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# Multi-Drug/Extensively Drug Resistant Tuberculosis (Mdr/Xdr-Tb): Renewed Global Battle Against Tuberculosis?

Claude Kirimuhuzya
*Department of Pharmacology and Toxicology*
*Faculty of Biomedical Sciences*
*Kampala International University-Western Campus*
*Uganda*

## 1. Introduction

### 1.1 Background

Tuberculosis is the world's second deadliest infectious disease, with nearly 9.3 million new cases diagnosed in 2007. According to the WHO, an estimated 1.8 million people died from TB in 2007. One-third of the world's population is infected with the TB bacillus and current treatment takes 6–9 months. The current TB vaccine, Bacille Calmette-Guérin (BCG), developed almost 90 years ago, reduces the risk of severe forms of TB in early childhood but is not very effective in preventing pulmonary TB in adolescents and adults — the populations with the highest rates of TB disease. TB is changing and evolving, making new vaccines more crucial for controlling the pandemic. Tuberculosis is now the leading cause of death for people living with HIV/AIDS, particularly in Africa. Multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are hampering treatment and control efforts. New control measures, diagnostic tools and guidelines for treatment as well as development of new drugs and vaccines have been made a priority and the battle is now raging to restore the grip on the magement and control of MDR/XDR TB. Winning the battle against tuberculosis will depend on the outcomes of the extensive research that is on going to produce new, more effective and fast acting diagnostic tools, drugs and vaccines.

### 1.2 Drug-resistant TB

Drug-resistant TB is a result of mycobacterial strains that do not respond to drug treatment. Drug resistance has in the recent past become a serious global public health problem especially in the populations of the poor countries of the world. Multidrug-resistant tuberculosis (MDR-TB) refers to organisms that are resistant to at least two of the first-line drugs, isoniazid (INH) and rifampin, (RIF). In recent years, the world has seen a rapidly emerging epidemic of drug-resistant TB or multi drug-resistant (MDR-TB) and/or extensively drug-resistant XDR-TB ), which is highly lethal and extremely expensive leave alone being complicated to treat. Extensively drug-resistant tuberculosis (XDR-TB) is a type of multidrug-resistant tuberculosis (MDR-TB) that is resistant to two of the first-line drugs -

isoniazid and rifampicin - as well as to the second-line medications that include a fluoroquinolone such as ciprofloxacin and at least one of the injectable drugs which may be an aminoglycoside such as amikacin or kanamycin, or a polypeptide like capreomycin, or a thioamides such as ethionamide, or cycloserine or p-aminosalicylic acid.

Because the treatment regimen for TB is long and complex, many patients are unable to complete the course of treatment, enabling their disease to develop drug-resistance. Once a drug-resistant strain has developed, it can be transmitted directly to others. XDR TB being resistant to the front-line drugs and two or more of the six classes of second-line drugs, this makes it virtually untreatable and HIV positive people are particularly at a greater risk. Therefore, XDR TB could have a bigger impact on developing nations considering the fact that there is high prevalence of HIV and lack of capacity to quickly and effectively diagnose and identify the disease. To prevent XDR-TB from spreading, there is an urgent need for new diagnostic tools and new and more effective anti TB drugs and vaccines to be developed. An estimated $5bn is required to confront the spread of DR TB.

### 1.3 Inadequate treatment

The current first-line TB drug regimen of four drugs is nearly 50 years old, takes six to nine months to complete and has significant side effects. Very often, these shortcomings cause patients to default on their treatment which, consequently, results in resistance to TB drugs which then spreads throughout the world. Treatment for MDR-TB or XDR-TB can last up to 30 months, consists of many drugs, (including injectables), many of which have significant side effects, are extremely expensive and resource-intensive to deliver. With the rapid and lethal spread of drug-resistant TB, expediting the development of new, simpler and more effective drug regimens is now a major public health emergency.

### 1.4 Nature of resistance

In a study conducted by Ioerger et al.,(2009) titled "Genome Analysis of Multi- and Extensively-Drug-Resistant Tuberculosis from KwaZulu-Natal, South Africa", which was designed to investigate the causes and evolution of drug-resistance, it was observed that polymorphisms among the strains was consistent with the drug-susceptibility profiles, in that well-known mutations correlated with resistance to isoniazid, rifampicin, kanamycin, ofloxacin, ethambutol, and pyrazinamide. It was however, realised that the mutations responsible for rifampicin resistance in rpoB and pyrazinamide in pncA are in different nucleotide positions in the multi-drug-resistant and extensively drug-resistant strains, which was taken to be an indication that they acquired these mutations independently, and that the XDR strain could not have evolved directly from the MDR strain though it could have arisen from another similar MDR strain.

The researchers reported that the MDR and XDR strains contain typical mutations in gyrA, rpoB, rrs, katG, and the promoter of inhA that explain resistance to fluroquinalones, rifampicin, kanamycin, and isoniazid. Although susceptibilities to ethambutol and pyrazinamide were not determined clinically, mutations in embB and pncA were observed as well. They further argued that the fact that the MDR and XDR strains have different mutations in rpoB and pncA suggests that they arose separately, and that these mutations were acquired independently after divergence. This observation contradicts the hypothesis

that the XDR strain might have evolved directly from the MDR strain (though it could have arisen from another similar MDR strain). While resistance to streptomycin is usually associated with mutations in rpsL or rrs, the KZN MDR and XDR strains showed a rare 130 bp deletion in gidB. Although recent studies have begun to show that mutations can cause low-level resistance to streptomycin, through abbrogation of ribosomal methylation, this mutation was unique and had never been reported before.

Consistent with what was already known, the researchers found that only the XDR strain KZN-R506 showed a mutation in rrs, the 16S rRNA, at position 1400, which explains the kanamycin resistance as put forward by Suzuki et al., (1998) and that only the XDR strain had the A90V mutation in gyrA responsible for resistance to fluoroquinolones as presented by Aubry et al., (2006). They further reported that the mutation at 1400 in rrs which is the most commonly observed mutation associated with kanamycin resistance, found in 60% of rifampicin-resistant clinical isolates was consitent with findings of Suzuki et al., (1998). The A90V in gyrA, the second-most frequently observed mutation conferring fluoroquinolone resistance, found in 24% of fluoroquinolone-resistant clinical isolates, is also reported to show agreement with the work of van Doorn et al.,(2008) on fluoroquinolone resistance.

With respect to isoniazid (INH) resistance, it is also reported that both strains have the mutation of S315T in katG, the catalase/peroxidase that activates the pro-drug isoniazid as reported by Zang et al.,(1992). The finding that this is the most frequently observed mutation associated with isoniazid resistance was also consistent with the report by Hazbón et al.,(2006) and Pym et al.,(2002). The role of the c-15t inhA promoter mutation, and mutations in katG in ETH/INH co-resistance is also presented as put forward by Morlock et al., (2006)

Resistance to rifampicin (RIF) can be explained by mutations in rpoB (beta-subunit of RNA polymerase). The mutation of Asp 435 in rpoB, was observed to confer rifampicin-resistance as put forward by Ramaswamy and Musser (1998). Ioerger et al.,(2009) further report that this is in the core 507–533 region, in which numerous mutations have been observed to cause resistance to RIF, although they agree that mutations at other sites in this region are more frequent. However, they report that the two Kwazulu Natal strains have different mutations within the same codon, leading to different amino acid substitutions. Strain KZN-V2475 was found to have a G->T substitution in frame 1, producing D435Y, and KZN-R506 with an A->G substitution in frame 2, producing D435G, a case that led the researchers to suggest that the two strains acquired rifampicin resistance independently. They also noted that the XDR strain, KZN-R506, contains two additional mutations in rpoB, L452P and I1106T; the former also being thought to cause RIF-resistance, while the latter does not.

Ioerger et al.,(2009) further contend that streptomycin (STR) resistance is most likely due to a 130 bp deletion in gidB found in both MDR and XDR strains, but not the wild-type. The classic STR-R mutations that have been correlated with streptomycin-resistance in the 530-loop or 915-region of rrs, the 16S ribosomal RNA, or in rpsL, the ribosomal protein S12, were not observed in either strain. However, they also state that mutations in these two genes explain only about 70% cases of STR resistance in clinical isolates (Sreevatsan et al., 1997) implying that there must be other loci that can be responsible. They further add that, despite the mutations in gidB having previously been observed in clinical isolates of M. tuberculosis by Nishimura et al., (2007) that, this 130 bp deletion is distinct from every other gidB

mutation previously reported. They report that the 130 bp gidB deletion observed in the KZN MDR and XDR strains spans amino acids 50–93, which encompasses the SAM-binding site (Romanowski et al., 2002) and causes a frame shift for C-terminal remainder, which is presumed to abbrogate function completely. They report that both strains also show classic mutations in embB, pncA, and the promoter region of ethA, which are associated with resistance to ethambutol (EMB), pyrazinamide (PZA), and ethionamide (ETH), though susceptibility to these drugs was not tested. It is further reported that the M306V mutation in the transmembrane protein embB is one of the most frequently observed mutations in EMB-resistant strains as reported by Sreevatsan et al.,(1997) and that this mutation putatively prevents ethambutol from interfering with biosynthesis of the arabinogalactan layer in the cell wall. In the case of pncA, they further report that the two drug-resistant KZN strains showed different mutations in pncA, a pyrazinamidase, which is thought to be involved in nicotinamide biosynthesis. They futher report that the MDR strain KZN-V2475 has a G132A mutation, and that mutations of this residue have previously been reported to cause resistance to PZA Sreevatsan et al.,(1997). They further report that strain KZN-R506 has a frame-shift mutation in amino acid 152 caused by an insertion of 1 bp, and missense mutations that cause resistance that have been observed downstream of this site and that they believe that the C-terminus of the 186-residue gene product must be important. They add that the two drug-resistant strains also share a mutation at position −8 upstream of the translational start site of ethA, which is a monooxygenase that activates thioamides such as ethionamide, isoxyl, and thioacetazone as pro-drugs as reported by Dover et al.,(2007). The researchers further contend that a mutation in the upstream region could potentially confer resistance by increasing expression although susceptibility of the KZN strains to these drugs was not determined

It is further reported by the study that the MDR and XDR strains contain typical mutations in gyrA, rpoB, rrs, katG, and the promoter of inhA that explain resistance to fluroquinalones, rifampicin, kanamycin, and isoniazid. Mutations in embB and pncA were also observed. It is further argued that the fact that the MDR and XDR strains have different mutations in rpoB and pncA which suggests that they arose separately, and that these mutations were acquired independently after divergence. The researchers further report that, the Kwazulu Natal MDR and XDR strains studied showed a rare 130 bp deletion in gidB although resistance to streptomycin is usually associated with mutations in rpsL or rrs. The researchers coclude by recommending further analysis and comparison of the genome sequences they have reported in order to bring out a better understanding of the nature of the virulence XDR-TB strains.

### 1.5 Epidemiology of drug-resistant TB

In South Africa, an epidemic of XDR-TB was reported in 2006 as a cluster of 53 patients in a rural hospital in KwaZulu-Natal of whom 52 died - Tugela Ferry case. What was particularly worrying was that the mean survival from sputum specimen collection to death was only 16 days and that the majority of patients had never previously received treatment for tuberculosis. This was the epidemic for which the acronym XDR-TB was first used, although TB strains that fulfil the current definition have been identified since then, though retrospectively. This was the largest group of linked cases ever found; after the initial report in September 2006, cases have now been reported in most provinces in South Africa, the

neghbouring countries and the world at large, with more than 50 countries on all the inhabited continents having reported XDR-TB cases.

MDR/XDR-TB can develop in the course of the treatment of fully sensitive TB and this is always the result of patients missing doses or failing to complete a course of treatment. Although there are reports that these resistant strains appear to be less fit and less transmissible, the high mortality rate especially where there is co-infection with HIV or during use of immunosuppressive drugs, this warrants that the epidemic has to be taken seriously. There is strong evidence that the spread of XDR-TB strains is very much associated with a high prevalence of HIV and poor infection control, and in some countries the upsurge of XDR-TB has been attributed to mismanagement of cases or poor patient compliance with drug treatment.

XDR-TB does not respond to any of the drugs currently available in most developing countries for first- or second-line treatment. Considering the fact the problem is wide spread globally, strict isolation procedures have been suggested to mitigate rapid spread of XDR-TB. The World Health Organization (WHO) recommends improving basic TB care to prevent emergence of resistance, the development of proper laboratories for detection of resistant cases, and when drug-resistant cases are found, it recommended prompt and appropriate treatment to prevent further transmission.

Collaborative care for both HIV and TB is also recommended to help limit the spread of tuberculosis, both sensitive and resistant strains. The spread of drug-resistant cases has also been linked to overcrowding in places such as seen in prison populations, although the major reason for the development of resistance is poorly managed TB care which may be in form of poor patient compliance, inappropriate dosing or prescribing of medication, poorly formulated medications, and/or an inadequate supply of medication.

### 1.6 Challenges presented by MDR/XDR TB

First, research has revealed that drug-susceptible (regular) TB and MDR/XDR TB are transmitted in the same way. Transmission of XDR TB is in clusters and follows similar transmission patterns as ordinary TB. This makes it difficult to put appropriate barriers to the transmission of the deadly strains. To make matters worse, proper diagnosis involving culture and sensitivity tests is the most commonly used diagnostic method especially in the poor countries. This may take from 6 to 16 weeks, before XDR TB is confirmed during which time it is likely to have spread to other patients and possibly health workers. There have been no new diagnostic tests invented for many years and therefore most laboratories in these areas have limited capacity to respond to XDR-TB. Most laboratories, especially those in developing countries lack the facilities and guidelines for the use of conventional and rapid culture-based or molecular methods for detection of M. tuberculosis and drug resistance and this impedes the widespread use of these tests. The laboratory confirmation of TB in HIV-infected persons is even more difficult and time consuming and highly sensitive and sophisticated and requires technically challenging diagnostic tests that are not universally available in all settings with a high burden of HIV and TB. There is, therefore, poor surveillance especially in the poor developing countries and this presents serious difficulties in identifying and locating the XDR TB cases. A further complication is that TB

affects mostly poor people who live in places where health care is not easily accessible and where the patients have to pay for their own transportation

The next challenge is that there are limited treatment options for XDR-TB especially in the developing countries and this makes the disease virtually untreatable. Considering the fact the majority of patients infected with XDR-TB are co infected with HIV/AIDS and that co-infection has been found to be virtually 100% fatal, this makes the situation more serious. In spite of this serious threat, the world is not responding fast enough and with enough resources as was the case with SARS, avian flu or swine flu. Stop TB estimates that through 2015, it will take about $2.4 billion for further discovery and early-stage development work and another $2.4 billion for clinical trials for new anti TB drugs. Considering the fact that the currently available resources are believed to total about $600 million, this leaves a substantial funding gap. More funding has to be directed towards research and development of new TB drugs and vaccines if the pandemic is to be defeated effectively.

With regard to anti-tuberculosis drugs and vaccines, the world's only vaccine (BCG) is almost 100 years old and only effective in children and for over 40 years there has been no new TB drug put on the market. This may be attributed to the high rates of failures of new drugs at clinical trials but it could also partly be due to complacency that tuberculosis was a defeated disease whose prevalence was on the decline especially in the USA. Another handicap has been that clinical trials required to register a TB drug can take a minimum of 6 years, much longer than trials for other infectious diseases.

A further complication is from drug-drug interactions in patients with TB/HIV co-infection. This is a serious hindering factor in finding treatments for people co-infected with TB and HIV. For example it is reported that rifampicin, which inhibits RNA polymerase, interacts with cytochrome P450 isozyme and causes some HIV drugs to be cleared quickly. To make matters worse clinicians, laboratory technologists, health-care professionals, public health officials, and policy makers do not possess up-to-date knowledge of what constitutes appropriate laboratory capabilities and capacities.

## 2. The global MDR/XDR response plan 2007-2008

Objectives for the Response were the following: (1) Strengthen basic activities to control TB and HIV/AIDS, as detailed in the Stop TB Strategy; (2) Scale-up the programmatic management of MDR-TB and XDR-TB to reach the targets set forth in the Global Plan; (3)Strengthen laboratory services for adequate and timely diagnosis of MDR- TB and XDR-TB; (4) Expand surveillance of MDR-TB and XDR-TB to better understand the magnitude and trends of drug resistance and the links with HIV; (5) Foster sound infection control measures to avoid MDR-TB and XDR-TB transmission to protect patients, health workers, others working in congregate settings, and the broader community, especially in high HIV prevalence settings; (6) Strengthen advocacy, communication and social mobilization for sustained political commitment and a patient centred approach to treatment; (7) Pursue resource mobilization at global, regional and country levels to ensure that necessary resources are available; and (8) Promote research and development into new diagnostics, drugs, vaccines, and operational research on MDR-TB management to shorten treatment. (Adopted from: WHO Report,2007)

## 3. Treatment of MDR/XDR -TB

### 3.1 Monitoring DOTS-plus

The WHO extended the DOTS programme in 1998 to include the treatment of MDR-TB (called "DOTS-Plus"). Implementation of DOTS-Plus requires the capacity to perform drug-susceptibility testing and the availability of second-line agents, in addition to all the requirements for DOTS. DOTS-Plus is therefore much more resource intensive than DOTS, and requires much greater commitment from countries wishing to implement it. Resource limitations mean that the implementation of DOTS-Plus may lead inadvertently to the diversion of resources from existing DOTS programmes and a consequent decrease in the overall standard of care (Dauby et al., 2011;Tam et al.,2009; Li et al., 2006).

Monthly surveillance until cultures convert to negative is recommended for DOTS-Plus, but not for DOTS. If cultures are positive or symptoms do not resolve after three months of treatment, it is necessary to re-evaluate the patient for drug-resistant disease or non-adherence to drug regimen. If cultures do not convert to negative despite three months of therapy, some physicians may consider admitting the patient to hospital so as to closely monitor therapy.

### 3.2 Management of TB/HIV co-infection

In patients with HIV, treatment for the HIV should be delayed until TB treatment is completed, if possible. The current UK guidance, provided by the British HIV Association, is that for a CD4 count over 200, treatment should be delayed until the six months of TB treatment are complete; for a CD4 count of 100 to 200, treatment should be delayed until the initial two-month intensive phase of therapy is complete ; while for a CD4 count less than 100, the situation is unclear and they recommend clinical trials to examine the issue. There is need for patients in this category to be managed by a specialist in both TB and HIV so that they are not compromised for either disease.

If HIV treatment has to be started while a patient is still on TB treatment, it is recommended that the advice of an HIV specialist should be sought. In general, reports say that there is no significant interactions with the NRTI's. Nevirapine should not be used with rifampicin. Efavirenz may be used, but the dose used depends on the patient's weight (600 mg daily if weight less than 50 kg; 800 mg daily if weight greater than 50 kg). Efavirenz levels should be checked early after starting treatment. The protease inhibitors should be avoided if at all possible because patients on rifamycins and potease inhibitors have an increased risk of treatment failure or relapse. The WHO also warns against using thioacetazone in patients with HIV, because of the 23% risk of potentially fatal exfoliative dermatitis.

### 3.3 Specific treatment of MDR-TB

The treatment and prognosis of MDR-TB are much more akin to that for cancer than to that for infection. It has a mortality rate of up to 80%, which depends on a number of factors, including: (1) How many drugs the organism is resistant to (the fewer the better); (2) How many drugs the patient is given (patients treated with five or more drugs do better); (3) Whether an injectable drug is given or not (it should be given for the first three months at least); (4) The expertise and experience of the physician responsible; (5) How co-operative

the patient is with treatment (treatment is arduous and long, and requires persistence and determination on the part of the patient) ; and (6) Whether the patient is HIV positive or not (HIV co-infection is associated with an increased mortality).

Treatment courses take a minimum of 18 months and may last for years; it may require surgery, though death rates remain high despite optimal treatment. That said, good outcomes are still possible. Treatment courses that are at least 18 months long and which have a directly observed component can increase cure rates to 69%.

Treatment of MDR-TB must be done on the basis of sensitivity testing since it is impossible to treat such patients without this information. When treating a patient with suspected MDR-TB, the patient should be started on streptomycin, isoniazid, rifampicin, ethambutol, pyrazinamide + moxifloxacin + cycloserine (SHREZ+MXF+cycloserine) pending the result of laboratory sensitivity testing. A gene probe for rpoB is available in some countries and this serves as a useful marker for MDR-TB, because isolated RMP resistance is rare, except when patients have a history of being treated with rifampicin alone. If the results of a gene probe (rpoB) are known to be positive, then it is reasonable to omit RMP and to use SHEZ+MXF+cycloserine. The reason for maintaining the patient on INH despite the suspicion of MDR-TB is that INH is so potent in treating TB that it would be irrational to omit it until there is microbiological proof that it is ineffective. There are also probes available for isoniazid-resistance (katG and mabA-inhA), but these are less widely available.

When sensitivities are known and the isolate is confirmed as resistant to both INH and RMP, five drugs should be chosen in the following order (based on known sensitivities): (1) an aminoglycoside such as amikacin, kanamycin or a polypeptide antibiotic such as capreomycin; (2) pyrazinamide; (3) ethambutol; (4) a fluoroquinolones (moxifloxacin is preferred and ciprofloxacin should no longer be used]); (5) rifabutin; (6) cycloserine; (7) a thioamide: prothionamide or ethionamide; (8) PAS; (9) a macrolide such as clarithromycin; (10) linezolid; (11) high-dose INH (if low-level resistance); (12) interferon-γ; (13) thioridazine; and (14) meropenem and clavulanic acid. Drugs near the top of the list are more effective and less toxic while drugs placed near the bottom of the list are less effective or more toxic, or more difficult to obtain.

Resistance to one drug within a class generally means resistance to all drugs within that class, but a notable exception is rifabutin for which rifampicin-resistance does not always mean rifabutin-resistance and the laboratory should be asked to test for it. It is only possible to use one drug within each drug class and if it is difficult to find five drugs to use then the clinician can request that high level INH-resistance be looked for. If the strain has only low level INH-resistance (resistance at 1.0 μg/ml INH, but sensitive at 0.2 μg/ml INH), then high dose INH can be used as part of the regimen.

When counting drugs, PZA and interferon are counted as zero i.e. when adding PZA to a four drug regimen, you must still choose another drug to make five. It is not possible to use more than one injectable (capreomycin or amikacin), because the toxic effect of these drugs is additive: if possible, an aminoglycoside should be given daily for a minimum of three months (and perhaps thrice weekly thereafter). Ciprofloxacin should not be used in the treatment of tuberculosis if other fluoroquinolones are available.

There is no intermittent regimen validated for use in MDR-TB, but clinical experience is that giving injectable drugs for five days a week (because there is no-one available to give the drug at weekends) does not seem to result in inferior results. DOTS Plus strategy has been found to help in improving outcomes in MDR-TB and it is recommended that it should be an integral part of the treatment of MDR-TB.

Response to treatment must be obtained by repeated sputum cultures (monthly if possible). Treatment for MDR-TB must be given for a minimum of 18 months and cannot be stopped until the patient has been culture-negative for a minimum of nine months. It is not unusual for patients with MDR-TB to be on treatment for two years or more.

To be able to contain the spread of resistance, patients with MDR-TB should be isolated in negative-pressure rooms, if possible. Patients with MDR-TB should not be accommodated on the same ward as immunosuppressed patients (HIV-infected patients, or patients on immunosuppressive drugs). Careful monitoring of compliance with treatment is crucial to the management of MDR-TB and hospitalisation should be encouraged for this reason. If possible these patients should be isolated until their sputum is smear negative, or even culture negative, a process that may take many months, or even years. Since keeping these patients in hospital for long periods may not be practicablel, the final decision depends on the clinical judgement of the physician treating that patient. In addition, the attending physician should make full use of therapeutic drug monitoring (particularly of the aminoglycosides) both to monitor compliance and to avoid toxic effects.

Some supplements may be useful as adjuncts in the treatment of tuberculosis, but for the purposes of counting drugs for MDR-TB, they count as zero (if you already have four drugs in the regimen, it may be beneficial to add arginine or vitamin D or both, but you still need another drug to make five). The supplements include arginine (peanuts are reported to be a good source) and Vitamin D.

There are also some drugs which have been used in desperation and for which it is uncertain whether they are effective at all or not, but which are used when it is not possible to find five drugs from the list above. They include imipenem, co-amoxiclav, clofazimine, prochlorperazine and metronidazole.

There is also increasing evidence for the role of surgery (lobectomy or pneumonectomy) in the treatment of MDR-TB, although whether this is should be performed early or late is not yet clearly defined (Mohsen et al, 2007).

### 3.4 Specific treatment for XDR-TB

Can XDR TB be treated and cured? Yes, in some cases. Some TB control programs have shown that aggressive treatment, using the current drug regimens can make it possible to effect cure for an estimated 30% of affected people. Researchers have shown that a cure is possible with a combination of at least five drugs as is the case with MDR-TB. Tailored treatment in 600 patients in Russia with at least five drugs showed that almost half of XDR-TB patients had treatment cure on completion of the course. The study reported that aggressive management of the disease is feasible and can prevent high mortality rates and further transmission of drug-resistant strains of TB. However, the treatment is extremely labour and resource intensive and has to be done within extremely well structured TB

programmes. It is further reported that successful outcomes depend greatly on the extent of the drug resistance, the severity of the disease, whether the patient's immune system is weakened, and adherence to treatment. There are no newly approved drugs or vaccines specifically for the treatment of XDR-TB although a number of drugs and vaccines are reported to be in various stages of development (Dauby et al., 2011).

### 3.5 New drugs in the pipeline

There is a desperate need for new and better TB treatments to address today's growing pandemic, which kills nearly 2 million people each year. There have been no new TB drugs for nearly 50 years and, until the past decade, there was no pipeline of TB drug candidates. Now, with increased investments in TB R&D, there are 9 promising TB compounds in the pipeline from six antibiotic classes, making combination testing of new TB drugs possible.

The eperimental drugs PA-824 (manufactured by PathoGenesis Corporation, Seattle, Washington), and R207910 (under development by Johnson & Johnson) are experimental compounds that are not commercially available, but which may be available from the manufacturer as part of a clinical trial or on a compassionate basis because their efficacy and safety are not yet properly understood. There are also reports that a Ukrainian herbal product which has been the subject of several small, open label clinical trials in TB patients and in patients with TB/HIV coinfection has produced promising results. Furthermore, Open Label trials with Dzherelo/Immunoxel have been reported to produce positive results in MDR and XDR-TB patients.

Stirling Products Ltd of Australia has also announced further work on drug-resistant TB and TB/HIV with trials being carried out in Nigeria. V-5 Immunitor (known as "V5"), an oral hepatitis B and hepatitis C treatment vaccine and administered as simple tablets is being developed for patients co-infected with hepatitis C and tuberculosis. It is reported to produce TB sputum clearance within only one month. Further blinded studies at multiple trial centres have reported that V5 is equally effective against multiple drug resistant tuberculosis (MDR-TB).

Currently, about 30 compounds have been identified for potential development of new anti TB drugs. However, new treatment for XDR TB is expected to be available not earlier than 2012. Drugs in the pipeline include, among others, combination regimens containing the fluoroquinolones moxifloxacin and gatfloxacin. Moxifloxacin (from Bayer and TB Alliance) is being looked at as a substitute for isoniazid or ethambutol and should now be undergoing final clinical trials while gatfloxacin (from OFLOTUB) is being developed to replace ethambutol. Other drugs in the pipeline include LL3858 (from Lopin) which should have by now gone through Phase I clinical trials.Work also continues on rifabutin (related to rifampicin) (from Pfizer) which is under study to replace rifampicin and on rifapentine, which was approved in 1998.

PA-824, a nitroimidazole, (from Chiron –part of Norvatis) is under Phase II Clinical trials while OPC-67683, a nitrodihydroimidazo-oxazole derivative (from Japan's Otsuk Pharmaceuticals) is in advanced stages of clinical trials for treatment of MDR TB. TMC-207 (from Johnson & Johnson), an ATP synthase inhibitor that is selective for MTB is under

development at Tibotec for MDR TB and is being considered as substitute for rifampicin and isoniazid to shorten the dosage period for MDR TB.

FAS20013, a sulfonyl tridecamide (from FASgen) is also being developed against MDR TB. It interferes with MTB cell wall synthesis and is expected to be effective against dormant bacteria.

SQ109, a 1, 2-ethylene diamine (from Sequella) is reported to inhibit cell wall synthesis and to have shown synergistic effect with rifampicin and isoniazid. It is also reported to be effective against MDR and latent forms. SQ609, a dipiperidine (from Sequella but got from Sankyo, Japan), which is an inhibitor of translocase, involved in cell wall synthesis, is in pre-clinical studies.

Source: U.S. National Institute of Allergy and Infectious Diseases (NIAID)

### 3.6 Ongoing research: New paradigm shift

Treating active TB requires a combination of drugs to prevent the development of drug resistance. Traditionally, researchers tested one new drug at a time in a series of lengthy and expensive clinical trials, meaning it would take decades to develop a completely novel drug combination. The individual TB drug candidates were developed and registered separately, by being substituted (or added) one at a time to the existing standard, four-drug-combination TB therapy. Because each substitution (or addition) could take six years or longer, the approval of a new four-drug TB regimen, through successive trials, could take nearly a quarter of a century to develop under this framework. With nearly 2 million people dying of TB each year, the world cannot wait that long for the tools needed to stop this devastating disease.

The push in this direction is because there is a possibility of developing one TB drug regimen capable of treating both drug-sensitive and multidrug- and extensively drug-resistant tuberculosis using combination therapy. Combination drug regimen may especially transform MDR/XDR-TB treatment, resulting in reduction of treatment duration from 2 years to less than six months. This new approach to drug development is expected to expedite the development and production of regimens that can be availed to patients in a much smaller period of time compared to the traditional approach of drug development.

This research approach is being championed by the Critical Path to TB Drug Regimens (CPTR), an initiative established to tackle the regulatory and other challenges associated with TB drug development. CPTR was founded in March 2010 by the Bill & Melinda Gates Foundation, the Critical Path Institute, and the TB Alliance. CPTR focuses on shifting the unit of development from an individual drug to combinations of drugs, which can be tested together and developed as a regimen from early clinical testing. Advances in regulatory science will help clearly evaluate experimental TB drugs both on their own and within the context of a regimen.

This new approach has the potential to shorten the time needed to develop new TB treatment regimens by decades, as well as significantly reduce development costs. However, to be able to test promising combinations together, there must be a change in today's

thinking about TB research— a paradigm shift - and the change must be adopted by everyone: drug sponsors, global regulators, WHO, patients, and other stakeholders throughout the TB landscape. This new approach to drug development enables combinations of previously unregistered TB drugs to be tested together, with the goal of introducing truly innovative regimens in only a fraction of that time. Nearly a dozen pharmaceutical companies, civil society organizations, the European and Developing Countries Clinical Trials Partnership (EDCTP), and others have signed on to the initiative's guiding principles. The US Food and Drug Administration, other regulatory bodies, and the World Health Organization have all shown support for this initiative.

In persuit of this paradigm shift, the 41st Union World Conference, the Global Alliance for TB Drug Development (TB Alliance) in Berlin, Germany on Nov. 8, 2010 announced the launch of the first clinical trial to test a novel tuberculosis regimen designed to expedite new treatments to patients. The novel three-drug combination has shown promising results towards treating both drug-sensitive (DS-TB) and multidrug-resistant TB (MDR-TB), and also being able to alter the course of the TB pandemic by shortening and simplifying treatment worldwide.

The combination now in Phase III clinical trials is called NC001 or New Combination 1. The new combination TB drug candidate being tested contains PA-824 and moxifloxacin in combination with pyrazinamide, an existing antibiotic commonly used in TB treatment today. The developers have reported that preclinical data have revealed that the combination has potential to shorten treatment time for virtually all tuberculosis patients and to harmonize the treatment of drug susceptible tuberculosis (DS-TB) and MDR-TB and possibly XDR-TB treatment with a single three-drug regimen. This is a particularly significant advance for MDR-TB patients, who today must take multiple types of drugs, including injectables, daily for up to two years. It is envisaged that, if successful, the experimental regimen will offer a shorter, simpler, safer, and more affordable treatment option for MDR-TB, an emerging global health threat. The new compounds are being developed by TB Alliance, but with moxifloxacin being developed in partnership with Bayer HealthCare AG.

The trial involves 68 participants at two centers in South Africa, each receiving two weeks of treatment and three months of follow-up to evaluate effectiveness, safety, and tolerability. NC001 is an early bactericidal activity trial and is supported financially by United States Agency for International Development, the Bill & Melinda Gates Foundation, and the United Kingdom's Department for International Development.

NC001, is also testing additional two-drug combinations (TMC207/pyrazinamide and PA-824/pyrazinamide) that may prove to be the building blocks of future regimens. Regimen development may become the new gold standard in TB research and offer lessons for other diseases requiring combination treatment, such as cancer, hepatitis C, and malaria. However, there remains a vital need for funding to bring new TB regimens through late-stage clinical trials.

Table 1 gives a summary of the various compounds and combinations that are in various stages of development.

| **Discovery** | | | **Pre-clinical Development** | **Clinical Development** | | |
|---|---|---|---|---|---|---|
| Target or cell-based screening | Lead identification | Lead optimization | | Clinical Phase I | Clinical phase II | Clinical phase III |
| Natural Products IMCAS | Whole-Cell Hit to Lead Program GSK | Mycobacterial Gyrase Inhibitors GSK | Nitroimidazoles U. of Auckland/ U. Ill Chicago | | PA-824 Novartis (NTBRD) | Moxifloxacin (+H, R, Z) Bayer |
| TB Drug Discovery Portfolio NITD | | Pyrazinamide Analogs Yonsei | Preclinical TB Regimen Development JHU/U. Ill Chicago (NTBRD) | | Preclinical TB Regimen Development JHU/U. Ill Chicago (NTBRD) | Moxifloxacin (+R, Z, E) Bayer |
| Topoisomerase I Inhibitors AZ/NYMC | Gyrase B Inhibitors AZ | Diarylquinolines Tibotec/U. of Auckland | | | PA-824/Pyrazinamide (NTBRD) | |
| | Folate Biosynthesis Inhibitors AZ | Riminophenazines IMM/BTTTRI | | | TMC207/Pyrazinamide (NTBRD) | |
| | Whole-Cell Hit to Lead Program AZ | | | | PA-824/TMC207 (NTBRD) | |
| | RNA Polymerase Inhibitors AZ | | | | PA-824/ Moxifloxacin/ Pyrazinamide (NTBRD) | |
| | Energy Metabolism Inhibitors AZ/U. Penn | | | | | |

Key: AZ = AstraZeneca, Bayer = Bayer Healthcare AG, BTTTRI = Beijing Tuberculosis and Thoracic, Tumor Research Institute, GSK = GlaxoSmithKline, IMM = Institute of Materia Medica, IMCAS = Institute of Microbiology, Chinese Academy of Sciences, JHU = Johns Hopkins University, Tibotec = Johnson & Johnson / Tibotec, NYMC = New York Medical College, NITD = Novartis Institute for Tropical Diseases, Novartis = Novartis Pharmaceutical, U. of Auckland = University of Auckland, U. Penn = University of Pennsylvania School of Medicine, Yonsei = Yonsei University, (NTBRD) = Novel TB regimen development, Source: Global Alliance for TB Drug Development . June 2011

Table 1. TB Alliance Portfolio for TB drug development

## 4. TB vaccines and immunizations

Vaccines work by stimulating the immune system to retain a memory of particular molecules from a microbe that will trigger a rapid immune response if the microbe is encountered later. The best candidates for vaccines are those that trigger the strongest response from the immune system. The existing Bacille Calmette Guerin (BCG) vaccine,

which came into the market in 1921, has limited effectiveness in protecting people from TB. BCG is based on a live but attenuated strain of Mycobacterium bovis, which is the species that causes TB in cattle but can also infect humans. It is given at birth throughout the developing world but the problem is that BCG is not very effective - a fact made obvious when you consider that about 2 million people a year still die from TB. It is also reported that the BCG vaccine, which is used to prevent childhood TB, may not be safe for children living with HIV.

The development of a vaccine from a pool of potential candidates through clinical trials to delivery in a healthcare system is a costly and time-consuming process with a very high failure rate along the way. However, this problem not withstanding, a number of groups from around the world are collaborating in major partnerships, on vaccine development where two main vaccine strategies are being pursued: (1) a pre-infection vaccine delivered early in life improved from the current BCG vaccine and (2) a post-exposure vaccine that would invoke immunity to clinical disease after infection. With these stragies in mind, a number of products has reached various phases of clinical trials.

Researchers in the TB-VAC project will select vaccines for TB that work in adults and are suitable for use in resource-poor settings and are safe for HIV-infected individuals. MUVAPRED (Mucosal Vaccines against Poverty Related Diseases) is aimed at stimulating local immunity to neutralise M. tuberculosis where the organism enters the body in the lungs. The focus is on developing vaccines that can be administered orally or as a nasal spray thus avoiding the risks involved in using needles.The momentum to develop a new and more effective vaccine is gathering pace and although there is still much work to be done, there is genuine optimism that a new effective vaccine can be delivered in the next ten years.

### 4.1 New tuberculosis vaccines in pipeline

TB vaccines under development are designed to work in one or several of the following ways: (1) Prevent infection; (2) Prevent primary disease; (3) Prevent latent infection; (4) Prevent reactivation of latent infection or (5) Shorten the course and improve the response to chemotherapy.

#### 4.1.1 Tuberculosis Vaccine Pipeline - 2010

In the 2010 Tuberculosis Vaccine Pipeline, tuberculosis vaccine candidates are presented in three categories:

a. Candidates Tested in Clinical Trials (Section I): TB vaccine candidates that were in clinical studies in 2010. Certain candidates that have been in clinical studies but are not currently in clinical trials are listed as 'completed.'
b. Candidates in Preclinical Studies & GMP-2010 (Section II): TB vaccine candidates that as of 2010 were not yet in clinical trials, but have been manufactured under good manufacturing practice (GMP) for clinical use and have undergone some preclinical testing that meets regulatory standards.
c. Next Generation Candidates-2010 (Section III): TB vaccine candidates that are in the research and development stage with some preclinical testing performed to show that they may confer protection.

| Type of vaccine | Products | Product description | Sponsor | Indication | Status as of 2010 |
|---|---|---|---|---|---|
| Recombinant Live | VPM 1002 | rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation | Max Planck, Vakzine Projekt Management GmbH, | Prime rBCG, Booster | TBVI Phase Ib |
| | rBCG30 | rBCG Tice strain expressing 30 kDa Mtb antigen 85B; phase I completed in U.S.. | UCLA, NIH, NIAID, Aeras | Prime | Phase I [completed] |
| | AERAS-422 | Recombinant BCG expressing mutated PfoA and overexpressing antigens 85A, 85B, and Rv3407 | Aeras | Prime | Phase I |
| Viral Vectored | Oxford MVA85A / AERAS-485 | Modified vaccinia Ankara vector expressing Mtb antigen 85A | Oxford Emergent Tubcerulosis Consortium (OETC), Aeras | Boost, Post-infection, Immuno-therapy | Phase IIb |
| | AERAS-402/ Crucell Ad35 | Replication-deficient adenovirus 35 vector expressing Mtb antigens 85A, 85B, TB10.4 | Crucell, Aeras | Boost | Phase IIb |
| | AdAg85A | Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A | McMaster University in Canada. | Prime , Boost | Phase I |
| Recombinant Protein | M72 + AS01 (GSK M72) | Recombinant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 & adjuvant AS01 | GSK, Aeras, othrers | Boost, Post-Infection | Phase II |
| | Hybrid-I+ IC31 (SSI Hybrid 1 (H1)) | Adjuvanted Recombinant protein (Ag85B plus ESAT 6) fusion molecule with adjuvant (IC31). recombinant protein composed of Mtb antigens 85B and ESAT-6 | Statens Serum Institute (SSI), TBVI, EDCTP, Intercell | Prime, Boost, Post-infection | Phase I/II |
| | Hybrid-I+ CAF01 | Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT6 | SSI | Prime, Boost, Post-inection. | Phase I – |

| Type of vaccine | Products | Product description | Sponsor | Indication | Status as of 2010 |
|---|---|---|---|---|---|
| | HyVac 4/AERAS 404, +IC31 Recombi-nant protein (Ag85B plus TB10.4) fusion molecule with adjuvant (IC31). | Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4 | SSI, Sanofi Pasteur, Aeras, Intercell | Boosting vaccine for prevention of new TB in BCG vaccinated infants. | Phase I |
| Whole Cell, Inactivated or Disrupted | M. vaccae (Investiga-tional heat-killed preparation derived from rough variant of an environmental isolate). | Inactivated whole cell non TB mycobacterium; phase III in BCG primed HIV+ population completed; reformulation pending | NIH, Immodulon (with Aeras). | Booster to BCG, for HIV infected. Post-infection, Immuno-therapy | Phase III [completed] |
| | Mw [M. indicus pranii (MIP)] | Whole cell saprophytic non TB mycobacterium | Department of Biotechnology (Ministry of Science & Techno-logy, Govern-ment of India), M/s. Cadila Pharma-ceuticals Ltd. | Immuno-therapy | Phase III |
| | RUTI | Fragmented Mtb cells Based on detoxified cellular fragments of M. tuberculosis. | Archivel Farma, S.I. Being develop-ed by Germans Trias i Pujol Health Science Research | Targets subjects with latent new TB infection (LTBI). | Phase II |

| Type of vaccine | Products | Product description | Sponsor | Indication | Status as of 2010 |
|---|---|---|---|---|---|
| | M. smegmatisa | Whole cell extract; phase I completed in China – | - | Boost, Post-infection, Immuno-therapy | Phase I [completed] |

Table 2. Candidates Tested in Clinical Trials (SECTION I)

The vaccine candidates are further subdivided into specific vaccine types: (1) Recombinant Live (2) Viral Vectored (3) Recombinant Protein or (4) Other. A brief description is also provided. The Table lists vaccines intended to be used as a Prime (P) or Booster (B) vaccine, as a Post-infection vaccine (PI) or in immunotherapy (IT). The information contained here was provided and updated by the vaccine developers unless otherwise indicated. In cases where an update regarding a previously listed vaccine candidate was not received in 2010, the 2009 listing was retained.

| Type of vaccine | Products | Product description | Sponsor | Indication |
|---|---|---|---|---|
| Recombinant Live | Mtb [ΔlysA ΔpanCD ΔsecA2] | Non replicating, Mtb strain auxotrophic for lysine and pantothenate; attenuated for secA2 | Albert Einstein College of Medicine | Prime |
| | MTBVAC [ΔphoP, Δfad D26] | Live vaccine based on attenuation of Mtb by stable inactivation by deletion of phoP and fad D26 genes | University of Zaragoza, Institute Pasteur, BIOFABRI, TBVI | Prime |
| Recombinant Protein | HBHA | Naturally methylated 21 kDa purified protein from M.bovis BCG | Institute Pasteur of Lille, INSERM, TBVI | Prime, Boost, Post-infection, Immuno-therapy |
| | Hybrid 56 + IC31 | Adjuvanted recombinant protein composed of Mtb antigens 85B, ESAT6 and Rv2660 | SSI, Aeras, Intercell | Prime , Boost, Post-Infection. |
| Other | HG85 A/B | Chimeric DNA vaccines— Ag85A/Ag85B | Shanghai H&G Biotech | Boost, Immuno-threapy |
| | Spray-dried BCGb | Live attenuated BCG Danish Strain spray-dried for nasal administration | MEND | Prime |

Table 3. Candidates in Preclinical Studies & GMP 2010 (SECTION II)

| Type of vaccine | Products | Product description | Sponsor | Indication |
|---|---|---|---|---|
| Recombi-nant Live | HG856, BCG | rBCG overexpressing chimeric ESAT6/Ag85A DNA fusion protein | Shanghai Public Health Clinical Center | Boost, Post-infection, Immunotherapy |
| | IKEPLUS M. smegmatis with ESX3 deletion/ complementation | Live M. smegmatis with deletion of ESX3 encoding locus and complementation with Mtb locus | Albert Einstein College of Medicine, Aeras | Boost |
| | paBCG | BCG with reduced activity of anti apoptotic microbial enzymes including SodA, GlnA1, thioredoxin, and thioredoxin reductase | Vanderbilt University | Prime |
| | Proapoptotic rBCG | Recombinant BCG expressing mutated PfoA and including mutations shown at AECOM to induce macrophage apoptosis | Aeras, Albert Einstein College of Medicine | Prime |
| | rBCG(mbtB)30 | rBCG with limited replication overexpressing the 30 kDa Mtb Antigen 85B | UCLA, NIH, NIAID | Prime |
| | rBCG T+B rM. smegmatis T+B | rBCG and rM. smegmatis expressing multiple T and B epitopes of Mtb | Finlay Institute, Universiti Sains Malaysia | Prime, Boost, Post-Infection |
| | rBCG TB Malaria | Expresses multiple epitopes of Mtb fused to malarial epitopes and antigens | Universiti Sains Malaysia | Prime , Boost, Ppost-Infection |
| | rBCG38 | rBCG Tice strain overexpress the 38 kDa protein | Universidad Nacional Autónoma de México | Prime, Boost |
| | rBCGMex38 | rBCG Mexico strain overexpress the 38 kDa protein | Universidad Nacional Autónoma de Mexico | Prime, Boost |
| | rBCG overexpressing L,D Transpeptidase | Recombinant M. bovis BCG overexpressing an Mtb L,D Transpeptidase | Johns Hopkins University | Prime |

| Type of vaccine | Products | Product description | Sponsor | Indication |
|---|---|---|---|---|
| | Replication deficient rBCG | Recombinant BCG expressing PfoA and classical, latency, and resuscitation antigens in live, non replicating background | Aeras | Prime |
| | rM.microti30 rM.microti38 | rM.microti strain overexpress the 30 or 38kDa protein | Universidad Nacional Autónoma de Mexico | Prime |
| | Streptomyces live vector | Recombinant streptomyces expressing multiple T and B epitopes from M.tb | Finlay Institute, Institute of Pharmacy and Food, Cuba | Prime, Boost, Post-infection, |
| Recombi-nant Protein | ID93 in GLASE adjuvant | Subunit fusion protein composed of 4 Mtb antigens | Infectious Disease Research Institute | Boost, Post-infection, Immunotherapy |
| | Latency fusion proteins | Recombinant fusion proteins composed of antigens 85A85B,Rv3407, Rv3407,Rv1733, Rv2626, Rv0867,R1884,Rv2389 | Aeras | Boost |
| | | 30kDa Mtb Ag85B protein purified from rM. Smegmatis | UCLA, NIH, NIAID | Boost, Post-infection |
| | R32Kda (recombinant 85A) | Purified recombinant 85A protein from BCG | Bhagawan Mahavir Medical Research Center, LEPRA Society Blue Peter Research Centre | Boost, Postinection ,Immuno-therapy |
| Viral Vectored | Recombi-nant LCMV | Recombinant lymphocytic choriomeningitis virus expressing Ag85A, Ag85B, or Ag85BESAT6 | University of Geneva | Prime, Boost, Post-infection, Immunotherapy |
| | pND 14 vector | With tpa factor expressing esat6, cfp10, hspx, Ag85A, Ag85B, or Ag85 | HEC Pakistan | Prime, Boost, |

| Type of vaccine | Products | Product description | Sponsor | Indication |
|---|---|---|---|---|
| Other | Ac2SGL Diacylated Sulfoglycolipid | Mycobacterial lipids with Ac2SGL, a novel glycolipid antigen | Institut de Pharmacologie et Biologie Structurale du CNRS | Prime, Boosr, Post-infection, Immunotherapy |
| | HG856A | Chimeric DNA vaccines— ESAT6/Ag85A; Ag85A/Ag85B | Shanghai H&G Biotech | Boost, Immun-otherapy |
| | HG856SeV | Recombinant Sendai virus overexpressing chimeric ESAT 6/Ag85A protein | Shanghai H&G Biotech | Boost |
| | Hsp DNA vaccine | Codon optimized heat shock protein from M. leprae, a CpG island | Cardiff University, Sequella | Boost |
| | HVJ Envelope/HSP65 DNA+IL12 DNA | Combination of DNA vaccines expressing mycobacterial heat shock protein 65 & IL12 | Osaka University | Boost, Post-infection, Immuno-therapy |
| | Liporale BCG | Live attenuated BCG Danish Strain in a novel lipid adjuvant and delivery system for an oral vaccine | Immune Solutions Ltd. | Prime, Boost |
| | Mycobacterial liposomes and proteosomes | Liposomes from M. smegmatis and proteoliposomes from BCG and M. smegmatis | Finlay Institute Universiti Sains Malaysia | Prime, Boost, Post-inection, Immuno-therapy |
| | NasL3/AM85B conjugate | Nasal vaccine with man capped Arabinomannan oligosaccharide conjugated to Ag85B in Eurocine L3TM adjuvant | Karolinska Institute | Boost |
| | NasL3/HtkBCG (BCG adjuvant) | Intranasal heat killed whole BCG Copenhagen strain in Eurocine L3TM adjuvant | Karolinska Institute | Prime, Boost, Post-infection, Immunotherapy |
| | PS conjugate | Subunit Mtb polysaccharide protein conjugate | Albert Einstein College of Medicine | Boost |

| Type of vaccine | Products | Product description | Sponsor | Indication |
|---|---|---|---|---|
| | pUMVC6/7 DNA | DNA vaccine plasmid vectors pUMVC6 or pUMVC7 expressing Rv3872, Rv3873, Rv3874, Rv3875 or Rv3619 | Kuwait University | Prime |
| | Recombinant B/HPIV | Recombinant B/HPIV vector encoding fusion of antigens 85A85B,Rv3407, Rv3407, Rv1733, Rv2626, Rv0867, Rv1884, Rv2389 | NIH, Aeras | Boost |
| | TBioVax | Heat shock HspC protein antigen complexes | ImmunoBiology Ltd. | Boost |
| | TBVax | T cell epitope based DNA prime/peptide boost vaccine | EpiVax , Inc. | Boost, Post-inection |

Key: BCG – Bacille Calmette Guérin, IL – Interleukin, GMP – Good Manufacturing Practices, GSK – GlaxoSmithKline Biologicals, M. bovis – Mycobacterium bovis, Mtb – Mycobacterium tuberculosis, NIAID– National Institute of Allergy and Infectious Diseases, NIH – National Institutes of Health, OETC – Oxford Emergent Tuberculosis Consortium, Ltd. SSI – Statum Serum Institute, TBVI – Tuberculosis Vaccine Initiative, UCLA – University of California Los Angeles,
Source: Tuberculosis Vaccine Pipeline 2010

Table 4. Next Generation Candidates – 2010 (SECTION III)

## 5. Tuberculosis diagnostics

Despite substantial investments and progress made in expansion of the directly observed therapy, short course (DOTS and DOTS Plus) strategy and improved treatment completion rates, inadequate case detection is still a major problem in the efforts to ensure global control of tuberculosis. There is need for health workers to be able to quickly detect resistant forms of tuberculosis and also to be able to distinguish clearly between active and latent forms.Efforts during the past decade to consistently diagnose and treat the most infectious cases have not been very successful. Insufficient access to advanced diagnostic tests has contributed to limited performance in the effort to control tuberculosis in general and MDR/XDR –TB in particular. Up to now, national tuberculosis programmes in disease endemic countries continue to rely largely on antiquated and inaccurate methods such as direct smear microscopy, solid culture, chest radiography, and tuberculin skin testing. There is still no rapid test that can allow early detection of active tuberculosis at health clinics , the biggest challenge bing presented by diagnosis of smear-negative tuberculosis in adults infected with HIV and in children.

To these shortcomings is added the fact that even the existing diagnostics are not used to their full potential because of poor access to health care and failures in health-care delivery systems, including poor coordination between national HIV/AIDS and tuberculosis programmes. There are rampant diagnostic delays, misdiagnoses, and inadequate implementation of existing tests leading to increased morbidity and mortality in patients,

leave alone allowing continued transmission of MDR/XDR strains. The shorcomings of present-day case detection approaches are most pronounced in countries with a high prevalence of HIV infection or MDR/XDR tuberculosis, or both which heralds a bleaque picture for the control of the disease.

### 5.1 Barriers to development of new tuberculosis diagnostics

The most important barries have been (1)market failure because industry tends to avoid developing and marketing products that will be mainly used for poor patients in resource-limited countries because such products will not generate profits; and (2) health systems in developing countries are generally weak due to poor management, insufficient financial resources, inadequate human resources, and poor laboratory capacity, making them unable to take advantage of tuberculosis diagnostics to achieve best possible performance, and to introduce new advances in diagnostic technologies.

### 5.2 Tuberculosis diagnostics pipeline

Over the past decade, there has been an unprecedented level of interest and activity focused on the development of new tools for TB diagnosis, with agencies like the Stop TB Partnership's New Diagnostics Working Group (NDWG), the Foundation for Innovative New Diagnostics (FIND), the Global Laboratory Initiative (GLI), the World Health Organization (WHO) and the Special Programme for Research and Training in Tropical Diseases (TDR), several industry partners, non-governmental agencies, and national TB programs being heavily involved. The impetus has been boosted by funding agencies such as the Bill & Melinda Gates Foundation, the Global Fund to Fight AIDS, TB and Malaria (GFATM), and UNITAID that have provided the much needed resources. As a result of this involvement, there is now a strong pipeline of improved or new tools for TB diagnosis.

Fluorescence microscopy is widely used in high income countries since it offers increased sensitivity, and has logistical advantages such as less technician time, but is rarely used in resource-limited countries. Several light-emitting diode (LED) microscopes that can be used in fluorescence microscopy have been developed in the past few years. They are inexpensive, robust, consume little electricity, are highly sensitive, and need less technician time than does Ziehl-Neelsen microscopy. WHO recommended that conventional fluorescence microscopy be replaced by LED microscopy in all settings and that LED microscopy be phased in as an alternative for conventional Ziehl-Neelsen microscopy in both high-volume and low-volume laboratories. Efforts are also underway to minimise diagnostic delays and to improve system efficiency by optimising the number of specimens that are needed and the way in which they are collected (eg, so-called same-day diagnosis, using two sputum smears collected on the same day).

### 5.3 Limitations of the existing diagnostics pipeline

Although promising work has either been done or is the pipeline we are yet to see a simple, rapid, inexpensive point-of-care test for active tuberculosis that can perform as well or better than conventional smear microscopy, and which can deliver results within minutes without sophisticated equipment or laboratory requirements. Such equipment that can be able to do

point-of-care diagnostic tests are necessary if we are to be able to control diseases such as tuberculosis that need lengthy standardised, decentralised therapy. However, with patient, community, and activist groups providing increased funding and resources to develop such tests, an ideal diagnostic system can be availed in afew years to come.

## 6. Biomarkers for tuberculosis

### 6.1 Importance of biomarkers

It is an established fact that biomarkers are important tools for provision of prognostic information about future health status, for individual patients or cohorts in clinical trials. They can be used to indicate normal or pathogenic processes, or pharmacological outcomes of therapeutic interventions. Basing on epidemiological, therapeutic, pathophysiological, or other scientific evidence, biomarkers can form the basis of surrogate endpoints, which can serve as substitutes for clinical endpoints in clinical trials. By using this approach, it possible to use them in drug candidate selection during drug discovery and accelerating dose selection in early clinical research, as well as shortening the time to licensing of new drugs and vaccines. In day-to-day clinical care, biomarkers can allow stratification of individual patients according to outcome risks, thus easing targeted interventions that might not otherwise produce overall benefit. Use of biomarkers can also play a vital role in the advancement of basic knowledge of disease pathogenesis.

With regard to tuberculosis research, the need for biomarkers is paramount in the areas of: (1) patients with active disease, to predict durable or non-relapsing treatment success; (2) patients with latent M. tuberculosis infection, to indicate reactivation risk and predict treatment success; and (3) people other than those with active disease, to indicate protection from tuberculosis by new vaccines. Although a number of studies have been undertaken in this area outstanding breakthroughs are yet to be made.

## 7. Existing gaps in research on XDR TB

In the majority of areas where XDR -TB has been identified, the actual prevalence of resistance to first- and second-line drugs among TB cases is unknown. The figures being used are maily estimates and, therefore, there is need to determine the exact global prevalence and incidence rates of XDR-TB.

The risk factors for and transmission dynamics of XDR-TB in domestic and international settings are not completely understood and the survival rates among patients with XDR-TB have not been adequately analyzed. Furthermore, host/pathogen determinants of survival, including the effect of co-morbidities, are yet to be completely elucidated.

In the field of diagnostics, the methods for detecting and documenting outbreaks of XDR-TB both domestically and internationally are not currently optimized to allow a rapid response and to these is added lack of effective and safe treatment regimens for XDR-TB which are yet to be established. Rapid, point-of-care identification of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB among HIV-negative and HIV-positive adults and pediatric populations and reliable early identification of latent M. tuberculosis infection are not yet possible.

Another scientific obstacle impeding progress is that up to now we do not have a icomplete understanding of the biology of M tuberculosis and its nteractions with the human host. These knowledge gaps impede the development of biomarkers that can distinguish between the different forms and stages of tuberculosis especially in immunocompromised patients and in children. The present diagnostic tests for latent M. tuberculosis infection do not adequately distinguish resolved from persistent infection, and are unable to efficiently identify individuals who are at highest risk of reactivation.

Furthermore, studies into the predictive value of Interferon-γ–release assays (IGRAs) have only shown modest outcomes, and several studies show similarly low rates of progression in people with positive tuberculin skin test and IGRA results. Other gray areas are in the area of diagnosis of smear-negative tuberculosis in children and HIV-infected individuals, as well as inablity to carry out rapid and accurate identification of resistance to second-line antituberculosis drugs. Although molecular markers have been identified and can be used as rapid and accurate tests for isoniazid and rifampicin resistance, testing for the resistance that characterises extensively drug-resistant tuberculosis is still a problem. Well-validated surrogate markers to rapidly assess clinical efficacy of new chemotherapeutic agents and regimens against XDR-TB are yet to be put in place although a lot of research is on going.

With regard to treatment of MDR/XDR-TB, effective treatments specifically designed for active or latent MDR/XDR-TB infection have not been established. Coupled with this is the fact that the complete pharmacology of existing and new TB drugs, including interactions with antiretroviral medications commonly used among high-risk populations, has not been adequately assessed.

Furthermore, there are still gaps in the areas of characterisation of the efficacy, safety and pharmacology of TB chemotherapeutics in special populations such as children, injection drug users and persons with HIV/AIDS, among other situations.

Further still, the quality of currently available services and treatments for MDR/XDR-TB patients has not been monitored or evaluated sufficiently and safe and more effective treatment regimens and appropriate follow-up procedures for managing contacts of XDR-TB patients are yet to be properly established. Another area of concern has been the fact that, despite M. tuberculosis having been known for a long time, there have been gaps in the knowledge of its characteristics with regard to growth, physiology, biochemistry, genetics, and molecular biology although this situation is now being addressed, as more and more research has been undertaken in these areas.

Finally, there is need to have in place, a comprehensive and up-to-date estimate of the costs of diagnosing, treating, and managing XDR-TB if cost-effective strategies to prevent XDR-TB are to be established.

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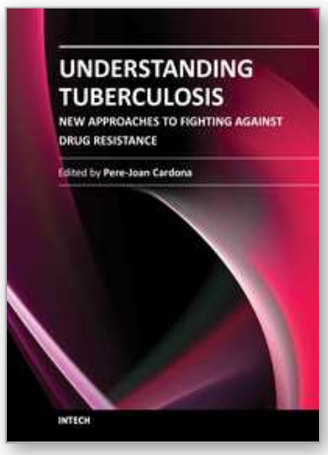


**Understanding Tuberculosis - New Approaches to Fighting Against Drug Resistance**

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In 1957, a Streptomyces strain, the ME/83 (S.mediterranei), was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphael, France. This drug was the base for the chemotherapy with Streptomicine. The euphoria generated by the success of this regimen lead to the idea that TB eradication would be possible by the year 2000. Thus, any further drug development against TB was stopped. Unfortunately, the lack of an accurate administration of these drugs originated the irruption of the drug resistance in Mycobacterium tuberculosis. Once the global emergency was declared in 1993, seeking out new drugs became urgent. In this book, diverse authors focus on the development and the activity of the new drug families.



**InTech Europe**
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166
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