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Tuberculosis (TB) remains the leading cause of infectious disease death among adults worldwide. In recent years, drug-resistant TB has emerged as an expanding threat, with an estimated 489,000 new cases in 2006. Treatment of multidrug-resistant TB (MDR-TB) is more than 100 times as costly as treatment of drug-susceptible TB (DSTB) and drug-susceptible TB cases.

Results Among 13,293 DSTB cases, 18 (0.07%) were XDR-TB cases, compared with 25107 TB cases (0.07%) in 2007. In the United States, defining the scope of the XDR-TB epidemic and describing its epidemiology is important.
for health care professionals, public health programs, and policy makers. Identifying unique factors among patients with XDR-TB will aid clinicians in making evidence-based decisions about which patients are at greatest risk of developing such highly drug-resistant forms of TB. This may enable earlier diagnosis, implementation of appropriate infection control measures, and initiation of early, aggressive treatment, critical steps in improving patient outcomes and curbing transmission.\textsuperscript{25-28} The availability of and access to a greater number of TB drugs in the United States should allow for better treatment success rates compared with resource-limited settings, where the prognosis may be far worse. Knowledge of the response to treatment and survival among patients with XDR-TB in the United States will assist in providing accurate information to patients and the public.

We analyzed 15 years of national surveillance data to describe XDR-TB cases. In an effort to more accurately determine disease burden, we considered all reported drug susceptibility test results for case counting and analysis of trends. To identify distinct features of XDR-TB, we compared the epidemiologic and clinical characteristics, treatment outcomes, and survival of XDR-TB cases with both MDR-TB and fully drug-susceptible TB cases.

**METHODS**

**Case Reporting**

This analysis was based on all culture-confirmed cases reported by the 50 states and the District of Columbia from 1993 through 2007. Local health departments verify and report incident cases of TB diagnosed within their jurisdiction to state health departments. States compile and transmit these data to the Centers for Disease Control and Prevention (CDC) using a standardized case report form.\textsuperscript{29} The national TB surveillance system has been evaluated and captures information on nearly all TB cases diagnosed in the United States.\textsuperscript{30,31}

The TB case reports include both the initial and follow-up drug susceptibility test results along with demographic and clinical information. The initial drug susceptibility test result is based on the first positive culture (sputum or other body fluid/tissue). The follow-up drug susceptibility test result is based on a specimen collected at least 30 days after the initial specimen. The reporting format for drug susceptibility test results includes recording options for 14 specific drugs as resistant, susceptible, not done, or unknown.

The TB case reports record HIV status as positive, negative, or unknown (including cases who were not offered or refused testing and those with indeterminate or missing results). Reporting of HIV status for California TB cases differs from other states and is based on annual matching of the TB and AIDS registries. Patients whose names appear on both TB and AIDS registries are reported to the US National TB Surveillance System as having AIDS. All other California TB cases have unknown HIV status (ie, HIV-negative test results and HIV-positive cases who do not appear on the AIDS registry are not reported). This process delays HIV data from California by approximately 2 years (California HIV data for this analysis are considered complete through 2004). Case reports do not include information about CD4 T-lymphocyte count, HIV viral load, or antiretroviral treatment.

**Case Definitions**

A drug-susceptible TB case was defined as a person in whom both an initial and a follow-up (if available) drug susceptibility test result was reported as susceptible to isoniazid and a rifamycin (rifampin or rifabutin). An MDR-TB case was defined as a person with reported resistance to at least isoniazid and a rifamycin, excluding cases in the subset confirmed to have XDR-TB. Multidrug-resistant TB cases who had resistance to a fluoroquinolone and a second-line injectable drug were defined as XDR-TB cases. Cases with other resistance patterns (eg, isoniazid monoresistance, rifampin monoresistance, or polyresistance other than MDR-TB) were excluded.

We included rifamycins as a class in our case definition of MDR-TB and XDR-TB. Although testing for rifampin susceptibility is a routine part of first-line drug susceptibility panels in the United States, these results were reported as unknown or missing in a subset of TB cases in whom rifabutin susceptibility results were available. Cross-resistance among different rifamycins is nearly 100%. We also included results of initial and follow-up drug susceptibility testing in case counts.

**Main Outcome Measures**

To understand epidemiologic and clinical differences among XDR-TB cases, we compared them with MDR-TB and drug-susceptible TB cases. We evaluated sociodemographic characteristics, prior TB, HIV status, extent of TB disease, chest radiography result, sputum smear result, and vital status at the time of TB diagnosis.

Reporting of patient outcomes is delayed by approximately 2 years from the time a case is reported in part because of the length of treatment (approximately 6-9 months for drug-susceptible TB and 24 months for MDR-TB and XDR-TB). Thus, for analysis of treatment outcomes (including sputum culture conversion and survival), the data were restricted to the subset of cases who were alive at the time of diagnosis, who started anti-TB therapy, and who were reported initially from 1993 through 2005.

In the US National TB Surveillance System, treatment outcomes are reported as the reason for stopping treatment. This was categorized as “completed treatment” (regardless of length of time), “died” (includes death during treatment, irrespective of cause), and “all other” (includes cases who moved, were lost, were uncooperative or refused, or had some other reason to stop therapy).

For sputum culture conversion, the data were restricted further to cases with a positive baseline sputum culture. Time to conversion was the difference
in days between the date of starting treatment and the specimen collection date of the first negative sputum culture (defined as 1 or more consistently negative sputum cultures). Cases with missing date of starting treatment or date of culture conversion were excluded from the calculation of time to conversion.

Survival time in days was the difference between the treatment start and stop dates. Cases who died before therapy started were not included. Cases who had not yet completed therapy (eg, MDR-TB or XDR-TB cases from recent years) were censored at the date this data set was closed (April 23, 2008).

**Statistical Analysis**
We compared the frequency distributions of XDR-TB cases, MDR-TB cases, and drug-susceptible TB cases across levels of categorical variables using conventional 2-way contingency tables. We calculated prevalence ratios (PRs) and 95% confidence intervals (CIs) for all comparisons as the percentage of cases with a specific characteristic who had XDR-TB (vs MDR-TB) divided by the percentage of cases who did not have the characteristic.32 The same calculation was used for PRs of XDR-TB compared with drug-susceptible TB cases. The $\chi^2$ test was used to compare proportions. Tests of significance were 2-sided, and $P<.05$ was considered statistically significant.

For continuous variables, we compared means (standard deviations) and/or medians (percentiles) depending on the underlying distributions. For comparison of unadjusted survival rates, we used Kaplan-Meier and actuarial life table methods, stratifying by drug resistance group. Kaplan-Meier survival curves were compared using the log-rank test. Death was the event variable and other outcomes were censored. All analysis was done using SAS software, version 9.1 (Cary, North Carolina).

This project was reviewed by the CDC and approved as public health surveillance, which is exempt from human subjects review and does not require informed consent.

### RESULTS
#### Case Estimates and Trends
From 1993 to 2007, a total of 212,896 culture-confirmed TB cases were reported in the United States, of which 201,399 (95%) had drug susceptibility test results reported for isoniazid and a rifamycin. A total of 183,536 cases met the study case definition for drug-susceptible TB. There were 3379 cases with resistance to at least isoniazid and a rifamycin (ie, MDR-TB), of which 2087 (62%) also had enough drug susceptibility test results to evaluate for a diagnosis of XDR-TB (ie, tested for $\geq 1$ fluoroquinolone and $\geq 1$ second-line injectable drug). Ultimately, 83 of these cases met criteria for XDR-TB (0.04% of 201,399 with reported drug susceptibility test results; 2.5% of 3379 MDR-TB cases; and 3.9% of 2087 evaluable MDR-TB cases with sufficient reported second-line drug susceptibility test results). Of these 83 cases of XDR-TB, 49 were included in a previous report.33 We excluded 14,484 cases with other drug resistance patterns.

The annual number of XDR-TB cases decreased from 18 (in 1993) to 2 (in 1997) and has fluctuated around a median of 3.5 cases per year over the past decade ($\chi^2$ test for linear trend, 2.46; $P=.12$) (FIGURE 1). Of 40 XDR-TB cases reported during 1993-1997, 25 (62%) were known to be HIV-infected. During 1998-2007, only 6 (14%) of 43 XDR-TB cases were known to be HIV-infected ($P<.001$).

#### Sociodemographic Characteristics
Of the 83 XDR-TB cases, the majority were aged 25 to 44 years (n=48 [58%]), male (n=53 [64%]), US-born (n=45 [54%]), and unemployed (n=44 [53%]) (TABLE 1). Thirty-three XDR-TB cases (40%) were Hispanic. Three cases (4%) occurred among health care workers.

Sociodemographic characteristics did not differ between XDR-TB and MDR-TB cases (Table 1). However, compared with drug-susceptible TB cases, XDR-TB cases were significantly less likely to be in the older age groups (PR, 0.45; 95% CI, 0.26-0.78 for age 45-64 years; PR, 0.28; 95% CI, 0.14-0.57 for age $\geq 65$ years). Extensively drug-resistant TB cases were more likely to be Hispanic (PR, 2.16; 95% CI, 1.19-3.93) and correctional facility residents (PR, 2.35; 95% CI, 1.08-5.10) compared with drug-susceptible TB cases.

#### Clinical Characteristics
Ten XDR-TB cases (12%) reported a previous diagnosis of TB compared with 570 MDR-TB cases (17%) and 8667 drug-susceptible TB cases (5%) (PR,
Most XDR-TB cases had pulmonary disease, either with (n=15 [18%]) or without (n=62 [75%]) extrapulmonary involvement. Disseminated disease (ie, pulmonary and extrapulmonary) was more than twice as likely among XDR-TB cases compared with MDR-TB (PR, 2.06; 95% CI, 1.19-3.58) and drug-susceptible TB cases (PR, 2.14; 95% CI, 1.22-3.76). Sputum smear microscopy result was positive among 57 XDR-TB cases (74%), which was significantly more likely than among MDR-TB (PR, 1.84; 95% CI, 1.05-3.24) and drug-susceptible TB cases (PR, 2.98; 95% CI, 1.69-5.27).

Among XDR-TB cases with HIV test results, 31 (53%) were HIV-positive. This did not differ significantly from MDR-TB cases but was more than 3 times higher prevalence than that among drug-susceptible TB cases (PR, 3.76; 95% CI, 2.25-6.30).

### Treatment Outcomes

Sputum culture conversion to negative, a measure of treatment response, was documented in 40 XDR-TB cases (66%), with a median time to culture conversion of 183 days (interquartile range, 104-344 days) (Table 3). Culture conversion was significantly less likely among XDR-TB cases compared with both MDR-TB and drug-susceptible TB cases (PR, 0.57; 95% CI, 0.34-0.99 and PR, 0.55; 95% CI, 0.33-0.94, respectively). Time to conversion, an indication of duration of infectiousness, was longer among XDR-TB cases than for MDR-TB cases (P < .001) and drug-susceptible TB cases (P < .001).

### Survival Analysis

Figure 2 displays Kaplan-Meier plots of the conditional probability of survival among TB cases who remain in treatment. Survival was significantly worse among XDR-TB cases com-

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### Table 1. Sociodemographic Characteristics of Extensively Drug-Resistant Tuberculosis (XDR-TB), Multidrug-Resistant Tuberculosis (MDR-TB), and Drug-Susceptible TB Cases, United States, 1993-2007

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>XDR-TB (n = 83)</th>
<th>MDR-TB (n = 3296)</th>
<th>Drug-Susceptible TB (n = 183,536)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-14</td>
<td>2 (2)</td>
<td>61 (2)</td>
<td>3425 (2)</td>
</tr>
<tr>
<td>15-24</td>
<td>7 (8)</td>
<td>351 (11)</td>
<td>16,615 (9)</td>
</tr>
<tr>
<td>25-44</td>
<td>48 (58)</td>
<td>1676 (51)</td>
<td>66,505 (36)</td>
</tr>
<tr>
<td>45-64</td>
<td>17 (20)</td>
<td>869 (26)</td>
<td>52,197 (26)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>9 (11)</td>
<td>339 (10)</td>
<td>44,755 (24)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (36)</td>
<td>1236 (38)</td>
<td>65,910 (36)</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>33 (40)</td>
<td>950 (29)</td>
<td>41,620 (23)</td>
</tr>
<tr>
<td>Hispanic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>16 (20)</td>
<td>493 (15)</td>
<td>43,622 (24)</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
<td>18 (22)</td>
<td>946 (29)</td>
<td>50,560 (32)</td>
</tr>
<tr>
<td>Asian</td>
<td>15 (18)</td>
<td>859 (26)</td>
<td>34,376 (19)</td>
</tr>
<tr>
<td>Foreign-born nationality</td>
<td>37 (45)</td>
<td>1774 (54)</td>
<td>78,306 (43)</td>
</tr>
<tr>
<td>Occupation during 2 years prior to diagnosis</td>
<td>44 (53)</td>
<td>1546 (47)</td>
<td>93,735 (51)</td>
</tr>
<tr>
<td>Unemployed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health care worker</td>
<td>3 (4)</td>
<td>118 (4)</td>
<td>4737 (3)</td>
</tr>
<tr>
<td>Residence history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correctional facility resident</td>
<td>7 (8)</td>
<td>147 (4)</td>
<td>6856 (4)</td>
</tr>
<tr>
<td>Homeless in the year prior to diagnosis</td>
<td>3 (4)</td>
<td>160 (5)</td>
<td>12,455 (7)</td>
</tr>
</tbody>
</table>

*Statistically significant at P < .01.
*One XDR-TB case (1%), 49 MDR-TB cases (1%), and 4412 drug-susceptible TB cases (2%) were American Indian/Native Alaskan, Native Hawaiian/Pacific Islander, or had multiple or unknown/missing racial/ethnic designations.
*Nationality was unknown or missing for 1 XDR-TB case (1%), 16 MDR-TB cases (<1%), and 943 drug-susceptible TB cases (1%).
*Occupation was unknown or missing for 16 XDR-TB cases (19%), 628 MDR-TB cases (19%), and 2766 drug-susceptible TB cases (12%).
*Cases with any type of known employment are the reference group.
*Cases with other, non-high-risk employment are the reference group. This excludes correctional facility employees (n = 221) and migrant workers (n = 2104).
*Correctional facility residence history was unknown or missing for 41 MDR-TB cases (11%) and 1619 drug-susceptible TB cases (11%). Cases without reported correctional facility residence history are the reference group.
*Homelessness history was unknown or missing for 18 XDR-TB cases (22%), 453 MDR-TB cases (14%), and 9764 drug-susceptible TB cases (5%). Cases without reported homelessness history are the reference group.
### Table 2. Clinical Characteristics of Extensively Drug-Resistant Tuberculosis (XDR-TB), Multidrug-Resistant Tuberculosis (MDR-TB), and Drug-Susceptible TB Cases, United States, 1993-2007

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>XDR-TB (n = 83)</th>
<th>MDR-TB (n = 32,96)</th>
<th>Drug-Susceptible TB (n = 183,536)</th>
<th>Prevalence Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior TB diagnosis</td>
<td>10 (12)</td>
<td>570 (17)</td>
<td>8667 (5)</td>
<td>0.66 (0.34-1.28)</td>
</tr>
<tr>
<td>Location of TB disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary alone</td>
<td>62 (75)</td>
<td>2675 (81)</td>
<td>137,309 (75)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Pulmonary and extrapulmonary</td>
<td>15 (18)</td>
<td>306 (9)</td>
<td>15,518 (8)</td>
<td>2.06 (1.19-3.58)</td>
</tr>
<tr>
<td>Extrapulmonary alone</td>
<td>6 (7)</td>
<td>314 (10)</td>
<td>20,682 (17)</td>
<td>0.83 (0.36-1.90)</td>
</tr>
<tr>
<td>Positive sputum microscopy result</td>
<td>57 (74)</td>
<td>1959 (66)</td>
<td>81,605 (44)</td>
<td>1.84 (1.05-3.24)</td>
</tr>
<tr>
<td>Chest radiograph result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>72 (87)</td>
<td>2910 (88)</td>
<td>156,049 (85)</td>
<td>0.82 (0.41-1.62)</td>
</tr>
<tr>
<td>Cavitary disease</td>
<td>24 (33)</td>
<td>973 (33)</td>
<td>43,260 (28)</td>
<td>1.01 (0.62-1.64)</td>
</tr>
<tr>
<td>HIV test result</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>31 (53)</td>
<td>818 (44)</td>
<td>20,543 (23)</td>
<td>1.46 (0.88-2.42)</td>
</tr>
<tr>
<td>Negative</td>
<td>27 (47)</td>
<td>1049 (56)</td>
<td>67,396 (67)</td>
<td>0.93 (0.23-3.73)</td>
</tr>
<tr>
<td>Vital status at diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dead</td>
<td>2 (2)</td>
<td>85 (3)</td>
<td>5742 (3)</td>
<td>0.76 (0.19-3.11)</td>
</tr>
<tr>
<td>Alive</td>
<td>81 (98)</td>
<td>3207 (97)</td>
<td>177,670 (97)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Total</td>
<td>83 (100)</td>
<td>3296 (100)</td>
<td>183,536 (100)</td>
<td></td>
</tr>
</tbody>
</table>

A person is considered to have had a prior episode of TB if TB was verified in the past and the person completed therapy or was lost to supervision for more than 12 consecutive months and has verified TB again.

### Table 3. Directly Observed Therapy (DOT) Use and Treatment Outcomes of Extensively Drug-Resistant Tuberculosis (XDR-TB), Multidrug-Resistant Tuberculosis (MDR-TB), and Drug-Susceptible TB Cases, United States, 1993-2005

<table>
<thead>
<tr>
<th>DOT</th>
<th>XDR-TB (n = 75)</th>
<th>MDR-TB (n = 2,920)</th>
<th>Drug-Susceptible TB (n = 156,832)</th>
<th>Prevalence Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No DOT (self-administered therapy only)</td>
<td>16 (21)</td>
<td>658 (23)</td>
<td>46,136 (29)</td>
<td>0.93 (0.51-1.70)</td>
</tr>
<tr>
<td>Partial DOT (DOT combined with some self-administered therapy)</td>
<td>30 (40)</td>
<td>1100 (38)</td>
<td>37,280 (24)</td>
<td>1.04 (0.63-1.73)</td>
</tr>
<tr>
<td>Complete DOT</td>
<td>28 (37)</td>
<td>1068 (37)</td>
<td>70,315 (45)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Sputum culture conversion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture conversion documented</td>
<td>40 (66)</td>
<td>1807 (73)</td>
<td>85,531 (75)</td>
<td>0.57 (0.34-0.99)</td>
</tr>
<tr>
<td>Time to conversion, median (interquartile range), d</td>
<td>183 (104-344)</td>
<td>93 (49-173)</td>
<td>55 (29-88)</td>
<td>P &lt; .001</td>
</tr>
<tr>
<td>Treatment outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completion of therapy</td>
<td>33 (44)</td>
<td>1665 (57)</td>
<td>127,600 (81)</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Death due to any cause</td>
<td>26 (35)</td>
<td>709 (24)</td>
<td>16,447 (10)</td>
<td>1.82 (1.10-3.02)</td>
</tr>
<tr>
<td>Other, unknown, or missing</td>
<td>15 (20)</td>
<td>546 (19)</td>
<td>12,785 (8)</td>
<td>1.38 (0.75-2.51)</td>
</tr>
</tbody>
</table>

Number and percentage are based on cases who were alive at diagnosis and initially treated with 1 or more TB drugs (provided in total for this Table). Cases counts have been censored at 2005 to allow sufficient time for reporting of end-of-treatment results.

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pared with both MDR-TB cases (P = .04) and drug-susceptible TB cases (P < .001). Within 1 year, 17 XDR-TB cases (23%) had died during treatment compared with 502 MDR-TB cases (17%; P = .22) and 15,543 drug-susceptible TB cases (10%; P < .001).

**Acquired Resistance**

Of the 83 XDR-TB cases, 55 were identified based on the first positive culture and 28 more from a follow-up culture and drug susceptibility test result, indicating the possibility of acquired resistance during treatment. In 21 of the 28 cases, initial drug susceptibility results showed susceptibility and follow-up results showed resistance to the same drug (ie, one of the drugs included in the definition of XDR-TB). Comparing these 2 groups of XDR-TB cases, there were no significant differences in most sociodemographic characteristics (including sex, race/ethnicity, prior TB, correctional or long-term care facility residence, injecting drug or excess alcohol use, unemployment, and health care worker status), clinical characteristics (including extent of disease, sputum smear or chest radiography result, cavitary disease, and HIV status), and outcomes (including sputum culture conversion and treatment completion).

However, acquired XDR-TB cases were more likely to be US-born (PR, 2.47; 95% CI, 1.18-5.15), to have received treatment under partial rather than total directly observed therapy (PR, 6.55; 95% CI, 2.18-19.65), and to die during treatment (PR, 1.83; 95% CI, 1.03-3.27).

**COMMENT**

This study provides the first comprehensive assessment of the burden of XDR-TB in the United States and represents 15 years of surveillance data from the beginning of TB drug resistance surveillance in 1993. From 1993 through 2007, there have been 83 cases of XDR-TB, accounting for 0.04% of all culture-confirmed TB cases with reported drug susceptibility results that occurred in the United States. Although the number of cases has declined since 1993, XDR-TB cases continue to occur each year.

The emergence of XDR-TB globally has raised concern about a return to the preantibiotic era in TB control, since XDR-TB cases face limited therapeutic options and consequently have poor treatment outcomes and high mortality. In this study, we similarly found that outcomes were significantly worse for XDR-TB cases compared with MDR-TB and drug-susceptible TB cases. Death rates were nearly 2 times greater than among MDR-TB cases and more than 6 times greater than among drug-susceptible TB cases. Infection with HIV played an important role in both the occurrence and the outcomes of XDR-TB cases, consistent with prior reports. Human immunodeficiency virus–infected patients had higher death rates than HIV-uninfected patients and accounted for most but not all XDR-TB deaths. Most deaths occurred prior to the widespread implementation of highly active antiretroviral therapy in the United States in the late 1990s. Indeed, im-

**Figure 2. Survival Among XDR-TB, MDR-TB, and Drug-Susceptible TB Cases, United States, 1993-2005**

Among patients included in the survival analysis, there were 26 deaths (35%) in the extensively drug-resistant tuberculosis (XDR-TB) group, 707 deaths (24%) in the (MDR-TB) group, and 16,398 deaths (11%) in the drug-susceptible TB group. Survival curves were compared using the log-rank test (P = .04 for XDR-TB vs MDR-TB and P < .001 for XDR-TB vs drug-susceptible TB). Numbers differ slightly from Table 3 because patients with missing data for start or end dates were excluded from the survival analysis.
Extensively Drug-Resistant Tuberculosis in the United States

Improvements in both HIV care and TB control in the United States have improved outcomes for coinfected patients, with death rates for TB/HIV-coinfected patients declining by more than 50% from 1993 to 2002. This is likely to contribute to better outcomes observed in this study compared with resource-limited settings. Strengthening both HIV and TB programs locally and globally through improved prevention, diagnosis, and treatment will be necessary to improve XDR-TB outcomes given the inextricable links between the 2 diseases.

We identified important differences between XDR-TB cases and patients with MDR-TB and drug-susceptible TB that may have affected the course of disease and have implications for case management. Extensively drug-resistant TB cases were more likely to be infectious, with 74% having positive sputum smear results for acid-fast bacilli. In addition, the higher prevalence of disseminated disease among XDR-TB cases may indicate delays in diagnosis, longer duration of disease, greater virulence of XDR-TB strains, or a more immunocompromised state (not limited to HIV infection) among patients. The prolonged infectious period of approximately 6 months until sputum culture conversion underscores the urgent need for improving the prevention, diagnosis, and treatment of XDR-TB, as well as infection control measures.

We found that suboptimal treatment supervision by TB programs may be one modifiable factor that contributed to poor outcomes. Only one-third of XDR-TB patients received directly observed therapy throughout treatment, while the remainder had only partial or no supervision of therapy. Incomplete treatment and incomplete supervision of XDR-TB reflects a public health failure, which may have led to increased risk of acquiring more drug resistance (through amplification) and ongoing transmission of XDR-TB to others. In this study, the change from susceptible to resistant was documented in 21 (75%) of 28 XDR-TB cases diagnosed on follow-up testing, suggesting possible selection for additional drug resistance during treatment. Although 44% of XDR-TB cases completed treatment, an aggressive approach to XDR-TB treatment has been observed to yield cure rates of 60% among HIV-negative patients, similar to what is achievable in MDR-TB patients.

Ensuring sufficient resources, training, and supervision for appropriate TB treatment should be a priority to prevent and control drug-resistant TB.

This study introduces 2 methodological advances in reporting surveillance data. First, it applies the concept of classwide cross-resistance among rifamycins to the case definitions. Rifabutin has an established role in TB treatment among HIV-coinfected patients receiving protease inhibitors. Because resistance to rifabutin eliminates rifampin as a treatment option, we included patients with resistance to either rifamycin in case counts of MDR-TB and XDR-TB. Other settings that routinely test for rifabutin drug susceptibility should be encouraged to do the same. Second, this study extends the case definition to include all reported drug susceptibility test results, regardless of whether it was the initial or a subsequent sample, to provide a more realistic estimate of the actual number of MDR-TB and XDR-TB patients in the United States.

This study has several limitations. Drug susceptibility testing for second-line drugs is not routine. The Clinical and Laboratory Standards Institute recommends testing for a full panel of first- and second-line drugs for all isolates with resistance to rifampin or any 2 anti-TB drugs. However, only 61% of MDR-TB cases had enough drug susceptibility test results reported to be able to identify an XDR-TB case if it had occurred. Multidrug-resistant TB cases who undergo second-line drug susceptibility testing may differ in substantial ways from cases who were not tested, and selection bias may have occurred. Thus, among the remaining 39% of MDR-TB cases, it is not possible to estimate the number of XDR-TB cases that were undiagnosed. The number of XDR-TB cases in this study may still underestimate the true burden of this disease in the United States but it is based on the most complete analysis possible with currently available national data.

Detailed TB treatment history, exposure history, and genotyping data are not included in case reporting, so it is undeterminable whether XDR-TB was due to primary vs acquired drug resistance. Acquired resistance followed by transmission of drug-resistant strains to others is projected to result in large increases in MDR-TB and XDR-TB cases. The relative importance of XDR-TB transmission in the United States compared with the emergence of XDR-TB as a consequence of inadequate treatment needs to be determined.

Human immunodeficiency virus status was not known for 45% of XDR-TB cases. Although HIV testing and reporting has increased steadily since 1993, the number of XDR-TB cases has declined during this same period. Personal identifiers are not reported to the CDC, so follow-up with clinicians to obtain more detailed clinical information (including HIV status) is not possible.

Important changes to TB therapy are likely to be made once drug susceptibility test results are available to clinicians and MDR-TB or XDR-TB is diagnosed. However, only the initial treatment regimen at the time of TB diagnosis is reported in our surveillance system. Thus, we were not able to include information about the treatment regimen in our analysis of outcomes. However, the CDC has launched an MDR/XDR-TB registry to collect information on the regimen prescribed at the time of TB diagnosis, the regimen at MDR-TB diagnosis, and the regimen at XDR-TB diagnosis to investigate this further.

Extensively drug-resistant TB has raised awareness and concern about incurable forms of TB and provides an important opportunity to mobilize ef-
forts to improve TB control. Preventing the further emergence of drug resistance is paramount and must include not only TB program strengthening to ensure that patients complete their treatment regimen but also general health system interventions to improve infection control. Greater vigilance regarding drug resistance must include systematic second-line drug susceptibility testing according to published guidelines. Lessons gained from MDR-TB in the 1990s should be applied: Patients must be identified early, treated effectively, and assisted to complete treatment, and infection control precautions must be in place to prevent further emergence and transmission of XDR-TB.

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