Assessment of school based screening for tuberculosis infection in Norway: comparison of positive tuberculin skin test with interferon-gamma release assay

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Abstract

Background
In Norway, screening for tuberculosis infection by tuberculin skin test (TST) has been offered for several decades to all children in 9th grade of school, prior to BCG-vaccination. The incidence of tuberculosis in Norway is low and infection with M. tuberculosis is considered rare. QuantiFERON®TB Gold (QFT) is a new and specific blood test for tuberculosis infection, but with few data so far from screening of predominantly unexposed, healthy, TST-positive children, including first and second generation immigrants. In order to evaluate the current TST screening and BCG-vaccination programme we aimed to (1) measure the prevalence of QFT positivity among TST positive children identified in the school based screening, and (2) measure the association between demographic and clinical risk factors for tuberculosis infection and QFT positivity.

Methods
This cross-sectional multi-centre study was conducted during the 2005-6 school year and the TST positive children were recruited from seven public hospitals covering both rural and urban areas in Norway. Enrolment included a QFT test and a questionnaire regarding demographic and clinical risk factors for latent infection.

Results
Among 511 TST positive children only 9% (44) had a positive QFT test. QFT positivity was associated with size of TST induration, origin outside western countries and known exposure to tuberculosis. Most children (79%) had TST reactions in the range of 6-14 of whom 5% were QFT positive. Discrepant results between the tests were common even for TST reactions =>15 mm, as only 22 % had a positive QFT. The results support the assumption that previous BCG-vaccination and infection with
non-tuberculosis mycobacteria contribute to most of the positive TST results in this group and indicate the improved specificity of QFT for latent tuberculosis. However, sensitivity or differences in the nature of the immune responses measured by the two tests might also explain the discrepant test results.

**Conclusions**

Our study suggests a very low prevalence of latent tuberculosis infection among 9th grade school children in Norway and has given key input to the discussion of the usefulness of the current TST screening and BCG-policy in Norway.

**Background**

The incidence of tuberculosis in Norway is generally low (6.3/100 000 population in 2006), but high among immigrants from countries where tuberculosis is endemic [1]. Although the tuberculin skin test (TST) has low specificity, it is still the major tool for detecting tuberculosis infection. In Norway, screening for tuberculosis infection by TST has been offered to all children in 9th grade of school (age 14-15) for several decades. Historically, there have been three objectives of this screening: (1) to measure the transmission rate of tuberculosis in the society, (2) to identify cases with latent tuberculosis infection for preventive treatment, and (3) to ensure that only tuberculin negative children receive Bacillus Calmette-Guérin (BCG) vaccine, which is offered in the national vaccination programme to all previously unvaccinated, TST negative children at the age of 14 years. Children born in Norway of parents from high prevalence countries and a limited number of other children assumed to be at risk are offered BCG-vaccination at birth or on other occasions [2]. Today, testing prior to BCG-vaccination remains the main objective of the screening.
Each year, this screening results in several hundred children with a positive TST (defined as => 6 mm) being referred to hospitals for medical evaluation, chest X-ray and a three year follow up procedure, which demands great resources and causes concern among the affected families. No case of tuberculosis disease has been identified through this screening for many years. We suspect that previous BCG-vaccination or infection with non-tuberculosis mycobacteria (NTM) are the causes of most TST reactions as few of the children have any known exposure to tuberculosis and the transmission rate in Norway, based on molecular epidemiology, is known to be very low [3,4].

New in vitro assays based on cellular production of interferon-gamma (IFN-γ) in response to the *M. tuberculosis* specific antigens ESAT-6, CFP10, and TB7.7 have been developed. These protein antigens are absent in all vaccine strains of *M. bovis*-BCG and most NTM, except *M. marinum, M. zulga*, and *M. kansasii* [5,6]. In contrast to TST, these tests can therefore distinguish *M. tuberculosis* infection from infections with non-tuberculosis mycobacteria or previous BCG-vaccination. The assays seem to be accurate and valid diagnostic tools for both active and latent tuberculosis infection with high specificity [6-10]. Among the commercially available and regulatory approved IFN-γ release assays, the QuantiFERON®TB Gold (QFT) test offers both logistic and economical advantages, which makes it suitable for mass screening. Such tests have now been evaluated and used in different contexts but with few data so far from screening of predominantly unexposed and healthy TST-positive children, including first and second generation immigrants [6,8,11,12].
The policy of universal TST screening and BCG-vaccination of school children in Norway is under discussion. In order to evaluate the current TST screening and BCG-vaccination programme and inform the discussion on any future targeted screening approach, we aimed to (1) measure the prevalence of QFT positivity among TST positive children identified in the school based screening and (2) measure the association between demographic and clinical risk factors for tuberculosis infection and QFT positivity.

**Methods**

TST with purified protein derivative (PPD) RT 23 (2 TU) from Statens Serum Institute, Denmark was applied according to the Mantoux method and read by public health nurses in the schools. A test was considered positive if the induration was $\geq 6$ mm after 72 hours. Children with a positive TST are referred to the public hospital serving the area. In this cross-sectional study in the school year 2005-6, we aimed to include all 9th grade children referred to seven hospitals serving both rural and urban areas in Norway. After the parents or guardians had given written informed consent, a QFT test was obtained and a questionnaire regarding demographic and clinical risk factors for latent infection was completed. Regardless of participation in the study, the nationally recommended follow up procedures were followed.

Statistics Norway provided the number and demographic characteristics of all children born in 1991 (proxy for 9th graders) living in the geographical regions covered by the seven hospitals. The Regional Ethics Committee for Medical Research recommended the study (S-05160) and permission was given from the Norwegian Data Inspectorate (23147).
The QuantiFERON®TB Gold in-tube-test (Cellestis Ltd, Victoria, Australia) was used. One ml of venous blood was drawn into each of two pre-coated tubes with and without synthetic peptide antigens respectively. Mitogen positive control was not included since this was not available in this first version of the test. The samples were processed and stored in accordance with the manufacturer’s instructions at the local hospital before they were transported to the Norwegian Institute of Public Health, where harvested plasma was subjected to Enzyme-Linked Immunosorbent Assay (ELISA) analysis, including IFN-γ standard for quantification. The quality of all laboratory analysis and calculation of the results was controlled by the accompanying QFT analysis software. A sample was considered positive if exceeding the standard cut-off value at 0.35 IU IFN-γ/ml. All positive results were confirmed by re-analysis of the same plasma sample before they were reported as positive. If the confirmatory test was negative, the QFT result was reported as non-conclusive and the participant was offered a new test.

Participating hospitals entered data into Excel 2003 in a standardized format and the data were later validated and merged at the Norwegian Institute of Public Health. Exact confidence intervals were calculated for proportion of single samples. Statistical analyses were performed in STATA 9.2 (Statacorp, Texas, 77845, USA). For analysis the origin of children was grouped in three: (1) born in a western country with parents of western origin (further referred to as western-born), (2) born in a western country with one or both parents of non-western origin (second generation immigrant), and (3) born in a non-western country (first generation immigrant). Western countries were defined as USA, Australia, Japan, Canada, New Zealand, and European countries other than Turkey, the Balkan States, and countries of the former
Soviet Union. The size of the TST indurations was grouped into three: 6-9 mm, 10-14 mm, and 15 mm or more. Presence of scar was considered as evidence of BCG vaccination (scar/no scar) and self-reported known exposure to an infectious tuberculosis case was reported as exposure (yes/no). History and duration of travels to non-western countries was collected on the questionnaire and accumulated duration of travel(s) was grouped as none, or \(</\> 3\) months.

Unconditional multivariate analysis (logistic regression) was performed with QFT as outcome variable. The independent variables; origin, gender, BCG-vaccination, exposure to tuberculosis and history of travel were all included in a preliminary multivariable regression analysis. Spearman correlation coefficient was used to check for correlation among pairs of independent variables. We subtracted one variable at the time using the likelihood ratio test as elimination criterion (p<0.05). The same approach was used to test the significance of the two-way interaction terms between the independent variables in the final model. This could not be run due to the low number of QFT positives. The odds ratios in the final model were used to measure the strength of association. A separate univariate regression analysis was performed to measure the strength of association between QFT positivity and travel history for western-born and second generation immigrant children.

**Results**

**Study population and characteristics**

The 33456 children in the catchment areas of the seven participating hospitals constituted 53\% of the children in Norway born in 1991. They had the same gender distribution as all children born in 1991, while children with immigrant parents were significantly overrepresented (table 1). Among the western-born children 86\% were
born in Norway, the remaining in other low-prevalence countries, mainly in Scandinavia and in USA. A total of 531 TST positive children were referred and 519 (98%) consented to participate. Eight of 16 children with a non-conclusive first QFT test, submitted a new blood sample where two became positive and six were negative. The remaining eight were excluded from the study. Thus, altogether 511 had a conclusive QFT result and formed the study group. Among these 511 children, the median TST indurations for unvaccinated children were 10 mm (range 6-30 mm) and for previously BCG-vaccinated children 11 mm (range 6-45 mm). First and second generation immigrant children significantly more often presented with a positive TST compared to western-born children (table 1). None of the children were diagnosed with tuberculosis disease during clinical evaluation or reported any previous history of tuberculosis.

**Prevalence of positive QFT result**

Only 44 (9%) of the 511 TST positive children had a positive QFT result. Positive QFT tests were seen with all sizes of TST indurations (figure 1), although the proportion increased with the size of the TST induration, in both genders and regardless of BCG vaccination and origin (table 2). First generation immigrants significantly more often had a positive QFT test (18% of the TST positives), while the percentage was similar for western-born and second generation immigrants (6% in both groups). Among the 16 western-born children with positive QFT results, 15 were born in Norway. Seven of these children came from one coastal city south in Norway, which contributed to only 14% of the children in the study. Three of the them came from the same school where additional nine children were identified with a positive TST, while the QFT turned out negative. They were all assessed for history of symptoms or clinical findings concurrent with *M. marinum, M. kansasii* or *M. zulga*. 
bot none reported such. Discrepant results were common even for TST reactions =>15 mm, as only 22% had a positive QFT. Among the 83 participants with TST =>15 mm and negative QFT, 31 were previously unvaccinated.

**Predictors of a positive QFT result**
Altogether, 46% of the TST positive children had a BCG-scar, 84% among first generation immigrants, 89% among second generation immigrants and 13% among western-born children (table 2). Exposure to an infectious case of tuberculosis was reported by 27 children. Immigrant children reported a median 9 years (range 1 month-15 years) stay in a non-western country, prior to arrival to Norway. Second generation immigrant children (76%) reported travels to non-western countries more often than western-born children (34%), but the median accumulated duration of their travels was comparable (6 weeks). Only origin and exposure to tuberculosis were associated with QFT positivity (table 3). Both BCG-vaccination and travel history were correlated to origin (Spearman’s rho 0.735 and 0.663 respectively) and did not fit into the same model. Travel was not significantly associated with a positive QFT for western-born or second generation immigrant children in univariate regression analysis (data not shown).

**Discussion**
In this study, we have shown that only 9% of TST positive school children, including first and second generation immigrants tested positive with the QuantiFERON®TB Gold test. QFT positivity was associated with size of TST induration, origin outside western countries and known exposure to tuberculosis.
Low prevalence of positive QFT-results

First and second generation immigrants were more likely to have a positive TST reaction. Most of them are already BCG-vaccinated, a factor known to affect the specificity of TST. The assumption that previous BCG-vaccination and NTM are widely contributing to positive TST reactions among schoolchildren in Norway is supported by this study, as only 9% had a positive QFT. Our study thus indicates the improved specificity of QFT compared to TST. Sensitivity or differences in the nature of the immune response measured by the two tests should however also be considered. Other studies from low-prevalence countries mainly including recent contacts or suspects of tuberculous disease have reported moderate agreement between the tests, but differences in design and populations make comparison between such studies difficult [6-10,12,13].

TST reactions caused by previous BCG-vaccination or infections with NTM are expected to be moderate and in the range of 6-14 mm [14-16], consistent with our study where 79% of the positive TST reactions occurred within this range. The effect of BCG-vaccination received in infancy on TST is perceived to be minimal, especially more than 10 years after vaccination [17]. Contrary to our results, other studies have reported a significantly better agreement between the tests for unvaccinated than vaccinated groups [8,18]. Different risk profile for tuberculosis exposure between the vaccinated and unvaccinated participants in our study may explain the lack of difference among the groups. Infections from NTM could explain the high number of TST positive children, as these infections are quite frequent in Norway (250 notifications from laboratories every year, unpublished data from
Tuberculosis Register) compared to the 300 notified cases of tuberculosis. They are endemic also in countries with high levels of tuberculosis [19].

Among the children with TST 15 mm or more, only 22% had a positive QFT. This discordance is not as easily explained by poor specificity of TST since reactions exceeding 15 mm have been interpreted as true tuberculosis infection [14-16]. The sensitivity of QFT for detection of latent infection has been extrapolated from data obtained from patients with active disease and found to be variable (75 - 97%) depending on the study population and design [12,20,21]. Discrepant results between TST=> 15 mm and QFT have also been documented in other studies [19,22]. The two tests measure different immune responses. Tuberculin induces a delayed-type hypersensitivity reaction reflecting a memory response, while the blood tests are believed to detect cellular IFN-γ release reflecting an effector response to an ongoing infection. Thus, IFN-γ release assays may detect recent and persistent infection whereas TST react to previous infections [7,12]. However, this may be of less relevance in our study as the population studied is very young.

None of the 7 western-born QFT positive cases from the same costal area reported exposure and careful source case investigations have revealed no links or index case. Despite the high specificity of the QFT, false positive results caused by one of the species that share the antigens used in the QFT assay with the M. tuberculosis-complex cannot be ruled out [12,23]. All of them were assessed for M. marinum, M. zulgaï, or M. kansasii infections, but none reported such and culture is necessary to confirm diagnosis. In this study QFT was following a tuberculin skin test. There is no
evidence of a potential influence of TST on the QFT result and having a QFT following a TST is also in agreement with the European Consensus Report [24,25].

**Predictors of positive QFT**

Origin of the child and known exposure to tuberculosis were predictors of a positive QFT. We assume that most first generation immigrant children with latent infection were infected in their home country prior to arrival in Norway. This is supported by results from Restricted Fragment Length Polymorphism (RFLP) fingerprinting routinely performed on all *M. tuberculosis* isolates in Norway since 1994, indicating that most tuberculosis cases are due to importation of new strains rather than transmission within the country [3,4]. Second generation immigrant children have been regarded as a risk group for tuberculosis as the disease is mainly affecting the immigrant population and they often travel for extended periods to their parents' country of origin and live close to the indigenous population. Over the last five years, 4-5 cases of tuberculosis disease have been reported annually among second generation immigrant children in Norway, compared to approximately one case in western-born children. In this study history of travel was not associated with QFT positivity for any of the groups, even though a substantial number reported accumulated duration of travel exceeding three months. The study was based on a well-run, public, school-based programme and enrolment was almost complete. However, we believe that some schools may not have tested previously BCG-vaccinated children or not referred children with marginally positive TST-results. Thus, we may have missed some TST-positive children.
Even though only few participants reported exposure to an infectious case of tuberculosis, this was, as reported in other studies, significantly related to a positive QFT [6,8,9,18,26]. Cultural concepts of “being exposed” may differ as none of the western-born children and only one of the second generation children reporting exposure, were QFT positive. Importantly, we observed a significant association between the increase in TST indurations and the proportion of QFT positive. This is consistent with the expected association between the increase in TST indurations and the proportion of tuberculin reactions caused by *M. tuberculosis* [27].

With only 44 QFT positives in the study group of 511 children, we had limited power to detect associations between background variables and QFT positivity. As positive mitogen control was not available as a part of the assay used in this study, we may theoretically have missed some QFT positives. However, this is not so relevant in this population where all participants were TST positive and immunosuppression is considered to be very rare.

**Implications for the screening programme**

The study suggests that the prevalence of latent infection among 9th grade school children in Norway is very low and that TST screening results in many false positive reactions. Thus, the current screening programme is hardly justified as a cost-effective tool for preventing tuberculosis in latently infected children. The few children where infection with *M. tuberculosis* is most likely may be identified by improved immigrant entry-screening and testing of contacts of cases with infectious tuberculosis. The usefulness of TST as pre-screening before routine BCG vaccination
needs to be carefully evaluated in conjunction with the current evaluation of the BCG vaccination programme as a whole.

**Conclusions**

Our results indicate that most positive TST reactions among children in Norway are caused by NTM or previous BCG-vaccination. The poor agreement between the tests is therefore mainly explained by the increased specificity of the QFT. Latent infection seems to be almost absent among western-born TST positive children, including second generation immigrants, while first generation immigrant children are at increased risk. First generation immigrant children are already targeted by entry screening and improved programme performance of this screening is a better control measure in a low prevalence country. The study supports the need to evaluate the current national screening and BCG-vaccination programme in Norway.

**Competing interests**

IH has been paid by Astra Zeneca for holding a lecture on mandatory screening of tuberculosis infection in health care services.

The remaining authors declare that they have no competing interests.

**Authors' contributions**

BAW has been responsible for study design, planning, data collection, data analysis and interpretation of data and the writing process, FO has been responsible for the laboratory components of the study and has made substantial contributions to the writing process, TM contributed to planning of the study, interpretation of data and input in the writing process, GEK carried out laboratory work and contributed to interpretation of data, AMDR, INL and IH contributed in planning of the study, data
collection, data analysis and the writing process and EH contributed to planning of the study, data interpretation and analyses of results as well as giving substantial input in the writing process. All authors read and approved the final manuscript.

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Figures

Figure 1 – Number of QuantiFERON®TB Gold positive results distributed by mm tuberculin skin test induration

Distribution of QuantiFERON®TB Gold results among 511 tuberculin skin test positive children detected in the Norwegian school based screening programme in the school year of 2005-6. Tuberculin skin test indurations measured as 25mm or more were grouped together as 25mm+

Tables

Table 1 - Characteristics of source population and study group: number and prevalence of positive TST

Characteristics of children born in 1991 in nation and project area and 531 children referred because of positive tuberculin skin test result in the school based screening programme in Norway in the school year of 2005-6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Population in nation born in 1991</th>
<th>Population in project area born in 1991</th>
<th>No. TST positives in project area</th>
<th>Prevalence of TST positives in project area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>No. (%)</td>
<td>No.</td>
<td>% (95% CI)</td>
</tr>
<tr>
<td>Total</td>
<td>63662</td>
<td>33456 (53)</td>
<td>531</td>
<td>1.6 (1.5 - 1.7)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>32617</td>
<td>17127 (53)</td>
<td>286</td>
<td>1.7 (1.5 - 1.9)</td>
</tr>
<tr>
<td>Female</td>
<td>31045</td>
<td>16329 (53)</td>
<td>245</td>
<td>1.5 (1.3 - 1.7)</td>
</tr>
<tr>
<td>Origin of child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western-born</td>
<td>57775</td>
<td>29712 (51)</td>
<td>288</td>
<td>0.9 (0.9 - 1.1)</td>
</tr>
<tr>
<td>Second generation immigrant</td>
<td>2867</td>
<td>2052 (72)</td>
<td>111</td>
<td>5.4 (4.5 - 6.5)</td>
</tr>
<tr>
<td>First generation immigrant</td>
<td>3020</td>
<td>1692 (56)</td>
<td>132</td>
<td>7.8 (6.6 - 9.2)</td>
</tr>
</tbody>
</table>
Number of QuantiFERON®TB Gold positive results among 511 tuberculin skin test positive children detected in the Norwegian school based screening programme in the school year of 2005-6.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total study group</th>
<th>TST 6-9 mm</th>
<th>TST 10-14 mm</th>
<th>TST =&gt;15 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TST QFT</td>
<td>TST QFT</td>
<td>TST QFT</td>
<td>TST QFT</td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Study group</td>
<td>511 9 (18)</td>
<td>207 8 (4)</td>
<td>198 13 (7)</td>
<td>106 23 (46)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>275 8 (30)</td>
<td>110 6 (6)</td>
<td>110 7 (6)</td>
<td>55 8 (15)</td>
</tr>
<tr>
<td>Female</td>
<td>236 15 (65)</td>
<td>97 2 (2)</td>
<td>88 6 (7)</td>
<td>51 15 (57)</td>
</tr>
<tr>
<td>Origin of child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western-born</td>
<td>280 6 (18)</td>
<td>131 6 (5)</td>
<td>110 7 (6)</td>
<td>39 3 (8)</td>
</tr>
<tr>
<td>Second generation immigrant</td>
<td>108 4 (10)</td>
<td>41 1 (2)</td>
<td>44 1 (2)</td>
<td>23 4 (17)</td>
</tr>
<tr>
<td>First generation immigrant</td>
<td>123 16 (13)</td>
<td>35 1 (3)</td>
<td>44 5 (11)</td>
<td>44 16 (36)</td>
</tr>
<tr>
<td>BCG-scar</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scar</td>
<td>236 14 (6)</td>
<td>80 2 (3)</td>
<td>89 5 (6)</td>
<td>67 16 (24)</td>
</tr>
<tr>
<td>No scar</td>
<td>262 18 (55)</td>
<td>125 6 (5)</td>
<td>101 7 (7)</td>
<td>36 5 (14)</td>
</tr>
</tbody>
</table>

- **Table 2 - QuantiFERON®TB Gold positive results distributed by TST-induration, gender, BCG-status, and origin**
Table 3 - Associations between background variables and positive QuantiFERON®TB Gold test

Results from multivariate regression analysis with positive QuantiFERON®TB Gold test as outcome variable among 511 tuberculin skin test positive children detected in the Norwegian school based screening programme in 2005-6. Final model; 505 observations, p-value< 0.001 and Log likelihood = -139.20399

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>QFT+</th>
<th>a OR</th>
<th>p-value for variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Origin of child</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western-born</td>
<td>280</td>
<td>16</td>
<td>ref</td>
<td>0.001</td>
</tr>
<tr>
<td>Second generation immigrant</td>
<td>108</td>
<td>6</td>
<td>0.9 (0.3 - 2.4)</td>
<td></td>
</tr>
<tr>
<td>First generation immigrant</td>
<td>123</td>
<td>22</td>
<td>3.3 (1.6 - 6.2)</td>
<td></td>
</tr>
<tr>
<td>Exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>478</td>
<td>37</td>
<td>ref</td>
<td>0.034</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>7</td>
<td>2.9 (1.1 - 7.6)</td>
<td></td>
</tr>
</tbody>
</table>