DEPARTMENT OF DEFENSE
ARMED FORCES EPIDEMIOLOGICAL BOARD
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258

AFEB

MAY 14 2003

MEMORANDUM FOR

Assistant Secretary of Defense (Health Affairs)
Surgeon General of the Army
Surgeon General of the Navy
Surgeon General of the Air Force

SUBJECT: QuantiFERON®-TB's Application in the U.S. Military - 2003-09

1. References:

a. Memorandum, OASD/HA(FHP&R), 3 October 2002, QuantiFERON®-TB's Application in the U.S. Military.

b. Bellete B, Coberly J, Barnes GL, et al. Evaulation of a whole-blood interferon-γ release assay for the detection of *Mycobacterium tuberculosis* infection in 2 study populations. Clin Infect Dis 2002;34:1449-56.

c. Mazurek GH, LoBue PA, Daley CL, et al. Comparison of a whole-blood interferon-γ assay with tuberculin skin testing for detecting latent *Mycobacterium tuberculosis* infection. JAMA 2001;286:1740-7.

d. Keep, et al. Unpublished.

e. FDA, Center for Devices and Radiological Health. QuantiFERON-TB – PO10033 [Letter]. Rockville MD;Food and Drug Administration, 2002. Available at http://www.fda.gov/cdrh/pdf/PO10033b.pdf

f. CDC. Guidelines for using the QuantiFERON-TB test for diagnosing latent *Mycobacterium tuberculosis* infection. MMWR 2002:52(RR02);15-19.

g. Howell MR. Screening for *Mycobacterium tuberculosis* in the U.S. military: Considerations for a cost-effectiveness model. The Johns Hopkins University, Division of Infectious Diseases.

h. Hirsch CS, Toossi Z, Othieno C, et al. Depressed T-cell interferon-γ responses in pulmonary tuberculosis: analysis of underlying mechanisms and modulation with therapy. J Infect Dis 1999;180:2069-73.

2. In October 2002, the Deputy Assistant Secretary of Defense for Force Health Protection and Readiness requested that the Armed Forces Epidemiological Board re-examine the use of the whole blood assay, QuantiFERON-TB (QFT), as a substitute for current skin testing policies. The Board had last addressed this question in February 2000. At that time, the Board was impressed with the potential role this assay could play, but felt there were a number of issues and concerns that needed to be addressed before a recommendation regarding its use could be made.

Those issues raised with regard to the assay were as follows:

- Additional head-to-head comparisons of tuberculin skin tests versus the whole cell blood assay should be done
- Cohort studies of personnel should be undertaken to determine sequential behavior of the whole blood assay, including reproducibility of results
- The cohort of personnel who are skin test negative, but whole cell assay-positive should be followed to determine their risk for active tuberculosis
- Test reproducibility should be studied by splitting samples between laboratories to gauge consistency of results
- Studies should be done to determine the feasibility of using whole blood assays given the 12-hour time constraint for the test to be run
- Cost analysis is needed to determine the cost impact of switching to a whole blood cell assay and changing screening policies

In addition, the Board felt it was inappropriate to make a recommendation regarding the whole cell blood assay until the Food and Drug Administration (FDA) licensed the test for general use in the United States.

3. Since the Board last assessed the whole blood cell assay, additional studies have been accomplished and efforts have been made to address the concerns raised in 2000 (Reference b-d). These studies have been conducted in both military settings and among non-military populations. In July 2002, the manufacturer of QFT submitted in writing to the Office of the Army Surgeon General a response to the Board's concerns. In November 2002, FDA licensed the QFT whole cell blood assay (Reference e), and in December 2002, the Centers for Disease Control and Prevention (CDC) published guidelines for use of the assay for diagnosing latent *Mycobacterium tuberculosis* infection (LTBI) (Reference f).

4. The CDC guidelines recommended cutoffs for a positive test result in low-risk populations and suggested that the test was appropriate for "initial and serial testing of

persons who are, by history, at low risk for LTBI but whose future activity might place them at increased risk for exposure, and others eligible for LTBI surveillance programs (e.g. health-care workers and military personnel)". The guidelines further indicate: "When the probability of LTBI is low, confirmation of a positive QFT result with a tuberculin skin test (TST) is recommended before initiation of LTBI treatment. LTBI therapy is not recommended for persons at low risk who are QFT-negative or who are QFT-positive but TST-negative."

5. At its February 2002 meeting, the Board heard a series of presentations from the manufacturer and from a representative of the Division of Tuberculosis Elimination, CDC updating the information contained in the July 2002 letter. The Board also reviewed the response in that letter. The Board's conclusion was that the manufacturer did address the issues raised by the Board. This recommendation will not summarize all of the studies and findings. However, additional head-to-head comparisons, reproducibility studies, and cost analysis studies have been conducted to address the Board's concerns. Additional testing has been conducted in military settings. Although these studies have not utilized overseas facilities, there is no reason to believe the test could not be conducted in such settings even with the required 12-hour processing time. Concerning the long-term follow-up of QFT-positive, TST negative individuals, the Board recognizes that in a low-risk population few cases of active tuberculosis would be expected in any given year and it would take many years for such a study to produce scientifically meaningful results.

6. In its previous review, the Board was concerned that the QFT produced a significantly higher number of positive results than the TST. This raised concerns that this would result in a much larger number of individuals who would require preventive therapy. However, given the revisions of the cutoff value in low-risk populations, more recent data suggest that the positivity rates for QFT and TST are similar, with higher levels of concordance. Data also suggest that when a positive QFT is coupled with follow-up skin testing, the number of individuals requiring preventive therapy will likely decrease within military populations.

7. The Board remains concerned about ongoing problems with tuberculin skin testing in military settings, including continued clusters of false-positive TST results leading to unnecessary preventive therapy. Given that screening for tuberculosis infection remains an important preventive measure in military settings, the recent licensure of the QFT assay, and the recent CDC recommendations, the Board concludes that use of the QFT assay is a reasonable alternative to the TST. The QFT appears to have distinct advantages over the TST, including removal of the need for a 48-hour follow-up visit to

read a TST and the more objective test results with the QFT. Although quantification is difficult, the Board also believes that use of the QFT assay in place of the TST should be relatively cost-neutral (Reference g). While the QFT test is more expensive, these costs are likely to be balanced by reductions in health care costs related to the follow-up visit for TST reading and the reduction in persons requiring preventive therapy. However, since cost savings in the medical care system may not be transferred to the laboratory testing system, there may be additional costs for DoD laboratories to implement the QFT test.

8. Use of the QFT test in the military does raise some concerns. First, it must be widely adopted. As members move from location to location, they cannot have a QFT assay done at one location and a TST at another location, as epidemiologic studies have demonstrated that many persons who do not have LTBI are QFT-negative but TST-positive (examples include those who have been given BCG vaccination and persons exposed to non-tuberculous mycobacteria) (Reference e). Hence there must be consistency between facilities within each of the services and between the services, since members often receive health care in other services' facilities. Second, the QFT is not widely utilized in other settings. Therefore, as members leave the service or are tested in non-military settings, the same problem with subsequent use of a TST in a QFT-negative person could occur.

9. In light of these findings, the Board makes the following recommendations:

a. **The QuantiFERON-TB test is an appropriate screening test for latent tuberculosis infection in military and other low-risk populations. It can be used as an alternative to the tuberculin skin test (TST) and appears to have distinct advantages in a military setting.**
b. **Persons with a positive QuantiFERON-TB test should not be considered infected with *Mycobacterium tuberculosis* unless a tuberculin skin test is also positive. The TST should be done after the QuantiFERON-TB test, as the TST may affect the results obtained in the QuantiFERON-TB test and produce false-positives. The QuantiFERON-TB test may be done if at least 12 months have elapsed since the last TST was administered.**
c. **The QuantiFERON-TB test should not be used to test for the presence of active tuberculosis, as studies have shown persons with active disease may have suppressed immunity and may be negative in this assay (Reference h). Persons being evaluated for active disease should continue to be assessed with tuberculin skin tests, radiological examinations, microbiologic cultures, and other appropriate studies.**

d. If the services decide to use the QuantiFERON-TB test in place of the TST, an initial pilot program should be conducted to examine cost and logistical implications or a phased implementation should be used to assess any unanticipated difficulties, particularly in overseas or post-deployment settings, or cost differences, before total force use. Ready availability of blood samples in the post-deployment and recruit settings may favor utilization of the QuantiFERON-TB test.

e. To the degree feasible, the services should harmonize approaches to tuberculosis screening, including test methodology and test frequency.

f. The services should keep the Board informed of any changes in tuberculosis screening policies and on the current status of tuberculosis screening programs on an annual basis.

10. The above recommendations and observations were unanimously approved.

FOR THE ARMED FORCES EPIDEMIOLOGICAL BOARD:

STEPHEN M. OSTROFF, MD
AFEB President

JAMES R. RIDDLE, DVM, MPH
Colonel, USAF, BSC
AFEB Executive Secretary

Enclosures
Memorandum, OASD/HA(FHP&R), 3 October 2002, QuantiFERON®-TB's Application in the U.S. Military.

CF:
Board Members and Consultants (w/encl)
J4-MRD (w/encl)
OASD(HA)/C&PP (w/encl)
Library of Congress (w/encl)
SAAA-PPO (w/encl)

OFFICE OF THE ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, DC 20301-1200

HEALTH AFFAIRS

OCT 3

MEMORANDUM FOR EXECUTIVE SECRETARY, ARMED FORCES EPIDEMIOLOGICAL BOARD

SUBJECT: QuantiFERON®-TB's application in the U.S. Military

The Armed Forces Epidemiological Board (AFEB) was asked in February 2000 to make recommendations concerning risk-based tuberculosis screening policies and new technologies. The Board's recommendations were submitted in May 2000 and included an assessment of the whole blood assay, QuantiFERON®-TB, as a substitute for current skin testing policies. With Food and Drug Administration approval in November 2002 of the whole blood assay, the Joint Preventive Medicine Policy Group (JPMPG) has been asked to evaluate QuantiFERON®-TB's application in the U.S. Military.

In this regard, I would like the AFEB to review and provide comment on the report and additional research submitted to the JPMPG by Cellestis Incorporated, addressing the questions raised by the AFEB in the May 2000 recommendation. I further request the Board provide recommendations on QuantiFERON®-TB's application in the U.S. Military.

Ellen P. Embrey
Deputy Assistant Secretary of Defense
(Force Health Protection and Readiness)

Attachments
As Stated