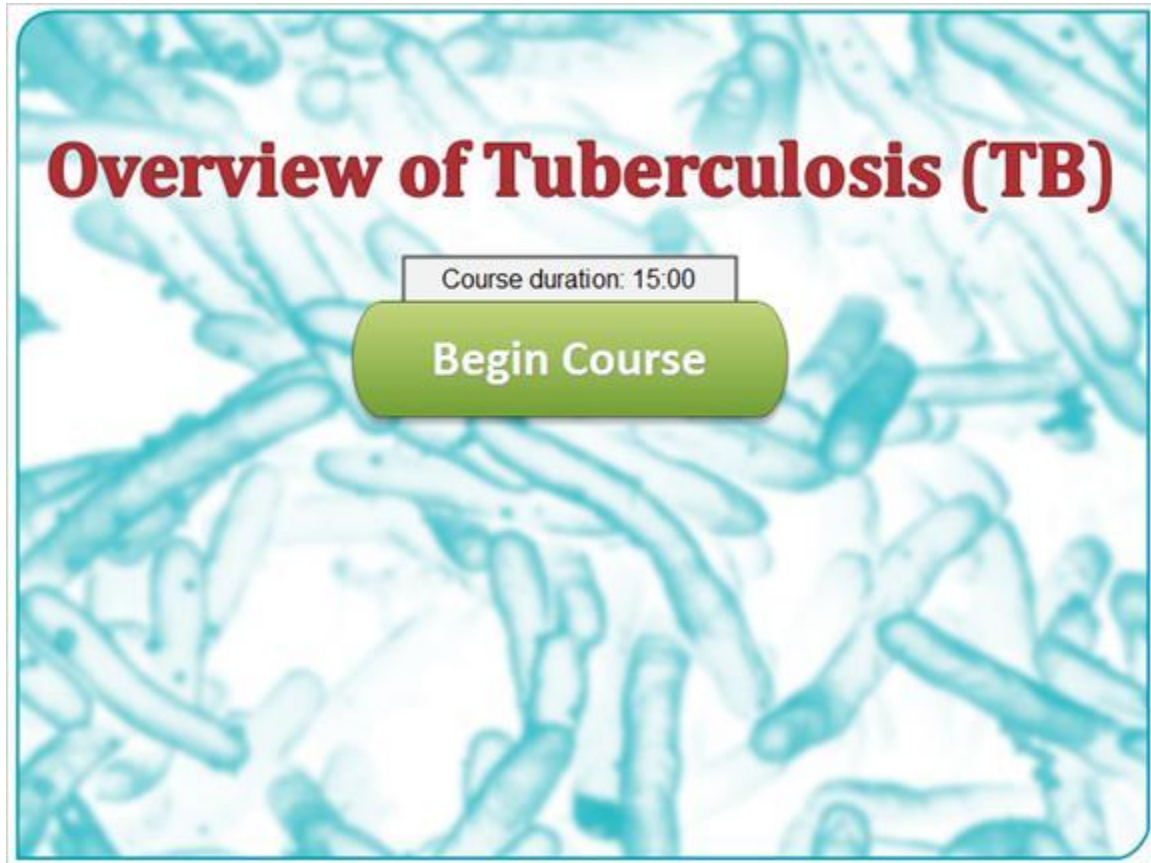


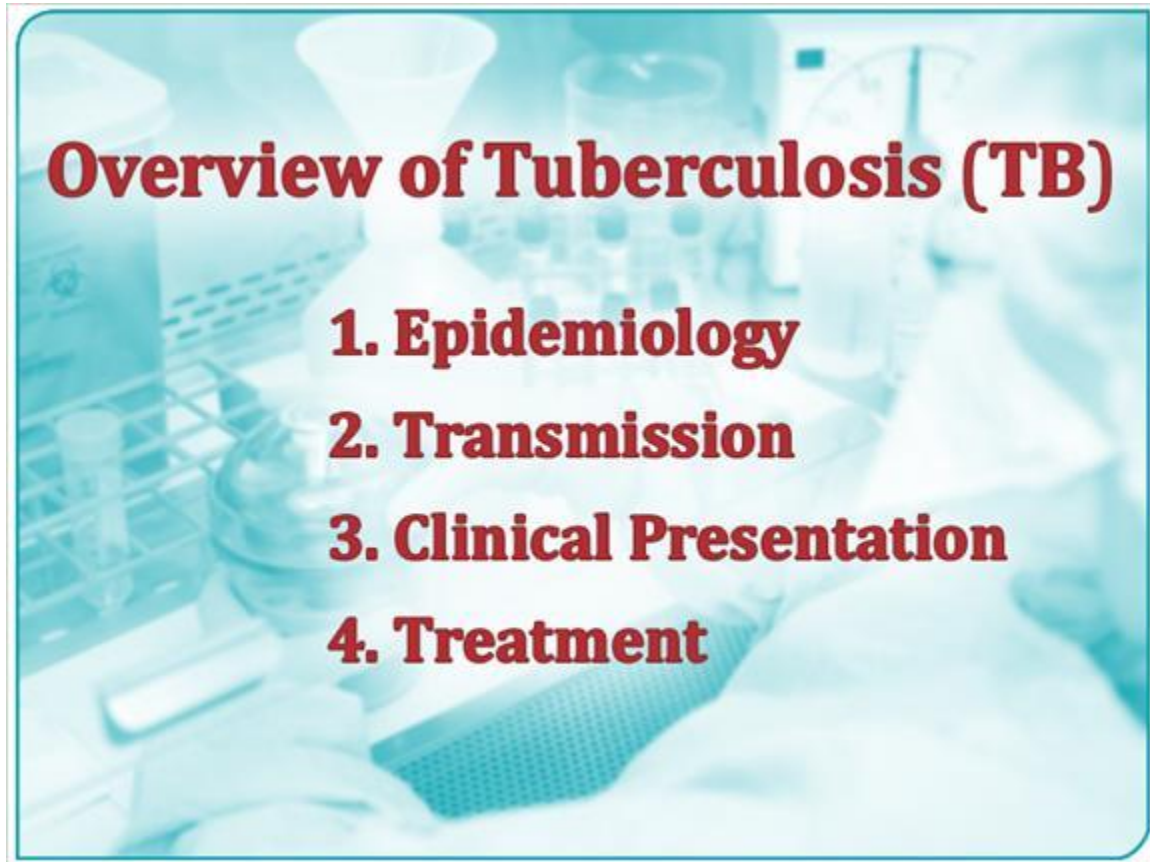


Overview of Tuberculosis (TB)



1. Overview of Tuberculosis

1.1 Introduction



Notes:

Welcome to the Association of Public Health Laboratories essentials for the Microbacteriology Laboratory promoting quality Practices. This is module number one, Overview of Tuberculosis. The goal of this module is to put your work in the Microbacteriology Laboratory in a public health context. This presentation will provide a national and global scope of tuberculosis disease. It will discuss the epidemiology, transmission, clinical presentation and treatment of tuberculosis.

By the end of the module, you will begin to appreciate that the microbacteriology laboratory is the frontline of a multifaceted public health system for TB control and ultimately TB elimination.

1.2 Tuberculosis

Tuberculosis (TB)

- Airborne disease caused by the bacterium *Mycobacterium tuberculosis* (M. tb)
- M. tb complex (MTBC) includes other mycobacteria that can cause TB: *M. bovis*, *M. africanum*, *M. canettii*, *M. microti*
- Expelled when a person with infectious TB coughs, sneezes, shouts, or sings
- Transmission occurs when droplet nuclei (airborne particle about 1-5 microns) are inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi
- 2 billion people infected worldwide (1/3 of the world's population)
- Estimated 8.7 million new cases in 2011
- 13% of new cases co-infected with HIV
- 1.4 million deaths in 2011

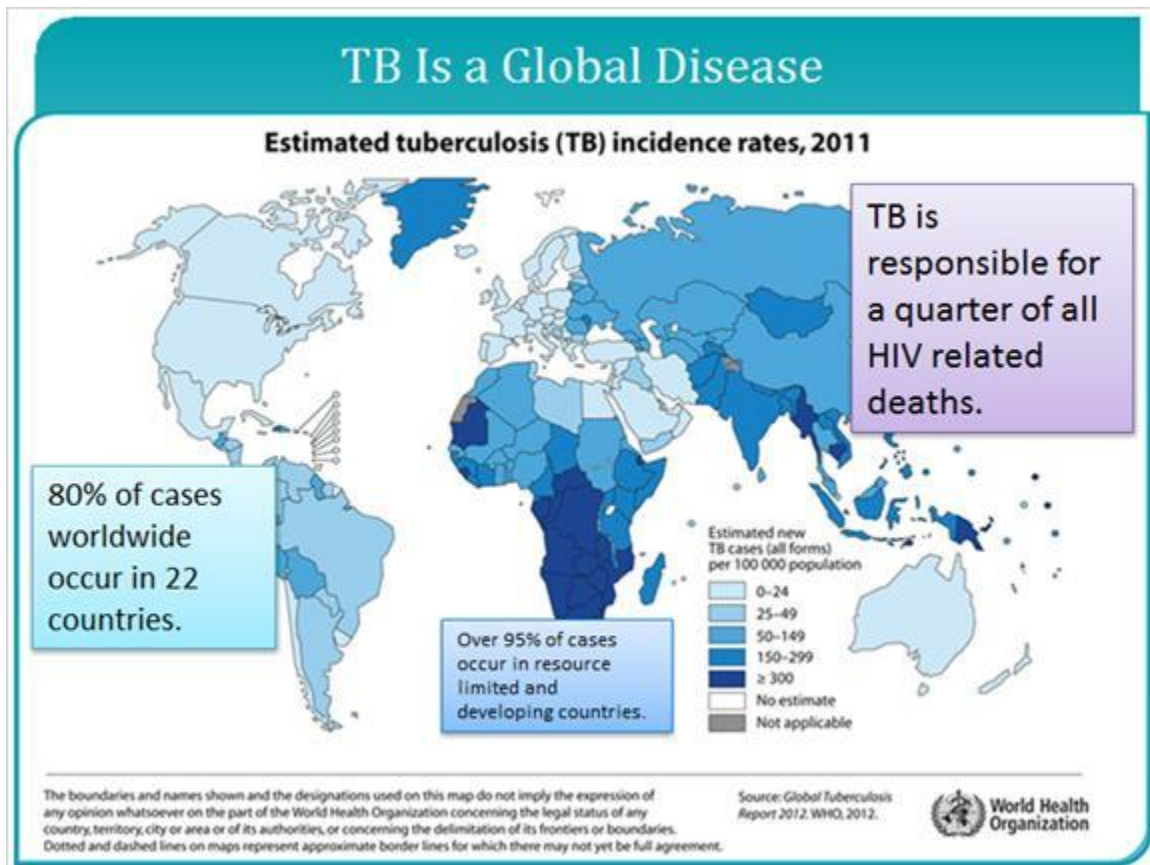
Notes:

Tuberculosis is an airborne disease caused by *Mycobacterium tuberculosis* (M. tb). M. tb complex or MTBC includes other mycobacteria that can cause TB such as *M. bovis*, *M. africanum*, *M. canettii*, and *M. microti*. The bacilli are expelled when a person with infectious TB coughs, sneezes, shouts, or sings.

Transmission occurs when droplet nuclei defined as airborne particles about 1-5 microns are inhaled and reach the alveoli via the lungs, via the nasal passages, respiratory tract, and bronchi. Droplet nuclei can remain airborne for an extended period of time; therefore, a person may still be exposed to suspended droplets even after the infectious person has left the room.

It is estimated that two billion people are infected with TB worldwide, accounting for approximately one third of the world's population. There were an estimated 8.7 million new TB cases globally, with 13% being co-infected with HIV and 1.4 million deaths from TB disease in 2011.

1.3 TB Is a Global Disease

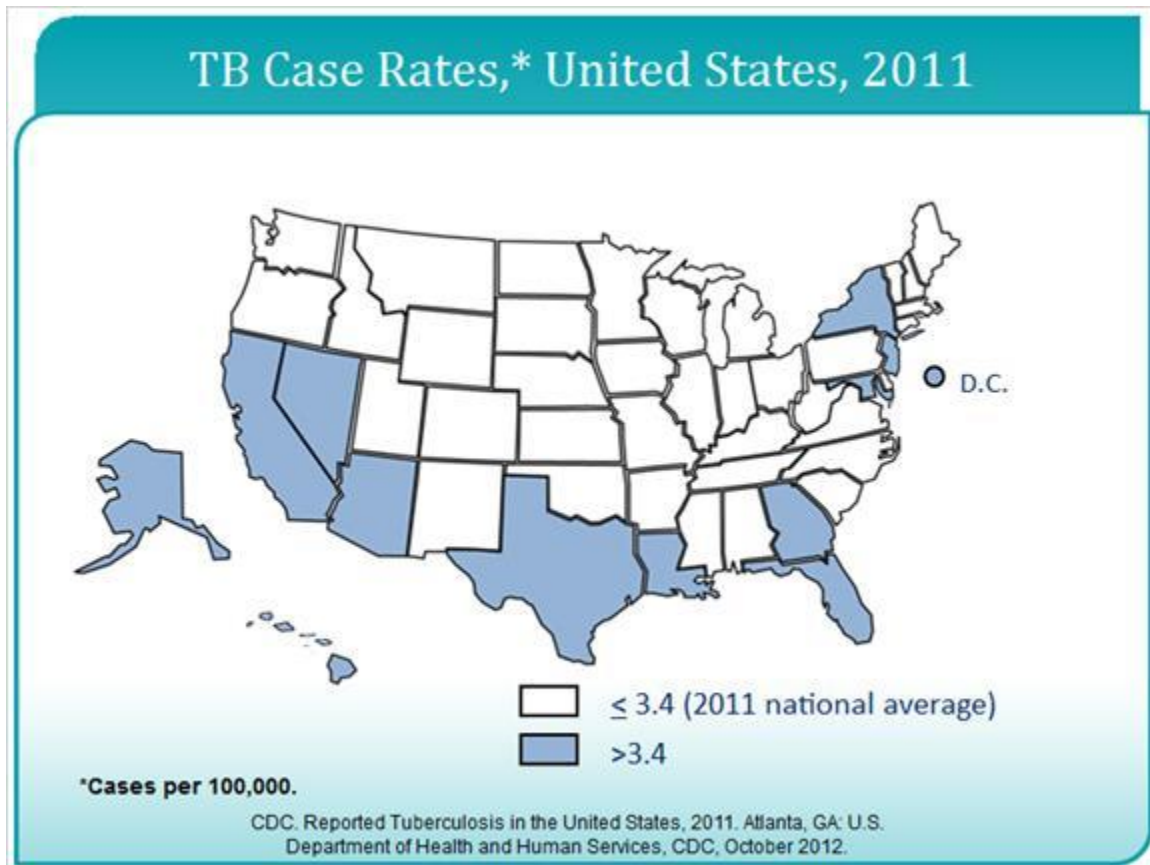


Notes:

The map displayed here shows that TB is found in virtually every country with the highest incidence rates occurring in Africa and Asia; especially sub Saharan Africa and Southeast Asia. Over 95% of TB cases and deaths occur in resource limited and developing countries and 80% of reported cases worldwide occur in 22 countries. These statistics highlight the importance of laboratory capacity for the early detection and treatment of TB disease.

In many parts of the world, TB incidence is underestimated or unavailable as a result of inadequate laboratory and surveillance infrastructure. Additionally, TB is one of the leading killers of those living with HIV and is responsible for a quarter of all HIV related deaths.

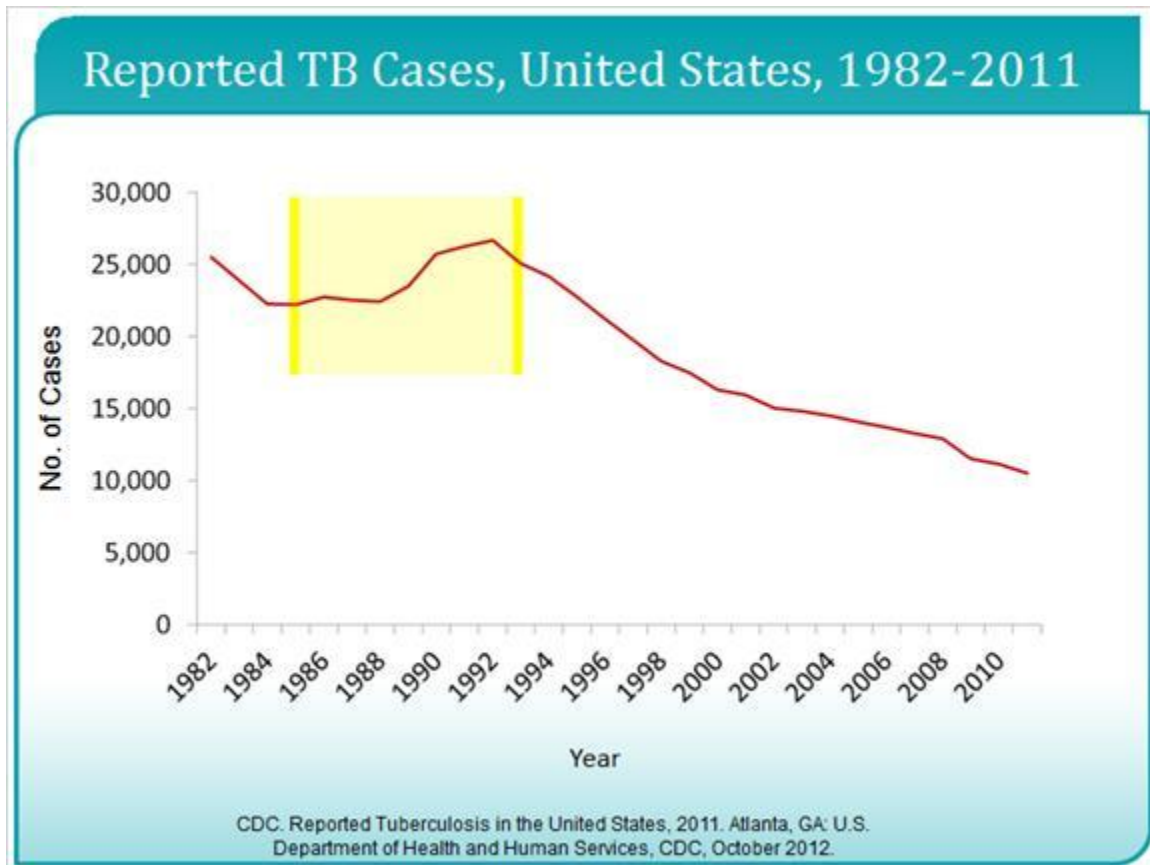
1.4 TB Case Rates,* United States, 2011



Notes:

In the United States, the national average TB case rate is declining. In 2009, an average TB case rate was 3.6 per 100,000 populations and declined 5.8% to 3.4 per 100,000 in 2011. However, there were still thirteen states including the District of Columbia that reported a TB case rate above 3.4 per 100,000. These areas accounted for 67% of the national total case rate.

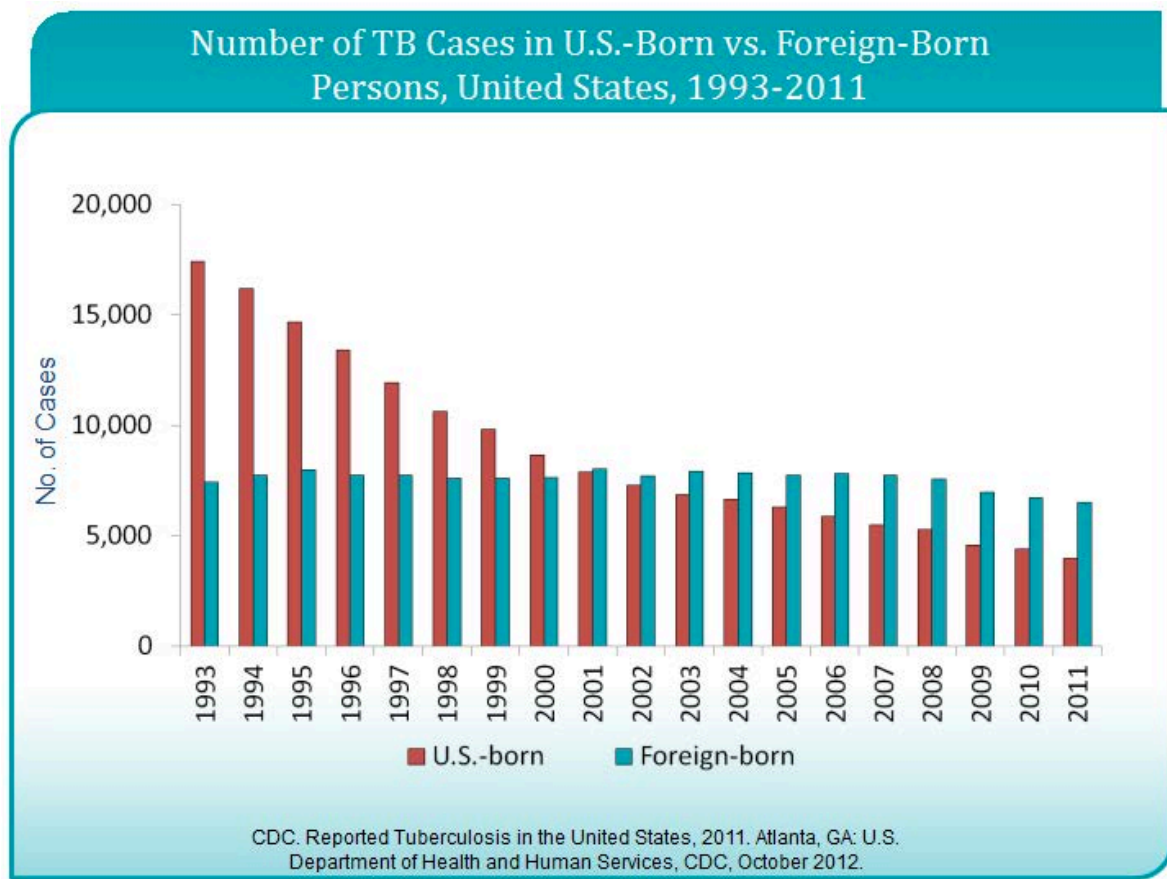
1.5 Reported TB Cases, United States, 1982–2011



Notes:

Here we see the trend in the annual number of reported TB cases between 1982 and 2011. The mid 1980's saw a resurgence of TB marked by several years of increasing case counts peaking in 1992. This peak in the early 1990's was partially due to the AIDS epidemic in that time.

1.6 Number of TB Cases in U.S.-Born vs. Foreign-Born Persons, United States, 1993–2011



Notes:

This next graph shows the trend in annual TB cases between US born and foreign born persons starting from the first year of decline after resurgence in 1993 through 2011. Over this time period we see a declining number of US born cases juxtaposed with virtually level number of cases among foreign-born persons.

This translates to an increase in overall percentage of cases that are foreign-born. For example, the percentage of cases of foreign-born persons increased from 29% in 1993 to 62% in 2011. Five countries of birth account for the highest proportion of cases among foreign-born persons reported with TB in the United States in 2011. They are Mexico at 22%, Philippines at 12%, India with 8%, Vietnam with 8% and China with 6% of the foreign-born cases.

1.7 TB Infection vs. TB Disease

TB Infection vs. TB Disease	
Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Not a TB case	A TB case
Does not require respiratory isolation	May require respiratory isolation
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does not feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal

Notes:

It is important to differentiate latent TB infection or LTBI with TB disease. This chart shown on this slide describes the characteristics that contribute to defining LTBI versus active TB disease. Persons with LTBI have a small number of bacilli antibodies that are alive but inactive and cannot spread the bacteria to others. Also, the bacteria will not be detected by AFB smear and culture. Persons with LTBI are not considered a TB case and don't require isolation. However treatment for LTBI should be considered.

Individuals with TB disease are infectious and potentially have AFB smear and culture positives specimens. Cases of TB disease must be reported to the public health authorities.

1.8 Risk Factors for TB Infection

Risk Factors for TB Infection

- Sharing air space with someone sick with TB disease (e.g., live, work, or play together)
- Crowded living conditions
- Residency or travel in a country with a high-incidence of TB disease
- High risk occupations including laboratory and health care jobs

Notes:

Environmental risk factors for TB infection would include any circumstance which may increase shared air space with and thus expose a person to someone who is sick with TB disease. Examples include crowded living conditions such as prisons, homeless shelters and long term care facilities as well as residency or travel in a country with a high-incidence of TB disease.

Additionally, occupations including those in laboratory and healthcare settings are considered higher risk for TB infection than the general population.

1.9 Risk of Progression to TB Disease

Risk of Progression to TB Disease

- Untreated, 5% of infected persons with normal immunity develop TB in the first 1-2 years post infection, another 5% develop TB later in life
- Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated

Notes:

The risk of progression from LTBI to active TB disease is highest during the first two years of infection. Left untreated it is estimated that 5% of infected persons with normal immunity will develop TB in the first 1-2 years post infection, with an additional 5% later in life. Thus, there is about a 10% lifetime risk for infected persons if left untreated.

1.10 Risk Factors for TB Disease

Risk Factors for TB Disease

- Low socioeconomic status
- Homelessness
- Diseases, conditions, or drugs that weaken the immune system:
 - Cancer
 - Transplantation
 - Malnutrition
 - Diabetes
 - Alcoholism
 - HIV infection
 - TB is the leading cause of death worldwide in HIV-infected individuals
 - 10% lifetime risk for developing active TB among HIV-uninfected
 - 10% annual risk for developing active TB among HIV-infected
- Major surgical procedures may occasionally trigger dissemination

Notes:

Additionally, comorbidities, especially diabetes, are becoming increasingly important in terms of how TB disease is treated.

1.11 Approximately how many cases of TB disease are reported in the United States each year?

Knowledge Check

Approximately how many cases of TB disease are reported in the United States each year?

- ☐ < 100
- ☐ 500 - 1,000
- ☒ 10,000
- ☐ 25,000 - 30,000

1.12 Since 1992, the overall number of TB cases in the United States has decreased, and the proportion of these cases attributed to foreign-born persons has

Knowledge Check

Since 1992, the overall number of TB cases in the United States has decreased, and the proportion of these cases attributed to foreign-born persons has

- ☒ Increased
- ☐ Decreased
- ☐ Remained the same
- ☐ No clear pattern is evident

1.13 True or False: A negative TB culture indicates the absence of TB disease.

Knowledge Check

True or False: A negative TB culture indicates the absence of TB disease.

- ☐ True, culture confirmation is required to diagnose TB disease.
- ☒ False, TB disease can be diagnosed based on signs and symptoms in the absence of a positive TB culture.

1.14 Signs and Symptoms of TB Disease

Signs and Symptoms of TB Disease

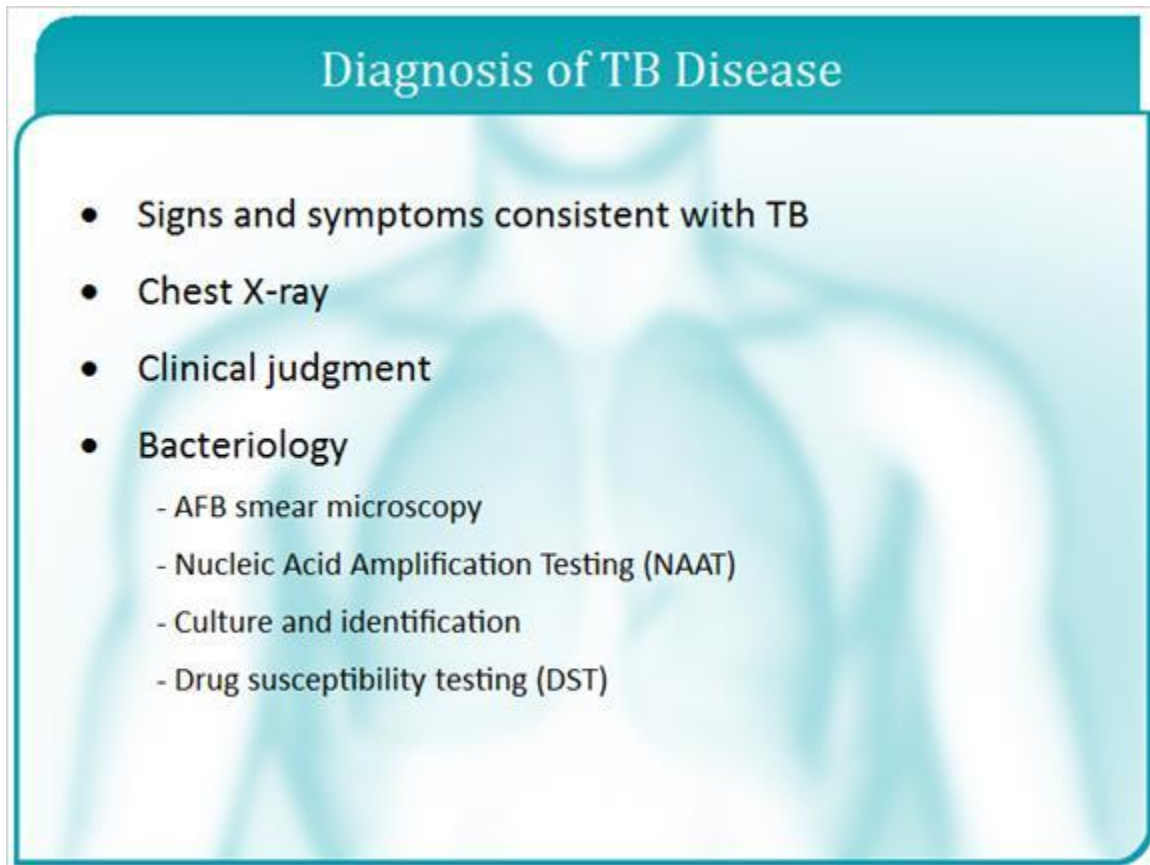
- **Extrapulmonary TB**
 - *M. tuberculosis* can infect any organ of the body
 - Symptoms vary by site of disease

- **Pulmonary TB**
 - Cough >2 weeks, often productive (sputum), can be bloody
 - Fever
 - Night sweats
 - Weight loss
 - Chest pain

Notes:

M. tuberculosis can infect any organ of the body and TB disease is thus classified as pulmonary, extrapulmonary or both for symptoms varying by site of infection. Signs and symptoms of active pulmonary TB disease include a cough of greater than two weeks that is often productive and bloody as well as fever, weight loss, night sweats and chest pain.

1.15 Diagnosis of TB Disease



Notes:

Diagnosis of TB disease is based on a number of factors including signs and symptoms consistent with TB disease, chest X-ray, clinical judgment, and laboratory examinations including AFB smear microscopy, Nucleic Acid Amplification Testing (NAAT) and Culture and identification. Drug susceptibility testing (DST) is required to ensure effective treatment is initiated.

In the United States, only about 75% of TB cases are culture confirmed so clinicians may choose to provide a clinical diagnosis based on the entire clinical picture and associated risk factors even in the absence of laboratory confirmation. Patients with a clinical diagnosis of TB without laboratory confirmation will be treated empirically with anti-tuberculosis medications.

1.16 TB Treatment Regimens

TB Treatment Regimens

- TB infection - LTBI treatment options
 - 9 months isoniazid
 - 4 months rifampin
 - 3 months isoniazid plus rifapentine
- TB disease - pulmonary, drug-susceptible TB, 6-month standard regimen
 - Intensive phase: 2 months isoniazid, rifampin, ethambutol, and pyrazinamide
 - Continuation phase: 4 months of isoniazid and rifampin

Notes:

Preventing tuberculosis by treating latent infection is the cornerstone of the US strategy for TB elimination. However treatment for LTBI is voluntary. There are currently three LTBI treatment options: 9 months isoniazid, 4 months rifampin or 3 months isoniazid plus rifapentine. All three treatment regimens are considered equivalent in effectiveness.

In 2011, three randomized control trials showed that isoniazid and rifapentine administered weekly for three months under directly observed therapy is more likely to be completed than nine months of daily isoniazid without DOT. The nine month isoniazid regimen requires abstinence from alcohol due to risks of hepatotoxicity which may add to the difficulty of strict compliance.

For pulmonary, drug-susceptible TB, there is a 6-month standard treatment regimen consisting of two phases. The first, known as the intensive phase generally includes 2 months of treatment with isoniazid, rifampin, ethambutol, and pyrazinamide. The second, known as the continuation phase generally includes 4 months of treatment with isoniazid and rifampin.

1.17 Drug-Resistant TB

Drug-Resistant TB

- Multi-drug-resistant TB (MDR-TB)-resistant to at least rifampin (RIF) and isoniazid (INH)
- 3.7% of new cases worldwide are estimated to have MDR-TB (20% among previously treated TB cases)
- 50% of all MDR-TB cases are estimated to occur in India and China
- Globally, outcome data for MDR-TB is limited. Highest death rates among MDR-TB patients seen in Africa (19%)
- Extensively drug-resistant TB (XDR TB)-MDR-TB plus resistance to at least one fluoroquinolone and one second-line injectable drug

http://www.who.int/tb/publications/global_report/en/index.html

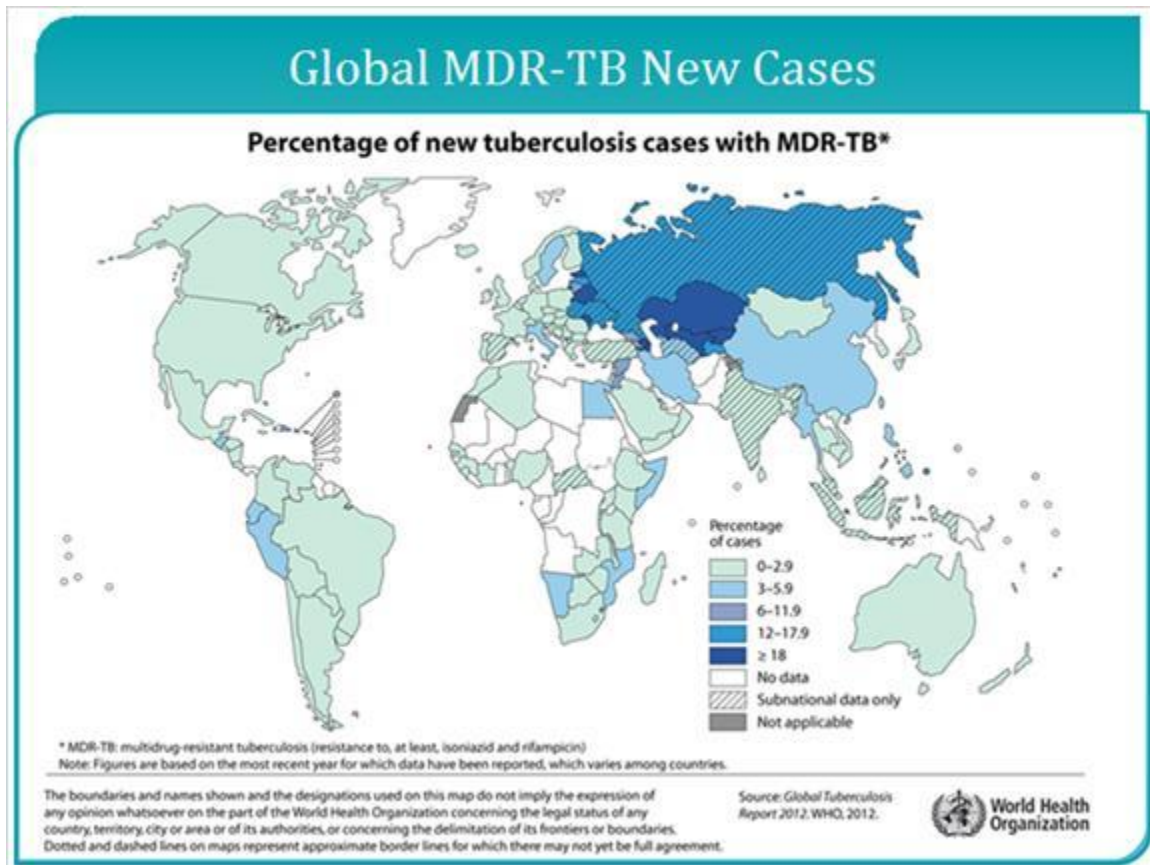
Notes:

Rifampin and isoniazid are the two most effective first line drugs used to treat TB. Multi-drug-resistant TB or MDR-TB is defined as resistant to at least rifampin (RIF) and isoniazid (INH). 3.7% of new TB cases worldwide are estimated to be MDR-TB. Among previously treated TB cases this proportion increases to 20%.

In 2011 in the United States, the proportion of MDR-TB was 1.3% in patients without previous TB and 7.8% for patients who have been previously treated. It is estimated that 50% of all MDR-TB cases are estimated to occur in India and China. Globally, there is limited data about the outcome for patients with MDR-TB.

Extensively drug-resistant TB (XDR TB) is defined as MDR-TB plus resistance to at least one fluoroquinolone and one second-line injectable drug. Second-line injectables include amikacin, kanamycin and capreomycin.

1.18 Global MDR-TB New Cases

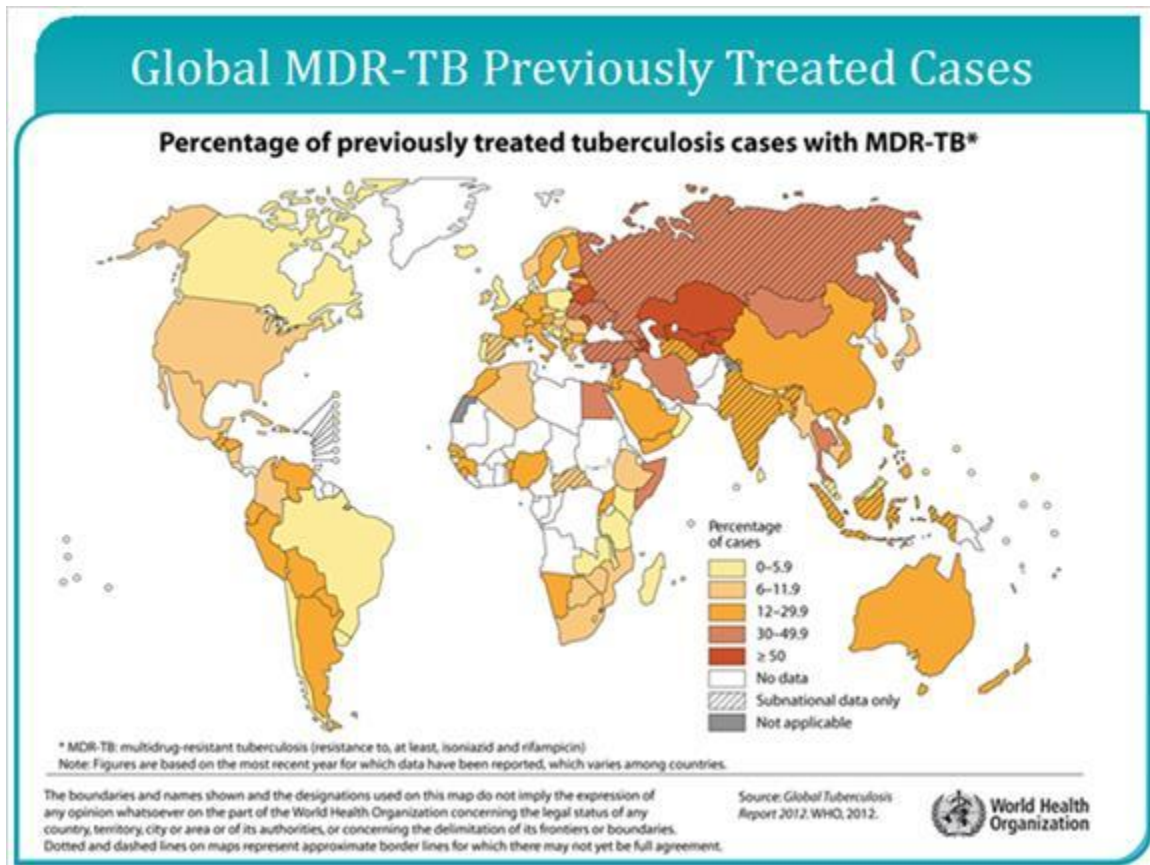


Notes:

As previously mentioned, the proportion of MDR among new TB cases is highest in Eastern Europe and Central Asia. Standard anti-TB drugs have been used for decades and resistance of these anti-tuberculosis medications is growing. The primary cause of MDR is inappropriate and incorrect use of these drugs along with poor quality medications.

Directly Observed Therapy or DOT is optimal for successful outcomes of individuals treated with TB. With DOT, an individual is observed taking all of their medications. This also allows the individual to be closely monitored for adverse events and tolerance issues. Unfortunately, resources do not often exist to allow DOT for all patients.

1.19 Global MDR-TB Previously Treated Cases



Notes:

This map shows a similar distribution of MDR-TB among previously treated cases. Also, notice on the color-coded map there are areas that are white in color, including many countries in Africa indicating no data is available regarding drug resistance. The lack of data in these countries is a result of the limited laboratory capacity for drug resistance monitoring.

1.20 MDR-TB Treatment

MDR-TB Treatment

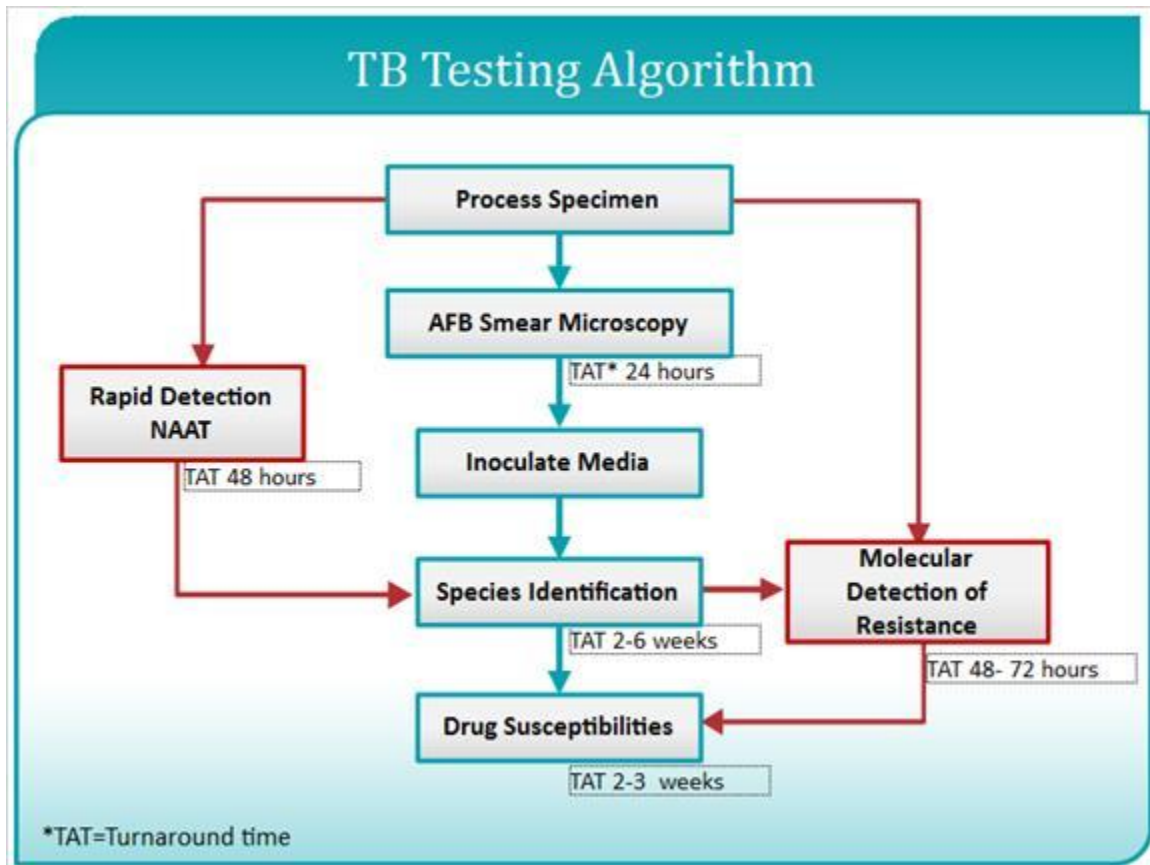
- Two years of therapy with second-line drugs
- Expensive and drugs may not be readily available
- Second-line drugs often cause severe adverse effects and are very difficult for patients to tolerate
- Increasing resistance to second-line drugs due to frequent changes in regimens (often due to toxicity), poor adherence, and too few drugs available for regimen

WHO; Guidelines for the programmatic management of drug-resistant tuberculosis: Emergency Update 2008

Notes:

Treatment for MDR-TB requires at least two years of therapy with second-line drugs. These drugs are expensive and not readily available. Additionally, second-line drugs often cause adverse effects and can be difficult for patients to tolerate. Increasing resistance to second-line drugs is due to frequent changes in regimens often due to toxicity, poor adherence and too few drugs available for an effective regimen.

1.21 TB Testing Algorithm



Notes:

The following is an example of a laboratory algorithm incorporating conventional and molecular methods for detection, identification and drug susceptible testing to provide a time efficient, comprehensive approach to Tb diagnostics that can contribute to clinical decision making.

1.22 The Laboratory Is Essential

The Laboratory Is Essential

- Laboratory is a critical partner in the diagnosis of TB
- Rapid, reliable results are essential for early detection of M. tb complex (MTBC) to prevent ongoing transmission
- Drug susceptibility test results identify drug resistance and help guide the clinician in providing appropriate treatment
- Laboratory results important for monitoring patient response to therapy

Notes:

This brings us to why the laboratory is an essential and critical partner in the diagnosis of TB. The microbacteriology laboratory provides rapid and reliable results for early detection of M. tb complex (MTBC) to prevent ongoing transmission and drug susceptibility test results to help guide the clinicians in providing appropriate treatment. Lastly, laboratory results important for monitoring patient response to therapy.

This is the end of the overview of tuberculosis which is the first module in the series from the Association of Public Health Laboratories Essentials of Microbacteriology Laboratory promoting quality practices. Please see the CDC and APHL websites for more information on the topics presented here.

1.23 MDR TB is defined as resistance to what drug(s)?

Knowledge Check

MDR TB is defined as resistance to what drug(s)?

- ☐ Pyrazinamide
- ☐ Streptomycin and Isoniazid
- ☐ Pyrazinamide, Ethambutol, and Isoniazid
- ☒ Rifampin and Isoniazid

1.24 According to standard laboratory testing algorithms for TB, what is the next step after a single positive NAA test result?

Knowledge Check

According to standard laboratory testing algorithms for TB, what is the next step after a single positive NAA test result?

- ☐ Report final result as positive for M. tuberculosis and do not perform culture
- ☐ Wait until confirmed by culture before reporting results to healthcare provider.
- ☒ Positive NAAT result should be reported and culture performed.
- ☐ Not enough information provided to determine the next step.

1.26 Course Complete



Notes:

This brings us to why the laboratory is an essential and critical partner in the diagnosis of TB. The microbiology laboratory provides rapid and reliable results for early detection of *M. tb* complex (MTBC) to prevent ongoing transmission and drug susceptibility test results to help guide the clinicians in providing appropriate treatment. Lastly, laboratory results important for monitoring patient response to therapy.

This is the end of the overview of tuberculosis which is the first module in the series from the Association of Public Health Laboratories Essentials of Microbiology Laboratory promoting quality practices. Please see the CDC and APHL websites for more information on the topics presented here.