Tuberculosis 5

Global tuberculosis drug development pipeline: the need and the reality

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Drugs for tuberculosis are inadequate to address the many inherent and emerging challenges of treatment. In the past decade, ten compounds have progressed into the clinical development pipeline, including six new compounds specifically developed for tuberculosis. Despite this progress, the global drug pipeline for tuberculosis is still insufficient to address the unmet needs of treatment. Additional and sustainable efforts, and funding are needed to further improve the pipeline. The key challenges in the development of new treatments are the needs for novel drug combinations, new trial designs, studies in paediatric populations, increased clinical trial capacity, clear regulatory guidelines, and biomarkers for prediction of long-term outcome. Despite substantial progress in efforts to control tuberculosis, the global burden of this disease remains high. To eliminate tuberculosis as a public health concern by 2050, all responsible parties need to work together to strengthen the global antituberculosis drug pipeline and support the development of new antituberculosis drug regimens.

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This is the fifth in a Series of eight papers about tuberculosis

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Introduction

Rifampicin, discovered 40 years ago, represents the last novel class of antibiotics introduced for the first-line treatment of tuberculosis. Drugs in this class are part of a 6-month, regimen that is ineffective against multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis, and are difficult to use with many antiretroviral drugs. Ten compounds have progressed to the clinical development pipeline for the treatment of tuberculosis. These compounds, if properly developed, have the potential to become part of a future regimen that could greatly affect the global tuberculosis control effort. The potential benefits of new drugs in development were investigated in a modelling study.[1] The results of this study suggest that the combination of a 2-month treatment regimen that cures 95% of MDR tuberculosis, a generalised nucleic acid amplification test, and a joint pre-exposure and post-exposure vaccine could potentially reduce the incidence of this disease by 71% by 2050.[1] The combination of preventive treatment for latent tuberculosis infection and a 2-month drug regimen might reduce incidence by 94%.[1]

In this review, we discuss the unmet needs in the treatment of tuberculosis, the global pipeline of new compounds that are in clinical development, and draw attention to the challenges in drug research and development. Issues associated with vaccines and diagnostic tests are reviewed in other reports in *The Lancet* Series about tuberculosis.[2,3]

Search strategy and selection criteria

The databases we searched included PubMed, Medline, SciFinder, and Cochrane Library. We mainly focused on papers published during the past 5 years in peer-reviewed journals. Some older papers were also included if they were judged to be important by the authors. Search terms included "tuberculosis", "multidrug-resistant tuberculosis", "latent tuberculosis infection", "tuberculosis and human immunodeficiency virus", "paediatric tuberculosis", "tuberculosis therapy", "tuberculosis regimen", "new tuberculosis drug", "tuberculosis drug development", "tuberculosis drug clinical trial", "novel regimen for tuberculosis", "fluoroquinolone", "nitroimidazole", "diarylquinoline", "rifamycin", "oxazolidinone", "ethylenediamine", "moxifloxacin", "gatifloxacin", "PA-824", "OPC-67683", "TMC-207", "rifapentine", "linezolid", "PNU-100480", "SQ-109", and "LL-3858". There were no language restrictions. Reviewers suggested several references. Additional information was obtained from our personal collections of peer-reviewed papers.

Key messages

- Drugs for tuberculosis are inadequate to address the many inherent and emerging challenges of treatment. Development of new technology for biomedical intervention should be a top priority of the global tuberculosis control and elimination agenda.
- Substantial progress has been made in development of new drugs during the past decade, with ten compounds progressing through the clinical development pipeline, including six new compounds specifically developed for tuberculosis.
- Despite this progress, the global tuberculosis drug pipeline is insufficient to address the unmet needs for treatment. Additional and sustainable funding is needed to further improve the pipeline.
- The main challenges in the development of new treatments are the needs for novel drug regimens, new trial designs, studies in paediatric populations, increased clinical trial capacity, clear regulatory guidelines, and biomarkers for prediction of the long-term outcome.
- Despite substantial progress in efforts to control spread of tuberculosis, the disease burden remains high globally. To eliminate tuberculosis as a public health concern by 2050, all responsible parties need to work together to support the development of new regimens for treatment of tuberculosis.

Panel 1: **Bactericidal and sterilising activities and the role of antituberculosis drugs**

Bactericidal activity indicates the rapid killing of metabolically active microorganisms, and affects the degree to which the drug will prevent transmission of *Mycobacterium tuberculosis* infection and prevent development of resistance to co-administered drugs. Sterilising activity is the ability of a drug to kill all viable microorganisms, including those tolerant to drug treatment; a good sterilising drug will have potential for shortening treatment.

Grosset and Mitchison postulated that some drugs (eg, isoniazid) have excellent bactericidal activity but poor sterilising activity, whereas others (eg, rifampicin) are less bactericidal but possess potent sterilising activity. Any future treatment regimen should consist of bactericidal and sterilising drugs for shortening treatment, and preventing the development of drug resistance.[4–6]

Present treatment and unmet needs

First-line treatment

Standardised short-course chemotherapy—rifampicin and isoniazid for 6 months, supplemented with pyrazinamide and ethambutol in the first 2 months—is effective against drug-susceptible tuberculosis under controlled conditions (panel 1). However, its effectiveness is compromised by the long treatment, which necessitates structured programmes to improve adherence. Although rates of treatment-limiting side-effects vary, mild adverse effects are common.[7] The potential for drug–drug interactions is high, largely due to the induction of the cytochrome P450 system, mediated through the activation of the pregnane-X receptor by rifampicin, which increases oral clearance of concomitant medications.[8] Intermittent dosing, reduced rifampicin exposure, low drug concentrations, poor adherence to treatment, advanced disease, and immunosuppression predispose patients to disease relapse[9,10] and development of drug resistance.[11] The limitations of control programmes are most evident in settings that are frequently characterised by poverty, high levels of HIV co-infection, and poor access to a high standard of treatment.[10,12] Short and simple regimens that are effective, safe, and robust during routine programmatic conditions are urgently needed.

Second-line treatment

MDR tuberculosis has become increasingly prevalent, and the XDR form is emerging.[13] Combinations of first-line and second-line drugs are used for the treatment of MDR and XDR tuberculosis according to results of drug-susceptibility testing. Second-line drugs include aminoglycosides (kanamycin and amikacin), cycloserine, terizidone, ethionamide, protionamide, capreomycin, aminosalicylic acid, and fluoroquinolones (including ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin). Treatment regimens for MDR and XDR tuberculosis are longer, less effective, less tolerable, and more expensive than is standardised short-course chemotherapy, and include the use of injectable drugs. The percentage of patients with MDR tuberculosis who are cured is estimated to be no more than 69% on the basis of results from retrospective cohort studies, even when treated for more than 18 months with directly observed treatment.[14] Toxicity frequently leads to drug discontinuation,[15] and mortality in patients with HIV infection is particularly high.[16–18] In 2008, only about 1% of cases of MDR tuberculosis were estimated to have received proper treatment according to WHO's recommended standards.[19] Containment of the spread of the MDR and XDR tuberculosis will be extremely difficult without treatment regimens that are shorter, safer, more effective, and less expensive than are those that are available. New drugs with novel mechanisms of action are needed for the effective management of MDR and XDR tuberculosis.

Treatment of tuberculosis and HIV co-infection

Mycobacterium tuberculosis and HIV co-infection is a major challenge in the control of tuberculosis since HIV infection increases the risk of developing active tuberculosis. Interaction between standardised short-course chemotherapy and antiretroviral drugs when administered together is a serious concern. Under-resourced health systems are not sufficiently equipped to provide the complex individualised care required for patients with *M tuberculosis* and HIV co-infection.[20] Efavirenz-based HIV regimens are compatible with the standardised short-course treatment for tuberculosis; and in patients with contraindications to efavirenz, standard twice-daily doses of nevirapine provide acceptable efficacy and safety.[21,22] However, treatment for co-infected patients taking protease inhibitor-based regimens is complicated. Rifampicin increases the expression of CYP3A4 and p-glycoprotein, thus rendering the concentrations of protease inhibitors ineffective.[23,24] Superboosted protease inhibitors (ie, addition of ritonavir to counteract the effect of rifampicin) are poorly tolerated and can cause hepatotoxicity.[25,26] Rifabutin, an alternative rifamycin, has less effect on concentrations of protease inhibitors than does rifampicin, but a safe and effective standardised dose when used with protease inhibitors has not yet been defined,[27] and suitable paediatric formulations are not available. New antituberculosis drugs that do not interact with protease inhibitor-based treatments are needed for the effective treatment of the co-infected population.

Treatment of latent infection

About a third of the world's population is infected with *M tuberculosis* and serves as a reservoir for active tuberculosis (panel 2). The spread of HIV infection in many parts of the world further helps the tuberculosis epidemic. The objective of treatment of latent tuberculosis

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Panel 2: Latent tuberculosis infection and chemotherapeutic strategy

Latent tuberculosis infection arises when an individual is infected with *Mycobacterium tuberculosis*, the causative pathogen of tuberculosis, but does not have active disease. Understanding the physical location and physiological state of *M tuberculosis* in latent disease is important because it could suggest potential chemotherapeutic strategies to eradicate such infections. One hypothesis is that *M tuberculosis* persists in a lazy state within granulomatous lesions, but periodically recrudesces; another hypothesis suggests that the bacterium persisting in a dormant state resides within alveolar epithelial cells in the lung apices and adipocytes.[28,29] The exact physical state of *M tuberculosis* in latent infection is still not clear. Isoniazid, a bactericidal drug that is supposedly active only against replicating microorganisms, has been used successfully for the treatment of latent tuberculosis infection, suggesting that at least sporadic recrudescence occurs. Some new drug candidates that are in development, such as TMC-207 and PA-824, are active against *M tuberculosis* in the non-replicating state and might be effective for the treatment of latent infection.

infection is to prevent the development of active disease in high-risk populations, such as people who have had recent contact with a person with infectious tuberculosis, or individuals who are HIV-positive. Isoniazid monotherapy has long been recommended for the treatment of latent tuberculosis infection,[30] and can reduce the risk of disease in people who have had contact with someone with active tuberculosis when taken for 6–9 months. Results of a meta-analysis showed that isoniazid monotherapy reduced the risk of tuberculosis by about 60% in individuals who were HIV positive.[31] Rifampicin-based regimens of 3 months or 4 months, with or without isoniazid, have been reported to be effective in the treatment of latent tuberculosis infection.[32–34] Further studies are needed to address the efficacy, cost-effectiveness, optimum duration, and potential long-term adverse events of tuberculosis prophylaxis. Shorter and safer treatments, than are available, are needed for latent tuberculosis infection.

Treatment of paediatric infection

Children account for up to 20% of incident cases of tuberculosis in high-burden settings[35,36] and have a higher risk than do adults of developing severe and rapidly progressive forms of the disease, such as disseminated disease and meningitis.[37,38] However, the study of antituberculosis treatment in children is difficult.[39] Evidence to support dosing recommendations in children is inadequate, and results from studies suggest that internationally recommended doses of first-line drugs result in suboptimum drug exposure;[40] and there is even less information available to guide the use of second-line drugs. Uncertainties about the safety of ethambutol and fluoroquinolones in children also restrict their use. Development of paediatric drug formulations to suit high-burden settings, and specific studies for investigation of the appropriate dosing and safety in children are important.

Drugs in clinical development

Important attributes of new drugs

Drug combinations are needed to eradicate various bacterial subpopulations and prevent the development of resistance. The contribution of a particular drug in a regimen can be altered substantially by the other drugs in the regimen, which makes the extrapolation of data for safety and efficacy for that drug from one regimen to another unreliable. Nevertheless, drugs are essential components of regimens, and high-quality drug candidates are needed before a substantially improved regimen can be identified and developed. Table 1 summarises some of the most important attributes that a new drug must have to contribute to a future regimen.

Ten compounds are in clinical development for tuberculosis—four existing drugs that are redeveloped or repurposed for tuberculosis and six new chemical compounds that are specifically developed for tuberculosis (figure 1). LL-3858, another antituberculosis compound, was first reported in a scientific meeting in 2004, but no peer-reviewed publications were available since the initial report to assess its status and potential; therefore, LL-3858 is not included in this review.

Fluoroquinolones

Fluoroquinolones are broad-spectrum antimicrobial drugs that target DNA gyrase.[41] Several members of this class have been used as second-line drugs for the treatment of MDR tuberculosis.[42] Gatifloxacin and moxifloxacin, the most recently developed fluoroquinolones, have shown better in-vitro activity against *M tuberculosis* than have ofloxacin and ciprofloxacin, the older fluoroquinolones.[43] According to results from a mouse model of tuberculosis infection, moxifloxacin-containing regimens have the potential to shorten treatment of drug-susceptible tuberculosis from 6 months to 4 months.[44] Rates of 2-month sputum culture conversion seemed better in phase 2 trials in which gatifloxacin or moxifloxacin was substituted for ethambutol or isoniazid in the control regimen (table 2).[45–48] Phase 3 trials are in progress for investigation of whether treatment of drug-susceptible tuberculosis can be shortened to 4 months by substitution of gatifloxacin for ethambutol, or moxifloxacin for ethambutol or isoniazid.

Nitroimidazoles

Nitroimidazoles are antimycobacterial compounds that are equally active against drug-susceptible and drug-resistant tuberculosis.[49] These compounds exert their antimycobacterial activity through bioreduction of the nitroimidazole pharmacophore that is mediated by two deazaflavin-dependent enzymes.[50] Reactive chemical

	Desired attributes	Therapeutic objectives
Mechanism of action	Novel mode of action	Active against MDR and XDR tuberculosis
Potency and efficacy	Active against both replicating and non-replicating *Mycobacterium tuberculosis*	Shorten treatment; effective against latent infection, and prevent development of resistance to co-administered drugs
Drug–drug interaction	Reduced interaction with P450 enzymes	Co-administration with antiretroviral drugs
Pharmacokinetics	Orally bioavailable, acceptable pharmacokinetic and pharmacodynamic profiles	Suitable for oral, once daily or less frequent administration
Safety and tolerability	Improved safety and tolerability profiles	Acceptable for treatment of drug-susceptible and drug-resistant tuberculosis, including acceptability for treatment of children and pregnant women
Cost	Low cost	Ensure affordability

MDR=multidrug-resistant. XDR=extensively drug-resistant.

Table 1: **Important attributes that new tuberculosis drug candidates should have and their therapeutic objectives**

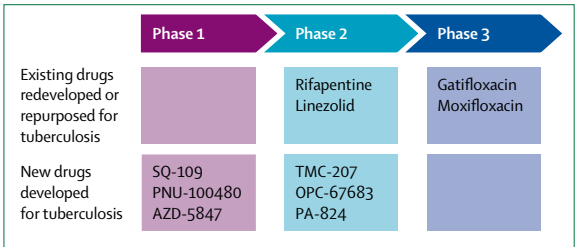

Figure 1: **Compounds in clinical development for the treatment of active tuberculosis**

species generated through the bioreduction are presumed to be responsible for the bactericidal activity. Nitroimidazoles are active against replicating and non-replicating bacteria, indicating their potential in shortening treatment for active disease, and in the management of latent infection. In mice, nitroimidazoles show bactericidal activity during both the initial intensive phase and the continuation phase of treatment. The compounds are effective against *M tuberculosis* that persists throughout the initial 2-month intensive treatment with rifampicin, isoniazid, and pyrazinamide.[51,52]

Two nitroimidazoles are in clinical development. PA-824 is a member of the nitroimidazo-oxazine family. Phase 1 trials and a study to assess the early bactericidal activity in drug-sensitive, smear-positive, adult patients with pulmonary tuberculosis have been completed in South Africa.[53,54] PA-824 was efficacious at 200 mg per day, 600 mg per day, 1000 mg per day, or 1200 mg per day for 14 days (data from TB Alliance). The four doses resulted in essentially equivalent early bactericidal activity, with a steady reduction in the number of viable bacteria in the sputum (about 0·1 log decline in colony-forming units per day for 14 days). The results of this study suggest that the maximum efficacy of PA-824 might be achieved at a dose lower than 200 mg per day; an additional study at lower doses is in progress.

For more on data from **TB Alliance** see http://www.tballiance.org

OPC-67683 is a member of the nitroimidazo-oxazole family.[55] Phase 1 and early bactericidal activity studies have been completed, and the compound is being assessed in a phase 2 trial for the treatment of MDR tuberculosis.

Diarylquinoline

TMC-207, an ATP synthase inhibitor, was discovered from high-throughput screening against *Mycobacterium smegmatis*.[56] It is highly potent against drug-susceptible and drug-resistant strains of *M tuberculosis*. In a mouse model of established infection, the combination of TMC-207, rifapentine, and pyrazinamide given once a week was much more efficacious than was the standard regimen of isoniazid, rifampicin, and pyrazinamide given five times per week, and was more active than TMC-207 was alone or in other combinations.[57] Compared with isoniazid or rifampicin, TMC-207 showed no early bactericidal activity for at least the first 4 days, but showed similar activity to rifampicin or isoniazid from 5–7 days when administered at 400 mg per day.[58] This delayed onset of activity could be explained by the time requirement for depleting ATP stocks, and drug accumulation because of the long terminal half-life of TMC-207.

The safety, tolerability, and efficacy of TMC-207 when added to individualised treatment for newly diagnosed MDR tuberculosis are being investigated in a phase 2 placebo-controlled, double-blind, randomised trial.[59] Results from the initial 2-month treatment phase show that the addition of TMC-207, compared with placebo, to standard treatment for MDR tuberculosis significantly reduced the time to conversion to a negative sputum culture (p=0·003), and increased the proportion of patients with conversion of sputum culture (48% *vs* 9%) after 2 months of treatment.[59] These results validate ATP synthase as a viable drug target for the treatment of tuberculosis, and its potential role in shortening treatment, and in the management of MDR tuberculosis. The second stage of the study is in progress to assess the microbiological outcome of the addition of TMC-207 to the first 6 months of individualised treatment for MDR tuberculosis.

Rifamycins

Rifamycins are potent inhibitors of bacterial RNA polymerase.[60] Three semisynthetic rifamycins—rifampicin, rifapentine, and rifabutin—have been introduced for the treatment of various microbial infections. Rifampicin is the key component of the first-line treatment for tuberculosis.

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	Trial design	Regimens	Primary endpoint	Patients (n)	Results
OFLOTUB[45]	Fluoroquinolone (ofloxacin, gatifloxacin, or moxifloxacin) replaced ethambutol; open-label RCT	Rifampicin, isoniazid, pyrazinamide, and ethambutol* or a fluoroquinolone (ofloxacin, gatifloxacin, or moxifloxacin)	Serial sputum colony counts during the first 8 weeks	217	Moxifloxacin substitution seemed better during the early phase of a biexponential fall in colony counts, but significant and similar acceleration of bacillary elimination during the late phase occurred with gatifloxacin and moxifloxacin (p=0·002); substitution of ofloxacin had no effect
JHU[46]	Moxifloxacin replaced ethambutol; double-blind RCT	Rifampicin, isoniazid, pyrazinamide, and ethambutol* or moxifloxacin	Sputum culture conversion by week 8	170	Culture conversion to negative in 59 (80%) of 74 patients in moxifloxacin group versus 45 (63%) of 72 in ethambutol group (difference 17·2%, 95% CI 2·8–31·7; p=0·03)
TBTC27[47]	Moxifloxacin replaced ethambutol; double-blind RCT	Rifampicin, isoniazid, pyrazinamide, and ethambutol* or moxifloxacin	Sputum culture conversion by month 2	336	Culture conversion to negative in 99 (71%) of 139 patients in moxifloxacin group versus 98 (71%) of 138 in ethambutol group (p=0·97); more patients in the moxifloxacin group had negative cultures than did those in the ethambutol group after 4 weeks of treatment
TBTC28[48]	Moxifloxacin replaced isoniazid; double-blind RCT	Rifampicin, moxifloxacin (or isoniazid*), pyrazinamide, and ethambutol	Sputum culture conversion by week 8	433	Culture conversion to negative in 90 (54·9%) of 164 participants in isoniazid group versus 99 (60·4%) in moxifloxacin group (p=0·37); substitution of moxifloxacin for isoniazid resulted in a small but non-significant increase in culture negativity at 8 weeks

RCT=randomised controlled trial. *Control group.

Table 2: **Summary of phase 2b studies done to assess safety and efficacy of fluoroquinolone-containing regimens**

Increased exposure to rifampicin leads to improved bactericidal activity in mice[61] and in human beings,[62] and the use of high doses for drug-susceptible tuberculosis might shorten treatment to 3 months.[63] Rifapentine, a more potent analogue with a longer half-life than has rifampicin, is an attractive candidate for shortening treatment, and for intermittent treatment.[64,65] However, as with rifampicin, rifapentine induces the expression of P450 enzymes.[66] A combination of rifapentine (600 mg) and isoniazid (900 mg) once a week in the continuation phase of treatment compared with rifampicin (600 mg) and isoniazid (900 mg) twice a week seems suboptimum, especially in patients with advanced disease or HIV co-infection who are at high risk of acquiring rifamycin resistance.[67,68] Crude rates of failure or relapse were 9·2% in individuals given rifapentine once a week versus 5·6% in those given rifampicin twice a week (p=0·04).[68] Clinical studies are in progress to assess the effects of high doses of rifapentine once or twice per week given with moxifloxacin and daily rifapentine in the first-line regimen to shorten treatment.

Oxazolidinones

Oxazolidinones exert their antimicrobial activity by inhibiting protein synthesis by binding to the 70S ribosomal initiation complex.[60] These compounds have a broad spectrum of activity against anaerobic and gram-positive aerobic bacteria, and mycobacteria.[69] Linezolid, the only approved drug in the class, has low in-vitro activity against *M tuberculosis*. Although linezolid has been used off-label in combination regimens for the treatment of MDR tuberculosis, its contribution to such combinations is unclear. Linezolid showed weak early bactericidal activity against *M tuberculosis* in patients with cavitary pulmonary tuberculosis.[70] Long-term use of linezolid has been associated with cumulative toxicity, including peripheral and optic neuropathy.[71]

PNU-100480 is an analogue of linezolid that is being developed for tuberculosis. It showed slightly better activity against *M tuberculosis* in vitro than did linezolid, but substantially improved activity in mouse models of tuberculosis.[72] A combination regimen of PNU-100480, moxifloxacin, and pyrazinamide was more active than was the standard regimen of rifampicin, isoniazid, and pyrazinamide. These findings suggest that PNU-100480 has the potential to shorten treatment of drug-susceptible and drug-resistant tuberculosis.[73,74] Phase 1 clinical trials are in progress.

Ethylenediamines

SQ-109 is a derivative of ethambutol, but seems to differ in its mode of action.[75] It interacts synergistically with isoniazid and rifampicin.[76] In a mouse model of established *M tuberculosis* infection, substitution of SQ-109 for ethambutol in the standard regimen improved activity.[77] The oral bioavailability of SQ-109 in mice, rats, and dogs is low (3·8%, 12·0%, and 2·4–5·0%, respectively), and it is metabolised rapidly by mouse, rat, dog, and human liver microsomes.[78] SQ-109 is in phase 1 clinical trials.

Future challenges

Need for novel regimens

Since the unsuccessful development of streptomycin as a single agent for tuberculosis, the need for multidrug

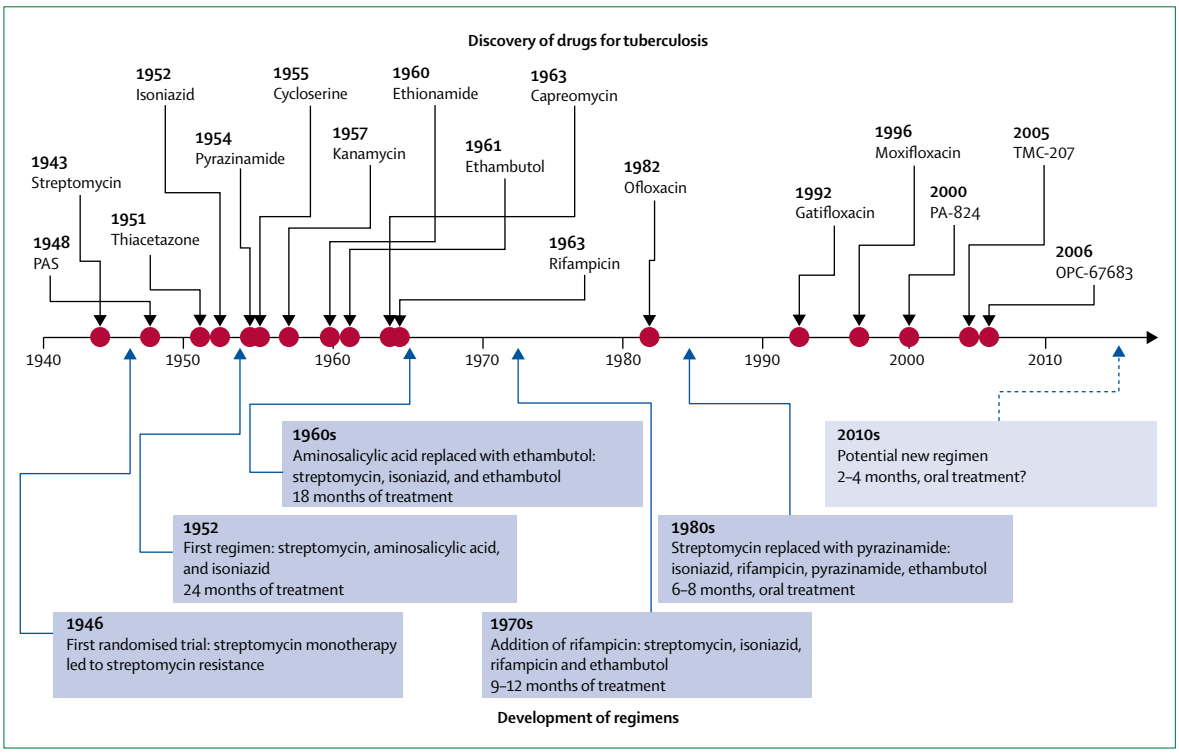

Figure 2: **History of drug discovery and development of treatment regimens for tuberculosis**
Compounds that are in the early-stage of development, but for which there are no human proof-of-concept data, are not shown. Arrow with dashed line represents future regimen. Red dots represent when the drugs were first reported.

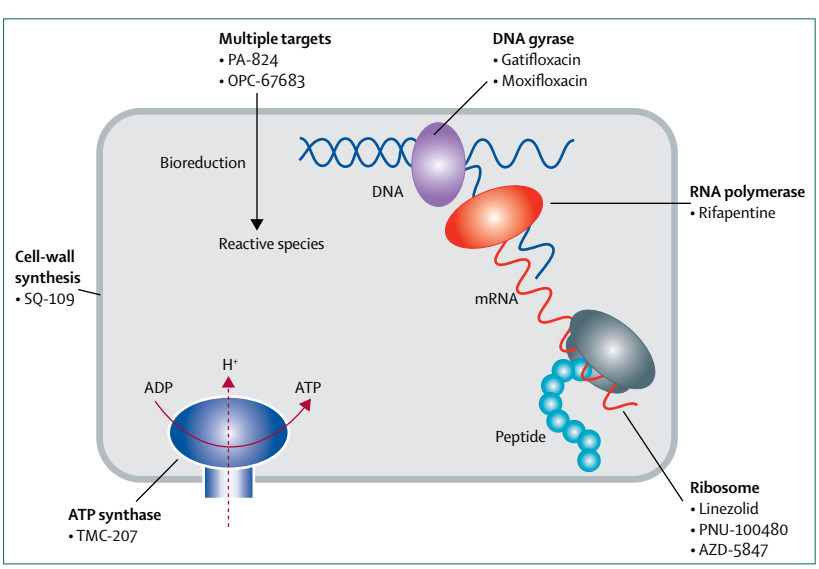

Figure 3: **Mechanisms of action of new compounds in clinical development for tuberculosis**

combinations for the treatment of tuberculosis to prevent the rapid development of drug resistance is widely recognised. Accordingly, the focus of drug development has always been on regimens rather than single drugs.[79] Figure 2 shows some of the major milestones in the discovery and development of drugs and regimens for tuberculosis.

The identification and development of novel drug combinations are essential to address the challenges associated with the present treatments for tuberculosis.[80] An ideal drug combination should consist of at least three drugs that are active against MDR and XDR tuberculosis, and have potent, synergistic, and complementary activities against various subpopulations of *M tuberculosis*. Such a combination should be equally effective against drug-susceptible and drug-resistant tuberculosis, and produce a stable cure in a much shorter period than does the standard treatment. Additionally, such novel combinations should be useful for the treatment of patients with *M tuberculosis* and HIV co-infection because the drug interactions with antiretroviral drugs could be avoided by removal of rifampicin from the regimen.

Several challenges exist in the development of such drug regimens. First, a large number of new drug candidates with novel mechanisms of action need to be available to allow for the selection of optimum regimens. Second, owners of each drug or drug candidate need to work collaboratively and allow their compounds to be developed with other new drugs. Third, regulatory agencies can help by developing clear guidelines to aid the development of new regimens that contain several new chemical compounds. Figure 3 shows the mechanisms of action of compounds that are in development, and table 3 summarises the potential roles of these compounds in a future regimen.

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Global clinical trial capacity

Inadequate global capacity to do controlled clinical trials to support registration of new regimens for treatment of tuberculosis has become increasingly problematic as more drug candidates progress into clinical trials. Development of adequate clinical trial capacity to fully assess even those compounds now in clinical trials will require much capacity-building effort during the next few years.[81] Such efforts necessitate wide investment in knowledge transfer, infrastructure upgrading, and capacity building to increase the number of sites capable of running clinical trials under good clinical and good laboratory practice standards.[82]

Clinical trial designs

The standard clinical development pathway consists of a 7–14-day assessment of the early bactericidal activity for dose finding, followed by an 8-week drug combination study, and eventually phase 3 trials with a long follow-up (generally lasting 12–24 months) for safety and clinical and microbiological cure. Many patients need to be recruited and followed up as part of a non-inferiority trial. This trial design is necessary since, under controlled conditions, the 6-month standard regimen for drug-susceptible tuberculosis is highly efficacious (>95% cure rate). New drugs are unlikely to show better efficacy after 6 months of treatment but improvement could come from shortening or simplifying treatment. Analyses should be done on the intention-to-treat population and on a per-protocol population, and similar positive conclusions are needed from both analyses.[83]

Predictive biomarkers

One of the major challenges for drug development for tuberculosis is the lack of predictive biomarkers.[3] Phase 3 trials are large and lengthy, requiring up to 12–24 months of follow-up after treatment for cure or relapse. A predictive biomarker, like the markers used in trials of HIV/AIDS treatment, to replace the measurement of long-term cure or relapse could greatly reduce the duration and number of patients needed for the trials, and hasten the development of new tuberculosis treatments.[84]

Paediatric-specific studies

Assessment of new treatments for tuberculosis should include children, with and without HIV infection, and the development of child-friendly formulations suitable for high-burden settings. Pharmacokinetic, and safety and tolerability profiles of all new drugs for tuberculosis should be established in paediatric populations, and could be used to develop optimum dosing in children. Technological advances that allow quantification of drug concentrations in low-volume blood samples, simplified sample handling and storage, and the use of sparse sampling with population pharmacokinetics, will assist pharmacokinetic assessment in the relevant paediatric populations. Although definitive assessment of efficacy is limited by the complexities of diagnosis and characterisation of treatment response, standardised methods for microbiological and clinical assessment (such as sputum induction and clinical definitions, respectively) should be used to improve assessment of efficacy as a secondary endpoint.[39]

	Drug target	Potential for treatment of MDR and XDR tuberculosis	Potential in shortening treatment
Moxifloxacin, gatifloxacin	DNA gyrase	Pre-existing resistance in clinical isolates; potential for treatment of MDR tuberculosis, but these drugs are not suitable for treatment of XDR disease; high bactericidal activity should assist the prevention of development of resistance to co-administered drugs	Active against drug-persistent culture in vitro; more effective than standard regimen in animal models and phase 2 trials[44-48]
Rifapentine	RNA polymerase	Cross-resistance with rifampicin; not suitable for the treatment of MDR and XDR tuberculosis	Active against drug-persistent culture in vitro; more effective than standard regimen in animal models[64]
Linezolid, PNU-100480, AZD-5847	Ribosome	Novel mode of action; active against MDR and XDR tuberculosis	Unknown potential
TMC-207	ATP synthase	Novel mode of action; active against MDR and XDR tuberculosis	Highly active against drug-persistent culture in vitro; more effective than standard regimen in animal models;[57] potential for treating latent tuberculosis infection
PA-824, OPC-67683	Many targets	Reductive activation of prodrug; novel mode of action; active against MDR and XDR tuberculosis	Active against drug-persistent culture in vitro; more effective than standard regimen in animal models;[52] potential for treating latent tuberculosis
SQ-109	Unknown (lead compound ethambutol is a cell-wall synthesis inhibitor)	Unknown mechanism of action; potentially active against MDR and XDR tuberculosis	Unknown potential

MDR=multidrug resistant. XDR=extensively drug resistant.

Table 3: **Modes of action and potential roles of new drug candidates in future regimens**

Funding and market incentive issues

As a result of the high attrition rate,[85] the drug pipeline for tuberculosis, without further improvement in the number and quality of compounds, will not be able to produce the number of new drugs needed in the coming years to support the rational selection and development of new drug regimens needed to eradicate tuberculosis. The funding shortfall to support tuberculosis drug research and development is 75%, according to a new report by Médecins Sans Frontières.[86] It is a major challenge to access increased and sustainable funding to bring the next generation of tuberculosis treatments to the patients.

Development of new drugs for tuberculosis is lengthy, expensive, and risky, and the expected revenues are too small to justify commercial investment. There is little market incentive for the private sector to get involved in drug discovery and development activities. New financing and market incentive mechanisms are needed to encourage pharmaceutical and biotechnology companies to invest in drug discovery and development, particularly in late-stage clinical trials. Combined push and pull funding mechanisms, such as multitiered pricing, fast-track options, patent extensions, and free patent pools, should be considered to increase industry investment.

Conclusions

To achieve the goal of elimination of tuberculosis by 2050, all responsible parties need to work together to support the discovery of new drugs and the development of novel regimens for tuberculosis. Governments of developed countries and emerging economies should invest more in drug research and development, and in capacity building to allow for rapid progress in the development of new regimens. Regulatory agencies worldwide could help by developing, streamlining, and harmonising regulatory guidelines to allow for testing of several new drugs in combination, and by addressing other clinical development issues. Pharmaceutical and biotechnology companies could increase their contributions of resources and expertise in tuberculosis drug research and development for the common good. International agencies and communities should come together to develop innovative funding and market incentive mechanisms to promote and support the development and rapid adoption of new regimens. With a joint effort, we have reasons to be optimistic that the challenges of tuberculosis drug research and development are surmountable, and a new revolutionary treatment for tuberculosis will soon become reality.

Contributors

All authors contributed equally to literature search, information analysis, and drafting and reviewing the paper. ZM was responsible for the final editing.

Steering Committee

This review is part of *The Lancet* Series about tuberculosis, which was developed and coordinated by Alimuddin Zumla (University College London Medical School, London, UK), Mario Raviglione (Stop TB Department, WHO, Geneva, Switzerland), and Ben J Marais (University of Stellenbosch, Stellenbosch, South Africa).

Conflicts of interest

We declare that we have no conflicts of interest.

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