Strategies to Prevent Tuberculous Infection and Active Disease

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There are many approaches to tuberculosis (TB) prevention, ranging from basic public health measures to technologically complex interventions. In the broadest sense, improvements in the standard of living, particularly less crowded housing and better health status overall, probably contributed the most to reducing the incidence of TB earlier this century and maintaining it since then at relatively low levels in the United States compared with many other countries. Over the past three decades, the development of effective medical treatment for TB has drastically reduced the period of infectivity in individuals with active disease and allowed for cure in the majority of cases treated (see chapter 5). Public health efforts to find cases of active TB, deliver curative treatment, investigate possible contacts of infectious cases, test them for infection, offer information about the disease, and deliver preventive treatment have become efficient means to break the chain of transmission (91). In hospitals, prisons, homeless shelters, and other congregate settings where infectious patients may be in close contact with others, infection control measures of various types are used to protect the uninfected from respiratory exposure to infectious individuals.

Once tuberculous infection occurs in an individual, measures can also be taken to lessen the chance that active disease will develop months or years later. Preventive treatment (after infection) and bacillus Calmette-Guerin (BCG) vaccination (before infection) are the two main approaches used to prevent the active TB.

This chapter examines three of these approaches—infection control measures to prevent transmission in institutional settings, preventive treatment, and BCG vaccination. The recent resur-

gence of TB, along with multidrug resistant-TB (MDR-TB) transmission and confection with human immunodeficiency virus (HIV), has brought some of the old issues in TB prevention to light and created new ones. Current issues and problems, along with developments in progress to improve each approach, are also summarized.

INFECTION CONTROL

In the past several years, a series of large outbreaks of MDR-TB in hospitals, prisons and other facilities have renewed concern about TB transmission and prompted debate over the need for and usefulness of various approaches to prevent further spread of infection (20,101,223, 348,350,352a). Thus far, more than 250 individuals contracted MDR-TB in these outbreaks, the majority of whom died within a few months of diagnosis. In nearly all cases, the outbreak strain was resistant to isoniazid (INH) and rifampin (RIF), the two most effective anti-tuberculous drugs. Some cases were resistant to seven drugs. Sixteen health-care workers (HCWS) and one prison guard also developed MDR-TB, seven of whom have died. Eighty percent of the patients, inmates, and staff who developed active disease in these outbreaks were known to be HIV-seropositive or otherwise immunocompromised (e.g., resulting from radiation treatment for cancer) (80,382). Epidemiologic investigations confirmed that the cases were acquired by airborne infection within the facilities.

At two of the hospitals, about a third of HCWS exposed to patients with MDR-TB were found to have been recently infected around the time of the outbreaks. At another hospital, more than 50 previously uninfected HCWS tested positive for tuberculous infection following exposure to hospitalized inmates with MDR-TB. Transmission of MDR-TB infection to HCWS in the other hospitals could not be determined because of a lack of comparative test results (324,382). While it is impossible to exclude the possibility that some of the HCWS may have acquired tuberculous infection outside of the hospital, it is assumed that most of the HCWS infections occurring during the outbreak periods resulted from exposure to infectious patients without adequate infection control measures in place.

It has been suggested that medical housestaff, nurses, and other HCWS have recently experienced high rates of new TB infection (151), but recent data on rates of tubercuIous infection among HCWS have not yet been published. Although tuberculous infection has long been recognized as an occupational hazard for HCWS, the magnitude of the risk of infection has not been well characterized in recent years because routine annual screening for tuberculous infection among most HCWS has been discontinued in many areas or is not collected systematically or is not reported publicly. Several surveys have reported higher rates of tuberculous infection among physicians and hospital personnel than the general population, though not all cases of infection could be identified as having been acquired through occupational, rather than community, exposure (15,109,234).

Some evidence indicates that HCWS in certain job categories are at higher risk of infection than other HCWS. A 1983 national survey comparing TB infection rates among physician trainees found that physicians training in pulmonary medicine had a greater risk of infection than similarly exposed physicians training in infectious disease (182). The higher risk was thought to be due in large part to the pulmonary physicians' likelihood of exposure to patients with pulmonary TB and involvement with certain invasive respiratory procedures (such as bronchoscopy and endotracheal incubation) that stimulate the patient's coughing reflex.

The Centers for Disease Control and Prevention (CDC) recommends that routine surveillance of HCWS by tuberculin skin testing be conducted to monitor for possible infection in health care facilities (359). The particular vulnerabilities of HIV-infected HCWS to occupational TB expo-

sure has recently prompted CDC and others to examine that issue (22,214).

Two features clearly distinguish the recent outbreaks from those of the past: undiagnosed or inadequately treated MDR-TB as a potent source of infection, and heightened vulnerability of immuocompromised individuals to rapid development of active TB. The fact that these outbreaks occurred in facilities in different regions of the country suggests that the problem is not specific to certain hospitals or local populations, but is a broader issue affecting individuals with HIV, HCWS, prison staff, and the community at large. The potential exists for nosocomial (acquired within the hospital) transmission of TB in many urban areas, given increasing numbers of hospitalized, incarcerated, and homeless individuals with acquired immunodeficiency virus (AIDS), rising rates of TB in these populations, and inadequate infection control measures for preventing the spread of infection within the facilities (80,87). Transmission of drug-susceptible TB may also be occurring, although it is less likely that such clusters would be recognized since they would be indistinguishable from most other cases in the community.

Investigations of the outbreaks revealed a common set of problems and deficiencies that allowed the disease to spread unchecked (20,87,223). Failure or delay in diagnosing TB in patients and inmates was cited as a major factor, One reason for this was the often unusual clinical and radiographic presentation of TB in individuals with AIDS, which may obscure or complicate the diagnosis. Further, a "low index of suspicion" for TB among HCWS unaccustomed to seeing patients with the disease was cited for HCWS' failure to order appropriate diagnostic tests upon admission so that potentially infectious patients could be isolated until they were determined to be noninfectious. In addition, laboratory procedures caused additional delays in obtaining diagnoses, confirmation, and drug susceptibility results. In one hospital, for example, a median of 15 weeks elapsed between the time patients' specimens were obtained and the time results were available due (223), in large part, to the slow growth rate of the bacilli.

Failure to render MDR-TB patients noninfectious through adequate treatment was another major factor in the outbreaks. In many cases, prolonged periods of infectiousness occurred despite treatment, either because the specific type of resistance was not yet identified and ineffective drugs were prescribed, or because the few remaining drugs available to treat patients with multiple resistance were not effective. The latter undoubtedly applied to the cases in which resistance to seven drugs was documented, but even in cases resistant only to INH and RIF, successful outcomes are far more diffficult to obtain (see chapter 5). Treatment failure then led to the persistence of symptoms (such as coughing), longer hospital stays, and a greater risk of transmission of infection to others.

Despite these serious problems, it is likely that transmission of tuberculous infection within the facilities could have been substantially reduced, if not totally prevented, by better use of recommended infection control measures. Investigations of the outbreaks revealed a number of common problems in applying and maintaining infection control measures. In various ways, respiratory isolation of infectious patients was either not achieved (i.e., the facility was not designed to handle infectious TB patients) or isolation was not consistently maintained. For example, ventilation systems permitted air from the patients' rooms to mix with surrounding areas rather than providing negative pressure relative to the corridors and other rooms. Often these systems recirculated the air within the facility rather than exhausting it directly to the outside. Patients who were in respiratory isolation sometimes left their rooms to walk to bathrooms down the hall, or their doors were left open to the corridors. Also noted was an insufficient number of properly equipped isolation rooms to accommodate the number of patients with suspected or confirmed TB. In some cases, isolation precautions were

Box 4-A-Summary of Recommendations for Preventing the Transmission of Tuberculosis in Healthcare Settings, 1992

Early identification and treatment of persons **with active** tuberculosis

- Maintain a high **index** of suspicion for TB to identify cases rapidly.
- **promptly initiate effective multidrug anti-TB** therapy based on clinical and drug-resistance surveillance data.

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

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

Surveillance **for TB transmission**

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

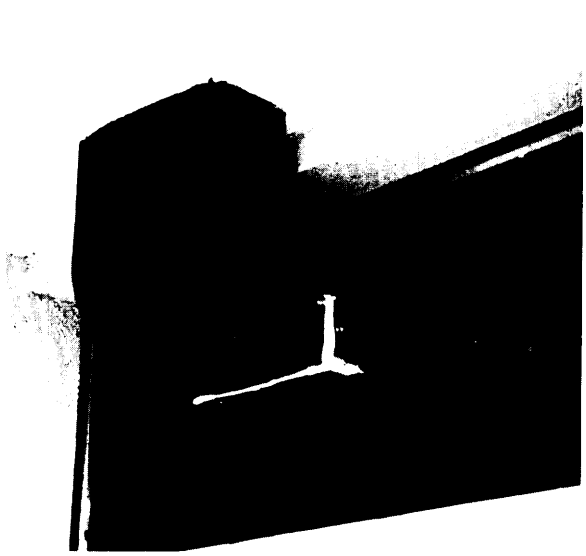
SOURCE: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, 1992.

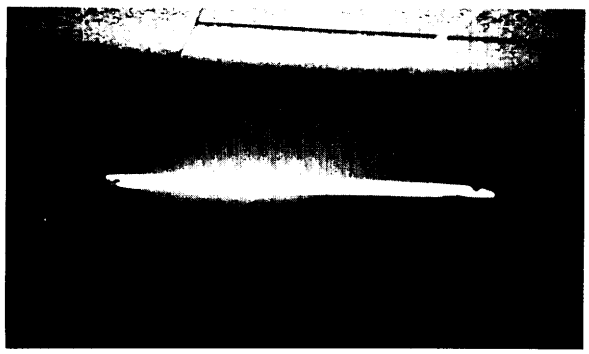
discontinued prematurely, while patients were still infectious.

A number of specific circumstances further increased the probability that infection would be spread. Most notably, two commonly used procedures-pentamidine aerosol treatment for patients with AIDS and sputum induction to collect samples for TB diagnosis-elicit forceful coughing, propelling infectious particles into the air unless contained in specially-designed booths (52). Both procedures have previously been associated with increased transmission of tuberCU1OUS infection in health care facilities (345).

Infection Control Measures

For many years, the merits and drawbacks of various infection control strategies have been debated. CDC recently updated and expanded its comprehensive guidelines for preventing transmission of tuberculous infection within hospitals and other facilities (359). These guidelines (which are now undergoing further revision) call for stricter application of a broad range of strategies (see box 4-A), some of which involve relatively simple modifications of procedures, while others involve the incorporation of sophisticated and expensive technologies. It is believed that such





CDC and NYU MEDICAL CENTER

Adequate ventilation and ultraviolet-B light can both decrease the likelihood of acquiring TB infection. Here an ultraviolet light (above) and an exhaust fan (left) have been ***added*** to *some hospital rooms housing patients with infectious TB to help control the spread of the disease.*

measures have not yet been widely adopted by health care facilities (254).

CDC'S guidelines emphasized a ''hierarchy of controls, ' emphasizing first the implementation of source control and administrative measures to reduce or eliminate the production of infectious particles or confine them to the patient where they originate<. g., rapid identification of infectious patients, prompt initiation of treatment, respiratory isolation of infectious patients, and instructing patients to wear masks or cover their mouths when they cough. These measures are generally considered to comprise the first and most important line of defense against transmission of tuberculous infection in institutional settings (21).

Additional measures to be used after the previous and administrative ones are in place included environmental controls for eliminating infectious particles after they have been released into the air (such as redirecting air flow and faltering or irradiating the air to remove infectious particles). Adequate ventilation generally includes directional air flow into isolation rooms from adjacent areas, air filtration, and direct exhaust of air to the outside. A minimum of six air exchanges per hour in isolation rooms is specified in CDC'S guidelines. Such measures are not necessarily easy to implement in modern facilities that are designed to recirculate air for energy conservation or in older buildings with no central air circulation. New devices are currently in development to filter and recirculate air within individual rooms, although their usefulness is far from demonstrated (205).

Disinfection of air with ultraviolet (UV) light sources has also been advocated (252). It is known from experimental data that tubercle bacilli are readily killed by UV-C irradiation (ultraviolet radiation of a shorter wavelength than UV-B present in sunlight), but data on efficacy in killing airborne tubercle bacilli under actual use conditions are lacking. Relevant variables include the intensity of the radiation, duration of contact, and humidity of the air. The minimum effective dose is unknown. Special fixtures have been developed for overhead installation but precise recommendations for their design and installation have not yet been developed. Such devices could be particularly appropriate where adequate ventilation and air filtration are impossible **to** attain. At present, a number of practical issues limit the effectiveness and application of such lights under different conditions; however, modifications are

likely to be made to permit wider use. These lights pose a potential risk for temporary but painful photokeratitis (inflammation of the cornea of the eye), which can result from exposure to high-intensity *W-C* light **(206),** so care needs to be taken to prevent direct exposure. The safety of properly designed UV-C lights on patients and HCWS under actual conditions has not been studied systematically. Anecdotal reports point to success with *W* systems in some high-risk settings (151).

The final type of measure discussed in CDC'S guidelines on infection control was personal protection devices, such as particulate respirators. Standard surgical face masks probably do not protect adequately against TB infection because they allow inhalation of airborne particles around the outside of the mask, although there is no evidence **that they** have failed to protect against infection. Masks designed to fit tightly around the nose and mouth (disposable particulate respirators) are believed to provide at least some protection against tubercle bacilli, but again, relevant data are lacking.

One of the most controversial aspects of infection control concerns the use of ''powered air purification respirators' (PAPRs), which are powered, halfmask respirators equipped with high-efficiency particulate falters. They are commonly used in industrial settings to protect workers from toxic fumes and other substances. The National Institute for Occupational Safety and Health (NIOSH), an agency within CDC, proposed in a recent report to the Occupational Safety and Health Administration, that PAPRs be used to protect high-risk HCWS from occupational exposure to tuberculous infection (371); NIOSH is mandated by the Occupational Safety and Health Act of 1970 to ''formulate science-based assessments of risk and preventive recommendations, which, if implemented, would assure that no worker develops illness as a consequence of exposure at work. Many experts have argued that such devices are unnecessary, uncomfortable, and impracticalin clinical situations (151,328).

To review the underlying data and practical implications of this recommendation, CDC convened a group of experts in TB infection control, biosafety, occupational safety and health, and representatives of labor groups and other organizations. William L. Roper, CDC'S director, concluded from the meeting that current evidence was inadequate to determine the effectiveness of such respirators in protecting HCWS from nosocomial transmission and that their routine use in health-care settings was not recommended (254).

There appear to be no clinical studies evaluating the efficacy of any of the various infection control measures to exist in preventing transmission of tuberculous infection (or other airborne infections). One reason for this is the difficulty of studying effects of single interventions in a clinical setting. Accordingly, precise judgments cannot yet be made about the efficacy or cost-effectiveness of the various measures. It is believed, however, that combinations of measures taken to improve infection control were responsible for the cessation of some of the outbreaks (e.g., in a Miami hospital) (219), the most important measure being rapid diagnosis and isolation of infectious patients. Nevertheless, data on the clinical efficacy, efficiency, and feasibility of the various measures will be needed in the long run to help guide these decisions.

In the short term, decisions about the necessity and appropriateness of individual measures in a given site will probably be determined largely by the prevalence of TB in that resident population, available resources, and the physical characteristics of each facility that influence the risk of transmission and the applicability of different interventions. Different combinations of interventions would be appropriate for different settings (see boxes 4-B through 4-D), e.g., acute care hospitals, prisons, HIV clinics, and homeless shelters. Infection control experts have recently recommended that such decisions be based on an individualized risk assessment for each local area, rather than on a universal set of requirements for both high- and low-prevalence areas (21).

Box 4-B—Changes in Infection Control Measures at Bellevue Hospital, New York City

Bellevue Hospital, one of New York City's largest municipal hospitals, admits mom than 400 patients with active TB per year to its 1,232-bed facility. To protect against transmission of tuberculous infection within the hospital, extensive changes have recently been made in its infection control capabilities and procedures.

In addition to standard ventilation, which provides two fresh air exchanges per hour in each mom, Bellevue's isolation and bronchoscopy rooms each have a window exhaust fan that allows four additional air exchanges per hour, with air expelled directly outside through a high-efficiency particulator air filter. This ventilation system is designed to create negative air flow relative to the corridor.

Each room also has been fitted with an air filtration system that recirculates air (at the rate of eight room volumes per hour) through a prefilter in tandem with a high-efficiency particulator air (HEPA) filter. This system is designed both to trap and remove airborne tubercle bacilli and also to facilitate mixing of the air, which enhances the bactericidal activity of ultraviolet lights.

The cost of these ventilation changes is estimated at $10,000 per isolation room.

Ultraviolet *(W)* light fixtures have also been installed in each respiratory isolation room and in some of the common areas where patients with active TB are likely to be present, including waiting and examination areas, bronchoscopy rooms, radiology areas, and chest clinics, Each isolation room has two 30-watt ***UV fixtures,*** mounted on the wall above eye level to provide *W* light for up to 200 square feet of floor space.

All hospital staff entering respiratory isolation rooms are required to wear a dust-mist particulate respirator. Health care workers performing certain high-risk procedures on patients with active TB, such as sputum induction, aerosolized pentamidine administration, and endotracheal incubation and suctioning, are required to wear a particulate respirator. Patients with active TB are required to wear masks only when outside of their isolation rooms.

SOURCE: W. Rem, Director and Professor, Department of Medicine, Division of Pulmormy and Critical Care Medicine, New York University Medical Center, New York NY, personal communication June 1993.

TUBERCULIN SKIN TESTING AND PREVENTIVE TREATMENT

Since the 1950s, when the anti-TB drug isoniazid (INH) was introduced and frost evaluated for efficacy in treating active TB (see chapter 5), it has also been possible to use this drug for the treatment of tuberculous infection to prevent subsequent development of the active disease. A number of clinical trials aimed at evaluating the efficacy of INH as a preventive treatment have shown over 90 percent effectiveness afforded by completion of 12 months of INH preventive treatment (IFT) among individuals with tubercu-1ous infection caused by INH-susceptible bacilli (64,113). Unless reinfection occurs later in life (generally unlikely in most U.S. populations), the benefits of IPT are presumed to be lifelong (1 13,131). IPT would not be expected to benefit individuals infected with INH-resistant tubercle bacilli.

Not all individuals with tuberculous infection are equally likely to develop active TB. Some develop it within a year or two after infection, while others harbor the infection for decades before becoming sick; most never develop the disease at all (249,300). The reasons for these differences are largely unknown, although some specific risk factors associated with a greater likelihood of progression have been identified. From a public health standpoint, the most important of these is HIV infection.

Public health efforts to prevent TB concentrate, for practical and economic reasons, on screening for tuberculous infection where it most likely is to be found—in identifiable high-risk groups (see tables 4-1 and 4-2). In total, an estimated 10 to 15 million individuals in the United States have

Box 4-C-infection Control Measures at Cook County Hospital, Chicago

Cook County Hospital (CCH), a 950-bed municipal hospital on Chicago's near-west side, was built in 1910. Its physical plant is antiquated: 30-bed open wards still exist, heating is provided by radiators, and there is no conditioning. Each year, approximately one-quarter of Chicago's newly diagnosed TB patients are diagnosed at CCH (168 patients in 1991); over 300 with active T.B were admitted to CCH in 1990. A long-suspectedproblern with occupational exposure to TB was recently documented in a study of tuverculin skin test conversions among CCH staff physicians; purified protein derivative conversions after 1 year of clinical work at CCH were noted among 46 percent of housestaff training in internal medicine, compared with 5 percent of other physician trainees (in emergency medicine, family practice obstetrics/gynecology, pediatrics, and radiology).

To address the problem, CCH implemented infection control measures according to the Centers for Disease Control and Prevention's 1990 guidelines, with adjustment for the hospital's physical plant, available resources, and patient care and health-cam workers (HCWS) concerns. All 51 single rooms with bathrooms were outfitted with fans that expel room air outside at a rate sufficient to provide 6 or more air changes per hour and negative air flow relative to the halls, and with a ultraviolet light. Common areas of the hospital where occupational exposure might occur, including the pulmonary function test laboratory and a labor and delivery room, were also outfitted with fans and UV lights.

A triage protocol was developed for CCH'S emergency room and walk-in clinics to speed identilfication and isolation of patients with known or suspected TB. Sputum induction booths were installed in the emergency room, HIV clinic, and the admitting ward. Emergency room laboratory personnel were trained and equipped to perform sputum smear examination on site to avoid sending specimens out to the microbiology laboratory for processing. Admitting procedures were changed so that patients with active TB could be admitted directly to isolation rooms without going through the common admitting ward.

Surgical masks were replaced with particulate respirator for all HCWS and visitors entering respiratory isolation rooms. HCWS were given training sessions on nosocornial transmission of TB and measures to protect themselves from infection. Two nurses were hired to serve as a roving employee health service team to offer tuberculin skin testing to HCWS at their worksites within the hospital.

The **total** cost of ventilation changes, UV lights, particulate respirators, and additional personnel was estimated at $350,000 in 1992, with ongoing annual costs of approximately $100,000. Since these infection control measures have been implemented, tuberculin skin test conversions among CCH housestaffhave dropped from 15 perwmt per year in 1991 to around 6 percent in 1992 and 1993. The tubenwlin skin testing program is currently reaching about half of the hospital's HCWS at risk for occupational exposure to 'I'B.

SOURCE: City of Chicsgo, Department of Health "Tuberculosis Morbidity and Mortality Report. 1991," Tuberculosis Control Program City of Chicago, Chicago, IL, August 25, 1992; L. Cocchiarélla . R. Muzaffar, "PPD "PPI) Conversion Among Housestaffin a Public Hospital" ***(abstract) American Review*** of Respiratory Diseases 145(4): (Suppl) A102, 1992; Rebecca M. Wurtz Director, Section of Epidemiology, Department of Infectious Diseases, Cook County Hospital, Chicago, IL, personal communication, June 1993.

tuberculous infection (357). However, the prevalence of tuberculous infection in specitlc populations and geographic areas is unknown, since the practice of regular screening among children and adults was abandoned during the 1970s and 1980s. No national surveys of tuberculous infection have been conducted in the United States in over 20 years. Recent small surveys of children in certain urban areas, however, have shown high rates of infection, particularly among foreign-born children (307). At present, only three States (Indiana, Missouri, and Kentucky) require reporting of tuberculin skin test results in children under six (307).

The medical community and public health officals in the United States have long advocated the policy of selective use of IPT. Recent increases in the incidence of TB in communities with high rates of HIV, along with evidence of rapid progression to active TB among those with

Box 4-D-infection Control Measures at the Rikers Island Correctional System, New York City

The tuberculosis case rate in the New York City correctional system is close to 600 cases per 100,000 population-three times the highest case rate in the general population of New York City. Montefiore Medical Center, a private not-for-profit hospital in the Bronx, in a tripartite agreement with the New York City Department of Health and Correction, provides comprehensive health services to the 14,000 men and women incarcerated on Rikers Island Correctional Complex. The Montefiore Rikers Island Health Servicea has worked closely with both agencies over the past few years on the implementation of infection control measures in the jails to curb the increase in TB. Currently, 125 individuals are being treated for active tuberculosis. The TB control program is challenged by the high turnover of the population, the short average length of stay of 59 days (with half of new admissions discharged from the system within a week), and the rapid transfer of inmates between different facilities. The creation of a respiratory isolation area, the development of a computerized tracking system, and the increasing ability of the Department of Correction to locate prisoners within the system have facilitated their ability to treat patients on TB medications.

To complement a TB control system that includes systematic screening, diagnosis, treatment, and contact tracing among inmates, Rikers Island has instituted a series of environmental changes in its facilities to help stop the spread of the disease.

In May 1992, the Department of Correction in conjunction with the Department of Health, Montefiore Rikers Island Health Services and other city agencies opened its first 42 isolation beds. There are 140 such respiratory isolation beds. Tent structures erected for housing of inmates were retrofitted to achieve levels of respiratory isolation that exceed all State, city, and CDC guidelines. Each room has approximately 10 to 12 air exchanges per hour, vents air to the outside, and has an anteroom with positive pressure. The corridor has approximately 18 air exchanges per hour. An extensive computer system monitors any cessation of negative pressure or other malfunction and makes appropriate adjustments or notifications.

All patients with suspected or confirmed TB are placed in respiratory isolation until TB is ruled out or until they are no longer infectious and have been evaluated for placement in the general jail population.

The facility has medical and nursing personnel 24 hours a day. Mental health services are provided daily for the many patients who also suffer from mental illness or who have mental health crises triggered by their isolation or adverse side effects from their medications. An estimated 60 percent are dually diagnosed with HIV infection and have complicated medical conditions. TB patients wear surgical masks when outside of their rooms; the more confining particulate respiratory masks may impair their breathing.

Upon release from jail, all patients receiving treatment for TB receive an appointment card that lists their medications, diagnosis, and the location of a community-based clinic that will provide directly obsexved therapy (DOT) to ensure continuity of treatment. These clinics include the Department of Health Chest Clinics and private providers who provide DOT through the State Medicaid program.

Due to the high prevalence of TB in connectional settings, all Montefiore employees receive a purified protein derivative (PPD) skin test every 6 months. Employees working in high-risk areas receive a PPD skin test every 3 months. Rikers Island has developed a computerized tracking system that automatically generates lists of those employees due for a skin test and documents the results of those tests, Rikers Island also provides education about TB for non-clinical staff including the appropriate use of particulate respirator masks worn in the presence of suspected or confirmed TB patients.

SOURCE: L. Richmond, Assistant to the Director, Montefiore Rikers Island Health Services, Montefiore Medical Center, The University Hospital for the Albert Einstein College of Medicine, New York NY, personal communication, 1 9 9 3 .

Table 4-l—Risk Factors for Tuberculous Infection

- Close contact with infectious tuberculosis cases (e.g., in the same household).
- Immigration from areas **of high** TB prevalence (i.e., parts of Asia, Africa, Latin America, and the Caribbean).
- Low- income status (including homeless people and migrant farm workers).
- Racial or ethnic minority (including African American, Hispanic, Native American).
- Substance abuse (especially alcohol and intravenous drugs).
- Residence in correctional institution, nursing home, mental institution, or other long-term care facility.

SOURCES: A.B. Bloch, H.L. Rieder, G.D. Kelly, et al., "The Epidemiology of Tuberculosis in the United States. Implications for Diagrmsis and Treatment," C/inics *in Chest* **Medicine 10(3):297-313, 1989; U.S. Department of Health and Human Services, Public Health Servke, U.S. Centers for Disease Control and Prevention, "Screening for Tuberculosis and Tuberculous Infection in High-Risk Populations. Recommendations of the Advisory Committee for Elimination of Tuberculosis," Morbidity and Mortality Weekly Report 39(RR-8):1-12, 1990.**

both HIV and tuberculous infection (278,290), have prompted renewed calls for expanding the use of PT. Even in many developing countries, where IPT has never been feasible because of the sheer number of people involved and the lack of adequate resources to deliver treatment (387), the escalating cost of treating the enormous number of active cases expected in the near future now makes IPT appear to be a relatively less expensive option for controlling TB (76,202,203).

For several decades, it has been theoretically possible to prevent the majority of new TB cases in the United States with the available diagnostic and preventive treatment methods. As TB has receded from the general population and become more concentrated among particular populations defined by ethnicity, race, geography, and age (see chapter 3), such targeted efforts at prevention should have become more feasible (28). However, because of limited resources available to TB control programs, controversies about adverse effects of IPT, problems with access to medical care, difficulties in ensuring completion of lengthy treatment regimens, among other reasons, IPT has not been widely applied, even in the high-risk populations for which it is most highly recommended (2,17,1 15,381). According to national data collected by CDC, fewer than half of all individuals with tuberculous infection identified by TB control programs through contact investigation receive an adequate course of preventive treatment (11 1).

Notable efforts have recently been made in some areas to overcome these obstacles, as in a program to offer IPT under direct observation to residents of a Seattle homeless shelter (208). In a nationwide effort involving 25 sites, CDC recently funded a project to evaluate the feasibility of onsite screening for tuberculous infection and for provision of IPT for clients at drug-treatment centers and inmates at Federal and State correctional facilities (355). Among the more than 38,000 individuals tested, 16 percent were found to have tuberculous infection (13 percent of drug-treatment clients and 25 percent of inmates); 66 percent of the infected drug-treatment clients, compared with 94 percent of infected inmates, subsequently completed IPT. Although the project showed that screening could be successfully conducted at these sites, ensuring completion of

Table 4-2—Fiisk Factors for Progression from Tuberculous Infection to Active TB

- **Symptoms suggestive of** TB.
- HIV infection.
- Previously untreated TB,
- Underweight (at least 10 percent below ideal body weight).
- Medical conditions known to increase the risk of **TB once infected (e.g., silicosis, diabetes mellitus, chronic renal failure, gastrectomy, some forms of cancer, treatment with immunosuppressive agents).**
- **Extremely young age.**

SOURCES: A.B. Bloch, H.L. Rieder, G.D. Kelly, et al., "The Epidemiology of Tuberculosis in the United States. Implications for Diagnosis and Treatment," *Clinics in Chest* **Medicine 10(3):297-313, 1989; U.S. Department of Health and Human Services, Centers for Disease Control, "Screening for Tuberculosis and Tuberculous Infection in High-Risk Populations. Recommendations of the Advisory Committee for Elimination of Tuberculosis," Morbidity andA.forta/ity Week/y Report 39(RR-8):1-12, 1990.**

CENTERS FOR DISEASE CONTROL AND PREVENTION

The TB skin test, **in** *which a purified protein derivative is injected under the skin, produces a reaction like the one on the right in about 95 percent of immunocompetent individuals infected with the bacilli that cause TB. The test detects infection in a much small percentage of peep/e with HIV or other types of immunosupression.*

IPT still posed substantial difficulties in the drug-treatment setting.

The following section briefly describes the available methods for identifying individuals with tuberculous infection and for preventing the development of active TB.

Identifying Individuals with Tuberculous Infection

At present, methods for directly detecting the presence of tubercle bacilli in the body (see chapter 5) are applicable only for those with active TB, which normally creates a large number of bacilli in the body. By contrast, latent tuberculous infection creates much smaller populations of bacilli in the body and is not directly detectable with current microbiologic methods (isolating, culturing, and identifying populations of organisms) or histologic methods (staining a sample containing bacilli and visually identifying them under the microscope).

The preferred means to identify individuals with tuberculous infection is the tuberculin skin test, developed in the 1890s and still in widespread use (268). As an indirect approach, the tuberculin skin test is designed to show a type of immune response (a delayed-type hypersensitiv-

ity (DTH) response mediated by T-lymphocytes) to tuberculin, proteins derived from a culture of tubercle bacilli (see chapter 2). Normally, the immune system of individuals infected with tubercle bacilli will be sensitized to tuberculin and will react (within 48 to 72 hours) to the test substance, as shown by a small raised area (usually greater than 10 mm) in the skin on the arm where the tuberculin is given. Individuals without previous exposure to tubercle bacilli should show no reaction on the skin to the test substance, unless they have had BCG vaccination or have been infected with nontuberculous mycobacteria.

For various reasons, responses to the tuberculin skin test are not ''all or nothing' small reactions (5 to 10 mm) could mean infection in some and no infection in others. The test results must be interpreted in light of the individual's risk for TB infection, previous BCG vaccination, age, immunocompetence, and exposure to mycobacteria other than tubercle bacilli, among other factors. A complex system for interpreting the test result for each individual based on risk factors, medical history, and size of the skin reaction has been developed (7,357).

In healthy individuals, the test has about 95 percent sensitivity and variable specificity (18,268). In individuals who are infected with HIV or who are acutely ill (with various viral infections, or, ironically, acute or overwhelming TB), its sensitivity is consistently lower or nonexistent; the test cannot be used in these circumstances to exclude the possibility of tuberculous infection (18,361). For practical purposes, negative results in individuals with late stage HIV me uninterpretable (126,143,361). Unless the tuberculin skin test is given early in the course of HIV infection, detection of true infection is much less likely, and thereby reduces the efficacy and usefulness of preventive treatment. CDC recommends that since HIV-infected individuals with tuberculous infection are at such high risk for developing active TB, IPT should be given to those with HIV who show small skin test reactions of 5 mm or more or to those who are anergic and who are at high risk for tuberculous infection (344). Others have argued for bypassing skin tests in HIV-infected individuals and offering IPT to all individuals with AIDS where the prevalence of tuberculous infection is high (165).

The accuracy of the tuberculin skin test also varies with the prevalence of tuberculous infection in the population being tested. In high prevalence groups (more than 25 percent infected), such as immigrants from high-prevalence areas of Asia, Africa, or Latin America, and recent, close contacts of active cases, tuberculin screening is generally considered to be informative and reliable. For many other populations, prevalence data are likely to be unavailable, so unless an individual is known to have been exposed to an infectious case or has other risk factors, interpreting the results of tuberculin skin tests is problematic. In very low-risk populations (prevalence of tuberulous infection less than 1 percent), such as the general U.S. adult population or, in many areas of the country, children entering school, the vast majority of positive results are likely to be falsely positive (18). Screening in these populations could lead to unnecessary isolation, testing, and treatment based on an erroneous presumption of TB. For that reason, tuberculin skin testing in low-risk populations is generally discouraged.

Limitations of the current tuberculin skin test may become increasingly apparent as screening is expanded to include more individuals with HIV, including homeless individuals, foreign-born individuals, and others. Improvements in the diagnostic capabilities for detecting infection are clearly needed. Specifically, a test that can be read without a long waiting period would be particularly useful in institutional settings where individuals may be difficult to locate several days later (e.g., jails and homeless shelters). A test that accurately and directly detects the infection and identifies the drug resistance pattern of the bacilli without depending on adequate immune re-

sponses to the infection would be essential for use in HIV-infected populations.

Isoniazid Preventive Treatment

The purpose of preventive treatment is to eliminate the living tubercle bacilli in the body, thereby reducing the risk of subsequent disease. These bacilli may be growing slowly, intermittently, or not at all. A treatment regimen based on the use of a single antibiotic drug for a long period of time (6 to 12 months) is necessary to substantially reduce the risk of subsequent disease. The chance of creating drug resistance in the process is considered low, since there are so few bacilli to begin with and only a remote chance that any drug-resistant ones are present. In the absence of disease, distinguishing infection with drug-resistant bacilli from infection with drug-sensitive bacilli is impossible with current diagnostic methods. Epidemiologic investigations could suggest the likelihood of drug resistance, and assist with the choice of drugs to be used in preventive treatment (13).

So far, INH is the only drug evaluated in human studies for efficacy in preventing progression of tuberculous infection. The American Thoracic Society, medical section of the American Lung Association, recommendations state that when INH cannot be tolerated, or if infection with INH-resistant bacilli is suspected, rifampin (RIF) can be used for preventive treatment in high-risk individuals (6,13). Data on the efficacy of RIF and other antibiotics in preventing TB are currently lacking. Animal data suggest that shorter regimens, e.g., 2 months of twice-weekly treatment, using RIF and pyrazinamide (PZA), are good candidates for study (150), and several clinical trials are in progress (e.g., in Haiti) (60). A recent placebo-controlled trial conducted in Hong Kong found that 3 months of RIF was as effective as 6 months of INH in preventing the onset of TB (138). It is not yet known whether regimens consisting of RIF and PZA for 2 months' duration will replace longer courses of INH for preventive treatment (131). The effectiveness and costs of these new approaches have not been examined in detail.

The efficacy of INH in preventing TB is well established through a series of randomized controlled trials involving more than 125,000 subjects. Results indicate that IPT can reduce the risk of active TB among adults with tuberculous infection by as much as 90 percent in those who complete a full course of treatment and by about 50 to 60 percent if those who don't complete treatment are included in the analysis (1 3,97, 148). In children, the reduction in risk approaches 100 percent (142).

The efficacy of preventive treatment for TB in HIV-infected individuals with tuberculous infection has not yet been reported from controlled trials (although such trials are in progress in Zambia (383) and elsewhere) (202). Preliminary results from one of the trials suggest that a 12-month course of IPT can lead to a 89 percent reduction in TB among HIV-infected individuals compared with a placebo. In its 1989 report on TB and HIV infection, CDC recommended that HIV-infected individuals with tuberculous infection should be offered IPT for a 12-month period, based on evidence of effectiveness in HIV-negative populations and observations of success with curative treatment for active TB in HIV-infected patients (344). Subsequent observational data supported the use of IPT in HIV-infected patients (279). The National Institute of Allergy and Infectious Diseases (NIAID) is currently supporting two clinical trials to evaluate the efficacy of IIT in HIV-infected individuals (96).

One of the main reasons to evaluate alternatives to INH in preventive treatment is to avoid the risk of rare, though serious, adverse effects from the use of INH (in individuals who are not sick with TB and not infectious to others). The major concern is with toxic effects on the liver and potentially fatal hepatitis. Although the drug is well tolerated in most cases, particularly in children, between 2 to 3 percent of adults overage 50 develop liver inflammation (which can lead to

Table 4-3-Criteria for Determining Need for Preventive Therapy for Persons with Positive Tuberculin Reactions, by Category and Age Group

Category	Age group (years)	
	<35	>35
With risk factor[a]	Treat at all ages if reaction to 5TU PPD 210 mm (or 25 mm and patient is recent contact, HIV-infected, or has radiographic evidence of old TB).	Treat at all ages if reaction to 5TU PPD 210 mm (or 25 mm and patient is recent contact, HIV-Infected, radiographs radiographic evidence of old TB).
No risk factor. High-incidence group[b]	Treat if PPD >IOmm.	Do not treat.
No risk factor. Low-incidence group	Treat if PPD >15mnF.	Do not treat.

a Risk factors include HIV infectlon, recent contact with infectious person, recent Skintf3st conversion, abnormal chest radiograph, intravenous drug abuse, and certain medical risk factors (see text).
b High-incidence groups include foreign-born persons, medically underserved low-income populations, and residents of long-term care facilities.
c Lower or higher cut points may be used for identifying positive reactions, depending on the relative prevalence Of *Myobacterium tuberculosis* infection and nonspecific cross-reactivity in the population.
KEY: PPD = purified protein derivative; TU = tuberculin unit.

SOURCE: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention, "The Use of Preventive Therapy for Tuberculous Infection in U.S. Recommendations of the Advisory Committee for Elimination of Tuberculosis," *Morbidity and Mortality Review* 29(RR-8):6-8, 1990.

hepatitis if the drug is not stopped as soon as serum tests indicate the condition). A recent review of available case reports of fatal hepatitis possibly associated with INH indicates that such cases seem to be decreasing infrequency since the early 1970s (possibly because of more limited use of IPT, but also because of better biochemical and clinical monitoring of patients on IPT). However, such cases are still occurring, especially among African American and Hispanic women (294). The postpartum period may be an especially high-risk time. Factors that increase the risk of INH-associated hepatitis may include alcohol or drug abuse, previous hepatitis, or simultaneous use of hepatotoxic drugs. The magnitude of the risk, and the specific factors contributing to it, are still largely unknown.

If IPT were harmless, there would be little controversy about offering it to virtually anyone with tuberculous infection would exist. Since it is not, disputes over balancing the risks and benefits in low-risk populations are difficult to resolve (65). A series of decision analyses comparing the risks of INH-induced hepatotoxicity with the benefits of preventing TB in low-risk populations have been published, with conflicting results (102,164,220,256,292,320). CDC developed criteria for determining how the use of IFT could be limited to minimize the risks of hepatoxicity and benefit those at highest risk. These criteria recommend avoiding use of IPT in low-risk populations (see table 4-3). Until alternative regimens with drugs posing fewer and less serious side effects are available, IPT will likely be limited to these high-risk groups.

BCG VACCINATION

Since the early 1950s, the World Health Organization (WHO) has advocated widespread vaccination with BCG as a preventive measure against TB. At present, over 70 percent of children worldwide are given BCG in infancy or childhood (386). Recommendations for vaccination schedules differ widely among countries, ranging from a single dose at birth (recommended by the WHO Expanded Programme on Immunization) to a single dose at age 13 (United Kingdom Policy) to repeated vaccinations through-

out childhood (as in many Eastern European countries). BCG vaccination is compulsory in 64 countries and officially recommended in 118 others (58). As a result of these policies, BCG has become the most widely used vaccine in the world, with more than 3 billion doses administered over the past 40 years (98).

Despite its widespread acceptance and long-standing use, controversy persists concerning the variation and lack of predictability in BCG'S protective efficacy against TB in different populations. In part because of questions about its efficacy and low expected utility in populations in which the rate of transmission of TB is relatively low, BCG vaccination has never been applied on a national basis in the United States. As of 1988, when CDC'S Immunization Practices Advisory Committee and Advisory Committee for Elimination of TB last issued recommendations on BCG use, a very circumscribed role for BCG vaccines was specified (343), Reexamination of the policy, along with renewed calls for development of an improved vaccine, are likely in the near future as CDC and others consider options for containing the current spread of TB.

This section briefly summarizes BCG'S nature, intended effects, efficacy and safety, overall impact, and policy issues concerning its role in TB control efforts in the United States. Because of the enormity of the international literature on this subject dating back to the 1920s, only a brief overview is possible in the context of this report.

The Nature and Rationale for BCG Vaccines

BCG refers to several strains of *Mycobacterium bovis* derived from the original strain, which was produced about 70 years ago in France by Albert Calmette and Camille Gue'rin at the Pasteur Institute. Using a virulent strain of *Mycobacterium bovis, the* bacillus that causes tuberculosis in cattle and in humans.[1] Calmette and Guérin produced an attenuated bacterial isolate (a strain of tubercle bacilli unable to cause TB). Their product, consisting of a liquid preparation of live bacilli, was first used as an anti-TB vaccine in French subjects (infants born to mothers with TB).

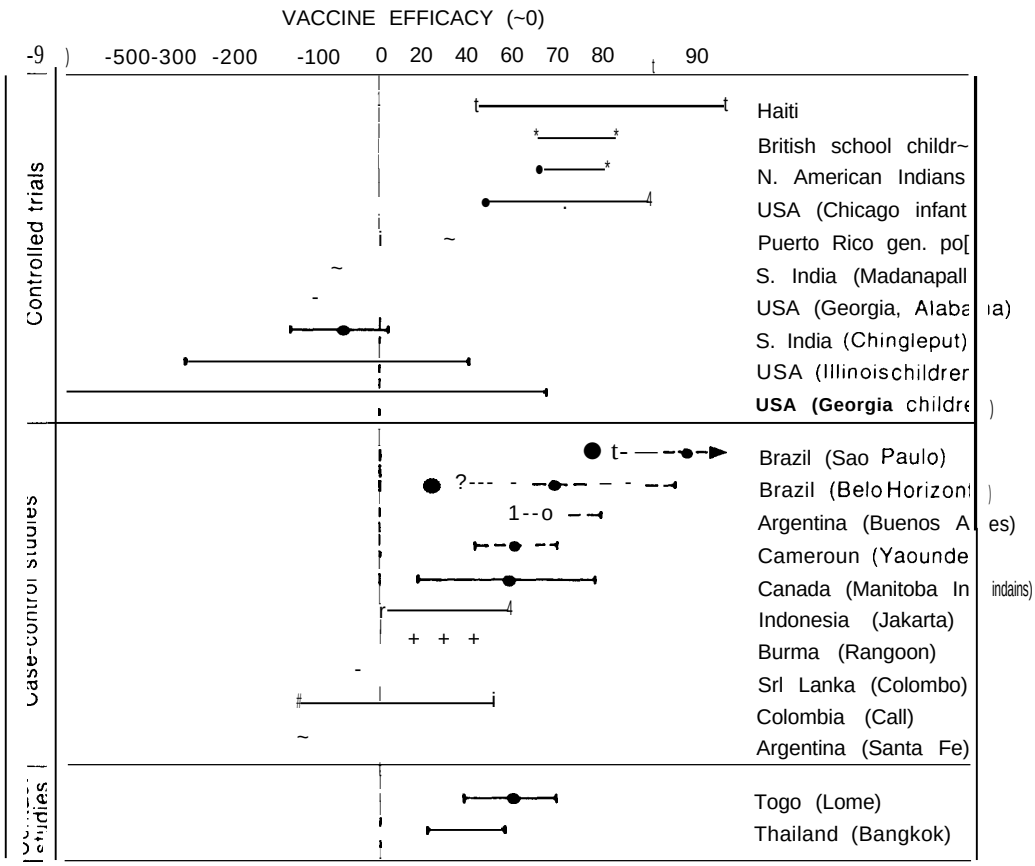
Literature describing this early work often notes that the original culture of BCG bacteria was never saved, i.e., no bacteriologically identical samples were made. Instead, the original strain was distributed to several different laboratories around the world, where it was maintained under different conditions, thereby leading to the generation of bacteriologically distinct strains. As a result, vaccines currently marketed as BCG actually comprise a group of related vaccines with differing characteristics, e.g., potency. This is one of several issues complicating the interpretation of clinical trials in which BCG was evaluated for efficacy (see below).

One freeze-dried strain of BCG containing live bacteria (referred to as Tice) is currently manufactured and sold in the United States, with Food and Drug Administration approval for use in the prevention of TB (and recently also in the treatment of bladder cancer) (10). The Tice strain is administered by multiple puncture only, not by the intradermal method generally preferred for BCG vaccination.

It is generally believed that BCG does not prevent initial infection with tubercle bacilli. Instead, BCG enhances the cellular immune response to *M.tb*. (by mechanisms that are not fully understood), thereby lowering the risk of developing active disease. It also seems to reduce multiplication of bacilli and dissemination of the disease to various parts of the body, thereby lowering the risk of extrapulmonary TB (305). How HIV-related immunodeficiency affects BCG's initial or subsequent immunologic actions is not clear, However, because a functional T-cell im-

[1] *Mycobacterium bovis* can cause TB in humans who have extensive contact with infected animals or who drink milk laden with tubercle bacilli.

Figure 4-l Summmary of Estimates of the Efficacy of BCG Vaccines Against Tuberculosis



SOURCE: Reprinted with printed with permission from P.E.M/ fine, " The "The BCG Story: Lessons From the Past and Implications for the Future," Review of the Infectious *Diseases* 11 (Suppl. 2):S353-S359, 1989.

mune system is believed necessary for BCG to work, it is not known whether the vaccine would protect against TB in HIV-infected individuals (103).

Unfortunately, there is currently no reliable immunologic measure of protective immunity to TB following BCG administration, so it is difficult to monitor and evaluate its effects. Tubberculin sensitivity (by skin testing) following BCG (referred to as a BCG-induced DHT response) does not correlate with protective immunity to TB (98).

Efficacy and Safety of BCG Vaccination

Ten major randomized clinical trials and many nonrandomized studies of BCG vaccination have been conducted in various populations since the 1930s (summarized in figure 4-1). These trials are noteworthy not only for their size (only the Salk polio vaccine trials involved more subjects), but also for the duration of followup. The most recent trial, begun in 1968, involved 115,000 subjects followed for 7.5 years in Chingleput, South India (327).

Despite the enormous international effort to determine the protective efficacy of BCG (defined as the percent reductionin risk of TB among BCG recipients, compared with similary exposed nonvaccinated subjects), the issue remains unresolved; a strikingly broad range of protective efficacy, from zero (or negative) to 80 percent, was found (98,99). As a result, there are major differences in expert opinion on the subject, and a continuing controversy surrounding the analysis of the data (59,98).

Why the vaccine worked well in some study populations and failed in others is still not known and may never be known. Various biological and statistical factors accounting for the variability have been proposed and debated, including:

- variations among the strains of BCG used in the studies;
- confounding immunologic effects of widespread infection with other types of mycobacteria commonly found in soil and tap water in some areas, some of which can induce a similar immunologic effect against tubercle bacilli as BCG;
- regional differences in virulence of the tubercle bacilli;
- nutritional and genetic differences in the populations studied; and
- methodologic differences in trial design (59, ***98,99).***

Some or all of these factors, or others not yet identified, may have influenced the trial results, producing observed differences in efficacy. Current efforts to conduct a meta-analysis of the data may clarify some of these issues (198). Development of a reliable animal model *to* compare potencies of the BCG strains currently available may be necessary to select vaccines likely to be potent in the human population and to avoid those likely to be affected (63).

The data from these studies suggest that BCG offers greater protection for children against disseminated forms of TB (including a reduction in incidence of TB meningitis and miliary TB that ranges from 52 to 100 percent) than it offers against pulmonary TB (58,134,343).

Side effects and adverse reactions to BCG vaccination are rare in immunocompetent individuals (179,343). The increasing prevalence of HIV in some populations, however, has raised concern over the safety of BCG vaccination in immunodeficient individuals since BCG is an attenuated live vaccine and thereby poses potential risks of dissemination in immunodeficient individuals (42,238). Case reports of serious complications of BCG vaccination in HIV-infected infants (141,210) and adults with AIDS (11,33,341) have been reported. CDC notes that HIV-infected individuals may be at greater risk for complications from BCG vaccine, but current data are insufficient to determine the magnitude of the risk and level of immunodefiency at which the effect might manifest (343).

Impact of BCG Vaccination on the Incidence of TB

Although BCG vaccination has long been conducted in many parts of the world with the intent of reducing the incidence of pulmonary TB in the population, its impact on the control of pulmonary TB is not easily discernible. The large burden of TB in many countries over the years suggests that even if BCG vaccination has reduced the incidence of TB (which some argue it must have, given the billions of doses administered over the years and some potential for benefit) (99), it is obviously not a sufficient strategy to prevent the disease. The degree to which it contributed to previous declines in TB incidence (e.g., in Western Europe) may never be known, given other contemporaneous factors, such as socioeconomic improvements and increased availability of anti-TB drugs. Within the next decade, the rising prevalence of HIV may substantially reduce the impact of BCG vaccination,

Most experts agree, however, that BCG may reduce the incidence of the serious (and noncontagious) childhood forms of TB (TB) meningitis and other disseminated forms of TB). In some high-risk countries, BCG vaccination may provide good protection against these forms of the disease, but it is not likely to prevent transmission of pulmonary TB among young and older adults, who are the main sources of infection to children and other adults in the population. Ironically, global BCG vaccination campaigns may have actually contributed more to complacency about TB over the years, with a corresponding decline in interest in developing better methods of prevention and treatment, than to TB eradication itself (98).

BCG Vaccination Policy in the United States

BCG vaccination of children or adults has never been carried out on a routine basis in the United States. CDC cites two main reasons for this policy-a low risk of tuberculous infection in the general population, and the variable efficacy of the vaccine (378). In its most recent policy summary, however, CDC does recommend selected use of the vaccine in certain high-risk infants and children such as those with negative tuberculin skin tests who are in unavoidable and close contact with infectious individuals and who cannot be treated with INH preventive therapy, or those who are continuously exposed to individuals with MDR-TB. CDC also recommends BCG vaccination in:

> ''. . . tuberculin-negative infants and children in groups in which the rate of new infections exceeds 1 percent per year and for whom the usual treatment and control programs are not effective. These groups include persons without regular access to health care, those for whom health care is culturally or socially unacceptable, and groups who have demonstrated an inability to use existing health care" (378).

It is not clear whether the rationale for this recommendation is narrow (i.e., to prevent the childhood disseminated forms of TB), or broad (i.e., to offer a prevention, albeit uncertain for those who are either unreachable or not covered by current TB control efforts). Previous policy statements issued by CDC and the American Thoracic Society made similar recommendations (6), although they were not limited to infants and children, also specifying ''alcoholics, drug addicts, migrants, and refugees" as those without regular access to health care for whom BCG might be appropriate (170).

BCG vaccination may itself cause subsequent reaction to tuberculin skin tests, thereby making interpretation of the skin test more difficult in some cases. Currently, no reliable method for distinguishing between tuberculin skin test reactions caused by BCG and those caused by tuberculous infection exists (378) but the reaction due to BCG is believed to wane after 3 to 5 years (307). In general, some judgments can be made on the basis of the size of the tuberculin reaction (with ''significant'' reactions more likely indicating true infection), the individual's risk of infection, presence of BCG "scar," and how long ago BCG was given (291,378). Framed as a policy choice between alternative strategies for TB prevention, skin testing and preventive treatment have long been favored in the United State over mass BCG vaccination, even though efforts to deliver preventive treatment have not been widely implemented.

In its 1988 statement on BCG, CDC reversed its 1979 recommendation for high-risk HCWs to receive BCG vaccination, citing a lack of evidence for increased rates of infection or tuberculin skin test conversion among HCWs (343). They opted instead for promoting greater use of skin testing and preventive therapy and of hospital infection control measures.

Because of possible risks of adverse effects from BCG vaccination among individuals with HIV, CDC did not recommend BCG vaccination for anyone known or suspected to be infected with HIV, except in selected populations where the risk of TB is high (343). Further data on

complications of BCG in HIV-infected individuals (most likely reported from developing countries) may help to clarify these issues for which there is little experience in the United States. Data on the efficacy of BCG in HIV-infected individuals are nonexistent. All previously mentioned clinical trials were conducted prior to 1980.

Issues Concerning Future Use of Vaccination Against TB

The current resurgence of TB in the United States highlights the continuing need for a vaccine that is effective and safe, particularly for individuals infected with HIV, who are at highest risk for developing active TB. Those who are tuberculin-negative and in close contact with individuals who have active, infectious MDR-TB, such as prison staff and inmates, HCWS and patients, and homeless shelter staff and residents, have the most to benefit from effective vaccination, along with HIV-seronegative individuals who are at high risk for becoming infected with HIV.

Until an improved vaccine is developed, an expanded role for BCG vaccination in HIV-seronegative (and ‘‘ asymptomat’ HIV-seropositive) groups needs to be considered in light of the risks, possible benefits to the affected individuals, and potential drawbacks to infection monitoring and preventive treatment efforts.

The need for new, improved vaccines against TB was noted in CDC’S recent “National Action Plan to Combat MDR-TB. ” Ideally, such a vaccine would effectively prevent infection progressing to active TB and would not interfere with interpretation of tuberculin skin testing (166). In order to develop and test a new TB vaccine, a number of unresolved issues in TB immunology may need to be addressed, including: identification of immunogenic and virulence components of the tubercle bacillus and which of these elicit protective immune responses, characterization of these immune responses, and development of animal models for TB prevention that correlate well with human responses (363,373). The possibility of deriving an effective vaccine against TB using a genetically engineered recombinant BCG vaccine containing antigen-encoding genes has been explored in recent studies (3,313). NIAID is currently funding several research efforts aimed at developing a new TB vaccine (see chapter 7) (104).