Tuberculosis Control: the Relevance of Classic Principles in an Era of Acquired Immunodeficiency Syndrome and Multidrug Resistance

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INTRODUCTION

The estimated 64,000 excess cases of tuberculosis which occurred in the United States between 1985 and 1993 (1) are part of a global pandemic (2). Years before industrialized countries started to experience a resurgence in tuberculosis, the disease had persisted in neglected groups within their own borders and in developing nations (3). With outbreaks of multidrug-resistant tuberculosis in the United States, the threat of "casual transmission of a highly fatal disease" (4, p. 648) led to a renaissance of interest in, and expansion of funding for, tuberculosis epidemiology, studies on the emergence of multidrug-resistant strains, and control programs in the United States. Global tuberculosis control programs, however, remain woefully underfunded (5) and are often poorly structured.

Even in the age of multidrug resistance and the acquired immunodeficiency syndrome (AIDS), the classic principles of tuberculosis control are as relevant as ever. These principles include diagnosis and appropriate and complete treatment of persons with active tuberculosis, and, after treatment is effective, contact investigation and preventive therapy as resources permit. Indeed, both the tuberculosis epidemic and the emergence of drug-resistant strains of Mycobacterium tuberculosis have been propelled, in part, by neglect of these basic principles by medical and public health establishments.

In this review, we summarize the findings of recent epidemiologic studies on the resurgence of tuberculosis and the emergence of multidrug-resistant strains, and the implications of these findings for tuberculosis prevention and control. In the last section of this review, we describe how New York City's Bureau of Tuberculosis Control analyzed and responded to the city's epidemic, and review critical gaps in our knowledge and ability to control tuberculosis.

DEFINITIONS

A verified case of tuberculosis is, for the purposes of public health surveillance and prevention, defined by 1) the isolation of M. tuberculosis in a culture grown from a clinical specimen, 2) the finding of acid-fast bacilli in clinical specimens for which a culture has not been or cannot be obtained, and/or 3) a clinical presentation consistent with tuberculosis (e.g., a positive tuberculin skin test, symptoms compatible with tuberculosis, and an abnormal or unstable chest radiograph) in a patient who is started on two or more antituberculosis drugs (6, 7).

Multidrug-resistant tuberculosis is usually defined as disease caused by M. tuberculosis organisms which are resistant to at least isoniazid and rifampin, the two most effective antituberculosis medications. Drug resistance may be primary, in a patient who has never before been treated for tuberculosis and was infected by drug-resistant bacilli, or secondary (acquired), in a patient who initially had drug-susceptible M. tuberculosis but received inappropriate or inadequate treatment, was nonadherent to a prescribed regimen, or absorbed prescribed medication poorly, and thus developed drug-resistant tuberculosis organisms (8).

NATURAL HISTORY

Infection

Generally, tuberculosis infection depends on exposure to an active case while progression from infection to disease depends on the immune status of the infected person (9). Most tuberculosis infections result from inhalation of airborne droplets containing the bacillus M. tuberculosis (10); these droplets are emitted most efficiently by patients with laryngeal tuberculosis, cavitary disease on chest radiographs, and...
sputum samples which show acid-fast bacilli on smear. *M. tuberculosis* is an acid-fast mycobacterium; of the four species in the *M. tuberculosis* complex (*M. tuberculosis*, *Mycobacterium bovis*, *Mycobacterium africanum*, and *Mycobacterium microti*) (11), it is the one primarily responsible for tuberculosis in humans.

An undiagnosed and untreated smear-positive patient has been estimated to infect 10–14 persons per year (12). The likelihood of infection following exposure to infectious droplets increases with increasing concentration of *M. tuberculosis* droplet nuclei in the air and increasing length of exposure (9, 13).

The efficacy of the Bacille Calmette Guerin (BCG) vaccine in protecting against tuberculosis is variable and partial, although the vaccine does appear to offer protection against disseminated and meningeal tuberculosis in children (14).

**Risk of disease progression**

Once in the lungs, *M. tuberculosis* evokes a nonspecific inflammatory response (primary complex) in the lung tissue and in adjacent lymph nodes (15). Approximately 10 percent of infected persons develop disease at some point in their lives. Of those who develop active disease, most (50–80 percent) do so within 2 years of infection (16, 17).

Young children are especially likely to progress to active disease after infection (18). Active cases among young children are sentinel health events and indicate recent transmission within a community (9).

Characteristics of the host which affect the likelihood of progression from infection to active disease include infection with human immunodeficiency virus (HIV), fibrotic lung lesions, silicosis, some malignancies, hemophilia, immunosuppressive medical treatment, low body weight, diabetes, heavy smoking, and certain genotypes (human leukocyte antigens A11, B15 and DR2) (9).

Treatment to prevent disease progression, usually with isoniazid, is recommended in the United States for all persons younger than 35 years of age who are infected with tuberculosis. Persons at high risk for progressing to active disease should receive preventive therapy, regardless of age; those at high risk include recent skin test converters, close contacts to active cases, and persons with any of the risk factors mentioned above, especially HIV infection (19).

Reactivation of latent infection had been considered the most important mechanism in the pathogenesis of active tuberculosis, but some recent studies suggest that rapid progression of recent infection may be an important cause of active disease in San Francisco, California, and New York, New York (20, 21). In addition, exogenous reinfection has been the mechanism responsible for two outbreaks of multidrug-resistant tuberculosis among homeless and HIV-infected patients (22, 23).

**The effect of treatment on the natural history of tuberculosis**

Without treatment, the case fatality rate for all forms of tuberculosis combined is 50–60 percent (12). Case fatality for tuberculous meningitis and miliary tuberculosis, however, may approach 100 percent.

Treatment for tuberculosis requires a minimum of 6 months, using a combination of isoniazid, rifampin, pyrazinamide, and either ethambutol or streptomycin for 2–3 months, and then, if the patient’s strain of *M. tuberculosis* is susceptible, continuing with isoniazid and rifampin for at least 4 more months (14). This short-course regimen replaces earlier regimens which required 12–24 months of treatment. If patients with drug-sensitive *M. tuberculosis* are treated appropriately and are fully compliant with their medical regimen for its entire duration, cure rates exceed 95 percent (12).

**Development of drug resistance**

Shortly after the discovery of antituberculosis drugs, it was recognized that therapy with a single agent can lead to drug resistance and treatment failure. In *M. tuberculosis*, resistance arises by spontaneous single-step mutation, which occurs at different frequencies for different medications. Previous treatment with antituberculosis drugs has been found to be the most important predictor of drug resistance (24–26). Multidrug resistance has drastic implications for the treatment of tuberculosis and for disease control programs, as patients with multidrug-resistant tuberculosis generally require at least 18 months of treatment with antituberculosis drugs, which are more costly and toxic than those used routinely, and may be more likely to relapse even after longer periods of treatment.

**SURVEILLANCE CHALLENGES**

It remains impossible to measure the full impact of tuberculosis on human well-being in much of the developing world because systems for surveillance of morbidity and mortality are inadequate (2). In some developing countries, detection of most tuberculosis cases may be entirely on the basis of physical examination and history; even where sputum microscopy and/or chest radiography are available, these procedures may be performed without adequate quality control or be inaccessible to populations at highest risk. Overreliance on radiography and underutilization of sputum smears for diagnosis and monitoring of treat-
ment are common. In most industrialized countries, on the other hand, cases are confirmed through bacteriologic culture and species identification of mycobacteria. Susceptibility testing of microorganisms is not available in many developing countries, while it is a routine procedure in several industrialized ones.

The New York City experience suggests that even in developed countries, the enumeration of smear- and culture-negative tuberculosis cases may be extremely labor-intensive. In New York City, health-care providers are legally mandated to report all suspected tuberculosis cases. Most verified cases (in 1994, approximately 83 percent) are confirmed by positive culture reports from laboratories (27). If suspected cases are not confirmed by positive cultures, health department staff must determine whether they may be confirmed clinically (e.g., through the demonstration of patient improvement in symptoms and radiographs while on antituberculosis medication).

International comparisons of tuberculosis morbidity and mortality are tenuous. To better estimate the burden of morbidity imposed worldwide by tuberculosis, a method has been devised to estimate the annual risk of tuberculosis infection through skin test surveys of persons who have not been vaccinated with BCG (2, 28). It has been estimated that 50 smear-positive tuberculosis cases per 100,000 population occur for every 1 percent increase in the annual risk of tuberculosis infection (2, 29). Limitations to this method include variability between regions in the specificity of tuberculin skin tests, in access to medical care, and in other factors that affect progression from infection to active disease (30), as well as the labor-intensiveness and expense of such surveys and increasing coverage with the BCG vaccine, which complicates interpretation of the skin test.

ADVANCES IN MICROBIOLOGY

Tuberculosis diagnosis in industrialized countries has already been strengthened by rapid detection, identification, and susceptibility testing of specimens from highly contagious smear-positive patients (31). This approach incorporates use of broth-based media with radiometric or fluorometric indicators to detect M. tuberculosis, a nucleic acid probe to identify species, and radiometric susceptibility testing.

Recently developed tools for DNA amplification (e.g., polymerase chain reaction and transcription-mediated amplification) hasten identification of M. tuberculosis directly from respiratory specimens (32), rather than after growth of mycobacteria in culture. Smears and cultures will still be needed for grading of infectivity and susceptibility testing, respectively. The clinical utility and cost effectiveness of DNA amplification techniques have not yet been demonstrated.

Restriction fragment length polymorphism (RFLP) analysis (33) has been used to determine whether microorganisms cultured from patients with active tuberculosis are genetically related. This technique has been helpful in outbreak investigations (23) and has been applied in population-based investigations to estimate the proportion of cases which arise from recent transmission of tuberculosis (20, 21). RFLP analysis, while helpful, complements, but does not replace, conventional epidemiologic analysis.

RECENT EPIDEMIOLOGY

National trends

In the United States, tuberculosis incidence reached its nadir in 1985 when there were 22,201 cases (9.3 per 100,000 population). Since 1953, when national data were first collected, annual numbers of cases had, with a few minor exceptions, declined steadily. Between 1974, when there was a change in the surveillance definition for tuberculosis, and 1985, the average annual decrease in cases was approximately 5 percent (9). Between 1985 and 1992, the national number of cases increased by almost 3 percent per year to reach 26,673 in 1992 (10.5 cases per 100,000 population); this upturn resulted in an estimated excess of 64,000 cases, compared with the number expected based on earlier trends (1, 6). Starting in 1993, the national number of cases has declined annually, to 25,313 (9.8 cases per 100,000 population) in 1993 (6), to 24,361 cases (9.4 per 100,000 population) in 1994 (34), and to 22,813 cases in 1995 (35).

The national increase between 1985 and 1992 was driven by an upsurge of tuberculosis in large cities (36). Trends in tuberculosis incidence in New York City heralded the national epidemic by 6 years: After reaching a low of 1,307 cases in 1978, the number of cases started to rise, to reach a peak of 3,811 cases (52.0 per 100,000 population) in 1992 (27, 36). Along with the increase in cases between 1985 and 1992, there was a shift in their age distribution. By 1992, reactivation of tuberculosis among the elderly no longer accounted for the highest percentage of total cases; instead, most cases occurred among persons aged 25–44 years (36, 37). The increasing incidence of primary and reactivated tuberculosis among HIV-infected adults contributed to this shift in age distribution, as did increasing numbers of young adult immigrants and refugees with tuberculosis.

In the 1960s (38) and 1970s (39), levels of single and multidrug-resistant tuberculosis were relatively low, although variation between localities and ethnic/
racial groups was considerable. In 1976, 8.6 percent of a national sample of \textit{M. tuberculosis} cultures showed primary drug resistance to one or more antimicrobial drugs, with the highest levels observed among Asian and Hispanic patients (20.7 and 15.0 percent, respectively) (39).

Although community-based transmission of multidrug-resistant tuberculosis had been documented earlier (40, 41), institutional outbreaks between 1988 and 1991 focused attention on the problem of emerging drug resistance. In 1989, after exposure in a residential drug-treatment facility to an HIV-infected man with smear-positive multidrug-resistant tuberculosis, 22 percent of contacts had documented skin-test conversions (42). Between 1988 and 1990, breaks in isolation precautions and delayed diagnosis of both tuberculosis and multidrug resistance contributed to the nosocomial spread of multidrug-resistant tuberculosis, primarily among HIV-infected persons, in several hospitals in New York City and Miami, Florida (43–45). By 1992, the Centers for Disease Control and Prevention (CDC) had investigated outbreaks of multidrug-resistant tuberculosis in eight hospitals and a state correctional system. The mortality rate for the 297 patients who had multidrug-resistant tuberculosis in these outbreaks was approximately 70 percent, and the median interval from tuberculosis diagnosis to death ranged from 4–16 weeks (43–46). More recently, however, lower mortality has been documented among multidrug-resistant tuberculosis patients who were promptly diagnosed and treated with appropriate drugs, especially if they were not HIV-infected (47, 48).

In response to outbreaks of multidrug-resistant disease, the CDC included as part of the National Action Plan to Combat Multidrug-Resistant Tuberculosis (49) the recommendation that local surveillance systems collect information on drug susceptibility patterns of initial and final \textit{M. tuberculosis} isolates from all persons with culture-positive tuberculosis. The CDC reported that initial drug susceptibility results were available for 81.7 percent of \textit{M. tuberculosis} isolates for 1994 cases—8.0 percent of isolates were resistant to at least isoniazid, and 2.2 percent were resistant to at least isoniazid and rifampin (34).

\textbf{International trends}

Trends in tuberculosis incidence in industrialized countries have varied. Case notification rates continue to decline in some Western European countries (Belgium, Finland, Germany, and Portugal) and in Japan (where, however, the rate of decline is slowing); rates have plateaued in other European countries (Great Britain and Sweden) and in Australia; and rates have increased in Denmark, Austria, Ireland, The Netherlands, Norway, Italy, France, and Switzerland (2, 50, 51).

Tuberculosis rates are higher in countries in eastern Europe and the former Soviet Union than in Western industrialized nations, and the quality of surveillance in eastern European and former Soviet bloc countries is variable (2). While tuberculosis incidence continues to decline in some Eastern European and former Soviet bloc countries, the rate of decline has slowed in several; in Romania and in some of the central Asian and Baltic countries, tuberculosis incidence rates have increased (2, 52).

Tuberculosis remains a leading cause of mortality and morbidity in developing countries. Seven percent of all deaths in developing countries are attributed to tuberculosis; 95 percent of the 90 million new tuberculosis cases which have occurred or will occur during the 1990s will be in developing countries (2, 32).

The impact of the HIV epidemic on tuberculosis in sub-Saharan Africa became apparent during the 1980s when, after years of steady decline, reported cases of tuberculosis increased dramatically (2, 53). The great majority of the estimated 305,000 excess tuberculosis cases which have occurred worldwide and which are attributable to HIV infection have thus far occurred in Africa (31, 53). Because the largest proportion of the world's tuberculosis-infected people live in Asia, and because HIV infection is increasing in several large Asian cities, the number of people in Asia who could develop tuberculosis because of dual infection may multiply nearly sevenfold (54).

In some developing countries, low adherence rates and availability of antituberculosis drugs without prescription have led to rates of acquired and primary drug resistance which are higher than those seen in developed countries (2, 55). The spectre of rising multidrug-resistant tuberculosis, and especially of rifampin resistance, threatens to turn back the clock on tuberculosis treatment and control by 30 years, dimming the prospect for international control. Fortunately, as will be documented later in a description of New York City's recent experience, effective control programs have demonstrated that it is possible to both prevent and reverse increases in multidrug-resistant tuberculosis.

\textbf{ECONOMIC IMPACT}

The resurgence of tuberculosis is associated with economic costs which are staggering for both developed and developing countries. In the United States, a 1992 analysis estimated that the average hospital cost per tuberculosis patient was approximately $25,000 (56, 57); in 1990, it was estimated that inpatient care...
for patients with multidrug-resistant tuberculosis approached $100,000 per patient (40, 56). In New York City, Arno et al. (57) found that the public sector shouldered a large share of the $179 million spent in 1990 for tuberculosis-related hospitalizations (57).

Because the burden of tuberculosis in developing countries falls most heavily on adults during the most productive years of their lives, its cost in terms of the World Bank's latest development indicator (the DALY, or disability-adjusted life year) is enormous (31, 58). Treatment of tuberculosis in developing countries is an extremely cost-effective health intervention and an appropriate investment in development. The great expense involved in curing patients with multidrug-resistant tuberculosis means that spread of this form of the disease in developing countries puts tuberculosis programs back into the pre-antibiotic era, as ineffectively treated patients remain sources of infection in their communities.

REASONS FOR THE REEMERGENCE OF TUBERCULOSIS

Host Susceptibility

HIV infection. By the year 2000, it is projected that worldwide as many as 17,454,000 people will be infected with HIV, of which 1,495,000 will be in North America (59).

Some of the earliest epidemiologic evidence suggesting that HIV infection had contributed to the resurgence of tuberculosis was ecologic in nature—it was noted that the highest incidence of tuberculosis occurred in geographic areas and among racial/ethnic groups with higher numbers of cases of AIDS (60, 61). For example, between 1980 and 1989, New York had more AIDS patients than any other city, and the incidence of tuberculosis increased by 68 percent (60–63). Because HIV-infected persons have a high frequency of extrapulmonary tuberculosis, the increase in proportion of extrapulmonary cases which occurred between 1984 and 1989 may have been due to increasing incidence of disease in dually-infected persons (61, 63). That HIV infection greatly increased the risk for developing active tuberculosis was demonstrated most convincingly by the finding that progression to active tuberculosis is far higher among HIV-infected persons with positive skin tests than among persons infected only with tuberculosis (60, 64, 65).

HIV infection increases the incidence of active tuberculosis by increasing the risk of reactivation of latent tuberculosis, of rapid progression to active disease following recent infection with tuberculosis, and of exogenous reinfection (22, 32). Findings of clustered M. tuberculosis strains among HIV-infected persons in two separate studies (20, 21) suggest that much active tuberculosis in HIV-infected persons may be due to rapid progression of recent infection.

Delayed diagnosis of tuberculosis in dually-infected people may be caused by atypical presentation, sometimes resembling that of other opportunistic infections, on the chest radiographs of HIV-infected patients with pulmonary tuberculosis (44). Some reports have shown, however, that delayed diagnosis was more often due to errors in routine management than to atypical presentation (60, 66, 67).

A HIV seroprevalence survey of all patients who attended 20 tuberculosis clinics in cities throughout the United States between 1988 and 1989 revealed a median clinic seroprevalence rate of 3.4 percent, with highest rates (over 20 percent) in the Northeast and Atlantic coastal areas (68).

Substance abuse. Injecting drug use is a risk factor for the progression of tuberculosis infection to active disease (17), and the high prevalence of HIV infection among injecting drug users further increases that risk. Buskin et al. (69) found that, after adjustment for age and smoking status, heavy drinkers were twice as likely as nonhabitual drinkers to have tuberculosis.

Population migration

Migration from areas of the world with relatively high tuberculosis prevalence to areas with relatively low prevalence may be an important contributor to the rising incidence of tuberculosis in industrialized countries. In some of the western European countries, where tuberculosis rates have recently increased, large proportions of cases (38 percent in Denmark, 41 percent in The Netherlands, and 51 percent in Switzerland) occurred among immigrants (2, 50).

In the United States between 1977 and 1979, foreign-born persons accounted for 15 percent of tuberculosis cases reported from 11 sites (70). McKenna et al. (3) reported that, from 1986 to 1993, the United States experienced increases in the number and proportion of foreign-born tuberculosis cases, from 4,925 cases in 1986 (21.6 percent of the total) to 7,346 cases in 1993 (29.6 percent of the total).

California's recently approved Proposition 187 requires publicly funded health-care providers to deny nonemergency care to undocumented immigrants and to report them to government officials. Such legislation could lead to increased tuberculosis morbidity and mortality by deterring persons with active tuberculosis from seeking treatment (71).

Events which place large populations of dislocated, malnourished people in crowded living conditions are likely to increase tuberculosis case rates (2). Combat in El Salvador (72) and the former Yugoslavia, and
wars in parts of Africa, have lead to forced migrations and may facilitate the spread of tuberculosis.

**Living conditions**

*Homelessness.* Tuberculosis disproportionately affects the poor and disenfranchised, and has historically been associated with homelessness. In the 1980s and 1990s, the problem of homelessness in many American cities was exacerbated by the deinstitutionalization of the mentally ill (without development of community-based housing), the increasing scarcity of jobs for unskilled persons, and drug abuse (36). Transmission of tuberculosis may be increased by the housing of homeless persons in large congregate shelters (73). A survey of homeless men attending a shelter-based clinic in New York City showed that 42.8 percent of those screened were infected with *M. tuberculosis* and 6 percent had active disease (74). Clinical presentation of patients in one outbreak of multidrug-resistant tuberculosis in a homeless shelter in Boston, Massachusetts, as well as phage-typing of their *M. tuberculosis* cultures, suggested that exogenous re-infection rather than reactivation of earlier infection was mainly responsible for the outbreak, and thus provided evidence for transmission of tuberculosis within the shelter (22). Because taking antituberculosis drugs may be a low priority for homeless persons, and because many such persons may be quite mobile, the achievement of high treatment completion rates in this population requires a concerted effort on the part of public and private providers (73).

*Correctional settings.* Inmates are at increased risk for infection by tuberculosis and other respiratory diseases in poorly ventilated and crowded correctional facilities (36, 75), and because they are often afflicted by HIV-infection, substance abuse, and homelessness, they are also at increased risk for disease progression. Ensuring continuity of treatment for inmates with active tuberculosis, and appropriate management of their contacts within and outside the correctional system, is hampered by frequent movement between and within facilities and by unexpected discharges (36).

An outbreak of multidrug-resistant disease occurred among prisoners and a guard in the New York State correctional system (36, 76). In 1989, to address the increased risk of tuberculosis among prisoners, the CDC published recommendations for the control of tuberculosis in correctional facilities (36, 77).

**Demographic trends**

*Increasing urbanization in developing countries.* By the year 2000, 71 percent of the world’s urban population will live in developing countries; if present conditions prevail, one quarter of these city dwellers will live in extreme poverty (78). In some countries, certain health indices (e.g., nutritional status) are worse among the urban poor than among their rural counterparts (79). As more people live in the crowded and poorly ventilated dwellings common in slums of the developing world, rates of tuberculosis may increase still further. Mobility of residents and lack of accessible medical and public health services within some of these poor urban communities may make it difficult to implement tuberculosis control programs.

*Changing population age structure.* Regions with recent high rates of population growth now have increasing proportions of their population in age groups with the highest likelihood of tuberculosis morbidity and mortality. Even if age-specific tuberculosis incidence rates remain constant, therefore, numbers of tuberculosis deaths and new cases will increase in the developing world (2).

**Public health programs and medical practices**

The medical and public health establishments together share some responsibility for the resurgence of tuberculosis, as they countenanced the dismantling of tuberculosis control programs and neglected sound infection control practices (80).

Brudney and Dobkin (73) chronicled the series of cuts in public health expenditures in New York City which contributed to the abysmal 11 percent rate of therapy completion by tuberculosis patients at a public hospital in 1988. Hospital tuberculosis beds were eliminated, yet resources intended for outpatient care never materialized; in the midst of New York City’s fiscal crisis in the 1970s, state and federal funding for tuberculosis control activities also decreased. Reichman (81) popularized the phrase “the U-shaped curve of concern” to describe the interaction between public health funding and health indices—as incidence of a targeted condition decreases, public health funding diminishes to the point where the condition once again begins to increase. A major decline in funding occurred when federal project grants, specifically for tuberculosis control, were replaced by block grants to the states, resulting in reallocation of federal monies previously used for tuberculosis control to other programs (81).

Medical mismanagement of patients with multidrug-resistant tuberculosis (for example, through late diagnosis, treatment with drugs against which tuberculosis organisms are resistant, or failure to administer medication in a program of directly observed therapy) may cause these patients to remain infectious longer (24, 44).
Lapses in adherence to guidelines for preventing tuberculosis in health-care settings have caused several nosocomial outbreaks of drug-susceptible and drug-resistant tuberculosis among patients and health-care workers (43-45). As summarized by Menzies et al. (82), factors which facilitated transmission of tuberculosis in hospital included delayed diagnosis (which leads to late institution of isolation), poor ventilation with positive pressure isolation rooms, and aerosolization of bacilli through procedures such as mechanical ventilation, bronchoscopy, and autopsy.

The resurgence of tuberculosis has also been facilitated by failure on the part of the medical and public health professions to make adequate and appropriate use of a simple tool, tuberculin skin testing (83), and to follow up with preventive therapy for infected patients at high risk for progression to active disease.

**IMPLICATIONS FOR CONTROL**

**Effective treatment of active disease**

The cornerstone of an effective tuberculosis control program is the detection and treatment of persons with active tuberculosis, particularly smear-positive disease. The World Health Organization (84) and the CDC (14) recommend short-course (6-8 month) therapy, consisting of a 2-3 month multidrug initial phase followed by a 4-6 month continuation phase. Short-course regimens have proven more cost effective than conventional regimens of 12-18 months, and patients are far more likely to complete shorter courses of treatment.

To help ensure that recommended regimens are completed, directly observed therapy has been advocated internationally as the standard of care (84). This simple intervention (i.e., having a specially trained worker observe patients as they swallow each dose of their antituberculosis medicines) has been found to reduce the frequency of primary and acquired drug resistance and relapse (85). By reducing the emergence of resistance to rifampin, directly observed therapy ensures that one of the most effective weapons in our antituberculosis armory remains useful for the next generation of tuberculosis patients. Savings accrued through preventing the emergence of multidrug-resistant tuberculosis more than compensate for costs of implementing directly observed therapy programs (86). With almost 1,400 fewer tuberculosis cases, including 300 fewer multidrug-resistant cases, in 1995 than in 1992, New York City saved hospitalization costs of more than $40 million in the past year alone, and more than $110 million since 1992 (87).

In 1993, the World Health Organization declared tuberculosis a global health emergency (5). They emphasized both the large death toll from tuberculosis, which kills more people than any other single infectious agent, and that tuberculosis is easily curable. In the years since this declaration, funding for tuberculosis control has increased and some national programs have improved their structure and management. The World Health Organization promotes a strategy of directly observed therapy, short course (DOTS) (84). The "S" for short course could also represent other critical elements of a control strategy—Smear-based diagnosis, with quality assurance of microscopy findings, Sputum examinations for follow-up to document cure, and Systematic monitoring with Simplified registers to ensure program accountability. The World Health Organization estimates that in the decade of the 1990s, more than 30 million people will die from tuberculosis. Many of these deaths could be prevented using directly observed therapy.

**Screening and prevention**

Adherence to, and completion of, a course of preventive therapy by persons infected with tuberculosis has been documented to be highly effective in preventing progression to tuberculosis disease (88). Preventive therapy becomes more complicated in cases of exposure to drug-resistant cases and infection with *M. tuberculosis* strains that are possibly drug resistant. When the infecting strain is thought to be resistant to isoniazid but susceptible to rifampin, rifampin may be used for preventive therapy (89). If the infecting strain is thought to be resistant both to isoniazid and rifampin, infected contacts should be categorized according to their risk of developing active tuberculosis—those at high risk should receive preventive therapy with two drugs to which the probable infecting strain is susceptible, though the efficacy of such preventive regimens remains to be determined; "watchful waiting" may be more appropriate for those who are not at such high risk (90).

In developing countries, resources must be prioritized for case detection and improvement of cure rates among smear-positive cases. Preventive therapy, however, may be appropriate for identified HIV-infected persons (84). In areas with high prevalence of HIV infection, institution of effective preventive therapy programs may prolong the productive lives of young adults, helping to maintain family and social structure.

**Infection control in health-care settings**

The infection control guidelines issued in 1994 by the CDC (90) recommend a "hierarchy of control measures" to decrease transmission of tuberculosis. The most important level of the hierarchy includes...
Interventions for HIV-infected persons

Measures must be taken to reduce the exposure of HIV-infected persons to those with infectious tuberculosis, and to improve tuberculosis prevention and treatment for HIV-infected patients (36). Persons with infectious tuberculosis should not be housed in congregate settings, and HIV-infected individuals should not be housed near persons with tuberculosis (36).

Improved screening and treatment services for immigrants and refugees

The increasing proportion of foreign-born tuberculosis patients among cases counted in the United States highlights the need for more effective international control programs and for increased support of such programs by developed nations. Improved management of persons entering the United States with active tuberculosis requires better screening of immigration applicants overseas, better communication of screening results to public health authorities in the United States, and better evaluation by local health-care providers of immigrants with suspicious chest radiographs but negative sputum smears (3). Location and evaluation of recent immigrants will require greater cooperation between local health departments and the US Immigration and Naturalization Service. Reduction of rates of tuberculosis infection, however, must be accomplished overseas.

Surveillance

Effective tuberculosis control requires that resources be allocated for surveillance as well as for direct service delivery. Population-based surveillance can improve case management and allow accurate monitoring of trends in tuberculosis and multidrug-resistant tuberculosis. Surveillance should include information on susceptibilities of M. tuberculosis, where feasible.

The Tuberculosis Epidemic in New York City: Analysis and Response

Because the upsurge in New York City of tuberculosis cases preceded the national epidemic by 6 years, the city offered a laboratory for analysis of contributing factors and for piloting interventions. We outline below how some early epidemiologic observations were translated by the health department, with guidance from the CDC, into new policies and programmatic interventions, and describe changes in the course of the tuberculosis epidemic in New York City.

Then, from the perspective of health department-based tuberculosis controllers, we suggest avenues for further epidemiologic study.

A survey of all M. tuberculosis isolates in New York City in April 1991 showed that the proportion which were drug resistant had increased dramatically since the last survey 8 years earlier (24). By 1991, 19 percent of tested isolates showed resistance to two or more drugs, and 26 percent to at least isoniazid.

In response to these findings, the New York City Department of Health strengthened its surveillance operations by mandating, in 1991, that results of any susceptibility tests performed be reported to the health department, and incorporating into its routine functions active surveillance for positive cultures and susceptibility results at mycobacteriology laboratories. The health department thus became a source of essential information for physicians throughout the city who could call with questions about prior treatment and susceptibility results of their patients.

Simultaneously, political leaders were informed about the impact that an epidemic of drug-resistant tuberculosis could have on the city, and on methods for control. It was emphasized that, unlike many other health and social problems, tuberculosis was curable and the epidemic reversible.

Recognizing that the single most important step toward controlling the tuberculosis epidemic and the emergence of multidrug resistance was treatment of active cases until completion of therapy, the Bureau of Tuberculosis Control emphasized directly observed therapy and instituted cohort reviews to monitor the therapy of every active tuberculosis case in New York City. Directly observed therapy was established as the standard of care at New York City chest clinics, and health-care providers outside the public system were informed about how to refer their patients into directly observed therapy programs, which were established by both the New York City and the New York State health departments. For those few patients who are unable or unwilling to adhere to prescribed treatment, a credible threat of detention was established, with passage of regulations which balanced individual lib-
erties against protection of the public safety—a locked tuberculosis treatment ward was created at a municipal hospital.

During the early part of the tuberculosis epidemic in New York City, large numbers of HIV-infected persons were housed in commercial hotels while awaiting permanent placement. The health department established directly observed therapy and directly observed preventive therapy in the hotels for both HIV-infected and HIV-negative clients; high rates of patient adherence were achieved, in part through the use of financial incentives (36).

The impact of these interventions is reflected in figure 1. Since the peak of the recent epidemic in 1992, tuberculosis cases have declined by 35.8 percent, from 3,811 in 1992 (52.0 cases per 100,000 persons) to 2,445 in 1995 (33.4 cases per 100,000 persons) (87). Multidrug-resistant tuberculosis cases have declined by approximately 75 percent since 1992, from 441 (11.6 percent of the total) in 1992 to approximately 108 (4.4 percent of the total) in 1995 (27, 87, 91–93).

As the recent tuberculosis epidemic has been brought under better control, there has been a sharp drop in US-born cases, while foreign-born cases have continued to increase in number and in proportion of total cases. The number of foreign-born cases recorded in 1995, 1,010 (41 percent of the total), is 37 percent greater than the number reported in 1993, 739 when foreign-born cases comprised 23 percent of the total. The New York City Department of Health has established an Immigrants and Refugees Unit to improve follow up and treatment of persons who enter the United States with radiologic evidence of tuberculosis, assuring complete evaluation and treatment of more than 90 percent of such persons within weeks of their arrival in New York City.

Although there is a rich history of tuberculosis epidemiology and control, large gaps remain in both our knowledge about tuberculosis and in our ability to apply this knowledge to controlling the epidemic.

On the therapeutic side, an effective vaccine against tuberculosis would be one of the greatest medical discoveries of the century. Better antituberculosis medications would also be helpful—only a tuberculosis specialist would use the term “short course” for a treatment regimen lasting 6 months or more.

On the epidemiologic side, we know surprisingly little about where and why most tuberculosis infections occur. We cannot identify those smear-positive persons who are most likely infectious, although we know that there is marked variability between smear-positive persons in terms of the number of contacts they infect. We have only a poor understanding of host characteristics which help determine infection, and we do not know whether they differ from those which determine progression to disease. We do not know whether different strains of \( \text{M. tuberculosis} \) vary in their ability to be transmitted or in their virulence.

Although RFLP analysis has expanded our knowledge of the molecular epidemiology of tuberculosis, it has also raised many questions: Why do some strains appear to be common “background” strains? Why do some strains have few insertion sequences? Are some strains less genetically “plastic” than others?

Perhaps the most significant and intriguing area of our current ignorance centers on the proportion of patients with tuberculosis disease arising from recent transmission. Classically, only 10–20 percent of patients were thought to have been infected or reinfected...
within the 2 years before disease onset (80). Recent studies indicate that this proportion may be 30–40 percent (20, 21), and in New York City at the peak of the epidemic, it may have exceeded 50 percent (New York City Department of Health, unpublished data). It was because so much tuberculosis disease resulted from recent transmission that New York City was able to control the disease so rapidly—improving treatment outcomes quickly interrupted transmission of infection and progression to active disease.

In developing countries, on the other hand, most adults have already been infected with tuberculosis, and as a result may have some level of immunity. Thus, in high-prevalence countries, unless reinfection is common, the proportion of tuberculosis resulting from recent transmission may be lower. HIV infection adds to the complexity of this question. We believe that New York City experienced a biphasic HIV-associated epidemic. The first phase, beginning in the mid-1980s through the early 1990s, was associated with reactivation of disease in HIV-infected persons who had been infected with tuberculosis years or decades previously. The second, much more explosive, stage, from 1990 to 1992, was characterized by microepidemics in hospitals, prisons, and communities, with a very rapid increase in cases and as many as three generations of cases in a year. Whether this second phase would have been less marked if more HIV-infected persons had prior tuberculosis infection, and, thus, some degree of protective immunity, is unknown.

The proportion of patients with disease resulting from recent transmission is of great practical importance. If, in developing countries, only 10–20 percent of cases are from transmission in the past 2 years, then, no matter how effective the treatment programs, new cases are unlikely to decrease by more than 5–10 percent per year, although prevalence may decrease rapidly by cure of cases. If, on the other hand, 30–50 percent of cases are from recent transmission, as we think was the case in New York City, tuberculosis in developing countries may be brought under control much more quickly through intensive emphasis on identification of cases and completion of therapy, following the pattern seen in New York City, where US-born cases decreased by nearly two-thirds in 3 years.

In calling for the development of new methods for tuberculosis control, Comstock (94) pointed out that much of our knowledge on the natural history of tuberculosis comes from studies conducted in the early and middle parts of this century. New epidemiologic investigations are needed to answer basic questions about risks for infection and disease progression in the 1990s.

Maintenance of adequate tuberculosis control programs requires that policy makers and politicians continue the fight against tuberculosis. It remains to be seen whether the recent brush with a major public health disaster leads to any change in the "U-shaped curve of concern" (81). As our recent epidemic begins to recede, policy makers must remain aware that, as long as tuberculosis persists at unacceptably high rates in underserved groups here in the United States and in developing countries, the potential for a new epidemic remains.

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