CLINICAL ASPECTS OF ESSENTIAL COMPONENTS DOCUMENT

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END TB NYC

Cole B, Nilsen DM, Will L, Etkind SC, Burgos M, Chorba T. Essential Components of a Public Health Tuberculosis Prevention, Control, and Elimination Program: Recommendations of the Advisory Council for the Elimination of Tuberculosis and the National Tuberculosis Controllers Association. MMWR Recomm Rep 2020;69(No. RR-7):1–27

OUTLINE

- Laboratory and Other Testing
  - IGRAs
  - Molecular Testing/WGS
  - Importance
- Identification, Management, and Treatment of Persons with LTBI
  - Overview
  - Importance of Screening, Testing, and Treatment of LTBI
  - Principles for Risk Assessment, Testing, and Treatment of LTBI
- Identification, Management, and Treatment of Persons with TB Disease
  - Overview
  - Available Services for TB Control
  - Protocols for TB Case Management and Treatment
  - Identifying Persons with Clinically Active TB Disease: Diagnostic Methods

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OUTLINE - 2

- Management and Treatment: Medical and Case Management Collaboration
  - Overview
  - Case Management Plan
  - Patient Interview
  - Case Management Team
  - Medical Manager
  - Case Manager
  - Accessing and Promoting Adherence
  - Medical Management Plan
  - Initiation of Treatment and Case Management Plan
- Clinic Services
- Clinical Consultative Services
- DR/MDR TB

OUTLINE - 3

- Referral System for Other Medical Problems
- TB Care in Inpatient and Other Clinical Settings
- Epidemiologic Investigation
  - Overview
  - Contact Investigation
  - Genotyping and Clustering
  - TB Outbreaks
  - Investigations of Laboratory Cross-Contamination
  - Source-Case Investigations

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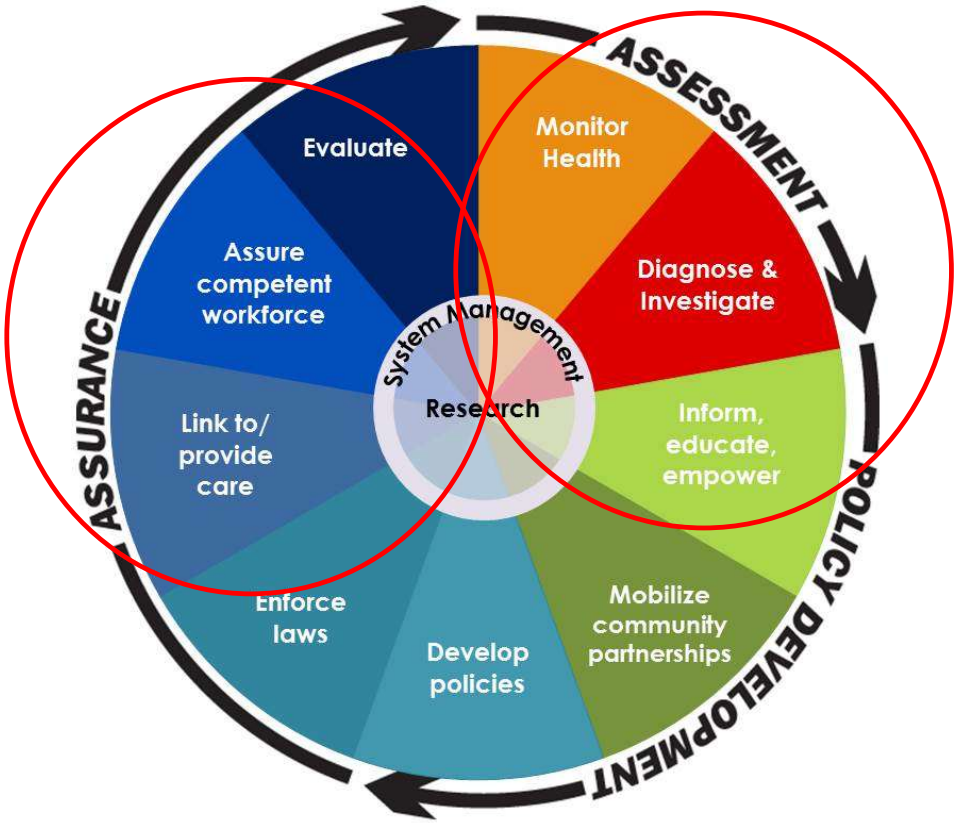
CORE PUBLIC HEALTH FUNCTIONS & ESSENTIAL SERVICES



LABORATORY AND OTHER TESTING-1

Two types of immunological-based testing to for detecting *M.tb* infection

- IGRAs: QuantiFERON® TB Gold Plus, T-Spot®.*TB*
  - differentiate between infection with *M.tb* versus the effect of bacillus Calmette-Guérin (BCG) vaccine and other NTMs
  - allow identification of TB infection regardless of BCG status
  - may be used for patients ≥ 2 years of age
- TST
  - still a valid test
  - is an acceptable alternative, especially in situations where an IGRA is not available, too costly, or too burdensome
  - results should be evaluated within the context of each patient's epidemiologic risk factors for infection
  - important for staff to maintain proficiency

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IGRAS
QUANTIFERON®-TB PLUS & T.SPOT®.*TB* TEST (T-SPOT)

- The preferred method of testing for:
  - Persons who have poor rates of returning to have their TST read
  - Persons who have received BCG vaccine
- Confirming and arranging for delivery of the blood sample within a specific timeframe is vital for ensuring viability of white blood cells in the blood samples

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TB TESTING IN CHILDREN

- According to 2017 ATS/IDSA/CDC guidelines, because of the relative sensitivity of the test, TST is the preferred method of testing (over IGRA) for children aged <5 years (*E1,E2*), although IGRA is acceptable (*E4*)
- Because IGRA has increased specificity for TB infection among children vaccinated with BCG, the American Academy of Pediatrics changed its recommendations in 2018 to a preference for IGRA over TST for children aged ≥2 years

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CRITERIA FOR TST POSITIVITY, BY REACTION INDURATION CUTOFF LEVEL AND RISK GROUP (BOX 5)

≥5 mm of induration

Persons with human immunodeficiency virus (HIV) infection
Close contacts of a person with infectious tuberculosis (TB)
Persons with chest radiographs consistent with previous untreated TB
Organ transplant recipients
Other immunosuppressed persons†

≥10 mm of induration

Recent immigrants
Injection drug users
Residents or employees of congregate settings
Mycobacteriology laboratory personnel

≥15 mm of induration

Persons with no known risk factors for TB

Source: CDC. Targeted tuberculin testing and treatment of latent tuberculosis infection. MMWR Recommend Rep 2000;49(No. RR-6).

* From highest (≥5 mm) to lowest (≥15 mm) risk for developing active TB disease. These cut points apply both to adults and children and can be modified on the basis of local epidemiology.

† Patients taking the equivalent of >15 mg/day of prednisone for 1 month or those taking tumor necrosis factor-α antagonists or other immunomodulators.

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COMPARISON IGRA & TST (TABLE E1)

IGRA	TST
In vitro test	In vivo test
Specific antigens	Non-specific antigens
Requires blood test	No phlebotomy
No boosting	Boosting phenomenon
One patient visit	Two patient visits
Fixed interpretation criteria	Risk stratified interpretation
Minimal interreader variability	Interreader variability
Variability with serial testing	Low variability with serial testing
Results in minimum of 2 days; depends on whether laboratories batch samples for testing	Results in 2-3 days
Not affected by BCG vaccine and majority of non-TB mycobacteria	Cross-reacts with BCG and non-TB mycobacteria

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TRADITIONAL TESTS FOR DIAGNOSING *M.tb*

- AFB staining (smear)
  - rapid but low sensitivity and specificity
  - does not distinguish *M.tb* vs. NTM
- Culture
  - gold standard
  - slow, taking 1-8 weeks
- Drug susceptibility testing
  - MGIT
  - conventional agar plate

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NEWER MOLECULAR TESTS FOR TB

- Molecular diagnostic tests rapidly identify both *M.tb* and genetic markers of drug resistance
  - NAATs (e.g., polymerase chain reaction, GeneXpert®)
  - GeneXpert: *rpoB* mutation can identify rifampin resistance
  - can be done within hours of receiving the specimen, without waiting for culture-based DST
- Molecular Detection of Drug Resistance (MDDR) CDC program
  - molecular testing can supplement conventional DST by looking at mutations for resistance, because all mutations and combinations of mutations are not known
- Whole-genome sequencing (WGS)
  - can identify *M.tb* and genetic mutations associated with drug resistance
  - can provide more discriminatory genotyping
  - needs culture growth

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MOLECULAR METHODS TO DETECT DRUG RESISTANCE BY DRUG & GENE TARGET

		RIF	INH		EMB	PZA		ETA	FQN		SMN	KM	AK	CM		BDQ
Test Type	GENE(S)	• rpoB	• inhA • katG	• oxyR-ahpC PR • mabA-inhA PR • mabA	• embB	• pncA	• pncA PR	• mabA-inhA PR • ethA	• gyrA	• gryB	• rrs • rpsL	• rrs • eis PR	• rrs	• rrs	• tlyA	• atpe
Xpert® MTB/RIF		✓														
GenoType MTBDR*plus* (Hain)		✓	✓						✓	✓		✓	✓	✓		
Pyrosequencing		✓	✓						✓	✓						
Sanger sequencing		✓	✓		✓		✓		✓			✓	✓	✓	✓	
Whole genome sequencing		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Research mutation only; Observed in laboratory-induced resistant strains																✓

Abbreviations Used: RIF=rifampin; INH=isoniazid; FQN=fluoroquinolone; KM=kanamycin; AK=amikacin; CM=capreomycin; SM= Streptomycin; EMB=ethambutol; PZA=pyrazinamide; ETA=ethionamide; BDQ=bedaquiline; PR=promoter region

Molecular Detection of Drug Resistance (MDDR) testing at the CDC is done using Sanger sequencing

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IMPORTANCE OF NEWER MOLECULAR TESTS

- Newer modalities allow for
  - earlier identification of *M.tb*
  - earlier initiation of recommended therapy for TB
  - resulting in decreased transmission of *M.tb*
- Specimens should still be cultured for phenotypic drug susceptibility testing
- Tests and methods are constantly changing
- Programs should have access to the most updated tests:
  - results should be reported as they become available
  - used for managing complex cases
  - remove persons from isolation in a timely fashion
  - identify cases with epidemiologic and genotypic linkages

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Identification, Management and Treatment of Persons with LTBI

IMPORTANCE OF SCREENING, TESTING, AND TREATMENT FOR LTBI

- LTBI – presence of *M.tb* organisms without signs, symptoms, radiographic, or bacteriological evidence of infection
  - asymptomatic
  - non-transmissible
  - absence of clinical illness
- LTBI can persist for decades
  - persons with LTBI can remain at risk for progressing to TB disease
  - heightened by immune system impairment
- 80% of active TB is thought to be caused by reactivation of LTBI
- Focus has shifted to identifying and treating persons with LTBI in order to eliminate TB
- However, benefit must outweigh risk to patient

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PRINCIPLES FOR RISK ASSESSMENT, TESTING, AND TREATMENT FOR LTBI

- When to test for LTBI:
  - diagnostic evaluation can be performed
  - therapy can be prescribed
  - therapy is likely to be completed
- Risk assessment should be conducted to identify groups who are at high risk for TB in order to reduce waste of resources and prevent non-essential treatment
- US Preventive Services Task Force (USPSTF) recommends guidelines for incorporating TB prevention into primary care
- Importance of engaging primary care providers for TB elimination

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PRINCIPLES FOR RISK ASSESSMENT, TESTING, AND TREATMENT FOR LTBI - 2

- Risk assessments should be based on state and local epidemiology
- Guidelines and documented risk factors provided by ATS/IDSA/CDC
- 2 categories of risk factors (see appendix F):
  - TB exposure
  - progression to active TB disease after becoming infected
- Only re-test a negative person(s) when there are new risk factors
  - close contact of person with infectious TB
  - new immunosuppression
  - new residence and/or travel to a high-risk area or country
- Collaborate with other local TB programs

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USPSTF RECOMMENDATION: PATIENT POPULATION

- Asymptomatic adults ≥18 years who are at increased TB risk
  - Born, resided, or traveled in countries with increased TB prevalence

    (e.g. Any country other than the U.S., Canada, Australia, New Zealand, or a country in Western or Northern Europe)
  - Lived or worked in high-risk settings

    (e.g., hospitals, long-term care facilities, correctional facilities, homeless shelters)

Consult updated recommendations for TB screening, testing, and treatment of health care personnel.

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CDC MMWR: NEW LTBI TREATMENT GUIDELINES

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Recommendations and Reports / Vol. 69 / No. 1
February 14, 2020

Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

Timothy R. Sterling, MD[1]; Gibril Njie, MPH[2]; Dominik Zenner, MD[3]; David L. Cohn, MD[4]; Randall Reves, MD[4]; Amina Ahmed, MD[5]; Dick Menzies, MD[6]; C. Robert Horsburgh, Jr., MD[7]; Charles M. Crane, MD[8]; Marcos Burgos, MD[8,9]; Philip LoBue, MD[2]; Carla A. Winston, PhD[2]; Robert Belknap, MD[4,8]

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CDC MMWR: NEW LTBI TREATMENT GUIDELINES

- TB disease should be ruled out before treatment for LTBI is initiated
- New shorter treatment regimens available
  - generally well-tolerated
  - lead to improved treatment completion
  - non-inferior to INH
- Short-course rifamycin-based regimens are preferred over longer course isoniazid therapy
  - daily rifampin (RIF) for 4 months
  - once weekly isoniazid (INH) + rifapentine for 12 weeks
- INH can be given for 6 - 9 months
- 3 mo daily INH + RIF; however, this regimen is not routinely used

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LTBI TREATMENT REGIMENS (APPENDIX TABLE F1)

Drug	Duration* (mos.)	Interval	Minimum doses
Isoniazid (INH) and Rifapentine (3HP)†	3	Once weekly§	12
Rifampin (RIF)§	4	Daily	120
INH and RIF**	3	Daily	90
INH¶	9	Daily**	270
		Twice weekly**	76
	6	Daily	180
		Twice weekly**	52

Source: CDC. Guidelines for the treatment of latent tuberculosis infection: recommendations from the National Tuberculosis Controllers Association and CDC, 2020. MMWR Recommend Rep 2020;69(No. RR-1);1–11.

* Completion of therapy is based on the total number of doses administered, not on duration of therapy alone.

† 3HP treatment is regarded as complete with 11 or 12 doses taken within 16 weeks. If treatment is interrupted, doses can be caught up by administering them no more frequently than every 72 hours.

§ Rifampin treatment can be regarded as complete if taken within 6 months.

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Identification, Management, and Treatment of Persons with TB Disease

AVAILABLE SERVICES FOR TB CONTROL

- Services available should meet the needs of the community
- Can be provided by state or federal funding
- Patients may be treated by other entities, but health department should monitor all activities

PROTOCOLS FOR TB CASE MANAGEMENT AND TREATMENT

- Public health goals of TB patient management
  - initiate treatment promptly
  - ensure treatment is completed and disease is cured
  - reduce transmission
  - prevent development of drug resistant TB
- Goals achieved through case management
- TB program needs protocols in place for successful case management
- Program, alongside HCP, should ensure that patient completes treatment in a timely manner

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IDENTIFYING PERSONS WITH CLINICALLY ACTIVE TB DISEASE: DIAGNOSTIC METHODS

- TB programs should be familiar with and have access to new diagnostic tools
  - Blood-based IGRAs
  - NAATs
  - Others as they become available
- Sputum & other specimens should be collected and tested asap for AFB smear & culture
  - Rapid identification with NAATs and molecular testing as indicated
- Patients should receive medical evaluation including:
  - CXR
  - Additional imaging of other infected areas
  - HIV tests
  - Medical regimen should be started based on patient clinical & epidemiologic characteristics

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Management and treatment: Medical and case management collaboration

CASE MANAGEMENT

Patient centered case management

- Case Management Plan
- Patient Interview
- Case Management Team
- Medical Manager
- Case Manager

CASE MANAGEMENT PLAN

- Case management includes:
  - DOT
  - side effects assessment
  - patient monitoring and adherence
  - other public health activities
- Case management works closely with medical care team
- Patient is educated on:
  - TB/TB treatment
  - importance of adhering to treatment
  - importance of identifying close contacts so they can be evaluated and treated for LTBI
- Case management helps ensure that the treatment is patient-centered and successfully completed
- This is unchanged from the previous document

CLINIC SERVICES

- Clinic services must be accessible and acceptable to the community served by the clinic
  - convenient hours, including evening or weekend hours
  - ideally located
  - accessible by public transportation/transportation provided
- Appointments & wait times at the clinic should be kept to a minimum
- In busy clinic settings, priority should be given to:
  - persons with TB disease
  - persons being evaluated for TB disease
  - persons receiving TB medications
- Clinic services should be provided regardless of patient's ability to pay
- Clinic staff should be representative of the community served
- Language interpretation services should be available

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CLINICAL CONSULTATIVE SERVICES

- Expert medical consultation should be available to the TB program and providers in the community
- Consultative services provided by:
  - the TB program directly
  - regional consultant collaborating with the health department
  - CDC's TB Centers of Excellence

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DRUG-RESISTANT AND MDR-TB

- Should be considered in patients
  - with a history of previous TB treatment
  - who are from countries with high rates of MDR TB
- Treatment can be guided by molecular testing sent to:
  - CDC Molecular Detection of Drug Resistance (MDDR) Service,
  - National Jewish Health (fee for service)
  - other laboratories (NYS Wadsworth, California)
- Familiarity with recent developments in treatment is required
- Consultative services available via jurisdictional MDR consultative services, TB Centers of Excellence, and Curry Guidelines
  - newer guidelines from ATS, CDC, ERS and IDSA

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REFERRAL SYSTEM FOR OTHER MEDICAL PROBLEMS

- A system should be in place for patient referrals for other comorbidities
- If care is received in more than one location, it should be coordinated between the providers to ensure continuity and completion of therapy, avoid drug interactions, and avoid duplication of efforts
  - the TB program will take primary responsibility for TB treatment
  - when referring patients, the TB program should notify providers if the patient is infectious

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TB CARE IN INPATIENT AND OTHER CLINICAL SETTINGS

- A rapid reporting system should be in place to alert the DOH of new or suspected diagnoses
- Hospitals should have effective infection control measures
  - airborne infection isolation (AII) rooms or HEPA filters
  - confirmed or suspected patients be kept separate
  - effective ventilation
- Medications should be available in the facility
- Diagnostic services available to monitor response to treatment
- Inpatient providers should be taught about DOT in order to approve pt adherence
- Monitor for adverse events and other existing or new medical issues
- Discharge planning begins when patient is admitted; TB program needs to work with hospital to facilitate

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Epidemiologic Investigation

CONTACT INVESTIGATION

- Key component to any TB program
- Process involves interviewing persons with TB disease to identify persons with close and prolonged contact
  - household, close friends, close work
  - contacts are tested according to CDC and NTCA guidelines
- Investigation is conducted using concentric circle model
  - initial focus on those at highest risk
- Priority, speed & extent of contact investigation should be guided by likelihood of transmission to the source patient, environment and exposed persons
  - can identify undiagnosed active TB cases and persons with LTBI
- Contact investigation begins as soon as program is notified of presumed or confirmed case of infectious pulmonary TB

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CONTACT INVESTIGATION - 2

- To identify persons accurately as contacts, program should determine infectious period for index patients
  - infectious period calculated to identify the period when the exposure is most intense and when it stops (treatment initiation)
  - should calculate an 8-10-week window period for treatment of those with increased risk for progression to disease
    - children < 5
    - immunocompromised
- Communicating with non-health department providers is crucial to ensure exposed patients are evaluated in a timely manner and retested after the window period
- Expand the CI after assessing transmission of the closest contacts

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GENOTYPING AND CLUSTERING

- Laboratory based approach that distinguishes different *M.tb* strains
- When combined with epidemiologic data, genotyping can be used to identify:
  - persons with TB disease involved in the same chain of recent transmission
  - recent reinfection vs relapse in patients with a history of TB disease
  - unsuspected transmission associations
  - interjurisdictional transmission
  - the early signs of an outbreak
  - laboratory contamination
- A cluster occurs when two or more isolates are matched by genotyping methods, and suggests possible recent transmission

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TB OUTBREAKS

- An outbreak investigation is triggered by transmission that is higher than expected, given the population demographics, the local epidemiology or the strain genotype
- What is considered an outbreak depends on the local epidemiology and is relative to the local context and can be defined by either:
  - two or more contacts identified as having active TB disease
  - two or more cases that have occurred within 1 year of one another and are discovered to be linked
- Requires a surge in public health resources

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INVESTIGATIONS OF LABORATORY CROSS-CONTAMINATION

- A false-positive *M.tb* specimen is a positive culture that is not the result of disease but is caused by contamination of a clinical device, a clerical error, or laboratory cross-contamination during processing
- Investigation of potential false-positive results may be triggered by:
  - single positive culture reported
  - review of genotyping results (i.e., lab strain, matching results in different patients)
  - clinician suspicion
- Identifying false-positives allows for:
  - correcting erroneous medical diagnosis & discontinuing unnecessary treatment
  - discontinuing contact or source case investigations
  - correction of the local or national surveillance system

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SOURCE CASE INVESTIGATIONS

- Source case investigation is triggered when TB disease is identified in a U.S.-born child ≤ 5 years who has never lived or traveled outside the US
  - sentinel event
- Assumption: the child must have been exposed recently to someone with unrecognized TB disease
- Parents or guardians (associates) are usually the best informants, with specific attention to all associates who have symptoms of TB disease
  - investigation begins with the closest associates; household members
  - follows the same overall procedure as a standard contact investigation
- Should also be considered for children ≤ 5 years with LTBI, including those who were born or traveled to high-prevalence countries, as their family members might also have LTBI and be candidates for treatment
  - if resources allow

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THANK YOU

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Questions?