TB and LTBI Beyond the Basics

Top 10 to improve our role in the global strategy

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Disclosure

- Consultant to Oxford Immunotec

Learning Objectives

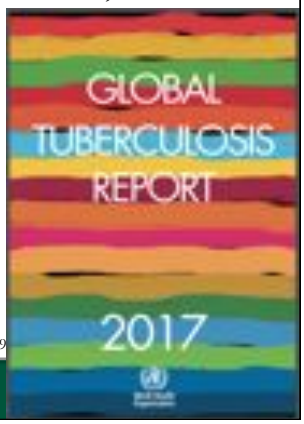
1) Participants will be able to define local and global epidemiological trends to better screen and treat groups at high risk for tuberculosis.

2) Participants will be able to describe current recommendations for assessing risk, testing and treating TB infection to prevent development of disease.

3) Participants will be able to describe available resources and best practices for the diagnosis, treatment and management of routine and complex TB cases.

Efficient TB and LTBI Diagnosis

- Globally in 2016, TB 9th leading COD, 1st among IDs
  - ~10.4M new cases of TB (2% decrease)
  - ~1.4M died from TB (3% decrease)
  - Delayed diagnosis results in increased transmission, costs and patient morbidity and mortality
- In US in 2016
  - 9,287 new cases of TB (2.7% decrease)
    - 68% were in foreign-born persons
  - ~13M are infected with *M. tuberculosis*
    - Reservoir of TB, major focus for ending TB



WHO/HTM/TB/2017.22; Schmit KM, et al. Tuberculosis — US, 2016. MMWR 2017;66:289–29

1 New TB/LTBI Diagnosis Guidance

- Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children.
  - Lewinsohn DM et al. CID 2017; 64:111.
- Guidance on use of GeneXpert® MTB/RIF for making decisions for release from Airborne Isolation.
  - NTCA/APHL, April 2016
- Screening for LTBI in Adults. USPSTF Rec Statement
  - USPSTF. JAMA 2016; 316(9):962-9.

GeneXpert is a registered trademark of Cepheid

Why, Who, How?

LATENT TB INFECTION

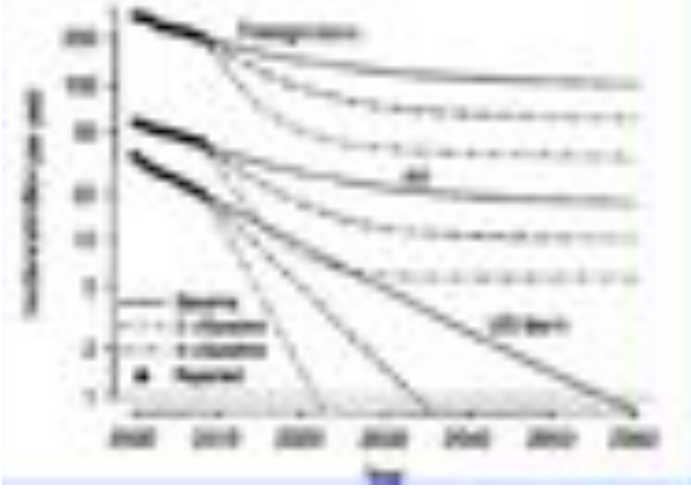
TBI Reservoir

WHO/HTM/GTB/2015.09, Image used with permission

- In low-incidence countries most TB is from reactivation
  - In US >80%
- 4.2% of US pop 1999-2000 have TBI
  - Reservoir of untreated TBI ~8.8M
- TBI dx/tx in high-risk groups is **priority action** for TB elimination strategy

Horsburgh. NEJM 2011;364(154):1441-8

US TB Elimination Must Address TBI



Horsburgh. NEJM 2011;364(154):1441-8; PLoS One 2015;10:e0140881; Epidemiol Infect 2012;14

TBI Challenges

- Confusion regarding testing interpretation
- Lengthy treatment leading to limited adherence
- Adverse effects influencing patient and provider agreement
- Perception of risk
- Cost

Targeted Testing

WHO ARE WE GOING TO TEST?

Targeted Testing

- Mass screening and treatment?
- Identify, evaluate, and treat persons at high risk for
  - LTBI or
  - Progression LTBI to TB

TB "Risk"

- You should be clear when talking about who is at "high risk"
  - High risk for being infected with *M. tuberculosis* <u>or</u> progressing to TB disease

High Risk for TB Infection

- Close contacts to TB patients
- Non-US-born persons
- Low-income groups and homeless persons
- Individuals who live and/or work in high risk settings
- Healthcare workers who serve high-risk groups
- People who inject drugs

It's all about risk of TB contact

High-Risk for Progression to TB Disease

- People living with HIV
- People with medical conditions known to increase the risk for TB
- People infected with *M. tuberculosis* within past 2 years
- Infants and children <4 years old
- People who inject drugs

It's all about host factors for progression

Summary Statements

HOW ARE WE GOING TO TEST?

What Tests are Available?

Tuberculin Skin Tests

- TUBERSOL® (Tuberculin Purified Protein Derivative)
  - Sanofi Pasteur, Canada
- Aplisol (Tuberculin Purified Protein Derivative)
  - JHP Pharmaceuticals LLC

Blood Tests

- QuantiFERON-TB Gold Plus
  - Qiagen, Hilden Germany
- T-SPOT.*TB*
  - Oxford Immunotec, Abingdon, UK

Both measure immune response to TB antigens.
TST is *in-vivo*; IGRA is *in-vitro*.
IGRAs use smaller number of specific TB antigens.

Tuberculin Skin Tests

Pro

- Test materials are relatively inexpensive
- Does not require lab
- Does not require sample transport
- Well studied and public health familiarity
- Recommended for children under 5

Con

- **Cannot diagnose active TB**
- Requires 2 visits
- Placement, reading and interpretation subject to human error
- Three cut points cause confusion
- False-positive tests occur (BCG and NTM)
- Baseline for serial testing may require two-step TST (4 visits)

Interferon Gamma Release Assays

Pro

- Require single encounter
- No cross reaction with BCG-vaccine and *most* NTMs*
- May have better acceptance in some populations
- Standardized laboratory test with controls
- "Objective" results

Con

- **Cannot be used to diagnose active TB**
- More expensive
- Requires phlebotomy
- Requires lab
- Requires specific specimen collection, handling, transport and lab processing

M. marinum, kansasii, szulgai, flavescens

"IS IGRA BETTER THAN TST?"

TST and IGRA Similarities

- Reduced sensitivity in immunocompromised
- Cannot differentiate between LTBI and active TB
- Neither predicts risk for progression to active TB
- Each with specificity issues
  - TST false positives if nontuberculous or BCG history
  - IGRA false positives in low incidence populations
    - 2 Quantitative results are meaningful
      - Among 1,335 close contacts, if QFT >10 IU, 6.36 times higher chance of progression to TB
      - Among 2,512 healthy babies in MVA85A trial, QFT > 4 IU had TB rate 28/100 p-y vs QFT negative 0.7/100 p-y

Altet et al. Ann Am Thor Soc 2015; 12(5):680; Andrews J et al. Serial QFT . . . Lancet 2017.

3 QuantiFERON-TB Gold Plus

- Usual ESAT-6/CFP10 = TB1
  - Removes TB7.7 to improve specificity
- New shorter peptide ESAT-6/CFP10 = TB2
  - Targets CD8 > CD4 response
  - Postulated for recent infection or active TB

What is the Plus?

- 162 bacteriologically confirmed TB patients and 212 *Mycobacterium tuberculosis*-uninfected volunteers
- ROC curve AUC for both 0.99
  - Using cut-off 0.35 IU/mL, QFT-Plus had lower sensitivity of 91.1% compared to 96.2% ($p = 0.008$) at its optimum cut-off (0.168 IU/mL) with same specificity
- Among older ages, [IFN-γ] significantly lower in QFT-GIT but not in QFT-Plus
- In TB patients, [IFN-γ] QFT-Plus < QFT-GIT

Yi L et al. Eval of QFTG Plus for detection of MTB infection in Japan. Sci Rep 2016; 6: 30617

4 LTBI vs TB?

- 19 uninfected, 58 LTBI, 33 cured and 69 active TB
- QFT-Plus and QFT-GIT agreement
  - Similar sensitivity in active TB (~90%)
  - Same specificity in healthy donors (0%)
  - LTBI more likely positive both TB1 and TB2 (97%) compared with active TB (81%)
    - Selective response to TB2 associated with active TB (9%)
- Isolated positive TB2 may reflect CD8 T-cell response suggestive of active or recent infection?

Petruccioli E et al. Analytical eval of Q-Plus and Q-GIT . . . Tuberculosis 2017;106:38-43.

5 Identify Recent Transmission?

- Prospective recruitment of TST+ adult contacts comparing QFT-GIT and QFT-Plus
- Strong agreement, but 12 discordants Plus positive
  - All but one of which in patient with TST>10
- Plus showed stronger infection risk association based on time and proximity to source case
- TB2 minus TB1 may be proxy for recent infection
  - 15% QFT Plus positive contacts had values >6 IU/mL
    - Associated with proximity to index case
    - European origin

Barcellini L et al. Eur Resp J 2016; 47: 1587-90

TST or IGRA?

- Either, if likely LTBI and high risk of progression
- Perform IGRA rather than TST* in individuals ≥5 years who:
  - Are likely to be infected,
  - Have low or intermediate risk of disease progression,
  - Testing for LTBI is warranted, and
  - Either have history of BCG vaccination or are unlikely to return to have their TST read
- *Strong recommendation, moderate-quality evidence*

* TST is an acceptable alternative

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

LTBI: Low Risk for LTBI

- Do NOT test. But …
- Suggest performing an IGRA instead of TST*
  - *Conditional recommendation, low-quality evidence*
- If initial test is positive, suggest second diagnostic test, either IGRA or TST
  - When such testing is performed, person is considered infected only if both tests are positive
  - *Conditional recommendation, very low-quality evidence*

* TST is an acceptable alternative

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official ATS/IDSA/CDC Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

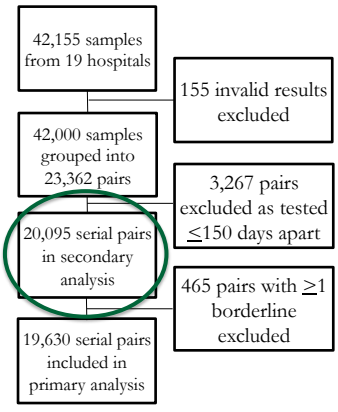
The TBES HCW Serial Testing Study

- Largest prospective study of serial IGRAs in low risk HCWs
- 4 sites: Denver, Houston, Baltimore, NYC with rates 4-9/100,000
- TST and IGRA every 6 months over 3 years Feb 2008–Mar 2011
- Conversions (neg to pos) occurred in all 3 tests
  - TST: 21 of 2293 (0.9%)
  - QFT: 138 of 2263 (6.1%)
    - 76.4% reverted – less likely if contact to TB
  - T-SPOT.*TB* test: 177 of 2137 (8.3%)
    - 77.1% reverted
- Reversions (pos to neg) were less likely for those with higher baseline values for both IGRAs

Dorman SE, Belknap R, Graviss EA et al. IGRA and TST for Diagnosis of LTBI in HCW in the US. *Am J Respir Crit Care Med.* 2014;189(1):77-87
T-SPOT and Oxford Diagnostic Laboratories registered trademarks of Oxford Immunotec, Ltd.; QuantiFERON registered trademark of Cellestis, Inc.

T-SPOT.*TB* Test in Serial HCW Screening[1]

Analysis of the ODL database: Jan 2010-June 30 2014



- Invalid results excluded (0.4%)
- Each HCW's test results grouped into pairs
- Results ≤ 150 days apart excluded
- Secondary analysis included 465 pairs with borderline results

1. King TC, Upfal M, Gottlieb A, et al. *Am J Respir Crit Care Med.* 2015:150527134833008.

King Study Results

Analysis	With Borderlines
Baseline positivity	2.3% overall; 8.4% high risk
Concordance	98.9%
Invalid rate	0.4%
Conversion rate	0.8% overall; 2.3% high risk
Reversion rate	17.6% (0.4% of all pairs); 13.9% high risk
Specificity (minimum)	98.6%

- Retesting after borderline result
  - 79% moved out of borderline
    - 23% positive
- Variance with Dorman: 4 different labs, no borderline

1. King TC, Upfal M, Gottlieb A, et al. *Am J Respir Crit Care Med.* 2015:150527134833008.

Global and US Recommendations

HOW ARE WE GOING TREAT?

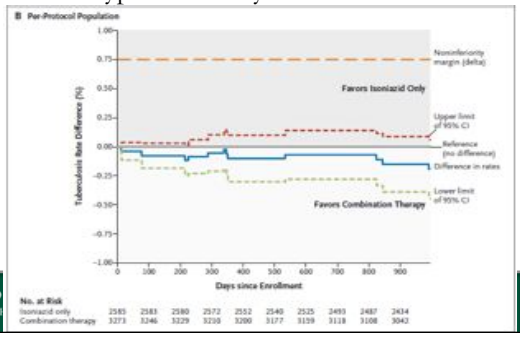
Treatment Regimens for TBI

Drugs	Months of Duration	Interval	Minimum Doses
INH	9*	Daily	270
		2x wkly**	76
INH	6	Daily	180
		2x wkly**	52
RIF	4	Daily	120
INH-RPT	3	Weekly**	12

*Preferred, ** Intermittent treatment only with DOT

INH and Rifapentine for 12 weeks

- Efficacy similar: 0.19% v 0.43% developed TB disease
- Completion 82% in INH-RPT vs. 69% in INH
- Permanent drug discontinuation due to AEs in INH-RPT group, although fewer AEs in INH-RPT
  - More hepatotoxicity in INH alone group
  - More 'possible hypersensitivity' reactions in INH-RPT



NEJM 2011; 365(23)

3HP Recommendations

- Equivalent to 9 months INH in otherwise healthy individuals ≥ 12 years old + high risk for progression to TB disease:
  - Close contact
  - Converter
  - Fibrotic changes on CXR
  - *HIV not on ART, otherwise healthy*
- Children 2-11 years old esp if unlikely to complete 9m + high risk to progress to TB disease
- 6 Recent study showed self-administered 3HP noninferior to DOT in US

Rec for Use of INH-RPT Regimen with DOT to Treat LTBI. MMWR / December 9, 2011 / Vol. 60 / No. 48
Villarino et al., JAMA Pediatrics, 2015; Belknap R. CROI 2015. Abstract 827LB.

Emphasis on diagnosis, MDR

ACTIVE TB

Nucleic Acid Amplification

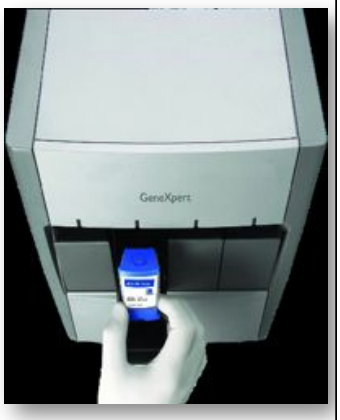
- Rec 7: A diagnostic NAAT should be performed on initial respiratory specimen from patients suspected of having pulmonary TB (*Conditional recommendation, low quality evidence)*
  - Appropriate NAATs include the Hologic Amplified Mycobacteria Tuberculosis Direct (MTD) test (San Diego, California) and the Cepheid Xpert® MTB/Rif test (Sunnyvale, CA)
  - References are pre-Xpert
- Comments:
  - AFB smear-pos, NAAT-neg sputum makes TB disease unlikely
  - In AFB smear-neg patients with an intermediate to high level of suspicion for disease, positive NAAT can be used as presumptive evidence of TB disease

Xpert is a registered trademark of Cepheid

Lewinsohn DM, Leonard MK, LoBue PA, *et al.* Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clinical Infectious Diseases.* 2017;64(2):e1-e33.

7 Xpert MTB/RIF (Cepheid)

- Automated, real-time PCR
  - 100 mins to TB and rifampin resistance
    - 92% sensitivity for TB
    - 95% sensitivity for rifampin resistance
- Simple, modular system
  - Cartridges for other diseases
- 2010 WHO, Aug 2013 FDA
- 2013 WHO policy expanded for all *instead of* AFB sm and culture
  - MDR, HIV-TB and CNS TB suspects



http://www.cdc.gov/mmwr/pdf/wk/mm6241.pdf; WHO/HTM/TB/2013.14

8 Xpert Omni, Ultra, Xtend

- Omni is GeneXpert platform improvement
  - Portable, 4 hour battery for point of care
- Ultra cartridge improves sensitivity
  - Lower specificity? "Trace calls" in paucibacillary disease
    - Detects dead organisms (decreased specificity for TB diagnosis)
  - Improved rifampin resistance specificity
- Xtend XDR cartridge for INH, FQ, SLIDs

http://www.pipelinereport.org/sites/default/files/TB%20Diagnostics.pdf

Alland D, et al. Xpert MTB/RIF Ultra: A New Near-Patient TB Test With Sensitivity Equal to Culture. CROI Feb 23-26, 2015, Seattle WA Abstract #91

TB Treatment

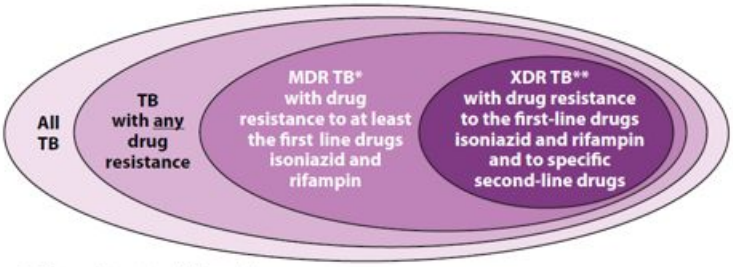
Drug	Properties	Dose	Common Side Effects
Isoniazid (INH)	Cidal	300mg/d	Hepatitis, neuropathy
Rifampin (RMP)	Cidal	600mg/d	Hepatitis, flu reaction, drug interactions
Pyrazinamide (PZA)	Cidal for intracellular organisms	15-30mg/kg/d	Hepatitis, GI, rash, myalgias
Ethambutol (EMB)	Static, used to prevent resistance	15-25mg/kg/d	Ocular toxicity

INH+RMP+PZA+EMB 2m (intensive phase)

Then, if sensitive, INH+RMP 4m (continuation phase).

The international standard is to administer by DOT.

Antimicrobial Resistance Definitions



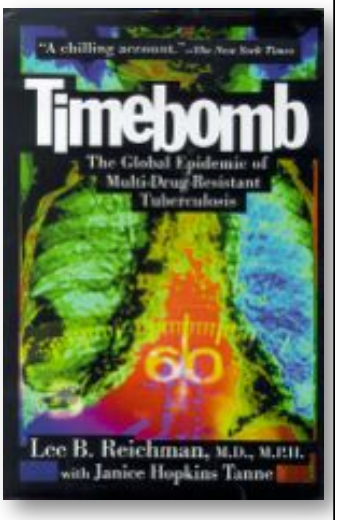
* Often resistant to additional drugs

** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

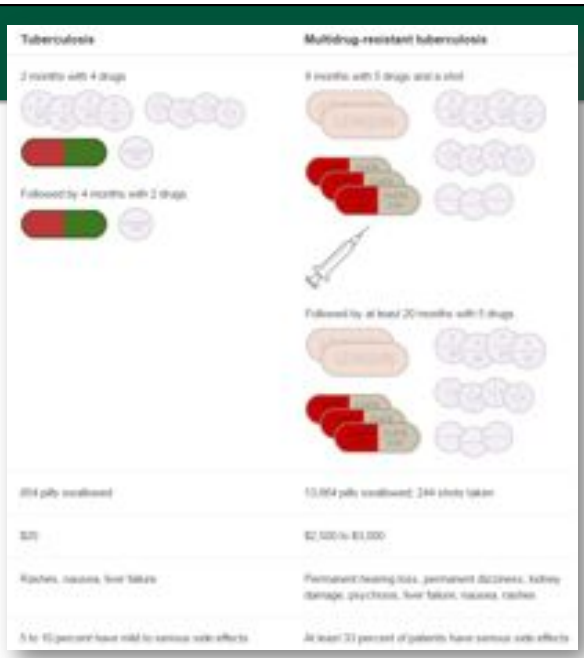
- RR: Rifampin resistant (an Xpert MTB/RIF era definition)
- MDR: Multi-drug resistant ≥INH+RMP
- XDR: Extensively drug-resistant MDR+FQ+SLIDs
- TDR: Totally drug resistant: XDR+cycloserine, PAS, all injectables

Impact of M/XDR TB

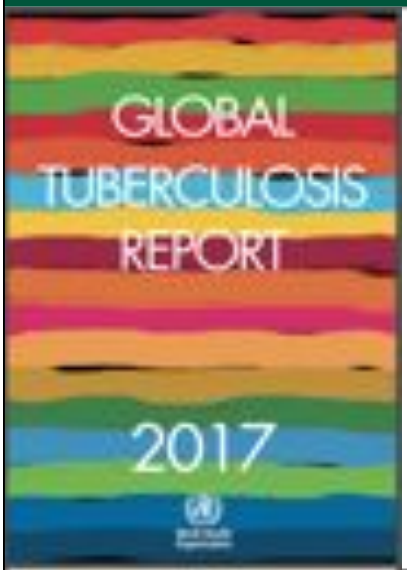
- In US, individualized not standardized treatment
- Major impact to patient
  - Prolonged treatment, monitoring
  - Prolonged isolation, inability to work
- Enormous resource sink, often by public sector
  - $17,000 per DS TB patient
  - $134,000 per MDR TB patient
  - $430,000 per XDR TB patient
- No proven therapy for contacts



MDR=>H+R; WHO, R Menzies of Montreal Chest Institute; Marks SM, et al. *EID* 2014;20(5):812-21



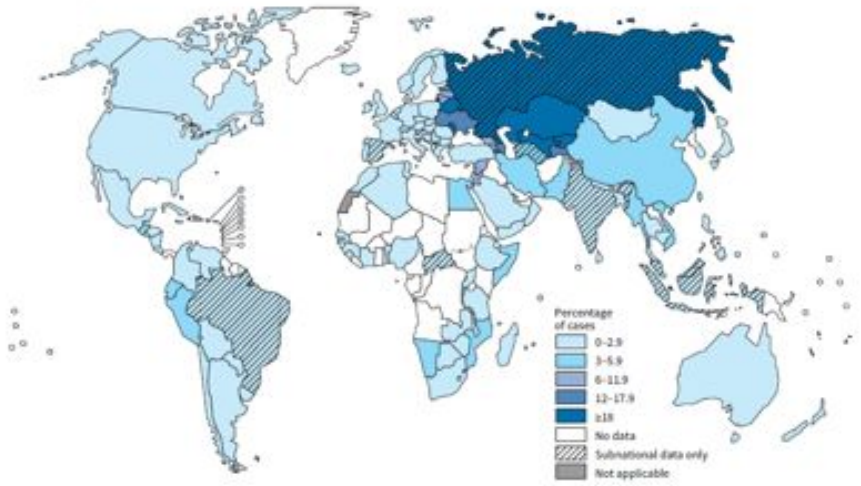
Global M/XDR TB



- Testing for ≥ rifampin
  - 33% of new patients
  - 60% of retreatment
- ~600,000 cases RR/MDR
  - 10% XDR
  - India, China, Russia 45%
- Increasing (22%) treated
  - Treatment success rate 52%
    - 28% for XDR

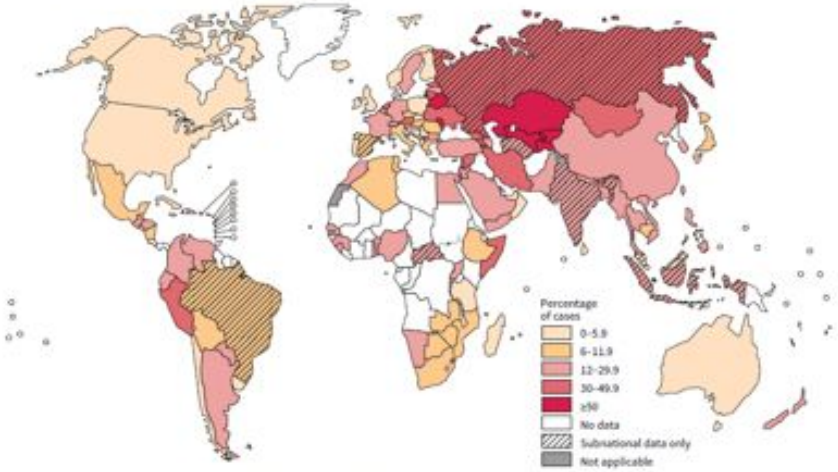
WHO/HTM/TB/2017.22; RR=rif resistance; MDR=>H+R; XDR= MDR+FQ+AG

3.3% of New Cases with MDR-TB



* Figures are based on the most recent year for which data have been reported, which varies among countries.

20% of Previously Treated with MDR-TB



* Figures are based on the most recent year for which data have been reported, which varies among countries. The high percentages of previously treated TB cases with MDR-TB in Bahrain, Bonaire, Israel, Saint Eustatius and Saba, and Sao Tomé and Principe refer to only a small number of notified cases (range: 1–8 notified previously treated TB cases).

Global M/XDR Projections

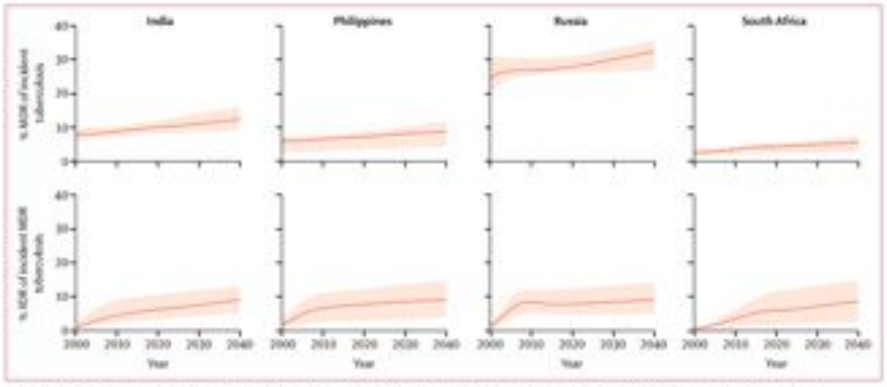
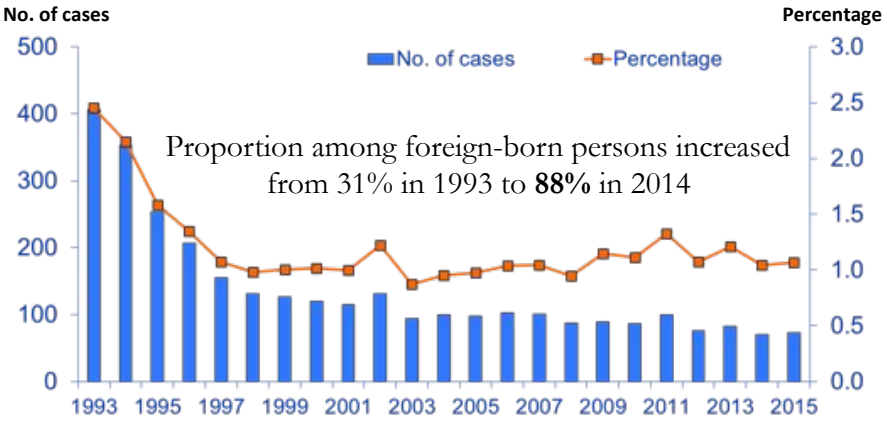


Figure 2: Projected trends of the proportion of individuals with MDR tuberculosis of those with incident tuberculosis, and the proportion with XDR tuberculosis of those with incident MDR tuberculosis
Data are for India, the Philippines, Russia, and South Africa from 2000 to 2040. MDR=multidrug-resistant. XDR=extensively drug-resistant. Solid lines represent medians of projections. Shaded areas represent 95% prediction intervals.

Sharma A et al for PETTS. Estimating the future burden . . . Lancet 2017; 17:707-15.

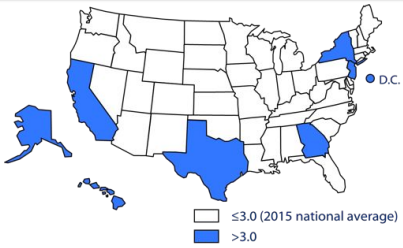
MDR in the United States



*As of June 9, 2016.

Note: Based on initial isolates from persons with no prior history of TB; multidrug resistant TB (MDR-TB) defined as resistance to at least isoniazid and rifampin.

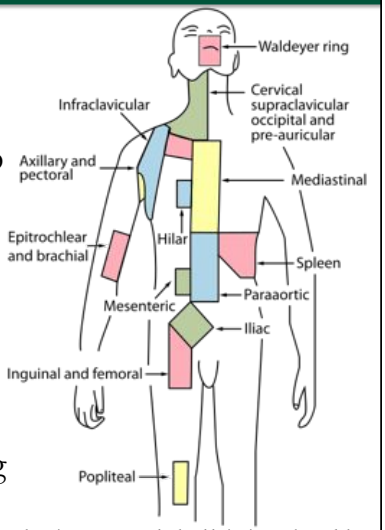
What is Our Regional Role?



- When should you suspect MDR TB?
- How do you diagnose MDR TB?
  - How do you interpret the test results?
- How do you build an MDR regimen?
- What innovations are coming?

Case: Globus with History of LTBI

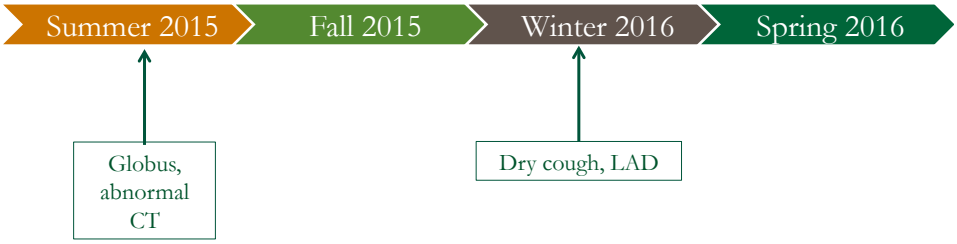
- 41M from Bhutan
  - 1996 purulent right cheek lump resected in Nepal
  - 2009 came to US
    - TST positive, neg CXR[1]
    - 9m INH through July 2010
- July 2015 develops globus
  - CT#1 prominent Waldeyer ring



By Lymph_node_regions.jpg: http://training.seer.cancer.gov/ss_module08_lymph_leuk/lymph_unit02_sec02_reg_lns.htmlderivative work: Fred the Oyster - Lymph_node_regions.jpg, Public Domain, https://commons.wikimedia.org/w/index.php?curid=9828280

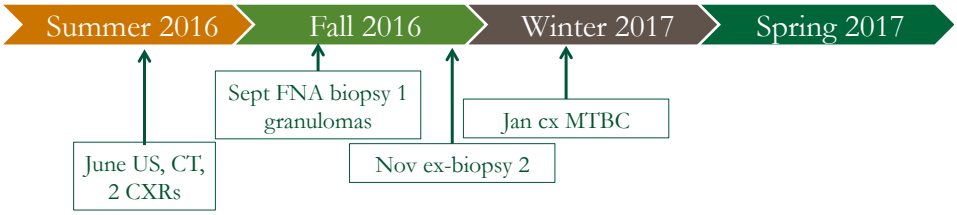
Patient, Clinician Delay

In a high risk patient, previously LTBI treated:



Patient, Clinician, Organism Delay

In a high risk patient, previously LTBI treated:



Most important MDR TB topic in northeast US

COULD THIS BE MDR TB?

Why Does He Have TB?

1. He did not complete treatment
2. He's been re-infected
3. 9m INH treatment not effective
   - He got poor quality, wrong dose *or*
   - He had MDR LTBI so INH had no power to prevent TB

E Victor Hugo's character Fantine (*Les Miserables*) 1886 painting by Margaret Bernadine Hall

Risk Factors for MDR TB

- Caused when TB drugs are misused or mismanaged
  - Patient does not complete full course of TB treatment
  - Providers prescribe wrong treatment (drug, dose or duration)
  - Drugs are not available or of poor quality
- Drug-resistant TB is more common in people who
  - Do not take their TB drugs regularly or completely
  - Have spent time with someone with drug-resistant TB
  - Develop TB disease after being treated for TB disease
  - Come from areas where drug-resistant TB is common
    - Nepal 2.2% new and 15% retreatment cases have MDR
    - Bhutan 38% retreatment cases have MDR

Corollary topic for public health and clinicians in the northeast US

HOW DO I DIAGNOSE MDR TB?

Detecting MDR TB in the U.S.

Method	Description	Advantages	Disadvantages	Sens/Spec	Time
Proportion method	Solid (agar) culture	Conventional	Expertise, BSL3, time	(Reference)	<42d
MGIT DST	Liquid culture DST	Automated or manual	Expertise, BSL3, time, cost, contamination (10%)	100/99	10-22d
Cartridge-based NAAT (GeneXpert)	Automated modular PCR	Fast, simple, accurate, RR	Cost, only rifampin resistance	TB: 88/98 RIF: 94/98	90min
Line Probe Assay (Hain, INNO LiPA)	Molecular probes for detection of DR mutations	Fast, accurate, cost less than MGIT	Expertise, culture isolate or sm+ sputum, lab space, still need culture capacity	85-98 sens 99 specif	6h
MDDR	Probe for genes known associated with DR	MDR confirmation, SLD info	Approval through TB program, not all mutations identified yet	Varies	Few days
Sequencing	Whole or targeted genome	Surveillance method	Not practical as clinical tool	Varies	Few days

Next Steps?

- Clinicians delay treatment until phenotypic DST
- NH DHHS sent specimen for Molecular Detection of Drug Resistance (MDDR)

Edvard Munch, *The Sick Child*, 1885–86, Nasjonalgalleriet, Oslo

9 Molecular Detection of Drug Resistance

- Examine DNA of specific genes for mutations known to be associated with phenotypic resistance
  - Not all mechanisms of resistance are known
    - Absence of mutation does not necessarily mean susceptible
- Since 2009, available to TB control programs
  - Rapid MDR TB confirmation
  - Second line drug resistance
- (Easy) approval process

Pyrosequencing instrument used for MDDR

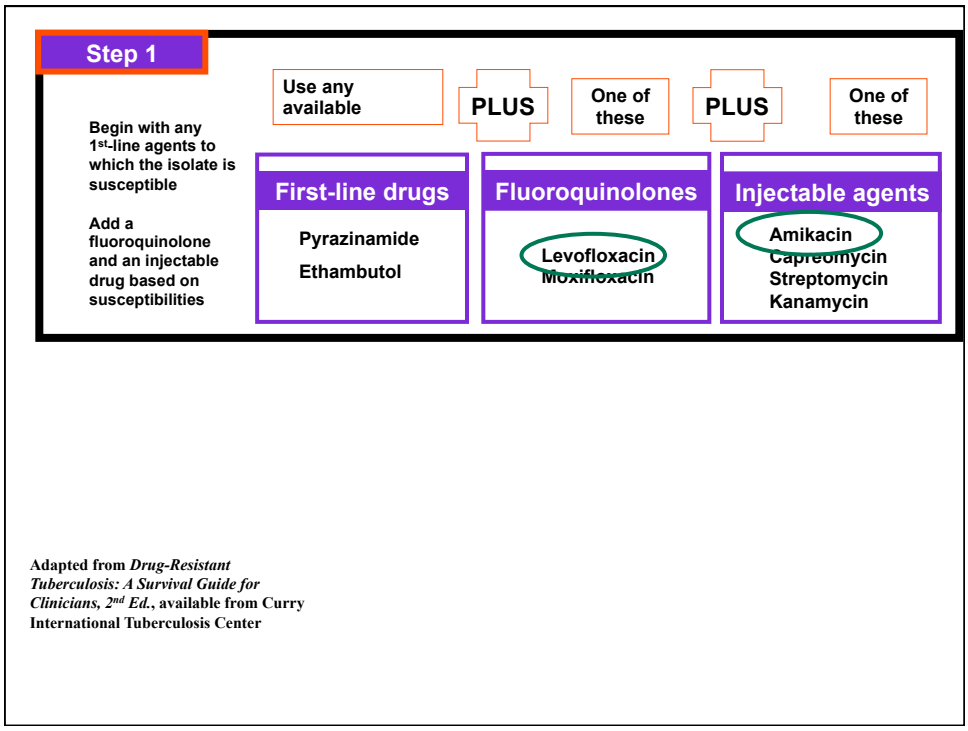
Molecular Detection of Drug Resistance Request Form

DST and MDDR

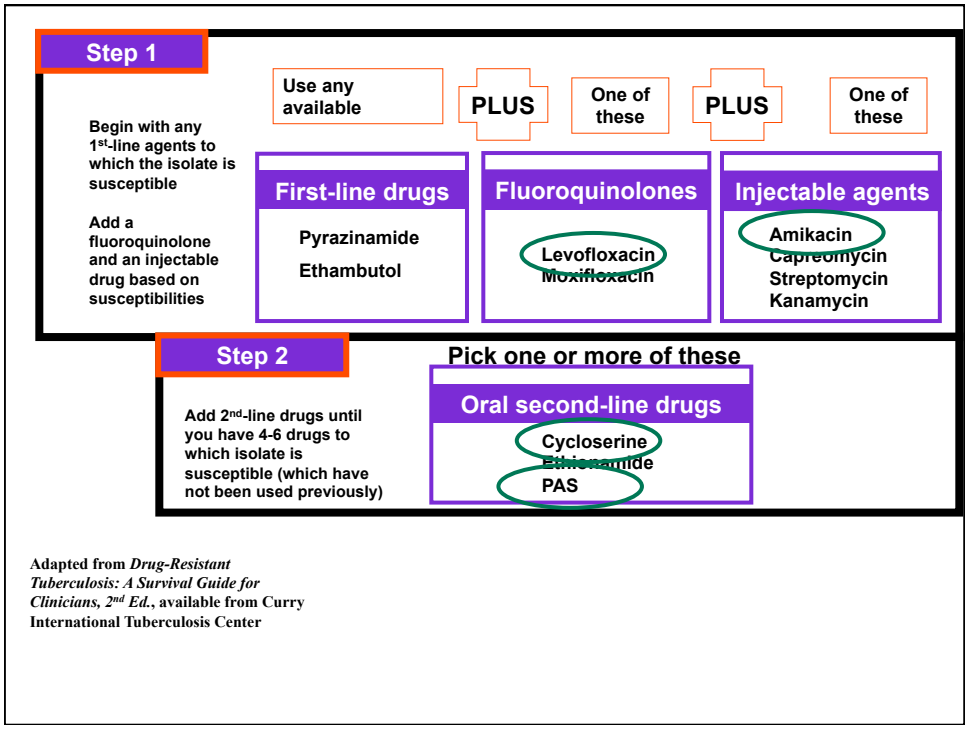
	MGIT	LJ	MDDR
INH 0.1 ug/ml	R	R	Kat G, not inhA
INH 0.4 ug/ml	R	R	
EMB 5.0 ug/ml	R	R	R
RMP	R	R	R
PZA 100 ug/ml	R	R	
Ethionamide	S	R	
Capreomycin	S	S	
Amikacin	S	S	
Moxifloxacin	S	S	GyrA not detected

Now what?

HOW DO I TREAT MDR TB?



Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center



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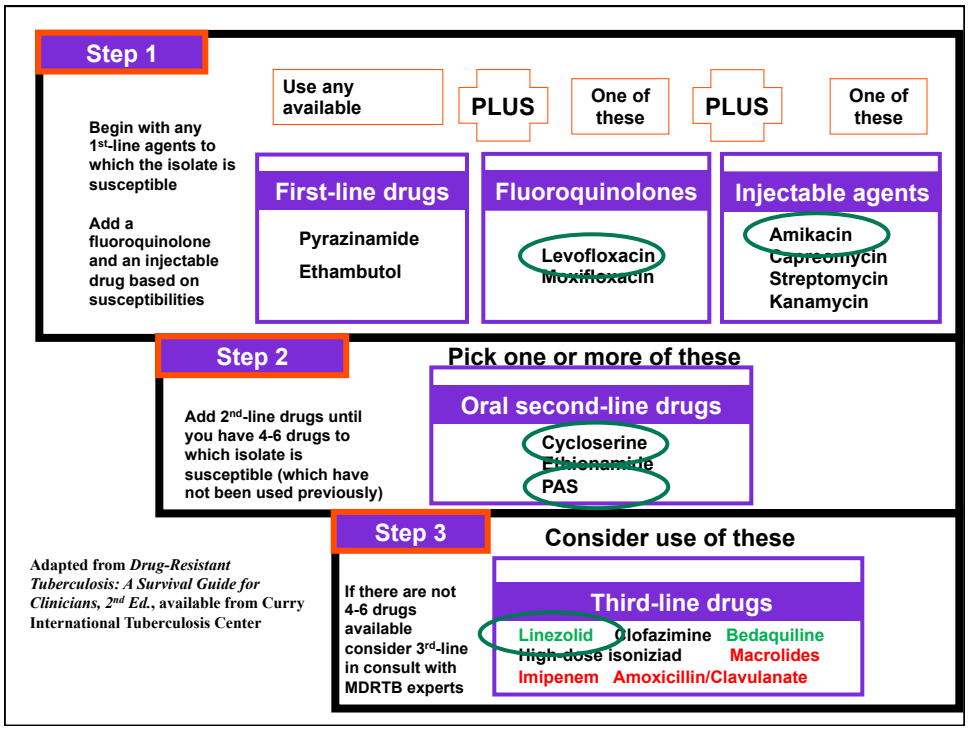
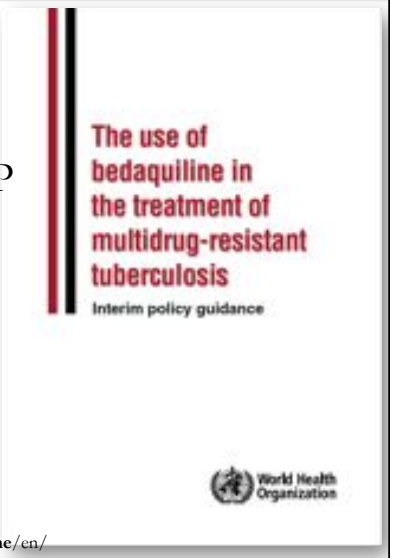


Complications

- Sensorineural hearing loss with tinnitus
- Bilat upper extremity neuropathy
- Rash (resolved with prednisone)
- July 2017 escalating "10/10" myalgias
  - Stopped linezolid and resolved
- Paradoxical reaction

9 Sirturo (Bedaquiline, J+J)

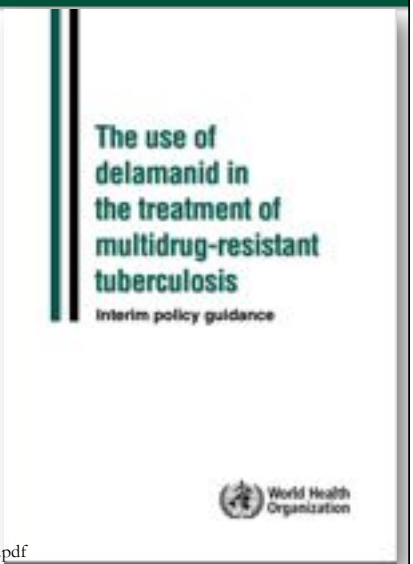
- Approved 2012
  - First new TB drug since 1970
- Diarylquinolone: inhibits ATP synthase
- First in its class, no resistance
- Common side effects nausea, joint pain, HA
  - QTc prolongation



www.who.int/tb/challenges/mdr/**bedaquiline**/en/

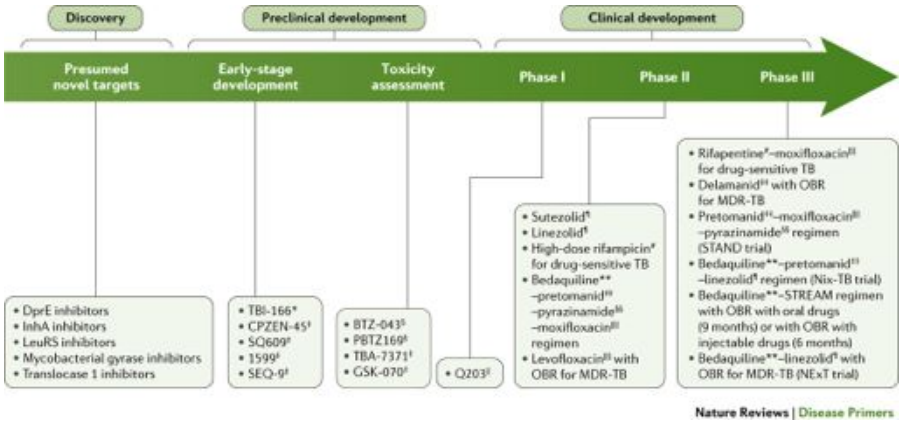
10 Delaminid (Otsuka)

- Nitro-dihydroimidazooxazole derivative: inhibits mycolic acid synthesis
- Approved 2014
- No resistance yet
- Common side effects HA, nausea and dizziness
  - QTc prolongation



WHO_HTM_TB_2014.23_eng.pdf

Global TB Drug Pipeline



Pai, M. *et al.* (2016) Tuberculosis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

Conclusion

- We must be ready to assist in efficient diagnosis of LTBI, TB and MDR-TB
- New guidelines available
- Both TST and IGRAs have issues of specificity
- Xpert improving, underutilized
- M/XDR TB awareness
- Xpert, MDDR, other methods available


GEISEL
SCHOOL OF
MEDICINE
AT DARTMOUTH
ADMISSIONS
Thank you!
The Next Pelé / China's Hackers / The World's Hardest Job
TIME
CONTAGION
Why drug-resistant tuberculosis threatens us all
BY KRISTA MAHR WITH PHOTOGRAPHS BY JAMES NACHTWEY