Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

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Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

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Abstract

Introduction

Interferon Gamma Release Assays (IGRAs) are considered a supplement to confirm Tuberculin Skin Tests (TST) for the diagnosis of Latent Tuberculosis Infection (LTBI). The impact of the recent introduction of IGRAs in the LTBI screening program of the Canadian Armed Forces (CAF) is being investigated.

Methods

This retrospective study compares the TST positivity in the CAF during 18 months before and after the implementation of IGRA. The study analyzes the agreement between TST and IGRA and the impact of IGRA on treatment in the 18 months post-IGRA period.

Results

Of the total 13,499 TSTs included in this study, 102 were positive in the pre-IGRA and 113 were positive in the post-IGRA period. In the post-IGRA period, 54 had IGRA tests with 17 positive and 37 negative (TST-IGRA agreement of 31.5%). TST positivity was significantly increased in the post-deployment group from 0.97% in the pre-IGRA to 1.88% in the post-IGRA period. In all other groups, the difference was not significant. Proportion of TST positive cases receiving isoniazid chemoprophylaxis was significantly reduced by 41.1% in the post-IGRA period.

Conclusions

Frequency of TST positive cases was significantly higher in the post-IGRA period compared with the pre-IGRA period, possibly due to the changing role of the CAF from that of battle to mentoring. The data indicates that the agreement in positive results between TST and IGRA is poor at 26.6%. Isoniazid prescriptions were significantly reduced after the implementation of IGRA suggesting that the use of IGRA prevents much unnecessary use of the antibiotic.

Keywords: LTBI (Latent Tuberculosis Infection), Tuberculosis, IGRA (Interferon Gamma Release Assay), TST (Tuberculin Skin Test), Isoniazid
Résumé

Introduction

Le test de libération d’interféron gamma (TLIG) est considéré comme un complément visant à confirmer le résultat du test cutané à la tuberculine (TCT) pour le diagnostic de l’infection tuberculeuse latente (ITL). On étudie actuellement l’impact de l’introduction récente du TLIG dans le programme de dépistage de l’ITL des Forces armées canadiennes (FAC).

Méthodologie

Cette étude rétrospective compare le nombre de membres des FAC qui ont eu un TCT positif au cours des 18 mois précédant l’introduction du TLIG et au cours des 18 mois où ce test a été utilisé. L’étude analyse la concordance des résultats du TCT et du TLIG ainsi que l’impact du TLIG sur le traitement administré aux personnes qui ont reçu leur diagnostic durant la période de 18 mois suivant l’introduction du TLIG.

Résultats

Sur l’ensemble des 13 499 TCT visés par cette étude, 102 résultats positifs ont été obtenus durant la période où le TLIG n’était pas utilisé et 113 résultats positifs ont été obtenus durant la période où le TLIG était utilisé. Durant la période où le TLIG a été utilisé, ce test a été administré à 54 personnes : 17 ont obtenu un résultat positif et 37 ont obtenu un résultat négatif (taux de concordance du TCT et du TLIG de 31,5 %). Le taux de positivité au TCT a augmenté de façon significative dans le groupe où le TLIG a été utilisé : ce taux est passé de 0,97 % lorsque le TCT était utilisé seul à 1,88 % lorsque les deux tests ont été utilisés en combinaison. Dans tous les autres groupes, aucune différence significative n’a été observée. Durant la période où le TLIG a été utilisé, on a observé une importante diminution (41,1 %) de la proportion de cas positifs au TCT à qui une chimiothérapie par l’isoniazide a été prescrite.

Conclusions

La prévalence des TCT positifs était nettement supérieure durant la période où le TLIG a été utilisé, comparativement à la période où le TCT a été utilisé seul, peut-être en raison du fait que le rôle des FAC a changé, passant du combat à la surveillance. Selon les données, le taux de concordance des résultats positifs entre le TCT et le TLIG est faible (26,6 %). Le nombre d’ordonnances d’isoniazide a grandement diminué après l’introduction du TLIG, ce qui donne à penser que l’utilisation de ce test permet d’empêcher le recours inutile à cet antibiotique.

Mots-clés : LTBI (Infection tuberculeuse latente), Tuberculose, IGRA (Tests de libération d'interféron gamma), TST (Test cutané à la tuberculine), Isoniazide
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<thead>
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<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guérin vaccine</td>
</tr>
<tr>
<td>CAF</td>
<td>Canadian Armed Forces</td>
</tr>
<tr>
<td>CFP-10</td>
<td>Culture Filtrate Protein 10</td>
</tr>
<tr>
<td>D FHP</td>
<td>Directorate of Force Health Protection</td>
</tr>
<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>ELISPOT</td>
<td>Enzyme-Linked Immunosorbent Spot</td>
</tr>
<tr>
<td>ESAT</td>
<td>Early Secreted Antigenic Target protein</td>
</tr>
<tr>
<td>IFNγ</td>
<td>Interferon gamma</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon Gamma Release Assay</td>
</tr>
<tr>
<td>INH</td>
<td>Isoniazid</td>
</tr>
<tr>
<td>ISAF</td>
<td>International Security Assistance Force</td>
</tr>
<tr>
<td>LSHTM</td>
<td>London School of Hygiene and Tropical Medicine</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent Tuberculosis Infection</td>
</tr>
<tr>
<td>NATO</td>
<td>North Atlantic Treaty Organization</td>
</tr>
<tr>
<td>NTM</td>
<td>Non-Tuberculous Mycobacteria</td>
</tr>
<tr>
<td>PBMC</td>
<td>Peripheral Blood Mononuclear Cells</td>
</tr>
<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
</tr>
<tr>
<td>PPD-S</td>
<td>Purified Protein Derivative-Standard</td>
</tr>
<tr>
<td>QFT-GIT</td>
<td>QuantiFeron Gold In-Tube</td>
</tr>
<tr>
<td>SFU</td>
<td>Spot Forming Units</td>
</tr>
<tr>
<td>SGHRB</td>
<td>Surgeon General Health Research Board</td>
</tr>
<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin Skin Test</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

Introduction

Background

Tuberculosis (TB) is one of the most important global public health concerns today. According to the World Health Organization (WHO), in 2011, 1.4 million people died from TB and there were 8.7 million new cases reported. (WHO 2012) TB is caused by an infection with *Mycobacterium tuberculosis*, a slow growing bacterium. TB infection can either be latent or active. Active TB is a serious disease and infectious to others. Latent TB Infection (LTBI) occurs when the immune system is able to control the growth of the bacteria, but is unable to completely eradicate it from the body. Therefore, the risk always remains of the bacteria actively starting to grow again in the body and hence cause pathogenic active infection. It is estimated that there are 2 billion people worldwide with latent tuberculosis, and there is a 10% chance over their lifetime that the disease will become active (Pommerville 2007).

The pathogen is primarily transmitted by the inhalation route. During active tuberculosis, the patient’s cough, sneeze, or even singing may produce minute infectious aerosol droplets which if inhaled may infect a healthy person. (Louden 1968)

Antibiotic treatment during latent TB infection is an important way of preventing active TB – and indeed a way of preventing community-wide infection. Thus, in public health, the overall goal of TB control is to reduce the incidence of disease and the spread of infection by early case detection and treatment of active TB, and to identify and treat persons with LTBI. (WHO 2012) Routinely in Canada, a positive diagnosis for LTBI will be treated with up to a 9-month course of isoniazid (INH) antibiotic. The drug has a relatively high rate of side effects and it disturbs the patients’ lives – e.g., women are recommended to not get pregnant while on this antibiotic. (PHAC 2007) The treatment is paid for by the government in Canada, which means the cost burden associated with treatment comes from the tax payer dollars.

Tuberculin Skin Test (TST) and Interferon Gamma Release Assay (IGRA) are two diagnostic tests used in the diagnosis of LTBI. In Canada, Tubersol® (Sanofi Pasteur, Toronto, Ontario) is the only purified protein derivative available for use in the TST. Two IGRA products are available in Canada – QuantiFERON Gold In-Tube (QFT-GIT) (Cellestis, Inc., Chadstone, Australia) and T-Spot.TB (Oxford Immunotec, Inc., Abbingdon, England).

Literature Review

Making the diagnosis of LTBI and a decision to prescribe preventive antibiotics (or indeed for the patient to agree to take it) can be a complex matter. The diagnosis of LTBI is reliant on immunologic methods. For decades, a century old test in medicine, the TST has been utilized. However, it is widely recognized that TST alone has significant limitations in terms of test performance, resources required and patient convenience. More recently however, in the last 8 years (and last 2 years for the Canadian Armed Forces),
a new test, IGRA has become available. This in-vitro diagnostic test takes advantage of the fact that white blood cells of people who have been exposed to *M. tuberculosis* release interferon-γ (IFNγ) when exposed to antigens in the test kit. The test measures the adaptive immune response of *M. tuberculosis*-specific effector T-cells’ ability to release IFNγ. They measure either the IFNγ directly (QFT-GIT), or indirectly (T-Spot.TB), the number of white blood cells releasing IFNγ when exposed to specific *M. tuberculosis* antigens.

Many studies have been performed to observe the usefulness of IGRA in screening for LTBI. Pai et al. (2008) published a systematic review of a total of 38 publications and compared the sensitivity and specificity of TST, QFT-GIT and T-Spot.TB. The authors recognize that the studies they used to pool the sensitivity and specificity had limitations such as small sample sizes and no reference standard test for diagnosing LTBI. These results, along with a number of other interesting variables, are compared in the table below.

### Table 1: Characteristics of TST, QFT-GIT and T-Spot.TB.

<table>
<thead>
<tr>
<th></th>
<th>TST</th>
<th>QFT-GIT</th>
<th>T-Spot.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigens</strong></td>
<td>Purified Protein Derivative</td>
<td>ESAT-6, CFP10, TB7.7</td>
<td>ESAT-6, CFP10</td>
</tr>
<tr>
<td><strong>Internal controls</strong></td>
<td>None</td>
<td>+ve and –ve</td>
<td>+ve and –ve</td>
</tr>
<tr>
<td><strong>Sensitivity</strong></td>
<td>77%</td>
<td>70%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Specificity (BCG Naive)</strong></td>
<td>97%</td>
<td>99%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Specificity (BCG vaccinated)</strong></td>
<td>59%</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td><strong>Boosting effect in repeat test</strong></td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Visits to clinic</strong></td>
<td>Twice</td>
<td>Once</td>
<td>Once</td>
</tr>
<tr>
<td><strong>Time to results</strong></td>
<td>48 – 72 hours</td>
<td>16 – 24 hours</td>
<td>16 – 20 hours</td>
</tr>
<tr>
<td><strong>Reader bias</strong></td>
<td>Subjective (reader)</td>
<td>Computerized</td>
<td>Computerized</td>
</tr>
<tr>
<td><strong>Sample</strong></td>
<td>Injection into skin</td>
<td>Blood draw</td>
<td>Blood Draw</td>
</tr>
</tbody>
</table>

* From pooled results from a number of studies analyzed by Pai et al. 2008. Sensitivity based on diagnosis of active TB.

A history of BCG vaccination is a substantial negative factor in TST specificity. In Canada, BCG was a routine vaccination up until the 1970s in most provinces but was used until 1987 in Saskatchewan. The vaccine is still offered to many First Nations (the aboriginal and Inuit population of Canada) communities who are considered high risk for TB and at least in one territory (Nunavut), the vaccine is still offered to all newborns. (PHAC 2007) In the population where BCG is given, TST specificity is as low as 60%. (PHAC 2008) In addition to BCG, to a lesser extent, exposure to non-tuberculous mycobacteria (especially in a population with a very low TB prevalence) can cause a higher number of false positives with TST (Farhat M 2006).

There is no complete agreement amongst public health agencies of various nations on exactly how to utilize IGRA most effectively. Denkignier et al. (2011) summarized recommendations of various nations for the use of TST and IGRA in tuberculosis prevention and control guidelines. As an example, for screening for LTBI in immigrants, TST followed by IGRA if TST is positive, is recommended by countries such as Italy.
Switzerland, Spain, Norway, Ireland, Bulgaria, Slovakia, and the Netherlands. However, the UK and Czech Republic recommend both TST and IGRA simultaneously. USA, Canada and Australia recommend either TST or IGRA. France is the only nation that recommends IGRA alone in this population. Similarly, the guidelines differ for screening children, healthcare workers or the immunocompromised for LTBI.

Significant discordance in positive results has been reported between the TST and IGRA tests in the literature. A study in Baltimore City Health Department patients that assessed the impact of routine IGRA implementation found that a final diagnosis of LTBI (based on patient history, x-ray, HIV status, blood chemistry and TST or TST+QFT-GIT) was made significantly more frequently in the pre-QFT-GIT period (445 of 452 evaluated) compared to the post-QFT-GIT period (397 of 567 evaluated). (Shah 2012) The implementation of IGRA in this setting significantly reduced the proportion of individuals in whom LTBI was diagnosed, leading to a possibility that significantly less number of patients were prescribed INH. In a similar study in French healthcare workers, Moucaut et al. (2013) found that the agreement for positive results between TST and IGRA was only 26.7%.

Another prospective study sought to assess diagnosis of LTBI based on the standard of care alone (TST, patient history, chest x-ray) and then the standard of care plus IGRA and also change in prescription practice based on IGRA results. The study included all patients referred for LTBI testing at the Respiratory Medicine and TB Clinic of Royal Infirmary of Edinburgh. This study determined that agreement for positive results between TST and IGRA was 30%. The remainder TST+ve (70% of cases), the positive LTBI diagnosis based on standard of care alone was changed to negative after negative IGRA results were obtained. All cases with positive TST but negative IGRA underwent a change of practice for chemoprophylaxis. (Tiernan 2013).

A study of military personnel in the Netherlands sought to re-assess positive TST results with IGRA. This study found that agreement in positive results between TST and QFT-GIT tests was 41.2% in new military recruits but was only 6.9% in military members returning from deployment. This low agreement in results was even lower when the patients were re-tested with IGRA several months later. (van Brummelen 2010) It is possible that during deployment, members may be infected with non-tuberculous mycobacteria which will show positive TST but will not be IGRA positive.

Another study in US military recruits had a cross-sectional analysis of TST, QFT-GIT and T-Spot.TB. The study found that of the 88 subjects with at least one positive result, only ten were positive in all three tests and twenty were positive in at least two. It was suggested that the false positives in TST were likely due to infection with non-tuberculous mycobacteria and a history of BCG vaccination. (Mancuso 2012).

Isoniazid is the antibiotic of choice for preventing LTBI from becoming active TB. There is good evidence that in TST converting population, for example, that of the military upon return from a deployment, INH prophylactic therapy will prevent tuberculosis disease. (Veening 1968) Isoniazid is prescribed as a daily dosage for 6 to 9 months as a prophylactic measure in those with LTBI. This is a relatively large drug burden for patients considering the relative high number of INH related adverse side effects. The common adverse side effects include INH related lupus-like syndrome, peripheral neuropathy, gastrointestinal distress and CNS abnormalities. Much less common but serious and fatal reactions include liver disease, including hepatitis (Kopanoff 1978). Therefore, although INH therapy is very effective, it is not justified especially if the diagnostic specificity is poor. In addition to the clinical risk/benefit, the cost/benefit of using INH has also been questioned. In a study comparing the cost of INH for 20-, 50- and 70-year old low-risk patients with positive TST, the authors concluded that although the costs are reasonable from a societal perspective (by reducing the incidence of TB), they are not justified from the patient perspective based on the increased life expectancy resulting from chemoprophylaxis. (Fitzgerald 1990)
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Canadian Armed Forces Setting

The Canadian Armed Forces (CAF) is the military population of Canada. The population consists of approximately 67,000 members in its Regular Force, about 1300 of whom are currently on deployment – largely in Afghanistan, sub-Saharan Africa and the Middle East. (Forces, 2013)

In accordance with the Canadian Tuberculosis Standards (PHAC 2007), members of the CAF are generally considered a “low risk” population. It is important though to consider that many active duty personnel would have received BCG vaccination in their childhood according to the Canadian provincial vaccination practices and the CAF personnel also have very low TB rate – therefore, TST specificity in this population might plausibly be lower than the pooled result reported by Pai and colleagues above.

Certain groups within the CAF are recommended for routine LTBI screening. Members of the CAF are often deployed in regions of the world with high rates of TB infection and active disease. The deployments are often for a prolonged period of time – six months or more. Members of the CAF also often encounter living conditions that may include close contacts (i.e., during recruit training or on missions). These conditions may increase the risk of transmission of TB if there is an active TB case among the group. For these reasons and primarily to allow for consideration of antibiotic prophylaxis therapy to converters, the Canadian Forces Health Services has a screening programme for LTBI. (D FHP 2011) It is very important to accurately diagnose LTBI in the CAF in order to limit unnecessary use of INH, the resources of which could be utilized towards other health care.

In the early version of LTBI screening during 1975 to 2003, all regular members of the CAF and all new entrants to the CAF were annually tested using the TST method. In addition to annual testing of all members, all new entrants and all members just before and just after deployments (pre-deployment and post-deployment) were also tested. (Tepper 2013)

In 2003, the screening programme evolved and the policy change eliminated annual testing of all members and all pre-deployment testing. At this time, all new entrants and all members post-deployment were tested. Screening for LTBI was reduced further in 2004 and instead of all new entrants, only a subset such as; foreign born and members of First Nations (aboriginals in Canada), were screened for LTBI. The change in screening reduced the number of TSTs from over 50,000 to fewer than 23,000 tests per year from pre-2003 to post-2004. (Tepper 2013)

In 2006, IGRAs were approved by Health Canada as diagnostic assays for LTBI. The two approved products in Canada, QFT-GIT and T-Spot.TB, became commercially available and much new evidence started coming to light about the usefulness of these assays. With the growing evidence, the CAF decided in 2011 to introduce IGRA to the screening for LTBI in the CAF members.

The current Directorate of Force Health Protection (D FHP) standard includes LTBI screening in the CAF targeting specific groups in the following way:

a) New entrants on initial training: Initially, all new entrants are screened with a questionnaire in order to identify the high-risk individuals. In essence, four criteria are applied, including the individuals’ country of birth, their status as an aboriginal or Inuit person, contact in the past with someone with active TB or a positive/worrisome TST result in the past. Those who fall within these groups are administered TST as the primary screening tool;
b) Members of the CAF are not tested pre-deployment. All CAF members who are returning from a deployment to a country where TB disease is common (smear positive pulmonary TB incidence of 50 – 99 per 100,000 for 12 months or longer, 100 – 199 per 100,000 for 6 months or longer and > 200 per 100,000 for 3 months or longer), are referred for a TST. In certain cases where large groups are deployed (i.e., Afghanistan), the need for TST is directed by D FHP along with screening tools, such as a questionnaire based on the risk to the individual. Post-deployment TST is to be done within 3 months after return to Canada;

c) CAF members who perform clinical duties (e.g. embedded within a hospital) may be screened using TST as per the national or regional tuberculosis standard. However, a routine periodic screening program is not recommended for the CAF health services personnel who may be relatively low risk; and

d) Other situations when CAF members are screened for LTBI include persons with newly diagnosed immune disorders (including HIV), contact with an active TB case or symptoms suggestive of TB.

In October 2011, the CAF introduced IGRA as a supplement to TST. IGRA is used to confirm or rule out LTBI in members newly identified with positive TST in low risk situations such as the post-deployment group and healthcare provider group (groups ‘b’ and ‘c’ above, respectively). IGRA are not recommended for new entrants (who are already considered high risk according to the screening questionnaire) and for active TB cases or their contacts.

Specific Aims of this Study and Research Question

The overall aim of this study was to determine the impact, on overall LTBI diagnosis and on INH prescriptions, of implementing IGRA testing in the Canadian Armed Forces. This included the following more specific objectives:

1) To determine the uptake of IGRA testing (adherence to D FHP standard and availability of results);

2) To compare the frequency of LTBI diagnosis in the CAF population in the pre-IGRA (April 2010 to Sep 2011) with the post-IGRA (Oct 2011 – Mar 2013) periods by reason for testing (new entrant, post-deployment, occupational or other);

3) To compare the frequency of INH prescriptions during the same time periods; and

4) To determine agreement in positive test results between TST and IGRA.

Methods

Study Design

This was a retrospective analysis to evaluate LTBI screening before and after the implementation of IGRA in the CAF TB program.

In accordance with the D FHP Standard # CDCP/2011/20: Tuberculosis Control in the Canadian Armed Forces, all clinics should report monthly (before IGRA implementation) or quarterly (after IGRA implementation), all TST tests. In addition, further details of each positive TST results should also be reported. These reports are routinely maintained by the Directorate of Force Health Protection. This data was
mired in order to conduct a retrospective analysis of all testing for LTBI reported in the study periods. Each report contained the basic information pertaining to the TB specific tests performed on that patient. The data was put into two cohorts based on 18 months before and 18 months after the date of introduction of IGRA in the Canadian Armed Forces – October 2011.

The study also compared the frequency of LTBI diagnosis with the number of INH prescriptions during the pre-IGRA and post-IGRA periods.

**Study Site**

This study was completed at Canadian Forces Health Services Group Headquarters in Ottawa, Ontario, Canada. Across Canada, there are 43 Canadian Forces Health Services units and their detachments that follow the D FHP standard for LTBI screening. The size of the units and the reasons for testing for LTBI at these units differ greatly depending on past or present operations – for example, some units may primarily test for LTBI in new entrants, while others may do so because their local contingent has recently returned from a long term deployment in Afghanistan. All units report to D FHP at the headquarters, a summary of screening for LTBI which was the primary data source analyzed in this study.

**Study Population**

The study population was the Regular Forces members of the Canadian Armed Forces – the military of Canada. The population was 86% male and 14% female, 52% between 16 and 34 years old and 48% between 35 to 70 years as of 23 August 2013.

This population, due the nature of its occupation is relatively healthy. The population by virtue of its occupation may be deployed to areas of the world where TB is endemic, however, generally the population is not considered at high-risk of becoming TB positive after any of its deployments due to limited contact with the local population.

**Study Period**

The study aimed to compare the 18 month periods before and after the policy implementation that includes use of IGRA to confirm TST positive tests. These time periods are referred to as pre-IGRA and post-IGRA periods in the remainder of this report. The pre-IGRA period was 1 April 2010 to 30 September 2011 and the post-IGRA period was 1 October 2011 to 31 March 2013.

**End Points**

The primary outcome of interest was the diagnosis of LTBI. This was compared between the pre-IGRA and the post-IGRA periods. The secondary outcome of interest was the comparative amount of INH prescriptions during the same periods.

For the LTBI diagnosis section, the outcome was differentiated by the reason for testing. These included testing of the new entrants to the CAF who were identified as being high risk; testing post-deployment of high-risk deployments; testing for occupational required reasons (i.e., working in healthcare field) or other. The last category, “others”, included reasons such as testing required prior to starting certain medications or prior to certain medical procedures, suspected active TB cases and contacts of active TB cases. Comparative frequency of TST-positive results in pre-IGRA and post-IGRA periods was statistically analyzed using the
statistical chi-squared test for comparison of proportions. Agreement for positive test results between TST and IGRA was also measured.

The number of INH prescriptions in pre-IGRA and post-IGRA periods was compared with TST-positive numbers in the same periods. A rate was measured by dividing the INH prescriptions by total TST-positives. A statistical odds ratio was calculated for INH prescriptions in the post-IGRA period compared with the pre-IGRA period.

**Tuberculin Skin Test**

Tuberculin skin testing is routinely performed according to the Mantoux method using 5 tuberculin units of Purified Protein Derivative-Standard (PPD-S) Tubersol® (Sanofi Pasteur). The PPD-S is administered by intradermal injection into the forearm. Approximately 48 to 72 hours is required for the development of the delayed type hypersensitivity reaction. The extent of induration at the injection site is measured after 48 to 72 hours by a standard ruler in millimetres (mm). In the CAF, a reaction of ≥10 mm is considered positive.

**Interferon Gamma Release Assay**

In accordance with the current D FHP policy, all positive TST cases are referred for IGRA testing, if available. Quantiferon-TB Gold In-Tube (Cellestis Ltd.) or T-Spot.TB (Oxford Immunotec Ltd.) are available in Canada. In the CAF, local medical laboratories are utilized for routine lab based testing. Therefore, whichever IGRA test used by the local contract laboratories would be utilized to confirm TST-positive cases in the post-IGRA period.

The QFT-GIT test uses peptides from early secreted antigentic target-6 (ESAT-6), culture filtrate protein 10 (CFP-10), and a portion of TB7.7. In this assay, one millilitre (mL) of blood is drawn into each of three tubes: a nil control, a positive mitogen control, and a tube that contains the *M. tuberculosis* specific RD-1 antigens CFP-10, ESAT-6 and TB7.7. The tubes are incubated at 37°C for 16 to 24 hours and then centrifuged. Plasma is removed and assayed for IFN-gamma by enzyme linked immunosorbent assay (ELISA). The plasma is stable for up to four weeks at 4°C or can be frozen at -20°C for three months. Using the software provided with the commercial kit, the ELISA read-out is used to calculate the amount of IFN-gamma as IU/mL. After correcting for the negative control, an IFN-gamma value of ≥0.35 IU/mL is considered positive. (Cellestis 2006)

The T-Spot.TB test also measures the IFN-gamma release following T-cell exposure to ESAT-6 and CFP-10. The product is available in two formats – a 96 well plate or an 8-well strip. In this assay, 8 mL of blood is collected into sodium citrate cell preparation tubes. Peripheral blood mononuclear cells (PBMC) are isolated and added to four plates – a nil control, a positive control, and two patients test wells containing ESAT-6 and CFP-10. The assay incubates the PBMC in these wells and measures the number of T-cells producing IFN-gamma by enzyme linked immunospot (ELISPOT) assay. The results are compared to the number in negative and positive control wells. A result of ≥8 Spot Forming Units (SFUs) would be considered a positive result. (Oxford 2012)

**Study Procedure**

Inclusion Criteria:

a) All monthly (May 2010 to Sep 2011) and quarterly (Oct 2011 to Mar 2013) reports were included; and
b) All filled INH prescriptions were included in accordance with the drug usage database (Blue Cross).

Exclusion Criteria:

a) All TSTs administered but “not read” (i.e., patient did not return for induration to be read) were excluded from the study;

b) Any IGRA results in the pre-IGRA period were excluded; and

c) All INH prescriptions without a corresponding TST or IGRA were excluded.

Data Collection, Organization and Analysis:

a) All monthly (pre-IGRA) and quarterly (post-IGRA) reports were collected and printed;

b) The reports were read one-at-a-time and tabularized by the unit reporting and then by reason for testing. Microsoft Excel was used to organize the data in this format;

c) Using Microsoft Excel, the total frequency of LTBI in the pre-IGRA and the post-IGRA periods was determined;

d) The pharmacy prescription database (Blue Cross) was mined to determine total number of INH prescriptions in the pre-IGRA and the post-IGRA periods; and

e) Statistical analysis was done using the software MedCalc – version 12.7.2. (MedCalc 2013)

Ethical Approval

This research was approved under the Canadian Armed Forces Surgeon General Health Research Program. This program includes requirements for research ethics considerations. In accordance with the instructions, this proposal was submitted to the Surgeon General Health Research Board (SGHRB) and was approved on 14 Feb 2013 (Reference: 2013-01-067-006-0001). Specific Research Ethics Board approval was not required by the SGHRB as all data was collected as part of routine public health surveillance and was provided in an anonymized form to the investigator. London School of Hygiene and Tropical Medicine MSc Research Ethics Committee also approved the proposal for this study (Reference: 012-012) on 8 April 2013.

Potential Bias and Confounders

Selection bias may possibly occur as the results are completely reliant on reporting practices of health clinics. Reporting may not always be accurate or complete. The healthcare provider staff at clinics is made up of members of the CAF. Military members are routinely rotated approximately every three years – meaning the reporting nurse at any given clinic may be new to the process and therefore, reporting practices may be inconsistent or inaccurate.

Results

All quarterly reports during the pre-IGRA and post-IGRA periods were tabulated and analyzed for total numbers of TST and IGRA tests completed and their results. In total, 13,908 TST were performed, but 409 (2.9%) of these were excluded because the results were not read – likely due to patients not returning to the clinic within 48 to 72 hours after the initial visit.
Of the 13,499 TST results included, 8,594 were in the pre-IGRA and 4,905 were in post-IGRA periods. In total, 13,284 (98.4%) tests were TST-negative. In the pre-IGRA period, 102 (1.19%) TST tests were positive and in the post-IGRA period, 113 (2.30%) TST tests were positive. (Difference: 1.11%, 95% CI: 0.636% to 1.618%, DF = 1, P < 0.0001).

In both the pre-IGRA and the post-IGRA periods, the reports from clinics were divided by the reason for testing. Each report included total numbers screened and then tested for new entrants, total numbers tested for post-deployment, occupational or “other” reasons. In most cases, occupational reasons included personnel going to work in a medical setting or due to requirements to attend or apply to a school such as a paramedic training facility. In the “other” category, three primary reasons were noted: contact with an active TB case, symptoms of TB, or the patient was starting an immune suppressant drug therapy such as adalimumab.

**Compliance with D FHP Standard**

D FHP Standard recommends that any positive TST result in a CAF member post-deployment should be followed by an IGRA test; if available, in order to confirm an LTBI diagnosis. In the post-IGRA period, there were a total of 113 positive TST reports, 71 of which were in the post-deployment group. Of these, 38 had IGRA performed, but 33 of these did not. Therefore, uptake of IGRA in the CAF based on the D FHP Standard was 53.5%.
Screening for LTBI in the Canadian Armed Forces

Table 2 shows TST positivity in the CAF during the pre-IGRA and the post-IGRA periods. Of the total 8,594 TST performed during the pre-IGRA period, 102 (1.19%) were positive. The distribution of tests performed by reason for testing shows that the post-deployment group was by far the largest group of the CAF population who had TST performed on them at 7095/8594 (82.6%). The remainder of the testing was for new entrants 977/8594 (11.4%), for occupational reasons 456/8594 (5.31%), and for other reasons 66/8594 (0.77%). The number of positive TST varied between the groups. In the new entrants group, 2.46% of the TSTs were positive compared with 0.97% in the post-deployment group, 1.31% in occupational group and 4.54% in the “other” group.

<table>
<thead>
<tr>
<th>Reason for TST</th>
<th>Pre-IGRA Period</th>
<th>Post-IGRA Period</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total TST</td>
<td>Positive TST</td>
<td>% TST Positive</td>
</tr>
<tr>
<td>New entrant</td>
<td>977</td>
<td>24</td>
<td>2.46%</td>
</tr>
<tr>
<td>Post-deployment</td>
<td>7095</td>
<td>69</td>
<td>0.97%</td>
</tr>
<tr>
<td>Occupational</td>
<td>456</td>
<td>6</td>
<td>1.31%</td>
</tr>
<tr>
<td>Other</td>
<td>66</td>
<td>3</td>
<td>4.54%</td>
</tr>
<tr>
<td>Total</td>
<td>8594</td>
<td>102</td>
<td>1.19%</td>
</tr>
</tbody>
</table>

* P-value is derived from a chi-squared test comparing the two proportions.

In the post-IGRA period, a total of 4905 TST were performed and 113 (2.30%) of them were positive. Again, in this period, the post-deployment group was the largest at 3774/4905 (76.9%) followed by 672/4905 (13.7%) in new entrants. There were 333/4905 (6.79%) tests for occupational reasons and 126/4905 (2.57%) were for other reasons. Of the four subgroups only the post-deployment group had a significant difference in TST positivity between pre-IGRA and post-IGRA periods (Difference: 0.91%, 95% CI: 0.43% to 1.44%, chi-squared: 15.36, P = 0.0001).

IGRA Testing in the Canadian Armed Forces

Table 3 shows the results of IGRA testing by the four groups. Only TST positive cases were tested using IGRA. Of the total 113 positive TST, 54 (47.8%) had IGRA performed on them. There were 37 negative IGRA and 17 positive IGRA results. Agreement in positive results between TST and IGRA then was 60% in new entrants, 26.3% in the post-deployment group, 0% in the occupational group and 50% in the “other” group. Overall, agreement in positive results between TST and IGRA was 31.5%.
In accordance with the D FHP Standard, only the post-deployment group should have IGRA testing. All other groups are considered at relative “high-risk” and TST positive results should be used along with patient history, chest x-ray and other medical tests for decisions to recommend prophylactic INH.

Comparing TST test results alone in the pre-IGRA and the post-IGRA periods, for both groups of interest, the new entrants and the post-deployment, the proportion of TST positive results increased by 1.26% and 0.91% respectively. However, the difference is statistically significant only for the post-deployment group.

**Isoniazid Prescriptions**

Table 4 compared the number of positive TST with number of INH prescriptions during the pre- and post-IGRA periods. In the pre-IGRA period, a total of 102 TSTs were positive and in the post-IGRA period, a total of 113 TSTs were positive. In the pre-IGRA period, a total of 71 new patients obtained INH. However, two were excluded because they were not tested with either TST or IGRA, but were prescribed INH simply based on the fact that they were in contact with an active TB case for a prolonged time. In the post-IGRA period, there were a total of 31 new patients who filled INH prescriptions – however, one was excluded because this patient was tested in the US and had started a 9-month course of INH in the US, but was completing the regimen in Canada.

<table>
<thead>
<tr>
<th>Reason for TST</th>
<th>Positive TST</th>
<th>Number of IGRAs</th>
<th>Negative</th>
<th>Positive</th>
<th>% +ve Agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>New entrant</td>
<td>25</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>60</td>
</tr>
<tr>
<td>Post-Deployment</td>
<td>71</td>
<td>38</td>
<td>28</td>
<td>10</td>
<td>26.3</td>
</tr>
<tr>
<td>Occupational</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>50</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>113</strong></td>
<td><strong>54</strong></td>
<td><strong>37</strong></td>
<td><strong>17</strong></td>
<td><strong>31.5</strong></td>
</tr>
</tbody>
</table>

The absolute difference in the proportion of TST positive cases who obtained INH between the pre-IGRA and post-IGRA period was 41.1%. The ratio of the odds of being prescribed INH in the post-IGRA period compared to pre-IGRA period was 0.17 (95% CI: 0.10 to 0.31, z-statistic: 5.85, P < 0.0001).
Discussion

Study Population

Due to the use of anonymized reports for analysis in this study, the exact characteristics of the study population are not known. However, according to the CAF Human Resources Reporting System, as of 23 Aug 2013, the total Regular Force population of the CAF is comprised of 67,342 members with 86% males and 14% females. The age distribution of the population is approximately 48% between 16 to 34 years, 39% between 35 to 49 years and 13% over 50 years of age.

The sub-groups of this population that were of interest to this study were the new entrants and the post-deployment groups. These were the largest populations screened for LTBI and any policy change would need to consider these groups. The occupational and the “other” groups are not discussed in detail in this section because of their relatively small numbers.

Table 5: Size of the Total CAF Population by Fiscal Year and the Size of the Groups of Interest by Study Periods.

<table>
<thead>
<tr>
<th></th>
<th>Total CAF Reg Force*</th>
<th>New Entrants* during the:</th>
<th>On Deployment** during the:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pre-IGRA Period:</td>
<td>Pre-IGRA Period:</td>
</tr>
<tr>
<td>31 Mar 2010</td>
<td>68,136</td>
<td>6,947</td>
<td>12,263</td>
</tr>
<tr>
<td>31 Mar 2011</td>
<td>68,250</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31 Mar 2012</td>
<td>67,719</td>
<td>Post-IGRA Period:</td>
<td>Post-IGRA Period:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5,629</td>
<td>5,436</td>
</tr>
<tr>
<td>31 Mar 2013</td>
<td>67,686</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data received from Public Affairs, Chief Military Personnel.
** Deployed overseas for 3 months or longer. Data received from Strategic Joint Staff.

The total size of the CAF population has largely remained constant between the pre-IGRA and the post-IGRA periods. At the beginning of the study period, there were 68,138 members and at the end of the study period, there were 67,868 members in the CAF. The number of new recruits was lower in the post-IGRA period compared to the pre-IGRA period. More noticeable though, the numbers of CAF members on deployments were significantly lower in the post-IGRA period compared with the pre-IGRA period.

It was noted that 2.9% of patients administered TST did not return for the result to be read 48 to 72 hours after the initial test. This is likely due to the highly mobile population of the CAF. Many members, upon return from a deployment are posted to new positions which may involve moving to another location and loss of medical follow-up.

IGRA Uptake

There are 43 CAF clinics (units) across Canada to which the D FHP Standard CDCP/2011/20 applies. All clinics are requested to submit monthly (pre-IGRA) or quarterly (post-IGRA) reports to D FHP even with nil entries. However, only 23 units have provided the reports found in the database used for this study. It is unknown whether the remaining clinics did not have any LTBI screening or whether they did not submit
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

reports. However, it is reasonable to imagine that because the population is relatively uniform, the pattern of TST positivity would follow a normal distribution within the CAF population.

In October 2011, D FHP promulgated the policy for tuberculosis control in the CAF (D FHP 2011). This updated standard recommended the use of IGRA in all TST positive cases in the CAF for members returning from deployments. In the period between Oct 2011 and Mar 2013, 113 TST positive cases were reported and 71 of these were in the post-deployment group. Although all 71 should have had IGRA tests performed, only 38 actually reported IGRA results. Therefore, during this period, the IGRA uptake rate can be said to be 53.5%.

There could be several possible explanations for the poor uptake. For example, a few of the CAF clinics are located in remote areas with no access to diagnostic laboratories. Physicians may perceive the CAF population as low-risk for tuberculosis and may be comfortable making decisions based on TST alone, plus chest x-ray and patient history (BCG vaccination, deployment or contact history). IGRA is a relatively new test and its uptake in the larger Canadian population is as yet unknown. Most physicians are familiar with TST as it has been used widely for decades.

In essence, the use of IGRA in the CAF is in general agreement with the recommendations from the Public Health Agency of Canada and the US Centers for Disease Control and Prevention.

TST Conversions During Deployments

Seventy percent of the CAF members deployed overseas in the last three years for 3 months or longer have been deployed to Afghanistan. (Tepper 2013) Smaller numbers were deployed on ships, sub-Saharan Africa and the Middle East. The incidence of TB in Afghanistan has been steady at 189 per 100,000 since 2008. (WHO 2012) In the post-deployment group, a statistically significant difference was noted in the frequency of TST positive tests between the pre-IGRA and post-IGRA periods. In the post-IGRA period, 1.88% CAF members returning from deployment were TST positive compared to 0.97% in the pre-IGRA period. This statistically significant difference could be due to a number of reasons. Canada is part of NATO’s International Security Assistance Force (ISAF) in Afghanistan. The role of the CAF changed from pre-IGRA to post-IGRA periods. In the pre-IGRA period, large components of the CAF members in Afghanistan were located within the ISAF base. There was very limited contact with the local population – and the contact that did exist during this time was of a combat nature. In the post-IGRA period, the CAF became more involved in community mentorship and had a higher frequency of contact with the local population, including training and mentorship of the Afghan security force, healthcare facilities and schools. Therefore, due to the nature of the mission in the pre-IGRA period, the risk of a CAF member coming into contact with an active case of TB was lower than in the post-IGRA period, which included frequent peaceful contact with local security force, healthcare workers (and patients) and children.

The agreement between TST and IGRA was lowest in the post-deployment group at 26.3%, although it had the highest number of IGRA tests performed. This could also be explained by the more sociable role in the post-IGRA period, which provided the opportunity for exposure to environmental mycobacteria. In a study of the Dutch military population, re-testing with IGRA at 0, 2, 6 and 12 months post-deployment resulted in positive results reverting to negative over time. The authors concluded that the majority of the TST conversions post-deployment are probably not caused by actual infection with *M. tuberculosis* but could be related to exposure to non-tuberculous mycobacteria. (van Brummelen 2010) This could also be the case in the Canadian military population and prospective studies with repeat testing using IGRA could support this speculation.
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

Rates of LTBI in New Entrants

This was the group with the second highest number of TST performed at about 11% of all cases in the pre-IGRA and 14% in the post-IGRA periods. Between the two periods, the rate of positivity increased slightly from 2.46% to 3.72%. This increase was not statistically significant. New entrants represent the highest risk group within the CAF, and therefore, the current standard infers that all TST positive new entrants be considered positive for LTBI. If all recruits are screened and treated with INH if positive, the remainder of the CAF population should be largely LTBI-free, unless exposed during their duty, especially deployment missions.

New entrants are first screened with a questionnaire to identify those at higher risk – immigrants from a high TB prevalence country, aboriginals (First Nations and Inuit of Canada), history of positive TST and recent contact with an active TB case. In both high TB prevalence countries and the aboriginal population in Canada, BCG vaccination is common. Therefore in these sub-groups, the specificity of TST is likely low and use of IGRA in these groups may prevent much unnecessary INH prescriptions.

Although not required to do so by the standard, 10 of the 25 TST positive cases of new entrants were tested with IGRA in the post-IGRA period. Six of these were positive and 4 negative, giving a 60% agreement between TST and IGRA. This is consistent with the assumption that new entrants are the highest risk population of the CAF and inference that TST positives are likely true LTBI positives. However, 40% IGRA negative is still a significant number over time – in the 18 months of the post-IGRA period, of the 25 TST positive cases, this accounts for ten patients who may not have needed INH for 9 months.

In a study of United States Navy new entrants, Mazurek and colleagues (2007) found that QFT-GIT is a more specific test than TST when a cut off of > 10 mm induration is used as positive TST. However, when a 15 mm cut-off is used, the difference was not statistically significant. In a similar study several years later, Mancuso et al. (2012) found that in low-prevalence populations (originating from a country with TB incidence of < 20 per 100,000) in the US military new entrants, most of the discordance was due to false-positives in TST. But the authors could not find a statistical difference in the “higher-risk” new entrants.

The usefulness of IGRA in the new entrants in the CAF should be assessed further in prospective studies.

Rates of LTBI in Occupational and Other Groups

Although these two groups made up the smallest portion of total TSTs, it is worth briefly discussing the impact of IGRA on these groups. Majority of the cases screened in the occupational group were for requirements of entry into formalized training. It was impossible to differentiate this population in any way, except that they were all members of the CAF. There were four IGRA tests done in this group and all were negative. This complete disagreement between TST and IGRA in this group could simply be attributed to the relatively small sample size. Similarly, in the “other” group, out of 2 IGRA, one was positive and one negative. It is impossible to assess reasons as the sample size was too small to judge the difference.

Use of Prophylactic Antibiotics

Although the proportion of TST positive cases overall increased from 1.19% in the pre-IGRA period to 2.30% in the post-IGRA period, the proportion of TST positive cases who obtained INH prescriptions was reduced significantly from 67.6% to 26.5%. This suggests that introducing IGRA in the LTBI screening program in the CAF had a large impact – even though only about half of TST positive cases had IGRA done on them.
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

The CAF is generally considered to be at a “very low” risk of TB (D FHP 2011). Since 2000, there has been only one case of active TB reported in the CAF and it was acquired outside of CAF activities. (Tepper 2013) Having such a low INH prescription rate in the TST positives, with no active cases of TB reported in the study periods, supports the theory that the CAF is at a very low risk of TB. This may also account for the relatively low proportion of TST positive cases actually acquiring INH prophylaxis.

A risk/benefit analysis for INH then would suggest that using TST alone for LTBI diagnosis increases the risk of adverse events in the patient with little impact on the benefit. Although not formally analyzed in this study, it was noted that several prescriptions that were filled once were not filled again (in Canada, INH is once-a-day tablet available in 100 tablets/bottle and is usually prescribed for 9 months, requiring a minimum of two re-fills). It is also possible that patients, even if prescribed INH, did not fill the prescription or they declined the prescription altogether.

The odds ratio of getting INH prescription in the post-IGRA period compared to the pre-IGRA period was 0.17. Therefore, TST positive patients were significantly less likely to receive INH in the post-IGRA period compared to TST positive patients in the pre-IGRA period.

A significant reduction in INH prescriptions in the CAF as noted by this study is supported by Tiernan and colleagues (2013) who found that including results of IGRA testing significantly lowered clinical practice of INH prescriptions. Similarly, Shah et al. (2012) found that introduction of QFT-GIT significantly reduced diagnosis of LTBI and therefore, the practice of prescribing chemoprophylaxis.

Limitations of the Study

1) In general, it can be argued that the CAF population is a niche population with narrow age and sex distribution, relatively good health and different risk factors compared to the general population. The results of this study may not apply to other population groups, but may be applicable to the militaries of allied nations of the Western world.

2) Due to the retrospective nature of this study, it was impossible to confirm complete reporting. Under-reporting in the CAF is a problem which could have caused the results to become skewed. Although this is unlikely if a normal distribution of CAF population across all clinics is assumed.

3) Two separate databases were used in this study – TB converters database and a drug utilization database. These systems are not linked. Therefore, it was impossible to tell whether the positive TST cases were the same as those who filled INH prescriptions. This is particularly limiting for the assessment of impact of IGRA in the post-IGRA period because an assumption had to be made that in this period, TST-positive cases without IGRA testing were considered positive for LTBI as well as those with TST-positive and IGRA-positive.

4) The agreement between TST and IGRA is only analyzed for positive TST results. For complete concordance/discordance analysis of the two tests, a prospective study needs to be completed where negative TST cases are also tested with IGRA. Additionally, IGRA negative cases should be followed up long term to determine that the prognosis actually is negative. This could be very difficult though as LTBI can take decades to become active and in large proportion of LTBI positive cases, may never become active. As reported by almost every researcher in this field, there is no “gold-standard” for LTBI diagnosis.
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

5) There are two IGRA tests approved for use in Canada – QFT-GIT and T.Spot-TB. It was impossible to determine which of these tests were used for the CAF patients – likely a combination of both. The CAF clinics purchase specialty laboratory services, including IGRA tests, from local private labs. In speaking with some experienced CAF laboratory personnel, most of the private laboratories use QFT-GIT.

Conclusions

1) Uptake of IGRA as a confirmatory test in positive TST cases in the post-deployment group is poor at 53.5% in the CAF.

2) Frequency of TST positive cases was significantly higher in the post-IGRA period compared with the pre-IGRA period.

3) Agreement in positive test results between TST and IGRA was poor at 26.3% in the post-deployment group and 31.5% overall.

4) INH prescriptions were significantly reduced after the implementation of IGRA.

Recommendations

• In order to validate the CAF TB screening standards, compare the screening guidelines in the military for US, UK, France, the Netherlands, Germany and Australia. These are likely not publicly available therefore, active requesting through proper chain of command and through existing medical R&D agreements will need to occur.

• Determine costs of TST+IGRA or IGRA alone in the CAF population and compare with cost of INH. In addition to the risk/benefit comparison of the screening options, a cost/benefit comparison may inform future policy changes.

• Encourage CAF physicians to comply with the D FHP Standard # CDCP/2011/20. If the physicians were educated on the false positivity rate of TST and the impact of INH, they may become more likely to utilize IGRA.

• Consider studying the impact of NTM as the reason for TST positivity in the CAF. A repeat IGRA several months after return from deployment could further reduce INH prescriptions in the CAF.
Acknowledgements

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First and foremost, I would like to thank my supervisor at LSHTM, Dr. Richard Lessells for the outstanding scientific guidance throughout this project. I would like to acknowledge Canadian Forces Health Services for providing me with the opportunity to carry out this research and specifically Dr. Martin Tepper, Mrs. Fiann Crane and Dr. Janice Ma for their indispensable guidance, helpful suggestions and insights on the CAF standards, processes and realities. Thanks also to Mrs. Michelle Lanouette and Dr. Slavica Dragisic for editing my work.

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Lastly, I would like to thank my loving wife Ragini, and my family for their continuous support, encouragement and understanding while I pursued my studies.
Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces
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Use of Interferon Gamma Release Assays as Confirmatory Test for Tuberculin Skin Test-Positive Patients in the Canadian Armed Forces

Patel, M.

February 2014

Technical Report

SGR-2013-011

Approved for Public Release; Distribution Unlimited

Unlimited Announcement
Introduction

Interferon Gamma Release Assays (IGRAs) are considered a supplement to confirm tuberculin skin tests (TST) for the diagnosis of latent tuberculosis infection (LTBI). The impact of the recent introduction of IGRAs in the LTBI screening program of the Canadian Armed Forces (CAF) is being investigated.

Methods

This retrospective study compares the TST positivity in the CAF during 18 months before and after the implementation of IGRA. The study analyzes the agreement between TST and IGRA and the impact of IGRA on treatment in the 18 months post-IGRA period.

Results

Of the total 13,499 TSTs included in this study, 102 were positive in the pre-IGRA and 113 were positive in the post-IGRA period. In the post-IGRA period, 54 had IGRA tests with 17 positive and 37 negative (TST-IGRA agreement of 31.5%). TST positivity was significantly increased in the post-deployment group from 0.97% in the pre-IGRA to 1.88% in the post-IGRA period. In all other groups, the difference was not significant. Proportion of TST positive cases receiving isoniazid chemoprophylaxis was significantly reduced by 41.1% in the post-IGRA period.

Conclusions

Frequency of TST positive cases was significantly higher in the post-IGRA period compared with the pre-IGRA period, possibly due to the changing role of the CAF from that of battle to mentoring. The data indicates that the agreement in positive results between TST and IGRA is poor at 26.6%. Isoniazid prescriptions were significantly reduced after the implementation of IGRA suggesting that the use of IGRA prevents much unnecessary use of the antibiotic.

Introduction

Le test de libération d’interféron gamma (TLIG) est considéré comme un complément visant à confirmer le résultat du test cutané à la tuberculine (TCT) pour le diagnostic de l’infection tuberculeuse latente (ITL). On étudie actuellement l’impact de l’introduction récente du TLIG dans le programme de dépistage de l’ITL des Forces armées canadiennes (FAC).

Méthodologie

Cette étude rétrospective compare le nombre de membres des FAC qui ont eu un TCT positif au cours des 18 mois précédant l’introduction du TLIG et au cours des 18 mois où ce test a été utilisé. L’étude analyse la concordance des résultats du TCT et du TLIG ainsi que l’impact du TLIG sur le traitement administré aux personnes qui ont reçu leur diagnostic durant la période de 18 mois suivant l’introduction du TLIG.
Résultats
Sur l’ensemble des 13 499 TCT visés par cette étude, 102 résultats positifs ont été obtenus durant la période où le TLIG n’était pas utilisé et 113 résultats positifs ont été obtenus durant la période où le TLIG était utilisé. Durant la période où le TLIG a été utilisé, ce test a été administré à 54 personnes : 17 ont obtenu un résultat positif et 37 ont obtenu un résultat négatif (taux de concordance du TCT et du TLIG de 31,5 %). Le taux de positivité au TCT a augmenté de façon significative dans le groupe où le TLIG a été utilisé : ce taux est passé de 0,97 % lorsque le TCT était utilisé seul à 1,88 % lorsque les deux tests ont été utilisés en combinaison. Dans tous les autres groupes, aucune différence significative n’a été observée. Durant la période où le TLIG a été utilisé, on a observé une importante diminution (41,1 %) de la proportion de cas positifs au TCT à qui une chimioprophylaxie par l’isoniazide a été prescrite.

Conclusions
La prévalence des TCT positifs était nettement supérieure durant la période où le TLIG a été utilisé, comparativement à la période où le TCT a été utilisé seul, peut-être en raison du fait que le rôle des FAC a changé, passant du combat à la surveillance. Selon les données, le taux de concordance des résultats positifs entre le TCT et le TLIG est faible (26,6 %). Le nombre d’ordonnances d’isoniazide a grandement diminué après l’introduction du TLIG, ce qui donne à penser que l’utilisation de ce test permet d’empêcher le recours inutile à cet antibiotique.

13. KEYWORDS, DESCRIPTORS or IDENTIFIERS (Technically meaningful terms or short phrases that characterize a document and could be helpful in cataloguing the document. Use semi-colons as delimiters.)

LTBI, Tuberculosis, IGRA, TST, Isoniazid