Tuberculosis in Pregnancy

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Tuberculosis (TB) is a communicable disease that is a major cause of ill health and one of the leading causes of death worldwide. until the coronavirus (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent, ranking above human immunodeficiency virus (HIV) /acquired immunodeficiency syndrome (AIDS). Globally, the estimated number of deaths from TB increased between 2019 and 2021, reversing years of decline between 2005 and 2019. In 2023, there were an estimated 1.4 million HIV-negative people with TB; and 187,000 deaths among HIV-positive people with TB, for a combined total of 1.6 million. An estimated 10.6 million people fell ill with TB in 2023, in increase of 4.5% form 10.1 million, in 2020. The burden of drug-resistant TB is also estimated to have increased between 2020 and 2021, with 450,000 new cases of rifampicin-resistant (1). There is a strong and enduring relationship between TB incidence rates per capita and the indicators of development such as average income and undernourishment. Economic and financial barriers can affect access to healthcare for TB diagnosis and completion of TB treatment; about half of TB patients and their households face catastrophic total costs' due to TB disease. Progress towards universal health coverage (UHC), better levels of social protection and multisectoral action on broader TB determinants area are all essential to reduce the burden of TB disease. TB in pregnancy poses a substantial risk of mortality and morbidity to both the pregnant woman and the fetus, if not diagnosed and treated in a timely manner.

The purpose of this document is assessing the risk of having *Mycobacterium tuberculosis* infection during pregnancy and its evidence-based management. Obstetricians and gynecologists are in a unique position to identify individuals with infection and facilitate further evaluation and follow up as needed. TB evaluation consists of a TB risk assessment, medical history, physical examination, and a symptom screen; a TB test should be performed if indicated by the TB evaluation. If a pregnant woman has signs and symptoms of TB or if the test result for TB infection is positive, active TB disease must be ruled out before delivery, with a chest radiograph and other diagnostics as indicated. Treatment should be coordinated with the TB Control Program, within the respective jurisdiction. The World Health Organization (WHO) End TB Strategy is also discussed.

Epidemiology and Surveillance

Although the incidence of active TB disease is lower in the United States (U.S.) than many other countries, active TB disease during pregnancy remains associated with a substantially elevated risk for poor maternal and fetal outcomes, including a 3-fold increase in maternal morbidity (e.g., antenatal admission, anemia, and cesarean delivery), 9-fold increase in miscarriages, 2-fold increase in preterm birth and low birthweight, and 6-fold increase in perinatal death (2). Between 3.1% and 5.0% of the U.S. population are estimated to be living with latent TB infection (3). Only 5 – 10% of individuals with latent TB infection will progress to active TB disease over

their lifetimes; most individuals with TB infection will remain asymptomatic (3). It is difficult to predict who will progress from latent TB infection to active TB disease. Screening individuals at risk for TB infection or at risk for progressing to active TB disease and ensuring proper treatment are important to reduce complications of the disease and are critical for the efforts to control TB in the U.S.

The perinatal period is an important opportunity for TB to screen, diagnose and treat those at high risk for this infection. Nearly one fourth of the world population has TB infection. As the number of children in immigrant families in the U.S. has increased overtime, understanding the implications for TB infection during pregnancy is important. Five-most common countries of origin being moderately to very high-burden TB countries are: Mexico, Philippines, Vietnam, India, and China.

Risk Factors for TB Infection and/or Progression

Risk factors for TB infection in pregnant women are the same as risk factors among general population. These are (4):

High-risk of TB Infection

1. Contacts of people with active tuberculosis disease;
2. People from a country where tuberculosis is common, including most countries in:
    a) Africa,
    b) The Caribbean,
    c) Eastern Europe,
    d) Latin America,
    e) Russia
3. Living or working in high-risk setting (depending on local epidemiology), including:
    a) Correctional facility,
    b) Healthcare facility working with patients at increased risk for tuberculosis,
    c) Homeless shelter,
    d) Long-term care facilities or nursing homes.

High-risk of TB progression

1. HIV infection,
2. Tuberculosis infection within the past 2 years,
3. Intravenous drug user,
4. Immunocompromise.

Pathophysiology

Tuberculosis is caused by infection with one of seven acid-fast bacilli that make up the *Mycobacterium tuberculosis* complex most commonly *M tuberculosis* in the U.S. (5). After exposure, a proportion of people will have *M tuberculosis* infection without experiencing any signs or symptoms of active TB disease. These people have latent TB infection, which is not contagious, but without treatment latent TB infection can progress to active TB disease, most commonly in the first 2 years after infection (6).

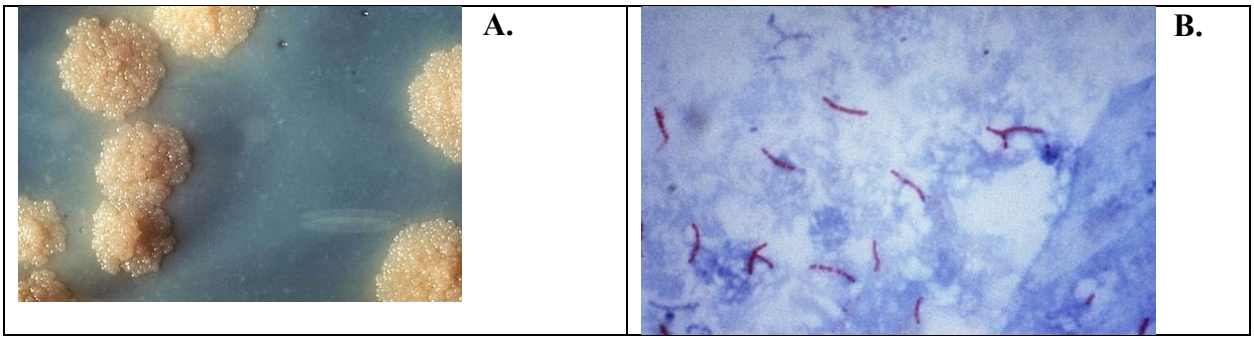


Figure 1. A. *Mycobacterium tuberculosis* colonies; **B.** Microscopic visualization of acid-fast bacteria (*M tuberculosis*) by Ziehl-Neelsen stain;

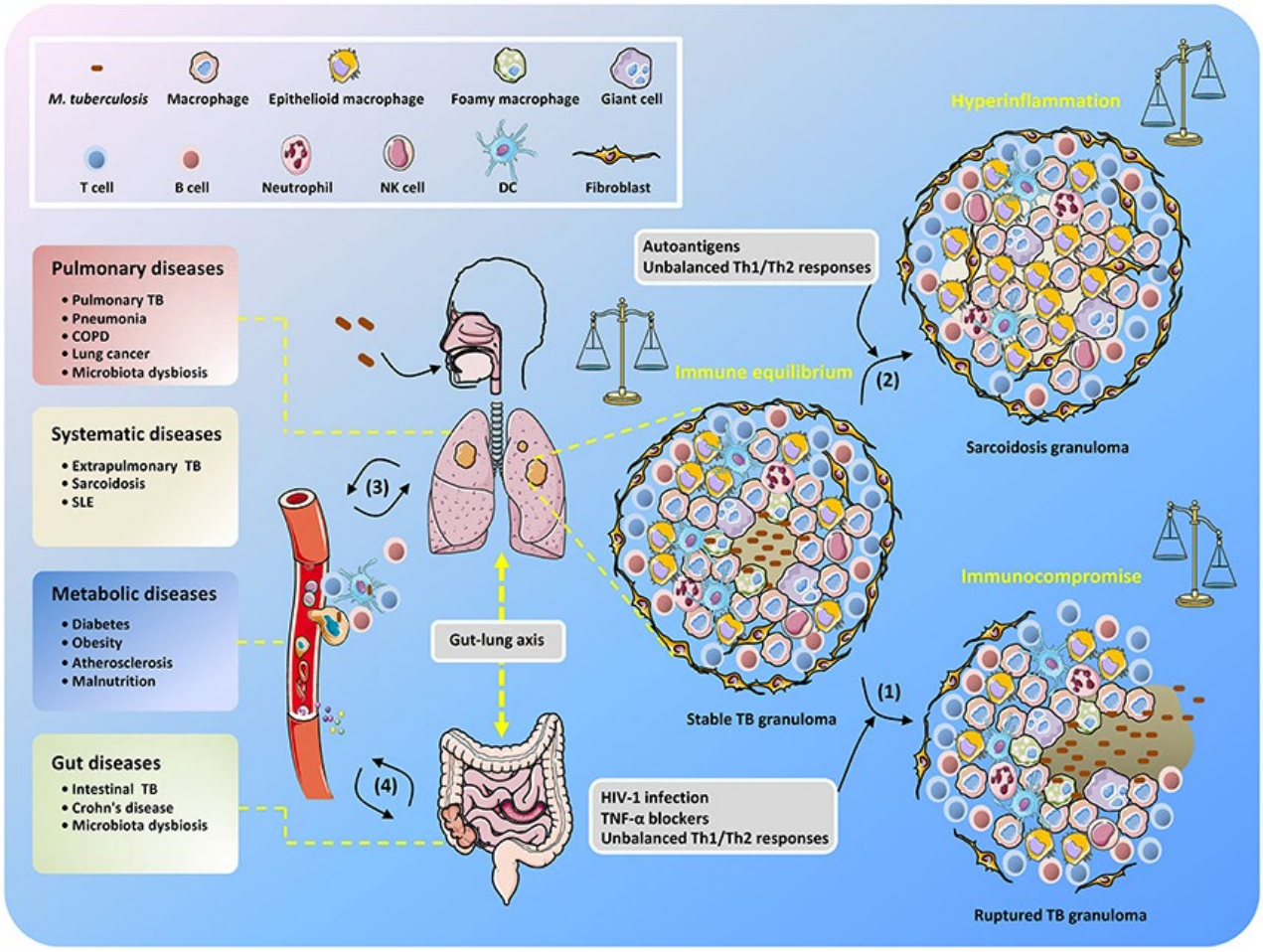


Figure 2. Unbalanced immune system in TB patients results in the development of diverse diseases. After inhalation of *Mycobacterium tuberculosis*, granuloma are formed with piles of immune cells to sequester the uncleared bacteria that subsequently step into latency. When the host becomes immunocompromised, *M tuberculosis* is reactivated to replicated and disseminate, which is accompanied by granuloma caseating, liquefying, and cavitating (6).

Non-caseating granuloma may continuously exist after bacteria elimination and present as sarcoidosis because of excessive host inflammatory immune responses (7). The infected cells, *M. tuberculosis* components, metabolites, and host immune molecules such as cytokines and chemokines are able to be exchanged and transmitted via the circulatory system, thus increasing

the risk of disease development (8). The gut microbiota is also involved in the interplay between *M. tuberculosis* and TB comorbidity via the gut-lung axis (9).

Differentiating Active Tuberculosis Disease and Latent Tuberculosis Infection

Most people with a TB infection have latent TB infection, and never experience any manifestations of their infection, that is, within 2-8 weeks, macrophages ingest and surround the tubercle bacilli. The cells form a barrier, called a *granuloma*, which keeps the bacilli contained.

Feature	Active TB Disease	Latent TB Infection
Signs and symptoms	May include one or more: Chest pain, cough, decreased appetite, fatigue, fever, hemoptysis, night sweats, weight loss	None
IGRA or TST	Usually positive; negative test result does not rule out active TB	Usually positive
Chest radiograph (X-Ray)	Usually abnormal*	Usually normal
Respiratory specimens	Usually smear- or culture-positive†	Smear- and culture negative‡
Infectious	Yes	No

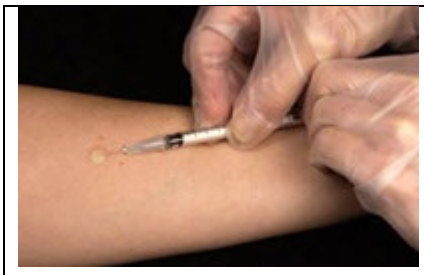
Table 1. Source**:** Center for Disease Control and Prevention (CDC); Abbreviations: TB – tuberculosis; IGRA-interferon-gamma release assay; TST – Mantoux tuberculin skin test.
*Chest radiograph may be normal in persons with advanced immunosuppression or extrapulmonary disease.
†Respiratory specimen smears or culture may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease.
‡Respiratory specimens are obtained only if ruling out active TB disease based on abnormal chest radiograph, symptoms, or clinical suspicion.

Diagnosing and TB Testing in Pregnancy

Everyone should be evaluated for TB on initiating antenatal care by assessing symptoms, performing a physical examination, and ascertaining TB risk factors. Healthcare providers can use WHO's lists to determine whether an individual is from one of the 48 high-burden countries. Additionally, pregnant women should be further evaluated if they have a high-risk of progressing to active TB disease, this includes people who have HIV infection, people who are IV drug users, and people who are immunocompromised. The Mantoux tuberculin skin test or a TB blood test (i.e., interferon-gamma release assay [IGRA] may be used to test for TB in pregnancy (10).

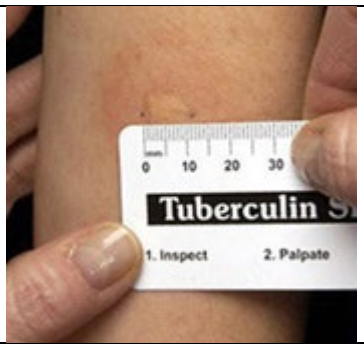
The **Mantoux tuberculin skin test (**TST) is one method of determining whether a person is infected with *Mycobacterium tuberculosis.* Reliable administration and reading of the TST requires standardization of procedures, training, supervision, and practice. The TST is performed by injecting 0.1 ml of tuberculin purified protein derivative (PPD) into the inner surface of the forearm. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. The TST is an ***intradermal*** injection. When placed correctly, the injection should produce a pale elevation of the skin (a wheal) 6 to 10 mm. in diameter.

The skin test reaction should be read between 48 to 72 hours after administration by a healthcare working trained to read TST results. A patient who does not return within 72 hours will need to be rescheduled for another skin test. Most persons can receive a TST. It is the recommended method of testing for children younger than 5 years of age. It should be noted that the American Academy of Pediatrics (AAP) recommends that either TST or TB blood test (IGRA), can be used in children 2 years and older. In children and adults – previously vaccinated with bacilli Calmette-Guérin (BCG), a TB blood test is preferred to avoid a false positive TST result caused by a previous vaccination with BCG (10).



A.

Administering TB skin test



B.

Reading the result of TB Skin Test Should be measured in millimeters of the induration.

Figure 3. Mantoux Tuberculin skin test (TST). A. injecting 0.1 ml of tuberculin purified derivative (PPD) into the inner surface of the forearm. B. Skin test is read between 48 to 72 hours after administration. Reaction should be measured in millimeters of the induration (firm swelling).

Classification of the Tuberculin Skin Test Reaction: Skin test interpretation depends on two factors – a) Measurement in millimeters of the induration; and b) Person's risk for TB infection or the risk of progression to TB disease if infected. The reaction should be measured of the induration (firm swelling). The reader should not measure erythema (redness). The diameter of the indurated area should be measured across the forearm (perpendicular to the long axis.

False-Positive and False-Negative TST Test

Some people may react to the TST even though they are not infected with *M tuberculosis*. The causes of these false-positive reactions my include, but not limited to the following:

1. Previous TB vaccination with the BCG vaccine;
2. Infection with non-tuberculosis mycobacteria (mycobacteria other than *M tuberculosis*);
3. Incorrect measurement or interpretation of reaction;
4. Incorrect antigen used.

TB blood test is the preferred method of testing for people who have received the BCG vaccine in order to prevent false-positive reactions. TB blood tests are also called interferon-gamma release assays or IGRAs. Some people may not react to the TST even though they are infected with *M tuberculosis*. The reasons for these false-negative reactions may include, but are not limited to the following:

1. Anergy (reduction or lack of immune response);
2. Recent TB infection (withing the past 8 to 10 weeks);
3. Very young age (younger than 6 months);
4. Recent live-virus measles or smallpox vaccination;
5. Incorrect method of giving the TST;
6. Incorrect measuring or interpretation of TST reaction.

Interpretation of Tuberculin Skin Test Reaction

Induration of 5 or more millimeter, Considered positive in:	**Induration of 10 or more millimeter, Considered positive in:**	**Induration of 15 or more millimeter Considered positive in:**
People living with HIV, Recent contact of a person with infectious TB disease, People with chest X-ray findings suggestive of previous TB disease, People with organ transplants. Other immunosuppressed people (e.g., patients on prolonged therapy with corticosteroids equivalent to/greater than 15 mg per day of prednisone or those taking TNF-a antagonists).	People born in countries where TB disease is common, including Mexico, Philippines, Vietnam, India, China, Haiti and Guatemala, or other with high-rates of TB. People who abuse drugs, Microbiology laboratory workers. People who live or work in high-risk congregate settings (nursing homes, homeless shelters, or correctional facilities). People with certain medical conditions that place them at high risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions). People with a low body weight (<90% of ideal body weight). Children younger than 5 years of age, Infants, children, and adolescents are exposed to adults in high-risk categories.	People with no known risk factors for TB.

Table 2. Interpretation of tuberculin skin testing

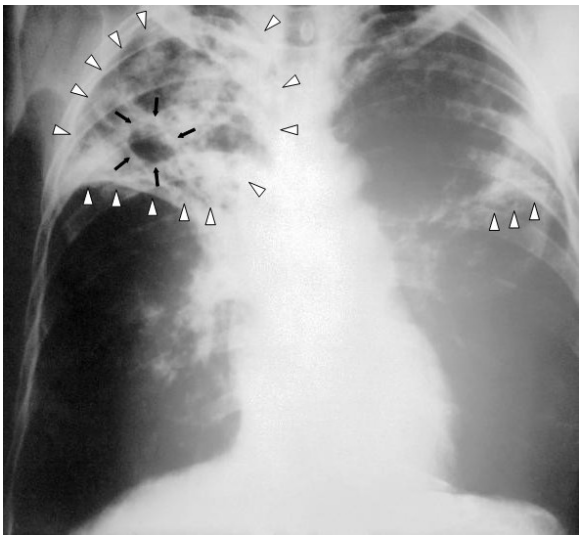
Diagnosis

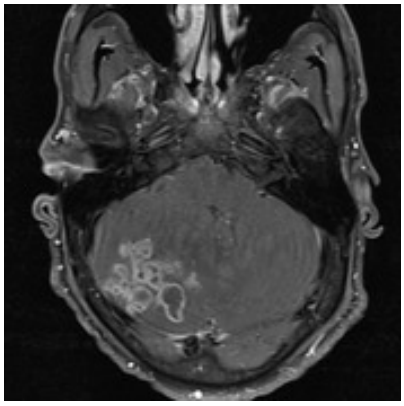
Diagnosis of Latent TB Infection

A diagnosis of latent TB infection is made if a person has a positive TB test result and a medical evaluation does not indicate TB disease. The decision about treatment for latent TB infection will be based on a person's chances of developing TB disease by considering their risk factors.

Radiologic Diagnosis of TB Disease

TB disease is diagnosed by medical history, physical examination, chest X-ray, and other laboratory tests. *See an example figure 4.*





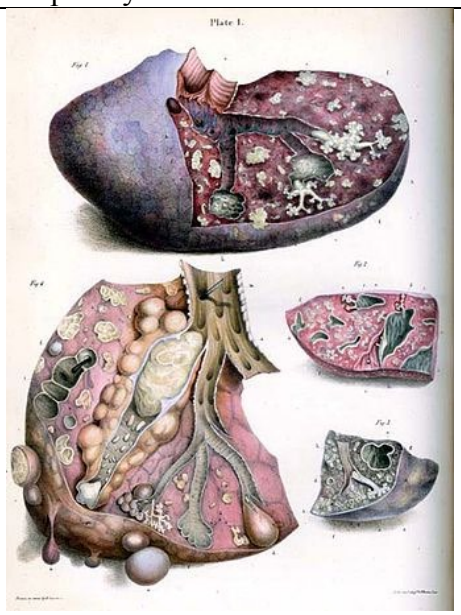
B.

A.

Figure 4. A. Chest X-Ray of a person with advanced tuberculosis: infection in both lungs is marked by white arrow-heads, and formation of a cavity is marked by black. arrows. **B.** MRI of Tuberculoma or tuberculous granuloma are well defined focal masses that result from *M tuberculosis* infection and are one of more severe forms of tuberculosis. It commonly occurs in the brain.

Histopathology

Macroscopically: a tuberculum is well defined firm nodule with a central caseous necrotic center.



A.

B

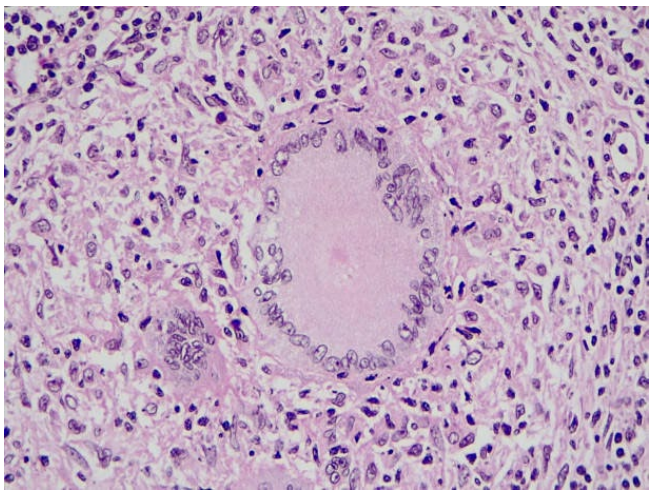


Figure 5. A. Illustration of tubercles in the lungs; **B.** Microscopy of tuberculosis; H & E Stain, multinucleated giant cells in tuberculosis lymph nodes. Microscopic appearance: histologically it consists of a central core of caseating necrosis with a surrounding wall of a florid granulomatous reaction containing Langhans giant cells, epithelioid histiocytes and lymphocytes. Unlike tuberculosis abscesses, organisms are uncommon or absent, and acute inflammatory infiltrate is not a prominent feature.

Effects of Pregnancy on Tuberculosis

Pregnancy does not appear to increase susceptibility to TB infection or progression from latent TB infection to active TB disease (11). Pregnancy also does not affect susceptibility to any particular site of TB infection (11). However, pregnancy can make the diagnosis of TB more difficult owing to hesitancy to perform radiographs and the similarly of screening symptoms with those of the pregnant state, for example, weakness, weight changes, and shortness of breath. A higher incidence of TB disease has been reported in the postpartum period than would otherwise be expected based on individual demographic (12). This may be a reflection of the immunological changes of pregnancy that may increase susceptibility to TB (e.g., suppression of the T-helper inflammatory response); these changes may mask symptoms during pregnancy but reverse postpartum with a corresponding exacerbation of symptoms.

Effects of Tuberculosis on Pregnancy

Adverse maternal and neonatal outcomes are increased with inadequate treatment, advanced disease, and late diagnosis of TB in pregnancy compared with earlier diagnosis (11). In a global systematic review and meta-analysis of 13 studies, including 3,384 pregnancies in which the pregnant woman had active TB disease, maternal and perinatal outcomes were consistently poorer with active TB disease than without (13). Active TB disease was associated with a 9-times greater rate of miscarriage. In pregnancies in women with active TB disease, perinatal death increased 4.2-fold, preterm birth increased 1.6-fold, acute fetal distress increased 2.3-fold, and low birth weight increased 1.7-fold. The risk of untreated active TB disease on the pregnant woman and on the fetus is greater than the risks of treatment (14).

Congenital TB may be transmitted form a mother with active TB disease to the fetus transplacental route through the bloodstream or lymphatics; it is also possible for *M tuberculosis* to be aspirated or ingested through the amniotic fluid during birth (15). Congenital TB may present in early neonatal period with sepsis or in the first 3 months of life with broncho-pneumonia and hepatosplenomegaly. Although rare, congenital TB has a high mortality rate (14). If congenital TB is suspected, evaluation should include histologic and mycobacterial culture of the placenta, in addition to the neonatal evaluation. It is difficult to distinguish between TB acquired as a fetus and TB acquired in the neonatal period. Current diagnostic criteria for congenital TB include a proven tuberculosis lesions in the first week of life, a primary hepatic TB complex or caseating hepatic granulomas (due to transmission through the umbilical vein, hence, forming a primary TB complex, in the fetal liver), TB of the placenta or maternal genital tract, or exclusion of postnatal transmission (16).

TB Treatment and Pregnancy

All four first-line medications used to treat TB (i.e., isoniazid [INH], rifampin [RIF], ethambutol [EMB], and pyrazinamide [PZA]) were classified by the Federal Drug Administration's (FDA's) prior letter-based system of medications in pregnancy as category C (17). However, the use of pyrazinamide during pregnancy is controversial in the U.S. given the lack of evidence about its

safety. If a drug susceptibility of active TB disease is diagnosed, a minimum of 9 months of therapy with isoniazid, rifampin, and ethambutol should be given (18).

Pyrazinamide is given in the standard four-drug regimen to people who are not pregnant; however, given possible risk, U.S. guidelines do not include this medication unless the pregnant woman has extrapulmonary or severe active TB disease or has co-infection with HIV (18). All treatment for active TB disease should be with directly observed therapy, in which a healthcare worker watches as a person takes each medications, which can be facilitated by the health department. Active TB disease treatment in pregnancy should occur with the support of an infectious disease specialist, especially in the context of antibiotic resistance, allergic reactions, extensive disease, or medication compliance concern (19).

TB Treatment Regimens for Pregnant Women

Diagnosis	Treatment
TB Disease	Preferred initial treatment regimen in INH, RIF, and EMB, daily for 2 months, followed by INH and RIF daily or twice weekly for 7 months (for a total of 9 months of treatment). Streptomycin should **not** be used because it has been shown to have harmful effects on the fetus. PZA is not recommended to be used because its effect on the fetus is unknown.
Latent TB	4-month daily regimen of RIF (4R); 3-month of daily regimen of INH and RIF (3HR); 6- or 9- month daily regimen of INH (6H or 9H), with pyridoxine (vitamin B6) supplementation; 3-month weekly INH and rifapentine (3HP) regimen is not recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety during pregnancy has not been studied.
HIV-Related TB Disease	Treatment of TB disease for pregnant women co-infected with HIV should be the same as for non-pregnant women, but with attention given to additional considerations.

Table 3. Abbreviations: INH: isoniazid; RIF: rifampin; EMB: ethambutol; PZA: pyrazinamide.
Source: Center for Disease Control and Prevention (CDC), United States of America (19). .

Main reason immediate treatment for latent TB infection in pregnancy should be considered is if the woman contracted TB in the past 2 years owing to the high-risk of progression to active TB disease (20). Hepatotoxicity with INH treatment might occur more frequently in pregnancy and in the early postpartum period (21). This risk must be balanced with the risk for developing active TB disease and the resultant potential consequences.

Few studies have examined teratogenicity of TB medications. INH crosses placenta, although it is not teratogenic even when given during the first trimester (22). RIF may have a small risk of teratogenicity; one study demonstrated that 3% of 446 exposed fetuses had abnormalities, including limb reductions, central nervous system abnormalities, and hypoprothrombinemia, as compared with 1% of those in control group (22). Additionally, hemorrhagic disease has been described in neonates born to a person taking RIF (23). Given the decades of experience with

RIF and limited data about potential teratogenicity, most experts agree that using RIF in pregnancy is appropriate. PZA has not been studied with regards to its effect on the fetus, and as such is avoided during the pregnancy, unless a person has co-infection with HIV. Streptomycin, which is not commonly used in the U.S. as a result of former high rates of resistance, should not be used in pregnancy owing to potential 8th cranial nerve toxicity in the fetus (24).

Contraindication of Antituberculosis Drugs in Pregnancy
Streptomycin;
Kanamycin;
Amikacin;
Capreomycin;
Fluoroquinolones.

Drug Resistant TB in Pregnancy
Pregnant women who are being treated for drug-resistant TB should receive counseling concerning the risk to the fetus because of the known and unknown risks of second-line antituberculosis drugs.

Postpartum Care and Breastfeeding

Notification of the pediatric team about maternal TB status is important for proper evaluation and care of the infant. Untreated active TB disease is a contraindicated to breastfeeding (25). Once treated with first-line drugs for at least 2 weeks and non-infectious (i.e., negative sputum culture), women with latent TB infection or active TB are encouraged to breastfeed. Pyridoxine supplementation should be given to all breastfeeding mothers taking INH, and their infants should be monitored for jaundice (26). Breastfed infants do not themselves require pyridoxine supplementation unless they are taking isoniazid. No infant toxic effects of TB medications delivered in breast milk have been reported (26). To minimize the dose the infant receives, a breastfeeding mother can take the medication immediately after a feeding and at the start of the infant's longest sleep period. The amount of isoniazid in breast milk is not prophylactic nor therapeutic for the infant.

There are rare cases of reports of tuberculosis mastitis and breast abscesses (14). If these conditions are diagnosed, breastmilk from the affected breast should be discarded until the mother is no longer contagious but breastfeeding can continue from the unaffected breast.

Treatment Completion

Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame. The duration of therapy depends on the drugs used, the drug susceptibility test results of the isolate, and patient's response to therapy. Most patients with previously untreated pulmonary TB disease can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is used for the majority of patients. All 6-month regimens must contain INH, RIF, and initially, PZA. **The goal is to complete all doses within 1 year.**

Co-Infection with Human Immunodeficiency Virus (HIV)

Pregnant women living with HIV need to be screened for TB early in pregnancy and evaluated thoroughly. The same treatment should be used for a person with HIV who is not pregnant. It is recommended that pregnant women with untreated HIV (i.e., not taking antiretroviral therapy) and active TB disease or latent TB infection should be treated for TB immediately (27). People with untreated HIV and latent TB progress to active TB disease at a rate of 10% per year (28).

HIV-infected patients are on numerous medications, some of which interact with anti-TB drugs. It is therefore strongly recommended that experts in the treatment of HIV-related TB be consulted. Due to the increased risk of developing acquired drug resistance, TB treatment may not be effective, with two exceptions (28);

1. Once-weekly administration of INH and rifapentine (RPT) in the continuation phase should **not** be used in any HIV-infected patient; and
2. Patients with advanced HIV (CD4 counts less than 100) should be treated with daily or three times weekly therapy in both the initial and continuation phase.

Every effort should be made to use a rifamycin-based regimen for the entire course of therapy in co-infected patients. The key role of rifamycin is the success of TB disease treatment mandates that the drug-drug interactions between the rifamycin and antiretroviral drugs be managed appropriately, rather than using TB treatment regimens that do **not** include a rifamycin or by withholding antiretroviral therapy until completion of anti-TB therapy. Of particular concern is the interaction of rifamycins with antiretroviral agents and other anti-infective drugs. Rifampin can be used for the treatment of TB with certain combinations of antiretroviral agents. Rifabutin, which has fewer drug-drug interactions due to its decreased induction of cytochrome P450 system, may also be used in place of rifampin and appears to be equally effective, although the doses of the rifabutin and antiretroviral agents may require adjustments and should be administered with expert consultation.

Therefore, patients with HIV- related TB disease should be treated with a regimen including a rifamycin for the full course of TB disease treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins.

Treatment Duration – 6 months should be considered the minimum duration of treatment for HIV-infected adults, even for patients with culture-negative TB disease. If there is evidence of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), the continuation phase should be prolonged 7 months (a total of 9 months of treatment). Directly observed therapy (DOT) and other adherence-promoting strategies should be used in all patients with HIV-related TB disease.

Extrapulmonary Tuberculosis Disease

In the U.S., 67% of TB cases are exclusively pulmonary, but TB can occur in any part of the body (15, 28). This is known as *extrapulmonary TB* and usually not infectious unless the person

also has pulmonary TB, or extrapulmonary disease has contact with air such as in infections of the oral cavity or an open abscess. The most common sites of extrapulmonary TB are lymph nodes, pleura, bones, meninges, and the urogenital tract (15).

As a general rule, the principles used for the treatment of pulmonary TB disease also apply to extrapulmonary form of the disease. A 6-month treatment regimen is recommended for patients with extrapulmonary TB disease, unless the organisms are known or strongly suspected to be resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months. The exception to these recommendations is central nervous system TB, for which the optimal length of therapy has **not** been established but some experts recommend 9 to 12 months. Most experts do recommend corticosteroids to be used as additional therapy for patients with TB meningitis and pericarditis. Consultation with a TB expert is recommended.

Drug-Resistant TB Disease

Drug-resistant TB disease can develop in two different ways:

- Primary Resistance – occurs in persons who are initially exposed to and infected with resistant organisms.
- Secondary Resistance, or acquired resistance – develops during TB therapy because of patient being treated with an inadequate regimen; patients not taking prescribe regimen appropriately; drug malabsorption; or drug to drug interaction leading to low serum levels.

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multi-drug-resistant) are at high risk for: Treatment failure; Relapse; Further acquired resistance; or Death.

Management of patients with drug-resistant TB disease is based on the following guidelines (28):

1. A single new drug should never be added to a failing regimen;
2. In patients with multi-drug-resistant (MDR) organisms resistant to first-line drugs in addition to INH and RIF, regimens employing 4 to 6 drugs that are new to the patient and to which the isolate shows in vitro susceptibility appear to be associated with better results;
3. Patients with MDR organisms should receive the highest priority for DOT, which should be administered either in the hospital, home, or other facility;
4. The use of drugs to which there is demonstrated in vitro resistance is **not** encouraged because there is little or no efficacy of these drugs and alternative medications may be available;
5. Resistance to RIF is associated with nearly all instances with cross-resistance to rifabutin and rifapentine (RPT);
6. There is no cross-resistance between streptomycin (SM) and other injectable agents, amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events); cross resistance between amikacin and kanamycin is not universal but frequently seen;

7. Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if monoresistance to PZA is observed, consideration must be given to the possibility that the disease is caused by *M. bovis,* **not** *M. tuberculosis*; and
8. Intermittent therapy should **not** be used in treating TB disease caused by drug-resistant organisms, except perhaps for injectable agents after the initiation phase (usually 2 to 3 months) of daily therapy.

Second-Line Drugs: Aminoglycosides and capreomycin; quinolones; thioamides; cycloserine; p-Aminosalicylic acid. Treatment is based on laboratory drug-resistance testing and epidemiological information – for 4 to 6 drugs for 2 years.

Congenital Tuberculosis

Congenital tuberculosis (CTB) is a relatively rare disease which occurs when the fetus is infected by *M.* tuberculosis acquired with in-utero or during delivery. Most patients are describe in case reports. Maternal TB status during pregnancy, the epidemiological history, T-SPOT. TB and other TB-related etiological tests and imaging are important for the early diagnosis and treatment of CTB, and are associated with favorable outcome (29). CTB has a mortality rate of 40-100%, and in many cases are only detected postmortem (30). According to the 1994 Cantwell diagnostic criteria, infants should be diagnosed with tuberculosis disease if they have at least one of the following:

i. Lesions in the 1st week of life;
ii. A primary hepatic complex or caseating hepatic granulomas;
iii. Tuberculosis infection of the placenta or the maternal genital tract; or
iv. Exclusion of possibility of postnatal transmission by a thorough investigation of contacts, including the infant's hospital attendants, and by adherence to existing recommendations for treating infants exposed to TB.

At present, there is no standard regimen for the treatment of CTB. Most children with CTB have no specific clinical manifestations and their condition is severe. Onset is usually within 4 weeks of birth.

Infants and Children

In the U.S., BCG vaccination should only be considered for those children who have a negative TST or IGRA result and who continually exposed to, and cannot be separated from, adults who:

1. Are untreated or ineffectively treated for TB disease (if the child cannot be given long-term treatment for infection); or
2. Have TB disease caused by strains resistant to isoniazid and rifampin.

The BCG vaccination is **contraindicated** in children infected with HIV.

Infants and children with TB disease should be treated with the regimens recommended for adults, with the exception that EMB is **not used** routinely in children. For children, whose clarity or sharpness of vision cannot be monitored, EMB is usually not recommended except when the risk of drug resistance is high or for children who have "adult-type" (upper lobe infiltration,

cavity formation) TB disease. In infants, TB is much more likely to disseminate; therefore, treatment should be started as soon as the diagnosis is established. Children commonly develop primary TB disease which generally affects the middle and lower lung. Children should be treated with three (rather than four) drugs in the initial phase: INH, RIF, and PZA). In general extrapulmonary TB in children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated TB and tuberculous meningitis, for which there are inadequate data to support 6-month therapy; thus 9 to 12 months of treatment is recommended.

Policies and Practices for Airborne Infectious Isolation All Rooms in Healthcare Settings

TB **Airborne Infection Isolation (AII)** rooms are designed to prevent the spread of droplet nuclei by a patient with TB disease. Healthcare facilities that provide care for patients with suspected or confirmed TB disease should have at least one AII room. In TB clinics, hospitals, and other inpatient settings, patients known to have TB disease or suspected of having TB disease should be placed in a TB AII room immediately. One characteristic of AII rooms is the negative pressure relative to other parts of the facility. Negative pressure allows air to flow from the corridors into the AII room. Healthcare settings with **AII** rooms observe the policies and practices indicated below (31):

i. Keep doors and windows closed as much as possible.
ii. Maintain an adequate number of AII rooms.
iii. Check negative pressure by monitoring and recording the direction of airflow on a daily basis.
iv. Perform diagnostic and treatment procedures in the AII room.
v. Ensure patients adhere to AII precautions.
vi. Group AII rooms in one part of the healthcare setting.
vii. Schedule patients with suspected and confirmed infectious TB disease for procedures when few Health-care Workers (HCWs) and no other patients are present.
viii. Provide a surgical mask for patients with suspected or confirmed infectious TB disease during transport, in waiting areas, and when others are present; and
ix. Review environmental control maintenance procedures and logs to determine if maintenance is being conducted properly and regularly.

WHO TB Infection Prevention and Control (IPC) Recommendations

The **administrative controls** are management measures aimed at reducing the risk of exposure to *M. tuberculosis* for individuals attending health facilities or a congregate setting. The **environmental controls** are intended to prevent the spread of infectious droplets and reduce their concentration in the ambient air. The **respiratory protection** comprises the use of personal protective equipment to limit the risk of acquiring *M. tuberculosis* infection. The following recommendations provide suggestions on how countries can integrate TB-specific actions into broader national IPC programs (32):

Recommendation 1: Triage people with TB signs and symptoms, or with TB disease, is recommended to reduce *M. tuberculosis* transmission to health workers (including community

health workers), persons attending health care facilities or other persons in settings with a high risk of transmission.
Recommendation 2: Respiratory separation/isolation of people with presumed or demonstrated infectious TB is recommended to reduce *M. tuberculosis* transmission to health workers or other persons attending healthcare facilities.
Recommendation 3: Prompt initiation of effective TB treatment of people with TB disease is recommended to reduce *M. tuberculosis* transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high-risk of transmission.
Recommendation 4: Respiratory hygiene (including cough etiquette) in people with presumed or confirmed TB is recommended to reduce *M. tuberculosis* transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high-risk of transmission.
Recommendation 5: Upper-room germicidal ultraviolet systems are recommended to reduce *M. tuberculosis* transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high-risk of transmission.
Recommendations 6: Ventilation systems (including natural, mixed-mode, mechanical ventilation and recirculated air through high-efficiency particulate air filters) are recommended to reduce *M. tuberculosis* transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission.
Recommendation 7: Particulate respirators, withing the framework of a respiratory protection program, are recommended to reduce *M. tuberculosis* transmission to healthcare workers, persons attending healthcare facilities or other persons in settings with a high risk of transmission.

To achieve the optimum impact on TB transmission, the recommended interventions given above should be implemented as a package, not selectively. In settings where there is a high-risk of *M. tuberculosis* transmission, it is important to develop and implement integrated, well-coordinated and multisectoral actions for TB IPC across the health and non-health sectors.

The bacilli Calmette-Guérin (BCG) Vaccination

The BCG vaccine is a live, attenuated (weakened) vaccine derived from a strain of *Mycobacterium bovis* that was developed over several years by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humansij1921. Since then, many different strains have been derived and used throughout the world. BCG vaccination is **not** generally recommended, routinely, in the U.S., because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the U.S., and vaccine interference with the ability to determine TST reactivity. Many highly TB-prevalent countries vaccinate infants with BCG as part of their TB control effort to prevent children from contracting severe disseminated TB or TB meningitis.

BCG vaccination in the United States, may be considered in limited circumstances for selected persons who meet specific criteria. The use of the BCG vaccine should be undertaken only after consultation with local health departments and experts in the management of TB. Recent BCG vaccination may cause a subsequent false positive reaction to the TST. Thus, it may complicate

decisions to prescribe treatment for latent TB infection for BCG-vaccinated persons who have a positive TST result. In such cases, IGRA would be the test of choice for latent TB diagnosis.

BCG vaccination is contraindicated in children infected with HIV. In the U.S., the BCG vaccination should only be considered in infants and children, who have a negative TST or IGRA result and who are continually exposed to, and cannot be separated from adults who:

(a) are untreated or ineffectively treated for TB disease (if the child cannot be given long-term treatment for infection); or
(b) have TB disease caused by strains resistant to isoniazid and rifampin (33).

Healthcare workers: BCG vaccination should be considered on an individual basis. It should **not** be required for employment or for assignment of healthcare workers in specific work areas.

Contraindications to BCG Vaccination

1. HIV infection;
2. Pregnancy;
3. Congenital immunodeficiency;
4. Leukemia;
5. Lymphoma;
6. Generalized malignancy;
7. High-dose steroid therapy;
8. Alkylation agents;
9. Antimetabolites; and
10. Radiation therapy.

It is also prudent to avoid giving BCG vaccination to pregnant women, although no harmful effects of BCG on the fetus have been observed.

World Tuberculosis (TB) Day

World Tuberculosis (TB) Day commemorates the discovery of the organism that causes TB (*Mycobacterium tuberculosis)* by Dr. Robert Koch on 24 March 1882. It is celebrated on this date each year to raise awareness among public and policy makers that TB remains an epidemic in most parts of the world, and a public health concern in developed countries, causing the deaths of about one and a half million people each year. Hundreds of recognized species of mycobacteria, in addition to *Mycobacterium tuberculosis,* can cause pulmonary disease and other illnesses. These organisms are diverse in their ability to cause human disease and can be pathogenic, opportunistic, or non-pathogenic.

Of the 10 million people estimated to have fallen ill with TB in 2019, nearly half million developed TB resistant to RIF, and over 1 million developed TB susceptible to RIF but resistant to INH. Drug resistance must be detected rapidly and accurately to initiate appropriate and effective treatment. Tuberculosis laboratories around the world can use the catalogue as a support in the interpretation of genome sequencing results. The catalogue can also guide the development of new molecular drug susceptibility tests, including next-generation sequencing (34).

The Global TB Report and requested progress reports for the World Health Assembly and the UN General Assembly in 2019 – 2020 and 2022 – 2023 are reinforcing global accountability to end TB. Resolution A/RES/73/3 adopted by the United Nations General Assembly on 10 October 2018 following approval by the high-level meeting of the General Assembly on the fight against tuberculosis on 26 September 2018. Details: https://www.who.int/publications/m/item/political-declaration-of-the-un-general-assembly-high-level-meeting-on-the-fight-against-tuberculosis

Strengthening Multi-sectoral Accountability to end Tuberculosis
https://www.who.int/activities/strengthening-multisectoral-accountability-to-end-tb

Summary

Untreated TB disease represents a greater hazard to a pregnant women and her fetus than does its treatment. Because of the risk of TB to the fetus, treatment of TB in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do **not** appear to have teratogenic effects. Streptomycin is the only anti-TB documented to have harmful effects on the human fetus (congenital deafness) and should **not** be used. Although detailed teratogenicity data are **not** available, PZA can probably be used safety during pregnancy and is recommended by the WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD). If PZA is **not** included in the initial treatment regimen, the minimum duration of therapy is 9 months. For pregnant women with multidrug resistant (MDR) TB treatment should be done in consultation with the multidrug resistant TB expert. Many of currently medications currently used for treatment of multidrug resistant TB may be harmful to the fetus.

Tuberculosis during pregnancy confers an elevated risk for maternal and infant mortality and morbidity. Clinicians who care for pregnant women should assess everyone for signs and symptoms as well as risk for TB infection or progression to active TB, if they have infection. Consultation and collaboration with disease experts, including infectious disease specialists, TB control programs, TB medical consultants and health departments, is highly suggested, to ensure timely and accurate diagnosis, linkage to care, and treatment compliance.

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