Principles for designing future regimens for multidrug-resistant tuberculosis

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Abstract Fewer than 20% of patients with multidrug-resistant (MDR) tuberculosis are receiving treatment and there is an urgent need to scale up treatment programmes. One of the biggest barriers to scale-up is the treatment regimen, which is lengthy, complex, ineffective, poorly tolerated and expensive. For the first time in over 50 years, new drugs have been developed specifically to treat tuberculosis, with bedaquiline and potentially delamanid expected to be available soon for treatment of MDR cases. However, if the new drugs are merely added to the current treatment regimen, the new regimen will be at least as lengthy, cumbersome and toxic as the existing one. There is an urgent need for strategy and evidence on how to maximize the potential of the new drugs to improve outcomes and shorten treatment.

We devised eight key principles for designing future treatment regimens to ensure that, once they are proven safe in clinical trials, they will be clinically effective and programmatically practicable. Regimens should contain at least one new class of drug; be broadly applicable for use against MDR and extensively drug-resistant Mycobacterium tuberculosis complex strains; contain three to five effective drugs, each from a different drug class; be delivered orally; have a simple dosing schedule; have a good side-effect profile that allows limited monitoring; last a maximum of 6 months; and have minimal interaction with antiretrovirals. Following these principles will maximize the potential of new compounds and help to overcome the clinical and programmatic disadvantages and scale-up constraints that plague the current regimen.

Background

Multidrug-resistant (MDR) tuberculosis, defined as tuberculosis resistant to at least rifampicin and isoniazid, is an increasing worldwide threat. According to the Global tuberculosis report 2012 of the World Health Organization (WHO), approximately 4% of new tuberculosis cases and 20% of retreated cases fall under this definition, with some countries reporting substantially higher figures.

Less than 20% of patients with MDR tuberculosis are currently receiving treatment and there is an urgent need to scale up treatment programmes. Scale-up is being severely hampered by financial, political, logistical and technical obstacles. The high costs and difficulty of implementing regimens prevent many national tuberculosis programmes from offering treatment for MDR tuberculosis or from investing sufficiently in scaling up MDR tuberculosis treatment programmes to meet the growing need. This in turn is allowing the spread of MDR tuberculosis.

One of the biggest barriers to scaling up MDR tuberculosis programmes is the treatment regimen, which is lengthy, complex, ineffective, poorly tolerated and expensive. The current WHO-recommended regimen for treating MDR tuberculosis requires daily injections for a minimum of 8 months and has a total duration of at least 20 months. The drugs are less effective than those used to treat drug-susceptible tuberculosis and have more adverse effects. Each course of therapy costs around 4000 United States dollars (US$) per patient.

The poor efficacy of treatment and the challenges involved in the programmatic implementation of the current recommended MDR tuberculosis regimen result in poor outcomes. A recent meta-analysis of outcomes for over 9000 patients receiving treatment for MDR pulmonary tuberculosis reported only a 54% success rate; treatment default, mortality and treatment failure rates were 23%, 15% and 8%, respectively. Analysis of outcomes from tuberculosis programmes operated by the medical humanitarian agency Médecins Sans Frontières showed results similar to those of the meta-analysis, with an overall treatment success rate of 55% for MDR tuberculosis and only 13% for extensively drug-resistant (XDR) tuberculosis (defined as tuberculosis resistant to at least isoniazid, rifampicin, a fluoroquinolone and an injectable second-line drug; unpublished data, TB Working Group, Médecins Sans Frontières, 2012).

For the first time in over 50 years, new drugs have been developed specifically to treat tuberculosis. The drugs currently in phase II or later clinical trials are derived from four classes of compounds: nitroimidazoles, diarylquinolines, oxazolidinones, aminoglycosides and fluoroquinolones. However, few have been approved for use in tuberculosis due to their toxicities, delay in development and the high costs associated with regulatory approval. The new drugs have the potential to revolutionize the treatment of drug-resistant tuberculosis.

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zolidinones and diamines. Bedaquiline was registered by the Food and Drug Administration of the United States of America in December 2012 and has been recommended for use in adults with MDR pulmonary tuberculosis by WHO. Although delamanid has recently received a negative opinion for registration with the European Medicines Agency, licensure and registration applications are pending at the Food and Drug Administration and at the Pharmaceutical and Medical Devices Agency of Japan, respectively. There is therefore real potential that two new drugs will be available for the treatment of MDR tuberculosis in the near future (Table 1). In addition, existing drugs not yet licensed for the treatment of MDR tuberculosis, such as linezolid, clofazimine, moxifloxacin and those at an earlier stage in the drug development pipeline (e.g. PA-824 and sutezolid), have shown promise (Table 1). While the development of new drugs is good news, there is limited knowledge on how to use bedaquiline and delamanid to treat patients with MDR tuberculosis and no evidence for the safety or efficacy of the regimens in which these drugs are combined. Although organizations and collaborations such as the TB Alliance, Critical Path to TB Drug Regimens and Research Excellence to Stop TB Resistance are working on new tuberculosis treatment regimens, no new MDR tuberculosis regimen containing new compounds is imminent.

Randomized controlled trials can be useful for determining the efficacy of treatment regimens. However, for MDR tuberculosis, trials are not easy to implement in many high-burden settings because of considerable diagnostic difficulties, which limit the accuracy of disease confirmation. These high-burden settings also have a lack of sites with the capacity to conduct randomized controlled trials.

In addition to the efficacy of a new regimen, it is important to consider factors associated with successful programmatic implementation – if new drugs are merely added to the current MDR tuberculosis regimen, the resulting regimen will remain lengthy, cumbersome and toxic. There is an urgent need for a regimen-development strategy that will make it possible to maximize the potential of the new drugs to improve outcomes among patients with MDR tuberculosis and minimize or eliminate the adverse attributes of the current regimen.

With no improvement seen in success rates despite considerable investment in scaling up treatment programmes, it is time for a fresh approach to designing MDR tuberculosis treatment regimens. Speed and pragmatism are essential in this process. With this in mind, we have devised eight key principles that should be used in designing future MDR tuberculosis regimens to ensure that the regimens are effective and programmatically feasible and that they can be scaled up. We propose that these principles be debated, refined and adopted by all tuberculosis research groups, agencies and policy-makers currently working on or making decisions about future regimens. To our knowledge, this is the first attempt to consider an approach that uses guiding principles to ensure that the opportunity offered by the development of new tuberculosis drugs is not squandered.

**Principles for designing future regimens**

Any future regimen should satisfy the following principles: (i) it should contain at least one new class of drug; (ii) it should be broadly applicable for use against MDR and XDR *Mycobacterium tuberculosis* complex strains; (iii) it should contain three to five effective drugs, each from a different drug class; (iv) it should have an exclusively oral delivery; (v) it should have a simple dosing schedule; (vi) it should have a good side-effect profile that allows limited monitoring; (vii) it should have a maximum duration of 6 months; and (viii) it should have minimal interaction with antiretroviral drugs. Here, we discuss and present the evidence underlying each principle.

**Inclusion of one or more new drug classes**

For any future MDR tuberculosis regimen, the use of at least one new drug class (whether it is added to a novel combination of antituberculosis drugs or to a standard antituberculosis regimen) has the potential to greatly improve outcomes. The addition of drugs from one new class to which patients have not previously been exposed would guarantee that most strains of *M. tuberculosis* complex are susceptible to the regimen. The few wild-type strains with resistance would be likely to succumb to the combined effects of the other efficacious drugs in the regimen. The addition of two new drug classes could increase the efficacy of the new regimen, if the agents can be safely combined. Care should be taken when choosing the drug combinations because studies of bactericidal activity in whole blood specimens have shown less than fully additive activity between bedaquiline and PA-824. Bedaquiline and either delamanid or PA-824 have shown some

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**Table 1. New and repurposed drugs available for the treatment of multidrug-resistant tuberculosis**

<table>
<thead>
<tr>
<th>Drug (Chemical)</th>
<th>New or repurposed</th>
<th>Class</th>
<th>Stage of development and comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delamanid (OPC 67683)</td>
<td>New</td>
<td>Nitroimidazole</td>
<td>Phase III trial under way; submitted for FDA and PMDA approval</td>
</tr>
<tr>
<td>Bedaquiline (TMC-207)</td>
<td>New</td>
<td>Diaryquinoline</td>
<td>Phase III trial to commence in 2014; FDA approval in December 2012</td>
</tr>
<tr>
<td>PA-824</td>
<td>New</td>
<td>Nitroimidazole</td>
<td>Developed by TB Alliance; as part of a regimen in a phase IIb trial that has completed recruitment</td>
</tr>
<tr>
<td>Sutezolid (PNL-100480)</td>
<td>New</td>
<td>Oxazolidinone</td>
<td>Phase II</td>
</tr>
<tr>
<td>AZD-5847</td>
<td>New</td>
<td>Oxazolidinone</td>
<td>Phase II</td>
</tr>
<tr>
<td>SQ-109</td>
<td>New</td>
<td>Ethylenediamine</td>
<td>Phase II</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Repurposed</td>
<td>Oxazolidinone</td>
<td>Phase II</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>Repurposed</td>
<td>Riminophenazine</td>
<td>Phase II</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Repurposed</td>
<td>Fluoroquinolone</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

antagonism in murine models, although when combined with pyrazinamide they were still significantly more efficacious than the combination of rifampicin, isoniazid and pyrazinamide.\textsuperscript{3}

**Activity against MDR and XDR strains**

In areas where MDR tuberculosis is common, susceptibility testing of first-line drugs is uncommon and that of second-line drugs is more uncommon still. Even when testing is available, substantial delays in obtaining results can seriously impair the ability to construct optimal regimens. To avoid reliance on complex and lengthy drug susceptibility testing, any new regimen for MDR tuberculosis should contain only drugs to which resistance is highly unlikely to have developed. This is where new classes of drugs offer a distinct advantage.

WHO estimates that 9\% of patients with MDR tuberculosis have XDR tuberculosis.\textsuperscript{1} Since susceptibility testing for second-line drugs is not commonly available in many settings, these estimates are probably conservative.\textsuperscript{16,17}

With the advent of new compounds not previously used in antituberculosis treatment, reliance on conventional susceptibility tests involving second-line agents could be reduced, and the emphasis on cheap, rapid molecular tests for a limited number of key agents could be increased.

**Inclusion of three to five drugs**

One drug is unlikely to be active against all populations of *M. tuberculosis* complex bacilli (i.e. actively multiplying bacilli, slowly or sporadically multiplying bacilli and dormant bacilli). Two-drug regimens might, in theory, be active against all populations and three-drug combinations might show even more activity.\textsuperscript{16} A review of MDR tuberculosis treatment from the era before rifampicin was available revealed that use of three antituberculosis drugs ensured favourable outcomes in patients with tuberculosis resistant to streptomycin, isoniazid and para-aminosalicylic acid.\textsuperscript{19}

The review concluded that a second-line regimen should contain at least four drugs likely to be active against the infecting strain and that such drugs chosen should, in combination, have rapid bactericidal activity (e.g. show evidence of bactericidal activity early after treatment initiation), prevent the easy formation of resistance to any single drug and have sterilizing activity.

A report of a seven-drug regimen with improved efficacy does not suggest that more drugs are better, but rather that, when resistance patterns are unknown, additional drugs may be necessary to account for the possibility that several may not be contributing.\textsuperscript{20} However, such regimens will unavoidably lead to increased toxicity without clinical benefit. Thus, to ensure that a regimen is effective and unlikely to generate further resistance, it should contain a minimum of three efficacious drugs; the value of including more than five drugs is unclear.\textsuperscript{1}

Each drug in the new regimen should ideally have a different mechanism of action – use of two drugs from the same class is not likely to have an additional benefit and could lead to more side-effects and lower tolerability. If new drugs are developed within the same class, the drug with the better efficacy and toxicity profile should be used in the regimen.

**Exclusively oral delivery**

Injectable agents (kanamycin, amikacin and capreomycin) play a key role in the current recommended MDR tuberculosis regimen. WHO’s recently updated guidelines on treating drug-resistant tuberculosis extend the recommended minimum duration for administration of injectable drugs.\textsuperscript{2} However, resistance to the injectable drugs in the MDR tuberculosis treatment regimen is increasing. Overall, strains in approximately 20\% of patients with MDR tuberculosis are resistant to the injectable agents and in some settings the prevalence of resistance is as high as 47\%.\textsuperscript{2} Thus, the role of these injectable agents in the current MDR tuberculosis regimen is declining. An exclusively oral regimen would be better tolerated and accepted by patients and would be easier for treatment programmes to administer.

For the patient, the daily intramuscular and/or intravenous injection of drugs for the treatment of MDR tuberculosis is a painful procedure that can be exacerbated by the low body mass index common among many patients with MDR tuberculosis. In addition, the injectable agents can cause severe side-effects, including deafness, with some programmes reporting rates of attributable hearing loss as high as 20 to 30\%.\textsuperscript{2,21} They are also associated with electrolyte imbalances and an increased risk of renal impairment. These side-effects necessitate regular monitoring, which is an additional strain for patients and programmes.

For treatment programmes, the requirement to provide daily injections is burdensome. Because of this, in some settings patients living far from health facilities have to be hospitalized to ensure the availability of appropriately trained staff. If treatment is community based, the need for injections has additional implications in terms of human resources and personnel training.

**Simple dosing schedule**

With the current adherence strategy for MDR tuberculosis treatment relying on direct observation by staff while the patient takes their medicine, drugs whose administration is complex, such as injectable or nebulized agents, present considerable barriers to programmes. Oral agents are easier to administer, but drugs requiring administration more than once daily or at specific times need to be carefully considered to ensure that their benefits outweigh the programmatic complexity of ensuring that they are properly administered.

**Good side-effect profile**

The current regimen is plagued with side-effects.\textsuperscript{24} Adverse gastrointestinal reactions are most common but deafness, renal and liver failure and psychosis are among the severe side-effects that can occur. Side-effects have been noted in 69\% of patients, requiring treatment modification in 55\%.\textsuperscript{25} The two drugs furthest along the development pipeline (bedaquiline and delamanid) and two of the repurposed drugs (moxifloxacin and clofazimine) can prolong the QT interval,\textsuperscript{26,27} which may pose an obstacle to use in tuberculosis programmes. It is essential to consider the influence of side-effects on treatment adherence and loss to follow-up when planning future regimens.

**Maximum duration of six months**

The feasibility of large-scale regimen implementation would be greatly enhanced by reducing the duration of treatment. The two-year duration of MDR tuberculosis treatment is a major barrier to treatment adherence and programme scale-up. There is evidence that a six-month course of tuberculosis treatment can lead to good clinical outcomes if the right combination of drugs to which the infecting *M. tuberculosis* complex bacilli...
are susceptible is used.1,24 Future MDR tuberculosis regimens containing new classes of drugs to which there is no recorded resistance, such as bedaquiline and delamanid, could produce similar outcomes.

A recently published study from Bangladesh was one of the first to look at using existing drugs in new ways to shorten and improve the outcomes obtained with MDR tuberculosis treatment.15 This observational study described the outcomes seen after a nine-month regimen in patients never exposed to second-line drugs. Good outcomes were reported; the treatment success rate was 87.9% and the default rate was 6%, much lower than seen with longer regimens.15 Since this research was conducted in a specific setting with a low prevalence of human immunodeficiency virus (HIV) infection, the results must be interpreted with caution until testing of the regimen in a multicentre randomized controlled trial (STREAM) is completed. These results, coupled with those already published from Bangladesh and other countries in which modified versions of this regimen were implemented, show the potential to dramatically reduce the duration of treatment in some patients with MDR tuberculosis.

In the United States, a six-month course of bedaquiline has been approved for concomitant use with the current regimen27 and studies of delamanid have focused on a similar treatment length.29 Incorporating new classes of drugs into an MDR tuberculosis regimen so that it contains drugs to which there is no background resistance should enable a substantial reduction in treatment duration. A pragmatic starting goal is to design a six-month regimen with the aim of further reducing treatment duration.

**Minimal interaction with antiretrovirals**

Tuberculosis is the major killer of HIV-infected patients. With 430,000 deaths reported in patients coinfected with HIV and *M. tuberculosis* complex in 2011,1 it is important for any new regimen to be suitable for this vulnerable group of patients. Use of this regimen with first-line antiretroviral agents for HIV infection should yield minimal, if any, clinically relevant drug–drug interactions or overlapping toxicity.

**Conclusion**

The current MDR tuberculosis regimen requires radical changes. It should be shorter, more tolerable and capable of being implemented rapidly within tuberculosis programmes in countries with a large burden of tuberculosis. Research into new regimens has not provided an answer to the immediate question of how to use the new tuberculosis drugs that are approved or pending approval. This is a critical research gap that must be addressed quickly. There is opportunity now to develop the strategies needed for evaluating new regimens that are suited to the current global tuberculosis situation. To ensure that the process is sped up to match the urgent need, there has to be a fundamental change in how regimens are developed and tested. Such change will require bold ideas and a willingness to challenge some of the current thinking with respect to tuberculosis treatment, clinical trials and drug development.

An important first step is to determine the compatibility of the first two new drugs likely to become available – bedaquiline and delamanid – with each other and with commonly used antiretroviral agents. In the absence of incompatibility, they could be the building blocks for new regimens that would meet many of the criteria that we have outlined. However, compatibility is not ensured. Existing tuberculosis clinical trial networks need to make compatibility studies their highest priority. Nontraditional participants in drug development research, such as Médecins Sans Frontières and Partners in Health, should engage the clinical trials community to collaborate, speed up and ensure rapid and pragmatic development and implementation of new regimens.

The potentially increased cost of new drugs could deter many centres from considering the inclusion of these drugs in new regimens. The current regimen costs about US$ 4000 per patient,1 exclusive of laboratory, human resource and patient opportunity costs. Although the price of bedaquiline has yet to be confirmed, a tiered pricing strategy is being proposed, with costs being lowest for countries supplied by the Global Drug Facility.25 Because repurposed drugs are cheaper, we hypothesize that drug costs for a regimen containing fewer drugs and of shorter duration would be equal to those of the current regimen. However, given the much shorter target duration and, consequently, the fewer laboratory and human resource requirements, the new regimens must have the potential to be cheaper for countries with a high burden of MDR tuberculosis. These considerations merit further investigation. The key principles that we have described should inform the development of future regimens so that the potential benefits of new compounds can be maximized while simultaneously addressing the clinical and programmatic disadvantages and constraints to scale-up that plague the current regimen.

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MLUX

ملخص

مبادئ تصميم النظم المستقبلية للسل للأدوية المتعددة

معدلات العلاج للمرضى ذوي السل للأدوية المتعددة لا يتفYe\n
قة أقل من 20% من مرضى السل للأدوية المتعددة العلاج، وتوجد حاجة للمجأة لزيادة حجم برام� العلاج. وتتمثل إحدى العقبات الكبرى التي تحول دون زيادة حجم النظام العلاجي في أن طول وتعقيد وراءسع النمط النموذجي. والعملية التكنولوجية الأولى فيما يزيد عن 50 سنة تم طويل دورة أدوية جديدة لأسباب لعلاج السل، باستخدام البيداكيلين وربما الديلامانيد المتوقع إتاحتهما قريباً لعلاج حالات السل المقاومة للأدوية المتعددة. ومع ذلك، إذا لم يتم سوى إضافة الأدوية الجديدة إلى النظام العلاجي الراهن، فسوف يكون النظام الجديد على الأقل طويلاً ومزعجًا وساماً مثل النظام القائم. وتأخذ حاجة ملحة لاستراتيجية وبيانات بشأن كيفية مضاعف احتمالات الأدوية الجديدة في تحسين الحصائل وتقصير مدة العلاج. وقمنا باستحداث ثمانية مبادئ رئيسية لتصميم النظم العلاجية المستقبلية لضمان فعاليتها من الناحية السريرية وقابلتها للتطبيق من الناحية البرمجية بمجرد إثبات سلامتها في التجارب السريرية. وينبغي أن تحتوي النظم على فئة دواء واحدة جديدة على الأقل، وأن يتم تطبيقها على نطاق واسع لاستخدامها ضد السل للأدوية المتعددة والسلاليات المعقدة من البكتيريا المفطرة السلية، وقد تم على ثلاثة إلى خمسة أدوية ناجحة، ينبغي أن تأتي جزء من كل منها إلى دواء واحدة مختلفة وتم تناولها عن طريق الفم، وتكون ذات جدول جرعات بسيط، محل ضعيف ضعافياً لتأخير الأداء جيداً بسبب الرصد المحدود؛ وتستغرق 6 أشهر على الأكثر، وتكون أقل فاعلية مباشراً مع مضادات الفيروسات الفطرية. وسوف يضاعف احتمالات الأدوية الجديدة لتزويج الحكم الذي يتعارض النظام الراهن. وسوف يضاعف احتمالات الأدوية الجديدة لتزويج الحكم الذي يتعارض النظام الراهن. وسوف يضاعف احتمالات الأدوية الجديدة لتزويج الحكم الذي يتعارض النظام الراهن. وسوف يضاعف احتمالات الأدوية الجديدة لتزويج الحكم الذي يتعارض النظام الراهن. وسوف يضاعف احتمالات الأدوية الجديدة لتزويج الحكم الذي يتعارض النظام الراهن.

Résumé

Principes de conception de futurs schémas thérapeutiques pour traiter la tuberculose multirésistante

Moins de 20% des patients atteints de tuberculose multirésistante (MDR) reçoivent actuellement un traitement et il est urgent de renforcer les programmes de traitement. Un des plus grands obstacles à ce renforcement est le schéma thérapeutique qui est long, complexe, inefficace, mal toléré et coûteux. Pour la première fois depuis plus de 50 ans, de nouveaux médicaments ont été développés spécifiquement pour traiter la tuberculose, dont la bedaquiline et potentiellement la delamanid qui devraient être rapidement disponibles pour traiter les cas de MDR. Cependant, si ces nouveaux médicaments sont ajoutés au schéma thérapeutique actuel, le nouveau schéma thérapeutique sera au moins aussi long, lourd et toxique que celui qui existe déjà. Il est urgent d'élaborer une stratégie et d'obtenir des preuves concernant la façon de maximiser le potentiel des nouveaux médicaments pour améliorer les résultats et raccourcir la durée du traitement. Nous avons mis au point huit principes clés pour la conception des futurs schémas thérapeutiques afin de s'assurer que, une fois qu'ils aient été éprouvés comme sûrs dans des essais cliniques, ils soient cliniquement efficaces et utilisables dans le cadre d'un programme. Les schémas thérapeutiques doivent comprendre au moins une nouvelle classe de médicament; être généralement applicables pour une utilisation contre les MDR et plus largeement contre les souches complexes de Mycobacterium tuberculosis multirésistantes; comprendre trois des cinq médicaments efficaces, chacun provenant d'une classe de médicament différente; être administré par voie orale; avoir un schéma posologique simple; avoir un bon profil d’effets secondaires permettant un suivi limité; durer au moins 6 mois et avoir le moins d'interaction possible avec les antirétroviraux. Suivre ces principes maximisera le potentiel des nouveaux composés et permettra de surmonter les inconvénients cliniques et programmatiques, ainsi que les contraintes qui plombent le schéma thérapeutique actuel.

Резюме

Принципы составления перспективных схем лечения туберкулеза с множественной лекарственной устойчивостью

Лечение проходит лишь менее 20% пациентов, страдающих туберкулезом с множественной лекарственной устойчивостью (МЛУ), поэтому необходимо срочно расширить охват населения программами по лечению данного заболевания. Одним из
Resumen

Principios para el diseño de programas futuros contra la tuberculosis multirresistente

Menos del 20% de los pacientes con tuberculosis multirresistente (MDR) recibe tratamiento, al tiempo que existe una necesidad apremiante de ampliar los programas de tratamiento. Uno de los mayores obstáculos para la ampliación es el propio programa de tratamiento, el cual resulta largo, complejo, ineficaz, caro y no se tolera bien. Por primera vez en más de 50 años se han desarrollado fármacos nuevos específicos para tratar la tuberculosis y se espera que la bedaquilina y, posiblemente, otros fármacos nuevos al programa de tratamiento actual, el programa nuevo recientemente autorizado, se pueda aplicar de forma amplia para su uso contra la tuberculosis multirresistente. Con la introducción de nuevos fármacos y el desarrollo de metadatos y protocolos, se maximizará el potencial de los fármacos nuevos para mejorar los resultados y acortar el tratamiento. Hemos establecido ocho principios esenciales para el diseño de los programas de tratamiento futuros.

References


Policy & practice

Future regimens for multidrug-resistant tuberculosis