

MDRTBWAR  
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# TB Update

March 21, 2018

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I have no actual or potential conflict of interest in regards to this presentation.



International Union Against  
Tuberculosis and Lung Disease  
Health solutions for the poor



# FIRS Organizations

# 2018 – Big year for TB

UN meeting:  
Sept 26, 2018



# 90(90)90

**THE TUBERCULOSIS REPORT  
FOR HEADS OF STATE AND GOVERNMENTS**

GLOBAL PLAN TO END TB 2016 - 2020

**First WHO Global Ministerial Conference  
Ending TB in the Sustainable Development Era: A Multisectoral Response  
Moscow, Russian Federation, 16-17 November 2017**

**MOSCOW DECLARATION TO END TB**

**Preamble:**

**74 ministers from 125 countries  
FIRS: professional societies role**

We, the Ministers of Health and from across Governments acknowledge that despite concerted efforts, tuberculosis (TB), including its drug-resistant forms, causes more deaths than any other infectious disease worldwide<sup>a</sup> and is a serious threat to global health security.

TB kills more than five thousand children, women and men each day and leaves no country untouched.<sup>a</sup> It is one of the leading killers among people of working age which creates and reinforces a cycle of ill-health and poverty, with potential catastrophic social and economic consequences for families, communities, and countries. While recognizing the higher prevalence of TB among men, women and children are also vulnerable to the consequences of TB due to gender-

# *Why TB?*

TB is a disease  
that should not exist!  
It's curable.  
It's preventable.  
It's contagious.



# *World TB*

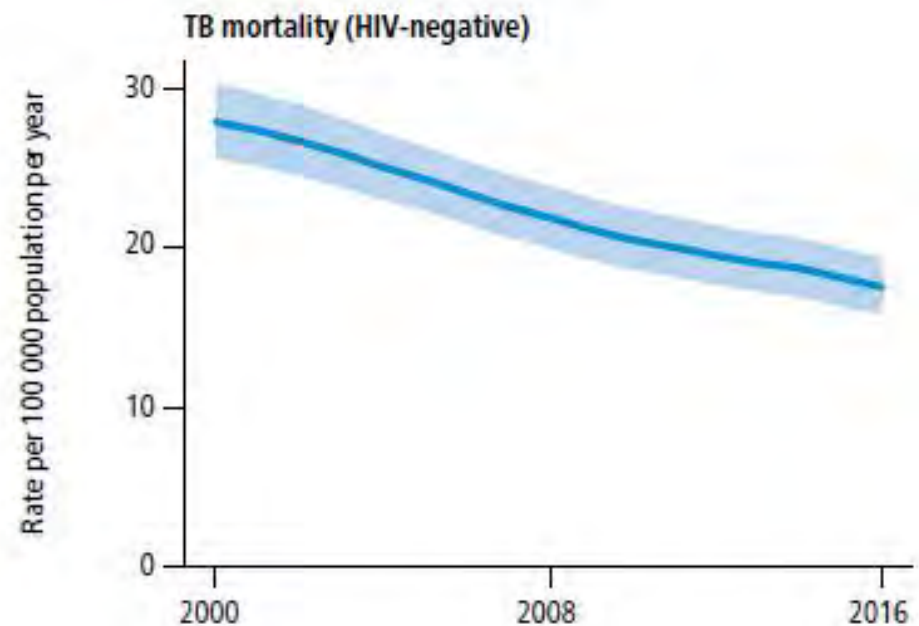
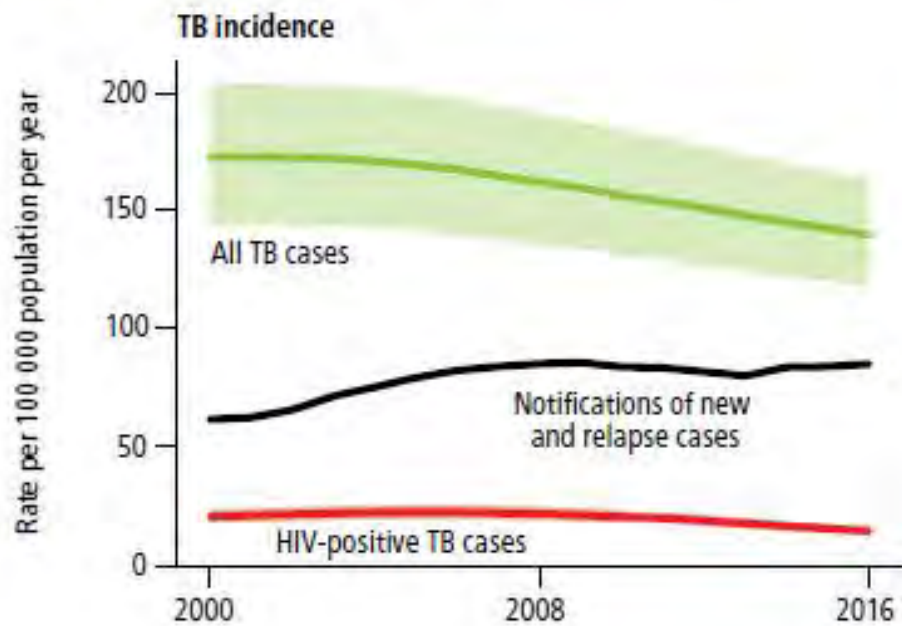
- Most fatal infectious disease in the world!
- 10.4 M new cases
- 1.8 M deaths
- Resistant TB
  - 600,000 rifampin
  - 490,000 MDRTB (HR)
  - 9% of MDRTB → XDRTB (FQL & injectable)
    - WHO Global Tuberculosis Report 2017

# *World TB*

- TB cure rate
  - Drug sensitive – 83%
  - MDR – 52%
    - (2017: new regimens ~75%)
  - XDR – 28%
    - WHO Global Tuberculosis Report 2016

# World TB trends

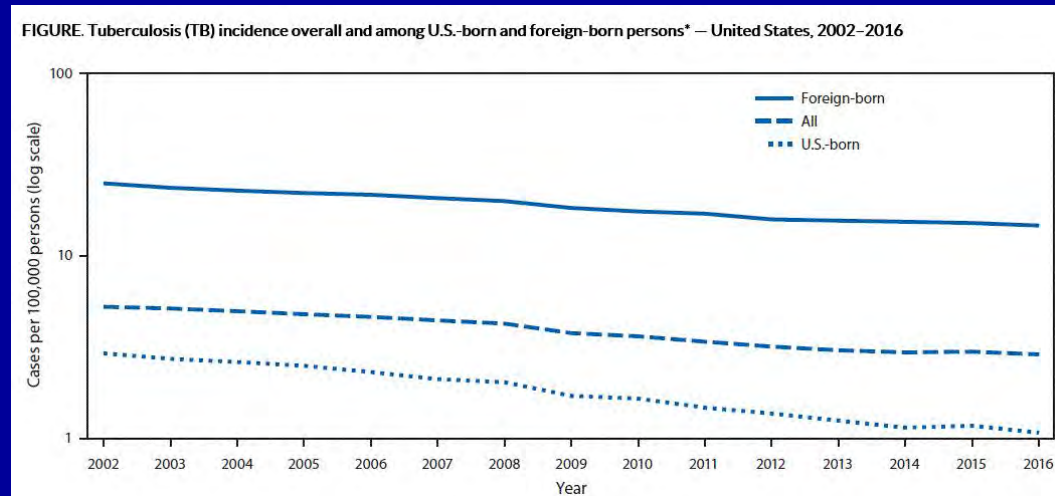
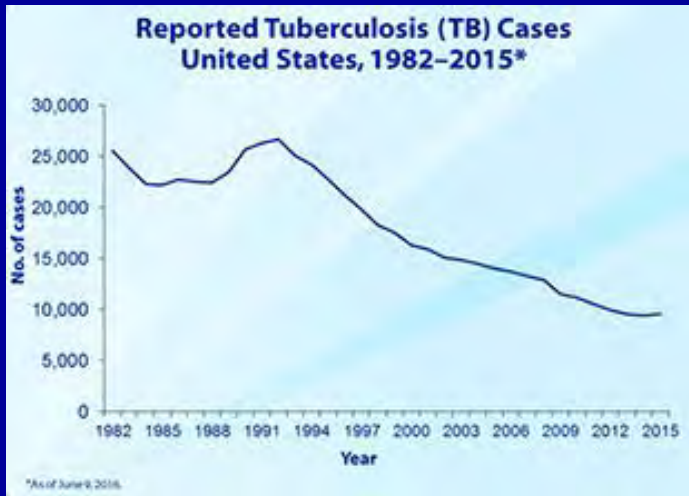
Global trends in estimated TB incidence and mortality rates, 2000–2016. Shaded areas represent uncertainty intervals.





# USA TB

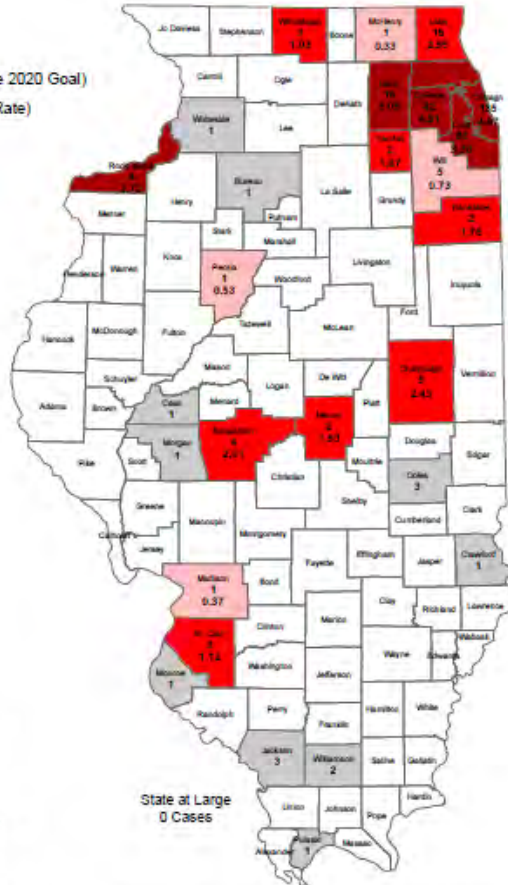
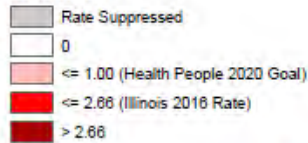
- 2016: 9287 new cases (lowest ever)
  - 2.7% decreased from 2015
- 2016: incidence  $2.9 \times 10^{-5}$
- 2015: 1.3% MDR (94 cases)
  - 1953: 84,304 cases, 19,707 deaths;  $52.6 \times 10^{-5}$



# Illinois TB

## Illinois Tuberculosis Case Rates per 100,000 Population 2016

### 2016 Rates



United States  
Total Cases: 9,287  
Rate: 2.9  
From: MMWR Vol. 66 No. 11

Illinois (including Chicago)  
Total Cases: 342  
Population: 12,873,761  
Rate: 2.66

Illinois (outside Chicago)  
Total Cases: 207  
Population: 10,156,227  
Rate: 2.04

City of Chicago  
Total Cases: 135  
Population: 2,717,534  
Rate: 4.97

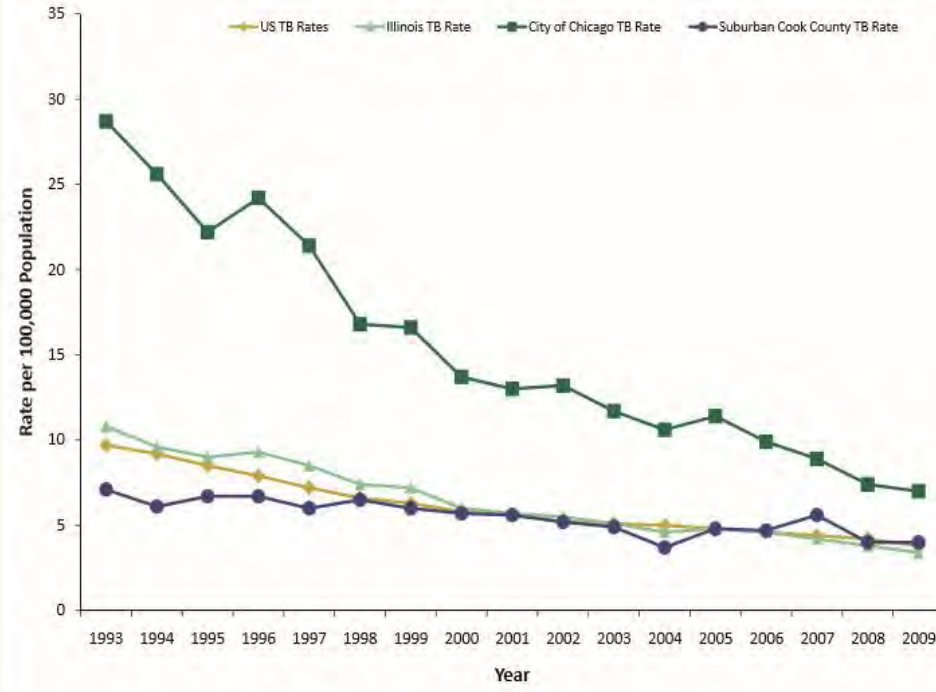
Suburban Cook County  
Total Cases: 83  
Population: 2,518,859  
Rate: 3.30

Illinois (outside Cook County)  
Total Cases: 124  
Population: 7,637,368  
Rate: 1.62

Source for population data:  
U.S. Census Bureau, 2011-2015  
American Community Survey  
5-Year Estimates.

Rates are suppressed for areas  
with a population < 100,000.

Illinois case counts as of 23 March, 2017; are still subject to change/revision



Nearly constant in this decade

2010:372; 2011:359; 2012:347; 2013:327; 2014:329; 2015:343; 2016:342

# *Epidemiology*



# *TB Epidemiology*

- 10% of TB occurs in children
  - » WHO TB Report 2017
- Smoking doubles risk
  - » Bates, et al., Arch Intern med 2007;167:335-42
- Death rates ↓ >100 fold 1900-1980
- China: halved its prevalence, reduced mortality by 80% from 1990-2010
  - » Wang et al., Lancet 2015;383:2057-64

# *TB Epidemiology*

- Average duration of infectiousness 1 year  
(based on incidence to prevalent ratio)
  - » Onozaki et al., Trop med Int Health 2015; 20: 1128-45
- 50% have no prolonged cough
- 25% have no symptoms at all
  - » Hoa et al., Bull WHO 2010; 88: 273-80
- Latent ↔ active subtle
  - Transmissible
    - » Dowdy et al., J Respir Crit Care Med 2013; 187: 545-551

# *Latent tuberculosis*



# *Latent basics*

- Definition: immune response
  - No symptoms or signs
  - Persistent bacilli
  - Adenopathy, capping, granuloma
- **“LTBI” misleading**
  - “Infection” ≠ lack of disease
- ¼ world (2 B) infected

# *All latent TB is not a like*

- Healthy long-term reactor
- Recent converter
- Reactor with risk factors
- Person going into and out of active disease



# *Dormancy basics*

- Persisters  $\equiv$  bacilli surviving with known effective drugs
  - **Noncultureable** (ordinary lab conditions)
    - » McDermott. Yale J Biol Med 1948; 30:257-291
- Dormancy  $\equiv$  bacterial state dependent on its environment
  - Predominant bacilli in latent TB

# *Dormancy*

- Stress → metabolic shift
  - 10X increase in glyoxylic acid cycle
    - » Wayne and Lin. Infect Immun 1977;37:1942-9
- dosR → regulates into dormancy
  - » Mayuri et al., FEMS Microbiol Lett 2002;211:231-7
- Resuscitation-promoting factors
  - Phospholipids
  - **Quorum sensing**
    - » Bassler and Losick. Cell 2006;125:237-246

# *Treatment of latent TB*

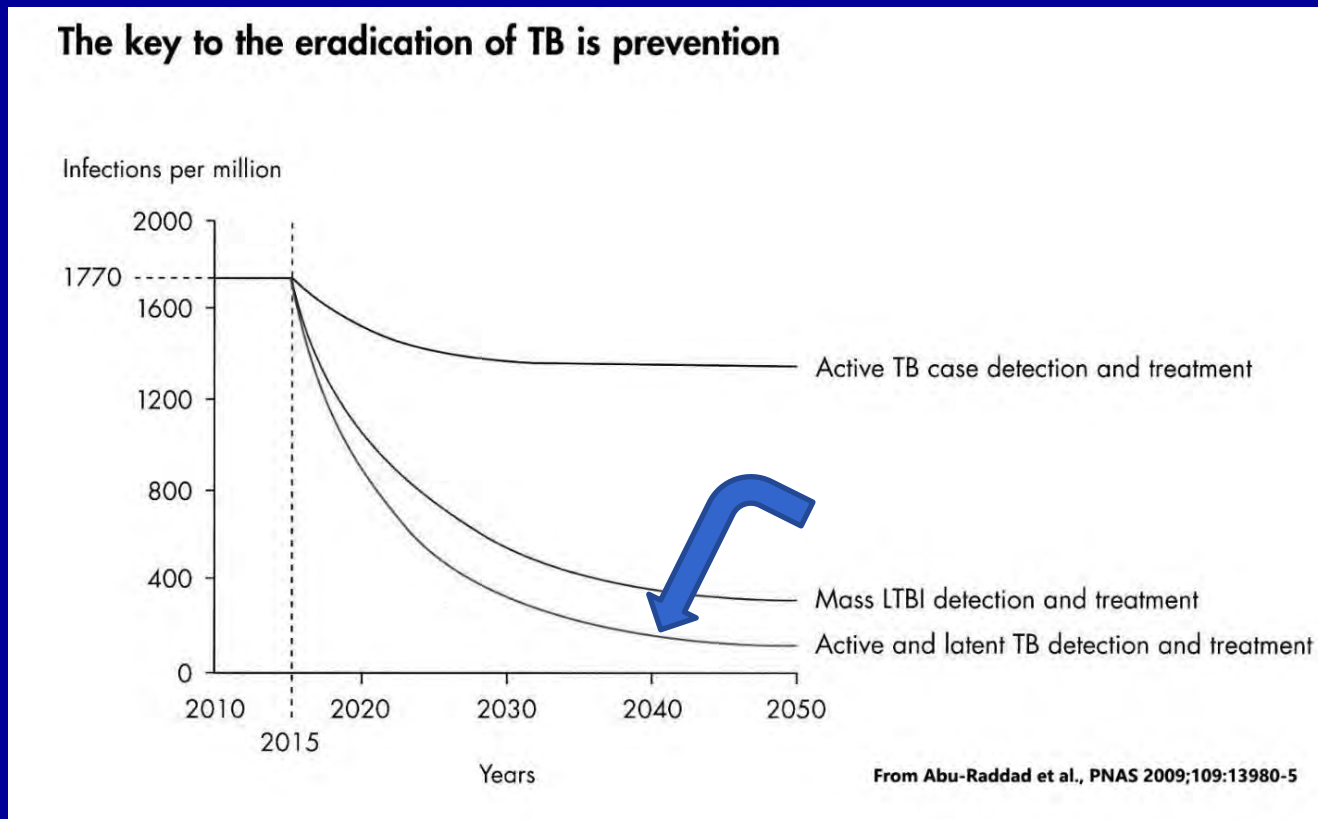


# *Decision to Rx*

- Risk-benefit considerations 50 years old
- Risk of TB vs. toxicity of INH for 12 mo
- Did not consider
  - Long-term protection
  - Careful follow-up (less chance of serious SA)
  - Shorter regimens
  - Patient time, worry
  - Public health

# *Treating latent* → ↓ *prevalence*

- Treat before spread → cost effective



# *Syphilis*

- Latent phase has similarities to TB
- Of 50 pts – only 19% progressed
  - » Eng et al., Bull WHO Org 1963;28:533-5
- 10% cardiac, 6.5% neuro, 16% late benign
  - » Clark and Danbolt. J Chronic Dis 1955;2:311-44
- All would treat–risk-benefit (penicillin)

# *Currently recommended*

- Isoniazid 9 months
- Rifampin 4 months
- Rifapentine + isoniazid weekly for 12 doses
- Not recommended RZ 2 mo (toxicity)
  - Therapy for active 2 months - adequate

# *Isoniazid*

- Success
  - Must await awakening to kill → long duration
- Long duration
  - Associated with toxicity, cost, treatment failure
    - Cost → HCW & patient's time
    - Dropout  $\propto$  treatment duration
      - Many studies



# *Why not kill dormant?*

- Pyrazinamide, quinolones, injectables, rifamycins, linezolid, clofazimine, bedaquiline, delamanid are active against dormant bacilli
- Isoniazid and ethambutol are not
  - » Wayne and Hayes. Infect Immun 1996; 64: 2062-2069
  - » Piccaro et al., Antimicro Agent Chemo 2013; 57: 1428-1433

# *Regimens against dormant*

- Rifamycins
  - Kill dormant bacilli
  - Should shorten regimens
- Daily rifampin 3-4 months effective
  - Hong Kong Chest Service. *Am Rev Resp Dis* 1992;145:36-41
- Rifapentine & INH - 12 doses weekly dose
  - As effective as 9-month daily isoniazid
  - Less toxicity (0.5%)
  - Higher completion rate (82% vs. 69%)
    - Sterling et al., *N Engl J Med* 2011;365:2155-2166

# *Treatment summary*

- Shorter and safer regimens
  - Treat all with latent TB
- Treating latent → TB elimination
- Treating helps patient *and* society

# *What is not in the conclusion*

- Mass screening → not cost effective
  - High false positives in low burden settings
    - » ATS. Am J Respir Crit Care Med 2000; 161: S221-47
- Nontargeted mass Rx → less effective
  - Without regard for infection
  - S. Africa: High reinfection
    - » Churchyard et al., N Engl J Med 2014; 370: 301-10
- PPD negative → no benefit
- Infrastructure needed to ensure success
  - Well-functioning clinic, education, access, follow-up

# *Drug resistance*



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# MDR-TB map

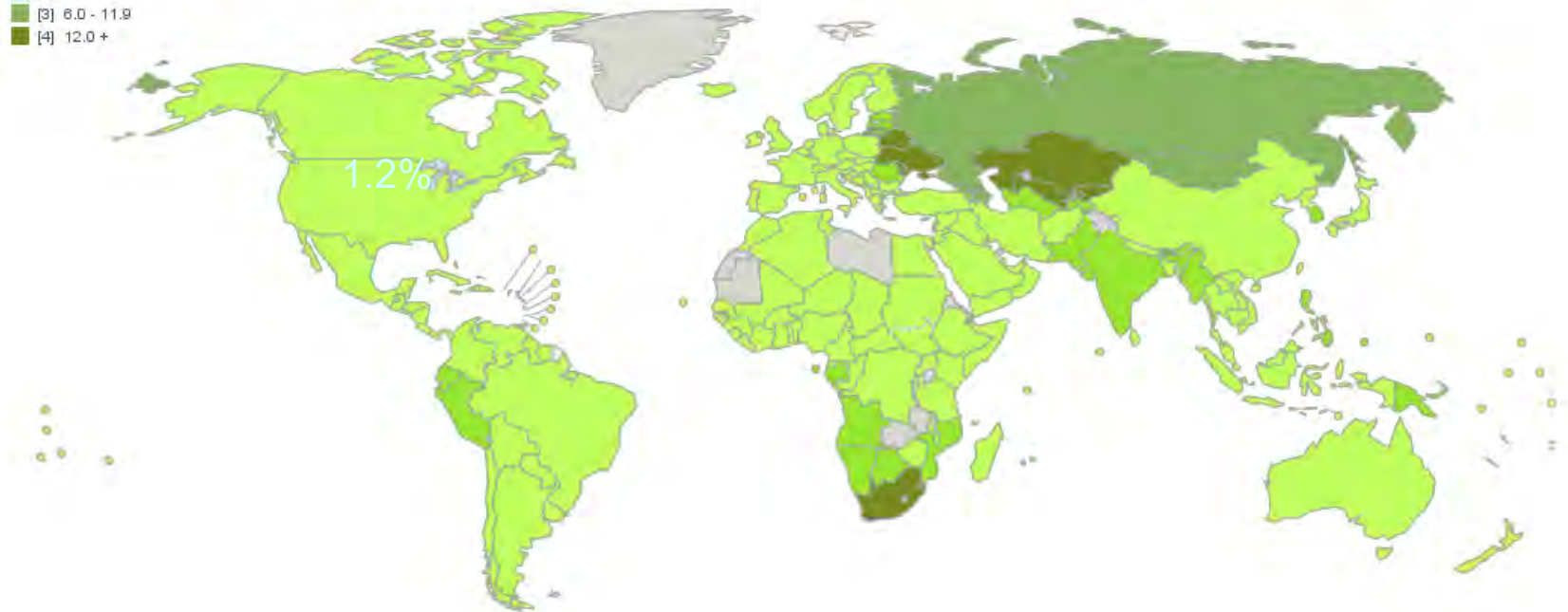
## Diagnosis and notification of multidrug-resistant TB

Notified MDR-TB cases (number per 100 000 population) ▾



Notified MDR-TB cases (number per 100 000 population), 2014

- [0] No Data
- [1] 0.0 - 0.9
- [2] 1.0 - 5.9
- [3] 6.0 - 11.9
- [4] 12.0 +



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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# *Resistance types*

- Genotypic (DNA tests)
  - Resistance genes known for most drugs
- Phenotypic (culture-based)
  - Epigenetic or protein modifications
  - E.g. treatment stress **induces efflux pumps**

# *Culture vs. genetic resistance*

- Genotype may vary with culture
- Culture: slow, biohazardous, requires lab infrastructure and training and may soon be more expensive
  - E.g. pyrazinamide
- Future will be gene based



# *10 commandments of TB Rx*

- 1. Never add a single drug to a failing regimen.
- 2. Never add a single drug to a failing regimen.
- 3. Never add a single drug to a failing regimen.
- 4. Never add a single drug to a failing regimen.
- 5. Never add a single drug to a failing regimen.
- 6. Never add a single drug to a failing regimen.
- 7. Never add a single drug to a failing regimen.
- 8. Never add a single drug to a failing regimen.
- 9. Never add a single drug to a failing regimen.
- 10. Never add a single drug to a failing regimen.



**Isoniazid monoresistance**

# *Isoniazid*

- Prodrug activated by catalase-peroxidase
  - **Only affects active organisms**
- 9% of world isolates resistant
  - » WHO Global Tuberculosis Report 2014
- Mutations
  - katG (50-95%) (high, MIC 0.2-5 µg/mL) (lose virulence?)
  - inhA (8-43%) (low, MIC=0.1-0.2 µg/mL)
- Others
  - katG promoter, inhA promoter, fabG1, embB, kasA, ahpC (+ promoter), oxyR, iniA, iniB, iniC, ndh
    - » Zhang and Yew. Int J Tuberc Lung Dis 2015; 19: 1276-89

# *Monoresistance isoniazid*

- BMRC trials (aggregate) small effect vs. RMP
  - » Mitchison & Nunn. Am Rev Respir Dis 1986;133:423-30
- INH resist vs. pansensitive → ↑ failure (10.9) and relapse (1.8)
  - » Menzies et al., PLOS Med 2009;6:e1000146
- katG mixed (or worse) outcome than inhA
  - » Stagg et al., Int J Tuberc Lung Dis 2017;21:129-39
- Replacing INH with FLQ – no difference
  - » Merle et al. N Engl J Med 2014;371:1588-98

# *Monoresistance isoniazid treatment*

- WHO

- No DST: High background: HRZE<sub>2</sub>RZE<sub>4</sub>

- DST available: RZE<sub>±</sub>F<sub>6-9</sub>

- WHO, 2014.

- [http://www.who.int/tb/publications/pmdt\\_compagnionhandbook/en/](http://www.who.int/tb/publications/pmdt_compagnionhandbook/en/)

- R<sub>p</sub>ZEM<sub>4</sub> + R<sub>p</sub>M<sub>2</sub> = standard RHZE

- Jindani et al., N Engl J Med 2014; 371: 1599-608

- For me: R<sub>p</sub>F<sub>±</sub>ZE<sub>6-9</sub>

# *High-dose isoniazid*

- High-dose  $\equiv$  16-20 mg/kg/d
- $\uparrow$  success (Rx-failure, relapse, death combined)
  - » Katiyar et al. Int J Tuberc Lung Dis 2008; 12: 139-45
- Not for *katG* mutations

# Resistance other drugs



# Rifamyicins





# *Rifamycins*

- Rifampin, rifapentine, rifabutin
- Similar sensitivity spectrum (5-20% difference)
  - » Jamieson et al., J Clin Microbiol 2014;52:2157-62
- Different safety profile: Side effects to one, can switch
- Low blood levels
  - Fewer pts reach  $C_{max}$  for RMP compared with other drugs
    - ↓RMP pts sicker (↑APACHE)
      - » Koegelenberg et al., S. Afr Med J 2013;103:394-8
- Autoinducer → ↓levels after starting
  - » Prasad and Singh, Int J Tuberc Lung Dis 2012;16:232-4
- High dose RMP >10 mg/kg or >600 mg/d
  - 14 trials (not all high quality) → suggest 900 mg → ↑culture conversion
    - » Steingart et al., Int J Tuberc Lung Dis 2011;15:305-16

# *Alternate therapy*

- Intolerance – switch rifamycins
- Check RBT sensitivity
- HEFZ<sub>2</sub> – **12**-18 mo
- HEZ – 18 mo
- HSZ – 9 mo
- FLQ do not replace rifamycins

# *Case*

- 1/16: 82 y. o. Indian ♀ DM dyspnea cough
  - CXR: mass, hilar adenopathy
  - PET/CT, bronchoscopy, EBUS TBNA
  - No CA;
- 4/16: chest pain, “URI” sx
  - CT chest, abd, pelvis, mass cavitated
    - 3 different hospital evaluation
- 10/17: hip fracture: cavitory mass larger
- 11/17: QFT positive

# Case

- 11/21 admitted: ↑T, ↑RR, ΔMS, AKI
- GeneXpert: MDRTB
  - PZA, EMB, LIN, AMK, LFX
  - ARF: AMK stopped, PTL 85K, Hb 9 →?LIN
    - Consider adding BDQ; SM added without side-effect
- WGS: rpoB mutation: Leu533Pro
  - Sensitive to RBT (despite DST)
  - INH (katG mutation) = complete resistance
- DST resistant to SM

# *Case outcome*

- Renal function returned to normal
  - AMK for SM
- Platelets stabilized on less LIN
- RBT added
- Sx gone, sput clear, cavity less
- Little recovery of CNS, cardiac status



**Pyrazinamide**

# *Pyrazinamide*

- Most effect against dormant (persistors)
  - Prodrug: PZA → Pyrazinoic acid (POA)
  - POA enters cell: pH-dependent passive diffusion
  - Must be pumped out (energy-dependent)
  - More toxic to bacilli in low energy state
- Mutations: *pncA* (72-99%); *RpsA* (low resist)
  - » Zhang and Yew. *Int J Tuberc Lung Dis* 2015;19:1276-89
- PZA-monoresistant → worse outcome
  - » Yee et al., *Int J Tuberc Lung Dis* 2012;16:604-9
- Rx 9 mo HR

# Quinolones





# *Quinolones*

- LFX, MFX, GFX (removed from market)
  - CFX no role
- Mutations: *gyrA*, *gyrB*
- Best role: replace isoniazid, not RMP
- Side effects
  - LFX 750 mg (tendon, joint)
  - MFX 400 mg (arrhythmias)
  - All prolong QT

**TABLE 4. ANY ADVERSE DRUG REACTIONS AMONG PARTICIPANTS WITH MULTIDRUG-RESISTANT TUBERCULOSIS**

	Levofloxacin Group (n = 78)	Moxifloxacin Group (n = 77)	P Value
Gastrointestinal trouble	30 (38.5%)	29 (37.7%)	0.92*
Musculoskeletal abnormalities	28 (35.9%)	11 (14.3%)	0.002*
Neurologic abnormalities	8 (10.3%)	11 (14.3%)	0.44*
Dermatologic abnormalities	9 (11.5%)	7 (9.1%)	0.62*
Others <sup>†</sup>	7 (8.9%)	9 (11.7%)	0.58*
Hepatotoxicity	8 (10.3%)	7 (9.1%)	0.81*
Ototoxicity	5 (6.4%)	4 (5.2%)	1.00 <sup>‡</sup>
Allergic reaction	1 (1.3%)	6 (7.8%)	0.06 <sup>‡</sup>
Cardiovascular abnormalities <sup>§</sup>	3 (3.8%)	2 (2.6%)	1.00 <sup>‡</sup>
Eye toxicity	1 (1.3%)	2 (2.6%)	0.62 <sup>‡</sup>
Endocrinologic abnormalities	0	1 (1.3%)	0.50 <sup>‡</sup>
Hematologic abnormalities	0	0	—
Any adverse drug reactions	54 (69.2%)	46 (59.7%)	0.22 <sup>‡</sup>

\* P value from chi-square test.

<sup>†</sup> Others include general weakness, fatigue, sweating, and chills.

<sup>‡</sup> P value from Fisher's exact test.

<sup>§</sup> QT prolongation was not reported in both groups.

Grade 3 or 4 toxicity	7.7%	5.2%	NS
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**Linezolid**



# *Linezolid*

- Oxazolidinones –X tRNA
- Side effects in 59% (prolonged therapy)
  - 68% of these - major
  - Anemia 38%, neuropathy 47%, GI 17%; optic neuritis 13%, ↓platelets 12%
  - Proportional to duration
  - More if dose > 600 mg/d
    - Sotgiu et al., Eur Resp J 2012; 40: 1430-42
- New oxazolidinones: sutezolid, posizolid, torezolid, radezolid

# Bedaquiline



# *Bedaquiline*

- Diarylquinoline –X ATPase synthesis
- No cross resistance
- EBA (400 mg)  $\approx$  INH & RMP after 5 days
  - Rustomjee et al., Antimicrob Agents Chemother 2008; 52: 2831-5
- ↓ Conversion time, rate, & cure
  - Diacon et al., N Engl J Med 2014; 371: 723-32
- XDR: with KAN, OFX, EIO, PZA, CYC
- Monitor liver, ECG
- \$6000 per month

# Diagnostics



# *IGRA Sources of variability*

- Around cut point
  - 0.25-0.34 → 26% of conversions
  - 0.35-0.80 → 18% of reversions
- Preincubation delay
  - 6 h → 50%; 12 h → 67% reversions
  - ↑ Mito-nil (Herrera et al. J Clin Microb 2010;48:2672-6)
- Blood volume (for QFT)
  - For each 0.2 mL ↑ volume → ↓ 0.11 IU
- Other: lots, shaking, labs, storage temp
  - » Tagmouti et al. Annals ATS 2014 (in press)



GeneXpert

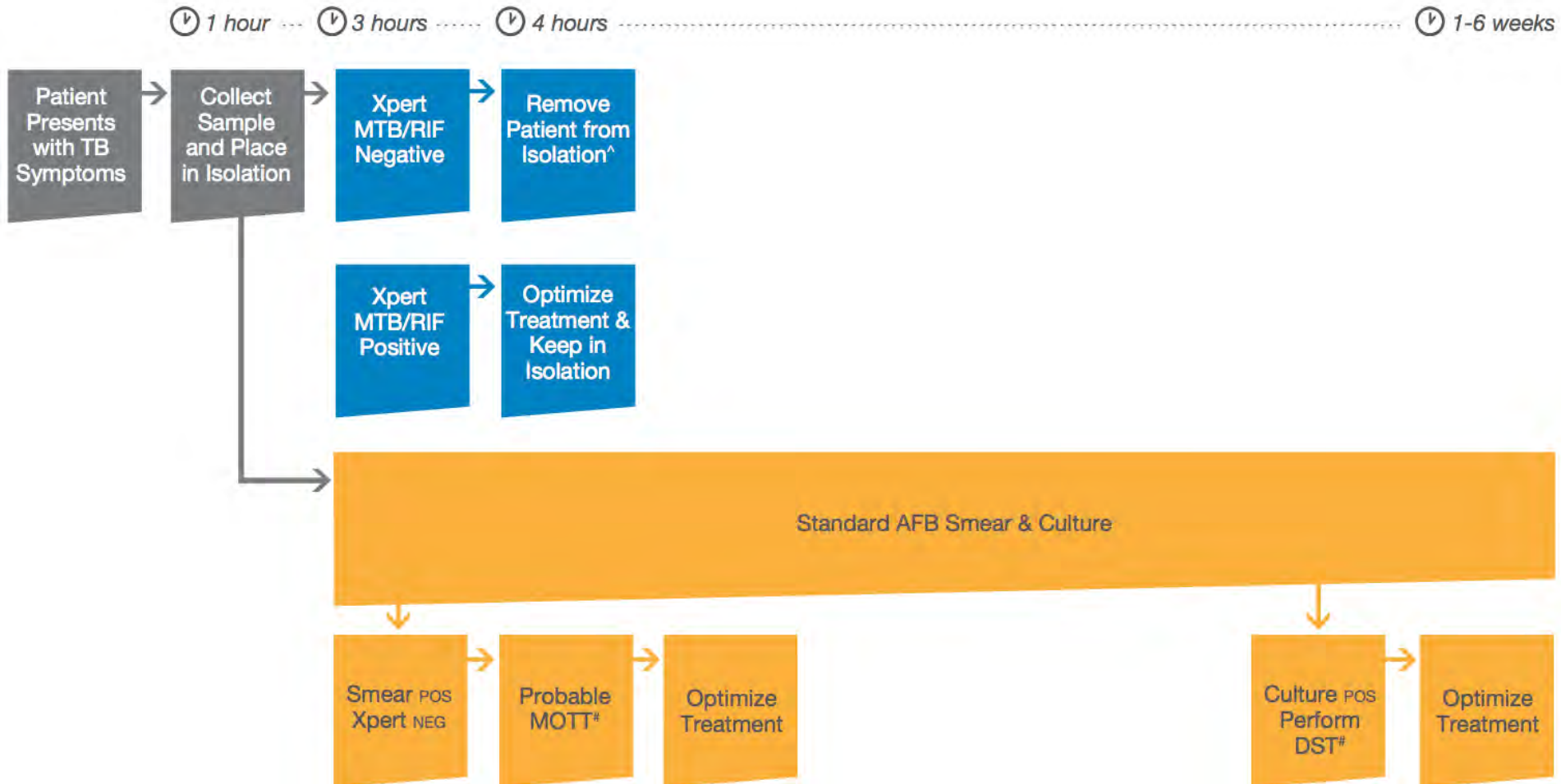


# *GeneXpert*

- Automated DNA probe for rpoB gene
- Point of care, low resource setting
- Better than smear
- Detect RFM resistance
- Sputum, other sites



# Isolation removal



# New diagnostics



Smear misses  $\frac{1}{2}$  of TB cases

# *Quantiferon Gold Plus*<sup>®</sup>

- 4 tubes
  - Nil
  - Mitogen
  - CD4 (ESAT-6, CFP-10, long peptides)
    - Stimulates CD4 lymphocytes
  - CD8 (short peptides antigens)
    - Stimulates CD4 and CD8 lymphocytes
    - CD8 lymphocytes  $\propto$  active disease

# Quantiferon Plus<sup>®</sup> results

QFT-Plus  
Positive

- ***M. tuberculosis* infection is likely**
- Nil  $\leq 8.0$ ; and
- TB1 and/or TB2 minus Nil  $\geq 0.35$  and  $\geq 25\%$  of Nil

QFT-Plus  
Negative

- ***M. tuberculosis* infection is NOT likely**
- Nil  $\leq 8.0$ , Mitogen minus Nil  $\geq 0.5$ ; and
- TB1 and TB2 minus Nil  $< 0.35$  or  $\geq 0.35$  and  $< 25\%$  of Nil

QFT-Plus  
Indeterminate

- **Likelihood of *M. tuberculosis* infection cannot be determined**
- Nil  $> 8.0$
- Nil  $\leq 8.0$  and TB1 and TB2  $< 0.35$  or  $\geq 0.35$  and  $< 25\%$  of Nil and Mitogen minus Nil  $< 0.5$

# *Diagnostic innovations*

- Alere's lipoarabinomannan (LAM) test
  - POC urine dipstick
  - Detects active TB
  - ↑ yield with ↓CD4
    - » Peter et al., Lancet 2016; 19:1187-97
- GeneXpert Omni (battery)
- GeneXpert Ultra
  - More sens (post-PCR melt curve analysis)
  - Approaches liquid media
  - Less specific
    - » <http://apps.who.int/iris/handle/10665/254792>

# *New GeneXpert*

- 25 mutations in 6 genes and promoter regions account for most FLX, INH, amino resistance
- Combined in GeneXpert cartridge
- Sensitivity 92.7-98.1
- Specificity 99.6%
- Expected out in end of 2019

» Xie et al., N Engl J Med 2017;377:1043-54



Thank you.



# መስኮት በመክፈት ቲቢን እንከላከል




# Stop TB



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ቅዳሜ መጋቢት 14 2005

Anti TB Walk Campaign

4km / Saturday 23 March 2013

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Registration: 1. St. Paul Hospital 2. St. Peter 's TB Specialized Hospital  
3. Ministry of Health Public Relations Division



የቅዱስ ጳውሎስ  
ቲቢ ስፔሻላይዥድ ሆስፒታል



IOM • OIM