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# Multi Drug-Resistant Tuberculosis in Children: A Challenge In 21st Century

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## Abstract

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## Introduction

Multidrug-resistant tuberculosis (MDR-TB) is a growing global health crisis; it is estimated there are more than five million people infected and sick with drug-resistant forms of TB in the world today (World Health Organization, 2011). Children represent a significant proportion of these cases yet they lack the same access to diagnosis and treatment as their adult counterparts. A recent meta-analysis of treatment for MDR-TB among children showed that more than 80% had positive outcomes when treated for MDR-TB and that pediatric patients tolerated second-line medications well (Ettehad, D. *et al*, 2012).[1] Urgent action is needed to address this gap in care. Based on experiences with pediatric HIV, equitable access for children with MDR-TB will only occur once systematic approaches to diagnosing and treating children are developed and once access to pediatric formulations of second-line medications is widespread. Finally the term "children" encompasses a broad range of individuals and ages with widely different needs. A 2-year-old child requires a different approach to a 12-year-old, and the treatment of children with MDR-TB will never be a "one size fits all" approach. In essence, children older than 12 years of age can be managed as adults, although the specific emotional needs of adolescent children and their caregivers should be considered.

### *Epidemiology and Global Burden*

Tuberculosis (TB) is a major health concern worldwide and the main cause of death caused by Mycobacterium tuberculosis (MTB). In 2010, it was estimated that 8.8 million incident TB cases occurred in the world. Of the 12 million prevalent TB cases, around 650,000 were estimated to be multidrug-resistant (MDR) (resistant to at least isoniazid and rifampicin). Another cause of concern is

that the highest frequencies of MDR-TB ever reported occurred in recent years. In countries such as Belarus and parts of the Russian Federation, more than a quarter of new TB cases now have MDR-TB. Swaziland reported the highest level of primary MDR ever reported in Africa in 2009 (7.7%).[2] Over 60% of newly diagnosed MDR-TB in 2010 occurred in China, India, the Russian Federation and South Africa alone ("RICS" countries).[2] Extensively drug-resistant (XDR) TB (defined as MDR-TB with additional resistance to at least a fluoroquinolone and one of the injectables, i.e., kanamycin, amikacin or capreomycin) has been reported in 77 countries across the globe by October 2011. Resistance to ethambutol, pyrazinamide and ofloxacin has emerged and demonstrated in over 50% of MDR-TB strains.[1] With total drug resistant (TDR-TB reported in India[2],the situation is now grim. Given the fact that childhood TB represents at least 10–20% of the total cases in areas with poor epidemic control, this translates into a minimum global estimate of around 40,000 pediatric cases of MDR-TB per year. Data on DR-TB in children are sparse and are in the form of case series or observational studies.[4–6] This is due to lower culture yields and drug susceptibility testing (DST) done in children because of paucibacillary disease and difficulties in getting adequate specimen in children. Furthermore, treatment duration, drug doses, drug metabolism and chemoprophylaxis in children with MDR-TB remain poorly understood. Treatment with second-line drugs is more expensive, less effective, more toxic and may need longer duration of therapy (18–24 months)[2]

*Definitions*

*1. Drug Resistant TB*

This is a patient of TB excreting bacilli resistant to one or more anti tuberculosis drugs.

*Mono Resistance:* A patient whose TB is due to tubercle bacilli that are resistant in vitro to exactly one anti TB drug tested from an accredited laboratory.

Poly resistance- a patient whose TB is due to tubercle bacilli that are resistant in vitro to more than one anti TB drug, except not both isoniazid and rifampicin tested from an accredited laboratory.

*2. Multi Drug Resistant (MDR) TB*

MDR TB is defined as in vitro resistance to at least isoniazid and rifampicin, the two main AT drugs from an accredited laboratory. Therefore it is an MDR TB suspect who is smear culture positive and has tubercle bacilli resistant to isoniazid and rifampicin with or without resistance to other anti tuberculosis drugs.

*3. Extreme Drug Resistant (XDR) TBu*

XDR TB is defined as resistance to atleast isoniazid and rifampicin plus resistance to any one of the fluoroquinolones and any one of the three second line injectable drugs (amikacin, kanamycin or capreomycin) based on dst results from and accredited laboratory.

*4. MDR TB Suspect*

An MDR TB suspect is defined as a TB suspect who fails an RNTCP I or III category treatment regimen.

Any RNTCP category two patient who is sputum smear positive at the end of the fourth month of treatment or later

MDR TB may be suspected in the following circumstances:

*Failure of Treatment:* This is smear positive TB patient excreting bacilli at 5 months or more after starting category i who treatment regimen given under direct observation by a health worker. Failure also includes a patient who was initially smear/culture negative but becomes smear/ culture positive during category iii treatment. These patients are placed under category ii treatment afresh.

*Failure of Retreatment:* This is defined as a smear positive patient who remains smear

positive at four months or more of category ii who retreatment regimen.

*Chronic Case:* The failure of a fully supervised WHO retreatment regimen given by health worker under direct observation. A chronic case must have received at least two or more courses of chemotherapy complete or incomplete. These cases are usually but not always excretors of acquired resistant MDR bacilli.

*Types of Resistance*

1. *Primary Resistance:* In patients who have not had any prior treatment with anti-tuberculosis drugs, the bacterial resistance is called primary resistance.
2. *Initial Resistance:* In after clinical assessment, it is doubtful that the patient has received prior treatment, this is called initial resistance. initial resistance is thus the mixture of primary resistance and undisclosed/unknown acquired resistance.
3. *Acquired Resistance:* In patients with some record of previous anti tuberculosis treatment, the bacterial resistance is called acquired resistance. in new patients, the WHO standard first line regimens (6 months) overcome the risk of failure due to primary resistance while majority of previously treated patients (taken ATD for > 1 month), the WHO standard retreatment regimen (8 months) reduces the risk of failure due to acquired resistance.

*Microbiological Basis of Drug Resistance*

1. *Natural Resistance (NR):* This is a species specific resistance to a drug without the strain ever been exposed to it. M. Tuberculosis, m. Bovis, M. Africanum are naturally resistant to penicillin, pyrazinamide and thioacetazone respectively. Therefore, NR is used as taxonomic marker for species.
2. *Primary Drug Resistance:* This is observed in a patient without prior treatment. It follows an infection with:
   A. A wild strain when the organism develops resistance usually to single drug without ever coming in contact with it. Wild type resistance is the result of random spontaneous mutation in an naturally susceptible strain which has never been exposed to anti tuberculosis drug. This spontaneous mutation within the bacteria occur at a rather predictable rate. For example isoniazid and streptomycin resistance develops at a frequency of 1 in 1 million organisms while for ethambutol at 10000 and rifampicin at 100000000.
   B. An infection with an isolate of M. Tuberculosis that is already resistance to the given ATT when the patient comes in contact and acquires infection from an already drug resistant case.
3. *Secondary (Acquired) Drug Resistance:* This exists if the organisms with which the patient is infected were initially drug susceptible, but develop resistance during the course of ATT.

*Molecular Basis of Drug Resistance*

Drug resistance (DR) is caused by specific mutation in independent genes of M. Tuberculosis. It is not transferrable form one organisms to another and is not interlinked between ATT drugs, however bacilli show cross resistance to drugs of similar nature. Understanding the mechanisms DR by gene mapping and recognizing the specific gene mutation is used for the development of molecular test for rapid detection DR bacilli and future anti tubercular drugs.

*Resistance to AT Drugs*

1. `Rifampicin - mis - sense mutation in gene rpo B encoding b unit rna polymerase.
2. Isoniazid - complete absence or mutation of gene kat G, inh A.
3. Streptomycin - mutation of 16 s ribosomal RNA gene.

**Algorithm For Suspected MDR TB[7]**