DEPARTMENT OF HEALTH
Republic of South Africa

THE MANAGEMENT OF MULTIDRUG RESISTANT TUBERCULOSIS IN SOUTH AFRICA

2nd Edition June 1999

PREFACE TO FIRST EDITION

The following guidelines are intended for use by health care professionals involved in the complex and difficult task of management of multidrug- resistant tuberculosis patients in South Africa. This document draws heavily from policy guidelines on the issue by the World Health Organization, the International Union Against Tuberculosis and Lung Disease and the Centers for Disease Control and Prevention. However, South Africa has a unique blend of health care services and resources and adaptations to existing policies had to be made in order to accommodate the great diversity in the country. These guidelines also reflect an integration of various provincial approaches to the problem of multidrug-resistant tuberculosis and present consensus decisions on many difficult issues.

The guidelines have been prepared with the idea that they will be used by health professionals working in regional tuberculosis management or lung disease referral centres. Some background detail has been included concerning laboratory testing and the dosages and side effects of drugs. Although this information will be known to the majority of physicians working in this field it may be useful to nurses, social workers and those physicians who are new to the care of patients with MDR tuberculosis. This background information, although not exhaustive, should also be useful to medical registrars and pulmonologists in training.

Furthermore, the day to day care of patients with MDR TB (whether or not they are on treatment) may often be conducted at designated and approved ambulatory care clinics, and the nursing and medical staff working in these clinics may require some technical background to the recommendations in this document.

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National Tuberculosis Research Programme
Medical Research Council, Pretoria December 1997

PREFACE TO SECOND EDITION

The second edition has been updated by advocating the use of ethambutol in place of cycloserine in the standard regimen should the TB bacilli culture be found sensitive (implying that all diagnoses of MDR- TB should be confirmed by testing for rifampicin, full INH and ethambutol resistance), recommending external laboratory quality control and adding a section on diagnosis. There is also more emphasis on the danger of spreading MDR-TB in HIV positive patients in hospital settings and in how to decrease this risk. This guide needs to be updated regularly. Comments and suggestions from those in the field are essential. Please forward to the TB Programme Manager, Department of Health, Private Bag X 828, Pretoria 0001 June 1999

EXECUTIVE SUMMARY: CRUCIAL ISSUES IN THE MANAGEMENT OF MDR TUBERCULOSIS

I *Mulltidrug Resistant TB is defined as TB disease where there is demonstrated resistance to both INH and rifampicin with or without resistance to other anti-TB drugs. As INH and rifampicin are the two most important 1st line TB drugs, their removal (via resistance) from the anti-TB drug armamentarium has serious implications. Based on current estimates, there should be at least 2000* ***newly active cases*** *of MDR tuberculosis in South Africa each year. The full cost of treating one MDR TB patient is about R 30, 000.* ***Cure rates are generally below 50%*** *even in the best circumstances. At least* ***30% of cases are fatal*** *within two years: the remainder are chronic and continue to be infectious, posing a threat to communities.*

II. *Prevention is the key to effective control of MDR TB. There is no point using scarce health care resources for the treatment of MDR tuberculosis while neglecting to properly implement the National Tuberculosis Control Programme, since most cases of MDR tuberculosis arise as a result of a poorly applied Tuberculosis Control Programme. The district and provincial health departments must aim at a cure rate of over 85% for at least all new smear positive cases.*

III. *Rifampicin should not be available as a single drug for the routine treatment of tuberculosis in hospitals or clinics.*

IV. *Laboratory results are sometimes wrong. Remember to treat the patient not the laboratory result. The most common mistake is a wrongly labled specimen or result. If the patient is getting better clinically on routine treatment and the laboratory result seems to contradict this, contact the lab for verification and, if necessary, repeat the specimen. Do not neglect to get expert advice.*

V. *Provinces are* ***not advised*** *to embark on programmes for the treatment of MDR tuberculosis unless they are able to furnish a properly staffed referral clinic and ensure a regular supply of appropriate drugs, with treatment taken under direct supervision.*

VI. ***Counselling*** *of patients and families is important. Offer emotional support, educate about prevention and to ensure that patients are given the best chance of cure.*

VII. *There are two approaches to the selection of treatment regimen in MDR tuberculosis patients.* ***Approach 1*** *involves a standard treatment regimen, with follow up decisions not based on susceptibility results.* ***Approach 2*** *involves a tailor-made regimen for each patient based on susceptibility results. Provincial Health Authorities should adopt one approach to be consistently applied in the province.* ***Approach 1 is strongly advocated as it minimises the chance for error in most cases****.*

VIII. *Irrespective of the approach used, patients should receive* ***5 drugs*** *during a* ***4 month intensive phase*** *followed by* ***3 drugs*** *during a* ***continuation phase of between 12 and 18 months****.*

Treatment should be given 7 days per week in hospitals and 5 days per week outside hospitals.

IX. *Patients with MDR TB are ideally treated **in hospital**, at least until 3 consecutive monthly sputa are culture negative. The most cost-effective way of doing this is to provide special, well ventilated, wards in existing hospitals. Separate "MDR" hospitals built far from the patient's social support network are not recommended.*

X. ***Clinic based care** for MDR TB patients without hospitalization is possible provided certain conditions are met.*

XI. ***Contact management** is the same as for the contacts of ordinary pulmonary tuberculosis. There is, as yet, no evidence to support the giving contacts of other, expensive and often poorly tolerated, chemoprophylaxis regimens.*

XII. *Reducing the risk of the spread of TB especially when many patients are HIV positive, is an essential part of clinic and hospital management. If there is not a negative pressure ward, MDR TB patients should be treated in wards with doors closed and the windows open. Sputum collection should take place if at all possible in the open air on the sunny side of the ward. A special glass roofed veranda, open to the outside should be built for this purpose. Inside the ward it should be mandatory for ward staff to wear particulate respirator masks which are impermeable to droplet nuclei. Patients should wear ordinary masks to prevent explosive spread.*

The positioning and installation of extract fans is a specialised job; expert help should be obtained. The value of ultraviolet lights is, as yet, not determined.

XIII. ***Health care workers in TB laboratories and MDR TB wards** should be well informed about the risks of their becoming ill with MDR TB, as well as ways of minimising this risk. They should be medically examined at employment and encouraged to report any illness to facilitate early diagnosis and treatment. A baseline medical examination will make compensation easier. Health workers who suspect they are HIV positive should be encouraged to be transferred to areas where the risk of TB infection is low.*

XIV *Every TB hospital must use one of their most competent nurses as infection control practitioners. They should have special skills in monitoring procedures and be able to communicate excellently.*

***A register of all health workers** who develop MDR TB should be kept at the referral centre in order to help determine the risk involved and to inform future policy.*

XV. ***Every case of MDR TB should be reviewed as to the reasons for the case developing** . Annual reviews should be compiled for each referral centre of the probable causes of MDR TB, the outcome of treatment and the costs involved. A report should be forwarded for the personal attention of the Provincial Head of Health, outlining the problems which led to the people developing*

MDR TB.

It must also be born in mind that many cases of MDR TB will be part of the group who have dropped out of treatment and therefore not under the direct control or influence of the health service. Only by curing a very high proportion of patients with ordinary Pulmonary TB at the first attempt and using combination drugs, not single drug in clinics and hospitals, can we contain the MDR TB rate.

XVI. *All laboratories which perform TB drug susceptibility tests must be part of an external quality control system.*

XVII *Periodic surveys of MDR TB incidence and prevalence need to be undertaken in each province.*

The above principles have been accepted as policy at the Provincial Health Restructuring Committee as of the 11th of June 1999.

The Department acknowledges the contribution of Dr Karin Weyer of the National Tuberculosis Research Programme Medical Research Council, who put together and edited the first edition of this document with the support from the MDR Working Group with contributions from Prof Eric Bateman, Dr Lucille Blumberg, Dr Neil Cameron, Dr Alistair Calver, Dr Gavin Churchyard, Dr Bernard Fourie, Dr Brendan Girdler-Brown, Dr Refiloe Matji and Dr Paul Wilcox. Valuable comments have been received from the TB Provincial Co-ordinators and other experts. Further suggestions will be appreciated. These guidelines should be updated at least annually.

These policy guidelines are meant for those directly involved in treating MDR TB. Please check that you have the latest copy. Copies may be obtained from the Provincial TB Coordinator, see annexure 4 for details.

GUIDELINES FOR THE MANAGEMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS PATIENTS IN SOUTH AFRICA

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1. INTRODUCTION

At no time in recent history has tuberculosis been as widespread a concern as it is today. Despite highly effective drugs, disease and deaths due to *Mycobacterium tuberculosis* are increasing worldwide and are being fuelled by the widespread HIV epidemic. A most serious aspect of the problem has been the emergence of multidrug-resistant (MDR) tuberculosis, which poses a threat both to the individual patient as well as to communities.

Recent studies by the MRC National Tuberculosis Research Programme in 3 provinces indicate a rate of approximately 1% MDR in new tuberculosis cases and 4% in previously treated cases. This translates into about 2 000 new cases of MDR tuberculosis in South Africa each year. MDR tuberculosis is difficult and expensive to treat, while current cure rates range from 30-50%. Two year case fatality rates are around 30% to 50%, being higher in HIV positive patients. The cost of treating a case of MDR tuberculosis in South Africa is 10 to 20 times the cost of treating an uncomplicated drug-susceptible case.

***It is of the utmost importance that MDR tuberculosis be prevented by rigorous adherence to the principles of the Tuberculosis Control Programme (The DOTS strategy*) and by patiently and consistently building partnerships with patients, their families and communities to cure TB at the first attempt .**

MDR tuberculosis is defined as tuberculosis disease caused by strains of *M. tuberculosis* that are resistant *in vitro* to both rifampicin and isoniazid, with or without resistance to other drugs. As with other forms of drug resistance, MDR tuberculosis is a man-made problem, being largely the consequence of human error in any or all of the following:

- Management of drug supply
- Prescription of chemotherapy
- Patient management
- Patient adherence

1.1 Most common medical errors leading to the selection of resistant bacilli

- Prescription of inadequate chemotherapy (e.g. three drugs during the initial phase of treatment in a new patient smear-positive with bacilli initially resistant to isoniazid);
- Adding one extra drug in the case of treatment failure, and often adding a further drug when the patient relapses after what amounts to monotherapy.

1.2 Most common errors observed in the management of drug supply

- Frequent or prolonged shortages of antituberculosis drugs due to poor management; especially when rifampicin is available as a single drug.
- Use of one or two drugs when three or four standard drugs should be given
- Use of TB drugs (or drug combinations) of unproven bioavailability

1.3 The following poor management practices also have the effect of multiplying the risk of successive monotherapies and selection of resistant bacilli

- Health care workers not ensuring that a good relationship is built with the patient from the start. Not taking time to show that you understand the patient's situation nor taking a problem solving approach.
- Patients' lack of knowledge (due to poor information or not repeatedly obtaining feedback of patient understanding and practice).
- Poor case-management (careless attitudes, lack of friendly support, treatment is not directly observed)
- Frequent staff changes (Clinic teams not built to manage all aspects of health care. No focal point for ensuring correct clinic practice)
- Poor staff morale (Lack of regular support and supervision.)
- Poor record keeping

1.4 Patient-related factors:

Patient cooperation or adherence is most often a problem when the patient is homeless, has a alcohol or drug problem, is unemployed, looking for a job, a family member has been unsuccessfully treated previously or when access to health care is difficult. An indepth discussion with the patient at the initiation of treatment clarifying the expectations of both the patient and the health care staff, helping the patient try to solve barriers to adherence and building a supportive relationship help decrease these constraints.

1.5 Mycobacteria Other Than Tuberculosis

Finally, it should be emphasised that MDR tuberculosis is not the same as disease due to mycobacteria other than tuberculosis (MOTT). The latter are commonly resistant to both isoniazid and rifampicin but should not be confused with MDR tuberculosis. These guidelines are relevant for the management of MDR tuberculosis only and not for disease caused by MOTTs. The incidence of MOTTs in patients with a positive culture is about 0.2%. This proportion is however likely to increase as those who are HIV positive are more susceptible also to MOTTs. MOTT infection is also more common in miners with silica dust disease.

Identification of a MOTTs infection is made after culture has been referred for special investigation. MOTTs are often a contaminant in the culture and are only of clinical significance if the patient is not responding to routine treatment. If the infection is not responding to treatment and MOTTs are reported in the sputum culture, the patient should be referred to a respiratory physician for advice.

2. MECHANISMS OF TUBERCULOSIS DRUG RESISTANCE

Natural resistance

M. tuberculosis has the ability to undergo spontaneous, slow but constant mutation, resulting in resistant mutant organisms. This natural phenomenon is genetically determined and varies from drug to drug. The probability of spontaneous resistance to the individual antituberculosis drugs is as follows:

Isoniazid	:	1 in every 10^6 cell divisions
Rifampicin	:	1 in every 10^9 cell divisions
Streptomycin	:	1 in every 10^6 cell divisions
Ethambutol	:	1 in every 10^5 cell divisions
Pyrazinamide	:	1 in every 10^5 cell divisions

Usually, the chromosomal location of resistance to different drugs is not linked; therefore, spontaneously occurring multidrug resistance is extremely rare. For example, the probability of mutation resulting in resistance to isoniazid is 10^{-6} and for rifampicin it is 10^{-9}. The likelihood of spontaneous resistance to both isoniazid and rifampicin is the product of the two probabilities, i.e. 10^{-15}. Since the probability of naturally occurring resistant mutants is very low, a large bacterial load (eg. in lung cavities) is needed for MDR tuberculosis strains to emerge.

Acquired resistance

Drug resistance, therefore, is the result of selection of resistant mutants in the bacterial population, due to killing of susceptible bacilli by tuberculosis drugs. The problem is greatly exacarbated by inadequate treatment, such as direct or indirect monotherapy, resulting from intake of a single antituberculosis drug or from intake of a combination of drugs where the minimal inhibitory concentration of only one drug may be optimal. Susceptible cells are killed rapidly and resistant mutants are then able to multiply. The speed at which resistance to individual antituberculosis drugs emerges has been calculated to be 45 days for streptomycin and 2 to 5 months for rifampicin.

3. DEFINITIONS

Drug resistant tuberculosis: This is defined as disease (usually pulmonary) caused by *M. tuberculosis* bacilli resistant to one or more antituberculosis drugs. Drug resistance is further classified into “primary”, “initial” or “acquired” according to history of previous tuberculosis treatment.

Primary resistance: Resistance in cultures from patients with no history of previous tuberculosis treatment.

Initial resistance: Drug resistance in new tuberculosis patients, allowing for undisclosed previous treatment, i.e. “initial resistance” refers to primary plus undisclosed acquired resistance. This rate may be up to twice the rate for true primary resistance and the term is preferred by some authors when dealing with population-based studies.

Acquired resistance: Resistance in cultures from patients with one or more previous tuberculosis

treatment episodes (totalling more than one month).

Treatment failure: A tuberculosis patient who remains or becomes again smear-positive at five months or later during treatment. is still excreting bacilli at the end of treatment (at five to six months for new cases or seven to eight months for retreatment cases).

Chronic case: The failure of a *fully supervised retreatment regimen*. A chronic case has received at least two courses of chemotherapy, and sometimes more than two courses (complete or incomplete). Chronic cases are often, but not always, excreters of MDR bacilli. Likewise, patients with retreatment failure are more likely to be harbouring multidrug resistant organisms.

MDR tuberculosis occurs either through infection by *M. tuberculosis* already resistant to isoniazid and rifampicin (primary resistance) or through the selection of drug resistant mutants of the original (susceptible) strain as a consequence of inadequate therapy or poor patient adherence (acquired resistance).

Since the early 1990s, several outbreaks of MDR tuberculosis have been reported in different regions of the world, as a consequence of inappropriate use of essential antituberculosis drugs. Usually MDR tuberculosis occurs in chronic cases after failure of retreatment regimens and represents a significant proportion of tuberculosis patients with acquired resistance. Exceptionally, MDR tuberculosis is observed in new cases, ie. in patients who have never taken antituberculosis drugs, and who have been infected by MDR bacilli. In South African studies, about 1% of new culture positive tuberculosis patients are found to have MDR TB.

4. RELEVANCE OF TUBERCULOSIS DRUG RESISTANCE IN TUBERCULOSIS CONTROL

During the early stages of implementation of an effective national tuberculosis control programme, retreatment cases may represent up to half of registered cases. In this situation, the rate of acquired resistance is usually high. The top priority however is to standardise treatment for new and retreatment cases of ordinary tuberculosis.

Primary and acquired resistance differ in terms of their prevalence and severity. The rate of primary resistance is always lower than the rate of acquired resistance. Primary resistance is usually 5% or less in good national programmes, and 15% or more in new programmes implemented after a period of disorganised and chaotic tuberculosis chemotherapy. In South Africa the primary resistance rate as measured in 3 provinces in 1995 was about 1 %. This is probably due to the widespread use of combination TB drugs.

Primary resistance is also usually less serious than acquired resistance because fewer drugs are usually involved and the level of resistance is lower.

Drug susceptibility testing should be reserved for the following individuals:

- Patients who remain sputum smear positive after two to three months' of intensive therapy;
- Treatment failure and interruption cases;
- Close contacts of MDR tuberculosis cases who have signs and symptoms of tuberculosis;
- High risk individuals who have signs and symptoms of tuberculosis, e.g. health care workers, laboratory workers and prisoners.

5. PREVENTION OF MULTIDRUG-RESISTANT TUBERCULOSIS

Standardised first line regimens

Ensuring cure of (especially) new smear-positive patients the first time around will prevent significant development and subsequent spread of MDR tuberculosis. This is only possible on the scale required by the use of standard regimens. Every effort should be made to ensure that people on the retreatment course complete it as their risk of developing MDR TB is high.

Health system compliance

Compliance refers here to how well the health care system (doctors and nurses) comply with management guidelines as laid down by the Tuberculosis Control Programme. It is essential that adequate drugs, in the correct combinations and dosages, be prescribed for the correct period of time. In a high proportion of MDR TB cases either a single drug is added when a patient does not respond or a "shot gun" approach is used whereby a range of drugs are prescribed in ad hoc fashion eroding the patient's confidence in the treatment.

It is also important that clinicians and nurses make efficient use of resources. The ordering of expensive drugs and investigations in an unsystematic manner leaves fewer resources available for more important interventions such as tracing patients who have missed treatment appointments.

Patient adherence

Here, adherence refers to how well patients manage to complete the full course of prescribed medication. This often depends on adequate counseling, accessibility of the service, the attitudes and ongoing support of health care staff.

Directly observed therapy during at the very least the intensive phase of treatment is the national policy. Excellent adherence during the intensive phase of treatment, during which time the total bacterial load in the patient is being reduced, is crucial to the prevention of MDR TB. This is especially true for sputum smear positive patients who have a higher bacterial load. DOT in the follow up phase is also important to help prevent relapse.

Drug supply

The uninterrupted supply of tuberculosis drugs to treatment points is crucial in preventing drug resistance. This is especially important if combination formulations are not used, e.g. if a treatment point runs out of specific individual drugs, the temptation might be to administer only the drugs which are available. It is therefore recommended that single formulations of tuberculosis drugs be withdrawn from provincial stocks and only be provided through referral hospitals.

Forecasting of consumption at the district level should be done based on the numbers of new and retreatment patients seen and registered during the preceding ordering period. These should be approximately equal to previous quarterly consumption plus 10%. Inventory should fluctuate between one and four months' supply. If inventory is to be reduced, then the re-order interval will need to be shortened. Much will depend on the reliability and cost of transport so that more remote districts might settle for fewer orders per year and larger inventory holdings, while metropolitan districts might prefer to order monthly. Treatment for TB should continue to be free of charge.

Supervision of therapy

Directly observed therapy is considered the optimal form of drug administration for the majority of patients especially during the intensive phase of treatment, and preferably for the entire treatment period. If rigorously applied, especially for sputum smear positive patients, retreatment patients and patients with MDR TB, it will make a major contribution to the limitation of MDR TB.

6. THE DIAGNOSIS OF MDR TUBERCULOSIS

- MDR TB is a laboratory diagnosis.
- It should be suspected in a patient who fails to respond to treatment despite good documented adherence but must always be confirmed by sputum culture and susceptibilities showing resistance to isoniazid and rifampicin with or without additional resistance to additonal drugs.
- If there is a history of close contact with an MDR patient, culture and susceptibilities should be requested on the initial sputum.
- Usually the first indication that the patient may be drug resistant organisms is when the patient fails to respond to treatment despite documented good adherence. This is usually supported by the smear at 2 months being positive which prompts a culture and susceptibility being done.
- If the smear at 2 months is negative and treatment continued and the smear done at 5 months is positive, culture and susceptibilities should be requested. If smear is negative but patient has not clinically responded, culture and susceptibilities should be requested.
- Do not add streptomycin or any single drug to a failed regimen as this may result in a single

agent being added to drugs to which the organism is resistant. Always await laboratory confirmation of drug susceptibilities.

The diagnosis of MDR TB is made by finding that the TB organisms in the sputum are resistant to at least rifampicin and isoniazid. When requesting sensitivity testing, ethambutol should be included.

The classification of a patient as MDR TB carries very serious consequences and should only be made by or at the very least in consultation with a physician experienced in managing MDR TB patients. A list of names and contact details is available from the provincial or national TB programme.

A person with bacteriologically proven PTB who continues to produce positive smears despite regular observed swallowing of standard treatment and is not improving clinically, with at least 1 positive culture and susceptibility tests which show resistance to at least rifampicin and isoniazid should be started on treatment for MDR TB. If in the opinion of an experienced chest physician at the referral clinic the patient´s history and clinical condition and CXR makes the diagnosis of MDR TB very likely, standard MDR TB therapy can be started while awaiting laboratory results.

Annexure 1: Assessing the individual case of apparent MDR tuberculosis should be read carefully.

7. LABORATORY ASPECTS

Identification of MDR strains of *M. tuberculosis* can only be established through culture and susceptibility testing of the organism. Routine susceptibility testing should be carried out for patients at risk of harbouring MDR strains, i.e. patients qualifying for the retreatment regimen and for whom this regimen has failed.

The so-called “proportion method” is commonly used for determining drug susceptibility of *M. tuberculosis* isolates in the laboratory. The results of this method are reported as the percentage of the total bacterial population resistant to a specific drug, which is defined as the amount of growth on a drug-containing medium as compared with growth on a drug-free control medium.

When 1% or more of the bacillary population become resistant to the so-called “critical concentration” of a drug, the *M. tuberculosis* isolate is regarded as resistant to that drug. The critical concentration is the concentration that inhibits the growth of most cells of susceptible strains of *M. tuberculosis.*

Drug concentrations for susceptibility testing

The quality of laboratory susceptibility testing is of paramount importance and impacts directly on tuberculosis treatment. Laboratory methodology and reporting must be standardised and appropriate

controls must be used. Each drug should be tested at its critical concentration, i.e. the concentration that inhibits growth of the majority of wild strains of *M. tuberculosis* without markedly affecting the growth of resistant mutants present. Some critical concentrations are listed in Table I.

Table I: Critical drug concentrations for routine susceptibility testing (µ/ml)

Drug	Radiometric	Conventional	
	Bactec 12B	Middlebrook 7H10	Löwenstein-Jensen
Isoniazid	0.1	0.2	0.2
Rifampicin	2.0	1.0	40.0
Ethambutol	2.5	5.0	2.0
Streptomycin	2.0	2.0	4.0

The quality of susceptibility tests carried out in central laboratories should be checked regularly as errors are not uncommon. A single report of MDR tuberculosis without additional clinical evidence should be regarded with caution. Labs detecting resistance to more than one drug (for the first time on a patient) should fax and/or telephone the results to the requesting facility.

Cultures (not susceptibility testing) should be done monthly, until three consecutive monthly cultures have become negative. Thereafter, cultures should be performed every three months until the completion of treatment. Treatment should be continued for 12 months after cultures first become negative.

All laboratories doing cultures and tests of drug susceptibility must be part of a recognised external quality control system.

8. MANAGEMENT OF PATIENTS WITH SINGLE DRUG RESISTANT TUBERCULOSIS

Standard short course TB drug therapy is the best way to prevent MDR tuberculosis. Standard regimens are also effective in patients with bacilli singly resistant to isoniazid and/or streptomycin. Reported rifampicin-only resistance does occasionally occur. If the patient is deteriorating clinically, MDR TB treatment should be considered. Culture and sensitivity tests should be repeated.

In the group of patients previously treated with one or several courses of chemotherapy and who remain smear/culture positive, three sub-populations can be observed:

- patients excreting bacilli still susceptible to all antituberculosis drugs;

- patients excreting bacilli resistant to at least isoniazid, but susceptible to rifampicin;
- patients excreting bacilli resistant to isoniazid *and* rifampicin

The respective proportion of the three sub-populations varies according to the chemotherapy applied in the community during the past years. It varies also with the number of courses of chemotherapy received by the patients:

- In patients who are still smear positive after the *first course of chemotherapy,* the proportion of patients excreting bacilli still susceptible to all drugs is usually higher than the proportion of the two other sub-populations. For this reason, the standard *retreatment* regimen of eight months given under direct observation can cure the majority of patients including those still harbouring susceptible bacilli, and those having bacilli resistant to isoniazid and/or streptomycin, but still susceptible to rifampicin.

- In patients whose treatment has failed after *two courses of chemotherapy* (the second being the fully supervised standard *retreatment* regimen), the majority (up to 80%) will harbour INH and rifampicin resistant bacilli. The proportion of patients with MDR tuberculosis can be as high as 50% of this group of patients. For this reason, a second application of the standard retreatment regimen is likely to fail and these patients should be considered eligible for MDR treatment.

  It cannot be emphasised strongly enough that a patient improving clinically and radiologically with a resistant TB bacilli lab report should be considered to have an abnormal lab report and investigated again rather than put on MDR TB treatment immediately.

9. MANAGEMENT OF PATIENTS WITH MULTIDRUG RESISTANT TUBERCULOSIS

Specialised facilities or specialised management teams

Treatment of patients with MDR tuberculosis involves second line, reserve drugs. These are much more expensive, less effective and have more side effects than standard tuberculosis drugs. Treating MDR patients requires experience and special expertise. It is therefore recommended that each province establish a specialised referral facility or management team to which MDR tuberculosis patients can be referred for evaluation, prescribing of treatment and follow-up, as well as for specialised counseling as already described. In provinces where the incidence of MDR tuberculosis is too low to make this a viable option, this team could also provide a referral facility for patients with other lung diseases and ordinary tuberculosis, who are referred from clinics with problems such as

allergic reactions to drugs and who may need specialist attention.

Specialised management teams should at the least consist of a respiratory physician or a specially trained medical officer, supported by a dedicated MDR TB-trained nurse, a social worker and an administrative assistant. These teams should oversee all aspects of MDR tuberculosis management and should be solely responsible for decisions about treatment and surgery.

Particular attention must be paid to **full documentation** of patient particulars and every effort must be made to ensure that all patients are seen by the management team at least once during the course of the disease to ensure an adequately detailed management plan but preferably on a monthly basis. Routine treatment of MDR tuberculosis patients at primary health care clinics should not be attempted. However, supervision of therapy for those patients being treated as outpatients may be available at certain clinics. In this case the required drugs should be made available to the approved clinic on a named-patient basis only, and on prescription from the MDR TB referral centre. Provincial health authorities should restrict the use of second-line reserve drugs in order to reduce the incidence of incurable tuberculosis.

Referral centres are not necessarily centres for the admission of patients, although they should be linked to hospitals with isolation facilities or special wards, since many patients will be referred from far away and will need admission during evaluation. The main function of these clinical management teams will be the evaluation of patients, prescribing of treatment, follow up, specialised counseling, training of staff and problem solving for special cases.

Some patients with MDR-TB will be admitted for at least the first few months until they have produced three consecutive monthly culture negative sputa. During this time, plans should be made for the provision of treatment at designated clinics which should be supplied with the drugs required prior to the patient's discharge from hospital, *on a patient named basis.*

Home Care of MDR TB

After evaluation at a specialised clinic, many patients can be successfully managed with ambulatory treatment provided DOT is ensured, therefore reducing costs, freeing up scarce beds, enabling patients to remain in employment and therefore preventing treatment interruption. Patients are educated on basic infection control procedures: safer coughing and sputum disposal, seperate sleeping place, ventilation and sunlight. It must be remembered that the person has already had contact over a long period with those he/she lives with, so the extra risk is small. If any of the following

criteria are applicable, the patient should be admitted.:

- Poor clinical condition
- Previous treatment interrupter.
- Complications (ie haemoptysis)
- Major adverse drug reactions.
- Poor social circumstances

Management of MDR tuberculosis patients should be characterised by:

- rational drug susceptibility testing of specimens from MDR-tuberculosis patients;
- provision of a social worker for counseling and support;
- provision of key nursing staff to provide continuity and direct observation of treatment;
- keeping updated registers;
- monitoring compliance;
- developing measures for rapid recall if patients interrupt their treatment;
- increased education and motivation of patients;
- tracing and evaluating contacts rapidly.

With the foregoing considerations in mind, specialised facilities and management teams for dealing with MDR tuberculosis may be regarded as an expensive luxury which are only affordable where national/provincial resources are adequate and after full implementation of standardised treatment regimens for new and retreatment patients has been achieved. A gross waste of resources will occur unless these facilities / teams consist of skilled and experienced staff who are given long-term responsibility. Treatment decisions should not be made by untrained and unsupervised persons on an *ad hoc* basis. Provincial protocols for the referral assessment and management of MDR tuberculosis patients should be worked out in consultation with all role players. An approach to assessing patients with MDR tuberculosis is given in Annexure 1.

Counselling of patients

Patients with MDR tuberculosis face the prospect of lengthy and often unpleasant treatment as well as the real possibility of premature death. Therefore counselling and emotional support are particularly important, much as in any other chronic life threatening illness (i.e. malignancies or HIV related diseases). Proper early counselling will also help to ensure good adherence to the treatment regimen and increase the likelihood of a successful outcome.

Once the patient is on treatment, further support will be required in order to maintain the patient's commitment and to help to identify social and emotional problems early so that they may be addressed before they interfere with the treatment programme. If treatment has been unsuccessful and further treatment becomes futile then it becomes very important that the patient is not merely abandoned, but

that s/he should continue to receive sympathetic and palliative care from the health team.

It should be clear, therefore, that skilled counselling services are an essential part of the team approach to the management of this disease. All staff however should show empathy to patients and provide support at every contact.

Training and review

Specific training programmes should be arranged in each province to ensure that policy details are communicated to all doctors and nurses who might be involved with the diagnosis, referral and treatment of MDR tuberculosis patients.

Training should be ongoing and practice should be reviewed annually. This should be facilitated by the Provincial Tuberculosis Coordinator in close co-operation with the head of the specialised MDR centre.

Every case of MDR tuberculosis should be reviewed and the reasons for the case developing should be documented.

Each centre should conduct an annual review on the probable causes of MDR TB, the outcome of treatment and the costs involved. Each centre should provide such a report to the Provincial Head of Health annually.

It must also be born in mind that most cases of MDR TB will be part of the group who have dropped out of treatment and therefore not under the control or influence of the health service. The treatment of MDR TB is to help individual patients and their families. The strict control of known patients with MDR TB may decrease the spread but will not control the MDR TB epidemic. Only curing a very high proportion of patients with ordinary Pulmonary TB at the first attempt and using combination drugs not single drug tablets in clinics and hospitals can we hope to contain the TB MDR rate.

10. TREATMENT REGIMENS

Health teams in the Provinces should elect to follow either Approach 1 in which all patients are offered the same regimen, only substituting ethambutol for cycloserine, should the organism be sensitive (to ethambutol), or Approach 2 in which the regimen is selected after consulting the detailed results of susceptibility testing. In reality, the two options are similar due to the limited number of reserve drugs available, but fewer mistakes are likely to be made with approach 1. Approach 1 is strongly recommended as the regimen of choice for provinces. Approach 2 leaves far greater margin for error.

Approach 1 STANDARD TREATMENT REGIMEN

The standard treatment regimen for MDR tuberculosis patients consists of a four-month intensive phase with five drugs (kanamycin, ethionamide, pyrazinamide, ofloxacin, and cycloserine or ethambutol), followed by a 12-18 month continuation phase with three drugs (ethionamide, ofloxacin and cycloserine or ethambutol) as indicated in Table II. Drugs should be administered five times per week in clinics and seven times per week in hospitals. The continuation period may be shortened provided that 12 months of treatment has been given after sputum conversion as demonstrated by three consecutive monthly negative cultures. A description of these drugs is given in Annexure 2 and their side-effects are presented in Annexure 3. The approach is summarised in Table II.

Table II: Approach 1 for the treatment of MDR tuberculosis

Intensive phase: 4 months

Drug	Daily dosage	
	Average (mg/kg)	Maximum (mg)
Kanamycin	15	1 000
Ethionamide	10-20	1000
Pyrazinamide	20-30	1 600
Ofloxacin or Ciprofloxacin	7.5-15 7.5-15	800 1500
Ethambutol or Cycloserine	15-25 10-20	1200 1000

Continuation phase: 12-18 months

Drug	Daily dosage	
	Average (mg/kg)	Maximum (mg)
Ethionamide	5-10	750
Ofloxacin or	7.5-15	800
Ciprofloxacin	7.5-15	1500
Ethambutol or	15-25	1200
Cycloserine	10-20	1000

Approach 2 : INDUVIDUALISED TREATMENT REGIMEN

With this approach, treatment regimens are based on the results of drug susceptibility tests. This implies that treatment be delayed until susceptibility results are available, or that patients are started on the standardised regimen if the sputum smear is still positive after the retreatment course while awaiting drug susceptibility.

- Monitor progress initially by monthly smears and cultures until at least 3 consecutive cultures are negative and then every 3 months until treatment is completed. Only request susceptibilities at month 3 of 6 if culture is still positive. CXR can be done every 3 months until treatment is completed.
- Ideally patients should be followed up for 2 years following completion of treatment with 6 monthly sputum culture and CXR's.
- Minimum duration of treatment with either regimen is 12 months after the first negative sputum culture. Usual duration of treatment is 18 months.
- An aminoglycoside should be given daily for a minimum of 4 months. Once the culture is negative, it is possible to reduce the dose to three times per week until 6 months treatment is completed.

Designing an appropriate regimen needs experience and skill. It is necessary to summarise previous treatment(s), drug susceptibility results, adherence history, clinical course and adverse reactions to drugs used previously. It is, therefore, recommended that Approach 2 be followed only in those provinces where the necessary referral mechanisms, specialised centres and medical, laboratory, and administrative expertise exists.

Drugs for the treatment of MDR tuberculosis patients are classified according to their bacteriological activity, toxicity and patient tolerance. The main criteria are based on biological data, which determine three groups of drugs available according to their activity and cross-resistance.

Classification of drugs available for MDR tuberculosis treatment

- drugs with moderate bactericidal activity: aminoglycosides, thioamides and, under acid pH conditions, pyrazinamide;
- drugs with low bactericidal activity: fluoroquinolones;
- drugs with bacteriostatic effect when given at usual dosages in man: ethambutol, cycloserine, PAS.

The ranking of drugs for treatment of MDR tuberculosis is presented in Table III on the following page. Drugs should be selected from the higher ranking categories if possible (i.e. if the bacteria are susceptible).

Table III: Ranking of antituberculosis drugs for treatment of MDR tuberculosis

Rank	Drugs	Average daily dosage	Type of activity (Category)	Peak serum level:MIC
1	Aminoglycosides		Bactericidal (actively multiplying organisms)	
	Streptomycin	15 mg/kg		20-30
	Kanamycin	15 mg/kg		5-7.5
	c. Amikacin	15 mg/kg		10-15
2	Ethionamide	5-10 mg/kg	Bactericidal	4-8
3	Pyrazinamide	20-30 mg/kg	Bactericidal (acid pH)	7.5-10
4	Fluoroquinolones			
	a. Ofloxacin	7.5-15 mg/kg	Weakly bactericidal	2.5-5
	b. Ciprofloxacin	7.5-15 mg/kg	Weakly bactericidal	-
5	a. Ethambutol	15-20 mg/kg	Bacteriostatic	2-3
	b. Cycloserine	5-10 mg/kg	Bacteriostatic	2-4

The initial regimen should consist of at least four drugs to which the bacilli have been shown to be susceptible. At least three of these should not have been administered to the patient previously (i.e. for three months or more). **Not more than 1 drug should be chosen from each of the categories in Table III, and all patients should receive an aminoglycoside during the intensive phase of treatment**.

Apart from the acceptable daily dosages, other criteria should also be considered:

_ toxicity;

_ patient tolerance;

_ acceptability (e.g. bulk or volume of drug to be injected/swallowed; taste, pain).

Approach 2 requires considerable time and expertise, access to drug susceptibility testing (also of the second-line drugs) and close monitoring of individual patients, with changes in treatment as indicated by susceptibility results. The approach in inexperienced hands can result in too frequent changes of medication, especially if laboratory tests are treated rather than patients. Approach 1 requires less access to routine culture facilities and monitoring of patients is mainly for side effects and culture conversion. MDR TB is difficult to treat. The margin of error in approach 1 is far less and this approach

is therefore strongly recommended.

Results from a meta-analysis of several controlled trials of the drugs used in the treatment of MDR TB are summarised in Table IV.

Table IV: Formulation, acceptable daily dosages and main characteristics of antituberculosis drugs available for the treatment of MDR tuberculosis

Drugs	Formulation	Daily dosage (mg)			Tolerance	Toxicity
		Minimum	Maximum			
Aminoglycosides						
- Streptomycin	Vial, 1g	750	1 000	Injection	Moderate	Medium
- Kanamycin	Vial, 1g	750	1 000	Injection	Poor	Medium
- Amikacin	Vial, 1g	750	1 000	(Painful)	Poor	Medium
- Capreomycin*	-	750	1 000	Injection	Moderate	Medium
Thioamides						
- Ethionamide	Tab, 250 mg	500	750	Good	Moderate	Medium
- Prothionamide*	-	500	750	Good	Moderate	Medium
Pyrazinamide	Tab, 400 or 500 mg	1 200	1 600	Good	Moderate	Low
Fluoroquinolones						
- Ofloxacin	Tab, 200 mg	600	800	Good	Good	Low
- Ciprofloxacin #	Tab, 250 mg	1 000	1 500	Good	Good	Low
Ethambutol	Tab, 400 mg	1 000	1 200	Good	Good	Low
Cycloserine	-	500	750	Good	Moderate	High
PAS acid*	- -	10 000 10 000	12 000 12 000	Bad (bulk, taste) Good	Poor Moderate	Low Low

*Not available in South Africa

#Ciprofloxacin can be substituted for ofloxacin.

11. GENERAL MANAGEMENT PRINCIPLES

Irrespective of whether Approach 1 or Approach 2 is followed, certain essential management principles should be adhered to under all circumstances:

- Directly observed therapy throughout the treatment course is essential.

- Aim for 18-24 months of treatment, always with an initial 4 months of intensive therapy. The continuation period may be shortened provided that 12 months of treatment have been given after sputum conversion as demonstrated by 3 consecutive negative monthly cultures.

- Establishing the HIV status is of clinical importance, since HIV sero-positive patients may suffer increased side effects from anti-tuberculosis drugs.

- When side-effects occur that are not potentially life threatening, every effort should be made to coach patients through with palliation and psychological support. Drugs with known severe side effects may be given in divided doses to improve tolerance. Patients with severe side effects should be treated in hospital.

The Management of Nausea and Vomiting as the most common side effect of drugs

- try to get patient to identify the drug
- ethionamide often implicated but also ethambutol, ofloxacin and isoniazid
- give antiemetics ie metaclopromide 10 mg tid (beware long term use can induce extrapyramidal signs)
- if continues stop ethionamide
- when settles restart with 250 mg/day
- if tolerated build up to 250 mg bid and then 250 mg tid at 3 or 4 day intervals.
- Retry 750mg/day
- If the patient is very intolerant despite all of these measures, stop the offending drug; continuation will often lead to treatment interruption.

- Patients should be warned that ototoxicity may occur with prolonged use of aminoglycosides, and should be asked to report any loss of hearing immediately.

- Clinical progress should be documented regularly and a chest radiograph should be obtained every three months.

With approach two:

- On referral, summarise previous treatment regimens and drug resistance results.
- Select an appropriate regimen.
- Never add a single drug to a failing regimen.
- Do not use drugs indiscriminately, i.e. in a “shotgun” approach.
- Treatment should never be changed without laboratory support. However, laboratory errors do occur. If a single discrepant result is received and it does not accord with the clinical assessment, the test should be repeated and treatment should not be changed while awaiting laboratory results. **Treat the patient, not the laboratory result!**

12. THE ROLE OF SURGERY

Surgical intervention was widely practised before the advent of chemotherapy. In the chemotherapy era it became apparent that drug treatment alone was sufficient to cure most patients. It is stressed that the treatment of MDR tuberculosis is first and foremost chemotherapeutic. There are however four indications for surgery; all presume the disease is mainly unilateral and that there is adequate cardiopulmonary reserve.

Definite indications

- Persistence of positive sputum cultures and lack of radiographic and clinical improvement after six months of adequate therapy and patient adherence;
- Relapse in the same site after a previous adequate course of chemotherapy in a patient who has been adherent.
- **Lesser indications**
- In a patient who has undergone sputum conversion but the original profile of drug resistance is so great (i.e. four or more drug resistance) that if relapse did occur it may be difficult to re-establish sputum culture conversion;
- In a patient who has undergone sputum conversion but there is residual cavitation or gross lobe or lung destruction and hence the potential for relapse.

At least 6 months of treatment should be given before surgery if at all feasible. The decision to perform surgery and the extent of surgery i.e. lobectomy or pneumonectomy should be made after anatomical

localisation of disease by CT scan. Often the apex of a lower lobe is involved together with a corresponding upper lobe and the former should also be removed. Perfusion scans are useful in establishing how much functioning lung is likely to be removed. Basic spirometry (i.e. FEV1 and FVC) is adequate in assessing lung function in the majority of patients. The electrocardiogram is useful for excluding pulmonary hypertension which would contraindicate surgery.

The resected specimen should be sent for histology and culture and susceptibility. Sputum cultures should be performed immediately post surgery and then monthly until three consecutive negative cultures have been obtained. If the patient was positive at the time of surgery the treatment should continue for 12 months after a negative culture.

Final points

In a patient who has not undergone sputum culture conversion, surgery should only be performed when there is no further possibility of an adequate chemotherapeutic regimen. There is no place for segmental/limited resection.

13. ETHICAL ISSUES

If a patient remains smear/culture positive after 4 months of intensive and 3 - 5 months of follow-up treatment, a decision needs to be taken to shift the treatment to palliative care. The situation should be fully and sympathetically explained to the patient, and to the family. Full, empathetic and supportive care should be made available to the patient and family. Patients in this situation should understand that although cure is unlikely they have not been abandoned. Patients should have been educated on basic infection control procedures after returning to their households/communities, e.g. safe coughing and sputum disposal, not sharing sleeping space with children, adequate ventilation, etc. Patients who have survived this long should still be followed up to help them deal with their situations if at all possible by the same staff who have been helping them so far.

Should an MDR patient miss more than two weeks treatment on two occasions, the patient should be interviewed by an empathetic counsellor. The patient should be informed that further interruption may result in curative treatment being terminated. This policy must be carefully explained to patients as part of initial counselling and their response documented. Expensive MDR TB treatment should not be restarted for a third time, except in very exceptional circumstances.

Patients with MDR tuberculosis who have late stage AIDS have in general a very poor prognosis. There will be occasions where a patient's condition as a consequence of AIDS is so poor that it will be

inappropriate to embark on a course of toxic chemotherapy for MDR tuberculosis. Under these circumstances it may be more appropriate to give only symptomatic treatment and advice on infection control. The decision not to treat such individuals should be taken at the referral centre by the management team, and it presupposes that full palliative and supportive care will continue to be given. It should be emphasised that patients in the early stages of HIV disease may respond well to chemotherapy. HIV status alone should not be used as a justification not to treat with curative intent.

14. CONTACTS OF MDR TUBERCULOSIS PATIENTS

Infection with MDR bacilli will be the cause of treatment failure in very few individuals. Even when transmission of drug resistant TB bacilli from a chronic patient to a new patient has been clearly demonstrated, there is no evidence that the success rate with standardised regimens is less than for new cases. This is probably because any population of TB bacilli has a proportion of resistant and susceptible bacilli. The immune system takes care of most if not all of the bacilli, with first line TB drugs helping to kill off most of the rest.

The effectiveness of preventive therapy in persons exposed to or infected with MDR tuberculosis organisms is not known. Factors which should be considered in the management of contacts include the likelihood of infection with MDR tuberculosis among contacts thought to be *newly* infected and the likelihood that the contact, if infected, will develop active tuberculosis. Contacts who have had exposure to a patient with MDR tuberculosis and are likely to be newly-infected should be evaluated to assess the likelihood of the actual infection being a MDR strain of *M. tuberculosis*.

Factors that should be considered include:

- the infectiousness of the MDR tuberculosis source case;
- the closeness and intensity of the exposure;
- the likelihood of exposure to persons with drug-susceptible tuberculosis;

Infectiousness of the source case

Tuberculosis patients including MDR cases who cough and have smear-positive sputum are substantially more infectious than those who do not cough or who have smear-negative sputum.

Closeness and intensity of MDR tuberculosis exposure

Persons who share air space with an MDR tuberculosis patient for a prolonged time (e.g. a household

member, hospital roommate) are at higher risk for infection than those with a brief exposure. Further, exposure in a small, enclosed, poorly-ventilated space is more likely to result in transmission than exposure in a large, well-ventilated space. Finally, exposure during cough-inducing procedures (eg. sputum induction, bronchoscopy) may greatly enhance transmission.

Contact history

Persons exposed to several sources of *M. tuberculosis*, including infectious tuberculosis patients with drug-susceptible strains, are less likely to become infected with an MDR tuberculosis strain than those whose only known exposure was to an infectious MDR tuberculosis case.

Recentness of infection also contributes to the risk of developing active tuberculosis: Persons with recently acquired *M. tuberculosis* infection are at relatively high risk of developing active disease: In immunocompetent persons, the risk of developing tuberculosis is highest within the first two years following infection, after which this risk declines markedly. In general, 5%-10% of infected immunocompetent persons will develop active disease within the first two years. Child contacts of MDR tuberculosis patients (especially those under two years of age) are at increased risk.

The most potent factor, however, that increases the probability that a person infected with MDR tuberculosis will develop active disease is impaired immunity. Impaired immunity is increasingly seen in persons infected with the AIDS virus. It should be remembered however that there are many other medical causes of impaired immunity, including malnutrition, some congenital syndromes, certain haematological diseases, and endocrine, or renal disease (notably diabetes mellitus). In addition, patients who are receiving immunosuppressive drugs (steroids, anti-cancer chemotherapy) or radiation therapy may also be considered to be at increased risk.

Management of contacts of MDR tuberculosis patients

- Manage contacts of sputum smear *negative* MDR tuberculosis patients according to the standard recommendations for infected contacts of drug-susceptible tuberculosis patients;
- Identify contacts of sputum smear *positive* MDR-tuberculosis cases rapidly;
- Child contacts aged five years and younger should be placed on preventive therapy irrespective of state of health and tuberculin response. In the absence of information on the effectiveness of preventive therapy for MDR tuberculosis the national guidelines for contacts of susceptible tuberculosis cases apply;
- Child contacts aged five years and younger who have reactive Mantoux PPD reactions

(>=14mm) should also be placed on preventive therapy according to the national guidelines;

- In children older than five years as well as in adult contacts, a strongly reactive tuberculin test indicates infection but not necessarily disease. The decision to start these persons on treatment depends on clinical history, examination and investigation. Routine preventive therapy in ordinary contacts is not considered appropriate. The patient should report the first signs of possible TB. There should be a careful risk assessment. Sputum should be sent for smear, culture and sensitivity and a CXR taken. Presumptive MDR-TB treatment, in general, should be avoided. Remember that the treatment is toxic and compliance difficult. Those contacts who are HIV positive should be followed up 3 monthly and encouraged to report symptoms and signs early on.

15. HEALTH CARE WORKERS AND MULTIDRUG-RESISTANT TUBERCULOSIS

Transmission of tuberculosis, including MDR tuberculosis, is a recognised risk for health care workers (HCWs). In addition, persons with HIV are at greater risk for TB disease as evidenced by explosive and lethal outbreaks of MDR tuberculosis in HIV-infected patients and HCWs in hospital environments elsewhere in the world.

It is not possible to cover every risk. What follows is a reasonable compromise. Health workers in TB wards who are not immune compromised have not been found to be at a much higher risk of TB or MDR TB than the general population.

Transmission of tuberculosis

The infectious source of *Mycobacterium tuberculosis* (and by implication also MDR tuberculosis) is mainly adults with pulmonary disease, especially where cavitation is present. Infective particles are usually derived from moist particles discharged into the air by forced expiration through the mouth and nose, e.g. coughing, sneezing, spitting or by procedures liberating aerosols. Once aerosolised materials dry out to form droplet nuclei about 1-5 microns in size, infective particles are formed. Droplet nuclei remain airborne and are inhaled and trapped in resident lung alveolar macrophages, where they initiate infection.

The risk for an individual of becoming infected with tubercle bacilli depends on the concentration of organisms in the source case, the duration of exposure to air contaminated with tubercle bacilli and the aerodynamics of the droplet nuclei: Patients with infectious tuberculosis may have between 10^7 and 10^8 organisms in a cavitating lesion. A 10µ droplet nucleus may carry three to ten tubercle bacilli. In indoor environments, droplet nuclei can remain suspended in the air for long periods of time, unless

they are removed by ventilation or filtration. Virtually all transmission occurs in enclosed environments. The infective dose is very low and may constitute fewer than 10 tubercle bacilli, Only about 6% of inhaled organisms reach the lung alveoli; the majority of inhaled particles settle in the upper respiratory track and are expelled or harmlessly swallowed and digested. The probability of a person becoming infected during a one hour exposure period has been estimated to range from 1 in 600 (0.2%) to 1 in 4 (25%).

Contaminated clothing, bedding, eating utensils and books etc. are not involved in the spread of tuberculosis infection and need no special attention. Infection rarely occurs when bacilli are introduced through the skin. This is occasionally seen among pathologists and laboratory workers handling infected specimens. Human sputum is, however by far, the most important source of infection and other infected body fluids present no practical risk to the majority of HCWs.

Contact therefore does not mean infection.

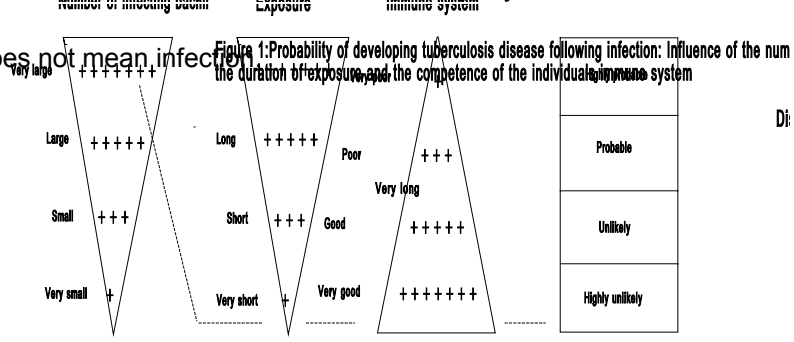

Figure 1:Probability of developing tuberculosis disease following infection: Influence of the num the duration of exposure, and the competence of the individual's immune system

Pathogenesis of tuberculosis

It is useful to understand the pathogenesis of TB, in order to understand the risk.

Most people do not develop tuberculosis disease following infection, since specific cell-mediated immunity usually develops within two to ten weeks after the initial infection. In most cases, this immunity arrests multiplication and averts clinical disease. In immunocompetent persons who are exposed to infectious tuberculosis for a prolonged period (hours or days rather than minutes), 20% to 50% may become infected. In 90% of infected individuals the organisms become dormant and cause no clinical disease. 5% may develop early tuberculosis (usually within two years after infection). A

further 5% may develop disease at some point during their lifetime, usually as a result of physical or emotional stress that adversely affects the immune system. Infection with the human immunodeficiency virus (HIV) is presently the most important risk factor for developing disease following infection. HIV kills T-helper cells (T4 lymphocytes), which reduces the infected individual's defence against *M. tuberculosis*. HIV infection therefore increases the risk of reactivation of dormant tuberculosis infection, as well as the risk of progressive disease following new infection.

The relationship between tuberculosis and disease and the associated risk factors are illustrated in Figure 1. Putting the risk into perspective means that, for the establishment of a tuberculosis infection sufficient to produce tuberculosis disease, exposure must be close and prolonged, the environment heavily laden with infectious droplet nuclei and the prospective host unprotected by his/her own immune mechanisms. Over-crowded living conditions with poor housing and sanitation increase the ease of transmission of *infection*, while factors adversely affecting the immune status of individuals (e.g. HIV, alcohol abuse, diabetes, cancer) increase the likelihood of the development of *disease*. The declining cellular immunity caused by HIV is associated with reactivation of old, endogenous tuberculosis foci; *and increases* susceptibility to new *TB* infection.

RISK ASSESSMENT

It has been well established that the risk of infection with tuberculosis depends on the severity of disease in the source case and on prolonged, intensive exposure to this case. It follows, therefore, that all HCWs are not at equal risk of acquiring infection, and that for many cadres of HCWs the risk is almost equal to that of the general community. The following categories of risk may be surmised:

High risk

- HCWs in prolonged close contact with infectious (smear-positive) MDR tuberculosis cases, e.g. nursing staff and other medical staff in MDR tuberculosis wards/centres;
- HCWs involved in aerosol-producing procedures, e.g. pulmonary physicians, respiratory technicians and other medical staff performing bronchoscopy, sputum induction, tracheal intubation, aerosolised pentamidine therapy and autopsy procedures;
- HCWs who are HIV-positive and who are involved in regular tuberculosis patient management.

Medium risk

- HCWs in primary health care centres who are involved in sputum collection procedures from tuberculosis suspects;
- HCWs in prolonged close contact with retreatment tuberculosis patients, especially if such patients have a history of more than one previous treatment episodes and a record of poor

adherence;

Low risk

- HCWs in primary health care centres involved in management of tuberculosis patients on therapy;
- Health care facility support staff, such as porters, cleaners and administrative staff;
- HCWs in general hospitals and community health centres.

IRRESPECTIVE OF THE LEVEL OF RISK, THE FOLLOWING PRINCIPLES APPLY:

- HCWs should receive ongoing education and training on the transmission and pathogenesis of tuberculosis and the consequences of MDR tuberculosis;
- The importance of a continuous awareness of risk situations and their avoidance should be stressed;
- HCWs should be informed about the increased risk of acquiring tuberculosis (and MDR disease) should they become HIV positive. Confidential HIV testing and alternative employment should be offered to those testing HIV positive;
- Universal infection control procedures should be implemented in all health care facilities, including safe waste disposal.
- Coughing behaviour should be strictly controlled. Sputum collection is especially dangerous (see the procedures described in the Practical Guidelines). All the patients in every hospital who are coughing should be isolated as far as possible. In clinics and outpatient settings, these patients should not be allowed to sit in waiting rooms for any length of time. Consideration should be given to setting up an adult cough clinic at every hospital where patients can be rapidly assessed, entered into a cough register for proper follow up and encouraged to come for re-evaluation.
- Inpatients who are coughing should be in a single ward with good outside ventilation and large windows if at all possible. They should be nursed with the door shut and the windows open as far as possible if the ward is

not under negative pressure.

IN HIGH RISK ENVIRONMENTS ONLY, THE FOLLOWING ADDITIONAL PRINCIPLES APPLY:

The assumption is that TB if discovered early has a higher cure rate.

Disease monitoring programme for HCWs in high risk environments

Each HCW should have a confidential disease monitoring file in which screening procedures for tuberculosis as well as other health-related data are recorded. The elements of a disease monitoring programme include the following:

Employment profiles and baseline screening of employees

A standardised health questionnaire should be completed for each employee for purposes of compensation. This questionnaire should relate past tuberculosis disease, BCG vaccination status, underlying medical conditions which may increase susceptibility of HCWs to tuberculosis and previous contact with confirmed tuberculosis cases. A baseline chest x-ray and a Mantoux tuberculin skin test (TST) should be performed.

A baseline blood serum sample should be collected and stored untested. The taking of such specimens should be optional but may be useful should improved serum testing for tuberculosis become available. These samples could also be tested for HIV antibodies or hepatitis B, at the request of the employee after counselling. HCWs should be made aware of the serious consequences which may occur in HIV positive individuals who become infected with MDR tuberculosis strains.

* *A health worker and colleagues should be encouraged to report the first symptoms and signs of TB disease: Tiredness, weight loss, persistent cough and loss of appetite. These symptoms tend to come on gradually and may be passed off as flu or stress. Many health workers have put off being investigated until the disease has caused permanent lung damage. Health workers should encourage colleagues to report at the first suspicion. Two sputum specimens, collected on successive days, should be investigated for tuberculosis by microscopy and culture.*

Annual screening for those who continue to work in high risk situations

HCWs should be offered an annual full size chest x-ray examination for evidence of recent tuberculosis disease. Individuals exhibiting changes on serial examination or recent skin test converters should be evaluated for tuberculosis, both clinically and microbiologically.

HCWs with TST reactions of <10mm should be re-tested. Strongly positive reactors with skin test diameters of >15mm should be evaluated clinically and microbiologically.

Quarterly record of health status in high risk situations

HCWs should declare information on their health status in the form of answers to specific questions relating to the early signs and symptoms of TB. These include cough for longer than three weeks, weight loss, anorexia, night sweats and the frequent occurrence of colds or other respiratory infection episodes in recent weeks.

The HCW's weight should be recorded during each monitoring visit and an unexplained loss of 10% or more of body weight during the previous quarter should be followed up with clinical and microbiological investigations for tuberculosis. Quarterly information on health status can be obtained by using a simple structured questionnaire.

Post-exposure monitoring

If other HCWs have been heavily exposed to an infectious MDR patient for more than two hours or to aerosolised infected material (e.g. in autopsy rooms), their monitoring files should be consulted and their chest x-ray and TST records reviewed. The HCW should be carefully monitored clinically. Eight weeks after the exposure episode, a chest x-ray examination should be performed, together with a TST in cases where the previous reaction diameter was <10mm.

Findings at eight weeks after exposure should be managed according to the guidelines described earlier.

Preventive measures in medium to high risk situations

The prevention of MDR tuberculosis focuses on both the infectious patient (or infected material) and on the HCW who is at risk of becoming infected.

All patients should be instructed to cover their mouths and noses with gauze or a tissue during coughing and other forms of forced expiration. Wearing an ordinary paper mask is another option to prevent widespread droplet dispersal. Immediately after use these materials should be disposed of in small plastic or paper refuse bags which should be regularly changed and discarded into larger refuse bags for incineration. Alternatively, a synthetic phenolic such as Hycolin 2% or 5% concentrations of an iodine-containing or a hypochlorite solution containing 10 000 ppm active chlorine should be used for disinfection and disposal.

HCWs should wear specially designed masks (particulate respirators) which are impermeable to droplet nuclei. An industrial mask with a 1μ m particle size and a filter efficiency of more than 95% is recommended (3M Health Care 1860 Particulate Respirator Type N95 or equivalent). These masks

should be discarded after eight hours of use.

Collection of sputum specimens should take place if at all possible in the open air on the sunny side of the ward. A special veranda should be built for this purpose. The correct procedure for sputum collection has been described in the Practical Guidelines of the National Tuberculosis Control Programme. These must be read carefully and followed to decrease the risk for everyone in that area.

16. MDR TB WARDS

The risk of MDR TB is greatly increased in a hospital ward where MDR TB patients and HIV positive patients sleep in the same room. Any patient especially those with possible TB or chronic TB who is coughing should be nursed in a single bed ward with the doors closed and the windows open or a properly placed extractor fan. Extractor fans should be installed. It should be mandatory for staff in such wards to wear masks impermeable to droplet nuclei. Patients who are coughing should wear ordinary paper masks.

Although many MDR TB patients are treated for long periods in ordinary TB wards while awaiting drug susceptibility results, MDR TB patients should probably be housed in separate wards with properly placed extractor fans and sealed windows. Airconditioning may be necessary. The use of ultraviolet lights also in the passage outside should be considered even though their value has not been determined conclusively.

The design or conversion of MDR TB wards should be done in consultation with experts and ward management, in order to create and maintain negative air pressure.

PLACE TO COUGH

Coughing is the source of airborne infectious particles. This risk increases when sputum is being collected. One option is to build a glass roofed veranda or cubicle or balcony on the sunny side of the ward or clinic. The side facing outside should be largely open down to floor level to promote full sunlight and ventilation.

17. WORKERS' COMPENSATION

Relevant legislation dealing with contamination by any infectious substance includes the Occupational Health and Safety Act (Act 85 of 1993) and the Compensation for Occupational Injuries and Diseases Act (Act 130 of 1993). All HCWs are covered by these Acts, with compensation provided at an amount determined by the Compensation Commissioner.

Tuberculosis and infections by mycobacteria other than M. tuberculosis (MOTTS) are covered by the

Act, but employees have to keep records of baseline and follow-up procedures in order to show that infections were acquired during the course of duties carrying a risk of contracting these infections. Compensation under the Act is payable whether or not there was negligence on the part of the employer. The right to compensation shall lapse if the Commissioner is not informed within 12 months from the start of the disease. It should be noted that HCWs may acquire subclinical tuberculosis infection (as shown by TST conversion) and may only become ill with reactivation tuberculosis many years later. These cases are also covered by the Act, subject to proof that the initial infection was acquired in the workplace.

The Commissioner may refuse to award the whole or a portion of compensation and may hold the employer responsible for medical costs in cases where willful misconduct or neglect of either the HCW or the employer could be proven.

It is the responsibility of the employer to see that patients and health workers comply with the policies to decrease the risk to themselves and others.

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ASSESSING THE INDIVIDUAL CASE OF APPARENT MDR TUBERCULOSIS **Annexure 1**

The suspicion of MDR tuberculosis occurs in two situations:

- When you receive a report from the laboratory indicating *Mycobacterium tuberculosis* resistant to isoniazid and rifampicin (with or without other drugs);
- When you observe in a patient no response to the standard *retreatmen*t regimen.

Some provisos

- Apparent MDR stains reported by a local laboratory should not be taken uncritically at face value. Errors occur in laboratories as elsewhere. Some laboratories are less reliable than others. The specimen may have been mislabeled or may have come from another patient. If the result is a single one, and if it does not accord with clinical data (see below), repeat at least one, and preferably two tests;

- If there is no response to the standard *retreatment* regimen, remember that many apparent treatment failures are due to the patient having failed to take his treatment and not due to MDR bacilli. Such patients should respond to the *fully supervised* standard retreatment regimen;

- Explain to the patient how essential it is to know exact details of his previous treatment. The patient may not bring himself to admit that failure is own fault, so also question his family if possible. Also check his previous records and consult his previous care givers if possible;

- Just because there are standard national regimens, do not assume that the patient has necessarily received them. Check the records, the patient's history and question the patient's previous health care providers. In some cases the patient may have received other and unreliable treatment. From your knowledge of local conditions you can judge how likely this is. Enquire also whether the patient has been given advice or a prescription in writing. If so note the dose of each drug, its frequency of administration, the accompanying drugs, and the dates when each drug was started and stopped.

Considering the criteria of failure of the *retreatment* regimen

The criteria of failure are mainly bacteriological, but not all positive bacteriological results necessarily mean "failure". Reasons for apparent failure may include the following:

Persistently positive sputum

If the patient is still smear-positive at two to three months of the *retreatment* regimen, check carefully that he/she has taken the drugs as prescribed. This is the commonest cause of failure. However, some patients with severe disease may take longer to convert from smear-positive to negative. Do not rush into changing treatment. If the number of bacilli on direct smear has been reduced and the patient is improving clinically and radiologically, this is particularly reassuring. If drug susceptibility testing is available, request susceptibility tests on positive cultures at three months in order that results be available as early as possible.

Persistent positivity at six to seven months makes genuine treatment failure much more likely. Again the commonest cause is failure to take the drugs. If you are certain that the patient is

taking the drugs, it is highly probable that the bacilli are resistant to the drugs he/she is receiving. Check the apparent persistent positivity by further sputum smears. For example, occasionally a patient with a large cavity or cavities may have intermediately positive smears, due to dead bacilli for a month or two after negative culture. If drug susceptibility testing is available, request susceptibility tests on positive cultures at seven months in order that results be available as early as possible.

Positive *cultures* at three and six months are even more important. If direct smears have become negative, but cultures are still positive (eg. at three months), this may only be a stage towards complete sputum conversion. Do not attempt changes in the retreatment regimen until drug susceptibility results become available.

Fall and rise phenomenon

Sputum smears may initially become negative (or less positive), and then later become persistently positive. This indicates failure usually due to either the patient having ceased to take the drugs or sometimes to the development of resistance to the drugs he/she is receiving. Check by further cultures and susceptibility tests.

Report of drug resistance

Do not accept such a report uncritically. As mentioned above, laboratories vary in reliability and errors may occur. Look at the clinical evidence, especially the trends in smear and culture positivity. If the susceptibility test results do not fit in, discuss them with the bacteriologist (if possible) and repeat the test. Do not rush into changing treatment. You should decide the appropriate treatment in the light of all the evidence available for the particular patient.

Radiological deterioration

Deterioration in a chest X-ray may be a sign of failure but deterioration may be due to one of the following:

- intercurrent pneumonia
- pulmonary embolism
- supervening carcinoma

A repeat chest X-ray after two to three weeks will probably show improvement in the case of intercurrent pneumonia or pulmonary embolism. Apparent radiological deterioration, if it is not accompanied by bacteriological deterioration, is less likely to be due to tuberculosis.

Clinical deterioration

This is the least reliable evidence of failure. It may be due to many conditions other than tuberculosis. If there is no accompanying bacteriological or radiological deterioration, clinical deterioration is unlikely to be due to tuberculosis.

Interpreting the data for an individual patient

Use an assessment form based on one of the examples to tabulate information on the patient's previous treatment history and drug susceptibility results. Use the criteria of failure above to decide whether resistance was likely to have developed during each regimen which the patient received. Remember that, if definite failure occurred, (principally bacteriological failure) it must have been due either to the patient not taking the drugs or to the development of resistance to the drugs being used (usually for more than three months). If you have all the relevant details, it is usually possible to assess to what drugs the patient's bacilli will be resistant. This can in due course be confirmed by susceptibility tests.

Although it is vital to collect all available information, in some cases it may remain uncertain which drugs the patient has received. Health care workers may have neglected serial sputum tests or requesting any sputum tests at all. You will therefore have to make the best estimate you can in the light of whatever evidence is available. This will include what you know of the most likely treatment which might have been used in the area where the patient was treated. It may also include what you may know about the frequency of resistance to individual drugs in that community.

Essential antituberculosis drugs

Streptomycin: Resistance to streptomycin has become less common since its routine use for tuberculosis was abandoned in South Africa in the late seventies. The use of streptomycin during the first two months in the standard retreatment regimen only allows for its use to be considered in the *individualised approach* to MDR tuberculosis treatment, provided that susceptibility has been proved.

Pyrazinamide: Resistance to pyrazinamide is neither easy to acquire nor to prove by susceptibility testing. As pyrazinamide has a bactericidal effect in an acid medium (bacilli inside macrophages), it is advisable to use pyrazinamide in combination with streptomycin or another aminoglycoside (active against bacilli actively multiplying, outside macrophages) to obtain a maximal bactericidal effect against all populations of bacilli.

Ethambutol: Ethambutol is used during the continuation phase of the standard retreatment regimen. In South Africa, the rate of acquired resistance to ethambutol is around 3%, but even in MDR TB about half of patients carry strains sensitive to ethambutol. Ethambutol is then a valuable bacteriostatic agent for preventing the emergence of resistance to other active drugs, in place of cycloserine, which is more expensive and tends to be more poorly tolerated.

Second-line antituberculosis drugs

Aminoglycosides: When resistance to streptomycin is proved or highly suspected, one of the othe aminoglycosides can be used as a bactericidal agent against actively multiplying organisms: *Kanamycin*, the least expensive, but largely used for indications other than tuberculosis in South Africa. *Amikacin*, as active as kanamycin and better tolerated, but much more expensive. Streptomycin-resistant strains of *M. tuberculosis* usually are susceptible to kanamycin and amikacin. Kanamycin-resistant strains can exhibit resistance to streptomycin and show high cross-resistance with amikacin.

Thioamides: *Ethionamide* and *prothionamide* are two different presentations of the same active substance, with bactericidal activity against *M. tuberculosis*. The pharmacokinetics of the two preparations are very similar, but prothionamide may be better tolerated than ethionamide.

Fluoroquinolones: *Ofloxacin* and *ciprofloxacin* are two different fluoroquinolones, but with complete cross-resistance inside the group. These drugs have a low bactericidal activity, and are useful in association with other antituberculosis drugs. The pharmacokinetics of ofloxacin are better than the pharmokinetics of ciprofloxacin but the latter is less expensive. Sparfloxacin should be avoided because of severe cutaneous side effects (photo-sensitisation). Norfloxacin should not be used because it does not provide adequate serum levels.

Cycloserine: *Cycloserine* is bacteriostatic at the usual dosage. It is a valuable companion drug to prevent resistance to other second-line drugs, since it does not share cross-resistance with other active TB drugs. It has a high incidence of side effects.

CROSS RESISTANCE

Consideration of cross-resistance is important for selecting drugs acceptable for the treatment of MDR tuberculosis. As usual in the treatment of infectious diseases when the combination of several drugs is required, it is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance.

Thioamides: Ethionamide, in the group of thioamides, induces complete cross-resistance with prothionamide. They should therefore be considered as the same drug.

Aminoglycosides: Strains resistant to streptomycin are susceptible to kanamycin and amikacin. Resistance to kanamycin induces complete cross-resistance with amikacin: they should therefore be considered as the same drug. Resistance to kanamycin or amikacin induces also resistance to streptomycin.

Fluoroquinolones: Ofloxacin, ciprofloxacin and sparfloxacin induce complete cross-resistance for all fluoroquinolones. There is no cross-resistance with other classes of drugs.

Kanamycin and amikacin: ***Preparation and dose****:* Kanamycin (Novo) is available in injection formulation containing 1g/3ml vial. Amikacin (B-H Squibb) is available as an injection containing 1g/ml or as injection formulations. The drug should be dissolved (Intramed) at concentrations 100mg/2ml, 250mg/2ml and 500mg/2ml respectively. The optimal dose for both kanamycin and amikacin is 15mg/kg bodyweight, usually 750mg to 1g given daily or five days per week, by deep intramuscular injection. Rotation of injection sites reduces local discomfort. The duration of daily therapy is usually three to four months. When necessary, it is possible to give the drug at the same dose two to three times weekly during the continuation phase, under close monitoring for adverse reactions. ***Adverse reactions***: These are similar to the side-effects associated with streptomycin. Ototoxicity, deafness or vertigo may occur, as well as reversible nephrotoxicity. ***Precautions:*** In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased, to avoid accumulation of the drug. In these patients, renal function should be monitored regularly during use. Kanamycin and amikacin should not be used in pregnant women except as a last resort.

Ethionamide: ***Presentation and dose:*** Ethionamide (Healthcare Generica) is provided in 250mg tablet formulation. The maximum optimum daily dose is 15-20 mg/kg or 1g. The usual dose is 500mg to 1g daily, depending upon body weight and tolerance. Few persons can take more than 750mg daily. (750mg for patients weighing 50kg or more, 500mg for patient weighing less than 50kg). Patients may find the drug more acceptable if it is administered with orange juice or milk or after milk, or at bed-time to avoid nausea. Among patients on directly observed treatment, a daily dose of 750mg can be given as 250mg and 500mg administered 10-12 hours later. ***Adverse reactions***: The main problems are epigastric discomfort, anorexia, nausea, metallic taste and sulphurous belching. Vomiting and excessive salivation can occur. Tolerance varies in different populations: the drug is usually well tolerated in Asia and in Africa. Psychotic reactions including hallucinations and depression may occur. Hypoglycaemia is a rare but dangerous occurrence, obviously particularly important in diabetic patients. Hepatitis may occur in about 10% of cases, but is rarely serious. When major liver damage occurs, jaundice and highly symptomatic disease is created, with prolonged elevation of transaminases (6-8 weeks). Drug administration should be interrupted during this period. Other rare side-effects have included gynaecomastia, menstrual disturbance, impotence, acne, headache and peripheral neuropathy. ***Precautions:*** Ethionamide is teratogenic in animals and should not be given in pregnancy. It should be very carefully monitored if given to patients with diabetes, liver disease, alcoholism or mental instability.

Ofloxacin and ciprofloxacin: *Presentation and dose:* Ofloxacin (Tarivid, Noristan) is supplied in 200mg and 400mg tablet formulation, while ciprofloxacin (Ciprobay, Bayer Healthcare) is available in 250mg, 500mg and 750mg tablet formulation as ciprofloxacin hydrochloride monohydrate. The usual daily dose is 600-800mg (3-4 tablets) of ofloxacin or 1000-1500mg (4-6 tablets) of ciprofloxacin during the initial phase. If the dose of 800mg ofloxacin is poorly tolerated, the daily dose can be reduced to 400mg during the continuation phase. Either can be given in single daily dose (especially applicable in directly observed treatment) or the daily dose can be divided into 12-hour intervals. ***Adverse reactions:*** Adverse reaction are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (dizziness, headache, mood changes and, rarely, convulsions). ***Precautions:*** Ofloxacin and ciprofloxacin should not be used in pregnant women or growing children because they may impair growth and produce injury to growing cartilage. **Because of adverse interaction, the following drugs should be avoided during fluorquinolones therapy: antacids, iron, zinc, sucralfate**.

Cycloserine: Cycloserine (Eli Lilly) is supplied in 250mg tablet formulation. The maximum daily dose is 15-20mg/kg, the maximum dose being 750mg. The daily dose can be divided into 250mg in the morning and 500mg in the evening. ***Adverse reaction:*** These include dizziness, slurred speech, convulsions, headache, tremor, insomnia, confusion, depression and altered behaviour. The most serious risk is suicide and mood should be carefully watched. Very rarely there may be hepatitis or general hypersensitivity. ***Precautions:*** In view of the above adverse reactions, monitoring for central nervous system reactions is essential. Minor adverse reactions such as insomnia can be managed by small doses of an appropriate tranquilliser. Pyridoxine may decrease central nervous system effects. Health care staff and family members of patients receiving cycloserine should be educated to report undue depression or personality changes immediately, since depression-related suicide is a definite risk.

Cycloserine should be avoided in patients with a history of epilepsy, alcoholism and mental illness especially depression. It should be used very cautiously in patients with renal failure.