What's in a name? The future of drug-resistant tuberculosis classification

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Due to a recent resurgence in tuberculosis research focused on drug development, several new antituberculosis drugs are in the pipeline, and the standard of care for tuberculosis might soon change. If new drugs replace the current first-line treatment, then existing classifications of resistance, including multidrug-resistant and extensively drug- resistant tuberculosis, might become less relevant. When much needed new drugs reach the market, a new classification system for resistance might need to be devised to describe resistance to these novel agents. Many options for such a system exist, each with its own inherent benefits and challenges. The adoption of new terminology for resistance should be guided by outcomes data from clinical trials in progress, and should be accompanied by increased support for drug susceptibility testing in developing countries to be clinically useful. Consideration of these issues now will hopefully help foster an informed approach to the classification of drug-resistant tuberculosis in the era of new drugs.

Introduction

In December, 2011, four cases of tuberculosis that were resistant to all first-line and second-line drugs were described in India,[1] following similar reports from Italy in 2007, and Iran in 2009.[2,3] Soon after the Indian cases were reported, this strain of tuberculosis, labeled totally drug-resistant tuberculosis, began to garner widespread international media attention.

In response to the discovery in India and other reports of patients infected with totally drug-resistant tuberculosis strains, the WHO Stop TB Department convened a meeting in March 2012, to discuss the notion of totally drug-resistant tuberculosis and the actual existence of such strains. This expert group concluded that because of inadequate drug susceptibility testing (DST) for some second-line tuberculosis drugs—a crucial requirement for classification of tuberculosis strains as drug- resistant—terms like totally drug-resistant should not currently be used in relation to tuberculosis.[4] Instead, they proposed that the drug-resistant tuberculosis classification be restricted to the existing multidrug-resistant and extensively drug-resistant tuberculosis terms, for which DST is more reliable.

The multidrug-resistant and extensively drug- resistant terms signify that the disease is resistant to some of the most frequently used antituberculosis drugs; however, through advances in drug discovery, the standard of tuberculosis care might soon change. When much needed new drugs reach the market, some important questions will arise about the future of drug- resistant tuberculosis classification: should the terms multidrug-resistant and extensively drug-resistant be redefined to reflect resistance to the new regimens? Or should this terminology be abandoned and replaced by a more nuanced classification system? In this Personal View, we discuss the evolution of drug-resistant

tuberculosis classification, briefly present new tuberculosis drugs and regimens in the pipeline, and propose three possible approaches to classification of resistant cases in the coming era as new drugs reach the market.

Lastly, we emphasize the importance of reliable DST in the development of a new, clinically relevant classification system.

The history of drug-resistant tuberculosis terminology

The development of bacterial resistance was identified soon after initial antibiotic treatments for tuberculosis were introduced in the 1940s.[5] Although regimens containing isoniazid and rifampicin were developed throughout the next 20 years, the term multidrug- resistant tuberculosis, which denotes resistance to both of these drugs, did not gain widespread use until the early 1990s.[6] Soon afterwards, increasingly resistant strains of tuberculosis were reported, and in 2006, WHO introduced the definition of extensively drug-resistant tuberculosis—an upgrade from multidrug-resistant tuberculosis—defined as strains resistant not only to isoniazid and rifampicin, but also to any fluoroquinolone and one of the three second-line injectable antituberculosis drugs (kanamycin, amikacin, or capreomycin).[7,8]

This 2006 definition of extensively drug-resistant tuberculosis was a revision of a previous classification, set in 2005, that defined extensively drug-resistant tuberculosis as a subset of multidrug-resistant tuberculosis with additional resistance to any three second- line antituberculosis drugs.[9,10] The revised, more precise definition was deemed necessary by a task force convened by WHO because susceptibility testing for many tuberculosis drugs (particularly ethambutol, pyrazinamide, the thioamides, the serine derivatives, and para-aminosalicylic acid) was not straightforward,[11–13] and the reproducibility of DST for these drugs only ranged from 50–80%. By contrast, DST methods for drugs covered by the new definition were considered to be more than 90% reproducible. Additionally, the revised definition supported more accurate case detection and surveillance in the short term, since DST was not available for at least three second-line drugs. This partly shows the complex reasoning behind WHO's recommendation of the term extensively drug-resistant tuberculosis. [14]

In 2007, when cases of tuberculosis that were resistant to all first-line and second-line drugs were first publically identified, the term extremely drug-resistant was initially used to qualify these strains,[2] but this resistance pattern was renamed totally drug-resistant in subsequent publications. WHO has recommended against definitions of resistance beyond extensively drug-resistant tuberculosis, again citing poorly reproducible DST for second-line tuberculosis drugs and a shortage of evidence to show that these strains, defined as totally resistant when grown in vitro, actually correlate with clinical outcomes.[4]

The terms multidrug-resistant and extensively drug- resistant, however, have clinical significance. These terms were initially chosen not only because they denote reproducible resistance patterns, but also because they describe resistance to the most potent antituberculosis drugs. Patients with multidrug-resistant tuberculosis have high rates of treatment failure and death,[15,16] and outcomes are even poorer in patients with extensively drug-resistant

tuberculosis.[17] Particularly high mortality rates have been reported in those co-infected with extensively drug-resistant tuberculosis and HIV.[18] The poor outcomes in patients with multidrug-resistant and extensively drug-resistant tuberculosis have been attributed to the decreased efficacy and increased toxicity of second-line drugs, and the lengthy treatment course. Developing safer, more efficacious drugs to combat drug- resistant tuberculosis has been identified as a priority by WHO,[19] and several new drugs and regimens are in the development pipeline.

New treatments for tuberculosis

After a period of rapid drug development in the 1950s and 1960s, tuberculosis was deemed under control, and no new first-line tuberculosis treatments were developed for the next 40 years. Amid recent renewed interest in tuberculosis drug discovery, more than ten drugs are now in the clinical development pipeline,[20] including novel agents and existing drugs that are being repurposed for tuberculosis treatment. For example, the drugs bedaquiline (TMC207) and delaminid (OPC67683), which are new classes of antituberculosis drugs, have already shown promising results in phase 2 trials.[21,22]

A major goal of tuberculosis drug development is to find better treatments for drug-resistant tuberculosis, and some of the drugs in the pipeline have shown activity against multidrug-resistant tuberculosis.[21,23,24] Another goal is to establish shorter, simpler regimens for drug-sensitive tuberculosis, [19] and such trials are now underway. WHO has suggested that, if research efforts can be increased, by 2015 a new 4-month regimen for drug-sensitive tuberculosis will be available, and a 9-month regimen for drug-resistant tuberculosis will be in phase 3 trials.[1]

In the era of new drugs: three options for a new classification system

With the advent of new drugs and regimens, the current terminology for drug-resistant tuberculosis might become less clinically relevant. For example, two new regimens under investigation do not include isoniazid or rifampicin,[25,26] and if they were to become first-line regimens, the current classifications of multidrug-resistant and extensively drug-resistant tuberculosis would lose much of their prognostic implications.

Meanwhile, resistance to new drugs in these regimens (such as bedaquiline and PA-824, another antituberculosis drug that has entered human trials) would become more important, and a new classification of drug resistance would be needed. Therefore, we anticipate that the classification for multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis will evolve into one of three options (figure).

If a new first-line regimen that does not include isoniazid and rifampicin replaces the current standard of care, one option (option 1 in the figure) would be for the definitions of multidrug-resistant and extensively drug- resistant tuberculosis to be changed to reflect resistance to the newer drugs. Multidrug-resistant tuberculosis could be redefined to reflect resistance to two new drugs, and the extensively drug-resistant term could be updated to denote higher levels of

resistance. The benefits of this approach would be that the familiar classification system could be retained, and it would still stratify patients into simple, easily defined groups. The major drawbacks would be that these terms would need to be redefined whenever a more effective drug is incorporated into first- line regimens, and as new drugs enter the market, these new definitions might quickly become outdated. Additionally, changing these definitions would complicate any comparison of multidrug-resistant and extensively drug-resistant cases from different eras. A second option (option 2 in the figure) would be to leave the multidrug-resistant and extensively drug-resistant terms unchanged and develop new terms to classify cases of tuberculosis that are resistant to the newer drugs. As data from tuberculosis drug trials are released, new patterns of resistance will probably become apparent, and a new system of classification could be devised. This approach would prevent some of the confusion that would be created by redefining the multidrug-resistant and extensively drug-resistant terms, but would also necessitate the introduction of more, potentially confounding terminology.

As more tuberculosis treatment options become available, a third approach (option 3 in the figure) might be to simply abandon further attempts to classify patients by broad definitions of drug resistance. If reproducible and affordable DST becomes more widespread, perhaps tuberculosis treatment will become increasingly personalized, and grouping patients into categories of resistance might become less useful. Instead, the approach to tuberculosis drug resistance might become similar to that for HIV, with complex drug susceptibility data used to guide individual treatment regimens. This option would only be realistic if affordable DST for new and existing drugs becomes more widely available, especially in low-resource settings.

In the era of new antituberculosis drugs, the use of the term totally drug-resistant will probably not be straightforward. As new drugs reach the market, the notion of total drug resistance would need to be repeatedly readdressed, and, similar to any redefinition of the terms multidrug-resistant and extensively drug-resistant, this term would be poorly reproducible for research or clinical purposes. Even as DST improves, the totally drug- resistant terminology is unlikely to be useful.

The importance of DST

The usefulness of any new system for classification of resistant tuberculosis in the era of new drugs would depend heavily on the cost, availability, and reliability of DST for the new drugs. In 2012, WHO recommended a target of one laboratory with the capacity to undertake DST for every five million people in the population, but also noted that of the 36 countries with high burdens of either tuberculosis or multidrug-resistant tuberculosis, less than half met this goal.[27] The Global Plan to Stop TB has identified strengthening of laboratory systems as a key objective, and estimated that to meet this goal by 2015, 2000 new laboratories would need to be built and 20000 new technicians trained, at a cost of US$4 billion over 5 years.[19]

When new drugs reach the market, the need to test the susceptibility of tuberculosis to these treatments would probably introduce additional challenges

to the already struggling tuberculosis diagnostic laboratories in developing countries. Without more support for laboratories to undertake reliable, efficient DST for both established and novel drugs, a new classification system is not likely to be clinically helpful. Companies developing new drugs should probably validate in parallel simple and accurate DST methods for their compounds. This would prevent the development of resistance to the new molecules by providing accurate, personalized DST profiles for patients who are drug-resistant at the onset of treatment.[8]

The future of drug-resistant tuberculosis classification

The long-overdue release of new antituberculosis drugs will hopefully usher in an exciting new era in the management of this deadly disease. As these new treatments reach the market, the classification of drug- resistant cases will probably need to be redefined.

The existing definitions of multidrug-resistant and extensively drug-resistant tuberculosis are the result of years of careful consideration and debate among experts in the field. Definitions of future categories of resistance will probably need similar deliberation and thought, because many possible approaches exist, each with its own inherent benefits and challenges.

Because new drugs might become available soon, these approaches should be considered now, although establishment of a new classification system would be unwise without additional outcomes data related to the new drugs and regimens. Just as the multidrug-resistant and extensively drug-resistant terms have been shown to have prognostic significance, the development of new terminology should be guided by knowledge of the way in which resistance to new drugs affects survival, treatment success, and other outcomes. As tuberculosis drug trials are completed, new clinically important patterns of resistance might become evident.

In addition to outcomes data, the development of a meaningful new classification system will undoubtedly rely on improvements in DST in low-income countries where drug-resistant tuberculosis is most prevalent. Our review underscores the crucial role of DST in the management of tuberculosis. Such considerations also emphasize the suboptimum state of tuberculosis laboratory technology and infrastructure worldwide and the undeniable need for additional support to ensure reliable, affordable DST for both established and new drugs in coming years.

The tuberculosis community has been waiting for almost half a century for new drugs and regimens, and in view of reports of increasingly resistant tuberculosis strains in recent years, the need for new treatment options has never been more pressing. As promising new drugs finally begin to emerge, the standard of care for tuberculosis might soon evolve, and the framework for classification of drug-resistant cases will need to evolve along with it. Reconsideration of that framework will hopefully help to foster an informed approach to the classification of drug-resistant tuberculosis in the era of new drugs.

Contributors
Both authors contributed to the planning, writing, and editing of this manuscript.

Conflicts of interest
We declare that we have no conflicts of interest.

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