MDR TB: Core Curriculum

Our local role in the global strategy

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Disclosure

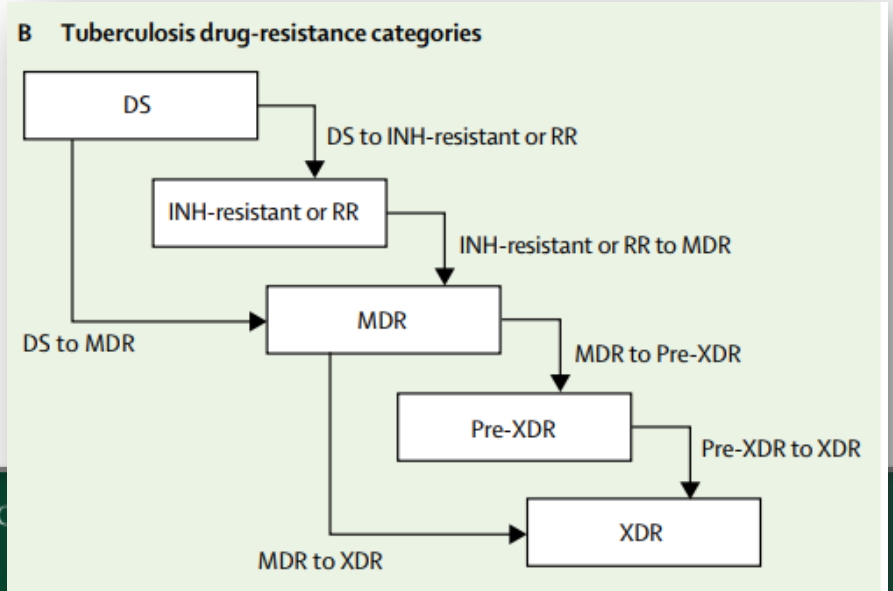
- Consultant to Oxford Immunotec

AMR Prioritized

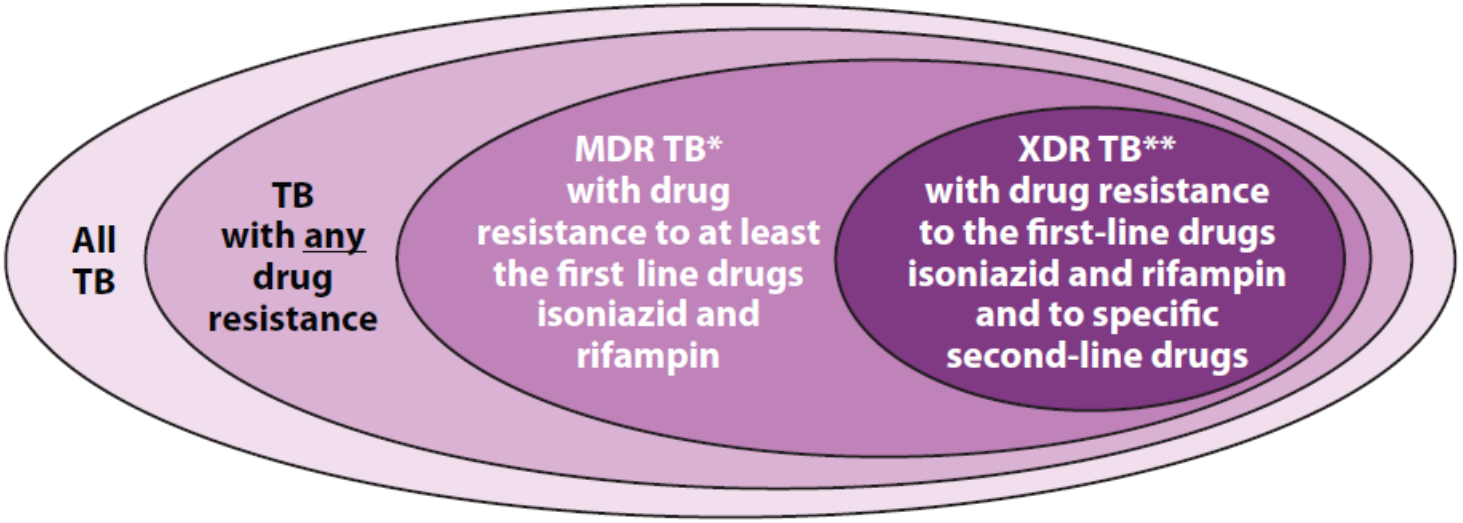
- 2014 National Strategy for Combating Antibiotic-Resistant Bacteria
  - Presidential Executive Order directs USG to "work domestically and internationally to reduce the emergence and spread of antibiotic-resistant bacteria."
- Sept 2016 political declaration endorsed UN General Assembly. Oct 2017 WHO declared
  - Coordinated action is required
  - All countries need national action plans on AMR
  - Greater innovation and investment are required in R+D of treatment, vaccines, and diagnostic tools

Tuberculosis Prioritized Among AMR

- TB is the leading infectious cause of death
  - ~29% of deaths caused by antimicrobial infections are due to drug-resistant TB
- UK estimates over 35 years, MDR will
  - Kill 75M people
  - Cost global economy $16.7 trillion



TB AMR Definitions



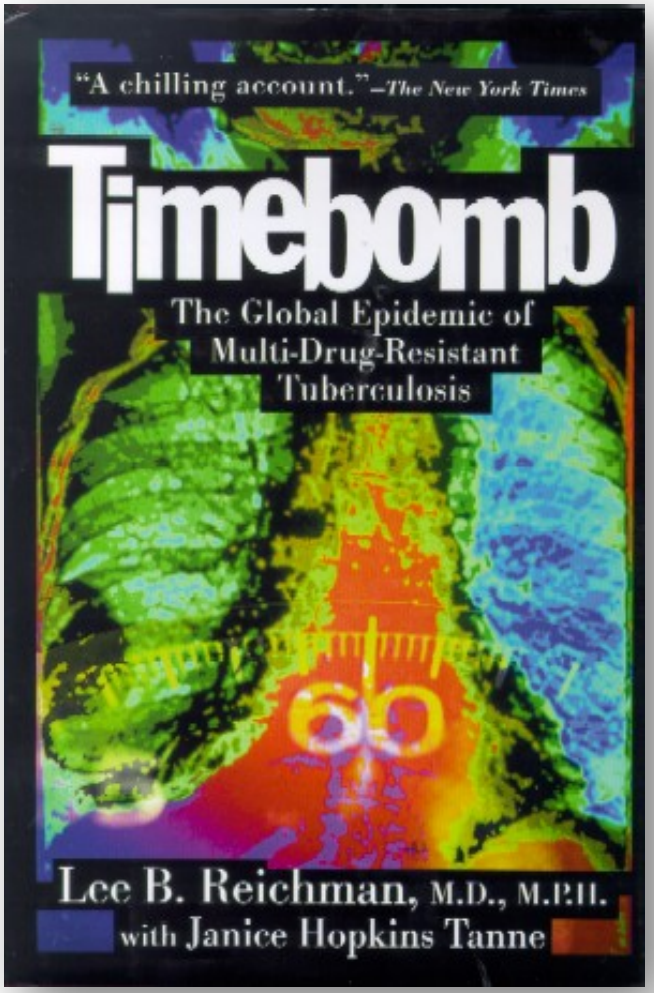
* Often resistant to additional drugs

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

- RR: Rifampin resistant, necessitated by Xpert MTB/RIF
- 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

Tuberculosis	Multidrug-resistant tuberculosis
2 months with 4 drugs 	8 months with 5 drugs and a shot 
854 pills swallowed	13,664 pills swallowed, 244 shots taken
$20	$2,500 to $3,000
Rashes, nausea, liver failure	Permanent hearing loss, permanent dizziness, kidney damage, psychosis, liver failure, nausea, rashes
5 to 10 percent have mild to serious side effects	At least 33 percent of patients have serious side effects

Inadequate Treatment

Today, treatment for drug-resistant TB is long, toxic, complicated and expensive.

6 months

INJECTIONS

1/day for at least 6 months.

9-24 months

PILLS

12-24/day for as many as 24 months.

6-24 months

IV INFUSIONS

2/day for 6-24 months.

14,000 pills

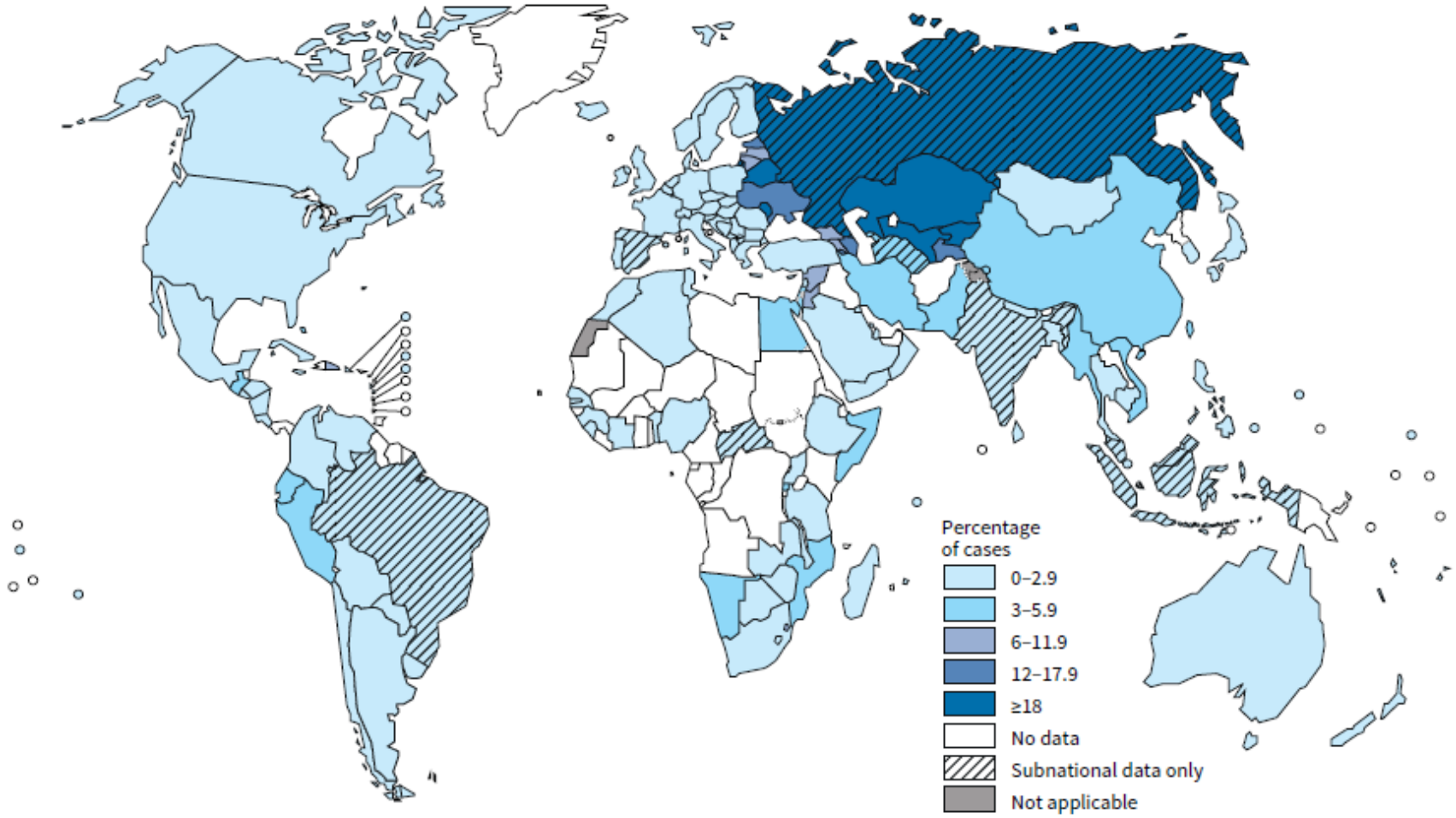
It takes 14,000 pills to treat one patient with drug-resistant TB.

Global M/XDR TB

- Testing for ≥ rifampin
  - 24% of new patients
  - 53% of retreatment
- ~580,000 cases RR/MDR
  - 10% XDR
  - India, China, Russia 45%
- Increasing (20%) treated
  - Treatment success rate 52%
    - 28% for XDR

WHO/HTM/TB/2016.22; RR=rif resistance; MDR=>H+R; XDR= MDR+FQ+AG

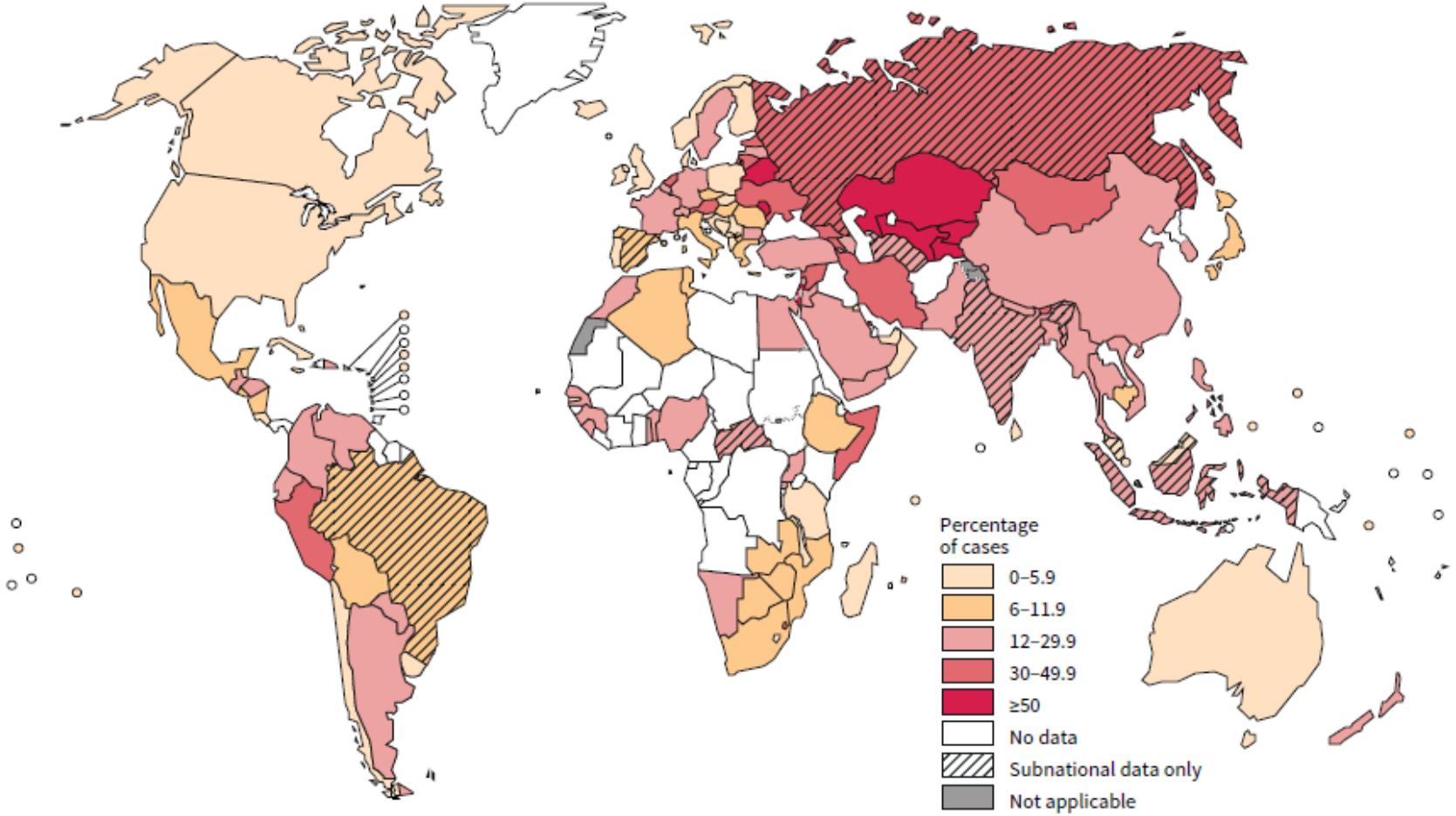
3.3% of New Cases with MDR-TB



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

WHO/HTM/TB/2016.22; MDR=>H+R

20% of Previously Treated with MDR-TB



[a] 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).

WHO/HTM/TB/2016.22; MDR=>H+R

Global M/XDR Projections

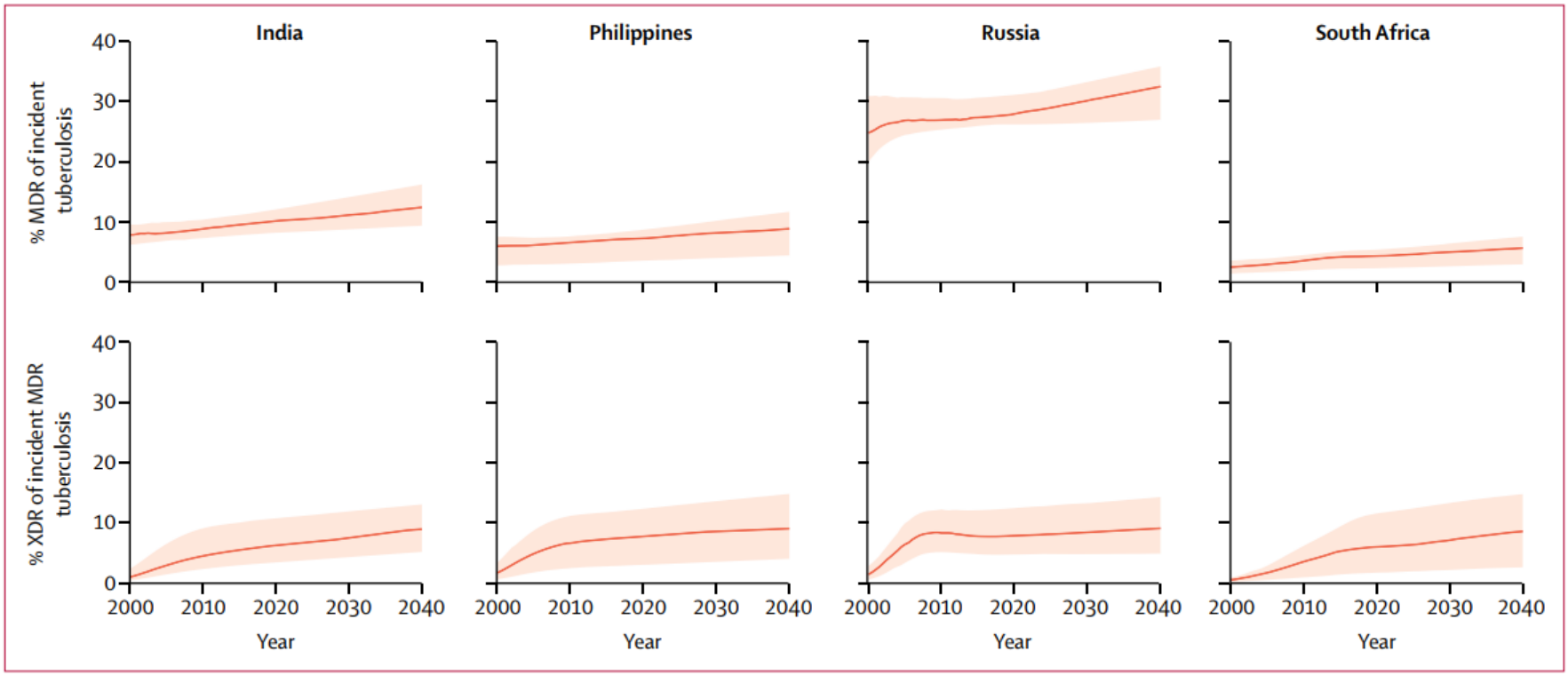
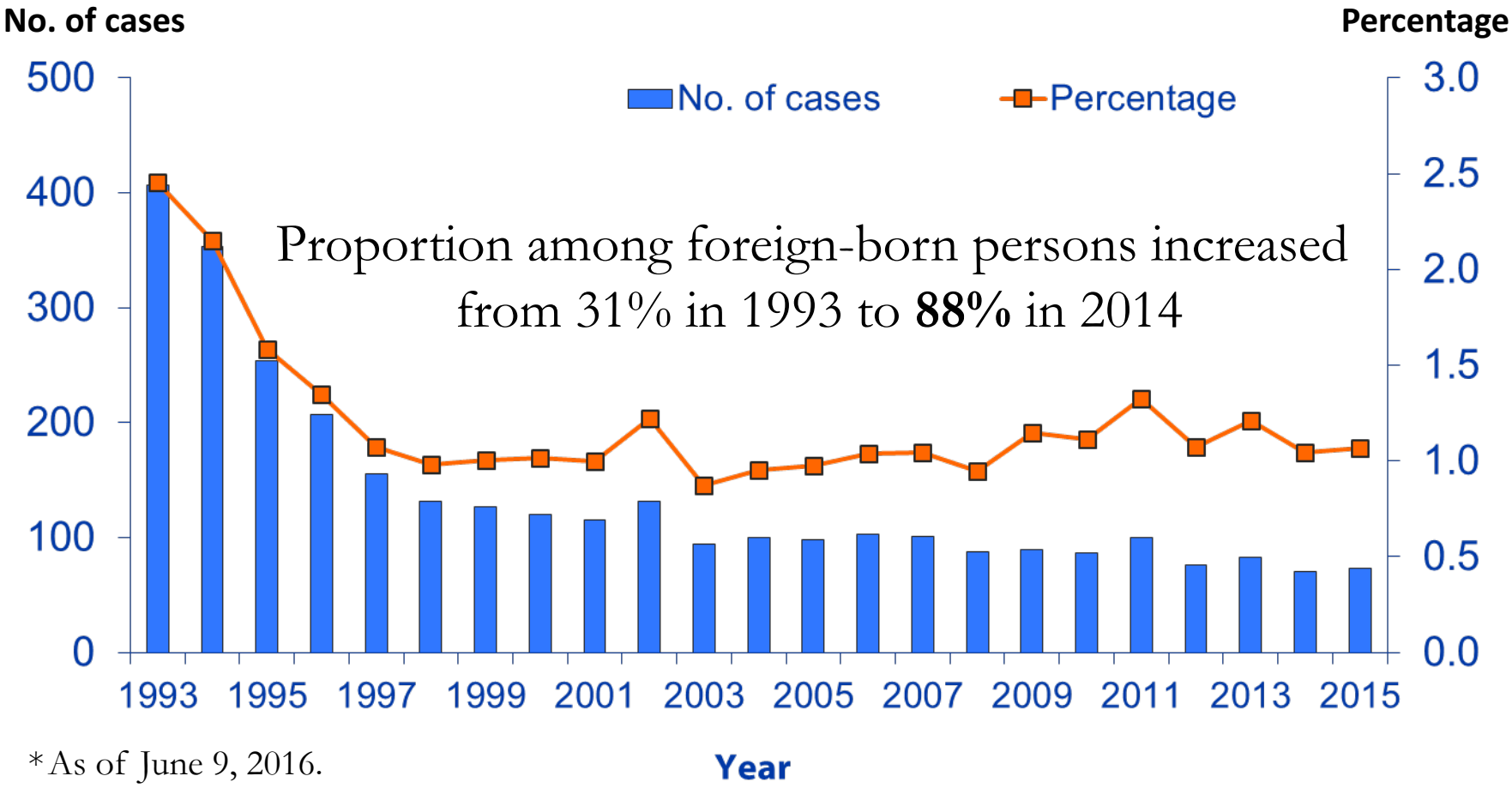


***Figure 2*: Projected trends of the proportion of individuals with MDR tuberculosis of those with incident tuberculosis, and the proportion with XDR tuberculosis of those with incident MDR tuberculosis**

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.

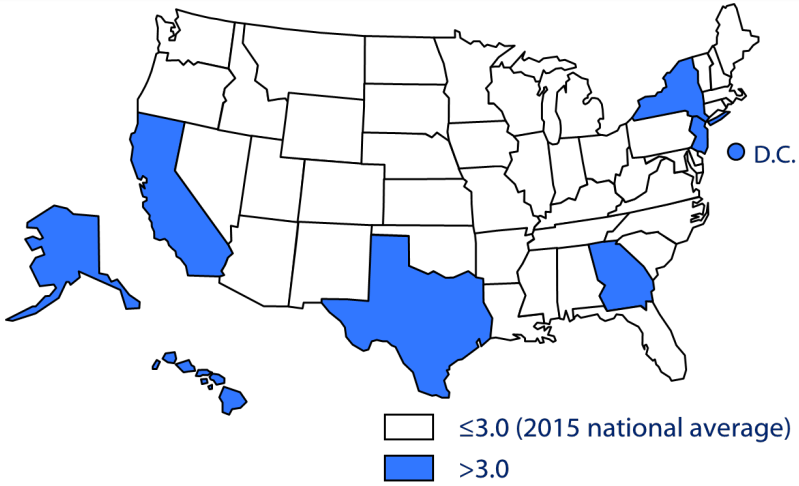
MDR in the United States



*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.

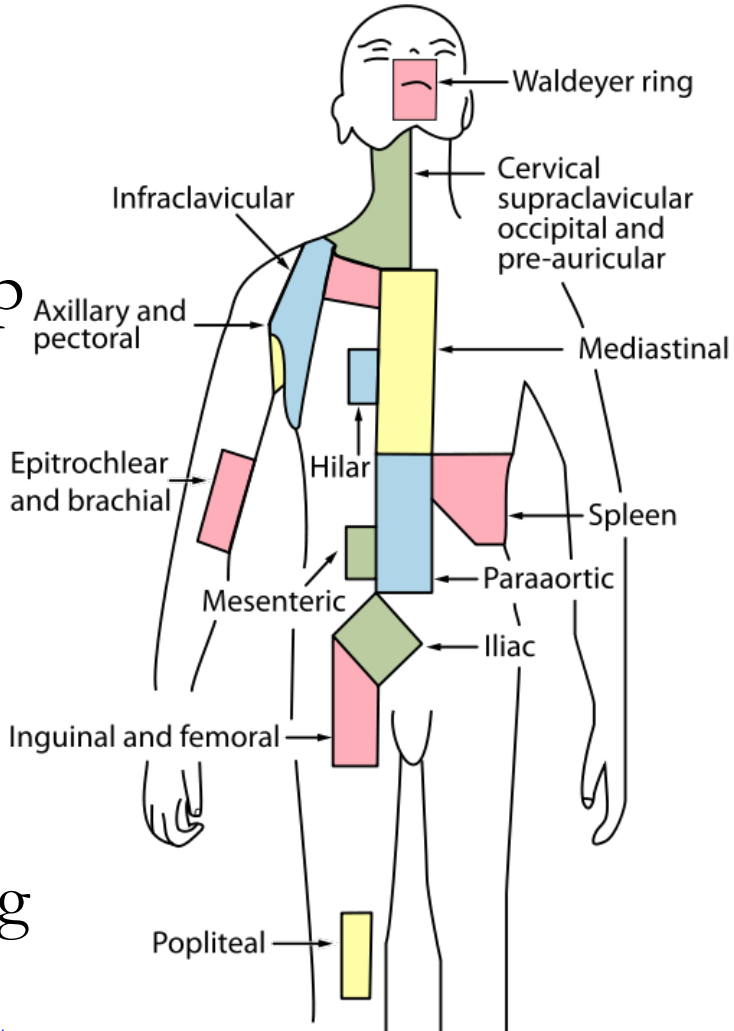
What is Our Regional Role?



- 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

Case: Cervical Lymphadenopathy

- 7m later in February 2016
  - Chronic dry cough, worse globus
    - CXR[2] normal, AFB sputum smears and cultures negative
  - Growing tender lump in neck
- 4m later "R inferior anterior cervical chain with multiple firm, tender, mobile" nodes

Diagnostic Evaluations Summer 2016

- CXR[3] neg
- Ultrasound[1] LAD <1–3cm in size
- Referred to ENT[1]
  - Flexible laryngoscopy no masses/lesions
- CT[2] 3.5 x 4 x 2.5cm LAD mass, some anechoic
- August 2016 still with dry coughing
  - QuantiFERON +
  - CXR[4] negative

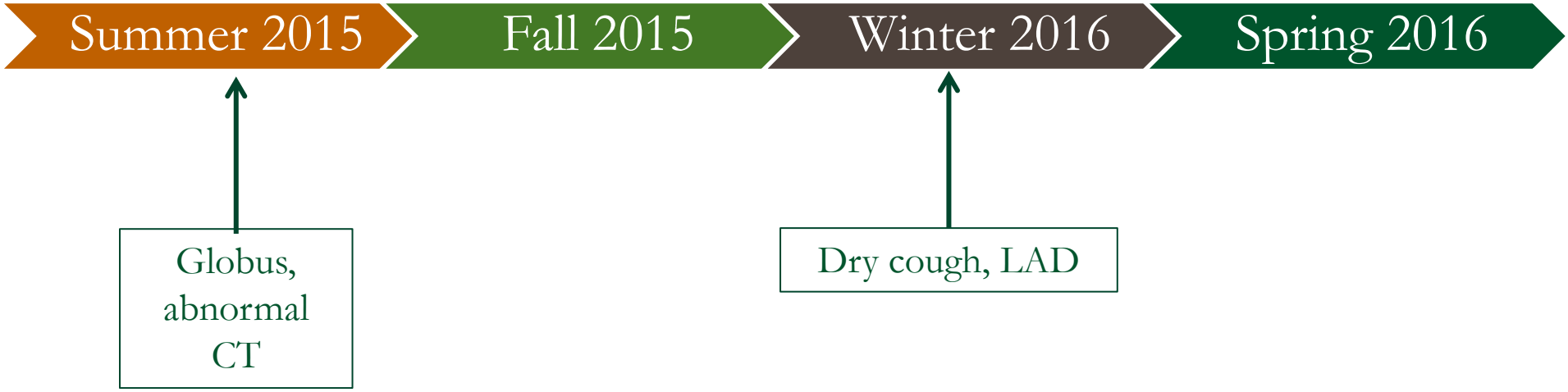
TB Scrofula Confirmed

- September 2016 20-gauge aspiration showed lymphoid tissue with granulomas and caseous necrosis
  - Biopsy[1] AFB smear and culture negative
- Nov 2016 ultrasound[2] 17/18 gauge biopsy[2] AFB sm-
  - Histology shows caseating granulomas
  - Jan 12 2017 MTBC **culture growth**

Engraving by André Du Laurens (1558-1609), showing King Henry IV of France touching scrofula sufferers

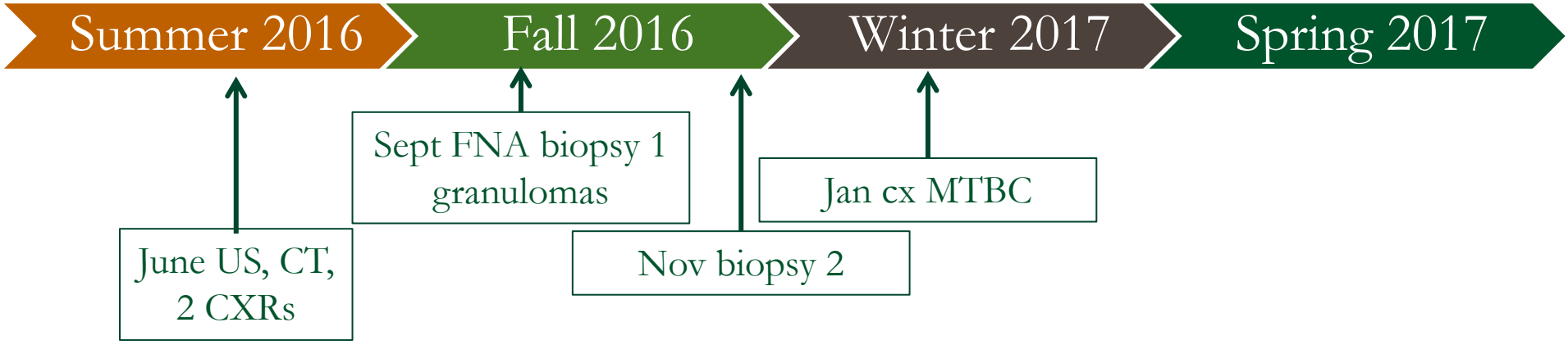
Patient, Clinician Delay

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?

MDR=>H+R; XDR= MDR+FQ+AG

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

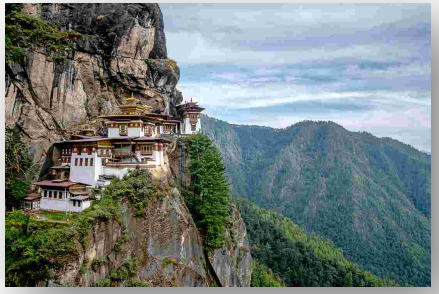
Victor Hugo's character Fantine (*Les Miserables*)
1886 painting by Margaret Bernadine Hall

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

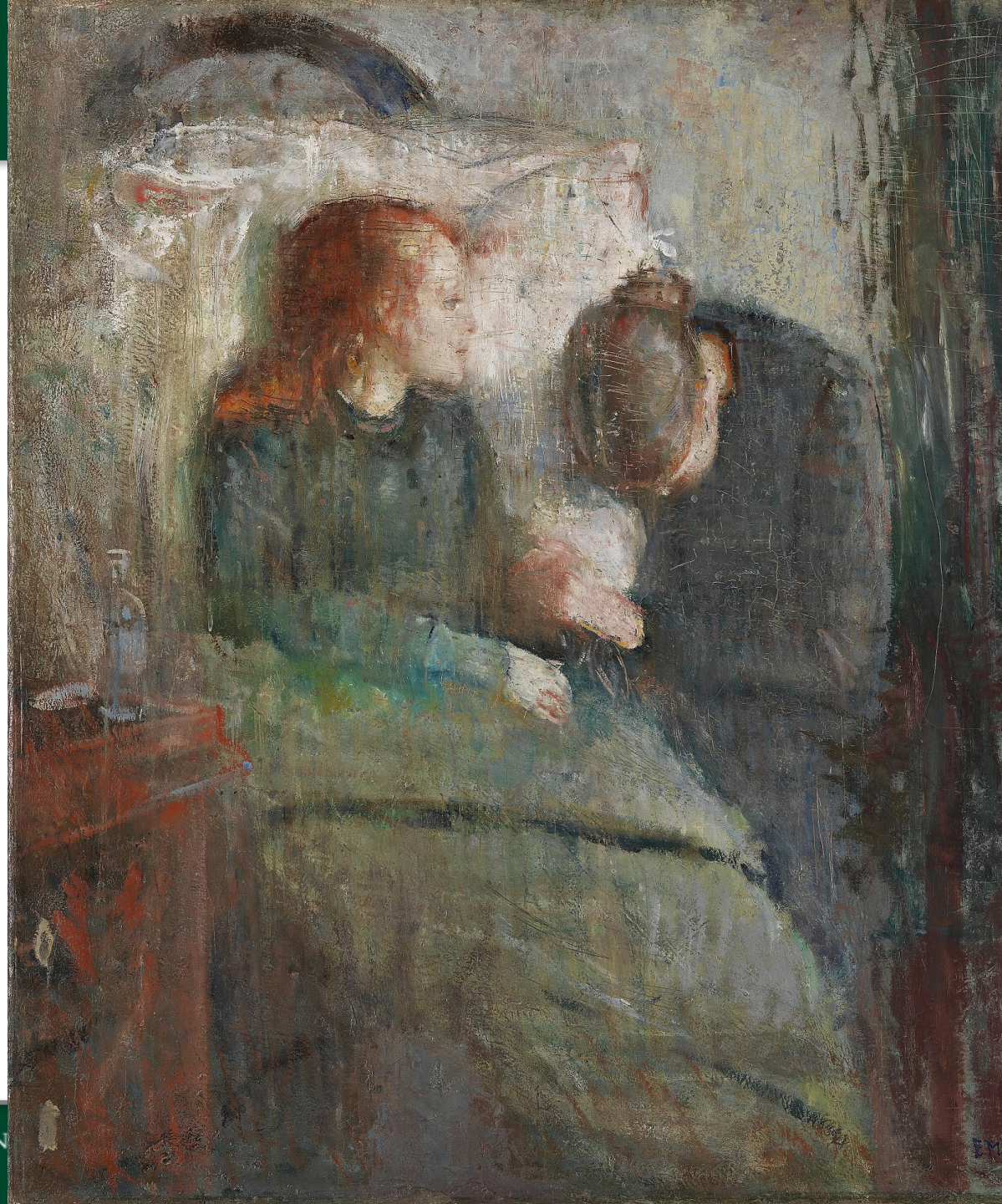
Empiric Treatment Now?

A. Yes: first line regimen (assume DS-TB)
B. Yes: empiric MDR regimen such as PZA/EMB/FQ/AG/SLDs. Adjust later
C. No: wait to treat based on molecular detection of drug resistance (MDDR).
D. Get consultation



Next Steps?

- ID elected to delay treatment pending drug sensitivity testing (DST)
- NH DHHS sent specimen for Molecular Detection of Drug Resistance (MDDR)



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

Corollary topic for public health and clinicians in the northeast US

HOW DO I DIAGNOSE MDR TB?

Detecting MDR TB in the U.S.

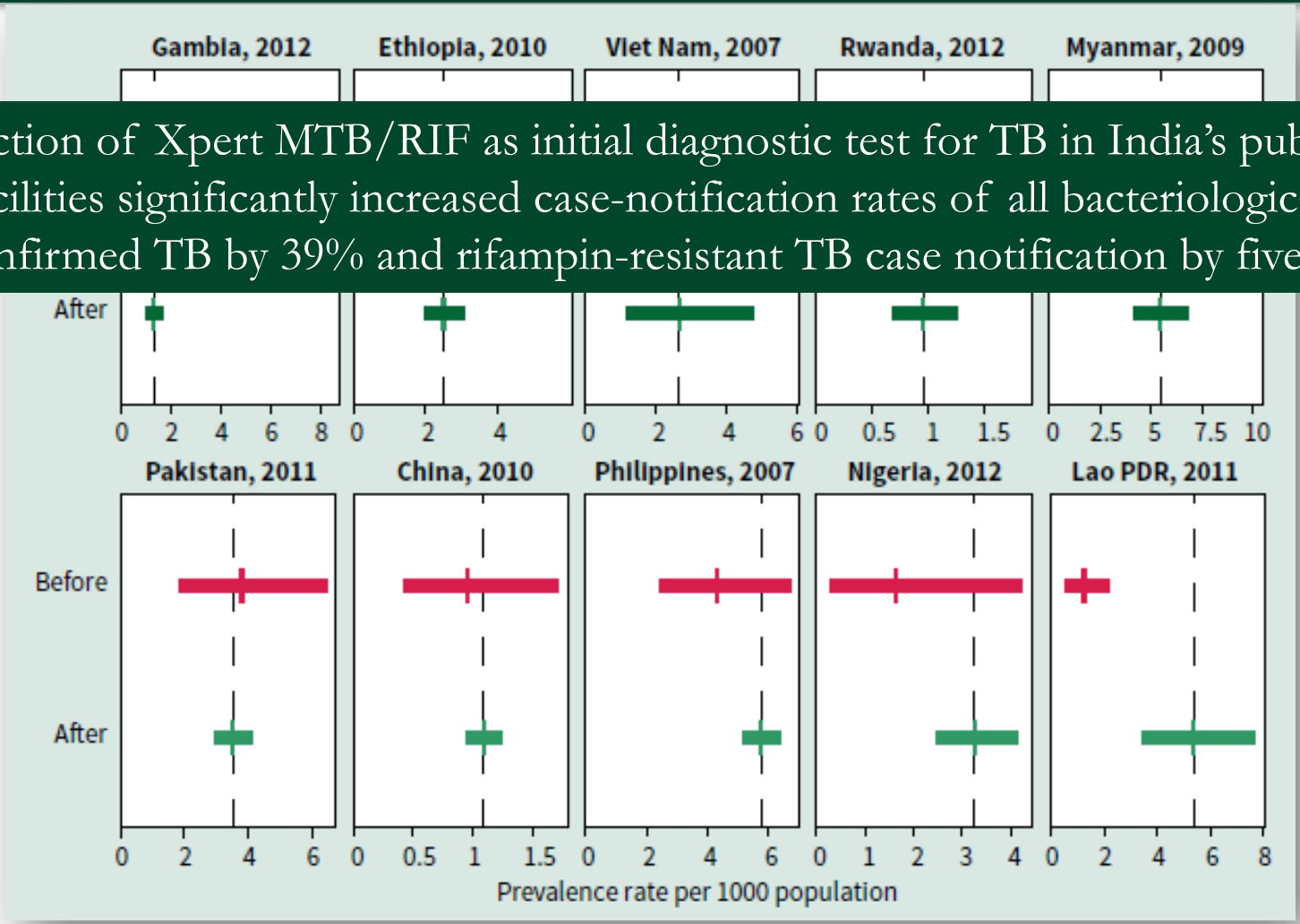
Method	Description	Advantages	Disadvantages	Sens/Spec	Time
Proportion method	Solid (agar) culture	Conventional	Expertise, BSL3, time	(Reference)	<42d
MGIT DST	Liquid culture DST	Automated or manual	Expertise, BSL3, time, cost, contamination (10%)	100/99	10-22d
Cartridge-based NAAT (GeneXpert MTB/RIF)	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

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

Xpert is Informing Global TB Control



Introduction of Xpert MTB/RIF as initial diagnostic test for TB in India's public health facilities significantly increased case-notification rates of all bacteriologically confirmed TB by 39% and rifampin-resistant TB case notification by fivefold

WHO/HTM/TB/2014.08, Sachdeva KS et al. Use of Xpert MTB/RIF in decentralized public health settings and its effect on pulmonary TB and DR-TB case finding in India. PLoS ONE 10(5): e0126065. doi:10.1371/journal.pone.0126065

Xpert Omni, Ultra, Xtend

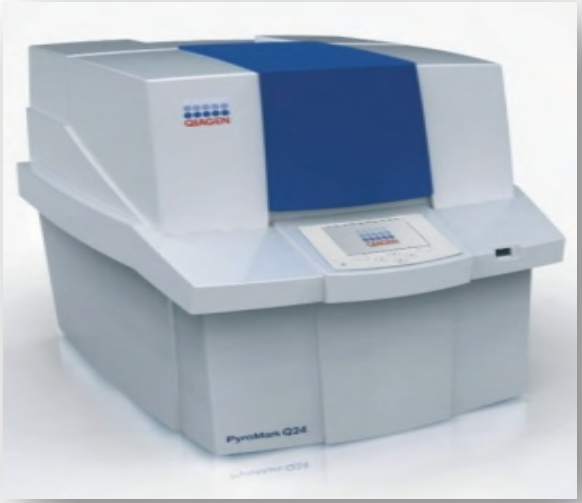
- Omni is GeneXpert platform improvement
  - Portable, 4 hour battery for point of care
- Ultra cartridge improves sensitivity*
  - "Trace calls" detect paucibacillary disease
    - Detects dead organisms (decreased specificity for TB diagnosis)
  - Improved rifampin resistance specificity
- Xtend XDR cartridge for INH, FQ, SLIDs
  - Intended to follow finding of RR; 2018

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

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
- Approval process



Pyrosequencing instrument used for MDDR

Molecular Detection of Drug Resistance Request Form

Laboratory Branch / Division of TB Elimination/ CDC
1600 Clifton Road, Atlanta, GA 30333
Phone 404-639-2455 FAX 404-639-5491 TBLab@cdc.gov

Instructions: Please provide the following information and submit the completed form via email to TBLab@cdc.gov or fax at 404-639-5491. An email notification will be provided upon approval with further instructions.

Section 1. Laboratory Contact Information

Date of Request

Submitting Laboratory

Contact Name

Phone Number

Fax Number

E-mail Address

Section 2. TB Program Contact Information

Contact Name

Phone Number

Fax Number

E-mail Address

Section 3. Type of specimen

☐ Isolate; Specify medium:

☐ NAAT+ sediment; Specify specimen source:

Section 4. Submission Criteria (check all that apply)

☐ Known MDR; Test method:

☐ Known RMP resistant; Test method:

☐ Contact to known MDR ☐ Previously Treated for TB

☐ From a country with a high rate of drug resistant TB; Specify:

☐ Travel to / lived in a country with a high rate of drug resistant TB; Specify:

☐ Mixed culture ☐ Non-viable in culture ☐ No / poor growth in DST media

☐ Other; Explain

Has a sample from this patient been previously submitted to CDC? ☐ Yes ☐ No

If yes, please provide reason for resubmission:

Feb 2017 DST and MDDR

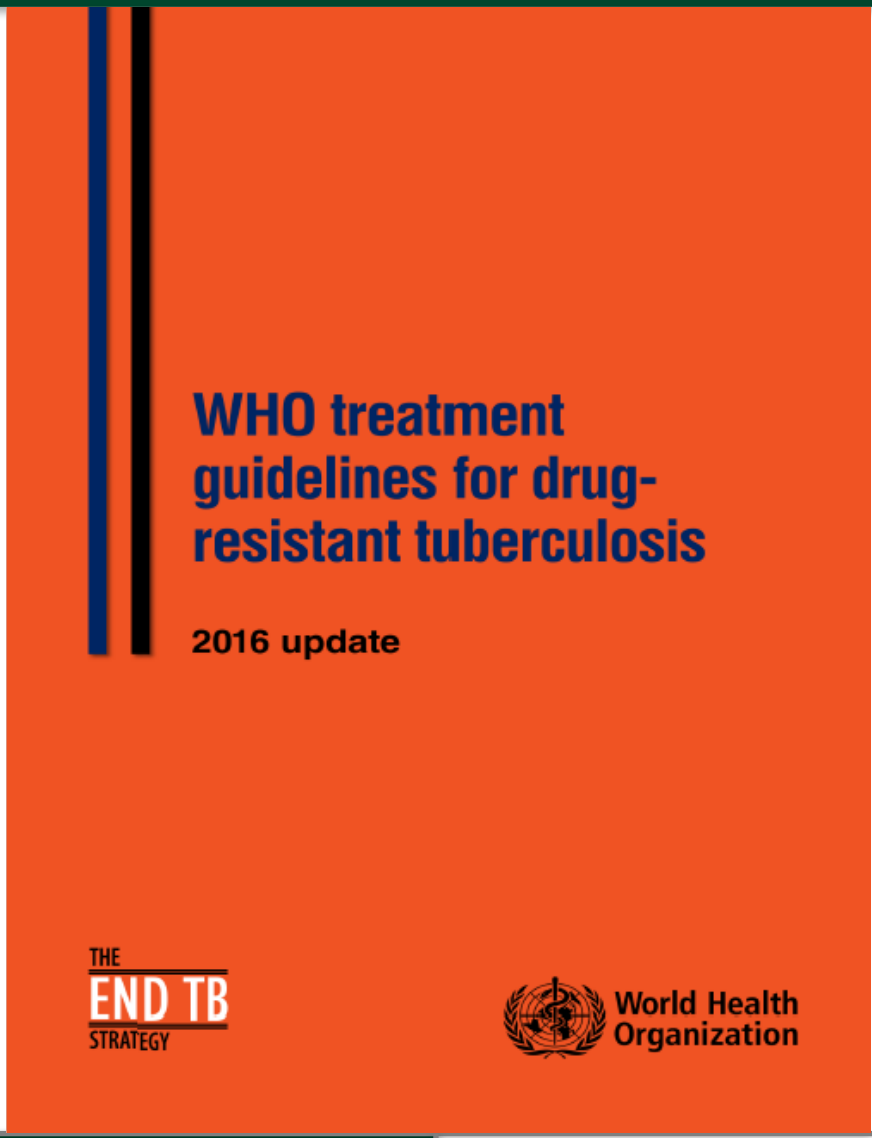
	MGIT	LJ	MDDR
INH 0.1 ug/ml	R	R	Kat G mutation, not inhA
INH 0.4 ug/ml	R	R	
EMB 5.0 ug/ml	R	R	R
RMP	R	R	R
PZA 100 ug/ml	R		R
Ethionamide	S	R	
Capreomycin	S	S	
Amikacin	S	S	
Moxifloxacin	S	S	GyrA not detected

Now what?

HOW DO I TREAT MDR TB?

New MDR Treatment Guidelines

- MDR-TB treatment recommended for RR-TB
  - Even if INH resistance is not confirmed
- Medicines in individualized MDR-TB treatment regimens are regrouped
- Recommendations on role of surgery

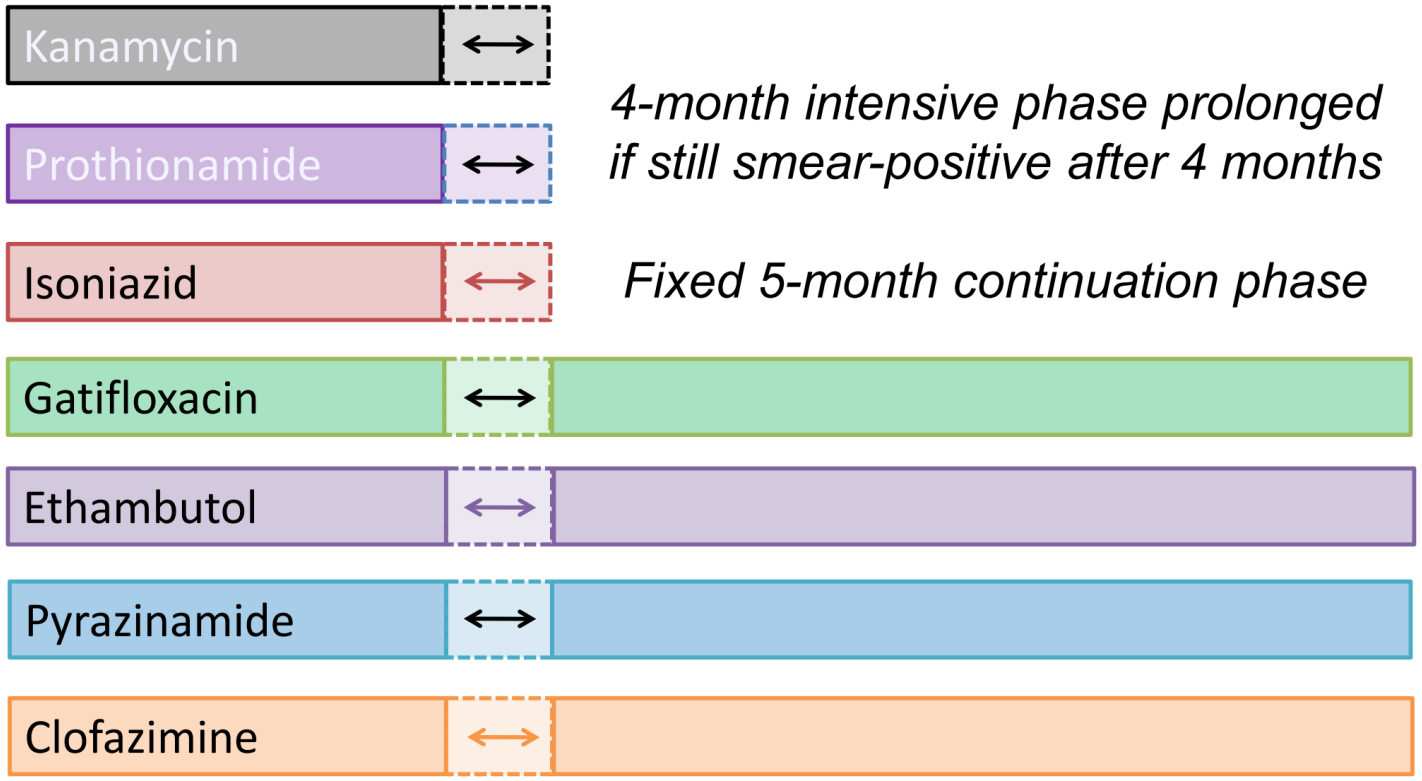


Big Change

SHORTER STANDARDIZED TREATMENT FOR MDR TB

7-Drug Bangladesh Regimen

The (minimum) 9-month regimen for MDR in Bangladesh (220 €)



Van Deun A, et al. Am J Respir Crit Care Med 2010;182:684-92

Efficacy of Short Course for MDR

7-drug standardized regimen showed efficacy similar to outcomes reported for drug sensitive TB

Resistance pattern	*Shorter MDR-TB regimen*		*Conventional MDR-TB regimen*	
	N	% (95% CI)	N	% (95% CI)
All cases regardless of pyrazinamide and fluoroquinolone susceptibility	1008/1116	*90.3% (87.8%- 92.4%)*	4033/5850	*78.3% (71.2%- 84%)*
Pyrazinamide resistant; fluoroquinolone resistant	19/28	67.9% (47.6%-84.1%)	81/137	59.1% (50.6%-67.1%)
Pyrazinamide resistant; fluoroquinolone susceptible	90/100	88.8% (47.3%-98.6%)	840/1075	81.4% (71.6%-88.4%)
Pyrazinamide susceptible; fluoroquinolone resistant	12/15	80.0% (50.0%-94.1%)	72/120	64.4% (49.6%-76.9%)
Pyrazinamide susceptible; fluoroquinolone susceptible	121/125	96.8% (77.3%-99.6%)	890/1119	83.5% (75.7%-89.2%)

Van Deun A et al. Am J Respir Crit Care Med Vol 182. 684–692, 2010; Aung et al, IJTLD 18(10):1180–1187, 2014

WHO RECOMMENDATIONS

ON THE USE OF THE SHORTER MDR-TB REGIMEN

In May 2016, WHO issued a conditional recommendation on the use of the shorter MDR-TB regimen. A flow chart outlining selection of patients on the shorter MDR-TB regimen is presented below.

CHOOSING THE MDR-TB TREATMENT REGIMEN IN PATIENTS WITH CONFIRMED RIFAMPICIN-RESISTANT OR MDR-TB

CRITERIA: Do any of the following apply ?

- ✓ Confirmed resistance or suspected ineffectiveness to a medicine in the shorter MDR-TB regimen (except isoniazid resistance)
- ✓ Exposure to ≥1 second-line medicines in the shorter MDR-TB regimen for >1 month
- ✓ Intolerance to ≥1 medicines in the shorter MDR-TB regimen or risk of toxicity (e.g. drug-drug interactions)
- ✓ Pregnancy
- ✓ Extrapulmonary disease
- ✓ At least one medicine in the shorter MDR-TB regimen not available in the programme

NO

Shorter MDR-TB regimen

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

FAILING REGIMEN, DRUG INTOLERANCE, RETURN AFTER INTERRUPTION >2 MONTHS, EMERGENCE OF ANY EXCLUSION CRITERION

YES

Individualised ("conventional") MDR/RR-TB regimens

Intensive phase
Duration: Up to 8 months
Composition: 4 or more second-line drugs

Continuation phase
Duration: 12 months or more
Composition: 3 or more second-line drugs

Also a big change

APPROACH TO INDIVIDUALIZED MDR REGIMEN

Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs	Fluoroquinolones	Injectable agents
Pyrazinamide	Levofloxacin	Amikacin
Ethambutol	Moxifloxacin	Capreomycin
		Streptomycin
		Kanamycin

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

Step 1

Begin with any 1st-line agents to which the isolate is susceptible

Add a fluoroquinolone and an injectable drug based on susceptibilities

Use any available

PLUS

One of these

PLUS

One of these

First-line drugs

- Pyrazinamide
- Ethambutol

Fluoroquinolones

- Levofloxacin
- ~~Moxifloxacin~~

Injectable agents

- Amikacin
- ~~Capreomycin~~
- Streptomycin
- Kanamycin

Step 2

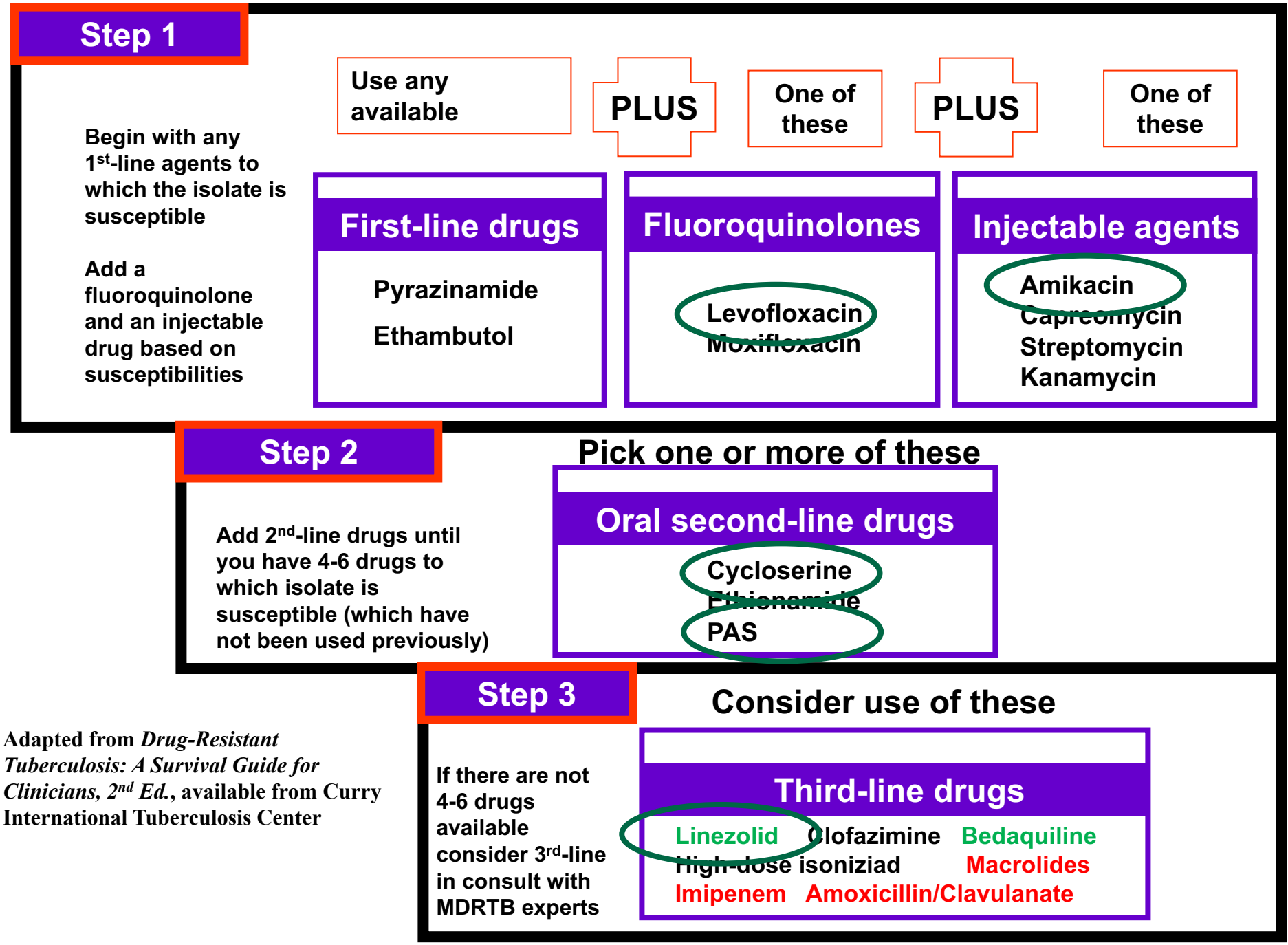
Add 2nd-line drugs until you have 4-6 drugs to which isolate is susceptible (which have not been used previously)

Pick one or more of these

Oral second-line drugs

- Cycloserine
- ~~Ethionamide~~
- PAS

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



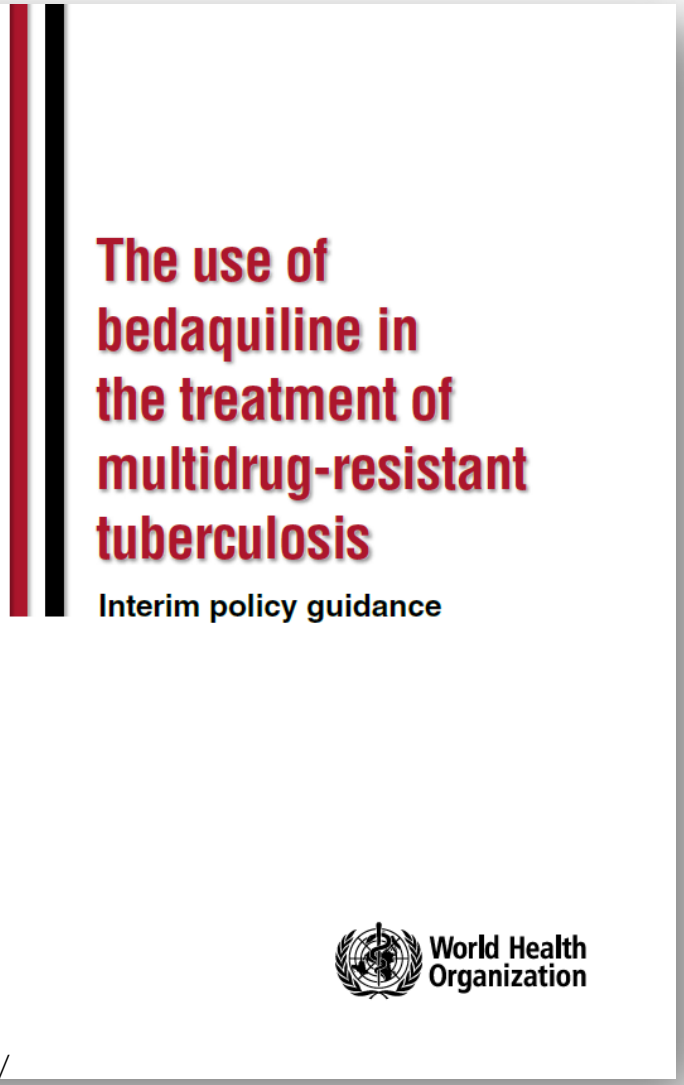
Adapted from *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2nd Ed.*, available from Curry International Tuberculosis Center

Complications

- Sensorineural hearing loss with tinnitus
- Bilateral symmetric upper extremit neuropathy
- Rash resolved with prednisone
- July 2017 escalating “10/10” myalgias
- Stopped linezolid and resolved
- Paradoxical reaction

Sirturo (Bedaquiline, J+J)

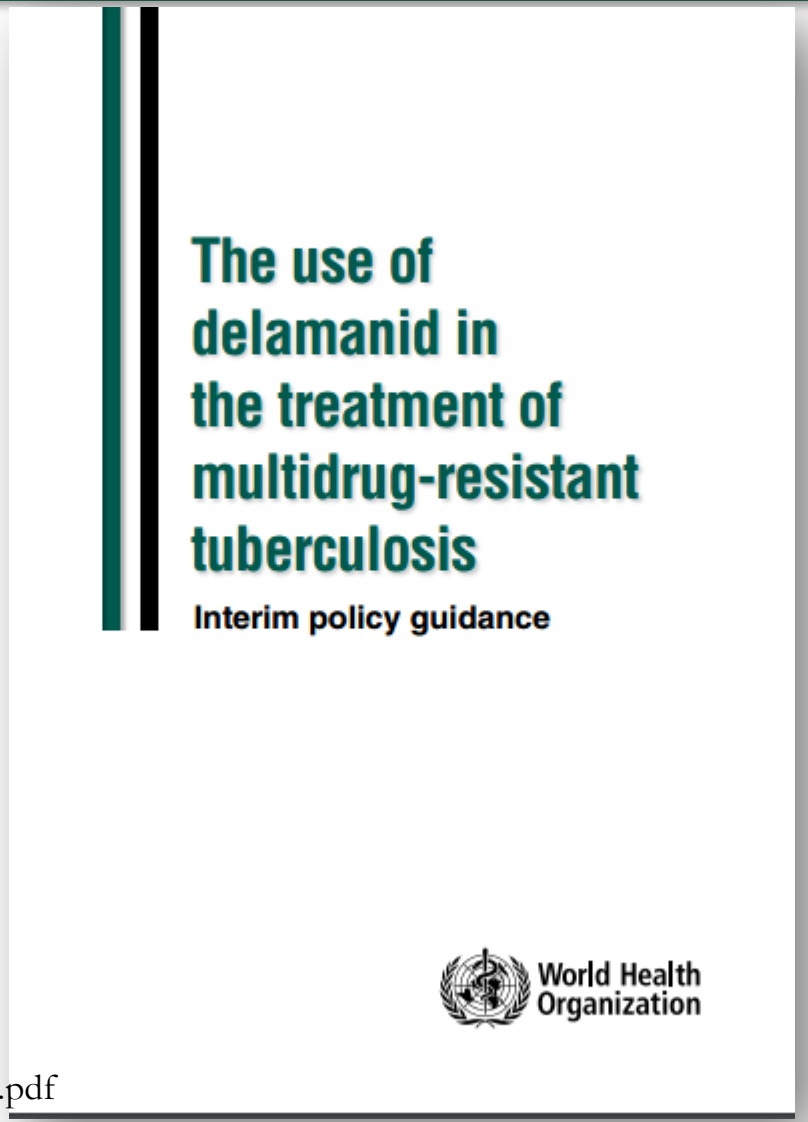
- Approved 2012
  - First new TB drug since 1970
- Diarylquinolone: inhibits ATP synthase
- First in its class so no resistance
- Common side effects nausea, joint pain, HA
  - QTc prolongation



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

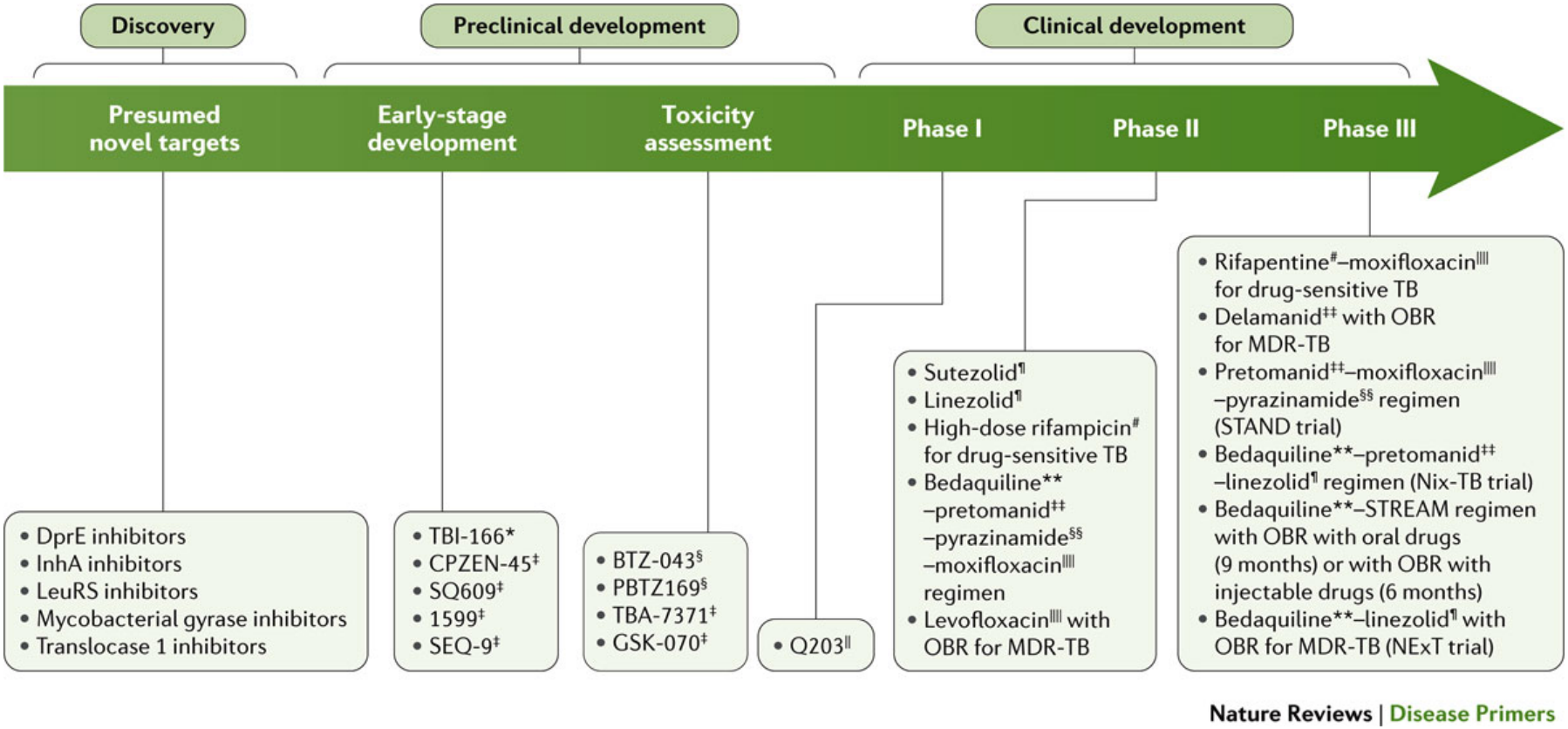
Delaminid (Otsuka)

- 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



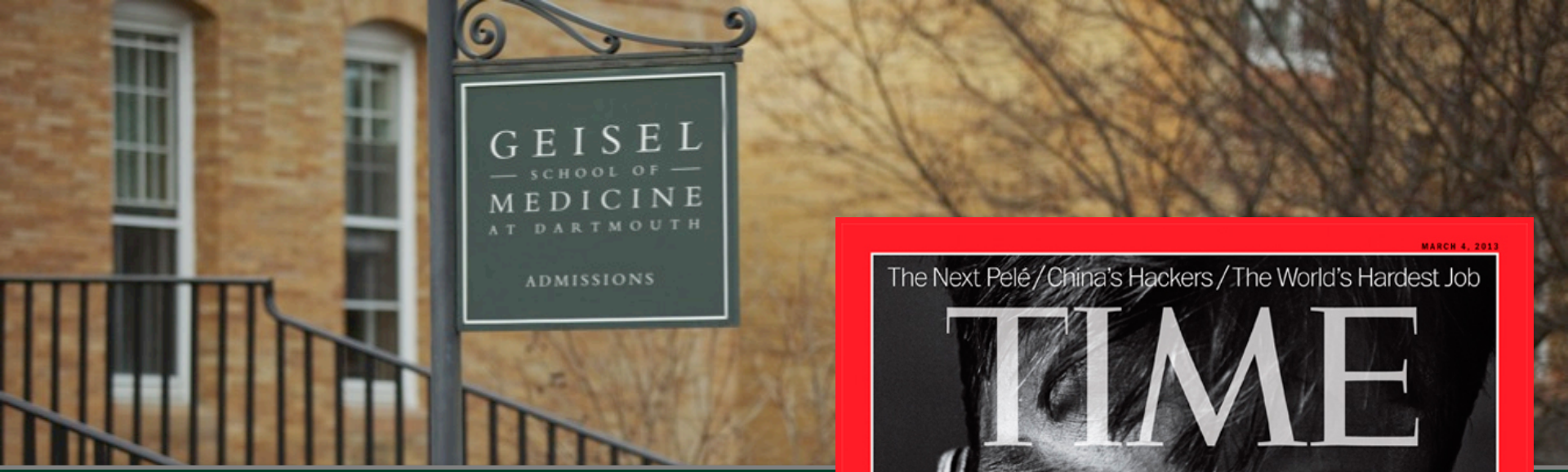
Pai, M. *et al.* (2016) Tuberculosis. *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2016.76

Q. Treatment for MDR LTBI?

1. No treatment
2. INH 9m
3. RMP 4m
4. Levofloxacin or Moxi 9m
5. Levofloxacin or Moxi + PZA 4 m
6. Fluoroquinolone + EMB
7. Delaminid
8. **Call an expert**

Conclusion

- M/XDR TB has an appropriate place on any AMR agenda
- Beyond thinking TB, we need to educate regarding when to think M/XDR
- We must be ready to assist in efficient diagnosis
- Knowledge of the dynamic changes to MDR treatment is appropriate, although consultation is available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Thank you!


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TIME
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Why drug-resistant tuberculosis threatens us all
BY KRISTA MAHR WITH PHOTOGRAPHS BY JAMES NACHTWEY
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