Novel diagnostics and therapeutics for drug-resistant tuberculosis

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Accepted 14 April 2014

Abstract

Introduction: Drug-resistant tuberculosis (DR-TB) is associated with increased mortality and morbidity. This is at least partly due to late diagnosis and ineffective treatment of drug-resistant status.

Sources of data: Selective search of the literature on DR-TB supplemented by recent guidelines from the World Health Organization.

Areas of agreement: Better and more rapid diagnosis of DR-TB by new techniques such as Xpert Mtb/RIF are likely to make a substantial impact on the disease. New therapeutics for DR-TB are entering, or about to enter the market for the first time in decades.

Areas of controversy: It is not clear whether new treatments should be restricted for DR-TB or also used for drug-susceptible tuberculosis.

Growing points: With several new agents on the horizon, there is the real possibility of an entirely new regimen for tuberculosis.

Areas timely for developing research: An inexpensive ‘near-patient’ diagnostic test is still needed. Optimizing new drug combination regimens in a timely manner is urgently required.

Key words: MDR-TB, XDR-TB, drug-resistant tuberculosis, diagnostics, new antibiotics

Introduction

Despite being largely treatable, tuberculosis (TB), caused by Mycobacterium tuberculosis, still causes in excess of 1.4 million deaths annually.1 Although the total annual burden of tuberculosis, and in particular drug-susceptible TB has declined 2.2% from its peak in 2010, partly due to the successful implantation of the World Health Organization’s
(WHO’s) directly observed therapy (short course) regimen (DOTS); the number of drug-resistant TB cases are increasing. Diagnostic and therapeutic strategies, unchanged for decades, had not kept up with the changing drug-resistant landscape for tuberculosis. However, change has come, albeit slowly, in how TB is managed. The last year has seen a license for the first completely new therapeutic for tuberculosis, bedaquiline, for over 40 years and novel diagnostics aimed specifically at identifying drug-resistant TB will become more routine in areas where tuberculosis is endemic. This review will give a brief overview of some of the advances recently implemented in the diagnosis and treatment of drug-resistant tuberculosis, as well as a glimpse of some others on the horizon.

Definitions and burden of disease

Strains of M. tuberculosis resistant to at least both the first-line drugs rifampicin and isoniazid are defined as ‘multi-drug-resistant’ tuberculosis (MDR-TB) and were first described in the resurgence of TB in the context of HIV in New York. If the strain is further resistant to quinolones and at least one ‘injectable’ drug (amikacin, kanamycin or capreomycin), the strain is defined as ‘extensively drug-resistant’ (XDR). Both MDR- and XDR-TB have increased mortality and lower cure rates than drug-susceptible disease, and current treatment regimens take at least 20 months compared with 6 months for drug-susceptible disease.

Every country of the world that has been surveyed has identified cases of MDR-TB, and 84 countries have identified at least one case of XDR-TB. The total global burden of MDR-TB in 2012 was estimated to be 3.6 and 20% of new and previously treated TB cases, respectively. The vast majority of MDR cases are in Asia, with China representing the nation with the single largest prevalence. In some countries, notably from the former Soviet Union and Eastern Europe, it is estimated that >20% of new cases of TB are MDR-TB and 50% of previous cases of drug-susceptible TB develop into MDR-TB. In these ‘high MDR burden’ countries, the DOTS strategy of treating all cases as drug-susceptible unless there is treatment failure clearly does not hold, and DOTS-plus ‘Directly Observed Therapy for MDR-TB’ has been implemented in its stead.

Not only is the number of MDR-TB cases on the rise, in 2009 it was also estimated that only ~7% of total estimated cases of MDR-TB (440 000) were diagnosed and fewer than 3% of patients with MDR-TB received appropriate treatment. Initial assumptions about the decreased ‘fitness’ and transmissibility of MDR-TB have not borne out, making prompt diagnosis and treatment of drug-resistant tuberculosis an essential arm in the fight against the disease. Second-line agents used in the treatment of MDR- and XDR-TB have a number of limitations. They are less potent than first-line drugs, necessitating longer treatment times. Their tolerability and side-effect profile are also unfavourable, further decreasing patient compliance. There are additional logistical problems surrounding the use of second-line drugs in that they are not readily available and are more costly than first-line drugs. For example, the estimated cost of treatment for XDR-TB in South Africa is US $26392/patient, compared with US$6772/patient for MDR-TB and US$257/patient for drug-susceptible disease.

Novel diagnostics for drug-resistant TB

For more than a century, particularly in countries in which TB is endemic, sputum smear microscopy has been the mainstay of diagnosis. Coupled with a low sensitivity of ~40% (compared with culture), smear microscopy cannot reveal any information about antibiotic susceptibility. In developed countries and higher level, e.g. regional level hospitals in developing countries, mycobacterial culture has supplemented smear microscopy. Given the slow growth rate of M. tuberculosis, the time-to-initial diagnosis can take up to 3 weeks, and drug susceptibility testing (DST) a further 2- to 4 weeks. Therefore, the time elapsed between first presentation and subsequent diagnosis of drug resistance takes at least 1–2 weeks, and as much as 1–3 months. If a patient is not on adequate treatment, they could potentially transmit drug-resistant bacilli in that time.

A further drawback to mycobacterial culture is that it requires specialized biosafety facilities for safe
handling of pathogenic \textit{M. tuberculosis}, limiting its utility and availability in resource poor settings. Therefore, novel diagnostic tests developed for the diagnosis of drug-resistant tuberculosis should be rapid, available to patients in a rural setting, have no requirements for specialized training or facilities for their use, and ideally, inexpensive. Recently rolled out diagnostic tests incorporate some but not all of these specifications (Table 1). The accurate identification of MDR-TB remains the highest priority in diagnostics, because of the important therapeutic and public health implications. Rifampicin resistance is almost always (>96% of all clinical samples) due to mutations in the drug-target gene, \textit{rpoB}, which codes for the \( \beta \) subunit of RNA polymerase.\(^{17}\) The target of isoniazid is InhA, a protein involved in mycolic acid synthesis,\(^{18}\) however, isoniazid, as a pro-drug, requires activation by the mycobacterial catalase encoded by \textit{katG}, and high level isoniazid resistance is usually due to missense mutations in \textit{katG} rather than \textit{inhA}.\(^{19}\)

Two recent innovations in the diagnosis of drug-resistant TB have already been rolled out in the clinical setting. The in-line probe assay involves DNA amplification of mycobacterial resistance determinants by PCR, followed by hybridization to probe-containing strips. Genotype MTBDRPlus, developed by HAIN lifesciences, is capable of identifying \textit{M. tuberculosis} and resistance to isoniazid and/or rifampicin from either pulmonary specimens or cultured samples.\(^{20}\) The probes are directed against mutations in \textit{rpoB} for rifampicin resistance, \textit{katG} for high-level isoniazid resistance and \textit{inhA} for low-level isoniazid resistance, and sensitivities are comparable to culture and conventional DST.\(^{21}\) MTBDR Plus takes approximately 5 h to complete, and its use in a trial setting has led a significant reduction in time to introduction of specific therapy directed against MDR-TB of 55 days compared with 80 days with conventional DST.\(^{22}\) However, actual time from sample acquisition to result determination and communication to patients and their treating physicians can vary considerably. These can be due to laboratory based delays—for example in waiting to pool samples before running a test, to delays based on infrastructure and relaying of clinical information.\(^{22}\)

\begin{table}
\begin{tabular}{|c|c|c|c|}
\hline
Technology & Drug resistance detected & Run time & Status & Developers \\
\hline
Genotype® MTBDR Plus & RIF resistance & 5 h & Available & HAIN (Nehren, Germany) \\
\hline
DNA·STRIP® technology & INH resistance & & Available & \\
\hline
Xpert® MTB/RIF & RIF resistance & 2 h & Available & Cepheid, Inc. (Sunnyvale, CA, USA) \\
\hline
whole-genome sequencing & Multiple & <7 days & Available but not routinely used & Various \\
\hline
B-SMART™ & First-line anti-TB drugs & <2 days & Under development & Sequella, Inc. and LabCorp (USA) \\
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A further drawback to the test is the requirement for technical expertise in running the assay and the possibility of sample cross-contamination, limiting its utility as a point of care diagnostic.\textsuperscript{23}

The Xpert Mtb/RIF test marketed by Cepheid, only tests for the presence of rifampicin resistance, but is relatively straightforward to use and deploy in the field. In keeping with the line-probe assay, Xpert Mtb/RIF uses amplification of mycobacterial DNA from samples. However, in contrast, the test uses molecular beacon technology in an automated hemi-nested PCR assay (Fig. 1). Since mutations resulting in rifampicin resistance are confined to a small, 81-bp region of the \textit{rpoB} gene\textsuperscript{17} designated the rifampicin resistance-determining region (RRDR), identification of rifampicin resistance is particularly suited to diagnosis by molecular beacon technology. Being automated, the device and test are straightforward to use, and results can be obtained from sputum samples in as little as 2 h.\textsuperscript{24} Sensitivity overall, at 90\% compared with culture, is good, although it drops significantly to 67\% in smear negative samples.\textsuperscript{25} At present, the platform can deal with a maximum of four cartridges at one time, limiting throughput, and costs for each test, at US$10/cartridge is significant in a resource-limited setting, notwithstanding the expense of the machine itself.\textsuperscript{1} Modelling the effect that Xpert Mtb/RIF may have on the health and economy of countries in Southern Africa suggested the potential to significantly reduce mortality and morbidity associated with TB, and over time, reduce disease transmission and latent TB reservoirs as secondary effects.\textsuperscript{26}

A major limitation of the Xpert Mtb/RIF assay in its current format is that it can only detect rifampicin resistance. The binary diagnostic outcome of a sample that is positive for \textit{M. tuberculosis} is classified as rifampicin-resistant – in which case the patient is treated as MDR-TB, or rifampicin sensitive, when they are treated as drug-susceptible TB. Although relatively uncommon, rifampicin monoresistance does occur, particularly in association with HIV co-infection and poor compliance.\textsuperscript{27} More serious potentially is the mis-classification of isoniazid monoresistance as drug-susceptible tuberculosis. Although controversial, some studies have identified worse outcomes for isolated isoniazid-resistant tuberculosis than pan-susceptible disease\textsuperscript{26,28,29} whilst others have not.\textsuperscript{30,31} In the study by Thomsen et al., rapid determination of isoniazid resistance resulted in a regime change, possibly explaining the favourable outcomes.\textsuperscript{30} Although still in the developmental stage, molecular beacon technology, coupled with extended colour spectrum detection, opens the potential for diagnosis of multiple drug resistances, e.g. to quinolones,\textsuperscript{32} as well as rifampicin on the same Cepheid/Xpert platform within the one sample.

Rather than targeting one or a limited number of resistance mechanisms, the dramatic decrease in costs associated with rapid whole-genome sequencing (WGS) potentially allows the diagnosis of most, if not all, resistance mechanisms in a relatively short time frame.\textsuperscript{15} Although as yet, not all resistance mechanisms have clearly defined or identified genetic markers, many of the most commonly used antibiotics—rifampicin, isoniazid, fluoroquinolones, pyrazinamide, aminoglycosides, amongst others—do. Whilst WGS is still only used as a research tool, its use in developed countries may be rolled out soon initially in parallel with standard DST, and with further research, it may be used as the primary method for diagnosing drug resistance—as is the case currently with HIV. A step change in pricing and technology would be required, however, before it might be used in a developing world setting as a near-patient diagnostic.

The above technologies leverage DNA amplification technologies with target-specific mechanisms of drug resistance. In contrast, the B-SMART assay, not yet in commercial use, developed by Sequella, Inc. and LabCorp utilizes phenotypic resistance to antibiotics—the same as conventional DST—but coupled with DNA amplification to detect a non-specific signal for bacterial viability. Briefly, the assay involves infecting a sputum sample with a modified mycobacteriophage—that will specifically and efficiently only infect mycobacterial species. The phage encodes a unique nucleic acid marker (SML—surrogate marker locus) that will only be synthesized in the presence of metabolically active mycobacteria. The samples are treated with a panel of antibiotics. Bacteria susceptible to the antibiotics will stop growing and thus the phage will not produce the SML. If the bacterium is
Fig. 1 Molecular Beacons and the Xpert MTB/RIF assay. Molecular probe sequences are designed based on the RRDR of \(rpoB\). Molecular probes are complementary to different, overlapping target sequences of 15–20 nucleotides of the RRDR of \(rpoB\) and can be combined in the same single rt-PCR assay (A). Molecular beacons contain probe sequences as well as two complementary arms which are covalently linked to a fluorophore (coloured and black sphere, respectively). DNA sequences from a sample are amplified by real-time PCR. Different molecular beacons with different fluorophore colours are used in the same multiplex reaction. When a molecular beacon hybridizes to an amplicon from rifampicin-susceptible strains (black), the conformational change allows for fluorescence which is measured during the annealing step in the rt-PCR reaction. However, a mutation in RRDR in the template (light blue) prevents hybridization and the quencher continues to suppress fluorescence from the fluorophore. Mutations in \(rpoB\) from samples result in suppression of fluorescence from the corresponding molecular beacon with capabilities of single nucleotide discrimination (B). Amplification of a region-specific for \(M. tuberculosis\) \(rpoB\), but outside of the RRDR confirms the diagnosis of tuberculosis. Fluorescence from all the probes suggests a rifampicin-susceptible isolate. One or more probes that fail to fluoresce suggest a rifampicin-resistant isolate.
resistant to the antibiotic, it will support growth of
the phage and SML production, which will be
detected in an automated fashion by nucleic acid
amplification.\textsuperscript{16} Theoretically, the B-SMART assay
can be used for any antibiotic that rapidly shuts down
mycobacterial metabolism without the need of spe-
cific knowledge of resistance mechanisms. However,
unlike line-probe assays and the Xpert Mtb systems,
B-SMART is unable to distinguish between infection
by \textit{M. tuberculosis} and non-tuberculous mycobacteria
(NTM) since the phage is able to infect most myco-
bacterial species. NTM are often highly pan-resistant
to most anti-TB medication—raising the possibility of
misdiagnosing NTM infection as MDR- or XDR-TB.

\textbf{Novel drugs for drug-resistant TB}

At the end of December 2012, the US Food and
Drug Administration (FDA) approved the use of
Bedaquiline for combination use in MDR-TB. This
was the first entirely novel anti-tuberculosis medica-
tion approved for clinical use in over 40 years and
underlined the gradually increasing priority given to
development of novel anti-TB medications after a
long period of neglect. Bedaquiline is joined by
several other agents in late clinical development
(Table 2), and whilst there is a need for an even more
robust pipeline, the next 5–10 years will likely
witness at least two or three more novel anti-TB
drugs. For reasons that are poorly understood, hori-
zontal gene transfer is not observed in clinical strains
of \textit{M. tuberculosis}. This means that acquisition of
drug resistance is always due to mutations in
chromosomal DNA. As such, almost all new anti-TB
agents, if they have a novel mechanism of action, are
likely to be active against both drug-susceptible and
drug-resistant tuberculosis—raising a dilemma of
whether they should be ‘kept in reserve’ for the most
intractable cases, or whether to be rolled out more
widely—with the increased risk of strains acquiring
resistance to the new agent.

The molecular target for bedaquiline, the first of a
new class of agents known as diarylquinolines, is the
mycobacterial ATP synthase.\textsuperscript{34} Not only did its dis-
covered target validate bacterial metabolism as a \textit{bona fide}
biological target, but also that antibiotics could act
on highly conserved targets that are in both bacterial
and eukaryotic cells.\textsuperscript{40} Although none are yet in clinical
development, other promising candidates target-
ning mycobacterial metabolism have subsequently
been discovered,\textsuperscript{41} suggesting that disruption of bac-
terial metabolism may be a promising new avenue to
explore for antibiotic discovery.\textsuperscript{42} The FDA’s accel-
erated approval of bedaquiline was on the basis of
promising results from Phase IIIb trials. Used in combi-
nation with a second-line agents for the treatment of
MDR-TB, bedaquiline-treated patients had a
much faster time to clearance of their mycobacterial

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Drug/regimen & Status & Developers/sponsor & Target/mode of action/notes \\
\hline
Delaminid/OPC-67683 & Phase III & Otsuka Pharmaceutical Co., Ltd. & Mycolic acid synthesis inhibition\textsuperscript{33} \\
Bedaquiline/TMC-207 & Phase III/IV & Janssen & ATP synthase\textsuperscript{34} \\
Linezolid & Phase II & TBTC, Pfizer & 50S ribosomal subunit, inhibits bacterial protein synthesis\textsuperscript{35} \\
Sutezolid & Phase II & Sequella & 50S ribosomal subunit\textsuperscript{36} \\
PA-824 & Phase II & TB Alliance & Inhibition of mycolic acid and nitric oxide (NO) generation\textsuperscript{37} \\
SQ-109 & Phase II & Sequella, NIH & Targets MmpL3, disrupts cell wall synthesis\textsuperscript{38} \\
Bedaquiline/sutezolid/SQ109 & Phase II & — & Whole blood early bactericidal study\textsuperscript{39} \\
STREAM trial\textsuperscript{a} & Phase III & MRC & Duration shortening (non-inferiority) trial \\
\hline
\end{tabular}
\caption{Antibiotics currently in late stage (Phase II or later) clinical development for DR-TB}
\end{table}

\textsuperscript{a}4 months kanamycin/clofazamine/moxifloxacin/ethambutol/isoniazid/pyrazinamide/protonamid followed by 5 months moxifloxacin/
ethambutol/pyrazinamid/clofazime versus 20–24 months standard MDR therapy.

sputum cultures (83 days) compared with placebo-treated controls (125 days) on similar background regimens. The bedaquiline-treated group also had a higher cure rate (38/66) compared with the control arm (21/66).

The potency of bedaquiline in clinical use, which, if borne out by further trials, may potentially reduce treatment times of MDR-TB from their current 20-month regimen, is very exciting. However, some questions remain regarding its safety. Bedaquiline causes QTc prolongation—making its use with other potentially cardio-toxic agents such as moxifloxacin problematic. As a substrate of cytochrome P450, bedaquiline dosing may need to be adjusted with HIV medications inducing the cytochrome, such as efavirenz, although no dose adjustment was needed with rifampicin. Furthermore, in the extended Phase IIb trial, there was a statistically significant increase in all-cause mortality in the bedaquiline arm (10/79 compared with 2/81 in the control arm). Although bedaquiline was not implicated in the cause of deaths, until larger studies report their findings, the use of bedaquiline comes with a ‘black box’ warning label. Nonetheless, it should be stressed that use of bedaquiline was found to be safe in a review by the WHO and there is now limited experience of its use on a compassionate use basis outside of clinical trials with no adverse effects. The newly discovered cross-resistance between clofazamine and bedaquiline, which is probably due to a shared efflux pump, may also further its utility in areas where clofazamine has been used in MDR and XDR regimens.

Another entirely novel agent currently undergoing Phase III trial assessment is delamanid (OPC-67683). Delaminid inhibits mycolic acid synthesis—an essential component of mycobacterial cell walls. In a large Phase IIb study, delaminid use for 2 months over background regimen for MDR-TB was associated with faster sputum conversion rates and 2-month sputum sterilization. A follow-up study of the original trial participants was conducted in which they were invited to participate in an open-label study of guaranteed access to delamanid for a further 6 months. Comparison of patients who received 6–8 months of delamanid with those receiving 0–2 months (who did not participate in the follow-up study) showed a clear benefit in terms of overall mortality (1% vs 8.3) and cure (57.3 vs 48.5%). Delaminid does not have interactions with most current anti-tuberculous or anti-HIV medications and Phase III trials are ongoing, including a sub-trial specifically with a cohort of HIV-positive patients and delaminid is currently in the process of undergoing regulatory approval and should be approved for clinical use shortly.

Earlier in the pipeline, the nitroimidazole (nitroimidazo-oxazine) PA-824 is bactericidal against both replicating and non-replicating M. tuberculosis. As with other nitroimidazoles such as metronidazole, PA-824 is a pro-drug, requiring activation by the bacterium. Its mechanism of action is complex. Metronidazole is active only against M. tuberculosis cultured under anaerobic conditions, whereas PA-824 is active under aerobic and anaerobic conditions—with possibly differing modes of action in the two conditions. PA-824 is well tolerated and safe, and does not interact with cytochrome P450—making its use with anti-retrovirals relatively straightforward. In Phase II trials, PA-824 is being assessed in combination with pyrazinamide and moxifloxacin (PaMZ regimen) for drug-resistant tuberculosis. The PaMZ combination has shown promise in a murine infection model, where it was able to sterilize mice infected by M. tuberculosis within 4 months unlike standard therapy. Early bactericidal activity in human subjects was also superior to second-line agents but similar to first-line therapy.

Also under Phase II development, SQ109 also targets cell wall mycolic acid synthesis through inhibition of the essential transporter MmpL3. SQ109 is a [1,2]-diamine-based ethambutol analogue and substitution of ethambutol by SQ109 was superior in a murine chronic infection model. Despite its structural similarity to ethambutol, there is no cross-resistance between the two agents, which is unsurprising given their different cellular targets. Since SQ109 shows promising synergism with new and established anti-TB drugs, its clinical development has been fast tracked. One question that remains to be resolved is why several unrelated compounds from recent anti-mycobacterial drug screens appear to share the same molecular target. In
addition to SQ109, indoleamides,57 diphenyl pyroles58 and adamantyl ureas59 all appear to target MmpL3—suggesting it may either be a particularly vulnerable target, or not the true molecular target, but an intermediate transporter or activator of at least some of these agents.

In addition to the novel compounds discussed above, a number of drugs have been repurposed for anti-mycobacterial activity, given the lack of good options amongst existing second-line agents. The fluoroquinolone moxifloxacin has been used ‘off-label’ for tuberculosis for some time. Given promising data from pre-clinical studies,60 it had been hoped that moxifloxacin may prove effective in reducing treatment times of drug-susceptible disease to 4 months. Although the Phase III trial data are not yet available, analysis of 2-month sputum sterilization data suggest that the outcomes of the RIFAQIN and REMoxTB trials may be disappointing.61 The combination use of moxifloxacin with PA-824 in drug-resistant tuberculosis may be more promising (see above).

The first oxazolidinone, linezolid, was developed to treat antibiotic-resistant gram-positive infections. Binding to the 23S portion of the 50S ribosomal subunit and inhibiting initiation complex formation,35 linezolid is bacteriostatic in keeping with most antibiotics that inhibit protein synthesis. In a boldly designed trial, which went against the usual maxim of ‘never add a single drug to a failing regimen’, linezolid was assessed in a group of South Korean patients with XDR-TB and few therapeutic options and not responding to their current therapy. Linezolid (on top of the failed background regimen) showed remarkable activity, converting patients that had previously been sputum culture positive for years to culture negative status within a median of 75 days.62 Culture negativity was prolonged for a majority of patients, but drug resistance did emerge in a few patients62 sounding a note of caution in using effectively monotherapy outside of a trial setting. Side effects, such as peripheral and optic neuropathy, probably due to mitochondrial toxicity (since mitochondria have 70S ribosomes, similar to bacteria), may limit the duration and dosage of linezolid that may be used. The surprisingly strong and positive data resulting from linezolid use in a clinical setting has encouraged investigation of other class members such as PNU-100480 (sutezolid) for anti-TB activity, which appear to be more potent, and hopefully, less toxic.63

Historically, beta-lactam antibiotics have not been used to treat tuberculosis since M. tuberculosis encodes for a single and broadly active beta-lactamase. However, the carbapenem meropenem, given in combination with the beta-lactamase inhibitor clavulanate, is bactericidal against M. tuberculosis.64 Given its requirement for parenteral administration, and cost, its utility is likely to remain in resource-rich settings or as a last resort.

Although several novel regimens are in development for treatment shortening for drug-susceptible tuberculosis, advanced clinical trials specifically aimed at treatment shortening in drug-resistant TB are relatively few. An observational study using seven second-line agents for MDR-TB (Table 2) showed promising results after a short, 9-month regimen,65 and a clinical trial, STREAM, evaluating this regimen against standard therapy is currently under way (trial # ISRCTN78372190). An early bactericidal activity in whole blood assay of bedaquiline/sutezolid/SQ109 showed additive activity, although no synergy.66

**Conclusion**

MDR- and XDR-TB currently represent <10% of the total global tuberculosis disease burden. However, unlike drug-susceptible tuberculosis, whose incidence has peaked, the number of cases of drug-resistant disease is still on the rise.67 Furthermore, drug-resistant disease contributes disproportionately to the morbidity and mortality due to tuberculosis.1,67 This is not because of increased pathogenicity, but rather due to late diagnosis of drug-resistant status and a far inferior second-line armamentarium with which to tackle the disease. Second-line drugs are not used in the first instance precisely because they are less effective than first-line drugs.

Traditional diagnostic methods were unable to identify drug-resistant cases, and patients were
treated as drug-susceptible unless they continuously failed to respond to therapy after many months—all the while remaining infectious. This had led to a recent change in WHO policy whereby in countries with a particularly high prevalence of MDR-TB (such as some member nations of the former Soviet Union), patients should be presumed drug-resistant until proven otherwise.68 However, countries such as China and South Africa, which harbour the greatest burden of MDR-TB, continue to treat patients as drug susceptible in the first instance.

The near future allows a potential change to this landscape. New diagnostics such as Xpert Mtb/RIF will allow rapid diagnosis of drug-resistant tuberculosis, if not in the patient’s village, at least in a nearby health clinic, and on the day of presentation, making partly tailored therapy a reality for the first time. The next decade will also witness enough new potent antibiotics for tuberculosis to construct an entirely new effective regimen—something not previously possible for 50 years. The challenge and controversy is whether to keep these new drugs ‘in reserve’ for MDR- and XDR cases, or to revolutionize the entire backbone regimen for all patients diagnosed with tuberculosis. Since these new agents have novel molecular targets and therefore will not have cross-resistance to currently circulating clinical strains, the challenge of needing to diagnose drug-resistant tuberculosis may become irrelevant—at least for a time. However, with mass usage of the new drugs will come the inevitable rise of new drug resistance, and the arms race between pathogen and human host will again need to be escalated. If the new agents were rendered ineffective due to rapid acquisition of drug resistance, we would be back to ‘square one’, with potentially even fewer treatment options and the novel pipeline of agents, several decades in the making, shattered. Pharmaceutical companies, historically reluctant to enter this unprofitable niche market, but recently making forays, might be discouraged from further efforts in expanding the pipeline. For now, the decision has been to keep the new agents in reserve, whilst exploring the infrastructure and health-care delivery requirements for regimen change.69 To realistically tackle the goal of eliminating tuberculosis as a major public health menace, in addition to investment in new drugs and diagnostics, we must address the continuing need for research in effective preventative and therapeutic70 vaccines, and in fundamental pathophysiology of the organism. One of the barriers to effective treatment is the current long treatment times. Identification of mechanisms of antibiotic tolerance—that allows susceptible bacteria to survive in the face of drug treatment71,72 opens up new avenues in the fight against this ancient pathogen.

Funding

This work was in part funded by a Phase I Grand Challenges Explorations grant from the Bill & Melinda Gates Foundation and start-up funds from Tsinghua University.

Conflict of interest

B.J. is a Tsinghua-Janssen scholar. Janssen had no role in the writing or submission of this study.

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