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Tuberculosis: Epidemiology, Diagnosis, Treatment, Prevention and Control in the United States and Worldwide

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Tuberculosis: Epidemiology, Diagnosis, Treatment, Prevention and Control in the United States and Worldwide

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Capstone

Presented to the Faculty of the Graduate School of

The University of Texas Medical Branch

in Partial Fulfillment

of the Requirements

for the Degree of

Master of Public Health

The University of Texas Medical Branch

May, 2013

Dedication

I would like to dedicate this capstone to my husband and three children for their continuous support and encouragement throughout the many years I have been in school.

Acknowledgements

I would like to begin by thanking my committee chair, Dr. C. Glen Mayhall, for his support and continuous assistance in guiding me through the work to complete this Capstone. I would also like to thank the other members of my committee, Dr. Christine Arcari and Dr. Melanie de Boer, for their support and guidance throughout my years in the MPH program. I would like to acknowledge Elsa Calzada in the Department of Healthcare Epidemiology, Dr. Natalie Williams-Bouyer in the Department of Clinical Microbiology along with Paula Clarner, and the Galveston County Health District, especially Elizabeth Reza-Mann and Eileen Dawley, for assisting me in gaining the knowledge I would need to complete this project and will need for my future endeavors. I thank each of you for allowing me to follow you around and observe TB prevention and control in action. Finally, a very special thank you to my PhD mentor, Dr. Janice Endsley, for supporting my decision to join the MPH program; without your support this would not have been possible.

Tuberculosis: Epidemiology, Diagnosis, Treatment, Prevention and Control in the United States and Worldwide

Publication No._____

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The University of Texas Medical Branch, 2013

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TB is one of the most common infectious diseases worldwide. Approximately one-third of the world's population is infected with TB. In 2011, there are about 9 million new infections and almost 1.4 million deaths. Furthermore, TB is the leading cause of death in HIV-positive individuals. With the global HIV pandemic and the emergence of MDR- and XDR-TB, new diagnostics and treatments are urgently needed for the control and prevention of TB. Ultimately, the coordinated efforts of international and national government agencies, non-government agencies, healthcare professionals, and the public is needed to ensure the implementation and adherence of control strategies that will lead to the eradication of TB.

This capstone will focus on the epidemiological and clinical aspects of TB, and the TB prevention and control measures as recommended by national and international organizations. The objectives of this project were accomplished through the direct observation of TB control and prevention measures in the hospital (UTMB) and public health (Galveston County Health District) settings. In addition, an extensive literature review was performed to gain a complete understanding of TB epidemiology, diagnostics, treatments, and prevention and control strategies.

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ACET	Advisory Committee for Elimination of Tuberculosis
AFB	acid-fast bacilli
AIDS	acquired immunodeficiency virus
AII	airborne infection isolation
ART	antiretroviral therapy
ATS	American Thoracic Society
BCG	*M.bovis* bacilli Calmette-Guérin
CDC	Centers for Disease Control and Prevention
CFP-10	culture filtrate protein 10 (CFP-10)
CNS	central nervous system
CPTR	critical path to TB drug regimens
CSF	cerebrospinal fluid
DOT	directly observed therapy
DOTS	directly observed therapy short-course
EMB	ethambutol
ESAT-6	early secretory antigenic target-6
FDA	Food and Drug Administration
HCW	healthcare workers
HEPA	high-efficiency particulate air
HGC	hard-gel capsule
HIV	Human Immunodeficiency Virus
IDSA	Infectious Diseases Society of America
IFN-γ	interferon-gamma
IGRA	interferon-gamma release assay
INH	isoniazid
IRIS	immune reconstitution inflammatory syndrome
LTBI	latent tuberculosis infection
MDG	Millennium Development Goals
MDR-TB	multi-drug resistant tuberculosis
mm	millimeter
MODS	microscopic observation drug susceptibility
M.tb	*Mycobacterium tuberculosis*
NGO	non-governmental organizations
NAA	nucleic acid amplification
NNRTI	non-nucleoside reverse transcriptase inhibitors
NTCA	National Tuberculosis Controllers Association
PCR	polymerase chain reaction
PPD	purified protein derivative
PZA	pyrazinamide
QFT-GIT	QuantiFERON®-TB Gold In-Tube
RIF	rifampin
RPT	rifapentine

TB	Tuberculosis
TDR-TB	totally-drug resistant tuberculosis
T-Spot	T-SPOT®.TB
TST	tuberculin skin test
SGC	soft-gel capsule
UN	United Nations
U.S.	United States
USPHS	United States Public Health Service
XDR-TB	extensively-drug resistant tuberculosis
Xpert MTB/RIF	GeneXpert *Mycobacterium tuberculosis*/Rifampin
WHO	World Health Organization

CHAPTER 1 INTRODUCTION

Tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*M.tb*) [1]. Approximately one third of the world's population, or two billion people, are latently infected with TB [1, 2]. In 2011, there were about 9 million new infections with a majority of cases occurring in Sub-Saharan Africa [1, 2]. Illustration 1 represents the global TB incidence [1]. With almost 1.4 million deaths in 2011, TB ranks as the second leading cause of death among infectious diseases worldwide [1, 2]. Since the 1800s, efforts to control TB have been established at the national and international level.

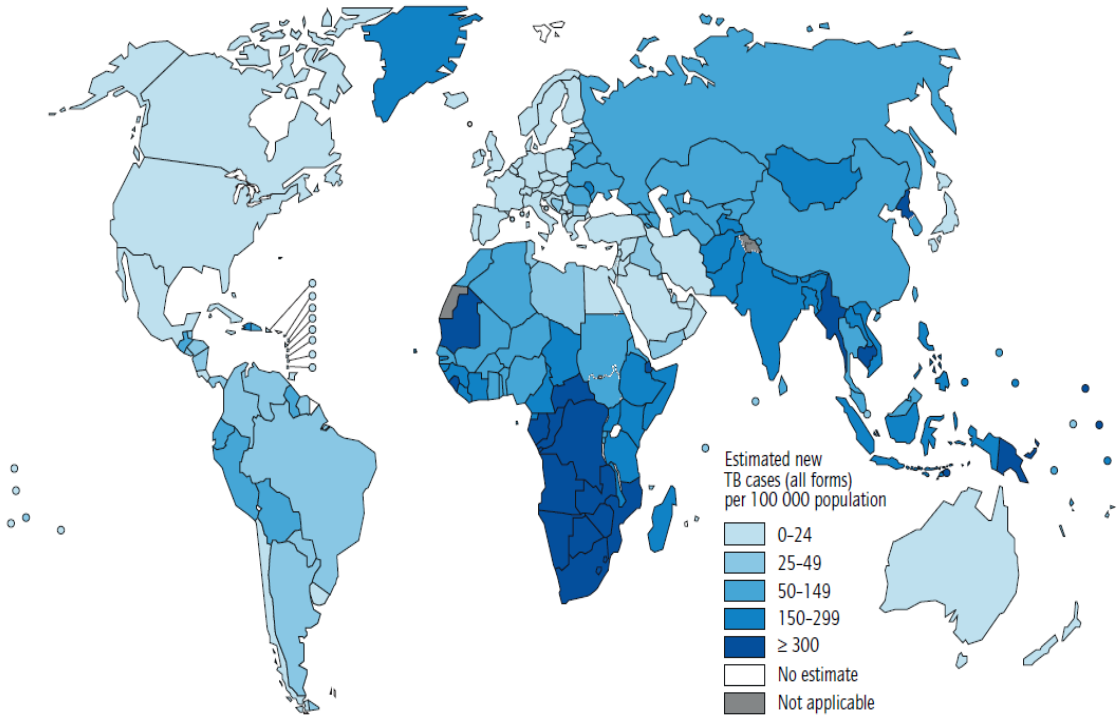


Illustration 1. Estimated TB Incidence Rates, 2011 (Taken from Reference [1])

SPECIFIC AIMS

TB is one of the most common infectious diseases worldwide [2]. Although rates of TB have declined in the U.S., it remains a major global health problem [1]. Implementation and adherence to TB prevention and control measures along with the development of novel diagnostics and treatments is important in TB elimination, especially with the emergence of multi-drug resistant (MDR)- and extensively-drug resistant (XDR)-TB, and co-existence of human immunodeficiency virus (HIV). The overall goal of this capstone is to review the epidemiological and clinical aspects of TB, and TB control and prevention measures as recommended by the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO). This will be accomplished through two objectives:

(1) understanding the epidemiological and clinical aspects of TB, including identifying the presentation of various forms of TB, assessing diagnostic methods and treatment regimens, the emergence of drug resistance, and analysis of the effects of HIV on the TB epidemic;

(2) understanding the control and prevention measures associated with TB infection, including identification of TB suspects, identification of contacts through contact investigations, targeted testing and treatment of high-risk populations, and infection-control measures within high-risk settings.

These objectives will be accomplished through the observation of TB control measures in the hospital and the public health settings. Additionally, these objectives will involve an extensive literature search regarding TB epidemiology, diagnostics, treatments, and control and prevention measures.

CHAPTER 2 AN INTRODUCTION INTO PREVENTION AND CONTROL

ESTABLISHMENT OF NATIONAL TB CONTROL MEASURES

TB was the leading cause of death in the early nineteenth century [3]. In the late nineteenth century mortality rates began to decrease with improved standards of living, and establishment of public health measures [3, 4]. Sanatoriums were also introduced with treatment that included rest, isolation, nutrition, and fresh air [3].

During this time, TB was considered a public health issue [3]. As a result, resources became available and public health programs were established that focused on TB control [3, 5]. On June 6, 1904, the National Association for the Study and Prevention of Tuberculosis (later known as the National Tuberculosis Association and currently the American Lung Association) was formed [3-5]. They were involved in TB surveillance and data collection [3]. Subsequently, the American Sanatorium Association (later the American Trudeau Society and currently the American Thoracic Society) was created [4]. In 1920, the *Diagnostic Standards and Classifications of TB* was published by the National Tuberculosis Association [3]. These criteria would allow officials to accurately understand the magnitude of TB incidence, morbidity, and mortality; additionally control measures could be effectively evaluated [3]. In the 1920s and 1930s, chest radiograph (x-ray) screening played a significant role in TB diagnostics; allowing for the diagnosis of TB patients prior to the onset of symptoms and identification of patients for isolation at sanitaria [3, 6]. In 1944, the United States Public Health Service Act created a national TB control program [3]. In 1951, recommendations for TB case reporting and counting were published and in 1952 the United States Public Health Service (USPHS) Tuberculosis Control Program implemented procedures for the reporting of new TB cases [3, 7]. By 1953, the national TB surveillance system officially began when reports were submitted from every state [3].

Between 1930 and 1960, along with TB control programs, the introduction of antibiotics dramatically decreased mortality rates by 93%, from 71 to 6 deaths per 100,000 in the population [3]. Starting in 1953, there was a gradual decline in the incidence rate of reported TB cases and by 1985 there was an 83% reduction, from 53 to 9 cases per 100,000 in the population (84,304 to 22,201 new cases, respectively) [8]. Ultimately, these results show that efficient TB control programs can be effective in reducing the burden of TB nationally and possibly internationally.

With the decline in TB, many believed that it was on the verge of being eliminated and would no longer be a public health problem; as a result, funding was reduced and TB control programs were eliminated [3, 9]. In 1986, the incidence rate of TB increased by 2.6% indicating resurgence and reintroduction of TB as a public health threat [3]. Factors that contributed to the resurgence of TB included deterioration of TB control infrastructure, increased HIV infections, hospital-acquired TB, MDR-TB, and increased immigration of individuals from countries with high TB incidence [10]. In 1987, an Advisory Committee for the Elimination of Tuberculosis (ACET) was established to provide recommendations for technology development, implementation of prevention and control measures, and management of TB elimination programs at the state and local level [11]. In 1989, the CDC published a plan to eliminate TB in the U.S. [10]. This lead to an influx of resources for TB control at the national, state, and local level which resulted in a 44% reduction in TB incidence between 1993 and 2003 with a 'historic' low of 5.1 per 100,000 in the population (14,835 cases) reached in 2003 as depicted in Figure 1 [8, 10]. In 2011, there were 3.4 new TB cases per 100,000 in the population (10,528 cases) which was a 5.8% decrease of reported TB cases compared to 2010 [2, 8]. Despite these decreases, elevated TB rates continue to be seen above the national average in certain states and populations (e.g. HIV-positive and foreign-born populations) [3].

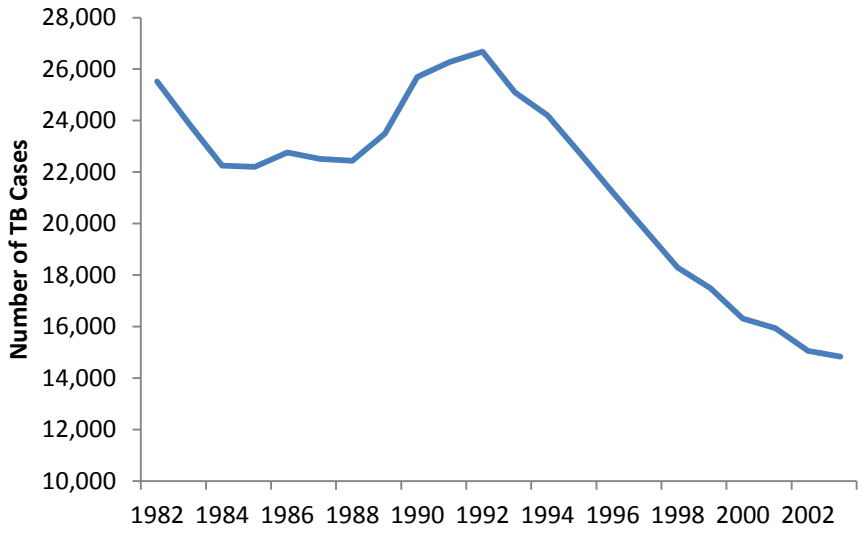


Figure 1: Number of reported TB cases in the United States, 1983-2011 (plotted from data in Reference 6)

ESTABLISHMENT OF INTERNATIONAL TB CONTROL MEASURES

In 1993, the WHO declared TB a 'global public health emergency'; shortly thereafter the WHO developed a TB control strategy, also known as directly observed therapy short-course (DOTS), to reduce the TB incidence and mortality globally [1, 12]. The components of this strategy included government commitment, sputum smear microscopy diagnosis, anti-TB drug supply of first-line treatments, short-course therapy, and a recording and reporting system of the number of TB cases and treatment outcomes [1, 12]. This strategy lead to a 53% detection rate among smear-positive cases and 85% treatment success rate among these cases [1, 12]. In 2006, the WHO also established the Stop TB Strategy for the care and control of TB, along with the Millennium Development Goals (MDGs) and the Stop TB Partnership; the global targets are to stop and reverse the rate of new TB infections by 2015, reduce TB prevalence and mortality by 50% compared to rates in 1990 by 2015, and eliminate TB as a public health threat by 2050 [1, 12].

TB control strategies implemented by national and international organizations have greatly reduced the global incidence, prevalence, and mortality of TB. This decrease is attributed to the coordinated efforts at the local, state, federal, and international levels [10]. Although despite these efforts, TB continues to be a major global burden and health threat [1].

CHAPTER 3 TUBERCULOSIS

EPIDEMIOLOGY IN THE U.S.

In the United States (U.S.) there were 10,528 cases of TB in 2011 [8]. The highest numbers of cases were reported in California, Florida, New York, and Texas with over 500 cases each; these states accounted for over 50% of the national cases [8]. Factors associated with increased TB are age, race and ethnicity, and country of origin [8]. In 2011, TB incidence was highest among the elderly (aged ≥65 years), who account for 21% (5.4 cases per 100,000) of the total cases [8]. Asians also had the highest incidence of TB, accounting for 30% (20.9 cases per 100,000) of cases [8]. TB rates were also increased in foreign-born individuals (62%; 17.2 cases per 100,000) compared to U.S.-born individuals (38%; 1.5 cases per 100,000) [8].

M.tb is primarily transmitted from person to person in airborne particles 1-5 microns in size when the infected individual coughs, talks, sneezes, or sings [2, 10, 13, 14]. These particles can remain suspended in the air for up to 30 minutes and can travel long distances by drafts or through ventilation systems [10, 13]. Exposure to an infected person or aerosolized droplets does not mean an exposed person will become infected with TB. The risk of infection is dependent upon several factors as seen in Table 1, including characteristics of the infected individual and the exposed individual, intensity, duration, location of the exposure, and virulence of the strain [10, 13]. Fortunately, not everyone who becomes infected will develop disease; there are two forms of TB infection: latent TB infection (LTBI) and active TB disease [2].

Table 1: Factors determining *M.tb* transmission (Adapted from Reference [10])

Characteristics of the source case
Concentration of the organism
Presence of a cavity on chest radiograph
Cough frequency and strength
Characteristics of the exposed person
Prior *M.tb* infection
Resistance to *M.tb* infection
Genetic susceptibility to *M.tb*
Characteristics of the exposure
Frequency and duration
Dilution effect (volume of air containing the infectious particle)
Ventilation
Exposure to ultraviolet light, such as sunlight
Virulence of the *M.tb* strain

PATHOGENESIS

Inhaled *M.tb* travel down the bronchus and enter the lung alveoli where they are taken up by alveolar macrophage [14]. Infection within the lung is known as pulmonary TB [1, 2]. The ability of the bacteria to circumvent the host's immune response allows for replication within the macrophages [14]. *M.tb* is a slow growing organism; as a result a cellular immune response is not elicited for 2 to 12 weeks after initial infection which is subsequently detected by the tuberculin skin test (TST) [14]. The ability of the host to mount a strong immune response, arrests the organism's ability to persist and limits its

presence to the lung and local draining lymph nodes; this is known as the "Ghon complex" [15]. A granuloma, the pathologic hallmark of tuberculosis, is formed and responsible for containing the bacteria in a dormant, non-replicative state [14, 16]. Granulomas are composed of various immune cells such as activated macrophages, T cells, B cells, dendritic cells, neutrophils, and natural killer cells [16]. Unfortunately, the bacteria are not completely eliminated and infected individuals are at risk of developing active TB disease [2, 16].

The inability of the host to eliminate or contain the organism results in bacterial dissemination [14]. Following inhalation and multiplication, the bacteria travel from the lung to the lymph nodes, then to the lymph channels which connect to the bloodstream where they migrate to other parts of the body; infection within areas of the body beyond the lung is known as extrapulmonary TB [1, 2, 6, 14].

PULMONARY TUBERCULOSIS

LATENT TB

As previously stated, two billion people are infected with LTBI worldwide [1, 2]. In the U.S., approximately 11 million people are infected with latent TB [13]. A latently infected individual does not have symptoms, is not infectious, and cannot spread TB to others [2, 14]. Individuals with LTBI are able to mount an adequate immune response that contains the bacteria and inhibits its growth within a granuloma; thus a granuloma is characteristic of latent infection [2, 16, 17]. On a chest radiograph most latent pulmonary TB infections will not be detected [14].

Latent infection occurs in approximately 90% of individuals who become infected with TB [2, 17]. People at highest risk of LTBI are immigrants from countries where TB is endemic, elderly who were alive when TB was endemic in the U.S., and individuals recently exposed to TB from an active TB case [13]. Individuals with LTBI should be started on treatment immediately to prevent the risk of developing active TB disease.

ACTIVE TB

Active TB infection or TB disease occurs when the individual's immune system is unable to prevent the bacteria from growing [2]. Approximately 10% of individuals infected with TB will develop TB disease; about 5% within 18 months of infection and 5% within their lifetime if untreated [2, 17]. Active TB which occurs immediately after infection is known as primary infection, while active TB that results from latent infection is known as post-primary infection or reactivation [6]. Post-primary infection manifests in 1-2% of LTBI cases each year [6]. During primary infection, a chest radiograph will display an area of infiltrate in the middle to lower lung region; progressive infection following primary infection will subsequently result in a cavity formation [14]. Reactivation will show upper lobe abnormalities in one or both lungs that may also result in cavitation [14].

There are several risk factors that increase an individual's chance of developing TB disease including recent TB infection (within 2 years), incorrect treatment of previous TB infection, or a weakened immune system such as HIV infection [2]. Factors for individuals at high risk of developing TB disease are listed in Table 2.

In the U.S., there were less than 5000 active TB cases among US-born individuals in 2009 [13]. During active TB infection, individuals are sick and able to spread the bacteria to others [2]. Symptoms of active TB disease include persistent cough lasting more than 3 weeks, chest pain, and coughing up blood or sputum; other symptoms may include weakness or fatigue, weight loss, loss of appetite, chills, fever, and night sweats [2].

Table 2: Risk Factors for the Development of TB disease (Adapted from Reference [2])

Individuals Recently Infected with TB	Individuals with Medical Conditions that Weaken the Immune System
• Close contact of a person with infectious TB disease • Persons who have immigrated from areas of the world with high rates of TB • Children <5 years old who have a positive TB test • Groups with high rates of TB transmission, such as homeless persons, injection drug users, and persons with HIV infection • Persons who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV	• HIV infection • Substance abuse • Silicosis • Diabetes mellitus • Severe kidney disease • Low body weight • Organ transplants • Head and neck cancer • Medical treatments such as corticosteroids or organ transplant • Specialized treatment for rheumatoid arthritis or Crohn's disease

EXTRAPULMONARY TUBERCULOSIS

Extrapulmonary TB develop in different organs including the lymph nodes, bones and joints, heart, central nervous system (CNS), gastrointestinal tract, and reproductive organs [6, 17]. As previously mentioned, after initial infection through the lungs, the bacteria can travel through the lymphatic system and bloodstream to other organs [1, 2, 6]. Approximately 10-42% of individuals infected with TB may develop a form of

extrapulmonary TB depending on age, race or ethnicity, underlying disease, *M.tb* strain, or immune status [17]. In the U.S., extrapulmonary TB accounted for 22% of cases [18]. Symptoms may arise within a month following primary infection or remain dormant for years; they include chills, joint pain, pale skin, or swollen lymph nodes [6].

LYMPHADENITIS

The most common form of extrapulmonary TB is lymphadenitis, or inflammation of the lymph nodes [19, 20]. It accounts for approximately one-third of extrapulmonary cases [21]. Within the U.S. and throughout the world, lymphadenitis is common among women, immigrants (particularly Indian or African ethnicity), and HIV-positive individuals [19-21]. In TB-endemic regions, it accounts for 10-34% of TB in HIV-negative populations and 50-70% of TB in HIV-positive populations [20].

Typically the nodes present as discrete, firm, and non-tender; although over time they may develop into visible, firm masses [14, 19]. HIV-positive individuals also present with fever, night sweats, and weight loss [19, 22]. Untreated lymphadenitis leads to fluctuant (movable and compressible) nodes that spontaneously drain [19].

Preferred diagnosis is biopsy of the lymph node with histology [14, 19, 21]. Alternative techniques may include fine-needle aspiration, acid-fast bacilli (AFB) stain, bacterial culture, or molecular detection [19, 21]. In HIV-negative cases, the chest radiograph is usually normal; in HIV-positive cases, the chest radiograph is often abnormal [19, 22]. Along with anti-TB treatment for 6 months, drainage by aspiration or incision of fluctuant lymph nodes that are ready to drain has been shown to benefit the patient [19, 23].

SKELETAL (BONE & JOINT)

Tuberculosis in the bone and joints accounts for up to 35% of extrapulmonary TB cases [19]. Involvement includes the spine, weight-bearing bones, and joints with pain

and tenderness [19, 21]. Infection is commonly found in immigrants (originating from India or Africa) and women [24].

Tuberculosis of the spine, also known as Pott's disease, involves the middle part of the spine; patients present with local pain, constitutional symptoms (e.g. weight loss, shaking, chills, fever, and vomiting), or destruction of the spine that results in paraplegia [19, 21]. Tuberculosis of the joints such as the hip and knee presents with pain, swelling, and reduces range of motion [19]. Radiographic images show tissue swelling, joint space narrowing, and erosion [19, 25]. Tuberculosis of the bone can include any bone and presents with local pain [19].

Diagnosis of skeletal TB is determined from synovial fluid or biopsy samples using histology and bacterial culture [14, 19, 21, 24, 25]. Culture will yield a positive result in 80-95% of cases [19, 21]. Anti-TB treatment is recommended, which should be administered for 6 to 9 months; surgery is also recommended to drain abscesses, clean infected tissue, or stabilize the spine to relieve compression on the spinal cord [19, 23, 24].

PERICARDITIS

Tuberculosis pericarditis is uncommon in developed countries, accounting for only 4-7% of cases [21, 26]. It develops from tuberculosis of the lungs, lymph nodes, spine, or during miliary spread [19]. If untreated, mortality occurs in up to 85% of cases within 6 months [26]. Progression can take weeks to years with symptoms arising gradually or suddenly and include chest pain, difficulty breathing, excessive fluid levels surrounding the tissue, and decreased blood pressure [14, 19, 21].

Diagnosis includes AFB stain, biopsy, bacterial culture, and molecular analysis [19, 21]. Sensitivity of AFB stain is 0-42% with 98% specificity; while histology from a biopsy sample is 10-87% sensitive with 100% specificity [26]. Molecular analysis, specifically nucleic acid amplification (NAA), also yields variable sensitivity (15-80%)

and specificity (75-100%) [26]. Chest radiography will display an enlarged heart, which is seen in over 80% of patients, along with fluid build-up within the pleural space [21]. Treatment involves anti-TB treatment for 6 months along with corticosteroids during the initial 11 weeks of treatment; corticosteroids accelerate the resolution of symptoms and reabsorption of fluid preventing re-accumulation [19, 23, 26]. Pericardial drainage is also recommended [19, 26]

MENINGITIS

Tuberculosis that affects that CNS can be life-threatening, especially when it affects the meninges [21]. TB meningitis is the most devastating form of extrapulmonary TB since it has high morbidity and mortality with a 60% death rate in developing countries [23, 27, 28]. Mortality rate is highest in children under 5 years of age, elderly patents over 50 years of age, and patients presenting with illness longer than two months [19]. TB meningitis is rare, affecting about 1.5% of extrapulmonary cases in developed countries and 6.3% of extrapulmonary cases in the U.S. alone [21, 27]. It is commonly seen in children under the age of 5 and the elderly [21]. Prior to the development of symptoms, inflammation occurs from the rupture of a tubercle below the epithelial membrane close to the meninges in the brain [19, 21]. Symptoms include nausea, headache, fever, vomiting, and behavioral and mental changes; within two to three weeks headache, vomiting, and confusion occur [19].

Diagnosis is difficult given the inconsistent clinical presentation and lack of adequate tests [21]. Thus diagnosis is usually based on clinical characteristics, cerebrospinal fluid (CSF), molecular analysis, and radiological imaging [21, 27, 28]. AFB smear and bacterial culture are unreliable given the low bacterial levels in the CSF; an AFB smear is positive in 10-90% of cases while culture is positive in 45-90% of cases [19, 21, 27]. Molecular analysis through polymerase chain reaction (PCR) has a sensitivity of 56% and specificity of 98% [19]. Optimal treatment length is not defined,

although 9-12 months of treatment is recommended; corticosteroid therapy for the first 6-8 weeks has been shown to reduce mortality and neurologic sequelae [19, 23]. HIV infection increases the risk of meningitis; clinical presentation in HIV-positive individuals is modified with acellular CSF and high bacterial loads as determined through AFB smear [27].

MILIARY

Miliary TB accounts for up to 20% of extrapulmonary cases [18]. Its name is derived from the Latin word "miliarius" and refers to the 'millet-seed size' nodules found in the affected organ [14, 18]. The organs usually affected are liver, spleen, bone marrow, lungs, and meninges [18]. Disease can occur following initial dissemination or after years of untreated TB [19]. Initially considered a disease of childhood, it has increasingly been seen in adults [18]. Incidence and prevalence has particularly grown in immunocompromised (i.e. HIV infected) individuals; 10% of acquired immunodeficiency syndrome (AIDS) and pulmonary TB patients, and 38% of AIDS and extrapulmonary TB patients have miliary TB [18, 19]. Miliary TB may also present with TB meningitis. In adults, 10-30% of miliary TB cases also have TB meningitis; similarly, 20-40% of children with miliary TB also suffer from TB meningitis [18]. Miliary TB symptoms include fever, chills, weight loss, anorexia, and cough [14, 18, 19]. Temperature spikes every morning and night sweats are characteristic; while choroidal tubercules and skin lesions offer clues to miliary TB diagnosis [18].

Diagnosis includes AFB stain, bacterial culture, or liver and bone marrow biopsy [19]. The hallmark of miliary TB is the chest radiograph that displays one to two millimeter nodules scattered within the infected organ; this is observed in over 85% of pulmonary cases [14, 18, 19]. If left untreated, miliary TB can be fatal within 1 year [18]. Treatment is recommended for 6 months or 9 to 12 when present with TB meningitis [18]. Mortality is observed in 25-30% of adults and 15-20% of children; although this is

dependent upon age, bacterial load, when treatment is initiated, and severity of disease [18].

TB DURING HIV INFECTION

TB infection is the most common co-infection and leading cause of death among individuals infected with HIV [2, 10]. In 2011, there were 1.1 million HIV-positive individuals among the 8.7 million TB cases with almost 80% of HIV/TB cases located in Africa as represented in Illustration 2 [1]. Whereas an HIV-negative individual has a 10% risk of developing active TB in their lifetime, an HIV-positive individual has a 7-10% risk of developing active TB each year [10]. HIV-positive individuals are also at greater risk of TB disease progression from latent infection (reactivation), rapid progression to active TB following infection, and reinfection [2, 10]. Moreover, HIV infected individuals are at an increased risk of extrapulmonary TB, which is seen in over 50% of cases [18]. In 2011, there were approximately 400,000 HIV-associated TB deaths worldwide [1].

In the U.S., there has been a decline in HIV infections among TB cases, from 29% in 1993 to 16% by 2002 [8]. By 2011, 10% of TB cases also reported HIV-positive status; a rate that has remained constant since 2008 [8]. For individuals with TB, the CDC recommends voluntary HIV counseling, testing, and referral [2, 3].

Worldwide, diagnosis of TB in HIV populations by sputum smear and chest radiograph has proven to be challenging. HIV-associated TB is characterized by asymptomatic TB with AFB-negative sputum smear and normal chest radiograph [17]. In TB endemic regions, it is believed that up to 25% of HIV-positive individuals have undiagnosed active TB [17]. Identification of HIV/TB cases may be based on the presence of one of the following symptoms: cough, fever, night sweats, or weight loss; this has been shown to be 80% sensitive, even in TB-endemic regions [17]. HIV-positive, smear-negative TB cases also have higher mortality than individuals with smear-positive

TB, particularly in resource-limited countries [29]. This is assumed to be the result of limited and inaccurate diagnostics that delays the initiation of treatment, and incorrect treatment [29]. For HIV-positive populations, the development of TB diagnostics and treatments is essential to reduce the burden of co-infection. Proper identification of HIV/TB individuals with effective diagnostics will aid in preventing transmission of TB and reduce the risk of extrapulmonary disease among HIV-positive populations. Rapid identification may also lead to early initiation of treatment and reduce mortality.

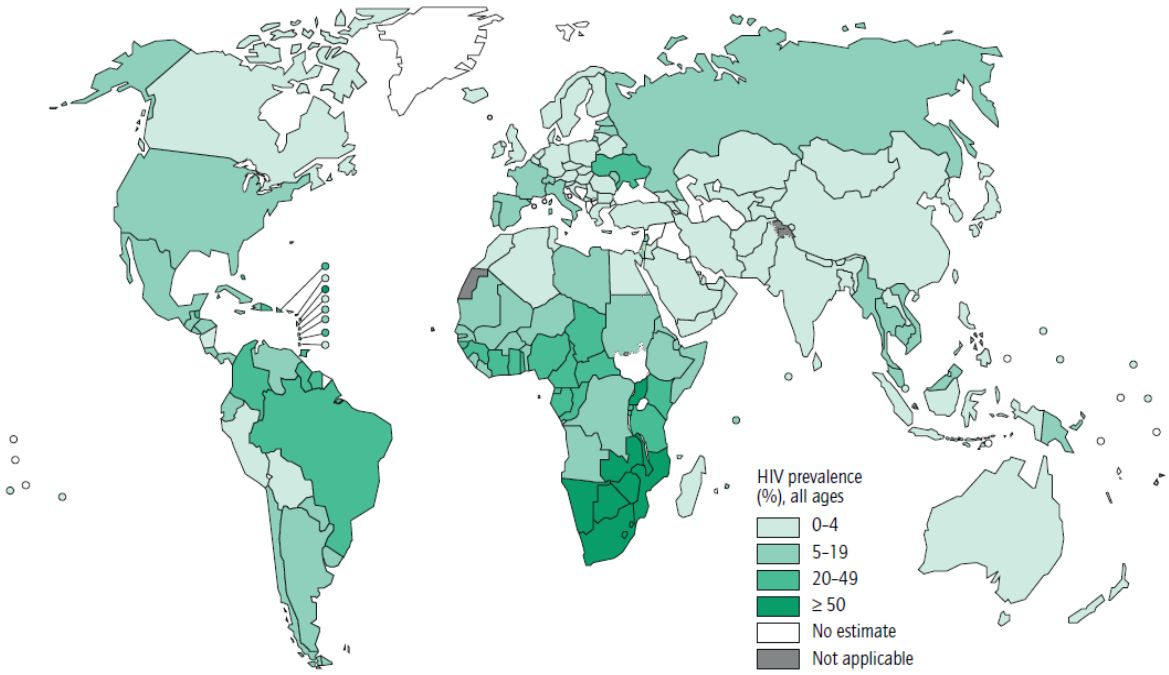


Illustration 2. Estimated HIV prevalence in new TB cases, 2011 (Taken from Reference [1])

CHAPTER 4 TB DIAGNOSTICS

Control of TB requires quick and efficient case identification. To determine whether an individual is infected with *M.tb* several tests can be administered, such as a TST, blood test, chest x-ray, AFB sputum smear for microscopy, bacterial culture, and molecular analysis [2, 30]. A TST and blood test primarily determines if an individual is infected with *M.tb*; they do not determine if the individual has latent or active TB [2]. Further detection for active TB is verified through x-ray, sputum smear, bacterial culture, and molecular analysis [2].

DIAGNOSIS OF LATENT TB

Screening for LTBI is done for high-risk groups such as foreign-born populations from TB endemic countries, immunocompromised populations, and individuals in recent contact with a TB infected patient [17, 31]. This is typically performed using the TST or blood test.

TUBERCULIN SKIN TEST

The TST is the most commonly used diagnostic test in the U.S. [6]. Also known as the Mantoux tuberculin skin test, the TST is a relatively inexpensive test that involves intradermal injection of a small amount of tuberculin or purified protein derivative (PPD) in the lower arm; 48 to 72 hours after administration, the individual that received the tuberculin will return to a healthcare worker to determine whether a reaction has occurred and for documentation of the result [2, 17, 31]. A positive skin test is identified by a raised area that is hard or swelling known as an induration [2]. The induration is measured with a ruler in millimeters (mm) by a trained healthcare worker [2]. To improve the chance of detecting *M.tb* infected individuals from non-infected individuals, three induration size cut-points have been established and are discussed in Table 3: ≥5

mm for the highest risk populations such as HIV-positive, ≥10 mm for populations with possible recent infection or other clinical condition such as immigrants or healthcare workers, and ≥15 mm for low risk populations who would not normally receive a TST [31]. Though a positive skin test shows that an individual has been infected with *M.tb*, additional testing is required to determine if the individual is latently or actively infected [2].

Table 3: Criteria for positive tuberculin skin test (Adapted from Reference [31])

≥5 mm induration	≥10 mm induration	≥15 mm induration
HIV infection Immunosuppressive therapy Recent contact with active TB case Abnormal chest radiograph suggestive of prior TB infection	Immigrated within 5 years from high prevalence region Injection drug user Resident or employees of high-risk congregate settings (e.g. hospitals, prisons, nursing homes, homeless shelters) Laboratory personnel Clinical condition (e.g. silicosis, diabetes mellitus, leukemias and lymphomas, carcinoma of the lung/head/neck, weight loss ≥10% of ideal body weight Children < 4 years of age or infants/ children/ adolescent exposed to high-risk adults	Low risk populations with no risk factors for TB

There are several limitations to the TST such as lot-to-lot variation, improper administration, subjective interpretation of the induration measurement, and

noncompliance by individuals in not returning to a healthcare worker for documentation of the results. Additionally, low specificity or false-positive is commonly seen in individuals that have been vaccinated with the *M.bovis* bacilli Calmette-Guérin (BCG) vaccine -a vaccine to prevent TB disease- or infected with environmental strains of mycobacterium –a nontuberculous mycobacterium [31, 32]. There are over 200 antigens present in PPD; though these antigens are not specific for *M.tb*, they are also found in the BCG vaccine and environmental mycobacteria [16, 32, 33]. For improved specificity, induration size should be increased; although sensitivity is reduced [31]. Low sensitivity or false-negative is commonly seen in HIV infected or immunocompromised individuals [16, 31, 32]. Given these limitations, it is evident that new diagnostic tools with higher sensitivity and higher specificity are urgently needed. Improved specificity would reduce or eliminate the unnecessary treatment of false-positive cases while improved sensitivity would properly identify HIV/TB co-infected cases, perhaps earlier in infection, preventing the delay of treatment and reducing mortality.

INTERFERON-GAMMA RELEASE ASSAY

An advancement in the development of a *M.tb* diagnostic tool was reached in 2001 when the Food and Drug Administration (FDA) approved the use of blood tests known as the interferon-gamma release assay (IGRA) for the detection of *M.tb* infection [6]. The IGRA is a blood test that measures an individual's immune response, specifically the release of the interferon gamma (IFN-γ) cytokine, following incubation with *M.tb* proteins [2, 33]. Currently, the two FDA approved IGRA's are QuantiFERON®-TB Gold In-Tube Test (QFT-GIT) and T-SPOT®.TB test (T-Spot) [2]. The QFT-GIT measures the amount of IFN-γ produced from whole blood following stimulation with early secretory antigenic target-6 (ESAT-6) and culture filtrate protein 10 (CFP-10), which are found in *M.tb* but not the BCG vaccine or nontuberculous mycobacterium, and the TB7.7 protein [16, 33]. The T-SPOT measures the number of T-

cells producing IFN-γ after stimulation with ESAT-6 and CFP-10 [16, 33]. A positive IGRA indicates an individual has been infected with *M.tb*; although, similar to the TST, the IGRA does not indicate whether an individual has latent or active TB so additional tests need to be performed [2].

An important advantage of the IGRA is it only requires one visit for diagnosis, thus it should be administered to individuals unlikely to return to a healthcare professional for TST evaluation [2, 13]. It is also more specific compared to the TST, although the sensitivity is comparable between the IGRA and TST [13, 32, 33]. Improved specificity is observed in BCG-vaccinated individuals [2, 33]. Unfortunately, the IGRA is more expensive than the TST and requires immediate transportation to a laboratory for processing [13]. Additional differences between the TST and IGRA are listed in Table 4.

Though the IGRA is an advancement made in TB diagnostics, limitations still exist. For implementation in TB-endemic, a resource-limited country, development of diagnostic tools requires cost-effectiveness. This is also important for developed countries, such as the U.S., considering that TB is increasingly being found in foreign-born populations and immigrants from countries where TB is endemic [6, 8, 17]. Furthermore, diagnostics with increased sensitivity are greatly needed for detection of *M.tb* in HIV-positive populations which will allow for early treatment of infection and possibly assist in reducing the worldwide epidemic of HIV/TB co-infection.

Table 4: Evaluation of tuberculin skin test (TST), QuantiFERON-TB Gold In-Tube, and T-SPOT.TB assay (Adapted from Reference [16])

	TST	QuantiFERON-TB Gold In-Tube	T-SPOT.TB
Antigens used	PPD	ESAT-6, CFP-10, TB 7.7(p4)	ESAT-6, CFP-10
Result reported as	Skin induration in mm	IFN-gamma concentration	Spot-forming number
Result interpretation	Subjective	objective	Objective
Result availability	48-72 hours	24 hours	24 hours
Visits required	Two	One	One
Influence of BCG vaccination	Yes	No	No
Cross-reaction with non-TB mycobacteria	Yes	No	No
Sensitivity	Moderate*	Moderate*	Moderate*
Specificity	Moderate‡	High	High
Side effects	Yes	No	No

*Low in HIV-infected individuals
‡Low in BCG-vaccinated individuals

DIAGNOSIS OF ACTIVE TB

The standard diagnostic methods to determine active TB infection are AFB sputum smear and bacterial culture in liquid medium along with drug-susceptibility

testing [17]. These may be further supplemented by molecular analysis and biopsy for histological analysis [17].

CHEST RADIOGRAPH (X-RAY)

Chest radiograph is commonly performed following a positive TST to exclude pulmonary or extrapulmonary TB infection [31]. During LTBI, a chest radiograph is typically normal; a TST-positive individual with normal chest radiograph will begin on treatment for latent infection [31]. If abnormalities are observed on the chest radiograph, it may suggest prior or active TB infection [31]. Characteristics of prior TB include well-defined, dense nodules in the upper lung lobes with or without calcification accompanied by smaller nodules with or without fibrosis and loss of air volume [31]. Fibrotic lesions may contain bacteria, increasing the potential for progression to active TB; on the other hand, calcified lesions possess a lower reactivation risk [31]. A chest radiograph showing possible pulmonary or extrapulmonary TB would require further evaluation to verify active TB; this would include a medical evaluation, various bacterial examinations -AFB sputum smear, bacterial culture, molecular analysis- and, if possible, comparison of old and new chest radiographs [31].

ACID-FAST BACILLI SPUTUM SMEAR

Worldwide, microscopy of a Ziehl-Neelsen stained sputum smear is the gold standard of diagnostic methods in detecting active TB infection [6, 31, 34]. The Ziehl-Neelsen stain cannot be removed from tubercle bacilli when the smear is treated with acid; thus tubercle bacilli are known as acid-fast bacilli [35]. AFB are rarely observed in sputum smear of persons with LTBI [31]. Individuals presenting with an abnormal chest radiograph suggestive of tuberculosis, excluding calcified nodules, will have three consecutive sputum samples obtained over 8 to 24 hours; these samples will be submitted for AFB stain and culture [31, 36]. Important advantages of this diagnostic method are its

low cost, relatively low complexity, and high specificity [6, 36]. Unfortunately, a significant disadvantage of the sputum smear is its low sensitivity; in the U.S., 10-43% of TB cases are smear-negative but culture-positive [30, 34, 36]. Low sensitivity has been shown to be the result of the limited expertise of the personnel examining the specimen, the amount of time devoted to examining each specimen, and the type of microscopy used; light microscopy yields lower sensitivity than fluorescent microscopy [13, 30].

In HIV-positive populations, smear-negative TB is commonly seen with sensitivity as low as 20% [34]. HIV infected individuals that have respiratory symptoms but a normal chest radiograph must submit samples for AFB sputum smear along with culture [31]. An HIV-positive individual with AFB negative smear and culture negative results, in addition to an alternative explanation for clinical symptoms, will be recommended for LTBI treatment [31]. An HIV-positive individuals with abnormal chest radiograph but negative AFB smear and culture will undergo further diagnostic testing, either by needle aspiration biopsy or bronchoscopy, to exclude or confirm active TB infection [31]. It is important to exclude active TB infection before administering treatment for LTBI [31].

Though its low cost and relatively simplistic methodology makes sputum smear ideal for use throughout the world, especially in TB endemic regions, a diagnostic test with increased sensitivity is urgently needed. This type of diagnostic will efficiently identify individuals with active TB infection so that treatment can be provided during early infection and the risk of transmission reduced. Furthermore, with the high prevalence of HIV in countries where TB is endemic, such a tool could greatly reduce the rate of undiagnosed cases.

BACTERIAL CULTURE

The gold standard for confirmation of active TB within a laboratory setting is culture [30]. In the U.S., bacterial culture in liquid medium is performed in conjunction

with AFB sputum smear to determine active TB infection, as previously stated [31, 34, 36]. In resource-limited countries, liquid bacterial culture can be costly; so culture on solid medium is preferred since it is cost-effective [17, 36]. Unfortunately, the process of culture is slow, requiring about 6 to 8 weeks to grow; four weeks are needed for drug susceptibility testing [6, 30]. It is evident that new culture methods which rapidly detect *M.tb* are urgently needed to reduce the delay of treatment, especially in drug-resistant cases.

MOLECULAR ANALYSIS

Nucleic acid amplification by PCR detects *M.tb* by identifying specified DNA sequences [30]. Results can be acquired within hours and sensitivity is high; up to 95% sensitivity for smear-positive specimens and 50-80% for smear-negative specimens [13]. Specificity is 100% [13]. Though this method is quick and highly accurate, molecular tests can be complex and costly; as a result, they are rarely used in limited-resource countries with a high prevalence of TB [30, 36].

A new molecular diagnostic tool is the GeneXpert system also known as the Xpert MTB/RIF [30]. It is a real-time PCR-based tool that can detect *M.tb* and drug-resistant *M.tb* within 2 hours [17, 30]. When compared to sputum smear, it has a higher sensitivity (99% for smear-positive samples and 80% for smear-negative samples) and 45% increased detection rate in HIV-positive populations [13, 17]. Specificity is almost 100% [13]. Currently, the Xpert MTB/RIF is being utilized in Europe and multiple other countries with high TB prevalence; in the U.S. it is still being tested for approval [1, 13, 17]. Molecular analysis may prove to be the most effective method for *M.tb* detection, although considering its high cost and complexity, application in endemic regions may prove to be difficult.

Though several diagnostic methods are available, a cost-effective diagnostic tool with high sensitivity and high specificity is missing. A highly sensitive and specific

diagnostic that is cost-effective will be required for utilization in countries with limited-resources. This is especially important since these regions have a high prevalence of BCG-vaccination and high incidence of HIV infection. It is anticipated that an improved diagnostic tool will improve identification of TB infected individuals and allow for the quick initiation of treatment.

CHAPTER 5 TB TREATMENTS

Initiation of treatment is dependent on clinical symptoms, pathological and radiographic findings, AFB sputum smear, and bacterial culture. First-line and second-line antibiotics are available for the treatment of TB as shown in Table 5 and Appendix A. It is important that treatment regimens for latent or active TB not be administered to patients with drug resistance [13].

Table 5: First-line Antibiotics for the TB Treatment (Adapted from Reference [23])

First-line Agents
Isoniazid
Rifampin
Rifabutin
Rifapentine
Pyrazinamide
Ethambutol

LATENT TB

Currently there are three anti-TB drugs available in four regimens for the treatment of LTBI [2]. The drugs include isoniazid (INH), rifampin (RIF), and rifapentine (RPT). The treatment regimens are shown in Table 6.

Table 6: Latent TB Infection Treatment Regimens (Taken from Reference [2])

Drug(s)	Duration	Interval	Minimum Doses
Isoniazid	9 months	Daily	270
		Twice weekly*	76
Isoniazid	6 months	Daily	180
		Twice weekly*	52
Isoniazid & Rifapentine	3 months	Once weekly*	12
Rifampin	4 months	Daily	120

*Use Directly Observed Therapy (DOT)

ISONIAZID

The most commonly used drug for treatment of LTBI is INH [13, 31]. In 1965, INH was recommended for the treatment of latent infection by the American Thoracic Society (ATS) [31]. Currently, it is the only FDA approved antibiotic for treatment of LTBI [37]. It is bactericidal (able to eliminate the bacteria), easily administered, relatively non-toxic, inexpensive, and highly effective, when taken properly [13, 31]. The preferred and most effective regimen is 9 months of INH alone; though 10-20% less effective, 6 months of treatment is also acceptable [2, 31]. Completion rates vary from 30-65%, which are largely attributed to the length of treatment and rare but severe side effects [13, 37]. Adverse effects include liver toxicity (hepatotoxicity), rash, fever, seizures, acne, arthritis, and peripheral neuropathies (numbness of the hands and feet) [13, 23, 31, 38]. Hepatotoxicity has been seen in approximately 1% of patients and 2% or higher in older individuals and those with preexisting liver disease [13].

RIFAMPIN

RIF is also recommended for the treatment of LTBI [2, 31, 37]. It is a rifamycin-derived drug that is also bactericidal [31]. For adults, a daily dose for 4 months is recommended; for children, a daily dose is recommended for 6 months [37]. This

treatment is administered if the individual has INH-resistance or is not able to tolerate INH [13, 31, 37]. Adverse effects include rash, flu-like symptoms, fever with chills, hepatotoxicity, orange discoloration of bodily fluids, and gastrointestinal problems [23, 31]. Drug toxicity in RIF-containing regimens is greater than regimens that do not contain RIF [17].

RIFAPENTINE

RPT is a rifampin-derived drug with a longer half-life and greater potency against *M.tb* than RIF [37, 38]. Though it should be noted that most *M.tb* strains resistant to RIF will also be resistant to RPT [37]. RPT has recently been recommended for use with INH [13, 37]. This regimen is taken once-weekly for 12 weeks; although it is only effective at preventing TB if administered by directly observed therapy (DOT) [13, 17, 37]. DOT is the observed ingestion of each dose of anti-TB medications; this process is meant to maximize completion of therapy and improve effectiveness of treatment [23, 31]. Patients taking INH-RPT are more likely to complete treatment compared to the 9 month INH regimen without DOT (82% versus 69%, respectively) [37, 38]. RPT and INH treatment was also shown to have lower rates of drug-related hepatotoxicity when compared to the INH-only treatment (0.4% versus 2.7%, respectively) [37, 38]. Discontinuation of treatment was also higher in patients taking the INH-only treatment (2.0% versus 0.3%) [38]. Currently studies are underway for the daily treatment regimen of RPT and INH for 1 month [17].

INH-RPT is recommended for LTBI cases who are otherwise healthy patients over the age of 12 and likely to develop active TB; additionally, it is recommended for HIV-positive patients who are otherwise healthy and not taking antiretroviral medications [37]. Further, INH-RPT can be administered to individuals with latent infection who are unlikely to complete the standard 9 months INH regimen or those who are in high-risk congregate settings [37]. INH-RPT is not recommended for children under the age of 2,

HIV-positive patients also taking antiretrovirals, pregnant women or women who may become pregnant during treatment, and cases believed to have INH- or RIF-resistant *M.tb* [37]. Since the INH-RPT treatment regimen is relatively new, a complete understanding of adverse effects is lacking and will only be fully known after wide implementation.

TREATMENT MONITORING

An initial clinical evaluation should be performed on individuals diagnosed with LTBI [31]. At this time, patients should be given information about possible treatment side effects, and advised to stop treatment and talk with a healthcare professional if side effects occur [31]. Since liver toxicity is an adverse effect associated with TB treatment, baseline laboratory testing may be conducted, especially for HIV-positive patients, pregnant women and women that delivered within 3 months, individuals with or at risk for chronic liver disease, and individuals who regularly use alcohol. Subsequently, monthly follow-up evaluations should be administered in patients receiving INH- or RIF-only; these evaluations include a physical assessment and the gathering of information regarding side effects that the patient may be experiencing [31].

ACTIVE TB

There are four first-line anti-TB drugs for the treatment of active TB disease; they include INH, RIF, ethambutol (EMB), and pyrazinamide (PZA) [2]. There are three treatment regimens for these first-line drugs as shown in Table 7. In all, 10 drugs are available for the treatment of active TB disease [2].

The typical treatment regimen for active TB is 6 months; 2 months of INH, RIF, EMB, and PZA following by 4 months of INH and RIF [2, 23]. For maximum efficacy and to reduce the risk of drug resistance, treatment for cases with active TB should be given under DOT [23]. Duration of treatment should be extended to 9 months in cases with cavitary lesions, continued sputum smear-positive after 2 months, extensive disease,

and immunosuppression [13, 23]. Figure 2 diagrams the various TB treatment regimens [23].

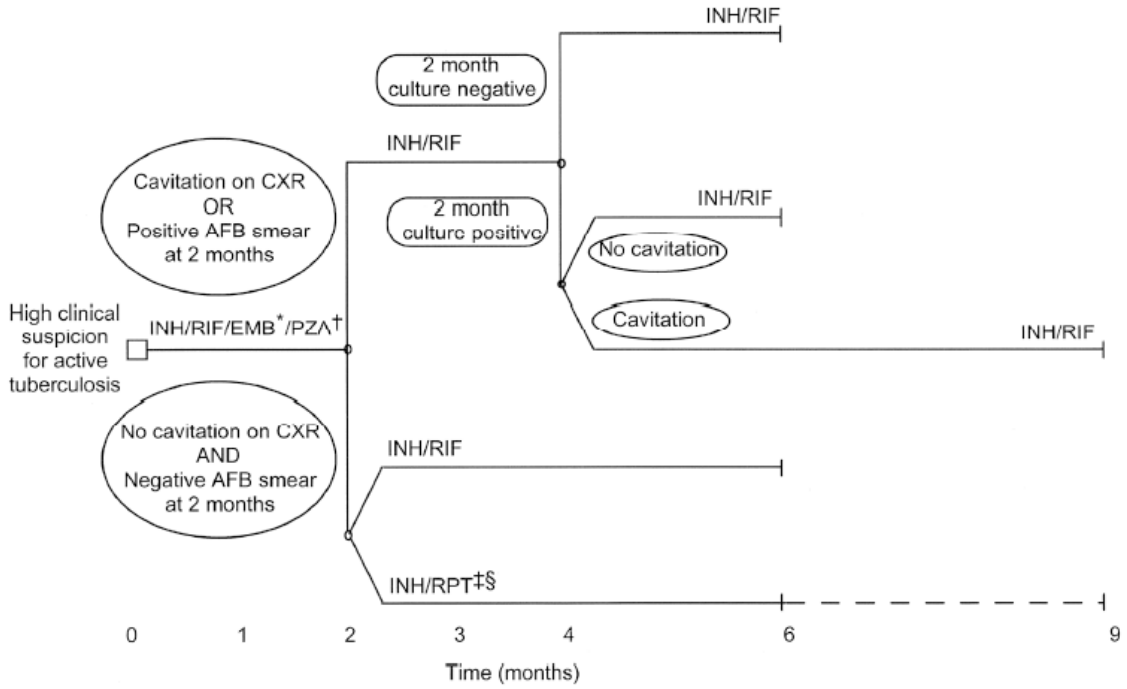
Table 7: TB Disease Treatment Regimens (Adapted from Reference [2])

	Preferred Regimen	Alternative Regimen	Alternative Regimen
Initial Phase	Daily INH, RIF, PZA, EMB* for 56 doses (8 weeks)	Daily INH, RIF, PZA, and EMB* for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)	Thrice-weekly INH, RIF, PZA, and EMB* for 24 doses (8 weeks)
Continuation Phase	Daily INH and RIF for 126 doses (18 weeks) or Twice weekly INH and RIF for 36 doses (18 weeks)	Twice weekly INH and RIF for 36 doses (18 weeks)	Thrice-weekly INH and RIF for 54 doses (18 weeks)

*Discontinue EMB if susceptibility is shown to first-line drugs

A recent modification to the regimen is substituting RPT for RIF during the last four months of treatment [13]. Although this substitution is not ideal for all cases, specifically HIV-positive patients or those with a AFB positive smear after 2 months [13].

There are many disadvantages to the current 6 month regimen. First, completion is relatively low with only 85% of patients completing therapy in the U.S.; second, there is a high rate of adverse effects; third, there is a risk of drug interaction between RIF and antiretrovirals, limiting the availability of treatment options in the HIV-positive populations; finally, the current standard of treatment is not effective for individuals with rifampin-resistance or multi-drug resistance [13]. Additional challenges include drug quality, ensuring administration of therapy, interruption of treatment, and reduced completion rates owing to long treatment periods [17].



*EMB may be discontinued when results of drug susceptibility testing indicate no drug resistance.
†PZA may be discontinued after it has been taken for 2 months (56 doses).
‡RPT should not be used in HIV-infected patients with tuberculosis or in patients with extrapulmonary tuberculosis.
§Therapy should be extended to 9 months if 2-month culture is positive.

Figure 2: Treatment algorithm for tuberculosis (Taken from Reference [23])

HIV/TB CO-INFECTION

TB treatment regimens for HIV-positive populations are similar to HIV-negative populations with a few exceptions [23]. HIV-positive individuals with advanced immunosuppression, which is a $CD4^+$ T cell count of less than 100, should not begin antiretroviral therapy (ART) until 2 to 4 weeks after TB therapy; in addition, administration of daily or thrice-weekly regimens are important to avoid the development of RIF-resistance TB [13, 17, 23, 39]. For HIV-positive cases with a $CD4^+$ T cell count of 100-200, ART should not begin until after the initial phase of TB therapy [23, 39]. For HIV-positive individuals with a higher than 200 $CD4^+$ T cell count, ART should not be started until week 8 or the continuation phase of TB therapy [13, 17, 39]. Cases with a

$CD4^+$ T cell count over 350, should wait to begin ART until after the completion of TB therapy [39]. DOT is also especially important in HIV-positive individuals [23].

There are disadvantages to the simultaneous treatment of HIV and TB; they include high pill burden which may affect adherence, higher toxicity and adverse effects that may be unknown, the development of immune reconstitution inflammatory syndrome (IRIS), and drug-drug interactions [40]. Treatment of HIV and TB increases the risk of IRIS [39]. IRIS results from the restored immune system's ability to produce an inflammatory response; symptoms range from mild and self-limiting (fever or cough) to severe (recurrent, new, worsening of initial clinical manifestations) and even death [39, 41]. The incidence of IRIS ranges from 11-71%; increased risk is associated with starting ART early during anti-TB treatment in HIV-positive individuals with a $CD4^+$ count less than 50 [41]. Drug-drug interactions between the anti-TB drug rifamycin and the antiretroviral drugs, protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs), which are shown in Table 8, have led to the development of new treatment guidelines and recommendations [3, 42]. For the treatment of active TB, a regimen lacking rifamycin may be employed if the patient is taking a complex combination of protease inhibitors or NNRTIs; although it is not optimal nor recommended [42]. For the treatment of LTBI in HIV-positive populations, INH does not interact with protease inhibitors or NNRTIs; thus the 9 month standard regimen is recommended [31, 42]. Ultimately, the management of care and treatment in HIV/TB co-infected patients should be directed by a highly experienced physician [42].

Table 8: Recommendations for Coadministering different Antiretroviral Drugs with the Antimycobacterial Drugs Rifabutin and Rifampin (Adapted from Reference [42])

Antiretroviral	Used in combination with rifabutin	Used in combination with rifampin
Saquinavir • Hard-gel capsule (HGC) • Soft-gel capsule (SGC)	Probably (if regimen also includes ritonavir) Probably	Possibly (if regimen also includes ritonavir) Possibly (if regimen also includes ritonavir)
Ritonavir	Probably	Probably
Indinavir	Yes	No
Nelfinavir	Yes	No
Amprenavir	Yes	No
Nevirapine	Yes	Possibly
Delavirdine	No	No
Efavirenz	Probably	Probably

TB IN CHILDREN

In infants and children less than age 4, treatment is initiated immediately after TB is diagnosed given the high risk of TB, especially disseminated TB and meningeal TB [23, 31]. The recommended regimens for latent and active TB in infants, children, and adolescents are similar to adults [23, 31]. For the treatment of LTBI, the American Academy of Pediatrics recommends the standard 9 month regimen or, if INH-resistance is suspected, 6 months of RIF treatment [31]. In active TB cases, EMB is not recommended unless INH-resistance is suspected [23, 31]. Although if a fourth drug is required, streptomycin, kanamycin, or amikacin can be utilized [23]. Studies have shown a success rate of over 95% and an adverse reaction rate of less than 2% in children that

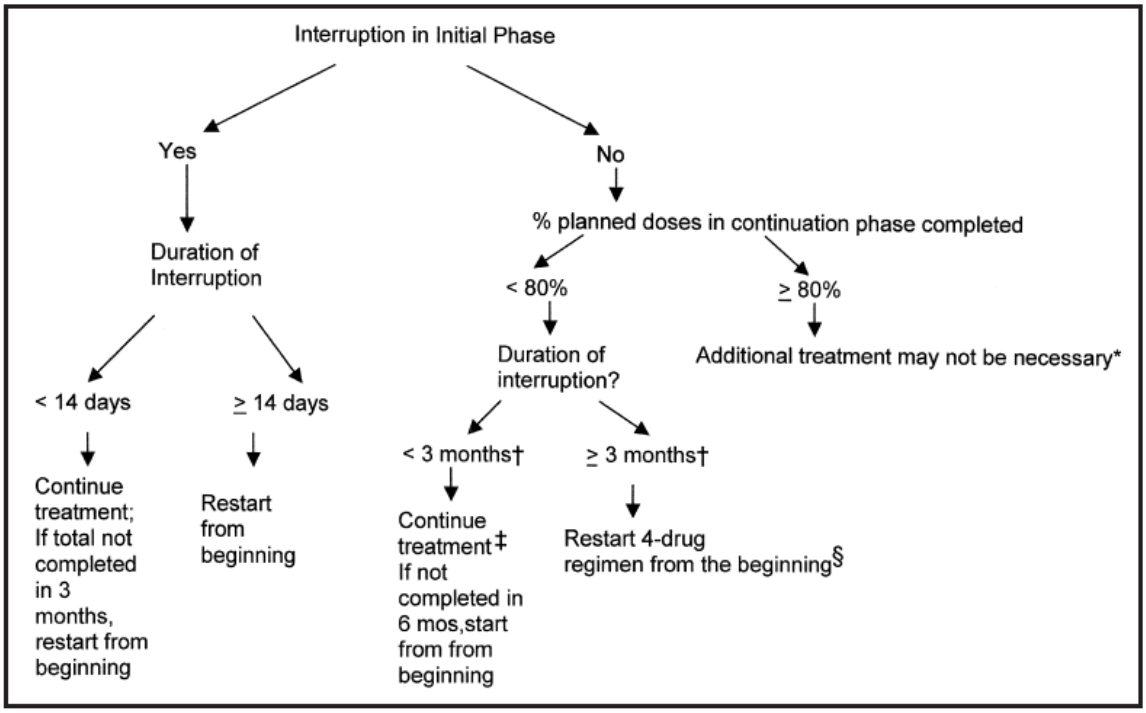
were administered the standard regimen of 2 months with INH, RIF, and PZA followed by 4 months with INH and RIF [23]. Since children are at increased risk of extrapulmonary TB, 9 to 12 months of therapy is recommended for disseminated TB and TB meningitis, [23]. DOT is also essential when treating children for TB [23].

TREATMENT COMPLETION & INTERRUPTION

Completion of TB therapy is determined by the number of doses ingested over a specific period of time, not length of treatment [2, 31]. Interruption of therapy is common in TB treatment because of the treatment duration required [23]. An expert in TB control should be consulted when determining whether interruptions in treatment should be continued or treatment be restarted; continuation of treatment following an interruption is based on bacterial load within the patient, point at which treatment was stopped, and length of interruption [23, 31]. It can be assumed that interruptions early during treatment and for longer durations will result in the need to restart treatment [23]. Detailed recommendations regarding treatment interruptions are not available and should be handled on a case-by-case basis [23]. The CDC has put forth an example by the New York City Bureau of Tuberculosis Control Clinical Policies and Protocols shown in Figure 3 [23]. Whether continuing or restarting treatment, DOT should be implemented; if DOT was already being used, additional measures should be employed to ensure that the patient completes treatment [23]. Treatment completion is vital to the elimination of TB; incomplete treatment may result in progression disease progression, transmission, and possibly death. Incomplete treatment may also result in the development of drug-resistant strains of *M.tb*.

Although several treatment options and anti-TB drugs are available, gaps still exist in providing an effective treatment for TB elimination. The development of a short-course treatment regimen with low toxicity drugs is urgently needed. Ultimately, these

improvements in treatment may increase completion rates, prevent treatment interruptions, and aid in the eradication of tuberculosis.



* Patients who were initially AFB smear-positive should receive additional therapy.
† Recheck smears and cultures (if positive, check drug susceptibility results). Start DOT if not already being used.
‡ If repeat culture is positive, restart four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, continue therapy to complete regimen within 9 months of original start date.
§ If repeat culture is positive, continue four-drug regimen while waiting for drug susceptibility results. If repeat culture is negative, consider stopping therapy if patient has received a total of 9 months of therapy.

Figure 3: Management of treatment interruptions (Taken from Reference [23])

CHAPTER 6 MDR- & XDR-TB

Drug-resistant TB has resulted from the misuse and mismanagement of antibiotics [2]. Humans are the primary cause of drug resistance, owing to the fact that: individuals do not take the drugs as directed, treatment is not completed, and healthcare providers prescribe the incorrect treatment/dose/duration [2]. Drug resistance may also be caused by the unavailability and poor quality of the antibiotics [2]. MDR-TB is defined as having "no previous history of TB disease and resistance to at least INH and RIF" [2, 8]. XDR-TB is defined as having "resistance to INH and RIF, plus any fluoroquinolone and at least one of the three injectable anti-TB drugs (i.e. amikacin, kanamycin, or capreomycin)" [2, 8].

EPIDEMIOLOGY

Worldwide, there were approximately 310,000 cases of MDR-TB in 2011; of which about 9% have XDR-TB [1]. Over half (60%) of MDR-TB cases are located in India, China, and the Russian Federation [1]. MDR-TB has been diagnosed in about 3.7% of new TB cases and 20% of previously treated TB cases [1]. The global percentage of new and previously treated TB cases with MDR-TB are shown in Illustration 3 and 4 [1]. Since the availability of drug-susceptibility testing labs and equipment are scarce in countries where TB is endemic, assessing the full burden of drug-resistance is difficult [6, 17].

In the U.S., there were 98 cases of MDR-TB in 2011; 81 of these cases (82.7%) occurred primarily among foreign-born individuals [8]. The same year, 6 cases of XDR-TB were reported, an increase from previous years (5 cases in 2008, 0 cases in 2009, and 1 case in 2010); of the 12 cases between 2008 and 2011, 11 occurred among foreign-born individuals [8].

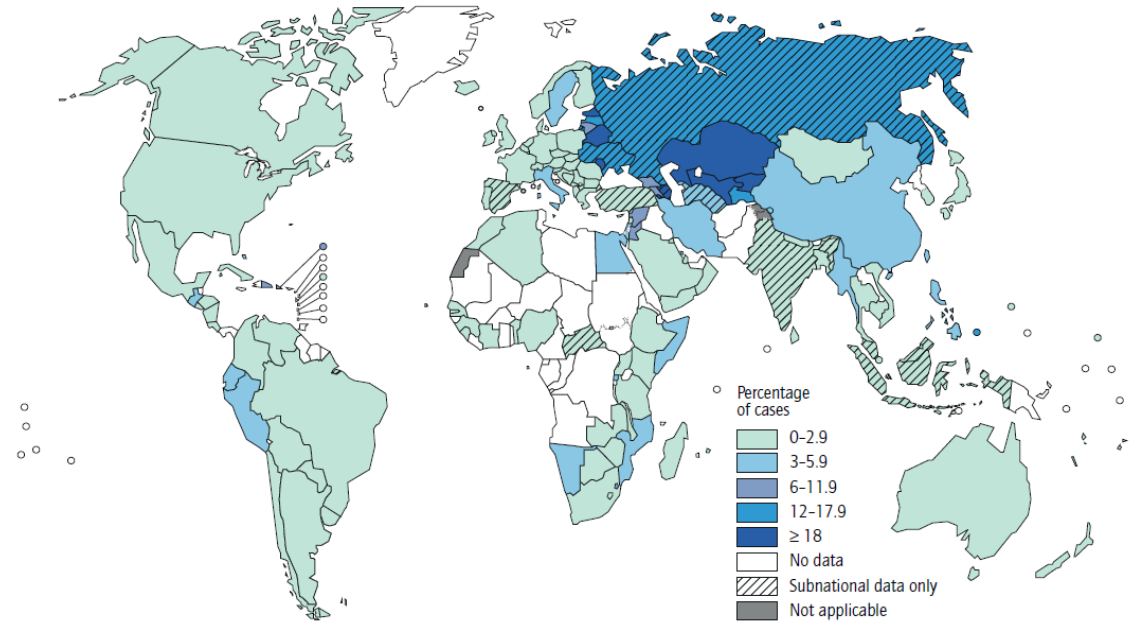


Illustration 3. Percentage of new TB cases with MDR-TB, 2011 (Taken from Reference [1])

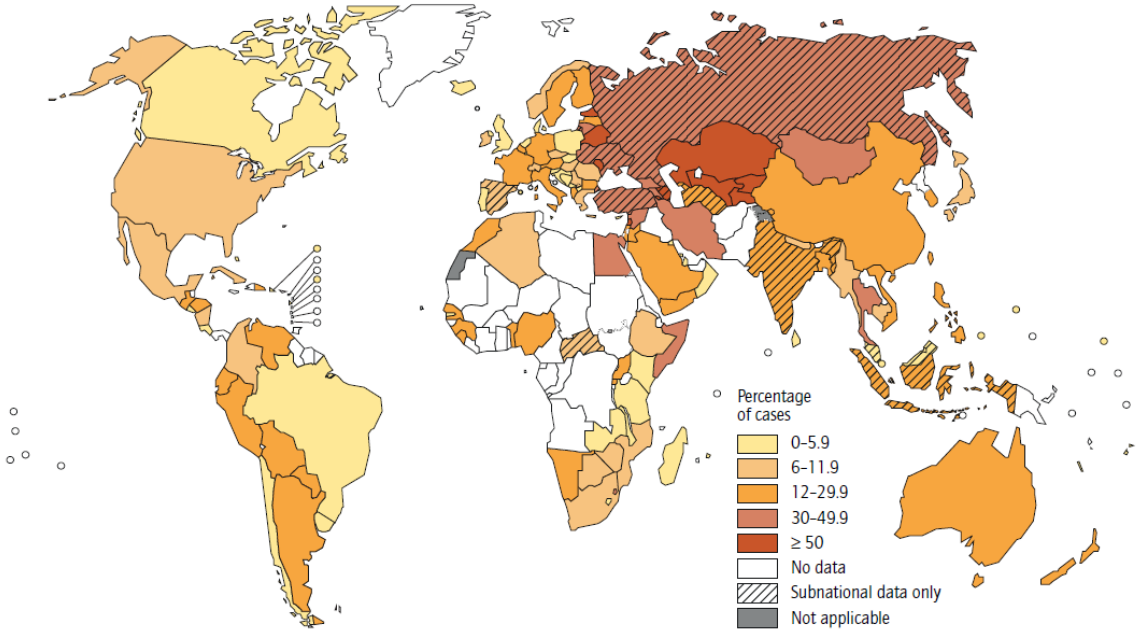


Illustration 4. Percentage of previously treated TB cases with MDR-TB (Taken from Reference [1])

DIAGNOSTICS

Determination of drug-susceptibility from *M.tb* infected individuals involves determining the growth level of *M.tb* in the presence of anti-TB drugs at various concentrations within culture [30]. This technique is time-consuming, technically demanding, not reproducible, and requires at least 21 days for results [30]. Fluorescent dyes or radioisotopic detection within liquid culture have been introduced for detection of drug-susceptible *M.tb*; however this method requires well-trained personnel and runs the risk of sample contamination [30]. Microscopic observation drug susceptibility (MODS), which also uses liquid culture, has also been introduced for the diagnosis of drug-susceptibility [17, 30, 43]. MODS provides results quicker with lower cost and increased sensitivity when compared to the standard drug-susceptibility technique [43]. The disadvantages of MODS are it requires higher containment facilities, an experienced microbiologist, and samples are at risk of contamination [30].

As previously mentioned, the Xpert MTB/RIF is new diagnostic tool in the detection of *M.tb* and drug-resistant TB. More specifically, it provides information about resistance to rifampin from sputum samples [30]. The WHO has recently provided recommendations regarding its use: (1) Xpert MTB/RIF should be the initial diagnostic method in individuals with suspected drug-resistance or HIV-associated TB and (2) Xpert MTB/RIF may be used as a subsequent diagnostic method in countries where MDR and/or HIV infection is less prevalent [30, 44]. However, given the cost of the instrument, cartridges required for it use, and regular maintenance for its proper function widespread use may prove to be difficult [30].

As with latent and active TB infection, diagnostic tools are required for the detection of drug-resistant *M.tb* strains. Given the high rate of mortality among populations with MDR- and XDR-TB and the difficulty in identifying such populations, a cost-effective molecular-based diagnostic tool may prove to be beneficial. Further, with

the addition of HIV-associated drug-resistant *M.tb*, rapid detection may provide the much needed relief of mortality among such populations.

CURRENT TREATMENTS

Individuals diagnosed with drug-resistant TB must be referred to a specialist for consultation on appropriate treatment regimens [23]. When an individual is initially diagnosed with TB, treatment with the standard regimen should begin immediately; the regimen should be tailored to each patient dependent on the results of the drug-susceptibility testing [17].

Guidelines have been established by the WHO regarding recommendations on the composition of a multi-drug resistant regimen:

- during the intensive/initial phase of treatment, at least four second-line drugs should be included along with PZA;
- the regimen should include PZA, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and cycloserine (or para-aminosalicylic acid);
- no more than four second-line drugs should be administered to patients with XDR-TB, unless the effectiveness of other drugs is uncertain; and
- group 5 drugs can be used although they should not be included in the standard regimen [45].

Duration of therapy should be 8 months of intensive phase treatment followed by a continuous phase [45]. For patients who have not received previous multi-drug resistant treatment, duration of therapy should be a total of 20 months; for patients who have received previous multi-drug resistant treatment, duration of therapy should be a total of 30 months [45]. For individuals with HIV infection, ART should be administered regardless of CD4 level within the first 2 months of initiating anti-TB therapy [45]. XDR-TB can also be difficult to diagnose, manage, and treat; especially in developing

countries where TB is endemic [17]. Among HIV-positive patients, XDR-TB can have a mortality rate as high as 98% [17].

NEW TREATMENTS

Currently there are several trials ongoing to identify anti-TB drugs for the treatment of drug-resistant TB. The FDA has recently approved bedaquiline for the treatment of MDR-TB; bedaquiline has been shown to be effective and cause conversion to culture-negativity by 8 weeks of treatment [17]. Studies involving combination treatment are also underway. A three-drug combination of moxifloxacin, PZA, and PA-824 has been shown to have bactericidal effects within 14 days similar to the 4-drug standard treatment [17, 46]. For the treatment of XDR-TB, linezolid has been shown to achieve culture-negative conversion [17, 47]. Additional clinical trials are shown in Appendix B.

Along with low cost, highly effective diagnostics, effective treatments are also needed in the fight against drug-resistant TB. Reduced treatment lengths and low toxicity would allow for improved completion rates and reduce the global health burden of drug-resistant TB. This may be especially important given the recent emergence of a new strain of drug-resistant TB, totally drug-resistant (TDR)-TB, which has been shown to be resistant to all first- and second-line drugs [48, 49].

CHAPTER 7 PREVENTION & CONTROL IN THE U.S.

In the U.S., TB control is aimed at reducing morbidity and mortality [10]. This goal is being achieved through four strategies: (1) rapid detection, diagnosis, and reporting of individuals with TB, (2) rapid identification of contacts of individuals with TB, (3) targeted testing and treatment of high-risk individuals within the general population, and (4) identification of high-risk settings and implementation of infection-control measures [10, 50]. Ultimately, these strategies will reduce the risk of transmission and prevent disease progression.

CASE DETECTION & MANAGEMENT

Case detection is important for the control of TB. The process of case detection includes presentation of disease at a healthcare facility, evaluation of the suspected case, confirming diagnosis, and case reporting [10]. Identifying cases requires educated medical personnel that are able to recognize clinical symptoms and individuals at risk of TB [10]. A few general guidelines in TB case detection are shown in Table 9. After identification of suspected TB cases, case management is the process taken by healthcare professionals and public health agencies to ensure a case is properly treated [10].

Case detection can also occur through screening, this is known as active TB case finding [10]. Active TB case finding is typically seen with immigrants and refugees with Class B1 or B2[1] TB notification status, during TB outbreaks, with working populations at risk of TB, and in certain congregate settings (e.g. jails and prisons) [10]. Various studies have shown screening to be an effective method of case finding [10].

Case detection and screening are essential TB prevention and control measures. The ability of trained healthcare professionals to identify the signs, symptoms, and risk

[1] Suspected of having active noninfectious (Class B1) or inactive (Class B2) TB notification status

factors of TB will determine whether progression or transmission can be prevented. For this these strategies to be effective, education of healthcare personal and public health officials is crucial.

Table 9: Guidelines for evaluating pulmonary TB in adults in five clinical settings (Adapted from Reference [10])

Patient	Evaluation
Any patient with a cough of ≥2-3 week duration, with at least one additional symptom (fever, night sweats, weight loss, or hemoptysis)	Chest radiograph: if suggestive of TB, collect three sputum specimens for AFB smear microscopy and culture
Any patient at high risk for TB with an unexplained illness, including respiratory symptoms, of ≥2-3 week duration	Chest radiograph: if suggestive of TB, collect three sputum specimens for AFB smear microscopy and culture
Any patient with HIV infection and unexplained cough and fever	Chest radiograph, and collect three sputum specimens for AFB smear microscopy and culture
Any patient at high risk for TB with a diagnosis of community-acquired pneumonia who has not improved after 7 days of treatment	Chest radiograph, and collect three sputum specimens for AFB smear microscopy and culture
Any patient at high risk for TB with incidental findings on chest radiograph suggestive of TB even if symptoms are minimal or absent	Review of previous chest radiographs if available, three sputum smear specimens for AFB smear microscopy and culture

CONTACT INVESTIGATIONS

Contact investigations are another essential part of TB control and prevention. Contact investigations (1) identify, diagnose, and treat individuals exposed to a TB case (index case) and (2) prevent the further progression and transmission of *M.tb* in contacts [10, 51]. Table 10 lists characteristics of the index case that increases the risk of transmission [51].

Table 10: Characteristics of the index case and behaviors associated with increased risk for tuberculosis transmission (Taken from Reference [51])

Characteristic
Pulmonary, laryngeal, or pleural TB
AFB positive sputum smear
Cavitation on chest radiograph
Adolescent or adult patient
No or ineffective treatment of TB disease
Behavior
Frequent coughing
Sneezing
Singing
Close social network

INDEX PATIENT

Initiation of a contact investigation should be considered based on the site of disease (pulmonary, laryngeal, or pleural TB), sputum smear or NAA results, and chest radiograph findings as shown in Figure 4 [10, 51].

During a contact investigation, the index case will be interviewed for information regarding characteristics of their disease (i.e. site of disease and symptoms), onset of illness, names of contacts, locations of transmission and exposure, and current treatment regimen [51]. The infectious period also needs to be determined to identify which contacts are at greatest risk; in general, it is recommended that the infectious period is dated 3 months prior to the diagnosis of TB [10, 51]. Table 11 describes characteristics that would warrant the start of an infectious period. An infectious period ends when treatment has been successfully administered for more than 2 weeks, symptoms have

decreased, clinical response has improved (e.g. reduced AFB in sputum smear), and all contacts have been identified, evaluated, and started on treatment if needed [10, 51]. Ultimately, quick identification of an index patient will allow for rapid identification of contacts to prevent further transmission.

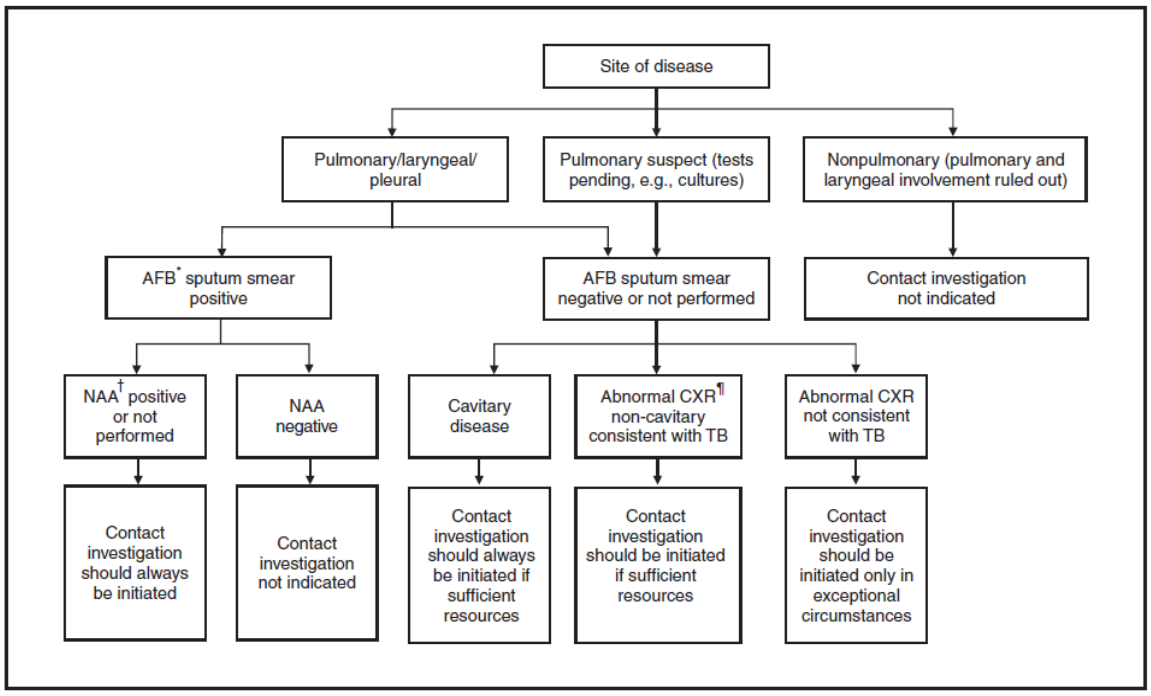


Figure 4: Decision to initiate a TB contact investigation (Taken from Reference [51])

Table 11: Guidelines for estimating the start of the infectious period of persons with TB, by index case characteristics (Taken from Reference [51])

Characteristics			Recommended initiation of infectious period
TB Symptoms	AFB Sputum Smear Positive	Cavitary Chest Radiograph	
Yes	No	No	3 months prior to symptom onset or first positive manifestation (e.g. abnormal chest radiograph) consistent with TB disease, whichever is longer
Yes	Yes	Yes	3 months prior to symptom onset or first positive manifestation consistent with TB disease, whichever is longer
No	No	No	4 weeks prior to suspected diagnosis
No	Yes	Yes	3 months prior to positive manifestation consistent with TB

FIELD INVESTIGATION

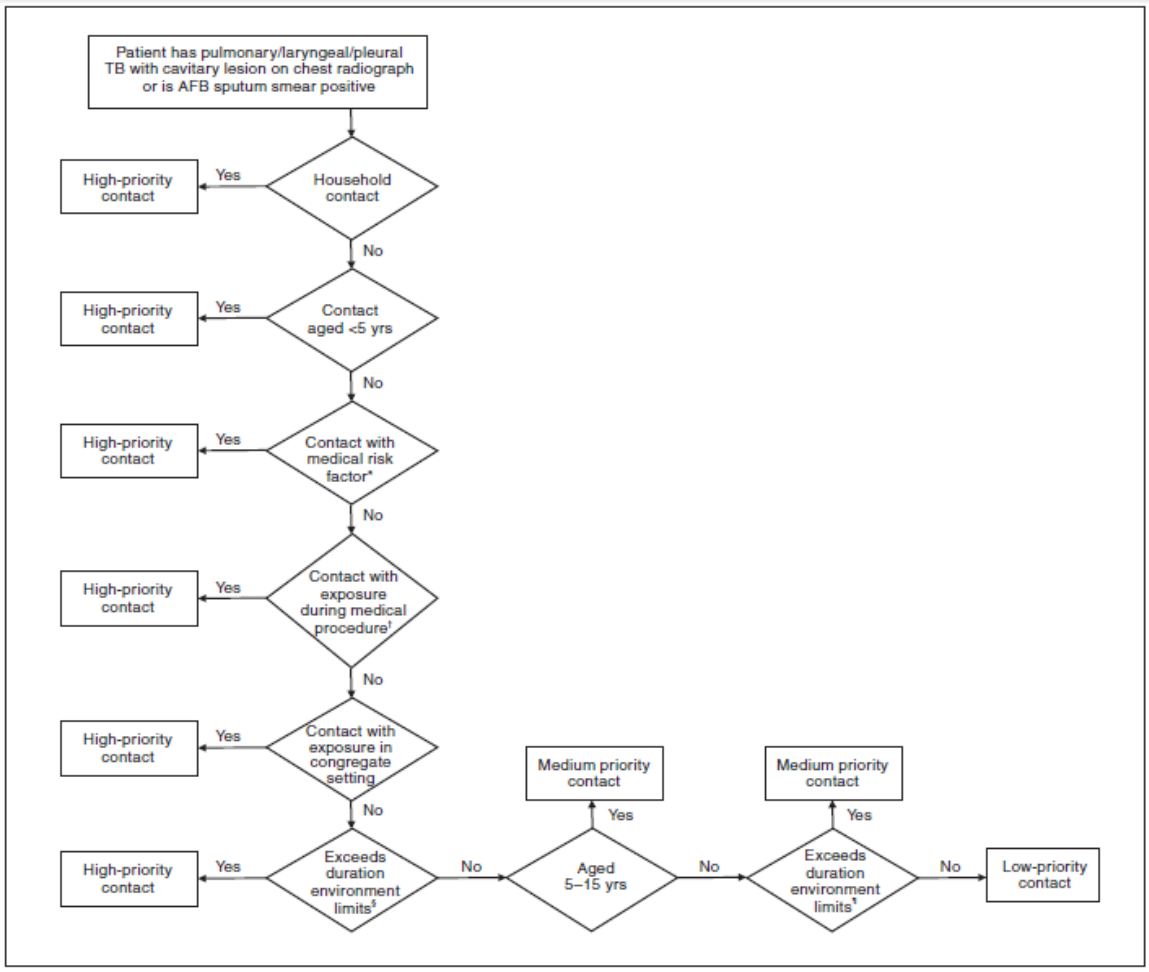
Following index case interview, site visits or visits to areas where transmission and exposure occurred need to be performed [10, 51]. Site visits should be made less than 3 days after the first interview with the index case [51]. These visits allow for re-interviewing of the index case, interviewing and testing of contacts by TST, collection of sputum samples, observing for symptoms of TB within contacts, scheduling clinic visits and making referrals, identifying potential new contacts, and providing education about TB and the contact investigation [51]. Site visits also allow the investigator to observe the physical environment where transmission occurred and gather information about the conditions such as crowding, room size, ventilation, and airflow [10, 51]. During interviews, it is critical that the investigator build rapport and trust with the case and

contacts; this will allow the case and contacts to feel more comfortable disclosing information which may be important for the investigation [10, 51].

PRIORITY ASSIGNMENT OF CONTACTS

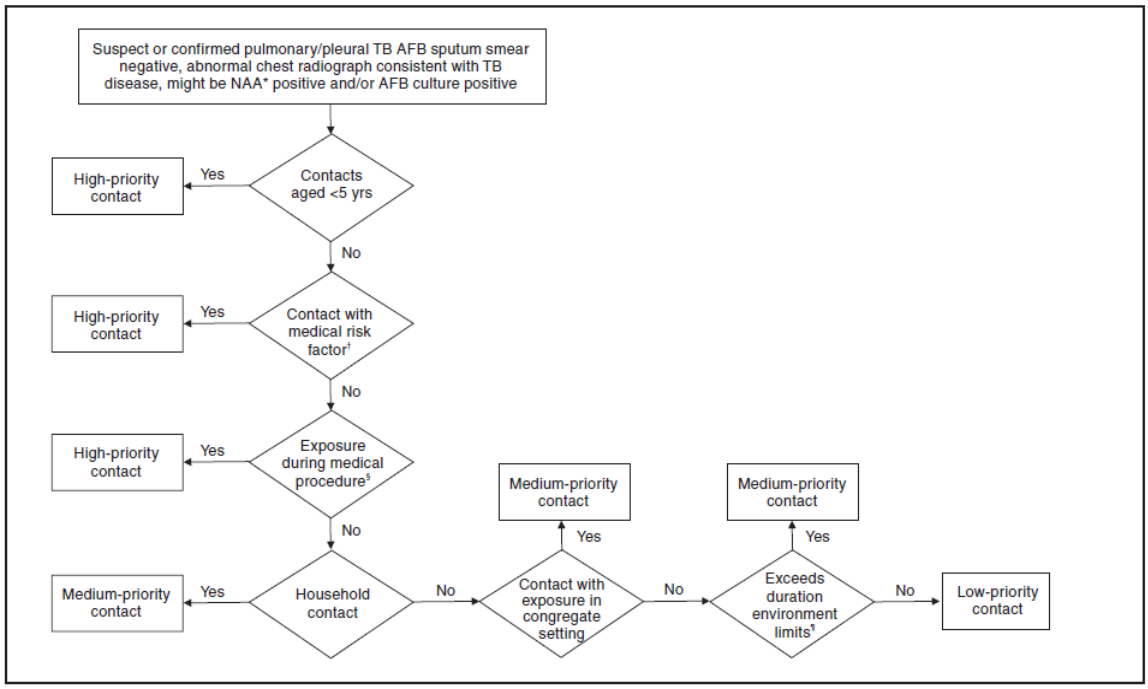
Priority is assigned to contacts to determine if there is an immediate risk of TB progression, and treatment needs to be administered; priority levels include high-, medium-, and low-priority [51]. Assignment of priority to contacts is dependent upon various factors, including the extent of disease in the index case, the length of interaction between the index case and contact, and air circulation in the environment where transmission occurred [51]. Medical conditions, which can impair the immune response and increase a contact's risk of infection, also contributes to the priority assignment [51]. Other factors that may contribute to priority assignment but have yet to be understood include virulence of the *M.tb* strain, previous infection, and predisposition of the contact to infection [51].

The highest priority should be assigned to contacts with a high-risk of progression to TB disease [10, 51]. Factors in a contact that may increase the risk of progression are age and immune status; children under 5 years of age and individuals with HIV infection [10, 51]. The contact's risk of infection and assignment of priority is also dependent upon the intensity (how much), frequency (how often), and duration (how long) of exposure [10, 51]. Exposure includes air volume, exhaust rate, and circulation within a closed area [51]. A method that has been used to determine exposure is categorizing the environment by size: "1" being a vehicle, "2" being a bedroom, "3" being a house, and "4" being larger than a house [51, 52]. Figures 5-7 show priority classification of contacts based on the index case's characteristics, the contacts susceptibilities/vulnerabilities, and exposure circumstances [51]. Utilization of the recommended criteria for assignment of priority will allow for precise identification of high- and medium-priority contacts to prevent progression to disease and any further transmission.



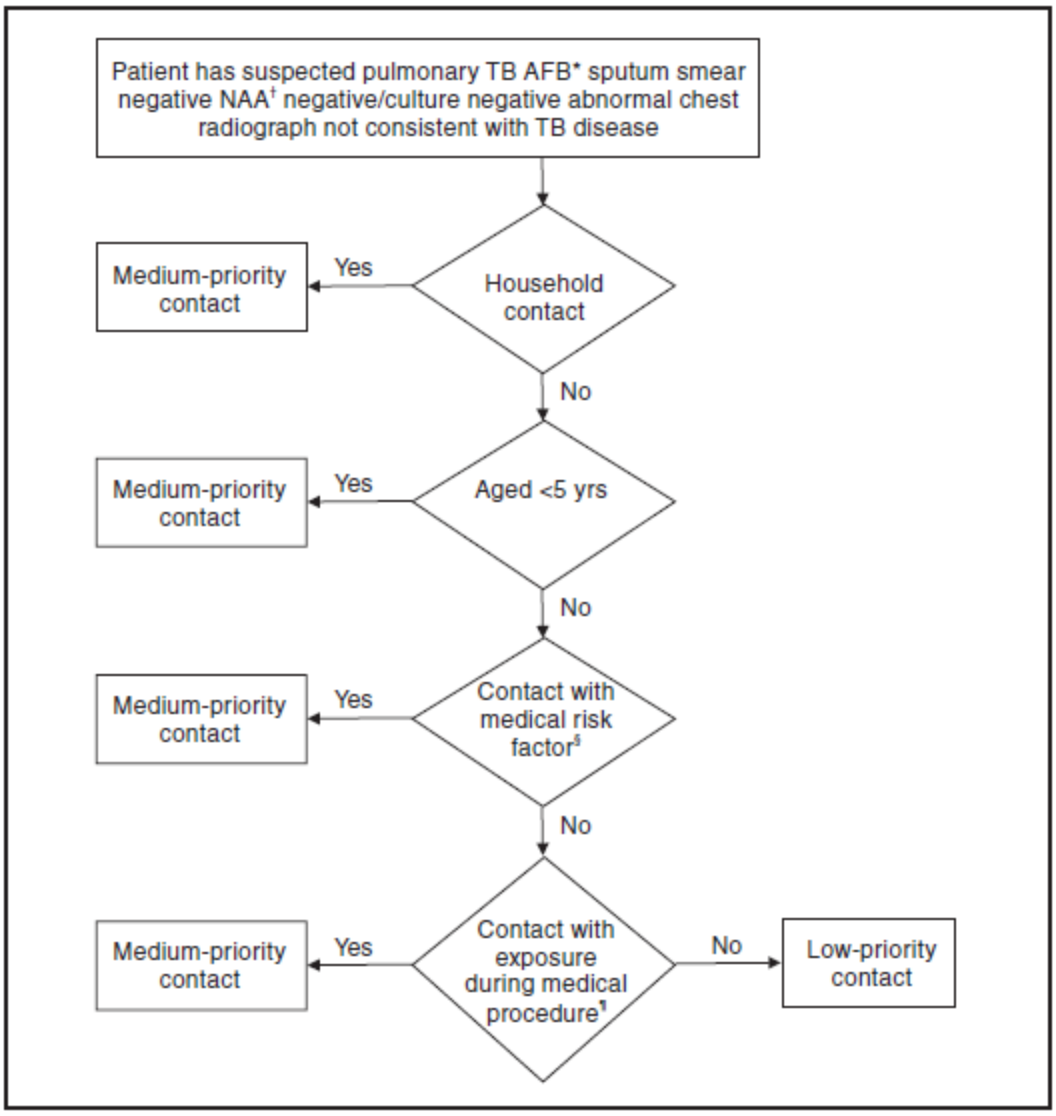
* Human immunodeficiency virus or other medical risk factor.
† Bronchoscopy, sputum induction, or autopsy.
§ Exposure exceeds duration/environment limits per unit time established by the health department for high-priority contacts.
¶ Exposure exceeds duration/environment limits per unit time established by the health department for medium-priority contacts.

Figure 5: Priority of contacts exposed to cases with AFB sputum smear-positive or cavitary TB (Taken from Reference [51])



* Nucleic acid assay.
† Human immunodeficiency virus or other medical risk factor.
§ Bronchoscopy, sputum induction, or autopsy.
¶ Exposure exceeds duration/environment limits per unit time established by local TB control program for medium-priority contacts.

Figure 6: Priority of contacts exposed to cases with AFB sputum smear-negative TB (Taken from Reference [51])



* Acid-fast bacilli.
† Nucleic acid assay.
§ Human immunodeficiency virus infection or other medical risk factor.
¶ Bronchoscopy, sputum induction, or autopsy.

Figure 7: Priority of contacts exposed to cases with suspected TB with abnormal chest radiograph not consistent with TB disease (Taken from Reference [51])

TESTING & TREATMENT OF CONTACTS

A TST should be administered to high- and medium-priority contacts, if there is not a previously documented positive result or previous TB disease [10, 51]. A TST for a high-priority contact should be performed within 7 days; while a TST for a medium-priority contact should be performed within 14 days [51]. An induration greater than 5 is indicative of a positive TST result [10, 51]. TST positive contacts will need further testing including a chest radiograph and medical evaluation [10]. It is important to note that an initial negative TST does not exclude the contact from possibly being infected because there is a window period between infection and detection by TST; thus the CDC and National Tuberculosis Controllers Association (NTCA) recommend a second TST be administered 8 to 10 weeks after the last exposure with the index case [10, 51]. Contacts with a second TST that is positive (induration of greater than 5 mm) or reporting of TB-like symptoms should undergo additional testing beginning with a chest radiograph [10, 51]. A TST positive contact with a normal radiograph will be referred for LTBI treatment; a TST positive contact with an abnormal radiograph will be referred for further evaluation for TB disease [10].

For children under the age of 5 and immunocompromised contacts, a full diagnostic medical exam is recommended, including chest radiograph, regardless of TST result [10, 51]. If the TST induration in these populations is less than 5 mm and the time since last exposure is less than 8 weeks, LTBI treatment is recommended following exclusion of active TB disease [10, 51]. In children, if the second TST is negative, treatment can be stopped; if it is positive, treatment for LTBI should be completed [10, 51]. In immunocompromised contacts, if the second TST is negative, it is recommended that treatment for LTBI still be completed [10, 51]. Completion of treatment in HIV-positive, TST negative contacts is based on two factors: (1) the frequency, duration, and intensity of exposure to the index case, and (2) likelihood that transmission from the

index patient to the contact occurred [51]. The evaluation, treatment, and follow-up of children under age 5 and immunocompromised contacts are further shown in Appendix C and D, respectively.

Immunocompetent adults and children over the age of 5 with a high- or medium-priority can be evaluated and treated based on the criteria in Figure 8; while contacts with low priority can be evaluated and treated as described in Figure 9 [51]. For contacts with documentation of previous positive TST, evaluation and treatment should be followed as shown in Figure 10; while contacts with previous positive TST and no documentation can follow the evaluation and treatment in Figure 9 [51]. Rapid identification of contacts with TB infection allows for immediate treatment and aids in preventing progression to TB disease.

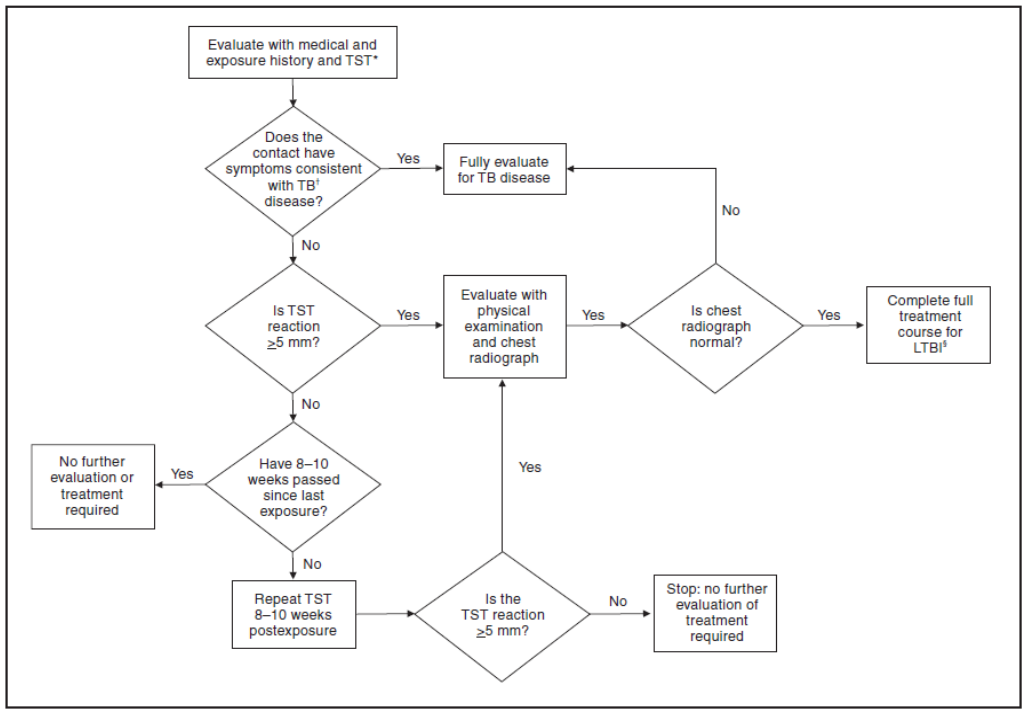


Figure 8: Evaluation, treatment, and follow-up of immunocompetent adults and children aged ≥5 years with high- and medium priority (Taken from Reference [51])

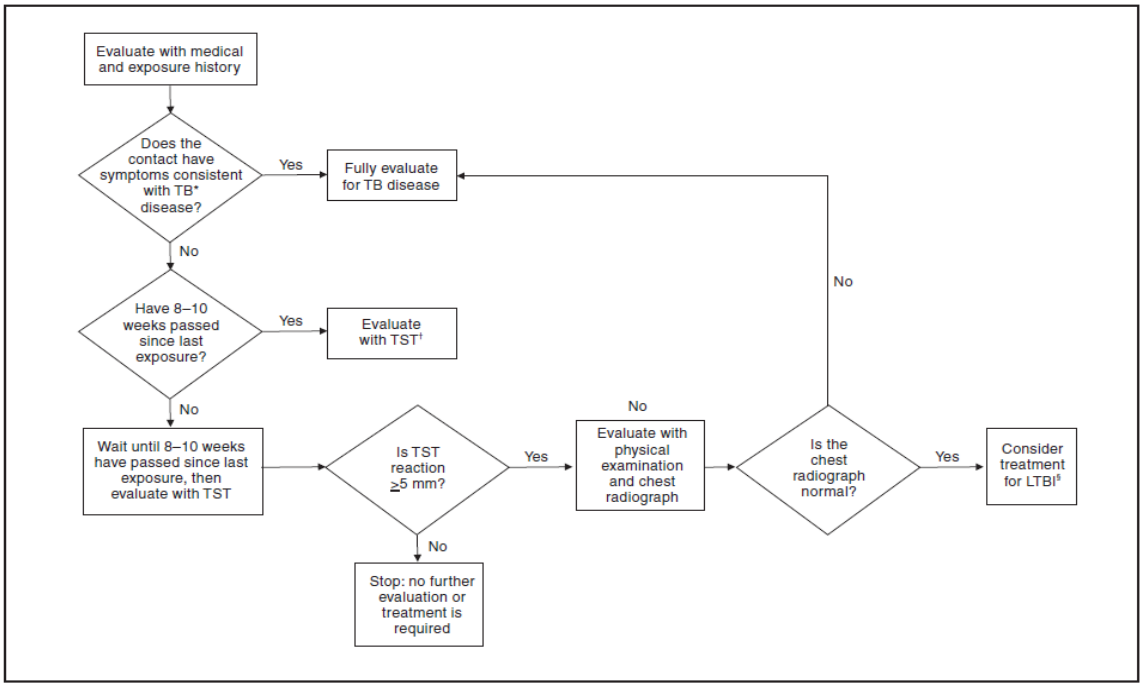


Figure 9: Evaluation, treatment, and follow-up of low-priority contacts (Taken from Reference [51])

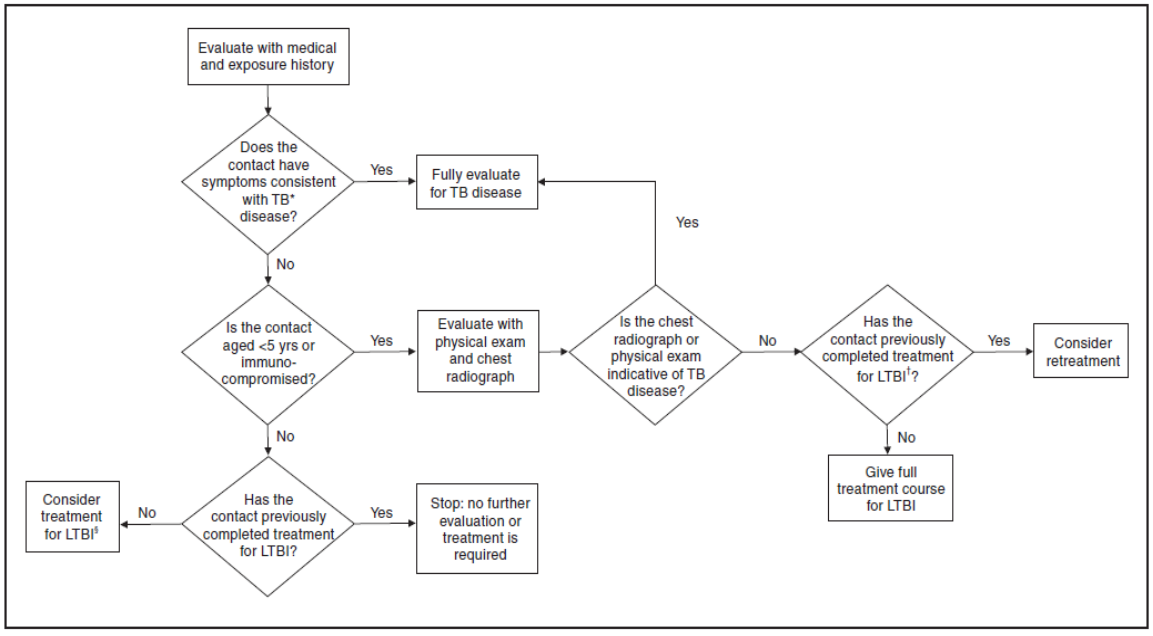


Figure 10: Evaluation, treatment, and follow-up of contacts with a documentation of previously positive TST (Taken from Reference [51])

EXPANDING A CONTACT INVESTIGATION

A contact investigation may be expanded to lower-risk contacts once the investigation of high- and medium-priority contacts is complete. Factors that warrant expanding a contact investigation include high-priority contacts experiencing an unexpected increase in TB disease, low-priority contacts developing TB disease, TST conversions (i.e. negative to positive skin test), and secondary transmission [10, 51].

IDENTIFICATION OF HIGH-RISK POPULATIONS

Elimination of TB in the U.S. requires targeting individuals that are at high-risk of acquiring LTBI or developing TB disease and treating individuals who have LTBI [10, 31]. Two approaches have been developed to increase targeted testing and treatment: (1) clinic-based testing, which identifies individuals with a medical condition (e.g. HIV infection or diabetes mellitus) that may increase their risk of acquiring TB and (2) program-based testing, which targets certain populations that have an increased LTBI prevalence (e.g. foreign-born populations or homeless) or are at an increased risk of developing TB disease [10].

Clinic-based testing is seen with individuals that are regularly seen by a healthcare professional [10]. This approach requires well-trained healthcare personnel that are able to identify risk factors and symptoms for TB infection [10]. Program-based testing assumes that high-risk populations have been separated based on incidence and prevalence of TB, risk for progressing to TB disease if exposed, likelihood of accepting and adhering to treatment, and ability to access the population [10]. Table 12 groups high-risk populations into three tiers based on the criteria described above. Tier 1 includes populations that would have a high prevalence of LTBI and TB disease; they would also be easily identifiable, accessed, and followed and as a result, they would be most likely to complete treatment [10]. Tier 2 includes populations also relatively easy to identify and access, although treatment completion might be lower [10]. Tier 3 includes

foreign-born populations with a high prevalence of TB that recently arrived in the U.S.; identification of these populations could prove to be difficult since reaction to the TST could be from either the BCG vaccine or TB infection; additionally access to health care, language barriers and inability to provide education would be difficult and result in low treatment completion rates [10]. Given the high prevalence of LTBI in these high-risk populations, specifically the increasing incidence in foreign-born and HIV-positive populations in the U.S., identification and treatment of these individuals is important in elimination of TB within the U.S.

Table 12: Priority of subpopulations and sites for targeted treatment of LTBI (Taken from Reference [10])

Tier 1
Individuals working in or served by clinics or community health organizations providing care to HIV-infected persons
Prisoners
Legal immigrants and refugees with Class B1 and B2 TB notification status
Recently-arrived refugees
Other defined groups in congregate living facilities
Tier 2
Jail detainees
Individuals working or living in homeless shelters
Immigrants reporting for adjustment of status
Tier 3
Other foreign-born populations at high risk (i.e. immigrated within 5 years from countries with a high incidence of TB)

INFECTION-CONTROL IN HEALTHCARE FACILITIES

M.tb transmission is a serious threat in healthcare facilities and HCWs are at an increased risk for TB infection [2, 53]. Transmission can occur through close contact with TB infected patients and procedures that generate or produce aerosols including bronchoscopy, endotracheal intubation, suctioning, autopsy, sputum induction, or inducing coughing [53]. Implementation of TB control measures is important to prevent transmission among HCWs and patients. TB prevention and control in healthcare settings includes: (1) implementation of infection-control programs that involve detection of suspected TB cases, immediate isolation, and administration of proper treatment regimen; and (2) identification and testing of *M.tb* exposed HCWs [2, 50, 53].

INFECTION-CONTROL

Infection-control programs are composed of a three level hierarchy: administrative measures, environmental controls, and respiratory protection [2, 53]. Administrative measures are the primary and most important infection-control measures, they are implemented to reduce exposure of uninfected individuals to patients suspected of having TB disease [2, 10, 53]. Control measures include screening for suspected TB cases during admission, isolation of suspected TB cases, diagnosing TB infection, and starting treatment [10]. Environmental controls prevent the risk of *M.tb* dissemination by using airborne precautions including airborne infection isolation rooms (AII room), exhaust ventilation, diluting and exchanging the air, and using a high-efficiency particulate air (HEPA) filter to clean the air [2, 10, 53]. Respiratory protective equipment prevents HCWs from exposure in high-risk areas; this measure involves training HCWs on the use of respiratory protection and training patients on respiratory hygiene and cough etiquette as shown in Appendix E [2, 10, 53].

TB SCREENING CLASSIFICATION

Healthcare facilities are classified according to TB screening risk: low risk, medium risk, and current transmission possible [10, 53]. HCWs in settings with low risk will not be exposed to TB patients; screening for low risk HCWs includes baseline TST upon start of employment and repeat TST when *M.tb* exposure is suspected; if baseline or subsequent TST is positive, a chest radiograph will be administered to exclude TB disease [10, 53]. HCWs in settings with medium risk will possibly be exposed to TB patients or specimens; screening for medium risk HCWs includes baseline TST upon start of employment and annual TB screening; if a TST is positive, a chest radiograph will be administered to exclude TB disease [10, 53]. For HCWs with an initial TST that is positive, they will undergo education about TB disease symptoms and receive an annual symptom screening rather than repeated chest radiograph [53]. These HCWs are advised to immediately report TB disease symptoms to the occupational health clinic [53]. HCWs in a setting with current transmission possible includes areas where person-to-person transmission has occurred within the past year [10, 53]. Person-to-person transmission includes TST conversion within a group, increased rate of conversion, confirmed TB disease within a HCW, HCWs or a patient with TB disease from an unknown origin, or identical *M.tb* strain within patients or HCWs [10, 53]. Screening for HCWs in possible transmission settings includes repeated testing, every 8 to 10 weeks, until evidence of transmission is eliminated; once the transmission has ceased a medium risk screening will be implemented [53]. TB screening classifications are important for infection-control measures; these control measures assist in preventing transmission or further transmission of TB and protecting patients and HCW.

MANAGING PATIENTS WITH TB DISEASE

Individuals suspected or confirmed to have TB disease need to be identified and separated from other patients, immediately evaluated by a medical professional and

transferred to an AII room where HCWs follow airborne precaution procedures; during isolation, suspected TB patients should wear a surgical mask and follow respiratory hygiene and cough etiquette procedures [53]. AII rooms should be for a single-patient with controlled entry to reduce the risk of transmission; additionally all HCWs and visitors should be required to wear at least an N95 disposable respirator [53]. Standard treatment should be started immediately for patients with confirmed or suspected TB disease [53]. Precautions can cease when the patient is no longer infectious or an alternative diagnosis has been made or the patient has three consecutive AFB negative sputum smears, each sample is collected 8 to 24 hours apart with one collected in the early morning allowing secretions to pool overnight [10, 53]. Prompt identification and isolation of suspected TB cases, is important to reduce the risk of transmission to other patients and HCWs.

COORDINATION WITH LOCAL OR STATE HEALTH DEPARTMENTS

Confirmation or suspicion of an individual with TB disease requires immediate notification to the local or state health department [53]. This allows for immediate follow-up and continuation of treatment by DOT after the patient is discharged; additionally, this allows the health department to conduct a contact investigation [53].

CHAPTER 8 GLOBAL PREVENTION AND CONTROL

Worldwide, TB prevention and control needs to be a coordinated effort among international organizations, national agencies, non-governmental organizations (NGOs), local health departments, and public and private healthcare professions. New strategies are being developed and implemented to reduce the global burden of TB. Identification and treatment of TB infected individuals in each country is important for control throughout the world and will aid the eradication of TB.

CURRENT STRATEGIES

BCG VACCINE

BCG vaccination is currently used throughout the world to protect against TB infection; although its protective effects are known to wane over time [1, 31]. BCG is an attenuated vaccine that was developed in 1908 by Albert Calmette and Camille Guérin [4, 50]. In 1921, it was first administered in humans; by 1924, over 600 infants had been vaccinated with the BCG vaccine [4, 50]. BCG vaccination has been shown to be protective, particularly in infants, from severe forms such as TB meningitis and miliary TB [1, 4]. Studies on the efficacy of BCG show varying rates from 0 to 80%; however, a recent meta-analysis demonstrated the vaccine to be approximately 50% protective [4, 54]. Over time the protective effects of BCG vaccination wanes and after 10 years may no longer persist within the individual [31, 50]. In the U.S., BCG vaccination is not recommended, because the risk for *M.tb* infection is low, the varying effectiveness in preventing TB, and reactivity with the TST [10, 50]. Given its variable protective effects, it is evident that a new vaccine would be beneficial in the prevention of TB infections.

TB SCREENING IN FOREIGN-BORN POPULATIONS

TB among foreign-born populations contributed to the resurgence of TB in the late 1980s and early 1990s within the U.S [3]. There has consistently been a higher rate of foreign-born TB cases compared to U.S.-born cases as shown in Figure 11 [3, 8]. Though the rate of U.S.-born and foreign-born TB cases has declined, the decreasing rate among the foreign-born population has been less substantial [8]. In 2011, 62% of TB cases were among foreign-born individuals, and the top five countries of origin were Mexico, Philippines, India, Vietnam, and China [8].

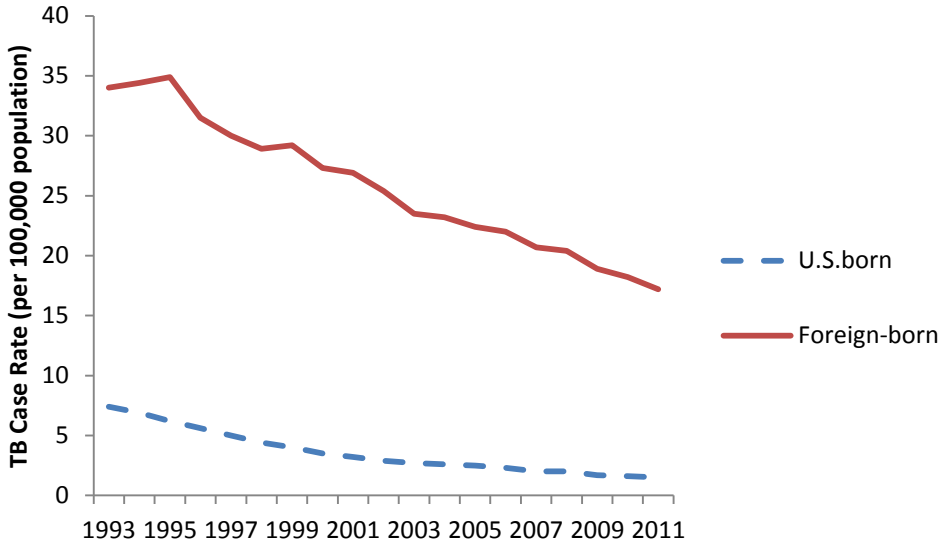


Figure 11: Case rate of reported TB cases among U.S.-born and Foreign-born populations, 1993-2011 (plotted from data in Reference [8])

TB screening among immigrants and refugees is being improved in developing and developed countries [3]. Since *M.tb* infections primarily occur in the country of origin, evaluation of immigrants prior to and immediately following their arrival in the U.S. and other developed countries will assist in identifying potential risks and individuals eligible for therapy [3]. Unfortunately, the primary role of screening in immigrant populations is for the detection of active TB [55]. A major disadvantage to this

screening process is reactivation of LTBI is responsible for the increase in TB cases among foreign-born populations [55]. Thus screening and treatment for LTBI along with active TB is required to reduce the rate of TB cases among foreign-born populations in the U.S. and other developed countries.

However, many of the countries of origin for foreign-born individuals lack the adequate resources needed to control and prevent TB. Thus several organizations are involved in helping these limited resource countries reduce transmission and control of the spread of TB; they include the United Nations, the Stop TB Partnership, the WHO, and the Bill and Melinda Gates Foundation.

LOOKING TOWARDS THE FUTURE

UNITED NATIONS

In 2000 at the United Nations (UN) Millennium Summit, the MDGs were established which were focused on eliminating or reducing poverty, hunger, and child mortality and disease, while promoting education, maternal health, gender equality, environmental sustainability and global partnerships [56]. As previously stated, the MDG 6, Target 6c is aimed at stopping and reversing the TB incidence, prevalence and mortality rate by 2015, and eliminating TB as a public health threat by 2050 [12]. A description of the MDGs as it relates to TB control is shown in Table 13.

The UN believes that sports are the cornerstone to assist in achieving the MDGs by bringing people together [56]. The position of the UN is "involvement of celebrity athletes and the use of mass sports events can increase reach and impact of malaria, tuberculosis and other education and prevention campaigns" [56]. On target to achieve this goal, the 2012 MDG Report has noted a decline in the incidence rates of TB since 2002 and a decline in the mortality and prevalence of TB [57]. There has also been an increase in the number of patients successfully treated for TB [57].

Table 13: Millennium Development Goal, Target and Indicators relevant to TB (Adapted from Reference [12])

Millennium Goal 6	Combat HIV/AIDS, malaria, and other diseases
Target 8	By 2015, halt and begin to reverse the incidence of malaria and other major diseases such as TB
Indicator 23	Prevalence and death rates associated with TB
Indicator 24	Proportion of TB cases detected and cured under DOTS

STOP TB PARTNERSHIP

The Stop TB Partnership, an organization of the UN established in 2000, is an international collaboration whose purpose is to reduce the burden of TB and ultimately eliminate TB from the world [58]. It consists of over 900 countries, donors, national and international organizations, governmental organizations, NGOs, academic institutes, foundations, and patient groups [59]. The mission of the Stop TB Partnership is to: ensure diagnostic tools and treatments are available to all TB patients, stop TB transmission, reduce the social and economic burden caused by TB, and develop and implement new diagnostic tools and treatment strategies to eliminate TB [59]. A full description of the vision, mission, and targets is shown in Table 14.

In 2005, the Global Plan to Stop TB was created that sets out strategies for research and development to improve the prevention, diagnosis, and treatment of TB, along with a plan for implementation of these strategies worldwide [58]. The Global Plan to Stop TB 2011-2015 also sets out the strategies needed to accomplish the targets of MDGs and the Stop TB Partnership [58]. The plan is divided into two sections: (1) Implementation and (2) Research and Development [58]. Implementation focuses on TB control by increasing diagnostic and treatment interventions, and introducing new

diagnostic technologies; the four elements involved in implementation include: expanding and enhancing DOTS, drug-resistant TB, HIV in TB infections, and improving laboratories [58]. Research and Development focuses on understanding and developing new technologies for TB prevention, diagnosis, and treatment; the elements involved in research and development include: basic research, new diagnostics/drugs/vaccines, and operational research [58]. The Global Plan to Stop TB also describes the funding that will be required to accomplish the targets; which was estimated at $47 billion (U.S.) for five years [58].

Table 14: Stop TB Partnership (Adapted from Reference [59])

Vision	A TB-free world with children seeing TB eliminated in their lifetime
Mission	• Ensure that every TB patient has access to effective diagnosis, treatment, and cure • Stop TB transmission • Reduce the inequitable social and economic toll of TB • Develop and implement new preventive, diagnostic, and therapeutic tools and strategies to stop TB
Targets	• By 2015: reduce the global prevalence and mortality of TB disease by 50% compared to 1990 levels • By 2050: elimination of TB as a global public health problem (reduce the global incidence of TB disease to <1 per 1,000,000 in the populations)

WHO

With the declaration that TB is a 'global public health emergency,' the WHO has developing several strategies for TB control. The Stop TB Strategy provides strategies that national TB control programs can adopt to guarantee that all individuals with TB have access to the care they need [12]. These strategies are in line with the MDGs and the Stop TB Partnership as previously mentioned. A full description of the vision, goal, objectives and targets is shown in Table 15.

Table 15: The Stop TB Strategy at a Glance (Taken from Reference [12])

Vision	A World Free of TB
Goal	• To reduce dramatically the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets
Objectives	• Achieve universal access to high-quality care for all people with TB • Reduce the human suffering and socioeconomic burden associated with TB • Protect vulnerable populations from TB, TB/HIV, and MDR-TB • Support development of new tools and enable their timely and effective use • Protect and promote human rights in TB prevention, care and control
Targets	• MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015 • Targets linked to the MDGs and endorsed by the Stop TB Partnership: - By 2015: reduce prevalence and deaths due to TB by 50% compared with a baseline of 1990 - By 2050: eliminate TB as a public health problem
Components of the Stop TB Strategy	
1. Pursue high-quality DOTS expansion and enhancement a. Secure political commitment, with adequate and sustained financing b. Ensure early case detection, and diagnosis through quality-assured bacteriology c. Provide standardized treatment with supervision, and patient support d. Ensure effective drug supply and management e. Monitor and evaluate performance and impact 2. Address TB-HIV, MDR-TB, and the needs of poor and vulnerable populations a. Scale-up collaborative TB/HIV activities b. Scale-up prevention and management of multi-drug resistant TB (MDR-TB) c. Address the needs of TB contacts, and of poor and vulnerable populations 3. Contribute to health system strengthening based on primary health care a. Help improve health policies, human resource development, financing, supplies, service delivery and information b. Strengthen infection control in health services, other congregate settings and households c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL) d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health 4. Engage all care providers a. Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches	

b. Promote use of the International Standards for Tuberculosis Care (ISTC)
5. Empower people with TB, and communities through partnership
   a. Pursue advocacy, communication and social mobilization
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients' Charter for Tuberculosis Care
6. Enable and promote research
   a. Conduct program-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

The WHO has made substantial progress in the care and control of TB as stated in the Global Tuberculosis Report, 2012 [1]. There has been an increase in the number of TB infected individuals with access to care, with the successful treatment of approximately 50 million TB infected individuals [1]. There have also been improvements in testing strategies to identify HIV infection among TB infected individuals; within the African Region alone, HIV testing was performed in 69% of TB patients in 2011 [1]. In addition, ART was started in 48% of HIV/TB co-infected patients worldwide [1]. New diagnostics are also being implemented worldwide, specifically the newly developed Xpert MTB/RIF which has been adopted by 67 low- and middle-income countries [1]. Progress has also been made in the development of new drugs and vaccines; currently 11 vaccine candidates are in Phase I or Phase II clinical trials and 11 new or repurposed drugs are in clinical trials (7 in Phase II and 4 in Phase III) [1].

BILL & MELINDA GATES FOUNDATION

The Bill and Melinda Gates Foundation is dedicated to contributing to the reduced incidence of TB worldwide [60]. The strategy proposed for 2011-2016 addresses vaccine development, shorter treatment regimens, more efficient diagnostic tools, and adequate financing against TB [60].

The foundation has created several programs aimed at drug and treatment discovery. The TB Vaccine Accelerator program was created to aid in the understanding of the vaccine-induced protection since these mechanisms are poorly understood; this can

lead to the discovery and development of more effective vaccines [60]. By 2016, it is the goal of the Bill and Melinda Gates Foundation to have a TB vaccine candidate in Phase III clinical trials and have alternative vaccine candidates ready for clinical trials [60]. The Critical Path to TB Drug Regimens (CPTR) has also been created to accelerate TB drug testing since the process of TB drug development can take decades [60]. The CPTR involves the coordinated efforts of international pharmaceutical companies, public health experts, NGOs, and regulatory agencies [60]. Additionally, the TB Drug Accelerator program has been created to develop shorter treatment regimens, new TB drugs against drug-resistant TB, and new drug discovery tools [60].

The Bill and Melinda Gates Foundation are involved in the development of new diagnostic tools that are less expensive and more efficient which would allow for immediate diagnosis at the 'point of care' instead of requiring a lab for processing [60]. They have also provided funding to the GeneXpert, which was previously described [60]. In addition, the foundation is involved in rapid and cost-effective dissemination of new TB diagnostic tools to areas in need of these diagnostics [60].

The Bill and Melinda Gates Foundation assists the Global Fund to Fight AIDS, Tuberculosis and Malaria, the WHO, and UNITAID to distribute and implement new TB technologies in the most cost-effective way [60]. The foundation also works with donors, governmental organizations, multinational institutions, pharmaceutical and biotechnology industries, and governments from countries where TB is endemic in supporting the efforts to raise the funding needed for TB research and development [60].

CONCLUSIONS

TB is a significant global health threat. Strategies to prevent and control TB infection have been implemented by national and international organizations. These approaches have been shown to be effective at reducing the incidence, prevalence, and mortality of TB worldwide. None the less, TB continues to plague the world, especially

in HIV-positive populations and with the emergence of drug-resistance. As a result, improved prevention and control measures are urgently needed to eliminate TB as a public health problem.

Identification, diagnosis, and treatment are the foundations of TB prevention and control. Education on the signs, symptoms, and risks of TB along with knowledge on infection-control measures are essential to combat TB. Additionally, the coordinated efforts of government organizations, NGOs, local and state health departments, academic institutes, public and private healthcare facilities, and patient groups are essential for the development and implementation of new TB diagnostics, treatments, and vaccines. Early detection with highly effective diagnostics and the rapid initiation of high-quality treatments are needed to stop the progression, transmission, and deaths from this disease. Ultimately, these prevention and control measures will lead to the elimination of TB as a public health problem.

Appendices

APPENDIX A FIVE GROUPS OF SECOND-LINE AGENTS (ADAPTED FROM REFERENCES [17, 23])

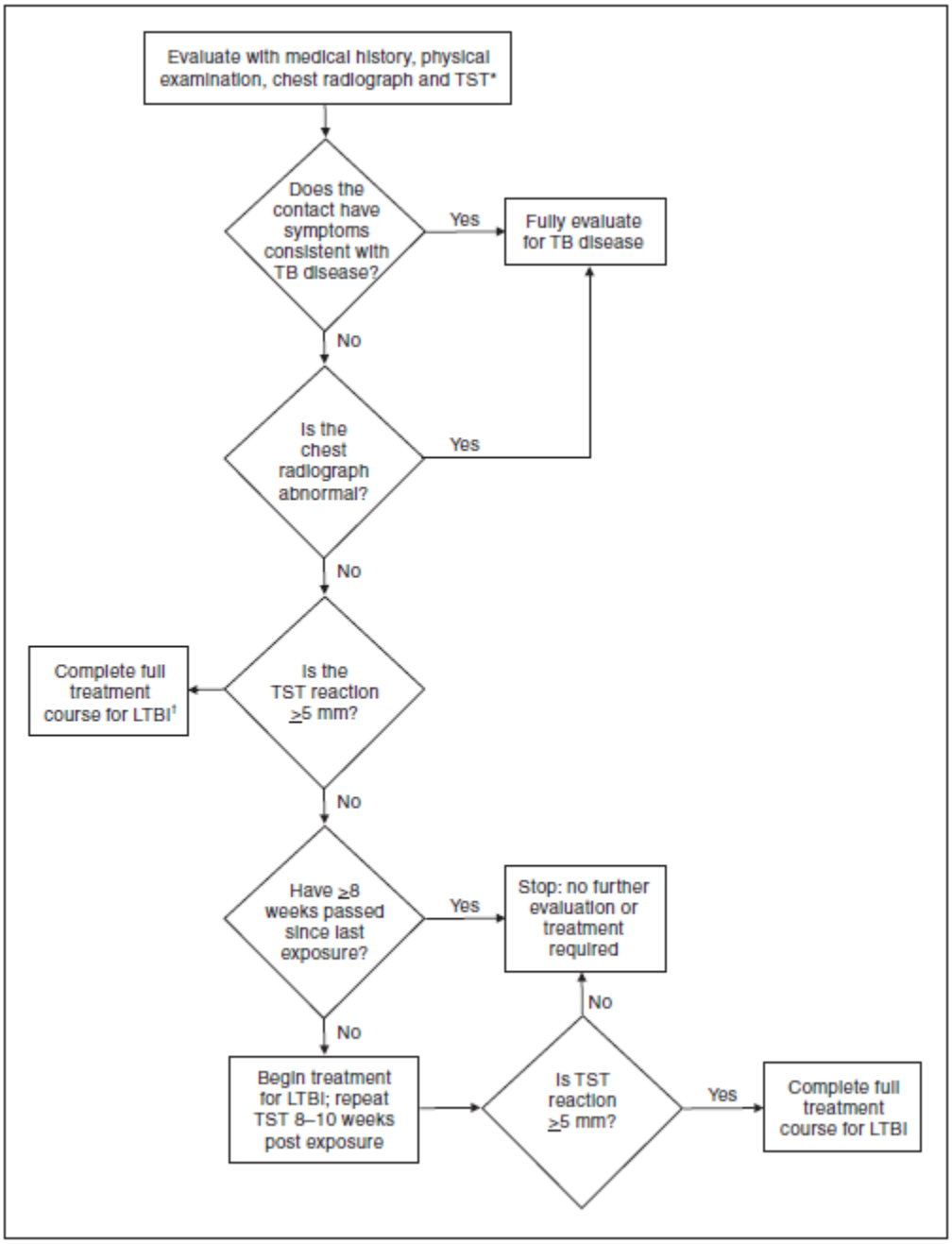
Second-line Agents	
Group 1 First-line oral	Pyrazinamide
	Ethambutol
Group 2 Second-line parenteral (injectable)	Amikacin
	Kanamycin
	Capreomycin
Group 3 Fluoroquinolones	Levofloxacin
	Moxifloxacin
	Ofloxacin
Group 4 Oral bacteriostatic	Para-Aminosalicylic Acid
	Cycloserine
	Ethionamide
	Prothionamide
	Terizidone
Group 5	Amoxicillin/Clavulanate
	Clarithromycin
	Clofazimine
	Imipenem/Cilastin
	Linezolid

APPENDIX B ANTI-TUBERCULOSIS DRUG CANDIDATES IN CLINICAL TRIALS (ADAPTED FROM REFERENCE [17])

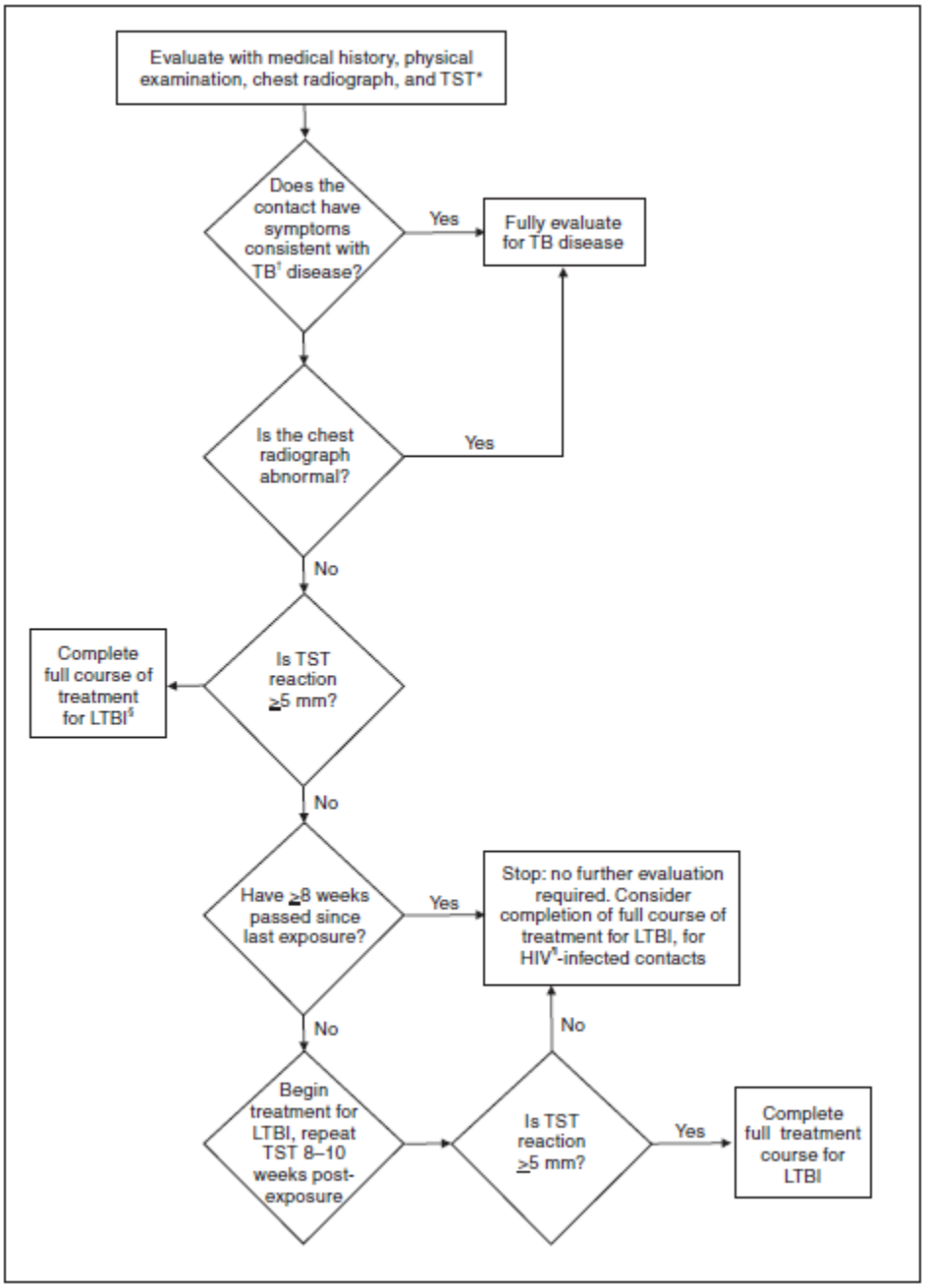
CLASS	DRUG	TRIAL PHASE	DEVELOPER
Fluoroquinolone	Levofloxacin	3	Janseen; generics available
	Moxifloxacin	3	Bayer/GATB
Nitroimidazole	Delamanid (OPC-67683)	3	Otsuka
	PA-824	2	GATB
Dairylquinoline	Bedaquiline (TMC-207)	2	Janssen
Oxazolidinone	Sutezolid (PNU 100480)	2	Pfizer
	AZD 5847	2	Astra Zeneca
Ethylenediamine	SQ109	2	Sequella

*GATB = The Global Alliance for Tuberculosis Drug Development

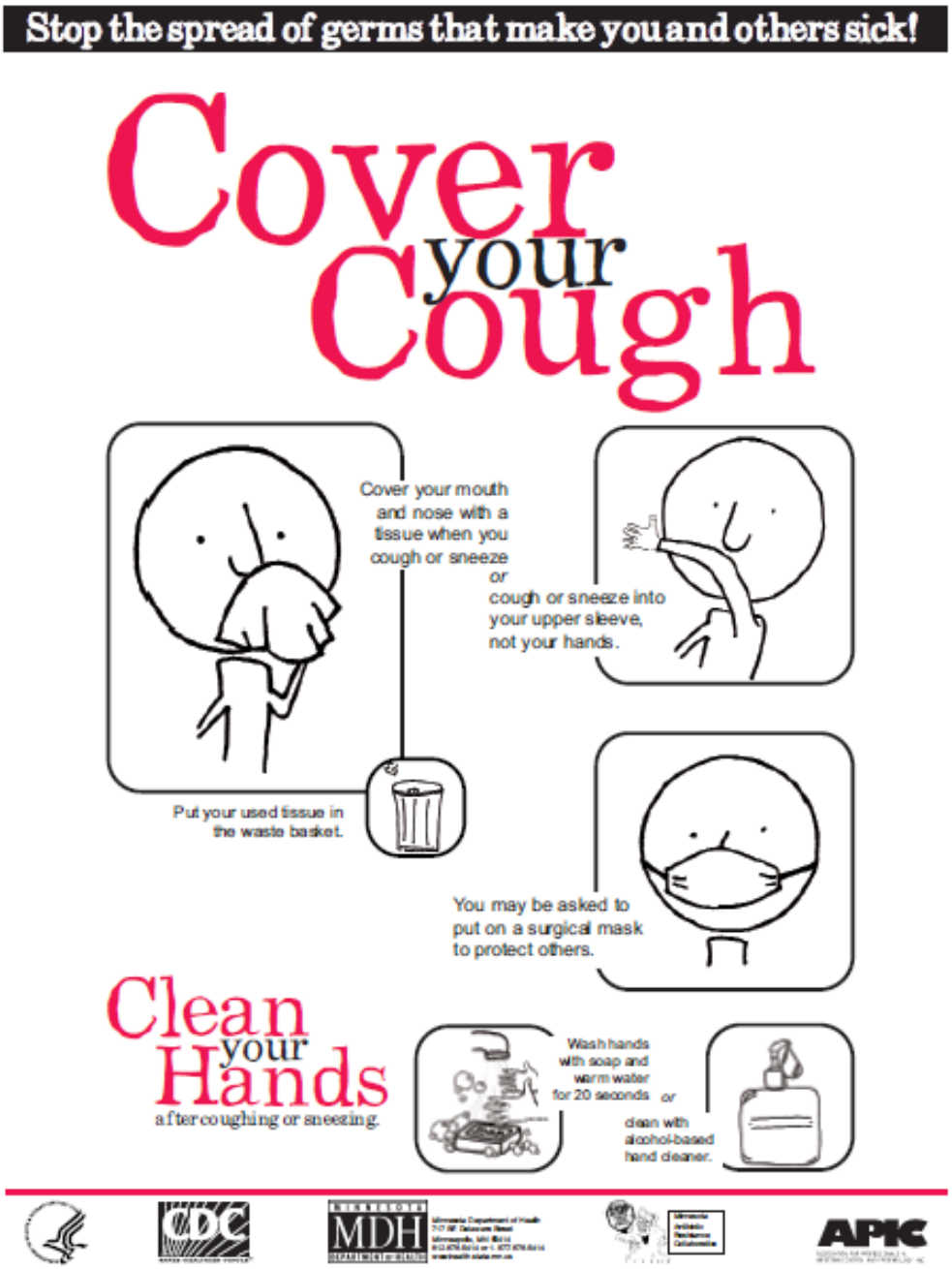
APPENDIX C EVALUATION, TREATMENT, AND FOLLOW-UP OF TB CONTACTS AGED <5 YEARS (TAKEN FROM REFERENCE [51])



APPENDIX D EVALUATION, TREATMENT, AND FOLLOW-UP OF IMMUNOCOMPROMISED CONTACTS (TAKEN FROM REFERENCE [51])



APPENDIX E RESPIRATORY HYGIENE AND COUGH ETIQUETTE PROCEDURES (TAKEN FROM REFERENCE [61])



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Publications

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