

# Extensively Drug-Resistant Tuberculosis - -- United States, 1993--2006

The worldwide emergence of extensively drug-resistant tuberculosis (XDR TB) and a provisional definition\* for this form of TB were first reported in November 2005 (1,2). A more detailed description of these findings and preliminary data from the U.S. National TB Surveillance System (NTSS) were published in 2006 (3). The U.S. data indicated that 74 TB cases reported during 1993--2004 met the case definition for XDR TB (3). Subsequent reports suggested different definitions for XDR TB (4,5). In October 2006, the World Health Organization convened an Emergency Global Task Force on XDR TB, which revised the case definition to specify resistance to at least isoniazid and rifampin among first-line anti-TB drugs, resistance to any fluoroquinolone, and resistance to at least one second-line injectable drug (amikacin, capreomycin, or kanamycin) (6). This report updates the 2006 report on XDR TB in the United States, using the revised case definition and provisional data for 2006. NTSS data were analyzed for reported XDR-TB cases during 1993--2006; a total of 49 cases (3% of evaluable multidrug-resistant [MDR] TB cases) met the revised case definition for XDR TB. Of these, 17 (35%) were reported during 2000--2006. Compared with 1993--1999, cases from 2000--2006 were more likely to be in persons who were foreign born and less likely to be in persons with human immunodeficiency virus (HIV) infection. XDR TB presents a global threat and a challenge to TB-control activities in the United States. To prevent the spread of XDR TB, renewed vigilance is needed through drug-susceptibility testing, case reporting, specialized care, infection control, and expanded capacity for outbreak detection and response.

TB cases reported to NTSS from 50 states and the District of Columbia (DC) were analyzed for the period 1993--2006.<sup>†</sup> All culture-confirmed cases with initial drug-susceptibility test (DST) results reported for at least isoniazid and rifampin were included in the analysis. Because susceptibility testing is time consuming, especially for second-line drugs, initial DST results are reported separately to avoid delaying reporting of routine TB case data. At the end of treatment, the outcome is reported in a second follow-up report. The HIV status of TB cases reported to NTSS was available through 2006, except in California, where only data on positive HIV test results<sup>§</sup> were available through 2004.

TB cases reported during 1993--1999, a period of rapidly decreasing incidence of both TB and MDR TB, were compared with cases reported during 2000--2006, a period of slower decline in TB and MDR-TB rates. During 1993--2006, a total of 202,436 culture-confirmed TB cases were reported to NTSS; 190,312 of these cases had initial DST results for at least isoniazid and rifampin, including 2,927 (2%) with initial resistance to both drugs (i.e., MDR TB). Of the 2,927 MDR-TB cases, 1,665 (57%) had DST results reported for at least one fluoroquinolone and one injectable second-line drug. Of these, 49 cases (3%) met the revised definition of XDR TB, including 32 cases reported during 1993--1999 and 17 cases during 2000--2006 (Table).

The 49 XDR-TB cases were reported from nine states and one city, with the largest numbers in New York City (19 cases) and California (11 cases) ([Figure](#)). HIV status was known for 29 (59%) of the 49 persons with XDR TB ([Table](#)); 16 (55%) were HIV positive. During 1993--1999, a total of 19 persons with XDR TB had known HIV status, of whom 14 (74%) were HIV positive; during 2000--2006, 10 persons had known HIV status, of whom two (20%) were HIV positive. The number and percentage of persons with XDR TB in the group aged 25--44 years decreased from 21 (66%) during 1993--1999 to six (35%) during 2000--2006.

When the two periods were compared, the number of XDR-TB cases among foreign-born persons did not change substantially, but the percentage of XDR-TB cases among foreign-born persons increased from 39% (12 cases) in 1993--1999 to 76% (13 cases) in 2000--2006 as the number of XDR-TB cases among U.S.-born cases decreased ([Table](#)). Among racial/ethnic populations, nine (28%) of 32 XDR-TB cases during 1993--1999 were reported among non-Hispanic blacks, decreasing to two (12%) of 17 cases during 2000--2006. Conversely, the number and percentage of cases among Asians increased from three (9%) during 1993--1999 to seven (41%) during 2000--2006. Sputum microscopy for acid-fast bacilli was positive in 27 (69%) of the 39 cases with known results. Mortality in XDR-TB cases was strongly associated with HIV infection. Among 41 persons with XDR TB and known outcomes, 12 (29%) persons died; 10 of those had HIV infection, and the other two did not have HIV test results reported.

**Reported by:** *NS Shah, MD, Albert Einstein College of Medicine, Bronx, New York. R Pratt, S Althomsons, T Navin, MD, KG Castro, MD, VA Robison, DDS, PhD, JP Cegielski, MD, Div of Tuberculosis Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (proposed), CDC.*

### **Editorial Note:**

After approximately 30 years of declining trends, a TB epidemic occurred in the United States during 1985--1992. From 22,201 cases in 1985 (9.3 per 100,000 population), reported TB increased to 26,673 cases in 1992 (10.4 per 100,000 population) (7). Although the incidence of MDR TB in the United States was largely unknown before 1993, the number of cases began increasing in New York City in the early 1980s (8), and numerous outbreaks of MDR TB were described in the late 1980s and early 1990s (9). With implementation of elements of the 1992 National Action Plan to Combat Multidrug-Resistant Tuberculosis, reported MDR-TB cases declined rapidly (10). TB-control activities included improving laboratory services for rapid, accurate culture and DST, improving infection control, and strengthening NTSS to include DST and HIV test results beginning in 1993. The rapid decrease in MDR-TB cases during 1993--1999 likely correlated with the 34% decline in TB cases overall in the United States to 17,501 (6.3 per 100,000) in 1999 (7).

Effective treatment of MDR TB requires administration, for 18--24 months, of four to six drugs to which the infecting organism is susceptible, including multiple second-line drugs. Beginning in the 1980s, the use of second-line drugs increased substantially as

physicians and TB-control programs treated growing numbers of MDR-TB cases. Increased use of these drugs resulted in MDR-TB strains with extensive resistance to both first- and second-line drugs. Thus, XDR TB in the 1990s likely represented the legacy of the 1985--1992 TB epidemic in the United States and treatments to combat the spike in MDR-TB cases.

Characteristics of XDR-TB cases changed during 2000--2006 in parallel with the changing epidemiology of TB in general and MDR TB in particular. These changes included an overall decrease in the number of cases, a decrease in the proportion of cases in HIV-infected persons, an increase in the proportion of cases among foreign-born persons, and an increase in the proportion of Asians among persons with XDR TB, compared with 1993--1999 (7).

The findings in this report are subject to at least five limitations. First, the number of XDR-TB cases is a minimum estimate because of incomplete DST data. Although 57% of MDR-TB cases had DST results reported for at least one fluoroquinolone and at least one of the three second-line injectable drugs, only 22% had DST results reported for all drug combinations in the definition of XDR TB, taking into consideration cross-resistance among drugs and data available in NTSS. Initial TB isolates with any resistance to rifampin or resistance to any two first-line drugs should be tested for susceptibility to a full panel of anti-TB drugs, and the results should be reported accordingly. Second, aggregate reporting of drug resistance traditionally has been based only on initial DST results, not on drug resistance that develops during treatment. Because of the complexity of second-line DST, results can be delayed by several months and might not be included in the report of initial DST results. Third, approximately 20% of reported TB cases do not have positive cultures that would enable DSTs to be performed. Fourth, NTSS data for 2006 are provisional, and final case counts, including XDR-TB cases, are subject to revision. Finally, HIV test results usually are reported to NTSS after both TB and HIV surveillance systems have verified their annual case counts. Thus, HIV test results lag behind TB case counts, and data on HIV status are complete through 2005 but provisional for 2006, except for California, which provided data only through 2004. In addition, HIV test results from California are less complete.

The NTSS surveillance data summarized in this report represent an updated measurement of XDR TB in the United States. However, surveillance data do not enable a detailed understanding of how most XDR-TB cases arise. For example, the relative importance of person-to-person XDR-TB transmission compared with the emergence of XDR TB in individual patients as a consequence of inadequate treatment cannot be determined.

Use of second-line drugs to treat drug-resistant TB is increasing throughout the world, presaging substantial increases in XDR TB internationally. Accurate measures of the incidence, prevalence, and determinants of XDR TB are needed to target public health responses. Attention to fundamental aspects of TB control (e.g., surveillance, prompt culture and DST, directly observed treatment, contact investigation, rapid containment of outbreaks, and infection control) is needed to control XDR TB in the United States in the same manner that MDR TB was addressed during the previous decade. The Federal TB

Task Force is developing a domestic and international response for U.S. government agencies regarding XDR TB. A senior-level interagency meeting will be convened to formulate a comprehensive response and to assign responsibilities for a unified strategic approach. Additional information regarding XDR TB is available at <http://www.who.int/tb/xdr/en/index.html>.

## References

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\* Provisionally defined as disease caused by *Mycobacterium tuberculosis* that is resistant in vitro to at least isoniazid and rifampin among first-line drugs, and at least three or more of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and para-aminosalicylic acid).

† Local health departments verify cases of TB and report to the state health department only those diagnosed within their own jurisdictions (to prevent duplicate counting of cases). State health departments validate, compile, and transmit selected data to NTSS, using the standardized form, *Report of Verified Case of Tuberculosis*.

§ Because only positive results were reported from California, persons with TB who tested HIV negative could not be distinguished from those who were not tested or whose results were unknown.

## Table

TABLE. Reported cases of tuberculosis (TB), multidrug-resistant (MDR) TB, and extensively drug-resistant (XDR)\* TB — U.S. National TB Surveillance System,† 1993–1999 and 2000–2006

Characteristic	1993–1999		2000–2006	
	No.	(%) <sup>§</sup>	No.	(%) <sup>§</sup>
Total number of culture-confirmed TB cases with initial drug-susceptibility test (DST) results reported for at least isoniazid and rifampin	111,758	—	78,554	—
No. of cases with initial resistance to at least isoniazid and rifampin (i.e., MDR TB <sup>§</sup> ) (% of total TB cases)	2,005	(2)	922	(1)
No. of cases with reported initial DST results sufficient to rule in XDR TB** (% of MDR-TB cases)	1,069	(53)	596	(65)
No. of cases with reported initial DST results sufficient to rule out XDR TB** (% of MDR-TB cases)	360	(18)	291	(32)
<b>No. of XDR-TB cases under revised definition (% of MDR-TB cases)</b>	<b>32</b>	<b>(2)</b>	<b>17</b>	<b>(2)</b>
Country of origin (% of XDR-TB cases)				
U.S. born	19	(59)	4	(24)
Foreign born	12	(38)	13	(76)
Unknown	1	(3)	0	—
Human immunodeficiency virus (HIV) status†† (% of XDR-TB cases)				
HIV positive	14	(44)	2	(12)
HIV negative	5	(16)	8	(47)
HIV test not administered or status unknown	13	(40)	7	(41)
Age group (yrs) (% of XDR-TB cases)				
0–14	1	(3)	0	—
15–24	1	(3)	4	(24)
25–44	21	(66)	6	(35)
45–64	3	(9)	6	(35)
≥65	6	(19)	1	(6)
Race/ethnicity (% of XDR-TB cases)				
Hispanic	11	(34)	5	(29)
Asian, non-Hispanic	3	(9)	7	(41)
Black, non-Hispanic	9	(28)	2	(12)
White, non-Hispanic	8	(25)	3	(18)
Other race, non-Hispanic	1	(3)	0	—
Sex (% of XDR-TB cases)				
Female	9	(28)	9	(53)
Male	23	(72)	8	(47)
TB history (% of XDR-TB cases)				
Previous TB <sup>§§</sup>	4	(13)	3	(18)
No previous TB	27	(84)	14	(82)
Unknown	1	(3)	0	—
Results of sputum microscopy for acid-fast bacilli (% of XDR-TB cases)				
Positive	15	(47)	12	(71)
Negative	9	(28)	3	(18)
Not done/Unknown	8	(25)	2	(12)
Treatment outcome (% of XDR-TB cases)				
Completed treatment	11	(34)	6	(35)
Died during treatment	10	(31)	2	(12)
Outcome not yet reported	3	(9)	5	(29)
Moved, lost to follow-up, or other	8	(25)	4	(24)

\* Defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and to at least one second-line injectable drug (amikacin, capreomycin, or kanamycin).

† On the basis of cases reported from 50 states and the District of Columbia (DC), through February 8, 2007. Cases reported from U.S.-affiliated island territories excluded.

§ Percentages might not add to 100% because of rounding.

† Defined as resistance to at least isoniazid and rifampin.

\*\* On the basis of DST results in the U.S. National TB Surveillance System for drugs included in the definition of XDR TB: isoniazid, rifampin, ciprofloxacin, ofloxacin, kanamycin, amikacin, and capreomycin.

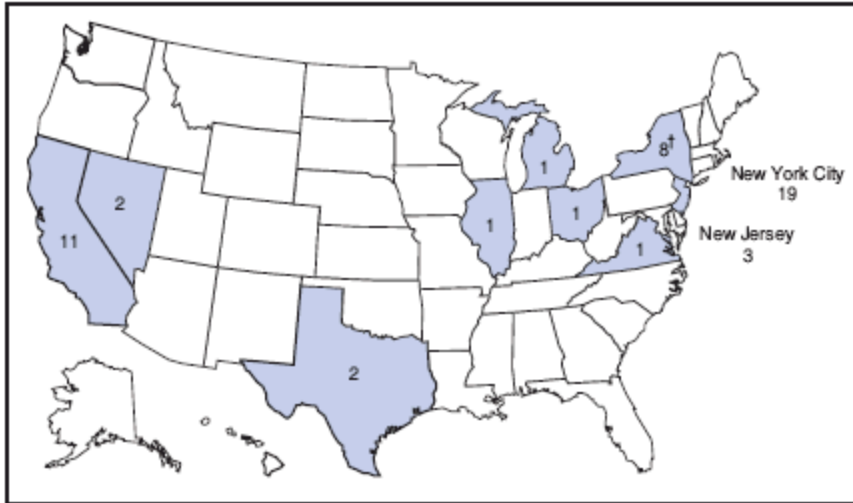
†† HIV reporting for California, which only reports HIV-positive results, completed through 2004; no HIV positives were reported from California. HIV reporting for 49 states other than California and DC completed through 2005, provisional for 2006.

§§ Persons who had verified TB disease in the past, were discharged (e.g., completed therapy) or lost to supervision for >12 consecutive months, and had verified disease again.

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**Figure**

**FIGURE. Number of reported cases of extensively drug-resistant tuberculosis (XDR TB)\* — United States, 1993–2006**



\* XDR TB defined as resistance to at least isoniazid, rifampin, any fluoroquinolone, and at least one second-line injectable drug (kanamycin, amikacin, or capreomycin).

† Excludes New York City.