IGRA Use in a Local Public Health Setting

LAURIE HICKSTEIN, RN, BSN
SENIOR PUBLIC HEALTH NURSE

HALEY BLAKE
DISEASE INVESTIGATION AND INTERVENTION SPECIALIST

Disclaimer

- We have done no research for companies
- We have not received funding from companies
- Use QuantiFERON®-Gold In Tube; only available IGRA without shipping samples out of state

Objectives

- Describe the difference between tuberculosis skin tests and IGRAs (Interferon-Gamma Release Assays)
- List three benefits of using IGRAs in contact investigations and for certain populations

Meeting the Challenge of Tuberculosis

- Diagnosis TB infection and disease is a primary care issue….
- Preventing TB is a primary care issue….
- Know the TB status of your *at risk* patients
  - Not just medical/social history
  - Black box warning on current medications
- Ensure evaluation and appropriate treatment
  - Decision to test is a decision to treat

Meeting the Challenge of LTBI

- Latent TB Infection should be treated as a condition in itself which is a precursor to a serious and potentially fatal disease
- Much the same way we treat hypertension as a condition in itself because it significantly heightens risk of heart disease, renal failure, and stroke or place infants in car seats because of the significant risk of injury without them, so should we approach latent TB infection
- While the condition in itself is asymptomatic, the risks assumed by ignoring it are substantial

Source: Carey Jackson, MD. Internal Medicine. International Clinic, Harborview Medical Center, Seattle, Washington

Methods for detecting *M. tb* infection

- Mantoux tuberculin skin test (TST)
- IGRAs
  - QuantiFERON-TB Gold In-Tube (QFT-GIT)® (2007)
  - T-Spot.*TB*® (2008)
- These tests do not exclude LTBI or TB disease
- Decisions about medical management should include other information, and not rely solely on TST/TGRA results

TB Screening with TST & IGRA

- Tests should not be mixed
  - If baseline/annual is TST then TST should be done for post-exposure screening
- Negative reaction to either test does not exclude active disease
  - Some data suggests IGRAs may not be a good predictor of active disease
  - If suspected, CXR and consider sputum

Nevada Administrative Code

- 441A.192 “Tuberculosis screening test”
- Means any tuberculosis screening test that has been
  - Approved by the Food and Drug Administration; and
  - Endorsed by the Centers for Disease Control and Prevention

- 441A.350 Health care provider to report certain cases and suspected cases within 24 hours of discovery.
  - Active or suspected active disease
  - Not solely positive TST or IGRA results

TST Considerations

- 100+ years old
- Staff must be trained in correct placement and measurement
  - Wheal must form upon injection of PPD solution
  - Measure induration only, not redness
  - Cutoff depends on individual risk factors
  - Must be recorded in millimeters
- Boosting
- Concerns abound about lack of sensitivity and specificity resulting in false positive and false negative results

Factors Affecting TST Reaction

Type of Reaction	Possible Cause
False-positive	• Nontuberculous mycobacteria • BCG vaccination • Problems with TST administration
False-negative	• Anergy • Viral, bacterial, fungal coinfection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid disease • Low protein states • Immunosuppressive drugs • Problems with TST administration

Interferon Gamma Release Assays (IGRAs)

- Detect *M. tb* infection by measuring immune response in blood
- Cannot differentiate between TB and LTBI
- Use in place of, not in addition to, TST
- Especially preferred when testing persons
  - Who might not return for TST reading
  - Who have received BCG vaccination
- Generally not used in children <5 years

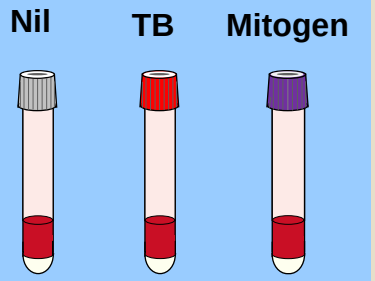
IGRAs

- Specific antigens: ESAT6 and CFP10
  - Found in all *M. tb* complex organisms
  - Not present in BCG
  - Not present in most non-TB mycobacteria (including MAI)
- If individual has been TB infected, memory CD4 cells should react to ESAT 6 and CFP10
- ESAT 6/CFP10 release interferon gamma that can be measured
  - Serum level or by staining cells
- Magnitude of the measured INF-γ cannot be correlated to stage or degree of infection

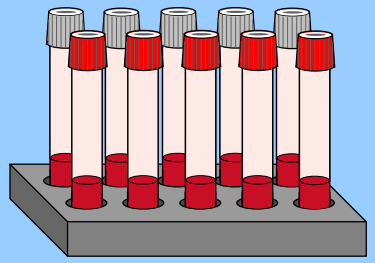
Tuberculosis complex	Antigens		Environmental strains	Antigens	
	ESAT-6	CFP-10		ESAT-6	CFP-10
M tuberculosis	+	+	M abcessus	-	-
M africanum	+	+	M avium	-	-
M bovis	+	+	M branderi	-	-
BCG Substrain			M celatum	-	-
gothenburg	-	-	M chelonae	-	-
moreau	-	-	M fortuitum	-	-
tice	-	-	M gordonae	-	-
tokyo	-	-	M intracellulare	-	-
danish	-	-	**M kansasii**	+	+
glaxo	-	-	M malmoense	-	-
montreal	-	-	**M marinum**	+	+
pasteur	-	-	M oenavense	-	-
			M scrofulaceum	-	-
			M smegmatis	-	-
			M szulgai	+	+
			M terrae	-	-
			M vaccae	-	-
			M xenopi	-	-

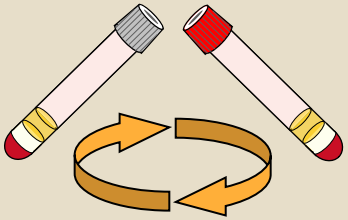
QuantiFERON®-Gold In Tube

- Stage 1 – Blood collection and harvesting



3x1mL blood collection


Incubation at 37ºC for 16-24 hours

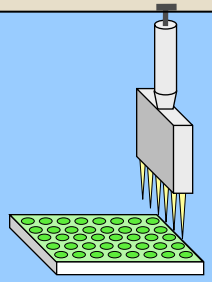

Centrifuge tubes for 5 min

IFN-γ stable refrigerated for at least 8 weeks.

- Option 1: Shipment of the blood collection tubes within 16 hours to a laboratory prior to incubation
- Option 2: Shipment of blood collection within 3 days after incubation to the laboratory
- Possibility to batch samples

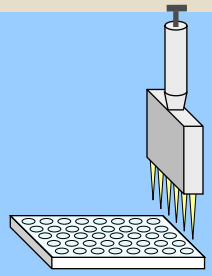
QuantiFERON®-Gold In Tube

- Stage 2 – Interferon-γ ELISA

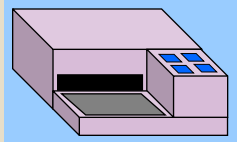


Add plasma and conjugate

Incubate for 120min at room temperature



Wash and add substrate



Add stop-solution and read absorbance

Software calculates and prints resuls

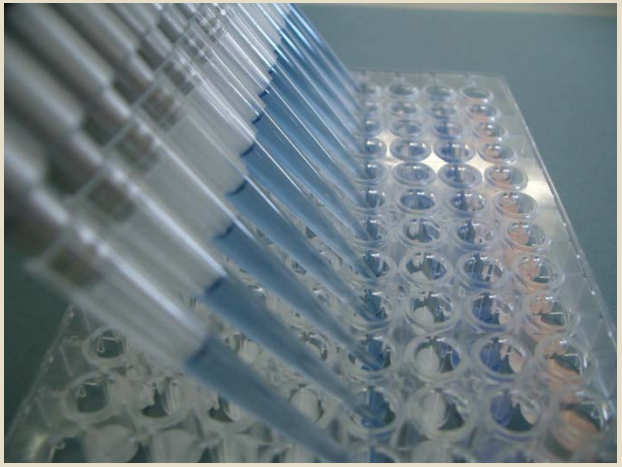
- Easy “Standard”-Elisa
- Software supplied free-of-charge from Cellestis
- No need for new equipment

QuantiFERON®-Gold In Tube

Nil (IU/mL)	TB Antigen minus Nil (IU/mL)	Mitogen minus Nil (IU/mL)	RESULT	REPORT/ INTERPRETATION
≤ 8.0	≥ 0.35 and ≥ 25% of Nil value	Any	POSITIVE	*M. tuberculosis* infection likely ESAT-6 and/or CFP-10 responsiveness detected
	< 0.35 OR ≥ 0.35 and < 25% of Nil value	≥ 0.5	NEGATIVE	*M. tuberculosis* infection unlikely No ESAT-6 or CFP-10 responsiveness detected
		< 0.5	INDETERMINATE	MTB infection status cannot be determined as a result of impaired immunity and/or incorrect performance of the test
> 8.0	Any	Any		

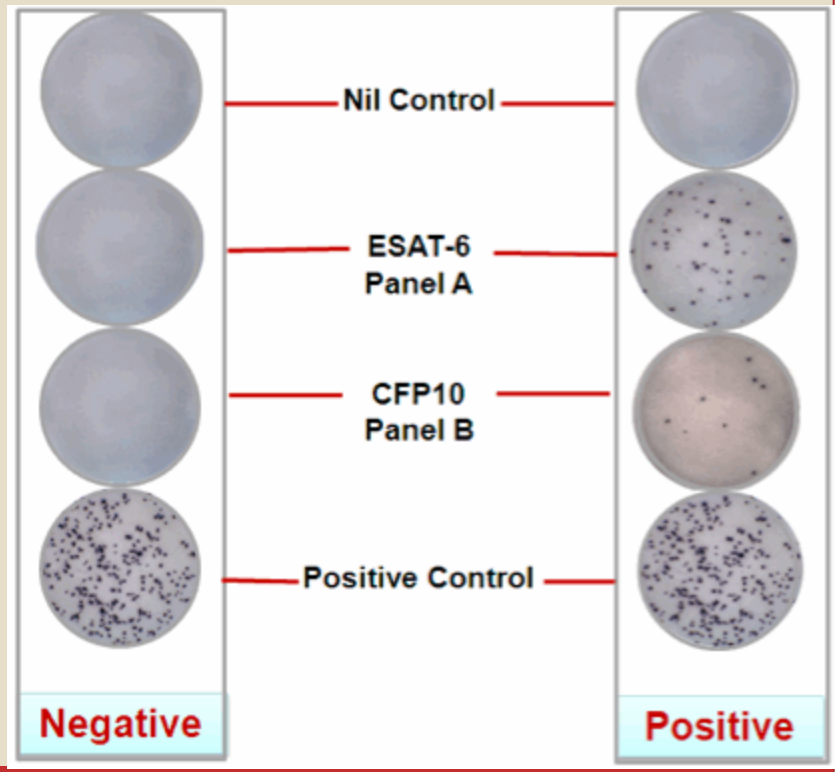
T-Spot®.*TB*

- Step 1 – Preparation of cells
  - Blood collected into Vacutainer CPT™ tube
  - Tube centrifuged
  - Lymphocyte band removed
  - Cells washed & counted
  - Cells added to 96-well plate
  - Antigens added to wells
  - Incubate overnight



T-Spot®.*TB*

- Step 2 – Forming spots
  - Plate washed
  - Add detection reagent for 60 minutes
  - Plate washed
  - Add substrate
    - Spots in 7 minutes
  - Plate washed and dried



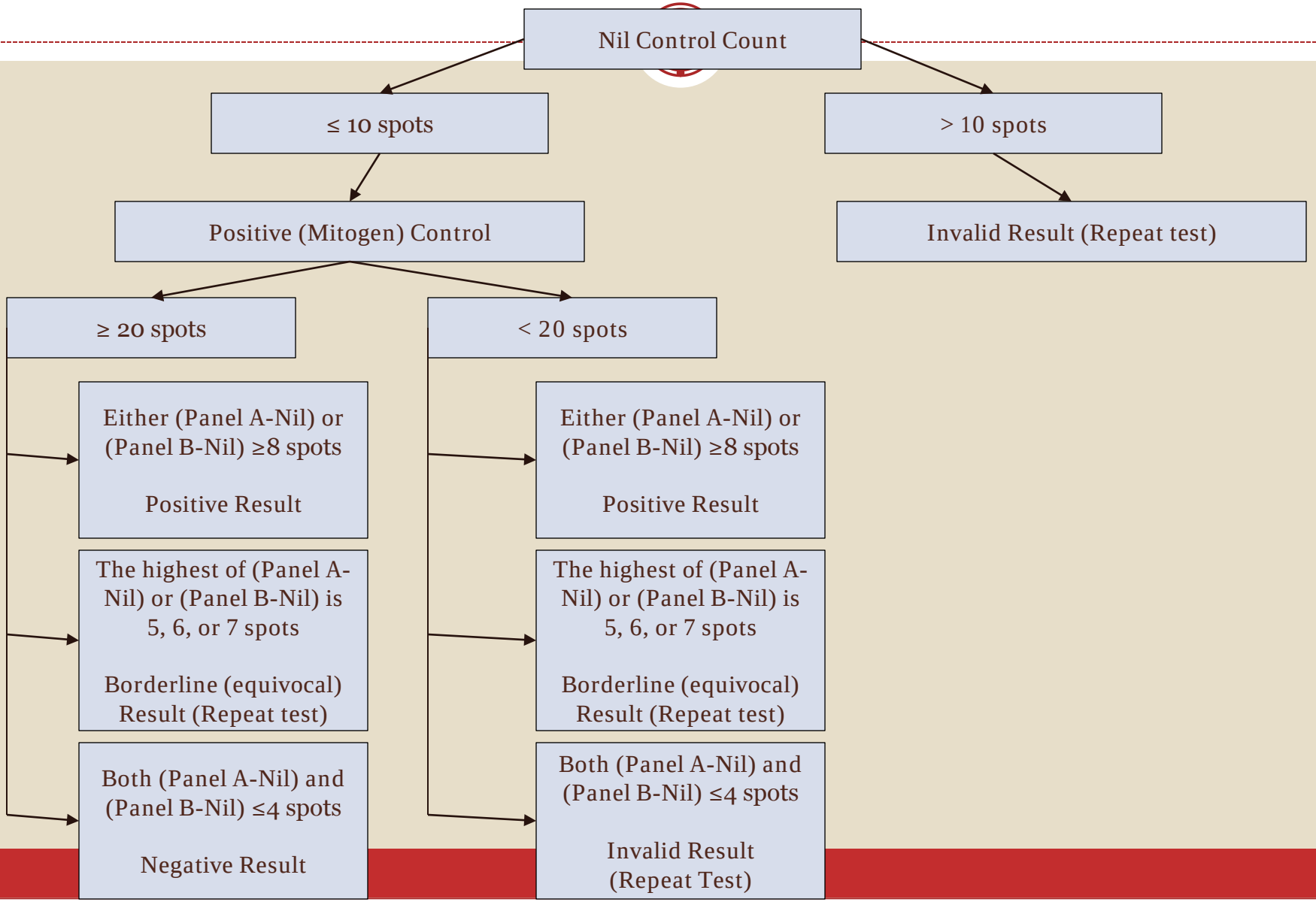
T-Spot®.*TB*

- Step 3 – Counting spots
  - Count spots by “eye” using a magnifying glass or dissecting microscope
  - Alternatively use an automated elispot reader

Above: Automated T-SPOT plate reader

- Plate placed in reader and read automatically
- Computer stores all images, a tamperproof audit log, and calculates the number of spots in each well
- Camera and analysis settings set automatically

T-Spot®.*TB*


Nil Control Count
≤ 10 spots
> 10 spots
Positive (Mitogen) Control
Invalid Result (Repeat test)
≥ 20 spots
< 20 spots
Either (Panel A-Nil) or (Panel B-Nil) ≥8 spots
Positive Result
The highest of (Panel A-Nil) or (Panel B-Nil) is 5, 6, or 7 spots
Borderline (equivocal) Result (Repeat test)
Both (Panel A-Nil) and (Panel B-Nil) ≤4 spots
Negative Result
Either (Panel A-Nil) or (Panel B-Nil) ≥8 spots
Positive Result
The highest of (Panel A-Nil) or (Panel B-Nil) is 5, 6, or 7 spots
Borderline (equivocal) Result (Repeat test)
Both (Panel A-Nil) and (Panel B-Nil) ≤4 spots
Invalid Result (Repeat Test)

General Recommendations for IGRA Use

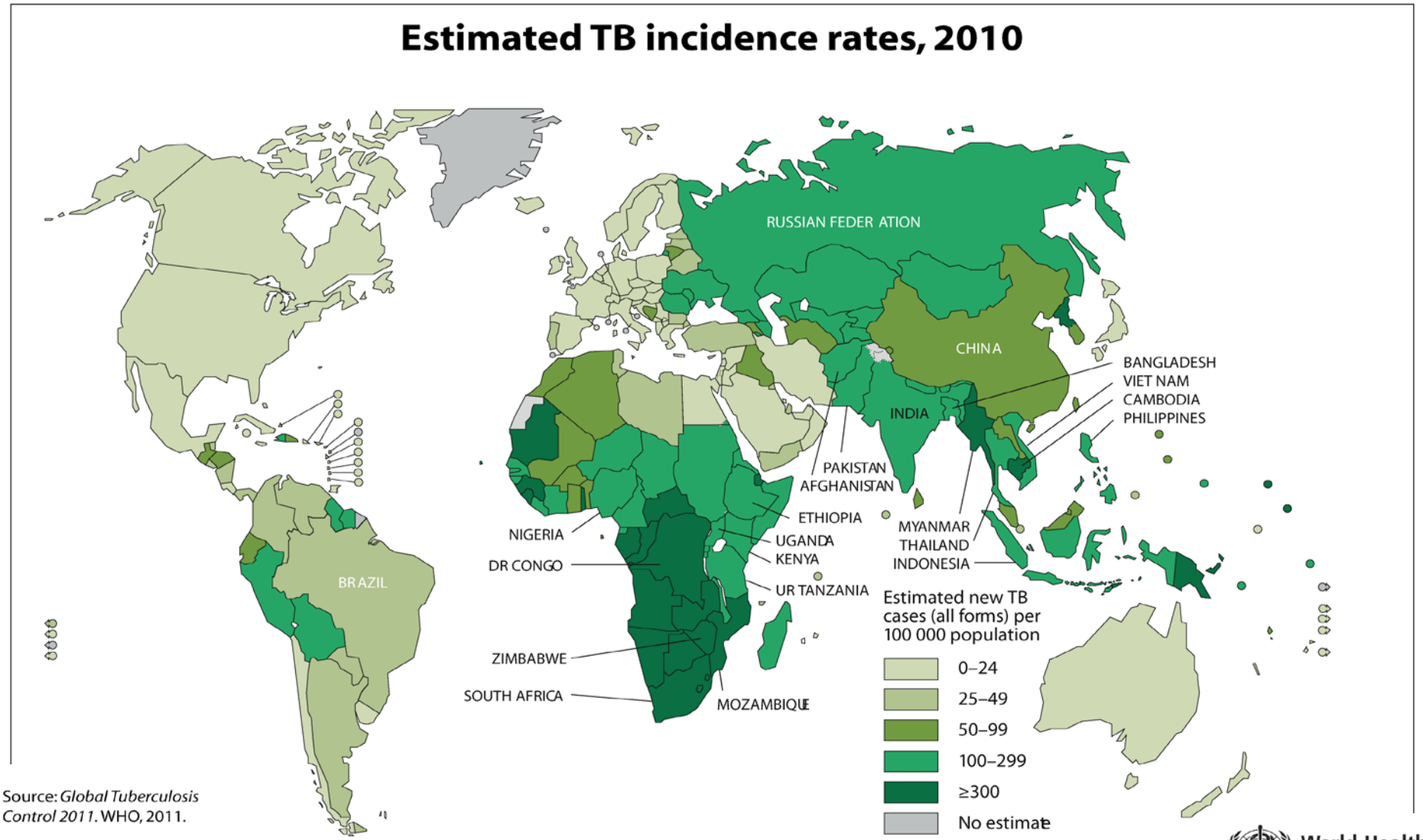
May be used in place of TST to test recent contacts of infectious TB

- Detect *M. tb* infection with greater specificity than TST
- Data are limited on ability to predict subsequent TB
- In contact investigations, confirm negative via retest 8-10 weeks post exposure
- Use same test for repeat testing to reduce misclassification errors

General Recommendations for IGRA Use

- May be used for periodic screening (health care workers)
- IGRAs do not boost subsequent test results
- Administered with one patient visit
- Results from both IGRA and TST may be useful when initial test is
  - Negative, and patient has high risk of TB infection or disease
  - Unclear or indeterminate

Immigration Screening



World Health Organization

Immigration Screening

- HHS/CDC regulations require all immigrants/refugees coming to USA be screened for TB (also adoptees)
- Specific testing requirements are based on age and country of origin
- Prior receipt of BCG does not change screening requirements or required actions

SNHD Immigration Screening

- Applicants require medical history, physical examination, TST or IGRA, and CXR. If suggestive of TB 3 sputum specimens should be collected.
- Release for travel dependent on sputum results
- If active TB, treatment initiated prior to travel release & must be non-communicable to travel
- Re-evaluated upon arrival in USA (SNHD)
- Adults receive IGRA, CXR, 3 sputum specimens
- Children receive IGRA (PPD if <5) and CXR

Immigration Screening

	2010		2011	
Immigrants completing evaluation process	307		353	
Latent TB Infection	253	82.4%	249	70.5%
Active Disease	4	1.3%	4	1.1%
No treatment needed (not infected or active)	50	16.3%	100	28.3%

	2010		2011	
LTBI started treatment	253	100%	249	100%
LTBI completed treatment	89*	35.2%	100	40.2%
Not completed (Reasons)	20*	7.9%	12	4.8%
Death	1*	0.4%	0	0.0%
Lost to follow-up	5*	2.0%	1	0.4%
Moved: follow-up unknown	14*	5.5%	11	4.4%

*Completion data is year to date comparison, not total number complete

Immigration Screening

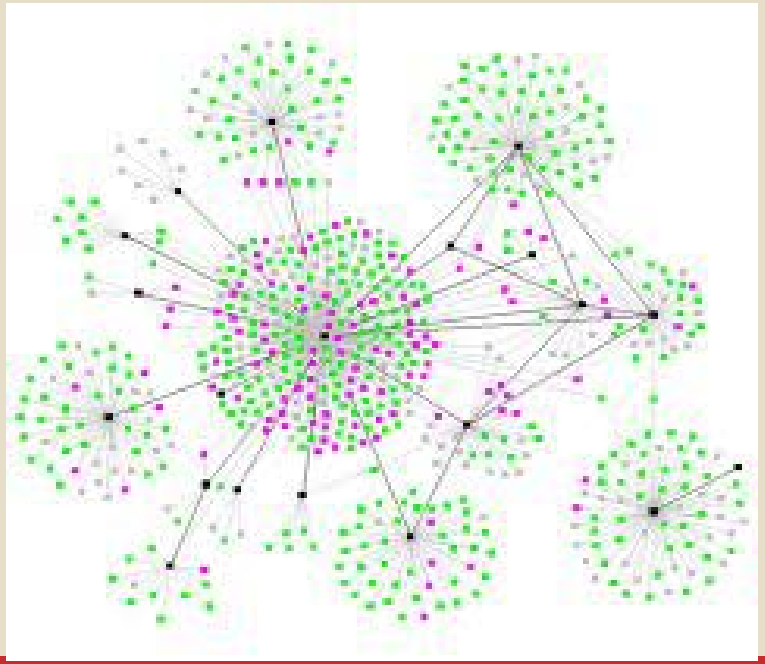
- Fewer QFT positives
- Similar LTBI treatment acceptance rate
- Higher rate of completion
  - Greater believability of blood test vs. TST
  - Intensified follow-up efforts on those that are late for refills

IGRA Use in SNHD Contact Investigations

- Research shows exposure characteristics associated with increased risk of infection correlate better with IGRAs than TST
- High percentage of foreign born active cases = high percentage of contacts with history of BCG vaccination
- Many contacts see blood tests as more reliable
  - "My arm always does that when I go to jail."
- When clients have more faith in the test they are more likely to accept LTBI treatment

IGRA Use in SNHD Contact Investigations

- One step test eliminates need for return reading
  - If needing 8-10 week follow-up, cuts total number of visits from 4 to 2
- Reduces time DIIS spends locating those that do not return for reading
  - Allows more time for further contact identification and LTBI treatment follow-up



Conclusions

- IGRAs are highly specific resulting in a lower number of positive results compared to TST
  - No evidence to date that cases are being missed
- Blood-based TB testing is a superior surveillance tool with more believable results
- IGRAs are most useful in nonadherent and BCG-vaccinated populations
- IGRAs may remain positive even after appropriate treatment of active or latent TB
- NEVER use an IGRA to rule out active disease…it's another tool from the toolbox

References

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- World Health Organization. Global Tuberculosis Control 2011