



Tuberculosis—advances in development of new drugs, treatment regimens, host-directed therapies, and biomarkers

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Tuberculosis is the leading infectious cause of death worldwide, with 9·6 million cases and 1·5 million deaths reported in 2014. WHO estimates 480 000 cases of these were multidrug resistant (MDR). Less than half of patients who entered into treatment for MDR tuberculosis successfully completed that treatment, mainly due to high mortality and loss to follow-up. These in turn illustrate weaknesses in current treatment regimens and national tuberculosis programmes, coupled with operational treatment challenges. In this Review we provide an update on recent developments in the tuberculosis drug-development pipeline (including new and repurposed antimicrobials and host-directed drugs) as they are applied to new regimens to shorten and improve outcomes of tuberculosis treatment. Several new or repurposed antimicrobial drugs are in advanced trial stages for MDR tuberculosis, and two new antimicrobial drug candidates are in early-stage trials. Several trials to reduce the duration of therapy in MDR and drug-susceptible tuberculosis are ongoing. A wide range of candidate host-directed therapies are being developed to accelerate eradication of infection, prevent new drug resistance, and prevent permanent lung injury. As these drugs have been approved for other clinical indications, they are now ready for repurposing for tuberculosis in phase 2 clinical trials. We assess risks associated with evaluation of new treatment regimens, and highlight opportunities to advance tuberculosis research generally through regulatory innovation in MDR tuberculosis. Progress in tuberculosis-specific biomarkers (including culture conversion, PET and CT imaging, and gene expression profiles) can support this innovation. Several global initiatives now provide unique opportunities to tackle the tuberculosis epidemic through collaborative partnerships between high-income countries and middle-income and low-income countries for clinical trials training and research, allowing funders to coordinate several national and regional programmes for greatest overall effect.

Introduction

WHO estimated that in 2014, 9·6 million people (5·4 million men, 3·2 million women, and 1 million children) fell ill with tuberculosis worldwide.¹ The resulting 1·5 million deaths made tuberculosis the leading infectious cause of death globally.¹ WHO further estimated 480 000 cases (and 190 000 deaths) were multidrug resistant (MDR; defined as resistant at a minimum to rifampicin and isoniazid; figure 1), and only a quarter of these cases were reported. An estimated 9·7% of cases of MDR tuberculosis were extensively drug resistant (XDR; defined as MDR plus additional resistance to at least one fluoroquinolone and one second-line injectable drug), and have been reported in 105 countries.¹ In 2014, MDR tuberculosis accounted for 3·3% of new tuberculosis cases and 20% of previously treated cases.¹ Only half of these patients will successfully complete treatment. Of those patients with outcome data, death (16%), loss to follow-up (16%), and treatment failure (10%) are common¹ due to weaknesses in current regimens, national programmes, and operational challenges. MDR tuberculosis thus constitutes a major threat to global public health security. WHO's 2015 annual tuberculosis report¹ states that “without new tuberculosis drugs and regimens, it will be very difficult to improve treatment outcomes in the near future”, adding “intensified research and development is one of the three pillars of WHO's Post-2015 Global Tuberculosis Strategy, and will play a crucial role in accelerating the

reductions in tuberculosis incidence and mortality required to reach global tuberculosis targets by 2035”.

Many unmet medical needs exist for all forms of tuberculosis (panel). In this Review we describe how these needs can be addressed by recent developments in new and repurposed antimicrobial drugs and host-directed therapies, advances in biomarkers, strategies for regimen development, and opportunities afforded by regulatory innovation.

New and repurposed antimicrobial drugs

Regimens comprising entirely new drugs would be an important therapeutic advance, because they would reduce the present requirement for drug-susceptibility testing, thus simplifying patient care. The current tuberculosis antimicrobial drug pipeline shows eight drugs in phase 2–3 trials (figure 2). Two new drugs (bedaquiline and delamanid) are in confirmatory phase 3 trials, having received accelerated approvals for MDR tuberculosis based on phase 2 data in 2012, and 2014, respectively. However, of the six remaining drugs, only two (sutezolid [an oxazolidinone] and pretomanid [PA-824; a nitroimidazole]) are new compounds. No trials of sutezolid are being done and hepatic safety concerns emerged during the largest trial of pretomanid. Ongoing studies of rifamycins (rifapentine [a long-acting but highly protein-bound rifamycin] and rifampicin) and fluoroquinolones (levofloxacin and moxifloxacin) seek mainly to optimise or define their roles in drug-susceptible

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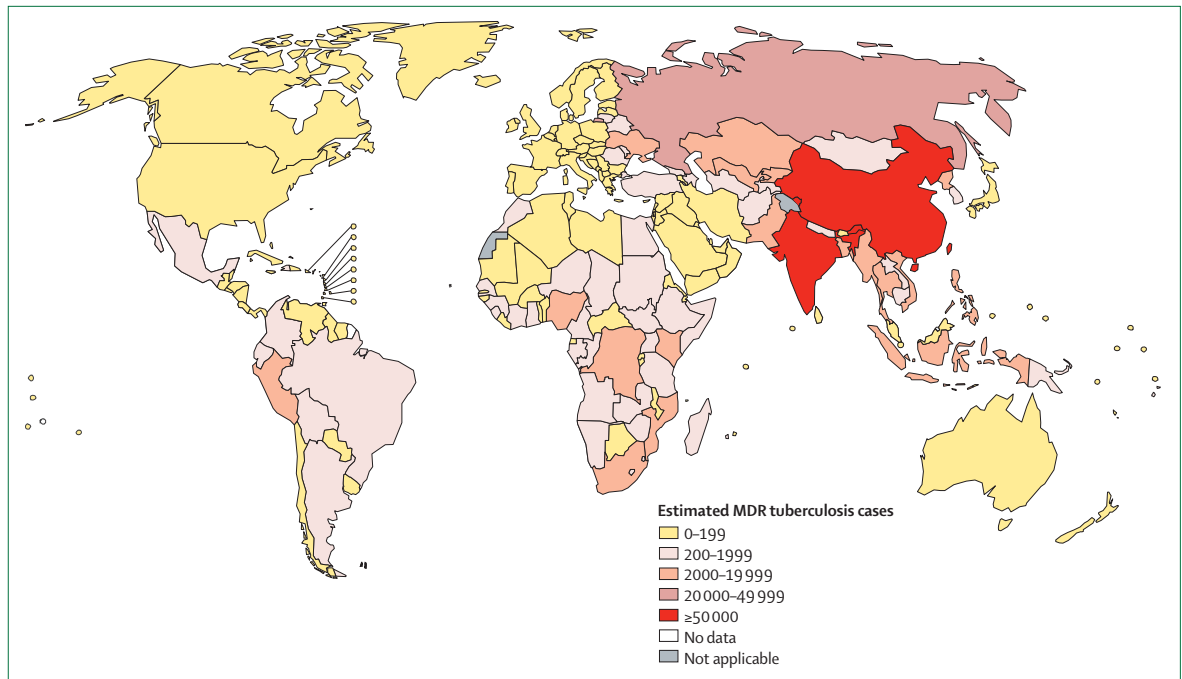


Figure 1: Estimated global distribution of MDR tuberculosis cases in 2014
Figure adapted from and by permission of WHO.¹ MDR=multidrug resistant.

Panel: Unmet medical needs in tuberculosis

- New regimens to shorten treatment duration without increasing the risk of patient relapse. Current targets are less than 6 months for drug-sensitive tuberculosis and less than 12 months for drug-resistant disease. Shorter regimens will improve patient adherence, reduce cumulative drug toxicities, and reduce clinics' workloads.
- Better-tolerated treatments than those available and that can effectively eradicate drug-resistant *Mycobacterium tuberculosis* infection while preventing new resistance and treatment failure. Drugs used for multidrug-resistant (MDR) tuberculosis are poorly tolerated, resulting in reduced patient adherence and increased risk of unsuccessful treatment.
- Treatments to prevent permanent lung injury and functional impairment, which in half of patients results in chronic cough, breathlessness, impaired lung function, and reduced longevity, despite treatment success. These risks seem to be increased in patients with MDR tuberculosis.
- Improved biomarkers to guide patient care and accelerate drug development.
- Improved survival in patients with drug-resistant tuberculosis and HIV co-infection.
- Improved treatments for suspected latent *M tuberculosis* infection, including of drug-resistant strains.

tuberculosis. Only two new compounds have entered phase 1 trials: Q203, a novel ATP synthetase inhibitor (ClinicalTrials.gov NCT02530710), and TBA-354, a

nitroimidazole (NCT02606214). However, as of January, 2016, the only study of TBA-354 had suspended recruitment. So far, studies of SQ109—an asymmetrical diamine—have not shown antituberculosis activity in sputum, alone or in combination with rifampicin over 14 days,² or in either of two rifampicin-containing regimens over 3 months³ (table 1). Additional studies of SQ109 to establish its maximum tolerated dose and to examine pharmacokinetic drug–drug interactions with rifampicin more closely will be needed if SQ109 is to advance further. Thus, the near-term availability of additional drugs representing new antimicrobial drug classes to be combined with bedaquiline and delamanid in entirely new regimens will not be sufficient. As a result, existing antimicrobial drug classes have to be relied on or consider host-directed therapies for development of new tuberculosis regimens.

Oxazolidinones act by binding to 23S RNA, blocking translation and thereby protein synthesis. Their clinical success depends on differential effects on bacteria versus mitochondria. Mitochondrial effects manifest over time as haematological, neurological, and ophthalmological toxicities. A landmark study¹⁴ of linezolid added to an unsuccessful regimen in 39 patients with XDR tuberculosis reported that sputum-culture conversion on solid culture medium occurred in 35% after 2 months, and 87% after 6 months, thus showing the remarkably low frequency of spontaneous oxazolidinone resistance in vitro. However, this study¹⁴ also reported that 82% of patients experienced linezolid toxicity, which led to three permanent discontinuations of treatment. As a result, studies of

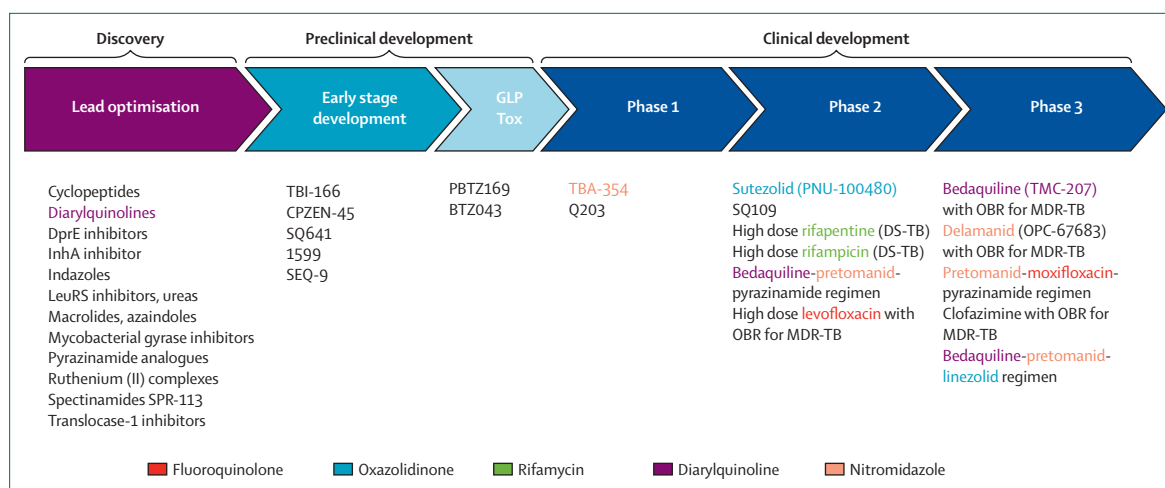


Figure 2: Research and development pipeline for new antituberculosis drugs

Adapted from and by permission of the STOP TB Partnership Working Group on New TB Drugs. GLP tox=good laboratory practice toxicology studies. DS-TB=drug-sensitive tuberculosis. OBR=optimised background regimen. MDR-TB=multidrug-resistant tuberculosis.

For more about the **Stop TB Partnership Working Group on New TB Drugs** see <http://www.newtbdrugs.org/pipeline.php>

| | Patients | Trial design | Key findings |
|--|--|---------------------------------------|--|
| Boeree and Hoelscher (2015) ³ | Drug-sensitive tuberculosis adults (N=296) | Multi-arm phase 2b culture conversion | Substitution of 35 mg/kg for standard dose rifampicin was most active (hazard ratio 1.75), but still yielded 10% of patients positive at week 8; two SQ109 drug regimens did not meet a prespecified target |
| Dorman et al (2015) ⁴ | Drug-sensitive tuberculosis adults (N=334) | Phase 2b culture conversion | Rifapentine of up to 1200 mg once a day in place of rifampicin was deemed safe and well tolerated, decreasing the week 8 positive-patients rate from 18.7% to 10.3% |
| Dawson et al (2015) ⁵ | Drug-sensitive tuberculosis, MDR tuberculosis adults (N=207) | Phase 2b culture conversion | In drug-sensitive tuberculosis, those with culture positive at 8 weeks were 17% for pretomanid 100 mg plus moxifloxacin and pyrazinamide, 5.7% for pretomanid 200 mg plus moxifloxacin and pyrazinamide, and 12.5% in controls; the combination regimen seemed to be less effective in a small number patients with MDR tuberculosis |
| Tang et al (2015) ⁶ | MDR tuberculosis adults (N=105) | Phase 3 | Clofazimine 100 mg once a day accelerated sputum culture conversion and increased number of patients cured; nearly all patients reported skin discolouration or icthyosis |
| Gillespie et al (2014) ⁷ | Drug-sensitive tuberculosis adults (N=1931) | Phase 3 | Substitution of moxifloxacin for isoniazid or ethambutol in regimens lasting 4 months increased relapse rates to 17.8% and 12.5%, respectively, vs 5.2% for standard 6-month treatment |
| Merle et al (2014) ⁸ | Drug-sensitive tuberculosis adults (N=1836) | Phase 3 | Substitution of gatifloxacin for ethambutol in a 4-month regimen increased relapse rates to 15.7% vs 7.8% for standard 6-month treatment |
| Jindani et al (2014) ⁹ | Drug-sensitive tuberculosis adults (N=827) | Phase 3 | Substitution of moxifloxacin for isoniazid in a 4-month regimen with weekly rifapentine plus moxifloxacin in the continuation phase increased relapse rate to 16%; a similar 6-month moxifloxacin regimen had 2.7% relapses vs 3.1% relapses in standard 6-month treatment |
| Pym et al (2015) ¹⁰ | MDR tuberculosis adults (N=205) | Open-label cohort | Bedaquiline was given for 6 months; at 120 weeks, culture conversion rates in patients were 73.1% in those with MDR tuberculosis, 70.5% with pre-XDR tuberculosis, and 62.2% in those with XDR tuberculosis, with 6.9% deaths |
| Piubello et al (2014) ¹¹ | MDR tuberculosis adults (N=65) | Open-label cohort | In patients who previously not received treatment, were given the Bangladesh regimen for 12 months and resulted in 89.2% of patients cured; no relapses were reported 1 year after end-of-treatment |
| Kuaban et al (2015) ¹² | MDR tuberculosis adults (N=150) | Open-label cohort | The Bangladesh regimen was given for 12 months and resulted in 89% cured and 8% deaths; no relapses were reported |
| Kuaban et al (2015) ¹³ | MDR tuberculosis adults (N=408) | Open-label cohort | A Bangladesh-type regimen substituting moxifloxacin for gatifloxacin given for 9 months resulted in 75% converting by month 2 and 82% cured at end-of-treatment |

MDR=multidrug resistant. XDR=extensively drug resistant.

Table 1: Phase 2b and phase 3 clinical trials of new antituberculosis drugs and regimens, 2014–15

linezolid seek to identify doses that minimise toxic effects without compromising efficacy. However, it might be challenging because efficacy and toxicity are due to similar mechanisms (inhibition of protein synthesis) in similar targets (bacteria and mitochondria). Sutezolid is a linezolid analogue with greater antimycobacterial activity than linezolid *in vitro*,¹⁵ in various intracellular and animal models^{16–19} and in *ex-vivo* whole blood cultures.²⁰ Sutezolid is active against non-replicating *Mycobacterium tuberculosis*

in vitro and *in vivo*.²¹ Studies²² using hollow fibre culture models showed more-than-additive effects for combination of this drug with rifamycins. No haematological toxic effects were recorded in phase 1 trials at 600 mg twice a day for 28 days, which is thought to represent reduced inhibition of mitochondrial protein synthesis.^{20,23} Sutezolid dose of 600 mg twice a day and 1200 mg once a day were well tolerated and showed sputum early bactericidal activity (EBA) in patients with tuberculosis of -0.09 log/day

and -0.07 log/day, respectively, over 14 days.²⁴ AZD5847 is the only other oxazolidinone that has been clinically assessed for antimycobacterial activity. In one trial,²⁵ doses from 500 mg once a day up to 800 mg twice a day were studied in 75 patients over 14 days; EBA was -0.04 log/day for 500 mg twice a day dose and -0.02 log/day for those receiving 800 mg twice a day.²⁵ However, 17 severe or life-threatening adverse events, including serious hepatic and haematological toxicities, occurred in patients treated with AZD5847, whereas no adverse events were reported in controls. No further studies are planned.

Rifamycins act by binding *rpoB* and blocking RNA synthesis. The introduction of rifampicin 40 years ago permitted treatment to be shortened from 16 months to 8 months.²⁶ Interest is renewed to assess higher doses than approved. Rifabutin, a rifampicin derivative approved by US Federal Drug Administration (FDA) in 1992 for prevention of disseminated *Mycobacterium avium* infection, is unique among licensed rifamycins in that it seems to be active against MDR tuberculosis strains with *rpoB* mutations at codon 516. These strains remain rifabutin susceptible (minimum inhibitory concentration twice as wild-type) despite rifampicin resistance (minimum inhibitory concentration >ten times that of wild-type).^{27,28} These predominate among MDR isolates in the South African Eastern Cape, and seem to represent a third of South Africa's MDR tuberculosis isolates overall, which can be detected by the B probe of the Cepheid GeneXpert TB-RIF (Cepheid, Sunnyvale, CA, USA). A Cochrane review²⁹ of five trials in 924 patients with drug-sensitive tuberculosis compared rifabutin and rifampicin and reported no differences in rates of treatment success, recurrence, or adverse events.²⁹ Rifabutin has minimal induction of CYP3A4, permitting its use with many rifampicin-incompatible drugs due to its pharmacokinetic drug–drug interactions.

Clofazimine is a fat-soluble rimonophenazine with both antimicrobial^{30,31} and anti-inflammatory³² properties, and is used with rifampicin and dapsone in the treatment of leprosy. A benefit of clofazimine in MDR tuberculosis suggested by uncontrolled trials^{33,34} was supported in a randomised controlled trial⁶ (table 1). Clofazimine shows treatment-shortening activity in Balb/c mice,³⁵ but not in C3HeB/FeJ mice that form necrotic granulomas.³⁶ Concerns regarding skin discolouration (and as a result possible stigmatisation), increased QT, and pharmacokinetic drug–drug interactions will hinder its advance in use for drug-sensitive tuberculosis.

Carbapenems might have a role in MDR tuberculosis regimens, based on in-vitro activity and uncontrolled case reports.^{37–41} Early trials of faropenem (NCT02349841) and meropenem (NCT02393586) are underway. Sulfonamides have also been proposed as antituberculosis drugs based on in-vitro susceptibility, but no prospective trials have yet been done. Several studies of cotrimoxazole prophylaxis in HIV-infected people in Africa reported no effect on tuberculosis incidence.^{42–44}

Host-directed therapeutics to eradicate infection and prevent lung damage

Scientific interest has recently increased in targeting of host factors to identify new treatments for MDR tuberculosis. Host-directed therapies (HDTs)—including new and repurposed drugs, biologics, and cellular therapies—have been proposed to shorten treatment duration, prevent resistance, and reduce lung injury, by promoting autophagy, antimicrobial peptide production, other macrophage effector mechanisms, and inhibiting mechanisms causing lung inflammation and matrix destruction.^{45–47} Lung damage in tuberculosis is pervasive and permanent. Findings from a study⁴⁸ showed that at diagnosis, patients with tuberculosis had lost a third of their expected 1 s forced expiratory volume (FEV1), recovering only a small fraction by the end of treatment. Another study⁴⁹ reported abnormal spirometry in 48 (68%) of 71 patients up to 16 years after being cured of tuberculosis, in relation to radiographical extent of disease and amount of sputum at diagnosis. A study⁵⁰ in 27660 South African gold miners after 5 years noted progressive FEV1 loss with each tuberculosis recurrence. Patients who have previously had tuberculosis are at an increased risk of death due to pneumonia and septicaemia,⁵¹ and have reduced longevity⁵² despite being cured of tuberculosis. Several inflammatory mechanisms contribute to lung destruction in tuberculosis, including local production and activation of matrix metalloproteinases (MMPs) by tumour necrosis factor (TNF).⁵³

Although lung injury has largely not been assessed in modern tuberculosis trials, several trials completed in the 1960s assessed the pulmonary effects of adjunctive corticosteroids. A review⁵⁴ in 1997 concluded that corticosteroids generally hastened resolution of signs and symptoms, but yielded no long-term benefit. Findings from a 2013 meta-analysis⁵⁵ showed corticosteroids reduced tuberculosis mortality, but its interpretations were heavily influenced by studies of CNS disease. A 2014 meta-regression analysis⁵⁶ reported dose-dependent acceleration of sputum-culture conversion by corticosteroids. Several mechanisms have been identified that reduce antimycobacterial drug effects against intracellular bacilli in activated macrophages including impaired lesional drug penetration,⁵⁷ reduced mycobacterial drug uptake,⁵⁸ and enhanced drug efflux.⁵⁹ Additionally, experiments completed in the past year suggest that the low concentrations of nitric oxide produced by macrophages in this setting substantially change bacillary replication, metabolism, and biosynthesis, inducing a state of phenotypic tolerance to currently available tuberculosis drugs (Russell D, Cornell University, personal communication). These mechanisms increase the risk of treatment failure (ie, the inability to eliminate replicating *M tuberculosis* from sputum due to genetic selection of drug-resistant mutants and patient relapse by reducing antituberculosis drug activity),⁶⁰ thereby broadening the possible

objectives for anti-inflammatory host-directed therapies beyond that of lung protection.

The Host-Directed Therapies Consortium Network was launched in April, 2015, with 64 global partners to take forward trials of tuberculosis host-directed therapies. It concluded that several drugs approved for other diseases are ready for clinical assessment in phase 2 trials, including imatinib, metformin, doxycycline, and CC-11050 (Celgene, Summit, NJ, USA).

Imatinib is a tyrosine kinase inhibitor approved for the treatment of chronic myelogenous leukaemia. In *M tuberculosis*-infected mice and macrophages, low doses of imatinib promoted myelopoiesis, phagosome maturation and acidification, and autophagy, thereby reducing bacillary survival.^{61–64} Favourable interactions of imatinib and pyrazinamide are anticipated based on imatinib's mechanism of action (phagosome acidification). Ongoing studies at the Emory University (Atlanta, GA, USA) and the Tulane University (New Orleans, LA, USA) are examining the activity of low dose imatinib added to moxifloxacin, pyrazinamide, and ethambutol in chronically *M tuberculosis*-infected macaques. Imatinib is generally very well tolerated,⁶⁵ especially at the doses anticipated for treatment of human tuberculosis. Imatinib's metabolism is greatly affected by rifampicin because of effects on CYP3A4. As an autophagy inducer, imatinib might have additional anti-inflammatory properties. However, a potential concern regarding neutrophil-induced lung damage makes its initial study, in our opinion, most applicable in patients with MDR tuberculosis, in whom the benefit-to-risk balance is more favourable. Generic forms of this drug became available internationally in 2015.

Metformin is a treatment of choice for diabetes. It was identified as an autophagy inducer in a screen of adenosine monophosphate-activated protein kinase activators that inhibited intracellular growth of *M tuberculosis*.⁶⁶ Subsequent studies⁶⁶ have reported that clinically achieved doses and concentrations of metformin reduced colony-forming unit counts in *M tuberculosis*-infected macrophages in vitro and in acutely infected mice. To assess the potential effect of metformin on human tuberculosis, a study⁶⁶ assessed the records of patients with tuberculosis and diabetes of the Singapore tuberculosis control programme. Singhal and colleagues⁶⁶ showed that those receiving metformin were less likely to have cavitary disease at diagnosis and were less likely to die during the first year after diagnosis.

Doxycycline non-specifically inhibits MMPs at subantimicrobial concentrations. MMPs cause tissue damage through the loss of collagen and other structural proteins; they have been shown in animal models of tuberculosis to play an important part in lung destruction.⁶⁷ An adjunctive role has been proposed for doxycycline on the basis of MMP inhibition in the lung. MMPs and products of collagen turnover can be readily measured in sputum, plasma, and urine.

CC-11050 is a type 4 phosphodiesterase inhibitor and was the backup compound for apremilast (a drug now approved for several anti-inflammatory diseases).^{68,69} Similar to apremilast, CC-11050 inhibits production of several pro-inflammatory cytokines (including TNF) by increasing cellular cyclic AMP. In mice and rabbits chronically infected with *M tuberculosis*, CC-11050 reduces the number and size of lung granulomas and accelerates isoniazid-induced bacillary clearance.^{70–72} As a result, this drug seems to have potential to reduce tuberculosis treatment duration and might reduce permanent lung injury due to tuberculosis.

Advances in tuberculosis biomarkers

Biomarkers are measurable characteristics that can form the basis of surrogate endpoints, thereby accelerating drug development.⁷³ However, progress in tuberculosis biomarkers has been slow.^{74–76} In 2015, a blueprint identified important research steps for advances in this area and emphasised collaboration and harmonisation of efforts.⁷⁷ Four areas of particular interest for new tuberculosis regimens are sputum-culture status, PET, whole-blood bactericidal activity, and gene expression profiles. Sputum-culture status on solid medium after 8 weeks of treatment is the most studied tuberculosis biomarker predictor for treatment failure and relapse (figure 3). An analysis⁷⁸ of 1712 patients with MDR tuberculosis showed culture conversion after 2 months was strongly associated with treatment success versus treatment failure or death (odds ratio 3·6, positive predictive value 80%). Findings from a 2015 study⁶ of clofazimine in 105 patients with MDR tuberculosis supported this conclusion. An analysis of 7793 patients enrolled in a prospective, randomised, clinical trial⁸⁰ identified 2-month culture status and duration as independent predictors of relapse in a simple statistical model. The model was independently validated with data from the eight arms of the REMox,⁷ RIFAQUIN,⁸ and OFLOTUB⁹ trials, showing that noted and predicted relapse rates were highly correlated (R^2 0·86).⁷⁹ A simplified, updated version of the model using the combined dataset of 11 181 patients can be accessed via an online calculator.⁸¹ The model predicts that if a new 4-month regimen reduces the proportion of patients positive on solid culture at month 2 to 1%, it would reduce to a 10% risk of a relapse to more than 10% in a phase 3 trial with 680 participants per group. About 15% are positive at month 2 during standard therapy. The 1% target for a 4-month regimen is far lower than anticipated. Culture status after 8 weeks of treatment is the sole tuberculosis biomarker meeting the regulatory criteria proposed by Chau and colleagues⁸² as “known valid”, based on independent confirmation in several studies.

PET scanning is an emerging technology used to assess the lung in patients with tuberculosis.^{83–85} Positrons emitted by ¹⁸F-fluorodeoxyglucose quickly collide with electrons, yielding two high-energy photons travelling in

For more about the Host-Directed Therapies Tuberculosis Consortium Network see <http://www.unza-uclms.org/hdt-net>

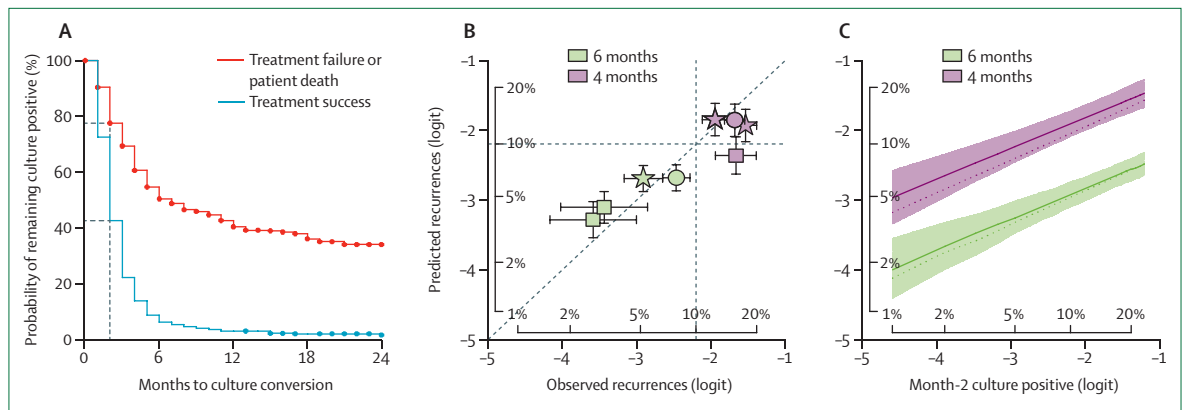


Figure 3: Month-2 sputum culture as a tuberculosis biomarker

(A) Predicted treatment failure and death or treatment success in patients with multidrug-resistant tuberculosis; reproduced from Kurbatova and colleagues,⁷⁸ by permission of Elsevier. (B) Predicted relapse in patients with drug-susceptible tuberculosis; error bars show 80% CI, insets show proportions of patients. (C) Updated model; solid lines are updated model predictions and dotted lines are original model predictions. Parts B and C were reproduced from and by permission of Wallis and colleagues,⁷⁹ under terms of the Creative Commons licence (CC BY).

opposite directions. Detection of these simultaneous events permits accurate three-dimensional localisation of nuclear events. The combination of PET with CT radiograph imaging gives combined information about inflammation and structure. PET with CT combination could be an important non-invasive method to assess disease activity, response to therapy, and risk of relapse. The potential role of PET with CT in the early rapid assessment of new tuberculosis drugs is being evaluated in the NexGen EBA trial (NCT02371681).

Whole-blood bactericidal activity against intracellular *M tuberculosis* is a candidate biomarker for assessment of protective antimycobacterial immunity and chemotherapy.^{86,87} Use of this method during tuberculosis treatment is better in the intensive than the continuation phase, is better for standard versus MDR regimens, and correlates with 2-month culture status.⁸⁸ Measurement of whole-blood bactericidal activity has accelerated the development of sutezolid and bedaquiline.^{19,24,89} Whole-blood bactericidal activity is uniquely suited to assess the combined effects of host-directed chemotherapy and antimicrobial chemotherapy. It is being assessed in the TB-host-directed therapies (not yet registered), TB-SEQUEL (not yet registered), and faropenem (NCT02393586) trials.

Gene expression profiles are technical advances in high-throughput techniques that now help with the investigation of genetic, epigenetic, and proteomic signatures of tuberculosis.⁹⁰ A study⁹¹ prospectively assessed 6363 South African adolescents with latent tuberculosis infection to identify gene signatures predicting progression to active tuberculosis. Two signatures, comprising splice junctions from 16 to 21 signal genes and ten reference genes, showed about 66% sensitivity and 81% specificity for active tuberculosis in the next 12 months.⁹¹ These findings⁹¹ were validated in two independent cohorts that included adults. The signatures, which include interferon module genes and

other markers of lung inflammation, seem to suggest the response to therapy and predict risk of relapse. This signature is being assessed in the TB-HDT trial (table 2).

Shortening of treatment in drug-susceptible tuberculosis

Relapse (the epigenetic persistence and subsequent reactivation of drug-susceptible but phenotypically tolerant, non-replicating bacilli) is the most common adverse clinical outcome in patients with drug-susceptible tuberculosis. The risk of relapse increases as the duration of treatment is reduced.⁸⁰ Identification of shorter regimens that do not unacceptably increase the relapse risk has been a major research focus.

Efforts to shorten treatment have so far been diverse. Some trials have attempted to identify patient characteristics compatible with shorter treatment. One trial⁹³ reported 4 months of standard treatment (2 months of daily isoniazid, rifampicin, ethambutol, and pyrazinamide followed by 2 months of daily isoniazid and rifampicin) yielded an acceptable relapse rate of 7% when restricted to patients without cavitory disease at diagnosis and who had negative sputum cultures at 8 weeks. However, this finding⁹³ will not be applicable for most patients with tuberculosis in whom cavitation is present at diagnosis. As a result, most trials have tested new regimens, including new compounds and approved drugs.

Moxifloxacin and gatifloxacin have been the subject of several phase 2 and 3 treatment-shortening trials. Phase 2 studies of these drugs in drug-susceptible tuberculosis generally showed small incremental benefits on month-2 sputum culture conversion.^{94–98} However, three large, multicentre phase 3 trials (REMOx,⁷ OFLOTUB,⁸ and RIFAQUIN⁹) reported this benefit to be insufficient to support shortening treatment from 6 months to 4 months, because relapse risks increased from less than 5% in the 6-month groups to more than

| | Sponsor; phase | Patients | Trial design | Primary endpoint | Start and expected end date |
|---|-------------------------------------|--|--|--|--|
| Antimicrobials | | | | | |
| STREAM (NCT02409290) | BMRC; phase 3 | MDR tuberculosis adults (N=1155) | A=standard treatment; B=Bangladesh regimen; C=B treatment plus bedaquiline; D=C treatment without kanamycin | Proportion of favourable outcomes at week 76 | July, 2015, to December, 2021 |
| Delamanid (NCT01424670) | Otsuka; phase 3 | MDR tuberculosis adults (N=511) | Bedaquiline vs placebo, both plus standard treatment | Time to sputum culture conversion | September, 2011, to May, 2017 |
| Delamanid (NCT01859923) | Otsuka; phase 2 | MDR tuberculosis (aged 6–17 years; N=36) | Open label extension of NCT01856634 | Safety and pharmacokinetics | August, 2013, to April, 2017 |
| NEXT (NCT02454205) | University of Cape Town; phase 2–3 | MDR tuberculosis adults (N=300) | A=standard treatment; B=linezolid and bedaquiline, plus standard treatment without kanamycin for 9 months | Favourable outcome at 24 months | October, 2015, to January, 2019 |
| Nix-TB (NCT02333799) | TB Alliance; phase 3 | XDR tuberculosis adults (N=200) | Single arm, open-label; bedaquiline, pretomanid, plus linezolid for 6–9 months | Failure or relapse at month 24 | March, 2015, to October, 2021 |
| endTB [®] (not yet registered) | PIH, MSF, and UNITAID; phase 3 | MDR tuberculosis adults (N=600) | Novel regimens including bedaquiline and delamanid | To be decided | December, 2015, to December, 2019 |
| Rifapentine, moxifloxacin (NCT02410772) | CDC; phase 3 | Drug-sensitive tuberculosis adults (N=2500) | A=standard treatment; B=4-month regimen substituting rifapentine for rifampicin; C=treatment B with added moxifloxacin | Tuberculosis disease-free survival 1 year after end-of-treatment | June, 2015, to December, 2019 |
| STAND (NCT02342886) | TB Alliance; phase 3 | Drug-sensitive tuberculosis and MDR tuberculosis adults (N=1500) | A=4 months of pretomanid (100 mg) plus moxifloxacin and pyrazinamide in patients with drug-sensitive tuberculosis; B=treatment A but pretomanid at 200 mg; C=treatment B for 6 months; D=treatment C in patients with MDR tuberculosis | Failure and relapse 12 months after start of therapy | February, 2015, to unknown (currently suspended) |
| NC-005 (NCT02193776) | TB Alliance; phase 2 | Drug-sensitive tuberculosis and MDR tuberculosis adults (N=240) | Drug-sensitive tuberculosis: bedaquiline with or without a loading dose, plus pretomanid and pyrazinamide; MDR tuberculosis: bedaquiline, pretomanid plus pyrazinamide | Sputum colony-forming units over 8 weeks | November, 2014, to February, 2016 |
| TB-PRACTECAL (NCT02589782) | MSF; phase 2/3 | MDR tuberculosis adults (N=630) | Three novel regimens with combinations of bedaquiline, clofazimine, pretomanid, moxifloxacin, and linezolid | Stage 1: culture conversion; stage 2: favourable outcomes | February, 2016, to March, 2020 |
| Lamprene in MDR tuberculosis (CLAM320B2202) | Novartis; phase 2b/3 | MDR tuberculosis adults (N=380) | A=standard treatment plus clofazimine; B=standard treatment | Number of patients cured at 30 months | April, 2016, to April, 2021 |
| Host-directed therapies | | | | | |
| Tuberculosis host-directed therapies (not yet registered) | Aurum; phase 2 | Drug-sensitive tuberculosis adults (N=200) | CC-11050, everolimus, auranofin, vitamin D, all plus rifabutin-substituted standard treatment | Sputum culture conversion | July, 2016, to July, 2018 |
| TB-SEQUEL (not yet registered) | LMU Aurum; phase 2 | Drug-sensitive tuberculosis adults (N=40) | N-acetylcysteine vs placebo both plus standard treatment | Intracellular glutathione concentration | October, 2016, to October, 2017 |
| Preventing tuberculosis IRIS, meloxicam (NCT02060006) | University of Stellenbosch; phase 2 | HIV tuberculosis adults (N=200) | Meloxicam vs placebo both plus standard tuberculosis and HIV treatment | Incidence of tuberculosis IRIS | April, 2014, to April, 2015 |
| Preventing tuberculosis IRIS, prednisone (NCT01924286) | University of Cape Town; phase 2 | HIV tuberculosis adults (N=240) | Prednisone vs placebo both plus standard tuberculosis and HIV treatment | Incidence of tuberculosis IRIS | August, 2013, to August, 2016 |
| MDR=multidrug resistant. BMRC=British Medical Research Council. CDC=US Centers for Disease Control. PIH=Partners in Health. MSF=Médecins Sans Frontières. LMU=Ludwig Maximilian University of Munich. IRIS=immune reconstitution inflammatory syndrome. | | | | | |
| Table 2: Pending phase 2b and 3 clinical trials of antimicrobials and host-directed drugs for tuberculosis | | | | | |

10% in the 4-month groups (table 1). The transition from phase 2 to phase 3 tuberculosis trials requires the use of biomarker endpoints to predict clinical endpoints. With no success from the three phase 3 fluoroquinolone trials,^{7–9} shortening of tuberculosis treatment has stimulated interest in the application of pharmacometrics and mathematical modelling as applied to tuberculosis biomarkers to guide the progression of studies of new regimens.^{79,80}

High doses of rifampicin and rifapentine have also been studied for their use to shorten tuberculosis

treatment. In the PanACEA MAMS-TB-01 trial,³ rifampicin 35 mg/kg per day added to standard doses of isoniazid, pyrazinamide, and ethambutol yielded an improved hazard ratio for stable culture conversion in liquid medium over 12 weeks (hazard ratio 1.75, 95% CI 1.21–2.55) compared with standard doses (table 1). However, the effect on culture status at 8 weeks using solid medium (10% positive vs 15% in controls) is predicted to yield a relapse rate of 13% if administered for only 4 months.^{79,81} In studies of rifapentine the 1200 mg once a day dose proposed for a phase 3 trial

(NCT02410772) also resulted in 10% of patients with positive cultures using solid medium at 8 weeks in a phase 2 trial⁴ (table 1). Regimens yielding 13% of patients with relapse are not likely to be judged acceptable by tuberculosis control programmes.

Pretomanid (formerly known as PA-824), is a nitroimidazole active against both replicating and non-replicating *M tuberculosis*. In aerobic cultures, pretomanid inhibits ketomycolate and cell wall synthesis,⁹⁹ whereas in hypoxic cultures nitroimidazole-derived nitrous oxide poisons the respiratory chain and depletes ATP.¹⁰⁰ The NC-002 phase 2b trial⁵ examined the efficacy of regimens consisting of pretomanid 100 mg or 200 mg once a day, plus moxifloxacin and pyrazinamide. In patients with drug-sensitive tuberculosis, this study⁵ reported culture positive using solid medium after 8 weeks in 17% of patients receiving the 100 mg per day and 5.7% in those receiving 200 mg per day groups, compared with 12.5% of patients receiving standard therapy (table 1). If administered for only 4 months, these drugs are predicted to yield 16% (in those given 100 mg) and 10% (in those given 200 mg) relapses. The trial⁵ also enrolled a small number of patients with MDR tuberculosis treated at the 200 mg dose. Three (37.5%) of eight patients remained culture positive at week 8, a result predicted to yield 10% relapses if administered for 6 months. Nonetheless, on the basis of this study⁵ a phase 3 trial (NCT02342886; STAND) began in 16 countries in February, 2015, under the sponsorship of the TB Alliance (table 2). The phase 3 study has five treatment groups, of which four groups will be tested in 350 patients (per group) with susceptible tuberculosis (two groups with pretomanid plus moxifloxacin and pyrazinamide [at 100 mg and 200 mg pretomanid once a day] for 4 months, one at 200 mg a day for 6 months, and one standard therapy group). The fifth group will be of 350 patients with drug-resistant tuberculosis (to be given 6 months of pretomanid plus moxifloxacin and pyrazinamide [at 200 mg a day]). Enrolment in the trial was suspended in October, 2015, due to serious hepatic safety concerns. In January, 2016, the concerns have not been resolved and the study remains on clinical hold.

The TB Alliance NC-003 trial (NCT01691534) examined the EBA of various combinations of clofazimine, bedaquiline, pretomanid, and pyrazinamide over 14 days in patients with drug-susceptible tuberculosis. The study found that the combination bedaquiline plus pretomanid and pyrazinamide was safe and highly active in sputum after 14 days. This study was followed by a phase 2b trial, TB Alliance NC-005 (NCT02193776) which started in October, 2014 (trial is ongoing; table 2). The study is assessing regimens that include two different doses of bedaquiline plus pretomanid, and pyrazinamide in drug-sensitive tuberculosis, and these drugs in combination with moxifloxacin in MDR tuberculosis. Its main endpoint is the decrease in counts of colony-forming units in 8 weeks. No results are available.

Improvement of outcomes in patients with MDR tuberculosis

By contrast with drug-susceptible tuberculosis, poor outcomes in MDR tuberculosis more often are representative of treatment failure rather than relapse.¹⁰¹ Treatment failure precludes patient relapse.¹⁰² Relapses are less common in MDR tuberculosis than drug-sensitive tuberculosis, even after accounting for this competing endpoint.¹⁰³ However, relapse will likely become more important in MDR tuberculosis trials as more effective regimens are studied and shorter treatment durations are judged.

Delamanid (a nitroimidazole) and bedaquiline (a diarylquinoline inhibitor of ATP synthesis) received accelerated approvals based on small trials showing accelerated sputum culture conversion. Both drugs were compared against placebo when added to a standardised background regimen. For delamanid, doses of 100 mg and 200 mg twice a day decreased rates of positive cultures at month 2 from 67% (placebo) to 45% (100 mg) and 37% (200 mg) on solid culture media.¹⁰⁴ Data from subsequent non-randomised rollover studies¹⁰⁵ suggest patients treated with delamanid for 6 months or more had reduced mortality compared with placebo (1% vs 8%, $p < 0.001$). Bedaquiline showed similar effects to delamanid on culture conversion, reducing the proportion of positive in liquid culture media from 91% to 52%.¹⁰⁶ However, in long-term follow-up, mortality increased in those patients who had previously received bedaquiline (ten of 79 patients) compared with those in the placebo group (two of 81 patients).¹⁰⁶ The long interval between drug exposure and death (nearly 1 year) hindered assessment of causality, even when the long terminal half-life of bedaquiline was considered. The possible mortality imbalance did not preclude accelerated approval, which illustrated the few options and poor outcomes for patients with MDR tuberculosis generally.¹⁰⁷ A 2015 uncontrolled report¹⁰ of bedaquiline in patients with MDR and XDR tuberculosis noted 16 (6.9%) of 233 deaths during follow-up to week 120.¹⁰ For both bedaquiline and delamanid accelerated approval did not remove the requirement to complete conventional phase 3 trials. WHO has issued interim guidance on the use of bedaquiline¹⁰⁸ in 2013 and delamanid¹⁰⁹ in 2014. By January, 2014, 43 countries reported using bedaquiline as part of treatment regimens to treat specific patients with severe forms MDR tuberculosis.¹¹⁰ Uptake of bedaquiline and delamanid have been slowed, however, by scarcity of knowledge as to their optimum use, prompting further studies assessing these drugs as components of new MDR tuberculosis regimens.

A series of MDR tuberculosis regimens studied sequentially in Bangladesh culminated in the report in 2010 that 9 months of treatment with gatifloxacin, clofazimine, ethambutol, and pyrazinamide supplemented by prothionamide, kanamycin, and high-dose isoniazid during an intensive phase of at least 4 months,

yielded relapse-free treatment success in 181 (87.9%) of 206 patients.^{33,34} Two observational studies have since reported high long-term effectiveness of similar 12-month regimens in Cameroon¹¹ and Niger¹² in patients with MDR tuberculosis who had not previously received second-line drugs (table 1). Most recently, findings from a preliminary report¹³ of a 9-month Bangladesh-type regimen (in which moxifloxacin replaced gatifloxacin) noted that 75% of patients had converted to culture negative by month 2, and 82% seemed to be cured at end-of-treatment. The 25% month-2 culture positive rate is likely sufficient to support a 9-month regimen, yielding a predicted relapse rate of 3%. All three studies^{11–13} very likely benefited from the low prevalence of pre-XDR, XDR, and HIV in their study populations. The Bangladesh regimen is being studied in the STREAM trial (NCT02409290),¹¹ with the addition of bedaquiline in some study groups (table 2). A phase 2b/3 randomised controlled trial of clofazimine in MDR tuberculosis is presently being planned by Novartis (Basel, Switzerland; table 2).

An ongoing phase 3 clinical trial (NCT01424670) is assessing delamanid plus an optimised background regimen in MDR tuberculosis, in which delamanid is given for the first 6 months. A 10-day, open-label pharmacokinetic trial (NCT01856634) of delamanid plus optimised background regimen in children with MDR tuberculosis is ongoing. Patients who successfully complete this trial will then be enrolled in a second, open-label study (NCT01859923) to assess the safety, tolerability, pharmacokinetics, and efficacy of delamanid plus optimised background regimen for 6 months. Delamanid and bedaquiline will also both be studied, given separately and in combination, in MDR tuberculosis (ACTG study A5343, NCT02583048) to examine effects on the cardiac conduction QT interval.

Several studies are assessing the possible role of linezolid in phase 3 trials (table 2). The NEXT trial (NCT02454205) is comparing linezolid, bedaquiline, levofloxacin, pyrazinamide, plus ethionamide with standard therapy. NiX-TB (NCT02333799) is a phase 2b, open-label, adaptive design trial that began enrolling patients with XDR tuberculosis at three South African sites in 2015. The study will investigate the safety and efficacy of 6-month regimens that include bedaquiline, pretomanid, and linezolid. The primary endpoint is a composite endpoint of bacteriological or clinical failure and relapse, with follow-up for 24 months after the end of treatment. The phase 3 endTB trial⁹² (not yet registered) will be undertaken by Partners in Health and Médecins Sans Frontières in Georgia, Kazakhstan, Kyrgyzstan, Lesotho, and Peru, with support from UNITAID. It will assess five short oral regimens for MDR tuberculosis, each containing combinations of delamanid or bedaquiline, moxifloxacin or levofloxacin, linezolid and clofazimine, plus pyrazinamide.⁹² Lastly, TB-PRACTECAL (NCT02589782) is a randomised, controlled, open-label,

phase 2/3, adaptive-design trial that is assessing the safety and efficacy of 6-month regimens that contain bedaquiline, pretomanid, and linezolid with or without moxifloxacin or clofazimine, in patients with MDR or XDR tuberculosis. It will be undertaken in Uzbekistan and Swaziland by Médecins Sans Frontières.

Innovative strategies for new drugs, regimens, and research capacity in MDR tuberculosis

These previously stated observations illustrate the challenges faced by tuberculosis drug developers. In drug-sensitive tuberculosis, researchers must contend with a 6-month regimen that is relatively well tolerated and efficacious in trial conditions, even though it has been difficult to implement in real-world settings and yet more difficult to improve. In MDR tuberculosis, researchers must contend with control regimens requiring up to 3 years of treatment and follow-up, consisting of drugs that precede the modern regulatory era, to be tested in a patient population that can be difficult to recruit.

Four factors now create an unprecedented opportunity for the rapid assessment and licensing of improved new MDR tuberculosis regimens in short innovative trials. Three have been previously discussed in this Review: the availability of new antimycobacterial drugs with novel mechanisms of action and improved safety and tolerability; the increasing recognition of the potential role of host-directed therapies; and the validation of sputum-culture conversion as a predictive biomarker for treatment failure and patient relapse. The last, but perhaps most crucial factor is that of regulatory innovation, the creation of the special medical use and adaptive licensing pathways for registration of new treatments for drug-resistant infections based on small clinical trials. These could potentially replace the requirement for conventional phase 3 trials with enhanced post-licensing outcome reporting. The coalescence of these four factors for MDR tuberculosis, and for tuberculosis generally, could be transformative.

Regulatory agencies balance potential risk against benefit as they assess new therapies. An imbalance of these factors 25 years ago in antiretroviral drug development resulted in accelerated approvals (subpart H 21CFR314) by the FDA, and conditional market authorisations (EC507/2006) by the European Medical Agency (EMA). These mechanisms substituted a biomarker (plasma HIV RNA) for a clinical endpoint (survival), thus relieving an ethically unacceptable bottleneck in drug development. We now face a similar crisis for drug-resistant bacterial infections,¹¹² and as a result are at the threshold of further regulatory innovation. New antibacterials are currently tested in large studies of patients who have been readily treated with other drugs, hoping that a small number with highly-resistant infections will enter the new treatment group. The US Presidential Executive Order Combating Antibiotic-Resistant Bacteria¹¹³ and PCAST report¹¹⁴

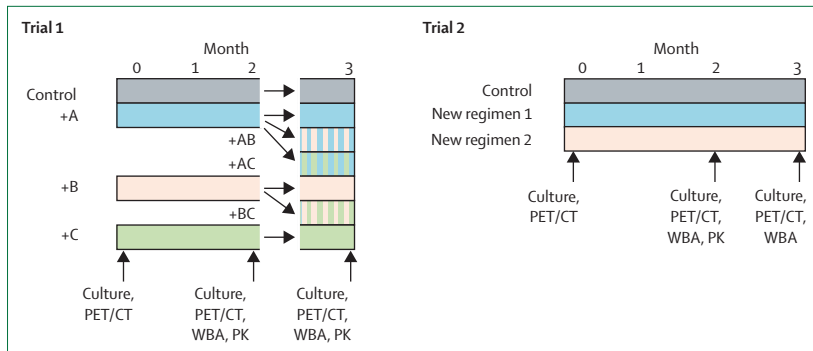


Figure 4: Proposed plan for the development of new MDR tuberculosis regimens, including three new drugs. Figures are based on two 3-month trials, making use of innovative regulatory approval pathways. Patients enrolled in both trials would resume standard treatment after 3 months. A, B, and C represent new drugs. MDR=multidrug-resistant. WBA=whole-blood bactericidal activity. PK=pharmacokinetics. PET/CT= 18 F-FDG and CT imaging.

Search strategy and selection criteria

We restricted our searches to reports published after Jan 1, 1996, in English. We did several searches of PubMed using the search term “tuberculosis” plus “clinical trials”, “biomarkers”, and “drug development”, and individual searches for each of the drugs Q203, SQ109, TBA-354, bedaquiline, delamanid, levofloxacin, moxifloxacin, pretomanid, pyrazinamide, rifapentine, rifampicin, and sutezolid (PNU-100480), and compounds identified by the Stop TB Partnership Working Group for New TB Drugs website. We searched the ClinicalTrials.gov website using the term “tuberculosis” alone, and in combination with each of the drugs identified by previous searches (including drugs Q203, SQ109, TBA-354, bedaquiline, delamanid, levofloxacin, moxifloxacin, pretomanid, pyrazinamide, rifapentine, rifampicin, and sutezolid [PNU-100480]). We contacted Novartis for information regarding their trial of clofazimine. Finally, we searched the UNITAID website using the term “tuberculosis”.

For more on the Stop TB Partnership Working Group for New TB Drugs see <http://www.newtbdrugs.org/>

created a new trials framework (small studies in patients with highly-resistant infections) and a new approval mechanism (eg, special medical use; restricted to specific types of patients with few therapeutic alternatives). The approach is consistent with the 21st century Cures Act¹¹⁵ and the emerging adaptive licensing concept at EMA.¹¹⁶

A clinical strategy to advance tuberculosis research through trials in MDR tuberculosis incorporating these four innovative elements is shown in figure 4. It describes the evaluation as one, and in combination, of three hypothetical candidates. Chances for real-world success might be enhanced by careful selection of these candidates based on preliminary evidence for efficacy, safety, and pharmacokinetic compatibility. Of the drugs we have discussed, sutezolid, rifabutin, imatinib, metformin, doxycycline, and CC-11050 would meet these criteria. These drugs should be prioritised for assessment in future innovative trials.

MDR tuberculosis was unlikely to have the main consideration of legislators when the special medical use pathway (or its equivalent) were first proposed. However, one cannot imagine a better exemplar to test feasibility and its effect. Treatment of MDR tuberculosis offers rapid diagnostics, validated biomarkers, specially trained physicians, dedicated treatment facilities, globally accepted reporting mechanisms, and the normative roles of several international organisations. Opportunities might arise to coordinate such an effort with planned revisions of the MDR tuberculosis recommended drug categories by WHO. Implementation of this concept could remove the requirement to complete large phase 3 trials in hard-to-recruit patient populations, substituting enhanced post-licensing reporting of clinical and safety outcomes.¹⁷ Large risks are deemed acceptable in MDR tuberculosis versus drug-sensitive tuberculosis, due to the greater unmet need and greater potential for patient benefit. Advances in turn can have great effect on patient care, health policy, and capacity strengthening for tuberculosis and infectious diseases generally. Global

initiatives—eg, the second programme of the European and Developing Countries Clinical Trials Partnership,¹¹⁸ the German Ministry for Science and Education, and the US National Institutes of Health—now provide unique opportunities to tackle the tuberculosis epidemic through development of partnerships between high-income countries and middle-income and low-income countries for clinical trials research and training, thus permitting funders to better coordinate national and regional research programmes.

Contributors

RSW and AZ developed the first draft of the manuscript. RSW developed the second draft of the manuscript. All authors reviewed and contributed to revisions and manuscript drafts.

Declaration of interests

We declare no competing interests.

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