

GLOBAL TUBERCULOSIS CONTROL: LESSONS LEARNED FROM NEW YORK AND OTHER PLACES

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Tuberculosis (TB) maintains its grim historical notoriety as one of the leading infectious causes of death worldwide. Ironically, it is preventable and, in most cases, treatable. Infection-control precautions can help reduce the risk of TB transmission. Medical treatment of persons with latent TB infection can prevent the subsequent development of active TB disease. TB disease can usually be cured with anti-TB drugs taken exactly as prescribed. Even persons with drug-resistant strains can often be cured by alternative regimens of medications.

The International Union of Tuberculosis and Lung Disease (IUATLD) recognized that the TB treatment program outcomes in industrialized countries and developing countries were very different: mortality decreased but the number of chronic infectious cases, often patients who were excreting drug-resistant tubercle bacilli, actually increased compared with the effects of no treatment at all. Under the auspices of the IUATLD, TB control

programs were developed and introduced in extremely poor countries. The powerful impact of a well-organized nationwide system of case finding and chemotherapy became apparent by 1985, when the evaluation was made of the first series of patients enrolled in the IUATLD-assisted National Tuberculosis Program in Tanzania; a 10-year follow-up confirmed the beneficial results [6].

At the 1990 World Congress in Boston, USA, organized by the American Thoracic Society (ATS) and IUATLD, the type of mutual-assistance program introduced and refined in Tanzania by IUATLD was recognized as the best method to treat TB in developing countries. At the same time, a study entitled Health Sector Priorities Review, which was centered at Harvard University and sponsored by the World Bank, evaluated the cost-effectiveness of various programs for health intervention in developing countries. The resulting analysis determined that the beneficial outcome of the TB program developed by

the IUATLD in Tanzania was among the most cost-effective of all available interventions, including measles vaccination and oral rehydration in children, and was the most cost-effective intervention in adults [21].

New York City

In the 1890s, the New York City Department of Health, under the leadership of Hermann Biggs, established what was probably the first modern TB control program. This program eventually consisted of mandatory reporting, free laboratory services, education, forced isolation for some patients, and significantly, intensive nursing follow-up of individual patients [1,15]. This nursing follow-up, conducted by the health department as well as the Visiting Nurse Service of New York, emphasized adherence with the medical treatment of the time, including diet, exercise, and disposal of sputum.

Programs to control TB became victims of their own success. In 1960, New York City had more than 2400 beds for patients with TB in hospitals and sanitariums and a comprehensive system of treatment. But as the incidence of the disease declines, so did programs to control it. By 1988, the staff of the Bureau of TB Control had been reduced to approximately 140, the number of clinics had declined from 24 to 8, and combined public health and chest clinics in municipal and voluntary hospitals had been disbanded. As a result, in 1989 less than

half of patients who began treatment were cured [11]. In a section of New York City, Central Harlem, however, 89% failed to complete treatment [2]. The human immunodeficiency virus (HIV) epidemic, diminished public health efforts to control TB, rising poverty and homelessness, overcrowded conditions in congregate settings, and immigration from countries with high prevalence of TB all led to a resurgence of the disease in the 1980s [2].

As a result of inadequate treatment, the proportion of patients with drug-resistant isolates of *Mycobacterium tuberculosis* increased. Drug resistance among patients who had never been treated increased from 10 percent in 1983 to 23 percent in 1991. Such resistance increases the likelihood of treatment failure and relapse and greatly complicates the control of the disease. By 1992, the situation in New York City looked bleak. The number of cases of TB had nearly tripled in 15 years. In central Harlem, the case rate of 222 per 100,000 people exceeded that of many developing countries. Outbreaks of multidrug-resistant TB had been documented in more than half a dozen major hospitals, with case fatality rates greater than 80 percent, and health care workers were becoming ill and dying of this disease. Nearly one in five patients with TB in New York City had multidrug-resistant strains, and the proportion of new patients with multidrug-resistance had more than doubled in seven years. In the first quarter of 1991, with 3 percent of the country's population, New York City accounted for a remarkable 61 percent of

cases of multidrug-resistant TB in the United States [as reviewed in 11].

In New York City, the first substantial decline of TB in 15 years began in 1993 and continued through 2002. Federal, state, and local governments responded to the deteriorating situation by directing monies to improve the local infrastructure for TB control. The partnership between different levels of government was crucial to helping the New York City Department of Health develop its large-scale Directly Observed Therapy (DOT) program entailed a “sea of change”, in attitudes of staff in the Bureau, the medical establishment, public health administrators, and patients. There was skepticism and debate on whether DOT should and, perhaps more importantly, could be effective. Overcoming reluctance and inertia required the use of a multi-pronged approach. Utilizing the commitment, involvement, and persuasive efforts of key organizations and leaders, among them the Centers for Disease Control and Prevention, the New York City Commissioner of Health, the New York City and State TB Control Programs’ directors and staff, and chiefs of pulmonary medicine and infectious diseases at local university hospitals. Senior medical staff gave presentations to the medical and academic communities, policymakers, hospital discharge planners, and the public, citing published literature documenting that DOT improved patients’ chances for cure and enabled more effective TB control. New York City TB Control also developed a set of key DOT concepts, highlighting the

benefits of DOT for patients, physicians, and public health [12].

Baltimore

From 1958 to 1978, Baltimore maintained one of the highest numbers of pulmonary TB cases in the United States [5]. In 1978, the Baltimore City Health Department implemented a limited program of supervised therapy for its high-risk patients, targeting the homeless, unemployed, and substance abusers [4]. In 1981, the DOT program was expanded citywide using a community-based strategy of home visitation and treatment. Cases were identified by physician report, laboratory report, or through a 1976 city ordinance that required reporting of anti-TB drugs dispensed by physicians.

All patients received standard anti-TB drugs endorsed by ATS/Centers for Disease Control and Prevention, with an induction phase of 3-4 drugs given 5 days/week for 15-60 days, followed by biweekly DOT for the remainder of treatment. DOT was provided predominantly at the patient’s home/workplace/school/drug treatment facility/city jail, or nursing home. Patients who regularly missed clinic appointments or were absent for the outreach nurse visit were aggressively pursued by the nurse outreach investigators. If improved compliance was not achieved, legal measures were invoked in the form of commissioner’s orders, involuntary hospitalization, or incarceration. As an interesting innovation, clinic staff were recruited from the affected Baltimore community.

From 1978 to 1992, while the rest of the United States was experiencing an upsurge in the incidence of TB, Baltimore's rate declined by 64% [4]. Baltimore's DOT program had a consistently high proportion of patients with documented sputum conversion after 3 months of therapy and average annual treatment completion rate of 90% between 1986 and 1992. Multidrug-resistance remained rare, at a rate of 0.57%. Within Baltimore, the sputum conversion rate was significantly higher among DOT-managed cases than among non-DOT managed cases. Disease relapse rates were low, even among patients with HIV infection. Within Maryland, Baltimore accounted for 44.4% of all TB cases in 1978, compared with 28.7% in 1992. These trends could not be attributed to differentials in AIDS, immigration, poverty, or unemployment [4].

DOTS

The World Health Organization (WHO) responded to the globally expanding TB problem by establishing the fundamentals of a new strategic approach to TB, emphasizing specialized managerial functions at central, regional, and district. The principles of integration of case-management delivery into the primary health care infrastructure were maintained. Standard 12-month treatment regimens were abandoned; short-course chemotherapy with rifampin became the standard treatment for every new patient; direct observation of drug intake was no longer an option carrying the same weight

as self-administered treatment, but the highly preferred way of administering drugs during the initial phase to both hospitalized patients and outpatients. In 1991, the World Health Assembly adopted the new strategy and formulated the two global targets for the year 2000 of curing 85% of infectious cases detected and detecting 70% of cases. Later, targets proved a crucial stimulus in many countries to focus efforts [as reviewed in 19].

The new strategy, subsequently labeled DOTS (directly observed treatment, short course), provided a framework for effective TB control. The strategy comprised five essential elements. Two elements are technical: case finding through bacteriological examinations of patients with respiratory symptoms attending primary health care units and administration of short-course chemotherapy mostly by direct observation. The other three elements are managerial: generating greater political commitment to mobilize sufficient resources for TB control; securing a regular supply of antituberculosis drugs; and establishing a reliable information system to provide data for monitoring and assessing case finding and treatment activities [as reviewed in 19].

DOTS-Plus

At a meeting held in April 1998 [10], cosponsored by Harvard Medical School, WHO's global TB program, and Partners in Health (a non-governmental organization focusing on TB in Latin America), to assess

the scope and dynamics of the emerging problem of multidrug-resistant TB, the strengths and limitations of existing control strategies, and the potential contribution of community based efforts. Since the presence of multidrug-resistant TB signals a failure to adhere to a TB program, the key need in global control of TB remains the adoption of DOTS. In settings where multidrug-resistant TB is already a problem, however, DOTS alone will be insufficient for three reasons: (1) those already ill with the disease would not be cured with short course chemotherapy based on isoniazid and rifampin; (2) nosocomial transmission is likely when untreated patients continue to seek care in clinics and hospitals; and (3) patients with primary resistance to isoniazid and rifampin who receive standard, short course chemotherapy are likely to develop resistance to pyrazinamide and ethambutol as well. Since empirical retreatment regimens are often based on the same four drugs plus a short course of streptomycin, patients initially resistant to two drugs may become resistant to as many as five.

In some settings involving multidrug-resistant TB, DOTS alone is clearly insufficient. With DOTS in place, a DOTS-Plus strategy may be implemented to assist with control of multidrug-resistant TB using second-line drugs and enhanced laboratory capabilities, such as real-time drug susceptibility testing for first and second-line drugs.

A national program to treat chronic TB patients using a directly observed standardized 18-month daily regimen,

consisting of kanamycin, ciprofloxacin, ethionamide, pyrazinamide, and ethambutol was established in Peru in 1997. Peru's National TB Program was able to achieve a compliance rate of nearly 90%, a cure rate of almost 50% among all patients enrolled, and a cure rate of 63% among those who completed the full course of treatment. The total program cost was affordable in the context of the National TB Program's budget. A key factor was that the new service was built on a TB control program that had already achieved WHO's global TB control targets with first-line drugs. Additionally, there was a special committee to filter requests for access to second-line drugs using experts available in the country, and allowed the National TB Program to screen out candidates for whom treatment with first-line drugs was a more appropriate option. Third, there was multidrug-resistant TB unit in the Program's framework, facilitating coordination and management [20].

HIV-related TB

HIV infection is a potent risk factor for TB. Not only does HIV increase the risk of reactivating latent *M. tuberculosis* infection, it also increases the risk of rapid TB progression soon after infection or reinfection with *M. tuberculosis*. In persons infected with *M. tuberculosis* only, the lifetime risk of developing TB ranges between 10% and 20%. In persons coinfecting with *M. tuberculosis* and HIV, however, the annual risk can exceed 10%. The TB burden in countries with a

generalized HIV epidemic has therefore increased rapidly over the past decade, especially in sub-Saharan Africa [reviewed in 7].

There were an estimated 8.3 million new TB cases in the year 2000. TB incidence rates were highest in the WHO African Region (290/100,000 per year), as was the annual rate of increase in the number of cases (6%). Nine percent of all new TB cases in adults (aged 15-49 years) were attributable to HIV infection, but the proportion was much greater in the WHO African Region. The HIV pandemic presents a massive challenge to global TB control. The prevention of HIV and TB, the extension of WHO DOTS programs, and a focused effort to control HIV-related TB in areas of high HIV prevalence are matters of great urgency [7].

Genotyping of TB strains

Recent technical advances in the field of molecular biology, in conjunction with an increased understanding of the molecular genetics of mycobacteria, have provided the means to reliably type strains of *Mycobacterium tuberculosis* at the DNA level. Genotyping or DNA fingerprinting of *M. tuberculosis* provides epidemiological data to assess whether a manifest TB episode represents 1) a reactivation of the disease, 2) current transmission of disease, 3) an exogenous reinfection, or 4) whether a positive culture result was due to cross-contamination in the laboratory or in the bronchoscopy suite. In addition, it is able to

lend ideas of transmission of *M. tuberculosis* within a community. Most often, restriction fragment length polymorphism (RFLP) patterns are generated by using the IS6110 as a probe, one of the numerous mycobacterial mobile genetic elements. IS6110 is a naturally occurring transposable genetic element, which appears to be detectable in species of the *M. tuberculosis* complex only. Each strain of *M. tuberculosis* contains a different number of identical copies of this transposable element, except some Asian strains that are devoid of the IS6110 element. Using a standardized protocol, the number of copies of IS6110 elements and the molecular size of the restriction fragments obtained after *PvuII* digestion vary in such a way that two unrelated strains do not produce identical patterns when hybridized with a labeled IS6110 probe, forming unique genetic fingerprints. Patterns as well as dendrograms, which illustrate the degree of relatedness among the isolates, can easily be assessed by computer analysis. Spoligotyping, as well as other methods such as mycobacterial interspersed repetitive unit (MIRU)-variable number tandem repeat (VNTR) analysis provide even more rapid typing, inasmuch as they utilize polymerase chain reaction to amplify the relevant genetic material. CDC, through its National TB Genotyping and Surveillance Network, offers nationwide rapid and accurate strain typing at no cost [8]. For additional information, please refer to Driscoll, et al [9].

False-positive Laboratory Results

The recent Institute of Medicine report on the quality of care, entitled 'To Err Is Human', has awakened much of the health care system [14]. The report states that errors cause between 44,000 and 98,000 deaths every year in American hospitals. Already in 1994, Leape [16] in his insightful and provocative article on medical error asked the question 'Why is the error rate in the practice of medicine so high?' and gave the following answer: 'But it is apparent that the most fundamental change that will be needed if hospitals are to make meaningful progress in error reduction is a cultural one. Physicians and nurses need to accept the notion that error is an inevitable accompaniment of the human condition, even among conscientious professionals with high standards. Errors must be accepted as evidence of systems flaws not character flaws. Until and unless that happens, it is unlikely that any substantial progress will be made in reducing medical errors.' In recent years, it seems that microbiologists, health care providers, and public health officers are taking this concepts to heart and are publishing a growing number of studies concerning false laboratory results. Burman and Reves [3] undertook a Medline literature search and reviewed the mechanisms of false-positive TB cultures and their frequency, clinical consequences, and laboratory characteristics. They found 14 large studies involving more than 100 patients. The median false-positive rate was 3.1% (interquartile range, 2.2%-10.5%).

However, much higher rates have been seen when there has been a major error in laboratory techniques or conditions.

The impact of false-positive cultures may reach from unnecessary multidrug therapy with its potential of adverse reactions, placing the patient in respiratory isolation, investigation of close contacts, unnecessary diagnostic tests, including bronchoscopy, and hospitalizations. Among people with proven TB, the occurrence of false-positive cultures during or after treatment can result in an inappropriate diagnosis of treatment failure or relapse.

Cross-contamination of specimens in the laboratory has received the greatest attention in studies of false-positive cultures thus far. However, events before the arrival of a specimen in the laboratory can also cause false-positive results. Unsupervised sputum collection allows the patient to substitute a specimen that is not his/her own. The channels of the fiberoptic bronchoscope may be difficult to sterilize once contaminated with mycobacteria or residual DNA sequences of *M. tuberculosis* in sterile bronchoscope may leading to false-positive PCR results. Finally, mislabeling of specimens on the patients' ward or in the laboratory is a documented cause of false-positive results [18].

Working Together

In recent years there has been a growing body of new and exciting methods in mycobacteriology, but there is no single test

that can yet stand alone. Most importantly, complementary techniques should be used to generate complete and rapid information. It is the laboratory director who needs to decide which tests will be best performed in-house and which specimens should be sent to a reference laboratory, on the basis of the community to be served and the resources available, as well as in consultation with the TB Control program, infectious disease practitioners, pneumologists, or other physicians involved. With this partnership, the health care provider and the TB Control program will then share the responsibility for the quality and the timeliness of the laboratory results

In addition, laboratory test results should always be correlated with the patient's clinical presentation, and the clinician should notify the laboratory when results are not consistent. An established and ongoing professional relationship between health care providers, TB Control program, and the laboratory enables the recognition of inaccurate results earlier, and therefore may minimize the potential harm to the patient. Previous reports demonstrated the occurrence of an unacceptable high rate of false-positive TB cultures. In studies analyzing drug-resistant TB or specimens from patients with negative AFB smears and only one positive culture, erroneous results were reported in 13 % and 56%, respectively. However, one needs to be aware of the possibility that the error may have occurred in the pre-testing phase. These reports underscore the fact that

laboratory results alone (i.e., positive culture, drug resistance) are not enough to dictate a particular strategy in the patient's care, and that a careful clinical correlation is necessary in making the correct diagnosis. Health care providers, TB Control program and laboratory staff need to communicate and cooperate to bridge any gap between them. Only when all parties work together can clinical outcomes be optimized and transmission of TB reduced.

Green Light Committee

In 1999, the WHO established the Working Group on DOTS-Plus for MDR-TB (Working Group) to address the various issues related to the programmatic management of multidrug-resistant (MDR) TB. The Working Group is an open group of over 50 institutions including academic institutions, civil society organizations, donor agencies, bilateral donors, the for-profit private sector, governments of resource-limited countries, and the United Nations agencies. It is convened by WHO which also serves as Secretariat for the Working Group. The Working Group aims to advise WHO in developing policy for the management of MDR-TB in resource-limited settings. Structured under this Working Group are four subgroups: a Scientific Panel to develop programmatic guidelines for implementing DOTS-Plus, the Subgroup on Laboratory Issues, the Subgroup on Drug Procurement Issues, and the Green Light Committee [13].

In 1999, the Subgroup on Drug Procurement Issues highlighted the high cost of second-line drugs as one of the major impediments to implementing DOTS-Plus pilot projects. Ultimately, a mechanism had to be established to increase access to these drugs, but under tightly supervised conditions to promote their rational use and minimize the emergence of resistance to this last line of defense against TB. To promote access to and rational use of the concessionally priced drugs, WHO formed (in 2000) the Green Light Committee as a subgroup of the Working Group. Subsequently, the cost of second-line drugs has fallen by up to 99% [13].

Paradigm shift

Concluding with Jonathan Mann [17], one may ask 'yet at such times of profound change, another kind of value becomes all the more vital. To build bridges – between medicine and public health, and between ethics and human rights – the critical underlying question may be, Do we believe that the world can change? Do we believe that the long chains of human suffering can be broken? Do we agree with Martin Luther King that “the arc of history is long, but it bends towards justice?”

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