Surveillance for latent tuberculosis in the Workplace: Pitfalls of Screening Low Risk Workers

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Definition of “pitfall” [Google dictionary]

- pit-fall
- /ˈpit fəl/
- noun: pitfall; plural noun: pitfalls
- a hidden or unsuspected danger or difficulty.
- synonyms: hazard, danger, risk, peril, difficulty, catch, snag, stumbling block, drawback
- “home schooling has its pitfalls”

Why screen asymptomatic persons for latent tuberculosis [TB]?

1. TB is the leading cause of death from infectious disease worldwide; TB caused massive epidemics in the past centuries
2. Now kills 1.8 mill/year worldwide: also disables
3. 1/3 of the world’s population is infected
4. There is a real potential of recurrent epidemics from reactivation of latent dz

Disclosure page

- I have nothing to disclose
- Pictures came from WikiMedia Commons Public Domain
- Some slides Include images of victims of tuberculosis to rescue you from looking at too many slides of TB data
- Opinions expressed are my own, and represent my perspective as an occupational medicine provider for 28 years

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Evolving definition of Screening versus Diagnostic Testing for Latent TB [2016 US Preventative Services Task Force]

- Screening is an evaluation of asymptomatic persons for the purpose of identifying candidates for medication to prevent progression to active TB
- Diagnostic testing is administering a Tuberculin skin test (TST) or Interferon-gamma release assay (IGRA) for screening purposes

“Latent tuberculosis infection” definition (I) [Center for Disease Control (CDC) 2013]

- “The presence of Mycobacterium tuberculosis in the body without signs and symptoms, or radiographic or bacteriologic evidence of tuberculosis (TB) disease.”
- “Detected by” IGRA or TST
- Once the decision has been made to test, latent TB is defined by diagnostic test results. No corroborating signs or symptoms and no confirmatory diagnostic tests of higher accuracy are required.
- “The intention to test should be a targeted intention to trust and treat the result” [van Zyl-Smit 2015]

CDC definition of Latent tuberculosis is not related to pretest probability

- This definition does not take into account the pre-test probability of TB disease.
- Almost half of all counties in California had no TB in 2016 (> 1/3 of counties had no TB in 10 years)
Yet a nurse who works in Amador County, which has no reported TB cases in the last 10 years, could be considered to have latent TB if their mandatory annual testing was positive in the absence of any TB exposure, even though the false positive rate of the screening test is known to be 3%.
- A potential pitfall of screening low risk workers is diagnostic error during serial testing.

2017 Clinical Practice Guidelines made important changes for the diagnosis of latent TB in low risk settings [American Thoracic Society/CDC]:

- Recommend low risk persons not be tested
- For low risk persons: Suggest a second diagnostic test [either an IGRA or a TST] if the initial test is positive (however the evidence is “very low” for this recommendation)
- Infection is diagnosed if both tests are positive
- The actual risk of TB disease, or the probability that a positive result is truly positive is still not factored into this diagnostic algorithm
- Medium and low risk are not defined in this document.
- Providers may not know which workers are “low risk”
What type of worker is “low risk”? I: CDC [MMWR 2005] defines Health Care Worker (HCW) risk according to risk of exposure

- Low risk: ... applied to HCWs who will never be exposed to persons with TB disease....
- Medium risk: ...HCW will or will possibly be exposed to persons with TB disease...
- Many providers feel all HCW with patient contact are medium risk by this criteria.
- Therefore another potential pitfall for providers is assigning the appropriate risk category for tested workers.

What type of HCW is “low risk”? II: CDC also defines low risk by setting:

- Low risk: ...settings in which persons with TB disease are not expected to be encountered, and therefore exposure to M. tuberculosis is unlikely... a low risk hospital setting has less than 6 persons with TB disease in the last year for a hospital with > 200 beds in the preceding year.
- Low risk outpatient/small hospital settings: exposure to <3 persons with TB in the preceding year.
- A HCW in a large hospital taking care of 5 TB patients in one year may be low risk by settings criteria but medium risk by exposure criteria
- Providers may be confused by the settings risk vs. exposure risk categories.

The rationale for annual testing of all low risk HCW in California [CA] involves the concept that annual testing provides the most protection due to:

- Dx of early infection; annual testing may identify seroconversions earlier than other protocols
- Detection of infection in the absence of a source
- CA has higher rates of TB than the US and needs more testing
- CDC HCW risk classification may not be accurate due to unrecognized exposure to infected persons
- [Vivian Leigh]

Possible reasons NOT to test all low risk HCW annually I. [California Department of Public Health (CDPH) 2016 and Contra Costa County Dept Public Health]:

- Incidence of TB is low (Number of TB cases in County dropped from 105 in 2001 to 40 in 2016)
- Scant longitudinal data for interpreting serial testing results
- Limited information regarding how to interpret conflicting results when more than one test is performed
Possible reasons not to test all low risk HCW annually, II: Risk of occupational transmission may be quite low:

- Youakim 2016, British Columbia: found only 8 cases of occupational TB in 10 years of testing (2 million workers); No risk for first responders was found
- Pederson, 2016, Denmark: found only 27 cases were likely occupational in 21 years of annual HCW testing.
- Rates of occupational TB in CA are unknown but likely very low

Possible reasons not to test all low risk HCW annually III: Risk of TB in HCW in CA is not elevated [CDPH 2015, Crowder et al 2018, unpublished]

- Rates of TB in HCW were not higher than non-HCW [RR: 0.84 (95% CI: 0.71-1.0)]
- In 2016 there were 80 cases of TB in HCW in CA (1.4 mill. HCW)
- 85% of these were foreign borne and likely infected outside of US
- Rate of TB in foreign borne HCW is 74 times that of US-borne (95% CI:43-129)
- [Rene Laennec]

Possible reasons not to test low risk HCW annually, IV. Apparently RANDOM false positive QuantiFERON –TB (QFT) results could be caused by:

- Tube defects [e.g. endotoxin contamination; Gamsky 2008, Slater 2012, Couturier 2014, Seto 2016, Igari 2017, FDA 2016]
- Handling/processing problems: blood draw, tube handling after draw, incubation [Pai 2014, Banaei 2016]
- Analytical/data entry error
- Skin contaminants [Banaei 2016, Gaur 2014]

Possible reasons not to test all low risk HCW annually, V. Apparently NONRANDOM positive QFT results could be caused by:

- The ESAT-6 and CFP-10 antigens used in IGRAs are also found in other nontuberculous mycobacterium and can cross react [van Pittius 2001, Arend 2005, Vordermeier 2007]
- Immune boosting by the TST [Igari 2007, Perry 2008, Baker 2009]
- Persons drawn multiple times using unrecognized contaminated tube lots
Nevertheless, annual testing of all HCWs, emergency responders and paramedics in California is required by state law [CDPH Jan 2018]

- California Code of regulations (B CCR 5199), subsection 5199(h)(3) Airborne Transmissible Disease (ATD) Act.
- CCR Title 22, Div. 5, Ch.1-12: requires most HCW to have annual TB screenings (with a TB test if their prior result was negative).
- [Henry VII England]

Contra Costa County has been testing first responders since 1970s with Tuberculin Skin Test

In 2007 testing changed to QFT-TB-Gold and 2008 QFT-Gold-In-Tube

This cohort is low risk

County first responders are “Low risk” due to:

- The low County rate of TB disease [3.5 cases/100,000/year in 2016]
- The predominant “US-born” nature of cohort
- No persons known to be Bacillus Calmette-Guerin (BCG) immunized
- No known occupational cases of TB disease
- No known occupational TB exposure 2000-2017
- No TST conversion from negative to positive from 2000-2017
- This essentially meets low risk CDC settings criteria

Case presentation: First Responder latent tuberculosis testing program 2000-2017

Case study: Mr. A

- First Responder x 5 years [US born]
- No BCG, no symptoms
- No exposure to tuberculosis or to persons with an unidentified illness or cough
- Prior to this exam he had yearly negative TST (zero mm) x 4; negative x-ray; He had no TST the year before.
Mr A’s longitudinal QFT results for 10 years: He had a subsequent negative x-ray and 5 negative TSTs; Does he have latent TB?

Mr A. QFT Result IU/ml by year

False positive QFT results were found in new persons in the cohort each year of testing 2007-13

- For 6 years: No false pos
- False + started in 2007: most were random. However, 20% of group with false + had multiple + results
- Cumulatively, 1/7 of the TST negative cohort tested false + with QFT
- False + results were identified by subsequent negative TST and negative QFT on follow up.

The most important risk factor for false positive results was the number of tests a group had

- The more tests a group had, the higher the percentage of persons with at least one false positive result.
- About 3% of the group tested once had at least one false positive result, but over 27% of the group tested yearly for 7 years had at least one false positive result [Gamsky 2016]
- The slope is about 3%/yr
- Consistent with random event

Corroborating evidence in the medical literature

- US Preventive Services Task Force [USPTF 2016]: finds a pooled 3% false positive QFT rate
- Moses et al [2016]: Mathematical modeling of false positive QFT testing results estimating 25% of HCW tested annually for 10 years would have at least one false positive QFT result
Random vs nonrandom false positive testing results

- Both the TST and the QFT have a pooled false positive rate of 3% [USPSTF 9/2016].
- For serial screening purposes, does it matter if these false positive rates are random or nonrandom [biological]?

If the 3% false positive results are random, what percent of the cohort would eventually have at least one false positive result after years of serial testing?

- Estimated cumulative % of tested group with at least one false positive result by # years tested:
  - Year 1: 3%
  - Year 2: 5.9%
  - Year 5: 14.1%
  - Year 10: 26.2%
  - Year 20: 46%

For comparison, how many HCW in CA are found with TB disease during annual testing?

- California Department of Public Health [(CDPH document 3/30/17)] found an average of 4-6 HCW/year with TB disease in CA during testing programs 2012-16.
- There are 1.4 million HCW in CA. 100K have latent TB; If we test the other 1.3 million, on average 39,000 HCW will have a false positive result each year.
- In order to find one case of tuberculosis with annual testing we need to falsely identify 6,500-9,750 persons with positive results; If these false positive results are random, these may be new persons each year.

Why false positive results matter: false positive results may cause:

- Costs: unneeded tests, staff time, X-ray, etc
- Medical restrictions
- Missed opportunity for prevention after actual infection
- Removal of uninfected persons from screening program reduces the screened population which undermines the program
- Medical risk from unneeded prophylaxis
Few studies have identified ALL the medical risks of prophylaxis: INH can cause varied adverse effects [Denholm 2014 n/100 patients]

Reactive metabolites of INH cause free radical generation
- Total % adverse effect 56
- Total % grade 3-4 rxn [Severe/life threatening] 6
- Hepatitis 5
- Dermatologic 15
- Neuropsychiatric 19
- Lethargy 7
- Cognitive impairment 9
- Peripheral neuropathy 4

Adverse reactions to TB prophylaxis among 363 HCW with latent TB [Perez 2017]
- INH: 41% had adverse reaction
- Rifampin: 49%
- Rifapentin/INH: 73%
- 5% had grade 3-4 reaction
- 25% required d/c of prophylaxis due to reaction
- Therefore prophylaxis itself may cause illness in a large percent of treated persons

How do we evaluate whether these positive testing results represent true latent TB? Positive Predictive Value [PPV]
- PPV is the probability in percent that a person with a positive testing result has true disease
- Providers who test low risk persons should become familiar with estimating and calculating this proportion.
- PPV is dependent upon test sensitivity, specificity, and disease prevalence [Mausner 1985]

Screening terminology
- Sensitivity= proportion of persons with disease who are correctly IDed by test
- Specificity=proportion of persons without disease correctly identified [=1 minus false pos rate]
- Prevalence=the proportion of persons who are affected by a medical condition
Bayes Theorem to estimate PPV
[Molinaro 2015]

\[
PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}
\]

Positive Predictive Value (y axis) is related to disease prevalence (x axis) in a curvilinear fashion. [Mausner 1985]

- On the right side of this chart, disease prevalence approaches 100%. PPV nears 100% as all positive results likely represent true disease.
- However, on the left side, disease prevalence approaches zero. PPV also approaches zero as almost all positive results are likely false.

Calculated Positive Predictive Value of QFT in County First Responders [Bayes Theorem and US Preventive Services Task Force Sept/2016]

- QFT Sensitivity [0.80]
- QFT Specificity [0.97]
- Prevalence of Latent tuberculosis = persons with both a positive QFT and a positive TST in Cohort= 0.7%
- Cohort First responder PPV =0.16=16%
- Bayes Theorem predicts that less than one out of six cohort first responders with positive QFT results will have latent tuberculosis;
- Given this low PPV, we asked for more confirmatory information than the screening result alone before diagnosing latent tuberculosis (follow-up TST, etc)

Risk/benefit analysis: California Department of Public Health (CDPH) TB Control Branch March 2017

- Only 9% of HCW identified with TB disease were found by routine screening during 2012-2016
- Positive predictive value of any screening test for latent TB in CA HCW is less than 25%
- Evaluating only liver effects: 40-400 health care workers/year may suffer liver damage whereas only 200 persons would have latent TB treated.
- Therefore annual testing of low risk HCW was not recommended
Proposed solutions for screening low risk persons:

- Raising the cut point separating positive from negative QFT results
- Retesting all low risk QFT positives
- Creating a “borderline” zone for QFT retesting
- Targeted testing: avoiding testing low risk persons

Published data imply that raising the “cut point” for diagnosis of TB infection may decrease QFT sensitivity

- Jonsson [2017-Sweden] 10% of TB cases may be missed by QFT cut point 0.99 IU/ml
- Dyrhol-Riise [2017-Norway] 13% of TB cases may be missed by cut point 0.88 IU
- Torres-Costa [2011 Portugal] 33% of TB cases may be missed by a QFT cut point of 0.99 IU/ml
- Nemes [2017] 8% of TB cases may be missed by a cut point of 0.7 IU/ml

Why not retest all positive QFT results in low risk workers (I)?

- Retesting is problematic: costs, staff time, difficulty reaching persons for retesting, etc
- It is unknown if retesting positive results during annual QFT testing is cost-effective or superior to skin testing, targeted testing or post-exposure testing

Why not retest positive QFT results for annual screening of low risk workers (II)

- Drawing another specimen should only be done if it will change your treatment plan.
- The assumption is that a second sequential positive QFT result will define infection for treatment purposes, but a second negative result will define no infection
- There is very little longitudinal data to support this practice in low risk persons
Multiple persons with serially false positive results were found in County first responders

- 10 TST negative persons had multiple sequential false positive results over 7 years [Gamsky 2016]
- These data question whether serial positive QFT results should be a diagnostic criteria for TB infection in low risk persons

Creating a “borderline” range for QFT retesting: How many would need to be retested?

- Jonsson et al [2017] 9% of QFT results were “borderline” on first test (0.2-0.99 IU/ml).
- Schlabon [2014] 9.4% of HCW were 0.2-0.7 IU/ml;

Problems with use of a borderline range for QFT:

- Finding and retesting large numbers of HCW can be “Kafkaesque” in the occupational setting
- No consensus in the US re: which borderline to use
- False positive results above the borderline cut point may be missed
  [Franz Kafka]

Percent of positive results above the borderline range which revert to negative and are likely false positive

- Dorman [2014] found 13% of US HCW with QFT result >1.00 IU/ml reverted to negative on the next test
- Schablon [2014] found 13.3% of German HCW with QFT > 1.0 reverted
- These data imply repeating only the borderline range may miss false positives above the cut point which increases the false positive rate
Alternatives to annual testing:

- Targeted testing: Screening the population but only testing those persons in higher risk groups.
- Post-exposure testing: Testing persons with exposure to an index case.

Mulie et al. [2017] compared annual testing to targeted testing to post-exposure testing of intermediate-risk HCW:

- Outcome was cost and number of TB cases prevented/1000 HCW tested yearly for 20 years.
- Post-exposure tested with TST prevented the most TB cases (average of 3.03 cases) and was cheapest.
- Targeted testing with TST prevented less TB cases (2.83) (additional cost $426k/case found).
- Annual testing with TST: prevented the least # cases (2.68), and cost the most ($1.7 Million/case > targeted testing).

Mulie et al. 2017 continued:

- Use of QFT, including use of confirmatory 2nd QFT was more expensive than TST with no benefit for intermediate risk HCW testing.
- More intensive testing was counterproductive: Yield of true positives decreased with more intensive testing.
- IGRAs do not improve the cost-effectiveness of testing.
- Annual testing of HCW was not cost effective.

The California Tuberculous Controllers Association [CTCA] no longer supports universal annual testing of HCWs [Oct 2016]

- Testing leads to false positives in 80-90% of HCWs, unnecessary tests and treatment which could cause harm.
- Only 8% of hospitals in California meet CDC criteria for testing.
- [Eleanor Roosevelt]
Statewide recommendations for testing low risk workers

- Intervention 2C: To reduce false positive tests and avoid treatment of individuals without true infection, routine testing of low risk individuals should be minimized.
- Bring the CalOSHA annual screening regulations for health care workers into alignment with federal [risk based] guidance on preventing TB transmission.

California Tuberculosis Risk Assessment User Guide: Adults June 2017 [CDPH, CTCA]

- Published guidelines identifying groups at highest risk
- This tool is meant to be used in targeted testing programs for deciding who needs further testing [Kamala Nehru]

For example, testing college/university students: 3 groups at highest risk [CDPH 2017]

- 1) Birth, travel, or residence > 1 mo in country with elevated risk for TB
- 2) Immunosuppressed (e.g., HIV, TNF alpha inhibitor use, steroids, organ transplant)
- 3) Contacts of known TB patients

There are currently 3 recent laws aimed at replacing annual testing with a CDPH TB risk assessment in CA

- SB 1038 [2016] addresses community college employees
- SB 792 [2015]: preschool teachers and volunteers
- AB 1667 [2014]: K-12 school employees and volunteers
- [James Monroe]
Conclusion 1: Testing programs

- Annual testing of low risk persons for latent tuberculosis in California may be inefficient, costly, counter-productive, and may harm more persons than are benefitted; therefore should be carefully considered.

Conclusion 2: Legal/advisory issues for providers

- Providers should be knowledgeable about recent legal and advisory changes to annual testing programs for low risk persons in CA;

Conclusion 3: Diagnosis of latent TB

- To avoid the pitfall of diagnostic error, providers who must test low risk persons should understand the limitations of each test and the test positive predictive value before they diagnose latent tuberculosis based on positive testing results alone.

  - [Henry David Thoreau]

Conclusion 4: Provider needs

- From a provider’s perspective, we urgently need a universally accepted framework for interpreting unexpectedly positive testing results [which should include positive predictive value] when testing low risk persons.
- The definitions of risk categories and of latent tuberculosis need to be clarified.
- Support for legal and administrative efforts to avoid testing low risk workers is needed.
**Resources**

- Center for Disease Control and Prevention: [https://www.cdc.gov/tb/default.htm](https://www.cdc.gov/tb/default.htm)
- California Tuberculosis Controllers Association [https://www.ctca.org/](https://www.ctca.org/)
- California Department of Public Health [https://www.cdph.ca.gov/](https://www.cdph.ca.gov/)
- County Public Health Departments: e.g. Contra Costa County Department of Public Health [http://cchealth.org/public-health/](http://cchealth.org/public-health/)

**Questions?**

**Q1:** Which of the following is LEAST useful for estimating the probability that an asymptomatic low risk persons with a positive test result has latent tuberculosis?

A. Prevalence of diagnosed tuberculosis in the cohort  
B. Prevalence of latent tuberculosis in cohort  
C. Screening test sensitivity [proportion of positives that are correctly identified as such]  
D. Screening test specificity [proportion of negatives that are correctly identified as such]

**Q2:** False positive QuantiFERON-TB results have been found to be causally related to all of the following except:

A. Tube handling and tube defects  
B. Nontuberculous mycobacteria infection  
C. Data entry error  
D. Bacille Calmette-Guerin [BCG] immunization
Q3: Which of the following is currently required for a diagnosis of latent tuberculosis?

A. Exposure to a patient with tuberculosis
B. Immunocompromised health status
C. Positive Tuberculin skin test or Interferon-gamma release assay
D. Living in a high-tuberculosis prevalence country for 1 month or longer

Answer key

- Q1: A
- Q2: D
- Q3: C