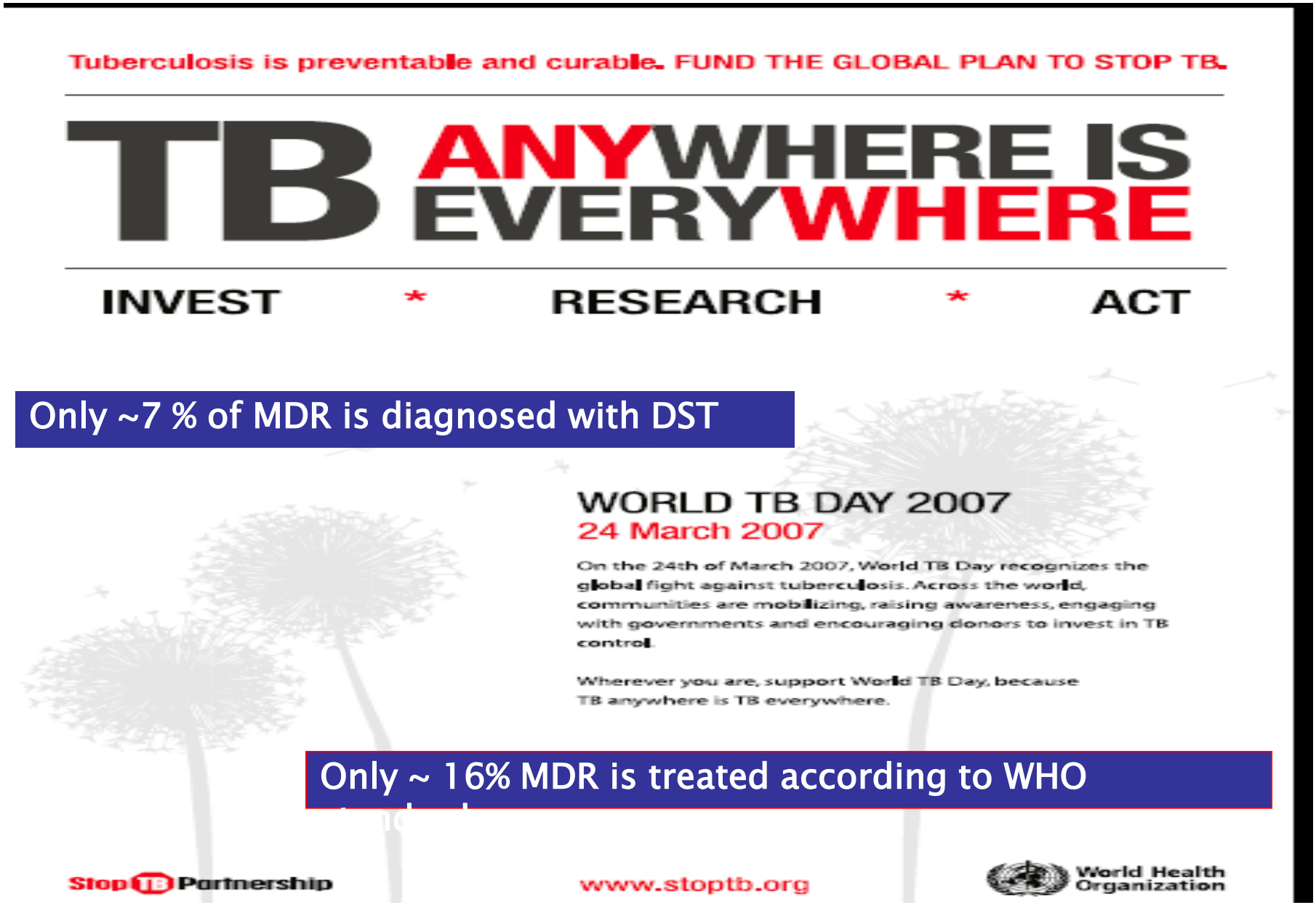
XDR TB:
The Laboratory's Dilemma
vs
The Clinician's Dilemma

Barbara J. Seaworth, MD, FIDSA, FACP, Heartland National TB Center, San Antonio, TX

Kenneth Jost, Jr., M(ASCP) Laboratory Services Section, Texas Department of State Health Services



Only ~7 % of MDR is diagnosed with DST

Only ~ 16% MDR is treated according to WHO

Dangerous TB Patient Detained on U.S. Mexico Border

In medical isolation in South Texas, 100 miles or so from Mexico's border, is a man who embodies one of U.S. health officials' greatest worries: He is the first person to cross and be held in detention while infected with one of the most severe types of drug-resistant tuberculosis known today. His three-month odyssey through 13 countries—from his homeland of Nepal through South Asia, Brazil, Mexico, and finally into Texas—shows the way in which dangerous new strains of the disease can migrate across the world unchecked

WSJ March 1, 2013

Potential Global Exposure

Asia

1. India
2. Dubai
3. Brazil
4. Bolivia
5. Peru
6. Ecuador
7. Columbia
8. Panama
9. Costa Rica
10. Nicaragua
11. El Salvador
12. Guatemala
13. Mexico

United States

Photo and map courtesy of Dr. Richard Wing, TB medical director, DSHS, Region 11

Multiple Exposures Over Hundreds of Miles

- Airplane flight > 12 hours
- Traveled by car across several countries in South and Central America
- Detained for > 1 week in a cell in Panama
- 48 hours in a safe house with > 30 people (2 rooms, no windows) in Reynosa
- 3 Days in Border Patrol Custody in a crowded cell

Case Study

- 24 year old Asian male - ICE custody 12/1/2012
  - Abnormal CXR bilateral disease consistent with TB
  - TST + 13mm

- Placed in isolation within three hours of arrival

- INH, rifampin, ethambutol and PZA treatment initiated 12/5/2012

- Denies history of prior TB or exposure to persons with TB or chronic cough

Initial Assessment

- Patient noted cough and back pain
  - Several episodes of blood streaked sputum
- Wheezing on exam
- No other medical problems
  - Laboratory assessment normal
  - HIV negative - Hepatitis panel negative

Sputum Specimen Results
December 2012

12/1	Sputum Collected
12/3	Received specimen
12/4	4+ smear positive
12/12	Mtb culture positive
12/17	MGIT DST

Initial Drug Susceptibility Tests

Drug	Lab A MGIT	Austin GeneXpert	CDC MDDR	Lab A 7H10	Austin 7H10	CDC 7H10
INH High Conc.	R		unknown mutation	R	R	R
RMP	R	R (Probe E)	R (Ser531Leu)	R	R	R
EMB	R/S		Probably R (Met306Ile)	S	R	R
PZA	R		unknown mutation		R	R
OFL			R (Asp94Ala)	R	R	R
KAN			R (A1401G)	R	R	R
AMK						R
CAP				S	R	R
RBT				R	R	R
ETH				R	R	R

Days post collection	16	19	25	30	47	55

Additional Drug Susceptibility Tests
Some Good News

- Linezolid S Day 36
- Cycloserine S Day 53
- PAS S Day 53
- Clofazimine S Day 58

PAS Drug Susceptibility Test Results

- Day 53, Lab 1, 7H11 (8 mcg/ml), Susceptible (0%R)
- Day 55, Lab 2, 7H10 (2mcg/ml), Resistant (100%R)

WHO Drug Susceptibility Test Methodology and Critical Concentrations

Table 2. Current status of DST methodology and critical concentrations for second-line DST

Drug group[a]	Drug	DST category	DST method available	DST critical concentrations (μg/ml)				
				Löwenstein-Jensen[b]	Middlebrook 7H10[b]	Middlebrook 7H11[b]	BACTEC460	MGIT960
Group 1 First-line oral anti-TB agents	Isoniazid	I	Solid, liquid	0.2	0.2	0.2	0.1	0.1
	Rifampicin	I	Solid, liquid	40.0	1.0	1.0	2.0	1.0
	Ethambutol	II	Solid, liquid	2.0	5.0	7.5	2.5	5.0
	Pyrazinamide	II	Liquid	-	-	-	100.0	100.0
Group 2 Injectable anti-TB agents	Streptomycin	II	Solid, liquid	4.0	2.0	2.0	2.0	1.0
	Kanamycin	II	Solid, liquid	30.0	5.0	6.0	4.0	-
	Amikacin	II	Liquid	-			1.0	1.0
	Capreomycin	II	Solid, liquid	40.0	10.0	10.0	1.25	2.5
	Viomycin	V	None	-	-	-	-	-
Group 3 Fluoroquinolones	Ciprofloxacin[d]	III	Solid, liquid	2.0	2.0	2.0	2.0	1.0
	Ofloxacin	III	Solid, liquid	2.0	2.0	2.0	2.0	2.0
	Levofloxacin	IV	Solid, liquid	-	2.0	-	-	2.0
	Moxifloxacin	IV	Liquid	-	-	-	0.5	0.25
	Gatifloxacin	IV	Solid	-	1.0	-	-	-
Group 4[c] Oral bacteriostatic second-line anti-TB agents	Ethionamide	IV	Solid, liquid	40.0	5.0	10.0	2.5	5.0
	Prothionamide	IV	Solid, liquid	40.0	-	-	1.25	2.5
	Cycloserine	IV	Solid	40.0	-	-	-	-
	Terizidone	IV	None	-	-	-	-	-
	P-aminosalicylic acid	IV	Solid, liquid	1.0	2.0	8.0	2.0	-
	Thioacetazone	V	None	-	-	-	-	-
Group 5[c] Antituberculosis agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine	V	Liquid	-	-	-	4.0	-
	Amoxicillin/clavulanate	V	None	-	-	-	-	-
	Clarithromycin	V	None	-	-	-	-	-
	Linezolid	V	Liquid	-	-	-	1.0	1.0

[a] WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* (*5*).
[b] Indirect proportion method recommended. Other solid media methods (resistance ratio, absolute concentration) have not been adequately validated for second-line drugs.
[c] Routine DST for group 4 and 5 drugs is not recommended.
[d] Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB (*5*).
[d] Gatifloxacin only to be used in exceptional circumstances (*5*).

PAS Agar MIC Follow-up Test Results

PAS (mcg/ml)	% Resistance	
	7H10	7H11
2	50%	100%
4	25%	50%
8	3%	3%

- **Categorical equivalence**
- **But are equivalent critical concentrations actually equivalent?**

Moxifloxacin MIC Distribution for Isolates with gyrA GAC>GCC; Asp94Ala

Mox MIC (mcg/ml)	# of isolates:		
	Study 1 MGIT	Study 2 7H11	Study 3 7H10
0.5	1		1
1	4	4	7
2	1	3	1
4			2
8			1

Asp94Ala associated with moderate FQ resistance

Study 1 Lin G, Desmond E, Schecter G, Jost K, Ortiz, E. 2010 ASM General Meeting
Study 2 Bottger et al. Clin Microbiol Infect 2011, 17: 1128-34
Study 3 CDC unpublished data

Fluoroquinolone MICs

Lab	Method	Ofloxacin		Levofloxacin		Moxifloxacin	
		MIC	Interp.	MIC	Interp.	MIC	Interp.
A	Sensititre	8				4.0	
B	BACTEC 460	4	MS	2.0	MS	1.0	S *
C	MIGT 960					1.0	**
D	7H10 AP					4.0	
D	7H10 AP (repeat)			2.0		2.0	
D	Sensititre	8				4.0	

* Subsequent patient isolate moxifloxacin MIC = 1.0 reported as Resistant

** No MIC interpretation but MGIT critical conc. 0.25mcg/ml reported as Resistant

Best Approach?

- 12/18/2012 laboratory reports resistance to INH and rifampin
  - Treatment held
- CXR (#2) 12/18/2012
  - "Increasing bilateral densities"
- CXR (#3) 12/28/2012
  - Increasing opacities compared to 12/18"

Do No Harm

When Should I Start Empiric Treatment for MDR TB?

- If patient is stable and they can be separated from high risk contacts in the home, it is best to wait until molecular tests and/or 2nd line susceptibility tests available.
  - Avoid surprises
  - Avoid amplification of drug resistance

- If patient is unstable, start treatment while waiting for molecular and standard test results. Most experts would start with 6 or more drugs and then withdraw extra drugs later

When Can We Start Therapy?

WHO and CDC Guidelines Recommend at least 4 drugs to which isolate is likely to be susceptible

Susceptibility Studies

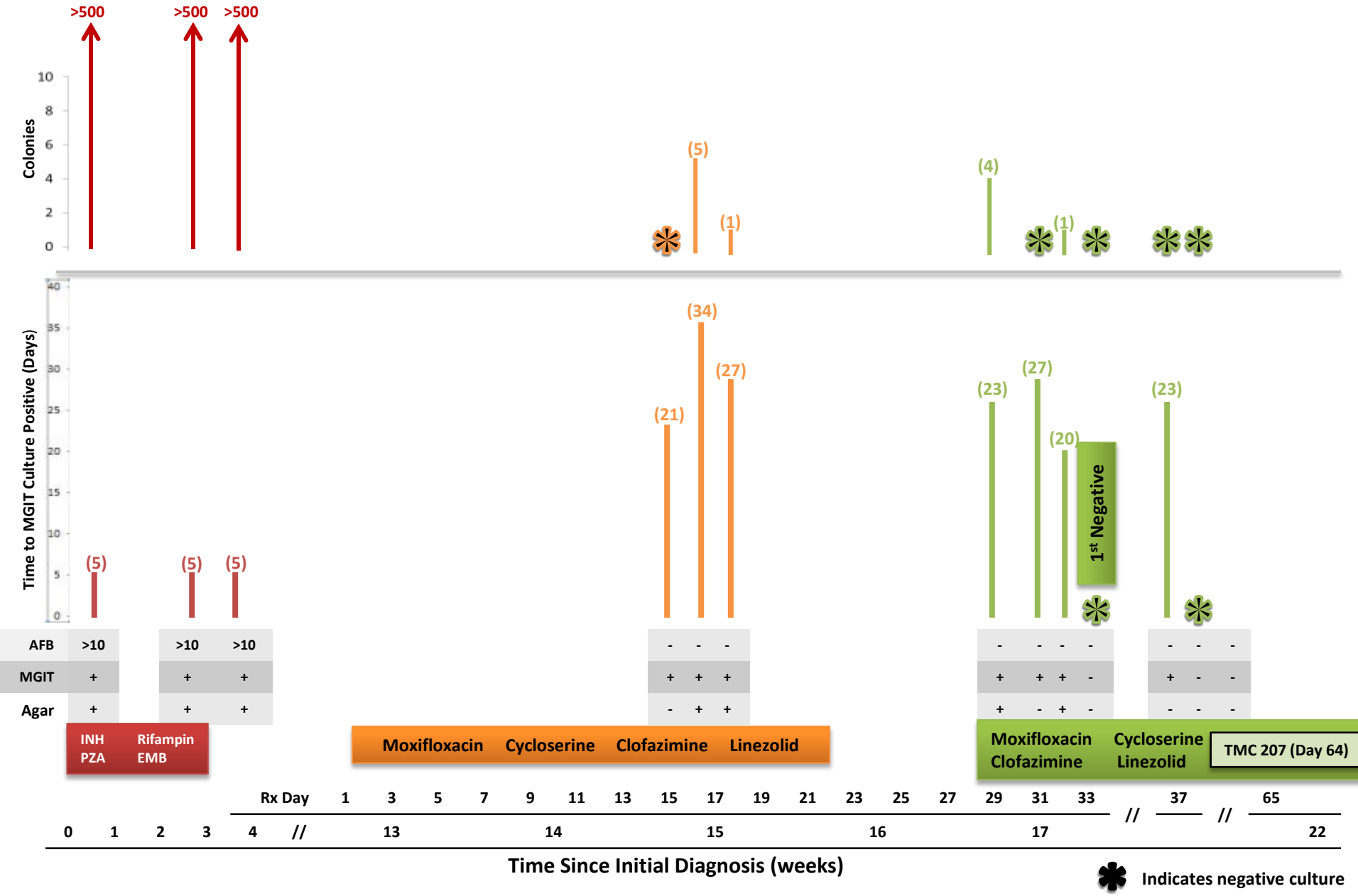
- **Susceptible**
  - Linezolid ≤ 4.0 mcg/ml
  - Cycloserine
  - Clofazimine < 0.06 mcg/ml
  - Moxifloxacin ≤1.0 mcg/ml

4 drugs Does Moxi Count ?

Treatment Course

- **Treatment started 2/22/2014 with:**
  - **Moxifloxacin**
  - **Linezolid**
  - **Cycloserine**
  - **Clofazimine**
  - **(Vitamin B 6)**
- **TMC207 anticipated within 2 weeks**
- **Back pain and hemoptysis resolve; Cough better**

Bacteriological Response to Treatment



Environmental Assessments at Border Patrol Stations

- Cell capacities between 45–100 detainees
- 0–3 air changes per hour (ACH) in cells
- 6 –9 ACH in isolation rooms
  - ≥12 ACH is recommended for buildings constructed after 2001*
- Pressure differential meters not functioning properly in one station
  - *CDC. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare settings, 2005. MMWR 2005(54)R-17:1–

Conclusions

- **Did transmission occur?**
  - No secondary TB cases have been identified
  - No known test conversions among BP or ICE staff
  - Detainee TST conversions may not indicate recent transmission
- **Only one other case with matching genotype in a person born in the same country as the index patient**
- **Collaboration among all partners is critical to the success of multi-jurisdictional TB contact investigations**

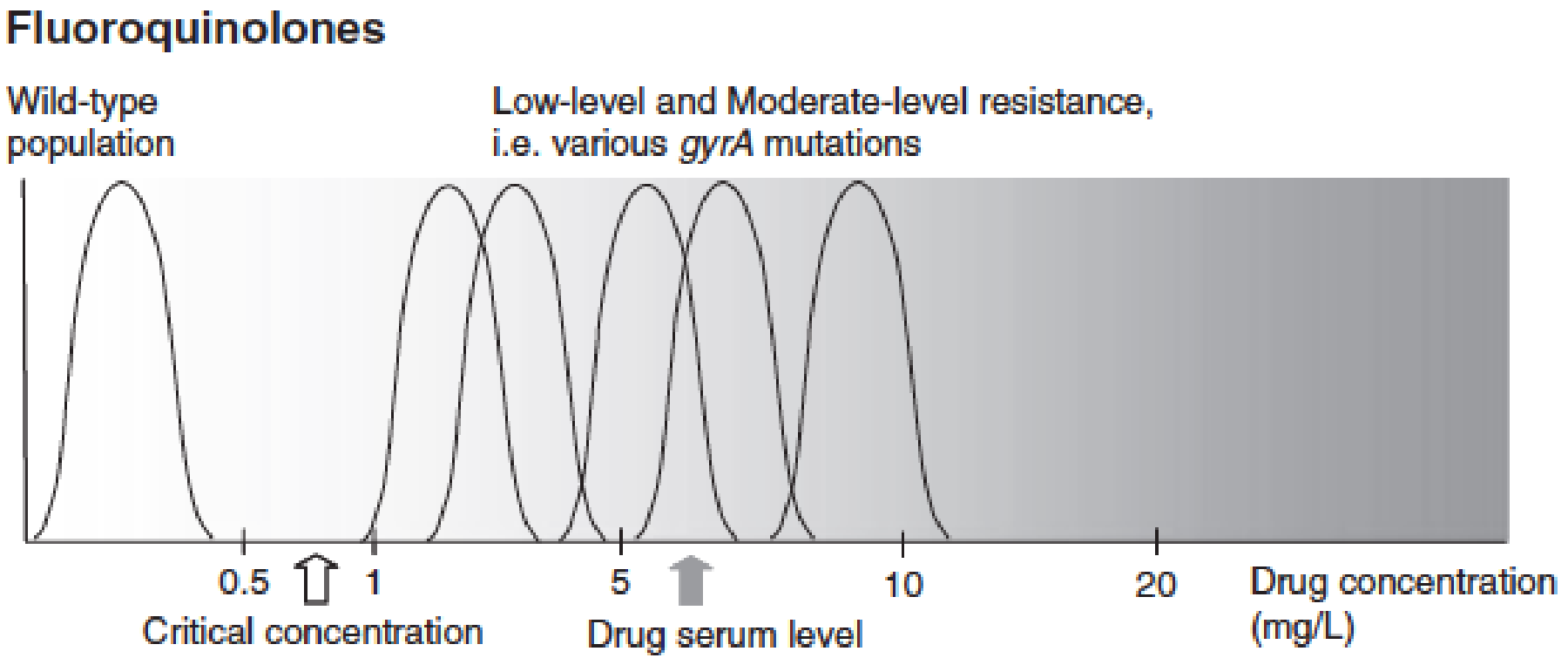
What About The Contacts Who Convert?

- Very few converters noted but most close contacts were not identified.

- Will moxifloxacin have any effect on LTBI?

Can labs and clinicians evaluate various DST systems and better identify critical cut points/MICs that correlate with clinical outcomes?

gyrA Mutation & FQ MIC Distribution



Mark Nicol, IOM/IMCAS Workshop on DR TB, Beijing 16-18 Jan 2013

http://www.iom.edu/~/media/Files/Activity%20Files/Research/DrugForum/2013-JAN-16/Presentations/January%2017%20%20Session%20III%20%20Nicol%20MarkRedacted.pdf


You can’t prevent TB with a fence.