Mycobacterium tuberculosis: A Survey

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Abstract

Tuberculosis is an infectious disease caused by the airborne transmission of the Mycobacterium tuberculosis organism. The disease has been a part of human history from the inception and continues to represent a significant disease burden for much of the global community. The disease has prompted important scientific discoveries, and the organism’s microbiology explains its tenacious grip on human populations. The recent emergence of various strains of drug-resistant tuberculosis is an urgent concern to public health professionals today.

*Keywords:* mycobacterium, tuberculosis, drug resistance, TB epidemic, pulmonary
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Mycobacteria tuberculosis: A Survey

Tuberculosis (TB) is an infectious disease caused by the airborne transmission of *Mycobacterium tuberculosis* and other mycobacteria belonging to the Mycobacterium tuberculosis (Mtbc) complex. This Mtbc complex consists of (Todar, n.d.):

- *M. tuberculosis* - the most common causative agent of tuberculosis and the focus of this paper
- *M. bovis* - transmitted by unpasteurized milk and currently found in a small percentage of developing countries
- *M. caprae* and *M. pinnipedii* - isolated to small groups in Central and West Africa

Tuberculosis is believed to be as ancient and as widespread as human prehistory. To appreciate the current socioeconomic burden of the disease and the challenges to its treatment, both globally and in the U.S., it is useful to review its course throughout human history.

**Mycobacterium tuberculosis: Antiquity and Modern Times**

Forensic archaeologists have uncovered evidence of its presence in skeletal human remains in Europe (8000-5000 B.C.), Egypt and Middle East (3000 B.C.), Asia and Pacific Islands (2200 B.C.), South America (700 A.D.) and North America (900 A.D.) (Boire, et.al, 2013).

The Greek physician Hippocrates (460-370 B.C.) was one of the earliest documenters of tuberculosis; he described the disease as a major cause of death at the time and named it “phthisis” (meaning “to waste away”). Although the pathology was unknown, Hippocrates suspected that that the disease was contagious and observed the presence of tubercles in tissues of various animals (sheep, pigs, and cows) (Frith, 2014).

* For an explanation of a superscripted term, refer to the Medical Dictionary section.
The collapse of the Roman Empire in 480 A.D. brought about a reduction in living standards, as well as a decline of arts, science and culture. During the subsequent Medieval Ages, illness was often seen as a punishment by God. People suffering from tuberculosis and other “evil ailments” were banned from living within town or city limits. Tuberculosis cervical adenitis, or “scrofula”, was prevalent, particularly in children; the causative organism was \textit{M. bovis} (Firth-1, 2014).

Frequent epidemics of infectious diseases such as bubonic plague, cholera, leprosy, diphtheria, yellow fever, smallpox, and influenza continued to decimate populations. Researchers believe that tuberculosis was a major contributor to the mortality of the repeated contagion outbreaks during this time. (Boire, et.al, 2013)

\textbf{Émile Léon Poincaré} - \textit{Prophylaxie et géographie médicale: des principales maladies tributaires de l'hygiène} (1884)
Retrieved from \url{Center for the History of Medicine/ Francis A. Countway Library of Medicine—Harvard Medical School}

Tuberculosis reached its peak prevalence of approximately 1000 deaths per 100,000 per year in the 18\textsuperscript{th} and 19\textsuperscript{th} century urban centers of Europe. Social conditions linked to the Industrial Revolution, such as overcrowded and poorly ventilated housing, crude sanitation, widespread malnutrition, and poor air quality were contributing risk factors. The phrases “White
Plague” and “consumption” were coined as descriptions, due to the pallor\(^5\) and emaciation\(^6\) of those affected by the disease (Mandal, 2014).

Major clinical developments surrounding tuberculosis at that time involved diagnosis rather than cure. They include Leopold Auenbrugger’s publication, *Inventum novum ex percussione thoracis humani ut signo abstrusos interni pectoris morbos detegendi* in 1761, which described percussion\(^7\) of the chest. R. T. H. Laennec’s 1891 paper *Del’ascultation mediate* described his invention and use of the stethoscope\(^8\) (Harvard.edu, n.d.).

Wealthy sufferers of tuberculosis went to sanatoria\(^9\) -- so-called “hospital hotels” in a variety of locales and climates -- in droves. Fresh air and sunshine, nutritious food, rest and exercise were prescribed. Those of a lower socioeconomic level, however, initially were cared for in dark, poorly ventilated rooms by family members, who would succumb a few years later of the same disease. Towards the end of the 19\(^{th}\) century, sanatoria were also built for the poorer classes. However, four years after discharge from sanatoria, an average of 80\% of tubercular patients were either dead or invalid (Frith-2, 2014.).

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Cristóbal Rojas - La Miseria (1886).
Retrieved from [http://plaguesandepidemics.tumblr.com/post/53959596966/crist%C3%B3bal-rojas-la-miseria-1886-the](http://plaguesandepidemics.tumblr.com/post/53959596966/crist%C3%B3bal-rojas-la-miseria-1886-the)
During the 19th century, physicians and scientists, in developing the germ theory\textsuperscript{10} of disease, determined that tubercles, along with cholera and several other illnesses, was an infectious disease rather than hereditary or a cancer. They also established that tubercles, scrofula, and phthisis were manifestations of a single disease, rather than separate disease entities. In 1882 Robert Koch discovered the bacterium responsible for the disease, named it *Tubercle bacillus* and was awarded the 1905 Nobel Prize for this achievement. The organism was renamed *Mycobacterium tuberculosis* in 1896. The professional community thereafter referred to the disease as either tuberculosis or TB, while the term “consumption” remained in layperson\textsuperscript{11} usage (Goetz, 2014).

In the 1860s, Louis Pasteur developed a method (subsequently called “pasteurization”) to rid milk of infectious microbes using a “quick boil”. This dramatically reduced the prevalence of *M. bovis*, the pathogen found in the milk of tubercular cattle (Goetz, 2014).

The discovery in 1895 of X-rays by Wilhelm von Rontgen was an important contribution to the diagnosis and control of the tuberculosis. “Röntgenograms” depicted tuberculosis in its various stages and were important in screening groups of the population. Röntgen was awarded the 1901 Nobel Prize for his work (Firth-2, 2014).

Recalling Edward Jenner’s successful development, beginning in 1796, of a vaccine against smallpox, research efforts turned once again to tuberculosis. Over a 13-year period, Albert Calmette and Camille Guérin developed a vaccine against TB. The Bacille de Calmette et Guérin (BCG) vaccine in 1921 was found to offer good protection against TB in children. However, its efficacy\textsuperscript{12} against adulthood pulmonary tuberculosis was very limited (Nor, 2014).
Without a successful treatment for *M. tuberculosis*, efforts during the remainder of the 19th century and into the middle 20th century centered around personal hygiene (particularly sputum\textsuperscript{13}), mandatory reporting by physicians, and segregation of tubercular patients in sanatoria. The American Lung Association was created in 1904 and was originally called the National Association for the Study and Prevention of Tuberculosis (NASPT). The NASPT launched the Modern Health Crusade, including a comprehensive anti-spitting campaign. Tuberculosis continued to be the leading cause of death in the U.S. during the nineteenth and early 20th century (Virginia.edu, n.d.).

Surgical treatments to manage symptoms of pulmonary tuberculosis ushered in the “hospital era” of care. These procedures (some helpful, others harmful) included the following (Brynum, 2012):

- **pneumothorax\textsuperscript{14}** - the injection of air or nitrogen into the intrapleural\textsuperscript{15} space until the lung collapsed. This was intended to allow the lung to rest and heal. The process reversed naturally, and treatments would be repeated as needed.

- **phrenic paralysis\textsuperscript{16}** - a reversible procedure where one of the phrenic nerves from the neck to the diaphragm\textsuperscript{17} on the left and right sides of the body was crushed. “Phrenic crush” blocked transmission of signals from the central nervous system to the diaphragm and interrupted the involuntary contractions responsible for lung inflation and deflation.

- **thoracoplasty\textsuperscript{18}** - the removal of several ribs at a time to cause partial deflation of the lung. Considered a more radical treatment because it was irreversible, thoracoplasty was used primarily when other treatments failed to cause improvements for the patient.
In 1910, Paul Ehrlich discovered a chemical that killed the microorganism that caused syphilis. Another scientist Gerhard Domagk discovered, in 1935, that organic compounds containing sulfur (sulfanilamide) were effective in the treatment of many bacterial infections. Alexander Fleming’s discovery, in 1928, of penicillin, described as the first “antibiotic”, followed by additional research in purification and stability, led to its widespread production and distribution in 1945. Tuberculosis was, however, resistant to these drug classes (Aminov, 2010).

The scientific observations that pathogenic bacteria do not survive for long periods in enriched soil, prompted investigations. In 1943, Selman Waksman, a soil scientist, discovered that a soil-borne fungus called Streptomyces griseus produced an antibiotic effect against Mycobacterium tuberculosis. The resulting compound, called “streptomycin”, was found to be effective in the treatment of tuberculosis. A cure had for TB had finally been discovered! Waksman won the Nobel Prize in 1952 for his efforts (NobelPrize.org, 2003).

Unfortunately, early in the studies, it became apparent that Mycobacterium tuberculosis bacteria were becoming resistant to streptomycin, a problem that anticipated challenges to
eradication in future years. In 1943, another drug, called para-aminosalicylic acid (PAS) was developed, that, when used in combination with streptomycin, was more effective. A third drug called “isoniazid” was developed in 1952 and found its place in tuberculosis drug therapy. Then, as now, patients had to be take combinational drugs for long periods of time to be cured, foreshadowing the problem of noncompliance²¹ (NobelPrize.org, 2003).

In the second half of the 20th century, rates of tuberculosis plummeted throughout the developed world. By the middle of the 1950s, effective treatments prompted U.S. health officials to predict that TB, like the scourge of smallpox, was on the brink of extinction. Tuberculosis research dwindled, and treatment facilities closed. By 1985, however, the number of new tuberculosis cases had plateaued²² and then began to rise. First reported in 1981, HIV/AIDS cases would skyrocket to over 200,000 by 1991. Within this decade, multi-drug resistant strains of tuberculosis (MDR-TB) began to appear in AIDS patients, challenging a healthcare system that was ill-equipped to study and treat them. By 1992, there were a total of 26,673 reported TB cases in the U.S., an increase of 20% from 1985. Federal funding was increased in the mid-1990s to combat this recent resurgence of tuberculosis, particularly in the areas of research, treatment and control. The CDC dedicated most of these new funds to support laboratories and clinics, conduct clinical epidemiological and clinical research, investigate latent strains of tuberculosis, and expand surveillance to monitor the impacts of these activities (pbs.org, 2015).
Those efforts began to pay off, and the incidence of tuberculosis in the U.S. began to decline. Between 2013 and 2014, the number of TB cases (9,421) and the case rate (3.0 cases per 100,000) both decreased, respective declines of 1.5% and 2.2%. Since the resurgence peak in 1992, the number of tuberculosis cases reported annually has decreased by 65% (Ananya, 2014).

*Mycobacterium tuberculosis*: Disease Process & Treatment Protocols

**Epidemiology**

While there has been a decline in the U.S. of the overall number of cases since 1993, new cases continue to be reported. Epidemiological studies have concluded the following (CDC.1, 2013):

Foreign-born persons account for a persistently high percentage of TB cases. These individuals are often coming from high TB disease burden counties. In 2002, for the first time, TB cases among foreign-born persons accounted for the majority (51.2%) of cases in the U.S. Seven countries accounted for 61% of the cases:
- Mexico (22%)
- Philippines (11%)
- Vietnam (8%)
- India (8%)
- China (6%)
- Guatemala (3%)
- Haiti (3%)

In the U.S., there is a disproportionate burden of TB in minority communities due to several factors, including:

- infection frequently acquired in country of origin
- increased exposure to TB
- lower socioeconomic living conditions, including overcrowding

HIV/AIDS-infected persons are at higher risk for developing TB disease after infection with *M. tuberculosis*. This is due to the immunosuppressive nature of the HIV/AIDS disease. In 2011 in the U.S., the percentage of HIV/AIDS and TB coinfection was 6%.

Other population groups at risk for TB infection and TB disease include the following:

- homeless shelters
- correctional and detention facilities
- facilities providing long-term residential care
- migrant farm work camps
- intravenous, illicit drug users

Overall, the U.S. case rate (cases per 100,000) in 2011 was:

- Asian (20.9)
- African-American (6.3)
- Hispanic (5.8)
- American Indian and Alaska Native (5.6)
- non-Hispanic white (0.8)

**Microbiology**

*M. tuberculosis* is a nonmotile, nonsporulating, weakly gram-positive, aerobic organism. Under microscopic examination, it appears as straight or slightly curved
slender rods, 2 to 4 μm in length and 0.2 to 0.5 μm wide. The pathogen has a waxy cell wall with the following characteristics:

- acid-fastness
- extreme hydrophobicity
- resistance to drying, acidity/alkalinity, and many antibiotics

This slow-growing bacterium has a 12- to 24-hour division rate and an extended culture period of up to 21 days. It is not well understood why *M. tuberculosis* grows so slowly. Possibilities include limits on nutrient uptake through its impermeable cell wall and slow rates of RNA synthesis (Sakamoto, 2012).

**Pathogenesis**

*M. tuberculosis* is transmitted on airborne particles, called “droplet nuclei,” which are produced when a person with pulmonary tuberculosis disease coughs, sings, or shouts. These tiny particles can remain suspended in the air for hours. Transmission occurs when a person inhales the droplet nuclei containing tubercular bacilli. The droplet nuclei, while navigating the mouth, nasal passages, and upper respiratory tract, will encounter the body’s mechanical
defenses, including the mucociliary transport\textsuperscript{37} system. If the droplet nuclei evade those physical defenses, they will migrate through the lungs’ bronchi\textsuperscript{38} and reach the alveoli\textsuperscript{39} (CDC.1, 2013). Note that \textit{M. tuberculosis} is not transmitted by surface contact.

Factors that determine the probability of transmission of \textit{M. tuberculosis} include the following (CDC.1, 2013):

- susceptibility (immune status) of the exposed individual
- infectiousness of the person with TB disease (concentration of bacilli in the droplet nuclei)
- environmental factors that affect the concentration of \textit{M. tuberculosis} organisms (e.g. ventilation)
- duration, frequency and proximity of exposure

Once the tubercle bacilli are present in the alveoli of the lungs, they are consumed by alveolar macrophages\textsuperscript{40} (sometimes referred to as “dust cells”). These specialized white blood cells serve as the body’s “front line” of cellular defense against respiratory pathogens. Their function is to clear the air spaces of infectious, toxic, or allergic particles that have escaped the mechanical defense systems of the respiratory tract. (Rubins, 2003). The macrophages typically destroy or inhibit most of the tubercular bacilli. A small number, like a “Trojan Horse”, however, continue to multiply within the macrophages and are released when the macrophages die (UBC, 2008).

These \textit{M. tuberculosis} bacilli then either remain in the lung or enter the bloodstream and spread throughout the body. This triggers an immunological response; within 2 to 8 weeks, macrophages will surround the bacilli in clustered structures called “granulomas”\textsuperscript{41}. These granulomas are thought to contain \textit{M. tuberculosis}-infected macrophages in the center,
surrounded by different kinds of immune cells, including T-lymphocytes[^42] and activated macrophages (CDC.1, 2013).

![Diagram of infection with *M. tuberculosis*](http://www.cell.com/cell-host-microbe/fulltext/S1931-3128(08)00154-6)

In healthy individuals, the immune system is sufficient to keep *M. tuberculosis* in check so that the disease will not develop. This stage is referred to as latent tuberculosis infection (LTBI). It is important to note that individuals with LTBI cannot transmit *M. tuberculosis*; they are not “contagious”. (CDC.2, 2013).

The exact status of *M. tuberculosis* bacilli within the granulomas is not clearly understood. It is not known whether they are “dormant” or whether they are actively dividing. It is clear, however, that *M. tuberculosis* can persist for a very long time, even up to the lifetime of the host[^43] (individual person). Therefore, the granuloma structure can be thought of as a balance between a potentially dangerous pathogen and the host immune system (Pieters, 2008).
Clinical Manifestations

If the granuloma aggregates are not maintained by the immune system, however, and become degraded, the tubercular bacilli can escape the shell-like structures and begin to multiply. This stage is referred to as tuberculosis disease (TB disease). Typically, these bacilli persist in the apices (upper extremities) of the lungs. This is described as pulmonary or respiratory tuberculosis, the focus of this paper. In 2011, 67% of the TB cases in the U.S. were exclusively pulmonary (CDC.1, 2013).

Other possible anatomical sites of TB disease, also characterized by high oxygen tension, include: cerebral cortex, renal cortex, and metaphysis of bones. The disease in these locations is called extra-pulmonary tuberculosis and can co-exist with pulmonary TB. In 2011, 33% of TB cases in the U.S. included an extra-pulmonary component (CDC.1, 2013).
Symptoms of pulmonary tuberculosis include cough, sputum production, hemoptysis, dyspnea, nocturnal hyperhidrosis and other systemic symptoms (such as fever or weight loss) (Davies, 2016).

**M. tuberculosis: Treatment and Drug Resistance**

*M. tuberculosis*’ resistance to chemotherapeutic solutions has been observed from the initial discovery of streptomycin. The following biological factors may be contributory (Gillespie, 2002):

- its long generation time; its capacity for dormancy; low metabolic activity
- located where penetration of antibiotics is difficult (e.g. solid caseous material)
- located in areas of low pH that inhibit the activity of most antibiotics
- its genetic variability

Other reasons for TB’s drug resistance include:

- improper use of antibiotics
  - missed doses
  - altered dosing intervals or amounts
  - incomplete treatment
- counterfeit drugs (Khazan, 2013)

Drug-susceptibility testing (DST) of the initial *M. tuberculosis* specimen is done to direct the health-care provider in the selection of the appropriate drugs to treat the patient with TB disease or LTBI. The specimen should be tested for resistance to the “first-line” of anti-TB drugs. Generally, two testing methods are used (Davies, 2016):

- Culture-based growth of organism in drug-free and drug-containing media
  - time-consuming (3 weeks to 2 months)
  - the “gold standard”
- Detection of certain nucleic acid sequences\textsuperscript{53} in the mycobacterial genome\textsuperscript{54}
  - quicker results
  - not widely available on a global basis

Laboratories are required by regulation to promptly report results of DST \textit{M. tuberculosis} specimens to the health-care provider and the health department.

The results of drug-susceptibility testing of the specimen are described as (CDC.\textsuperscript{1}, 2013):

- **Drug-susceptible TB** - responsive to first-line oral drugs
- **Multidrug-Resistant TB (MDR-TB)** - definite resistance to two first-line drugs, with probable resistance to other first-line drugs.
- **Extensively Drug Resistant TB (XDR-TB)** - definite resistance to two first-line drugs and two second-line drugs, with probable resistance to other first-line drugs and other second-line drugs.

The goals of treatment for LTBI and TB disease are: (CDC.\textsuperscript{1}, 2013):

- **LTBI**: Reduce the risk of progression to TB disease in the individual patient
- **LTBI**: Reduce the potential for transmission of \textit{M. tuberculosis} to other persons
- **TB disease**: Cure the individual patient
- **TB disease**: Minimize the risk of disability and death to the patient
- **TB disease**: Reduce the actual transmission of \textit{M. tuberculosis} to other persons

Currently, there are 10 drugs approved by the FDA for the treatment of TB disease; an additional 5 drugs are commonly used “off-label” to treat TB disease in the case of drug resistance or intolerance. Common first- and second-line antitubercular drugs include (Davies, 2016):

<table>
<thead>
<tr>
<th>Drug (administration)</th>
<th>Daily dose relative to body weight (in mg/kg)</th>
<th>3/week dose relative to body weight (in mg/kg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First line drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid* (oral/IM/IV)</td>
<td>5</td>
<td>10</td>
<td>Bacterial, rapidly absorbed</td>
</tr>
<tr>
<td>Rifampicin* (oral/IV)</td>
<td>10</td>
<td>10</td>
<td>Bacterial; inhibits DNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Pyrazinamide*</td>
<td>25</td>
<td>35</td>
<td>Nicotinamide analogue; weakly bacterial; strongly sterilizing activity in inflammatory tissue</td>
</tr>
<tr>
<td>Ethambutol*</td>
<td>15</td>
<td>30</td>
<td>Synthetic bacteriostatic</td>
</tr>
<tr>
<td>Drug</td>
<td>Dosage</td>
<td>Duration</td>
<td>Notes</td>
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<tr>
<td>Rifabutin**</td>
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<td>Used as a substitute for Rifampicin</td>
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<tr>
<td>Rifapentin</td>
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<td>Used as a substitute for Rifampicin</td>
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<tr>
<td><strong>Second line drugs</strong></td>
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<tr>
<td>Streptomycin (IM/IV)</td>
<td>15</td>
<td>15</td>
<td>First antitubercular agent to be</td>
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<td></td>
<td></td>
<td>invented</td>
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<tr>
<td>Cycloserine</td>
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<td>--</td>
<td>Reserved for situations such as drug</td>
</tr>
<tr>
<td>Capreomycin</td>
<td></td>
<td></td>
<td>intolerance or resistance</td>
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<tr>
<td>p-Aminosalicylic Acid</td>
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<tr>
<td>Levofoxacin**</td>
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<td>Moxifloxacin**</td>
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<td>Gatifloxacin**</td>
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<tr>
<td>Amikacin/Kanamycin**</td>
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<tr>
<td>Ethionamide**</td>
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</tbody>
</table>

* form the core of initial treatment regimen  
** not approved by the FDA for use in treatment of TB; use is “off-label”

There are several treatment regimens available for the treatment of LTBI and TB disease. Clinicians will choose the appropriate protocol based on (CDC.1, 2013):

- Results of drug-susceptibility testing of the specimen (susceptible, MDR-TB, XDR-TB)
- Coexisting medical issues (e.g. pregnancy, HIV/AIDS status, hepatic or renal disease)
- Possible drug-drug interactions

Most patients with (previously untreated) pulmonary TB disease are treated with either a 6-month or 9-month regimen of four drugs.

Due to the long treatment duration, interruptions in treatment of TB disease are common. The health-care provider is responsible for deciding whether to restart a complete course of treatment or to resume treatment as intended. This is based on when the interruption occurred and the duration of the interruption.

Patient medical evaluation and monitoring by the health-care provider is critical to the successful treatment of TB disease. This includes (CDC.1, 2013):

- Clinical evaluations (at least monthly)  
  - Assess adherence  
  - Determine treatment efficacy
Routine laboratory monitoring
  - bacteriologic examinations
  - chest radiographs

Treatment follow-up
  - possible adverse drug reactions - relatively rare, but may be severe
  - other medical conditions

The responsibility for successful treatment is assigned to the health-care provider, not the patient. The provider should consult the TB control program of the relevant municipal health department to ensure their patient can adhere to a prescribed TB treatment regimen. The TB control program should assist the provider in evaluating patient barriers to adherence and, if appropriate, recommend directly observed therapy (DOT) and the use of incentives and enablers to assist the patient in completion of treatment (CDC.1, 2013).

Treatment completion is defined as the ingestion of the prescribed drugs within the specified time. The duration of the therapy depends on the drugs used, the drug susceptibility test results of the *M. tuberculosis* specimen(s), and the patient’s response to therapy. The goal is to complete all doses within one year (CDC.1, 2013).

**Prevention**

Tuberculosis is a preventable and curable disease if detected and treated early. It has a low prevalence in the U.S., so the risk of acquiring TB is low. In general, this means that individuals do not need to take special precautions to prevent the disease.

Safeguards for less common situations include the following (WebMD, 2014):

- Avoid long periods of time in poorly ventilated, enclosed areas with anyone who has TB disease until that person has been treated for 2 weeks.

- Use face masks or other protective measures if you work in a facility that cares for people who have untreated TB disease.

- Anyone living with someone who has TB disease should help the person follow and complete their treatment plan.
The CDC has published guidelines for individuals in the following environments:

- In health-care settings (Jensen, P., et.al., 2005)
- Along the U.S.-Mexico border (Lobato, M., et.al., 2001)
- Among homeless persons (CDC.3, 1992)
- In correctional and detention facilities (Fenton, K., 2006)
- In facilities providing long-term care to the elderly (CDC.4, 1990)
- Among migrant farm workers (CDC.5, 1992)
- Among foreign-born persons (CDC.6, 1998)
- International travelers who anticipate prolonged exposure to TB (LoBue, 2015)

**Mycobacterium tuberculosis: Research & Outlook**

Four main factors necessitate the development of new drugs to treat TB. Some of these points are more urgent in countries outside the U.S., but all are important to consider (Davies, 2016):

1. Inadequacy
   a. The lengthy treatment regimen results in poor compliance
   b. The treatment protocol is complex to administer, placing an increasing burden on resource-challenged public health authorities

2. Drug Resistance
   a. There has been a continuous rise of MDR-TB and XDR-TB during the last few decades.
   b. A sharp increase of MDR-TB has occurred since 2008.
   c. The treatment for these strains is longer and more complex, typically involving injectable drugs.

3. HIV/AIDS and TB Co-Infection
   a. Co-infection of HIV/AIDS and TB complicates the treatment regime because of drug-drug interactions
   b. Treatment options for dual-infected patients are considerably more limited.
4. Economic Burden

a. The control of TB places a significant burden on the world economy; the world poor countries are estimated to lose $1-3 trillion over the next 10 years due to TB.

b. Countries where 95% of the TB cases occur rely on donor countries to obtain TB drugs and treat their patients.

c. The disease burden also slows economic development; 75% of TB cases occur during a person’s most productive years (15-54 years).

Many drugs are being investigated for the treatment of TB disease. The following four are currently in phase II and III trials:

1. Fluoroquinolones - inhibition of mycobacterial DNA synthesis (Schluger, 2013).

2. Delamanid - inhibition of mycobacterial cell wall components (Xavier, 2014).

3. Bedaquiline - inhibits mycobacterial $\text{ATP}^{58}$ and depletes cellular energy stores (Diacon, 2014).

4. Pretomanid - potent antibacterial; active against all tested drug resistant TB strains (TBAlliance, 2014).

At least ten TB drugs are being evaluated as candidates for TB vaccines. Their aims vary: some control infection at the latent stage, others eradicate *M. tuberculosis* from the human body. The Ag85B vaccine, currently in mouse trials, instructs the immune system to target critical *M. tuberculosis* bacterial proteins (Sjøgren, 2014).

**Conclusion**

The barriers to controlling TB disease on a global level are significant and numerous, including its association with poverty and inadequacies in health systems that lead to drug resistance. Gaps in funding also play a significant role. The Global Fund’s grant funding decisions in 2015 confirm this shortfall:
• $ 121.0 billion - Malaria
• $ 78.0 billion - HIV/AIDS
• $ 42.0 billion - Tuberculosis

Tuberculosis remains one of the top 10 causes of death worldwide; it is the second highest cause of death from infectious disease, behind malaria, and ahead of HIV/AIDS. The World Health Organization describes this global prevalence as a TB epidemic and notes the following (WHO, 2016):

• In 2015, there were 10.4 million new TB cases worldwide, with people living with AIDS accounting for 11%.

• In 2015, an estimated 4.6% of new TB cases were multi-drug resistant TB (MDR-TB); however, only 20% of these MDR-TB diagnosed cases were enrolled in MDR-TB treatment.

• In 2015, there were 1.4 million TB deaths worldwide, with 29% being HIV/AIDS-related.

• Finally, in 2015, over 95% of TB deaths occurred in low- and middle-income countries.

As it has for millennia, tuberculosis continues to thrive in deprived, isolated communities within wealthy environments, as well as economically-disadvantaged regions with inadequate healthcare services and delivery systems (Zaman, 2010).
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https://www.cdc.gov/mmwr/preview/mmwrhtml/00001711.htm


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http://www.cdc.gov/mmwr/preview/mmwrhtml/00032773.htm


https://www.cdc.gov/mmwr/PDF/rr/rr4716.pdf


PBS.org (Feb. 10, 2015). The Forgotten Plague: Tuberculosis in America. DVD from Public Broadcast System. Available from

http://www.pbs.org/wgbh/amERICANexPERIENCE/films/plague/


Mycobacterium tuberculosis


### Medical Terminology

<table>
<thead>
<tr>
<th>#</th>
<th>Term</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><em>Mycobacterium tuberculosis</em></td>
<td>rod-shaped bacterial organism that is the cause of tuberculosis disease</td>
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<tr>
<td>2</td>
<td>causative</td>
<td>functioning as an agent or cause</td>
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<tr>
<td>3</td>
<td>tubercle</td>
<td>swelling or nodule, especially a mass of epithelioid cells and lymphocytes; characteristic lesion of tuberculosis</td>
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<td>4</td>
<td>cervical adenitis</td>
<td>inflammation of the lymph node or gland in the neck</td>
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<tr>
<td>5</td>
<td>pallor</td>
<td>abnormal or extreme paleness</td>
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<tr>
<td>6</td>
<td>emaciation</td>
<td>wasted condition of the body</td>
</tr>
<tr>
<td>7</td>
<td>percussion</td>
<td>striking the body with the fingers to determine characteristics of the parts by the sound produced</td>
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<tr>
<td>8</td>
<td>stethoscope</td>
<td>instrument used to listen to sounds produced within the body</td>
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<tr>
<td>9</td>
<td>sanatoria (singular: sanatorium)</td>
<td>facility to house patients with long-term illnesses</td>
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<tr>
<td>10</td>
<td>germ theory</td>
<td>theory that infectious diseases are caused by microorganism activity in the body</td>
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<tr>
<td>11</td>
<td>layperson</td>
<td>someone who is not a professional in a particular field</td>
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<tr>
<td>12</td>
<td>efficacy</td>
<td>ability of a drug to achieved desired effect</td>
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<tr>
<td>13</td>
<td>sputum</td>
<td>material that is coughed up and ejected from the mouth</td>
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<tr>
<td>14</td>
<td>pneumothorax</td>
<td>collection of air in the chest that causes lung collapse</td>
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<tr>
<td>15</td>
<td>intrapleural</td>
<td>relating to between the membranes that enclose each lung and line the chest</td>
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<tr>
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<tr>
<td>phrenic paralysis</td>
<td>relating to lack of movement by the diaphragm</td>
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<tr>
<td>diaphragm</td>
<td>muscular portion separating the chest from the abdomen</td>
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<tr>
<td>thoracoplasty</td>
<td>surgical removal of one or more ribs to allow the retraction of the chest</td>
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<tr>
<td>resistant (drug resistance)</td>
<td>the ability of the pathogen to withstand exposure to drugs that were previously toxic to them</td>
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<tr>
<td>pathogenic</td>
<td>relating to an agent that causes disease (usually a virus, bacteria, or fungus)</td>
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<tr>
<td>noncompliance</td>
<td>failure to follow a prescribed medical treatment</td>
<td></td>
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<tr>
<td>plateaued (verb: to plateau)</td>
<td>to flatten or level</td>
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<tr>
<td>disease burden</td>
<td>quantitative impact of a health problem, described by mortality, morbidity, and financial cost</td>
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<tr>
<td>nonmotile</td>
<td>not capable of movement</td>
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<tr>
<td>nonsporulating</td>
<td>not capable of producing or releasing spores</td>
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<tr>
<td>gram-positive</td>
<td>retaining the color of the violet stain in the Gram stain.</td>
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<tr>
<td>aerobic</td>
<td>in the presence of molecular oxygen</td>
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<tr>
<td>acid-fastness</td>
<td>physical property of certain bacteria's resistance to coloration by acids during stain testing</td>
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<tr>
<td>hydrophobicity</td>
<td>repelling or not dissolving in water</td>
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<tr>
<td>acidity/alkalinity</td>
<td>quality of being acid or alkaline; uniting with either positively- or negatively-charged ions</td>
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<tr>
<td>division rate</td>
<td>time required by a parent cell to divide into two or more daughter cells</td>
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<tr>
<td>culture period</td>
<td>time to propagate microorganism in a special growth media</td>
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<tr>
<td>nutrient uptake</td>
<td>absorption of ingredients that are sources of nourishment</td>
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<tr>
<td>impermeable</td>
<td>not permitting passage</td>
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<tr>
<td>RNA synthesis</td>
<td>essential part of the transfer of genetic material</td>
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<tr>
<td>droplet nuclei</td>
<td>very small particles formed by aerosolizing of infective material</td>
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<tr>
<td>mucociliary transport</td>
<td>movement that is related to the interaction of mucous and associated ciliated epithelium</td>
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<tr>
<td>bronchi (singular: bronchus)</td>
<td>subdivisions of the trachea that transport air to and within the lungs</td>
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<tr>
<td>alveoli (singular: alveolus)</td>
<td>tiny sacs in the lungs where oxygen and carbon dioxide are exchanged by capillary action</td>
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<tr>
<td>macrophage</td>
<td>round granular phagocyte that ingests inhaled particulate matter</td>
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<tr>
<td>granulomas (singular: granuloma)</td>
<td>cluster of macrophages surrounding a target foreign to the body</td>
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<tr>
<td>T-lymphocytes</td>
<td>white blood cells that form in bone marrow and mature in the thymus to become immunologically active cells</td>
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<tr>
<td>host</td>
<td>the organism that shelters and provides support to another organism (the parasite)</td>
<td></td>
</tr>
<tr>
<td>apices (singular: apex)</td>
<td>upper rounded extremity of either lung</td>
<td></td>
</tr>
<tr>
<td>oxygen tension</td>
<td>partial pressure of oxygen molecules dissolved in blood plasma</td>
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<tr>
<td>cerebral cortex</td>
<td>outer layer of the main portion of the brain</td>
<td></td>
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<tr>
<td>renal cortex</td>
<td>outer layer of the kidney</td>
<td></td>
</tr>
<tr>
<td>metaphysis</td>
<td>wide part at the end of the shaft of a long bone</td>
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Mycobacterium tuberculosis

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<td>hemoptysis</td>
<td>coughing up blood or bloody sputum from the lungs</td>
</tr>
<tr>
<td>dyspnea</td>
<td>difficult or labored breathing</td>
</tr>
<tr>
<td>nocturnal hyperhidrosis</td>
<td>excessive sweating during nighttime hours</td>
</tr>
<tr>
<td>caseous</td>
<td>resembling curd or cheese</td>
</tr>
<tr>
<td>nucleic acid sequences</td>
<td>order of materials that encode, transmit and express genetic information</td>
</tr>
<tr>
<td>genome</td>
<td>complete set of hereditary factors</td>
</tr>
<tr>
<td>hepatic</td>
<td>pertaining to the liver</td>
</tr>
<tr>
<td>renal</td>
<td>pertaining to the kidney</td>
</tr>
<tr>
<td>radiograph</td>
<td>image produced on processed film by x-rays</td>
</tr>
<tr>
<td>ATP</td>
<td>material present in cells that stores and transports energy needed for metabolic reactions</td>
</tr>
</tbody>
</table>