



accp consensus statement

Institutional Control Measures for Tuberculosis in the Era of Multiple Drug Resistance

ACCP/ATS Consensus Conference

A Joint Consensus Statement of the American College of Chest Physicians and the American Thoracic Society in cooperation with American Hospital Association; Centers for Disease Control and Prevention; National Heart, Lung and Blood Institute; and Society for Hospital Epidemiology of America

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AC/h=air changes per hour; BCG=bacillus Calmette-Guerin; CDC=Centers for Disease Control and Prevention; HEPA=high-efficiency particulate air; INH=isoniazid; MDR=multidrug resistant; NIOSH=National Institute for Occupational Health and Safety; OSHA=Occupational Safety and Health Administration; PAPR=powered air-purifying respirator; TB=tuberculosis; UV=ultraviolet; UVGI=ultraviolet germicidal irradiation

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The risk for transmission of *Mycobacterium tuberculosis* from hospitalized patients to other patients and hospital employees was well established by 1950. Before that time, the risk to hospital employees was debated and indeed minimized, perhaps for fear that acknowledging the risk would frighten young people away from health-care careers.¹ Heimbeck,² in 1928, was one of the first to demonstrate that nurses were at high risk of converting the tuberculin skin test and developing clinical tuberculosis (TB); of 220 tuberculin-negative nursing students, 95% had converted by graduation and 22% developed clinical TB. Subsequent reports from large hospitals in Philadelphia, New York, and Boston during the 1930s showed that most nurses working in these institutions converted their tuberculin skin test and were at risk of developing clinical TB at a rate much higher than were workers not involved in the health-care field.³⁻⁵ In 1930,

Myers⁶ made a series of recommendations for TB control for hospital employees that have relevance today, including tuberculin skin tests and chest radiographs for new employees, isolation of clinical cases, and having a high index of suspicion of TB among all new patients admitted to hospital. Gradually hospitals implemented these and other control measures as their benefits were demonstrated. But as highly effective chemotherapy for TB became the rule and preventive treatment became routine, the incidence of TB in the United States progressively declined, and the risk of TB infection and clinical TB among hospital employees fell sharply. As the risk became less and less, concern about this occupational hazard fell rapidly so that only scattered reports of hospital outbreaks appeared in the 1960s, 1970s, and early 1980s.⁷⁻¹⁰

As has happened with other public health problems, when the incidence of TB decreased, government and private efforts for TB control diminished markedly. In 1944, the Public Health Service Act authorized the establishment of a TB control program for the United States and the Surgeon General established the Tuberculosis Control Division in the Public Health Service. In 1961, the US Congress provided a substantial increase of funds for TB control through project grants; 29 projects were funded in 1962 with a total appropriation of \$500,000, and by 1969 the number of projects had increased to 80 funded at a level of approximately \$20 million. Funding for TB control by state and local government agencies increased from \$1.5 million in 1962 to \$40 million in 1969. Support began to be phased down after 1969 and the project grant program ended in 1972. Throughout the 1970s and 1980s, federal funding for TB decreased and special funds for TB control at the federal level were halted altogether for several years in the 1980s. This

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decrease in funds available for TB control together with the emergence of the HIV epidemic, the large increase in the homeless population, the growing number of elderly Americans, the dramatic increase in the US prison population, and outbreaks of TB caused by multidrug-resistant (MDR) *M tuberculosis* laid the basis for the reemergence of TB as a major public health problem.

A number of alarming hospital outbreaks have been recognized in recent years.¹¹⁻¹³ In one hospital, 21 of 60 employees had a documented tuberculin skin test conversion after exposure to a patient whose condition was not promptly diagnosed after hospital admission; in another hospital, 14 of 45 exposed employees converted.¹² The Centers for Disease Control and Prevention (CDC) reported a number of hospital and institutional outbreaks in which TB spread among hospitalized patients and employees, resulting in several deaths due to occupationally acquired MDR *M tuberculosis*.¹¹⁻¹³ The risk of TB among health-care workers was the subject of a recent review.¹⁴ A recent survey of American medical schools indicated a mean estimated annual conversion rate for students of 1.8%, although schools in areas with more than twice the national incidence rates for TB tended to be overrepresented among the survey respondents.¹⁵

The increase in incidence of TB in the United States noted over the past few years is a first in this century. Indeed, TB rates fell progressively throughout the United States beginning in the latter half of 19th century.¹⁶ This increase must be viewed with the realization that for much of the United States, TB remains under control. In 1992, nearly half of all counties in the United States reported having not a single person with TB for that year, and over the past decade, the number of counties having no TB in a given year steadily increased.¹⁷ The increase in TB has been observed primarily in states with large metropolitan centers, where there is also a substantial minority population together with persons who are foreign born.¹⁸ Most persons having MDR TB are from New York, New Jersey, and Florida, but MDR TB has been reported by many other states.¹⁹ For 1993, only 16 states reported an increase in the number of TB cases and the total number reported for the United States fell by 5.1%, the first decrease since 1988.²⁰

Today, many hospitals and their employees have been placed under difficult circumstances. They are treating more and more patients who have TB, some of whom harbor MDR strains. Several governmental actions were taken in response. The CDC published guidelines that provide for major changes in hospitals regarding TB control.²¹ These guidelines were the subject of considerable controversy within the medical community and among various agencies and interest groups.²²⁻²⁵ A common criticism has been absence of

scientific data on which to base recommendations. A recent retrospective cohort study in a New York City teaching hospital suggests that the implementation of interventions similar to those recommended by the CDC in 1990 resulted in reduced TB transmission to patients and health-care workers.^{26,27} Implementation of similar precautions also appeared to have controlled transmission of MDR TB on an HIV ward and among health-care workers at a large Miami hospital.²⁸ Unfortunately, it is usually not possible to determine by retrospective analysis which of the several interventions enacted were effective and which were ineffective.

In October 1993, the Occupational Safety and Health Administration (OSHA) issued a compliance memorandum that establishes an enforcement policy for protecting exposed workers against *M tuberculosis*. Employers found in violation of the policy mandates have been fined. The current OSHA enforcement policy for TB is based primarily on the 1990 CDC guidelines, but it is expected that OSHA will soon issue an airborne pathogen standard based on the revised 1994 CDC guidelines.²¹ The current OSHA enforcement policy and an independent interpretation have been published.²⁹

In response to these important clinical, epidemiologic, and regulatory developments regarding TB, the American College of Chest Physicians and the American Thoracic Society (the medical advisory arm of the American Lung Association) convened a panel of persons having special expertise in TB to review the subject of "Institutional Control Measures for Tuberculosis in the Era of Multiple-Drug Resistance." The objective of this conference was to review and analyze the risk of TB transmission in health-care facilities today, and the means available for protecting workers, patients, and visitors from the perspective of clinicians who have worked closely with the disease over the years. The following is a report from this group.

BACKGROUND INFORMATION: AIRBORNE TRANSMISSION OF TB VIA DROPLET NUCLEI

TB spreads when airborne particles produced by an infectious person are inhaled by a susceptible host. Many details regarding the precise nature of this process have been described. In 1934, Wells³⁰ pointed out that droplets ejected into air evaporate rapidly. The residues of these evaporated droplets are called droplet nuclei. He showed that the death rate of organisms in the transition from droplet to droplet nucleus is very high. Wells et al³¹ demonstrated that the size of the inhaled particle is important. Rabbits inhaling 2 or 3 tubercle bacilli dispersed as single, respirable particles developed more lung lesions than rabbits inhaling 10,000 bacilli dispersed in large aggregates. Study of tissue sections showed that the large clumps of bacilli

reach the alveolar space, whereas the small droplets containing a single bacillus were deposited on the vulnerable alveolar membrane. The large particles, deposited on the mucous blanket of the larger airways, were removed without producing any evidence of infection. Ratcliffe³² reported a series of animal experiments designed to study airborne transmission of tubercle bacilli in mice, hamsters, guinea pigs, and rabbits. Infections in these animals were induced by inhalation of an infectious aerosol produced by an atomizer that generated particles from an aqueous suspension of tubercle bacilli. From these experiments, it was found that only 0.8% of the organisms remained viable after transfer to the aerosol stage. The killing of 99% of the bacilli as they were put into the airborne state is not explained nor is it known whether this same degree of killing occurs when humans generate droplet nuclei.

Ratcliffe and Palladino³³ showed that in the guinea pig, mouse, and rat, almost all tubercle bacilli inhaled as single organisms reach the alveolar space and produce a tubercle. They also observed that it was most unusual for more than a single organism to be deposited at any one site. From this work, they postulated that TB in man develops in the same manner, *ie*, by inhalation of a single droplet nucleus containing one or at most a few tubercle bacilli. The details of this work and extensive supporting experimental material were reported by Riley and O'Grady.³⁴

To test the droplet nucleus hypothesis Riley et al^{35,36} studied patients with newly diagnosed pulmonary TB who had just been placed on a regimen of chemotherapy and were likely to have tubercle bacilli in their sputum. These patients were placed in hospital rooms with controlled ventilation so that the room air was discharged through an exposure chamber containing guinea pigs located in a penthouse above the ward. Infection rate for the guinea pigs was determined by periodic tuberculin tests. Infectious particles capable of passing through the ventilation ductwork to the exposure chamber above had the aerodynamic characteristics of droplet nuclei. This experiment showed that humans with TB create droplet nuclei containing tubercle bacilli that remain viable and infectious for guinea pigs while suspended in room air.

The human respiratory tract emits droplets of different size during quiet breathing, coughing, sneezing, speaking, or singing. Respiratory droplets must obey the physical laws of small particles suspended in air. The largest droplets settle quickly onto surfaces where they aggregate with dust, and are resuspended only briefly when disturbed by air currents produced by open windows or people walking in the room. Considerable energy is required to fragment large dust particles into particles of a respirable size. To our knowledge, there is no evidence of dust-borne TB

transmission or infection from contaminated surfaces. The small droplets, which evaporate almost instantly on exiting from the mouth and nose, settle so slowly that air currents normally present in any occupied room keep them airborne indefinitely. Although the size of droplet nuclei generated by infectious patients with TB has not been measured directly, aerodynamic principles governing airborne transport and alveolar deposition dictate that the infectious units of TB must be approximately 1 to 5 μm in diameter. Particles under 1 μm in diameter might not accommodate the organism and are unlikely to settle out in the alveolus, whereas particles larger than 5 μm in diameter are unlikely to remain airborne or reach the alveolus if inhaled.

The estimated number of infectious droplet nuclei generated by a patient with TB is highly variable. The great majority of infectious patients have cavitary TB with smear-positive sputum. Patients with laryngeal TB are especially infectious. Some patients have been termed "disseminators" and are usually dangerous sources of infection, but not all patients with smear-positive sputum are disseminators.³⁷ Brief exposure to some infectious cases has resulted in high infection rates.^{10,11} Investigators have paid little attention to factors that relate to the TB patient as an effective or ineffective producer of droplet nuclei and to the biology of *M tuberculosis* that determines its stability and long-term viability while suspended in a droplet nucleus.

HOST RESISTANCE

Resistance to TB is expressed in two ways: resistance against acquisition of infection and resistance to the development of disease after infection is established. Although the mechanisms by which uninfected persons resist infection with *M tuberculosis* are uncertain, the macrophage is believed to play a central role in this process, initially through ingestion of bacilli, then synthesis and release of substances that directly destroy bacilli, and ultimately through production of cytokines that enhance immune defenses.

Racial differences in susceptibility to TB infection have been reported. In a provocative report, blacks were approximately twice as likely as whites to develop TB infection after equivalent exposure to a source case, possibly because macrophages from blacks are more permissive for growth of *M tuberculosis*.^{38,39} This racial difference in susceptibility has been attributed to the prolonged selection pressure brought on whites by the TB epidemic throughout Europe for many generations prior to the first introduction of TB into sub-Saharan Africa.¹⁶ Although the human genes that might regulate resistance to TB have not been identified, several studies in animals indicate that this resistance is expressed in the capacity of the host macrophage to kill

phagocytized bacilli. In the mouse, Vidal and coworkers⁴⁰ have designated this gene as the "natural resistance-associated macrophage protein gene of Nrap"; it encodes an integral membrane protein that has macrophage-specific membrane transport function.

Additional factors that influence acquisition of TB infection remain undefined, but they are likely to involve genetic and acquired factors that determine the capacity of the alveolar macrophage to effectively eliminate tubercle bacilli. For example, HIV infection results in macrophage dysfunction and this may increase the likelihood of TB infection, although this has not been shown.

After TB infection is established, interactions between T lymphocytes and macrophages are pivotal in preventing progression of TB infection to disease. A major factor known to markedly reduce the risk for recently inhaled tubercle bacilli to replicate and progress to cause disease is a prior positive tuberculin reaction. In TB outbreaks in which the prior tuberculin reaction of exposed individuals was known, only 0 to 2% of those previously positive developed TB compared with 9 to 59% of those who converted the skin test.⁴¹ Thus, a positive tuberculin reaction provides substantial protection for employees who work in areas where they are likely to be exposed to infectious patients. Exceptions to this rule include HIV-infected persons and possibly others with impaired host defenses heavily exposed to infection.^{42,43}

Numerous risk factors have been reported to increase the risk for development of TB, probably through defects in T-lymphocyte and/or macrophage function. Factors most relevant to those concerned with hospital infection control are chronic renal failure, silicosis, jejunioileal bypass, and immunosuppressive therapy with cytotoxic agents or long-term corticosteroids. Although infection control strategies are designed to protect all health-care workers, patients, and visitors, persons at greater risk should be especially careful to avoid unprotected exposure to infectious TB patients. Other factors such as malnutrition, alcoholism, diabetes mellitus, postsubtotal gastrectomy status, and heavy tobacco smoking have been stated to increase the risk of reactivation TB twofold to fivefold.⁴⁴

IMPACT OF INFECTION WITH HIV

Infection with HIV accelerates the progression of TB, but HIV does not fundamentally change the possible results of infection with the tubercle bacillus. The clinical presentation of dually infected persons can be more complicated because (1) nonspecific symptoms such as fever and weight loss may be caused by either disease, (2) the sensitivity of the tuberculin skin test decreases, (3) the typical manifestations of TB such as apical cavitory disease are less commonly seen, and (4)

extrapulmonary TB, which is more difficult to diagnose, is more frequent. These factors together cause some cases of TB to go undiagnosed. Despite the widely recognized increased risk of TB, potentially infectious pulmonary TB may not even be suspected against a background of frequent respiratory symptoms and signs in HIV-infected persons. This greatly compromises the application of effective infection control precautions.

The infectiousness of the HIV-infected patient who also has pulmonary TB has been studied by several observers. For any given extent of radiographic involvement, the HIV-infected patients in one study had more tubercle bacilli in their sputum than did comparable patients who were HIV seronegative.⁴⁵ In most instances, however, skin test conversions have been less frequent among contacts of the HIV-infected persons.^{45,46} The impact of effective chemotherapy on infectiousness among these patients has not been studied fully; however, the time required to sterilize sputum is comparable to that observed before the AIDS era, and quantitative studies of the bacillary response in HIV-infected persons show no delay in the bactericidal effect of chemotherapy.⁴⁷ To our knowledge, there are no data regarding this question in HIV-infected persons who harbor MDR organisms, but a reasoned view holds that therapy with ineffective agents will not reduce infectiousness, and chemotherapy with drugs less effective than the "first-line tuberculosis agents" will reduce infectiousness less rapidly.

Conclusive data are available demonstrating that coinfection with HIV and *M tuberculosis* increases the risk for immediate and delayed progression from infection to disease. Studies have shown the risk of progression to disease for coinfecting persons is 5 to 10% per year compared with an estimated 5 to 10% lifetime risk for HIV-negative persons.^{48,49} Although it is not known whether HIV infection will increase the risk for an individual to develop TB infection after inhaling viable tubercle bacilli, defects in macrophage function of HIV-infected persons support a reasonable hypothesis that inhaled tubercle bacilli would be more likely to result in infection.⁵⁰ Although to our knowledge there are no data on the risk of initial TB infection, the available scientific evidence suggests that HIV-seropositive health-care workers should be allowed to remove themselves voluntarily from work environments in which they are likely to be exposed to patients with infectious TB. This decision is more than an issue of scientific evidence; questions of confidentiality, individual freedom to assume personal risk, employer liability, and the Americans with Disabilities Act are involved.

Thus, when HIV-infected persons develop pulmonary symptoms, there must be a high level of suspicion of TB, especially in persons with additional risk factors

for TB. HIV status of patients should not enter importantly into the decision concerning when a TB patient can be removed from isolation. However, close contacts with persons with infectious TB, whether tuberculin positive or negative, require that their HIV infection status must be considered since rapid progression to disease after infection can occur in the seropositive subject. Every effort should be made to avoid TB exposure of HIV-infected persons.

Among persons who are infected with HIV, the usual approach to contact investigation should be altered. Although tuberculin skin testing should be performed, isoniazid (INH) preventive therapy should be provided for all persons who have had significant contact, after current TB has been excluded. Symptoms suggestive of TB should be sought more diligently and there should be a low threshold for thorough clinical evaluation. Moreover, because of the rapidity with which HIV-infected persons can progress from infection to clinical TB, contact investigations should be initiated and completed promptly.

SPECIAL PROBLEMS IN PRISONS AND JAILS

Among the growing number of Americans who are incarcerated is a disproportionate percentage of minorities and urban poor. TB infection among new inmates in the New York prison system correlates better with the number of previous admissions to the New York City jail than with the total duration of previous incarcerations, suggesting that crowded conditions in city jails, like homeless shelters, may be foci of transmission.⁵¹ The prevalence of HIV infection among prison inmates in the United States is not known, but in New York it is estimated to be 15%. The tuberculin skin test reactor rate in many prisons ranges between 20 and 30%. Thus, jails and prisons bring persons infected with HIV together with persons infected with TB (and some individuals infected with both agents) under conditions conducive to transmission. When TB develops in a correctional facility, rapid progression from infection to communicable disease may favor accelerated propagation of infection among inmates and guards, and a number of epidemics in prisons have been reported.⁵² Given the high rate of release and reincarceration in the United States, correctional facilities contribute importantly to TB case rates in the community. Frequent transfers of prisoners among facilities spreads TB and hinders control activities. Prisoners and staff have died of MDR TB when prisoners with unrecognized TB were transferred from another facility where an outbreak of TB was in progress.⁵³ Health-care workers in hospitals caring for prisoners have also been infected. TB should be suspected among prisoners admitted to health-care facilities for any reason, especially those with respiratory symptoms. Guidelines for controlling TB in cor-

rectional facilities have been published.⁵⁴ A greater role for environmental controls has recently been emphasized.⁵⁵

SPECIAL CONSIDERATIONS IN CHILDREN

In 1993, there were 1,721 cases of TB in children reported in the United States. This was a 35% increase over 1985, indicating a marked increase in community transmission.⁵⁶ Although the initial infection in children usually produces no symptoms, approximately 5 to 10% develop a clinical illness that may include pneumonia, pleural effusions, fever, or chronic cough. Since the tuberculin reaction may not be positive at the onset of these findings, the diagnosis of TB can be missed.⁵⁷ Most infected children are discovered through contact investigations of adults who have TB.

It is widely believed that children with TB are usually not infectious, but only a few studies have addressed this issue carefully.⁵⁷ One report from a pediatric hospital describes 3 of 50 health-care workers who converted their tuberculin skin test after exposure to 2 small children with pulmonary TB; however, the father of the children with whom the employees had some contact had infectious pulmonary TB.⁵⁸ A second report describes a young boy with AIDS and cavitary TB (no sputum smear was performed) who exposed 28 health-care workers, 2 of whom had tuberculin skin test conversions; these converters had no other known exposure and only 3 of 774 remaining workers were found to be tuberculin positive.⁵⁹ There are little data concerning the prevalence of tuberculin skin test reactivity and conversion rates among health-care workers at children's hospitals. In 1993, at Texas Children's Hospital, where 10 to 15 children with TB are seen each year, 2.9% of 2,800 employees were tuberculin positive, 70% of whom were foreign born (Jeffrey Starke, MD, personal communication, 1994). At the same hospital 1 year later, 1.3% of employees had new positive skin tests, but none had exposure to children with known TB. This rate of tuberculin positivity was estimated to be comparable to that of persons in the community without known exposure to TB.

TUBERCULIN SKIN TESTING AND PREVENTIVE TREATMENT

Tuberculin skin testing and INH preventive treatment are essential components of a good TB control program for hospitals, correctional facilities, and other institutions providing long-term care. A positive tuberculin skin test serves to identify persons with any one of four conditions: (1) persons with or without clinical evidence of tuberculous disease infected with actively replicating *M tuberculosis*; (2) persons without evidence of tuberculous disease who are infected with viable but metabolically dormant *M tuberculosis*; (3) persons harboring *M tuberculosis* organisms that have

become nonviable; or (4) persons immunized with bacillus Calmette-Guerin (BCG) or infected with nontuberculous mycobacteria stimulating a "false-positive" skin test reaction. The tuberculin skin test may give false-negative reactions in all categories of persons infected with *M tuberculosis*. INH preventive treatment is highly effective in preventing TB, but (1) it is associated with some toxicity and is not recommended for all infected persons, (2) it requires a relatively protracted course of treatment to be effective, and (3) it is not effective when the infection is caused by INH-resistant organisms. Technical aspects of the tuberculin test antigen, its application, and test interpretation have been reviewed elsewhere.^{60,61}

Skin testing should be performed using an intracutaneous injection (Mantoux technique) of a standardized dose of purified protein derivative of tuberculin. By varying the reaction size of the tuberculin reaction to define a positive test, the sensitivity and specificity of the test can be adjusted as required by a particular test situation. In this way, a lower threshold for positive is used (eg, 5 mm of induration) in settings where reactivity may be reduced due to host factors (eg, HIV infection) and/or it is deemed especially important to identify as many infected persons as possible (ie, close contacts of an infectious patient), knowing there will be some degree of "overdiagnosis." In practice, lowering the threshold of "positive" for HIV-infected persons may not increase the prevalence of positive skin tests in this group; thus, the merit of this approach requires continued evaluation.⁶² Conversely, when reactivity due to sensitization with cross-reacting species of mycobacteria (ie, nontuberculous mycobacteria, BCG vaccination) is common relative to TB infection, or when preventive treatment is less critical, the threshold for a positive reaction can be increased with a resulting increase in test specificity.⁶³

Several issues related to skin testing are of special concern in institutional settings. These include anergy, boosting, and skin test reactivity in older adults.⁶⁴ Absent or reduced delayed-type hypersensitivity to test antigens (ie, anergy) is a problem among debilitated persons and other immunocompromised hosts, particularly those with advanced HIV infection. Although tuberculous infection may be identified in some of these persons by decreasing the threshold for a positive reaction, many will be completely nonreactive. The use of several other common skin test antigens (anergy testing) to accompany the tuberculin skin test to check for anergy is theoretically attractive, but these companion antigens have not been carefully standardized, may not be readily available, and their use adds cost and logistic complexity to a skin test program. Anergy skin tests should probably not be used routinely, but should be reserved for situations in which the determination of anergy results in a clearly defined

clinical response, ie, additional diagnostic tests in symptomatic persons or preventive chemotherapy in persons in whom TB infection is considered highly likely. A recent study of the usefulness of anergy testing in HIV-infected persons suggests that the best predictor of anergy is the patient's degree of immunosuppression as defined by CD4⁺ lymphocyte count. The frequency of anergy increases progressively as the CD4⁺ counts falls below 400/mm³.⁶⁵

Boosting can be associated with prior TB infection, BCG immunization, or infection with nontuberculous mycobacteria.⁶⁶ Boosting of waned tuberculin sensitivity occurs in situations in which skin tests are applied repeatedly over some period of time.⁶⁷ This can be a problem in institutions in which employees or residents undergo repeated testing as part of a TB control program. Because serial testing programs may overestimate the rate of new infection, those persons who show apparent skin test conversion must be evaluated for the "booster effect."^{66,68} Results of repeated tuberculin testing among 2,469 Southeast Asian refugees analyzed by CDC showed that boosting rather than recent infection accounted for most apparent skin test conversions.⁶⁹ Based on these findings, routine sequential tuberculin testing was specifically not recommended for this population, but institutional employees who are tested often include persons from groups in whom boosting may be likely. It is a particular problem in older individuals in whom there has been ample opportunity for previous hypersensitivity to tuberculin and cross-reacting antigens to have waned.⁷⁰ Application of a second skin test at the time an initial tuberculin test is read as being negative is a strategy used to distinguish skin test boosters from true converters.⁷¹ Two-step tuberculin testing of persons older than 35 years helps prevent unnecessary INH prophylaxis in persons at increased risk from INH hepatotoxicity. When two-stage initial testing is performed and when accurate records are maintained, it is appropriate to consider any subsequent increase in induration of 10 mm or more for persons younger than 35 years as true infection.⁶⁸ For persons older than 35 years in whom boosting is more likely and INH prophylaxis more risky, increasing the threshold for conversion (ie, new infection) to a 15-mm change has been recommended.

APPROACH TO INSTITUTIONAL SKIN TESTING PROGRAMS

A skin testing program should be developed in all hospitals and other institutions providing ongoing care or shelter for adults or children. All employees should be skin tested at the time of initial employment. Although 10-mm induration is recommended as positive for health care workers in general, for employees with little risk of TB exposure, this threshold for positivity will likely overestimate the prevalence of in-

fection. Patients in long-term care should also have baseline tuberculin testing and periodic retesting at a frequency dependent on the estimated risk of TB transmission in the institution. The misleading results of skin test boosting among geriatric patients entering a long-term care facility should be minimized by using a two-step test procedure.⁷¹ All persons with a negative initial test reaction should be immediately retested and the second test result recorded as the baseline reading. Although additional boosting might be elicited by further testing, it is not practical to go beyond a two-step process. In settings in which sequential testing of all employees is anticipated, a two-step process should be used for all employees. Although health-care worker tuberculin skin test conversions are assumed to be work related, high rates of initial skin test positivity among workers at some inner-city hospitals suggest that the risk of infection in the community may in some cases be comparable to that of the health-care setting. Epidemiologic contact investigations of skin test converters usually fail to uncover a source of infection either in the community or in the health-care setting.

Nonresidential programs providing long-term services to groups with a high incidence of TB (eg, drug treatment centers, HIV treatment centers, immigrant education programs serving persons from countries with high rates of TB) should develop skin testing programs for their employees and clients. Routine tuberculin skin testing of patients admitted to acute-care facilities is usually not warranted unless the risk of TB is high and both reading of skin test results and follow-up evaluation for preventive therapy can be assured. Shorter hospital stays, poor communication of medical data, and competing priorities during short-term hospitalizations sometimes render routine in-patient tuberculin testing an ineffective public health and personal health intervention.

PREVENTIVE TREATMENT

Preventive treatment of persons with positive tuberculin skin tests with INH daily for a period of 6 to 12 months can reduce their risk of developing active disease by up to 90%.⁷² Because INH has been associated with a number of side effects, including hepatitis, guidelines have been developed to help select candidates for preventive therapy to maximize the benefit and minimize the risk.⁶⁴ These guidelines focus on the risk and benefit to the individual rather than to the community, but important public health benefits are also associated with INH preventive therapy. High priority for preventive treatment should be given to tuberculin reactors, regardless of age, who are HIV seropositive, documented recent skin test converters, IV drug users, persons who have chest radiographic abnormalities suggestive of tuberculous infections but have normal results of bacteriologic studies, or persons

who have medical conditions predisposing them to activation of a tuberculous infection.⁶⁴ Tuberculin-negative persons recently exposed to persons with acid-fast smear-positive sputum under conditions conducive to transmission should be considered for INH prophylaxis until they retest negative 6 to 12 weeks after their last exposure. Because the risk of INH-associated hepatitis is increased in persons older than 35 years of age, persons over this age without additional risk factors predisposing to TB generally should not receive INH preventive treatment.

Several factors can limit the utility of INH preventive therapy; these include patient reluctance to accept the long duration of a course of preventive treatment, the increasing prevalence of INH-resistant strains of *M tuberculosis*, exogenous reinfection among HIV-infected persons, and the difficulty of ensuring adherence to prescribed treatment.^{42,64}

Because INH must be provided for 6 to 12 months, resources must be available for that period to monitor treatment. Recently, multidrug regimens of shorter duration have shown substantial efficacy in the treatment of smear and culture-negative pulmonary TB.^{73,74} Such regimens require a 4-month course of treatment and may be given on a twice-a-week basis. These reports raise the potential for providing "short-course" prophylaxis to selected high-risk groups, but experience with these regimens is limited.

In situations in which infection with an INH-resistant strain of *M tuberculosis* is deemed likely, prophylaxis should be provided with another drug or drugs to which the organism is known or believed to be sensitive.¹⁸ Selection of a particular regimen depends on the susceptibility pattern of the infecting strain. Use of rifampin is desirable if the organism is sensitive to it.

Although there is indisputable evidence that exogenous reinfection does occur, it has rarely been documented in the United States among persons who are immunocompetent. Persons who are tuberculin reactors and otherwise healthy should not have repeated courses of preventive treatment upon reexposure to persons with infectious TB.

Because of the limitations of preventive therapy, vaccination with BCG has received renewed interest. Use of BCG also has limitations. These include the fact that it produces tuberculin skin test reactivity that renders skin testing programs less effective, it provides protection estimated most recently by meta-analysis at approximately 50% for most reported studies, and it exposes persons who are immunocompromised to the potential complication of disseminated infection. BCG is best reserved for situations in which other forms of preventive therapy cannot or will not be accepted by immunocompetent hosts who are known to be tuberculin skin test negative, and who have unavoidable exposure to potentially infectious cases of TB.⁷⁵ For

otherwise healthy, tuberculin-negative health-care workers frequently exposed to patients having MDR TB, BCG remains an option.^{76,77}

ADMINISTRATIVE PROCEDURES AND RISK ASSESSMENT

The modern-day hospital is a complex enterprise consisting of a physical facility, a wide array of employees from professionals to support staff, and a range of patients, visitors, and volunteers. There is often construction taking place to meet changing needs. The objective to control a communicable airborne disease in this setting is challenging. To effect TB control in this environment, an individual or a defined group must be held responsible and must be given authority to ensure that TB is recognized, treated, and prevented from spreading. Of great importance for any hospital is the education of staff to have a high index of suspicion for TB among its patients and employees. The infectious person with undiagnosed disease accounts for many episodes of transmission of tuberculous infection to employees and patients. At a teaching hospital over a 5-year period, 57 of 108 patients (52%) had conditions diagnosed within 3 days after hospital admission, but 25% required more than 10 days before a correct diagnosis was made.⁷⁸ In a nonteaching community hospital, pulmonary TB was not suspected on initial assessment after hospital admission in 42% of 31 patients subsequently diagnosed as having TB, and the delay in instituting proper isolation measures for the elderly patients with TB averaged 6 days.⁷⁹ In another hospital, a nursery supervisor with smear-positive pulmonary TB exposed 528 newborns over a 3-month interval.⁸⁰ There must be an ongoing educational program for employees at all levels to maintain an awareness regarding the possibility of TB in all persons who have unexplained pulmonary infiltrates, chronic cough, or pneumonic episodes that do not respond to prescribed therapy. The American Thoracic Society/CDC/American Academy of Pediatrics/Infectious Disease Society of America statement on the control of TB provides a basis for this education.⁸¹ Recent legal proceedings regarding TB transmission in hospitals will also provide convincing reasons to implement control measures.⁸²

The hospital or institutional infection control program is responsible for monitoring and preventing nosocomial infection in hospitals.⁷⁹ The hospital accreditation process requires proof of the existence and efficacy of infection control.⁸³ It is this group that should direct TB control activities and set policies within hospitals. Infection control committees should include representatives from nursing, infection control, infectious disease, occupational health, pulmonary medicine, and hospital engineering. In other institutions that serve long-term residents, a suitably trained person or group should be given this responsibility.

Not all hospitals have the same risk for TB transmission. In making plans for TB control, the infection control group should use all available information from the recent past to assess the magnitude of a particular hospital's exposure to TB. Others have called this institutional risk assessment for TB.⁸⁴ Hospital microbiology laboratory reports, the number of patients with TB diagnosed at the hospital, records of the local and state health departments on TB, and consideration of the populations served by a hospital are important parameters to be reviewed when assessing a hospital's risk for encountering TB. Then, depending on the risk for TB, the steps to develop a control plan can be appropriately individualized. These risks may change and the assessment parameters must be regularly reviewed for changes.

DEVELOPING A PLAN TO CONTROL TB

Any TB control plan should take the entire hospital into account.^{21,83,84} The plan should consider the risk beginning at the first patient contact in emergency or admitting departments through the time of patient discharge. Risks, preventive measures, and monitoring of both risks and safety precautions should be considered for all areas. The objective should be to protect patients, health-care workers, and visitors. Inpatient areas, outpatient facilities, waiting rooms, public spaces, procedure rooms, and special treatment facilities, such as HIV clinics, should each be considered independently for measures needed to ensure safety for all. Hospital laboratories deserve special consideration since they handle potentially contaminated and infectious patient specimens. These laboratories should fully implement the National Institutes of Health/CDC biosafety recommendations. New construction, renovations of existing space, and routine building maintenance procedures may have an impact on the safety of everyone if building ventilation is interrupted.

Each hospital should charge its Infection Control Committee with the responsibility to develop an effective TB control plan. The CDC has published guidelines that are useful for all such committees to review.²¹ The elements of any plan must include the following: risk assessment for TB transmission; development of policies to aid in early identification of patients who may have TB; establishment of a detailed protocol to provide for isolation of patients having or suspected of having infectious TB; monitoring of isolation and procedure room ventilation system performance to ensure that infectious respiratory droplets are controlled; appropriate use of air filtration and ultraviolet (UV) air disinfection to reduce risk of transmission; development of policies and procedures for use of personal respiratory protective devices; provision for periodic screening of employees for TB infection and for the treatment of those who become infected; and

cooperation with the appropriate public health agencies by reporting of all persons with proved or suspected TB.

The assessment of risk for TB transmission must be done for all employees. A beginning point would be to determine the number of persons with TB admitted to or diagnosed in the hospital each year. The TB case rate for the community served by the institution is also important. Some states have only a few TB patients diagnosed statewide each year and almost half the counties in the United States have had no patients diagnosed each year. Thus, many hospitals are at very low risk of encountering an infectious TB patient. For hospitals at very low risk, initial risk assessment would include tuberculin skin testing of all workers who have patient contact. If, as expected, the tuberculin skin test positivity rate is very low and not above that found in the community, these data will support the decision to declare the hospital at very low risk. The frequency of repeated skin testing for a hospital at very low risk can be much less than for those hospitals where patients with TB are treated more frequently. After initial skin testing, if the hospital and community continue to see few or no TB patients, the frequency of repeated skin tests for employees "at risk" should be determined by the Infection Control Committee. For a very low-risk facility, testing as infrequently as once every 3 years might be appropriate. For hospitals that do encounter TB patients, skin testing of employees should be required more frequently to promptly identify recently infected workers. Testing health-care workers yearly or more often has been recommended for hospitals caring for specific numbers of TB patients each year, although there are no scientific data on which to set any arbitrary thresholds. If frequent testing over several years fails to turn up evidence of nosocomial transmission, testing frequency should be reassessed and adjusted to the actual risk of infection. Skin testing should be done on the anniversary date of employment. For the hospital where transmission is thought to be likely or where patients infected with MDR strains are encountered, skin testing will be required frequently, perhaps as often as every 3 months until control is well established and risk to employees has been reduced to a very low level.

Despite efforts to refine and improve tuberculin skin testing over several decades, the procedure remains a very imperfect diagnostic tool that gives a distressing number of false-positive and false-negative readings. Repeated testing of low-risk persons will invariably produce a certain number of false-positive reactions that then may lead to personal anxiety, institutional disruption, expense, and potential for drug toxic reactions that can outweigh the benefits of preventing TB in this group. For these reasons, the Infection Control Committee in a hospital having very low risk for TB

transmission must continuously reevaluate its skin testing policy.

ENVIRONMENTAL CONTROL OF TB

The currently recommended environmental approach to the control of TB is built around the concepts of isolation and mechanical ventilation. Mechanical ventilation serves two distinct functions: (1) to dilute and remove droplet nuclei, and (2) to ensure that air flows *into* isolation and procedure rooms from adjacent low-risk areas. Isolation requires that hospital staff be able to reliably identify most persons who might have TB soon after initial contact. When potentially infectious persons cannot be identified and isolated, this infection control strategy becomes less effective. The problem of identifying persons with potentially infectious TB varies greatly by institution and by region, depending on the prevalence of the disease in the population served. At a high-prevalence hospital where nearly 200 patients with TB are admitted each year, seven patients have been isolated for suspected TB for every patient with true active disease.⁸⁵ In low-prevalence institutions, the nonspecificity of TB symptoms may lead to the isolation of a higher ratio of suspect patients who ultimately prove not to have the disease. Scott and colleagues⁸⁶ estimated that in a large, mid-western university medical center, 92 patients presenting with one or more of the currently accepted clinical and epidemiologic risk factors for TB would require isolation to isolate just one patient with active disease. Thus, depending on the prevalence of tuberculosis, too little surveillance and isolation results in delayed or missed diagnoses, whereas aggressive surveillance leads to isolation of a disproportionate number of suspects without disease, with potential adverse health-care consequences for patients and economic consequences for institutions.

The number of patients isolated determines not only an institution's need for special isolation rooms, but also its utilization of respirators for staff who care for patients in isolation. To our knowledge, there are no published data indicating that inappropriate isolation for TB impacts adversely on the care of patients by delaying diagnostic studies and treatment. The inability of clinicians to accurately predict which patients should be isolated means that environmental control measures must be deployed widely in high-risk facilities to prevent transmission from persons with unsuspected disease.⁸⁷ Environmental control measures to prevent TB have been the subject of a recent review.⁸⁸

To our knowledge, there have been no scientific studies of the effect of various levels of building ventilation on TB transmission; current recommendations are based on the use of ventilation to control odor and other indoor air contaminants.^{89,90} Because of the variable character of TB transmission, large, controlled

epidemiologic trials of ventilation or other means of air disinfection would be required to mitigate the influence of the occasional highly infectious case. In the absence of field trials, mathematical modeling of airborne infection is used to analyze the effect of building ventilation as a transmission factor in airborne infection.^{11,91-93} Engineers employ mathematical models to design ventilation systems that provide protection against inhaling droplet nuclei containing tubercle bacilli.⁹² In addition to building ventilation, other transmission factors required to calculate the risk of infection under various conditions include (1) the duration of exposure, (2) the estimated volume of air inhaled by exposed building occupants (average ventilatory rate), and (3) the estimated average number of airborne infectious droplet nuclei generated by one or more patients with TB. Although the number of infectious droplet nuclei generated by TB patients cannot be measured directly, this factor has been calculated for patients on an experimental TB ward and in several outbreaks in which the risk of infection and the other major transmission factors were known or estimated.^{10,36,93} Using these calculated values for the numbers of droplet nuclei generated by patients who were known sources of transmission, it has been possible to calculate the theoretical risk of infection under various exposure conditions, for example, where building ventilation was theoretically better or worse than was actually the case.^{92,93} As with all mathematical models used to predict the complex interrelationship among multiple factors, certain assumptions are required, and the results of modeling calculations must be interpreted with these assumptions in mind.

In modeling TB transmission using the Wells-Riley equation, it is assumed that transmission factors are in a steady state over the period of exposure, including the average number of infectious droplet nuclei generated by the source case.⁹³ In reality, infectiousness probably varies over time, depending on such factors as cough frequency and sputum viscosity.³⁷ Patients may become more infectious over time as the disease progresses, or less infectious due to treatment. Environmental conditions such as outdoor ventilation may also change over time. In predicting transmission risk, the model further assumes that exposed persons have approximately equal susceptibility to tuberculous infection. As discussed previously, this is probably not true for individuals or for groups, depending on such variables as genetically determined innate immunity to TB.⁴⁰ Despite these limitations, for a given population exposed under defined conditions, mathematical modeling is useful for assessing the relative importance of environmental factors such as ventilation compared with source factors such as the average number of infectious droplet nuclei generated by a person with TB.^{10,92,93}

Within the limits of the assumptions stated, the probability of infection is directly proportional to the concentration of infectious droplet nuclei in the air and the volume of air inhaled, which is primarily a function of the duration of exposure.⁹¹ The concentration of droplet nuclei is a function of the rate at which infectious droplet nuclei are added to the air and the rate at which they are diluted, removed, die, or are inactivated.

To an engineer, "effective" ventilation refers to contaminant-free outdoor air entering and completely mixing with ambient room air.²¹ Air entering and leaving a room without completely mixing with ambient air, so called "short-circuiting," provides less effective ventilation. The measurement of effective ventilation requires tests of clearance using tracer gases or particulates sampled from various locations within a room. Except for special types of ventilation called "laminar flow" or "displacement ventilation," good room air mixing is essential for all forms of air disinfection whether it is ventilation, filtration, or upper room UV air disinfection. Incomplete mixing means less effective clearance of droplet nuclei than the room ventilation rates would predict. For TB control, dilution by air from any source that is free of tubercle bacilli is "equivalent" ventilation, even though it may not be outdoor air. Disinfected air or air recirculated from low-risk areas in a building should be as effective as outdoor air in diluting droplet nuclei.

In a hypothetical room with a number of viable tubercle bacilli evenly dispersed in the form of droplet nuclei, only two factors determine the rate of disappearance of infectious particles: effective ventilation, and death or inactivation of the organisms. The rate of decrease in the number of microorganisms is proportional to the number of air changes per unit of time. A single room air change occurs when the volume of outdoor air ventilation equals the volume of air in the room. If the organisms are well mixed within the room and the ventilation is evenly dispersed throughout the room, one air change will reduce the number of infectious droplet nuclei to 37% of the starting number. To the extent that droplet nuclei are not well distributed in the room and ventilation is not uniform, the particle clearance rate predicted by calculated room air changes may not reflect actual conditions. The reciprocal of concentration of droplet nuclei is the volume of air in which a single droplet nucleus is contained. The studies of Riley et al³⁶ on a TB ward found that the concentration of infectious particles was less than 1 in 10,000 cu ft of air. Under these conditions, when an individual inhales 10,000 cu ft of air, there is a 63% chance of inhaling an infectious particle and a 37% chance of escaping infection. Every doubling of the volume of ventilation halves the chance of infection, or doubles the length of exposure time required to have

a 63% chance of becoming infected.

Several outbreaks of TB provided sufficient information to apply the Wells-Riley equation. During a 150-min bronchoscopy and intubation, 10 of 13 occupants of an ICU were infected by a patient with unsuspected TB generating approximately 250 infectious units per hour.¹⁰ The hazard of this unusually infectious patient was compounded by low outside air ventilation (150 cubic feet/min, or 1.23 room air changes per hour). In this case, increasing total ventilation to six room air changes per hour would have reduced the infection rate from 80% to about 20%, or two to three of the room occupants infected rather than ten.

A second outbreak occurred in an office building where one worker with undiagnosed TB infected 27 of 67 (40%) coworkers over a 4-week (160 h) exposure period.⁹³ Infections occurred throughout both floors of the building, in no particular relation to the work station of the index case. Infection was believed to have been widely distributed by recirculated ventilation and by the movement of the infectious person within the building. Outdoor air ventilation averaged 15 cfm per occupant, the low end of the acceptable range of ventilation.⁸⁹ In this case, the Wells-Riley equation predicted that increasing the outdoor air ventilation rate to 35 cfm per person, a high ventilation rate for an office building, would have reduced infection rate only by half, suggesting practical limits to the protection achievable in a building under actual outbreak conditions.

The two illustrations differ in the level of ambient ventilation, the duration of exposure, and the infectiousness of the source cases. For both outbreaks, substandard ventilation contributed to high levels of transmission, but the protection predicted by increasing ventilation differed between the two examples. In the ICU example, increasing ventilation to protective levels should have been readily achievable despite a highly infectious source case. In the office building example, practical levels of increased ventilation would have protected only half of those infected, primarily because of prolonged exposure to an unusually infectious source case. Although engineering controls to prevent TB transmission would not be appropriate to office buildings, the principles elucidated are directly applicable to health-care facilities. Ventilation is important but has limitations as the fundamental environmental strategy for protecting building occupants against TB transmission. Depending on the exposure conditions, increasing ventilation may become progressively less efficient as it becomes more and more costly. Engineering, construction cost, operating cost, and occupant tolerance place upper limits on the amount of ventilation that is practical.

Building ventilation, natural or mechanical, serves to dilute and remove droplet nuclei in the air, but also to transport infection within rooms and buildings.^{9,11} Within spaces contiguous to the infectious patient, convection currents, drafts, and forced air movement rapidly disperse and dilute airborne droplet nuclei to low concentrations. Even at low concentrations the chance of infection persists if the duration of exposure is long enough. Immediate proximity to the infectious TB patient is likely to increase the risk of infection, but only transiently as droplet nuclei disperse rapidly within the available space. Epidemiologic patterns of TB transmission in developed countries such as the United States rarely implicate transient close contact as being important; instead, the data suggest that prolonged exposure and the clinical characteristics of the source case are the critical factors.^{18,81} However small the risk to the individual for becoming infected through casual contact, recent studies of the molecular epidemiology of transmission within large populations suggest that some persons without apparent epidemiologic linkages to one another may have become infected as a result of brief contact—for example, in public places.⁸³

The role of convection air currents as a mode of transmission in a hospital was demonstrated by a TB outbreak where proximity to the room of the source case was an important transmission factor.¹¹ The patient had a soft-tissue abscess that was ultimately diagnosed as TB. Respiratory precautions were not in place. Investigation showed that air flowed out of the patient's room into the corridor due to a malfunction of the ventilation system. Fifty-eight patients were exposed over 3 days in rooms off the same corridor. Infection rates ranged from 0.67 across the hall from the source case, to 0.37, 0.29, 0.1, and 0% as the distance from the source increased. The other rooms were found to be pressure neutral with respect to the corridor. Convection currents generated by personnel and visitors apparently carried droplet nuclei down the corridor, the infectious units being progressively diluted by air in the corridor.

Mechanical ventilating systems have facilitated transmission of infection throughout entire buildings, as in the office building previously described. In a clinic treating HIV-infected patients, a case-control investigation of risk factors for infection found that the greatest risk was simply being in the building for 40 or more hours per week.⁹⁴ Because the ventilation system recirculated droplet nuclei, exposure was nearly universal and not solely dependent on proximity to the source cases. Since air in most health-care facilities is recirculated, unsuspected TB cases in almost any area may contribute to infection throughout a building. Air from isolation rooms is routinely exhausted directly to

the outside, but single-pass, nonrecirculating ventilation is prohibitively expensive for an entire building. Air disinfection within ducts using UV germicidal irradiation (UVGI) or high-efficiency particulate air (HEPA) filters is a less expensive, highly effective way to permit safe recirculation of air within high-risk areas.^{21,95,96} Because filters and UV lamps in ventilation ducts are out of sight, routine maintenance schedules are essential to assure proper function.

PATIENT ISOLATION: DIRECTIONAL AIRFLOW, NEGATIVE PRESSURE, AND ANTEROOMS

Negative pressure isolation uses directional airflow from low- to high-risk areas to protect persons in areas adjacent to potentially infectious source cases. To produce directional airflow, room air is exhausted at a rate greater than it is supplied by the ventilation system, with make-up air drawn from adjacent areas. Airflow into rooms around doors can easily be monitored with a smoke stick or wisp of cotton, although the direction may be different at the top and bottom of the door due to gradients of pressure and temperature. Air pressure fluctuation outside (through leaky windows) or elsewhere inside the building may negate a small gradient in pressure and intermittently reverse airflow direction. Directional airflow can reverse when ventilation filters become clogged or fan belts slip. In seven hospitals in one US city, the number of isolation rooms was highly variable, and testing with isolation room doors closed found that 45% of 115 rooms had airflow into corridors.⁹⁶⁻⁹⁸ Continuous room air pressure monitors are available, but they are expensive because of the small pressure gradients involved, and frequent pressure fluctuations may lead to unnecessary alarm.²¹

Some air leakage from negative pressure isolation rooms normally occurs due to the turbulence generated by opening and closing doors. Anterooms can minimize isolation room air leakage, but these rooms add complexity and cost and may interfere with patient care by discouraging staff interaction with patients. Among the many factors that influence TB transmission in hospitals, small leaks from properly functioning negative pressure isolation rooms are unlikely to rank high in importance. As previously emphasized, it is the unsuspected person with TB, not the isolated patient, who poses the greatest risk of transmission in institutions.

The adequacy of air mixing within a room to achieve dilution and removal of droplet nuclei is as important as the number of room air changes. In some instances, ventilation supply diffusers and exhaust ducts may be located too close together, producing poor mixing and inadequate room air changes. In addition, when the same forced air system serves both heating and cooling functions, diffuser locations that encourage air mixing during one cycle (cooling from ceiling diffusers)

often encourage stagnation during the other cycle (heating from ceiling diffusers). Since room air mixing is essential for effective air disinfection by all methods—dilutional ventilation, filtration, and upper room UVGI—ventilation systems should be constructed to provide optimal air mixing within rooms during both the heating and cooling cycles. So-called *displacement ventilation* aims to produce an infection-free breathing zone by preventing mixing with contaminated air.²¹ Given the variety and complexity of the many indoor spaces where transmission occurs, this strategy is unlikely to be an effective or practical approach for hospitals.

AIR FILTRATION MACHINES

Portable and permanently installed air filtration devices providing "equivalent" air changes for infection control are being used as an alternative to additional ventilation. HEPA filters remove particles in the size range of droplet nuclei. Equipped with a fan or blower, these filtration units serve to recirculate and disinfect air within rooms. A large variety of room air disinfection devices are available, but few have been subjected to rigorous, independent testing of their ability to clear airborne particles under field conditions. In some instances, enclosed UV air disinfection is incorporated with filtration, although there is no rationale to employ both technologies in the same unit since HEPA filters remove 99.97% of all particulate over 0.3 μm in diameter. Irradiation of filter surfaces is ineffective and unnecessary. Some room units use enclosed intensive UV irradiation as the only means of air disinfection. The main advantage of UV over HEPA air disinfection is far lower resistance to airflow, allowing the use of smaller, quieter blowers, but a malfunction of the UV defeats the system, whereas HEPA is less subject to total failure. While any added air disinfection in rooms is likely to be beneficial, there is a danger of overreliance on room units while other administrative and environmental precautions are neglected. These devices are designed primarily for use in isolation and procedure rooms and do not address the problems of the unsuspected case elsewhere in the hospital. Filtered, recirculated air does not replace required outdoor air ventilation which must still meet specifications.²¹ Portable devices have been employed during building renovations to provide temporary protection.

The following are specific concerns regarding fan-driven air filtration and UV filtration devices. First, is the volume of air sterilized sufficient to substantially reduce the risk of infection? Because TB appears to be transmitted by low concentrations of droplet nuclei, large volumes of air must be sterilized to substantially reduce the risk of transmission.⁹³ A reasonable goal would be to provide at least ten equivalent air changes in addition to the existing ventilation air changes.

Higher rates of air movement are more likely to cause unacceptable noise and drafts. Second, is room air mixing adequate to prevent air stagnation? Although these devices may agitate the room air, there is the possibility of refiltering air primarily in the immediate vicinity of the device. When this occurs, the magnitude of the protective effect is decreased. Third, is the device constructed to prevent damage and leakage around filters, particularly as portable units are moved from room to room? Initial on-site testing of filters for leakage before use and after such devices are moved has been recommended.

Fan-driven filtration and fan-UVGI devices should be standardized and tested for their effectiveness, and guidelines for their use developed.

Air filtration devices have been adapted to create effective negative pressure isolation rooms by recirculation of filtered/irradiated air from the patient's room through a duct to an anteroom.⁹⁹ For some institutions, a "retrofit" isolation room of this type may be preferable to the cost of construction and operation of standard negative pressure isolation rooms, exhausting large volumes of heated or cooled air to the outside. Several HEPA-filtered, self-contained booths for administering pentamidine aerosol therapy and for sputum induction are on the market and provide a cost-effective way to perform these procedures safely.

ULTRAVIOLET GERMICIDAL IRRADIATION

UVGI began to be used to control airborne infection soon after droplet nuclei were recognized as being critically important in the transmission of certain respiratory infections.¹⁰⁰ Successful laboratory tests of air disinfection and successful field trials preventing measles transmission in schools and influenza transmission in hospitals were counterbalanced by failed experiments, where the sites of air disinfection were not the only sites of transmission.¹⁰¹⁻¹⁰⁴ Air disinfection in classrooms failed to prevent measles in settings where children were exposed outside of school—for example, on school buses or in crowded urban housing. Safety concerns, lack of familiarity with the technology, wide use of chemotherapy for TB, and immunization for some viral respiratory diseases led to loss of interest in UV air disinfection. UVGI is again of interest, however, due to increased concern with TB transmission in institutions ranging from hospitals to shelters and jails, especially from persons with unsuspected pulmonary disease.^{21,56,95,96,105,106} Three types of evidence favor the use of upper-room UVGI to control transmission: (1) data regarding susceptibility of airborne tubercle bacilli to UV irradiation;^{101,102,107-109} (2) data regarding convective air mixing between the upper and lower room areas to achieve effective UV air disinfection;¹¹⁰⁻¹¹² and (3) data regarding safety of UV light for room occupants.¹¹³⁻¹¹⁷

SUSCEPTIBILITY OF AIRBORNE TUBERCLE BACILLI TO UV IRRADIATION

Because both room ventilation and UV irradiation reduce the numbers of viable airborne organisms in a logarithmic fashion when plotted against time, inactivation of organisms by UV can be expressed as equivalent air changes per hour (Eq AC/h). Although this is not the only way to express the germicidal effect of UV, it is useful because (1) the equivalent air changes produced by UV and those produced by ventilation are additive, and (2) upper room germicidal efficacy depends in part on air mixing within the room, which can also be expressed as room air changes per hour between the upper and lower part of the room. Exposure chamber experiments using virulent *M tuberculosis* organisms determined the lethal dose for 90% of airborne organisms to be $576 \mu\text{W}/\text{s}\cdot\text{cm}^{-2}$.¹⁰⁷ Because the biologic effects of UV irradiation exposure intensity and duration act reciprocally (Bunsen-Roscoe Reciprocity Law), exposure to as little as $1 \mu\text{W}/\text{cm}^2$ for as long as an hour would, by calculation, inactivate organisms at a rate equivalent to 15 AC/h, where 1 AC/h equals a reduction of infectious droplet nuclei to 37% of the starting number. This calculation serves simply to equate the air disinfection of UV irradiation and ventilation, not to suggest that UV can substitute for other important functions of ventilation such as the dilution of carbon dioxide and other indoor air contaminants. Because upper-room exposure of airborne tubercle bacilli is likely to last only seconds in duration, UV intensity well over $1 \mu\text{W}/\text{cm}^2$ is required. Since even $1 \mu\text{W}/\text{cm}^2$ of UV irradiation is in excess of the intensity permitted for prolonged exposure of people, germicidal irradiation must be confined to the upper part of the room, with lower room air disinfection dependent on good air mixing between the upper and lower regions of the room. As previously noted, germicidal irradiation can also be used within ducts and fan-driven air disinfection units, but these methods cannot ordinarily approach the numbers of equivalent air changes possible by upper-room UV under optimal conditions.^{95,96,105} High humidity greatly reduces the germicidal effect of UV against ordinary bacteria. Mycobacterial killing may not be as affected by humidity because of the organism's hydrophobic cell wall, but these experiments have yet to be performed.¹¹⁸

Because of the large cross-sectional area, substantial mixing can occur between upper and lower parts of a room without detectable drafts, as in the case of a room heated by a radiator in a single location. The rate of air mixing within a room through convection currents is independent of the exchange of air between the room and the external environment (ventilation room air changes). The time of an equivalent air change is how long it will take to reduce the number of infectious

particles to 37% of the original number. When the irradiation is confined to the upper part of the room, the time required to produce additional equivalent air changes will be longer. If the irradiation is confined to the upper one fifth of the room, the time to produce equivalent air changes in the lower part of the room will be five times longer than if the entire room was irradiated, assuming complete mixing.

To avoid direct exposure of people, UV fixtures are normally installed at 7 ft above floor level, and fixtures are louvered to prevent both downward radiation and reflection off of ceilings. Using fixtures recently designed to prevent reflection into the lower part of the room, rooms with ceilings as low as 8 ft can be safely equipped for upper air disinfection.¹¹⁹ A 30-W UV source is usually adequate to disinfect the air above a floor area of 200 sq ft, except under crowded conditions in which additional UV wattage is recommended. Heat sources (including people) in the lower part of the room usually provide good mixing by convection between upper and lower room air. Where forced air heating is supplied to the upper room, layering of air is encouraged, and fans may be desirable to achieve better room air mixing.^{107,110-112} The quantitative assessment of mixing within rooms is not done routinely, and requires further study.

Permutt¹¹³ has derived an equation showing the independent contributions to lower-air disinfection of air mixing and upper-air disinfection. These two rates, both expressed as AC/h, appear in the equation as reciprocals and thus are in terms of time required per air change. In the lower part of the room, the time required for an air change due to air mixing and the time required due to air disinfection are additive. The sum of the two times determines the actual time required for an equivalent air change in the lower part of the room.

The greatest efficiency is achieved when the two component times are approximately equal. For example, if the time per air change in the lower part of the room due to mixing is 2 min, and the time required per air change due to upper-air disinfection is 2 min, the total time per air change in the lower part of the room is 4 min, or 15 AC/h. If the upper-air volume is one fifth of the total room volume, this implies an air disinfection rate in the upper part of the room equivalent to approximately 150 AC/h. Based on the relationship of UV air disinfection to equivalent ventilation previously mentioned, this air disinfection rate requires a mean upper-room UV intensity of approximately 10 $\mu\text{W}/\text{cm}^2$ which is safely achieved using modern equipment and constitutes a reasonable goal for a good upper-room UV installation.

However, room air mixing between the upper and lower parts of the room can easily exceed the 30 room air changes postulated above, which is only 800 cfm for

a room with 200 sq ft floor area. Vertical air mixing two or three times this rate can be achieved without discomfort and would result in lower room air disinfection equivalent to well over 20 AC/h, in addition to ambient outdoor air ventilation. The effects of room air mixing on air disinfection have been demonstrated in room experiments using airborne surrogate bacteria.¹¹⁰⁻¹¹²

SAFETY OF UV IRRADIATION

UVGI uses a narrow-band (95% 253.7-nm wavelength, UV-C) of the UV portion of the electromagnetic spectrum to inactivate airborne pathogens. Upper-room UV irradiation achieves intensity levels in the upper part of the room that are rapidly lethal for airborne bacteria, while the exposure of occupants in the lower part of the room remains well within the limits of safety. UV light of longer wavelength (UV-A and UV-B) has a greater penetrating capacity than does UV-C, and long-term exposure to UV-A and UV-B has been associated with skin cancer and cataracts.¹²⁰ UV-C is almost completely (95%) absorbed by the outer layer of the stratum corneum.¹¹³ Accidental direct exposure to high-intensity UV-C can cause temporary, painful irritation of eyes (photokeratoconjunctivitis) or skin erythema.¹¹⁴ Hospital workers have experienced photokeratoconjunctivitis due to accidental direct UV-C exposure from working in the upper part of the room without first turning off UV fixtures. Because UV-C does not penetrate the cornea, it does not reach the lens to cause cataracts.¹¹⁴ Prolonged high-intensity irradiation of hairless mice with UV-C has produced skin cancers at the level of exposure permitted for people, but in the lower part of the room more than 300 years of exposure would be required to produce skin cancer.^{115,116} Although systemic immunosuppression has been induced by UV-B irradiation of mice, the UV dosage required is relatively large and requires UV penetration to the cellular level—readily achieved with UV-B but unlikely with the low-penetrating UV-C.¹²¹ There is no evidence (to our knowledge) of systemic immunosuppression in humans from UV-C exposure. Activation of the HIV in cell cultures exposed to UV-B or UV-C has been reported, and concerns have been raised that UV light therapy and sunbathing could be an activation factor for HIV-infected persons.¹²² To our knowledge, there are no data for sunlight-induced HIV activation in humans, and indoor exposure to germicidal UV is normally far less than exposure outdoors to UV-A and B in sunlight.

Exposure safety guidelines for UV-C are based on a combination of animal data and voluntary human exposures using eye irritation as the end point.¹²³ The exposure limit for 254-nm UV, 0.2 $\mu\text{W}/\text{cm}^2$ over 8 h, incorporates a margin of safety and assumes continuous eye exposure at the maximum level. Movement

within rooms, angles of incidence of UV reflected from walls, and shielding by eyebrows and lids serve to reduce exposure to the cornea. The safety margin is maximized with fixtures of improved design that confine the irradiation more effectively to the upper part of the room.¹¹⁹

PERSONAL RESPIRATORY PROTECTION

For decades, surgical face masks have been part of an isolation ritual, religiously placed outside of hospital rooms of TB patients, but only recently has the question of their efficacy been raised. To our knowledge, there have been no field trials demonstrating that personal respiratory protection of any kind is effective in preventing transmission of TB. Such trials would be difficult if not impossible because of the unpredictable numbers and infectiousness of patients with TB. As in the case of ventilation, air filtration, and UV irradiation, basic principles and analogies with other applications have been used as criteria in the absence of field trial data.

The ability of respirators to protect workers from certain airborne hazards has been well established. To the extent that respirators reduce the risk of inhaling droplet nuclei, they will reduce the chance of TB infection. Respirators require worker cooperation, but they cannot be worn continuously, and they will not be worn in some situations where TB is not suspected. Therefore, personal respiratory protection is properly considered last in the three-tiered hierarchy of control strategies of occupational and industrial hygiene—after administrative and environmental controls. However, the three strategies should not be considered independently, since their effects are often complementary or additive in reducing risk. A respirator that is only 80% efficient in excluding droplet nuclei provides protection approximately equivalent to increasing ventilation by over four times, since each doubling of effective ventilation reduces by half the risk of infection. If such a respirator was properly worn at the time the hazard was present, its protection would be equivalent to approximately an 80% reduction in exposure. Given the engineering difficulties of increasing ventilation and the administrative difficulties in reducing exposure duration, the potential benefit of even less than perfect personal respiratory protection can be significant. In the reported episode of TB transmission associated with bronchoscopy, previously discussed in relation to ventilation, correcting deficient ventilation would have theoretically reduced the number of persons infected from ten to about two or three.¹⁰ This change in ventilation, together with the use of a respirator that was only 80% efficient, would have been nearly fully protective against one of the most infectious cases of TB on record. In contrast, in those situations in which the numbers of infectious

particles in the air are few, further increments in filtration efficiency of respirators would be predicted to contribute minimal added protection. It is important to recognize that as part of a comprehensive infection control program, respirators need not be 100% efficient to be useful. In the two retrospective reviews of precautions implemented in hospitals in New York and Miami, previously cited, use of respirators less efficient than HEPA appear to have been effective when used together with administrative and environmental controls.^{25,26}

SELECTION OF RESPIRATORS

The reduction of transmission of infectious particles through the filtration material of face masks and respirators is accomplished by the impaction of particles on the filter or by electrostatic attraction. Five factors affect leakage of aerosols through a filter: (1) the filtration characteristics of each type of filter; (2) the size distribution of the aerosol; (3) the linear velocity through the material; (4) filter loading; and (5) the electrostatic charges on the filter and aerosol. Equally important as the efficiency of the filtration material is face-seal leakage, the ability of unfiltered air to penetrate a respirator between the respirator's edge and the wearer's face.^{21,124-128} Both filtration efficiency and face-seal leakage determine the effective protection of personal respirators. In general, the more efficient the filtration material, the greater the airflow resistance, the greater the tendency for face-seal leakage, and the better the face-seal required. For example, two respirators, one with 99.97% filter efficiency (HEPA) and another with 95% filter efficiency, may provide similar protection if the face-seal leakage of both respirators averages 10 to 20%, as is often the case.²³

The filtration characteristics of a variety of single-use masks and respirators have been assessed using mycobacterial aerosols of a particle size distribution believed to be representative of infectious droplet nuclei (1 to 5 μm respirable particles).¹²⁹ In this investigation, face masks and respirators were sealed to the test apparatus to prevent leakage around the filtration material. As expected, HEPA respirators excluded a mean of more than 99.99% of the aerosolized mycobacteria. However, the filtration materials of most other masks and respirators tested were also highly efficient, trapping a mean of 96.9% or more of airborne mycobacterial aerosol. When masks and respirators are worn by people rather than sealed to a test apparatus, particles that reach the respiratory tract are likely to be due to leakage around the face seal. As of this writing, no respirator class other than HEPA is certified by the National Institute for Occupational Health and Safety (NIOSH) for the particle size range of droplet nuclei (Note: since this document was approved for publication, NIOSH has finalized a new certification standard

for particulate respirators and has certified a broad range of respirator models for TB protection. Additional information may be obtained by calling the NIOSH toll-free at (1-800-35NIOSH) or from the NIOSH worldwide web home page (<http://www.cdc.gov/niosh/homepage.html>). New testing procedures and standards have been proposed by NIOSH, which should result in certification of respirators of lower efficiency than HEPA for use in TB control.¹³⁰ CDC has proposed 95% efficiency for particles 1 μm in diameter, with no more than 10% face-seal leakage, as satisfactory protection for most TB control applications.²¹ Positive-pressure respirators designed to minimize face-seal leakage (powered air-purifying respirators [PAPRs] and air-line respirators) are still recommended for the most hazardous applications, such as autopsies of patients with MDR TB.²¹

Face-seal leakage is affected by the match between size and shape of the face piece and facial features, facial hair, faulty respirator positioning, incorrect placement of head straps, facial oils, perspiration that leads to slippage, and damage to the respirator. Face-seal leakage is minimized by training regarding respirator usage and by fit testing. Only qualitative fit testing is possible for disposable respirators and should be done prior to respirator selection. In addition, workers should perform fit checks on themselves every time they put on a respirator, given the potential for damage as disposable respirators are reused. Disposable respirators can be reused by workers as long as the mask remains clean and structurally intact.²¹ Given the limited availability of respirator sizes, their reuse, and the inability to quantitatively fit test disposable respirators, the potential for significant (10 to 20%) face-seal leakage remains. In contrast, PAPRs and line respirators can be quantitatively fit tested and have an estimated face leakage of only 2%.²¹ About 15 to 20% of workers are unable to obtain a tight fit with available negative-pressure respirators, and these persons should use a PAPR when a respirator is required. Workers with beards cannot be fitted with negative-pressure respirators due to excessive face-seal leakage, and may also require positive-pressure respirators in hazardous settings. It is anticipated that once the new certification procedures for respirators are finalized and implemented, a wider range of sizes and styles of disposable and reusable respirators will become available.

The new certification procedures for respirators should lead to a better adaptation of technology developed for industrial applications to the very different risks and needs of health-care personnel. Adaptation must take into account worker comfort, the need to communicate with patients, the need to protect visitors and patients as well as workers, a wide range of TB risks among institutions, and cost-effectiveness considerations.^{22-24,131-133}

Two recent cost-effectiveness analyses based on the current HEPA respirator recommendations calculated the cost of preventing a single case of TB. Based on survey data from 159 Veterans Affairs facilities in the United States, the cost estimate was \$7 million per case of TB prevented, and \$100 million per life saved.¹³⁴ At a 700-bed university teaching hospital in Virginia with 47 TB isolation rooms, the cost estimate to prevent a single TB case ranged from \$1.3 million under optimal conditions, to \$18.5 million if respirator utilization was suboptimal and more workers were exposed than necessary.¹³⁵ This approach to the issue of respirators has sparked controversy, with some critics pointing out that respirators should not be considered apart from administrative and environmental precautions.¹³⁶⁻¹⁴² While some critics may consider it unethical to consider the economic cost of lowering risks for workers, another view holds that it would be more unethical not to consider cost, since the large sums of money spent on respirators will be unavailable for other, potentially more cost-effective interventions.¹⁴³ Whereas the broad application of high-efficiency personal respiratory protection appears to result in expenditures well out of proportion to risk, selective use of less costly respirators of sufficient efficacy pushes the cost-efficacy analysis back toward an acceptable balance.²²⁻²⁴ As expressed in an insightful commentary on risk as it applies to public policy, effective decisions about risk requires an understanding that total risk reduction is rarely possible, that choices between competing objectives invariably transfers risks to others, and that explicit analysis of the necessary trade-offs relative to societal values is necessary.¹⁴³

In view of both the potential utility and the inherent limitations of respirators to prevent TB transmission, and the cost considerations just discussed, efforts must be undertaken to tailor the application of respirators of various efficiencies to specific TB risks. Effective respiratory protection is currently required for three settings: isolation rooms, high-risk procedure rooms, and in the transport of potentially infectious patients.^{21,29} The use of respirators in isolation rooms and the categories of patients who require care in isolation rooms should be guided by standards set by the Infection Control Committee of each institution.⁸³ The committee should establish a graduated scale setting out the characteristics of patients who range from highest risk to lowest risk for TB transmission. An institution located in a geographic area where TB is uncommonly diagnosed and where drug-resistant strains are very rare would require only a minority of patients be placed in isolation with full respiratory protection. In contrast, in high-risk areas, nearly all cases will require full respiratory protection. Individual institutional risk assessment and isolation policies are essential to avoid unacceptable levels of overisolation that

are likely to adversely affect patient care directly, but also result in the misallocation of limited funds for respirator usage. It is also important to emphasize that the risk for any particular patient will change over time. The risk can be increased, decreased, or eliminated altogether. The four-tier ranking set out below is one model for institutions to consider; each institution should adapt a classification that is flexible, but provides a practical system that protects patients and employees.

HIGHEST-RISK PATIENTS

Isolation room and respirator are required. The respirator may be any type approved by NIOSH for TB use. Depending on the risk of TB and of MDR TB, HEPA and positive-pressure respirators may be considered. Patients in this group have newly diagnosed conditions that are untreated, having pulmonary TB with cough and positive sputum smears. Also included are (1) patients who have negative sputum smears but are high risk for drug-resistant tuberculosis with cough and lung infiltrate, and (2) patients who are suspected of having pulmonary TB, but sputum smear laboratory reports are pending.

HIGH RISK

Isolation room and respirator are required. Patients in this group include those who are smear positive and receiving effective chemotherapy. In most instances of newly diagnosed TB, chemotherapy is started before drug susceptibility results are known. For most patients, developing an "effective regimen" will not be difficult (a four-drug regimen is used in areas where drug resistance is uncommon). It will be uncommon for such patients to remain hospitalized for prolonged periods. However, when hospitalization is prolonged, the infectiousness of each patient should be re-evaluated from time to time. After 2 weeks of effective chemotherapy, the infectiousness of almost all patients will be reduced markedly (particularly when the patient is clinically improved and cough frequency is reduced) and the requirement to use a respirator in the isolation room should be reviewed, with the expectation that in most cases its use can be discontinued. Patients with smear-negative pulmonary TB receiving effective chemotherapy become very low risk after 1 to 2 weeks of treatment.

LOW-MODERATE RISK

Persons in this group include those suspected of having TB, but have three or more negative sputum smears. (All three separate specimens may be collected in 1 day's time.) Such patients may remain in isolation rooms, depending on the level of suspicion, but respirators are not required. This situation is most applicable in geographic areas of low risk where drug

resistance is uncommon. In geographic areas at high risk for TB and drug resistance, respirator use should be required longer, pending repeated or more aggressive diagnostic studies.

LOW RISK

These patients include those in whom the diagnosis of TB is possible, but unlikely. These patients may or may not be placed in isolation, but a respirator is not required. This is most applicable to those areas of low risk where drug resistance is uncommon. Persons having a previous diagnosis of TB who have satisfactorily completed chemotherapy and who are smear negative need not be placed in isolation.

APPENDIX

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