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

Robert S Wallis, Markus Maeurer, Peter Mwaba, Jeremiah Chakaya, Roxana Rustomjee, Giovanni Battista Migliori, Ben Marais, Marco Schito, Gavin Churchyard, Soumya Swaminathan, Michael Hoelscher, Alimuddin Zumla

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.

Lancet Infect Dis 2016; 16: e34–46

Aurum Institute, Johannesburg, South Africa (Prof R S Wallis MD, Prof G Churchyard FRCP); **Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, USA** (Prof R S Wallis); **Therapeutic Immunology, Departments of Laboratory Medicine and Microbiology, Tumour and Cell Biology, Karolinska Institute, Stockholm, Sweden** (Prof M Maeurer FRCP); **UNZA-UCLMS Research and Training Project, University Teaching Hospital, Lusaka, Zambia** (P Mwaba FRCP, Prof A Zumla FRCP); **Kenya Medical Research Institute, Nairobi, Kenya** (J Chakaya MD); **Advancing Care for TB/HIV** (Prof R S Wallis), **South African Medical Research Council** (R Rustomjee FRCP), **Cape Town, South Africa; WHO Collaborating Centre for TB and Lung Diseases, Fondazione S Maugeri Care and Research Institute, Tradate, Italy** (Prof G B Migliori FRCP); **Children's Hospital at Westmead and the Centre for Research Excellence in Tuberculosis, University of Sydney, Sydney, NSW, Australia** (Prof B Marais PhD); **Critical Path to TB Drug Regimens, Critical Path Institute, Tucson, AZ, USA** (M Schito PhD); **Department of Infectious Diseases, London School of Hygiene & Tropical Medicine, London, UK** (Prof G Churchyard); **School of Public Health, University of Witwatersrand, Johannesburg, South Africa** (Prof G Churchyard); **National Institute for Research on Tuberculosis, Chennai, India** (S Swaminathan MD); **Division of Infectious Diseases and Tropical Medicine, Medical Centre of the University of Munich, Munich, Germany** (Prof M Hoelscher FRCP); **DZIF German Centre for Infection**

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 common[1] 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 report[1] 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

Research, Munich, Germany (Prof M Hoelscher); **and Centre for Clinical Microbiology, Division of Infection and Immunity, University College London (UCL), London, UK** (Prof A Zumla); **National Institute for Health Research Biomedical Research Centre, UCL Hospitals NHS Foundation Trust, London, UK** (Prof A Zumla)

Correspondence to: Prof Alimuddin Zumla, UCL Division of Infection and Immunity, Centre for Clinical Microbiology Royal Free Hospital, London NW3 2QG, UK **a.i.zumla@gmail.com**

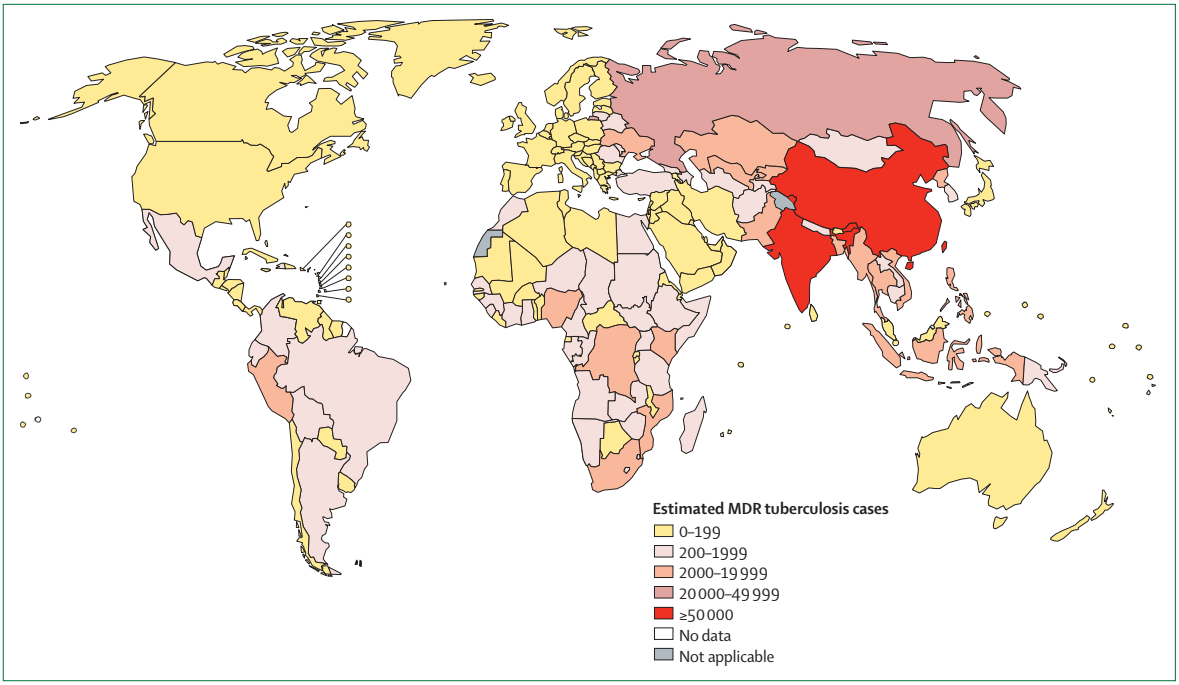

Figure 1: **Estimated global distribution of MDR tuberculosis cases in 2014**
Figure adapted from and by permission of WHO.[1] MDR=multidrug resistant.

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 months[3] (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 study[14] 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 study[14] also reported that 82% of patients experienced linezolid toxicity, which led to three permanent discontinuations of treatment. As a result, studies of

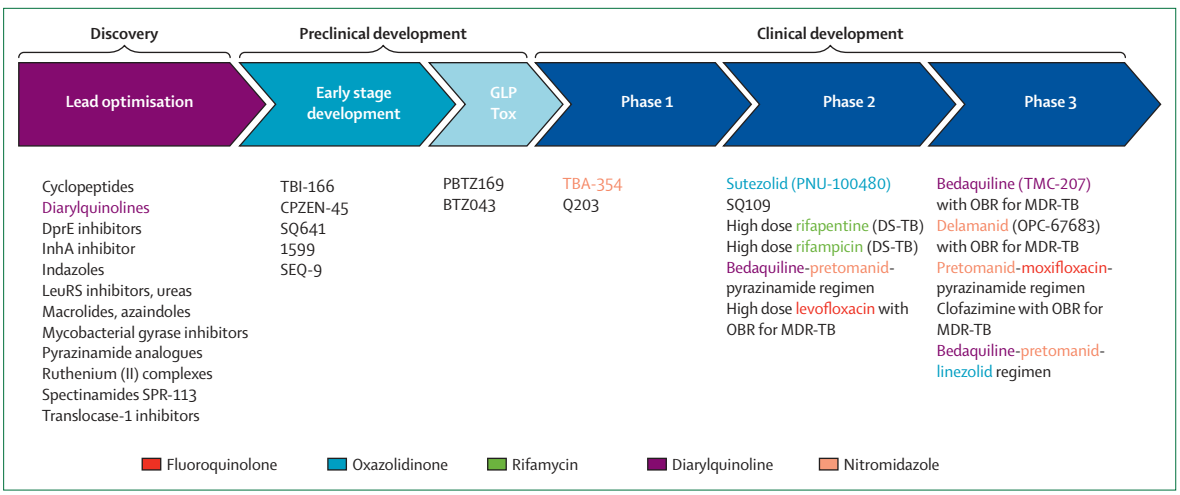

Figure 2: **Research and development pipeline for new antituberculosis drugs**
Adapted from and by permission of the STOP TB Partnership Working Group on New TB Drugs. GLP tox=good laboratory practice toxicology studies. DS-TB=drug-sensitive tuberculosis. OBR=optimised background regimen. MDR-TB=multidrug-resistant 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] Studies[22] 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 review[29] 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 riminophenazine with both antimicrobial[30,31] and anti-inflammatory[32] 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 trial[6] (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 co-trimoxazole 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 study[48] 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 study[49] 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 study[50] in 27 660 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 longevity[52] 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 review[54] in 1997 concluded that corticosteroids generally hastened resolution of signs and symptoms, but yielded no long-term benefit. Findings from a 2013 meta-analysis[55] showed corticosteroids reduced tuberculosis mortality, but its interpretations were heavily influenced by studies of CNS disease. A 2014 meta-regression analysis[56] 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 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 studies[66] 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 study[66] assessed the records of patients with tuberculosis and diabetes of the Singapore tuberculosis control programme. Singhal and colleagues[66] 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 analysis[78] 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 study[6] of clofazimine in 105 patients with MDR tuberculosis supported this conclusion. An analysis of 7793 patients enrolled in a prospective, randomised, clinical trial[80] 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 OFLOTUB[9] 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 colleagues[82] 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 ^{18}F-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

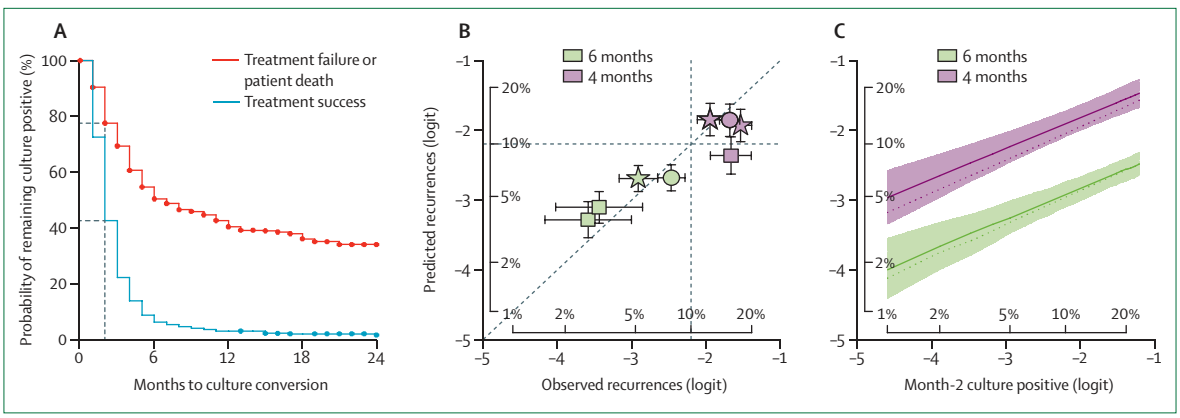

Figure 3: **Month-2 sputum culture as a tuberculosis biomarker**
(A) Predicted treatment failure and death or treatment success in patients with multdrug-resistant tuberculosis; reproduced from Kurbatova and colleagues,[78] by permission of Elsevier. (B) Predicted relapse in patients with drug-sensitive 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 study[91] 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 findings[91] 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-sensitive 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 trial[93] 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 cavitary disease at diagnosis and who had negative sputum cultures at 8 weeks. However, this finding[93] 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-sensitive 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 RIFAQUIN[9]) 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[92] (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 trial[4] (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 trial[5] 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 study[5] 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 trial[5] 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 study[5] 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 studies[105] 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 report[10] 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 bedaquiline[108] in 2013 and delamanid[109] 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 Cameroon[11] and Niger[12] in patients with MDR tuberculosis who had not previously received second-line drugs (table 1). Most recently, findings from a preliminary report[13] 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),[111] 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 trial[92] (not yet registered) will be undertaken by Partners in Health and Médecins Sans Frontierès 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 Bacteria[113] and PCAST report[114]

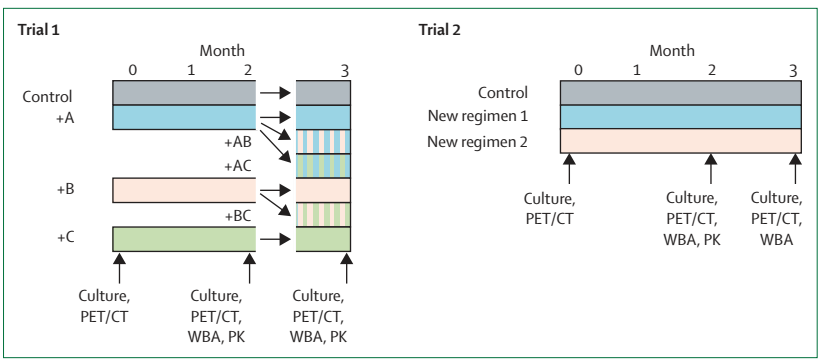

Figure 4: **Proposed plan for the development of new MDR tuberculosis regimens, including three new drugs**
Figures is based on two 3-month trials, making use of innovative regulatory approval pathways. Patients enrolled in both trials would resume standard treatment after 3 months. A, B, and C represent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

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 Act[115] 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.[117] 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.

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".

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.

Acknowledgments
RSW and GC receive support from German Ministry for Science and Education, the Bill & Melinda Gates Foundation, the South Africa Medical Research Council, USAID, and US National Institutes of Health. MM is supported by Vetenskapsradet, Vinnova, and the Heart and Lung Foundation, Sweden. MH is supported by German Ministry for Science and Education grants, European & Developing Countries Clinical Trials Partnership—Pan African Consortium for the Evaluation of Anti-tuberculosis Antibiotics (PanACEA) 2007 32011 013. AZ receives support from the European Union FW7 RiD-RTI Project, European Developing Countries and the National Institute for Health Research Biomedical Research Centre at UCL Hospital (London, UK).

References
1 Anderson L, Dean A, Falzon D, et al. Global tuberculosis report 2015, 20th edition. Geneva: World Health Organization, 2015.
2 Heinrich N, Dawson R, du Bois J, et al. Early phase evaluation of SQ109 alone and in combination with rifampicin in pulmonary TB patients. *J Antimicrob Chemother* 2015; **70:** 1558–66.
3 Boeree MJ, Hoelscher M. High-dose rifampin, SQ109, and moxifloxacin for treating TB: the PanACEA MAMS-TB trial. Conference on Reteroviruses and Opportunistic Infections; Seattle, WA, USA; Feb 23–26, 2015. Session O-7: abstr 95LB.
4 Dorman SE, Savic RM, Goldberg S, et al. Daily rifapentine for treatment of pulmonary tuberculosis. A randomized, dose-ranging trial. *Am J Respir Crit Care Med* 2015; **191:** 333–43.

5 Dawson R, Diacon AH, Everitt D, et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015; **385:** 1738–47.

6 Tang S, Yao L, Hao X, et al. Clofazimine for the treatment of multidrug-resistant tuberculosis: prospective, multicenter, randomized controlled study in China. *Clin Infect Dis* 2015; **60:** 1361–67.

7 Gillespie SH, Crook AM, McHugh TD, et al. Four-month moxifloxacin-based regimens for drug-sensitive tuberculosis. *N Engl J Med* 2014; **371:** 1577–87.

8 Merle CS, Fielding K, Sow OB, et al. A four-month gatifloxacin-containing regimen for treating tuberculosis. *N Engl J Med* 2014; **371:** 1588–98.

9 Jindani A, Harrison TS, Nunn AJ, et al. High-dose rifapentine with moxifloxacin for pulmonary tuberculosis. *N Engl J Med* 2014; **371:** 1599–608.

10 Pym AS, Diacon AH, Tang SJ, et al. Bedaquiline in the treatment of multidrug- and extensively drug-resistant tuberculosis. *Eur Respir J* 2015; **47:** 564–74.

11 Piubello A, Harouna SH, Souleymane MB, et al. High cure rate with standardised short-course multidrug-resistant tuberculosis treatment in Niger: no relapses. *Int J Tuberc Lung Dis* 2014; **18:** 1188–94.

12 Kuaban C, Noeske J, Rieder HL, Ait-Khaled N, Abena Foe JL, Trebucq A. High effectiveness of a 12-month regimen for MDR-TB patients in Cameroon. *Int J Tuberc Lung Dis* 2015; **19:** 517–24.

13 Kuaban C, Kashongwe Z, Bakayoko A, et al. First results with a 9-month regimen for multidrug-resistant tuberculosis (MDR-TB) in francophone Africa. 46th Union World Conference on Lung Health; Cape Town; Dec 2–6, 2015. Session 41.7.

14 Lee M, Lee J, Carroll M, et al. Linezolid for the treatment of chronic extensively drug-resistant tuberculosis. *N Engl J Med* 2012; **367:** 1508–18.

15 Alffenaar JW, van der Laan T, Simons S, et al. Susceptibility of clinical *Mycobacterium tuberculosis* isolates to a potentially less toxic derivate of linezolid, PNU-100480. *Antimicrob Agents Chemother* 2011; **55:** 1287–89.

16 Converse PJ, Lee J, Williams KN, et al. Activity of PNU-100480 and its major metabolite in whole blood and broth culture models of tuberculosis. *Am Soc Microbiol* 2012; **112**: abstr GM-A-2052.

17 Williams KN, Stover CK, Zhu T, et al. Promising anti-tuberculosis activity of the oxazolidinone PNU-100480 relative to linezolid in the murine model. *Antimicrob Agents Chemother* 2009; **53:** 1314–19.

18 Williams KN, Brickner SJ, Stover CK, et al. Addition of PNU-100480 to first-line drugs shortens the time needed to cure murine tuberculosis. *Am J Respir Crit Care Med* 2009; **180:** 371–76.

19 Zhu T, Friedrich SO, Diacon A, Wallis RS. Population pharmacokinetic/pharmacodynamic analysis of the bactericidal activities of sutezolid (pnu-100480) and its major metabolite against intracellular *Mycobacterium tuberculosis* in ex vivo whole-blood cultures of patients with pulmonary tuberculosis. *Antimicrob Agents Chemother* 2014; **58:** 3306–11.

20 Wallis RS, Jakubiec W, Kumar V, et al. Pharmacokinetics and whole blood bactericidal activity against *Mycobacterium tuberculosis* of single ascending doses of PNU-100480 in healthy volunteers. *J Infect Dis* 2010; **202:** 745–51.

21 Zhang M, Sala C, Dhar N, et al. In vitro and in vivo activities of three oxazolidinones against nonreplicating *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2014; **58:** 3217–23.

22 Louie A, Eichas K, Files K, et al. Activities of PNU-100480 (PNU 480) alone, PNU 480 plus its major metabolite PNU-101603 (PNU 1603) and PNU 480 plus PNU 1603 in combination with rifampin (RIF) against *Mycobacterium tuberculosis*: comparison with linezolid. Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, IL; Sept 17–20, 2011. A1–1737.

23 Wallis RS, Jakubiec W, Kumar V, et al. Biomarker assisted dose selection for safety and efficacy in early development of PNU-100480 for tuberculosis. *Antimicrob Agents Chemother* 2011; **55:** 567–74.

24 Wallis RS, Dawson R, Friedrich SO, et al. Mycobactericidal activity of sutezolid (PNU-100480) in sputum (EBA) and blood (WBA) of patients with pulmonary tuberculosis. *PLoS One* 2014; **9:** e94462.

25 Furin JJ, Du Bois J, van Brakel E, et al. Early bactericidal activity of AZD5847 in pulmonary tuberculosis. 46th Union World Conference on Lung Health; Cape Town; Dec 2–6, 2015. Session 41.5.

26 Councils EA-BMR. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis. Second report. *Tubercle* 1980; **61:** 59–69.

27 Sirgel FA, Warren RM, Bottger EC, Klopper M, Victor TC. The rationale for using rifabutin in the treatment of MDR and XDR tuberculosis outbreaks. *PLoS One* 2013; **8:** e59414.

28 ElMaraachli W, Slater M, Berrada ZL, et al. Predicting differential rifamycin resistance in clinical *Mycobacterium tuberculosis* isolates by specific *rpo*B mutations. *Int J Tuberc Lung Dis* 2015; **19:** 1222–26.

29 Davies G, Cerri S, Richeldi L. Rifabutin for treating pulmonary tuberculosis. *Cochrane Database Syst Rev* 2007; **4:** CD005159.

30 Noufflard H, Berteaux S. Antituberculous activity of compound B-663. *Ann Inst Pasteur (Paris)* 1958; **95:** 449–55 (in French).

31 Barry VC, Buggle K, Byrne J, Conalty ML, Winder F. Absorption, distribution and retention of the riminocompounds in the experimental animal. *Ir J Med Sci* 1960; **416:** 345–52.

32 Karat AB, Jeevaratnam A, Karat S, Rao PS. Double-blind controlled clinical trial of clofazimine in reactive phases of lepromatous leprosy. *BMJ* 1970; **1:** 198–200.

33 Van Deun A, Salim MA, Das AP, Bastian I, Portaels F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int J Tuberc Lung Dis* 2004; **8:** 560–67.

34 Van Deun A, Maug AK, Salim MA, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010; **182:** 684–92.

35 Tyagi S, Ammerman NC, Li SY, et al. Clofazimine shortens the duration of the first-line treatment regimen for experimental chemotherapy of tuberculosis. *Proc Natl Acad Sci USA* 2015; **112:** 869–74.

36 Irwin SM, Gruppo V, Brooks E, et al. Limited activity of clofazimine as a single drug in a mouse model of tuberculosis exhibiting caseous necrotic granulomas. *Antimicrob Agents Chemother* 2014; **58:** 4026–34.

37 Esposito S, D'Ambrosio L, Tadolini M, et al. ERS/WHO Tuberculosis Consilium assistance with extensively drug-resistant tuberculosis management in a child: case study of compassionate delamanid use. *Eur Respir J* 2014; **44:** 811–15.

38 De Lorenzo S, Alffenaar JW, Sotgiu G, et al. Efficacy and safety of meropenem-clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB. *Eur Respir J* 2013; **41:** 1386–92.

39 Chambers HF, Turner J, Schecter GF, Kawamura M, Hopewell PC. Imipenem for treatment of tuberculosis in mice and humans. *Antimicrob Agents Chemother* 2005; **49:** 2816–21.

40 Hugonnet JE, Tremblay LW, Boshoff HI, Barry CE 3rd, Blanchard JS. Meropenem-clavulanate is effective against extensively drug-resistant *Mycobacterium tuberculosis*. *Science* 2009; **323:** 1215–18.

41 Hugonnet JE, Blanchard JS. Irreversible inhibition of the *Mycobacterium tuberculosis* β-lactamase by clavulanate. *Biochemistry* 2007; **46:** 11998–2004.

42 Anglaret X, Chêne G, Attia A, et al, and the Cotrimo-CI Study Group. Early chemoprophylaxis with trimethoprim-sulphamethoxazole for HIV-1-infected adults in Abidjan, Côte d'Ivoire: a randomised trial. *Lancet* 1999; **353:** 1463–68.

43 Walker AS, Ford D, Gilks CF, et al. Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort. *Lancet* 2010; **375:** 1278–86.

44 Hoffmann CJ, Chaisson RE, Martinson NA. Cotrimoxazole prophylaxis and tuberculosis risk among people living with HIV. *PLoS One* 2014; **9:** e83750.

45 Zumla A, Maeurer M, Host-Directed Therapies Network, et al. Towards host-directed therapies for tuberculosis. *Nat Rev Drug Discov* 2015; **14:** 511–12.

46 Zumla A, Maeurer M, Host-Directed Therapies Network (HDT-NET) Consortium. Host-directed therapies for tackling multi-drug resistant tuberculosis: learning from the Pasteur-Bechamp debates. *Clin Infect Dis* 2015; **61:** 1432–38.

47 Wallis RS, Hafner R. Advancing host-directed therapy for tuberculosis. *Nat Rev Immunol* 2015; **15:** 255–63.

48 Ralph AP, Kenangalem E, Waramori G, et al. High morbidity during treatment and residual pulmonary disability in pulmonary tuberculosis: under-recognised phenomena. *PLoS One* 2013; **8:** e80302.

49 Willcox PA, Ferguson AD. Chronic obstructive airways disease following treated pulmonary tuberculosis. *Respir Med* 1989; **83:** 195–98.

50 Hnizdo E, Singh T, Churchyard G. Chronic pulmonary function impairment caused by initial and recurrent pulmonary tuberculosis following treatment. *Thorax* 2000; **55:** 32–38.

51 Shuldiner J, Leventhal A, Chemtob D, Mor Z. Mortality after anti-tuberculosis treatment completion: results of long-term follow-up. *Int J Tuberc Lung Dis* 2016; **20:** 43–48.

52 Hoger S, Miller T, Katz D, Beavers S, Lykens K. Longevity loss among cured tuberculosis patients and the potential value of prevention. *Int J Tuberc Lung Dis* 2014; **18:** 1347–52.

53 O'Kane CM, Elkington PT, Friedland JS. Monocyte-dependent oncostatin M and TNF-alpha synergize to stimulate unopposed matrix metalloproteinase-1/3 secretion from human lung fibroblasts in tuberculosis. *Eur J Immunol* 2008; **38:** 1321–30.

54 Dooley DP, Carpenter JL, Rademacher S. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clin Infect Dis* 1997; **25:** 872–87.

55 Critchley JA, Young F, Orton L, Garner P. Corticosteroids for prevention of mortality in people with tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2013; **13:** 223–37.

56 Wallis RS. Corticosteroid effects on sputum culture in pulmonary tuberculosis: a meta-regression analysis. *Open Forum Infect Dis* 2014; **1:** ofu020–ofu020.

57 Kjellsson MC, Via LE, Goh A, et al. Pharmacokinetic evaluation of the penetration of antituberculosis agents in rabbit pulmonary lesions. *Antimicrob Agents Chemother* 2012; **56:** 446–57.

58 Sarathy J, Dartois V, Dick T, Gengenbacher M. Reduced drug uptake in phenotypically resistant nutrient-starved nonreplicating *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 2013; **57:** 1648–53.

59 Adams KN, Takaki K, Connolly LE, et al. Drug tolerance in replicating mycobacteria mediated by a macrophage-induced efflux mechanism. *Cell* 2011; **145:** 39–53.

60 Wallis RS, Patil S, Cheon SH, et al. Drug tolerance in *Mycobacterium tuberculosis*. *Antimicrob Agents Chemother* 1999; **43:** 2600–06.

61 Bruns H, Stegelmann F, Fabri M, et al. Abelson tyrosine kinase controls phagosomal acidification required for killing of *Mycobacterium tuberculosis* in human macrophages. *J Immunol* 2012; **189:** 4069–78.

62 Napier RJ, Rafi W, Cheruvu M, et al. Imatinib-sensitive tyrosine kinases regulate mycobacterial pathogenesis and represent therapeutic targets against tuberculosis. *Cell Host Microbe* 2011; **10:** 475–85.

63 Yogalingam G, Pendergast AM. Abl kinases regulate autophagy by promoting the trafficking and function of lysosomal components. *J Biol Chem* 2008; **283:** 35941–53.

64 Napier RJ, Norris BA, Swimm A, et al. Low doses of imatinib induce myelopoiesis and enhance host anti-microbial immunity. *PLoS Pathog* 2015; **11:** e1004770.

65 Gotta V, Bouchet S, Widmer N, et al. Large-scale imatinib dose-concentration-effect study in CML patients under routine care conditions. *Leuk Res* 2014; **38:** 764–72.

66 Singhal A, Kumar P, Hong GS, et al. Metformin as adjunct anti-tuberculosis therapy. *Sci Transl Med* 2014; **6:** 263ra159.

67 Ong CW, Elkington PT, Brilha S, et al. Neutrophil-derived MMP-8 drives AMPK-dependent matrix destruction in human pulmonary tuberculosis. *PLoS Pathog* 2015; **11:** e1004917.

68 Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014; **73:** 1020–26.

69 Paul C, Cather J, Gooderham M, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate-to-severe plaque psoriasis over 52 weeks: a phase III, randomized controlled trial (ESTEEM 2). *Br J Dermatol* 2015; **173:** 1387–99.

70 Subbian S, Tsenova L, O'Brien P, et al. Phosphodiesterase-4 inhibition combined with isoniazid treatment of rabbits with pulmonary tuberculosis reduces macrophage activation and lung pathology. *Am J Pathol* 2011; **179:** 289–301.

71 Subbian S, Tsenova L, O'Brien P, et al. Phosphodiesterase-4 inhibition alters gene expression and improves isoniazid-mediated clearance of *Mycobacterium tuberculosis* in rabbit lungs. *PLoS Pathog* 2011; **7:** e1002262.

72 Koo MS, Manca C, Yang G, et al. Phosphodiesterase 4 inhibition reduces innate immunity and improves isoniazid clearance of *Mycobacterium tuberculosis* in the lungs of infected mice. *PLoS One* 2011; **6:** e17091.

73 Wallis RS, Pai M, Menzies D, et al. Biomarkers and diagnostics for tuberculosis: a review of progress and current needs and translation into practice. *Lancet* 2010; **375:** 1920–37.

74 Maertzdorf J, Kaufmann SH, Weiner J 3rd. Toward a unified biosignature for tuberculosis. *Cold Spring Harb Perspect Med* 2015; **5:** a018531.

75 Ueberberg B, Kohns M, Mayatepek E, Jacobsen M. Are microRNAs suitable biomarkers of immunity to tuberculosis? *Mol Cell Pediatr* 2014; **1:** 8.

76 Walzl G, Haks MC, Joosten SA, Kleynhans L, Ronacher K, Ottenhoff TH. Clinical immunology and multiplex biomarkers of human tuberculosis. *Cold Spring Harb Perspect Med* 2014; **5:** a018515.

77 Nicol MP, Gnanashanmugam D, Browning R, et al. A blueprint to address research gaps in the development of biomarkers for pediatric tuberculosis. *Clin Infect Dis* 2015; **61** (suppl 3): S164–72.

78 Kurbatova EV, Cegielski JP, Lienhardt C, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: a secondary analysis of data from two observational cohort studies. *Lancet Respir Med* 2015; **3:** 201–09.

79 Wallis RS, Peppard T, Hermann D. Month 2 culture status and treatment duration as predictors of recurrence in pulmonary tuberculosis: model validation and update. *PLoS One* 2015; **10:** e0125403.

80 Wallis RS, Wang C, Meyer D, Thomas N. Month 2 culture status and treatment duration as predictors of tuberculosis relapse risk in a meta-regression model. *PLoS One* 2013; **8:** e71116.

81 Wallis RS. TB relapse risk calculator. 2015. http://www.rswallis.com/Pages/TBrelapsecalculator.aspx (accessed Dec 28, 2015).

82 Chau CH, Rixe O, McLeod H, Figg WD. Validation of analytic methods for biomarkers used in drug development. *Clin Cancer Res* 2008; **14:** 5967–76.

83 Skoura E, Zumla A, Bomanji J. Imaging in tuberculosis. *Int J Infect Dis* 2015; **32:** 87–93.

84 Coleman MT, Chen RY, Lee M, et al. PET/CT imaging reveals a therapeutic response to oxazolidinones in macaques and humans with tuberculosis. *Sci Transl Med* 2014; **6:** 265ra167.

85 Chen RY, Dodd LE, Lee M, et al. PET/CT imaging correlates with treatment outcome in patients with multidrug-resistant tuberculosis. *Sci Transl Med* 2014; **6:** 265ra166.

86 Fletcher HA, Tanner R, Wallis RS, et al. Inhibition of mycobacterial growth in vitro is enhanced following primary BCG vaccination but not BCG revaccination of human subjects. *Clin Vaccine Immunol* 2013; **20:** 1683–89.

87 Wallis RS. Assessment of whole blood bactericidal activity in the evaluation of new anti-tuberculosis drugs. In: Donald PR, van Helden P, eds. Antituberculosis chemotherapy. Basel: Karger, 2011: 220–26.

88 Wallis RS, Vinhas SA, Johnson JL, et al. Whole blood bactericidal activity during treatment of pulmonary tuberculosis. *J Infect Dis* 2003; **187:** 270–78.

89 Good CE, Healan AM, Blumer JL, et al. Whole blood mycobactericidal activity (WBA) of bedaquiline (BDQ, TMC207) alone and in combination with rifampin (RIF) or rifabutin (RBT) after oral dosing of healthy volunteers. *ICAAC* 2012; **52:** A-1257.

90 Esterhuyse MM, Weiner J 3rd, Caron E, et al. Epigenetics and Proteomics Join Transcriptomics in the Quest for Tuberculosis Biomarkers. *MBio* 2015; **6:** e01187–15.

91 Zak DE, Penn-Nicholson A, Scriba TJ, et al. A blood RNA signature for tuberculosis disease risk: a prospective cohort study. *Lancet* 2016; (in press).

92 UNITAID. UNITAID joins health partners to launch new treatment for drug-resistant TB. 2015. http://www.unitaid.eu/en/statements/1433-unitaid-joins-health-partners-to-launch-new-treatment-for-drug-resistant-tb (accessed Dec 28, 2015).

93 Johnson JL, Hadad DJ, Dietze R, et al. Shortening treatment in adults with noncavitary tuberculosis and 2-month culture conversion. *Am J Respir Crit Care Med* 2009; **180:** 558–63.

94 Wang JY, Wang JT, Tsai TH, et al. Adding moxifloxacin is associated with a shorter time to culture conversion in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2010; **14:** 65–71.

95 Dorman SE, Johnson JL, Goldberg S, et al. Substitution of moxifloxacin for isoniazid during intensive phase treatment of pulmonary tuberculosis. *Am J Respir Crit Care Med* 2009; **180:** 273–80.

96 Conde MB, Efron A, Loredo C, et al. Moxifloxacin versus ethambutol in the initial treatment of tuberculosis: a double-blind, randomised, controlled phase II trial. *Lancet* 2009; **373:** 1183–89.

97 Rustomjee R, Lienhardt C, Kanyok T, et al. A Phase II study of the sterilising activities of ofloxacin, gatifloxacin and moxifloxacin in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2008; **12:** 128–38.

98 Burman WJ, Goldberg S, Johnson JL, et al. Moxifloxacin versus ethambutol in the first two months of treatment for pulmonary tuberculosis. *Am J Respir Crit Care Med* 2006; **178:** 331–38.

99 Manjunatha U, Boshoff HI, Barry CE. The mechanism of action of PA-824: novel insights from transcriptional profiling. *Commun Integr Biol* 2009; **2:** 215–18.

100 Singh R, Manjunatha U, Boshoff HI, et al. PA-824 kills nonreplicating *Mycobacterium tuberculosis* by intracellular NO release. *Science* 2008; **322:** 1392–95.

101 Cegielski JP, Dalton T, Yagui M, et al. Extensive drug resistance acquired during treatment of multidrug-resistant tuberculosis. *Clin Infect Dis* 2014; **59:** 1049–63.

102 Hicks D. How can I miss you when you won't go away? Japan International: Epic and Sony Music, 1969.

103 Gelmanova IY, Ahmad Khan F, Becerra MC, et al. Low rates of recurrence after successful treatment of multidrug-resistant tuberculosis in Tomsk, Russia. *Int J Tuberc Lung Dis* 2015; **19:** 399–405.

104 Gler MT, Skripconoka V, Sanchez-Garavito E, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012; **366:** 2151–60.

105 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. *Eur Respir J* 2012; **41:** 1393–400.

106 Diacon AH, Pym A, Grobusch MP, et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. *N Engl J Med* 2014; **371:** 723–32.

107 Cox E, Laessig K. FDA approval of bedaquiline–the benefit-risk balance for drug-resistant tuberculosis. *N Engl J Med* 2014; **371:** 689–91.

108 Lienhardt C, Weyer K, Falzon D, et al. The use of bedaquiline in the treatment of multi-drug resistant tuberculosis: interim policy guidance. Geneva: World Health Organization, 2013.

109 Lienhardt C, Jaramillo E, Falzon D, et al. The use of delamanid in the treatment of multidrug-resistant tuberculosis: interim policy guidance. Geneva: World Health Organization, 2014.

110 Friends of the Global Fight Against AIDs, Tuberculosis, and Malaria. The Global Fund and Partners: fighting tuberculosis across the globe. 2015. http://theglobalfight.org/wp-content/uploads/TB-Nov15.pdf (accessed Feb 26, 2016).

111 Nunn AJ, Rusen ID, Van Deun A, et al. Evaluation of a standardized treatment regimen of anti-tuberculosis drugs for patients with multi-drug-resistant tuberculosis (STREAM): study protocol for a randomized controlled trial. *Trials* 2014; **15:** 353.

112 Spellberg B, Shlaes D. Prioritized current unmet needs for antibacterial therapies. *Clin Pharmacol Ther* 2014; **96:** 151–53.

113 Obama B. Executive order—combating antibiotic-resistant bacteria, 2014. http://www.whitehouse.gov/the-press-office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria (accessed Dec 28, 2015).

114 Holdren JP, Lander E. Report to the President on combating antibiotic resistance. Washington DC, 2014. http://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf (accessed Dec 28, 2015).

115 Upton F. 21st century cures act, 2015. https://www.congress.gov/bill/114th-congress/house-bill/6/text (accessed Dec 28, 2015).

116 Eichler HG, Baird LG, Barker R, et al. From adaptive licensing to adaptive pathways: delivering a flexible life-span approach to bring new drugs to patients. *Clin Pharmacol Ther* 2015; **97:** 234–46.

117 Wallis RS, Peppard T. Early biomarkers and regulatory innovation in multidrug-resistant tuberculosis. *Clin Infect Dis* 2015; **61** (suppl 3): S160–63.

118 Zumla A, Petersen E, Nyirenda T, Chakaya J. Tackling the tuberculosis epidemic in sub-Saharan Africa–unique opportunities arising from the second European Developing Countries Clinical Trials Partnership (EDCTP) programme 2015–2024. *Int J Infect Dis* 2015; **32:** 46–49.