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MULTIDRUG-RESISTANT TUBERCULOSIS IN THE END TUBERCULOSIS ERA

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ABSTRACT

Multidrug-resistant (MDR) tuberculosis (TB) emerged shortly after introduction of rifamycins in the 1960s; isoniazid resistance had already emerged by the mid-1950s. Without these two drugs, tuberculosis is very difficult and costly to treat, with unacceptably high rates of treatment failure, death, loss to follow-up, and no known preventive treatment. Global attention first focused on MDR TB in the early 1990s when nosocomial outbreaks with high case fatality rates were reported in many countries. Prevalence data for MDR TB on a global scale first became available in 1997. In 2016, about 4.1% of estimated ~10.4 million new TB patients plus 19% of ~1 million previously treated patients, that is ~600,000 people develop MDR TB or rifampicin resistant TB; 250,000 die annually. Ten years ago, <5% of them were diagnosed and enrolled on treatment, increasing to about 21.6% in 2016, leaving much room for improvement. Over that same period of time, momentum has been building to combat MDR TB, including advances in diagnostics, therapeutics, and care; decentralizing patient-centered care coupled with social support; growing improvements in prevention of transmission; increasing use of highly effective antiretroviral treatment; communications, advocacy, and social mobilization; leadership and updated policy guidance. Taking into account long-term epidemiological trends, all of these factors coupled with funding from the Global Fund and other major donors, suggest we may be on the verge of accelerating declines in MDR TB morbidity and mortality. Extreme poverty, which allows tuberculosis to flourish, has actually decreased by about one billion people over the past 25 years. What is needed now is political will on the part of national governments to apply these advances diligently and further reductions in poverty, pushing epidemiological trends past the inflection point to the downward slope. All these can be accelerated with increased support for science leading to better diagnosis, treatment and an effective vaccine to sustain and accelerate the meager declines reported thus far.

Keywords: Tuberculosis; Antitubercular Agents; Tuberculosis, Multidrug-Resistant (source: MeSH NLM).

TUBERCULOSIS MULTIDROGO RESISTENTE EN LA ERA FINAL DE LA TUBERCULOSIS

RESUMEN

La tuberculosis multidrogo resistente (TB-MDR) surgió poco después de la introducción de rifampicina en la década de 1960, cuando la resistencia a la isoniazida ya había emergido a mediados de la década de 1950. Sin estos dos medicamentos, la tuberculosis es muy difícil y costosa de tratar, con tasas inaceptablemente altas de fracaso del tratamiento, muertes, pérdidas durante el seguimiento y ningún tratamiento preventivo conocido. La atención global se centró por primera vez en la TB-MDR en la década de 1990 cuando se reportaron brotes hospitalarios con altas tasas de letalidad en muchos países. Los datos de prevalencia para TB-MDR a escala global estaban por primera vez disponibles en 1997. En 2016, 4,1% de aproximadamente 10,4 millones de pacientes nuevos más el 19% de un millón de pacientes tratados previamente, hacían un aproximado de 600 000 personas que desarrollaron TB-MDR o resistencia a la rifampicina; y 250 000 murieron dicho año. Hace diez años, menos del 5% de ellos fueron diagnosticados e iniciaron el tratamiento, aumentando a aproximadamente en 21,6% en 2016, dejando un amplio margen para mejorar. Durante ese mismo período de tiempo, se han fomentado avances para combatir la TB-MDR, incluidos los avances en diagnóstico, terapéutica y atención; descentralizando la atención en el paciente junto con el apoyo social; crecientes mejoras en la prevención de la transmisión; uso cada vez mayor de tratamientos antirretrovirales de alta efectividad; comunicación, abogacía y movilización social; liderazgo y actualización del enfoque de las políticas. Teniendo en cuenta las tendencias epidemiológicas a largo plazo, todos estos factores junto con el financiamiento del Fondo Mundial y otros donantes importantes, sugieren que podemos estar a punto de acelerar la disminución de la morbilidad y mortalidad por TB-MDR. La pobreza extrema, que permite el incremento de la tuberculosis ha disminuido en aproximadamente mil millones de personas en los últimos 25 años. Lo que se necesita ahora es voluntad política por parte de los gobiernos nacionales para aplicar estos avances con diligencia y buscar una mayor reducción de pobreza, empujando las tendencias epidemiológicas más allá del punto de inflexión hacia una pendiente descendente. Todo esto se puede acelerar con un mayor apoyo para la ciencia que conduzca a un mejor diagnóstico, tratamiento y una vacuna efectiva para sostener y acelerar las reducciones reportadas hasta el momento.

Palabras clave: Tuberculosis; Antibióticos Antituberculosos; Tuberculosis Resistente a Múltiples Medicamentos (fuente: DeCS BIREME).

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INTRODUCTION

Ending the multidrug-resistant (MDR) tuberculosis (TB) epidemic is poised to gather momentum like never before. MDR TB is defined as TB with resistance to at least isoniazid and rifampin, the two most important anti-TB drugs. Molecular diagnostic technologies, new and re-purposed drugs, better/shorter and less costly treatment regimens, increasing attention to airborne infection control, decentralized patient-centered care and social support, combined with financial resources from the Global Fund and other major donors herald an inflection point in progress against TB and MDR TB [1,2]. What is needed now is the political will to implement these advances energetically. Increased support for science is needed to generate tomorrow's advances to accelerate these trends because funding for TB research has stagnated [3]. Political will is starting to gain momentum, unevenly among middle- and low-income countries, pulled by the dire public health need and pushed by communication, advocacy and social mobilization. The unprecedented call by the Minister of Health of South Africa, Aaron Motsoaledi, for a United Nations high level meeting on TB [4], the Global Ministerial Conference on TB in Moscow in November 2017, and inclusion of TB at the UN General Assembly in 2018 [5,6], may create opportunities for global and country commitments to accelerate implementation of targets set forth in the End TB strategy and in the Sustainable Development Goals agenda [7].

The movement of major tuberculosis epidemics through populations is measured in centuries, not months or years. Ending the global TB epidemic, including MDR TB, is a marathon not a sprint like Severe Acute Respiratory Syndrome (SARS) or Ebola. Much of Europe and the United States are at the tail end of an epidemic that began in medieval Europe [8,9]. Peaking in the 19th century when tuberculosis was the leading cause of death, TB declined steadily through the 20th century (except for two World Wars), accelerating only modestly after the advent of chemotherapy [8,9]. On this same scale, Latin America, Africa, and Asia are just passing the peaks of their epidemics, which started much later following European colonization [8,9]. The human immunodeficiency virus (HIV) changed this trajectory, especially in sub-Saharan Africa. Massive global efforts beginning in the 1990s have just started turning the tide, even in regions with high HIV prevalence, mortality decreasing much faster than incidence. Thus, with sustained effort we are on the verge of substantial progress with steeper declines in TB, including MDR TB, through increasing application of advances in science to public health, international funding, and social/political mobilization over the past two decades. The convergence of these trends is "keeping alive the interest of all social classes in the fight against tuberculosis" as originally called by Robert Koch, the founder of modern TB science [10]. To this same end, poverty, the common denominator of TB everywhere, has actually decreased by about one billion people over the past 25 years [11].

Paradoxically, drug-resistant TB was an untoward by-product of chemotherapy, beginning with the first human trials of the first anti-TB drug. With streptomycin in 1947, over two-thirds of the patients developed streptomycin-resistant TB; streptomycin was the only available effective drug at that time. Today, an estimated 4.1% of new TB patients have MDR TB, but MDR TB spreads about the same as drug-susceptible TB, and not all new patients are cured with chemotherapy [1]. Varying by country, from 1% to over 20% of patients will require treatment again, and 21% of these previously treated TB patients have MDR TB [1]. Until recently, controlling MDR TB required diagnostics and therapeutics that were 10 to 100-fold more costly per patient than those needed for drug-susceptible TB, and personnel costs were at least 4-fold higher than drug-susceptible TB. While today's program managers see these costs as part of the total cost of managing TB, before the Global Fund, most TB programs were vastly underfunded, with insufficient resources even to diagnose and treat half of the people with active TB, those who could be diagnosed by microscopy and treated with standardized short-course chemotherapy [12]. An influential communications campaign, ignited by World Health Organization's first-ever declaration of a global public health emergency in 1993 brought much needed attention to TB which has again surpassed HIV as the single most lethal human pathogen [1].

BUILDING THE FOUNDATION

Although MDR TB emerged soon after the introduction of rifamycins [13-15], MDR TB did not emerge into global awareness until the early 1990s following reported outbreaks with high case fatality rates in United States, Argentina, Italy and subsequently many other countries. These outbreaks, clearly, were the tip of an iceberg, but the true magnitude of the problem was completely unknown. The first major multinational response was the World Health Organization (WHO) / International Union Against TB and Lung Disease (the Union) Global Project on Anti-Tuberculosis Drug Resistance Surveillance supported by a Supranational TB Reference Laboratory Network, both in 1994 [16]. The first volume of results, published in 1997, confirmed that MDR TB was present in every country surveyed with a median prevalence of 3.5% among new cases and 20% among previously treated cases [13]. "Hot zones" with much higher prevalence were identified in specific geographic regions, most notably countries of the former Soviet Union. Subsequent reports have affirmed and extended these results, by 2014 covering over 150 countries or subnational regions of larger countries representing >95% of the world's populations [17-20].

In this context, leading tuberculosis experts, public health policy leaders and decision-makers were divided as to how best to approach MDR TB given lack of evidence on the feasibility and effectiveness of managing MDR-TB in limited resources settings at that time. On the one hand, hard core supporters of the WHO-recommended DOTS (Directly Observed Treatment, Short Course) strategy prioritized all efforts, infrastructure, human resources, and economic inputs on strengthening and expanding DOTS over management of MDR TB, smear-negative TB (children, people with HIV infection) and extrapulmonary TB. The DOTS strategy evolved from highly effective demonstration projects in several of the world's poorest countries in the 1970s and 1980s, when public funding for TB control was at historic lows. By focusing on microscopy and standardized short-course chemotherapy, about 50% of TB cases, the sickest and most contagious, could be diagnosed and treated relatively easily and inexpensively [12]. This half, however, was the source of infection for 70% to 80% of tomorrow's tuberculosis cases. Mathematical models indicated that if this strategy were implemented diligently, TB incidence overall would decline ~5% per year; the low priority assigned to MDR-TB was reinforced by the assumption that MDR TB would decline in parallel, partly from decreasing the reservoir, partly due to a presumed loss of fitness of drug resistant TB strains [12,21].

On the other hand, health care providers, laboratories, program officers, patients and affected communities were facing increasing numbers of MDR TB patients, with disproportionate suffering, mortality, and catastrophic costs. Vigorously promoting a commensurate medical and humanitarian response was the only humane, ethical path forward.

Major barriers to progress in developing a response to MDR TB was the lack of laboratory capacity to diagnose MDR TB in most middle- and low-income countries and the high cost of second-line medicines needed for treatment. This high cost was partly because the real size of the economic market for second line anti-tuberculosis drugs (which differs from the public health need) was small, and located in countries with ability to pay for drugs. Markets such as this were, and remain, not very attractive to the pharmaceutical industry. Consequently the cost of these drugs remained high. Recognizing this, Partners in Health at Harvard Medical School brought together WHO, non-governmental organizations, major pharmaceutical companies, national and multilateral public health agencies, donors and bilateral aid agencies to agree on setting up a pooled procurement mechanism for quality-assured second-line drugs to be made available to all middle- and low-income countries [22]. This mechanism was aimed at increasing economic demand, making it more consistent, improving predictability, and timely payment for quality-assured second line drugs. In return major pharmaceutical manufacturers such as Eli Lilly, and Jacobus, working with the pharmaceutical drug wholesaler International Dispensary Association, offered 60% to 90% discounts on their specific drug products under specified conditions [22].

The lessons of history are clear in this respect. Essentially all pathogens progressively develop resistance to the antimicrobial agents with which we treat them especially when those agents are used imperfectly. Using second line drugs in programs with a high burden of MDR TB, predictably, would generate resistance to these same second line drugs. At that time, these drugs were the last hope, the last line of defense against MDR TB. Hosted by WHO, with financial support from the Bill and Melinda Gates Foundation, Harvard/Partners in Health, KNCV Tuberculosis Foundation (KNCV), Médicos Sin Fronteras (MSF), Centers for Disease Control and Prevention (CDC), and Estonia's National TB Program established the "Green Light Committee" (GLC), to increase access, prevent acquired drug resistance, and increase knowledge, ultimately helping launch by 2009 around 140 pilot MDR TB programs in 90 countries, ensuring that programs gaining access to these high quality low cost drugs had the capacity and appropriate plans to use these drugs properly without generating further drug resistance [23]. These programs served as a nucleus for subsequent nationwide expansion of services for MDR TB, to which countries committed at the 62nd World Health Assembly [24]. Indeed, 110 of the 253 applications received and approved by the GLC from 2000-2011 were second and third applications from approved programs to expand pilot projects established under their first application; thus, moving into major expansion phases with Global Fund money [23]. Subsequent research indicated participation in the GLC initiative reduced the incidence of acquired resistance to second line drugs and improved treatment outcomes even compared with higher income countries [25-26]. GLC approval became recognized as a sign of programmatic excellence at that time.

DEVELOPMENTS IN FUNDING AND POLICY

For middle- and low-income countries, the Global Fund Against AIDS, TB, and Malaria (Global Fund), a multilateral pooled donor mechanism for public health programs, changed everything. Cost was no longer a legitimate reason to forego appropriate services for MDR TB. While the BRICS countries (Brazil, Russia, India, China and South Africa) rely on the Global Fund for a portion of their TB control program costs, many other middle- and low-income countries rely heavily on the Global Fund for a majority of their program costs [1]. Because of the substantially reduced drug cost and program quality that came with GLC approval, the Global Fund came to rely heavily on the GLC not only to procure high-quality drugs at reduced prices, but also to evaluate applications to the

Global Fund that included MDR TB. By 2002, the Global Fund required countries to obtain GLC approval to use Global Fund grants for MDR TB, saving the Global Fund an estimated $100 million in drug costs [27]. Moreover the GLC established a model of thorough evaluation and close monitoring of programs based on initial and repeated site visits to ensure that implementation in each country followed the policies and practices proposed by the program itself.

Interestingly however the world was unprepared in several respects. At the policy and leadership level, momentum did not change overnight. Reliance on acid-fast microscopy for diagnosis meant that both laboratory capacity for culture and drug susceptibility testing (DST) and radiology services were grossly under-developed low- and middle-income countries. In addition, biosafety and infection prevention and control measures were rudimentary at best but mostly non-existent in healthcare facilities except for wealthy countries. Before 2006, the GLC was one of the few mechanisms supporting countries in addressing MDR TB until WHO's Stop TB Strategy in 2006 called for making this an essential part of the response to TB everywhere [28]. This situation changed further with the World Health Assembly's resolution 62.15, passed in 2009, affirming the public health imperative and the right to appropriate diagnostic and therapeutic services of all TB patients, as well as people being evaluated for TB, including MDR TB [24]. Therefore, it was not until after 2009 that WHO had a firm legal base from which to advocate for growth and expansion of efforts to address MDR TB. This political decision would transform radically the GLC model described above, which was not suitable anymore for a response to MDR-TB driven by ministries of health committed to universal access to MDR-TB management, rather than by the demand of countries and subnational units with the capacity to meet the requirements of the GLC model.

The experience of wealthy countries with MDR TB outbreaks in the 1990s led to the development of a policy base that could serve as guidance and that could be adapted to middle and lower income settings. Similarly the accumulated experience of reference laboratories in affluent countries served as major sources of expertise for policymakers and laboratory managers in middle and low income countries, offering consultation, training, mentorship, proficiency testing, referral testing, and in many cases material support [29-31].

Seminal funding from the Bill and Melinda Gates Foundation, launching the Foundation for Innovative New Diagnostics (FIND), the Global Alliance for TB Drug Development, the Critical Path Institute, Aeras Vaccine Foundation, and the GLC, among many other initiatives, has been crucial in transforming the landscape of the global campaign against tuberculosis more than any other single donor.

ADVANCES IN DIAGNOSIS

Advances in diagnostic technology, perhaps more than any other factor, have led us to the verge a massive global scale up in efforts to prevent and control MDR TB. Although phenotypic methods have advanced too, for the first time in history, we are able to detect nanogram quantities of specific bacterial DNA directly in sputum specimens within two hours rather than looking for AFB under a microscope or cultivating them on nutrient medium. Of these, the most revolutionary has been Gene Xpert MTB/RIF® (Cepheid, USA), with simple, one-step sample preparation and an automated, self-contained system for nucleic acid amplification and detection of specific DNA sequences identifying both Mycobacterium tuberculosis (M.tb.) and mutations in the rpoB gene responsible for 95% of rifampin resistance [32]. The Xpert MTB/RIF assay is revolutionizing the detection and diagnosis of TB in general, and rifampin-resistant TB specifically. In return for public support in the development of Xpert TB/RIF, negotiated by the Foundation for Innovative New Diagnostics (FIND), Cepheid, the manufacturer, in a prime example of corporate citizenship in the domain of public health, offered the instrument and the Xpert MTB/RIF assay to middle- and low-income countries at deeply reduced prices eventually reaching less than $10 per specimen [33]. This test could be carried out in relatively small urban centers, for example at the district level, without extensive infection control and biosafety measures already in place; the biohazard is no worse than smear microscopy. The next generation, Xpert Ultra®, is even more sensitive and will become widely available in 2018.

Competitors to Xpert MTB/RIF such as Truenat MTB® (Molbio Diagnostics, India) and the MeltPro MTB® family of tests (Zeesan Diagnostics, China) have now entered the market with alternative assays [34,35]. Stepwise improvements in line probe assays and the rapid evolution and decreasing cost of whole genome sequencing suggest we are on the verge of an era of widely distributed molecular diagnostic services that may help identify hundreds of thousands of individuals with MDR TB who remain undiagnosed and inadequately treated today [36-38]. In affluent countries, targeted gene sequencing for well-characterized resistance-determining genes for as many as nine drugs has become routine, with turn-around-times of 48 hours, starting with either culture or the sediment of processed sputum [39]. These technologies and practices should be extended to national reference laboratories everywhere.

The main shortcoming of Xpert MTB/RIF at the moment is that it does not include isoniazid even though isoniazid resistance is much more common than rifampin resistance. Commercially available line probe assays such as the Hain MTBDRplus®, can fill this gap, although they require more sophisticated laboratory infrastructure and trained personnel suitable for urban centers [36]. Recent improvements to the Hain MTBDRsl® (Hain Life Sciences, Germany) for

second-line drugs made it sensitive and specific enough to recommend in routine practice where available [37]. Again, Hain Life Sciences is not the only company in this market. Competition is leading to better products with diverse profiles at lower cost.

Phenotypic methods have advanced in the past 20 years as well. Direct susceptibility testing on solid media using the nitrate reductase (Griess) method and the Microscopic Observation Drug Susceptibility (MODS) test have been decentralized to state- or province-level laboratories, demonstrably improving patient outcomes, especially among patients who present as diagnostic challenges [40,41].

ADVANCES IN TREATMENT

This accelerating detection of rifampicin resistance worldwide is pulling along behind it the need for expanding access to prompt and effective treatment. The advent of extensively drug-resistant tuberculosis (XDR TB) (a subset of MDR TB with additional resistance to the two most important classes of second-line drugs, fluoroquinolones and aminoglycosides) in the 2000s was a major impetus to science and industry, spurring development of new diagnostics, new drugs, and better uses of existing drugs. Fluoroquinolones were developed for gram-negative urinary tract infections in the 1980s. Fortuitously, they were found to be effective against MDR TB in the 1990s, and newer fluoroquinolones are even more effective. Apart from these, no new drugs had been developed against tuberculosis since the rifamycins in the 1960s. Treatment was based on obscure second-line drugs that had been relegated to the back shelf because they were more expensive, less effective, or more toxic, so the therapeutic outlook was relatively dismal, with only 50%-60% successful treatment outcomes [1,42,43].

In the past five years, linezolid, originally approved for treatment of methicillin-resistant *Staphylococcus aureus*, has been shown to be effective against MDR TB, although bone marrow suppression and neuropathy limit dosage and longer-term use. In addition, the anti-TB activity of clofazimine is receiving renewed attention, adding two recently re-purposed drugs to the ammunition [44].

In 2012 and 2013 the first two truly new anti-tuberculosis drugs, bedaquiline and delamanid, were approved by the US FDA (bedaquiline) and the European Medicines Association (delamanid) [45,46]. Although Phase 2 controlled clinical trials show these drugs to be effective against MDR TB, safety concerns and cost considerations have prevented rapid widespread uptake. More recent experience with case series and observational studies report safety and tolerability better than the original Phase 2B clinical trials that led to provisional approvals for marketing, contigent on completion of proper, full-scale Phase 3 trials, currently underway [47,48].

Preliminary results of the Global Alliance's trial NC005 of the novel regimens of bedaquiline / pretomanid / pyrazinamide with and without moxifloxacin with a target duration of 6 months treatment show the regimen to be as effective as standard short-course chemotherapy for drug-susceptible TB in terms of time to stable culture conversion [49]. Moreover, early results from the NiX-TB study of bedaquiline, pretomanid and linezolid for treatment of XDR TB, reported in October 2016 suggest these regimens are on track to provide substantial improvements in treatment [50]. Together with other clinical trials that are underway or being planned, the future of chemotherapy for MDR TB is much brighter than the past. Promising newer drugs such as Q203 and PBTZ169 have entered Phase 1 trials [51-53].

Apart from new and repurposed drugs, better uses of existing drugs are also contributing to our stronger position vis-à-vis MDR TB. First the Damien Foundation in Bangladesh demonstrated the effectiveness of an intensified regimen of seven drugs for 4-5 months followed by 4 drugs for 5-7 months (9 to 12 months total) including the anti-leprosy drug clofazimine, the fluoroquinolone gatifloxacin, and isoniazid doses three-fold higher than normal, led to >80% cure rates [54]. Subsequently, their experience has since been replicated prospectively in much larger cohorts in Bangladesh [55], throughout francophone Africa, Central Asia, and elsewhere consistently showing >80% treatment success rates versus ~60% with standard MDR TB regimens [56,57]. More recently, WHO formally recommended this regimen for patients who have not been previously treated for MDR TB and who do not have additional resistance to drugs in the regimen [58]. These exceptions, however, exclude 1/3-1/2 of MDR TB patients depending on location. These individuals would benefit from the new drugs described above.

CONCLUSION

These developments in diagnostics and therapeutics, in financing and increasing advocacy, have led WHO to update global policy guidelines with unprecedented frequency. Since 2009, policy guidelines have been formally evidence-based using information and communication technology to take best advantage of the broader, collective public knowledge in a rigorous, transparent manner. The fly in the soup is stagnant investment in science that will bring about tomorrow's advances crucial for meeting tomorrow's challenges. Consider only the massive output of science in response to HIV/AIDS beginning in the 1980s, transforming HIV from a horrible death sentence to a manageable chronic condition. That kind of investment can bring about that kind of change. Diagnosis and treatment of MDR TB is reaching only one-fourth of those affected by it, increasing far too slowly from <5% ten years ago. We must bend that curve upward until it exceeds 90%. Advocacy, communications, and social mobilization like the Stop TB Partnership, Treatment Action

Group, and many others are crucial to accelerate progress against TB. Their efforts push governments and others to fund science and the governments of high-burden countries to fully support TB prevention and control in their own populations because the Global Fund is not a permanent solution. Nevertheless, in this environment, donors are investing in further refinement and adoption of these new tools, countries are modernizing TB laboratory diagnostics, research into new drugs is finally bearing fruit, and the market for drugs and diagnostics is growing. While some countries are moving ahead vigorously, setting an example for the rest, others are still to slow to step up to the challenge of reducing suffering and death due to tuberculosis. With increasing political commitment, the future holds more hope than the past for people affected by MDR TB.

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