The Changing Epidemiology of Tuberculosis 3

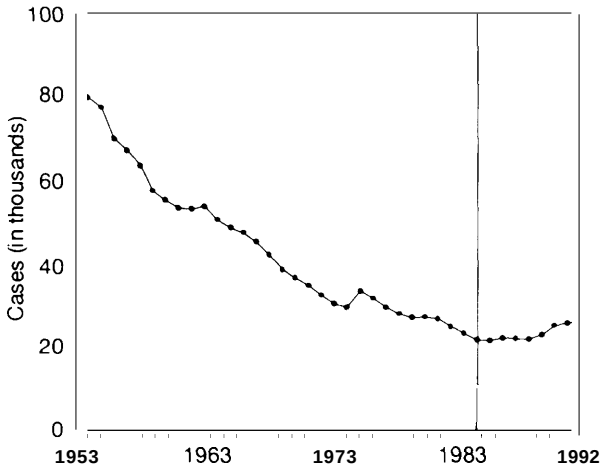
After decades of steady decline in the number of new cases each year, tuberculosis (TB) is now on the increase in the United States. This turnabout has received considerable attention in the news media, medical literature, and public health sector. Reports of clusters of TB cases, particularly the more dangerous multidrug-resistant (MDR-TB) forms occurring recently in several hospitals and prisons, have been highlighted. These reports raise the specter of a serious, accelerating public health problem with the potential to spread regionally and nationally. For a disease that was widely considered to have been headed toward elimination in this country, the resurgence seems surprising and disturbing.

While many of the basic features of TB and its transmission are the same as those described decades ago, there are new elements that have changed the nature and magnitude of the problem. This chapter reviews current epidemiologic features of TB in the United States, including overall incidence, high-risk groups in the population, rates of confection with human immunodeficiency virus (HIV), and the cases of MDR-TB. Although the focus is on TB in the United States, some international data are included for comparison. Various factors that may be responsible for the recent changes in TB are discussed at the end of the chapter.

OVERALL TRENDS IN TB INCIDENCE

In 1953, the U.S. Public Health Service began a nationwide reporting system for TB, based on annual summaries of total TB cases reported in each State. In 1979, the Centers for Disease Control (CDC) began to phase in the "Report of a Verified Case of Tuberculosis' (RVCT) surveillance system, based on individ-

Figure 3-l—Reported Tuberculosis Cases In the United States, **1953-92**



SOURCE: Office of Technology Assessment, 1993, based on data **from U.S. Department of Health and Human Services, Public Health Service, Centers for** Disease Control and Prevention, 1992.

ual case reports from all 50 States, the District of Columbia, and New York City (159).1 The system was fully implemented in 1985. By using a standardized case definition and collecting data on individuals with TB (including age, sex, race, ethnicity, and country of origin), the RVCT system permitted a more detailed picture of TB epidemiology in the United States than was previously possible with aggregate data. In general, incidence rates based on case reports underestimate the true incidence of a disease, since many factors can influence the likelihood that any given case will actually be reported. It is unlikely that changing the TB reporting requirements in the RVCT system affected the overall ascertainment of cases, although it clearly produced more information about each case reported. The increased number of cases reported since the mid-1980s is much greater than could be accounted for by changes in the reporting system. In fact, significant underreporting of TB may still be occurring (28,250,307).

In 1953, there were 84,304 reported cases of TB, equivalent to a case rate of 53.0/100,000 population (27). Over the next 31 years, incidence declined steadily, with a few exceptions,[2] to 22,255 new cases in 1984 (case rate of 9.4/100,000 population) (233). The rate of decline averaged about 6 percent per year between 1953 and 1974, and about 5 percent per year between 1975 and 1984 (159,249). By 1984, the incidence of TB had declined 74 percent from its 1953 level (see figure 3-l).

This longstanding downward trend began to change in 1985. First, the decline in incidence slowed to just 0.2 percent in 1985, and then increased by 2.6 percent in 1986. Then, in 1987 and 1988 the decline in new cases resumed, but by only 1.1 and 0.4 percent, respectively. Further increases occurred in 1989 (4.7 percent), 1990 (the largest to date, 9.4 percent), 1991 (2.3 percent), and 1992 (1.5 percent) (334b). The number of reported cases in 1991 was 26,283 (case rate of 10.4/100,000), and in 1992 it was 26,673 (10.5/100,000) (353,356). This 1992 case total represented an 20 percent increase over 1985.

Averaged over the 6-yea period, these data suggest a current upward trend of about 3 percent per year in cases, compared with the previous 5 to 6 percent annual decrease observed before 1984. Based on data indicating much sharper upturns in case rates in certain areas (see discussion below), it is possible that national rates may possibly continue to rise 2 percent per year, or go even higher, in the next decade.

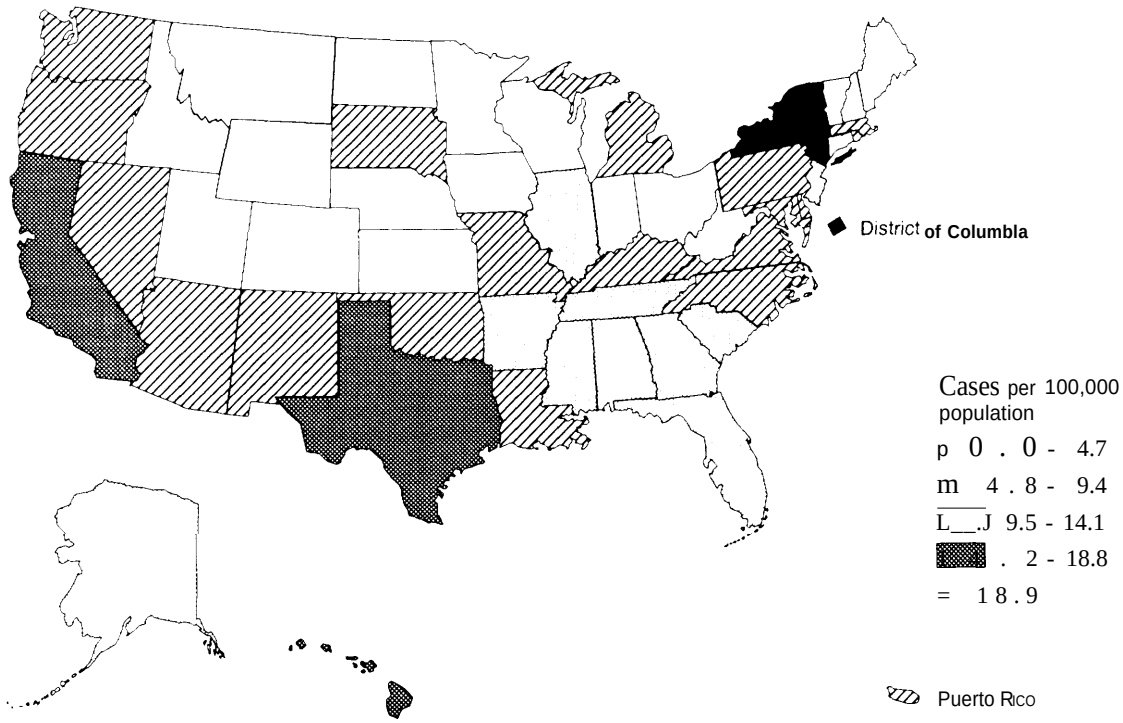
DEMOGRAPHIC CHANGES IN TB

One of the most striking changes in TB epidemiology in the United States in recent decades has been a gradual shift in TB occurrence

[1] Data from Puerto Rico and the Virgin Islands are also collected, but are not referred to in the data cited in this report.

[2] A l-year increase occurred in 1980 following a large influx of Indochinese refugees into the United States, and artificial increases were recorded in 1963 and 1975 due to changes in reporting criteria.

Figure 3-2—Rates of New Tuberculosis Cases in the United States, by State, 1991



SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1991.

from broader to narrower demographic populations (295), identified to some extent by geography, age, sex, race, ethnicity, and country of origin, A description of these changing characteristics can reveal where and in whom TB is occurring, It offers only limited information, however, about the epidemiology of the disease, since these characteristics are not causally related to TB; at best, they may be only indirectly associated with causal factors. Historically, TB has been linked primarily with environmental conditions that increase the likelihood of transmission, such as crowded, poorly ventilated housing and working conditions. Current data, described below, indicate that TB now occurs disproportionately among individuals who lack stable housing, abuse intravenous drugs or alcohol, become incarcerated, or are employed as migrant farm workers. A common element in these cases may also be environmental. The increasing **occurrence** of TB among individuals with HIV reflects a causal risk factor due to immunosuppression, **as well as lifestyle** factors such **as drug** abuse.

This section describes the current distribution of TB among demographic groups and summarizes the available data on the prevalence of TB in some high-risk populations. The epidemiologic association between TB and HIV is discussed later in the chapter.

Geographic Distribution

In 1991, more than half of the Nation's new cases came from five of the most populous States--California, New York, Texas, Florida, and Illinois (334). The highest TB case rates (the number of cases per 100,000 population), however, are found not only in these States but **also in** many smaller ones (see figure 3-2). New York

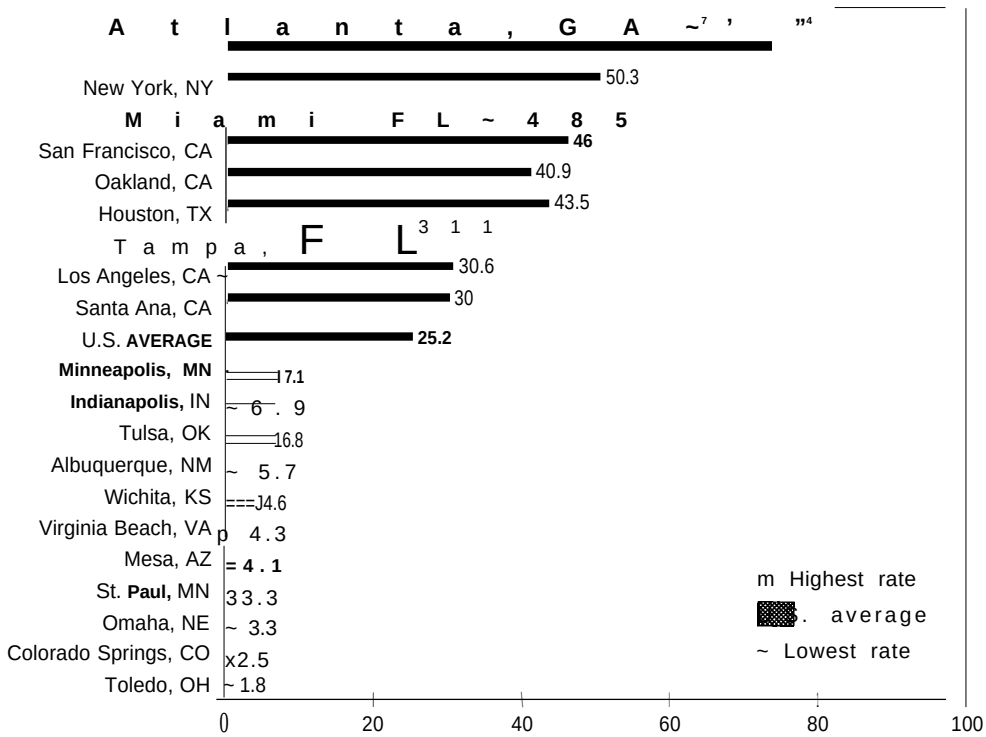
State ranked highest with a case rate of 24.5. Twelve other States recorded case rates above the national average of 10.4 for the same year: in descending order, Hawaii, California, Texas, Georgia, Florida, New Jersey, Alaska, Arkansas, Mississippi, Tennessee, South Carolina, and Alabama. The Southern region as a whole has long been above the national average in TB case rates (235). The lowest rates in 1991 were found in New Hampshire, Wyoming, North Dakota, Idaho, Nebraska, and Vermont (334).

Large urban areas as a group account for a disproportionate number of TB cases. In 1991, cities over 250,000 population accounted for 18 percent of the population, but more than 43 percent of new TB cases. About 14 percent of the Nation's cases came from New York City alone. The other major urban centers accounted for a much smaller percent of cases; Los Angeles, the city with the second highest number of new cases, accounted for about 4 percent of the Nation's cases, while Chicago, with the third highest, less than 3 percent (334a).

The ranking of cities by TB case rate indicates where TB is most concentrated. In 1991, the highest case rates were noted in Atlanta (76.4), Newark (71.8), New York City (50.3), Miami (48.5), and San Francisco (46.0) (see figure 3-3) (334a). Philadelphia and Chicago had relatively fewer cases, given their population size.

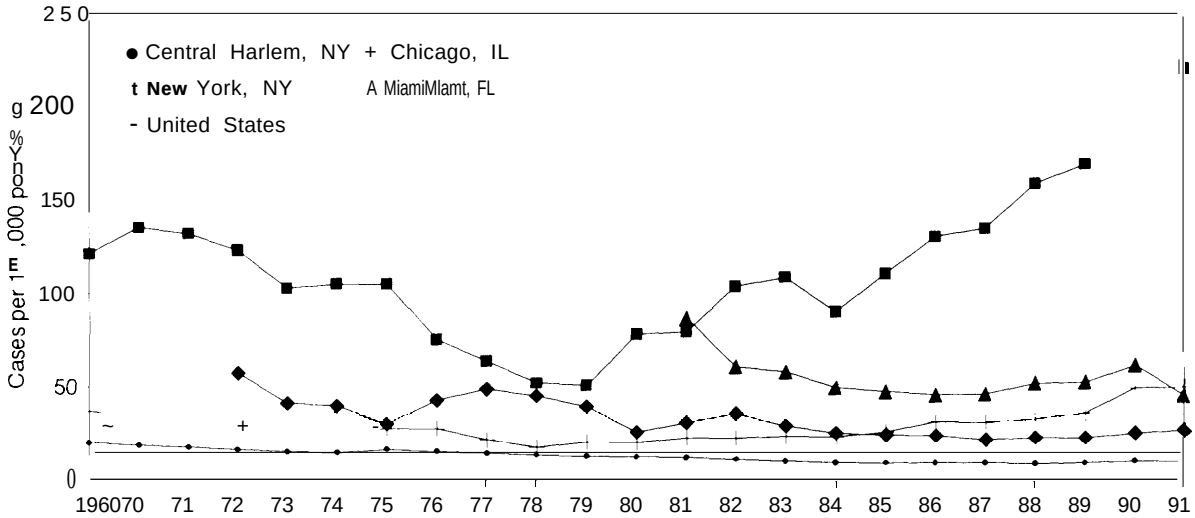
Some of the cities with currently high TB case rates have consistently had a high burden of TB for many years, even while the U.S. average case rates were declining. For example, figure 3-4

Figure 3-3-Highest and Lowest Rates of Active Tuberculosis in U.S. Cities of *250,000* or More, 1991



SOURCE: Office **of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Pubtic Health Service, Centers for Disease Control and Prevention, 1991.**

Figure 3-4—U.S. Localities With Highest Tuberculosis Case Rates Compared With U.S. National Rates, 1969-91



SOURCES: Office of Technology Assessment, 1993, based on data from Janice M. Burr, Medical Director of Tuberculosis Control Program, Dade County Department of Health, Miami, FL, personal communication, 1993; John Kuharik, Director, Tuberculosis Program, Chicago Department of Health, Chicago, IL, personal communication, 1993; K. Brudney and J. DobkM, "Resurgent Tuberculosis in New York City: Human Immunodeficiency Virus, Homeles-sness, and the Decline of Tuberculosis Control Programs," American Review of Respiratory Disease 144:745-749, 1991.

shows TB case rates in Central Harlem New York City, (one of the areas of New York with the highest case rates), Chicago, and Miami, along with the national average rates since 1969 (45). Although the downward trend in U.S. rates began to change in the mid-1980s, case rates in New York City began to rise in 1979, and in Miami and Chicago, in the late 1980s; all three cities have been dealing with case rates well above the national average for many years. The exceptionally high rates of TB in Central Harlem all through the 1970s and 1980s show that TB remained endemic for decades even while the disease was receding nationally, presumably moving toward elimination (128).

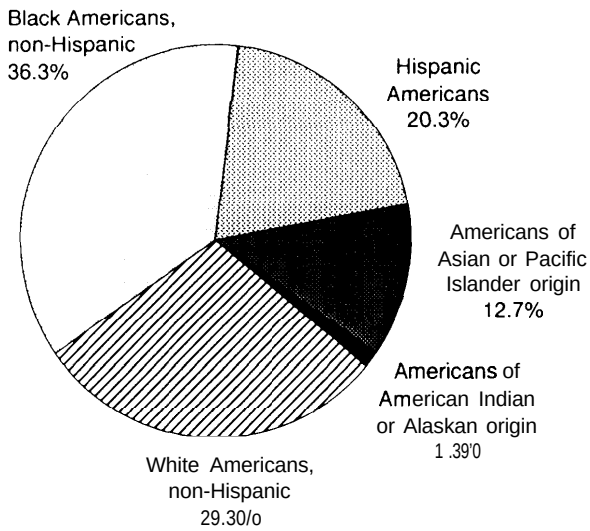
Race, Ethnicity, Age, and Sex

Historically, TB in the United States has been most prevalent among ethnic and racial minorities living in impoverished areas (245), and today this trend still holds, In 1991, 71 percent of new cases occurred in racial and ethnic minorities (see **figure 3-5).** From 1985 to 1991, relatively large increases in numbers of TB cases occurred among Hispanic Americans (increasing 72 percent), Americans of Asian or Pacific Islands origin (increasing 32 percent), and black Americans (increasing 26 percent). During the same period, reports of cases decreased among non-Hispanic white Americans 9 percent and among Native Americans, 13 percent (293). Approximately two-thirds of cases in 1991 were reported in males, although the percent increase was slightly higher for females than males (293).

TB cases and rates generally increase with age, except among 5- to 14-year-olds, who have the lowest case rate of all age groups (159). Since 1985, however cases increased in all age groups except for those 65 or older. The largest increase by far, however, occurred among the 25- to 44-year-olds, who now constitute 39 percent of all cases (see figure 3-6) (293).

A comparison of the age distribution of cases divided according to race and ethnicity (see figure

Figure 3-5-Racial and Ethnic Distribution of Tuberculosis Cases in the United States, 1991



SOURCE: Office of Technology Assessment, 1993, based on data **from U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1991.**

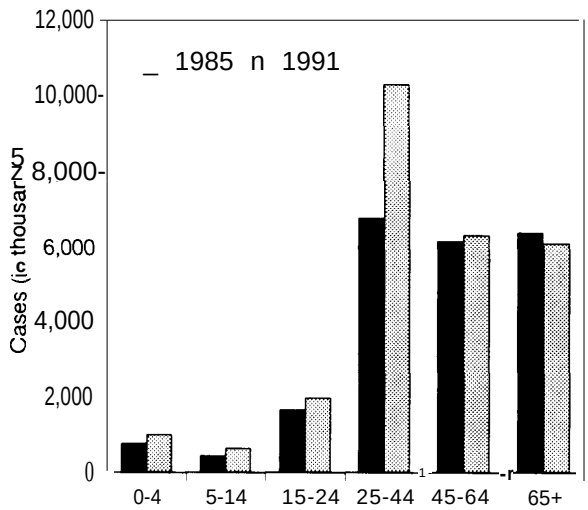
3-7) shows a dramatically different pattern among whites compared to black Americans and Hispanic Americans. Among white Americans, the majority of cases occur among elderly individuals, while among black and Hispanic Americans, an increasing number of cases is occuring among young adults in the 25- to 44-age-group. Minorities are disproportionately represented, particularly in this age group; of the 10,263 cases reported in 1991 among 25- to 44-year-olds, 45 percent occurred among black Americans, 22 percent among Hispanic Americans, 19 percent among white Americans, and 13 percent among Americans of Asian or Pacific Islands origin (293).

Children

Unlike cases among adults, TB among children is evidence of recent transmission of the disease-suggesting the presence of other individuals (usually adults) with active, infectious TB in the community (163,302,307). While transmission to children could occur in group settings such as family homes, schools, family day care homes, or nursery schools, a large TB clinic in Houston traced 80 percent of the cases to an infectious adult contact in the child's household (302). In some areas of the country, immigration from countries with high rates of TB may also account for high rates of TB among children.

Nationally, new cases of TB in children declined an average of 6 percent annually from 1962 until 1987, but then began to rise in 1988. In 1991, 1,662 new cases were reported in children under 15 years of age, an increase of 32 percent over 1985; most of the increase occurred among Hispanic American children, so that in 1991 Hispanic Americans accounted for nearly half of all cases in children. Overall, 86 percent of cases occurred in racial and ethnic minorities, compared with 80 percent in 1985 (302). Cases declined, however, not only among white American children, but also among Americans of Asian or Pacific Islands origin, American Indian, and Alaskan Native children during this period (293).

Figure 3-6-Reported Tuberculosis Cases in the United States by Age, 1985 and 1991

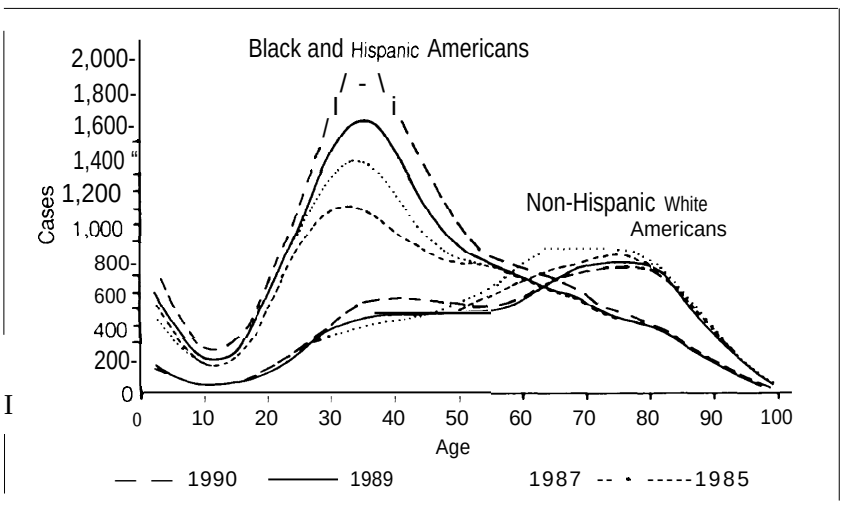


SOURCE: Office of Technology Assessment, 1993, based on data **from U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1991.**

BENJAMIN SMITH and ON LOK SENIOR HEALTH SERVICES

Individuals at high risk of TB in the United States include elderly people and economica//y-disadvantaged people, especially those who are members of racial and ethnic minority groups, children, and those born in other countries.

Figure 3-7—U.S. Tuberculosis Cases Among Black and Hispanic Americans Compared With Non-Hispanic White Americans, 1985, 1987, 1989 and 1990



SOURCE: M.E. Villarino, L.J. Geiter, and P.M. Simone, "The Multidrug-Resistant Tuberculosis Challenge to Public Health Efforts to Control Tuberculosis," Public Health Reports 107(6):616-625, 1992.

In 1991, three States contributed almost 60 percent of the cases among children: California (with 563 cases), Texas (with 219 cases), and New York (with 198 cases). Large percent increases in recent years, however, occurred in New Jersey and Arizona (293). High rates of TB among immigrants such as in California and increases in TB among parents of the 25 to 44 age group may account for the observed increases among children.

Elderly Individuals

In 1991, elderly individuals accounted for nearly a quarter of all new TB cases; the case rate among individuals 65 or older is currently the highest of any age group (358). The vast majority of these cases result from infection acquired earlier in life when TB was more prevalent, with the infection then progressing to active disease in older age (31 1). Some evidence suggests, however, that some TB cases among the elderly individuals result from recent infection or active transmission (309,31 1). Residents of nursing homes or other long-term care facilities maybe at greater risk for TB than those living in single family homes (312). Data from a CDC survey of over 15,000 TB cases among elderly individuals living in nursing homes compared with noncongregate sites between 1984 and 1985 showed an annual case rate in nursing homes nearly twice as high (358). A smaller, more intensive survey among cases reported in Arkansas suggested an even higher relative risk for nursing home residents (312).

High-Risk Populations

Immigrants and Refugees

As a group, U.S. residents born outside of the United States tend to have higher rates of TB than those born in this country (360). This trend reflects the fact that TB is more prevalent in many areas of the world, particularly regions of Asia, Africa, and Latin America, than in the United States (199,316). In 1991,27 percent of the 6,982 new cases were reported among the foreign-born; this is increased from 22 percent in 1986 (293).

The vast majority of these cases were reported in people of either Hispanic, Asian, or Pacific Islands origin. Such cases made up sizable proportions of all cases within each of these ethnic groups: 55 percent of all Hispanic American cases and 89 percent of all cases among Americans of Asian or Pacific Island origin were reported as foreign-born in 1991 (293),

Residents of Homeless Shelters

Various surveys among selected clinics and shelters serving homeless individuals indicate that the prevalence of active TB may range from 2 to 7 percent (184,275,289). The prevalence is likely to be highly variable, however, depending on the site, population, and time period studied. The proportion of TB patients who are also homeless may be high. In New York City, 20 percent of new TB cases reported in 1991 were also identified as homeless, based on a computerized matching of shelter addresses to TB cases in the registry (57).

There are several factors that make homeless individuals generally more vulnerable to development of active TB. The prevalence of tuberculous infection among homeless individuals is reported to be quite high-up to 50 percent in some studies (16,184,285,289,342). Factors predisposing homeless individuals with TB infection to progress to active disease include impaired immunity (due to poor nutrition, poor health status overall, substance abuse, and/or HIV infection) and lack of access to preventive treatment (184).

In addition, homeless shelters typically provide ideal conditions for transmission of tuberculous infection-large numbers of people in close proximity, poor ventilation, the presence of undiagnosed or untreated infectious cases, and prolonged exposure due to lengthy stays particularly in winter months (325). Studies have also shown that previously infected residents may also become reinfected in the shelter and progress rapidly to active disease (207). In recent years, several outbreaks of TB disease in homeless shelters have been reported (207,212,342,351).

Drug Users

Drug users are another population that overlaps with several other identifiable groups at high risk for TB, particularly the HIV-infected and homeless. Results of a recent study of MDR-TB in New York City indicated that intravenous drug use was an independent risk factor for the development of MDR-TB in that population (107). A survey

conducted in the early 1970s of drug-dependent individuals identified through New York City drug addiction treatment centers and methadone maintenance treatment programs showed a high prevalence of TB in this population (246). A recent report documented an outbreak of TB among crack cocaine users in Contra Costa County, California (349). In 283 cases of TB reported during a 42-month period, 16 percent (44 individuals) were found to have occurred among crack cocaine users. Fifteen of the 44 drug users frequented one or more crack houses, environments that may facilitate active transmission of TB. Crack use, which damages the lungs and promotes coughing, can lead to increased active transmission of TB among users in close quarters and in poorly ventilated surroundings typical of crack houses. No direct link of crack use in the risk of infection was documented.

Prisoners and Inmates

The prevalence of TB in correctional institutions (including prisons, jails, and detention centers) is related both to the prevalence of tuberculous infection and HIV in the incarcerated population and to conditions within the institutions favoring spread of tuberculous infection. On both accounts, TB has become a significant and increasing health problem within the correctional system (23). These factors are an issue not only for the correctional system itself (with its average daily population of 1.2 million in 1990) (1 12), but for the country as a whole, since inmates who develop TB within the system carry it with them into the community following release (308); in addition, correctional staff who become infected and develop active TB can, in turn, transmit the disease to their family and other contacts in the community (346).

Population groups at high risk for TB—individuals who abuse drugs, who are HIV-infected, and who are homeless—are disproportionately represented in the connectional system (112,346). In the New York State system, 26 percent of the women and 16 percent of the men were also found to be HIV-infected in a recent blinded serosurvey. Almost one-third of newly admitted inmates in New York State reported having been homeless just prior to incarceration, and the majority of inmates had histories of substance abuse (209).

TB may be at least three times more prevalent among inmates and prisoners than in nonincarcerated adults (335). In the New York State, New Jersey, and California correctional systems, for example, the prevalence of TB in the mid- 1980s was 6 to 11 times higher than in the general population of those States (41,346). In New York State, the incidence of TB began rising in the early 1980s (before any confections with HIV were identified) but accelerated its rise in 1986; it increased four-fold from under 25 cases per 100,000 in the late 1970s to over 100 per 100,000 in 1986. Approximately one-half of the cases between 1985 and 1986 were found to have HIV infection, based on a study matching TB and AIDS registries. Most TB cases were in minority men between 30- and 49-years-old with histories of intravenous drug use (41).

Since 1985, at least 11 outbreaks of TB have occurred in correctional institutions in eight States (346); the most recent one involved a cluster of MDR-TB cases in which 13 inmates and one correctional officer died of the disease. The presence of inmates with active, infectious disease in close proximity with large numbers of highly susceptible individuals in poorly ventilated surroundings creates a scenario for rapid and widespread infection (308). Frequent transfers of prisoners within and between facilities may also serve to broaden the scope of the problem.

Migrant Farm Workers

Evidence suggests that migrant farm workers,[3] many of whom are immigrants from counties with a high prevalence of TB, may also be at high risk

[3]Migrant farm workers are defined as seasonal agricultural workers who move from area to area for jobs.

for TB. A 1988 study of 543 migrant farm workers in North Carolina found an overall prevalence of active TB in 2 percent of workers (0.47 percent in Hispanic American workers and 3.6 percent in black American workers), along with high rates of TB infection (33 percent of Hispanic Americans, 54 percent of black Americans, and 76 percent of Haitian immigrants) (55). High rates of tuberculous infection have also been noted in other migrant worker populations (2%,362). Since there is no regular monitoring of this population, the overall prevalence of TB in the U.S. migrant farm worker population is unknown.

Data from the North Carolina study suggest that TB in migrant farm workers maybe at least partly an occupational problem, since those with longer migrant work histories had greater risks of TB. Lack of access to health services and substandard working and housing conditions are likely factors in this heightened risk. Characteristics of the migrant population also predispose them to TB. A high percentage of workers, mostly black Americans, are recruited from homeless shelters, soup kitchens, and alcohol rehabilitation centers. While immigrants (generally from Central America, Mexico, and Haiti) constitute a large part of the migrant work force, the North Carolina study found much higher rates of TB disease among U.S.-born black workers compared with the foreign-born workers (55).

HIV AND AIDS: EPIDEMIOLOGIC ASSOCIATION WITH TB

Reports in the mid-1980s were the first to describe an association between TB and AIDS, based on clinical studies of Haitian immigrants in Florida (23 1) and intravenous drug users (IVDUS) in New Jersey (319). In recent years, a significant physiologic interaction between the two infections has become clear. This interaction is relevant not only to the medical care of individuals confected with tubercle bacilli and HIV, but also to the resurgence of TB in many areas.

Current evidence indicates that HIV-related immunsuoppression impairs the body's ability to contain infection with tuberculous mycobacteria. As a result, individuals infected with TB and HIV, particularly those with advanced immunosuppression, are at high risk of progressing rapidly to active TB disease; this is true whether they have recently become infected with TB or previously harbored the latent TB infection (69,77,81,278). Rapid progression to active TB disease among individuals with AIDS seems to be a more dangerous course of TB, with death often occurring before treatment for TB begins or within the first month of treatment (290). The estimated annual risk of progression to active TB disease among dually-infected individuals has been estimated to be as high as 8 percent per year (278), compared with an average risk among HIV-seronegative individuals of 10 percent per lifetime.

In addition, preliminary observations suggest some individuals with HIV infection may be more likely than a healthy individual to acquire the initial TB infection after contact with someone who has active, infectious TB (69). Heightened susceptibility and prolonged periods of infectivity have been cited as potential factors in several recent outbreaks of MDR-TB among HIV-infected individuals in congregate settings (48,69,77,81,195).

An estimated 10 million people in the United States are infected with tubercle bacilli (248) and an estimated 1 million are infected with HIV. As has been seen in some areas, the presence of HIV can profoundly affect the incidence of TB, particularly where populations with TB and HIV overlap to a large extent (202,229,249,315). According to a recent CDC analysis of trends in reported cases of TB among U.S.-born individuals between 1985 and 1991, the largest increases in numbers of TB cases were found in groups of States with the highest incidence of AIDS (defined as 138 to 636/100,000 population); TB incidence was found to have declined in States with the lowest cumulative AIDS incidence (5 to

46/100,000), and remained at the same level in those with an intermediate incidence of AIDS (48 to 97/100,000) (293). These data suggest that HIV may be having a direct impact on TB, accounting for at least some of the resurgence of TB in these areas. Common factors, such as the occurrence of both diseases in some of the same demographic groups, may also be contributing to the observed association, Inmates and IVDUS, for example, are at higher risk for TB than the general population because a greater proportion of individuals in these groups have tuberculous infection and are also at high risk for HIV infection; in addition, noninfected inmates and IVDUS are also at high risk for TB due to the potential for transmission within correctional facilities, crack houses, and other settings (23,355).

A recent analysis of U.S. death certificates filed between 1980 and 1990 indicated an increase in deaths due to TB in young adults, believed to be associated with the AIDS epidemic. In 1990, more than half of the deaths with TB in individuals 20- to 49-years-old occurred in those who also had AIDS listed on their death certificates (39).

In developing countries, particularly in sub-Saharan Africa and Haiti where both AIDS and TB are more prevalent than in the United States, AIDS appears to be having a substantial impact on TB. According to World Health Organization (WHO) estimates, 4 million people worldwide are dually infected with tubercle bacilli and HIV, the majority of whom live in developing countries; as many as two-thirds of TB patients in some countries may be HIV-seropositive (236). Internationally, TB is one of the most common opportunistic infections of AIDS and is the AIDS-defining condition in about 30 percent of cases (132). This could lead to a dramatic increase in the number of deaths from TB over the next decade in regions where TB and AIDS are endemic (135,201).

The Prevalence of TB Among Individuals With AIDS

Studies of individuals with AIDS in the United States have consistently shown a higher prevalence of TB compared with the general population, even after adjustment for age, race, and sex (67,232). Overall, 4.9 percent of AIDS cases reported up to 1990 also appeared on TB registries, according to a CDC analysis of TB and AIDS registries in 43 States and 11 localities (293,344). Substantially higher prevalence rates of TB among individuals with AIDS have recently been reported in certain populations: for example, 26 percent of men with HIV infection and 40 percent of men with AIDS or AIDS-related complex living in a homeless shelter in New York City and 13 percent of patients with AIDS in a New York City hospital were found to have active TB (177,325). The 1990 overall proportion of 4.9 percent increased from 4.0 percent 2 years earlier (344).

Another indicator that the prevalence of TB may be increasing among individuals with AIDS is the disproportionate increase in the incidence of extrapulmonary TB, which rose by 20 percent nationwide, compared with pulmonary TB, which rose by 3 percent, between 1984 and 1989. Extrapulmonary TB is more often seen among individuals with AIDS (see chapter 2) (27,218).[4] *M.tb.* isolates may represent only 10 percent of mycobacterial infections in patients with AIDS, however. Infection with nontuberculous mycobacteria such as *M.avium* is very common among AIDS patients; these infections occur in later stages of AIDS (when CD4 cell counts are below $100/mm^3$), are untreatable, and may be life-threatening.

[4] According to CDC'S 1987 definition of AIDS, an HIV-infected individual with extrapulmonary TB would be reportable as AIDS (40). In 1993, this definition was broadened to include, among other conditions, pulmonary TB as a defining condition of AIDS among HIV-infected individuals with CD4+ lymphocyte counts waler 200 cells/mm^3 (365).

MULTIDRUG-RESISTANT TUBERCULOSIS

Drug-resistant TB is not a new phenomenon, but in recent years, the predominant types of MDR-TB have changed, as has the overall number of cases in the United States.

Three general categories of drug resistance apply to TB, although, in practice, it is not always possible to determine which one applies in any given case: primary resistance, which is a naturally occurring biological phenomenon that rarely results in resistance to more than one drug, but also refers to a drug resistance in a patient not known to have received prior treatment; acquired resistance, which is a manmade problem caused by inadequate or erratic treatment and can result in resistance to one or more drugs in each case; and transmitted resistance, which occurs in active transmission to contacts from infectious cases (e.g., in institutional settings) and results in resistance to the same number and types of drugs as in the source case (154).[5]

Until the past several years, TB experts generally assumed that most cases of MDR-TB were acquired through inadequate or erratic treatment in an individual case. Increasingly, however, transmitted resistance is being implicated in reported cases of MDR-TB (48). For example, in New York City, a survey of all TB cases reported during April 1991 suggested that most patients with drug-resistant isolates had drug resistance because they were initially infected with resistant bacilli (107). Although both categories of resistance appear to be important at present, the actual proportion of each in the U.S. population is unknown. Genetic fingerprinting technology has recently been used to track the spread of specific strains of tubercle bacilli among infected individuals in an outbreak situation, thus providing strong evidence of active transmission in certain cases (69).

From a public health standpoint, the most significant forms of drug-resistant TB are resistant to both isoniazid (INH) and rifampin (RF), two of the most powerful anti-TB drugs. Such cases of MDR-TB are generally far more difficult and costly to treat than drug-sensitive TB, and can be fatal despite the best available treatment (see chapter 5 for further details).

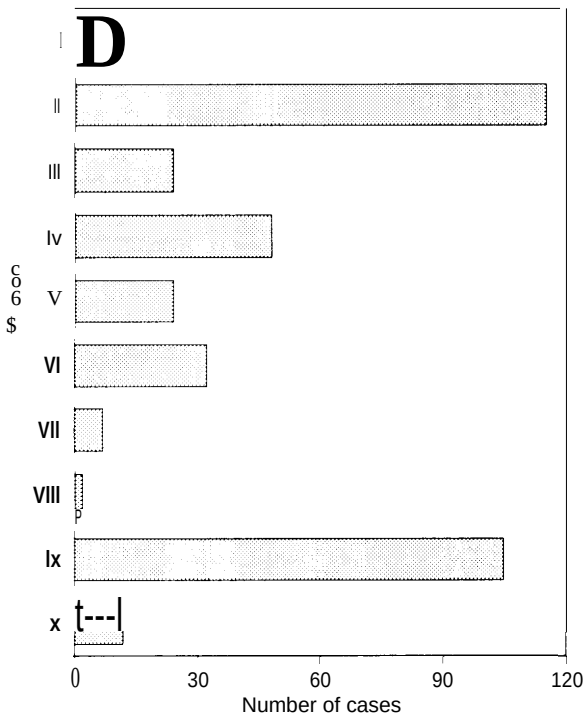
The proportion of cases with drug-resistant TB in the United States, Canada, and Europe has traditionally been lower than in many other countries. In many areas of Latin America, Asia, and Africa, higher rates of TB overall, inadequate TB control programs, uncontrolled dispensing of drugs, and ineffective treatment delivery systems all contribute to higher rates of drug-resistant TB (156). On entry to the United States, immigrants from these areas can harbor tuberculous infection that may be drug-resistant.

Current national data on the incidence and prevalence of drug-resistant TB in the United States are unavailable because, until 1993, the TB surveillance system did not collect information on drug-susceptibility of reported cases (382). Although some States or communities regularly preform susceptibility testing on TB cases, others test only on some individuals on an optional basis (156). As of 1993, reports of each case of TB will be required to include drug susceptibility data (26). Since 1961, CDC conducted periodic national surveys of primary drug resistance, but discontinued the practice in 1986, partly due to evidence of stable or declining proportions of patients with drug resistance but also due to competing priorities for CDC resources. Several large national surveys conducted over the past few decades do offer some information on the epidemiology of drug-resistant TB in the United States.

---

[5] Although these definitions are accepted by most TB experts, the CDC uses a different scheme to distinguish among types of resistance. The CDC classification uses the term ''primary resistance" to refer to all TB not previously treated; this category combines "primary" and "transmitted' resistance as they are defined in the text. The CDC's term "secondary resistance" is equivalent to "acquired resistance" as defined in the text.

Figure 3-8-Culture-Positive Cases of Tuberculosis Resistant to One or More Drugs, by Region, 1991



REGION I
Connecticut
Maine
Massachusetts
New Hampshire
Rhode Island

REGION II
New Jersey
New York
Puerto Rico
Virgin Islands

REGION III
Delaware
District of Columbia
Maryland
Pennsylvania
Virginia
West Virginia

REGION IV
Alabama
Florida
Georgia
Kentucky
Mississippi
North Carolina
South Carolina
Tennessee

REGION V
Illinois
Michigan
Minnesota
Ohio
Wisconsin

REGION VI
Arkansas
Louisiana
New Mexico
Oklahoma
Texas

REGION VII
Indiana
Kansas
Missouri
New England

REGION VIII
Colorado
Montana
North Dakota
South Dakota
Utah
Wyoming

REGION IX
Arizona
California
Hawaii
Nevada

REGION X
Alaska
Idaho
Oregon
Washington

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1991.

The incidence of primary resistance to anti-TB drugs remained under 3 percent from the 1940s, when antibiotics were first used to treat TB, through the 1960s (82). An average rate of primary resistance of 7.1 (range of 3.3 to 15.1 percent) was found in a national survey of over 7,500 patients tested in 19 city and State laboratories by CDC between 1975 and 1977, with higher rates found among Asian and Hispanic American patients than other racial and ethnic groups. Another survey of 20 State and city labs involving over 11,000 patients, conducted between 1975 and 1982, found a declining incidence of primary resistance over the period of the study, with a 6.9 percent rate overall and variation by geography, race, and ethnicity (172,338,340).

A higher average incidence of primary resistance to one or more drugs (9.0 percent) (with 0.5 percent resistant to two or more drugs during this same period) was found in a 1982-86 survey conducted by CDC, (based on 3,760 samples from 31 health departments across the country (51,297). Results showed a decreased rate of primary resistance during the 4-year survey. Because of different methods of sampling and data collection, however, results of the 1975-82 survey and the 1982-86 survey are not comparable.

More recent and comprehensive data are available from a nationwide CDC survey of drug resistance among new TB cases reported during the frost 3 months of 1991. This survey did not include data on drug resistance in prevalent cases, so it provides only a minimal estimate on the number of drug-resistant cases in the United States. Provisional analysis of these data show that drug resistant TB is present in many areas of the country (see figure 3-8); cases resistant to at

least one drug were reported from 36 States and to both INH and RIF from 13 States.

A total of 114 cases of TB in newly diagnosed cases resistant to both INH and RIF were found, with more than half of these reported from New York City.[6] Resistance to both INH and RIF was 3.5 percent, representing cases in which the two best anti-TB drugs could not be given. Overall, 14.2 percent of the cases had resistance to at least one drug (the majority to INH) (19,363).

Rates of drug-resistance among selected populations of TB patients have also been described (54). A recent study of drug resistance among TB cases reported in New York City gives an indication of the magnitude of the problem in that area. In a collaborative study with CDC, the New York City Department of Health conducted a systematic survey of TB cases to measure drug resistance among all patients in New York City who had a positive culture for TB during the month of April 1991 (107). Overall, 33 percent of cases were resistant to one or more drugs, and 19 percent were resistant to both INH and RIF.

Divided according to primary and acquired resistance, the study found that among cases not previously treated, 23 percent were resistant to one or more drugs and 7 percent to both INH and RIF; among those currently or previously treated, 44 percent were resistant to one or more drugs and 30 percent to both INH and RIF. The New York City Department of Health reported that for the entire year of 1991, a total of 366 new cases of TB resistant to both INH and RIF were reported in New York City-about 10 percent of all cases that year (57). No other area of the country currently has as high a level of MDR-TB. Further, limited evidence suggests that the prevalence of MDR-TB in New York is increasing. During a recent 3-year period at a large hospital center in Brooklyn, the prevalence of TB cases resistant to two or more drugs increased from 12 percent (31 *cases* per *265* patients) to 18 percent (39 cases per 221 patients) (280).

Recent Outbreaks of MDR-TB in Institutional Settings

Although community outbreaks of drug-resistant TB (237,339) are not an entirely new occurrence, a recent series of reports indicate that such outbreaks have become more common, larger in scope, and more dangerous.

Since 1990, CDC has investigated nine outbreaks of MDR-TB in the United States (370). At least seven additional clusters of drug-resistant TB, however, have been reported in 1990 and 1991 but not investigated by CDC (in Illinois, Mississippi, New York, and Michigan). They have occurred in several hospitals in New York City and Miami; in New York State and New Jersey; and in prison facilities in New York State (see table 3-l). The total number of individuals who developed active MDR-TB in these outbreaks had risen to 297 as of October 1992 (78). Most, though not all, were HIV-seropositive. The majority (79 to 89 percent) of the individuals affected by these outbreaks have died from the disease, including six health care workers and one prison guard; the median interval between diagnosis and death was just 4 to 16 weeks (363). Almost all cases were resistant to at least INH and RIF, and some to as many as seven drugs (80). It is not known whether the high rate of mortality observed in these outbreaks applies to other individuals with MDR-TB, whether or not they are HIV-infected.

In these institutional settings, MDR-TB was transmitted from patient to patient, from patient to health care worker, from inmate to inmate, and from inmate to prison staff. A number of common factors have been investigated as possible causes of the rapid transmission of the disease in these different settings (80). The immediate factor in

[6] Cases of TB resistant to both INH and RIF: 51 from New York City, 9 from New Jersey, 7 from Florida, 6 from California, 5 from Texas, 3 from Alabama, 3 from Illinois, and 1 each from Hawaii, Arizona, Virginia, Washington, Georgia, and Pennsylvania (26).

Table 3-1—Nosocomial HIV-Related Multidrug-Resistant Tuberculosis Outbreaks, 1988 to October 1992

Facility	Location	Time period	Total cases	Resistance pattern[a]
Hospital A	Miami	1988-91	65	INH, RIF (EMB, ETA)
Hospital B	New York City	1989-91	51	INH, SM (RIF, EMB)
Hospital C	New York City	1989-92	70	INH, RIF, SM (EMB, ETA, KM, RBT)
Hospital D	New York City	1990-91	29	INH, RIF (EMB, ETA)
Hospital E	New York State	1991	7	INH, RIF, SM (EMB, ETA, KM, RBT)
Hospital F	New York City	1990-91	16	INH, RIF, SM (EMB, ETA, KM, RBT)
Hospital i	New Jersey	1990-92	13	INH, RIF (EMB)
Hospital J	New York City	1991-92	28	INH, RIF (SM, EMB, ETA, KM)
Prison system[b]	New York State	1990-92	42	INH, RIF (SM, EMB, ETA, KM, RBT)
Total cases[b]			297	

KEY: EMB = Ethambutol; ETA- Ethionamide; HIV- human immunodificiency virus; INH _-Isoniazid; KM Kanamycin; RBT = Rifabutin; RIF = Rifampin; SM = Streptomycin.
a All cases are resistant to first group of drugs listed. Some cases are also resistant to the drugs listed within the parentheses.
b 24 prison cases are also counted with Hospital C.

SOURCE: Office of Technology Assessment, 1993, based on data from U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, 1992.

each case is the presence of individuals with active, infectious TB in close proximity to others; such patients remain infectious until at least several weeks into appropriate therapy under the best of circumstances, or, in untreatable cases, remain infectious indefinitely. Furthermore, delayed diagnosis and delayed initiation of appropriate therapy in treatable cases increase the chances of spreading the disease. For a number of reasons, HIV-seropositive individuals with MDR-TB maybe more difficult to diagnose. In addition, drug susceptibility testing, which is necessary to assure an appropriate treatment regimen, usually takes several weeks to months to complete. Heightened vulnerability to the rapid development of active TB among HIV-seropositive individuals infected with tubercle bacilli also contribute to these outbreaks,

Delayed implementation of infection control measures, premature discontinuation of isolation, delayed reporting of drug-resistance, and lack of isolation facilities were major factors in the spread of MDR-TB within these institutions. Given the medical limitations cited above, infection control practices adequate to the task may be essential to prevent further spread of the disease in these circumstances (see chapter 5 for further details). In at least one setting where an outbreak occurred, the adoption of improved infection control practices was believed to be largely responsible for the absence of further cases of transmitted MDR-TB (20).

FACTORS UNDERLYING THE TB RESURGENCE IN THE UNITED STATES

Recent changes in the nature and magnitude of TB involve a broad range of interrelated factors. No one factor appears to be the predominant cause of the resurgence. Medical factors (such as HIV-related immunsuppression), social factors (e.g., hopelessness and incarceration), and health policy issues (such as reduced resources for TB

control in general) (see chapter 7) have all contributed to the problem in various ways (31).

One of the most basic and often overlooked reasons for the resurgence is inadequate control of the disease in some areas, even though its overall incidence steadily declined in the general population (277). The maintenance of a reservoir of TB permitted the larger resurgence to occur when conditions favored its spread. Certain communities in New York City, such as Central Harlem, are examples of areas where TB rates remained consistently high in the 1960s and 1970s compared with regional and national rates. The incidence of TB in Harlem began to rise in the late 1970s (before AIDS became prevalent and well before national TB rates began to rise). The rise was driven by a variety of factors, particularly hopelessness, intravenous drug use, and the decline of TB control programs (45). TB rates began to increase more quickly in Harlem in the mid- 1980s, as HIV became prevalent in the same population (57).

Social and public policy issues figure prominently in the resurgence. Some of the most intractable social problems are generally believed to play a role, directly or indirectly, in furthering the spread of TB, including, poverty, hopelessness, substance abuse, poor health status, language barriers, and crowded, substandard living conditions. The AIDS epidemic in some of the same populations provided the vechile for an accelerated rate of increase in TB. Immigration of individuals from certain countries has added to the level of disease in some areas, and has been a continuing source of TB, although it is not clear whether immigration in recent years has contributed substantially more to TB than it has in the past (31). Growing numbers of inmates in correctional institutions, of residents in homeless shelters, and of patients with AIDS in health care facilities may also have contributed to rapid increases in TB in some areas. It is likely that a combination of many of these factors in the same populations produced the most volatile situation for TB.

Despite the multitude of social factors favoring its spread, most of which are not new, most TB cases are curable and preventable by traditional public health and medical approaches (see chapters 4 and 5). The withdrawal of public resources and the dismantling and defunding of community control programs credited with the earlier decline in the disease appear to have played a major role in the resurgence (31,45,240). Although the proportion of current cases that could have been prevented by surveillance and treatment is not known, the majority of them potentially could have been prevented. Moreover, the emergence of MDR-TB is a sensitive indicator of deficiencies in the process of ensuring treatment until cure, one of the main responsibilities of TB control programs.