VIRGINIA
EPIDEMIOLOGY BULLETIN

Robert B. Stroube, M.D., M.P.H., Commissioner
Grayson B. Miller, Jr., M.D., Epidemiologist
Editor: Carl W. Armstrong, M.D., F.A.C.P.

October, 1993 Volume 93, Number10

Initial Therapy for Tuberculosis in the Era of Multidrug Resistance

Recommendations of the Advisory Council for the Elimination of Tuberculosis*

Summary

These recommendations update previous CDC/American Thoracic Society (ATS) recommendations for the treatment of tuberculosis (TB) among adults and children. The most notable changes are in response to the increasing prevalence of drug-resistant TB in the United States. These recommendations include the need for a) in vitro drug susceptibility testing of *Mycobacterium tuberculosis* isolates from all patients and reporting of these results to the health department, b) initial four-drug regimens for the treatment of TB, and c) initial directly observed therapy for persons with TB. Adherence to these recommendations will help prevent the occurrence of more cases of drug-resistant TB, reduce the occurrence of treatment failure, and reduce the transmission of TB in the United States.

Introduction

The number of tuberculosis (TB) cases reported in the United States has declined from more than 84,000 cases in 1953 to 22,255 cases in 1984. However, since 1984 dramatic changes in TB morbidity trends have occurred, and these changes jeopardize the control of TB. From 1985 through 1991, reported TB cases increased 18% — representing approximately 39,000 more cases than expected had the previous downward trend continued. The excess number of cases is due to many factors, including the human immunodeficiency virus (HIV) epidemic, a deterioration in the health-care infrastructure, and increases in the number of cases among foreign-born persons.

The recent emergence of drug-resistant TB also has become a serious concern. For example, in New York City in 1991, 33% of TB cases were resistant to at least one drug, and 19% were resistant to both isoniazid (INH) and rifampin (RIF) — the two most effective drugs available for treating TB. Resistance to both INH and RIF substantially increases the cost and duration of treatment, while decreasing the efficacy.

Based on surveys of all TB cases reported to CDC during the first quarter of 1991, cases of TB resistant to one or more drugs were reported from all 10 Health and Human Services/Public Health Service regions of the United States. Moreover, during the period 1982-1986, 0.5% of new TB cases were resistant to both INH and RIF, whereas preliminary analysis of data for the first quarter of 1991 suggests that this proportion was about 3%. Among recurrent cases, 3% were resistant to both drugs during the period 1982-1986, compared with 6.9% in 1991.

Outbreaks of multidrug-resistant TB (MDR-TB) — resistant to both INH and RIF, as well as to other drugs — have occurred in a variety of institutional settings. From 1990 through 1992, CDC has investigated nine outbreaks of MDR-TB in hospitals and prison facilities in Florida and New York. These outbreaks have been characterized by a high prevalence of HIV infection among the outbreak cases, range 20%-100%; a high mortality rate among patients with MDR-TB, range 72%-89%; a short median interval between TB diagnosis and death, range 4-16 weeks; and transmission of MDR-TB to health-care and correctional facility workers, at least 17 of whom have developed active MDR-TB.

Drug-resistant tubercle bacilli are transmitted in the same manner as drug-susceptible organisms. A study comparing infection rates among contacts of TB patients suggested that the likelihood of transmission was similar for both drug-resistant and drug-susceptible organisms. In institutional TB outbreaks investigated from 1991 to 1992, tuberculin skin-test conversions among health-care workers were more likely to be associated with exposure to patients with drug-resistant organisms than to patients with drug-susceptible organisms — probably reflecting the persistent infectiousness of patients with unrecognized drug-resistant TB who were not on effective therapy.

Mycobacterium tuberculosis becomes drug resistant through random, spontaneous genetic mutation. The proportion of naturally occurring resistance has been established for several of the primary anti-TB drugs: RIF, $1/10^8$; INH and streptomycin

(SM), $1/10^6$; and ethambutol, (EMB) $1/10^4$. Assuming that the mutations are independent, the likelihood of an organism spontaneously developing resistance to more than one drug is the product of probabilities; for example, the probability of INH and RIF resistance occurring in the same organism is $1/10^8$ times $1/10^6$ ($1/10^{14}$). Because the total number of bacilli in an infected person, even with advanced cavitary disease, does not approach this number (10^{14}), spontaneous evolution of MDR tubercle bacilli occurs infrequently.

Treatment

Because administration of a single drug often leads to the development of a bacterial population resistant to that drug, effective regimens for the treatment of TB must contain multiple drugs to which the organisms are susceptible. When two or more drugs are used simultaneously, each helps prevent the emergence of tubercle bacilli resistant to the others. However, when the in vitro susceptibility of a patient's isolate is not known — which is generally the case at the beginning of therapy — selecting two agents to which the patient's isolate is likely to be susceptible can be difficult. Improper selection of drugs for the treatment of drug-resistant TB (i.e., providing only one drug to which most organisms are susceptible) may subsequently result in the development of additional drug-resistant organisms.

A four-drug regimen with INH, RIF, pyrazinamide (PZA), and SM or EMB is preferred for the initial, empiric treatment of TB (Tables 1,2). When adherence with the regimen is assured, such as with directly observed therapy (DOT), the four-drug regimen is highly effective even for INH-resistant organisms. Based on the prevalence and characteristics of drug-resistant organisms, at least 95% of patients will receive an adequate regimen (at least two drugs to which their organisms are susceptible) if this four-drug regimen is used at the beginning of therapy. Even with susceptible organisms, sputum conversion is accomplished more rapidly from positive to negative with a four-drug regimen than with a three-drug regimen of INH, RIF, and PZA. DOT is more easily managed with the four-drug regimen since it can be administered intermittently 3 times/week from the beginning of therapy. The four-drug regimen also can be administered 2 times/week following a 2-week induction phase of daily therapy. Finally, a patient who is treated with the four-drug regimen, but who defaults therapy is more likely to be cured and not relapse when

Table 1. Regimen Options for the Initial Treatment of TB Among Children and Adults

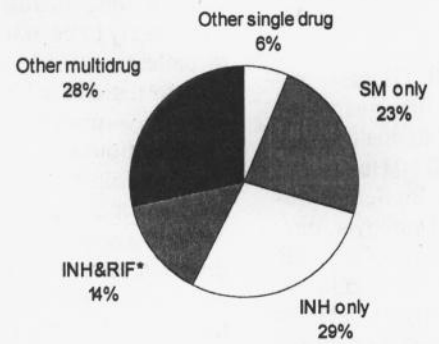
TB Without HIV Infection			
Option 1	**Option 2**	**Option 3**	**TB with HIV infection**
Administer daily INH, RIF, and PZA for 8 weeks followed by 16 weeks of INH and RIF daily or 2-3 times/week* in areas where the INH resistance rate is not documented to be <4%. EMB or SM should be added to the initial regimen until susceptibility to INH and RIF is demonstrated. Continue treatment for at least 6 months and 3 months beyond culture conversion. Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.	Administer daily INH, RIF, PZA, and SM or EMB for 2 weeks followed by 2 times/week* administration of the same drugs for 6 weeks (by DOT§), and subsequently, with 2 times/week administration of INH and RIF for 16 weeks (by DOT). Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.	Treat by DOT, 3 times/week* with INH, RIF, PZA, and EMB or SM for 6 months.† Consult a TB medical expert if the patient is symptomatic or smear or culture positive after 3 months.	Options 1, 2, or 3 can be used, but treatment regimens should continue for a total of 9 months and at least 6 months beyond culture conversion.

**All regimens administered 2 times/week or 3 times/week should be monitored by DOT for the duration of therapy.*

†The strongest evidence from clinical trials is the effectiveness of all four drugs administered for the full 6 months. There is weaker evidence that SM can be discontinued after 4 months if the isolate is susceptible to all drugs. The evidence for stopping PZA before the end of 6 months is equivocal for the 3 times/week regimen, and there is no evidence on the effectiveness of this regimen with EMB for less than the full 6 months.

§DOT-Directly observed therapy.

Resistance Pattern for Drug-Resistant TB Cases (N=78), Virginia, 1990-92



*Resistance to INH and rifampin or INH, rifampin, and one or more other drugs

compared with a patient treated for the same length of time with the three-drug regimen.

Recommendations

To avoid the emergence of drug-resistant organisms, the Advisory Council for the Elimination of Tuberculosis (ACET) recommends the following approach to beginning therapy for TB.

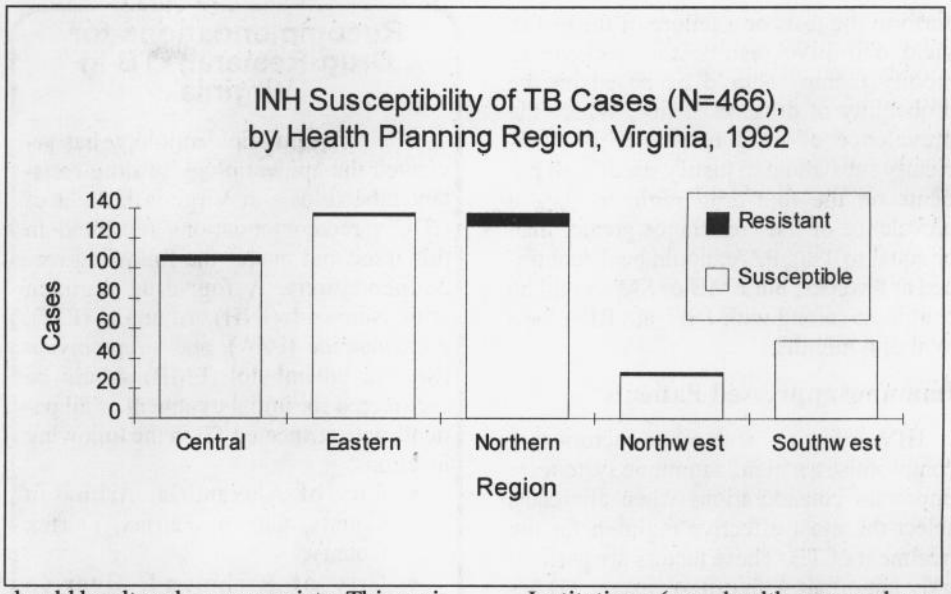
Susceptibility Testing

All persons with TB from whom *M. tuberculosis* is isolated should have drug susceptibility testing performed on their first isolate; these results should be reported promptly to the health-care provider and to the health department.

Such testing will provide the basis for clinical therapeutic decisions. In addition, surveillance of drug-susceptibility reports will help identify emerging drug resistance and help monitor control efforts in areas where resistance is already established. Drug-susceptibility testing also should be performed on additional isolates from patients whose cultures fail to convert to negative within 3 months of beginning therapy, or if there is clinical evidence of failure to respond to therapy. To monitor changes in drug susceptibility patterns in the United States, the "Report of Verified Cases of Tuberculosis" reporting form has been revised to include a section relating to drug susceptibility results from the initial isolate for all reported TB cases.

Initial Regimen

The initial treatment of TB should include four drugs. During the first 2 months, the drug regimen should include INH, RIF, PZA, and EMB or SM. When drug susceptibility results are available, the regimen should be altered as appropriate. This regimen should be administered to all patients unless the likelihood of INH or RIF resistance is low.



General Principles

Analysis of local rates of drug resistance provides the best basis for determining when the four-drug regimen might not be necessary. Local data may indicate that the population in general is at low risk for drug resistance or that specific and definable subgroups in the population can be defined that are at low risk for drug resistance. In the past, when national INH-resistance rates were about 4% and declining, two- and three-drug regimens were considered adequate. Community rates of INH resistance less than 4% may be an indication that an initial regimen with fewer than four drugs may be acceptable. However, continued surveillance of drug susceptibility patterns is necessary to ensure that low rates of drug resistance continue.

Institutions (e.g., health-care and correctional facilities) that are experiencing outbreaks of TB resistant to INH and RIF or that are resuming treatment for a patient with a prior history of anti-TB therapy may need to begin five-drug or six-drug regimens as initial therapy. These regimens should include the four-drug regimen and at least three drugs to which the suspected multidrug-resistant strain may be susceptible.

When the results of drug susceptibility tests become available, regimens should be specifically defined on the basis of those results. For example, patients whose TB organisms are susceptible to INH and RIF should receive a regimen of INH and RIF for a full 6 months, supplemented with PZA during the first 2 months. The treatment regimen of patients with drug-resistant organisms should be determined in consultation with physicians experienced in the treatment of drug-resistant TB.

When results of drug susceptibility tests are not available, either due to a failure to

Table 2. Dosage Recommendation for the Initial Treatment of TB Among Children* and Adults

	Dosage					
	Daily		2 times/week		3 times/week	
Drugs	Children	Adults	Children	Adults	Children	Adults
Isoniazid	10-20mg/kg, max. 300mg	5mg/kg, max. 300mg	20-40mg/kg, max. 900mg	15mg/kg, max. 900mg	20-40mg/kg, max. 900mg	15mg/kg, max. 900mg
Rifampin	10-20mg/kg, max. 600mg	10mg/kg, max. 600mg	10-20mg/kg, max. 600mg	10mg/kg, max. 600mg	10-20mg/kg, max. 600mg	10mg/kg, max. 600mg
Pyrazinamide	15-30mg/kg, max. 2gm	15-30mg/kg, max. 2gm	50-70mg/kg, max. 4gm	50-70mg/kg, max. 4gm	50-70mg/kg, max. 3gm	50-70mg/kg, max. 3gm
Ethambutol†	15-25mg/kg, max. 2.5gm	5-25mg/kg, max. 2.5gm	50mg/kg, max. 2.5gm	50mg/kg, max. 2.5gm	25-30mg/kg, max. 2.5gm	25-30mg/kg, max. 2.5gm
Streptomycin	20-30mg/kg, max. 1 gm	15mg/kg, max. 1gm	25-30mg/kg, max. 1.5gm	25-30mg/kg, max. 1.5gm	25-30mg/kg, max. 1gm	25-30mg/kg, max. 1gm

**Children ≤12 years of age.*

†Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<6 years of age). However, ethambutol should be considered for all children with organisms resistant to other drugs, when susceptibility to ethambutol has been demonstrated, or susceptibility is likely.

perform the tests or a failure of the test to yield definitive results, the decision to modify therapy should be based on the probability of drug resistance. Where the prevalence of drug resistance is sufficiently substantial to justify starting all patients on the four-drug regimen (i.e., a prevalence of INH resistance greater than or equal to 4%), PZA should be discontinued at 8 weeks, but EMB or SM should be continued (along with INH and RIF) for a total of 6 months.

Immunosuppressed Patients

HIV infection and other factors that compromise a patient's immune system are important considerations when clinicians select the most effective regimen for the treatment of TB. These factors are particularly important with drug-resistant TB because of the potential for rapid disease progression and death when patients receive inadequate treatment. Because data from controlled clinical trials are not available to determine if a 6-month regimen is adequate treatment for HIV-infected patients with TB, ACET recommends that such patients be treated for a total of 9 months and for at least 6 months after sputum conversion. No evidence suggests that intermittent therapy — 2 times/week or 3 times/week — will not be as effective for the treatment of TB among HIV-infected persons when compared with TB treatment for persons who are not HIV positive.

If drug susceptibility results are not available, EMB or SM should be continued for the entire course of therapy because of the risk of rapid disease progression while the patient is on inadequate therapy.

Treatment of Extrapulmonary TB

Regimens that are adequate for treating adults and children with pulmonary TB also should be effective in treating extrapulmonary disease. However, some experts extend the duration of therapy to 9 months for patients with disseminated disease, miliary disease, disease involving the bones or joints, or tuberculous lymphadenitis. The use of adjunctive therapies, such as surgery and corticosteroids, may be beneficial.

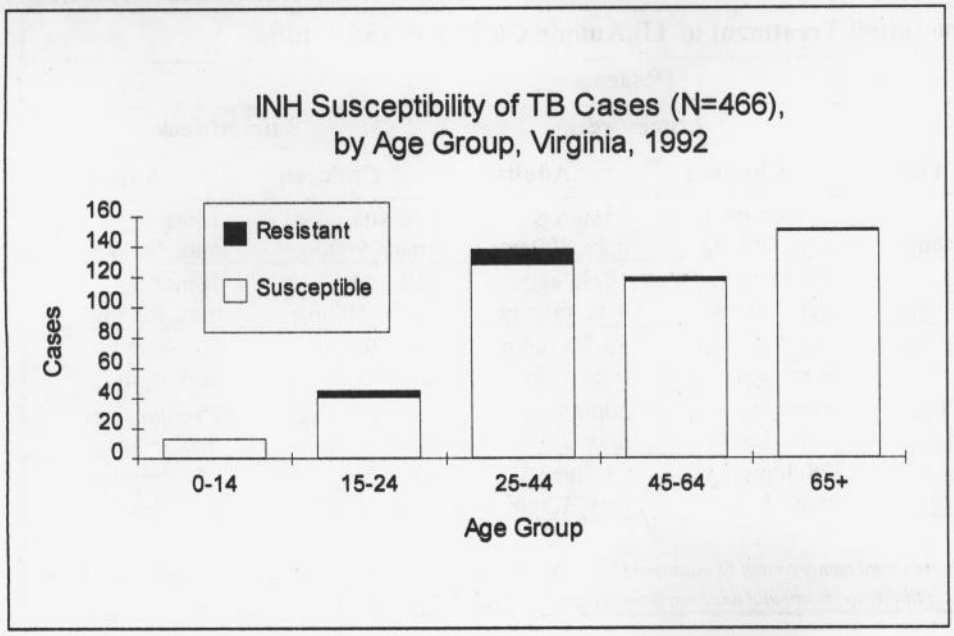
Recommendations for Drug-Resistant TB in Virginia

The Office of Epidemiology has reviewed the epidemiology of drug-resistant tuberculosis in Virginia in light of CDC's recommendations reprinted in this issue and makes the following recommendations. A four-drug regimen with isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and streptomycin (SM) or ethambutol (EMB) should be considered for initial treatment of all patients with suspected TB in the following locations:

- City of Alexandria, Arlington County, City of Fairfax, Fairfax County;
- City of Richmond, Henrico County, and Chesterfield County; and
- Cities of Virginia Beach, Norfolk, and Portsmouth.

In other areas a three-drug regimen may be used for initial treatment but physicians should maintain a high index of suspicion for drug-resistant TB, especially in patients with exposure to a known or suspected drug-resistant TB case, and in foreign-born patients from areas with a high incidence of drug-resistant disease (Central and South America, Southeast Asia and Africa).

As outlined in the accompanying article, regimens should be adjusted to the results of drug susceptibility tests, when reported.



Treatment of Infants and Children

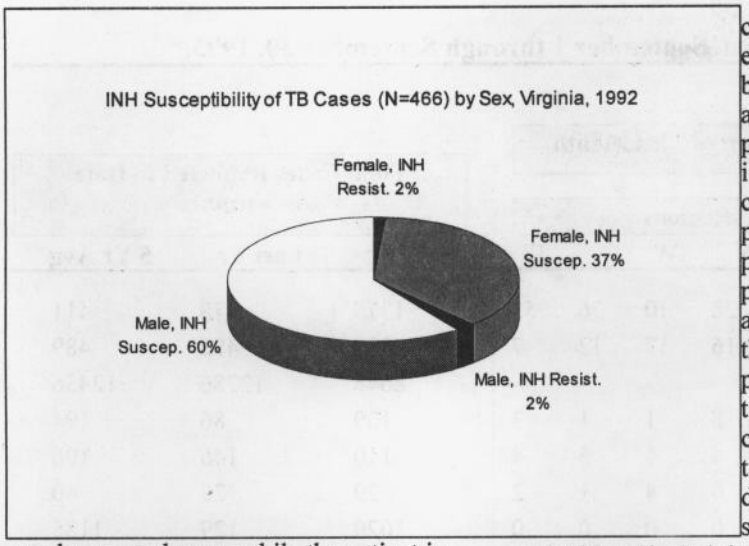
Infants and children with TB should be treated with the same regimens recommended for adults; however, dosage may vary for some drugs (Table 2). Further, EMB is generally not used for children whose visual acuity cannot be monitored (e.g., those less than 6 years of age); SM is an alternative. The inclusion of EMB in the treatment regimen should be considered, however, for all children with organisms resistant to other drugs when susceptibility to EMB has been demonstrated or when susceptibility is likely. Because the risk of dissemination of TB is greater among infants than adults, prompt and vigorous treatment should begin as soon as the diagnosis is suspected.

Treatment of TB During Pregnancy

Effective therapy for TB is essential for pregnant women with TB. However, the treatment regimen must be adjusted since SM may cause congenital deafness. SM is the only licensed anti-TB drug documented to have harmful effects on the fetus. Routine use of PZA also is not recommended during pregnancy because the risk of teratogenicity has not been determined. In addition, since the 6-month treatment regimen cannot be used and a minimum of 9 months of therapy is recommended, the preferred initial treatment regimen is INH, RIF, and EMB. If resistance to other drugs is likely and susceptibility to PZA also is likely, the use of PZA should be considered and the risks and benefits of the drug carefully weighed. Because the small concentrations of anti-TB drugs in breast milk do not produce toxicity in the nursing newborn, breast feeding should not be discouraged. Further, because these drug levels are so low in breast milk they cannot be relied upon for either prophylaxis or therapy for nursing infants.

Directly Observed Therapy (DOT)

A major cause of drug-resistant TB and treatment failure is patient nonadherence to prescribed treatment. Treatment failure and drug-resistant TB can be life-threatening and pose other serious public health risks because they can lead to prolonged infectiousness and increased transmission of TB in the community. DOT is one method of ensuring adherence; it requires that a health-care provider or other desig-



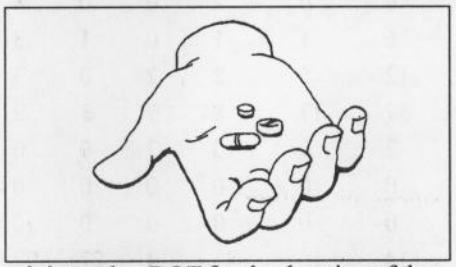
nated person observe while the patient ingests anti-TB medications.

DOT should be considered for all patients because of the difficulty in predicting which patients will adhere to a prescribed treatment regimen. Decisions regarding the use of expanded or universal DOT should be based on a quantitative evaluation of local treatment completion rates. If the percentage of patients who complete therapy within 12 months is less than 90% or unknown, the use of DOT should be expanded. If greater than or equal to 90% of patients beginning therapy complete a recommended course of therapy within 12 months, the expanded use of DOT may not be necessary. However, even in these circumstances, consideration should be given to extending the use of DOT to increase the treatment completion rate. All patients with TB caused by organisms resistant to either INH or RIF and all patients receiving intermittent therapy should receive DOT.

DOT programs increase adherence in both rural and urban settings and provide effective treatment for TB. A hospital in New York City reported that only 11% of patients under care for TB reported to an outpatient clinic for further treatment when discharged from the hospital. In contrast, a program in which DOT is routinely used for all patients had a completion rate of 98%.

Although expanding the use of DOT may require additional resources, intermittent, directly observed regimens are cost effective. DOT can be conducted with regimens given once a day, 2 times/week, or 3 times/week.

When TB is initially diagnosed, medical providers should explain to the patient about the disease, treatment, and the importance of completing the recommended course of therapy. Medical providers should also verify that the patient understands this information. When DOT is administered, the method must be specifically defined for each patient and be based on a thorough assessment of each patient's needs, living/employment conditions, and preferences. The patient and the provider should agree on a method that ensures the best possible DOT routine and maintains confidentiality. Patients who receive daily therapy can be successfully managed with self-administered therapy. Public health officials responsible for TB treatment should be notified when patients not receiving DOT miss appointments or demonstrate other nonadherent behaviors. These patients should be placed on DOT, and all regimens administered 2 times/week or 3 times/week should be administered as DOT for the duration of therapy.



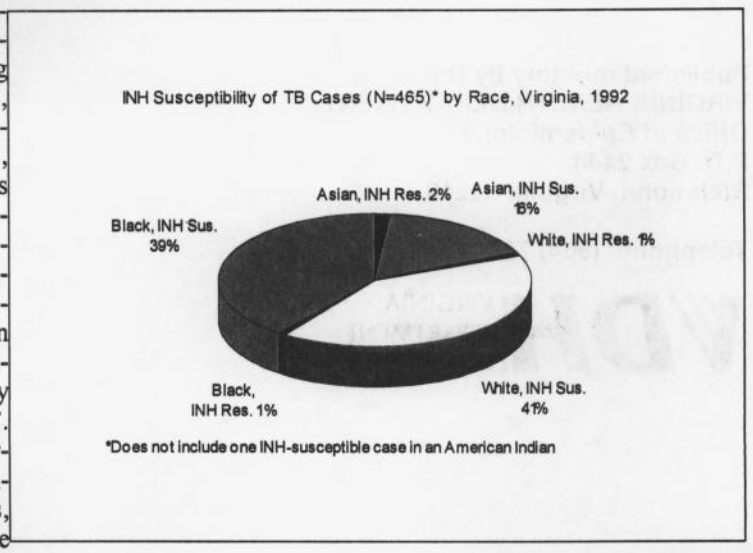
Effective use of DOT sometimes requires an outreach worker to go into the community to locate a patient and administer each dose of medication. However, most patients can receive the daily, 2 times/week, or 3 times/ week treatment at a location agreed on by both the provider and the patient. DOT can be arranged and administered in various settings, including TB clinics, community health centers, migrant clinics, homeless shelters, prisons or jails, nursing homes, schools, drug treatment centers, hospitals, HIV/AIDS clinics or hostels, or occupational health clinics. In some situations, another responsible person other than a health-care worker may administer DOT. Persons administering DOT may include physicians, nurses, health care aides, nursing home staff, correctional facility personnel, staff of community-based organizations, school nurses or teachers, reliable volunteers, drug treatment center employees, social and welfare caseworkers, and clergy or other community leaders. These arrangements require careful supervision by the medical provider. The use of incentives or enablers (e.g., providing transportation or car/bus fare to the DOT site) may promote patient adherence to a DOT program. The use of combined preparations of INH and RIF (e.g., Rifamate Registered) or INH, RIF, and PZA (not available in the United States) may also improve patient adherence.

Poor patient adherence is a multifaceted problem; additional research is needed to clarify the role of operational, environmental, behavioral, and other factors in determining adherence. A research agenda is described in "Problem 38" of the *National Action Plan to Combat Multidrug-Resistant Tuberculosis*.

Conclusion

These recommendations update previous CDC/American Thoracic Society (ATS) recommendations for the treatment of TB among adults and children. The ATS Statements Committee is revising that previous report with representatives from CDC, the American Academy of Pediatrics, and the Infectious Disease Society of America and may offer similar recommendations. Questions concerning these recommendations should be made to: CDC, National Center for Prevention Services, Division of TB Elimination, Clinical Research Branch, 1600 Clifton Road, MS E-10, Atlanta, GA 30333, (404) 639-2530.

**Adapted from: Centers for Disease Control and Prevention. Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1993;42(RR-7):1-8.*



Cases of Selected Notifiable Diseases, Virginia, September 1 through September 30, 1993.*

Disease	Total Cases Reported This Month						Total Cases Reported to Date in Virginia		
		Regions							
	State	NW	N	SW	C	E	This Yr	Last Yr	5 Yr Avg
AIDS	136	9	28	10	36	53	1375	478	411
Campylobacteriosis	61	9	16	17	12	7	528	492	489
Gonorrhea†	663	-	-	-	-	-	8648	12786	12436
Hepatitis A	14	1	8	1	1	3	109	86	194
Hepatitis B	17	0	4	4	5	4	110	146	196
Hepatitis NANB	7	0	0	4	1	2	29	28	40
Influenza	0	0	0	0	0	0	1020	129	1185
Kawasaki Syndrome	5	0	2	1	0	2	20	20	18
Legionellosis	2	0	0	1	0	1	6	19	12
Lyme Disease	11	1	3	3	1	3	57	95	74
Measles	1	0	0	1	0	0	2	15	64
Meningitis, Aseptic	46	3	14	6	0	23	217	196	218
Meningitis, Bacterial‡	10	3	0	0	1	6	72	89	110
Meningococcal Infections	6	0	2	0	0	4	37	48	43
Mumps	6	1	1	0	1	3	25	49	84
Pertussis	12	5	2	2	0	3	50	10	19
Rabies in Animals	37	17	8	7	3	2	287	266	220
Reye Syndrome	2	0	0	2	0	0	3	0	1
Rocky Mountain Spotted Fever	0	0	0	0	0	0	8	17	16
Rubella	0	0	0	0	0	0	0	0	2
Salmonellosis	114	15	31	14	27	27	724	720	1016
Shigellosis	62	3	10	1	33	15	510	177	262
Syphilis (1° & 2°)†	39	1	3	0	2	33	470	564	552
Tuberculosis	10	1	6	1	1	1	309	281	275

Localities Reporting Animal Rabies: Augusta 2 raccoons, 1 skunk; Chesterfield 1 skunk; Fairfax 2 groundhogs, 1 raccoon; Floyd 1 raccoon; Frederick 2 raccoons; Goochland 1 raccoon; Greene 1 skunk; Hanover 1 fox; Loudoun 1 bat, 3 raccoons, 1 skunk; Louisa 1 raccoon; Montgomery 1 raccoon, 1 skunk; Page 1 groundhog, 2 raccoons, 1 skunk; Pulaski 1 raccoon; Rockbridge 1 bat; Rockingham 1 raccoon; Scott 1 skunk; Spotsylvania 1 raccoon; Stafford 1 raccoon; Waynesboro 1 raccoon, 1 skunk; Wythe 1 cat, 1 cow; York 2 raccoons;
Occupational Illnesses: Asbestosis 12; Carpal Tunnel Syndrome 66; Coal Workers' Pneumoconiosis 12; Loss of Hearing 14.

*Data for 1993 are provisional. †Total now includes military cases to make the data consistent with reports of the other diseases. ‡Other than meningococcal.

Published monthly by the
VIRGINIA HEALTH DEPARTMENT
Office of Epidemiology
P.O. Box 2448
Richmond, Virginia 23218

Telephone: (804) 786-6261

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