Community-Wide Implementation of Targeted Testing for and Treatment of Latent Tuberculosis Infection

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Treatment of latent infection due to Mycobacterium tuberculosis will likely increase in importance as a strategy to prevent tuberculosis in the United States. This review was undertaken to assess how targeted testing and treatment of latent tuberculosis infection are currently organized, with a focus on the extension of those services from public health clinics to other community sites. Targeted testing programs are now being implemented in primary care neighborhood clinics, syringe-exchange programs, jails, and teen health clinics. Organizational issues at those new sites include the need for a tracking system for clinical follow-up and for incentives to promote adherence. There is increasing experience with directly observed treatment of latent tuberculosis infection. Communities that receive large numbers of immigrants and refugees should prioritize the evaluation of those whose chest radiographs are suggestive of tuberculosis. Current studies continue to point out imperfections in the current tools, such as the tuberculin skin test and isoniazid. Finally, the advent of managed care, especially for Medicaid recipients, presents both opportunities and challenges for expansion of population-based preventive health services.

Tuberculosis Commentaty

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nities and challenges for population-based preventive services such as treatment of latent tuberculosis infection [10].

In 1995 the Advisory Council for the Elimination of Tuberculosis (ACET) proposed a number of innovations in the organization and delivery of treatment of latent tuberculosis infection [11], reviewed below. Given the scenario of a changing landscape from a number of perspectives, it is appropriate to review the current status of targeted testing and treatment of latent tuberculosis infection. The emphasis will be to highlight efforts to implement the 1995 ACET recommendations at the local level, with a focus on the extension of those services from public health tuberculosis clinics to other community sites.

The underlying principles of targeted testing and treatment of latent tuberculosis infection and the current tools, i.e., the tuberculin skin test and isoniazid, will not be reviewed here. For background information, the reader is referred to recent authoritative reviews [11–14].

In this review, the phrase “treatment of latent tuberculosis infection” is used instead of the conventional terminology “preventive treatment for tuberculosis [infection].” This new terminology has been recommended by an expert committee convened by the American Thoracic Society and the Centers for Disease Control and Prevention (CDC) as reflecting more accurately the intervention in which drug therapy is administered to terminate tuberculosis infection in its latent phase.

Current Recommendations for the Organization and Delivery of Targeted Testing and Treatment of Latent Tuberculosis Infection

In the ACET Strategic Plan for the Elimination of Tuberculosis in the United States [15], published in 1989, the responsibility for treatment of latent tuberculosis infection in high-risk groups was assigned directly to public health agencies, following the conventional belief that the expertise in skin test administration and reading, as well as the intensive follow-up required to ensure compliance with and to prevent side effects of isoniazid treatment, were beyond the scope of most medical practices. However, the ACET 1995 recommendations [11] emphasized the concept of community-based targeted testing for latent tuberculosis infection. It was acknowledged that health departments generally lack resources to undertake community-wide targeted testing programs among high-risk populations. The participation of other health care providers in diagnosing and treating latent tuberculosis infection was called for to ensure the successful implementation of community-wide efforts to prevent tuberculosis in high-risk groups.

The 1995 recommendations also established targeted testing and treatment of latent tuberculosis infection as activities of lower priority than those of identifying and treating all active tuberculosis cases and evaluating and protecting contacts of active cases. Except for special purposes, targeted testing for its own sake was discouraged except for situations in which there are sufficient resources and a plan to complete a course of treatment for persons found to have latent tuberculosis in a targeted testing program. Screening of low-risk persons was discouraged.

Finally, a flexible approach to identifying high-risk groups was recommended, and state and local public health agencies were encouraged to analyze their own data to identify high-risk groups of local or regional importance, on the basis of current trends in the epidemiology of tuberculosis and latent tuberculosis infection.

Defining “High-Risk” Status for Tuberculosis

Although current strategies for targeted testing and treatment of latent tuberculosis infection are predicated on reaching target groups that are at increased risk of tuberculosis, explicit criteria for assignment of the “high risk” designation for groups of persons are not available. A precise way to assess the risk of tuberculosis in a group of individuals is to compare the group’s risk with that of the general United States population, which in 1997 was 7.4 cases per 100. Available data, in some cases formal and in others informal, suggest that in all groups designated at the national level as having a high risk of tuberculosis, the incidence of tuberculosis is 2–5 times that of the general population. In Seattle and its surrounding county, among the main high-risk groups—foreign-born persons from areas of high tuberculosis incidence, homeless persons, and those with HIV infection—the annual incidence rates, based on the best available population information, are >50 per 100,000 persons, at least 7 times that of the region’s general population, which is currently 7 per 100,000.

Another approach to group-associated risk assessments for tuberculosis is to determine the rate of reactive tuberculin skin tests in epidemiologically defined population subgroups, in order to identify those with an increased group-derived risk of tuberculosis due to the increased prevalence of latent tuberculosis infection in its members. This is a feasible undertaking at a local level, through well-conducted skin test surveys as well as through review of available data from existing skin test programs throughout the community.

The question of what rate of tuberculin reactivity characterizes a high-risk group has yet to be addressed on a formal level. In Seattle, two high-risk groups—foreign-born persons and homeless persons—have rates of reactive skin tests (≥10 mm) of 20%–50%, 5–10 times higher than those of surveyed groups without risk factors, e.g., firefighters and police, who show rates of reactive skin tests (≥10 mm) of <5% (author’s unpublished observations).

Current Trends in the Organization and Delivery of Targeted Testing and Treatment of Latent Tuberculosis Infection

As noted, there is a growing awareness that health departments lack the resources as well as the access to target popu-
lations to be the sole managers of tuberculosis preventive services in most communities. For example, the Seattle–King County Department of Public Health Tuberculosis Control Program currently administers treatment of latent tuberculosis infection to ~1,400 high-risk persons per year and estimates that other providers treat only a small fraction of that number. However, the program has also estimated that there are presently 30,000–50,000 persons from high-risk groups in the community who are likely to have latent tuberculosis infection and are candidates for treatment.

Furthermore, the pool of persons at risk is dynamic, undergoing constant replenishment through primary and secondary migration and the transmission of infection among homeless persons. If this information can be applied generally throughout the United States, it indicates that public health agencies must find new ways of reaching high-risk groups if they wish to increase the treatment of latent tuberculosis infection as a means of reducing the incidence of tuberculosis in a community.

**Targeted testing of children.** The changing concept of screening and targeted testing of children was reviewed by Starke in a recent editorial [16]. Writing in support of revised recommendations from the American Academy of Pediatrics (AAP) [17] that discourage the routine screening of children, Starke laid the responsibility to prevent tuberculosis in children squarely on the shoulders of public health departments, which have the potential to prevent up to one-third of tuberculosis cases involving children simply by performing or organizing timely and thorough contact investigations of adult tuberculosis cases.

Screening of low-risk children continues, despite evidence that it is not cost-effective. Cheng et al. [18] surveyed 1,272 community pediatricians and family physicians from the mid-Atlantic area and found that 64% of respondents tested low-risk children periodically. Furthermore, 29% used multiple-puncture skin tests exclusively, despite the 1994 AAP recommendation against their use [17].

Screening of children from low-income neighborhoods—included among high-risk groups in national recommendations [17]—was not productive in at least two recent studies. Servint et al. [19] reported that among inner-city children in Baltimore the prevalence rate of positive skin tests was only 0.8%, while Christy et al. [20] found that among children screened at a hospital-based pediatric primary care center in Rochester, New York, serving families from a low-income neighborhood, the rate was only 1.4%. On the basis of the latter data, the authors concluded that the recommended policy of annual testing of that population of children was not likely to be cost-effective.

**Targeted testing of foreign-born persons.** Effective access to foreign-born persons for treatment of latent tuberculosis infection is a major issue in current tuberculosis control. A working group convened by the Division of Tuberculosis Elimination of the CDC [21] concluded that barriers to tuberculosis control among the foreign-born can be linguistic, cultural, and social, and that those barriers can best be overcome by partnerships between tuberculosis control programs and organizations that provide basic health services to immigrants and refugees.

Health care facilities that serve as sites of primary health care for foreign-born persons are logical places for targeted testing and treatment of latent tuberculosis infection. Nelson et al. [22] reported on an evaluation of opportunities for health promotion and disease prevention among recent Vietnamese immigrants presenting for primary care to two neighborhood health centers in Boston. Among a group of 99 persons, 32% were smokers, 17% were depressed, 14% were chronic hepatitis B carriers, 51% had intestinal parasites, and 70% were tuberculin-positive. Among patients with positive skin tests, treatment of latent tuberculosis infection was recommended for the majority.

In Seattle, in response to recommendations of a 1993 Health Community Tuberculosis Task Force, the Tuberculosis Control Program has been working to develop partnerships with primary care clinics to increase preventive services for tuberculosis in the community. Such clinics include health department primary care clinics and publicly funded neighborhood clinics that serve ethnic and foreign-born clients such as Hispanics and Asians. The responsibilities of the tuberculosis program are to provide tuberculosis education to health care providers, patient education materials, isoniazid for the clinics to dispense, chest radiography with interpretation for patients who cannot undergo the procedure elsewhere, and a tracking system for clinical follow-up of clients receiving treatment of latent tuberculosis infection. The responsibilities of the primary care sites are to conduct targeted testing and treatment of latent tuberculosis infection programs among their primary care patients, using recommended protocols for monitoring and follow-up of persons with drug toxicity, and to collect statistics on numbers of persons screened and those offered and completing treatment of latent tuberculosis infection.

The most successful partnership in the Seattle program is with the International District Community Health Center (IDCHC), which serves Asian and Pacific Island clients, >90% of whom are immigrants. During 1997 the IDCHC screened 471 of its clients, read 94% of applied skin tests, had a 29% rate of positive skin tests, recommended treatment of latent tuberculosis infection to 63% of tuberculin-positive reactors, and achieved a completion rate of ~80%. As an unexpected benefit, skin-test targeted testing at the IDCHC has led to the diagnosis, during follow-up evaluations of tuberculin reactors, of one to three asymptomatic cases of tuberculosis in each of the past 3 years. A key factor in the success of this program is the assignment and training of a specific clinic staff member to manage the tracking and follow-up of clients receiving treatment of latent tuberculosis infection.
It is recommended that considerable attention be given to the targeted testing of immigrants and refugees identified overseas as tuberculosis suspects. On the basis of examination of acid-fast-bacilli smears of sputum and chest radiographs, applicants for immigration are classified as class A, if smear-positive; class B1, if smear-negative, but with a chest radiograph compatible with active tuberculosis; or class B2, if smear-negative and with a chest radiograph compatible with inactive tuberculosis. Persons with B1 or B2 status are allowed to immigrate to the United States but are required to report for follow-up evaluation at a health department in their intended state of residence. It is estimated that ~6,000 persons with B1 status, and twice that number of persons with B2 status, enter the United States each year [21].

Several follow-up studies of class B1 and B2 immigrants in the United States have now been published [23–26]. Surveys from Hawaii, Seattle, San Francisco, New York City, New York State, and Portland, Oregon, found that the burden of tuberculosis caused by classified immigrants in certain communities and states was substantial. In Hawaii, 95 (77%) of 124 immigrants for whom active tuberculosis was diagnosed within 1 year of arrival had been classified as B1 or B2. The surveys also showed high rates of active tuberculosis in class B immigrants. The proportion of class B1 immigrants found to have confirmed active tuberculosis on the basis of health department evaluations ranged from 3.3% to 14.0%; among B2 immigrants, 0.4%–3.8% of those screened had active disease. Finally, it was shown in several cities that 39%–62% of evaluated class B immigrants were eligible for treatment of latent tuberculosis infection.

On the basis of these data showing high yields of tuberculosis cases and candidates for treatment of latent tuberculosis infection among class B refugee and immigrant arrivals, cities and states receiving large numbers of class B immigrants and refugees should give such persons their highest priority for active case finding and targeted testing. Catlos et al. [27] recently evaluated yields and costs of letters, telephone calls, and home visits in motivating class A and B immigrants to present for evaluation. Letters sent by the health department to the patient immediately upon notification from the CDC that a classified immigrant had arrived in the community had the highest yield and lowest cost of the three interventions that were studied.

Recent studies have cast doubt on the efficacy of targeted testing programs for immigrants and refugees as currently constituted. Menzies modeled the outcome of targeted testing and treatment with isoniazid for immigrants to Canada from five regions of the world: Africa, the Caribbean, Central/South America, Asia, and Europe [28]. Employing assumptions from published work on region-specific rates of positive skin tests, rates of false-positive tuberculin reactions due to nontuberculous mycobacteria and BCG, adherence with referral for evaluation, completion of treatment of latent tuberculosis infection, rates of breakdown with active tuberculosis, and protective efficacy of isoniazid treatment of latent tuberculosis infection, Menzies found that the targeted testing of 50,000 immigrants aged 0–20 years, 10,000 from each geographic region, would result in the prevention over the lifetime of the cohort of only 210 cases of tuberculosis.

Furthermore, those cases projected to be prevented represented only 20% of cases expected to arise from the cohorts over their lifetime. Applying conservative estimates for costs of targeted testing, evaluation, and treatment, Menzies determined that the cost of the program per case of tuberculosis prevented was ~$10,000 (Canadian currency).

In a study still in progress, Mageto et al. are finding that the refugee screening program for Southeast Asian refugees in Seattle has achieved questionable success in preventing tuberculosis in that population. The authors analyzed all 120 cases of tuberculosis reported in Southeast Asian refugees from Seattle–King County, Washington, during the 6-year period of 1992–1997. They found that 81 of the cases (68%) had been screened and evaluated at their own program at least 6 months prior to their diagnosis of tuberculosis and that 47 of those who had been screened, 36% of subsequent cases, had received isoniazid treatment for latent tuberculosis infection.

Whether these refugees did not complete the course of treatment of latent tuberculosis infection and whether they may have originally been infected with isoniazid-resistant organisms is under study. However, it is disquieting that the majority of cases of tuberculosis in Southeast Asian refugees in Seattle during the past 6 years arose in persons who were evaluated by the public health tuberculosis program and who, in many cases, received treatment for latent tuberculosis infection. This emphasizes that further work is necessary to achieve an effective strategy to prevent tuberculosis in that population.

Targeted testing of intravenous drug users, persons in jail, and inner-city homeless persons. Several recent studies explore targeted testing for tuberculosis in venues where persons from high-risk groups are followed for health services or other purposes. Perlman et al. [29] described implementation of tuberculosis testing at a syringe-exchange program in New York City. Fifteen percent of participants had skin test reactions of ≥10 mm. The authors employed a direct cash incentive for persons to return for the skin test reading and provided assistance for subsequent medical evaluations.

The program is achieving a high rate of completion of evaluation for tuberculosis, and focus groups suggest that participants are favorably inclined toward the availability of tuberculosis services at the syringe-exchange program. A majority of clients screened for tuberculosis reported using the exchange two or more times a week for 6 months or more, a finding suggesting that the program could be considered as a site for directly observed treatment of latent tuberculosis infection.
Bock et al. [30] conducted a targeted testing program through a coalition of facilities and providers serving high-risk inner-city residents in Atlanta. Testing was done at sites where the target population had most extensive contact with the health care system—in the waiting areas of the public hospital that served inner-city residents; the city jail; and neighborhood clinics—and by outreach teams in neighborhoods frequented by drug users. Follow-up services were arranged through the tuberculosis clinic at the public hospital.

During a 3-year period, tuberculin skin tests were administered to 7,246 persons in the identified access points; 65% of administered tests were read, and 17% of those were positive. However, only half of the skin test-positive persons were <35 years of age and met indications for preventive therapy; furthermore, only 20% of those who started treatment for latent tuberculosis infection completed the course. The authors concluded that there is a need for regimens that are shorter, to enhance compliance, and safer, to be suitable for use by older persons with latent tuberculosis infection.

The unique challenges of targeted testing for tuberculosis in jails were highlighted by Tulsky et al. [31], in their report of the results of such testing in the San Francisco jail, where most inmates were foreign-born Hispanics. Twenty-seven percent of tested inmates were tuberculin-positive, and isoniazid treatment was initiated for 45% of them. However, the majority of those beginning treatment were released before completion of therapy, and among those, only 3% went to the San Francisco Health Department Tuberculosis Clinic to continue therapy.

In another study those authors found that the use of standardized tuberculosis education, with or without a cash incentive, improved adherence (24% vs. 3%) of this population to follow-up at the tuberculosis clinic following release from jail [32].

Nolan et al. developed an integrated program in which outreach workers became acquainted with inmates found to have latent tuberculosis infection on jail-based testing [33]. Those outreach workers then administered directly observed treatment of latent tuberculosis infection in the community after release. Even with this individualized approach, 40% of released inmates could not be located. Among the remainder, however, 63 of 105 (60%) who accepted directly observed treatment completed the regimen, compared with a completion rate of 29% among 52 released inmates who chose self-supervised treatment of latent tuberculosis infection (P = .0002).

Pilote et al. evaluated interventions to improve adherence to advice for tuberculosis evaluation among homeless persons screened in shelters and food lines in San Francisco [34]. The authors found that a monetary incentive of $5 or assistance from a peer health adviser produced higher rates of follow-up appointments at the tuberculosis clinic (84% and 75%, respectively) than usual measures (referral slips and bus tokens only [53%]). Among 173 homeless persons completing their evaluation in this targeted testing program, 72 (42%) started treatment for latent tuberculosis infection and 3 cases of active tuberculosis were identified.

**Directly Observed Treatment of Latent Tuberculosis Infection**

A number of recent studies have reported the implementation of directly observed treatment of latent tuberculosis infection. In the project with released jail inmates described above, Nolan et al. found that although directly observed treatment produced a higher completion rate than self-supervised treatment of latent tuberculosis infection, the program was costly [33]. Applying accepted figures for preventive efficacy of a completed course of isoniazid treatment and lifetime risk of tuberculosis in persons with latent tuberculosis infection, the authors estimated that only 4.4 future tuberculosis cases were prevented during the course of a project that utilized three full-time health professionals for 2.5 years. On the basis of these results, the authors concluded that funds for tuberculosis control, if limited, should not be diverted to jail-based testing and post-release directly observed treatment.

Kohn et al. [35] also reported a higher rate of completion of treatment of latent tuberculosis infection with directly observed treatment than with self-supervision (88% vs. 50%; P = .001) in a school-based clinic at an inner-city New York City high school. In contrast to the Seattle jail study, however, the authors concluded that since directly observed treatment was administered on-site by existing personnel, the program was likely to be cost-effective. Heal et al. [36] compared results of self-supervised and twice-weekly directly observed isoniazid therapy among aboriginal persons with latent tuberculosis infection. In a program in which patients selected their mode of therapy, 75.2% of those choosing directly observed treatment completed 6 months of isoniazid therapy and 50.9% completed 12 months. Among the group that chose self-administered isoniazid, the completion rates at both time intervals were significantly lower: 60.9% at 6 months and 36.6% at 12 months.

Using a different analytic approach, Graham et al. [37] found that during a 6-year period when access to directly observed treatment of latent tuberculosis infection was expanded more than threefold, a population of 2,960 injection drug users in Baltimore in which the prevalence of HIV infection was 30% experienced a decline in tuberculosis incidence of 83%. No cases of tuberculosis occurred in the population that received treatment for latent tuberculosis infection, whereas 12 cases occurred among those not receiving such treatment.

Gourevitch et al. [38] performed a cost-effectiveness analysis of directly observed treatment of latent tuberculosis infection, using data from clients at a methadone treatment program in the Bronx, New York. The authors concluded that in that setting directly observed treatment is likely to be a highly
cost-effective intervention, producing net savings in tuberculosis-related hospital costs, if it is able to improve adherence by as little as 10% over self-supervised therapy.

**Treatment of Latent, Isoniazid-Resistant Tuberculosis Infection**

Several investigations have addressed the issue of treatment of latent tuberculosis infection for persons with a high probability of latent infection with isoniazid-resistant *M. tuberculosis*. Polesky et al. [39] analyzed the outcome of several modes of preventive treatment that had been used during an outbreak of isoniazid- and streptomycin-resistant tuberculosis in the homeless population in Boston in the 1980s. Among 204 homeless persons whose skin test status converted during the outbreak, active tuberculosis had subsequently been reported in 6 (8.6%) of 71 untreated converters, in 3 (7.9%) of 38 who received preventive treatment with isoniazid, and in none of 95 who received prophylactic rifampin or isoniazid plus rifampin. The three cases of tuberculosis following isoniazid treatment were caused by organisms that were resistant to isoniazid.

Villarino et al. followed 157 high school students who were given rifampin for treatment of latent tuberculosis infection following exposure to a highly infectious student with isoniazid-resistant tuberculosis [40]. Only two required discontinuation of rifampin therapy due to adverse effects, and six stopped receiving treatment for other reasons. During 2 years of follow-up, no cases of tuberculosis occurred among treated students, whereas seven cases of tuberculosis (5% of those exposed) would have been expected with no intervention.

Sterling et al. performed a decision analysis to assess the benefit of isoniazid treatment of latent tuberculosis infection in areas with high rates of isoniazid-resistant tuberculosis [41]. They concluded that in young, HIV-negative tuberculin reactors there is a net benefit, in terms of days of life gained from isoniazid treatment of latent tuberculosis infection, if the rate of isoniazid resistance is 25% or less. Recent tuberculin converters received somewhat greater benefit because of their greater risk of disease.

**Managed Care and Tuberculosis Targeted Testing: Opportunities and Challenges**

One-quarter of the United States population is now enrolled in health maintenance organizations. This new trend in the organization of health care delivery in the United States may have tremendous impact on tuberculosis preventive services in a community, because it is becoming the dominant mode of health care for Medicaid recipients, a group that includes many persons at high risk of tuberculosis. At the end of 1996, managed care programs provided care for one-third of Medicaid beneficiaries, with enrollment in such programs growing at a rate of 30%–40% annually [9].

There is a growing body of literature outlining the challenges that face public health agencies with the transition to managed care [9, 10, 42, 43]. Rutherford [42] pointed out that for many years tuberculosis diagnosis, treatment, and prevention have been the almost exclusive province of public health agencies. This fact has led to a perception in the public health sector that the private medical sector has neither the knowledge or capability nor interest to do clinical tuberculosis-oriented public health practice.

Halverson et al. [10], on the other hand, expressed the view that managed care organizations are particularly attractive partners for public health agencies in their disease control efforts. Those authors encourage health departments to engage health plans actively in the adoption of a community-wide tuberculosis prevention and control protocol. However, they caution that such joint efforts are likely to succeed only if the parties recognize that it will take time, effort, and expense to overcome differences between organizations in mission, culture, and financial incentives. Likewise, Friedman [43] called for an acknowledgment of the shared vision of public health agencies and managed care organizations, which she sees as the willingness to invest time, effort, and resources to keep people healthy.

Examples of arrangements between managed care organizations and health departments are beginning to appear. Groups contracting with Medi-Cal, the California Medicaid Organization, are required to develop memoranda of understanding with local health departments to clarify the roles and responsibilities of each [42]. In another approach, the Pacific Business Group on Health, a large employer and Medicaid purchasing coalition, requires health plans that wish to do business with its members to include in their benefit package the clinical preventive services identified by the United States Preventive Services Task Force [42, 44].

An interesting collaborative project has been described [45] between Medicaid managed care organizations and the San Diego school system, which includes tuberculosis skin testing among its package of services. Miller et al. [46] have recently published a standard set of contract specifications concerning treatment and prevention of tuberculosis for purchasers, such as state Medicaid agencies, of contracted services from managed care organizations.

**Conclusion**

For treatment of latent tuberculosis infection to increase in importance as a tool for tuberculosis control in communities throughout the United States, it will be necessary for public health agencies to develop strategies to improve their access to populations at high risk of tuberculosis and to increase acceptance and completion of treatment of latent tuberculosis infec-
tion among high-risk populations. There is a particular need for improvement in access to foreign-born persons, the most prevalent high-risk group.

Successful targeted testing programs will increasingly be community-based and dependent upon the delineation of high-risk groups at the local level and the development of partnerships between public health agencies and a variety of patient care providers and payor groups. Given the rapid increase in persons enrolled in managed health care, there will be considerable mutual benefit, to enrollees and to the public, if preventive health services such as treatment of latent tuberculosis infection are extended to that venue.

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