

AFRL-AFIOH

Birthplace, Home and Future of Aerospace Medicine

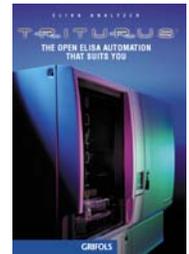


U.S. AIR FORCE

**QuantiFERON[®]-TB
Gold In-Tube Trial**



- **QuantiFERON®-TB Gold In-Tube** (aka **QFT-GIT**) blood test (manufacturer: Cellestis, Inc)
- **Triturus** instrument (manufacturer: Grifols USA, Inc) to automate ELISA processing
- **Automated export of QFT-GIT results** to military medical record



Funded Study: A **10-month*** comparison trial of the TST run in parallel with an automated QFT-GIT to screen **2400 USAF BMTs** for evidence of TB infection.

*Implementation planned for 1 Oct 2006



QFT-GIT CHARACTERISTICS



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- Uses a **blood test** (no second visit needed to read results)
- Uses an **automated** analytical method, assay results interpretation and export
- Produces test **results in 24 hours**
- Enables **flexible timing** (ELISA reading can be delayed 2 months without loss of test accuracy)
- **Specificity* improved by $\geq 30\%$** (33-78% fewer positives)
- **Sensitivity* maintained** ($\geq 80\%$ for active TB)

**Based upon QFT-Gold compared to current TST standards*



TIME LINE



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Oct 2006 → Aug 2007

Begin Oct–Nov '06

- 1) Study begins: Instrument calibration
- 2) Staff hiring & training

Accession and initial TB screening Nov–Apr '07

- 3) Recruit BMTs and enroll until reach 2400 subjects
- 4) Consent (until reach 2400)
- 5) Complete epidemiological questionnaire
- 6) Screen for TB infection by TST & QFT-GIT

Follow-up TB screening – Blood Donors Dec–Jun '07

- 7) Screen for TB infection by TST & QFT-GIT

Jul–Aug '07 **End**

- 8) Data analysis and report writing



TRIAL COSTS (Total: \$465,240)



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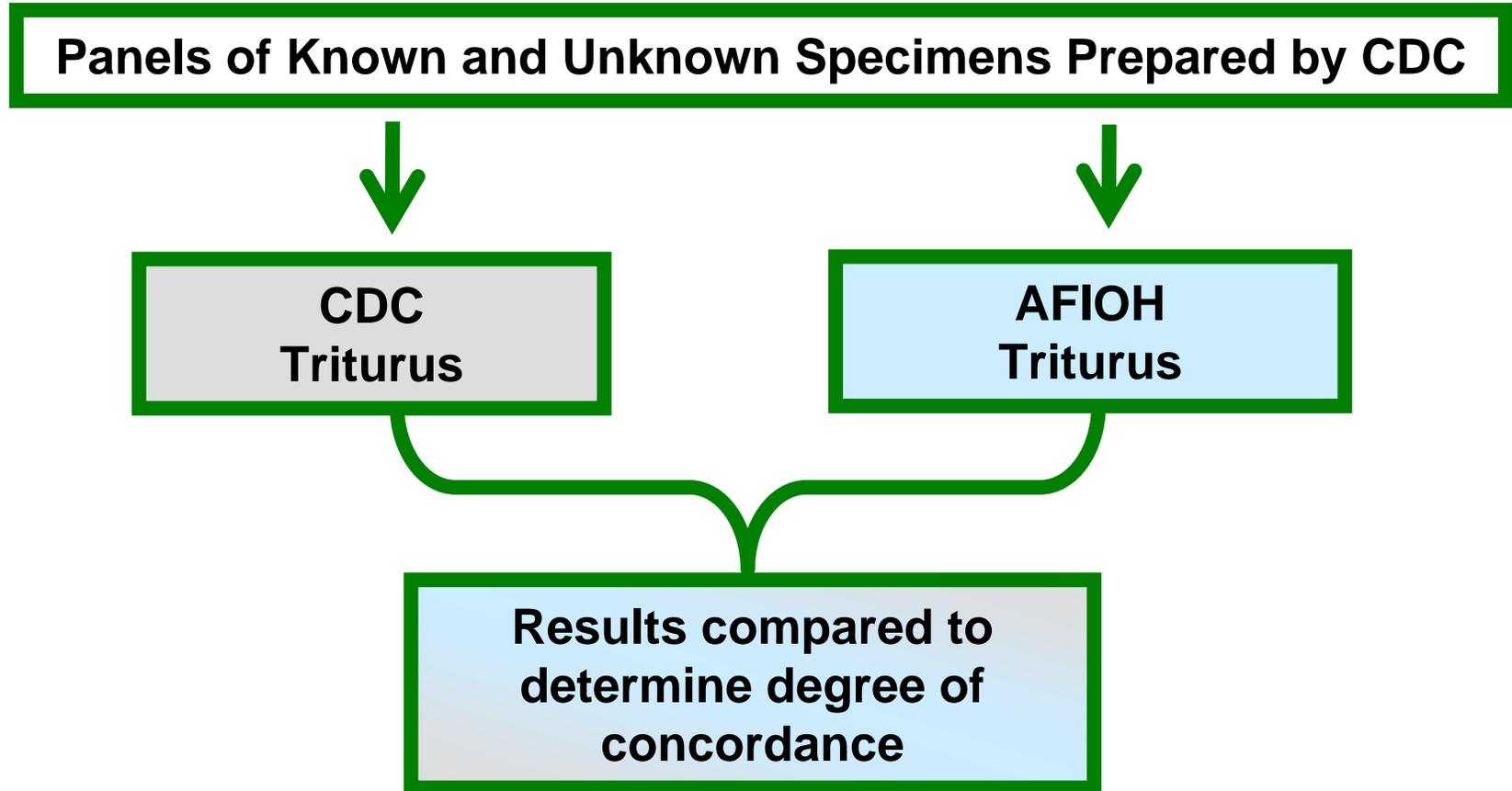
- **Money** – Trial program **funding from AETC**. Follow-on sustainment will be a service (DHP) O&M bill.
- **Manpower and Supplies (\$185,240 + \$280,000)**
 - **Contract personnel** – (**\$118,240**); 1 trial coordinator, 2 phlebotomists, 2 laboratory technicians
 - **Supplies** -- (**\$32,000**); AFIOH Epidemiology Laboratory and CDC/NCHSTP Laboratory support
 - **Consultation** – (**\$35,000**) CDC technical support staff, training, protocol development, problem solving, associated travel
 - **Cellectis Inc: Donating all QFT-GIT tests needed (\$100,000)**
 - **Grifols USA: Donating 2 Triturus instruments (\$180,000)**
- **Facilities** - Use existing **WHMC & AFIOH Epi Lab** facilities
- **Risk** - Low
- **Opportunities** - High



QFT-GIT PRE-TRIAL VALIDATION STUDIES



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SPECIMEN PROCESSING OVERVIEW



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Blood Specimens Received at WHMC Laboratory from Reid Clinic and/or Blood Donor Center



Incubate overnight (37°C)



Centrifuge to separate plasma from cells

**Specimen
Transport**



**AFIOH Epi Lab
for QFT-GIT Assay**



Residual plasma stored at AFIOH for future use with other candidate TB tests



QFT-GIT results sent to military medical record



BMT TRAINING WEEK-1



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**BMT Enrollment – Reid Clinic, Lackland AFB
Informed Consent Obtained**

**Not
In Study**

No

Yes

**Bloods drawn* & TB
screening via TST**

**3cc blood collected
for QFT-GIT assay**

**AFIOH
Epi Lab**

**TST results read
after 48-72 hours**

**TST & QFT-GIT results entered
into military medical record**

*Blood drawn for other standard screenings



BMT TRAINING WEEK-6



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**BMT Blood Donation – WHMC, Lackland AFB
Trial Participants Who Volunteer to Donate**

No

Yes

STOP

**Routine blood
drawn for donor
screening**

**Extra 3cc of blood
collected for QFT-
GIT assay**

**AFIOH
Epi Lab**

**TST test placed at
Blood Donor Center &
read after 48-72 hours**

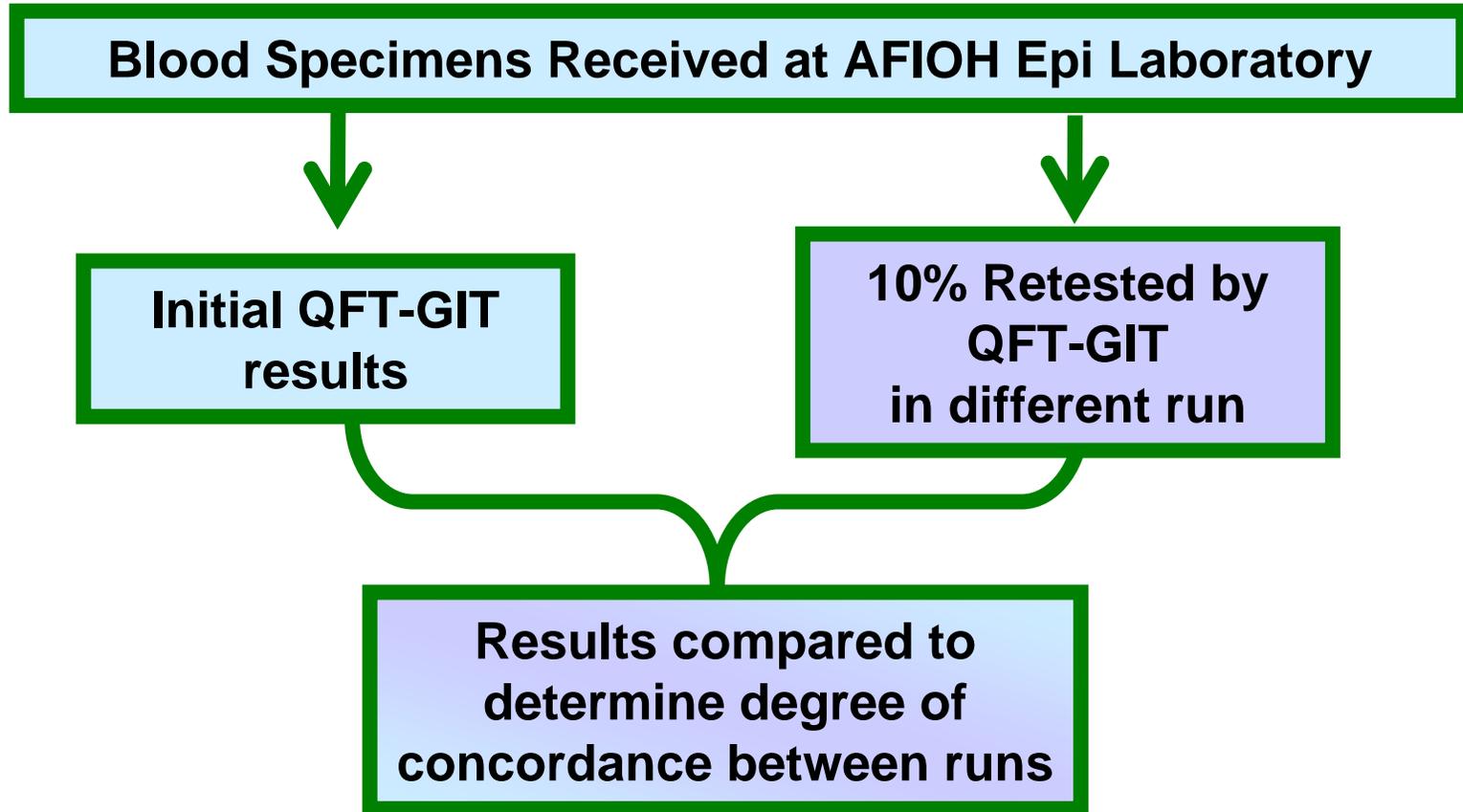
**TST & QFT-GIT results entered
into military medical record**



QFT-GIT VALIDATION STUDIES



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QFT-GIT VALIDATION STUDIES



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**Blood Specimens Tested at AFIOH Epi Lab by QFT-GIT
and Parallel TST Screening Results**

**WEEK-1 QFT-GIT
results & TST
screening results
(N = 2400)**

**WEEK-6 QFT-GIT
results (~1000) & TST
screening results
(N = ~ 1000)**

**Results compared to
determine degree of
concordance between
initial and second test at
an approx 6 week interval**



QFT-GIT VALIDATION STUDIES



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QA ISSUES TO BE CONSIDERED

1. **Impact of time-of-day of specimen collection**
2. **Impact of variations in duration of specimen processing times:**
 - **Blood collection to incubation**
 - **Incubation duration (37°C)**
 - **Centrifuge duration**
 - **Holding & transport time from end of centrifuge cycle at WHMC until arrival at AFIOH (refrigerated)**
 - **Holding time from arrival at AFIOH to ELISA reading**



PARTNERS & SUPPORTERS



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AFRL (AFIOH): Dr. Donald Goodwin (PI)

CDC/NCHSTP: Dr. Gerald Mazurek (Co-PI)

AFIOH: Col Paul Barnicott, Col Grover Yamane,
LtCol Paul Sjoberg, LtCol Ronald Rippetoe,
Dr. Huge Neisler & Maj Diane Calimlim

59AMDS: Col Mike Bunning, LtCol Lorie Brosch &
Dr., Kevin West, & Capt Patricia Rohrbeck

859 MDTS: LtCol Brian Casleton, Robert Purkhiser

CELLESTIS, INC: Scott Weiss, Mark Boyles, Brenda Robles
& Jim Rothel
(QFT-GIT Manufacturer)

GRIFOLS USA, INC: Raymond Zane, David Shell, & John Morris
(Triturus Manufacturer)

AETC/SGPM: LtCol Brian Ortman
(Sponsor)



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Questions?



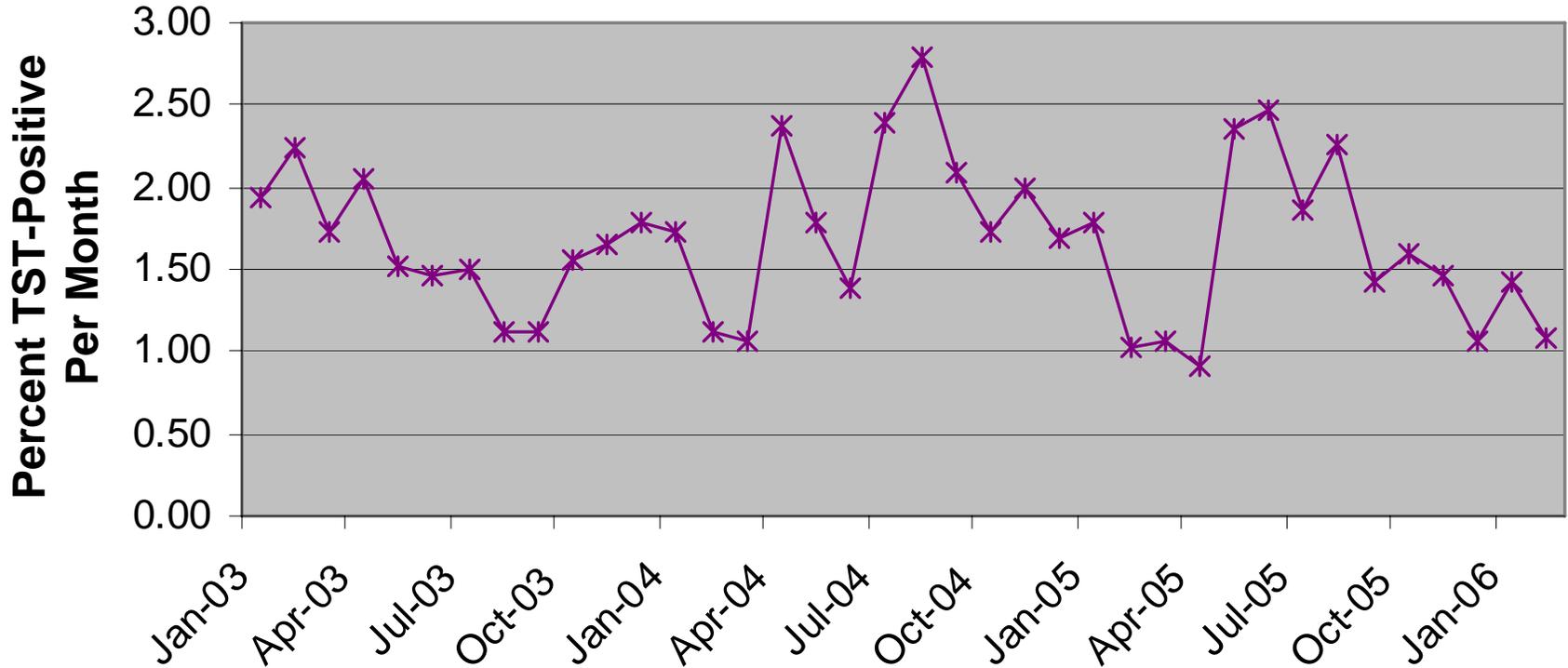
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Back-up Slides

MANTOUX TUBERCULIN SKIN TEST RESULTS AMONG 62,048 USAF BASIC MILITARY TRAINEES (Jan 2003 thru Feb 2006)



Range: 0.91% to 2.79%
Mean: 1.67%
Std Dev: 0.47%

ELISA ANALYZER

TRITURUS®

THE OPEN ELISA AUTOMATION
THAT SUITS YOU



GRIFOLS

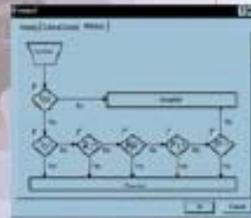


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Immunoassay System



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or Disposable Tips**

**High Precision Dispensing
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and Bar Code Reading**

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REPLY TO
ATTENTION OF

DEPARTMENT OF THE ARMY
OFFICE OF THE SURGEON GENERAL
5109 LEESBURG PIKE
FALLS CHURCH VA 22041-3258



AFEB (15-1a) 00-4

12 May 2000

MEMORANDUM FOR THE ASSISTANT SECRETARY OF DEFENSE (HEALTH AFFAIRS)
THE SURGEON GENERAL, DEPARTMENT OF THE ARMY
THE SURGEON GENERAL, DEPARTMENT OF THE NAVY
THE SURGEON GENERAL, DEPARTMENT OF THE AIR FORCE

SUBJECT: Armed Forces Epidemiology Board (AFEB) Recommendations
Regarding "Risk-based Tuberculosis Screening Policies and New
Technologies"

1. At the 28-29 February meeting of the AFEB, the Board was asked by the Air Force Medical Operations Agency (AFMOA) to review current Armed Forces tuberculosis screening policies and make recommendations for modifications to the current policies



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e. Because of the low rates of active tuberculosis and problems administering the tuberculin skin test, there is a desire to review and simplify current policies related to tuberculosis screening. Such simplification can take several forms, including changing the frequency of, and criteria for, tuberculosis screening. Another is to change to a different test method for evidence of infection.

1) There has long been a desire to develop a test for tuberculosis infection which is more reliable than the skin test method. Recently, a whole blood cell assay has been developed which detects the presence of t-lymphocytes activated against *M. tuberculosis* due to prior exposure. The assay comes as a kit which also determines immune responsiveness and prior infection with non-tuberculous *Mycobacterium avium* complex. These additional assays improve test performance by eliminating two of the common causes of false-positive and false-negative assays with the skin test. The Australian developers of the assay have already successfully marketed a similar test for bovine tuberculosis.



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2) To date, the whole blood cell assay has only been tested in research settings and is not licensed for use by the Food and Drug Administration. CDC is currently funding a series of studies to address its performance against the TST in the United States. The U.S. Navy has done a head-to-head comparison of the two tests at the Great Lakes Training Center. Although these studies have not been published, data were presented to the Board which showed generally similar results. Recognizing that there is no "gold standard" for tuberculosis infection, there is significant correlation between the two tests. However, there are also significant numbers of discrepancies, with TST-positive individuals who are whole blood cell assay-negative, and vice-versa. In the Great Lakes study, the whole blood cell assay appeared to be more "sensitive," in that the percent of recruits who were positive with this assay 8% was significantly higher than the percent who were positive with the TST 2.7%, even when different cutoff values for the TST were applied. Because the whole blood cell assay is unlicensed, individuals who were positive in this test but negative by TST were not given preventive therapy. Unfortunately, due to the nature of the study, it is not possible to follow these individuals in longitudinal fashion with the two tests or to determine whether they are at higher risk of developing tuberculosis.



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e. WHAT ARE THE PRIORITIES FOR RESEARCH?

1) THE WHOLE BLOOD CELL TUBERCULOSIS ASSAY HOLDS GREAT PROMISE AS AN ALTERNATIVE METHOD FOR TUBERCULOSIS SCREENING OF MILITARY PERSONNEL.

WHILE THE INCIDENCE OF ACTIVE TUBERCULOSIS IS LOW, IT HAS THE POTENTIAL TO RISE IN THE FUTURE DUE TO PEACETIME OPERATIONS IN HIGH RISK SETTINGS, AND THE INCREASING NUMBER OF FOREIGN-BORNE PERSONS WHO WILL BE ENTERING MILITARY SERVICE.

2) AT PRESENT, THIS ASSAY IS NOT LICENSED FOR USE IN THE UNITED STATES, AND THESE ARE A NUMBER OF QUESTIONS WHICH SHOULD BE ADDRESSED BEFORE IT COULD BE CONSIDERED FOR GENERAL USE IN MILITARY POPULATIONS. OBSERVATIONS AT GREAT LAKES SUGGEST THAT THIS TEST COULD SIGNIFICANTLY INCREASE THE NUMBER OF RECRUITS FOUND TO BE INFECTED, GREATLY INCREASING THE NEED FOR EFFECTIVE PREVENTIVE THERAPY.



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- STUDIES SHOULD BE DONE TO DETERMINE COMPLIANCE WITH PREVENTIVE THERAPY AMONG RECRUITS AND SKIN TEST CONVERTERS. THIS SHOULD INCLUDE ADDRESSING RISK FACTORS FOR NONCOMPLIANCE.
- A COST EFFECTIVENESS STUDY OF DIRECTLY OBSERVED PREVENTIVE THERAPY SHOULD BE UNDERTAKEN, INCLUDING ALTERNATIVE DOSING REGIMENS.

- ADDITIONAL HEAD-TO-HEAD COMPARISONS OF TST 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. SUCH STUDIES SHOULD BE DONE IN THE TYPES OF SETTINGS WHERE
- SCREENING WILL LIKELY OCCUR IN THE MILITARY.