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Association of Tuberculin Sensitivity in Dutch Adults with History of Travel to Areas of a High Incidence of Tuberculosis

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International travel may be a source of introduction of tuberculosis into low-incidence countries. We assessed whether, in The Netherlands, sensitivity to tuberculin was associated with a history of travel to countries with a high incidence of tuberculosis. Immunocompetent adults with no history of Bacille Calmette-Guérin vaccination or sensitivity to tuberculin were skin-tested simultaneously with 1–tuberculin unit (TU) purified protein derivative (PPD) of Mycobacterium tuberculosis and 1-TU sensitin of Mycobacterium scrofulaceum. Tuberculin sensitivity was defined as a reaction to PPD of ≥10 mm that was ≥3 mm larger than the reaction to M. scrofulaceum sensitin. Tuberculin sensitivity was found in 7 (0.7%) of 1014 participants (95% confidence interval [CI], 0.3%–1.4%); it was independently associated with a cumulative history of >3-months’ travel to high-incidence areas (odds ratio, 6.0; 95% CI, 1.2–31.2; \( P < .016 \)) and increased in association with total duration of travel (\( P = .02 \)). Travel to high-incidence areas increases the risk of tuberculin sensitivity and, consequently, of latent tuberculous infection. In countries with a low incidence of tuberculosis, cases of infection acquired during travel may account for a substantial proportion of new infections in the resident population.

International travel may contribute to the spread of infectious diseases across the globe [1, 2]. Tuberculosis, which is still highly endemic in large parts of the world [3], also has potential for introduction into and further spread within countries where it has become rare. Although much attention has focused on immigrants as a source of introduction of tuberculosis into Western Europe and North America [4–6], few studies have addressed the potential role of international travel [7]. Tuberculosis has been identified as a risk for persons who travel from low-incidence to high-incidence areas [8]. In a case-control study, children who were born in the United States were found to have a 4.7-fold increased risk of a positive tuberculin skin test (TST) result if they had traveled abroad during the preceding 12 months [9]. We report the results of a study of the association of travel history with tuberculin sensitivity among BCG-naïve adults who presented for pretravel testing at 5 travel immunization clinics in The Netherlands.
PATIENTS AND METHODS

The study was conducted at the Municipal Health Services of Amsterdam, Rotterdam, The Hague, and Utrecht, which have departments of both travel immunization and tuberculosis control, and at the travel clinic of the Academic Medical Center in Amsterdam. From 1 November 1994 through 31 October 1996, all persons who were born in The Netherlands since 31 December 1944, who were at least 15 years old, and who intended to travel to areas with a high incidence of tuberculosis for a period of 3–12 months were offered pretravel TST screening to serve as a baseline measurement for posttravel follow-up. After giving written informed consent, eligible persons underwent pretravel TSTs with purified protein derivative (PPD) of M. tuberculosis and a sensitin of environmental mycobacteria, and they completed self-administered questionnaires regarding their occupational and travel history, exposure to patients with known cases of tuberculosis, previous TSTs, and health status. Questionnaires were completed before the test results were assessed.

Exclusion criteria were a history of tuberculosis and/or positive TST result; positive BCG vaccination status; presence of known immunodeficiencies, insulin-dependent diabetes mellitus, or HIV infection, irrespective of CD4 lymphocyte count; current or recent receipt of immunosuppressive therapy, including corticosteroid use, radiotherapy, and cancer chemotherapy; current presence of febrile illness; pregnancy; and a history of immunization with live-attenuated vaccines (within the 6 weeks that preceded the TST). BCG status was ascertained on the basis of history and inspection for typical scars, and, in cases of doubt, was checked against the BCG registry in the participant’s home town.

Tests were performed simultaneously on either forearm according to the Mantoux method, with use of 0.1 mL of 1-tuberculin unit (TU) PPD of M. tuberculosis and a sensitin of M. scrofulaceum in Tween 80 and 0.1 mL of 1-TU sensitin of M. scrofulaceum in Tween 80 (Rijksinstituut voor Volksgezondheid en Milieuhygiëne). This PPD was used for several decades as the standard in The Netherlands. No data exist on direct comparisons with the international standard of 5-TU PPD-Seifert (PPD-S). However, 1 TU of the Dutch PPD was shown to be slightly less sensitive than 2 TU of the Danish PPD Rt23, which is bioequivalent to 5-TU PPD-S [10, 11]. Test results were assessed after 72–96 h and are expressed as millimeters of induration. Results of ≥0 mm were assessed by a second observer; a final result was obtained by consensus. Tests were administered and assessed by experienced staff.

“Tuberculin sensitivity” was defined as a reaction to PPD of ≥10 mm that was ≥3 mm larger than the reaction to the sensitin of M. scrofulaceum [12]. “High-incidence areas” were defined as countries with a reported or estimated annual risk of tuberculous infection of ≥1% since 1975 [13].

Data were entered twice into Epi Info, version 6.0 (Centers for Disease Control and Prevention). Analyses were performed by use of Stata software, version 6.0 (Stata). For point estimates, exact binomial 95% CIs were calculated [14]. For comparison of categorical and numerical variables, Fisher’s exact tests, Cuzick’s test of trend across ordered categories, unpaired Student’s t tests, and Wilcoxon’s rank sum tests were used where appropriate. In the stratified analysis, adjusted summary ORs were calculated by use of the Mantel-Haenzel method [14]. Unless stated otherwise, all tests were 2-sided, and a P value of .05 was considered statistically significant.

RESULTS

Of 1070 persons who met the inclusion criteria, TST results were available for 1050. Of these persons, 36 were excluded because of incomplete data. Therefore, data from 1014 subjects (94.8%) were available for analysis. Mean subject age (± SD) was 27.3 ± 5.5 years (range, 18–50 years), 428 subjects (42.2%) were male, and 241 (23.8%) had worked in health care. A TST had been performed previously for 370 subjects (36.5%); the TST had been performed <2 years prior to the study period for 115 subjects (11.3%). Using a 5-point scale, 956 subjects (94.7%) described their health status as “good” or “very good.”

Nine subjects (0.9%) had a reaction to PPD of ≥10 mm (table 1); the reaction to the sensitin of M. scrofulaceum was larger in one subject and <3 mm smaller in another subject (differences, 10 mm and 2 mm, respectively). Therefore, 7 subjects (0.7%) had reactions that met the definition of tuberculin sensitivity (95% CI, 0.3–1.4%). In all 7 patients, chest radiographs showed no abnormalities consistent with past or active tuberculosis.

Tuberculin sensitivity was not associated with age, sex, history of tuberculin testing, history of tuberculosis in a family member, or known occupational exposure to patients with tuberculosis (table 2). There was a nearly significant association with health care work that involved direct contact with patients (P = .087). The risk of tuberculin sensitivity was significantly associated with the total time spent in countries with a high incidence of tuberculosis (P = .028); it increased in relation to increasing cumulative duration of travel (tests for trend, P = .02; table 2).

The risk of tuberculin sensitivity among subjects with no history of travel was similar to that of subjects who spent a total of <3 months in such areas. The crude OR for tuberculin sensitivity among subjects who spent a total of ≥3 months compared with those who spent <3 months in high-incidence countries was 6.0 (95% CI, 1.2–31.2; P = .016). This was not affected by stratification by sex (summary OR, 6.0; P = .016), history of health care work (summary OR, 5.9; P = .017), or history of tuberculosis in a family member (summary OR, 6.1; P = .012).
Table 1. Distribution of reactions to simultaneous tuberculin tests with 1–tuberculin unit (TU) purified protein derivative (PPD) of Mycobacterium tuberculosis and 1-TU sensitin of Mycobacterium scrofulaceum, among 1014 BCG-naïve Dutch adults who intended to travel to areas with a high incidence of tuberculosis.

<table>
<thead>
<tr>
<th>Reaction to PPD, mm</th>
<th>Reaction to M. scrofulaceum sensitin</th>
<th>Difference in reaction to PPD and M. scrofulaceum sensitin</th>
<th>Reaction to PPD &gt;3 mm larger than to M. scrofulaceum sensitin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>66 (6.7)</td>
<td>912 (93.3)</td>
<td>0 (0)</td>
<td>978</td>
</tr>
<tr>
<td>2–5</td>
<td>9 (45.0)</td>
<td>7 (35.0)</td>
<td>4 (20.0)</td>
<td>20</td>
</tr>
<tr>
<td>6–9</td>
<td>4 (57.1)</td>
<td>2 (28.6)</td>
<td>1 (14.3)</td>
<td>7</td>
</tr>
<tr>
<td>10–14</td>
<td>1 (14.3)</td>
<td>1 (14.3)</td>
<td>5 (71.4)</td>
<td>7</td>
</tr>
<tr>
<td>≥15</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>2</td>
</tr>
<tr>
<td>Total, no. (%)</td>
<td>80 (7.9)</td>
<td>922 (90.9)</td>
<td>12 (1.2)</td>
<td>1014</td>
</tr>
</tbody>
</table>

* Row percentages are given.

* Including 2 patients whose M. scrofulaceum sensitin test results were missing.

Of 7 subjects with tuberculin sensitivity, 6 had either worked in patient care or had traveled to high-incidence areas for ≥3 months. This included 1 subject who had worked in patient care in Southeast Asia. The negative predictive value for tuberculin sensitivity, given the low prevalence in this population in The Netherlands, was 99.5% for persons with a history of health care work that involved patient care (95% CI, 98.8%–99.9%), 99.7% for persons with a history of ≥3 months of travel to areas with a high incidence of tuberculosis (95% CI, 99.0%–100%), and 99.8% for both predictors together (95% CI, 99.1%–100%).

DISCUSSION

Even with the small numbers identified among this Dutch-born, BCG-naïve population with no history of positive TST results, the risk of tuberculin sensitivity was significantly associated with a history of travel to areas with a high incidence of tuberculosis. Although this cutoff may be somewhat arbitrary, the association was particularly apparent for subjects with a cumulative duration of travel to such areas of ≥3 months, which had a 6-fold increased risk, and was not affected by adjustment for differences in sex, history of health care work, or history of tuberculosis in a family member. This suggests that in countries with a low incidence of tuberculosis, persons who travel to high-incidence areas may be a more important source of tuberculous infection than has been acknowledged thus far.

The cases of tuberculin sensitivity in this study are likely to represent true latent infections with M. tuberculosis. In immunocompetent persons, a reaction to PPD of ≥10 mm is generally considered to represent latent tuberculous infection [15]. Cross-reactions may occur because of delayed-type hypersensitivity to BCG or infections with environmental mycobacteria [16]. None of the subjects of the study had received BCG vaccination, and we controlled for cross-sensitivity to environmental mycobacteria by means of dual testing, which allowed distinction between M. tuberculosis and environmental mycobacterial infection, because homologous TST antigens elicit larger reactions than do heterologous antigens [17, 18]. A sensitin prepared from M. scrofulaceum is particularly suitable, because it is closer to the nontuberculous sources of sensitization than is PPD and it is the broadest cross-reacting environmental mycobacterial sensitin in the Dutch population [18, 19]. By using the criterion of a 3-mm difference for the indication of the dominant reaction, as has been suggested by similar studies, we also controlled for reading errors that have been shown to be within this range for experienced observers [20, 21].

Therefore, we are confident that our definition of tuberculin sensitivity was sufficiently specific for the identification of latent tuberculous infections. Its sensitivity may have been somewhat lower. Although false-negative reactions were unlikely, because waned hypersensitivity to M. tuberculosis is rare among persons in the age group that we studied [16], and because subjects with impaired cellular immunity were excluded, the sensitivity of the TST for detecting tuberculosis at the cutoff point of 10 mm does not exceed 90%–95%, even in immunocompetent persons [22]. Therefore, the single intermediate-range (6–9 mm) reaction to PPD that was dominant may reflect true tuberculous infection, particularly because 1 TU of the PPD that we used is considered slightly less sensitive for detection of tuberculous infections than 5-TU PPD-S [10, 11].

In addition, the 3-mm criterion may have been too stringent (i.e., there may have been cases of true tuberculous infection among those persons in whom the reactions did not differ by >2 mm). Limited sensitivity of the outcome measure is unlikely to have affected our risk estimate; however, it will have resulted in reduced statistical power [14], thus strengthening the signif-
In 1990, the annual risk of tuberculous infection was estimated to be 0.01% [25], and the current prevalence of latent tuberculosis among persons who were born after 1944 does not exceed 4% [26]. Our study suggests that, under these epidemiological conditions, a substantial proportion of new cases of infection and, therefore, of new cases of active tuberculosis in the resident population may be due to exposure that occurs abroad during travel to areas with a high incidence of tuberculosis. This is cause for concern. First, international travel from industrialized countries to the developing world is increasing rapidly [27]. Second, adolescents and young adults, who constitute the predominant age group engaging in such travel (in particular, travel for longer periods), have a relatively high rate of progression to infectious pulmonary tuberculosis [28, 29]. Third, there is the rapidly growing problem of the drug resistance of M. tuberculosis strains that are found in many countries with high rates of endemicity, particularly in Asia [30]. As a consequence, young travelers may serve as the vehicles for introduction of drug-resistant strains of tuberculosis into low-incidence areas.

Therefore, prevention of tuberculosis in international travelers must be given serious attention. BCG has incomplete or unpredictable efficacy in the prevention of active tuberculosis [31]. Therefore, several countries that do not routinely vaccinate persons during childhood, including The Netherlands, use TST screening that is performed 2–3 months after travelers return and, subsequently, chemoprophylaxis for those persons who have positive TST results as tools for prevention of tuberculosis among international travelers. Compliance with TST screening programs tends to be low, however [8, 32], and this may be caused in part by the requirement of pretravel testing to exclude existing infections. Our data suggest that, at least among young Dutch travelers, virtually all tuberculin reactors can be identified before travel by testing only those persons with a history of ≥3 months of travel to high-incidence areas or of health care work that has involved direct patient care. In this population, which has tuberculin sensitivity of <1%, testing other travelers only after return may decrease the burden upon them and thereby improve compliance with the screening program. However, in populations with higher background prevalences of tuberculin sensitivity, these negative predictive values will be lower, and additional selection criteria for pretravel testing may be needed.

**ACKNOWLEDGMENTS**

We thank the immunization clinic and tuberculosis control nurses at the participating health services for their assistance in data collection and, in particular, Hannelore Speenhof, Tally Drost, and Wilma op den Beek (deceased), for follow-up of the study subjects. We also thank Anne Leentvaar-Kuijper, Willem Beaumont, and Jan van den Homberg, for assistance in data collection and comments on the study protocol; Matthijs

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**Table 2. Univariate associations of potential risk factors with tuberculin sensitivity in 1014 BCG-naive Dutch adults who intended to travel to areas with a high incidence of tuberculosis.**

<table>
<thead>
<tr>
<th>Characteristic or risk factor</th>
<th>Subjects whose tuberculin-sensitivity test results were</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Negative (n = 1007)</td>
<td>Positive (n = 7)</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>27.3 ± 5.5</td>
<td>27.0 ± 1.9</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>426 (99.5)</td>
<td>2 (0.5)</td>
</tr>
<tr>
<td>Female</td>
<td>581 (99.1)</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>History of tuberculin testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>640 (99.4)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Yes</td>
<td>367 (99.2)</td>
<td>3 (0.8)</td>
</tr>
<tr>
<td>History of tuberculosis in family member b</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>853 (99.3)</td>
<td>6 (0.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>38 (97.4)</td>
<td>1 (2.6)</td>
</tr>
<tr>
<td>Worked in health care</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>847 (99.5)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Yes</td>
<td>160 (98.2)</td>
<td>3 (1.8)</td>
</tr>
<tr>
<td>Known occupational exposure to tuberculosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>944 (99.3)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Yes</td>
<td>61 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cumulative duration of travel to high-incidence countries c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>388 (99.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>&lt;3 months</td>
<td>322 (99.7)</td>
<td>1 (0.3)</td>
</tr>
<tr>
<td>3–12 months</td>
<td>201 (99.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>&gt;12 months</td>
<td>96 (97.0)</td>
<td>3 (3.0)</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of subjects, unless otherwise indicated.

a Wilcoxon’s rank sum test; all other P values are based on 2-sided Fisher’s exact tests.

b Family history unknown for 116 subjects.

c Annual risk of tuberculosis infection, >1%; test for trend, P = .02.

icance of the association with travel history that we found. Finally, although we did not perform “initial 2-step” testing to control for false-positive conversions due to boosting by repeated TSTs, this is unlikely to have affected the validity of our results. Apart from cross-sensitivity to BCG or environmental mycobacteria, for which we controlled by means of exclusion and dual testing with the M. scrofulaceum sensitin, respectively, boosting may occur in cases of waned delayed-type hypersensitivity to M. tuberculosis [16, 23, 24]. Waned immunity is rare among patients in the age group we studied, however, and subjects with suspected cellular immune deficiencies were excluded.

In The Netherlands, tuberculosis has become a rare disease. In 1990, the annual risk of tuberculous infection was estimated to be 0.01% [25], and the current prevalence of latent tuberculosis among persons who were born after 1944 does not exceed 4% [26]. Our study suggests that, under these epidemiological conditions, a substantial proportion of new cases of infection and, therefore, of new cases of active tuberculosis in the resident population may be due to exposure that occurs abroad during travel to areas with a high incidence of tuberculosis. This is cause for concern. First, international travel from industrialized countries to the developing world is increasing rapidly [27]. Second, adolescents and young adults, who constitute the predominant age group engaging in such travel (in particular, travel for longer periods), have a relatively high rate of progression to infectious pulmonary tuberculosis [28, 29]. Third, there is the rapidly growing problem of the drug resistance of M. tuberculosis strains that are found in many countries with high rates of endemicity, particularly in Asia [30]. As a consequence, young travelers may serve as the vehicles for introduction of drug-resistant strains of tuberculosis into low-incidence areas.

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Bleiker, for advice on the skin test methods; Melchert Visser, for assistance in coordination of the study; Gesina Sandstra, for entering the data; and Piet Kager, for his comments on the manuscript.

References


