NATIONAL TUBERCULOSIS GUIDELINES

PALAU

Ministry of Health

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ABBREVIATIONS

ACSM	Advocacy, communication and social mobilization
AFB	Acid-fast bacilli
ART	Antiretroviral therapy
ATS	American Thoracic Society
BCC	Behavior Change Communication
BCG	BacilleCalmette–Guérin
BNH	Belau National Hospital
CDC	Centers for Disease Control and Prevention (USA)
CDU	Communicable Disease Unit
CXR	Chest X-ray
DAO	Disease Assistance Officer
DIA	Disease Intervention Assistant
DIS	Disease Intervention Specialist
DLS	Diagnostic Laboratory Services (in Hawaii)
DM	Diabetes mellitus
DOTS	Directly Observed Treatment, Short-Course
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
EPTB	Extrapulmonary tuberculosis
EQA	External quality assurance
FLD	First line TB drugs
GFATM	The Global Fund to fight HIV, Tuberculosis and Malaria
HIV	Human immunodeficiency virus
IEC	Information, Education, Communication
INH	Isoniazid
ISTC	International Standards of Tuberculosis Care
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
LTBI	Latent TB infection
M&E	Monitoring and evaluation
MDR-TB	Multidrug-resistant tuberculosis
NSP	New Smear Positive
NTM	Nontuberculous mycobacteria
NTP	National TB Control Program
PAL	Practical Approach to Lung Health
PPD	Purified protein derivative
PPM	Public-private mix
PTB	Pulmonary tuberculosis
RR	Rifampicin-Resistant
SPC	Secretariat of the Pacific Community
STD	Sexually Transmitted Diseases
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World Health Organisation
XDR-TB	Extensively drug-resistant TB

ANNEXES

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FOREWORD

Tuberculosis continues to be a problem of important public health significance in the Republic of Palau. However, the total number of cases has fallen in recent years and the number of cases has reduced by about one third compared to the year 2000.

The National TB Program was established in Palau in the 1970's and the internationally recommended TB control strategy, Directly Observed Treatment Short-course is in place. Since this time the National TB Program has expanded and now Palau has health care workers dedicated to the care of persons with presumptive TB and patients. The National TB Program has enhanced its activities by training health care workers to better identify and manage TB, strengthening laboratories to diagnose TB, recruiting staff dedicated to support TB patients throughout their course of treatment and by implementing community campaigns designed to educate the community about tuberculosis. These combined efforts aim to not only strengthen the National TB Program but to reduce the burden of TB in the local community.

Within the framework of the Stop TB Strategy and policies developed by the US Centers for Disease Control and Prevention, the Republic of Palau can reduce the burden of TB. The Republic of Palau will continue to fight to prevent TB, effectively treat TB when diagnosed and eventually eliminate TB. In collaboration with other health professionals within the health system, our technical agency partners, non-government organisations and affected individuals we will continue to strive to reduce the scourge of TB on our Micronesian people.

1. INTRODUCTION

The National TB Program of the Palau works in close collaboration with its technical partners; CDC, SPC and WHO.

The national Government's efforts, supported by technical partners, has led to substantial progress in TB control in Palau. These national guidelines are designed to further support TB control efforts in Palau.

These national TB guidelines are based on the *Treatment of tuberculosis: guidelines* (4th edition)[1]. WHO's 4th edition has some major changes compared to the 3rd edition (*Treatment of Tuberculosis: Guidelines for National Programs*, WHO, 3rd edition, WHO/CDS/TB/2003.313). The guidelines are also in line with CDC documents and policies and the *International Standards of Tuberculosis Care*[2].

These guidelines contain the general policy for tuberculosis control in Palau and are intended to be a reference to guide health care workers in the diagnosis, treatment and prevention of tuberculosis in Palau.

This guideline should be updated periodically to reflect new evidence and best practices. The National TB Program Manager is responsible for the review process and modifications over time, to reflect new evidence and best practice from reputable sources.

Acknowledgements

The Ministry of Health, Palau would like to thank everyone who was involved in the development and review of these national TB guidelines.

[1] Treatment of tuberculosis: guidelines – 4th edition, WHO/HTM/TB/2009.420 (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf)

[2] While in the first edition (2006), there were 17 standards, there are now 21 standards in the 2nd edition. (http://www.istcweb.org/ISTC_Documents.html).

2. TUBERCULOSIS CONTROL IN PALAU

The Republic of Palau is an island nation located in the Pacific Ocean. It is a sovereign state in free association with the United States.

Palau has sixteen states, which is further sub-divided into 76 hamlets or smaller administrative units similar to villages; almost two-thirds of the population lives in the state of Koror. The overall population of Palau is approximately 20,288 and among these, roughly 7,700 are foreign-born (over 5,000 of them are from the Philippines). Palau is an upper middle income country and the economic activity consists primarily of tourism, subsistence farming and fishing.

2.1 DOTS and Stop TB strategy in Palau

In the mid-1990s, the concept of DOTS (directly observed treatment, short course) was introduced in Palau as it was proven to be an affordable and cost effective strategy for controlling TB in other parts of the world. The five basic components of DOTS Strategy are:

i. Government and political commitment to sustaining the NTP
ii. Reliable sputum smear microscopy for case detection
iii. An effective, uninterrupted supply of anti-TB drugs
iv. Directly observed standardized short-course treatment for all patients with TB, and
v. A standardised recording and reporting system to monitor each patient's progress and treatment outcomes.

The Stop TB Strategy was launched in 2006 to build upon and enhance the achievements of DOTS and to address the key challenges of TB-HIV and MDR-TB. The national TB program in Palau aligns implementation of TB care activities with the Stop TB Strategy that aims to ensure access to care for all TB patients, to reach the 2015 Millennium Development Goal for TB and to reduce the burden of TB worldwide. The six components of the Stop TB strategy highlighted in Annex 1are as follows:

i. Pursue high quality DOTS expansion and enhancement
ii. Address TB-HIV, MDR-TB and the needs of poor and vulnerable populations
iii. Contribute to health system strengthening based on primary health care
iv. Engage all care providers
v. Empower people with TB, and communities through partnership
vi. Enable and promote research

2.2 The International Standards of TB Care

The International Standards for Tuberculosis Care (ISTC) were developed by the Tuberculosis Coalition for Technical Assistance (TBCTA) with funding from the United States Agency for International Development (USAID). The standards describe the internationally accepted level of care in managing patients who have or are presumed of having TB and include the principles of diagnosis, treatment and public health responsibilities. The standards are the accepted level of TB management, while the WHO recommended DOTS and STOP TB strategies provide a practical means of implementing those standards.

2.3 DOTS based TB Care in Palau

Case registration

According to WHO data, DOTS coverage in Palau was 100% in the year 2002. The case detection rate (new smear-positive cases and all forms of TB) ranged between 75-90% from 2002 to 2010. TB case notification rates during the period have increased significantly from 45 cases per 100,000 in 1990 to 153 cases per 100,000 in 2011. Table 1 presents the number of new and relapse cases and sputum smear positive TB cases for the years 2004-2012.

Table 1: Total number of new and relapse TB notifications in Palau: 2004-2012

	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Number of new and relapse cases	5	10	12	11	18	19	19	12	4	8
Number of new smear positive cases	5	3	6	5	7	6	8	4	3	

Sources: (i) Global TB Reports 2008-2013 (WHO) (ii) NTP data from Palau

Diagnosis

The main diagnostic tools for TB case finding in Palau are sputum smear microscopy, and chest x-ray for all presumptive TB cases and GeneXpert starting from Q1 2013.Sputum samples from Palau are routinely sent to Hawaii for microscopy, culture and drug susceptibility testing (DST) to Diagnostic Laboratory Services, Inc. (DLS) in Honolulu.The Belau National Hospital (BNH) and the Communicable Disease Unit (CDU) is the main facility for the treatment of TB. All TB cases are referred to BNH for diagnostic work-up, treatment, and contact investigation.

Treatment supervision

Treatment supervision is health facility-based directly observed therapy (DOT). In 2009, people from the communities were recruited to become TB-DOTS workers after intensive training lasting nearly 12 – 15 months. The TB-DOTS workers receive comprehensive training on all public health aspects including TB. Termed Disease Intervention Assistants (DIA), they hold jobs similar to the profile of Assistant Nurses and ensure DOT for TB care while also providing care for other diseases as well.

Treatment outcome

The treatment success rate (for new sputum smear positive cases) has fluctuated over the past five years, which is expected due to the very small number of new sputum smear positive patients in Palau. From 2002 to 2012, the sputum smear positive treatment success rate ranged from 67-100%.

Drug management

The TB first line drugs are procured directly by the pharmacy of MoH in Palau from different companies across the world using MoH funding. Most of these drugs are ordered biannually based on consumption and availability of buffer stocks. Second-line TB medicines are available through a regional stock pile (in Manila, Philippines). BNH houses the central warehouse where the TB medicines are stocked.

Financing

The National TB Program is mostly financed by the national budget, with significant support coming from the Centers for Disease Control and Prevention (CDC) and the Global Fund to Fight AIDS, TB and Malaria (Round 7 and TFM).

2.4 Objectives of the National TB Program

The two general objectives for the National Tuberculosis Program (NTP) based on the DOTS strategy:

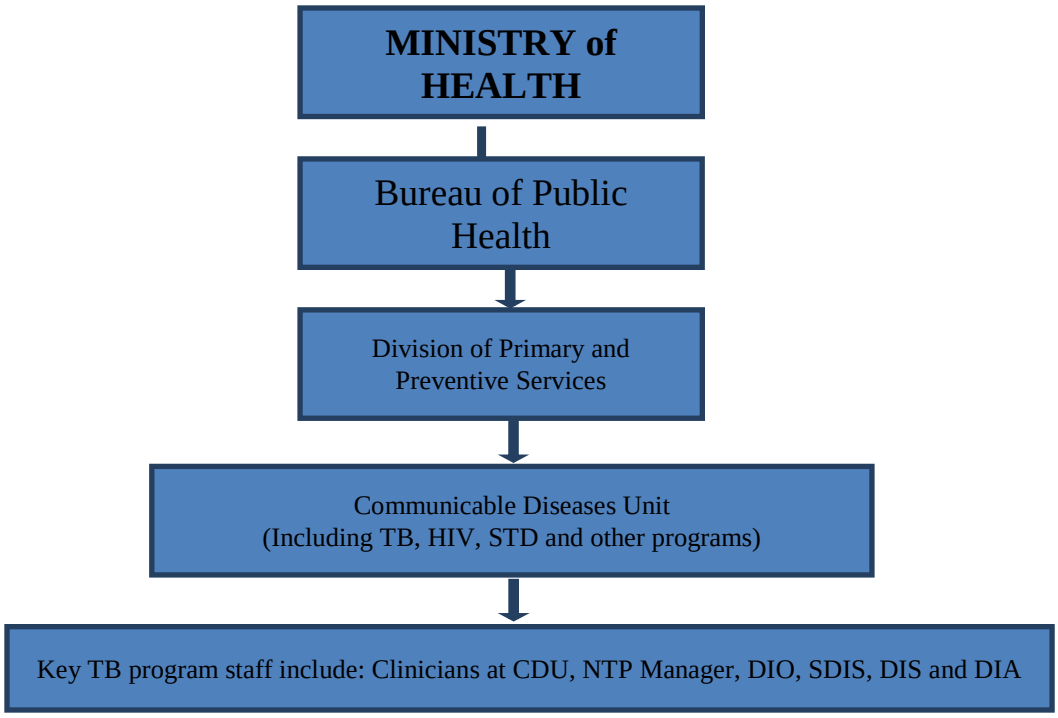
i. To reduce TB mortality and morbidity, and transmission of infection, and
ii. To prevent the development of drug resistance.

The Strategic Plan for TB Control in the Western Pacific 2011-2015 has been developed to provide countries with guidance on designing national strategic plans for TB control during the 5 years with an aim to achieve the 2015 Millennium Development goals for TB. The regional strategic plan sets out three core priorities:1) ensuring universal and equitable access to TB diagnosis and treatment for all people suffering from TB, 2) considerable scale up of the programmatic management of drug-resistant TB, and 3) strengthening TB-HIV collaborative activities.

2.5 Structure of the National TB Program

The National TB Program is part of the Communicable Disease Unit within the Bureau of Public Health, Ministry of Health (Fig 1). The Program is managed by a National TB Program Manager who oversees the work of Disease Intervention Officers and Disease Intervention Assistants. A summary of the key duties of each role is provided in Annex 2.

Figure 1: NTP structure within the Bureau of Public Health



3. CASE DEFINITIONS AND CLASSIFICATIONS

The TB case definitions incorporate recent revisions by WHO on case definitions that are based on the level of certainty of the diagnosis and recent rapid diagnostic developments. This document incorporates latest WHO standard case definitions for TB and drug-resistant TB, the categories used to assign outcomes, and the standard reporting framework for TB. The definitions incorporate less judgmental language, so the term defaulter has been replaced by Lost to follow-up and TB suspect by presumptive TB case.

- **Presumptive TB case**: A presumptive TB case is one who presents with symptoms or signs suggestive of TB (previously known as a TB suspect). The most common symptom of pulmonary TB is a productive cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, haemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).
- **Bacteriological confirmation or clinically diagnosed TB Case**: A bacteriologically confirmed TB case is one from whom a biological specimen is positive by smear microscopy, culture or WRD (WHO-approved rapid diagnostics such as Xpert MTB/RIF). All such cases should be notified regardless of whether TB treatment was started or not.
- **Clinically diagnosed TB Case**: A clinically diagnosed TB case is one who is started on a full treatment for active TB but who does not fulfil the criteria to be considered bacteriologically confirmed. This includes cases diagnosed on the basis of X-ray abnormalities, suggestive histology and extrapulmonary cases without a laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be re-classified as bacteriologically confirmed.

Cases of TB are also classified according to:

- Anatomical site of disease
- Bacteriological results
- History of previous treatment
- HIV status
- Drug resistance

Each of these key features of TB cases is discussed below.

The Centers for Disease Control and Prevention (CDC) has specific requirements for a TB case to be counted. To be officially counted the TB case must meet the following criteria:

1. Is a verified case of TB: A case of TB is defined as an episode of TB disease in person meeting the laboratory or clinical criteria for TB (see definition of confirmed case below)

2. Confirmed that it is not counted by another area

3. Meets surveillance definition and is not a recurrent case.

Non countable cases include cases counted by another area, TB treatment was initiated in another country or the case has recurrent TB within 12 months after completion of therapy. According to CDC, if TB disease recurs within a consecutive 12 month period after the patient completed therapy the recurrence is considered the same TB episode. If the TB disease recurs more than 12 months after the patient completed therapy the recurrence is counted as a separate TB episode and is counted as a new case.

In addition, the following case classifications are used for recording purposes for CDC:

1. Laboratory case definition

- Isolation of *M. tuberculosis* complex from a clinical specimen,*

OR

- Demonstration of *M. tuberculosis* complex from a clinical specimen by nucleic acid amplification test (nucleic acid amplification tests must be accompanied)

OR

- Demonstration of acid fast bacilli in a clinical specimen when a culture has not been or cannot be obtained or is falsely negative or contaminated

2. Clinical case definition

In the absence of laboratory confirmation of *M. tuberculosis* complex after a diagnostic process has been completed, persons must have <u>all</u> of the following criteria:

- A positive tuberculin skin test or positive interferon gamma release assay for *M. Tuberculosis*

  AND

- One of the following:
  - Signs and symptoms compatible with current tuberculosis disease (e.g., abnormal chest radiograph or other chest imaging study)

    OR

  - Clinical evidence of current disease (e.g., fever, night sweats, cough, weight loss, haemoptysis)

    AND

- Treatment with two or more anti-TB medications.

Confirmed case: A TB case that meets the clinical case definition or is laboratory confirmed.

3.1 Classification based on anatomical site of disease

Defining the site of TB is important for recording and reporting purposes and to identify the more infectious patients - those with pulmonary involvement (who are further subdivided by smear status).

Pulmonary tuberculosis (PTB) refers to a case of TB (defined above) involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Extrapulmonary tuberculosis (EPTB) refers to a case of TB (defined above) involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. EPTB cases could be either bacteriologically confirmed or clinically diagnosed. Identification of *M. tuberculosis* (as opposed to histology) should be the basis of bacteriological confirmation of EPTB. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease.

3.2 Bacteriological results

Bacteriology refers to the smear status of pulmonary cases and the identification of *M. Tuberculosis* for any case by culture or newer methods. All patients presumed of having pulmonary TB should submit at least three[3] sputum specimens for microscopic examination in a quality-assured laboratory. When possible, at least one early-morning specimen should be obtained, as sputum collected at this time has the highest yield. In Palau, three sputum specimens are being collected per presumed TB case.

3.2.1. Smear-positive pulmonary TB cases

A case of pulmonary TB is considered to be *smear-positive* if one or more sputum smear specimens at the start of treatment are positive for AFB (provided that there is a functional EQA system with blind rechecking[4]). In Palau, a case of pulmonary TB is considered to be *smear-positive* if at least one sputum smear is positive for AFB in Palau or MTB+ through Gx ***and/or*** the specimen is smear-positive and culture-positive in Hawaii. The following cases of PTB are also classified as sputum smear positive:

- AFB negative in Palau, AFB positive and culture positive in Hawaii
- AFB negative in Palau with positive CXR and clinical indication of TB and AFB positive but culture negative in Hawaii
- MTB+ in Palau from nucleic acid amplification test, GeneXpert-TB
- If a presumptive TB case is: 1) AFB negative in Palau, 2) has a CXR not clearly suggesting TB and 3) there is no clear clinical indication of TB and the laboratory in Hawaii (DLS) finds that the same patient is AFB positive and culture negative, then the clinician in charge should conduct a careful review of the patient. Re-submission of sputum is indicated, and – depending on the number of weeks passed since the first chest x-ray – a second chest x-ray may also be indicated.

3.2.2. Smear-negative pulmonary TB cases

There are two classes of sputum smear negative PTB cases: those with bacteriological proof and those without bacteriological proof.

The first class: those with bacteriological proof:

A. Sputum is smear-negative but at least two specimens grow culture-positive for *M. tuberculosis* (i.e. the 3 sputum specimens at the start of treatment are negative for AFB in Palau and in Hawaii, but at least 2 specimens are culture positive for *M. tuberculosis).*

Or

B. Sputum is smear-negative (in Palau and Hawaii) but at least ***one*** specimen is culture-positive for *M. Tuberculosis* ***and*** the clinician in Palau decides to start treatment.

C. Sputum is smear negative in Palau and Hawaii, but GeneXpert is positive for MTB-DNA, Clinician in Palau will decide whether or not to start treatment

Sputum samples from Palau are routinely sent to the partner reference laboratory in Hawaii (i.e. Diagnostic Laboratory Services) for microscopy, culture and DST.

The second class: those without bacteriological proof:

[3]For countries with functional EQA systems and with a human resource crisis, WHO recently advised to reduce for the initial sputum examination the number of samples to be examined from three to two specimens. In Palau, there is no need to implement this new recommendation.

[4] Palau is, through the collaboration with the laboratory in Hawaii, considered to have EQA.

These smear-negative PTB patients meet the following diagnostic criteria:

- decision by a clinician to treat with a full course of anti-TB therapy; and
- radiographic abnormalities consistent with active pulmonary TB and
  either:
  - no improvement in response to a course of broad-spectrum antibiotics (excluding anti-TB drugs and fluoroquinolones and aminoglycosides) if HIV-negative or unknown HIV status,

  Or:
  - laboratory evidence or strong clinical evidence of HIV infection

3.2.3. Pulmonary TB cases whose smear was not examined: Pulmonary TB cases without smear results are labelled "smear not done" in the TB register; they are no longer classified as smear-negative

3.3 Classification based on history of previous TB treatment (patient registration group)

These classifications focus on history of previous treatment only and are independent of bacteriological confirmation or site of disease.

- **New patients** have never had treatment for TB, or have taken anti-TB drugs for less than 1 month.
- **Previously treated patients** have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:
  - **Relapse patients** are previously treated for TB, were declared cured or treatment completed at the end of their most recent treatment episode and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by re-infection).
  - **Treatment after failure patients** are previously treated for TB and whose treatment failed at the end of their most recent treatment episode.
  - **Treatment after loss to follow-up patients** are previously treated for TB and were declared Lost to follow-up at the end of their most recent treatment episode. (These were previously known as Treatment after default patients).
  - **Other previously treated patients** are previously treated for TB but with an unknown or undocumented outcome for their most recent treatment episode.
- **Patients with unknown previous TB treatment history** do not fit into any of the categories listed above.
- New and relapse cases of TB are **incident** TB cases.

3.4 Classification based on HIV status

- **HIV-positive TB patients** are patients with TB (bacteriologically confirmed or clinically diagnosed) who have a documented HIV-positive result (e.g. there is documented evidence of enrolment in HIV care such as enrolment in the pre-ART register or in the ART register once started on ART) or have a positive HIV result from testing conducted at the time of TB diagnosis.
- **HIV-negative TB patients** are patients with TB (bacteriologically confirmed or clinically diagnosed) who have a documented negative HIV result from a test conducted at the time of TB diagnosis. HIV-negative TB patients subsequently found to be HIV-positive should be re-classified as HIV-positive TB patients.

- **HIV status unknown TB patients** do not have a documented HIV test result. If HIV-status is subsequently determined the patient should be re-classified as per the HIV test result.

3.5 Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing in clinical isolates confirmed to be Mycobacterium tuberculosis:

- **Monoresistance**: resistance to one first-line anti-tuberculosis drug only.
- **Polydrug resistance**: resistance to more than one first-line anti-tuberculosis drug, other than both isoniazid and rifampicin.
- **Multidrug resistance (MDR-TB)**: resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance (XDR-TB)**: resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance (RR-TB)**: resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating RR-TB, for instance, MDR-TB and XDR-TB are also included. While it has been the practice until now to limit the definitions of monoresistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents as well as any other anti-TB drug for which reliable DST becomes available.

4. DIAGNOSIS OF TUBERCULOSIS

Tuberculosis (TB) affects the lungs in more than 85% of cases. This form of the disease is called pulmonary tuberculosis. Pulmonary tuberculosis is an infectious disease and spreads mainly by droplet infection. Sputum positive pulmonary TB patients are the main source of infection. It is estimated that an untreated smear positive pulmonary TB patient infects 10-15 persons annually. Therefore, it is very important to identify presumed TB cases and diagnose them early in order to effectively treat and make them non-infectious.

4.1 TB case finding

The main steps in diagnosing TB are: (i) medical history; (ii) bacteriology; and (iii) radiographic examination (x-ray).

4.1.1 Medical History

The medical history includes social, family, medical, and occupational information on the patient. For evaluation of a presumed TB case or patient, the patient history should include the following information:

- Symptoms of TB disease
- Onset (date of the start of symptoms)
- Previous treatment for TB infection or TB disease
- Known exposure to a person who has infectious TB
- Risk factors for developing the disease – HIV infection, diabetes mellitus, renal disease, malnutrition, advanced age, receiving treatments that suppress immunity and lifestyle factors such as smoking and heavy alcohol consumption
- Medical conditions that might impact treatment (e.g., renal disease, liver disease, pregnancy).

The tools for identifying a TB case are not limited to clinical indicators, sputum examination and chest x-ray findings; other factors (i.e., exposure, risk factors, and medical conditions) should also be considered.

The Role of the Tuberculin Skin Test

The tuberculin skin test (TST) is the recommended method of skin testing to determine whether a person is infected with *M. tuberculosis*. These national TB guidelines **do not recommend** using the TST for diagnosing tuberculosis among adults. The use of the TST should be limited to diagnosing TB among pediatric cases and for contact tracing. The TST is often misleading because of false-negative and false-positive results.

4.1.2 Bacteriologic Examination

Sputum collection and transport to the laboratory

The presumptive TB case should be properly instructed on how to produce three sputum specimens; at least one specimen should be an early morning specimen. Obtaining a good sputum specimen is crucial for quality sputum microscopy. The following steps have to be observed to get good sputum specimen:

- **Tasks performed before sputum collection:** Before a health worker collects a sputum specimen, the reasons for sputum collection have to be explained to the patient. The Laboratory technician/ health worker must ensure that the patient's full address is entered in the laboratory form.
- **Tasks performed during sputum collection:** A specimen collected under the proper guidance of a health worker is likely to yield more conclusive results than one produced by a patient without any

guidance. The health-care provider needs to show the patient how to provide good sputum samples by taking a deep breath and coughing hard from deep in the lungs to produce good quality sputum. Sputum should preferably be collected in open air or in a vacant room with open windows. The health worker or the laboratory technician should stand behind the patient. The health worker should also ensure that no-one stands in front of the patient. If a patient coughs out only saliva, s/he should be asked to try again to bring out sputum. Patient must be asked to rinse the mouth before bringing out the sputum samples.

- Leak-proof sterile containers made of clear thin unbreakable plastic of sufficient size should be used. The sputum container should be wide-mouthed so that collection of sputum is not difficult.
- If the sputum container becomes contaminated on the outside, it should be discarded and the patient asked to produce another sputum sample.
- As soon as sample collection is completed the lid of the container should be closed tightly.
- The provider should then wash hands well with soap and water and/or rinse with alcohol.

There will be three samples: SPOT-EARLY MORNING-SPOT to be collected within two days:

- The first is a spot specimen, collected during the consultation
- The second is an early-morning specimen, the very first sputum produced by the presumptive TB case when getting up, and
- The third specimen is again a spot specimen, collected when the presumptive TB case comes back to the health facility to submit the second specimen. This should be one day after the consultation when the first sputum specimen was collected.

A health facility without adequate facilities for collecting and transporting sputum should refer the patient to the nearest health facility able to collect sputum, or direct the patient to the laboratory. Once collected, staff should check if the sputum samples are properly labeled (full name of the patient, not to be written on the lid). The date of collection should be affixed to the sputum container. The sputum samples are registered at the time of collection. Each sputum container is packed in the recommended transport kit and kept at cool temperatures (ideally 4 to 8 degrees Celsius) not exposed to light, then sent to the laboratory. **TAT 24 hours.**

A completed *Laboratory Request Form for TB Microscopy* accompanies each patient's sputum samples.

Sputum examination and recording

On arrival of a sputum specimen at the laboratory, each sample is recorded in the *TB Laboratory Register*, based on the information of the *Laboratory Request Form for TB Microscopy* accompanying the sputum specimen.

Direct smear microscopy for the detection of acid-fast bacilli is performed by the Ziehl-Neelsen (ZN) staining method (the staining is done after smearing and fixing). The slides are then read. The laboratory worker reading the slide should take at least 5 minutes per slide to read 100 fields (10 minutes is optimal). The recording/reporting of the results of sputum smear microscopy must be not only qualitative (whether AFB are present or not), but also semi-quantitative (give some indication of the number of AFB present).

In accordance with international guidelines, AFB smear results should be reported as follows:

Table 2: Recording of acid fast bacilli smear results in the local laboratory (in Palau)

AFB Counts	***Recording / Reporting***
No AFB in at least 100 fields	0 (negative)
1 to 9 AFB per 100 fields	Specify the actual number of AFB per 100 fields
10 to 99 AFB per 100 fields	1 +
1 to 10 AFB per field in at least 50 fields *	2 +
>10 AFB per field in at least 20 fields *	3 +

* In practice, most microscopists read a few fields and confirm the finding by a quick visual scan of the remaining fields

As soon as the results are available, the results of the examination have to be relayed to the facility that requested the sputum examination by sending back the filled in *Laboratory Request Form* to the referring unit.

Improper preparation of smears or incorrect staining of slides may lead to false-negative results. Therefore, the following needs to be avoided:

- Too little material has been spread on the slide, so that the smear is too thin;
- The smear is too thick, so that sufficient light cannot pass through it;
- The slide was overheated during fixing of the smear;
- The smear has not been sufficiently fixed and parts of the material have been washed off;
- The staining with carbol fuchsin was too short or was overdone by boiling;
- The counterstaining was too intense, so that the AFB have been obscured.

Interpretation of results

The definition of a sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacillus (AFB+) in at least one sputum sample in countries with a well-functioning EQA system. Still, a finding of 1 to 3 bacilli in 100 fields does not correlate well with culture positivity and the interpretation of the significance of such a result should be left to the clinician and not to the microscopist. If the clinical picture does not strongly suggest TB it is appropriate to prepare a new smear from the same sputum specimen and re-examine it.

Shipping of sputum specimens to DLS

Specimens should be stored at 4-8 degrees Celsius until they are shipped to Hawaii. Specimens should be shipped in a timely manner to DLS as detailed in the TB specimen shipping protocol provided by Pacific Islands Health Officers Association[5]. Specimens should be shipped within 10 days of receipt by the laboratory.

[5] Reference: A protocol for shipping and mycobacterial culture and anti-mycobacterial susceptibility testing and for the US-affiliated Pacific island laboratories

4.1.3 Radiographic examination (x-ray)

No radiographic pattern is diagnostic of tuberculosis. Many diseases of the lung show a similar radiographic appearance and can easily mimic tuberculosis. Similarly, the lesions of pulmonary tuberculosis can take almost any form on a radiographic picture. Reliance on chest radiography as the only diagnostic test for TB results in either over-diagnosis or missed diagnoses of TB and other diseases. Radiographic examination is useful when applied as part of a systematic approach with sputum examination as the key diagnostic tool. A chest x-ray is most useful for the purpose of:

- Increasing the predictive value of a TB diagnosis in a person, especially when HIV positive, with persistent TB symptoms with negative sputum smears
- Evaluating persons with a newly identified positive reaction to the tuberculin skin test.

Although clinicians working with pregnant women should attempt to minimize interventions especially in the first trimester, it is always necessary to balance the risks of a procedure with the benefits to be gained. It should be remembered that undiagnosed TB may have severe consequences in pregnancy. A diagnostic chest x-ray may be necessary for the investigation of TB in some pregnant women. The minimum radiation dose should always be used with fetal shielding where possible. Routine contact screening chest x-rays however if they are required should be deferred at least until after the first trimester and sometimes can be deferred until after delivery depending on the indication.

4.2 Diagnosis of smear-negative TB and extrapulmonary TB

For smear-negative and extrapulmonary TB, a diagnosis by a clinician specially trained in TB may be required as well as radiographic examination. As no chest radiographic pattern is absolutely specific for pulmonary TB, the diagnosis of smear-negative TB is always presumptive and should be based on other clinical and epidemiological information, including failure to respond to a course of broad-spectrum antibiotics (excluding fluoroquinolones and aminoglycosides)[6]and exclusion of other pathology.

Figure 2 shows the various possible diagnostic pathways where the experience and clinical judgment of the physician will influence which pathway to take when there are options (e.g. the next step after the chest x-ray). Figure 3 illustrates the laboratory testing algorithm using GeneXpert while Figure 4 highlights the diagnostic work-up based on recent revisions shared by CDC for USAPI countries.

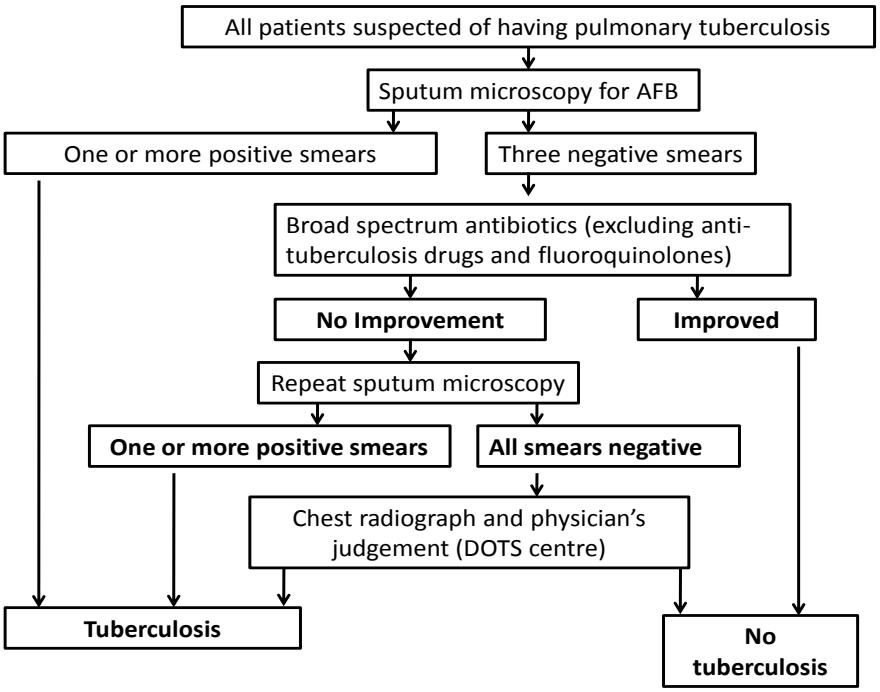
DLS[7] provide culture and species identification[8] for all presumptive TB cases, which makes identification of smear-negative TB less difficult. However, culture results may not be available until after a decision to begin treatment has been made, therefore treatment may be subsequently stopped if cultures are negative, if non-tuberculous mycobacteria are identified, and if the patient has not responded clinically to treatment and the clinician has decided to seek a differential diagnosis. If the sputum results from DLS are not the same as the results from Palau laboratory, it is important to consider the clinical picture to decide if TB treatment is needed. Annex 3 provides diagnostic and treatment guidance based on laboratory results from Palau laboratory and DLS. In Palau, culture results are available after approximately 1- 2 months. Annex 4 provides the sputum collection and GeneXpert protocol.

[6]Empiric fluoroquinolone monotherapy for respiratory tract infections has been associated with delays in initiation of appropriate anti-tuberculosis therapy and acquired resistance to the fluoroquinolones. Consequently, use of these agents is discouraged for treatment of infections in which there is a reasonable possibility of TB being in the differential diagnosis.

[7]Diagnostic Laboratory Services, Inc. (DLS), Honolulu, Hawaii.

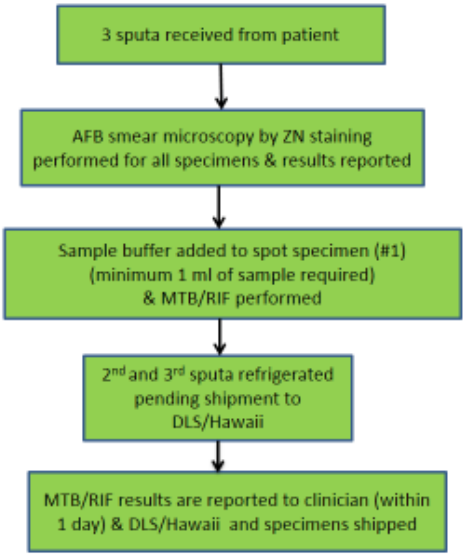
[8]In addition to increasing the yield of confirmed TB cases, mycobacterial culture is the only way to differentiate *M. tuberculosis* from other non-tuberculous mycobacteria.

Figure 2: Approach to the diagnosis of presumptive pulmonary tuberculosis case*



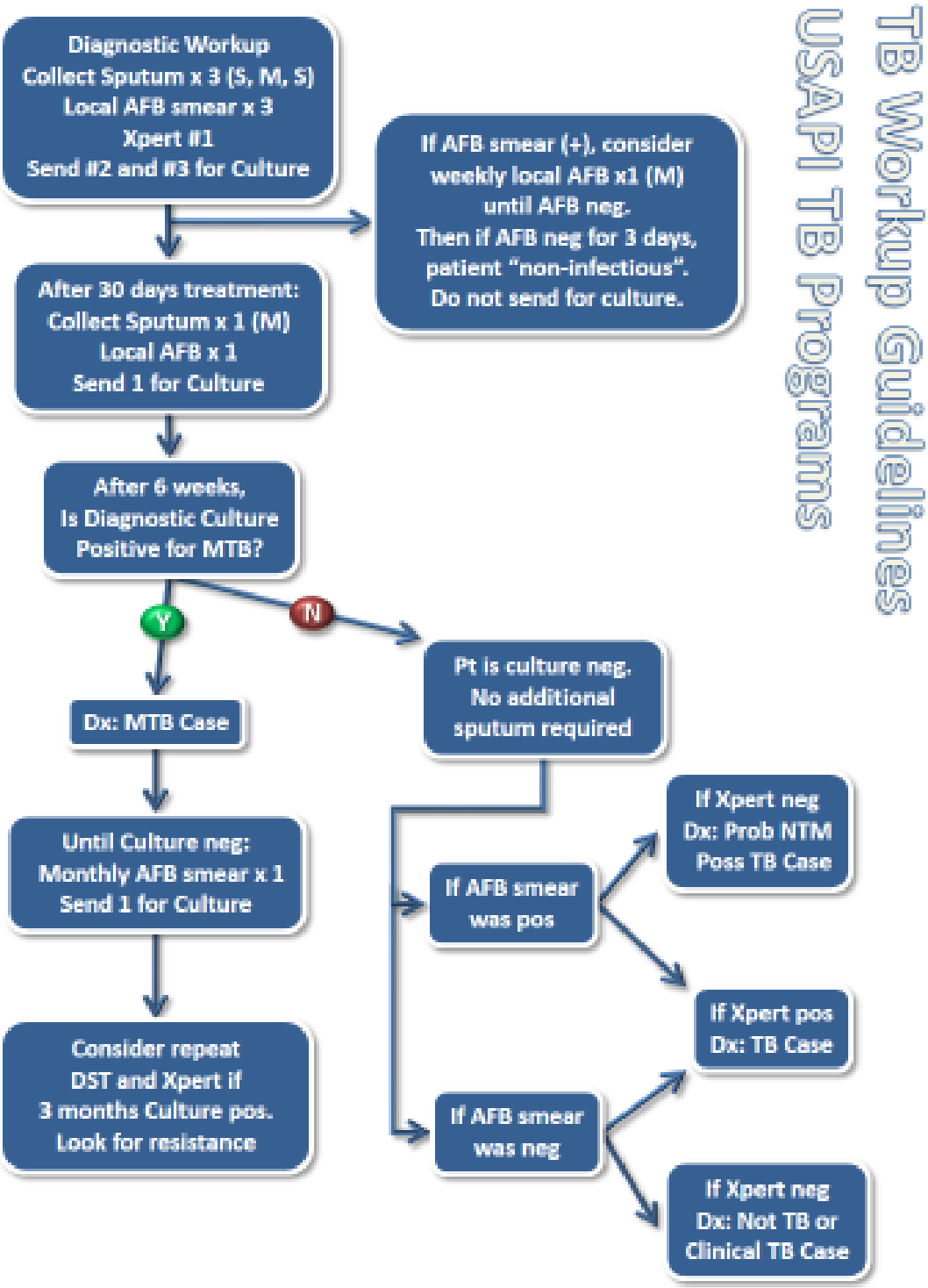
Note: *For HIV+ TB presumptive cases, sputum microscopy should be repeated prior to antibiotic trial treatment. Also, the results of culture are very important. It is important to be aware of the limited utility of CXR for HIV+ TB presumptive cases. When the initial sputum examination is smear-negative, completion of all of the steps requires a substantial amount of time; thus, it should not be used for patients with an illness that is worsening rapidly.This is especially true in patients with HIV infection in whom tuberculosis may be rapidly progressive. For HIV positive TB presumptive cases, using culture is crucial (because many HIV positive TB presumptive cases are sputum smear negative but culture positive).

Figure 3: Laboratory Testing Algorithm for GeneXpert MTB/RIF



Note: Only 1 specimen is tested by Xpert and others are referred to DLS.

Figure 4: TB work-up guidelines, USAPI, CDC, 2013



Extrapulmonary TB

Extrapulmonary TB involves relatively inaccessible sites and, because of the nature of the sites involved, fewer bacilli can cause much greater damage.

Common forms of EPTB are:

- TB of the central nervous system (CNS), including TB meningitis and brain tuberculoma
- Tuberculosis of the spine (Pott's disease)
- Tuberculosis of the cervical lymph nodes (scrofula)
- Tuberculous pleural effusion
- Tuberculous pericarditis
- Disseminated tuberculosis, including miliary TB
- Genito-urinary tuberculosis.

A person with EPTB may have the following general symptoms (note that these systemic symptoms can also be found among pulmonary TB cases):

- Weight loss
- Fever
- Night sweats
- General malaise and fatigue
- Loss of appetite

Other symptoms and signs depend on the affected site:

- Swelling (occasionally with pus drainage when lymph nodes are affected)
- Pain and swelling when joints are involved
- Headache, neck stiffness and drowsiness suggesting TB meningitis (usually children).

The diagnosis of extrapulmonary TB should be based on one culture positive specimen (any smear-negative specimens obtained from cases with clinical diagnosis of EPTB should be sent for culture and identification of *M. tuberculosis*) or strong histological and clinical evidence consistent with active extrapulmonary TB, followed by a decision by a clinician to treat for TB. Therefore, for patients presumed of having EPTB, specimens should be obtained from the suspected sites of involvement and culture and histopathological examination should be requested. Given the low yield of microscopy, both culture and histopathological examination of tissue specimens (i.e., needle biopsy of lymph nodes), are important diagnostic tests for extrapulmonary TB. Patients diagnosed with extrapulmonary TB should also be investigated for PTB and be offered HIV testing.

4.3 Diagnosis of drug-resistant TB (DR-TB)

To diagnose drug resistant TB, a patient requires sputum microscopy, culture, species identification, and DST. Chapter 9 *Diagnosis and Management of drug-resistant TB cases* discusses diagnosis of drug-resistant TB. Mono-resistance to INH was noticed in previous years, but mono-resistance to Rif was noticed in 2011 and the first MDR-TB case was diagnosed in 2011.

5. TREATMENT OF TUBERCULOSIS

5.1 Standard regimens and drug dosing

The overall goals of treatment of TB are: to cure the individual patient, to minimize the transmission of TB to others, to prevent the development and transmission of drug resistance, to prevent death from active TB and prevent relapse of TB cases.

There are three standard TB regimens:

1. New patient regimen: 2HRZE/4HR
2. Re-treatment regimen (formerly called Category 2 regimen): 2HRZES/1HRZE/5HRE
3. MDR-TB regimen

Dosing of the TB medications is presented in Table 3.

Table 3: Recommended dosing of first-line TB medicines for adults and children

Drug	**Recommended dose for adults (daily regimens)**		**Recommended pediatric dose (daily regimens)**	
	Dose (range) in mg/kg body weight	**Maximum**	**Dose (range)** in mg/kg body weight	Maximum
Isoniazid (H)	5 (4-6)	300 mg	10 (10-15)	300 mg
Rifampicin (R)	10 (8-12)	600 mg	15 (10-20)	600 mg
Pyrazinamide (Z)	25 (20-30)	-	35 (30-40)	-
Ethambutol (E)	15 (15-20)	-	20 (15-25)	-
Streptomycin* (S)	15 (12-18)	1000mg	15 (12-18)	

* Notes about streptomycin:
a) Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group.
b) Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily.

A. New patient regimen 2HRZE/4HR

The standard regimen for new TB patients (presumed, or known, to have drug-susceptible TB) is two months of intensive phase treatment with four TB medications (rifampicin, isoniazid, pyrazinamide and ethambutol) followed by four months of continuation phase treatment with two TB medications (rifampicin and isoniazid). Drug intake is daily. It is presumed that all TB cases have pan-susceptible TB when treatment is started. When culture results arrive from DLS in Hawaii, treatment is adjusted if necessary.

The following points should be considered when deciding on the regimen to be taken by a TB patient:

1. Extrapulmonary TB:
    a. Expert advice recommends 12 months of treatment for TB of bones or joints because of the difficulties of assessing treatment response and 12 months of treatment for TB meningitis given the serious risk of disability and mortality.

b. Because penetration of some drugs (e.g. rifampicin and streptomycin) into the cerebrospinal fluid is poor, treatment regimens for TB meningitis and miliary TB will most likely benefit from the upper end of the recommended dose ranges.

c. In tuberculous meningitis, ethambutol should be replaced by streptomycin.

d. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis.

e. Although sometimes required for diagnosis, surgery plays little role in the treatment of extrapulmonary TB. It is reserved for management of late complications of disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis and neurological involvement from Pott's disease (spinal TB). For large, fluctuant lymph nodes that appear to be about to drain spontaneously, aspiration or incision and drainage appear beneficial.

2. Pulmonary TB: length of the continuation phase of treatment:

   a. For TB patients with diabetes mellitus (DM) or other immunocompromised conditions, prolongation of the continuation phase from 4 months to 7 months may be useful.

   b. TB patients whose follow-up sputum examination (at two months) is culture-positive ***and*** whose initial chest x-ray showed cavities should receive 9 months of treatment by prolonging the continuation phase by three months, i.e. the regimen should be 2 months of HRZE and 7 months of HR.

B. Retreatment patient regimen 2HRZES/1HRZE/5HRE

In Palau, streptomycin has not been used for the few identified re-treatment cases over the past few years because drug susceptibility results are expected around 2 to 3 months after the start of treatment, enabling Palau to provide the most appropriate therapy for each individual TB patient.

For cases not undergoing rapid drug susceptibility testing, once conventional DST results are known, re-treatment patients should receive or continue to receive[9] two months of HRZE and four months of HR (with the possibility of extending the continuation phase as mentioned above) if pan-susceptible TB is found. If there is drug resistance, individualized treatment should be provided based on the results of GeneXpert with TB Consultation.

However, whether rapid drug susceptibility tests or conventional DST is done (although more so when conventional DST is done), the clinician should carefully consider the option of starting empirical MDR-TB treatment[10] for the following patients:

- Close contacts of MDR-TB patients, especially if these contacts are seriously ill.
- Re-treatment cases who are seriously ill
- All re-treatment cases who have had ***more than*** one previous anti-TB treatment (lasting for at least one month)

The reason for this is that such patients may die while the National TB Program waits for the culture and DST results.

[9] In Palau, most patients undergoing conventional DST are already on HRZE when the DST result is issued.
[10] The design of this empirical MDR-TB treatment should be decided in collaboration with CDC.

C) Treatment for MDR-TB cases

Chapter 9 discusses diagnosis and treatment of MDR-TB. Briefly, treatment of MDR-TB cases should be with at least 4 drugs with either certain, or almost certain, effectiveness. MDR must be treated at least 18-24 months after culture conversion. Each dose in an MDR regimen is given strictly under directly observed therapy throughout the treatment.

D) Hospitalization of TB patients

In Palau, all TB patients are hospitalized at the beginning of treatment. Among the sputum smear positive patients, every one to two weeks, three sputum samples maybe examined (but not sent to DLS) until the patient converts to sputum negativity which then normally leads to discharge from hospital. Among the sputum smear negative patients, approximately two weeks after treatment start, three sputum samples are examined (but not sent to DLS) to check if the patient really is sputum smear negative. Once confirmed, the patient is discharged from hospital. For all MDR-TB patients, hospitalization for the first few months of treatment is warranted. Children with severe forms of TB should be hospitalized.

5.2 Drug formulations

In Palau, all TB medicines are supplied by the Government of Palau. Patient kits or fixed dose combination tablets maybe used under specific circumstances.

5.3 Side effects of TB medicines (adverse drug reactions)

Patients need adequate information about the possibility of experiencing side effects, and how to recognize adverse drug reactions. Complaints about side effects should be promptly referred for evaluation to identify the offending drug so as to minimize interruptions in treatment and/or unnecessary cessation of important first-line drugs. Toxicity and hypersensitivity reactions may require the offending drug(s) to be discontinued; however, changes to the recommended regimen should be done only after careful evaluation. Side effects can be classified as minor and major. In general, a patient who develops minor side effects should continue TB treatment. Often, reassurance and symptomatic treatment are sufficient. If a patient develops a major side effect, the treatment or the responsible drug is stopped; the patient should be urgently referred to a clinician or health care facility for further assessment and treatment. Patients with major adverse reactions should be managed in a hospital. Adverse reactions to drugs should be recorded on the *TB Treatment Card* under “Case review”. Table4provides an overview of common side effects of the first line TB medications andTable 5 gives more detailed information with a symptom-based approach to the management of the most common side effects.

Table 4: Common side effects of the first-line TB medicines

Drug	Side effects
Rifampicin	Hepatitis; flu-like illness (usually only with intermittent administration); thrombocytopenia; drug interactions
Isoniazid	Hepatitis; peripheral neuropathy; hypersensitivity reactions
Pyrazinamide	Hepatitis; hyperuricemia; arthralgias; gastrointestinal symptoms
Ethambutol	Retrobulbar neuritis (dose related)
Streptomycin	Vertigo; tinnitus; deafness; renal failure
All drugs	Rash, nausea, and fever

Table 5: Symptom-based approach to managing side effects of TB medicines

Side-effects	Drug(s) probably responsible	Management
Major		*Stop responsible drug(s) and refer to clinician urgently*
Skin rash with or without itching	Streptomycin, isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs
Deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti-TB drugs
Confusion (suspect drug-induced acute liver failure if there is jaundice)	Most anti-TB drugs	Stop anti-TB drugs
Visual impairment (other cause excluded)	Ethambutol	Stop Ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin
Decreased urine output	Streptomycin	Stop streptomycin
Minor		*Continue anti-TB drugs, check drug doses*
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin, isoniazid	Give drugs with small meals or just before bedtime, and advise patient to swallow pills slowly with small sips of water. If symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side effect to

		be major and refer to clinician urgently.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti-inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50–75 mg daily
Drowsiness	Isoniazid	Reassurance. Give drugs before bedtime
Orange/red urine	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal
Flu syndrome (fever, chills, malaise, headache, bone pain)	Intermittent dosing of rifampicin	Change from intermittent to daily rifampicin administration

5.4 Adherence to treatment

Support and treatment supervision

An important task of the National TB Program is to find ways to optimize patient adherence to treatment. The patient needs support to ensure treatment adherence. Clear and culturally appropriate communication, relevant health education, empathy by the health care provider and good counseling skills are important. Some people consider directly observed therapy (DOT)to be the main approach to enhance adherence. However, rigid forms of supervision may be an intolerable burden for the patient. It may mean high expenditures for transportation costs, having to stop work, losing privacy and confidentiality, and a loss of self-worth. Particular attention should be paid to the poorest and most vulnerable groups. The geographical peculiarities of Palau (i.e. isolated islands) also need to be taken into account.

The following actions can improve treatment adherence:

1. Provision or financing of transportation, and other treatment enablers that can compensate patients for the indirect costs of care;
2. Provision of incentives such as food or hygienic packages for patients and their families, if appropriate for the context and for the patient;
3. Patient and peer support groups, which may help also reduce stigma;
4. Referrals for psychological, social and legal support and other services including substance abuse treatment; joint (integrated) support for TB patients with addictive behaviors;
5. Full availability of concomitant HIV treatment.

Addressing missed treatment

The National TB Program also needs to make sure that each time a patient misses two consecutive days of treatment, the patient is immediately visited by a health care worker to make sure treatment is not missed again and to address the reason for the missing of treatment.

For patients with treatment interruptions lasting for more than just a few days, the management takes into consideration several factors, each of which, if present, will necessitate further caution and possibly additional treatment:

- Is the patient smear or culture-positive upon returning from treatment interruption
- Is the treatment interruption in the intensive or the continuation phase
- Has the treatment interruption occurred earlier (rather than later) in the continuation phase.
- Is the treatment interruption of long duration
- Is the patient immuno-compromised (living with HIV, diabetes or another condition)
- Has the patient had a poor response to treatment before the treatment interruption
- Is drug-resistant TB known or suspected.

For patients with treatment interruptions of ***up to one month only***; two things need to be done once the non-attending patient has been found or come back for treatment:

1. Solve the problem(s) that caused the treatment interruption
2. Continue treatment and prolong it to compensate for missed doses.

For patients with longer treatment interruptions (i.e. more than 1 month), Table 6shows what steps need to be taken once the non-attending patient has been found or come back for treatment and the problem(s) that caused the treatment interruption have been addressed:

Table 6: Steps to be taken when a TB patient interrupts treatment

Treatment interruption for 1 – 2 months		
Action 1	Lab result	Action 2
Re-start treatment and do 3 sputum smears with GeneXpert	If ss-, cu- or EPTB:	Continue treatment and prolong it to compensate for missed doses.
	If ss+ and/or cu+	*If less than 5 months of treatment received*: Continue treatment and prolong it to compensate for missed doses while waiting for DST result: if found pan-susceptible, complete the prolonged treatment. If drug resistance found, re-start treatment that is adequate for the resistance pattern.
		a) If more than 5 months of treatment received as new patient: start new treatment (HRZE and then – if needed – adjust the regimen when DST results are reported). *b) If more than 5 months of treatment received as re-treatment patient*: presumptive MDR-TB case: re-start re-treatment regimen (including S) while waiting for DST results.
Treatment interruption for more than 2 months (Lost to follow-up)		
Do 3 sputum smears with GeneXpert but do not re-start treatment	If ss-, cu- or EPTB:	Clinical decision on individual basis whether to start the re-treatment regimen or continue treatment, or no further treatment.
	If ss+ and/or cu+	*If the patient was a new patient*: Start re-treatment regimen (HRZE and then – if needed – adjust the regimen when DST results are reported).
		If patient was a re-treatment patient: presumptive MDR-TB case: re-start re-treatment regimen (including S) while waiting for DST results (ask for rapid DST)

5.5 Treatment of TB in special situations

5.5.1 Pregnancy and breastfeeding

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for successful outcome of pregnancy. With the exception of streptomycin, the first line TB medicines are safe for use in pregnancy (streptomycin is ototoxic to the foetus and should not be used during pregnancy).

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of TB to the baby. Mother and baby should stay together and the baby should continue to breastfeed.

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid. Palau follows US CDC/WHO recommendations of 25-50 mg per day.

5.5.2 Liver disorders

Patients who carry a hepatitis virus, patients with a past history of acute hepatitis and patients currently consuming excessive alcohol can receive the usual TB regimens provided that there is close monitoring for clinical evidence of chronic liver disease. However, hepatotoxic reactions to TB medicines may be more common among these patients.

Isoniazid, rifampicin and pyrazinamide are all associated with hepatitis. Pyrazinamide is the most hepatotoxic. Rifampicin is least likely to cause hepatocellular (severe liver) damage, although it is associated with cholestatic jaundice.

In patients with unstable or advanced liver disease, liver function tests should be done more frequently .The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used. In some cases of concurrent acute (i.e. viral) hepatitis not related to TB or TB treatment, it may be possible to defer TB treatment until the acute hepatitis has resolved.

Possible regimens include:

- Two hepatotoxic drugs (rather than the three in the standard regimen):
  - 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented);
  - 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
  - 6–9 months of rifampicin, pyrazinamide and ethambutol.
- One hepatotoxic drug:
  - 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
- No hepatotoxic drugs:
  - 18–24 months of streptomycin, ethambutol and a fluoroquinolone.

Expert consultation is advisable in treating patients with advanced or unstable liver disease.

Clinical monitoring and liver function tests (if possible) of all patients with pre-existing liver disease should be performed during treatment. Pyridoxine supplementation should be considered.

5.5.3 Renal failure and severe renal insufficiency

The recommended initial regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4-7 months of isoniazid and rifampicin. Isoniazid and rifampicin are eliminated by biliary excretion, so no change in dosing is necessary. There is significant renal excretion of ethambutol and metabolites of pyrazinamide and doses should therefore be adjusted.Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25mg/kg), and ethambutol (15 mg/kg)[11].

While receiving isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy (see also next page).

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored if possible.

5.5.4 TB patients with diabetes mellitus (DM)

Diabetes mellitus (DM) triples the risk of developing tuberculosis and therefore the rates of TB are higher in people with diabetes than in the general population. Diabetes can also worsen the clinical course of TB, and TB drugs can worsen glycaemic control in people with diabetes. All non-diabetic TB patients should be screened for DM. Also, if a patient with diabetes has signs and symptoms of TB they must be referred as a TB presumptive case.

Currently, there is sufficient evidence to support the recommended standard TB treatment regimens or making specific recommendations for clinical case management of TB in people with diabetes. It is common clinical practice in some settings to extend the duration of TB treatment in people with diabetes. There are published trials and studies done on the effectiveness of extending the duration of treatment. Supplementary treatment with pyridoxine is recommended for all TB patients with diabetes.

A recent framework on the management and control of TB and DM has been developed by US CDC, WHO, and the International Union Against Tuberculosis and Lung Disease (The Union) and provides guidance on the establishment of mechanisms for collaboration between TB and DM programs, detection and management of TB in patients with DM and the detection and management of DM in patients with TB. The recommendations outlined by this framework are detailed in Annex 5.

In addition, United States Affiliated Pacific Islands Standards for the Management of Tuberculosis and Diabetes has been finalized for implementation..

5.5.5 Treatment for Women Taking the Oral Contraceptive Pill

Rifampicin interacts with the oral contraceptive pill, with a risk of decreased protective efficacy against pregnancy. A woman who usually takes the oral contraceptive pill may choose between the following two options while receiving treatment with rifampicin:

- Following consultation with a physician, she could take an oral contraceptive pill containing a higher dose of estrogen (50 mcg)
- Alternatively, she could use another form of contraception (e.g., barrier) to supplement oral contraceptive use.

[11]These are the same mg/kg doses as those used for daily treatment.

All women who are diagnosed with TB and who commence TB treatment should be questioned about oral contraceptive use and counselled about the need to use alternative methods of contraception to avoid unplanned pregnancies.

5.5.6 The use of pyridoxine

Isoniazid may interfere with pyridoxine metabolism and may cause peripheral neuropathy. Pyridoxine (25 mg daily) should be considered for all patients when prescribing isoniazid. It is especially important for patients with diabetes, renal failure, malnutrition, HIV infection, liver disease, substance abuse or significant alcohol intake or women who are pregnant or breastfeeding because of the increased risk of symptoms related to pyridoxine deficiency.

5.5.7 Treatment of non-tuberculous mycobacteria

Nontuberculous mycobacteria (NTM) refers to all the species in the family of mycobacteria that may cause human disease, but do not cause tuberculosis. The most common NTM's that require treatment are *M. avium, M. intracellulare, M. kansasii, M. abscessus, M. chelonae, M. fortuitum, M. terrae, M. xenopi*and *M. simiae.*

Most of the nontuberculous mycobactera infections are naturally resistant to many common antibiotics. It is often necessary to use some of the same medications that are used to treat TB. Because many of these medications have side effects, close monitoring is important. Furthermore, treatment may be necessary for as long as two years. Sometimes treatment is ongoing, depending on the severity of the disease.

The most common organisms involved in human infection are *M. kansasii, M. avium, M. intracellulare, M. chelonae* and *M. abscessus*. *M. kansasii* is easier to treat and often can be killed with only three anti-TB medications. On the other hand, organisms such as *M. avium, M. chelonae* and *M. abscessus* are more difficult to treat. Three to five medications may be needed. Depending on how localized the disease is, surgery also may be helpful. Expert advice is important when there is suspicion or laboratory evidence that a patient harbors NTM.

5.5.8 Treatment among foreign-born residents

More than one third of the population is foreign-born in Palau. It is, therefore, crucial that the Palau NTP has good coordinating relationships with the NTPs of those countries that have a high number of migrant workers in Palau, e.g. the Philippines. Often, TB treatment will begin in Palau and may be continued in the home country of the migrant. Therefore referral and collaboration between National TB Programs is important.

5.6 Treatment of TB patients co-infected with HIV

HIV testing

Palau offers all TB patients HIV testing with pretest counseling and informed consent in a confidential setting. HIV-positive TB patients may have household members who are also living with HIV. Testing and counselling should be recommended for children and other immediate family members of all people living with HIV.

As per national policy, all patients who are diagnosed with TB are counselled and offered an HIV test. . TB patients are tested for HIV in accordance with the HIV testing algorithm. Blood samples are initially screened for HIV using a rapid test assay kit (call Evelyn @ lab to verify test type). Blood samples that are reactive to the screening test undergo local confirmatory testing using two further rapid test assay kits done in parallel (Trinity Biotech Uni-Gold and BiolyticalInsti HIV-1/HIV-2). HIV test results are reported based on the reactivity of the blood samples to the combination of the three rapid tests. For local reactive tests; blood samples are sent to DLS for Western Blot, viral load, CD4 and resistance testing. Patients who are diagnosed HIV antibody positive are counselled and offered treatment and care.

TB treatment for HIV-positive patients

Generally, TB treatment is the same for HIV-infected as for non-HIV-infected TB patients on strict DOT.

HIV-positive TB patients who have been previously treated for TB should receive the same re-treatment regimen as HIV-negative TB patients. When Streptomycin is being used, ensuring the use of ***sterile*** needles and syringes is crucial.

Deaths during treatment, partly due to TB itself and partly due to other HIV-related diseases, are more frequent in HIV-infected patients; particularly in the advanced stages of immunodeficiency (case-fatality is higher with smear-negative pulmonary and extrapulmonary TB, as these patients are generally more immunosuppressed than those with smear-positive TB).

When TB is diagnosed in patients already receiving antiretroviral therapy (ART), TB treatment should be started immediately. There are two issues to consider in such cases: whether ART needs to be modified because of drug–drug interactions or to reduce the potential for overlapping toxicities, and whether the presentation of active TB in a patient on ART constitutes ART failure that requires a change in the ART regimen.

The three I's

Three I's for reducing the burden of TB in persons living with HIV are: (i) ***I***ntensified case-finding; (ii) ***I***NH preventive therapy (daily INH for 9 months[12]); and (iii) TB ***I***nfection control for people living with HIV.

Co-trimoxazole and antiretroviral therapy (ART) for HIV-positive patients

The first priority for HIV-positive TB patients is to initiate TB treatment, followed by co-trimoxazole (sulfamethoxazole and trimethoprim 5:1) and ART. Co-trimoxazole preventive therapy should be initiated as soon as possible and be given throughout TB treatment. Continuation after completion of TB treatment should be considered. The recommended dose for adults is 960 mg once daily, and for children, sulfamethoxazole 20 mg/kg, trimethoprim 4 mg/kg once daily.

[12]The consultant was informed during his stay in Palau, that should a HIV+ patient be identified, the treatment of INH given to this person would be for 12 months, not 9 months.

Antiretroviral therapy (ART) should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count. TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment. Antiretroviral therapy improves survival in HIV-positive patients and reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50%.

WHO recommends that the first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI). The preferred NRTI backbone is zidovudine (AZT) or tenofovirdisoproxilfumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, WHO recommends either efavirenz (EFV) or nevirapine (NVP). The recommended first-line ART regimens for TB patients are those that contain efavirenz (EFV) because interactions with anti-TB drugs are minimal. **For the most up-to-date WHO guidance on ART regimens, reference should be made to www.who.int/hiv/pub/guidelines/en.**

Side effects
Adverse drug reactions are common in HIV-positive TB patients, and some toxicities are common to both ART and TB drugs. Overlapping toxicities between ART, TB therapy and co-trimoxazole include rash (and, more rarely, hepatic dysfunction). Vigilant monitoring of side effects is therefore essential.

Support for co-infected patients
To improve treatment success, the special needs of particular groups (e.g. drug users, prisoners, migrant populations, other marginalized groups) should be assessed and addressed; their care should be integrated with other services. Adequate measures of support and patient-friendly, proper treatment supervision are crucial.

Contact tracing regarding HIV
HIV-positive TB patients may have household members who are also living with HIV. Testing and counseling should be recommended for children and other immediate family members of all people living with HIV.

Screening for latent TB infection
Isoniazid preventive therapy (IPT) reduces the risk of HIV-infected persons with latent TB infection developing active TB. Adults living with HIV should be screened for TB and those who do not report any one of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have active TB and should be offered IPT. Treatment of TB disease with a single anti-tuberculosis drug can lead to the development of drug resistance. It is therefore critical to rule out TB disease before attempting to treat latent infection. TB preventative therapy should not be given to people with HIV infection who have any symptoms of TB disease.

Isoniazid (5 mg/kg daily, to a maximum of 300 mg) should be given for 9 months with monthly follow-up. In addition, pyridoxine should be given to all patients with HIV infection who are on isoniazid in order to prevent peripheral neuropathy. People living with HIV infection who have a positive TST benefit more from IPT and TST can be used where feasible to identify such patients. If a TST is performed an induration size of $\geq$5mm is considered a positive test in people living with HIV infection.

5.7 TB and tobacco

Recent studies and reviews of existing studies have shown that there is a link between tobacco users and 2nd hand smokers with TB outcomes including infection, response to treatment, relapse rates and mortality[13].

Therefore, TB patients who smoke should be identified and offered counseling and other smoking cessation treatments. Also, every TB patient who is not a smoker must be made aware of the consequences of being exposed to secondhand smoke.

Brief routine advice and some pharmacological treatments can be offered routinely by the medical staff in charge of managing TB patients in primary health care services. Every TB patient should be asked if s/he smokes or chews tobacco and those who smoke or chew tobacco should be advised to quit.

[13]As an example, a very recent study found that passive smoking accounted for 18.5% of culture-positive TB in a cohort of 15,486 female never-smokers (Leung et al., Passive smoking and tuberculosis. Arch Intern Med 2010 (Febr 8);170(3):287-292).

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6. MONITORING RESPONSE TO TREATMENT AND TREATMENT OUTCOMES

6.1 Monitoring treatment

All patients should be monitored to assess their response to therapy. Regular monitoring of patients also facilitates treatment completion and allows the identification and management of adverse drug reactions. It also assures the patients that good care is being offered to them.

All patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruption.

Patient weight should be monitored each month, and dosages should be adjusted if weight changes.

A written record of all medications given and bacteriological response should be maintained for every patient on the TB Treatment Card.

Each patient put on treatment should have a monitoring consultation at least once a week during the intensive phase of treatment and at least every month during the continuation phase.

Case management Review should be done once a month to ensure optimal standards of care.

Bacteriological follow-up examinations

a) for pulmonary TB patients on the new treatment regimen (6 months)

Follow-up bacteriological examinations are done monthly after the start of treatment until culture conversion. If there is no culture conversion, expert consultation is recommended. Possibility of drug-resistant TB should be seriously considered and empirical MDR treatment started, especially if the patient deteriorates clinically. Otherwise, the result of the DST needs to be awaited.

A positive sputum smear at the end of the intensive phase may indicate any of the following:

- the initial phase of therapy was poorly supervised and patient adherence was poor;
- poor quality of anti-TB medicines;
- doses of TB medicines are below the recommended range;
- resolution is slow because the patient had extensive cavitation and a heavy initial bacillary load;
- there are co-morbid conditions that interfere either with adherence or with response;
- non-viable bacteria remain visible by microscopy;
- the patient may have drug-resistant *M. tuberculosis* that is not responding to first-line treatment.

b) for extrapulmonary TB patients

For patients with EPTB, no follow-up sputum examinations are required, but monthly clinical monitoring is done.

6.2 Treatment outcomes

The new treatment outcome definitions make a clear distinction between two types of patients:
a) Patients treated for drug-susceptible TB;
b) Patients treated for drug-resistant TB using second-line treatment

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that the management of the standard TB register and the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment episodes.

6.2.1 Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

All bacteriologically confirmed and clinically diagnosed tuberculosis cases should be assigned an outcome from this list, except those with rifampicin-resistant TB (RR-TB) or multidrug-resistant TB (MDR-TB) who are placed on a second-line drug regimen.

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed tuberculosis at the beginning of treatment and who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT there is no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because they were not done or because results were not available.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and where the treatment outcome is unknown to the reporting unit).
Treatment success	The sum of cured and treatment completed.

TB patients found to have a rifampicin-resistant (RR-TB) or multidrug-resistant (MDR-TB) strain at any point in time should be placed on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those in table above.

6.2.2 Outcomes for RR-TB / MDR-TB / XDR-TB patients treated using second-line treatment

Outcomes for RR-TB / MDR-TB / XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.
Treatment failed	Treatment terminated or need for permanent regimen change of ≥2 anti- TB drugs because of - lack of conversion in the continuation phase, or - bacteriological reversion* in the continuation phase after conversion* to negative, or - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or -adverse drug reactions (ADRs)
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more. (This category was previously known as defaulted.)
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed

* The terms conversion and reversion of culture results as used here are defined as follows:

- Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures taken at least 30 days apart are found to be negative. In such case, the specimen collection date of the first negative culture is used as the date of conversion.
- Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures taken at least 30 days apart are found to be positive. For the purpose of defining Treatment failed, reversion is only considered when it occurs in the continuation phase.

The revised definitions should be applied by the NTP at a set changeover date (eg 1 January). All cases on treatment on that date will be assigned outcomes as per the revised definition. This means that patients started on treatment in the previous year may be assigned outcomes according to two different definitions of "Cured" or "Treatment failed", depending on whether they completed treatment before or after the changeover date. This may be the most practical option for the transition period given that retrospective reassignment of outcomes is not always feasible. In Palau, treatment outcomes are also reported in accordance with CDC definitions and these are presented in the below table.

Definitions of treatment outcomes (reason therapy stopped or never started) for reporting to CDC

Outcome	Definition
Completed therapy	Patient completed prescribed course of therapy per the medical record as recorded by the clinician caring for the patient
Lost	Patient could not be located before the start or the completion of treatment (e.g., the patient moved to an unknown location, or the forwarding address is known but the patient was not found at that address). Patients who move outside of Palau and cannot be followed are coded as Other.
Uncooperative or refused	Patient refused to complete therapy (e.g., stopped taking drugs)
Adverse treatment event	Therapy was permanently stopped because of an adverse event due to anti-TB medications (this option is only selected if the patient lived). If the patient died because of an adverse TB treatment event, select Died as the Reason Therapy Stopped And then select Related to TB Therapy for Cause of Death even if the patient stopped TB therapy prior to death due to an adverse treatment event. This determination has to be made by a clinician.
Not TB	Completed diagnostic evaluation did not substantiate the diagnosis of TB (e.g., *M avium* was isolated from clinical specimen)
Died	Patient was alive at diagnosis but died before the start or completion of treatment. This also applies to a patient classified as alive for Status at TB diagnosis if the patient was taking at least 2 anti- TB drugs before the day of death, even though the TB case was not verified and counted until after death.
Other	Therapy was discontinued for a known reason not included in the above choices and is not Unknown (e.g., patient moved outside of Palau).
Unknown	Reason that therapy was stopped is not known.

7. DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IN CHILDREN

Children can present with TB at any age. The frequency of childhood TB is influenced by the intensity of the TB epidemic locally, the age structure of the population, the availability of diagnostic tools, and whether contact investigation is routinely conducted.

Transmission of TB to a child usually results from exposure to an infectious adult or adolescent in her/his close environment, often within the household. On acquiring TB infection, children frequently develop a primary parenchymal lesion in the lungs, with subsequent spread to the regional lymph nodes. The immune response halts further progression in most situations; however, very young children (below 5 years of age) and those with weakened immune systems are at great risk for disease progression.

7.1 Clinical presentation of TB in children

Most children with TB have pulmonary TB; however, PTB is more difficult to recognize because many children present with primary PTB. In addition, the majority of children with TB are too young to produce sputum for smear microscopy.

The most common type of EPTB seen in children is intrathoracic. Other forms of EPTB frequently seen in children include TB lymphadenopathy, TB meningitis, miliary TB, TB effusions (pleural, pericardial, and peritoneal), and spinal TB.

Among children with advanced HIV infection, dissemination of TB becomes more common and patients may present with TB meningitis, miliary TB or widespread tuberculous lymphadenopathy.

7.2 Diagnosis of TB in children

Although most children with TB have pulmonary TB, the diagnosis in children may be difficult. Diagnosis requires a careful assessment of the history, clinical findings and relevant investigations. Bacteriological confirmation of TB is not always feasible but should be sought whenever possible. A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB and when a decision has been made to treat a child, the child should be treated with the full treatment course.

The most important risk factors for TB in a child are; a household contact of a newly diagnosed smear-positive case, age less than five years, HIV infection and severe malnutrition.

The following five steps should be taken to diagnose TB in children:

*7.2.1. **Careful history** (symptoms consistent with TB and history of TB contact)*

a) Symptoms

In most cases, children with symptomatic TB develop chronic symptoms. The commonest are:

- Chronic cough: an unremitting cough that is not improving and has been present for more than 21 days.
- Fever: Body temperature above 38 °C for 14 days, after common causes such as pneumonia have been excluded.
- Weight loss or failure to thrive: In addition to asking about weight loss or failure to thrive, it is necessary to look at the child's growth chart.

b) Contact
Close contact is defined as living in the same household as the source case or in frequent contact with a source case (e.g. the child's caregiver) with sputum smear positive TB (source cases that are sputum smear negative but culture-positive can also be infectious, but to a much lesser degree).

7.2.2. Clinical examination (including growth assessment)

There are no specific features on clinical examination that can confirm that the illness is due to pulmonary TB. Some signs, although uncommon, are highly suggestive of extrapulmonary TB. Other signs are common and should prompt an investigation into the possibility of childhood TB.

a) Physical signs highly suggestive of extrapulmonary TB:

- gibbus (an anterior angular deformity of the lower back), especially of recent onset (resulting from vertebral TB)
- non-painful enlarged cervical lymphadenopathy with fistula formation

b) Physical signs requiring investigation to exclude extrapulmonary TB:

- meningitis not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure
- pleural effusion
- pericardial effusion
- distended abdomen with ascites
- non-painful enlarged lymph nodes without fistula formation
- non-painful enlarged joint
- signs of tuberculin hypersensitivity (e.g. phlyctenular conjunctivitis, erythema nodosum).

Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation program, is a good indicator of chronic disease in children, of which TB may be the cause.

7.2.3. Tuberculin skin test (TST)

Tuberculin skin testing (TST) is the intradermal injection of a combination of mycobacterial antigens which elicit an immune response, represented by induration, which can be measured in millimeters. When a person is infected with *M. tuberculosis*, a TST is often (but not always) positive. A positive TST indicates TB infection, but not necessarily TB disease. However, the TST can be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and when used in conjunction with other diagnostic tests. A TST is useful to support a diagnosis of TB in children with suggestive clinical features who are sputum smear negative or who cannot produce sputum.

TST using the Mantoux method is the test recommended. In Palau, 5 tuberculin units of tuberculin purified protein derivative (PPD)-S14 is used. Health-care workers must be trained in performing and reading a TST.

A TST should be regarded as positive when the induration measures $\geq$ 10 mm (the induration, not the redness) irrespective of BCG immunization[15]. A TST is also positive if $\geq$ 5mm in HIV-infected, children under 5 years of age or severely malnourished children.

[14] Currently, only Chuuk uses 5 units; the other three states use 10 units.

The TST can be used to screen children exposed to TB (such as household contacts with TB) and as an aid in the diagnosis of TB (note that fewer HIV-infected children will have a positive TST, as a normal immune response is required to produce a positive test). A positive TST does not distinguish between TB infection and active disease. A negative TST never rules out a diagnosis of TB in a child.

7.2.4 Bacteriological confirmation whenever possible

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available. Appropriate specimens from the suspected sites of involvement should be obtained for microscopy and for culture (and also histopathological examination). Appropriate clinical samples include sputum, gastric aspirates and certain other material (e.g. lymph node biopsy or any other material that is biopsied). Fine-needle aspiration of enlarged lymph glands – for both staining of acid-fast bacilli and histology – has been shown to be a useful investigation, with a high bacteriological yield.

The following are ways of obtaining samples for smear microscopy:

a) Expectoration: Sputum should always be obtained in adults and older children (10 years of age or older) who are presumptive pulmonary TB cases. Among younger children, sputum is difficult to obtain and most children are sputum smear-negative. However, in children who are able to produce a specimen, it is worth sending it for smear microscopy and culture.

b) Gastric aspiration: Gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. A gastric aspirate should be obtained on each of three consecutive mornings (obtained in the early morning after overnight fast)

c) Biopsied lung, peripheral lymph node, or other tissue

7.2.5 Investigations relevant for presumptive pulmonary TB and extrapulmonary TB cases

a) Presumptive pulmonary TB case

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have radiographic changes suggestive of TB. The commonest picture is that of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent opacification which does not improve after a course of antibiotics should be investigated for TB.

Adolescent patients with TB have radiographic changes similar to adult patients with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease with hilaradenopathy and collapse lesions visible on CXR.

It is essential to have a high index of suspicion for TB disease in children living with HIV. As with the non-HIV infected child, a definitive diagnosis of TB disease requires isolation of *M. tuberculosis.*

Bronchoscopy is not recommended for the routine diagnosis of TB in children.

b) Presumptive extrapulmonary TB case

[15]WHO, in its 2006 Guidance on paediatric TB care, states that for high-risk children (HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor), an induration of at least 5 mm is considered positive; for all other children the cut off is 10 mm.

Table 8 shows the investigations usually used to diagnose the common forms of extrapulmonary TB in children. Often, TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

Any child presumed to have TB should have an HIV test. A positive test also directed the need for other HIV-related care for the child and possibly other family members.

Table 8: Common forms of extrapulmonary TB in children, and suggested approach to diagnosis

Site	***Practical approach to diagnosis***
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest x-ray and lumbar puncture (to test for meningitis)
TB meningitis	Lumbar puncture (and computerized tomography where available)
Pleural effusion (older children and adolescents)	Chest x-ray, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound and ascitic tap
Osteoarticular	X-ray, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

Modified from: Guidance for national tuberculosis programs on the management of tuberculosis in children. World Health Organization, 2014.

7.3 Standard case definitions of TB in children

As with adult TB patients, all children with TB should be registered with the NTP as smear-positive pulmonary, smear-negative pulmonary TB or extrapulmonary TB, and as a new case or a previously treated case.

7.4 Treatment

Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Severe and disseminated TB (e.g. TB meningitis and miliary TB) may occur more frequently, especially in young children (less than 3 years old). Treatment outcomes in children are generally good, even in young and immunocompromised children who are at higher risk of disease progression and disseminated disease, provided that treatment starts promptly.

Table 9: Recommended treatment regimens for children in each TB diagnostic category

TB Diagnostic Category	TB cases	Anti-TB Drug Regimen	
		Intensive phase	**Continuation phase**
Low HIV prevalence (and HIV-negative children) and low Isoniazid resistance settings[16]	Smear negative PTB Intrathoracic lymph node TB Tuberculous peripheral lymphadenitis	2HRZ	4HR
	Extensive pulmonary disease Smear-positive pulmonary TB Severe forms of extrapulmonary TB(other than tuberculous meningitis/osteoarticular TB)	2RHZE	4HR
High HIV prevalence or high isoniazid resistance or both[17]	Smear-positive PTB Smear-negative PTB with or without extensive parenchymal disease All forms of EPTB except tuberculous meningitis and osteoarticular TB	2RHZE	4RH
All Regions	Tuberculous meningitis and osteoarticular TB	2HRZE[18]	10HR
	MDR-TB	Individualized regimens (see chapter7)	

Modified from: Guidance for national tuberculosis programs on the management of tuberculosis in children. Geneva, World Health Organization, 2nd Edition 2014; Rapid advice: Treatment of tuberculosis in children. Geneva, World Health Organisation, 2010.

[16] The standard code for anit-TB treatment regimens uses an abbreviation for each anti-TB drug: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases – the initial and continuation phases. The number at the front of each phase represents the duration of that phase in months. Example, 2HRZ: Duration of this phase is 2 months and drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide

[17] See "Definitions and distinctions" section for discussion of WHO definitions or high and low prevalence of HIV and Isoniazid resistance

[18] The decision on the regimen for a child with tuberculous meningitis should be made by an experienced clinician. It is suggested that the patient be treated in a hospital.

8. CONTACT INVESTIGATION (CONTACT TRACING)

8.1 Objective and rationale

The primary objective in TB contact tracing is to identify and manage any person at risk of developing TB disease after being exposed to an infectious case of TB. This will contribute to a reduction in TB morbidity and in the spread of TB.

A review of contact investigations carried out in low-income and middle-income countries showed that 4.5% of identified household contacts of new pulmonary TB cases had TB at the time of the evaluation. Among contacts aged under 5 years, 8.5% were found to have TB. More than 50% of household contacts had latent TB infection (page 56 of WHO, *Implementing the WHO Stop TB Strategy – A handbook for national tuberculosis control programs*. 2008. WHO/HTM/TB/2008.401).

8.2 Target population for contact tracing and procedures for high-risk contacts

All household contacts of a sputum smear positive TB patient (the so-called index case)[19] should be traced. People outside the household of the sputum smear positive TB patients who have been in regular close contact with the index case may also be traced. The likelihood that a contact is infected with TB depends on (i) the extent of disease in the index case, (ii) the duration that the source and the contact are together and their proximity, (iii) local air circulation; and (iv) the contact's medical condition as it is related to the immune competence. Less clearly understood factors are the virulence of the particular *M. tuberculosis* strain and a contact's intrinsic predisposition for TB infection or disease.

When detecting a sputum smear positive index case, the following contacts are first priority in contact tracing:

- Household contacts aged below 5 years
- Household contacts with a medical risk factor (e.g. HIV-positivity, diabetes mellitus), irrespective of age
- People aged below 5 years or HIV-positive people who live outside the household of the sputum smear positive TB case but have been in regular close contact with the case
- Contacts with exposure to TB bacilli during a medical procedure (bronchoscopy, sputum induction, autopsy).

Contacts who have documentation of a previous positive tuberculin skin test result or with previous TB disease have a different procedure: all should be examined for TB disease. Those not having TB disease will have no further examination. In general contacts with previous +ve tst w/out previous TB prevention should be offered IPT.

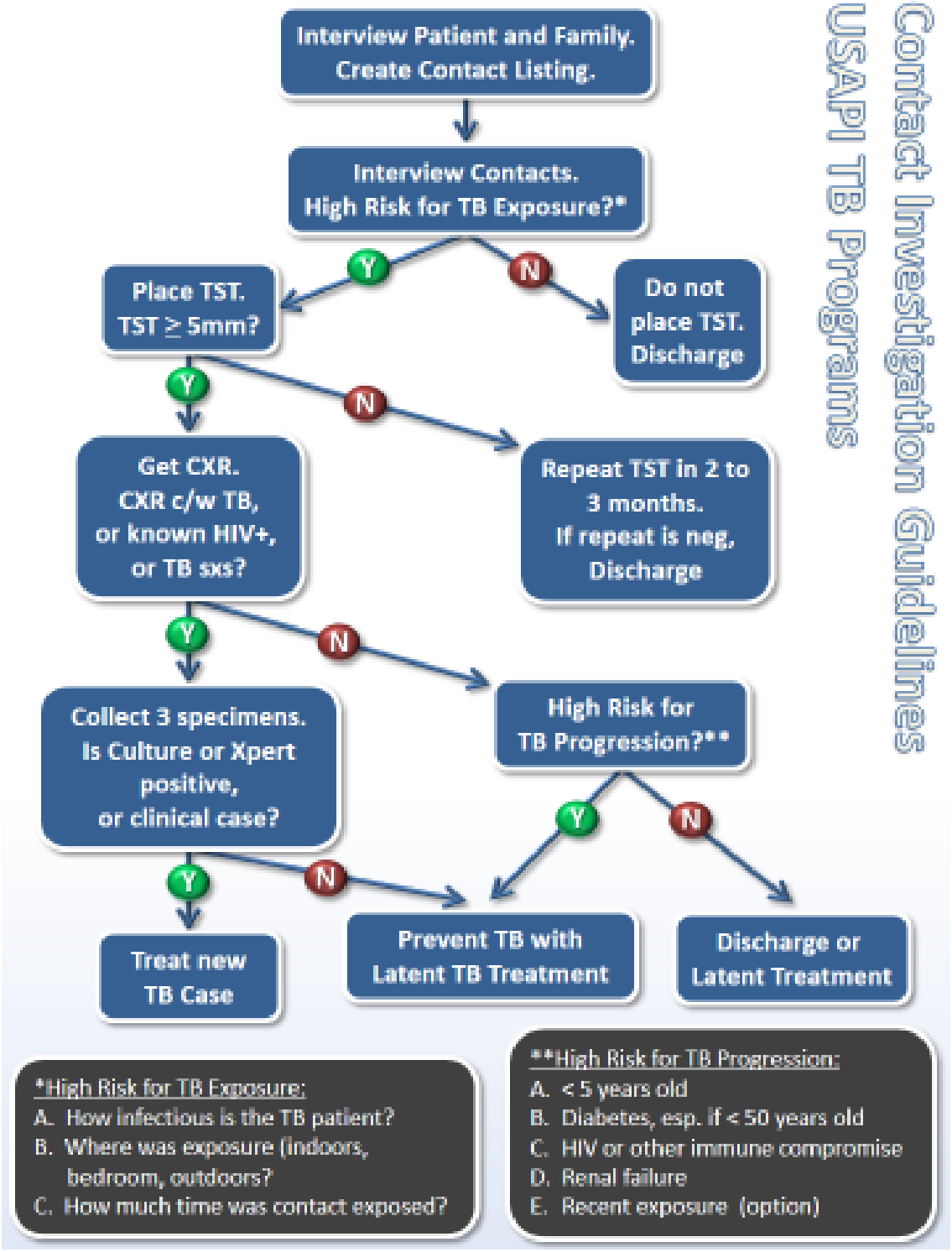
Figure 5 highlights the recent contact tracing guidelines for USAPI countries provided by CDC (2013).

[19] Smear-negative TB patients, especially those whose chest radiograph indicates the presence of cavities in the lung, also have the potential to spread TB. Culture+ index cases are, therefore, included though priority are the smear-***positive*** index cases.

In contact investigations, the two main tasks are to find out who has TB disease and who has TB infection. During the initial contact encounter, it is crucial to identify TB disease and latent TB infection (LTBI) efficiently; during an investigation the following should be recorded:

- Contact's previous *M. tuberculosis* infection or disease and related treatment;
- Contact's verbal report and documentation of previous TST results; a positive TST in a BCG-vaccinated person should be interpreted as evidence of recent *M. tuberculosis* infection in persons who are contacts of an infectious case.
- Current symptoms of TB illness;
- Medical conditions or risk factors making TB disease more likely (mainly HIV infection, diabetes mellitus, chronic renal failure, prolonged corticosteroid therapy, other immunosuppressive therapy).

Figure 5: Contact investigation guidelines for USAPI, CDC, 2013



9. DIAGNOSIS AND MANAGEMENT OF MDR-TB

In Palau, management of MDR-TB[20] and other drug-resistant cases is done in close collaboration with CDC; this close collaboration with CDC is crucial for the management of drug-resistant TB (DR-TB) in Palau. The 2008 edition of the WHO Guidelines for the programmatic management of drug resistant TB[21] is a useful reference. Palau can ask for clinical support for presumptive and confirmed cases of MDR-TB through the Curry International TB Center (warmline service; tbcenter@nationaltbcenter.ucsf.edu) or the TB Support service via SPC (tb-support@lists.spc.int). To date, Palau has reported one case of MDR-TB in 2011.

9.1 Diagnosis of multi drug resistant TB

Effective treatment and management of MDR-TB requires prompt recognition and diagnosis of drug-resistant disease. Health care workers assessing TB patients must be constantly aware of the risk factors for drug resistance, such as a history of prior TB treatment, contact with MDR-TB, treatment failure or relapse or residence in a community/ country with high levels of MDR-TB. Specimens from patients with identified risk factors should be sent for mycobacterial culture and DST.

The most important predictors of drug-resistant TB are:

- A previous episode of TB treatment
- Progressive worsening clinical and/or radiographic findings while on TB treatment
- Exposure to an individual with infectious drug-resistant TB
- Origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance

Collaborating with the reference laboratory (i.e. DLS), sputum samples from Palau are routinely being sent to Hawaii for sputum microscopy, culture, species identification and drug susceptibility testing. In general, turn-around-time is 2 to 3 months for first-line DST results. When liquid culture is used, it is around 1 to 2 months. However, rapid DST is now also available. Rapid DST can identify the presence of genetic mutations associated with resistance to rifampicin and INH within 1 to 2 days.

9.2 Treatment

Treatment of MDR-TB cases should be with at least 4 drugs with either certain, or almost certain, effectiveness. For MDR treatment, TB medicines are grouped according to efficacy, experience of use and drug class. The medicines belonging to Group 1 are the most powerful drugs, those belonging to Group the least powerful drugs (Table 11).

[20] In these guidelines, XDR-TB is included in the term 'MDR-TB'. MDR-TB: multidrug-resistant TB; it is caused by organisms that are resistant to at least isoniazid and rifampicin. XDR-TB: extensively drug-resistant TB, defined as MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of threeinjectable second-line drugs (amikacin, capreomycin or kanamycin).

[21] *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

Table 10: Group of drugs to treat MDR-TB

Group	Drugs (abbreviations)
Group 1: First-line oral agents	• Pyrazinamide (Z) • Ethambutol (E) • Rifabutin (Rtb) [a]
Group 2: Injectable agents	• Kanamycin (Km) • Amikacin (Am) • Capreomycin (Cm) • Streptomycin (S)
Group 3: Fluroquinolones	• Levofloxacin (Lfx) • Moxifloxacin (Mfx) • Ofloxacin (Ofx)
Group 4: Oral bacteriostatic second-line agents	• Para-aminosalicylic acid (PAS) • Cycloserine (Cs) • Terizidone (Trd) • Ethionamide (Eto) • Protionamide (Pto)
Group 5: Agents with unclear role in treatment of drug resistant-TB	• Clofazimine (Cfz) • Linezolid (Lzd) • Amoxicillin/clavulanate (Amx/Clv) • Thiocetazone (Thz) • Imipenem/Cilastatin (Ipm/Cln) • High-dose isoniazid (high-dose H)b • Clarithromycine (Clr)

[a]Rifabutin is not on the WHO List of Essential Medicines. It has been added here as it is used routinely in patients on protease inhibitors in many settings. Rifabutin has a very high cross-resistance to rifampicin.

[b] High-dose isoniazid is defined as 16–20 mg/kg/day. Some experts recommend using high-dose isoniazid in the presence of resistance to low concentrations of isoniazid (>1% of bacilli resistant to 0.2 μg/ml butsusceptible to 1 μg/ml of isoniazid), whereas isoniazid is not recommended for high-dose resistance (>1% of bacilli resistant to 1 μg/ml of isoniazid).

Adapted from Table 7.1. and Figure 7.2. of Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402)

The following principles should be applied when treating MDR-TB:

- Use at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present.
- Regimens should be based on the history of drugs taken by the patient. The longer a drug has been taken previously, the higher the chance that there is resistance towards this drug.
- Fluoroquinolones are believed to have variable cross-resistance between each other, with in vitro data showing that some later-generation fluoroquinolones (Levofloxacin, Moxifloxacin) remain susceptible when earlier-generation fluoroquinolones are resistant. In these cases, it is unknown if the later-generation fluoroquinolones remain effective clinically. Amikacin and kanamycin have very high cross-resistance. Other aminoglycosides and polypeptides have low cross-resistance. Prothionamide and ethionamide have 100% cross-resistance.
- Design treatment regimens with a consistent approach based on the hierarchy of the five groups of TB medicines.
- DST should generally be used to guide therapy; however, one cannot depend on the results of drug susceptibility for ethambutol, PZA, Group 4 drugs and Group 5 drugs (due to the low reliability of DST for these drugs, especially for the Group 4 and Group 5 drugs).
- Treatment should be continued for a total of 18 to 24 months beyond culture conversion. MDR-TB patients who are culture-negative at start of MDR-TB treatment, therefore, generally have 18 months of treatment if response to treatment is good. For many MDR-TB patients, treatment lasts for around 24 months.
- The recommended duration of administration of the injectable agent, or the intensive phase, is guided by culture conversion. The injectable agent should be continued for another 4 months after culture conversion[22]. If patient was culture-negative at the start of MDR treatment[23], the injectable agent should be given for a minimum of 6 months.
- Each dose in an MDR regimen is given under directly observed therapy throughout the treatment. This is not negotiable.
- When possible, pyrazinamide, ethambutol and fluoroquinolones should be given once per day as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs depending on patient tolerance; however ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.
- Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many patients with drug-resistant TB have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs.

[22]The use of an individualized approach that reviews the cultures, smears, X-rays and the patient's clinical status may also help in deciding whether to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness is questionable for an agent(s), or extensive or bilateral pulmonary disease is present. In rare cases, the injectable agent may be used for a much longer period. This may be the case when other medicines that are effective against MDR-TB cannot be used (because of resistance or due to unmanageable side effects).

[23] In order for a patient to be considered culture- or sputum smear-positive at the start of treatment, the following criteria must be met: at least one pre-treatment culture or smear was positive; the collection date of the sample on which the culture or smear was performed was less than 30 days before, or 7 days after, initiation of MDR treatment.

- The drug dosage should be determined by body weight. Dosage should be adjusted continuously as the weight changes.
- Most drugs should be started at full dose, except cycloserine, ethionamide/prothionamide, and PAS, in which case the dose of the drug can be increased over a two-week period.
- Use adjunctive measures appropriately, including surgery[24] and nutritional[25] as well as social support. Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine or terizidone to help prevent peripheral neurpathy. The recommended dose is 50mg of pyridoxine for every 250mg of cycloserine (or terizidone) prescribed.
- Treat adverse drug reactions immediately and adequately. Drugs to counter side effects should be available at no cost to the patient.
- Persistently positive sputa and cultures for AFB should be assessed for non-tuberculous Mycobacteria (NTM), as overgrowth with NTM in lung damage secondary to TB is not uncommon. In such cases, although DR-TB may be adequately treated, treatment may need to be directed towards the NTM as well.
- Augmenting a re-treatment regimen or the standard 2HRZE / 4HR regimen by a fluoroquinolone or an injectable second-line drug should not be done – it jeopardizes second-line drugs that are critical treatment options for MDR patients. Second-line drugs should be used only for MDR regimens and only if quality-assured drugs can be provided by DOT for the whole course of therapy.

The management of drug-resistant TB is often complicated by drug toxicities and long duration of therapy. Successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, especially when multidrug-resistance is present.

In addition, strong stigma is often attached to MDR-TB. Therefore, emotional support is crucial to increase the likelihood of completion of this demanding treatment. It is vital that health-care providers dealing with MDR-TB patients are well equipped to support the MDR-TB patients not only medically but also emotionally and socially.

Empirical MDR treatment

Empirical MDR treatment is treatment with second-line drugs even though the drug susceptibility pattern is not yet known. When the rapid, molecular-based DST method is being used, then there is no need to start empirical MDR treatment because there is only minimal delay until the clinician knows the drug susceptibility pattern of the patient. However, if the DST results are expected to arrive after more than one month it may be appropriate to start empirical MDR treatment for TB patients who have a high likelihood of harbouring MDR-TB. Empirical MDR treatment is especially important for TB patients in poor clinical condition or when the disease is progressing rapidly[26]. Once the DST results are issued, the regimen is adjusted accordingly.

[24] The most common operative procedure in patients with pulmonary DR-TB is resection surgery (taking out part or all of a lung). Large case-series analysis has shown resection surgery to be effective and safe under appropriate surgical conditions. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available. It is not indicated in patients with extensive bilateral disease.

[25]Without nutritional support, patients, especially those already suffering from baseline hunger, can become enmeshed in a vicious cycle of malnutrition and disease. The second-line drugs can also further decrease appetite, making adequate nutrition a greater challenge. Vitamin B6 (pyridoxine) should also be given to all patients receiving cycloserine or terizidone to prevent neurological adverse effects. Vitamins (especially vitamin A) and mineral supplements can be given in areas where a high proportion of patients have these deficiencies. If minerals are given (zinc, iron, calcium, etc.) they should be dosed apart from the fluoroquinolones, as they can interfere with the absorption of these drugs.

[26]In general, HIV-positive TB patients are also considered for empirical MDR treatment.

9.3 Monitoring of treatment for multi-drug resistant TB

Close monitoring is essential during treatment of MDR-TB. Monitoring of treatment and management of adverse effects may have to be more intensive in patients with co-morbid conditions (diabetes mellitus, renal insufficiency, acute or chronic liver disease, thyroid disease, mental illness, drug or alcohol dependence, HIV infection, pregnancy, lactation and others)[27]. Methods of avoiding pregnancy during treatment for women of child bearing age should be discussed.

To assess treatment response, sputum smears and cultures should be performed monthly until smear and culture conversion. Conversion is defined as two consecutive negative smears and cultures taken 30 days apart. Specimens for monitoring do not need to be examined in duplicate, but doing so can increase the sensitivity of the monitoring.

The recommended initial laboratory evaluations and monitoring during treatment are shown in Table 12.

After conversion, the minimum frequency recommended for bacteriological monitoring is monthly for smears and quarterly for cultures. WHO recommends that programs with adequate culture capacity choose to do cultures more frequently, every 1–2 months, after conversion. Monitoring of MDR-TB patients by a clinician should be at least monthly until sputum conversion, then every 2–3 months.

Chest radiographs should be taken at least every six months, when a surgical intervention is being considered, or whenever the patient's clinical situation has worsened. Each patient's weight should be monitored monthly.

Table 11: Monitoring during treatment of MDR-TB

Monitoring evaluation	**Recommended frequency**
Evaluation by clinician	At baseline, and at least monthly until conversion, then every 2–3 months
Screening by DOT worker	At every DOT encounter
Sputum smears and cultures	Monitor smears and cultures monthly throughout treatment. (Note: programs with limited resources may choose to do smears monthly but cultures only every other month)
Weight	At baseline and then monthly
Drug susceptibility	At baseline in programs doing individualized treatment testing (DST) or in programs doing standardized treatments that need to confirm MDR-TB. For patients who remain culture-positive, it is not necessary to repeat DST within less than 3 months of treatment
Chest radiograph	At baseline, and then every 6 months
Serum creatinine	At baseline, then monthly if possible while receiving an injectable drug. Every 1–3 weeks in HIV-infected patients, diabetics and other high-risk patients
Serum potassium	Monthly while receiving an injectable agent. Every 1–3 weeks in HIV-infected patients, diabetics and other

[27] The management of drug-resistant TB when these conditions exist is described in Chapter 9 of WHO's *Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008*.

	high-risk patients
Thyroid stimulating hormone (TSH)	Every 6 months if receiving ethionamide/prothionamide and/or PAS; and monitor monthly for signs/ symptoms of hypothyroidism. TSH is sufficient for screening for hypothyroidism; it is not necessary to measure hormone thyroid levels
Liver serum enzymes	Periodic monitoring (every 1–3 months) in patients receiving pyrazinamide for extended periods or for patients at risk for or with symptoms of hepatitis. For HIV-infected patients, do monthly monitoring
HIV testing	At baseline, and repeat if clinically indicated
Pregnancy testing	At baseline for women of childbearing age, and repeat if indicated
Hemoglobin and white blood count	If on linezolid, monitor weekly at first, then monthly or as white blood count needed based on symptoms; there is little clinical experience with prolonged use For HIV-positive patients on an ART regimen that includes AZT, monitor monthly initially and then as needed based on symptoms
Lipase	Indicated for work up of abdominal pain to rule outpancreatitis in patients on linezolid, D4T, ddI, ddc.
Lactate	Indicated for work up of lactic acidosis in patients on linezolid or ART
Serum glucose	If receiving gatifloxacin, monitor glucose frequently (weekly) and educate patient on signs and symptoms of hypoglycaemia and hyperglcycaemia

Source: Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update 2008. World Health Organization, 2008.

9.4 Treatment of contacts of MDR-TB index cases (prophylactic MDR-TB treatment)

Close clinical follow-up of people exposed to MDR-TB is recommended as it may assist in early diagnosis and treatment. Therefore, contacts of index cases with MDR-TB should be traced. There are no internationally accepted, evidence-based recommendations available to guide treatment of latent TB infection in persons exposed to MDR-TB.

However, in Palau, based on advice from the CDC, prophylactic MDR-TB treatment consists of 12 months of moxifloxacin for adults and 12 months of levofloxacin plus ethionamide for children. If DST shows only RH-resistance, the prophylactic regimen is moxifloxacin plus ethambutol for 12 months for adults; for children it is levofloxacin plus ethambutol for 12 months. It is important to consider the DST results of the index patient when deciding how to treat a contact of an MDR-TB case.

9.5 Extensively drug-resistant TB (XDR-TB)

XDR-TB is defined as MDR-TB that is resistant as well to any one of the fluoroquinolones and to at least one of the three injectable second-line drugs (amikacin, capreomycin or kanamycin). The two strongest risk factors for XDR-TB are:

1. Failure of an anti-TB regimen that contains second-line drugs including an injectable agent and a fluoroquinolone.
2. Close contact with an individual with documented XDR-TB or with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

Treatment of XDR-TB is a challenge. Treatment of XDR-TB will involve group 5 agents and management should always be in consultation with an expert in the management of drug-resistant TB.

10. INFECTION CONTROL

TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within populations. The foundation of infection control is early and rapid diagnosis, and proper management of TB patients. Infection control is a crucial part of TB control and is especially important in settings where drug-resistant TB is common.

TB infection control should be part of national infection prevention and control policies because it complements such policies – in particular, those that target airborne infections.

M. tuberculosis is nearly always transmitted through an airborne route, with the infecting organisms being carried in droplets of secretions (droplet nuclei) that are expelled into the surrounding air. Droplet nuclei are produced when persons with pulmonary or laryngeal tuberculosis cough, sneeze, speak, or sing. They also may be produced by aerosol treatments, sputum induction, aerosolization during bronchoscopy, and through manipulation of lesions or processing of tissue or secretions in the hospital or laboratory.

Person-to-person transmission of *M. tuberculosis* is determined by certain characteristics of the source case and of the person exposed to the source person and by the environment in which the exposure takes place. The virulence of the infecting strain of *M. tuberculosis* might also be a determining factor for transmission.

TB infection control has three components. By order of importance, they are:
1) Administrative controls,
2) Environmental or engineering controls, and
3) Personal respiratory protection.

Table 12: Key components of TB infection control

Key components of TB infection control are:
- Administrative controls
  - Prompt identification of people with TB
  - Separate infectious patients
  - Control the spread of pathogens (cough etiquette and respiratory hygiene)
  - Minimize the time spent in health-care facilities
- Environmental or engineering controls
  - Use of ventilation systems
  - Use of ultraviolet germicidal irradiation, at least when adequate ventilation cannot be achieved
- Personal respiratory protection
  - Particulate respirators

Particulate respirators

Particulate respirators (e.g. N95 masks) should be used by health care providers. Visitors should also wear particulate respirators when in enclosed space with infectious cases. It is important that correct use of the mask is enhanced by the fit test (how the mask covers the face closely) and by regularly exchanging old masks. Respirators are especially important when health workers are involved in high-risk aerosol-generating procedures associated with high risk of TB transmission (e.g. bronchoscopy, intubation, sputum induction procedures, aspiration of respiratory secretions, and autopsy or lung surgery with high-speed devices) and when health workers or visitors interact with infectious MDR-TB or XDR-TB patients

or presumptive cases. TB presumptive cases and infectious TB patients should wear surgical masks (face masks) to reduce the spread of mycobacteria from them[28] to others.

10.1 Congregate settings and households

Reduction of overcrowding in any congregate setting (e.g. military barracks, homeless shelters, prisons) is an important measure to decrease TB transmission in such settings. At the household level, reducing overcrowding is often not possible. Behavior and social change campaigns can help reduce TB transmission at the household level. Particular attention should be given to the quality of information, education and communication messages to avoid any unintended increase of stigma.

Effective health communication between a provider and a TB patient is crucial so that each TB patient on treatment does her/his part to minimize the spread of TB bacilli. During the first few weeks of treatment, sputum smear patients should spend as much time as possible outdoors, sleep along in a separate, adequately ventilated room (if possible), and spend as little time as possible in congregate settings or in public transport.

10.2 Bio safety during diagnostic procedures

To decrease the risk of infection with TB bacilli during the diagnostic process, the following should be adhered to:

- Treat all sputum samples as potentially infectious and use leak proof containers for collection and transportation.
- Use bacteriological safety hood while carrying out all procedures involving sputum. However, in a well-ventilated area, direct smear microscopy can be performed without biological safety cabinets.
- Dispose of the sputum cups by incineration, autoclaving or treating with 5% phenol or 2% freshly prepared hypochlorite solution, whichever is feasible.
- Take special precautions while transporting the specimens to the reference laboratories with emphasis on containers which don't get broken in the event of an accident.
- Wash hands with soap and water frequently especially after touching the sputum.
- Do not eat, drink or smoke in the laboratory area.
- Clean laboratory bench tops with a disinfectant (phenol or hypochlorite solution) at the end of each day.
- Quality assurance must be applied to safe laboratory arrangement, equipment, collection and transportation of specimen, reagents and methods and reporting of results. Use standard operating procedures, equipment should meet the manufacturer's claims and specifications and agents should be of good quality. Analyze laboratory results on a weekly or monthly basis. Adequately trained and motivated staff is crucial to the generation of quality results.

[28] Little is known about whether surgical masks placed on coughing patients affect transmission of TB, or whether masks are better than other barrier interventions (piece of cloth, tissue, coughing into elbow) at minimizing the spread of droplet nuclei. There is a strong theoretical basis for use of masks, particularly when infectious patients are moving through areas housing susceptible individuals. Surgical masks may be useful for patients who are unable to cover their mouth for any reason.

11. EMPOWERMENT OF PEOPLE WITH TB AND OF COMMUNITIES

11.1 Advocacy, communication and social mobilization (ACSM)

In the context of wide-ranging partnerships for TB control, advocacy, communication and social mobilization (ACSM) activities are fundamental:

Advocacy to influence policy changes and sustain political and financial commitment;

Two-way communication between the care providers and people with TB as well as communities to improve knowledge of TB control policies, programs and services, making TB services more patient-friendly;

Social mobilization to engage society, especially the poor, and all allies and partners in the campaign to control TB.

11.2 Community participation in TB control

Community participation in the daily patient care and other aspects of TB control such as training and policy making implies establishing a working partnership between the health sector and the community – the local population, especially the poor, and TB patients, both current and cured. Cured patients can be very effective encouragers and supporters of TB patients who are on treatment: the experiences of TB patients help fellow-patients to cope better with their illness. Cured TB patients, especially when organised in a "patient association" or "patient groups" can also share their experiences and insights to care providers in order to guide NTPs in delivering services responsive to the needs of patients.

A tool to involve the patients more closely in the fight against TB is the so-called *Patients' Charter.* Developed by patients from around the world, the Patients' Charter outlines the rights and responsibilities of people with TB. Its purpose is to empower people with TB and communities and to make the patient–provider relationship mutually beneficial. The Charter (www.wcc-tb.org/charter2006.php) provides guidance on how patients, communities, health-care providers and governments can work as partners and enhance the effectiveness of health services in general and TB care in particular.

It is important that the NTP trains and supports their frontline health workers to help them create an empowering environment, for example by facilitating the creation of patient groups, encouraging peer education and support, and linking with other self-help groups in the community. Ensuring that patients and communities alike are informed about TB, enhancing general awareness about the disease and sharing responsibility for TB care can lead to effective patient empowerment and community participation, increasing the demand for health services and bringing care closer to the community.

Bringing TB treatment closer to the communities where the patients live reduces the burden of treatment for the patients. Selecting community volunteers and identifying how they could contribute to TB care should be the joint responsibility of the local NTP staff, TB patients and representatives of the community.

12. MONITORING AND EVALUATION (M&E)

A reliable monitoring and evaluation system is one of the key elements of a good national TB program. Such a system is useful not only to monitor progress and treatment outcomes of individual patients, but also to evaluate the overall performance of the TB control program at the local and national level.

A strong monitoring and evaluation system has three components:

1. A monitoring and evaluation plan (M&E plan) at the level of the ministry
2. A data management unit
3. Data collection and reporting systems.

The monitoring and evaluation system in Palau consists of a suite of recording and reporting tools, quarterly reporting of programmatic and laboratory data, annual cohort analysis, an online surveillance and reporting tool (EpiAnywhere™), supervisory visits from the national level to the States, technical visits from external technical experts, and reporting to Government, donors and others on a set of predefined indicators to monitor progress.

Recording and reporting

Records and **registers** are the primary tools for collecting and recording data needed to track what is happening at the patient level, the facility level, the district level, the state level, the country level and ultimately at the global level. Some of the data gathered through these forms allows for tracking progress towards targets.

Reports are used for monitoring and evaluation, activity planning, implementation and budgeting purposes. During supervisory visits, it is fundamental that the recording and reporting is thoroughly checked and corrective measure taken if needed. Palau produces quarterly reports on programmatic and laboratory data for internal reporting and sends quarterly reports of aggregated TB data to SPC and DLS. In addition, Palau completes annual online reports for WHO and submits mid-year and annual reports to CDC.

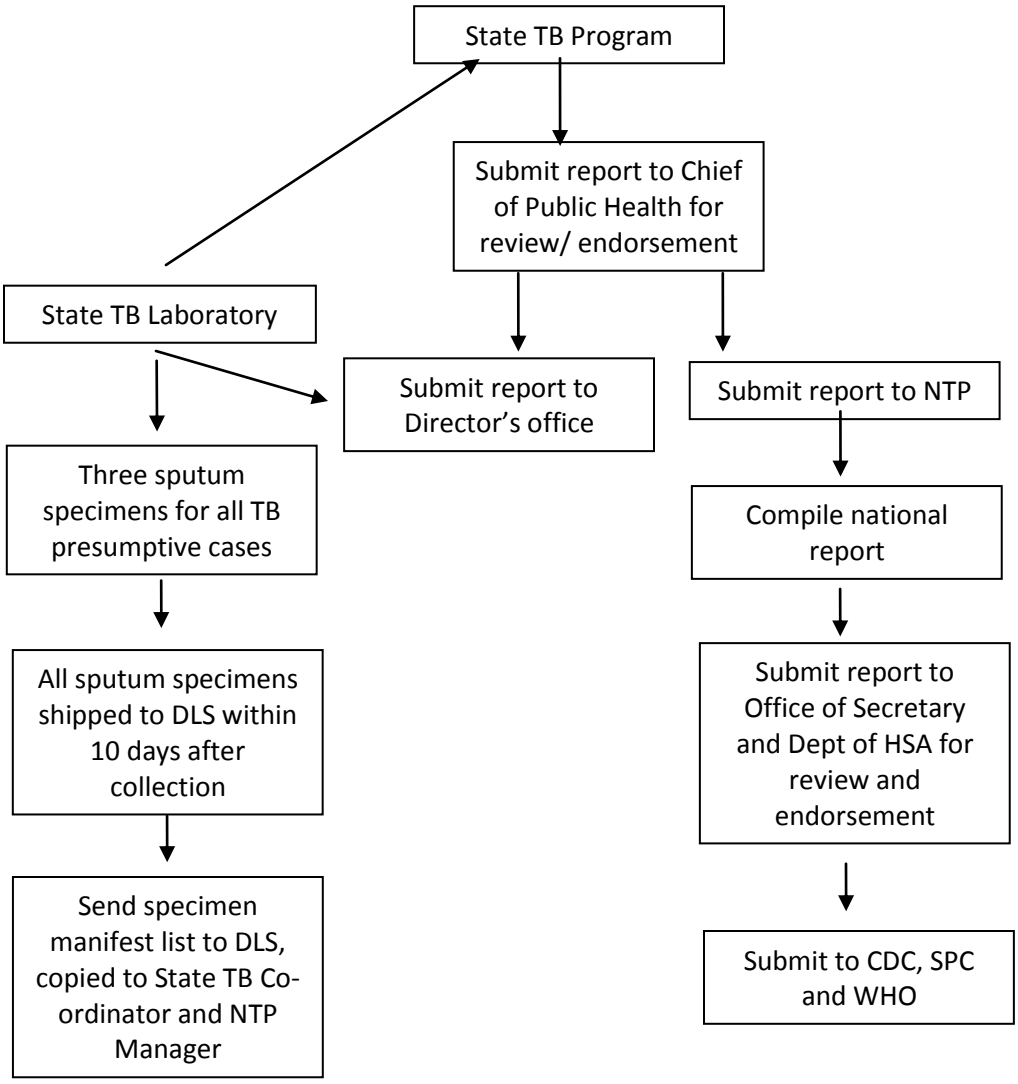
The forms used in the National TB Program in Palau are included in Annex 7.

The following forms are used in Palau:

1. *Laboratory Request Form for TB Microscopy*
2. *TB Laboratory Register*
3. *TB Patient Register*
4. *Tuberculosis Treatment Card*
5. *Quarterly Workload Statistics and Performance Indicators Report (laboratory)*
6. *Interjurisdictional Tuberculosis Notification Form*

The process of preparing reports and seeking approval prior to sending them from State level to the national level and to international agencies is described in Figure 6.

Figure 6: Process of reporting and verification for state and national TB reports



1. Laboratory Request Form for TB Microscopy

This form is available at the DOTS centres. The health worker completes it when a presumptive tuberculosis case or a follow up case produces his/her sputum specimens. A form should accompany the corresponding sputum specimen to the laboratory (i.e. one form per specimen).

2. TB Laboratory Register

This register is kept in the laboratory at the DOTS centre. The TB laboratory Officer fills in the register when the sputum specimen arrives at the laboratory, the information on the form "*Laboratory Request Form for TB Microscopy*" should be entered into the register. Each patient will have three sputum specimen examined. All should be entered on the same line and given a laboratory register number. This number is then entered on the "Request" form together with the smear results and returned to the OPD or TB ward. The serial number shall start with number 01 in January and ends 31st December each year. Follow-up sputum specimens will not need a new serial number as the previous number must be used.

3. TB Patient Register

The State TB Co-ordinators (or someone else delegated to do this task), registers the patients whenever they are admitted for treatment. The State TB Co-ordinators, based on the information from the treatment card and laboratory register, will also update information on each patient. The results of sputum examinations are also entered into this register. All forms of TB should be registered in this register. Monitoring of treatment and treatment outcome for every patient is completed regularly soon after the patient finishes treatment. This is done from the complete copy of the treatment card once it is received from the supervising treatment partner at the completion of the continuation phase of treatment.

4. Tuberculosis Treatment Card

When a presumptive case is confirmed to have TB, the TB nurse in-charge or the medical officer at the TB ward making the diagnosis completes the tuberculosis treatment card. There are two sides to the card.

Side one of the card records information regarding the treatment regimen (for the intensive and continuation phases), DOTS worker, TB /HIV treatment and treatment outcome. For each day that the patient is observed to take their medication the DOT worker must put a cross in the date box.

The second side of the card contains information on the demographic data of the patient, disease classification, type of patient, other health conditions and laboratory examinations results. It is important that the card is filled in as completely as possible.

If the patient transfers to another DOTS centre the treatment card should be sent to the receiving health care facility and a copy should be kept with the sending DOTS centre.

5. Quarterly Workload Statistics and Performance Indicators Report (laboratory)

The *Quarterly Workload Statistics and Performance Indicators Report* should be filled in on a quarterly basis by the TB laboratory technician. They should also calculate the performance indicators. Once completed the TB laboratory technician should use the information to assess performance and if any issues related to poor performance exist these should be fixed. The *Quarterly Workload Statistics and Performance Indicators Report* should be sent to the State TB Co-ordinator, the National TB Program Manager, Diagnostic Laboratory Services and the Regional Laboratory Co-ordinator (Pacific Island Health Officer's Association).

6. Interjurisdictional Notification Form

The*Interjurisdictional Notification Form* is used when a TB patient is transferred from Palau out to another DOTS centre. It should be completed by the NTP staff sending the TB patient and is faxed ahead of time to the receiving DOTS centre. A list of all national TB programs in the Pacific is found on the Secretariat of the Pacific Community website (and a list of all of the national TB programs in US affiliated Pacific islands and mainland US states is available on the National TB Controllers Association website (http://tbcontrollers.org/?p=10).

EpiAnywhere™

EpiAnywhere™ is a web-based, case-level TB surveillance, reporting, and analysis tool. PALAU uses EpiAnywhere™ to record individual patient data and each patient that is registered in the TB Register should be entered into EpiAnywhere™. Information entered into EpiAnywhere™ is used to track cases, analyze TB trends and program performance, and reports case data automatically to national and international health authorities.

EpiAnywhere™ contains an electronic copy of the *Report of a Verified Case of Tuberculosis* (RVCT) form. The RVCT is the national surveillance form used by the Division of TB Elimination, CDC and is used in all states and territories of the United States. An online RVCT should be completed for each verified case of tuberculosis. The RVCT comprises three data collection reports:

1. Report of Verified Case of Tuberculosis
2. Initial Drug Susceptibility Report (Follow-up Report), and
3. Case completion Report (Follow-up Report 2).

The two follow up reports supplement the RVCT. The three reports in the RVCT form are not necessarily completed for all patients and are not completed all at one time.

The RVCT includes data about patient demographics, laboratory results and risk associated with TB. It should be completed for all patients with a verified case of TB disease and is competed over time.

The *Initial Drug Susceptibility Report* includes genotyping information and drug susceptibility testing results and should be completed for all patients who has a positive culture result for *Mycobacterium tuberculosis* complex and should be completed after the susceptibility test results are received. It should not be completed for patients with a negative culture or no results for culture.

The *Case Completion Report* includes treatment outcome information and should be completed for all patients who were alive when TB was diagnosed. The case completion report is due no later than 2 years after the initial RVCT.

Further information on CDC definitions and the RVCT is available in EpiAnywhere™. National TB Program staff in Palau have been trained on the use of the RVCT and on how to use EpiAnywhere™.

Indicators

Annex 6 includes a list of key TB control indicators that make up a minimum set of indicators for assessing the performance of the NTP.

Supervision

Supervision is an activity which must be conducted on a regular basis. The aim of supervision is to identify factors that inhibit or enhance implementation of NTP policies and to ensure that weaknesses are corrected so as to provide motivation for staff and ultimate achievement of the program's goals and objectives. During

supervisory visits, the weaknesses and strong points of current performance assessment should be discussed and compared with the previous assessment. Praise and recognition where it is due should be given and action points for further improvement as well as actions for resolution of problems clearly stated. Monitoring regarding the implementation of these remedial action points should also be done.

Cohort analysis

A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually one quarter of a year). Evaluation of treatment outcome in new smear-positive pulmonary patients is used as a major indicator of program quality. Outcome in other patients (pulmonary smear-negative, extrapulmonary, re-treatment) is analysed in separate cohorts.

Evaluation of the results of treatment and trends must be done at the state and national levels to allow any necessary corrective action to be taken. It can also identify states or areas who are performing well and allows for positive feedback to be provided to staff.

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