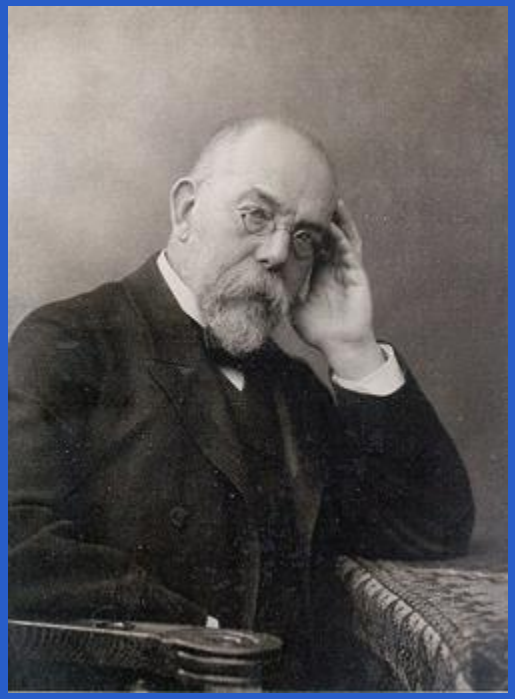
Photo shown:

Who is ???



TB “JA PERDY”

2013 JA

Diagnostics	Latent TB	Clinical TB	Special Features	Drugs	TB Control
100	100	100	100	100	100
200	200	200	200	200	200
300	300	300	300	300	300
400	400	400	400	400	400
500	500	500	500	500	500

This adds 5% to 10% in yield in diagnosis

What is sputum induction; direct observed sputum evaluation; Bronchial lavage?

Sputum evaluation

Jour Global In Dis
Oct 2011
Gastric lavage in adults

Spontenous Sputum

Supervised Sputum "DOSE"

Induced Sputum

Related to pooling of specimens: Refrigeration OK
IUAT April 2011

Chang et al Eur Resp J 2008 May ; (5) 1085-90

The issues

- Little supervision; the “give the cup” approach
- Bacterial contamination
- Only 30 % positivity in the first sputum although incremental yield beyond 3 is doubtful
- (S:47%/C:74% to S:58%/ C: 90%)
- Depends upon cavitary disease or non cavitary disease
- Single vs.24-72 hour pooled specimen: No difference except increased bacterial contamination (2%) increased to 15 %

Krasnow et al Appl Micro 1969;18:915-917
Kestle DG et al Am J Clin Path 1967;48:347-349

of sputum samples : Debate

- ILH data
- 451 times 3 sputum submitted on 426 patients since Nov 2008
-
- **Smear Positive Inpatients (n=53):**
- 83% positive on first smear, 90.5% positive with 2 smears
- 9.4% (5 pts) not positive until 3rd smear (of these 5 , 2 had TB)

  - Of the 5 pts who were not smear positive until 3rd sputum:
    - 2 with TB
      - 1 high suspicion (would have remained in isolation)
      - 1 low suspicion (HIV positive, discharged to hospice before 3rd sputum returned with diagnosis of PCP. He died the day the smear result became available)
    - 1 with Mkansasii
    - 2 with RG/MAC
-
- **Culture Results**
  - 26 (49%) with TB: 23 TB only, 2 TB/RG, 1 TB/MAC
  - 15 (28.3%) with MAC: 12 MAC only, 3 MAC/RG
  - 8 (15.1%) with M kansasii
  - 3 (5.7%) RG
  - 1 (1.9%) Szulgai
-

Bullets

- 2 sputum smears as good as 3 even for infection control purposes but….
- Volume of sputum 5cc or more improves sensitivity
- If ES negative; SI adds up to 19–30 % in sensitivity in suspected cases
- FOB with Bronchial washing if less than 50 cc, there is no difference in sensitivity
- FOB with BAL better if return more than 50 cc and sensitivity increased if PCR also done

Ref: Thorax 2002 : 57 1010
Nelson et al J Clin Micro 1999 36 (2)

Extraction of DNA; hybridization of labeled PCR products with oligonucleotide probes; according to the CDC, this must be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where diagnosis has not yet been established

What are nucleic acid amplification tests?

3% to 7% of sputum specimens have this,
Less than 50% of labs do this

What are tests for NAA inhibitors?

Molecular Methods

- STEPS
  1. Extraction of DNA
  2. PCR
  3. NA sequence amplication
  4. Hybridization of labeled PCR products with Oligo nucleotide probes

CID 2011 :52

"No home grown brew"

NAA

- CDC recommends that standardized NAA testing be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where Dx has not yet been established, and for whom the result will alter management and TB control measures/contact investigations

MMWR Jan 2009/58(01);7-10

NAA

Ampl MTB direct test
MTD (Gen-probe)

Enhanced Amplicor (Roche) test

Greater PPV /NPV and SS in smear positive cases) 80-95%
Lower sensitivity and PPV in smear negative cases 50% appx
Earlier Detection
Less inappropriate use of FQ as empiric monotherapy for pneumonia
Reliance by MDs: 20-50% of cases
NAA testing should be considered as Critical test value notification
Report time less than 48 hours.
If clinical suspicion is low, do not do NAA as PPV low
If clinical suspicion moderate or high: single NAA negative should not be relied upo

MMWR Jan 2009

NAA inhibitors: Importance

- 3–7% sputum specimens have inhibitors
- 50–75 % labs do this test; probably less

Interpretation

CLINICAL SUSPICION	AFB smear	NAA result	
HIGH	positive	positive	MTB (PPV 95%) Rx Isolate and Contact investigation
HIGH	Negative	positive	Repeat NAA; if positive or clinical suspicion high: Rx as TB as above
	Positive	negative	Repeat; test for Inhibitors, if none This is probably MOTT If Inhibitors present NAA no use Decision to Rx ??

Adapted from AJRD 1997 #155 pg 1804

This is based on mycobacterial genomics and antigen specific T cell response, Antigenic targets include ESAT-6 and CFP-10

What is IGRA test based on?

This is performed in homeless/transient resident population and has a higher PPV and NPV

What is IGRA?

The blood test for TB!!

TIGRA* update

Advantages

Disadvantages

TIGRA preferred but TST acceptable — Homeless /Transitional Care / Substance abusers

TST is preferred — Children less than 5 years of age

Equally acceptable: — Contact screening* (although higher PPV and NPV seen (3% vs 13 % and 99% vs 100% when compared with TST

ILH current priority list

5mm)

1. Employees
2. Immune compromised patients
3. Patients with Hx of BCG
4. Specific cases where differential Dx of pneumonia includes TB or MAC
5. Referral from Transitional Homes / Shelters to UCC

Am j Resp Crit Care 2011 jan

Relationship of timing of TST to TIGRA: Variable conflicting data ; Present consensus : no effect on either test results or booster phenomenon or false positivity

Ref MMWR /CDC Rep 2010 : 59 (RR-5 :1-28

INTERFERON GAMMA RELEASE ASSAYS (IGRAs)

AN OVERVIEW

Two Disclosures

PERSONAL

INSTITUTIONAL

Juzar Ali MB.,BS (MD); FRCP(C); FCCP

Interim LSU Public Hospital (ILH) & CLINICS System
Interim CEO /
Medical Director ; UMOB, 2025 Gravier St., 7th Floor NEW ORLEANS , LA 70112
Off: (504) 903 4900, 4907, 4917,; Fax : 504 903 4952
Email: JALI@lsuhsc.edu **Cell : 504 444 3975**
**Russell C. Klein, LSU-Alumni Professor of Clinical Medicine) ; **Faculty: Section of Pulmonary & Critical Care Medicine, LSUHSC
1901 Perdido , Suite 3205, MEB, New Orleans, LA 70112 LSUHSC Academic Office: 504 568 4634 Fax 504 568 4295
** Adjunct Professor, School of Nursing , LSUHSC**
** Medical Director : Region 1 OPH ; Metro-Wetmore TB Clinics**
** Adjunct Professor , Dept of Tropical Medicine, Tulane University School of Public Health and TM & Faculty:
Tulane University Dept of Preventive Medicine & Community Medicine**
** Guest Faculty: Ege University & Hospital , Chest Unit , IZMIR Turkey**
websites www.tbeducation.org www.tbinfo.lsuhsc.edu

ACKNOWLEDGEMENTS

WETMORE TB CLINIC TEAM ; TB CONTROL OFFICE LEADERSHIP
Ms Maureen Vincent , Clinic Coordinator;
Drs Dean Ellithorpe & Louis Trachtman
Mr Charles DeGraw et team

Timeline of Advancements in TB Screening

1900

1907 – Tuberculin skin test developed by Dr. Charles Mantoux

2000

2001 – US launch of QuantiFERON®-TB

2004 – US launch of QuantiFERON®-TB Gold

QFT® QuantiFERON-TB Gold

2007 – US launch of QuantiFERON®-TB Gold In-Tube

2008 – US launch of the T-SPOT®.*TB* test

2010 – US launch of approved overnight storage protocol for the T-SPOT®.*TB* test

Tuberculin Skin Test (TST) vs Interferon-Gamma Release Assays (IGRAs)

Tuberculin Skin Test

- 2 visits required (minimum)
- Method: injection into skin
- Results affected by BCG
- Results in 48–72 hours
- Subjective results

IGRAs

- 1 visit required
- Method: blood draw
- Results not affected by BCG
- Next-day results
- Objective results

Updated CDC Guidelines

CDC guidelines[1] allow the use of IGRA or TST for screening healthcare workers:

- "An IGRA or a TST may be used without preference for periodic screening of persons who might have occupational exposure to *M. tuberculosis* (eg, surveillance programs for healthcare workers)."
  - **IGRA preferred testing for groups with low rates of return**
  - **IGRA preferred testing for individuals who have received BCG**

- "Prior to implementing IGRAs, each institution and tuberculosis-control program should evaluate the availability, overall cost, and benefits of IGRAs for their own setting."

- LSU/ILH guidelines : When DDx includes Pneumonia/MAC/MOTT
- & with employees screening

1. Updated Guidelines for Using Interferon Gamma Release Assays to Detect *Mycobacterium tuberculosis* Infection - 2010. CDC MMWR 59 RR-5.

Commercially Available IGRAs

QuantiFERON®-TB Gold In-Tube[1]

- ELISA technology
- Measures IFN-γ release
- "One and done"
- PI sensitivity: 88.2%
- PI specificity: 99.1%
- 3 specialized tubes
- Provides qualitative results
- Sample stability: 16 hours
- Can be run in hospital lab
- Available nationally through reference laboratories (eg, Quest)

The T-SPOT®.TB Test[2]

- ELISpot technology
- Enumerates effector T cells
- "One and done"
- PI sensitivity: 95.6%
- PI specificity: 97.1%
- 1 standard tube
- Provides quantitative and qualitative results
- FDA-approved borderline category
- Sample stability: 32 hours
- Can be run in hospital lab
- Available nationally through Oxford Diagnostic Laboratories®

1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.
2. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec; 2010. T-SPOT is a registered trademark of Oxford Immunotec, Ltd. QuantiFERON is a registered trademark of Cellestis, Inc.

QuantiFERON®-TB Gold (QFT) Kit[1]

- ELISA-based assay in a 96-well format
  - 1-mL control, mitogen, and TB antigen collection tubes for each patient
  - 3 wells used per patient; 26 wells per plate
- Uses specialized collection tubes requiring 0.8−1.2 mL of blood per tube

1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.

Blood Collection for QFT Testing[1]

- Collection tubes include:
  - Nil control (grey cap)
  - TB antigen (red cap)
  - Mitogen control (purple cap)

- Tubes require shaking (10 times each) to mix blood with antigens coated on the inside of the tubes, but too much shaking could cause aberrant results
- Blood in collection tubes must be incubated for 16−24 hours at 37°C within 16 hours of collection[2,3]

1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.
2. Herrera V, Yeh E, Murphy K, Parsonnet J, Banaei N. *J Clin Microbiol*. 2010;48(8):2672–2676.
Doberne D, Gaur RL, Banaei N. *J Clin Microbiol*. 2011;49:3061-3064.

The Science Behind QFT Technology[1]

- Blood samples are incubated with antigen to stimulate IFN-γ release
- Plasma containing IFN- γ is harvested
- Plasma, standards, and conjugate are added to appropriate wells of QFT ELISA plate and incubated
- Substrate is added to each well and incubated
- Stop solution is added to all wells and absorbance read
- Computer software is used to interpret results

1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.

Interpreting QFT Results[1]

QFT Result	Nil (IU/mL)	TB Ag-Nil (IU/mL)	Mitogen-Nil (IU/mL)
Positive	≤ 8.0	≥ 0.35 and ≥ 25% Nil value	Any
Negative	≤ 8.0	< 0.35	≥ 0.5
Indeterminate	≤ 8.0	≥ 0.35 and < 25% of Nil value	< 0.5
Indeterminate	> 8.0	Any	Any

1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.

T-SPOT.®*TB* Test Kit[1]

- Flexible, 96-well format
  - 12 eight-well strips
  - 4 wells used per patient; 24 patients per kit
  - Positive and negative control for each patient test
  - A minimum of 1 patient test can be run
- Uses standard blood collection tubes
- No special lab equipment required

1. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec; 2010.

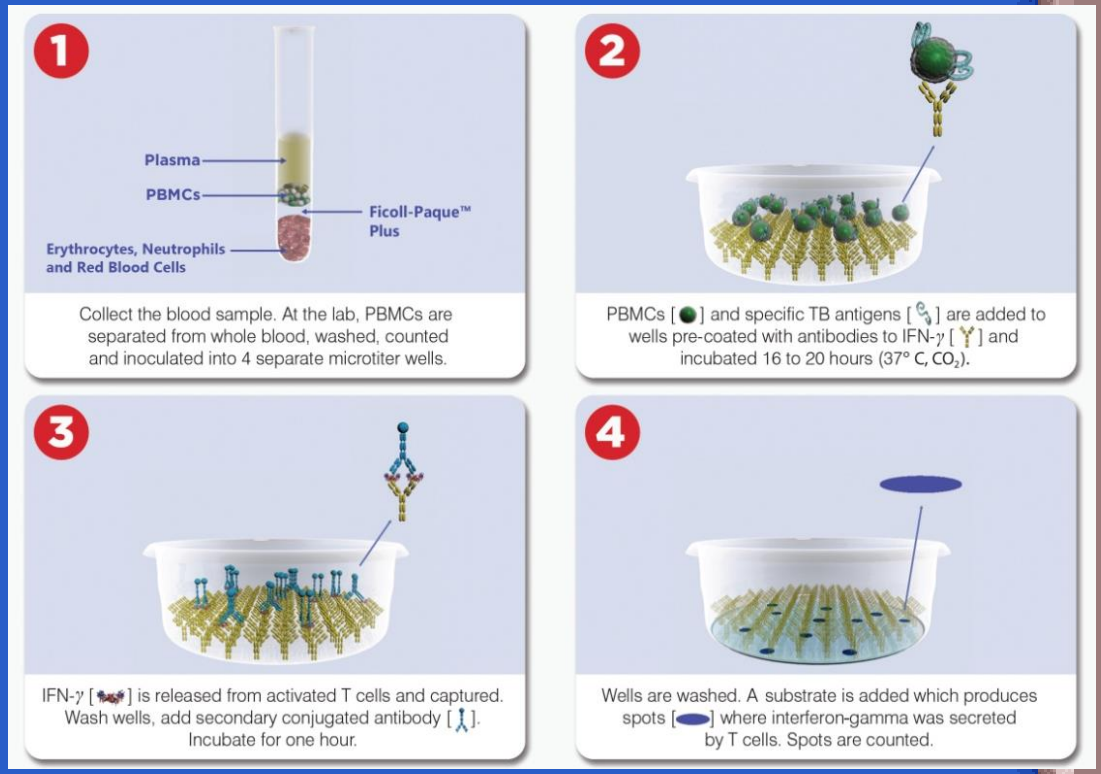
Blood Collection for T-SPOT.*TB*[1]

- No special phlebotomy training required
- Uses a standard lithium or sodium heparin tube
- Less sensitive to preanalytical variables than QFT
  - Time from collection to analysis
  - No specialized tubes needed
  - No specific order of draw
  - No shaking of tubes
  - No incubation required
  - Specimens maintained at room temperature for up to 32 hours

1. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec; 2010.

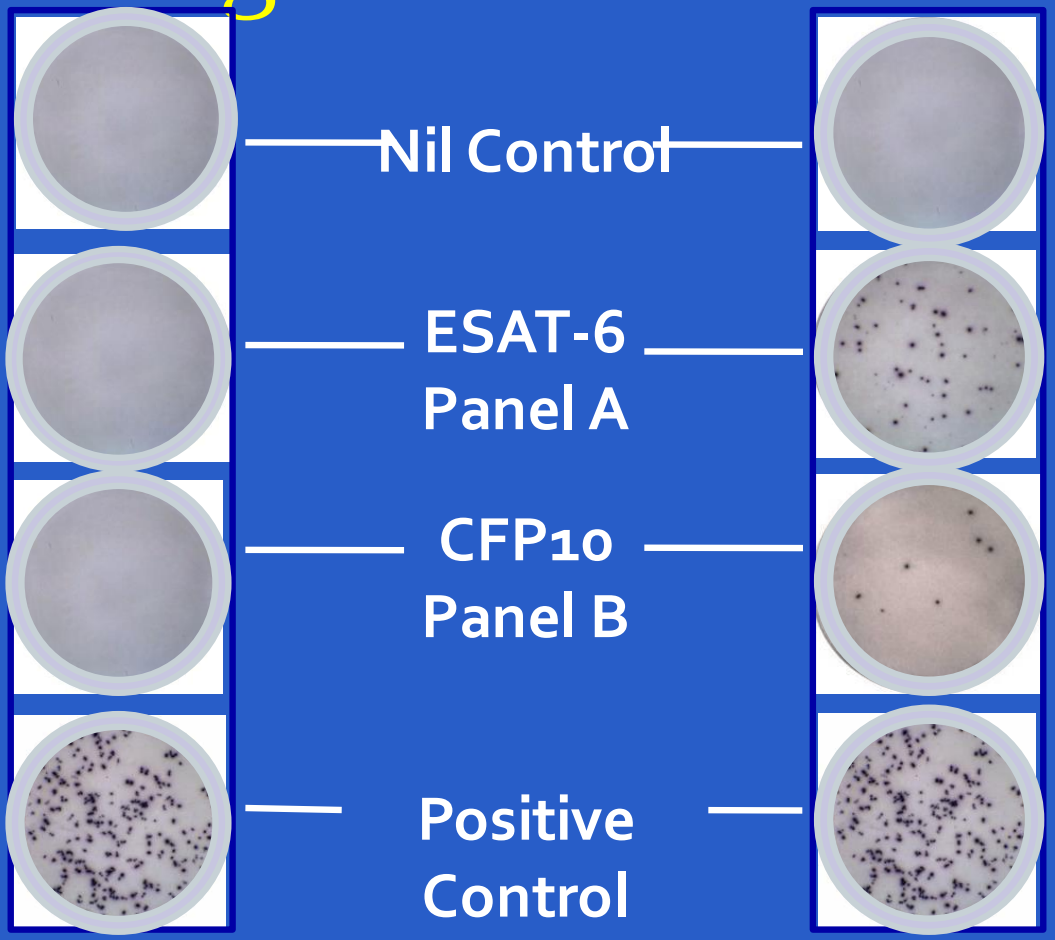
The Science Behind T-SPOT.*TB* Technology[1]

- Density gradient isolation of mononuclear cells
- Quantitation of cells and adjustment of concentration
- Incubation with specific antigens on ELISPOT microtiter plate



1. T-SPOT.*TB* Package Insert. Marlborough, MA. Oxford Immunotec, 2010.

Interpreting T-SPOT.*TB* Results[1]



1. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec; 2010.

Interpreting T-SPOT.*TB* Results[1]

- The test result is **Positive** if Panel A-Nil and/or Panel B-Nil **≥ 8 spots**
- The test result is **Borderline** (equivocal) where the higher of Panel A-Nil or Panel B-Nil spot count is **5, 6, or 7** and retesting by collecting another sample is recommended
- The test result is **Negative** if Panel A-Nil and/or Panel B-Nil **≤ 4 spots.** This includes values less than zero.

1. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec; 2010.

Consideration of TB Blood Test Logistics

Phlebotomy Steps	QuantiFERON®-TB Gold In-Tube[1]	T-SPOT®.*TB* Test[2]
Collection tubes	3 specialized tubes	Standard tube
Tubes drawn in specific order	Required; Nil, TB antigen, mitogen	N/A
Blood volume	1 mL (0.8–1.2 mL); under- or overfilling outside the 0.8- to 1.2-mL range may lead to erroneous results	Fill 6-mL tube
Shake collection tubes	Required; vigorously shake the tubes up and down 10 times	Not required
Purge tube with butterfly	Required when a butterfly needle is used	Not required
Sample stability	Specimens must be incubated as soon as possible but within 16 hours	Up to 32 hours

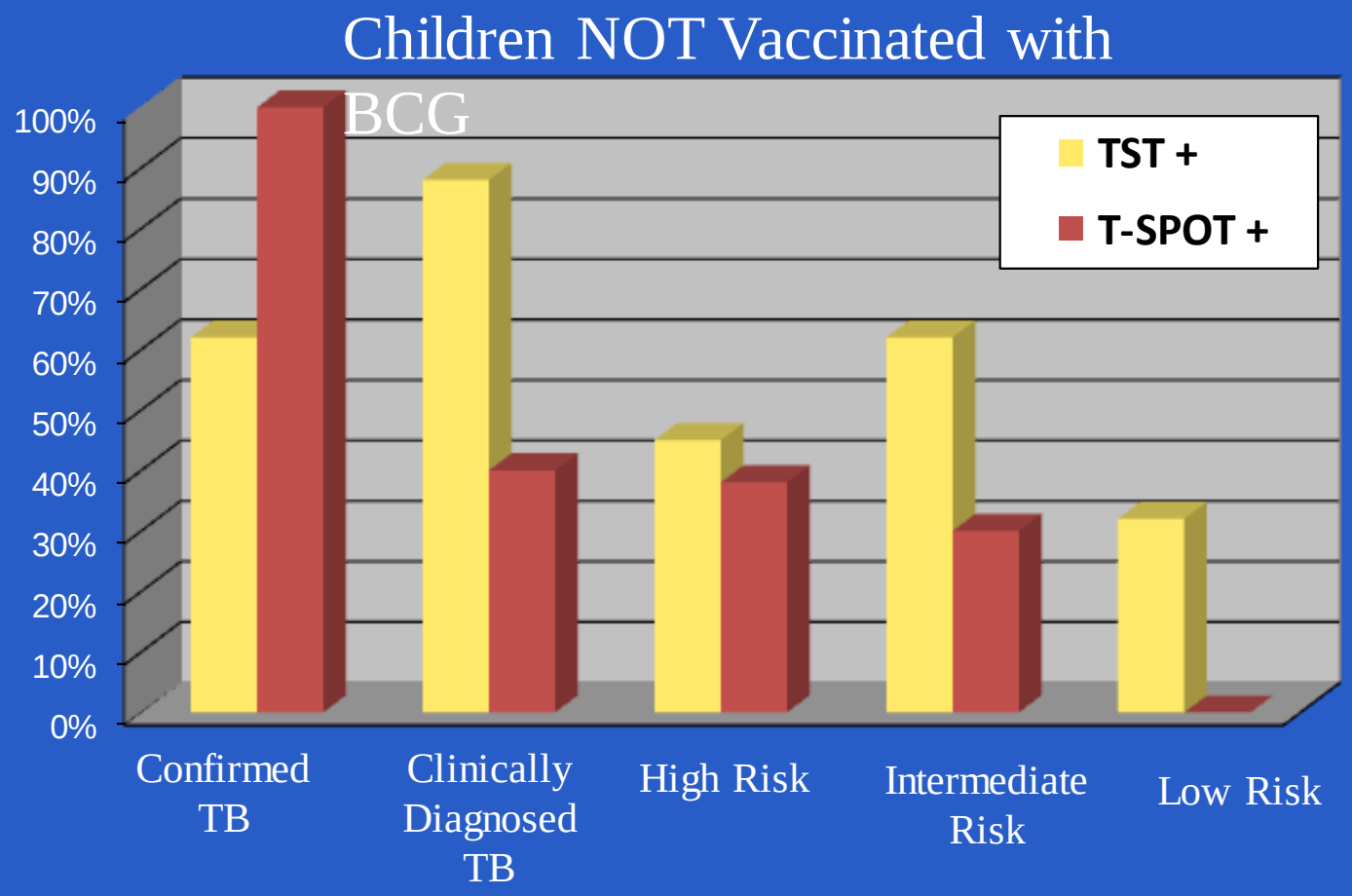
1. QuantiFERON-TB Gold Package Insert. Cellestis, Inc. Valencia, CA. Doc. No. US05990301K, July 2011.
2. T-SPOT.*TB* Package Insert. Marlborough, MA: Oxford Immunotec, 2012.

TB Screening in Children Using TST and T-SPOT.*TB*

- **Study objective:** To compare the diagnostic performance of an IGRA (T-SPOT.*TB*) to the TST in children seen in US tuberculosis clinics[1]
- A prospective study of 210 children (ages 1 month to 18 years) from 3 pediatric TB clinics in Houston, Texas
- 4 levels of epidemiologic risk:
  - Low (no identifiable risk factor, n = 27)
  - Intermediate (birth in or travel to high-prevalence country or contact with adults with risk factors, n = 78)
  - High (recent contact with a person with TB, n = 74)
  - Active disease (n = 31)
- BCG vaccine status was also used to compare the performance of the 2 tests

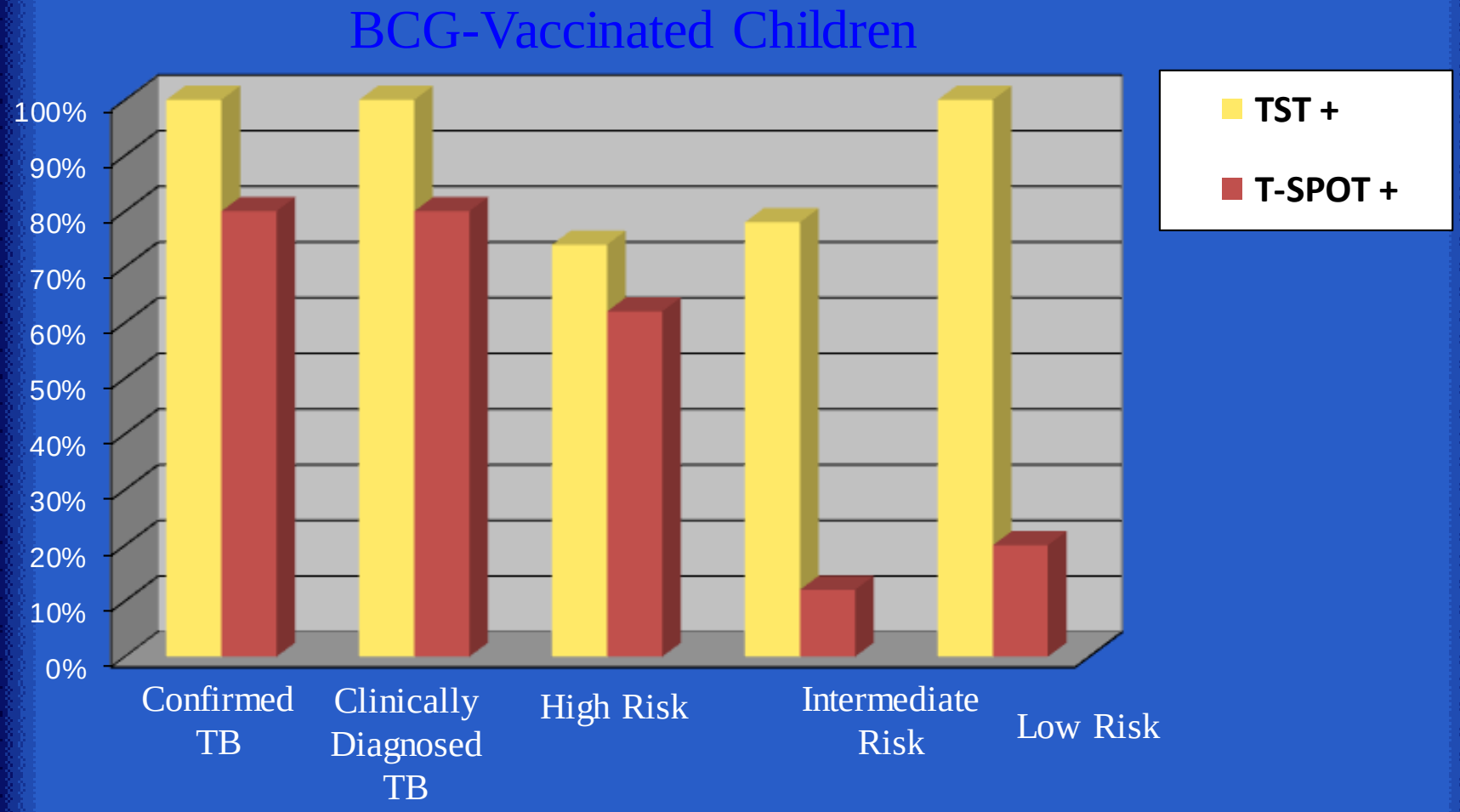
1. Cruz AT, Geltenmeyer AM, Starke JR et al. *Pediatrics*. 2011;127(1):e31-e38.

TB Screening in Children[1] Using TST and T-SPOT.*TB*



1. Cruz AT, Geltenmeyer AM, Starke JR et al. *Pediatrics*. 2011;127(1):e31-e38.

TB Screening in Children[1] Using TST and T-SPOT.*TB*



1. Cruz AT, Geltenmeyer AM, Starke JR et al. *Pediatrics*. 2011;127(1):e31-e38.

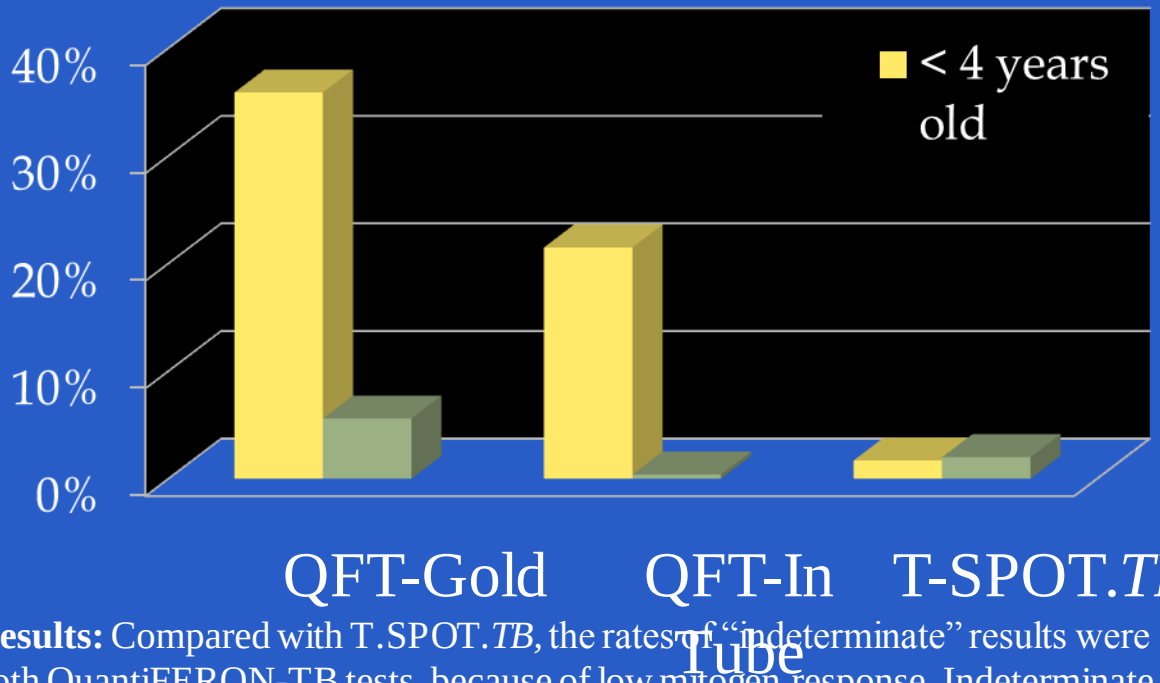
TB Screening in Children and Adolescents Using QFT and T-SPOT.*TB*

- **Study objective:** To evaluate the impact of age on the performance of various IGRAs when used in a hospital setting among children tested for suspected active or latent TB[1]
- A retrospective study of 496 children (ages 0 to 19 years of age) at the University of Modena in Italy who had been tested with the TST and at least one IGRA:
  - 181 with QuantiFERON-TB Gold only
  - 315 with QuantiFERON-TB Gold In-Tube only
  - 87 with QuantiFERON-TB Gold & T-SPOT.*TB*
  - 67 with QuantiFERON-TB Gold In-Tube & T-SPOT.*TB*

1. Bergamini BM, Losi M, Vaienti F, et al. *Pediatrics.* 2009;123(3):e419-e424.

TB Screening in Children and Adolescents[1] Using QFT and T-SPOT.*TB*

Indeterminate IGRA Results in Children



- **Results:** Compared with T.SPOT.*TB*, the rates of "indeterminate" results were significantly higher for both QuantiFERON-TB tests, because of low mitogen response. Indeterminate results were seen more frequently in children < 4 years old than in those ≥ 4 years old.
- **Conclusion:** Different TB blood tests in children seem to perform differently, because both QuantiFERON-TB tests were more likely than T.SPOT.*TB* to give indeterminate results in children < 4 years old.

1. Bergamini BM, Losi M, Vaienti F, et al. *Pediatrics.* 2009;123(3):e419-e424.

No cross-reactivity to BCG and most NTMs

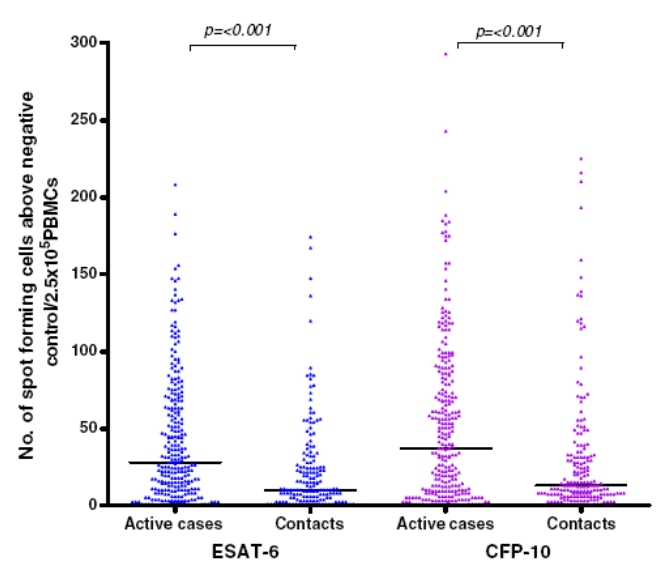
Tuberculosis Complex	Antigens		Environmental Strains	Antigens	
	ESAT-6	CFP 10		ESAT-6	CFP 10
M. tuberculosis	+	+	M. abcessus	-	-
M. africanum	+	+	M. avium	-	-
M. bovis	+	+	M. branderi	-	-
BCG substrain			M. celatum	-	-
gothenburg	-	-	M. chelonae	-	-
moreau	-	-	M. fortuitum	-	-
tice	-	-	M. gordonae	+	+
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. xenopii	-	-

Watch for *M. MSGK*

Active Vs latent

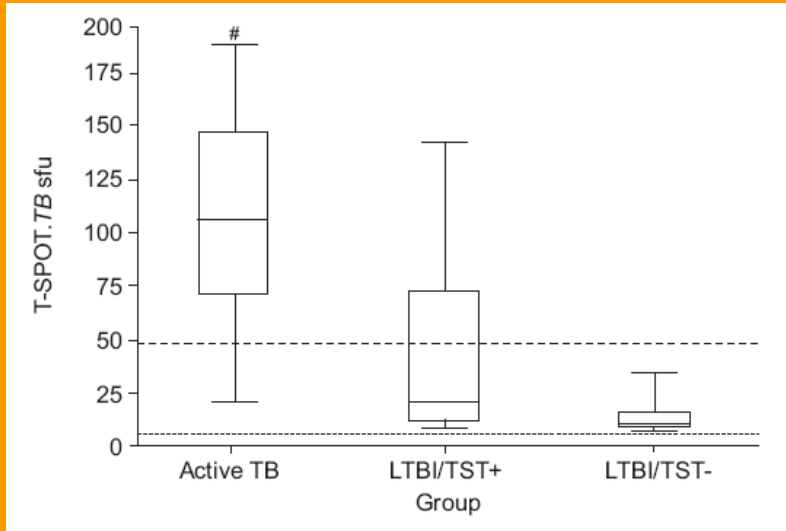
- IGRA responses are higher in active disease than in LTBI
  - **However, there is a very large overlap in the results so it will not be possible to use IGRAs to differentiate between active disease and latent infection**

Chee *et al* Eur J Clin Microbiol Infect Dis (2008)



T-SPOT.*TB* spot numbers in subjects with active disease compared to LTBI

Janssens *et al* ERJ (2007)



T-SPOT.*TB* spot numbers in subjects with active disease compared to LTBI (TST+ve and TST-ve)

OTHER CONSIDERATIONS

- COST BENEFIT ANALYSIS

The SWITCH Study

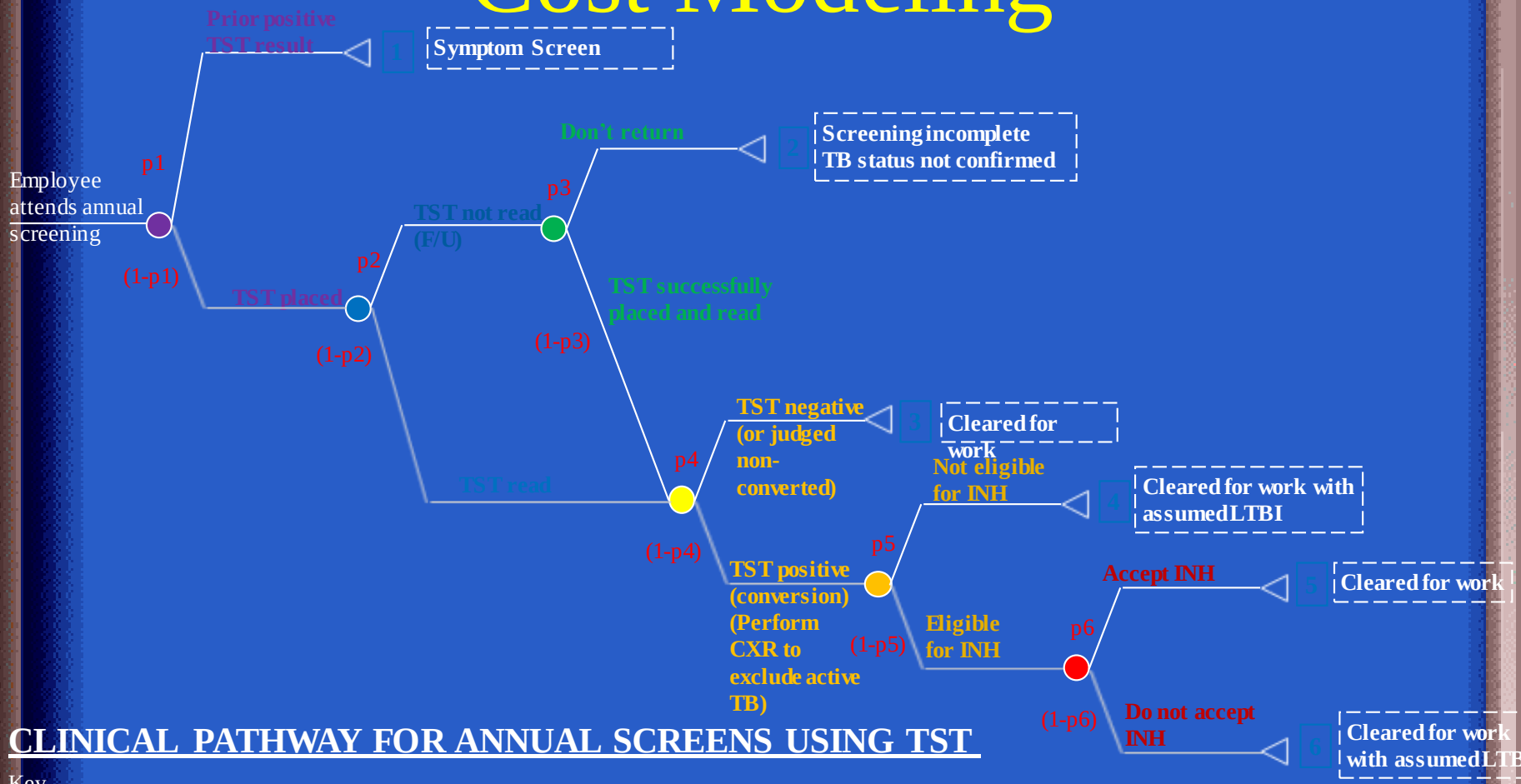
*S*creening Health Care *W*orkers with *I*nterferon-γ Release Assay Versus *T*uberculin Skin Test: Impact in *C*osts and Ad*h*erence to Testing

Authors: Wrighton-Smith, P.; Sneed, L.; Humphrey, F.; Tao, X.; Bernacki, E.

Publication: *Journal of Occupational and Environmental Medicine*. 54(7):806-815, July 2012

Study Sites: Johns Hopkins Healthcare System (JHHS) and Johns Hopkins Medical School, Baltimore, MD

Cost Modeling



CLINICAL PATHWAY FOR ANNUAL SCREENS USING TST

Key

Red text denotes probabilities of taking a particular branch at each decision point

Blue numbers are used to label each of the possible final pathways that an employee could take during screening. The costs of these pathways were individually determined.

For example, pathway 5 has the following costs associated with it: TST placement (material and labor cost), TST reading (lab or cost), chest X-ray (material and labor cost), INH treatment (drug costs, monitoring test costs, etc.)

Highlights:

- First study to analyze the actual cost of a TB screening program using both the TST and the T-SPOT.*TB* test by obtaining direct measurements of all program components.

- Study exposes the "false economics" of the TST, demonstrating that it actually costs $73.20 per test to perform when taking into account all the components of a TST program.

- Using the T-SPOT.*TB* test resulted in 99% compliance (with no follow-up required).

- Cost savings were realized when the material cost of the T-SPOT.*TB* test is at or below $54.83 per test.

Results:

- 75/113 prior positive TST employees were T-SPOT.*TB* negative
- 10x more employees preferred the T-SPOT.*TB* test over the TST
- The average cost of using the TST at JHHS for their TB screening program costs an average of $73.20 per employee
- The TST screening adherence rate was 70.8% without EH staff follow-up, and modeled to be 98.5% with staff follow-up (at an additional cost of $20.59 per employee)

Discussion:

- 9/10 significant costs associated with TST screening programs were related to staff times.
- With TST, institutions are forced to weigh costs against the desired adherence rate. When using the T-SPOT.*TB* test, that decision is not necessary.
- 10% of the TST non-returners were positive with the T-SPOT.*TB* test, demonstrating a risk to the hospital if the staff did not follow-up with the non-returners.
- SWITCH study results demonstrating TST screening costs of $52 to $73 per employee are similar to results from a study

What is your current case rate and volume of testing?

- Louisiana reported 218 cases with a 5.2 case rate in 2009
- Performed 4,901 PPDs
  - 90 HIV positives
  - 2,625 in high risk contacts
  - 427 in foreign-born
  - 1,849 in low risk screening

Cost Comparison

- Mantoux PPD: Clinic $23.80 Field $52.20
- Private Laboratories (QFG-IT): $150 to $260
- State Laboratory (T-SPOT): $85.00
- Oxford Diagnostic Laboratories (T-SPOT): $60.00

Implementation

- Guidelines
- Supplies
- Forms
- FedEx
- Venipuncture training
- Reports - Submitter and TB Control Program
- Payment

Evaluation

9 Months: 2898 T-SPOT.*TB* tests performed

	2009 (PPD)	**2010 (T-SPOT.*TB*)**
Contacts	23%	21%
Foreign-born	98%	38%
PPD Positive	83%	65%
HIV Positive	45%	54%

Evaluation (cont.)

9 Months: 113 T-SPOT.*TB* tests performed

Cases	2009 (PPD)	2010 (T-SPOT.*TB*)
Culture +	76%	89%
HIV Positive Culture +	85%	100%
Clinical	75%	60%

Summary of Benefits

- Restructure contact investigations
  - Eliminated second visit
  - Time to identify additional contacts
  - Increase the number of contacts placed on DOT for LTBI
- Place more HIV positives to DOPT
- Improve prevention services and reduce overall budget

Questions We Ask ?

- TST and IGRAs : predictors of disease : General
- Does quantifying help in either case ?
- Specific Quantification in TB spot test : Culture filtrate protein 10 spot count, but not early secretary antigenic target 6 spot count, was significantly associated with subsequent TB development. (Hongkong study in silicotic pts)
- Issue of discordance & Borderline data
- Effect of Smoking **Negative effect of smoking on the performance of the QuantiFERON TB gold in**
- **tube test** *BMC Infectious Diseases* 2012, **12**:379 doi:10.1186/1471-2334-12-379
- **IMPORTANCE OF DEFINITION OF CONVERTORS OR REVERSION SPECIALLY IN HCWs**

Challenges of IGRAs conversion in serial testing of HCW : Fong et al Chest 2012 ;142 (1): 55-62

Issue of Borderline results

- **Both IGRAs are biological assay so results will have some variation around the cut-off**
- **Using a cut-off reduces fluctuations in results that are near the cut-off**
- **Benefit of cut-off is highlighted by CDC in 2010 guidelines:**
  - **"Use of a borderline category might address test variation and uncertainty for results near a dichotomous cut point."**
- **Re-testing borderline results 2 weeks later should give definitive result**
- **Bordeline zones used by IGRAs:**
  - **T-SPOT.*TB* has a borderline of 5, 6 and 6 spots throughout the world**
  - **QFT only has borderline zone in Japan (0.1 - 0.35 IU/IFN gamma)**

Explaining discordant results; Contact tracing

Zellweger *et al*., Int J Tuberc Lung Dis (2005)

	T-SPOT.*TB*			TST		
	OR	*P* value	95% CI	OR	*P* value	95% CI
Being in high exposure group	5.00	0.029	1.05–23.86	1.85	0.161	0.78–4.36
Having received BCG vaccine	1.32	0.733	0.27–6.56	n/a*	0.0003	n/a
Age of subject†	3.31	0.116	0.70–15.80	2.66‡	0.041	1.02–6.92

"These findings support the extensive literature showing that measurement of TB-specific T-cells using the ex vivo ELISPOT technique (upon which the T-SPOT.*TB* test is based) is more accurate than the TST, as it has closer correlation to exposure history and is unaffected by prior BCG vaccination."

Explaining discordant results; Contact tracing

Zellweger *et al*., Int J Tuberc Lung Dis (2005)

Setting: contact tracing in an institution for alcoholics in Lausanne, Switzerland

Index case:

- 47-year old female, born in Brazil
- Smear-positive pulmonary TB, infectious for 1 month
- She had stopped TB treatment 3 years before so possibility of MDR-TB

Background

- Preventive treatment associated with liver toxicity (most contacts >35 years old, residents all had history of alcoholic liver disease)

Explaining discordant results; TNF screening

Vassilopoulus *et al.*, J Rheumatology (2008)

- 70 subjects attending a rheumatology clinic in Athens
- All candidates for anti-TNF therapy
- 43/70 on immunosuppressive drugs
- 15/70 had co-morbid conditions (e.g. chronic liver disease, diabetes, COPD)
- Results of TST and the T-SPOT.*TB test* compared, multivariate analysis used to analyse discordant results

		TST		
T-SPOT.*TB*		+	-	Total
	+	12	4	16
	-	15	39	54
	Total	27	43	70

"(BCG) vaccination was associated with TST+/Elispot– discordant results (p = 0.01), whereas steroid use was linked to TST–/Elispot+ discordant results (p = 0.04)." p 1

Borderline results

- Both IGRAs are biological assay so results will have some variation around the cut-off
- Using a cut-off reduces fluctuations in results that are near the cut-off
- Benefit of cut-off is highlighted by CDC in 2010 guidelines:
  - "Use of a borderline category might address test variation and uncertainty for results near a dichotomous cut point."
- Re-testing borderline results 2 weeks later should give definitive result

Indeterminate results

- **Indeterminate results occur when nil or positive controls fail. Caused by:**
  - **Errors during processing (usually resolved when re-tested)**
  - **Maybe patient specific (not usually possible to resolve)**
- **Indeterminate results should be repeated 2 weeks later**
  - **~ two thirds will then give a reportable result**

Black and white and Grey

The discussion about discordant results

A "positive" TST / IGRA : suggested plan

steps

A : DATA	B: EVALUATE	C: SCAN	D : RECAP	E: TREAT
QUANTIFY ASSESS BORDERLINE INDETERMINATE DISCORDANT RESULTS	RULE OUT ACTIVE DISEASE	RULE OUT EXTRA-PULM DISEASE	SIZE OF TST: is it helpful? IN CHILDREN; Degree of IGRA ??	**Dx; LTBI** **Should we offer Rx? Based on many factors**
DOCUMENT	SYMPTOMS H/P	ROS LN EXAM	GO BACK to STEPS B&C IF IN DOUBT	**RISK OF ADR***
CHECK HIV	CXR CT Scan if needed	CORRELATE with Chest imaging		**PRE-LAB CHECK**
STRATIFY RISK, CHECK SOURCE CASE **WHY???**	SPUTUM INDUCE if needed	PRE-TEST PROBABILITY?	IF SURE GO TO STEP E	TREAT FOR LTBI. ASSESS RISK BENEFIT RATIO
CONCLUDE AFTER FULL EVALUATION; IF POSITIVE STEPS B-E	PRE-TEST PROBABILITY? TREAT FOR ACTIVE TB ?	TREAT FOR TB ?		**MONITOR** **SIDE EFFECTS*** **AND Rx**

*ATS 2006 DILI consensus statement

TEŞEKKÜRLER

teşekkür ederim/ sağ olun for your kind attention

LA

And …You all are welcome to LSU and New Orleans, USA

Hoş geldin to USA

ILH /Bogalusa MC data

- 1130 tests performed last 6 months *
- 55/1130 4.9 % positive… HOP and 4W
- 982/1130 86.9 % negative
- Rest either invalid, borderline , other causes
- ** previous year 3063 performed

Is it better to get LTBI than not?

- Relative to risk of developing progressive TB after reinfection compared to uninfected indivduals
- In a review of 23 cohort studies prior to LTBI Rx (1950's) 79% lower risk of developing progressive TB

CID Oct 2011

NTM/MOTT
BCG
Technique

What are the drawbacks of TST/Mantoux test/PPD?

TST phenomenon
Two step
Confusion to treat or not

What is the booster phenomenon?

Granulomas
TST/TIGRA
Th1 response
Not infectious

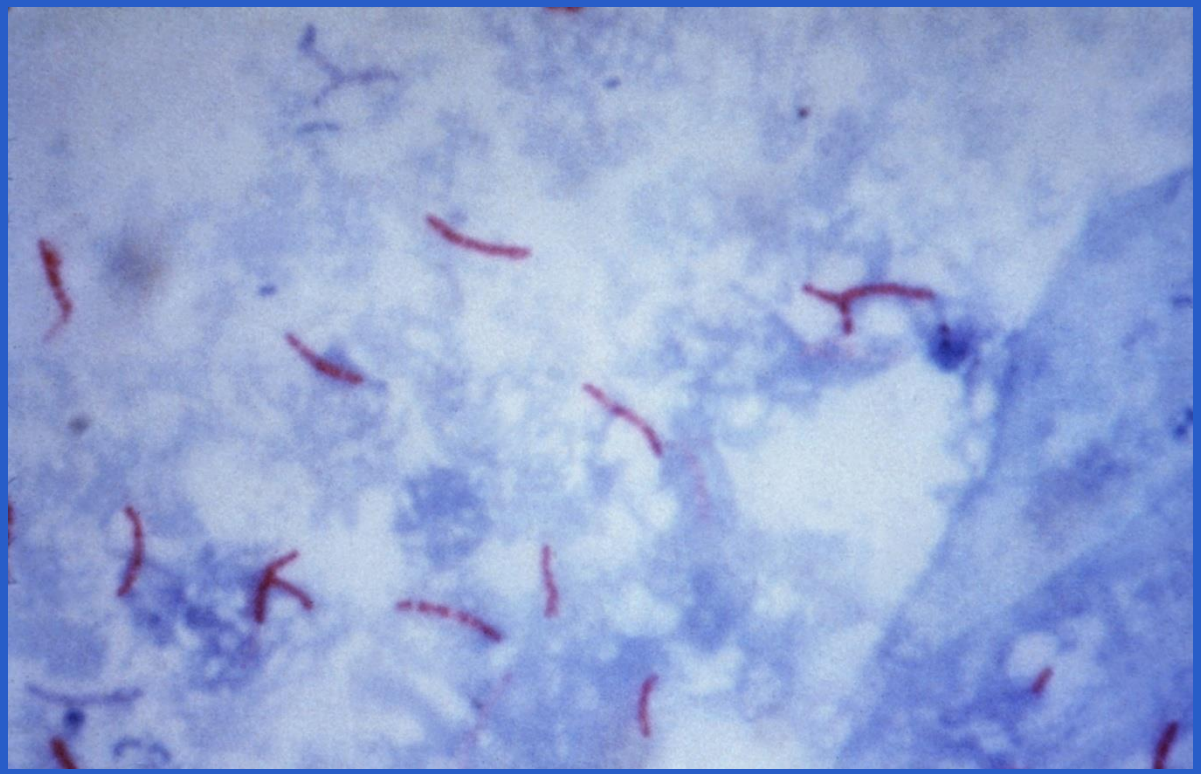
What is latent TB?

Check for active TB

What do you do before starting treatment for latent TB?

Must be DOT and it is not treatment for active TB

What is chemoprophylaxis for latent TB by intermittent therapy?

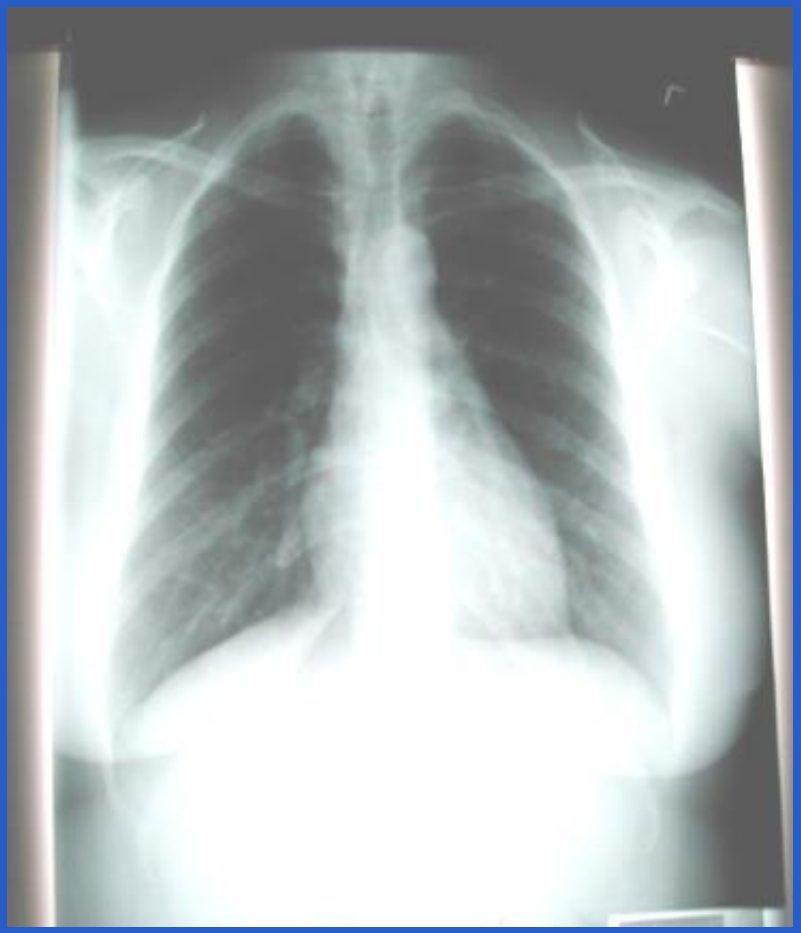


TB
MOTT
Nocardia
Leprosy

What is a Positive AFB smear?

HIV 5 mm
Contact 5mm
Congregate setting 10 mm
No risk 15mm

What are the criteria for a positive TST requiring consideration for chemoprophylaxis?



Normal chest x-ray

What is the CXR finding in 15% of HIV patients with TB?

13% to 22% of cohort can acquire disease form this group

What is

Smear negative TB?

The hidden reservoir of TB

- Smear negative cases: 13-22 % of cohort can acquire disease from smear negative contacts
- Undocumented immigrants with prolonged symptoms with poor access to health care

(CID 2008 Tostmann et al)

(Achkar et al Clin Infec Dis 2008 Nov)

Delay in Dx, Index of suspicion (Surgical specialties)

Am J Med science 340 Nov 2010)

Note:
Infectious period 3 months prior to onset of symptoms
Only 20% of contacts with LTBI complete Rx.; Need to expand contact screening for Smear negative TB

(

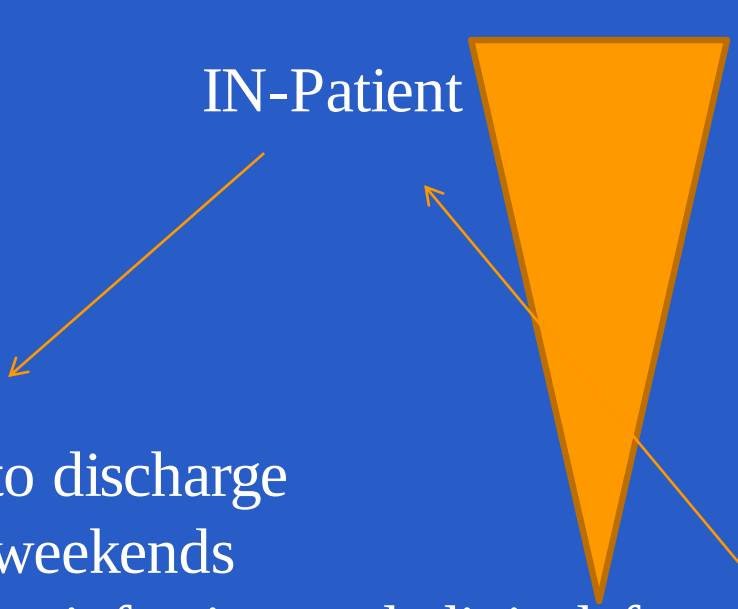
Suspect cases

ILH data

- Suspect TB cases require Resp Isolation
- Average cost of care 20 K per pt
- ALOS : 22.7 days

When to hospitalize and when to discharge

Basis: NYC Health Dept criteria



When to discharge
Avoid weekends
Check pt infection and clinical factors
Co morbid conditions
Home and follow up situations.
Depends upon where discharged to

When to admit?

Cavitary disease / Hx Substance abuse
Unstable medical /psych /social
or societal or follow up situations

Compliance

No DOT

Increase bacterial burden

Development of secondary resistance

Malabsorption of Drugs

Host variation in response to drugs

“lab error”

What are

The causes of delayed sputum conversion and/or treatment failure?

Reasons for delayed conversion and /or treatment failure

- Compliance/ No DOT used; though 16% failure rates in DOT programs too (**)
- Increased bacterial burden ; cavitary disease
- Development of secondary resistance
- Malabsorption of drugs
- Host variation in response
- “lab error”

1: 28.6 %

**Region

No SM

No PZA in USA

9 months at least

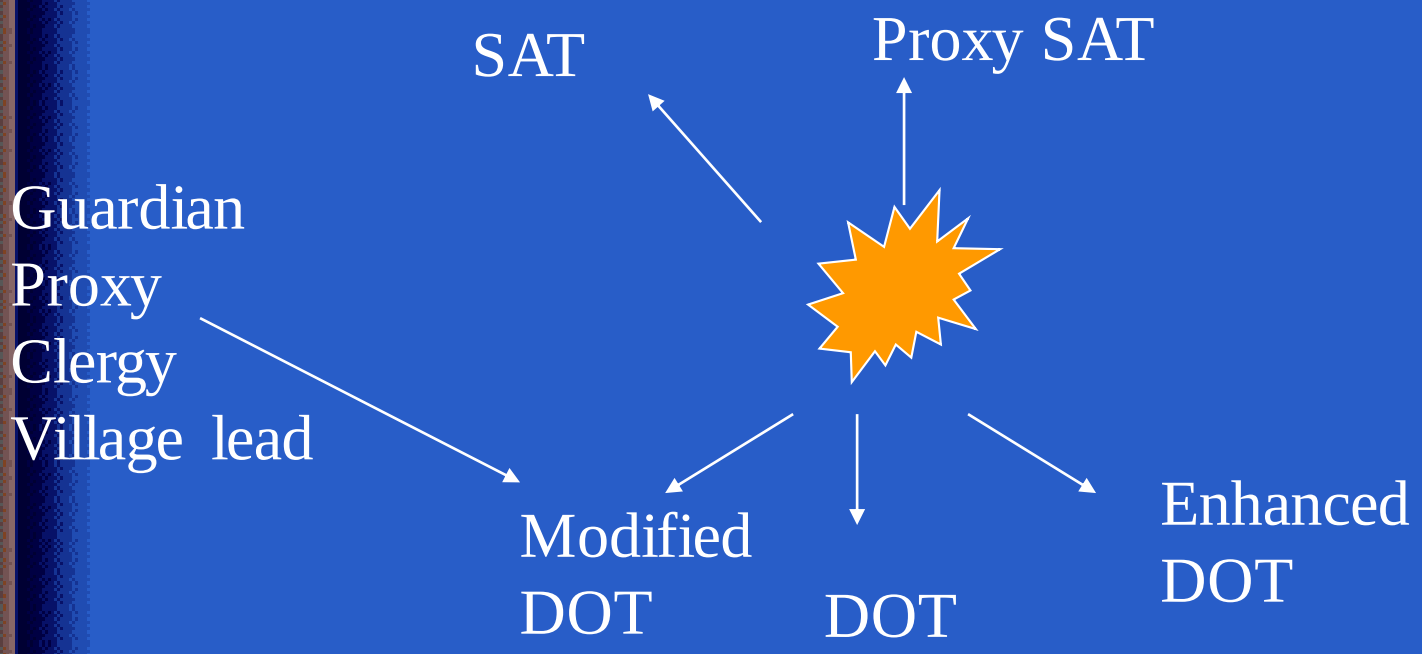
Vitamin B6 a must

What is

TB treatment in pregnant womem?

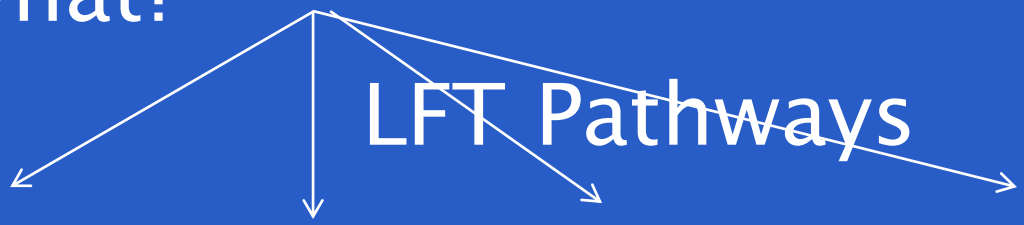
Rx protocols

Single drugs versus FDC
No inferiority
JAMA 2011;305 (14):1415-1423



You start RIPE

- And then……
- LFTS become abnormal (multiple Criteria)
- Skin rash develops…Culprit ? * PZA /Rif in HIV
- Now What?



Stop Rx Review Dx , Choose second line drugs , Re initiate in a step wise manner ; choose drugs based on likely culprit etc , Modify and de-escalate

Therapy

- Ideal Rx: DOT "RIPE"
  Duration: 6 months …..* 9 months in special case scenarios

* When sputum culture is still positive at the end of 2 months
* CXR showed cavitary disease/ Initial high bacterial load
* When initial induction phase did not include PZA
* When induction phase was not "standard" i.e. once weekly doses

TB Pleural effusion**

17% cases had Pleural fluid lymphocyte count of less than 50%
And this count was inversely related to positive culture
(63 % positive culture on liquid medium) Thorax March 2012

	ADA*	PCR	INFγ
*Sens	88%	85.7 %	73.8 %
*Spec	85.7%	97.1%	90%

* Maintained over a wide range of prevalence; note cutoff point and

The Pleural fluid triad*
ADA,LDH,L:N ratio of > 0.
>90 % s/s

Ghanei et al 2004
Asian CT Annals , Iran

**Confirmed by culture or pleural bx

Villegas et al: Chest 2000 118:1355-1364

** May be helpful to remember in other fluid evaluation*

Extra pulmonary TB

- 1993–2006 US data ; 18.7 %
- 40% Lymph nodes, 20% Pleural effusion
- 10% combined
- Female sex, foreign birth
- Not associated with usual Pulm TB risk factors
- Relationship between *MTB* and phylogenetic lineage and clinical site !!

- CID 2009;49:1350–7
- CID 2012;54(2): 211–9

23% of MDR-TB
are this

What is XDR-TB?

RISK Factors for DR; MDRTB and XDRTB

- Inadequate Rx protocols and non compliance
- Question of low level resistance and importance there of
- Previous TB Rx OR 11; HIV OR 3 , Homelessness OR 3, ETOH abuse OR 2 (Annals June 2009)
- Rifampin Resistance is an excellent marker for MDRTB

XDRTB in the limelight, but this has existed…..up to 34 % of MDRTB

Lancet 2006: Gandhi et al from the Natal Province South Africa

- Dx – Death period: 16 days; mortality 85-98%
- HIV population; median CD4 : 64 with only 34 % receiving ART
- Epidemiological survey: 41 % MDRTB; 23 % of these were XDRTB

It is not coming soon

It is here

90% sensitive/specific

What is

The XPERT Test?

Where are we moving forward ?

- Old drugs ; Newer drugs and newer class of drugs *(focus has moved to out of USA to Japan , India)*
- Other approaches : targeting *MTB* proteins*
- Drug delivery : Inhaled administration
- Revisit Rifampins (Dose, toxicity concerns (immunologic and idiosyncratic) , association with PZA , Drug levels, D-D interaction)
- Caution about Flouroquinoles

Mitnick et al NJMRC Denver Expert Opinion Pharmacoth 2009

*(*Nature 2009 : Lin et al)*

Not recommended in USA generally
May be considered in special circumstances of continued exposure/MDR-TB exposure
Not recommended in HIV/impaired immunity/Pregnancy

What is BCG?

Rifapentine

Rifabutin

What are

Other forms/types of rifamycin?

KatG gene

aphC gene

What are

the genetic basis of INH resistance?

Detecting drug resistance

- **Rifampicin resistance: Mutations in β subunit of RNA polymerase**
- >90% of mutations in 81 base pair region

Isoniazid resistance – more complex

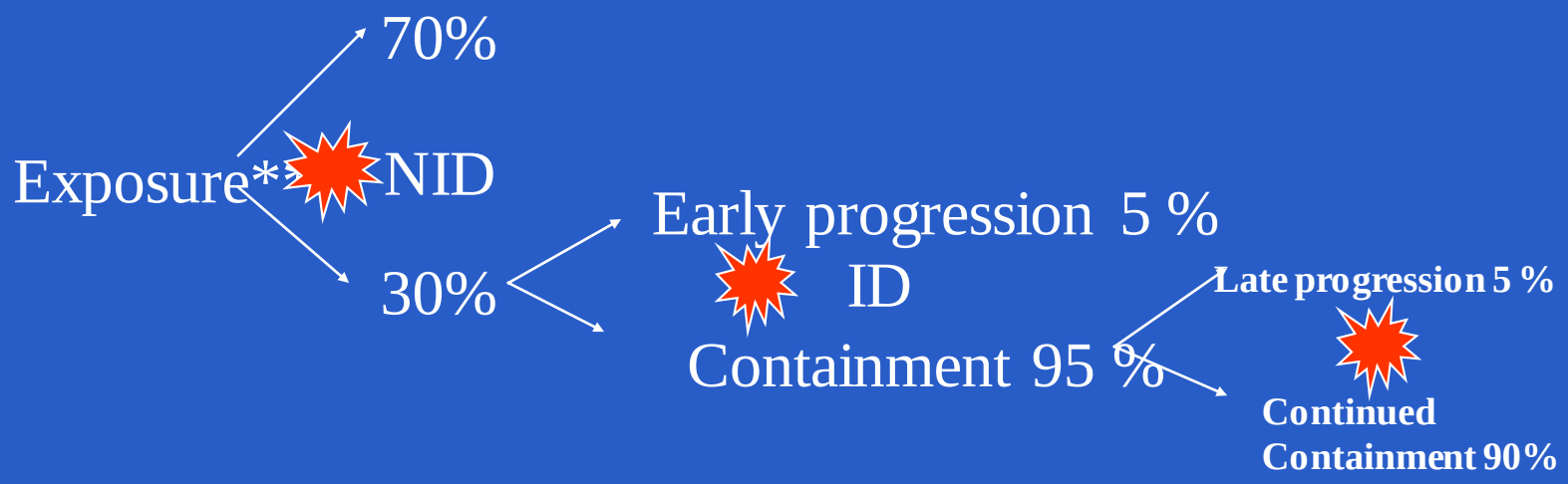
- katG gene (peroxidase) mutations
- inhA gene mutations – cell wall synthesis
- others - aphC gene mutations

PZA : mutations in gene pncA

- **PCR-based detection line probe assay**
- GenoType MTBDRplus (Hain Lifescience)

TB: 2012 update of contemporary topics

Exposed ... Now what?



** transmission factors NID=Non-Imm Defenses ID=Imm Defenses

Latent TB Infection Definition?

- A paucibacillary infection with no detectable bacilli present
- Animal models: Bacilli “stunted” due to nutritional depletion, hypoxia or genetic factors

Ref: Mol Micro 2002 ; 43: 717

Annu Rev Microbio 2001; 55: 133-163

The triple issues of LTBI

TST

↓

*Poor Specificity in BCG vaccinated persons
*Low sensitivity in Immune compromised hosts
*Logistical drawbacks
*Overall no show rate for reading test is 40-60 %

LTBI

INFγ

ELISPOT test
ELISA Quantiferon Gold

Based on Mycobacterial genomics and antigenic Specific T cell response
Deleted segment Region of Difference (ROD1)
Early secretory antigenic target-6 ESAT-6
Culture filtrate Protein 10 CFP-10
Checking for the "TB footprint"
Technical & Cost ?

A "positive" TST / IGRA : suggested plan

steps

A : DATA	B: EVALUATE	C: SCAN	D : RECAP	E: TREAT
QUANTIFY	RULE OUT ACTIVE DISEASE	RULE OUT EXTRA-PULM DISEASE	SIZE OF TST: is it helpful? IN CHILDREN; Degree of IGRA ??	**Dx; LTBI Should we offer Rx? Based on many factors**
DOCUMENT	SYMPTOMS H/P	ROS LN EXAM	GO BACK to STEPS B&C IF IN DOUBT	**RISK OF ADR***
CHECK HIV	CXR CT Scan if needed	CORRELATE with Chest imaging		**PRE-LAB CHECK**
STRATIFY RISK, CHECK SOURCE CASE **WHY???**	SPUTUM INDUCE if needed	PRE-TEST PROBABILITY?	IF SURE GO TO STEP E	TREAT FOR LTBI. ASSESS RISK BENEFIT RATIO
CONCLUDE: IF POSITIVE STEPS B-E	PRE-TEST PROBABILITY? TREAT FOR ACTIVE	TREAT FOR TB ?		**MONITOR SIDE EFFECTS* AND Rx**

*ATS 2006 DILI consensus statement

IGRA tests

- LTBI: low burden of dormant bacilli, which are not directly detectable or quantifiable
- No gold standard for LTBI, surrogate marker used such is active TB
- Strong cellular immune response: LTBI serves as an amplied signal
- TST : first measure: DTH
- Whole blood: ELISA (Q TB gold in Tube)
- T cell secretion Enzyme - linked immunospot ELISpot assay (T-SPOT TB)

Quantiferon TB Gold

- Unaffected by BCG and NTM
- TB-specific antigens are only present in M.TB
- INF-Gamma in whole blood with an ELISA measurement
- 90% SENSITIVITY IN Culture + TB
- 98% SPECIFICITY IN Culture + TB

www.cellestis.com

Further references : lancet 2004 Dec Volume 4;

QUANTIFERON - GOLD
INF-Gamma based assay

- Advantages: More Specific ,(BCG/MOTT), One visit; good correlation with TST
- Disadvantages: Technical, Analysis software, Blood, Cost,Usage, Refrigerated
- Components: Early secretory antigen target (ESAT-6 antigen), Culture Filtrate protein (CFP)-antigens and others

ELISPOT & ELISA

- Both tests have higher specificity than TST
- Higher diagnostic sensitivity than TST 70-97%
- Further increase in sensitivity with T cell INF γ release assay (IGRA)
- ?? Decreased levels as a marker for treatment response???
- Excellent specificity ,but we still need higher sensitivity

Ref: Lalvani Chest 2007;131:1898-1906

Pai et al Annals 2008; 149: 177-184 (meta analy

IGRAs & TB progression

- Of 41 QFT-G pos – 6 (14.6%) developed TB
- Of 219 TST pos – 5 (2.4%) developed TB

- Of 545 QFT-G neg – 0 developed TB
- Of 181 QFT-G neg/TST pos – 0 developed TB
- Of 358 TST neg – 1 developed TB

Diel et al. AJRCCM 2008;177:1164

IGRA* update

Advantages

Disadvantages

IGRA preferred but TST acceptable — Homeless /Transitional Care/ Substance abusers

TST is preferred — Children less than 5 years of age

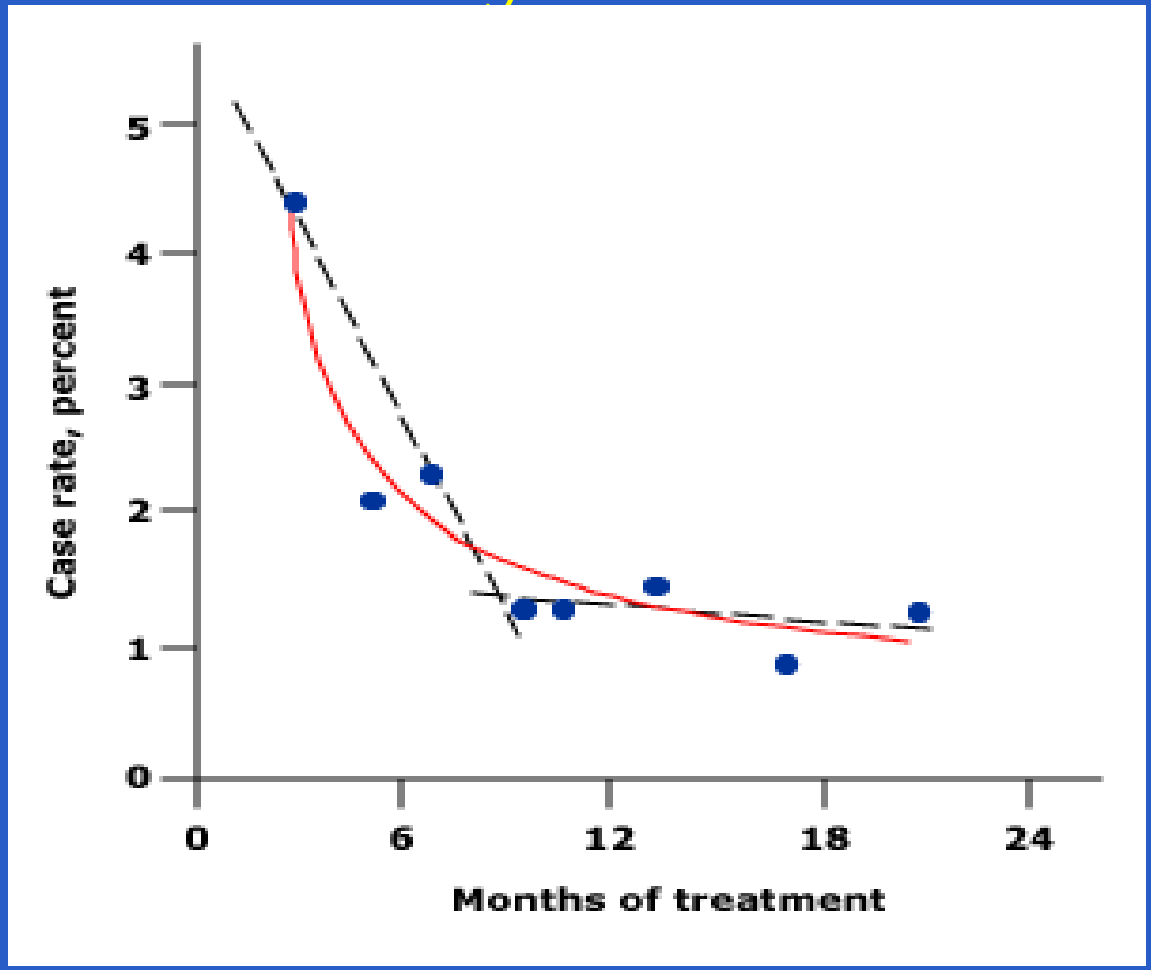
Equally acceptable: — contact screening

ILH priority list under consideration

1. Employees
2. Immune compromised patients
3. Patients with Hx of BCG
4. Specific cases where differential Dx of pneumonia includes TB or MAC
5. Referral from Transitional Homes/ shelters

Ref MMWR /CDC Rep 2010 : 59 (RR-5 :1-28

Why Rx ?



Rx options

- INH 6 months
- INH 9 months
- RIF 4 months
- RIF& INH 4 months
- RFT / INH
- *If index case MDRTB or XDRTB , then a big problem*

NAA

- CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with clinical suspicion of TB, where Dx has not yet been established, and for whom the result will alter management and TB control measures/contact investigations

MMWR Jan 2009/58(01);7-10

NAA contd

Ampl MTB direct test
MTD (Gen-probe)

Enhanced Amplicor (Roche) test

Greater PPV
Earlier Detection
Less inappropriate use of FQ as empiric monotherapy for pneumonia
Reliance by MDs: 20-50% of cases
NAA testing should be considered as Critical test value notification
Report time less than 48 hours.
If clinical suspicion is low, do not do NAA as PPV low
If clinical suspicion moderate or high: single NAA negative should not

NAA inhibitors

- 3-7% sputum specimens have inhibitors
- 50-75 % labs do this test; probably less
- AFB positive, NAA negative x2 and no inhibitors present…it is probably NTM
- If AFB positive, NAA negative and Inhibitors detected, NAA test is of no use
- If AFB is negative, NAA negative, Inhibitors negative, use clinical judgement as sens of NAA in smear negative , culture positive cases is 50-80% only

Interpretation

CLINICAL SUSPICION	AFB smear	NAA result	
	positive	positive	MTB (PPV 95%)
	Negative	positive	Repeat NAA; if positive or clinical suspicion high: Rx as TB
	Positive	negative	Repeat; test for Inhibitors ….will discuss

Pleural effusion**

	ADA	PCR	INFγ
*Sens	88%	85.7 %	73.8 %
*Spec	85.7%	97.1%	90%

* Maintained over a wide range of prevalence

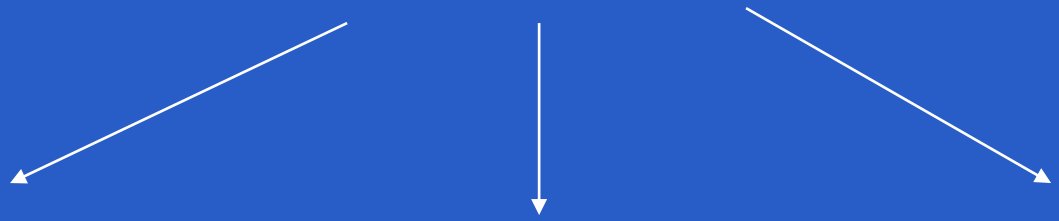
ADA,LDH,L:N ratio of > 0.75

**Confirmed by culture or pleural bx >90 % s/s

Villegas et al: Chest 2000 118:1355-1364

Ghanei et al 2004
Asian CT Annals , Iran

Sputum evaluation



Spontenous Sputum

Supervised Sputum "DOSE"

Induced Sputum

Chang et al Eur Resp J 2008 May ; (5) 1085-90

Supervised and induced sputum among patients with smear-negative pulmonary tuberculosis

K. C. Chang1, C. C. Leung1, W. W. Yew2 and C. M. Tam1

ERJ 2008

From a cohort of 660 patients ; prospectively for collection of one specimen each of supervised and induced sputum in succession. Among 78 patients with culture-proven pulmonary tuberculosis, analysis of matched sputum culture results showed that: 1) induced sputum outperformed supervised sputum; 2) the second unsupervised sputum was significantly inferior to the first and redundant in the presence of the others; 3) adding one specimen each of supervised and induced sputum to two unsupervised specimens increased culture yield significantly; and 4) patients with either extent of disease less than right upper lobe or no respiratory symptoms were more likely to benefit.

The issues

- Little supervision; the “give the cup” approach
- Bacterial contamination
- Only 30 % positivity in the first sputum although incremental yield beyond 3 is doubtful
- (S:47%/C:74% to S:58%/ C: 90%)
- Depends upon cavitary disease or non cavitary disease
- Single vs.24-72 hour pooled specimen: No difference except increased bacterial contamination (2%) increased to 15 %

Krasnow et al Appl Micro 1969;18:915-917
Kestle DG et al Am J Clin Path 1967;48:347-349

Bullets

- 2 sputum smears as good as 3 even for infection control purposes but….
- Volume of sputum 5cc or more improves sensitivity
- If ES negative; SI adds up to 19-30 % in sensitivity in suspected cases
- FOB with Bronchial washing if less than 50 cc, there is no difference in sensitivity
- FOB with BAL better if return more than 50 cc and sensitivity increased if PCR also done

Ref: Thorax 2002 : 57 1010
Nelson et al J Clin Micro 1999 36 (2)

The Real Life Algorithm*

.. 2/4 or 2/7 or 3/3

Dx of TB (Class 3 or 5 Start RIPE DOT DAILY/Bi weekly*

RIPE***

****

Culture back

****

Pan sensitive

***RIP(drop E)

2 month Sputum culture negative

***Drop PZA

|

*** RI ******

0…… 2-4 weeks……..6 weeks 8-12 wks …….6mths

……9mths

* Check dosage; ***Watch for ADR/LFTs/DILI

Therapy

- Ideal Rx: DOT "RIPE"

  Duration: 6 months …..* 9 months in special case scenarios

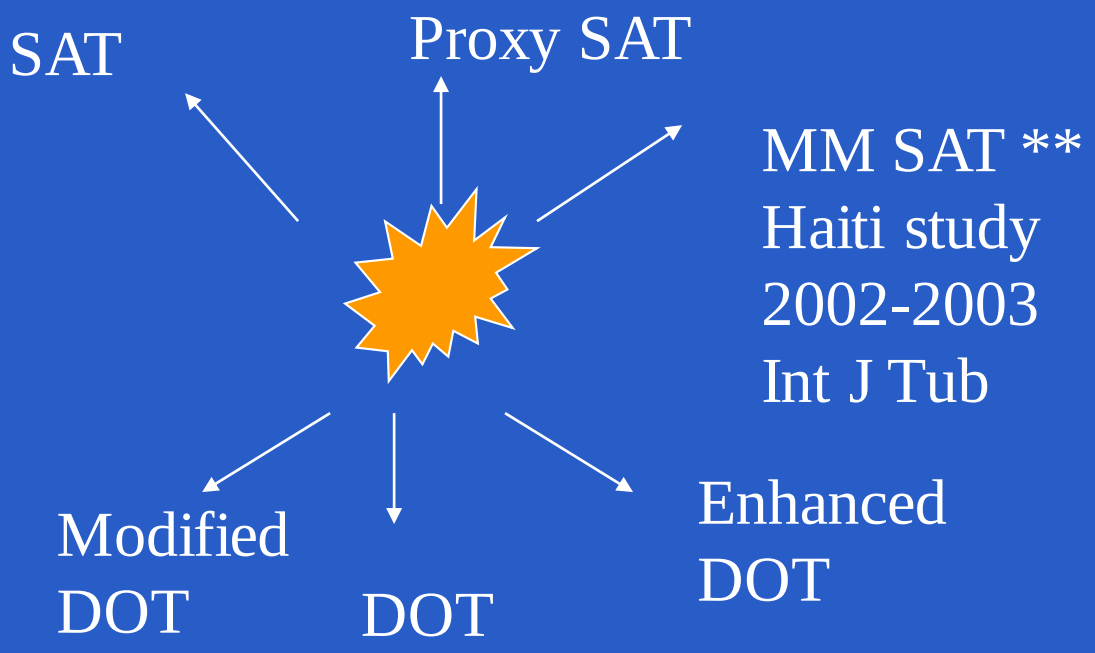
(a) When sputum culture is still positive at the end of 2 months

(b) CXR showed cavitary disease

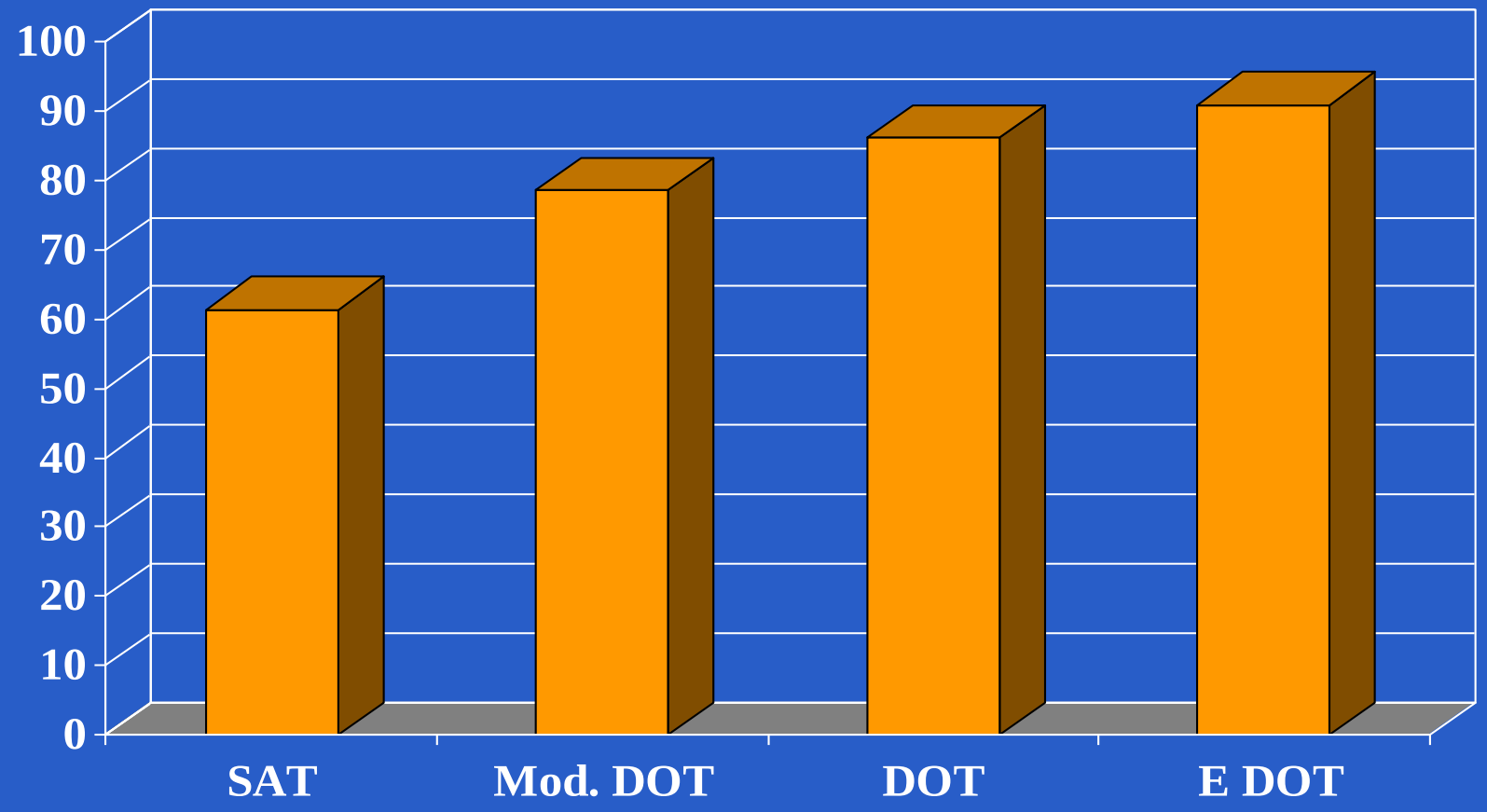
(c) When initial induction phase did not include PZA

(d) When induction phase was with once weekly drugs i.e. INH/Rifapentine

Rx protocols



Completion range of Rx strategies



JAMA 1998; 279: 943-948

Yield of continued monthly sputum evaluation after culture conversion

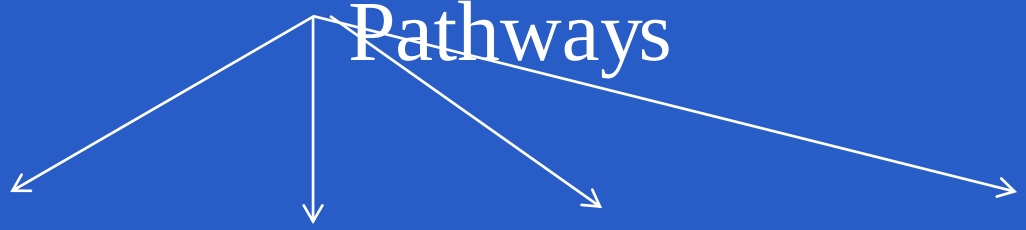
- Retrospective analysis
- Pan sensitive disease
- RI containing regimens
- 56 % initial smear positive
- At the end of 5 month 5.3 % smear positive
- 1.3 % culture reversions

NY city Health Dept IUATLD 2002 6 (3)

National data: 10% of cases culture positive after 12 weeks of Rx

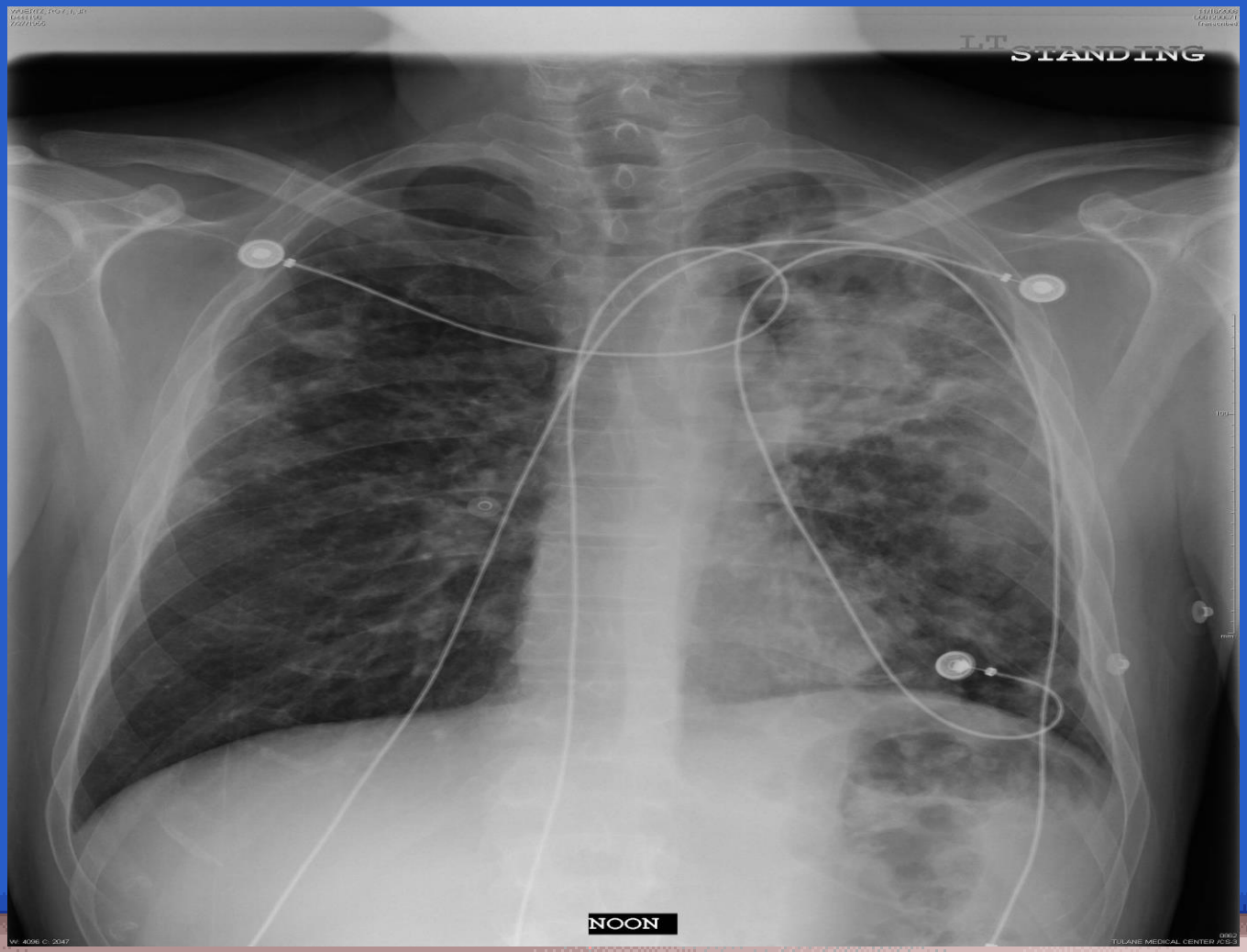
You start RIPE

- And then……
- LFTS become abnormal (multiple Criteria)
- Now What?



Stop Rx Review Dx , Choose second line drugs , Re initiate in a step wise manner ; choose drugs based on likely culprit etc , Modify and deescalate

A problem or multiple problems ?



Reasons for delayed conversion and /or treatment failure

- Compliance/ No DOT used; though 16% failure rates in DOT programs too (**)
- Increased bacterial burden ; cavitary disease
- Development of secondary resistance
- Malabsorption of drugs
- Host variation in response
- “lab error”

**Region 1: 28.6 %

Done at wetmore

•*Thee et al In J Tuberc 2007 (

•**Um et al In J Tuberc 2007

Drug levels

- Body weight or Body surface* especially in children
- **Low 2 hr serum conc was 46% INH and Rifampin mainly associated with dose/kg weight
- INH associated with acetyl INH/INH ratio and ETH associated with Cr Cl;
- However significant scatter noted and clinical relevance unclear

Relapses

- In nearly all patients with TB caused by drug susceptible organisms and who are treated with Rif –containing regimens using DOT Rx, relapses occur with susceptible organisms

High risk for treatment failure or relapse

HIV / DM
When second line Rx used

**Cavitation on initial CXR

**Positive Sputum Culture after 8 weeks of Rx.

** When PZA is not used in the Intensive phase

US PHSS 22 TB Consortium trial 1993-2002 cohort and ATS guidelines

Relapse of PTB after sputum conversion after SCC

- Followed for 3 years
- 3.29 %
- Those who became smear negative after 3 months of Rx had a relapse rate of 8.8 %

CDC data from NC Public health dept

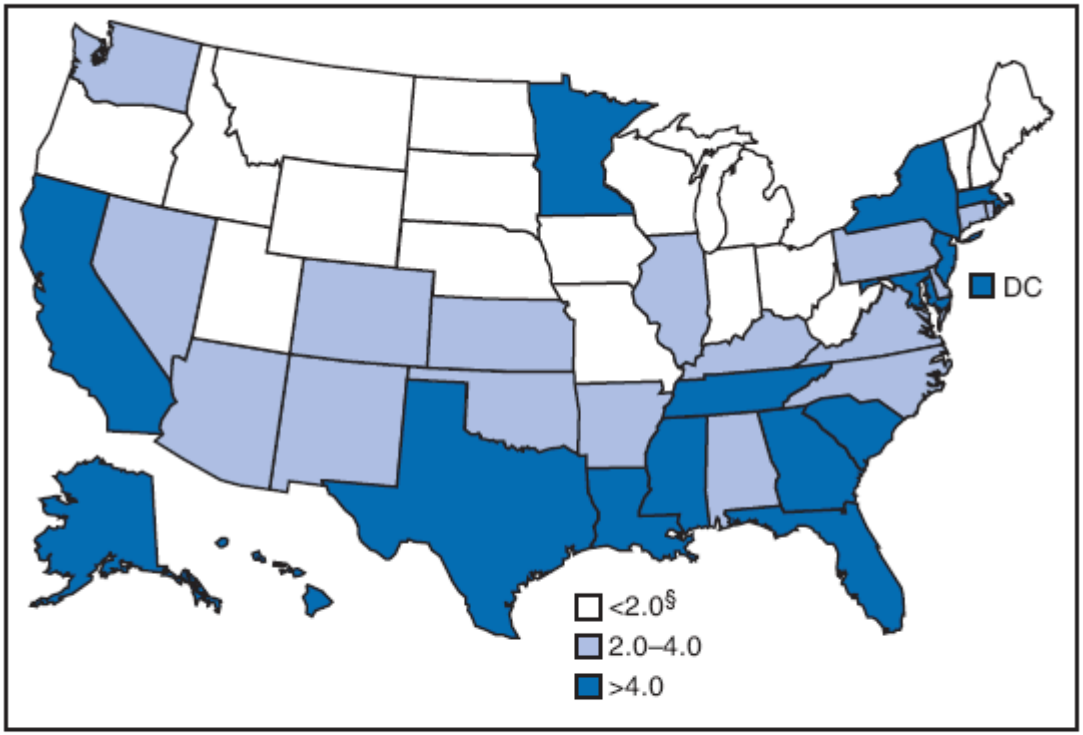
Latest National Statistics* MMWR 2007

- 13767 TB cases in 2007 @ 4.6 per 100K
- 3.2 % decline from 2005
- Less decline than previously (7.3 %)
- Highest rates in foreign born individuals
- Blacks 8.4 times higher
- Asians 2 times higher
- Hispanics 7.6 times higher than whites

The cone of caution

Figure 1

FIGURE 1. Rate* of tuberculosis (TB) cases, by state/area — United States, 2008†

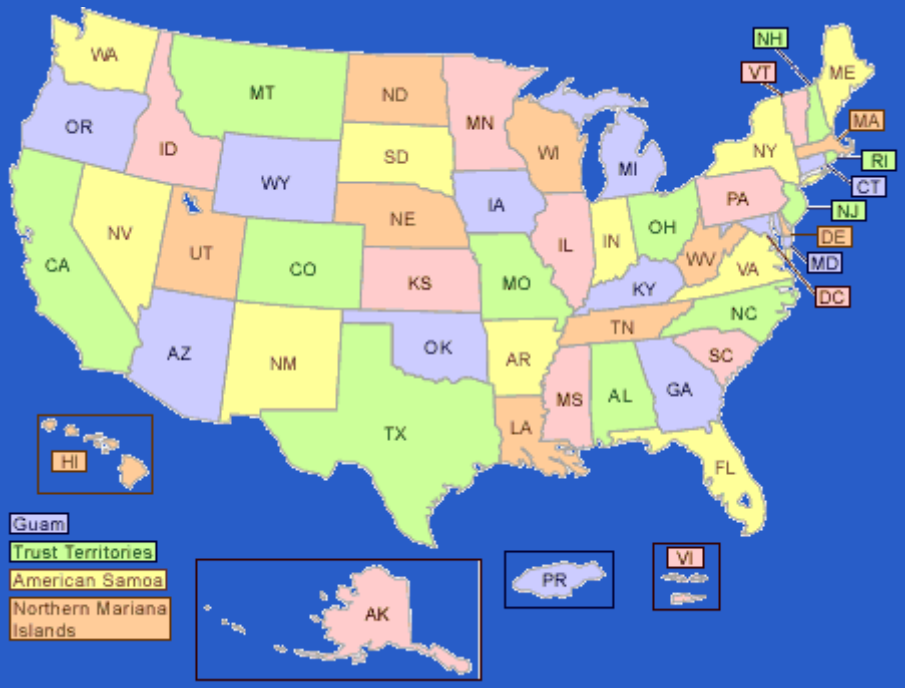


SOURCE: National TB Surveillance System.

* Per 100,000 population.

† Data updated as of February 18, 2009. Data for 2008 are provisional.

§ TB rate cutoff points were based on terciles: 18 states had TB case rates of <2.0 (range: 0.46–1.99) per 100,000, 17 states had TB case rates of 2.0–4.0 (range: 2.03–3.92) per 100,000, and 15 states and the District of Columbia had TB case rates of >4.0 (range: 4.02–9.63) per 100,000.


WA
OR
CA
ID
NV
MT
WY
UT
AZ
CO
NM
ND
SD
NE
KS
OK
TX
MN
IA
MO
AR
LA
WI
IL
MS
MI
IN
KY
TN
AL
OH
WV
GA
FL
SC
NC
VA
PA
NY
ME
VT
NH
MA
RI
CT
NJ
DE
MD
DC
HI
AK
PR
VI
Guam
Trust Territories
American Samoa
Northern Mariana Islands

- **LOUISIANA TUBERCULOSIS (TB) CASES / RATES FOR 2008**
- **cases by parish/ case rates per 100,000**
- **State Total = 227 cases/ 5.4 cases per 100,000***

LA 2008 examples

Parish	# of case	Rate/100K
Jefferson	25	5.6
Orleans	28	12.2
E Baton Rouge	20	4.5
St. Bernard	2	15.4
Terrebonne	4	3.6
5 parish here	55	7.7

Drug Resistance

Primary drug-resistance is said to occur in a patient who has never received antituberculosis therapy.

Secondary resistance refers to the development of resistance during or following chemotherapy, for what had previously been drug-susceptible tuberculosis

Detecting drug resistance

- **Rifampicin resistance: Mutations in β subunit of RNA polymerase**
- >90% of mutations in 81 base pair region

Isoniazid resistance – more complex

- katG gene (peroxidase) mutations
- inhA gene mutations – cell wall synthesis
- others - aphC gene mutations

- **PCR-based detection**
- GenoType MTBDRplus (Hain Lifescience)

USED THIS IN ONE CASE RECENTLY AT WETMORE

This report summarizes the results of that survey, which determined that, during 2000--2004, of 17,690 TB isolates, 20% were MDR and 2% were XDR.

Population-based data on drug susceptibility of TB isolates were obtained from the United States (for 1993--2004), **Latvia (for 2000--2002), and South Korea (for 2004),** where 4%, **19%,** and **15%** of MDR TB cases, respectively, were XDR.

MMWR 3/2006
55(11);301-305

- DRTB: The term "drug-resistant tuberculosis" refers to cases of tuberculosis caused by an isolate of Mycobacterium tuberculosis, which is resistant to one of the first-line antituberculosis drugs: isoniazid, rifampin, pyrazinamide, or ethambutol.

- Multidrug-resistant tuberculosis (MDR-TB) is caused by an isolate of M. tuberculosis, which is resistant to at least **isoniazid and rifampin, and possibly additional chemotherapeutic agents.**

- Extensively drug-resistant tuberculosis (XDR-TB) is caused by an isolate of M. tuberculosis, which is resistant to at least isoniazid, rifampin, fluoroquinolones, and either aminoglycosides (amikacin, kanamycin) or capreomycin, or both

The Story of MDRTB

- Exists and ongoing throughout the world over the years. Russia, Far East, South Asia;
- Globally 400K cases reported
- 1990s Several outbreaks in hospitals and correctional facilities in NY and Florida; Mostly HIV, 80% mortality; Dx-Death time 4-16 weeks
- Nosocomial transmission; not more contagious but more difficult to treat
- Lower cure rate and Cost differential

Contd…

- Mainly from Mexico, Philippines, Vietnam , China and India
- 124 MDRTB in 2005
- Foreign born 81 % of MDRTB
- XRDTB: 17 cases reported between 2000 - 2006

RISK Factors for MDRTB

- HIV, clusters, inadequate Rx protocols and non compliance
- Rifampin Resistance is an excellent marker for MDRTB

XDRTB in the limelight, but this has existed…..up to 34 % of MDRTB

Lancet 2006: Gandhi et al from the Natal Province South Africa

- Dx - Death period: 16 days; mortality 85-98%
- HIV population; median CD4 : 64 with only 34 % receiving ART
- Epidemiological survey: 41 % MDRTB; 23 % of these were XDRTB

FIGURE 2.12
Countries that had reported at least one case of XDR-TB by the end of 2008

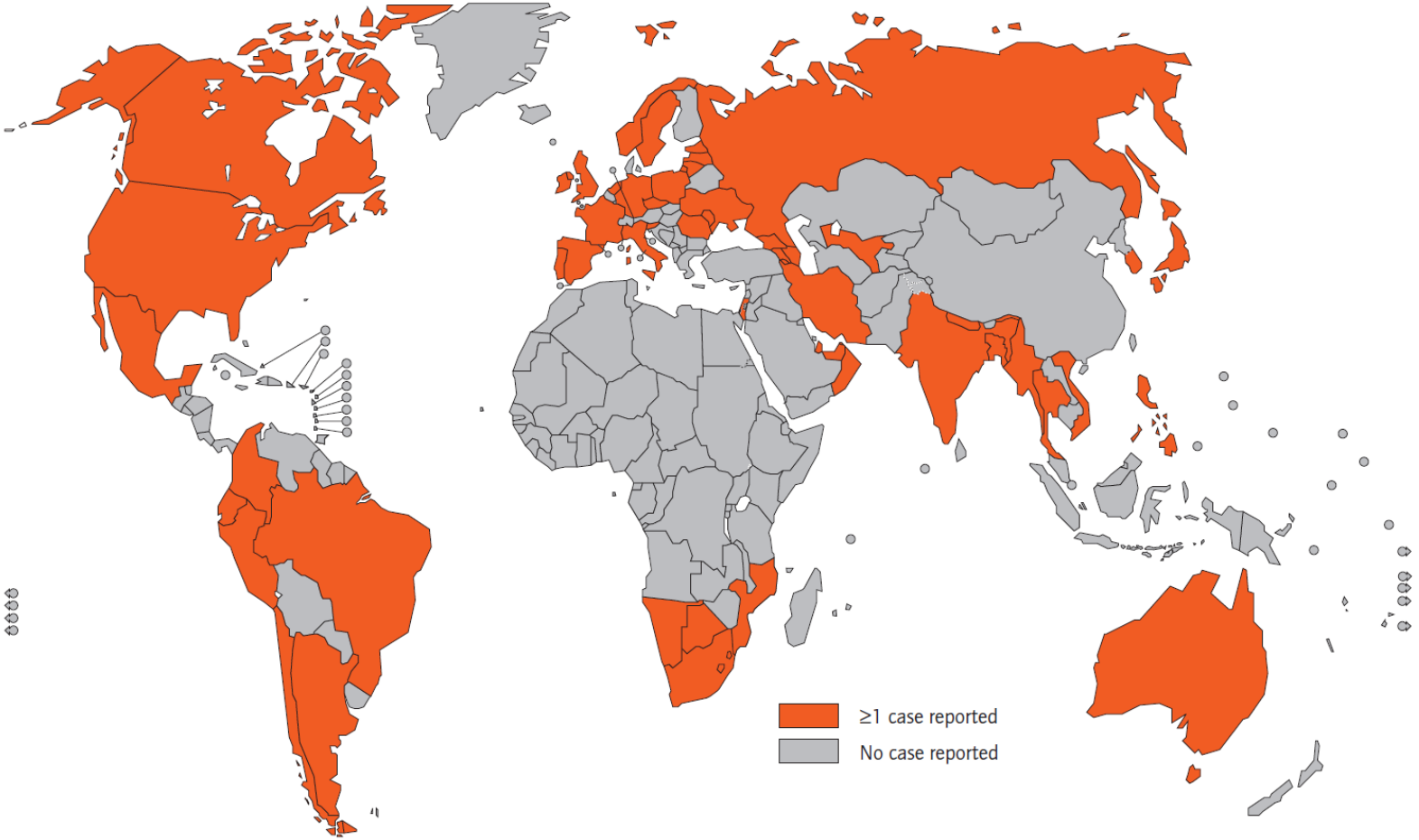
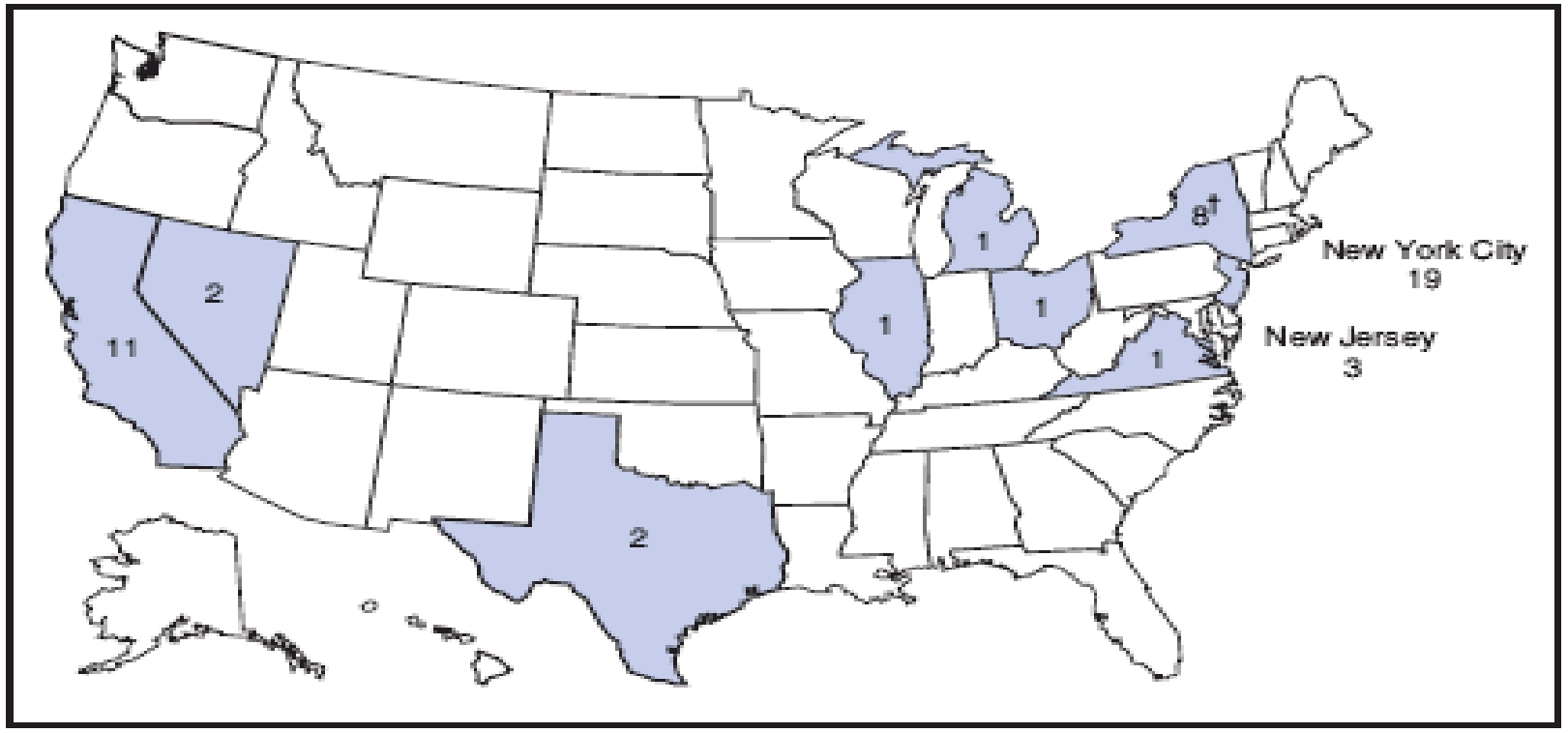


FIGURE. Number of reported cases of extensively drug-resistant tuuberculosis (XDR TB)* — United States, 1993–2006



* XDR TB defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin).
† Excludes New York City.

Newer Drugs…….in the pipeline

TB vaccine developments

Boosting BCG responses

- Subunit vaccines, combined with novel T-cell adjuvants
- Ag85B-ESAT6 (or Ag85B-TB10.4) fusion molecules
- Immunogenic and safe in phase I study
- MTB72f
- MVA85A
- Modified vaccinia virus expressing Ag 85A

Andersen. Nat Rev Microbiol 2007;5:484

Hoft. Lancet 2008;372:164

Side effects may be due to longer intervals of dosing rather then the actual dose

We may be using a lower dose than is needed

What is

Rifampin and ?
issues with
standard dosage?

Dec levels Reported in TB patients

Receptor polymorphism associated with increase susceptibility to MTB

Can suppress intracellular growth of MTB in vitro

Induces expression of autophagy, phagosomal maturation, antimicrobial peptides such as cathelicidin

Enhances the activity of PZA

What is Vitamin D?

VITAMIN D

- TB and nutritional deficiency : A historical fact
- Vit D deficiency reported in TB pts
- Vit D receptor polymorphism associated with increased susceptibility to *MTB*
- Vit D can suppress intracellular growth of *MTB* in vitro
- Vit D also induced expression of autophagy, phagosomal maturation, antimicrobial peptides (cathelicidin,
- Enhanced activity of PZA
- Amer Jour Med Sciences 341 June 2011 Science Tran s Med Oct 11

Seen in at least one TB drug in about 46% of cases

Data shows significant scatter

What are

Low drug levels?

Done at wetmore

•*Thee et al In J Tuberc 2007 (
•**Um et al In J Tuberc 2007
•*** Kimerling et al Chest 199

Drug levels

- Due to PK and PD variability it is better to use Body surface* area ,especially in children to decide dosage and achieve better therapeutic levels
- **Low 2 hr serum conc of at least one Anti TB drug was seen in about 46%
- INH associated with acetyl INH/INH ratio and ETH associated with Cr Cl;
- However significant scatter noted, many variables such as ETOH use , fixed combination etc and hence clinical relevance unclear. Importance of looking at the therapeutic level range

Drug levels ? Some questions

- Present practice; why the doses? RIF specially*
- *(Ingen et al CID 2011: 3 reasons*
- *Drug conc above MIC, Fear of side effects, economic*
- *600mg is at a lower end of the dose response curve; side effects not dose related : idiosyncratic and immunological more, cost?)*
- *Weight/gender/genetic variations/BSA may determine different dose*
- Any reason to change practice since in most cases of Rx failure , causes are multifactorial
- Side effects may be due to longer intervals of dosage rather than dose
- Importance of tailoring Rx
- Do we re-set the clock?

TUBERCULOSIS DISEASE: DRUG LEVEL TESTING

CRITERIA FOR TESTING

1)Recurrent MTB disease of any site

2)MTB cases not converting to negative sputum smear @ 4 weeks

3)MTB cases not converting to negative sputum culture @ 8 weeks

4)MTB case with known drug resistant organisms

5)MTB case with HIV co-infection

Continued

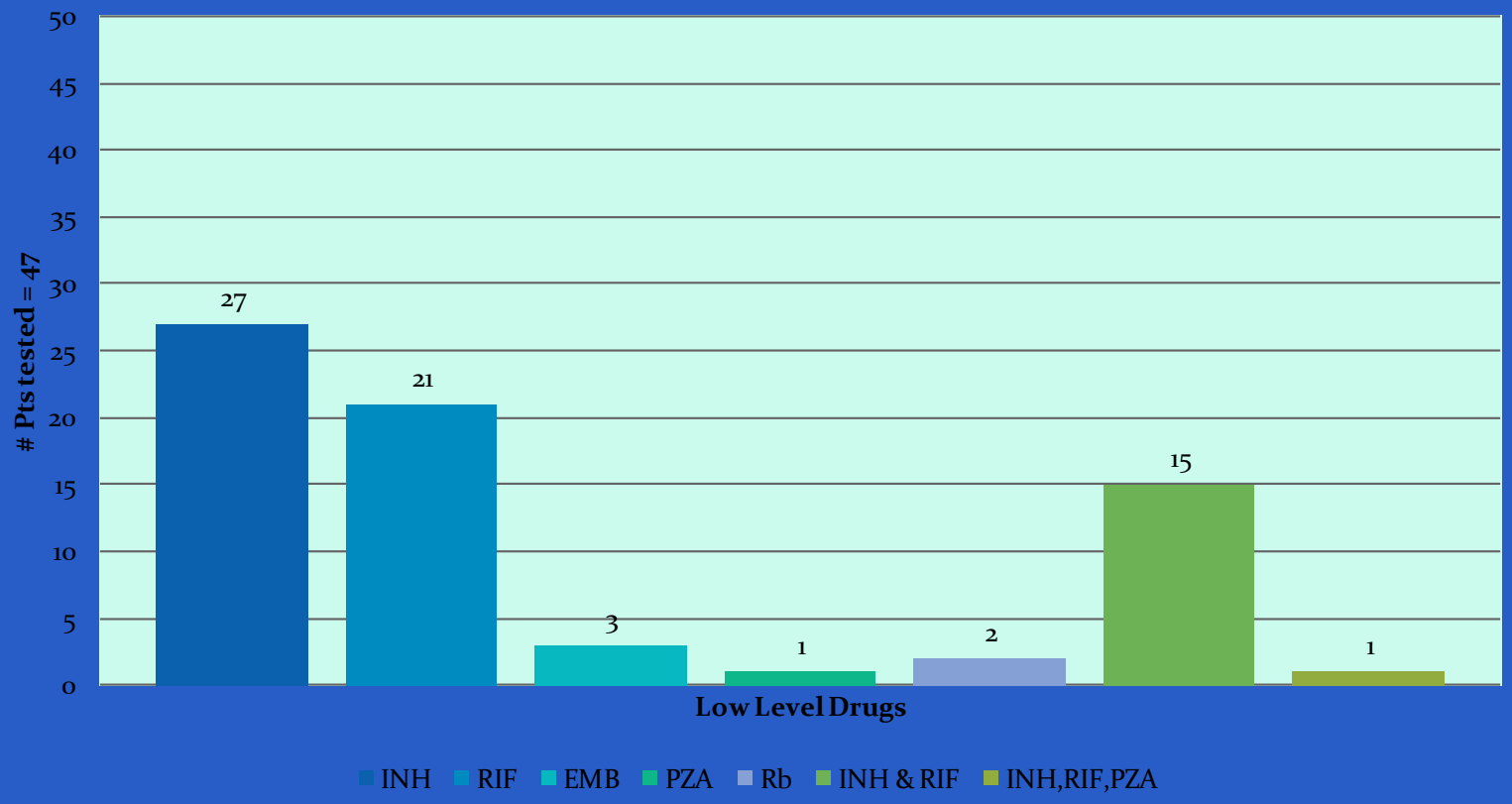
6)MTB cases with abnormal Drug Blood Level results

7)Other MTB cases with administrative approval

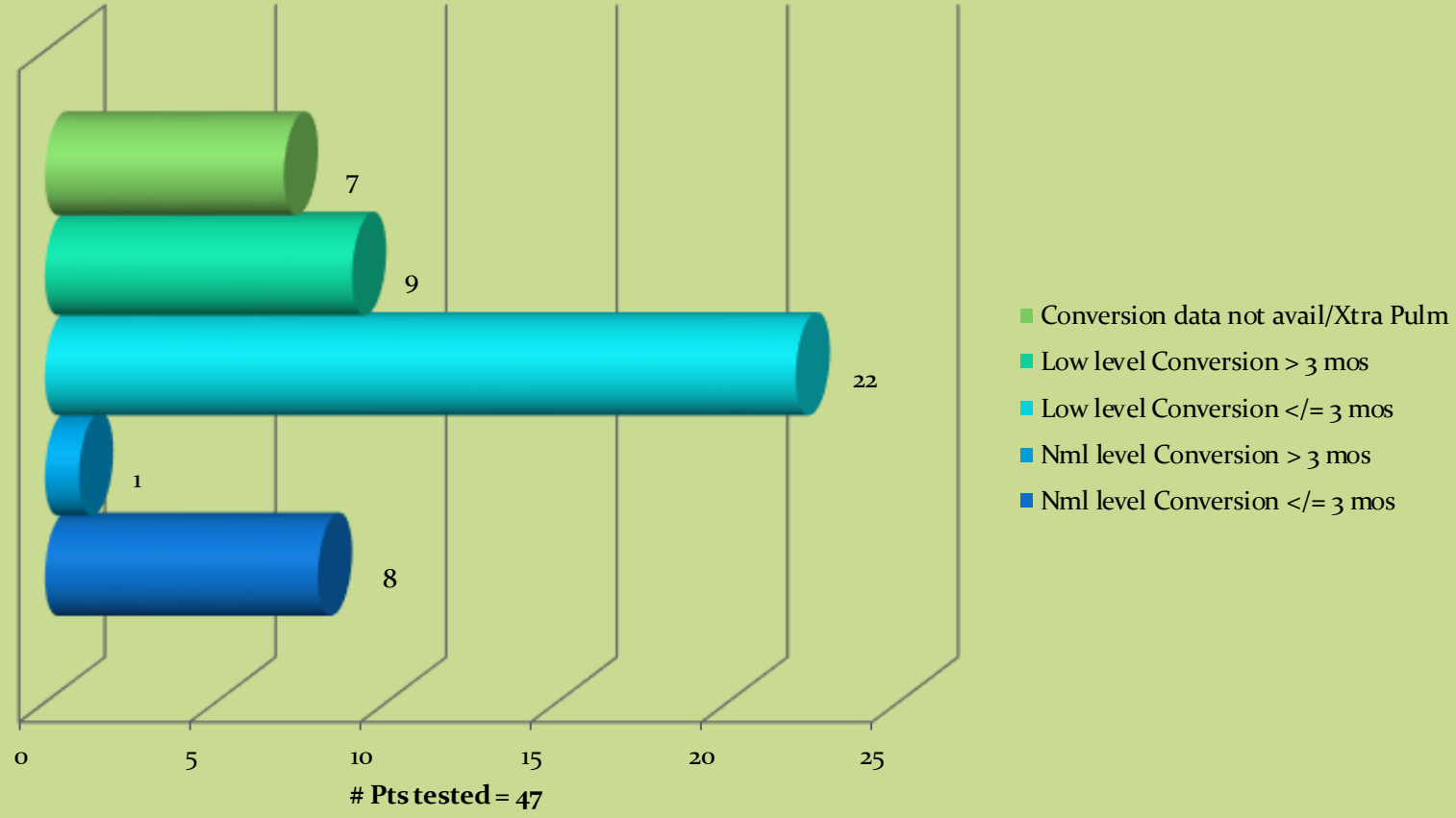
Drug levels that should be tested include INH, Rifampin or Rifabutin, PZA and

Drug Level Testing in TB Patients

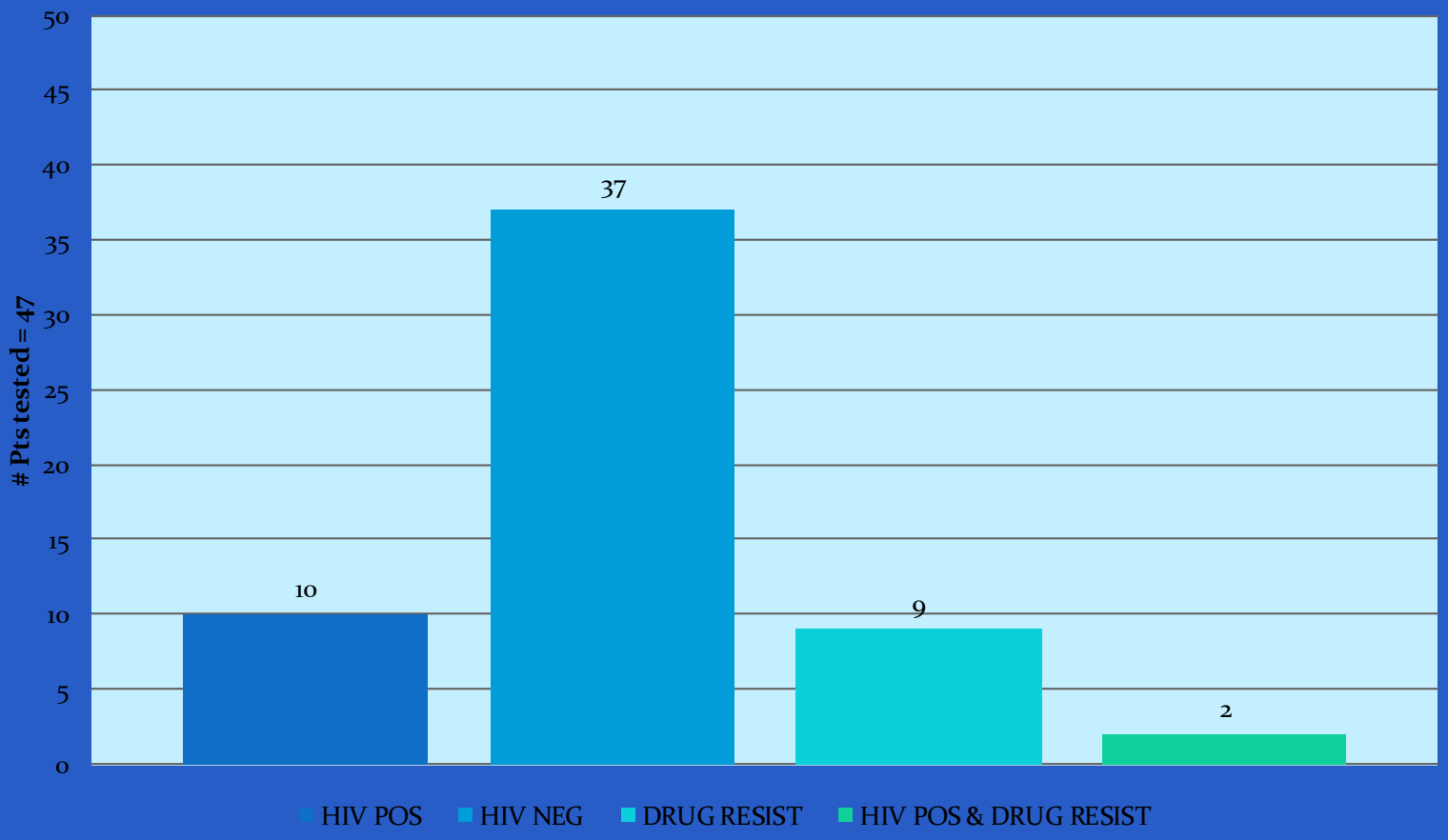
2009 - 2012



Positive Culture Conversion to Negative: Nml Levles vs Low Drug Levels



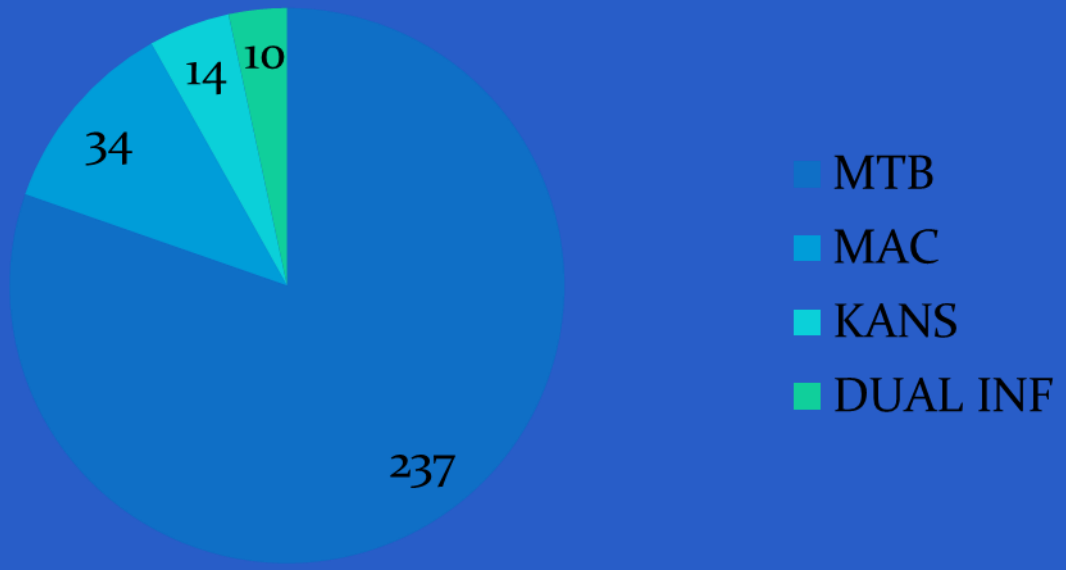
HIV & DRUG RESISTANCE



MYCOBACTERIUM TUBERCULOSIS AND MOTT

Over the course of 4 years, data were collected on Mycobacterium tuberculosis and MOTT, basically to compare the number of patients infected with each of these organisms. Patients with MTB are provided treatment at no cost through the Public Health System. However, those unlucky patients diagnosed with MOTT are on there own when it comes to seeking treatment for their condition.

MTB vs MOTT
TOTAL 295 PTS



DUAL INFECTIONS

- As noted in the previous chart, there were 10 dual infections. Eight (8) of these were MTB and Mycobacterium Avium Complex (MAC), one (1) was MTB and Mycobacterium fortuitum and one (1) was MTB and Mycobacterium kansasii.

MTB

M. bovis

M. africanum

M. microti

M. canetti

M. Mungi

What is MTB Complex?

HIV/AIDS
Immigration
Congregate setting
Funding cuts

What are

The factors that caused an increase in TB post 1981?

Sputum culture is positive after 2 months

Cavitary, heavy smear positive disease

PZA of RIPE not used.

When

Do you extend treatment beyond 6 months?

Relapse of PTB after sputum conversion after SCC

- Followed for 3 years
- 3.29 %
- Those who became smear negative after 3 months of Rx had a relapse rate of 8.8 %

CDC data from NC Public health dept

High risk for treatment failure or relapse

HIV / DM* **BMC Med 2011**
When second line Rx used

**Cavitation on initial CXR

**Positive Sputum Culture after 8 weeks of Rx.

** When PZA is not used in the Intensive phase

US PHSS 22 TB Consortium trial 1993-2002 cohort and ATS guidelines

HIV
Silicotic lung disease
Immunocompromised
Diabetes
Congregate settings
Travel to high endemic countries

What are

The conditions in which there is increased risk of infection to disease?

Proximity, frequency, duration of exposure

Environmental concentration

Infectiousness of index case

Susceptibility of exposed person

What are

Factors that increase transmission of TB?

FINAL

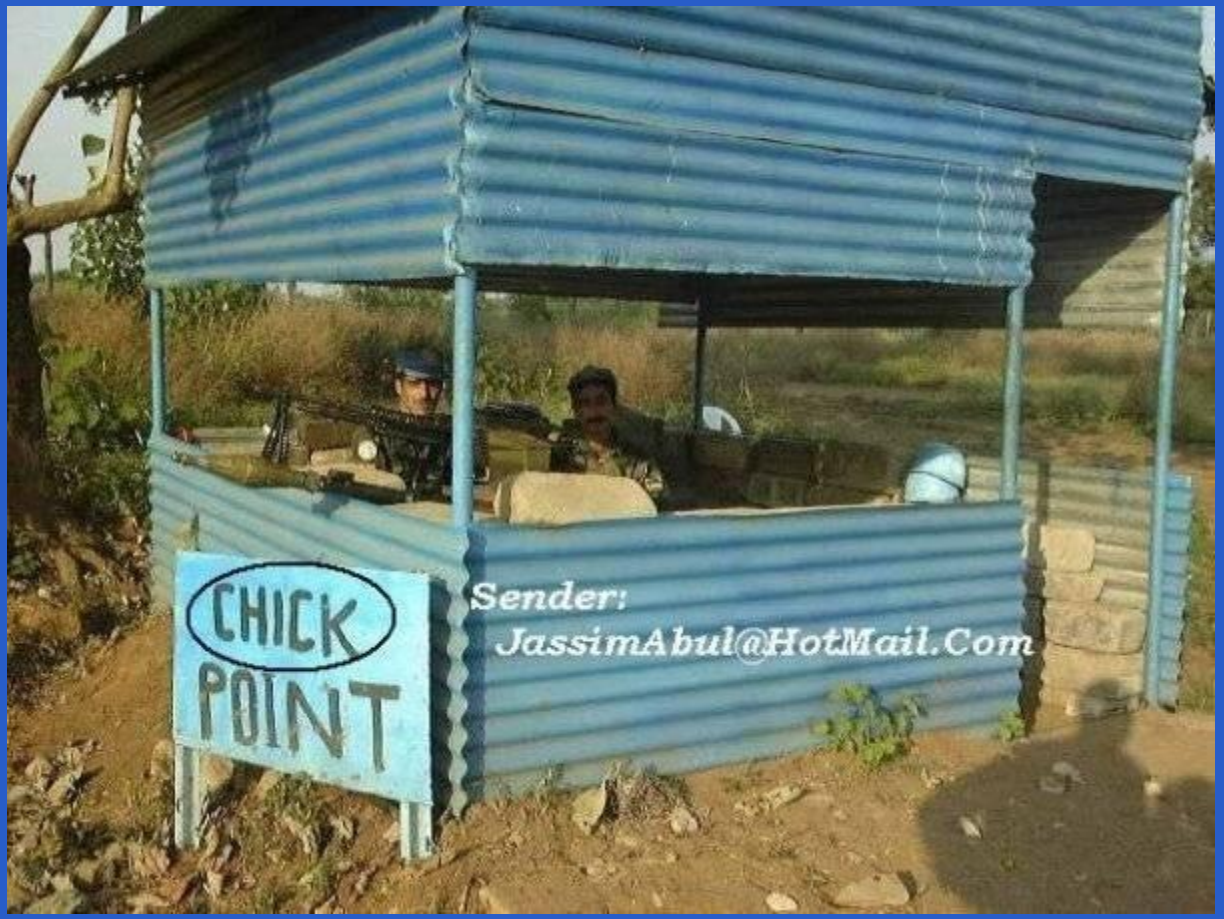
Jeopardy

TOPIC History

Final Jeopardy

The monster that is associated with tuberculosis.

What are Vampires?



Tempting the enemy !!