TESTING AND TREATMENT OF TUBERCULOSIS (TB) INFECTION IN CHILDREN

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WHY IS SCREENING IMPORTANT?

- A diagnosis of TB infection in a child is a **public health sentinel event**

- Goal:
  - Eliminate TB reservoirs (LTBI)
  - Eliminate TB disease

http://www.searo.who.int/nepal/documents/communicable_diseases/WTBD_2019/en/

GLOBAL: EPIDEMIOLOGY OF TB DISEASE IN CHILDREN AND ADOLESCENTS

- 1.2 million cases of TB disease in children
- Approximately 230,000 tuberculosis-related deaths in children <15 years of age in 2019

Source: World Health Organization. Global Tuberculosis Report 2020. Geneva, Switzerland: World Health Organization; 2020. https://www.who.int/tb/publications/global_report/en/

SUMMARY OF EPIDEMIOLOGY OF TB

- TB in children
  - Highest risk for disease:
    - <5 years of age
    - Non-U.S.-born children
      - Most common countries of birth: Mexico, Philippines, India
        - Varies depending on immigration patterns
    - Racial and ethnic minorities

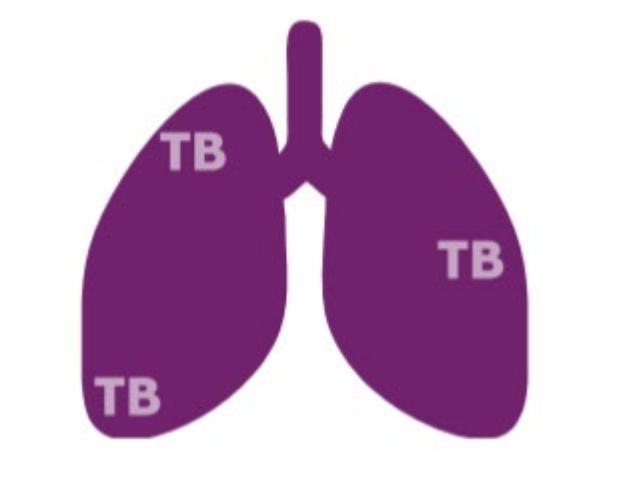
Source: CDC Reported Tuberculosis in the United States, 2019

SIGNIFICANCE OF TB IN CHILDREN

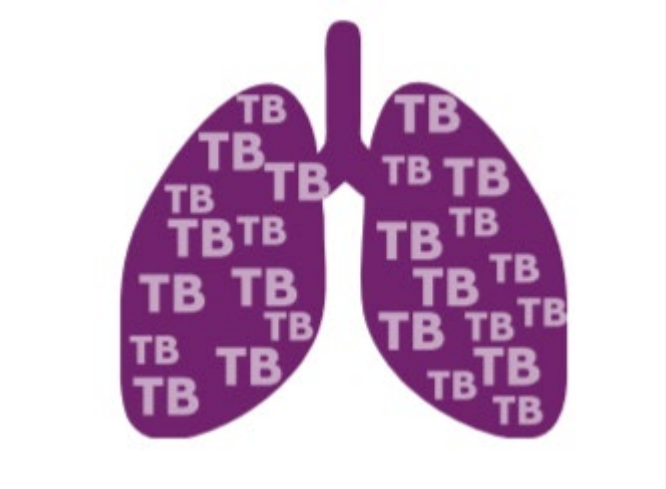
- A case of tuberculosis in a child is considered a "sentinel healthcare event" representing recent transmission of TB within the community

TB INFECTION DEFINITION

- TBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without signs and symptoms or radiographic or bacteriologic evidence of TB disease in children <15 years of age



TB Infection



TB Disease

Source: CDC Infographic

DEFINITIONS

- TB infection (TBI):
  - *M. tuberculosis* infection with a
    - Positive tuberculin skin test (TST) or interferon-gamma release assay (IGRA)
    - No physical findings of disease
    - Chest radiographs: normal or evidence of a healed infection (calcified lesion)

- TB disease:
  - *M. tuberculosis* infection
    - Positive TST or IGRA test
    - Symptoms and signs of disease – pulmonary, extrapulmonary or both
    - Radiographic manifestations of disease

Source: Redbook AAP 2021

POLLING QUESTION #1

Can children <10 years of age who have TB, transmit it to others?

- Yes
- No
- Unsure

INFECTIOUSNESS

- Children have few tubercle bacilli in lungs, therefore, are rarely infectious
- Children less than 10 years of age usually lack the pulmonary force to produce airborne bacilli
- For a case of childhood TB infection, it is likely that an adolescent or adult transmitted TB bacilli to the child
  - It is important to find the source case

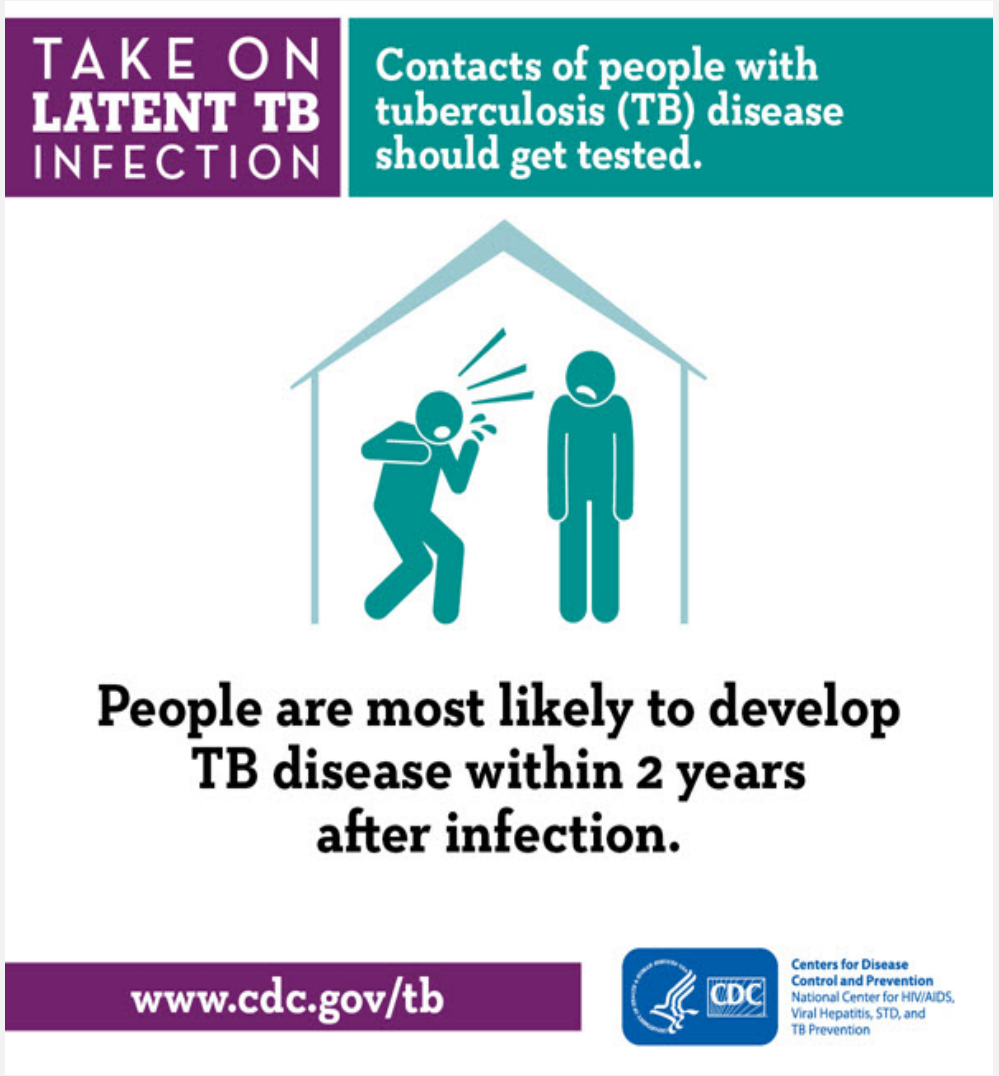
TARGETED TB TESTING AND TREATMENT OF TBI

- Identifies persons at high risk of infection with *M. tuberculosis*
- Identifies persons at high risk of progressing to disease should they be infected
- Reduces unnecessary testing, evaluations and treatments

Slide courtesy Dr. George McSherry

IMPORTANT FACTS

- Highest risk of TB disease is during the first 6 months after exposure
- Risk is still elevated for up to 2 years later
- Always ask about recent travel or visitors



AAP RECOMMENDATIONS: TARGETED TUBERCULIN TESTING

- Risk of exposure to TB should be assessed at routine healthcare evaluations
- Only children with an increased risk of acquiring TB infection or disease should be considered for testing
- Frequency of testing should be according to the degree of risk of acquiring infection
- "Screening" is an inefficient way to manage tuberculosis

AAP VALIDATED QUESTIONNAIRE FOR TB SCREENING

- Has a family member or contact had tuberculosis disease?
- Has a family member had a positive tuberculin skin test result?
- Was your child born in a high-risk country (countries other than the US, Canada, Australia, New Zealand or Western or Northern European countries)?
- Has your child traveled to a high-risk country?
  - How much contact did your child have with the resident population?
  - Re-assess with each trip

- Add: Immunosuppression, HIV (annual TB screening)

Source: AAP Red Book®, 2021

TARGETED TUBERCULIN TESTING RISK ASSESSMENT QUESTIONNAIRE

- Depending on local epidemiology and priorities, other possible questions include:
  - Does your child spend time with anyone who has been in jail or a shelter, uses drugs or has HIV?
  - Has your child had raw milk or eaten unpasteurized cheese?
  - Is there a household member born outside the US?
  - Is there a household member who has traveled outside the US?

Source: Pediatrics 2004; 114:1175, supplement

CALIFORNIA PEDIATRIC TB RISK ASSESSMENT TOOL

LTBI testing is recommended if any of the boxes below are checked.

☐ **Birth, travel, or residence** in a country with an elevated TB rate for at least 1 month

- Includes any country other than the United States, Canada, Australia, New Zealand, or a country in western or northern Europe
- If resources require prioritization within this group, prioritize patients with at least one medical risk for progression (see the California Adult Tuberculosis Risk Assessment User Guide for this list).
- Interferon Gamma Release Assay is preferred over Tuberculin Skin Test for non-U.S.-born persons ≥2 years old

☐ **Immunosuppression,** current or planned

HIV infection, organ transplant recipient, treated with TNF-alpha antagonist (e.g., infliximab, etanercept, others), steroids (equivalent of prednisone ≥2 mg/kg/day, or ≥15 mg/day for ≥2 weeks) or other immunosuppressive medication

☐ **Close contact** to someone with infectious TB disease during lifetime

Treat for LTBI if LTBI test result is positive and active TB disease is ruled out.

☐ **None**; no TB testing is indicated at this time.

https://www.cdph.ca.gov/Programs/CID/DCDC/CDPH%20Document%20Library/TBCB-CA-Pediatric-TB-Risk-Assessment.pdf

TST AND IGRA

- IGRAs (QuantiFERON®-TB Gold Plus and T-Spot®.*TB*) are the preferred tests in asymptomatic children >2 years of age who have received the BCG vaccine
- TST is the preferred test in children <2 years
- Positive results in either test is considered significant
- IGRA preferred, TST acceptable
  - Children ≥2 years of age who have received the BCG vaccine
  - Children ≥2 years of age who are unlikely to return for TST reading
  - "The published experience testing children with IGRAs demonstrates IGRAs consistently perform well in children 2 years and older, and some data support their use in even younger children"

Source: Red Book 2021

POLLING QUESTION #2

Why is the BCG vaccine given?

- To provide lifetime protection from TB infection
- To prevent infants from developing severe forms of TB
- To prevent the transmission of TB
- Unsure

Table 3.74. Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents[a,b]

Induration 5 mm or greater

Children in close contact with known or suspected contagious people with tuberculosis (TB) disease

Children suspected to have TB disease:

- Findings on chest radiograph consistent with active or previous TB disease
- Clinical evidence of TB disease[c]

Children receiving immunosuppressive therapy[d] or with immunosuppressive conditions, including human immunodeficiency (HIV) infection

Induration 10 mm or greater

Children at increased risk of disseminated TB disease:

- Children younger than 4 y
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition (see Table 3.75)
- Children born in high-prevalence regions of the world
- Children with significant travel to high-prevalence regions of the world[e]
- Children frequently exposed to adults who are living with HIV, experiencing homelessness, or incarcerated, or to people who inject or use drugs or have alcohol use disorder

Induration 15 mm or greater

Children without any risk factors

[a]See **www.cdc.gov/tb/publications/guidelines/pdf/ciw778.pdf.**

[b]These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization (see Testing for *M tuberculosis* Infection, p 791); erythema alone at TST site does not indicate a positive test result. Tests should be read at 48 to 72 hours after placement.

[c]Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (eg, meningitis).

[d]Including immunosuppressive doses of corticosteroids (see Corticosteroids, p 807) or tumor necrosis factor-alpha antagonists or blockers (see Biologic Response-Modifying Drugs Used to Decrease Inflammation, p 82) or immunosuppressive drugs used in transplant recipients (see Solid Organ Transplantation p 84).

[e]Some experts define significant travel as travel or residence in a country with an elevated TB rate for at least 1 month.

Source: Red Book, 2021 (Table 3.74 pg. 788)

MANTOUX TUBERCULIN SKIN TEST (I)

- TST is administered by injection
- Tuberculin is made from proteins derived from inactive tubercle bacilli
- Most people who have TB infection will have a reaction at injection site

Syringe being filled with 0.1 ml of liquid tuberculin

MANTOUX TUBERCULIN SKIN TEST (2)

- 0.1 ml of 5 tuberculin units of liquid tuberculin are injected between the layers of skin on forearm

HCW administering Mantoux TST

MANTOUX TUBERCULIN SKIN TEST (3)

- Forearm should be examined within 48 to 72 hours by HCW
- Reaction is an area of induration (swelling) around injection site
  - Induration is measured in millimeters
  - Erythema (redness) is not measured

Only the induration is measured

NEXT STEPS...

Positive TB test

Asymptomatic and normal exam

Order a 2 view Chest X-ray-AP, lateral

If negative, start TBI treatment

TREATMENT INITIATION:

- Counsel and educate patient and family
  - Discuss patient's risk for progressing to TB disease
  - Emphasize benefits of treatment
  - Assess whether patient willing to be treated for full treatment period
  - TBI treatment 90%+ effective
- Routine bloodwork is not recommended
- Determine if exposure was to a susceptible *M. tb* isolate and not MDR-TB

Adapted slide; courtesy of Dr. George McSherry

NEW CHANGES

- CDC released updated LTBI treatment recommendations on February 14, 2020
  - Guidelines for the Treatment of Latent Tuberculosis Infection: Recommendations from the National Tuberculosis Controllers Association and CDC, 2020

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm

TREATMENT REGIMENS FOR LTBI

Drugs	Months of Duration	Interval	Minimum Doses
INH-RPT	**3**	**Weekly**	**12**
RIF	**4**	**Daily**	**120**
INH+RIF	**3**	**Daily**	**90**
INH	6/9	Daily	**180/** 270

Adapted from slides of Dr. George McSherry and CDC

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TREATMENT OPTION 1- RIFAPENTINE (3HP) + INH

Dosing:

- Ages >11 years
  - INH: 15mg/kg rounded to nearest 50 or 100mg (900mg max dose) once a week
- Ages 2 – 11 years:
  - 25mg/kg rounded to nearest 50 or 100mg (900mg max dose) once a week
  - Rifapentine- for ages ≥ 2 years
    - 10-14kg 300mg **2 pills**
    - 14-25kg 450mg **3 pills**
    - 25.1-32kg 600mg **4 pills**
    - 32.1-49.9kg 750mg **5 pills**
    - >50kg 900mg **6 pills**
- **Some experts prefer this regimen for children 2 years and older**

Formulations:

- INH: 100mg, 300mg ,suspension
- Rifapentine: 150mg in blister packs
- Both pills can be crushed
- Side effect profile similar to Rifampin

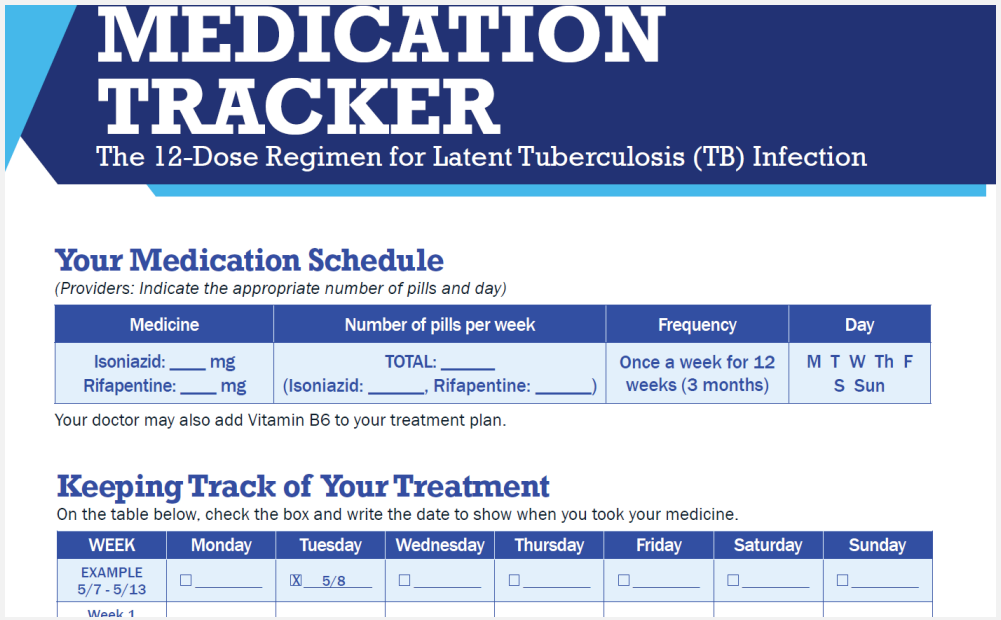
- **Completion: 12 doses within 16 weeks**

Source: Red Book 2021

INH + RIFAPENTINE (3HP)

PROS

- Once a week x 12 weeks
- Increased adherence and completion rates
- Recommended for ≥ 2 years of age



MEDICATION TRACKER

The 12-Dose Regimen for Latent Tuberculosis (TB) Infection

Your Medication Schedule

(Providers: Indicate the appropriate number of pills and day)

Medicine	Number of pills per week	Frequency	Day
Isoniazid: ____ mg Rifapentine: ____ mg	TOTAL: _____ (Isoniazid: _____, Rifapentine: _____)	Once a week for 12 weeks (3 months)	M T W Th F S Sun

Your doctor may also add Vitamin B6 to your treatment plan.

Keeping Track of Your Treatment

On the table below, check the box and write the date to show when you took your medicine.

WEEK	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
EXAMPLE 5/7 - 5/13	☐_____	☒ 5/8	☐_____	☐_____	☐_____	☐_____	☐_____
Week 1							

CONS

- Pill burden (up to 10 pills)
- Can be given by two methods based on local practice and risk of progression:
  - Directly observed or self-administered
- Check with your local pharmacy for availability and for cost

MMWR . Recommendations for Use of an Isoniazid–Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w
https://www.cdc.gov/tb/publications/pamphlets/LTBI_Medication_Tracker.pdf

Adapted from slides of Dr. George McSherry

TREATMENT OPTION 1– PRECAUTIONS

- Not recommended in children <2 years of age
- Not recommended for HIV-infected persons taking antiretroviral medications
- May reduce effectiveness of hormonal contraceptives
- Causes orange staining of urine
- Can cause liver toxicity, flu-like symptoms, or allergic reaction
- These reactions are rare, especially in children

TREATMENT OPTION 1– IMPORTANT CONSIDERATIONS

- Adherence to treatment is most important, considering this is a 12 dose regimen
- Directly observed therapy ensures adherence, but is not always feasible
- Give an observed dose at time of visit
- Provide family with a Medication Tracker so doses given at home can be documented. This should be brought to each visit
- Give dosage packets for a single month

TREATMENT OPTION 2 – RIFAMPIN (4R)

Dosing:

- 15-20 mg/kg/day PO (max 600mg dose)
  - Formulations: 150mg, 300mg capsules
- Given on an empty stomach

- Capsules can be opened and mixed with a small amount of semi-soft food
- Nausea, vomiting, abdominal pain, orange discoloration of secretions or urine, contact lenses staining, rash, thrombocytopenia, pruritus, influenza like reaction
- Monitor with oral contraceptive pills (decreased effectiveness) and other medication

Completion: 120 doses within 6 months

TREATMENT OPTION 3 – ISONIAZID (9H)

- 10-15 mg/kg/day PO daily (max 300mg dose)
  - Formulations: scored tablets 100mg, 300mg, suspension
  - Preferable route: crushed tablets not suspension
    - INH suspension causes abdominal pain and cramping in at least 50% of children from sorbitol
      - https://www.heartlandntbc.org/pedi-toolkit/assets/Tools/DosingTips/tips_for_admin_med.pdf
- Mild liver toxicity, peripheral neuritis, hypersensitivity
- 9- month duration preferred over 6 month (greater efficacy)
- Ensure index case has an INH susceptible isolate, if not use alternative drugs

Completion: 270 doses within 1 year

ASSESSING FOR ADVERSE REACTIONS

- Generally, children tolerate TB medications well and adverse reactions are rare
- It is important to monitor for such reactions and consult with the healthcare provider
- Medications should be stopped immediately if the child develops
  - Nausea
  - Vomiting
  - Anorexia
  - Abdominal pain
  - Jaundice
- Tell parents to seek advice from the child's healthcare provider if any of these symptoms occur

TREATMENT OPTION 4: INH+RIF DAILY

- Isoniazid: 10–15 mg/kg ; 300 mg maximum

- Rifampin: 15–20 mg/kg
  - 600 mg maximum dose
  - Formulations: 150mg, 300mg capsules

Completion: 90 doses within 90 days

https://www.cdc.gov/mmwr/volumes/69/rr/rr6901a1.htm?s_cid=rr6901a1_e&deliveryName=USCDC_921-DM19851
https://www.cdc.gov/mmwr/volumes/69/rr/pdfs/rr6901a1-H.pdf

MEDICATION MONITORING

- Review common side effects
- Establish treatment and monitoring plan
- Follow-up every month with a health care provider while on treatment
- Fill prescriptions on a monthly basis

MANAGEMENT OF PATIENT WHO MISSED DOSES

- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- When treatment has been interrupted for more than 2 months, patient should be evaluated to rule out TB disease
- Recommend and arrange for directly observed therapy as needed to ensure completion

Source: CDC TB slide set

DIRECTLY OBSERVED THERAPY (DOT)

- DOT is the observing the ingestion of anti-TB medications by a trained outreach worker or healthcare worker

- Can be supervised by:
  - Physician
  - Health Department Nurse
  - Trained Outreach Worker
  - School Nurse

- Should *not* be supervised by:
  - Parents or other close family member

WHAT TO DO AFTER TREATMENT OF TBI?

- Monitor and re-screen patient based on symptoms
- Repeat TB testing is not recommended
- Complete the record →

Record of Treatment Completion

To Whom It May Concern:
The following is a record of evaluation and treatment for *M. tuberculosis* infection:
Name:_____ Date of birth:_____
TST: Date:_____ Results (in millimeters of induration):____
IGRA: Date:_____ Type of test:_____ Result:_____
Chest radiograph: Date:_____ Results:_____
Date medication started:_____ Date completed:_____
Medication(s):_____
This person is not infectious. He/she may always have a positive TB skin test, so there is no reason to repeat the test. If you need any further information, please contact this office.
Signature of Provider_____
Date_____

https://www.cdc.gov/tb/publications/ltbi/appendixe.htm

TB INFECTION IN CHILDREN - SUMMARY

- In children, TB is more serious than in adults
- Young children, especially under the age of 4, have difficult fighting off infections and can have serious forms of TB if left untreated
- Treating TB infection can prevent the child from getting active TB disease in the future
- Treating TB Infection is essential in preventing tuberculosis in children and subsequently, in adults

Thank you!

A decision to test, is a decision to treat

TIPS FOR ADMINISTERING MEDICATION TO CHILDREN

- For additional tips and resources:
  Tricks of the Trade: Strategies for Pediatric TB Case Management
  Presented by: Suzanne Tortoriello, APN-C and Lillian Pirog,BSN, RN, PNP

- Pediatric TB Consultation

- Please contact us if you have additional questions