AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Original manuscript submission Blue-201502-0232OC R1

American Journal of Respiratory and Critical Care Medicine

Risk assessment of tuberculosis in contacts by interferon-γ release assays (IGRAs).

A TBNET study.

Authors: Jean-Pierre Zellweger[1], Giovanni Sotgiu[2], Michael Block[3], Simone Dore[2], Neus Altet[4,5], Rebecca Blunschi[6], Matthias Bogyi[7], Graham Bothamley[8], Christina Bothe[9], Luigi Codecasa[10], Patrizia Costa[11], Jose Dominguez[12], Raquel Duarte[13,14], Andreas Fløe[15], Isabelle Fresard[16], José-María García-García[17], Delia Goletti[18], Petra Halm[19], Doris Hellwig[20], Eveline Henninger[21], Helga Heykes-Uden[22], Liane Horn[23], Katarzyna Kruczak[24], Irene Latorre[12#], Geneviève Pache[25], Heidrun Rath[26], Felix C. Ringshausen[27], Asunción Seminario Ruiz[4§], Ivan Solovic[28], Maria-Luiza de Souza-Galvão[4], Ursula Widmer[29], Peter Witte[30], Christoph Lange[3,31-34] for the TBNET*

Authors affiliations: [1]Swiss Lung Association, Berne, Switzerland; [2]Epidemiology and Medical Statistics Unit, Department of Biomedical Sciences, University of Sassari-Research, Medical Education and Professional Development Unit, AOU Sassari, Sassari, Italy; [3]Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Germany; [4]Unitat de Tuberculosis Vall d'Hebron-Drassanes, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [5]Catalan Health Institute and Primary Healthcare University Research Institut-IDIAP Jordi Gol, Barcelona, Spain; [6]Swiss Lung Association Zürich, Switzerland; [7]Department of Child and Adolescent Medicine, Wilhelminenspital, Wien, Austria; [8]Homerton University Hospital, London, United Kingdom; [9]Public

Health Service Braunschweig, Brauschweig, Germany; [10]Regional TB Reference Centre, Villa Marelli Institute, Niguarda Ca'Granda Hospital, Milan, Italy; [11] Swiss Lung Association Ticino, Lugano, Switzerland; [12]Servei de Microbiologia, Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol, Universitat Autònoma de Barcelona, Ciber Enfermedades Respiratorias, Instituto de Salud Carlos III, Badalona, Spain; [13]Centro Hospitalar de Vila Nova de Gaia/Espinho, Portuguese Reference Centre for M/XDR-TB, Vila Nova de Gaia, Portugal; [14]Department of Clinical Epidemiology, Predictive Medicine and Public Health, Institute of Public Health University of Porto, Porto, Portugal; [15]Department of Respiratory Diseases and Allergy, Aarhus University Hospital, Aarhus, Denmark; [16]Centre antituberculeux, Geneva, Switzerland; [17]S. Neumología, Hospital San Agustín, Avilés, Asturias, Spain; [18]Translational Research Unit, Department of Epidemiology and Preclinical Research, "L. Spallanzani" National Institute for Infectious Diseases (INMI), Rome, Italy; [19]Public Health Service Wilhelmshaven, Wilhelmshaven, Germany; [20]Public Health Service Göttingen, Göttingen, Germany; [21]Swiss Lung Association Fribourg, Fribourg, Switzerland; [22]Public Health Service Hannover, Hannover, Germany; [23]Swiss Lung Association St. Gallen, St. Gallen, Switzerland; [24]Jagiellonian University Medical College, Department of Medicine, Cracow, Poland; [25]Swiss Lung Association Vaud, Lausanne, Switzerland; [26]Public Health Service Lübeck, Lübeck, Germany; [27]Department of Respiratory Medicine, Hannover Medical School, Hannover, Member of the German Center for Lung Research (DZL), Germany; [28]Catholic University Ruzomberok, Slovakia; [29]Swiss Lung Association Aargau, Aarau, Switzerland; [30]Public Health Service Minden, Minden, Germany; [31]International Health/Infectious Diseases, University of Lübeck, Germany; [32]Tuberculosis Unit, German Center for Infection Research (DZIF), Borstel, Germany; [33]Department of Medicine University of Namibia School of Medicine, Windhoek, Namibia; [34]Department of Medicine, Karolinska Institute, Stockholm, Sweden.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

***Additional contributors in the TBNET study group:**

Myriam Aeby, Swiss Lung Association Fribourg, Fribourg, Switzerland; Gilda Cuzzi, Enrio Girardi, Valentina Vanini, Eleonora Vecchi, from the Department of Epidemiology and Preclinical Research and Francesco Nicola Lauria and Marco Vecchi from the Clinical Department L. Spallanzani National Institute for Infectious Diseases (INMI), Rome, Italy; Maurizio Ferrarese, Alice Repossi, both Regional TB Reference Centre, Villa Marelli Institute, Niguarda Ca'Granda Hospital, Milan, Italy; Silke Gerdes, Public Health Service Hannover, Hannover, Germany; Martina Haller, Swiss Lung Association Aargau, Aarau, Switzerland; Andrea Glaewe, Center for Clinical Studies, Research Center Borstel, Germany; Ole Hilberg, Department of Respiratory Diseases, Aarhus University Hospital, Denmark; Jean-Paul Janssens, Centre antituberculeux, Geneva, Switzerland; Christof Rübsamen, Public Health Service Wilhelmshaven, Wilhelmshaven, Germany; Stephan Schlösser, Department of Occupational Medicine, University Hospital Bergmannsheil, Bochum, Germany; Manuel-Angel Villanueva- Montes, S. Neumología, Hospital San Agustín, Avilés, Asturias, Spain.

Present address: [§]Servei de Pneumologia, Hospital Universitari Arnau de Vilanova, Lleida, Spain. [#] Molecular Microbiology Department, Hospital Universitari Sant Joan de Déu, University of Barcelona, Barcelona, Spain.

Corresponding author contact information: Christoph Lange, Division of Clinical Infectious Diseases, Medical Clinic, Research Center Borstel, Parkallee 35, 23845 Borstel, Germany, T +49 4537 188-332 (-0), F +49 4537 188-313, clange@fz-borstel.de

Author contributions: Jean-Pierre Zellweger initiated the study. Jean-Pierre Zellweger and Christoph Lange made substantial contributions to the conception and design of the work, to the acquisition, analysis and interpretation of data for the work, wrote the draft of the manuscript, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. Giovanni Sotgiu and Simone Dore made substantial contributions to the interpretation of data for the work, performed statistical analysis, wrote the manuscript, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. Michael Block made a substantial contribution to the conception and design of the work and the management of the data, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. All other authors made a contribution to the acquisition of the data for the work, critically revised the manuscript for important intellectual content, and gave final approval of the current version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Sources of support: This study was investigator initiated and was funded by the German Ministry of Education and Research (Bundesministerium für Bildung und Forschung, BMBF, reference 01KI0784). CL is supported by the German Center of Infection Research (DZIF); FCR is supported by the German Center for Lung Research (DZL).

Running head: Risk of TB in recent contacts

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Descriptor number: 11.1 - Diagnosis of Tuberculosis or Latent Infection

Total word count: 3499

At a glance commentary

Scientific Knowledge on the Subject: Interferon-γ release assays (IGRAs) are routinely used for the diagnosis of latent infection with *M. tuberculosis*, but only few, mostly monocentric studies have evaluated the impact of IGRAs to predict the development of tuberculosis in recent contacts in low incidence countries of tuberculosis.

What This Study Adds to the Field: Progression towards tuberculosis is generally low in contacts of tuberculosis patients in Western Europe and poorly predicted by either IGRA. The number needed to treat to prevent one case of incident tuberculosis with chemotherapy among IGRA-positive close contacts was 37 with the T-SPOT.TB test and 38 with the QuantiFERON-Gold in-Tube test, respectively.

Online data supplements: This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournal.org.

Key words: Tuberculosis, TB, LTBI, IGRA, QuantiFERON, T-SPOT.TB

Abstract

Rational: Latent infection with *Mycobacterium tuberculosis* is defined by a positive interferon-γ release assay (IGRA) result in the absence of active tuberculosis.

Objectives: Only few, mostly monocentric studies have evaluated the role of IGRAs to predict the development of tuberculosis in recent contacts in low incidence countries of tuberculosis. We analyzed IGRA results and the effect of preventive chemotherapy on tuberculosis progression rates among recent contacts.

Methods: Results from contact investigations at 26 centers in 10 European countries including testing for latent infection with *Mycobacterium tuberculosis* by the QuantiFERON-Gold in-Tube (QFT) test or the T-SPOT.TB (TSPOT) were prospectively collected and analyzed.

Main Results: Among 5,020 contacts of 1,023 index cases, 25 prevalent secondary cases were identified at screening. Twenty-four incident cases occurred among 4,513 contacts during 12,326 years of cumulative follow-up. In those with a positive IGRA result, tuberculosis incidence was 0.2 (QFT) and 0 (TSPOT) per 100 patient years when contacts received preventive chemotherapy versus 1.2 (QFT) and 0.8 (TSPOT) per 100 patient years in those not treated (38 and 37 patients needed to be treated to prevent one case, respectively). Positive and negative predictive values were 1.9% (95%CI 1.1-3.0) and 99.9% (95%CI 99.7-100) for the QFT and 0.7% (95%CI 0.1-2.6) and 99.7% (95%CI 99.1-99.9) for the TSPOT.

Conclusions: Tuberculosis rarely developed among contacts and preventive chemotherapy effectively reduced the tuberculosis risk among IGRA-positive contacts. Although the negative predictive value of IGRAs is high, the risk for the development of tuberculosis is poorly predicted by these assays.

.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Introduction

Contact investigation is an important part of the global policy for the control of tuberculosis (1). Especially in geographical areas of the world with a low tuberculosis incidence, e.g. Western Europe, contact investigation is part of the procedures recommended by national guidelines for tuberculosis control (2). Contact investigation detects secondary cases of tuberculosis who developed the disease in the same population. In addition, it aims to identify contact persons latently infected with *Mycobacterium tuberculosis* who are at risk for later development of tuberculosis and who may benefit from a preventive treatment and/or close clinical surveillance (3).

In healthy individuals who are latently infected with *Mycobacterium tuberculosis* direct detection of viable mycobacteria is not possible by current routine microbiological culture or molecular methods. Therefore, latent infection with *M. tuberculosis* is ascertained indirectly by the evaluation of the presence of an adaptive immune response to antigens of *M. tuberculosis* in the absence of active disease (4). Adaptive immune response is classically assayed by the tuberculin skin test (5-7), and more recently, by interferon-γ release assays (IGRAs; QuantiFERON-Gold in-Tube (QFT) test, Qiagen, Hilden, Germany or T-SPOT.TB (TSPOT) test, OxfordImmunotec, Abingdon, UK) (8).

A large number of publications describe the use of IGRAs for the diagnosis of latent infection with *M. tuberculosis*. However, only few studies have evaluated their role in predicting the development of tuberculosis in recent contacts in low tuberculosis incidence countries (9-12). As these studies were mono-centric, their results may not be representative.

To gain more generalizable data and to ascertain the role of IGRAs in predicting the risk for tuberculosis in recent contacts the Tuberculosis Network European Trialsgroup (TBNET; www.tb-

net.org) (13) performed an international, multi-center, observational cohort study in Western Europe.

Methods

Study population and data collection

Contacts of tuberculosis index cases for whom an IGRA (QFT or TSPOT) was performed as part of the routine screening procedure according to national guidelines (**Table S1**) were consecutively recruited between April 2009 and March 2011 from European healthcare facilities and followed up for the occurrence of tuberculosis until March 2013. Contacts living in the same household as the index patient were defined as *close contacts/relatives*. Contacts with short but intensive contact not living in the same household were defined as *close contacts/not relatives*. Those not belonging to these categories but having contact to an index patient during work, school activities, leisure, or travel for more than 8 hours were defined as *prolonged contacts*. When contact investigation was considered to be necessary by the responsible public health authorities, although the intensity and duration of exposure could not be verified, contacts were defined as *other contacts*.

Data on demographic, epidemiological, and clinical parameters, data related to the conditions of *M. tuberculosis* exposure, IGRA test results, and the decision for preventive chemotherapy were electronically recorded on a structured questionnaire, pseudonymized and transmitted to the coordinating center (Research Center Borstel, Germany), where potential inconsistencies or missing entries were assessed. Completion of follow up data included information whether the patient was still alive or died, was lost to follow-up, was transferred out, or whether she/he developed tuberculosis after 24 months following enrollment in the study. Follow-up information on the occurrence of tuberculosis after initial testing was actively carried out by the participating

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

centers; however, the proportion of contacts completing preventive chemotherapy was not recorded.

When tuberculosis cases were notified among the contacts before the median interval between index case notification and contact case notification (*i.e.*, 81 days) they were considered to be prevalent; the others were considered to be incident. The ethics committee of the coordinating center (University of Lübeck, Germany) approved the study.

Statistical analysis

According to the IGRA results (*i.e.*, positive, negative, and indeterminate) demographic, epidemiological, and clinical variables were analyzed using relative frequencies (percentages). The risk of development of tuberculosis during the follow-up in patients exposed and not exposed to preventive chemotherapy was measured by computing the incidence density and its 95% confidence intervals (CI).

The diagnostic test performances of QFT and TSPOT test were evaluated by calculating sensitivity, specificity, positive and negative likelihood ratios and positive and negative predictive values. Logistic regression analyses were performed using different cut-offs in order to prove the best value for tuberculosis diagnosis for both QFT (0.35, 0.7, 1.0, 4.0 IU IFN-γ /ml) and TSPOT (5, 9, 20 spot forming cells (sfc)/250,000).

Statistical analysis was carried out using STATA®13 (StataCorp, College Station, TX, USA).

Results

Study population

Twenty-six centers in 10 European countries (**Table S2**) were enrolled in the study and collected data on 1,023 index cases and 5,020 contacts (**Figure 1**). Mean age of the index cases was 41.0 years (standard deviation (SD) 19.5). Five hundred and ninety-nine (58.6%) of the index cases were male. The median (interquartile range) number of contacts per index case was 2 (1-4). For 3,895 (77.6%) of the contacts IGRA testing was performed by QFT and in 1,125 (22.4%) by TSPOT. Among all contacts, 1,367/5,020 (27.2%) had a positive IGRA test result (1,068/3,895, 27.4%, for QFT and 299/1,125, 26.6%, for TSPOT). The proportion of positive test results was highest in the age group 5 to 14 years (43.1%), among contacts of smear-positive index cases (41.8%) and among close relatives (45.4%). Indeterminate test results were observed in only 27/5,020 tests (0.5%) (**Figure 1, Table 1**).

Prevalent and incident cases

The median interval between index case notification and contact case notification was 81 days. Within this interval of contact screening, 25/5,020 (0.5%) prevalent cases of tuberculosis were identified. Of those 18/23 (78.3%) had symptoms or an abnormal chest X-ray at the time of screening (for 2 cases information was not available). In addition, 24/4,513 (0.5%) cases of secondary incident tuberculosis occurred during the follow-up period, with a range of 84-968 days after the screening of the index case, (**Table 2**) among the 89.9% contacts for whom complete follow-up data were available (**Figure 1, Table S3**). Thirty-one cases of tuberculosis occurred among 1,022 close relatives (3%) against 18 among 3,998 other contacts (0.5%). Twenty-one cases occurred among 495 contacts aged 0 to 14 years (4,2%), against 28 among 4,525 older contacts (0.6%).

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Preventive chemotherapy was offered to 1,485 contacts and initiated in 971 (793/1,367, 58.0%, with a positive IGRA and 176/3,653, 4.8%, with a negative IGRA). Contacts with a negative IGRA result were more likely to receive preventive chemotherapy when they were less than 15 years of age ($p<0.0001$), closely related to the index case ($p<0.0001$) or foreign born ($p<0.003$).

Progression rates to tuberculosis

The progression rate to tuberculosis was generally low (**Table 3**). Overall 14/421 (3.3%) QFT positive contacts and 2/73 (2.7%) TSPOT positive contacts without preventive chemotherapy developed tuberculosis during follow up of a median of 2.5 years (interquartile range (IQR): 1.9-3.5). Among contacts with a positive QFT test at screening who started preventive chemotherapy 3/481 cases (0.6%) of tuberculosis occurred, after 47, 95, and 125 days of therapy, respectively. In contrast 3/2,419 (0.1%) and 2/722 (0.3%) cases of tuberculosis occurred among QFT and TSPOT negative individuals in the absence of preventive chemotherapy. No cases of tuberculosis occurred during follow-up in QFT (n=104) or TSPOT (n=58) negative individuals and TSPOT (n=208) positive individuals who received preventive chemotherapy.

Predictive values

While the negative predictive values were 99.9% (95% CI: 99.7-100.0) for the QFT and 99.7% (95%CI: 99.1-99.9) for the TSPOT, positive predictive values were only 1.9% (95%CI 1.1-3.0) for the QFT and 0.7% (95%CI 0.1-2.6) for the TSPOT (**Table 4**). Both IGRAs poorly predicted the development of tuberculosis.

Number needed to treat

The number needed to treat to prevent a case of tuberculosis in case of a positive IGRA was 38 and 37 for QFT and the TSPOT, respectively; in case of a negative IGRA the number needed to treat was 807 and 361 for QFT and the TSPOT, respectively (**Table 3**).

Cut-offs for positive IGRA test results

We ascertained whether the cut-offs for the concentration of IFN-γ in the QFT or of the number of spot-forming-cells (sfc) in the TSPOT that define a positive test result had an influence on the ability to predict tuberculosis. The incidence ratios varied between 0.017 and 0.024 when cut-offs between the 0.35 and >10 IU/ml for the IFN-γ concentration in the QFT were tested. The incidence ratio for a QFT test result below 0.35 IU IFN-γ /ml was 0.001.

Similarly, various cut-offs between >4 sfc/250,000 and >50 sfc/250,000 in the TSPOT had comparable incidence ratios for tuberculosis, ranging between 0.007 and 0.01, while the incidence ratio for tuberculosis for a cut-off <5 sfc/250,000 was 0.003. Logistic regression analysis demonstrated that the current QFT cut-off is the best predictor for progression to active tuberculosis, showing an area under the curve (AUC) of 0.779 (P< 0.0001). The TSPOT cut-off of 5 sfc/250,000 showed the best AUC (*i.e.*, 0.615), although no TSPOT cut-offs were statistically significant (**Table S4**).

Discussion

We evaluated the role of IGRAs in predicting the risk for tuberculosis in contacts in an international, multi-center prospective, observational cohort study carried out in Western Europe.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

The main findings from this study are that the risk of tuberculosis is comparatively low in tuberculosis contacts in this geographic region irrespectively of the IGRA test result, that preventive chemotherapy is highly effective to reduce the risk of tuberculosis in contacts with a positive IGRA result and that IGRAs predict poorly the development of tuberculosis during the first 2 years after screening. Our results highlight the limitations of IGRAs to function as a basis for the decision to initiate preventive chemotherapy in tuberculosis contacts or other populations at risk for the development of tuberculosis in low tuberculosis incidence countries (14-17).

This prospective observation of 5,020 tuberculosis contacts in 26 centers in 10 European countries demonstrated that the proportion of infected contacts, defined by a positive IGRA test result, is approximately one quarter of the population screened but that the occurrence of tuberculosis during the follow-up time of 2.5 years on average is actually a rare event. Prevalent and incident tuberculosis were observed more frequently among close contacts, among contacts of smear-positive cases and among young contacts below the age of 14 years. More than 96.5% of contacts with a positive IGRA result did not develop tuberculosis, even in the absence of preventive chemotherapy. However, contacts with a positive IGRA result have a relatively higher risk of tuberculosis than contacts with a negative result. Despite the limited impact, immunodiagnostic testing for latent infection with *M. tuberculosis* is still the most efficient way to reduce the number needed to treat to prevent a case of tuberculosis in contacts (18). The prescription of preventive treatment in contacts decreased the risk of subsequent tuberculosis (from 1.20 to 0.23/100 persons-years for contacts with a positive QFT and from 0.81 to 0/100 persons-years for contacts with a positive TSPOT), however confounding by indication could not be excluded by the study design.

Several studies assessed the proportion of tuberculosis and latent infection with *M. tuberculosis* among contacts of index cases. A large meta-analysis concluded that the proportion of prevalent

cases of tuberculosis among contacts was 4.5% and the proportion of latent infection (defined by a positive tuberculin skin test) was 51.4% (19). This meta-analysis did not evaluate the number of incident cases who were diagnosed after screening. A more recent meta-analysis found similar rates of tuberculosis and latent infection in contacts living in low-income (and high-incidence) countries, with 3.1% and 51.5% prevalent tuberculosis and latent infection respectively, but lower rates in high-income (and low prevalence) countries, with 1.4% prevalent cases of tuberculosis and 28.1% latent infection (20). The proportion of prevalent tuberculosis and latent infection was higher among contacts of smear-positive index cases (20). Studies from single centers or regions in countries with low/intermediate incidence of tuberculosis demonstrated comparable rates of prevalent tuberculosis and latent infection among contacts to our study (1.5%/35.0% in Australia (21); 0.8%/18.1% in Portugal (22); 1.0%/27.8% (23) and 2.0%/36.0% in the US (24), respectively)

We found a similar proportion of prevalent (0.5%) and incident (0.6%) secondary tuberculosis. The distribution of prevalent and incident cases detected in the course of contact tracing depends on the interval definition of prevalence following screening and the observation period. In a recent study from the Netherlands prevalence for secondary cases was defined as the occurrence within 180 days of screening (11). Applying that definition to the secondary cases in our cohort, the number of prevalent cases would have been >2 times the number of incident cases (33 prevalent cases and 16 incident cases). The decrease in the number of incident cases among contacts with a positive IGRA result who received preventive treatment (from 3.2% to 0.4%) is comparable to the decrease observed in a study from the US (from 1.5% to 0.4%) (23).

The contacts of extra-European origin, born in countries with a prevalence of tuberculosis higher than in Western Europe, had a higher rate of IGRA positivity (up to 50% among Africans), indicating that a large proportion of the positive test results among the contacts may be the consequence of a remote exposure in the country of birth and not the result of the current

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

contact. A study among US army recruits demonstrated that subjects born in a country with a high incidence of tuberculosis had a much higher frequency of positive TST (23.8%) and IGRA (9.5% for QFT and 11.1% for TSPOT) than recruits born in a low-incidence country (1.1., 1.6 and 1.4% respectively) (25). This highlights the difficulty in the interpretation of test results among migrants, who may represent a large proportion of index cases and contacts in some regions in Europe (26, 27).

This study underlines the fact that investigation of the close contacts of a case of tuberculosis reveals additional cases of active tuberculosis who will benefit from a full course of treatment. Using a higher cut-off for the definition of latent infection with *M. tuberculosis* did not substantially change the risk for the development of tuberculosis in this study. This is an important finding, which contrasts with previous results from Germany suggesting that raising the cut-off of the QFT could result in an improvement in the prognostic value of this test (9, 12).

As half of the tuberculosis cases observed among contacts (25/49) were detected during the first 81 days following the notification of the index case, contact investigation has an important role in detecting cases who are already active and may further spread *M. tuberculosis*. For the detection of such cases, the screening with IGRA is of limited sensitivity and specificity and one must rely on the history of complaints, the clinical examination and the chest radiograph of suspected cases. In some settings, where the contact investigation was performed several weeks or months after the notification of the index case, some incident cases were detected at screening. In such case also, the screening with IGRA was not helpful but the detection of tuberculosis relied on clinical and radiological signs. Screening with IGRAs seems only helpful in contacts without symptoms and with a normal chest radiograph at the time of screening, in order to identify those with recent latent infection who have the greatest benefit from a preventive therapy. This also highlights the fact that screening contacts for latent infection should be performed soon after the notification of

index cases, preferably 8 weeks following the last contact to allow generation of an adaptive *M. tuberculosis*-specific immune response (28). We suspect that in some cases, late screening was performed because some contacts developed symptoms of tuberculosis in the meantime.

In practice, among contacts with a positive IGRA, the risk of future tuberculosis is low but can be further reduced by a preventive treatment. Among contacts with a negative IGRA at screening without additional risk factors for tuberculosis (like young age or immunosuppression), one may confidently assume a negligible risk of future tuberculosis, unless they are re-exposed and infected later. In our study, among 5 contacts with a negative IGRA result at screening who developed tuberculosis, 2 were young children (2 and 8 years), one adult was immunocompromized. Among the 5 cases, 2 adults and one child were diagnosed with tuberculosis between one and three years after the notification of the index case, so that we cannot exclude another exposure or an additional risk factor.

The risk for tuberculosis observed in this study was lower than in some previous monocentric studies (9, 10) but similar to others (10). Globally, the percentage of cases observed among contacts (1% within two years) was lower than the traditionally mentioned figures of 10% (29), half of it during the initial period after screening. The risk observed among contacts with a positive IGRA but no active tuberculosis at screening and who did not receive preventive chemotherapy (3.2% for the QFT and 2.7 for the TSPOT) is similar to those reported before (30). We may speculate that in some studies the population of contacts included more migrants from high-prevalence countries with a corresponding higher rate of latent infection and higher risk of reactivation of tuberculosis (27), whereas in our study the vast majority of contacts (3885/5020) were of European origin. A recent study from a single center in the Netherlands reported a global cumulative risk of tuberculosis (prevalent and incident) of 9.5% among 4774 contacts within 5 years or a risk of incident tuberculosis of 2,4% for contacts with LTBI at screening who did not start

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

a preventive chemotherapy (11). Progression rates to tuberculosis in that study were very similar to our data although the impact of preventive treatment on the risk for tuberculosis was less obvious.

Our results confirm previous studies demonstrating that prescribing preventive treatment in contacts latent infection with *M. tuberculosis* decreased the risk of future tuberculosis (31-33), despite a comparatively high number needed to treat to prevent one case. As we do not know for all individuals if the preventive treatment was really followed until the scheduled end in the contacts who did not develop tuberculosis, this assumption is probably an underestimation and the protective effect may be higher. Only 3 among 24 contacts who developed incident tuberculosis were prescribed a preventive treatment, which was followed for 47, 95 and 125 days, respectively, and was likely not sufficient to offer a significant protective effect. The other 21 contacts who developed tuberculosis did not receive preventive chemotherapy despite a positive IGRA test result. This clearly underlines the fact that persons with a documented tuberculosis contact and a positive IGRA result may benefit from a preventive treatment. Recent guidelines from the WHO propose to offer a preventive treatment to persons living in countries with a low or medium incidence of tuberculosis who have latent tuberculosis infection and additional risk factors for the development of tuberculosis, like HIV infection, recent contact with a case of pulmonary tuberculosis, TNF-antagonists treatment, dialysis, silicosis or organ or hematologic transplantation (1, 34). The fact that only 58% of contacts with recent exposure and latent infection with *M. tuberculosis* received a preventive treatment illustrates poor adherence to previous recommendations. Recent surveys from Germany demonstrated that in some federal states of this country less than 30 % of contacts with a positive IGRA test result received preventive chemotherapy (9, 12, 35), whereas in other settings the adherence after prescription

may reach up to 80% (36). It is hoped that rates of preventive treatment for latent infection with *M. tuberculosis* will increase now that new guidelines have been issued by the WHO (1).

This study has several limitations. One of them is the fact that the procedures for contact investigations followed different national recommendations and were not standardized. Therefore, the results are not fully comparable between the centers and rather represent operational data. Similarly, we could not control for the laboratory procedures and cannot exclude technical differences in the IGRA procedure between the centers. Furthermore, although the centers were instructed to register all contacts for each index case, we cannot exclude a selection bias in that some centers probably tended to include in priority contacts with a positive IGRA result. This may have induced an overestimation of the risk of subsequent tuberculosis but does not change the magnitude of the effect of preventive treatment. Although 26 centers in 10 different European countries participated in this study, centers were selected on their agreement to participate in the country and may not be representative for their country or other countries in Western Europe.

On the other side, the strength of this study is its multi-centric and multi-national character that allows representativeness beyond single centers or regions, the large population of contacts, and the high proportion of contacts with follow-ups (in spite of the fact that many contacts were foreign-born migrants who may move from one region to another during the follow-up).

In conclusion, we found that progression towards tuberculosis is generally low in contacts of tuberculosis patients in Western Europe and poorly predicted by either IGRA, and that in contacts without signs of infection this risk is even lower. Although preventive chemotherapy effectively reduced the risk for tuberculosis among IGRA-positive contacts, identification of individuals at risk for the development of tuberculosis could be improved substantially by more predictive biomarkers.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Acknowledgement: The authors thank Martina Sester PhD, Homburg, Germany, for a critical manuscript review.

References

1. World Health Organization. Guidelines on the management of latent tuberculosis infection. Geneva, Switzerland: WHO; 2014 No. WHO/HTM/TB/2015.01.
2. Bothamley GH, Ditiu L, Migliori GB, Lange C. Active case finding of tuberculosis in Europe: a Tuberculosis Network European Trials Group (TBNET) survey. *Eur Respir J* 2008; 32: 1023-1030.
3. Erkens CG, Kamphorst M, Abubakar I, Bothamley GH, Chemtob D, Haas W, Migliori GB, Rieder HL, Zellweger JP, Lange C. Tuberculosis contact investigation in low prevalence countries: a European consensus. *Eur Respir J* 2010; 36: 925-949.
4. Mack U, Migliori GB, Sester M, Rieder HL, Ehlers S, Goletti D, Bossink A, Magdorf K, Hîlscher C, Kampmann B, Arend SM, Detjen A, Bothamley G, Zellweger JP, Milburn H, Diel R, Ravn P, Cobelens F, Cardona PJ, Kan B, Solovic I, Duarte R, Cirillo DM, Lange C. LTBI: latent tuberculosis infection or lasting immune responses to M. tuberculosis ? A TBNET consensus statement. *EurRespirJ* 2009; 33: 956-973.
5. von Pirquet C. Die Allergieprobe zur Diagnose der Tuberkulose im Kindesalter. *Wien Med Wochenschr* 1907; 57: 1370-1374.
6. Mendel F. Die von Pirquetsche Hautreaktion und die intravenîse Tuberkulinbehandlung. *Med Klin* 1908; (No. 12): 402-404.
7. Mantoux C. L'intradermo-reaction de la tuberculine et son interpretation clinique. *Presse Med* 1910; (no 2): 10-13.
8. Salje H, Andrews JR, Deo S, Satyanarayana S, Sun AY, Pai M, Dowdy DW. The importance of implementation strategy in scaling up Xpert MTB/RIF for diagnosis of tuberculosis in the Indian health-care system: a transmission model. *PloS Med* 2014; e1001674: doi:10.1371/journal.pmed.1001674.
9. Diel R, Loddenkemper R, Niemann S, Meywald-Walter K, Nienhaus A. Negative and positive predictive value of a whole-blood interferon-γ release assay for developing active tuberculosis: an update. *Am J Respir Crit Care Med* 2011; 183: 88-95.
10. Haldar P, Thuraisingam H, Patel H, Pereira N, Free RC, Entwisle J, Wiselka M, Hoskyns EW, Monk P, Barer MR, Woltmann G. Single-step QuantiFERON screening of adult contacts: a prospective cohort study of tuberculosis risk. *Thorax* 2013; 68: 240-246.
11. Sloot R, Schim van der Loeff MF, Kouw PM, Borgdorff MW. Yield of tuberculosis contact investigations in Amsterdam: opportunities for improvement. *Eur Respir J* 2014; 44: 714-724.
12. Geis S, Bettge-Weller G, Goetsch U, Bellinger O, Ballmann G, Hauri AM. How can we achieve better prevention of progression to tuberculosis among contacts? *Eur Respir J* 2013; 42: 1743-1746.
13. Giehl C, Lange C, Duarte R, Bothamley G, Gerlach C, Cirillo DM, Wagner D, Kampmann B, Goletti D, Juers T, Sester M. TBNET - Collaborative research on tuberculosis in Europe. *Eur J Microbiol Immunol* 2012; 2: 264-274.
14. Sester M, van Leth F, Bruchfeld J, Bumbacea D, Cirillo DM, Dilektasli AG, Dominguez J, Duarte R, Ernst M, Eyuboglu FO, Gerogianni I, Girardi E, Goletti D, Janssens JP, Julander I, Lange B, Latorre I, Losi M, Markova R, Matteelli A, Milburn H, Ravn P, Scholman T, Soccal PM, Straub M, Wagner D, Wolf T, Yalcin A, Lange C, Tbnet. Risk Assessment of Tuberculosis in Immunocompromised Patients. A TBNET Study. *Am J Respir Crit Care Med* 2014; 190: 1168-1176.
15. Dorman SE, Belknap R, Graviss EA, Reves R, Schluger N, Weinfurter P, Wang Y, Cronin W, Hirsch-Moverman Y, Teeter LD, Parker M, Garrett DO, Daley CL, Tuberculosis Epidemiologic Studies C. Interferon-gamma release assays and tuberculin skin testing for diagnosis of latent tuberculosis infection in healthcare workers in the United States. *Am J Respir Crit Care Med* 2014; 189: 77-87.
16. Slater ML, Welland G, Pai M, Parsonnet J, Banaei N. Challenges with QuantiFERON-TB Gold assay for large-scale, routine screening of U.S. healthcare workers. *Am J Respir Crit Care Med* 2013; 188: 1005-1010.
17. Gutsfeld C, Olaru ID, Vollrath O, Lange C. Attitudes about Tuberculosis Prevention in the Elimination Phase: A Survey among Physicians in Germany. *PLoS One* 2014; 9: e112681.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

18. Diel R, Wrighton-Smith P, Zellweger JP. Cost-effectiveness of interferon-gamma release assay testing for the treatment of latent tuberculosis. *Eur Respir J* 2007; 30: 321-332.
19. Morrison J, Pai M, Hopewell PC. Tuberculosis and latent tuberculosis infection in close contacts of people with pulmonary tuberculosis in low-income and middle-income countries: a systematic review and meta-analysis. *Lancet Infect Dis* 2008; 8: 359-368.
20. Fox GJ, Barry SE, Britton WJ, Marks GB. Contact investigation for tuberculosis: a systematic review and meta-analysis. *Eur Respir J* 2013; 41: 140-156.
21. Dobler CC, Marks GB. Risk of tuberculosis among contacts in a low-incidence setting. *Eur Respir J* 2013; 41: 1459-1461.
22. Mendes MA, Gaio R, Reis R, Duarte R. Contact screening in tuberculosis: can we identify those with higher risk? *Eur Respir J* 2013; 41: 758-760.
23. Anger HA, Proops D, Harris TG, Li J, Kreiswirth BN, Shashkina E, Ahuja SD. Active case finding and prevention of tuberculosis among a cohort of contacts exposed to infectious tuberculosis cases in New York City. *Clin Infect Dis* 2012; 54: 1287-1295.
24. Marks SM, Taylor Z, Qualls NL, Shrestha-Kuwahara RJ, Wilce MA, Nguyen CH. Outcomes of contact investigations of infectious tuberculosis patients. *Am J Respir Crit Care Med* 2000; 162: 2033-2038.
25. Mancuso JD, Tribble D, Mazurek GH, Li Y, Olsen C, Aronson NE, Geiter L, Goodwin D, Keep LW. Impact of targeted testing for latent tuberculosis infection using commercially available diagnostics. *Clin Infect Dis* 2011; 53: 234-244.
26. Kik SV, Franken WPJ, Arend SM, Mensen M, Cobelens FGJ, Kamphorst M, van Dissel JT, Borgdorff MW, Verver S. Interferon-gamma release assays in immigrant contacts and effect of remote exposure to Mycobacterium tuberculosis *IntJTubercLung Dis* 2009; 13: 820-828.
27. Pareek M, Bond M, Shorey J, Seneviratne S, Guy M, White P, Lalvani A, Kon OM. Community-based evaluation of immigrant tuberculosis screening using interferon gamma release assays and tuberculin skin testing: observational study and economic analysis. *Thorax* 2013; 68: 230-239.
28. Lee SW, Oh DK, Lee SH, Kang HY, Lee CT, Yim JJ. Time interval to conversion of interferon-gamma release assay after exposure to tuberculosis. *Eur Respir J* 2011; 37: 1447-1452.
29. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and adolescence. *Am J Epidemiol* 1974; 99: 131-138.
30. Rangaka MX, Wilkinson KA, Glynn JR, Ling D, Menzies D, Mwansa-Kambafwile J, Fielding K, Wilkinson RJ, Pai M. Predictive value of interferon-g release assays for incident active tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2011; 12: 45-55.
31. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Adv Tuberc Res* 1969; 17: 28-106.
32. Landry J, Menzies D. Tuberculosis. State of the Art series. Number 2 in the series. Preventive chemotherapy. Where has it got us? Where to go next? *Int J Tuberc Lung Dis* 2008; 12: 1352-1364.
33. Leung CC, Rieder HL, Lange C, Yew WW. Treatment of latent infection with Mycobacterium tuberculosis: update 2010. *Eur Respir J* 2011; 37: 690-711.
34. Goletti D, Sanduzzi A, Delogu G. Performance of the tuberculin skin test and interferon-gamma release assays: an update on the accuracy, cutoff stratification, and new potential immune-based approaches. *J Rheumatol Suppl* 2014; 91: 24-31.
35. Robert-Koch-Institute. Anwendung und Akzeptanz der präventiven Behandlung bei Kindern mit Kontakt zu Tuberkulose-Erkrankte. *Epidemiol Bull Nr 12* 2013.
36. Sarivalasis A, Bodenmann P, Langenskiold E, Lutchmaya-Flick C, Daher O, Zellweger JP. High rate of completion of preventive therapy for latent tuberculosis infection among asylum seekers in a Swiss Canton. *Swiss Med Wkly* 2013; 143: w13860.

Figures and Tables

Figure 1 legend: Flow chart of test results and occurrence of secondary cases with tuberculosis (TB) in tuberculosis contacts included in the study. Secondary cases were defined as prevalent, if they were detected within the median interval between index case notification and contact case notification of 81 days found in this study. QFT = Quantiferon-Gold in-Tube test; TSPOT = T-SPOT.TB test; TB = tuberculosis.

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Table 1: IGRA results among contacts by demographic characteristics

	IGRA neg.	IGRA pos.	IGRA ind.	Total. n (%)
Total. n (%)	3626 (72.2)	1367 (27.2)	27 (0.5)	5020 (100.0)
Sex of contact. n (col %) (row %)				
Female	2027 (55.9)(74.5)	678 (49.6)(24.9)	16 (59.3)(0.6)	2720 (54.2)
Male	1599 (44.1)(69.5)	689 (50.4)(30.0)	11 (40.7)(0.5)	2299 (45.8)
Age group. n (col %) (row %)				
0- to 4-yr-old	73 (2.0)(76.0)	23 (1.7)(24.0)	0 (0.0)(0.0)	96 (1.9)
5- to 14-yr-old	226 (6.2)(56.6)	172 (12.6)(43.1)	1 (3.7)(0.3)	399 (7.9)
15- to 34-yr-old	1561 (43.0)(75.9)	481 (35.1)(23.4)	15 (55.6)(0.7)	2057 (41.0)
35- to 64-yr-old	1613 (44.5)(73.0)	585 (42.8)(26.5)	9 (33.3)(0.4)	2207 (44.0)
65-yr-old and older	138 (3.8)(58.2)	97 (7.1)(40.9)	2 (7.4)(0.8)	237 (4.7)
Unknown	15 (0.4)(62.5)	9 (0.7)(37.5)	0 (0.0)(0.0)	24 (0.5)
Type of contact. n (col %) (row %)				
Close. relatives	549 (15.1)(53.7)	464 (33.9)(45.4)	9 (33.3)(0.9)	1022 (20.4)
Close not related but intensive	711 (19.6)(70.3)	296 (21.7)(29.3)	5 (18.5)(0.5)	1012 (20.2)
Prolonged. work	1792 (49.4)(77.8)	502 (36.7)(21.8)	9 (33.3)(0.4)	2303 (45.9)
Other	573 (15.8)(84.1)	104 (7.6)(15.3)	4 (14.8)(0.6)	681 (13.6)
Unknown	1 (0.0)(50.0)	1 (0.1)(50.0)	0 (0.0)(0.0)	2 (0.0)
Place of birth of contacts. n (col %) (row %)				
Africa	120 (3.3)(48.8)	124 (9.1)(50.4)	2 (7.4)(0.1)	246 (4.9)
Americas	219 (6.0)(61.3)	134 (9.8)(37.5)	4 (14.8)(1.1)	357 (7.1)
Asia	299 (8.3)(64.4)	161 (11.8)(34.7)	4 (14.8)(0.9)	464 (9.2)
Europe	2938 (81.0)(75.6)	931 (68.1)(24.0)	16 (59.3)(0.4)	3885 (77.4)
Oceania	2 (0.1)(100.0)	0 (0.0)(0.0	0 (0.0)(0.0	2 (0.0)
Unknown	48 (1.3)(72.7)	17 (1.2)(25.8)	1 (3.7)(1.5)	66 (1.3)
Screening test. n (col %) (row %)				
QFT	2803 (77.3)(71.9)	1068 (78.1)(27.4)	24 (88.9)(0.6)	3895 (77.6)
TSPOT	823 (22.7)(73.1)	299 (21.9)(26.6)	3 (11.1)(0.3)	1125 (22.4)
Preventive chemotherapy. n (col %) (row %)				
Not initiated	3127 (86.2)(88.5)	383 (28.0)(10.8)	23 (82.1)(0.7)	3533 (70.4)
Initiated	499 (13.8)(33.6)	982 (71.8)(66.1)	4 (14.8)(0.3)	1485 (29.6)

Unknown	0 (0.0)(0.0)	2 (0.2)(100.0)	0 (0.0)(0.0)	2 (0.0)
Preventive therapy. n (col %) (row %)				
Not received	3414 (94.2)(85.1)	574 (42.0)(14.3)	25 (92.6)(0.6)	4013 (79.9)
Received	176 (4.9)(18.1)	793 (58.0)(81.7)	2 (7.4)(0.2)	971 (19.3)
Unknown	36 (1.0)(100.0)	0 (0.0)(0.0)	0 (0.0)(0.0)	36 (0.7)
Prevalence TB. n (col %) (row %)				
Non-prevalent cases	3624 (99.9)(72.5)	1344 (98.2)(26.9)	27 (100.0)(0.6)	4995 (99.5)
Prevalent cases	3 (0.1)(12.5)	22 (1.8)(87.5)	0 (0.0)(0.0)	25 (0.5)

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Table 2: Characteristics of 24 incident patients who developed tuberculosis during follow up

Time since index case notification	Age	Sex	Country of origin	Country of residence	Contact type	Index case	PT	QFT (IU/ml)	TSPOT (sfc/250.000)
84	8	female	Spain	Spain	relative	sputum smear+	no	2.17	-
84	43	female	United Kingdom	United Kingdom	relative	sputum smear+	no	0.38	-
87	21	male	Latvia	United Kingdom	work	sputum smear+	no	13.99	-
99	1	female	Poland	Poland	relative	sputum smear+	no	21.94	-
112	14	female	United Kingdom	United Kingdom	relative	sputum smear+	yes	12.07	-
125	47	male	Nicaragua	Spain	work	sputum smear+	yes	11.05	-
133	2	male	United Kingdom	United Kingdom	close	sputum smear+	yes	0.24	-
155	56	male	Poland	Poland	close	sputum smear -/culture+	no	5.66	-
182	49	male	Switzerland	Switzerland	relative	sputum smear+	no	-	0
231	11	male	China	Spain	close	sputum smear+	no	3.67	-

261	37	female	Sri Lanka	Switzerland	relative	sputum smear+	no	-	8
331	13	female	Pakistan	Spain	relative	sputum smear+	no	1.46	-
332	11	female	Pakistan	Spain	relative	sputum smear+	no	13.24	-
343	70	female	Bangladesh	United Kingdom	relative	sputum smear+	no	0.08	-
344	29	female	Poland	Poland	relative	sputum smear -/culture+	no	21.94	-
372	60	male	Poland	Poland	work	sputum smear+	no	0.8	-
394	15	female	Pakistan	Spain	relative	sputum smear+	no	14.79	-
400	36	male	United Kingdom	United Kingdom	other	sputum smear+	no	2.045	-
427	31	female	Poland	Poland	relative	sputum smear -/culture+	no	0.52	-
444	26	female	Somalia	United Kingdom	other	sputum smear -/culture-	no	0.07	-
476	24	female	Pakistan	Spain	relative	sputum smear+	no	3.09	-
810	25	male	Eritrea	Switzerland	relative	sputum	no	-	50

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

						smear+			
882	17	male	Bolivia	Spain	work	sputum smear+	no	1.08	-
968	8	female	France	Spain	close	sputum smear+	no	-	1

Table 3. Development of tuberculosis during follow-up depending on IGRA test result and preventive chemotherapy.

	Test result	n	Prophylaxis	TB cases	Progression rate (%)	Person time (Years)	Incidence/100 py	Number needed to treat
QFT	negative	2419	no	3	0.12	6349.8	0.047	807
	negative	104	yes	0	0	326.4	0	
	positive	421	no	14	3.33	1169.1	1.198	38
	positive	481	yes	3	0.62	1296.5	0.231	
TSPOT	negative	722	no	2	0.28	1790.1	0.112	361
	negative	58	yes	0	0	316.1	0	
	positive	73	no	2	2.73	247.8	0.807	37
	positive	208	yes	0	0	829.7	0	

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Table 4: Diagnostic performance of the Quantiferon-Gold in-Tube (QFT) test and the T-SPOT.TB (TSPOT) test for active tuberculosis in contacts.

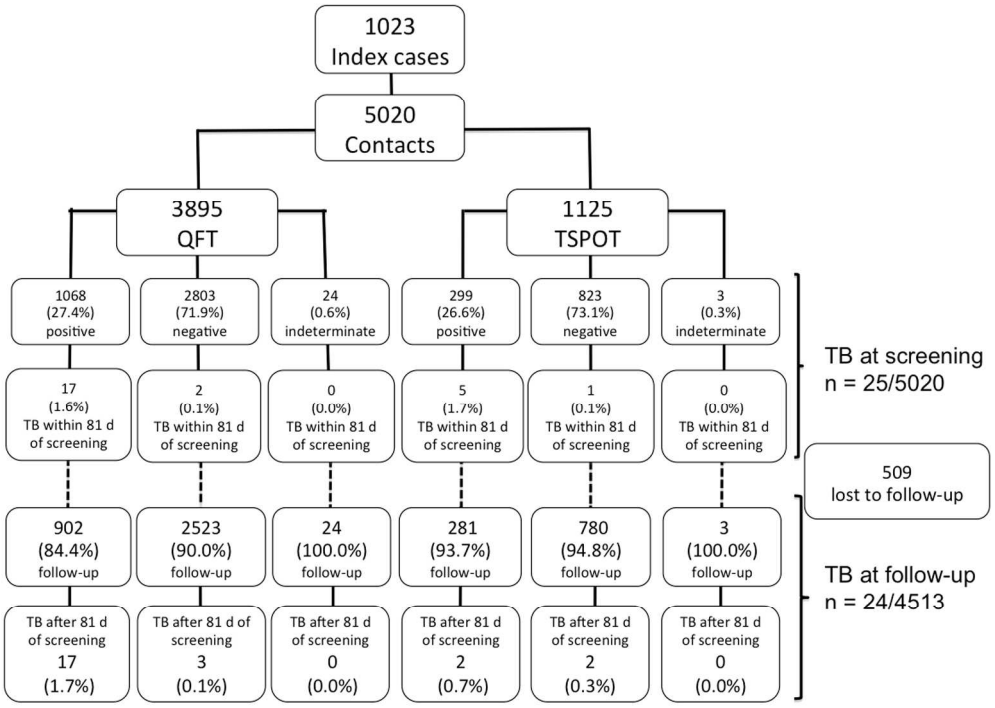
			95% Confidence Interval
QFT	Sensitivity (%)	85.0	62.1 – 96.6
	Specificity (%)	74.0	72.5 – 75.5
	Positive Likelihood Ratio	3.3	2.7 – 4.0
	Negative Likelihood Ratio	0.2	0.1 – 0.6
	Positive Predictive Value (%)	1.9	1.1 – 3.0
	Negative Predictive Value (%)	99.9	99.7 – 100.0
TSPOT	Sensitivity (%)	50.0	8.3 – 91.7
	Specificity (%)	73.6	70.8 – 76.2
	Positive Likelihood Ratio	1.9	0.7 – 5.1
	Negative Likelihood Ratio	0.7	0.3 – 1.8
	Positive Predictive Value (%)	0.7	0.1 -2.6
	Negative Predictive Value (%)	99.7	99.1 – 99.9

Table 5: Concentration of IFN-γ in the QuantiFERON–Gold in-Tube (QFT) test and net number of spot forming cells (sfc)* in the T-SPOT.*TB* (TSPOT) test and 2.5 year risk for tuberculosis in contacts not receiving preventive chemotherapy

	IFN-γ concentration (IU/ml)	n	Incident TB cases	Ratio
QFT	< 0.35	2410	3	0.001
	> 0.35	1015	17	0.017
	> 0.7	796	15	0.019
	> 1.0	740	14	0.019
	> 1.4	677	13	0.019
	> 2.0	615	12	0.020
	> 5.0	441	8	0.018
	> 10.0	287	7	0.024
	SFC	**n**	**Incident TB cases**	**Ratio**
TSPOT	< 5	784	2	0.003
	> 4	305	2	0.007
	> 7	271	2	0.007
	> 10	246	1	0.008
	> 20	204	1	0.005
	> 50	102	1	0.010
	> 100	40	0	-
	> 200	1	0	-

*highest value of sfc in response to either ESAT-6 or CFP-10 antigen

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC



Flow chart of test results and occurrence of secondary cases with tuberculosis (TB) in tuberculosis contacts included in the study. Secondary cases were defined as prevalent, if they were detected within the median interval between index case notification and contact case notification of 81 days found in this study. QFT = Quantiferon-Gold in-Tube test; TSPOT = T-SPOT.TB test; TB = tuberculosis.
414x294mm (300 x 300 DPI)

Supplementary data

Table S1: Comparison of national guidelines for tuberculosis contact investigations in European countries from which centers participated in this study.

	Austria[1]	Denmark[2]	Germany[3]	Italy[4]	Poland[5]	Portugal[6]	Slovakia[7]	Spain[8]	Switzerland[9]	UK[10]
National TB contact investigation guideline present?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Is there a recommended delay for performing screening for TB and LTBI in adults	no	8-12 weeks after the notification of the index case	8 weeks after the notification of the index case	8-10 weeks after the notification of the index case	8 weeks after the notification of the index case	8 weeks after the notification of the index case	6 weeks after the notification of the index case	no	8 weeks after the notification of the index case	no
Is re-screening recommended if screening was performed within 8 weeks of the last contact to the index case?	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Which screening method for LTBI is recommended in symptom-free contacts ?	TST or IGRA	TST or IGRA	IGRA (in children <5 y.: TST)	BCG-unvaccinated: TST (in immunocompromized hosts a negative TST should be confirmed by an IGRA) BCG-vaccinated: IGRA	TST or IGRA In immunocompromized hosts and children <5 y.: TST and IGRA	TST or IGRA	TST or IGRA	BCG-unvaccinated: TST (in immunocompromized hosts and children < 5 y. a negative TST should be confirmed by an IGRA) BCG-vaccinated: TST (if the TST is positive it must be confirmed by an IGRA)	TST or IGRA	TST followed by IGRA if positive (only contacts <36 y. are screened)
Is a CXR recommended if a TST or IGRA	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

result is positive ?										
For whom is preventive therapy recommended?	- in children < 6y. who are recent contacts chemoprevention is recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 3 months - recent contacts with positive TST or IGRA	- < 35 y. recent contacts with positive TST or IGRA - individual judgement by the attending physician in recent contacts with positive TST or IGRA ≥ 35 y.	- in children < 5y. who are recent contacts chemoprevention is recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 2 months - recent contacts with positive TST or IGRA	- in children < 5y. who are recent contacts chemoprevention is recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 8-10 week - recent contacts with positive TST or IGRA (depending on BCG-vaccination status)	- in children < 5y. who are recent contacts chemoprevention is recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 2 months - < 35 y. recent contacts with positive TST or IGRA - in immunocompromized hosts who are recent contacts chemoprevention is also recommended when the TST or IGRA is negative	- in children < 5y. who are recent contacts chemoprevention is also recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 2 months - recent contacts with positive TST or IGRA - in immunocompromized hosts who are recent contacts chemoprevention is also recommended when the TST or IGRA is negative	- in children < 5y. who are recent contacts chemoprevention is recommended when the TST or IGRA is negative, chemoprevention is discontinued when the TST or IGRA result is still negative after 2 months - recent contacts with positive TST or IGRA	- recent contacts with positive TST or IGRA < 35 y. - individual judgement by the attending physician in recent contacts with positive TST or IGRA ≥ 35 y - in children and teenager who are recent contacts chemoprevention is recommended when the TST or IGRA is negative; chemoprevention is discontinued when the TST or IGRA result is still negative after 2 months - in recent contacts who are immunocompromized any TST induration is indicative	- in children < 5y. even when the TST or IGRA is negative. PT may be stopped if TST/IGRA is still negative at retesting after 2 months - recent contacts with positive TST or IGRA	- recent contacts with positive TST and IGRA < 36 y.
What is the preferred treatment for LTBI ? ----- dosage	- isoniazid (daily over 9 months) --------- children: 10 mg/kg adults: 5 mg/kg	- isoniazid (daily over 6 months) --------- adults: 5 mg/kg children: 10 mg/kg	- isoniazid (daily over 9 months) -------- adults: 5 mg/kg children: 200 mg/m²	- isoniazid (daily over 6 months) --------- Isoniazid in adults: 5 mg/kg in children: 10 mg/kg	- isoniazid (daily over 6-9 months) or - isoniazid and rifampicin (daily over 3 months) --------- Isoniazid in adults: 5 mg/kg in children: 5-10 mg/kg rifampicin in adults and children: 10 mg/kg	- isoniazid (daily over 6-9 months) --------- adults: 5 mg/kg children: 10 mg/kg	- isoniazid (daily over 6 months) or --------- Isoniazid in adults: 5 mg/kg children: 10 mg/kg	- isoniazid (daily over 6-9 months) or - isoniazid and rifampicin (daily over 3 months) --------- isoniazid in adults: 5 mg/kg in children: 5-10 mg/kg rifampicin in adults and children: 10 mg/kg	- isoniazid (daily over 9 months) or - rifampicin (daily over 4 months) --------- Isoniazid in adults: 5 mg/kg	A - isoniazid (daily over 6 months) or - isoniazid and rifampicin (daily over 3 months) if > 16 y. and HIV- B - isoniazid (daily over 6 months) in HIV+ C

									in children: 10 mg/kg rifampicin in adults and children: 10 mg/kg	- rifampicin (daily over 6 months) in isoniacid resistance in persons <36 y. D - special recommendations apply to neonates and children --------- dosage recommendations are not provided
Is a CXR follow-up recommended?	yes - 1 year after completion of PT or - 1 year after the diagnosis of LTBI if PT was not taken	yes - 3 and 6 months after start of PT or - 6 and 12 months after the last contact if PT was not taken	yes - 9 months after screening if PT was not taken or at the end of PT	no	no	no	no	no	no	yes - 3 and 12 months after the last contact if PT was not taken
Is it recommended to document completion of preventive therapy ?	yes	yes	no	no	yes	yes	yes	yes	yes	yes

BCG = *Mycobacterium bovis* Bacille Calmette Guérin; CXR = chest x-ray; IGRA = interferon–γ release assay; PT = preventive chemotherapy; TST = tuberculin skin test.

[1] Rendi-Wagner P, Bogyi M, Hagel E, Hirtl T, Klein JP. Österreichische Leitlinie zur Tuberkulose – Umgebungsuntersuchung. Bundesministerium für Gesundheit, Wien, Austria 2013

[2] Seersholm N, Andersen PH, Bengård Andersen A, Østergaard Thomsen V, Hilberg O, Ravn P, Høgh B, et al. Tuberkulosebekæmpelse i Danmark Et nationalt tuberkuloseprogram needs. Dansk Lungemedicinsk Selskab, Dansk Selskab for Infektionsmedicin, Dansk Pædiatrisk Selskab, Dansk Selskab for Klinisk Mikrobiologi og Statens Seruminstitut. Copenhagen 2010

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

[3] Diel R, Loytved G, Nienhaus A, Castell S, Detjen A, Geerdes-Fenge H, Haas W, et al. [New recommendations for contact tracing in tuberculosis]. Gesundheitswesen. 2011 Jun;73(6):369-88.

[4] Lauria FN, Jefferson TO, Palmieri F, Goletti D, Loffredo MR, Gualano G, Mancini R, et al. Aggiornamento delle raccomandazioni per le attività di controllo della tubercolosi. "Gestione dei contatti e della tubercolosi in ambito assistenziale", Rome, 2009

[5] Augustynowicz-Kopeć E, Demkow U, Grzelewska-Rzymowska I, Korzeniewska-Koseła M, Langfort R, Michałowska-Mitczuk D, Rowińska-Zakrzewska E, et al. Guidelines of Polish Respiratory Society concerning diagnosis, treatment and prevention of tuberculosis in adults and in children. Pneumonologia i Alergologia Polska 2013, tom 81, nr 4, strony 323–379

[6] Correia AM, Valente P, Duarte R. Planeamento do Rastreio de Contactos de Doentes com Tuberculose; Programa Nacional para a Tuberculose, Portugues Ministry of Health, Lisbon 2013

[7] Rozborilová E, Solovic I. Metodické odporúčanie hlavného odborníka mz sr pre odbor pneumológia a ftizeológia. Bratislava 2011

[8] González-Martín J, García-García JM, Anibarro L, Vidal R, Esteban J, Blanquer R, Moreno S, et al. Consensus Document on the Diagnosis, Treatment and Prevention of Tuberculosis. Arch Bronconeumol. 2010;46(5):255-274

[9] Barben J, Berger C, Bodmer T, Egger JM, Helbling P, Janssens JP, Merlani G, et al. Tuberculosis in Switzerland, the key issues. Swiss Lung Association (SLA), Berne, 2011

[10] Abubakar I, Bell C, Bradley S, Chapman A, Collyns T, Drobniewski F, Longson D, et al. Clinical diagnosis and management of tuberculosis, and measures for its prevention and control, National Institute for Health and Care excellence (NICE), London 2011.

Table S2 : Recruitment centers, index cases, contacts and secondary TB patients

				Follow-up complete				
Country	**Center**	**Index cases n**	**Contacts n**	**n**	**%**	**Prev. cases n**	**Inc. cases n**	**All TB cases n**
Austria	Wien	12	24	10	41.7	0	0	0
Denmark	Aarhus	49	164	164	100.0	2	0	2
Italy	Milan	61	142	140	98.6	0	0	0
Italy	Rome	73	229	189	82.5	0	0	0
Germany	Bochum	1	143	143	100.0	0	0	0
Germany	Braunschweig	9	18	18	100.0	0	0	0
Germany	Göttingen	12	349	334	95.7	0	0	0
Germany	Hannover	80	673	627	93.2	0	0	0
Germany	Luebeck	48	335	328	97.9	0	0	0
Germany	Minden	12	66	66	100.0	0	0	0
Germany	Wilhemshaven	6	103	103	100.0	0	0	0
Poland	Cracow	17	176	176	100.0	0	5	5
Portugal	Villa Nova de Gaia	32	84	1	1.2	0	0	0
Slovakia	Visne Hagy	6	25	25	100.0	0	0	0
Spain	Aviles	29	164	164	100.0	0	0	0
Spain	Badalona	3	74	74	100.0	0	0	0
Spain	Barcelona	252	662	659	99.5	19	9	28
Switzerland	Aargau	23	223	145	65.0	0	0	0
Switzerland	Fribourg	13	44	41	93.2	0	1	1
Switzerland	Genève	13	158	2	1.3	0	0	0
Switzerland	St. Gallen	1	4	4	100.0	0	0	0
Switzerland	Ticino	8	21	21	100.0	0	0	0
Switzerland	Valais	15	56	14	25.0	0	0	0
Switzerland	Vaud	28	122	115	94.3	0	0	0
Switzerland	Zürich	72	450	444	98.7	0	2	2
United Kingdom	London	148	511	506	99.0	4	7	11
		1023	5020	4513	89.9	25	24	49

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Table S3: Demographic characteristics among contacts with follow-up, stratified by IGRA results

	IGRA neg.	IGRA pos.	IGRA ind.	Total. n (%)
Total. n (%)	3303 (73.2)	1183 (26.2)	27 (0.6)	4513 (100.0)
Sex of contact. n (col %) (row %)				
Female	1878 (56.9)(75.7)	588 (49.7)(23.7)	16 (59.3)(0.6)	2482 (55.0)
Male	1425 (43.1)(70.2)	595 (50.3)(29.3)	11 (40.7)(0.5)	2031 (45.0)
Age group. n (col %) (row %)				
0- to 4-yr-old	68 (2.1)(80.0)	17 (1.4)(20.0)	0 (0.0)(0.0)	85 (1.9)
5- to 14-yr-old	216 (6.5)(56.3)	167 (14.1)(43.5)	1 (3.7)(0.3)	384 (8.5)
15- to 34-yr-old	1408 (42.6)(76.2)	424 (35.8)(23.0)	15 (55.6)(0.8)	1847 (40.9)
35- to 64-yr-old	1475 (44.7)(74.7)	490 (41.4)(24.8)	9 (33.3)(0.5)	1974 (43.7)
65-yr-old and older	132 (4.0)(60.3)	85 (7.2)(38.8)	2 (7.4)(0.9)	219 (4.9)
Unknown	4 (0.1)(100.0)	0 (0.0)(0.0)	0 (0.0)(0.0)	4 (0.1)
Type of contact. n (col %) (row %)				
Close. relatives	495 (15.0)(55.4)	389 (32.9)(43.6)	9 (33.3)(1.0)	893 (19.8)
Close not related but intensive	658 (19.9)(71.9)	252 (21.3)(27.5)	5 (18.5)(0.6)	915 (20.3)
Prolonged. work	1587 (48.1)(77.6)	449 (38.0)(22.0)	9 (33.3)(0.4)	2045 (45.3)
Other	562 (17.0)(85.4)	92 (7.8)(14.0)	4 (14.8)(0.6)	658 (14.6)
Unknown	1 (0.0)(50.0)	1 (0.1)(50.0)	0 (0.0)(0.0)	2 (0.0)
Place of birth of contacts. n (col %) (row %)				
Africa	113 (3.4)(49.3)	114 (9.6)(49.8)	2 (7.4)(0.9)	229 (5.1)
Americas	212 (6.4)(61.8)	127 (10.7)(37.0)	4 (14.8)(1.2)	343 (7.6)
Asia	280 (8.5)(65.3)	145 (12.3)(33.8)	4 (14.8)(0.9)	429 (9.5)
Europe	2648 (80.2)(76.8)	785 (66.4)(22.8)	16 (59.3)(0.5)	3449 (76.4)
Oceania	2 (0.1)(100.0)	0 (0.0)(0.0)	0 (0.0)(0.0)	2 (0.0)
Unknown	48 (1.5)(78.7)	12 (1.0)(19.7)	1 (3.7)(1.6)	61 (1.4)
Screening test. n (col %) (row %)				
QFT	2523 (76.4)(73.2)	902 (76.3)(26.2)	24 (88.9)(0.7)	3449 (76.4)
TSPOT	780 (23.6)(73.3)	281 (23.8)(26.4)	3 (11.1)(0.3)	1064 (23.6)
Preventive chemotherapy. n (col %) (row %)				

Not initiated	2821 (85.4)(88.2)	353 (29.8)(11.0)	0 (0.0)(0.0)	3197 (70.9)
Initiated	482 (14.6)(36.7)	829 (70.1)(63.0)	4 (14.8)(0.3)	1315 (29.1)
Unknown	0 (0.0)(0.0)	1 (0.1)(100.0)	0 (0.0)(0.0)	1 (0.0)
Preventive therapy. n (col %) (row %)				
Not received	3141 (95.1)(85.8)	494 (41.8)(13.5)	25 (92.6)(0.7)	3660 (81.1)
Received	162 (4.9)(19.0)	689 (58.2)(80.8)	2 (7.4)(0.2)	853 (18.9)
Follow-up TB. n (col %) (row %)				
Non-incident cases	3298 (99.8)(73.5)	1164 (98.4)(25.9)	27 (100.0)(0.6)	4489 (99.4)
Incident cases	5 (0.2)(20.8)	19 (1.6)(79.2)	0 (0.0)(0.0)	24 (0.5)

AJRCCM Articles in Press. Published on 12-March-2015 as 10.1164/rccm.201502-0232OC

Table S4. Logistic regression analysis of the IGRA results using different cut-offs

	Test result	OR (95% CI)	p-value	AUC
QFT	0.35	13.67 (4.00 – 46.74)	<0.0001	0.779
	0.70	10.08 (3.65 – 27.82)	<0.0001	0.760
	1.00	8.61 (3.30 – 22.48)	<0.0001	0.743
	4.00	4.14 (1.68 – 10.19)	0.002	0.631
TSPOT	5	2.70 (0.38 – 19.23)	0.323	0.615
	9	1.06 (0.11 – 10.23)	0.960	0.505
	20	4.30 (0.44 – 41.86)	0.209	0.589