Epidemiologic Notes and Reports

During 1990 and 1991, outbreaks of multidrug-resistant tuberculosis (MDR-TB) in four hospitals (one in Miami and three in New York City) were investigated by CDC in collaboration with the reporting hospitals and state and local health departments. This report summarizes preliminary findings of the investigations and recommendations for prevention and control of MDR-TB outbreaks. Hospital A

From January 1988 through January 1990, 29 patients diagnosed with MDR-TB (case-patients) had Mycobacterium tuberculosis isolates resistant to at least isoniazid (INH) and rifampin (RIF) (1). For nine of these patients, isolates were also resistant to ethambutol (EMB). Of the 29 patients, 27 (93%) were known to be infected with human immunodeficiency virus (HIV); 23 had acquired immunodeficiency syndrome (AIDS)-defining conditions (2). Of the 29 total patients, 21 (72%) died a median of 7 weeks after diagnosis of MDR-TB.

The 29 case-patients were compared with 29 randomly selected HIV-infected patients with tuberculosis (TB) who had M. tuberculosis isolates susceptible to INH, RIF, and other drugs tested (controls). Before onset of TB, case-patients were more likely to have been patients in the hospital's HIV ward or outpatient HIV clinic at the same time as another case-patient with infectious pulmonary MDR-TB (14/29 vs. 1/29; odds ratio (OR)=26.1; 95% confidence interval (CI)=3.2-1143.0) (1).

From February 1990 through February 1991, 36 additional patients were diagnosed with M. tuberculosis resistant to at least INH and RIF; 30 of these cases were diagnosed during the first 6 months of that period and before, or within 2 months after, hospital A had implemented a substantial number of control measures (see box) with the assistance of the state and local health departments and CDC. Of the 36 additional patients, 35 were known to have HIV infection. Hospital B

From February 1990 through February 1991, 36 additional patients were diagnosed with M. tuberculosis resistant to at least INH and rifampin (RIF); 30 of these cases were diagnosed during the first 6 months of that period and the estimated incubation period for TB in case-patients ranged from 30 to 105 days.
For 13 of 14 outbreak isolates analyzed, typing by restriction fragment length polymorphism (RFLP), an experimental method of DNA analysis for identifying genetic differences between M. tuberculosis strains (5), yielded identical DNA fingerprints. From May 1990 through January 1991, 17 additional patients (all infected with HIV) were diagnosed with M. tuberculosis resistant to at least INH and SM. Hospital C

From September 1989 through March 1991, 17 patients diagnosed with MDR-TB had isolates resistant to at least INH, RIF, and SM (case-patients); for 10 case-patients, isolates were also resistant to EMB. Of the 16 patients who were known to be HIV-seropositive, 11 had AIDS-defining conditions. Of the 17 total patients, 14 (82%) died a median of 6 weeks after diagnosis of TB. For 10 case-patients, the cause of death appeared to be TB.

Case-patients were compared with the 69 patients with TB diagnosed during the same period with M. tuberculosis isolates susceptible to INH, RIF, SM, and other drugs tested (controls); 59 of the controls were known to be HIV-positive. Case-patients were more likely to have been hospitalized at hospital C at least 30 days before their first positive M. tuberculosis culture (when limited to case-patients and controls with HIV infection, 13/16 vs. 21/59; OR=7.8; 95% CI=1.8-46.4).

Since March 31, 1991, four additional patients have been diagnosed with M. tuberculosis resistant to at least INH, RIF, and SM; all four had HIV infection.

Hospital D

From January 1990 through March 1991, 23 patients diagnosed with MDR-TB had isolates resistant to at least INH and RIF (case-patients). For 13 of these patients, the isolates were resistant to other anti-TB drugs (four with resistance to INH, RIF, SM, and EMB). Of the 21 (91%) patients who were known to be HIV-seropositive, 20 had AIDS-defining conditions. Of the 23 total patients, 19 (83%) died a median of 4 weeks after diagnosis of TB. For 16 patients, the cause of death appeared to be TB.

The 23 case-patients were compared with 23 patients diagnosed with TB during the same period with M. tuberculosis isolates susceptible to INH, RIF, and other drugs tested (controls); 11 of the controls were known to be HIV-positive. Before onset of TB, case-patients were more likely to have been hospitalized at hospital D (when limited to case-patients and controls with HIV infection, 19/21 vs. 2/11; OR=42.8; 95% CI=4.0-576.5).

Since April 1, 1991, three additional patients have been diagnosed with M. tuberculosis resistant to INH and RIF; all three had HIV infection. Other Outbreak Characteristics

Late Diagnosis of TB and Recognition of Drug Resistance. In all four hospitals, because radiologic and bacteriologic signs often were inconclusive, the timely diagnosis of TB was delayed for some case-patients. For example, cavitation on chest radiograph was present in only seven (8%) of the 87 outbreak cases. In three hospitals, acid-fast bacilli (AFB) were not detected in sputum smears of 14 (25%) of the 55 MDR-TB case-patients who had sputum submitted for AFB examination. In the fourth hospital, sputum smears were not routinely examined for AFB. Furthermore, the time taken to complete and verify drug-susceptibility testing and report the results to hospitals and clinicians often contributed to delayed recognition of drug resistance. In general, drug-susceptibility testing took at least 8 weeks to complete. In many instances, several factors, including repeating susceptibility tests to confirm results, extended this time up to 6 months.

Ineffective Patient Isolation. Reviews of medical records indicated that, because of late diagnosis and recognition of drug resistance, AFB isolation precautions were sometimes delayed and/or not maintained
until the patient was rendered noninfectious (3). In addition, hospital personnel reported that, in some instances, doors to isolation rooms were left open, health-care workers (HCWs) and visitors entered AFB isolation rooms wearing no masks or using masks improperly, and patients in AFB isolation left their rooms without wearing masks. Finally, testing of direction of air flow with smoke tubes in all four hospitals indicated that many AFB isolation rooms had positive pressure relative to hallways.

Probable Nosocomial Transmission to HCWs. Eight cases of TB have been reported among HCWs in these hospitals. Two of the eight had known exposure to outbreak case-patients and had M. tuberculosis isolates resistant to the same drugs as outbreak cases. One of these two HCWs was infected with HIV and died after a fulminant clinical course of TB; the other, who was HIV-seronegative and had clinical and radiographic signs compatible with primary TB, has improved with therapy.

Of the other six HCWs with TB, three had known or possible exposure to outbreak case-patients but had isolates with different drug-susceptibility patterns; one had M. tuberculosis isolated, but drug susceptibility and clinical information is incomplete; and two were diagnosed clinically and did not have M. tuberculosis isolated. Of the six HCWs, four were HIV-seropositive; HIV serostatus for the other two was unknown.

In two of the hospitals, positive tuberculin skin-test reactions were recorded after outbreak exposure in 13 (33%) of 39 and six (50%) of 12 other HCWs, respectively, who had reported negative skin-test reactions within the previous 2 years. Reported by: M Fischl, MD, R Uttamchandani, MD, R Reyes, MD, T Cleary, PhD, J Otten, A Breeden, Univ of Miami/Jackson Memorial Medical Center; W Bigler, PhD, H Valdez, R Cacciatore, J Witte, MD, RS Hopkins, MD, State Epidemiologist, Florida Dept of Health and Rehabilitative Svcs. MH Grieco, MD, J Williams, E Sordillo, MD, ME Gilligan, N Schneider, St. Luke's/Roosevelt Hospital Center, New York; VL Sharp, MD, P Rivera, A Pitta, MD, St. Clare's Health and Hospital Center; MP Mullen, MD, MT Gordon, MA, CP Busillo, MD, JF Boyle, PhD, New York; J Adler, MD, KR Ong, MD, New York City Dept of Health; GT DiFerdinando, Jr, MD, DL Morse, MD, State Epidemiologist, New York State Dept of Health. Div of Tuberculosis Elimination, National Center for Prevention Svcs; Div of Bacterial and Mycotic Diseases, Div of HIV/AIDS, and Hospital Infections Program, National Center for Infectious Diseases; Div of Field Epidemiology, Epidemiology Program Office; Div of Surveillance, Hazard Evaluations, and Field Studies, and Div of Physical Sciences and Engineering, National Institute for Occupational Safety and Health; Special Programs Group, Office of the Director, National Center for Environmental Health and Injury Control, CDC.

**Editorial Note**

Editorial Note: The findings in this report illustrate the increased susceptibility of HIV-infected persons, particularly those with severe immunosuppression, to life-threatening nosocomially transmitted TB; underscore the importance of implementing infection-control precautions to prevent transmission of M. tuberculosis to patients and HCWs (3); and identify additional issues related to the prevention and control of TB outbreaks caused by organisms resistant to the two major anti-TB drugs, INH and RIF. Although the investigations focused on MDR-TB, the findings also underscore the infectiousness of TB cases in general, the susceptibility of HIV-infected patients (6-8) to rapid progression to clinical TB after infection with M. tuberculosis, and the potential for rapid spread of TB when immunocompromised patients and HCWs are exposed to patients who have infectious TB. Of the 83 patients identified with HIV infection, 76 had clinical diagnosis of AIDS, indicating advanced immunosuppression.

At least two categories of factors may have contributed to these outbreaks. First, diagnosis of TB in HIV-infected patients was delayed, in many cases, because of unusual clinical and radiographic characteristics, and recognition of drug resistance was delayed because of the lengthy time required for
laboratory identification, confirmation, and reporting of drug-resistance patterns. Until M. tuberculosis drug resistance was identified as a problem and the pattern of resistance known, no reliably effective therapeutic regimens could be prescribed. Thus, treatment regimens had to be adjusted empirically when patients failed to respond, and patients sometimes remained infectious for prolonged periods.

Second, in all four hospitals, AFB isolation precautions sometimes were delayed on admission or readmission of symptomatic TB patients because of delays in TB diagnosis and in identification of drug resistance. Furthermore, AFB precautions were not always maintained for an adequate period. In addition, lapses occurred in AFB isolation precautions, and AFB isolation rooms often did not have appropriate negative pressure ventilation. Other factors that may have contributed to these outbreaks included the clustering of highly susceptible (i.e., immunocompromised) HIV-infected patients in these hospitals and inadequate numbers of appropriate rooms for AFB isolation.

In at least one of the four hospitals (hospital A), sufficient time has elapsed to begin to assess the impact of control measures (see box). Although the number of MDR-TB cases decreased substantially after implementation of these measures, the specific contribution of each strategy to the decrease in cases is unknown. Evaluation of the effectiveness of this comprehensive approach is under way at each of the other three hospitals. Because of the likelihood that MDR-TB was also spread in the community, local health departments are collaborating with the hospitals to identify and examine community contacts of the outbreak case-patients.

These outbreaks underscore the need for all health-care facilities, especially those in which persons with HIV infection receive care, to implement published recommendations for prevention of TB transmission (3) (see box). However, the involvement of organisms resistant to INH and RIF suggests the need for additional measures. Anti-TB drug-susceptibility testing should be performed on initial M. tuberculosis isolates from all TB patients. Isolates obtained after relapse or apparent treatment failure should also be tested for drug susceptibility. Drug-susceptibility testing should be completed rapidly, and results should be reported promptly to the health-care provider and the health department, even if confirmatory tests are planned. The use of radiometric culture and RFLP techniques may facilitate rapid detection of drug-resistant M. tuberculosis strains and should be used when appropriate. Hospitals and health departments should periodically examine MDR-TB incidence and resistance patterns to detect outbreaks and to provide a basis for drug regimens for patients with suspected MDR-TB.

Until rapid methods for determining M. tuberculosis drug susceptibility are routinely available, however, suspicion of drug resistance based on clinical and epidemiologic grounds is the only means available for early detection of MDR-TB and prevention of outbreaks by effective treatment. Persons at high risk for developing MDR-TB include 1) immunocompromised persons and others who have recently been exposed to infectious MDR-TB and 2) persons who have been previously treated for TB but who failed to take medications as prescribed or were prescribed an inadequate or ineffective treatment regimen.

No data are available from controlled trials regarding the treatment of patients with TB resistant to INH and RIF. However, pending drug-susceptibility test results, patients likely to have MDR-TB should be treated promptly with regimens containing INH, RIF, and pyrazinamide (since these drugs may be effective) plus at least two other drugs to which the M. tuberculosis strain is likely to be susceptible (based on surveillance of local drug-resistance patterns). Expert consultation, often available through the state or local health department, may be advisable--especially if clinical specimens are AFB-smear- and/or culture-positive and the patient fails to respond to treatment. Treatment should be modified accordingly when drug-susceptibility results are available.

All hospital personnel, including volunteers, who may be exposed to patients with suspected or known TB
should be educated about the medical consequences of becoming infected with MDR-TB and should follow appropriate precautions for minimizing such exposure (3). Their education should include information about the risk for life-threatening clinical TB in persons with immunocompromising conditions, including HIV infection. HCWs and other persons exposed to patients with potentially infectious TB for whom appropriate AFB isolation precautions are not in place should be promptly evaluated to determine whether treatment for TB or preventive therapy for tuberculous infection is indicated (3). HCWs who are diagnosed with active pulmonary or laryngeal TB should have temporary work restriction (3). Preventive therapy recommendations for persons exposed to or infected with multidrug-resistant strains of M. tuberculosis will depend on drug-susceptibility patterns. CDC, in consultation with additional experts, is developing guidelines for clinicians managing such patients.

It is unknown whether vaccination with BCG (bacille Calmette-Guerin) vaccines licensed for use in the United States will protect HCWs against TB (9). Furthermore, BCG vaccination is contraindicated for persons with HIV infection. The Immunization Practices Advisory Committee and the Advisory Council for Elimination of Tuberculosis are being consulted to determine if recommendations on BCG vaccination for HCWs should be modified in view of these MDR-TB outbreaks.

All TB cases identified in hospitals should be reported promptly to the appropriate health departments to facilitate community contact identification procedures. Outbreaks of MDR-TB should be promptly investigated and reported through state and territorial health departments to the Division of Tuberculosis Elimination, National Center for Prevention Services, CDC; telephone (404) 639-2519. Health departments can usually provide additional services to prevent development or spread of MDR-TB, including directly supervised administration of TB medications in the patient's home or other settings; arrangements for temporary housing for TB patients who may be infectious and who are homeless; initiation of legal quarantine procedures for infectious TB patients, when needed; medical and nursing case management; expert consultation; and educational materials on TB.

References


2. CDC. Revision of the CDC surveillance case definition for acquired immunodeficiency syndrome. MMWR 1987;36(no. 1S).

3. CDC. Guidelines for preventing the transmission of tuberculosis in health-care settings, with special focus on HIV-related issues. MMWR 1990;39(no. RR-17).


Summary of Recommendations for Preventing the Transmission of Tuberculosis in Health-Care Settings*

1. Early identification and treatment of persons with active tuberculosis (TB)
   - Maintain a high index of suspicion for TB to identify cases rapidly.
   - Promptly initiate effective multidrug anti-TB therapy based on clinical and drug-resistance surveillance data.
   - Initiate acid-fast bacilli (AFB) isolation precautions immediately for all patients who are suspected or confirmed to have active TB and who may be infectious. AFB isolation precautions include use of a private room with negative pressure in relation to surrounding areas and a minimum of six air exchanges per hour. Air from the room should be exhausted directly to the outside. Use of ultraviolet lamps and/or high-efficiency particulate air filters to supplement ventilation may be considered.
   - Persons entering the AFB isolation room should use disposable particulate respirators that fit snugly around the face.
   - Continue AFB isolation precautions until there is clinical evidence of reduced infectiousness (i.e., cough has substantially decreased, and the number of organisms on sequential sputum smears is decreasing). If drug resistance is suspected or confirmed, continue AFB precautions until the sputum smear is negative for AFB.
   - Use special precautions during cough-inducing procedures.

2. Prevention of spread of infectious droplet nuclei by source control methods and by reduction of microbial contamination of indoor air

3. Surveillance for TB transmission
   - Maintain surveillance for TB infection among health-care workers (HCWs) by routine, periodic tuberculin skin testing. Recommend appropriate preventive therapy for HCWs when indicated.
   - Maintain surveillance for TB cases among patients and HCWs.
   - Promptly initiate contact investigation procedures among HCWs, patients, and visitors exposed to an untreated, or ineffectively treated, infectious TB patient for whom appropriate AFB procedures are not in place. Recommend appropriate therapy or preventive therapy for contacts with disease or TB infection without current disease. Therapeutic regimens should be chosen based on the clinical history and local drug-resistance surveillance data. *Adapted from reference 3.