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DASG-PPM-NC

25 SEP 2008

MEMORANDUM FOR SEE DISTRIBUTION

SUBJECT: Supplemental guidance for the Army Latent Tuberculosis Infection (LTBI) Surveillance and Control Program

1. Purpose. The enclosed document provides supplemental guidance to the Army LTBI Surveillance and Control Program document, 27 May 2003. The 2003 guidance is still in effect unless specifically changed in this document.

2. Scope. This guidance applies to all medical activities in the US Army.

3. Summary of Guidance.

a. LTBI Screening Tests: There are now two US Food and Drug Administration approved diagnostic aid modalities available for diagnosis of LTBI - the tuberculin skin test (TST), and the interferon-gamma release assays (IGRAs) QuantiFERON®-TB Gold and QuantiFERON®-TB Gold-In-Tube. Interpretation of results of either the TST or the IGRA requires consideration of all relevant epidemiological, historical, medical, and diagnostic findings. Contemplated changes in choice of diagnostic aid should be thoroughly staffed at the local level before implementation.

b. Targeted Screening: LTBI testing should only be done for individuals with known risk factors including persons at high risk for TB who have either been exposed recently with *M. tuberculosis* or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB. A complete list of risk factors is included in tables 2 and 3 in reference d. For Soldiers returning from deployment, exposure to TB will be assessed in the Post-Deployment Health Assessment (PDHA) and only Soldiers with high-risk exposures will be screened. If the PDHA provider determines that a Soldier is at increased risk, the Soldier will receive an LTBI screening test at the time of redeployment, with appropriate medical evaluation and treatment as indicated for positive results.

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Encl
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SUPPLEMENTAL GUIDANCE TO THE ARMY LATENT TUBERCULOSIS INFECTION (LTBI) SURVEILLANCE AND CONTROL PROGRAM

1. Purpose. This document provides supplemental guidance to the Army LTBI Surveillance and Control Program document, 27 May 2003. The 2003 guidance is still in effect unless specifically changed in this document.

2. References.

a. Army Regulation (AR) 40-5, Preventive Medicine, 25 May 2007.

b. DA Pam 40-11, Preventive Medicine, 22 July 2005.

c. Core Curriculum on Tuberculosis, US Department of Health and Human Services, Centers for Disease Control and prevention, National Center for HIV, STD and TB Prevention, Division of Tuberculosis Elimination, Fourth Edition, 2000.

d. Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, MMWR Recommendations and Reports, 9 June 2000, 49(RR-6);1-54, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm, accessed 23 January 2008.

e. QuantiFERON®-TB Gold In-Tube package insert, http://www.cellestis.com/IRM/Company/ShowPage.aspx?CPID=1370, accessed 14 December 2007.

f. Pai M et al. Serial testing for tuberculosis: can we make sense of T-cell assay conversions and reversions? PLoS Med. June 2007;4(6):e208.

g. Mazurek et al. Detection of Mycobacterium tuberculosis infection in United States Navy recruits using the tuberculin skin test or whole blood interferon-gamma release assays. Clin Infect Dis. 2007 October 1;45(7):826-36.

h. Diel R et al. Cost effectiveness of interferon-gamma release assay screening for latent tuberculosis infection treatment in Germany. Chest 2007; 232:2424-1434.

i. Sbarbaro JA and Iseman M. Editorial Response: “Koch’s Lymph” 107 Years Later – An Oldie but not a Goldie, CID 1997 September;25(3):664.

j. World Health Organization’s Annual Report on Global Tuberculosis Database http://www.who.int/globalatlas/dataQuery/default.asp.

SUBJECT: Supplemental Guidance to the Army Latent Tuberculosis Infection (LTBI) Surveillance and Control Program

3. Screening Tests for LTBI.

a. There are now two US Food and Drug Administration (FDA) approved diagnostic aid modalities available for diagnosis of LTBI - the tuberculin skin test (TST) and interferon-gamma release assays (IGRA) such as QuantiFERON® technology; QuantiFERON®-TB Gold (QFT-G), and QuantiFERON®-TB Gold In-Tube (QFT-GIT).

(1) Interpretation of results of either test modality requires consideration of all relevant epidemiological, historical, medical, and diagnostic findings.

(2) Comparing sensitivities of TST and IGRAs is difficult because there is no gold standard test by which to determine whether a patient has LTBI. QFT-G is less sensitive than QFT-GIT. Specificity of QFT-GIT is marginally better than TST at 10mm, but the two tests are equivalent in specificity at 15mm.

(3) Screening program options include TST only, IGRA only, or TST followed by IGRA among those positive by TST.

(4) Personnel responsible for the local TB control program should take into account local conditions in deciding which diagnostic aid for latent TB should be used. Contemplated changes in choice of diagnostic aid should be thoroughly staffed at the local level before implementation.

b. TST.

(1) The TST using purified protein derivative (PPD) has been, until recently, the only diagnostic aid available to clinicians trying to establish whether a patient may have LTBI. The US Army Medical Department has traditionally used the Mantoux test for all TB screening. The Mantoux test is the intradermal injection of 0.1 milliliter of PPD tuberculin containing 5 tuberculin units. Administration, classification and interpretation of reactions are done in accordance with (IAW) guidelines published by the Centers for Disease Control and Prevention (CDC).

(2) Administration and reading of TSTs requires special training. Local policies should define who is qualified to administer and read TSTs and should require written certification of such individuals. Qualified personnel will receive annual retraining in the administration and reading of TSTs.

(3) Based on decades of prospective data, strong evidence exists to show that conversion of the skin test is associated with risk of progression to actual disease and that treatment of individuals with conversions reduces risk of progression to active TB.

Thresholds for defining TST conversions are also based on evidence. The skin test has been used successfully in the United States and around the world to control TB.

(4) Disadvantages of the TST include the following:

(a) Need for two patient visits.

(b) Technical and logistical difficulty of administering and reading the test and recording test results.

(c) Potential for false positive results due to bacille Calmette-Guérin (BCG) vaccination or exposure to non-tuberculosis mycobacteria.

(d) Possibility of boosting and consequent possible necessity for a two-step baseline test. In some persons who are infected with *M. tuberculosis*, the ability to react to tuberculin may wane over time. When given a TST years after infection, these persons may have a false-negative reaction. However, the TST may stimulate the immune system, causing a positive or negative reaction to subsequent tests. Giving a second TST after an initial negative TST reaction is called two-step testing which is useful for the initial skin testing of adults who are going to be retested periodically, such as healthcare workers or nursing home residents.

(5) To minimize false positive skin test results, Tubersol® brand tuberculin (Sanofi Pasteur) should be used preferentially over Aplisol® brand tuberculin (Parkedale Pharmaceuticals). Aplisol has been associated with many reports in the literature of false positive results. Experts have written that “Aplisol likely contains more antigens shared with [non-tuberculous mycobacteria] than does Tubersol. Therefore, Aplisol should continue to produce greater numbers of false-positive tests when used in general populations.” (Reference i)

c. QFT-GIT Testing.

(1) In October 2007, the FDA approved QFT-GIT as an in vitro diagnostic test. QFT-GIT is an interferon-gamma release assay (IGRA). When a person has been previously exposed to a disease, their lymphocytes “remember” the antigens of the disease agent. Subsequently, if that person is tested with an IGRA their lymphocytes will produce interferon-gamma (IFN-gamma) and they are likely to return a positive response on the test. QFT-GIT is an improvement over QFT-G because incubation of whole blood with the antigens begins immediately on drawing the blood into the mini-tubes, obviating the need to process the specimens within 12 hours, and because an additional antigen may increase sensitivity. Analysis of data and calculation of results can be done through purchased proprietary QFT-GIT software or manually through

generation of a standard curve with appropriate quality control parameters.

(2) IGRAs have been developed, in part, to overcome some of the disadvantages of the TST. Using IGRAs, boosting does not occur, only one patient visit is required, and the technical challenges are limited to laboratory personnel and equipment instead of relying on the variability that occurs with placing, reading and recording TSTs. Using QFT-GIT, there should be fewer false positives due to BCG vaccination and, perhaps, to non-tuberculous mycobacteria than with TST.

(3) Because TB control program personnel and laboratory personnel are less likely to be familiar with QFT-GIT than with TST, more detail is provided below regarding technical and logistical challenges with QFT-GIT, of which there are many. Complete information is available in the QFT-GIT package insert.

(a) False positive or negative results can result from incorrect blood-collection procedures, incorrect blood-specimen handling, or incorrect use of the QFT-GIT assay.

(b) Interpretation of QFT-GIT dichotomous 'positive' and 'negative' results requires consideration of all relevant epidemiological, historical, medical, and diagnostic findings. Clinicians should not accept that a 'positive' or 'negative' QFT-GIT lab result is necessarily true. Unreliable or indeterminate results may result from deviations from the procedure described in the QFT-GIT package insert or from characteristics of the individual being tested, such as excessive levels of circulating IFN-gamma or presence of heterophile antibodies.

(c) Few if any data are available regarding variation, over time, of IFN-gamma levels in individuals, making determination of the optimal IGRA cut-point difficult, but critically important since minor changes in IFN-gamma level could result in opposing interpretations of the patient's TB status. IGRA conversion (negative to positive) could be a result of random biological variation in IFN-gamma levels in an individual and is not necessarily reflective of LTBI. For serial testing, knowledge of the actual IFN-gamma value of a test, not just a dichotomous positive/negative interpretation, may be important for clinicians to be able to interpret. It has been postulated that high and/or rising levels of IFN-gamma may be prognostic markers for active disease, but this theory has not been confirmed in large-scale cohort trials.

(d) Conversions and reversions of IGRAs may be frequent, and there are insufficient data to fully interpret IGRA conversions and reversions. Possible reasons that IGRAs revert include clearing of TB infection, either spontaneously or due to treatment; biological variations among IGRA-positive individuals; variability in lab and test procedures; permanent or temporary cessation of secretion by *M. tuberculosis* of early secreted antigen target 6 (ESAT-6), culture filtrate protein 10 (CFP-10), and

TB7.7(p4).

(e) There is a lack of prospective data demonstrating the likelihood of progression to disease among those with positive and negative test results.

4. Targeted Screening.

a. The US CDC recommends that tuberculin testing programs should be targeted to individuals at high risk and discouraged in those at low risk. Personnel responsible for the local tuberculosis should ensure that testing for LTBI is, to the extent possible and given current Joint and Army regulations and requirements, targeted at those with true risk of TB.

b. Persons at high risk for TB have either been infected recently with *M. tuberculosis* or have clinical conditions that are associated with an increased risk of progression of LTBI to active TB. A complete list of risk factors is included in tables 2 and 3 in reference d. http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4906a1.htm.

c. Increased risk in deployed Soldiers is defined as indoor exposure to locals or third country nationals of greater than one hour per week in a highly-endemic active TB region. Highly endemic is defined as greater than 25 cases per 100,000 persons annually. Country-specific incidence rates of TB are provided in the World Health Organization's annual report on Global Tuberculosis. http://www.who.int/globalatlas/dataQuery/default.asp. (Reference j)

d. TST should not be routinely performed in-Theater. Soldiers' exposure to TB will be assessed in the Post-Deployment Health Assessment (PDHA) upon redeployment. If the PDHA provider determines that a Soldier is at increased risk of contracting TB, the Soldier will be screened at the time of redeployment. Soldiers with a positive screening test (TST or IGRA) will be referred for appropriate medical evaluation and treatment. High-risk Soldiers with a negative TST result on initial post-deployment screening require a repeat TST at 90-180 days after redeployment, with appropriate medical evaluation and treatment as indicated for positive results.

e. Any Soldier with signs or symptoms suggestive of active TB requires immediate medical evaluation.

5. Documentation and Tracking.

a. TSTs will be entered into the Military Occupational Database System/Medical Protection System (MODS/MEDPROS) and medical records IAW the 27 May 2003 guidance.

b. IGRA testing dates and results will be entered into medical records. Because IGRAs are performed by the laboratory, results are logged into AHLTA and then automatically downloaded into MEDPROS.