Extensively Drug-Resistant (XDR) Tuberculosis: A Review

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Abstract:

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). This definition in immensely valuable for more uniform surveillance in varied international settings. The prevalence of tuberculosis drug resistance has risen to the highest rate ever recorded. Although the gold standard for drug-susceptibility testing has been the agar proportion method; due to it's time consumption, more sensitive, specific and rapid diagnostic tests are required. It is difficult to differentiate XDR tuberculosis from non-XDR tuberculosis clinically, although the former is associated with greater morbidity and mortality. 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.

Key words: Extensively drug-resistant (XDR) tuberculosis, Mycobacterium tuberculosis

Introduction:

Extensively drug-resistant (XDR) tuberculosis has received substantial attention since the initial report of an association of XDR-TB with extremely high mortality in patients co-infected with *M. tuberculosis* and HIV in a rural area of South Africa in the year 2006.[1] XDR strains of *M. tuberculosis* have now been identified in at least 49 countries around the globe.[2]

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".[3, 4] Such statements were premature - strains of streptomycin-resistant Mycobacterium tuberculosis were found within months of the drug's widespread use.[5] 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.[6]

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. Researchers initially suspected that these resistant organisms had reduced fitness and thus could be classified as being less virulent.[7, 8] 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.[9] Substantial attention was focused upon New York City (NY, USA) where a virulent and transmissible strain had spread among immunocompromised populations.[10, 11] 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.[12]

Definition of XDR tuberculosis:

The term XDR tuberculosis was first developed by the US Centers for Disease Control and Prevention (CDC) in March, 2005.[13] It came to public focus in October, 2005, at the 36th Union World Conference on Lung Health in Paris, France.[14, 15] The original definition

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was proposed in March, 2006, in CDC's Morbidity and Mortality Weekly Report, defining it 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).[16] 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 least one of three injectable second-line drugs (capreomycin, kanamycin or amikacin).[17] The revision was made to facilitate reproducibility of drug-susceptibility testing and to focus attention on drugs accessible in resource-limited settings. Moreover, the classification has also been shown to have value in its ability to predict poorer outcomes.[18]

Epidemiology:

In the face of rising cases of MDR tuberculosis, WHO and the International Union Against Tuberculosis and Lung Diseases (IUATLD) established the Global Project on Anti-tuberculosis Drug Resistance Surveillance in the early 1990s.[19] One of the most important outcomes of the project was the formation of an international quality assurance programme supervised by supranational reference laboratories (SRLs).[20] There are currently 26 SRLs that assist over 100 national laboratories in six continents by standardizing culture and drug-susceptibility techniques. To determine the rate of XDR tuberculosis, CDC and WHO assessed 17,690 M tuberculosis isolates collected by 25 SRLs from 2000—2004.[16] 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.[16]

In a rural hospital in Tugela Ferry, KwaZulu-Natal Province, South Africa, 1539 individuals were 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 tuberculosis, 53 had XDR tuberculosis.[21] 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.[22, 23]

The occurrence of MDR tuberculosis has reached its highest level, with cases reported in a record 49 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.
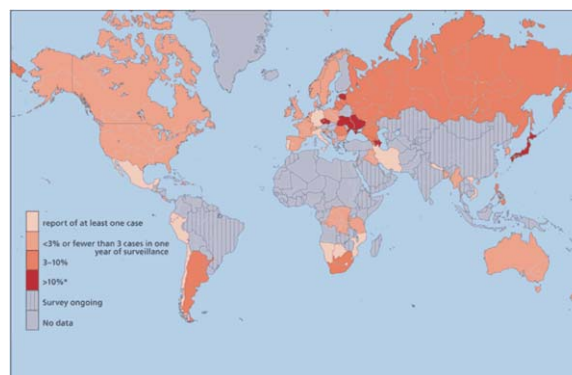
The USA, a country with a low tuberculosis prevalence, recently reclassified 1·9% of MDR-tuberculosis cases as XDR tuberculosis.[3]
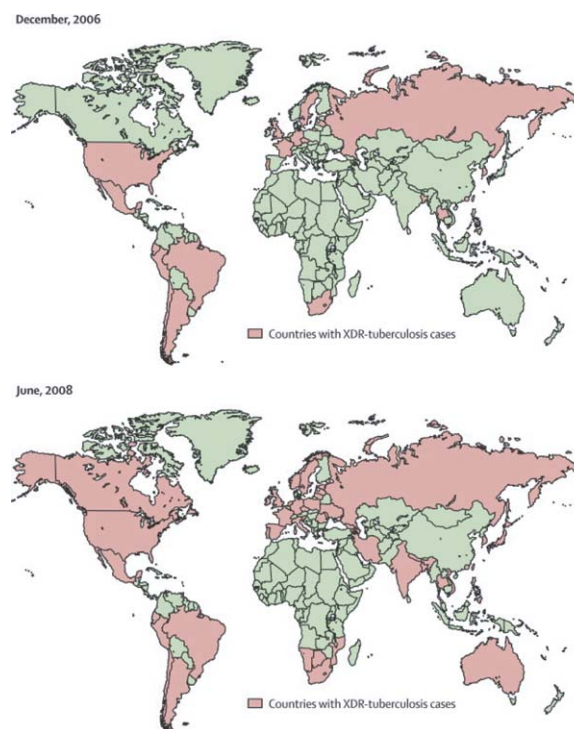
Figure: Countries with XDR-tuberculosis cases in December, 2006, and June, 2008

According to ICDDRB report, MDR surveillance is continuing at Shyamoli TB clinic, Dhaka, Bangladesh in collaboration with National TB control programme (NTP). In their observation, out of 657 isolates, multi-drug resistance was observed in 5.5% isolates. It was significantly higher among persons who received tuberculosis treatment for e" one month. (15.4% vs 3.0%)

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.[24, 25] 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).[26]

Acquired and amplified drug resistances are the primary means by which tuberculosis drug-resistant strains have been generated. However, the key determinant that has 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.[27] 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.[21] The transmission of drug-resistant tuberculosis largely depends on the virulence of the mutated organism.[28-30]

Diagnostic tests for XDR tuberculosis:

The gold standard for drug-susceptibility testing has been the agar proportion method on Lowenstein-Jensen medium and Middlebrook 7H11 agar.[31] But, there are several disadvantages. 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 finalized results. Thus, the inability to detect drug resistance rapidly could increase the likelihood of an isolate developing resistance through ineffective chemotherapy,[32] likelihood of transmission of resistant strains and the potential to produce clusters of secondary infections.[33] Line-probe hybridization 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.[35]

Other molecular methods that could be used in the detection of drug-resistant tuberculosis strains [34] 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. A median time of only 7 days (IQR 6—8 days) is needed for both disease identification and drug-susceptibility testing.[36]

Clinical course of XDR tuberculosis:

MDR tuberculosis is associated with a high mortality in individuals with HIV or other immunosuppressive conditions.[37] The even poorer clinical outcomes associated with XDR tuberculosis was initially documented in the first CDC report of the disease in 2006.[13] During 1993—2002, patients with XDR tuberculosis were 64% more likely to die during treatment than patients with MDR tuberculosis.[10, 13]

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.[21] Fifty two (98%) of 53 patients with XDR tuberculosis died during the study period. Forty four (83%) of the 53 XDR-tuberculosis patients agreed to HIV testing and all tested positive for co-infection.

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.[37] All the patients with XDR tuberculosis died within 2-6 months of diagnosis. A recent study from South Korea described the clinical

outcomes of 43 HIV-uninfected patients with XDR tuberculosis.[38] 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. A five-fold increase in the risk of death in patients with XDR tuberculosis was seen in a study done in Germany and Italy.[39] XDR-tuberculosis patients required longer hospital stays and longer treatment durations, mainly because of clinical complications (ie, sputum conversion).

Treatment of XDR tuberculosis:

The principles of treatment for MDR-TB and for XDR-TB are the same. Treatment requires extensive chemotherapy for up to two years. Second-line drugs are more toxic than the standard anti-TB regimen and can cause a range of serious side-effects including hepatitis, depression and hallucinations. Patients are often hospitalised for longer periods, in isolation. In addition, second-line drugs are extremely expensive compared with the cost of drugs for standard TB treatment.

Strategies to treat drug-resistant tuberculosis can be categorized as either standardized or individualised.[40] Standardized regimens are determined on representative drug-resistance surveillance data of specific regions. Individualized regimens are more specific in that they take into account previous antituberculosis treatments and drug-susceptibility testing of the particular isolate. XDR tuberculosis requires individualized treatment given the inability of standardized regimens to accurately address both first-line and second-line treatment resistance.[41, 42] Individualized regimens are also the only reliable means by which the amplification of drug resistance may be avoided.[43] 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.[44]

The length of treatment for XDR tuberculosis has not been firmly established and is often based on individual clinical presentations.[45] Key factors determining treatment duration include cost, drug availability, toxicity, bactericidal capacity, clinical improvement, and patient adherence.[41] 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 [46, 47] 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.[48] Treatment with this regimen should be continued for a minimum of 18—24 months.

Grouping of anti-tubercular drugs:

Grouping	Drugs (Abbreviation)
Group 1- First-line oral antituberculosis agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2 - Injectable antituberculosis agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vi)
Group 3 Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lfx); Moxifloxacin (Mfx);e Gatifloxacin (Gfx)°
Group 4 -Oral bacteriostatic second-line antituberculosis agents	Ethionamide (Eto); Protionamide (Pto); Cycloserine (Cs); Terizidone (Trd)°; Raminosalicylic acid (PAS); Thioacetazone (Th)h
Group 5 -Antituberculosis agents efficacy (not recom-mended by WHO for routine use in MDR TI3 patients)	Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/ with unclear Clv); Clarithromycin (Clr); Linezolid (Lzd)

A possible treatment regimen is as follows- The treatment is divided into 2 phages: An initial phase of 6 months, which is extended to 9 months if the sputum culture is positive at 4th month; to be followed by a continuation phase of minimum 18 months. Sputum smear examination should be conducted monthly during initial phase and quarterly during continuation phase. Sputum culture should be done at least at 4, 6, 12, 18, 24th month.

A study in the Tomsk oblast of Russia, reported that 14 out of 29 (48.3%) patients with XDR-TB successfully completed treatment.[49] In Hong Kong the overall treatment success rate of XDR tuberculosis compared to MDR tuberculosis is 38% vs 63%.

Surgical treatment should also be considered if clinically significant parenchymal lung disease is localized and high-grade resistance is present.[50] 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.[51]

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).[52-54] Moreover, tuberculosis vaccines are currently being tested which might serve as immunotherapeutic agents to accompany tuberculosis drug regimens.[55]

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 recognizing the impact of the disease.[56]

Recommendations of the WHO Global Task Force on XDR-TB, Oct 9, 2006.

• 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

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

Conclusion:

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 development of highly sensitive and rapid laboratory tests for tuberculosis diagnosis also remains an area worthy of further investigative efforts. 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

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