

Laboratory Role in Tuberculosis Control

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ABSTRACT

The term “tuberculosis” (TB) refers to infection with the bacterium *Mycobacterium tuberculosis* that has progressed to active disease. This disease is a public health threat because it is caused by a microorganism that is potentially fatal for humans, and transmission is commonly through the inhalation of airborne droplets expelled by infectious persons with active disease. The World Health Organization (WHO) estimates that there are more than 8 million new cases of TB each year, 2 million deaths from the disease each year, and that one-third of the world population is infected with *M. tuberculosis* and at risk for active disease.¹ In 2003, the 100-year anniversary of the founding of the Wisconsin State Laboratory of Hygiene (WSLH), TB is recognized as a disease that is preventable and now almost always treatable. An early and accurate diagnosis of TB is perhaps the most significant intervention step in TB control. Early diagnosis permits expedited treatment and limitation of spread. An effective TB laboratory program plays an essential role in the early and accurate diagnosis and appropriate treatment of TB. This article examines that role.

INTRODUCTION

Tuberculosis (TB) remains a leading infectious cause of death worldwide and a leading public health priority in Wisconsin, the United States, and the world. The United States made important gains in TB control in the 20th century and envisioned the eventual elimination of the disease in this country, only to see a resurgence in the mid-1980s. The public health community in the United States and Wisconsin has rededicated itself to the goal of TB elimination. Challenges include the changing demographics and evolving epidemiology of TB in this country and the impact of the global TB epidemic upon the United States.

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HISTORICAL PERSPECTIVE

TB has affected humans since before recorded history, but it was not until the 1600s that TB grew to epidemic proportions in Europe as urban migration intensified and population densities increased.² By 1892, the year that Dr Robert Koch announced the discovery of the infectious agent that causes tuberculosis, TB killed 1 out of every 7 people living in the United States and Europe. By the early 1900s, laboratories had the ability to demonstrate the etiologic agent in acid-fast sputum smears (it was one of the handful of tests offered by the WSLH in its first decade of existence), and the clinician had use of the chest x-ray to diagnose TB. At the same time, improving social and economic conditions and the institution of a public health infrastructure to help control the transmission of infection contributed to the beginning of a decline of TB in this country and Europe. Except for interruptions during World War I and World War II, the decline in TB continued through most of the 20th century. The decline was propelled by the discovery of effective antituberculosis antimicrobial agents in the 1940s and 1950s, and it accelerated with the development of effective antituberculosis combination therapy in the early 1960s. From 1953, the year a national surveillance system was established for reporting new cases of active TB disease, to 1985, the United States saw a consistent 5%-6% per year average decline in TB incidence.³

The decline in TB incidence in the United States leveled off after 1985 and then the incidence started to increase. In 1992, TB incidence had increased by 20% since 1985.⁴ Reasons for the sudden increase have been attributed to the human immunodeficiency virus (HIV) epidemic, increasing numbers of people in congregate settings (homeless shelters, correction facilities, residential health care centers), immigration from countries with high rates of TB, outbreaks of multi-drug-resistant strains of TB (Figure 1), and perhaps most importantly, a decline in the public health infrastructure for TB control.⁵⁻⁸ Unfortunately, the declining TB rate had bred a sense of complacency rather than a sense of what should be accomplished, and TB control was neglected, begin-

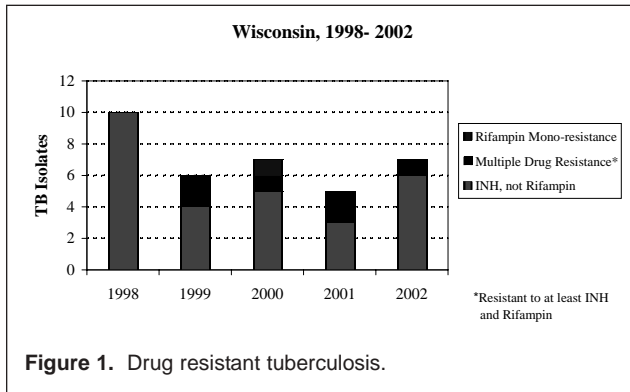


Figure 1. Drug resistant tuberculosis.

ning in the early 1970s. Federal funding for tuberculosis control programming was systematically reduced, and categorical funding was entirely eliminated from the Centers for Disease Control and Prevention (CDC) budget in 1972. Categorical funding for TB control was not reinstated for 9 years, and it did not reach its peak 1969 level again until 1989.^{3,7}

In 1989, the CDC and the Advisory Council for the Elimination of Tuberculosis (ACET) published a strategic plan wherein the public health community would rededicate itself to the elimination of TB in the United States, defined as less than 1 new case per million population per year. The plan was to achieve this goal by the year 2010, with an interim goal of 3.5 cases per 100,000 population by the year 2000.⁹

The resurgence of TB promoted a reinvestment in the resources to combat the increase in cases and renewed the interest in the elimination of the disease in the United States. This concerted effort has achieved good results. The 15,078 TB cases reported to CDC in 2002 represent the lowest rate of reported TB in the United States since reporting started in 1953. The 2002 US TB rate continues a 10-year period of yearly declines that began in 1993.⁸ This same picture is seen in Wisconsin, with 78 active cases reported in 2002, down from 106 in 1992. Even with this success, the United States and Wisconsin are still a long way from achieving the goal of TB elimination, and the gains made in reestablishing control over TB transmission are now prompting a shift in focus to addressing latent infection. The increased rates of transmission in this country in the late 1980s and early 1990s plus the continuing immigration from countries with high rates of TB infection have resulted in a large number of cases of latent TB infection in the United States.⁵ The CDC estimates that there are 10 to 15 million people latently infected with TB in this country.¹⁰ If active transmission is under better control in this country, the challenge now is to prevent the emergence of active disease in the pool of latently infected individuals.^{6,11}

CONTROL OF TB USING LABORATORY-BASED STRATEGIES

In January, 2000, the US Department of Health and Human Services published *Healthy People 2010—Understanding and Improving Health*. Among the numerous public health goals and objectives presented in this report were 4 tuberculosis goals, 1 of which was to reduce the average time for the laboratory to confirm and report TB cases.¹² The steady decline in TB incidence over the past 10 years indicates that the program for elimination of TB in the United States is achieving some success. The laboratory is playing an important part in this success through advances made in applied diagnostics including new methods that reduce the time needed to detect growth of *M. tuberculosis* in diagnostic specimens.¹³

Advances in Diagnostic Testing

Starting in the 1980s, improvements in laboratory methodology were developed beyond the standard smear for acid-fast bacilli (AFB) and solid media for culture and drug susceptibility testing. With increasing federal funding for public health in the early 1990s, TB laboratory improvement efforts were intensified to actively upgrade laboratory facilities, procedures, and reporting protocols in order to provide a safe working environment and the fastest turn-around-time of results possible. An increase in the numbers of multi-drug-resistant (MDR) strains of *M. tuberculosis* between 1985 and 1992 prompted stronger enforcement of safety standards for TB laboratories. In 1996, WSLH completed the construction of a new Biosafety Level III laboratory for its Mycobacteriology Unit at a cost of over \$400,000. This state-of-the-art 1200-square-foot facility provides a safe and efficient working environment that also minimizes the opportunity for laboratory cross-contamination of cultures. New diagnostic testing procedures and reporting protocols that were developed in the 1980s and 1990s and instituted at the WSLH are included in Table 1.

Genotyping Methodologies and Serologic Testing for TB Control

The development and use of molecular genetic typing (genotyping) methodologies and protocols for the subtyping of *M. tuberculosis* strains is proving to be a potent tool for TB control. *M. tuberculosis* genotyping has refined our understanding of TB transmission dynamics and proven its utility in confirmation of epidemiologically implicated outbreaks, distinguishing unresolved cases as relapses versus exogenous re-infections, and identifying suspected laboratory cross-contamination

Table 1. Laboratory Testing Improvements

Procedure or Protocol Change	Year
Fluorochrome stain for AFB smear examination that is less time consuming than the older carbol fuchsin method	Mid-1970s
Commercial broth systems for culture, starting with the radiometric BACTEC system	Early 1980s
Molecular methodologies (DNA probes) for the identification of <i>M. tuberculosis</i> in positive cultures	Late 1980s
Automated broth systems for culture	Early 1990s
High performance liquid chromatography (HPLC) of mycolic acids on AFB-positive cultures for the speciation of mycobacteria	Early 1990s
Commercial broth systems for drug susceptibility testing for first-line anti-TB drugs, starting with the radiometric BACTEC system	Early 1990s
Use of nucleic acid amplification (NAA-TB) testing on all new smear-positive patients	1996
Use of a courier to transport specimens to the laboratory within 24 hours of collection	1997
Use of NAA-TB testing on smear-negative patients with signs and symptoms of TB and risk factors for TB infection	2000
Reporting all results by facsimile as soon as results are available	2000

cases.¹⁴ WSLH and the Wisconsin Division of Public Health (WDPH) TB Control Program are presently involved in a study with CDC in the development of a universal genotyping scheme that incorporates rapid PCR-based methodologies. Wisconsin was chosen to participate in this study because WSLH has a repository of TB isolates from virtually all culture-positive Wisconsin TB cases since 2000 and a majority of the isolates from cases in the 6 years prior to 2000. In addition, the WDPH has excellent demographic and epidemiological information on all these cases. Universal genotyping of all new TB isolates is proving its usefulness in the examination of ongoing community transmission and the identification of unsuspected transmission links. Universal TB genotyping will soon be available to all TB control programs in the country.¹⁵

For the past 100 years, the only test available for diagnosing latent TB infection (LTBI) was the tuberculin skin test (TST). In 2001 the FDA approved a commercial blood test which detects cell-mediated immunity *in vitro* to TB infection. This testing methodology, which has many potential advantages over the TST, creates a role for the laboratory in detection of LTBI. An increased focus on the detection of LTBI is being promoted in light of the estimated 10 million to 15 million people in this country who have LTBI.^{10,16} In collaboration with the WDPH and CDC, the WSLH is presently involved in the evaluation of this new testing methodology when used on individuals recently exposed to TB cases.

PARTNERSHIPS AND COLLABORATIONS

TB patients must have access to state-of-the-art laboratory services wherever they may live. No single approach to achieving this level of service in the United States is necessarily the best, but rather the level must be achieved through innovative approaches tailored to

the situation and location.¹⁷ The development and strengthening of partnerships and collaborations is the approach that has been successful in Wisconsin. A TB laboratory white paper was produced in 1998 by the major players in TB control in Wisconsin. This white paper assessed the status of TB laboratory testing in Wisconsin and provided recommendations for improvements. A major goal proposed by the TB white paper was that all TB laboratory testing in Wisconsin be of the highest quality available and *consistent regardless of the laboratory facility*.¹⁸ The Wisconsin Mycobacteriology Laboratory Network (WMLN) was developed specifically to address this goal. The WSLH has taken the leadership role in developing and sponsoring this network. The WMLN:

- is an ongoing collaboration of all 30 or so laboratories in Wisconsin that perform some level of testing for TB to share expertise and data critical to the state's TB control efforts and to improve TB testing quality overall in Wisconsin.
- is a forum for assisting all Wisconsin TB laboratories to be in compliance with the recommendations of the first, second, third, fourth, and future National Conferences on Laboratory Aspects of Tuberculosis, which are sponsored by the Association of Public Health Laboratories (APHL) and the CDC.
- acts as a conduit for transfer of technical information from CDC, APHL, and the WDPH TB Control Program.
- holds an annual statewide conference and periodic regional meetings. Issues addressed include laboratory safety, adherence to recommended methods, use of appropriate media, isolation rates, laboratory result turn around times, reporting processes, and maintaining proficiency in small volume laboratories.

- provides a laboratory-based mechanism for monitoring the incidence of mycobacteria and *M. tuberculosis* isolation and drug-resistance rates. Network members report the identification of all new mycobacterial isolates to WSLH on a monthly basis. WSLH generates isolation reports monthly, quarterly, and annually, which are distributed to network members and state and local public health departments.
- provides the means for developing a central repository for all of Wisconsin's new patients' TB isolates for the purpose of DNA fingerprinting analysis. This analysis will help identify transmission links.

WSLH has also developed strong partnerships and collaborations on a national level. WSLH has worked closely with CDC for the past 7 years to provide an international performance evaluation program for laboratories performing molecular amplification testing for *M. tuberculosis*. WSLH is also collaborating with CDC in the development of a universal genotyping scheme for *M. tuberculosis* and in the evaluation of an *in vitro* laboratory test to diagnosis latent TB infection, both of which were discussed earlier in this article.

SUMMARY

On March 24 each year, the international medical community observes World TB Day to recognize the effect that TB still has on millions of people. Even though TB is again declining in the United States and Wisconsin, the global TB epidemic continues in many other countries and remains a significant source of new US cases in immigrants and refugees.¹⁹ Elimination of TB in the United States will not be possible without a substantial reduction in the global burden of TB.¹⁹

The reemergence in the mid-1980s of TB as a serious public health threat in this country demonstrated that there is a price to pay for complacency. It reinforced the notion that public health services for TB control, including TB laboratory services, must be maintained even during periods of decreasing case rates. Essential priorities of an effective TB control program include finding all cases of active TB in a timely manner and ensuring completion of therapy, and finding all cases of latent TB infection who are at high risk of progressing to active disease and ensuring completion of appropriate treatment.^{20,21} A successful TB public health laboratory must engage in those activities that are essential to help achieve these priorities. WSLH's challenge as Wisconsin's public health laboratory is to maintain those activities that promote the present low incidence of TB in Wisconsin and to ensure progress toward elimination of TB in Wisconsin and the United States.

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