

International Council
of Nurses

TB GUIDELINES

**for Nurses in the Care
and Control of Tuberculosis
and Multi-drug Resistant
Tuberculosis**

3rd Edition



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Abbreviations

AFB	Acid-fast bacilli
ART	Antiretroviral therapy
BCG	Bacille Calmette Guerin
CPT	Co-trimoxazole prophylaxis therapy
CT	Computer tomograph
DOT	Directly observed treatment
DOTS	The internationally recommended strategy for TB control
DRS	Drug resistance surveillance
DST	Drug-susceptibility testing
EPTB	Extrapulmonary TB
FDC	Fixed-dose combination
G	Gram
GLC	Green Light Committee
HIV	Human immunodeficiency virus
ICN	International Council of Nurses
IGRA	Interferon-gamma release assay
ILO	International Labour Organization
IPC	Infection prevention and control
IPT	Isoniazid preventive therapy
IRIS	Immune reconstitution inflammatory syndrome
LPA	Line probe assay
LTBI	Latent TB infection
MDR-TB	Multi-drug resistant tuberculosis
Mg	Milligram
MRI	Magnetic resonance imaging
NGO	Non-governmental organisation
NTP	National TB Programme
PPE	Personal protective equipment
PTB	Pulmonary TB
RR-TB	Rifampicin-resistant TB
SL-LPA	Second-line line probe assay
TB	Tuberculosis
TST	Tuberculin skin test
The Union	The International Union Against Tuberculosis and Lung Diseases
UVGI	Ultraviolet germicidal irradiation
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis

Anti-tuberculosis drug abbreviations

Am	Amikacin
Bdq	Bedaquiline
Amx/Clv	Amoxicillin/Clavulanate
Cfx	Ciprofloxacin
Cfz	Clofazimine
Clr	Clarithromycin
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delaminid
E	Ethambutol
Eto	Ethionamide
FQ	Fluoroquinolone
Gfx	Gatifloxacin
H	Isoniazid
Imp/Cln	Imepenem/Cilastatin
Km	Kanamycin
Lfx	Levofloxacin
Lzd	Linezolid
Mfx	Moxifloxacin
Mpm	Meropenem
Ofx	Ofloxacin
PAS	<i>Para</i> -aminosalicylic acid
PAS-Na	<i>Para</i> -aminosalicylate sodium
Pto	Protionamide
R	Rifampicin
Rfb	Rifabutin
S	Streptomycin
T	Thioacetazone
Trd	Terizidone
Z	Pyrazinamide

Preface

Tuberculosis (TB) has reached epidemic proportions in many parts of the world. Nearly one and a half million people die every year from a disease that is curable and preventable in most cases, even in very resource poor settings. Everywhere in the world, nurses encounter patients with TB, suspected TB and those who have symptoms of the disease.

The information in these guidelines by the International Council of Nurses (ICN) is intended to help nurses in their important role of detecting TB cases, providing care and managing TB treatment. It sets out a nursing approach to planning and delivering patient care, aimed at improving access and quality of care throughout the treatment period.

These guidelines offer a review of TB and multi-drug resistant TB (MDR-TB). The new *End TB Strategy* (2016 – 2035) has been developed to replace and to continue the successes of the previous *Global Plan to Stop TB* (2011-2015) and the *Stop TB strategy* (2006-2011). Also included is an overview of organisational issues that can have an important impact on TB control programmes.

This publication is a continuation in a series of ICN products on TB and is intended to be a comprehensive guide for the busy nurse. Other ICN publications on TB address practice development with regard to TB care, TB-related stigma, infection prevention and control, and occupational issues. ICN trusts that the series will provide a complete understanding of TB and MDR-TB and strengthen nursing competence in tackling this growing epidemic.

The second edition of these guidelines was prepared by Gini Williams, former ICN TB Project Director. The revision of this third edition was prepared by Carrie Tudor, ICN TB Project Director, and Gini Williams.

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Introduction

The International Council of Nurses (ICN) prepared these guidelines to strengthen nursing capacity related to TB and to enhance the effectiveness of TB control measures worldwide. Because nurses play a crucial role in TB control programmes, it is essential for them to have a solid understanding of TB: its aetiology, pathogenesis, epidemiology and treatment, as well as the best practices for TB control. This strengthened understanding is essential in the light of the current resurgence of TB and drug-resistant TB in many countries.

Undetected and improperly treated cases of tuberculosis resulting from ineffective TB management are major reasons for the spread of the disease and the development of MDR-TB. More recently the emergence of extensively drug-resistant TB (XDR-TB) has added to the complexity of TB care and treatment. Ineffective TB management of this type often results from a scarcity of adequately trained personnel, poor capacity at a management level, and/or inadequate resources to sustain treatment.

If they are properly informed and mobilised, nurses can positively influence TB disease prevention and management, particularly because of their close involvement with patients. Some nurses specialise and work solely with TB programmes, but the vast majority work within general health services, encountering patients for a wide variety of reasons – pregnancy, injury, illness, or to receive immunisations. Thus, nurses are in an ideal position to detect previously unsuspected cases of TB, since the patients they see for other reasons may also have symptoms of TB.

This publication approaches TB control from a best practices perspective and provides practical TB information for nurses in their day-to-day work. A section on organisational issues gives the reader a useful perspective for managing TB control.

ICN believes that information is only valuable when it is utilised at the local level. Blending the measures of the expanded TB control strategy with local customs enhances nursing practice and provides the best of both worlds – standardised care that is individualised to meet the constraints and the needs of local nursing practice. ICN sincerely hopes that the best practice approach offered in these guidelines enhances TB control programmes in your local community and strengthens your own individual nursing practice.

Chapter 1: Tuberculosis: the Clinical Context

History of tuberculosis

Mycobacterium tuberculosis (TB) is as old as the human species. Fragments from the spinal column of Egyptian mummies dating from 2400 BC show definite pathological signs of tubercular decay. The name "tuberculosis" has been used from the middle of the last century.

Tuberculosis, also called phthisis or consumption, and nicknamed "white plague", first appeared in Greek literature. At around 460 BC Hippocrates described it as the most widespread disease of its time.

Exact aetiological and pathological descriptions of TB began to appear in the 17th Century when the earliest references to the infectious nature of the disease appeared in Italian medical literature. Although this allowed for some progress to be made towards prevention, a cure was still not within sight.

The introduction of the sanatorium provided the first hope for a TB cure. These special centres were located in areas with a healthier climate, where patients were continuously exposed to fresh air. Improving social and sanitary conditions and ensuring adequate nutrition were all that could be done to strengthen the body's defence against TB. It is still unknown whether sanatoria really helped people with TB. There were also many people with TB who could not afford to go to a sanatorium, and who died at home.

In 1865, a French military doctor, Jean-Antoine Villemin, demonstrated that TB could be passed from humans to cattle and from cattle to rabbits. On the basis of this evidence he postulated that TB was contagious and a microorganism was the cause of the disease.

In 1882, a German scientist, Robert Koch, discovered the *Mycobacterium tuberculosis* under the microscope and the fight against TB really began.

A further milestone came in 1895, when Wilhelm Konrad von Roentgen discovered radiation. Now the progress and severity of a patient's disease could be followed and reviewed.

The French bacteriologist, Albert Calmette, worked together with Camille Guérin to develop a vaccine against TB. By 1921, they had developed a bacillus harmless to man, yet with the ability to stimulate the production of antibodies. From 1924, the vaccination of newborns was practiced. The Bacille Calmette Guérin (BCG) vaccine is still used in immunization programmes today.

In 1943, in the middle of the Second World War, an American scientist, Selman A. Waksman, discovered streptomycin, an antibiotic that could

kill TB bacteria. In the following years, a rapid succession of anti-TB drugs appeared. This was essential because with streptomycin monotherapy, resistant mutants began to appear, endangering the success of antibiotic therapy. Following streptomycin, isoniazid (1952), pyrazinamide (1954), ethambutol (1962) and rifampicin (1963) were introduced as anti-TB agents. These anti-TB drugs are still used today and their application will be described later in greater detail. The effects of TB on the population during the last centuries and its current global situation and epidemiological trends will be described in the next section - Epidemiology of Tuberculosis.

Epidemiology of tuberculosis

TB caused great public concern in the 19th and early 20th centuries as the endemic disease of the poor. After the development of the antibiotic streptomycin in 1943, medical treatment rather than prevention became a possibility. Prior to this medical treatment, only surgical intervention was possible along with the purported benefits of sanatoria.

Following the development of effective treatment for TB in the 1950s the general view, especially in industrialised countries, was the disease no longer posed a public health threat (Raviglione, 2003, Frieden et al., 1995). In industrialised countries there was a steady decline in TB incidence from the 1950s to the 1980s. Due to the drop in TB cases many countries decreased funding for TB control programmes. As a result, there was a decline in successful treatment outcomes which gave rise to drug-resistant TB.

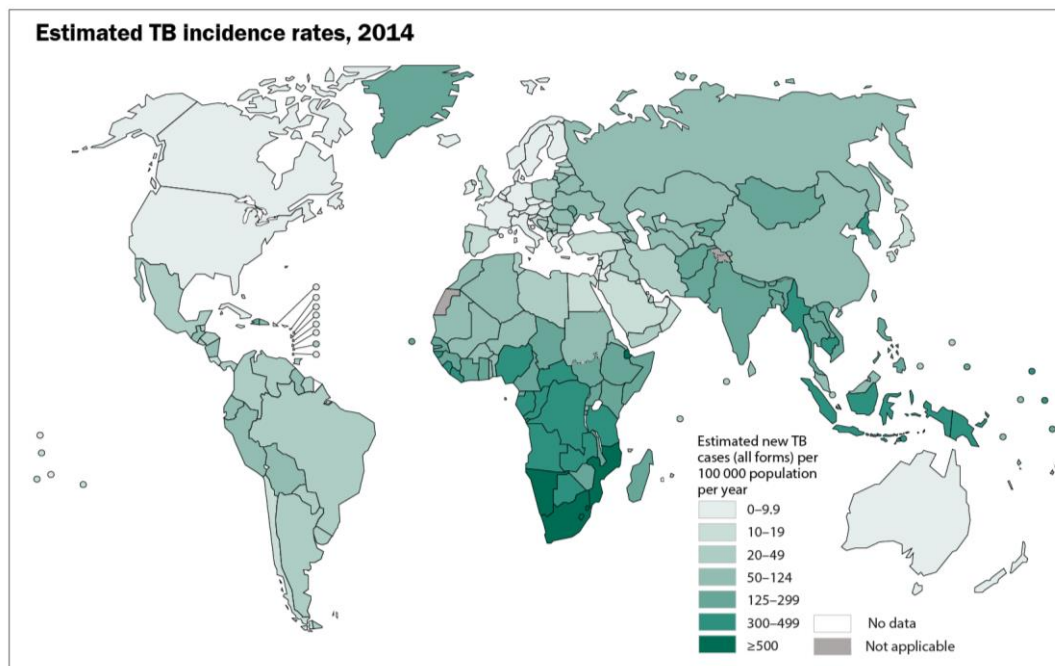
Increases in TB figures, seen in both the United States and Europe, were alarming in the late 1980s, highlighting the need to refocus efforts on TB control. The reasons for the increases in the USA were largely attributed to the rising rates of human immunodeficiency virus (HIV), worsening poverty in urban areas, decrease in funding for TB control programmes, and poor TB control practices. Hopes that TB could be completely eliminated have been dashed since the rise of multi-drug resistant strains in the 1980s. In Europe, the increases were mainly associated with urban poverty. In recognition of the fact that, in both the United States and Europe, increases in TB prevalence were associated with immigration from countries with high rates of TB, the disease had to be addressed as a global issue (Raviglione, 2003). In order to intensify efforts to limit its spread, in 1993, TB was declared a “global emergency” by the World Health Organization (WHO).

TB remains a major public health problem worldwide and is the second leading cause of death due to an infectious disease, second only to HIV/AIDS. While much progress has been made over the past 20 years since TB was declared a public health emergency, there is still much funding needed and work to do to control the disease. Since 1995, more than 56 million patients have been treated for TB resulting in an

estimated 22 million lives saved. In addition, the global TB mortality rate has decreased by 45% compared with 1990 rates. While progress has been made, TB will continue to remain a major killer for many years to come (World Health Organization, 2013c). The following figures from the WHO's *Global tuberculosis report 2015* (World Health Organization, 2015c) highlight the current state of the global TB epidemic:

- Two billion people, i.e. one-third of the total human population, are estimated to be infected with *M. tuberculosis*.
- 9.6 million new cases of TB occurred globally in 2014 including among 1.2 million living with HIV.
- TB remains a disease of poverty. Of the 9.6 million new TB cases in 2014, approximately 85% lived in Africa and Asia. The majority of TB cases (80%) occur in 22 countries and 95% of TB cases and deaths occur in low-resourced countries.
- In 2014, 1.5 million people died worldwide from TB including 400,000 individuals co-infected with HIV.
- In 2014, there were an estimated 480,000 new cases of multidrug-resistant TB (MDR-TB) worldwide however, only 110,000 were registered on treatment. It is estimated that there were 190,000 deaths due to MDR-TB globally in 2014.
- Between 1990 and 2012, the TB mortality rate decreased by 47%.
- TB is one of the leading causes of death among women of reproductive age and in 2014 nearly 3.2 million TB cases were among women resulting in approximately 480,000 deaths due to TB. Moreover, it is estimated that 140,000 women with TB/HIV died.
- In 2014 an estimated 1 million children were diagnosed with TB and 140,000 died from TB (HIV-negative children).

Figure 1. Map of global estimated TB incidence rates 2014



Source: (World Health Organization, 2014d, World Health Organization, 2015c)

Pathology

TB is a bacterial infection caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) also referred to as tubercle bacilli. The *M. tuberculosis* is a Gram-positive aerobic bacterium. It is a small rod-like bacillus with a complex cell wall, which can withstand weak disinfectants and survive in a dry state for weeks, but can only grow in a host organism.

It most commonly affects the lungs, producing pulmonary TB. However, transported by the blood or lymphatic system, the TB bacilli can infect almost any part of the body, including lymph glands, joints, kidneys, and bone - extrapulmonary TB. It is critical to understand the disease, its aetiology and its epidemiology to develop a strong TB control programme.

Early symptoms of pulmonary TB are often vague and easily attributable to other conditions, with the result that many cases of active, infectious TB can remain undetected for some time. Thus, the disease spreads from one person to another.

TB is spread when an infectious person coughs, sneezes, talks or sings, releasing droplets containing the bacilli into the air. However, TB can also be spread when TB bacilli are aerosolised by treatments, such as irrigating a wound that is infected with TB, organ transplants, or bronchoscopy. In either case, a susceptible person inhales the airborne droplets, which then traverse the upper respiratory tract and bronchi to reach the alveoli of the lungs. Once in the alveoli, alveolar macrophages take up the TB bacilli, holding some in the lungs, and

transporting others throughout the body. Usually within 2-10 weeks, the immune response limits further multiplication and spread of the bacilli.

Some patients may go on to active disease from this stage while others may be able to contain the infection and may never develop active TB. In the patients who contain the infection some may eliminate all the bacteria; however, in many of the patients, the bacilli remain dormant and viable for many years, resulting in a condition referred to as latent TB infection (LTBI). Persons with LTBI usually have positive TB skin tests but have no symptoms of the disease and are not contagious. See Table 1.1 for a list of differences between latent TB infection and active TB disease (Centers for Disease Control and Prevention, 2012). In fact, most people who are infected with TB never go on to develop active disease and therefore present no risk to the people around them.

Table 1.1: Differences between latent TB infection and TB disease

Latent TB infection	TB disease (active TB)
<ul style="list-style-type: none"> No symptoms 	<ul style="list-style-type: none"> Symptoms are present, which may include: <ul style="list-style-type: none"> Bad cough that lasts ≥ 2 weeks Pain in the chest Coughing up blood or sputum Weight loss Fever Night sweats Weakness or fatigue No appetite
<ul style="list-style-type: none"> Does not feel sick 	<ul style="list-style-type: none"> Usually feels sick
<ul style="list-style-type: none"> Not contagious 	<ul style="list-style-type: none"> Contagious
<ul style="list-style-type: none"> Tuberculin skin test (TST) or blood test (IGRA) results will be positive indicating TB infection 	<ul style="list-style-type: none"> Tuberculin skin test (TST) or blood test results will be positive indicating TB infection
<ul style="list-style-type: none"> Chest x-ray is negative and a negative sputum smear 	<ul style="list-style-type: none"> Possible abnormal chest x-ray, or positive sputum smear, Xpert[®] MTB/RIF or culture
<ul style="list-style-type: none"> Treatment for latent TB infection to prevent active TB disease 	<ul style="list-style-type: none"> Treatment to treat active TB disease

Adapted from (Centers for Disease Control and Prevention, 2012)

Pulmonary TB

Pulmonary TB (PTB) is the most common and potentially most contagious type of active TB. Small areas in the lung infected with the bacilli gradually merge to form a bigger lesion filled with infected material. This material can become liquid, which is then coughed out, leaving a cavity in the lung (Rieder et al., 2009). The process continues causing extensive damage to the lung tissue and its blood vessels, generating more infectious material and inflammation – the damage to blood vessels can result in some patients coughing up blood

(haemoptysis). Some healing may occur in parts of the lung resulting in scar tissue.

In the early stages of this process, someone with pulmonary TB may well not be infectious and have few easily definable symptoms. As the disease progresses and causes more damage, they will become infectious and experience worsening symptoms. The challenge is to identify people in the early stages to prevent transmission.

Extrapulmonary TB

Extrapulmonary TB (EPTB) is TB that occurs outside of the lungs and it is estimated to account for 20 to 25% of all TB cases globally (World Health Organization, 2009a). EPTB can affect any organ in the body including:

- cervical lymph glands (most common)
- bone (particularly the spine)
- pleural cavity (causing pleural effusion)
- kidney and genitourinary tract
- intestines and peritoneum
- pericardium
- meninges
- skin

Although extrapulmonary TB is treatable in most forms, the lasting damage may be permanently crippling (in the case of spinal TB) or even fatal (in TB meningitis). Bacillary load, extent of disease and anatomical site determine the severity of EPTB. One of the most lethal forms of tuberculosis is TB meningitis.

Some forms of extrapulmonary TB are more common in particular geographical areas, ethnic groups or age groups. By knowing the most common types of EPTB in the local community, the nurse is more alert to the symptoms and may detect a case of extrapulmonary TB that would otherwise have gone unnoticed. Extrapulmonary TB is also common in patients infected with HIV.

Signs and symptoms of pulmonary and extrapulmonary TB

The symptoms of pulmonary and extrapulmonary TB may differ but some are common to both. Most people have only a few of these symptoms. It is recommended that anyone reporting a cough which has lasted for two or more weeks should have their sputum tested for TB. However, for patients living with HIV, it is recommended to test their sputum for TB if they have had a cough of any duration. As a general rule, the presence of three or more symptoms for two or more

weeks increases the suspicion of any form of the disease. Common signs and symptoms of both pulmonary and extrapulmonary TB are detailed in Table 1.2.

Table 1.2: Signs and symptoms of TB

General symptoms	Pulmonary symptoms	Extrapulmonary symptoms
Fever	Dry or productive cough	Localised pain/swelling (depending on site of disease)
Night sweats	Chest pain	
Weight loss	Shortness of breath	
Fatigue	Traces of blood are coughed up in the sputum (haemoptysis)	
Loss of appetite		

Risk factors for TB

Risk factors combined with TB symptoms are strong indicators for further diagnostic workup and early detection of the disease.

Some of the main risk factors for TB include:

- history of TB
- contact with a known TB case, e.g. family member or friend
- compromised immunity due to illness, e.g. HIV infection, cancer or diabetes
- compromised immunity due to medications such as steroids
- migration from a country with a high incidence of TB
- history of travel to an area with a high incidence of TB
- smoking
- alcohol and/or drug abuse
- malnutrition
- homelessness

Managing and preventing risks

Those who are responsible for managing TB programmes must consider the five levels that can be ascribed to the risks of TB transmission and progression. The risks must be considered in relation to the population of the region and local community, but also how they apply to the nurses and other TB programme staff. The risk levels are the following (Rieder, 1999):

- 1) the risk of exposure
- 2) the risk of infection
- 3) the risk of developing active disease
- 4) the risk of developing drug-resistant TB (MDR-TB/XDR-TB), and
- 5) the risk of death

The number and severity of risk factors present in any given community affects the epidemiology of TB disease in that community. Successful TB control programmes recognise, assess and manage these risk factors effectively.

Risk of exposure

The risk of exposure is associated with the frequency and duration of contact with an infectious case of TB/MDR-TB.:

- Exposure is very much linked to time spent with potentially infected individuals in confined and poorly ventilated spaces, and overcrowded accommodation due to poverty or social norms of living together in extended family groups; working conditions; and other social habits and behaviours, e.g. communal drug-taking.
- A higher risk of exposure to TB is also associated with urban areas where people are living, travelling and working in cramped conditions.
- TB is more prevalent in residential institutions such as prisons, hostels, and healthcare facilities where accommodation may be overcrowded.
- The higher the prevalence of the disease in a community, the greater the likelihood of contact with an infected person, and the higher the risk of exposure to TB bacilli.

Risk of infection

The risk of infection depends on:

- numbers of TB bacilli inhaled
- duration of the exposure
- virility of the bacilli
- strength of the person's immune system (Rieder et al., 2009, Centers for Disease Control and Prevention, 1994).

For example, some people exposed to just a few TB bacilli may be naturally more susceptible and will develop active TB disease. Others when exposed to a large number of bacilli will only develop a latent TB infection. Others may be exposed, but develop neither a latent TB infection nor active TB disease.

The longer a person with active TB who is smear positive remains undetected and untreated, the higher the likelihood that others will be

exposed and infected. The more people there are living in overcrowded conditions with a person with undetected TB, the higher the risk of someone contracting the infection. It is estimated that individuals with active TB disease can infect between 10 to 15 people a year if not placed on appropriate treatment (World Health Organization, 2015f).

Risk of developing active disease

WHO estimates that one-third of the world's population is infected with *Mycobacterium tuberculosis* (World Health Organization, 2015f). In general, people who become infected with *M. tuberculosis* have approximately 5 to 10% risk of developing active disease in their lifetime and as high as 50% among those living with HIV (World Health Organization, 2015f). This risk is greatest during the first two years after infection. The risk of developing active disease relates to the individual's health status, and most particularly to the status of the immune system. HIV increases the risk of developing active TB once infected.

WHO estimated that approximately one-third of the 35 million people living with HIV at the end of 2012 had latent TB infection and were roughly 30 times more likely to develop active TB disease compared with persons without HIV (World Health Organization, 2014e). Other factors contributing to the risk of developing active disease, once the TB infection takes hold, are smoking (more than 20% of TB incidence may be due to smoking) (World Health Organization, 2009b); diabetes (World Health Organization and The International Union Against Tuberculosis and Lung Disease, 2011); exposure to smoke from biomass stoves (Perez-Padilla et al., 2001); Vitamin D deficiency (Wilkinson et al., 2000); malnutrition often associated with poverty, alcohol and substance abuse, and other debilitating conditions (Crofton et al., 1999). Internally displaced people, asylum seekers, migrant workers and refugees all face difficulties compounding their vulnerability to TB, including crowded and poorly ventilated housing, poor access to health and social care, and reduced personal security.

Risk of developing multi-drug resistant TB (MDR-TB)

The WHO estimates that approximately 3.5% of all new TB cases and up to 20% of retreatment cases worldwide have MDR-TB. Roughly 10% of all MDR-TB cases are estimated to be extensively drug-resistant TB (XDR-TB) cases. However, incidence of MDR-TB varies greatly by region and country. More than 50% of all MDR-TB cases in 2014 occurred in China, India, and the Russian Federation (World Health Organization, 2014d). Given the increasing trend toward globalisation, trans-national migration and tourism, all countries are potential targets for outbreaks of MDR-TB.

Risk factors for developing MDR-TB are:

- improper use of first-line anti-TB drugs;

- inadequate laboratory capacity to diagnose MDR-TB;
- patients who failed previous first-line treatment;
- new TB patients who remain smear positive after two or three months of anti-TB treatment;
- close contact with known MDR-TB case;
- poor infection control especially in healthcare facilities; and
- people who are living with HIV or other immunosuppression disease (diabetes).

Risk of death

Among infectious diseases, TB is a leading cause of adult mortality, resulting in more than one million deaths a year worldwide (World Health Organization, 2015c). In addition, TB kills more people with HIV than any other associated disease or opportunistic infection. Two main factors are the principal determinants of TB case fatality: 1) the site and type of disease; and 2) the appropriateness and timeliness of the intervention and care provided. Inadequate treatment is likely to result in early death: 30-40% of untreated sputum smear-positive TB cases will die within a year, and 50-60% will be dead within five years (Rieder, 1999). HIV infection, malnutrition and severe pulmonary disease are all associated with a greater risk of death from TB. Inadequate treatment for those suffering from drug-resistant TB (MDR/XDR-TB) also increases the risk of death.

TB and HIV

HIV is one of the main risk factors for developing active TB from both recently acquired and latent TB infection and poses one of the greatest challenges to TB control. In addition, TB is the most common opportunistic infection among people living with HIV. In 2014, WHO estimated that there were 1.2 million new cases of TB among people living with HIV worldwide and approximately 75% of these cases occurred in sub-Saharan Africa. More people living with HIV die from TB than any other condition accounting for about 24% of all HIV-related mortality (World Health Organization, 2015c). The association between the two diseases is so significant that one cannot be managed without consideration of the other.

With better care and treatment opportunities becoming available to those infected with HIV, there is now a greater incentive for individuals to know their HIV status. With adequate treatment, a TB patient who is co-infected with HIV is as likely to make full recovery from TB as a HIV-negative patient. The top priority must be early diagnosis of TB and effective and efficient treatment for both HIV and TB in order to give him/her the best chance of recovery. In recent years, many countries have begun to integrate TB and HIV care services to better treat co-infected patients. It is important for patients to know their HIV status and therefore all TB patients should be tested for HIV and all people

living with HIV should be regularly screened for TB and offered preventive therapy such as isoniazid preventive therapy (IPT) and co-trimoxazole prophylaxis (CPT) (World Health Organization, 2014e).

Those in the early stages of HIV infection are more likely to develop sputum smear-positive pulmonary disease and present in a similar way to their immuno-competent counterparts. In the later stages of HIV infection, due to suppression of the immune response, patients are more likely to be smear negative, or suffer from EPTB and present with less definable symptoms. Immuno-compromised patients with TB may present different clinical pictures, according to their level of immunodeficiency (Raviglione et al., 1997). In addition, TB skin tests may be negative and x-rays may not show the typical TB picture. In fact, in rare cases, x-rays may appear as normal (Centers for Disease Control and Prevention, 1994).

The WHO recommends regularly screening people living with HIV for the following four most common symptoms: (World Health Organization, 2013a)

- current cough
- fever
- weight loss
- night sweats

If a patient living with HIV presents with any one of the above four symptoms, they are to undergo further screening for active TB. Those patients living with HIV diagnosed with active TB should be screened for drug-resistant TB and started on appropriate anti-TB treatment as soon as possible. If it is determined that the patient does not have active TB, they should be counselled and offered IPT to protect them against developing active TB described below (World Health Organization, 2011a). See Annex 1 for an algorithm for diagnosing TB in HIV-positive adults and adolescents.

For more information, please see: *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource constrained settings*. WHO, Geneva, Switzerland. 2011: (http://who.int/tb/challenges/hiv/ICF_IPTguidelines/en/) and *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. WHO, Geneva, Switzerland June 2013: http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1

Numerous studies have found that starting TB patients co-infected with HIV on antiretroviral therapy (ART) within eight weeks of starting anti-TB treatment irrespective of CD4 count significantly improves TB treatment outcomes and significantly reduces mortality among co-infected patients compared with deferring the initiation of ART until after completion of TB treatment (Abdool Karim et al., 2010, Abdool

Karim et al., 2011, Blanc et al., 2011, World Health Organization, 2013a). Therefore, the most recent 2013 WHO guidelines recommend initiating ART naïve TB/HIV co-infected patients within eight weeks of starting anti-TB treatment including patients co-infected with MDR-TB/HIV. For patients with a CD4 count < 50 cells/mm³, it is recommended to initiate ARTs within the first two weeks of starting anti-TB treatment. However, it has been shown that co-infected patients with a CD4 < 50 cells/mm³ starting ARTs within two weeks of starting anti-TB treatment are more likely to experience immune reconstitution inflammatory syndrome (IRIS) (Abdool Karim et al., 2011, Havlir et al., 2011, World Health Organization, 2013a).

Please visit the following link for more information:

http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1

As TB and HIV are becoming increasingly common co-infections, nurses must follow national TB and HIV treatment guidelines and recommendations for treatment with ART and anti-TB treatment of co-infected patients. In addition, nurses should be familiar with preventive therapy such as IPT and CPT.

Isoniazid preventive therapy

Isoniazid preventive therapy (IPT) – the use of isoniazid to prevent latent tuberculosis infection from developing into active TB disease – has been shown to be effective in treating LTBI and has been used globally for many years in HIV-negative individuals (Comstock et al., 1967). More recently, IPT has been promoted for the prevention of TB among people living with HIV (World Health Organization, 2011a, World Health Organization and UNAIDS, 1998, World Health Organization, 2008b) and is estimated to reduce the incidence of TB among people living with HIV taking IPT by 32% (Akolo et al., 2010). Current WHO guidelines call for the provision of IPT for all individuals living with HIV regardless of TST results (World Health Organization, 2011a). The most recent WHO HIV guidelines released in 2013 recommend providing at least six months of IPT for any HIV-positive patient with either known positive TST or unknown TST with no signs and symptoms of active TB (World Health Organization, 2013a). However, individual national guidelines may differ and IPT should be provided based on current national guidelines.

For more information please visit:

http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf?ua=1

http://apps.who.int/iris/bitstream/10665/85321/1/9789241505727_eng.pdf?ua=1

Co-trimoxazole prophylaxis therapy

Co-trimoxazole is a broad-spectrum antibiotic comprised of sulfamethoxazole and trimethoprim used to treat a range of common opportunistic and bacterial infections among people living with HIV

such as *Pneumocystis jirovecii (carinii)* pneumonia (PCP), toxoplasmosis, etc. (World Health Organization, 2006b). The WHO recommends that all TB/HIV co-infected patients should be given co-trimoxazole (480 mg 1 tablet twice daily or 960 mg 1 tablet once daily) regardless of CD4 count. Co-trimoxazole prophylaxis therapy (CPT) has been shown to substantially reduce mortality among TB cases living with HIV (Harries et al., 2009, World Health Organization, 2006b, Uyei et al., 2011, Nunn et al., 2008).

It is important for the nurse to check for allergies to sulpha drugs and patients with such allergies should not be given co-trimoxazole prophylaxis therapy. Dapsone is the recommended alternative drug for those with sulpha drug allergies (World Health Organization, 2006b).

For more information please visit:

www.who.int/hiv/pub/guidelines/ctxguidelines.pdf?ua=1

TB and diabetes

Diabetes is estimated to affect 422 million people worldwide and approximately 80% of deaths due to diabetes occur in low- and middle-income countries – in many cases the same countries with a high burden of TB. The global prevalence of diabetes is expected to continue to increase in the foreseeable future. WHO estimates that roughly 15% of all TB cases also have diabetes and those with diabetes have a three-fold greater risk of TB compared with those without diabetes. In addition, patients co-infected with TB and diabetes are more likely to die while on TB treatment and are more likely to suffer a relapse following TB treatment than those who do not have diabetes.

All people with diabetes should be screened regularly for TB, especially in settings with a high burden of TB, in order to diagnose and treat TB early as a means to improve treatment outcomes and the control of both diseases. It is also recommended that TB patients should be screened for diabetes (World Health Organization and The International Union Against Tuberculosis and Lung Disease, 2011, World Health Organization, 2016b).

For more information please visit

http://whqlibdoc.who.int/publications/2011/9789241502252_eng.pdf, and http://www.who.int/tb/publications/diabetes_tb.pdf.

TB in children

In recent years there has been an increasing awareness of the major impact TB has on childhood morbidity and mortality worldwide, especially in high TB burden countries. According to the latest WHO estimates, the annual global burden of TB in children aged less than 15 years in 2014 was approximately one million cases, and that up to 140,000 children died from TB in 2014 – equating to approximately 200 children dying of TB every day. However, it is likely that the true burden

of childhood TB is underestimated, because in areas with a high HIV burden, children co-infected with TB and HIV are often classified as an HIV death (World Health Organization, 2015c).

The majority of TB cases among children occur in those less than five years of age. While infants and children are likely to suffer from more severe forms of TB, such as TB meningitis, the majority of children will suffer from pulmonary TB. Additionally, infants and children are more likely to experience a faster onset of disease than older children or adults and it is expected that 90% of children under five years old who become infected with TB will progress to TB disease within one year of infection. TB can often be difficult to diagnose in children because there is often considerable overlap of TB symptoms with other common childhood diseases resulting in many TB cases being missed, including the more severe and often fatal cases that present as severe pneumonia, malnutrition or meningitis. In countries with a high burden of TB, it is estimated that between 10 to 20% of all TB cases occur in children (World Health Organization, 2013c, World Health Organization, 2013e, The International Union Against Tuberculosis and Lung Disease, 2010).

TB in women

Women are greatly affected by TB, which is one of the top five causes of death among women of reproductive age. WHO estimates that the global burden of TB disease among women in 2014 amounted to approximately three million cases and 480,000 deaths. Women from Africa and Southeast Asia are most affected accounting for nearly 70% of all TB cases among women. Approximately 140,000 TB deaths among TB/HIV co-infected individuals were among women – approximately 50% of all such deaths in 2014 (World Health Organization, 2015c). In addition, it is believed that in 2012 approximately half of the estimated cases of TB among women were undetected which is greater than the estimated number of undetected cases in the general population (World Health Organization, 2014d).

It is important for nurses to routinely screen women of reproductive age for signs and symptoms of TB especially in high TB burden settings regardless of their HIV status. This can be done through prenatal and well-baby check-ups as well. It is important to get women diagnosed and on treatment as a means to protect them, but to also protect other family members including children (World Health Organization, 2014g).

Drug-resistant tuberculosis

Among the bacteria multiplying and causing disease in someone with TB, there will always be a few bacteria that will be resistant to any one of the anti-TB drugs. If only one drug is used, a population of bacteria resistant to this drug will develop. If more than one drug is used, then

any bacteria resistant to one drug will be dealt with by another. This is why it is recommended that TB is treated with multiple drugs.

A person may become infected with a TB strain that is already drug resistant. This is termed *primary drug resistance*. This is the principal reason why patients fail the standard six-month TB treatment regimen when properly administered. If multi-drug resistance develops while the person is receiving drug therapy, the resistance is called *acquired drug resistance*. It often develops because a patient is treated incorrectly or the patient is not able to adhere to the treatment regimen. In both cases, the patient has not been receiving a strong enough dosage of the drugs over a long enough period of time to kill the bacilli, so the organisms are given time to develop resistance to one or more of the drugs.

Drug-resistant TB can only be defined through laboratory confirmation of in vitro resistance to one or more anti-TB drugs. Results are defined according to the pattern of resistance – please see page 29 for more details.

Multi-drug resistant tuberculosis (MDR–TB)

Although MDR-TB varies widely across regions, it occurs in all geographical settings able to produce data and is therefore a significant global public health threat. WHO estimated the global prevalence of MDR-TB cases was roughly one million with approximately 480,000 new incident cases in 2013. China, India and the Russian Federation account for more than 50% of the annual incidence of MDR-TB cases (World Health Organization, 2014d). Of the estimated 480,000 new cases of MDR-TB in 2013, roughly 3.6% were new TB patients (primary drug resistance) and up to 20% had been previously treated for TB (acquired drug resistance) although these percentages can vary greatly by country. It is estimated that the average MDR-TB patient may infect up to 20 other people in her/his lifetime. In 2013, approximately 48% of MDR-TB patients who started treatment in 2011 were treated successfully (World Health Organization, 2014d).

Drug resistance can emerge from the improper use of first-line anti-TB agents in the therapy of drug-susceptible TB patients and is found in all countries. Some programmes do not yet have adequate laboratory capacity and resources for treating MDR-TB cases. Nonetheless, all TB programmes in poor-resourced areas should develop, in conjunction with a good TB control programme, adequate laboratory facilities to diagnose MDR-TB and an effective strategy for MDR-TB treatment. Treatment for MDR-TB is effective, feasible and cost-effective. Table 1.3 lists some of the most common causes of inadequate anti-TB treatment which may contribute to drug resistance.

Aside from the clinical care, the importance of maintaining a positive attitude towards patients and ensuring strong support for them throughout diagnosis and treatment cannot be underestimated.

Extensively drug-resistant tuberculosis (XDR-TB)

Extensively drug-resistant TB (XDR-TB) is a rare type of drug-resistant TB resistant to first- and second-line drugs. As a result, patients with XDR-TB are left with treatment options that are more toxic and less effective. However, if XDR-TB can be identified early, it can be treated and cured under proper TB control conditions. Successful treatment outcomes depend on the extent of the drug resistance, the severity of the disease and the immune response of the patient.

Table 1.3: Causes of inadequate anti-tuberculosis treatment

HEALTHCARE PROVIDERS: INADEQUATE REGIMENS	HEALTH SYSTEM ISSUES: INADEQUATE SUPPLY /QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
<ul style="list-style-type: none"> • Inappropriate guidelines • Noncompliance with guidelines • Absence of guidelines • Poor training • No monitoring of treatment • Poorly organized or funded TB control programmes 	<ul style="list-style-type: none"> • Poor quality • Unavailability of certain drugs (stock-outs or delivery disruptions) • Poor storage conditions • Wrong dose or combination 	<ul style="list-style-type: none"> • Poor adherence (or poor direct observed treatment (DOT)) • Lack of information • Lack of money (no treatment available free of charge) • Lack of transportation • Adverse effects • Social barriers/stigma • Malabsorption • Substance dependency disorders

(World Health Organization, 2008a)

XDR-TB strains have been found in all regions of the world and, as of late 2014, 100 countries had reported at least one XDR-TB case. While XDR-TB remains rare, in some parts of the world 19% of MDR-TB cases had XDR-TB and in 2013 WHO estimated that globally approximately 10% of all MDR-TB cases are XDR-TB (World Health Organization, 2015c). This percentage varies by country and region and is likely an underestimate based on the lack of second-line drug-sensitivity testing capabilities in many countries.

XDR-TB remains a grave global public health threat, especially in populations with high rates of HIV and drug-resistant TB. In 2013, approximately 3,000 XDR-TB patients worldwide were reported to be on treatment (World Health Organization, 2014d). XDR-TB is most often a result of a poorly functioning TB control programme and poor management of MDR-TB. The best way to prevent XDR-TB is to ensure prompt diagnosis of pulmonary TB and drug-resistant TB (both RR-TB and MDR-TB) in the early stages of disease and successfully manage, treat, and cure patients with both drug-susceptible and drug-resistant TB. Effective infection prevention and control measures in

health facilities play a key role in preventing nosocomial transmission. Moreover, there is a need for the development of new TB diagnostics, treatments and vaccines, since the current tools are outdated and insufficient. In 2008 an international response to the XDR-TB emergency began with the establishment of a WHO Global Task Force on XDR-TB. The recommendations of this Task Force can be found at the following website:
http://whqlibdoc.who.int/hq/2007/WHO_HTM_TB_2007.375_eng.pdf

Chapter 2: Global Measures for Tuberculosis Control

The End TB Strategy (Post-2015 Global Tuberculosis Strategy)

While wealthy industrialised countries with good public healthcare systems can be expected to keep TB under control, in much of the developing world the disease remains an urgent public health problem and is the second leading cause of death globally.

A concerted effort has been made by the WHO together with national TB programmes to expand the coverage of effective TB control measures based on first the DOTS (Direct Observed Therapy Short Course) strategy and then the broader Stop TB Strategy through the *Global Plan to Stop TB 2006-2015*. This concerted effort has meant that since the 1990s the TB mortality rate has decreased by 45% resulting in an estimated 22 million lives saved and 56 million patients cured. However, even though the incidence of new cases is coming down, the decline is still too slow and there remains an alarming increase in all forms of drug-resistant TB, so there is no room for complacency.

The WHO has approved a new strategy to continue the fight against TB – *The End TB Strategy*. This new strategy builds on previous strategies with a much greater emphasis on patient-centredness and the need to work with a much broader range of partners to address ongoing challenges. It will form the basis of a new *Global Plan to Stop TB* which is being devised under the leadership of the Stop TB Partnership.

The incidence of TB currently is declining at a rate of 2% per year and, in order to meet the target of a 90% reduction in incidence by 2035, this rate of decline will need to be increased to approximately 10% per year (World Health Organization, 2015a). *The End TB Strategy* also calls for a 95% reduction in mortality due to TB compared with 2015 and no families or patients afflicted with TB should suffer catastrophic costs due to TB. In order to reach these targets the WHO has adopted the following principles: 1) government stewardship and accountability, with monitoring and evaluation; 2) a strong coalition with civil society organisations and communities; 3) protection and promotion of human rights, ethics and equity; and 4) adaptation of the strategy and targets at country level, with global collaboration.

The strategic framework is comprised of three main pillars and components (World Health Organization, 2015a):

1. Integrated, patient-centred care and prevention

- a. early diagnosis of TB including universal drug-susceptibility testing and systematic screening
 - b. treatment of all people with TB (including drug-resistant TB) and patient support
 - c. collaborative TB/HIV activities and management of co-morbidities
 - d. preventive treatment of individuals at high risk
2. Bold policies and supportive systems
- a. political commitment with adequate resources for TB care and prevention
 - b. engagement of communities, civil society organisations, and public/private care providers
 - c. universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
 - d. social protection, poverty alleviation and actions on other determinants of TB
3. Intensified research and innovation
- a. discovery, development and rapid uptake of new tools, interventions and strategies
 - b. research to optimise the implementation and impact and promote innovation

Figure 2. Post-2015 global tuberculosis strategy: Pillars and Principles (World Health Organization, 2015b)



Source: *WHO Gear up to end TB: Introducing the End TB Strategy* (World Health Organization, 2015b)

For more information on the current global TB strategy, please visit: www.who.int/tb/End_TB_brochure.pdf?ua=1. The WHO has also published an implementation guide on how to implement the new End

TB Strategy titled: *Implementing the end TB strategy: the essentials* (http://www.who.int/tb/publications/2015/end_tb_essential.pdf) (World Health Organization, 2015d).

WHO has declared MDR-TB a global health risk and drafted priority actions to address this threat (World Health Organization, 2014c).

Five priority actions to address the global MDR-TB crisis are to:

- prevent MDR-TB through strengthening drug-susceptible TB treatment control programmes
- scale up rapid diagnosis of drug-resistant TB cases
- ensure immediate access to MDR-TB treatment
- prevent transmission through effective infection prevention and control
- ensure political will and funding

Table 2.1 The WHO End TB strategy indicators and selected targets

<i>Vision</i>	A world free of TB <i>(zero deaths, disease and suffering due to TB)</i>		
<i>Goal</i>	End the global TB epidemic		
<i>Indicators</i>	Milestones		Targets
	2020	2025	2035
<i>Reduction in number of TB deaths compared with 2015 (%)</i>	35%	75%	95%
<i>Reduction in TB incidence rate compared with 2015 (%)</i>	20% (<85/100,000)	50% (<55/100,000)	90% (<10/100,000)
<i>Percentage of TB-affected families experiencing catastrophic costs due to TB</i>	0	0	0

Source: *The WHO End TB strategy* (World Health Organization, 2015a)

The Stop TB strategy (2006 – 2015)

While new tools such as drugs and vaccines were recognised as essential to combating TB in the longer term, WHO understood that the targets set for 2015 would only be achieved if more people had access to existing good quality diagnosis and treatment. For this reason, *The Global Plan to Stop TB 2006 - 2015* adopted the WHO-recommended *Stop TB Strategy* which consisted of the following six key elements:

1. Pursue quality DOTS expansion and enhancement (based on the five elements of the DOTS strategy), improving case-finding and cure through an effective patient-centred approach to reach all patients, especially the poor.
2. Address TB/HIV, MDR-TB and other challenges, by scaling up TB/HIV joint activities, DOTS-Plus, and other relevant approaches.

3. Contribute to health system strengthening by collaborating with other health programmes and general services, for example in mobilising the necessary human and financial resources for implementation and impact evaluation, and in sharing and applying achievements of TB control.
4. Involve all care providers, public, nongovernmental and private, by scaling up approaches based on a public-private mix, to ensure adherence to the International Standards for TB Care (TB CARE I, 2014).
5. Engage people with TB and affected communities to demand, and contribute to, effective care. This will involve scaling up community TB care; creating demand through context specific advocacy, communication and social mobilisation; and supporting development of a patients' charter for the TB community.
6. Enable and promote research for the development of new drugs, diagnostics and vaccines. Research will also be needed to improve programme performance.

While the *Stop TB Strategy* ends in 2015, the need to provide care to all TB patients, whether the disease is caused by drug-susceptible or drug-resistant bacilli continues. Nurses are absolutely crucial to ensuring the successful treatment of patients continues.

The DOTS strategy (1995 – 2005)

The DOTS strategy (1995 – 2006) remained at the heart of the *Stop TB Strategy* and continues to be a guide for good TB management and is consistent with many components of Pillar 2 of the new *End TB Strategy*. It combines five elements or essential principles that must be fully implemented to achieve effective TB control:

1. Political commitment to effective TB control.
2. Case detection by bacteriological confirmation (sputum smear microscopy, Xpert MTB/RIF, culture, etc.) among symptomatic people.
3. Standardised treatment regimen of six months with first-line anti-TB drugs, administered under proper case management conditions.
4. Uninterrupted supply of all essential anti-TB drugs.
5. Standardised recording and reporting system, allowing monitoring and evaluation of treatment results.

1. Political commitment

Only political commitment to the TB control programme can ensure its successful implementation. Political support at community, regional, national and global level will provide technical guidance, and required financial and human resources. Sustainable partnerships will guide the

achievement of short, middle and long-term goals in fighting TB. Concerted efforts of communities, non-governmental organisations, faith-based organisations and patient groups can improve political commitment and increase access to care.

2. Case detection and monitoring by sputum smear microscopy

In order to control TB effectively, it is necessary firstly to reduce the infectious pool in the community by finding and treating the most infectious cases. While sputum smear microscopy remains a reliable and cost-effective method of identifying infectious cases of TB, the Xpert MTB/RIF test is becoming more widely used as the initial method for diagnosis. This varies between and within countries and in all circumstances nurses need to be aware of and follow local policies. Some countries and settings have rolled out the Xpert MTB/RIF for initial diagnosis.

3. Standardised treatment regimen

The objective of anti-TB treatment is to cure as high a percentage of smear-positive patients as possible. Well-run programmes can cure greater than 90% of all detected smear-positive cases.

The main requirements for adequate anti-TB treatment are the:

- right combination of anti-TB drugs,
- right dosage,
- right schedule, taken regularly without interruption,
- right length of treatment,
- patient entry is not in a critical or severe condition, and
- bacilli are not resistant to isoniazid and rifampicin.

Establishing a treatment regimen that is adequate and adapted to the situation of the individual patient can be facilitated by placing each patient on appropriate TB treatment. The diagnostic classifications are used for each new or current TB patient, and they can be modified to account for culture and drug-susceptibility testing (DST) results obtained.

4. Regular, uninterrupted drug supply

Since it is imperative for a TB patient to complete a full, uninterrupted course of treatment to prevent drug resistance, and since in most countries TB drugs are procured centrally with a nation-wide system for ordering and distribution, the government must commit to organise and manage resources to ensure a consistent supply of drugs. Enough medication to effectively treat all patients is based on the number of cases detected and on the roster, including a reserve amount. This is imperative to prevent treatment interruptions. Thus, accurate reporting and recording systems are vital. Also, security is essential for storage

and transport of supplies. Drugs must be protected from adverse conditions, such as extreme temperatures, water damage, accidents, animal interference, etc. Governments must ensure that they are procuring quality medications from trustworthy manufacturers. The Global TB Drug Facility (GDF) is available to help governments and non-governmental organisations procure a continuous supply of quality TB drugs.

5. Standardised recording and reporting systems

Standardised recording and reporting systematically evaluate patient progress and treatment outcome and give a picture of how the programme is performing overall. There are four essential components: the laboratory register, the patient treatment card, the TB register and quarterly reports. These components should be able to be cross-checked to evaluate completeness, accuracy and promptness of record keeping, and programme accountability.

- The **laboratory register** logs all patients who have submitted a sputum sample for analysis by biological examination (smear, Xpert MTB/RIF) or by culture and sensitivity testing. Completed by the laboratory technician, it includes basic patient details, dates of the tests and results.
- **Patient treatment cards** contain basic patient details and clinical information, including the medication, dosage and dates prescribed for each patient. The card has a calendar grid for recording each dose of medication, allowing the nurse and the patient to see the treatment status, get timely sputum tests and ensure adequate medication supplies. The treatment card is an important indicator of treatment completion and is particularly important if the patient is unable to produce a sputum specimen at the end of the treatment or if the TB was extrapulmonary. If medications are self-administered or supervised at home, the patient or a family member maintains the card and needs training to use it.
- The **TB patient register** lists all persons who have been diagnosed with TB, including drug resistance (RR-TB, MDR-TB, or XDR-TB), HIV status, anatomical site of TB, and previous history of TB and who are under treatment at a particular facility. It is maintained locally and allows the facility to monitor its own performance. This register feeds into a district registry that enables monitoring of the TB situation at district level, as well as consolidating information about the overall epidemic.
- **Quarterly cohort analysis** includes data on all TB patients registered during a three-month period. This type of report enables health facilities to monitor their performance, identify and address local problems, and order appropriate quantities of drugs and supplies. At a district and national level, cohort analysis compares TB programme progress to TB control targets.

The DOTS strategy and drug-resistant tuberculosis

The DOTS framework with its five elements also applies for the management of drug-resistant TB. DOTS programmes ensure that second-line drugs are used safely and appropriately within a comprehensive management system. Without this strategic approach, drug supplies may become erratic, recording is likely to be inadequate, and the use of second-line drugs risks inconsistent, which can lead to second-line drug resistance. Second-line drugs should only be used by a project that follows the published WHO protocols for standardised or individualised DOTS treatment regimens for MDR-TB (World Health Organization, 2009a, World Health Organization, 2011b). Effective TB control based on the DOTS strategy is the first step in the fight against drug resistance.

Chapter 3: Diagnosis of Tuberculosis

Screening tests for TB

Systematic symptom screening for active TB is recommended to detect TB early and get patients initiated on appropriate treatment as soon as possible. In general clinical settings in high-burden TB and TB/HIV settings, it is recommended to use a standard screening tool for all patients at each clinic visit (or hospital admission) to screen for common symptoms of TB (cough, unexplained loss of weight, night sweats, and persistent fever) and to collect sputum samples from those with symptoms for testing. (World Health Organization, 2013f). See Annex 2 for a sample screening tool.

For more information on the systematic screening of patients for active TB, please visit:

www.who.int/tb/publications/Final_TB_Screening_guidelines.pdf.

Tuberculin skin test (TST): In this test, a substance called tuberculin is injected into the skin of the arm. Tuberculin is protein derived from tubercle bacilli that have been killed by heating. In most infected people, the immune system will recognise the tuberculin because it is similar to the tubercle bacilli that caused infection. This will cause reaction to the tuberculin. A positive TST reaction does not distinguish between TB infection and active TB disease and a negative TST reaction alone does not rule out TB disease.

The TST is read by measuring the induration in millimetres. A TST is considered to be positive if:

≥ 5 mm induration	≥ 10 mm induration
<ul style="list-style-type: none">patients living with HIV or those who are severely malnourished	<ul style="list-style-type: none">children irrespective of BCG immunisation
<ul style="list-style-type: none">those who have a history of recent contact with a known TB case	<ul style="list-style-type: none">those who work in high-congregate settings (like prisons, healthcare facilities, etc.)

- TST results take 48 -72 hours and require two patient visits (once to have the TST set and again 48-72 hours later to have the TST read).
- The test is inexpensive and does not require special laboratory infrastructure.

Interferon-gamma release assay (IGRA): The WHO also recommends this blood test to screen for latent TB infection. The IGRA

tests for an immune response to the TB bacilli from a prior exposure to TB but does NOT detect actual TB bacilli.

- IGRA results take 24-48 hours.
- It is more expensive and technically challenging than TST requiring special laboratory resources.

It is important to note that while both TST and IGRA can be useful in identifying patients who have been exposed to TB and may require additional work-up to rule out active TB, **the TST and IGRA should not be used to diagnose active TB**. Additionally, these tests do not predict which patients will develop active TB disease (World Health Organization, 2011c).

Diagnosis of pulmonary TB

Several measures are used to diagnose pulmonary TB, the most common and infectious form of the disease. The most common method used to diagnose pulmonary tuberculosis is sputum smear microscopy which will diagnose the most infectious cases, i.e. those that are sputum smear positive. A new molecular diagnostic test is now being used called Xpert MTB/RIF (also called GeneXpert) which can confirm the presence of *M. tuberculosis* as well as rifampicin resistance. If facilities are also available for drug-sensitivity testing, it will be possible to identify drug resistance. Culture remains the gold standard for diagnosing TB. Different methods for diagnosing TB are described below.

For accuracy of diagnosis, at least two quality sputum specimens should be taken from someone presumed to have TB. Ideally, the initial specimen is collected at the first patient interview under the nurse's supervision and, if possible, it is recommended for the other sputum specimen to be an early morning specimen. Depending on the availability of laboratory services, if acid-fast bacilli (AFB) are seen on direct microscopy, the specimen should be cultured to confirm the identity of the bacilli and check their sensitivity to first-line anti-TB drugs, especially isoniazid and rifampicin. If AFB are not seen and laboratory services allow, the sputum specimen should be cultured before being considered negative, or evaluated using Xpert MTB/RIF, if available (World Health Organization, 2009a). In countries and settings where Xpert MTB/RIF is used as the initial test, these recommendations may vary and it is important to follow the national guidelines.

The tubercle bacillus has a number of unique properties. It has an unusually thick cell wall, which is impermeable by acids, alkalis and detergents, and it is very slow growing. This means that specific tests are required to investigate TB. To confirm active disease, the patient's sputum must be examined.

- **Sputum smear microscopy:** *M. tuberculosis* is identified microscopically by its staining characteristics: it retains certain stains after being treated with acid solution. Therefore, it is classified as an “acid-fast bacillus” (AFB). The most common staining technique is the Ziehl-Neelsen stain. AFB are stained bright red, which stands out clearly against a blue background. Auramine staining followed by fluorescence microscopy is faster although not universally available.
- **Xpert MTB/RIF:** The newest diagnostic test for TB, Xpert MTB/RIF is a rapid molecular diagnostic test useful for detection of *M. tuberculosis* and rifampicin resistance which is used as a proxy for MDR-TB. This test can provide results within two hours. Introduced in 2010, the Xpert MTB/RIF was available in more than 100 countries as of June 2014. This test is also helpful in diagnosing TB among patients living with HIV who are more likely to be sputum smear negative (World Health Organization, 2014f, World Health Organization, 2014d).
- **Molecular-amplification assays**
 - **Line probe assay (LPA):** A molecular test used for rapid detection of MDR-TB. Results are available within one to two days and include drug-sensitivity testing for isoniazid and rifampicin.
 - **MTBDRsl or second-line LPA (SL-LPA):** A rapid molecular DNA-based test that can detect genetic mutations in MDR-TB strains which make them resistant to fluoroquinolones and injectable second-line anti-TB drugs. This test can also be used to detect XDR-TB. Results are available within one to two days; much faster than current culture methods which can take up to two months (World Health Organization, 2016c).
- **Culture:** In addition to smear microscopy and Xpert MTB/RIF, all specimens should also be isolated and identified by means of a sputum culture. Culturing the specimen means growing the mycobacteria on media, substances that contain nutrients, in the laboratory. When the mycobacteria have formed colonies, they can be identified. Liquid culture is the preferred culture method over solid culture as it is more sensitive in detecting mycobacteria and provides more rapid results to drug-sensitivity testing.
- **Chest x-ray:** This is helpful to look for cavitations areas of consolidation and infiltration, enlargements of the hilar lymph nodes and pleural effusion in symptomatic patients found to be smear negative (World Health Organization, 2016a).
- **Computer tomography (CT) and magnetic resonance imaging (MRI):** These are useful for guiding the diagnosis process in some difficult cases, but frequently are not available.

Examples of the most commonly utilised tests and procedures to diagnose TB are listed in Table 3.1.

Table 3.1: TB Diagnostic tests and procedures

Pulmonary	Extrapulmonary
<ul style="list-style-type: none"> • Sputum smear microscopy • Sputum culture • Xpert MTB/RIF • Line probe assay (LPA) • Chest x-ray • Bronchoscopy • Imaging, e.g. by CT or MRI • Tuberculin skin test (TST) (most valuable in children) • Gastric washing (or gastric aspirate) (in children) 	<ul style="list-style-type: none"> • Biopsy at site • Fine needle aspiration at site • Lumbar puncture (if TB meningitis is suspected) • Imaging, e.g. by CT or MRI • Tuberculin skin test (TST) (most valuable in children)

Children are often treated empirically since it is harder to get a sputum specimen. Gastric lavage and/or bronchoscopy are not often used since it is not always fruitful and is difficult to do in many resource-poor settings (Shingadia and Novelli, 2003). See more information on the diagnosis of TB in children on page 33.

Diagnosis of extrapulmonary TB

The diagnosis of extrapulmonary TB can be difficult as it is less common than pulmonary disease and there may be numerous differential diagnoses. It is therefore essential to recognise the general symptoms of TB that are common to both pulmonary and extrapulmonary TB. Specific symptoms for extrapulmonary TB vary according to the site of disease but severe pain is common – this can be excruciating when it causes destruction in bones and joints.

In some cases, particularly with regard to TB of the lymph node, it may be possible to collect pus by aspirating the infected site. Biopsies may also be useful, but it is important to remember to send specimens for both histo-pathological as well as microbiological examination. If at all possible, diagnosis should be based on a culture-positive specimen, or historical or strong clinical evidence consistent with active TB, followed by a decision by a clinician to treat with a full course of anti-TB treatment. A list of diagnostic tests is included in the table above. There is likely to be varied availability of these tests especially imaging and culture, according to local resources.

Diagnosis of drug-resistant TB

A multidrug-resistant organism requires treatment with second-line drugs. While treatment of MDR-TB is more complicated, expensive and longer than treatment with first-line drugs, it has been proven

efficacious. Patients who are identified early with MDR-TB can have greater than an 85% chance of cure. The treatment is also feasible in low-resourced areas. It is extremely important to treat MDR-TB patients both to prevent their deaths and to prevent those who remain infectious from spreading drug-resistant TB in the community.

Good history taking is essential when people present with TB symptoms to determine previous TB treatment, its length and the drugs used. In addition, during history taking, the patient may reveal contact with someone who suffered from drug-resistant disease. This patient's sputum should be examined by Xpert MTB/RIF or cultured for drug-sensitivity testing when risk factors for MDR-TB are detected. In some areas there are no resources for culture and sensitivity testing, but in those settings, a history of inadequate treatment, or past treatment with only one drug, or a past default on treatment, followed by a return of symptoms, may be considered as reasonable suspicion that one is dealing with MDR-TB.

Drug-resistant TB can only be defined through laboratory confirmation of in vitro resistance to one or more anti-TB drugs. In well-resourced settings all specimens are sent for culture and drug-sensitivity testing, in areas where there are fewer resources, specimens of high-risk cases may be sent for further investigation but in some areas it is not possible to offer any culture and sensitivity testing. Results are defined according to the pattern of resistance as follows:

- **Mono-resistant TB:** TB in patients whose infecting isolates of *M. tuberculosis* are confirmed to be resistant to one first-line anti-TB drug.
- **Poly-resistant TB:** TB which is resistant to more than one first-line drug, other than isoniazid and rifampicin.
- **Rifampicin-resistant TB (RR-TB):** Active TB resistant to rifampicin, with or without resistance to isoniazid or other anti-TB drugs. This is a newer description following the rollout of the Xpert MTB/RIF rapid molecular diagnostic test.
- **Multidrug-resistant TB (MDR-TB):** Active TB which is resistant to at least both isoniazid and rifampicin, the two most powerful anti-TB agents; an MDR-TB strain can be resistant to more than these two antibiotics and in many cases patients are resistant to other first-line drugs as well.
- **Extensively drug-resistant TB (XDR-TB):** Active TB resistant to at least rifampicin and isoniazid, in addition to any fluoroquinolone (FQ), and to at least one of the three following injectable drugs used in anti-TB treatment: capreomycin (Cm), kanamycin (Km) or amikacin (Am).

Diagnosis of TB in children

Diagnosing TB in children can be difficult as many of the symptoms are similar to other more common childhood diseases like pneumonia. The most important role nurses can play in diagnosing TB in children is careful history taking. It is important to ask about symptoms of TB, as well about a history of a household or other close contact with a known or presumed case of active TB or contact with an adult who has had a chronic cough. Children less than five years old are more likely to have a household contact with active TB than older school-aged children who could potentially have been exposed to TB outside of the home (The International Union Against Tuberculosis and Lung Disease, 2010, World Health Organization, 2006a).

The most common symptom and clinical sign of pulmonary TB in children is a persistent cough and poor weight gain or failure to thrive. Younger children (less than one year of age) and children who are HIV-positive often present with acute pneumonia. Below is a list of the most common signs and symptoms of TB in children under 10 years old.

The approach to diagnosing TB in HIV-positive children is similar to that for HIV-negative children.

Common symptoms of TB in children < 10 years old

- persistent cough \geq 2 weeks that does not improve on its own or with antibiotics
- loss of weight or failure to thrive
- persistent fever > 10 days
- night sweats
- fatigue which may present as reduced playfulness
- respiratory distress – in severe cases

Because many children less than five years of age do not cough and produce sputum effectively, culture of gastric washings obtained by nasogastric tube lavage or induced sputum has a higher yield than spontaneous sputum (Shingadia and Novelli, 2003). Tuberculin skin tests (TST) can also be useful in supporting a diagnosis of TB in children with clinical symptoms suggestive of TB, but who are not able to produce sputum (The International Union Against Tuberculosis and Lung Disease, 2010).

Signs and symptoms and diagnosis of pulmonary TB among children under 10 years old and adolescents are similar to the symptoms present in adults. It is important to note that TB disease can be more severe and have a much faster onset in younger children and infants. Just as with adult TB cases, child TB cases should be screened for HIV in settings with high HIV prevalence (The International Union Against Tuberculosis and Lung Disease, 2010, World Health Organization, 2014a).

Box 1. Recommended approach to diagnose TB in children (World Health Organization, 2006a)

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
6. HIV testing (in high HIV prevalence areas)

For more information on diagnosing TB in children, please visit:

www.theunion.org/what-we-do/publications/technical/english/pub_tbdeskguide_eng.pdf,
http://whqlibdoc.who.int/hq/2006/WHO_HTM_TB_2006.371_eng.pdf?ua=1,
and www.who.int/tb/challenges/Child_TB_Training_toolkit_web.pdf?ua=1.

Contact investigation

In some countries, contact tracing is initiated at the initial assessment. The patient provides a list of those people closest to him/her. These people are then invited for screening: a symptoms check, a TST or sputum examination if TB symptoms are present. If resources are scarce, the patient is encouraged to identify anyone he/she knows who is showing signs or symptoms of the disease and to encourage them to come to the health clinic for investigation. At a minimum, all children under the age of five living in the patient's household are examined. Whatever the circumstances, this is a distressing process, since the patient may not want others to know that he/she has TB. Contact tracing offers a good opportunity to educate others about TB, infection control in the home, and address stigma, thus increasing the patient's support system. Contact tracing must always be conducted sympathetically, with the greatest possible effort to maintain confidentiality.

TB Classification

Once diagnosed, patients should be classified by whether they have had previous treatment for TB, and the outcome of this treatment. This helps to identify patients at increased risk of drug resistance and to prescribe appropriate treatment. In 2013, the WHO updated TB case definitions and reporting recommendations and now recommends national TB programmes use the following definitions detailed below and in Table 3.2 (World Health Organization, 2009a, World Health Organization, 2013b).

TB case definitions

- **Presumptive TB** refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a *TB suspect*).
- A **bacteriologically confirmed TB case** is a case with a confirmed biological diagnosis by smear microscopy (smear positive), Xpert MTB/RIF or other diagnostic tests, such as culture or LPA.
- A **clinically diagnosed TB case** is a case which cannot be confirmed bacteriologically but has been diagnosed with active TB by a clinician or other medical practitioner and the medical provider has prescribed a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. If a clinically diagnosed case is later confirmed to have TB by bacteriologic means either before or after starting TB treatment, they should be reclassified as a bacteriologically confirmed TB case (World Health Organization, 2013b).

Bacteriologically confirmed or clinically diagnosed cases of TB are further classified according to:

- anatomical site of disease
- history of previous treatment
- drug resistance
- HIV status

Classification based on anatomical site of disease

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs.

Patients with pulmonary TB are referred to as either smear positive or smear negative

This is an important distinction as smear-positive patients tend to have more advanced disease with more damage to their lungs so they cough up more infectious material and are therefore more contagious. Without treatment, the outcome of their disease is poorer than that of smear-negative patients.

Pulmonary TB; sputum smear positive (PTB+)

- is the most infectious form of TB
- refers to patients who have enough TB bacilli (AFB) in their sputum that they can be identified under a microscope when a Ziehl-Neelsen or auramine stain is used:
 - at least two initial sputum smear examinations need to be positive for AFB; or

- one sputum specimen AFB+ and radiographic abnormalities consistent with active pulmonary TB; or
- one sputum specimen AFB+ culture positive for TB bacilli
- one sputum specimen bacteriologically confirmed with Xpert MTB/RIF

Pulmonary TB; sputum smear negative (PTB-)

If a patient has symptoms suggestive of TB, at least two sputum examinations negative for AFB, and radiographic abnormalities consistent with active PTB, the patient should receive a full course of anti-TB therapy. Individuals living with HIV are more likely to be smear negative. If available, Xpert MTB/RIF should be used to diagnose TB in those living with HIV.

Knowing whether the patient is smear negative or smear positive is important for two reasons:

1. Sputum conversion from smear positive to smear negative or vice versa is one of the key indicators of a patient's progress and response to treatment.
2. The status of the sputum smear can determine how to allocate scarce resources. In such situations smear-positive patients take priority in treatment over less infectious smear-negative cases although every effort must be made to treat all cases of TB as soon as possible.

Extrapulmonary tuberculosis refers to any bacteriologically confirmed or clinically diagnosed case of TB occurring outside of the lungs and involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, joints and bones, meninges, etc.

A patient with **both** pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Classification based on HIV status

HIV-positive TB patient refers to any patient diagnosed with TB by bacteriologic or clinical means who is known to be HIV-positive or who has tested positive to an HIV test at the time of TB diagnosis. An HIV-positive TB case may or may not be on antiretroviral therapy.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. If a HIV-negative TB patient is later found to be HIV-positive, they should be reclassified as a HIV-positive TB case.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and has no evidence of being enrolled in HIV care. If the

patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

Classification based on drug resistance

Cases are classified in categories based on drug-susceptibility testing of clinical isolates confirmed to be *M. tuberculosis* and include: mono-resistant, poly-drug resistant, multidrug resistant, extensively drug-resistant, and rifampicin resistant. Any patient with drug-resistant TB can fit into more than one of the above categories. For example, if a patient is diagnosed with RR-TB they must also be recorded as being either MDR-TB or XDR-TB. (World Health Organization, 2013b)

It is important for nurses to be familiar with the case definitions, reporting and classification definitions in the national TB Programme (NTP) guidelines of their country. For more information on the WHO classification and reporting guidelines, please see http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf.

Table 3.2: Definitions of TB case classifications

Type of case	Definition
New patient	No previous treatment for TB or treatment for less than one month
Previously treated patients	Have previously received at least one month or more of anti-TB treatment including the outcome of the most recent course of anti-TB treatment.
Relapse patients	Previously treated and declared cured, or treatment completed in the past, and now diagnosed with smear-positive or culture-positive TB. (This can be either true relapse or a new episode of TB caused by reinfection).
Treatment after failure patients	Previously treated for TB and whose treatment failed at the end of treatment, e.g. remained smear positive after five months of treatment.
Treatment after loss to follow-up patients (Previously referred to as treatment after default)	A patient returning to treatment who is smear or culture positive, after being classified as lost to follow-up at the end of their most recent TB treatment.
Other previously treated patients	Patient previously treated for TB without any documented history of treatment outcome.
Patients with unknown previous TB treatment history	Patients who do not fit into any of the other categories.

*New and relapse cases of TB are **incident** TB cases.

Source: *Definitions and reporting framework for tuberculosis – 2013 revision* (World Health Organization, 2013b)

Chapter 4: Treatment of Tuberculosis

TB treatment: Essential drugs against TB

More than 10 million bacteria exist in the actively multiplying bacterial population in any given patient, and there are always a few mycobacteria resistant to one or another of the anti-TB drugs. If only one drug is used, bacteria resistant to that drug will continue to develop and multiply. However, if more than one drug is used, the bacteria that may be resistant to the first drug are killed by the second drug – this is the rationale behind the use of multiple-drug therapy.

Anti-TB drugs have three main actions: bactericidal activity, sterilising activity and the ability to prevent resistance. Isoniazid and rifampicin are the most powerful bactericidal drugs. Rifampicin is the most potent sterilising drug and pyrazinamide and streptomycin are also bactericidal. Ethambutol is used in association with more powerful drugs to prevent the development of resistant TB bacilli. Table 4.1 below shows (World Health Organization, 2009a) the main first-line TB drugs and recommended dose. The range is shown in parentheses. The WHO still recommends the use of fixed-dose combination (FDC) tablets for the treatment of TB. Details are provided in Table 4.2 below.

Standard code for TB treatment regimens

TB treatment regimen should have a standard code. Each anti-TB drug has an abbreviation:

Isoniazid	H
Rifampicin	R
Pyrazinamide	Z
Ethambutol	E
Streptomycin	S

Table 4.1: Essential first-line anti-TB drugs and recommended doses

Drug (abbreviation)	Recommended dose			
	Daily		3 times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid (H)	5 (4-6)	300	10 (8-12)	900
Rifampicin (R)	10 (8-12)	600	10 (8-12)	600
Pyrazinamide (Z)	25 (20-30)	2000	35 (30-40)	2000
Ethambutol (E)	15 (15-25)	1200	30 (20-35)	1200
Streptomycin (S)	15 (12-18)	1000	15 (12-18)	1000

*WHO no longer includes the use of thioacetazone as a first-line drug because of the risk of severe toxicity in HIV-infected individuals (World Health Organization, 2009a).
Source: *Treatment of tuberculosis: guidelines - 4th ed* (World Health Organization, 2009a)

Table 4.2: Fixed-dose combination of first-line drugs

Drug	Dose form	Strength for daily use	Strength for use 2-3 times weekly
Isoniazid + rifampicin	Tablet	75 mg + 150 mg; 150 mg + 300 mg	150 mg + 150 mg
	Tablet or pack of granules*	30 mg + 60 mg	60 mg + 60 mg
Isoniazid + ethambutol	Tablet	150 mg + 400 mg	--
Isoniazid + rifampicin + pyrazinamide	Tablet	75 mg + 150 mg + 400 mg	150 mg + 150 mg + 500 mg
	Tablet or pack of granules*	30 mg + 60 mg + 150 mg	--
Isoniazid + rifampicin + pyrazinamide + ethambutol	Tablet	75 mg + 150 mg + 400 mg + 275 mg	--

*For paediatric use.

Source: *Treatment of tuberculosis: guidelines - 4th ed* (World Health Organization, 2009a)

For new patients with PTB and EPTB, treatment with the drugs recommended by WHO is divided into two phases:

- 1. Intensive phase** – four drugs given daily (isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E)) in fixed dose combination, and directly observed for at least two months. This rapidly improves clinical symptoms and reduces the bacterial population without allowing drug resistance to develop.
- 2. Continuation phase** – a combination of two drugs (isoniazid and rifampicin) in fixed-dose combination, daily or three times per week, for four more months to eliminate remaining bacilli and prevent relapse. The WHO now recommends drug treatment regimens containing at least six months of rifampicin for new TB patients.

In the standard code, the number before a phase is the duration of the phase in months. Letters in parentheses indicate fixed-dose combinations of those drugs. A number in subscript (e.g. 3) after a letter or letters in parentheses indicates the number of doses of that drug per week. If there is no subscript number, treatment is daily (or 6 times weekly, excluding for instance Sundays). One example is shown below:

2 (HRZE) / 4 (HR)₃

The initial phase is 2 (HRZE). The duration of this phase is two months. Drug treatment is daily, with isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) in FDC.

The continuing phase is 4 (HR)₃. The duration is four months, with isoniazid and rifampicin, in fixed-dose combination, three times per week.

The current WHO recommended standard anti-TB treatment regimens for new and presumed TB patients are detailed in Table 4.3 below. For more information, please visit the latest WHO *Treatment of tuberculosis: guidelines – fourth edition*:

http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1.

Table 4.3: Recommended treatment regimens for new and presumed TB patients

TB case classification	Dosing frequency	TB treatment regimen	
		Initial phase	Continuation phase
Presumed, or new patients known, to have drug-susceptible TB (includes smear-negative, smear- and culture-positive patients), both HIV-positive and HIV-negative patients, and those with EPTB ^a (except TB meningitis ^b , CNS, joint and bone).	PREFERRED treatment regimen Daily for initial and continuation phases	2 HRZE	4HR
	Daily for intensive and three times per week for continuation phase Acceptable if patient receives directly observed therapy for continuation phase	2 HRZE	4 HR ₃
	Three times per week for intensive and continuation phase Acceptable if patient is receiving directly observed therapy NOT recommended for patients living with HIV or patients living in areas with high prevalence of HIV	2 HRZE ₃	4 HR ₃
New TB patients in areas where isoniazid resistance among new TB patients is high	Daily	2 HRZE	4 HRE

Notes:

^a Except for the following types of EPTB cases: TB meningitis, TB of the bone, joint or TB of the CNS. WHO recommends treating EPTB for 9 – 12 months (TB meningitis) and 9 months (for TB of bone or joint) with standard regimen – 2 HRZE / 4 HR) (World Health Organization, 2009a).

^b In TB meningitis ethambutol should be replaced by streptomycin.

Source: *Treatment of tuberculosis: guidelines - 4th ed* (World Health Organization, 2009a)

For previously treated patients with access to DST or rapid molecular tests and who have drug-sensitive TB, the initial phase is two months of daily drug treatment with isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), and streptomycin (S) followed by one month of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). The continuation phase is five months with isoniazid (H), rifampicin (R), and ethambutol (E) for a minimum of eight months of treatment.

The WHO recommends that DST be done for all patients (new and previously treated) before starting anti-TB treatment to ensure that each patient is placed on appropriate therapy. With the rollout of Xpert MTB/RIF many countries now have the ability to test for rifampicin resistance at the initial diagnosis and can perform confirmatory DST prior to starting anti-TB treatment. However, many countries and regions still do not have access to this rapid diagnostic test. Therefore, WHO recommends that all previously treated patients especially among those who failed prior treatment and all patients living with HIV have DST performed for at least isoniazid and rifampicin prior to starting anti-TB treatment. In addition, DST is recommended for new patients with a history of contact with a known MDR-TB case and in all new patients living in countries or settings where more than 3% of new TB patients are expected to be MDR-TB. Table 4.4 below details the WHO recommended treatment regimens for previously treated patients.

Nurses must be familiar with the adverse reactions of anti-TB drugs and refer to WHO and national tuberculosis programme (NTP) guidelines on essential drugs and national treatment guidelines.

For more information on WHO recommendations for TB treatment, please visit: http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf?ua=1.

Table 4.4: TB treatment regimens for previously treated patients based on availability of access to DST

DST availability	Likelihood of MDR-TB (based on patient registration group/classification)	
	High likelihood of MDR-TB (i.e. patients who have failed first-line treatment)	Low or medium likelihood of MDR-TB (i.e. relapse or loss to follow-up patients)
Xpert MTB/RIF	If RR-TB to be started on empiric MDR regimen *Regimen to be revised once confirmatory DST results become available	If not RR-TB start retreatment regimen ^a 2 HRZES / 1 HRZE / 5 HRE ^b
Rapid molecular-based method (line probe assay)	DST results available within 1 – 2 days to confirm or exclude MDR to guide choice of regimen	DST results available within 1 – 2 days to confirm or exclude MDR to guide choice of regimen
Conventional method (liquid or solid culture)	While waiting for DST results Empirical MDR regimen *Regimen to be revised once DST results become available	2 HRZES/ 1 HRZE /5 HRE ^a for full course of treatment *Regimen to be revised once DST results become available
DST not available	Empirical MDR regimen *Regimen to be revised once DST results or drug-resistant survey (DRS) data become available	2 HRZES/ 1 HRZE /5 HRE ^a for full course of treatment *Regimen to be revised once DST results or DRS data become available

^a This is based on international guidance and policies regarding regimens may vary between countries. It is essential that nurses are familiar with and follow locally recommended treatment regimens and policies.”

^b Daily regimen – intermittent or thrice weekly regimens of first-line drugs are not recommended for previously treated patients.

TB treatment regimens for children

The standardized treatment regimens for children are similar to those for adolescents and adults with the exception of certain types of extrapulmonary TB as shown in Table 4.5 below. Intermittent anti-TB treatment is not recommended for children with HIV. Table 4.6 provides information on daily dosage of anti-TB medications for paediatric TB cases.

As of late 2015, child-friendly formulations or doses of anti-TB medications are available. The new child-friendly formulations are

available in FDC making it simpler and easier to give the correct dose to children weighing < 25 kg without having to cut or crush pills. The new formulations can be dissolved in water making it easier to give to younger children (World Health Organization, 2015e). However, there are still no child-friendly formulations or doses of second-line anti-TB medications for children with drug-resistant TB.

For more information on treatment regimens for paediatric TB patients please visit: http://www.who.int/tb/FDC_Factsheet.pdf, and www.theunion.org/what-we-do/publications/technical/english/pub_tdeskguide_eng.pdf.

Table 4.5: Recommended treatment regimens for new paediatric patients in HIV endemic settings*

TB disease category	Recommended regimen	
	Intensive phase	Continuation phase
All forms of PTB and EPTB except TB meningitis & osteoarticular TB	2 HRZE	4 HR
TB meningitis & osteoarticular TB	2 HRZE	10 HR

*An HIV endemic setting is a setting/country where prevalence of HIV adult pregnant women is greater than 1% or the prevalence of HIV among TB patients is more than 5%.

Source: (World Health Organization, 2010, The International Union Against Tuberculosis and Lung Disease, 2010)

Table 4.6: Recommended doses according to weight for children

Drug	Daily dosage in mg/kg (range)
Isoniazid (H)	10 mg/kg (range 7-15)
Rifampicin (R)	15 mg/kg (range 10-20)
Pyrazinamide (Z)	35 mg/kg (range 30-40)
Ethambutol (E)	20 mg/kg (range 15-25)

Source: (World Health Organization, 2010, The International Union Against Tuberculosis and Lung Disease, 2010, World Health Organization, 2015e)

Treatment of MDR-TB

When MDR-TB is confirmed by DST (rapid molecular or culture methods), is suspected based on the patient's history, or rifampicin resistance is identified by Xpert MTB/RIF the first phase of treatment should include at least four second-line drugs susceptible to the infecting strain. This intensive phase should include pyrazinamide (Group 1), a parenteral agent (Group 2), a fluoroquinolone (Group 3), and ethionomide or prothionomide (Group 4), and cycloserine (or PAS if cycloserine is not available). Drugs listed in Group 5 in Table 4.7

below may be used, but these drugs are not recommended as they are of unknown efficacy. **It is no longer recommended to add additional second-line drugs to the standard MDR-TB regimen of four second-line drugs.** The first phase, which uses an injectable agent, should be a minimum of six to eight months and many programmes extend treatment if the patient has not converted both smear and culture. However, the duration of the intensive phase may be modified based on the patient's condition, for example, if the patient converts before eight months the intensive phase may be modified to less than eight months. The evidence to support this is not of high quality however. The entire treatment period should not be less than 20 months past smear and culture conversion (World Health Organization, 2011b, World Health Organization, 2014b).

Box 2. Example of a standardized MDR-TB regimen

8Km⁶-Lfx⁷-Eto⁷-Cs⁷-Z⁷/12Lfx⁷-Eto⁷-Cs⁷-Z⁷

The initial phase consists of five drugs and lasts for eight months in most patients. Kanamycin is given six days a week and all other drugs are given seven days a week. The continuation phase in this example - the phase without the injectable - continues all the oral agents for a minimum of 12 months. The total minimum treatment will last at least 20 months.

Patients with MDR-TB take more tablets for a longer period of time, may experience more adverse effects and require increased support to continue treatment and/or to monitor adverse effects. Detecting and controlling adverse effects in a timely manner prevents adherence problems and patients defaulting treatment. Nurses play a critical role in the rapid detection of adverse effects, management and adherence issues. See Annex 5 for common adverse effects of essential and reserve medications used in treating drug-sensitive and drug-resistant TB. Patients co-infected with HIV and MDR-TB often experience more adverse effects in addition to drug to drug interactions between second-line TB medications and antiretrovirals. See the WHO's *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (World Health Organization, 2014b) for more information.

http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf?ua=1&ua=1

Table 4.7: Conventional groups of second-line anti-tuberculosis agents used to treat MDR-TB

Group name	Anti-tuberculosis agent	Abbreviation
Group 1: First-line oral drugs	Isoniazid Rifampicin pyrazinamide ethambutol rifabutin ^a	H R Z E Rfb
Group 2: Second-line parenteral agent (injectable anti-tuberculosis drugs)	kanamycin amikacin capreomycin streptomycin ^b	Km Am Cm S
Group 3: Fluoroquinolones ^c	levofloxacin moxifloxacin gatifloxacin ^d	Lfx Mfx Gfx
Group 4: Oral bacteriostatic second-line anti-tuberculosis drugs	ethionamide protionamide cycloserine terizidone <i>para</i> -aminosalicylic acid <i>para</i> -aminosalicylate sodium	Eto Pto Cs Trd PAS PAS-Na
Group 5: Drugs with limited data on efficacy and/or long term safety in the treatment of MDR-TB	Bedaquiline Delamanid clofazimine linezolid amoxicillin/clavulanate thioacetazone clarithromycin imipenem/cilastatin* High-dose isoniazid meropenem*	Bdq Dlm Cfz Lzd Amx/Clv Thz Clr Ipm/Cln High-dose H Mpm

^a Rifabutin has similar microbiological activity as rifampicin. Rifabutin is not on the *WHO list of essential medicines*, however it has been added here as it is used routinely in patients on protease inhibitors in many settings.

^b There are high rates of streptomycin resistance in MDR-TB; therefore it is not considered a second-line anti-TB injectable agent.

^c Ofloxacin is considered a weaker fluoroquinolone against TB and is no longer recommended.

^d Gatifloxacin is known to have life-threatening side effects including serious diabetes (dysglycemia) and has been removed from the formula in several countries.

^e Terizidone has limited programme data and effectiveness data as compared to cycloserine.

^f Clavulanate (Clv) is recommended as an adjunctive to imipenem/cilastatin and meropenem.

^g Limited data on the role of thioacetazone and clarithromycin in MDR-TB treatment has resulted in many experts not including these drugs as options for Group 5.

Source: *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (World Health Organization, 2014b)

New shortened treatment for MDR-TB

As of May 2016, WHO recommends a shortened treatment regimen for patients with MDR-TB (World Health Organization, 2016d). The new MDR-TB regimen shortens the MDR-TB treatment course from 20 to 24 months to nine to 12 months. The new recommended regimen

should contain a second-line injectable plus a fluoroquinolone (moxifloxacin), prothionamide (or ethionamide), clofazimine, high-dose INH, pyrazinamide, and ethambutol for an initial phase of four months. This is to be followed by five months of four drugs (moxifloxacin, clofazimine, pyrazinamide, and ethambutol). Please see Box 3 for a sample regimen. More detailed information can be found at <http://www.who.int/tb/MDRTBguidelines2016.pdf?ua=1> (World Health Organization, 2016d).

Box 3. Example of new shortened MDR-TB treatment regimen (World Health Organization, 2016d)

4-6 Km-Mfx-Pto-Cfz-Z-Hhigh-dose-E / 5 Mfx-Cfz-Z-E

The WHO has revised the list and grouping of medications for the treatment of MDR-TB and RR-TB. Please see Table 4.8 below for the updated groupings.

Table 4.8. Updated anti-TB medications for the treatment of RR-TB and MDR-TB

Group name	Anti-TB medication		Abbreviation
A. Fluoroquinolones ^a	Levofloxacin Moxifloxacin Gatifloxacin		Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin) ^b		Am Cm Km (S)
C. Other core second-line agents	Ethionamide / Prothionamide Cycloserine/Terizadone Linezolid Clofazimine		Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents	D1	Pyrazinamide Ethambutol High-dose isoniazid	Pza E H ^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	<i>p</i> -aminosalicylic acid Imipenem-cilastatin ^c Meropenem ^c Amoxicillin-clavulanate (Thioacetazone) ^d	PAS Ipm Mpm Amx-Clv (T)

^a Medications in Groups A and C are shown by decreasing order of preference for use.

^b Streptomycin is not appropriate for substitution for other injectable agents. Please see the text for more detailed information. (<http://www.who.int/tb/MDRTBguidelines2016.pdf?ua=1>)

^c Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin.

^d HIV status must be tested and confirmed to be negative before thioacetazone is started.

New drugs to treat drug-resistant TB

Bedaquiline

Bedaquiline (TMC207) is the first new drug to be approved for treatment of tuberculosis in 40 years. A WHO expert panel has recommended that bedaquiline may be added to a standardized MDR-TB treatment regimen for pulmonary MDR-TB in adults only. There remains limited data available on the use of bedaquiline and long-term adverse effects among other safety issues. Therefore, the use of bedaquiline is very limited and controlled as of late 2014. There are five conditions that must be met for use of bedaquiline to be used to treat MDR-TB patients and it is not yet available in most countries. The five conditions are:

- 1 Treatment is administered under closely monitored conditions.
- 2 Proper patient inclusion (pulmonary MDR-TB patients > 18 years old).
- 3 Informed consent from patient.
- 4 Adherence to WHO recommended standardized MDR-TB regimen.
- 5 Management of adverse drug events (World Health Organization, 2013g).

For more detailed information on bedaquiline please visit: www.who.int/tb/challenges/mdr/bedaquiline/en/index.html.

Delamanid

Delamanid (OPC-67683) is another new drug which has been approved in several countries as of 2014. WHO convened an expert panel to develop recommendations for the use of delamanid for the treatment of pulmonary MDR-TB in adults. At present there is limited data available on the use delamanid, safety issues and long-term side effects. (World Health Organization, 2014h)

The conditions for use of delamanid are:

- 1 Proper patient inclusion (adults \geq 18 with pulmonary MDR-TB – including those with HIV).
- 2 Adherence to WHO recommended standardized MDR-TB regimen.
- 3 Treatment is administered under closely monitored conditions.
- 4 Active pharmacovigilance and management of drug adverse events including drug interactions.
- 5 Informed consent obtained from the patient.

For more detailed information on delamanid please visit:

http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf?ua=1&ua=1&ua=1

Monitoring TB treatment

During the course of TB treatment, sputum smears must be taken at least three times for monitoring purposes for new smear-positive pulmonary TB/MDR-TB cases (see Table 4.9).

Treatment outcome definitions

The 2013 revised WHO definitions and reporting guidelines now make a distinction between drug-susceptible and drug-resistant TB patients (those taking second-line drugs) and the reporting should reflect this. For example, if a patient initially started first-line treatment and is then later found to have drug-resistant TB, they must be removed from the drug-susceptible TB register and outcome cohort and added to the drug-resistant register and outcome cohort.

Treatment outcome definitions are described in Table 4.10 for drug-susceptible TB patients and Table 4.11 for drug-resistant TB patients (RR-TB and MDR-TB).

Table 4.9: Monitoring of TB treatment by smear microscopy for new pulmonary TB patients (6-month regimen)

Time of sputum collection	New smear-positive pulmonary TB patients (6-month regimen)	Retreatment smear-positive pulmonary TB patients
1 st time	At the end of the 2nd month of treatment when 75-85% of initially sputum smear-positive patients should be sputum smear negative (sputum conversion) If smear positive – repeat sputum again at the end of month 3 and if still smear positive at the end of month 3, request culture and DST	At the end of the 3rd month of treatment when sputum smear-positive patients should be sputum smear negative (sputum conversion) If still smear positive at the end of month 3, request culture and DST
2 nd time	At the end of the 5th month of treatment in order to confirm TB cure. If smear positive – request culture and DST	At the end of the 5th month of treatment in order to confirm TB cure. If smear positive – request culture and DST
3 rd time	At the end of the 6th month of treatment in order to confirm TB cure. If smear positive – request culture and DST	At the end of the 8th month of treatment in order to confirm TB cure. If smear positive – request culture and DST

Source: *Treatment of tuberculosis: guidelines - 4th ed* (World Health Organization, 2009a)

Conversion (to negative): A patient is considered to have converted to negative if two consecutive sputum smears (drug-susceptible TB or cultures (RR-TB and MDR-TB), taken at least 30 days apart, are found to be negative. The date the specimen of the first negative culture was collected is used as the date of conversion.

Reversion (to positive): A patient is considered to have reverted to positive when, after an initial conversion, two consecutive sputum smears (drug-susceptible TB) or cultures (RR-TB and MDR-TB), taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failure, reversion is considered only when it occurs in the continuation phase (World Health Organization, 2009a, World Health Organization, 2014b).

Table 4.10: WHO treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

Outcome *	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the start of treatment 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 negative sputum smear or negative culture results in the last month of treatment and at least on one previous occasion and without evidence of treatment failure. This may be because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture remains positive at the 5 th month 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 as well as cases for whom the treatment outcome is not known.
Treatment success	The sum of cured and treatment completed.

Adapted from WHO *Definitions and reporting framework for tuberculosis – 2013 revision* (World Health Organization, 2013b)

*All bacteriologically confirmed and clinically diagnosed TB cases should have a recorded outcome from the above list **except** those with RR-TB or MDR-TB, who are placed on a second-line drug regimen – see treatment outcomes for RR-TB and MDR-TB patients below in Table 4.11.

Table 4.11: Treatment outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed 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 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 at least two anti-TB drugs because of: <ul style="list-style-type: none"> • lack of conversion^a by the end of the intensive phase, <i>or</i> • bacteriological reversion in the continuation phase after conversion to negative^a, <i>or</i> • evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, <i>or</i> • 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 two consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned – includes cases who "transferred out" to another facility and whose treatment outcome is unknown.
Treatment success	The sum of cured and treatment completed

Source: Definitions and reporting framework for tuberculosis – 2013 revision (World Health Organization, 2013b)

^a The terms "conversion" and "reversion" of culture are defined as follows:

Medication adverse effects

Minimising medication adverse effects helps ensure patient adherence to treatment. The nurse should teach every patient about the possible adverse effects and encourage them to report any symptoms as soon as possible. Adverse effects fall into two groups depending on their severity, minor and major.

Minor adverse effects include:

- discolouration of urine
- nausea, occasional vomiting, abdominal discomfort, loose stools
- lack of energy
- mild rash, itching

The patient experiencing minor adverse effects needs support to complete his/her treatment. The nurse may need to think of ways to

help alleviate suffering such as changing the medication time, diet and/or offering mild anti-emetics, antacids or anti-histamines.

Treatment is usually stopped if the patient suffers any of the following major adverse effects:

- persistent vomiting
- hepatic toxicity/jaundice
- peripheral neuropathy
- severe rash

After a short break in treatment to permit some recovery from the adverse effects, each drug is reintroduced, one at a time, to identify the problem drug. Once identified, the problem drug is replaced with an alternative. This does mean that the treatment period is extended.

For more detailed guidance, please see Adverse Effect Management in Annex 5 (page 80).

Treatment Adherence

To encourage adherence to treatment protocols, TB services must be flexible enough to give the patient a choice about where they receive treatment, e.g. at home, in the clinic or in the workplace (TB CARE I, 2014, Williams et al., 2007). If the patient chooses to take the drugs in his home or workplace, treatment observers, other than those associated with the clinic, are encouraged. These observers can be anyone who is willing, trained, responsible, acceptable to the patient and accountable. Close family members, such as spouses, may not always make the best treatment observers as they may be manipulated by the patient and caution is needed to ensure adherence.

Failure to adhere to standardised treatment due to adverse effects or other reasons can lead to treatment failure and the emergence of MDR-TB. Therefore, the patient's commitment to the prescribed therapy plays a key role in successful treatment outcomes. Nurses must listen to patients' concerns and provide information and education that is tailored to each patient's needs. The importance of treatment adherence and obtaining patient commitment are vital for treatment success.

Please see Annex 6 (page 90) for more information on factors affecting adherence and suggestions to improve adherence.

Chapter 5: Guidelines for Patient Care: Nursing Principles and Processes

Role of Nurses in TB Care and Management

Nurses make up by far the largest group of healthcare workers in any part of the world and as in most areas of healthcare they often undertake the bulk of the work in TB control. According to the ICN Code of Ethics, “Nurses have four fundamental responsibilities: to promote health, to prevent illness, to restore health and to alleviate suffering. The need for nursing is universal.” (International Council of Nurses, 2012) In relation to TB, nurses promote health in order to prevent people becoming vulnerable to the disease in the first place; they prevent illness by reducing transmission of TB in the community by finding and treating active cases; they restore health by ensuring patients receive the treatment they need; and alleviate suffering by organising support for patients according to their individual needs.

Many people are extremely shocked when they are told they have TB; some refuse to accept it; and others simply take it in their stride. The reaction depends on many factors including cultural beliefs and values, previous experience, and knowledge of the disease. TB sometimes has a high profile in the media; the reports are often alarmist and a stigma still remains attached to the disease. Even though TB is more common among vulnerable groups, it can affect anyone and it is important for patients to be able to discuss their concerns. Nurses are well-placed within communities, working closely with patients and their families, to play a crucial role in providing a caring environment for all patients suffering from TB. This is essential to the success of TB control programmes which need to offer good access to effective diagnostic and treatment facilities. With the inclusion of patient-centred care as one of the three main pillars of the *End TB Strategy*, the WHO has recognised the vital importance of this approach to the success of any TB programme. Individualised patient-centred care underpins the nursing process and, as such, should encourage nurses to take the lead in this area.

The nurse’s role in relation to national TB control strategies

The roles that nurses play in TB management and control vary according to their work setting. While some will be involved in all of the activities described below, others will take on various elements. Nurses with additional qualifications may change their job titles thereby becoming less visible as nurses, but continuing, nonetheless, to carry out nursing activities. With the new WHO *End TB Strategy* as described in Chapter 2, there is now a larger role for nurses to play in ensuring care is patient-centred from the moment a patient seeks diagnosis to the very end of their treatment. There is also a larger emphasis on working with a broader range of partners, something which nurses are

well-placed to do with their understanding of the needs of their clients and their potential to identify and work closely with other clinical partners and community organisations.

Nurses working in primary healthcare settings are often first to see people who present with symptoms and are crucial to the early identification and management of presumed TB and MDR-TB cases. To ensure a high level of case detection, a cornerstone of TB control, nurses working with individuals, families, communities and other services need to understand their role in controlling this preventable disease.

The nursing process, DOTS and MDR-TB management strategies

The nursing process is a systematic approach to providing individualised, patient-centred care through a cycle of assessment, planning, implementation and evaluation. It offers a scientific basis for decision making and improves the quality of planning. Actions made explicit during the planning phase allow for evaluation of the effectiveness of the interventions undertaken.

Like the nursing process, DOTS and MDR-TB management strategies have quality and effectiveness at their core. The DOTS strategy in particular offers a standardised approach for the control and management of TB. The management of MDR-TB is much more complex although there are some opportunities for standardising certain aspects such as elements of diagnosis and treatment monitoring. Although the technical aspects of TB control are standardised, to be effective, TB services must be flexible and based on the needs of the patient, their family and the local community (Table 5.1).

Patient-centred approach to TB control and care

The patient-centred model links nursing process with the DOTS and MDR-TB management strategies, identifying case finding and patient holding as intertwined cycles of intervention. Cases are constantly being found, prompting further investigation, which leads to more cases being discovered. Since the individual patient's needs may change during the time they are on treatment, the nurse's constant evaluation and reassessment ensures appropriate care at each stage and enhances the patient's adherence to TB treatment protocols.

Case finding

Patients enter the patient roster through passive case finding or active case finding. Active case finding is TB screening of populations, recommended only in areas where treatment success is at least 85% and where treatment and follow-up services are available. Screening can be expensive, so it is more cost effective to target the highest risk

groups based on epidemiological trends within a local population. Often screening is targeted at hard-to-reach groups, which means identified cases are a challenge to treat (Williams et al., 2007).

Table 5.1: The role of the nurse in relation to the five elements of the DOTS strategy

Element	Strategy and rationale	Nurses' role
Political commitment	Investment essential at national and local levels to implement and sustain a successful TB control programme	Advocacy and lobbying Experience of working closely with patients and communities can inform policy and strategic decision making and assist implementation
Case detection by smear microscopy (and other bacteriologic tests e.g. Xpert MTB/RIF)	Most cost-effective option Identifies infectious cases	Identification of presumed cases Support for worried patients Advise patients on how to produce a good sputum sample Access for delivery of sample Documentation (dates & results)
Standardised treatment with DOT	To ensure effective treatment prescribed and good adherence to medication Treatment observers should be willing, trained, responsible, and acceptable to the patient	Ensuring equitable access Individualised care planning Education of patient and family Monitoring and documentation of medication and progress Support for patient, family and treatment observer
Standardized reporting and recording	Systematic evaluation of a) patient progress and treatment outcome b) overall programme performance	Clear, accurate and prompt record keeping –Laboratory register –Treatment cards –TB register Communication re individual and collective progress
Regular uninterrupted drug supply	Minimising the possibility of treatment interruption	Ensuring there is a sufficient supply for patients seen according to level of responsibility (manager of a TB Unit to DOTS supervisor)
Additional logistical aspect: Training and supervision	Vital to ensure quality and proper management of actual and possible TB cases	Personal professional development Provision of education for patients their families, communities and volunteers etc.
Additional operational aspect: Flexibility	The range of geographical, environmental and cultural contexts requires flexibility in the implementation of DOTS components	Nurses play a key role in providing flexible TB services by providing individualised patient-centred care

Passive case finding occurs when people present themselves with symptoms. It relies on good public information and accessible services for people to recognise TB symptoms and know where to get help. If TB is suspected, the person is tested.

If diagnosed with active TB, the nurse registers the patient and starts him/her on treatment. Diagnosis usually leads to an investigation of the patient's contacts to see if any of them have active TB (active case finding). Those with TB are registered and treated, and so on.

Patient holding

Once diagnosed, the patient enters the patient holding cycle and remains there until TB cure or treatment is complete. In this cycle, the nurse ensures that the patient can adhere to the drug treatment as easily as possible. She assesses his/her status, implements the treatment plan, and continuously evaluates progress and problems.

To ensure appropriate assessment, planning and implementation, the nurse needs a range of skills: clinical skills; detecting and managing adverse effects; counselling; communication and teaching; as well as organisational skills for co-ordinating the patient's care, especially if a number of different care givers are involved, e.g. advocates, community workers, volunteers (Williams et al., 2007).

Assessment

Assessment includes evaluating the patient's physical, psychological, social and nutritional status in relationship to the management of his/her TB care by collecting data from medical notes, and communicating with and observing the patient. The nurse must listen to the patient and assess what is important to him/her, what he/she is trying to achieve, and how the TB diagnosis has affected him/her.

The TB patient often cares for him/herself and may not appear to have problems. Yet, there may be something happening that prevents adherence to treatment – depression, financial difficulty, pregnancy, alcohol or drug dependency, working illegally, bereavement, homelessness, poor nutrition, etc (Williams et al., 2007).

Planning

Defining treatment goals and expected outcomes at the beginning of treatment reduces confusion and misunderstandings. Planning as a team, the nurse and the patient agree on short term, intermediate and/or long term goals with specified and measurable outcomes. Including his/her personal goals in the treatment plan gives the patient a vision beyond the absence of disease.

Planning must be realistic and achievable, and services promised must be accessible. To do this, each person must understand his role and

the role of the others, know the available services, and have an accurate understanding of the treatment goals.

A clear understanding of the patient's situation is key. For instance, if the patient has to work from early in the morning until late at night or has to leave home for several weeks during his treatment, directly observed treatment at the clinic will not be successful. The nurse and patient must establish a different treatment plan. Once the patient's concerns are known, the nurse can work with him/her to develop an individualised plan including support systems. Doing so minimises disruption in his/her life, motivates adherence and enhances completion of drug treatment.

Implementation

Having assessed and planned care with the patient, it is essential to do what was agreed. A range of skills is required to provide care for patients, only few of which are manual such as tuberculin testing, injections, wound care and so on. Core skills include counselling, communication and teaching. As discussed below, good organisational skills are also required to ensure, for instance, that the correct medication is available and provided as prescribed.

The nurse should record the patient's progress promptly, clearly and accurately and any changes or problems should be referred as appropriate. Obviously, the availability of support services will vary from place to place and best use needs to be made of local resources.

Evaluation

During long-term TB treatment (especially in patients with MDR-TB), many factors could change so the nurse must evaluate the patient's progress at regular intervals as agreed with the patient. This may involve a weekly review to begin with, followed in later stages by fortnightly or even monthly follow up. Any changes in the patient's clinical condition, personal circumstances, mood, attitude and appearance should be noted.

In addition, the patient should be assessed and their progress documented at specific intervals in accordance with the local TB control programme:

- Usually after two months of treatment to ensure progression to non-infective condition, sputum conversion from smear positive to smear negative.
- With MDR-TB patients:
 - usually at 3-4 months to ensure the patient's sputum has converted to negative; and
 - 8 months after this point (when the injectable medication, which is used in the first phase of treatment for a minimum of 8 months, is stopped) as this is the point when many patients move from inpatient to outpatient treatment settings.

- At the end of treatment, to evaluate and record the treatment outcome.

Patient-centred care and treatment adherence

While emphasising the need for a patient-centred approach, it is still imperative to stress the importance of treatment adherence – both the adherence of healthcare workers to following correct protocols as well as the adherence of the patient to the treatment prescribed. Adherence to TB treatment, a major factor in the successful outcome of TB treatment, reduces the potential for developing acquired MDR-TB and is the main reason the DOTS strategy was developed in the first place. Adherence is the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes – follows the agreed healthcare recommendations (World Health Organization, 2009a).

Adherence is complex, with a number of factors that can adversely impact treatment completion including: socio-economic factors and issues related to the organisation of TB treatment in the community; patient variables; treatment variables; treatment of adverse effects; disease variables; and organisational variables. The nurse must understand the barriers for adherence to treatment regimens and reduce or eliminate these barriers. A patient-centred approach which includes facilitating access to treatment, deciding with the patient the most convenient time and place for direct observation of treatment (DOT), and when possible providing other social and medical services, is more effective than tracing patients lost to follow up (World Health Organization, 2009a). DOT is a key element of the policy package for TB control and requires that an observer watch the patient swallow the medicines. The observer can be a health worker or a trained and supervised member of the community.

Best adherence indicators include:

- smear conversion from positive to negative,
- improvement in symptoms, and
- clinical improvement.

The use of incentives to motivate the TB patient to adhere to treatment can be effective and enhance the patient/nurse relationship. Some ideas for incentives are: support groups; award ceremonies on successful completion of treatment; reimbursement for travel, food, visits and phone calls; "Thank you teas" for patients and their families; and birthday or anniversary greetings. In many countries, malnutrition is a serious problem and food is considered an enabler – necessary for treatment success – rather than an incentive.

Giving incentives carries responsibility for both the patient and the nurse. Both must keep their promises. If the nurse promises the

incentive and does not deliver it, the relationship with the patient and credibility in the community may be adversely affected. To effectively use incentives, the nurse must also get to know the patient and recognise the difference between the nurse's perception of the patient's needs and his/her reality.

Chapter 6: Organisational and Workforce Issues

Organisational issues

Organisational issues related to a successful TB control programme include:

- human resource issues, such as staffing and worker protection
- practice development issues including training and quality assurance
- programme evaluation and TB research
- social advocacy and community mobilisation

Some of the **most common and important organisational issues** were identified by WHO in the 2002 survey of National TB Programme Managers in 22 high-burden countries. These issues are: (World Health Organization, 2003)

- lack of qualified staff
- weak political commitment
- inadequate health infrastructure
- non-compliance of the private sector with DOTS

Workforce issues

While no further study has been undertaken since then it is clear from the WHO's progress report on Strengthening Nursing and Midwifery that there are many challenges still affecting the healthcare workforce (World Health Organization, 2013d). The following issues remain in all six regions of WHO although the severity of each may vary from country to country. Key challenges to strengthening nursing and midwifery services were identified as:

- inadequate human resources at all levels of the health-care system
- difficulty in retaining healthcare workers in rural areas after completion of training
- increased migration within countries, regions and globally
- low salaries, lack of career incentives, an ageing workforce, poor professional image
- poor working conditions/environments
- difficulties implementing and reinforcing existing policies
- lack of high-quality local education programmes

- delayed or inadequate responses to crises and/or disasters
- limited access to information and communication technologies
- funding and training resource constraints exacerbated by the global economic situation

By understanding the problems and potential resolutions, nurses can advocate for strong TB control programmes at a local, regional or national level.

In addition to these general issues which disproportionately affect lower and middle income countries where TB is more common, there are a number of additional challenges associated with the disease namely:

- unsafe work environment through poor or lack of infection control measures
- stigma
- work-related stress
- lack of protective devices such as filtering facepiece respirators (N95 or FFP2)

Some of the main issues are discussed here as they relate to TB.

Infection prevention and control

Effective infection prevention and control (IPC) in healthcare facilities plays an important role in providing a safe environment for both patients and healthcare workers. The hierarchy of infection control measures consists of: 1) managerial/facility level controls, 2) administrative controls, 3) environmental controls, and 4) personal protective equipment (Table 6.1).

Managerial and administrative controls are at the top of the hierarchy and are the most effective and often the least expensive IPC measures. The most effective way to protect staff and patients from TB exposure is to be alert to potential cases and to separate coughing patients and patients with suspicious symptoms until a diagnosis of active TB can be ruled out. The healthcare facility should institute a policy allowing the nurse to place a patient in a separate waiting area or isolation if he/she suspects that the patient has active TB. This helps minimise exposure that can occur while waiting for a diagnosis.

Since patients with active TB are the most infectious, they should remain separated from patients who do not have TB for the first two weeks of treatment. Patients being treated for MDR-TB generally convert by the third or fourth month. In facilities where there are a high number of patients with HIV infection, it is particularly important to separate TB patients and TB suspects from HIV-positive patients. After two weeks of treatment, most patients with TB are no longer infectious (Rouillon et al., 1976). However, if there is a suspicion that the patient

has MDR-TB, he/she should be separated from other patients until there are good signs of clinical improvement and, if possible, until sputum becomes smear negative. Prompt diagnosis and initiation of appropriate treatment are also an effective method of decreasing and preventing transmission.

Environmental controls are the next level of the infection control hierarchy and include measures to maximize natural ventilation (open windows and doors) to reduce the amount of airborne droplet nuclei to decrease the risk of transmission. Other environmental controls include mechanical ventilation, such as negative pressure isolation rooms and ultraviolet germicidal irradiation (UVGI). In most low-resourced settings natural ventilation will be the only environmental control available and it is important for environmental controls to be implemented in conjunction with administrative controls. Natural ventilation is inexpensive while mechanical ventilation and UVGI are much more expensive and require considerable monitoring and maintenance (World Health Organization, 2009c).

The lowest level of the infection prevention and control hierarchy is personal protective equipment (PPE) such as wearing filtering facepiece respirators like N95 or FFP2 respirators. Respirators should not be used alone, but rather it is recommended they be used as part of an overall infection control strategy, especially in addition to effective administrative control measures. Moreover, it is important for healthcare workers to be fit-tested prior to using respirators as a one size respirator does not fit all face shapes (World Health Organization, 2009c).

More resources on infection control are available at the following links:

http://whqlibdoc.who.int/publications/2009/9789241598323_eng.pdf
www.tbcare1.org/publications/toolbox/tools/ic/TB_IC_Implementation_Framework.pdf (Tuberculosis Coalition for Technical Assistance, 2010)

Infection prevention and control is the responsibility of everyone working in health facilities and it is important for nurses, physicians, support staff and management to all work together to ensure a safe environment for patients, healthcare workers and visitors. ICN has created a toolkit to help guide inter-professional collaboration in healthcare facilities on infection control (International Council of Nurses, 2011). The toolkit can be found at the following link: www.icn.ch/es/tb-mdr-tb-project/training-resources/training-package/tb-infection-control-toolkit.html.

Table 6.1: Infection prevention and control measures

Type of control	Examples
Managerial controls (facility-level controls)	<ul style="list-style-type: none"> • Conduct a risk assessment plan of facility infection control measures • Create a multidisciplinary infection control committee • Develop and implement a comprehensive infection control plan • Monitor and evaluate infection control plan • Surveillance of TB among healthcare workers
Administrative controls	<ul style="list-style-type: none"> • Triage coughing patients and TB suspects (routinely ask patients about cough upon entering facility/hospital) and separate coughing patients from others • Minimize time spent in health facilities (fast track patients with cough) • Separate HIV-positive patients from TB patients/suspects in waiting areas and in wards. • Ensure patients are not crowded in hallways or waiting areas (casualty, etc.). • Educate patients on cough hygiene (coughing into tissue, ask patients to wear a surgical mask, etc.) • Provide tissues, cloths or surgical masks for patients to cough into • Sputum samples are collected in a designated area (i.e. outside) • Separate smear-positive and smear-negative patients in wards • Rapidly diagnose and start patients on appropriate treatment • Natural ventilation (open windows and doors) • Mechanical ventilation (negative-pressure isolation rooms, extraction fans, etc.) • Ultraviolet germicidal irradiation (UVGI)
Environmental controls	<ul style="list-style-type: none"> • Filtering facepiece respirators (N95 or FFP2) • Fit testing • Gowns, aprons, gloves, eye protection
Personal protective equipment (PPE)	

Adapted from: *WHO Policy on TB infection control in health-care facilities, congregate settings and households* (World Health Organization, 2009c).

Maintaining a healthy workforce

A healthcare facility is a workplace as well as a place for giving and receiving care. Nurses need protection from workplace hazards. Yet, protection and safety of nurses and other health professionals is often a neglected area. In order to protect themselves from TB infections and to maintain a continued high level of patient care, it is important for nurses to understand the risks of contracting TB and to know the recommended methods of protection.

Given the global prevalence of TB, protection of the nurse's health is pertinent to every TB discussion. The prevalence of disease in the wider community has always been a significant factor in determining occupational exposure for nurses. Historically, TB has long been a recognised hazard for healthcare workers, especially nurses. In fact, it has been reported that entire nursing classes had been infected with TB within the first year of nursing training (Israel et al., 1941). It is estimated that more than 50% of healthcare workers globally have LTBI placing them at a greater risk of developing active TB. Moreover, healthcare workers are two to three times more likely to develop active TB than the general population (Joshi et al., 2006, Menzies et al., 2007).

Although it is important for countries to establish regulations and legislation to protect nurses, with or without that legislation, employers still have a responsibility to protect their workers. In most countries, according to the International Labour Organization (ILO), the employer is responsible for occupational safety and health programmes. Moreover, ILO contends that disease and injury are not inevitable consequences of work, and poverty does not excuse an employer's disregard for his employee's safety and health. This is true for nurses as well as other workers.

While some measures recommended to protect nurses are costly, others can be implemented at a low cost including:

- pre-employment and routine (annual) screening for TB symptoms
- checking BCG status
- TB skin testing
- giving BCG vaccination
- taking a chest x-ray, if indicated
- educating nurses about the signs and symptoms of TB and encouraging them to seek medical attention promptly if signs appear
- confidential and voluntary HIV counselling and testing
- reassigning HIV-positive healthcare workers to work in areas with low risk of being exposed to TB patients or TB suspects
- provision of HIV treatment services including IPT for healthcare workers living with HIV.

In 2011, the ILO/WHO/UNAIDS released a guidance note on improving healthcare workers' access to prevention, treatment and care for HIV/AIDS and TB. Below are several actions recommended to be implemented in the workplace to protect healthcare workers affected by TB and/or HIV.

- Make occupational health services available for all healthcare workers to ensure access to HIV and TB prevention, treatment, support and care can be attained.
- Strengthen existing IPC programmes, especially with respect to TB and HIV to ensure a safe work environment.
- Provide regular, free, voluntary and confidential HIV counselling and testing, and TB screening, as well as general wellness services including screening of family members of health workers with TB.
- Implement good practices in occupational health and the management of HIV and TB in the workplace
- Provide information on benefits and risks of post-exposure prophylaxis (PEP) to all staff and provide PEP free of charge for all exposed health workers in a timely manner.
- HIV and TB treatment should be provided free of charge for healthcare workers in need. Services for healthcare workers affected by HIV and TB should be provided in a confidential, non-stigmatizing, and patient-centred manner.
- Provide universal access to prevention and care services for all HIV-positive health workers, such as isoniazid preventive therapy and co-trimoxazole prophylaxis.
- Provide training for all healthcare workers on TB and HIV prevention, treatment, support, and care including information on the rights of both employers and workers and measures to reduce stigma. (International Labour Organization, 2011)

For more information, please visit: www.ilo.org/wcmsp5/groups/public/---ed_protect/---protrav/---ilo_aids/documents/publication/wcms_149714.pdf.

Practice development

Practice development encompasses a broad range of interventions designed to improve practice and patient care services (Bryar and Griffiths, 2003). Training and quality assurance are essential elements of practice development.

Staff training

Training and supervision of health personnel are essential to the success of any TB control programme. They are equally important at all levels of nursing – those working specifically in TB control programmes as well as primary healthcare workers, who are often the first to identify suspect cases. Participatory education with regular follow-up is usually more effective than didactic approaches that simply disseminate information (Centers for Disease Control and Prevention, 2005). The best training provides ongoing support and helps integrate the learning into practice.

Evaluation is essential to reinforce, maintain and disseminate best practices. Developing new practices requires establishing measures for evaluating change. Since changes in community nursing practice may have a far reaching impact on a variety of stakeholders, no developments should be planned without outlining expected measurable outcomes, including looking downstream at the impact on the wider community.

The type of data collected during an evaluation should also reflect the purpose of the evaluation. If the purpose is to influence physicians and TB coordinators, quantitative data may be most appealing. However, for nurses and patients, qualitative data may be more meaningful.

Data collection is absolutely intrinsic to the DOTS programmes – gathering the right data is essential for correctly identifying a problem, developing a practice to resolve the problem, and evaluating the impact of the change:

- Quarterly cohort analysis gives regular feedback about overall programme performance and highlights rates of sputum conversion, defaulting, etc.
- Comparing laboratory records with the TB patient registry shows how many sputum smear positive cases started treatment, and within what time period.
- Treatment outcome data demonstrates rates of success, default, failure or death.
- Patient record cards illustrate treatment adherence patterns.
- In addition to evaluating nursing practices and patient outcomes, worker health protection must be regularly evaluated to determine if it is successfully protecting healthcare workers from contracting TB. In most settings, TB skin tests are done when new staff is first employed, every six months or annually thereafter (based on the level of TB found in the community and in the health facility), and whenever an employee has signs and symptoms of active TB (World Health Organization, 2009c). In addition, mechanical ventilation and negative-pressure isolation rooms are routinely checked to ensure that the controls are functioning properly. Nurses wearing respiratory protection must also perform fit tests regularly to ensure that the respirator fits their faces appropriately. If a respirator does not fit correctly, its protection is compromised.

Table 6.2: Key nursing capabilities in TB control and prevention

<p>CAPABILITY REQUIRED</p> <ul style="list-style-type: none"> recognise a suspect case describe the local TB situation explain how TB is spread discuss the main principles of TB management 	<p>KNOWLEDGE</p> <ul style="list-style-type: none"> signs and symptoms of TB local and national statistics how TB is transmitted local and national policy for treatment and management of TB
<p>Primary/Community Care facilities</p> <p>In addition to the above:</p> <ul style="list-style-type: none"> order appropriate tests give the patient / family basic information, e.g. TB is curable refer to the appropriate service complete appropriate documentation 	<p>In addition to the above:</p> <ul style="list-style-type: none"> diagnostic tests available for TB support required by patient when suspected of having TB local services responsible for TB recording and reporting procedures associated with TB management
<p>Acute hospital services</p> <p>In addition to the above:</p> <ul style="list-style-type: none"> apply hospital infection control procedures appropriately observe treatment given during patient's stay in hospital recognise and report adverse effects discuss treatment with patient (and family) plan discharge to local TB services/unit 	<p>In addition to the above:</p> <ul style="list-style-type: none"> infection control strategy for inpatient facilities treatment for TB adherence issues range of adverse effects from TB medication
<p>TB Units</p> <p>In addition to the above:</p> <ul style="list-style-type: none"> support and monitor patients throughout their treatment order subsequent tests at the correct time and record results accurately refer or manage adverse effects as appropriate liaise with other support services according to patient need complete reports as appropriate 	<p>In addition to the above:</p> <ul style="list-style-type: none"> recommended TB control and management procedures complexity of patients' needs; methods to maximise adherence essential monitoring issues, e.g. patient progress; sputum conversion TB treatment, possible minor and severe adverse effects reporting procedures

Social mobilisation and advocacy

Social mobilisation, the active recruitment of patients and community members to support TB control strategies, is necessary to sustain support for TB control. TB affects whole communities and has social and economic as well as physical consequences. Social mobilisation means that community representatives become partners in the TB

control programme and work closely with the health services involved. It requires a strong relationship between the community and the TB control programme.

The four main activities of social mobilisation are:

- advocacy
- health education
- DOT treatment support
- programme support

Not all activities have to be implemented to achieve successful social mobilisation. In fact, the local community and the setting determine which activities are appropriate.

Advocacy

A suitable environment can be created for sustainable TB control when a community has strong and effective leadership and mobilises to demand appropriate services and political commitment. Advocacy can happen on many levels from high-level international lobbying to local advocacy to improve services and working conditions. Patient advocacy is an important part of a nurse's role as many nurses have demonstrated in the field of TB. Over the years, numerous examples have been given by nurses attending training reviews where they have made significant changes to their services and improved patient care as well as staff and patient safety. Changes have been made from the provision of the correct respirators, to separation of infectious from non-infectious patients, to the building of entirely new clinic areas. By identifying problems and targeting efforts real practical changes can be made and, ultimately, lives can be saved.

More details about nurses' achievements through advocacy can be found at www.icn.ch/tb-mdr-tb-project.html

The common thread was that they all

- knew what was required to make an improvement
- presented the suggestion to the right people who could help
- involved all the key partners and colleagues
- were patient and persistent
- made a personal commitment

Events, such as World TB Day on March 24th each year, raise TB awareness and help establish the need for commitment to effective TB control, adequate government funding and appropriate organisation of services.

Health education

Education of the public about TB is important. It should be part of an effective control programme that has a good cure rate and raises awareness about access to care and treatment. Increasing the knowledge of TB usually increases the demand for services and can result in advocacy for people's right to treatment and improved quality of care.

The health education plan must be relevant to available services and community needs. Before initiating a campaign, planners must carefully consider who should be involved and clarify the aim of the education. For example, one area for educational campaign could be to combat the stigma associated with TB patients. Stigma can be attached to any number of falsely held beliefs and myths. People may believe, for instance, that TB is incurable, runs in the family, is caused by having a dirty household, or is the result of a curse. The stigmas must be exposed and addressed before public TB education will be successful.

DOT treatment support

As mentioned earlier, members of the community can often provide invaluable support to patients on treatment. With appropriate training and support from the nurse, they can supervise a patient's treatment using the patient's treatment card and drugs provided by the TB service. Receiving treatment from a community member is often a very convenient alternative to the health clinic. This can enhance the patient's adherence to the treatment regimen and facilitate successful completion and cure. For example, in South Africa, local pharmacists and shopkeepers are trained to offer DOT and, in Malawi, volunteers act as guardians for TB patients. In Peru, for the two-year treatment of MDR-TB in 2002-2004, community volunteers were trained to observe two or three patients. In return, the volunteers received a basket of staples each month valued at US\$ 30. Nurses trained and supervised the volunteers.

Programme support

Community-based approaches rely on good organisation and support from the health services responsible for treating TB patients and require strong support from the district and national level.

The types of support needed for a successful community programme are:

- ongoing training and supervision of involved community members;
- a mechanism for providing essential supplies, such as TB drugs and sputum containers; and
- good communication between the community and the local health service to address questions and concerns.

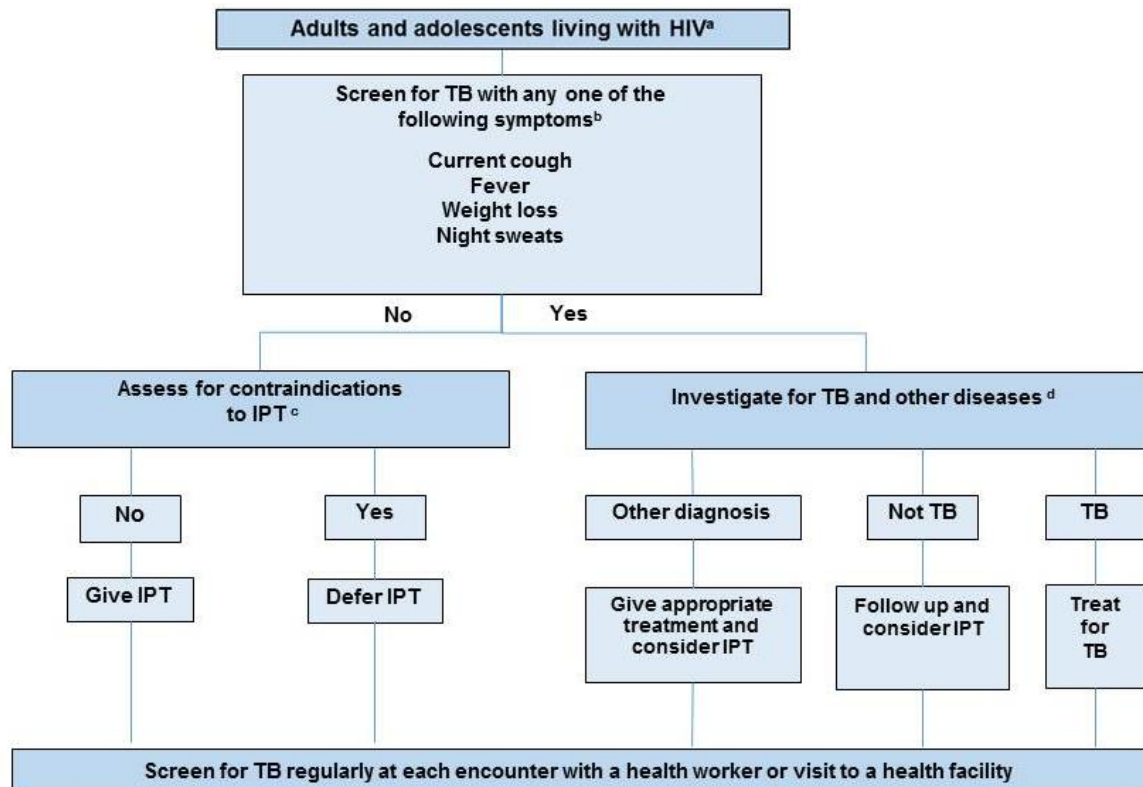
Conclusion

Nurses play a significant role in the control of drug-sensitive and drug-resistant TB all around the world. To be effective, the nurse must understand the disease, recognise the signs and symptoms of TB, and support patients' adherence to TB treatment. By adapting the best practice standards described in the next section of this guide to local settings and advocating for strong TB control programmes, nurses can maximise their role and have a real impact on TB control practices. However, nurses must also be protected while they care for others, and worker protection programmes must be instituted to enhance the nurse's ability to provide high quality care. On-going programme evaluation ensures programme effectiveness and enables continuous process improvement.

TB control involves all levels of the health system – international and national policy makers, regional and district TB coordinators and TB specialty nurses, as well as primary care nurses working in a variety of settings. The general practice nurse is the first line of defence in TB control worldwide, and this important role must be recognised and strengthened. ICN encourages you to learn more about TB in your community and to actively participate in establishing effective TB control programmes.

ANNEXES

Annex 1: Algorithm for Screening for TB among Adults and Adolescents



^a Every adult and adolescent should be evaluated for eligibility to receive antiretroviral therapy, infection prevention and control measures should be implemented to reduce TB transmission in all healthcare settings.

^b Chest radiography can be done if available, but is not required to classify patients into TB and non-TB groups. In settings with high HIV prevalence and a high TB burden among people living with HIV, strong consideration must be given to adding other sensitive investigations.

^c Contraindications include: active hepatitis (acute or chronic), regular and heavy alcohol consumption and symptoms of peripheral neuropathy. Past history of TB and current pregnancy should not be contraindications for starting IPT. Although not a requirement for initiating IPT, tuberculin skin testing may be performed as part of eligibility screening in some settings.

^d Investigations for TB should be performed in accordance with existing national guidelines.

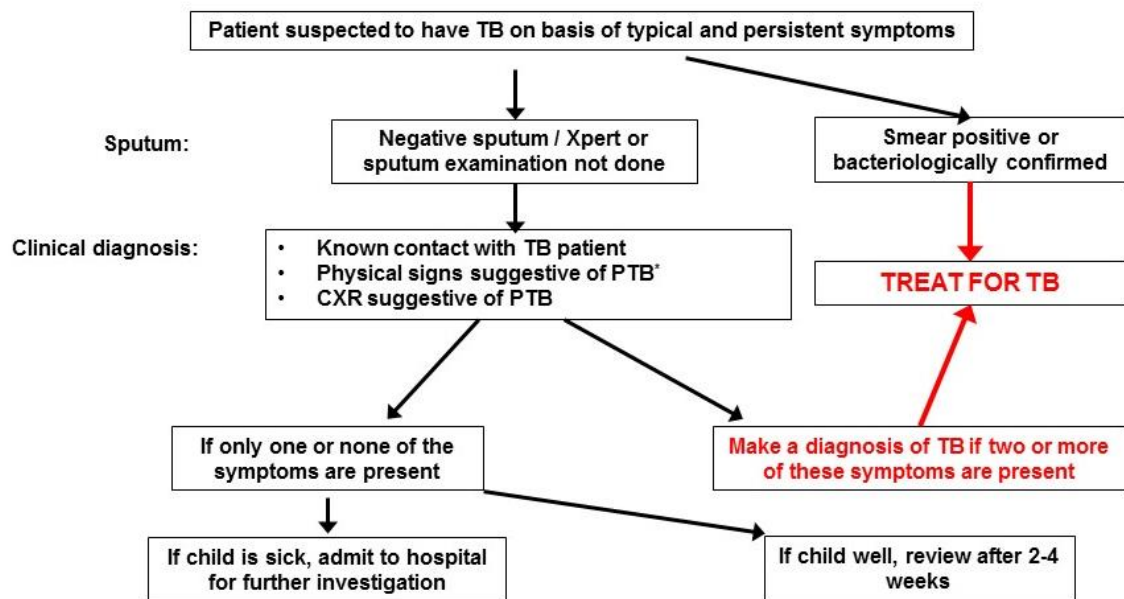
Source: *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: summary of key features and recommendations* (World Health Organization, 2013a)

Annex 2: TB Symptom Screening Tool Sample

TB SYMPTOM SCREENING TOOL FOR ADULTS AND CHILDREN			
PATIENT DETAILS			
Surname:		First Name:	
Physical Address:		Age:	
Telephone Number:		Patient folder Number:	
MEDICAL HISTORY			
Close contact of a person with infectious TB:	Yes	No	Unknown
Type of index patient:	DS-TB	Rif Resistant TB	MDR-TB or XDR-TB
Diabetic:	Yes	No	Unknown
HIV Status:	Positive	Negative	Unknown
Other: (Specify)	_____		
TB SYMPTOM SCREEN			
1. ADULTS			
Symptoms (Tick v)	Yes	No	
Cough of 2 weeks or more OR of any duration if HIV positive			
Persistent fever of more than two weeks			
Unexplained weight loss >1.5kg in a month			
Drenching night sweats			
2. CHILDREN			
Symptoms (Tick v)	Yes	No	
Cough of 2 weeks or more which is not improving on treatment			
Persistent fever of more than two weeks			
Documented weight loss/ failure to thrive (check Road to Health Card)			
Fatigue (less playful/ always tired)			
<p><i>If "Yes" to one or more of these questions, consider TB.</i></p> <p><i>If the patient is coughing, collect sputum specimen and send it for Xpert testing.</i></p> <p><i>If the patient is not coughing but has the other symptoms, clinically assess the patient or refer for further investigation.</i></p>			
Date of last TB test:			
Patient referred for assessment and investigation:		Yes	No
Date of referral:		Facility name:	
Name:		Date:	

Source: National tuberculosis management guidelines 2014 (Department of Health Republic of South Africa, 2014).

Annex 3: Algorithm for Diagnosing TB in Children



* The clinical and CXR signs suggestive of TB are listed on page 26.

Source: *Desk-guide for diagnosis and management of TB in children 2010 (The International Union Against Tuberculosis and Lung Disease, 2010)*

Annex 4: TB Drugs used for MDR-TB in Five Groups

Medication (drug abbreviation), (common presentation)	Daily dose	Weight Class					
		Dose range (use in patients ≥ 30 kg)					
		30-35 kg	36-45 kg	46-55 kg	56-70kg	>70 kg	
Isoniazid (H) (100, 300 mg)	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg	
Rifampicin (R) (150, 300 mg)	8-12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg	
Pyrazinamide (Z) (500 mg)	20-30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg	
Ethambutol (E) (100, 400 mg)	15-25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg	
Rifabutin (Rfb)	5-10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg	
Group 2: Injectable anti-TB drugs							
	Daily dose	30-33 kg	34-40 kg	41-45 kg	46-50 kg	51-70 kg	>70 kg
Streptomycin (S) (1 gram vial)	12-18 mg/kg once daily	500 mg	600 mg	700 mg	800 mg	900 mg	1000 mg
Kanamycin (Km) (1 gram vial)	15-20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Amikacin (Am) (1 gram vial)	15-20 mg/kg once daily	500 mg	625 mg	750 mg	875 mg	1000 mg	1000 mg
Capreomycin (Cm) (1 gram vial)	15-20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg
Group 3: Fluoroquinolones							
	Daily dose	30-35 kg	36-45 kg	46-55 kg	56-70kg	>70 kg	
Levofloxacin (Lfx) (250, 500 mg)	750-1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg	
Moxifloxacin (Mfx)	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg	

(400 mg)	once daily					
Gatifloxacin (Gfx)	400 mg	400 mg	400 mg	400 mg	400 mg	400 mg
(400 mg)	once daily					

Group 4: Oral bacteriostatic second-line anti-TB drugs

	Daily dose	30-35 kg	36-45 kg	46-55 kg	56-70kg	>70 kg
Ethionomide (Eto)	500-750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionomide (Pto)	500-750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine (Cs) (250 mg)	500-750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid (PAS) (4 gram sachets)	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8-12 g

Group 5: Anti-TB drugs with limited data on efficacy and/or long term safety in the treatment of drug-resistant TB (This group includes new anti-TB agents)

	Daily dose	30-35 kg	36-45 kg	46-55 kg	56-70kg	>70 kg
Bedaquiline (Bdq)		400 mg once daily for 2 weeks then 200 mg 3 times per week				
Clofazimine (Cfz)		200-300 mg (2 first months) then 100 mg				
Linezolid (Lzd)	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic acid 7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic acid 8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
High-dose isoniazid	16-20 mg/kg once daily	600-1000 mg	1000-1500 mg	1500 mg	1500 mg	1500 mg
Imipenem/cilastatin		1000 imipenem / 1000 mg cilastatin twice daily				
Meropenem		1000 mg three times daily (alternative dosing is 2000 mg twice daily)				

Adapted from the *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (World Health Organization, 2014b) and *Tuberculosis: Practical guide for clinicians, nurses, laboratory technicians and medical auxiliaries. 2014 edition* (Médécins Sans Frontières and Partners In Health, 2014).

Annex 5: Adverse Effects, Suspected Agents and Management Strategies in MDR-TB Treatment

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Rash, allergic reaction and anaphylaxis	Any drug	<ol style="list-style-type: none"> 1) For serious allergic reactions, stop all therapy until the reaction is resolved. If the patient experiences anaphylaxis, follow standard emergency protocols. 2) Eliminate other potential causes of allergic skin reaction. 3) For minor rash – agents such as antihistamines, hydrocortisone creams, low dose prednisone (10 to 20 mg/day for several weeks), and moisturizing lotion for dry skin. 4) Once rash resolves, reintroduce drugs one at a time with the most likely to cause the reaction last. 5) Suspend any drug permanently identified to be the cause. 	<ol style="list-style-type: none"> 1) History of previous drug allergies should be carefully reviewed and any known drug allergies should be noted on the treatment card. 2) Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with isoniazid and tyramine containing foods like cheese and red wine. If this occurs advise patients to avoid these foods. 3) Any of the drugs can cause hives (urticaria). To identify the drug, introduce the drugs one at a time. In the case of hives a desensitization attempt can be made. 4) Any drug that resulted in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced.
Arthralgia	Bedaquiline (Bdq), Pyrazinamide (Z), Fluoroquinolones (FQs)	<ol style="list-style-type: none"> 1) Initiate therapy with NSAIDs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day). 2) Lower dose of suspected drug (most commonly pyrazinamide), if this can be done without compromising regimen. 3) Discontinue suspected drug without compromising regimen. 4) Initiate exercise regimen. 	<ol style="list-style-type: none"> 1) Symptoms of arthralgia generally diminish over time, even without intervention. 2) Uric acid levels may be elevated in patients on pyrazinamide. Allopurinol should be used if gout is present. 3) If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.
Dysglycaemia and hyperglycaemia	Gatifloxacin (Gfx), Ethionomide / Prothionomide (Eto/Pto)	<ol style="list-style-type: none"> 1) Stop gatifloxacin and replace with different later generation fluoroquinolone like moxifloxacin. 2) Treat diabetes as needed. Good glucose control is important during treatment. 	

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Gastritis and abdominal pain	Para-aminosalicylic acid (PAS), Ethionomide (Eto), Protionomide (Pto), Clofazimine (Cfz), Fluoroquinolones (FQs), Isoniazid (H), Ethambutol (E), and Pyrazinamide (Z)	<p>1) Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.</p> <p>2) If symptoms are consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of fluoroquinolones.</p> <p>3. For severe abdominal pain stop suspected agent(s) for short periods of time (1 to 7 days).</p> <p>4. Lower the dose of or discontinue the suspected agent, if this can be done without compromising the regimen.</p>	<p>1) Severe gastritis, as manifested by blood in the vomit or stool is relatively rare.</p> <p>2) Dosing of antacids should be carefully timed so as to not interfere with the absorption of anti-TB drugs (<i>take two hours before or after anti-TB medications</i>).</p> <p>3) Stop any nonsteroidal anti-inflammatory drugs (NSAIDS) the patient may be taking.</p> <p>4. Diagnose and treat for <i>Helicobacter pylori</i> infections.</p> <p>5. Severe abdominal distress has been reported with clofazimine. Although this is rare, if this occurs, clofazimine should be suspended.</p> <p>6) Reversible upon discontinuation of suspected agent(s).</p>
Diarrhoea and/or flatulence	Para-aminosalicylic acid PAS), Ethionomide (Eto) Prothionomide (Pto)	<p>1) Educate patients that some degree of loose stools and flatulence may occur.</p> <p>2) Encourage fluid intake.</p> <p>3) Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24 hours.</p> <p>4) Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe.</p> <p>5) Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than an adverse effect of anti-TB drugs.</p>	<p>1) Consider other causes of diarrhoea:</p> <ul style="list-style-type: none"> • Pseudo-membranous colitis related to broad-spectrum antibiotics (such as the FQs) is a serious and even life threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudomembranous colitis. •parasites and common waterborne pathogens in the area should be evaluated in the patient and treated. •lactose intolerance, especially if patient has been exposed to new foods not normally part of their diet. <p>2) Loperamide can be used in children over two years of age.</p>
Lactic acidosis	Linezolid (Lzd)	<p>1) Stop linezolid if lactic acidosis occurs.</p>	<p>1) Lactic acidosis can be monitored with a blood test that measures lactic acid.</p>

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Hepatitis	Rifampicin (R), Isoniazid (H), Pyrazinamide (Z), Ethionomide (Eto), Prothionomide (Pto), Para-aminosalicylic acid (PAS), Ethambutol (E) Fluoroquinolone (FQs)	<p>1) Stop all therapy pending resolution of hepatitis.</p> <p>2) If enzymes are more than 5 times the upper limit of normal, stop all hepatotoxic drugs and continue with at least 3 non-hepatotoxic medications (for example, the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the 3-drug regimen, then stop all drugs.</p> <p>3) Rule out other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis).</p> <p>4) Consider suspending most likely agent permanently Re-introduce remaining drugs, one at a time with the most hepatotoxic agents first, while monitoring liver function.</p>	<p>1) History of prior hepatitis should be carefully analyzed to determine most likely causative agent(s); these should be avoided in future regimens.</p> <p>2) Viral serology should be done to rule out other aetiologies of hepatitis if available, especially to hepatitis A, B and C.</p> <p>3) Assess patient for alcohol abuse and refer for treatment if appropriate.</p> <p>4) Generally reversible upon discontinuation of suspected agent.</p>
Hypothyroidism	Para-aminosalicylic acid (PAS), Ethionomide (Eto), and Prothionomide (Pto), especially when given in combination.	<p>1) Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: Young healthy adults to be started on 75–100 mcg daily.</p> <ul style="list-style-type: none"> • Older patients should start treatment with 50 mcg daily. • Patients with significant cardiovascular disease should start at 25 mcg daily. <p>2) Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.</p>	<p>1) Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate.</p> <p>2) Do not start treatment unless TSH is above 1.5 – 2.0 time of the upper normal limit.</p> <p>3) It is completely reversible upon discontinuation of PAS and/or Eto/Pto.</p> <p>4) The combination of ethionamide/protonamide with PAS is more frequently associated with hypothyroidism than when each individual drug is used.</p>
Optic neuritis	Ethambutol (E), Ethionomide (Eto), Prothionomide (Pto), Linezolid (Lzd), Clofazimine (Cfz), Isoniazid (H), Rifabutin (Rfb)	<p>1) Stop ethambutol (E) and do not restart.</p> <p>2) Refer patient to an ophthalmologist.</p>	<p>1) Usually reverses with cessation of ethambutol (E).</p> <p>2) Improve diabetes control in diabetic patients.</p>

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Nausea and vomiting	Ethionomide (Eto), Prothionomide (Pto), Para-aminosalicylic acid (PAS), Bedaquiline (Bdq), Amoxicillin/Clavulanate (Amx/Clv), Isoniazid (H), Ethambutol (E), Pyrazinamide (Z), Clofazimine (Cfz)	<p>1) Assess for dehydration Initiate rehydration therapy if Indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin (Hgb) and treat for possible bleeding ulcers.</p> <p>2. Initiate a stepwise approach to manage nausea and vomiting.</p> <p><u>Phase 1:</u> —Give Eto/Pto at night —Give Eto or PAS twice or three times daily —Give a light snack (biscuits, bread, rice, tea) before the medications —Give PAS two hours after other anti-TB drugs.</p> <p><u>Phase 2:</u> Start antiemetic(s): —Metoclopramide 10 mg, 30 minutes before anti-TB medications. —Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose.</p> <p><u>Phase 3:</u> Lower the dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.</p>	<p>1) Nausea and vomiting are common in early weeks of therapy and usually decrease with time on treatment and supportive therapy. Some nausea and vomiting may be unavoidable in the initial period.</p> <p>2) Electrolytes and creatinine should be monitored if vomiting is severe. Give intravenous fluids and replace electrolytes as needed.</p> <p>3) Reversible upon discontinuation of suspected agent.</p> <p>4) Ondansetron is a serotonin 5-HT₃ receptor antagonist and considered to have strong antiemetic properties. It is on the WHO essential drug list. A number of other antiemetics from this class of serotonin 5-HT₃ receptor antagonists exist. Trying different antiemetics, even if from the same class may be helpful for some patients. <i>Ondansetron prolongs the QT interval; avoid with bedaquiline.</i></p> <p>5) Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).</p> <p>6) For patients particularly anxious about the nausea, (and with “anticipatory nausea and vomiting”) a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs.</p>
Metallic taste	Ethionomide / Prothionomide (Eto/Pto), Clarithromycin (Clr), Fluoroquinolones (FQs)	<p>1) Educate patients about this possible side effect.</p> <p>2) Sucking hard candy or chewing gum can be helpful.</p>	<p>1) Resolution occurs after treatment is stopped.</p>

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Vestibular toxicity (Tinnitus and dizziness)	Streptomycin (S), Kanamycin (Km), Amikacin (Am), Capreomycin (Cm), Cycloserine (Cs), Fluoroquinolones (FQs), Isoniazid (H), Ethionomide (Eto), Linezolid (Lzd)	<p>1) If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice or three times a week. Also, consider using Cm if an aminoglycoside had been the prior injectable in the regimen.</p> <p>3. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.</p>	<p>1) Ask the patient about tinnitus and unsteadiness every week.</p> <p>2) Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity.</p> <p>3) A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, H or Lzd. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve on withholding medications.</p>
Hearing loss	Streptomycin (S) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm) Clarithromycin (Clr)	<p>1) Document hearing loss and compare to baseline audiometry.</p> <p>2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using Cm if an aminoglycoside had been the prior injectable in the regimen.</p> <p>3) Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing.</p>	<p>1) Patients with prior exposure to aminoglycosides may have baseline hearing loss. In such patients, it may be helpful to obtain audiometry at the initiation of MDR-TB therapy.</p> <p>2) <i>Hearing loss is almost always permanent. Continuing the injectable agent despite hearing loss almost always results in irreversible deafness.</i></p> <p>3) The risk of further hearing loss must be weighed with the risks of stopping the injectable in the treatment regimen.</p> <p>4) While the benefit of hearing aids is minimal to moderate in auditory toxicity, consider a trial use to determine if a patient with hearing loss can benefit from their use.</p>
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Streptomycin (S) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)	<p>1) Check Potassium</p> <p>2) If Potassium is low also check magnesium (and calcium if hypocalcemia is suspected)</p> <p>3) Replace electrolytes as needed. Dose oral electrolytes apart from FQs as they can interfere with FQ absorption.</p>	<p>1) If severe hypokalaemia is present, consider hospitalization.</p> <p>2) Amiloride 5-10 mg daily or spironolactone 25 mg daily may decrease potassium and magnesium wasting and is useful in refractory cases.</p> <p>3) Oral potassium replacements can cause significant nausea and vomiting. Oral magnesium may cause diarrhoea.</p>

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Seizures	Cycloserine (Cs), Isoniazid (H), Fluoroquinolones (FQs), valproic acid	<p>1) Suspend suspected agent (Cs, H, FQs) pending resolution of seizures.</p> <p>2) Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid).</p> <p>3) Consider increasing pyridoxine to maximum daily dose (200 mg daily).</p> <p>4) Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride.</p> <p>5) Restart suspected agent or reinstitute suspected agent at lower dose, if essential to the regimen. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If Cs is reinstated, start a dose one weight band lower.</p>	<p>1) Anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agent discontinued.</p> <p>2) History of prior seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well-controlled and/or the patient is receiving anticonvulsant therapy (Do not include Cs if an alternative drug is available).</p> <p>3) Patients with history of prior seizures may be at increased risk for development of seizures during MDR-TB therapy.</p> <p>4) Always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of Cs, which can cause seizures. Adjusting the dose of Cs in the presence of low creatinine may be all that is needed to control the seizures.</p>
Peripheral neuropathy	Cycloserine (Cs), Linezolid (Lzd), Isoniazid (H), Streptomycin (S), Kanamycin (Km), Amikacin (Am), Capreomycin (Cm), Ethionomide /Prothionomide (Eto/Pto), Ethambutol (E), Fluoroquinolones (FQs)	<p>1) Correct any vitamin or nutritional deficiencies. Consider increasing pyridoxine to 300 mg daily.</p> <p>2) Initiate therapy with NSAIDS or acetaminophen (may help alleviate symptoms), tricyclic anti-depressants, gabapentin (300 mg three times per day), carbamazepine (100 – 400 mg twice per day) if available.</p> <p>3) Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.</p> <p>4) Consider whether the dose of Cs can be reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible, switching the aminoglycoside to Cm may also be helpful.</p>	<p>1) Patients with co-morbid disease (e.g. diabetes, HIV, alcohol abuse) may be more likely to develop peripheral neuropathy, but these conditions are not contraindications to the use of the agents listed here.</p> <p>2) Neuropathy may be irreversible; however, some patients may experience improvement when offending agents are suspended. The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be strongly considered when neuropathy develops due to linezolid.</p>

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Renal failure (Nephrotoxicity)	Streptomycin (S) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)	<ol style="list-style-type: none"> 1) Discontinue suspected agent. 2) Consider using Capreomycin if an aminoglycoside had been the prior injectable drug in regimen. 3) Consider other contributing aetiologies (NSAIDs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated. 4) Follow creatinine (and electrolyte) levels closely, every one to two weeks. 5) Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent. 6) Adjust all TB medications according to the creatinine clearance. 	<ol style="list-style-type: none"> 1) History of diabetes or renal disease is not a contraindication to the use of the agents listed here, although patients with these co-morbidities may be at increased risk for developing renal failure. 2) Renal impairment may be permanent.
Haematological abnormalities	Linezolid (Lzd)	<ol style="list-style-type: none"> 1) Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosuppression resolves and if linezolid is considered essential to the regimen. 2) Consider nondrug related causes of the haematological abnormality. 3) Consider blood transfusion for severe anaemia 	<ol style="list-style-type: none"> 1) Haematological abnormalities (leukopenia, thrombocytopenia, anaemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. 2) There is little experience with prolonged use of linezolid
Suicidal ideation	Cycloserine (Cs), Isoniazid (H), Ethionomide / Prothionomide (Eto/Pto)	<ol style="list-style-type: none"> 1) Hospitalize the patient and put under 24-hour surveillance. 2) Discontinue cycloserine. 3) Request psychiatric consultation. 4) Initiate antidepressant therapy. 5) Lower the dose of Eto/Pto to 500 mg daily until the patient is stable. 	<ol style="list-style-type: none"> 1) Keep the patient in the hospital until risk of suicide has passed. 2) If no improvement occurs after stopping Cs, hold H and/or Eto/Pto.

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Psychotic symptoms	Cycloserine (Cs), Isoniazid (H), Fluoroquinolones (FQs)	<p>1) Hold suspected agent for a short period of time (one to four weeks) while psychotic symptoms are brought under control. (The most likely drug is cycloserine followed by high dose isoniazid.)</p> <p>2) Initiate anti-psychotic drugs (haloperidol) if severe symptoms persist.</p> <p>3) Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.</p> <p>4. Increase pyridoxine to the maximum daily dose (200 mg per day).</p> <p>5) Lower dose of suspected agent (most commonly cycloserine 500 mg/day), if this can be done without compromising regimen.</p> <p>6) Discontinue suspected agent if this can be done without compromising regimen.</p> <p>7. Once all symptoms resolve and patient is off Cs, antipsychotic therapy can be tapered off. If Cs is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.</p>	<p>1) Some patients will need to continue anti-psychotic treatment throughout MDR-TB therapy.</p> <p>2) Prior history of psychiatric disease is not contraindicated with Cs, but may increase the likelihood of development of psychotic symptoms developing during treatment.</p> <p>3) Some patients will tolerate Cs with an antipsychotic drug but this should be done in consultation with a psychiatrist, as these patients will need to be under special observation; this should only be done when there is no other alternative.</p> <p>4) Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent.</p> <p>5) Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.</p>
Gynaecomastia	Ethionomide / Prothionomide (Eto/Pto)	<p>1) Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported.</p> <p>2) Educate patients about this potential side effect.</p>	1) Resolution occurs after treatment is stopped.
Superficial fungal infection and thrush	Fluoroquinolones (FQs) and other antibiotics with antibacterial properties	<p>1) Topical antifungal agents or short-course oral antifungal drugs are helpful.</p> <p>2) Exclude other diseases if response to treatment is not prompt (such as HIV).</p>	

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Depression	Socioeconomic circumstances, chronic disease, Cycloserine (Cs), Fluoroquinolones (FQs), Isoniazid (H), Ethionomide / Prothionomide (Eto/Pto)	1) Assess and improve socioeconomic conditions. 2) Group or individual counselling. 3) Initiate anti-depressant drugs (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid. 4) Lower dose of suspected agent, if this can be done without compromising the regimen. (Example: reduce the dose of Cs and Eto to 500 mg daily to see if the depression improves) 5) Discontinue suspected agent if this can be done without compromising regimen. 6). Assess patients for coexisting substance abuse and refer to treatment if appropriate.	1) Importance of socioeconomic conditions and chronic illness should not be underestimated as a contributing factor to depression. 2) Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3) History of prior depression is not a contraindication to the use of the agents listed here, however, these patients may be at increased risk for developing depression during MDR-TB treatment. If significant depression is present at the start of treatment, avoid a regimen with Cs, if possible. 4) Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
QT prolongation	Bedaquiline (Bdq), Fluoroquinolones (FQs), Clarithromycin (Clr), Clofazimine (Cfz)	Any patient found to have a QTc value greater than 500 ms should be managed carefully. <ul style="list-style-type: none"> • Repeat ECG and confirm the prolongation. • Bedaquiline should be stopped for QTc value greater than 500 ms. Consider stopping other drugs that prolong the QT interval. • Check potassium, calcium and magnesium levels. Electrolyte levels should be maintained in the normal range. • It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl. • Avoid other drugs that increase the QT interval. Monitor the patient's renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present. Consider suspension of fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug.	1) The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard ECG. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. A normal QTc is generally <440 ms. 2) Values above QTc 440 ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. Patients with QTc greater than 500 ms are at the greatest risk for developing these arrhythmias. 3) The fluoroquinolones cause prolongation of the QTc. Moxifloxacin and gatifloxacin cause the greatest QTc prolongation, while levofloxacin and ofloxacin have a lower risk. 4) Currently, ECG monitoring prior to initiation and during MDR-TB therapy is only required with the use of bedaquiline.

Adverse Reaction	Suspected Agent(s)	Suggested management strategies	Comments
Headache	Cycloserine (Cs) Bedaquiline (Bdq)	1) Rule out more serious causes of headache including meningitis, and other infections of the central nervous system. 2) Start analgesics like ibuprofen (NSAID) or paracetamol. Also encourage good hydration. 3) Consider low dose tricyclic antidepressants for refractory headaches.	1) Headaches are common during the initial months of MDR-TB treatment. They can present as migraine or cluster headaches. 2) To minimize headaches at the start of treatment, cycloserine can be started at a lower dose of 250-500 mg and gradually increased over one to two weeks to achieve the target dose. 3) Headaches due to cycloserine and bedaquiline are usually self-limited. 4) Pyridoxine should be given to all patients receiving cycloserine to help prevent neurotoxicity. The recommended dose is 50 mg for every 250 mg of cycloserine prescribed.
Alopecia	Isoniazid (H), Ethionomide / Prothionomide (Eto/Pto)	1) Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2) Educate patients about the possibility of hair loss.	1) Significant cosmetic change has not been reported.

Adapted from *Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis* (World Health Organization, 2014b).

Annex 6: Factors Affecting Adherence

Tuberculosis	Factors affecting adherence	Interventions to improve adherence
Social/economic Factors	<p>(-) Lack of effective social support networks and unstable living circumstances; culture and lay beliefs about illness and treatment; stigma; ethnicity, gender, and age; high cost of medication; high cost of transport; criminal justice involvement; involvement in drug dealing</p>	<p>Assessment of social needs, social support, housing, food tokens, and legal measures; providing transport to treatment settings; peer assistance; mobilization of community-based organizations; optimizing the cooperation between services; education of the community and providers to reduce stigma; family and community support</p>
Health system/ healthcare team factors	<p>(-) Poorly developed health services; inadequate relationship between healthcare provider and patient; healthcare providers who are untrained, overworked, inadequately supervised or unsupervised in their tasks; inability to predict potentially non-adherent patients</p> <p>(+) Good relationships between patient and physician; availability of expertise; links with patient support systems; flexibility in the hours of operation</p>	<p>Uninterrupted, ready availability of information; training and management processes that aim to improve the way providers care for patients with tuberculosis; support for local patient organizations/groups; management of disease and treatment in conjunction with the patients; multidisciplinary care; intensive staff supervision; training in adherence monitoring; use of DOT</p>
Condition-related factors	<p>(-) Asymptomatic patients; drug use; altered mental states caused by substance abuse; depression and psychological stress</p> <p>(+) Knowledge about TB Education on use of medications; provision of information about tuberculosis and the need to attend for treatment</p>	<p>Education on use of medications; provision of information about tuberculosis and the need to attend for treatment</p>
Therapy-related factors	<p>(-) Complex treatment regimen; adverse effects of treatment; toxicity</p>	<p>Education on use of medications and adverse effects of medications; adherence education; use of fixed dose combination preparations; tailor treatment support to needs of patients at risk of non-adherence; agreements (written or verbal) to return for an appointment or course of treatment; continuous monitoring and reassessment</p>
Patient-related factors	<p>(-) Forgetfulness; drug abuse; depression; psychological stress; isolation due to stigma</p> <p>(+) Belief in the efficacy of treatment; motivation</p>	<p>Therapeutic relationship; mutual goal-setting; memory aids and reminders; incentives and/or reinforcements; reminder letters, telephone reminders or home visits for patients who default</p>

Adapted from *International Standards for Tuberculosis Care (ISTC)* (Tuberculosis Coalition for Technical Assistance, 2006).

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