ARIZONA DEPARTMENT OF HEALTH SERVICES
PREPAREDNESS

It's Resistant, So What?

Mycobacterium tuberculosis-Complex rpoB mutations; characterization of rifampin-resistant genotypic and phenotypic clinical isolate concordance in Arizona.

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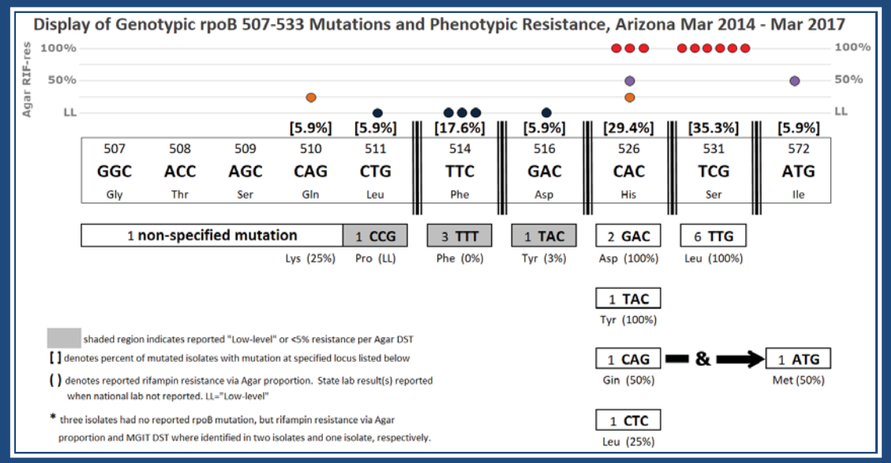
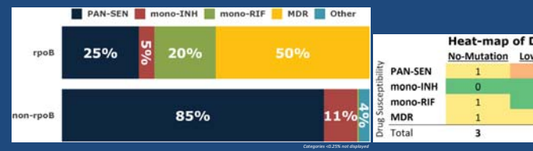
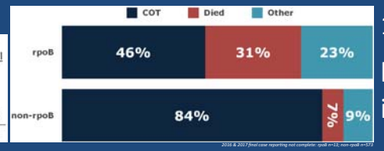
BACKGROUND: The presence of drug-resistant tuberculosis (TB), including multidrug-resistant TB, creates an emerging concern in the Americas for early and accurate detection of resistance and the initiation of an adequate treatment regimen. Usage of molecular testing for resistance provides earlier results compared to conventional drug susceptibility testing (DST); however, the concordance between the genotypic and phenotypic display of rifampin resistance (RR) has not been adequately characterized in the state of Arizona. Additionally, epidemiologic-based data is often lacking in this type of analysis.

METHODS: Twenty clinical *M. tuberculosis*-complex (MTBC) isolates from 20 different Arizona TB cases were included in this review. Inclusion criteria consisted of: 1) culture-confirmed Arizona-counted MTBC case, and 2) identified molecular rpoB mutation and completed rifampin DST or identified RR DST and completed molecular rpoB testing. Molecular rpoB mutations were recorded along the 81-base pair region of codon 507 to codon 533. Silent mutations were classified as having an agar proportion RR DST of <5% at 1.0 µg/ml or as "low-level" when no percentage was reported. Case-level demographics were collected from state surveillance data.





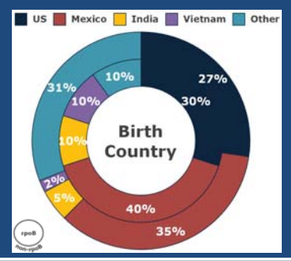


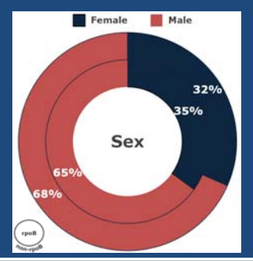
35% Genotypic-Phenotypic Discordance

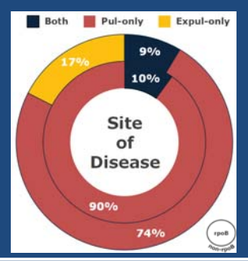
29.4% rpoB Mutations w/ Low-Level RIF-res

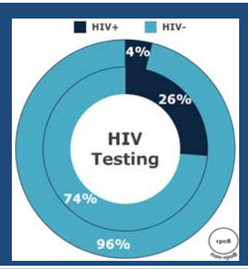
	1st (+) Specimen Collected to Tx Start[1]		If sputum(+), Culture Convert[1]		If non-U.S.-born, Years in US before Dx[2]		Age at Time of TB Dx[2]	
	rpoB	non-rpoB	rpoB	non-rpoB	rpoB	non-rpoB	rpoB	non-rpoB
Min	1	-25	22	1	0	0	22	0
Median	3	7	41.5	46	9.5	5	43.5	43
Max	27	104	287	526	48	65	77	100
Skewness	1.503	5.568	2.856	4.737	1.18	1.267	0.372	0.214
Count	20	480	12	276	14	422	20	607

[1] Time in days
[2] Time in years









RESULTS: Of the 20 assessed isolates, a rpoB mutation was identified in 17 [85%] of the isolates. Eight unique rpoB mutations were identified; three were silent mutations [Leu-511-Pro, Phe-514-Phe, Asp-516-Tyr]. Silent mutations accounted for five [29.4%] of the 17 reported mutations and were most notably linked to persons born in Mexico. Eleven [64.7%] mutations were identified at codons 526 and 531. Homogeneity of six [35.3%] mutations was observed at codon 531 [Ser-531-Leu] where all were 100% RR at 1.0 µg/ml. Codon 526 accounted for four unique mutations and five [29.4%] total mutations with a RR range of 25% to 100% at 1.0 µg/ml. Discordance between genotypic and phenotypic display was observed in seven [35%] of the 20 isolates.

CONCLUSIONS: Although this sample size is relatively small, generalizations for future comparison may be useful. Silent mutations were found in a higher than expected proportion of isolates and account for the majority of observed genotypic-phenotypic discordance. The genotypic-phenotypic discordance suggesting more research is needed to better understand their interrelation and clinical translatability.

Review period: Mar 2014—Mar 2017; only accounts for Arizona confirmed, counted, & reported active tuberculosis cases; **Cohort rpoB**: n=20; **Cohort non-rpoB**: n=607; When final reporting is pending or variables omitted/missing, Tables & Figures may not reflect the entire cohort sample.