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Amanda Panepento Date

Effect of Acquired Resistance to Streptomycin or Ethionamide on Treatment Outcomes in Patients with Multidrug-Resistant Tuberculosis

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2015

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An abstract of

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Abstract

Effect of Acquired Resistance to Streptomycin or Ethionamide on Treatment Outcomes in Patients with Multidrug-Resistant Tuberculosis

By Amanda Panepento

With millions of people contracting it and billions of dollars spent researching and treating it annually, the world-wide burden of tuberculosis (TB) is staggering and thus, many public health organizations are constantly seeking ways to decrease the morbidity, mortality, and the financial burden it places on communities across the globe. What's especially concerning has been the rising development of bacterial resistance to key antibiotics and the increase in cases of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB. This study used data prospectively collected from 1254 subjects in nine countries as part of the Preserving Effective TB Treatment Study (PETTS) to identify whether acquiring resistance to streptomycin or ethionamide is associated with worse outcomes in patients being treated for MDR TB. Consecutive consenting adults ages 18 years and older with pulmonary MDR TB were enrolled. Baseline and monthly sputum samples were collected and sent to the CDC in Atlanta, GA for drug-susceptibility analysis. We developed two multivariable logistic regression models, one for each drug, in order to assess whether developing resistance to either of these drugs during treatment increases the odds of poor treatment outcomes. Among 432 subjects who had *M. tuberculosis* strains that were susceptible to streptomycin at baseline, 42 (9.7%) of them developed resistance to streptomycin during treatment. Among the 1022 subjects who had strains susceptible to ethionamide at baseline, 176 (17.2%) of them developed resistance to ethionamide. Through our analysis, no significant association between acquired resistance to streptomycin and treatment outcomes was found. In contrast, acquired resistance to ethionamide increased the odds of poor treatment outcomes by 82% (OR = 1.82, 95% CI 1.47 - 2.25, $p < 0.0001$) in patients being treated for MDR TB. Therefore, we concluded that acquired resistance to ethionamide was associated with worse patient outcomes. By increasing our understanding of the impact that acquiring resistance to specific antibiotics has on treatment outcomes, the scientific community can develop better antibiotic therapies to maximize good outcomes for patients with MDR TB.

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Table of Contents

Background

Nearly 25% of the world's population is infected with *Mycobacterium tuberculosis* and WHO estimates that 10 million people developed the disease in 2018. Due to the disease burden, the United Nations identified tuberculosis (TB) as a priority and created Sustainable Development Goal Target 3.3 in hopes of ending the TB epidemic by 2030. This requires a 90% reduction in deaths compared to 2015 and mobilizing $2 billion for TB research and $13 billion for universal access to TB diagnosis, treatment and care (1). Multidrug resistant tuberculosis (MDR TB) is defined as a *Mycobacterium tuberculosis* infection that is resistant to at least rifampin and isoniazid, the two most important first-line drugs used to treat TB (2). With some experts estimating that MDR TB alone could cost the world $16.7 trillion by 2050, this disease deserves increased attention (3).

Previous studies have shown that treatment outcomes in patients with MDR TB deteriorate as levels of drug resistance increase compared to patients whose isolates have lower levels of drug resistance (4). Unfortunately, there is still a significant proportion of TB cases that are not microbiologically confirmed and that do not get comprehensive susceptibility testing to identify drug resistance (5,6). Ideally, MDR TB is treated for a minimum of 15-24 months, with the first phase being a 5-7-month intensive phase and the second phase being a continuation phase for the remainder of the treatment duration (6). At least five effective drugs should be used in the intensive phase and four drugs should be used in the continuation phase (7). Throughout the years, drug resistance has developed for nearly every antibiotic we have used to treat *Mycobacterium tuberculosis* infections, and this pattern will likely continue.

Recently, three new drugs, bedaquiline, delamanid, and pretomanid have shown promise in treating MDR TB, but like many newer therapies, their cost makes make them

inaccessible for many low- and middle-income countries with a high burden of TB (9). For those reasons, medical and public health authorities must optimize currently available, less expensive therapies. This analysis builds on findings of the Preserving Effective TB Treatment Study (PETTS), which found that resistance to fluoroquinolones and second-line-injectable drugs was significantly associated with poorer treatment outcomes in patients with MDR TB. Resistance acquired during treatment had a greater impact than baseline resistance (10). To date, PETTS has not investigated the effect of acquired resistance to other drugs used to treat MDR TB. This analysis seeks to identify the effect of acquired resistance to two commonly used second-line antibiotics, streptomycin and ethionamide, on treatment outcomes in patients treated for MDR TB. These drugs are inexpensive, used widely, and easily accessible to communities most affected by TB. The findings of this study are relevant to public health programs, healthcare providers, and their patients around the world and may influence the case for universal and comprehensive drug susceptibility testing for patients being treated for *Mycobacterium tuberculosis* infections. By having detailed knowledge about the effects of acquired resistance on treatment outcomes, we can make informed decisions about treating individuals with MDR TB and that will help us make progress toward our goal of ending the TB epidemic by 2030.

Methods

Study Population

Data used for this analysis were collected as part of the Preserving Effective Treatment of Tuberculosis Study (PETTS), the largest prospective cohort study of MDR TB treatment to date. The study enrolled consenting adults ≥18 years old with locally confirmed pulmonary MDR TB from January 2005 through December 2008 and followed them until their treatment was completed or until December 2010. Subjects were enrolled across 26 clinical sites in nine different countries: Estonia, Latvia, Peru, the Philippines, Russia, South Africa, South Korea, Taiwan, and Thailand. Details about the study and study population have been previously published (2). The study was approved by the CDC's IRB and the IRB in all nine participating countries.

Procedures

Data were collected from subjects' medical records in real time concurrently with their medical care across all sites using a standardized data collection system. Baseline sputum specimens were collected, cultured in duplicate, and tested locally for *Mycobacterium tuberculosis* and for susceptibility to at least isoniazid and rifampin (so as to determine if they qualified as MDR TB). Follow-up sputum was collected and cultured in duplicate monthly throughout treatment. All labs used internationally recommended methods. Duplicates of positive baseline and follow up cultures were sent to the CDC in Atlanta where they were tested for susceptibility to 12 drugs by the indirect agar proportion method according to the Clinical Laboratory Standards Institute procedures as previously reported (2). The samples were tested for susceptibility to streptomycin and ethionamide, along with isoniazid, rifampicin, rifabutin, ethambutol, ofloxacin, ciprofloxacin, kanamycin, capreomycin, amikacin, and para-

aminosalicylic acid. Pyrazinamide testing was carried out by sequencing the pncA gene. Further details on the procedures of this study have been previously published (2).

Statistical Analysis

Subjects were divided into two groups – those who acquired resistance (to each drug, separately) and those who did not. Subjects' baseline isolates had to be susceptible to the given drug in order to be able to develop resistance. Subjects who had an initial sputum culture that was susceptible to ethionamide and streptomycin and never had a follow up culture that was positive (and therefore not tested for resistance) were included in the group that did not acquire resistance because their treatment eliminated the bacilli. Subjects with baseline resistance could not acquire resistance, so they were excluded. A total of 24 risk factors were cross-tabulated with acquired drug resistance (AR) to either ethambutol or streptomycin. Dichotomous variables included were: patient's natal sex, occupational risk of TB, history of incarceration, current smoking status, diabetes, history of prior TB, a history of prior treatment with a second-line drug, previous treatment with a fluoroquinolone, previous treatment with a second-line injectable, hospitalization at enrollment, and whether they were located in a Green Light Committee (GLC)-approved site. Non-dichotomous variables were: age, marital status, level of education, employment status, homelessness status, HIV status, sputum culture results, number of prior episodes of TB, prior treatment for MDR TB, extent of cavitary disease (unilateral vs. bilateral and cavitary vs. non-cavitary), and extent of pulmonary radiographic abnormalities. These variables were divided into groups and recoded based on naturally occurring group levels.

A Pearson's Chi-Square test or Fisher's Exact test were run on each of these cross tabulations and the odds ratios (OR) with corresponding 95% confidence intervals were

calculated for the relationship between each risk factor and acquired resistance. P values of < 0.05 were considered significant. Odds ratios (OR) are reported in the tables for ease of comparison with the logistic regression output. The variables for acquired resistance to ethionamide and for streptomycin included two levels: acquired resistance and continued susceptibility. This process was repeated for treatment outcomes where the variable for this included only two levels: poor outcomes (failure/death) and good outcomes (cure/completion = C/C). For this analysis, we were particularly interested in the relationship between acquired resistance to streptomycin or ethionamide and clinically relevant treatment outcomes.

To investigate for possible confounding variables, we stratified our cross-tabulation of acquired resistance versus treatment outcomes by variables that were found to be significantly associated with both. The covariates that had a Mantel-Haenszel adjusted relative risk more than 10% different from the crude measurement were included in subsequent logistic regression models as potential confounders. For streptomycin, these were: previous treatment with second-line injectables, HIV status, and number of effective drugs used to treat the current infection. For ethionamide, these were: hospitalization status at the time of enrollment, HIV status, and the number of effective drugs used to treat the current infection.

To identify potential interaction variables, a Breslow-Day test for Interaction was performed for each covariate by stratification of acquired resistance vs. treatment outcomes with the threshold for interaction as $p < 0.10$. For both streptomycin and ethionamide, employment status was identified as a possible interaction variable. Once potential confounding and interaction variables were identified, two logistic regression models were

created, one using acquired resistance to streptomycin and the other using acquired resistance to ethionamide as the independent variables of interest and poor treatment outcomes as the dependent variable of interest.

To assess the importance of employment status as an interaction term, we used the likelihood ratio test: we took the difference of -2LogL values of each full model with and without the interaction term. This difference has a chi-squared distribution, and we determined the p-value corresponding to this difference was not significant ($p > 0.05$). Therefore, employment group and its interaction term were dropped from the models. Final models can be seen in the Appendix. All statistical analyses were performed using SAS 9.4.

Results

Of the 1254 subjects enrolled in the PETTS study, 804 (64.1%) were male and 450 (35.9%) were female (Table 1). Subjects ranged from 18-79 years old and were grouped based on prior PETTS publications where 191 (15.2%) were 18-28 years old, 354 (28.2%) were 29-36 years old, 35 (2.8%) were 37-45 years old, and 674 (53.8%) were 46-79 years old (4, 10). One-hundred and sixty-one (12.8%) were HIV positive and 125 (10.0%) had been previously treated for MDR TB. Of the total 1254 subjects enrolled, one did not have data for baseline streptomycin susceptibility and was excluded from analysis. Of the remaining 1253, 432 (34.5%) subjects had *M. tuberculosis* strains susceptible to streptomycin at baseline (Table 1). Of the 1254 that had baseline susceptibility data for ethionamide, 1022 (81.5%) subjects had strains susceptible to ethionamide at baseline.

Section One: Acquired Resistance

Streptomycin

Of the 432 subjects who had streptomycin-susceptible strains at baseline, 42 (9.7%) developed resistance to streptomycin (Table 2). Of the 42 subjects with strains that acquired resistance, 32 (76.2%) were male and the majority (n = 25, 59.5%) were between 25-44 years of age (Table 2). Similar proportions were seen among the 390 subjects whose strains did not acquire resistance. Among those who had strains that did acquire resistance to streptomycin, 9 (21.4%) were HIV positive and 7 (16.7%) had been previously treated with a second line injectable (SLI) drug. Comparatively, among the 390 subjects who had strains that did not acquire streptomycin resistance, only 37 (9.5%, p = 0.017) subjects were HIV positive and 19 (4.9%, p = 0.002) had been previously treated with an SLI. Additionally, 11 (26.2%) of those whose cultures acquired resistance had been previously treated for MDR

TB, compared to 43 (11.0%, p = 0.005) of those who did not. Among subjects whose strains had baseline susceptibility to streptomycin, the strongest predictors of acquired resistance were prior treatment with a third line drug (40.0%, p = 0.001) and prior treatment with a second-line injectable drug (26.9%, p = 0.002).

Ethionamide

Of the 1022 subjects who had strains susceptible to ethionamide at baseline, 176 (17.2%) developed resistance to ethionamide (Table 1). Of these 176, 109 (61.9%) were male and 93 (52.8%) were between 25-44 years of age (Table 3). Again, similar proportions were seen among those with strains that did not acquire resistance. Among those who did have strains that acquired resistance, 39 (22.2%) were HIV positive, compared to 94 (11.1%, p = 0.0001) among those who did not. Additionally, among the subjects with strains that acquired resistance, 20 (11.4%) had been previously treated with an SLI and 119 (67.6%) were hospitalized at the time of treatment. This is compared to 56 (6.6%, p = 0.029) and 363 (42.9%, p < 0.0001), respectively, among those who did not acquire resistance. Finally, 129 (73.3%) of those with strains that acquired resistance were treated with less than the recommended four effective drugs, compared to 486 (57.4%) among those whose strains remained susceptible. Among subjects with strains that had baseline susceptibility to ethionamide, the number of effective drugs used to treat the subject's MDR TB was the strongest predictor of acquired resistance. Of the subjects treated with only one effective drug, 32.7% (n = 18) developed strains with resistance to ethionamide.

Section Two: Treatment Outcomes

When examining the association between acquired resistance to streptomycin or ethionamide and clinically relevant treatment outcomes, we focused our analysis on subjects who had good or poor outcomes and excluded those who were lost to follow-up and those whose strains were resistant at baseline (n = 546 total excluded for streptomycin, n = 375 total excluded for ethionamide).

Streptomycin

Of the 42 subjects whose strains developed resistance to streptomycin, n = 15 (35.7%) were excluded because they were lost to follow up. Among the remaining 27 subjects whose strains acquired resistance to streptomycin, 10 (37.0%) had poor treatment outcomes, compared to 56 (19.6%) of the 286 subjects whose strains did not acquire this resistance (crude OR 2.42, 95% CI 1.05 – 5.56, p = 0.03) (Table 4). Of the 24 risk factors mentioned previously, three were found to be confounding variables in the logistic regression model for streptomycin. These factors were: previous treatment with second-line injectable drugs, HIV status, and number of effective drugs being used to treat the current MDR TB infection. Controlling for these factors with multivariable logistic regression model, we found that subjects whose strains developed resistance to streptomycin had 35% greater odds of having poor treatment outcomes than those who remained susceptible, although this was not statistically significant (adjusted OR = 1.35, 95% CI 0.86 – 2.11, p = 0.20).

Ethionamide

Of the 176 subjects whose strains acquired resistance to ethionamide, n = 36 (20.5%) were excluded because they were lost to follow up. Subjects with strains that acquired resistance to ethionamide were 4.86 times more likely to have poor treatment outcomes than those whose strains did not develop resistance (crude OR 4.86, 95% CI 3.30 – 7.15, p<0.0001).

For the logistic regression model, three variables were found to be confounders: HIV status, the number of drugs used to treat the current MDR TB infection, and whether or not the subject was in the hospital at the time of enrollment. Controlling for these factors with our multivariable logistic regression model, we found that subjects whose strains developed resistance to ethionamide had 82% greater odds of having poor treatment outcomes than subjects whose strains did not develop resistance (adjusted OR = 1.82, 95% CI 1.47 – 2.25, $p < 0.0001$).

Discussion

This analysis aimed to quantify the incidence of acquired resistance to streptomycin or ethionamide and the relationship between acquired resistance to streptomycin or ethionamide with treatment outcomes in patients being treated for multidrug-resistant pulmonary tuberculosis. Logistic regression models found a significant association between acquired resistance to ethionamide, but not streptomycin, and poor treatment outcomes. Acquired resistance to ethionamide conferred an 82% increase in odds of treatment failure among patients being treated for MDR TB. Conversely, the weaker association (35%) seen between acquired resistance to streptomycin and poor treatment outcomes in the adjusted model was not statistically significant, which may have been due to the decreased power of the study as a result of a small sample size (n = 27). These findings add to the body of literature showing that both acquired resistance and the number of effective drugs used to treat MDR TB have a significant effect on patient outcomes. Previously, PETTS demonstrated that increasing drug resistance was associated with a stepwise increase in poorer treatment outcomes (10). Additionally, the PETTS study also found that the risk of poor treatment outcomes increases as the number of potentially effective drugs used for treatment decreases (4).

Data regarding the individual treatment regimen that each subject received were not analyzed, but there are multiple reasons why our study may have found an association between acquired resistance to ethionamide and increased odds of death or treatment failure. It is estimated that less than 60% of patients with newly diagnosed TB receive susceptibility testing (1) and although all of our patients did receive proper testing, they may not have been tested for ethionamide, and they still may have received inappropriate drug regimens. Their regimens could have been incongruent with their susceptibility profile because the

comprehensive susceptibility test results from the CDC were available only after the fact and therefore not used for clinical management. In non-GLC sites, patients may have received drugs that were of low quality or questionable strength. A much simpler explanation is that subjects who were given drugs to which they developed resistance were less likely to have successful outcomes because the treatment was less effective or became less effective. If treatment regimens are not altered in response to newly acquired resistance, it makes sense that continued treatment with these ineffective drugs may yield poor results.

Strengths and Limitations

While the results of this analysis fall in line with conclusions drawn by prior studies, our work is not without its limitations. For this particular analysis (not PETTS overall), we looked at differences in baseline and follow-up resistance only. We did not use genotyping to determine if the pair of isolates were the same strain. Genotyping of *Mycobacterium tuberculosis* bacterial strains was performed on patients who had acquired resistance to fluroquinolones and second-line injectable drugs, but it was not performed on all patients whose strains acquired resistance to streptomycin or ethionamide. Therefore, it is possible that patients who were deemed to have strains with acquired resistance were re-infected with a strain of *M. tuberculosis* that was resistant to one of the two drugs of interest or had a mixed infection at the start, making it look like their original infection had acquired resistance. Also, the reproducibility of the susceptibly test for streptomycin and ethionamide is less than that for the other drugs tested. This intrinsic testing variability could have led to the introduction of random error and therefore the association of acquired resistance with treatment outcomes may be diminished compared to reality. An additional limitation was that the sample size for streptomycin was small, which may explain why the association between acquired resistance to streptomycin and treatment outcomes was not found to be significant. Finally, PETTS

data were based on self-selected participating countries and did not include subjects from China or India, two countries with the highest burdens of MDR TB, so the results cannot be considered globally representative (9). The statistical analyses performed in this study assumed that the data were from a simple random sample of a hypothetical population but without data from these two countries, our results are likely not generalizable to MDR TB patients as a whole. To mitigate the effects of this limitation, future studies could stratify the logistic regression models by country as the data obtained from each country *is* believed to be a representative sample of that country's population.

However, our study does have important strengths. As mentioned, data were collected from nine different countries and across 26 different sites, resulting in a large heterogenous study population. The researchers used a standardized system for prospective data collection with diligent quality assurance procedures to ensure its accuracy and validity. Our culture samples were analyzed at the Centers for Disease Control and Prevention, so the quality of the lab work done, and results reported, was superior. Finally, while the sample size for this particular analysis, especially for streptomycin, was small, overall, the PETTS study is the largest prospective MDR TB study done to-date and was groundbreaking in that it was the first to look at acquired resistance in MDR TB. Most importantly, the results of our analysis are logical. If a patient's cultures developed resistance, their physician would not have been aware that they were treating their patient with a regimen that was no longer effective. Thus, patients who developed resistance may have had poor outcomes because they were being treated with ineffective drugs. We further speculate that, if a patient acquired resistance to a drug, they were likely not on a good treatment regimen in the first place because an adequate regimen would prevent the development of acquired resistance. In theory, a patient who is on a drug for which they have baseline susceptibility and the drug is

administered appropriately (with proper frequency, duration, strength, etc.) in combination with at least three or four other effective drugs, should not develop resistance to the drug in question.

Conclusion

In previous works, we have seen that acquired resistance to other drugs negatively impacts treatment outcomes, but no prior publications have focused on streptomycin and ethionamide specifically (2, 5, 10, 11). Streptomycin is no longer used as a first-line treatment for tuberculosis in many countries, but it was at the time of this study, and more recent data show it is effective clinically when laboratory test results show susceptibility. Ethionamide, as a second-line drug, is still used widely. Many of the countries that are most significantly impacted by TB are countries that have limited medical resources and funding to fight the disease, making newer more expensive drugs more difficult to obtain. Therefore, it is still relevant to evaluate the impact of acquired resistance to older drugs as long as they continue to be used for patients with MDR TB, as these are likely to be used in lower income countries and rural areas for years to come. As we have seen throughout the years, resistance to TB drugs continues to be a problem, with resistant strains becoming ever more prevalent (7,11). Eventually, it is likely that TB will be resistant to all new drugs and for that reason, knowing how to use older drugs remains relevant and important (14). If we, as a global community, are going to reach our Sustainable Development Goal by 2030, future research needs to focus on better understanding the frequency and consequences of resistance to specific antibiotics. This way, we can improve our antibiotic stewardship, increase our tuberculosis cure rates, and potentially slow down the development of MDR tuberculosis.

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Tables

Table 1. Subject Population Demographics and Clinical Characteristics

Characteristic	Category	Number (%) (N=1254)
PATIENT CHARACTERISTICS		
Sex	Male	804 (64.1)
	Female	450 (35.9)
Age group (years)	18-28	191 (15.2)
	29-36	354 (28.2)
	37-45	35 (2.8)
	46-79	674 (53.8)
Marital Status	Never Married	458 (36.5)
	Previously Married	161 (12.8)
	Currently Married or Cohabitating	540 (43.1)
Employment	Unemployed	475 (37.9)
	Employed	581 (46.3)
	Not Seeking Work	192 (15.3)

Education	Primary or Less	289 (23.1)
	Secondary	336 (26.8)
	Postsecondary	561 (44.7)
Occupational Risk	Yes	166 (13.2)
	No	1088 (86.8)
Homelessness	Yes	29 (2.3)
	No	1088 (86.8)
History of Imprisonment	Yes	81 (6.5)
	No	992 (79.1)
Current Smoker	Yes	281 (22.4)
	No	957 (76.3)
Alcohol Abuse	Yes	186 (14.8)
	No	1016 (81.0)
Human Immunodeficiency Virus (HIV) Infection	Positive	161 (12.8)
	Negative	1093 (87.2)
Diabetes mellitus	Yes	168 (13.4)
	No	1081 (86.2)
History of Tuberculosis	Yes	1185 (94.5)
	No	69 (5.5)
Number of Previous TB Episodes	0	443 (35.3)
	1	396 (31.6)
	2	207 (16.5)
	3	139 (11.1)
	4+	69 (5.5)
First Treatment for MDRTB	Yes	1127 (89.9)
	No	125 (10.0)
Prior Treatment with any SLD	Yes	186 (14.8)
	No	1068 (85.2)

Prior Treatment with any Fluoroquinolone	Yes	159 (12.7)
	No	1095 (87.3)
Prior Treatment with any SLI	Yes	98 (7.8)
	No	1156 (92.2)
Prior Treatment with 3rd line drugs	Yes	28 (2.2)
	No	1226 (98.8)
In Hospital at the Time of Enrollment	Yes	584 (46.6)
	No	670 (53.4)
Extent of Cavitary Disease on Chest X-ray	None	457 (36.4)
	Unilateral cavities	477 (38.0)
	Bilateral cavities	293 (23.4)
Pulmonary Radiographic Abnormality	Bilateral	993 (79.2)
	Unilateral	236 (18.82)
Sputum Smear Test at Diagnosis	Positive	1087 (86.7)
	Negative	116 (9.2)
Green Light Committee Approval	Yes	465 (37.1)
	No	789 (62.9)
TREATMENT REGIMEN		
Number of Effective Drugs in Current Treatment Regimen	0-1	110 (8.8)
	2	280 (22.3)
	3	443 (35.3)
	4	357 (28.5)
	5-6	54 (4.3)
INITIAL DRUG RESISTANCE BY DRUG		
Streptomycin		
	Resistant	821 (65.5)
	Susceptible	432 (35.4)
Ethionamide		

	Resistant	232 (18.5)
	Susceptible	1022 (81.5)
TREATMENT OUTCOME		
Treatment outcome	Cured	659 (52.5)
	Completed	66 (5.2)
	Died	80 (6.4)
	Treatment failed	172 (13.7)
	Defaulted	234 (18.7)
	Transfer out	26 (2.1)
	Continuing treatment	17 (1.4)

*Table adapted from prior PETTS publications (2, 4). Not all variables add to 1254 due to missing data.

Table 2. Risk Factors for Acquired Resistance to Streptomycin (SM)

Characteristic	Category	Acquired Resistance to Streptomycin N (%)	No Acquired Resistance to Streptomycin N (%)	Crude OR (95% CL)	P-value
PATIENT CHARACTERISTICS					
Total	1253				
Total at risk	432	42 (9.7)	390 (90.3)		
Sex	Male	32 (11.07)	257 (88.93)	1.65 (0.79, 3.47)	0.179
	Female	10 (6.99)	133 (93.01)	Ref.	.
Age Group (years)	18-24	8 (12.7)	55 (87.3)	1.23 (0.53, 2.87)	0.636
	25-44	25 (10.59)	211 (89.41)	Ref.	.
	45-64	9 (7.44)	112 (92.56)	0.68 (0.31, 1.50)	0.337
	65+	0 (0)	12 (100)	N/A	0.235

	Data missing: 0				
Marital Status	Never Married	16 (10.39)	138 (89.61)	1.38 (0.66, 2.88)	0.396
	Previously Married	0 (0)	41 (100)	N/A	N/A
	Currently Married or Cohabitating	15 (7.77)	178 (92.23)	Ref.	.
Education	Primary or Less	9 (7.89)	105 (92.11)	0.75 (0.33, 1.71)	0.493
	Secondary	20 (10.26)	175 (89.74)	Ref.	.
	Postsecondary	9 (8.33)	99 (91.67)	0.80 (0.35, 1.81)	0.586
Occupational Risk	Yes	5 (26.32)	14 (73.68)	4.25 (1.43, 12.63)	0.005
	No	29 (7.75)	345 (92.25)	Ref.	.
Employment Status	Unemployed	22 (15.49)	120 (84.51)	2.49 (1.32, 4.7)	0.004
	Not Seeking Work	6 (9.52)	57 (90.48)	1.53 (0.61, 3.82)	0.363
	Employed	14 (6.22)	211 (93.78)	Ref.	.
History of Imprisonment	Yes	2 (15.38)	11 (84.62)	2.19 (0.46, 10.38)	0.313
	No	27 (7.67)	325 (92.33)	Ref.	.
History of Homelessness	Yes	1 (25.0)	3 (75.0)	3.73 (0.38, 36.94)	0.228
	No	31 (8.2)	347 (91.8)	Ref.	.
Alcohol Abuse	Yes	8 (18.18)	36 (81.82)	2.38 (1.02, 5.54)	0.040
	No	32 (8.56)	342 (91.44)	Ref.	.
Current Smoker	Yes	12 (18.46)	53 (81.54)	2.52 (1.22, 5.23)	0.011
	No	30 (8.24)	334 (91.76)	Ref.	.

HIV Infection	Yes	9 (19.57)	37 (80.43)	2.6 (1.16, 5.86)	0.017
	No	33 (8.55)	353 (91.45)	Ref.	.
Diabetes mellitus	Yes	4 (5.26)	72 (94.74)	0.47 (0.16, 1.37)	0.159
	No	37 (10.51)	315 (89.49)	Ref.	.
History of Tuberculosis	Yes	41 (9.74)	380 (90.26)	1.08 (0.14, 8.64)	0.943
	No	1 (9.09)	10 (90.91)	Ref.	.
Number Previous TB Episodes	0	1 (9.09)	10 (90.91)	Ref.	.
	1	14 (11.29)	110 (88.71)	1.27 (0.15, 10.7)	0.825
	2	12 (7.69)	144 (92.31)	0.83 (0.10, 7.07)	0.868
	3	9 (10.98)	73 (89.02)	1.23 (0.14, 10.79)	0.851
	4+	6 (10.17)	53 (89.83)	1.13 (0.12, 10.45)	0.914
First Treatment for MDRTB	No	11 (20.37)	43 (79.63)	2.86 (1.82, 32.27)	0.005
	Yes	31 (8.2)	347 (91.8)	Ref.	.
Prior Treatment with any SLD	Yes	11 (17.74)	51 (82.26)	2.35 (1.12, 4.98)	0.021
	No	31 (8.38)	339 (91.62)	Ref.	.
Prior Treatment with any FQ	Yes	9 (16.07)	47 (83.93)	1.99 (0.90, 4.42)	0.086
	No	33 (8.78)	343 (91.22)	Ref.	.
Prior Treatment with any SLI	Yes	7 (26.92)	19 (73.08)	3.91 (1.54, 9.93)	0.002

	No	35 (8.62)	371 (91.38)	Ref.	.
Prior Treatment with 3rd Line Drugs	Yes	4 (40)	6 (60)	4.44 (1.96, 10.06)	0.001
	No	38 (9)	384 (91)	Ref.	.
In Hospital at Time of Enrollment	Yes	22 (15.6)	119 (84.4)	2.51 (1.32, 4.76)	0.004
	No	20 (6.87)	271 (93.13)	Ref.	.
Cavitary Disease	Unilateral	14 (9.21)	138 (90.79)	1.39 (0.61, 3.17)	0.429
	Bilateral	16 (15.38)	88 (84.62)	2.50 (1.11, 5.62)	0.024
	None	11 (6.79)	151 (93.21)	Ref.	.
Pulmonary Radiographic Abnormality	Bilateral	34 (10.21)	299 (89.79)	1.25 (0.53, 2.93)	0.606
	Unilateral	7 (8.33)	77 (91.67)	Ref.	.
Sputum Smear Test at Diagnosis	Positive	33 (8.85)	340 (91.15)	0.68 (0.25, 1.85)	0.448
	Negative	5 (12.5)	35 (87.5)	Ref.	.
Green Light Committee	Yes	22 (8.53)	236 (91.47)	0.72 (0.38, 1.36)	0.308
	No	20 (11.49)	154 (88.51)	Ref.	.
Number of Effective Drugs Used During Current Treatment					
	1	4 (21.05)	15 (78.95)	2.95 (0.88, 9.95)	0.069
	2	7 (9.86)	64 (90.14)	1.21 (0.48, 3.08)	0.689

	3	14 (9.59)	132 (90.41)	1.17 (0.55, 2.49)	0.677
	4+	16 (8.29)	177 (91.71)	Ref.	.

*Not all variables add to 432 due to missing data.
* "At risk" subjects are those with baseline streptomycin susceptibility who have the potential to develop resistance.

Table 3. Risk Factors for Acquired Resistance to Ethionamide (THA)

Characteristic	Category	Acquired Resistance to Ethionamide N (%)	No acquired Resistance to Ethionamide N (%)	Crude OR (95% CL)	P-value
PATIENT CHARACTERISTICS					
Total	1254				
Total at risk	1022	176 (17.2)	846 (82.7)		
Sex	Male	109 (16.87)	537 (83.13)	0.94 (0.67, 1.31)	0.699
	Female	67 (17.82)	309 (82.18)	Ref.	.
Age Group (years)	18-24	28 (17.61)	131 (82.39)	1.0 (0.65, 1.65)	0.873
	25-44	93 (17.06)	452 (82.94)	Ref.	.
	45-64	49 (17.13)	237 (82.87)	1.01 (0.69, 1.47)	0.980
	65+	6 (18.75)	26 (81.25)	1.12 (0.45, 2.80)	0.806
Marital Status	Never Married	71 (18.78)	307 (81.22)	1.26 (0.87, 1.81)	0.222
	Previously Married	31 (23.31)	102 (76.69)	1.65 (1.02, 2.67)	0.039
	Currently Married or Cohabitating	67 (15.55)	364 (84.45)	Ref.	.

Education	Primary or Less	39 (16.6)	196 (83.4)	0.84 (0.56, 1.27)	0.411
	Secondary	92 (19.13)	389 (80.87)	Ref.	.
	Postsecondary	37 (14.57)	217 (85.43)	0.72 (0.48, 1.09)	0.123
Occupational Risk	Yes	12 (24)	38 (76)	1.43 (0.73, 2.8)	0.293
	No	160 (18.08)	725 (81.92)	Ref.	.
Employment Status	Unemployed	90 (22.39)	312 (77.61)	2.28 (1.57, 3.31)	<0.0001
	Not Seeking Work	32 (21.19)	119 (78.81)	2.13 (1.31, 3.45)	0.002
	Employed	52 (11.23)	411 (88.77)	Ref.	.
History of Imprisonment	Yes	31 (43.66)	40 (56.34)	3.86 (2.33, 6.39)	<0.0001
	No	134 (16.73)	667 (83.27)	Ref.	.
History of Homelessness	Yes	5 (20.83)	19 (79.17)	2.33 (1.57, 3.45)	0.770
	No	163 (18.48)	719 (81.52)	Ref.	.
Alcohol Abuse	Yes	46 (29.11)	112 (70.89)	1.94 (1.45, 2.60)	<0.0001
	No	123 (14.98)	698 (85.02)	Ref.	.
Current Smoker	Yes	65 (28.14)	166 (71.86)	2.43 (1.72, 3.46)	<0.0001
	No	108 (13.86)	671 (86.14)	Ref.	.
HIV Infection	Yes	39 (29.32)	94 (70.68)	2.28 (1.50, 3.45)	0.0001
	No	137 (15.41)	752 (84.59)	Ref.	.
Diabetes mellitus	Yes	12 (9.84)	110 (90.16)	0.49 (0.27, 0.92)	0.023
	No	162 (18.1)	733 (81.9)	Ref.	.
History of tuberculosis	Yes	160 (16.67)	800 (83.33)	0.58 (0.32, 1.04)	0.0648
	No	16 (25.81)	46 (74.19)	Ref.	.

Number Previous TB episodes	0	16 (25.81)	46 (74.19)	Ref.	.
	1	87 (22.54)	299 (77.46)	0.84 (0.45, 1.55)	0.571
	2	50 (16.03)	262 (83.97)	0.55 (0.29, 1.05)	0.065
	3	15 (9.68)	140 (90.32)	0.31 (0.14, 0.67)	0.002
	4+	8 (7.48)	99 (92.52)	0.23 (0.09, 0.58)	0.001
First Treatment for MDRTB	No	17 (16.5)	86 (83.5)	0.95 (0.54, 1.62)	0.853
	Yes	158 (17.23)	759 (82.77)	Ref.	.
Prior Treatment with any SLD	Yes	29 (19.73)	118 (80.27)	1.22 (0.78, 1.90)	0.385
	No	147 (16.8)	728 (83.2)	Ref.	.
Prior Treatment with any FQ	Yes	24 (19.2)	101 (80.8)	1.17 (0.72, 1.88)	0.532
	No	152 (16.95)	745 (83.05)	Ref.	.
Prior Treatment with any SLI	Yes	20 (26.32)	56 (73.68)	1.81 (1.06, 3.10)	0.029
	No	156 (16.49)	790 (83.51)	Ref.	.
Prior Treatment with 3rd line drugs	Yes	1 (5.26)	18 (94.74)	0.26 (0.03, 1.98)	0.164
	No	175 (17.45)	828 (82.55)	Ref.	.
In Hospital at Time of Enrollment	Yes	119 (24.69)	363 (75.31)	2.78 (1.97, 2.92)	<0.0001
	No	57 (10.56)	483 (89.44)	Ref.	.
Cavitary Disease	Unilateral	78 (19.8)	316 (80.2)	1.65 (6.45, 42.12)	0.0122
	Bilateral	48 (20.43)	187 (79.57)	1.71 (1.10, 2.65)	0.0158
	None	48 (13.04)	320 (86.96)	Ref.	.

Pulmonary Radiographic Abnormality	Bilateral	144 (18.07)	653 (81.93)	1.32 (0.86, 2.04)	0.204
	Unilateral	29 (14.29)	174 (85.71)	Ref.	.
Sputum Smear Test at Diagnosis	Positive	117 (14.75)	676 (85.25)	0.50 (0.33, 0.76)	0.001
	Negative	39 (25.66)	113 (74.34)	Ref.	.
Green Light Committee	Yes	98 (15.68)	527 (84.32)	0.79 (0.61, 1.04)	0.102
	No	78 (19.65)	319 (80.35)	Ref.	.
Drug Effect					
Number of Effective Drugs Used During Current Treatment	1	18 (32.73)	37 (67.27)	3.73 (1.97, 7.07)	<0.0001
	2	50 (28.74)	124 (71.26)	3.09 (1.97, 4.83)	<0.0001
	3	60 (15.87)	318 (84.13)	1.45 (0.96, 2.18)	0.078
	4+	47 (11.55)	360 (88.45)	Ref.	.

*Not all variables add to 1022 due to missing data.
* "At risk" subjects are those with baseline ethionamide susceptibility who have the potential to develop resistance.

Table 4. Predictors of treatment outcome (C/C = Cured/Treatment Completed)

Characteristic	Category	Failure/Death N (%)	C/C N (%)	Crude OR (95% CL)	P-value
PATIENT CHARACTERISTICS					
Total	1254				
Total at risk	1254				
Sex	Male	159 (25.98)	453 (74.02)	1.03 (0.76, 1.38)	0.863
	Female	93 (25.48)	272 (74.52)	Ref.	.
Age Group (years)	18-24	37 (27.21)	99 (72.79)	1.04 (0.68, 1.60)	0.845
	25-44	139 (26.38)	388 (73.62)	Ref.	.
	45-64	68 (23.94)	216 (76.06)	0.88 (0.63, 1.23)	0.449
	65+	8 (26.67)	22 (73.33)	1.02 (0.44, 2.33)	0.972
Marital Status	Never Married	107 (30.48)	244 (69.52)	1.67 (1.21, 2.31)	0.002
	Previously Married	28 (21.71)	101 (78.29)	1.05 (0.66, 1.71)	0.820
	Currently Married or Cohabitating	91 (20.78)	347 (79.22)	Ref.	.
Education	Primary or Less	64 (29.09)	156 (70.91)	1.20 (0.83, 1.72)	0.329
	Secondary	111 (25.52)	324 (74.48)	Ref.	.
	Postsecondary	49 (18.56)	215 (81.44)	0.67 (0.46, 0.97)	0.034
Occupational Risk	Yes	10 (20)	40 (80)	0.80 (0.39, 1.62)	0.527
	No	205 (23.92)	652 (76.08)	Ref.	.
Employment Status	Unemployed	119 (33.06)	241 (66.94)	2.0 (1.46, 2.77)	<0.0001
	Not Seeking Work	41 (25.95)	117 (74.05)	1.43 (0.94, 2.18)	0.098
	Employed	90 (19.69)	367 (80.31)	Ref.	.

History of Imprisonment	Yes	17 (34)	33 (66)	1.79 (0.98, 3.30)	0.058
	No	178 (22.33)	619 (77.67)	Ref.	.
History of Homelessness	Yes	3 (14.29)	18 (85.71)	0.54 (0.16, 1.84)	0.314
	No	205 (23.73)	659 (76.27)	Ref.	.
Alcohol Abuse	Yes	45 (31.91)	96 (68.09)	1.59 (1.07, 2.35)	0.019
	No	181 (22.71)	616 (77.29)	Ref.	.
Current Smoker	Yes	66 (31.13)	146 (68.87)	1.47 (1.05, 2.06)	0.025
	No	177 (23.54)	575 (76.46)	Ref.	.
HIV Infection	Yes	69 (50.36)	68 (49.64)	3.64 (2.51, 5.29)	<0.0001
	No	183 (21.79)	657 (78.21)	Ref.	.
Diabetes mellitus	Yes	25 (18.8)	108 (81.2)	0.71 (0.45, 1.12)	0.050
	No	225 (26.79)	615 (73.21)	Ref.	.
History of Tuberculosis	Yes	243 (26.1)	688 (73.9)	1.45 (0.69, 3.05)	0.323
	No	9 (19.57)	37 (80.43)	Ref.	.
Number Previous TB episodes	0	9 (19.57)	37 (80.43)	Ref.	.
	1	104 (29.3)	251 (70.7)	1.71 (0.79, 3.66)	0.168
	2	72 (24)	228 (76)	1.29 (0.60, 2.82)	0.509
	3	42 (25.61)	122 (74.39)	1.41 (0.63, 3.18)	0.399
	4+	25 (22.32)	87 (77.68)	1.18 (0.50, 2.77)	0.703
First Treatment for MDRTB	No	33 (44.59)	41 (55.41)	2.52 (1.56, 4.09)	0.0001
	Yes	218 (24.2)	683 (75.8)	Ref.	.
Prior Treatment with any SLD	Yes	43 (32.82)	88 (67.18)	1.49 (1.00, 2.21)	0.048

	No	209 (24.7)	637 (75.3)	Ref.	.
Prior Treatment with any FQ	Yes	40 (35.71)	72 (64.29)	2.54 (1.54, 4.17)	0.011
	No	212 (24.51)	653 (75.49)	Ref.	.
Prior Treatment with any SLI	Yes	31 (44.93)	38 (55.07)	2.54 (1.54, 4.17)	0.0002
	No	221 (24.34)	687 (75.66)	Ref.	.
Prior treatment with 3rd Line Drugs	Yes	7 (31.82)	15 (68.18)	1.24 (0.67, 2.31)	0.514
	No	245 (25.65)	710 (74.35)	Ref.	.
In Hospital at Time of Enrollment	Yes	179 (38.58)	285 (61.42)	3.79 (2.78, 5.16)	<0.0001
	No	73 (14.23)	440 (85.77)	Ref.	.
Cavitary Disease	Unilateral	85 (22.67)	290 (77.33)	1.06 (0.75, 1.51)	0.714
	Bilateral	86 (38.74)	136 (61.26)	2.30 (1.59, 3.33)	<0.0001
	None	78 (21.55)	284 (78.45)	Ref.	.
Pulmonary Radiographic Abnormality	Bilateral	224 (28.72)	556 (71.28)	2.40 (1.54, 3.74)	0.0001
	Unilateral	26 (14.36)	155 (85.64)	Ref.	.
Sputum Smear Test at Diagnosis	Positive	186 (24.16)	584 (75.84)	0.98 (0.65, 1.49)	0.935
	Negative	35 (24.48)	108 (75.52)	Ref.	.
Green Light Committee	Yes	105 (17.18)	506 (82.82)	0.31 (0.23, 0.42)	<0.0001
	No	147 (40.16)	219 (59.84)	Ref.	.
Drug Effect					
Number of Effective Drugs Used During Current Treatment	1	45 (58.44)	32 (41.56)	10.02 (5.71, 17.61)	<0.0001

	2	87 (38.33)	140 (61.67)	4.43 (2.89, 6.80)	<0.0001
	3	80 (22.73)	272 (77.27)	2.10 (1.38, 3.18)	0.0004
	4+	39 (12.30)	278 (87.70)	Ref.	.
Acquired Resistance	Streptomycin Susceptible → Resistant	10 (37.04)	17 (62.96)	2.42 (1.05, 5.56)	0.034
	Streptomycin Resistant → Resistant	152 (38.48)	243 (61.52)	2.57 (1.80, 3.67)	<0.0001
	Streptomycin Susceptible → Susceptible	56 (19.58)	230 (80.42)	Ref.	.
	Ethionamide Susceptible → Resistant	73 (52.14)	67 (47.86)	4.86 (3.30, 7.15)	<0.0001
	Ethionamide Resistant → Resistant	50 (52.63)	45 (47.37)	4.95 (3.16, 7.76)	<0.0001
	Ethionamide Susceptible → Susceptible	118 (18.32)	526 (81.68)	Ref.	.

* "At risk" are those who are capable of having a good or poor outcome.

Appendix

Full Logistic Regression Models

Streptomycin

TRT2OUTCOME = DST2SM + PREVSLJ + HIV + DRUGGROUP + EMPGROUP + EMPGROUP*DST2SM

Ethionamide

TRT2OUTCOME = DST2THA + HIV + DRUGGGROUP + TBHOSP + EMPGROUP + EMPGROUP*DTS2THA

Final Logistic Regression Models

Streptomycin

TRT2OUTCOME = DST2SM + PREVSLJ +HIV + DRUGGROUP
TRT2OUTCOME = 2.6381 + 0.2969(DST2SM) – 1.0796(PREVSLJ) – 0.0655(HIV) – 0.4998(DRUGGROUP)

Ethionamide

TRT2OUTCOME = DST2THA + HIV + DRUGGROUP + TBHOSP
TRT2OUTCOME = 2.3771 + 0.5980(DST2THA) + 0.1122(HIV) - 0.6336(DRUGGROUP) – 0.9526(TBHOSP)

Where:

*TRT2OUTCOME = treatment outcome (1 = FAIL/DEATH, 3 = C/C, as coded)

*DSTSM = acquired resistance to streptomycin

*PREVSLJ = previous use of second line injectable drugs

*HIV = HIV status

*DRUGGROUP = the number of drugs used to treat the MDR TB infection

*DST2THA = acquired resistance to ethambutol

*TBHOSP = in hospital at time of enrollment