The epidemiology, pathogenesis, transmission, diagnosis, and management of multidrug-resistant, extensively drug-resistant, and incurable tuberculosis


Global tuberculosis incidence has declined marginally over the past two decades, and tuberculosis remains out of control in several parts of the world including Africa and Asia. Although tuberculosis control has been effective in some regions of the world, these gains are threatened by the increasing burden of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis. XDR tuberculosis has evolved in several tuberculosis-endemic countries to drug-incurable or programmatically incurable tuberculosis (totally drug-resistant tuberculosis). This poses several challenges similar to those encountered in the pre-chemotherapy era, including the inability to cure tuberculosis, high mortality, and the need for alternative methods to prevent disease transmission. This phenomenon mirrors the worldwide increase in antimicrobial resistance and the emergence of other MDR pathogens, such as malaria, HIV, and Gram-negative bacteria. MDR and XDR tuberculosis are associated with high morbidity and substantial mortality, are a threat to health-care workers, prohibitively expensive to treat, and are therefore a serious public health problem. In this Commission, we examine several aspects of drug-resistant tuberculosis. The traditional view that acquired resistance to antituberculous drugs is driven by poor compliance and programmatic failure is now being questioned, and several lines of evidence suggest that alternative mechanisms—including pharmacokinetic variability, induction of efflux pumps that transport the drug out of cells, and suboptimal drug penetration into tuberculosis lesions—are likely crucial to the pathogenesis of drug-resistant tuberculosis. These factors have implications for the design of new interventions, drug delivery and dosing mechanisms, and public health policy. We discuss epidemiology and transmission dynamics, including new insights into the fundamental biology of transmission, and we review the utility of newer diagnostic tools, including molecular tests and next-generation whole-genome sequencing, and their potential for clinical effectiveness. Relevant research priorities are highlighted, including optimal medical and surgical management, the role of newer and repurposed drugs (including bedaquiline, delamanid, and linezolid), pharmacokinetic and pharmacodynamic considerations, preventive strategies (such as prophylaxis in MDR and XDR contacts), palliative and patient-orientated care aspects, and medicolegal and ethical issues.

Introduction

With the notable exception of sub-Saharan Africa, the incidence of tuberculosis has declined over the past two decades in most regions of the world. However, gains in tuberculosis control are threatened by the emergence of resistance to antituberculosis drugs. Approximately 20% of tuberculosis isolates globally are estimated to be resistant to at least one major drug (first-line or group A or B second-line), with approximately 10% resistant to isoniazid. WHO has defined multidrug-resistant (MDR) tuberculosis as resistance to at least isoniazid and rifampicin, when first-line therapy is unlikely to cure the disease and a switch to a second-line drug regimen is recommended. Similarly, extensively drug-resistant (XDR) tuberculosis is MDR tuberculosis that is also resistant to the fluoroquinolones and second-line injectable drugs, indicating the probable failure of the standardised second-line treatment regimen. Two modes exist by which patients contract drug-resistant tuberculosis. Primary resistance results from infection with a drug-resistant strain, whereas resistance that develops during therapy is referred to as secondary or acquired resistance. Amplification of resistance might occur when resistance to additional drugs emerges during the treatment course, often in association with inadequate therapy. Globally, approximately 5% of patients with tuberculosis are estimated to have either MDR or XDR types, but the distribution of cases is not uniform; it is substantially higher in some regions, and increasing incidence has been reported in several countries. The high mortality due to most patients remaining untreated is a key reason for this apparently stable estimated global rate of drug-resistant tuberculosis. Approximately 30% of MDR tuberculosis isolates are either fluoroquinolone-resistant or aminoglycoside-resistant, and approximately 10% of MDR tuberculosis isolates can be classed as XDR tuberculosis, or as having resistance to additional drugs beyond XDR tuberculosis (ie, totally drug resistant). This expansion of resistance has
ushered in an era of programmatically incurable tuberculosis, in which insufficient effective drugs remain to construct a curative regimen. The availability of newer drugs, such as bedaquiline and delamanid, has not averted this problem and resistance to both bedaquiline and delamanid in the same patient has already been reported. The effect on patients is profound, because drug resistant tuberculosis is associated with a higher morbidity than drug-sensitive tuberculosis and is responsible for approximately 20% of the global tuberculosis mortality, with mortality rates estimated at around 40% for patients with MDR tuberculosis and 60% for those with XDR tuberculosis. Provision of effective first-line treatment was hoped to prevent the emergence of drug-resistant tuberculosis as a public health problem. However, data suggest that primary transmission of MDR and XDR tuberculosis is now driving the spread of resistance, including in high-burden countries such as China, India, and South Africa. The inability to cure infectious patients raises ethical and medicolegal questions regarding the freedom of affected individuals to work and travel and how to prevent onward transmission. Drug-resistant tuberculosis causes a strain on health systems because of the chronic nature of the disease, and because of the risk of transmission to health-care workers. Drug-resistant tuberculosis also jeopardises tuberculosis control through its economic effect, because the high cost of managing drug-resistant tuberculosis is not sustainable in some settings and an anticipated shortfall in global resources has been reported by the STOP TB partnership. In the USA, average inpatient costs have been estimated to be US$81 000 for patients with MDR tuberculosis and $285 000 for those with XDR tuberculosis. In South Africa, management of MDR and XDR tuberculosis, despite only accounting for less than 5% of all tuberculosis cases, is estimated to cover over a third of the total tuberculosis programme resources. Of the US$6·3 billion available in 2014 to respond to the global tuberculosis epidemic, $3·8 billion was used for diagnosis and treatment of drug-susceptible tuberculosis, and $1·8 billion (47%) for MDR tuberculosis. Tuberculosis and drug-resistant tuberculosis are no longer the concern of individual countries, because international travel and migration support transmission across international boundaries and around the world.

Addressing drug-resistant tuberculosis requires an urgent and concerted effort to manage the disease and prevent onward transmission with sustained research to develop and assess new tools. In this Commission, we report on the global status of drug-resistant tuberculosis and how it emerges, followed by state-of-the-art detection and patient management options; we discuss transmission and intervention to reduce transmission; and research needs are assessed and prioritised. We therefore present for consideration a contemporary situational analysis and roadmap for combating and eradicating drug-resistant tuberculosis as a global public health problem. An array of views is presented on drug-resistant tuberculosis with the aim to highlight challenges and to provide practicable solutions and a roadmap for progress. A patient-oriented perspective is also presented, including audio and video interviews with patients with drug-resistant tuberculosis (panel 1).

Epidemiology and risk factors for MDR and XDR tuberculosis, and resistance beyond XDR

Global epidemiology of MDR and XDR tuberculosis

Historically, knowledge of drug-resistant tuberculosis has been limited by the absence of reliable data from many of the countries with a high burden of tuberculosis. Drug susceptibility testing is technically challenging and requires specialist laboratory facilities that are not widely available in many tuberculosis-endemic countries. In 1994, WHO and International Union Against Tuberculosis and Lung Disease (IUATLD) launched a global surveillance programme to standardise methods and improve data quality. Data was collected for susceptibility to the first-line drugs isoniazid, rifampicin, ethambutol, and streptomycin. Pyrazinamide was excluded because of technical difficulties and the poor reliability of testing methods. Increased laboratory capacity for testing and progress in surveillance activities has made it possible to estimate the global burden of MDR tuberculosis and look at trends over time. As of 2014, 153 countries have provided data on drug-resistant tuberculosis to WHO. Some countries have undertaken national surveillance studies, and others have submitted national (regional) data. Data are provided as a population, South Africa should also be considered a high-burden country (figure 1 C). India, China, and Russia have the highest number of estimated MDR tuberculosis cases with the three countries accounting for over 50% of all MDR tuberculosis cases in notified patients with pulmonary disease worldwide. Although the global burden of MDR tuberculosis remained unchanged between 2008 and 2013, the number of detected rifampicin-resistant cases increased substantially in several countries (eg, China, India, Pakistan, Nigeria, South Africa, Indonesia, Bangladesh, and DR Congo).
from 2009 to 2013. Of the two drugs associated with MDR tuberculosis, resistance to isoniazid is more common, with an estimated global average monoresistance in 2014 of 9-5% (95% CI 8.0–11.0; 8.1% in new cases and 14.0% in previously treated tuberculosis). Regardless, routine testing for isoniazid resistance is not done as a front-line test in most settings and as a result most isoniazid-monoresistant tuberculosis will remain undetected. Approximately one in five tuberculosis isolates worldwide are resistant to at least one major first-line (rifampicin, isoniazid, pyrazinamide, or ethambutol) or second-line drug (fluoroquinolone or a second-line injectable agent).11

As the incidence of MDR tuberculosis has increased, cure rates have decreased in some countries; the WHO southeast Asia region reported that cure rates dropped from more than 70% in 2006 to less than 50% in 2014.1 Information on XDR tuberculosis is more scarce, but available data suggest that 9-7% of MDR tuberculosis cases also had XDR tuberculosis. The proportion of MDR tuberculosis with XDR tuberculosis was highest in Belarus in 2014 (29%) and Lithuania in 2013 (25%).1 Notably, the proportion of MDR tuberculosis cases that were also resistant to any fluoroquinolone was 21% worldwide, whereas resistance to either a fluoroquinolone, a second-line injectable agent, or both, was more than 30%. The global burden of drug resistance in children has rarely been quantified; two recent high-quality modelling studies generated plausible estimates of 31 948 cases (95% CI 25 594–38 663) of paediatric MDR tuberculosis in 2010 and 24 800 cases (16 100–37 400) in 2014.12,13

Further resistance to the drugs used to treat XDR tuberculosis has been reported in several countries and has resulted in the phenomenon of programmaticallly incurable tuberculosis (ie, when insufficient susceptible drugs remain for a curative regimen).14 Of particular concern is the occurrence of programmaticallly incurable strains in countries such as China, India, and South Africa that are poorly equipped to prevent onward transmission.15

Determinants of drug resistance

The primary vehicle by which drug resistance arises in Mycobacterium tuberculosis is via mutations in genes encoding drug targets or enabling enzymes. Unlike other bacteria that often acquire resistance through promiscuous gene transfer systems such as plasmid exchange, changes in the genomic DNA of M tuberculosis usually result from single-nucleotide polymorphisms (SNPs), indels, or, more rarely, large deletions.16 In principle, the effect of drug treatment is to diminish the pool of susceptible bacteria, which enables the clonal expansion and enrichment of resistant bacteria and the emergence of a strain able to withstand drug treatment. Sequential mutations in additional genes can lead to resistance to additional drug targets and the emergence of strains resistant to multiple drugs. Several studies in individual patients who have developed progressive drug resistance over time have documented the initial acquisition of isoniazid resistance as a result of one or more mutations, followed by acquisition of resistance to rifampicin or ethambutol (or both), pyrazinamide, and finally, the second-line and third-line drugs.15–17 The order in which resistance is acquired might reflect the number of different mutations that lead to resistance to a specific drug,18 the relative fitness costs associated with specific mutations (ie, mutations might lead to less successful survival and reproduction of the organism),19 or pheno-tipic changes following an initial drug-resistance mutation that might facilitate the acquisition of further mutations.20 When resistance to one or more drugs is acquired in this way, it is referred to as secondary resistance.

By contrast, primary resistance occurs when resistant strains are transmitted to a new host in the same manner as a drug-susceptible strain. Because the mutations that lead to resistance can be deleterious and produce a fitness cost, many observers hypothesised that resistant strains were less virulent or less easily transmitted than drug-sensitive strains. However, recent work has shown that additional mutations often follow or coincide with drug resistance mutations, and that these mutations can compensate for deleterious effects, restoring their initial growth capacity.21,22 Although some epidemiological studies have found that drug-resistant strains are less transmissible than drug-sensitive strains, others have shown the opposite,23 and the question of the effect of resistance on transmission remains an open one.

Risk factors

Several studies have investigated host, bacterial, ecological, or health-system determinants of MDR and XDR tuberculosis in children.1,24

Panel 1: Audiovisual material outlining a researcher perspective and interviews with patients with MDR and XDR tuberculosis

- This video, produced by Meera Senthilingam, gives an introduction to the tuberculosis and drug-resistant tuberculosis epidemic in South Africa through the eyes of the lead author (KD) and a patient undergoing treatment for MDR tuberculosis, and the tribulations she faces in day to day life. The video shows the township setting in which the majority of patients in South Africa reside to provide insight into the environment and living conditions of those most affected and at high risk of tuberculosis.
- Interview by Meera Senthilingam with Kirt Ross, a patient with XDR tuberculosis whose treatment has failed to cure his condition and who is no longer receiving drug treatment for tuberculosis. Kirt discusses his experiences with treatment, stigma, and how he lives day to day knowing he carries a contagious and deadly infection.
- Video showing the lifelong effects that treatment for drug-resistant tuberculosis can have on an individual. Through her story, Phumeza Tisile shows that, although the disease is curable, the ramifications of drug-resistant tuberculosis forever change a patient’s life. The Human Spirit Project is a collaboration between Visual Epidemiology, the Stop TB Partnership, TB PROOF, and WHO.

Courtesy of Meera Senthilingam (Multimedia producer).
XDR tuberculosis. Nonetheless, identifying the initial causes of the problem by studying human populations is challenging, in part because of the multiple steps or transitions involved both in the pathogenesis of tuberculosis and in the emergence and transmission of resistance. Not only does each of the tuberculosis transitions (exposure, infection, and disease progression) have its own set of specific determinants, but distinct risk factors for resistance exist at each of these stages. We briefly review non-biomedical risk factors for the acquisition of MDR tuberculosis.

Previous exposure to antituberculosis drugs is consistently identified as a strong risk factor for MDR, but other host risk factors can vary in different geographical settings. Few studies have examined risk factors for primary MDR tuberculosis and the associations that have been reported have been inconsistent. A common finding across multiple studies is that patients with MDR tuberculosis tend to be younger than those with a drug-sensitive infection, with one meta-analysis reporting that patients with tuberculosis younger than 65 years were 2·5 times more likely to have MDR than those who are older than 65 years. A possible explanation for this is that older patients might have tuberculosis due to activation of a latent infection acquired before the emergence of drug resistance. Such data are consistent with findings from molecular epidemiological studies that show that younger age is a risk factor for recent transmission.

Many studies have identified socioeconomic or behavioural risk factors for MDR, although unsurprisingly, these factors vary across settings, most serving as indicators of poor access to high-quality health care. For example, foreign-born individuals in the Netherlands had almost twice the risk for MDR as people born locally. In Shanghai, internal migrants from other regions of China were 1·4 times more likely to develop MDR than individuals born in the city. Other groups at high risk in some settings include prisoners, who were shown to have double the incidence of MDR compared with civilians in Samara.
Oblast in Russia; 28 abusers of alcohol (odds ratio [OR] 8·53 in patients admitted to tuberculosis hospitals in St Petersburg and Ivanovo, Russia); intravenous drug users; and homeless people.

Although most studies focus on individual characteristics, these host risk factors might not lead directly to MDR tuberculosis but serve as indicators of poor access to high-quality care. Rather than identifying individual risk factors for resistance, recent research has increasingly focused on the attributes of communities and health systems in spatially distinct areas with a high burden of MDR tuberculosis. For example, a study in Moldova found that communities with a larger proportion of previously incarcerated patients with tuberculosis were more likely to be MDR hotspots than communities with fewer of these patients.39 Similarly, using county-level data from China, another group showed that factors such as health resources, health services, tuberculosis treatment, and tuberculosis detection, but not socioeconomic status, were associated with drug resistance.39

Comorbidities as risk factors for MDR
Two common comorbidities, HIV and diabetes mellitus, have been inconsistently associated with drug-resistant tuberculosis. A systematic review found that several studies have reported a high proportion of resistant cases in patients with tuberculosis co-infected with HIV in specific outbreak settings such as prisons and hospitals, but few studies have systematically compared prevalence of multidrug resistance between HIV-infected and uninfected patients after controlling for other factors. A 2009 systematic review that summarised 32 eligible studies noted a statistically significant association between HIV co-infection and primary but not secondary multidrug resistance, but most of the studies included patients with MDR tuberculosis. For example, a study in Kazakhstan showed that, although risk factors for HIV and MDR tuberculosis largely overlapped, HIV was not a risk factor for MDR once the socioeconomic risk factors for both diseases had been taken into account.10

A study in Kazakhstan showed that, although risk factors for HIV and MDR tuberculosis largely overlapped, HIV was not a risk factor for MDR once the socioeconomic risk factors for both diseases had been taken into account.10 Studies on diabetes as a risk factor for MDR tuberculosis have been similarly heterogeneous. Although multiple studies have reported a positive association, with ORs ranging from 1·2 to 8·5, others have found no association.11–14 Furthermore, many studies did not control for body-mass index, which is often high in people with type 2 diabetes, and can be associated with subtherapeutic serum drug concentrations that might lead to acquired resistance. In addition, the classification of patients simply as having type 2 diabetes without further stratification by glycaemic control, treatment modality, or renal function might result in the mixing of patients with substantially differing susceptibilities to drug resistance.

Modelling MDR epidemics
Mathematical models provide a means to explore the dynamics of drug-resistant tuberculosis in different epidemiological and intervention contexts. The simplest approach entails the construction of a compartmental model that describes the emergence of an epidemic as a function of the transmissibility of an infectious organism, the rate of person-to-person contact, and the duration of infectiousness. More elaborate simulations can be generated through individual or agent-based models that assign specific characteristics to each individual in a population. Early work on modelling MDR tuberculosis suggested that potential fitness costs concomitant with resistance-causing mutations might be offset by the longer duration of infectiousness of patients with MDR tuberculosis for whom access to effective therapy was delayed.36,37 More recent studies have modelled the potential effect of improving detection of drug resistance and access to effective treatment, or of reducing acquired resistance by enhancing treatment of drug-susceptible tuberculosis. These dynamic models have linked transmission models to economic models to predict the cost-effectiveness of specific intervention strategies.40,41 One study examined the estimated incidence of new and retreatment cases in countries with a high tuberculosis burden, and concluded that more than 95% of MDR tuberculosis is due to primary transmission of resistant strains.42 Consistent with the results described above, these findings suggest that a focus on early detection and improved treatment of MDR tuberculosis is needed to curtail future incidence.

Summary of epidemiology and risk factors for MDR and XDR tuberculosis
Despite technical challenges in the laboratory testing of drug susceptibilities and gaps in the data map, evidence from WHO-monitored surveillance activities suggests that drug-resistant tuberculosis is a global problem. Advanced resistance to first-line and second-line drugs has emerged as a significant threat to public health in several countries, including nations with a high burden of tuberculosis. Although previous exposure to tuberculosis drugs remains a major determinant for MDR tuberculosis, several social and behavioural risk factors have been identified, some of which relate to poor access to health care and social support networks. Further monitoring of resistance to second-line drugs is needed to enable assessment of XDR and resistance beyond XDR, including programmatically incurable forms of the disease.

Molecular epidemiology and transmission dynamics of drug-resistant tuberculosis in high-burden countries
Drug-resistant tuberculosis continues to be a threat to tuberculosis control.43 Molecular epidemiology has been important in advancing the knowledge of drug-resistant tuberculosis.44 A study in Kazakhstan showed that, although risk factors for HIV and MDR tuberculosis largely overlapped, HIV was not a risk factor for MDR once the socioeconomic risk factors for both diseases had been taken into account.10 Studies on diabetes as a risk factor for MDR tuberculosis have been similarly heterogeneous. Although multiple studies have reported a positive association, with ORs ranging from 1·2 to 8·5, others have found no association.11–14 Furthermore, many studies did not control for body-mass index, which is often high in people with type 2 diabetes, and can be associated with subtherapeutic serum drug concentrations that might lead to acquired resistance. In addition, the classification of patients simply as having type 2 diabetes without further stratification by glycaemic control, treatment modality, or renal function might result in the mixing of patients with substantially differing susceptibilities to drug resistance.
tuberculosis epidemics (figure 2). First, on a population basis, strain typing identifies strain relatedness, thus identifying chains of transmission (a cluster of isolates with identical genotypes according to IS6110 DNA fingerprinting,\(^5\) mycobacterial interspersed repetitive units–variable numbers of tandem repeat [MIRU–VNTR] typing,\(^6\) or whole-genome sequencing; figure 2) and providing an indication of how well a tuberculosis control programme functions with respect to transmission control.\(^{6,48}\) High clustering of drug-resistant tuberculosis strains is indicative of high levels of transmission, which might be because of the absence of appropriate case detection and diagnosis-associated delays (and hence treatment delays). By contrast, predominance of unique drug-resistant tuberculosis strains reflects the acquisition of drug resistance or reactivation of drug-resistant tuberculosis acquired many years earlier\(^5\) (panel 2). Second, on a patient level, strain typing provides insight into the mechanism whereby drug-resistant tuberculosis develops in an individual\(^6,15\)—ie, whether resistance developed in the patient during treatment (acquired resistance) or whether a patient was infected with an already resistant strain of *M tuberculosis* (primary resistance).\(^3\) Third, since drug resistance is caused mainly by particular mutations in the genome of *M tuberculosis* complex strains, molecular epidemiology tools using gene or genome sequencing are increasingly involved in the identification of drug resistance in clinical isolates.\(^5,15\)

Combined strain typing and targeted gene sequencing improve the accuracy of transmission studies of drug-resistant tuberculosis.\(^13\) Identification of resistance-conferring mutations forms the foundation of commercially available molecular diagnostics tests endorsed by WHO, including the Xpert MTB/RIF assay for simultaneous detection of *M tuberculosis* and rifampicin resistance, and the molecular line probe assays MTBDRplus and MTBDRsl for detection of resistance to first-line and second-line drugs.\(^52,62\)

The discourse around drug-resistant tuberculosis continues to rely on two deeply-rooted epidemiological dogmas. First, resistance has a fitness cost rendering drug-resistant strains less transmissible (in this case, we can regard fitness cost to be when bacilli grow more slowly in vitro; however, whether this is relevant in a clinical case is debatable).\(^11,14\) Second, resistance is believed to primarily be acquired by patients who were previously exposed to antituberculosis drugs (secondary resistance).\(^17\) Consequently, for decades, tuberculosis control policies have targeted prevention of drug-resistant tuberculosis through the WHO directly observed treatment, short course (DOTS) strategy and focused on detection of drug-resistant tuberculosis in individuals with a history of prior treatment for active tuberculosis (high-risk group).\(^65\) International policies have largely ignored patients who develop primary resistance. Only with the advent of molecular

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**Figure 2:** Timeline of key molecular epidemiological findings using different genotyping tools

Genotyping tools used for each finding are indicated by different colours. MDR=multidrug resistant. MIRU–VNTR=mycobacterial interspersed repetitive units–variable numbers of tandem repeat. XDR=extensively drug-resistant.
evidence for herd immunity.

### Epidemiology Tools and Terminology

**Table 1: Molecular epidemiological genotyping methods**

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For the SITVIT global database see http://www.pasteur-guadeloupe.fr:8081/SITVIT_ONLINE
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- **Panel 2: Strain typing definitions and interpretation**

**Cluster**

Isolates collected within a defined time period and geographical region with identical patterns on IS6110 RFLP, spoligotyping, or MIRU-VNTR are hypothesised to reflect recent transmission. This definition of a cluster can be flexible to allow for minor variation in the IS6110 RFLP or MIRU-VNTR patterns and evolutionary events. Within the context of drug-resistant tuberculosis, supporting the definition of a cluster with resistance-conferring SNP data is crucial.

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**Unique**

Drug-resistant isolates with unique IS6110 RFLP banding patterns, spoligotype patterns, or MIRU-VNTR types, and drug-resistant isolates with identical IS6110 RFLP banding patterns, spoligotype patterns, or MIRU-VNTR types but different mutations conferring resistance, reflect the acquisition of drug resistance (ie, secondary resistance). Similarly, isolates whose whole genome sequences differ by more than ten SNPs are interpreted to reflect the acquisition of resistance or reactivation of a previous drug-resistant tuberculosis infection or influx from a different community (migration).

RFLP—restriction fragment length polymorphism. SNP—single-nucleotide polymorphism.

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mutations might occur in genes coding the same protein or in the same or a linked metabolic pathway or pathways, thereby balancing fitness deficits or even raising the comparative fitness of drug-resistant isolates to surpass their drug-susceptible counterparts.90,91,92 Compensatory mutations have been described for rpoA or rpoC,93,94,95 ahpC,96 and 16S rRNA.97 Highly transmissible MDR outbreak clones with specific combinations of low-cost resistance and compensatory mutations have already emerged in several areas of the world.98,99,100 The transmissibility of these drug-resistant strains remains intact, even in the presence of up to nine resistance-conferring mutations.93,94,95 However, even strains with mutations associated with high fitness cost have emerged and spread in immunocompromised hosts.96,97

Challenging the dogma that drug-resistant tuberculosis is predominantly acquired

The 3·3% worldwide MDR tuberculosis prevalence in new cases versus 20% in previously treated cases has led to the widely held belief that most cases of MDR tuberculosis arise from acquisition of resistance during treatment rather than transmission of resistant strains. Using molecular epidemiological tools, various mechanisms for the development of drug-resistant tuberculosis have been described: 1) primary infection with a drug-resistant strain;92 2) re-infection with a drug-resistant strain during treatment for drug-susceptible tuberculosis;84 3) re-infection with a drug-resistant strain after successful treatment for drug-susceptible tuberculosis;84 4) mixed infection with a susceptible and resistant strain with unmasking of the resistant strain during treatment for drug-susceptible tuberculosis;84 and 5) acquisition of resistance during therapy.84 A major outcome of large-scale genotyping studies was that, in several high-incidence settings, the contribution of transmission for fuelling the drug resistance epidemic was underestimated.92,93,94,95

In most regions of the world, drug-resistant tuberculosis is now predominantly caused by transmission rather than acquisition of resistance, with an estimated 95-9% of MDR tuberculosis in new tuberculosis cases and 61-3% in previously treated cases being due to transmission.92 Even the epidemiology of XDR tuberculosis—defined as resistance to isoniazid, rifampicin, a fluoroquinolone, and an injectable agent—is now better understood as acquisition of resistance, with an estimated 95·9% of XDR tuberculosis in new tuberculosis cases and 61·3% in previously treated cases being due to transmission.92 Furthermore, since full DST profiling and individualised therapy are rarely done, strains with second-line resistance often continue to transmit. Consequently, drug-resistant strains can circulate and persist for decades, as has been shown in Argentina,99 South Africa,100 eastern Europe,92,101 and Portugal.102 However, our knowledge of the global extent of such

Clinical implications of the findings of molecular epidemiology

Clinical and public health practices for MDR tuberculosis management have been slow to change, partially reflecting the insufficient worldwide investment in MDR tuberculosis diagnosis and treatment. For example, drug susceptibility testing (DST) continues to focus on previously treated patients,103 and universal DST or DST beyond rifampicin is rarely done. Pyrazinamide, isoniazid (high dose), and ethambutol are still recommended as add-on agents in MDR tuberculosis treatment regimens, even in the absence of documented sensitivity—reflecting the low number of active agents available.104 Consequently, many patients with MDR tuberculosis are never appropriately treated for MDR tuberculosis or are treated with ineffective regimens, allowing for amplification of resistance and continued transmission. In 2014, only a quarter of all new MDR tuberculosis cases were detected and reported.104 Furthermore, since full DST profiling and individualised therapy are rarely done, strains with second-line resistance often continue to transmit. Consequently, drug-resistant strains can circulate and persist for decades, as has been shown in Argentina,99 South Africa,100 eastern Europe,92,101 and Portugal.102 However, our knowledge of the global extent of such
drug-resistant tuberculosis strains is limited to countries in which culture and molecular strain typing has been done. The observation that most drug-resistant tuberculosis is the result of transmission nevertheless raises hope, because reducing transmission through early and effective MDR tuberculosis treatment should halt transmission and thus control MDR tuberculosis epidemics. Indeed, some settings—from Estonia to New York—have seen steeper declines in the incidence of drug-resistant tuberculosis than in tuberculosis as a whole after adopting interventions to control the transmission of drug-resistant tuberculosis. Typically, these measures included universal DST, individualised treatment, access to tuberculosis care, and sustained efforts to improve treatment completion, which is only achieved in two-thirds of cases, even in well functioning programmes. The recent recommendation of a shorter-course MDR tuberculosis regimen in patients with rifampicin-resistant or MDR tuberculosis not previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable drugs has been excluded or is considered highly unlikely, could substantially improve treatment compliance and thus reduce transmission from patients who might otherwise fail to adhere to the standard 24-month toxic MDR tuberculosis regimen. For those diagnosed with pre-XDR tuberculosis (resistance to either a fluoroquinolone or second-line injectable drugs) and XDR tuberculosis, the availability of new drugs, including bedaquiline and delamanid, promises better treatment outcomes in those patients who previously had very low treatment success rates, potentially interrupting the spread of drug-resistant strains.

Figure 3: Inter-country and intra-country spread of drug-resistant tuberculosis according to *M* tuberculosis genotype

(A) Worldwide spread of drug-resistant strains of *M* tuberculosis. Red=Beijing strain, Green=LAM9 strain, Light blue=Haarlem1 strain, Purple=T1 strain.

(B) Ongoing intra-country spread of extensively drug-resistant tuberculosis strains in South Africa. Red=atypical Beijing strains. Green=LAM4 strain. Intra-country spread has also been reported in Portugal and Spain.
However, in the absence of careful stewardship the effectiveness of these drugs might be rapidly lost thereby potentiating the cycle of transmission.

The future of molecular epidemiology of drug-resistant tuberculosis: whole-genome sequencing

The advent and accessibility of whole-genome sequencing could revolutionise the field of molecular epidemiology because this method provides the ultimate resolution for strain classification, and has thereby challenged the accuracy of genotyping methods that have been used previously. As with other typing methods, transmission of *M tuberculosis* strains is measured by the relatedness of each strain’s whole-genome sequencing results. Recent reports have suggested that strains differing by less than 10 single nucleotide variations reflect transmission (figure 4). Deciphering tuberculosis transmission dynamics is crucial for the optimisation of local and global control measures and the early detection of MDR and XDR outbreaks. Whole-genome sequencing also provides a robust system for differentiating clinical isolates into major lineages and sublineages using an accurate nomenclature framework, paving the way for investigations of lineage-specific pathobiological characteristics.

Whole-genome sequencing also allows for the simultaneous characterisation of virtually all resistance markers in a given isolate. However, before whole-genome sequencing information can be used in routine clinical practice, several important issues need to be resolved. Whole-genome sequencing is complicated by the need for culture before DNA extraction, incomplete knowledge of all resistance-conferring mutations, and the need for a validated pipeline to accurately predict resistance. A relational sequencing tuberculosis data platform (ReSeqTB) is being developed in a partnership between the Foundation for Innovative Diagnostics and Critical Path to TB Drug Regimens to catalogue genotypic and phenotypic data and to provide a validated pipeline for the analysis of whole-genome sequencing. However, in the absence of a complete understanding of the association between genotype and phenotype, whole-genome sequencing or targeted sequencing will remain a rule-in assay for the presence of resistance. Further challenges will be the need to rapidly process whole-genome sequencing data and to communicate in a clinically and programatically relevant timeframe. This will be challenging, especially in high-burden countries in which whole-genome sequencing will most likely only occur at centralised reference laboratories. Finally, data will need to be presented in a clear, easily interpretable manner to clinicians and programme managers who are unfamiliar with sequencing technology. The application of whole-genome sequencing information to clinical care and tuberculosis control will thus benefit from research by microbiologists to establish the mutations conferring resistance and strain classification, and by experts in implementation science to optimally translate whole-genome sequencing results into policy and practice.

Next-generation molecular epidemiology

The diagnostic pipeline has recently undergone unprecedented innovation, with the development of several new molecular tests for diagnosis of tuberculosis and drug-resistant or MDR tuberculosis. WHO has endorsed Xpert MTB/RIF and the MTBDRplus, MTBDRsl, and Nipro line probe assays. New tests such as Xpert Ultra (Cepheid) or targeted whole-genome sequencing are in the advanced stages of development. Used in routine care, these molecular tests not only provide a diagnosis in an individual patient, but could also potentially be modified to provide mutation-specific information and phylogenetic data (eg, Xpert Ultra will detect IS6110 transposable elements) at a population level that could be used for monitoring drug resistance surveillance, detecting epidemics, and contact tracing. The potential utility of these tests (and evidence to support their use) for public health interventions unfortunately remains quite unexplored.

Examples of potential applications of molecular epidemiological data from diagnostic tests do exist. A preliminary study from South Africa found that Xpert MTB/RIF probe information, which differed substantially by geographical region, could be used for near real-time national surveillance using connected software, such as GXalert (open-source data connectivity for the GeneXpert). By documenting the increasing frequency of a specific mutation, these data could be used for identifying the emergence of drug-resistant tuberculosis or hotspots of MDR tuberculosis. Targeting these hotspots might be highly effective for controlling drug-resistant tuberculosis. However, as described by the routine strain typing service in the UK, the effect of molecular epidemiological data on patient care and public health response might not be useful if those data are not reported and acted upon quickly. To achieve this, major technical and systems barriers must be overcome, including the strengthening of information technology systems to facilitate timely capture, export, and potentially automated analysis of complex data, such as in web-based systems; linking molecular data to key epidemiological data (eg, geographical location); improving local scientific capacity; and providing decision makers with sufficient autonomy and resources to act in response to such data.

Summary of molecular epidemiology and transmission dynamics

Whole-genome sequencing and new molecular diagnostics promise to revolutionise our understanding of the epidemiology of *M tuberculosis*. Advances in these technologies have raised the prospect that molecular
The Lancet Respiratory Medicine Commission

epidemiology could be integrated into routine care. However, numerous challenges still remain with respect to the utility of these methods for the direct analysis of clinical specimens and whether such methods can be implemented in low-resource settings in which the burden of tuberculosis disease is highest. Whole-genome sequencing is computationally intense, delaying its real-time application for diagnosis and rapid programmatic interventions. Furthermore, analysis tools have some limitations: the definition of a transmission cluster remains poorly defined; repeat regions of the genome are excluded from the analyses; genomic deletions are missed; and the sensitivity for detecting heteroresistance and mixed infections is low. Resolution of these problems, together with more basic clinical and implementation research, will allow us to address the knowledge gaps regarding transmission, pathophysiology, and the association between mutations, microbiological resistance, and clinical impact.

The rise of drug-resistant tuberculosis

Historical notions on how drug resistance arises

In the past, the proximate cause of acquired drug resistance had been ascribed to poor adherence. However, acquired drug resistance was dealt with using a programmatic approach, specifically the DOTS strategy, to improve adherence. The idea of DOTS arose from the move from sanatoria-based care to ambulatory care, on the basis of studies in India and Hong Kong in the late 1950s and the 1960s, the main outcomes of which were for ambulatory patients to achieve the same rates of treatment compliance as was achieved in hospitalised patients, to attain the same treatment success. To achieve this compliance, supervision of outpatient therapy—not just in these countries but also in Western countries—and the development of intermittent therapy regimens was needed. The Styblo model, which included strict supervision and active case finding, expanded supervised outpatient therapy into international tuberculosis programme contexts, with trials in east Africa. These early efforts have evolved to the point at which supervised treatment is now universally advocated and is a pillar of the WHO DOTS policy. The DOTS programme has five elements: political commitment from governments, improved laboratory services, a continuous supply of high-quality drugs, lower cost anti-TB drugs, treatment of drug-resistant tuberculosis, and evaluation of programme performance.

Figure 4: IS6110 DNA fingerprint of 26 outbreak isolates

Genotypic analysis of 26 outbreak isolates. (A) IS6110 DNA fingerprint and spoligotype patterns and (B) genome analysis (modified from Kohl and colleagues). IS6110 DNA RFLP and spoligotyping patterns are identical (clustered), suggesting transmission. Whole-genome sequence analysis identified a total of 264 single-nucleotide polymorphisms between the different isolates which allowed for a higher differentiation of the outbreak strains in the minimum spanning tree. Four outlier strains with more than 50 single-nucleotide polymorphisms were identified. Colours depict strains from patients with direct epidemiological links—source case is coloured purple. RFLP = restriction fragment length polymorphism.
a reporting system to document the progress (and failure) of treatments for individual patients and for the programme, and direct observation to ensure that patients swallow all their pills. Strengthening DOTS programmes was credited with stopping the outbreaks of MDR tuberculosis in many regions in the USA, especially in New York City, the Dallas–Fort Worth Metroplex, and Baltimore.\(^{161–164}\) Emergence of acquired drug resistance eventually became equated with poor adherence, and high rates of acquired drug resistance were considered to be an indicator of poor performance of DOTS programmes. Thus, high numbers of patients defaulting from therapy is now considered an indicator of poor treatment outcomes in its own right, as bad as therapy failure. Acquired drug resistance continues to be a major problem in many places, including in programmes in which patients achieve high rates of adherence.\(^{165,166}\) Indeed, careful historical documentation has shown that the problem of \(M\) \(tuberculosis\) acquired drug resistance arose as soon as drug therapy first became available, and has continued being a problem from the 1950s to the present.\(^{25}\)

Several mechanisms were proposed for how poor compliance could lead to acquired drug resistance. In 1970, Hugo David performed fluctuation tests to identify \(M\) \(tuberculosis\) mutation rates, and identified average mutation rates (as mutation per bacterium per generation) of \(2.56 \times 10^{-8}\) for isoniazid, \(2.56 \times 10^{-7}\) for ethambutol, and \(2.25 \times 10^{-10}\) for rifampin.\(^{27}\) The probability of acquired drug resistance to two or more drugs is the product of these mutation rates, so the probability of acquired drug resistance for these three drugs in combination would be \(\sim 1 \times 10^{-25}\). In view of this low predicted probability, the only way acquired drug resistance was thought to be possible was with inadvertent monotherapy because of inappropriate prescribing, irregular drug supplies, or most importantly, poor patient adherence.\(^{28}\) Four scenarios or mechanisms were proposed for this inadvertent monotherapy.\(^{29}\) First, given the high bacillary burden in which mutants probably pre-existed, and that each antibiotic in the combination only works on specific metabolic sub-populations of the bacteria (eg, isoniazid is the only effective drug against rapidly growing bacteria; thus, monotherapy is effectively being given), isoniazid-resistant mutants would be selected if patients took the combination treatment for 2 days and then stopped. The second mechanism would arise during the sterilising effect, given that pyrazinamide would be the only effective drug for semidormant \(M\) \(tuberculosis\) under acidic conditions, and rifampicin for non-replicating persistent bacteria under hypoxia; mathematical models predicted that poor compliance would lead to acquired drug resistance in this situation.\(^{30}\) The third mechanism involves regrowth during subinhibitory concentrations of drugs, especially for drugs (such as isoniazid) that have a high therapeutic margin and a long half-life, because they remain present in the body after the clearance of other drugs. This is essentially a version of the pharmacokinetic mismatch hypothesis. The fourth scenario involves differential bacteriopausal mechanisms in which a drug such as rifampicin, whose post-antibiotic effect is shorter than of a companion drug such as isoniazid, selects isoniazid-resistant mutants during regrowth.\(^{31}\)

The lessons learned from the study of other bacteria, such as \(Staphylococcus aureus\) and Gram-negative bacilli, and simple evolutionary principles should not have been ignored. In the clinical setting, poor adherence is not the main driver of acquired drug resistance in many other bacteria. In fact, suboptimal antibiotic concentrations lead to acquired drug resistance as a result of simple evolutionary pressure, and some bacterial genetic hypermutable backgrounds could predispose some strains to a higher propensity for acquired drug resistance. Doses and dosing schedules that lead to suboptimal concentrations and a bacterial genetic background that facilitates acquired drug resistance cannot be overcome simply by improved adherence. Fortunately, in recent years, a better understanding that is supported by studies in standard bacteriology and pharmacology has emerged to explain \(M\) \(tuberculosis\) acquired drug resistance.\(^{75–77}\) Consideration of resistance mechanisms beyond gene mutations has also begun. However, this pharmacological approach does not exclude the role of tuberculosis programmes; rather it emphasises that the policy for abrogating acquired drug resistance that programmes implement should continue being revised to conform to the latest scientific understanding, which would strengthen the effectiveness of these programmes.

### The role of adherence in emergence of acquired drug resistance: preclinical models and evidence-based clinical approaches

One explanation of how non-adherence causes acquired drug resistance is pharmacokinetic mismatch. During periods of non-adherence, the drugs with shorter half-lives disappear so that \(M\) \(tuberculosis\) bacilli are exposed to monotherapy with the drug that has the longer half-life for periods of their growth, leading to resistance to that drug. This concept also applies to HIV drugs such as efavirenz with a half-life of 58 h, and stavudine and lamivudine with half-lives of 5–12 h. If the viral burden is \(10^{20}\) virions in the body with a mutation rate of \(4 \times 10^{-3}\) to \(2 \times 10^{-5}\) per base per cell and a doubling time of 10 h, the virus would be exposed to efavirenz monotherapy for a period of 2 weeks (ie, >30 doubling times).\(^{28}\) In the standard antituberculosis regimen, rifampicin and isoniazid both have a short half-life of 2–3 h and pyrazinamide has a half-life of 10 h, while \(M\) \(tuberculosis\) has a doubling time of 14–96 h and the mutation rates (\(2.56 \times 10^{-8}\) for isoniazid, \(2.56 \times 10^{-7}\) for ethambutol, and \(2.25 \times 10^{-10}\) for rifampin) identified by David,\(^{167}\) with a
total bacterial burden of $10^8$ in a cavity. The antibiotics are no longer present because clearance occurs before a single $M$ tuberculosis has replicated, and certainly by the second and third replications. This timing makes the probability of generation of mutants, or even amplifying pre-existing ones, less likely, particularly for non-probability of generation of mutants, or even amplifying second and third replications. This timing makes the single model of tuberculosis, on the basis of $M$ tuberculosis doubling times of 2.4 h and 2.40 h. This preclinical model was chosen because of the ease in which acquired drug resistance arises in the model. Acquired drug resistance did not arise with mismatched regimens, even when the inoculum was spiked with 0.5% rifampicin-resistant and isoniazid-resistant isogenic strains; rather, microbial kill was actually better with the most deliberately mismatched regimens compared with the most perfectly matched regimen, supporting a role for sequential dosing. The success of sequential dosing is probably because of reduced isoniazid–rifampicin antagonism in the most mismatched regimens. Thus, at least in the laboratory, pharmacokinetic mismatch was not likely to be involved in the emergence of XDR and MDR tuberculosis.

The hollow fibre model was also used to directly test the non-compliance hypothesis for acquired drug resistance and for amplification of pre-existent (0.5%) rifampicin and isoniazid resistance. This experimental model—which has a forecasting accuracy of 94% for clinical therapeutic events in patients with tuberculosis, based on evidence gathered for regulatory approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA)—enables experiments to be done that could be too dangerous in patients (eg, the deliberate generation of acquired drug resistance). Different degrees of adherence, from 0% to 100% of doses missed, and different adherence patterns (on–off; on–off–on–off, random missed doses) were used, and population size of the resistant subpopulations was captured via repetitive sampling with treatment of up to 56 days. No emergence of MDR tuberculosis was seen (except transient isoniazid resistance which eventually disappeared) in any system in a set of six repeat experiments, including those with a pre-existent resistant population of less than 1%. Similar findings were seen in the mouse model, in which no MDR tuberculosis arose with non-adherence. Thus, at least in two laboratory pre-clinical models, missing doses did not seem to lead to either MDR $M$ tuberculosis or amplification of acquired drug resistance.

In the past, the role of non-adherence in acquired drug resistance has been established in clinical settings by consensus on the basis of low-quality retrospective studies. These were the only type of studies available and thus represented the best available evidence at the time. Since then, at least five randomised controlled trials and five prospective observational studies, in which patients were assigned to self-administered therapy or supervised therapy (ie,DOTS, have been reported.

Recent meta-analyses of these prospective studies, in which quality was assessed and studies were ranked using standard evidence-based medicine criteria, examined the outcomes of therapy failure and acquired drug resistance. These meta-analyses are summarised in table 2. The three meta-analyses were concordant in showing that supervised therapy was effective in reducing non-adherence and improving treatment completion. The meta-analyses also showed that no benefits were associated with DOTS compared with self-administered therapy when microbiological failure and relapse were examined as clinical endpoints. Pasipanodya and colleagues showed that

<table>
<thead>
<tr>
<th>Study design</th>
<th>Number of subjects and study location</th>
<th>Hypotheses examined</th>
<th>Conclusions</th>
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</thead>
<tbody>
<tr>
<td>Volmink and Garner</td>
<td>Ten RCTs</td>
<td>Effects of DOT on tuberculosis cure, tuberculosis treatment completion, adherence, and latent tuberculosis treatment efficacy and adherence</td>
<td>DOT did not improve overall cure (RR 1.02, 95% CI 0.86 to 1.21). There was a possible small effect with home-based DOT compared with clinic DOT (RR 1.10, 95% CI 1.02 to 1.18)</td>
</tr>
<tr>
<td>(1997, updated 2007)</td>
<td>3985 patients from Tanzania, Nepal, Taiwan, Pakistan, Thailand, USA, and South Africa</td>
<td></td>
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</tr>
<tr>
<td>Pasipanodya and Gumbo (2013)</td>
<td>Ten RCTs and prospective studies</td>
<td>Compared DOT versus SAT on tuberculosis treatment failure, relapse, and ADR</td>
<td>DOT was not significantly better than SAT in preventing microbiological failure, relapse, or ADR; the pooled risk difference was 0.00 (95% CI -0.01 to 0.01) when DOT (n=415) was compared with SAT (n=532) for ADR</td>
</tr>
<tr>
<td>(2013)</td>
<td>8774 patients from Tanzania, Nepal, Taiwan, Pakistan, Thailand, USA, and South Africa</td>
<td></td>
<td></td>
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<tr>
<td>Karumbi and Garner</td>
<td>11 RCTs, including nine individual patient RCTs and two cluster RCTs</td>
<td>Effects of different forms and intensity of DOT on tuberculosis cure, tuberculosis treatment completion, adherence, and latent tuberculosis treatment efficacy and adherence</td>
<td>Proportion of patients whose disease was cured was still low and ranged between 41% and 65%. DOT did not improve overall proportion cured (RR 1.08, 95% CI 0.91–1.27); no significant difference in proportion whose disease was cured was seen between different forms of DOT (facility based vs community based) or the person supervising (health care worker, family, or community member)</td>
</tr>
<tr>
<td>(2015)</td>
<td>5662 patients from Tanzania, Nepal, Taiwan, Pakistan, Thailand, Australia, USA, and South Africa</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DOT=directly observed therapy. SAT=self-administered therapy. ADR=acquired drug resistance. RCT=randomised controlled trial. RR=relative risk.
acquired drug resistance developed in seven of 415 (1.69%) patients randomised to supervised therapy (i.e., DOTS) versus five of 532 (0.94%) who were randomised to self-administered therapy, with a risk difference of 0.00 (95% CI: -0.01 to 0.01). The incidence of acquired drug resistance was the same whether supervised therapy was given at home, in a health facility, by a family member, or by a community health-care provider. None of these analyses identified single study effect or bias.

Despite this apparent absence of an effect, the DOTS programme is useful because it is an example of political commitment by governments and ensures the continuous supply of good-quality drugs, which directly affects pharmacokinetic variability. Equally important are good laboratory services, which affect the accuracy of susceptibility testing and measurement of minimal inhibitory concentrations (MICs), which are crucial in defining MDR and XDR tuberculosis, and, in triaging patients to different regimens. Accumulating evidence, based on the latest evidence-based approaches, indicate that causes of acquired drug resistance in tuberculosis should be sought elsewhere other than poor adherence.

**Pharmacokinetic variability and acquired drug resistance**

To demonstrate the common scenarios that lead to acquired drug resistance in patients with tuberculosis, we refer to a paediatric case report by Garcia-Prats and colleagues. They described a boy aged 25 months infected with drug-susceptible tuberculosis, who was treated with a meticulous directly observed therapy, but sequentially developed isoniazid acquired drug resistance after 2 months of therapy, and then rifampicin acquired drug resistance after 5 months. The reason was established as low serum isoniazid and rifampicin concentrations, due in part to rapid metabolism of isoniazid by NAT2*4/2*7B in the child, who was given the standard therapy at the time. Thus, despite the paucibacillary nature of this disease in children, pharmacokinetic variability was crucial in the emergence of MDR tuberculosis. This scenario has also emerged as an important and common proximate cause of acquired drug resistance in adult patients with tuberculosis.

Hollow fibre studies in tandem with in-silico clinical trials predicted that, given the xenobiotic metabolism patterns in the Western Cape in South Africa, a proportion of patients would actually be on monotherapy despite being given the full multidrug regimen and being part of a DOTS programme. This is because of the differential rapid elimination of some drugs in the regimen, leading to prolonged monotherapy with the drug that is not rapidly or extensively metabolised over tens to hundreds of rounds of bacterial replication. The in-silico study predicted that 0.68% of patients would develop acquired drug resistance and MDR tuberculosis within 2 months despite 100% adherence, because of such differential pharmacokinetic variability of regimen components. A prospective clinical study in the same population was performed, and identified suboptimal drug concentrations due to pharmacokinetic variability as the cause of failure of therapy in more than 90% of patients. Acquired drug resistance, including MDR tuberculosis, was encountered in 0.7% of patients during the first 2 months, despite adherence to standard doses of isoniazid, rifampicin, pyrazinamide, and ethambutol. All cases of acquired drug resistance, including MDR tuberculosis, were preceded by suboptimal drug concentrations due to pharmacokinetic variability.

A meta-analysis of 13 randomised studies with 1631 rapid isoniazid acetylators and 1751 slow acetylators showed that rapid acetylators had 2.0 times higher occurrence of isoniazid acquired drug resistance compared with slow acetylators. This increased microbial failure and acquired drug resistance was due to pharmacokinetic variability to only one of the three main drugs in the regimen. Recent studies have extended this finding to aminoglycosides in patients with MDR tuberculosis. Dhera and colleagues have proposed and tested further pharmacokinetic variability at the level of drug penetration into tuberculosis lesions, which is dependent on the architecture of the tuberculosis lung cavity, for more than eight drugs. The lung cavity and surrounding fibrosis, depending on the size, will create a physicochemical barrier to drug entry, leading to anatomical site-based monotherapy. Indeed, this differential penetration has also been identified in pericardial and meningeal tuberculosis.

Some problems exist in the tuberculosis programme that will exacerbate pharmacokinetic variability, such as drug stock shortages, and that many drug stocks include counterfeit drugs with low concentrations of active pharmaceutical ingredient, so the drug is unknowingly taken at low concentrations even when first administered. In addition, health-care workers might prescribe lower doses than those needed to achieve the required optimal drug concentrations because of error.

**Figure 5: Antibiotic resistance timeline**

Exposure to low drug concentrations caused by various factors often initiates the process of antibiotic resistance. Low concentrations of active pharmaceutical ingredient is a common problem, with low-quality drugs produced by some manufacturers as well as from counterfeit drugs. Early events include induction of multiple efflux pump genes, with RNA upregulation of up to 50 times. Phenotypic low-level resistance can then occur, which is reversed by efflux pump inhibitors. Over time, a subpopulation of the bacteria replicate, with mutations in the antibiotic target site and efflux pumps. In the event that there is heteroresistance at the start of therapy, the process is still operational for both the resistant and susceptible subpopulations. Additionally, part of the susceptible bacterial subpopulation is killed at high drug exposures, leaving the resistant subpopulation.
or weight-based capping dosing practices (when dosing is capped at a particular maximum for the individual patient weight), which are often used in tuberculosis programmes, especially when fixed-dose formulations are given. All these factors converge to increase the chances of delivering suboptimal drug concentrations.

The role of efflux pumps in antibiotic resistance

Laboratory experiments and clinical observations, combined with the consideration of non-adherence, biological variability, evolution, and efflux pumps, have led to another theory of the mechanisms underlying drug resistance, in which efflux pumps and chromosomal mutations represent a single process of acquired drug resistance.\(^\text{171–173,194,195}\) In this theory of drug resistance (figure 5) several initiating factors exist such as low drug dosage due to poor dosing practices, pharmacokinetic variability, or inadvertent mono-therapy with, for example, quinolones for bacterial pneumonias and other conditions that turn out to be tuberculosis. As part of the bacterial stress reaction to the suboptimal antibiotic concentrations—and to effective monotherapy—efflux pumps in the bacilli are upregulated within hours. This increase can be demonstrated by quantifying transporter messenger RNA, and is followed within a few days by phenotypically demonstrable low-level resistance that is reversed by efflux pump inhibitors such as verapamil. This process is evolutionarily conserved in \(M\) \(tuberculosis\), \(Mycobacterium avium\) complex, \(Mycobacterium leprae\), \(Mycobacterium marinum\), \(Mycobacterium abscessus\), and \(Mycobacterium ulcerans\).\(^\text{200}\) This efflux pump-dependent low-level resistance process allows the bacteria time to undergo multiple rounds of replication under suboptimal antibiotic pressure or monotherapy, allowing for development of mutations in the canonical drug resistance genes, in efflux pump genes, or in negative regulators of efflux pumps.\(^\text{206}\) The mutations in efflux pump regulators lead to high-level resistance, usually to multiple antibiotics. The demonstration of co-occurrence of canonical mutations in drug target genes and MICs that decrease in the presence of an efflux pump inhibitor, as well as recent studies in clinical isolates, seem to support this new idea.\(^\text{197,198,199–201}\)

Some phylogenetic lineages of \(M\) \(tuberculosis\) (genotypes) and the strains of these lineages have greater propensity to cause acquired drug resistance—this theory has been especially recognised since the Beijing strain started gaining notoriety in the MDR tuberculosis epidemic.\(^\text{209}\) Ford and colleagues\(^\text{210}\) did Luria-Delbrück fluctuation analysis on a panel of laboratory and clinical isolates from lineage 2 and lineage 4, to which the Beijing strain belongs, and found the number of mutants per cell plated in a single culture ranged from \(2.42 \times 10^9\) for the CDC-1551 strain (lineage 2) to \(1.94 \times 10^8\) for the HN878 strain (lineage 4), which was a significant difference.\(^\text{211}\) In the case of \(M\) \(tuberculosis\) genotypes associated with higher mutation rates, there could be a pre-existing subpopulation already resistant to one or two antibiotics before commencement of therapy.\(^\text{209}\) Indeed, mathematical modelling predicted a probability of the emergence of resistance to both isoniazid and rifampicin of \(1 \times 10^{-5}\) to \(1 \times 10^{-4}\) before commencement of therapy, suggesting that prior existence of MDR might be common.\(^\text{206}\) These patients would have a mixture of both drug-susceptible \(M\) \(tuberculosis\) and drug-resistant \(M\) \(tuberculosis\) that have arisen from a single strain. By contrast, there are also groups of patients infected by mixed strains, one resistant and the other susceptible. These scenarios lead to so-called heteroresistance, which is encountered in 7–25% of patients with MDR tuberculosis, patients previously treated for tuberculosis, and those in whom first-line therapy failed.\(^\text{70,205,246}\)

Treatment with standard regimens or MDR tuberculosis regimens would lead to rapid selection of the drug-resistant subpopulations, either on the basis of classic Luria-Delbrück considerations, or the antibiotic resistance process shown in figure 5.\(^\text{207}\)

Redefining drug resistance, MDR tuberculosis, and XDR tuberculosis by changing susceptibility breakpoints

\(M\) \(tuberculosis\) is considered drug resistant when >1% of \(M\) \(tuberculosis\) cultures grow in the presence of critical drug concentrations. Critical concentrations are derived from epidemiological cutoff values on the basis of their ability to kill 95% of wild-type isolates or the 95% MIC on a normal distribution curve.\(^\text{208}\) The problem with this definition is logical and mathematical: what do the parameters of the Gaussian curve of the MIC distribution have to do with how well a patient will respond to therapy?\(^\text{209}\) Wild-type MIC distributions of any organism vary between regions because of local evolutionary drivers, so it is unclear which to use.\(^\text{209}\) The idea that all wild-type distributions are the same is assumed in general microbiology—but they aren’t the same, and data show that \(M\) \(tuberculosis\) is no exception. Using pharmacokinetic–pharmacodynamic principles, and the knowledge that microbial kill with a fixed ceiling concentration decreases as MIC of the drug increases, Gumbo\(^\text{209}\) proposed that drug resistance should be defined.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Standard or WHO MIC</th>
<th>Proposed MIC</th>
<th>Breakpoint, above* which therapy fails</th>
<th>Lowest MIC in mutants carrying resistance mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>0.2; 1.0†</td>
<td>0.03; 0.125†</td>
<td>0.0312</td>
<td>0.03-0.125</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1</td>
<td>0.06-0.25</td>
<td>0.125</td>
<td>0.125-0.6-0.25†</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>5; 7.5†</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>100</td>
<td>50</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
<td></td>
</tr>
</tbody>
</table>

MIC=minimal inhibitory concentrations. *shown a range. †unknown value. *Since MICs are determined on the basis of two-fold dilution steps, but classification and regression tree analyses calculate exact MIC breakpoints, the values presented in the table indicate the nearest observed MICs that fulfill the non-strict inequality values. †Where two values are given, this indicates the high and low level of resistance. Data are from several sources.\(^\text{171–173,194,195}\)

Table 3: Clinical and microbial evidence to support proposed susceptibility breakpoints of different antibiotics

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as the MIC at which the antibiotic fails to kill *M tuberculosis* in a patient taking the maximum tolerated dose. If the drug cannot kill the bacteria in the lungs of patients because its MIC is high, then the bacteria are resistant. In view of this, mathematical modelling and simulations have identified the MICs at which isoniazid, rifampicin, ethambutol, pyrazinamide, and moxifloxacin fail (table 3).10 These MIC values differ substantially from the consensus breakpoints that are used by WHO, suggesting that the problem of MDR tuberculosis, and thus also XDR tuberculosis and incurable tuberculosis, is much more severe than appreciated.
Confirmation of these lower critical concentrations have come from clinical studies209–213 and several investigations214–221 of drug resistance-associated mutations in isolates with MICs below the standard breakpoint. Clinical studies using assumption-free methods such as machine learning have confirmed that these values (table 3) are in fact the MICs above which tuberculosis patients fail combination therapy.209,212,213 As an example, on the basis of an analysis of 207 patients with MDR tuberculosis in China, Zheng and colleagues213 identified the same proposed susceptibility breakpoint for pyrazinamide as the pharmacokinetic–pharmacodynamic breakpoint (table 3), and calculated a sensitivity of 89% and a specificity of 93% for treatment success. Thus, the proposed breakpoints are relevant in terms of patient outcomes. Additionally, studies have been done in which treatment failed in patients who were infected with M tuberculosis who had drug target site mutations, but MICs were lower than current breakpoints, and were more consistent with the newly proposed breakpoints.218,221 Therefore, the proposed concentrations have higher sensitivity for clinical decision making, and should be used to estimate the global burden of MDR tuberculosis.

Mutations identified by whole-genome sequencing that are associated with XDR or MDR tuberculosis

Acquired drug resistance in M tuberculosis is considered to be mostly caused by chromosomal mutations that lead to drug-target modification, as is the case with rifampicin and rpoB. Drug resistance can also occur in enzymes that convert prodrugs to active moiety—eg, catalase-peroxidase and isoniazid. Another common mechanism resulting in acquired drug resistance involves mutations that lead to activation of efflux pumps. Traditional sequencing targeted at some antibiotic targets and the use of whole-genome sequencing for an unbiased identification of mutations associated with drug resistance have revealed a myriad of mutations directly leading to resistance on the basis of these three mechanisms, as well as compensatory mutations. A comprehensive list of these mutations is provided in table 4.198,232,76,223–225,77

Summary of the rise in drug-resistant tuberculosis

New efforts have been made to understand how acquired drug resistance and MDR tuberculosis arise in patients. Preclinical studies, prospective clinical studies, and meta-analyses have not identified the role of adherence in acquired drug resistance, contrary to common beliefs. Pharmacokinetic variability has emerged as an important proximate cause of acquired drug resistance in vitro, in mathematical simulations, in prospective clinical studies, and in meta-analyses. Another new hypothesis is that efflux pumps and final-target mutations associated with acquired drug resistance are linked and part of one process. One pivotal study210 proposed different mutation rates for the different phylogenetic lineages of M tuberculosis, which could explain why drug resistance emerges commonly in some locations. Finally, we propose that the susceptibility breakpoints should be revised on the basis of pharmacokinetic–pharmacodynamic approaches and patient outcomes.

Diagnosis of MDR and XDR tuberculosis

Drug-resistant tuberculosis occurs when M tuberculosis bacilli undergo mutations that enable it to survive the effects of tuberculosis drug treatments. Unlike many other bacteria, no horizontal acquisition of resistance has been shown in M tuberculosis, and a drug-resistant strain can be defined as one that differs significantly from wild strains in its degree of susceptibility because of the increased proportion of resistant mutants.289 Testing the susceptibility of M tuberculosis to antituberculosis drugs might be done either for patient management or as part of a surveillance programme to monitor the effectiveness...
of local treatment protocols. An important distinction between the two is the need for urgency; patients on inappropriate treatment are unlikely to recover. They could remain infectious and therefore a source of onward transmission. Drug resistance testing reveals drugs of reduced or no curative benefit, thus facilitating construction of an individualised, optimised treatment regimen. Other factors deserving consideration in the treatment of drug-resistant tuberculosis are drug toxicity and individual patient tolerance. In most high-income countries with a low prevalence of tuberculosis, all patient isolates are routinely screened for susceptibility to the major antituberculosis drugs.227 In settings with a high incidence of disease or scarce resources, testing is often restricted to those cases for which drug resistance is suspected. Previously, in high-burden countries and in locations where second-line drug therapies were not available, routine drug susceptibility testing was not considered a priority.228 However, the emergence of MDR and XDR tuberculosis prompted a change in WHO strategy in 2006229 and the capacity for testing has been expanded since.230 Despite these efforts, access to tests for MDR remains poor (figure 6).

Facilities for drug susceptibility testing are scarce in many parts of the world, and less than a quarter of the estimated tuberculosis cases with resistance to rifampicin are confirmed by laboratory tests.

Phenotypic testing
Culture-based phenotypic drug-susceptibility testing (DST) methods provide a measure of the susceptibility of bacteria to a drug. Routine DST is normally based on qualitative methods that assess in-vitro growth using a single critical concentration of the drug.231 The results are typically reported as susceptible or resistant and are less precise than those generated by semiquantitative methods, whereby bacteria are grown at a range of drug concentrations so the MIC can be established.232 Semi-quantitative data have therapeutic implications because it differentiates between susceptible and resistant strains, and it also detects moderate or low-level resistance where increased dosage might be beneficial to the patient.233,234 The first DST methods were developed and validated for solid culture using Löwenstein-Jensen slopes or agar plates. For the proportion method, bacteria are grown on drug-containing and drug-free media.233 The numbers of colonies on the drug-containing media are counted and expressed as a percentage of those on the drug-free media. If the proportion exceeds the critical proportion for that drug then the strain is classed as resistant. To ascertain the MIC, the bacteria are exposed to a series of media containing serial two-times (log₂) dilutions of the drug. MICs of test strains are compared with the upper MIC limit or the epidemiological cutoff value of wild-type strains.232 WHO defines the MIC for *M tuberculosis* as the lowest concentration of drug that inhibits 95% of a wild-type strain (that has never been exposed to drug) while allowing clinically resistant strains to grow.

DST is also performed in the commercial automated liquid-based culture systems such as the MGIT 960, for which results can be obtained in 7–12 days.233 Alternative low-cost DST methods have been developed
that use microscopic observation of colonies or oxidation-reduction dyes to indicate growth of bacteria.\textsuperscript{24,25,26}

From a clinical perspective, the main drawback of DST is the time taken to obtain a result. To increase the speed of detection, clinical specimens can be screened directly so that the delays incurred during isolation and pre-culture are avoided.\textsuperscript{27} However, this is only feasible for a small number of drugs and is not a suitable method for measuring MICs.

Phenotypic testing is technically demanding and can be affected by interactions of the drug with the culture media and the propensity of hydrophobic \textit{M tuberculosis} bacilli to form clumps. Different critical drug concentrations have been adopted for different culture systems.\textsuperscript{28} In 1994, WHO and the IUATLD established a Global Surveillance Project with a network of supranational reference laboratories to standardise methods and introduce international quality standards for drug susceptibility testing.\textsuperscript{29} DST is considered the reference standard by which new genotypic tests are compared. However, discrepancies between methods are not uncommon and it has been suggested that for rifampicin, genotypic analysis offers a more reliable reference standard.\textsuperscript{20,29,30}

Simple binary classification on the basis of a single critical concentration into susceptible and resistant is evidently not sufficient. Drug susceptibility tests for pyrazinamide, ethambutol, ethionamide, and para-aminosalicylic acid are less reproducible than phenotypic tests for the drugs for which resistance defines MDR and XDR tuberculosis (isoniazid, rifampicin, fluoroquinolones, and second-line injectable drugs) and the data obtained are considered less reliable.\textsuperscript{26} The critical concentrations need to be reconsidered in accordance with modern principles of setting clinical breakpoints (wild-type MIC distributions, pharmacokinetic–pharmacodynamic considerations, and outcome data).

Genotypic testing

Genotypic tests predict resistance to a drug but do not establish susceptibility, and a negative genotypic test result is usually reported as no resistance detected. Drug resistance in \textit{M tuberculosis} can arise from mutations in the bacterial DNA that render the organism immune to the action of the drug. The most frequently observed cause of resistance are SNPs in genes encoding drug targets or converting enzymes, but large deletions might also result in resistance.\textsuperscript{31,32} A summary of loci implicated in resistance to antituberculosis drugs is presented in table 4. A review of the loci is not included in this Commission, and for a comprehensive list of resistance-causing mutations (1325 polymorphisms [SNPs and indels] at 992 nucleotide positions from 31 loci, 6 promoters, and 25 coding regions) and corresponding aminoacid changes, we refer the reader to the London School of Hygiene & Tropical Medicine TB Profiler.

\textit{M tuberculosis} is naturally resistant to several antibiotics because of the impermeable nature of the cell wall.\textsuperscript{26} Transmembrane transporter molecules and efflux pumps might aid in the emergence of resistance, but no putative diagnostic efflux gene polymorphisms have been identified. Epigenetic factors are likely to be involved in the regulation of such transporter mechanisms but have not been extensively investigated in \textit{M tuberculosis}.\textsuperscript{26} Considerable progress has been made in understanding the mechanisms of resistance for most key first-line and second-line antituberculosis drugs, but further work is needed to identify the full range of mutations and to define their clinical efficacy.\textsuperscript{26}

Resistance to rifampicin is almost entirely due to changes in the \(\beta\) subunit of DNA-dependent RNA polymerase, which is encoded by the \textit{rpoB} gene.\textsuperscript{26} Molecular tests targeting this gene are more accurate than using phenotypic DST.\textsuperscript{26} However, caution must be used when interpreting data from some molecular tests because not all mutations have the same effect. Silent mutations can occur, where replacement of a nucleotide does not necessarily result in resistance. An example of a silent mutation can be seen in \textit{rpoB} (TTC→TTT; Phe514Phe), which does not result in an aminoacid change, and tests that only detect changes at that nucleotide position without identifying the nucleotide involved might give false-positive resistance results.\textsuperscript{26}

Regardless, the high sensitivity and specificity of the molecular targets (SNPs) for rifampicin resistance,\textsuperscript{26} and their value as a tool for predicting MDR tuberculosis has supported commercial in-vitro diagnostic products to enter the market.

Xpert MTB/RIF

Xpert MTB/RIF is an easy-to-use automated PCR-based test that diagnoses tuberculosis and detects mutations predictive of resistance to rifampicin in less than 2 h. The test was endorsed by WHO in 2010\textsuperscript{26} and is recommended as a front-line diagnostic test and tool to assist in the management of MDR tuberculosis.\textsuperscript{26} Regulatory approval has also been granted by the FDA who recognised the potential for false-negative results, with the recommendation that phenotypic testing should also be performed.\textsuperscript{26} Concerns about the accuracy of the Xpert MTB/RIF test and reports of false-positive rifampicin resistance results have led countries such as Brazil and South Africa to adopt a policy of confirmatory testing.\textsuperscript{26,29,30,31} The manufacturers have reported that a new version of the Xpert MTB/RIF test is under development (Xpert ULTRA) in which the diagnostic targets and rifampicin-resistance detection chemistry have been changed, with the aim of increasing test accuracy. The test is being assessed by its developers and is expected to be released for sale and independent assessment in 2017.

The GeneXpert test combines sample extraction and analysis within a single sample cassette that is processed and analysed by placing it within the GeneXpert
instrument, thus is very simple to use; however, the test has high costs associated with manufacture. A four-module GeneXpert instrument and ancillary equipment costs ~US$20,000 (ex-factory) and a single-use test cassette costs ~$10. To test every individual with suspected tuberculosis the estimated cost is $434–468 million per year. A consortium of international donors led by UNITAID is providing financial support to facilitate reduced pricing for public-sector procurers in countries with a high tuberculosis burden. However, annual maintenance costs and periodic replacement of the modules might mean that affordability and sustainability of this technology for routine use in countries with a high burden of tuberculosis is unlikely.

**Line probe assays (LPAs)**

In addition to the GeneXpert technology, WHO has endorsed LPA molecular technology for detecting drug resistance. Following amplification of the target gene, LPA technology reverse-hybridises samples to a series of oligonucleotide probes immobilised on a membrane. The most widely studied tests are the GenoType MTBDRplus for rifampicin and isoniazid and the GenoType MTBDRsl-v1.0 assay for fluoroquinolones, aminoglycosides, and ethambutol. The GenoType MTBDRsl-v1.0 was the first commercially available test for XDR tuberculosis. A Cochrane systematic review of published performance data found a pooled sensitivity compared with DST of 83·1% (95% CI 78·7–86·7) and a pooled specificity of 97·7% (94·3–99·1) when testing cultured bacteria for resistance to fluoroquinolones. The test maintained similar accuracy to that seen when testing cultured bacteria when used to test samples of smear-positive sputum, with a sensitivity of 85·1% (71·9–92·7) and specificity of 98·2% (96·8–99·0). When testing cultured isolates for resistance to second-line injectable drugs, pooled sensitivities were 87·9% (82·1–92·0) for amikacin, 66·9% (44·1–83·8) for kanamycin, and 79·5% (58·3–91·4) for capreomycin. Specificities were 99·5% (97·5–99·9) for amikacin, 98·6% (96·1–99·5) for kanamycin, and 93·8% (93·4–97·3) for capreomycin. Few studies reported testing smear-positive sputum for second-line injectable drugs; the pooled sensitivity was 94·4% (25·2–99·9) and the pooled specificity was 98·2% (88·9–99·7). Wide variation in sensitivities was observed across study sites, ranging from 1% to 100%. Clonal spread during transmission of resistant strains increases the prevalence of particular polymorphisms and the sensitivity and predictive value of a test might vary by geographical location and population. The suboptimal sensitivity of the LPA tests for extensive drug resistance suggests that a negative test result does not rule out resistance, and DST should be undertaken to confirm the susceptibility of the strain. High specificity is crucial because false-positive results might lead to the unnecessary rejection of effective drugs and, in some cases, misclassification of patients as having MDR or XDR tuberculosis.

A newer version of the Hain XDR test is available (GenoType MTBDRsl-v2.0), which incorporates an extended range of loci using 27 probes for the detection of fluoroquinolones and aminoglycosides. Fewer data have been published on this new test, but a European study found similar sensitivity to the previous version of the test when testing isolates for detection of fluoroquinolone resistance (83·6%; 95% CI 73·4–90·3) and a high specificity of 100% (97·6–100). For detection of resistance to second-line injectable drugs, sensitivity was 86·4% (79·9–91·0) and specificity was 90·1% (81·7–94·9). Similar results were obtained when testing smear-positive clinical samples for fluoroquinolone resistance with a sensitivity of 93·0% (83·3–97·2) and a specificity of 98·8% (95·1–99·4), and for resistance to second-line injectable drugs; 88·9% (78·8–94·5), and 91·7% (86·5–95·0).

LPA requires an operator who is skilled in molecular techniques, and precautions are needed to avoid ampicillin contamination that would render the results invalid. Additionally, considerable laboratory infrastructure is needed, so LPA is only suited for use in tertiary centres and reference laboratories. Semi-automated and robotic systems are available to assist sample preparation, and although colorimetric readouts can be read by eye, instrumentation is highly recommended. The costs of LPA technology are negotiable and vary according to location and customer status, and preferential pricing for Hain Biosciences products is available for the public sector in low-income and middle-income countries with a high burden of tuberculosis. Start-up equipment costs are approximately US$50,000 and the test and DNA extraction kit cost is approximately $15 per patient. Three other manufacturers have developed LPA products for drug-resistant tuberculosis, including the REBA MTB-XDR test (YD Diagnostics, Korea), which tests for rifampicin and isoniazid or ofloxacin, or kanamycin and streptomycin; the tuberculosis resistance module (Autoimmun Diagnostika GmbH, Germany), which tests for rifampicin and isoniazid, streptomycin, fluoroquinolones, second-line injectable drugs and ethambutol; and TM/MDR TB LPA (Nipro Co, Japan), which tests for rifampicin and isoniazid, or pyrazinamide or fluoroquinolones. These tests have not yet been subjected to extensive independent assessment, and robust data on their performance and pricing was not available at the time of writing.

**Compensatory mutations**

One of the challenges when assessing the effect of polymorphisms on drug efficacy is the accumulation of compensatory mutations. These changes can abrogate the negative effects of resistance mutations on the bacteria, restoring fitness and giving selective advantage. Such compensatory changes in the genome might be strongly associated with resistance but are not causative and so should not be used to diagnose resistance. A second form of compensatory mutation has recently been described
in which susceptibility of a drug-resistant mutant is restored by additional mutations in the gene.260 Fluoroquinolone resistance often arises because of changes in DNA gyrase caused by mutations in GyrA. However, susceptibility to ofloxacin can be restored by additional mutations in the gene that infers hypersensitivity.261 Therefore, strains should be checked for the resistance-conferring mutations and the restorative compensatory mutations. Although this phenomenon is rare, it has great significance for patients, because a false-positive test for fluoroquinolone resistance could result in a misdiagnosis of XDR tuberculosis and unnecessary treatment with drugs of heightened toxicity. Commercial tests for fluoroquinolones do not incorporate the hypersensitivity mutations in their analysis and so might overdiagnose XDR tuberculosis. Notably, phenotypic tests are not affected by compensatory mutations.

Differentiating resistance levels
Phenotypic identification of MICs shows variation in the tolerance of bacteria to antibiotics. The degree of disruption caused by a mutation is associated with its position within a gene, and the part played by that gene in the action of the drug. Increased dosage can provide a therapeutic solution for some drugs for which there is low-level resistance, because the resistance can be overcome by high-dose treatment. An example is the common first-line drug rifampicin, in which changes in the conformation of the drug binding site cause high-level resistance, but mutations at sites outside of that region result in lower MICs.260 Similarly, mutations in inhA typically confer low-level resistance to isoniazid, whereas katG mutations confer high-level resistance.260

Mutation analysis also offers some advantages in differentiating susceptibilities to closely related drugs; cross-resistance in drug families is common, but not universal. DST for each fluoroquinolone, aminoglycoside, and rifampicin used in the treatment of tuberculosis would be slow and costly; however, mutation analysis can be used to predict susceptibility for individual drugs within a family. Thus, the Ala90Val mutation in gyrA causes lower resistance to levofloxacin (2 μg/mL) and moxifloxacin (1 μg/mL) than to ofloxacin (4 μg/mL), and for such cases, treatment with a higher dose of moxifloxacin might succeed while treatment with ofloxacin might be unsuccessful.261 Similarly, mutations at codon 516 in rpoB cause resistance to rifampicin but do not increase the MIC of rifabutin to above the critical threshold of 0.5 μg/mL.262 Further studies are required to validate these observations, but providing additional treatment options for patients with extensive resistance would be highly beneficial. One phenomenon that neither genotypic or phenotypic testing can assess is environmentally induced phenotypic changes. Bacilli that have become dormant might resist the action of bacteriostatic drugs, and changes in cell wall structures can hinder drugs from entering the bacilli. Such conditions, if temporary, will not be observed during in-vitro growth and do not represent the emergence of a transmissible drug-resistant strain.

Sequencing approaches
For patients with rifampicin-resistant tuberculosis, follow-on testing to identify resistance to additional drugs is advisable because it will allow treatment regimens to be optimised. Use of ineffective second-line drugs might inadvertently promote amplification of resistance and the emergence of XDR tuberculosis. Timely access to curative treatment would reduce opportunities for onward transmission and might reduce morbidity and mortality. The use of multidrug cocktails to treat tuberculosis has resulted in the identification of a complex array of polymorphisms that are responsible for resistance. Although a single gene is involved for rifampicin resistance (rpoB), several genes might be involved for some other drugs (table 4 presents a summary list of loci and common mutations). Molecular tests are limited in the number of loci they can analyse at one time, and although sequential testing of a few drugs at a time is possible, it will increase costs and might delay access to effective therapy. DNA sequencing examines all nucleotide positions, can provide higher accuracy,263 and in some settings might be more time-efficient and cost-efficient than the LPA and probe-based tests. Several sequencing strategies are available, including targeted sequencing, where specific genes or loci are amplified before sequencing, and can be performed directly from sputum samples.266 Pyrosequencing is a real-time method for rapid sequencing of small segments of genomic DNA, and is capable of reliably detecting mutations that confer first-line and second-line drug resistance in M tuberculosis. Pyrosequencing not only shows the presence or absence of these mutations, but also displays detailed sequence data, which enables users to distinguish mutations conferring resistance from silent mutations as well as from those conferring different levels of resistance.260 Commercial kits are available but have not yet received regulatory approval for diagnostic use. For example, the Ion AmpliSeq TB Research Panel examines eight genes involved in resistance to first-line and second-line drugs (embB, eis, gyrA, inhA, katG, pncA, rpoB, and rpsL).

Considered the ultimate drug resistance test by some, whole-genome sequencing has the potential to provide resistance profiles for all drugs within a single analysis (figure 7). Sequencing has previously been the preserve of sophisticated research laboratories, but reductions in costs and development of more robust and user-friendly instrumentation has led to its introduction in clinical settings and pathology laboratories. Sequencing is considered a referral-level test to be used in tertiary centres in which, if found to be cost-effective, it might eventually replace LPA. A comparison of whole-genome sequencing with the follow-on tests (DST and LPA) for samples found positive for resistance to rifampicin is presented in table 5. Whole-genome sequencing should
be introduced for tuberculosis control for two main reasons: first, it can potentially accelerate access to effective treatment for individuals who are likely to fail standardised treatment for MDR or XDR, and it can prevent amplification of resistance through inadequate treatment. Second, it reduces the hazards associated with handling highly resistant and sometimes incurable strains of M tuberculosis. Molecular approaches for detecting drug resistance promise rapidity, safety, accuracy, and accessibility, but developers of tests for tuberculosis

**Figure 7: Process of next-generation sequencing**

The first step in detecting drug resistance by whole-genome sequencing is extraction of the Mycobacterium tuberculosis DNA from the clinical specimen or cultured isolate. After the creation of a library of DNA fragments, an amplification step creates multiple amplicons, which are aligned using computing technology to give multiple overlapping layers of sequence reads across the genome. Comparison (alignment) to a reference genome permits mutations to be detected, and those associated with drug resistance can be recognised by software using databases of the known resistance-causing mutations. The end readout will be a report of the genotypic resistance patterns to assist selection of an effective cocktail of drugs for treating the patient. With small bacterial genomes such as M tuberculosis, multiple samples can be analysed in a single run, greatly reducing costs.

**Table 5: Comparison of test characteristics of whole-genome sequencing with current drug-resistance tests**

<table>
<thead>
<tr>
<th>Phenotypic tests</th>
<th>Xpert MTB/RIF</th>
<th>Line probe assays</th>
<th>Whole-genome sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to result</td>
<td>Slow (weeks or months)</td>
<td>Less than 2 h</td>
<td>Rapid (hours or days) when done directly from samples</td>
</tr>
<tr>
<td>Sensitivity for detecting resistance</td>
<td>High</td>
<td>High for rifampicin; no other drugs included</td>
<td>Sensitivity limited by the number of loci incorporated in test; high for rifampicin</td>
</tr>
<tr>
<td>Resistance levels</td>
<td>Ability to determine MICs</td>
<td>Does not assess MIC</td>
<td>Does not assess MIC; some tests provide knowledge of mutations that can be used to predict levels of resistance but have poor clinical validity</td>
</tr>
<tr>
<td>Safety</td>
<td>High risk, requiring sophisticated microbiological protection</td>
<td>Low risk</td>
<td>Moderate microbiological risk when testing clinical samples. High risk if bacterial cultures are used</td>
</tr>
<tr>
<td>Quality assessment</td>
<td>Quality assurance via WHO and International Union Against Tuberculosis and Lung Disease reference laboratory network</td>
<td>Test-specific quality assurance schemes not widespread</td>
<td>Test-specific quality assurance schemes not widespread</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Separate tests for each drug</td>
<td>Detects resistance to one drug only</td>
<td>Two or three drugs per test</td>
</tr>
</tbody>
</table>

MIC=minimum inhibitory concentration.
have some considerable improvements to make. Whole-genome sequencing requires more *M tuberculosis* DNA than is usually found in sputum samples, and sequencing is performed on cultured isolates. For genotypic tests to fully exploit their potential they need the capacity to test clinical specimens directly without recourse to culture. The scarcity of *M tuberculosis* bacilli in sputum and the complexity of the sample matrix provides a serious challenge to the provision of a user-friendly DNA isolation device at an affordable manufacturing cost.

Efforts to enhance sequencing directly from sputum are ongoing and proof of concept has been obtained, but further studies are required. Strategies being investigated include selective removal of human DNA and enrichment of samples for *M tuberculosis* DNA. However, selective whole-genome amplification approaches, which have been used across a range of other pathogens might provide a cost-effective alternative.

The use of whole-genome sequencing for the rapid drug susceptibility profiling of *M tuberculosis* for tuberculosis treatment management will be dependent on a routinely curated high-quality drug resistance database. Building on the TBdream database, the tuberculosis profiling tool provides the most complete knowledge of the relationship between mutations and resistance in *M tuberculosis*, with high predictive ability for 14 drugs. However, concerted efforts in tuberculosis research are required to identify new markers of resistance, and develop knowledge databases containing clinical, phenotypic, and sequence data that can be used routinely in tuberculosis research and health care. One such initiative is the Relational Sequencing TB Data Platform (ReSeqTB), which is a collaborative project funded by the Bill & Melinda Gates Foundation. Once established, the platform will provide a validated whole-genome sequencing analysis pipeline and a one-stop source of curated, clinically relevant genetic data and associated metadata for drug-resistant tuberculosis.

The economic benefits of sequencing approaches remain a matter of speculation because studies have not been done, and the cost of sequencing is highly dependent on throughput. *M tuberculosis* has a relatively small genome of approximately 4.5 million basepairs compared with 3 billion in the human genome, so batched analysis of multiple samples is possible, greatly reducing costs. The capacity of sequencing platforms vary widely, with instruments costing from thousands to hundreds of thousands of US dollars. Whole-genome sequencing costs for each tuberculosis genome (excluding data analysis) are approximately $30–100. Whichever technology is preferred, studies are needed to inform sampling strategies. To assess cost-effectiveness, clinical trials are needed to measure the effect of rapid diagnostic testing on treatment practices and on important patient outcomes such as treatment success, morbidity, and mortality.

**Summary of diagnosis of drug-resistant tuberculosis**

Susceptibility testing remains severely inaccessible in most high-burden countries. For patients with drug-resistant disease, inaccessibility prevents or delays effective treatment and provides opportunity for transmission, and in some cases it allows amplification of resistance to further drugs. Urgent action is needed to address this gap in service provision. New technology might aid this situation, and molecular testing methods have the advantage of speed, with results available in hours or days, compared with days or weeks for phenotypic methods. Molecular testing is also considered safer, removing the need to culture and manipulate large numbers of highly infectious bacteria. However, major reservations about the use of molecular testing include the imperfect understanding of the clinical effect of some polymorphisms and the cost and sophistication of the technology required. A further impediment is the technical challenge of sequencing directly from clinical specimens to avoid the need for isolation and culture of the bacteria.

We suggest that improved access to effective treatment for people with resistance to multiple drugs will require tests capable of assessing the full range of available drugs. The most promising technology to deliver improved access is whole-genome sequencing. Further development of this technology is needed to allow direct testing of sputum samples, complemented by the construction of a well characterised library of resistance mutations to profile drug resistance. New diagnostics, including portable targeted sequencing, are yet to show their full potential, and greater convergence of technologies and approaches is needed to accelerate the development of improved tests to provide rapid access to effective treatment for all patients. Above all, greater investment is urgently needed, to implement the tools already available and to develop and assess new tools for the detection of drug-resistant tuberculosis.

**Medical and surgical management of drug-resistant tuberculosis: general principles and treatment of children, patients with HIV, and in other specific clinical contexts**

The management of drug-resistant tuberculosis is complex and several factors must be considered, including the prioritisation of effective treatment. Priorities should be decided upon while accounting for multiple clinical contexts, including HIV co-infection, diabetes, and vulnerable populations, such as pregnant women and children. More effective new and repurposed drugs are now routinely being used to treat drug-resistant tuberculosis, but resistance to these agents is already emerging. The key principles of developing a treatment regimen for MDR and XDR tuberculosis are outlined in panel 3; however, these recommendations are mostly based on observational studies. Other important aspects of management include well-functioning laboratories for
bacteriology and DST, infection control in health-care facilities to minimise transmission, adherence-promoting mechanisms, attention to psychosocial factors and patient-specific economic matters, access to quality drugs, appropriate training of health-care workers, rolling out appropriate information systems to track patients and audit data, and overall strengthening of national tuberculosis programmes.

Empirical regimens in use
WHO recommendations (2016) state that the conventional treatment for rifampicin-resistant tuberculosis or MDR tuberculosis should include at least five drugs (panel 4) that are likely to be effective in a regimen, including pyrazinamide and four core second-line drugs—one chosen from group A, one from group B, and at least two from group C, and additional drugs from group D when appropriate.4 This approach is an attempt to improve the poor efficacy (favourable outcome ~50%) of conventional MDR tuberculosis treatment. Nevertheless, drawbacks of significant toxicity and pill burden, poor adherence, and 6–8 months of painful injections with second-line injectable drugs remain. Also in 2016, WHO has recommended a standardised shorter MDR tuberculosis treatment regimen that has been used with second-line drug treatment-naive patients with MDR tuberculosis in Bangladesh,77 Niger,78 and Cameroon.79 The shorter MDR tuberculosis regimen (9–12 months) is successful in approximately 90% of cases, and includes three drugs (kanamycin, prothionamide, and high-dose isoniazid) for 4–6 months, with additional drugs (moxifloxacin, clofazimine, pyrazinamide, and ethambutol)

Panel 3: Recommended principles to be used when designing a regimen for the medical management of MDR and XDR tuberculosis
MDR tuberculosis
• Ideally use at least four drugs, in addition to pyrazinamide, to which the strain has proven or probable susceptibility (drugs previously taken for ≥1 month are generally avoided)18
• Use a backbone of a later-generation fluoroquinolone (eg, moxifloxacin or levofloxacin; group A drug), plus a second-line injectable drug (amikacin or kanamycin, or capreomycin; group B drugs; used for ≥4 months after culture conversion and for a minimum of 6 months)20
• Add any first-line drug and additional group C drugs (eg, cycloserine or terizidone, ethionamide or prothionamide, clofazimine, or linezolid if appropriate) to which the isolate is susceptible
• The WHO recommended treatment duration is 20 months; however, this recommendation is based on very low-quality evidence)18
• Bedaquiline or delamanid (group D2) can be added to the regimen if toxicity or resistance precludes formulation of a regimen containing ≥4 drugs that are likely to be effective, particularly if a group A or B drug cannot be used (both prolong QT interval, and thus require monitoring)19,20
• Oxazolidinones (linezolid) can be used (group C drug), particularly in fluoroquinolone-resistant MDR or XDR tuberculosis, but monitoring for toxicity (neuropathy and bone marrow suppression) is required20,21
• Given the specific and conditional nature of the recommendation (poor-quality evidence), the decision to use the newer WHO-recommended 9–12–month short course versus the~20-month regimen in selected patients will be dependent on several factors, including previous treatment, local resistance profiles, patient acceptance, and the requirement for proven or highly likely fluoroquinolone and aminoglycoside isolate susceptibility, and absence of probable or proven resistance to any of the components of the regimen (except isoniazid)18
• Whatever the duration of the regimen used, psychosocial and financial support are crucial elements to maintain adherence
• Patients should be monitored for adverse drug reactions, which are common20
• A single drug should not be added to a failing regimen
• The patient’s HIV status should be established and antiretroviral therapy initiated in all HIV-infected patients
XDR tuberculosis and resistance beyond XDR tuberculosis
• Regimens should be constructed on the basis of prevailing patterns of drug resistance and on similar principles to those outlined for MDR tuberculosis (use of ≥4 drugs is likely to be effective)
• We recommend a backbone of bedaquiline or delamanid, or both, plus linezolid, inclusion of a later-generation fluoroquinolone, and addition of other drugs such as clofazimine, para-aminosalicylic acid, pyrazinamide, high-dose isoniazid, and other drugs depending on the likelihood of susceptibility
• Bedaquiline and delamanid can be used in combination (with careful monitoring for corrected QT prolongation—eg, every 2 weeks for the first 12 weeks)
• Adverse events such as renal failure, hypokalaemia, hypomagnesaemia, and hearing loss are associated with capreomycin, which has high levels of cross-resistance with aminoglycosides20
• Differential susceptibility to fluoroquinolones might occur20
• Group D3 drugs such as meropenem plus clavulanate can be used, but their clinical effectiveness is uncertain

WHO classification of drugs used for the treatment of MDR tuberculosis:
group A=fluoroquinolones; group B=second-line injectable agents; group C=other core second-line agents; group D=add-on agents. MDR=multidrug resistant. XDR=extensively drug resistant. Adapted from Dheda K.2

[28x20]314
given throughout the course of treatment. WHO now recommends the shorter MDR tuberculosis regimen for selected patients with MDR tuberculosis or rifampicin-resistant-tuberculosis irrespective of patient age or HIV status, on the basis of a systematic review of the observational studies and following their standard practice for making recommendations on the treatment of MDR tuberculosis. Patients are eligible for this regimen unless they have confirmed or suspected resistance to any of the shorter MDR tuberculosis regimen drugs (except isoniazid, but especially to fluoroquinolones or second-line injectable drugs), prior exposure to any second-line drug contained within the shorter MDR tuberculosis regimen for more than 1 month, intolerance or toxicity to any of the drugs, unwanted drug–drug interactions, pregnancy, extrapulmonary disease, or drug inaccessibility. This newly recommended 9–12-month MDR tuberculosis regimen might be limited to specific patients and regional settings for various reasons, including the high frequency of M tuberculosis drug resistance to pyrazinamide, ethambutol or second-line antituberculosis drugs, resistance of patients and clinicians to use clofazimine because of adverse events like hyperpigmentation and potential induction of bedaquiline resistance, and substantial rates of previous tuberculosis in settings with high prevalence of MDR tuberculosis. Use of this conditional recommendation (weak evidence based only on a few small cohort studies) must be guided by patient and geographical context. Thus, until the results of the STREAM 1 study are available, the shorter MDR tuberculosis treatment regimen can be conditionally recommended in carefully selected patients, taking into account prevailing drug resistance profiles and previous treatment. Adherence is expected to be much better with the short duration regimen. Ineligible patients should receive the 20-month 5-drug regimen unless they have resistance or intolerance to the injectable agents or fluoroquinolones, in which case they should receive bedaquiline or delamanid, according to WHO guidelines.

Principles of formulating a treatment regimen for MDR and XDR tuberculosis

Several factors that might affect the selection of drugs and regimens are outlined in panel 4; these include the presence of HIV co-infection, age of the patient, presence of extrapolmonary tuberculosis, history of previous first-line or second-line antituberculosis treatment, disease severity, and access to reliable DST results, including second-line DST (often no standardisation of testing methods exists or testing is unavailable). Treatment is often complicated by a high rate of adverse drug reactions, which is more common in MDR and XDR tuberculosis than in drug-susceptible tuberculosis. The scarcity of comprehensive and rapid susceptibility readouts directly from sputum means that empirical regimens are still frequently necessary.

Randomised controlled trials are required to establish the minimum number of drugs, duration of treatment, and what specific drugs should constitute an effective regimen (table 6). However, better outcomes are associated with use of a greater number of effective drugs, the use of antiretroviral therapy in HIV-infected persons, and the use of new and repurposed drugs, such as bedaquiline, delamanid, and linezolid. The high mortality of patients with MDR and XDR tuberculosis has been strongly linked to the scarcity of effective drugs.

Although capreomycin is an option in patients with XDR tuberculosis, it is associated with substantial toxicity, and there is a high level of cross-resistance with aminoglycosides. Capreomycin, or aminoglycosides, can be dosed three times per week after culture conversion to decrease toxicity. High-dose isoniazid can be a useful addition for patients with inhA gene mutations conferring resistance.

Panel 4: WHO categorisation of second-line antituberculosis drugs recommended for the treatment of rifampicin-resistant and multidrug-resistant tuberculosis

Group A: fluoroquinolones
- Levofloxacin
- Moxifloxacin
- Gatifloxacin

Group B: second-line injectable agents
- Amikacin
- Capreomycin
- Kanamycin
- Streptomycin

Group C: other core second-line agents
- Ethionamide or prothionamide
- Cycloserine or terizidone
- Linezolid
- Clofazimine

Group D: add-on agents (not part of the core multidrug-resistant tuberculosis regimen)
- Thioacetazone
- Ibafacine
- Rifampicin or ethambutol
- Pyrazinamide
- High-dose isoniazid
- Bedaquiline
- Delamanid
- Paro-aminosalicylic acid
- Imipenem plus clavulanate
- Meropenem
- Amoxicillin plus clavulanate
- Thioacetazone

This grouping is intended to guide the design of conventional regimens. *These medicines are shown by decreasing order of usual preference for use. †Streptomycin might substitute other injectable agents under specific conditions. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant tuberculosis. ‡Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin. §HIV status must be tested and confirmed to be negative before thioacetazone is started.
<table>
<thead>
<tr>
<th>New drug in regimen</th>
<th>Official trial title</th>
<th>Description</th>
<th>Status</th>
<th>Phase</th>
<th>Trial Registry Identifier (link)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otsuka 233 Delamanid</td>
<td>Phase 2, open-label, multiple-dose trial to assess the safety, tolerability, pharmacokinetics, and efficacy of delamanid in paediatric patients with MDR tuberculosis</td>
<td>Safety, efficacy, and pharmacokinetic study of delamanid in paediatric patients with MDR tuberculosis</td>
<td>Enrolment completed for participants aged 6 years or older; enrolment open for participants younger than 6 years in the Philippines</td>
<td>Phase 2</td>
<td>NCT01859923</td>
</tr>
<tr>
<td>Janssen C211 Bedaquine</td>
<td>A phase 2, open-label, multicentre, single-arm study to assess the pharmacokinetics, safety, tolerability and antimycobacterial activity of TMC207 in combination with a background regimen of MDR tuberculosis medications for the treatment of children and adolescents younger than 18 years who have confirmed or probable pulmonary MDR tuberculosis</td>
<td>Investigate the pharmacokinetics, safety, tolerability, and antimycobacterial activity of bedaquiline in combination with MDR tuberculosis therapy for HIV-negative children and adolescents</td>
<td>Currently enrolling participants in Russia and South Africa</td>
<td>Phase 2</td>
<td>NCT02354014</td>
</tr>
<tr>
<td>NC-005 Pretomanid and bedaquine</td>
<td>A phase 2, open-label, partially randomised trial to assess the efficacy, safety, and tolerability of combinations of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide during 8 weeks of treatment in adult subjects with newly diagnosed drug-sensitive tuberculosis, MDR tuberculosis, or smear-positive pulmonary tuberculosis</td>
<td>Study of combinations of bedaquiline, moxifloxacin, pretomanid, and pyrazinamide for 8 weeks in patients with drug-sensitive or MDR tuberculosis, with one arm for patients with MDR tuberculosis adding moxifloxacin to bedaquiline, pretomanid, and pyrazinamide</td>
<td>Fully enrolled</td>
<td>Phase 2</td>
<td>NCT02193776</td>
</tr>
<tr>
<td>ACTG S343 Bedaquine and delamanid</td>
<td>A trial of the safety, tolerability, and pharmacokinetics of bedaquiline and delamanid separately and in combination, in participants taking multidrug treatment for drug-resistant tuberculosis</td>
<td>Study of drug-drug interactions and combined QT effects of bedaquiline and delamanid</td>
<td>Enrolling participants in South Africa</td>
<td>Phase 2</td>
<td>NCT02583048</td>
</tr>
<tr>
<td>ACTG S312 Isoniazid</td>
<td>The early bacteriological activity of high-dose or standard-dose isoniazid in adult participants with isoniazid-resistant or drug-sensitive tuberculosis</td>
<td>Safety and efficacy study of different doses and generic variants of isoniazid-resistant tuberculosis</td>
<td>Currently enrolling participants in South Africa</td>
<td>Phase 2</td>
<td>NCT01936831</td>
</tr>
<tr>
<td>Opti-Q Levofloxacin</td>
<td>Prospective, randomised, blinded phase 2 pharmacokinetic/pharmacodynamic study of the efficacy and tolerability of levofloxacin in combination with optimised background regimen for the treatment of MDR tuberculosis</td>
<td>Efficacy and safety study of increasing doses of levofloxacin in combination with optimised background therapy</td>
<td>Fully enrolled</td>
<td>Phase 2</td>
<td>NCT01918397</td>
</tr>
<tr>
<td>MDR-END Delamanid</td>
<td>Shortening treatment of MDR tuberculosis using existing and new drugs</td>
<td>Comparing efficacy of a treatment regimen that consisted of delamanid, linezolid, levofloxacin, and pyrazinamide for 9–12 months, with a control arm of the standard treatment regimen (including an injectable drug) for 20–24 months for the treatment of quinolone-sensitive MDR tuberculosis</td>
<td>Currently enrolling participants in South Korea</td>
<td>Phase 2</td>
<td>NCT02619994</td>
</tr>
<tr>
<td>Janssen Japan Trial Bedaquine</td>
<td>An open-label study to explore the safety, efficacy, and pharmacokinetics of TMC207 in Japanese patients with pulmonary MDR tuberculosis</td>
<td>Open-label, single-arm, multicentre trial to explore safety, efficacy, and pharmacokinetics of bedaquiline in Japanese participants with pulmonary MDR tuberculosis</td>
<td>Enrolling participants in Japan</td>
<td>Phase 2</td>
<td>NCT02365623</td>
</tr>
</tbody>
</table>

(Table 6 continues on next page)
<table>
<thead>
<tr>
<th>New drug in regimen</th>
<th>Official trial title</th>
<th>Description</th>
<th>Status</th>
<th>Phase</th>
<th>Trial Registry Identifier (link)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB-PRACTECAL</td>
<td>Bedaquiline and pretomanid</td>
<td>Pragmatic clinical trial for a more effective, concise, and less toxic MDR tuberculosis treatment regimen</td>
<td>Enrolling participants in Uzbekistan</td>
<td>Phase 2–3</td>
<td>NCT02589782</td>
</tr>
<tr>
<td>STREAM Stage 1</td>
<td>Modified Bangladesh regimen</td>
<td>The assessment of a standardised treatment regimen of antituberculosis drugs for patients with MDR tuberculosis: a multicentre international parallel group randomised controlled trial</td>
<td>Comparison of standard WHO MDR tuberculosis regimen with 9-month modified Bangladesh regimen</td>
<td>Recruitment complete; follow-up ongoing</td>
<td>ISRCTN78372190</td>
</tr>
<tr>
<td>Otsuka 213</td>
<td>Delamanid</td>
<td>A phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel group trial to assess the safety and efficacy of delamanid administered orally as 200 mg total daily dose for 6 months in patients with pulmonary sputum culture-positive, MDR-TB</td>
<td>Safety and efficacy study of delamanid vs placebo for 6 months in combination with optimised background therapy for 18–24 months</td>
<td>Recruitment complete; follow-up ongoing</td>
<td>NCT01424670</td>
</tr>
<tr>
<td>STREAM Stage 2</td>
<td>Bedaquiline</td>
<td>Assessment of a standard treatment regimen of antituberculosis drugs for patients with MDR tuberculosis: a prospective open-label randomised controlled trial</td>
<td>Comparison of a 6-month (containing an injectable) and 9-month (all oral) bedaquiline-containing regimen versus the WHO and Bangladesh regimen</td>
<td>Enrolling participants in Ethiopia, Vietnam, Mongolia, and South Africa</td>
<td>NCT02409290</td>
</tr>
<tr>
<td>NoXT</td>
<td>Bedaquiline</td>
<td>Investigating a new treatment regimen for patients with MDR tuberculosis: a prospective open-label randomised controlled trial</td>
<td>Open label RCT of a 6–9-month injection-free regimen containing bedaquiline, linezolid, levofloxacin, ethionamide or high-dose isoniazid, and pyrazinamide</td>
<td>Enrolling participants in South Africa</td>
<td>NCT02454205, PACTR201409000848428</td>
</tr>
<tr>
<td>NiX-TB</td>
<td>Bedaquiline, pretomanid, linezolid</td>
<td>A phase 3 open-label trial assessing the safety and efficacy of bedaquiline plus PA-824 plus linezolid in subjects with pulmonary infection of either XDR tuberculosis, treatment-intolerant tuberculosis, or pre-XDR non-responsive MDR tuberculosis</td>
<td>Study of bedaquiline, pretomanid, and linezolid in patients with XDR tuberculosis and MDR tuberculosis for 6 months with an option of 9 months’ treatment</td>
<td>Enrolling participants in South Africa</td>
<td>NCT02333799</td>
</tr>
<tr>
<td>STAND</td>
<td>Pretomanid</td>
<td>A phase 3 open-label, partially randomised trial to assess the efficacy, safety, and tolerability of the combination of moxifloxacin plus PA-824 plus pyrazinamide after 4 and 6 months of treatment in adults with smear-positive pulmonary drug-sensitive tuberculosis, and after 6 months of treatment in adults with smear-negative pulmonary MDR tuberculosis</td>
<td>Efficacy, safety, and tolerability of a combination of moxifloxacin, PA-824, and pyrazinamide treatments after 6 months of treatment in patients with MDR tuberculosis compared with a combination of moxifloxacin, PA-824, and pyrazinamide treatments in drug-sensitive tuberculosis subjects; there will be a comparitor arm for MDR tuberculosis</td>
<td>On hold; participant recruitment suspended</td>
<td>NCT02342886</td>
</tr>
<tr>
<td>China PZA Trial</td>
<td>Pyrazinamide</td>
<td>Optimisation of an MDR tuberculosis treatment regimen based on the molecular drug susceptibility results of pyrazinamide</td>
<td>Efficacy study of introducing molecular testing of pyrazinamide susceptibility in optimising the MDR tuberculosis treatment regimen</td>
<td>Unknown</td>
<td>NCT02120638</td>
</tr>
</tbody>
</table>

(Table 6 continues on next page)
isoniazid resistance (in the absence of \textit{katG} gene mutations), although the rate of hepatotoxic and neurotoxic adverse events are quite high.\textsuperscript{285} A dose of 10–15 mg/kg three times per week is often better tolerated than 16–18 mg/kg per day, except in children, in whom 16–18 mg/kg is well tolerated.\textsuperscript{286} This tolerance is present because children eliminate isoniazid faster than adults, especially young children.\textsuperscript{286} Clofazimine might be a useful drug because it has been shown to have sterilising properties in experimental studies; it might require co-administration with pyrazinamide for optimal activity, but is a less potent antituberculosis agent with minimal early bactericidal activity, and could theoretically induce cross-resistance to bedaquiline (though this remains unproven in clinical practice). Clofazimine is also associated with several problematic adverse effects, including prolongation of the corrected QT (QTc) interval and hyperpigmentation, which often affects adherence. The potential usefulness of meropenem plus clavulanate or imipenem plus clavulanate has been highlighted, but it is expensive, requires long-term intravenous access, and insufficient clinical evidence of its usefulness or effectiveness exists.\textsuperscript{287,288}

\textbf{Use of linezolid, bedaquiline, and delamanid}

For the first time in nearly half a century, multiple promising new and repurposed agents are available to treat MDR tuberculosis; and experience of the new drugs bedaquiline and delamanid and the repurposed drug linezolid is increasing. These drugs should be considered part of the routine management of highly resistant strains of tuberculosis.\textsuperscript{289} Recommendations for the use of bedaquiline and delamanid are outlined in panel 3, mechanisms of action, drug interactions, and key adverse events are described in table 7, and planned and ongoing clinical trials, including MDR tuberculosis regimen shortening to 6 or 9 months are presented in table 6. Although the merits of the regimen composition, duration, and adverse event profile in these trials can be debated, we view the different studies as complementary because they address different questions and regimens that are relevant to different cases, depending on the clinical and programmatic context.

<table>
<thead>
<tr>
<th>New drug in regimen</th>
<th>Official trial title</th>
<th>Description</th>
<th>Status</th>
<th>Phase</th>
<th>Trial Registry Identifier (link)</th>
</tr>
</thead>
<tbody>
<tr>
<td>endTB Bedaquiline, delamanid</td>
<td>Evaluating newly approved drugs for multidrug-resistant tuberculosis: a clinical trial</td>
<td>This is a phase 3, randomised, controlled, open-label, non-inferiority, multicountry trial assessing the efficacy and safety of new combination regimens for MDR tuberculosis treatment</td>
<td>Not yet recruiting</td>
<td>Phase 3</td>
<td>NCT02754765</td>
</tr>
<tr>
<td>FS-1 Trial FS-1*</td>
<td>Randomised, placebo-controlled study of safety and therapeutic efficacy of the drug FS-1 in the oral dosage form in drug-resistant pulmonary tuberculosis</td>
<td>Safety and efficacy of FS-1 administered orally to patients with drug-resistant pulmonary tuberculosis</td>
<td>Enrolling participants in Kazakhstan and Kyrgyzstan</td>
<td>Phase 3</td>
<td>NCT02607449</td>
</tr>
<tr>
<td>V-QUIN Levofloxacin</td>
<td>A randomised controlled trial of 6 months of daily levofloxacin for the prevention of tuberculosis in household contacts of patients with MDR tuberculosis</td>
<td>Investigating 6 months of daily levofloxacin versus placebo as preventive therapy in contacts of MDR tuberculosis; enrolling HIV-positive and HIV-negative household contacts with a positive tuberculin skin test. Enrolment of children &lt;15 years is on hold. Household randomisation</td>
<td>Enrolling participants in Vietnam</td>
<td>Phase 3</td>
<td>ACTRN12616000215426</td>
</tr>
<tr>
<td>TB-CHAMP Levofloxacin</td>
<td>Tuberculosis child and adolescent multidrug-resistant preventive therapy trial</td>
<td>Randomised double-blind placebo-controlled, multicentre superiority trial to assess the efficacy of levofloxacin versus placebo for the prevention of MDR tuberculosis in child and adolescent household contacts</td>
<td>Not yet recruiting</td>
<td>Phase 3</td>
<td>ISRCTN92634082</td>
</tr>
<tr>
<td>PHOENiX MDR TB Delamanid</td>
<td>Protecting households on exposure to newly diagnosed index multidrug-resistant tuberculosis patients (A5300B/12003B/PHOENiX)</td>
<td>Open label, multi-centre trial with a cluster-randomised superiority design to compare the efficacy and safety of delamanid versus isoniazid for 26 weeks for preventing confirmed or probable active tuberculosis during 96 weeks of follow-up in high-risk household contacts of patients with MDR tuberculosis</td>
<td>Not yet recruiting</td>
<td>Phase 3</td>
<td>AS3008</td>
</tr>
</tbody>
</table>

MRR=multidrug resistant. XDR=extensively drug resistant. *FS-1 is an immunomodulatory agent that is only available in Kazakhstan.

Table 6: Currently registered phase 2 and 3 clinical trials for MDR-tuberculosis
Monitoring treatment response and predicting outcome

The monitoring of patients on MDR tuberculosis treatment regimens should follow a holistic approach with consideration given to clinical, laboratory, microbiological, and radiological parameters.296 WHO guidelines suggest monthly sputum smear microscopy and culture as an adjunct to clinical monitoring of patients to assess treatment outcome.296 For example, the duration of second-line injectable drug therapy and the definition of treatment failure are based on this information. However, sputum culture conversion at 2–3 months has poor sensitivity for predicting successful final treatment outcomes using the conventional MDR tuberculosis regimen297–299 (many culture positives later converted and had a successful outcome). 6-month conversion has a high sensitivity (approaching 90%) and a successful outcome. 6-month conversion has a high sensitivity (approaching 90%) and a successful outcome. 6-month conversion has a high sensitivity (approaching 90%) and a successful outcome. 6-month conversion has a high sensitivity (approaching 90%) and a successful outcome.

### Table 7: Novel, repurposed, and conventional drugs for the treatment of drug-resistant tuberculosis, including mechanism of action, key adverse events, and drug interactions

<table>
<thead>
<tr>
<th>WHO group</th>
<th>Mechanism of action</th>
<th>Mechanism of resistance</th>
<th>Common adverse events or cautions</th>
<th>Pharmacology and drug interactions with rifampicin* and antiretrovirals*</th>
<th>Important shared toxicity with antiretrovirals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedaquiline/TMC 2071</td>
<td>Inhibition of Mycobacterium tuberculosis ATP synthase</td>
<td>ApH gene mutation (encodes subunit c of ATP synthase); mutations in Rv067 coding for repressors of M tuberculosis efflux pumps; some resistance with clofazimine; high barrier to resistance</td>
<td>Increased rates of unexplained deaths in the bedaquiline arm (11.4% vs 2.5% in the control group),297 not apparent in pharmacovigilance studies to date; prolonged corrected QT interval; caution in patients with liver dysfunction</td>
<td>Rifampicin reduces steady-state bedaquiline concentrations by 79%; efavirenz reduces steady-state bedaquiline concentrations by 52%;298,299 lopinavir plus ritonavir significantly increases steady-state bedaquiline concentration (uncertain clinical significance);298 nevirapine shows no significant interaction</td>
<td>Hepatotoxicity; caution use with nevirapine, lopinavir plus ritonavir, and NRTIs</td>
</tr>
<tr>
<td>Pretomanid/PA-8241</td>
<td>Unclassified Inhibition of mycolic acid biosynthesis and generation of mycobactericidal nitrogen oxide derivatives (dormant M tuberculosis)</td>
<td>Mutations in fhuA, fhuB, fhuC leads to impaired coenzyme F420 synthesis; mutation in Rv3547 coding for deazaflavin-dependent nitroreductase (inhibit activation of pro-drug); could have a low barrier to resistance</td>
<td>Hepatotoxicity, caution in patients with renal dysfunction, gastrointestinal tract toxicity</td>
<td>Rifampicin reduces pretomanid by 66%; efavirenz reduces pretomanid 35%293</td>
<td>Hepatotoxicity; caution use with nevirapine, lopinavir plus ritonavir, and NRTIs</td>
</tr>
<tr>
<td>Delamanid/OPC 67683</td>
<td>D2 Inhibits mycolic acid biosynthesis</td>
<td>Mutation in mycobacterial Rv3547 prevents activation of delamanid, could have a low barrier to resistance</td>
<td>Prolonged corrected QT interval (linked to metabolite); potential CNS toxicity when used with isoniazid or fluoroquinolone; caution with hypoalbuminaemia (&lt;2.8 g/dL)</td>
<td>Rifampicin reduced delamanid concentrations by 45%; no clinically significant interaction with efavirenz;298 lopinavir plus ritonavir might increase delamanid concentration293 (uncertain clinical significance); twice daily dosing (once daily dosing during maintenance phase is under study); taken separately from other companion drugs</td>
<td>Potentially no significant anticipated drug-drug interactions with antiretrovirals</td>
</tr>
<tr>
<td>SQ-109f§</td>
<td>Unclassified Infection of mycolic acid biosynthesis</td>
<td>Mutation in the mmpL3 gene could potentially confer resistance</td>
<td>Gastrointestinal tract toxicity</td>
<td>No clinical data available</td>
<td>No clinical data available</td>
</tr>
<tr>
<td>Linezolid or sutezolid/PNU-100480© (oxazolidinones)</td>
<td>C Inhibits protein synthesis</td>
<td>Mutations in the 23S rRNA; mutations in the spc encoding ribosomal protein L3; other mechanisms with possible involvement of efflux pumps; might have high barrier to resistance</td>
<td>Peripheral neuropathy; hepatotoxicity</td>
<td>Rifampicin induces clearance of linezolid, possibly through P-glycoprotein expression; sutezolid is metabolised by flavin mono oxygenases with small contribution by cytochrome P450 isoenzyme 3A</td>
<td>Peripheral neuropathy; caution use with high-dose isoniazid (INH mutation) and with antiretrovirals such as didanosine and stavudine; myelosuppression: caution use with zidovudine</td>
</tr>
</tbody>
</table>

NRTI=nucleoside reverse transcriptase inhibitors. *A reduction in the concentrations of the parent drug due to a co-administered inducing drug might be compensated for by an increase in concentrations of the active metabolite. Unless otherwise stated, the % changes are in the area under the curve. †Phase 2B trials completed. ‡This mechanism might confer resistance to clofazimine, but the clinical significance of this is unclear. §The STAND study investigating a 4-month regimen for drug-sensitive tuberculosis has been stopped because of concerns of hepatotoxicity. ¶Phase 2A trials completed.
Managing treatment failure, resistance beyond XDR tuberculosis, and programmatically incurable tuberculosis

Treatment failure is generally defined as the presence of two consecutive positive cultures approximately 30 days apart (one intervening culture might be missed or contaminated), and either the need for a permanent regimen change of at least two major antituberculosis drugs, or treatment is terminated (stopping 2 or more drugs) at a specified timepoint, or both. A consensus definition has been proposed. Treatment failure might occur in the context of no culture conversion from the outset, initial response with subsequent culture reversion, or the need for a regimen change because of adverse events or acquired drug resistance.

Despite the presence of significant drug-specific resistance, patients might improve transiently. A rescue regimen will depend on the results of patient DST and prevailing DST profiles. However, other factors must first be considered, including adherence and malabsorption of drugs (e.g., in patients who are HIV-positive), and drug quality might occasionally be a problem. When appropriate, a concomitant alternative diagnosis must be considered. In areas where the MDR tuberculosis prevalence is less than 10%, a significant proportion of Xpert MTB/RIF rifampicin-resistant results could theoretically be false positive (approximately 10–15%). Although confirmation by additional methods is advocated, this often does not occur in tuberculosis-endemic countries. Occasionally, despite considering all other factors, patients who persistently remain culture positive with bacilli susceptible to aminoglycosides and fluoroquinolones fail to respond to MDR treatment and might have heteroresistance. Resistance profiles that are not detectable in the sputum using tools such as DNA amplification techniques, or an MIC in the cutpoint grey zone are often the cause. In such cases, empirical use of an XDR tuberculosis regimen, after exclusion of other causes, is reasonable.

Totally drug-resistant tuberculosis has been used in the literature to refer to strains of M tuberculosis that show in-vitro resistance to all medications that are available for testing. However, this term is a misnomer, since many of the new and repurposed agents that have been shown to be effective against tuberculosis are not assessed in in-vitro resistance testing panels. Such individuals would probably benefit from inclusion in clinical trials of new drugs or regimens, or consideration of surgical resection (panel 5). Regardless, many patients with resistance beyond XDR tuberculosis are not given effective medical treatment options, which has already been highlighted as a problem in South Africa and is likely occurring in other countries such as India, China,

320

www.thelancet.com/respiratory Vol 5 April 2017
and Russia. Indeed, in India—the region with the majority of the world’s patients with MDR tuberculosis—there is no widespread access to new life-saving drugs such as bedaquiline and delamanid, despite these drugs having received approvals by the FDA in 2012, and the EMA in 2014. However, a small compassionate use programme and an early pilot project for bedaquiline access has begun. Apart from some initial attempts to access these drugs via compassionate use programmes and vigorous campaigning by activists, these drugs remain unavailable to the patients who need them the most. Many patients with treatment failure reside in the community because tuberculosis hospitals are full, which raises several ethical and medicolegal issues. Thus, the provision of palliative care and long-term-stay community facilities is urgently needed. Access to these services is extremely difficult in most tuberculosis programmes and must be improved as part of the patient-centred approach to treatment.

Management in special situations

Patients with HIV, those who are pregnant, and those with liver or kidney disease need to be optimally managed in a comprehensive fashion in which specific treatment regimens are designed that take into account the risks of poor outcomes from drug-resistant tuberculosis—including the development of adverse events—versus the risks of the comorbid conditions (panel 6). HIV is commonly encountered in people with drug-resistant tuberculosis, and in some settings, as many as 80% of drug-resistant tuberculosis patients are also HIV positive. For this reason, it is imperative that all people with MDR tuberculosis be screened for HIV at the time of diagnosis. Management of HIV-infected patients is complicated by several factors, including higher rates of drug toxicity, HIV-related organ dysfunction (eg, nephropathy, neuropathy, and anaemia), drug–drug interactions and overlapping toxicities, pill burden, and immune reconstitution inflammatory syndrome. As a set of general management principles, people with MDR tuberculosis and HIV should be started on antiretroviral therapy as soon as possible—usually within 2–8 weeks of starting MDR tuberculosis treatment—regardless of CD4 count. The selection of the drug-resistant tuberculosis regimen should be done on the basis of WHO principles, but should also minimise the use of drugs with overlapping toxicities if at all possible. Although people with HIV were largely excluded from the phase IIb clinical trials of both bedaquiline and delamanid, some data on the safety and efficacy of bedaquiline have emerged in cohorts in South Africa and Swaziland. Bedaquiline should not be given with efavirenz, however, since efavirenz decreases the serum concentration of bedaquiline. Delamanid does not appear to have significant interactions with any of the antiretroviral mediations (table 7).

Decision on the timing of drug-resistant tuberculosis treatment during pregnancy should account for the clinical condition of the mother, gestational age of the fetus, and risks of teratogenicity. Women who are pregnant and develop drug-resistant tuberculosis should be included in all discussions on management plans with a multidisciplinary team. All women of childbearing age should be offered contraception free of charge as part of the management of drug-resistant tuberculosis. Compared with children born to women who have untreated drug-resistant tuberculosis, children born to women treated for drug-resistant tuberculosis during pregnancy appear to have excellent birth outcomes (ie, no evidence of neurological dysfunction or hearing or visual abnormalities), and long-term follow-up of small cohorts of such children do not document any negative effects.

Surgical management

Various principles underlie the surgical management of patients with drug-resistant tuberculosis (panel 5). Although no controlled trials have been performed and patients undergoing surgery are selected for low severity of disease (thus biasing towards a favourable outcome), recent meta-analyses using observational data found that surgical intervention was associated with better outcomes compared with medical treatment, particularly in patients with XDR tuberculosis. Newer, non-invasive bronchoscopic approaches using valves and other methods might offer alternative approaches in selected patients who refuse surgery or are not surgical candidates. Surgical mortality is <5%, but the rate of complications varies between 12% and 30%. Several questions remain unanswered, including timing of surgery, use of adjunctive therapy, and optimal investigation in those patients with borderline lung function who might be eligible for surgery, and these have been reviewed in detail by Calligaro and colleagues. The 2016 WHO update on the MDR tuberculosis treatment guidelines examined the effectiveness of surgery for MDR tuberculosis and suggested (on the basis of low quality evidence) that elective partial lung resection (lobectomy or wedge resection), when used alongside a recommended MDR tuberculosis regimen, improves prognosis compared with chemotherapy alone. The duration of antituberculous therapy for people undergoing surgery should be a minimum of 18–24 months from the time of culture conversion, which is often 18–24 months after surgery has been done. In patients with minimal disease burden, as assessed by PET or CT, shorter treatment durations could be considered depending on patient tolerance, but no data exist to guide the optimal timing and duration of medical therapy after surgical resection of disease.
Panel 6: Management of MDR tuberculosis in different clinical contexts

Patients with HIV and MDR tuberculosis

- Commence antiretroviral therapy, irrespective of CD4 count, usually within 8–12 weeks of tuberculosis treatment initiation.\(^{38}\)
- Start antiretroviral therapy within 2 weeks of tuberculosis treatment initiation in those with CD4 count less than 50 cells/mL, which is the case with drug-susceptible tuberculosis (given the higher mortality) despite the additional risk of immune reconstitution inflammatory syndrome.\(^{39–42}\)
- Bedaquiline can be combined with two nucleoside reverse transcriptase inhibitors and nevirapine, or a combination of lopinavir plus ritonavir (use with caution given increased concentrations of drugs; see table 7), or an integrase strand transfer inhibitor.
- Delamanid is potentially safe when co-administered with antiretroviral therapy.
- If treatment for hepatitis B is indicated, antiretroviral therapy should be initiated with the combination of at least two agents active against hepatitis B virus—e.g., tenofovir + emtricitabine or tenofovir + lamivudine. In hepatitis C and hepatitis B virus coinfection, drug interactions and overlapping toxicities must be considered.

Pregnancy

- Start treatment immediately if medically indicated, using the principles outlined in panel 3.
- Given the high risk of teratogenicity in the first trimester, in stable and selected cases, treatment with second-line drugs can be deferred until the second trimester with appropriate monitoring.
- Avoid aminoglycosides regardless of gestational age (concern about fetal ototoxicity).
- If deemed to be lifesaving for the mother, capreomycin can be given (three times per week, if appropriate, to decrease fetal drug exposure and the risk of ototoxicity).
- Avoid ethionamide because of concerns about teratogenicity and worsening of pregnancy-associated nausea and vomiting.
- Ethionamide and aminoglycosides or other second-line injectable drugs may be reintroduced after delivery to strengthen the regimen.

Liver disease

- Ethionamide, prothionamide, high-dose isoniazid, para-aminosalicylic acid, and bedaquiline might be hepatotoxic; use with caution in chronic stable liver disease with close monitoring.
- Avoid pyrazinamide in patients with underlying chronic liver disease.
- Avoid other potentially hepatotoxic non-tuberculosis agents in patients with underlying chronic liver disease.
- No formal studies of drug–drug interactions between the hepatitis C protease inhibitors and the second-line tuberculosis drugs have been done; if a patient has stable liver function, treatment of MDR tuberculosis should be initiated first.
- Alcohol use might substantially exacerbate liver disease in some settings, although studies have found that no increased risk of hepatic adverse events exists in people with MDR tuberculosis.\(^{33}\)

Renal disease

- Frequency and dosage should be adjusted by creatinine clearance for aminoglycosides, capreomycin, pyrazinamide, ethambutol, cycloserine, either ethionamide or prothionamide, and para-aminosalicylic acid.\(^{43–45}\)
- Bedaquiline is often used to substitute second-line injectable drugs in cases of significant pre-existing or aminoglycoside-related renal dysfunction.
- Bedaquiline does not require any dose adjustments for patients with mild to moderate renal dysfunction (ie, not on dialysis) and may be used with caution in advanced renal failure.

Management of MDR and XDR tuberculosis in children

A substantial proportion of worldwide MDR tuberculosis cases occur in children. Conservative estimates suggest that about 32 000 children (younger than 15 years) developed MDR tuberculosis in 2010.\(^{39}\) Children with MDR tuberculosis usually have considerably better treatment outcomes than adults; treatment is successful in 80–90% of children given individualised therapy, probably due to the paucibacillary nature of most paediatric tuberculosis. MDR tuberculosis in children usually results from direct transmission from an adult, and treatment of MDR tuberculosis in children is particularly challenging. Bacteriological confirmation of MDR tuberculosis in children could be complicated because of its paucibacillary nature, because the tuberculosis is often extrapulmonary, and because sample collection is challenging. Although bacterial confirmation should be attempted, most children can be presumptively diagnosed with MDR tuberculosis on the basis of the presence of signs and symptoms of tuberculosis and a positive contact history, because there is high concordance between DST patterns of children and their source cases.\(^{59,316}\) The hesitance of health-care providers to treat probable MDR tuberculosis in children is particularly challenging.
is a major reason for few children with drug-resistant tuberculosis receiving adequate treatment. The principles of MDR tuberculosis treatment in adults and children are the same; all second-line drugs are used in children, although formal pharmacokinetic studies are sparse and child-friendly formulations are not usually available (panel 7). Notably, theoretical concerns about the effects of the fluoroquinolones on developing bones and joints that emerged from animal studies have not been observed in children on long-term fluoroquinolone use for the treatment of MDR tuberculosis or for other chronic infectious diseases. Shorter overall treatment durations (12–15 months) can be considered in children with non-severe disease. A notable exception is irreversible sensorineural hearing loss caused by the injectable adenine nucleotide analogue aminoglycosides, which is seen in up to 25% of children. Hence, treatment are rare. Additionally, adverse effects are more difficult to assess in children, and could therefore be underestimated. A notable exception is irreversible sensorineural hearing loss caused by the injectable drugs, which is seen in up to 25% of children. Hence, a high-priority research objective is developing an all-oral programme for children.

**Summary of medical and surgical management**

We have described the key principles for designing an effective regimen for MDR and XDR tuberculosis (panel 3) and the management of MDR tuberculosis in special situations, including in HIV-infected individuals (table 7 and panel 6). However, several other factors are critical for successful treatment outcomes, including ensuring adherence support, a good laboratory infrastructure, and a well-functioning tuberculosis programme.

Furthermore, we suggest that an entirely new framework for the treatment of drug-resistant tuberculosis be adopted and that the conventional regimen no longer be used to treat the majority of individuals with drug-resistant tuberculosis. Rather, we suggest a precision medicine-orientated treatment approach in which universal access to rapid DST for isoniazid, rifampicin, the second-line injectables, and the fluoroquinolones is available, to guide individualised therapy. In the interim, patients without resistance to the second-line drugs would receive the shortened drug-resistant tuberculosis treatment regimen, and those with resistance to the second-line drugs would receive novel agents such as bedaquiline or delamanid, or both, in combination with other drugs shown to be effective in randomised trials, such as linezolid and clofazimine. All-oral regimens that maximise potency and minimise toxicity should be rapidly implemented as evidence emerges. The ideal length of therapy would be calculated, taking into account clinical, laboratory, microbiological, and radiographic parameters, and

<table>
<thead>
<tr>
<th>Panel 7: Recommended dosing of second-line drugs in children, with maximum daily dose in brackets</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pyrazinamide</strong></td>
</tr>
<tr>
<td>• 30–40 mg/kg per day (2000 mg)</td>
</tr>
<tr>
<td><strong>Kanamycin, amikacin, or capreomycin</strong></td>
</tr>
<tr>
<td>• 15–20 mg/kg per day (1000 mg)</td>
</tr>
<tr>
<td><strong>Levofloxacin</strong></td>
</tr>
<tr>
<td>• 15–20 mg/kg per day (1000 mg)</td>
</tr>
<tr>
<td><strong>Moxifloxacin</strong></td>
</tr>
<tr>
<td>• 10 mg/kg per day (400 mg)</td>
</tr>
<tr>
<td><strong>Ethionamide or prothionamide</strong></td>
</tr>
<tr>
<td>• 15–20 mg/kg per day (1000 mg)</td>
</tr>
<tr>
<td><strong>Cycloserine or terizidone</strong></td>
</tr>
<tr>
<td>• 15–20 mg/kg per day (750 mg)</td>
</tr>
<tr>
<td><strong>Para-aminosalicylic acid</strong></td>
</tr>
<tr>
<td>• 150–200 mg/kg per day (12 g)</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
</tr>
<tr>
<td>• 2–3 mg/kg per day (100 mg)</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
</tr>
<tr>
<td>• In children 10 years or older: 10 mg/kg per day (600 mg)</td>
</tr>
<tr>
<td>• In children younger than 10 years: 10 mg/kg twice daily (600 mg)</td>
</tr>
<tr>
<td><strong>Delamanid</strong></td>
</tr>
<tr>
<td>• Weight of 35 kg or more: 100 mg twice daily</td>
</tr>
<tr>
<td>• Weight of 20–34 kg: 50 mg twice daily</td>
</tr>
<tr>
<td>• Weight of less than 20 kg: consult with expert</td>
</tr>
<tr>
<td><strong>Bedaquiline</strong></td>
</tr>
<tr>
<td>• Weight of 33 kg or more: 400 mg daily for 14 days followed by 200 mg three times a week for 22 weeks</td>
</tr>
<tr>
<td>• Weight of less than 33 kg: consult with expert</td>
</tr>
<tr>
<td><strong>Amoxicillin plus clavulanate</strong></td>
</tr>
<tr>
<td>• 80 mg/kg of amoxicillin component divided into two doses (4000 mg amoxicillin plus 500 mg clavulanate)</td>
</tr>
<tr>
<td><strong>Meropenem</strong></td>
</tr>
<tr>
<td>• 20–40 mg/kg intravenously every 8 h (6000 mg)</td>
</tr>
</tbody>
</table>

*Meropenem is only to be used in combination with amoxicillin plus clavulanate.*
comorbidities that affect outcomes, including poorly controlled HIV, malnutrition, and diabetes. Thus, improved biomarkers and scoring systems are urgently required to accurately predict outcomes, facilitate clinical management, and streamline the assessment of new therapeutic interventions for MDR tuberculosis.

Patients with XDR tuberculosis and additional resistance to second-line drugs should be offered access to clinical trials and to new medications through compassionate use and expanded access programmes. Surgical therapy should be considered a key adjuvant to medical management of highly resistant forms of tuberculosis. Children merit special attention in the diagnosis, prevention, and treatment of drug-resistant tuberculosis, and the long delays in access to innovation in this vulnerable population must be eliminated. Other vulnerable populations, including pregnant women, people with hepatic disease, and those with other risk factors for poor outcomes such as diabetes, HIV, or renal disease, can have successful outcomes if they are treated in a comprehensive programme. In tandem, adherence-promoting mechanisms, antibiotic stewardship, and attention to appropriate dosing and monitoring is crucial to prevent the amplification of resistance and rapid loss of these agents. Insufficient effective approaches will only enlarge the pool of patients with programmatically incurable tuberculosis, which is a substantial problem in tuberculosis-endemic countries. Other innovative approaches such as community-based isolation facilities will be required to deal with this ongoing problem.

New drugs and strategies for treating drug-resistant tuberculosis
Developing new regimens for drug-resistant tuberculosis is challenging. Tuberculosis drugs work in combination, and an effective regimen should include at least one drug with potent bactericidal activity to rapidly reduce mycobacterial burden. This role is filled by isoniazid in drug-susceptible tuberculosis. Drugs with potent sterilising activity (eg, rifampicin and pyrazinamide in drug-susceptible tuberculosis), which effectively kill semidormant, persisting organisms that will cause relapse if they are not eradicated, are even more important. Companions drugs with different mechanisms of action that protect these main bactericidal and sterilising drugs against the emergence of resistance (like ethambutol in drug-susceptible tuberculosis) are also essential. Additionally, an ideal regimen that can be used for drug-resistant tuberculosis worldwide will have the following features: compatibility with antiretroviral therapy, good penetration into cavitary lung lesions and areas undergoing caseous necrosis, few requirements for safety monitoring, ease of use in programmatic settings, and oral formulations.

Tuberculosis is a millennia-old disease and to defeat it (or even abate the advance of ever more drug-resistant tuberculosis), scientists must think creatively and marshal all available resources, including repurposing existing drugs and developing new ones. Fortunately, a pipeline of drugs is now in development for tuberculosis. However, this pipeline is not yet robust, several drugs are newly in clinical use or are in clinical development, and some old drugs are being reassessed or optimised for drug-resistant tuberculosis (tables 7 and 8).

New or repurposed drugs for drug-resistant tuberculosis: the building blocks
Repurposed drugs are antimicrobials that were developed for other bacterial infections, but which have useful antimycobacterial activity. Substantial information on the pharmacokinetics and pharmacodynamics, safety and tolerability, and drug–drug interactions is typically available for repurposed drugs, which accelerates their adoption for tuberculosis treatment. However, further optimisation of drug dosing for safety and efficacy, as is being done for levofloxacin (OptiQ Study; NCT01918397), is needed in the context of the long treatment durations and multidrug regimens used to treat drug-resistant tuberculosis.

Fluoroquinolones
Fluoroquinolones are well-tolerated oral agents that are used to treat a wide variety of bacterial infections. These drugs are already considered cornerstone agents for the treatment of MDR tuberculosis, and the use of late-generation drugs of this class against susceptible isolates was associated with an adjusted odds ratio of 2·5 for treatment success in an individual patient meta-analysis. Repurposed drugs are antimicrobials that were developed for other bacterial infections, but which have useful antimycobacterial activity. Substantial information on the pharmacokinetics and pharmacodynamics, safety and tolerability, and drug–drug interactions is typically available for repurposed drugs, which accelerates their adoption for tuberculosis treatment. However, their bactericidal effect is mediated through subsequent chromosomal fragmentation and generation of reactive oxygen species, as well as at least one other poorly characterised mechanism. Available fluoroquinolones differ in their MIC against M tuberculosis, with the late-generation fluoroquinolones moxifloxacin and gatifloxacin being most potent, followed by levofloxacin and then ofloxacin, but clinical trials comparing fluoroquinolones are few in number and narrow in scope. Ofloxacin has been shown to be less efficacious than the others and should be abandoned for tuberculosis therapy. Moxifloxacin, gatifloxacin, and high-dose (ie, 1 g daily for patients weighing >50 kg) levofloxacin display similar early bactericidal activity in drug-susceptible tuberculosis. Sputum culture conversion rates were similar for levofloxacin and moxifloxacin in a small randomised controlled trial in patients with MDR tuberculosis. Evidence is emerging that moxifloxacin and gatifloxacin might retain activity against some ofloxacin-resistant isolates, especially those with A90V and D94A mutations in gyrA. Increasing the moxifloxacin or gatifloxacin dose would be expected to further increase the activity against such isolates and mediated through subsequent chromosomal fragmentation and generation of reactive oxygen species, as well as at least one other poorly characterised mechanism. Available fluoroquinolones differ in their MIC against M tuberculosis, with the late-generation fluoroquinolones moxifloxacin and gatifloxacin being most potent, followed by levofloxacin and then ofloxacin, but clinical trials comparing fluoroquinolones are few in number and narrow in scope. Ofloxacin has been shown to be less efficacious than the others and should be abandoned for tuberculosis therapy. Moxifloxacin, gatifloxacin, and high-dose (ie, 1 g daily for patients weighing >50 kg) levofloxacin display similar early bactericidal activity in drug-susceptible tuberculosis. Sputum culture conversion rates were similar for levofloxacin and moxifloxacin in a small randomised controlled trial in patients with MDR tuberculosis. Evidence is emerging that moxifloxacin and gatifloxacin might retain activity against some ofloxacin-resistant isolates, especially those with A90V and D94A mutations in gyrA. Increasing the moxifloxacin or gatifloxacin dose would be expected to further increase the activity against such isolates and...
suggests opportunities for more personalised approaches to MDR tuberculosis therapy in conjunction with resistance genotype information.\textsuperscript{193} However, gatifloxacin poses a risk of hyperglycaemia or hypoglycaemia, so has been removed from the market in many regions. Further study should establish whether higher doses of levofloxacin or moxifloxacin would be more efficacious with acceptable toxicity. Fluoroquinolones cause modest QT interval prolongation (with the effects of moxifloxacin greater than those of levofloxacin), and this should be kept in mind when constructing multidrug regimens or treating concurrent illnesses with drugs that also have this risk.

**Oxazolidinones**

Oxazolidinones are orally available drugs developed for resistant Gram-positive infections, which inhibit bacterial protein synthesis by binding to 23S ribosomal RNA. Mutations in the **rrl** gene encoding 23S rRNA confer high-level resistance to oxazolidinones, whereas mutations in the **rplC** gene encoding ribosomal L4 protein confer low-level resistance.\textsuperscript{343} Because these mutations occur spontaneously in only approximately 1 in 10\textsuperscript{8} bacilli, this class has a high genetic barrier to drug resistance. Linezolid, the first drug in this class, has good in-vitro activity against *M tuberculosis*, and is the best-studied oxazolidinone in tuberculosis. Linezolid also has good pulmonary and cerebrospinal fluid penetration.\textsuperscript{343}

Linezolid has been used off-label in patients with MDR tuberculosis with promising efficacy in observational studies.\textsuperscript{272} The addition of linezolid to a failing regimen in patients with XDR tuberculosis resulted in culture conversion in 87% of patients by 6 months, and resistance emerged in 4 of 38 patients.\textsuperscript{272} In another trial in which patients with XDR tuberculosis were randomised to receive linezolid or placebo, added to an individually optimised treatment regimen, culture conversion at 24 months was significantly higher for patients receiving linezolid (79% vs 38%).\textsuperscript{272}

Linezolid commonly causes haematological or neuropathic toxicity by virtue of its inhibition of protein synthesis in human mitochondria, and sometimes treatment must be stopped temporarily or permanently. This toxicity is both dose-dependent and duration-dependent. Although the approved dose for Gram-positive bacterial infections is 600 mg twice daily, clinicians treating MDR or XDR tuberculosis commonly initiate therapy with 300–600 mg once daily in an effort to mitigate toxicity. However, increasing bactericidal

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**Table 8: Drugs used in current WHO standard or shortened treatment of multidrug-resistant tuberculosis**

<table>
<thead>
<tr>
<th>Standard treatment*</th>
<th>Shortened treatment</th>
<th>Key role</th>
<th>Adverse events and tolerability</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluoroquinolone: levofloxacin or moxifloxacin</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Key bactericidal agent</td>
<td>Generally well tolerated; tendinitis; insomnia; QT prolongation</td>
</tr>
<tr>
<td><strong>Injectable agent: amikacin, kanamycin, or capreomycin</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Undefined</td>
<td>Ototoxicity, common and often irreversible; nephrotoxicity; injections painful</td>
</tr>
<tr>
<td><strong>Ethionamide or prothionamide</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Treat isolates whose isoniazid resistance is mediated by inhA mutation</td>
<td>Nausea and vomiting common</td>
</tr>
<tr>
<td><strong>Cycloserine or terizidone</strong></td>
<td>Yes</td>
<td>No</td>
<td>Bacteriostatic drug</td>
<td>Neuropsychiatric side-effects common</td>
</tr>
<tr>
<td><strong>Linezolid</strong></td>
<td>No</td>
<td>No</td>
<td>Protect against emergence of resistance</td>
<td>Peripheral neuropathy and bone marrow toxicity common</td>
</tr>
<tr>
<td><strong>Clofazimine</strong></td>
<td>No</td>
<td>Yes</td>
<td>Sterilising drug</td>
<td>Skin discoloration in almost all people; QT prolongation</td>
</tr>
<tr>
<td><strong>High-dose isoniazid</strong></td>
<td>No</td>
<td>Yes</td>
<td>Treat isolates whose isoniazid resistance is mediated by inhA mutation</td>
<td>Peripheral neuropathy, preventable by vitamin B6</td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Sterilising drug; synergy with other drugs</td>
<td>Arthralgias common; hepatitis</td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>No</td>
<td>Yes</td>
<td>Protection against resistance</td>
<td>Optic neuritis, rarely</td>
</tr>
</tbody>
</table>

*In 2016, WHO recommendations were updated to recommend the following as standard treatment: a fluoroquinolone, an injectable, two of the following—ethionamide or prothionamide, cycloserine or terizidone, linezolid, and clofazimine—and pyrazinamide. Other agents (ethambutol, bedaquiline, delamanid, etc) could be added, if needed, to construct a regimen. Before 2016, linezolid and clofazimine were not components of WHO-recommended standard MDR-TB treatment, but they now are.
activity has been observed with increasing total daily doses between 300 and 1200 mg. Administration of higher doses intermittently (eg, 900–1200 mg three times per week), with or without an initial phase of daily therapy, might be a promising strategy to better separate the efficacy of linezolid from its toxicity. Linezolid is a weak inhibitor of monoamine oxidase A and B and cannot be given with serotonin reuptake inhibitors because this might result in development of the serotonin syndrome. Cost has restricted linezolid usage, but the availability of generic linezolid and the inclusion of linezolid in the WHO Model List of Essential Medicines since 2015 have improved drug accessibility.

Newer oxazolidinones with potential for more favourable risk-to-benefit ratios than linezolid need to be explored for use in drug-resistant tuberculosis. Tedizolid is an oxazolidinone that is newly approved for the treatment of bacterial skin and soft tissue infections. In vitro it is active against *M tuberculosis* and might have less mitochondrial toxicity than linezolid, but tedizolid has not been tested in patients with tuberculosis or given for prolonged periods. Sutezolid is an investigational oxazolidinone in phase 2 testing for tuberculosis (table 8). Preclinical data suggest it could be more efficacious than linezolid, but a high incidence (14%) of liver enzyme elevations in an early bactericidal activity study was reported.

**Clofazimine**

Clofazimine is an oral riminophenazine dye that is used to treat leprosy. Although its mechanisms of action are not completely understood, it results in the intracellular generation of reactive oxygen species via redox cycling that involves a mycobacterial NADH dehydrogenase and molecular oxygen. In mouse models, clofazimine shows delayed-onset bactericidal activity as monotherapy, and significant sterilising activity in combination with first-line and second-line regimens. However, in C3HeB/FeJ mice that develop large caseous granulomas, clofazimine is less effective, perhaps because of the hypoxic conditions or reduced diffusion through caseous tissue, or both. Clofazimine shows no bactericidal activity in patient sputum over the first 14 days of treatment. However, in a phase 2 clinical trial, adding clofazimine at a dose of 100 mg daily for 21 months to multidrug background therapy (ie, the MDR tuberculosis treatment regimen) improved MDR tuberculosis treatment success versus placebo (74% vs 54%). Clofazimine is also considered a key component of a short-course regimen (ie, 9–12 months) recently endorsed by WHO for treatment of MDR tuberculosis after several observational cohorts reported good treatment success.

Clofazimine is highly lipophilic, it has a very large volume of distribution, and has a terminal half-life of 70 days. The drug becomes highly concentrated in fat, organs, and skin with long-term use. Clofazimine accumulation causes slowly reversible red-black skin discolouration in nearly all patients, which is a barrier to widespread implementation because there is a stigma against hyperpigmentation in many countries in which tuberculosis is endemic. The extent of hyperpigmentation and the time to resolution depends on both dose and duration and might, therefore, be mitigated by shorter treatment durations or lower doses, or both, should they prove effective. Clofazimine also causes modest QT extension.

**β-lactams**

β-lactams as a class of drugs have received little attention as antituberculosis drugs, primarily because *M tuberculosis* has a constitutively active broad-spectrum β-lactamase (Blac). However, carbapenems such as meropenem are inefficiently hydrolysed by Blac. Further, carbapenems are active against *M tuberculosis* in vitro, and clavulanate, an irreversible inhibitor of Blac, further enhances the activity of carbapenems. The combination of a carbapenem and a penicillin might also have additive or synergistic effects. To examine the activity of a carbapenem–penicillin–clavulanate combination in vivo, a recent phase 2A proof-of-concept trial was done. In this study, a combination of meropenem, amoxicillin, and clavulanate showed quantifiable early bactericidal activity in patients with pulmonary drug-susceptible tuberculosis. However, all drugs were administered three times per day, and meropenem (like imipenem) requires intravenous infusion. Faropenem, an oral penem, in combination with amoxicillin-clavulanate had no bactericidal activity, perhaps because the drug exposure was too low at the tested dose.

**Bedaquiline**

Bedaquiline is a new oral diarylquinoline drug developed for tuberculosis that inhibits the *M tuberculosis* ATP synthase. Bedaquiline is the first representative of a new class of drugs to be approved for treatment of tuberculosis in over 40 years. In preclinical testing, bedaquiline plus pyrazinamide had better sterilising activity than rifampicin, pyrazinamide, and isoniazid. Bedaquiline displays notable synergy with pyrazinamide. Spontaneous mutations conferring resistance to bedaquiline occur in approximately 1 in 10^7 or 10^8 bacteria (similar to rifampicin). High-level resistance to bedaquiline results from mutations in the ATP synthase binding site, *Rv0678*. These resistant mutants show cross-resistance to rifampicin and have been selected for during treatment of patients with pre-XDR and XDR tuberculosis with bedaquiline. In human beings, bedaquiline is highly protein-bound (99–99%), is metabolised by cytochrome P450 isoenzyme 3A (CYP3A) to a less active metabolite (M2),
In human beings, delamanid is the QT interval, so clinicians should minimise the use of delamanid and antiretroviral drugs: bedaquiline concentrations are estimated to be reduced by about 50% with concurrent efavirenz treatment, and increased two-times with concurrent lopinavir and ritonavir.

In phase 2 trials, 2-month sputum culture conversion increased after 8-week therapy from 9% with multidrug background therapy and placebo to 48% with background therapy and bedaquiline, and the increase was sustained at 6 months. Mortality was higher in the bedaquiline group than the placebo group, but most of the deaths in the bedaquiline group occurred after completion of the 6-month course of bedaquiline treatment, and causes of death were widely variable. This suggests that the increased mortality associated with bedaquiline in the small phase 2 study is a chance finding. In post-marketing studies, an increase in mortality was not seen. WHO recommends that bedaquiline be given for 6 months for treatment of MDR tuberculosis in adult patients who don't have other treatment options. Mortality concerns in the phase 2 study and the reduction in bedaquiline concentrations by more than 50% with the concurrent use of rifampicin has prevented its investigation as a first-line treatment-shortening regimen.

Bedaquiline causes moderate prolongation (10–15 ms) of the QT interval, so clinicians should minimise the use of other QT-prolonging drugs, including non-tuberculosis drugs and tuberculosis drugs such as clofazimine, delamanid, and the fluoroquinolones (apart from levofloxacin, which has a minor effect on QT) and undertake rapid correction of electrolyte abnormalities and regular ECG monitoring. Substantial hepatotoxicity has been reported (7.7% in the bedaquiline arm vs 2.5% in the control arm). In-vitro studies using human mononuclear cells suggest that bedaquiline induces phospholipidosis with ultrastructural cellular changes; however, the implications for toxicity from this drug-induced phospholipidosis are unclear. Drug interactions with the concurrent use of bedaquiline and antiretroviral therapy is outlined in table 2. The extremely long terminal elimination half-life (6 months) and intracellular drug accumulation might have beneficial mycobactericidal effects, although concerns have been raised about the development of resistance in individuals lost to follow-up who could have been exposed to long periods of bedaquiline monotherapy.

The need for rapid use of bedaquiline in sub-populations with significant mortality and toxicity (eg, people with pre-XDR or XDR tuberculosis, and those with MDR tuberculosis with intolerance of other drugs such as aminoglycoside ototoxicity) but at the same time clarify important unknowns through phase 3 trials (efficacy, optimum duration and use with companion drugs, and adverse events), raises important ethical and medicolegal questions.

Although encouraging initial observations have been made of faster culture conversion in early bactericidal activity and phase 2 studies of bedaquiline, and high rates of culture conversion in French and South African patients with XDR tuberculosis (100% in the French cohort and 85% in the South African cohort), another analysis indicated that the 120-week culture conversion rate was 70% in patients with pre-XDR tuberculosis and 62% in XDR tuberculosis when bedaquiline was used with companion drugs and an optimised background regimen. Thus, even with newer drugs such as bedaquiline, treatment failure will be common in patients with XDR tuberculosis or those with resistance beyond XDR tuberculosis, for which no effective therapy is available and so it remains programmatically incurable. Measures will need to be taken to strengthen the drug development pipeline and to minimise drug resistance. In addition to addressing patient-specific and programme-specific issues that promote the development of drug resistance, novel drug dosing and administration strategies, monitoring strategies, and adjunct therapies (eg, efflux pump inhibitors and immune modulation strategies) will need to be investigated.

### Nitroimidazoles

Nitroimidazoles have been developed specifically for tuberculosis. They have two mechanisms of action—the inhibition of mycolic acid (mycobacterial cell wall) synthesis and the liberation of toxic nitric oxide within M tuberculosis. These drugs act against actively dividing and non-replicating bacilli and show potent sterilising activity in mouse models.

Delamanid is a nitroimidazole registered for use in the treatment of drug-resistant tuberculosis and is a prodrug that is activated by an F420-dependent mycobacterial nitroreductase. Mutations across the nitroreductase gene, or in any of four genes involved in the synthesis or activation of the F420 cofactor, could cause high-level delamanid resistance. Spontaneous mutations conferring resistance to delamanid are relatively frequent, occurring in approximately one in 100000 to 1000000 bacilli. In human beings, delamanid is highly protein bound (>99.5%), is metabolised by albumin, has a half-life of 34 h, and its DM-6705 metabolite has a half-life of more than 180 h. Delamanid has low oral bioavailability, so it has to be given with food, and dosing must be separated in time from dosing of other medications. Co-administration with ritonavir-boosted protease inhibitors or efavirenz does not markedly affect delamanid exposure.

In a phase 2 randomised controlled trial in patients with MDR tuberculosis, treatment with delamanid resulted in higher rates of culture conversion at 2 months compared with placebo (45.4% vs 29.6%, p=0.008) after 8 weeks of treatment compared with placebo; the
Delamanid causes moderate QT prolongation (10–15 ms) but is otherwise well tolerated. QT prolongation appears to be associated with concentrations of the DM-6705 metabolite. A phase 3 trial of delamanid (NCT01424670) has completed the enrolment and treatment phase (table 6), and full results are expected in 2018.

Global access to delamanid has been poor, but the drug has been made available through the Global Drug Facility and there is increasing experience of its use. Delamanid has a low threshold for resistance development, therefore it should be used in combination with drugs with higher genetic barriers to resistance, such as bedaquiline (with careful ECG monitoring). Delamanid is contraindicated in people who have an allergy to metronidazole. The twice-daily dosing regimen complicates the use of delamanid in DOT programmes, and a single daily dose of delamanid is being assessed in clinical trials. Delamanid is recommended for 24 weeks of therapy, but longer courses have been given without additional safety issues both in the industry-sponsored observational study and in individual patients. Patients given delamanid should have a baseline and monthly ECG to measure the QTc interval and a baseline albumin test because the drug is metabolised by albumin and there might be an increase in adverse events with albumin concentrations below 28 g/L. Delamanid is not recommended in patients with moderate to severe hepatic impairment. Delamanid has few drug–drug interactions and no significant interactions have been seen with the antiretrovirals efavirenz and lopinavir–ritonavir.

**Pretomanid** (PA-824) is another nitroimidazole agent that is being developed as part of combination therapy for tuberculosis and MDR tuberculosis by the TB Alliance. Pretomanid is in phase 3 testing, and its characteristics are shown in table 7. On the basis of early bactericidal activity studies and the superior bactericidal activity of pretomanid, moxifloxacin, and pyrazinamide versus rifampicin, isoniazid, pyrazinamide, and ethambutol for drug-sensitive tuberculosis at 8 weeks, the phase 3 STAND study was launched (table 6; NCT02342886), but this study was placed on partial clinical hold because of hepatotoxicity and further enrolment was stopped, but follow up will continue as per protocol. Pretomanid is also being studied as part of combination therapy for XDR tuberculosis (NIX Trial, NCT02333799; table 6). Complete cross-resistance exists between delamanid and pretomanid.

**Constructing regimens: tools and strategies**

Although the majority of MDR tuberculosis strains are resistant to additional drugs beyond isoniazid and rifampicin, detailed susceptibility profiles are rarely available at the initiation of treatment. The standard of care to construct empirical drug-resistant tuberculosis regimens, pending the outcome of full susceptibility results, or for standardised drug-resistant tuberculosis regimens used in low-resource settings is given in panel 3. Treatment with a large number of tuberculosis drugs is commenced in an effort to provide at least 3–4 active drugs (ie, drugs that the organism is susceptible to). Standardised MDR tuberculosis treatment regimens typically consist of a fluoroquinolone, a second-line injectable drug, ethionamide or prothionamide, and cycloserine or terizidone; however, these drugs do not have good sterilising activity. The first-line drugs pyrazinamide and ethambutol are often included, despite high prevalence of resistance in MDR tuberculosis isolates. In 2016, WHO recommended a 9–12 month, 7-drug MDR tuberculosis regimen for selected patients that uses largely the same drugs, with the addition of clofazimine and high-dose isoniazid. There is a need for a more rational approach to selecting newer drug-resistant tuberculosis regimens, with a focus on safer and shorter regimens.

With the new or repurposed drugs that we have described in this Commission, existing first-line and second-line drugs commonly used in drug-resistant tuberculosis, and experimental drugs that have entered or will be entering the clinical research pipeline, the number of potential combinations of drugs, durations, and doses to construct new regimens appears almost limitless. However, considering that the regimen ought to be rapidly bactericidal (to interrupt transmission), have good sterilising activity (to completely cure), minimise resistance emergence (to be durable), and to be well tolerated (considering overlapping toxicities and drug–drug interactions), the number of promising regimens shrinks substantially, and assessing them becomes more manageable.

The absence of a validated surrogate efficacy marker that can be measured early in the course of treatment and predict long-term treatment outcomes is a major impediment to the clinical development of new tuberculosis drugs and regimens. Non-clinical models therefore fulfil an essential role, enabling exploration of exposure–response relationships and the efficacy of novel drug combinations. The ultimate goal of non-clinical efficacy studies is to inform the design of clinical trials that will establish the optimal dose of individual drugs, the contribution of individual drugs to the efficacy of novel regimens, and the efficacy of novel regimens relative to the standard of care. A variety of non-clinical models have been used, each with advantages and disadvantages. Largely for reasons of availability, cost, and tractability, murine models have been used most extensively. Although the lung pathology produced in the commonly used mouse strains does not reproduce the caseous pathology observed in human tuberculosis, demonstration of the treatment-shortening potential of rifampicin and pyrazinamide have established the utility...
of murine models. Studies in mice were used to justify phase 3 trials investigating the potential of late-generation fluoroquinolones to shorten the treatment of drug-susceptible tuberculosis. However, the failure of these treatment-shortening trials showed potential pitfalls in the way non-clinical and early clinical data have been used to inform trial design, including over-reliance on murine models that might not fully represent the distribution and activity of drugs in caseating lung lesions, and underappreciation of the effect of individual pharmacokinetics and drug–drug interactions on efficacy.

A key lesson that has been learned is that defining optimal drug doses is a necessary step in optimising regimen efficacy and preventing the emergence of resistance. Repetition of the mistake of underdosing with new drugs should be avoided in drug-resistant tuberculosis regimens, because resistance could rapidly emerge. For repurposed drugs, doses used to treat other infections should not be assumed to be optimal for drug-resistant tuberculosis treatment, in which disease-specific pharmacokinetic–pharmacodynamic associations, longer treatment durations, overlapping toxicities, and drug–drug interactions associated with combination therapy are important factors in establishing optimal doses. Even for new drugs specifically developed for drug-resistant tuberculosis, such as bedaquiline and delamanid, it should not be assumed that doses used for regulatory approval are necessarily optimal. Although additive or synergistic drug combinations could be exploited to lower individual drug doses, this could undermine the ability of regimens to suppress the emergence of drug resistance. The role of rifabutin in MDR tuberculosis also requires clarification (panel 8).

A more revolutionary approach uses non-clinical model results together with early clinical data to rapidly advance novel, short-duration drug combinations containing two or more new drugs or multiple regimens. The combination of pretomanid with moxifloxacin and pyrazinamide was first shown to be superior to the first-line regimen for drug-susceptible tuberculosis in a murine model and has subsequently shown activity that is superior to the standard of care over the first 2 months of treatment in patients with drug-susceptible tuberculosis. Pyrazinamide also appeared to be effective in patients with pyrazinamide-susceptible and fluoroquinolone-susceptible MDR tuberculosis. A confirmatory phase 3 study of pyrazinamide in patients with MDR tuberculosis is underway (China PZA trial; table 6). Similarly, following the promising effects in mice, the three-drug combination of bedaquiline, pretomanid, and pyrazinamide is under investigation in patients with drug-susceptible tuberculosis, with the addition of moxifloxacin in patients with MDR tuberculosis (STAND; table 6). Combining bedaquiline and pretomanid (or delamanid) with linezolid could be the best opportunity for a much-desired three-drug regimen that is effective against virtually all circulating drug-resistant and drug-sensitive M tuberculosis isolates. This combination has shown sterilising activity superior to the first-line drug-susceptible tuberculosis regimen in mice and is now being studied in patients with XDR tuberculosis or MDR tuberculosis with intolerance of other regimens. A graphic summary of the effect of relevant novel regimens on duration of therapy in murine models is shown in figure 8. However, when developing regimens containing two or more new drugs for which safety data are scarce, special attempts should be made...
to assign causality of adverse events to individual drugs, and to understand the mechanisms of toxicity.

The proposal to use a new phase 2C trial design, which is a hybrid phase 2/3 study, to accelerate the development of novel treatment-shortening regimens in drug-susceptible tuberculosis is equally applicable to drug-resistant tuberculosis, and is being pursued by several groups.

**Challenges and opportunities for the treatment of paediatric MDR tuberculosis**

Although the second-line antituberculosis drugs are routinely used for treating paediatric MDR tuberculosis, all are prescribed off-label and none had been prospectively assessed in pharmacokinetic studies in children until recently. These studies show substantially lower exposures to key second-line tuberculosis drugs, including levofloxacin and moxifloxacin, compared with adult target values, indicating considerable opportunity for dose optimisation. There are few palatable, child-friendly formulations of the second-line antituberculosis drugs, making safe and appropriate dosing difficult, especially in young children, complicating adherence, and making both providers and families reluctant to initiate MDR tuberculosis therapy for children. The high pill burden and paucity of child-friendly formulations are even more challenging in children who are co-infected with HIV. Available MDR tuberculosis regimens with existing second-line antituberculosis drugs are long, often require hospitalisation, and are associated with frequent and serious toxicity, including permanent sensorineural hearing loss due to injectable tuberculosis drugs in up to 24% of children. Safer, shorter, simpler, and injectable-sparing treatment regimens are urgently needed. Trials investigating such regimens are already underway in adults.

Children have traditionally been excluded from trials of novel tuberculosis treatment regimens because of the perceived low public health significance of paediatric tuberculosis, a disregard for the significant tuberculosis-associated morbidity and mortality in children, few regulatory incentives, practical challenges of including children in trials, and scarce commercial incentives. For novel tuberculosis drugs, given proof of efficacy from phase 2B or 3 trials in adults, the priority for children is pharmacokinetic and safety studies to establish the optimal and safe doses in children of different ages and weights. In parallel to the opening of adult efficacy trials, paediatric formulations should therefore already be developed to allow for the clinical assessment of these drugs in paediatric-appropriate regimens. Considering the extensive clinical assessment and licensure of the novel drugs bedaquiline and delamanid in adults with MDR tuberculosis, the rare assessment of these drugs in children to date represents a serious neglect of paediatric tuberculosis by researchers.

Delamanid seems to be safe and well tolerated in children aged 6–17 years, and with appropriate exposures achieved using the adult formulation, but very few controlled data for children have been collected. Studies in younger age groups are ongoing. Paediatric studies for bedaquiline are ongoing. Such studies are urgently needed to improve children’s access to trials assessing injectable-sparing short-course MDR tuberculosis therapy and for routine care. Paediatric formulations should be developed and used in these trials.

**Summary of new drugs and strategies**

The approach of assessing new drugs by comparing them with placebo added to multidrug background therapy has identified drugs that are promising candidates for new regimens. Murine models are used extensively to assess novel regimens, several of which are now being studied in phase 2 and 3 clinical studies. Enough new drugs now exist to enable discontinuation of the use of toxic drugs with low efficacy, at least for MDR tuberculosis. The 9–12-month regimen now recommended by WHO for selected patients with MDR tuberculosis is welcome, but it includes seven drugs, some of which are quite toxic or unlikely to be effective (table 8). With the new drugs, much better regimens can be constructed. Injection-free regimens of 6–9 months are highly likely to replace the problematic drug-resistant tuberculosis regimens in the medium term. New regimens that are shown to be

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**Figure 9: Pill burden for patients with MDR tuberculosis**

(A) Pill burden for a child aged 8 years. (B) Pill burden in an adult, including morning dose (left panel) and evening dose (right panel). These photos exclude any injectable agents, which are usually given in addition to pills, for 6–8 months intramuscularly without anaesthesia. Images with courtesy and permission of CAPRISA.
effective should be rapidly available to all patients with drug-resistant tuberculosis, including children and individuals with HIV co-infection.

**Pharmacokinetic-pharmacodynamic factors in drug-resistant tuberculosis**

A direct association exists between acquired drug resistance and drug pharmacokinetics and is best explained by use of antimicrobial pharmacokinetic–pharmacodynamic science. Similarly, drug exposures predict the clearing of viable *M tuberculosis* from the sputum. \(^{191,195}\)

**Capturing pharmacokinetic variability**

Each patient treated with a fixed dose achieves a different concentration-time curve from the next. This difference between patients is due to differences in absorption, speed of xenobiotic metabolism, elimination, and volume of distribution. Evolution, lifestyle habits such as smoking and diet, and anthropometric factors such as weight, nutritional state, height, and other immeasurable factors, are responsible for this between-patient pharmacokinetic variability. For example, obesity has emerged as a major driver of pharmacokinetic variability, based on changes in organ size and physiological maturation, including that of enzymes responsible for xenobiotic metabolism.\(^ {198-403}\) Furthermore, variation exists from day to day in the same patient, which is termed inter-occasion variability. Thus, a given dose of a drug (even when given in mg/kg rather than an absolute concentration) will achieve many different peak concentrations (*C*\(_\text{max}\)) and area under the curve (AUC) values, as well as different lengths of time for which the drug concentration persists above the MIC (*T*\(_\text{mic}\)). This variability is captured and quantified in population pharmacokinetic analyses. Therefore, population pharmacokinetic parameter values of anti-tuberculosis drugs should be established for each locale in which the tuberculosis burden is high. The pharmacokinetic parameters for standard first-line drugs and for drugs used in both MDR and XDR tuberculosis are shown in table 9, mainly based on publications from South Africa, India, and the USA.\(^ {494-496}\) Predicting what concentration a patient will achieve is difficult, given the multiple determinants of pharmacokinetic variability.\(^ {111}\) Therefore, to identify the specific concentration-time profile, the drug concentrations should be measured in the patient directly.

**Pharmacokinetic-pharmacodynamic indices and microbial kill versus acquired drug resistance: fraternal twins**

The pharmacokinetic–pharmacodynamic exposure is the drug concentration at a site divided by the MIC. This calculation is based on the fact that the drug concentration (*C*\(_\text{max}\) or AUC) achieved as well as the MIC will affect how well an antibiotic kills *M tuberculosis*. *M tuberculosis* MICs for antibiotics are variable, and have a distribution. Thus, commonly used statements that specify a typical MIC do not reflect the distribution of susceptibility to a particular drug.\(^ {203,427}\) As a result of this MIC distribution and the pharmacokinetic variability, when patients are given the same dose of antibiotics, wide distributions of *C*\(_\text{max}\) divided by MIC, AUC\(_{0-24}\) divided by MIC, and T\(_\text{mic}\) are achieved in different individuals. Since it is difficult to guess the effect of such distributions from patient to patient, the drug concentration and MIC should be measured in each patient to establish the exact exposure achieved.

The associations between pharmacokinetic–pharmacodynamic exposure and microbial kill or acquired drug resistance were first established using preclinical models such as the hollow fibre system, murine models, and guineapig models. Since the pharmacokinetic–pharmacodynamic relationships are intrinsic to the interaction between bacteria and different drug exposures, the relationships are invariant, and follow the exposure–response curves shown in figure 10A, on the basis of an inhibitory sigmoid maximal effect (E\(_\text{max}\)) model. The model has four parameters: 1) the effect without any drug treatment; 2) E\(_\text{max}\); 3) the exposure associated with 50% of E\(_\text{max}\) (EC50); and 4) the slope on the steep portion of the curve (Hill factor). This relationship can be translated from preclinical models to humans. In some models these data have been found to accurately forecast therapeutic events with 94% accuracy.\(^ {183,421-425}\) The bactericidal effect of isoniazid is an example that has been shown in several preclinical models and patients (table 10).\(^ {494}\) The pharmacokinetic–pharmacodynamic exposure patterns or indices important in preventing or amplifying acquired drug resistance have been established for several agents in preclinical models, and at least in the case of first-line antituberculosis drugs and quinolones, they have been validated in clinical studies.\(^ {393-420,425}\) Table 11 shows the pharmacokinetic–pharmacodynamic exposure and pharmacokinetic–pharmacodynamic index associated with the suppression of acquired drug resistance for several drugs that are used in clinical practice; these often differ from those associated with optimal microbial kill for the same drug.\(^ {493,393,395,398,399,402,404,407}\) Mistakenly, many regimens were designed for the treatment of tuberculosis with a focus on microbial kill, ignoring the problem of acquired drug resistance. The theory was that directly observing the patients swallowing the pills, and using one drug to prevent resistance to another, would solve the acquired drug resistance problem.\(^ {103}\) As a result, MDR and XDR tuberculosis developed. Each drug in a given combination will need optimisation for both microbial kill and acquired drug resistance, which can be achieved with awareness of pharmacokinetic variability, followed by understanding the relationship between pharmacokinetics and pharmacodynamics, and pharmacokinetics and acquired drug resistance.
The relationship between the pharmacokinetic–pharmacodynamic exposure and acquired drug resistance is described by a system of quadratic functions (figure 10). This U-shaped relationship, first described in hollow-fibre models for isoniazid and pyrazinamide for *M tuberculosis*, has since been identified with other antibiotics in their relationships with other mycobacteria, including *M abscessus*.432,433 For *M tuberculosis*, the relationship between exposure and the bacterial burden of the drug-resistant subpopulation forms a U-shaped curve early during therapy (figure 10). As drug exposure increases (e.g., as \(C_{\text{max}}/\text{MIC}\) increases) there is a progressive decrease in the size of the drug-resistant subpopulation, indicating suppression of acquired drug resistance. However, a point is reached that as exposure increases the drug-resistant subpopulation begins to increase again, then as therapy duration increases, the curve starts to flatten, eventually flipping into an inverted U-shape. Thus, as drug exposure increases from zero, amplification of the drug-resistant subpopulation occurs. This amplification of the drug-resistant subpopulation reaches a point after which increases in exposure lead to a decrease in the size of the resistant population, eventually to zero. That drug concentration or exposure, which is associated with a zero size of drug-resistant subpopulation, is the target for suppression of acquired drug resistance. However, with increasing duration of therapy at concentrations below this point, acquired drug resistance is amplified and a high level of drug resistance is established that cannot be overcome with any achievable drug exposures. Thus, acquired drug resistance is determined by both pharmacokinetic–pharmacodynamic exposure and duration of therapy; longer is not necessarily better. Thus, in dosing to

<table>
<thead>
<tr>
<th>Age range</th>
<th>Total clearance in L/h (interindividual variability)</th>
<th>Central volume in L (interindividual variability)</th>
<th>Absorption constant per h (interindividual variability)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid404-405 (n=191; India)*</td>
<td>Younger than 15 years</td>
<td>7.8 (67.8%)</td>
<td>5.2 (34.3%)</td>
</tr>
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<td></td>
<td></td>
<td>5.2 (34.3%)</td>
<td>0.8 (64.8%)</td>
</tr>
<tr>
<td>Rifampicin406-407 (n=191; India)</td>
<td>Younger than 15 years</td>
<td>11.0 (120.0%)</td>
<td>21.8 (27.0%)</td>
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<td></td>
<td></td>
<td>21.8 (27.0%)</td>
<td>1.1 (126.0%)</td>
</tr>
<tr>
<td>Pyrazinamide408 (n=191; India)</td>
<td>Younger than 15 years</td>
<td>2.2 (41.9%)</td>
<td>12.8 (48.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12.8 (48.4%)</td>
<td>2.5 (77.2%)</td>
</tr>
<tr>
<td>Ethambutol409 (n=31; South Africa)</td>
<td>Younger than 15 years</td>
<td>20.6 (29.61%)</td>
<td>135 (15.7%)</td>
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<td></td>
<td></td>
<td>135 (15.7%)</td>
<td>1.7 (123.5%)</td>
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<tr>
<td>Linezolid410 (n=100; USA), full term (per kg)</td>
<td>Full-term birth to 28 days</td>
<td>0.31 (22.0%)</td>
<td>0.66 (29.0%)</td>
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<td></td>
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<td>0.66 (29.0%)</td>
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<tr>
<td>Linezolid410 (n=100; USA), infants (per kg)</td>
<td>28 days to 3 months</td>
<td>0.32 (32.0%)</td>
<td>0.79 (27.0%)</td>
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<td></td>
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<td>0.79 (27.0%)</td>
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<tr>
<td>Linezolid410 (n=100; USA), child (per kg)</td>
<td>Aged 3 months to 11 years</td>
<td>0.23 (53.0%)</td>
<td>0.69 (28.0%)</td>
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<td></td>
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<td>0.69 (28.0%)</td>
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<tr>
<td>Moxifloxacin411 (n=23; USA), infants (per kg)</td>
<td>0–1 years</td>
<td>0.35 (27.0%)</td>
<td>2.23 (31.3%)</td>
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<td></td>
<td></td>
<td>2.23 (31.3%)</td>
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<tr>
<td>Moxifloxacin411 (n=23; USA), toddlers (per kg)</td>
<td>1–4 years</td>
<td>0.26 (24.3%)</td>
<td>1.61 (22.9%)</td>
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<tr>
<td></td>
<td></td>
<td>1.61 (22.9%)</td>
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<tr>
<td>Moxifloxacin411 (n=23; USA), school age (per kg)</td>
<td>4–9 years</td>
<td>0.25 (36.87%)</td>
<td>2.08 (33.37)</td>
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<td></td>
<td></td>
<td>2.08 (33.37)</td>
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<tr>
<td><strong>Adults</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Isoniazid409 (n=235; South Africa)†</td>
<td>18 years or older</td>
<td>7.8, fast acetylator (18.4%); 9.7, slow acetylator (18.4%)</td>
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<td></td>
<td></td>
<td>57.7 (16.5%)</td>
<td>1.85</td>
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<tr>
<td>Rifampicin410 (n=261; South Africa)</td>
<td>18 years or older</td>
<td>19.2 (52.8%)</td>
<td>53.2 (43.4%)</td>
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<td></td>
<td></td>
<td>53.2 (43.4%)</td>
<td>1.15 (66.3%)</td>
</tr>
<tr>
<td>Ethambutol411 (n=189; South Africa)§</td>
<td>18 years or older</td>
<td>39.9 (20%)</td>
<td>82.4</td>
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<td></td>
<td></td>
<td>82.4</td>
<td>0.5 (39%)</td>
</tr>
<tr>
<td>Pyrazinamide407 (n=227; South Africa)</td>
<td>18 years or older</td>
<td>3.4</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29.2</td>
<td>3.56, fast absorbers 1.25, slow absorbers</td>
</tr>
<tr>
<td>Linezolid410 (n=455; Japan, USA)¶</td>
<td>18 years or older</td>
<td>1.3 (46.6%)</td>
<td>47.0 (25.9%)</td>
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<td></td>
<td></td>
<td>47.0 (25.9%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Moxifloxacin411 (n=241; South Africa)</td>
<td>18 years or older</td>
<td>10.6 (18.6%)</td>
<td>114</td>
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<tr>
<td></td>
<td></td>
<td>114</td>
<td>1.5 (69.9%)</td>
</tr>
<tr>
<td>Levofloxacin412 (n=372; USA)</td>
<td>18 years or older</td>
<td>9.3 (46.5%)</td>
<td>64.8 (51.3%)</td>
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<tr>
<td></td>
<td></td>
<td>64.8 (51.3%)</td>
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</tr>
<tr>
<td>Bedaquiline413 (n=480)</td>
<td></td>
<td></td>
<td>18 years or older</td>
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<td></td>
<td></td>
<td>164 (39.1%)</td>
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</tr>
<tr>
<td>Para-aminosalicylic acid414 (n=73; South Africa)</td>
<td>18 years or older</td>
<td>9.4 (47.5%)</td>
<td>51.8 (74.8%)</td>
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<tr>
<td></td>
<td></td>
<td>51.8 (74.8%)</td>
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</tr>
<tr>
<td>Amikacin415 (n=88, Belgium)**</td>
<td>18 years or older</td>
<td>2.2 (71.9%)</td>
<td>19.2 (39.0%)</td>
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<td></td>
<td></td>
<td>19.2 (39.0%)</td>
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</tbody>
</table>

Values for which there is no inter-individual variability published have no percentage indicated. The clearance and central volume in children are expressed as per kg because children's weights change rapidly and regularly. -- not estimated. *Isoniazid intercompartmental clearance in children was 15.4 L/h (16.9%), and volume of peripheral compartment 7.5 L (21.0%). Isoniazid intercompartmental clearance in adults was 3.34 L/h (93.1%), and volume of peripheral compartment 1730 L. Ethambutol intercompartmental clearance in adults was 3.41 L/h, and volume of peripheral compartment 623 L. Slope of effect of weight on clearance (per kg) was 0.43; slope of effect of weight on volume (per kg) was 0.43. *Linezolid intercompartmental clearance was 2.1 L/h (33.9%), and volume of peripheral compartment 89.8 L (A 4-compartment disposition model. **Amikacin intercompartmental clearance was 4.3 L/h (16.5%), and volume of peripheral compartment 9.3 L (34%).

Table 9: Pharmacokinetic parameter estimates and variability of antituberculosis agents in adults and children

The relationship between the pharmacokinetic–pharmacodynamic exposure and acquired drug resistance is described by a system of quadratic functions (figure 10). This U-shaped relationship, first described in hollow-fibre models for isoniazid and pyrazinamide for *M tuberculosis*, has since been identified with other antibiotics in their relationships with other mycobacteria, including *M abscessus*.432,433 For *M tuberculosis*, the relationship between exposure and the bacterial burden of the drug-resistant subpopulation forms a U-shaped curve early during therapy (figure 10). As drug exposure increases (e.g., as \(C_{\text{max}}/\text{MIC}\) increases) there is a progressive decrease in the size of the drug-resistant subpopulation, indicating suppression of acquired drug resistance. However, a point is reached that as exposure increases the drug-resistant subpopulation begins to increase again, then as therapy duration increases, the curve starts to flatten, eventually flipping into an inverted U-shape. Thus, as drug exposure increases from zero, amplification of the drug-resistant subpopulation occurs. This amplification of the drug-resistant subpopulation reaches a point after which increases in exposure lead to a decrease in the size of the resistant population, eventually to zero. That drug concentration or exposure, which is associated with a zero size of drug-resistant subpopulation, is the target for suppression of acquired drug resistance. However, with increasing duration of therapy at concentrations below this point, acquired drug resistance is amplified and a high level of drug resistance is established that cannot be overcome with any achievable drug exposures. Thus, acquired drug resistance is determined by both pharmacokinetic–pharmacodynamic exposure and duration of therapy; longer is not necessarily better. Thus, in dosing to
suppress acquired drug resistance, it would be necessary to achieve the pharmacokinetic–pharmacodynamic exposure that suppresses resistance (i.e., target concentration) but delivered for shorter durations that minimize resistance. The idea of increased drug resistance with longer therapy duration is counterintuitive, because in clinical practice the tendency is to lengthen therapy duration to improve outcome.

The importance of drug penetration to the infection site

Antituberculosis drugs are administered at a site that is remote from the infection that is being treated, so whether antibiotics are administered orally, intramuscularly, or intravenously, they need to reach infections in different anatomical compartments. The physical barriers to drug transit toward the site of infection include the normal histopathology of the infected organ, physiological barriers such as the blood–brain barrier, and the pathological lesion such as a lung tuberculosis cavity that has layers of different cells and tissues. The concentration-time profiles that M tuberculosis will be exposed to are defined by these barriers; these local profiles will either kill the M tuberculosis, amplify acquired drug resistance, or suppress acquired drug resistance. Antituberculosis drug penetration indices into the lung cavity, macrophages, epithelial lining fluid, bone, the pericardial space, and the meninges are shown in table 12. In 2016, Dheda and colleagues showed that entry into the human tuberculosis cavity leads to a concentration gradient map, and they directly linked this gradient to the MICs (and hence resistance) in the different parts of the lung cavity for several antituberculosis drugs that patients were taking. Studies are ongoing that aim to associate this drug penetration indices into the lung cavity, macrophages, epithelial lining fluid, bone, the pericardial space, and the meninges are shown in table 12. In 2016, Dheda and colleagues showed that entry into the human tuberculosis cavity leads to a concentration gradient map, and they directly linked this gradient to the MICs (and hence resistance) in the different parts of the lung cavity for several antituberculosis drugs that patients were taking. Studies are ongoing that aim to associate this drug penetration indices into the lung cavity, macrophages, epithelial lining fluid, bone, the pericardial space, and the meninges are shown in table 12.

Therapeutic drug monitoring

Three main aims exist for therapeutic drug monitoring. First, drug concentration measurements should be used to individualise the dose to achieve optimal exposures in patients, giving them a better possibility of cure. This measurement is especially important in patients with comorbid conditions associated with worse tuberculosis outcomes, such as immunosuppressed patients or those with diabetes. Ideally, if resources permit, then specific measurements should be done in all tuberculosis patients, as is already the case in several countries. Second, therapeutic drug monitoring could be used to suppress resistance emergence, especially for those drugs whose mutation frequencies have weak barriers to acquired drug resistance. Third, implementation of therapeutic drug monitoring could be used to ameliorate concentration-dependent toxicity, for example with aminoglycosides, many second-line drugs, and even new antituberculosis compounds. For example, Modongo and colleagues examined the main determinants of amikacin ototoxicity and identified them to be an amikacin cumulative AUC of 87232 days per mg/h/L, a patient weight of less than 51 kg, and duration of

![Figure 10: Microbial kill and acquired drug resistance versus exposure](image-url)

(A) The inhibitory sigmoid $E_{max}$ curve for the relationship between drug exposure (linezolid AUC/MIC in this case) and the total bacterial population, modelled from receptor theory. At low exposures, no change in effect is seen with large exposure changes, until the exposure reaches an inflection point. After that, small exposure changes result in large changes in effect, with steep bacterial burden decline. An inflection point is eventually reached, probably because most target sites are occupied by the antibiotic. Increased exposure does not result in much change in effect beyond that. Adapted from Deshpande and colleagues. (B) System of quadratic functions explaining the size of the drug-resistant subpopulation with time versus exposure, based on the model by Gumbo and colleagues. At time $t_1$, there is a decline in the size of the resistant subpopulation with increasing exposure, until a nadir is reached after which, paradoxically, increasing exposure leads to an increase in the drug-resistant subpopulation towards baseline. This shows suppression of acquired drug resistance over time. As the duration of therapy increases, the graph straightens and then flips, so that at $t_2$, the relationship is opposite, indicating resistance amplification. However, at high exposures, resistance is suppressed below baseline. As the duration of therapy increases beyond that, the descending arm straightens out, and no amount of drug exposure can suppress the acquired drug-resistant subpopulation. AUC=area under the curve. CFU=colony-forming units. EC$_{80}$=80% of maximum efficacy. $E_{max}$=maximum efficacy. MIC=minimal inhibitory concentration. T$_{max}$=length of time for which the drug concentration persists above the MIC.
therapy of 166 days. Peak and trough concentrations were not predictive of ototoxicity. These observations were also made in carefully planned amikacin experiments in guineapigs based on audiometry: cumulative AUC was associated with hearing loss but not peak or trough. By contrast, a C\textsubscript{max} more than 67 mg/L and a C\textsubscript{max}/MIC more than ten were identified as the drivers of amikacin efficacy in tuberculosis. Thus, a good strategy is intermittent dosing with these targets, with identification of both C\textsubscript{max} and AUC during the first week to calculate the duration of therapy upfront in order to avoid the cumulative AUC of 87.23 days per mg/L that is associated with toxicity. In this scenario, the practice of also measuring trough concentration would be abandoned. Another potential drug for therapeutic drug monitoring and MIC identification could be pyrazinamide, especially when used for patients with MDR tuberculosis. For pyrazinamide treatment, exposures and MICs are the major determinants of clinical outcomes. Accounting for both the pyrazinamide exposures and actual MIC in each patient is crucial since the much lower proposed susceptibility breakpoint of 50 mg/L means that many patients will probably have isolates naturally resistant to pyrazinamide. Furthermore, many patients might not achieve the serum AUC/MIC ratio of 11.3, which has been associated with optimal sterilising effect. Increasing the pyrazinamide dose would of course entail

Table 10: The invariant relationship between isoniazid exposure and microbial effect in different disease models and patients

<table>
<thead>
<tr>
<th>Microbial kill</th>
<th>Acquired drug resistance</th>
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<tr>
<td><strong>Preclinical models</strong></td>
<td><strong>Clinic</strong></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>C\textsubscript{max}/MIC; AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>C\textsubscript{max}/MIC; AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Linezolid</td>
<td>AUC\textsubscript{0–24}/MIC</td>
</tr>
<tr>
<td>Amikacin</td>
<td>C\textsubscript{max}/MIC</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>C\textsubscript{max}/MIC</td>
</tr>
<tr>
<td>Pretomanid</td>
<td>%T\textsubscript{mic}</td>
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</tbody>
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Table 11: Antimicrobial pharmacokinetic-pharmacodynamic parameters linked to microbial kill and resistance suppression

<table>
<thead>
<tr>
<th>Tissue-to-serum penetration ratio for drug AUCs</th>
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<tbody>
<tr>
<td>Cerebrospinal fluid</td>
</tr>
<tr>
<td>Rifampicin</td>
</tr>
<tr>
<td>Isoniazid</td>
</tr>
<tr>
<td>Pyrazinamide</td>
</tr>
<tr>
<td>Ethambutol</td>
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<tr>
<td>Moxifloxacin</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Linezolid</td>
</tr>
<tr>
<td>Amikacin</td>
</tr>
<tr>
<td>Bedaquiline</td>
</tr>
</tbody>
</table>

= data not available. *Bone-to-serum ratio for foci inside sclerotic wall: sclerotic wall of vertebrae: other apparently abnormal bone. †Single-point sampling, not AUC or C\textsubscript{max}, thus could be subject to hysteresis. ‡Estimated from published graph of caseum-to-plasma ratio at steady state by Prideaux and colleagues (Pericardial fluid in tuberculosis pericarditis had pH 7.34 (thus pyrazinamide might not work), and a protein 61 g/L which would bind most rifampicin.

Table 12: Tissue-to-serum penetration ratio for drug AUCs
closer follow-up of adverse events, and frequent liver function tests.

Summary of pharmacokinetic-pharmacodynamic factors

Given the pharmacokinetic variability and the variability of MICs in patients, drug exposures that could lead to acquired drug resistance and therapy failure could be achieved. More data about drug exposure targets that would minimise therapy failure is available. Most data about acquired drug resistance was collected from preclinical models, except for one analysis of clinical studies in which all acquired drug resistance was preceded by low drug concentrations. Drug concentrations are also likely to be lower than the optimal concentration in some anatomical compartments, such as the meninges and pericardial fluid, because of poor penetration of drugs into those compartments. Thus, to choose the most effective therapy for different anatomical locations, having an idea of drug penetration indices is crucial. The research agenda should involve examining the penetration of alternative antibiotics for sites such as the pericardial fluid in which rifampicin, ethambutol, and pyrazinamide do not achieve high enough concentrations to be effective. Therapeutic drug monitoring targets must be those that were derived to optimise patient response, and to minimise toxicity. Work still needs to be done to validate concentration targets associated with suppression of acquired drug resistance in patients, using knowledge garnered from preclinical models.

Prevention and containment of transmission of highly drug-resistant (MDR and XDR) tuberculosis

Managing patients with highly drug-resistant tuberculosis is a rigorous process, so prevention of these infections is a far better option than treatment. Therefore, health-care delivery systems are crucial in ensuring that treatment of tuberculosis is effective, thereby preventing the emergence of drug resistance (panel 9). A full discussion of the effect of health-care delivery systems (private, public, inpatient, ambulatory, community-based, vertical, integrated) on the prevention of MDR tuberculosis is beyond the scope of this Commission; however, here we will discuss interventions that aim to prevent the generation, transmission, and reactivation of highly drug-resistant tuberculosis.

Sources of drug resistance

Mutations in *M tuberculosis* that confer drug resistance can be acquired through several processes. These drug-resistant bacilli can then be transmitted from an infectious patient to another person. Knowing the relative contributions of acquired drug resistance and person to person transmission to the burden of drug-resistant tuberculosis is crucial to target setting-specific tuberculosis control measures. For example, if most drug resistance is acquired, interventions to correct pharmacokinetic mismatch, promote adherence, and return patients to treatment with quality-assured drugs, are more likely to be effective. However, if most drug-resistant tuberculosis is transmitted (figure 11), interventions to rapidly reduce the infectiousness of patients (eg, by active case finding, rapid diagnosis, prompt and effective treatment, and transmission control interventions) are required. Molecular epidemiology studies in high-burden settings have shown high degrees of strain clustering—which is indicative of transmission rather than acquisition—in the majority of known MDR tuberculosis cases and a significant proportion of XDR tuberculosis cases. Indeed, the proportion of drug-resistant tuberculosis cases that are new tuberculosis cases, and hence have not had an opportunity to acquire resistance, has increased and is up to 80% in some settings. Some previously treated patients assumed to be due to acquired drug resistance, would likely be attributed to transmission if molecular typing were more widely available. Furthermore, a recent mechanistic mathematical modelling approach based on WHO prevalence data estimated the proportion of MDR tuberculosis due to transmission in different settings. Although the transmission-attributable fraction varied widely from 48% in Bangladesh to 99% in Uzbekistan, with the remainder probably being driven by acquired resistance, this model further underscores the importance of interrupting MDR tuberculosis transmission to prevent new cases. For several years, it has been established that only 20% of patients with MDR tuberculosis are given

### Panel 9: Effective treatment: the role of health-care delivery systems

- Community-based treatment of drug-susceptible and drug-resistant tuberculosis is more likely to be effective because of better adherence and cost-effective because of reduced hospital admissions thus preventing both the emergence of MDR tuberculosis and its transmission
- Successful community-based programmes have credited various key features, including the employment of paid and trained community members (rather than volunteers)—eg, in Cambodia, Haiti, Peru, and Rwanda—together with incentives and enablers such as food baskets, transportation vouchers, telephone credits, contracts, bonds, cash payments, and patient support groups
- Community-based programmes have been shown to be as effective or more effective than hospitalisation, and their cost is 33–70% less
- Unfortunately, with insufficient beds and resources for the growing numbers of patients with MDR tuberculosis, some programmes—eg, those in South Africa—have rapidly transitioned from hospital-based care, without first building the community-based infrastructure that is needed to assure treatment success
effective treatment (and less than half of these successfully treated), and thus the infectious pool of patients with undiagnosed, often unsuspected, drug resistance will continue to grow unabated. Estimating the burden due to ineffective or poorly adherent treatment is further complicated by data that suggest that approximately 1% of patients will still acquire resistance despite having uninterrupted treatment. Additionally, the association between treatment effectiveness (which can vary widely) and the degree of acquisition of drug resistance is not well understood.

Importance of unsuspected drug resistance
Tuberculosis transmission commonly and efficiently occurs in congregate settings from patients with unsuspected or undiagnosed drug-resistant disease, people not on therapy at all, or those on inadequate treatment. For example, in Tomsk, Russia, Gelmanova and colleagues reported a six-times greater risk of MDR tuberculosis for drug-susceptible, adherent patients with a history of hospitalisation compared with drug-susceptible, adherent patients treated entirely on an ambulatory basis. Commonly in Russia and around the world, patients diagnosed by sputum smear or radiography are treated for drug-susceptible tuberculosis in a room with many other patients with tuberculosis. In many regions of the world, drug susceptibility testing is only ordered when patients fail to clinically respond to treatment, with long delays in obtaining results using culture-based conventional methods. Commonly, MDR tuberculosis is recognised several months into treatment, and then effective treatment started, but during those months MDR tuberculosis transmission and re-infection of other patients and staff can occur. With the increasing use of Xpert MTB/RIF and other rapid molecular diagnostic tests, exposure to patients with unsuspected tuberculosis or unrecognised MDR tuberculosis can be substantially reduced. In a tuberculosis hospital in Veronesh, Russia, 932 patients with suspected pulmonary tuberculosis were hospitalised from May, 2013, to March, 2014; 923 underwent Xpert MTB/RIF testing, of whom 863 (93.5%) were tested within 2 days of admission. 407 (44%) of 923 that underwent testing were positive for tuberculosis; of these, 161 (40%) were rifampicin-resistant, of whom 159 (99%) were started on MDR tuberculosis treatment within three working days of receiving the result. An initiative to refocus attention on the speed of diagnosis and effective treatment for the purpose of transmission control has been branded FAST: Find cases Actively, Separate, and Treat effectively. Following the widely publicised and high-mortality outbreak of XDR tuberculosis at the Church of Scotland Hospital in KwaZulu-Natal, South Africa, a series of similar targeted interventions have dramatically reduced transmission in the hospital and in the community.

Insights into the effect of treatment on transmission using the guineapig and cough aerosol sampling models
Once diagnosed and started on effective treatment, another important practical issue is how long patients remain infectious. How long, if at all, do patients with MDR tuberculosis require isolation or separation in hospital, and do they actually require hospitalisation for transmission-control purposes? On the basis of household contact studies, Rouillon and colleagues in 1976 first proposed 2 weeks of effective treatment as the minimum duration necessary to render tuberculosis patients non-infectious. The authors emphasise that most patients are not smear-negative or culture-negative after 2 weeks (converting, on average, at about 2 months), concluding that smear and culture predicted patient infectiousness before the onset of effective therapy, but not once started. Three human to guineapig natural transmission studies spanning more than 50 years on three continents all found that transmission occurred almost exclusively from patients not on effective therapy. The original Riley study found that the 98% reduction in infectiousness from patients with drug-susceptible tuberculosis occurred almost immediately, since treatment was started only on hospital admission, not 2 weeks before. Since then, in South Africa, Dharmadhikari and colleagues found transmission only from patients with unsuspected XDR tuberculosis who were inadequately treated with MDR drugs rather than those...
patients that received effective treatment. In their study, more than a hundred patients with MDR tuberculosis just started on effective therapy were exposed to hundreds of sentinel guineapigs. 27 patients without molecular mutations for XDR tuberculosis and given effective treatment infected just one guineapig over 3 months, suggesting the effectiveness of MDR treatment in halting transmission.

By contrast, Fennelly and colleagues cultured bacilli from captured cough aerosol sampling using novel apparatus (figure 12), and found that aerosol cultures in four patients with MDR tuberculosis who were on effective treatment declined exponentially and much faster than sputum smears or cultures. However, aerosol cultures in one patient remained positive for up to 3 weeks, suggesting the potential for transmission. These data raise concerns, because cough aerosol cultures of M tuberculosis have been found to be the best predictors of recent infection in contacts of untreated patients and have also been associated with incident disease in contacts. Thus, once a patient is on antimycobacterial therapy with an appropriate threshold of effective drugs (ie, drugs to which the isolate is susceptible), the sputum smear for acid-fast bacilli is not a good marker of infectiousness.

Following current national guidelines, many hospital infection control practitioners assume infectiousness while sputum remains positive by smear or culture, resulting in prolonged isolation or hospitalisation, with important resource implications for the inpatient management of drug-resistant tuberculosis—even as ambulatory and community-based treatment expands globally. Some studies show that patients on effective therapy based on rapid drug susceptibility testing require little, if any, added precautions. They can be treated at home or in the hospital and do not require isolation. Other studies have indicated that despite effective therapy, patients with positive sputum smears or positive cough aerosol cultures might pose a risk of transmission. However, to our knowledge, there are no reports of transmission to contacts by patients with tuberculosis who were on effective therapy. In the absence of a broad consensus on this important question, it remains an important topic for additional research, including the effect of newer drugs on XDR tuberculosis transmission.

**Environmental controls**

Although rapid diagnosis and effective treatment are the most effective means to stop transmission, not all cases of tuberculosis will be rapidly diagnosed and treated, even with active case finding. Traditional environmental control strategies and respiratory protection have a role in reducing the risk in congregate settings, especially in emergency rooms, general medical and specialty areas, and non-medical settings, such as jails and prisons.

In the WHO tuberculosis infection prevention and control guidelines, natural ventilation is emphasised because it is widely available in areas with suitable climates, and presumably much more sustainable than the alternative engineering strategies such as mechanical ventilation, germicidal UV air disinfection, and air filtration (room air cleaners). Little high-level evidence exists to support any tuberculosis infection environmental control interventions. Although natural ventilation should be the centrepiece of environmental control strategies, it has its limitations. Many buildings have not been designed for effective natural ventilation, wind direction and speed are usually unpredictable, windows are often closed on cold nights even in tropical or temperate climates, and access to outdoor waiting areas might not be feasible in many urban settings. Natural ventilation cannot be used in very cold climates, and even in hot climates, windows are often closed as...
split-system cooling is increasingly introduced for comfort. If available, mechanical ventilation systems in high-burden settings often simply cannot be maintained by most hospital engineering staff because they do not have the expertise or targeted resources. Room air cleaners are attractive to hospital administrators, but are often oversold, and invariably undersized in terms of clean air delivery rate—usually producing no more than a fraction of one equivalent room air change per hour (ACH) when tested in situations in which 6–12 ACH are recommended. Another option is upper-room germicidal ultraviolet air disinfection with air mixing, which, unfortunately, has usually been poorly applied and poorly maintained (figure 13). However, of the three technologies available to supplement or replace natural ventilation (at night, for example), germicidal ultraviolet air disinfection holds the greatest potential for sustainable effectiveness. Some studies have shown effectiveness under experimental hospital conditions in Peru and South Africa, and recent advances in dosing and fixture technology and conditions in Brazil, Haiti, Kenya, India, Peru, South Africa, Tanzania, Thailand, and Zimbabwe suggest that combining simple disposable respirators with enhanced air disinfection can lower the risk substantially. For very high-risk procedures, for example, for chest surgery, bronchoscopy, or autopsy of patients with known or suspected MDR tuberculosis, powered air purifying respirators (PAPRs) can be used, which increase the protection factor to more than 90% because the breathing space is under positive pressure. Important limitations of respiratory protection include that respirators cannot be worn continuously, that they are more likely to be used for known, non-infectious patients with MDR tuberculosis who are on effective therapy, and are not worn for unsuspected cases.

Respiratory protection
The third and final recourse in the transmission control hierarchy are personal respirators, which are tight-fitting masks designed to protect the wearer from inhalation hazards. By contrast, surgical masks are loose fitting, designed to protect the wearer from inhalation hazards. By contrast, surgical masks are loose fitting, originally designed to prevent the exhalation of infectious particles onto a sterile field. Surgical masks on patients were shown to be about 50% effective in preventing transmission of tuberculosis from people to guineapigs. This risk reduction is equivalent to doubling the building ventilation, so is neither insignificant, nor completely effective.

The treatment of latent tuberculosis infection is considered crucial to global tuberculosis elimination, and can also have life-saving implications for individual patients. Targeted contact investigations of MDR tuberculosis cases could prevent future cases and avert deaths. In a systematic review and meta-analysis of household contacts of drug-resistant tuberculosis cases, household contacts had a high yield of tuberculosis transmission of tuberculosis from people to guineapigs.467

<table>
<thead>
<tr>
<th>Intervention</th>
<th>TB-CHAMP</th>
<th>V-QUIN</th>
<th>PHOENix</th>
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<tbody>
<tr>
<td>Design</td>
<td>Cluster randomised; superiority; community based</td>
<td>Cluster randomised; superiority; community based</td>
<td>Cluster randomised; superiority; community based</td>
</tr>
<tr>
<td>Target population</td>
<td>0-5 years regardless of TST or HIV status</td>
<td>TST-positive and paediatric enrolment on hold</td>
<td>HIV-positive; children 0-5 years TST-positive or interferon gamma release assay-positive if older than 5 years</td>
</tr>
<tr>
<td>Assumptions</td>
<td>Levofloxacin decreases tuberculosis incidence by 50% from 7%; 80% power</td>
<td>Levofloxacin decreases tuberculosis incidence by 70% from 3%; 80% power</td>
<td>Delamanid decreases tuberculosis incidence by 50% from 5%; 90% power</td>
</tr>
<tr>
<td>Sample size</td>
<td>778 households; 1556 contacts</td>
<td>1326 households; 2785 contacts</td>
<td>1726 households; 3452 contacts</td>
</tr>
<tr>
<td>Sites</td>
<td>South Africa</td>
<td>Vietnam</td>
<td>AIDS Clinical Trials Group and International Maternal, Pediatric, Adolescent AIDS Clinical Trials network sites, including Botswana, Brazil, Haiti, Kenya, India, Peru, South Africa, Tanzania, Thailand, and Zimbabwe</td>
</tr>
<tr>
<td>Start of recruitment</td>
<td>Open (fourth quarter of 2016)</td>
<td>Open (first quarter of 2016)</td>
<td>Fourth quarter of 2017</td>
</tr>
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TST=tuberculin skin test.

Table 13: Planned treatment trials for the prevention of MDR-TB infection. All have a Cluster randomised, superiority design targeting household contacts.
disease (7·8%) and latent infection (47·2%). The majority of secondary cases occurred within a year of the source case diagnosis. More than 50% of secondary cases had drug susceptibility patterns concordant with the source case, particularly in children, who have greater exposure in the household than in the community.

Young children (aged <5 years) and HIV-infected children of all ages who are exposed to a source case with MDR tuberculosis are at high risk of developing MDR tuberculosis disease. Although no formal guidelines on preventive therapy regimens exist, analysis of many studies suggest efficacy and safety of a fluoroquinolone-based 6–12-month preventive therapy regimen. However, because of the scarce evidence from randomised clinical trials, WHO does not recommend treatment, but advises 2 years of follow up for any person who has been exposed to tuberculosis in the household. Three clinical trials investigating the use of levofloxacin (TB-CHAMP, V-Quin) or delamanid (PHOENIx MDR TB/A5300B) for treatment of child and adult household contacts are underway or will be starting soon (table 13). Until clinical trial evidence becomes available, the WHO guidelines advise clinicians as part of good clinical practice to consider individually tailored preventive treatment, for which operational guidelines now exist. Challenges to treating MDR tuberculosis infection include the few tests available to identify whether tuberculosis infection is drug resistant and whether the treatment results in a cure; adhering to long courses of potentially toxic drugs; and concerns of generating resistance. In addition to treatment, an effective tuberculosis vaccine could also contribute to preventing MDR tuberculosis.

Summary of drug-resistant tuberculosis prevention

We have discussed an unconventional approach to preventing drug-resistant tuberculosis transmission, focusing not on patients with identified drug resistance who are already on effective treatment, but on preventing the transmission from patients with unsuspected tuberculosis or unsuspected drug-resistant disease. We maintain that MDR tuberculosis is best prevented by earlier diagnosis and more effective treatment of susceptible and resistant disease, in order to prevent acquired mutations and to prevent their transmission. One intensified, refocused administrative approach to preventing transmission through active case finding, rapid diagnosis, and prompt effective therapy (FAST) is reducing exposure duration in a variety of settings. Preventing transmission in congregate settings by conventional environmental control interventions remains important, but widespread sustainable implementation proves challenging. Although natural ventilation can be sustainable, greater use of rationally applied upper-room germicidal ultraviolet air disinfection, including new LED technology, should be anticipated. Contact investigations and preventive therapy have some potential to prevent the reactivation of latent MDR tuberculosis infection, but evidence to inform policy is needed. Children exposed to MDR cases are an especially compelling risk population for the treatment of latent drug-resistant infection. Health-care workers risk their own lives in the interest of treating drug-resistant tuberculosis cases, often themselves becoming infected, and also deserve consideration for preventive treatment because of their enhanced exposure.

Patient-centred care for drug-resistant tuberculosis

The treatment of drug-resistant tuberculosis requires careful attention not only to the medical aspects of the disease but also to the psychosocial aspects. A patient-centred approach to tuberculosis is a central pillar in WHO’s new End TB strategy, and there are multiple opportunities to enhance this type of care in the treatment of drug-resistant tuberculosis, including adherence support, treatment discontinuation, and palliative care. The fundamental underpinning of the patient-centred strategy is a diagnostic and treatment programme that is grounded in human rights.

Patient-centred adherence support

Successful therapy for drug-resistant tuberculosis requires patient adherence for the entire treatment course. However, drug-resistant tuberculosis adherence is challenging for many reasons, including the high pill burden, the frequency of drug-related adverse events, the lengthy duration of treatment, low efficacy of the regimen, and the added common burden of HIV co-infection (panel 1). People with MDR tuberculosis, particularly those with highly resistant strains, are often hospitalised for treatment, which increases costs for the health-care system and the patient, increases the chance of nosocomial transmission of disease, and also loss to follow-up, compared with community-based care. Although drug-resistant tuberculosis therapy is still almost always given as DOT, a recent Cochrane systematic review questioned the effectiveness of DOT. Indeed, some evidence showed that DOT might actually represent a barrier to adherence through increased transportation costs, inability to work or go to school, and discrimination experienced from health-care providers, other patients, and the community.

The successful decentralisation of drug-resistant tuberculosis care in Khayelitsha, Cape Town, showed that improved cure rates could be achieved simultaneously with the delivery of a more patient-responsive service closer to patients’ homes; indeed, much of the improvement in cure rates was likely to be due to these patient-responsive services (figure 14 A). Programmes in Lesotho, India, and Peru led by non-governmental organisations have challenged health services to recognise different ways, appropriate to the local context, to manage drug-resistant tuberculosis other than in hospitals.
Supporting adherence is therefore one of the most important aspects of drug-resistant tuberculosis treatment and might be achievable outside the strict confines of DOT. Counselling and treatment literacy delivered by trained and paid lay health counsellors or drug-resistant tuberculosis survivors are crucial. Such counselling should be individualised and include ongoing assessments of barriers to adherence and strategies for addressing them, because an individual's ability to adhere can change over time depending on his or her life circumstances. Since many people living with drug-resistant tuberculosis face other pressing health and social concerns—including catastrophic illness-related costs—nutritional, economic, and transportation support are essential for continued adherence to therapy and in keeping with the WHO’s goal to eliminate such costs by 2020. Peer support groups are also a key part of patient-centred care.

The development of drug-resistant tuberculosis was previously thought to be amplified from drug-susceptible tuberculosis as the result of inadequate adherence. As a result, patients with drug-resistant tuberculosis were often labelled as problematic (non-adherent) and subsequent management decisions were coloured by this erroneous perception of patient irresponsibility. Attributing treatment failure to the behavioural choices of the patient, without making any effort to address these underlying risk factors for non-adherence, is both an ethical failure on the part of the health system and a likely violation of patient rights (figure 14 B). As recent South African evidence shows, drug-resistant tuberculosis is often contracted via primary transmission and that when amplification is responsible for the development of drug-resistant tuberculosis, it is usually due to service and regimen failings rather than poor adherence.

Nonetheless, some individuals will be non-adherent even when optimal support is provided, as a result of psychological factors or the denial that is commonly seen in people with serious illness. Denial might be more common in people with drug-resistant tuberculosis, given the high degree of stigma and discrimination. Difficulties in adherence should prompt careful investigation of underlying factors associated with non-adherence, preferably by a multidisciplinary team. If an individual is unable to adhere after individualised interventions are attempted, then cessation of treatment could be considered but must be based on objective evidence of likely future non-adherence rather than judgments about patient behaviour.

Patient-centred approach to treatment discontinuation and palliative care

Deciding when treatment is failing and needs to be discontinued is not a simple task, given the paucity of data on the natural course of treated drug-resistant tuberculosis. A study in the Western Cape province of South Africa using cohort data from four South African treatment sites, identified criteria for treatment failure, including duration of uninterrupted treatment for 12 months, three consecutive positive sputa, and a declining clinical condition. Decisions on treatment discontinuation should always be made by a multidisciplinary team, including the individual being treated and his or her support network.

Treatment discontinuation raises ethical questions about health risks posed by infectious patients to household contacts, close family, and to the community (panel 1). Should such patients be confined involuntarily to a health facility to protect third parties from infection, heralding a return to the days of the sanatorium? This is the classic trade-off between the rights of the individual (to autonomy, freedom of movement, and respect) and that of the community (to an environment that is not harmful to health). Although forced isolation and treatment might be a consideration in some settings, this should only be done as a last resort if there is demonstrable evidence of the risk of infection to vulnerable contacts (eg, children or HIV-positive people).
and after all other treatment and infection control options have been exhausted.492

Relying on enforced confinement of patients with drug-resistant tuberculosis that has failed treatment to achieve control of infection risk to third parties is problematic for many reasons. Patients might abscond from confinement, and court orders compelling them back to hospital are largely ineffective in practice.493 Other methods exist for infection control, including increasing ventilation in the home and providing patients with surgical masks, which might be effective and less invasive of patient rights.494,495 Furthermore, from a programmatic point of view, focusing solely on prevention of infection risk late in the course of the disease overlooks the fact that most transmission probably occurs before diagnosis in the community.496–499 Enforced confinement is a poor strategy to prevent transmission at a community level, might drive the epidemic underground, and is not justified as a routine measure.

Discontinuation of tuberculosis treatment is often associated with the discontinuation of any form of care, essentially abandoning the patient when he or she is in greatest need of palliative care, and contact with the health system remains essential. Given that palliative care pertains to the provision of services aimed at providing individuals with relief from the pain, physical symptoms, and mental distress that accompany chronic conditions, palliative care should clearly be offered to all individuals diagnosed with drug-resistant tuberculosis. This should include counselling and psychological support for people living with drug-resistant tuberculosis and their families, oxygen therapy, inhaler therapy for reactive airways disease, aggressive prevention and management of adverse events, pain control, physical and occupational therapy, and pulmonary rehabilitation and nutritional support.500

The component of palliative care that includes end-of-life care is particularly important for patients whose treatment has failed—not only to ensure dignity and respect for the dying person and that they are able to die in comfort without pain, but also to restrict the opportunity for transmission by including infection control in the palliative care received. In high-burden settings, the need to strike a balance between inpatient palliation and palliative care delivered in the home must be tailored to local conditions. The transmissibility of the disease might lead to strong feelings of guilt or shame about the risk to others in the household, where most people receive end-of-life services, which complicates end-of-life care for drug-resistant tuberculosis.501 Even though antiretroviral therapy continuation in co-infected patients might increase opportunities for drug-resistant tuberculosis transmission though prolonged survival, it would be unethical to withdraw antiretroviral treatment in these patients.

Apart from isolation and natural ventilation, engineering interventions applicable in congregate settings, such as germicidal ultraviolet irradiation, air filtration, or mechanical ventilation, are impractical for home use and respirators are difficult for family members to wear continuously. One potentially novel intervention being investigated to reduce infectiousness during end-of-life care is the use of the inhaled antibiotic, dry powder colistin, commonly used for patients with cystic fibrosis.502

<table>
<thead>
<tr>
<th>Component</th>
<th>Rationale</th>
<th>Key elements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integration with HIV and other services</td>
<td>Intensified screening of those with high risk for tuberculosis or high risk of poor outcomes; facilitation of seeking care; coordinated management of multiple medications and side-effects</td>
<td>Integration of tuberculosis screening and treatment with HIV services, maternal and child health services, and diabetes services (and screening for and treating diabetes and HIV in people with tuberculosis)</td>
</tr>
<tr>
<td>Decentralisation</td>
<td>Reduces need for hospital beds or other infrastructure, which can be costly and lead to delayed care or loss to follow-up; people with tuberculosis can continue working or other daily activities and still receive care</td>
<td>Provision of care close to home where supportive structures are more likely; strong health-care systems</td>
</tr>
<tr>
<td>Supportive health-care system</td>
<td>People with tuberculosis disease or infection are more likely to seek and stay in care if it is provided in a comfortable, safe environment; an effective health-care system can reduce many barriers that people with tuberculosis face with obtaining a diagnosis and completing treatment</td>
<td>Sound infrastructure with proper infection control and necessary resources (electricity, clean water, and medical and laboratory supplies); professional and respectful clinical and administrative staff; provision of nutritional or other support; peer support; treatment literacy training, and counselling</td>
</tr>
<tr>
<td>Optimal diagnosis and treatment</td>
<td>Poor availability of and access to optimal biomedical interventions nationally and locally contribute to undiagnosed cases of drug-resistant tuberculosis, lower cure rates because of less effective or less tolerable treatment, and increased transmission due to longer infectiousness and inadequate preventive measures</td>
<td>Rapid diagnosis of tuberculosis, drug susceptibility testing to guide treatment choice, screening, treatment, counselling, and support for families of people with tuberculosis; effective prevention and treatment that is safe, tolerable, and easy to complete, and appropriate for all ages; auxiliary care such as monitoring for and managing side-effects</td>
</tr>
<tr>
<td>Supportive environment for addressing tuberculosis beyond the health-care system</td>
<td>Many factors outside the health-care system influence a person’s ability to seek and stay in care; when someone has tuberculosis, the health and wellbeing of others around them are also affected and need attention</td>
<td>Education about tuberculosis in communities to reduce stigma and encourage care-seeking behaviour; infection control in homes, public spaces, prisons, and schools; improved transportation and infrastructure to facilitate care seeking</td>
</tr>
</tbody>
</table>

Table 14: Components of optimal care for multidrug-resistant and extensively drug-resistant tuberculosis
The Lancet Respiratory Medicine Commission

Panel 10: Patient case histories illustrating the real-world challenges and practical realities of dealing with drug-resistant tuberculosis in low-resource settings

Patient story 1

KP is a woman aged 27 years who was living in a one-room shanty home in South Africa with her boyfriend and her three children, who are aged 3, 6, and 7 years. Her boyfriend had returned to the household after a 6-month period of incarceration for petty theft. KP occasionally works selling sunglasses on the street, but the family struggles to earn enough to survive.

The family’s tenuous situation took a turn for the worse when KP’s boyfriend started coughing up blood. She took him to the health centre where they tested him for HIV and tuberculosis, and his HIV test came back positive and the Xpert MTB/RIF® test done on his sputum showed M tuberculosis with rifampin resistance. He was told by the nurse he has “strong tuberculosis” and that he must come to the clinic daily to take his medication and receive his daily injection. He and KP were deeply frightened and, because he was too exhausted to walk, they arranged for a small taxi to take him to the clinic daily so he could start on his daily treatment of kanamycin, high-dose isoniazid, ethionamide, pyrazinamide, moxifloxacin, and terizidone. Unfortunately, he developed severe nausea and vomiting with the medication, and everyone in the household feared that he would die.

1 month after starting this gruelling treatment regimen, KP’s boyfriend went to the clinic but did not return. KP went to the health centre to find him, only to be told by the nurse that he was taken to the hospital after additional test results showed he had “killer tuberculosis.” The clinic had received a report that morning from second-line line probe assay testing that showed additional resistance to both ofloxacin and kanamycin, and KP’s boyfriend was taken to the hospital for admission, as is required of all patients with XDR tuberculosis. KP was told that he would probably die and that the family could not visit him because they might “get sick too.” The nurse also told KP that this killer tuberculosis that her boyfriend had was a result of him not taking his medication properly, which made KP afraid and embarrassed.

KP’s worry intensified when she herself began to develop a cough and fever and to lose weight, which she attributed to a change in the weather and to having less food to eat since her boyfriend was hospitalised. Understandably, KP was reluctant to go to the clinic because she was worried that the nursing sister would scold her again and because she didn’t want to be sent to the hospital, where people “only go to die.” However, when her 5-year-old child began to cough and have drenching night sweats, she took him to the health centre. The clinic team examined the child and KP and diagnosed both of them with tuberculosis on the basis of clinical findings, chest radiograph, and Xpert MTB/RIF® tests showing the presence of M tuberculosis and rifampin resistance.

Her son was taken to the paediatric ward and placed under the care of physicians there, and the nurse caring for KP noted during her contact screening questions that KP’s boyfriend had XDR tuberculosis and was worried that KP might have it as well. The nurse wanted to have KP admitted to the hospital, but KP refused, reporting that she will have nobody to care for her other two children. The nurse asked for assistance from the MDR tuberculosis counsellor working in the clinic—who herself had survived MDR tuberculosis—and the counsellor and KP spent almost an hour talking. Meanwhile, the nurse learned that no open beds were available for women in the MDR tuberculosis hospital and that KP had to wait to begin therapy until a bed opens, which can take several weeks.

Given KP’s situation, her contact history, and the low availability of beds, she was offered treatment through a community-based project that is being run by the National TB Programme in partnership with a local non-governmental organisation. The programme uses new drugs to treat people with XDR tuberculosis, and they were able to start KP on a regimen of bedaquiline, linezolid, clofazimine, pyrazinamide, high-dose levofloxacin, pyrazinamide, and terizidone. She was also started on antiretroviral therapy, because she also has HIV. She received ongoing support from her counsellor, in addition to taking treatment daily at the health centre. She also attended a support group twice a month for people who are on new tuberculosis drugs.

KP was devastated when she heard her boyfriend had died in the hospital. This news increased her anxiety for her two children at home and the one in the hospital, who was also being treated for XDR tuberculosis. KP has been hoping that her son too can get one of the new drugs for his XDR tuberculosis, so her nurse got in touch with the children’s hospital (KP was unable to visit him because of her own XDR tuberculosis). However, the drug was not available for children younger than 6 years or those who weigh less than 20 kg; and although her son, aged 5 years, weighed 21 kg, he did not qualify to get the medication because it is only available straight from the drug company, and not licensed for use in the country. So KP was told that they screened her son for participation in a trial of the drug but he did not qualify, and she did not understand why they could consider her child for drug testing in the trial, but he cannot get the drug for treatment. Now all she can do is worry almost about her other two children, and what might happen if they too become ill.

(Panel 10 continues on next page)
(Continued from previous page)

**Patient story 2**

PI is a man aged 32 years, who works in a garment factory outside of Kolkata in eastern India. He was grateful for the job—which opened when one of his cousins who was working at the factory died of pneumonia—because it allows him to better support his wife, sister, and the five children they have living with them in an informal settlement on the edge of town. He usually worked for 16 h per day, 7 days per week, so he ignored the fatigue and weight loss that he had had since his second month of work. Only when his incessant cough caught the attention of his co-workers, was he taken to the nearby health clinic. The doctor suspected tuberculosis, and a sputum smear confirmed the presence of acid-fast bacilli. PI’s chest radiograph showed a right upper lobe cavity lesion, so he was started on directly-observed therapy and fired from his job.

PI lived far away from the factory, and the clinic at which he was diagnosed, and he was deeply ashamed of having tuberculosis. He confided in his sister who helped him locate a hospital nearby that he could attend for his treatment. He reported almost daily for his medications, but occasionally he found some work picking scrap metal out of a nearby dump, so could not go to the clinic for his treatment, because it was only open during his work hours. Despite the treatment, he continued to cough and lose weight, and after 6 months he was told he had “failed” treatment and must start second-line therapy, which includes a daily injection. During his treatment he couldn’t work, and his infant daughter was hospitalised with malnutrition. His sputum smears never converted, his treatment was stopped, and an additional sputum was sent for culture and drug susceptibility testing.

6 weeks later, a community health worker visited PI at home, because he could no longer get out of bed, and the family reported that he coughs—sometimes with blood—and has shivers “all the time.” The family was distraught, because their infant daughter died 3 weeks before and they were about to be evicted from their home. The health worker found a taxi and took PI to the hospital, telling them he had tuberculosis. The nurse at the hospital contacted his clinic and found out that his sputum tests showed he has MDR tuberculosis, with resistance to isoniazid, rifampin, ethambutol, and streptomycin. He was started on a regimen of kanamycin, levofloxacin, ethionamide, pyrazinamide, cycloserine, and ethionamide, and admitted to the hospital. He shared a single bed in an open ward with 17 other men who had also been diagnosed with MDR tuberculosis.

Initially PI experienced some improvement because he was given nutritional support along with his medications. However, after 1 month of therapy he began to hear a buzzing in his ears, and one morning he woke up completely deaf. This caused deep depression in PI, and although psychological support was offered to him, he had trouble participating since he could not hear and was unable to read or write.

After 3 months on treatment, PI’s sputum cultures became positive for M tuberculosis once again, and a chest radiograph showed progression of the disease, with bilateral upper lobe cavities seen as well as scarring, fibrosis, and near-total destruction of the right lung. His left lung also had ulceroinfiltrative disease throughout the upper lobe, and scarce normal lung tissue remained. Another sputum sample was sent for culture, and a research study also investigated the sputum using rapid second-line drug susceptibility testing. Unfortunately, his sputum sample came back with resistance to all the drugs tested, including isonizid, rifampin, ethambutol, streptomycin, amikacin, kanamycin, ethionamide, cycloserine, ofloxacin, low-dose moxifloxicin, and para-aminoosalicylic acid. In view of this, his physicians considered starting him on a regimen containing new drugs, but although bedaquiline was registered in the country, it was only available at a small number of sites, and none of these were in Kolkata.

PI was considered a terminal case and the nurses tried to contact his family to let them know to come and collect him. However, when the community health worker went to the family’s old house there was nobody there, and the neighbours told her the family left long ago. The hospital staff were frightened of catching tuberculosis from PI, and refused to help him eat or wash. The other patients were also frightened of him, and he was moved to an isolated corner of the hospital ward. Eventually, he died in isolation of “untreatable” tuberculosis.

Patient-centred care and human rights

The problem of drug-resistant tuberculosis is essentially a consequence of a systematic violation of human rights arising from the failure to develop pharmaceuticals for this neglected disease.503 The unpalatable rights arising from the failure to develop pharmaceuticals have been considered untreatable. However, without sustained investment in the promotion of access to new licensed in the 1970s. With the recent recognition of the global tuberculosis crisis and the formation of global initiatives to accelerate drug development, some new and repurposed drugs have appeared in the tuberculosis drug development pipeline. Preliminary studies with linezolid, bedaquiline, and delamanid suggest that they substantially improve treatment outcomes, offering hope to patients who would previously have been considered untreatable. However, without sustained investment in the promotion of access to new
Panel 11: Key messages

- Resistance to antituberculosis drugs is a global problem of considerable public health importance that threatens to derail efforts to eradicate the disease. Advocacy is needed in national and transnational fora to ensure the urgency of the situation is understood and that appropriate funding is made available.
- Practices for the management of individual patients in settings with a high tuberculosis burden are not sufficient to prevent the emergence, amplification, and spread of drug-resistant tuberculosis. These practices include empirical treatment with standardised second-line drug regimens for people who are found to have rifampicin-resistant tuberculosis.
- Access to drug resistance testing is scarce in most countries and urgently needs to be expanded to allow curative second-line treatment regimens to be implemented.
- Knowledge regarding the safe use—including dose and length of treatment—of new and repurposed drugs must be improved through clinical trials.
- Models for care of people with drug-resistant tuberculosis, including programmatically incurable disease, must ensure that the rights and dignity of individual patients are respected.
- Assessment of the performance, health effects, and potential economic benefits of molecular tools such as genome sequencing for detecting resistance, must be accelerated to facilitate effective implementation.
- Greater investment is needed in the development of new drugs and diagnostics.

Summary of patient-centred care

For the individual patient, pursuing the best possible treatment regimen or keeping a patient on a costly but failing regimen has opportunity costs and might lead to fewer available options for other patients with a better chance of cure if treated early. However, at a programmatic level, the current approach of protecting new drugs from development of resistance has restricted access to potentially life-saving treatments when fears of resistance might not be evidence-based. Increasingly, better treatment is being recognised earlier in the course of the disease, and will not only improve individual patient outcomes, but likely enhance programmatic effectiveness in terms of cure rates and reduced community transmission. We suggest expanding models of care, providing comprehensive packages of support for people who are living with drug-resistant tuberculosis, to replace any remaining restrictive tuberculosis delivery approaches. Patient-centred care for all forms of drug-resistant tuberculosis must become the norm, linked to community-based models, with hospitalisation reserved only for those with clinical indications. Access to new shorter regimens, as recommended by WHO in 2016, is already a reality in some countries, and should be increasingly common as new tuberculosis drugs become available, which will help considerably to alleviate the ethical problem of stopping drug-resistant tuberculosis treatment that is suspected to be failing. However, patients who are unable to adhere to treatment or those whose drug-resistant tuberculosis cannot be cured require palliative care interventions from multidisciplinary teams aimed at maintaining their dignity while minimising transmission risk. In the interim, retention of patients with XDR tuberculosis in care, even if their treatment has failed and cure is no longer a realistic prospect, is crucial for reducing community transmission. Development of robust evidence-based protocols for reducing community transmission is an important research priority in this context.

Components of patient-centred and community-centred care for MDR and XDR tuberculosis: an advocacy perspective

The weak, vertical, unsupportive approach to treating MDR and XDR tuberculosis is failing. Of the estimated 480,000 new MDR tuberculosis cases in 2014, only 26% were diagnosed and only 23% were treated. People on treatment suffer from toxic side-effects of drugs, stigma, and economic loss. About 50% of patients who get treatment for MDR tuberculosis and 26% of those treated for XDR tuberculosis are cured. The failure of approaches to combat tuberculosis can be overcome; through not only patient-centred but also family-centred and community-centred approaches to care. We outline the key components of a framework for ideal MDR and XDR tuberculosis care, most of which are achievable immediately (table 14).

Integration: one patient, one file, one health-care worker

Tuberculosis is a leading cause of illness and death in people who are HIV-positive. Initiating antiretroviral therapy during tuberculosis treatment improves survival; integrating tuberculosis and HIV care is cost-effective; early initiation of antiretroviral therapy in people with MDR tuberculosis and HIV substantially reduces mortality; and, in patients with XDR tuberculosis and HIV, more deaths occur among those not receiving antiretroviral therapy. Despite this overwhelming supportive evidence and guidelines for integration, implementation is scarce. Globally, only a third of people with tuberculosis and HIV receive antiretroviral therapy. Patients with tuberculosis and HIV who are in care must make multiple visits to healthcare centres and interact with multiple clinicians, which is challenging for the patient and complicates the management of adverse effects, dosing, and regimen adjustments.
<table>
<thead>
<tr>
<th>2-year goals</th>
<th>Outcome</th>
<th>Barriers to achievement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improve knowledge of genetic predictors of resistance to the key first-line and second-line drugs</td>
<td>Accurate genetic markers for predicting multidrug and extensive drug resistance, and pyrazinamide resistance</td>
<td>Poor knowledge regarding clinical effect of genetic markers of resistance</td>
</tr>
<tr>
<td>Expand current rapid software tools to include all drugs and provide estimated accuracy data from in-silico validation studies</td>
<td>Software tool for predicting resistance and minimum inhibitory concentration values to antituberculosis drugs from genome sequence data</td>
<td>Several such tools are being developed but independent assessment of their comparative performance and regulatory approval have not been done</td>
</tr>
<tr>
<td>Develop DNA extraction and sequencing methodology suitable for routine use in a diagnostic laboratory</td>
<td>Methodology for sequencing from clinical specimens</td>
<td>Technical challenges might be insurmountable using current technology</td>
</tr>
<tr>
<td>Complete studies of the clinical significance of heteroresistance as detected by molecular methods</td>
<td>Improved documentation of the significance of heteroresistance in clinical outcomes</td>
<td>Low availability of funding might restrict the geographical spread of data collection</td>
</tr>
<tr>
<td>Complete epidemiological studies to determine the contribution of diabetes to drug resistance</td>
<td>Overview of the effect of diabetes on drug-resistant tuberculosis</td>
<td>Low funding might restrict the geographical spread of data collection</td>
</tr>
<tr>
<td>Complete intervention studies to assess the effect of different psychosocial and behavioural interventions on MDR tuberculosis transmission, progression, and treatment outcomes</td>
<td>Targeted interventions to address the social and behavioural factors associated with morbidity and mortality from MDR tuberculosis and the emergence of further resistance, including substance abuse</td>
<td>Buy-in from the necessary agencies and stakeholders might be difficult to achieve in some countries. Low funding might also restrict the geographical spread of studies; prioritisation of various interventions will need to be done</td>
</tr>
<tr>
<td>Strengthen engagement with civil society and affected community organisations to ensure research is applicable and accessible to all those affected by MDR tuberculosis</td>
<td>A research agenda grounded in a human rights approach to preventing, diagnosing, and successfully treating drug-resistant tuberculosis</td>
<td>Low engagement because of poor communication with civil society; input of civil society not valued by tuberculosis policy makers; insufficient interest (political will) from service providers in the formal sector</td>
</tr>
<tr>
<td>Complete and launch studies to confirm the efficacy of dispensable formulations, other dosing strategies, and pharmacokinetic assessments of the second-line drugs in adolescents and children</td>
<td>Child-friendly formulations and dosing recommendations for all second-line drugs, including novel therapeutic agents</td>
<td>Insufficient investment from pharmaceutical companies and public or philanthropic funding bodies; regulatory challenges for drug developers and stringent regulatory authorities; small market in the paediatric population</td>
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<thead>
<tr>
<th>5-year goals</th>
<th>Outcome</th>
<th>Barriers to achievement</th>
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</thead>
<tbody>
<tr>
<td>Develop and validate technology platforms for assessing genetic markers of resistance</td>
<td>Affordable rapid tests for MDR and XDR tuberculosis for use at the point at which care is provided</td>
<td>Insufficient financial investment; failure to develop technology that is considered affordable in low-income countries</td>
</tr>
<tr>
<td>Initiate economic and health system service delivery studies to understand how to include genome sequencing technologies</td>
<td>Strategies for providing full resistance profiles for patients with MDR tuberculosis that is also resistant to additional drugs</td>
<td>Failure of countries or donor agencies to use such technologies for regimen design</td>
</tr>
<tr>
<td>Develop affordable tests that could be used in routine diagnostic laboratories</td>
<td>A test to monitor drug concentrations at the point at which care is provided</td>
<td>Insufficient financial investment; failure to develop technology that is considered affordable in low-income countries</td>
</tr>
<tr>
<td>Complete pharmacokinetic and pharmacodynamic studies to determine the contribution of subtherapeutic serum drug concentrations to the acquisition of drug resistance</td>
<td>Contribution of subtherapeutic serum drug concentrations to the emergence of resistance</td>
<td>Availability of funding</td>
</tr>
<tr>
<td>Investigate the biological mechanisms by which diabetes contributes to the emergence of drug resistance</td>
<td>Improved strategies for managing diabetic patients with tuberculosis</td>
<td>Tuberculosis immunology and metabolism in the diabetic host is not fully understood, availability of funding insufficient</td>
</tr>
<tr>
<td>Initiate interventional studies to reduce acquisition and transmission of MDR tuberculosis in prisons and in other high-risk institutions</td>
<td>Strategies to reduce risk of nosocomial and institutionalised spread of resistance</td>
<td>Insufficient human rights-based approach to tuberculosis transmission in congregate settings; insufficiency in hospitalisation for treatment of MDR tuberculosis, XDR tuberculosis, or use of new drugs; Not enough buy-in from stakeholders</td>
</tr>
<tr>
<td>Complete studies to determine community and health system risk factors for spread of drug resistance</td>
<td>Strategies to eliminate spread of drug resistance</td>
<td>Complicated social networks with migration playing a major role in transmission; availability of funding</td>
</tr>
<tr>
<td>Develop and test innovative procedures for personal protection and sterilisation</td>
<td>Strategies for interrupting transmission</td>
<td>Insufficient investment</td>
</tr>
<tr>
<td>Strengthen joint initiatives to explore and assess the contribution of community groups and faith-based organisations to prevent emergence and spread of drug-resistant tuberculosis</td>
<td>Strategies for community involvement for ending drug-resistant tuberculosis</td>
<td>Not enough buy-in from stakeholders; low recognition of the importance of such groups in optimal management of drug-resistant tuberculosis</td>
</tr>
<tr>
<td>Assess how targeted drug delivery (to the lung) affects drug concentrations in the various lung compartments</td>
<td>Improved strategies for drug delivery</td>
<td>Technical difficulties in ascertaining drug concentrations; failure to attain ethical review approval</td>
</tr>
<tr>
<td>Undertake interventional studies on enhanced adherence support strategies, especially those that allow for dignified partnerships between people living with tuberculosis and their care providers</td>
<td>Improved strategies for individualised adherence support other than directly observed therapy</td>
<td>Buy-in from care providers; failure to identify acceptable strategies</td>
</tr>
<tr>
<td>Complete formal studies on specific psychosocial, nutritional, and economic strategies that address the links between tuberculosis and poverty</td>
<td>Support package for patients living with highly drug-resistant tuberculosis</td>
<td>Failure to identify effective generalisable interventions; scarce systems, funding, and will to implement effective interventions in these areas</td>
</tr>
<tr>
<td>Develop and test models of integrated care to address medical, housing, and infection control needs</td>
<td>Care package for patients living with highly drug-resistant tuberculosis</td>
<td>In many countries, tuberculosis control measures are highly vertical and housing needs might be considered outside the scope of tuberculosis programmes</td>
</tr>
</tbody>
</table>

(Table 15 continues on next page)
Research goals and activities with anticipated outcomes and deliverables: a 10-year programme of priority research to control drug-resistant tuberculosis

such research priorities have previously been published by WHO and STOP-TB Partnership.521,523 In addition, considerable gaps remain in our understanding of the emergence and spread of resistance and how to

For drug-resistant tuberculosis to be controlled and eradicated, increased investment is needed in tools for case detection and for developing shortened treatment regimens and drugs with low toxicity. Lists of

Integrating diabetes and tuberculosis screening and management, and tuberculosis screening in maternal and child health programmes, is also crucial. Integration will increase detection and survival, and would also reduce numbers of visits and streamline care for individuals, which could positively affect adherence and mental wellbeing.

Decentralisation: take treatment to the people
With centralised MDR tuberculosis care, patients must travel further to access care, disrupting work and social life. Decentralisation improves access to treatment without compromising treatment outcomes and is cost effective.237–239 Successful decentralisation requires relatively robust health-care infrastructure.238

Table 15: Research goals and activities with anticipated outcomes and deliverables: a 10-year programme of priority research to control drug-resistant tuberculosis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Barriers to achievement</th>
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<tbody>
<tr>
<td><strong>5-year goals</strong></td>
<td></td>
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<tr>
<td>Clinical trials, including safety and efficacy of (i) oxazolidinones (linezolid, tedizolid, and sutezolid) and (ii) delamanid and pretomanid in drug-resistant tuberculosis; the optimum dose and duration of linezolid, moxifloxacin, and levofloxacin for drug-resistant tuberculosis; phase 3 trial of bedaquiline, delamanid or pretomanid, and linezolid for drug-resistant tuberculosis (or combinations of the abovementioned drugs to optimise favourable outcome)</td>
<td>Knowledge on safety and efficacy of new drugs, and when used in novel, injection free, shortened (&lt;12 months duration) regimens</td>
</tr>
<tr>
<td>Complete clinical trials and observational studies on post-exposure prevention of MDR tuberculosis, including clinical trials on the use of the fluoroquinolones, isoniazid, and delamanid</td>
<td>Strategies to prevent MDR tuberculosis, including treatment of infection before progression to active disease</td>
</tr>
<tr>
<td>Continue clinical trials to measure the effect of active case finding and early treatment of previously undiagnosed MDR tuberculosis on individual treatment outcomes and transmission</td>
<td>Polices to improve case finding and identification of resistance</td>
</tr>
<tr>
<td>Develop and validate an affordable portable tool for rapid identification of infectious patients</td>
<td>A tool to assess infectiousness of individuals</td>
</tr>
<tr>
<td>Launch formal studies on MDR tuberculosis elimination strategies in multiple high-burden countries, regions, or cities</td>
<td>Pilot strategies of comprehensive packages of services that might be effective in eliminating MDR tuberculosis in high-burden settings</td>
</tr>
<tr>
<td>Continue and report on findings of clinical trials to measure contribution of new-generation sequencing to personalised treatment</td>
<td>Implementation policies for new detection technologies</td>
</tr>
<tr>
<td>Implementation policies for novel therapeutic approaches</td>
<td>Complete and report on findings of clinical trials of novel therapeutic regimens</td>
</tr>
</tbody>
</table>

**10-year goals**

| Continue and expand research and development to identify and explore new drug targets and potential compounds through basic science research | New candidate drugs | Insufficient investment from pharmaceutical companies and public or philanthropic funding bodies |
| Continue and expand the programme of all clinical trials | An all-oral regimen of less than 12 months duration that can cure 90% of people with all forms of MDR tuberculosis | Insufficient investment from pharmaceutical companies; insufficient funding from public and philanthropic bodies; insufficient new trial sites and low capacity or fatigue of existing sites |
| Launch interventional studies of targeted drug delivery with optimised doses and doses levels at the site of disease | Refined treatment algorithms and delivery systems to provide optimum dosage | Requires acceptance and buy-in from national tuberculosis control programmes |
| Continue to adapt, validate, and adopt new and improved detection platforms and incorporate new drugs | Expanded access to resistance testing | Dependent on funding and the emergence and availability of new drugs |
| Complete and analyse early vaccine trials and identify appropriate candidates to move forward | Candidate vaccine for large-scale testing in vulnerable populations | Incomplete understanding of host protective immunity leading to unsatisfactory vaccine candidates; reduced funding from public and philanthropic bodies |
| Scale-up interventions, including treatment of MDR tuberculosis infection, active case finding, improved management of comorbid disease, and poverty reduction, which have been pilot-tested at high-burden sites | Comprehensive package of services that have been effective in eliminating MDR tuberculosis at selected sites | Insufficient sustained funding from national governments and international donors; poor political leadership in high-burden countries |

For drug-resistant tuberculosis to be controlled and eradicated, increased investment is needed in tools for case detection and for developing shortened treatment regimens and drugs with low toxicity. Lists of such research priorities have previously been published by WHO and STOP-TB Partnership.524,525 In addition, considerable gaps remain in our understanding of the emergence and spread of resistance and how to interrupt transmission. We highlight here only critical research topics to be addressed and their outcomes. The major challenge facing the goals is access to adequate funding, which reflects the insufficient political will of some governments and international bodies to resolve this public health crisis. MDR=multidrug resistant; XDR=extensively drug resistant.
Supportive health-care systems: make care-seeking a positive experience

Supportive health-care systems that create a positive experience, including physical infrastructure, human resources, and nutritional support, are important to retention in care. The environment should be comfortable, safe, and clean, should have appropriate infection control, a stable electrical and potable water supply, and uninterrupted medication and supply stocks. Food supplementation can enhance supportive health care.

Providers must show commitment, capability, proactivity, respect for confidentiality, and empathy for several aspects of the patient experience, including drug toxicity and the considerable pill burden (figure 9). Psychosocial support, patient involvement, education, and treatment literacy are important for good outcomes. DOT for tuberculosis is disempowering. Preferential adherence to antiretroviral therapy over MDR and XDR tuberculosis treatment might be because antiretroviral therapy is the patient's responsibility; patients receive education and counselling for antiretroviral therapy and understand it, whereas tuberculosis notification is incriminating and XDR tuberculosis is clinically isolating.

Improved diagnosis and treatment

Access to culture, line probe assays, and nucleic acid amplification testing can greatly improve the scarce MDR and XDR tuberculosis detection perpetuated by a reliance on sputum smear microscopy, which has low sensitivity and is unable to detect drug resistance. Active case finding by identifying and screening individuals at risk—including those with close contacts with smear-positive tuberculosis—not just people who present to the health-care system with symptoms, is essential for early detection and prevention of transmission.

But merely finding cases is insufficient: rapid initiation of acceptable, effective treatment must follow. The pill burden of MDR tuberculosis treatment (figure 9), lengthy duration, poor tolerability, and inadequate efficacy contribute to adherence challenges and poor outcomes. Wider and more effective MDR and XDR tuberculosis treatment options are urgently needed, as well as validated MDR tuberculosis prevention options and child-friendly formulations for the 30,000 children who develop MDR tuberculosis each year.

Additionally, improved access to underused drugs such as delamanid, bedaquiline, linezolid, and clofazimine could improve outcomes. Screening for hearing loss, nerve damage, and depression to mitigate toxicities of older drugs, such as the injectables and cycloserine, can and should be widely implemented immediately to save lives and prevent disability.

A holistic approach: creating a supportive environment

Addressing tuberculosis requires a multi-angle approach. The real-world challenges and practical realities of dealing with drug-resistant tuberculosis in low-resource settings are difficult (panel 10). People with HIV and XDR tuberculosis report far more stigma and isolation associated with their tuberculosis than with their HIV status, which deters health-care seeking. Community education about tuberculosis symptoms and transmission should emphasise that the disease can be cured, and should explain simple infection control strategies such as ventilation. With increased understanding of and confidence in preventing disease, we anticipate decreased stigma. Improved transportation options and roads, economic opportunities, and uncrowded housing options can facilitate care seeking, improve overall health, and reduce transmission.

Summary of community-centred care for MDR and XDR tuberculosis

With new and repurposed drugs to treat tuberculosis, improved diagnostic tests, and more research underway, progress is being made in addressing the clinical drivers of MDR and XDR tuberculosis, but much more can be done with existing tools. Investment in tuberculosis research and development was US$674 million in 2014, which is a third of the $2 billion needed annually to eliminate tuberculosis, estimated by the Stop TB Partnership. Investment in health-care systems and the social factors surrounding tuberculosis, such as poverty, overcrowding, and stigma, is essential to empower patients with MDR and XDR tuberculosis and communities, to reduce stigma, and create supportive environments for detection and treatment.

Conclusion

MDR tuberculosis, XDR tuberculosis, and resistance beyond XDR tuberculosis remains a major threat to global tuberculosis control because of the increasing burden it creates on health-care systems, economies, and societies, the threat to health-care workers in tuberculosis-endemic countries, the high mortality, and the unsustainably high costs of treating drug-resistant tuberculosis. Additionally, the development of totally drug-resistant or programmatically incurable tuberculosis has raised several ethical and medicolegal challenges. The global epidemiology of drug-resistant tuberculosis shows a worrying increase in the prevalence and incidence of drug-resistant tuberculosis in several countries and regions. Also, the proportion of cases of tuberculosis that are MDR and fluoroquinolone-resistant or aminoglycoside-resistant—ie, pre-XDR—or that are programmatically incurable has increased greatly. New molecular tools such as next-generation whole-genome sequencing are shedding further light on the transmission, diagnosis, and pathogenesis of drug-resistant tuberculosis. Particularly, several lines of evidence challenge the traditional view that resistance is acquired through non-adherence promoted by poor programmatic functioning. Although adherence is
clearly important for the prevention of drug-resistant tuberculosis, several other factors that promote pharmacokinetic mismatch drive the acquisition of drug-resistant tuberculosis even when adherence is good. However, newer methods to enable whole-genome sequencing directly from sputum and to assess its effect on clinical outcomes are needed.

Furthermore, a paradigm shift is required to take testing from the clinical setting into the community, thus promoting active case finding, and the detection of the undiagnosed and unsuspected cases of community-based drug-resistant tuberculosis. Newer drugs have improved the efficacy of the treatment of MDR and XDR tuberculosis, and therefore the prognosis, but resistance amplification will need to be minimised through strengthening tuberculosis programmes and other innovative approaches to prevent pharmacokinetic mismatch. Novel ways to reduce or eliminate the transmission of drug-resistant tuberculosis and to understand the fundamental biology of transmission are urgently required. These key messages are summarised in panel 11, and timeline-orientated research priorities and goals for drug-resistant tuberculosis are shown in table 15. All these priorities will need to be urgently addressed in tandem with the strengthening of health systems, reduction of poverty, and changing of political will.

Contributors
KD wrote the outline of the Commission and the text for the abstract, introduction, and conclusion sections. KD, JF, and RM reviewed and edited the entire Commission as it was developed by the other authors. Epidemiology and risk factors for MDR and XDR tuberculosis, and resistance beyond XDR: MMu was lead author; H-HL, SRA, RM, and KD were contributors. Molecular epidemiology and transmission dynamics of drug-resistant tuberculosis in high-burden countries: RMW was lead author; GT, PVH, SN, MMe, DD, AVR, and TGC were contributors. The rise of drug-resistant tuberculosis: TG and KD were lead authors; GKH5 and JGP were contributors. Diagnosis of MDR and XDR tuberculosis: RM was the lead author; CR, TGC, and FAS were contributors. Medical and surgical management of drug-resistant tuberculosis: general principles and treatment of children, patients with HIV, and in other specific clinical contexts: KD and JF were lead authors; HSS, KKC, CL, PN, ZFLU, CRH, GJC, AE, and DM were contributors. New drugs and strategies for treating drug-resistant tuberculosis: KED and GM were lead authors; ACH and EN were contributors. Pharmacokinetic–pharmacodynamic factors in drug-resistant tuberculosis: TG was the lead author; HM was a contributor. Prevention and containment of transmission of highly drug-resistant (MDR and XDR) tuberculosis: EAN was the lead author; GT, GJC, and KPF were contributors. Patient-centred care for drug-resistant tuberculosis: LL and JF were lead authors; EG and EJ were contributors. Components of patient-centred and community-centred care for MDR and XDR tuberculosis: an advocacy perspective: EL was the lead author; ML, CMJ, and NP were contributors.

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349


www.thelancet.com/respiratory Vol 5 April 2017
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