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Epidemiology and Treatment of Multidrug Resistant Tuberculosis

Carole D. Mitnick, Sc.D.[1], **Sasha C. Appleton, Sc.M.**[2], and **Sonya S. Shin, M.D., M.P.H.**[3]

[1] Department of Global Health and Social Medicine, Harvard Medical School, Boston, Massachusetts;

[2] Partners In Health, Boston, Massachusetts;

[3] Division of Global Health Equity, Brigham and Women's Hospital, Boston, Massachusetts

Abstract

Multidrug resistant tuberculosis is now thought to afflict between 1 and 2 million patients annually. Although significant regional variability in the distribution of disease has been recorded, surveillance data are limited by several factors. The true burden of disease is likely underestimated. Nevertheless, the estimated burden is substantial enough to warrant concerted action. A range of approaches is possible, but all appropriate interventions require scale-up of laboratories and early treatment with regimens containing a sufficient number of second-line drugs. Ambulatory treatment for most patients, and improved infection control, can facilitate scale-up with decreased risk of nosocomial transmission. Several obstacles have been considered to preclude worldwide scale-up of treatment, mostly attributable to inadequate human, drug, and financial resources. Further delays in scale-up, however, risk continued generation and transmission of resistant tuberculosis, as well as associated morbidity and mortality.

Keywords

Tuberculosis; drug resistance; surveillance; management; epidemiology

An estimated 489,139, or nearly 5% of all new cases of tuberculosis (TB) diagnosed in 2006 were multidrug resistant (MDR), that is resistant to isoniazid and rifampicin, the two most effective anti-TB agents. This represents an increase of 12% since 2004 and 56% since 2000.[1] An additional 1 to 1.5 million prevalent cases of MDR-TB were estimated in 2006, resulting in as many as 2 million people with active disease.[2] The successful treatment of MDR-TB requires the use of second-line drugs, which historically presented an insurmountable cost barrier in resource-poor settings. To alleviate this gap, the World Health Organization (WHO) established the Green Light Committee (GLC) in 2000 to facilitate access to and strictly supervise the use of second-line agents for TB control.

Even with the inception of the GLC and a significant reduction in cost of second-line drugs, drug resistant TB continues to grow and challenge the current capacity in most settings. Recognition of the magnitude of the MDR-TB problem and its associated morbidity and mortality has motivated recent calls for increased research and scaled-up treatment.[3,4] Several recent, excellent articles have reviewed the molecular mechanisms of resistance, risk factors for drug resistant TB (DR-TB), DR-TB and HIV, and global epidemiology of TB.[5–21] This article highlights the gaps in knowledge of the global epidemiology of MDR-TB, illustrates

Address for correspondence and reprint requests: Carole D. Mitnick, Sc.D., Department of Global Health and Social Medicine, Harvard Medical School, 800 Boylston St., 47th Fl., Boston, MA 02199 (cmitnick@pih.org).
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the elements of a programmatic response and confronts some of the perceived obstacles to scale-up of programmatic management of MDR-TB.

EPIDEMIOLOGY OF MDR-TB

Drug Resistance and Multidrug Therapy

DR-TB is defined as tuberculosis caused by a strain of *Mycobacterium tuberculosis* that grows, in vitro, in the presence of one or more antimycobacterial drugs. Spontaneous mutations leading to resistance occur at random in large populations of *M. tuberculosis* at a rate per cell division of 10^{-10} for rifampin (RIF), 10^{-8} for isoniazid (INH) and streptomycin, 10^{-6} to 10^{-8} for fluoroquinolones, 10^{-7} for ethambutol, and 10^{-3} for pyrazinamide. [22–24] Resistance can be engendered through inadequate treatment (Fig. 1). Exposure to drugs kills susceptible organisms, selecting for resistant mutants that become responsible for persistent disease, a phenomenon known as acquired resistance. Resistant organisms are also transmitted; the consequent TB episode is considered to have been caused by primary resistance.

The phenomenon of acquired resistance was first observed with the introduction of streptomycin (SM) in 1945. After initial bacteriologic and radiographic response, resistance to SM emerged in 85% of patients tested,[25] and monotherapy with SM afforded no long-term survival benefit.[26] Combination therapy was introduced to prevent the development of resistance[27] and remains one of the cornerstones of anti-TB therapy, which usually comprises four drugs, including INH and RIF.[28,29] The DOTS (directly observed therapy, short-course chemotherapy) strategy, introduced by the WHO in 1993, incorporates direct observation of multidrug therapy and several other elements to minimize the acquisition of drug resistance and facilitate TB control.[30]

The emergence of increasingly resistant strains of *M. tuberculosis*, however, is evidence that the DOTS strategy alone cannot successfully prevent drug resistance in all settings.[31,32] Of particular importance is MDR-TB, which severely compromises treatment outcomes. [33–38] Extensively drug resistant TB (XDR-TB) refers to MDR-TB isolates with further resistance to a second-line injectable agent and a fluoroquinolone. Treatment success among these patients has been reported to be worse than among patients with MDR-TB.[39–42]

The Global Epidemiology of Drug Resistant TB: Knowledge and Gaps

Considerable effort has been expended to estimate the number of cases of DR-TB and the percent of TB cases caused by resistant organisms. Through a standardized, four-survey, 14-year effort, the Global Project Anti-tuberculosis Drug Resistance Surveillance (GPADRS) reported the burden of DR-TB in 138 settings in 114 countries.[2,31,43,44] Based on reported figures and data on nine epidemiologic indicators, global estimates were derived for 2006: 489,139 (95% CI: 455,093 to 614,215) cases of MDR-TB, representing 4.8% (4.6 to 6.0) of all TB cases.[2]

These survey data, although extremely valuable, suffer from several limitations described in a recent article.[45] A few are highlighted here. First, the MDRTB burden was estimated to be lower in nonsurveyed places than in regions with survey data. Because poor TB control is an important risk factor for drug resistance, and some infrastructure is required to implement a survey of antituberculosis drug resistance, settings that have not conducted surveys may, in fact, have higher rates of MDR-TB.[23,43] Second, surveys provide, at most, limited information on important subpopulations that can have higher risks of MDR-TB. These include previously treated patients, who are often enrolled, but not in sufficient numbers to generate accurate estimates. Patients treated in the private sector[46–49] are generally not included in survey samples. Furthermore, HIV-infected TB patients may be underrepresented in surveys that require sputum-smear positivity for inclusion.[50] Finally, a substantial pool of chronic patients

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with MDR-TB suffers at home, with substantial delays in seeking care[51]; these patients, therefore, are likely to be excluded from health facility–based samples. These omissions may result in an underestimate of the burden of resistant disease and preclude design of effective standardized regimens.[52]

The foregoing summary results also mask significant variability (Table 1 [53–64]).* In some parts of the world, like the former Soviet Union and eastern Europe, the percent of new and previously treated TB cases with resistant disease is alarmingly high: in Baku, Azerbaijan, multidrug resistance was reported in more than 20% and 55% of new and previously treated patients, respectively, in 2006. The absolute MDR-TB burden, however, is relatively low at 431 cases. In contrast, in the Indian states surveyed, DR-TB among new patients remains relatively infrequent (0.5 to 3.4%). However, high frequency of MDR-TB among previously treated patients (e.g., 17.4% in Gujarat State in 2006), combined with high TB incidence, yield a disturbing estimate of the absolute number of MDR-TB cases: 110,132 (95% CI: 79,975 to 142,386). In China, MDR-TB incidence was estimated at 5%, resulting in 130,548 cases (95% CI: 97,663 to 164,900) in 2006. These examples, in which percent of TB cases that are MDR and absolute number of MDR-TB patients provide very different impressions of the magnitude of the problem, highlight the importance of deriving and comparing population incidence or prevalence to make policy decisions.[65]

An overall lack of current data defines the situation in much of Africa. Of the 22 African countries ever evaluated, only six were surveyed in the last 5 years. In 2006, 66,711 (95% CI: 55,607 to 137,264) cases of MDR-TB were estimated to have occurred (2.2% of TB patients) on the continent. Reports of 3.9% MDR-TB among new cases in Rwanda, 18% among previously treated cases in Senegal, and widespread MDR-TB and XDR-TB in southern Africa[66–69] suggest that the true burden of drug resistance in this region may be underestimated. In particular, more data are needed to refine estimates of MDR-TB in high-HIV incidence settings in Africa where an estimated 58,296 MDR-TB cases occurred; the upper confidence limit was more than two times that figure (118,506).

Even more uncertain is our current knowledge of the global burden of XDR-TB. The 2008 report summarized available data on XDR-TB, which has been documented in at least 46 countries (Fig. 2). Surveillance data revealed XDR-TB among 1.9% (95% CI: 1.1,3.1) of MDR-TB patients in the United States and 23.7% (95% CI: 18.5,29.5) in Estonia. Survey results ranged from 0% in Rwanda and Tanzania to 15.0% (95% CI: 3.2, 37.9) in Donetsk Oblast, Ukraine. Knowledge of the true extent of the XDR-TB problem is hampered for several reasons, in addition to those already mentioned. First, surveillance data are available from a very small number of patients in only a few countries, and only those with extensive drug susceptibility testing (DST) capacity. Second, the denominator in nearly all sites is confirmed MDR-TB, so the true burden of XDR-TB in the population remains unknown. Lastly, the short duration of surveys may yield biased results, particularly in light of oft-reported seasonal variation in TB notification.[70–76]

Nevertheless, existing data warrant intensive, rapid action. Given the heterogeneity of observed and estimated burden, a standardized approach is unlikely to be appropriate. However, certain principles of MDR-TB management apply across disparate settings and are essential to scale-up efforts.

*Results from the four reports of the Global Anti-Tuberculosis Drug Resistance Surveillance Project are adapted and summarized in Table 1. For countries for which no representative survey results have been published, data from the most recent published reports of convenience samples are included.

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PROGRAMMATIC MANAGEMENT OF MDR-TB

Laboratory Networks

Prominent among the challenges of scaling up MDR-TB treatment programs has been the process of building laboratory capacity. Although DOTS requires only smear microscopy, MDR-TB treatment demands culture and DST capacity for the following: individual regimen design, regional surveillance to guide standardized regimen composition, and treatment monitoring. These services are unlikely to be available at point of care in the immediate future. Implementation, therefore, requires a laboratory network to efficiently transmit samples and results between laboratories and clinical settings.

At present, many developing countries are unable to diagnose TB with certainty, much less MDR-TB or XDR-TB[77–80]; this is especially true in the presence of HIV coinfection.[81] Countries in the process of implementing MDR-TB treatment programs must therefore include a plan to enhance laboratory infrastructure. Adequate, local DST and culture capacity may lag behind treatment capacity but should not hamper swift "roll-out" of treatment services. Instead, "bridging" infrastructure can draw from a variety of resources, such as: established, quality-assured reference laboratories abroad; laboratory capacity built through translational and operational research[82]; and laboratory support from local private commercial or academic laboratories.

An MDR-TB laboratory network comprises not only participating local, regional, and national laboratories, but also clinical providers and policy makers who work with laboratory directors to establish and adhere to a rational plan for DST and culture capacity consistent with National TB Program policy.[82] Simple, rapid, and inexpensive DST methods, currently becoming available, should be implemented whenever possible.[83–85] However, the benefits of rapid DST will be limited if delays in specimen transport, test result communication, and treatment initiation are not simultaneously addressed.[86,87]

Programmatic Approaches to MDR-TB Treatment

There is a broad spectrum of programmatic approaches to MDR-TB management, with variability in the following elements: (1) when to screen and treat, (2) whether to use empirical therapy prior to laboratory confirmation of MDR-TB, (3) how much to individualize the regimen, (4) how to monitor treatment response, and (5) where to deliver care. Below, we recommend approaches for each of these elements, gleaned from management experiences in many sites.[88–92]

Delayed initiation of appropriate treatment in suspected MDR-TB cases is associated with excess morbidity.[93] Because drug resistance is often suspected before DST is performed, a proactive approach to identifying drug resistant cases optimizes the chances of timely initiation of therapy. All patients with prior TB treatment or delayed or unfavorable response to first-line treatment should be evaluated for drug resistance. Close contacts of cases with active MDR-TB—for instance, those exposed in prisons, hospitals, and households—should be screened for active disease and if confirmed, screened for MDR-TB. Moreover, in light of the poor prognosis among patients coinfected with HIV, prompt referral for diagnosis and treatment of MDR-TB in this population is critical. Additional indications for empirical MDR-TB treatment and/or DST should be guided by data on local or regional factors associated with drug resistance. Universal DST should be the ultimate goal. Figure 3 provides several examples of programmatic approaches, without being exhaustive. A common element among the examples is adherence to the principle of initiating empirical therapy when there is high clinical suspicion of MDR-TB in individual patients. *The importance of timely and adequate empirical MDR therapy cannot be overemphasized*. Improved outcomes have been demonstrated when

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patients with MDR-TB receive prompt therapy with multiple drugs that the patient has not received before.[94,95] The use of inappropriate therapy (e.g., a re-treatment regimen containing only first-line drugs or regimens containing an inadequate number of second-line drugs) while awaiting susceptibility results may fail to result in clinical improvement. Moreover, drug pressure may lead to amplification of drug resistance, rendering the DST data unreliable when they are finally available. Once effective, empirical therapy has been initiated, the regimen can be optimized if susceptibility results become available.

All MDR-TB treatment follows several basic principles. MDR-TB regimens are constructed using the most active drugs available. Agents used to treat MDR-TB are described in Table 2. A regimen typically consists of at least four to five drugs to which the infecting strain is likely susceptible, including a parenteral, a fluoroquinolone, and any first-line drugs to which the infecting strain is likely susceptible. Likely susceptibility is determined by several criteria, including extent of prior exposure: a patient-isolate is considered likely susceptible if the patient has not previously received the drug for more than 1 month. If the patient is a close contact of someone with MDR-TB and DST results on the new patient are not available, the contact can be presumed to have MDR-TB, although the specific resistance pattern may vary.[96,97] Drugs to which in vitro resistance is laboratory confirmed—or to which the patient has a documented allergy—should also not be prescribed. If individual DST results are not available or are incomplete, regional resistance data are considered; for instance, in regions where streptomycin resistance is endemic, the regimen should use an alternative parenteral agent.

In addition to the foundation of four to five drugs, reinforcement with additional drugs (e.g., drugs to which resistance is possible given prior exposure but not confirmed) may be considered in cases with advanced disease and/or confirmed high-grade drug resistance. Drugs that possess in vitro efficacy without proven in vivo effect may also be included for reinforcement. None of these drugs, however, should be considered part of the foundation. Other drugs—including new compounds in clinical development—have been suggested for use against MDR-TB, but additional safety and efficacy testing is still required.[98–112]

Much emphasis has been placed on whether regimens are tailored to each patient's drug susceptibility data and treatment history or standardized according to population resistance data. In reality, hybrid approaches, which combine available population and individual data, are most often applied. Irrespective of the degree of individualization, the principles of regimen design remain the same and depend on prudent attention to treatment history and timely, representative resistance data.[52]

Bacteriologic, clinical, and radiographic parameters all aid in monitoring treatment response. Because less active drugs may merely suppress bacillary growth without sterilization, current guidelines recommend monthly sputum smear and culture, at least prior to bacteriologic conversion. Culture conversion occurs at an average of 60 days into MDR-TB therapy and is associated with favorable treatment outcome.[113] In cases of delayed culture conversion (i.e., positive after 4 months of treatment) and/or lack of clinical and/or radiographic improvement, patients should be evaluated for surgery and reinforcement of their MDR-TB regimen. Adherence to treatment should be reassessed and repeat DST considered.

There is considerable debate around the optimal frequency of bacteriologic monitoring after initial conversion. Some have argued that the risk of reconversion, as well as its associated consequences, is high enough to warrant monthly follow-up with smear and culture. Others cite programmatic and laboratory burden and suggest less frequent monitoring, especially with culture. Current guidelines recommend at least quarterly monitoring, after conversion, with both smear microscopy and culture.[114] A parenteral agent should be provided for 6 months

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after achieving sputum-culture conversion. Oral MDR-TB treatment is recommended for at least 18 months after culture conversion.

Treatment support and directly observed therapy (DOT) of antimycobacterial agents are especially important for MDR-TB patients. Prolonged treatment with frequent adverse reactions presents adherence challenges for even the most motivated patients. Adverse events associated with MDR-TB medications, summarized in Table 2, should be managed aggressively to minimize risk of treatment default.[115,116] Therapy is best supervised by individuals trained in the use of second-line drugs. Experience notes, however, that these can include specially trained lay personnel.[117,118]

Both inpatient[119–121] and ambulatory[117,122,123] models of MDR-TB care have been successful.[124] Inpatient management allows close management of adverse events and facilitates treatment adherence. Ambulatory care permits increased flexibility, eliminates the bottleneck of inpatient treatment initiation, and decreases the risk of nosocomial transmission of drug resistant strains to other patients and health workers. With DOT and intensive monitoring, ambulatory care may be comparable (or superior) to inpatient modes of care.

There are several advantages to community-based MDR-TB treatment. First, scheduling and treatment locale can be flexible without compromising supervision or regularity. This permits treatment completion, usually of two doses a day for 18 to 24 months, without jeopardizing patients' family and work obligations. Second, community-based DOT should minimize MDR-TB transmission in health centers. Third, community health workers provide additional support, including emotional and educational support; monitoring of and referral for medical and/or psychosocial problems that may threaten treatment completion; and screening of household contacts for TB. Finally, task shifting to community health workers represents an important potential contribution to health systems strengthening beyond MDR-TB treatment.

Infection Control

Infection control in health establishments, households, and laboratories is an essential component of MDR-TB management. TB infection control measures can be planned at three levels: administrative, environmental, and personal, as described by the Centers for Disease Control and Prevention (CDC). First, and most often overlooked, are practical administrative measures to separate patients according to reduce risk of (and from) transmission of TB, including MDR-TB. In resource-poor settings, it can be difficult to screen and identify TB and/or MDR-TB patients in overcrowded waiting rooms with poor ventilation and minimal staff. However, simple strategies can be employed, such as (1) separating coughing patients from others in emergency and waiting rooms; (2) separating HIV-positive individuals in emergency wards and consultation services; (3) designating different times or spaces for consultations and DOT for pansusceptible versus MDR-TB patients. Whenever possible, inpatient contact between HIV-positive patients and patients with confirmed or suspected MDR-TB should be minimized. Similarly, HIV-positive health care workers may be protected by minimizing their exposure to smear- and culture-positive MDR-TB cases.

Infection control in patient homes and communities has been largely neglected, resulting in an absence of metrics of transmission risk. Nevertheless, adapting from hospital and laboratory infection control research, several practices may reduce transmission and stigma. First, there should be adequate ventilation [125,126] and space. Households should be assessed for transmission risk, and, if necessary, renovations (such as windows, to allow cross ventilation; or construction of a separate room to allow the MDR-TB patient to sleep alone). These measures should be undertaken by TB programs or social services as part of public health efforts to reduce community transmission. Families should also be counseled on behavior modifications to reduce transmission, such as using outdoor spaces whenever possible and

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minimizing intimate contact (e.g., breastfeeding, sexual relations) while a family member is culture-positive. Culture-positive patients should also be discouraged from attending work or school. Conversely, myths should be dispelled (e.g., refusing to share eating utensils or refraining from close contact once the patient is culture-negative).

MEETING THE CHALLENGE

"Universal access to high-quality diagnosis and patient-centered treatment" is the first objective of the 2006 Stop TB Strategy.[127] A companion document, the MDR-TB/XDR-TB Response Plan set as a target, treatment of 1.6 million MDR-TB patients by 2015.[3] This number represents only 25 to 50% of estimated cases expected to occur before then.[1] Even with unprecedented opportunities created through global advocacy and substantially increased funding for treatment of DR-TB, implementation remains daunting and the goal elusive. Limitations in available human resources, as well as in current diagnostic and treatment tools, give pause to scale-up efforts. The risks of accelerating scale-up with incomplete information and partial infrastructure, however, need to be weighed against the consequences of continued limited action. In this final section, we present some of the primary concerns that have been raised and propose pragmatic responses to this global crisis.

If MDR-TB Treatment Is Made Widely Available, Limited Second-Line Drugs Will Be Squandered through Emergence of Additional Resistance

MDR-TB and XDR-TB are humanmade epidemics that result from inadequate TB treatment, outdated policy, and transmission. Experiences in the former Soviet Union, parts of Asia, and Latin America reveal that historical poor TB control led to high levels of resistant TB.[128–130] Motivated by a perceived need for a universal, cost-effective solution and preservation of costly, toxic, second-line drugs, the response was to impose rigid TB control,[131] which relied on repeated courses of standardized treatment with first-line drugs[132–134] and severely restricted the distribution of second-line drugs.[135]

This strategy has been extremely successful in the treatment of drug-susceptible TB. In settings of important, extant resistance, however, this approach has been markedly less successful.[33–35,136] The 2004 GPADRS report suggests reasons for this failure: "present treatment practices create significant numbers of new resistant cases and amplify already present resistance," singling out DOTS re-treatment regimens as problematic: "These results corroborate recently emerging evidence that standard re-treatment regimens containing first-line drugs for failures of standard treatment should be abandoned in some settings."[137]

When second-line regimens are finally introduced in this context, they are often inadequate for the resistance profiles of circulating strains.[52] In two examples, Peru and Korea, outcomes of standardized second-line treatment were poor.[138,139] Evidence from Peru and South Africa —where a similar standardized regimen was used—also reveals that, not surprisingly, resistance was further aggravated.[140,141] Moreover, this approach has yet to yield a detectable reduction in the overall burden of resistant disease in Peru or Korea.[2] Stable and decreasing trends in drug resistance were documented, in contrast, only in places with TB control strategies that include universal DST at first TB diagnosis and treatment with second-line drugs when indicated by one or more of the following: DST, prior exposure, or contact history (Fig. 3, option 2). Examples include Hong Kong, the United States, Latvia, Estonia, and several western European countries.[2]

As with many infectious diseases, selection of resistant strains is inevitable in the presence of exposure to antimicrobial therapy. The rate at which they emerge, and the negative consequences of their emergence— morbidity, mortality, amplification of resistance, and transmission—can, however, be minimized through adherence to several principles. MDR-TB

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treatment with a consistent supply of quality-assured second-line drugs should be initiated early; advanced disease diminishes the chance of cure[117,142] and increases opportunity for transmission. Suboptimal regimens containing second-line drugs should be avoided,[52] and treatment adherence should be assured to impede resistance amplification. Measures must also be implemented to reduce transmission risk: these include hospitalizing only those patients who require it for medical reasons and improving administrative and environmental controls in hospitals, health centers, and communities. The GLC currently facilitates treatment consistent with these principles for a small number of TB programs that meet criteria for good TB control.

An alternative and dangerous reality, however, prevails: an estimated 71,000 patients are being treated *outside* GLC auspices in 2007–08; during that interval only 22,000 patients were even *approved* under the GLC mechanism, and many fewer treated. Outside the GLC, patients are often treated with drugs of unknown quality, with untested and unsupervised regimens. Patients are often forced to purchase their own medicines and can only do so sporadically. Consequently, although the GLC mechanism limits distribution and use of quality- assured, second-line drugs,[143] non-quality-assured drugs circulate widely.

Broader, not more limited, distribution of quality-assured drugs will be essential to achievement of targets. Control over their distribution will have to be exercised at the local, rather than the international level. When administered to new patients, or patients having failed only one prior treatment, second-line regimens will require fewer toxic drugs and will achieve better outcomes.[142] Nevertheless, regimens should be constructed to maximize probability of cure, not designed to "hold in reserve" some second-line drugs. The dangers of the alternatives are now well understood. And, with two new drugs already in clinical development for MDR-TB[110,111]—and a third showing promise in animal models[101]—treatment options will not always be so limited.

Global Drug Supply Is Too Limited to Permit Scale-Up

In addition to required policy changes described earlier, increased production is essential to permit wider distribution of quality-assured drugs. Current delays in delivery of orders through the GLC mechanism often exceed 6 months. Second-line drug manufacturers are stymied by inaccurate forecasting of drug needs. Lengthy lead time required to manufacture drugs, and, in some cases, shortages of raw materials, further aggravates the supply problem.† An additional obstacle to a growing drug supply is the perceived small market, represented by those initiating GLC-approved treatment.

Dramatic scale-up of second-line drug production is critical but will not occur without increased demand and/or new incentives: with more aggressive implementation of laboratory support and treatment programs, in the context of health-systems strengthening, patient numbers will increase. Supply could also be bolstered through increased prequalification of manufacturers and products through the WHO's Essential Drugs Program. Only 17 anti-TB products have been prequalified— among them one second-line drug—whereas 147 antiretroviral drugs or combinations are on the prequalification list.[144] Dozens of generic manufacturers are operating in high-burden MDR-TB countries, which have laws that preclude purchase of generic drugs made elsewhere. Enhanced access to prequalification could substantially increase the high-quality products available in and out of these settings. Lastly, novel incentives for drug discovery, development, and manufacturing must be explored.[145,146]

†Personal communication, P. Zintl, chair, drug-procurement subgroup, June 2008.

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MDR-TB Cannot Be Managed without Local Laboratory Capacity

Although current protocols recommend baseline drug-susceptibility testing and frequent monitoring by sputum culture, treatment need not be delayed until these tests can be performed locally. Partnerships with reference laboratories, often with excess capacity and little TB, can be established to fill the gap while laboratory capacity is developed locally. This approach provides additional training opportunities for staff in laboratories in low TB-incidence settings. The Laboratory Strengthening Sub-Group of the DOTS Expansion Working Group of the Stop TB Partnership should facilitate these partnerships by developing a directory of laboratories interested in collaborating to ensure the successful shipment of samples and timely transmission of reliable results. These partnerships can further help to develop local laboratory capacity and facilitate external quality assurance. [82]

Implementation of MDR-TB Treatment Should Follow Resistance Survey or Surveillance Data

Designing treatment strategies and forecasting drug demand are challenging without good data. Yet, available models and empirical evidence demonstrate the substantial risks associated with a "business as usual" approach[33–35,140,141] while awaiting better data. Even if DOTS coverage and cure targets are achieved, frequency of failure will likely rise as the proportion of patients with resistant disease increases relative to the number of all TB patients.[147] Inadequately treated patients will transmit resistant strains and ultimately die. This cycle will be accelerated in settings with high HIV prevalence due to the increased incidence of TB.[148]

It is essential to develop a range of mechanisms that facilitate treatment with second-line drugs in patients with risk factors for MDR-TB, or for poor outcomes. If local epidemiological data are not available to identify these groups, selection criteria should at least include patients in whom prior treatment failed to result in a sustained cure, those not responding to first-line TB treatment (especially if they are HIV coinfected), and individuals with close exposure to MDR-TB patients (e.g., household contacts, health care workers, prisoners, etc.). Empirical regimens can be constructed based on treatment history and available DST results.

There Are Too Few Hospital Beds and Too Few Health Care Workers to Scale Up MDR-TB Treatment

Inpatient initiation of MDR-TB therapy is unlikely to be the optimal strategy in settings where limited numbers of hospital beds, doctors, and nurses as well as the prohibitive cost of inpatient care result in enrollment bottlenecks. Moreover, the current lack of infection control virtually guarantees transmission to other patients and health care workers.[149,150] In some settings, forced hospitalization has raised serious human rights concerns,[151,152] especially in light of poor treatment outcomes.[149]

Ambulatory, especially community-based, treatment can alleviate these problems.[153] Task-shifting to community health workers—supervised by nurses and doctors—for the bulk of the patient contact also has significant benefits in light of the human resource and financial challenges confronting many health systems. Hospitalization should be reserved for patients for whom it is medically indicated. Infection control efforts should prioritize administrative and environmental measures.

In Light of Limited Resources for TB Control, Scaled-Up Treatment of MDR-TB Is Unrealistic

Building an MDR-TB program on an already fragile and burdened TB service is daunting. Management of adverse events, HIV-coinfected patients, and often-tenuous relationships with private providers represent significant challenges. Addressing MDR-TB, however, need not threaten the health system. Rather, it can infuse additional resources, including: access to new funding sources, training of new health care workers, and integration of services.[154,155]

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Moreover, it can be used to raise the standard of care: while still treating ~25,000 new TB patients annually in Peru, the National Tuberculosis Program (NTP) now assures culture and DST to all patients failing first-line treatment. This is especially true when ambulatory systems of treatment support are developed and used to deliver integrated primary care services. Private providers, who have been successfully engaged in the implementation of DOTS with quality-assured drugs, can also be trained to manage resistant disease. In addition, the funding climate has changed profoundly since the myths surrounding MDR-TB in resource-poor settings were first exposed in 1998[156]: the recent influx of international funding (e.g., from the Global Fund to Fight AIDS, Tuberculosis and Malaria and the International Drug Purchase Facility, referred to as UNITAID) and outside expertise should counter the scarcity mentality. Although the challenge of building a program is enormous, resources are no longer the obstacle.

There Is Too Little Expertise Available Globally to Support Scale Up

With GLC-approved projects functioning since 2000, there is growing global expertise in the management of MDR-TB. Consultants can be drawn from more experienced programs to support implementation and scale-up in settings with similar conditions. Regional centers of excellence in all elements of DR-TB management represent one possible approach to facilitating scale-up. Referral to the cadre of experts in management, scale-up, laboratory, and infection control, which is no longer limited to a handful of individuals from industrialized countries, should be facilitated by the MDR-TB Working Group of the STOP TB Partnership.

Treatment Recommendations Are Based on Expert Opinion, Rather than on Evidence from Randomized, Controlled Trials

Although no large-scale randomized, controlled trials of MDR-TB regimens have been implemented, a growing body of evidence from observational studies has been used to develop recommendations for MDR-TB management. [114] These recommendations do not advocate a single approach, rather they present a range of options, adaptable to local conditions. Questions about optimal drug combinations and duration persist.[157] Nevertheless, programs following existing recommendations have achieved cure in up to 80% of patients.[117,120,121,124] The dangers of waiting until these controversies have been resolved for broader implementation include ongoing transmission, morbidity, mortality, and generation of increasingly drug resistant strains.

CONCLUSION

We have reviewed existing data on the global burden of DR-TB, and argue that, despite gaps in knowledge, sufficient evidence exists to exhort global action. We have described a broad range of models, emphasizing the need to adapt these models based on local context. Finally, we confront some of the perceived obstacles that have resulted in exceptionally slow scale-up and urge innovation to permit achievement of targets.

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References

1. Zignol M, Hosseini MS, Wright A, et al. Global incidence of multidrug-resistant tuberculosis. J Infect Dis 2006;194:479–485. [PubMed: 16845631]
2. Anti-Tuberculosis Drug Resistance in the World: Fourth Global Report. Geneva: World Health Organization; 2008. WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance.

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3. World Health Organization, STOP-TB Partnership. The Global MDR-TB & XDR-TB Response Plan 2007. WHO/HTM/TB/2007; 2007. p. 387
4. Fauci AS: NIAID Tuberculosis Working Group. Multidrug-resistant and extensively drug-resistant tuberculosis: The National Institute of Allergy and Infectious Diseases Research Agenda and Recommendations for Priority Research. J Infect Dis 2008;197:1493–1498. [PubMed: 18426366]
5. Matteelli A, Migliori GB, Cirillo D, Centis R, Girard E, Raviglion M. Multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*: epidemiology and control. Expert Rev Anti Infect Ther 2007;5:857–871. [PubMed: 17914919]
6. Sharma SK, Mohan A. Multidrug-resistant tuberculosis: a menace that threatens to destabilize tuberculosis control. Chest 2006;130:261–272. [PubMed: 16840411]
7. Harries AD, Dye C. Tuberculosis. Ann Trop Med Parasitol 2006;100:415–431. [PubMed: 16899146]
8. Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. J Infect Dis 2007;196(Suppl 1):S86–S107. [PubMed: 17624830]
9. Yew WW, Leung CC. Management of multidrug-resistant tuberculosis: update 2007. Respirology 2008;13:21–46. [PubMed: 18197909]
10. Meya DB, McAdam KP. The TB pandemic: an old problem seeking new solutions. J Intern Med 2007;261:309–329. [PubMed: 17391107]
11. Ducati RG, Ruffino-Netto A, Basso LA, Santos DS. The resumption of consumption–a review on tuberculosis. Mem Inst Oswaldo Cruz 2006;101:697–714. [PubMed: 17160276]
12. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. Thorax 2006;61:158–163. [PubMed: 16254056]
13. Saltini C. Chemotherapy and diagnosis of tuberculosis. Respir Med 2006;100:2085–2097. [PubMed: 17113007]
14. Johnson R, Streicher EM, Louw GE, Warren RM, van Helden PD, Victor TC. Drug resistance in *Mycobacterium tuberculosis*. Curr Issues Mol Biol 2006;8:97–111. [PubMed: 16878362]
15. Singh P, Mishra AK, Malonia SK, et al. The paradox of pyrazinamide: an update on the molecular mechanisms of pyrazinamide resistance in Mycobacteria. J Commun Dis 2006;38:288–298. [PubMed: 17373362]
16. Woodford N, Ellington MJ. The emergence of antibiotic resistance by mutation. Clin Microbiol Infect 2007;13:5–18. [PubMed: 17184282]
17. van Helden PD, Donald PR, Victor TC, et al. Antimicrobial resistance in tuberculosis: an international perspective. Expert Rev Anti Infect Ther 2006;4:759–766. [PubMed: 17140353]
18. Goldman RC, Plumley KV, Laughon BE. The evolution of extensively drug resistant tuberculosis (XDR-TB): history, status and issues for global control. Infect Disord Drug Targets 2007;7:73–91. [PubMed: 17970220]
19. Shi R, Itagaki N, Sugawara I. Overview of anti-tuberculosis (TB) drugs and their resistance mechanisms. Mini Rev Med Chem 2007;7:1177–1185. [PubMed: 18045221]
20. Friedland G. Tuberculosis, drug resistance, and HIV/AIDS: a triple threat. Curr Infect Dis Rep 2007;9:252–261. [PubMed: 17430708]
21. Chakrabarti B, Davies PD. Key issues in multidrug-resistant tuberculosis. Future Microbiol 2007;2:51–61. [PubMed: 17661675]
22. David HL. Probability distribution of drug-resistant mutants in unselected populations of *Mycobacterium tuberculosis*. Appl Microbiol 1970;20:810–814. [PubMed: 4991927]
23. Anti-tuberculosis Drug Resistance in the World. Geneva: World Health Organization; 1997. WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance 1994–1997.
24. Alangaden GJ, Manavathu EK, Vakulenko SB, Zvonok NM, Lerner SA. Characterization of fluoroquinolone-resistant mutant strains of *Mycobacterium tuberculosis* selected in the laboratory and isolated from patients. Antimicrob Agents Chemother 1995;39:1700–1703. [PubMed: 7486904]
25. Crofton J, Mitchison D. Streptomycin resistance in pulmonary tuberculosis. BMJ 1948;2:1009–1015. [PubMed: 18100441]
26. Medical Research Council. Streptomycin treatment of pulmonary tuberculosis: a Medical Research Council Investigation. BMJ 1948;4582:769–782.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

27. Medical Research Council. Prevention of streptomycin resistance by combined chemotherapy. BMJ 1952;1:1157–1162. [PubMed: 14925407]
28. Mitchison DA. The diagnosis and therapy of tuberculosis during the past 100 years. Am J Respir Crit Care Med 2005;171:699–706. [PubMed: 15709048]
29. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of Tuberculosis. Am J Respir Crit Care Med 2003;167:603–662. [PubMed: 12588714]
30. An expanded DOTS framework for effective tuberculosis control. Int J Tuberc Lung Dis 2002;6:378–388. [PubMed: 12019913]
31. Aziz MA, Wright A, Laszlo A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet 2006;368:2142–2154. [PubMed: 17174706]
32. Balabanova Y, Drobniewski F, Fedorin I, et al. The Directly Observed Therapy Short-Course (DOTS) strategy in Samara Oblast, Russian Federation. Respir Res 2006;7:44. [PubMed: 16556324]
33. Espinal MA, Kim SJ, Suarez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. JAMA 2000;283:2537–2545. [PubMed: 10815117]
34. Coninx R, Mathieu C, Debacker M, et al. First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons. Lancet 1999;353:969–973. [PubMed: 10459906]
35. Kimerling ME, Kluge H, Vezhnina N, et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. Int J Tuberc Lung Dis 1999;3:451–453. [PubMed: 10331736]
36. Quy HT, Lan NT, Borgdorff MW, et al. Drug resistance among failure and relapse cases of tuberculosis: is the standard re-treatment regimen adequate? Int J Tuberc Lung Dis 2003;7:631–636. [PubMed: 12870683]
37. Migliori GB, Espinal M, Danilova ID, Punga VV, Grzemska M, Raviglione MC. Frequency of recurrence among MDR-TB cases ‘successfully’ treated with standardised short-course chemotherapy. Int J Tuberc Lung Dis 2002;6:858–864. [PubMed: 12365571]
38. Mak A, Thomas A, Del Granado M, Zaleskis R, Mouzafarova N, Menzies D. Influence of multidrug resistance on tuberculosis treatment outcomes with standardized regimens. Am J Respir Crit Care Med. 2008 May 29; [Epub ahead of print].
39. Jeon CY, Hwang SH, Min JH, et al. Extensively drug-resistant tuberculosis in South Korea: risk factors and treatment outcomes among patients at a tertiary referral hospital. Clin Infect Dis 2008;46:42–49. [PubMed: 18171212]
40. Kim HR, Hwang SS, Kim HJ, et al. Impact of extensive drug resistance on treatment outcomes in non-HIV-infected patients with multidrug-resistant tuberculosis. Clin Infect Dis 2007;45:1290–1295. [PubMed: 17968823]
41. Centers for Disease Control and Prevention. Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. MMWR Morb Mortal Wkly Rep 2006;55:301–305. [PubMed: 16557213]
42. Migliori GB, Besozzi G, Girardi E, et al. Clinical and operational value of the extensively drug-resistant tuberculosis definition. Eur Respir J 2007;30:623–626. [PubMed: 17690121]
43. Pablos-Mendez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization-International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 1998;338:1641–1649. [PubMed: 9614254]
44. Espinal MA, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. World Health Organization- International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001;344:1294–1303. [PubMed: 11320389]
45. Cohen T, Colijn C, Wright A, Zignol M, Pym A, Murray M. Challenges in estimating the total burden of drug-resistant tuberculosis. Am J Respir Crit Care Med 2008;177:1302–1306. [PubMed: 18369201]
46. Choi JC, Lim SY, Suh GY, et al. Drug resistance rates of *Mycobacterium tuberculosis* at a private referral center in Korea. J Korean Med Sci 2007;22:677–681. [PubMed: 17728509]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

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47. Lönnroth K, Lambregts K, Nhien DT, Quy HT, Diwan VK. Private pharmacies and tuberculosis control: a survey of case detection skills and reported anti-tuberculosis drug dispensing in private pharmacies in Ho Chi Minh City, Vietnam. Int J Tuberc Lung Dis 2000;4:1052–1059. [PubMed: 11092718]
48. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. Lancet 2001;358:912–916. [PubMed: 11567729]
49. Greaves F, Ouyang H, Pefole M, MacCarthy S, Cash RA. Compliance with DOTS diagnosis and treatment recommendations by private practitioners in Kerala, India. Int J Tuberc Lung Dis 2007;11:110–112. [PubMed: 17217139]
50. Harries AD, Maher D, Nunn P. An approach to the problems of diagnosing and treating adult smear-negative pulmonary tuberculosis in high-HIV-prevalence settings in sub-Saharan Africa. Bull World Health Organ 1998;76:651–662. [PubMed: 10191561]
51. Storla DG, Yimer S, Bjune GA. A systematic review of delay in the diagnosis and treatment of tuberculosis. BMC Public Health 2008;8:15. [PubMed: 18194573]
52. Rich ML, Socci AR, Mitnick CD, et al. Representative drug susceptibility patterns for guiding design of retreatment regimens for MDR-TB. Int J Tuberc Lung Dis 2006;10:290–296. [PubMed: 16562709]
53. Van Deun A, Aung KJ, Chowdhury S, et al. Drug susceptibility of *Mycobacterium tuberculosis* in a rural area of Bangladesh and its relevance to the national treatment regimens. Int J Tuberc Lung Dis 1999;3:143–148. [PubMed: 10091880]
54. Sanders M, Van Deun A, Ntakirutimana D, et al. Rifampicin mono-resistant Mycobacterium tuberculosis in Bujumbura, Burundi: results of a drug resistance survey. Int J Tuberc Lung Dis 2006;10:178–183. [PubMed: 16499257]
55. Kelly PM, Lumb R, Pinto A, da Costa G, Sarmento J, Bastian I. Analysis of *Mycobacterium tuberculosis* isolates from treatment failure patients living in East Timor. Int J Tuberc Lung Dis 2005;9:81–86. [PubMed: 15675555]
56. Tudo G, Gonzalez J, Obama R, et al. Study of resistance to anti-tuberculosis drugs in five districts of Equatorial Guinea: rates, risk factors, genotyping of gene mutations and molecular epidemiology. Int J Tuberc Lung Dis 2004;8:15–22. [PubMed: 14974741]
57. Menner N, Gunther I, Orawa H, et al. High frequency of multidrug-resistant *Mycobacterium tuberculosis* isolates in Georgetown, Guyana. Trop Med Int Health 2005;10:1215–1218. [PubMed: 16359400]
58. Ferdinand S, Sola C, Verdol B, et al. Molecular characterization and drug resistance patterns of strains of *Mycobacterium tuberculosis* isolated from patients in an AIDS counseling center in Port-au-Prince, Haiti: a 1-year study. J Clin Microbiol 2003;41:694–702. [PubMed: 12574269]
59. Mokaddas E, Ahmad S, Samir I. Secular trends in susceptibility patterns of *Mycobacterium tuberculosis* isolates in Kuwait, 1996–2005. Int J Tuberc Lung Dis 2008;12:319–325. [PubMed: 18284839]
60. Salaniponi FM, Nyirenda TE, Kemp JR, Squire SB, Godfrey-Faussett P, Harries AD. Characteristics, management and outcome of patients with recurrent tuberculosis under routine programme conditions in Malawi. Int J Tuberc Lung Dis 2003;7:948–952. [PubMed: 14552564]
61. Kehinde AO, Obaseki FA, Ishola OC, Ibrahim KD. Multidrug resistance to *Mycobacterium tuberculosis* in a tertiary hospital. J Natl Med Assoc 2007;99:1185–1189. [PubMed: 17987922]
62. Javaid A, Hasan R, Zafar A, et al. Prevalence of primary multidrug resistance to anti-tuberculosis drugs in Pakistan. Int J Tuberc Lung Dis 2008;12:326–331. [PubMed: 18284840]
63. Sharaf-Eldin GS, Saeed NS, Hamid ME, et al. Molecular analysis of clinical isolates of *Mycobacterium tuberculosis* collected from patients with persistent disease in the Khartoum region of Sudan. J Infect 2002;44:244–251. [PubMed: 12099732]
64. Yu MC, Wu MH, Jou R. Extensively drug-resistant tuberculosis, Taiwan. Emerg Infect Dis 2008;14:849–850. [PubMed: 18439381]
65. Zager EM, McNerney R. Multidrug-resistant tuberculosis. BMC Infect Dis 2008;8:10. [PubMed: 18221534]
66. Kapp C. XDR tuberculosis spreads across South Africa. Lancet 2007;369:729. [PubMed: 17340679]

NIH-PA Author Manuscript

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67. Jones KD, Hesketh T, Yudkin J. Extensively drug-resistant tuberculosis in sub-Saharan Africa: an emerging public-health concern. Trans R Soc Trop Med Hyg 2008;102:219–224. [PubMed: 18243260]
68. Alcorn, K. Two XDR TB cases reported in Botswana. [Accessed June 9, 2008]. http://www.aidsmap.com/en/news/1B5F0A58-9125-461F-9F37-36CC930B6E79.asp
69. Sibeene, P. Namibia: No Drugs for Virulent TB Strain. [Accessed June 9, 2008]. http://allafrica.com/stories/200805271002.html
70. Luquero FJ, Sanchez-Padilla E, Simon-Soria F, Eiros JM, Golub JE. Trend and seasonality of tuberculosis in Spain, 1996–2004. Int J Tuberc Lung Dis 2008;12:221–224. [PubMed: 18230258]
71. Akhtar S, Mohammad HG. Seasonality in pulmonary tuberculosis among migrant workers entering Kuwait. BMC Infect Dis 2008;8:3. [PubMed: 18179720]
72. Nagayama N, Ohmori M. Seasonality in various forms of tuberculosis. Int J Tuberc Lung Dis 2006;10:1117–1122. [PubMed: 17044204]
73. Leung CC, Yew WW, Chan TY, et al. Seasonal pattern of tuberculosis in Hong Kong. Int J Epidemiol 2005;34:924–930. [PubMed: 15851395]
74. Thorpe LE, Frieden TR, Laserson KF, Wells C, Khatri GR. Seasonality of tuberculosis in India: is it real and what does it tell us? Lancet 2004;364:1613–1614. [PubMed: 15519633]
75. Douglas AS, Strachan DP, Maxwell JD. Seasonality of tuberculosis: the reverse of other respiratory diseases in the UK. Thorax 1996;51:944–946. [PubMed: 8984709]
76. Schaaf HS, Nel ED, Beyers N, Gie RP, Scott F, Donald PR. A decade of experience with *Mycobacterium tuberculosis* culture from children: a seasonal influence on incidence of childhood tuberculosis. Tuber Lung Dis 1996;77:43–46. [PubMed: 8733413]
77. Addressing the threat of tuberculosis caused by extensively drug-resistant *Mycobacterium tuberculosis*. Wkly Epidemiol Rec 2006;81:386–390.
78. Dukes Hamilton C, Sterling TR, Blumberg HM, et al. Extensively drug-resistant tuberculosis: are we learning from history or repeating it? Clin Infect Dis 2007;45:338–342. [PubMed: 17599311]
79. Fisher M. Diagnosis of MDR-TB: a developing world problem on a developed world budget. Expert Rev Mol Diagn 2002;2:151–159. [PubMed: 11962335]
80. Raviglione MC, Smith IM. XDR tuberculosis: implications for global public health. N Engl J Med 2007;356:656–659. [PubMed: 17301295]
81. Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis 2007;196(Suppl 1):S15–S27. [PubMed: 17624822]
82. Shin SS, Yagui M, Ascencios L, et al. Scale-up of multidrug-resistant tuberculosis laboratory services, Peru. Emerg Infect Dis 2008;14:701–708. [PubMed: 18439349]
83. Martin A, Portaels F, Palomino JC. Colorimetric redoxindicator methods for the rapid detection of multidrug resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. J Antimicrob Chemother 2007;59:175–183. [PubMed: 17135182]
84. Palomino JC. Newer diagnostics for tuberculosis and multidrug resistant tuberculosis. Curr Opin Pulm Med 2006;12:172–178. [PubMed: 16582671]
85. Palomino JC. Nonconventional and new methods in the diagnosis of tuberculosis: feasibility and applicability in the field. Eur Respir J 2005;26:339–350. [PubMed: 16055883]
86. Nic Fhogartaigh CJ, Vargas-Prada S, Huancare V, Lopez S, Rodriguez J, Moore DA. Physician-initiated courtesy MODS testing for TB and MDR-TB diagnosis and patient management. Int J Tuberc Lung Dis 2008;12:555–560. [PubMed: 18419892]
87. Yagui M, Perales MT, Asencios L, et al. Timely diagnosis of MDR-TB under program conditions: is rapid drug susceptibility testing sufficient? Int J Tuberc Lung Dis 2006;10:838–843. [PubMed: 16898366]
88. Furin J. The clinical management of drug-resistant tuberculosis. Curr Opin Pulm Med 2007;13:212–217. [PubMed: 17414129]
89. World Health Organization. Guidelines for the Management of Drug-Resistant Tuberculosis. Geneva, Switzerland: WHO; 2006.
90. Partners In Health. The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis. Boston: Partners In Health; 2003.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

91. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474–481. [PubMed: 14962530]
92. Iseman MD. Treatment of multidrug-resistant tuberculosis. N Engl J Med 1993;329:784–791. [PubMed: 8350889]
93. Telzak EE, Sepkowitz K, Alpert P, et al. Multidrug-resistant tuberculosis in patients without HIV infection. N Engl J Med 1995;333:907–911. [PubMed: 7666876]
94. Park MM, Davis AL, Schluger NW, Cohen H, Rom WN. Outcome of MDR-TB patients, 1983–1993. prolonged survival with appropriate therapy. Am J Respir Crit Care Med 1996;153:317–324. [PubMed: 8542137]
95. Turett GS, Telzak EE, Torian LV, et al. Improved outcomes for patients with multidrug-resistant tuberculosis. Clin Infect Dis 1995;21:1238–1244. [PubMed: 8589149]
96. Schaaf HS, Shean K, Donald PR. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. Arch Dis Child 2003;88:1106–1111. [PubMed: 14670781]
97. Bayona J, Chavez-Pachas AM, Palacios E, Llaro K, Sapag R, Becerra MC. Contact investigations as a means of detection and timely treatment of persons with infectious multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2003;7(12 Suppl 3):S501–S509. [PubMed: 14677844]
98. Brooks JV, Furney SK, Orme IM. Metronidazole therapy in mice infected with tuberculosis. Antimicrob Agents Chemother 1999;43:1285–1288. [PubMed: 10223954]
99. Paramasivan CN, Kubendiran G, Herbert D. Action of metronidazole in combination with isoniazid & rifampicin on persisting organisms in experimental murine tuberculosis. Indian J Med Res 1998;108:115–119. [PubMed: 9805839]
100. Watt B, Edwards JR, Rayner A, Grindey AJ, Harris G. In vitro activity of meropenem and imipenem against mycobacteria: development of a daily antibiotic dosing schedule. Tuber Lung Dis 1992;73:134–136. [PubMed: 1421344]
101. Nuermberger E, Tyagi S, Tasneen R, et al. Powerful bactericidal and sterilizing activity of a regimen containing PA-824, moxifloxacin, and pyrazinamide in a murine model of tuberculosis. Antimicrob Agents Chemother 2008;52:1522–1524. [PubMed: 18285479]
102. Rodriguez JC, Ruiz M, Lopez M, Royo G. In vitro activity of moxifloxacin, levofloxacin, gatifloxacin and linezolid against *Mycobacterium tuberculosis*. Int J Antimicrob Agents 2002;20:464–467. [PubMed: 12458143]
103. Park IN, Hong SB, Oh YM, et al. Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis. J Antimicrob Chemother 2006;58:701–704. [PubMed: 16857689]
104. von der Lippe B, Sandven P, Brubakk O. Efficacy and safety of linezolid in multidrug resistant tuberculosis (MDR-TB): a report of ten cases. J Infect 2006;52:92–96. [PubMed: 15907341]
105. Fortun J, Martin-Davila P, Navas E, et al. Linezolid for the treatment of multidrug-resistant tuberculosis. J Antimicrob Chemother 2005;56:180–185. [PubMed: 15911549]
106. Huang TS, Liu YC, Sy CL, Chen YS, Tu HZ, Chen BC. In vitro activities of linezolid against clinical isolates of *Mycobacterium tuberculosis* complex isolated in Taiwan over 10 years. Antimicrob Agents Chemother 2008;52:2226–2227. [PubMed: 18391030]
107. Yew WW, Chau CH, Wen KH. Linezolid in the treatment of 'difficult' multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2008;12:345–346. [PubMed: 18284844]
108. Barry PJ, O'Connor TM. Novel agents in the management of *Mycobacterium tuberculosis* disease. Curr Med Chem 2007;14:2000–2008. [PubMed: 17691942]
109. Chambers HF, Turner J, Schecter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. Antimicrob Agents Chemother 2005;49:2816–2821. [PubMed: 15980354]
110. Matsumoto M, Hashizume H, Tomishige T, et al. OPC-67683, a nitro-dihydro-imidazooxazole derivative with promising action against tuberculosis in vitro and in mice. PLoS Med 2006;3:e466. [PubMed: 17132069]
111. Andries K, Verhasselt P, Guillemont J, et al. A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. Science 2005;307:223–227. [PubMed: 15591164]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

112. Rustomjee R, Diacon AH, Allen J, et al. Early bactericidal activity and pharmacokinetics of the Diarylquinoline TMC 207 in pulmonary tuberculosis. Antimicrob Agents Chemother. 2008 May 27; [Epub ahead of print].
113. Holtz TH, Sternberg M, Kammerer S, et al. Time to sputum culture conversion in multidrug-resistant tuberculosis: predictors and relationship to treatment outcome. Ann Intern Med 2006;144:650–659. [PubMed: 16670134]
114. World Health Organization. Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 2006.
115. Nathanson E, Gupta R, Huamani P, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 2004;8:1382–1384. [PubMed: 15581210]
116. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2001;5:648–655. [PubMed: 11467371]
117. Mitnick C, Bayona J, Palacios E, et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. N Engl J Med 2003;348:119–128. [PubMed: 12519922]
118. Shin S, Furin J, Bayona J, Mate K, Kim JY, Farmer P. Community-based treatment of multidrug-resistant tuberculosis in Lima, Peru: 7 years of experience. Soc Sci Med 2004;59:1529–1539. [PubMed: 15246180]
119. Riekstina V, Leimane V, Holtz TH, Leimans J, Wells CD. Treatment outcome cohort analysis in an integrated DOTS and DOTS-Plus TB program in Latvia. Int J Tuberc Lung Dis 2007;11:585–587. [PubMed: 17439686]
120. Shin SS, Pasechnikov AD, Gelmanova IY, et al. Treatment outcomes in an integrated civilian and prison MDR-TB treatment program in Russia. Int J Tuberc Lung Dis 2006;10:402–408. [PubMed: 16602404]
121. Tahaoglu K, Torun T, Sevim T, et al. The treatment of multidrug-resistant tuberculosis in Turkey. N Engl J Med 2001;345:170–174. [PubMed: 11463011]
122. Tupasi TE, Gupta R, Quelapio MI, et al. Feasibility and cost-effectiveness of treating multidrug-resistant tuberculosis: a cohort study in the Philippines. PLoS Med 2006;3:e352. [PubMed: 16968123]
123. Van Deun A, Salim MA, Das AP, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. Int J Tuberc Lung Dis 2004;8:560–567. [PubMed: 15137531]
124. Nathanson E, Lambregts-van Weezenbeek C, Rich ML, et al. Multidrug-resistant tuberculosis management in resource-limited settings. Emerg Infect Dis 2006;12:1389–1397. [PubMed: 17073088]
125. Menzies D, Fanning A, Yuan L, FitzGerald JM. Hospital ventilation and risk for tuberculous infection in Canadian health care workers. Canadian Collaborative Group in Nosocomial Transmission of TB. Ann Intern Med 2000;133:779–789. [PubMed: 11085840]
126. Escombe AR, Oeser CC, Gilman RH, et al. Natural ventilation for the prevention of airborne contagion. PLoS Med 2007;4:e68. [PubMed: 17326709]
127. Stop TB Partnership and World Health Organization. Global Plan to Stop TB 2006–2015. Geneva: World Health Organization; 2006.
128. Hopewell PC, Sanchez-Hernandez M, Baron RB, Ganter B. Operational evaluation of treatment for tuberculosis: results of a “standard” 12-month regimen in Peru. Am Rev Respir Dis 1984;129:439–443. [PubMed: 6200016]
129. Hopewell PC, Ganter B, Baron RB, Sanchez-Hernandez M. Operational evaluation of treatment for tuberculosis: results of 8- and 12-month regimens in Peru. Am Rev Respir Dis 1985;132:737–741. [PubMed: 3901842]
130. Manalo F, Tan F, Sbarbaro JA, Iseman MD. Community-based short-course treatment of pulmonary tuberculosis in a developing nation: initial report of an eight-month, largely intermittent regimen in a population with a high prevalence of drug resistance. Am Rev Respir Dis 1990;142(6 Pt 1): 1301–1305. [PubMed: 2123613]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

131. World Health Organization. Framework for Effective Tuberculosis Control. Geneva: World Health Organization; 1994. WHO/TB/94.179

132. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: strategies to beat multidrug- resistant tuberculosis. Science 2002;295:2042–2046. [PubMed: 11896268]

133. Maher, D.; Chaulet, P.; Spinaci, S.; Harries, A. Treatment of Tuberculosis: Guidelines for National Programmes. Geneva: World Health Organization; 1997.

134. Espinal MA, Dye C, Raviglione MC, Kochi A. Rational "DOTS Plus" for the control of MDR-TB. Int J Tuberc Lung Dis 1999;3:561–563. [PubMed: 10423218]

135. Crofton, J.; Chaulet, P.; Maher, D. Guidelines on the Management of Drug-Resistant Tuberculosis. Geneva: World Health Organization; 1996.

136. Bonnet M, Sizaire V, Kebede Y, et al. Does one size fit all? Drug resistance and standard treatments: results of six tuberculosis programmes in former Soviet countries. Int J Tuberc Lung Dis 2005;9:1147–1154. [PubMed: 16229227]

137. Anti-tuberculosis Drug Resistance in the World: Third Global Report. Geneva: World Health Organization; 2004. WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance.

138. Suarez PG, Floyd K, Portocarrero J, et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. Lancet 2002;359:1980–1989. [PubMed: 12076553]

139. Park SK, Lee WC, Lee DH, Mitnick CD, Han L, Seung KJ. Self-administered, standardized regimens for multidrug-resistant tuberculosis in South Korea. Int J Tuberc Lung Dis 2004;8:361–368. [PubMed: 15139476]

140. Pillay M, Sturm AW. Evolution of the extensively drug-resistant F15/LAM4/KZN strain of *Mycobacterium tuberculosis* in KwaZulu-Natal, South Africa. Clin Infect Dis 2007;45:1409–1414. [PubMed: 17990220]

141. Han LL, Sloutsky A, Canales R, et al. Acquisition of drug resistance in multidrug-resistant *Mycobacterium tuberculosis* during directly observed empiric retreatment with standardized regimens. Int J Tuberc Lung Dis 2005;9:818–821. [PubMed: 16013781]

142. Leimane V, Riekstina V, Holtz TH, et al. Clinical outcome of individualised treatment of multidrug-resistant tuberculosis in Latvia: a retrospective cohort study. Lancet 2005;365:318–326. [PubMed: 15664227]

143. McKinsey & Company McKinsey & Company. Independent External Evaluation of the Stop TB Partnership: Final Report. [Accessed June 9, 2008]. http://www.stoptb.org/resource_center/documents.asp

144. World Health Organization. Prequalification Programme: A United Nations Programme Managed by WHO. [Accessed June 9, 2008]. http://healthtech.who.int/pq/

145. Pogge T. Montreal Statement on the Human Right to Essential Medicines. Camb Q Healthc Ethics 2007;16:97–108. [PubMed: 17345971]

146. The Sixty-first World Health Assembly. Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property. [Accessed June 9, 2008]. http://www.who.int/gb/ebwha/pdf_files/A61/A61_R21-en.pdf

147. Blower SM, Gerberding JL. Understanding, predicting and controlling the emergence of drug-resistant tuberculosis: a theoretical framework. J Mol Med 1998;76:624–636. [PubMed: 9725765]

148. Nelson LJ, Talbot EA, Mwasekaga MJ, et al. Antituberculosis drug resistance and anonymous HIV surveillance in tuberculosis patients in Botswana, 2002. Lancet 2005;366:488–490. [PubMed: 16084258]

149. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients coinfected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575–1580. [PubMed: 17084757]

150. Basu S, Andrews JR, Poolman EM, et al. Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. Lancet 2007;370:1500–1507. [PubMed: 17964351]

151. Singh JA, Upshur R, Padayatchi N. XDR-TB in South Africa: no time for denial or complacency. PLoS Med 2007;4:e50. [PubMed: 17253901]

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152. McGregor, SS. Africa Urged to Isolate “Killer” TB Patients. [Accessed 2008, June 9]. http://www.alertnet.org/thenews/newsdesk/L23916489.htm

153. Goemaere E, Ford N, Berman D, McDermid C, Cohen R. XDR-TB in South Africa: detention is not the priority. PLoS Med 2007;4:e162. [PubMed: 17455997]

154. Keshavjee S, Gelmanova I, Pasechnikov A, et al. Treating multi-drug resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. Ann N Y Acad Sci. 2007 Oct 22; [Epub ahead of print].

155. Bonilla C, Bayona J. Building political commitment in Peru for TB control through expansion of the DOTS strategy. Bull World Health Organ 2007;85:402.

156. Farmer P, Bayona J, Becerra M, et al. The dilemma of MDR-TB in the global era. Int J Tuberc Lung Dis 1998;2:869–876. [PubMed: 9848606]

157. Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. Int J Tuberc Lung Dis 2006;10:829–837. [PubMed: 16898365]

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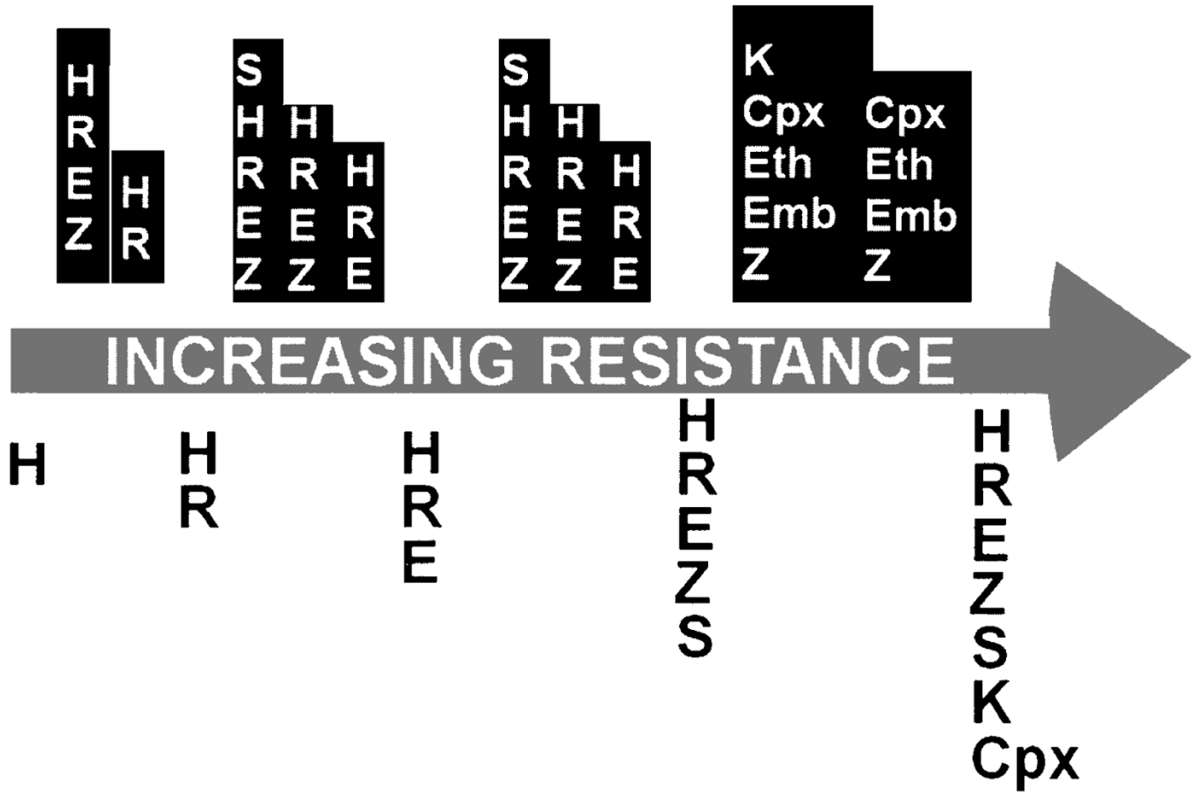

Figure 1.
Amplifier effect of repeated, standardized regimens. Example of how selective pressure of repeated standardized regimens (represented by white letters on dark background over arrow) can result in serial acquisition of resistance (represented by dark letters on light background under arrow), ultimately XDR-TB.

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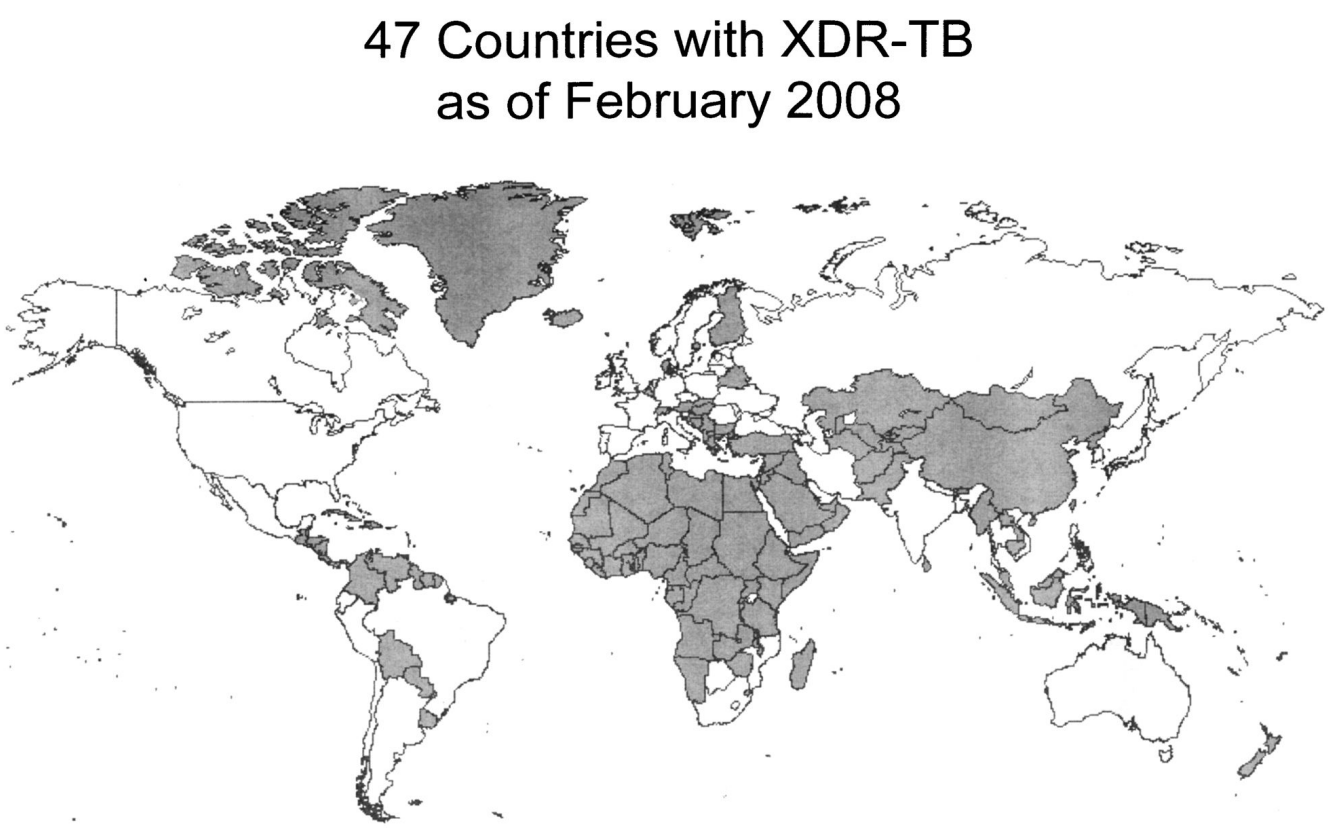

Figure 2.
Global distribution of XDRTB, reported through February 2008. Adapted from reference [2].

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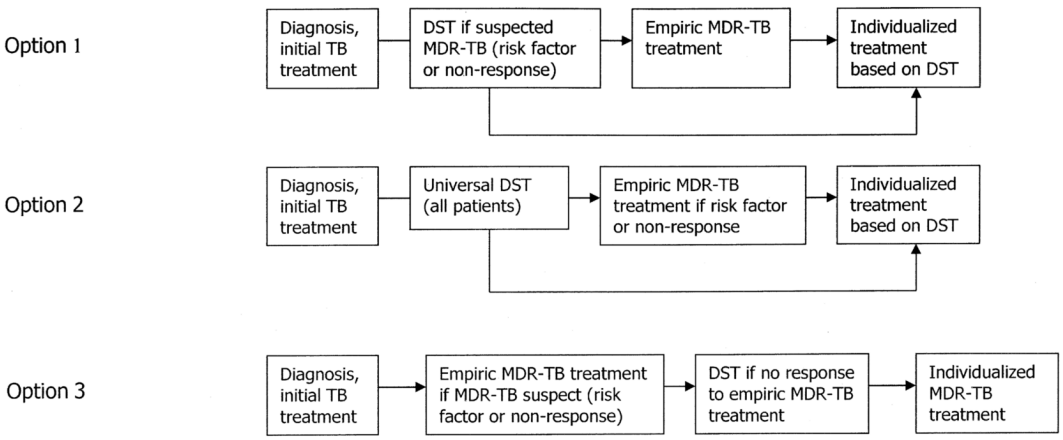

Figure 3.
Possible strategies for screening and referral to treatment for DR-TB.

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Table 1

Global Burden of MDR-TB (from Surveys, Surveillance, Convenience Samples, or Estimates) by Country

					MDR**		Drug-Resistant (Non-MDR)	
Country/Region	**Reference†**	**Period**	**Source Population; Sampling Strategy‡**	***N* Tested±**	***N***	**%**	***N***	**%**
Afghanistan	Report #4	2006	Estimated		2139 (671,8802)	4.9 (1.6,19.5)		
Albania	Report #4	2006	Estimated		14 (4,67)	2.1 (0.7,10.3)		
Algeria*	Report #4	2001	National; proportionate cluster	518	6	1.2	26	5
Andorra	Report #4	2005	National; 100% cases	9	0	0	9	11.1
Angola	Report #4	2006	Estimated		1665 (547,7144)	3.2 (1.1,13.1)		
Antigua and Barbuda	Report #4	2006	Estimated		0	1.3 (0.7,9.1)		
Argentina	Report #4	2005	National; proportionate cluster	819	36	4.4	66	8.1
Armenia	Report #4	2007	National; 100% diagnostic units	892	199	22.3	261	29.3
Australia	Report #4	2005	National; 100% cases	808	12	1.5	69	8.6
Austria	Report #4	2005	National; 100% cases	609	13	2.1	59	9.7
Azerbaijan	Report #4	2007	Subnational; Baku; 100% diagnostic units	1103	431	39.1	345	31.3
Bahamas	Report #4	2006	Estimated		3 (1,12)	1.9 (0.7,8.5)		
Bahrain	Report #4	2006	Estimated		11 (4,43)	3.5 (1.1,13.4)		
Bangladesh	Van Deun et al, 1999[53]	1994	Subnational; cluster; 5 health centers			0.02		18.6
Belarus	Report #4	2006	Estimated		1,096 (371,3,272)	15.7 (5.4,46.5)		
Belgium	Report #4	2005	National; 100% cases	758	11	1.5	36	4.8
Belize	Report #4	2006	Estimated		4 (1,15)	2.3 (0.8,10.2)		
Benin*	Report #1	1997	National; proportionate cluster	333	10	0.3	27	8.1
Bhutan	Report #4	2006	Estimated		28 (8119)	4.2 (1.3,17.5)		
Bolivia	Report #1	1996	National; proportionate cluster	605	11	1.8	160	26.5
Bosnia and Herzegovina	Report #4	2005	National; 100% cases	1141	11	1	30	2.6
Botswana	Report #3	2002	National; 100% diagnostic units	1288	21	1.6	126	9.8
Brazil	Report #1	1996	Nearly countrywide; proportionate cluster	2888	62	2.1	234	8.1
Brunei	Report #4	2006	Estimated		11 (3,47)	3.3 (1.1,13.8)		

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Country/Region	Reference†	Period	Source Population; Sampling Strategy‡	*N* Tested±	MDR**		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Bulgaria	Report #4	2006	Estimated		451 (143,1563)	13.2 (4.2,44.1)		
Burkina Faso	Report #4	2006	Estimated		1170 (369,5402)	2.9 (1.0,13.1)		
Burundi*	Sanders et al, 2006[54]	2002–2003	Subnational; 7 diagnostic units in Bujumbura; 100% cases			2.7		17.9
Cambodia	Report #3	2001	National; proportionate cluster	734	3	0.4	80	10.9
Cameroon	Report #4	2006	Estimated		786 (227,4036)	2.1 (0.6,11.0)		
Canada	Report #4	2005	National; 100% cases	1203	23	1.9	123	10.2
Cape Verde	Report #4	2006	Estimated		22 (7,102)	2.3 (0.8,10.7)		
Central African Republic	Report #2	1998	Subnational; 100% diagnostic units in Bangui	495	11	2.2	77	15.5
Chad	Report #4	2006	Estimated		807 (230,4297)	2.4 (0.7,13.3)		
Chile	Report #3	2001	National; proportionate cluster	1158	17	1.5	132	11.4
China	Report #4	2006	Estimated		130548 (97633,164900)		8.3 (7.0,10.2)	
Guandong Province	Report #2	1999	Proportionate cluster	524	24	4.6	60	11.4
Beijing Municipality	Report #4	2004	100% diagnostic units	1197	42	3.5	199	16.6
Shandong Province	Report #2	1997	Proportionate cluster	1229	72	5.9	215	17.5
Henan Province	Report #3	2001	Proportionate cluster	1487	192	12.9	333	22.4
Liaoning Province	Report #3	1999	Proportionate cluster	904	106	11.7	287	31.7
Heilongjiang Province	Report #4	2005	Proportionate cluster	1995	241	12.1	612	30.7
Hubei Province	Report #3	1999	Proportionate cluster	1097	70	6.4	185	16.9
Zhejiang Province	Report #2	1999	Proportionate cluster	942	85	9	117	12.4
Shanghai Municipality	Report #4	2005	100% diagnostic units	964	55	5.7	118	12.2
Inner Mongolia Autonomous region	Report #4	2002	Proportionate cluster	1114	188	16.9	310	27.8
China, Hong Kong SAR	Report #4	2005	100% cases	4350	41	0.9	439	10.1
China, Macao SAR	Report #4	2005	100% cases	284	9	3.2	38	13.3
Colombia*	Report #3	2000	National; proportionate cluster	1087	16	1.5	152	14
Comoros	Report #4	2006	Estimated		9 (3,45)	2.3 (0.7,11.9)		
Congo	Report #4	2006	Estimated		321 (90,1737)	2.1 (0.6,11.0)		
Costa Rica	Report #3	2006	National; 100% diagnostic units	284	5	1.8	15	5.2

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Country/Region	Reference[†]	Period	Source Population; Sampling Strategy[‡]	*N* Tested[±]	MDR[**]		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Côte d'Ivoire[*]	Report #4	2006	National; proportionate cluster	320	8	2.5	68	21.3
Croatia	Report #4	2005	National; 100% cases	647	6	0.9	16	2.5
Cuba	Report #4	2005	National; proportionate cluster	198	1	0.5	20	10.1
Cyprus	Report #4	2006	Estimated		1 (0,3)	1.3 (0.4,7.6)		
Czech Republic	Report #4	2005	National; 100% cases	582	13	2.2	38	6.6
Democratic Republic of the Congo	Report #3	1999	Subnational; Kinshasa, proportionate cluster	710	41	5.8	236	33.2
Denmark	Report #4	2005	National; 100% cases	325	5	1.5	16	5
Djibouti	Report #4	2006	Estimated		449 (150,1489)	6.2 (2.1,20.1)		
Dominica	Report #4	2006	Estimated		0 (0,1)	2.2 (0.8,10.2)		
Dominican Republic	Report #1	1995	National; proportionate cluster	420	43	10.2	141	33.6
East Timor	Kelly et al, 2005[55]	2000–2001	National; re-treatment failures			64.3		28.6
Ecuador	Report #3	2002	National; 100% diagnostic units	997	85	8.5	160	16
Egypt	Report #3	2002	National; proportionate cluster	849	97	11.4	245	28.8
El Salvador	Report #3	2001	National; 100% diagnostic units	711	9	1.3	48	6.7
Equatorial Guinea	Tudó et al, 2004[56]	1999–2001	Subnational; nearly 100% in 5 of 18 districts			3.4		14.8
Eritrea	Report #4	2006	Estimated		127 (36,681)	2.7 (0.8,14.1)		
Estonia	Report #4	2005	National; 100% cases	387	79	20.4	57	14.7
Ethiopia	Report #4	2005	National; proportionate cluster	880	22	2.5	231	26.3
Fiji	Report #4	2006	National; random cluster	38	0	0	0	0
Finland	Report #4	2005	National; 100% cases	315	3	1	11	3.4
France	Report #4	2005	National; 100% cases	1501	24	1.6	119	7.9
Gabon	Report #4	2006	Estimated		98 (31,460)	1.9 (0.6,9.1)		
Gambia	Report #3	2000	National; 100% diagnostic units	225	1	0.4	8	3.6
Georgia	Report #4	2006	National; 100% diagnostic units	1422	219	15.4	586	41.2
Germany	Report #4	2005	National; 100% cases	3886	105	2.7	373	9.6
Ghana	Report #4	2006	Estimated		1090 (288,6169)	2.2 (0.6,12.1)		
Greece	Report #4	2006	Estimated		45 (15,186)	2.0 (0.7,8.5)		

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Country/Region	Reference†	Period	Source Population; Sampling Strategy‡	*N* Tested±	MDR**		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Guam	Report #4	2002	National; random cluster	47	0	0	2	4.3
Guatemala	Report #4	2002	National; proportionate cluster	823	61	7.4	257	31.2
Guinea	Report #2	1998	SubNational; sentinel sites; random cluster	571	12	2.1	83	14.5
Guinea-Bissau	Report #4	2006	Estimated		109 (32,545)	2.8 (0.8,13.9)		
Guyana	Menner, Gunther, Orawa et al, 2005[57]	2001	Convenience; 36 patients from Georgetown Chest Clinic			11.1		22.2
Haiti	Ferdinand et al, 2003[58]	2000	Convenience; GHESKIO HIV VCT center in Port au Prince			8.9		20.4
Honduras	Report #3	2004	National; proportionate cluster	530	17	3.2	66	12.5
Hungary	Report #4	2006	Estimated		69 (23,258)	3.0 (1.0,11.1)		
Iceland	Report #4	2005	National; 100% cases	8	0	0	0	0
India	Report #4	2006	Estimated		110132 (79975, 142386)	4.9 (3.9,6.2)		
Mayhurbhanj District, Orissa State*	Report #4	2001	100% diagnostic units	282	2	0.7	13	4.6
Wardha District, Maharashtra State*	Report #3	2001	100% diagnostic units	197	1	0.5	38	19.3
Delhi State	Report #1	1995	100% diagnostic units	2240	298	13.3	428	19.1
Raichur District, Karnataka State*	Report #3	1999	100% diagnostic units	278	7	2.5	54	19.4
North Arcot District, Tamil Nadu State*	Report #3	1999	100% diagnostic units	282	8	2.8	70	24.9
Ernakulam district, Kerala State*	Report #4	2004	100% diagnostic units	305	6	2	79	25.9
Gujarat State	Report #4	2006	Proportionate cluster	2618	219	8.4	600	22.9
Tamil Nadu State*	Report #2	1997	Proportionate cluster	384	13	3.4	59	15.4
Hoogli district, West Bengal State*	Report #4	2001	100% diagnostic units	263	8	3	36	13.7
Indonesia*	Report #4	2004	Subnational; Mimika district, Papua Province; 100% diagnostic units	101	2	2	12	11.9

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Country/Region	Reference[†]	Period	Source Population; Sampling Strategy[‡]	*N* Tested[±]	MDR[**]		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Iran	Report #2	1998	National; random cluster	722	60	8.3	78	10.8
Iraq	Report #4	2006	Estimated		969 (334,3246)	5.6 (2.0,18.6)		
Ireland	Report #4	2005	National; 100% cases	273	3	1.1	10	3.7
Israel	Report #4	2005	National; 100% cases	217	12	5.5	34	15.7
Italy	Report #4	2005	Subnational; 100% cases in ½ the country	585	22	3.8	56	10
Jamaica	Report #4	2006	Estimated		4 (1,20)	1.8 (0.5,9.4)		
Japan	Report #4	2002	National; 100% diagnostic units	3122	60	1.9	278	8.9
Jordan	Report #4	2004	National; 100% diagnostic units	141	18	12.8	43	30.5
Kazakhstan	Report #3	2001	National; 100% diagnostic units	678	231	34.1	234	34.8
Kenya	Report #1	1995	Nearly countrywide; proportionate cluster	491	0	0	45	9.2
Republic of Korea	Report #4	2004	National; proportionate cluster	2914	110	3.8	288	9.9
Kuwait	Mokaddas et al, 2008[59]	1996–2005	National surveillance			0.9		12.5
Kyrgyzstan	Report #4	2006	Estimated		1368 (443,4026)	18.2 (6.2,51.5)		
Latvia	Report #4	2005	National; 100% cases	1055	160	15.2	249	23.6
Lebanon	Report #4	2003	National; 100% diagnostic units	206	12	5.8	37	18
Lesotho	Report #1	1995	National; proportionate cluster	383	6	1.6	41	10.7
Libyan Arab Jamahiriya	Report #4	2006	Estimated		33 (8,166)	3.1 (0.8,15.2)		
Lithuania	Report #4	2005	National; 100% cases	1739	338	19.4	243	14
Luxembourg	Report #4	2005	National; 100% cases	37	4	10.8	0	0
Macedonia	Report #4	2006	Estimated		19 (6,79)	2.8 (0.9,11.4)		
Madagascar	Report #4	2007	National; proportionate cluster	865	6	0.7	51	5.9
Malawi	Salaniponi, Nyirenda, Kemp et al 2003[60]	1999–2000	Convenience; all 43 nonprivate hospitals in Malawi			4		15
Malaysia	Report #2	1997	Subnational; peninsular Malaysia; proportionate cluster	1017	1	0.1	50	4.9
Maldives	Report #4	2006	Estimated		5 (2,24)	3.7 (1.1,16.4)		
Mali	Report #4	2006	Estimated		756 (177,4,363)	2.2 (0.5,12.8)		

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Country/Region	Reference†	Period	Source Population; Sampling Strategy‡	*N* Tested±	MDR**		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Malta	Report #4	2005	National; 100% cases	11	0	0	2	18.2
Mexico	Report #2	1997	Subnational; Baja California, Sinaloa, Oaxaca; 100% diagnostic units	441	32	7.3	59	13.3
Republic of Moldova	Report #4	2006	National; 100% diagnostic units	2879	1204	41.8	599	20.8
Mongolia*	Report #3	1999	National; 100% diagnostic units	405	4	1	115	28.4
Morocco	Report #4	2006	National; proportionate cluster	1238	28	2.3	84	6.8
Mozambique	Report #2	1999	National; proportionate cluster	1150	40	3.5	229	19.9
Burma/Myanmar	Report #4	2003	National; proportionate cluster	849	47	5.5	61	7.2
Namibia	Report #4	2006	Estimated		342 (103,1716)	2.0 (0.6,9.8)		
Nepal	Report #4	2007	National; proportionate cluster	930	41	4.4	113	12.2
Netherlands	Report #4	2005	National; 100% cases	841	7	0.8	67	8
New Caledonia	Report #4	2005	National; random cluster	5	0	0	1	20
New Zealand	Report #4	2006	National; 100% cases	255	1	0.4	25	9.8
Nicaragua	Report #4	2006	National; proportionate cluster	423	10	2.4	69	16.3
Niger	Report #4	2006	Estimated		750 (233,3667)	2.9 (0.9,13.5)		
Nigeria	Kehinde et al, 2007[61]	2005–2006	Convenience; network of clinical sites in Ibadan			53.6		NA
Northern Mariana Islands*	Report #4	2006	National; 100% cases	18	2	11.1	2	11.1
Norway	Report #4	2005	National; 100% cases	214	3	1.4	41	19.2
Oman	Report #4	2006	National; 100% cases	164	7	4.3	9	5.5
Pakistan*	Javaid et al, 2008[62]	NA	Convenience, 29 centers throughout the country			1.8		11.3
Palau	Report #4	2006	Estimated		1 (0,2)	5.4 (1.7,16.5)		
Panama	Report #4	2006	Estimated		47 (16,188)	2.7 (0.9,11.0)		
Papua New Guinea	Report #4	2006	Estimated		915 (285,3560)	5.3 (1.7,20.1)		
Paraguay	Report #4	2001	National; proportionate cluster	266	7	2.4	27	10.2
Peru	Report #4	2006	National; proportionate cluster	2169	180	8.3	390	18
Philippines	Report #4	2004	National; proportionate cluster	1094	66	6	180	16.5
Poland	Report #4	2004	National; 100% diagnostic units	3239	51	1.6	194	6

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Country/Region	Reference[†]	Period	Source Population; Sampling Strategy[‡]	*N* Tested[±]	MDR[**]		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Puerto Rico	Report #4	2005	National; 100% cases	94	0	0	3	3.2
Portugal	Report #4	2005	National	1579	28	1.8	210	13.3
Qatar	Report #4	2006	National; 100% cases	278	3	1.1	25	9
Romania	Report #4	2004	National; 100% diagnostic units	1251	67	5.4	181	14.5
Russian Federation	Report #4	2006	Estimated		36037 (28992,50258)	19.4 (17.1,24.6)		
Ivanovo Oblast	Report #3	2002	100% cases	505	133	26.3	147	29.1
Orel Oblast	Report #4	2006	100% cases	347	33	9.5	68	19.6
Mary El Oblast[*]	Report #4	2006	100% cases	304	38	12.5	53	17.4
Tomsk Oblast[*]	Report #4	2005	100% cases	515	77	15	105	20.3
Rwanda	Report #4	2005	National; 100% diagnostic units	701	32	4.6	50	7.2
Samoa	Report #4	2006	Estimated		2 (1,8)	5.2 (1.8,18.6)		
Saudi Arabia	Report #4	2006	Estimated		375 (124,1540)	3.4 (1.1,13.6)		
Senegal	Report #4	2006	National; proportionate cluster	279	12	4.3	26	9.3
Serbia	Report #4	2005	National; 100% cases	1233	9	0.7	38	3.1
Sierra Leone	Report #2	1997	Nearly countrywide; random cluster	130	4	3.1	33	25.4
Singapore	Report #4	2005	National; 100% cases	1000	3	0.3	66	6.6
Slovakia	Report #4	2005	National; 100% cases	311	8	2.6	21	6.7
Slovenia	Report #4	2005	National; 100% cases	245	1	0.4	13	5.3
Solomon Islands	Report #4	2004	National; random cluster	84	0	0	0	0
Somalia	Report #4	2006	Estimated		412 (113,2229)	2.1 (0.6,11.3)		
South Africa	Report #3	2002	National; proportionate cluster	5708	175	3.1	388	6.8
Spain	Report #4	2006	Estimated		48 (8,102)	0.3 (0.1,0.7)		
Galicia	Report #4	2005	100% cases	634	2	0.3	44	7
Aragon	Report #4	2005	100% cases	226	4	0.8	14	6.2
Barcelona	Report #4	2005	100% cases	538	4	0.7	49	9.2
Sri Lanka	Report #4	2006	National; 100% cases	624	1	0.2	10	1.6
Sudan	Sharaf-Eldin et al, 2002[63]	1998–1999	Convenience; two TB clinics in Khartoum State			4		33.3

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Country/Region	Reference[†]	Period	Source Population; Sampling Strategy[‡]	*N* Tested[±]	MDR[**]		Drug-Resistant (Non-MDR)	
					N	%	*N*	%
Swaziland	Report #1	1995	National; proportionate cluster	378	7	1.9	41	10.8
Sweden	Report #4	2005	National; 100% cases	442	4	0.9	52	11.8
Switzerland	Report #4	2005	National; 100% cases	457	5	1.1	19	4.2
Syria	Report #4	2006	Estimated		287 (90,1195)	4.4 (1.4,17.8)		
Taiwan	Yu et al, 2008[64]	2005	National; 100% cases			4		14.1
Tajikistan	Report #4	2006	Estimated		3204 (1072,8916)	20.0 (6.8,53.9)		
Tanzania	Report #4	2007	National; proportionate cluster	418	4	1	27	6.4
Thailand	Report #4	2006	National; proportionate cluster	1344	86	6.4	192	14.3
Togo	Report #4	2006	Estimated		667 (190,3449)	2.5 (0.7,12.6)		
Tunisia	Report #4	2006	Estimated		84 (22,413)	3.3 (0.9,15.7)		
Turkey	Report #4	2006	Estimated		889 (284,3320)	3.3 (1.1,12.3)		
Turkmenistan	Report #3	2002	Subnational; Dashoguz Velavat (Aral Sea Region); 100% diagnostic units	203	22	10.8	71	35
Uganda	Report #2	1997	Subnational; 3 of 9 NTLP zones representing 50% of national population; proportionate cluster	419	4	1	93	22.2
Ukraine	Report #4	2006	Donetsk; 100% diagnostic units	1497	379	25.3	367	24.5
United Arab Emirates	Report #4	2006	Estimated		27 (9,104)	3.8 (1.3,14.2)		
United Kingdom	Report #4	2005	National; 100% cases	4800	39	0.8	302	6.3
United States	Report #4	2005	National; 100% cases	10584	124	1.2	1132	10.7
Uruguay	Report #4	2005	National	368	2	0.5	8	2.2
Uzbekistan	Report #4	2005	Tashkent; 100% diagnostic units	292	83	28.4	97	33.2
Vanuatu	Report #4	2006	National; random cluster	29	0	0	1	3.4
Venezuela	Report #3	1999	National; proportionate cluster	873	18	2.1	72	8.2
Vietnam	Report #4	2006	National; proportionate cluster	826	84	4.6	242	29.3
Yemen	Report #4	2004	National; 100% diagnostic units	563	21	3.7	39	7
Zambia	Report #3	2000	National; proportionate cluster	489	9	1.8	48	9.9
Zimbabwe	Report #1	1995	Nearly countrywide; all diagnostic centers	712	16	2.2	11	1.6

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[*] Reported among new TB cases only.

[†] All reports are from the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance and can be accessed online at http://www.who.int/tb/publications/en/index.html.

[‡] Source population and sampling strategy are specified for those countries or regions for which sampling was conducted. In the absence of reported data, estimates were obtained with logistic regression modeling, as described in the 4th WHO/IUATLD report.

[±] The absence of the number tested indicates that the number and proportion of MDR-TB cases are estimates.

[**] Estimated burden and 95% confidence intervals are drawn from the 4th WHO/IUATLD report.

No information, either reported or estimated, was available for the following countries: Barbados, Grenada, Laos, Liberia, Liechtenstein, Mauritania, Monaco, Sao Tome e Principe, Suriname, Trinidad, and Tobago.

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Table 2

Chemotherapeutic Agents Used in the Treatment of Tuberculosis

Drug Name	Description	Administration (Adult Doses)	Side Effects
FIRST-LINE DRUGS			
Isoniazid (INH)[1]	Nicotinic acid hydrazide. Bactericidal. Inhibits mycolic acid synthesis most effectively in dividing cells. Hepatically metabolized.	Regular dose: 300 mg or 5 mg/kg PO once a day	**Incidence of adverse reactions:** 5.4%.
		High dose: 900 mg or 15 mg/kg PO 2x/wk (for strains resistant to low-dose INH)	**Common**: hepatitis (10–20% have elevated transaminases; INH discontinuation indicated in symptomatic hepatitis; increased risk with alcohol ingestion), peripheral neuropathy (dose-related; increased risk with malnutrition, alcoholism, diabetes, concurrent use of aminoglycosides or Prothio/Ethio)
		Administer with pyridoxine 150–300 mg once a day	**Less common**: fever, GI upset, gynecomastia, rash (2%)
			Rare: agranulocytosis, anemia, encephalopathy, eosinophilia, hypersensitivity, memory impairment, optic neuritis, positive antinuclear antibody, psychosis, seizure, thrombocytopenia, vasculitis
			Drug interactions: increases phenytoin levels
Rifampin (Rifampicin, RIF)	Bactericidal. Produced by *Streptomyces* spp. Inhibits protein synthesis by blocking mRNA transcription and synthesis. Hepatically metabolized.	600 mg or 10 mg/kg PO once a day	**Incidence adverse reactions**: <4%
			Common: orange-colored bodily secretions; transient transaminitis
			Less common: GI upset (1.5%), hepatitis
			Rare: cholestatic jaundice, drowsiness, fatigue, fever (0.5%), gynecomastia, headache, pruritis, rash (0.8%), renal insufficiency, thrombocytopenia (especially in conjunction with EMB), urticaria
			Drug interactions: decreased reliability of oral contraceptives, protease inhibitor (PI) levels decreased by RIF, decreased activity of drugs metabolized by P450 system (e.g., CPX, corticosteroids, dapsone, diazepam, digitoxin, fluconazole, haloperidol, methadone, oral hypoglycemics, phenytoin, quinidine, theophylline, warfarin)
Pyrazinamide (PZA)	Nicotinamide derivative. Bactericidal. Mechanism unknown. Effective in acid milieu (e.g., cavitary disease, intracellular organisms). Hepatically metabolized, renally excreted.	25–35 mg/kg PO once a day	**Common**: arthropathy, hepatotoxicity, hyperuricemia
			Less common: GI upset, impaired diabetic control, rash
			Rare: dysuria, fever, hypersensitivity reactions, malaise

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Drug Name	Description	Administration (Adult Doses)	Side Effects
			Drug interactions: none reported
Ethambutol (EMB)	Bacteriostatic at conventional dosing (15 mg/kg). Inhibits lipid and cell wall metabolism. Renally excreted.	15–25 mg/kg PO once a day	**Incidence adverse reactions**: <2%
		Adjust for renal insufficiency	**Less common**: arthralgia, GI upset, headache, malaise
			Rare: disorientation, dizziness, fever (0.3%), hallucination, peripheral neuropathy, pleuritis, rash (0.5%), retrobulbar neuritis (0.8%, dose-related and reversible, increased risk with renal insufficiency)
			Drug interactions: none reported
PARENTERAL AGENTS			
Aminoglycosides	Bactericidal. Inhibits protein synthesis through disruption of ribosomal function. Less effective in acid, intracellular environment. Renally excreted	Amikacin: 1 g or 15 mg/kg IM/IV once a day	**Incidence adverse reactions**: 8.2%
Amikacin (AMK)	SM least nephrotoxic. AMK has been shown to be highly mycobactericidal compared with other aminoglycosides in vitro. Cross-resistance rare between SM and other aminoglycosides. Frequent cross-resistance between KM and AMK	Kanamycin: 1 g IM/IV once a day	**Common**: pain at injection site
Kanamycin (KM)		Streptomycin: 1 g or 15 m/kg IM once a day	**Less common:** cochlear otoxocity (hearing loss, dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), facial paresthesia, nephrotoxicity (dose-related to cumulative and peak concentrations, increased risk with renal insufficiency, may be irreversible), peripheral neuropathy, rash, vestibular toxicity (nausea, vomiting, and vertigo)
Streptomycin (SM)		Adjust for renal insufficiency	**Rare**: anaphylaxis, hemolytic anemia, neuromuscular blockade, pancytopenia
		Every other day or biweekly dosing not recommended	**Drug interactions**: otoxocity potentiated by certain diuretics
Polypeptide Capreomycin (CM)	Polypeptide isolated from *Streptomyces capreolus*. Renally excreted. Varying degrees of cross-resistance reported between KM and CM; no cross-resistance reported between SM and CM; frequent cross-resistance between viomycin and CM.	1 g IM once a day	**Common**: pain at injection site
		Adjust for renal insufficiency	**Less common**: otoxocity and nephrotoxicity (dose-both to cumulative and peak concentrations, increased risk with renal insufficiency)
		Every other day or biweekly dosing not recommended	**Rarely**: electrolyte abnormalities, eosinophilia, hypersensitivity, neuromuscular blockade
			Drug interactions: Enhanced risk of neuromuscular blockade with ether anesthesia

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Drug Name	Description	Administration (Adult Doses)	Side Effects
FLUOROQUINOLONES			
Ciprofloxacin (CPX)	Likely bactericidal. DNA-gyrase inhibitor. Not FDA-approved for use during pregnancy (associated with arthropathies in studies with immature animals). Renally excreted. Levofloxacin active moiety and thus possibly the drug of choice. Cross-resistance among first-generation fluoroquinolones thought to be near complete.	Ciprofloxacin: 750 mg PO twice a day	Well-tolerated, well-absorbed
Levofloxacin (LFX)		Sparfloxacin: 200 mg PO twice a day	**Less common**: diarrhea, dizziness, GI upset, headache, insomnia, photosensitivity (8% occurrence with SPX), rash, vaginitis
Ofloxacin (OFX)		Ofloxacin 400 mg PO twice a day	**Rare**: arthralgia, interstitial nephritis, palpitations, psychosis, seizure, transaminitis (CNS effects seen almost exclusively in elderly)
Sparfloxacin (SPX)		Levofloxacin 500 mg PO once a day	**Drug interactions**: CPX, OFX prolong half-life of theophylline with increased risk of toxicity; $CaSO_4$ or $FeSO_4$ and antacids with Al, Mg may inhibit GI absorption of fluoroquinolones; altered phenytoin levels (increased and decreased); exacerbated hypoglycemic effect of glyburide; increased coumadin levels reported with CPX, OFX; probenacid increases CPX, OFX levels; use of SPX contraindicated in persons receiving any drug that prolongs the Q-T interval
Moxifloxacin (MFX)		Adjust doses for creatinine clearance <50 mL/min	
Gatifloxacin (GFX)			
OTHER SECOND-LINE DRUGS			
Cycloserine (CS)	Alanine analogue. Bacteriostatic. Interferes with cell-wall proteoglycan synthesis. Renally excreted. Recommended for TB of CNS given ready penetration into CNS.	750–1000 mg PO once a day	**Common**: neurological and psychiatric disturbances including headaches, irritability, tremors
		Administer with pyridoxine 150–300 mg once a day	**Less common**: hypersensitivity, psychosis, peripheral neuropathy, seizures (increased risk of CNS effects with concurrent use of ethanol, INH, Prothio/Ethio, or other centrally acting medications). Neurologic adverse effects may be lessened by pyridoxine coadministration.
		Increase gradually to maximum dose.	**Drug interactions**: phenytoin
Ethionamide (Ethio)	Derivative of isonicotinic acid. Bacteriostatic. Partial cross-resistance with thiacetazone. Hepatically metabolized, renally excreted. Efficacy profiles similar; prothionamide may cause fewer side effects.	Ethionamide: 750–1000 mg PO once a day	**Common**: GI upset (nausea, vomiting, abdominal pain, loss of appetite), metallic taste, hypothyroidism (especially when taken with PAS)
Prothionamide (Prothio)		Prothionamide: 500–1000 mg PO once a day	**Less common**: arthralgia, dermatitis, gynecomastia, hepatitis, impotence, peripheral neuropathy, photosensitivity

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Drug Name	Description	Administration (Adult Doses)	Side Effects
		Increase gradually to maximum dose	**Rarely**: optic neuritis, psychosis, seizure (Increased risk of CNS effects with concurrent use of ethanol, INH, CS, or other centrally acting medications)
		Administer with pyridoxine 150–300 mg once a day	**Drug interactions**: transiently increased INH levels
Para-aminosalicylic acid (PAS)	Bacteriostatic. Hepatic acetylation, renally excreted.	4 g PO three times a day	**Incidence adverse reactions**: 10%
		Delayed-release granules should be administered with acidic food or drink	**Common**: GI upset (nausea, vomiting, diarrhea), hypersensitivity (5–10%), hypothyroidism (especially when taken with ethionamide)
			Less common: hepatitis, electrolyte abnormalities
			Drug interactions: decreased INH acetylation, decreased RIF absorption in nongranular preparation, decreased B_{12} uptake
Rifabutin (RFB)	Bactericidal. Rifamycin spiropiperidyl derivative. Cross-resistance with rifampin >70%.	Rifabutin: 150–300 mg PO once a day	Similar or lesser side effect profile and drug interactions compared with RIF, including reduced activity of drugs metabolized by P450 system
Rifapentine (RFP)		Rifapentine: 600 mg PO 2x/wk	**Drug interactions**: RFB interacts less with PI levels than does RIF; RFB and RFP decrease protease inhibitor levels; RFB levels increased by PIs
Thiacetazone (THZ)	Weakly bactericidal. Inhibition of mycolic acid synthesis.	150 mg PO three times a day	**Common**: GI upset (nausea, vomiting), hypersensitivity
			Rare: cutaneous reactions (including Stevens-Johnson syndrome, increased risk in HIV-infected patients), jaundice, reversible bone-marrow suppression
			Drug interactions: may potentiate ototoxicity of aminoglycosides
THIRD-LINE DRUGS			
Amoxicillin-clavulanate	Beta-lactam antibiotic with a β-lactamase inhibitor. Bactericidal effect demonstrated in vitro.	500 mg PO three times a day	**Common**: GI upset
		Administer with food.	**Less common:** hypersensitivity
			Drug interactions: none reported
Clarithromycin	Semisynthetic erythromycin derivative. Demonstrated efficacy against *Mycobacterium avium* complex; in vitro bactericidal effect on susceptible strains of *Mycobacterium tuberculosis*.	500 mg PO twice a day	Well tolerated
			Less common: GI side effects (abdominal pain, diarrhea, metallic taste)
			Rare: ototoxicity
			Drug interactions: increased theophylline and carbamazepine levels; use of terfenadine is contraindicated
Clofazimine	Substituted iminophenazine bright-red dye. Bacteriostatic. Transcription inhibition by	200–300 mg PO once a day	**Common**: discoloration of skin and eyes, GI upset

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Drug Name	Description	Administration (Adult Doses)	Side Effects
	binding guanine residues of mycobacterial DNA.		
		Initiate dose at 300 mg; decrease dose to 200 mg when skin bronzes.	**Less common:** photosensitivity, malabsorption, severe abdominal distress due to crystal deposition
			Drug interactions: none reported

CNS, central nervous system; FDA, Food and Drug Administration; GI, gastrointestinal.