SUPPLEMENT ARTICLE

Drug-Resistant Tuberculosis—Current Dilemmas, Unanswered Questions, Challenges, and Priority Needs

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Tuberculosis was declared a global emergency by the World Health Organization (WHO) in 1993. Following the declaration and the promotion in 1995 of directly observed treatment short course (DOTS), a cost-effective strategy to contain the tuberculosis epidemic, nearly 7 million lives have been saved compared with the pre-DOTS era, high cure rates have been achieved in most countries worldwide, and the global incidence of tuberculosis has been in a slow decline since the early 2000s. However, the emergence and spread of multidrug-resistant (MDR) tuberculosis, extensively drug-resistant (XDR) tuberculosis, and more recently, totally drug-resistant tuberculosis pose a threat to global tuberculosis control. Multidrug-resistant tuberculosis is a man-made problem. Laboratory facilities for drug susceptibility testing are inadequate in most tuberculosis-endemic countries, especially in Africa; thus diagnosis is missed, routine surveillance is not implemented, and the actual numbers of global drug-resistant tuberculosis cases have yet to be estimated. This exposes an ominous situation and reveals an urgent need for commitment by national programs to health system improvement because the response to MDR tuberculosis requires strong health services in general. Multidrug-resistant tuberculosis and XDR tuberculosis greatly complicate patient management within resource-poor national tuberculosis programs, reducing treatment efficacy and increasing the cost of treatment to the extent that it could bankrupt healthcare financing in tuberculosis-endemic areas. Why, despite nearly 20 years of WHO-promoted

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activity and >12 years of MDR tuberculosis–specific activity, has the country response to the drug-resistant tuberculosis epidemic been so ineffectual? The current dilemmas, unanswered questions, operational issues, challenges, and priority needs for global drug resistance screening and surveillance, improved treatment regimens, and management of outcomes and prevention of DR tuberculosis are discussed.

The World Health Organization (WHO) is the directing and coordinating authority on international health within the United Nations system. Through WHO's policies and support, governments can tackle global health problems and improve people's well-being. It was almost 2 decades ago that WHO declared tuberculosis to be a global emergency and launched the cost-effective global tuberculosis control strategy named directly observed treatment short course (DOTS) [1, 2]. In 1999, with the growing threat of drug-resistant (DR) tuberculosis, WHO decided to tackle it through a complementary approach focused on provisions for treating multidrug-resistant (MDR) tuberculosis [3]. In 2000, recognizing that the cost and poor availability of high-quality drugs were barriers to successful implementation of a programmatic management of MDR tuberculosis, WHO, together with some other agencies, set up the Green Light Committee (GLC) to help countries gain access to affordable, high-quality second-line drugs [4]. In 2002, acknowledging that a critical lack of tuberculosis laboratory services capacity was a barrier to effective tuberculosis care, the DOTS Expansion Working Group of the Stop TB Partnership established a subgroup on laboratory capacity strengthening (now the Global Laboratory Initiative), hosted by WHO, to address this. These leadership initiatives coincided with an era of unprecedented funding for global tuberculosis control activities through organizations such as The Global Fund.

The slow decline in tuberculosis incidence observed in the past few years is encouraging, but there remains a great need to enhance control efforts because the global burden of tuberculosis remains very high and control efforts have been dogged by the emergence of DR strains of *Mycobacterium tuberculosis*. WHO estimates that approximately 640 000 cases were due to MDR tuberculosis in 2008 [5]. Multidrug-resistant tuberculosis is a man-made problem, resulting from improper use of antituberculosis drugs and likely the substandard quality of tuberculosis drugs used in certain settings. The identification and spread of MDR tuberculosis, extensively drug-resistant (XDR) tuberculosis , and more recently, totally drug-resistant (TDR) tuberculosis pose a major threat to global tuberculosis control. Of the estimated 290 000 cases of MDR tuberculosis that could be diagnosed if all notified tuberculosis cases were drug susceptibility tested, only 10% were reported to be enrolled in treatment for MDR tuberculosis, and a much smaller percentage received treatment from programs that use drugs approved by the GLC [6]. In the 27 high-burden, MDR tuberculosis countries, only 1% of new tuberculosis cases and 3% of previously treated cases are screened for DR tuberculosis by a laboratory. The occurrence of MDR tuberculosis and XDR tuberculosis greatly complicates patient management within resource-poor national tuberculosis programs, reducing treatment efficacy and increasing the cost of treatment to the extent that it could bankrupt healthcare systems in tuberculosis-endemic areas. Multidrug-resistant tuberculosis has great potential to bankrupt patients because of the more complicated, lengthy therapy involved [7–9] and the inability of these patient to work.

A serious question arises: Why, despite nearly 20 years of WHO-promoted activities in tuberculosis control and >12 years of MDR tuberculosis–specific activity, has the global response to the DR tuberculosis epidemic been so slow and ineffectual? In this article, we discuss current dilemmas, unanswered questions, operational issues, challenges, and priority needs for global drug resistance screening and surveillance, improved treatment regimens and management of outcomes in human immunodeficiency virus (HIV)–infected and uninfected adults and children, and infection control and prevention of DR tuberculosis.

DEFINITIONS, THEIR USEFULNESS, AND THEIR LIMITATIONS

Current definitions of DR tuberculosis are as follows: MDR tuberculosis is defined as resistance to the 2 key first-line antituberculosis drugs, isoniazid (INH) and rifampicin (RIF). The term XDR tuberculosis appeared in the literature for the first time in March 2006 in a report jointly published by WHO and the Centers for Disease Control and Prevention (CDC); later in the same year an outbreak of XDR tuberculosis associated with high mortality rates occurred among HIV-infected patients treated at a rural hospital in Tugela Ferry, South Africa [10]. It is presently defined as tuberculosis caused by *M. tuberculosis* strains that are resistant to at least INH and RIF (ie, MDR tuberculosis) *plus* any fluoroquinolone *and* at least 1 of 3 injectable anti-tuberculosis drugs—capreomycin, kanamycin, or amikacin. Totally drug-resistant tuberculosis is defined as tuberculosis caused by *M. tuberculosis* strains resistant to all first- and second-line licensed anti-tuberculosis drugs. Surveys of DR tuberculosis based on these definitions can be useful markers of efficiency and quality of national, regional, or global tuberculosis control programs and can be used as powerful advocacy tools for evoking political and community support. Furthermore, because treatment of DR tuberculosis is more costly, data on drug resistance can inform

health system budgetary planning. Identification of distinct groups of patients with MDR tuberculosis and XDR tuberculosis are important in clinical trials assessing the efficacy and duration of newer drugs or drug regimens. However, the current broad-based definition of MDR tuberculosis and XDR tuberculosis may not be sufficient to effectively randomize patient groups in clinical trials and may require subclasses of these groups based on actual drug resistance patterns to be studied.

The complexities of phenotypic mycobacterial drug susceptibility testing and the molecular mechanisms of *M. tuberculosis* drug resistance and cross-resistance [11] can make these definitions imprecise and confusing because drug concentrations used in definitions of drug resistance are not the same as drug concentrations achieved at the site of infection in vivo. Furthermore, the extent of resistance and cross-resistance conferred by distinct mutations differs substantially for INH, RIF, aminoglycosides, and fluoroquinolones [12]. Although necessary for treatment guidance, such complex diagnoses can only be made in a few quality-controlled tuberculosis reference laboratories, generally in developed countries where the burden of disease is lowest.

GLOBAL EPIDEMIOLOGICAL DATA AND ESTIMATES OF DRUG-RESISTANT TUBERCULOSIS

Drug-resistant strains of *M. tuberculosis* are globally dispersed, although the true scale of the threat remains undefined. Drug resistance surveillance data were patchy and often unreliable because of poorly standardized methodologies and biased patient selection, with the highest uncertainty in tuberculosis-endemic areas with limited resources where resistance testing is often not available. In a literature review of data published between 1985 and 1994, the authors found that rates varied widely between settings [13]. In 1994, WHO and the International Union Against Tuberculosis and Lung Diseases established a Global Surveillance Project to collect and assess data on the extent and type of anti-tuberculosis drug resistance and to monitor trends over time. Guidelines for surveillance of drug resistance were published, and a network of reference centers was established to aid standardization of procedures. The most recent report published in 2010 revealed that no high-burden country undertakes continuous surveillance, and although some countries undertake periodic surveys, only 47 countries have performed national surveys for drug resistance within the last decade [6]. World Health Organization estimates state that 3.6% of global tuberculosis cases (440 000 cases) were due to MDR tuberculosis in 2008, but these estimates are rather crude (Figure 1). The lack of laboratory capacity to test for drug resistance in much of Africa, Eastern Europe, and Asia makes it nearly impossible to accurately assess the situation, and the true global burden of DR tuberculosis may be higher than current estimates (Tables 1 and 2).

The large number of MDR tuberculosis cases reported from Eastern Europe and South Africa may only be the tip of the iceberg, although countries with limited or no access to second-line anti-tuberculosis drugs would not be expected to have a significant "home-grown" XDR tuberculosis problem, although immigration of patients from other countries is a potential source. The practice of reporting the prevalence of drug resistance as the proportion of cases with MDR tuberculosis is a further source of confusion regarding the global burden of drug resistance. Although a useful measure of the effectiveness of treatment, it does not indicate the absolute burden of MDR tuberculosis. For example, although the burden of MDR tuberculosis in South Africa appears low compared with that of Eastern European countries (when expressed as a proportion of the total tuberculosis caseload), the absolute number of cases is in reality very high because South Africa has the third highest tuberculosis caseload in the world [6, 14]. Similarly the absolute numbers of cases in India and China are very large, although as a proportion of total tuberculosis cases, the burden seems relatively small.

Mechanisms of drug resistance in *M. tuberculosis* originate either from spontaneous chromosomal mutations at low frequency (primary drug resistance) or from misuse of anti-tuberculosis drugs by physicians and patients, which leads to monotherapy or intermittent drug intake (secondary drug resistance) [11]. Secondary drug resistance is extremely rare in patients who adhere to their prescribed anti-tuberculosis regimen. Differentiation of drug-resistant cases is made for programmatic reasons in which incident cases arising from a transmission event are distinguished from those in which resistance has emerged during the course of an infection through inadequate therapy. WHO reports resistance in "previously treated cases" (defined as those who have received at least 1 month of treatment with anti-tuberculosis drugs), and resistance in "new cases" (defined as a newly registered episode of DR tuberculosis in a patient who, in response to direct questioning, denies having had any prior anti-tuberculosis treatment for more than 1 month, and, in countries where adequate documentation is available, patients for whom there is no evidence of such history) [6]. Of 12 686 confirmed new MDR tuberculosis cases reported worldwide in 2010, 11 646 were reported in the European region, the vast majority of which were from Eastern Europe. A total of 22 875 confirmed previously treated cases were reported to WHO in 2010, the majority of which again were from Eastern Europe [15]. The highest proportions of new and previously treated forms of MDR tuberculosis are found in Eastern Europe and Central Asia, with Azerbaijan, for example, reporting 22.3% and 55.8% MDR tuberculosis in new and previously treated tuberculosis cases, respectively [6]. The proportion of MDR tuberculosis

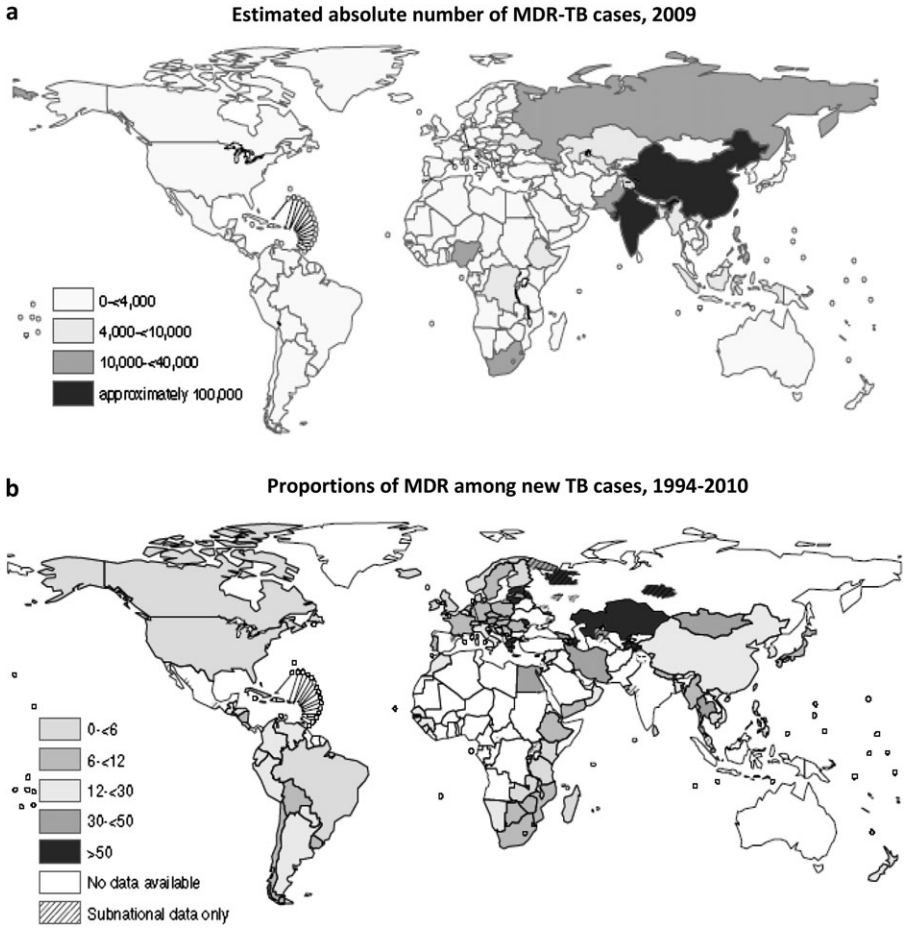

Figure 1. *A*, Estimated absolute number of multidrug resistance (MDR) among tuberculosis (TB) cases, 2009. *B*, Proportions of MDR among new tuberculosis cases, 1994–2010.

is always higher in previously treated tuberculosis cases than in new cases. India and China collectively accounted for almost half of the global cases of MDR tuberculosis in 2010, reporting high proportions of MDR tuberculosis in previously treated cases (17.2% and 25.6%, respectively) but relatively small proportions in new cases (2.3% and 5.7%, respectively) [15]. It was assumed that the incidence of MDR tuberculosis in new cases was an indicator of levels of transmission. However, genotyping studies have revealed the possibility of secondary infection, in which tuberculosis patients with drug-susceptible tuberculosis are infected with a new MDR *M. tuberculosis* strain, and thus an alternative measure of transmission is required to avoid underestimation of the problem.

DIAGNOSIS OF DRUG-RESISTANT TUBERCULOSIS

Sputum microscopy remains the most widely used diagnostic test and is frequently the only test available in tuberculosis-endemic areas. Although it allows detection of the most infectious cases, it is not a sensitive test and case detection rates remain low in developing countries [16]. In the WHO African Region, less than half of the estimated incident tuberculosis

Table 1. Limitations of Available Multidrug-Resistant Tuberculosis Data

Poor diagnostic, surveillance, and reporting systems for drug-resistant tuberculosis in most developing countries due to lack of resources and expertise.
Many tuberculosis-endemic areas are completely data deficient.
Continued surveillance occurs mainly in developed countries.
Periodic survey data are mostly old and outdated, although a number of surveys are currently under way.
The proportion of drug-resistant cases among new tuberculosis patients reflects transmitted disease, although retreatment cases probably represent a mix of transmitted (primary) and acquired (secondary) resistance.
Numbers of human immunodeficiency virus–infected patients with drug-resistant tuberculosis are poorly quantified.
No reliable pediatric data on multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis exist.

Table 2. Challenges for Global Control of the Drug-Resistant Tuberculosis Epidemic

Diagnostic dilemma	Microscopy-based diagnostics are unable to identify drug-resistant disease.
	Phenotypic diagnosis is most accurate, but requires a P3 lab and is costly and time consuming.
	Genotypic diagnosis offers rapid turnaround and fair accuracy; huge chance of false-positive diagnosis.
	Xpert MTB/RIF assay and false positives.
Infection control difficulties	Containment of aerosol transmission in healthcare facilities and transmission hot-spots within the community is difficult.
	Early diagnosis and effective treatment of infectious cases are essential, but even if this is achieved, treatment response is often slow.
	Prolonged isolation of infectious patients is costly and poses multiple legal and ethical dilemmas.
Complicated treatment	Second-line treatment is very expensive and is less potent and more toxic than first-line options.
	Treatment duration is for a minimum of 2 years with a combination of multiple drugs; adherence is a major challenge.
	Optimal drug regimens are poorly characterized, and no fixed-dose combination tablets are in existence.
Drug-resistant tuberculosis and HIV coinfection issues	The HIV epidemic has greatly increased the burden on tuberculosis programs, undermining treatment outcomes and fueling high rates of recurrent disease.
	Expansion of HIV care and treatment settings is very vulnerable to transmission and outbreaks of drug-resistant tuberculosis, affecting patients and healthcare workers.
	Second-line tuberculosis drugs and antiretroviral drugs have many shared toxicities, and patients with drug-resistant tuberculosis may be more susceptible to tuberculosis-immune reconstitution disease.
Limited international and domestic funding	Controlling the drug-resistant tuberculosis epidemic requires major investment.
	Most countries simply cannot afford or maintain the sophisticated infrastructure required to manage these patients in an optimal fashion.
	People with drug-resistant tuberculosis are usually poor and marginalized with little financial or political influence.
Lack of political commitment	Lack of awareness in general; no ''disease face.''
	Inaccurate numbers and poor quantification of the true disease burden.
	No immediate threat perceived; no easy/cheap answers.
	No international political pressure.

Abbreviation: HIV, human immunodeficiency virus.

cases each year are detected and notified [15]. Microscopy cannot differentiate drug-susceptible tuberculosis from DR tuberculosis. Drug susceptibility can be determined phenotypically by culture of *M. tuberculosis* isolates in the presence of the drug or genotypically via detection of mutations within the genome of *M. tuberculosis* that are known to confer resistance to specific anti-tuberculosis drugs. Culture-based methods are generally costly and time consuming and require a well-functioning, biosecure laboratory. Alternative lower-cost, more rapid culture-based methods, such as the microscopically observed drug susceptibility assay and the nitrate reductase assay, have also been endorsed for use by WHO, and a further rapid culture method, thin-layer agar culture, is also undergoing evaluation [17]. However, biosafety issues remain a stumbling block to more widespread implementation of these assays. Moreover, the technical infrastructure and expertise required means that in practice such assays remain largely confined to centralized reference laboratories. Access to such facilities is very poor in most high-burden countries, and not only do we fail to detect many tuberculosis patients, but also only a tiny proportion of those that are diagnosed are tested for drug resistance.

Rapid diagnosis is of paramount importance to improve patient outcomes and limit ongoing transmission. During the outbreak of MDR tuberculosis and XDR tuberculosis in rural KwaZulu Natal Province in South Africa in 2006, it was striking that many patients died during the period that sputum samples were obtained and the diagnosis was finally made [10]. Such delays in diagnosis allow clonal spread of drug resistant *M. tuberculosis* strains within vulnerable communities. Nucleic acid amplification tests (NAATs) provide a means for significantly more rapid detection of drug-resistant mutations, but it is important to note that other factors also contribute to resistance phenotype [18]. For some anti-tuberculosis drugs, genotypic drug susceptibility testing is complex, with multiple areas of the genome involved. Testing for large numbers of mutations is technically challenging and beyond the scope of real-time polymerase chain reaction (PCR) or line probe technology. Following the report of the South African XDR tuberculosis outbreak in 2008, WHO endorsed the use of line

probe assays in resource-limited settings for the rapid molecular detection of drug resistance in smear-positive specimens or culture isolates [19].

DEVELOPMENT OF NEWER ASSAYS FOR DETECTING DRUG RESISTANCE

In 2009, the GenoType MTBDR*sl* (Hain Lifescience) assay, which is able to detect resistance to fluoroquinolones, aminoglycosides, and ethambutol in culture isolates or smear-positive sputum specimens, became available [20]. A WHO expert committee reviewed the evaluation data for second-line drug susceptibility testing using the GenoType MTBDR*sl* test in 2010 but did not endorse it due to lack of sufficient evidence on its accuracy. When used in combination with the GenoType MTBDR*plus* assay, the GenoType MTBDR*sl* assay provides a means of rapid detection of XDR tuberculosis. Using such molecular assays reduces the time to diagnosis of MDR tuberculosis and XDR tuberculosis from weeks or months to a matter of days.

A further major step forward has occurred with the development of the Xpert MTB/RIF assay, a simplified NAAT that can be used outside the domain of reference laboratories in peripheral healthcare facilities [21]. This assay uses a series of molecular probes and real-time PCR technology to detect *M. tuberculosis* and the *rpoB* gene RIF resistance–associated mutations [22]. The cartridge-based system requires minimal laboratory expertise, and results are available in <2 hours, permitting a specific tuberculosis diagnosis and rapid detection of RIF resistance. A large multicountry evaluation found excellent performance characteristics [23], and an implementation study found that this technology could be used successfully at the district level, greatly reducing the time to tuberculosis diagnosis and showing high sensitivity for rapid detection of RIF resistance [24]. Further studies, however, have highlighted a problem with false-positive RIF resistance results [24, 25], and corrective measures are being instituted, including revisions to the diagnostic platform software and redesign of one of the assay oligonucleotide probes [22]. Thus, following detection of an RIF-resistant strain, WHO recommends further testing with another method to confirm RIF resistance and to assess susceptibility to other agents [21]. More details of this assay are outlined in McNerney et al's article (this issue) on tuberculosis diagnostics and biomarkers.

PATTERNS OF DRUG RESISTANCE

Single-drug (mono) resistance occurs commonly to INH. Historical studies demonstrated a high risk of acquiring INH resistance when tuberculosis patients with high bacillary loads were treated with INH monotherapy. The widespread use of INH preventive therapy (IPT) may fuel the emergence of INH monoresistance, which is usually the first step toward MDR tuberculosis if active tuberculosis disease is not adequately ruled out prior to IPT initiation. However, the available evidence suggests that the risk posed by IPT programs is less than anticipated, and the standard 4-drug treatment seems adequate even for those who fail IPT [26]. Rifampicin monoresistance used to be uncommon but seems to be increasing in frequency. This may be a false observation that reflects the increased sensitivity of genetic tests to detect RIF resistance compared with INH resistance. However, upward trends have been observed using phenotypic results as well in areas where poor quality of fixed-dose combination tablets have been used in the past. Rates of resistance may be affected by changes in treatment patterns, as some countries have only recently initiated RIF in the continuation phase of treatment. It is important to point out that the Xpert MTB/RIF assay only detects RIF resistance, which is often used as a surrogate for MDR tuberculosis. The failure to detect INH monoresistance is a significant limitation of the Xpert MTB/RIF assay. This poses 2 problems: (1) RIF or INH monoresistance would not be recognized, and (2) widespread usage will result in lower diagnosis of INH monoresistance. Furthermore, there have been particular challenges with the stability of some *rpoB* gene probes leading to false-positive RIF resistance results. This is a major concern because incorrect multidrug resistance identification would deprive these patients of optimal first-line therapy, which is more potent and less toxic and costs a fraction of the price of MDR tuberculosis treatment. Suggestions that these patients should not be started on an expanded first-line regimen until phenotypic confirmation of the actual drug susceptibility pattern are tempered by laboratory evidence that RIF induces efflux pump activation that significantly reduces flouroquinolone drug levels during cotreatment [27]. Resistance to other first-line drugs, pyrazinamide and ethambutol, are rarely tested for but seems to occur frequently among MDR tuberculosis cases. This is not unexpected in settings where first-line treatment often continues for months until treatment failure is recognized, and even the use of retreatment regimens that include streptomycin as a fifth agent offers poor protection against amplification of drug resistance.

MANAGEMENT OF DRUG-RESISTANT TUBERCULOSIS

It is estimated that <7% of MDR tuberculosis cases are diagnosed worldwide [6], and of these only 1% of patients receive treatment from programs that use quality-assured anti-tuberculosis drugs approved by the GLC. The GLC was set up to monitor tuberculosis program performance and restrict the availability of second-line anti-tuberculosis drugs, making them available only to countries that meet minimum performance targets. Whereas WHO and the GLC focus their attention on the public sector and national control programs,

the private sector is not regulated in most countries. Individuals with suspected MDR tuberculosis who cannot access second-line treatment in the public sector may turn to private providers, who may supply drugs, but of variable quality and without appropriate medical supervision, and thus the risks of amplified resistance or the emergence of XDR tuberculosis are high. Best practice guidelines need to be refined, taking into account drug cost, the cost of missed diagnosis or initial suboptimal treatment, side effects, and interactions with antiretrovirals. Although individualized regimens based on laboratory drug susceptibility data remains the ideal, standardized management algorithms based on local drug susceptibility patterns seem the only pragmatic alternative to assist treatment delivery at peripheral points of care. This should be done as an integrated tuberculosis and HIV service, with strict infection control measures.

COMPLEXITIES, DILEMMAS, AND PRIORITY NEEDS FOR DRUG-RESISTANT TUBERCULOSIS TREATMENT

Given that <1% of MDR tuberculosis patients are estimated to be on appropriate treatment [5, 28], massive treatment scale-up is urgently required to reduce individual suffering and to avoid ongoing transmission and a future scenario when DR tuberculosis strains cause the majority of tuberculosis cases [29]. Reasons for the lack of treatment scale-up include lack of diagnostic capacity in countries with the highest burdens of tuberculosis and DR tuberculosis, lack of political commitment, and lack of the financial resources needed to reach universal access for MDR tuberculosis treatment [30]. In addition, there are complexities around supply and pricing of existing second-line tuberculosis drugs, with ineffective global mechanisms to ensure access to quality-assured and effective regimens to treat MDR tuberculosis.

Early experience in the treatment of DR tuberculosis was primarily gleaned from small, well-resourced programs, and treatment was invariably individualized. Settings utilizing standardized or empiric treatment on a programmatic scale often report poorer outcomes, resulting in treatment success in approximately 62% of cases [31, 32]. More recent evaluations have reported higher success, up to 88% [33], but fundamental biases, such as nonrandom differences in how treatment is offered, influence the reported efficacy of regimens and also potentially lead to erroneous conclusions. In general, outcomes are suggested to be worse among HIV-infected individuals [34, 35]. Disappointing treatment outcomes are largely explained by the fact that treatment is lengthy and toxic, rendering adherence extremely difficult for patients. Even with good patient adherence, resistance amplification is common, resulting in treatment failure and the creation of highly resistant tuberculosis strains [36, 37].

Current recommendations for the treatment of DR tuberculosis are based on low-grade evidence. Randomized controlled trials have not been conducted to the same degree that ultimately led to the definition of the first-line tuberculosis regimen currently used [38]. Instead, guidelines for the management of MDR tuberculosis are based largely on expert opinion and limited observational data, resulting in the recommended use of drugs for which there is no or limited evidence of efficacy [39, 40]. Implementation of these guidelines results in a wide range of treatment regimens based on availability of drug susceptibility testing, physician preference, and drug availability and cost in many settings. Such individualized treatment approaches result in a modest improvement in outcomes (64% treatment success vs 54% for standardized treatment in meta-analyses) but no clear benefit in terms of mortality reduction (11% for both approaches) [32]. Clearly there is an urgent need for defined DR tuberculosis regimens that are shorter, more tolerable, and more effective and that have undergone trials under programmatic conditions [33, 41].

Given this bleak picture, it is encouraging that there are now several new promising compounds in the pipeline (see Leinhardt et al in this issue). The most advanced of these are TMC207 and OPC-67683, developed by Tibotec and Otsuka, respectively [42–44]. Early data on TMC207 suggested a significant negative interaction with RIF, a backbone first-line drug, and hence efforts have been directed from the outset toward DR tuberculosis treatment [45]. After promising phase 2 data, Tibotec has now approved the use of TMC207 under compassionate-use criteria for patients with limited treatment options. Due to poor treatment outcomes and high levels of treatment failure and defaulting, there is considerable pressure to make these drugs available sooner rather than later. Compassionate use can be seen as one way to speed up access to new drugs for patients whose therapeutic options are few and who therefore cannot afford to wait for the results of clinical trials. However, care must be taken to ensure that compassionate use does not result in inappropriate use and the early emergence of resistance.

METHODOLOGICAL ISSUES IN DRUG-RESISTANT TUBERCULOSIS TREATMENT

In addition to debates on priorities for new and existing tuberculosis drugs [46], there are important methodological difficulties in conducting clinical trials for DR tuberculosis (Table 3). The novel notion of the optimized background regimen enables assessment of individual drug effects, but it remains difficult to assess particular drug combinations in clinical trials [39]. If a similar approach to clinical trials for combinations of new and existing drugs with different durations is taken for DR tuberculosis, as was done for first-line

Table 3. Methodological Difficulties and Possible Solutions to Identify Optimal Treatment Regimens for Drug-Resistant Tuberculosis

Methodological Difficulties	Possible Solutions
Heterogeneous patient population; variable drug resistance profiles	Testing novel drugs against an optimized background regimen (difficult to assess particular drug combinations) tuberculosis
Little basic information regarding pharmacokinetics and other drug characteristics	Use of individual patient-level meta-analyses to better utilize existing observational data;expanded early bactericidal activity studies in patients with drug-resistant tuberculosis
Risk of selection bias, especially with program-based outcomes	Detailed pharmacokinetic and drug interaction studies for all second-line drugs
Hundreds of possible combinations of existing and new drugs and durations that could be tested against specific resistance profiles	Validate surrogate marker of response to therapy (eg, 6-month culture conversion rate)
Limited capacity to conduct large-scale trials in high multidrug resistance–burden settings	Develop capacity within tuberculosis control programs to conduct effectiveness trials of high quality
Length of time taken to achieve treatment success and therefore assess efficacy	Using animal models to test multiple drug combinations for potential synergy or antagonism, against infection with a variety of resistance profiles
Need for novel, innovative strategies to generate data that will inform drug-resistant tuberculosis regimen development; carefully guided prioritization of human trials	Support novel drug development and testing against drug-resistant strains

treatment, there could be a delay of 20–30 years before a well-evaluated regimen emerges [39]. Hence there is a need for novel, innovative strategies to generate data that will inform DR tuberculosis regimen development. Carefully guided prioritization is required in order to test regimens most likely to be efficacious, and importantly, able to be implemented under routine conditions in decentralized, nonspecialized programs in high-burden settings.

There have been some promising moves in this regard. The TB Alliance, through the Critical Path to New TB Regimens, has embarked on a series of early bactericidal activity (EBA) trials testing novel combinations of drugs, which aim to considerably reduce the time taken to develop full regimens [47]. There is debate in the tuberculosis clinical trial community about the appropriateness of EBA for evaluation of new drug combinations (see Phillips et al article in this issue). Furthermore, because the aim is to develop an entirely new regimen for all tuberculosis (both drug susceptible and resistant) [48], such a strategy will likely delay access to new drugs for DR tuberculosis patients and will not take advantage of the potential to combine new tuberculosis drugs with existing drugs currently used for DR tuberculosis. An entirely new tuberculosis regimen will likely take many years to establish, and in the meantime, DR tuberculosis will continue to exact an enormous toll on mortality and further threaten tuberculosis control efforts. Hence, there are strong arguments to concurrently develop better regimens for DR tuberculosis. Another promising approach is the use of individual patient-level meta-analyses to better utilize existing observational data on DR tuberculosis treatment and outcomes. An analysis drawing data from published meta-analyses aiming to assess drug choices and duration of treatment is currently under way with full results available soon [49]. This approach permits more extensive analysis of treatment factors than conventional meta-analyses but remains limited by the observational nature of the primary data and heterogeneity of treatment approaches.

SCALING UP DRUG-RESISTANT TUBERCULOSIS TREATMENT—CONCERNS AND DILEMMAS

Ultimately, if treatment is to be scaled up to the level required to meet the hundreds of thousands of patients in need each year and the millions currently waiting for treatment, some form of standardization will inescapably be required in order to improve access, reduce reliance on specialized services, and simplify patient adherence. However, in the absence of a full drug susceptibility profile, empiric regimens that take into account prevailing resistance patterns and HIV prevalence in different settings will be needed. With the expansion of case detection promised by the introduction of rapid PCR-based diagnostics, more programmatic data should be generated over the coming years. The question arises as to how these data should be best used to inform the design of clinical trials and advise national programs on what drug regimens should be implemented. One approach might be to draw on lessons learned from other diseases with regard to combined databases and information sharing. In hematology, for example, a shared database has been developed to draw data from multiple sites. This approach has the advantage of standardizing data collection, thus increasing the ability to undertake robust statistical analyses. This has improved survival for pediatric leukemia and increased the potential patient base for enrollment in clinical trials [50].

Other approaches are needed to inform the conduct of clinical trials that are most likely to result in usable,

efficacious regimens. This includes expanding efforts to develop new models (mathematical, animal, and human) to direct which drugs and which drug combinations should be taken forward to trials and efforts to characterize markers of disease progression and cure. In addition, various drug combinations may have the potential to result in positive synergistic interactions that may shorten treatment and increase efficacy. An example of this is the potential synergistic effects of ethambutol and pyrazinamide on clarithromycin [51, 52]. Unfortunately, data on potential drug synergies is severely limited for existing second-line tuberculosis drugs, mainly because many of these drugs are not well characterized in terms of mechanisms of action and pharmacokinetics [53]. Indeed, many currently used second-line tuberculosis drugs are not even registered for long-term use in tuberculosis treatment; the fluoroquinolones are a notable example of this. There is also potential for novel approaches to therapy, such as adjunctive therapy to limit tissue damage, [54] and novel drug delivery mechanisms, such as inhaled drugs [55]. Hence, in addition to novel methods of accumulating observational data on outcomes, significantly more targeted laboratory and pharmacokinetic studies are needed.

Encouragingly, there are several controlled trials under way aiming to improve DR tuberculosis treatment (see details at http://clinicaltrials.gov). Planning is also well advanced for a clinical trial aiming to evaluate the successful 9-month regimen used in Bangladesh in other high MDR–burden settings (STREAM study) [33, 56]. There are compelling reasons, both humanitarian and epidemiological, to scale up access to the best possible treatment for patients currently suffering from DR tuberculosis. Questions remain as to whether the limited global capacity for clinical trials in DR tuberculosis is being optimally used. A more directed and informed strategy that draws on the large range of mathematical and statistical tools that are available to help support complex decision making should be used to guide such decisions.

NEED FOR ANCILLARY OR ADJUNCT TREATMENTS

The poor treatment outcomes for XDR tuberculosis and MDR tuberculosis and the slow progress in development and evaluation of new tuberculosis drugs now calls for evaluation of novel adjunct therapies in addition to tuberculosis drug treatment. A range of immune modulators have been considered for use as adjunct treatment of DR tuberculosis [57]. These include immunoregulatory approaches, immunosuppressive therapy, and supplement effector cytokines. Immunoregulatory approaches, which seek to alter the nature of the immune response, can be divided into 3 subgroups: (1) those for which good manufacturing practices (GMP) manufacturing capacity exists (high-dose IVIg; HE2000-16α-bromoepiandrosterone; multidose heat-killed *Mycobacterium vaccae* or *Mycobacterium w*; anti–interleukin 4); (2) those for which GMP manufacturing capacity can be established (DNA vaccine [HSP65]), and (3) the others (Dzherelo; SCV-07 SciCLone; RUTI) [57]. Clinical trials with environmental *Mycobacterium* species have not shown any benefit as adjunct treatments. Trials with other preparations are hindered by availability of funding and the high cost of the immunotherapeutic agent. A phase 1 study in patients in Belarus with MDR tuberculosis and XDR tuberculosis is under way using autologous bone marrow–derived mesenchymal stem cell transfusions (M. Maeurer, personal oral communication, 2 December 2011) in an attempt to reinvigorate lung immune responses to enhance mycobacterial clearance.

PREVENTION AND CONTROL MEASURES FOR DRUG-RESISTANT TUBERCULOSIS—IDEAL VS REALITY

The existing BCG vaccine has played only a small role in preventing the acquisition and spread of DR tuberculosis. New effective vaccines against tuberculosis have the potential for a significant and durable effect on reducing DR tuberculosis globally. During the past decade, tuberculosis vaccine research has developed a number of new vaccine candidates that are under evaluation. Although the world eagerly awaits the results of these trials, current emphasis must remain on basic prevention and infection control measures. Pediatric data indicate effective human-to-human transmission within households, invalidating previous laboratory observations that drug-resistant strains are likely to be less fit and thus pose a reduced transmission risk [58]. The fitness cost associated with the acquisition of drug resistance seems unpredictable as compensatory evolution has been demonstrated to account for improved fitness of DR clinical strains with fitness approaching that of their progenitor strains [59]. The spread of DR tuberculosis is ominously linked to the HIV epidemic, as reflected by the clonal nature of the XDR tuberculosis outbreak documented at Tugela Ferry in KwaZulu Natal, South Africa [10], which showed that person-to-person spread of DR tuberculosis can occur quickly in hospitalized patients with HIV infection. Furthermore, all grades of healthcare workers are at increased risk of acquiring DR tuberculosis from patients because many hospitals in resource-poor countries do not have appropriate facilities for instituting infection control measures. There have been several reports of XDR tuberculosis occurring in South African hospital staff. This emphasizes the crucial importance of instituting effective infection control measures within hospitals, clinics, and confined institutions such as prisons, mines, and other congregate settings.

Patients with DR tuberculosis should be managed as inpatients in hospitals equipped with negative pressure isolation facilities, appropriate masks for patients and staff, and administrative protocols to deal with such patients; appropriate

environmental protective measures should also be taken. This may not be feasible in most resource-poor settings. In warm climates, adequate ventilation (>12 air changes per hour) obtained by opening windows and doors is the most important and easily implemented measure other than diagnosing and treating infectious cases early and effectively and separating suspected cases from high-risk patients, such as children and HIV-infected individuals. Cough etiquette is also a cost-effective intervention that needs to be urgently implemented at all levels. A recent modeling study on infection control outcomes estimated that half of anticipated XDR tuberculosis cases could be prevented by applying a combination of available strategies in developing countries [60]. Appropriate safety measures should be implemented by clinical and laboratory staff when dealing with biological samples from patients suspected of harboring DR tuberculosis strains.

INFECTION CONTROL MEASURES AND PATIENT RIGHTS

Balancing the rights of individual patients to have freedom of movement and association vs protecting the rights of the community at large to be protected from a dangerous pathogen is a difficult issue. During the severe acute respiratory syndrome outbreak, immediate implementation of strict patient isolation measures helped to avert a global epidemic. The situation with DR tuberculosis is more problematic because millions of people are affected already, disease is often indolent with slow progression over time, a prolonged course of treatment is required (at least 2 years), and cure cannot be guaranteed. Ensuring effective patient isolation during the time of infectiousness (sputum smear positivity) sounds like a logical intervention, but the scale of such an initiative is overwhelming. The threat of long-term isolation from loved ones and the huge economic consequences of having to visit and support the patients would be a major disincentive to present for diagnosis and treatment. Such a reaction may do more harm than good, negatively impacting control of both drug-susceptible and DR tuberculosis. The impact of various public health interventions to limit ongoing transmission within communities merits further discussion.

It is estimated that healthcare workers in South Africa have a 6-fold higher risk for contracting MDR tuberculosis and XDR tuberculosis compared with the general population [61]. WHO has published a policy on infection control that attempts to address the needs of resource rich and resource-limited settings [62]. This covers organizational activities (surveillance and assessment at all levels of the health system), administrative controls (triage, cough etiquette, reduction of unnecessary hospital stays, etc), environmental controls (natural ventilation, mechanical ventilation, ultraviolet irradiation, and health facility renovation), and personal protection (the use of respirators for health staff and masks for patients and the "package of prevention and care for healthcare workers" [including HIV prevention, antiretroviral therapy, and IPT for HIV-positive healthcare workers]). The WHO policy on infection control does not adequately distinguish between interventions that can be readily applied in resource rich and resource poor settings and not surprisingly in resource poor settings remains poorly implemented. Increased collaboration between HIV and tuberculosis screening and treatment programs will be essential as a means of infection control in endemic settings in order to mitigate the risk of transmission of tuberculosis, including in clinical spaces where HIV-infected individuals are kept in close contact with one another. Infection control management in clinical settings can include measures such as integrated tuberculosis and HIV care, early diagnosis and linkage to treatment, and appropriate ventilation and cough control, including triaging patients with cough to a separate waiting area. In addition to public health measures, early initiation of both antiretroviral therapy and second-line anti-tuberculosis drugs is a critical factor in survival of HIV-infected patients who are coinfected with MDR tuberculosis or XDR tuberculosis.

DRUG-RESISTANT TUBERCULOSIS—PEDIATRIC ISSUES

Published data on DR tuberculosis in children is sparse, but in general the pattern of drug resistance in children mirrors that of emergence within the adult population [63]. A rising incidence of DR tuberculosis has been reported in a longitudinal surveillance study from South Africa, in which MDR tuberculosis among children newly diagnosed with tuberculosis increased from 2.3% in the period 1994–1998 to 6.7% in the period 2005–2007; increases in drug resistance among adult cases in the same community were also tracked [58]. Successful transmission of MDR *M. tuberculosis* strains demonstrates the need to protect young and vulnerable children by limiting their exposure to infectious cases and considering preventive chemotherapy in the subgroup at highest risk of disease progression [64, 65]. The diagnosis of pediatric MDR tuberculosis is often delayed due to reliance on the diagnosis of the adult contact as a case of MDR tuberculosis, which depends on sputum culture and drug susceptibility results. Diagnosis requires a high index of suspicion because the culture yield in children makes definitive microbiological confirmation difficult. Resistance should be suspected if an index case has known resistant tuberculosis, if the child shows initial improvement on anti-tuberculosis treatment and then deteriorates, or if there is no response to initial treatment. Acquired drug resistance in the pediatric population is rarely reported; however, children with *M. tuberculosis*–HIV coinfection could have high bacterial loads as well as low drug levels, hence, they should be closely monitored and adherence to treatment should be ensured. Table 4

Table 4. Issues Related to Drug-Resistant Tuberculosis in Children

Preventive therapy	The best protection for vulnerable children is reduced exposure, which emphasizes the need for early diagnosis of adult cases and implementation of effective infection control measures.
	Children aged <3 years are most vulnerable to progress to disease following exposure/infection.
	High-dose INH preventive therapy (10–15 mg/kg) may offer some protection with low- or intermediate-level INH resistance.
	For INH or RIF monoresistance, either RIF (4 months) or INH (6–9 months) should provide adequate protection.
	As a general rule, the benefit-to-risk ratio for multidrug-resistant prophylaxis is likely to be highest in children aged <3 years. Using 2–3 oral drugs (6 months) to which the index strain is susceptible does provide some protection.
	Follow up of high-risk children is warranted for a period of at least 1 year.
Diagnosis	Always take a detailed contact history.
	Always collect at least 2–3 samples for culture and susceptibility testing before initiating treatment following exposure to a drug-resistant source case.
	Improved access to culture and molecular diagnostics should benefit children in whom microscopy performs poorly.
Management	Same principles apply as in adults, but children with minimal disease and low bacillary loads may be treated for shorter durations (9–12 months of prescription drugs).
	Always base treatment decisions on the drug susceptibility profile of the likely source case, and adjust as needed should any of the child's specimens yield a positive result.
	Pay attention to dosage because pediatric formulations of second-line drugs are often not available.
	Increased vigilance is required to monitor for adverse events (eg, transient hypothyroidism associated with ethionamide or PAS treatment has increased relevance in an actively growing and developing child).
	Ensure parental understanding of the need to complete a prolonged course of treatment and provide ongoing support.

Abbreviations: INH, isoniazid; PAS, para-aminosalicylic acid; RIF, rifampicin.

summarizes some of the principles related to prevention, diagnosis, and management of DR tuberculosis in children.

Definitive data regarding optimal therapy for pediatric DR cases are lacking, but treatment cure rates >90% have been reported for MDR cases [66], and children with XDR tuberculosis have been successfully treated as well [67]. This demonstrates that a rational approach to diagnosis and drug selection can lead to good outcomes if adherence is maintained and side effects are adequately managed [64, 66]. Most guidelines, although expert opinion based, recommend regimens that include at least 4–5 active drugs, of which 1 should be an injectable agent and, if possible, at least 2 should be bactericidal. In the absence of drug susceptibility results, the child should be treated according to the resistance profile of the most likely source case [64, 65]. The use of high-dose INH (15 mg/kg) is likely to confer clinical benefit with low or intermediate levels of INH resistance, which may be suggested by genetic mutational analysis [68, 69]. However, INH should not replace an active drug in the regimen, and combining high-dose INH with ethionamide is probably a good strategy to consider in the absence of sophisticated tests [68, 70].

Depending on the severity of disease and side effects experienced, parenteral agents should be given for at least 4–6 months. Although second-line anti-tuberculosis drugs have known and potentially serious side effects, limited evidence in children suggests that they tolerate these drugs at least as well as adults [65]. There is general consensus that the benefits of fluoroquinolones in the treatment of DR tuberculosis far outweigh potential risks [64, 65]. Ciprofloxacin has the weakest potency and should not be used if newer fluoroquinolones are available. Amikacin is generally the injectable agent of choice in children because it is less painful to inject intramuscularly and is associated with fewer adverse effects than other agents. However, prolonged use of any injectable agent is associated with renal and hearing/vestibular toxicities, which may be delayed in onset. Hearing should be monitored during and for at least 6 months after treatment completion because hearing disability may have major consequences for language and communication development [71]. Both ethionamide and para-aminosalicylic acid (PAS) have been associated with transient hypothyroidism, and thyroid replacement therapy may be warranted during prolonged treatment, especially in young children with active neurological development. Serine analogues such as cycloserine/terizidone as well as INH and some antiretroviral drugs can cause peripheral neuropathy; routine pyridoxine supplementation is advised, especially in HIV-infected children who frequently demonstrate persistently low pyridoxine levels [72].

CONCLUSIONS

Multidrug-resistant tuberculosis and XDR tuberculosis are spreading globally and now greatly complicate patient

management within resource-poor national tuberculosis programs, reducing treatment efficacy and increasing the cost of treatment to the extent that it could bankrupt healthcare systems in tuberculosis-endemic areas. There is an urgent need for program and laboratory infrastructure improvement and a dire need for funders, donors, and governments to take these issues seriously, especially in light of the current global economic recession.

Notes

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