Framework to address multidrug-resistant TB in the Pacific Island countries and territories

By
Dr Axel Wiegandt and Dr Richard Stapledon

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Secretariat of the Pacific Community
BP D5 98848 Noumea Cedex, New Caledonia
Tel: +687 26 2000 Fax: +687 26 3818
Web: http://www.spc.int

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The leading authors were Dr Rick Stapledon, Consultant Royal Adelaide Hospital Chest Clinic, and Dr Axel Wiegandt, Medical Officer Secretariat of the Pacific Community.

Members of the writing committee were:

Dr Ivan Bastian, Head, WHO Supranational Reference Laboratory, IMVS, Adelaide

Dr Chris Coulter, Director Queensland Mycobacterium Reference Laboratory

David Dawson, PATLAB coordinator

Dr Anastasios Konstantinos, Director Queensland TB Control Centre

Dr Sundari Mase, Division of TB Elimination National Centre for HIV, STD and TB, CDC

Dr Linh Nguyen, Medical Officer, Office of the WHO Representative in the South Pacific

Dr Nobuyuki Nishikiori, Medical Officer, Stop TB and Leprosy Elimination, WHO/WPRO

Dr Katsunori Osuga, Medical Officer, Stop TB and Leprosy Elimination, WHO/WPRO

Dr Daniel Sagebiel, Medical Officer, Stop TB and Leprosy Elimination, WHO/WPRO

Kerri Viney, TB Systems Specialist, Secretariat of the Pacific Community

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LIST OF ABBREVIATIONS

AFB	acid-fast bacilli
CDC	United States Centers for Disease Control and Prevention
DOT	directly observed treatment
DOTS	directly observed treatment, short course strategy
DST	drug-susceptibility testing
GLC	Green Light Committee
HIV	human immunodeficiency virus
IATA	International Air Travel Association
IPT	isoniazid preventive treatment
MDR-TB	multidrug-resistant tuberculosis
NTL	National Tuberculosis Laboratory
NTP	National Tuberculosis Programme
PATLAB	Pacific TB Laboratory Initiative
PICTs	Pacific island countries and territories
PMDT	programmatic management of drug-resistant TB
PPTC	Pacific Paramedical Training centre
PTRL	Pacific TB Reference Laboratory
SLD	second line drugs
SPC	Secretariat of the Pacific Community
TB	tuberculosis
WHO	World Health Organization
XDR-TB	Extensively drug resistant TB

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1. INTRODUCTION

The emergence of resistance to anti-tuberculosis (TB) drugs, particularly of multidrug-resistant TB (MDR-TB), has become a major public health problem worldwide and an obstacle to effective global TB control. The development of MDR-TB, defined as TB with an isolate resistant to at least the two most effective TB drugs, isoniazid and rifampicin, represents poor treatment practices and failures to conform to WHO TB programme guidelines and the International Standards for TB Care, and underscores the importance of patient centered management, to promote adherence to lengthy treatment regimens.

Although available data indicate an overall low level of drug resistance in the southern Pacific, alarmingly high levels in some Pacific Island Countries and Territories (PICTs), especially the Micronesian, have been observed. Survey data from the Northern Mariana Islands show a prevalence of MDR-TB among new TB cases to be as high as 11.1% (WHO 2008). Chuuk State in the Federated States of Micronesia reported two major MDR-TB outbreaks involving two separate isolates in the past year.

Most cases have been managed with laboratory support from the Pacific TB Laboratory Initiative (PATLAB) network and clinical support from external technical advisers on an informal basis. Major constraints have been timely procurement of second line drugs, long-term management of patients in isolation, training and education needs of staff and reliance on PATLAB expertise.

Thus one major recommendation of the Fourth Pacific Stop TB Meeting (WHO 2008) (Brisbane 11–14 March 2008) was that technical partners (i.e. the Secretariat of the Pacific Community (SPC), Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO)) should support the development of a framework of response to drug-resistant TB in the Pacific, to link the three critical aspects of case management of this disease, laboratory services, technical/clinical support for case management, and the timely provision of second line drugs.

In response, a working group of experts from the technical agencies and from PATLAB was established to develop this document. The framework it sets out is intended to offer simple and clear guidance to National TB Programme (NTP) managers and public health officials from the PICTs on critical aspects of MDR-TB treatment and case management, emphasizing an urgent network response and building on PATLAB and clinical partnerships.

Key components of the framework are the diagnosis of MDR-TB, the urgent response plan, management of MDR-TB cases and their contacts, infection control measures and monitoring and evaluation to promote a standardised and harmonised approach throughout the PICTs, while taking into account the unique aspects of MDR-TB treatment and management in the Pacific islands.

The central theme of the document is optimal MDR-TB management. Critical to success is assessing and strengthening the directly observed treatment (DOT) short course (DOTS) programme to enhance the management and control of drug sensitive TB, and prevent the emergence of MDR-TB.

2. MULTIDRUG-RESISTANT-TB IN THE PACIFIC

2.1 Epidemiology of MDR-TB

In 2008, there were an estimated 390,000 to 510,000 incident cases of MDR-TB globally (best estimate, 440,000 cases). Globally, among all incident TB cases, 3.6% (95% confidence interval: 3.0 to 4.4) are estimated to have MDR-TB and 50% of these cases are thought to occur in China and India. In 2008, MDR-TB caused an estimated 150,000 deaths (WHO 2010).

In 2008, the estimated number of MDR-TB cases in the Western Pacific Region (primary and acquired) (95% confidence interval) was 120,000 (100,000 to 140,000) with 31 (0 to 106) in the Pacific island region excluding Papua New Guinea (WHO 2010).

MDR-TB patients have been reported in several countries and territories in the Pacific, including Guam, Commonwealth of the Northern Mariana Islands (CNMI), the Federated States of Micronesia, the Republic of Marshall Islands (RMI), Kiribati, and Samoa.

MDR-TB has been reported in Guam and CNMI for several years. In both countries, many MDR-TB cases have been linked to migrant workers from countries with a high prevalence of MDR-TB.

Since early 2008, Chuuk State (one of the four states comprising FSM) has been confronted with two simultaneous outbreaks of MDR-TB. A total of 8 confirmed and 18 suspected MDR-TB cases have been identified. Seven patients died and 19 are currently receiving treatment (2010) with individualised regimens tailored to the susceptibility results of the isolates (15 as outpatients and 4 as inpatients). In addition, 112 close contacts of MDR-TB patients are being treated for presumed MDR with the goal of preventing progression to active MDR-TB disease. Most of the contacts have now completed treatment and will be followed for 3 years to assess the tolerability, safety and possibly the efficacy of MDR latent TB infection treatment regimens. The first outbreak of MDR-TB in Chuuk has been linked to an overseas source, a cluster of MDR-TB cases among migrants who arrived in Saipan, CNMI, from South East Asia. The second outbreak of MDR-TB in Chuuk is associated with the lack of quality DOT in the local setting.

From 2004 to 2009, 6 cases of MDR-TB were diagnosed in residents of RMI. The most recent case, diagnosed in 2008, was reported on Majuro Island in the Majuro atoll. A contact investigation conducted around this case in October 2009 revealed 4 additional cases of MDR-TB (3 probable and one confirmed), bringing the total number of MDR-TB cases to 10 occurring from January 2004 to November 2009. All 10 patients with MDR-TB were born in RMI and 9 out of 10 had a diagnosis of diabetes as a co-morbid condition. A total of 2 MDR-TB cases are currently being treated on Majuro. Contact investigations have shown the local epidemiological links of the index case in Majuro to be with a non compliant TB patient, who had died of TB.

Kiribati also experienced its first case of MDR-TB in 2005, the patient died during the first year of treatment. Samoa diagnosed its first MDR-TB case before 2000 and a second case in 2007. The latter is a migrant patient who had received TB treatment overseas before migrating to Samoa. This second patient successfully completed treatment with second line TB drugs in 2009.

The emergence of MDR-TB is a current and pressing issue and brings further challenges to countries with limited resources, and an already complex implementation environment. The number of cases recently diagnosed, at least in the Northern Pacific, means an increased need for a proactive approach to this alarming situation, including a need for stronger technical support for core DOTS programmes, and the creation of a solid public health infrastructure to respond to this crisis.

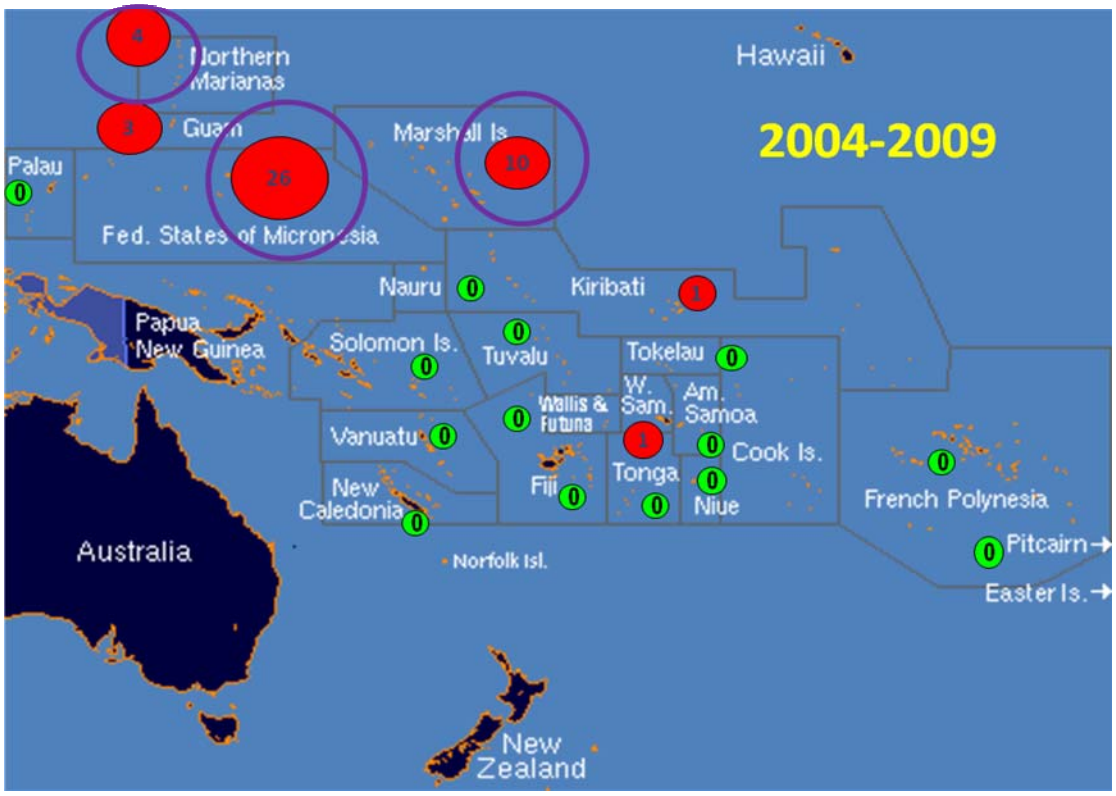

Figure 2.1 Number of MDR-TB cases in Pacific Island countries and territories 2004–2009 (probable and confirmed)

2.2 Strategic Plan for TB Control in the Western Pacific Region 2011–2015

The Strategic Plan for TB Control in the Western Pacific 2011–2015 (Regional Strategic Plan) provides guidance to member states on designing national strategic plans for TB control during the coming 5 years (WHO Regional Office of the Western Pacific 2006). The Regional Strategic Plan is in accordance with the Stop TB Strategy, developed by WHO to achieve the 2015 Millennium Development Goals for TB. Strategic priority 2 emphasises the need for scaling-up the programmatic management of drug-resistant TB (PMDT).

The Regional Strategic Plan sets out three core priorities:

Strategic Priority 1: Ensuring universal and equitable access to TB diagnosis and treatment for all people suffering from TB

Strategic Priority 2: Considerably scaling up the programmatic management of drug-resistant TB (PMDT)

Strategic Priority 3: Strengthening TB/HIV collaborative activities

Certain targets have been set for each priority, and these are shown in full in Appendix 1. Strategy 2 relates specifically to MDR-TB and the tables that follow show the target and a series of expected results.

Targets

Strategic Priority 2: Considerable scaling up of PMDT
A) Almost 100% of the region covered by PMDT by the end of 2015
B) In areas covered by PMDT almost 100% of suspects with X/MDR-TB screened by line probe assays and culture and drug-susceptibility testing (DST)
C) In areas covered by PMDT at least 90% of patients diagnosed with drug resistant tuberculosis enrolled on second line drug treatment regimens

To achieve these Strategic Priorities, certain Expected Results, or desired outcomes through actions, have been suggested:

Strategic Priority 2: **Considerably scaling up PMDT**		
	DESCRIPTION	**INDICATORS AND TARGETS**
Expected Result 2.1	Second line treatment, care and support system for all diagnosed M/XDR-TB patients in place	100% of PMDT treatment units with uninterrupted supply of second line anti-TB drugs in a given year
Expected Result 2.2	Evaluation of treatment outcomes of all MDR-TB cases enrolled on second line drugs	Treatment success rate ≥ 70%–75% Failure rate ≤ 5%–10% Death rate ≤ 10% Default rate ≤ 10%–15%
Expected Result 2.3	Prevention of nosocomial transmission of TB	100% of PMDT and TB/HIV health facilities with adequate infection control measures

Cross-Cutting Components have been identified. These components do not necessarily fall under one of the three Strategic Priorities, but rather span the broad aims of TB control.

Cross Cutting Component 1:	Sufficient financing for TB control
Cross Cutting Component 2:	Strengthening of the regional laboratory network
Cross Cutting Component 3:	Strengthening TB Infection Control
Cross Cutting Component 4:	Strengthening disease control, including TB through primary health care networks
Cross Cutting Component 5:	Human resource development
Cross Cutting Component 6:	Operational Research

3. DIAGNOSIS OF MULTIDRUG-RESISTANT TB

3.1 Risk groups

Effective treatment and management of MDR-TB requires prompt recognition and diagnosis of drug-resistant disease. Clinical personnel must constantly be aware of the risk factors for drug resistance, such as prior treatment history for TB, contact with MDR-TB, treatment failure or relapse. Specimens from patients with these risk factors should be submitted for acid fast bacilli (AFB) culture and DST to confirm the diagnosis of MDR-TB. Patient groups who should be prioritized for culture and DST include:

- **Failure or relapse after re-treatment regimen with first line drugs (previously category 2)**

(these patients have about an 80% likelihood of being MDR if their treatment has been well supervised)

- **Symptomatic close contacts of a proven MDR-TB case**

(investigating symptomatic children and HIV-positive contacts is especially important because these patient groups are at increased risk of progression to active disease)

- **Failure or relapse after new patient treatment regimen (previously category 1)**

(most relapses and failures after treatment of a new patient will still be drug-susceptible)

- **Retreatment patients sputum smear positive at end of intensive phase (month 3)**
- **New patients sputum smear positive at end of month 3**
- **All HIV positive patients diagnosed with active TB**

(mortality rates from MDR-TB are high in HIV positive cases unless detected early)

Box 3.1 Target groups for drug susceptibility testing

- Failure or relapse after retreatment regimen with first line drugs
- Symptomatic close contacts of a proven MDR-TB case
- Failures or relapse after new patient treatment regimen
- Retreatment patients sputum smear positive at end of intensive phase (month 3)
- New patients sputum smear positive at end of month 3
- All HIV positive patients diagnosed with active TB

NTP in PICTs should consider requesting culture/DST for:

- smear-positive TB suspects from an island or other locale where a proven MDR-TB patient has resided (as an informal survey for secondary MDR-TB cases);
- symptomatic smear-negative HIV-positive patients, to aid diagnosis of TB;
- prisoners or other patients living in congregate settings where MDR-TB would have exaggerated public health implications;
- all TB suspects if resources allow.

NTP in PICTs must be aware that culture/DST for MDR-TB is costly. Because the number of specimens submitted from PICTs depends on funding and the capacity of the receiving laboratories, patient groups requiring culture/DST need to be prioritised in consultation with WHO, SPC, CDC, funding organizations and the receiving laboratory.

3.2 PATLAB Network

The Pacific TB Laboratory Initiative (PATLAB) represents a collaborative partnership between PICTs and the mainland reference laboratories, Pacific TB Reference Laboratories (PTRL). Because DST is technically demanding, laboratories performing this procedure must have the appropriate infrastructure, skills, high-level safety equipment, consumables and be quality assured.

PTRL have agreed to provide technical support to NTP in the PICTs, including smear, culture, and DST for samples from patients considered high risk for having drug-resistant TB. (See below.)

Table 3.1 Pacific TB Reference Laboratories

Pacific Island Country and Territory	Pacific TB Reference Laboratory
Kiribati, Solomon Islands	WHO SRL, SA Pathology, Adelaide, Australia
Fiji, Nauru,Vanuatu	WHO CC, Brisbane, Qld, Australia
Samoa, Tonga, Cook Islands, Tuvalu, Niue	LabPlus, Auckland, NZ
All US-Affiliated PICTs	Diagnostic Laboratory Services, Honolulu, HA, USA
French-speaking Territories	Local reference laboratory

Contact details for PTRL are shown in Appendix 2

3.3 Laboratory Tests for Drug Susceptibility

Advance planning is the key to meaningful and efficient DST. Before embarking on specimen collection, NTP must ensure that:

- laboratory staff have current certification to act as shippers of dangerous goods/infectious materials;
- the laboratory has ample supplies of shipping materials;
- local air-lines have confirmed willingness to accept dangerous goods;
- there has been liaison with the appropriate PTRL to advise shipment and clarify transport arrangements.

(i) Specimen collection

For each patient, two sputum specimens of good quality must be collected. At least one early morning specimen should be collected. The appropriate collection of sputum specimens is well described in *Laboratory diagnosis of tuberculosis by sputum microscopy*, which has been distributed to all PICTs (Lumb and Bastian 2005).

These points are highlighted:

- Specimens must be collected under supervision (e.g. at the clinic).

- Suspect MDR-TB patients must be instructed to cover their mouth when coughing and the collection must be performed in an open, well-ventilated area to reduce the risk of transmission.

- Containers must be sterile, wide-mouthed; be made of clear, break-resistant plastic; have a screw-capped, leak proof lid; and have a label on which the patient's details can be written easily.

- The container (not the lid) must be labeled with the patient's name, another identifier (e.g. date of birth) and the date of collection. The request form must be completed with the same information plus the patient's address, name and contact of the prescribing physician, laboratory register number and reasons for culture/DST.

- Individual specimens should be enclosed in a sealed plastic bag (biohazard bag, or equivalent), and separated from request forms.

(ii) Packaging

Shipments must comply with international shipping requirements (IATA) which cover packing the samples, accompanying documentation, and the certification of the person packaging the samples.

IATA regulations require that the person doing the packaging has formal training and is certified. This certification must be renewed every 2 years. Each PICT requires at least two staff with IATA training, which is necessary not only for shipping TB specimens but also for shipping other samples for pathology investigations. This training/recertification must occur routinely and be integrated into the training activities for laboratory staff rather than being performed when a MDR-TB suspect is recognised. (PTRL can advise on certification options.)

NTP/NTL must develop a working relationship with their local courier company and be fully informed on local shipping requirements. Flight itineraries between the PICT and PTRL must be ascertained as part of pre-shipment planning.

Briefly, the shipping package must comprise:

- a watertight primary receptacle (i.e. the specimen container),
- a watertight secondary package (for liquid substances such as sputa; sufficient absorbent material to absorb the entire contents must be placed between the primary receptacle and the secondary packaging), and
- a rigid outer packaging of adequate strength for its capacity, weight and intended use.

Packaging materials are available commercially. It is recommended that NTP/NTL have a small stock of IATA-compliant packaging on hand at all times. Because these packages are expensive, the PICT may require funding support to purchase.

The respective PTRL will provide details of the documentation which must accompany each shipment. Most diagnostic samples can be shipped as Category B packages under IATA regulations.

For imports into Australia, the accompanying documentation should include:

- a copy of the receiving laboratory's import permit
- a quarantine letter and
- a customs declaration (Appendix 4).

A major portion of shipping cost is due to customs and handling charges at the destination. The cost is the same whether the parcel contains one or 10 samples. Therefore collections from multiple patients should be coordinated to allow batching in a single shipment.

Specimens must be shipped as soon as practicable after collection, and refrigerated at 4^{o}C where delay is unavoidable. Sputum specimens for culture/DST do not require shipment on dry-ice.

(iii) Shipment

The shipper must inform the receiving PTRL by fax and/or email on the day that a package is dispatched. The shipper must provide the name of the courier company, the consignment number and, ideally, a copy of the accompanying documentation. With this forewarning and information, the reference lab can investigate the whereabouts of a package if it is overdue.

(iv) Expected turnaround time (PTRL turnaround time)

Positive culture results on smear positive samples are expected within 2 to 3 weeks, though negative culture results will take at least 6 weeks. DST will usually take another 10 to 14 days after the primary culture. The entire culture/DST process for a sputum smear positive sample could therefore take 3 to 5 weeks.

Specimens not stored in a refrigerator are much more likely to yield contaminated cultures which require re decontamination. This will potentially cause long delays to obtaining a pure culture for DST.

The PTRL will forward the results to:

- the referring national TB laboratory;
- the responsible NTP officer
- the case manager and
- the nominated external MDR-TB consultant for the PICT.

Therefore the PTRL must have the email addresses of these individuals at the planning stage. NTP is responsible for ensuring efficient communications to/from the PTRL.

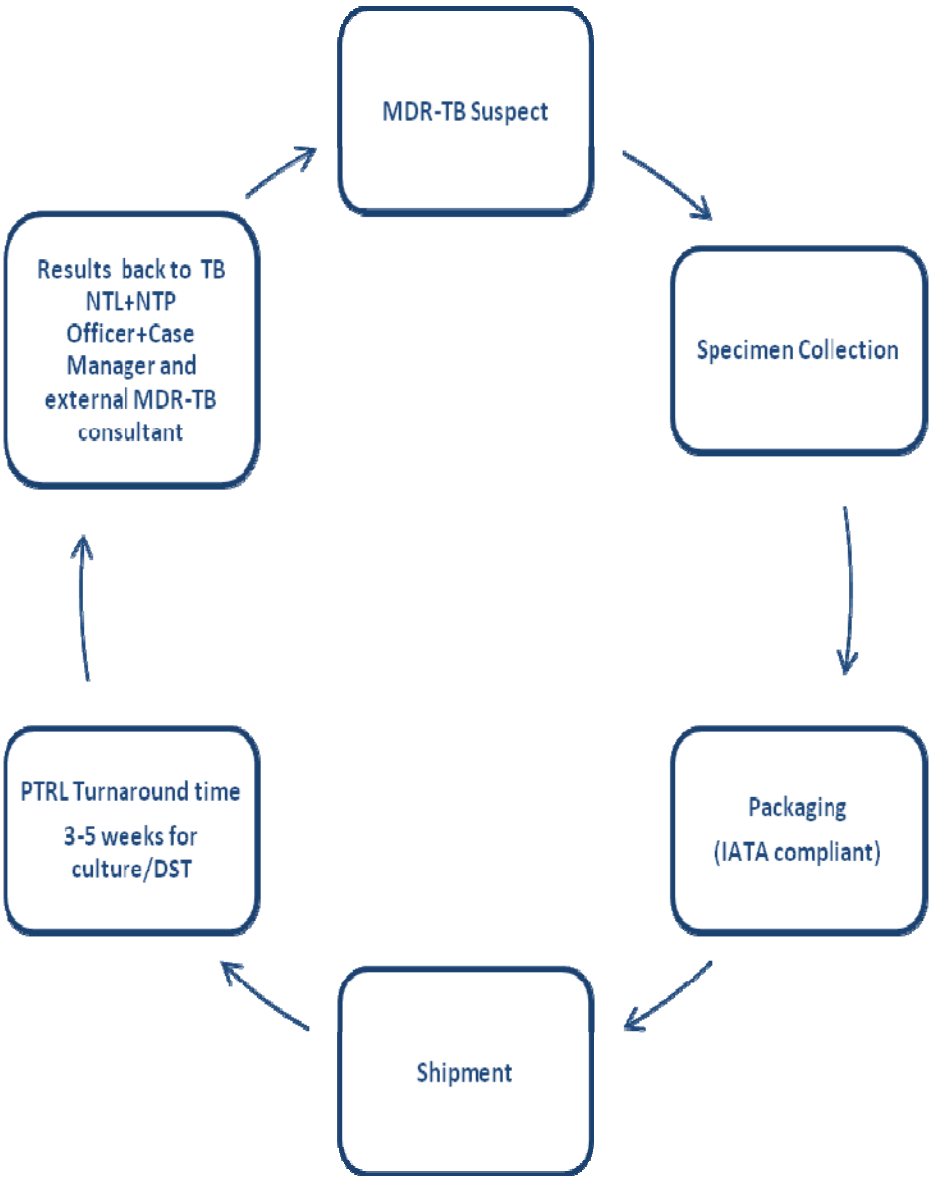

Figure 3.1 Process for a sputum smear positive sample

(v) Future prospects

New molecular technologies, such as Cepheid Gene Xpert System's *M. tuberculosis*/RIF assay, offer an integrated hands-free sputum-processing and real-time PCR system (Helb et al. 2010). The Cepheid assay requires minimal operator expertise, and can rapidly and simultaneously detect *M. tuberculosis* and rifampicin resistance in smear-positive samples. These assays may have a place in the future in a few PICTs with a high incidence of MDR-TB, where the investment in equipment, reagents and staff training would be justified. Further evaluation is required, however, to determine the performance of these assays on smear-negative samples and their sustainability in isolated, low-income countries such as the Pacific Islands.

4. URGENT RESPONSE PLAN

An urgent response plan is needed to:

- manage newly diagnosed MDR-TB cases and interrupt TB transmission
- provide a systematic, comprehensive and timely approach for MDR-TB treatment, case management and coordination of care.

This plan is critical, especially in areas where public health workers are usually "generalists" who work with several different programmes.

The goals of the MDR-TB urgent response plan are to:

(a) form the case management team including representatives from local pharmacies and laboratories, and assign responsibilities to define clear communication lines;

(b) contact the identified consultants for international technical support through the "TB treatment support network";

(c) initiate a public health response including infection control measures and contact investigation in a timely manner;

(d) prepare a Green Light Committee (GLC) application to procure second line TB drugs in close liaison with pharmacy and technical agencies;

(e) prepare a communication plan for public information and media (when appropriate).

4.1 The case management team

The case manager is the "team leader" of the case management team and coordinates the treatment and management strategy of the treating physician, the international consultant, and other health care workers such as DOT staff, nurses, the pharmacy and the TB laboratory.

The physician, in close liaison with the international MDR-TB consultant, through the "TB treatment and support network", performs the initial patient assessment, reviews the chest radiograph and drug susceptibility results, and designs the MDR-TB treatment regimen. Nurses have primary responsibility for ensuring DOT, following up sputum smear and culture results, monitoring for adverse effects and evaluating nutritional and social support. DOT workers supervise the administration of medications on a daily basis. Pharmacy personnel are responsible for the procurement and distribution of medications. Laboratory personnel oversee the AFB smear and culture testing, and DST. An international advisory board oversees all team activities and provides guidance to all members of the team.

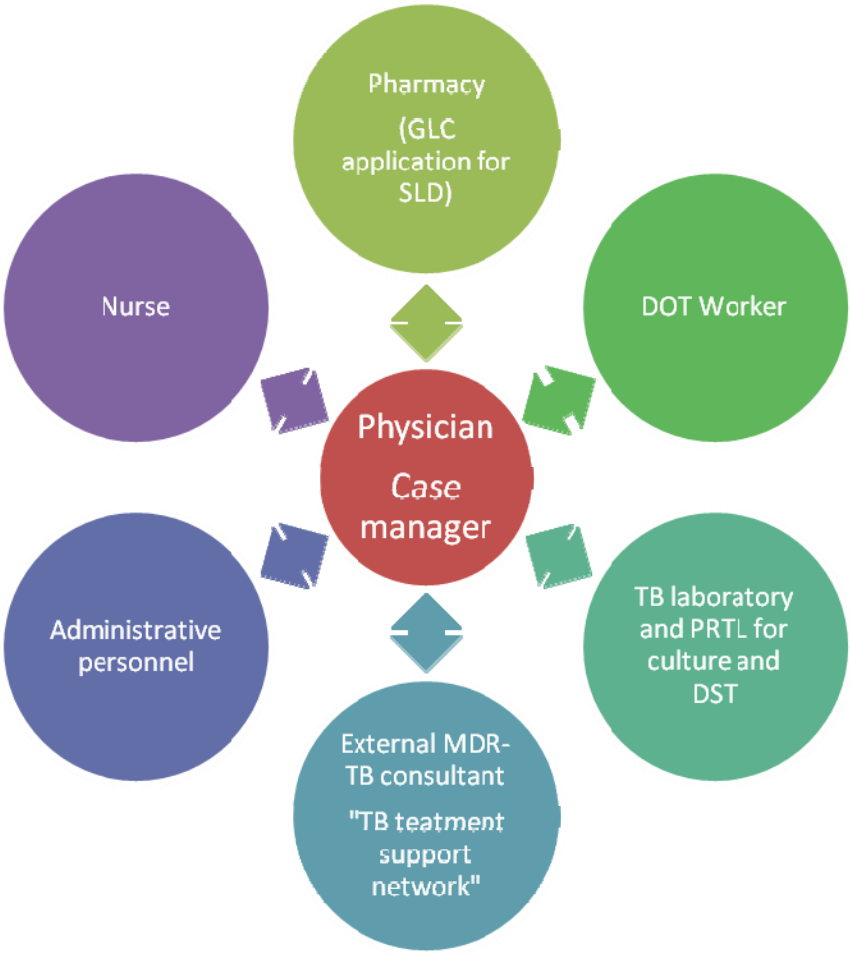

Fig 4.1 Organization of the case management team

4.2 TB treatment and support network

The aim of the TB treatment and support network is to provide expert clinical advice to NTP staff in 20 PICTS on all aspects of the care, treatment, management and follow up of TB cases, including retreatment cases, TB/HIV co-infected cases and cases of drug-resistant TB.

The TB treatment and support network comprises a listserv which is moderated by professional staff from SPC's TB Section. Expert consultants are available (by email) to provide clinical advice on any TB case, in particular MDR-TB. Contact details for expert consultants are shown in Appendix 3.

To join the listserv, members of the case management team need to go to the following page and enter their email address and a password:

http://lists.spc.int/mailman/listinfo/tb-support_lists.spc.int

Their subscription will then be activated by someone at SPC.

To access expert advice, members of the case management team need to email a request to this address:

tb-support@lists.spc.int

The request will then be passed on to an international consultant who can respond within a short time. If the email system is down and assistance is needed urgently the requesting health care provider can phone SPC's TB Section on +687 262 000 and ask for a TB Section staff member. The staff member will then follow up with a consultant by phone and respond in a timely manner.

When posting to the network, members of the case management team will be asked to provide a brief clinical history of the case (including dates of sputum specimens sent), the age and gender of the patient, history of previous TB treatment and any other information that might be considered useful for clinical decision-making (i.e. co-morbidities). The patient should be identified by their initials only in the interest of preserving patient confidentiality. At no time should the patient's name be used in an email conversation. Should NTP staff desire to send photos of chest radiographs they can do so, provided that the name of the patient is deleted. Files larger than 2MB will need to be sent to SPC using a gmail account set up for this task or a file sharing service such as "You Send It".

NTP staff from US affiliated Pacific islands will be asked if information shared in the listserv can also be shared with CDC and the Warm line service (Francis J Curry National TB Center). This will ensure that CDC is aware of any issues relating to TB management and control in these islands.

For enquiries that fall beyond the scope of the network (i.e. outbreaks, non clinical matters) SPC will be responsible for liaising with the relevant technical partners (i.e. CDC and WHO) and other stakeholders as appropriate. In this instance, advice should be provided and technical assistance arranged according to the urgency of the request.

Box 4.1 Summary Checklist Urgent Response Plan

- ✓ Case management team set up
- ✓ Relationship with PTRL established
- ✓ International MDR-TB expert contacted
- ✓ GLC fast-track application prepared
- ✓ Infection control measures taken
- ✓ Contact tracing in place
- ✓ Adequate DOT and patient support measures in place

5. PROCUREMENT OF SECOND LINE DRUGS

NTP managers are strongly encouraged to make full use of the GLC (www.who.int/tb/challenges/mdr/greenlightcommittee). This committee is a subgroup of the MDR-TB Working Group of the Stop TB Partnership, and an advisory body of WHO, and promotes access to (and monitors the use of) quality-assured, life-saving MDR-TB treatment.

GLC fast-track application

Whenever a country needs second line drugs (SLDs) from the regional preempted stock, the first step is to develop a GLC fast-track application (WHO 2008) with technical support from WHO and SPC (Appendix 5). Such applications are intended for projects to treat a small number of, mainly PICTS, cases. Advice on applications can be found at: www.who.int/entity/tb/challenges/mdr/greenlightcommittee/glc_fasttrack_application.pdf.

Deployment of second line drugs from regional store

Immediately after the fast-track application is approved by GLC, WHO Western Pacific Regional Office will requisition SLDs from the regional warehouse in Manila, where a virtual stock of 20 MDR treatments is readily available for PICTs. This has occurred through a regional pre-empted procurement by Western Pacific Regional Office using TB Round 7 multi-country grant for PICTs. Second line drugs are to be dispatched to the ordering country by courier (similar to that undertaken for leprosy drugs to PICTs). Alternatively, WHO regional office staff may physically take SLDs to the ordering country in person and release these immediately after GLC approval.

Regional storage

The procured SLDs will be stored together with the regular SLD stock of Philippines PMDT programme in a warehouse in Manila. The drugs for PICTs will be included as part of a buffer stock. This will eliminate the issue on expiry as the Philippines' programme supply has much higher turnover rate compared with the one for PICTs.

Storage conditions and stock management practices will be monitored and supported by GLC monitoring visits and technical assistance missions from WHO. Department of Health Philippines and WHO regional office will be accountable for ensuring the availability of SLDs whenever needed by PICTs.

Stock recovery

As the mechanism will be established under the multi-country grant for PICTs of Global Fund Round 7, PICTs do not need to reimburse or pay for the SLDs received. WHO regional office plans to procure the SLDs for 20 patients twice, under the current GF grant (Year 2010 and Year 2012), which is expected to be sufficient for 3 to 4 years. An additional funding source may be explored if consumption exceeds this expectation.

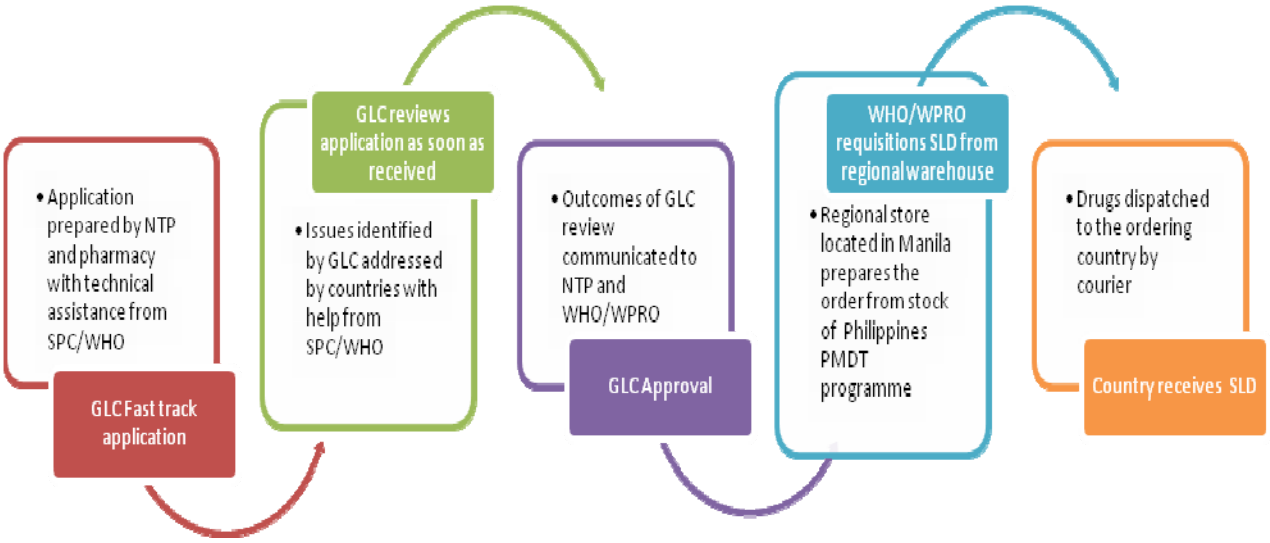

Figure 4.1 Second line TB drug procurement process

6. MULTIDRUG-RESISTANT TB MANAGEMENT

The recommendations for treating MDR-TB are based on a consensus of expert opinion. WHO (WHO 2010, WHO 2008) provides detailed guidance on suggested best practice to manage each MDR-TB case. This section summarises the key aspects.

6.1 Management plan

When notification of a new MDR-TB case is received from the PTRL, this checklist (Box 6.1) should be used to develop the patient treatment and care plan.

Box 6.1 Checklist for MDR-TB case management

1. Case management team to meet urgently to organise care plan in collaboration with External MDR-TB Consultant
    a. Refer to contact list for internal & external support network
    b. Assign responsibility for different tasks
    c. Determine who will oversee management of the patient
2. Initial information required to determine treatment regimen in combination with DST result
    a. Patient treatment history
    b. Current clinical assessment & medical history
    c. Baseline information – refer monitoring checklist
3. Develop treatment plan in consultation with External MDR-TB Consultant
    a. Treatment regimen plan
    b. Monitoring protocol – refer monitoring checklist
4. Patient Care
    a. Determine who will personally advise patient of their TB result & actions necessary
    b. Decide where the patient will be managed
    c. What actions to take if patient refuses to comply
    d. Determine plans for
        i. DOT/ side effect check with screening list
        ii. Infection control – specific to setting
        iii. Patient, family & staff education
        iv. Patient support measures: social, psychological, incentive payments

6.2 Treatment strategy

There are three different treatment strategies for MDR-TB, but confirmation by DST should be always attempted as misclassification of a suspect may result in inappropriate or unnecessary treatment.

Standardised Treatment – the same treatment is given to all MDR suspects based on representative drug resistance surveillance data.

Empirical Treatment – the regimen is determined by previous treatment history and any drug resistance surveillance survey data. It can be modified when DST information becomes available.

Individualised Treatment - the regimen is determined by previous treatment history and DST results

In the PICTs, the approach is mostly individualised.

6.3 Antituberculosis drug selection

WHO classifies five different groups of anti-TB agents available for use. These groups provide a systematic method for allocating drugs to an MDR treatment regimen.

Group 1 – ethambutol and pyrazinamide can be used if there is laboratory evidence of susceptibility but previous use potentially means that these drugs may be less effective. If the laboratory demonstrates low-level isoniazid resistance, then high dose isoniazid may be beneficial.

Group 2 – an injectable agent should be given to all MDR patients. If sensitive, streptomycin should be used. If the patient is streptomycin resistant, kanamycin is the preferred agent. If kanamycin resistant, capreomycin is recommended.

Group 3 – a quinolone antibiotic should be included if susceptible. Ofloxacin and moxifloxacin are the preferred choices. Ciprofloxacin is no longer recommended.

Group 4 – protionamide (or ethionamide) and cycloserine are the two most commonly used agents from this group. Para-aminosalicylic acid (PAS) is the next choice if a third drug is required.

Group 5 – the effectiveness of drugs in this group is unclear. They should be considered only when drug options are limited, e.g. XDR-TB where there is resistance to group 2 and 3 drugs.

Table 6.1 WHO classification of anti-TB drugs

Group	Drugs
Group 1 – First line agents (oral)	isoniazid, rifampicin, ethambutol, pyrazinamide
Group 2 – Injectable agents	streptomycin, kanamycin, amikacin, capreomycin
Group 3 – Quinolone group	ofloxacin, levofloxacin, moxifloxacin, gatifloxacin
Group 4 – Other, second line agents (bacteriostatic)	ethionamide, protionamide, cycloserine, PAS
Group 5 – Agents of uncertain efficacy (not routinely recommended)	clofazimine, amoxicillin-clavulanate, clarithromycin, linezolid

6.4 MDR treatment principles

Certain key principles should be observed when planning a treatment regimen for an MDR-TB patient. These are summarised in Table 6.2:

- The drug combination used to treat MDR-TB should be based on:
    - the results of DST from a quality assured laboratory and
    - the patient's history of previous TB drug use. This information should be forwarded to an external consultant using the "Initial Assessment" form (Appendix 6).
- At least four drugs should be selected from groups 2 to 4 as listed in Table 6.1 to prevent further drug resistance. Dosage is based on patient weight (and as applicable renal function). Refer to Table 6.4 for adult and children doses, and Table 6.5 for any adjustments based on renal function.
    - the use of an injectable agent (group 2) for at least 6 months and a quinolone (group 3) are critical to the best chance of a successful outcome;
    - 2 to 3 drugs from group 4 are also added. Ethionamide and cycloserine are the two most commonly recommended. The third option is PAS, but it has a significant rate of gastro-intestinal side effects and requires careful cold storage;
    - ethambutol and pyrazinamide should be used if DST confirms susceptibility but their reliability should be questioned, based on previous use and these drugs should be considered "extras".

- Duration of therapy for MDR-TB should be at least 18 months (more than 12 months beyond bacteriological clearance of the organism). Most guidelines would recommend at least 24 months treatment. Continuing therapy for a sufficient duration is important to minimise the risk of relapse. Table 6.3 summarises the treatment phases and duration.
- Treatment should be individualised in consultation with the MDR consultant in these situations:
    - Pregnancy
    - Liver disease
    - Kidney disease (see Table 6.5 for dosage adjustments)
    - Other chronic medical conditions such as diabetes

Table 6.2 Principles of MDR-TB treatment regimen

- Design regimen using drug susceptibility results and patient's treatment history
- Use at least 4 to 5 drugs
- Use any first line drugs (group 1) that are still reported susceptible (may be less reliable due to previous use!)
- Use an injectable agent (Group 2) for at least the first 6 months
- Use a quinolone (group 3)

Table 6.3 Summary of Treatment Phases

Treatment Phase	Duration
Initial (injectable)	Minimum 6 months – until sputum cultures negative for at least 2 consecutive months. Decision to stop injectable agent should also consider the clinical and radiological status.
Continuation	12–18 months

Note: it is assumed that services managing MDR-TB have an effective DOTS programme in place that meets WHO guidelines. It is important that further drug resistance is prevented by ensuring strict ongoing adherence to prescribed regimens.

Table 6.4 Second-line anti-tuberculosis drugs

Recommended adult dosage

Drug	Weight Group			
	Average daily dose	**33–50 kg**	**51–70 kg**	**> 70 kg (max dose)**
Group 1 – 1st line anti-TB agents				
ethambutol	25 mg/kg	800–1200	1200–1600	1600–2000
pyrazinamide	30–40 mg/kg	1000–1750	1750–2000	2000–2500
Group 2 – Injectable agents				
streptomycin	15–20 mg/kg	500–750	1000	1000
kanamycin	15–20 mg/kg	500–750	1000	1000
capreomycin	15–20 mg/kg	500–750	1000	1000
Group 3 – Quinolones				
ofloxacin	800 mg	800	800	800–1000
moxifloxacin	400 mg	400	400	400
levofloxacin	1000 mg	750	750–1000	750–1000
Group 4 – Bacteriostatic 2nd line anti-TB agents				
cycloserine	15–20 mg/kg	500	750	750–1000
ethionamide/protionamide	15–20 mg/kg	500	750	750–1000
PAS	150 mg/kg	8 g	8 g	8–12 g

* Injectable drugs are given intramuscularly.

Please note that:

- quinolones are given as a single daily dose;

- Group 4 drugs are usually given twice daily and can be introduced gradually over a few days to improve tolerability and minimize side effects;
- 50 mg pyridoxine (vitamin B6) should be given for every 250 mg of cycloserine, e.g. 150 mg of B6 with a 750 mg daily dose of cycloserine.

Recommended dosage for children

Drug	Dose	Maximum dose per day
Group 1 – 1st line anti-TB agents		
ethambutol	15 mg/kg	800
pyrazinamide	30–40 mg/kg	1500
Group 2 – Injectable agents		
streptomycin	20–40 mg/kg	1000
kanamycin	15–30 mg/kg	1000
capreomycin	15–30 mg/kg	1000
Group 3 – quinolones		
ofloxacin	15–20 mg/kg	800
moxifloxacin	7.5–10 mg/kg	400
levofloxacin	15–25 mg/kg	1000
Group 4 – Bacteriostatic 2nd line anti-TB agents		
cycloserine	15–20 mg/kg	1000
ethionamide/protionamide	15–0 mg/kg	1000
PAS	150 mg/kg	8 g

Table 6.5 Drug dosage recommendations for patients with renal impairment

Drug	Daily dose for patients with creatinine clearance < 30ml/min
Group 1 – 1st line anti-TB agents	
ethambutol	15–25 mg/kg per dose 3 times per week only
pyrazinamide	25–35 mg/kg per dose 3 times per week only
Group 2 – Injectable agents	
streptomycin	12–15 mg/kg per dose 2–3 times per week only
kanamycin	12–15 mg/kg per dose 2-3 times per week only
capreomycin	12–15 mg/kg per dose 2-3 times per week only
Group 3 – Quinolones	
ofloxacin	600–800 mg per dose 3 times per week only
moxifloxacin	400 mg once daily
levofloxacin	750–1000 mg per dose 3 times per week only
Group 4 – Bacteriostatic 2nd line anti-TB agents	
cycloserine	250 mg once daily or 500 mg per dose 3 times per week
ethionamide/protionamide	250–500 mg per dose daily
PAS	4 g per dose twice daily

Creatinine clearance can be calculated using the formula in Table 6.6.

Please note these instructions:

- Use a non-sodium formulation of PAS; a sodium salt formulation of PAS can result in sodium retention;
- Use injectable agents with caution in patients with renal impairment as these drugs have an increased risk of oto-toxicity and renal toxicity;
- Use ethambutol with caution as there is an increased risk of renal toxicity and optic neuropathy.

Table 6.6 Estimation of creatinine clearance from serum creatinine

Cr Cl (ml/min) = $\frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{815 \times \text{serum creatinine (mmol/L)}} \times 0.85$ for females Estimation of lean body weight:
Male: 50 kg + 0.9 kg for each cm > 150 cm
Female: 45 kg + 0.9 kg for each cm > 150 cm

6.5 Monitoring

Initial assessment

The initial patient visit is crucial to developing a good partnership with the patient and family. During this visit the patient should:

- be advised about MDR-TB and its treatment;
- provide information on previous treatment history and any special conditions that may influence treatment, and undertake baseline tests (check "initial assessment form", appendix 6 and "monitoring protocol" appendix 8);
- have infection control explained – measures that are required to protect others and where treatment will occur during the "injectable phase";
- gain some information about the drugs and possible side effects and the follow-up care;
- learn about the DOT process, and the other supportive care that will be offered, to help ensure adherence.

Follow-up care

Use the monitoring protocol (appendix 8) to determine the routine tests required and frequency at which they should be undertaken.

Regular follow-up is important to:

- provide patient support and reinforce information on MDR;
- assess clinical progress and monitor sputum smear and cultures to determine when conversion occurs and the injectable phase can cease;
- monitor side effects (use checklist at appendix 7) and determine whether treatment modifications may be required (seek advice from external MDR-TB consultant);

Figure 6.1 Flow chart for treating MDR-TB patients

Monitor adverse effects of MDR-TB treatment

It is important that adverse effects from treatment for MDR-TB are detected early. The "Symptom Monitoring Checklist" at appendix 7 provides a systematic method for DOT workers to use on a regular basis to screen for adverse drug reactions.

The following table summarises adverse effects and the likely drugs responsible. For more detailed information and guidance on managing a suspected adverse drug reaction, see Chapter 11 in *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008.* Geneva, World Health Organization; 2008. (WHO/HTM/TB/2008.402). Any treatment changes indicated should be made in consultation with an external MDR-TB consultant.

Table 6.7 Adverse effects of MDR-TB treatment

Adverse Effect	Drug(s) to consider	Suggested Action(s)
Persistent nausea or vomiting	May be caused by any drug ethionamide, PAS usually	o Assess hydration status o Take drugs with food o Use anti-emetic and ORS as indicated o Although a reduced dose may improve symptoms, such an action may reduce treatment efficacy. o Seek advice if severe
Abdominal pain	ethionamide, PAS usually	o Take drugs with food o Seek advice if doesn't settle
Heartburn (reflux)	PAS, ethionamide	Antacid, H2 blocker or proton-pump inhibitor Antacids should be used 2 hours before or 3 hours after TB drugs
Diarrhoea	PAS	May persist Try loperamide
Hepatitis (loss of appetite, jaundice)	pyrazinamide, isoniazid ethionamide PAS	Stop treatment until settled Consider possible non drug causes Seek advice on how to re-start treatment
Optic neuritis (visual disturbance)	ethambutol	Stop ethambutol
Hearing loss	Injectable agent	Exclude ear wax as cause

		Seek advice – 3 times weekly dosing may be considered
Pruritus (itching), skin rash	Any drug	Mild – use antihistamine Severe (generalized itch, skin peeling) – stop all treatment, seek advice
Arthralgia (joint pain)	pyrazinamide, fluoroquinolone	Use aspirin or non steroidal anti-inflammatory agent
Renal toxicity	Injectable agent	Stop injectable agent 2-3 times weekly dosing may be feasible depending on creatinine clearance
Hypokalaemia (low potassium)	Severely ill patient, vomiting, diarrhoea Injectable agents	Check potassium regularly during injectable phase Seek advice if abnormal potassium result
Hypothyroidism	PAS, ethionamide	Use thyroxine Low thyroid status usually reverses on cessation of these drugs
Peripheral neuropathy (burning sensation or pins and needles of feet, hands)	cycloserine, isoniazid Injectable agent, ethionamide, fluoroquinolone	Increase B6 to 200mg daily Seek advice
Balance disturbance	Injectable agent	Permanent loss of balance can result from vestibular toxicity Seek advice
Depression	cycloserine, fluoroquinolone, ethionamide	Consider social factors, counselling May need antidepressant Although a reduced dose may improve symptoms, such an action may reduce treatment efficacy.
Psychosis	cycloserine, isoniazid fluoroquinolone, ethionamide	Stop suspected drug Seek advice
Epilepsy	cycloserine Isoniazid, fluoroquinolone	Cease likely drug Start anti-convulsant Increase B6 to 200mg daily

Treatment failure

If there has been no clinical improvement, or sputum cultures are still positive at 4 months, the risk of treatment failure should be considered high and these actions should be taken:

- review treatment record and assess patient adherence (DOT is mandatory).
- review treatment regimen to ensure it is appropriate.
- review patient's clinical status – consider HIV or malabsorption.
- Perform culture/DST to check whether additional drug resistance has occurred.

Treatment failure should be suspected if there is:

- clinical deterioration (e.g. persistent weight loss);
- persistent positive sputum cultures at 8 months or more;
- positive sputum culture(s) after period of negative cultures;
- no further treatment option.

How to manage MDR treatment failure

The main risk from continued treatment in a failing situation is amplified resistance, i.e. XDR-TB or worse. If transmitted to others, such a highly resistant strain should be considered untreatable. The case management team will need to discuss:

- an approach to cessation of treatment;
- a care plan for the patient that ensures adequate discussion about stopping treatment and addresses issues such as supportive care and end of life management.
- infection control because of the importance of preventing transmission of a highly resistant infection to family, relatives and community.

Chapter 13 in *Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency update 2008* gives good guidance on management after MDR treatment failure.

6.6 Resistance other than MDR

If a different pattern of resistance is detected on DST then consultation with the external TB consultant of the Pacific network needs to be undertaken. Table 6.8 below suggests an appropriate regimen selection for a sample of resistance patterns.

Table 6.8 Recommended regimens for non-MDR resistance

Resistance Pattern	Regimen
H, HS	REZ 6–9 months
HE	RZQ 9–12 months
R	HEZQ 2 months + HEQ 10–16 months
Polyresistant (not MDR) HEZ	RQ + group 4 drug + injectable agent first 2–3 months
Injectable agent or quinolone	Consult

Abbreviations: H, isoniazid; R, rifampicin; Z, pyrazinamide; E, ethambutol; Q, quinolone

6.7 Treatment of MDR-TB in Special Situations

The following table summarizes treatment of MDR-TB in special circumstances. For more detailed information consult chapters 9 (Special conditions) and 10 (HIV infection and MDR-TB) in "*Guidelines for the programmatic management of drug-resistant tuberculosis Emergency update 2008.* Geneva, World Health Organization; 2008. (WHO/HTM/TB/2008.402)"

Table 6.9 Treatment of MDR-TB in special conditions

Special Condition	Considerations
Pregnancy	Pregnancy is not a contraindication to MDR treatment Treatment may be deferred until the second trimester depending on the clinical situation If possible avoid: o Injectable agents as they are potentially toxic to the ear of the developing foetus o ethionamide which can increase nausea and vomiting of pregnancy
Breastfeeding	Use of an infant formula is preferred Protection of the baby is very important in the absence of proven prevention treatment. Babies of smear positive mothers should be cared for by another family member until sputum is smear negative
Contraception	Oral contraception is not contraindicated in a regimen that does not include rifampicin. Vomiting may reduce contraceptive efficacy and require the use of a barrier method
Children	Children with evidence of active TB who are close contacts of an MDR case most likely have MDR-TB Children appear to tolerate MDR treatment but there is limited information Fluoroquinolones should be used despite a small theoretical risk of arthropathy Drug dosages are weight based and alterations will be necessary with weight gain (refer table 6.4) Consider treatment failure in children failing to gain or losing weight
Diabetes	Diabetes may increase the risk of adverse effects from treatment e.g. peripheral neuropathy, seizures The dose of oral hypoglycemic agents may need to be increased Renal function should be monitored regularly
Renal Impairment	Injectable agents can cause renal impairment Injectable agents need to be used very cautiously in patients with pre-existing impaired renal function (refer table 6.5)

Liver Dysfunction	pyrazinamide is the most hepatoxic drug when used in an MDR regimen – ethionamide and PAS are also potentially hepatotoxic pyrazinamide should not be used in patients with evidence of chronic liver disease. Liver function should be monitored regularly.
Psychiatric	Patients with a psychiatric disorder should be evaluated before treatment is started by a mental health specialist. Monitor the use of cycloserine closely as this drug may increase adverse effects.
Epilepsy	In known epileptics treatment may require adjustment cycloserine should be used cautiously – good seizure control is required Seizures occurring for the first time during treatment are likely treatment related
HIV co-infection (WHO 2004)	Case management team should have skills in both MDR-TB and HIV care MDR treatment is the same for HIV and non-HIV infected patients ART should be used and timing based on CD4 cell counts Adverse drug reactions are more frequent Close follow-up and additional support measures will be required

Box 6.2 PICT experience

History: Male/35 years, HIV negative:

- 2002 - Category 1 treatment for sputum smear negative pulmonary TB;
  - Outcome: treatment complete after six months DOT.
- 2006 – Category 2 treatment for relapse pulmonary TB (sputum smear positive);
  - Sputum converted to smear negative at two and three months ;
  - Again sputum smear positive at 8 months – high suspicion of MDR-TB.
- Further history revealed previous treatment for PTB in another country.
- Urgent advice sought from external TB and laboratory consultants.
- Through SPC
  - urgent sputum specimens sent for culture and DST.
  - patient isolated.
  - Category 2 treatment stopped to await DST result and plan.
- DST results: MDR-TB.
  - Resistant: isoniazid, rifampicin, ethambutol, streptomycin, ethionamide
  - Susceptible: kanamycin, capreomycin, amikacin, ofloxacin.
- In collaboration with external MDR-TB consultant management plan developed:
  - Second line anti-TB treatment regimen:
    - kanamycin, ofloxacin, cycloserine, PAS, pyrazinamide, pyridoxine.
  - Urgent request for second line anti-TB drugs made to WHO.
  - Patient hospitalized until completion of injectable phase.
- Infection control plan
  - Special room for isolation, N95 masks for staff & visitors.
  - Hospital security round the clock initially
- Family and friends
  - Education, counseling, support
  - wife took another partner after several months
- Monitoring
  - Sputum smear and culture monthly until conversion to culture negative confirmed at 4 months
  - Routine side effect screening and blood tests according to protocol
  - Injectable phase completed at 6 months; treatment completed after total 2 years (all DOT)
  - Close monitoring and screening of household contacts for 2 years
  - Family screening every three months.
- Health Staff encouragement.
- National Health Services provides facilities and meals free of charge
- **Crucial: international technical and consultancy support**

7. SUPPORTIVE MEASURES

The International Standards for TB Care clearly outline the standards for an acceptable level of care, which all practitioners (public and private) should seek to maintain when caring for patients with MDR and XDR-TB (Tuberculosis Coalition for Technical Assistance 2009).

The Patients Charter for Tuberculosis Care outlines the rights and responsibilities for people diagnosed with tuberculosis (Patients Charter for Tuberculosis Care 2006). Together with the International Standards for TB Care, these documents promote a patient centered approach.

7.1 Challenges for patients diagnosed with MDR-TB

Patients diagnosed with MDR-TB may face significant challenges when coping with the diagnosis and adhering to a treatment regimen. The treatment regimen is long (18 months or longer), hospitalization is often required, some medications need to be administered parenterally, side effects of medication may occur and the perceived stigma associated with a diagnosis of MDR-TB may be high.

7.2 Promoting adherence to therapy

Adherence to TB treatment is crucial for the patient to be cured, and the patient and health care workers need to work together to achieve this goal. DOT is recommended for all cases of MDR-TB, and it should be complemented by a number of other strategies to promote adherence. It is important that all of these strategies are implemented in collaboration with the patient. Adherence is a complex phenomenon determined by a range of factors which have been summarised into five dimensions:

- health system and health care team factors,
- social/ economic factors,
- treatment related factors,
- patient related factors and
- condition (i.e. diagnosis of TB) related factors (WHO 2003).

Therefore, promoting adherence to a course of second line drugs requires a multi-faceted approach, based on a partnership and mutual respect between the patient and the health care worker.

7.3 Directly Observed Therapy (DOT)

1. DOT is essential for all patients with MDR-TB.

Patients with MDR-TB are more likely to have had problems adhering to a TB treatment regimen in the past. Thus to achieve a cure, and to prevent transmission of drug resistant strains, DOT should be provided in a way that minimises the burden on the patient.

2. The mode of delivery should be agreed between the patient and the health care worker.

DOT can be delivered in the hospital initially with follow up in the community. At all times, the DOT worker should maintain strict confidentiality regarding a patient's TB diagnosis and treatment unless the patient consents to the release of this information. DOT workers should aim to be friendly, sympathetic, knowledgeable, professional and non-judgmental.

3. Barriers to receiving DOT should be removed wherever possible.

All actions should be taken to identify barriers to DOT services. These may include: long distance to DOT services, DOT services that are open only for certain hours, cost of transport to and from DOT services, perceived stigma of attending a DOT service and acceptability of the DOT worker. These barriers should be removed wherever possible.

4. Other treatment enablers and incentives should also be used and, when combined with DOT, these should form part of a patient centered management plan.

7.4 Patient education

Patients diagnosed with MDR-TB may be overwhelmed by their diagnosis and the perceived stigma may be high. Patients and their families should receive education at the time of diagnosis and throughout treatment. Community and health care workers may also require education on TB, in particular about managing MDR-TB. Education of health care workers who care for TB patients is important as the patient/health care worker relationship should be based on a common understanding of TB and its management. Educational materials should be adapted to the literacy levels of the patient and should be culturally appropriate and gender sensitive. The scope of education should include information on the diagnosis, the treatment regimen (including length of treatment, frequency of treatment, potential side effects and the importance of adherence), contact tracing, infection control and the need to provide DOT and adherence monitoring throughout treatment. Patients should have the opportunity to ask questions at any time, including outside scheduled appointment times.

7.5 Treatment enablers and incentives

Some patients may have a number of socioeconomic problems aside from their MDR-TB diagnosis. At times, and from the patient's perspective, these problems can take priority over TB treatment. Socioeconomic problems may include: homelessness, mental health problems, unemployment, crime, hunger, relationship problems and drug and/or alcohol dependence. Some can be managed with the help of treatment enablers and incentives, which may allow the patient to concentrate more fully on managing their TB. Enablers are goods or services that make adherence to the TB treatment regimen easier for patients, while incentives are goods or services that encourage patients to adhere to therapy. An example of an enabler is free transport for patients who come to the clinic for DOT, while an example of an incentive is a food parcel for a newly diagnosed TB patient. Treatment enablers and incentives should be used in accordance with National TB Program policies, provision of adequate funding and be adapted to the local situation. Examples of treatment enablers and incentives are:

- transport passes or subsidised transport;
- food parcels, hot meals;
- personal items (i.e. clothing, toiletries, stationery, magazines);
- temporary housing;
- nicotine replacement therapy;
- education and skills building, and

- entertainment (i.e. television, internet or DVDs for patients who are hospitalised for long periods).

Other treatment enablers and incentives may result from appropriate referral to other health care professionals (drug and alcohol services, social workers, pediatricians, sexual health clinics, HIV testing centre) and other services (a community legal service, housing service, prison service, and other social services).

7.6 Emotional and psychological support

For many patients, a diagnosis of MDR-TB is devastating news. Despite the best efforts of TB advocates, in many countries the diagnosis of TB still has considerable stigma. Thus emotional and psychological support may be needed at diagnosis and throughout treatment. Health care workers may be able to provide some of this support, but if they cannot, they should facilitate referral to an appropriate group or service. Providing emotional support to patients who have been diagnosed with MDR-TB should serve to lessen the patient's anxiety and may promote better adherence to the treatment regimen.

7.7 Managing side effects of therapy

Second line drugs to treat MDR-TB are associated with side effects and toxicities that make the drugs difficult for patients to tolerate. To promote adherence to the treatment regimen, any side effects should be recognised early during treatment, notified to a health care worker and managed in a timely manner. Early and effective management of side effects is an important way to promote adherence to MDR-TB treatment. TB patients should be educated about possible side effects, and should know who to contact should these occur. To increase patient tolerability and minimize adverse effects to SLDs, drugs such as ethionamide, PAS and cycloserine should be introduced using a lower dose for the first few days and then slowly increased until the target dose is reached. This approach may allow the patient to adjust to side effects. Side effects are best managed with expert consultation, because so few drugs are available to treat MDR-TB. Rather than stopping medication altogether, managing side effects will ensure that effective drug treatment continues whenever possible.

7.8 Addressing non adherence

Non adherence to the TB treatment regimen can occur at any time and should be dealt with quickly and effectively. It is important that the health care worker attempts to understand the reasons for non adherence, and works with the patient to overcome any barriers to adherence, or other problems. The NTP should have a system in place to monitor adherence to TB therapy (including a TB treatment card), and to promptly trace any patients who default from treatment or who do not attend routine clinic appointments.

Legal orders are sometimes required when a patient remains non adherent despite interventions to overcome barriers and gain the patient's cooperation. WHO states that forcibly isolating people with drug-resistant TB must be used only as the last possible resort when all other means have failed, and only as a temporary measure.

8. MANAGING CONTACTS

In view of increasing concern about transmission of MDR and XDR-TB, contact investigation may be a way to identify new cases of primary resistance promptly. Early detection may prevent further transmission of resistant *M. tuberculosis organisms*.

Standard 16 of the International Standard for Tuberculosis Care (Tuberculosis Coalition for Technical Assistance 2009) outlines the level of care that all practitioners should seek to achieve when managing the contacts of TB cases:

- All providers of care for patients with tuberculosis should ensure that persons (especially children under 5 years of age and persons with HIV infection) who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations.
- Children under 5 years of age and persons with HIV infection who have been in contact with an infectious case should be evaluated for both latent infection with *M. tuberculosis* and for active tuberculosis.

WHO has made the following key recommendations on drug resistant TB (WHO 1999):

- Multi drug resistant TB (MDR-TB) contact investigations should be given high priority, and NTPs should consider contact investigation for cases of extremely resistant TB (XDR-TB) as an emergency situation.
- Close contacts of drug resistant TB patients should receive careful clinical follow-up.

Due to the potential severity of MDR/XDR-TB, contacts of all cases of proven or suspected pulmonary (including laryngeal and pleural) MDR/XDR-TB should be given a high priority for investigation, regardless of the index patient's sputum smear result. Contact investigation should be initiated for suspected MDR-TB cases in the same way as for those with proven MDR-TB.

WHO does not recommend treating MDR-TB contacts with regimens tailored to the susceptibility pattern of the presumed source case because no evidence based data exist. But many experts would agree that the treatment of MDR latent tuberculosis infection (LTBI) may be appropriate and feasible in some circumstances. Factors to be considered in the decision to treat MDR-TB contacts include the likelihood of infection with an MDR strain, the risk of progression to active disease once infected, and availability of resources to implement treatment and monitoring.

The likelihood of infection with an MDR strain includes such factors as the infectiousness of the source case, the closeness and intensity of exposure and the history of exposure to pan-sensitive TB. On the basis of this assessment, close contacts of MDR-TB patients, especially children under 5 years and those who are immunocompromised, would be a high priority for TB screening and treatment, if appropriate.

Close contacts of MDR-TB patients are defined as people living in the same household, or spending many hours a day together with the patient in the same indoor living space. Household contacts of MDR-TB

cases who develop TB disease, especially children, are most likely to have MDR-TB also. Early detection of these cases provides the best chance of cure and limits morbidity and mortality.

When screening household contacts who have had contact with an MDR-TB index case:

- All contacts should be carefully assessed for signs and symptoms suggestive of TB disease.
- TB suspects should be evaluated expeditiously for MDR-TB; AFB smear, culture and DST should be performed if possible.
- Close contacts who have no suspicious features of TB disease as a minimum standard should be monitored clinically, radiographically and, if indicated bacteriologically, for at least 2 years.
- All contacts who receive clinical monitoring should be educated about their contact with an MDR-TB case and about the importance of seeking urgent medical attention should they develop signs and symptoms suspicious of TB disease.
- Where resources are available, preventive treatment tailored to the source case isolate drug susceptibility pattern should be considered in close contacts with a high risk for progression to TB disease – particularly young children and the immune-supressed.
- Close contacts offered treatment should receive a regimen containing at least two drugs to which the presumed source case isolate is susceptible.
- Contacts offered treatment should have active TB disease excluded before starting treatment for LTBI.
- All contacts on medication should be educated about and monitored closely for side effects/toxicities and for evidence of progression to active TB disease.
- Efficacy of any regimen depends on adherence and completion of therapy.
- The most effective, best-tolerated regimen, to which the isolate is likely to be sensitive, should be selected (see table 8.1).
- The recommended duration of treatment is generally 6 to 12 months (HIV-infected contacts should receive 12 months of treatment).
- The BCG vaccine should be considered in unvaccinated infants and children with a negative TST who are continually exposed to a case of MDR-TB and who cannot be removed from this exposure.
- If TB disease develops, MDR-TB treatment should be started promptly. The treating doctor should be provided with the drug susceptibility results of the index case.

When TB disease is suspected in a close contact of an MDR-TB case, advice should be sought immediately from a doctor who has expertise in the treatment and management of MDR-TB cases.

There is no proven prevention treatment for infected contacts of MDR-TB cases and the use of second line drugs for this purpose is a controversial area and not generally recommended by the WHO.

In 1992, CDC convened a group of 31 experts to reach consensus on the treatment of MDR TB contacts (CDC 1992). These experts could not reach a consensus, and thus no CDC guidelines on treating and managing MDR TB contacts were published. Unfortunately, there has been little progress in evidence based literature to guide the treatment and management of MDR-TB contacts.

Table 8.1: Potential Drug Regimens

Resistance Pattern	*LTBI Treatment Options*
INH	Adults: RIF 4 months; Children: RIF 6 months
INH, RIF	PZA/EMB or fluoroquinolone + EMB or PZA
INH, RIF, EMB	fluoroquinolone + PZA
INH, RIF, PZA	fluoroquinolone + EMB
INH, RIF, PZA, EMB	fluoroquinolone + ethionamide

9. INFECTION CONTROL FOR MDR-TB

All NTPs in PICTs should have formal written infection control policies for TB. These policies must be implemented and continuously reviewed to control the transmission of TB in healthcare facilities, whether or not MDR-TB is prevalent within their jurisdiction.

This chapter will only summarise the principles of infection control for MDR-TB after describing some background rationales. WHO published an excellent document in 1999 (WHO 1999), available at: http://www.who.int/entity/tb/publications/who_tb_99_269.pdf. Several updates have been produced addressing HIV-specific issues (http://whqlibdoc.who.int/hq/1999/WHO_TB_99.269_ADD_eng.pdf) and with other addendums (http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf). Interested parties are strongly advised to read these documents, particularly the original 1999 publication, for more details on infection control measures for TB.

9.1 Rationales

The causative organism of TB, *Mycobacterium tuberculosis*, is transmitted by aerosols produced mainly by coughing. The aerosols contain thousands of droplet nuclei, each nucleus being < 5 μm in diameter and containing 1 to 3 mycobacteria. These droplets are ideally sized to be inhaled deep into the lungs to establish infection. The risk of infection and disease progression is dependent on 4 factors:

1. The infectiousness of the host – smear-positive patients are more infectious than smear-negative cases; increasing frequency of coughing also increases infectivity.

2. Environment – crowded, poorly-ventilated, dark rooms increase transmission.

3. Duration of exposure – any exposure to an infectious TB patient can lead to transmission but the risk significantly increases when exposure is > 8 hours.

4. Immunocompetent individuals have a 10% lifetime risk of progressing to active TB disease after infection; HIV-positive patients on the other hand have > 50% risk of developing active TB disease; children < 5 years old are also at increased risk of progressing to active TB disease.

All infection control measures for TB try to address one of these four factors. Examples are listed in the Table 9.1.

Table 9.1 Infection control measures

Factors influencing Infection risk	Infection Control Measures
Infectiousness of the host	Suspect, diagnose and treat all TB patients as promptly as possible. The undiagnosed coughing TB patient represents the greatest threat of disease transmission.
Environment	Maximise ventilation and sunlight in building designs.
Duration of exposure	Segregate TB patients; shorten waiting times in out-patient clinics and radiology.
Immune susceptible individuals	Separate HIV and TB patients; avoid mixing babies or young children with TB patients.

9.2 Specific methods of infection control for TB

Three broad categories of infection control methods for TB are: administrative measures, engineering controls and personal protective equipment. Administrative measures are the cheapest, most-effective method, and most cost-effective to institute in PICTs. Engineering controls (e.g. negative-pressure ventilated rooms) and personal protective equipment (e.g. N95 face masks, respirators) are far more expensive (almost prohibitively so in PICTs), and will not work in the absence of administrative measures.

Administrative measures

Examples are:

- Conduct a risk assessment in your hospital – how many TB patients are admitted? How many MDR-TB cases? Where do TB suspects wait to be seen? How many healthcare workers have developed TB (as a measure of healthcare-associated transmission of disease)?
- Develop an infection control plan.
- Educate health care workers about TB transmission and prevention.
- Ensure that all TB suspects are promptly recognised and tested. For example, diagnostic algorithms including features such as cough > 3 weeks, loss of weight, HIV positivity can prompt health care workers to "think TB" and order sputum smear microscopy.

- Ensure sputum collection is performed in a well-ventilated sunlit area that provides some privacy for the patient.
- Avoid cross-infection between patients and staff: limit waiting times in out-patient clinics; triage TB suspects to separate clinics or waiting areas; avoid mixing TB suspects and HIV patients (noting that such measures must be instituted without compromising the HIV patient's confidentiality).
- Isolate TB patients, e.g. have a ward for medical patients, a separate ward for TB patients, another ward for MDR-TB patients, and yet another ward for HIV patients.
- Consider special areas such as theatres, sputum-induction or bronchoscopy suites, and post-mortem rooms.
- Continuously monitor the implementation of these infection control strategies and evaluate their effectiveness (e.g. follow the number of health care workers developing TB).

Engineering controls

Engineering controls attempt to reduce the number of infectious droplets in the atmosphere. These measures are generally "high-tech" (e.g. negative-pressure ventilation rooms and biosafety cabinets. The capital cost and on-going maintenance expenses make most engineering measures prohibitively expensive for PICTs. The most appropriate engineering control for PICTs is to ensure that their wards, waiting areas and laboratories have effective natural cross-ventilation, which may be augmented with window fans.

Personal protective equipment

NTPs and health care workers in PICTs must recognise that normal surgical masks provide no protection to the wearer. These masks are designed to prevent surgeons contaminating operative sites. Surgical masks may therefore be used to reduce aerosol production from TB patients in-transit around the hospital (such as between the TB ward and Radiology).

Masks that effectively protect HCWs are rated depending on their efficiency at filtering minute particles. Suitable masks for filtering mycobacteria are termed "P2" or "N95" masks in various countries. P2-N95 masks must fit snugly on the face to ensure that all inhaled and exhaled air actually travels through the filter. Healthcare workers must be trained on the proper use of P2-N95 masks and should fit-check their mask each time one is worn. Health care facilities in high-income countries also undertake fit-testing of masks. Further information about fit testing is available at: http://www.health.sa.gov.au/INFECTIONCONTROL/Default.aspx?tabid=143.

Beards or moustaches can compromise the facial seal of P2-N95 masks. High-income countries can provide bearded workers with an alternative respirator, such as a powered air-purifying respirator. Because such alternatives may be unavailable in PICTs, shaving should be considered.

P2-N95 masks are expensive as described above. "Duckbill"-style P2 masks cost about AUD$3 each and can only be used until they become moist or damaged. Providing adequate on-going stocks can therefore cost thousands of dollars. Pacific Island countries may therefore choose to limit P2-N95 masks to high-risk situations, such as:

- when working in isolation rooms for patients with MDR-TB;
- during sputum induction or other cough-inducing procedures;
- bronchoscopy suites;
- autopsy areas;
- spirometry rooms;
- during emergency surgery on potentially infectious TB patients

9.3 Specific measures to be taken when managing an MDR-TB patient

The above text summarises infection control measures for TB and MDR-TB. Certain specific measures must be taken when a PICT is confronted with caring for an MDR-TB patient. These should be an extension of and complement the pre-existing TB infection control strategy within the PICT.

1. Appoint an infection control officer to implement and monitor infection control measures.
2. Ensure daily direct observation of all treatment
    - keep record to verify;
    - poor adherence to treatment will risk further drug resistance and an untreatable infection.
3. Patient placement
    - Advise patient of reasons for isolation.
    - Isolate the MDR-TB patient until considered non infectious – consecutive negative sputum cultures (2) one month apart.
    - Separate the MDR-TB patient from other TB cases and immune-suppressed patients, e.g. HIV cases.
    - The room should have natural ventilation and the door should have a “Stop” sign” to limit entry.
    - There are no special requirements for linen.
4. Patient behavior
    - Cough hygiene – advise patient to cough into a disposable tissue and provide a plastic bag for disposal.
    - Encourage daily outdoor activity in the open air (not within buildings).

- Patient movement outside the room but within hospital buildings (e.g. transfers to Radiology, waiting for chest X-rays) should be limited and supervised; a surgical mask should be worn unless outdoors.

5. Sputum Collection

    - Sputum specimens should be collected in a private outdoor area with good natural ventilation (not in a toilet area).

6. Visitors

    - Visits by family or close friends should occur in an outdoor area, especially if visitors include young children.

7. Staff Protection

    - Staff entering the patients room should ideally wear an N95 standard mask, with a good face seal.

    - Surgical masks do not provide adequate protection.

    - Immune-compromised staff should not be involved in the patient care.

8. Staff Education

    - Staff should be informed about the measures required to protect other patients, visitors and themselves.

Box 9.1 Summary Checklist Infection Control

- ✓ Appoint Infection Control Officer
- ✓ Ensure DOT
- ✓ Patient placement (isolation and separation)
- ✓ Patient behavior (cough hygiene)
- ✓ Sputum collection (outdoors)
- ✓ Visitors (outdoors)
- ✓ Staff protection (N95 mask)
- ✓ Staff education

10. REPORTING AND RECORDING

A standardised method of recording and reporting should be implemented in drug-resistant TB control programmes.

10.1 Aims of the information system

The aims of the information system are:

• To allow NTP managers at different levels to monitor programme performance (such as patients started on treatment and treatment results), to follow trends in the number of cases notified, to plan drug supply, and to provide the basis for programme and policy developments.

• To aid clinical providers in management of individual patients.

10.2 Performance indicators

The performance indicators include:

• the number of patients in whom MDR-TB is detected in the laboratory;

• the number of MDR-TB patients started on treatment;

• interim treatment outcome at 6-months of MDR-TB cases;

• final outcome of MDR-TB treatment.

Table 10.1 MDR-TB performance indicators

1	MDR-TB suspects - Number of patients meeting the criteria for MDR-TB suspect (registered as new or re-treatment) who received diagnostic DST from a PATLAB Laboratory
2	MDR-TB cases registered based on PATLAB confirmed culture isolates that are resistant to at least isoniazid & rifampicin
3	MDR-TB cases treated with second line drugs
4	Treatment success: number of MDR-TB cases successfully treated (culture confirmed). For TB cases registered 2 calendar years earlier
5	Treatment failure, default or death: number of MDR-TB cases with an unsuccessful outcome

10.3 Main forms/registers and flow of information

The forms and registers include:

• MDR-TB treatment card;

• MDR-TB register;

• request for sputum examination;

• laboratory register for culture and DST.

Reports include:

• quarterly report on MDR-TB detection and MDR-TB treatment start;

• six-month interim outcome assessment of confirmed MDR-TB cases;

• annual report of treatment result of confirmed MDR-TB patients starting MDR-TB treatment.

Chapter 18 in *Guidelines for the programmatic management of drug-resistant tuberculosis Emergency update 2008* provides good guidance on the different forms and their use.

Because most PICTs will have very few MDR-TB cases, a MDR-TB specific reporting and recording system will not be required. The focus will be on ensuring that a system is in place to properly manage the MDR-TB cases using an MDR-TB treatment card.

10.4 MDR-TB Treatment Card

The staff should complete the MDR-TB treatment card when the patient is actually starting treatment. This card is a key instrument for DOT workers who administer drugs to patients daily. It should be updated daily by ticking off the supervised administration of drugs. The card, or a copy, must always follow the patient (e.g. from a specialised hospital to an ambulatory facility). A copy may be used as a notification form and later also to report the final outcome of treatment. A useful tool to monitor patients with MDR-TB, especially drug administration, is shown in Appendix 9: the "Drug-O-Gram" (Francis J. Curry National Tuberculosis Center 2008).

APPENDICES

Appendix 1. Strategic priorities and targets

Strategic Priority 1: Ensuring universal and equitable access to TB diagnosis and treatment for all people suffering from TB
A) Decline of ≥ 1% of the notification rate of new smear-positive pulmonary tuberculosis cases
B) Beyond 85% Cure Rate
Strategic Priority 2: Considerable scaling up of PMDT
A) Near 100% of the region covered by PMDT by the end of 2015
B) In areas covered by PMDT near 100% of suspects of X/MDR TB screened by line probe assay and culture and DST
C) In areas covered by PMDT at least 90% of patients diagnosed with drug resistant tuberculosis enrolled on second line drugs treatment regimens
Strategic Priority 3: Strengthening TB HIV collaborative activities
Case-fatality rate of HIV positive TB patients on anti-TB treatment ≤ 10%

To achieve the above Strategic Priorities, these Expected Results, or desired outcomes through actions, have been suggested:

Strategic priorities and expected results

Strategic Priority 1: Ensuring universal and equitable access to TB diagnosis and treatment for all people suffering from TB		
	DESCRIPTION	**INDICATORS AND TARGETS**
Expected Result 1.1	Suspects examined by direct microscopy per 100,000 people	Increasing or stable trend
Expected Result 1.2	Proportion of suspects with at least one positive smear	Target: ≥ 10% to ≤ 5%
Expected Result 1.3	Enhancing early reporting of suspects and detection of cases	Representative diagnostic delay studies carried out

Expected Result 1.4	Examination of household and close contacts of smear-positive index cases	Monitoring and evaluation for contact investigations implemented
Expected Result 1.5	Use of fixed dose combination tablets of assured quality	Proportion of cases treated with fixed dose combinations at least 90%
Expected Result 1.6	Electronic case based reporting system of suspects, cases and treatment results	Proportions of referral, diagnostic and treatment units linked to the system
Expected Result 1.7	Minimizing access barriers, especially for the poor and vulnerable	Programme for periodic screening of high risk groups implemented
Expected Result 1.8	Engaging all health care providers	Proportion of private providers engaged by the programme and proportion of additional cased notified by them
Expected Result 1.9	Increasing health communication and social mobilisation	Knowledge, Attitude and Practices studies carried out
Expected Result 1.10	Ensuring that TB treatment and care are consistent with ethics and human rights norms and promote social justice	NTPs have developed and applied policies to safeguard ethical norms and rights of patients, health staff and communities

Strategic Priority 2: **Considerable scaling up of PMDT**		
	DESCRIPTION	**INDICATORS AND TARGETS**
Expected Result 2.1	Second line treatment, care and support system for all diagnosed M/XDR TB patients in place	100% of PMDT treatment units with uninterrupted supply of second line anti-TB drugs in a given year
Expected Result 2.2	Evaluation of treatment outcomes of all MDR-TB cases enrolled on SLD	Treatment success rate ≥ 70% to 75% Failure rate ≤ 5% to 10% Death rate ≤ 10% Default rate ≤ 10% to 15%
Expected Result 2.3	Prevention of nosocomial transmission of TB	100% of PMDT and TB/HIV health facilities with adequate infection control measures

Strategic Priority 3: Strengthening TB HIV collaborative activities		
	DESCRIPTION	INDICATORS AND TARGETS
Expected Result 3.1	Ensured access of TB patients to provider initiated testing and counseling	At least 90% of TB patients are tested for HIV in Cat 1 and Cat 2 countries/areas
Expected Result 3.2	Implementation of ICF and IPT in those with HIV/AIDS	National AIDS programmes adopt ICF and IPT
Expected Result 3.3	Prevention of nosocomial transmission of TB	Infection control measures in place in all settings where those with HIV/AIDs are at risk of infection with TB

Appendix 2. Contact details for reference laboratories

	MAILING ADDRESS	CONTACT DETAILS
Adelaide	Mycobacterium Reference Laboratory Institute of Medical and Veterinary Sciences Frome Road Adelaide South Australia 5000 Australia	Mr Richard Lumb richard.lumb@imvs.sa.gov.au Tel: (08) 8222 3579 Fax: (08) 8222-3543
Brisbane	Mycobacterium Reference Laboratory Block 7 Royal Brisbane and Women's Hospitals Campus Herston Queensland 4006 Australia	Ms Robyn Carter Robyn_Carter@health.qld.gov.au Tel: (07) 3636 0032 Fax: (07) 3636 1336
Honolulu	Diagnostic Laboratory Services, Inc. Suite 300 650 Iwilei Road Honolulu Hawaii 96817 USA	Dr Matthew Bankowski mbankowski@dlslab.com Tel: (808) 589-5242 Fax: (808) 589-5215
Auckland	Phone 09 307 8995 extn 2044 LabPlus, Building 31 Auckland City Hospital Park Road AUCKLAND 1023	Dr Sally Roberts Tel: 09 307 8995 extn 2044 Pager 93-6156 sallyrob@adhb.govt.nz

Appendix 3. Contact details for TB treatment and support network

	MAILING ADDRESS	CONTACT DETAILS
Adelaide	South Australian TB Services Royal Adelaide Hospital Chest Clinic 275 North Terrace Adelaide, South Australia 5000	Dr Rick Stapledon Tel: 08 82225435 Fax: 08 82225398 E-mail: Richard.Stapledon@health.sa.gov.au
Brisbane	Queensland TB Control Centre (Specialised Health Services) Queensland Health Locked Bag 66 COORPAROO D.C4151	Dr A Konstantinos Tel: (617) 3896 3937 Mobile: 0410424756 Fax: (617) 3896 3984 E-mail : anastasios_konstantinos@health.qld.gov.au
Suva	Stop TB and Leprosy Elimination WHO South Pacific Po Box 113. Suva, FIJI	Dr Linh Nguyen Tel: (679) 323 4106 Fax: (679) 323 4177 Email: nguyenli@wpro.who.int

Noumea	Secretariat of the Pacific Community BP D5 Noumea Cedex	Dr Janet O'Connor Tel: (687) 26 20 00 Fax: (687) 26 38 18 Tel: (687) 26 01 16 (direct line) E-mail: janeto@spc.int Dr Axel Wiegandt Tel: (687) 26 01 42 (direct line) E-mail: axelw@spc.int
Manila	WHO Western Pacific Regional Office P.O. Box 2932, UN Avenue 1000 Manila, Philippines	Dr Daniel Sagebiel Tel:+63-2-528-9720 GPN: 89720 Fax:+63-2-521-1036 E-mail: sagebield@wpro.who.int
Atlanta	Division of Tuberculosis Elimination National Center for HIV, Hepatitis, STD and TB Prevention Centers for Disease Control and Prevention Mailstop E-10, 1600 Clifton Road Atlanta, GA - 30333	Dr Sundari Mase Tel: 404-639-5336 Fax: 404-639-8958 E-mail: : fyy0@cdc.gov

San Francisco	Francis J. Curry National Tuberculosis Center – TB Warmline 3180 18th Street, Suite 101 San Francisco, CA 94110	Warmline Coordinator Tel: 877-390-6682 or 415-502-4700 E-mail : tbcenter@nationaltbcenter.edu

Appendix 4. Templates for shipping documents

Template Quarantine Letter

To: Australian Quarantine Inspection Service (AQIS)

Re: AWB No: XXXXXXXXX

The fiberboard boxes contain X sputum samples that are being shipped to Australia for diagnostic testing & research purposes only.

The consignee is:

The sample has been packed in accordance with IATA packing instructions 650.

These are urgent samples that need refrigeration and should not be delayed in any circumstance.

A copy of the import permit is attached.

Should there be any query regarding Customs or AQIS clearance, please contact (give receiving laboratory's name, phone number & fax number)

Yours sincerely

_____

Template Customs Letter

Customs Declaration

To whom it may concern

This shipment contains X sputum specimens packed in accordance with IATA packing instructions 650. The samples are to be used for diagnostic testing & research purposes only. They have no real commercial value and are not for resale.

Nominal commercial value: USD$10

Contents:

Specimen:	sputum
Amount:	X mls (liquid)
Number of pots	X
Origin	Human
Country of Origin	X

From: Your name, address & phone number

To: Name, address, phone & fax number of receiving laboratory

Yours sincerely

Appendix 5. Fast-track application to the Green Light Committee

Projects for small a number of patients

The time for the application process for projects designed to treat a small number of patients (generally less than 50) can be minimised by using the fast-track option specifically intended for these cases. The procedure outlined below should be followed. It is important to note that although the application process is simplified, the requirements for approval have not been not downgraded in any way, especially evidence of sound TB control based on all elements of DOTS.

Access to the drugs will be provided based on the understanding that:

- the project will adhere to WHO technical guidelines;
- the drugs will only be used to treat the patients approved;
- all the drugs approved will be purchased through the GLC mechanism, and
- the project will provide regular information on the progress achieved to WHO.

Letter of support from the government (MOH) and/or NTP needs to be provided.

These issues should be addressed by the application:

1. Background

1.1 Brief information on the region/country in which project will be undertaken.

1.2 Epidemiology of TB.

1.3 Reasons for emergence of drug-resistant TB and justification for the project.

2. Existing TB control programme

2.1 DOTS performance in the country/region with aggregate data.

2.2 Method for case finding.

3. Information on drug-resistant TB in the area and past use of second line drugs

3.1 Drug resistance profile of the proposed treatment cohort (if only a few patients, the profile of each patient) from the quality assured laboratory or reliable drug surveillance data.

3.2 Use of second line drugs in the past in the country/region.

4. Commitment and partnerships

4.1 Evidence of commitment to TB control such as the budget for the project and support letters.

4.2 Verification stating that treatment of drug-resistant TB is provided free of charge to the patients.

4.3 Commitment of the project to regulate and account for the distribution of second line anti-TB drugs.

5. Organization, management and coordination

5.1 Number of patients planned for enrollment. Anticipated start date and duration of the project.

5.2 Organization/institution to manage the project; local facilities of the TB control system (including specialised units) that will be involved in treating patients with DR TB.

5.3 Local personnel in the TB control system who will be responsible for treating patients with DR TB, and their training/experience in managing such cases and use of second-line anti-TB drugs.

5.4 Infection control measures.

5.5 Plan for implementation.

5.6 Plan for the monitoring and supervision of the project by both internal and external body.

6. Case finding, diagnosis and definitions

6.1 Inclusion/exclusion criteria to be employed for selecting, out of all cases with drug resistant TB identified by the project, those to be enrolled in the project cohort.

6.2 Case definitions for patients with DR TB with brief description for each and rationale behind using them within a framework of this project.

6.3 Detailed definitions of all outcomes of the DR TB treatment and their implications for the further decisions to take.

6.4 Description of the laboratory to serve needs of the project and its affiliation/links with supranational laboratory network for quality control. Quality control results.

6.5 HIV testing.

7. Treatment and follow-up strategy

7.1 Treatment regimens (standardised or individualised) and algorithms for their design for both intensive and continuation phases.

7.2 Strategy and algorithms to manage the most frequently occurring/expected side effects.

7.3 Plan for ensuring complete treatment and follow up of all patients.

Appendix 6. MDR-TB Case - Initial assessment

Name:

Date of Birth:

District:

Gender: □ M □ F

Pre-treatment Assessment

Site of Disease:

Bacteriology Result:

Microscopy:

Culture:

DST Result:

Resistant:

Susceptible:

TB Treatment History

Year of treatment	Category used & duration	Outcome
1.		
2.		
3.		

Were fixed dose combination □ or individual drugs used □ ?

Has kanamycin or ofloxacin (or another quinolone) ever been used? □ Y □ N

If yes, please specify:

Clinical Assessment

Current medical status including associated medical disorders e.g. diabetes, epilepsy

Baseline investigations:

Height: (cms)

Weight: (kgs)

Urinalysis:

Complete blood picture

Electrolytes & Creatinine

Liver function

Thyroid function (if possible)

HIV test

Chest X-ray (please forward digital copy if possible)

Appendix 7. MDR-TB symptoms monitoring checklist

Patient Name:							
Date							
Symptom check							
CNS							
Dizziness							
Balance difficulty							
Headache							
Pins & needles							
Seizures							
Hearing							
Tinnitus							
Hearing difficulty							
Psychiatric							
Anxiety							
Depression							
Behaviour disturbance							
Thought disturbance							
Gastro-intestinal							
Nausea							
Vomiting							
Diarrhoea							
Abdominal pain							
Skin							
Rash							
Pruritus (itch)							
Petechiae/bruises							
Jaundice							
Vision							
Visual disturbance							
Colour vision disturbance							
Musculo-skeletal							
Joint pain							
Muscle cramps							

Appendix 8. MDR-TB Monitoring protocol

	MDR TB MONITORING PROTOCOL
Test	**Frequency**
Doctor check	Every 2 weeks first 1-2 months then monthly
Symptom check	Each DOT visit (refer checklist)
Weight	Baseline, monthly
Urinalysis	Baseline, monthly
Visual acuity	Baseline, monthly
Sputum	Monthly smear & culture until culture converts to negative
	Conversion = 2 negative cultures followed by 2 negative cultures one month apart
	Post conversion:
	Monthly smear, culture every 2 to 3 months
DST	If failure to culture convert by 4 months, DST should be repeated
Electrolytes	Baseline, monthly during injectable phase then 1-3 monthly
Creatinine	Baseline, monthly during injectable phase then 1-3 monthly
Liver function	Baseline, 1-3 monthly
Thyroid (TSH)	6 monthly (PAS and ethionamide can cause hypothyroidism)
Complete Blood Picture	Baseline & 1-3 monthly
Chest X-ray	6 monthly (of limited value in predicting clinical improvement, mainly
	to detect complicating events)

Appendix 9. "Drug-O-Gram"

SUMMARY DATE:	NAME:	DOB:	HEALTH DEPARTMENT:	TREATING PHYSICIAN:	FILE NO:

TREATMENT REGIMEN **BACTERIOLOGY**

Date	Wt.	INH	RMP	PZA	EMB	SM	KM	AK	CM	PAS	ETA	LFX	OFX	CS	Date	spec	sm/cult	Comments

SUSCEPTIBILITY RESULTS

Date	Spec.	Lab	INH	RMP	EMB	PZA	SM	KM	AK	CM	PAS	ETA	LFX	OFX	CPX	CS	RFB	IMI	Reported

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