

Ministry of Health and Population
National Tuberculosis control Program



Tuberculosis Control Guidelines

Egypt, 2017

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Preface

WHO's declaration of tuberculosis as a global public health emergency in 1993 ended a period of prolonged global neglect. Together, the subsequent launch of the directly observed treatment, short course (DOTS) strategy; inclusion of tuberculosis-related indicators in the Millennium Development Goals; development and implementation of the Stop TB Strategy that underpins the Global Plan to Stop TB 2006–2015.



We stand now at a crossroads as the United Nations move from the 2015 Millennium Development Goals (MDGs) to the Sustainable Development Goals (SDGs) for 2030. Integral to this transition, the world community is launching a dramatically accelerated fight against tuberculosis and for those most affected by it: the poorest, most vulnerable, socially marginalized and inequitably served. The World Health Organization's new and holistic strategy approved by the World Health Assembly of 194 Member States in 2014 is the End TB Strategy.

Under this strategy, new, ambitious yet feasible global targets are proposed for 2035. These include achieving a 95% decline in deaths due to tuberculosis compared with 2015, and reaching an equivalent 90% reduction in tuberculosis incidence rate.

Ministry of Health and Population in Egypt, through the National Tuberculosis Control Program, adopted this new strategy towards elimination of Tuberculosis through certain pillars. These include; integrated, patient-centered care and prevention to early diagnose the disease including universal drug susceptibility testing, and systematic screening of contacts and high-risk groups, treatment of all people with tuberculosis including drug-resistant tuberculosis, and patient support, collaborative TB/HIV activities.

Introduction of the new molecular rapid diagnostics is an important tool to achieve the target of the early diagnosing cases to minimize the infection transmission cycle and decrease morbidity of the patient.

Engagement of communities, civil society organizations, and public and private care providers is an important pillar that even was adopted by the Egyptian TB control program since the Stop TB Strategy was developed.

Another innovative approach is operational research. Research is considered the scientific backbone of the NTP through which the situational analysis and introduction of new policies and interventions can be made.

The Guide is meant for physicians involved in the management of TB in Egypt. Its content is based on the latest views and technologies in TB control.

The Guide provides the reader with practical guidelines and instructions on the management of TB. These guidelines are based on the national policies for tuberculosis control in Egypt and should be followed by all agencies involved in tuberculosis control activities. The guidelines in this Guide follow the international guidelines from the World Health Organization (WHO).

Minister of Health & Population

Prof. Ahmed Emad El Din Radi

A handwritten signature in blue ink, corresponding to Prof. Ahmed Emad El Din Radi. The signature is stylized and cursive, written over a light blue horizontal line.

Acknowledgement

It would have been impossible without the kind support and help of many individuals that these guidelines had been developed.

The national Tuberculosis control Program, NTP, of Egypt would like to extend sincere thanks to all of them those who shared in developing these guidelines.

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NTP Executive Manager

**Dr. Wagdy Abdel Moneim Amin
March 2017**

Editors of Guidelines

Scientific Committee

Prof. Mohamed Awad Tag El Din

- Chairman of Scientific committee and professor of chest diseases - Ain Shams University

Prof. Adel Khattab

- Chairman of Egyptian Board , professor of chest diseases - Ain Shams University

Prof. Ahmed El Hadidi

- Professor of chest diseases , Head of Chest departement - Cairo University

Prof. Yasser Mostafa

- Professor of chest diseases , Head of Chest departement - Ain Shams University

Prof. Mostafa Ragab

- Professor of chest diseases , Head of Chest departement - Zagazig University

NTP Staff

Dr. Wagdy Amin

General Director for Chest Diseases ,
NTP Manager

Dr. Magdy Fawzy

MDR Coordinator

Dr. Amal Galal

Surveillance Coordinator

Dr. Nabila Wahib

Supervision Coordinator

Dr. Amal Salah

Infection Control Coordinator

Dr. Mohamed Abdel Halim

PPM Coordinator

Dr. Abeer Shams

Training Coordinator

Dr. Magda Mahmoud

PSM Coordinator

Historical overview

Consumption, phthisis, scrofula, Pott's disease, and the White Plague are all terms used to refer to tuberculosis throughout history.

Signs of the disease have been found in Egyptian mummies dated between 3000 and 2400 BCE. It appears likely that Akhenaten and his wife Nefertiti both died from tuberculosis, and evidence indicates that hospitals for tuberculosis existed in Egypt as early as 1500 BCE

In 460 BC, Hippocrates identified phthisis (Greek word meaning "consumption") as the most widespread disease of the times and notes that it is almost always fatal.

In 1854 AC, Brehmer built the first sanatorium in Gorbardsdorf, Poland, to provide two main functions: guarantee isolation of the sick from the general population and assist the healing process through enforced rest and proper diet.

In 1882, Koch identified the tubercle bacillus and convicts it of causing tuberculosis.

In 1900, Calmette and Guérin discover the vaccine (BCG) that is obtained from attenuation of a strain of *Mycobacterium bovis*.

Streptomycin (1943), *p*-aminosalicylic acid (1949), Isoniazid (1952), Pyrazinamide (1954), Cycloserine (1955), Ethambutol (1962) and Rifampicin (1963) are introduced as anti-TB agents, leading to progressive decline in TB incidence in the industrialized countries.

In 1980s and 1990s, The AIDS epidemic has serious repercussions on TB epidemiology, increasing the incidence of TB both in industrialized countries and in developing countries. Multi drug resistance poses increasing problems with regard to the efficacy of the therapy in use.

GLOBAL AND REGIONAL TB STATUS¹

- The TB epidemic is larger than previously estimated, reflecting new surveillance and survey data from India. However, the number of TB deaths and the TB incidence rate continue to fall globally and in India.
- In 2015, there were an estimated 10.4 million new (incident) TB cases worldwide, of which 5.9 million (56%) were among men, 3.5 million (34%) among women and 1.0 million (10%) among children. People living with HIV accounted for 1.2 million (11%) of all new TB cases.
- Six countries accounted for 60% of the new cases: India, Indonesia, China, Nigeria, Pakistan and South Africa. Global progress depends on major advances in TB prevention and care in these countries. Worldwide, the rate of decline in TB incidence remained at only 1.5% from 2014 to 2015.
- This needs to accelerate to a 4–5% annual decline by 2020 to reach the first milestones of the End TB Strategy.
- In 2015, there were an estimated 480 000 new cases of multidrug-resistant TB (MDR-TB) and an additional 100 000 people with rifampicin-resistant TB (RR-TB) who were also newly eligible for MDR-TB treatment.² India, China and the Russian Federation accounted for 45% of the combined total of 580 000 cases.
- There were an estimated 1.4 million TB deaths in 2015, and an additional 0.4 million deaths resulting from TB disease among people living with HIV. Although the number of TB deaths fell by 22% between 2000 and 2015, TB remained one of the top 10 causes of death worldwide in 2015.

TB care and prevention results

- TB treatment averted 49 million deaths globally between 2000 and 2015, but important diagnostic and treatment gaps persist.
- In 2015, 6.1 million new TB cases were notified to national authorities and reported to WHO. Notified TB cases increased from 2013–2015, mostly due to a 34% increase in notifications in India. However, globally there was a 4.3 million gap between incident and notified cases, with India, Indonesia and Nigeria accounting for almost half of this gap.
- The crisis of MDR-TB detection and treatment continues.
- In 2015, of the estimated 580 000 people newly eligible for MDR-TB treatment, only 125 000 (20%) were enrolled. Five countries accounted for more than 60% of the gap: India, China, the Russian Federation, Indonesia and Nigeria. Globally, the MDR-TB treatment success rate was 52% in 2013.

¹ *DATA FROM THE 2015 WHO GLOBAL TB REPORT*

- In 2015, 55% of notified TB patients had a documented HIV test result. The proportion of HIV-positive TB patients on antiretroviral therapy (ART) was 78%.
- Access to TB preventive treatment needs to be expanded.
- A total of 910 000 people living with HIV were started on such treatment in 2015, as well as 87 000 children under five (7% of those eligible).

TB disease burden

- Upward revisions to estimates of the burden of TB disease in India for the period 2000–2015 follow accumulating evidence that previous estimates were too low. This evidence includes household surveys, a state-wide TB prevalence survey, studies of anti-TB drug sales in the private sector, notification data and new analysis of mortality data. Since India accounts for more than one quarter of the world's TB cases and deaths, these revisions have had a major impact on global estimates. Estimates for India are considered interim, pending a national TB prevalence survey scheduled for 2017/2018.
- The proportion of TB cases living with HIV was highest in the WHO African Region (31%), and exceeded 50% in parts of southern Africa.
- In addition to accelerating the annual decline in TB incidence, reaching the 2020 milestone for a 35% reduction in TB deaths requires reducing the global proportion of people with TB who die from the disease (the case fatality ratio or CFR) from 17% in 2015 to 10% by 2020.
- The CFR in 2015 varied from under 5% in a few countries to more than 20% in most countries in the WHO African Region. This shows considerable inequalities among countries in access to TB diagnosis and treatment that need to be addressed. If everyone with TB had a timely diagnosis and high-quality treatment, the CFR would be low in all countries.
- National notification and vital registration systems (with standard coding of causes of death) of high coverage and quality are needed in all countries. In the interim, national TB prevalence surveys will continue to provide the best method for directly measuring the burden of TB disease
- and identifying actions required to reduce that burden in an important subset of countries. In recent years, there has been enormous progress in implementing such surveys, with 22 completed between 2009 and August 2016.

Diagnosis and treatment: TB, HIV-associated TB and drug-resistant TB

- The global male: female (M: F) ratio for notifications was 1.7, varying from 1.0 in Pakistan to 3.1 in Viet Nam among the 30 high TB burden countries. Results from national TB prevalence surveys of adults show higher M:F ratios, indicating that notification data understate the share of the TB burden accounted for by men in some countries. Globally, children (aged <15 years) accounted for 6.3% of the new cases that were notified in 2015.

- In 2015, 30% of the 3.4 million new bacteriologically confirmed and previously treated TB cases notified globally were reported to have had drug susceptibility testing for rifampicin, with coverage of 24% for new TB patients and 53% for previously treated TB patients.
- The only WHO-recommended rapid diagnostic test for detection of TB and rifampicin resistance currently available is the Xpert MTB/RIF® assay. Of the 48 countries in at least one of the three new lists of high burden countries, 15 had adopted national algorithms positioning Xpert MTB/RIF as the initial diagnostic test for all people with signs and symptoms of pulmonary TB by the end of 2015. These countries accounted for 10% of the estimated global number of incident TB cases in 2015.
- In 2015, the gap of 4.3 million between notifications of new cases and the estimated number of incident cases reflects a mixture of underreporting of detected TB cases (especially in countries with large private sectors) and under diagnosis (especially in countries where there are major geographic or financial barriers to accessing care).
- Ten countries accounted for 77% of the total estimated gap: India, Indonesia, Nigeria, Pakistan, South Africa, Bangladesh, the Democratic Republic of the Congo, China, the United Republic of Tanzania and Mozambique.
- In the African Region where the burden of HIV associated TB is highest, 81% of notified TB patients had a documented HIV test result. The proportion of known HIV-positive TB patients on ART was above 90% in India, Kenya, Malawi, Mozambique, Namibia and Swaziland.
- The latest treatment outcome data show a treatment success rate of 83% for TB (2014 cohort), 52% for MDRTB (2013 cohort) and 28% for extensively drug-resistant TB (XDR-TB; 2013 cohort).
- At least 23 countries in Africa and Asia have introduced shorter regimens for treatment of MDR-TB or RR-TB. These have achieved high treatment success rates (87–90%) under operational research conditions. A standardized regimen of 9–12 months is recommended by WHO for all patients (excluding pregnant women) with pulmonary MDR/RR-TB that is not resistant to second-line drugs.
- As part of efforts to improve outcomes for MDR/XDR-TB, at least 70 countries had started using bedaquiline and 39 countries had introduced delamanid by the end of 2015.

Epidemiological situation in Egypt

Prevalence

In 1990, the WHO estimated the prevalence of tuberculosis in Egypt to be **82** (37-144)/100,000 population. The national population in 1990 was projected at 56,336,614 and the absolute number of prevalent TB cases in that year was estimated to be 46,000 (21,000 – 81,000).

Uncertainty intervals in the early estimates are wide. By 2013, the national population is projected to have increased by 46% to 82,056,378 while the (best) estimate of prevalence had declined to close to a third of the 1990 estimate to **27** (14-44) /100,000 population with the absolute numbers of prevalent TB estimated to be about 22,000 (12, -36,000) – and uncertainty intervals are less wide.

It is to be noted that despite the wide confidence intervals in the estimates (14 to 44 for the year 2013), the decline in prevalence is definite and the rate of decline varies between -7 to -9% annually during the period 1990 to 1999, between -3 to -6% annually during the period 1999 to 2005 and between 0 to -4% annually since then.

According to the latest WHO estimation, the prevalence is 25 cases per 100,000 population in the year 2014.

Incidence

In 1990, the WHO estimated the incidence of tuberculosis in Egypt to be 35 (32-39)/100,000 population. The national population in 1990 was 56,336,614 and the absolute number of TB cases occurring in that year was estimated to be 20,000 (18, – 22,000). By 2013, the national population had increased by 46% to 82,056,378 while the (best) estimate of incidence had declined by more than half to 16 (15-18)/100,000 population with the absolute numbers estimated to be about 13,000 (12,000 -15,000).

It is to be noted that the confidence intervals of this estimation provide more certainty to the estimations and that the decline in incidence is definite. The rate of decline varies – it is about -3% annually from 1990 to 1998, increases to -4% annually during the period 1999 to 2004 and is about -6% annually thereafter with some years (2008/9 and 2011/12) showing no change.

According to the latest WHO estimation, the incidence is 15 cases per 100,000 population in the year 2015.

Case notification

Annual case notification rates (all forms, new and relapses) declined at the national level from 16/100,000 in the year 2000, when the DOTS strategy had been expanded countrywide to 10/100,000 in 2013.

In 2013, the country notified 8,183 TB patients of which 7,876 were incident (new and relapses) and 307 were previously treated (excluding relapses). Relapses accounted for 4% (342/7,876) of incident TB in 2013. Retreatment accounted for 8% (649/8,183) of all cases notified that year.

Amongst new cases, 65% (4,906/7,534) had a diagnosis that was bacteriologically confirmed (smear or culture) and 34% (2,565/7,534) were extra-pulmonary forms of TB. The case detection rate, which approximates to the NTP's effort to detect and diagnose all incident TB cases annually was 67.26% in 2000 and exceeded 70% (the global target) for 10 out of the 14 years in the period 2000-2013. For 2015, it was 59%.

HIV associated TB

In the year 2013 (1,467) TB patients were tested for HIV (17%). Testing for HIV does not seem to be uniform sub-nationally. In September 2014, on-site data validation (OSDV) showed that in 12/27 governorates, not a single TB patient was tested for HIV in 2013.

Eight governorates had tested over 30% of their registered TB patients for HIV included Alexandria, Cairo, Damietta, Fayoum, Gharbia, Kafr El-Sheikh, Port Said and Suez. Three governorates – Gharbia, Port Said and Suez had tested over half of their TB patients and Port Said had the highest rate for HIV testing at 76%.

Amongst those tested (1467), 51 were positive; 38/51 (75%) positives were from just two governorates – Alexandria and Cairo (19 each) and a further 9 were from Giza. Positivity rate amongst those tested with a rapid test is estimated to be 3% from this report.

Drug resistant TB

The second national drug resistance survey was conducted between 2010 and 2012 and the results of the survey are abstracted in the table below. There is not much marked difference in the levels of multidrug resistant TB (MDR-TB) between the findings in this survey versus an earlier survey conducted in 2002 (the data from the earlier survey are within the uncertainty levels of this survey).

Background resistance to streptomycin is high with one in every five new and almost half of all retreatment TB patients notified demonstrating resistance to the drug; streptomycin is available for use within pharmacies in public health facilities.

Comparing results of the two conducted surveys

Resistance pattern	New		Previously treated	
	2012	2002	2012	2002
Any resistance				
R resistance	(12.8%)	7%	(43.2%)	50.5%
H resistance	(10.8%)	9.8%	(38.1%)	46.5%
S resistance	(21.0%)	23.6%	(44.1%)	53.5%
E resistance	(2.6%)	2.8%	(18.9%)	30.9%
Mono-resistance				
Resistance to R only	(8.6%)	3.5%	(7.8%)	6.9%
Resistance to H only	(1.9%)	2.7%	(2.4%)	2.8%
Resistance to S only	(12.0%)	15%	(9.7%)	7.8%
Resistance to E only	(1.0%)	0.5%	(0.5%)	0.9%
MDR-TB				
H+R	(1.05%)	0%	(4.3%)	2.3%
H+R+E	(0.19%)	0%	(0.3%)	0.9%
H+R+S	(2.1%)	0.8%	(11.6%)	9.7%
H+R+S+E	(0.9%)	1.4%	(16.2%)	25.3%
All MDR (final adjusted) estimate)	(3.4%)	(2.2%)	(32.4%)	38.4%

Treatment outcomes

For the cohorts of new and previously TB patients registered in 2012, the NTP reported treatment success of 88% and 61% respectively. For the cohort of MDR-TB patients registered for treatment in 2012, the NTP reported treatment success of 63% (with high lost to follow rates up to 26%). No extremely drug resistant (XDR-TB) patients have been registered for treatment.

Treatment success for new TB patients (all forms) has been consistently over 85% during the period 2008 to 2012. Cure rates for these cohorts however have been much lower with the lowest at 51% for the 2010 cohort and the highest at 72.3% for the 2009 cohort.

TB related mortality

TB mortality is the number of deaths from TB that occur in a given year (expressed as deaths per 100,000 population per year). There is currently no national level vital registration system with standard ICD-10 (10th revision of the International Statistical Classification of Diseases and Related Health Problems) coding in place in Egypt. As such, TB mortality in Egypt is based on WHO estimates. The underlying causes of deaths in patients with acquired immunodeficiency syndrome (AIDS), including the proportion of these who died of TB is also not well known.

Estimates of TB related mortality (excluding HIV associated TB) has consistently declined in Egypt from an estimated 3.5 / 100,000 population in 1990 to **0.24**/ 100,000 population in 2014.

National Tuberculosis Control Program of Egypt

Tuberculosis (TB) control refers to all aspects of health promotion, i.e. prevention of tuberculosis and its complications; early diagnosis; appropriate treatment; patient information and research in different areas related to tuberculosis.

The Ministry of Health and Population (MOHP) has established the National Tuberculosis Control Program, NTP, in 1979. It is the detailed plan of action for effective TB control. NTP is implemented through:

- 34 Chest Disease Dispensaries
- 32 Chest Disease Hospitals
- 85 chest clinics located in general and central hospitals
- 6 chest department located in general and central hospitals
- Tuberculosis control activities are currently integrated through the primary health care system which is constituted of more than 4000 PHCs.

MISSION STATEMENT OF NTP EGYPT

- To reduce the prevalence of tuberculosis in the community as quick as possible to a level where it ceases to be a public health problem.
- NTP is adopting the UN Millennium Development Goals, the four principal targets for global TB control are: by 2005, to detect 70% of new smear-positive patients arising each year, and to successfully treat 85% of these patients; by 2015, to halve TB prevalence and deaths rates, as compared with 1990.

VISION STATEMENT NTP EGYPT

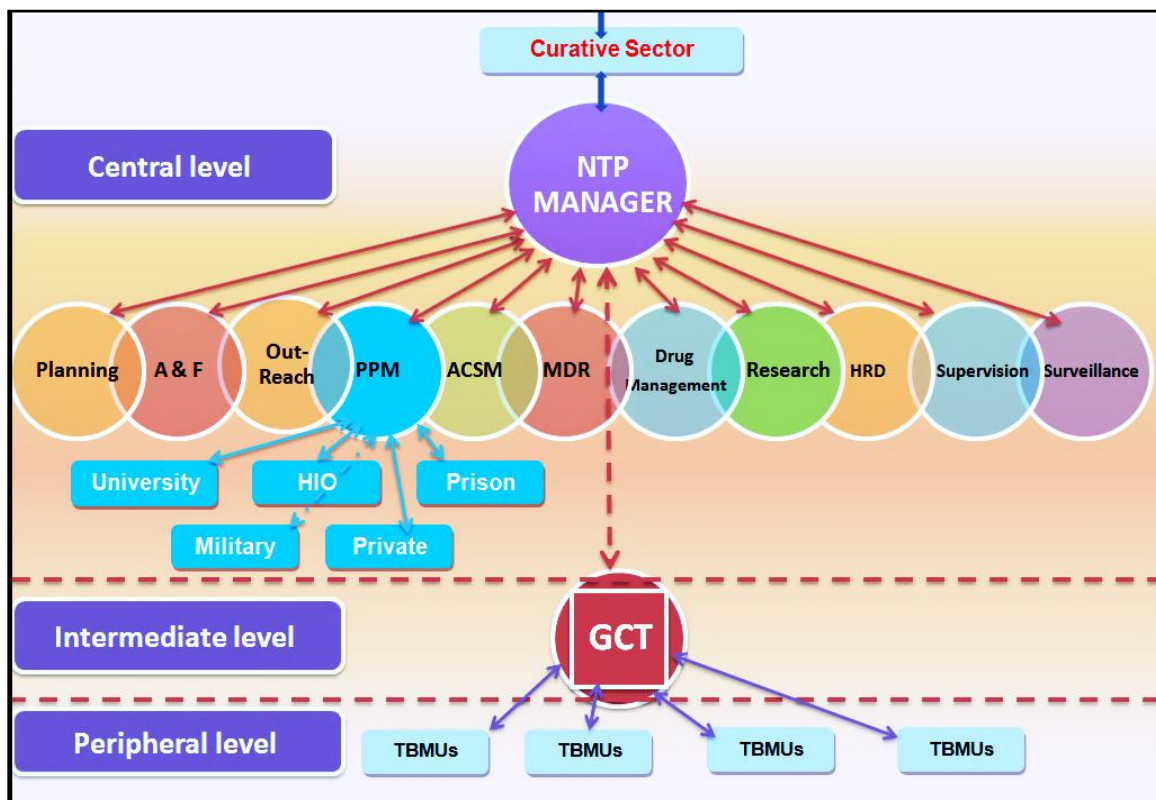
We see the NTP

- To pioneer the international effort of collaboration between similar programs and by sharing its experience contribute to the elimination of TB as a health problem in developing countries
- Expanding research activities to all fields of TB control and utilizing the results of our research in improving our performance
- To develop into a renowned center for national and international conferences
- As a data reference source both nationally and internationally as well as developing into a nationally renowned training center.

NTP STRUCTURE

The organization of TB control in Egypt is illustrated in the following diagram:

There are three levels of responsibility to ensure efficacy of TB control: peripheral, intermediate or governorate, and central levels. Each of these levels has well defined, but different tasks.



a) Peripheral level (district and health unit)

This is the actual implementation level, with the delivery of TB control services. Initially limited to chest facilities, TB services are now increasingly offered through Primary Health Care (PHC) Units. Most districts in Egypt are served by a chest facility. Usually, the director of the facility acts as the District Coordinator for TB.

b) Governorate level

At this level lies the responsibility for local level planning; program implementation; governorate inter-sector collaboration; monitoring and evaluation of the peripheral level; and provision of training. The Governorate Coordinator for Tuberculosis (GCT) carries these responsibilities as the governorate representative of the NTP.

c) Central level

The central level is responsible for policy making, planning and logistics, program co-ordination, training development, laboratory services (in collaboration with the Central Laboratories for Tuberculosis) and program monitoring and evaluation.

Role of the chest clinic (District):

- Registration in the TB Register
- Issue TB treatment card for each patient: one copy at chest clinic and one at PHC center
- Supply anti-TB drugs to PHC centers
- Health education for TB patients
- Ensure DOT with short course chemotherapy (ambulatory or hospitalized)
- Register & examine contacts of TB patients
- Monitor treatment at PHC center through:
 - Ensure PHC staff collects required drugs
 - Report new patients to director of district health directorate
 - Update TB Treatment cards through monthly reports from the PHC center
 - Monitor the treatment progress by timely sputum-smear examination
 - Evaluation of treatment & recording treatment outcome in the TB register

Role of the PHC center:

- Provide TB patients with daily supervised treatment with anti-TB drugs according to prescribed regimen, dosage and duration.
- Provide patients, who are unable to attend at the PHC centre on a daily basis (e.g. handicapped patients) with supervised treatment at the patient's home.
- Retrieve patients who did not attend the PHC centre for their daily treatment.
- Record daily attendance and anti-TB drug intake in the TB treatment card.
- Health education and counseling to TB patients, their contacts and the community.
- Timely referral of TB patients to the chest clinic for follow up sputum examination.
- Order and collect the required quantity of anti-TB drugs for TB patients.
- Refer contacts of TB patients to chest clinic.
- Refer TB presumptive cases to chest clinic.

Role of GCT (Governorate Coordinator for Tuberculosis):

- Carry out supervisory visits to the chest clinics and if possible to some PHC centers in order to monitor and evaluate the performance of health workers
- Provide in-service training, and solve problems if necessary
- Ensure that all anti-TB drugs and all consumables are supplied to the chest clinics on a timely and regular basis
- On a regular basis report progress to the governorate health director and the Director-General for Chest Diseases at the MOHP

TREATMENT STRATEGY ADOPTED BY NTP OF EGYPT (DIRECTLY OBSERVED TREATMENT WITH SHORT COURSE CHEMOTHERAPY, DOTS)

WHAT IS DOTS?

DOTS is not just a treatment method. It ensures that a TB patient takes the right anti-tuberculosis drugs, in the right doses, at the right intervals. This is fulfilled through an observer watches the patient swallowing their tablets in a way that is sensitive and supportive to the patient's needs.

WHO has initiated DOTS in an attempt to prove that simple supervision of anti-TB treatment will lead to a high cure rate.

WHY DOTS?

- Patient compliance to treatment and subsequently the cure rate issues are addressed in implementing DOTS e.g. poor patient compliance, poor health education, long distance to chest clinic, long duration of treatment, social problems...etc.
- To prevent emerging of drug-resistant strains.
- To integrate TB services into the general health services to increase accessibility.

WHAT ARE THE PRINCIPLES OF DOTS STRATEGY?

- Sustained government commitment to TB control
- Case detection through sputum-smear microscopy in the general health services
- Standardized short-course chemotherapy to all TB cases under proper case management conditions.
- Regular, uninterrupted supply of all essential anti-tuberculosis drugs
- Monitoring system for program supervision and evaluation

APPLYING DOTS IN EGYPT

The existing network of Primary Health Care Centers (PHCs) was increasingly utilized for the treatment of TB patients who had been detected in the chest facility. One demonstration area had been established in each governorate by the end of 1997.

One hundred percent of chest facilities adopted DOTS by August 2000, providing TB patients with the possibility to take their treatment at the health facility nearest to their home either the PHC or the chest unit.

By applying DOTS strategy, a successful treatment outcome was ensured. Success rates of 90 to 95 percent are not uncommon. The key to this successful treatment outcome is the commitment to treatment adherence by both patients and health staff.

TUBERCULOSIS INFECTION

- There are five closely related *Mycobacteria* responsible for tuberculosis: *M tuberculosis*, *M bovis*, *M africanum*, *M microti* and *M Canetti*. *Mycobacterium tuberculosis*, by far the commonest, is transmitted between humans through the airborne route.
- *Mycobacterium bovis* may penetrate the gastrointestinal mucosa or invade the lymphatic tissue of the oropharynx when ingested in milk from diseased cows.
- Human infection with *M bovis* has decreased significantly as a result of the pasteurization of milk and effective tuberculosis control amongst cattle.
- Infection with the other organisms is relatively rare.
- Tuberculosis is usually spread from person-to-person through the air by droplet nuclei that are produced when a person with pulmonary or laryngeal tuberculosis coughs or sneezes.
- Droplet nuclei may also be produced by aerosol-producing investigations such as sputum induction, bronchoscopy and through manipulation of lesions or processing of tissue or secretions in the laboratory.
- Micro-droplets, 1 to 5 μm in diameter containing 1-5 bacilli, are highly infectious. They can remain suspended in air for long periods of time. These droplets are small enough to reach the alveolar spaces within the lungs, where the organisms replicate.
- Three factors determine the likelihood of transmission of *M tuberculosis*:
 1. The number of organisms expelled into the air
 2. The concentration of organisms in the air, determined by the volume of the space and its ventilation
 3. The length of time an exposed person breathes the contaminated air
- Extra-pulmonary cases are almost non-infectious.
- Individuals with latent tuberculosis infection are not infectious, as they do not have replicating bacteria and cannot transmit the organism.
- Close contact and prolonged exposure increases the risk of transmission.

EVOLUTION OF INFECTION

- Progression to active disease is dependent on the immune status of the individual.
- Only 10% will develop active disease half of these within the first 2 years after infection.
- Those most at risk include children <5 years of age and the elderly.

NB. BCG immunization gives variable protection against the progression of TB from infection to disease. The main benefit of BCG is the protection against the development of the serious forms of TB in children in the first two years of life, such as TB meningitis and miliary TB.

PATHOGENESIS OF TUBERCULOSIS

- Primary infection occurs on first exposure to tuberculosis bacilli. This usually occurs in childhood so primary TB is often thought of as childhood TB. However, it can occur at any age in a previously unexposed individual.
- Droplet nuclei are carried down the bronchial tree and deposit in a respiratory bronchiole or alveolus usually just below the pleura in the lower part of the upper lobe or upper part of the lower lobe, where they are ingested by alveolar macrophages.
- These represent a non-specific response to the bacillus.
- The balance between bacterial virulence and the inherent microbicidal ability of the alveolar macrophage that ingests it is the key factor.
- The tubercle bacillus grows slowly, dividing approximately every 16 to 24 hours within the macrophage.
- The mycobacterium has no known endotoxins or exotoxins, so there is no immediate host response to the infection.
- The organisms grow for 2 - 12 weeks and reach 10^3 to 10^4 in number, when a cellular immune response is initiated that can be detected by a reaction to the tuberculin skin test.
- The destruction of macrophages and release of tubercle bacilli products and chemokines stimulates an immune response.
- Other macrophages and monocytes are attracted to the area and produce an inflammatory area is known as the Ghon's focus.
- Bacilli and antigens drain from the Ghon's focus via the lymphatic (causing lymphangitis) to the hilar lymph nodes (causing lymphadenitis) and these together (Ghon's focus, lymphangitis and lymphadenitis) form the primary complex.
- Before the development of cellular immunity, tuberculosis bacilli spread via the lymphatics to the hilar lymph nodes and from there may spread through bloodstream to more distant sites.

- Within the lymph node, the T-lymphocytes develop a specific immune response and activated macrophages inhibit the growth of the phagocytosed bacilli.
- In a few cases, the immune response is not strong enough to prevent multiplication of bacilli and bacilli may spread from the lymphatics into the bloodstream and throughout the body causing disease within a few months.
- The bone marrow, liver and spleen are almost always seeded with mycobacteria, but uncontrolled multiplication of the bacteria in these sites is unusual.
- Organisms deposited in the upper lung zones, kidneys, bones and brain find environment that favors their growth.
- Primary infection is usually asymptomatic and a positive tuberculin skin test 4-6 weeks after infection is the only evidence of infection.

Possible Outcomes of Primary Infection

<p>1. No clinical disease with Positive tuberculin skin test as only evidence of infection</p> <p>(Usual "outcome" in 90% of cases)</p>	<p>2. Hypersensitivity reactions</p> <p>e.g. erythema nodosum, phlyctenular conjunctivitis, dactylitis</p>
<p>3. Pulmonary and pleural complications</p> <p>e.g. tuberculosis pneumonia, lobar collapse (bronchial compression by enlarged LN), pleural effusion</p>	<p>4. Disseminated disease</p> <p>e.g. lymphadenopathy (usually cervical)</p> <p>meningitis, pericarditis, miliary disease</p>



Erythema nodosum in front of the leg



Phlyctenular conjunctivitis

POST-PRIMARY TB/SECONDARY TB

- Post-primary TB is the pattern of disease that occurs in a previously sensitized host. It occurs after a latent period of months or years after primary infection.
- It may occur either by reactivation of latent bacilli or by re-infection.
- Reactivation may be in response to a trigger such as weakening of the immune system by HIV infection.
- In a small number of cases it occurs as a progression of primary infection.
- Following primary infection, rapid progression to intra-thoracic disease is more common in children than in adults.

DIAGNOSIS OF TUBERCULOSIS

- The first step of TB diagnosis is to suspect a case
When to suspect TB (pulmonary TB)?



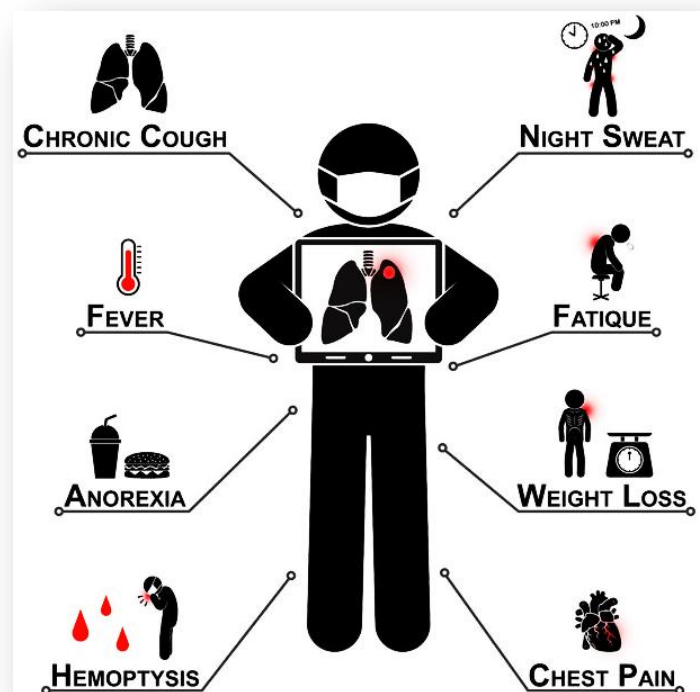
CLINICAL PRESENTATION OF TB

Pulmonary TB

1- Symptoms

The main symptoms of pulmonary tuberculosis are:

- Persistent cough of 2 weeks or more or any duration if HIV positive with or without Production of sputum which may be blood-stained not responding to non-specific treatment (including antibiotics with no anti-TB effect i.e. avoid Rifampicin, aminoglycosides and Quinolones)
- Fever for more than 2 weeks mainly at night.
- Night sweats
- Breathlessness
- chest pain
- loss of appetite and loss of weight
- History of contact sometimes could be detected.



2- Physical signs

- Physical signs are non-specific and may not be helpful in confirming the diagnosis
- Chest – there may be crackles in the lung apices more pronounced on deep breathing; localized wheeze in local obstruction or pressure; dullness where there is effusion and in chronic disease there may be extensive fibrosis with the trachea pulled to one side.

What to do for a presumptive pulmonary tuberculosis case?

1. The first step is to register the presumptive in the presumptive case register
2. **Request a sputum examination for Acid Fast Bacilli**, AFB (Smear stained by Z-N stain). Every pulmonary TB presumptive should submit three sputum samples (at least two samples) for microscopy.

The recommended method for sputum collection is described in the following table.

Routine sputum collection	
Day 1, Sample 1	- Patient provides, under supervision, an “on-the-spot” sample when he presents to the health facility (sputum production should be in an open-air area away from other individual) - Patient is given a sputum container to take home for an early-morning sample the following morning
Day 2, Sample 2	- Patient brings an early morning sample (just after getting up from bed)
Sample 3	- Patient provides another “on the spot” sample under supervision when he submits the second sample to the lab

It should be noted that sure TB diagnosis depends on visualization of the Mycobacteria on a smear or culture.

Same-day diagnosis

Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) in November 2009 acknowledged existing evidence that collecting two sputum samples in one day is equivalent, in terms of diagnostic accuracy, to the existing conventional previously mentioned approach.

The expected sputum smear examination results could be one of four. The following table shows the probable results and the corresponding action:

Result	Action
All the 3 smears are positive for AFB	This is a sure case of smear positive pulmonary Tuberculosis and treatment should be initiated
Only 2 are positive for AFB	This is also a sure case of smear positive pulmonary Tuberculosis and treatment should be initiated.
Only one is positive for AFB	This is a probable case. It should be noted that one positive sample maybe a false positive one. (See causes of false positive sputum below). Repeat sputum examination. Treatment is initiated only if there is supporting evidence e.g. x-ray chest consistent with tuberculosis and the decision of a specialist to start treatment if the condition of the patient is seriously ill.
All are negative for AFB	Follow the diagnostic protocol of smear negative pulmonary Tuberculosis (see below)

Causes of false positive direct sputum smear examination for AFB with ZN stain,

A false positive result means that the sputum smear result is positive even though the patient does not really have pulmonary TB. This may arise because of the following:

1. red stain retained by scratches on the slide,
2. accidental transfer of AFBs from a positive slide to a negative one (contamination),
3. Contamination of the slide or smear by environmental mycobacteria,
4. Various particles that are acid-fast (e.g. food particles, stain precipitates, other micro-organisms).

Smear negative pulmonary tuberculosis

When the patient presents with symptoms consistent with tuberculosis and dealt with as a presumptive case as previously mentioned, then all the received sputum smears results are negative, we come to a problem. To deal with this situation follow the following steps:

1. Do an x-ray chest If has not been done yet. X-ray chest may show any lesion pattern (infiltrations, pneumonic patch (s), pleural effusion, atelectasis, cavitation...etc.). It should be noted that there is no peculiar x-ray pattern specific for TB.
2. **Do sputum examination by GeneXpert.**
3. If there is neither clinical nor radiological improvement, in spite of non-specific treatment, and sputum re-examination is still negative by all means, investigate the case to exclude other underlying causes for the presenting complaints e.g. malignancy, Sarcoidosis, other lung infections...etc.

NB. In all previous cases the returning smear examination for AFB result may be in the form of one of the following probabilities of results:

Number of bacilli seen on a smear		Results reported
No AFB	Per 100 oil immersion field	0
1-9 AFB	Per 100 oil immersion field	Scanty (the number may be mentioned)
10-99 AFB	Per 100 oil immersion field	+
1-10 AFB	Per 1 oil immersion field (min 50 fields)	++
>10 AFB	Per 1 oil immersion field (min 20 fields)	+++

The number of bacilli (AFB) seen in a smear reflects the patient's infectivity.

Solid Conventional Culture (Lowenstein-Jansen medium)

- Culture of sputum is more sensitive (require from 10-100 mycobacteria /ml sputum) than smear examination (which will be positive if there are 10^4 - 10^5 mycobacteria/1 ml sputum),
- It takes from four to eight weeks before the result is known.
- It also requires well-equipped laboratories with skilled staff.

Indications of culture:

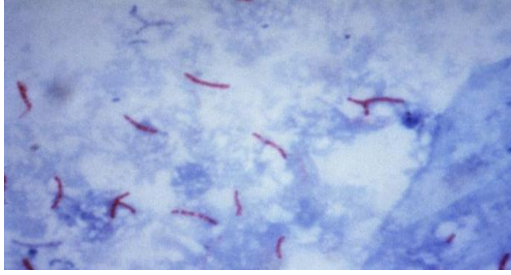
- a) For all cases of extra-pulmonary tuberculosis.
- b) For all cases of smear negative pulmonary tuberculosis and TB/HIV co-infection (together with GeneXpert or a substitute for it)
- c) For differentiating Mycobacteria tuberculosis complex from other non-Tuberculosis Mycobacteria.
- d) Culture is done with drug susceptibility testing, *DST*, for new smear positive pulmonary tuberculosis who remain positive at the end of the second month of treatment with Cat I treatment course and for all retreatment (after relapse, after failure and after lost to follow) before starting Cat II retreatment course.

Culture on liquid medium

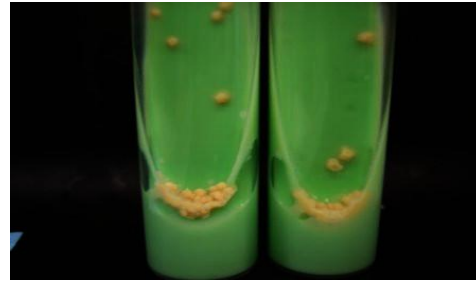
The BACTEC MGIT 960 System

The MGIT 960 system is a non-radio-metric (does not use radio-active material) automated system that uses the MGIT media & sensors to detect the fluorescence.

It can differentiate between TB complex & non-TB mycobacteria. Drug susceptibility tests are available for Streptomycin, INH, Rifampicin, Ethambutol and Pyrazinamide. The average time of detection with the MGIT 960 system is 12.7 days compared to 20 days with the solid media.



AFB stained in smear, tuberculosis bacilli are shown in red.



M. tuberculosis on Löwenstein Jensen



Mycobacterial Growth Indicator Tube (MGIT)

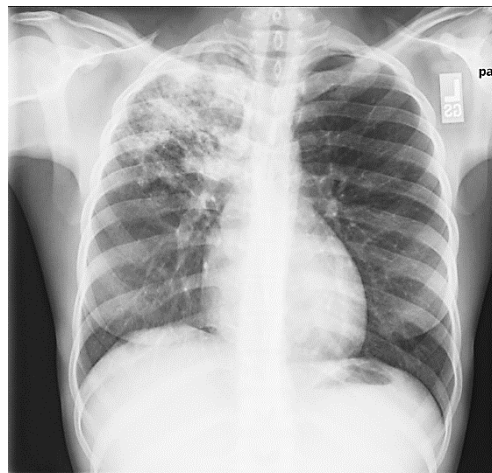
Radiology

As mentioned before, no radiological picture can be characteristic of the disease. Chest radiograph can be helpful in localizing abnormalities but not to establish the diagnosis of tuberculosis. Only bacteriology can provide the final proof. Radiological findings are relevant only to a certain extent and are therefore recorded as:

Chest x-rays are necessary in TB p who cannot produce sputum or who have negative smears, and where extra-pulmonary TB (such as pleural effusions and pericardial TB) is suspected. They must be interpreted in the light of the patient's history and other clinical findings.

Indications for the use of chest x-rays

1. To assist in the diagnosis of TB:
 - When smears are negative
 - Where extra-pulmonary or miliary TB is suspected
 - For primary TB in children
2. During or at the end of treatment to evaluate the response to treatment or when response to treatment is not satisfactory.
3. To assist in the diagnosis of suspected



complications:

- In a breathless patient to exclude a pneumothorax or pleural effusion.
 - For frequent or severe hemoptysis.
4. Computed tomography (CT) scan findings in tuberculosis are equally non-specific. However, in cases of mediastinal Lymphadenopathy, peripheral rim enhancement with relatively low attenuation centers can suggest a diagnosis of tuberculosis in the appropriate clinical setting. Also in extra-pulmonary case e.g. tuberculosis osteoarthritis (particularly MRI).

GeneXpert MTB/RIF

GeneXpert MTB/RIF is an automated molecular platform to detect *M. tuberculosis* and rifampicin resistance testing by targeting specific mutations in the *rpoB* gene. It is approved for use directly on raw sputum and results should be available within 2 hours in the laboratory but available in health facilities within 48 hours.

The test involves only three manual steps:

- Addition of reagent to liquefy and inactivate the sputum.
- Transfer of 2 ml of liquefied sputum to the cartridge
- Loading the cartridge into the device for the assay.

Advantages of the test

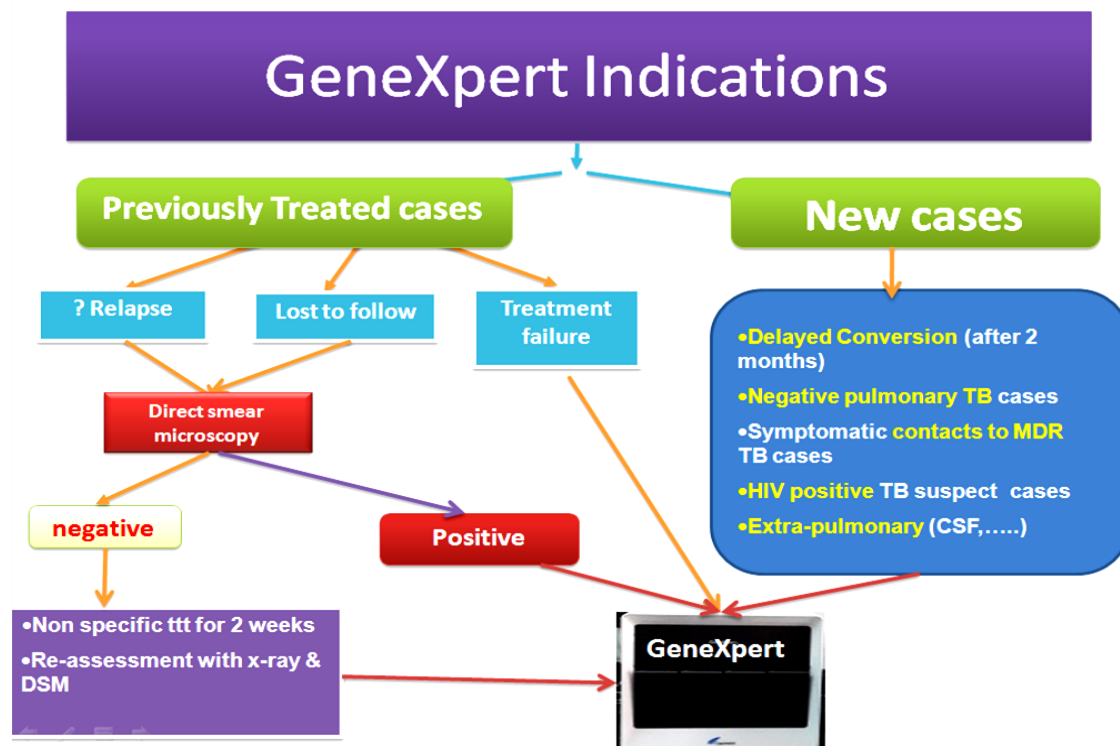
- It detects MTB and Rifampicin resistance from one specimen at the same time.
- Processing time for the test itself is 2 hours.
- It is specific for MTB complex.
- It can also be used on the following processed samples - CSF, aspirates (gastric, lymph node) and tissue (i.e. pleural biopsy)
- The test for each specimen is carried out in a closed system (cartridge), so there is a reduced risk of cross-contamination and human error.



The limitations of this test are that

- It cannot be used for monitoring treatment because it does not distinguish between live and dead bacilli, its use is therefore limited to diagnosis
- The assay is semi-quantitative and defines a positive test as “very low”, “low”, “medium”, and “high”. This grading is not reported on the laboratory result. There is no direct correlation between the Xpert semi-quantitative result and the smear grading of scanty, +, ++ and +++.

The test might be unsuccessful due to laboratory test errors, test failure or invalid results. In these instances a second specimen must be collected for a repeat Xpert test.



Line Probe Assay

This test has been approved for direct testing on smear positive specimens and on isolates from solid and liquid culture. It simultaneously detects MTB complex and specific mutations in the *rpoB* gene conferring rifampicin resistance and mutations on the *katG* gene which is associated with higher levels of isoniazid resistance and *inhA* gene mutations which is associated with lower levels of isoniazid resistance.

Compared to phenotypic DST this provides rapid diagnosis of drug resistant TB and results should be available within 48-72 hours in the laboratory.

Advantages of the test are that;

- It detects MTB and resistance to R & INH at the same time from one specimen
- It reduces time to diagnosis of MDR-TB
- It is specific for MTB complex.

The limitations of the test are that:

- The test is labor intensive and is prone to contamination and human error
- It requires a lot of space - at least 3 separate rooms for the different steps

TUBERCULIN SKIN TESTING

The tuberculin skin test (TST) has limited value in clinical work, especially where TB is common. The test shows hypersensitivity to proteins of the TB bacillus, as a result either of infection with *M. tuberculosis* or induced by Bacille Calmette-Guérin (BCG) vaccination. The test involves injecting tuberculin purified protein derivative (PPD) into the skin. Previous exposure results in a local delayed type hypersensitivity reaction within 24-72 hours. The reaction is identified as palpable induration (hardness) at the site of injection. The response only indicates hypersensitivity. It shows that the person has at some time been infected with *M. tuberculosis* or been vaccinated. By itself, it does not indicate the presence or extent of tuberculosis disease.

It should also be noted that a negative result does not rule out the diagnosis of TB disease.



Performing a Mantoux Tuberculin Skin Test

1. The Mantoux TST is the most reliable test available. The test requires:
2. 2 units of tuberculin purified protein derivative PPD-RT23 2TU or 5 units of PPD-S 5TU.
3. Use a single-dose tuberculin syringe and a short 27-gauge needle with a short bevel to do the test.
4. Draw up 0.1 ml of PPD of the correct strength into the syringe.
5. Clean an area of skin in the mid anterior section of the forearm. The PPD is injected between layers of skin (*intra*dermal). Keep the needle almost parallel to the skin, with the bevel pointing upwards during insertion. It is important to ensure that the injection goes into and not under the skin. A small *papule* should form at the injection site; if it does not, the PPD has been injected too deeply and the test should be repeated at a different site.
6. The reaction to the test at the site of the injection is measured 48-72 hours later by noting the widest transverse point across the edges of the raised, thickened area. This area of induration and not redness is measured.

- To help measure accurately, mark the edges of the induration at the widest point with a pen and measure the exact distance between the two points in millimeters.

Reading interpreting a positive Tuberculin Skin Test

Immune Status and age group	HIV positive, malnourished, severe illness at any age	HIV negative and not immune-compromised
Diameter of induration to consider the test positive	≥ 5 mm	If no history of BCG vaccination or after age of 6 years ≥ 10 mm If history of BCG vaccination or before age of 5 years ≥ 15 mm

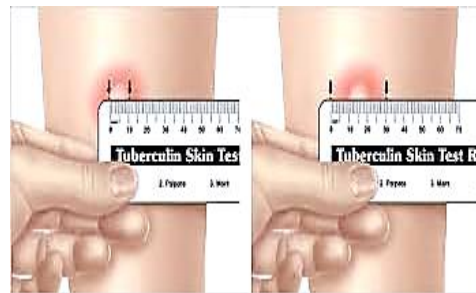
Limitation of TST

- TST will be positive in cases with either infection or active disease, so it cannot differentiate between both conditions.
- TST also cannot differentiate infection with *M tuberculosis* from other mycobacteria.
- After BCG vaccination, it is not possible to distinguish between a tuberculin skin test reaction caused by virulent mycobacterial infection or by vaccination itself.

False negative Reactions to Tuberculin:

1- Factors related to the person being tested:

- Infection:-
 - Viral (HIV, measles, chicken pox).
 - Bacterial (typhoid fever, brucellosis, typhus, leprosy pertussis, overwhelming TB).
 - Live virus vaccinations (measles, mumps, polio).
- Metabolic derangements (chronic renal failure).
- Nutritional factors (severe protein depletion).
- Disease affecting lymphoid organs (Hodgkin's disease, lymphoma, sarcoidosis)
- Age (new born).
- Recent or overwhelming infection with *M. tuberculosis*.
- Stress (surgery, burns...etc.).



2 - Factors related to the tuberculin used:

- Improper storage (exposure to light and heat).
- Improper dilutions.
- Chemical denaturation.
- Contamination.

3 - Factors related to the method of administration:

- Injection of too little antigen. ,
- Delayed administration after drawing into syringe.
- Injection too deep

4 - Factors related to reading the test and recording results:

- Inexperienced reading.
- Conscious or unconscious bias.
- Error in reading

Other tests

INTERFERON GAMMA RELEASE ASSAYS (IGRA)

- Interferon-Gamma Release Assay (IGRAs) is whole-blood test that can aid in diagnosing *Mycobacterium tuberculosis* infection.
- *They do not help differentiate latent tuberculosis infection (LTBI) from tuberculosis disease.*
- It is not affected by previous BCG vaccination.
- Test is expected to be more specific than a TST because the antigen used in this test is *RELATIVELY SPECIFIC* to *M. tuberculosis* and should produce fewer false-positive tests (i.e., they should not produce cross-reactions after sensitization by BCG and most non-tuberculosis mycobacteria, such as *M. avium* complex). However, in a study in which cohorts with similar risks for infection were compared, the specificity of IGRA using ESAT-6 or CFP-10 did not differ significantly between those vaccinated with BCG and those not vaccinated. The effect of BCG on specificity is difficult to assess because BCG is used predominately in populations already at increased risk for *M. tuberculosis* infection.
- WHO does not recommend these tests for program purposes in low and middle income settings.

Disadvantages and limitations of IGRAs

- Fresh blood samples must be processed within 8-30 hours after collection while white blood cells are still viable.
- Errors in collecting or transporting blood specimens or in running and interpreting the assay can decrease the accuracy of IGRAs.
- Limited data on the use of IGRAs for:
 - Children younger than 5 years of age;
 - Persons recently exposed to *M. tuberculosis*;
 - Immuno-compromised persons; and
- Tests are expensive.

- Estimates of IGRA sensitivity have varied widely in published studies which have involved predominantly adults with culture-confirmed active tuberculosis. In general, IGRA sensitivities are considered similar to those for TST.

BLOOD CULTURE

Blood cultures may be used to detect MTB and other species of mycobacteria in HIV-infected patients; especially those with low CD4 count where disseminated disease is suspected.

HISTOLOGICAL EXAMINATION

Histo-pathological examination may be conducted on tissue specimen. Samples that can be submitted for examination include;

- Fine needle aspiration from lymph nodes
- Tissue biopsies from serous membranes, skin, pleura, endometrium, liver

Extra-pulmonary TB

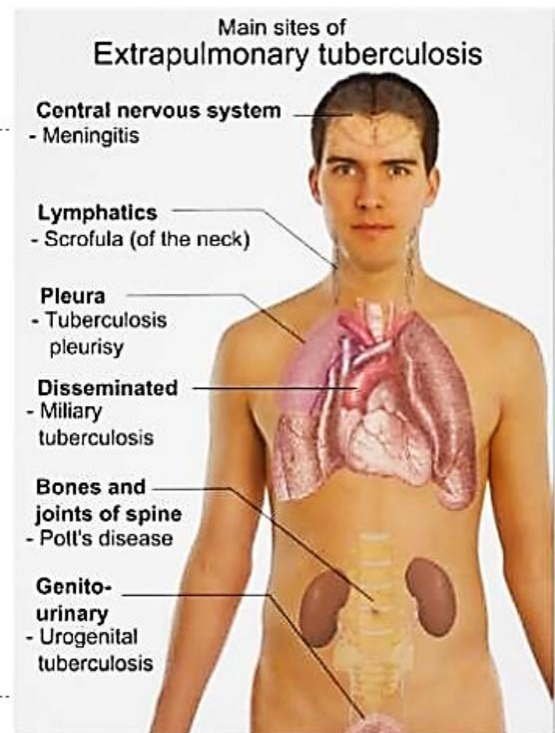
Extra-pulmonary TB can present with non-specific symptoms such as unexplained weight loss, night sweats and fever for more than 2 weeks. Other symptoms depend on the site or organ affected. The most common types of extra-pulmonary tuberculosis are:

- TB lymphadenitis
- Tuberculosis pleural effusion (usually single-sided)
- TB of the bones and joints
- Tuberculosis pericardial effusion
- TB meningitis
- Disseminated/miliary tuberculosis
- Tuberculosis empyema
- TB peritonitis

Disseminated tuberculosis and tuberculosis meningitis are severe forms of TB, often occurring soon after primary infection. They occur most commonly in children and young adults. These acute forms of TB are often fatal. When this form of disease is suspected, treatment should be commenced immediately without waiting for bacteriological proof of diagnosis. HIV positive patients particularly those with low CD4 counts may present with extra pulmonary disease.

Appropriate investigations for extra-pulmonary TB include the following where these are available.

- Ultrasound examination may be suggestive of abdominal TB (lymphadenopathy, ascites and/or splenic hypo-densities) or pericardial TB (pericardial effusion especially if there is stranding)
- TB blood culture.
- Culture of tissue or fluid from fine needle aspirate or biopsy.
- Histological examination of tissue.
- Cytological examination.
- GeneXpert of body fluids other than sputum (except blood) and processed tissues.



TB LYMPHADENITIS

Owing to the high frequency with which *M. tuberculosis* disseminates through the lymph vessels, lymphatic TB is one of the most common forms of extra-pulmonary TB presentation.

Lymphatic TB can be divided into two main groups: the first affects the peripheral lymph nodes (scrofula), and the second affects the internal adenopathies. TB of the peripheral lymph nodes affects the adenopathies in the head and neck principally, although it can affect any other area. The most important differential diagnosis should consider lymphadenitis caused by other mycobacteria. In children, *M. tuberculosis* is isolated in only 10% to 20% of peripheral lymphadenitis cases with *M. avium* and *M. scrofulaceum* isolated in the remaining instances. *M. tuberculosis* is isolated in 90% of adults with this clinical manifestation.

Awareness of the epidemiological differences between adults and children is of great importance since the vast majority of environmental mycobacteria that cause lymphadenitis in children are very resistant to anti-tuberculosis drugs.

Large lymph node masses may be produced in the mediastinum, which can compress and sometimes perforate the tracheobronchial tree. This process was considered relatively common in the past, especially before the advent of chemotherapy, with compressive symptoms reported in 67.8% of patients studied and bronchial perforations in 27.8%. Currently, with the availability of bactericidal treatments, this form of TB presentation and its complications is considered to be rare.

Involvement of the abdominal lymph nodes by TB is common, and adenopathies can normally be found in various sites.

A biopsy should be carried out, which can be complemented with use of imaging (an ultrasound scan or tomography). The adenopathies may obstruct the alimentary canal, urinary tract, or biliary tract (when their location is peri-portal or peri-pancreatic).

The treatment of lymphatic TB is the same as that for pulmonary TB, although some experts advocate prolonging the treatment for up to 9 to 12 months. One problem is that the size of the adenopathies decreases very slowly (over weeks or months), and in 5% to 10% of cases they are still the same size after the treatment has ended. This, however, does not mean that the treatment was unsuccessful.

One problem is that it is difficult for antibiotics to reach the lymphatic area, and the size of the adenopathy is largely due to a local immunological reaction. Consequently, adenopathies decrease in size extremely slowly (over weeks or months), and in 5% to 10% of cases they are still the same size after the treatment has finished,

Surgery may be indicated in cases of lymph node TB caused by other mycobacteria, and when the mediastinum has been affected (even with *M. tuberculosis*) and is extremely compressive.

However, in both adults and children in whom *M. tuberculosis* is isolated, medical treatment is preferred. This evidence underlines the importance of culturing the samples obtained from a biopsy or by aspiration using a thin needle (the only way to obtain a definite diagnosis), rather than just sending these specimens to the laboratory for histopathological analysis.

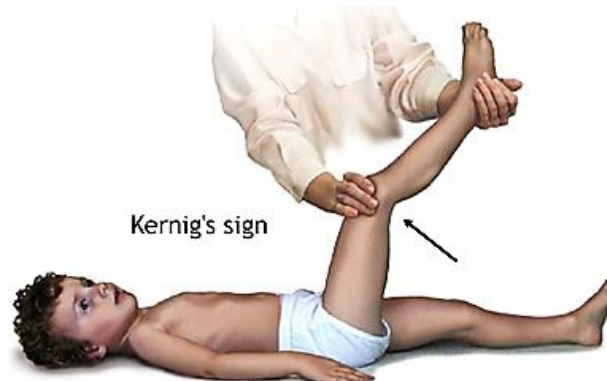
The most important differential diagnosis must consider lymphadenitis caused by environmental mycobacteria. *M. avium* complex is isolated in 70% to 80% of cases of lymphadenitis.

TB MENINGITIS

TB meningitis remains a potentially devastating disease that is associated with a high morbidity and mortality. HIV positive patients appear to be at increased risk for developing TB meningitis but the clinical features and outcome of the disease are similar to that in HIV-negative patients.

Clinical presentation and management:

- Fever and headache are the cardinal features, confusion is a late feature and coma bears a poor prognosis. Meningism is absent in a fifth of patients with TB meningitis. Patients may also have focal neurological deficits.
- Examination reveals neck stiffness and a positive Kernig's sign (flex one of the patient's legs at hip and knee with the patient lying on back, and then straighten the knee; resistance to straightening the knee and pain in the low back and posterior thigh suggest meningeal inflammation). Severe stiffness of the hamstrings causes an inability to straighten the leg when the hip is flexed to 90 degrees
- Diagnosis rests on clinical presentation and a lumbar puncture with examination of cerebrospinal fluid (CSF).



The following CSF features are highly suggestive of TB meningitis:

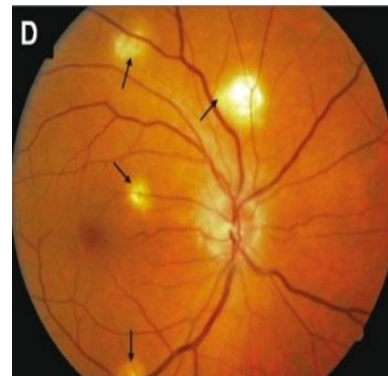
CSF normal values	CSF in TB meningitis
Gross appearance: Normal CSF is clear and colorless	Opening Pressure: Variable
Specific gravity: 1.006–1.009.	Glucose (mg/dL): <40 mg/dL (Low)
CSF opening pressure: 50–180 mmH2O	Protein (mg/dL): (moderate to marked increase) 50 -500 mg/dL
Glucose: 40–85 mg/dL.	WBCs (cells/μL): Variable (10 -1000 cells/μL) <500cells/μL.
Protein (total): 15–45 mg/dL.	Cell differential: Predominance of Lymphocytes
Lactate dehydrogenase: 1/10 serum level.	Culture: Positive for AFB
Lactate: less than 35 mg/dL.	•Negative India ink stain for Cryptococcus
Leukocytes (WBC): 0–5/μL (adults/children); up to 30/μL (newborns).	•Negative Cryptococci Antigen test
Differential: 60–70% lymphocytes; up to 30% monocytes and macrophages; other cells 2% or less.	

- Patients with suspected TB meningitis should be referred to hospital without delay as TB meningitis is life threatening, with serious complications if not treated promptly.
- Those presenting with more severe neurological impairment such as drowsiness or coma have a greater risk of neurological complications and a higher mortality.

DISSEMINATED / MILIARY TB

Disseminated TB results from widespread blood borne dissemination of TB bacilli. This is either the consequence of a recent primary infection or the erosion of a tuberculosis lesion into a blood vessel.

It occurs most often in children and young adults. Unlike pulmonary tuberculosis, acute disseminated TB is highly fatal. Disseminated TB is an under-diagnosed cause of end-stage wasting in HIV positive individuals and should be considered in all febrile patients presenting with HIV wasting syndrome.



Clinical features

- 1) The patient presents with constitutional symptoms such as high fever, night sweats, weight loss and shortness of breath.

- 2) Clinical signs may reflect the involvement of other organs: pleural effusion, digestive problems, hepato-splenomegaly and meningeal signs.
- 3) There may be choroidal tubercles on fundoscopy.
- 4) Differential diagnosis include: acute viral infections, as well as infections caused by staphylococcus aureus, salmonella species, Cryptococcus and malaria.

Diagnosis

- 1) Chest X-ray may show diffuse, uniformly distributed, small miliary (“like small millet seeds”) nodules.
- 2) Full blood count may show pancytopenia (this may also be seen as a result of HIV) or anemia.
- 3) Liver function tests may be abnormal.
- 4) Bacteriological confirmation is sometimes possible from sputum, C.S.F., or bone marrow.
- 5) Smear microscopy of sputum from cases with disseminated (miliary) tuberculosis is usually negative, as the disease is paucibacillary.

Tuberculosis serous effusions

- Inflammatory tuberculosis effusions may occur in any of the serous cavities of the body, i.e. pleural, pericardial or peritoneal cavities.
- They are a common form of TB in HIV positive patients.

1.1. Tuberculosis pleural effusion

Clinical features

- Non-productive cough, chest pain in the stage of pleurisy, shortness of breath after accumulation of the fluid.
- Systemic symptoms such as, anorexia, weight loss, fever.
- Findings on clinical examination may include:
 - Tracheal and mediastinal shift away from the side of the effusion
 - Decreased chest movement
 - Dullness on percussion on the side of the effusion.

Diagnosis

- Suspected pleural effusions should be confirmed immediately by chest x-ray.
- Pleural aspiration should be undertaken wherever possible: the fluid is usually a straw colored exudate and has protein content >30g/l.
- White cell count is high (1000-2500 per mm³) with predominant lymphocytes.
- Adenosine de-aminase (ADA) is raised >30 IU.
- Since the number of bacilli, if present, is relatively small, AFB are not usually seen on microscopy of centrifuged specimens of pleural fluid, however, culture may be positive. GeneXpert may be more helpful.
- Differential diagnosis of a pleural exudate includes malignancy, para-pneumonia effusion and pulmonary embolism.

- Plural biopsy may be needed to confirm diagnosis.

1.2. Tuberculosis pericardial effusion

Tuberculosis accounts for about 90% of pericardial effusions in HIV positive patients and for about half in HIV-negative patients.

Clinical features

- Cardiovascular symptoms include: chest pain, shortness of breath, cough, dizziness and weakness due to low cardiac output.
- Symptoms of right-sided heart failure include leg swelling, right hypo-chondrial pain (liver congestion), abdominal swelling (ascites).
- Signs include: tachycardia, low blood pressure, pulsus paradoxus (fall in systolic pressure >10mmHg on inspiration), raised jugular venous pressure, impalpable apex beat, distant heart sounds.
- Signs of right-sided heart failure include hepato-splenomegaly, ascites, and peripheral edema.

Diagnosis

Diagnosis usually rests on suggestive systemic features and ultrasound:

- Chest X-ray may show a large globular heart, clear lung fields and bilateral pleural effusions may be present.
- ECG may show tachycardia, flattening of ST and T waves, low voltage QRS complexes.
- Treatment without pericardiocentesis usually results in resolution of a tuberculosis pericardial effusion.
- Corticosteroids may help prevent constrictive pericarditis
- In cases of cardiac tamponade the patient should be referred to a specialist for aspiration of the effusion.

If not properly treated, TB pericarditis may evolve to constrictive pericarditis over months, with later evidence of calcification.

1.3. Tuberculosis empyema

- This usually arises when a tuberculosis cavity in the lung ruptures into the pleural space.
- The physical signs are similar to a pleural effusion, but aspiration reveals thick pus. Send the pus to the laboratory for examination for TB, gram stain and bacterial culture. The main differential diagnosis is bacterial empyema.

1.4. Peritoneal Tuberculosis

Peritoneal TB is the commonest type of abdominal TB.

Routes of spread of TB to the peritoneum include the following:

- a. from tuberculosis mesenteric lymph nodes;
- b. from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum);
- c. Blood borne.

Clinical features

- Patients present with constitutional features and ascites.
- Marked wasting is common in children.
- Signs of other causes of ascites such as nephrotic syndrome (peripheral edema) or portal hypertension (marked splenomegaly) are usually absent.
- There may be palpable abdominal masses (mesenteric lymph nodes).
- Adhesion of nodes to bowel may cause bowel obstruction.
- Fistulae may develop between bowel, bladder and abdominal wall.

Diagnosis

- Chest X-ray to look for associated PTB.
- Always do a diagnostic ascitic tapping. The aspirated fluid is usually straw-colored, but occasionally turbid or blood-stained.
- The fluid is an exudate, usually with more than 300 white cells per mm³ and predominantly lymphocytes. Ultrasound, if available, may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes.

NB. An ill, wasted patient with TB ascites may have a low serum albumin concentration. In this case, the usual threshold of 30 g/l albumin concentration for diagnosing an exudate is too high. Instead, calculate the difference between the albumin concentrations in serum and ascites. A serum–ascites albumin difference of less than 11 g/l means that the ascites is an exudate.

The diagnosis is usually presumptive. Definitive diagnosis rests on a peritoneal biopsy. Blind percutaneous needle biopsy of the peritoneum has a low pick-up rate and a high complication rate. Laparoscopy under local anesthetic has a high pick-up rate. Laparoscopy enables direct visualization and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is *too invasive* for routine use.

Differential diagnosis

- If transudates: heart failure, renal failure, nephrotic syndrome, chronic liver disease due to cirrhosis, hypoproteinemia.
- If exudates: malignancy, other infections causing peritonitis.

TUBERCULOSIS OF THE SPINE

TB of the spine is important. The disastrous consequence for the patient of a missed diagnosis of thoracic or cervical spinal TB is paralysis. TB starts in an intervertebral disc and spreads along the anterior and longitudinal ligaments, before involving the adjacent vertebral bodies. Plain X-ray of the spine is usually diagnostic. The typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. The disc space is narrowed laterally. The sites most commonly involved are the lower thoracic, lumbar and lumbosacral areas. The main differential diagnoses are malignancy and pyogenic spinal infections. Malignant deposits in the spine tend to erode the pedicles and spinal bodies, leaving the disc intact. Pyogenic infection tends to be more acute than TB, with more severe pain.

It is characterized by loss of bone density and slow bone erosion, with the disc space being maintained for a long time (differentiating it from pyogenic infections). In children, an acute form may develop with vertebral osteomyelitis, collapse of the vertebral body and neurological involvement. Collapse of adjacent vertebral bodies may lead to angulated kyphosis.

Spread may occur into the soft paravertebral tissue to form a so-called “cold abscess”. These form symmetrical masses; they may spread further and end up calcifying.

Clinical features

- back pain, stiff back, there may be referred pain radiating out from the site of origin
- A child that refuses to walk or has weakness or paralysis of the lower limbs.
- Involvement of cervical vertebrae may cause pain in the neck and shoulders and rigidity of the neck. A cold abscess can develop behind the sternocleidomastoid muscle. More rarely, neurological involvement leads to progressive tetraplegia.
- Involvement of the thoracic vertebrae causes localized back pain, deformity of the spine, and in extreme cases an angulated kyphosis (gibbus). The chief risk is spinal cord compression and paraplegia.
- Involvement of the lumbar vertebrae results in lower back pain. A “cold abscess” can drain along the psoas muscle towards the inguinal area.

Diagnosis

- X-rays of the spine show disc space narrowing and erosion of the adjacent vertebral bodies, wedge shaped collapse and angulation.
- Biopsy of cold abscess for microscopy and culture if possible, can confirm the diagnosis.

Genito-urinary tuberculosis

- Urinary tract TB is essentially a renal parenchymatous disease. It is produced as a result of dissemination through the bloodstream from a distant focus, which is generally pulmonary. It is therefore a bilateral disease, although it manifests as a localized one.
- In almost all cases there is a cured or active pulmonary lesion. It manifests when the lesion ulcerates a calyx or the renal pelvis, producing bacteriuria, pyuria, and abnormalities that can be detected radiographically; it is in this way that the rest of the urinary tract is most often affected.
- Symptoms include urinary frequency, dysuria, hematuria and loin pain/swelling. Urine analysis shows sterile pyuria.
- For diagnosis, it is necessary to take three urine samples over 3 consecutive days, preferably early in the morning when the patient wakes up. Because other environmental mycobacteria are present in the urethra and glans and thus smear microscopy is non-specific.

For this reason, a culture of urine sample is essential for a definite diagnosis.

- GeneXpert is also indicated for urine samples
- The genitals may also become affected, although this is extremely uncommon. Any organ may be affected in male subjects, although perhaps the most common presentation is epididymis TB.
- Likewise, any organ may be affected in female subjects; the most commonly affected areas are adnexa, which causes an inflammation of the fallopian tubes and frequently causes sterility.
- One curious point worth mentioning is that genital TB can also be caused as a result of direct inoculation during sexual intercourse.
- Treatment is the same as for pulmonary TB but duration may be needed to be extended, and surgical intervention should be evaluated in the event of complications or sequel.

Childhood tuberculosis

The key risk factors for childhood TB are:

- household contact with a newly diagnosed smear-positive case
- age less than 5 years
- Severe malnutrition.
- Immune-suppression

Diagnosis of TB in children, general considerations

- The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. TST, chest X-ray (CXR) and sputum smear microscopy.
- Most children with TB have pulmonary TB.
- Although bacteriological confirmation of TB is not always feasible, it should be tried whenever possible, e.g. by sputum microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample.
- A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB in children.
- The decision to treat a child should be carefully considered and once such a decision is made, the child should be treated with a full course of therapy.

Recommended approach to diagnose TB in children

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 extra-pulmonary TB

1. Careful history (including history of TB contact and symptoms consistent with TB)

Contact

Close contact is defined as living in the same household as or in frequent contact with a source case with sputum smear-positive pulmonary TB. Source cases that are sputum smear-negative but culture-positive are also infectious, but to a much lesser degree.

Symptoms

The commonest are:

- *Chronic cough*, an unremitting cough that is not improving (not responding to non-specific measures including antibiotics of no anti-TB effects) and has been present for more than 21 days.
- *Fever*, Body temperature of $>38^{\circ}\text{C}$ for 14 days, after common causes such as malaria or pneumonia have been excluded.

- *Documented weight loss or failure to thrive*, In addition to documenting weight loss or failure to thrive (through nutritional plan for 4 weeks), it is necessary to look at the child's growth chart.

2. Clinical examination (including growth assessment)

There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. Some signs, although uncommon, are highly suggestive of extra-pulmonary TB (i.e. TB of organs other than the lungs). Other signs are common and should prompt an investigation into the possibility of childhood TB. Important physical signs are:

a) physical signs highly suggestive of extra-pulmonary TB:

- gibbous, especially of recent onset (resulting from vertebral TB)
- non-painful enlarged cervical lymphadenopathy with fistula formation;

b) physical signs requiring investigation to exclude extra-pulmonary TB:

- Meningitis with a sub-acute onset or raised intracranial pressure and involvement of the cranial nerves.
- pleural effusion
- pericardial effusion
- distended abdomen with ascites
- non-painful enlarged lymph nodes without fistula formation
- non-painful enlarged joint
- Signs of tuberculin hypersensitivity (e.g. Phlyctenular conjunctivitis, erythema nodosum).

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

3. Tuberculin skin test (refer to above)

A positive TST occurs when a person is infected with *M. tuberculosis*, but does not necessarily indicate disease. However, the TST can also be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and when used in conjunction with other diagnostic tests. There are a number of TSTs available, but the TST using the Mantoux method is the recommended test.

Sometimes it is useful to repeat the TST in children once their nutritional status has improved or their severe illness (including TB) has resolved, as they may be initially TST negative, but positive after 2–3 months on treatment. A negative TST never rules out a diagnosis of TB in a child.

4. Bacteriological confirmation whenever possible

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available.

Appropriate specimens from the suspected sites of involvement should be obtained for GeneXpert, microscopy and culture (and also histopathological examination).

Appropriate clinical samples include sputum, gastric aspirates and certain other material (e.g. lymph node biopsy or any other material that is biopsied). Fine-needle aspiration of enlarged lymph glands – for both staining of acid-fast bacilli and histology – has been shown to be a useful investigation, with a high bacteriological yield.

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

Bacteriological confirmation is especially important for children who have:

- suspected drug-resistant TB
- HIV infection
- complicated or severe cases of disease

Common ways of obtaining samples for smear microscopy include the following.

a. Expectoration

Sputum should always be obtained in adults and older children (10 years of age or older) who are pulmonary TB presumptive cases. Among younger children, especially children under 5 years of age, sputum is difficult to obtain and most children are sputum smear-negative. However, in children who are able to produce a specimen, it is worth sending it for smear microscopy (and mycobacterial culture). Bacterial yields are higher in older children (more than 5 years of age) and adolescents, and in children of all ages with severe disease. As with adult TB presumptive cases, three sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), an early morning specimen and a second on-the-spot specimen (at a follow-up visit).

b. Gastric aspiration

Early morning gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. Gastric aspirates should be sent for smear microscopy and mycobacterial culture. A gastric aspirate should be obtained on each of three consecutive mornings.

c. Sputum induction

Several recent studies have found that sputum induction is safe and effective in children of all ages and the bacterial yields are as good as or better than for gastric aspirates. However, training and specialized equipment are required to perform this procedure properly. Precautions are also necessary particularly in patients with history of bronchospasm or bleeding tendency.

5. Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB

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

Common forms of extra-pulmonary TB in children and corresponding investigations

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

Other tests

Serological and nucleic acid amplification (e.g. polymerase chain reaction, PCR) tests are not currently recommended for routine diagnosis of childhood TB, as they have been inadequately studied in children and have performed poorly in the few studies which have been done. However, this is an area that requires further research; as such tests may prove to be useful in the future.

Recommended treatment regimens, see recommendations

Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. TB meningitis, complications of airway obstruction by TB lymph glands, and pericardial TB. The drug most frequently used is prednisone, in a dosage of 2 mg/kg daily, increased up to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks. The dose should then be gradually reduced (tapered) over 1–2 weeks before stopping.

Conditions that merit hospitalization include:

1. TB meningitis and miliary TB, preferably for at least the first 2 months,
2. respiratory distress,
3. spinal TB, and
4. Severe adverse events, such as clinical signs of hepatic toxicity (e.g. jaundice).

Follow-up

Adherence should be assessed by reviewing the treatment card. A follow-up sputum sample for smear microscopy at 2 months after treatment initiation should be obtained for any child who was smear-positive at diagnosis. Follow-up CXRs are not routinely required in children, particularly as many children will have a slow radiological response to treatment. A child who is not responding to anti-TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence. Weight gain and clinical improvement sometimes are the only prove of improvement.

BCG vaccination

BCG, or bacille Calmette-Guerin, is a vaccine for tuberculosis (TB) disease. The national policy in Egypt is to vaccinate all children at birth with BCG. However, BCG vaccination does not influence the transmission of infection. Its main value is to give protection against the serious forms of TB such as TB meningitis and miliary TB which is commonest in the under 5 year's age group.

Babies born to mothers who develop TB shortly before or shortly after delivery are not protected sufficiently quickly by BCG given at birth to avoid the possibility of becoming infected. Neonates should be given daily Isoniazid (5 mg/kg) for six months as prophylactic chemotherapy. BCG, which is inactivated by chemotherapy, can be given after it ends.

The maximum effect of BCG is in the first 3-5 years after vaccination. BCG causes a specific lesion that starts as a papule two or more weeks after vaccination. This then becomes ulcerated and heals after several months leaving a scar. Mild reactions are mostly local with or without regional lymph nodes manifestations. Axillary or cervical lymphadenitis usually heals spontaneously and it is best not to treat the lesion if it remains non-adherent to the skin. An adherent or fistulated lymph gland, however, may be drained and an anti-TB drug may be instilled locally. Some authors recommend systemic treatment of severe persistent lesions with erythromycin.

Spectrum of mild expected reactions

Immediate	Small raised lump appears. No need for interaction (disappear within 30 minutes).
after about two weeks	A red sore that is about the size of the end of an unsharpened pencil appears and remains for another two weeks and heals spontaneously.
After healing of the previous sore (after several months)	A small scar, about 5 mm across, remains. This is a sign that the child has been effectively immunized

Classification of BCG Disease:

- Local BCG disease at site of injection:
 - Severe BCG scar ulceration
 - Injection site abscess ≥ 10 mm x 10 mm
 - Regional BCG disease at site of injection:
 - Ipsilateral axillary, supraclavicular, cervical and upper arm lymph nodes enlargement.
 - Ipsilateral axillary, supraclavicular, cervical and upper arm lymph nodes suppuration and/or fistula formation.
 - Distant BCG disease:
 - Involvement of any site beyond a local or regional ipsilateral process. This may be in the form of meningitis, urinary tuberculosis, osteitis, distant skin lesion... Etc., Diagnosis should be confirmed by procedures like gastric aspirate, urine culture, CSF examination.
 - Disseminated BCG disease:
 - Confirmed from more than one remote site and/or from at least one blood or bone marrow culture.

Aspiration or excision with or without installation of local Streptomycin, even from the start, is indicated in:

- Fluctuant node
- Abscess formation
- Fistula formation
- Persistent rapidly enlarging node.
- Large injection site abscess
- **Post-BCG lymphadenitis**
 - BCG vaccine is prepared from live bacilli, which is why its use is associated with certain side effects. Although these side effects are generally rare, they vary greatly, from disseminated infection from BCG to death.
 - The likelihood of side effects, in particular the more adverse effects, increases in immuno-deficient children and those who suffer from severe malnutrition

- It is well known that intradermal BCG vaccination causes a primary reaction at the injection site. However, some individuals suffer an excessive reaction, with ulceration, subcutaneous abscess, or suppurative adenitis.
- The IUATLD performed two studies to investigate the incidence of complications from BCG vaccination: a retrospective study (1975-1976) and a prospective study (1979-1981). Six European countries participated in the second study, which involved approximately 5.5 million vaccinated children, half of them were over the age of 1 year when vaccinated. The observed risk of local complications and suppurated lymphadenitis was 387 cases per million in the younger age group, of which 93 per million registered positive histological or bacteriological results. In the older age group, the risk was 25 per million, and confirmation was attained in 18 cases per million.

Possible complications caused by BCG vaccination.

1. Abnormal primary reaction due to BCG vaccination:
 - 1.1. Ulcers, Koch's phenomenon, abscess
 - 1.2. Regional purulent adenitis
2. Disseminated BCG infection; generalized or local lesions; non-fatal cases
 - 2.1. Osteitis
 - 2.2. Retropharyngeal abscesses
 - 2.3. Specific tuberculosis-type cutaneous lesions: lupus, others
 - 2.4. Metastatic subcutaneous and intramuscular abscesses
 - 2.5. Bone and joint complications (including synovial lesions)
 - 2.6. Renal and urogenital complications
 - 2.7. Pulmonary and hilar complications
 - 2.8. Mesenteric adenitis
 - 2.9. Multiple adenitis and/or hepato-splenomegaly, or other locations
3. Disseminated BCG infection; generalized lesions; fatal cases
4. Post-vaccination syndromes or pathologies associated with BCG vaccination
 - 4.1. Chronic local cutaneous complications (keloids, histiocytomas)
 - 4.2. Acute cutaneous eruptions (erythema nodosum and other eruptions)
 - 4.3. Ocular complications
 - 4.4. Other syndromes; non-fatal cases
 - 4.5. Other syndromes; fatal cases

Mild adverse events

- In 90–95% of vaccine recipients, BCG causes a specific lesion that starts as a papule two or more weeks after vaccination. This then becomes ulcerated and heals after several months leaving a scar.
- More serious local reactions have also been described (Lotte et al., 1984): limited lupoid reaction, lasting a few months, keloids, and real tuberculosis lupus (1/200

000 inoculations) have been reported (Misery & Combemale, 1993; Marrak et al., 1991).

- Mild reactions are mostly local with or without regional manifestations. Local reactogenicity differs between vaccines, varying with both strain and number of viable bacilli. Thus the Pasteur and Copenhagen strains have generally been found to be more reactogenic than the Tokyo, Glaxo or Brazilian (Moreau) strains (Milstien, 1990). There were several reports in the late 1980s of “outbreaks” of BCG reactions, manifested as large ulcers and local lymphadenopathy or suppurative lymphadenitis.
- Axillary or cervical lymphadenitis usually heals spontaneously and it is best not to treat the lesion if it remains non-adherent to the skin.
- An adherent or fistulated lymph gland, however, may be drained and an anti-TB drug may be instilled locally.
- Some authors recommend systemic treatment of severe persistent lesions with erythromycin (Bandhari et al., 1980).

Severe adverse events

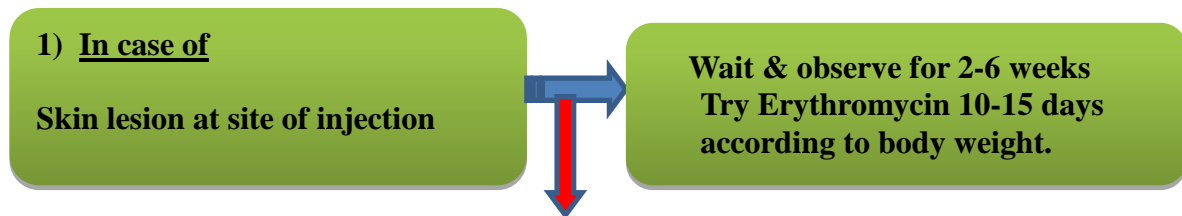
- Osteitis may occur as a BCG complication. BCG osteitis/osteomyelitis is another of the rare and severe consequences of BCG vaccination, and has been reported, in particular in Scandinavia and Eastern Europe, typically associated with changes in BCG vaccine strain. Thus there was a report of an increase in osteitis to 35 per million in Czechoslovakia after a shift from the Prague to Russian strain BCG (Lotte, 1988). Both Finland and Sweden reported increases in osteitis after 1971, when they shifted to a Gothenburg strain produced in Denmark. Sweden reported rates as high as 1 in 3000 vaccine recipients, which declined rapidly when the national programme shifted to a Danish (Copenhagen 1331) vaccine strain (Lotte, 1988).
- Those have been described mostly in Scandinavian countries and seem to be linked to the Göteborg strain. According to Kröger et al. (1994), the incidence rate of such complications ranged from 15 to 73 per 100 000 vaccinated between 1971 and 1978. Dittmann (1992) quotes a frequency between < 0.1 and 30 per 100 000 vaccine recipients. These accidents were also described rarely after injection of the Pasteur or Japanese strains.

Tuberculosis meningitis

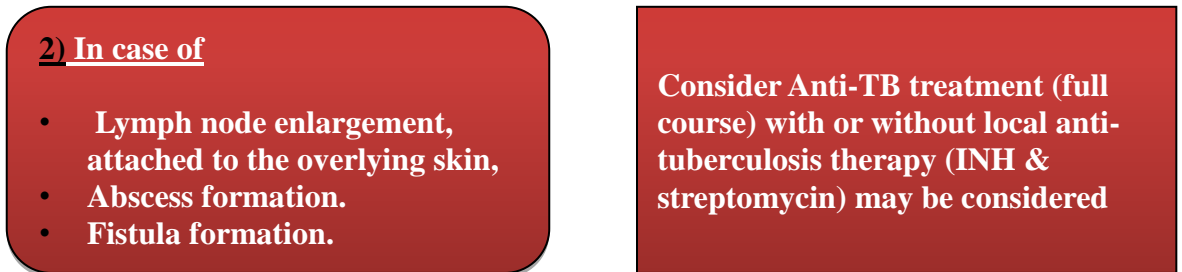
- The complication due to BCG has been described (Tardieu et al., 1988) but this is also exceptional.
- ***Generalized infection due to BCG vaccination*** has also been reported, sometimes being fatal. Systemic BCG-itis is a recognized but rare consequence of BCG vaccination, and traditionally has been seen in children with severe immune deficiencies.

- A recent multi-center study has identified the syndrome in children with severe combined immunodeficiency (SCID), chronic granulomatous disease, Di George syndrome and homozygous complete or partial interferon gamma receptor deficiency (Jouanguy, 1996; Jouanguy 1997; Casanova, 1995).
- Its frequency is reported as less than 5 per million vaccine recipients, reflecting the rarity of the underlying conditions (Lotte, 1988). If not properly managed, these cases may be fatal.

NATIONAL MANAGEMENT PROTOCOL FOR POST-BCG COMPLICATION



If there is no regression refer to chest unit



If there is no regression refer to chest hospital



The recommended regimen is 2RHZ/4HR according to body weight.

CASE FINDING

NATIONAL CASE FINDING POLICY

A. Passive Case Detection

Tuberculosis patients are detected among individuals who have symptoms and who seek health care. It is very important to create awareness in the community and among the medical professions about the symptoms suggestive of pulmonary TB.

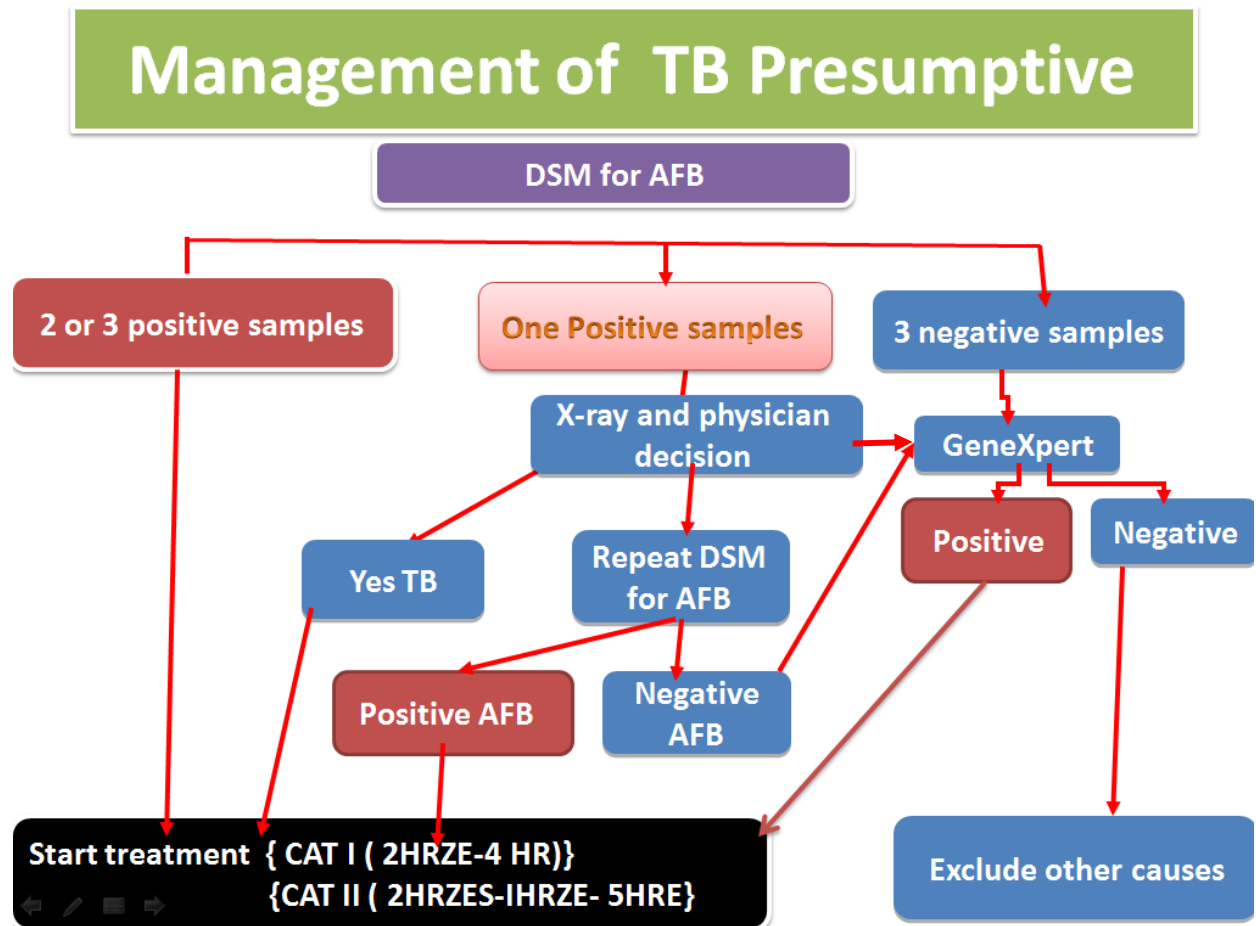
Active Case Detection

The health services go to the community to detect TB cases; e.g. screening in the army, prison, psychiatric wards and among contacts of identified pulmonary TB patients. Mass examination by X-ray of large numbers of persons has been abandoned because of its high costs and the small number of TB cases detected by this method. Currently, active case detection is applied only for certain risk groups:

1. Contacts of pulmonary TB patients
2. Individuals who are in need of a health certificate
3. Other risk groups:
 - Health staff, especially laboratory staff dealing with sputum examination
 - Closed communities, e.g. army, prison, etc.
 - Patients with immunosuppressive diseases, e.g. diabetes, renal failure, HIV infection
 - Patients under immunosuppressive treatment, e.g. corticosteroids, anti-cancer therapy

TB will be detected most efficiently where health care providers and community members are highly conscious of the symptoms suggestive of TB.

PRESUMPTIVE CASE MANAGEMENT



Case definitions

Purposes of defining a TB case

- Proper patient registration and case notification,
- Standardizing the process of data collection for TB control,
- Selecting appropriate treatment regimens,
- Evaluating the proportion of cases according to site, bacteriology and treatment history,
- Cohort analysis of treatment outcomes,
- Accurate monitoring of trends and evaluation of the effectiveness of TB programs within and across districts, countries and global regions.

Tuberculosis presumptive case: Any person who presents with cough for more than 2 weeks, which may be accompanied by other respiratory symptoms (shortness of breath, chest pains, hemoptysis) and/or constitutional symptoms (loss of appetite, weight loss, fever, night sweats, and fatigue).

Definite case of tuberculosis. A patient with *Mycobacterium tuberculosis* identified from a clinical specimen, either by smear, culture or by a newer.

Cases of TB are also classified according to the:

- Anatomical site of disease;
- Bacteriological results (including drug resistance);
- History of previous treatment;
- HIV status

Classified according to anatomical site of TB disease

Pulmonary tuberculosis (PTB) refers to a case of TB (defined above) involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculosis intra-thoracic lymph-adenopathy (mediastinal and/or hilar) or tuberculosis pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of pulmonary TB.

Extra-pulmonary tuberculosis (EPTB) refers to a case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed *M tuberculosis* or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease.

Classified according to bacteriological results

Smear-positive PTB cases: a case of pulmonary TB is considered to be smear-positive if one or more sputum smear specimens at the start of treatment are positive for AFB

Smear-negative PTB cases:

1. Presenting complaints consistent with Tuberculosis
2. Radiographic abnormalities consistent with pulmonary TB
3. Two sets of sputum smear negative for AFB separated by a course of antibiotic with no clinical or radiological improvement
4. Decision by a clinician to treat with a full course of anti-TB therapy

NB. Pulmonary TB cases without smear results are no longer classified as smear-negative; instead, they are recorded as “smear not done” on the TB register.

Classified according to history of previous treatment:

New patient has never had treatment for TB, or has taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously treated patient has received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment. NB. Patients whose sputum is smear-positive at the end of (or returning from) a second or subsequent course of treatment are no longer defined as “chronic”. Instead, they should be classified by the outcome of their most recent retreatment course: relapsed, lost to follow or failed.

The following table summarizes the different definitions of patient diagnostic and registration categories

Diagnostic/Registration category		Definition
New		A patient who has never had treatment for TB or who has taken anti-tuberculosis drugs for less than 4 weeks.
Re-treatment	Relapse	Previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
	Treatment after failure	Previously has been treated for TB and whose treatment failed at the end of their most recent course of treatment.
	Treatment after lost to follow	Previously has been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
Transfer in		Patient already registered for treatment in one district that has been transferred to another district to continue treatment is recorded as a “transfer in” at the referral site.
Other		Previously have been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Treatment of tuberculosis

Aims of treatment

- To cure the patient and restore quality of life and productivity;
- To prevent death from active TB or its late effects;
- To prevent relapse of TB;
- To reduce transmission of TB to others;
- To prevent the development and transmission of drug resistance.

First-line anti-tuberculosis drugs

The following table shows the first-line anti-TB drugs and their recommended dosages for adults based on the patient's weight.

Drug	Dose and range (mg/kg body weight)	Maximum dose per day
Isoniazid, H	5 (4-6)	300 mg/day
Rifampicin, R	10 (8-12)	600 mg/day
Pyrazinamide, Z	25 (20-30)	2000 mg/day
Ethambutol, E	15(15-20)	1500 mg/day
Streptomycin, S	15 (12-18)	1 gm/day

The recommended dosages of anti-TB medicines for the treatment of TB in children:

- Isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day
 Rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day
 Pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg)
 Ethambutol (E) 20 mg/kg (range 15–25 mg/kg)

The following table summarizes the mode of action and side effects of first-line

Drug	Side effects	Control	Interactions	Action
Isoniazid	Neuritis	SGOT	Phenytoin	Extra- + intracellular bactericide
	Hepatitis	SGPT		
	Hypersensitivity			
Rifampicin	Hepatitis	SGOT	Inhibits oral contraceptives	Bactericidal all populations
	Febrile reaction	SGPT		
	Purpura		Quinidine	Sterilizing
Pyrazinamide	Hyperuricemia	Uric acid		Intracellular bactericide Sterilizing
	Hepatitis	SGOT		
		SGPT		

Ethambutol	Optic neuritis	Red-green discrimination Visual acuity		Extra- + intracellular bacteriostatic
Streptomycin	VIII cranial nerve damage Hypersensitivity	Vestibular function Audiogram Creatinine	Neuromuscular blocker	Extracellular bactericide

TREATMENT REGIMENS

The following table shows the different patients categories and the corresponding treatment category (whether category I, *Cat I* or category II, *Cat II*) used to treat them.

Treatment Category	Patient category	Regimen	
		Intensive phase	Continuation phase
<i>Cat I</i>	All new TB cases	2HRZE (first 2 months)	4HR (following 4 months)
<i>Cat II</i>	All Previously treated TB cases – relapse – treatment after interruption – treatment after failure	2HRZES (first 2 months) Then 1HRZE (one month)	5HRE (following 5 months)

BASES OF TB TREATMENT

TB chemotherapy should be based on two important microbiological considerations:

1. The combination of drugs to avoid the development of resistance.
2. The need for prolonged treatment to prevent disease relapse.

All **mono-therapeutic** regimens (real or masked) lead to treatment failure and to the development of resistance.

When three or more drugs are administered, the risk of resistance is practically zero.

These treatment regimens were based on some characteristics of the *M. tuberculosis* and the drugs used:

M. tuberculosis is strict aerobe. Metabolic activity is proportional to the surrounding **oxygen partial pressure** and **PH**. The ideal conditions for the bacilli comprise a pH of 7.40 and an oxygen pressure of 100 to 140 mm Hg. **4 growth modalities** have been established:

A. Metabolically active and under conditions of continuous growth. They are Present in cavitary wall, located extracellular and responsible for treatment failure and

resistance if not homogeneously eradicated. Eradicated by bactericidal drugs, mainly **INH**, then less by **streptomycin & Rif**.

- B. Bacilli in the acid-inhibition phase.** They are scanty population (10^3 - 10^5 bacilli) Growth inhibited by the **acidic medium** in the **necrotic tissue** (for extra-cellular bacilli), or **in the phagocytes** (for intracellular bacilli). Their growth is also inhibited by the deficient oxygen. These can't be eradicated by the drugs as they lack metabolic activity. They represent the main cause of relapse. Most active drug against them is **Pyrazinamide**. This action of Pyrazinamide is referred to as sterilizing effect.
- C. Bacilli in the sporadic multiplication phase.** Often located in solid caseum where the PH is neutral. They show long dormant periods, with occasional & brief metabolic activity periods (for hours). Drugs are only able to destroy bacteria during these periods, which may not occur during the course of therapy. They are also **responsible for relapse**. The limited and occasional activity of these bacteria prevents them from developing resistances. Rifampicin is the drug of choice to eradicate these population during their brief metabolic action because of the rapid onset of its sterilizing action (15-20 minutes, versus 24 hours as in the case of isoniazid).
- D. Persistent or totally dormant populations.** Bacteria lack metabolic activity. Treatment is not effective against them. Probably only the individual host defense mechanisms are able to have some effect on this population. May be responsible for relapse in patients with severe immunodeficiency.

Rationale for an ideal initial treatment regimen

The drugs that selectively act upon the different bacterial populations are (H), (R), and (Z); these three drugs should constitute the basis for an effective TB treatment regimen. The combination 2HRZ/4HR is ideal in all initial cases of the disease. However, due to high **primary resistance rate to isoniazid (H)** found in many parts of the world, it is necessary to add a fourth drug to this initial phase of therapy.

Isoniazid and Streptomycin have been used extensively. This caused the primary resistance rates to these two drugs in many parts of the world. Considering the high proportion of **natural mutants resistant to Pyrazinamide**. Rifampicin is the sole remaining agent that can be used against very large microbial populations. Therefore, a fourth drug should be added during the first 2 months of treatment when the bacillary population is very high. By the second treatment phase, this population would have been reduced to such low levels that even with initial resistance to Isoniazid, the number of surviving bacilli would be too small to generate a mutant resistant to Rifampicin.

What is the ideal drug to add to isoniazid, rifampicin, and pyrazinamide in the initial phase?

Streptomycin or Ethambutol? The latter is preferable for both microbiological and practical reasons. Microbiologically, streptomycin has been as extensively used as isoniazid. Practically, streptomycin needs injection

Drug and food interactions with anti-tuberculosis drugs

A. Interactions at the drug absorption level.

The effect of food and antacids.

Such interactions can be attributed to:

- changes in the pH of the gastrointestinal contents,
- effects on gastric emptying, gastrointestinal motility
- fixation or chelation of drugs to form insoluble complexes,

Isoniazid, rifampicin, and Ethambutol require an acid medium for absorption; as a result, their absorption is worse in the presence of drugs that increase the gastric pH, or in patients with achlorhydria (a common condition in HIV-infected patients).

It is therefore advisable to administer these drugs at least 2 hour before taking antacids.

Drug	Effect of food	Effect of antacid
Isoniazid	<ul style="list-style-type: none"> • To be administered on empty stomach • Food reduces absorption by 57% particularly carbohydrates. • Isoniazid inhibits monoamine oxidase, avoid foods rich in Tyramine and alcohol 	Antacid reduces area under curve AUC*, by up to 19%
Rifampicin	<ul style="list-style-type: none"> • To be administered on empty stomach, absorption is reduced by up to 26% in the presence of food. 	Administration with antacid should be avoided but H2 blocker (Ranitidine) can be used
Pyrazinamide	<ul style="list-style-type: none"> • Minimum effect on bioavailability 	Can be administered with antacid
Ethambutol	<ul style="list-style-type: none"> • Minimum effect on bioavailability 	Reduce C _{max} (maximum (or peak) serum concentration) by 28% and AUC by 10%. Avoid combining both

**in a plot of concentration of drug in blood plasma against time, typically, the area computed starting at the time the drug is administered and ending when the concentration in plasma is negligible. In practice, the drug concentration is measured at certain discrete points in time and used to estimate AUC*

INTERACTIONS AT THE DRUG METABOLISM LEVEL

- The rifampicin *induces* cytochrome P450 enzyme activity; consequently, may reduce the therapeutic efficacy of drugs such as:
 - oral anticoagulants,
 - contraceptives,
 - glucocorticoids,
 - oral anti-diabetic drugs,
 - immune suppressors
 - methadone,
- Isoniazid can increase the concentrations of:
 - phenytoin
 - carbamazepine,

Probably as a result of inhibition of the liver metabolism of these antiepileptic drugs.

- **Isoniazid can also alter the metabolism of paracetamol, increasing the production of a toxic metabolite. High paracetamol doses should therefore be avoided when administering isoniazid.**

PHARMACO-DYNAMIC INTERACTIONS

- Aminoglycosides (impairing kidney functions), can reduce the elimination of anti-retroviral, which are mainly eliminated through the kidneys.
- Pyrazinamide can induce episodes of gout in patients at risk, since it competes with uric acid for renal elimination. This is more evident in patients receiving allopurinol. Allopurinol reduces the elimination of the main metabolite of pyrazinamide, which also reduces uric acid secretion.
- Ethambutol can cause optic neuritis, while rifabutin can cause uveitis. Patients who simultaneously receive several drugs capable of causing ocular toxicity must be closely monitored.
- Aminoglycosides need periodic hearing evaluation, particularly among those receiving other ototoxic agents in combination e.g. clarithromycin, ethacrynic acid and furosemide.

IMPORTANT CONSIDERATION FOR TB TREATMENT

1. All these drugs should be given as single daily dose (no more frequent administration as the Mycobacteria are slow multiplier almost once every day).
2. All these drugs should be given together, as a single dose, to get the simultaneous synergetic effect of all drugs. Dividing the dose or spacing the drugs interfere with that effect.
3. Most of the drugs are affected by the presence of food in the stomach or its PH, that is why, it is necessary to give all drugs on empty stomach (as in case of FDCs)

Treatment of tuberculosis in special situations

Pregnancy

Untreated tuberculosis represents a far greater hazard to a pregnant woman and the fetus than treatment of the disease. It is important to ask a woman if she is pregnant before starting TB treatment.

Most TB drugs, except for streptomycin, are safe for use in pregnant women.

Safety classification of anti-TB drugs during pregnancy

A = safety established in human studies.

B = safety presumed based on animal studies.

C = safety uncertain; no human or animal studies reveal an adverse effect.

D = safety uncertain; evidence of risk but use is justified in certain circumstances.

Isoniazid

- Safety class C
- Experience with patients suggests safety. Pyridoxine (vitamin B6) should be used during pregnancy.

Rifampicin

- Safety class C
- Experience with patients suggests safety.

Ethambutol

- Safety class B
- Experience with pregnant patients suggests safety

Pyrazinamide

- Safety class C
- Formal studies are limited but there is much clinical experience.

Streptomycin

- Safety class D
- **Documented toxicity to the developing fetal ear (8-11%).** Toxicity is higher in the first trimester.
- Risks and benefits should be carefully considered.
- Use should be limited to severe cases when clinical status and drug resistance warrants use.

NTP recommends that Streptomycin should not be used in pregnancy.

Breastfeeding women

A breastfeeding woman who has TB should receive a full course of TB treatment. All the TB drugs are compatible with breastfeeding and a woman taking them can safely continue to breastfeed her baby. If the mother is infectious (both smear-positive and smear-negative PTB) the child should be given prophylactic isoniazid (10mg/kg/day) for six months and continue breastfeeding. BCG vaccination should be postponed until the end of isoniazid prophylaxis as the TB treatment and INH can destroy the vaccine.

Women using contraceptives

Since Rifampicin reduces the effectiveness of oral contraceptives, women should be advised to choose between one of two options for contraception: she may use an oral contraceptive pill containing a higher dose of estrogen (50 µg); alternatively, a non-hormonal method of contraception may be used throughout Rifampicin treatment and for at least one month subsequently.

Diabetes mellitus

The drug regimen is same as in non-diabetic. Strict control of blood glucose is mandatory. Also, doses of oral hypoglycemic agents may have to be increased due to interaction with Rifampicin. Prophylactic pyridoxine is indicated.

Liver disorders

Patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of *chronic liver disease*:

- Hepatitis virus carrier,
- Patients with a past history of acute hepatitis,
- Current excessive alcohol consumption.

Hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated and closely monitored.

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment. If the serum alanine aminotransferase level is more than 3 times normal before the initiation of treatment, the following regimens should be considered.

In advanced liver failure, the administered regimen should always include Ethambutol and streptomycin, with a third drug that could be isoniazid if laboratory evidence indicates cholestasis conditions (high bilirubin only) (2HES/10HE), or rifampicin (R) in the event of necrosis (high liver enzymes) (2RES/10RE).

The more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used:

One hepatotoxic drug:

- 2 months of Isoniazid, Ethambutol and streptomycin, followed by 10 months of Isoniazid and Ethambutol.

Two hepatotoxic drugs:

- a) 9 months of Isoniazid and Rifampicin, plus Ethambutol (until or unless Isoniazid susceptibility is documented);
- b) 2 months of Isoniazid, Rifampicin, streptomycin and Ethambutol, followed by 6 months of Isoniazid and Rifampicin;

No hepatotoxic drugs: Ethambutol, Fluoroquinolone with/without aminoglycoside for 12-24 months.

Treatment of TB in a compensated cirrhotic liver.

Proposed regimens are:

- 1.rifampicin, isoniazid, pyrazinamide and Ethambutol for 2 months followed by 4 months rifampicin and isoniazid;
- 2.rifampicin, isoniazid, Fluoroquinolone/aminoglycoside and Ethambutol for 2 months followed by 4 months rifampicin and isoniazid;
- 3.Rifampicin, isoniazid, and Ethambutol for 2 months followed by 7 months rifampicin and isoniazid.

Treatment of TB in a decompensated cirrhotic liver.

Proposed regimens are:

- 1.rifampicin, Ethambetol, Fluoroquinolone with/without aminoglycoside for 9-12 months;
- 2.isoniazid, Ethambutol, Fluoroquinolone with/without aminoglycoside for 9-12 months;
- 3.Ethambutol, Fluoroquinolone with/without aminoglycoside for 12-24 months.

NB.

- Liver diseases expert consultation is advisable in treating patients with advanced or unstable liver disease.
- Clinical monitoring and liver function tests of all patients with pre-existing liver disease should be performed frequently during treatment.
- Note that TB itself may involve the liver and cause abnormal liver function.
- In some cases of concurrent acute (i.e. viral) hepatitis not related to TB or TB treatment, it may be possible to postpone TB treatment until the acute hepatitis has resolved.

Proposed treatment options according to Child’s class (could be evaluated with Liver diseases specialist)

Child’s class	Suggested Treatment
A	Two hepatotoxic drugs can be used namely isoniazid and rifampicin with/without pyrazinamide (low dose). Duration 6-9 months
B	Ideally one hepatotoxic drug is used in combination. Pyrazinamide generally avoided. Duration generally 9-12 months
C	No hepatotoxic drugs to be used. Ethambutol, Fluoroquinolones and Capreomycin/Amikacin/ kanamycin for extended duration of 12 months or more. Role of aminoglycosides may be limited due to reduced renal reserve in these patients.

The Child-Pugh score

Factor	1 point	2 points	3 points
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
PT INR	<1.7	1.71-2.30	>2.30
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (suppressed with medication)	Grade III-IV (or refractory)
	Class A	Class B	Class C
Total points	5-6	7-9	10-15
1-year survival	100%	80%	45%

In patients with advanced liver disease with complications of cirrhosis and signs of liver failure, it may not be possible to use even a single hepatotoxic drug.

The presence of hepato-renal syndrome or other renal dysfunction further complicates the situation, limiting the use of aminoglycosides.

Altered mental status may also prevent administration of oral drugs.

The outcome in such group patients is poor, with high mortality due to the underlying poor hepatic function.

Renal failure

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of Isoniazid, Rifampicin, Pyrazinamide and Ethambutol, followed by 4 months of Isoniazid and Rifampicin.

- Isoniazid and Rifampicin are eliminated by biliary excretion, so no change in dosing is necessary.
- There is significant renal excretion of Ethambutol and metabolites of Pyrazinamide, and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is recommended: Pyrazinamide (25 mg/kg), and Ethambutol (15 mg/kg).

While receiving Isoniazid, patients with severe renal insufficiency or failure should also be given pyridoxine in order to prevent peripheral neuropathy.

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

In all of these cases creatinine clearance should be done to adjust the dose and renal diseases expert should be consultant.

Monitoring and management of first-line anti-TB drugs side effects.

Prevention of adverse effects of drugs: Health personnel can prevent some drug-induced side-effects, for example Isoniazid-induced peripheral neuropathy. This usually presents as numbness or a tingling or burning sensation of the hands or feet and occurs more commonly in pregnant women and in people with the following conditions: HIV infection, alcohol dependency, malnutrition, diabetes, chronic liver disease, renal failure. These patients should receive preventive treatment with pyridoxine, 10-25 mg/day along with their anti-TB drugs.

Monitoring and recording adverse effects: Most TB patients complete their treatment without any significant adverse drug effects. However, a few patients do

experience adverse effects. It is therefore important that patients be clinically monitored during treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary except in some high risk group, see below.

Health personnel can monitor adverse drug effects by teaching patients how to recognize the symptoms of common effects, urging them to report if they develop such symptoms, and by asking about symptoms when patients come to collect drugs.

Adverse reactions to drugs should be recorded on the TB Treatment Card under “Observations”.

Risk groups/factors for side effects:

- Elderly patients
- Malnutrition
- Pregnancy or lactation
- Alcoholism
- Liver cell failure
- Chronic renal failure
- HIV infection
- Disseminated and advanced TB
- Atopy
- Anemia
- Diabetes mellitus
- Family history of adverse anti-tuberculosis drug reactions
- Patients receiving irregular anti-tuberculosis treatment
- Patients receiving medication for other disorders, in addition to anti-tuberculosis drugs

All these patients groups or with risk factors should be closely monitored during the whole course of treatment with frequent lab investigation to early detect the major side effects.

Side-effects	drug(s) probably responsible	Management
<i>Major</i>		<i>Stop responsible drug(s) urgently</i>
Skin rash with or without itching	Streptomycin, Isoniazid, Rifampicin, Pyrazinamide	Stop anti-TB drugs and manage accordingly. Start treatment of allergic reaction, then after the condition subsides, restart drugs one by one with the least likely drug and close observation to determine the responsible drug to exclude it.
deafness (no wax on otoscopy)	Streptomycin	Stop streptomycin

Side-effects	drug(s) probably responsible	Management
dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin
Jaundice (other causes excluded), hepatitis	Isoniazid, Pyrazinamide, Rifampicin	Stop anti-TB all drugs. Exclude other causes of jaundice e.g. viral hepatitis, wait until all symptoms subside, liver enzymes become normal and then reintroduce drugs one at a time. Start with R, then after 3 days add H then Z If the TB condition is severe and treatment can't be stopped or hepatitis didn't resolve, start non-hepatotoxic regimen, see before.
confusion (suspect drug- induced acute liver failure if there is jaundice)	most anti-TB drugs	Stop anti-TB drugs and accordingly
Visual impairment (other causes excluded)	Ethambutol	Stop Ethambutol
Shock, Purpura, acute renal failure	Rifampicin	Stop Rifampicin and accordingly
decreased urine output	Streptomycin	Stop Streptomycin and accordingly
Minor		Continue anti-TB drugs, check drug doses
Anorexia, nausea, abdominal pain	Pyrazinamide, Rifampicin, Isoniazid	Advise patient to swallow pills slowly with small sips of water. Give anti-emetic drugs and anti-TB drugs just before bedtime, and if symptoms persist or worsen, or there is protracted vomiting or any sign of bleeding, consider the side-effect to be major and hospitalize the patient.
Joint pains	Pyrazinamide	Aspirin or non-steroidal anti- inflammatory drug, or paracetamol
Burning, numbness or tingling sensation in the hands or feet	Isoniazid	pyridoxine 50–75 mg daily
drowsiness	Isoniazid	Reassurance. give drugs before bedtime
Orange/red discoloration of urine for few hours	Rifampicin	Reassurance. Patients should be told when starting treatment that this may happen and is normal. If continues all over the day, exclude

Side-effects	drug(s) probably responsible	Management
after dose of Rifampicin		jaundice
flu syndrome (fever, chills, malaise, headache, bone pain)	intermittent dosing of Rifampicin	change from intermittent to daily Rifampicin administration

Alternative regimens depend on which drug is implicated as the cause of the hepatitis.

- If Rifampicin is implicated, a suggested regimen without Rifampicin is 2 months of Isoniazid, Ethambutol and streptomycin followed by 10 months of Isoniazid and Ethambutol.
- If Isoniazid cannot be used, 6–9 months of Rifampicin, Pyrazinamide and Ethambutol can be considered.
- If Pyrazinamide is discontinued before the patient has completed the intensive phase, the total duration of Isoniazid and Rifampicin therapy may be extended to 9 months
- If neither Isoniazid nor Rifampicin can be used, the non-hepatotoxic regimen consisting of streptomycin, Ethambutol and a Fluoroquinolone should be continued for a total of 18–24 months.
- When hepatitis with jaundice occurs during the intensive phase of TB treatment with Isoniazid, Rifampicin, Pyrazinamide and Ethambutol: once hepatitis has resolved, restart the same drugs EXCEPT replace Pyrazinamide with streptomycin to complete the 2-month course of initial therapy, followed by Rifampicin and Isoniazid for the 6-month continuation phase.
- When hepatitis with jaundice occurs during the continuation phase: once hepatitis has resolved, restart Isoniazid and Rifampicin to complete the 4-month continuation phase of therapy.

Fixed-dose combinations of anti-TB drugs

Fixed-dose combinations (FDCs) of anti-TB drugs are to prevent acquisition of drug resistance due to mono-therapy, which may occur with separate (“loose”) drugs. With FDCs, patients cannot be selective in the choice of drugs to ingest. Prescription errors are likely to be less frequent because dosage recommendations are more straightforward, and adjustment of dosage according to patient weight is easier. The number of tablets to ingest is smaller and may thus encourage patient adherence.

Number of tablets of 4 fixed dose and two fixed dose combination per day **for adults and children weighing ≥ 25 kg.**

Pre-treatment body weight	Intensive Phase 7 days a week for 2 months		Continuation phase 7 days a week for 4 months	
	RHZE (150 mg,75 mg, 400 mg,275 mg)		RH (150 mg,75 mg)	RH (300 mg,150 mg)
children weighing ≥ 25 kg.	2 tabs		2 tabs	
30-37 kg	2 tabs		2 tabs	
38-54 kg	3 tabs		3 tabs	
55-70 kg	4 tabs		4 tab	2 tabs
>70kg	5 tabs		4 tab	2 tabs

FIXED-DOSE COMBINATIONS FOR CHILDREN

The new formulations available are:

For the intensive phase of TB treatment:

Rifampicin 75 mg + Isoniazid 50 mg + Pyrazinamide 150mg

For the continuation phase of TB treatment:

Rifampicin 75mg + Isoniazid 50 mg

The following dosing table provides information on the number of daily tablets needed to reach the proper dosing, based on the child’s weight:

Weight band	Numbers of tablets	
	Intensive phase: RHZ 75/50/150*	Continuation phase: RH 75/50
4-7 kg	1	1
8-11 kg	2	2
12-15 kg	3	3
16-24 kg	4	4
25+ kg	Adult dosages recommended	

**Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high*

MONITORING THE TREATMENT RESPONSE:

- The most important way to monitor treatment is following up sputum smear examination results at regular intervals during treatment (at the end of intensive phase, at end of the fifth month, and at the end of treatment).
- Clinical improvement, weight gain can also be used, in addition.
- X-ray chest may show slow improvement over the treatment period, so it can't be a good method to follow up the disease process. However, radiological imaging maybe the sole method of following up the disease in some extra-pulmonary cases e.g. Tuberculosis of bone and joints.

Practical issues when monitoring TB treatment:

- In pulmonary smear-positive cases, the conversion of sputum smears from smear-positive to smear-negative is the best early indicator that chemotherapy is taken regularly and effectively.
- After two months of chemotherapy more than 80 % of NEW pulmonary smear-positive cases should have converted to smear-negative, and after three months this rate should increase to more than 90 %.

TREATMENT OUTCOME:

The aim of the NTP is to detect and treat patients with TB, particularly patients with smear positive TB. One of the main objectives is to achieve a cure rate of 85% or more for new smear positive tuberculosis patients that were registered and put on treatment.

Determining the cure rate for new pulmonary smear positive cases is a useful way to evaluate the effectiveness of chemotherapy. Another way to assess the performance of the NTP is to determine the other possible treatment outcomes for new smear positive cases: determine the proportion of smear positive patients that failed to convert to smear negative after five months of treatment; the proportion that lost to follow; the proportion that died; and the proportion that was transferred to another governorate. In a similar manner smear positive retreatment cases should be evaluated.

The report on treatment outcome is one of the most important reports that are being prepared, as it provides information on the effectiveness of the NTP in the management of TB patients.

Definitions of Treatment Outcome

The following table shows the definitions of different expected outcomes:

<i>Cure</i>	A patient who is smear-negative in the last month of treatment and on at least one previous occasion.
<i>Treatment completed</i>	A patient who has completed treatment but who does not meet the criteria to be classified as a cure or a failure.
<i>Treatment failure</i>	A patient who remains or becomes again smear-positive at five months or later during treatment Also a patient who was initially smear-negative before starting treatment and became smear-positive after completing the initial phase of treatment
<i>Died</i>	A patient who dies for any reason during the course of treatment
<i>Lost to follow up</i>	A patient whose treatment was interrupted for two months or more
<i>Transfer out</i>	A patient who has been transferred to another <i>reporting unit</i> outside the Governorate and for whom the treatment outcome is not known

Management of treatment interruption (for new case on Cat I treatment regimen)

If a patient misses an arranged appointment to receive treatment, the NTP should ensure that the patient is contacted within a day after missing treatment dose.

The patient can be traced using the locating information previously obtained.

It is important to find out the cause of the patient's absence so that appropriate action can be taken and treatment can continue.

IF THE PATIENT INTERRUPTED TREATMENT FOR LESS THAN 1 MONTH

- Trace the patient
- Establish the cause for interruption of treatment
- Address the problem or concerns/counsel patient
- Continue treatment and add the missed doses at the end of the treatment phase:
 - a. If the interruption occurred during the intensive phase, the duration of this phase must be extended by the number of days that the patient did not take treatment.
 - b. If the interruption occurred during the continuation phase, the duration of this phase must be extended by the number of days that the patient did not take treatment.

IF PATIENT INTERRUPTS TREATMENT FOR 1 – 2 MONTHS

- Continue treatment and add the missed doses at the end of the treatment phase

IF PATIENT INTERRUPTED TREATMENT FOR TWO MONTHS OR MORE (LOST TO FOLLOW UP)

- If positive by GeneXpert and Rifampicin sensitive, start treatment category *II*
- If positive by GeneXpert and Rifampicin resistant, start treatment category *IV*

Management of treatment interruption (for retreatment cases on Cat II treatment regimen)

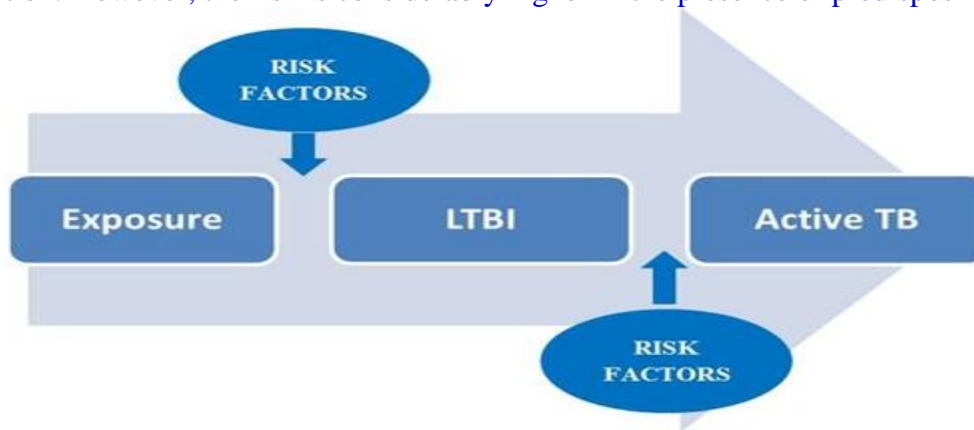
Duration of treatment before interruption	Length of interruption	Do a smear examination?	Sputum status	Register again as?	Treatment
Patient received treatment < 1 month	< 2 weeks	NO	-	No	Continue Cat II
	2-8 weeks	NO	-	No	Restart again Cat II
	> 8 weeks	YES	Positive	Treatment after interruption	Restart again Cat II
			Negative	Others	Continue Cat II
Patient received treatment 1-2 months	< 2 weeks	NO	-	No	Continue Cat II
	2-8 weeks	YES	Positive	No	Extend intensive phase of Cat II one month
			Negative	No	Continue Cat II
	> 8 weeks	YES	Positive	Treatment after interruption	Restart again Cat II
Negative			Others	Continue Cat II	
Patient received treatment > 2 months	< 2 weeks	NO	-	No	Continue Cat II
	2-8 weeks	YES	Positive	No	Restart again Cat II
			Negative	No	Continue Cat II
	> 8 weeks	YES	Positive	Treatment after interruption	Restart again Cat II
Negative			Others	Continue Cat II	

Latent tuberculosis infection

Latent tuberculosis infection (LTBI) is a state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active TB.

A direct measurement tool for *M. tuberculosis* infection in humans is currently unavailable. One-third of the world's population is estimated to have LTBI: they do not have active TB disease but may develop it in the near or remote future, a process called "TB reactivation".

The lifetime risk of reactivation for a person with documented LTBI is estimated to be 5–10%, with the majority developing TB disease within the first five years after initial infection. However, the risk is considerably higher in the presence of predisposing factors



How is LTBI diagnosed?

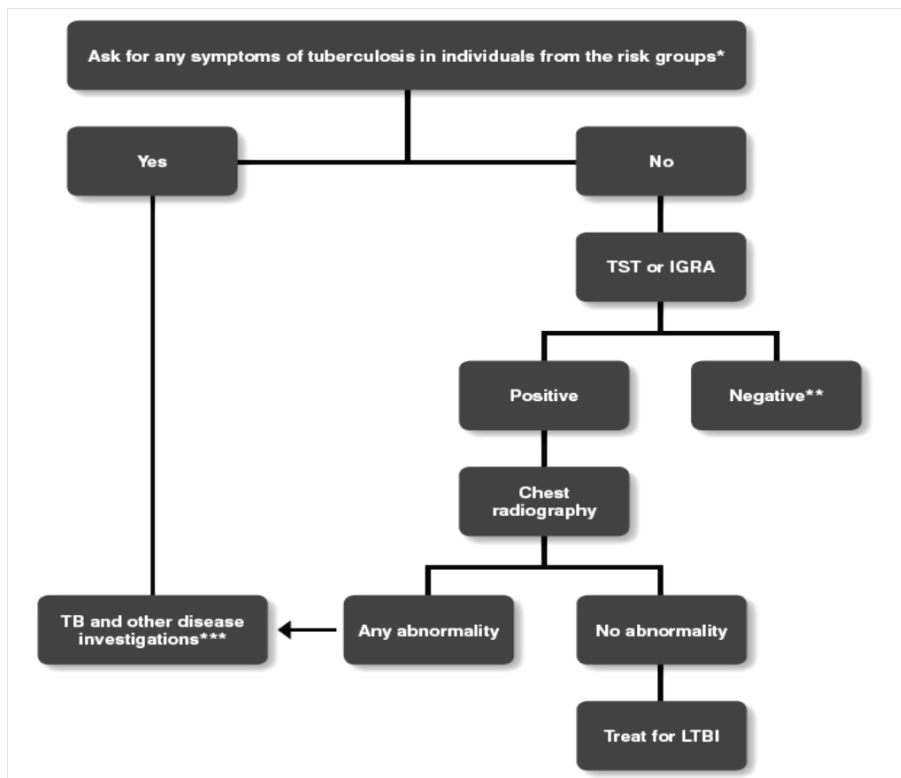
TST (Tuberculin Skin Test) and **IGRAs** (Interferon-Gamma Release Assays) are the main tests currently available for the diagnosis of LTBI.

Persons with LTBI have negative bacteriological tests: the diagnosis is based on a positive result of either a TST or IGRA test indicating an immune response to *M. tuberculosis*. Persons with LTBI have negative bacteriological tests: the diagnosis is based on a positive result of either a skin (tuberculin skin test, TST) or blood (Interferon-gamma release assay, IGRA) test indicating an immune response to *M. tuberculosis*.

However these tests have limitations as they cannot distinguish between latent infection with viable microorganisms and healed/treated infections; they also poorly predict who will progress to active TB.

Either TST or IGRAs can be used to identify candidates to LTBI treatment in high and upper-middle-income countries with estimated TB incidence less than 100,000. IGRAs should not replace TST in low and other middle-income countries.

- **Algorithm for diagnosis**



Who should be tested and treated for LTBI?

The risk of progression to active disease is considerably higher in infected individuals who belong to specific high risk populations. Major risk factors for TB activation include:

- HIV infection,
- recent contact with an infectious patient,
- initiation of an anti-tumour necrosis factor (TNF) treatment,
- receiving dialysis,
- receiving an organ or hematologic transplantation,
- silicosis

How can LTBI be treated?

LTBI can be effectively treated in order to prevent progression to active TB, thus resulting in a substantial benefit for both the individual and the community. Currently available treatment options allow to reduce by at least 60% the risk of developing active TB. However, safety concerns exist, mainly related to the development of hepatotoxicity.

Treatment options for LTBI

The following treatment options are recommended for the treatment of LTBI:

1. 6-month isoniazid, or
2. 9-month isoniazid, or
3. 3-month regimen of rifampicin plus isoniazid,
(*Strong recommendation, moderate to high quality of evidence*)

Preventive treatment for contacts of MDR-TB cases

Serious limitations of the quality of evidence prevent drawing any recommendations on MDR-TB preventive therapy as a public health measure. Strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases.

Risk of drug resistance following LTBI treatment

Isoniazid for 6- to 12-month duration: Thirteen studies comparing 6- to 12-month isoniazid preventive therapy versus no treatment or placebo were included in the systematic review (seven involving HIV uninfected populations); no difference in the risk of resistance among incident TB cases was found (risk ratio = 1.45 (95% CI: 0.85–2.47)). There was little evidence of heterogeneity ($p=0.923$) and the risk ratio for HIV-uninfected and HIV-infected populations was comparable. The quality of the evidence was moderate.

Isoniazid for 36 months in HIV-infected individuals: Three studies comparing 36- and 6-month isoniazid were reviewed but only one study provided resistance rates, and no significant difference in drug resistance was found (risk ratio = 5.96 (95% CI: 0.24–146)).

The two other studies reported that the observed proportion of resistant cases were similar to the expected rate in the background population, but did not provide a direct comparison of resistance rates between those receiving 36 months compared to those receiving 6 months treatment. Therefore, it was concluded that there is no evidence to indicate whether or not continuous use of isoniazid increases the risk of isoniazid resistance.

Rifamycin-containing regimens: Five studies were included in the comparison of Rifamycin resistance in individuals treated with a Rifamycin-containing regimen versus regimen not containing Rifamycin.

There were very few cases of Rifamycin resistance, a total of six (0.1%) cases in 5790 individuals receiving LTBI treatment with a Rifamycin and five (0.09%) cases in the 5537 individuals in the control group with a relative risk of 1.12 (95% CI: 0.41–3.08). The quality of the evidence was very low after downgrading for risk of bias, indirectness and imprecision.

Contact management

Prompt contact investigation is essential for TB control. Contact investigations should start with the persons who are most likely to be infected--those who most frequently come in contact with the person who has infectious TB. These close contacts are usually family members or other persons who live in the same household. Active case detection is indicated in this group of individuals.

Management of child contacts of infectious adults:

High priority should be given to examining children contact to an infectious TB case. Screening include: A thorough history, Clinical examination, TT and Chest x-ray

Detection of TB cases among adult household contacts:

When adult household contacts come to the health facility, ask whether the individual has a cough and, if the cough has persisted for 2 weeks or more, the individual is a presumptive case for pulmonary TB. Collect three sputum samples for sputum examination.

Contact tracing:

It is important following notification of a case of TB that appropriate contact procedures be initiated with a view to identifying other cases of TB. Contacts should be screened by T.T. and chest films. Negative skin reactors should be retested at 6 weeks to exclude the possibility of recent primary infection. Skin test conversion merits chemoprophylaxis.

Preventive chemotherapy:

The aim of preventive treatment is to prevent progression of *M. tuberculosis* infection to disease. Preventive treatment for all individuals infected with *M. tuberculosis* is not a recommended TB control strategy

Target groups for preventive treatment

- **Infants of mothers with PTB:** The infant should receive 6 months INH treatment, followed by BCG immunization. An alternative policy is to give 3 months INH, then perform a TST. If negative, stop the INH and give BCG. If positive, continue another 3 months INH, then stop INH and give BCG.
- **Children under 5 years of age:** If without symptoms should be given 6 months INH preventive treatment. If with symptoms need investigation for TB. If investigations show TB, the child receives anti-TB treatment. If investigations do not show TB, the child should receive INH preventive treatment.

TB/HIV

TB is the leading cause of death among people living with HIV. Almost one in four deaths among people with HIV is due to TB. In 2010 350,000 people died of HIV-associated TB. It is also the most common presenting illness among people living with HIV, including those who are taking antiretroviral treatment.

- There were an estimated 1.1 million HIV positive new TB cases globally in 2010. Around 82% of patients live in sub-Saharan Africa.
- At least one-third of the 34 million people living with HIV worldwide is infected with TB. Persons co-infected with TB and HIV are 21-34 times more likely to develop active TB disease than persons without HIV.
- People living with HIV are facing emerging threats of drug-resistant TB. Multidrug-resistant TB or MDR-TB is resistance to first-line anti-TB drugs; extensively drug-resistant TB or XDR-TB is resistance to second-line anti-TB drugs. Worldwide, there were an estimated 650,000 MDR-TB cases in 2010.

The risk of developing tuberculosis (TB) is estimated to be between 20-37 times greater in people living with HIV than among those without HIV infection.

People living with HIV are more likely to present with extrapulmonary or sputum smear-negative TB, especially as immunosuppression advances. This can result in misdiagnosis or delays in diagnosis and, in turn, higher morbidity and mortality.

HIV testing and counseling for all patients known or suspected to have TB

WHO recommends HIV testing for patients of all ages who present with signs or symptoms that suggest tuberculosis. TB is often the first clinical indication that a person has underlying HIV infection, and TB services can be an extremely important entry point to HIV prevention and treatment. In addition, the HIV status of TB patients makes a difference to their TB treatment.

Detecting HIV infection in a TB patient is also critical for the TB patient's household members:

- HIV-positive TB patients may have household members who are also living with HIV. Testing and counseling should be recommended for family members of all people living with HIV.
- Household contacts of an infectious TB case are a high priority for TB screening, especially if they are living with HIV and those who are found to have active TB disease need prompt treatment.

- Among household contacts, people living with HIV (and children, regardless of their HIV status) who do not have active TB are candidates for isoniazid treatment to prevent the development of active TB.

In the case of patient-initiated HIV testing, informed consent, counseling and confidentiality are essential.

- As with conventional HIV assays, a reactive result from the first, highly sensitive, rapid assay requires confirmation by a second, more specific test, typically another rapid assay. If the second test yields non-reactive or indeterminate results, a third test may be performed; if the result is reactive, follow-up HIV testing should be performed on a specimen collected 4 weeks after the initial test.
- The follow-up testing would rule out possible seroconversion at the time of the initial test as the cause of discrepant testing results and would reveal most technical or clerical errors. The use of rapid assay should be undertaken only with functional quality assurance in place and conducted according to the country's nationally validated testing algorithm.
- Appropriate post-test counseling should be ensured, with a strong focus on HIV prevention; this will also help prevent the spread of TB.

The recommendations of TB/HIV co infection treatment:

- **The recommended treatment regimen is 2 HRZE/4HR**
- TB patients with known positive HIV status and all TB patients living in HIV-prevalent settings should receive daily TB treatment at least during the intensive phase
- For the continuation phase, the optimal dosing frequency is also daily for these patients

In terms of duration of therapy, some experts recommend prolonging TB treatment in persons living with HIV in certain circumstances.

A systematic review found lower relapse rates in people living with HIV treated with 8 or more months of rifampicin-containing regimens compared with the current recommendation of 6 months.

HIV-positive TB patients who have been previously treated for TB should receive the same retreatment regimens as HIV-negative TB patients.

Rifampicin induces the activity of hepatic enzymes, leading to sub-therapeutic concentrations of some antiretroviral drugs.

Co-trimoxazole preventive therapy

In all HIV-positive TB patients, co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment.

Co-trimoxazole preventive therapy substantially reduces mortality in HIV-positive TB patients. The exact mode of activity is not clear but co-trimoxazole is known to prevent *Pneumocystis jirovecii* and malaria and is likely to have an impact on a range of bacterial infections in HIV-positive TB patients.

A system for providing co-trimoxazole preventive therapy to all people living with HIV who have active TB should be established by TB and HIV programs. Continuation after TB treatment is completed should be considered in accordance with national guidelines.

Antiretroviral therapy

Antiretroviral therapy improves survival in HIV-positive patients. In addition, antiretroviral therapy reduces TB rates by up to 90% at an individual level, by 60% at a population level and it reduces TB recurrence rates by 50%. ART should be initiated for all people living with HIV with active TB disease irrespective of CD4 cell count.

TB treatment should be started first, followed by ART as soon as possible and within the first 8 weeks of starting TB treatment.

What ART regimens to start?

WHO recommends that the first-line ART regimen contain two nucleoside reverse transcriptase inhibitors (NRTIs) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI).

These are efficacious, relatively less expensive, have generic and FDC formulations, do not require a cold chain, and preserve a potent new class of agents (protease inhibitors) for second-line regimens. .

The preferred NRTI backbone is zidovudine (AZT) or tenofovir disoproxil fumarate (TDF), combined with either lamivudine (3TC) or emtricitabine (FTC). For the NNRTI, WHO recommends either efavirenz (EFV) or nevirapine (NVP).

Drug susceptibility testing

High mortality rates have been reported among people living with HIV who have drug resistant-TB, and rates can exceed 90% in patients co- infected with extensively drug-resistant TB (XDR-TB) and HIV.

Prompt initiation of appropriate TB treatment (and subsequent initiation of ART) can reduce mortality among people living with HIV who have drug-resistant TB.

DST should be done at the start of TB therapy in all HIV-positive TB patients, to avoid mortality due to unrecognized drug-resistant TB, and strongly encourages the use of rapid DST in sputum smear-positive persons living with HIV.

Patient monitoring during TB treatment

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

Drug Resistance TUBERCULOSIS (DR-TB)

Recent updates, May 2016

Recent updates of the WHO policy recommendations for the treatment of MDR-TB

1. Shorter MDR-TB regimen for adults & children under specific conditions

In patients with rifampicin-resistant or multidrug-resistant TB who have not been previously treated with second-line drugs and in whom resistance to Fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9-12 months may be used instead of a conventional regimen (conditional recommendation, very low certainty in the evidence).

Shorter regimen composition

It consists of an intensive phase of 4-6 months containing Km- Mfx - Pto- Cfz -Z-H (high-dose)-E then followed by a continuation phase of 5 months containing Mfx – Cfz - Z- E.

This can be summarized in the following formula:

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

Km=Kanamycin; Mfx=Moxifloxacin; PTO=Prothionamide; Cfz=Clofazimine; Z=Pyrazinamide; H high-dose = high-dose Isoniazid; E=Ethambutol

Selection of patients on the shorter MDR-TB regimen

Do not use the shorter regimen if any of the following criteria applies

1. Confirmed resistance or suspected ineffectiveness of a medicine in the shorter regimen except isoniazid resistance.
2. Exposure to more than one second line medicines in the shorter regimen for more than one month.
3. Intolerance of more than one medicine or risk of toxicity (e.g. drug-drug interaction)
4. Pregnancy
5. Extra-pulmonary Tuberculosis.
6. At least one medicine in the shorter MDR-TB regimen not available in the program.

In such a case, use an individualized conventional RR/MDR-TB regimen (usual treatment regimen).

If all are absent, the short regimen can be used.

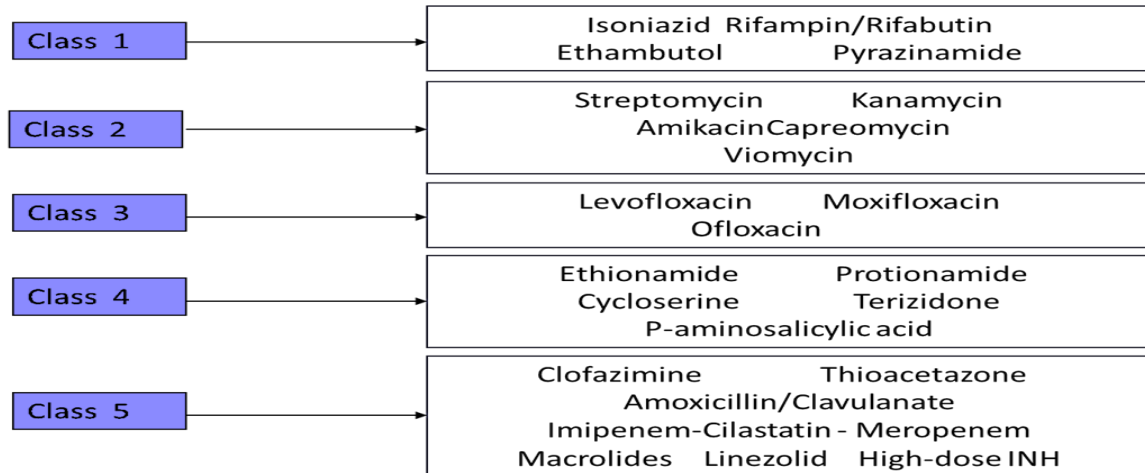
If a shorter regimen had been started then one of the following occurred:

- Failure of the regimen.
- Drug intolerance.
- Interruption more than two months.
- Emergence of any of the previously mentioned exclusion criteria.

Again, in such a case, use an individualized conventional RR/MDR-TB regimen.

2. **Medicines used for designing a conventional MDR-TB treatment regimens are now regrouped in a different way based upon current evidence on their effectiveness and safety.**

The old classification is shown below:



Regrouping of Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB¹

Group	Drugs Constituents	Abbreviations
Group A. Fluoroquinolones²	Levofloxacin, Moxifloxacin, Gatifloxacin	Lfx, Mfx, Gfx
Group B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin) ³	Am Cm Km (S)
Group C. Other core second-line agents²	Ethionamide / Protiomamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
Group D. Add-on agents (not part of the core DR-TB regimen)	D1 Pyrazinamide Ethambutol High-dose isoniazid	Z E Hh
	D2 Bedaquiline Delamanid	Bdq Dlm
	D3 p-aminosalicylic acid Imipenem-cilastatin ⁴ Meropenem ⁴ Amoxicillin-clavulanate ⁴ (Thioacetazone) ⁵	PAS Ipm Mpm Amx-Clv (T)

¹This regrouping is intended to guide the design of conventional regimens;

For shorter regimens lasting 9-12 months the composition is usually standardized.

² *Medicines in Groups A and C are shown by decreasing order of usual preference for use*

³ *Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB)*

⁴ *Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin*

⁵ *HIV-status must be tested and confirmed to be negative before Thioacetazone is started*

According to the new regrouping of the anti-TB medicines, designing a treatment regimen for an RR/MDR-TB patient goes through the following Steps:

1. Determine whether there are special circumstances that affect the regimen

These may be

- Additional resistance to fluoroquinolones, second-line injectable agents and extensive drug resistance (XDR-TB)
- Involvement of the CNS
- Patient is living with HIV
- Substance dependence
- Psychiatric disorder
- Liver disorder
- Seizure disorder
- Renal insufficiency
- Diabetes mellitus
- Childhood TB
- Breastfeeding
- Pregnant women
- Use of oral contraception
- Extra-pulmonary disease

2. Review the patient's DST results

- Make sure that the DST has been done in a quality assured laboratory.
- If the DST results show resistance to a certain medicine, this medicine should not be included.
- Only agents documented to have certain or almost certain effectiveness should be used.
- If the evidence about an agent's effectiveness is unclear, the agent may be included in the regimen but it should not be counted as one of the effective medicines.

3. Confirm the patient's history of anti-TB treatment

- Every effort should be made to supplement what the patient remembers about previous treatments with objective records.
- A detailed clinical history may indicate which medicines are likely to be ineffective.

- The probability of acquiring resistance to a medicine increases with the length of time that it has been used.

If a patient was treated with a medicine for longer than 1 month and persistently had positive smears or cultures, the strain should be considered as “probably resistant” to that medicine.

4. In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C.

5. Pyrazinamide is added routinely unless there is:

- Confirmed resistance from reliable DST, or
- Well-founded reasons to believe that the strain is resistant, or
- Risk of significant toxicity.
- If pyrazinamide is compromised or cannot be used, the regimen may be strengthened with an additional agent from group C or D (preferably D2, or if not possible, from D3).

6. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.

7. In patients with rifampicin-resistant or multidrug-resistant TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or Ethambutol (if strain is susceptible).

8. It is recommended that any patient – child or adult - with rifampicin-resistant TB in whom isoniazid resistance is absent or unknown be treated with a recommended MDR-TB regimen, either a shorter MDR-TB regimen, or if this cannot be used, a conventional MDR-TB regimen to which isoniazid is added.

9. Calculate doses

- Once the regimen has been designed, calculate the correct doses based on the patient’s weight and age
- You may need to adjust the doses if other circumstances are present, such as renal insufficiency

Other important points to remember

1. Early detection of MDR-TB and prompt initiation of treatment are important factors in achieving successful outcomes.
2. Regimens should be based on the national standardized regimen or pattern of drug susceptibility, and the medicines previously taken by the patient, particularly any first-line anti-TB medicines.
3. The intensive phase is generally recommended for **8 months** (subject to response to treatment), **and for at least 4 months past culture conversion**.
4. The total length of treatment is expected to be **continued for at least 12 months past the point at which culture converts** to negative and **not less than 20 months in total**.

5. Injectable anti-TB drugs should be given once daily.
6. If adverse effects are problematic in a patient, the injectable agent may be given **three times a week after culture conversion**.
7. Oral drugs are to be given **6–7 days a week under DOT**.
8. When possible, **pyrazinamide, Ethambutol and the fluoroquinolones should be given once per day**. This dosing may be more efficacious, and it facilitates DOT.
6. However, for children, the recommendation is to give fluoroquinolones twice a day.
7. In children with non-severe disease Group B medicines may be excluded. In the case of children with additional resistance to Fluoroquinolones, group B medication are best retained.
8. Ethionamide/Prothionamide, Cycloserine and para-aminosalicylic acid are preferably given in one dose. However, if circumstances so dictate, they may be given in divided doses as long as each dose is directly observed.
9. Pyrazinamide may be used for the **entire treatment** if it is judged to be effective. Many MDR-TB patients have chronically inflamed lungs that theoretically produce the acidic environment in which pyrazinamide is active.
10. The **dose should be determined by the patient's weight**. A suggested weight-based dosing scheme

Management of XDR-TB

1. Use pyrazinamide and any other first line agents that may be effective.
2. Use an injectable agent to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment).
3. If strain is resistant to all injectable agents consider designing the regimen with an injectable agent that the patient has never used before or **consider designing the regimen without an injectable agent**. This advice is made because while the accuracy and reproducibility of DST to injectables are good, *there is little data on clinical efficacy* of injectable resistant in DST. Options with XDR-TB are very limited and some strains may be affected in vivo by an injectable agent even though they are testing resistant in vitro.
5. If toxicity is a limiting factor for the use of the injectable agent, and one of the injectable agents is considered effective, **consider using inhaled version via a nebulizer**. **No experience** of the use of nebulization of injectable agents for TB has been published. Kanamycin and Amikacin have been used via nebulization for cystic fibrosis. The effectiveness and safety of delivering injectable **drugs via nebulization in TB is unknown**. Do not count nebulized aminoglycosides as one of the four effective second-line anti-TB drugs needed to form an effective regimen. **Renal toxicity and ototoxicity can still occur with nebulization**.
6. Use a higher-generation Fluoroquinolone such as Moxifloxacin or Gatifloxacin.
7. Use all **Group C** agents that have not been used extensively in a previous regimen or any that are likely to be effective.

8. Add two or more **Group D2** and **D3** drugs (consider adding *bedaquiline or delamanid*)
9. Consider high-dose isoniazid treatment if susceptibility is confirmed
10. Consider adjuvant surgery if there is localized disease.
11. Ensure rigorous respiratory infection control measures at the site where the patient is being treated.
12. Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities coexist, or a shelter if the social condition of the patient prevents proper home care.
13. Manage HIV co-infection.
14. Provide comprehensive monitoring and full social support to enable adherence to treatment.
15. Ensure that all patients have full access to palliative and end-of-life care services, with a patient-centered approach to relief the suffering of the disease and its treatment.

3. New RR/MDR-TB medicines

3.1. Bedaquiline

DRUG CLASS: DIARYLQUINOLINE

- Bactericidal: Inhibits ATP synthesis; novel method of action.
- The drug has a 5.5-month half-life.
- CYP3A4 is the major CYP isoenzyme involved in the metabolism of bedaquiline. The metabolism leads to the formation of N- mono-desmethyl metabolite.
- There is a reported cross-resistance of bedaquiline with Clofazimine (Cfz).
- Linear pharmacokinetics and better absorption when the drug is taken **With** food versus when taken fasting.
- There is no experience with use of bedaquiline in children, pregnant women, extra-pulmonary disease, and the elderly, and there is minimal information on its use in HIV-infected patients, whether on antiretroviral treatment (ART) or not.
- Bedaquiline can also cause hepatotoxicity.
- When bedaquiline is added to a regimen, it is only given for the **first 24 weeks of treatment**.
- Drug susceptibility testing (**DST**) **for bedaquiline has not yet been standardized.**

Absolute contraindications of Bedaquiline:

1. Patient refuses to consent
2. Hypersensitivity.
3. High risk for cardiac complications. Patient who has a QT interval greater than 500 ms, history of cardiac ventricular arrhythmias or severe coronary artery disease.

Relative contraindications

1. Children or persons under 18 years of age: the safety and dosing of bedaquiline has not been established in children and its use in this group should be avoided until further data are available.
2. Pregnancy: reproduction studies performed in rats and rabbits have revealed no evidence of harm to the fetus due to bedaquiline.
3. Nursing mothers: it is not known if bedaquiline and its metabolites are passed into human breast milk. Because of the potential for adverse reactions in nursing infants, a decision should be made on whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Cautions:

1. Geriatric use: Clinical studies of bedaquiline did not include sufficient numbers of patients aged 65 and over.
2. Hepatic impairment: no dose adjustment is necessary for bedaquiline in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment and should be used with caution in these patients and only when the benefits outweigh the risks.
3. Renal impairment: no dose adjustment is required in patients with mild or moderate renal impairment. Bedaquiline has not been studied in patients with severe renal impairment or end stage renal disease requiring hemodialysis or peritoneal dialysis and should be used with caution in these patients and only when the benefits outweigh the risks.
4. Serum potassium outside the normal range: because QT prolongation is associated with hypokalemia and arrhythmias are associated with hypokalemia or hyperkalemia, potassium should be corrected before starting bedaquiline and carefully monitored.

In addition, the following should be ensured

1. The drugs included in the regimen that are known to prolong the QTc (QT interval corrected to heart rate) interval should be minimized.
2. Clofazimine and Moxifloxacin should be avoided if possible, due to potential overlapping cardiotoxicity, unless an adequate MDR-TB treatment regimen cannot be constructed without them.
3. Aminotransferases are less than thrice the upper limit of normal and total bilirubin is less than twice the upper limit of normal.
4. The patient's serum potassium, calcium and magnesium have been obtained at baseline and levels are within normal limits or the patient has received appropriate electrolyte repletion
5. Bedaquiline should be reserved for the treatment of MDR-TB when a WHO standard recommended regimen cannot be otherwise provided; it cannot be utilized to treat drug-susceptible TB or drug-resistant TB cases in which another satisfactory regimen is available.

Dose of bedaquiline

Bedaquiline comes in 100 mg tablets.

Week 1–2: Bedaquiline 400 mg (4 tablets of 100 mg) daily (seven days per week).

Week 3–24: Bedaquiline 200 mg (2 tablets of 100 mg), three times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.

Week 25 (start of month 7) to end of treatment: Continue other second-line anti-TB drugs only

Safety profile of Bedaquiline in the treatment of MDR-TB

Non-clinical safety

Toxicology studies after repeated dosing of bedaquiline have been conducted with durations of up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs.

Key observations were:

1. **Cardiac safety**: (dog study, 6 months): QT prolongation of 12%-16% at 2 months of exposure to 40 mg/kg/day, which was above the maximum tolerated dose.

No prolongation after dose reduction to 20 mg/kg/day, and also no prolongation at 140 mg/kg twice weekly for 6 months.

Cardiac troponin/CPK was increased at all dose strengths.

No ECG changes or cardiac lesions were seen with lower doses (6 month dog at 10 mg/kg/day, and 9 month dog at 18 mg/kg/day).

2. **Hepatic safety**: Centri-lobular hypertrophy was seen in mice, rats, dogs. Severity was dose-related, and effects partially reversible. Liver function test (LFT) changes were also observed, associated with transaminase increases but no bilirubin changes or cholestasis

3. **Phospholipidosis**: Observed in all preclinical species and consisted of the accumulation of pigment laden and/or foamy macrophages or (micro)vacuolization in various tissues, mostly in lymphoid tissue (lymph nodes and spleen), lungs, liver, stomach, skeletal muscle, pancreas and/or uterus.

Phospholipidosis was seen in rats (minimal) at exposures similar to the clinical exposure for bedaquiline and M2 (the main metabolite of Bedaquiline).

In dogs, phospholipidosis was seen at 3- and 6 fold higher exposures compared to those in humans for bedaquiline and M2, respectively.

Human safety experience with Bedaquiline

Adverse drug reactions

1. Common:

- Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite),
- joint pain (arthralgia),
- Headache.
- Hemoptysis and chest pain were also more frequently reported in the group receiving bedaquiline than in the placebo treatment group).

2. Less common:

- QT prolongation,
- Hyperuricemia,
- Phospholipidosis (the accumulation of phospholipids in the body's tissues),
- Elevated aminotransferases.
- Possibly an increased risk of pancreatitis.

Drug interactions

- Bedaquiline is metabolized by CYP3A4. Rifampicin (a CYP3A4 inducer) reduces bedaquiline in blood by half.
- Efavirenz² based on a single dose study appears to reduce the amount of bedaquiline though inducing CYP3A4.
- CYP3A4 inhibitors (e.g. azole anti-fungal drugs, some macrolides, protease inhibitors, and many others) can raise the level of bedaquiline but can be considered for use if the benefits outweigh the risk.
- Avoid use with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. Clofazimine, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); any syncopal event (fainting) should prompt an immediate medical evaluation and ECG.

Monitoring

- An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12 and 24 weeks after starting treatment.
- ECG should be more frequently if heart conditions, hypothyroidism or electrolyte disturbances are present.
- Liver function tests should be done monthly.

Patient instructions and alerting symptoms

- The patient should be informed that bedaquiline is a new anti-TB drug and there could be unknown risks and side-effects.
- The following serious side-effects can occur with bedaquiline: death, heart rhythm abnormalities, and/or hepatitis.
- This medicine should be taken with food.
- Avoid alcohol.

The patient should be informed that in one clinical trial, more deaths were seen in people who were treated with bedaquiline compared to people who did not receive.

Instruct patients to inform their health care provider right away if any of the following occurs:

- Abdominal pain
- Yellowing of your skin or eyes
- Palpitations

²Non-nucleoside reverse transcriptase inhibitor (NNRTI used as part of highly active antiretroviral therapy (HAART) for the treatment of a human immunodeficiency virus (HIV)

- Chest pain
- Fainting and near fainting events

3.2. Delamanid

Drug class: Nitrodihydro-imidazo-oxazole.

Mechanism of action and metabolism: Inhibition of the synthesis of the mycobacterial cell wall components (methoxy-mycolic and keto-mycolic acid).

- The complete metabolic profile of delamanid in man *has not yet been fully elucidated*. Therefore the potential for drug-drug interactions of clinical significance to occur with delamanid and the possible consequences, including the total effect on the QTc (QT interval corrected to heart rate) interval, cannot be predicted with confidence.
- QTc prolongation is very closely correlated with the major delamanid metabolite DM-6705.
- Delamanid disappears from plasma with a t_{1/2} of 30-38 hours.
- Delamanid is not excreted in urine.

Dose

- Adults: 100 mg twice daily for 24 weeks. It is recommended to administer with water and to be taken with, or just after a meal.
- Children: Not yet determined

Preparation and administration.

- 50 mg film-coated tablets.
- Oral absorption is increased with a standard meal.

Special circumstances

Pregnancy/breastfeeding:

There are very limited data from the use of delamanid in pregnant women. Studies in animals have shown reproductive toxicity. Available pharmacokinetic data in animals have shown excretion of delamanid and/or its metabolites in milk.

Renal disease:

No dosage adjustment is required in patients with mild to moderate renal impairment. Dosing not established in severe renal impairment, use with caution and only when the benefits outweigh the risks.

Hepatic disease:

No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.

Adverse reactions

Common: The most frequently observed adverse drug reactions in patients treated with delamanid (i.e. incidence > 10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%).

Less common: QT prolongation.

Contraindications/caution

Do not use or discontinue delamanid in case of

- Clinically significant ventricular arrhythmia.
- A QTcF interval of > 500 ms (confirmed by repeat ECG).
- Severe liver disease.
- Serum Albumin less than 2.8.
- Abnormal electrolytes.

Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):

- Use with other QT prolonging drugs.
- A history of torsade de pointes.
- A history of congenital long QT syndrome.
- A history of hypothyroidism and bradyarrhythmias.
- A history of uncompensated heart failure.
- Serum calcium, magnesium, or potassium levels below the lower limits of normal.
- Use with caution in patients sensitive to lactose.

Drug Interactions

- Avoid concomitant administration of strong CYP3A inducers (e.g. rifampicin, carbamazepine). No clinically relevant reduction in delamanid exposure was observed with weak inducers.
- If co-administration of delamanid with any strong inhibitor of CYP3A (e.g. ritonavir, ketokonazole) is necessary, consider more very frequent monitoring of ECGs, throughout the delamanid treatment.
- Delamanid does not affect plasma exposure of co-administered anti-TB drugs, Rifater (isoniazid/rifampicin/pyrazinamide) + Ethambutol in a clinically relevant manner (25% increase in Ethambutol).
- Delamanid does not affect plasma exposure of ARV drugs tenofovir, Kaletra (lopinavir/ritonavir), or efavirenz.
- Antiretroviral drugs, tenofovir, efavirenz, and Kaletra (lopinavir/ritonavir), do not affect delamanid exposure in a clinically relevant manner (24% increase).
- Avoid using with other drugs that prolong the QT interval as additive QT prolongation may occur (e.g. Clofazimine, fluoroquinolones, bedaquiline, azole anti-fungal drugs, ondansetron, and several others).

Monitoring

An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12, and 24 weeks after starting treatment with delamanid.

Monitoring ECGs should be done weekly if taking other QT prolonging drugs (i.e. moxifloxacin, Clofazimine, etc.).

Patient instructions and alerting symptoms

- The patient should be informed that delamanid is a new anti-TB drug and there could be unknown risks and side-effects.
- One serious side-effect associated with delamanid is it can change the electrical conduction of the heart, which could put a patient at risk for arrhythmias.
- This medicine should be taken with food.
- Avoid alcohol.
- Instruct patient to inform health care provider right away if any of the following occurs:
 - Palpitations
 - Chest pain
 - Fainting and near fainting events

4. Other medicines to consider

4.1. Clofazimine

Drug class: Iminophenazine

Mechanism of action, and metabolism: In vitro activity against *M. tuberculosis* without much in vivo data. Generally reserved for cases with few other options. Tissue half-life estimated to be around 70 days.

Dose Adults: A regimen of 200 mg daily for 2 months, followed by 100 mg daily.

Dose Children: Limited data, but doses of 1 mg/kg/day have been given.

Preparation and administration: 50 and 100 mg capsules. Only oral formulae are available.

Improved tolerance and absorption with food.

Storage: Room temperature (15–25 °C).

Oral absorption: 70% absorption after an oral dose.

CSF penetration: Limited data are available regarding CNS penetration.

Special circumstances:

Use in pregnancy/breastfeeding: Not recommended due to limited data (some reports of normal outcomes, some reports of neonatal deaths).

Avoided with breastfeeding: due to pigmentation of the infant.

Use in renal disease: No dosage adjustment required.

Use in hepatic disease: Partially metabolized by the liver; use caution and/or adjust the dose for severe hepatic insufficiency.

Adverse reactions

Common:

- Orange/red discoloration of skin, conjunctiva, cornea and body fluids.
- Dry skin, pruritus, rash, ichthyosis (dry scaly skin).
- Gastrointestinal intolerance.
- Photosensitivity.

Less common:

- retinopathy,
- severe abdominal symptoms,
- bleeding and bowel obstruction;
- QT prolongation.

Contraindications: Allergy to Clofazimine.

Drug interactions:

Using with drugs that prolong the QT interval may cause additive QT prolongation (e.g. bedaquiline, fluoroquinolones, delamanid, azole anti-fungal drugs, and many others); further research is needed to understand potential interactions with antiretroviral.

Monitoring: Symptomatic monitoring.

Patient instructions and alerting symptoms

- Take with food to avoid stomach upset and improve absorption.
- This medicine may discolor your skin and body secretions are orange, red or brownish-black. This should go away after stopping the medicine, but may take a long time.
- Avoid the sun and use strong sunscreens.

Instruct patients to inform their health care provider right away if any of the following occurs:

- Bloody or black stools or diarrhea
- Yellowing of skin or eyes
- Severe nausea, vomiting, abdominal pain, cramps or burning
- Depression or thoughts of hurting oneself.

4.2. Imipenem (Imp)/Cilastatin (Cln)

Drug class: Beta-lactam – Carbapenem (it is related to the penicillin/Cephalosporin family of antibiotics but is classified as belonging to the Carbapenem class).

Activity, mechanism of action and metabolism: In vitro activity – very limited clinical experience. Given that imipenem is rapidly degraded by renal proximal tubule dipeptidases, it is used in combination with the dipeptidase inhibitor, Cilastatin. (Conversely, meropenem a similar drug as Imipenem is stable to renal dipeptidases and requires no Cilastatin).

Cilastatin is partially metabolized renally.

Dose

Adults: 1000 mg IV every 12 hours. (Dosed on the Imipenem component). *Should be given with clavulanate* (available as amoxicillin/clavulanate) 125 mg every 8–12 hours.

Children: Meropenem preferred.

Route of administration: IV or IM (total recommended IM dose is not more than 1.5 gram/day and therefore not very practical for treatment of drug-resistant TB). No oral absorption.

Preparation:

Lyophilized³ powder 1:1 ratio of Imipenem and Cilastatin. Vials available as 250 mg, 500 mg, 750 mg, or 1 gram and contain equal amounts of both drugs. (i.e. a “500 mg vial” contains 500 mg of Imipenem and 500 mg Cilastatin).

Storage:

Powder should be kept at room temperature (15–25 °C); suspended product should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.

CSF penetration:

Good CSF penetration, but children with meningitis treated with Imipenem had high rates of seizures (Meropenem preferred for meningitis and for children).

Special circumstances:

Use in pregnancy/breastfeeding: Little information is known

Use in renal disease: Adjustment in dose based on severity of renal failure – for example, 750 mg every 12 hours for creatinine clearance 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min. Dose after dialysis.

Use in hepatic disease: Elevated liver function tests have been noted in up to 6% of patients, but no definite liver damage has been documented.

Adverse reactions:

1. Common: Diarrhea, nausea, or vomiting.
2. Less common: Seizure (noted with CNS infection), palpitations, pseudomembranous colitis.

Contraindications:

- Carbapenem intolerance;
- Meningitis (use Meropenem rather than Imipenem).

Monitoring: Symptomatic monitoring.

Patient instructions:

- Make sure your health care provider knows if you are also taking Ganciclovir or have allergy to Penicillins or Cephalosporins.
- Instruct patients to inform their health care provider right away if any of the following occurs:

³Freeze-drying works by freezing the material and then reducing the surrounding pressure to allow the frozen water in the material to sublime directly from the solid phase to the gas phase.

- Fast or irregular heartbeat
- Seizures
- Severe diarrhea (watery or bloody)
- Skin rash, hives, or itching
- Swelling of the face, throat or lips
- Wheezing or trouble breathing.

4.3. Meropenem (Mpm)

DRUG CLASS: Beta-lactam – Carbapenem (It is related to the penicillin/Cephalosporin family of antibiotics but is classified as belonging to the Carbapenem class).

Activity, mechanism of action and metabolism: In vitro activity – very limited clinical experience (Meropenem is stable to renal di-peptidases and requires no Cilastatin).

Dose

Adults: No oral absorption. Recent case–controlled study used 1000 mg IV every 8 hours.

Must be given with clavulanate (available as amoxicillin/clavulanate), 125 mg every 8–12 hours.

Children: Not established for TB however for other bacterial infections in children: 20 mg/kg/dose and 40 mg/kg/dose for meningitis or particularly severe infections. Given IV every 8 hours up to 2 g per dose.

Renal failure/dialysis: Adjustment required – 750 mg every 12 hours for creatinine clearance of 20–40 ml/min; 500 mg every 12 hours for creatinine clearance <20 ml/min.

Route of administration: IV only; No oral absorption.

Preparation: Crystalline powder. Product is available in 500 mg, or 1 g vials.

Storage: Powder should be kept at room temperature (15–25 °C); **suspended product:** should be kept no more than 4 hours at room temperature or no more than 24 hours refrigerated.

CSF penetration: Adequate CSF penetration.

Special circumstances

Use during pregnancy/breastfeeding: There is little information regarding use during pregnancy; unknown safety during breastfeeding.

Use in renal disease: Dose adjustment required; dose after dialysis.

Use in hepatic disease: Liver disease does not alter the pharmacodynamics of Meropenem.

Adjustment in dose and interval are based on severity of renal failure and body weight – e.g. 750 mg every 12 hours for creatinine clearance of 20–40 ml/min, 500 mg every 12 hours for creatinine clearance <20 ml/min.

Adverse reactions:

- Diarrhea, nausea or vomiting.
- Seizure (noted with CNS infection), but rare compared to Imipenem.
- Rarely elevated LFTs, hematologic toxicity, hypersensitivity

Contraindications: Carbapenem intolerance.

Monitoring: Symptomatic monitoring.

Patient instructions and alerting symptoms

- Make sure your doctor knows if you are also taking valproic (Depakine) acid or have allergy to penicillins or Cephalosporins.
- Instruct patients to inform their health care provider right away if any of the following occurs:
 - Severe diarrhea (watery or bloody)
 - Skin rash, hives or itching
 - Swelling in the face, throat or lips
 - Wheezing or trouble breathing.

4.4. Linezolid (Lzd)

Drug class: Oxazolidinones.

Activity against TB, mechanism of action and metabolism: Has in vitro bactericidal activity; inhibits protein synthesis.

Linezolid (Lzd)

Dose

Adults: 600 mg, once daily. (Reduce to 400–300 mg/day if serious adverse effects develop).

Children: 10 mg/kg three times daily in children up to 11 years of age and 10 mg/kg (maximum dose 600 mg) twice daily in older children. 8 10 mg/kg/dose every 12 hours.

Vitamin B6: All patients should receive vitamin B6 while receiving linezolid.

Preparation:

Coated tablets: 400 and 600 mg;

Intravenous solution: 2 mg/ml: 100, 200 or 300 mg bags. Intravenous doses are administered over 30–120 minutes.

Oral powder for suspension: 100 mg/5 ml, 240 ml bottle.

Storage Store: at room temperature (15–25 °C).

Reconstituted oral suspension may be stored at room temperature for 21 days.

Parenteral preparation should be stored at room temperature (protect from light and do not freeze).

Oral absorption: Nearly complete oral absorption.

CSF penetration: CSF concentrations are about 1/3 of those in serum in animal models, and linezolid has been used to treat meningitis in humans.

Use in pregnancy/breastfeeding: Not recommended during pregnancy or breastfeeding due to limited data.

Use in renal disease: No dose adjustment is recommended, but metabolites may accumulate.

Use in hepatic disease: Rarely associated with increased transaminases.

Adverse reactions:

- Myelo-suppression (decreased level of platelets, decreased level of white blood cells, and/or anemia).
- Diarrhea and nausea.
- Optic and peripheral neuropathy may be irreversible and linezolid should be stopped if these develop; weigh against the risk of permanent blindness or disabling permanent neuropathy.
- Lactic acidosis – patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving linezolid should receive immediate medical evaluation, including a lactic acid blood test.

Contraindications: Hypersensitivity to Oxazolidinones. Symptoms of neuropathy (pain, numbness, tingling or weakness in the extremities).

Drug Interactions: Avoid use with patients taking serotonergic agents, such as monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (e.g. fluoxetine, paroxetine), lithium, tricyclic antidepressants, etc. as it may cause serious CNS reactions such as serotonin syndrome.

Monitoring:

- Monitor for peripheral neuropathy and optic neuritis (visual eye tests every two months or if symptoms develop, clinical examination for peripheral neuropathy monthly or if symptoms develop).
- Monitor a complete blood count weekly during the initial period, then monthly, and then as needed based on symptoms;
- There is little clinical experience with prolonged use.

Patient instructions and alerting symptoms

- This medicine may be taken with or without food.
- Take it with food if it irritates the stomach.
- Avoid food and drinks that contain Tyramine: aged cheeses, dried meats, sauerkraut, soy sauce, beers and red wines.
- Make sure your doctor knows if you are taking medicines for colds, congestion or depression.

Instruct patients to inform their health care provider right away if any of the following occurs:

- Pain, numbness, tingling or weakness in the extremities
- Black, tarry stools or severe diarrhea
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Headache, nausea or vomiting.

International Standards for Tuberculosis Care

(ISTC), 3RD EDITION, 2014

Purpose:

The purpose of the *ISTC* is to describe a widely accepted level of care that all practitioners, public and private, should seek to achieve in managing patients who have, are suspected of having, or are at increased risk of developing TB.

They are intended to promote the effective engagement of all providers in delivering high quality care for patients of all ages, including those with sputum smear-positive and sputum smear-negative pulmonary TB, extra-pulmonary TB, DR-TB and TB/HIV and other co-morbidities.

Thus, all providers who undertake evaluation and treatment of patients with tuberculosis must recognize that, not only are they delivering care to an individual, they are assuming an important public health function that entails a high level of responsibility to the community and to the individual patient.

Standards for Diagnosis

Standard 1

To ensure early diagnosis, providers must be aware of individual and group risk factors for tuberculosis and perform prompt clinical evaluations and appropriate diagnostic testing for persons with symptoms and findings consistent with tuberculosis.

Standard 2

All patients, including children, with unexplained cough lasting two or more weeks or with unexplained findings suggestive of tuberculosis on chest radiographs should be evaluated for tuberculosis.

Standard 3

All patients, including children, who are suspected of having pulmonary TB and are capable of producing sputum should have at least 2 sputum specimens submitted for smear microscopy or a single sputum specimen for Xpert MTB/RIF testing in a quality-assured laboratory.

Patients at risk for drug resistance, who has HIV risks, or who are seriously ill, should have Xpert MTB/RIF performed as the initial diagnostic test.

Blood-based serologic tests and interferon-gamma release assays should not be used for diagnosis of active tuberculosis.

Standard 4

For all patients, including children, suspected of having extra pulmonary TB, appropriate specimens from the suspected sites of involvement should be obtained for microbiological and histological examination.

An Xpert MTB/RIF test is recommended as the preferred initial microbiological test for suspected TB meningitis because of the need for a rapid diagnosis.

Standard 5

In patients suspected of having pulmonary TB whose sputum smears are negative, Xpert MTB/RIF and/or sputum cultures should be performed. Among smear- and Xpert MTB/RIF negative persons with clinical evidence strongly suggestive of TB, anti-TB treatment should be initiated after collection of specimens for culture examination.

Standard 6

For all children suspected of having intrathoracic (i.e., pulmonary, pleural, and mediastinal or hilar lymph node) TB , bacteriological confirmation should be sought through examination of respiratory secretions (expectorated sputum, induced sputum, gastric lavage) for smear microscopy, an Xpert MTB/RIF test, and/or culture.

Standards for Treatment

Standard 7 (practitioner responsibility)

- Any practitioner treating a patient for tuberculosis is assuming an important public health responsibility to prevent ongoing transmission of the infection and the development of drug resistance.
- To fulfill this responsibility the practitioner must not only prescribe an appropriate regimen, but also utilize local public health services and other agencies, when necessary, to assess the adherence of the patient and to address poor adherence when it occurs.

Standard 8 (TB Treatment)

- All patients (including those with HIV infection) who have not been treated previously should receive an internationally accepted first-line treatment regimen using drugs of known bioavailability.
- The initial phase should consist of two months of isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA), and Ethambutol (EMB).

- The continuation phase should consist of isoniazid and rifampicin given for four months.
- The doses of anti-tuberculosis drugs used should conform to international recommendations.
- Fixed dose combinations (FDCs) of two (isoniazid and rifampicin), three (isoniazid, rifampicin, and pyrazinamide) and four (isoniazid, rifampicin, pyrazinamide, and Ethambutol) drugs are highly recommended.

Standard 9 (Treatment adherence)

- To assess and foster adherence, a patient-centered approach to administration of drug treatment, based on the patient's needs and mutual respect between the patient and the provider, should be developed for all patients.
- Supervision and support should be individualized and should draw on the full range of recommended interventions and available support services, including patient counseling and education.
- A central element of the patient centered strategy is the use of measures to assess and promote adherence to the treatment regimen and to address poor adherence when it occurs.
- These measures should be tailored to the individual patient's circumstances and be mutually acceptable to the patient and the provider.
- Such measures may include direct observation of medication ingestion (directly observed treatment or DOT) and identification and training of a treatment supporter (for tuberculosis and, if appropriate, for HIV) who is acceptable and accountable to the patient and to the health system.
- Appropriate incentives and enablers, including financial support, may also serve to enhance treatment adherence.

Standard 10 (Response to therapy)

Response to treatment in patients with pulmonary TB (including those with TB diagnosed by a rapid molecular test) should be monitored by follow up sputum smear microscopy at the time of completion of the initial phase of treatment (two months). If the sputum smear is positive at completion of the initial phase, sputum microscopy should be performed again at 3 months and, if positive, rapid molecular drug sensitivity testing (line probe assays or Xpert MTB/RIF) or culture with drug susceptibility testing should be performed. In patients with extra pulmonary TB and in children, the response to treatment is best assessed clinically.

Standard 11 (DR TB)

An assessment of the likelihood of drug resistance, based on history of prior treatment, exposure to a possible source case having drug-resistant organisms, and the community prevalence of drug resistance (if known), should be undertaken for all patients.

Drug susceptibility testing should be performed at the start of therapy for all patients at a risk of drug resistance.

Patients who remain sputum smear-positive at completion of 3 months of treatment, patients in whom treatment has failed, and patients who have been lost to follow up or relapsed following one or more courses of treatment should always be assessed for drug resistance.

Standard 11 (DR TB)

For patients in whom drug resistance is considered to be likely an Xpert MTB/RIF test should be the initial diagnostic test.

If rifampicin resistance is detected, culture and testing for susceptibility to isoniazid, Fluoroquinolone, and second-line injectable drugs should be performed promptly.

Patient counseling and education, as well as treatment with an empirical second-line regimen, should begin immediately to minimize the potential for transmission.

Standard 12 (treatment of DR TB)

Patients with or highly likely to have TB caused by drug-resistant (especially MDR/XDR) organisms should be treated with specialized regimens containing quality-assured second-line anti - TB.

The doses of anti - TB drugs should conform to WHO recommendations.

The regimen chosen may be standardized or based on presumed or confirmed drug susceptibility patterns.

At least five drugs, pyrazinamide and four drugs to which the organisms are known or presumed to be susceptible, including an injectable agent, should be used in a 6–8 month intensive phase, and at least 3 drugs to which the organisms are known or presumed to be susceptible, should be used in the continuation phase.

Treatment should be given for at least 18–24 months beyond culture conversion.

Patient-centered measures, including observation of treatment, are required to ensure adherence.

Consultation with a specialist experienced in treatment of patients with MDR/XDR tuberculosis should be obtained.

Standard 13 (written record)

A written record of all medications given, bacteriologic response, and adverse reactions should be maintained for all patients.

Standards for Addressing HIV Infection and other Co-morbid Conditions

Standard 14 (TB/HIV)

- HIV testing and counseling should be recommended to all patients with, or suspected of having, tuberculosis.
- Testing is of special importance as part of routine management of
 - all patients in areas with a high prevalence of HIV infection in the general population,
 - In patients with symptoms and/or signs of HIV-related conditions, and in patients having a history suggestive of high risk of HIV exposure.
- Because of the close relationship of tuberculosis and HIV infection, in areas of high HIV prevalence integrated approaches to prevention and treatment of both infections are recommended.

Standard 15 (TB/HIV)

- All patients with tuberculosis and HIV infection should be evaluated to determine if antiretroviral therapy is indicated during the course of treatment for tuberculosis.
- Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment.
- However, initiation of treatment for tuberculosis should not be delayed.
- Patients with tuberculosis and HIV infection should also receive cotrimoxazole as prophylaxis for other infections.

Standard 16 (TB/HIV)

Persons with HIV infection who, after careful evaluation, do not have active tuberculosis should be treated for presumed latent tuberculosis infection with isoniazid for 6-9 months.

Standard 17 (co-morbid conditions)

- All providers should conduct a thorough assessment for co-morbid conditions that could affect tuberculosis treatment response or outcome.
- At the time the treatment plan is developed, the provider should identify additional services that would support an optimal outcome for each patient and incorporate these services into an individualized plan of care.
- This plan should include assessment of and referrals for treatment of other illnesses with particular attention to those known to affect treatment outcome, for instance care for diabetes mellitus, drug and alcohol treatment programs, tobacco smoking cessation programs, and other psychosocial support services, or to such services as antenatal or well-baby care.

Standards for Public Health

Standard 18 (contact management)

- All providers of care for patients with tuberculosis should ensure that persons who are in close contact with patients who have infectious tuberculosis are evaluated and managed in line with international recommendations.
- The determination of priorities for contact investigation is based on the likelihood that a contact:
 1. has undiagnosed tuberculosis;
 2. is at high risk of developing tuberculosis if infected;
 3. is at risk of having severe tuberculosis if the disease develops; and
 4. is at high risk of having been infected by the index case. The highest priority contacts for evaluation are:
 - Persons with symptoms suggestive of tuberculosis
 - Children aged <5 years
 - Contacts with known or suspected immuno-compromise, particularly
 - HIV infection
 - Contacts of patients with MDR/XDR tuberculosis
 - Other close contacts are a lower priority group.

Standard 19 (contact management)

Children <5 years of age and persons of any age with HIV infection who are close contacts of an infectious index patient and who, after careful evaluation, do not have active tuberculosis, should be treated for presumed latent tuberculosis infection with isoniazid.

Standard 20 (infection control plan)

Each healthcare facility caring for patients who have, or are suspected of having, infectious tuberculosis should develop and implement an appropriate tuberculosis infection control plan.

Standard 21 (Cases notification)

All providers must report both new and re-treatment tuberculosis cases and their treatment outcomes to local public health authorities, in conformance with applicable legal requirements and policies.

Annex I : WHO recommendation of TB diagnosis in Children

Some important definitions (according to WHO)

Infant: a child under 1 year of age.

Newborn (or neonate): an infant under 28 days of age.

Child: refers to the 0-10-year age group.

Adolescent: refers to the 10-18-year age group.

Contact: any person who has been exposed to an index case.

Close contact: a person who is not in the household but who shared an enclosed space, such as a social gathering place, workplace, or facility, with the index case for extended daytime periods during the 3 months before the start of the current treatment episode.

Household contact: a person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of the current treatment episode.

Important recommendations

Recommendation 1

– GeneXpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

Recommendation 2

– GeneXpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

Recommendation 3

– GeneXpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extra-pulmonary TB

Recommendation 4

– GeneXpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis

Recommendation 5

Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings.

Recommendation 6

Commercial sero-diagnostics should not be used in children suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status.

Recommendation 7

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB

Recommendation 8

The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

Isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day

Rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day

Pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg)

Ethambutol (E) 20 mg/kg (range 15–25 mg/kg)

Recommendation 9

Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two drug (HR) regimen for 4 months at the dosages specified in Recommendation 8

Recommendation 10

Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8

Recommendation 11

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing pediatric TB

Recommendation 12

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT)

Recommendation 13

Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculosis peripheral lymphadenitis.

Recommendation 14

Children with suspected or confirmed tuberculosis meningitis and children with suspected or confirmed osteo-articular TB should be treated with a four drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total

duration of treatment being 12 months. The doses recommended for the treatment of tuberculosis meningitis are the same as those described for pulmonary TB

Recommendation 15

In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants.

Recommendation 16

In children who are known to be HIV-infected, BCG vaccine should not be given.

Recommendation 17

In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors

Recommendation 18

Clinical evaluation of household and close contacts for active TB should be done on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts who are:

- Children with symptoms suggestive of TB;
- Children <5 years of age;
- Children with known or suspected immuno-compromising conditions (especially those living with HIV); and
- Child contacts of index cases with multidrug-resistant or extensively drug-resistant TB (proven or suspected)

Recommendation 19

It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- has sputum smear-positive pulmonary TB;
- has multidrug-resistant or extensively drug-resistant TB (proven or suspected);
- is a person living with HIV; or
- is a child <5 years of age

Recommendation 20

Contact investigation may be conducted for household and close contacts of all other index cases with pulmonary TB, in addition to the index cases covered in Recommendation

Recommendation 21

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be given 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day)

Recommendation 22

In settings of high HIV prevalence, all household and close contacts of people with TB should be counseled and tested for HIV

Recommendation 23

In settings of low HIV prevalence, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered counseling and testing for HIV as part of their clinical evaluation.

Recommendation 24

All household contacts of an index case who is a person living with HIV should be counseled and tested for HIV

Recommendation 25

Children living with HIV who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and who have no contact with a TB case:

- should be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if living in settings with a high TB prevalence
- might be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) if living in settings with a medium or low TB prevalence

Recommendation 26

Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses)

Recommendation 27

Children with proven or suspected pulmonary TB or tuberculosis meningitis caused by multidrug-resistant bacilli can be treated with a Fluoroquinolone in the context of a well-functioning MDR-TB control program and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing pediatric TB

Recommendation 28

All children treated for TB should be recorded and reported by the NTP in one of two age bands (0–4 years and 5–14 years)

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