

# Extensively drug-resistant tuberculosis

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Extensively drug-resistant (XDR) tuberculosis is defined as disease caused by *Mycobacterium tuberculosis* with resistance to at least isoniazid and rifampicin, any fluoroquinolone, and at least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin). The definition has applicable clinical value and has allowed for more uniform surveillance in varied international settings. Recent surveillance data have indicated that the prevalence of tuberculosis drug resistance has risen to the highest rate ever recorded. The gold standard for drug-susceptibility testing has been the agar proportion method; however, this technique requires several weeks for results to be determined. More sensitive and specific diagnostic tests are still unavailable in resource-limited settings. Clinical manifestations, although variable in different settings and among different strains, have in general shown that XDR tuberculosis is associated with greater morbidity and mortality than non-XDR tuberculosis. The treatment of XDR tuberculosis should include agents to which the organism is susceptible, and should continue for a minimum of 18–24 months. However, treatment continues to be limited in tuberculosis-endemic countries largely because of weaknesses in national tuberculosis health-care models. The ultimate strategy to control drug-resistant tuberculosis is one that implements a comprehensive approach incorporating innovation from the political, social, economic, and scientific realms.

## Introduction

Extensively drug-resistant (XDR) tuberculosis has received substantial attention in recent years, both from the general public and scientific communities.<sup>1,2</sup> Although clinical and basic-science research has led to an increased understanding of drug-resistant strains, far more comprehensive efforts have been advocated by various groups in the public-health arena.<sup>3–5</sup> Despite the keen awareness the epidemic has received, the prevalence of XDR tuberculosis continues to rise. A report published by WHO in February, 2008, shows that the number of cases of drug-resistant tuberculosis has reached the highest level ever recorded.<sup>6</sup>

From the advent of tuberculosis chemotherapy in the 1940s, hints of resistance were evident. When Selman Waksman accepted the Nobel Prize in 1952 for his laboratory's discovery of streptomycin, he claimed the drug would lead the path to the elimination of "The Great White Plague".<sup>7,8</sup> Such statements were premature—strains of streptomycin-resistant *Mycobacterium tuberculosis* were found within months of the drug's widespread use.<sup>9</sup> In fact, the classic 1948 British Medical Research Council (BMRC) trial that investigated the efficacy of streptomycin monotherapy showed that most patients who were treated with the drug developed resistant strains.<sup>10</sup>

In the same year as the discovery of streptomycin, Jorgen Lehman discovered para-aminosalicylic acid (PAS; now known as aminosalicylic acid), but without the acclaim that Waksman received.<sup>11,12</sup> The BMRC concluded that combination treatment with PAS and streptomycin was more effective than treatment with either agent alone.<sup>13</sup> Therefore, there were indications as early as the 1950s that treatment strategies with concurrent use of multiple drugs were necessary to minimise the generation of drug-resistant organisms.

As the tuberculosis chemotherapy era evolved, increasing cases of drug resistance continued to occur

mainly as a result of inadequate regimens and non-adherence to therapy.<sup>3</sup> Researchers initially suspected that these resistant organisms had reduced fitness and thus could be classified as being less virulent.<sup>14,15</sup> This assumption was reversed in the 1990s with the rise in multidrug-resistant (MDR) tuberculosis—ie, *M tuberculosis* resistant to at least rifampicin plus isoniazid.<sup>16</sup> Substantial attention was focused upon New York City (NY, USA) where a virulent and transmissible strain had spread among immunocompromised populations.<sup>17,18</sup> With an effective public-health response, both the epidemic and the public interest into the disease seemed to diminish. However, awareness of tuberculosis drug resistance was refocused with a study presented in August, 2006, at the XVI International AIDS Conference in Toronto, Canada, which described an epidemic of XDR tuberculosis in a rural hospital in KwaZulu-Natal Province, South Africa.<sup>19</sup>

## Definition

The term XDR tuberculosis was first developed by the US Centers for Disease Control and Prevention (CDC) in March, 2005.<sup>20</sup> In October, 2005, it was introduced into the public realm at the 36th Union World Conference on Lung Health in Paris, France.<sup>21,22</sup> 6 months later, in March, 2006, CDC's *Morbidity and Mortality Weekly Report* published the original definition of XDR tuberculosis. At that time it was characterised as *M tuberculosis* with resistance to at least isoniazid and rifampicin among the first-line tuberculosis drugs and resistance to at least three of the six main classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and aminosalicylic acid).<sup>23</sup>

This definition was subsequently revised in October, 2006, during the first meeting of the WHO Global XDR-TB Task Force. The classification, which continues to be accepted, requires resistance of *M tuberculosis* to at least isoniazid and rifampicin, any fluoroquinolone, and at

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least one of three injectable second-line drugs (amikacin, capreomycin, or kanamycin).<sup>24</sup> The revision was made to facilitate reproducibility of drug-susceptibility testing and to focus attention on drugs accessible in resource-limited settings.<sup>4</sup> Moreover, the classification has also been shown to have value in its ability to predict poorer outcomes.<sup>25</sup> This practical definition, with operational and clinical value in both resource-rich and resource-limited settings, has allowed for more uniform surveillance in varied international settings.<sup>26</sup>

### Epidemiology

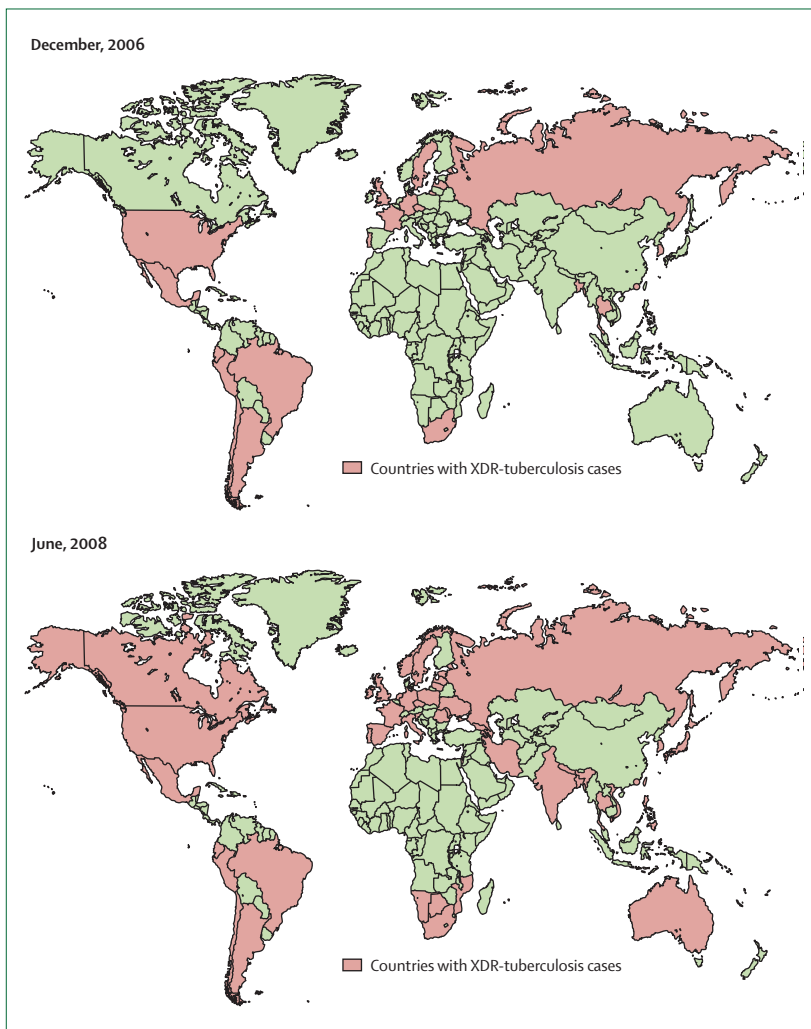
In the early 1990s, with the rise in MDR tuberculosis cases, WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD) established the Global Project on Anti-tuberculosis Drug Resistance

Surveillance.<sup>27</sup> One goal of the project was to develop guidelines to assess the extent of drug resistance through a standardised methodology. Such standards were intended to assist in policy development for national MDR-tuberculosis treatment programmes.<sup>28</sup> One of the most important outcomes of the project was the formation of an international quality assurance programme supervised by supranational reference laboratories (SRLs).<sup>29</sup> There are currently 26 SRLs that assist over 100 national laboratories in six continents by standardising culture and drug-susceptibility techniques. However, in tuberculosis-endemic regions such as southern Africa, there is only one SRL (Pretoria, South Africa).<sup>30</sup>

In 2000, the Stop TB Partnership's Green Light Committee (GLC) was created to provide access to preferentially priced second-line drugs to combat the rise in MDR tuberculosis.<sup>5</sup> The GLC systematically reviews new and ongoing programmes, approves the use of quality-assured second-line antituberculosis drugs, and provides technical assistance to programmes so that they can fully integrate drug-resistant tuberculosis treatment into their overall tuberculosis control strategies.<sup>31</sup> During assistance of national MDR-tuberculosis treatment programmes, the GLC encountered several cases of drug-resistant tuberculosis that were consistent with XDR-tuberculosis definitions. To determine the rate of XDR tuberculosis, CDC and WHO assessed 17 690 *M tuberculosis* isolates collated by 25 SRLs from 2000–04.<sup>23</sup> The study found that 20% of the isolates met MDR-tuberculosis criteria and 2% were classifiable as XDR tuberculosis. Population-based assessment showed that 4%, 15%, and 19% of XDR-tuberculosis cases were obtained from the USA, South Korea, and Latvia, respectively.<sup>23</sup>

Although the rate of XDR-tuberculosis cases was notably high in eastern Europe and Asia, little information could be discerned regarding the rates in Africa because of a lack of available data. The number of tuberculosis cases in sub-Saharan Africa has increased markedly in the past decade, largely as a result of the HIV epidemic.<sup>6,25</sup> WHO estimates that between 1990 and 2005, the average incidence of tuberculosis in the area doubled from 149 to 343 per 100 000 population.<sup>32</sup> In most of these countries, over 30% of patients with active tuberculosis are co-infected with HIV.<sup>32</sup> In areas of Lesotho, almost 90% of patients with tuberculosis also have HIV infection.<sup>33</sup> Despite the high prevalence of HIV/tuberculosis co-infection, the penultimate global resistance survey undertaken by WHO/IUATLD (1999–2002) measured MDR-tuberculosis rates of only 0.8–2.6% in the sub-Saharan African region.<sup>34</sup>

The true impact of drug-resistant tuberculosis in sub-Saharan Africa became evident with a report from a rural hospital in Tugela Ferry, KwaZulu-Natal Province, South Africa.<sup>19,35</sup> The study showed that of the 1539 individuals tested for tuberculosis from January, 2005, to March, 2006, 542 had at least one culture that was positive for *M tuberculosis*. Of these 542 patients with confirmed



**Figure 1: Countries with XDR-tuberculosis cases in December, 2006, and June, 2008**

The USA, a country with a low tuberculosis prevalence, recently reclassified 1.9% of MDR-tuberculosis cases as XDR tuberculosis. Of the six countries in Africa able to test for drug resistance, all had documented cases of XDR tuberculosis. Investigations of several tuberculosis-endemic countries, notably China, have not shown any cases of XDR tuberculosis. The data likely underestimate the true worldwide occurrence of the disease. Data adapted from reference 6.

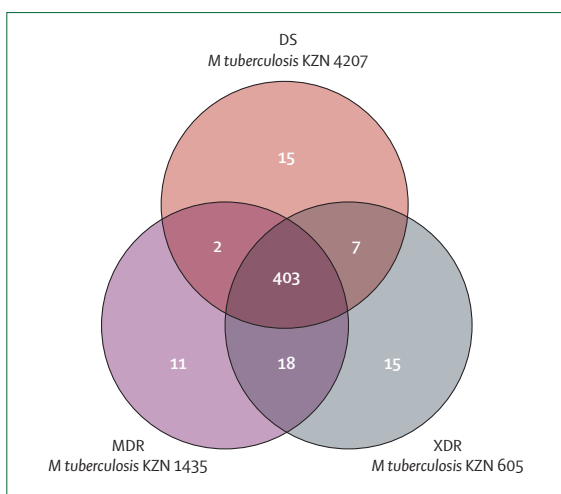
tuberculosis, 53 had XDR tuberculosis. The median time of death from sputum collection was 16 days (range 2–210 days) for the 52 of 53 patients who died. Concern for nosocomial infection was triggered by the findings that 26 (55%) of 47 patients with XDR tuberculosis had never been previously treated for tuberculosis and 28 (67%) of 42 had reported a recent stay in hospital before their tuberculosis diagnosis.

Factors that have fuelled this South African epidemic include ineffective tuberculosis treatment in the context of a high prevalence of HIV, lack of proper diagnostic testing, and poor infection control practices.<sup>23,36,37</sup> The effects of such universally prevalent factors were noted in the fourth report of the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance released in February, 2008 (figure 1).<sup>6</sup> Previous reports were released in 1997, 2000, and 2004, containing statistics from 35, 58, and 77 countries, respectively. The latest report contains information from 2002–07 on 91577 patients from 93 settings in 81 countries and two Special Administrative Regions of China. The report is far more comprehensive because of the inclusion of several countries with a high prevalence of tuberculosis and the representation of more than 35% of the worldwide total of new smear-positive tuberculosis cases. The occurrence of MDR tuberculosis has reached its highest level, with cases reported in a record 45 countries. In South Africa, Tomsk Oblast (Russian Federation), and Estonia—all countries with a high burden of tuberculosis—5.7%, 6.6%, and 23.7% of all MDR-tuberculosis cases were XDR, respectively. However, the reported rate of drug resistance in several tuberculosis-endemic regions, such as southern Africa, might be inaccurate because of lack of access to the proper laboratory tools for reliable diagnosis of second-line drug resistance.<sup>6</sup> Only six countries in Africa—the region with the highest incidence of tuberculosis—were able to test for XDR tuberculosis. However, the report did conclusively show a rise in MDR tuberculosis cases in this region, and thus valid considerations about the future rise in XDR tuberculosis may be inferred.<sup>38</sup>

### Mechanisms of resistance and fitness in XDR tuberculosis

The basis of tuberculosis drug resistance is the selection of bacterial mutants with innate resistance to chemotherapy.<sup>39,40</sup> Epidemics of drug-resistant disease can be generated by three interrelated mechanisms: (1) conversion of wildtype pan-susceptible strains to drug-resistant strains during treatment (acquired resistance); (2) increasing development of resistance in drug-resistant strains because of inappropriate chemotherapy (amplified resistance); and (3) transmission of drug-resistant cases (transmitted resistance).<sup>41</sup>

Acquired and amplified drug resistance are the primary means by which tuberculosis drug-resistant strains have been generated. However, the key determinant that has



**Figure 2:** Venn diagram depicting the number of genetic differences between drug-susceptible tuberculosis, MDR tuberculosis, and XDR tuberculosis for three KwaZulu-Natal (KZN) clinical tuberculosis isolates

XDR tuberculosis is shown to have 15 unique distinct single nucleotide polymorphisms (SNPs). A limited number of SNPs exist among the strains. MDR tuberculosis has 11 unique SNPs compared with drug-susceptible (DS) tuberculosis. XDR tuberculosis has 15 unique SNPs compared with MDR tuberculosis and DS tuberculosis. Image reproduced with permission from the Broad Institute.<sup>43</sup>

#### Panel 1: Single nucleotide polymorphisms of the KwaZulu-Natal strain that are unique to XDR tuberculosis

##### Mutation (annotation)

- A90V (DNA gyrase subunit A *gyrA*)
- L25I (transmembrane transport protein *mmpL13a*)
- Y207Y (arylsulfatase *atsD* [aryl-sulfate sulphohydrolase])
- D441G (DNA-directed RNA polymerase beta subunit *rpoB*)
- L458P (DNA-directed RNA polymerase beta subunit *rpoB*)
- I1112T (DNA-directed RNA polymerase beta subunit *rpoB*)
- A1401G (ribosomal RNA 16S *rrs*)
- L275P (hypothetical protein)
- V188A (conserved integral membrane protein)
- A84A (30S ribosomal protein S11 *rpsK*)
- D64E (hypothetical protein)
- G418W (PPE family protein)

The twelve single nucleotide polymorphisms listed are protein-coding mutations. Some mutations involve genes well-known to be involved in antibiotic resistance such as *gyrA* (encoding DNA gyrase, fluoroquinolone resistance) and *rpoB* (encoding the RNA polymerase  $\beta$  subunit, rifampicin resistance). Others may involve genes involved in membrane transport or cell wall synthesis (ie, *mmpL13a*), which could be associated with drug target modification or with antimicrobial accumulation. Several genes remain uncharacterised and hence may offer clues towards the elucidation of new antibiotic resistance mechanisms. Panel adapted from reference 43.

led to the exponential rise in XDR-tuberculosis cases is likely to have been transmitted resistance. The role of transmitted resistance can be elucidated by noting the clonal strains evident in tuberculosis outbreaks. The MDR-tuberculosis outbreak in the early 1990s in New York City, fuelled by the HIV epidemic and urban settings, was primarily associated with a clinically virulent strain of Beijing/W genotype.<sup>17,42</sup> Moreover, 39 (85%) of 46 isolated XDR-tuberculosis strains in the Tugela Ferry outbreak in South Africa belonged to the KwaZulu-Natal (KZN) genotypic family of strains.<sup>35</sup> The Broad Institute (Cambridge, MA, USA) has sequenced three KZN clinical isolates from Tugela Ferry: (1) drug-susceptible tuberculosis; (2) MDR tuberculosis; and (3) XDR tuberculosis (figure 2 and panel 1).<sup>43</sup> The KZN family was first described to have resistance to first-line tuberculosis treatments in 1996.<sup>44</sup> It is suspected that this strain has accumulated resistance to several second-line drugs within just 5 years.<sup>45,46</sup> However, a countrywide study in South Africa (which notably excluded the KwaZulu-Natal Province) isolated seven different XDR-tuberculosis genotype families of which the Beijing genotype was the most common.<sup>47</sup>

The transmission of drug-resistant tuberculosis largely depends on the virulence of the mutated organism.<sup>48–50</sup> Mutations may alter gene products that affect the organism's virulence and therein its reproductive fitness.<sup>14,39</sup> Even if negative fitness costs are apparent, compensatory mutations can occur that restore fitness potential.<sup>51–53</sup> Mathematical modelling has allowed for theoretical assessment of the contribution of microbial fitness to the transmission of drug-resistant strains. Blower and Chou<sup>41</sup> analysed the evolution of “hot zones” (areas that have an MDR-tuberculosis prevalence of more than 5%) and showed a high rate of drug-resistant tuberculosis can occur even if the MDR strains are less fit than the wildtype strains.<sup>41</sup> The study inferred that prediction of future drug-resistant tuberculosis transmission requires equal measurement of not only fitness, but also amplification probability, case-finding, and cure rates. These factors are more dependent on tuberculosis control strategies and less a function of biological potential.

Cohen and Murray<sup>54</sup> also developed a mathematical model of the emergence of MDR tuberculosis based on the assumption that drug-resistant strains have heterogeneous fitness. The model showed that even when the average microbial fitness is low and a properly functioning tuberculosis control programme is in place, a small population of drug-resistant strains might emerge from the background of drug-susceptible and less fit MDR-tuberculosis strains. The difference in the fitness between the circulating strains becomes the primary determinant of the future burden of transmitted MDR tuberculosis.

Ultimately, the only definitive way of determining bacterial fitness would be to observe its effects.<sup>55,56</sup> In animal modelling studies, certain endemic clinical

isolates and related recombinant *M tuberculosis* strains have shown a variety of phenotypic outcomes including that of hypervirulence.<sup>57–59</sup> Hence, the issue of the degree to which drug resistance alters the fitness of *M tuberculosis* remains an open research question.

## Diagnostics

Preventing transmission of *M tuberculosis* relies on an accurate and rapid diagnosis.<sup>60</sup> A key barrier to tuberculosis control is that current case detection rates are low.<sup>61</sup> WHO set a global target to identify 70% of new smear-positive tuberculosis cases in 2005; however, this goal was not met.<sup>62</sup> With the global rise in XDR tuberculosis, a key aspect of its initial containment will be the identification of the disease itself.

The currently available diagnostic tests for active and latent tuberculosis are a mixture of old and new technologies. Tuberculin skin testing, clinical signs, and sputum microscopy continue to be used in all international settings.<sup>63–65</sup> The sensitivity of such techniques is limited in those with HIV infection or extrapulmonary dissemination.<sup>66,67</sup> The proportion of cases of smear-negative pulmonary tuberculosis in HIV-positive patients with tuberculosis ranged from 24% to 61% in a systematic review of studies describing the pattern of HIV prevalence in patients with tuberculosis.<sup>68</sup> Recently developed diagnostic tests that are more sensitive and specific rely on such methodologies as nucleic-acid amplification and interferon- $\gamma$  release assays, the latter being the subject of much recent research, yet remarkable for their inability to distinguish latent from active infection.<sup>69,70</sup> The limited laboratory capacities and staff training in resource-limited settings currently preclude the widespread use of such advanced diagnostics.<sup>70,71</sup>

The gold standard for drug-susceptibility testing has been the agar proportion method on Lowenstein-Jensen medium and Middlebrook 7H11 agar.<sup>72</sup> Although this form of testing can detect drug resistance to standard tuberculosis drugs, the reproducibility and accuracy of drug-susceptibility testing for second-line antituberculosis drugs remains questionable. The technique can take up to 4–8 weeks for finalised results. The inability to detect drug resistance rapidly could increase the likelihood of an isolate developing resistance through ineffective chemotherapy.<sup>73</sup> Such delays in diagnosis might also enhance the likelihood of transmission of resistant strains and the potential to produce clusters of secondary infections—ie, transmission in nosocomial or congregate settings.<sup>41,74</sup> Drug-susceptibility testing can be accelerated by focusing on the identification of rifampicin resistance and using that as a surrogate marker for potential resistance to other drugs.<sup>75,76</sup> Line-probe hybridisation assays in conjunction with nucleic-acid amplification offer a promising route to rapid identification of isoniazid and rifampicin resistance and are currently being studied by the WHO SRLs.<sup>77</sup> One particular commercially

available line-probe assay, the Hain Genotype MTBDRplus, has proven itself as a reliable and rapid diagnostic test.<sup>78</sup> The assay, which can be used with culture-based isolates and directly on smear-positive sputum samples, has been successfully tested in high-tuberculosis burden settings and expanded testing is now occurring in several resource-limited settings.<sup>33</sup> Another advantage of the Hain Genotype MTBDRplus is that the cost is less than US\$3 per test.<sup>77</sup>

Other molecular methods that could be used in the detection of drug-resistant tuberculosis strains<sup>72,75</sup> include the molecular beacon assay, luciferase mycobacteriophage strategy, dideoxy fingerprinting, direct sequencing of PCR products, and heteroduplex analysis. These methods are generally described as providing results rapidly and being highly sensitive. However, they are also labour intensive and costly compared with the agar proportion method.

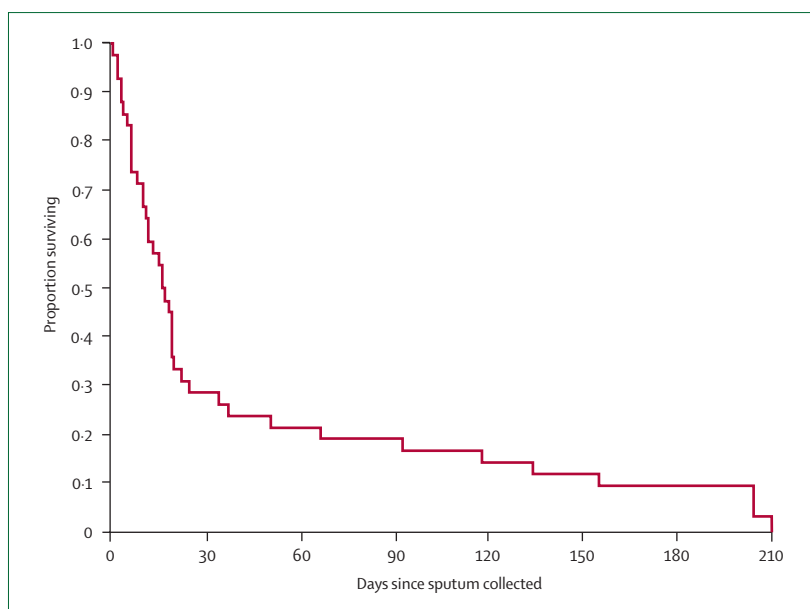
One particular form of testing that has received much attention because of its potential application in resource-limited settings is the microscopic-observation drug-susceptibility (MODS) assay. By use of liquid culture medium, the MODS assay depends on the microscopic observation of a cording pattern (ie, the aggregation of tuberculosis bacilli that form serpentine structures) that is unique to *M tuberculosis*.<sup>79</sup> A median time of only 7 days (IQR 6–8 days) is needed for both disease identification and drug-susceptibility testing.<sup>80</sup> The approximate cost for the MODS assay is less than \$2 per test.<sup>81</sup>

### Clinical course of XDR tuberculosis

The poorer clinical outcomes associated with MDR tuberculosis compared with fully drug-susceptible tuberculosis have been well documented. MDR tuberculosis is associated with a high mortality in individuals with HIV or other immunosuppressive conditions.<sup>82</sup> The even poorer clinical outcomes associated with XDR tuberculosis were initially documented in the first CDC report of the disease in 2006.<sup>23</sup> During 1993–2002, patients with XDR tuberculosis were 64% more likely to die during treatment than patients with MDR tuberculosis.<sup>21,23</sup>

An appreciation for the substantial morbidity and mortality associated with co-infection with XDR tuberculosis and HIV was heightened by the findings in KwaZulu-Natal (figure 3).<sup>35</sup> 52 (98%) of 53 patients with XDR tuberculosis died during the study period. 44 of the 53 XDR-tuberculosis patients agreed to HIV testing and all tested positive for co-infection. The median CD4 count at the time of sputum collection was 63 cells per  $\mu\text{L}$ .

HIV/XDR tuberculosis co-infection has also been reported in patient populations in Asia.<sup>83</sup> The first published case reports of XDR tuberculosis in India noted that among 54 HIV-positive patients, 4 (33%) of 12 diagnosed MDR tuberculosis cases were reclassified as XDR tuberculosis after drug-susceptibility testing.<sup>84</sup> In the study, the mean CD4 cell count was 102 cells per  $\mu\text{L}$  and all the patients with XDR tuberculosis died within



**Figure 3: Survival after sputum collection in patients with XDR tuberculosis**  
Kaplan-Meier survival curve depicting the rapid mortality among 52 of 53 patients with XDR tuberculosis and confirmed dates of death in an outbreak in a rural area in KwaZulu-Natal, South Africa. Reproduced from reference 35.

2–6 months of diagnosis. A recent study from South Korea described the clinical outcomes of 43 HIV-uninfected patients with XDR tuberculosis.<sup>85</sup> Treatment failure, defined as a lack of culture conversion, was noted in 19 (44%) patients with XDR tuberculosis compared with 46 (27%) non-XDR-tuberculosis patients. Moreover, the mortality was 14% in those with XDR tuberculosis and 8% in those with MDR tuberculosis.

Studies in Europe have also shown that the diagnosis of XDR tuberculosis is an independent predictor for treatment failure. A five-fold increase in the risk of death in patients with XDR tuberculosis was seen in a study done in Germany and Italy.<sup>86</sup> XDR-tuberculosis patients required longer hospital stays and longer treatment durations, mainly because of clinical complications (ie, sputum conversion). Regardless of how one defines clinical outcomes, the results in all settings indicate a higher probability of treatment failure and mortality with XDR tuberculosis.<sup>87–90</sup>

### Treatment

Strategies to treat drug-resistant tuberculosis can be categorised as either standardised or individualised.<sup>91</sup> Standardised regimens are determined on representative drug-resistance surveillance data of specific regions. Individualised regimens are more specific in that they take into account previous antituberculosis treatments and drug-susceptibility testing of the particular isolate.<sup>31</sup> XDR tuberculosis requires individualised treatment given the inability of standardised regimens to accurately address both first-line and second-line treatment resistance.<sup>92,93</sup> Individualised regimens are also the only

reliable means by which the amplification of drug resistance may be avoided.<sup>94</sup>

Unfortunately, the difficulty in performing drug-susceptibility testing in many resource-limited countries has led to long-term use of inadequate empiric regimens that could lead to further acquired resistance.<sup>95</sup> The issue of determining susceptibility to a core set of drugs is crucial because an isolate that is resistant to a fluoroquinolone and an aminoglycoside is likely to have cross-resistance to additional second-line drugs.<sup>96</sup> Moreover, certain second-line antituberculosis antibiotics are often difficult to obtain in resource-limited settings (panel 2). WHO's GLC has attempted to address these concerns by creating mechanisms by which all countries can obtain affordable and quality-assured second-line antituberculosis drugs.<sup>97-99</sup>

The length of treatment for XDR tuberculosis has not been firmly established and is often based on individual clinical presentations.<sup>100</sup> Key factors determining treatment duration include cost, drug availability, toxicity, bactericidal capacity, clinical improvement, and patient

adherence.<sup>36,92</sup> Typical MDR-tuberculosis regimens can consist of up to five drugs, and WHO recommends their use for a minimum of 18 months of treatment after culture conversion to negative.<sup>31,101,102</sup> Treatment of XDR tuberculosis should include agents that the strain of *M tuberculosis* has proven to be susceptible to. Any first-line agent to which the isolate has shown to be susceptible, and any appropriate second-line drugs should be used to achieve a regimen with a minimum of four to five effective medications.<sup>103</sup> Treatment with this regimen should be continued for a minimum of 18–24 months.

Surgical treatment should also be considered if clinically significant parenchymal lung disease is localised and high-grade resistance is present.<sup>104</sup> Bilateral disease can also be approached surgically but requires multiple, staged resections. Cure rates of MDR tuberculosis can be greater than 90% with post-surgical chemotherapy.<sup>105</sup>

In view of the multiple drug cross-resistance patterns, new antituberculosis drugs with novel mechanisms of action are necessary if XDR tuberculosis is to be successfully treated. Future treatment also requires development of drugs with minimal adverse events. Ideally, such agents would not have pharmacological interactions with antiretroviral drugs commonly used to treat HIV. Promising new compounds with high potency against *M tuberculosis* include a diarylquinoline compound (R207910, also called TMC207) and two nitroimidazole compounds (PA-824 and OPC-67683).<sup>106-108</sup> Moreover, tuberculosis vaccines are currently being tested which might serve as immunotherapeutic agents to accompany tuberculosis drug regimens.<sup>109</sup>

### Potential solutions and prevention

A multifaceted approach is advocated to address the XDR-tuberculosis epidemic. The WHO Global XDR-TB Task Force initially established comprehensive recommendations in 2006 after recognising the impact of the disease (panel 3). These proposals continue to be promoted as the basis of treatment and prevention strategies to address the increasing prevalence of drug resistance.<sup>110</sup>

### Improve global tuberculosis control by enhancing the testing and care of HIV-infected populations

In several countries throughout southern Africa, the proportion of individuals with HIV is greater than 25% among those diagnosed with active tuberculosis.<sup>32</sup> HIV co-infection enhances both the progression to active disease following primary infection and the reactivation of latent tuberculosis infection.<sup>111,112</sup> The increased likelihood of active tuberculosis disease, which is characterised by a high bacillary burden, has resulted in an amplification of drug-resistant tuberculosis cases.<sup>39,41</sup> Tuberculosis cases among HIV co-infected individuals are notably difficult to diagnose by use of conventional diagnostics and therefore ineffective treatment regimens

#### Panel 2: First-line and second-line drug regimens used in the treatment of tuberculosis

##### First-line regimen

- Isoniazid
- Rifampicin or rifapentine
- Ethambutol
- Pyrazinamide
- Streptomycin

##### Second-line regimen

- Aminoglycosides (amikacin, kanamycin)
- Polypeptides (capreomycin)
- Fluoroquinolones (moxifloxacin, levofloxacin, gatifloxacin)
- Thioamides (ethionamide, protionamide)
- Cycloserine
- Aminosalicilic acid

#### Panel 3: Recommendations of the WHO Global Task Force on XDR-TB, Oct 9, 2006<sup>110</sup>

- Improve global tuberculosis control by enhancing the testing and care of HIV-infected populations
- Develop programme management and treatment guidelines of XDR tuberculosis in high and low HIV prevalence settings
- Strengthen laboratory diagnostic services to ensure rapid and accurate drug-susceptibility testing
- Reducing transmission in health-care settings and other high-risk areas to improve infection control
- Increase disease surveillance efforts to accurately assess epidemiological trends
- Enhance educational advocacy and research funding to encourage development of new drugs and diagnostics

are often employed.<sup>66,67,113</sup> The result, as shown by the outbreak in KwaZulu-Natal, has been an increase in morbidity and mortality in individuals infected with drug-resistant tuberculosis and HIV.<sup>35,114</sup>

Solutions to this problem can be sought in both resource-rich and resource-limited environments by increasing detection of HIV co-infection in individuals diagnosed with tuberculosis.<sup>37,60,115</sup> Treatment with antiretroviral therapy in this population may reduce the number of immunocompromised patients that would be susceptible to progression to active tuberculosis.<sup>116</sup> Moreover, the diagnosis and treatment of latent tuberculosis infection in co-infected patients may reduce a major reservoir of the disease. Isoniazid has been shown to reduce tuberculosis incidence; however, worldwide, the drug is taken by less than 1% of HIV-infected patients with latent tuberculosis infection.<sup>117</sup> Isoniazid preventive therapy is a cost-effective strategy that can be used in resource-limited settings where latent tuberculosis infection is suspected to be drug susceptible. It has been reported that isoniazid therapy enhances the effects of HIV therapy and reduces the probability of tuberculosis disease when taken with antiretroviral treatment.<sup>117,118</sup>

Diagnostic and therapeutic algorithms that can be easily used by private and public-health practitioners for the treatment of HIV/tuberculosis co-infection have also been advocated.<sup>63,119</sup> Currently, few written guidelines exist that programmatically address XDR tuberculosis in HIV-endemic settings. Such documents would serve as the basis for future refinement of laboratory techniques that test for drug susceptibility in individuals with HIV/tuberculosis co-infection and scientific research into the use of second-line tuberculosis drugs with antiretroviral therapy.<sup>120,121</sup>

#### Strengthen laboratory capacity and diagnostics

The median survival time from sputum collection to death was 16 days in the study from KwaZulu-Natal.<sup>35</sup> It should be noted, however, that the short survival time must be interpreted in the context of an HIV-endemic, immunocompromised patient population. Regardless of the clinical circumstances, the rapid detection of drug resistance is essential for effective treatment strategies to be instituted before high rates of tuberculosis transmission and mortality occur. If existing highly sensitive technologies were better used, this could reduce tuberculosis prevalence and mortality by 20% or more.<sup>122</sup>

The availability of point-of-care diagnostic tests is crucial in the determination of appropriate therapy and the reduction of disease transmission.<sup>123</sup> As previously mentioned, examples of accurate and rapid testing include currently available rifampicin resistance assays such as line-probe hybridisation assays—eg, the Hain Genotype MTBDRplus. Although more reliable and rapid drug-susceptibility testing strategies are being developed,

#### Panel 4: Components of the Global Laboratory Initiative

- Global policy guidance on appropriate laboratory technology and best practices
- Laboratory capacity and resource mobilisation
- Laboratory capacity development and coordination
- Interface design with other laboratory networks to ensure appropriate integration
- Standardised laboratory quality assurance
- Coordination of technical assistance
- Effective knowledge sharing

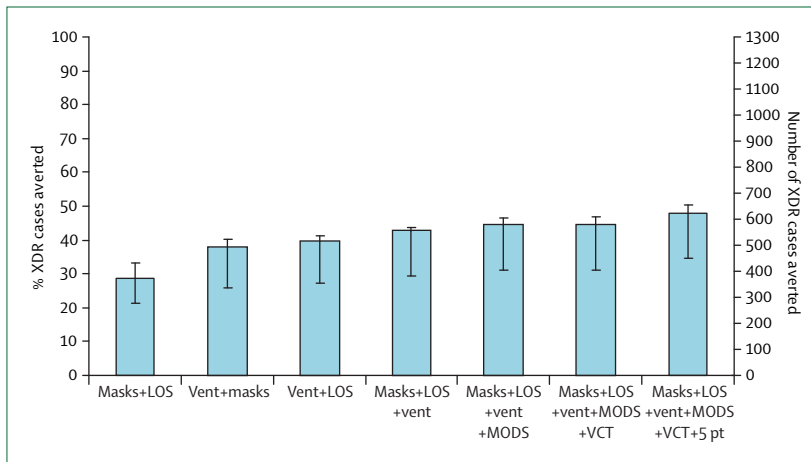
The aim of the Global Laboratory Initiative (GLI) is to universally strengthen tuberculosis laboratory services. The GLI Secretariat is hosted in the Stop TB Department at WHO (Geneva, Switzerland) and works closely with national tuberculosis programmes, non-governmental organisations, technical and financial partners, and WHO offices at country and regional levels.<sup>126</sup>

greater investment will be required to enhance laboratory infrastructure in resource-limited settings.<sup>120,124,125</sup> Current efforts to achieve this include the Global Laboratory Initiative (GLI), a strategic plan that aims to create a multifaceted and integrated approach to laboratory capacity strengthening (panel 4).<sup>126</sup> The country of Lesotho provides an example of how an enhanced laboratory infrastructure can be achieved in a resource-limited, high tuberculosis-endemic environment. Lesotho's national tuberculosis programme, with the assistance of Partners In Health and the Foundation for Innovative New Diagnostics (FIND), has transformed its national tuberculosis reference laboratory. Today, it can reliably perform first-line drug-sensitivity testing and is undertaking more rapid liquid media culture techniques with equipment provided by FIND.<sup>77</sup>

#### Improve infection control

Community and nosocomial spread of tuberculosis has been a growing concern. Primary infection appears to be the key means by which the MDR-tuberculosis and XDR-tuberculosis epidemics have progressed.<sup>17,90,127</sup> In a study at the Church of Scotland Hospital in Tugela Ferry, KwaZulu-Natal, exogenous re-infection, rather than treatment failure, was found to be responsible for the rise in MDR-tuberculosis and XDR-tuberculosis cases.<sup>128</sup> Therefore, infection control practices in both community and health-care facilities are crucial in disrupting the cycle of transmission of drug-resistant tuberculosis.

Infection control mechanisms in health-care settings can involve such varied approaches as isolation, ventilation, air filtration, ultraviolet germicidal radiation, respiratory masks, and staff-training programmes.<sup>129,130</sup> A recent mathematical model has shown that improvements in ventilation alone would be among the most effective measures (figure 4).<sup>131</sup> Opening windows and doors



**Figure 4: Mathematical modelling of the efficacy of rapidly available combinations of strategies to reduce nosocomial transmission**

Masks=both staff N95 respirators and patient masks with adherence enforcement. LOS=reducing average length of stay to 5 days. Vent=improvements in natural ventilation. MODS=microscopic-observed drug-susceptibility assay. VCT=voluntary counselling and testing in admitted patients, with subsequent antiretroviral therapy to those who qualify. 5 pt=isolating patients in groups of five patients. The figure shows that the implementation of a comprehensive approach, which uses all six described strategies, may be able to most effectively minimise the number of XDR-tuberculosis cases. Reproduced from reference 131.



**Figure 5: A street sign in Monsefú (Chiclayo, Peru) promotes the fight against tuberculosis, listing its signs and symptoms**  
Photo courtesy of Photoshare.

maximises natural ventilation and has been reported to be more efficacious than costly, mechanical ventilation systems.<sup>132</sup> Even methods as simple as the partitioning-off of wards based on infectious status are effective infection control measures.<sup>133</sup> Rapid isolation of tuberculosis patients or suspected tuberculosis patients has been shown by some authors to be able to resolve tuberculosis transmission.<sup>130</sup>

Health-care workers can be protected through the use of a personal respirator. Even a poor respirator or face mask that filters only 50% of inhaled particles has the equivalent effect, in theory, of doubling the ventilation of a room, and at a much lower cost.<sup>70</sup> Staff HIV testing is also important so that immunocompromised members can be assigned work duties that minimise exposure to drug-resistant tuberculosis cases.<sup>131</sup> Health-care workers are an essential aspect of any effective administrative response and serve as a key means by which nosocomial transmission can occur.<sup>134</sup>

### Develop comprehensive tuberculosis programme management strategies

The rising trends of resistant tuberculosis have led to mobilisation efforts to increase funding for tuberculosis care, prevention, and research. The Global Plan to Stop TB 2006–2015, has detailed a comprehensive approach to halve tuberculosis deaths and prevalence compared with 1990 levels by 2015.<sup>135</sup> The total cost of the programme over its 10-year period is \$56 billion, of which \$47 billion is for implementation of currently available interventions and \$9 billion are for research and development. The Treatment Action Group, in a survey of 100 institutions involved in tuberculosis research and development, noted that the top 40 donors invested only \$393 million in 2005.<sup>136</sup> The overall estimated funding gap for the Global Plan is \$31 billion and must be immediately addressed if the ultimate aim of tuberculosis elimination by 2050 is to be achieved.<sup>137,138</sup>

One particular aspect of any programme management strategy is an emphasis on improving drug-susceptible tuberculosis treatment completion rates and provision of appropriate medications in cases of drug-resistant tuberculosis.<sup>114</sup> The average treatment completion rate for tuberculosis is substantially below the WHO target of 85%.<sup>125</sup> The evolution of drug-resistant strains will continue if adherence to treatment is not further maximised. Building on the successes of directly observed treatment, short course (DOTS) programmes, WHO and partner agencies developed a strategy for treatment of MDR tuberculosis, termed “DOTS-Plus”, in 1999.<sup>139</sup> The DOTS-Plus strategy adapts the core components of DOTS to the needs of patients with drug-resistant tuberculosis. Although some experts have argued that MDR-tuberculosis treatment may divert resources from drug-susceptible tuberculosis treatment, empiric and modelling studies to date indicate that programme-based MDR-tuberculosis treatment is cost effective.<sup>124,140–142</sup> Moreover, some have argued that the incorporation of treatment of drug-resistant tuberculosis cases might strengthen DOTS programmes because of the attention they generate from a variety of funders (figure 5).<sup>143</sup>

The successful results that can be derived from a comprehensive, programmatic approach to XDR tuberculosis can be seen in a recently published retrospective study of patients referred for individualised tuberculosis treatment in Lima, Peru.<sup>144</sup> Of the 651 patients tested, 48 (7%) were diagnosed with XDR tuberculosis and none were co-infected with HIV. Reliable drug-susceptibility testing, notably undertaken at the Massachusetts State Laboratory Institute (USA), provided the basis of an aggressive, comprehensive treatment strategy that was able to cure 29 (60%) patients with XDR tuberculosis. The individualised treatment approach, which on average lasted more than 2 years, relied on the use of at least five drugs at the highest tolerated doses to ensure chemotherapeutic benefit. The regimens used drugs such as capreomycin,

aminosalicylic acid, and cycloserine, which are rarely available in Peru, but accessible through GLC mechanisms. Treatment adherence was maximised via direct observation of treatment in patient homes and health-care centres, and psychosocial needs were continually addressed to increase compliance. Although this study is undoubtedly fraught with uncertainties—for example, the achievability of such favourable results in HIV-endemic settings and the inherent flaws in retrospective study designs—its comprehensive strategy is now being implemented in Peru's national tuberculosis programme. Studies such as this can serve as the basis of future research into interventions that can be immediately implemented in resource-limited, tuberculosis-endemic areas to effectively address the XDR-tuberculosis epidemic.

## Conclusions

The rising prevalence of XDR tuberculosis has brought a resurgence of interest in drug-resistant tuberculosis. Because of a confluence of several epidemiological factors—such as the HIV pandemic and inadequate case detection and treatment completion—virulent XDR-tuberculosis strains have been increasingly reported worldwide. The public-health community have responded to this issue but much is yet to be accomplished. Inadequate treatment is present in many regions and the need to optimise current treatment strategies through the development of novel drugs is urgent. The development of highly sensitive and rapid laboratory tests for tuberculosis diagnosis also remains an area worthy of further investigative efforts. Resource-limited settings should not postpone active interventions to counter outbreaks of XDR-tuberculosis strains. Immediate action can be implemented through the use of currently available strategies such as enhanced HIV detection and treatment, improved tuberculosis diagnostics (ie, MODS and line-probe hybridisation assays), effective infection control policies (ie, isolation, natural ventilation, and respiratory masks), and increasing local advocacy/research efforts. Ultimately, the path to alleviating this epidemic is one that uses a comprehensive, universal approach that can reverse the current trends of drug resistance.

### Search strategy and selection criteria

Data for this Review were identified by searching PubMed. Search terms (alone or in combination) were “extensively drug resistant tuberculosis”, “XDR-TB”, “tuberculosis”, “drug resistance”, “diagnostics”, “treatment”, “individualized treatment”, “standardized treatment”, “empiric treatment”, “HIV”, “active pulmonary TB”, “DOTS”, “DOTS plus”, and “disease transmission”. Only articles published in English language were reviewed, without date restriction. Selected articles were also searched for relevant references.

### Conflicts of interest

We declare that we have no conflicts of interest.

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