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Acquired resistance to second-line drugs among persons with tuberculosis in the United States

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Abstract

Background—Acquired resistance to second-line drugs (SLD) is a problem in treating patients with drug-resistant tuberculosis (TB) worldwide. The objectives of this study were to identify risk factors for acquired resistance (AR) to injectable SLD and fluoroquinolones in the US National TB Surveillance System, 1993–2008.

Methods—We selected cases with initial and final drug susceptibility test (DST) results reported. We defined AR as resistance at the final DST but susceptibility to the same drug at the initial DST. We analyzed AR using 2-way frequency tables and multivariable logistic regression.

Results—Baseline prevalence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB was 12.6% (1864/14,770) and 0.38% (56/14,770), respectively. Of 2,274 individuals without initial resistance to injectable SLD, 49 (2.2%) acquired resistance. Of 1,141 initially susceptible to fluoroquinolones, 32 (2.8%) acquired resistance. AR to injectable SLD was associated with age group 25–44 years (adjusted Odds Ratio [aOR], 2.7; 95% confidence interval [CI], 1.2–6.3), positive HIV status (aOR, 2.5; 95% CI, 1.3–4.7), MDR at treatment initiation (aOR, 5.5; 95% CI, 2.9–10.5), and treatment with any SLD (aOR, 2.4; 95% CI, 1.2–4.7). AR to fluoroquinolones was associated with MDR TB at treatment initiation (aOR, 6.5; 95% CI, 2.9–14.6).

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Conclusion—Among patients with initial and final DST reported, risk factors for AR to injectable SLD included age, positive HIV status, MDR TB and initial treatment with any SLD, while the only predictor for AR to fluoroquinolones was MDR TB at treatment initiation. Providers should consider monitoring SLD DST for MDR TB patients in the indicated subgroups.

INTRODUCTION

Antituberculosis drug resistance is a major public health problem around the world. The World Health Organization (WHO) estimates the global burden of multidrug-resistant (MDR) tuberculosis (TB), defined as TB resistant to at least isoniazid and rifampicin, as approximately 650,000 cases in 2011 (1).

Primary resistance occurs when a person is infected with a strain of *M. tuberculosis* that is already resistant to antituberculosis drug(s). Acquired drug resistance (AR) occurs when a person is infected with a drug-susceptible strain of *M. tuberculosis* that becomes drug-resistant during treatment. AR occurs due to improper use of antibiotics such as inadequate treatment regimens or incomplete treatment (2–4). Acquisition of resistance to second-line drugs (SLDs) during MDR TB treatment (18–24 months) increases the risk of treatment failure (5–6) and the emergence of extensively drug-resistant TB (XDR TB) (7). XDR TB is a subset of MDR TB with further resistance to at least one of three injectable second-line drugs (SLDs) (amikacin, kanamycin, or capreomycin) and any fluoroquinolone (8). The latest WHO report of anti-tuberculosis drug resistance in the world estimated that 9.4% of MDR TB isolates were XDR TB (9). As of January 2012, 77 countries had reported to WHO at least one case of XDR-TB (10). Treatment outcomes among XDR TB patients are poor and mortality rates are similar to the pre-antibiotic era. According to the results of a recent meta-analysis of 13 observational studies, treatment of XDR TB succeeded in only 43.7 % of cases, and mortality was 20.8% (11).

In the United States, 63 cases of XDR TB based on initial DST results have been reported in 1993–2011 (12, plus 6 cases in 2011 CDC unpublished). Little is known about the causes of acquired resistance to SLD during treatment, as most published reports to date have been descriptive (11–19). As acquired resistance to the second-line TB medications severely compromises treatment options for patients with MDR TB, understanding the factors that lead to acquired resistance to SLD may help identify patients at risk and measures for prevention (3).

To determine the frequency of and risk factors for acquired resistance to key second-line antituberculosis drugs, we analyzed data from the U.S. National TB Surveillance System (NTSS) for the years 1993–2008.

METHODS

We analyzed data from all culture-positive TB cases in CDC's NTSS from all 50 states and the District of Columbia between January 1993 and December 2008 (20). The NTSS includes sociodemographic and clinical information, as well as initial and final drug susceptibility test (DST) results. While DST for first-line drugs on the initial positive culture is routine in the U.S., second-line DST and repeated DST are performed only when

indicated. Final DST data and treatment outcomes are reported within 12 to 24 months after the end of treatment. All injectable SLDs (amikacin, kanamycin, capreomycin) and FQs (ofloxacin, ciprofloxacin) considered in this analysis were available for treatment in the U.S. from 1993.

Case definitions

We included in the analysis culture-positive cases with both initial and final DST results reported for second-line anti-TB drugs, specifically amikacin, kanamycin, capreomycin (injectable second-line drugs, INJ SLD), ofloxacin and ciprofloxacin (fluoroquinolones, FQ). Initial DST is defined as the first available DST for a case; final DST is defined as the last available DST for the same drug. Acquired resistance was defined as drug resistance at the final DST but susceptibility to the same drug at the initial DST.

In this nested case-control analysis, we defined a case as an individual who acquired resistance to at least one INJ SLD or one FQ during treatment. A control was defined as an individual who did not acquire resistance. We excluded cases that had resistance at the initial DST to INJ SLD or FQ.

All variables were defined according to their standard usage in the NTSS which has been described in detail elsewhere (20).

Statistical analysis

We compared the distribution of demographic, social, and clinical characteristics among TB cases with versus without acquired SLD drug resistance, assessing differences in categorical variables with Pearson's chi square test. Specific demographic and social characteristics examined were gender, age, race/ethnicity, country of origin, illicit drug use, excess alcohol consumption, history of homelessness, occupation and imprisonment at the time of diagnosis. Clinical characteristics included a prior history of TB, sputum-smear status at diagnosis, chest radiograph results (normal versus abnormal), radiographic abnormalities (cavitary versus non-cavitary disease), anatomic site of disease (i.e., pulmonary or not pulmonary), HIV status, MDR TB, and specific drug regimens at the start of treatment.

We stratified the analysis of risk factors versus acquired resistance by other covariates to assess potential confounding and effect modification. Multivariable logistic regression was used to assess the independent associations between selected characteristics and acquired resistance. Criteria for including variables in the initial multivariable logistic regression model included a p-value <0.10 in univariate analysis or biologically plausible association with outcome of interest. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to measure the magnitude and precision of the association of each factor with the outcome of interest. We used two-sided tests of significance; P<0.05 was considered statistically significant.

These data were collected and analyzed as part of routine public health surveillance, not as human subject's research requiring IRB approval.

RESULTS

Among 222,897 culture-positive TB cases, reported in the United States from 1993 to 2008, 31,733 (14.3%) had initial DST results to at least one SLD (Figure 1). Of these, 31,226 (98.4%) cases had initial DST results to at least one injectable SLD and 15,337 (48.3%) to at least one FQ; 14,830 (6.7%) had initial DST results to both classes of SLD. Of these, 14,770 cases also had initial DST results to isoniazid and rifampin. MDR TB was diagnosed in 1,864 (12.6%) cases and 56 (0.38%) had XDR TB at treatment initiation (baseline XDR).

Among 31,226 cases with initial DST results to INJ SLD, 2,329 (7.5%) had final DST results to the same drug: 89% had both initial and final DST results for kanamycin, 16% for amikacin, and 70% for capreomycin. Of these, 43 cases had resistance to one INJ SLD at the initial DST but DST results for the other INJ SLDs were not reported; 12 cases were resistant to all INJ SLD at the initial DST. Therefore, 55 cases could not have acquired resistance and were excluded from the analysis (Figure 1). Kanamycin, amikacin and capreomycin were included in the initial treatment regimen for 13 (0.6%), 35 (1.5%) and 58 (2.6%) cases, respectively. Of 2,274 analyzed cases, 49 (2.2%) acquired resistance to at least one INJ SLD. The annual number of acquired INJ SLD resistance cases decreased from a maximum of 10 in 1995 to zero in 2008, fluctuating around a mean of 2.2 per year during the past decade (Figure 2).

Among 15,337 culture-positive TB cases with initial DST results to at least one FQ, 1,187 (7.7%) had final DST results to the same FQ. 39 culture-positive TB cases were resistant to one FQ on initial DST and did not have initial DST to other FQ; 17 cases were resistant to both FQs on initial DST, thus 56 cases could not have acquired resistance and were excluded from the analysis (Figure 1). Among 1,141 cases with both initial and final DST results to FQ, 32 (2.8%) acquired resistance to at least one FQ. The annual number of acquired FQ resistance cases decreased from a maximum of 4 in 1994 to 1 case in 2008, fluctuating around a mean 1.8 per year during the past decade (Figure 2).

Of 14,830 culture-positive cases with initial DST results to both INJ SLD and FQ, 1,155 (7.8%) had final DSTs to the same drug. Seventy-two cases were excluded: 22 cases were initially resistant to all reported INJ SLD and FQ; 50 cases were initially resistant to one INJ SLD and one FQ but DST results for the other INJ SLDs and FQs were not reported. Of the remaining 1,083 cases, 5 (0.5%) acquired resistance to both INJ SLD and FQ. All five had MDR TB at the initial DST, thus they became XDR TB. All five cases were HIV positive and occurred before 2001. Twenty-four (2.2%) of 1,083 individuals acquired resistance to INJ SLD only, and coincidentally 24 cases (2.2%) of 1,083 acquired resistance to FQ only.

Risk factors for acquired resistance to injectable second-line drugs

Of the 49 cases with acquired resistance to INJ SLD, the majority (36/49, 73.5%) were aged 25 to 44 years, 27 (55.1%) were male, 21 (42.9%) were Hispanic, 27 (55.1%) were US-born, and 22 (44.9%) were unemployed (Table 1). Twenty-two (45%) of these 49 cases were HIV-infected, 34 (69.4%) had MDR TB at the beginning of treatment, and 19 (38.8%) had an initial treatment regimen that included at least one SLD (Table 2). Most cases with

acquired resistance to INJ SLD had pulmonary disease (36, 73.5%). Among 40 individuals with abnormal chest radiographs, the majority had non-cavitary abnormalities (24, 60%).

In univariate analysis significant predictors of acquired resistance to INJ SLD included female gender (Odds Ratio [OR], 2.1; 95% CI, 1.2–3.6), age group 25 to 44 years (OR, 3.7; 95% CI, 1.7–8.4, versus the reference age-group 45–64), Hispanic ethnicity (OR, 4.0; 95% CI, 1.6–9.9, compared to non-Hispanic whites), positive HIV status (OR, 4.9; 95% CI, 2.8–8.7), extra pulmonary disease (OR, 3.3; 95% CI, 1.4–8.1), normal chest X-ray result (OR, 2.5; 95% CI, 1.1–6.0), MDR TB at initial DST (OR, 8.3; 95% CI, 4.5–15.3) and having at least one SLD in the initial treatment regimen (OR, 5.4; 95% CI, 2.9–10.2) (Table 3). Stratified analysis did not reveal any potential effect modifiers among sociodemographic and clinical characteristics.

In multivariable logistic regression, significant predictors of acquired resistance to INJ SLD included: age group 25–44 years (aOR, 2.7; 95% CI, 1.2–6.3), positive HIV status (aOR, 2.5; 95% CI, 1.3–4.7), MDR TB at initial DST (aOR, 5.5; 95% CI, 2.9–10.5), and initial treatment with any SLD (aOR, 2.4; 95% CI, 1.2–4.7).

Risk factors for acquired resistance to fluoroquinolones

Among 32 persons who acquired resistance to FQ, the majority were male (22/32, 68.8%), 15 were aged 25 to 44 years (46.9%), 13 (40.6%) were Hispanic, 17 (53.1%) were US-born, 19 (59.4%) were unemployed, 5 (15.6%) used illicit drugs and 2 (6.3%) were homeless (Table 1). Nine (28.1%) patients with acquired resistance to FQ were HIV-infected, 24 (75.0%) had MDR TB at the beginning of TB treatment, and 10 (31.3%) had an initial treatment regimen that included at least one SLD (Table 2). The majority had pulmonary disease (25/32, 78.1%). Six (21.4%) were sputum-smear negative at the start of treatment and 4 (12.5%) had previous TB episodes.

In univariate analysis significant predictors of acquired resistance to FQ were MDR TB at initial DST (OR, 6.5; 95% CI, 2.9–14.3) and having at least one SLD included in the initial treatment regimen (OR, 2.3; 95% CI, 1.1–4.9) (Table 4). In multivariable analysis, MDR TB at initial DST (aOR, 6.5; 95% CI, 2.9–14.6) was the only statistically significant risk factor for acquired resistance to fluoroquinolones.

DISCUSSION

The present study provides the first comprehensive assessment of predictors of acquired resistance to two key classes of second-line antituberculosis drugs, fluoroquinolones and second-line injectable agents. From 1993 to 2008, among culture-positive TB cases with both initial and final DST results, 49 (2.2%) acquired resistance to INJ SLD and 32 (2.8%) acquired resistance to FQ. Five baseline MDR TB cases acquired resistance to both INJ SLD and FQ, and thus developed XDR TB. The number of cases with acquired drug resistance declined after 1993. The decrease in the frequency of AR beginning in 1993 may be attributed to the public health response to the TB epidemic, including greatly improved TB control activities and increased proportion of patients treated under directly observed

therapy (DOT) in the US from that time. However, acquisition of resistance to SLD in the U.S. continues to occur.

MDR TB was an independent predictor of acquired resistance to INJ SLD and FQ, and it was the only predictor for acquired resistance to FQ. Acquired resistance to INJ SLD was also independently associated with HIV status and having any SLD in the initial treatment regimen. Age group 25–44 years was the only demographic predictor for acquisition of resistance to INJ SLD, increasing the odds 2.7-fold. In this age group, cases who acquired resistance include a substantially higher proportion of HIV infected cases and illicit drug users compared with controls. No statistically significant association was identified between previous TB treatment and the acquisition of resistance to either group of SLD. The risk factors for acquired resistance to the injectable drugs and the FQs could be different because injectable second-line drugs have been available in the US since the 1950s, while FQs have been used for TB treatment only since the 1990s. Therefore the sample size for acquired resistance to FQs is smaller than for injectable second-line drugs, especially in the 25–44 age group and among those who were HIV positive.

Several groups have reported the development of FQ-resistant TB and XDR TB during treatment (6–14), but not predictors for acquisition of resistance. There are very few publications on acquisition of second-line drug resistance, likely due to lack of capacity for the laboratory testing (21–22). Treatment with second-line drugs was associated with XDR TB in South Korea and also in Tugela Ferry, South Africa (21–22). Having MDR TB at the start of treatment appears to be the strongest consistent factor for acquired resistance to SLD.

Our study has several limitations. Drug susceptibility testing of *M. tuberculosis* to first-line drugs is performed and reported routinely in the United States, however testing of second-line drugs and repeat testing is performed on an individual basis, according to the physician's request. Most cases in NTSS had no reported DST results to SLDs and no repeat DST after the initial testing. Therefore, our results did not reflect SLD resistance among all reported TB cases, but only among those with reported results. In addition, among all cases with initial DST results reported, 10.3% (3,207/31,226) in the INJ SLD group and 9.9% (1,516/15,337) in the FQ group died; while about 3% (979/31,226 in the INJ SLD group and 501/15,337 in the FQ group) were lost to follow up without final DST result. Thus, this study underestimates the real number of cases with acquired SLD resistance in the United States, but it is based on the most complete national data currently available. Also, as genotyping of both initial and final isolates was not available, we could not ensure that the same strain was tested. Therefore, we could not exclude infection with mixed strains, re-infection, or laboratory errors. However, the risk of re-infection during TB treatment in the US is low (23–24). The U.S. National TB Genotyping Service database may help address these issues in the future (25). Finally, only the initial treatment regimen is reported in the NTSS, and important changes to TB therapy could be made during treatment. Accordingly we did not have detailed information about TB treatment for this analysis. The CDC has recently established an MDR/XDR TB registry collecting information on treatment regimens with the aim to further investigate this issue.

In conclusion, our study demonstrated that in spite of declining trends in SLD resistance, the problem of acquired SLD resistance, while rare, still persists in the United States. The proportion of acquired resistance was larger among MDR TB patients, patients with positive HIV status, and those with SLD in the initial treatment regimen. Since emergence of resistance to second-line TB medication severely compromises the treatment regimen options for TB patients, identification of patients at risk and prevention of further resistance is important. Patients in these subgroups should be prioritized for fast-track DST and rapid molecular tests for drug resistance and strictly follow supervised treatment based on the drug susceptibility test results. Earlier identification of patients at risk for developing XDR TB enables more diligent infection control measures, critical for preventing transmission of the disease.

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Summary

This study provides the first comprehensive assessment of predictors of acquired resistance to two key classes of second-line antituberculosis drugs that may help identify patients at greater risk for developing XDR TB.

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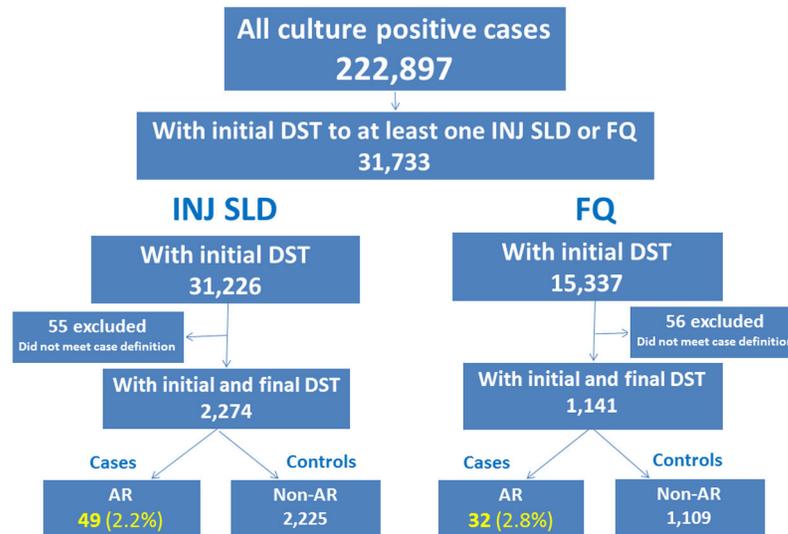


Figure 1. Selection of Patient Population

Note: DST - Drug Susceptibility Testing

SLD - Second-Line Drugs

INJ SLD – Injectable Second-Line Drugs

FQ – Fluoroquinolones

AR – Acquired resistance

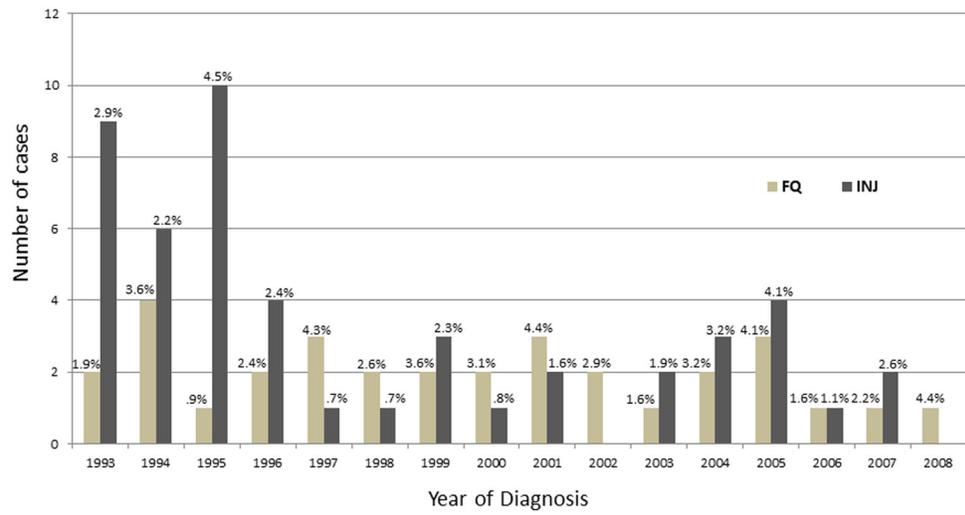


Figure 2. Number and percent of acquired resistance cases in the US by year, 1993–2008

Note: INJ – Injectable Second-Line Drugs

FQ – Fluoroquinolones

Table 1 Sociodemographic characteristics of tuberculosis cases with and without acquired resistance to second-line drugs, United States, 1993 – 2008

Characteristics	Injectable Second-Line Drugs				Fluoroquinolones					
	AR (n=49)	(%) ¹	non-AR (n=2225)	(%) ¹	p-value	AR (n=32)	(%) ¹	non-AR (n=1109)	(%) ¹	p-value
Gender										
Male	27	(55.1)	1,592	(71.6)	0.01	22	(68.7)	758	(68.4)	0.96
Female	22	(44.9)	633	(28.4)		10	(31.3)	351	(31.6)	
Age										
0 – 24	5	(10.2)	208	(9.4)	0.0001	2	(6.2)	128	(11.3)	0.6
25 – 44	36	(73.5)	951	(42.7)		15	(46.9)	538	(46.8)	
45 – 64	7	(14.3)	692	(31.1)		12	(37.5)	325	(28.8)	
65	1	(2.)	374	(16.8)		3	(9.4)	147	(13.2)	
Race/Ethnicity										
Hispanic/Latino	21	(42.9)	558	(25.1)	0.015	13	(40.6)	304	(27.4)	0.34
Black, non-Hispanic	14	(28.6)	385	(17.3)		8	(25.)	263	(23.7)	
White, non-Hispanic	6	(12.2)	647	(29.1)		6	(18.8)	313	(28.2)	
Other ²	8	(16.3)	635	(28.5)		5	(15.6)	229	(20.7)	
Origin										
United States	27	(55.1)	1,333	(59.9)	0.51	17	(53.1)	531	(47.9)	0.56
Foreign-born	22	(44.9)	891	(40.1)		15	(46.9)	577	(52.1)	
Occupation										
Not employed within the last 12 months	22	(44.9)	1,154	(51.9)	0.33	19	(59.4)	585	(52.8)	0.94
Health Care Worker	2	(4.1)	65	(2.9)		1	(3.1)	41	(3.7)	
Other ³	14	(28.6)	756	(33.8)		8	(25.)	370	(33.3)	
Unknown ⁴	11	(22.4)	250	(11.2)		4	(12.5)	113	(10.2)	
Homelessness within the Last 12 Months										

Characteristics	Injectable Second-Line Drugs				Fluoroquinolones				p-value
	AR (n=49)	(%) ^f	non-AR (n=2225)	(%) ^f	AR (n=32)	(%) ^f	non-AR (n=1109)	(%) ^f	
Yes	3	(6.1)	189	(8.5)	2	(6.3)	102	(9.2)	0.64
No	37	(75.5)	1,879	(84.6)	26	(81.3)	911	(82.3)	
Unknown ⁴	9	(18.4)	154	(6.9)	4	(12.5)	96	(8.5)	
Drug Abuse within the Last 12 Months									
Yes	9	(18.4)	202	(9.1)	5	(15.6)	109	(9.8)	0.45
No	27	(55.1)	1,754	(78.8)	24	(75.)	854	(77.)	
Unknown ⁴	13	(26.5)	269	(12.1)	3	(9.4)	146	(13.2)	
Alcohol Abuse within the Last 12 Months									
Yes	9	(18.4)	493	(22.2)	3	(9.4)	212	(19.1)	0.37
No	30	(61.2)	1,481	(66.6)	24	(75.)	764	(68.9)	
Unknown ⁴	10	(20.4)	248	(11.2)	5	(15.6)	133	(12.)	
At a Correctional Facility at Diagnosis									
Yes	3	(6.1)	90	(4.1)	3	(9.4)	37	(3.4)	0.07
No	46	(93.9)	2,135	(10.6)	29	(90.6)	1072	(96.6)	

Note:

AR - Acquired resistance

non-AR - no Acquired resistance

^f Column percent² Includes: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Missing and Unknown³ Includes: Correctional Employee, Migratory Agricultural Worker, Other Occupation⁴ Includes Missing**Bold:** statistically significant at alpha = 0.05

Clinical characteristics of tuberculosis cases with and without acquired resistance to second-line drugs, United States, 1993 – 2008

Table 2

Characteristics	Injectable Second-Line Drugs				Fluoroquinolones					
	AR (n=49)	(%) ¹	non-AR (n=2225)	(%) ¹	p-value	AR (n=32)	(%) ¹	non-AR (n=1109)	(%) ¹	p-value
Reported HIV Status										
Positive	22	(44.9)	317	(14.3)	<0.0001	9	(28.1)	208	(18.6)	0.23
Negative	14	(28.6)	1048	(47.1)		9	(28.1)	461	(41.6)	
Unknown ²	13	(26.5)	860	(38.6)		14	(43.8)	440	(39.8)	
MDR TB										
Yes	34	(69.4)	479	(21.5)	<0.0001	24	(75.)	350	(31.6)	<0.0001
No	15	(30.6)	1746	(78.5)		8	(25.)	757	(68.3)	
Unknown ²	0	(.)	6	(.3)		0	(.)	2	(.1)	
Anatomic Site of Disease										
Pulmonary	36	(73.5)	1941	(87.2)	0.008	25	(78.1)	946	(85.3)	0.26
Extrapulmonary	6	(12.2)	97	(4.3)		1	(3.1)	52	(4.7)	
Both	7	(14.3)	187	(8.5)		6	(18.8)	114	(10.)	
X-Ray										
Normal	6	(12.2)	118	(5.4)	0.002	2	(6.3)	69	(6.2)	0.8
Abnormal	40	(81.6)	2055	(93.3)		30	(93.8)	1019	(92.4)	
Unknown ²	3	(6.1)	29	(1.3)		0	(.)	15	(1.4)	
Cavitary Disease*										
Yes	15	(30.6)	882	(39.6)	0.06	15	(46.9)	421	(38.)	0.56
No	24	(49.)	1117	(50.2)		15	(46.9)	586	(52.8)	
Unknown ²	10	(20.4)	226	(10.2)		2	(6.2)	102	(9.2)	
Sputum Smear										

Characteristics	Injectable Second-Line Drugs				Fluoroquinolones				p-value	
	AR (n=49)	(%) ¹	non-AR (n=2225)	(%) ¹	p-value	AR (n=32)	(%) ¹	non-AR (n=1109)		(%) ¹
Positive	32	(65.3)	1623	(73.4)	0.2	24	(75.)	822	(74.5)	0.67
Negative	11	(22.4)	482	(21.8)		6	(18.8)	243	(22.)	
Unknown ²	6	(12.2)	107	(4.8)		2	(6.3)	39	(3.5)	
Previous Tuberculosis Treatment										
Yes	7	(14.3)	205	(9.2)	0.44	4	(12.5)	113	(10.2)	0.89
No	42	(85.7)	2010	(90.4)		28	(87.5)	993	(89.6)	
Unknown ²	0	(.)	9	(.4)		0	(.)	2	(.2)	
Initial Regimen										
Includes any SLD	14	(28.6)	154	(6.9)	<0.0001	7	(21.9)	85	(7.7)	0.004
No SLD ³	35	(71.4)	2071	(93.1)		25	(78.1)	1024	(92.3)	

Note:

AR - Acquired resistance

non-AR - no Acquired resistance

¹ Column percent² Includes Not Done and Missing³ Includes Missing and Unknown

* only for cases with abnormal X-Ray results: n(INJ)=40, n(FQ)=30

Bold: statistically significant at alpha = 0.05

Risk factors for acquired resistance to injectable second-line drugs during treatment of tuberculosis, United States, 1993–2008 (n=49)

Table 3

Risk factor	Crude OR	(95% CI)	Adjusted OR	(95% CI)
Gender				
Female	2.1	(1.2, 3.6)	Not included in the model	
Male	Reference			
Age				
0 – 24	2.4	(0.8, 7.5)	1.9	(0.6, 6.1)
25 – 44	3.7	(1.6, 8.4)	2.7	(1.2, 6.3)
45 – 64	Reference			
65	0.3	(0.03, 2.1)	0.4	(0.1, 3.4)
Race/Ethnicity				
Hispanic/Latino	4.0	(1.6, 9.9)	Not included in the model	
Black, non-Hispanic	2.2	(0.8, 6.4)		
White, non-Hispanic	Reference			
Other ¹	2.3	(0.8, 6.0)		
Drug Abuse within the Last 12 Months				
Yes	2.3	(1.1, 4.7)	Not included in the model	
Other ²	Reference			
Reported HIV Status				
Positive	4.9	(2.8, 8.7)	2.5	(1.3, 4.7)
Other ³	Reference			
MDR TB				
Yes	8.3	(4.5, 15.3)	5.5	(2.9, 10.5)
Other ²	Reference			

Risk factor	Crude OR	95% CI	Adjusted OR	95% CI
<i>Anatomic Site of Disease</i>				
Extrapulmonary	3.3	(1.4, 8.1)	Not included in the model	
Pulmonary	Reference			
Both	2.0	(0.9, 4.5)		
<i>X-Ray</i>				
Normal	2.5	(1.1, 6.0)	Not included in the model	
Other ⁴	Reference			
<i>Initial Regimen</i>				
Includes any SLD ⁵	5.4	(2.9, 10.2)	2.4	(1.2, 4.7)
No SLD ⁶	Reference			

Note:

- ¹ Includes: American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, Missing and Unknown
- ² Includes: No, Unknown, Missing
- ³ Includes: Negative, Not Done, Unknown, Missing
- ⁴ Includes: Abnormal, Not Done, Unknown, Missing
- ⁵ Include any INJ SLD (amikacin, kanamycin, capreomycin) or FQ (ofloxacin, ciprofloxacin)
- ⁶ Includes Missing and Unknown and do not include any above SLDs

Bold: statistically significant at alpha = 0.05

Table 4 Risk factors for acquired resistance to fluoroquinolones during treatment of tuberculosis, United States, 1993–2008 (n=32)

Risk factor	Crude OR	(95% CI)	Adjusted OR	(95% CI)
MDR TB				
Yes	6.5	(2.9, 14.3)	6.5	(2.9, 14.6)
Other ¹	Reference			
At a Correctional Facility at Diagnosis				
Yes	3.0	(0.9, 10.3)	Not included in the model	
No	Reference			
Initial Regimen				
Includes any SLD	3.4	(1.4, 8.0)	Not included in the model	
Other ¹	Reference			

Note:

¹ Includes No, Missing and Unknown

Bold: statistically significant at alpha = 0.05