

Tuberculosis in a Swiss army training camp: contact investigation using an Interferon gamma release assay

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Summary

Background: In tuberculosis (TB), the risk of exposure is determined mainly by the proximity to and the hours of direct contact with an infectious patient.

We describe the contact investigation after detection of an infectious form of TB in a military camp using an Interferon-g-Release-Assay (IGRA, QuantiFERON®-TB Gold In Tube [QFT-GIT]) eight weeks after detection of the index case.

Index patient: The index patient presented with fever, cough and weight loss in the military hospital six weeks after entering the camp. TB was suspected and anti-tuberculous therapy given immediately. Subsequently, TB was microbiologically confirmed.

Methods: Four exposure groups were formed *a priori* based on the proximity and the hours of direct contact to the index case. 168 (95.5%) agreed to be investigated:

- Group A: sharing the same dormitory (15 persons)
- Group B: same platoon, but not sharing the dormitory (20 persons)

- Group C: staff and patients of the military hospital (22 persons)
- Group D: other three platoons and senior military staff (111 persons)

Results: 34 (20.2%) out of 168 contacts tested positive in the QFT-GIT assay. For the exposure groups, the respective QFT-GIT testing results were: group A, 14/15 (93%); group B, 4/20 (20%); group C, 5/22 (22.7%); and group D, 11/111 (9.9%). No secondary TB cases were identified.

Conclusions: In our study, test results show a correlation with the risk of exposure, suggesting that IGRA may be useful for the assessment of TB infection in TB contacts. The high mobility of recruits reduced traceability of contacts. In this context, QFT-GIT allowed for an efficient screening of contacts at a single time point.

Key words: tuberculosis; contact investigation; Interferon-gamma release assay

Introduction

Migration, HIV infection, and the emergence of multidrug-resistant strains have heightened the awareness of tuberculosis (TB) as a global emergency. In developed countries, the aging of the population highlights the need for stringent strategies to maintain and improve TB control [1]. Key strategies for reducing the incidence of TB in low-prevalence areas are the timely diagnosis and adequate treatment of patients latently infected with *Mycobacterium tuberculosis* who have a definite risk of progression to TB [2]. It is of paramount importance to eliminate the infectious burden in young people who have, in face of the extended life expectancy, a higher risk of develop-

ing TB than the average population. Moreover, foreign-born immigrants from high-prevalence areas carry more than half of the burden of TB cases in developed countries [3–5].

The tuberculin skin test (TST) is the standard diagnostic tool for the diagnosis of latent TB infection (LTBI) with well-known limitations. The main drawback of the TST is poor specificity due to previous vaccination with *Bacille Calmette-Guerin* (BCG) and exposure to *nontuberculous mycobacteria* (NTM). There is a cross-reactivity of the purified protein derivative (PPD) used in the TST and BCG as well as with the most NTM [6]. Therefore, this test overestimates the population

at risk and is responsible for a substantial proportion of unnecessary antibiotic treatment [7]. Even more importantly, the sensitivity of the TST is particularly low in immunosuppressed patients for whom the risk of progression to TB is high, thus producing significant prevalence of false-negative results in this population [8].

Immunity to TB infection is primarily a cell-mediated response to TB antigens. The TST uses PPD in an attempt to measure this immune response. Interferon-gamma (IFN- γ)-Release-Assays (IGRA) have been developed as a potential replacement for the TST. T cells, stimulated by TB antigens, produce the cytokine IFN- γ that enables macrophages to eliminate this intracellular pathogen [9]. QuantiFERON®-TB Gold In Tube (QTF-GIT) is a whole-blood IGRA and uses a mixture of two antigens that are encoded by the *Region of Difference 1* (RD1) to stimulate T lymphocytes. These antigens are the *Early-Secretory-Antigenic-Target 6* (ESAT-6) and *Culture-Filtrate Protein-10* (CFP-10); in addition, the mixture contains TB7.7(p4), a third, *M. tuberculosis*-specific antigen. As RD1 is absent in all strains of *Bacille*

Calmette-Guérin (BCG), the vaccine strains, much of the cross-reactivity problems with PPD antigens that were used in older IGRA tests are avoided [10]. As a consequence, results of IGRA tests are not associated with previous BCG vaccination. Moreover, ESAT-6 specific T cells detected by the IGRA's are highly sensitive to *M. tuberculosis* infection in patients with positive smear tests and substantially higher than that for the TST [11]. In a pilot study, a correlation was found between quantitative ESAT-6 results and the extent of exposure to TB cases, whereas unexposed people tested uniformly negative [12]. In addition, a close relationship of proximity and duration of exposure was also found in a contact investigation in the UK [13].

In August 2005, we detected a case of infectious pulmonary TB in a Swiss military training camp. We describe the contact investigation activities in the setting of a military environment and the use of QTF-GIT, an Interferon-Gamma Release Assay (IGRA), as the sole diagnostic tool for the assessment of LTBI.

Case report

The index patient was a twenty year old male of Turkish origin who regularly visited his relatives in the eastern part of Turkey. Review of the patient's medical records at the time of Swiss army recruitment procedure indicated that auscultation had revealed rhonchi of the right lung. As a consequence, a lung function test was requested, but no radiology. Lung function tests revealed no abnor-

malities, and the patient was recruited for compulsory Swiss military service.

In July 2005, six months after being drafted, the patient began military service in a company of four platoons of armoured infantrymen. Six weeks after entering military service, he presented with high fever and productive cough at the military hospital. Physical examination revealed an am-

Figure 1

Cavernous lesion in the lower lobe of the right lung.

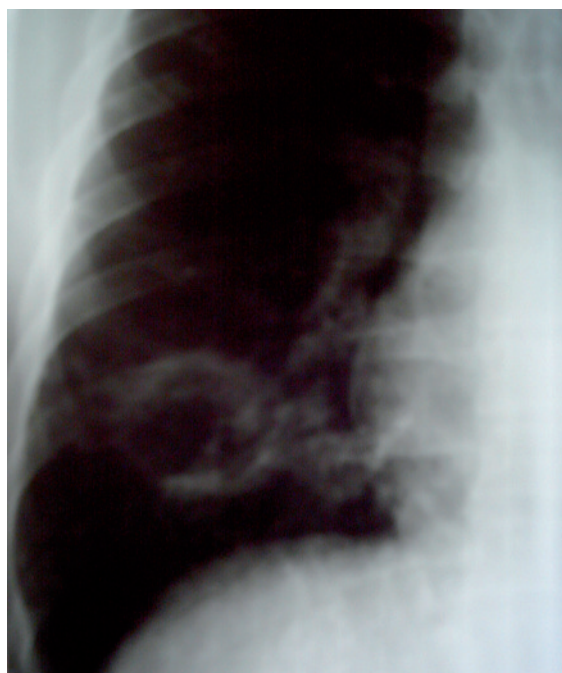


Figure 2

CT scan revealing the cavernous lesion with connection to the bronchial tree and military seeding to the left side.



phoric breath sound from the right hemi-thorax. A cavity was suspected and confirmed by radiology (fig. 1). TB was suspected, and the patient immediately evacuated to a civilian medical centre, where he was isolated. A CT-scan revealed cavernous TB on the right side and miliary seeding to both lungs (fig. 2). Sputum smears revealed numerous (4+) acid-fast bacilli, subsequently identified as *M. tuberculosis*, susceptible to the first-line anti-tuberculous drugs. The acute episode with fever and productive cough was attributed to a confirmed superinfection with *Haemophilus influenzae*. A quadruple therapy regimen with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol

was started. In the meantime, cure under this treatment was established.

During the contact investigation, it became evident that prior to resuming military training, ie, during the first term of 2005, the index patient had infected 6 of 15 classmates who shared the classroom for a few hours a week at school. The fact that the patient had presented with pulmonary symptoms at the Swiss Army Recruitment Centre in January and eventually infected 40% of his classmates during the first term of 2005 provides strong evidence that the patient had been contagious for a long time.

Methods

Contact Investigation

The military command accorded the highest priority to the identification and treatment of all recruits who might have acquired LTBI. Every person of the company, military staff and the staff of the military hospital in direct contact with the patient were considered potentially infected. Four exposure groups were formed *a priori* based on the proximity to the patient and the estimated hours of direct contact.

During this process it became evident that BCG vaccination probably still was prevalent in this cohort. This piece of information influenced the final decision to use IGRA rather than TST as the primary screening tool for this contact investigation.

QuantiFERON®-TB Gold In Tube Assay (QFT-GIT)

In this particular situation of a very mobile, BCG-vaccinated cohort, we identified QuantiFERON®-TB Gold In Tube (Cellestis Ltd., Carnegie, Australia) as a screening test that was not confounded by previous BCG vaccination and potentially suited to a single-point testing. Blood was collected from all contacts eight weeks

after detection of the index patient, ie, 14 weeks after exposure had started. Interferon-gamma (INF- γ) which is released from sensitised lymphocytes upon stimulation with Early-Secreted Antigen-6 (ESAT-6), Culture-Filtrate Protein-10 (CFP-10), and Protein TB7.7(p4) were determined as recommended by the manufacturer [14]. The mitogen control was included in all cases.

Statistical Analysis

Statistical analysis was performed with GraphPAD Prism®, version 4.02 (Graph PAD Software Inc., San Diego, CA, U.S.A.) and STATView®, version 5.0 (SAS Institute, Inc., Cary, NC, U.S.A.)

Fisher's exact test was used for contingency table analysis. Analysis were 2-sided, and p-values <0.05 were considered statistically significant.

Unadjusted odds ratios were calculated with group D as the reference group.

Furthermore, from a multivariate logistic regression model with age, sex and country of origin as covariates, adjusted odds ratios were calculated. Group D served as the reference group.

Results

Contact Investigation

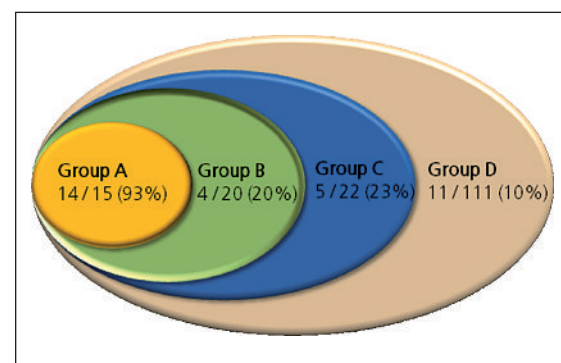
Overall, 176 contacts were identified. They were classified according to the proximity to the index patient and the estimated hours of direct contact as follows (fig. 3):

- Group A: persons of the index patient's platoon who shared the dormitory (n = 15)
- Group B: persons of the index patient's platoon not sharing the dormitory (n = 21)
- Group C: medical staff and patients of the military hospital having had contact with index patient (n = 23)
- Group D: persons of the company's other three platoons and the senior military staff (n = 117)

Overall, 168 (95.5%) contacts gave informed consent for being tested using the QFT-GIT Assay. The relative distribution per risk group of

contacts tested was 100%, 95%, 96%, and 95% for group A, B, C, and D respectively.

Figure 3



QuantiFERON® – TB Gold In Tube Assay

A total of 34 (18.9%) contacts had a positive QFT-GIT test result. The respective QFT-GIT results for the exposure groups are shown in table 1 and figure 3. Individual INF- γ responses above cut-off value (0.35 IU/ml) varied considerably (fig. 4a, left), ranging from 0.4 to >15 IU/ml (median, 2.5; interquartile range, 0.9 to 5.6). No indeterminate results were found (fig. 4b, right) as all mitogen controls were above the threshold level (≥ 0.5 IU/ml).

A total of 33 (97.6%) QFT-GIT-positive contacts agreed to undergo chemoprophylaxis with Isoniazid for six months while one person pre-

ferred a homeopathic treatment. 32 (97%) contacts completed the chemoprophylactic treatment, while in one (3%) patient chemoprophylaxis was discontinued due to mild hepatotoxicity.

The decision for a six-month chemoprophylaxis course instead of nine months was taken by the military medical command. Although the military authorities acknowledged, as specified in the Swiss national guidelines, that 9 months of Isoniazid treatment may confer a higher protection than six months, the shorter treatment regimen was taken to maximise compliance, similar to the NICE guidelines issued in 2006 [15].

Table 1

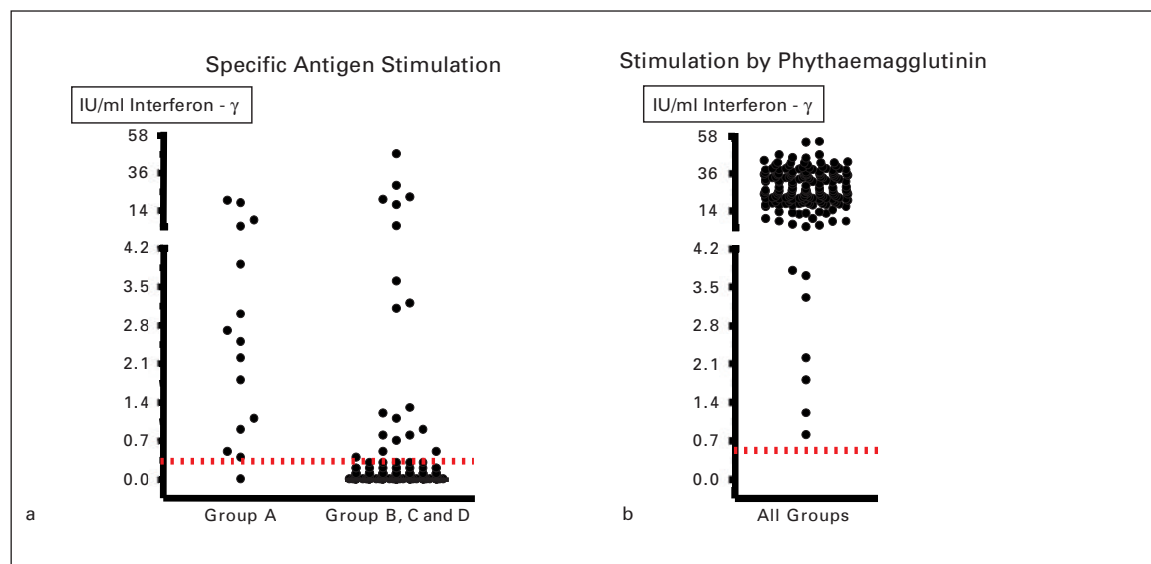
Odds ratio (OR) and 95% confidence intervals (CI) for a positive QFT-GIT in groups with long-term exposure (group D, B and A) and a group with short but intense exposure (group C). Those in group D, who should have the lowest risk for acquiring LTBI, were considered to be the reference group for calculating the odds ratios.

Contact group	Negative	Positive		Unadjusted OR (95% CI)	P – value	Adjusted OR ¹ (95% CI)	P – value
	NO	NO	%				
D	100	11	9.9	1			
C	17	5	22.7	2.7 (0.8 to 8.7)	0.10	3.1 (0.7 to 13.2)	0.12
B	16	4	20	2.3 (0.6 to 8.0)	0.20	2.2 (0.6 to 7.8)	
A	1	14	93.3	127 (15 to 1063)	<0.0001	124 (15 to 1038)	<0.0001

¹ Adjusted OR are calculated from a multivariate logistic regression model with age, country of origin and sex as covariates.

Figure 4

QTF – GIT results of all contacts. Dotted lines indicate cut-off values at 0.35 IU/ml and 0.5 IU/ml for TB-specific antigens (a, left) and Phytohaemagglutinin, ie mitogen (b, right).



Discussion

In developed countries, several factors have shown an association with the resurgence of TB: the deterioration of infrastructure for TB prevention and control, emerging HIV infection, immigration from countries with a high TB incidence, congregate settings and the occurrence of drug- and multidrug-resistant strains of *M. tuberculosis* [16]. In 2004, foreign-born persons living in

Switzerland contributed to 64% of the new TB cases [3] while representing only twenty percent of the country's population. This is comparable to the Nordic states, where foreign-born persons contributed for more than 70% of new TB cases [17]. However, our index patient was a Swiss citizen with Turkish parents, born and raised in Switzerland while still having a physical relation-

ship to the country of origin of his parents. Thus, he represents a member of the growing pool of naturalised Swiss citizens, who may have a higher than the average risk of being latently infected with *M. tuberculosis*.

The investigation of TB contacts in the context of a military training camp posed several challenges that finally led to the decision to use IGRA rather than TST: the rate of contacts with confirmed BCG vaccinations was as high as 61%; another 17% of contacts had an undetermined vaccination status. Due to the unexpectedly high rate of contacts with previous BCG vaccinations, two-step TST testing would have been required. This would have rendered the contact investigation even more complex, particularly because – at the time of designated contact investigation (eight weeks after detection) – the four platoons were involved in military exercises at different places in Switzerland. Therefore, the high specificity and the “single-sample-gives-diagnosis” format of QFT-GIT were particularly suited for this situation.

However, studies of IGRA sensitivity suggest that they are at least as sensitive as TST in TB patients but may be less sensitive than TST for detecting LTBI in immunocompetent individuals. Until further evidence has evolved, the confirmation of positive TST by IGRA might be the ideal approach for contact tracing in incidents where there is a known index case, as recommended by the Swiss and UK guidelines for contact tracing. Therefore, our approach should be reserved for contact tracing in highly mobile population subgroups.

Overall, the results of QFT-GIT correlated well with the risk of exposure: the high prevalence of infected contacts in the closest proximity of the index patient (95% infected), the index patient's platoon (20% infected) and the involved persons of the Military Medical Centre (22.7%) were strong arguments to extend the investigation to the other three platoons and the military staff. The prevalence of LTBI in this subpopulation was 9.9%. This rate most probably does not reflect the true prevalence of LTBI of the average Swiss population. However, the rate appeared to be reasonably low to reject the option of testing all members of the military training camp, regardless of the possibility of a contact to the index patient for economic reasons. In addition, the latter option would have created a dilemma on whom to treat, as testing for LTBI is only justified by the intention-to-treat those who tested positive. From an epidemiological standpoint, the low predictive value of a positive test result in this low prevalence population is prohibitive of any action.

Surprisingly, the rate of positive results in group C, ie, among contacts at the Military Medical Centre, where the patient had stayed for only 12 hours prior to the diagnosis, was found to be 22.7%. Two fellow recruits who had shared the room with the index patient, the attending physician, the nurse in charge and the soldier on call at the front desk had positive QFT-GIT test results (table 1 and fig. 3). We assume that the superposition of two factors contributed to this surprisingly high rate of infection. The index patient's condition had clearly deteriorated at the time when he presented at the Military Medical Centre: he was febrile and had productive cough. It is conceivable that the patient's infectivity had increased over time in relation to the deterioration of his physical condition due to the bacterial superinfection and thus transmission of *M. tuberculosis* had become more effective. In addition, staff members of the Military Medical Centre who tested positive were older than the average recruits by one or two decades, and thus positive test results in these age groups likely reflect both previously and recently acquired LTBI, respectively. However, the clarification of this question would require the availability of QFT-GIT test results obtained prior to exposure.

In summary, QFT-GIT was a reliable and practical tool for the investigation of a TB outbreak in a highly mobile population, and its high specificity was very valuable for the detection of LTBI in a cohort with a high background level of BCG vaccination. The “single-sample-gives-diagnosis” format was particularly suited to the requirements of highly mobile military populations. In addition, the case of our index patient highlights the changing TB epidemiology in Switzerland: in more than half of the detected new TB cases, foreign-born persons and their children were affected. As demonstrated in our case, TB transmission can occur even in the absence of overt clinical symptoms, and thus, as the clinical presentation of TB can be mild, introduction of IGRA testing and chest x-ray for selected persons in this young population may be valuable. Investment in preventive measures may help avoiding similar occurrences in the future.

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