The need to accelerate access to new drugs for multidrug-resistant tuberculosis

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The need to accelerate access to new drugs for multidrug-resistant tuberculosis

Helen S Cox, Jennifer J Furin, Carole D Mitnick, Colleen Daniels, Vivian Cox & Eric Goemaere

Abstract Approximately half a million people are thought to develop multidrug-resistant tuberculosis annually. Barely 20% of these people currently receive recommended treatment and only about 10% are successfully treated. Poor access to treatment is probably driving the current epidemic, via ongoing transmission. Treatment scale-up is hampered by current treatment regimens, which are lengthy, expensive, poorly tolerated and difficult to administer in the settings where most patients reside. Although new drugs provide an opportunity to improve treatment regimens, current and planned clinical trials hold little promise for developing regimens that will facilitate prompt treatment scale-up. In this article we argue that clinical trials, while necessary, should be complemented by timely, large-scale, operational research that will provide programmatic data on the use of new drugs and regimens while simultaneously improving access to life-saving treatment. Perceived risks – such as the rapid development of resistance to new drugs – need to be balanced against the high levels of mortality and transmission that will otherwise persist. Doubling access to treatment and increasing treatment success could save approximately a million lives over the next decade.

Introduction

Resistance to antimicrobial drugs threatens incremental gains that have been made in the global fight against tuberculosis. It has been estimated that 480,000 people develop multidrug-resistant (MDR) tuberculosis each year. In 2013, only 20% of these people received recommended second-line treatment regimens; yet only about 50% of the people that did receive such regimens had successful treatment outcomes. Therefore, most people with MDR tuberculosis transmit drug-resistant Mycobacterium tuberculosis to other members of their communities, since they go undiagnosed or are diagnosed but only treated with ineffective first-line drugs. There is an urgent need for accessible and improved treatments for MDR tuberculosis – to reduce mortality and avoid scenarios in which resistance becomes the norm rather than the exception. There needs to be a major scale-up of treatment for MDR tuberculosis that matches the scale-ups that have already been achieved in treatments for human immunodeficiency virus and drug-susceptible tuberculosis. The decentralization of diagnosis, care and management is essential. Specialist medical management needs to be largely replaced by nurse-led care, with hospitalization restricted to those patients for whom it is medically indicated. Treatment regimens need to be simplified, shortened and improved, so that treatment success exceeds 50%.

After more than 40 years without any new tuberculosis drugs, there are now several new drugs that are in development or becoming available. Examples include bedaquiline – which received conditional approval from the United States’ Food and Drug Administration in December 2012 and conditional marketing authorization by the European Medicines Agency in December 2013 – and delamanid – which received conditional authorization by the European Medicines Agency in April 2014. In phase II trials – compared with a placebo and within an optimized background regimen – both of these drugs appeared to be efficacious against MDR tuberculosis. Phase III trials of these drugs are planned or underway. Some so-called repurposed drugs – e.g. linezolid, which has been primarily used for the treatment of Gram-positive bacterial infections – also appear to be promising in the treatment of MDR tuberculosis.

Despite this apparent progress, access to new or repurposed drugs is associated with substantial challenges for the majority of patients in settings with high burdens of MDR tuberculosis. In addition to regulatory approval in Europe and the United States of America, specific country-level regulatory approval is often required and can be difficult to obtain. The level of difficulty depends mainly on the sophistication of national intellectual property laws and the regulatory authorities. After approval of a new treatment has been granted, national programmes often grapple with issues of cost and supply and require guidance on appropriate use. In general, such programmes rely on the World Health Organization (WHO) for policy recommendations. Guidance on the appropriate use of new drugs for MDR tuberculosis is currently constrained by limitations in the available evidence, which is often entirely based on the results of phase II and phase III trials in which the efficacies of current regimens with and without a new drug were compared. Much of the available guidance on the optimal use of new or repurposed drugs continues to rely on expert opinion. We need innovative and rigorous observational studies to be run concurrently with – and complementary to – randomized controlled trials. Such studies should be designed...
to investigate the incorporation of new drugs into more tolerable and practical regimens and to evaluate the novel regimens under routine conditions.

**Tolerability and practicality**

Clinical trials are designed to demonstrate the new drug’s efficacy and safety, for the purposes of obtaining drug approval and registration. They are not designed to identify the best possible treatment regimen to achieve large-scale effectiveness. The approach followed in clinical trials of bedaquiline and delamanid – i.e. adding either drug to an existing, long, toxic, complex regimen – is extremely unlikely to improve treatment access or patient outcomes substantially. Although inclusion of bedaquiline or delamanid has led to improved culture conversion, it has not led to overall treatment success levels that were substantially greater than those reported, in systematic reviews, for the currently recommended treatment regimens for MDR tuberculosis.4,5,6

Use of the currently recommended regimens is plagued by poor uptake and poor results.7 The large pill burden, treatment side-effects and the need for daily injections and routine, long-term hospitalization all lead to high demands on both patients and health systems. As a result, early discontinuation of treatment is consistently above 20% of patients in many settings and up to 52% in some settings.8,9

Compared with any currently recommended regimen, a better-tolerated regimen that can be administered in decentralized settings by the existing tuberculosis programmes should enhance treatment uptake and completion and have a greater impact. An entirely oral regimen – i.e. one that obviates the need for painful, daily injections administered by health workers – would have the combined benefits of improving adherence and treatment completion while reducing severe and debilitating adverse events10 and reducing the demands on the health system.

There is a clear need for innovative treatment regimens that incorporate new or repurposed drugs or older drugs in novel combinations that can be used in shorter treatment regimens. The focus of improvements needs to be broadened beyond efficacy and safety to the capacity to scale-up treatment and reach a much larger proportion of the disease burden with a better-tolerated and practical regimen. This approach is relevant for both clinical trials and innovative operational research.

**Clinical trials**

The limitations of currently recommended treatment regimens for MDR tuberculosis are largely due to the regimens’ dependence on old drugs, the use of which is generally poorly supported by evidence. It is noteworthy that most companion drugs for such tuberculosis are used off-label (in a manner that, according to the drug’s label, is not formally approved). In contrast to the treatment of drug-susceptible tuberculosis, there have been no clinical trials to guide the design of treatment regimens for MDR tuberculosis. Consequently, drugs have been combined into treatment regimens for MDR tuberculosis based only on expert opinion and observational experience obtained over the past 15 years.11 In this context, clinical trials are much-needed.

A phase III trial testing delamanid against placebo is underway, with results expected by 2017.12 Both treatment and placebo arms of the trial receive an optimized background treatment regimen. The United States Food and Drug Administration approved bedaquiline under the condition that a phase III trial of the drug be completed by 2022.13 Instead of conducting a separate phase III trial, there are plans to incorporate an entirely oral, bedaquiline-containing arm into an existing study (STREAM), which is examining shorter nine-month regimens using existing and repurposed drugs.16

In addition to the bedaquiline-containing arms in STREAM, a small number of trials that aim to test combinations of new, repurposed and existing drugs for MDR tuberculosis are being planned. Médecins Sans Frontières, Partners in Health and other groups are planning a set of clinical trials, using adaptive approaches, to design new regimens containing bedaquiline, delamanid and/or the nitroimidazole PA-824 and create shorter, better-tolerated and more effective regimens that have the potential to increase access to treatment in a range of settings.11 The Global Alliance for TB Drug Development is implementing a small one-arm study – the so-called Nix-TB trial – to assess a regimen that contains all the new drugs for extensively drug-resistant tuberculosis.17 The Global Alliance also plans to enrol a small number of MDR tuberculosis patients in a trial to test a combination of PA-824, moxifloxacin and pyrazinamide.17 Unfortunately, the AIDS Clinical Trials Group’s plans for a trial of new regimens for MDR tuberculosis ended in June 2014.

With the exception of the Nix-TB trial, none of the remaining trials that we have mentioned has obtained full approval for implementation or started recruiting patients. Trials to investigate combinations of bedaquiline and delamanid are contingent on the results of a study of drug–drug interaction and safety of the drugs in combination, planned by the United States National Institutes of Health. Although the fast-tracking of this study has been recommended, it remains in preparation and patient recruitment is unlikely to start before late 2015.14 Trials combining bedaquiline with PA-824 are also on hold until the safety of the combination can be assessed in the Nix-TB trial. In addition to the delays in planning and implementing clinical trials, clinical trials for tuberculosis are extremely slow. The results of recent tuberculosis trials have only been released 6–9 years after the first patient was allocated to a treatment arm.10–21

Even if the limited number of trials currently in process and planning produce promising results, it is unlikely that we will have data to guide regimen formulation for programmatic use until at least 2020. Given the urgent need for expanded and improved MDR tuberculosis treatment, this timeline appears untenable.

**Policy guidance**

WHO released interim policy guidance for the use of bedaquiline in June 2013.22 Given the limited data available, WHO recommended that bedaquiline be restricted to tuberculosis patients showing extensive drug resistance and a poor response to their current treatment and to patients affected by adverse events that limit the options for treatment with other drugs. WHO released guidance on the use of delamanid in November 2014.23 For delamanid, WHO made similar recommendations as for bedaquiline but also suggested that use of delamanid may not be warranted in situations where an effective regimen can be composed of older drugs. Given the lack of data on the concurrent use of delamanid and bedaquiline, WHO felt
under operational research conditions, while reflecting specific disease burdens and health system realities. Relatively short (nine- to 10-month) treatment of MDR tuberculosis with existing drugs, based on the regimen already used in Bangladesh, 32 is currently being assessed in several settings as well as in the STREAM trial. Such short regimens have produced excellent outcomes under operational research conditions in some settings, 11,32 and may be scaled up before the results of the formal STREAM trial become available. Since the operational research approach to the investigation of existing drugs, as supported by WHO, encompasses ethical review and close monitoring of patients, it could make valuable contributions to the evidence base. 11

While not using the rigid standards of clinical management and reporting required for clinical trials, observational studies can provide a better quality of care than that available in routine treatment. In order for observational studies to maximize patient safety and provide quality data, they should include: (i) assured access to laboratory and clinical tests, for safety assessment; (ii) strong community-based follow-up, to allow for proactive monitoring of patient outcomes; and, ideally, (iii) a standardized tool for the collection of basic safety and efficacy data (Box 1). While the number of patients included in clinical trials – after satisfying multiple criteria for eligibility – is often in the hundreds, operational studies can aim to treat all diagnosed cases within certain geographical regions and potentially offer treatment to thousands of patients. Instead of the complexities of randomization to different regimens, all patients can be treated with the same regimen. Observational studies can also build local clinical capacity and strengthen health systems – two key prerequisites for treatment scale-up and continued research.

**Risks and benefits**

Treatment as prevention has the dual aims of reducing mortality and interrupting disease transmission. The benefits and risks of accelerated access to new drugs – potentially leading to a greater proportion of patients receiving treatment and a greater treatment success – can be compared with those achieved through a more restricted and gradual introduction. For example, if the incidence of MDR tuberculosis stays the same for another decade, 4.8 million patients will develop MDR tuberculosis. Doubling access to treatment from the current level of 20% of patients, and increasing treatment success to 80%
Several researchers have expressed concern that the scaled-up use of new drugs will lead to the rapid development of widespread resistance to the drugs. 14–16 This concern motivates efforts to restrict the use of new drugs to small, well-functioning programmes and to use very restrictive criteria for patient eligibility. Current policies emphasize minimizing the risk of widespread resistance. However, this risk needs to be carefully weighed against the deaths that might be expected under different scale-up scenarios. The development of resistance to drugs used to treat tuberculosis and all other infectious diseases is inevitable. Resistance to almost every antimicrobial in clinical use has been detected. 17–19 Although resistance to some tuberculosis drugs has emerged rapidly, the mechanisms and drivers of such resistance remain poorly understood. 20–22 It also remains unclear if restricting access to a drug slows the acquisition of resistance to that drug. 23–26 The acquisition of resistance to the drugs used in the second-line treatment of tuberculosis appears to be driven by regimen composition, such that the risk of such resistance increases substantially as the number of effective drugs in the regimen decreases. 27 The acquisition of resistance was found to be relatively rare in programmes approved by the Green Light Committee Initiative, probably as the result of strict regimen guidance. 28 Accelerating access to new drugs – contained in improved, easier-to-administer regimens – may actually reduce the rate at which resistance develops. If treatment outcomes can be improved and the number of patients managed by a nurse or other health-care worker can be increased by the use of simplified, less toxic regimens, the encouraging results seen in programmes approved by the Green Light Committee Initiative ought to be achievable on a much larger scale.

Finally, the safety of a treatment regimen is considered paramount. The maxim of first do no harm can lead to a drug not being used because of rare, but serious, risks to patients. In the case of MDR tuberculosis, no cardiac event has yet been attributed to the use of bedaquiline and delamanid, despite the knowledge that both drugs can prolong the QT interval. However, sudden death, deafness, renal insufficiency, psychosis and irreversible peripheral neuropathy are some of the known adverse effects of the older drugs still used. 43–46

Conclusion

Although the development and approval of new drugs provide hope for the hundreds of thousands of people affected by MDR tuberculosis each year, we still need to know how to use such drugs at scale in the most effective way. If we can rapidly develop a knowledge base on how to use new drugs in combination with existing drugs, we may soon be able to offer effective treatment to all those in need – and not just to those few patients who are able to access specialist care in well-resourced settings. Scale-up of drug-resistant tuberculosis treatment has been singularly ineffective over the last decade. In the absence of innovative thinking, there is a danger that we will take a conservative
Policy & practice

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Aim for speeding up the access to drugs for多重抗药性联合治疗

Abstract

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Summary

Policy & practice

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approach in which access to new drugs is very restricted and scale-up is slowed. Flexibility and speed – combined with advocacy, political commitment, adequate resources and pragmatism – are now required.

Archaeological approaches are needed to achieve the goals of the Sustainable Development Goals. The Sustainable Development Goals are the umbrella under which the global health and development agendas will be pursued. The definition of the Sustainable Development Goals is that they are achieved through sustained and equitable progress in achieving a set of targets for reducing poverty, improving health, education, and other social indicators.

The Sustainable Development Goals are a framework for global action that aims to end poverty, protect the planet, and ensure prosperity for all. They are based on the recognition that economic growth and development must be sustainable and equitable. The goals are meant to be achieved over a period of time, with the aim of creating a world in which everyone can live a healthy and productive life.

The Sustainable Development Goals are a set of 17 global goals that are intended to address the world’s most pressing challenges, including poverty, hunger, climate change, and inequality. They were adopted by the United Nations in 2015 and are expected to be achieved by 2030. The goals cover a wide range of areas, including health, education, and economic growth.

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