

Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, United States, 2005–2007

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To describe factors associated with multidrug-resistant (MDR), including extensively-drug-resistant (XDR), tuberculosis (TB) in the United States, we abstracted inpatient, laboratory, and public health clinic records of a sample of MDR TB patients reported to the Centers for Disease Control and Prevention from California, New York City, and Texas during 2005–2007. At initial diagnosis, MDR TB was detected in 94% of 130 MDR TB patients and XDR TB in 80% of 5 XDR TB patients. Mutually exclusive resistance was 4% XDR, 17% pre-XDR, 24% total first-line resistance, 43% isoniazid/rifampin/rifabutin-plus-other resistance, and 13% isoniazid/rifampin/rifabutin-only resistance. Nearly three-quarters of patients were hospitalized, 78% completed treatment, and 9% died during treatment. Direct costs, mostly covered by the public sector, averaged \$134,000 per MDR TB and \$430,000 per XDR TB patient; in comparison, estimated cost per non-MDR TB patient is \$17,000. Drug resistance was extensive, care was complex, treatment completion rates were high, and treatment was expensive.

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Drug-resistant *Mycobacterium tuberculosis* poses substantial obstacles to tuberculosis (TB) control. In the United States, multidrug-resistant (MDR) TB (resistant to at least isoniazid and rifampin) comprises only 1.0%–1.5% of TB cases but requires lengthy regimens of toxic drugs, imposes high costs on the health care system and society, and causes high mortality rates.

Studies of MDR TB in the United States have been limited by small sample sizes, limited study periods, minimal information on outcomes and costs, or reliance solely on surveillance data (1–6), which omit some cases of acquired drug resistance and changes in regimens. Costs of treating MDR TB are not routinely collected or reported.

Our study describes and analyzes characteristics associated with drug resistance, timely diagnosis, treatment practices, outcomes, and costs associated with MDR TB for cases reported to the Centers for Disease Control and Prevention (CDC) by California, New York, and Texas during 2005–2007. These 3 areas contribute about half of US MDR TB cases annually.

Methods

CDC and local institutional review boards approved the study and granted a waiver of patient informed consent and patient authorization. We defined a 5-drug regimen (online Technical Appendix, wwwnc.cdc.gov/EID/article/20/5/13-1037-Techapp1.pdf) to be consistent with US and World Health Organization recommendations (7,8). All study definitions are in the online Technical Appendix.

Each site identified cases of MDR TB and extensively drug-resistant (XDR) TB reported to CDC during

2005–2007. The study included all XDR TB cases and a 75% simple random sample of MDR TB cases from California and New York (New York City), and a 50% sample from Texas. Using standardized forms, we abstracted hospital, laboratory, and public health clinic records retrospectively for patient demographic, socioeconomic, and clinical characteristics and for treatment, case management, outcomes, and costs. Total charges for each TB-associated hospitalization were abstracted from hospital UB-04 forms. To ascertain sputum-culture conversion and drug resistance, we examined all available culture and drug-susceptibility testing (DST) results from diagnosis through treatment.

To assess representativeness, we compared our sample with National TB Surveillance System data from all US sites. We identified characteristics among MDR TB patients associated with the following 3 dichotomous outcomes: drug resistance acquisition, expert consultation use, and death during TB treatment. Multivariable logistic regression was used with backward selection at $p < 0.05$ to identify variables remaining in final models (SAS version 9.2/9.3; SAS Institute, Cary, NC, USA). Adjusted odds ratios (AORs) significant at 95% CIs and Schwarz Criterion statistics are reported for goodness-of-fit. Variables included in initial models were patient demographics (gender, age group, race/ethnicity, foreign birth), socioeconomic factors (homelessness, unemployment, illicit substance use, excess alcohol use, smoking), medical risks (HIV infection, diabetes), TB history, disease severity (acid-fast bacilli [AFB]–smear positivity, cavitation, dissemination), drug-resistance pattern, receipt of TB clinic outpatient care, and additional relevant characteristics (for acquired resistance: receipt of ≥ 4 effective medications; for expert consultation: incarceration in a correctional institution, long-term-care facility residence, pregnancy, death during treatment, number of adverse events, private outpatient insurance; for death during treatment: pregnancy, incarceration in a correctional institution).

Inpatient costs were measured; outpatient costs and productivity losses were estimated (online Technical Appendix). Hospital charges were converted to costs by using hospital-specific operating cost-to-charge ratios (9). All costs were converted to 2010 US dollars (10) and were adjusted for cost of living (1.13 for California, 1.08 for New York City, and 0.94 for Texas) (11) to facilitate aggregation. For 17 patients for whom hospital charges data were missing, we multiplied hospitalization duration by average cost per day for patients for whom data were available (\$1,419).

Study total direct costs were compared with estimated direct costs for cases of non-MDR TB (online Technical Appendix). We report SEMs to display cost variability.

For productivity losses from hospitalization, we applied an updated 2010 dollar value of work-plus-home production of \$224/day for employed patients and \$40/day

for home-only production of unemployed patients (12). For TB-related deaths, we estimated the value of remaining lifetime productivity, updated to 2010 dollars, based on the age at death (12). For patients experiencing adverse events during treatment, we calculated a disability adjustment per patient (100%, 83%, 67%, 50%, 33%, 17%, 0%). We estimated direct and productivity-loss costs and examined associated characteristics by using multivariable linear regression with backward selection. Adjusted R^2 statistics are reported to show goodness-of-model-fit.

Results

The sample consisted of 135 patients (130 with MDR TB and 5 with XDRTB), representing 36% (130/364) of MDR TB and 56% (5/9) of XDR TB cases reported in the United States during 2005–2007. Among these patients, 87% were foreign born and 36% had prior TB disease (Tables 1–3). Among patients for whom information about concurrent medical conditions was available, 24 (20%) of 121 had diabetes and 14 (12%) of 116 had HIV infection. The study population resembled all US MDR TB patients; however, fewer study participants were White or unemployed, and more used noninjection drugs, had prior TB, or had AFB-positive smear specimens. Similar to all foreign-born TB patients in the United States, most foreign-born MDR TB study participants arrived from Mexico, the Philippines, India, and Vietnam. Of the 135 patients, 7% were homeless before diagnosis (6 patients) or during treatment (3 patients). Case management to obtain housing during treatment was needed by 23 (17%) patients; 38 (28%) patients had been unemployed before diagnosis, and of the 97 remaining patients, 27% stopped work because of MDR TB.

Of the 135 patients, disease was pulmonary for 85%, extrapulmonary only for 6%, and disseminated for 9%. Of 127 patients with pulmonary or disseminated disease, 69 (54%) had extensive disease. Of 8 patients with extrapulmonary-only disease, 2 (25%) had extensive disease. Of 134 patients alive at diagnosis, 77% (103) had at least 1 AFB-smear-positive specimen, 72% from sputum.

Drug Resistance

At various times during treatment, *M. tuberculosis* isolates were tested for susceptibility (median 14 medications, range 4–19) and were resistant to several (median 5 medications, range 2–16) at any time during treatment. The following mutually exclusive resistance patterns were identified: 4% XDR, 17% pre-XDR, 24% total first-line resistance, 43% isoniazid/rifampin/rifabutin-plus-other resistance, and 13% isoniazid/rifampin/rifabutin-only resistance (Figure 1). Initial *M. tuberculosis* isolates obtained within 30 days of treatment initiation revealed isoniazid/rifampin resistance among 122 (94%) of the 130 MDR TB patients and XDR among 4 (80%) of the 5 XDR TB patients. DST

was conducted for first-line drugs during the first month of treatment, for second-line drugs during the second month of treatment, for linezolid during the fourth month, and for clofazimine during the seventh month.

Among 128 patients for whom DST was conducted multiple times on separate dates, acquired resistance to an anti-TB medication during treatment was detected for 27 (21%). According to multivariable analysis, acquisition of drug resistance during treatment was more likely for patients who were recently homeless (AOR 5.8, 95% CI 1.2–28.9), who had pre-XDR or XDR TB (AOR 5.1, 95% CI 1.9–14.2), or who were Black (AOR 4.1, 95% CI 1.1–15.4) (Table 4). Acquisition of resistance to isoniazid or rifampin, resulting in MDR TB, occurred for 6% of patients, to fluoroquinolones for 3%, and to injectable drugs for 4%. Other medications to which resistance was acquired were ethambutol (10% of patients), pyrazinamide (6%), streptomycin (5%), ethionamide (5%), rifabutin (2%), cycloserine (1%), and clofazimine (1%). For 1 patient, fluoroquinolone resistance was acquired, resulting in XDR TB.

Time to Diagnosis

For 74 patients who had TB symptoms before diagnosis, a median of 1.6 months elapsed from symptom onset to initial TB diagnosis. Of 134 patients alive at diagnosis, 123 (92%) started receiving ≥ 2 second- or third-line medications a median of 2.4 months after initial TB diagnosis. The median duration of infectiousness was 10 months.

Treatment Practices

Among 105 patients who completed treatment, treatment duration varied. Median durations were 32.3 months (interquartile range [IQR] 30.6–37.8) for those with XDR,

25.1 months (IQR 23.6–29.2) for those with pre-XDR, 25.7 months (IQR 22.4–26.9) for those with total-first-line-resistant, 24.1 months (IQR 20.1–27.0) for those with isoniazid/rifampin/rifabutin-plus-resistant, and 20.0 months (IQR 19.4–24.5) for those with isoniazid/rifampin/rifabutin-only-resistant TB.

Providers changed medications for 134 patients alive at diagnosis a median of 7 times during treatment; 33% of 988 medication changes were because of adverse events and 10% because of DST results. Of 134 patients, 34% received a 5-drug regimen before sputum-culture conversion, and 61% ultimately received a 5-drug regimen. Of the 134 patients, 81% received an effective (i.e., medication to which their isolate was never resistant) injectable medication and 86% received an effective fluoroquinolone medication during treatment. Of 123 patients who received outpatient care, 90% received $>80\%$ of outpatient medication doses by directly observed therapy (DOT).

Most study patients were hospitalized for TB, often several times; 73% (98) were hospitalized at least 1 time and 29% were hospitalized ≥ 2 times (range 2–6). Detailed data were available for 83% of inpatients. Among multiple possible reasons, severe worsening of TB disease was the reason for 50% of hospitalizations, followed by the need to initiate or change treatment (40%), implement respiratory isolation (21%), manage adverse events (7%), manage concurrent conditions (3%), and perform surgery (1%). One patient had undergone TB-related lung lobectomy. Four XDR TB patients were hospitalized for a median of 282 days (range 14–850) and non-XDR patients for a median of 27 days (range 1–759). Home isolation was prescribed for 37% of patients; a median of 102 days (range 4–337) for non-XDR TB patients and 257 days for the 1 XDR TB patient.

Table 1. Demographic characteristics of study participants and all patients with MDR and/or XDR TB, United States, 2005–2007*

Characteristic	Study participants, no. (%), n = 135	All US MDR TB patients, no. (%), n = 370
Sex		
M	68 (50)	205 (55)
F	67 (50)	164 (44)
Age, y		
Median	38.2	
0–14	1 (1)	13 (4)
15–24	24 (18)	64 (17)
25–44	62 (46)	171 (46)
45–64	40 (30)	91 (25)
≥ 65	8 (6)	31 (8)
Race/ethnicity		
Hispanic	42 (31)	100 (27)
White†	4 (3)	31 (8)
Black	14 (10)	63 (17)
Asian	72 (53)	173 (47)
Other/unknown	3 (2)	3 (1)
Geographic origin		
Foreign born‡	118 (87)	305 (82)
US born	17 (13)	64 (17)

*Study patients were from California, New York City, and Texas. MDR, multiple-drug resistant; XDR, extensively drug resistant; TB, tuberculosis.

†Statistically significant differences between percentages of study patients and all US MDR TB patients at $p < 0.05$.

‡For 110 participants, median no. years after first entry into United States = 3.5.

Table 2. Socioeconomic characteristics of study participants and all patients with MDR and/or XDR TB, United States, 2005–2007*

Characteristic	Study participants, no. (%), n = 135	All US MDR TB patients, no. (%), n = 370
Unemployed†	38 (28)	187 (51)
Homeless	9 (7)	20 (5)
Correctional institution resident	6 (4)	7 (2)
Long-term care facility resident	4 (3)	6 (2)
Injection drug use	5 (4)	8 (2)
Noninjection drug use†	12 (9)	15 (4)
Excess alcohol use	15 (11)	31 (8)
Smoker	31 (23)	
Pregnant at treatment initiation	6 (4)	
Private health insurance, % of 112 known	24 (21)	
Public health insurance, % of 112 known	49 (44)	
Jail/prison health coverage, % of 112 known	2 (2)	
Other health insurance, % of 112 known	5 (4)	
No health insurance, % of 112 known	32 (29)	
HIV+	14 (10)	29 (8)
Receiving HAART	9 (64)	
Receiving ART	1 (7)	
Receiving neither HAART nor ART	3 (21)	
Receipt of ART not documented	1 (7)	
Not HIV infected	102 (76)	205 (55)
HIV status unknown	19 (14)	136 (37)
Diabetes, % of 121 known	24 (20)	
ESRD, % of 121 known	3 (2)	
Prolonged corticosteroid therapy, % of 121 known	2 (2)	
Other immunosuppressive therapy, % of 121 known	2 (2)	
Cancer, % of 121 known	3 (2)	
Hematologic diseases, % of 121 known	2 (2)	

*Study patients were from California, New York City, and Texas. MDR, multidrug resistant; XDR, extensively drug resistant; TB, tuberculosis; HIV+, HIV infected; HAART, highly active antiretroviral therapy; ART, antiretroviral therapy; ESRD, end-stage renal disease. Blank cells indicate data not available.

†Statistically significant differences between percentages of study patients and all US MDR TB patients at $p < 0.05$.

Of the 134 patients alive at diagnosis, 81% had documentation of physician consultation with an MDR TB expert during inpatient or outpatient care. Expert consultation was more likely for patients managed primarily by a TB clinic (AOR 5.7, 95% CI 1.9–16.8) and less likely for those with private insurance (AOR 0.2, 95% CI = 0.1–0.7) (Table 5). Overall, each patient received a median of 3 expert consultations.

Of the 134 patients alive at diagnosis, ≈90% were assigned a case manager. Case management activities included home visits (68%), social worker assistance (37%), transportation assistance (32%), incentives (25%), housing assistance (17%), and other activities including legal orders for DOT or isolation (9%–15%). Only 4% of patients received none of these case management services. Interpreter use was documented for 60% of 107 patients who understood some or no English.

Outcomes

Of 112 eligible patients, including all XDR TB patients, sputum culture converted to negative for 109 (97%). Patients considered ineligible for culture conversion included 1 patient whose TB was diagnosed after death, 6 who died during treatment, 3 who were transferred to another US jurisdiction or out of the United States, 7 who had extrapulmonary-only disease, and 6 without a positive sputum culture result. Of the 3 for whom no culture conversion

was documented, 1 was lost to follow-up after 166 days and 2 completed treatment. Culture conversion occurred within a median of 2 months from starting a 5-drug-regimen but varied by resistance pattern (online Technical Appendix).

Of the 134 patients alive at diagnosis, 78% completed treatment, 11% transferred within or outside the United States or were lost to follow-up, and 1% stopped treatment because of adverse events (Table 6). For no patients did treatment fail or TB recur within the year after treatment completion. Of the 134 patients, 12 (9%) died during treatment; 75% of these deaths were considered TB related. No XDR TB patient died. Death during treatment was significantly associated with age ≥ 65 years (AOR 20.2, 95% CI 2.3–181.0), smoking (AOR 6.4, 95% CI 1.0–39.4), or HIV infection (AOR 6.3, 95% CI 1.1–37.7) (online Technical Appendix). When TB medications and interaction terms were initially included in the model, HIV infection was no longer associated with death and receipt of an effective injectable medication was associated with lower odds of dying (AOR 0.02, 95% CI 0.002–0.2) (online Technical Appendix). No HIV-infected patient who received an effective injectable medication died. Of 9 patients who died of TB-related causes, only 2 who had received a 5-drug regimen died, both after 8 months; 1 had received 3 non-first-line medications and died after 5 months, and the remaining 6 never received ≥ 2 MDR TB second- or third-line medications and died within 49 days of treatment initiation.

Table 3. Clinical characteristics of study participants and other patients with MDR and/or XDR TB, United States, 2005–2007*

Characteristic	Study participants, no. (%), n = 135	All US MDR TB patients, no. (%), n = 370
History of LTBI, % of 130 known	21 (16)	
History of completing LTBI Rx, % of 21 with history of LTBI	14 (67)	
History of TB disease†	48 (36)	60 (16)
Contact with infectious TB patient, % of 87 known	10 (11)	
Contact with infectious MDR TB patient, % of 10 contacts	6 (60)	
Dead at TB diagnosis	1 (1)	5 (1)
Smear positive at any time, % of 134 alive at diagnosis†	103 (77)	223 (60)
Sites of TB disease		
Pulmonary	115 (85)	332 (90)
Extrapulmonary only	8 (6)	37 (10)
Disseminated at any time	12 (9)	
Extent of pulmonary disease at diagnosis		
Extensive	69	
Moderate	31	
Minimal	21	
Undocumented	6	
Description of extensive pulmonary disease, at any time		
Miliary	4	
Cavitary	58	127
Multiple lobes	70	
Collapsed lobes	6	
Extent of extrapulmonary disease at diagnosis		
Extensive	2	
Moderate	3	
Minimal	3	

*MDR, multidrug resistant; XDR, extensively drug resistant; TB, tuberculosis; LTBI, latent TB infection; Rx, treatment. Blank cells indicate data not available.

†Statistically significant differences between percentages of study patients and all US MDR TB patients at p<0.05.

Of the 4 HIV-infected patients who died of TB-related causes, 3 had a CD4 count of ≤ 50 cells/mm³ at initiation of TB treatment and the other had a CD4 count of ≤ 100 cells/mm³. Of these 4 patients, 2 were taking ≥ 3 anti-HIV medications.

Among patients alive at diagnosis, a median of 1 adverse event (average 2.9) resulted in medication change or adjustment, but only 2 patients completely stopped treatment. According to multivariate linear regression, use of clofazimine was significantly associated (p<0.05) with more adverse events but was not associated with death during treatment. Of 9 patients receiving clofazimine, 6 experienced postinitiation gastrointestinal effects that

resulted in their discontinuing clofazimine. Because of MDR TB or its treatment, of the 134 patients, 13% experienced hearing impairment, 13% hepatitis, 11% renal impairment, 8% difficulty ambulating, 7% visual impairment, and 1% seizures. Depression or psychosis was documented for 19% (80% of whom were taking cycloserine), and pulmonary impairment was documented for 4%. Of 103 impairments, 66% were mild, but another 7% were graded most severe and occurred for 6 patients, 3 of whom completed treatment; 2 of those patients died (lung and mobility impairments), and 1 transferred outside the country.

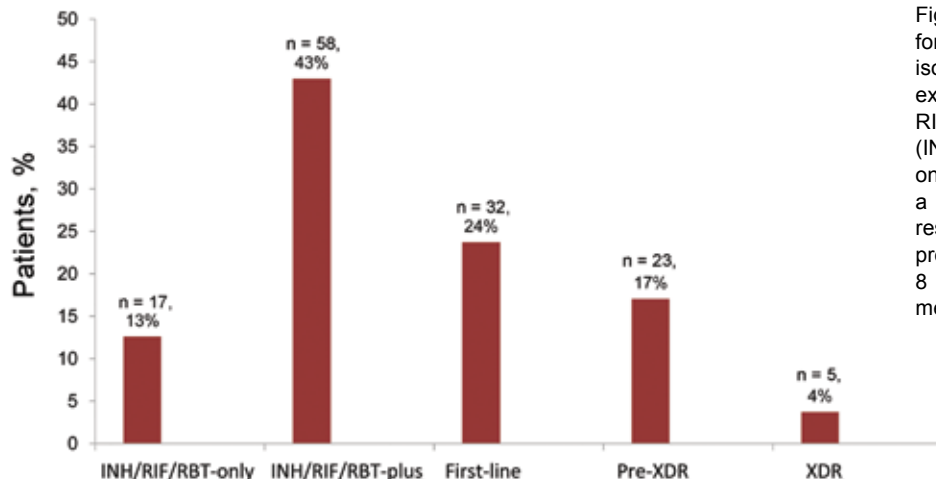


Figure 1. Percentage of 135 patients for whom *Mycobacterium tuberculosis* isolates had the following mutually exclusive resistance patterns. INH/RIF/RBT-only, resistant to isoniazid (INH)/rifampin (RIF)/rifabutin (RBT) only; INH/RIF/RBT-plus, resistant to a median of 4 medications; first-line, resistant to a median of 6 medications; pre-XDR, resistant to a median of 8 medications; XDR, resistant to a median of 11 medications.

Table 4. Characteristics associated with any acquired antimicrobial drug resistance during MDR TB treatment, 128 patients, California, Texas, and New York, NY, USA, 2005–2007*†

Variable	Initial OR estimate	Initial 95% CI	Initial Pr> χ^2	Final OR estimate	Final 95% CI	Final Pr> χ^2
Age \geq 65 y	<0.001	<0.001–>999.999	0.973			
Black race	33.19	0.80–>999.999	0.065	4.07	1.08–15.37	0.039
Recent homelessness	18.76	0.93–377.71	0.056	5.81	1.17–28.86	0.031
Pre-XDR or XDR TB	8.78	2.31–33.42	0.001	5.15	1.86–14.21	0.002
AFB-smear positive	5.34	0.86–33.22	0.072			
Age 25–44 y	4.83	0.65–36.03	0.124			
Hispanic ethnicity	4.83	0.11–216.20	0.417			
\geq 4 Effective medications	3.46	0.41–29.47	0.256			
Age 45–64 y	3.41	0.39–30.21	0.271			
Asian race	3.35	0.07–151.32	0.534			
Disseminated TB disease	2.28	0.21–24.20	0.495			
Foreign born	2.10	0.15–28.64	0.577			
Recent cigarette smoker	1.96	0.41–9.31	0.397			
Recent excess alcohol use	0.99	0.13–7.65	0.988			
TB clinic outpatient management	0.98	0.18–5.35	0.980			
Recent unemployment	0.97	0.24–3.93	0.964			
Cavitary disease	0.77	0.21–2.84	0.694			
Diabetes	0.76	0.16–3.70	0.732			
History of TB disease	0.44	0.12–1.59	0.208			
HIV infection	0.39	0.03–4.92	0.463			
Recent injection drug or noninjection drug use	0.15	0.00–5.08	0.291			

*MDR TB, multidrug-resistant tuberculosis; XDR TB, extensively drug-resistant TB; OR, odds ratio; AFB, acid-fast bacilli; Pr, probability. Boldface indicates significance in the final model. Blank cells indicate variables not retained in the final model.

†Model fit intercept and covariates: Akaike information criterion, initial 136.392, final 116.619; Schwarz criterion, initial 198.964, final 127.996; $-2\log L$, initial 92.392, final 108.619.

Cost of MDR TB and XDR TB

Direct costs averaged \$134,000 (SE \$9,683) per MDR TB patient and \$430,000 (SE \$73,109) per XDR TB patient. In comparison, costs are estimated at \$17,000 (SE \$1,210) per non-MDR TB patient (Figure 2 and online Technical Appendix). For isoniazid/rifampin/rifabutin-only, direct costs averaged \$77,000 (SE \$15,448) and direct-plus-productivity-loss costs averaged \$226,000 (SE \$73,338). Outpatient medications comprised \approx 40% of direct costs, averaging \$53,300 for MDR TB and \$164,000 for XDR TB patients. Direct-plus-productivity-loss costs averaged \$260,000 (SE \$23,212) per MDR TB patient and \$554,000 (SE = \$127,707) per XDR TB patient. Highest costs were nearly \$1.8 million. Applying these averages to 364 cases of MDR TB and 9 cases of XDR TB in the United States during 2005–2007, direct costs were \approx \$53 million and direct-plus-productivity-loss costs were \approx \$100 million.

When days hospitalized were controlled for, characteristics associated with greater direct costs, in descending order, were having XDR TB, residency in a long-term-care institution, non-injection-drug use, HIV infection, or having public insurance (adjusted $R^2 = 0.55$). When days hospitalized were controlled for, characteristics associated with greater direct-plus-productivity-loss costs were death, XDR TB, non-injection-drug use, HIV-infection, diabetes, or being male ($R^2 = 0.66$) (online Technical Appendix)

Table 2 shows that known insurance status was indicated on clinic records of 112 patients. Of 76 patients for

whom insurance coverage while hospitalized was known, 38% had public insurance (including 32% Medicaid), 36% had no insurance, 24% had private insurance, 4% were in jail/prison, and 1% had other insurance. The public sector covered (i.e., by public insurance, for outpatients who had no/unknown insurance, for uninsured inpatients cared for in publicly financed hospitals, for jail/prison inmates) 75% of MDR TB and 100% of XDR TB patients and incurred 80% of MDR TB direct costs (\$13,883,000/\$17,415,000) and 100% of XDR TB direct costs (\$2,149,000).

Discussion

In this population-based sample, which comprised 36% (130/364) of MDR TB and 56% (5/9) of XDR TB cases reported in the United States during 2005–2007, MDR/XDR TB diagnosis and treatment were very complex: *M. tuberculosis* isolates were resistant to a large number of medications, care was complicated by extensive disease and by concurrent conditions, and patients were highly infectious.

Despite this complexity, for nearly all eligible patients, sputum cultures converted to negative and 78% of patients completed treatment, including all those with XDR TB. Only 1% stopped treatment because of adverse events. The mortality rate (10%) was lower than that for other countries (13–17), and the mortality rate for patients during treatment (9%) was similar to that for US patients with isoniazid/rifampin-susceptible TB (8%) (L. Armstrong, pers. comm.). Among patients who died, 75% (9/12) of deaths

Table 5. Characteristics associated with expert consultation for 134 patients during MDR TB treatment, California, Texas, and New York, NY, USA, 2005–2007*†

Variable	Initial OR estimate	Initial 95% CI	Initial Pr> χ^2	Final OR estimate	Final 95% CI	Final Pr> χ^2
XDR TB	>999.999	<0.001–>999.999	0.939			
Recent homelessness	>999.999	<0.001–>999.999	0.887			
Correctional institution residence	>999.999	<0.001–>999.999	0.939			
Recent injection drug or noninjection drug use	61.63	0.00–>999.999	0.401			
Recent cigarette smoker	27.88	0.56–>999.999	0.096			
Diabetes	26.44	1.28–545.80	0.034			
Disseminated TB disease	9.49	0.18–501.11	0.266			
TB clinic outpatient management	7.96	1.50–42.32	0.015	5.67	1.93–16.64	0.002
Age 45–64 y	4.30	0.38–48.55	0.239			
Recent unemployment	3.81	0.52–28.18	0.190			
Age 25–44 years	2.92	0.58–14.63	0.192			
Long-term care facility resident	1.87	<0.001–>999.999	0.878			
5-drug regimen	1.13	0.22–5.82	0.882			
Total no. adverse events	1.12	0.88–1.42	0.371			
Total first-line resistance	0.63	0.11–3.77	0.614			
Acquired resistance	0.57	0.07–4.37	0.588			
Foreign born	0.55	0.03–12.28	0.705			
History of TB disease	0.53	0.13–2.10	0.363			
Age >65 y	0.50	0.02–14.97	0.687			
HIV infection	0.34	0.02–7.21	0.492			
Pregnant	0.28	0.02–5.15	0.393			
Private insurance	0.14	0.02–0.87	0.035	0.23	0.08–0.68	0.008
Pre-XDR	0.12	0.01–1.35	0.087			
Male	0.12	0.02–0.82	0.031			
Died	0.05	<0.001–3.46	0.165			
White race	0.05	<0.001–>999.999	0.988			
Recent excess alcohol use	<0.001	<0.001–0.06	0.002	0.19	0.05–0.72	0.014
Black race	<0.001	<0.001–>999.999	0.937			
Hispanic ethnicity	<0.001	<0.001–>999.999	0.938			
Asian race	<0.001	<0.001–>999.999	0.943			

*MDR TB, multidrug-resistant tuberculosis; XDR TB, extensively drug-resistant TB; OR, odds ratio. Boldface indicates significance in the final model.

Blank cells indicate variables not retained in the final model.

†Model fit intercept and covariates: AIC (initial 133.402, final 121.683), SC (initial 223.235, final 133.274); $-2\log L$ (initial 71.402, final 113.683).

were TB-related, and 67% (6/9) occurred within 49 days of TB diagnosis. Among HIV-infected patients, failure or inability to use an effective injectable TB medication was associated with TB-related death.

Some diagnostic and treatment practices contributed to successful outcomes. Among symptomatic patients, initial TB diagnosis was made relatively quickly, within 7 weeks of symptom onset. Nearly three-fourths (73%) of patients were hospitalized; duration was 1 month for non-XDR TB patients and 9 months for XDR TB patients. Extensive DST of first-line and second-line medications was conducted within 2 months of treatment initiation for most patients. At some point during treatment, 61% of patients were receiving a 5-drug regimen. For outpatient care, DOT was used nearly universally, including during home isolation as recommended by national guidelines (7). The physicians of most patients with MDR/XDR TB consulted with experts. However, patient management required intensive monitoring and numerous medication changes. Case management services were also intensive; a case manager was assigned to $\approx 90\%$ of patients.

Deficiencies in practices were identified. Despite CDC recommendations, $\approx 20\%$ of patients had no documentation

of expert consultation. Outcome was unknown for 3% who transferred within and 6% outside the United States and for 2% who were lost to follow-up. Acquisition of any drug resistance during treatment occurred for 21% of patients and was more likely to occur in populations difficult to treat (those who had pre-XDR TB or XDR TB or were homeless), suggesting a need for more vigilant treatment monitoring. There were delays of ≈ 3 months before patients started a 5-drug regimen. Today, the use of more rapid molecular diagnostic techniques could shorten the time to initiation of an appropriate treatment regimen (18). Since September 2009, CDC has offered US sites a molecular-based testing service (www.cdc.gov/tb/topic/laboratory/guide.html).

Because MDR TB treatment lasts >2 years (vs. 6 months for drug-susceptible TB), uses expensive medications, and requires hospitalization for $\approx 75\%$ of patients (vs. 50% with drug-susceptible TB), it was very costly to treat and manage; average direct cost was \$134,000 per MDR TB patient and \$430,000 per XDR TB patient. The estimated \$17,000 per non-MDR TB patient is 8 and 25 times lower than the costs for MDR TB and XDR TB, respectively. In contrast, lifetime care per HIV-infected

Table 6. Treatment outcomes of MDR/XDR TB study patients alive at diagnosis, by resistance pattern, California, Texas, and New York, NY, USA, 2005–2007*

Resistance pattern	Completed treatment, %	Transferred within United States, %	Transferred out of United States, %	Lost to follow-up, %	Stopped because of side effects, %	Died during treatment, %
All, N = 134	78	3	6	2	1	9
INH/RIF/RBT-only, n = 17	59	0	18	6	0	18
INH/RIF/RBT-plus, n = 58	83	3	7	0	0	7
First-line, n = 32	78	0	3	6	3	9
Pre-XDR, n = 22	77	9	0	0	5	9
XDR, n = 5	100	0	0	0	0	0

*MDR TB, multidrug-resistant tuberculosis; XDR TB, extensively drug-resistant TB; INH, isoniazid; RIF, rifampin; RBT, rifabutin.

patient costs \$380,000 (updated to 2010 dollars) (19) and lifetime care per breast cancer patient costs \$20,000–\$100,000 (20).

During 2005–2007, the 373 MDR/XDR TB cases cost the US health care system an estimated \$53 million; during this time there were ≈41,000 total TB cases. Direct costs for an average XDR TB patient were 3.2 times those for an average MDR TB patient, mostly because of hospitalization costs. Only 20% of XDR TB and 28% of MDR TB patients were managed solely as outpatients. The public sector incurred 80% of the MDR TB costs and 100% of the XDR TB costs.

With health care reform, a substantial proportion of uninsured TB patients are expected to become eligible for Medicaid coverage, which should increase access to health care and early TB diagnosis and decrease TB-associated hospitalizations and deaths. Prevention opportunities for MDR TB are limited. Maintaining the capacity of public health departments and of publicly financed hospitals to act as safety nets (regardless of patient insurance status) to quickly diagnose MDR/XDR TB and isolate and effectively treat the patients will be critical for preventing deaths and transmission of drug-resistant TB organisms. Investment in infection control infrastructure and the capacity to prevent TB among MDR TB patient contacts is also critical; our cost-of-illness estimates did not include

these programmatic costs of preventing cases. During the 1979–1994 TB resurgence and MDR TB outbreaks in the United States, New York City renovated hospitals and the Rikers Island prison and treated 20,000 excess TB patients at a cost of ≈\$1.7 billion (updated to 2010 dollars) (21).

This study had some limitations. Detailed hospitalization records were unavailable for 17 patients. Moreover, documentation of care for incarcerated patients was limited. Follow-up data for all patients were unavailable after 1 year of treatment. Because outpatient care was provided by a mixture of public and private providers, we used average wholesale medication prices to estimate medication costs, which overestimated actual costs to TB clinics that have access to reduced (often one half to one third) medication prices negotiated with pharmaceutical companies. Estimates of out-of-pocket costs were not included.

Conclusions

In this population-based sample of MDR/XDR TB patients in the United States, despite the extensive drug resistance found at the time of diagnosis, culture conversion and treatment completion rates were high and mortality rates were low. Records of treatment practices documented near-universal use of DOT. However, these outcomes came at a high cost to the public sector, providing incentives for

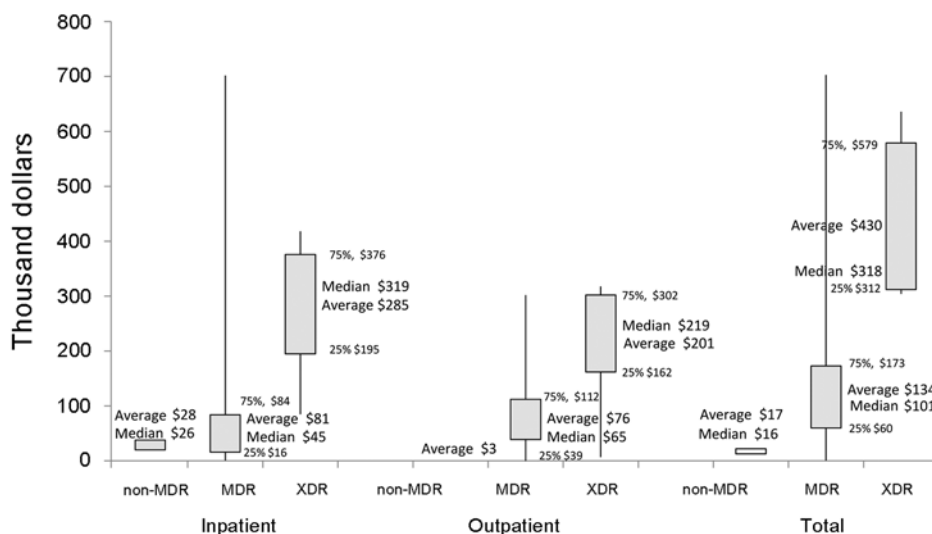


Figure 2. Average, median, and distribution of direct costs per patient in 2010 US dollars by drug resistance. This box-plot diagram shows the minimum and maximum values (vertical lines), the averages and medians (numbers), and the interquartile ranges (box). MDR, multidrug-resistant tuberculosis; XDR, extensively drug-resistant tuberculosis.

the United States to prevent MDR/XDR TB. Preventing MDR/XDR TB in the United States will require addressing factors associated with development of drug resistance in countries where foreign-born US patients originate, as well as rapid diagnosis, appropriate regimen selection, robust case management practices, and continued emphasis on DOT in the United States.

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etymologia

Papillomavirus

[pap-ĭ-lo-mə-vi-rəs]

From the Latin *papillo-* (“nipple”) + *oma* (“tumor”), papillomaviruses are nonenveloped DNA viruses that induce exophytic lesions of the skin and mucous membranes. The first animal papillomavirus was described in 1933 by Richard Shope, who researched papillomata in

“warty” wild cottontail rabbits. In 1975, Harald zur Hausen published the hypothesis that the human papillomavirus played a role in the etiology of cervical cancer, work for which he was awarded the Nobel Prize in Physiology or Medicine in 2008.

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Table of Contents
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Treatment Practices, Outcomes, and Costs of Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis, United States, 2005–2007

Technical Appendix

Contents

1. Additional Methods
 - a. Sampling
 - b. Data Collection
 - c. Data Analysis
2. Cost Analysis
 - a. Inpatient Cost Estimation
 - b. Outpatient Cost Estimation
 - c. Total Direct Cost Estimation
 - d. Productivity Loss Estimation
 - e. Cost Analyses
3. Definitions
4. Additional Results
 - a. Percent of Patients Having Isolates Tested within 30 days of Medications Start and Resistance to Medications
 - b. Percentage of Patients on Various Medications at Any Time During Treatment
 - c. Median Months to Event
 - d. Acquired Resistance Multivariate Model
 - e. Death During TB Treatment Multivariate Model A
 - f. Death During TB Treatment Multivariate Model B
 - g. Inpatient Direct Costs Boxplot
 - h. Outpatient Direct Costs Boxplot
 - i. Total Direct Costs Boxplot
 - j. Productivity Losses Boxplot
 - k. Direct Costs and Productivity Losses Boxplot
 - l. MDR TB Direct Costs Multivariate Model
 - m. MDR TB Direct Costs and Productivity Losses Multivariable Model
 - n. Cost Estimation of Drug-susceptible TB Costs

Additional Methods

Sampling

Each participating site identified MDR-TB and XDR-TB patients reported to CDC during 2005–2007. All XDR-TB patients were selected for participation in the study. From the sampling

frame of MDR-TB patients, a simple random sample of 75% was selected from California and New York and of 50% from Texas. In one instance in New York, a randomly selected patient whose records were unavailable was replaced with another randomly selected patient.

Data Collection

Data were abstracted onto standardized data collection forms, one for TB clinic records and one for each hospitalization, which were entered into separate databases. Separate Excel spreadsheets were used for direct entry of abstracted data on specimens, chest radiography/CT exams, and medications. All databases were converted to SAS for analysis.

Data Analysis

From the originally collected variables, we created the following new variables:

- First date of a positive specimen
- First and last date of positive specimen culture
- Sputum-culture-conversion date: the first date (at least 7 days after the date of last sputum-culture positivity) of 2 consecutive negative sputum-culture results, with 3 categories of exceptions:
 - If there were not 2 consecutive negative culture results 7 days after the last positive, used the available date 7 days after (3 patients).
 - If there were 2 consecutive negative culture results, but the 2nd result was more than a month after the first and the first is not quite 7 days from the last positive, use the first even though it is not quite 7 days after (1 patient)
 - If there were at least 2 negative culture results after the last positive, but none met the 7 day criteria, use the last one available (otherwise the patient would have qualified as no culture conversion) (1 patient)
- First date and duration of TB medications
- First date of diagnosis: earliest of report date, first medication, first positive specimen
- First date and duration of symptoms: from various documented symptoms
- First date and duration of respiratory isolation, intensive care unit, mechanical ventilation
- Days hospitalized: sum of days hospitalized over all TB-related hospitalizations
- Any resistance to each medication
- Initial resistance to each medication within 30 days of TB treatment start
- Acquired resistance to any medication: any resistant result after a susceptible result
- Five mutually exclusive categories of drug resistance: INH/RIF/RBT-only, INH/RIF/RBT-plus, First-line, Pre-XDR, XDR
- Milligrams per medication per week per patient: dose*frequency per week*weeks
- Days to culture conversion: date of culture conversion minus date of TB medications start
- Medication duration: days on each individual medication before and after culture conversion
- Effective medication duration: days on each individual medication to which the isolate was never resistant
- Start and duration of a 5-drug regimen: the date the patient started taking at least 5 medications (including an INJ and FQ) to which their TB isolate was never resistant
- Days infectious: number of days 12 weeks prior to first symptom or, if asymptomatic, prior to initial diagnosis through culture conversion or medications stop
- Number of outpatient DOT visits per patient: DOT regimen*frequency per week*weeks

- Total number of chest radiographs and CTs per patient
- Disseminated disease: TB in ≥ 2 noncontiguous sites at any time during treatment
- Died during treatment: if the reason for treatment stop was died, or hospital disposition was died
- History of TB: if there was a history of TB from either clinic or hospital records or patient self-report
- History of latent TB infection: if there was a history of LTBI from either clinic or hospital records or patient self-report
- Homeless: if in a homeless living situation within the year prior to TB treatment or hospitalization, or if homeless at TB diagnosis or during TB treatment
- Prison/jail inmate: if incarcerated within the year prior to TB treatment or hospitalization, or if an inmate at TB diagnosis or during treatment
- Unemployed: if primary occupation within the year prior to TB treatment was “unemployed”
- Uninsured: if no health insurance during TB treatment, separately for clinic and hospitalization
- Smoker: if patient smoked at least once within the year prior to clinic intake or hospitalization
- Long-term-care facility resident: if the patient was a resident of a long-term-care facility at TB diagnosis or within 3 months prior to TB treatment start

The following data analyses were performed:

- Compared the representativeness of study data with National TB Surveillance System (NTSS) data¹
- Examined homelessness prior to TB, during TB treatment, housing assistance
- Examined unemployment prior to TB, because of TB
- Summarized DST testing by medication, initial resistance, ever resistance, and acquired resistance
- Calculated the median number of DSTs on medications, median number of medications having resistance
- Assessed associations with pre-XDR and XDR combined vs. other MDR patients
- Examined resistance patterns by country of birth, compared with NTSS all-TB data by country of birth
- Identified medications to which resistance was acquired during treatment
- Identified factors associated with any acquired resistance
- Calculated the percentage of patients diagnosed while hospitalized
- Assessed symptoms
- Calculated the median days to initial diagnosis
- Calculated the median months of infectiousness
- Calculated the percentage of patients on each medication at any time during treatment
- Calculated the medication changes per patient, reasons
- Examined whether patients were hospitalized, the number of hospitalizations, and reasons for hospitalization
- Calculated the outpatient DOT use per medication
- Calculated the number of medications taken prior to culture conversion to which the patient’s isolate was never resistant

- Calculated the median days from medications start to 5-drug regimen start, 5-drug regimen to culture conversion, any regimen to culture conversion, 5-drug regimen to treatment stop, by drug resistance pattern
- Calculated the median treatment length and by resistance pattern and 5-drug regimen
- Identified factors associated with treatment longer than 2 years after culture conversion
- Assessed culture conversion by resistance pattern and by number of effective medications prior to culture conversion
- Analyzed treatment outcomes by resistance pattern, comparison with US MDR/XDR and U.S. drug-susceptible cases
- Calculated the number of days to TB-related death, by 5-drug regimen and for HIV+ by highly active antiretroviral treatment (HAART)
- Calculated the median days on effective medications before and after culture conversion by resistance pattern
- Identified characteristics associated with death during treatment
- Calculated the median and average number of adverse events by resistance pattern and association with individual and combined medications
- Calculated the median days of inpatient (inpatient days, respiratory isolation) and outpatient care (total outpatient, DOT days, outpatient isolation)
- Measured the number of outpatient procedures: chest radiographs, smears, cultures
- Assessed receipt of expert consultation, associations with expert consultation
- Calculated case management usage types and frequency
- Assessed use of interpreters by non-English speaking patients
- Analyzed impairment during treatment

Cost Analysis: Inpatient Cost Estimation

From total charges per TB-related hospitalization that were collected, inpatient costs were calculated by:

- Converting all charges to 2010 inflation-adjusted dollars using the Consumer Price Index for Medical Care²
- Converted charges to costs by multiplying the charges by each hospital's cost-to-charge ratio³
 - If a specific hospital's cost-to-charge ratio was unavailable, we used operating-cost-to-charge ratio average for the state (CA=0.32, NY=0.46, TX=0.40)
- Converted site-specific costs, using Medicare Geographic Adjustment Factors⁴ as the cost-of-living adjustment factor, to a US basis for aggregation (CA=1.13, NY=1.08, TX=0.94)
- Added in physician costs for each hospitalization day from the 2009 Physicians' Fee and Coding Guide of \$238.50 for the first day of hospitalization at Level 2,⁵ converted to a cost by multiplying by the average cost-to-charge ratio for pulmonary diseases 0.502,⁶ updated to 2010 dollars using the Medical Care CPI,² for a value of \$123.81. The remaining hospitalization days were calculated similarly from a 2009 charge of \$131 to a cost of \$68/day.
- For 17 patients for whom we were not able to obtain detailed hospital data, the length of stay (which was obtained for all patients) was multiplied by an average cost per day (\$1419) for hospitalizations for which we did have data

Cost Analysis: Outpatient Cost Estimation

Outpatient costs were estimated as follows:

- Computed the number of outpatient days of treatment
- Estimated outpatient diagnosis costs, using numbers of chest radiographs (2 views \$30.97), computed tomographies (\$308.99), AFB smears (\$7.70), *M.tuberculosis* cultures (\$15.48), DSTs (\$8.10), and other diagnostic tests, and applied Centers for Medicare and Medicaid Lab Schedule Fees⁷
- Often, DOT visits were not specified as taking place at the clinic or at home, so we estimated that 11% of DOT visits occurred in the clinic (5 days/week for 6 weeks=30 visits, plus 25 visits for the remaining 490 work days of a 2-year period of 520 work days), and the remaining 89% of DOT visits occurred in the patient's home. Costs for a home DOT visit (\$32.70) were estimated using the 2001 Physicians' Fee and Coding Guide Medicare Allowable Charge for a home DOT visit by a nurse (\$49)⁸ and updating it to 2010 dollars using the change in home health care average weekly earnings² and converting it to a cost by multiplying by 50.2%, the average cost to charge ratio for pulmonary diagnostic related group (DRG)⁶: $(49 * (484.58 / 364.51) * .502)$). Costs for clinic DOT visits (\$38.63) were estimated using the 2009 Physicians' Fee and Coding Guide average outpatient physician visit charge for an established level 2 patient (\$58.67 for Level 2 patient⁵), then updated to 2010 dollars using the CPI/MC, converted to a cost by multiplying by 0.502, plus 15 minutes of a nurse based on the cost of an outpatient DOT visit: $(58.67 * (388.436 / 375.613) * .502) + (.25 * (49 * (484.58 / 364.51) * .502))$.
- Estimated outpatient medication costs by multiplying the total outpatient mg. of each medication by its Red Book average wholesale price per mg.⁹ Added therapeutic monitoring costs (CBC \$11.14, LFT \$11.70), according to the Drug-Resistant Tuberculosis Survival Guide for Clinicians,¹⁰ for those on CYC, AMK, CAP, KAN.

Costs per mg by medication were:

- o INH=(0.000517778)
- o RIF=(0.006702778)
- o RBT=(0.102664)
- o RPT=(0.02765)
- o PZA=(0.002381)
- o EMB=(0.004448)
- o SM=(0.00432)
- o CAP=(0.175)
- o KAN=(0.006041667)
- o AMK=(0.06771)
- o CIP=(0.0026254)
- o LEV=(0.0385332)
- o MOX=(0.048954167)
- o GAT=(0.10723)
- o ETH=(0.0168836)
- o PAS=(0.000934417)
- o CYC=(0.024)
- o CLO=(0.2022)
- o LIN=(0.194871667)
- o CLR=(0.008477)

- o AZI=(0.04242)
- Estimated, using Centers for Medicare and Medicaid Lab Schedule Fees,⁷ outpatient lab tests for baseline tests (CBC with WBC differential [\$11.14], comprehensive metabolic panel \$15.14, LFT [\$11.70], HIV EIA initial [\$19.65] and follow-up Western Blot test [\$38.35] if positive, TSH [\$24.06] if on CYC or ETH, and 6 drug levels [\$21.59] for those on CAP, KAN, AMK, SM, or CYC). Estimated ongoing lab tests, based on the MDR-TB Survival Guide,¹⁰ for those on treatment longer than one week (monthly CBC, monthly LFT, monthly comprehensive metabolic panel for those on CAP, KAN, AMK, SM, monthly audiometry [\$34.38] if on AMK, CAP, KAN, SM, monthly visual function screening [\$3.06] if on EMB, CLO, RBT, LIN, quarterly TSH for those on CYC, ETH, PAS)
- Estimated case management costs, based on the frequency of each type of case management.
 - o Transportation costs were estimated at \$20/week in LA, \$29/week in NYC, \$17.50/week in TX.
 - o Housing costs were estimated at \$31/day in CA, \$37/day in NY, \$19/day in TX.¹¹
 - o Social worker costs were estimated at \$23.95 for 2 days consultation.¹²
 - o Interpreters were estimated at \$21.73/hour¹²
- Calculated outpatient direct costs as the sum of outpatient diagnosis, outpatient DOT, outpatient medication, outpatient lab, and case management costs.

Cost Analysis: Total Direct Cost Estimation

Estimated total direct costs as the sum of outpatient direct costs and inpatient direct costs.

Cost Analysis: Productivity Loss Estimation

Estimated productivity losses as follows:

- o Calculated a disability adjustment based on responses to Adverse Events variable on the clinic form, 100% divided into 6 segments (100%, 83%, 67%, 50%, 33%, 17%)
- o Estimated inpatient productivity losses as follows: Applied a value of work plus home production, updated to 2010 dollars using the change in average hourly earnings,¹³ at \$224/day for employed patients, and just home production (\$40) for non-employed to each day hospitalized¹⁴
- o Estimated outpatient productivity losses as follows: ½ day for each DOT day, a full day if in outpatient isolation, times the disability adjustment factor for all remaining outpatient days
- o Estimated one year of productivity losses for one year after treatment for one person who had documentation, at 50% disability, and discounted it using a 3% social discount rate.
- o For TB-related deaths (9/13 deaths), applied a value of remaining lifetime productivity, updated to 2010 dollars using the change in average hourly earnings,¹⁵ based on the age at death¹⁴
- o Estimated total productivity loss as the sum of inpatient productivity loss, outpatient productivity loss, after treatment productivity loss, and productivity loss due to premature death.

Cost Analyses

- Estimated 3 illness severity categories similar to analysis done in the previous TB hospitalization study:
 - o Category 1= those who died from TB-related causes
 - o Category 2= any comorbidities, pregnancy, disseminated or extensive disease
 - o Category 3= all remaining cases
- Calculated average costs by resistance pattern, by illness severity, and for each cost category
- Identified characteristics associated with high direct and societal costs
- Estimated U.S. MDR/XDR direct and direct-plus-productivity-loss costs during 2005-2007 by applying average costs per study patient to the U.S. cohort of cases during the period.
- Assessed who paid the costs by public sector/private sector insurance

Study Definitions

Initial diagnosis: earliest of TB medication start, collection of first positive specimen (AFB-smear, M. tuberculosis culture, PCR, HPLC, or NAA), or report date (date the health department first suspected a patient had TB)

First-line TB Medications: isoniazid (INH), rifampin (RIF), rifabutin (RBT), pyrazinamide (PZA), ethambutol (EMB), streptomycin (SM),

Second-line TB Medications: capreomycin (CAP), kanamycin (KAN), amikacin (AMK), any second-line injectable (INJ), ciprofloxacin (CIP), ofloxacin (OFL), levofloxacin (LEV), moxifloxacin (MOX), gatifloxacin (GAT), any fluoroquinolone (FQ), ethionamide (ETH), para-aminosalicylic acid (PAS), cycloserine (CYC),

Third-line TB Medications: clofazimine (CLO), linezolid (LIN), clarithromycin (CLR), azithromycin (AZI)

MDR TB: resistance to at least INH and RIF

Initial resistance: any resistance found on the initial TB isolate cultured within 30 days of specimen collection in the U.S.

Acquired resistance: any resistance found after a documented prior susceptible culture

Resistance patterns, mutually exclusive:

- INH/RIF/RBT-only
- INH/RIF/RBT-plus other resistance to any of the following: PZA, EMB, SM, PAS, ETH, or CYC (excluding total first-line resistance)
- Total First-line: resistance to INH, RIF, PZA, and EMB
- Pre-XDR: MDR TB plus resistance to a FQ or an INJ
- XDR: MDR TB plus resistance to both a FQ and a INJ

5-drug-regimen: an INJ, a FQ, and ≥ 3 other medications to which M. tuberculosis was never resistant

Infectious period: began 12 weeks before earliest of first symptom, first medication, first positive specimen collection, or report date; ended at culture conversion, or, if no culture conversion, censored at medications stop

Date of culture conversion: After the last positive-sputum-culture, the first date (≥ 7 days after last positive) of 2 consecutive negative-sputum-culture results

Disseminated disease: ≥ 2 non-contiguous sites of disease

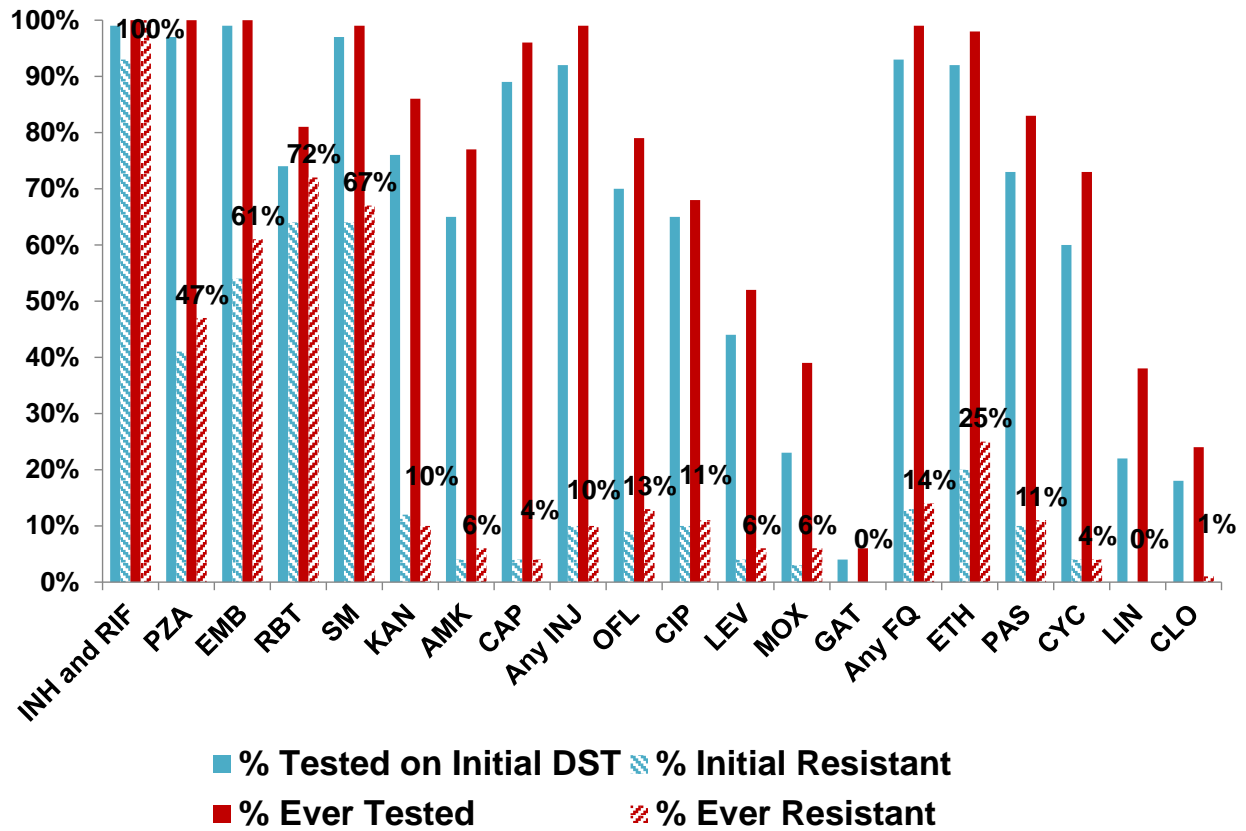
Extensive disease: incapacitating, preventing normal everyday activities

Moderate disease: sufficiently discomforting to interfere with normal everyday activities

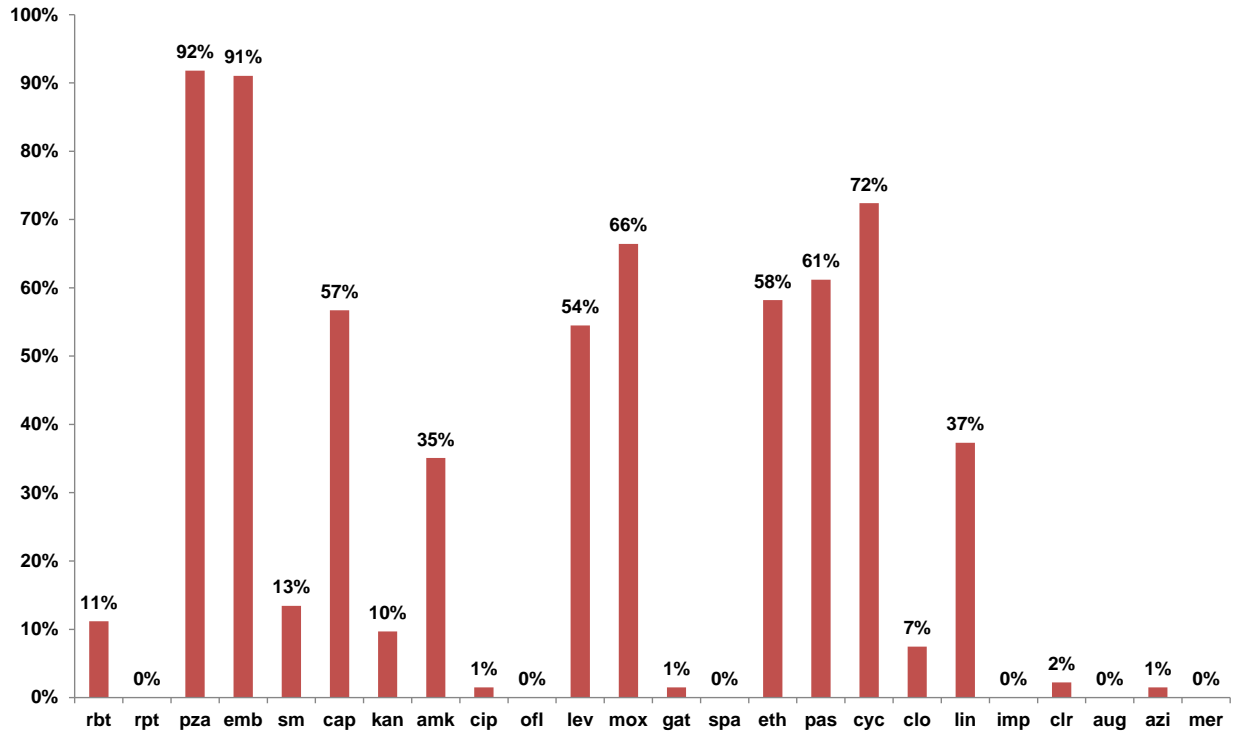
Minimal disease: causing minimal discomfort, easily tolerated, not interfering with everyday activities

Additional Results

Percent of Patients Having Isolates Tested within 30 days of Medications Start and Resistance to Medications, N=134

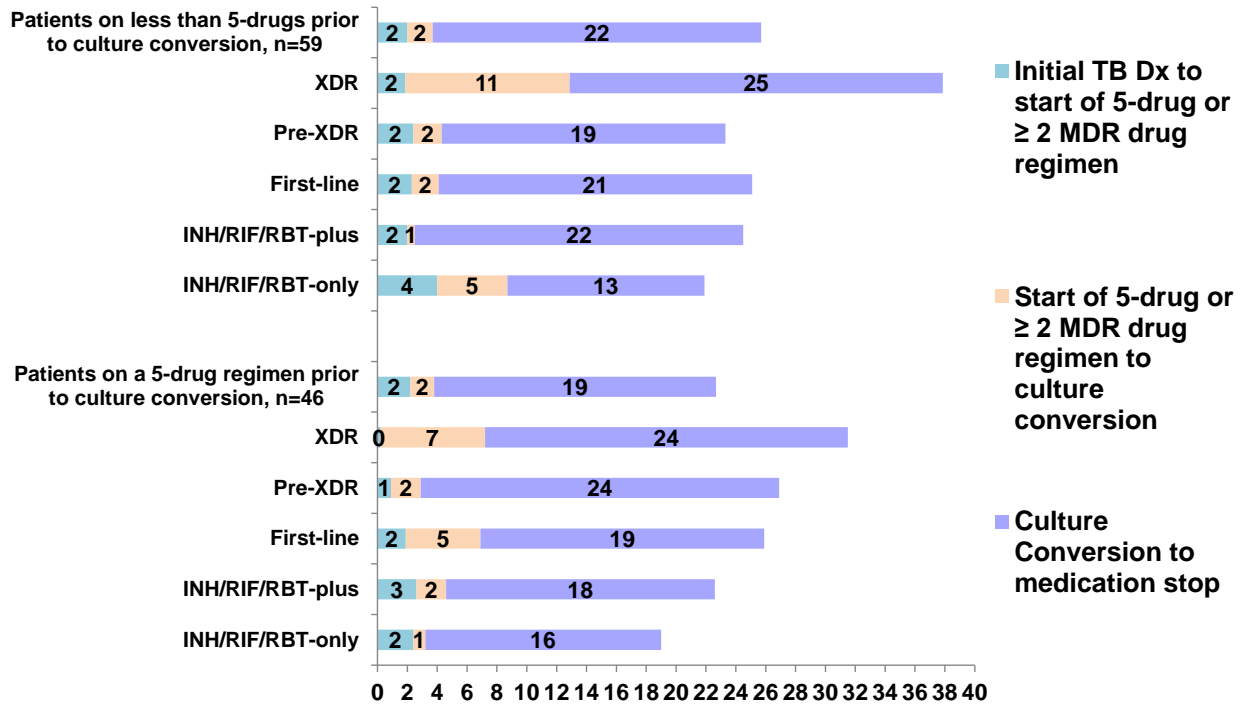


**Percentage of Patients on Various Medications at Any Time During Treatment
(N= 134 patients)***



* 1 patient was diagnosed at death and was not started on medications

Median Months to Event



Acquired Resistance Multivariate Models

Variable	Initial	Initial	Initial	Pr > ChiSq	Final	Final	Final	Final	
	95%	95%	95%		95%	95%	95%	95%	
	Odds Ratio	Confidence	Confidence		Odds Ratio	Confidence	Confidence	Odds Ratio	
Estimate	Lower Limit	Upper Limit	Estimate	Lower Limit	Upper Limit	Estimate	Lower Limit	Upper Limit	Pr > ChiSq
Age 65 or over	<0.001	<0.001	>999.999	0.973					
Black race	33.19	0.80	>999.999	0.065	4.07	1.08	15.37	0.039	
Recent homelessness	18.76	0.93	377.71	0.056	5.81	1.17	28.86	0.031	
Pre-XDR or XDR TB	8.78	2.31	33.42	0.001	5.15	1.86	14.21	0.002	
AFB smear positive	5.34	0.86	33.22	0.072					
Age 25-44 years	4.83	0.65	36.03	0.124					
Hispanic ethnicity	4.83	0.11	216.20	0.417					
≥ 4 effective medications	3.46	0.41	29.47	0.256					
Age 45-64 years	3.41	0.39	30.21	0.271					
Asian race	3.35	0.07	151.32	0.534					
Disseminated TB disease	2.28	0.21	24.20	0.495					
Foreign born	2.10	0.15	28.64	0.577					
Recent cigarette smoker	1.96	0.41	9.31	0.397					
Recent excess alcohol use	0.99	0.13	7.65	0.988					
TB clinic outpatient management	0.98	0.18	5.35	0.980					
Recent unemployment	0.97	0.24	3.93	0.964					
Cavitary disease	0.77	0.21	2.84	0.694					
Diabetes	0.76	0.16	3.70	0.732					
History of TB disease	0.44	0.12	1.59	0.208					
HIV infection	0.39	0.03	4.92	0.463					
Recent injecting-drug or non-injecting-drug use	0.15	0.00	5.08	0.291					
Model Fit Statistics									
	Initial Model	Final Model							
	Intercept	Intercept							
	and	and							
Criterion	Covariates	Covariates							
AIC	136.392	116.619							
SC	198.964	127.996							
-2 Log L	92.392	108.619							

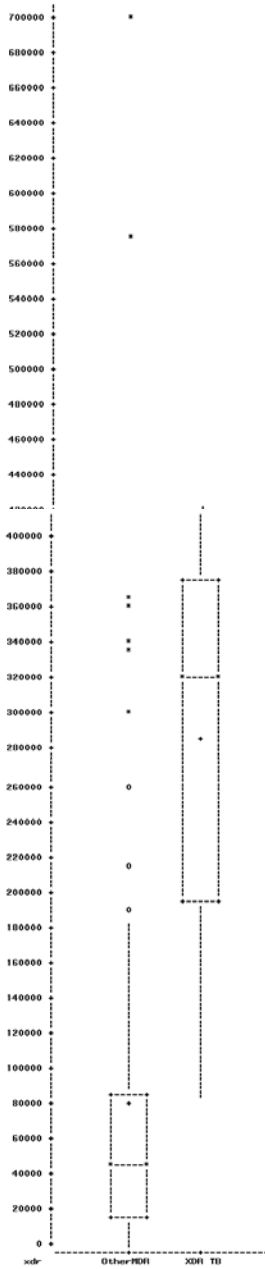
Death During TB Treatment Multivariate Model A

Death During Treatment Model A		Initial	Initial			Final	Final	
	Initial	95%	95%		Final	95%	95%	
	Odds Ratio	Confidence	Confidence	Initial	Odds Ratio	Confidence	Confidence	Final
Variable	Estimate	Lower Limit	Upper Limit	Pr > ChiSq	Estimate	Lower Limit	Upper Limit	Pr > ChiSq
Recent cigarette smoker	>999.999	2.60	>999.999	0.023	6.39	1.04	39.41	0.046
Age 45-64 years	>999.999	<0.001	>999.999	0.924				
Age 25-44 years	>999.999	<0.001	>999.999	0.947				
Age 65 or over	>999.999	<0.001	>999.999	0.890	20.21	2.26	180.98	0.007
Recent excess alcohol use	690.52	0.16	>999.999	0.126				
Foreign born	303.05	0.10	>999.999	0.164				
HIV infection	99.82	0.09	>999.999	0.201	6.31	1.05	37.73	0.044
TB clinic outpatient management	17.19	0.13	>999.999	0.251				
Hispanic ethnicity	17.14	0.00	>999.999	0.567				
Black race	14.02	0.00	>999.999	0.565				
Asian race	6.00	0.00	>999.999	0.682				
Disseminated TB disease	2.23	0.01	852.99	0.792				
Recent unemployment	0.83	0.05	14.21	0.900				
Recent homelessness	0.48	0.00	82.71	0.777				
Pre-XDR or XDR TB	0.36	0.01	16.56	0.598				
History of TB disease	0.26	0.01	6.02	0.401				
Diabetes	0.04	<0.001	12.94	0.268				
Male	0.02	<0.001	2.40	0.107				
Recent injecting-drug or non-injecting-drug use	0.01	<0.001	12.50	0.186				
Pregnant	0.00	<0.001	>999.999	0.990				
Correctional inmate	<0.001	<0.001	>999.999	0.971				
Model Fit Statistics								
	Initial Model	Final Model						
	Intercept	Intercept						
	and	and						
Criterion	Covariates	Covariates						
AIC	72.127	56.51						
SC	135.88	68.101						
-2 Log L	28.127	48.51						

Death During TB Treatment Multivariate Model B

Variable	Initial	Initial Pr > ChiSq	Final	Final	Final	Final
	Odds Ratio Estimate		Odds Ratio Estimate	95% Confidence Lower Limit	95% Confidence Upper Limit	Final Pr > ChiSq
Age ≥65	0.00	0.9774	61.926	3.099	>999.999	0.0069
Age ≥65*Excess alcohol	1.00
Age ≥65*Black race	1.00
Age ≥65*effluorom	1.00
Age ≥65*effective INJ med	>1000	0.9983
Age ≥65*Foreign born	1.00
Age ≥65*HIV-infection	1.00
Age ≥65*Homeless	1.00
Age ≥65*Hispanic	1.00
Age ≥65*IDU or NIDU	1.00
Age ≥65*Smoker	>1000	0.9984
Age ≥65*TB clinic	>1000	0.9791
Age ≥65*TB history	0.00	0.9774
Excess alcohol	0.00	0.9986
Excess alcohol*effective FQ med	1.00
Excess alcohol*effective INJ med	1.00
Excess alcohol*Smoker	>1000	0.9986
Excess alcohol*TB clinic	1.00
Excess alcohol*TB history	1.00
Black race	0.02	0.9959
Black race*Excess alcohol	1.00
Black race*effective FQ med	1.00
Black race*effective INJ med	0.00	0.9996
Black race*Foreign born	>1000	0.9994
Black race*HIV-infection	>1000	0.9996
Black race*Homeless	0.00	0.9968
Black race*IDU or NIDU	1.00
Black race*Smoker	>1000	0.9994
Black race*TB clinic	1.32	0.9992
Black race*TB history	1.00
effective FQ med	0.00	0.9792
effective INJ med	0.00	0.9629	0.017	0.002	0.176	0.0006
effective INJ med*effective FQ med	>1000	0.976
Foreign born	1.26	0.9997
Foreign born*Excess alcohol	0.05	0.9964
Foreign born*effective FQ med	1.00
Foreign born*effective INJ med	1.00
Foreign born*HIV-infection	>1000	0.9996
Foreign born*Homeless	1.00
Foreign born*IDU or NIDU	>1000	0.9983
Foreign born*Smoker	1.71	0.9991
Foreign born*TB clinic	4.60	0.998
Foreign born*TB history	1.00
HIV-infection	0.00	0.9995
HIV-infection*Excess alcohol	>1000	0.9983
HIV-infection*effective FQ med	1.00
HIV-infection*effective INJ med	1.00
HIV-infection*Homeless	>1000	0.9972
HIV-infection*IDU or NIDU	0.00	0.9976
HIV-infection*Smoker	0.05	0.9965
HIV-infection*TB clinic	1.00
HIV-infection*TB history	>1000	0.9982
Homeless	>1000	0.9969
Homeless*Excess alcohol	>1000	0.9982
Homeless*effective FQ med	1.00
Homeless*effective INJ med	1.00
Homeless*IDU or NIDU	1.00
Homeless*Smoker	>1000	0.9996
Homeless*TB clinic	1.00
Homeless*TB history	1.00
Hispanic	6.79	0.9978
Hispanic*Excess alcohol	>1000	0.9984
Hispanic*Black race	1.00
Hispanic*effective FQ med	0.01	0.9905
Hispanic*effective INJ med	71.72	0.9907
Hispanic*Foreign born	0.14	0.9975
Hispanic*HIV-infection	56.90	0.9965
Hispanic*Homeless	0.00	0.9969
Hispanic*IDU or NIDU	0.00	0.999
Hispanic*Smoker	0.52	0.9978
Hispanic*TB clinic	1.39	0.9984
Hispanic*TB history	2.03	0.9956
IDU or NIDU	>1000	0.9991
IDU or NIDU*Excess alcohol	0.00	0.9977
IDU or NIDU*effective FQ med	1.00
IDU or NIDU*effective INJ med	1.00
IDU or NIDU*Smoker	1.00
IDU or NIDU*TB clinic	1.00
IDU or NIDU*TB history	1.00
male	0.00	0.9755
male*Age ≥65	0.00	0.9994
male*Excess alcohol	10.85	0.996
male*Black race	1.68	0.9985
male*effective FQ med	>1000	0.9742
male*effective INJ med	42.97	0.9916
male*Foreign born	0.46	0.9989
male*HIV-infection	65.29	0.9963
male*Homeless	0.00	0.998
male*Hispanic	2.69	0.9937
male*IDU or NIDU	>1000	0.9982
male*Smoker	0.46	0.9984
male*TB clinic	1.17	0.9992
male*TB history	2.74	0.9934
Smoker	1.73	0.999	19.387	2.727	137.817	0.0031
Smoker*effective FQ med	1.00
Smoker*effective INJ med	1.00
Smoker*TB clinic	1.12	0.9997
Smoker*TB history	0.53	0.9979
TB clinic	0.22	0.9981
TB clinic*effluorome	0.14	0.9911
TB clinic*effective INJ med	5.50	0.9957
TB history	0.07	0.9948
TB history*effective FQ med	0.27	0.9939
TB history*effective INJ med	36.59	0.9924
TB history*TB clinic	1.05	0.9997
Model Fit Statistics						
	Initial Model	Final Model				
	Intercept	Intercept				
	and	and				
Criterion	Covariates	Covariates				
AIC	140.006	40.932				
SC	342.855	82.524				
-2 Log L	0.006	32.932				

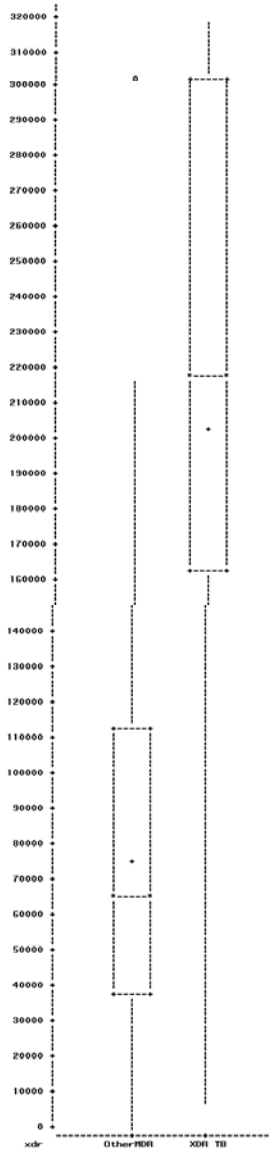
Inpatient Direct Costs



Standard error of the mean:

Other MDR	12,200
XDR	70,829

Outpatient Direct Costs

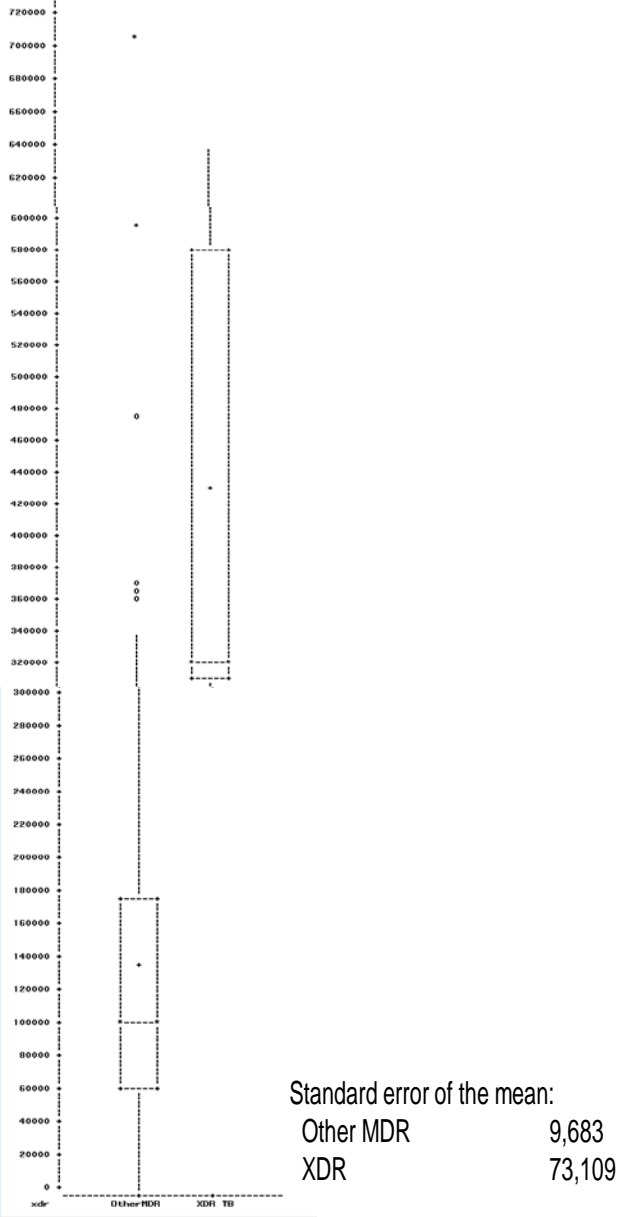


Standard error of the mean:

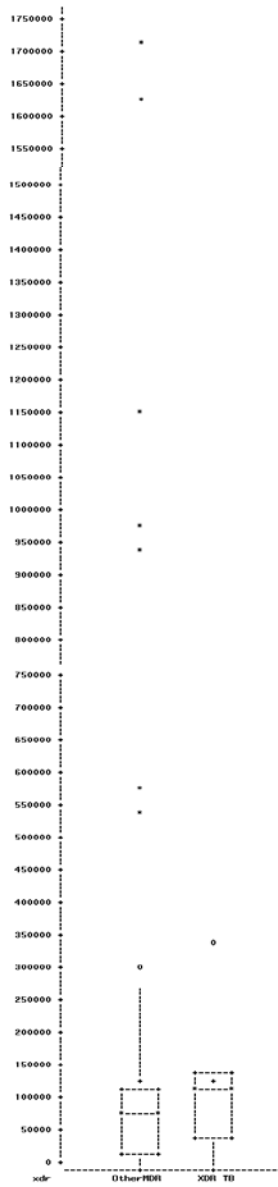
Other MDR 4,991

XDR 56,374

Total Direct Costs

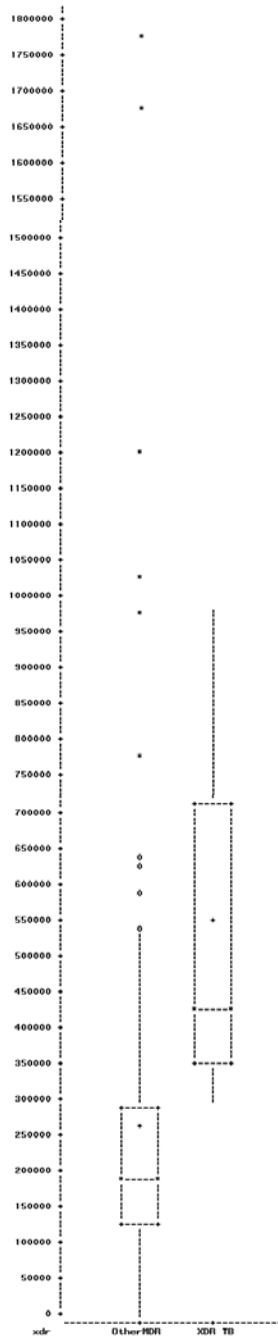


Productivity Losses



Standard error of the mean:
 Other MDR 22,520
 XDR 59,594

Direct Costs and Productivity Losses



Standard error of the mean:

Other MDR 23,212

XDR 127,707

MDR-TB Direct Costs Multivariate Model

Variable	Initial	Initial Pr > F	Final	Final	Final F Value	Final Pr > F
	Parameter Estimate		Parameter Estimate	Standard Error		
Intercept	29,310	0.559	80,807	11,139	52.620	<.0001
XDR TB	242,811	<.0001	219,438	42,494	26.670	<.0001
Long-term care facility resident	208,619	0.003	182,545	64,022	8.130	0.005
Recent non-injecting-drug use	119,934	0.065	112,203	42,984	6.810	0.010
Black race	86,395	0.054				
HIV infection	58,745	0.135	69,368	33,234	4.360	0.039
Asian race	54,566	0.238				
Recent homelessness	44,402	0.314				
Public insurance	43,185	0.053	57,221	17,052	11.260	0.001
Hispanic ethnicity	41,324	0.371				
Total firstline resistance	28,626	0.196				
Foreign born	11,142	0.747				
Male	9,828	0.606				
Pre-XDR TB	9,263	0.712				
Diabetes	3,845	0.889				
No. of days hospitalized	451	<.0001	426	60	50.540	<.0001
Recent injecting-drug use	-324,397	0.000	-315,716	70,089	20.290	<.0001
Recent excess alcohol use	-78,044	0.033	-74,682	33,009	5.120	0.026
Age 45-64 years	-34,156	0.240				
Age 65 or over	-30,517	0.487				
Correctional inmate	-24,708	0.632				
Recent unemployment	-14,145	0.535				
Age 25-44 years	-14,492	0.568				
Native Hawaiian/Other Pacific Islander	-1,829	0.986				
Model Statistics	Adj R-Square=.52		Adj R-Square = 0.55			
Analysis of Variance						
Source	Degrees of freedom		Sum of Squares	Mean Square	F Value	Pr > F
Model	8		1,160,877,000,000	145,109,600,000	18.84	<.0001
Error	111		854,750,200,000	7,700,452,335		
Corrected	119		2,015,627,000,000			

MDR-TB Direct Costs and Productivity Losses Multivariate Model

	Initial		Final	Final		
Variable	Parameter	Initial	Parameter	Standard	Final	Final
	Estimate	Pr > F	Estimate	Error	F Value	Pr > F
Intercept	41,006	0.688	175,161	27,059	41.900	<.0001
Died	837,849	<.0001	810,082	82,887	95.520	<.0001
XDR TB	322,504	0.001	315,817	91,413	11.940	0.001
Recent non-injecting-drug use	188,405	0.158	240,819	93,512	6.630	0.011
Hispanic ethnicity	151,102	0.112				
HIV infection	144,532	0.084	151,514	71,251	4.520	0.036
Asian race	137,699	0.154				
Native Hawaiian/Other Pacific Islander	104,329	0.628				
Diabetes	83,578	0.140	123,628	47,944	6.650	0.011
Male	63,478	0.104	65,679	35,964	3.340	0.071
Recent injecting-drug use	91,371	0.588				
Black race	52,318	0.566				
Public insurance	57,079	0.209				
Total firstline resistance	24,606	0.584				
Age 25-44 years	37,381	0.470				
No. of days hospitalized	525	0.000	424	128	11.020	0.001
Age 65 or over	-379,300	0.000	-428,817	80,756	28.200	<.0001
Long-term care facility resident	-357,057	0.020	-280,788	137,546	4.170	0.044
Correctional inmate	-158,124	0.134	-180,258	91,947	3.840	0.053
Recent excess alcohol use	-149,285	0.049	-179,858	67,536	7.090	0.009
Age 45-64 years	-67,604	0.253	-123,917	39,748	9.720	0.002
Recent unemployment	-68,354	0.146				
Pre-XDR TB	-50,252	0.328				
Foreign born	-35,118	0.627				
Recent homelessness	5,003	0.956				
Model Statistics	Adj R-Square=.64		Adj R-Square = 0.66			
Analysis of Variance						
Source	Degrees of freedom		Sum of Squares	Mean Square	F Value	Pr > F
Model	12		7,719,364,000,000	643,280,300,000	19.91	<.0001
Error	107		3,456,381,000,000	32,302,623,791		
Corrected	119		11,175,740,000,000			

Estimate of the Average Cost of Non-MDR TB, 2010 U.S. Dollars									
Site	Avg hospitalization length	1998\$ avg cost per patient hospitalized*	2010\$ avg cost per patient hospitalized**	2010\$ hospital physician cost***	2010\$ avg total hospitalization cost per patient	Weight	2010\$ weighted avg cost per pt. hospitalized	2010\$ outpatient cost per patient****	2010\$ avg cost per TB patient*****
1	17	\$11,987	\$19,233	\$1,290	\$20,523	6.2	\$127,485	\$3,419	
2	37	\$22,518	\$36,130	\$2,605	\$38,735	12.2	\$473,212	\$3,419	
3	35	\$12,231	\$19,623	\$2,474	\$22,097	7.1	\$157,255	\$3,419	
4	15	\$13,631	\$21,871	\$1,159	\$23,030	10.8	\$248,245	\$3,419	
5	22	\$15,114	\$24,250	\$1,619	\$25,869	5.5	\$141,508	\$3,419	
6	20	\$17,651	\$28,320	\$1,487	\$29,808	13.6	\$404,616	\$3,419	
7	24	\$17,009	\$27,290	\$1,751	\$29,040	14.1	\$409,356	\$3,419	
8	36	\$22,316	\$35,806	\$2,540	\$38,345	17.9	\$685,538	\$3,419	
9	23	\$10,438	\$16,746	\$1,685	\$18,431	13.8	\$254,907	\$3,419	
10	16	\$11,970	\$19,205	\$1,224	\$20,429	14.7	\$299,492	\$3,419	
Total						115.8	\$3,201,614		
Average							\$27,640	\$3,419	\$16,963
* From reference 16: 49% of TB patients were hospitalized; included MDR TB costs for 13/733 hospitalized patients									
** Converted from 1998 dollars to 2010 dollars using the consumer price index for medical care (388.436/242.1) reference 2									
*** Average of lower and upper physician fees (reference 5) for one day of initial hospital care (\$206,\$271)=\$238, and remaining days at Level 2 subsequent care (\$113,\$149)=\$131, converted to a cost using the cost-to-charge ratio for the respiratory Diagnostic Related Group (reference 6), multiplied by 0.502									
**** From reference 17, \$2985 from Nashville, TN, adjusted to a US basis using the Census Bureau Cost of Living Index 87.3 (reference 18)									
***** (Weighted average hospitalization cost X 49% of patients hospitalized)+average outpatient cost									

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