Tuberculosis 2

Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis

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

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Although progress has been made to reduce global incidence of drug-susceptible tuberculosis, the emergence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis during the past decade threatens to undermine these advances. However, countries are responding far too slowly. Of the estimated 440 000 cases of MDR tuberculosis that occurred in 2008, only 7% were identified and reported to WHO. Of these cases, only a fifth were treated according to WHO standards. Although treatment of MDR and XDR tuberculosis is possible with currently available diagnostic techniques and drugs, the treatment course is substantially more costly and laborious than for drug-susceptible tuberculosis, with higher rates of treatment failure and mortality. Nonetheless, a few countries provide examples of how existing technologies can be used to reverse the epidemic of MDR tuberculosis within a decade. Major improvements in laboratory capacity, infection control, performance of tuberculosis control programmes, and treatment regimens for both drug-susceptible and drug-resistant disease will be needed, together with a massive scale-up in diagnosis and treatment of MDR and XDR tuberculosis to prevent drug-resistant strains from becoming the dominant form of tuberculosis. New diagnostic tests and drugs are likely to become available during the next few years and should accelerate control of MDR and XDR tuberculosis. Equally important, especially in the highest-burden countries of India, China, and Russia, will be a commitment to tuberculosis control including improvements in national policies and health systems that remove financial barriers to treatment, encourage rational drug use, and create the infrastructure necessary to manage MDR tuberculosis on a national scale.

Introduction

> "Responding to drug-resistant tuberculosis is possibly one of the most profound challenges facing global health."[1]

The past 20 years have seen the worldwide appearance of multidrug-resistant (MDR) tuberculosis,[2–5] followed by extensively drug-resistant (XDR) tuberculosis,[6–9] and, most recently, strains that are resistant to all antituberculosis drugs.[10–12] MDR tuberculosis is caused by *Mycobacterium tuberculosis* that is resistant at least to isoniazid and rifampicin, and XDR tuberculosis by mycobacteria resistant to rifampicin and isoniazid, any fluoroquinolone, and one of the three injectable drugs, capreomycin, kanamycin, and amikacin. Drug resistance severely threatens tuberculosis control, since it raises the possibility of a return to an era in which drugs are no longer effective.[13]

Progress is being made in global control of drug-susceptible tuberculosis, as presented by Lonnröth and colleagues[14] in the first report in this Series. In 2008, 5·7 million (61%) of the estimated 9·4 million new and relapsed tuberculosis cases were identified and treated on the basis of the WHO Stop TB Strategy.[15] Partly as a result of these efforts, worldwide incidence of tuberculosis has been slowly falling since 2004.[15] Data are insufficient to indicate whether incidence of MDR tuberculosis is rising or falling globally. However, the fact that only 7% of the

Key messages

- An estimated 440 000 cases of multidrug-resistant (MDR) tuberculosis occurred worldwide in 2008 (3·6% of the estimated cases of tuberculosis in that year); most of these cases develop as a result of primary transmission (ie, in people never previously exposed to antituberculosis drugs).
- Drug-resistant tuberculosis poses a major threat to existing control programmes since treatment is less effective, more complex, and far more costly than is that for drug-susceptible disease.
- Tuberculosis control efforts are complicated by weak programmes with poor access to laboratory diagnosis and effective treatment. Investment in laboratory capacity and staff and the introduction of new rapid diagnostic tests are crucial.
- Driving forces behind the epidemic of drug-resistant tuberculosis include poor political commitment and weak health policies, regulation, and enforcement—especially uncontrolled drug availability in the private sector.
- Outbreaks of MDR and extensively drug-resistant (XDR) tuberculosis have emphasised the need for effective infection-control measures, which are absent in most high-burden settings.
- Nonetheless, some countries have reversed rising epidemics of MDR tuberculosis with wise use of existing technologies, and set an example for others.
- That new drugs, presently in the pipeline, are not exposed to the same health-system and programme weaknesses that created MDR and XDR tuberculosis is imperative.

Search strategy and selection criteria

We searched Medline using the search terms: "tuberculosis", "multidrug-resistant tuberculosis", "MDR-TB", "extensively drug-resistant tuberculosis", and "XDR-TB". Reference lists of identified articles were then searched for further relevant reports. Publications in English were reviewed. Reports published in the previous 10 years were selected mainly, but when relevant, we reviewed primary historical sources for frequently cited information or knowledge.

estimated 440 000 (95% CI 390 000–510 000) cases of MDR disease worldwide were reported to WHO in 2008, and of these, only a fifth (1·2% of the total) were treated according to WHO recommended standards, is of major concern.[15] These data show the depth of the challenge referred to by Upshur and colleagues[1]—that countries are confronted by huge political, structural, and economic constraints that have to be overcome to tackle the epidemic of drug-resistant tuberculosis. As a result, although the Millennium Development Goal of a reversal in the incidence of tuberculosis seems to have been achieved in 2004,[15] progress in the management of MDR tuberculosis has been poor, and milestones in the Stop TB Partnership's Global Plan to Stop TB 2006–2015, are being missed.[16] Unless countries can greatly intensify detection and treatment of drug-resistant cases, the possibility remains that MDR strains could become the dominant form of tuberculosis disease.[17,18]

In this Series report on drug-resistant tuberculosis, we will explore the size and causes of the MDR and XDR tuberculosis epidemic, and discuss the possible responses that are needed by policy makers globally and nationally if the challenge of drug-resistant tuberculosis is to be adequately faced.

What is the size of the problem?

WHO estimates that 440 000 cases of MDR tuberculosis occurred in 2008 (3·6% of the estimated total incident tuberculosis episodes).[19] Of these, 360 000 were new and relapse (recurrence after successful previous treatment) cases (ie, likely transmission of an MDR strain), and 94 000 were in individuals previously treated for the disease (ie, likely acquired resistance during previous treatment).

India and China together carry nearly 50% of the global burden, followed by Russia (9%). MDR tuberculosis caused an estimated 150 000 deaths in 2008.[19] These estimates are based on surveys done by local organisations, but coordinated, supported, and analysed by the Global Project on Anti-Tuberculosis Drug Resistance Surveillance (figure 1).[19] Since the surveillance project began in 1994, surveys have been undertaken in 114 countries (59% of 193 WHO member states). The surveys are intended to be representative of the entire population and thus test patients from all levels of health services, not only from central hospitals. To ensure laboratory results are accurate and comparable, the Supranational Reference Laboratory Network was formed in 1994, and now includes 28 laboratories in all six WHO regions.[20] Ideally, a culture and drug-susceptibility test should be done for every patient suspected to have tuberculosis, and surveillance would be based on these routinely obtained data. However, routine culture and drug-susceptibility testing happens in only 42 (22%) countries worldwide,[19] whereas 72 (37%) countries rely on periodic surveys, which are difficult to mount, often need external financial support, and can distract from routine programme activities. In the remaining 79 (41%) countries, drug-resistance surveys have never been done, mainly because laboratory capacity for culture and drug-susceptibility testing is insufficient (figure 1).[19]

On the basis of data from the Global Project on Anti-Tuberculosis Drug Resistance Surveillance, high rates of MDR tuberculosis (>3% of new tuberculosis cases) have been reported for at least one country in all six WHO regions (figure 2). Of particular note are several countries of the former Soviet Union, where more than 12% of new cases and more than 50% of previously treated cases are MDR tuberculosis (figure 2).[19] Nearly all cases of MDR tuberculosis in these countries are resistant to other first-line drugs besides isoniazid and rifampicin.[21] In Estonia, Lithuania, Latvia, Azerbaijan, Ukraine, and Tajikistan, XDR tuberculosis is present in more than 10% of all MDR cases (table 1). Additionally, MDR tuberculosis and HIV co-infection now occur frequently in the Ukraine and Latvia,[22,23] as well as southern Africa.[7,24,25] Although previously the HIV/AIDS epidemic was mostly focused in sub-Saharan Africa and the MDR tuberculosis epidemic was largely confined to eastern Europe, these epidemics are now clearly converging on both continents.[19,22,24–26]

Trends in drug resistance can be estimated for only 59 countries or subnational settings (eg, provinces) for which more than one drug-resistance survey was done between 1994 and 2009. Nonetheless, in six countries (Estonia, Hong Kong, Latvia, Russia [Orel and Tomsk oblasts], Singapore, and the USA) incidence of MDR tuberculosis is falling faster than is incidence of all forms of tuberculosis.[27] In other countries, such as Lithuania, incidence of MDR tuberculosis is decreasing, but more slowly than the rate for all tuberculosis cases. In countries such as Peru, incidence of all tuberculosis cases is decreasing, but incidence of MDR tuberculosis is rising. Most concerning are South Korea and Botswana, where all cases of tuberculosis are increasing in incidence, and MDR tuberculosis is increasing even faster.[19,23,26] The number of countries reporting at least one case of XDR tuberculosis had risen to 58 by January, 2010, although this change is probably a result of increased efforts to identify XDR tuberculosis rather than an increase in prevalence or distribution of the disease.[19]

Rising incidences of both tuberculosis and MDR tuberculosis in Botswana are being accelerated by high rates of HIV co-infection, which substantially increases progression to active disease after infection with *M tuberculosis*.[28] This example is especially concerning because no similar trend data are available for the rest of Africa, so similar prevalence rates in other countries might well be hidden.[29] Furthermore, MDR tuberculosis and HIV co-infection has a high early mortality rate, especially in low-income settings.[30,31] Together with insufficient laboratory capacity for detection of such cases, this mortality could be masking innumerable local outbreaks of HIV-associated MDR tuberculosis, preventing them from coming to medical or public

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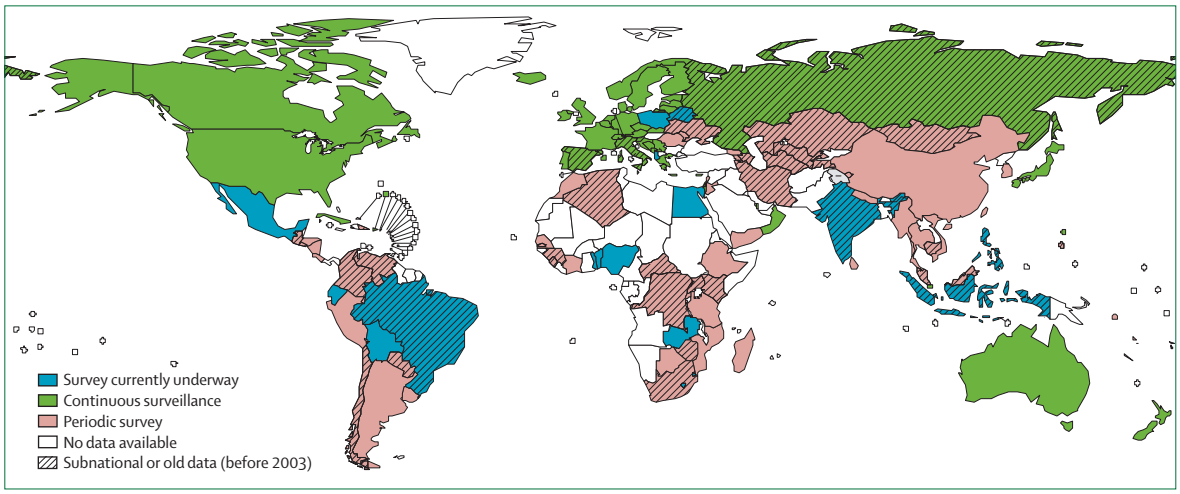

Figure 1: **Global coverage of surveillance for antituberculosis drug resistance**
Based on Global Drug Resistance Surveillance Project data.[19,32]

health attention. Because of insufficient laboratory capacity, only 22 (48%) of 46 countries in the WHO African region have ever undertaken a drug-resistance survey (figure 1).[19]

The usefulness of survey and estimate data is restricted in several other ways. First, surveys are generally done only in public facilities, excluding patients in the private sector. Second, in some countries, surveys have been done in only a few states or oblasts rather than nationwide, or the information is old; 38 (20%) countries last obtained data before 2003, and have not since repeated a survey (figure 1).[32] Third, surveys have used only standard culture-based diagnostic tests, and thus have not exploited the opportunities that are presented by new technologies.[33] Fourth, surveys focus on recently diagnosed patients and have had difficulties accurately surveying those infected with HIV, potentially biasing results.[34] As a result of these limitations and others, the question of whether drug resistance is increasing or decreasing worldwide remains unclear, despite the large effort put into this global survey.

A massive expansion of laboratory capacity will be needed before the global burden and patterns of drug resistance are fully understood. WHO is calling for establishment of continuous national surveillance systems, such that every country should be able to measure the magnitude of its drug-resistant tuberculosis epidemic and monitor the effectiveness of prevention and control measures.[35] These routinely obtained data would greatly improve global estimates of the epidemic, and the need to establish such systems was emphasised by a World Health Assembly resolution.[36] In view of the present limitations in laboratory capacity, initial efforts to establish continuous surveillance systems should target high-risk groups for MDR tuberculosis, such as patients not responding to treatment and those with previous history of tuberculosis treatment, then gradually expand to cover all tuberculosis cases.[35]

How did we reach the present situation?

Resistance to antituberculosis drugs arises as a result of spontaneous mutations in the genome of *M tuberculosis* and not as a result of horizontal gene transfer.[37,38] These resistance-conferring mutations occur at predictable rates for each antituberculosis drug (eg, isoniazid 10^{-6}, rifampicin 10^{-8}).[37] Thus, in patients with active tuberculosis disease, subpopulations of resistant mycobacteria spontaneously arise,[39] and can emerge as the dominant strain in the presence of drug-selection pressure.[40] Thus, drug-resistant tuberculosis is regarded as a man-made occurence.

With selection, drug-resistant organisms multiply to become the dominant strain; for example, isoniazid monotherapy selects for isoniazid-resistant mutants and allows them to multiply (figure 3).[40,41] Resistance to additional tuberculosis drugs can be added in a step-wise manner to create tuberculosis strains that are resistant to several drugs; for example, treatment of isoniazid-monoresistant tuberculosis with isoniazid and rifampicin selects for spontaneous rifampicin-resistant mutants. This process is referred to as acquired resistance (figure 3),[42,43] and is the rationale for the adage "never add a single drug to a failing regimen". However, for patients not responding to first-line tuberculosis treatment in high-burden settings, in the absence of drug-susceptibility test data, common practice is to replace standard first-line treatment with an extended regimen that adds streptomycin as the only additional drug (category II regimen).[44,45] This practice has predictably led to acquisition of further drug resistance.[46]

Once created, drug-resistant strains can be transmitted, giving rise to drug-resistant tuberculosis in individuals never previously exposed to antituberculosis drugs (primary resistance) (figure 4).[5,7,47] Drug-resistance mutations were initially postulated to exert a fitness cost, rendering those strains too weak to be transmitted.[48–50] However, results of many studies have now confirmed

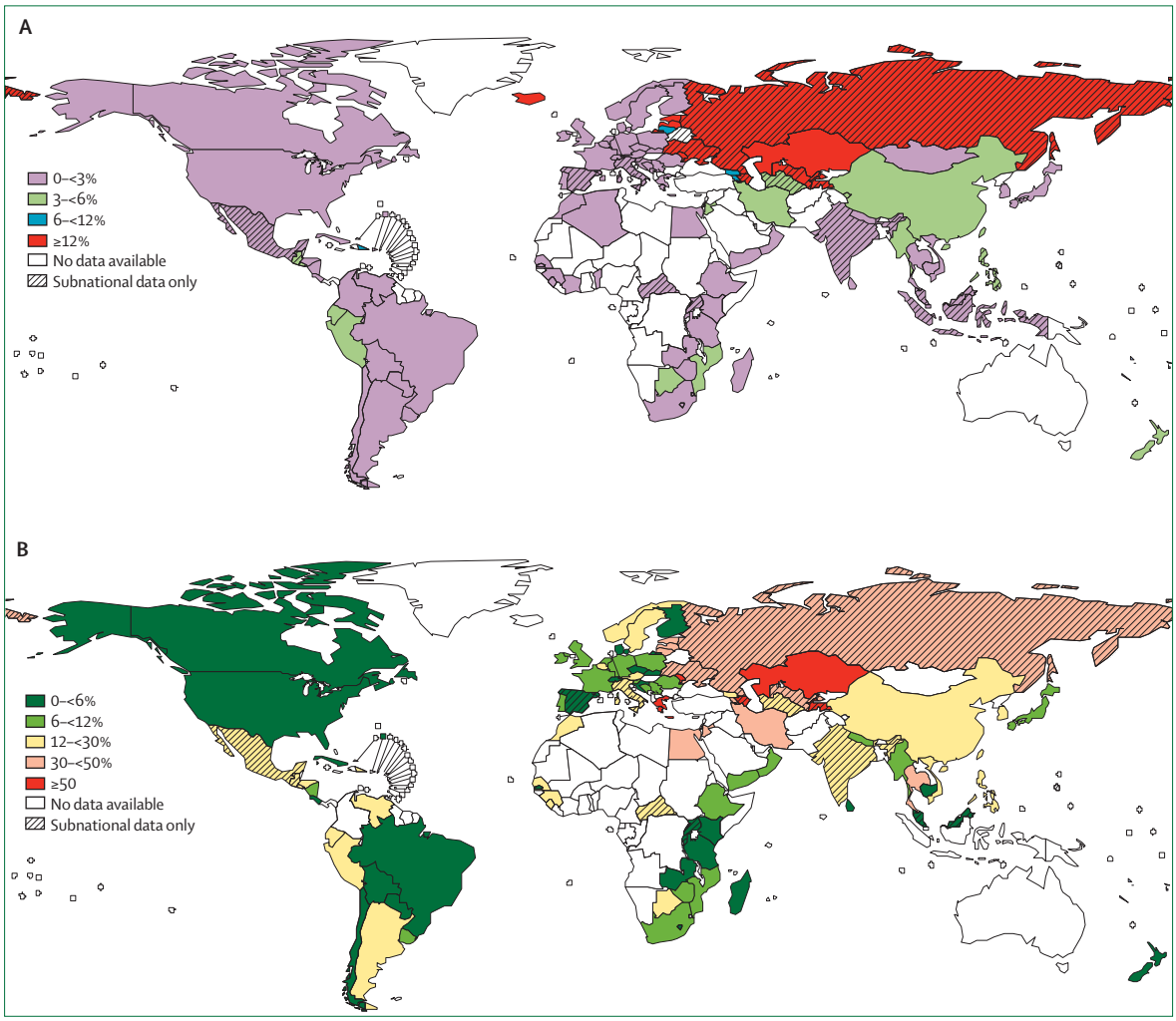

Figure 2: **Proportion of multidrug-resistant disease among (A) new cases and (B) previously treated cases of tuberculosis**
Based on Global Drug Resistance Surveillance Project data.[19,32] Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands, and Qatar reported data for combined new and previously treated cases.

that transmission of drug-resistant tuberculosis does occur,[2,5,42,47,51,52] although further studies are needed to elucidate the relation between resistance-conferring mutations and transmissibility.[53] Specific strain genotypes (eg, W/Beijing strain), and particular resistance or compensatory mutations (eg, position 315 of *katG* gene), seem to be important factors establishing transmissibility of particular drug-resistant strains.[54,55] Other clinical factors seem to promote transmission of drug-resistant tuberculosis, including delays in diagnosis using conventional drug-susceptibility methods and an increased time to sterilise sputum culture, due to the low potency of second-line drugs.[56]

The global epidemic of drug-resistant tuberculosis is due to a combination of acquired resistance and primary transmission,[46,47,52,57] although the relative contribution of each can only be estimated. Identification of the mechanisms through which drug-resistant cases develop is important to establish the interventions necessary to prevent further cases. Historically, tuberculosis control efforts have focused mainly on improvement of cure rates for drug-susceptible disease, in an attempt to reduce the number of drug-resistant cases arising from acquired resistance.[44] However, many health systems and national tuberculosis programmes have performed poorly during the past two decades, failing to recruit and train sufficient health workers[58] and to regulate drug suppliers and pharmacies.[59] Many have allowed antituberculosis drugs to be obtained without prescription,[60] have not ensured correct prescription or dispensing (irrational drug use), especially in the private sector,[61] and have not ensured adherence to treatment through patient-friendly supervision.

Another important issue has been the failure to provide free treatment for drug-susceptible disease.[62] As a result, cure rates have fallen short of the recommended 85%

	Year	Method*	MDR TB cases tested for second-line drug resistance	XDR cases among MDR TB cases tested	Proportion of MDR cases that were XDR (%)
Armenia	2007	Survey	199	8	4·0% (1·8–7·8)
Azerbaijan, Baku	2007	Survey	431	55	12·8% (9·8–16·3)
Bangladesh†‡	2008	Surveillance	168	1	0·6%
China†	2008	Survey	270	30	11·1% (7·6–15·5)
Estonia	2008	Surveillance	72	9	12·5%
Georgia	2006	Survey	70	3	4·3% (0·9–12·0)
India, Gujarat state†	2006	Survey	216	7	3·2% (1·2–6·6)
Kazakhstan	2008	Surveillance	373	16	4·3%
Latvia	2008	Surveillance	128	19	14·8%
Lithuania	2003–06	Surveillance	173	25	14·5%
Moldova	2006	Survey	47	3	6·4% (1·3–17·5)
Russia, Tomsk oblast†	2003–05	Surveillance	458	30	6·6%
South Africa†	2008	Surveillance	5451	573	10·5%
Tajikistan, Dushanbe and Rudaki	2009	Survey	100	21	21·0% (13·5–30·3)
Ukraine, Donetsk oblast	2006	Survey	20	3	15·0% (3·2–37·9)

Data are n or % (95% CI). MDR=multidrug resistant. TB=tuberculosis. XDR=extensively drug resistant. *Data derived from continuous surveillance systems versus from periodic drug-resistance surveys. †Countries with a high burden of tuberculosis, for which representative data for prevalence of XDR disease were available; XDR prevalence data were not available for any of the remaining high-burden countries. ‡Damien Foundation Area, previously treated cases only.

Table 1: **Second-line drug-resistance data for countries with high burdens of MDR tuberculosis[19]**

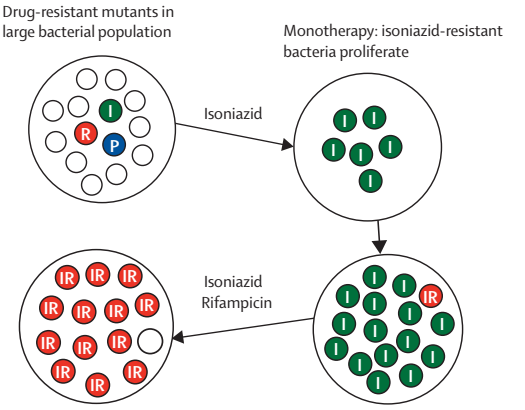

Figure 3: **Acquisition of resistance**
I=isoniazid. R=rifampicin. P=pyrazinamide. MDR=multidrug resistant. TB=tuberculosis. Adapted from Albino JA, Reichman LB. The treatment of tuberculosis. *Respiration* 1998; **65:** 237–55, by permission of S Karger AG, Basel, Switzerland.

benchmark. These programmes created an ideal environment for acquisition of drug resistance[18]—ie, treatment was given, but was not managed well enough to prevent development of resistance. Additionally, treatment costs for MDR tuberculosis can exceed yearly family income,[63] leading to similarly poor-quality treatment of MDR tuberculosis with second-line drugs, which has given rise to second-line drug resistance and emergence of XDR strains.[64] Treatment for other diseases can also contribute to acquired resistance—for instance, widespread use of fluoroquinolones for respiratory-tract and other infections might drive resistance to fluoroquinolones in tuberculosis.[65]

Problems with drug production, supply, and quality have been described,[66–68] and could contribute to development of acquired drug resistance. When faults in production or in the supply chain interrupt the availability of one or more drugs, patients' adherence is interrupted (through no fault of the patient). Similarly, if drug quality is not monitored or maintained, even if patients are adhering to their treatment, bioavailable drug concentrations can be subtherapeutic. The extent to which this problem leads to resistance is unknown and warrants further study, although the bioavailability of rifampicin, especially within fixed dose combinations, is well documented.[66]

Transmission is now also playing an increasing part in development of drug-resistant tuberculosis cases.[47,52] However, infection control to prevent transmission has largely been ignored. In most of the world, patients are admitted to large congregate hospital wards or spend time in crowded outpatient waiting areas with little or no ventilation. Modelling studies have shown that when a patient with infectious drug-resistant tuberculosis is admitted to such a setting, up to 50% of the patients exposed on that ward can become infected within 24 h.[69] Primary transmission in settings with little or no infection control has undoubtedly contributed to the spread of MDR and XDR tuberculosis and has led to outbreaks worldwide, particularly in patients co-infected with HIV.[2,5,7,51] Transmission in household and community settings has also been documented,[70,71] which is especially troubling with respect to children younger than 5 years (panel 1), since they are highly susceptible to progression to active disease. The proportion of MDR tuberculosis cases that arise because of transmission in health-care versus community settings remains unknown and also warrants further study.

Effect of HIV/AIDS

The association between HIV/AIDS and drug-resistant tuberculosis is complex and multifaceted.[83] HIV co-infection is not believed to increase the rate at which spontaneous resistance-conferring mutations occur, although it might increase the number of mutants that arise overall by enlarging the pool of individuals with active tuberculosis disease.[84] Additionally, HIV co-infection might increase selection for spontaneous mutations in several ways. Without proper management, individuals with HIV-associated tuberculosis could have diminished adherence due to increased pill burden, overlapping toxic effects, or fragmentation of care between separate tuberculosis and HIV/AIDS programmes.[85,86] They are also prone to having subtherapeutic concentrations of antituberculosis drugs because of malabsorption[87,88] or drug interactions.[89,90]

Patients with tuberculosis, with and without HIV co-infection, can be infected with drug-resistant tuberculosis strains, but those co-infected with HIV are much more likely than are their counterparts to progress to active tuberculosis disease after initial infection.[28] Thus, patients co-infected with HIV are more likely and are often the first to show active drug-resistant tuberculosis after transmission in an outbreak,[91,92] whereas HIV-negative individuals may become latently infected and manifest disease years later, if at all.

Finally, the risk factors for both drug-resistant tuberculosis and HIV/AIDS (eg, injection drug use) could be similar,[93] creating the appearance that drug-resistant tuberculosis has increased prevalence in patients co-infected with HIV, such as in eastern Europe.[22,23] In summary, although HIV infection might not itself be causing an increase in the rate of drug-resistance mutations, it certainly has the potential to increase the number of individuals who select for drug resistance or manifest active disease from resistant organisms, thereby potentially accelerating the propagation and spread of drug-resistant disease.

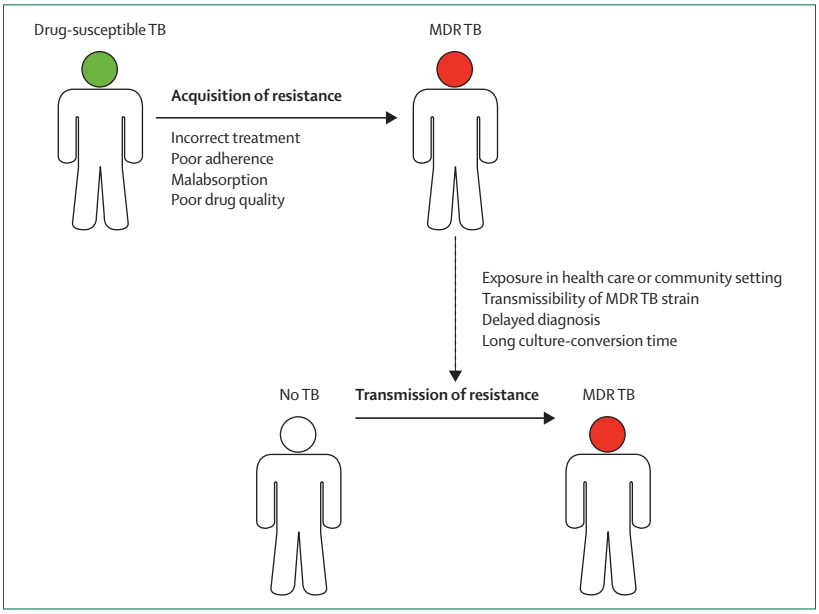

Figure 4: **Mechanisms in the development of resistance**
TB=tuberculosis. MDR=multidrug resistant. Adapted from Cohen T, Colijn C, Murray M. Mathematical modeling of tuberculosis transmission dynamics. In: Kaufman SH, van Helden P, eds. Handbook of tuberculosis: clinics, diagnostics, therapy, and epidemiology. Weinheim, Germany: Wiley-VCH, 2007: 227–43, by permission of Wiley-VCH Verlag GmbH & Co KGaA.

How can we use existing technologies to improve outcomes?

Overall, although restricted in their effectiveness, existing technologies seem sufficient to begin turning the tide against drug-resistant tuberculosis, if properly used.[17,27,94] These results have been achieved with political commitment, drug-susceptibility testing of every case of tuberculosis, and specialist management of MDR tuberculosis in centres of excellence, with currently available technologies. The countries that have achieved these results are small and centralised (Estonia and Latvia), wealthy (USA), politically very committed (Orel and Tomsk oblasts of Russia), or all three (Hong Kong, Singapore), which might allow them to more easily manage the health-system constraints that make implementation difficult in large countries. Nonetheless, are there specific steps involving existing components of tuberculosis control that all countries can consider implementing?

Diagnosis of drug resistance

Diagnosis of drug-resistant tuberculosis relies on establishment of the drug susceptibility of *M tuberculosis* strains,[76] which is either assessed phenotypically (ie, culture growth in the presence of drug) or, more recently, genotypically (ie, identification of resistance-conferring mutations). However, at present neither technique is available in most countries because of a scarcity of capable laboratories.[95,96] Improved access to diagnosis depends on expansion of laboratory capacity, improved use of present techniques, and development of new technologies that can be used peripherally and at point of care. The Global Laboratory Initiative was founded in 2007 to coordinate development of laboratory capacity; provide policy guidance for laboratory technology, best practices, and quality assurance; and stimulate expansion of the laboratory network.[97] The past decade has also seen a dramatic increase in refinement of existing techniques and development of new diagnostic methods to facilitate diagnosis of MDR tuberculosis (table 2).[98–100] As such tests are developed, specific attention should be paid to their performance in smear-negative and paucibacillary disease (eg, in children, HIV-infected patients), in which morbidity and mortality from drug-resistant tuberculosis are greatest, as well as in programmatic settings and in specimens other than sputum (eg, lymph-node aspirate, blood culture, bronchoalveolar lavage).

Finally, a change in thinking is needed to emphasise the importance of definitive diagnosis of drug-resistant tuberculosis and recognise that microscopic and clinical diagnoses are insufficient. Delays in diagnosis lead to clinical deterioration, death (especially in patients co-infected with HIV), and further transmission. Consequently, the goal should be rapid testing for susceptibility to isoniazid and rifampicin for all patients; however, until sufficient laboratory capacity is established, targeting of patients at high risk for MDR or XDR tuberculosis (eg, close contacts, first-line treatment failures, and retreatment cases) would be a reasonable interim step. Further studies to assess the cost-effectiveness of such approaches are also needed.[101]

Treatment

Although no randomised clinical trials have been done to guide optimum treatment strategies for MDR and XDR tuberculosis,[76,102,103] results of observational studies have

shown that treatment can be successful for some patients with MDR and XDR tuberculosis.[31,102,104,105] Treatment success rates are associated with degree of drug resistance;[30,105] rates of success in MDR tuberculosis are as high as 83%,[106] and 60% in patients with XDR tuberculosis[107] in the absence of HIV co-infection. Overall outcomes are substantially worsened with HIV co-infection, largely owing to very high mortality in both MDR and XDR tuberculosis within the first 2 months, before patients can be diagnosed and started on treatment.[30,31] However, if both drug-resistant tuberculosis treatment and antiretroviral therapy can be delivered early to patients co-infected with HIV, results might be expected to improve.[108,109] Further studies are needed to confirm these early findings—since most studies to date included few, if any, patients with HIV co-infection[104,105]—and also to investigate potential complications and challenges of combined treatment, such as overlapping toxic effects, immune reconstitution inflammatory syndrome, and effect on adherence to either therapy.[110]

Despite scarcity of rigorous evidence, some guiding principles have been developed for treatment of MDR tuberculosis on the basis of expert consensus and data from observational studies.[76] Patients should be treated with four to six drugs to which their strains are known or likely to be susceptible, including any first-line drugs, a fluoroquinolone, and a second-line injectable agent for an intensive phase of at least 4 months after culture conversion and a minimum of 6-months' duration.[76] Additional second-line oral agents should be added to achieve the target number of susceptible drugs. The same principles are used in regimens for XDR tuberculosis, although addition of third-line drugs might be necessary to achieve four to six susceptible drugs.[76] Timely initiation of treatment is crucial to lower morbidity and mortality, and to reduce transmission to others. Treatment in the continuation phase should continue with the remaining oral drugs for a minimum of 18 months after culture conversion.[76] If pulmonary disease is sufficiently localised and residual lung function is adequate, resective surgery should be considered as an adjunct to chemotherapy.[111] Some drugs are being considered for off-label use (eg, linezolid, meropenem-clavulanate), particularly for patients with XDR tuberculosis, for whom few other options remain.[112,113] Rigorous studies to examine their efficacy and safety are still needed.

Optimum duration of treatment is unknown,[102,103] and questions remain as to whether these recommendations should be applied to all cases. Should patients with rapid sputum conversion be treated for a shorter time than those with slower conversion?[114–116] Should extrapulmonary drug-resistant tuberculosis be treated for the same duration as pulmonary disease?[76] Should treatment duration be extended for patients with HIV co-infection? Clinical trials were undertaken during the past 40 years to establish treatment duration in susceptible tuberculosis,[117–119] and should also be done to establish the duration of MDR tuberculosis treatment.[120] In the future, tuberculosis biomarkers might have the potential to shorten treatment duration and facilitate clinical trials by serving as a surrogate endpoint for relapse or cure.[121]

Public health and programmatic approaches to treatment

From a public health perspective, the challenge of scaling up treatment for drug-resistant tuberculosis is immense. Management of MDR tuberculosis is more complex, costly, and time-consuming and less effective than is management of drug-susceptible tuberculosis.[122,123] The Green Light Committee was established in 2000 to provide a mechanism for responsible distribution of second-line drugs;[124] however, it sponsors treatment for only about 1% of global MDR tuberculosis cases every year.[15] Until recently, important barriers to availability of treatment in countries with low and middle incomes

Panel 1: Drug-resistant tuberculosis in children

Identification and diagnosis

- Drug-resistant tuberculosis in children is mainly due to transmission from an adult, although acquired resistance is possible in children older than 8–10 years with adult-type pulmonary tuberculosis.
- Drug-resistant tuberculosis is under-recognised and underdiagnosed in children. Children mainly have paucibacillary disease, making diagnosis difficult. Culture yields of induced sputum, gastric aspirates, and bronchoalveolar lavage vary between 30% and 70% on the basis of disease severity.[72,73]
- Every effort should be made to obtain a culture and drug-susceptibility test for children who are contacts of adults with drug-resistant tuberculosis to aid construction of treatment regimens and to avoid unnecessary exposure to toxic drugs. In the absence of a drug-susceptibility test, however, test results for the adult contact should be used to build the child's regimen[70,74,75] and to empirically start a second-line drug regimen.[76]
- Drug resistance should also be considered if a child does not respond to first-line treatment, despite good adherence. Clinical signs such as weight loss can be the only indication of clinical failure, since unchanged chest radiographs do not necessarily denote an absence of improvement.[76] Culture and drug-susceptibility testing should be repeated when failure is suspected.

Treatment

- Basic principles of treatment for childhood drug-resistant tuberculosis are the same as those for adults, although a reduced duration of treatment might be sufficient for children with early primary disease. Treatment should be daily and directly observed, with clinical and bacteriological follow-up.[76]
- Second-line drugs seem to be well tolerated in children, but adverse effects are difficult to assess.[74,75,77] Concerns have been raised about a potential relation between fluoroquinolones and arthropathy, although a link has not been proven.[78] Long-term use of aminoglycosides or capreomycin can cause hearing loss, and hearing screening should be routinely done when possible. Thioamides and para-aminosalicylic acid can cause temporary subclinical hypothyroidism.
- Treatment outcomes for children with drug-resistant tuberculosis are based on case reports and cohort studies.[74,77,79,80] In one study, investigators documented cure rates of 95% in 38 children treated in Peru, providing evidence that drug-resistant tuberculosis in children can be managed effectively, even in resource-constrained settings.[74] XDR tuberculosis does occur in children, and has been successfully managed.[81,82] Few data are available for paediatric co-infection with HIV and drug-resistant tuberculosis.[82,83]

	Description and comments	Manufacturer
Culture		
Microscopic observation drug-susceptibility assay*	Early detection of *Mycobacterium tuberculosis* in liquid culture media with an inverted light microscope; highly accurate, quick, and cheap	A standardised version under development with PATH
Thin-layer agar	Early growth detection on selective thin-layer agar with light microscopy or colorimetric detection; cheap, accurate, and easy to use	A standardised version under development with FIND
Nitrate reductase assay*	Early growth detected through a colour change mediated by the ability of *M tuberculosis* to reduce nitrate to nitrite (Griess reaction) in selective media; accurate and cheap	No standardised version available
Colorimetric redox indicator assays*	Growth detected by reduction of a coloured indicator added to a selective culture medium; accurate and cheap	No standardised version available
Nucleic acid amplification tests		
Line-probe assay*	PCR amplification of a segment of *rpoB* with hybridisation of the biotin-labelled amplicons to oligonucleotide probes on a membrane strip (line probe); the GenoType MTBDRplus assay detects rifampicin and isoniazid resistance; MTBDRsl version detects resistance to fluoroquinolones, aminoglycosides, capreomycin, and ethambutol	GenoType MTBDRplus assay (Hain Lifescience); GenoType MTBDRsl (Hain Lifescience); INNO-LiPA Rif.TB (Innogenetics)
Xpert MTB/RIF	Multiplex PCR amplification of *rpoB* with real-time detection with a fluorescent signal (molecular beacons); preliminary outcome data show good performance	Cepheid
Other technologies		
Bacteriophage assays	Based on detection of progeny phages, which infect *M tuberculosis*, as lytic plaques on a lawn of *Mycobacterium smegmatis*; few data available for clinical specimens	FASTPlaque
High-resolution melt assays	Novel method using DNA melting temperature during PCR to scan for mutations; no clinical data available	Experimental

PATH=Program for Appropriate Technology in Health. FIND=Foundation for Innovative New Diagnostics. MTBDR=*Mycobacterium tuberculosis* drug resistance. MTB=*Mycobacterium tuberculosis*. RIF=rifampicin. *Endorsed by WHO for use as a diagnostic test for drug-resistant tuberculosis.[11]

Table 2: **New and emerging technologies for diagnosis of drug-resistant tuberculosis[100]**

included a scarcity of evidence showing the effectiveness of large-scale treatment programmes and an absence of global guidelines for programmatic management of MDR tuberculosis. Now that these issues have been addressed,[76,123] the remaining major bottlenecks are inadequate capacity at country level to provide treatment for MDR tuberculosis and insufficient production of quality-assured drugs. National governments need to greatly increase support of treatment programmes for MDR tuberculosis and make use of resources available from the Global Fund to Fight AIDS, Tuberculosis and Malaria.

In an effort to meet the challenges of MDR and XDR tuberculosis, some countries will need to consider treating patients in the community because of insufficient hospital capacity and long waiting lists for treatment (panel 2).[130] Studies are needed to evaluate these different treatment models. At present, the most common approach is to admit patients to hospital for the intensive phase. But is this approach more effective at ensuring safety, treatment success, or prevention of acquired resistance than home-based or community-based treatment models? Similarly, how do programmes that centralise treatment to a provincial or national centre of excellence compare with those providing decentralised treatment at district or subdistrict levels? How should a particular locale decide which model would work best?

Prevention and control

Efforts to address the epidemic of MDR and XDR tuberculosis have to prevent both acquired and primary resistance. Prevention of acquired resistance relies on early case finding and effective treatment, encapsulated in the directly observed therapy, short course (DOTS) and Stop TB strategies,[131] which aim to improve treatment cure and completion rates and reduce failure and default. By contrast, prevention of transmission of drug-resistant strains needs not only early identification and initiation of treatment, but also infection control.

Transmission of tuberculosis occurs through droplet nuclei, aerosolised by patients with infectious pulmonary tuberculosis and inhaled by another individual. Probability of infection depends on site of disease and bacillary burden in the infectious patient,[132] duration and proximity of contact, surrounding air volume, and speed of replacement of air through ventilation.[133,134] The principles are the same for drug-susceptible and drug-resistant strains.

The mainstay of prevention of drug-resistant tuberculosis transmission is airborne infection control, which strives to reduce aerosol production, sterilise bacterial load, and prevent inhalation of droplet nuclei. A set of infection-control measures has been defined to support development of infection-control programmes, which includes: national and regional planning; facility design, construction and renovation; administrative, environmental, and personal control measures;

Panel 2: **Ethical dilemmas in treatment of drug-resistant tuberculosis in resource-poor settings**

Many patients with multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis have poor treatment outcomes.[108,125] Often, these patients have high-grade resistance, are not surgical candidates, and have received 12 months of inpatient therapy but continue to have positive cultures.[125] Among these patients, acute ethical dilemmas arise. Should they be discharged into their communities? If so, should treatment be suspended, to prevent further acquisition of resistance? Should they be isolated from society, to whom they pose a threat? Discharging of infectious and incurable patients back into the community might be criticised, but are there any alternative options in resource-poor settings? In the Western Cape Province of South Africa, the decision to suspend treatment is taken by a multidisciplinary review committee after all other options are exhausted. A social assessment is done to assess suitability for home discharge. However, is this decision justifiable, since many of these patients live with their families in single rooms or informal housing? Community and hospital-based settings with isolation facilities, such as hospices, might be needed to care for incurable or terminally ill patients with XDR tuberculosis.

Another concerning example is the (not infrequent) smear-positive patient with high-grade resistance, and alcohol or substance misuse, who has repeatedly defaulted from treatment. These patients are often difficult to manage in hospitals, absconding and even threatening or assaulting hospital staff and other patients. Should such patients be incarcerated? How should the right of the individual be balanced against the safety of society?[126,127] Although incarceration of patients who do not comply with treatment has been used in countries such as the USA,[128] resource-poor countries often have an inadequate legal framework and no suitable facilities to deal with such patients, who can break out or escape from existing tuberculosis facilities. Moreover, transmission occurs in prisons,[129] which often do not have adequate diagnostic and treatment facilities or policies for management of prisoners with drug-resistant tuberculosis. In the Western Cape, the review committee has withdrawn therapy from patients who persistently default to prevent acquisition of drug resistance, but incarceration is not imposed.

Patients unwilling to start treatment because of the risk of losing employment, or accept long-term inpatient admission because they are single parents with young children, will stimulate treatment programmes for drug-resistant tuberculosis to consider new models of care. As this epidemic grows, innovative solutions will be necessary to ensure safe completion of treatment for MDR tuberculosis, despite the long duration and many limitations.

necessary advocacy and communication steps; and monitoring, and assessment.[135] Drug resistance does not substantially change the basic infection-control strategies that are recommended,[76] but does increase urgency.

Few resources have been devoted to the creation or implementation of infection-control policies or programmes, even though the implementation of low-technological, readily available measures (eg, limitation of hospital admissions, natural ventilation, active case finding, N95 masks) could have a substantial effect, curbing transmission immediately and blunting the epidemic trajectory.[69,136] Most research into transmission of drug-resistant strains has focused on institutional settings and vulnerable populations.[2,5,31,51] In these settings, infection control has to include protection of clinical and laboratory health-care workers—precious resources in whom rates of MDR and XDR tuberculosis are several times higher than in the general population.[137,138] Finally, because of the need for community-based treatment, further studies are necessary to investigate infection control in household and community settings. Rates of transmission of MDR and XDR tuberculosis in households are similar to those for drug-susceptible tuberculosis, resulting in drug-resistance prevalence rates that are greater than 1000 cases per 100 000 population in household contacts of MDR and XDR tuberculosis index cases.[71]

What new knowledge or technologies do we need?

The epidemic of MDR and XDR tuberculosis worldwide has exposed defects in our attempts to control tuberculosis. Although much can be done to fight MDR and XDR tuberculosis with existing technologies, we would be unwise to rely on these techniques alone. The prospects for development of new diagnostic tests, drugs, and vaccines are the subject of past work[139] and reports in this Series,[140–142] and we will touch here only on some of the important implications for management of MDR tuberculosis (panel 3).

The development of new diagnostic tests is an active area of research for both drug-susceptible and drug-resistant tuberculosis, and tests for rifampicin resistance that can be used in district laboratories or health centres will probably be available in the next few years.[143] Point-of-care tests could become available thereafter. The challenge will be to make these tests truly available in countries and settings where need is greatest. This goal will necessitate substantial expansion of the laboratory network in most countries, in addition to advocacy and political will to mobilise the necessary capital investment. Cost-effectiveness studies assessing the effect on clinical outcomes and clarifying optimum algorithms for diagnosis of MDR and XDR tuberculosis will also be necessary. Finally, a reassessment of the role of the traditional tuberculosis laboratory might be necessary as new diagnostic tests that can be used in peripheral settings become widely available.

The impending arrival of new antituberculosis drugs also raises important issues related to drug resistance. Any new class of drugs is likely to be effective against existing drug-resistant tuberculosis strains, so there will be strong calls to use these drugs in patients with MDR and XDR tuberculosis. The most important issue will be to ensure that these new drugs are not exposed to the weak health systems and irrational drug practices that are currently giving rise to resistance. This process will necessitate strategic planning to balance accessibility to the new drug while ensuring that treatment is provided in accordance with international standards. Additionally, early in the drug-development process, consideration should be given to how clinical trials can establish the optimum regimen for a new drug (ie, the number, class, and dose of companion drugs). This process might

necessitate cooperation between drug companies, as well as research-funding agencies and international organisations, if several companies develop new drugs around the same time.[144]

An effective new vaccine, although some distance away, would revolutionise tuberculosis control. If it were a preinfection vaccine, however, patients with MDR or XDR tuberculosis that developed before introduction of the new vaccine would still need to be managed. Several new immunotherapeutic interventions, including high-dose intravenous immunoglobulin G, multiple-dose *Mycobacterium vaccae*, and others, need to be assessed in cohorts of patients with MDR and XDR tuberculosis.[145] Research in infection control in tuberculosis has recently been resurrected, notably in Peru and South Africa,[146,147] but a conceptual framework is needed for the assessment and validation of infection control methods and policies in the field.

Several new (and not so new) approaches are needed in health systems to address the causes and management of MDR and XDR tuberculosis. Every country needs a comprehensive framework for management and care of MDR and XDR tuberculosis, including direct observation of treatment in community-based and patient-centred care models, sufficiently trained and motivated staff, and involvement of all treatment providers, including private practitioners, prisons, and non-governmental organisations.[36] Above all, removal of the threat of financial ruin for the family of any patient with MDR tuberculosis is crucial, in view of the catastrophic cost of treatment. Uninterrupted supplies of quality-assured second-line drugs are essential. Appropriate legal frameworks and isolation facilities in high-burden settings need to be set up to deal with patients who default or who do not respond to treatment. Rational use of drugs needs to be enshrined in policies, implemented, and, if previous failures are to be overcome, enforced. Antituberculosis drugs should be sold by prescription only, written by accredited providers, in settings with a high burden of MDR tuberculosis.[148] Consideration should be given to setting of national targets to accelerate access to treatment.

Conclusions

MDR and XDR tuberculosis are major challenges to tuberculosis control, but are not yet being sufficiently addressed. National governments have yet to make available adequate resources for control efforts.[15] Unless countries invest substantially in management of MDR tuberculosis, the possibility remains that MDR strains could become the dominant form of tuberculosis.[17,18] Moreover, the future possibility of strains that are totally resistant to all antituberculosis drugs becoming widespread is not inconceivable. Although incidence of all forms of tuberculosis might be reduced in this scenario, the complexity, cost, and overall burden for communities and countries would be substantially

***Panel 3:* Strategies and research priorities to prevent new cases and manage existing cases of drug-resistant tuberculosis**

Prevention of acquired drug resistance

- Shorten and improve first-line treatment of drug-susceptible tuberculosis
- Strengthen and expand implementation of the Stop TB Strategy
- Provide universal drug-susceptibility testing for all patients with suspected tuberculosis
- In treatment failures and retreatment cases:
  - Undertake rapid drug-susceptibility testing for isoniazid and rifampicin
  - Treat patients empirically with second-line regimens until these test results are available
- Study efficacy and safety of concurrent antiretroviral and second-line tuberculosis treatment
- Undertake pharmacokinetic and pharmacodynamic studies of second-line antituberculosis and antiretroviral drugs

Transmission of drug resistance

- Identify factors associated with transmissibility and fitness of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains
- Determine sites and extent of transmission of MDR and XDR tuberculosis
- Examine effectiveness of infection-control strategies for prevention of transmission
- Develop infection-control programmes for health-care, congregate, community, and household settings
- Establish optimum strategies to prevent nosocomial transmission to health-care workers
- Establish how best to manage close or casual contacts of patients with MDR and XDR tuberculosis

Diagnosis of MDR and XDR tuberculosis

- Expand laboratory capacity to provide drug-susceptibility testing in every country and establish continuous surveillance for drug resistance
- Develop diagnostic tests for use at point of care and in peripheral facilities
- Develop and validate rapid diagnostic tests for XDR tuberculosis
- Assess effect of rapid diagnostic test use on transmission rates of MDR tuberculosis
- Validate new diagnostic tests for MDR and XDR tuberculosis in smear-negative, HIV co-infected, and paediatric patients and non-sputum specimens

New therapies for MDR and XDR tuberculosis

- Facilitate research and development of new tuberculosis drugs
- Enhance clinical trials capacity and funding to:
  - Establish optimum treatment regimen with currently available second-line drugs
  - Assess efficacy of new drugs and regimens
  - Evaluate new diagnostic tests
- Develop new adjunct immunotherapies
- Streamline regulatory approval of new drugs and immunotherapies

Programmatic priorities and capacity building

- Improve second-line drug supply, quality, access, and cost in high-burden settings
- Improve reporting systems of diagnostic test results between laboratories and clinicians
- Develop and assess alternative care delivery strategies for MDR and XDR tuberculosis (eg, community-based treatment)
- Undertake active case finding for individuals at high risk of MDR and XDR tuberculosis (eg, close contacts)
- Improve legal frameworks to manage patients who do not respond to or default from treatment
- Create voluntary-stay isolation facilities in hospitals, communities, and hospices in high-burden settings

heavier than they are at present. The consequences will depend on the progress achieved in other areas. If no new and effective antituberculosis drugs are found, we face the prospect of returning to the preantibiotic era. If new drugs are developed, more efficient case management and health systems will need to be implemented to prevent emergence of resistance to the new drugs. Transmission of drug-resistant tuberculosis will continue if new rapid diagnostic drug-susceptibility tests are not widely deployed and if infection control in health facilities is not improved and implemented.

What countries need to do is clear—they have to prevent creation of drug resistance by ensuring that all patients with drug-susceptible tuberculosis are rapidly diagnosed and effectively treated. At the same time, they have to scale up diagnosis and treatment to at least 80% of cases of MDR tuberculosis and prevent transmission by implementing infection-control measures.[149] Moreover, countries—particularly India, China, and Russia—will need to take decisive action that involves improvements in the health system (eg, rational drug use, free care for treatment of MDR tuberculosis) and beyond, if they are to successfully scale up good-quality management of MDR tuberculosis to near universal access. The price of inaction, or failure, will be immense. Estonia, Latvia, and two Russian oblasts have shown, however, that even high and rising incidence rates of MDR tuberculosis can be reversed. As some countries slowly put together management programmes for MDR tuberculosis, we hope that this Series will create the awareness that is needed to stimulate a substantial acceleration of drug-resistant tuberculosis control efforts worldwide.

Contributors

NRG and PN were responsible for the conception, design, and initial draft of this report. All authors contributed to writing specific sections and participated in critical revision of the report.

Steering committee

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Conflicts of interest

JB has received consultancy fees from Otsuka Pharmaceutical Development and Commercialization. NRG, PN, KD, HSS, MZ, DvS, and PJ declare that they have no conflicts of interest.

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