GENERAL ARTICLES

The Multidrug-Resistant Tuberculosis Challenge to Public Health Efforts to Control Tuberculosis

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Synopsis

After years of steady decline, there has been an unprecedented resurgence of tuberculosis (TB) in the United States and outbreaks of multidrug-resistant tuberculosis (MDR-TB). The authors assess the nature, epidemiology, and implications of MDR-TB; provide suggestions for preventing drug resistance among patients with drug-susceptible TB; and offer recommendations for managing patients with MDR-TB. They outline the National Action Plan to Combat MDR-TB. Close collaboration among medical practitioners and staff members of TB control programs is needed to ensure the most effective management of patients with TB and their contacts. This collaboration is one of the most important steps for successful control of MDR-TB.

AFTER YEARS OF STEADY DECLINE, there has been an unprecedented resurgence since 1985 in the number of cases of tuberculosis (TB) in the United States. More recently, drug-resistant TB has become a serious concern as increasing numbers of TB cases are reported to be caused by strains of *Mycobacterium tuberculosis* resistant to one or more antituberculosis drugs.

In a survey of new TB cases reported to the Centers for Disease Control (CDC) during the first quarter of 1991, 13.3 percent were resistant to at least one antituberculosis drug and 3.0 percent were resistant to both isoniazid (INH) and rifampin (RIF) (unpublished CDC data), the two most effective drugs presently available for the treatment of TB. Furthermore, from 1990 through 1992, several large institutional outbreaks of multidrug-resistant TB (MDR-TB), involving strains of *M. tuberculosis* resistant to both INH and RIF, have occurred in hospitals, outpatient clinics, and prison facilities (*1-9* and unpublished CDC data). The total number of cases of MDR-TB in these outbreaks combined now exceeds 200.

Preventing the emergence of drug-resistant TB in individual patients would seem relatively simple; if an effective antituberculosis drug therapy regimen is prescribed and taken correctly for the appropriate period of time, drug-resistant disease should not occur (*10*). However, successful treatment of TB requires months of therapy with multiple medications, and the problems associated with the provision and supervision of these services by TB control programs and medical practitioners are complex. A major cause of drug resistance is nonadherence with therapy. The control of drug-resistant TB in institutional settings is complicated and critically dependent on the institution's early detection and proper management of infectious patients. Institutions must intensify their efforts to reduce the risk of person-to-person transmission of TB, especially drug-resistant TB.

Recognition of drug-resistant TB can be delayed by clinicians' low levels of suspicion of resistance and by the several weeks required to perform drug susceptibility testing using traditional methods (*9*). Consequently, patients with drug-resistant TB may remain unrecognized as such, may not receive effective therapy, and may remain infectious for prolonged periods. The prevention and control of drug-resistant TB represents a significant challenge to public health officials and medical practitioners. In this article, we review the mechanism and

epidemiology of drug-resistant TB and discuss current strategies for managing, preventing, and controlling drug-resistant TB.

Mechanism of Drug Resistance

Resistance to antituberculosis drugs occurs in *M. tuberculosis* by random, spontaneous mutations of the bacterial chromosome (*11*). These mutations occur at a low but constant rate, which varies for different antituberculosis drugs. The probability of mutation to drug resistance is directly proportional to the size of the bacterial population. The rates of spontaneous resistance are 1 in 10^6 organisms for INH, 1 in 10^8 for RIF, 1 in 10^6 for ethambutol, and 1 in 10^5 for streptomycin (*12*). Assuming they are independent events, the probability of resistance to more than one drug is the product of the probabilities for each drug alone. The probability of INH and RIF resistance occurring in the same organism is 1 in $10^6 \times 1$ in 10^8, or 1 in 10^{14}. The bacterial population in a cavitary pulmonary lesion is estimated to be approximately 10^9 organisms (*13*). Therefore, the bacterial population of these lesions is likely to include a small number of mutants resistant to any single antituberculosis drug; only very rarely will the population include a significant number of mutants resistant simultaneously to two or more drugs. Monotherapy with a single antituberculosis drug does not induce drug-resistant mutants, but it suppresses the bacteria susceptible to that drug, thereby selecting for mutants resistant to that drug.

Drug-resistant TB occurs when there is a substantial increase in the proportion of organisms that are resistant to one or more antituberculosis drugs (*13*). There are two ways a patient can develop drug-resistant TB. Acquired or secondary drug resistance occurs when the small number of drug-resistant mutants are selected as a result of ineffective antituberculosis drug therapy. In TB, acquired drug resistance may appear after 2 weeks, but more usually from 1 to 4 months after the start of therapy, when the bacterial population is still relatively large (*14*).

Initial or primary drug resistance, on the other hand, occurs when the patient becomes infected with *M. tuberculosis* organisms resistant to one or more drugs, before the patient is treated with the drug(s) in question. Primary drug resistance is caused by person-to-person transmission of drug-resistant organisms. Primary drug resistance is not distinguishable clinically from acquired drug resistance except by history. In clinical practice, a patient with TB is said to have drug-resistant disease if that patient's bacillary population consists of organisms that would probably fail to respond to treatment with the drug concerned in normal dosage, for example, a dosage that will cause a response in patients infected with drug-susceptible organisms (*15*).

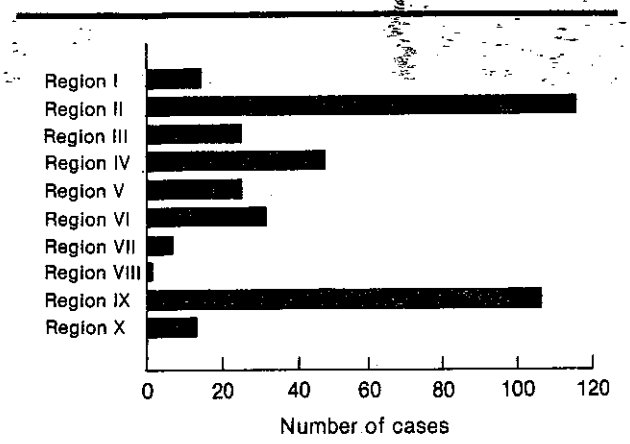
Epidemiology of Drug-Resistant TB

Nationwide reporting of TB cases was first fully implemented in the United States in 1953, and a national surveillance system currently is maintained at CDC. This system has not collected information on the drug susceptibility of reported cases of TB; thus, national data on the incidence and prevalence of drug-resistant TB are not available. However, information on the epidemiology of drug-resistant TB has been derived from the results of large national surveys of primary drug resistance and from reports of drug-resistant TB outbreaks.

There are two important limitations in the data available on drug-resistant TB (*16*). First, it is often difficult to distinguish between primary and acquired drug resistance. A history of previous treatment with antituberculosis drugs seldom can be accurately ascertained; thus, the primary drug resistance rate estimated by a survey will be falsely elevated if previously treated patients with acquired drug-resistance are misclassified and included. Second, the technical and methodologic differences in performing and interpreting drug susceptibility tests limit the comparability of the data reported by different investigators. In spite of these limitations, epidemiologic data on drug-resistant TB can provide valuable information if interpreted carefully.

National surveys of primary drug resistance. CDC has conducted national surveys of primary drug resistance at intervals since 1961 (*17–22*). The most recent survey was conducted between March 1982 and March 1986 in cooperation with 31 public health laboratories throughout the country (*22*). A concerted effort was made to investigate the medical history of the TB cases included in that survey and to exclude previously treated patients. Of the 3,760 isolates tested in the survey, 9.0 percent were resistant to at least 1 of the 10 drugs tested. The rate of primary resistance decreased significantly during the 4-year survey. Primary resistance rates varied among geographic areas, ranging from 2.0 percent in Indiana to 14.1 percent in Harlingen, TX. Rates also varied by the patient's race or ethnicity, and primary drug resistance was about twice

Culture-positive cases of tuberculosis resistant to one or more drugs, reported by HHS Region, United States, 1991, first quarter



NOTE: I. CT, ME, MA, NH, RI, and VT; II. NJ, NY, PR, and VI; III. DE, MD, PA, VA, DC, and WV; IV. AL, FL, GA, KY, MS, NC, SC, and TN; V. IL, IN, MI, MN, OH, and WI; VI. AR, LA, NM, OK, and TX; VII. IA, KS, MO, and NB; VII. CO, MT, ND, SC, UT, and WY; IX. AZ, CA, HI, and NV; X. AK, ID, OR, and WA.
SOURCE: CDC provisional data.

as likely in foreign-born patients as in U.S.-born patients.

Because the national surveys indicated a low and apparently decreasing rate of primary drug resistance in the United States, and because of resource constraints and competing priorities, CDC discontinued surveillance of drug resistance in 1986. However, prompted by the recent occurrence of several outbreaks of MDR-TB, CDC conducted a survey of drug resistance among TB cases reported to the national surveillance system January through March 1991 (unpublished CDC data).

The methodology used in the 1991 survey was different from that of the previous surveys. The survey was based on the results of susceptibility testing from local laboratories, whereas previous surveys were based on results of susceptibility testing at the CDC Mycobacteriology Laboratory. Therefore, technical and methodologic differences among the various laboratories may account for some of the geographic variation in the rates in the 1991 survey. In the 1991 survey, TB cases reported as new cases were assumed to have had no previous antituberculosis treatment and those reported as recurrent cases were assumed to have received previous treatment. No attempt was made, as in previous surveys, to verify this information.

Finally, in the provisional results of the 1991 survey reported in this paper, significant differences in the sample of isolates that were tested for drug susceptibility may possibly have biased the results. Of 4,031 culture-positive cases provisionally reported during the study period, 2,670 (66 percent) had results of susceptibility testing for at least two drugs, and 2,648 had results of testing for both INH and RIF. Among new TB cases, 13.3 percent were reported as being resistant to at least one antituberculosis drug. These cases were reported from all regions of the country (see figure). Of isolates tested for both drugs, 3.0 percent were reported as being resistant to INH and RIF.

The CDC surveys indicate that drug resistance is not distributed uniformly. This suggests that rates of primary resistance estimated for the entire country are not always characteristic of specific localities or certain subpopulations. The surveys illustrate the importance of local surveillance for primary drug resistance to distinguish areas or population subgroups where drug resistance is emerging, as well as to monitor control efforts in areas where drug resistance is already established.

Drug-resistant tuberculosis outbreaks. Until recently, reports of outbreaks of drug-resistant TB have been uncommon. An extensive review of community and school-based TB outbreaks published in 1965 found none which involved drug-resistant strains (*23*). In the 20-year period from 1970 through 1990, five TB outbreaks involving strains of *M. tuberculosis* resistant to two or more drugs were reported in the literature (*24–29*). The outbreaks occurred in families and households, schools, communities, and a shelter for the homeless.

Steiner and coworkers reported an outbreak among a large family in New York City, in which the source case was a female adolescent who was symptomatic for 6 months before being diagnosed with TB with primary resistance to INH, streptomycin, and para-amino salicylic acid (PAS) (*24*). All 23 members of the immediate household had positive tuberculin skin tests, and 6 developed active TB.

In a school-based outbreak in Mississippi, an 18-year-old high school student was symptomatic for 6 months before being diagnosed in November 1976 with TB resistant to INH, streptomycin, and PAS (*25*). A retrospective and prospective review of all TB cases reported from the county of residence of the source case was conducted from 1964 through 1980. During this time, 17 epidemiologically linked cases (including 4 cases among students and staff members exposed to the source case), with organisms resistant to the same 3 drugs, were detected. Thus, a prolonged outbreak of MDR-TB had occurred in the community.

Two community outbreaks of drug-resistant TB have both involved prolonged or repeated exposure to a source case, with relatively indolent but persistent patterns of transmission. In one, four epidemiologically-linked TB cases with resistance to INH, RIF, streptomycin, and ethambutol were detected as part of an outbreak that spanned 6 years (*26*). In another drug-resistant TB outbreak, eight members of an extended family and two persons who were close social contacts of members of the family were diagnosed with TB during a period of 18 years (*27*). Family members had interacted extensively and lived intermittently in three States. Contact investigations of the extended family found that 60 (47 percent) of 127 persons had positive tuberculin skin tests, including 30 children and adolescents. In both outbreaks, prolonged infectiousness of cases due to nonadherence to treatment regimens contributed significantly to propagation of the outbreak.

In Boston, reports of several drug-resistant TB cases among homeless persons led to recognition of a large outbreak of TB resistant to INH and streptomycin (*28, 29*). Twenty-seven drug-resistant TB cases were identified as being epidemiologically linked to a single large homeless shelter. The *M. tuberculosis* isolates from 22 of the cases had the same phage type. The cultures from five cases were nonviable and were not phage typed. The probable source case was a shelter resident with a long history of drug-resistant TB and nonadherence to treatment.

Beginning in 1990, several large outbreaks of primary MDR-TB have occurred. The recent outbreaks differ from most of the outbreaks just described in that they have propagated rapidly and have involved large numbers of patients in institutional settings, rather than small numbers of household and close social contacts. From 1990 through June 1992, CDC has worked with State and local health departments and hospital and prison officials to investigate MDR-TB outbreaks in seven hospitals in Florida, New York, and New Jersey, and in the New York State correctional system (*1-9*, and unpublished CDC data). The number of cases in each of the outbreaks has ranged from 5 to 65 (see table). The total number of cases for all the outbreaks combined is now approximately 235.

In the recent MDR-TB outbreaks, all but six of the patients had TB caused by strains of *M. tuberculosis* resistant to both INH and RIF. Most patients had isolates resistant to additional drugs; in three hospitals and in the correctional system, many isolates were resistant to seven drugs. In seven of the eight outbreaks, 80 percent or more of the TB patients were co-infected with human immunodeficiency virus (HIV). This is because most of the outbreaks have occurred in facilities providing care to persons with HIV infection, and because HIV-infected persons newly infected with *M. tuberculosis* are very likely to develop active TB within weeks to months of infection (*30-32*). Because many of the patients with MDR-TB were severely immunosuppressed because of HIV infection or other causes, and because of difficulty in rapidly recognizing drug resistance and devising an effective antituberculosis treatment regimen, the mortality rate in these outbreaks has been very high (60 percent to 89 percent) with rapid progression from diagnosis to death (median interval 4 to 16 weeks).

Health care and correctional workers have been affected by these outbreaks. At two hospitals, 13 of 39 (33 percent) and 9 of 23 (39 percent) exposed workers were found to have confirmed tuberculin skin test conversions at the time of the outbreaks. At a third hospital, more than 50 health care workers showed tuberculin skin test conversions following exposure to hospitalized inmates with MDR-TB. Transmission of MDR-TB to health care workers in the other hospitals investigated could not be ascertained adequately because of incomplete data on workers' baseline tuberculin skin tests. At least 16 health care workers and 1 correctional worker who guarded hospitalized inmates have developed active MDR-TB; 7 of the health care workers were known to be HIV-infected; the correctional worker was immunocompromised as a result of a malignancy. At least six of these workers have died, including five health care workers (four of whom were known to be HIV-infected) and the correctional worker.

Factors influencing the likelihood of drug resistance. Patients at increased risk for drug-resistant TB are believed to include immigrants from areas of high prevalence of TB and drug-resistant TB, such as Southeast Asia, India, and Mexico; persons who are contacts of patients with drug-resistant TB, such as household or other close social contacts or contacts identified in institutional outbreaks of drug-resistant disease; persons with cavitary disease; and persons with residence in areas of the country with a high prevalence of primary drug resistance (*33*). In addition, persons with increased likelihood of drug-resistant disease are those who have received previous treatment with antituberculosis drugs, especially if the treatment failed or the

Test the initial isolate of Mycobacterium tuberculosis *of all patients with tuberculosis for drug susceptibility, to distinguish those who have drug-resistant disease.*

disease reoccurred while the patient was still on drugs, or if treatment was ineffective, such as with an insufficient number of drugs, an inappropriate duration of therapy, or a history of nonadherence to the treatment regimen.

Several factors have contributed to the most recent MDR-TB outbreaks. For some HIV-infected patients, the diagnosis of TB was delayed because of clinicians' low suspicion or because of unusual clinical and radiographic features. Recognition of drug resistance was often delayed because of the lengthy time required for laboratory identification, confirmation, and reporting of drug susceptibility results. As a result, it was difficult to initiate reliably effective treatment regimens, and patients remained infectious for prolonged periods. The start of acid-fast bacilli (AFB) isolation precautions was sometimes delayed because of lags in diagnosis, and AFB precautions were not always maintained for an adequate period of time. Furthermore, lapses occurred in AFB isolation precautions, such as the doors of AFB isolation rooms were sometimes left open, patients sometimes left AFB isolation rooms without appropriate precautions, and isolation rooms often did not have appropriate negative pressure ventilation. Finally, in the correctional system outbreak, transfer of inmates with active infectious MDR-TB probably contributed to interruptions in patient care and to the transmission between and within correctional facilities.

MDR-TB Management, Prevention, and Control Strategies

To deal with the problem of drug-resistant TB effectively, three major areas need to be addressed: (*a*) effective management of patients with drug-susceptible TB to prevent them from developing drug-resistant disease and effective management of patients with drug-resistant TB to render them noninfectious, (*b*) intensification of infection control efforts in institutional settings to prevent transmission of TB, and (*c*) development and implementation of strategies in TB control programs to provide adequate and necessary services.

The role of drug susceptibility testing. Drug-susceptibility testing should be performed on the initial *M. tuberculosis* isolate of all patients with TB to distinguish those with drug-resistant TB (*34*). Drug-susceptibility testing should be performed on a second isolate of persons whose *M. tuberculosis* culture fails to convert to negative within 3 months after beginning therapy, or those who do not respond clinically to therapy. For the patient, such testing provides important information on the selection of drugs for treatment. Susceptibility testing also plays a crucial role in epidemiology by detecting the emergence of resistance in a community, potentially from breakdowns in providing and supervising effective antituberculosis therapy (*11*).

The preferred method of drug susceptibility testing achieves the shortest turn-around time for reporting results to the clinician. Radiometric techniques, such as the BACTEC (*A*) system, can reduce the time needed to identify drug-resistant organisms from the 7 weeks often needed for testing by conventional methods (solid media) to 3 weeks (*35*). In the BACTEC system, growth in a drug vial (drug-containing medium) is compared with growth in a control vial (drug-free medium) that contains a 1-to-100 dilution of the *M. tuberculosis* inoculum. Growth suppression in the drug vial and continuous growth in the control vial indicates that the isolate is susceptible to that drug. Resistant organisms show an increasing amount of growth in both the drug and control vial. The BACTEC system for drug susceptibility testing has been standardized and evaluated for five antituberculosis drugs (INH, RIF, pyrazinamide [PZA], ethambutol, and streptomycin). The results of the method are reported to the clinician as *M. tuberculosis* isolate susceptible or resistant to a specific drug. There is excellent correlation between radiometric and conventional methods (*36–38*).

The most popular conventional method for determining drug susceptibility of *M. tuberculosis* isolates is the proportion method using 7H10 Middlebrook solid media (*39*). The results of the method are reported to the clinician as the percentage of the total bacterial population resistant to a given drug. The percentage is defined as the amount of growth on a drug-containing medium compared with growth on a drug-free control medium. When 1 percent or more of the bacillary population is resistant to the critical concentration

Multidrug resistant tuberculosis outbreaks associated with human immunodeficiency virus infections, January 1990–June 1992

Facility and location	Year of investigation	Total cases[1]	Resistance pattern: All cases resistant to–	Resistance pattern: Many cases also resistant to–	Cases in denominator[2]	HIV infection (percent)	Mortality (percent)	Median interval from TB diagnosis to death
Hospital A, Miami	1990	65	I, R	E, T	29	93	72	7 weeks
Hospital B, New York City	1990	35	I, S	R, E	18	[3]100	89	16 weeks
Hospital C, New York City	1991–92	[4]51	I, R, S	E, T, K, B	51	94	82	4 weeks
Hospital D, New York City	1991	32	I, R	E, T	23	91	83	4 weeks
Hospital E[5], New York State	1991	5	I, R, S	E, T, K, B	5	20	60	4 weeks
Hospital F, New York City	1992	17	I, R, S	E, T, K, B	17	82	85	4 weeks
Hospital I, New Jersey	1992	13	I, R	E	13	100	85	4 weeks
Prison system, New York State	1991–92	17	I, R	S, E, T, K, B	17	91	74	4 weeks
Total cases		235						

[1] Cases identified during initial investigation and cases identified through followup surveillance.

[2] Denominator includes only cases for which outcome has been ascertained. Denominator applies to the percentages in HIV infection column, mortality column, and median interval column.

[3] HIV infection was part of case definition.

[4] 24 cases in hospital C were among prison system inmates.

[5] Investigated by the New York State Department of Health.

NOTE: I = isoniazid, R = rifampin, S = streptomycin, E = ethambutol, T = ethionamide, K = kanamycin, B = rifabutin, HIV = human immunodeficiency virus, TB = tuberculosis.

of a drug, the *M. tuberculosis* isolate is considered to have *in vitro* resistance to that drug and a normal dose of that drug is likely to be ineffective in clinical therapy. The critical concentration of a drug is the concentration that inhibits the growth of most wild strains of *M. tuberculosis*. When run in parallel with the radiometric method, conventional testing can provide confirmation of the more rapid radiometric results, as well as results on a wider range of drugs.

Drug resistance and therapy selection. Effective multidrug regimens are needed to prevent the emergence of drug resistance. The mainstay of an effective antituberculosis drug regimen is the simultaneous administration of two or more drugs to which the infecting organisms are susceptible, because each drug helps prevent the emergence of resistance to the other. In practice, however, when the *in vitro* susceptibility of a patient's *M. tuberculosis* isolate is not known, as is almost always the case when treatment begins, it can be difficult to select two agents to which the patient's isolate is susceptible. Effective treatment must also include factors that encourage the patient's adherence to the drug regimen.

An initial regimen consisting of four of the currently available first-line antituberculosis agents, INH, RIF, and PZA, plus ethambutol or streptomycin, is desirable. If primary drug resistance is present in the newly diagnosed patient, a regimen that contains fewer drugs might include only one drug to which the organisms are susceptible (monotherapy), and resistance to additional drugs may develop. Among patients that adhere to therapy, four-drug regimens have been shown to be 94 to 97 percent effective, even for those with tubercle bacilli resistant to INH or streptomycin alone (*40–42*). Conversion of sputum cultures to negative has been demonstrated to be faster with four-drug regimens than with a three-drug regimen of INH, RIF, and PZA (*43*), thus potentially reducing the period of infectiousness. A patient on a four-drug regimen who does not complete a full course of therapy may be more likely to be cured and not relapse than a patient treated for the same length of time with a three-drug regimen.

When drug susceptibility results become available, drug regimens should be individualized on the basis of these results. Patients with organisms shown to be susceptible to INH and RIF should receive a 6-month regimen consisting of INH and RIF with PZA during the first 2 months (*44*). Among patients co-infected with HIV, the three-drug regimen is deemed effective when given for at least 9 months and for at least 6 months beyond the time the sputum culture becomes negative (*45*). Among patients with tubercle bacilli resistant to RIF alone, the three- and four-drug regimens previously described are not effective when given for only 6 months. An 18-month regimen of INH and ethambutol, supplemented during the initial 2 months by PZA, should be effective (*13*).

Since nonadherence to treatment is a major cause of acquired drug-resistant TB, therapy for all TB patients should be directly observed unless adherence to self-administered therapy can be ascertained (*34*). With directly observed therapy (DOT), a health care worker or other designated person observes the patient ingest the medications. A

four-drug regimen facilitates DOT, since this regimen can be given intermittently (three times per week) from the start of therapy (*40*) or twice weekly with only a 2-week induction phase of daily therapy (*46*). In contrast, a three-drug regimen requires an 8-week induction phase of daily therapy.

Considerations in managing patients with MDR-TB. Treating a patient with MDR-TB usually is more difficult and much more expensive than treating a patient with drug-susceptible disease (*33*). The treatment of patients with MDR-TB requires prescribing multiple drugs that the patient has not received before and to which his organisms are susceptible *in vitro*. Thus, current drug-susceptibility results and a history of previous treatment with antituberculosis drugs should be considered in tailoring drug regimens for patients with MDR-TB. It usually is necessary to use second-line antituberculosis or other drugs that can be less effective and more toxic than the commonly used first-line agents (*13*). The second-line antituberculosis agents currently available are capreomycin, kanamycin, ethionamide, PAS, and cycloserine. Other drugs, including amikacin, quinolones (for example, ciprofloxacin and ofloxacin), and clofazimine, have been studied for activity against TB (*33*).

The recent increase in the occurrence of MDR-TB has created more situations in which the use of these drugs must be considered; however, these drugs have not been evaluated in well-designed, randomized trials for treatment of TB and therefore should not be used in place of effective first- or second-line antituberculosis drugs. The recommended duration of treatment is at least 18 months and preferably 24 months after conversion of sputum cultures to negative (*33*). Because of the complexity of the problem, clinicians who are not familiar with the management of patients with MDR-TB should seek expert consultation, usually available through State or local health departments.

Guidelines for infection control in institutional settings. In institutions where there is a risk for TB transmission, current CDC guidelines should be implemented to reduce the risk (*47*). The guidelines emphasize the following fundamental practices.

- Patients who may have active TB must be quickly identified. Identification requires a high clinical index of suspicion for TB and use of the most sensitive and rapid laboratory diagnostic methods available.
- Patients with suspected or confirmed infectious TB should be promptly placed in appropriate AFB isolation. Isolation precautions should be maintained until the patient improves clinically, until the cough decreases substantially, and until the number of AFB on sequential sputum smears decreases progressively. Usually, this occurs within 2 to 3 weeks after beginning antituberculosis therapy. When a patient is suspected of having a drug-resistant TB, AFB isolation precautions should be applied until the patient is improving clinically and until the sputum smear is negative for AFB.
- Effective antituberculosis therapy should be initiated promptly for all patients with confirmed or suspected TB.
- When cough-inducing procedures, such as bronchoscopy, sputum induction, and administration of aerosol treatments, are done with patients who may have TB, the procedures should be carried out in rooms or booths with negative air pressure.
- Patients and health care workers who come in contact with infectious patients with TB should be identified and evaluated for tuberculous infection or active disease.
- Routine, active surveillance should be conducted to identify TB cases among patients and health care workers, drug resistance patterns among TB cases, and tuberculin skin test conversions among health care workers.

Drug resistance and TB control programs. Local epidemiologic data on drug resistance is useful to TB control programs for several major reasons (*16*). Knowledge of the incidence and prevalence of resistance to specific drugs can help determine the most effective initial drug therapy regimen for patients within a given area, or for individual patients. Although the current recommendation for initial therapy of TB patients in this country is to use INH, RIF, and pyrazinamide, plus either ethambutol or streptomycin, there may be some areas in which this regimen would be inadequate for a significant proportion of patients.

Analysis of local rates may indicate, however, that the population in general is at low risk for drug resistance or that specific subgroups in the population can be defined that are at low risk for drug resistance. In communities where the rates of primary drug resistance are less than 4 percent, an initial regimen with fewer than four drugs may be acceptable (*34*), but continued surveillance is necessary to ensure that the low rates of drug resistance continue. When factors that increase the likelihood of drug resistance are identified, initial therapy

regimens can be modified for those at risk for drug-resistant TB.

In special situations, such as in institutions experiencing outbreaks of TB resistant to INH and RIF, five- or six-drug regimens may be required as initial therapy (*9*). When the results of drug susceptibility tests become available, regimens should be modified on the basis of those results. Every TB patient deserves the chance for the best and shortest regimen possible, whether at increased risk of resistance or not (*48*).

Ongoing or periodic surveys are useful in tracking trends in the incidence and prevalence of drug resistance, and they serve as an indicator of the success of TB control programs. For these programs, cases of primary drug-resistant TB may reflect ongoing transmission of drug-resistant organisms and suggest a need for improved casefinding and containment. In addition, defining the patterns of primary drug resistance in a community is essential to guiding the selection of initial drug therapy for TB.

Cases of acquired drug resistance indicate to TB control programs and medical practitioners a breakdown in ensuring that patients adhere to and complete therapy. Preventing the emergence of drug-resistant TB in individual patients would seem relatively simple; if an effective antituberculosis drug therapy regimen is prescribed and taken correctly for the appropriate time, drug-resistant disease should not occur (*10*). However, complex problems are associated with providing and supervising these services with TB control programs and medical practitioners. Patients with TB frequently have social problems and lifestyles that complicate therapy (*13*). TB control programs and medical practitioners must take into account other medical conditions, including co-infection with HIV, to provide the optimum therapy for TB. Since nonadherence to treatment is a major cause of acquired drug-resistant TB, staff members of TB programs need to use a variety of methods, including DOT, to ensure successful completion of a full course of therapy.

The National Response to MDR-TB

In response to the emergence of MDR-TB, a Federal task force was convened in December 1991 to develop a national action plan to combat the problem (*49*). The plan identifies a number of objectives to be undertaken at the national level. The objectives are summarized in this section.

An initial treatment regimen consisting of isoniazid, rifampin, and pyrazinamide, plus either ethambutol or streptomycin, is effective for most patients. . . . Effective treatment must also encourage the patient's adherence to the drug regimen.

Epidemiology and surveillance. To better define the magnitude and nature of MDR-TB, national surveillance will be expanded to capture information on the incidence of drug-resistant TB. Epidemiologic studies will be used to identify where MDR-TB is being spread, what activities are associated with increases or decreases in transmission, and which preventive strategies are effective in community and in institutional settings. The impact of HIV infection on recent trends in TB disease and infection, including MDR-TB, will be assessed.

Laboratory diagnosis. To improve the rapidity, sensitivity, and reliability of diagnostic methods for MDR-TB, widespread changes and improvements need to be implemented in clinical and public health laboratories. These changes include the use of the most sensitive and rapid laboratory diagnostic methods available, including the use of a primary susceptibility test panel of five drugs (INH, RIF, PZA, ethambutol, and streptomycin). New equipment, training courses, and information systems will be used in laboratories to achieve these objectives.

Patient management. Activities need to be implemented to prevent patients with drug-susceptible TB from developing drug-resistant disease and to manage patients optimally who have developed drug-resistant disease. To achieve these goals, effective initial antituberculosis therapy regimens and implementation of DOT for all TB patients who would benefit from it, regardless of their ability to pay for these services, will be promoted. Options for the long-term hospitalization of drug-resistant TB patients, when needed, will be explored. Efforts to facilitate access to diagnosis and treatment will be directed to those at high risk for both TB and nonadherence to therapy, such as persons who are homeless, mobile populations of migrant farm workers, refugees and immigrants from areas with a high prevalence of TB, and persons with substance abuse problems.

Screening and preventive therapy. To distinguish persons who are infected or at risk of developing MDR-TB to help prevent them from developing clinically active TB, widespread dissemination and implementation of recently published guidelines on management of persons exposed to MDR-TB will be promoted (*49*). Screening and preventive therapy (directly observed when necessary) among populations at risk for both TB and nonadherence to therapy will be implemented.

Infection and outbreak control. Given the circumstances of recent MDR-TB outbreaks in hospital and correctional institutions, the risk of transmission of MDR-TB to patients, workers, and others in institutional settings needs to be minimized. Implementation of current guidelines for reducing this risk is of the highest priority (*47*). Adequate screening and monitoring for TB infection among workers in settings where there is a substantial risk of TB transmission will be ensured.

Outbreaks represent a challenge to public health authorities in controlling TB. Various officials and organizations will collaborate to enhance the control of outbreaks of MDR-TB.

Program evaluation. TB control programs need to be evaluated for effectiveness in managing patients and preventing the development of MDR-TB. Local epidemiologic data will be used for assessing the adequacy of the TB control programs.

Information dissemination, training, and education. To disseminate information about MDR-TB and its prevention and control, high-risk populations, such as persons working in drug treatment centers, homeless shelters, HIV clinics, and correctional and other institutions with close living quarters, and their clients; refugees; and immigrants will be identified to be educated about TB. A system for the professional education of those involved in the prevention, control, diagnosis, and treatment of TB will be developed.

Research. Research is needed to identify better methods to combat MDR-TB. Increased knowledge of the basic genetics and biology of *M. tuberculosis* is necessary to understanding better the pathogenesis, immune response, and mechanisms of drug resistance of TB, so that improved diagnostic assays, drugs, and vaccines can be developed. A research subcommittee of the Public Health Service's National MDR-TB Task Force was recently formed to coordinate current and future TB research efforts among participating Federal agencies.

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Equipment

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