest in immigrants in the first 3 to 5 years after arrival in their adoptive country (5, 17, 23). However, it is well known that immigrants from countries where TB is common have a heightened risk of developing a clinical manifestation of TB compared with the risk of the native population in a country with a low incidence of TB, and this risk persists at least for some decades following entry (6, 28). In our study 58.1% of all immigrants developed disease within 5 years; of these, the asylum seekers with negative screening results at entry became ill significantly earlier after entry than other immigrants, but still after a mean period of residence in Germany of only 3.5 years.

Nearly one-third (108 of 334 [32.3%]) of the cases of infection in our study could be attributed to disease imported by asylum seekers. A small number of these cases (31 of 108 [28.7%]) could be diagnosed by screening shortly after entry into the country, and the overall proportion of cases detected by screening was 31 of 12,176 (0.25%), a tiny fraction of the number examined, even though most of these had come from countries with a high risk of TB. This finding corresponds to the results of a recent prospective study of screening of asylum applicants in Germany: of 14,307 asylum seekers in Lower Franconia screened by chest X ray between 1995 and 2001, there were 45 active cases (including several cases of lung TB without bacteriological or cultural proof of *M. tuberculosis* infection); i.e., the disease was found in 0.3% of the individuals screened (16).

Among the foreign-born individuals, clustered isolates represented approximately one-third of all isolates ($n = 86$ versus 248), indicating at first glance a low risk of recently transmitted disease, as indeed could be expected on the basis of the results of earlier molecular-epidemiological studies in these settings (1, 4). However, it should not be concluded from this that a person in the cluster has entered it through recent transmission. Several studies (3, 7, 8) have shown that the TB in patients belonging to a cluster may occur by chance, through coincidental reactivation during the observation period, and therefore, a superficial comparison based on proportions may not be an appropriate measure of the magnitude of TB transmission.

The in-depth analysis of patients with clustered isolates revealed that during the study period 23 of the 334 foreign-born patients fell ill because of a recent transmission (18 transmissions from foreign-born residents and 5 from German-born residents), so that 6.9% of the TB cases among foreign-born persons were due to infection acquired in Hamburg. This indicates that TB is transmitted within immigrant communities in the host country and foreign-born individuals cannot be regarded as sole sources of infection. Recent transmission from foreigners resulted in only 13 secondary cases in German-born individuals, corresponding to a transmission rate during the study period of 2.8% (13 of 462 German-born cases [796 total cases − 334 foreign-born cases]). This result is consistent with that of an RFLP study conducted in San Francisco, California (13), in which it was found that only about 2% of secondary cases arose from foreign-born cases. Additionally, in a Danish RFLP study of Somali immigrants (15), there was no evidence that foreign-born patients with TB generally transmit TB to large numbers of natives in their adoptive countries. Nevertheless, we found a surprisingly large number of clusters with both German-born and foreign-born individuals (10 of 20 clusters) without demonstrable fresh infection chains. This can be explained as the result of an undiscovered fresh transmission chain that occurred, in one direction or the other, among cluster members before the beginning of the study. It may therefore be concluded that the limitation of the study period to 5.5 years resulted in an underestimation of the real transmission rate between foreign-born and German-born individuals.

Not only was the proportion of isolates not in clusters in our analysis very high (248 of 334 [74.3%]), but also in 12 of the clusters with exclusively foreign-born individuals, no epidemiological connection between other members could be found (despite a thorough inquiry). Both of these observations confirm the widely accepted hypothesis that disease in foreign-born patients is basically more likely to have arisen from reactivation of latent infection acquired in the country of origin (18). It is very probable that most cases of infection among such cluster patients arise from dominant TB strains with complex and widely disseminated transmission chains in their home country or neighboring regions before these patients arrived in Germany and, given the emergence of coincidental reactivations within the study period, lead to an import of clusters. These clusters, however, should not be regarded as expressions of person-to-person transmission (7, 11).

Irrespective of this, it is remarkable from the viewpoint of TB control that the cluster patients, with or without recent transmission, are exposed to risk factors similar to those determined to be predictors of clustering for both groups (Table 5). These factors include the use of substances of abuse (alco-

hol and intravenous drugs), unemployment, a history of being a refugee, and, as expected, a known history of previous infection. It is precisely the cluster members (both asylum seekers and others) who show a significantly longer latent period between the time of entry into Germany and the time of the first manifestations of disease than the non-cluster members: asylum seekers on average over 4 years and other immigrants over 10 years (with considerable scatter) (Table 2).

The goals of this study were not only to determine the risk of recently transmitted disease in immigrants but also to make a contribution to controlling the spread of TB from this population. In conclusion, public health policy in our area should focus on the prevention of symptomatic disease in infected individuals and not on the detection of manifest symptoms at the time of screening: our data presented here suggest that only a fraction (less than 10%) of the TB cases among foreign-born individuals will be detected by screening of refugees at entry, and the predictive value of prospective conventional contact tracing by public health staff is also generally unsatisfactory (just over one-third). Thus, a reduction of TB among foreign-born individuals and the dissemination of TB by recent transmission to secondary cases may be achieved only by two complementary measures. First, tuberculin skin testing not only should be performed for asylum seekers but also should be conducted as it is in other European countries. For example, in The Netherlands everyone (except for residents of the European Union and certain industrialized countries where the prevalence of TB is low) applying for a permit for residence lasting over 3 months is screened for TB, and in Great Britain all immigrants from countries where the annual TB incidence exceeds 40 cases per 100,000 are screened (9). Persons testing positive should receive a chest X ray on a voluntary basis in order to exclude current TB disease. However, offering preventive chemotherapy to all high-risk foreigners, according to the recommendations of the American Thoracic Society (2), does not seem to be appropriate in Germany, because an increasing number of immigrants originate from Eastern Europe and are more likely to be infected by isoniazid-resistant strains (21).

Second, immigrants, (irrespective of whether they come from a country with a high incidence of TB) should be informed about the symptoms of manifest disease and should be instructed to seek medical support promptly if these occur. Because the period of patient delay (i.e., the latent period between the retrospectively determined onset of symptoms and the establishment of diagnostic procedures) is remarkably long (6.5 weeks among foreigners immigrating as asylum seekers and 4.9 weeks among non-asylum seekers), further efforts by public health service agencies are urgently needed.

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