Tuberculosis 2013: 5

Drug-resistant tuberculosis: time for visionary political leadership

Ibrahim Abubakar, Matteo Zignol, Dennis Falzon, Mario Raviglione, Lucica Ditiu, Susan Masham, Ifedayo Adetifa, Nathan Ford, Helen Cox, Stephen D Lawn, Ben J Marais, Timothy D McHugh, Peter Mwaba, Matthew Bates, Marc Lipman, Lynn Zijenah, Simon Logan, Ruth McNerney, Adam Zumla, Krishna Sarda, Payam Nahid, Michael Hoelscher, Michel Pletschette, Ziad A Memish, Peter Kim, Richard Hafner, Stewart Cole, Giovanni Battista Migliori, Markus Maeurer, Marco Schito, Alimuddin Zumla

Two decades ago, WHO declared tuberculosis a global emergency, and invested in the highly cost-effective directly observed treatment short-course programme to control the epidemic. At that time, most strains of *Mycobacterium tuberculosis* were susceptible to first-line tuberculosis drugs, and drug resistance was not a major issue. However, in 2013, tuberculosis remains a major public health concern worldwide, with prevalence of multidrug-resistant (MDR) tuberculosis rising. WHO estimates roughly 630 000 cases of MDR tuberculosis worldwide, with great variation in the frequency of MDR tuberculosis between countries. In the past 8 years, extensively drug-resistant (XDR) tuberculosis has emerged, and has been reported in 84 countries, heralding the possibility of virtually untreatable tuberculosis. Increased population movement, the continuing HIV pandemic, and the rise in MDR tuberculosis pose formidable challenges to the global control of tuberculosis. We provide an overview of the global burden of drug-resistant disease; discuss the social, health service, management, and control issues that fuel and sustain the epidemic; and suggest specific recommendations for important next steps. Visionary political leadership is needed to curb the rise of MDR and XDR tuberculosis worldwide, through sustained funding and the implementation of global and regional action plans.

Published **Online**
March 24, 2013
http://dx.doi.org/10.1016/S1473-3099(13)70030-6

This is the fifth in a **Series** of six papers about tuberculosis

Centre for Infectious Disease Epidemiology, Department of Infection and Population Health, University College London, London, UK (Prof I Abubakar FRCP); **Health Protection Agency, London, UK** (Prof I Abubakar); **Stop TB Department, WHO, Geneva, Switzerland** (M Zignol MD, D Falzon MD, Prof M Raviglione FRCP); **STOP TB Partnership, Geneva, Switzerland** (L Ditiu MD); **All Party Parliamentary Group on Global Tuberculosis, London, UK** (Baroness S Masham, S Logan MSc); **House of Lords, London, UK** (S Masham); **Medical Research Council, Banjul, The Gambia** (I Adetifa PhD); **Médecins Sans Frontières, Cape Town, South Africa** (N Ford PhD, H Cox PhD); **Centre for Infectious Disease Epidemiology and Research, University of Cape Town, Cape Town, South Africa** (N Ford, H Cox); **Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK** (S D Lawn FRCP, R McNerney PhD); **Sydney Emerging Infections and Biosecurity Institute, University of Sydney, Sydney, NSW, Australia** (B J Marais FCPaed); **Centre for Clinical Microbiology, Division of Infection and Immunity, University College London, London, UK** (Prof T D McHugh PhD, M Bates PhD, Prof Alimuddin Zumla FRCP); **University of Zambia-University College London Medical School (UNZA-UCLMS)**

Introduction

Tuberculosis is a leading cause of death by an infectious disease worldwide, despite global efforts and financial investment by governments and non-governmental organisations in disease-control programmes during the past 20 years.[1] In its 2012 global report on tuberculosis,[2] WHO estimates that 3·7% (range 2·1–5·2%) of new cases and 20% (range 13–26%) of previously treated cases have multidrug-resistant (MDR) tuberculosis (defined as tuberculosis caused by *Mycobacterium tuberculosis* isolates that are resistant to rifampicin and isoniazid). In many countries in eastern Europe and central Asia, 9–32% of new patients and more than 50% of previously treated patients have MDR tuberculosis.[2] After initial reports in 2006 from South Africa of extensively drug-resistant (XDR) tuberculosis (defined as tuberculosis caused by strains of *M tuberculosis* resistant to rifampicin, isoniazid, fluoroquinolones, and any of the second-line injectable drugs such as capreomycin, amikacin, and kanamycin),[3,4] the number of countries reporting cases of XDR tuberculosis has increased: 84 countries reported at least one case at the last count in 2011 (figure 1). Eastern European countries have the highest rates of drug-resistant tuberculosis worldwide, and most cases of MDR tuberculosis arise in populous Asian countries such as China, India, the Philippines, and Indonesia.

Although large gaps in our knowledge of the occurrence of MDR and XDR tuberculosis remain, much progress is being made in estimation of the burden of drug resistance through surveys and roll-out of rapid diagnostics in some countries. In 2011, nearly 60 000 cases of MDR tuberculosis were detected, treated, and notified.[2] Inappropriate

Key messages

- For many decades, the response to global tuberculosis by governments in both wealthy and disease-endemic countries has been complacent and politically neglectful
- Rising rates of multidrug-resistant and extensively drug-resistant tuberculosis threaten global control efforts in both developing and developed countries
- The development of new rapid diagnostics and tuberculosis drug pipelines need to be maintained and strengthened
- Rapid and accurate diagnosis of drug-resistant tuberculosis needs to be scaled up worldwide, and robust treatment programmes with quality assured drugs and patient support programmes should be provided
- The serious threat posed by drug-resistant tuberculosis needs to be acknowledged worldwide, before it rises to rates that overwhelm the health systems, as seen in several countries of the former Soviet Union
- Strong political commitment and adequate funding should underpin the implementation of a global strategy to tackle the wider societal and health-service determinants of multidrug-resistant and extensively drug resistant tuberculosis
- A major conceptual change and visionary global leadership are needed to move away from the conventional view that tuberculosis is only a disease of poor nations

Research and Training Project, University Teaching Hospital, Lusaka, Zambia (P Mwaba FRCP, Adam Zumla MD , M Bates); **Ministry of Health, Lusaka, Zambia** (P Mwaba); **Department of Respiratory Medicine, Royal Free Hospital NHS Foundation Trust, University College London, London, UK** (M Lipman FRCP); **University of Zimbabwe, College of Health Sciences, Harare, Zimbabwe** (Prof L Zijenah PhD); **School of Pharmacy, London, UK** (Adam Zumla); **India 800 Foundation, New Delhi, India** (K Sarda MD); **Division of Pulmonary and Critical Care, University of California, San Francisco, CA, USA** (P Nahid MD); **Department for Infectious Diseases and Tropical Medicine, Klinikum of the University of Munich, Munich, Germany** (Prof M Hoelscher FRCP); **Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland** (M Pletschette FRCP); **WHO Collaborating Centre for TB and Lung Diseases, Fondazione S Maugeri, Care and Research Institute, Tradate, Italy** (Prof G B Migliori FRCP); **Ministry of Health, Riyadh, Saudi Arabia** (Prof Z A Memish FRCP); **College of Medicine, Alfaisal University, Riyadh, Saudi Arabia** (Z A Memish); **Global Health Institute, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland** (Prof S Cole PhD); **Department of Microbiology, Karolinska Institute, Stockholm, Sweden** (Prof M Maeurer FRCP); **Henry M Jackson Foundation-Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA** (M Schito PhD); **and Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA** (P Kim MD, R Hafner MD)

Correspondence to:
Prof Alimuddin Zumla, Centre for Clinical Microbiology, Department of Infection, University College London Royal Free Campus, Royal Free Hospital, London NW3 2PF, UK
a.zumla@ucl.ac.uk

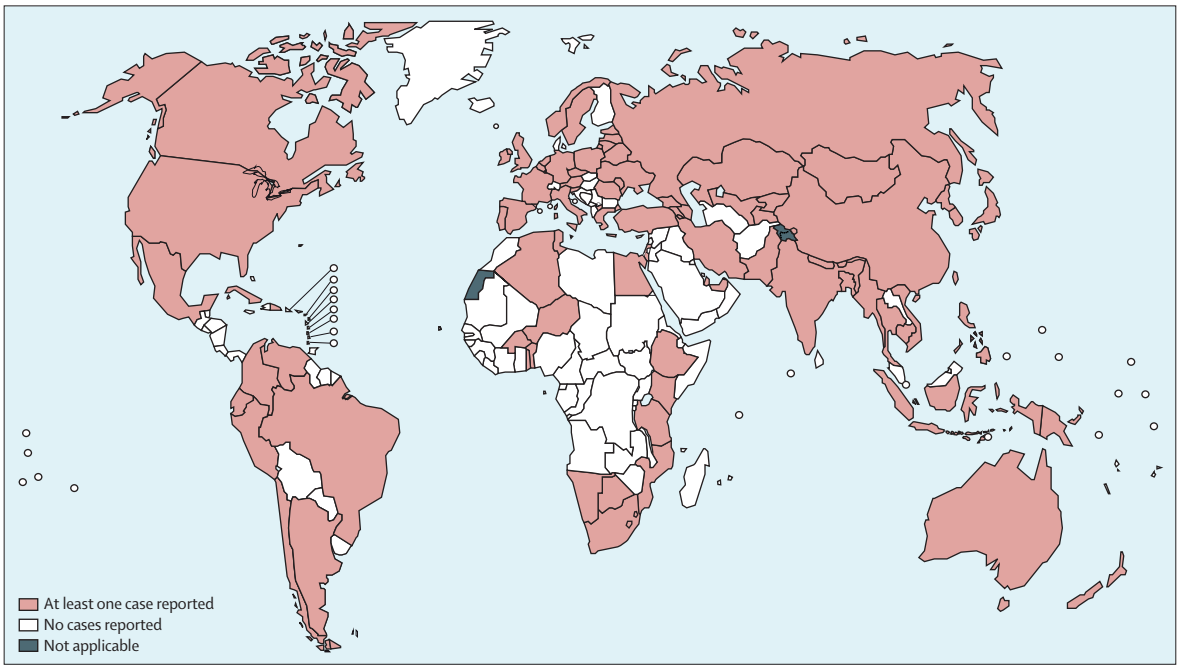

Figure 1: **Countries with at least one case of extensively drug-resistant tuberculosis by the end of 2011**
Reproduced from WHO's global tuberculosis report 2012,[2] by permission of the World Health Organization.

monotherapy and intermittent treatment are the main causes of drug resistance, and facilitate the selection and transmission of resistant strains of *M tuberculosis* within communities. Once MDR and XDR tuberculosis emerge in a population, several social, health service, management, and control issues help to transmit the disease within communities, health-care establishments, and congregate settings such as prisons and mines.

The widespread emergence of XDR tuberculosis could lead to virtually untreatable tuberculosis. With ease of international travel, and increased rates of MDR tuberculosis in eastern Europe, central Asia, and elsewhere, the threat and range of the spread of untreatable tuberculosis is very real.[5,6] Calls in 2012 to bring back sanatoria, indicate the desperate situation as perceived by practising physicians in Africa and Europe.[7] We provide an overview of the global burden of drug-resistant tuberculosis, and discuss the social, political, health service, management, and control issues that fuel transmission worldwide. We detail specific recommendations for the next steps needed to inform policy, establish research priorities, and ensure the best returns for investment in control of the disease.

The global burden of drug-resistant tuberculosis

In 2011, WHO estimated 12 million prevalent cases of tuberculosis worldwide,[2] of which about 630 000 (roughly 5%) were MDR tuberculosis (figure 2). Drug-resistance caused by primary transmission is a growing concern.[8] The frequency of MDR tuberculosis varies greatly between countries. In most resource-limited countries, data for drug resistance are collected through surveys of a representative sample of patients with the disease (table). Although nearly all countries with a high burden of tuberculosis and drug-resistant tuberculosis have information about prevalence of resistance to first-line drugs, this information might be old or not nationally representative. Unfortunately, because of insufficient diagnostic facilities, the number of MDR tuberculosis cases reported in 2011 represents only 19% of the estimated 440 000 cases of MDR tuberculosis in patients with pulmonary tuberculosis, and less than 10% in the two countries with the largest number of cases (China and India).[9]

In 2011, first-line drug-sensitivity testing was done in only a few patients worldwide: less than 4% of new bacteriologically confirmed cases and 6% of previously treated cases.[2] Data on the magnitude of drug resistance in children are scarce.[10] WHO estimates of MDR tuberculosis notification are made on the basis of either routine surveillance (for the few countries with data), or are modelled with data from countries that are regarded as similar.[2] The highest caseloads of MDR tuberculosis are reported in India, China, Russia, and South Africa, accounting for more than 60% of cases worldwide.[11] In 2007, a national survey estimating the incidence of drug-resistant tuberculosis in China showed that the country has a serious epidemic of drug-resistance, with one in ten patients estimated to have MDR tuberculosis.[8] In several eastern European and central Asian countries, such as Belarus, Kazakhstan, and regions of Russia such as Arkhangelsk Oblast, more than 30% of newly diagnosed patients with tuberculosis have MDR tuberculosis, suggesting the successful transmission of

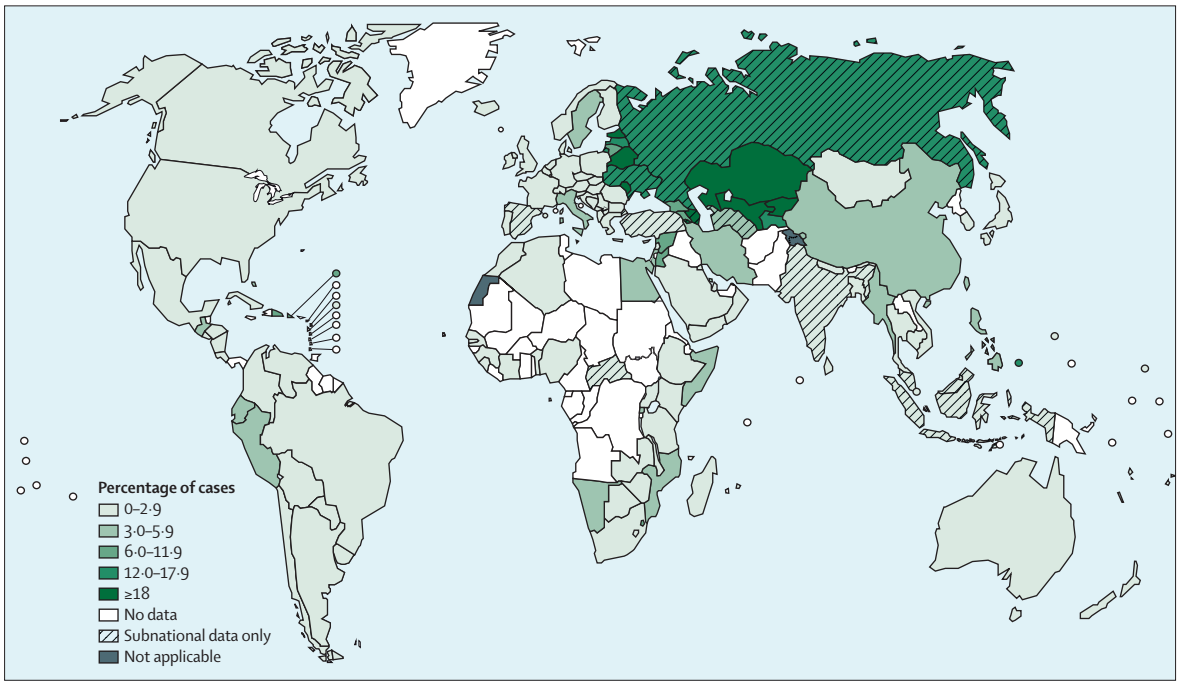

Figure 2: **Percentage of new tuberculosis cases with multidrug-resistant tuberculosis**
Based on the most recent year for which data have been reported, which varies among countries. Reproduced from WHO's global tuberculosis report 2012,[2] by permission of the World Health Organization.

drug-resistant *M tuberculosis* strains.[11] The levels of MDR tuberculosis are highest in previously treated cases (figure 3). Aside from MDR tuberculosis, the most severe drug resistance arises in eastern Europe and central Asia. Worldwide, 9% (95% CI 6·7–11·2) of patients with MDR tuberculosis have XDR tuberculosis, and 14·5% (11·6–17·4) have additional resistance to a fluoroquinolone—ie, pre-XDR tuberculosis. XDR and pre-XDR tuberculosis are underdetected in many countries.[2]

Although China and India are large emerging economies that have the resources to substantially reduce the prevalence of MDR tuberculosis, these countries have the highest number of MDR tuberculosis cases worldwide.[2] In 2000, the Chinese Government started to revitalise its tuberculosis programme; its acceptance of tuberculosis as a major health issue, and the subsequent strong political commitment have led to major successes in control of the disease.[12] In India's private sector, the national surveillance programme does not detect tuberculosis in many patients,[12] and the quality of diagnostic and treatment services by family doctors is a major issue. In December, 2012, doctors from Mumbai reported cases of totally drug–resistant tuberculosis (TDR),[13] which generated major political interest and concern. However, use of the term TDR is controversial since no reliable definition beyond XDR tuberculosis is practicable.[14–16] Tuberculosis has now been made a notifiable disease in India, laboratory and curative services have been strengthened, and efforts to increase private-sector participation in tuberculosis control have been stepped up.[17] A national drug resistance survey to measure the magnitude of drug-resistant tuberculosis in India has never been undertaken, although there are plans to conduct such a survey in 2013. Surveys in Andhra Pradesh, Gujarat, and Tamil Nadu states showed that up to 3% of new cases, and 13–17% of previously treated cases, were of MDR tuberculosis.[17] The first national survey of drug-resistance to measure the magnitude of drug-resistant tuberculosis across India is planned for this year.

15 of the 27 countries with the highest burden of MDR tuberculosis are in the WHO European region.[2] More than 80 000 cases of MDR tuberculosis occur in the region each year—almost a fifth of the world's total MDR tuberculosis burden.[18] The findings of a 2012 study showed that in Minsk, Belarus, almost 50% of reported tuberculosis cases, and 75·76% of previously treated cases in 2011, were multidrug resistant.[19] Precise data for MDR and XDR tuberculosis in Europe are not available because most eastern European countries have poor diagnostic services and suboptimum surveillance systems to detect drug-resistant tuberculosis.[20]

Global implications of the rising MDR tuberculosis levels in high-incidence countries

These developments are of importance outside the borders of high-incidence countries. Many countries with low incidence of tuberculosis, including western Europe and the USA, receive millions of travellers from India, Europe, Africa, and China. Many travellers settle in the countries they move to, but maintain regular

	Total confirmed cases of MDR tuberculosis*	Estimated cases of MDR tuberculosis among notified cases of tuberculosis
Worldwide		
2005	11 988	..
2009	46 897	..
2010	54 987	..
2011	61 690†	310 000 (220 000–400 000)
Africa		
2005	2445	..
2009	10 741	..
2010	9340	..
2011	12 384	45 000 (7900–82 000)
The Americas		
2005	4427	..
2009	2884	..
2010	2661	..
2011	3474	5900 (3400–8400)
Eastern Mediterranean		
2005	350	..
2009	496	..
2010	886	..
2011	841	17 000 (0–38 000)
Europe		
2005	4347	..
2009	28 157	..
2010	33 863	..
2011	33 984	76 000 (64 000–87 000)
Southeast Asia		
2005	68	..
2009	2560	..
2010	3942	..
2011	6615	89 000 (76 000–100 000)
Western Pacific		
2005	351	..
2009	2059	..
2010	4295	..
2011	4392	78 000 (60 000–95 000)

Data in parantheses are the range. MDR=multidrug resistant.*Includes cases with unknown previous treatment history. †Total number reported to have started appropriate treatment is 55 597 (<20% of all estimated MDR tuberculosis cases; treatment success rates for programmatic management of MDR tuberculosis are in the order of 50%). Data taken from reference 2.

Table: **Global estimates of multidrug-resistant tuberculosis by world region, 2005–11**

contact with their country of origin. In the UK, particularly London, the rates of tuberculosis have risen over the past 20 years,[21] especially in deprived groups.[22] The 2012 UK annual tuberculosis report[23] showed that the number of cases resistant to any first-line drug rose from 206 (6·4%) in 2000, to 431 (8·4%) in 2011.[23] The number of cases of MDR tuberculosis increased from 28 in 2000, to 81 in 2011; in 2011 alone, the number increased by 26%. Most cases of MDR tuberculosis are in patients born outside the UK, which suggests importation from abroad including eastern Europe, sub-Saharan Africa,[24] and the Indian subcontinent.[23] However, in London, isoniazid resistance is more common in UK-born patients than in non-UK-born patients because of an outbreak that has continued for more than a decade.[25] Cases of XDR tuberculosis pose challenges to clinical services.[26,27] Since 1995, 24 cases of XDR tuberculosis have been reported. The highest number of cases (six) was reported in 2011.

Although several countries with a low incidence of tuberculosis use pre-entry screening of immigrants to detect the disease,[27,28] these programmes focus on the identification of active tuberculosis cases. Even with entry measures to detect and treat latent tuberculosis infection, present prophylactic treatment with isoniazid or rifampicin, or both, would likely be useless in most individuals infected with strains of MDR tuberculosis. This issue should be addressed in the country of origin, and high-burden countries should be supported in their effort to control drug-resistant tuberculosis. As the global economic influence of China and India expands, these countries should contribute to drug-resistant tuberculosis control in poorer countries.

Social, health service, management, and control issues

Factors driving drug-resistant tuberculosis

MDR and XDR tuberculosis arise because of inadequate or interrupted administration of first-line treatment.[29–31] If patients are given too few drugs, for too short a period, or given drugs to which infecting strains are partly drug resistant, the resistant strains are favoured and will eventually predominate in the body.[32] However, once drug-resistant strains of *M tuberculosis* have been selected and occur in a community, they are directly transmitted to others. Many factors then propagate the spread of drug-resistant tuberculosis, and lead to widespread emergence of XDR tuberculosis. These factors include: lack of rapid, cheap, and accessible point-of-care diagnostic methods to rapidly diagnose drug-resistant tuberculosis as early as possible;[33] insufficient second-line drug options; poor patient adherence to prolonged treatment; inadequate case holding; poor treatment strategies;[31] social stigma; deprivation and poverty; absence of community engagement; insufficient political will; and inadequate resources.[34] The complex interaction between the host and *M tuberculosis*, affected by concomitant infections[35] and wider social determinants, compound these structural factors. The genetic makeup of some *M tuberculosis* strains could increase risk of drug resistance.[36,37] In several countries, primary transmission of MDR and XDR tuberculosis have been well documented,[38–42] and have drawn attention to the crucial need to implement infection control precautions in congregate settings.[40,43]

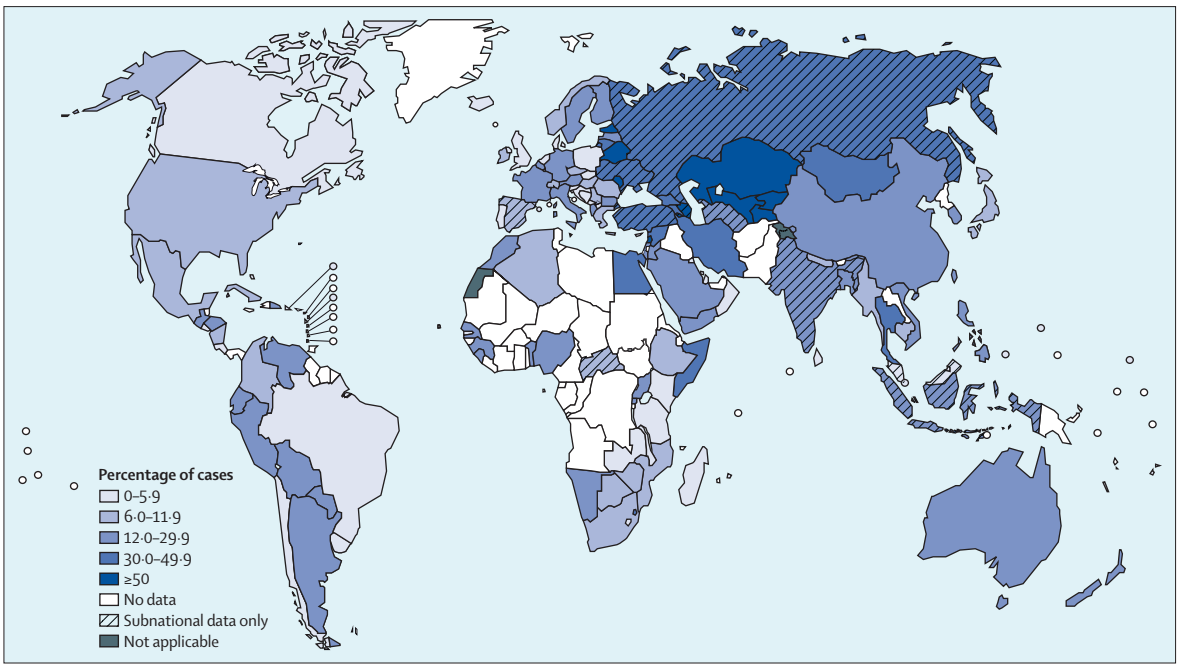

Figure 3: **Percentage of previously treated tuberculosis cases with multidrug-resistant tuberculosis**
*Based on the most recent year for which data have been reported, which varies among countries. Reproduced from WHO's global tuberculosis report 2012,[2] by permission of the World Health Organization.

Diagnostic and treatment challenges

The prevalence of MDR and XDR tuberculosis and the size of the recent increase are likely to be underestimated because of insufficient laboratory facilities for drug susceptibility testing in most countries with high tuberculosis burden. Unfortunately, most laboratories are ill equipped to detect and diagnose the extent of drug resistance, which represents a major bottleneck for continuous surveillance of drug-resistant tuberculosis based on routine drug-sensitivity testing of all microbiologically confirmed cases. Because most national programmes fail to diagnose and treat MDR and XDR tuberculosis, reported data are often unrepresentative; only 65 countries and three territories are deemed to report representative and good quality data.[2]

Diagnostic constraints are the first barrier to treatment; therefore, efforts to scale up the availability of drug-sensitivity testing should be the first step to improve treatment. The second barrier is the access to a quality assured treatment programme once the diagnosis has been established. In most high-burden settings, treatment programmes for drug-resistant tuberculosis are insufficient. Several countries have developed plans for the up-scaling of treatment programmes for MDR tuberculosis; however, these plans rely on international donor funding, have been negatively affected by the funding shortfall at the Global Fund,[44] and are not sustainable in the long term at present funding amounts. To contain the spread of drug-resistant tuberculosis would need a consistent supply of second-line drugs supported by adequate resources to ensure treatment uptake, prevention, management of adverse effects, and halting of transmission worldwide. The Global Plan to Stop TB 2011–15 set a target to successfully treat more than 75% of MDR tuberculosis cases by 2015. Unfortunately, only 30 of the 107 countries that reported outcome data for MDR tuberculosis treatment for 2011 reached this goal.[2] The universal availability of drug-sensitivity testing and scaling up of MDR tuberculosis treatment and control programmes need serious political commitment from national and international leaders, continued innovation, and implementation of bold and pragmatic approaches.

For the **WHO Global Plan to Stop TB 2011–15** see http://www.stoptb.org/global/plan/

Management of children

Epidemiologically, MDR tuberculosis in children is particularly important because tuberculosis in children is usually acquired because of recent exposure, suggesting continuing community transmission. Findings from several case series have shown that children are likely to develop MDR and XDR tuberculosis in settings where transmission is poorly controlled.[45] These children are at an additional disadvantage because bacteriological sampling to diagnose drug-resistance is difficult. The pill burden is huge, and age-appropriate paediatric formulations are unavailable for most second-line drugs.[46] Adverse effects, especially hearing loss induced by injectable agents, are a major concern in young and developing children (<16 years of age).[47] However, excellent outcomes can be achieved, with generally better treatment

outcomes than those achieved in adults.[48] Unfortunately, access to treatment is severely restricted, and few MDR treatment programmes offer treatment to young children.

Inadequate infection control

Insufficient infection control is a major cause of transmission of drug-resistant tuberculosis[49,50]—eg, the 2006 XDR tuberculosis outbreak in a high-HIV prevalence setting in Kwazulu Natal, South Africa, where infection control practices vary widely.[40,51] Attempts to control MDR tuberculosis worldwide need to include robust infection control measures in all health-care settings through containment of aerosol transmission. At a community level, the most effective strategy is early diagnosis and prompt initiation of appropriate treatment, although creative strategies to reduce transmission within identified transmission hotspots should be considered in high-burden communities.

Social and health service determinants

Health system failures generally underpin the emergence of drug resistance in a population. Factors such as poor diagnostic facilities, insufficient regulation of access to antibiotics, poor implementation of the directly observed treatment short-course programme, and lack of tuberculosis drugs lead to monotherapy and intermittent treatment. Factors related to society and health services that underlie the epidemic differ by region—eg, in Russia, high rates of tuberculosis in prisons with poor quality management contributed to the emergence of MDR transmission, with subsequent spread into the community.[52] In India, huge variations in the quality of management practices in public-sector and private-sector facilities probably play a major part in the emergence of drug-resistant tuberculosis.[53] Transmission, including nosocomial spread, has contributed to the rise in drug-resistant tuberculosis in China[8] and South Africa.[51] By contrast, properly resourced and organised health systems are less likely to generate drug-resistant tuberculosis, as shown by the low rates of MDR tuberculosis in patients in western Europe and North America.[54,55] The highest burden of drug resistance arises in countries that can afford first-line drugs, but have weak health-care systems that are likely to generate MDR and XDR tuberculosis.[2] This situation explains the relative over-representation in Brazil, Russia, India, China, and the emerging economies in the Asia-Pacific region.

Once drug resistance emerges, its subsequent transmission is facilitated by a complex interplay of several factors. Individuals living in poverty in overcrowded conditions, homeless people, alcohol and drug users, incarcerated individuals, and other susceptible groups are more likely to sustain transmission.[19,52,56] An additional factor is insufficient community engagement in tuberculosis control.[12] Countries with well run programmes supported by high-level political commitment, early diagnosis, and access to quality assured drugs tend to have better treatment outcomes,[57] although more operational data are needed to guide best practice.

In New York City, between 1979, and 1992, the number of patients with tuberculosis tripled, and the proportion of patients with MDR tuberculosis more than doubled.[55,56] Tuberculosis had resurfaced as a major public health problem because of reduced government funding of tuberculosis programmes and associated deterioration of tuberculosis public health services, compounded by an increasing number of poor communities and the advent of the HIV/AIDS epidemic. The detection of the large outbreak of MDR tuberculosis in New York City in the early 1990s, and MDR tuberculosis in prison guards, led to substantial political attention focused on tuberculosis resulting in resurgence of governmental financial and political commitment to the eradication of tuberculosis.[58,59] Nationwide, declining tuberculosis trends in the USA were reversed, and tuberculosis incidence increased by 20% between 1985 and 1992. This reversal resulted in 52 100 excess cases of tuberculosis during this time.[60] Subsequent political commitment and substantial investment have brought down tuberculosis rates in the USA to the lowest recorded so far.[61]

However, outbreaks of the disease among disadvantaged people continue to challenge control efforts[38,62]—eg, the outbreak of tuberculosis at a homeless shelter in Illinois in January, 2010. Since September, 2011, 28 outbreak-associated cases have been reported in shelter guests, suggesting continuing *M tuberculosis* transmission.[63] Unfortunately, outside the USA, western Europe, and Australia, major reservoirs of active tuberculosis exist. Since the 1980s, some European countries have also encountered a resurgence of tuberculosis[21]—eg among disadvantaged communities in the Netherlands. The Dutch Government pledged to control tuberculosis and drug-resistant tuberculosis with large financial investment into disease services. Tuberculosis control and surveillance is now an integral part of the health-care system in the Netherlands, and the country has one of the lowest tuberculosis rates in Europe.[64]

Although the rate of MDR tuberculosis is high in Estonia, the country has shown what is achievable with a coherent national programme underpinned by political will.[65] The centralised national tuberculosis-control programme supported specific measures including targeting of interventions to susceptible groups such as alcoholics, drug users, and their families; minimisation of drug misuse by stopping sale of antituberculosis drugs in pharmacies; high-quality training for medical staff; and reliable supply of quality assured drugs. The replication of this model in other larger countries could decrease the current burden, but would need increased resources and commitment. A comparative study of WHO Green Light Committee programmes in five resource-poor settings, including Estonia, Latvia, Russia, and Peru, shows that cure rates in patients with MDR tuberculosis can be similar to those noted in richer countries.[57]

Limitations of MDR and XDR tuberculosis management

Although 310 000 cases of MDR tuberculosis were estimated to occur in patients with pulmonary tuberculosis in 2011, only 55 597 patients (<20% of estimated cases) were started on second-line treatment.[2] This massive treatment gap shows that not enough is being done to help individual patients, and to contain the spread of MDR tuberculosis.

Regimens for treatment of MDR tuberculosis are very long (≥20 months), poorly tolerated, expensive, and substantially less effective than first-line treatment of drug-susceptible tuberculosis.[66,67] WHO reports show that only 48% of the more than 25 000 patients with MDR tuberculosis from 107 countries who started MDR tuberculosis treatment in 2009 completed their treatment successfully because of deaths (15%), treatment interruptions (14%), treatment failure (9%), and insufficient data (14%).[2] An individual meta-analysis of 9153 patients with MDR tuberculosis from 32 observational cohorts reported similarly dismal findings (success 54%, default 23%, failure or relapse 8%, and death 15%).[68] Patients with strains of tuberculosis that had acquired additional resistance to second-line injectable drugs, to fluoroquinolones, or both (XDR tuberculosis)[69] had poor outcomes, with treatment success rates of less than 50%,[70–73] which is similar to outcomes seen in the pre-chemotherapy era. These poor outcomes show the exhaustion of treatment options in patients who often have longstanding disease—although many patients with XDR tuberculosis have no history of previous tuberculosis treatment, suggesting failures in infection control.

Access to treatment is poor for drug-resistant tuberculosis;[74] however, in some high-burden countries, treatment success rates have improved, and cure rates of more than 75% are achievable.[75] A study by Van Deun and colleagues[76] in 2010, showed excellent results in patients with MDR tuberculosis from Bangladesh who were treated for 9 months with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout the treatment period, supplemented by protionamide, kanamycin, and high-dose isoniazid during an intensive phase of a minimum of 4 months. The STREAM trial is assessing this regimen. Improved use of existing drugs could provide opportunities to improve control programmes.

New drug development and treatment regimen approaches

Several national and international partners—eg, the Global Alliance for TB Drug Development (TB Alliance), the US National Institutes of Health (NIH), the US Centers for Disease Control and Prevention (CDC), and the European and Developing Countries Clinical Trials Partnership (EDCTP)—have started animal and human studies to test the efficacy of drug combinations rather than individual drugs. These studies aim to shorten the time taken to derive an entirely new treatment regimen for both drug-susceptible and drug-resistant tuberculosis.[77] However, this approach will probably take 8–10 years because of regulatory, study design, and research grant-awarding processes. Efforts through the clinical trial plan funded by the NIH, and the PANACEA consortium funded by EDCTP with adaptive designs could make the process quicker. Although this work has tremendous long-term value, it does little to address the immediate needs of drug-resistant patients who are underserved by present treatments. The recent US Food and Drug Administration accelerated approval of bedaquiline, the soon expected approval of delamanid by the European Medicines Agency, and the advanced development of drugs such as PA-824 (TB Alliance) beg the question: how should we use these new drugs in the treatment of drug-resistant tuberculosis?[78] Clinical trials such as the MARVEL study (ACTG 5319) in development by the AIDS Clinical Trials Group in collaboration with the TB Alliance, will investigate treatment regimens that include both old and new drugs, and will provide answers within the next 3–4 years. The dual goals of developing completely new regimens and optimising existing or partly new regimens are not incompatible, and the poor treatment success and high mortality associated with drug-resistant tuberculosis treatment means that both approaches should be taken as a matter of urgency.

For the **TB Alliance trials** see http://www.tballiance.org/

For the **MARVEL study** see http://www.resisttb.org

The beneficial effects of pharmaceutical companies and public–private partnerships providing drugs and access to drug information cannot be overstated and should be encouraged. The gap between clinical efficacy and programme effectiveness is well recognised,[79] and is especially important for second-line drugs because of the specific challenges associated with the delivery of complex combinations of drugs in a routine programmatic setting. Cross-resistance is more likely with repurposed drugs; however, drug resistance can occur when new antituberculosis agents, both novel compounds and repurposed drugs, are introduced into new combination treatment regimens. These are the first antibiotics that have been developed specifically against tuberculosis in nearly half a century. Cross-resistance is also likely when drugs with other indications repurposed as antituberculosis agents such as linezolid, meropenem, trimethoprim, and thioridazine are eventually introduced into tuberculosis treatment regimens.[80–86] Linezolid and clofazimine are increasingly used for MDR and XDR tuberculosis.

For the **STREAM trial** see http://www.controlled-trials.com/ISRCTN78372190/STREAM

The mechanisms to ensure new tuberculosis drugs are preserved for MDR treatment need to be considered in view of the need to assess all new drugs for use in shortening of drug-sensitive tuberculosis treatment. Parallel approaches are needed to implement regimen change in a way that takes into account both the short-term priority to improve treatment of drug-resistant tuberculosis for patients in need today, and the longer-term goal to develop and test the best regimen combinations for patients with drug-susceptible and

drug-resistant tuberculosis. Novel approaches and partnerships are needed to assess new drugs as part of regimens for drug-resistant tuberculosis. Examples of new partnerships include collaborations between the US CDC, the NIH, and the Bill & Melinda Gates Foundation, coordination of activities between the US and European clinical trials networks, and the support by the Bill & Melinda Gates Foundation for the Critical Path to TB Drug Regimens.[87] Until now, the resources needed to adequately treat patients with MDR and XDR tuberculosis have been inadequate, and have been dealt with as secondary to the broader goals of global tuberculosis control. With fewer than one in five patients with MDR tuberculosis being treated with second-line drugs,[2] and only around half of these patients achieving treatment success, the need for new treatment approaches has never been greater.

New and repurposed drugs need to be delivered through programmatic management of drug-resistant tuberculosis.[66] Treatment success is substantially compromised because of toxicity and complexity,[88,89] which leads to high rates of treatment discontinuation. Data from a recent systematic review[72] suggest that several programmatic factors significantly predict low default levels, including the use of standardised regimens and the flexible provision of treatment support and observation. The treatment of patients in small cohorts was also associated with improved adherence, presumably because programmes could devote more individualised care and support to patients.[72] These findings show the increased importance of integrated and well functioning control programmes to prevent the formation and limit the transmission of drug-resistant tuberculosis. Therefore, programme scale-up should be accompanied by planning and provision of adequate resources to ensure successful implementation.

Adverse events cause patients to default from treatments, and underscore the concern that the ability of patients to tolerate prescribed treatment regimens, and maintain the entire treatment course, is of fundamental importance to overall treatment success.[90] Shortening of treatment duration for drug-resistant tuberculosis is likely to reduce default, improve adherence, and benefit scale-up of treatment in many high-burden settings. A new regimen, which includes new drugs, but excludes some backbone drugs because of tolerability issues, could cure most patients with much shorter durations, albeit risking relapse in a small percentage of patients.[80–86] To effectively address these various needs will probably need the availability of several effective agents with low toxicity and quality assured use of the new drugs for drug-sensitive and drug-resistant tuberculosis in well resourced programmes.

Along with scale-up, simple diagnostic methods to detect drug-resistant tuberculosis are needed to ensure that patients are not put on failing drug regimens, or on regimens in which only one of the drugs in the combination is effective, resulting in functional monotherapy and the acquisition of additional resistance or amplification. This need for simple diagnostic laboratory methods is particularly important with the introduction of new compounds. Responsible access programmes with broad national and international acceptance should be rapidly designed to protect new drugs from inappropriate use that would quickly lead to the emergence of resistant strains.[80,91]

***Panel:* Recommendations**

- International and national policymakers should ensure that the global funding shortfall to support tuberculosis control is urgently met
- The plan to scale up rapid diagnostics to detect tuberculosis, multidrug-resistant, and extensively drug-resistant tuberculosis should be accelerated, and be accompanied by relevant training and support to ensure appropriate management of patients
- Effective infection control practices in health-care facilities should be implemented, and opportunities to reduce transmission risk within high-burden communities should be explored
- Quality assured second-line drugs for treatment using the WHO recommended regimen should be available worldwide, and should be accompanied by a clear plan for the rationale use of existing and new drugs
- National programmes should investigate wider social determinants of drug-resistant tuberculosis, and establish locally tailored solutions including direct observation of treatment, socioeconomic support, and a patient-centred approach to care
- Research activity should increase to ensure the development of new drugs and innovative approaches to clinical trials, accurate and cheap diagnostics for first-line and second-line drug resistance, and an effective vaccine against tuberculosis
- Global policy formulation and investment priorities should be focused on evidence-based approaches including those that tackle health-system failures; adequate support mechanisms for national programmes to implement WHO recommendations should be made available
- All countries should have quality assured surveillance, as recommended by the WHO Global Task Force on TB Impact Measurement, to inform control measures

Improved implementation

Many expert groups and WHO reports[66,92,93] have drawn attention to major issues in financing of tuberculosis control efforts, universal health coverage, the engagement of all care providers including private-for-profit practitioners, optimisation of disease management and care, improvement of laboratory capacity, ensuring of access to quality assured drugs, restriction of drug availability, and adequate infection control.[94–96] Many calls for action have not been heeded, despite evidence for an increase in MDR and XDR tuberculosis. The plans by European governments to address MDR tuberculosis[18,97] need to be accompanied by sustained implementation of these efforts among all involved. Thoughtful political decision making and investment of government resources on the basis of expert advice and scientific evidence is more likely to have lasting effects on the growing problem of drug-resistant tuberculosis than sporadic bursts of focused investments in response to predictable outbreaks of MDR tuberculosis.

Search strategy and selection criteria

We searched PubMed, Embase, and Google Scholar from Jan 1, 1990, to Nov 30, 2012, for all publications in English with the terms "tuberculosis", "drug resistance", "*Mycobacterium tuberculosis*", "multidrug resistant", "extensively drug resistant", "MDR", "XDR", "TDR", "determinants", "transmission", "etiology", and "epidemiology". We also searched from relevant references within previous reviews identified with this strategy.

The ineffectiveness of national diagnostic, treatment, and surveillance efforts has allowed the continued transmission of MDR tuberculosis, and the emergence of XDR tuberculosis. To prevent further cases of MDR and XDR tuberculosis, a radical change in political and scientific thinking, and the implementation of specific measures worldwide are needed (panel). The global economic crisis and reduced investments in health services threaten national tuberculosis programmes and the gains made in global tuberculosis control. The world needs to acknowledge the serious threat of drug-resistant tuberculosis, before it overwhelms health systems, as is being seen in several countries of the former Soviet Union.[19]

Conclusions

Major conceptual change and visionary global leadership are needed to move away from the conventional view that tuberculosis is only a disease of poor nations. United and motivated advocacy from tuberculosis care, control, research, and community participants is needed to raise awareness that the increase of MDR tuberculosis is a real and present danger for the developed nations and should be addressed now with effective planning and resource allocation. We need to learn from recent examples: drug-resistant tuberculosis will not subside until the problem is controlled globally.[72,97,98] Wealthy nations cannot ignore the worrying rise of MDR and XDR tuberculosis.

Contributors

Al Z, IA, and MS wrote the first and final drafts. All authors contributed to the writing of the Series paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

Al Z, PM, MB, and MH are supported by the European and Developing Countries Clinical Trials Partnership (grants REMOX, PANACEA, and TB-NEAT), Netherlands. AZ receives support from the UK Medical Research Council (MRC); UBS Optimus Foundation, Switzerland; University College London Hospitals (UCLH) Comprehensive Biomedical Research Centre, UK; and the UCLH National Health Service Foundation Trust, UK. IA is supported by the UK National Institute for Health Research and the UK MRC. SDL is supported by the Wellcome Trust, UK. The opinions expressed herein are those of the authors and should not be construed as representing the official views or policies of the US Department of Health and Human Services or the authors' national governments. Nor does mention of trade names, commercial practices, or organisations imply endorsement by the US Government or the authors' national governments. DF, MR, and MZ are staff members of WHO. The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.

References

1 Raviglione M, Marais B, Floyd K, et al. Scaling up interventions to achieve global tuberculosis control: progress and new developments. *Lancet* 2012; **379:** 1902–13.
2 WHO. Global tuberculosis report 2012. Geneva, Switzerland: World Health Organization, 2012.
3 WHO. Extensively drug-resistant tuberculosis (XDR-TB): recommendations for prevention and control. *Wkly Epidemiol Rec* 2006; **81:** 430–32.
4 Centers for Disease Control and Prevention (CDC). Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. *MMWR Morb Mortal Wkly Rep* 2006; **55:** 301–05.
5 Dara M, De Colombani P, Petrova-Benedict R, et al. Minimum package for cross-border TB control and care in the WHO European region: a Wolfheze consensus statement. *Eur Respir J* 2012; **40:** 1081–90.
6 Blumberg HM, Migliori GB, Ponomarenko O, Heldal E. Tuberculosis on the move. *Lancet* 2010; **375:** 2127–29.
7 Dheda K, Migliori GB. The global rise of extensively drug-resistant tuberculosis: is the time to bring back sanatoria now overdue? *Lancet* 2012; **379:** 773–75.
8 Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. *N Engl J Med* 2012; **366:** 2161–70.
9 World Health Organization. Tuberculosis MDR-TB and XDR-TB 2011 progress report. http://www.who.int/tb/challenges/mdr/factsheet_mdr_progress_march2011.pdf (accessed Feb 15, 2013).
10 Zignol M, Sismanidis C, Falzon D, Glaziou P, Dara M, Floyd K. Multidrug-resistant tuberculosis in children: evidence from global surveillance. *Eur Respir J* 2012; published online Dec 6. DOI:10.1183/09031936.00175812.
11 Zignol M, Van Gemert W, Falzon D, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bull World Health Organ* 2012; **90:** 111–19.
12 Bhatter P, Chatterjee A, Mistry N. The dragon and the tiger: realties in the control of tuberculosis. *Interdiscip Perspect Infect Dis* 2012; **2012:** 625459.
13 Udwadia ZF, Amale RA, Ajbani KK, Rodrigues C. Totally drug-resistant tuberculosis in India. *Clin Infect Dis* 2012; **54:** 579–81.
14 Migliori GB, Centis R, D'Ambrosio L, et al. Totally drug-resistant and extremely drug-resistant tuberculosis: the same disease? *Clin Infect Dis* 2012; **54:** 1379–80.
15 WHO. "Totally drug-resistant" tuberculosis: a WHO consultation on the diagnostic definition and treatment options. March 21–22, 2012. http://www.who.int/entity/tb/challenges/xdr/Report_Meeting_totallydrugresistantTB_032012.pdf (accessed Nov 19, 2012).
16 Velayati AA, Masjedi MR, Farnia P, et al. Emergence of new forms of totally drug-resistant tuberculosis bacilli: super extensively drug-resistant tuberculosis or totally drug-resistant strains in Iran. *Chest* 2009; **136:** 420–25.
17 Government of India. TB India 2012. Revised national TB control programme. Annual status report. March 2012. http://tbcindia.nic.in/pdfs/TB%20India%202012-%20Annual%20Report.pdf (accessed Nov 14, 2012).
18 WHO. Roadmap to prevent and combat drug-resistant tuberculosis. The consolidated action plan to prevent and combat multidrug and extensively drug-resistant tuberculosis in the WHO European Region, 2011–2015. Copenhagen: World Health Organisation, 2011. http://www.euro.who.int/__data/assets/pdf_file/0011/148376/RC61_InfDoc3.pdf (accessed Nov 12, 2012).
19 Skrahina A, Hurevich H, Zalutskaya A, et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J* 2012; **39:** 1425–31.
20 Jenkins HE, Plesca V, Ciobanu A, et al. Assessing spatial heterogeneity of MDR-TB in a high burden country. *Eur Respir J* (in press).
21 Abubakar I, Lipman M, Anderson C, Davies P, Zumla A. Tuberculosis in the UK—time to regain control. *BMJ* 2011; **343:** d4281.
22 French CE, Kruijshaar ME, Jones JA, Abubakar I. The influence of socio-economic deprivation on tuberculosis treatment delays in England, 2000–2005. *Epidemiol Infect* 2009; **137:** 591–96.

23 Pedrazzoli D, Fulton N, Anderson L, Lalor M, Abubakar I, Zenner D. Tuberculosis in the UK: 2012 report. London: Health Protection Agency, July 2012. http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1317134916916 (accessed Nov 14, 2012).

24 Cooke GS, Beaton RK, Lessells RJ, et al. International spread of MDR TB from Tugela Ferry, South Africa. *Emerging Infect Dis* 2011; **17:** 2035–37.

25 Ruddy MC, Davies AP, Yates MD, et al. Outbreak of isoniazid resistant tuberculosis in north London. *Thorax* 2004; **59:** 279–85.

26 Abubakar I, Moore J, Drobniewski F, et al. Extensively drug-resistant tuberculosis in the UK: 1995 to 2007. *Thorax* 2009; **64:** 512–15.

27 Lords Hansard Statement. Immigration: pre-entry screening for tuberculosis. 2010. http://www.publications.parliament.uk/ (accessed Jan 18, 2013).

28 Lowenthal P, Westenhouse J, Moore M, Posey DL, Watt JP, Flood J. Reduced importation of tuberculosis after the implementation of an enhanced pre-immigration screening protocol. *Int J Tuberc Lung Dis* 2011; **15:** 761–66.

29 Balaji V, Daley P, Anand AA, et al. Risk factors for MDR and XDR-TB in a tertiary referral hospital in India. *PLoS One* 2010; **5:** e9527.

30 Van der Werf MJ, Langendam MW, Huitric E, Manissero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J* 2012; **39:** 1511–19.

31 Zhao P, Li XJ, Zhang SF, Wang XS, Liu CY. Social behaviour risk factors for drug resistant tuberculosis in mainland China: a meta-analysis. *J Int Med Res* 2012; **40:** 436–45.

32 Van der Werf MJ, Langendam MW, Huitric E, Manissero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. *Eur Respir J* 2012; **39:** 1511–19.

33 Weyer K, Mirzayev F, Migliori G, et al. Rapid molecular TB diagnosis: evidence, policy-making and global implementation of Xpert(R)MTB/RIF. *Eur Respir J* 2012; published online Nov 22. DOI:10.1183/09031936.00157212.

34 Marais BJ, Raviglione MC, Donald PR, et al. Scale-up of services and research priorities for diagnosis, management, and control of tuberculosis: a call to action. *Lancet* 2010; **375:** 2179–91.

35 Cohen T, Van Helden PD, Wilson D, et al. Mixed-strain *Mycobacterium tuberculosis* infections and the implications for tuberculosis treatment and control. *Clin Microbiol Rev* 2012; **25:** 708–19.

36 Caws M, Thwaites G, Stepniewska K, et al. Beijing genotype of *Mycobacterium tuberculosis* is significantly associated with human immunodeficiency virus infection and multidrug resistance in cases of tuberculous meningitis. *J Clin Microbiol* 2006; **44:** 3934–39.

37 Hu Y, Ma X, Graviss EA, Wang W, Jiang W, Xu B. A major subgroup of Beijing family *Mycobacterium tuberculosis* is associated with multidrug resistance and increased transmissibility. *Epidemiol Infect* 2011; **139:** 130–38.

38 Barry PM, Gardner TJ, Funk E, et al. Multistate outbreak of MDR TB identified by genotype cluster investigation. *Emerging Infect Dis* 2012; **18:** 113–16.

39 Cohen T, Murray M, Abubakar I, et al. Multiple introductions of multidrug-resistant tuberculosis into households, Lima, Peru. *Emerging Infect Dis* 2011; **17:** 969–75.

40 Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet* 2006; **368:** 1575–80.

41 Kruijshaar ME, Watson JM, Drobniewski F, et al. Increasing antituberculosis drug resistance in the United Kingdom: analysis of National Surveillance Data. *BMJ* 2008; **336:** 1231–34.

42 Gavín P, Iglesias MJ, Jiménez MS, et al. Long-term molecular surveillance of multidrug-resistant tuberculosis in Spain. *Infect Genet Evol* 2012; **12:** 701–10.

43 Wells CD, Cegielski JP, Nelson LJ, et al. HIV infection and multidrug-resistant tuberculosis: the perfect storm. *J Infect Dis* 2007; **196** (suppl 1): S86–S107.

44 The Lancet. The Global Fund: a bleak future ahead. *Lancet* 2010; **376:** 1274.

45 Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev* 2011; **12:** 31–38.

46 Seddon JA, Thee S, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in children treated for multidrug-resistant tuberculosis. *J Infect* 2012; published online Sep 6. DOI:S0163-4453(12)00253-8. 10.1016/j.jinf.2012.09.002.

47 Seddon JA, Hesseling AC, Schaaf HS. Retooling existing tuberculosis drugs for children. *Clin Infect Dis* 2012; **56:** 167–68.

48 Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes of children with multi-drug resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012; **12:** 449–56.

49 Centers for Disease Control (CDC). Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons—Florida and New York, 1988–1991. *MMWR Morb Mortal Wkly Rep* 1991; **40:** 585–91.

50 Nodieva A, Jansone I, Broka L, Pole I, Skenders G, Baumanis V. Recent nosocomial transmission and genotypes of multidrug-resistant *Mycobacterium tuberculosis*. *Int J Tuberc Lung Dis* 2010; **14:** 427–33.

51 Farley JE, Tudor C, Mphahlele M, et al. A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *Int J Tuberc Lung Dis* 2012; **16:** 82–89.

52 Olson S, English RA, Guenther RS, Claiborne AB. The new profile of drug-resistant tuberculosis in Russia: a global and local perspective. Summary of a joint workshop. Washington DC; National Academies Press (US), 2011.

53 Olson S, English RA, Guenther RS, Claiborne AB. Facing the reality of drug-resistant tuberculosis in India: challenges and potential solutions. Summary of a joint workshop by the Institute of Medicine, the Indian National Science Academy, and the Indian Council of Medical Research. Washington DC; National Academies Press (US), 2012.

54 European Centre for Disease Prevention and Control, WHO Regional Office for Europe. Mar 19, 2012. Tuberculosis surveillance and monitoring in Europe 2012. http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=841 (accessed Aug 29, 2012).

55 Centers for Disease Control and Prevention (CDC).Trends in tuberculosis—United States, 2011. *MMWR Morb Mortal Wkly Rep* 2012; **61:** 181–85.

56 Keshavjee S, Gelmanova IY, Pasechnikov AD, et al. Treating multidrug-resistant tuberculosis in Tomsk, Russia: developing programs that address the linkage between poverty and disease. *Ann N Y Acad Sci* 2008; **1136:** 1–11.

57 Nathanson E, Lambregts-van Weezenbeek C, Rich ML, et al. Multidrug-resistant tuberculosis management in resource-limited settings. *Emerg Infect Dis* 2006; **12:** 1389–97.

58 Paolo WF, Nosanchuk JD. Tuberculosis in New York city: recent lessons and a look ahead. *Lancet Infect Dis* 2004; **4:** 287–93.

59 Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City-turning the tide. *N Engl J Med* 1995; **333:** 229–33.

60 Cantwell MF, Snider DE Jr, Cauthen GM, Onorato IM. Epidemiology of tuberculosis in the United States, 1985 through 1992. *JAMA* 1994; **272:** 535–39.

61 Hinman AR, Hughes JM, Berreth DA, et al. National action plan to combat multidrug-resistant tuberculosis. *MMWR Recomm Rep* 1992; **41:** 5–48.

62 Mitruka K, Oeltmann JE, Ijaz K, Haddad MB. Tuberculosis outbreak investigations in the United States, 2002–2008. *Emerging Infect Dis* 2011; **17:** 425–31.

63 Centers for Disease Control and Prevention (CDC). Tuberculosis outbreak associated with a homeless shelter-Kane County, Illinois, 2007–2011. *MMWR Morb Mortal Wkly Rep* 2012; **61:** 186–89.

64 Veen J, Migliori GB, Raviglione M, et al. Harmonisation of TB control in the WHO European region: the history of the Wolfheze Workshops. *Eur Respir J* 2011; **37:** 950–59.

65 Blöndal K, Viiklepp P, Blöndal P, Altraja A. Countrywide management of pulmonary tuberculosis reverses increasing incidence. *Int J Tuberc Lung Dis* 2011; **15:** 892–98.

66 WHO. Guidelines for the programmatic management of drug resistant tuberculosis. 2011 update. http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf (accessed Oct 18, 2012).

67 Falzon D, Jaramillo E, Schünemann HJ, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. *Eur Respir J* 2011; **38:** 516–28.

68 Ahuja SD, Ashkin D, Avendano M, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012; **9:** e1001300.

69 Falzon D, Gandhi N, Migliori GB, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. *Eur Respir J* 2012; published online Oct 25. DOI:10.1183/09031936.00134712.

70 Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS One* 2009; **4:** e6914.

71 Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infect Dis* 2009; **9:** 153–61.

72 Tocsec A, Cox H, Du Cross P, Cooke G, Fox N. Strategies for reducing treatment default in drug-resistant tuberculosis: systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2013; **17:** 299–307.

73 Migliori GB, Sotgiu G, Gandhi NR, et al. Drug resistance beyond XDR-TB: results from a large individual patient data meta-analysis. *Eur Respir J* 2012; published online Oct 11. DOI:10.1183/09031936.00136312.

74 Keshavjee S, Farmer PE. Picking up the pace—scale-up of MDR tuberculosis treatment programs. *N Engl J Med* 2010; **363:** 1781–84.

75 Nathanson E, Lambregts-van Weezenbeek C, Rich ML, et al. Multidrug-resistant tuberculosis management in resource-limited settings. *Emerging Infect Dis* 2006; **12:** 1389–97.

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

77 Spigelman M, Woosley R, Gheuens J. New initiative speeds tuberculosis drug development: novel drug regimens become possible in years, not decades. *Int J Tuberc Lung Dis* 2010; **14:** 663–64.

78 Voelker R. MDR-TB has new drug foe after fast-track approval. *JAMA* 2013; **309:** 430.

79 Nunn A. What is the role of clinical trials for the treatment of tuberculosis and what are the alternatives? *Int J Tuberc Lung Dis* 2010; **14:** 380–81.

80 Diacon AH, Pym A, Grobusch M, et al. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. *N Engl J Med* 2009; **360:** 2397–405.

81 Skripconoka V, Danilovits M, Pehme L, et al. Delamanid improves outcomes and reduces mortality for multidrug-resistant tuberculosis. *Eur Respir J* 2012; published online Sept 27. DOI:10.1183/09031936.00125812.

82 Diacon AH, Dawson R, Von Groote-Bidlingmaier F, et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet* 2012; **380:** 986–93.

83 De Lorenzo S, Alffenaar JW, Sotgiu G, et al. Efficacy and safety of meropenem/clavunate added to linezolid containing regimens in the treatment of M/XDR-TB. *Eur Respir J* 2012; published online Sept 20. DOI:10.1183/09031936.00124312.

84 Sotgiu G, Centis R, D'Ambrosio L, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MDR-TB and XDR-TB: systematic review and meta-analysis. *Eur Respir J* 2012; **40:** 1430–42.

85 Alsaad N, Van Altena R, Pranger AD, et al. Evaluation of co-trimoxazole in treatment of multidrug-resistant tuberculosis. *Eur Respir J* 2012; published online Oct 25. DOI:10.1183/09031936.00114812.

86 Amaral L, Udwadia Z, Abbate E, Van Soolingen D. The added effect of thioridazine in the treatment of drug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2012; **16:** 1706–08.

87 Peloquin CA, Berning SE, Nitta AT, et al. Aminoglycoside toxicity: daily versus thrice-weekly dosing for treatment of mycobacterial diseases. *Clin Infect Dis* 2004; **38:** 1538–44.

88 Törün T, Güngör G, Ozmen I, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005; **9:** 1373–77.

89 Bloss E, Kuksa L, Holtz TH, et al. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. *Int J Tuberc Lung Dis* 2010; **14:** 275–81.

90 Mitnick CD, Castro KG, Harrington M, Sacks LV, Burman W. Randomized trials to optimize treatment of multidrug-resistant tuberculosis. *PLoS Med* 2007; **4:** e292.

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

92 WHO. Towards universal access to diagnosis and treatmnent of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO Progress Report 2011. Geneva: World Health Organization, 2011.

93 Nathanson E, Nunn P, Uplekar M, et al. MDR tuberculosis—critical steps for prevention and control. *N Engl J Med* 2010; **363:** 1050–58.

94 Raviglione MC, Lange C, Migliori GB. Preventing and managing antimicrobial resistance: imperative for chest physicians. *Eur Respir J* 2011; **37:** 978–81.

95 Migliori GB, Langendam MW, D'Ambrosio L, et al. Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. *Eur Respir J* 2012; **40:** 814–22.

96 Sotgiu G, D'Ambrosio L, Centis R, et al. TB and M/XDR-TB infection control in European TB reference centres: the Achilles' heel? *Eur Respir J* 2011; **38:** 1221–23.

97 Abubakar I, Dara M, Manissero D, Zumla A. Tackling the spread of drug-resistant tuberculosis in Europe. *Lancet* 2012; **379:** 21–23.

98 Keshavjee S, Farmer PE. Tuberculosis, drug resistance, and the history of modern medicine. *N Engl J Med* 2012; **367:** 931–36.