Washtenaw County Health Department

Washtenaw County Health Department Latent Tuberculosis Infection Diagnosis and Management Protocol for HIV-Negative Adults

Introduction

This updated algorithm is provided by the Washtenaw County Health Department (WCHD). It is intended for the use by our local primary care providers based on guidelines from the Center for Disease Control (CDC) and United States Preventive Services Task Force (USPSTF) for screening, diagnosis and treatment of latent tuberculosis infection (LTBI) for HIV- negative individuals who are 18 years or older. This resource is for informational and educational purposes and is not intended as a substitute for clinical judgment. This algorithm was updated in October 2018 to include the CDC's updated treatment recommendations pertaining to HIV-negative adults' treatment options.

Scope of the Problem

In 2016, there were 9287 cases of tuberculosis in the United States. The national tuberculosis case rate was 2.9 per 100,000, a 2.7% decrease from the case rate in 2015 (1). Tuberculosis case rate in Washtenaw County in 2016 was 2.8 per 100,000 in comparison to case rate in the state of Michigan of 1.3 per 100,000 (see Michigan TB case rates by county).

Reactivation of LTBI is a significant source of TB disease. Of individuals exposed to *Mycobacterium tuberculosis*, 30% will develop LTBI (2, 3). If these individuals are not treated, an estimated 5-10% will progress to active TB disease (2, 3). More than 80% of cases of tuberculosis in the United States are the result of reactivated latent infection (4). A higher rate of disease progression is possible in individuals with certain risk factors or medical conditions such as HIV infection, diabetes, and immunosuppression, history of illicit drug use, or cigarette smoking. Therefore, the U.S. Public Health Service recommends screening and treatment of persons at increased risk for latent tuberculosis as a critical strategy for elimination of tuberculosis in the United States (3, 5).

Indications for screening

Diagnostic testing for LTBI is done based on risk of TB infection or risk of progression to TB disease, if infected. Important: Guidelines from the American Thoracic Society, Centers for Disease Control and Prevention, and Infectious Diseases Society of America recommend that persons at low risk for TB infection and disease progression NOT be tested for TB infection unless required by law or credentialing bodies (see CDC TB Guidelines: Testing & Diagnosis: Diagnosis of Tuberculosis in Children and Adults, 2017) (6).

Individuals at increased risk for TB infection or progression include:

- Individuals born in or who frequently travel to countries where TB is endemic (see high burden TB countries).
- Immunosuppressed individuals, e.g. patients with HIV infection, history of organ transplant, and use of active treatment with a TNF-alpha antagonist, steroids dose (10-15mg/ per day for more than one month), or other immunosuppressive medications (5).
- People who live in or have lived in high risk congregate settings, e.g. correctional facilities or homeless shelters (5).
- Individuals who are in close contact with a person who has active TB disease.

- Healthcare workers and others who work in hospitals, nursing homes and other types of healthcare facilities (5) (see https://www.cdc.gov/tb/topic/testing/healthcareworkers.htm).

Distinguishing TB Disease versus Latent TB Infection

Screening for LTBI requires obtaining a good medical history including work and travel history, and birth place, in addition to performing a thorough physical examination and diagnostic testing to rule out tuberculosis disease. Symptoms of tuberculosis disease include fever, night sweats, cough lasting several weeks, chest pain, hemoptysis, loss of appetite, fatigue, and unexplained weight loss (7). Chest radiological findings are usually abnormal. If any of the above symptoms are present and/or the healthcare provider has clinical suspicion of TB disease, the local health department should be contacted. Clinicians are required to report suspected or confirmed TB disease to the local health department within 24 hours (8).

Table 1: Differentiating Between LTBI and TB Disease

LTBI	TB Disease
• No symptoms or physical findings suggestive of TB disease. • TST or IGRA result usually positive. • Chest radiograph is typically normal. • If done, respiratory specimens are smear and culture negative. • Cannot spread TB bacteria to others. • Should consider treatment for LTBI to prevent TB disease.	• Symptoms may include: fever, cough, chest pain, weight loss, night sweats, hemoptysis, fatigue, and decreased appetite. • TST or IGRA result usually positive, though may be negative, especially in newly infected or immunosuppressed patients. • Chest radiograph is usually abnormal in pulmonary disease. However, may be normal in persons with advanced immunosuppression or extrapulmonary disease. • Respiratory specimens are usually smear or culture positive in pulmonary disease. However, may be negative in persons with extrapulmonary disease or minimal or early pulmonary disease. • May spread TB bacteria to others. • Needs treatment for TB disease

Source: Latent Tuberculosis Infection: A Guide for Primary Health Care Providers. Centers for Disease Control and Prevention: Division of Tuberculosis Elimination. https://www.cdc.gov/tb/publications/ltbi/diagnosis.htm (9)

Diagnostic Testing

There are 2 available testing methods to detect infection with TB. However, these tests do not distinguish between LTBI and TB disease (2, 10).

1. The Tuberculin Skin Test (TST): detects cell mediated immunity by delayed hypersensitivity reaction to purified protein derivative (PPD).
2. Interferon Gamma Release Assays (IGRA): measures the immune response to TB proteins in whole blood. There are 2 FDA approved and commercially available IGRAs - QuantiFeron®- TB Gold In tube (QFT- IT) and T-spot.

The IGRAs are often preferable to TST for adults with: low chance of returning for reading the test or past receipt of the BCG vaccine. Also, IGRA testing does not cause the booster phenomenon that can occur with using TST (11, 12). (See link for more information on testing for TB infection: https://www.cdc.gov/tb/publications/factsheets/testing/tb_factsheet.pdf).

Interpretation of Test Results (TST, IGRA)

For most individuals with a negative TST or IGRA result, no further evaluation is needed. It should be noted that some individuals may not react to the TST despite being infected with *Mycobacterium tuberculosis* (TB). These reasons include:

- Recent TB infection (within 8-10 weeks of exposure)
- Old TB infection (many years)
- Very young age (less than 6 months old)
- Recent live-virus vaccination (e.g., Measles/Mumps/Rubella, Varicella, and Smallpox)
- Overwhelming TB disease
- Some viral illnesses (e.g., measles and chicken pox)
- Incorrect method of TST administration
- Incorrect interpretation of reaction
- Cutaneous anergy

IGRA testing should be repeated if initial IGRA results are borderline (T-Spot only), invalid, or indeterminate. The Washtenaw County Health Department TB Program requests to be contacted by local providers for positive QuantiFeron® tests with quantitative measurements: TB Antigen minus Nil <1.0 IU/ML, prior to treatment initiation in order to further evaluate TB risk factors. Furthermore, recent 2017 guidelines suggest that a confirmatory test with either an IGRA or TST be done, if initial diagnostic testing is positive for individuals who are unlikely to be infected with *Mycobacterium tuberculosis*, e.g. individuals who require routine testing by law or credentialing bodies (12, 13). For more information on TB diagnostic testing, see: CDC TB Guidelines: Testing & Diagnosis: Diagnosis of Tuberculosis in Children and Adults, 2017 and CDC: Latent Tuberculosis Infection: A Guide for Primary Health Care Providers) (6, 9).

Treatment and Monitoring

Treatment

LTBI treatment should be initiated **only after** TB disease has been ruled out. There is a high risk of drug resistance and treatment failure if a patient with TB disease is treated with a single drug regimen. Patients with suspected TB disease are managed by the local health department and these patients should receive the recommended multidrug treatment regimen until the diagnosis is either confirmed or ruled out.

Before treatment is started, it is important to determine which patients need baseline liver function evaluation with liver function tests (LFT). If LFTs are within normal limits, the patient's treatment regimen may proceed, otherwise the course of action will be determined by transaminase levels (see table 1 and CDC Guide for Primary Health Care Providers' section on Monitoring: https://www.cdc.gov/tb/publications/ltbi/default.htm (14, 15, 16).

The CDC recommends several regimen options for LTBI treatment.

1. ^INH and Rifapentine (RPT), also known as 3HP, for 3 months once weekly under Directly Observed Therapy (DOT) or self-administered therapy (SAT) (17)
2. Rifampin (RIF) for 4 months daily
3. Isoniazid (INH) for 9 months daily or twice weekly under DOT
4. *INH for 6 months daily or twice weekly under DOT (1, 16)

Note: Patients are more likely to complete shorter treatment regimens, e.g. 3HP. Regimens commonly used by Washtenaw County Health Department Tuberculosis Clinic (in order of preference):

- ◊INH and RPT, 3HP, once weekly for 12 weeks (under DOT), or
- RIF once daily for 4 months, or
- INH once daily for 9 months

^For once-weekly isoniazid-rifapentine (3HP) for 12 weeks, the CDC now recommends that health care providers choose the mode of administration (DOT versus SAT) based on their local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease (17). ◊Washtenaw County Health Department prefers DOT for all regimens that have once weekly or twice weekly dosing intervals. *Washtenaw County Health Department does not recommend using the 6 months INH regimen because it is not optimal and only used in special circumstances.

Important: Treatment must be modified if the patient is a contact of an individual with drug-resistant TB disease. Contact our local health department TB program if the known source of TB infection has drug-resistant TB (16).

Note: It should be noted that INH is hepatotoxic and RPT and RIF may potentially cause drug-drug interactions. A proper medication history should be obtained and patients should be evaluated for potential drug-drug interactions. Pyridoxine B6 supplementation should be used with INH regimens in:

- pregnant and breastfeeding women
- adolescents with nutritional deficiencies
- people with seizure disorders
- patients who develop signs and symptoms of peripheral neuropathy while on INH
- patients with medical conditions that may be associated with peripheral neuropathy e.g. HIV, DM, chronic renal failure, chronic alcohol use, malnutrition (14,16).

Monitoring

Once LTBI treatment has been initiated, the level of monitoring that the patient requires should be determined and healthcare providers should periodically assess the patient's progress. These periodic assessments are to ensure that treatment is safe and effective. Furthermore, these assessments should involve 1) clinical monitoring (e.g. signs of hepatitis, adherence to the medication regimen, and symptoms of possible adverse drug reactions or interactions), 2) laboratory testing, and 3) patient education. See Table 1 and/or the CDC's Guide for Primary Health Care Providers' section on Monitoring: https://www.cdc.gov/tb/publications/ltbi/default.htm (14, 15, 16).

Please see the CDC Tuberculosis (TB): Treatment Options for Latent Tuberculosis Infection for more details on treatment regimens, monitoring, and side effects (14,15).

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Adult Latent Tuberculosis Infection (LTBI) Patients (HIV-Uninfected) Diagnosis and Treatment

Washtenaw County Health Department

ϕHigh-Risk Groups

Foreign Born - People born in Canada, Australia, New Zealand, or Western and Northern European countries are not considered at high risk for TB infection, unless they spent time in a country with a high rate of TB.

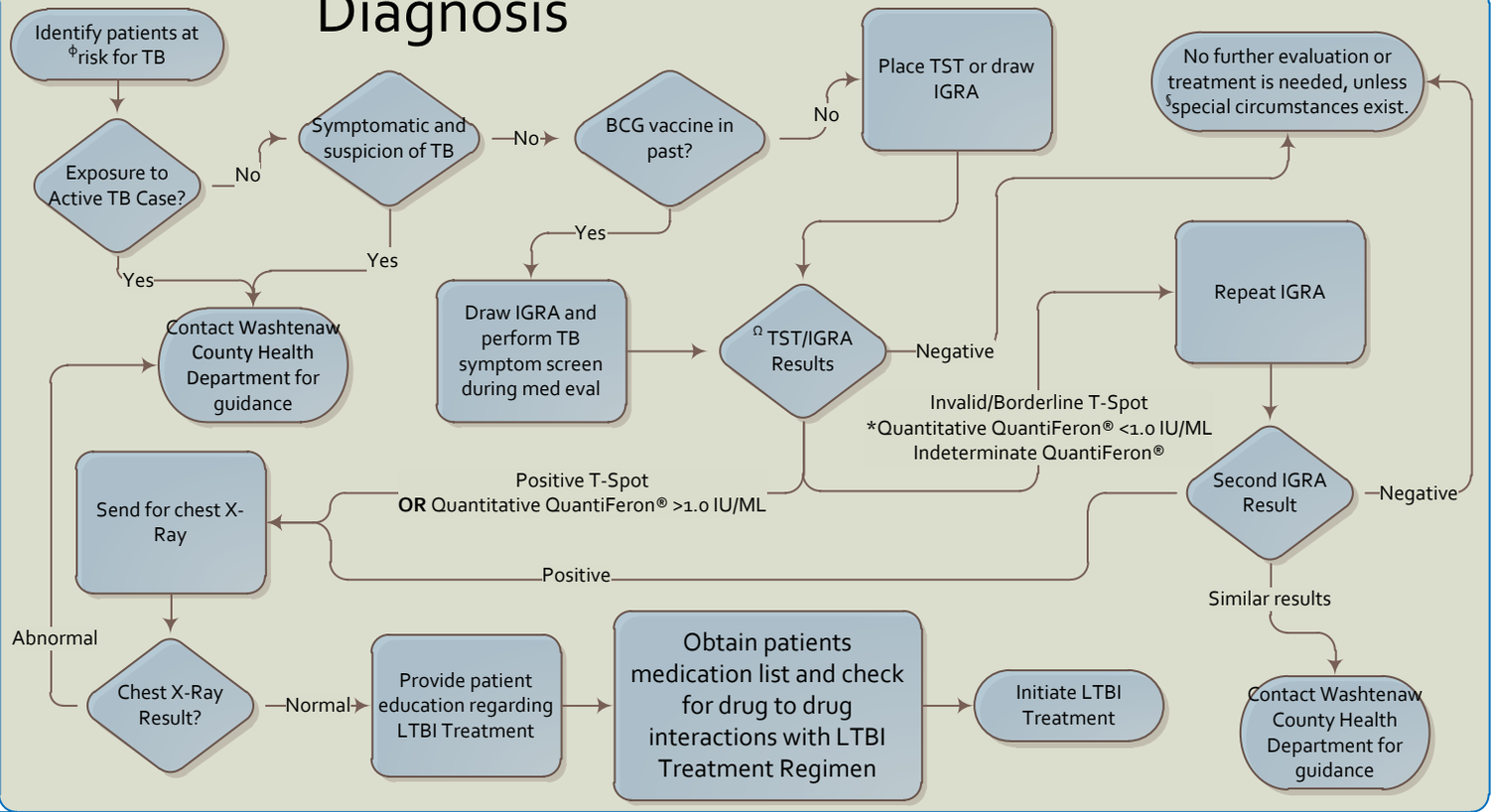
Foreign Travel or Residence - ≥ 1 month consecutively in any country other than the United States Canada, Australia, New Zealand or in Western and Northern Europe

Immunosuppression - HIV infection, organ transplant, treatment with TNF-alpha antagonist, steroids or other Immunosuppressive medication

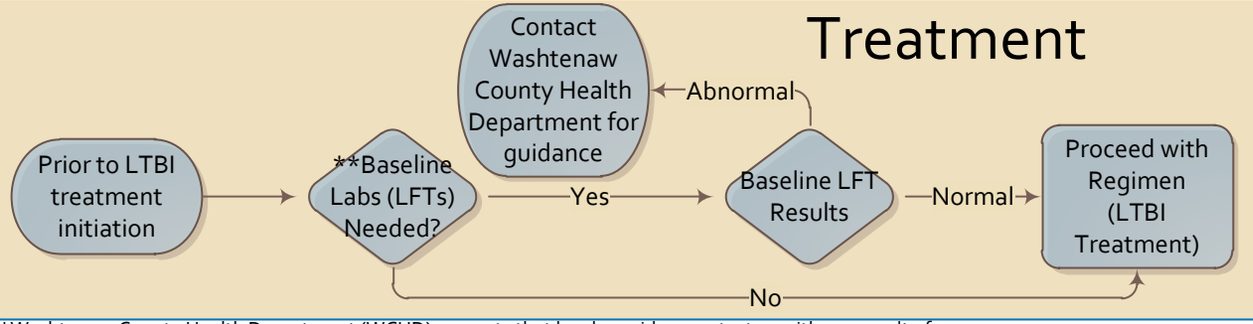
Close Contact - To someone with infectious TB disease at any time

High Risk Individuals / Congregate Settings - Illicit drug use, Correctional facilities, homeless shelters, health care facilities (including healthcare workers)

Diagnosis



Treatment



Commonly used Regimens by WCPH / TB Clinic

- **^INH** and **^^RPT** - Once-Weekly (DOT) 12 Weeks
- **^^RIF** – Daily 4 Months
- **^INH** – Daily 9 Months

See Table 1 for alternative treatment regimens

*Washtenaw County Health Department (WCHD) requests that local providers contact us with any result of a quantitative QuantiFeron®: TB Antigen minus Nil <1.0 IU/ML, in order to further evaluate client for TB risk factors.

Ω See TST reaction interpretation table on page 2 of companion document

** Baseline Labs are needed when there is a history of Liver Disease, Regular Alcohol Use, HIV Infection, Pregnancy (or within 3 months postpartum, Risk for Hepatic Disease)

§Special circumstances include: close contact of actively infected person, severely immunosuppressed, etc. (see page 2 of companion document for additional exceptions).

^INH-Hepatotoxic; Pyridoxine (B6) Supplementation should be considered
^^Rifamycins: Important and potentially prolonged drug interactions

Endorsed by the Tuberculosis Control Program of the Michigan Department of Health and Human Services.

This algorithm is for informational and educational purposes and is not intended as a substitute for clinical judgment. Please check with your local health department for any questions or concerns.

(UPDATED) RECOMMENDED DRUG REGIMENS FOR LTBI TREATMENT

Determine which regimen is most appropriate for your patient and support adherence to ensure successful completion. Evidence shows that patients are more likely to complete shorter regimens.

DRUG	INTERVAL AND DURATION	ADULT DOSAGE (MAX)	PEDIATRIC DOSAGE* (MAX)	COMPLETION CRITERIA	INDICATIONS	ADVERSE REACTIONS	CONSIDERATIONS WITH THIS REGIMEN	MONITORING FOR ALL PATIENTS
INH♦ and RPT	Once-weekly for 12 weeks	Adults and ^children ≥ 2 years of age: Adults and Children aged ≥ 12 years: INH:15 mg/kg rounded up to the nearest 50 or 100 mg (900 mg max) RPT: 10.0–14.0 kg (300 mg) 14.1–25.0 kg (450 mg) 25.1–32.0 kg (600 mg) 32.1–49.9 kg (750 mg) >50.0 kg (900 mg max) Children aged 2–11 years: INH: 25 mg/kg; 900 mg max RPT: as above ^DOT or SAT can be used with this 12-dose regimen. The CDC recommends basing the chosen mode of administration (DOT vs SAT) on local practice, individual patient attributes and preferences, and other considerations, including risk for progression to severe forms of TB disease.		12 doses within 16 weeks	Recommended for otherwise healthy persons ^aged ≥2 years who were recently in contact with infectious TB or who recently converted their TB test from negative to positive or who have radiographic evidence of healed pulmonary TB. Also, recommended for persons with LTBI who have ^HIV infection, including AIDS, and are taking antiretroviral medications with acceptable drug-drug interactions with rifapentine. **Not recommended for:** •Children less than 2 years old •Persons living with HIV/AIDS and taking antiretroviral medications with clinically significant or unknown drug interactions with rifapentine. •People presumed to be infected with INH or RIF-resistant M.tb. •Pregnant women or expecting to be pregnant while taking this regimen.	INH: Hepatic enzyme elevation, hepatitis (nausea, vomiting, abdominal pain, anorexia, yellow eyes/skin, light stools, dark urine), rash, peripheral neuropathy, mild CNS effects, drug interactions RPT: Hematologic toxicity, hypersensitivity reaction (e.g. hypotension or thrombocytopenia), GI symptoms, polyarthralgia, hepatotoxicity, pseudo jaundice, flu-like symptoms, orange discoloration of bodily fluids	Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine (B6) should be considered in certain populations. Vigilance for drug hypersensitivity reactions, ranging from mild reactions such as dizziness to more severe reactions including hypotension and thrombocytopenia. Consider possible rifamycin-associated drug interactions. Women who use any form of hormonal birth control should be advised to also use a barrier method. Educate patients that orange discoloration of bodily fluids is expected and harmless. Train DOT provider to ask patients about adverse reactions at each DOT visit.	•Evaluate at least monthly: Include careful questioning about adherence and side effects, and a brief physical examination. Check for evidence of hepatotoxicity, RPT hypersensitivity, or other adverse reactions: fever, anorexia, dark urine, icterus, rash, persistent parasthesia of hands and feet, fatigue or weakness lasting 3 or more days, abdominal tenderness (especially in the right upper quadrant), easy bruising or bleeding, arthralgia, nausea, or vomiting. •Routine monthly monitoring of LFTs is not generally indicated. •Baseline LFTs are indicated for: – HIV infection – Regular alcohol use – Pregnancy or <3 months postpartum – History of liver disease or liver disorders – Risks for hepatic disease, including other potentially hepatotoxic drugs (e.g. anti-convulsants) or over-the-counter drugs (e.g. acetaminophen) Periodic LFTs are indicated for persons at risk for, or with a history of, hepatic disease, persons who have abnormal baseline LFTs, or those who develop symptoms consistent with hepatotoxicity. • If side effects occur, a prompt physician's evaluation is necessary with treatment changes as indicated Medication should be withheld and patients evaluated if: • Transaminase levels >3 times upper limit of normal in presence of symptoms • Transaminase levels >5 times upper limit of normal in asymptomatic patient • If children taking LTBI treatment develop hepatitis, discontinue treatment and seek other causes, noting transaminase levels stated above. When LFTs have returned to normal, consider an alternate regimen, with close clinical and laboratory monitoring. Consult TB expert. **Report adverse events to CDC Division of Tuberculosis Elimination by sending an email to:** ltbidrugevents@cdc.gov
RIF	Daily for 4 mos.	RIF 10 mg/kg (600 mg)	10–20 mg/kg (600 mg)	120 doses within 6 mos.	For contacts of patients with INH-resistant, RIF-susceptible TB, persons with allergy/intolerance to or serious adverse effects from INH, or when shorter course treatment is preferred. In HIV-infected persons certain antiretroviral medications should not be given concurrently with RIF. An alternative with protease inhibitors is 150 mg of rifabutin daily. See www.aidsinfo.nih.gov for current guidelines.	GI intolerance, drug interactions, hepatitis, bleeding problems (from gums or other sites, easy bruising), flu-like symptoms, orange discoloration of bodily fluids	Consider possible rifamycin-associated drug interactions. Women who use any form of hormonal birth control should be advised to also use a barrier method. Educate patients that orange discoloration of bodily fluids is expected and harmless.	
INH♦	Daily for 9 mos.	5 mg/kg (300 mg)	10–20§mg/ kg (300 mg)	270 doses within 12 mos.	Not indicated for persons exposed to INH-resistant TB. In HIV-infected persons, INH may be given concurrently with NRTIs, protease inhibitors, or NNRTIs.	INH: as above	Hepatitis risk increases with age, alcohol use, and concurrent use of other hepatotoxic drugs. Supplementation with pyridoxine (B6) should be considered in certain populations.	
	Twice-weekly for 9 mos.	15mg/kg (900 mg)	20–40‡ mg/kg (900 mg)	76 doses within 12 mos.				
		DOT must be used with twice-weekly dosing						

Abbreviations: INH = isoniazid, RIF = rifampin, RPT = rifapentine, NRTIs = nucleoside reverse transcriptase inhibitors, NNRTIs = non-nucleoside reverse transcriptase inhibitors, LFT = liver function test, DOT = directly observed therapy, mos. = months, SAT = self-administered therapy

^ Updated with CDC 2018 guidelines

* An additional regimen, 3 months of daily INH and RIF is included in the AAP Red Book as a possible alternative regimen, but is not currently included in CDC recommendations.

♦ **Breastfeeding** is not contraindicated in women taking INH. The amount of INH in breast milk is inadequate for treatment of infants with INH. Supplementation with pyridoxine (B6) is recommended for nursing women and for breastfed infants.

§ AAP recommends 10-15 mg/kg ‡ AAP recommends 20-30 mg/kg.

MDR-TB exposure: Consult TB expert. Decision to treat must consider likelihood of recent infection with MDR-TB strain, likelihood of developing TB disease, host factors, effective alternative regimen, monitoring, and follow-up.

The 2015 Rutgers Global Tuberculosis Institute Diagnosis and Treatment of Latent Tuberculosis Infection (LTBI) table was modified and updated by Washtenaw County Health Department based on the CDC 2018 updated guidelines.