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CONCEPT NOTE

The Development of Tuberculosis Treatments and Policy

In 2011, 8.7 million people were diagnosed with tuberculosis (TB) and 1.4 million died as a result of TB. Tuberculosis has plagued humanity for millennium. DNA testing has documented TB infection in mummies from as early as 3000 BCE. Despite this long history of affliction, significant progress has been made in controlling TB in the past century. Since 1995, over 51 million people have been cured of TB and 20 million lives have been saved.[1] This paper will briefly review the history of TB control with a focus on the development of chemotherapy for the disease, the creation of public health programs to cure those infected, and the evolution of international TB control policy.

Global Tuberculosis Policy and Development

It was not until an international conference in 1867 that the medical community recognized TB as a communicable disease. In 1882, Robert Koch discovered a staining technique that enabled him to see the causative agent, *Mycobacterium tuberculosis*. Conferences focusing solely on TB followed, starting in 1888. Non-governmental organizations and government officials met to address TB together for the first time in 1899.

The Central Bureau for the Prevention of Tuberculosis was formalized in Berlin in 1902, and periodic meetings addressing clinical, research, and sociological aspects of TB were held until the First World War in 1914.[2] In 1920, 31 countries came together "to agree on the means to fight TB." They established the International Union Against Tuberculosis (IUAT). The following year, the Bacilli Calmette-Guérin (BCG) vaccination was introduced to humans to reduce the risk of disease. The IUAT organized international conferences and produced a regular bulletin until 1940, when activity was interrupted by the war.

In 1945, diplomats came together to form the United Nations and discussed what would be the World Health Organization (WHO) for the first time. The IUAT remobilized in 1946 and suggested that the new global health organization create a division of TB. The WHO signed its constitution into effect on April 7, 1948, and included fighting TB as one of its top priorities.

Interest in TB soon gained momentum through the development of new drugs and the possibility for true disease control and treatment through public health programs. The first medication for TB,

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streptomycin (SM), administered as an injection, became available in 1943 and was introduced for clinical use in 1946. Most patients had marked and rapid clinical improvement with SM. When TB isolates were obtained from patients who had failed therapy, they were found to be streptomycin-resistant. Para-aminosalicyclic acid (PAS) was introduced in 1946; Isoniazid (INH) and pyrazinamide in 1952. The rapid development of resistance led to the principle of multi-agent chemotherapy in order to prevent resistance.[3] Patients taking INH, PAS, and SM together had 97% cure rates.[4]

These somewhat experimental treatments were provided through public health programs focused solely on TB control. These "vertical" programs had dedicated staff from the central level down to the local level where delivery occurred. When industrialized countries saw declines in TB prevalence, the WHO recommended the same approach in less developed countries. The less developed countries did not see the same declines, however, and new research soon suggested moving away from TB-only vertical public health programs toward horizontal TB control measures that were integrated with the provision of general health services.

New research continued to move disease understanding forward. One of the first national prevalence surveys of primary drug resistance was carried out in England and Wales in 1955–1956 (see **Exhibit 1**).[5] In 1958, the IUAT supported the first international collaborative clinical trial for treatment of any disease, looking at 17,391 patients from 17 countries with possible drug resistance.

That same year, Wallace Fox worked with the British Medical Research Council (MRC) to compare ambulatory with sanatorium-based INH and PAS therapy in Madras, India. The study was scientifically rigorous, testing each patient for sensitivity to INH, SM, and PAS before enrolling.[6] The sanatorium patients receiving supervised therapy had better outcomes when controlling for other factors, underscoring the problem of irregularity of treatments and the need to ensure treatment adherence.[7]

Fox went on to explore the possibility and outcomes of supervised treatment for outpatients in Madras. "Despite the fact that the patients involved came from a poverty-stricken community in a city with a poor transport system and that travel of up to five miles to the clinics was necessary, it was possible to get patients to come to clinic six days a week for streptomycin injection and a supervised oral dose of pyrazinamide," Fox determined.[7] Fox concluded that "long term supervised administration can be organized under special circumstances, even in developing countries."[7]

1960s Global TB Policy and Development

By the 1960s, Dr. A.S. Moodie, the architect of Hong Kong's TB program, which had been in operation for 10 years, was adopting Fox's suggestion of supervised, outpatient provision of oral medication due to a significant percentage (2%) of the adult population having TB. The Hong Kong health system tried to make the ambulatory clinics as convenient as possible for patients, and with Moodie's approach, 70% of patients completed therapy for the two-and-a-half month period specified.[7]

Around the same time, Fox began to explore the possibility of moving away from daily doses of medication to an intermittent regimen. He compared twice-weekly, supervised SM and INH with daily, unsupervised INH and PAS; the study showed it was possible to cure patients by treating them with SM and INH only several times per week. Fox determined supervision and adherence were even more important with less frequent dosing.[7]

Physicians in London were working on developing TB treatment regimens as well. Concerned about self-medication and intermittent regimens, they required patients to come to the clinic six days per week for 18 months, giving them SM and INH. Their results were less impressive, however, as only 51% of patients

completed the long course of therapy. Many patients stopped taking their medication as soon as they felt better.

Almost everyone concerned with TB agreed that effective treatment required direct supervision of therapy. Many African programs had experience with supervised leprosy, filariasis, and malaria treatments that had proven successful.[8] The frequency of TB therapy, length of treatment, and necessary medications were still under debate, however, with some recommended short-course treatments lasting as little as three months and scores of drug combinations being used.[9]

The IUAT continued to evaluate other issues related to TB control, such as sputum smear microscopy, tuberculin skin testing and BCG vaccinations. The basic methods of smear examination, culture, sensitivity, and identification tests remained largely unchanged for many decades.[5] Ethambutol was introduced for treating TB in 1963 and rifampin (RIF), part of the last class of drugs ever introduced, in 1966. Karel Styblo with the IUAT established the Tuberculosis Surveillance Research Unit in 1966 while other national efforts to assess prevalence as well as primary and acquired resistance were underway.[5]

1970s Global TB Policy and Development

In 1974, the WHO Expert Committee on Tuberculosis endorsed the value of intermittent (twice weekly) chemotherapy and encouraged countries to decentralize health facilities to make them more accessible to patients.[9] Over the decade, TB control programs were being implemented in many places, but research slowed as resources were diverted to other issues. The WHO's Director General at the time, Halfdan Mahler, had just introduced the goal of "health for all by the year 2000" and planned to achieve it by strengthening basic primary health care in poor countries. International health concerns focused on issues such as family planning, population control, and immunization rather than disease control.[10] Some believe that TB program resources were cut because of Mahler's prior experience with TB in India that was rift with challenges. Others suggest that interest in TB declined with its importance as a cause of death in the places holding most of the power, where "'virtual elimination of the disease as a public health problem' was in sight."[11, 12] Academic institutions, ministries of health, and other organizations were also perceived to have lost interest. The IUAT broadened its focus to include other lung diseases in order to find sufficient research for publication and changed its name to the International Union Against Tuberculosis and Lung Disease (IUATLD).

Styblo was one exception to the slowdown in TB research. While the most accepted TB regimen was an 18-month course of treatment, Styblo worked to implement a strategy that included short-course treatment regimens of six months. He believed the shorter treatments would be more feasible in developing countries. In 1978, the Ministry of Health of Tanzania requested that the IUATLD help it establish a national TB program. Styblo created a program using short-course therapy there and later created a similar one in Mozambique.[13] He worked on the ground, visited countries, and gained the trust and respect of people as he implemented his novel approach.[14] He was the first to propose the idea of using existing basic health services to diagnose, initiate treatment, record and report patients' treatment progress, and manage supplies. The health services had the staff and resources necessary to manage the technical aspects of TB control, which made integrating the program smooth.[15]

Not many knew of Styblo's efforts, and those who did worried about the development of drug resistance with short-course treatment. Some also criticized the program's hospitalization of patients during their first two months of treatment, as ambulatory or outpatient care was accepted as the norm. Beyond the direct clinical component of a TB program, Styblo emphasized the practice of cohort analysis and maintaining a thorough reporting system. His approach employed delivery of TB control within dedicated,

vertical programs, which ran counter to the WHO's recommendation to decentralize these services and integrate them with the provision of primary health services.

1980s Global TB Policy and Development

The United States was one of the last countries to adopt the stance that direct supervision of TB treatment was necessary. The idea stirred many debates. Some argued that only patients who were unreliable should require supervision to save unnecessary diversions of resources, and many studies focused only on trying to identify characteristics of non-compliant people to allow programs to target such individuals. In 1985, the American Thoracic Society concluded that unemployed alcoholic patients in inner cities should be placed on supervised treatment. The US Centers for Disease Control and Prevention (CDC) encouraged supervised treatment only for patients who had documented circumstances that would make compliance with a treatment regimen difficult.

Rather than a service, directly observed therapy (DOT) was often viewed as an imposition that could be justified only with evidence that the patient would behave in a way that posed a threat to public health.[7] Some even argued that directly supervised therapy was a violation of a basic human right.

One researcher changed the direction of the argument when he used cost-benefit analyses. He noted that as many as 75% of patients could be classified as unreliable and asserted that "the health behavior of most people is unpredictable and does not conform with our expectation that patients will follow what their physicians recommend."[7] The decision about whether to mandate DOT remained open.

A rising number of TB and drug resistant TB cases soon emerged in the US and beyond, many of which were linked with the emerging HIV/AIDS epidemic. In 1985, following several smaller studies that suggested alarming rates of drug resistance, Michael Iseman wrote an editorial called "Tailoring a Time-Bomb: Inadvertent Genetic Engineering. " The *American Review of Respiratory Diseases* published the piece in which Iseman wrote:

> [M]any of these individuals are harbouring drug resistant bacilli. These individuals may spread infection with drug-resistant organisms to their contacts … What is to be done? May we only stand by as onlookers and bemoan this tragedy in the making? … It is sufficiently shameful that 30 years after recognition of the capacity of triple therapy (INH, streptomycin and PAS) to elicit 95%+ cure rates, tuberculosis prevalence for many nations remain unchanged. The fact that improper, unwise or otherwise suboptimal use of these therapeutic tools may be creating a potentially worse situation is simply not acceptable.

Iseman charged people to take action to combat the emergence of multi-drug resistant TB (MDR-TB).[16]

In 1986, the IUATLD published the first *Orange Guide* stating, "Frequent and careful supervision is required to ensure that the patient actually takes all the drugs prescribed. Respected individuals in the community … can be a great help to the health workers in their tasks of ensuring compliance." The guide recommended hospitalization for the first two months of therapy in developing countries where patients might not be able to receive the full initial phase otherwise, including all those in rural areas.[17] That same year, in 1986, the British Medical Research Council Tuberculosis Unit that had contributed significantly to modern TB interventions closed.

In 1989, with sharp increases in TB cases related to the HIV pandemic, the WHO appointed Arata Kochi as head of the WHO TB unit, which had shrunk to two professionals, to revamp its program.[8, 18] In addition, an international Ad Hoc Commission on Health Research, composed of international public health

figures and housed at Harvard University, identified TB as a neglected disease. Rising interest and concern in policy and programs related to TB soon followed.

1990s Global TB Policy and Development

The Ad Hoc Commission on Health Research met Styblo, one of the only people doing operational research in TB at the time, and did a cost: benefit analysis of his project in Tanzania. It found that short course, DOT was cost-effective, even in poor country settings. The results surprised many and inspired the WHO. The disability-adjusted life-year or DALY concept was developing around this time, stemming from the "desire to inject rationality into resource allocation decisions in developing countries."[18] Calculated based on the years of life lost (YLL) and years lived with disability (YLD) from a specific disease, the DALY concept helped support the need for investing in TB.

The World Bank, in line with its new attention to the health sector, argued that TB control should be a priority since treatment was inexpensive and the global burden was high. A World Bank economist and others joined Kochi to build up the TB unit that soon took on a formal evaluation of three countries, Tanzania, Malawi, and Mozambique, where the IUTALD and Styblo had set up sites. In 1991, the WHO and the World Bank formally tested Styblo's directly supervised treatment approach in China with a World Bank loan of USD 50 million. One WHO official claimed that if it could be done by a big country like China, then the approach could be implemented anywhere.

An article on Styblo's treatment design declared, "In terms of costs per death averted and per year of life saved, chemotherapy for smear-positive TB is the cheapest health intervention available in developing countries."[19] The evaluation confirmed that the short-course regimen was legitimate, and the WHO declared it had identified the solution to TB control in these settings. The organization sponsored research and meetings to develop policy for TB control and discussed strategy. Aims were to expand services and to achieve global targets of 70% case detection and 85% cure rates worldwide. The DOTS strategy was not effective for children, people with HIV, and those with drug-resistant TB.[11]

The World Bank became the single largest source of funding for TB control programs in developing countries, committing USD 350 million from 1989 over the next several years. With the financial power behind its policy, even long-established programs, such as India's, subscribed to the short-course therapy plan.

In the US, a New York City TB epidemic that had started in the 1980s was continuing due to lack of funding, poor internal communication, and social upheaval that made treatment adherence hard.[20] Directly observed therapy had been considered but was cited as too expensive.[21] A CDC study in 1991 and 1992 showed one-third of the New York City patients had a strain resistant to one or more drugs. The news sent fear into the middle and upper class.[22]

New York City revamped its program despite budget cuts by the federal government and promoted DOT. The new program requested patients sign a contract stating they would come to all scheduled clinic appointments. Patients were guaranteed the length of their visits would be limited, that all medications would be free, and that they would be reimbursed for all transportation to and from the clinic plus additional food incentives, up to USD 60 per month. Health workers who dedicated themselves to the patients were important in halting the epidemic that began to wane in terms of sheer numbers as well as the percent of resistant cases after 1992.[3] For the 20,000 cases diagnosed from 1979 to 1994, treatment alone cost more than USD 400 million.

The New York City experience led experts to link strong programs with low rates of resistant disease.[23] If a program was strong, they believed TB could be controlled "even in populations in which

immunosuppression is common and the prevalence of drug-resistant organisms is high."[23] Findings also "underscore[d] the importance of obtaining susceptibility testing in all patients who have cultures positive for *Mycobacterium tuberculosis*."[22]

The World Bank and the WHO stayed focused on international control of drug-susceptible TB. The Bank's new, large role in TB control stirred tension between the WHO and the World Bank, sparking a rivalry in global health leadership. To reassert itself after being criticized for having acted too slowly, the WHO hired a new advocacy expert, Kraig Klaudt, to help promote TB control and gain momentum. The WHO put on a major media event declaring TB a "global emergency" in London in April of 1993.

That year, the organization published the first *Treatment of Tuberculosis: Guidelines for National Programs.* The guidelines outlined different patient categories according to their priority for treatment (highest to lowest), and provided recommended regimens for each (see **Exhibit 2** for regimens). The highest priority was Category I, new patients, and the lowest priority was Category IV, chronic TB patients, usually patients with drug resistant TB. Those who spoke directly with the WHO representatives at the time said the organization "felt (but didn't state publicly) that [MDR-TB patients] would most likely die anyway."[3] Some scientists argued that MDR-TB was less of a problem because in the course of acquiring resistance, the bacteria became less virulent.

Arata Kochi clarified the definition of MDR-TB for the first time in an article. He defined it as tuberculosis bacilli resistant to at least INH and RIF. "This type of MDR-TB is very difficult to cure; even in very sophisticated specialized TB institutions, the cure rate is less than 50%. In many developing countries, this MDR-TB is virtually incurable," he wrote.[4] The article suggested that RIF resistance was a new phenomenon, increasing since 1985. It stated, "Data is quite limited at this time … An accurate picture of the drug resistance problem in the world is not available because a limited number of countries have a reliable drug resistance surveillance system."

More and more states and local health departments in the US began to implement DOT programs despite lack of federal support. In Mississippi in the early 1990s, 98% of TB patients were treated by DOT. Political commitment to the projects and a cultural climate in which supervision was not offensive were important in achieving success.

In 1993, the CDC's Advisory Council for the Elimination of Tuberculosis made DOT the standard of care by federal US policy. The policy decision was soon reflected at local levels and adopted by health departments. Positive trends in disease decline followed.[24] The United States was one of few countries that routinely treated any MDR-TB case that arose. In 1994, a year after Kochi's article was printed, the WHO and IUATLD began the first global study on anti-tuberculosis drug resistance, and the WHO set up a worldwide TB surveillance and monitoring system.

The same year, the WHO released a Framework for Effective TB Control, outlining policy on how to treat and control TB. The framework promoted a strong TB program as the best solution to resistance.[4] It condensed the most important ideas from Styblo's 200 page manual into 13 pages, consisting of nine key operations and five essential features of a program. The key components were reduced further to five key components, and eventually they began to brand the new TB policy—Directly Observed Therapy Short-course—as DOTS. The DOTS strategy included (1) government commitment to a TB program aiming at nation-wide coverage integrated into the existing health structure with technical leadership from a central unit; (2) case detection through predominantly passive case finding with confirmation of diagnosis by quality-assured microscopy; (3) administration of standardized short-course chemotherapy to at least all sputum smear positive cases of TB under proper management conditions; (4) establishment of a regular drug supply of all essential anti-TB drugs an effective procurement system; and (5) a monitoring and

evaluation system based on individual patient information used for program evaluation and supervision.[25] The standard WHO-DOTS treatment eliminated the need for intense clinical management of the disease.

By this time, it was established that there were differences in how TB was treated in high-income, low-incidence countries and low-income, high-incidence countries where resources for TB control were limited despite following the same basic principles. World Bank loans for health sector reform became tied to the implementation of WHO-DOTS. Within five years of the WHO-DOTS plan, 120 countries had adopted DOTS, including all 22 high-burden countries, and the WHO had released a second edition of *Treatment of Tuberculosis: Guidelines for National Programs* (see **Exhibit 2** for summary of treatment recommendations.).[26]

The WHO approach during this time focused on advocacy and communications. Donors and policy makers were the targets rather than scientists or academics. Advocacy, one WHO member argued, "is not an analytical undertaking; unlike the academic process, in advocacy, you start with a simple, clear message to grab attention and work down from there, filling in explanations and gaps later."[10] The WHO had to raise funds for TB and gain partners to implement its strategies in developing countries. At the international level, resources still largely came from multi-lateral donors such as the World Bank and bilateral agencies such as USAID or the UKs' DFID, and, on the ground, programs were implemented through government partnerships.

In 1997, the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance published findings showing that there was resistance in each of the 35 countries that participated. The WHO revised the treatment guidelines to address the potential for drug resistant cases and released *Guidelines for the Management of Drug-Resistant Tuberculosis*. The guidelines defined the disease and its causes, some basic principles for managing it, information on how to assess cases, available drugs and regimens, and the role of surgery. The guidelines reinforced "the top priority is not the management, but the prevention of MDR-TB."[27] Treatment was something to consider for "more economically prosperous countries" that "might wish to do so."[27] That year, the WHO also published the first annual report on global TB control that included data from all national control programs that reported to the WHO.

In 1998 the WHO published a report on the status of the high-burden countries and general constraints to global TB control. Of the 22 high-burden countries, 20 had not reached their targets.[28] The report suggested political will was a primary constraint that impacted four other identified constraints: financing, human resources, anti-TB drug supply, and confusion in health information systems.[29] That year the WHO also acknowledged that TB and HIV/AIDS, though recognized epidemiologically, had been overlooked "on the ground" as a public health problem.[30]

The WHO Director-General Dr. Gro Harlem Brundtland launched The Global Partnership to Stop TB that year, in 1998, to bring together TB specialists to share their knowledge and expertise in six working groups for the most critical elements of TB control: DOTS expansion; TB/HIV; new TB diagnostics; new TB drugs; new TB vaccines; and advocacy, communications, and social mobilization. The Partnership, soon known as the Stop TB Partnership, developed a five-year action plan to stop TB with an estimated cost through 2005 of USD 9.1 billion. Of the resources being spent on global TB control at the time, 70% were provided by endemic countries.[31]

A nonprofit organization that had been treating patients with drug resistant TB in resource-poor areas of Peru since 1996 cured its first cohort of patients and presented its results at a meeting of experts. At the meeting, for the first time participants agreed, "In some settings, DOTS alone is clearly insufficient." They agreed, "All patients with active tuberculosis, regardless of drug susceptibility patterns have a right to treatment." Experts coined the MDR-TB case management strategy using second-line drugs "DOTS-Plus," suggesting it was to be used within the DOTS strategy, and they formally introduced it in a journal article in 1999.[32] The WHO added a working group on DOTS-Plus for MDR-TB to the Stop TB Partnership to advise

on policy recommendations for member states. By 1999, at least 127 countries had adopted DOTS, but only 23% of cases worldwide were detected and treated according to the DOTS strategy, and "the success of DOTS was threatened by the rise of multidrug-resistant TB (MDR-TB)."[8, 33]

Global TB Policy and Development in the 21st Century

The turn of the century brought the WHO/IUATLD Global Project on Drug Resistance Surveillance's Second Anti-tuberculosis Drug Resistance in the World Report. Over 2 million people were dying annually from TB, and over a third of the world was infected. There was drug resistance in nearly every country, and many new settings had over 3% MDR-TB prevalence among new cases.[34]

The WHO published guidelines for starting DOTS-Plus pilot projects for MDR-TB. The Working Group determined DOTS-Plus programs should start as pilot projects "to generate the evidence to guide the creation of specific policy for the management of MDR-TB." The goal of DOTS-Plus projects was to "prevent further development and spread of MDR-TB." Though the ideal means for treating MDR-TB was with individualized, tailored treatment, catered to each patient's pattern of resistance, some—at least in certain countries—considered this to pose considerable operational and financial difficulties. They believed a standard regimen, geared to the most common local pattern of resistance, would be more practical. The pilot studies aimed to resolve this debate.

The Working Group identified access to second-line anti-TB drugs as one of the major obstacles to the implementation of DOTS-Plus and created the Subgroup on Drug Procurement Systems for Second-line Anti-TB Drugs. The subgroup worked with pharmaceutical companies to negotiate preferential prices on second-line anti-TB drugs for DOTS-Plus pilot projects. Projects could benefit from concessional pricing with approval from the Green Light Committee (GLC). The GLC ensured that all programs included the five tenet components of DOTS-Plus, similar to those of the DOTS strategy. It also evaluated proposals, promoted technical assistance, and reassessed projects as needed to determine ongoing qualifications for support. The committee believed that projects adhering to the DOTS-Plus guidelines would have "a great chance of programmatic success and the least chance of creating resistance to the last line of defense against TB."[35]

With this change in policy, the WHO reported:

> Initially, the great potential cost and high technical skills required to treat patients with MDR-TB seemed to put mass treatment of such cases beyond the reach of many poor countries … Understandably, priority was given to establishing effective TB programmes that use the DOTS strategy. If these were efficiently implemented, little MDR-TB would be created. However, it was soon realised, and has now been established by the WHO surveys, that in some countries, owing to poor previous programmes, there is an appreciable MDR-TB problem.

In 2001, the WHO was looking beyond the basics of TB. The organization published special reports on TB in women (2000) and in prisons (2001) and on involving private practitioners with national programs (2001).

By 2002, Médecins Sans Frontières, Harvard Medical School, and the WHO, through the GLC had helped lower the cost of second-line anti-TB drugs by up to 99%. Eli Lilly and Company had agreed to continue its support of DOTS-Plus by extending its concessional pricing agreement and doubling the quantities of drugs provided.[36] A long-term procurement arrangement between the International Dispensary Association and the WHO was finalized that would ensure sustained concessionary pricing.

The constraints on regular DOTS expansion at this time included: lack of qualified staff and management skills, shortage of laboratory equipment, absence of collaboration between TB and HIV

programs, an unregulated private sector, and decentralization of health services. In 2002, the WHO published *An Expanded DOTS Framework for Effective Tuberculosis Control.*[37] The expanded strategic framework advocated for: (1) sustained political commitment to increase human and financial resources and make TB control a nationwide activity integral to the national health system, (2) access to quality-assured TB sputum microscopy, (3) standardized short-course chemotherapy to all cases of TB under proper case-management conditions including direct observation of treatment, including technically sound and socially supportive treatment services, (4) uninterrupted supply of quality-assured drugs with reliable distribution and procurement systems, and (5) recording and reporting system enabling outcome assessment of each and every patient and assessment of the overall program performance.[37]

The WHO revised the guidelines for treatment of TB in 2003 for the third time to present information on HIV-related TB and MDR-TB and chronic cases. The revisions allowed countries some flexibility by providing reliable alternatives to suggested treatments. The third revision was 113 pages compared to the original guidelines of 13 pages.[38] Fixed-dose combinations of anti-tuberculosis drugs were available, meaning patients had to swallow fewer pills, and thrice-weekly treatment was proven effective, offering an alternative to daily treatments. The public health priority of identifying and curing infectious TB cases remained in place.

In 2004, the IUATLD/WHO Global Project on Anti-tuberculosis Drug Resistance Surveillance published data collected between 1999 and 2002, showing an increase in resistance. Of 77 settings, 74 had drug resistance. The survey reported, "As in previous phases of the Global Project, a link was found between poor programme performance, or insufficient coverage of a good programme, and drug resistance." It also acknowledged that because lab capacity was necessary for reporting MDR-TB, it was likely that resistance in unsurveyed areas was worse than what was reported.[39]

The world began looking at strengthening lab capacity and other essential infrastructure for the expansion of DOTS as well as connections between tobacco use and TB.[40] One hundred eighty-seven countries were already applying DOTS in 2005, and 89% of the world's population lived in areas with DOTS services.[41] A new Global Plan to Stop TB was put in place around that time, calling for USD 56.1 billion toward new tools and implementation working groups to save 14 million lives over 10 years.[42]

By 2006, the emergence of extensively drug-resistant TB (XDR-TB), defined as MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin), was documented in all regions of the world.[43] A cluster of XDR-TB cases in a hospital in South Africa was detected in which 52 of the 53 patients died. Of the 44 tested for HIV, all were positive, shining a spotlight on the emergence of XDR-TB.[44]

The WHO introduced the definition of XDR-TB formally in 2008 in *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis: Emergency Update 2008*. The guidelines updated recommendations on how to manage drug-resistant TB based on a rapid assessment of the evidence from the pilot projects and encouraged the use of drug susceptibility testing (DST) among all patients at risk of MDR-TB. They suggested adding community based care and support into national strategies and plans. There was only one chapter that was completely new: "Managing [drug-resistant TB] through Patient-centered Care." The chapter included sections entitled "understanding patient-centered care," "dignity, from day one," "staff as stakeholders, patients supporting peers," "communicating 'cure,'" and "forced isolation and respect for human rights." It suggested that "any patient in whom MDR-TB or XDR-TB is suspected or diagnosed should be provided with high-quality patient-centered care, as outlined in both the International Standards for Tuberculosis Care, the Patients' Charter for Tuberculosis Care, and in the WHO Good Practice in Legislation and Regulations for TB Control."[43]

In 2009, the *Implementing the WHO Stop TB Strategy Handbook for National TB Control Programmes* was released. It acknowledged several changes that had occurred in TB control over the years including the fact that efforts to control the disease were less focused on public health and more focused on patients; that current TB policy acknowledged the importance of universal access to care; and the recent increase in HIV had strained resources and made it essential for national TB programs to work not just in isolation but jointly with HIV control programs. The WHO was also encouraging national programs to think about contributing to general health system development and integrating with primary care as part of its broader movement for health system strengthening. The WHO suggested that the field of TB was ready for advances in research that would bring improved and rapid diagnostic tools; new classes of drugs for MDR -TB and XDR -TB, and shorter treatments.

The fourth Anti-Tuberculosis Drug Resistance in the World Report came out in 2009, showcasing data from 93 settings between 2004 and 2007. It found XDR-TB in 45 countries and MDR-TB at the highest rates ever.[45]

The fourth iteration of *Treatment of Tuberculosis Guidelines* also came out in 2009. The guidelines removed the categories that prioritized patients for treatment, acknowledging the Stop TB Strategy's emphasis on universal access to high-quality, patient-centered treatment. The new guidelines stated, "For treatment decisions it no longer makes sense to assign third priority to smear-negative patients given their high mortality if they are living with HIV. Equally, MDR-TB patients should not be assigned fourth priority, given their high mortality and the urgent need to prevent the spread of these deadliest TB strains." The guidelines instead grouped patients according to the likelihood of their having drug resistance and the outcome of their prior treatment course—failure, relapse, and default—and integrated HIV testing. They reaffirmed that all previously treated patients should have access to culture and drug susceptibility testing at the beginning of treatment to identify MDR-TB as early as possible. Given the new sources of international funding such as the Global Fund to Fight AIDS, Tuberculosis and Malaria and UNITAID, the guidelines suggested, "Lack of resources for MDR-TB treatment is no longer an acceptable rationale" for providing first-line drugs to patients with a high likelihood of MDR, and they no longer recommended "MDR treatment be introduced only in well-performing DOTS programmes" since "in some countries with limited DOTS coverage, there may be an appropriate setting for an MDR pilot project that, once established, can provide a model and an impetus for the expansion of basic DOTS into more areas."[46]

Funding for TB control reached USD 2.6 billion in 2010, a marked increase from what had been available a decade prior, but far less than what was needed to meet the global targets of halving the burden of TB between 1990 and 2015.[47] Much of the funding, about USD 4.3 billion between 2002 and 2010, came from the Global Fund to Fight AIDS, Tuberculosis and Malaria while other bilateral and private funding sources accounted for much of the remainder. Compared to what the Global Plan to Stop TB called for, there was a gap of USD 2.1 billion in 2010.[48]

Despite centuries of fighting tuberculosis, updating policy, and improving medical technologies, HIV/AIDS, increasing urbanization, poverty, malnutrition, smoking, indoor air pollution, and diabetes have all helped the disease thrive amidst the interventions. Continuing to increase funding, addressing social, economic, and demographic factors, keeping tuberculosis a global priority, engaging sectors beyond health, and improving access to health care will all help advance global tuberculosis control.

Exhibit 1 ***British Medical Research Council Tuberculosis Research Studies, 1946-1986***

Place	Year	Subject	Resistance to INH* (%)	Reference
England & Wales	1955–1956	Drug resistance	0.7	55, 506
	1963	Drug resistance	1.8	507, 508
Scotland	1968–1970	Notifications and treatment	2.0	509–511
England & Wales	1978–1979	Notifications and drug-resistance	1.9	512, 513
		Children	–	514
		Results of treatment	–	515
	1983	Notifications and drug-resistance	2.1	516–519
		Children	–	520
		Results of treatment	–	521
	1988	Notifications and drug-resistance	2.0	522
		Children	–	523
		Management	–	524
Hong Kong	1962	Drug resistance	14.2	525
Kenya	1964	Drug resistance and notifications	10.3	526
		Results of treatment	–	527
	1974	Drug resistance and notifications	10.1	528
		Results of treatment	–	529
	1984	Drug resistance and notifications	7.1	530
Tanzania	1969/1970	Drug resistance and notifications	6.3	531
		Results of treatment	–	532
	1978/1980	Drug resistance and notifications	10.1	533

* Primary or initial resistance.

Source: Fox, W., G.A. Ellard, and D.A. Mitchison, *Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946-1986, with relevant subsequent publications.* International Journal of Tuberculosis and Lung Disease, 1999. 3(10): p. S231-S279.

Exhibit 2 *Summary of WHO TB Treatment Guidelines, 1991-2010*[26, 27, 49]

1991 The World Health Assembly adopted Resolution WHO 44.8, recognizing "effective case management as the central intervention for tuberculosis control," and recommending the strengthening of national tuberculosis programs by introducing short-course chemotherapy and improving the treatment management system.

1993 *Treatment of Tuberculosis: Guidelines for National Programs* published, categorizing patients according to their priority for treatment (highest to lowest), and providing recommended regimens:

Category I: newly diagnosed cases of smear-positive pulmonary tuberculosis and other newly diagnosed seriously ill patients with clinically severe forms of tuberculosis.

Recommended treatment regimen: 2HRZS (E)/4H_3R_3 or 6HT[1]

Category II: relapse and smear-positive treatment failures suspected of having INH-resistant and or S-resistant disease.

Recommended treatment regimen: 2HRZES/1HRZE/5 H_3R_3 E_3

"… If patient is not smear negative by the end of 12 weeks, the initial phase can be extended by 4 weeks. If patient is still smear positive at the end of the fourth month, all drugs should be stopped for two to three days and a sputum specimen tested for DST. The patient should then start the continuation phase. If pre-treatment DST showed patients fully susceptible to all the drugs, then the continuation phase of Category I patients should follow the initial phase. If the pretreatment studies showed resistance to H or R, then the patients should start continuation under close supervision. If the pretreatment studies showed resistance to both H and R …. the chance of achieving sputum conversion is limited. If the patient remains smear positive after the completion phase, he or she is no longer eligible for the re-treatment regiment."

Category III: pulmonary smear negative tuberculosis with limited parenchymal involvement and extra pulmonary tuberculosis (this category usually includes children for whom pulmonary disease is almost always smear negative).

Smear negative pulmonary cases that will eventually become smear-positive are a higher priority than those with more benign forms of extrapulmonary tuberculosis.

Recommended regimen: 2HRZ/$2H_3$ R_3

Category IV: chronic tuberculosis

"Management of these patients who have a high likelihood of MDR-TB is highly problematic. Even with optimal therapy, cure may be possible in only half of such cases. Second-line drugs are very expensive, are generally more toxic and are significantly less effective than conventional regiments in drug-susceptible cases. More over, the patients must remain in the hospital for several months. If possible, the drug sensitivity of the bacilli should be established and a re-treatment program should

[1] Treatment regimens for TB have a standard code. Each antituberculosis drug has an abbreviation: isoniazid (H), rifampicin (R), pyradinamide (Z), streptomycin (S), ethambutol (E), thioacetazone (T). TB treatment consists of two phases; the number before a phase is the duration of that phase in months. Letters in parenthesis represent fixed-dose combinations. Subscript numbers indicate the number of doses per week of the letter they follow. No subscript number following a letter represents daily (6 times a week) doses of that drug. For example, 2HRZS (E)/4H_3R_3 represents two months of some dose of isoniazid, rifampicin, pyradinamide, and streptomycin with a fixed dose of ethambutol daily followed by four months if isoniazid and rifampicin three times a week.

be attempted with second line and experimental drugs. However, in countries, with limited resources, treatment of patients with chronic tuberculosis should be given the lowest priority and should not divert resources from higher priority patients. One option, available to programs with limited resources, is to prescribe lifelong isoniazid for such patients, in the hope that this will diminish their infectivity and reduce the transmission of resistant organisms."

1995 WHO Tuberculosis Control Workshop held in Geneva discussed simplifying the patient treatment categories and the use of second-line drugs. Participants "recommend that a country prepared to go to this expense should only provide these second-line drugs for a specialized unit (or units in large countries), in close connection with a laboratory able to carry out cultures and reliable susceptibility tests."

1997 *Treatment of Tuberculosis Guidelines for National Programs 1997, 2nd edition* published "to update the guidelines in the light of the experience gained since the first edition in assisting NTPs." The same basic regimens remained in place with some alternatives and flexibility to acknowledge variations in resources and circumstances across countries.

Guidelines for the Management of Drug-Resistant Tuberculosis published to advise "more economically prosperous" countries with "resources for second-line drugs" on how to "give some hope of cure" to patients who remained sputum smear-positive following fully supervised WHO retreatment regimen.

2009 To move towards universal access to MDR-TB treatment, the fourth edition includes a new recommendation for every country to include an MDR regimen in its standard regimens. This is essential while awaiting DST results for patients with a high likelihood of MDR (such as those whose prior treatment with a six-month rifampicin regimen has failed) and for patients in whom resistance to isoniazid and rifampicin is confirmed.

With new funding from international partners, lack of resources for MDR-TB treatment is no longer an acceptable rationale for providing the 8-month retreatment regimen with first-line drugs (formerly called the "Category II regimen") to patients with a high likelihood of MDR; this regimen is ineffective in treating MDR-TB and may result in amplification of drug resistance (5, 13).

The 8-month retreatment regimen is retained in this fourth edition in only two circumstances. In countries with access to routine DST using conventional methods, the 8-month retreatment regimen with first-line drugs is recommended while awaiting DST results or until laboratory capacity is available.

Sources: World Health Organization, *Treatment of Tuberculosis: Guidelines for National Programmes, 2nd Edition*; *Guidelines for the Management of Drug-Resistant Tuberculosis; and An Expanded Framework for Effective Tuberculosis Control*. Geneva, Switzerland: WHO; 1997, 2002.

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