

Transmission of *Mycobacterium tuberculosis* Depending on the Age and Sex of Source Cases

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This study estimated to what extent tuberculosis transmission in the Netherlands depends on the age and sex of source cases. DNA fingerprints of *Mycobacterium tuberculosis* isolates were matched to patient information in the Netherlands Tuberculosis Register for 1993–1998. Clusters were defined as groups of patients with pulmonary tuberculosis whose isolates had identical DNA fingerprints. Source cases were assigned by using two models. The first-case model assumed that the first diagnosed case was the source case. The incidence rate model estimated source case probabilities from the incidence rates of potential source cases and the time of diagnosis. DNA fingerprints of 6,102 isolates were matched to patient information on 5,080 (83%) cases, 3,479 of whom had pulmonary disease. According to both models, the number of infectious cases generated per source case was lower for female than for male source cases and decreased with increasing age of the source case. The authors concluded that transmission of tuberculosis is associated with the age and sex of source cases as well as the age of secondary cases. Increased transmission among immigrant groups in the Netherlands is largely attributable to the relatively young age of immigrant source cases. *Am J Epidemiol* 2001;154:934–43.

age distribution; polymorphism, restriction fragment length; sex; tuberculosis, pulmonary

Tuberculosis ranks seventh as a cause of global mortality and morbidity (1, 2). Most of this burden is found in developing countries (1, 2). In low-prevalence countries (e.g., western Europe), tuberculosis is changing from an endemic disease to a disease associated with immigration and risk groups, such as the homeless and drug users (3, 4). In these countries, increasing emphasis is given to active case finding. For instance, of 1,341 tuberculosis patients in the Netherlands in 1998, 60 percent were foreign born, 41 percent of the Dutch patients reportedly belonged to specific risk groups, and 21 percent of all patients were identified through active case finding (5).

The aim of active case finding is to detect tuberculosis cases early in the course of the disease to prevent development of severe disease and to limit transmission by reducing the infectious period. To focus active case finding on the most infectious cases, it would be useful to know which types of source cases are particularly effective in generating secondary cases.

Investigation of infection prevalence among contacts has been the main tool to determine the infectiousness of tuberculosis source cases. It has been used to compare the infectiousness of smear-positive and smear-negative pulmonary tuberculosis (6, 7), of source cases in various age groups (8), of source cases with and without human immunodeficiency virus infection (9–11), and of tuberculosis sensitive and resistant to isoniazid (12).

Recently, DNA fingerprinting has been used in population-based studies to determine the average number of infectious tuberculosis cases generated by a source case (13–15). These studies applied different methods for identifying source cases, and only a few risk factors were examined, particularly nationality (13), having a positive sputum smear (14), and ethnicity (15). However, one limitation of these models was that they did not include a multivariate analysis of risk factors such as age and sex for being an “effective” source case.

In the present study, we aimed to determine to what extent transmission of *Mycobacterium tuberculosis* from tuberculosis source cases is associated with the age and sex of the source case. We used DNA-fingerprinting results in a population-based study in the Netherlands during the period 1993–1998.

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Abbreviations: IS, insertion sequence; P^s , probability that a clustered case was the original source case of the cluster; P^t , probability that a potential source case will give rise to a cluster; RFLP, restriction fragment length polymorphism.

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MATERIALS AND METHODS

Study population

From January 1993 to December 1998, 9,463 tuberculosis cases were diagnosed in the Netherlands, 6,102 (64 percent) of whom were culture positive for *M. tuberculosis* and were subjected to restriction fragment length polymorphism (RFLP) typing (16). Demographic and clinical data were obtained from the Netherlands Tuberculosis Register, held by the Royal Netherlands Tuberculosis Association (KNCV), which receives data from municipal health services. To maintain patient confidentiality, the Netherlands Tuberculosis Register does not contain patient names and addresses. Therefore, we matched RFLP data with those in the register on the basis of postal area code, date of birth, and sex. This procedure resulted in 5,080 matching patients (83 percent). Of these, 4,465 (88 percent) matched perfectly while the other 12 percent showed at most one of the following differences: sex (6 percent) (for the vast majority, the laboratory file was missing information on sex), a one-digit difference in either day or month of birth (2 percent), or a one-digit difference in the postal area code (4 percent). No bias among nonmatched patients was found regarding sex, age, or proportion of isolates clustered.

Of the 5,080 patients whose patient information and RFLP results matched, 3,046 had pulmonary tuberculosis only, 1,550 had extrapulmonary tuberculosis only, and 484 had both. Because the main aim of the analysis was to determine the average number of infectious tuberculosis cases generated by a source case with infectious tuberculosis, and because patients with extrapulmonary tuberculosis only are very unlikely to transmit *M. tuberculosis*, these 1,550 patients were excluded. In addition, 51 patients with pulmonary tuberculosis and of unknown nationality were excluded, leaving 3,479 for analysis. Population data for calculation of incidence rates were obtained from the Netherlands Central Bureau of Statistics.

DNA fingerprinting

All *M. tuberculosis* cultures were subjected to standardized insertion sequence (IS)6110-based RFLP typing (16). Because differentiation of *M. tuberculosis* strains carrying few IS6110 copies is limited, all 423 strains (8 percent) harboring fewer than five IS6110 copies were subjected to subtyping, in which the polymorphic guanine-and-cytosine-rich sequence was used as a probe (17, 18). For computer-assisted analysis of IS6110 RFLP patterns, we used Gelcompar software (version 4.1 for Windows; Applied Maths, Kortrijk, Belgium) (19).

Clusters were defined as groups of two or more patients having isolates with identical RFLP patterns, that is, the same number of IS6110 copies at identical band positions. For isolates with fewer than five IS6110 bands, an additional requirement for clustering was having the same number of restriction fragments containing the polymorphic guanine-and-cytosine-rich sequence at identical band positions. The full 6-year period was used to define clustering.

Data analysis

Data analysis was based on the following reasoning. Potential source cases with a new DNA fingerprint arise in the population from endogenous reactivation or through immigration. Some of these source cases remain nonclustered, while others give rise to secondary cases through transmission of the disease. Because the rate of change of the DNA fingerprint is low (with a half-life of about 2–5 years during active disease (20, 21)), most of these secondary cases will have the same DNA fingerprint and, if occurring within the study period, will belong to the same cluster as the source case. An earlier study suggested that identical DNA fingerprints in the Netherlands are not likely to occur by chance (22). In the present analysis, we assumed that the original source case of the cluster was present in the data set and that all clustered cases with an identical DNA fingerprint were linked through transmission. The following procedures were used to identify the source cases of clusters.

First-case model. Because, according to the above assumptions, a cluster is generated by its first case, we assumed that the case with the earliest isolation date was its source case (14). In the present analysis, we referred to this assumption as the first-case model.

Incidence rate model. Because the delay from onset of symptoms to diagnosis and treatment varies between patients, the time sequence of isolation dates may differ somewhat from that of onset of symptoms. Because patients for whom there is a long delay in diagnosis are more likely to generate secondary cases but less likely to be identified as source cases if the first-case model is used (15), we supplemented this approach with the incidence rate model. With this model, the probability that a clustered case was the original source case of the cluster (P') is assumed to be proportional to the incidence rate of potential source cases in the patient's subgroup multiplied by the probability that a potential source case would give rise to a cluster (P') (figure 1) (13). Initially, P' is assumed to be the same for all subgroups, and the relative incidence rate of potential source cases is estimated from the incidence rate of nonclustered tuberculosis (figure 1). In further calculations, adjustment is made for different probabilities of potential source cases in different subgroups giving rise to a cluster; the correction factor $P'/(1 - P')$ is used (figure 1) (13). Previously, P' was estimated as

$$P_i = 1 - \exp(-R_e) \quad (1)$$

assuming that the number of secondary cases has a Poisson distribution, with a mean of R_e (13). R_e was calculated as follows:

$$R_e = TI/(TI + 1) \quad (2)$$

where R_e is the effective reproduction number and TI the transmission index. TI is calculated as

$$TI = (\text{number cases generated}) / (\text{sum } P^S + \text{number nonclustered}) \quad (3)$$

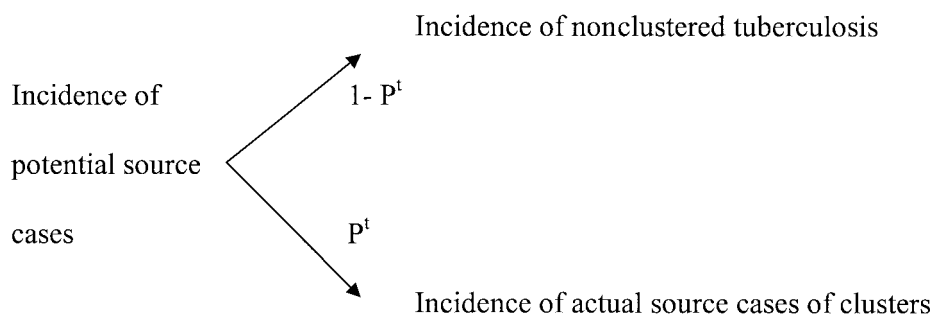


FIGURE 1. Diagram of the relation between the incidence of potential source cases and the incidence of nonclustered tuberculosis, the Netherlands, 1993–1998. P^t , probability that a potential source case will give rise to a cluster.

where

$$\begin{aligned} \text{Number of cases generated by case } i & \quad (4) \\ &= P_i^s (\text{cluster size} - 1). \end{aligned}$$

However, in the current analysis, $P^t/(1 - P^t)$ was estimated directly from the data, as follows:

$$P^t/(1 - P^t) = (\text{sum } P^s)/(\text{sum nonclustered}). \quad (5)$$

In some small subgroups without nonclustered cases, P^t was estimated as described previously by using expressions 1–4.

Adjustments, in which updates of P^s and P^t were used, were made until convergence was reached, generally within five cycles.

In this probability model, time of diagnosis was taken into account as follows. The probability of cases being the source was assumed to decrease exponentially by 0.77 percent per day, that is, by 50 percent for each 3 months since the first case occurred in the cluster (15).

Number of secondary cases generated per source case. After we determined the probability of each clustered case (P^s) being the source case of the cluster by using either the first-case model (which sets P^s at 1 for the first case and 0 for all others) or the incidence rate model, we calculated the number of cases generated by that source case as

TABLE 1. Incidence rates of culture-confirmed pulmonary tuberculosis (total and nonclustered) in the Netherlands, 1993–1998

	Total			Clustered (%)	Nonclustered		Rate ratio		
	Cases (no.)	Person-years* (x 1,000)	Incidence rate†		Cases (no.)	Incidence rate	Crude	Adjusted‡	95% confidence interval
Sex									
Male	2,264	45,916	4.9	47	1,193	2.6	1	1	
Female	1,215	46,965	2.6	40	726	1.5	0.59	0.62	0.57, 0.68
Age (years)									
<25	789	29,158	2.7	53	367	1.3	1	1	
25–34	925	15,592	5.9	50	463	3.0	2.4	1.94	1.69, 2.2
35–44	555	14,381	3.9	52	269	1.9	1.49	1.90	1.62, 2.2
45–54	299	12,589	2.4	49	151	1.2	0.95	1.74	1.43, 2.1
55–64	242	8,808	2.7	42	140	1.6	1.26	2.7	2.2, 3.3
≥65	669	12,352	5.4	21	529	4.3	3.4	10	9.0, 12
Nationality									
The Netherlands	1,657	88,628	1.9	48	861	1.0	1	1	
Central + eastern Europe	145	368	39.4	26	108	29.4	30	40	33, 50
Turkey	206	903	22.8	49	105	11.6	12	22	17, 27
Morocco	330	878	37.6	56	145	16.5	17	30	25, 36
Somalia	332	85	390.1	51	164	192.7	198	390	330, 470
Other Africa	266	167	159.0	41	156	93.2	96	150	120, 180
Asia	347	403	86.2	20	279	69.3	71	110	96, 130
Other	196	1,449	13.5	48	101	7.0	7.2	9.2	7.5, 11

* Calculated as the sum of the midyear populations of each year in the period 1993–1998.

† Per 100,000 population per year.

‡ Adjusted for age, sex, and nationality.

$P^s \times (\text{cluster size} - 1)$ (expression 4). Risk factors for generating secondary cases were determined by Poisson regression using the number of cases generated per tuberculosis patient as the outcome measure of interest. Confidence intervals were calculated by using the bootstrap method (23).

Because a positive sputum smear is a known risk factor for transmission of *M. tuberculosis* (6, 7, 14), we explored to what extent the observed differences by age and sex might be explained by different proportions of patients being sputum smear positive. Sputum smear results had been recorded in the Netherlands Tuberculosis Register only

TABLE 2. Transmission index for tuberculosis in the Netherlands, 1993–1998*

	Nonclustered cases (no.)	Source cases (no.)	Secondary cases generated (no.)	Transmission index			
				Crude	Relative crude	Relative adjusted†	95% confidence interval
First-case model							
Sex							
Male	1,193	264	833	0.57	1	1	
Female	726	126	337	0.40	0.69	0.74	0.49, 0.99
Age (years)							
<25	367	110	365	0.77	1	1	
25-34	463	118	385	0.66	0.87	0.84	0.41, 1.28
35-44	269	60	178	0.54	0.71	0.75	0.40, 1.10
45-54	151	29	72	0.40	0.52	0.38	0.00, 0.75
55-64	140	26	91	0.55	0.72	0.40	0.24, 0.56
≥65	529	47	79	0.14	0.18	0.24	0.14, 0.33
Nationality							
The Netherlands	861	179	572	0.55	1	1	
Central + eastern Europe	108	14	41	0.34	0.61	0.71	0.00, 1.25
Turkey	105	34	104	0.75	1.36	0.40	0.00, 0.99
Morocco	145	51	159	0.81	1.47	1.01	0.56, 1.46
Somalia	164	41	116	0.57	1.03	0.38	0.18, 0.58
Other Africa	156	29	98	0.53	0.96	0.69	0.35, 1.02
Asia	279	22	42	0.14	0.25	0.28	0.14, 0.42
Other	101	20	38	0.31	0.57	0.49	0.24, 0.73
Incidence rate model							
Sex							
Male	1,193	293.7	969.2	0.65	1	1	
Female	726	96.3	200.8	0.24	0.37	0.42	0.32, 0.51
Age (years)							
<25	367	104.5	354.1	0.75	1	1	
25-34	463	127.1	405.3	0.69	0.91	0.93	0.45, 1.41
35-44	269	61.0	188.1	0.57	0.76	0.76	0.33, 1.18
45-54	151	30.8	101.7	0.56	0.74	0.76	0.00, 1.53
55-64	140	21.5	47.1	0.29	0.39	0.42	0.21, 0.63
≥65	529	45.1	73.6	0.13	0.17	0.30	0.14, 0.46
Nationality							
The Netherlands	861	142.8	383.3	0.38	1	1	
Central + eastern Europe	108	16.5	48.9	0.39	1.03	1.00	0.11, 1.89
Turkey	105	39.1	106.1	0.74	1.93	1.42	0.51, 2.33
Morocco	145	59.5	228.3	1.12	2.92	2.11	0.73, 3.50
Somalia	164	45.3	134.9	0.64	1.69	1.12	0.81, 1.43
Other Africa	156	40.7	160.8	0.82	2.14	1.67	0.51, 2.83
Asia	279	27.1	51.8	0.17	0.44	0.49	0.23, 0.75
Other	101	19.1	55.8	0.46	1.22	0.92	0.12, 1.73

* The first case of a cluster was assumed to be the source case (first-case model), and source case probabilities accounting for time of diagnosis (incidence rate model) were used.

† Adjusted for age, sex, and nationality.

since 1996 and therefore could not be used for the complete study period.

RESULTS

From 1993 to 1998, 1,560 (45 percent) of the 3,479 cases with pulmonary tuberculosis were in 390 different clusters. Of all patients, 65 percent were male, and their mean age was 42 years. Dutch patients, 47 percent of the total, were on average much older (mean age 52 (standard deviation, 22) years) than non-Dutch patients (mean age 32 (standard deviation, 13) years) (t test $p < 0.001$).

The proportion of clustered patients was lower among females than males, lower for those aged at least 65 years than for younger patients, and lower for patients from central and eastern Europe and Asia than of other nationalities (table 1). Male sex, older age, and non-Dutch nationality were strongly associated with an increased incidence rate of nonclustered tuberculosis (table 1).

According to both the first-case model and the incidence rate model, female source cases generated fewer secondary cases than male source cases did (table 2). The number of cases generated per source case decreased with increasing

age. Figure 2 shows that although the pattern varied somewhat on the basis of nationality and model used, the transmission index tended to decline with increasing age among both Dutch and non-Dutch persons, according to both models.

Relatively few secondary cases were generated by source cases from Asia. When the first-case model was used, the transmission index was highest in Moroccan sources, although, after adjustment for age, the transmission index was similar for Dutch and Moroccan groups (table 2). All other non-Dutch groups had a lower transmission index. When we used the incidence rate model, we found that Moroccan source cases generated relatively many secondary cases, also after adjustment for age, although the difference with the Dutch was not significant (table 2).

Among both males and females, tuberculosis cases due to recent transmission were mainly attributed to a male source case (table 3). Of the Dutch tuberculosis cases, 12 and 20 percent were attributed to source cases of non-Dutch nationality by using the first-case model and the incidence rate model, respectively (table 3). The association between age of the source case and the ages of its secondary cases is presented in more detail in figure 3. According to both the first-

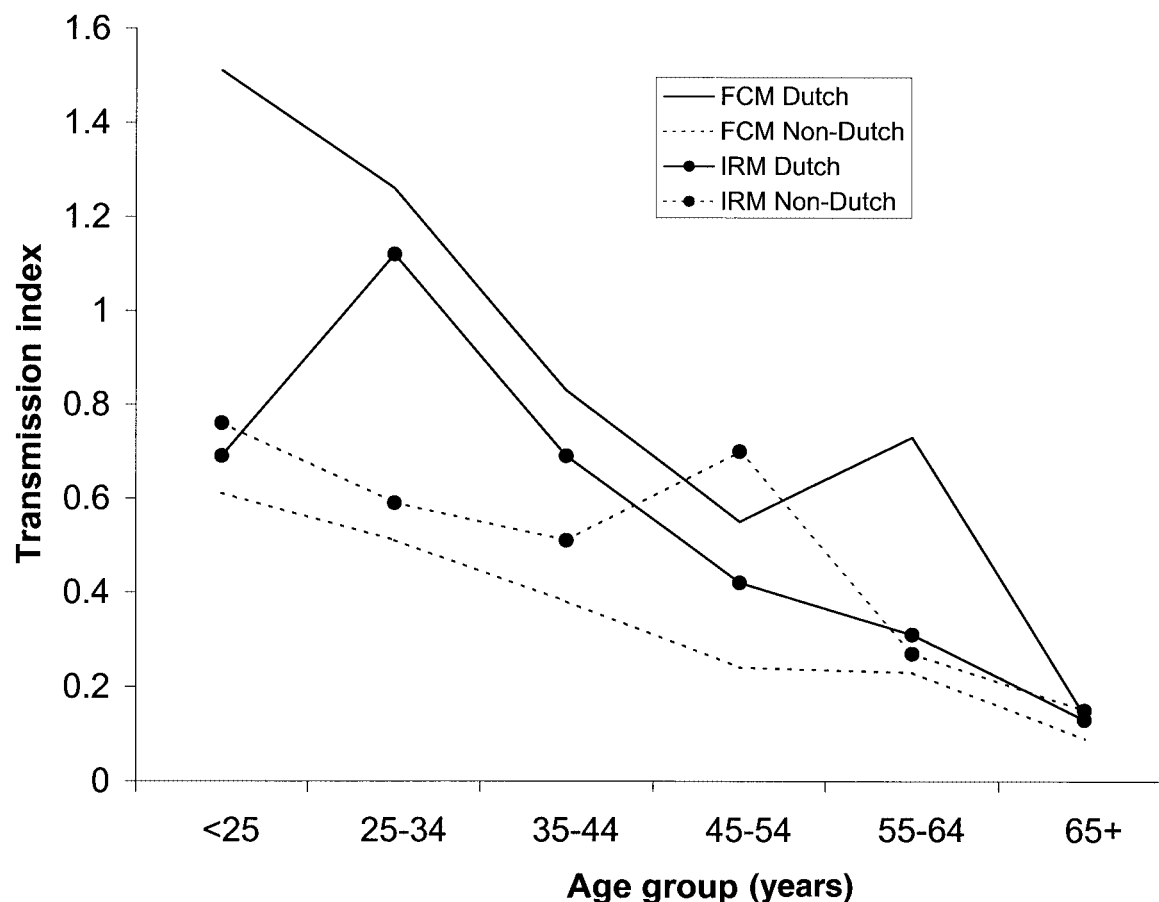


FIGURE 2. Transmission index of tuberculosis by age group (years) in Dutch and non-Dutch patients according to the first-case model (FCM) and the incidence rate model (IRM), the Netherlands, 1993–1998.

TABLE 3. Transmission of tuberculosis between subgroups in the Netherlands, 1993–1998, according to the first-case model and the incidence rate model

	Nonclustered cases (no.)	%	Source cases (no.)	%	Recent transmission from			
					Same group		Other group	
					No.	%	No.	%
First-case model								
Sex								
Male	1,193	53	264	12	585	26	222	10
Female	726	60	126	10	115	9	248	20
Age (years)								
<25	367	47	110	14	143	18	169	21
25-34	463	50	118	13	128	14	216	23
35-44	269	48	60	11	58	10	168	30
45-54	151	51	29	10	5	2	114	38
55-64	140	58	26	11	8	3	68	28
≥65	529	79	47	7	34	5	59	9
Nationality								
The Netherlands	861	52	179	11	422	25	195	12
Central + eastern Europe	108	74	14	10	0	0	23	16
Turkey	105	51	34	17	0	0	67	33
Morocco	145	44	51	15	0	0	134	41
Somalia	164	49	41	12	99	30	28	8
Other Africa	156	59	29	11	34	13	47	18
Asia	279	80	22	6	14	4	32	9
Other	101	52	20	10	11	6	64	33
Incidence rate model								
Sex								
Male	1,193	53	293.7	13	659.9	29	117.4	5
Female	726	60	96.3	8	83.4	7	309.3	25
Age (years)								
<25	367	47	104.5	13	141.6	18	175.8	22
25-34	463	50	127.1	14	129.0	14	205.9	22
35-44	269	48	61.0	11	56.5	10	168.5	30
45-54	151	51	30.8	10	6.0	2	111.2	37
55-64	140	58	21.5	9	3.5	1	77.0	32
≥65	529	79	45.1	7	30.0	4	64.9	10
Nationality								
The Netherlands	861	52	142.8	9	319.6	19	333.5	20
Central + eastern Europe	108	74	16.5	11	12.4	9	8.1	6
Turkey	105	51	39.1	19	42.2	20	19.8	10
Morocco	145	44	59.5	18	79.7	24	45.8	14
Somalia	164	49	45.3	14	109.4	33	13.3	4
Other Africa	156	59	40.7	15	34.7	13	34.6	13
Asia	279	80	27.1	8	14.4	4	26.6	8
Other	101	52	19.1	10	12.5	6	63.4	32

case model and the incidence rate model, young people generated most of the secondary cases, particularly among young people (figure 3). Secondary cases among people aged 65 years or more were relatively often attributed to source cases aged 65 years or more (figure 3).

Sputum smear results for patients with culture-positive tuberculosis since 1996 suggest that women

were somewhat less likely than men to have a positive smear (odds ratio = 0.8, 95 percent confidence interval: 0.7, 1.0) and that some immigrant groups (particularly those from Somalia and Asia) were less likely than Dutch patients to have a positive smear (table 4). Age was not associated with a positive sputum smear (table 4).

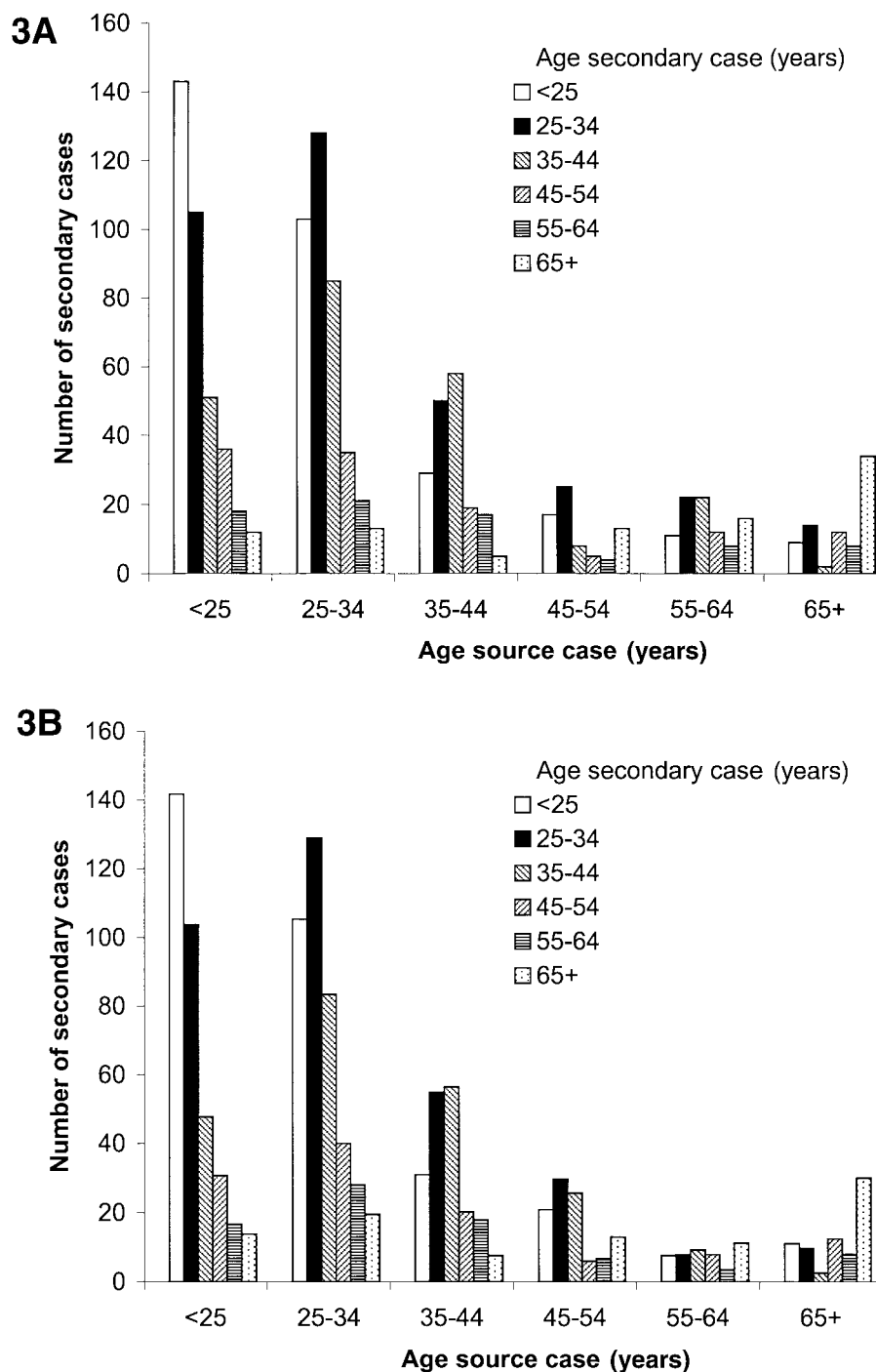


FIGURE 3. Transmission of tuberculosis between groups of source cases by age (years), according to the first-case model (3A) and incidence rate model (3B), the Netherlands, 1993–1998. Refer to the text for a description of these models.

DISCUSSION

This study suggests that the average number of secondary cases decreased with increasing age of the source case and that female source cases generated on average fewer secondary cases than male source cases did. The increased

crude transmission index for various non-Dutch compared with Dutch nationalities was largely attributable to the younger ages of source cases in these immigrant groups.

In most countries, tuberculosis is diagnosed more often in men than in women, in both routine notifications and prevalence surveys (24). In San Francisco, California, the sex dif-

TABLE 4. Sputum smear results in 1,376 tuberculosis patients in the Netherlands, 1996–1998

	Total (no.)	Smear positive (no.)	%	Odds ratio		
				Crude	Adjusted*	95% confidence interval
Sex						
Male	896	537	60	1	1	
Female	480	259	54	0.8	0.8	0.7, 1.0
Age (years)						
<25	275	151	55	1	1	
25–34	396	229	58	1.1	1.1	0.8, 1.5
35–44	258	147	57	1.1	0.9	0.7, 1.3
45–54	116	76	66	1.6	1.3	0.8, 2.1
55–64	94	58	62	1.3	1.1	0.7, 1.8
≥65	237	135	57	1.1	0.9	0.6, 1.3
Nationality						
The Netherlands	580	356	61	1	1	
Central + eastern Europe	43	23	53	0.7	0.7	0.4, 1.3
Turkey	75	47	63	1.1	1.0	0.6, 1.6
Morocco	132	73	55	0.8	0.7	0.5, 1.1
Somalia	147	66	45	0.5	0.5	0.3, 0.7
Other Africa	129	85	66	1.2	1.2	0.8, 1.8
Asia	165	85	52	0.7	0.6	0.4, 0.9
Other	84	50	60	0.9	0.9	0.5, 1.4

* Adjusted for age, sex, and nationality.

ference was larger in clustered cases (attributed to recent transmission) than in nonclustered cases (25). However, little appears known about sex differences in *generating* infections and secondary cases. In an earlier study in the Netherlands, restricted to clustered cases with epidemiologic confirmation of contact, source cases were significantly more likely than the average tuberculosis patient to be male (26). The sex difference suggested by the present study may at least in part be explained by a higher proportion of men with smear-positive disease. We found no evidence of assorted mixing by sex: similar proportions of male and female secondary cases were attributed to a male source case.

The importance of relatively young source cases for tuberculosis transmission observed in our study is supported not only by an earlier study restricted to epidemiologically confirmed contacts (26) but also by a study based on results of contact investigations (8). Index cases aged less than 40 years had more close contacts and more contacts in general than older index cases did (8). The contacts of young index cases were found in all age groups, whereas older index cases mainly reported older contacts (8). This contact pattern may explain both the declining transmission index with increasing age and the observed association between the ages of source cases and secondary cases. The latter finding is also supported by a study on clusters of two patients, which suggested that source cases in the Netherlands tend to transmit tuberculosis to persons close to their own age (27). The declining transmission index with increasing age cannot be explained by the proportion of patients with smear-positive tuberculosis decreasing with age, as such a decrease was neither observed nor expected (28).

The two models used in this study produced conflicting results on the importance of nationality. In the first-case model, all non-Dutch patient groups except the one from Morocco had a significantly lower transmission index than the Dutch. In the incidence rate model, only Asian immigrants had a significantly lower transmission index than the Dutch. For recent immigrants, a reduced transmission index might be expected, because many tuberculosis patients in these groups are detected through screening soon after arrival, which also may explain the lower proportion of patients with positive smears among immigrants from Somalia and Asia (29). Moreover, recent immigrants may have relatively few contacts among residents in the Netherlands; however, it is unclear whether a reduced transmission index should be expected among immigrants who arrived in the country some years ago. Diagnostic delay may be shorter for these groups (5), leading to reduced transmission rates. However, household size may be larger and contact investigations less complete, leading to increased transmission. Further research, for instance, that based on thorough contact investigations, is needed to clarify this issue.

Limitations of this study are the assumptions that identical DNA fingerprints suggest recent transmission and that the database is complete. Although identical fingerprints in different patients are probably due to linkage through transmission, this linkage may be indirect (through other patients), and the exact time period within which this linkage must have occurred is not clear. With a half-life of fingerprints of about 2–5 years (20, 21), this time period may vary from a few weeks (the minimum incubation period) to

years or even decades. Because our study covered the period 1993–1998, linkage through patients from before 1993 was not found in the present analysis. As a result, we may have somewhat overestimated recent transmission, particularly in the older age groups (30). Thus, this bias may also have somewhat reduced the observed decline of the transmission index with age. On the other hand, the 83 percent match of fingerprints to patients may have lowered observed clustering and therefore the estimate of recent transmission (31).

Finally, although our study conclusions probably also apply to other high-income, low-prevalence countries, they may not necessarily apply in developing countries with a high prevalence of tuberculosis. If contacts between young and old patients are more extensive than in the Netherlands, for instance, in extended families with elderly family members looking after the very young, tuberculosis transmission may be less strongly associated with age (32). RFLP studies in other settings are needed to determine whether our conclusions apply more widely.

This study has implications for active case finding through screening and contact investigations as well as the expected impact of tuberculosis control over time. When active case finding is undertaken, such as screening of immigrants, the age of the target group should be taken into account; in a contact investigation, the age of the index patient is important. For immigrant screening and contact investigations to be effective, coverage needs to be particularly high among immigrants aged less than 45 years and among contacts of index patients aged less than 45 years.

The decreasing transmission index with age suggests that, within a closed population, tuberculosis control should become easier over time (33). Over time, reduced tuberculosis transmission will lead to an increase in the average age of tuberculosis patients (33). This increase in the age of source cases may further reduce tuberculosis transmission.

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