Tuberculin reactivity: prevalence and predictors in BCG-vaccinated young Norwegian adults

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Abstract We studied tuberculin reactivity in young Norwegian adults and its possible dependency on age, gender, previous BCG vaccination, smoking habits, occupational exposure, diet as well as years of education as a measure of socio-economic status. Responders of a random sample of men and women aged 20–44 years living in Bergen, Norway were interviewed and tested with the adrenaline-Pirquet test with Norwegian-produced synthetic medium tuberculin at the out-patient chest clinic in the city of Bergen in 1992–1993. Nine hundred and three subjects out of 1200 met for the clinical examination (75%). Five hundred and eighty-eight subjects were tuberculin-tested and read, whereof 95% were BCG vaccinated by age 14. Mean tuberculin reactivity was 4.8 mm (SD: 3.0 mm). A positive reaction (≥4 mm) was found in 64%, whereof 7% had a strongly positive reaction (≥10 mm). A negative reaction (<4 mm) occurred in 36%, whereof 10% had no reaction (0 mm). Only 30% of the females and 36% of the males aged 21–25 years were tuberculin positive 7–12 years after BCG vaccination. Linear regression analysis demonstrated tuberculin reactivity to increase with increasing age, male gender with an increasing sex effect by age, and current smoking. Occupational dust or gas exposure, a diet rich in vitamin C or years of education did not influence tuberculin reactivity significantly.

INTRODUCTION

Although introduced almost a 100 years ago (1) tuberculin testing is still the most commonly used test for tuberculosis infection. However, the fraction of subjects reacting to tuberculin in a population is influenced by the rate of BCG vaccination (2) and non-tuberculous mycobacterial infections.

The incidence of tuberculosis in Norway in 1989–1993 was 6.4 per 100,000 inhabitants and for those born in Norway 4.4 per 100,000 inhabitants, respectively (3). Pulmonary tuberculosis accounted for approximately 70% of the cases. Immigrants from high incidence countries accounted for 40% of all incident cases of tuberculosis in Norway in the study period 1992–1993.

Tuberculin testing, BCG vaccination of the Norwegian population and screening with mass miniature chest X-ray were introduced by law in 1947. The BCG vaccination was attended by more than 95% of the population, usually given to pupils at school at age 14.

Non-tuberculous mycobacteria (NTM) are known to induce positive tuberculin reactions. This has been documented by Bjerkedal (4) in Norway (1961–1962) and Larsson (5) in Sweden (1986–1990), in large population studies of not-BCG-vaccinated children, when testing with tuberculin-like products produced from NTM (sensitins). They both concluded that NTM were responsible for most of the tuberculin reactivity in not-BCG-vaccinated Scandinavian children.

Eilertsen (6) demonstrated 30 years ago in his tuberculin studies (Danish old tuberculin), of young adults in Bergen, Norway, that BCG vaccination resulted in a positive tuberculin reaction in 94% of the subjects, stabilizing after 10–15 years at a positive tuberculin rate of about 65%. A recent study of 2629 pupils in 1990–1994 by The Norwegian Health Screening Service (7) showed a positive adrenaline-Pirquet tuberculin test (≥4 mm) 2 months after BCG vaccination in 84% of the pupils. Tuberculin reactivity has not been examined in Norway since the Waaler report in 1975 based on tuberculin data up to 1968 (2). Our routine tuberculin testing of young adults in the early 1990’s suggested that only one out of...
four subjects having been BCG vaccinated 7–12 years earlier reacted to tuberculin. This might indicate a substantial change in long-lasting tuberculin reactivity in BCG-vaccinated subjects of unknown reasons.

The objective of the paper is to describe tuberculin reactivity in a young Norwegian population with a high coverage of BCG vaccination. Furthermore, we wanted to evaluate possible predictors of tuberculin reactivity such as age, sex, smoking habits, as well as other factors related to lifestyle assessed as occupational dust exposure, socio-economical status judged by educational level and dietary intake of vitamin C.

METHODS AND SUBJECTS
Study population
A random sample of 1200 men and women aged 20–44 years, living in the city of Bergen, Norway August 1st 1990, was drawn by the Central Population Registry. The 1200 subjects, being selected from a population of about 90 000, were invited to participate in the Norwegian part of the European Community Respiratory Health Survey (ECRHS) (8). This selection of subjects was also included in a tuberculin survey. The interviews and investigations took place at the Hordaland County Chest Unit from September 1992 to June 1993. A questionnaire and an interview revealed prior tuberculin status, BCG vaccination, smoking habits, occupational dust or gas exposure, dietary vitamin C intake and age when finishing education as a measure of socio-economic status.

The tuberculin test
The standard Norwegian test, a modification of von Pirquet’s skin scarification method, with Norwegian-produced synthetic medium tuberculin (SMT) and adrenaline, was applied (9). Two drops of the SMT and adrenaline solution were placed on the volar side of the left arm, 5 and 10 cm below the cubital line, respectively. A 5 mm skin scratch was made with a lancet through the solution placed on the skin. The duplicate test reactions were to be read within 48–72 h and assessed as the greatest measure of the infiltration perpendicular to the scratch. The larger of the duplicate reactions was used. An experienced public health nurse performed all tuberculin testing and reading. We defined a positive reaction as an infiltrate ≥4 mm. A strongly positive reaction (≥10 mm) may indicate tuberculosis transmission despite previous BCG vaccination (7).

We have previously shown that the adrenaline-Pirquet tuberculin test as is reproducible (10) as the Mantoux PPD test (11), but less sensitive (12). The adrenaline-Pirquet tuberculin test gave 11–16% less positive reactors than the Mantoux PPD 5 TU and 2 TU tests (12).

BCG vaccination
BCG vaccination has been compulsory in Norway since 1947 with an adherence of 95% or more of the population. Since 1995 BCG vaccination has been recommended on a voluntary basis. As in earlier years all pupils in elementary school, usually at age 14, is BCG vaccinated by the public school health nurse. In Norway, the Bergen strain of BCG was applied up to January 1972 and thereafter the Copenhagen strain.

Smoking habits, occupational exposures, socio-economic status and diet
Smokers were subjects who reported to have been smokers for as much as one year, smoking at least 1 cigarette a day/l cigar a week or having smoked at least 400 cigarettes/360 g tobacco during their lifetime. The smokers were further divided into light smokers consuming 1–9 cigarettes daily, moderate smokers with 10–19 cigarettes daily and heavy smokers taking at least 20 cigarettes daily. Cigar or pipe tobacco smoking was registered as grams of tobacco smoked per day with 1 cigarette equaling 1 g of tobacco. Ex-smokers were subjects who reported to have been smokers according to the definition above and to have stopped smoking more than 1 month prior to answering the questionnaire. Never smokers were subjects who denied smoking according to the applied definition (8).

Occupational, airborne exposure to dust or gas was assessed by asking: “Have you ever had a job that exposed you to vapors, gas, dust or fumes?” The answers were given as yes or no. Dietary vitamin C intake was assessed by a semi-quantitative food-frequency questionnaire as the daily intake of orange or orange juice, potatoes, carrots or tomatoes. The questionnaire was originally developed by Channing Laboratory, Harvard Medical School, and has documented acceptable reproducibility and validity (13,14).

Socio-economic status was assessed as level of education (15). Information about age when education was finished was obtained from the questionnaire. A low level of education was defined as finishing education at age 16 or younger, a medium level when finishing education at age 17–19 years and a high level when finishing education at age 20 years or older.

Statistical methods
Non-attendants, attendants who did not complete the tuberculin test program and attendants tested and read were compared with respect to age and sex distribution by one-way analysis of variance and chi-square tests, respectively (16,17). Age was calculated from year of birth to test year (1992 or 1993). The mean adrenaline-Pirquet tuberculin reactivity was compared bet-
ween BCG-vaccinated and not-BCG-vaccinated groups and childhood tuberculin converters, using Student’s t-test (17).

To study the relationship of the adrenaline-Pirquet reaction with age, gender, smoking classification groups, occupational exposure, educational level and dietary vitamin C intake, we applied multiple linear regression analyses (17).

RESULTS

Nine hundred and three persons (75%) attended the study. The sex and age distribution for non-attendants (\(n = 297\)), attendants not included (\(n = 315\)) and attendants tuberculin tested and read (\(n = 588\)) are presented in Table 1. Attendants not included were either not tuberculin tested due to eczema (\(n = 12\)), tested but not read (\(n = 301\)) or they had only one adrenaline-Pirquet scratch (\(n = 2\)). The attendants had a higher mean age and a higher percentage of women than the non-attendants and those tested but not included.

Out of the study population of 588 subjects, 558 BCG-vaccinated subjects had a mean adrenaline-Pirquet tuberculin reactivity of 4.8 mm (SD: 3.0 mm). The 20 subjects who denied having had a BCG vaccination had a mean tuberculin reaction of 3.6 mm (SD: 2.5 mm) (\(P = 0.28\))

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Table 1 presents the results of the stepwise multiple linear regression analysis for predictors of tuberculin reactivity in this young adult population. Increasing age, smoking classification groups, occupational exposure, educational level and dietary vitamin C intake all significantly contributed to the variance of the outcome variable. There was a nonsignificant trend of tuberculin reactivity increasing with nutritional vitamin C intake (\(P = 0.06\)).
male sex with an increasing sex effect by age and current smoking predicted independently tuberculin reactivity after adjusting for educational level, a marker of socio-economic status. The sex and age interaction is more easily shown in Table 2, where tuberculin reactivity is higher in men than in women but differentially by age. The gender difference was most pronounced in the oldest age groups. No dose-response effect of tobacco smoking was found. No statistical significant effects were demonstrated for occupational dust or gas exposure and vitamin C intake when added to the multivariate model.

**DISCUSSION**

We observed that 64% of the subjects in a young BCG-vaccinated Norwegian population had a positive reaction (≥4 mm) to the adrenaline-Pirquet tuberculin test. A
A negative reaction (\(<4\ mm\)) occurred in 36%, while 10% had no reaction (0 mm). However, only 30% of the females and 36% of the males aged 21–25 years were tuberculin positive 7–12 years after BCG vaccination. Tuberculin reactivity was significantly predicted by gender, age and smoking habits.

Out of the random sample of 1200 men and women our study comprised 588 subjects who were tuberculin tested and read (49%). As in other population studies performed in the same area (18), those who completed the tuberculin study were older and included a greater proportion of women. We did not observe significant differences in the frequency of attendance when comparing those being spontaneous tuberculin converters with those having received previous BCG vaccination. We thus believe that the small age and gender differences observed should not have biased our results substantially.

However, we do not have the readings of the tuberculin reactions of 35% of those tested. One may speculate whether subjects with a small or a negative tuberculin reaction would be less likely to return for tuberculin readings. In addition, younger subjects have lower tuberculin reactivity and a lower attendance rate in this survey. Consequently, the proportion of tuberculin positive re-

### Table 2. Adrenaline-Pirquet tuberculin positive results (\(\geq 4\ mm\)) in 588 Norwegian adults aged 21–46 yr

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>n</th>
<th>Percent tuberculin positive</th>
<th>Mean tuberculin reactivity (mm)</th>
<th>Standard deviation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>21–25</td>
<td>44</td>
<td>36.4</td>
<td>2.9</td>
<td>2.7</td>
</tr>
<tr>
<td>Female</td>
<td>21–25</td>
<td>37</td>
<td>29.7</td>
<td>2.6</td>
<td>2.4</td>
</tr>
<tr>
<td>Male</td>
<td>26–30</td>
<td>64</td>
<td>59.4</td>
<td>4.3</td>
<td>3.0</td>
</tr>
<tr>
<td>Female</td>
<td>26–30</td>
<td>76</td>
<td>56.6</td>
<td>4.3</td>
<td>2.9</td>
</tr>
<tr>
<td>Male</td>
<td>31–35</td>
<td>61</td>
<td>65.6</td>
<td>5.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Female</td>
<td>31–35</td>
<td>57</td>
<td>57.9</td>
<td>5.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Male</td>
<td>36–40</td>
<td>67</td>
<td>80.6</td>
<td>6.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Female</td>
<td>36–40</td>
<td>65</td>
<td>72.3</td>
<td>4.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Male</td>
<td>41–46</td>
<td>61</td>
<td>88.5</td>
<td>6.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Female</td>
<td>41–46</td>
<td>56</td>
<td>71.4</td>
<td>5.1</td>
<td>2.8</td>
</tr>
<tr>
<td>Male</td>
<td>21–46</td>
<td>297</td>
<td>68.0*</td>
<td>5.2</td>
<td>3.1</td>
</tr>
<tr>
<td>Female</td>
<td>21–46</td>
<td>291</td>
<td>598*</td>
<td>4.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Total</td>
<td>21–46</td>
<td>588</td>
<td>63.9</td>
<td>4.8</td>
<td>3.0</td>
</tr>
</tbody>
</table>

* Males vs. females using Pearson’s chi-square test: \(P = 0.0002\).

### Table 3. Multiple linear regression model for adrenaline-Pirquet tuberculin reactions (mm) in young Norwegian adults (\(n = 558\))

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>Standard error</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>−1.802</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.186</td>
<td>0.024</td>
</tr>
<tr>
<td>Sex (male = 0, female = 1)</td>
<td>2.088</td>
<td>1.153</td>
</tr>
<tr>
<td>Sex (\times) age interaction</td>
<td>−0.083</td>
<td>0.033</td>
</tr>
<tr>
<td>Smoking(^a)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>0.213</td>
<td>0.349</td>
</tr>
<tr>
<td>Light smokers ((\leq 9) cigarettes/day)</td>
<td>1.083</td>
<td>0.372</td>
</tr>
<tr>
<td>Medium smokers (10–19 cigarettes/day)</td>
<td>0.723</td>
<td>0.310</td>
</tr>
<tr>
<td>Heavy smokers ((\geq 20) cigarettes/day)</td>
<td>0.779</td>
<td>0.425</td>
</tr>
<tr>
<td>Educational level</td>
<td></td>
<td>0.125</td>
</tr>
<tr>
<td>(17–19) yr</td>
<td>0.005</td>
<td>0.365</td>
</tr>
<tr>
<td>(\geq 20) yr</td>
<td>0.490</td>
<td>0.314</td>
</tr>
</tbody>
</table>

*Age when finishing education.

\(^a\) Regression coefficients are relative to the reference categories (zero) which are never smokers and \(\leq 16\) years, respectively.
actors would be even lower than what we have observed in our youngest 21–25 year age group, resulting in an under-estimate of the tuberculin reactivity in the youngest age groups.

The adrenaline-Pirquet test with Norwegian-produced synthetic tuberculin (9) has long historical stand-\(\text{ings and has been regularly quality assessed by the Norwegian National Health Screening Service (7). In co-}\),herence with clinical tradition (7) the tuberculin-setting and readings were performed by the same well-trained public health nurse. We have previously shown that the adrenaline-Pirquet tuberculin test is as reproducible (10) as the Mantoux PPD test (11), but less sensitive (12).

Tuberculin reactivity in this cross-sectional study increased with increasing age. Cross-sectional investiga-
\(\text{tions by the Norwegian National Health Screening Service (7) observed in 1990–1994 a tuberculin positive rate of 84% in children 2 months after BCG vaccination. Larson et al. (19) found 49% positive tuberculin (PPD RT23) reactors in 8–9-year-old Swedish children BCG vaccinated within their first 2 years of life. Miret-Cuadrás et al. (20), Spain, reported tuberculin (STU PPD RT23) reactivity in 13–25 year old subjects BCG vaccinated at birth and 20–25-year-old subjects BCG vaccinated at age 6–14. Positive reactions (≥ 5 mm) were found in 64% of the males and in 60% of the females. When using our (12) transition equation for the relationship between the adrenaline-Pirquet tuberculin test and the Mantoux PPD RT23 5 TU (12), we calculated that 52% of the subjects in our study would have reacted positively in the age-group 20–25 years. This difference between Spain and the Nordic countries is not a BCG effect as the same BCG strain has been applied. However, it may be related to the ten times higher risk of tuberculosis infection in Spain than in Norway (20).

Krøger et al. (21) studied tuberculin (PPD RT23) reactivity in 4–6-year-old Finnish children who were BCG vaccinated at birth and again at age 10–12. They found that the mean tuberculin reactivity decreased from 4.8 mm to 3.4 mm and concluded that contact with mycobacteria, either with Mycobacterium tuberculosis or environmental mycobacteria, was too rare to maintain tuberculin responsiveness. Eilertsen (6) studied the tuberculin reactivity in BCG Bergen strain vaccinated young adults in the 1960s and followed them for 15 years. The rate of positive tuberculin reactors dropped from 96% the first year to approximately 65% 15 years after vaccination. The decline in tuberculin reactivity in our study compared with Eilertsen’s data may partly be due to a cohort effect reflecting a higher risk of tuberculosis infections in the 1950–1960s. In addition, the cohort effect might be explained by other factors including exposure to environmental mycobacteria or tobacco smoking.

The lower tuberculin reactivity in women than in men in the older age groups, independent of tobacco smok-ing, is difficult to explain. Men may be more heavily exposed to mycobacteria or there may be gender differences in immune reactivity (22). Our observations are in accordance with previous reports (23).

We found a strong and independent effect on tubercu-
\(\text{lin reactivity by tobacco smoking, but no dose–response relationship. While Gulsvik et al. (24) found lower levels of}\), IgA, IgG and IgM in smokers, Omenaas et al. found in 1994 (25) that smokers had a higher IgE level than non-smokers. Anderson et al. (26) studied cigarette smoking and tuberculin conversion among inmates in prisons. They suggested that smokers were more likely to become tuberculin skin test converters than non-smokers reflecting a reduced mucociliary clearance of potential pathogens such as non-tuberculous mycobacteria or of Mycobacterium tuberculosis.

This study shows that the prevalence of a positive tu-
\(\text{berculin reaction in this young Norwegian population, BCG vaccinated at age 14, was 64%. Tuberculin reactivity was predicted significantly by increasing age, with an increasing male effect by aging and current smoking.}

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