Pediatric TB Meningitis: Protecting the Minds of Our Future

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World TB Day
March 20, 2024
Webcast

Lisa Armitige, MD, PhD has the following disclosures to make:

- No conflict of interests
- No relevant financial relationships with any commercial companies pertaining to this educational activity

Fighting Tuberculous Meningitis under 5

Risk Factors

- Children <24 months of age
- Immunocompromised
- Foreign-born
- Close contacts with individuals with infectious TB

CDC

Improving Outcomes

Prompt diagnosis and treatment is essential. Failure to begin treatment swiftly results in poorer outcomes, significant and permanent neurological sequelae, or death.

Window Prophylaxis

Close contacts to someone with infectious TB who are <5 years of age should receive treatment for latent TB infection once TB disease is excluded by chest radiograph and symptom review. Treatment is needed even when a TST and/or IGRA is negative. A second TST and/or IGRA should be administered 8 - 10 weeks after the last exposure to infectious TB.

CDC

Assessment & Medical Evaluation

Tuberculous meningitis is more difficult to diagnose than other forms of bacterial meningitis, but thinking of TB as a possibility and rapid screening using various methods in order to make a proper diagnosis is crucial.

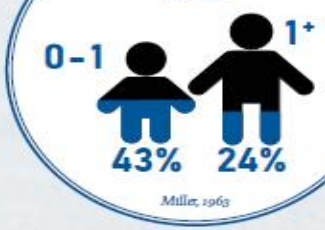
- Tuberculin Skin Testing (TST)
- Interferon Gamma Release Assay (IGRA)
- Physical Examination
- Chest X-Ray
- Lumbar Puncture *(for ALL infants <12 months with suspected TB)*
- MRI with Contrast

Outcomes for TB Survivors

On average, 54% of children who survived tuberculous meningitis developed neurological sequelae.

The Lancet, 2014

Percent Risk of Disease by Age



Miller, 1963

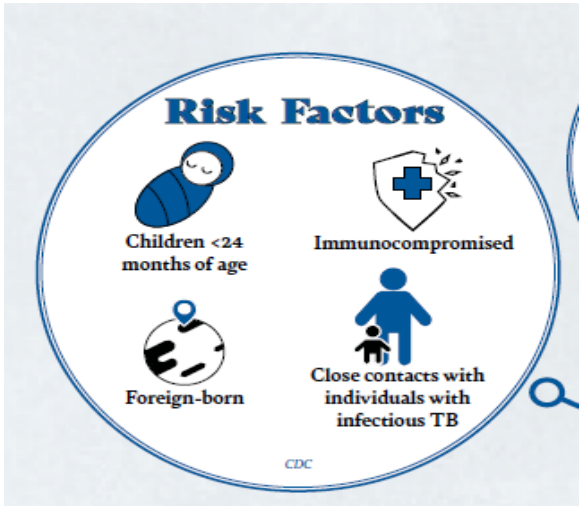
HEARTLAND NATIONAL TB CENTER
THE UNIVERSITY OF TEXAS AT TYLER HEALTH SCIENCE CENTER

For Medical Consultations:
(800) TEX-LUNG *or* (800) 839-5864
http://www.heartlandntbc.org/consultation

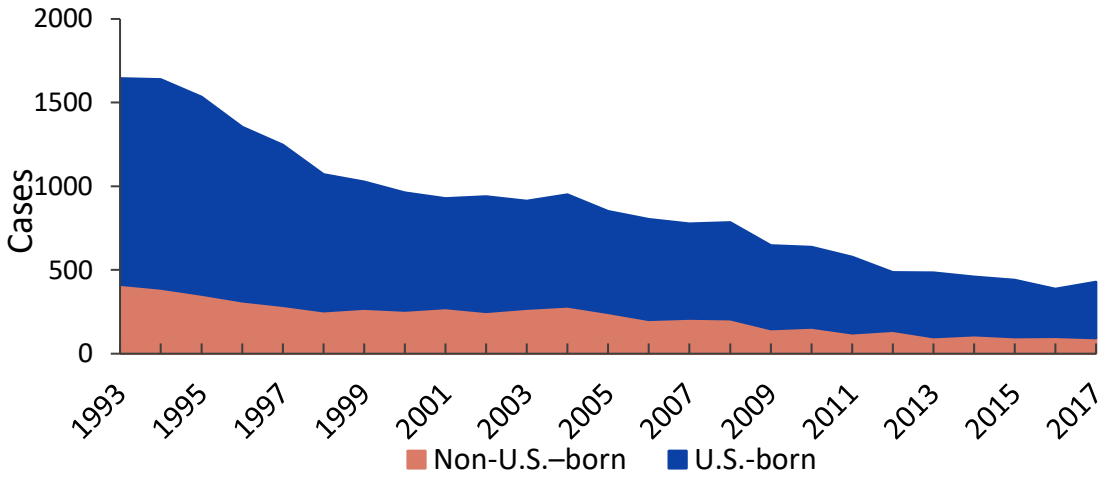
Watching for Early Signs & Symptoms

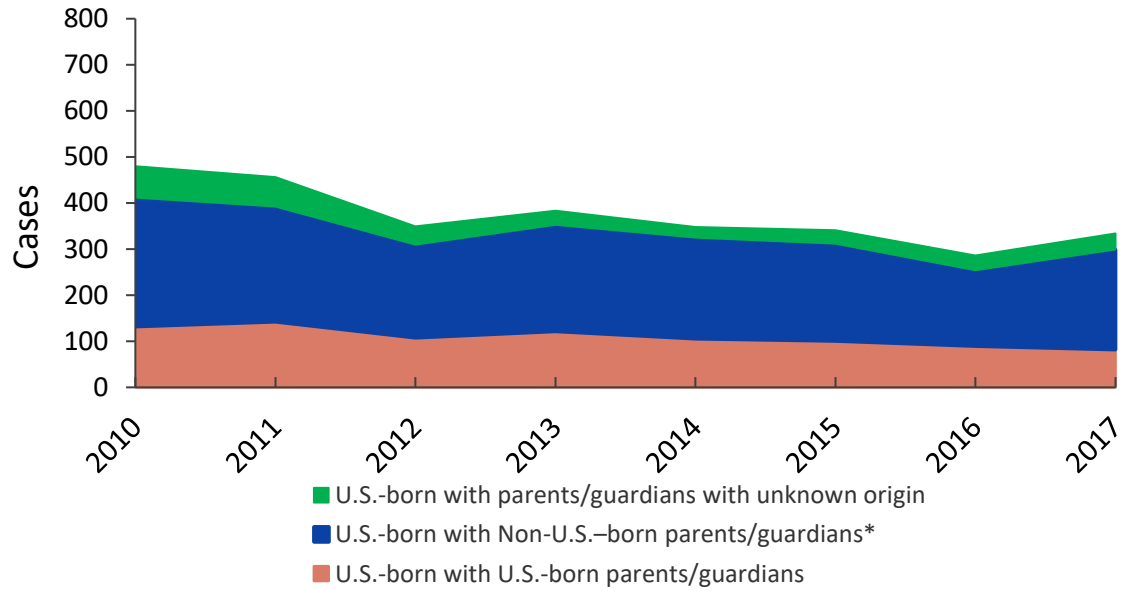
0-1	2+
Lethargy	Excessive Sleepiness
Vomiting	Vomiting
Excessive Sleepiness	Motor/Sensory Abnormalities
High Fever	Irritable
Seizures	Poor Feeding
Constant Crying	High Fever
Poor Feeding	Lethargy
	Persistant Headaches
	Constant Crying
	Seizures
	Cranial Nerve Findings

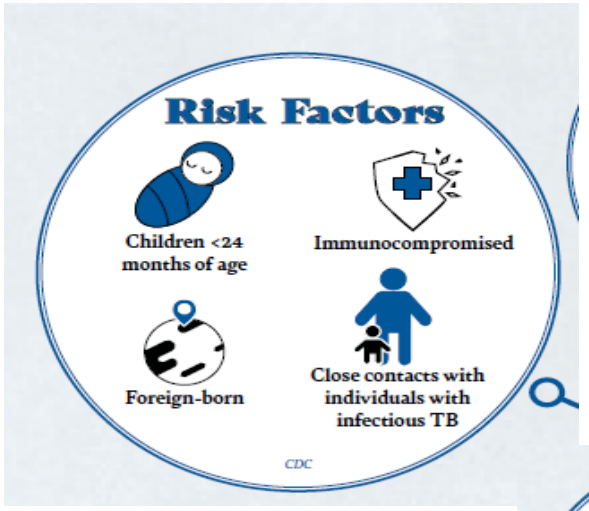
Note: Young children may not be able to share or verbalize these symptoms when asked, so collaborating with care givers will be imperative.

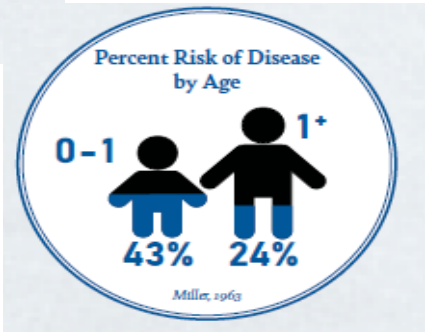


Age at Infection	Risk of Active TB
Birth – 1 year*	43%
1 – 5 years*	24%
6 – 10 years*	2%
11 – 15 years*	16%
Healthy Adults	5-10% lifetime risk
HIV Infected Adults+	30-50% lifetime









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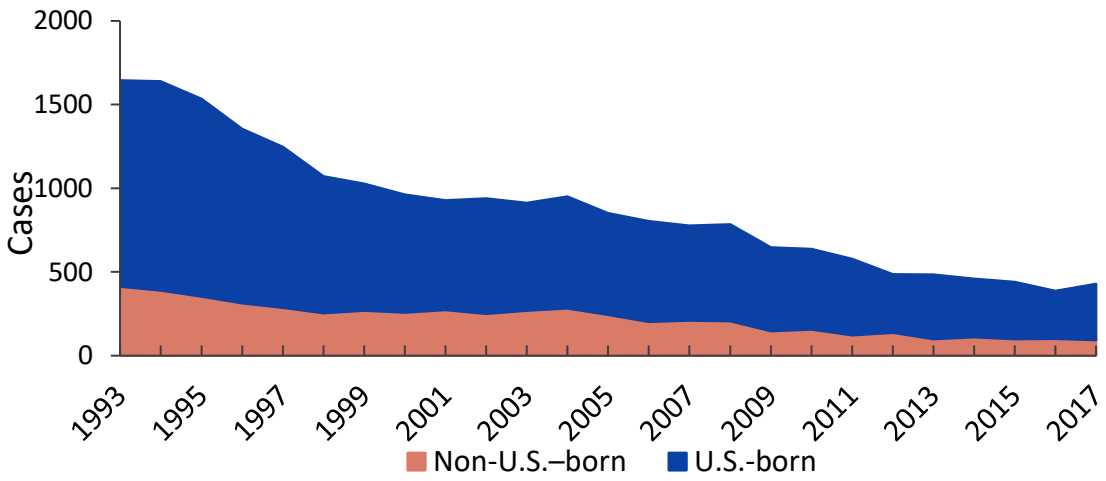

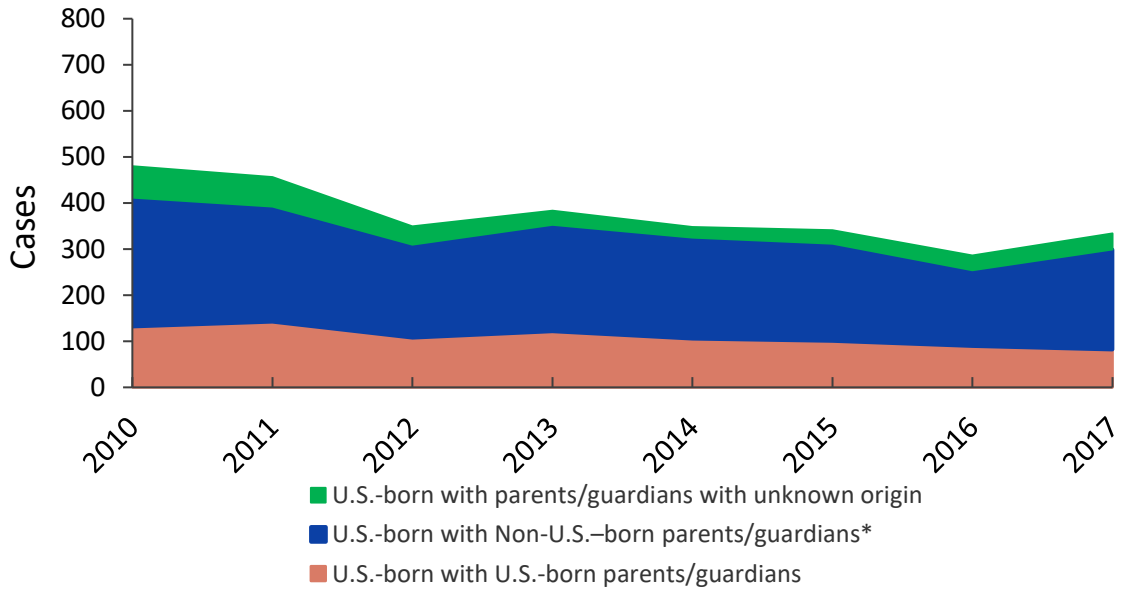

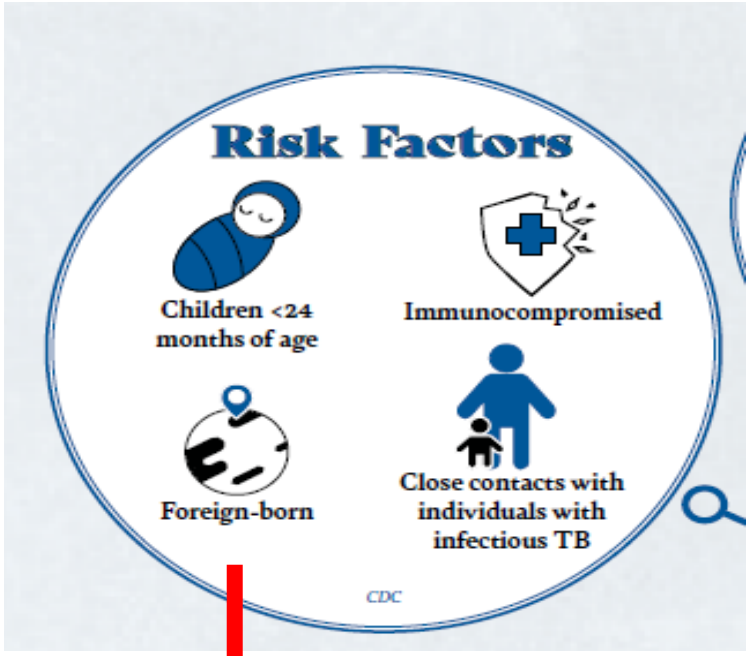

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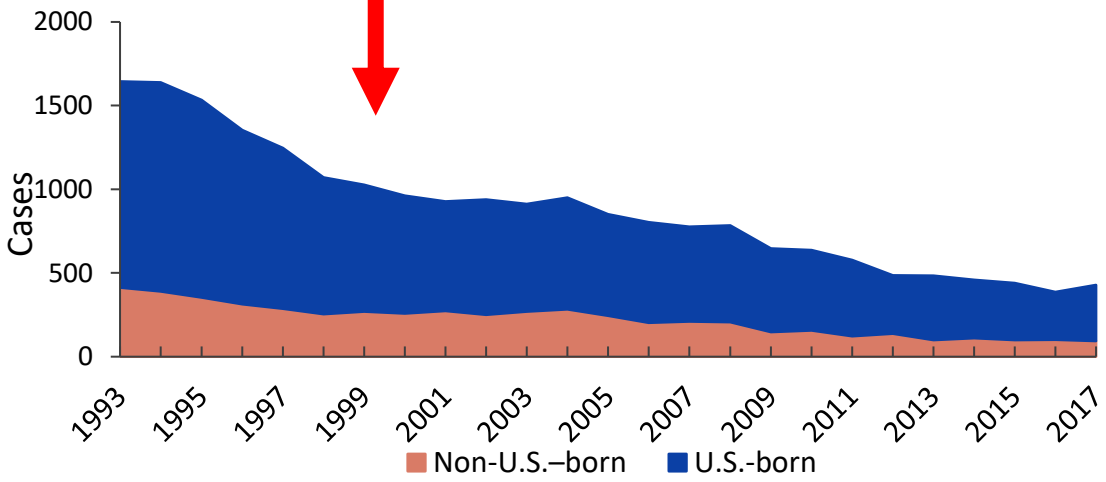
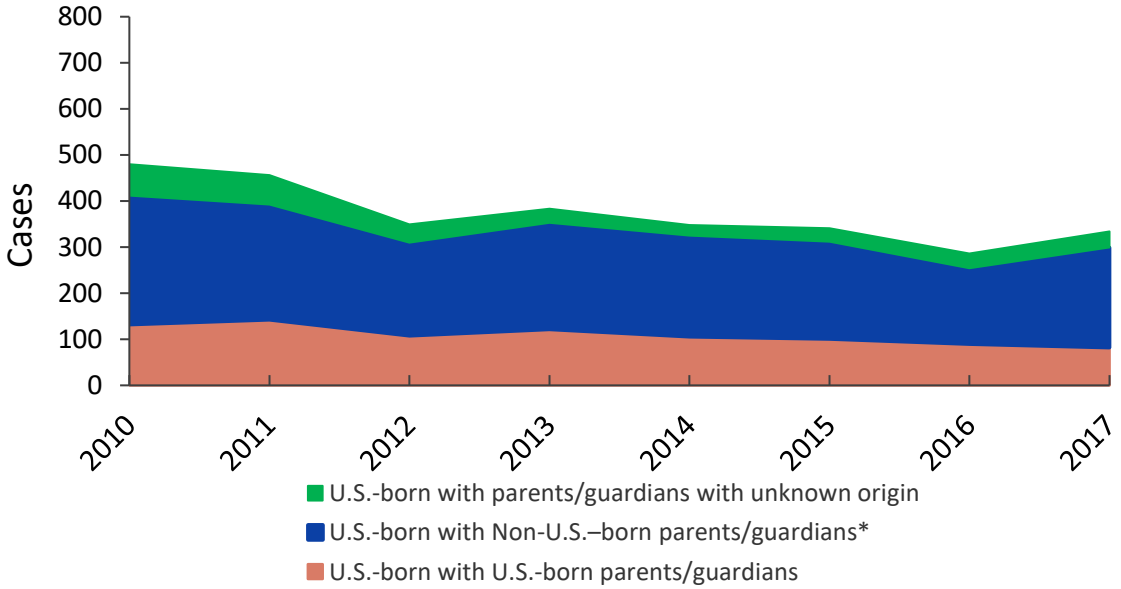
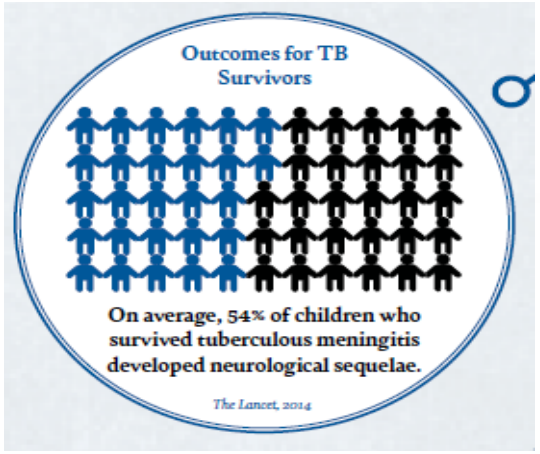


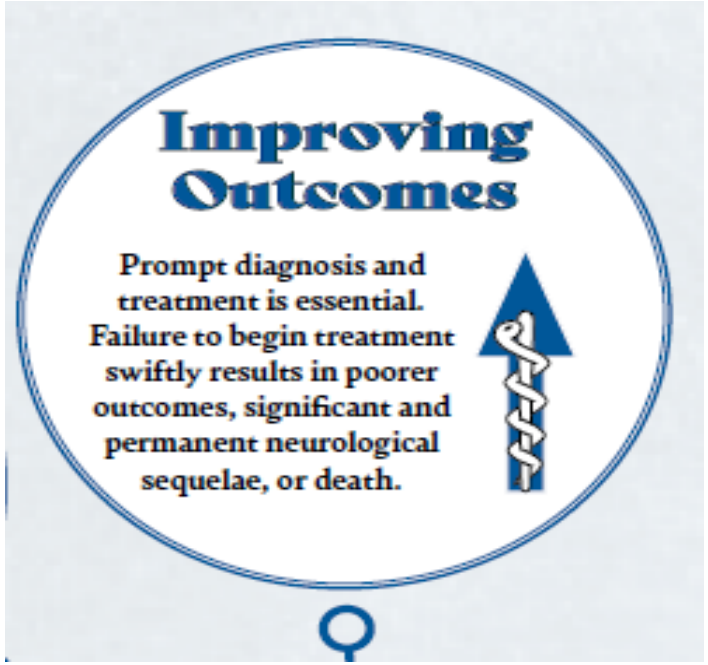


Treatment outcomes of childhood tuberculous meningitis: a systematic review and meta-analysis

Lancet Infect Dis 2014; 14: 947–57



- 19 studies, 1636 children
- Risk of death: **19.3%**
- Probability of survival without neurologic sequelae: **36.7%**
- Risk of neurologic sequelae: **53.9%**
- Diagnosis at stage 3: **47%** (associated with worse prognosis than early diagnosis)



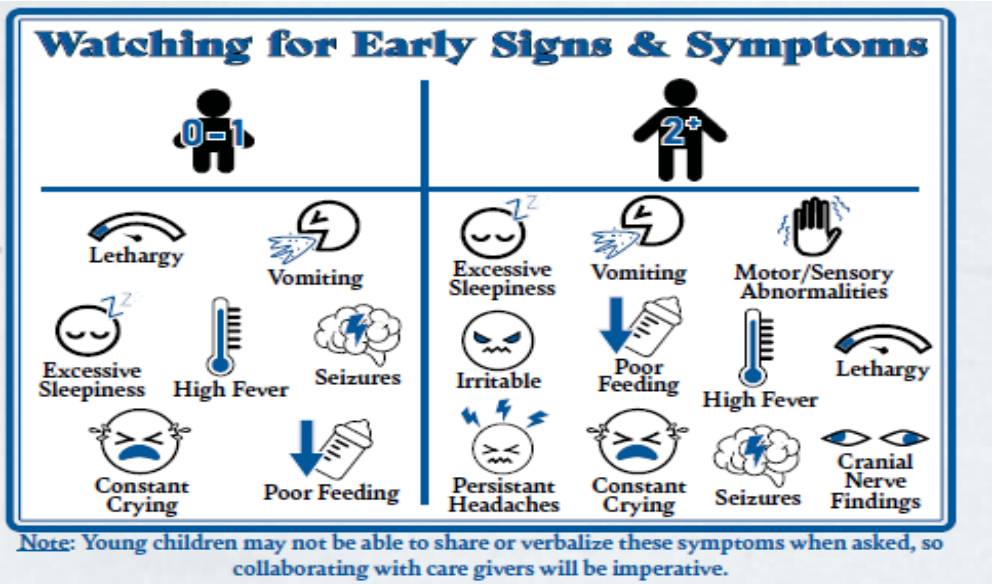
- **Stage I**
  - Notoriously nonspecific
  - Cough, low grade fever, vomiting, general listlessness
  - **Most valuable findings** are persistence of non-specific symptoms and signs, weight loss, recent contact with an active case of TB (70-80%)
- **Stage II**
  - Meningeal irritation
  - Other neurologic signs, loss of consciousness, signs of raised intracranial pressure, paralysis
- **Stage III**
  - Deep coma, progressive motor paralysis, cranial nerve palsies (especially 3rd, 6th), decerebration

J Neurol Neurosurg Psychiatry 2000; 68: 289-99

TABLE 1. British Medical Research Council clinical criteria for the severity of TBM[a]

Stage/grade	Classic criterion[b]	Contemporary criterion[c]
I	Fully conscious and no focal deficits	Alert and oriented without focal neurological deficits
II	Conscious but with inattention, confusion, lethargy, and focal neurological signs	Glasgow coma score of 14-11 or 15 with focal neurological deficits
III	Stuporous or comatose, multiple cranial nerve palsies, or complete hemiparesis or paralysis	Glasgow coma score of 10 or less, with or without focal neurological deficits

Death or Severe Disability HIV -	Death or Severe Disability HIV +
15%	25%
30%	50%
50%	80%



Stage I is when you want to diagnose

- Notoriously nonspecific
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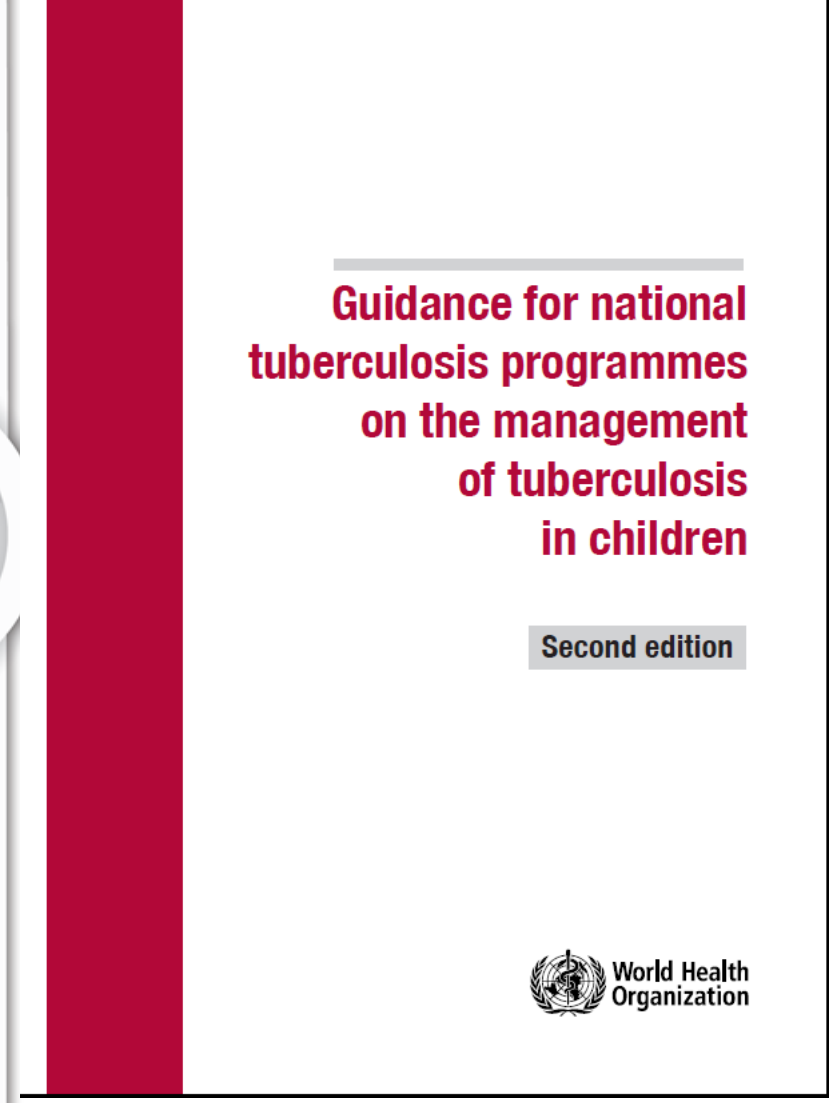
- **Most valuable findings** are persistence of non-specific symptoms and signs, weight loss, recent contact with an active case of TB (70-80%)

Clinical presentation

- In children, TBM tends to develop within 3 months of infection (with 75% presenting within 12 months of infection) and the pace of infections is often rapid (weeks to months)
- Children have headache less frequently than adults
- In small children, TBM appears to be closely associated with disseminated disease
  - Recommendation to do an LP on all children < 12 months of age with active TB disease is based on this association
- Clinical presentation at diagnosis is the strongest predictor of outcome
- Meta-analysis: Fever 89.9%

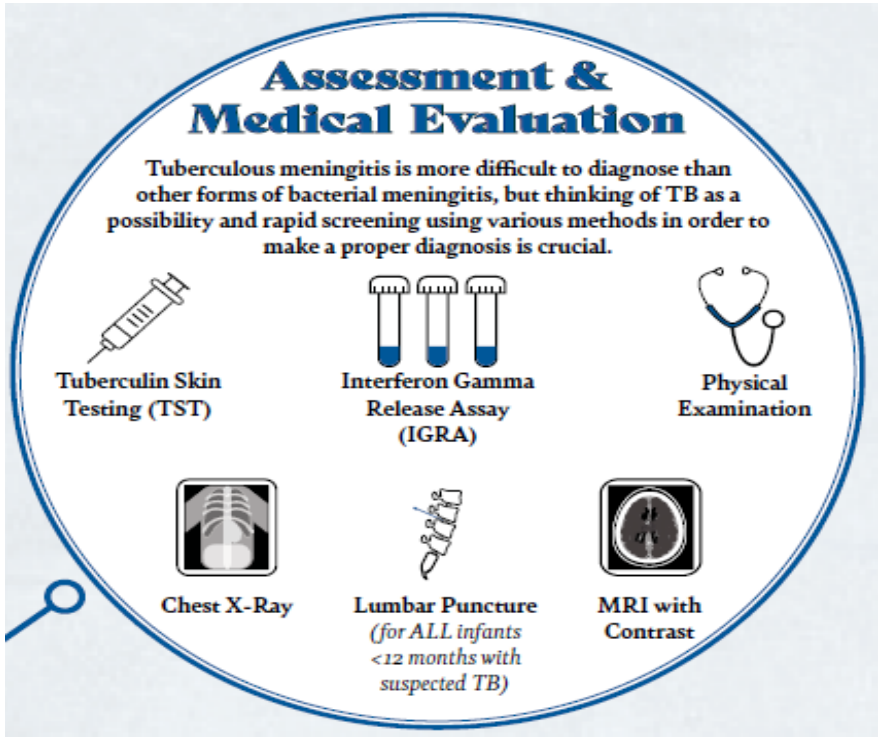


Symptoms

In most cases, children with symptomatic TB develop chronic unremitting symptoms, i.e. symptoms that persist for more than 2 weeks without sustained improvement or resolution following appropriate treatment for other potential diagnoses (e.g. antibiotics for pneumonia; antimalarials for fever; nutritional support for failure to thrive). The commonest symptoms include:

- cough
- fever
- not eating well/anorexia
- weight loss or failure to thrive
- fatigue, reduced playfulness, decreased activity.

The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are. However, no definite cut-offs, e.g. duration of symptoms, have been validated and accuracy will depend on context. Strict symptom criteria have lower sensitivity and specificity in those at greatest risk of severe disease and poor outcome such as infants or very young children (under 3 years), children living with HIV, or severely malnourished children *(1)*. These groups pose the greatest challenge for clinical diagnosis.



- AFB stain:
  - Sensitivity 10-20%
  - Large volume (10 ml), centrifuged, 30 minute examination by an experienced microscopist can increase detection to >80%

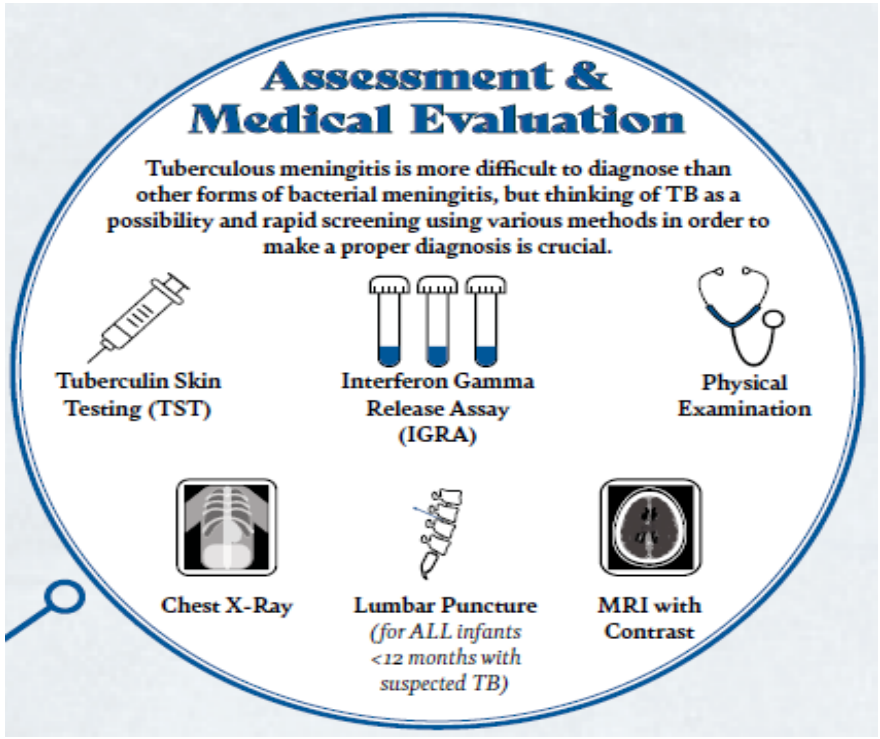
- Culture
  - More sensitive, not timely enough to effect decision making

- Xpert
  - Meta-analysis of 30 studies, found to be about 81-85% sensitive (enhanced by large volume tap, centrifugation)

- 22% TST/IGRA negative at diagnosis, consider doing both

- Typical CSF findings
  - Lymphocytes 100-1000 cells/mm^3 (first 10 days may have PMN predominance)
  - Elevated protein, decreased glucose

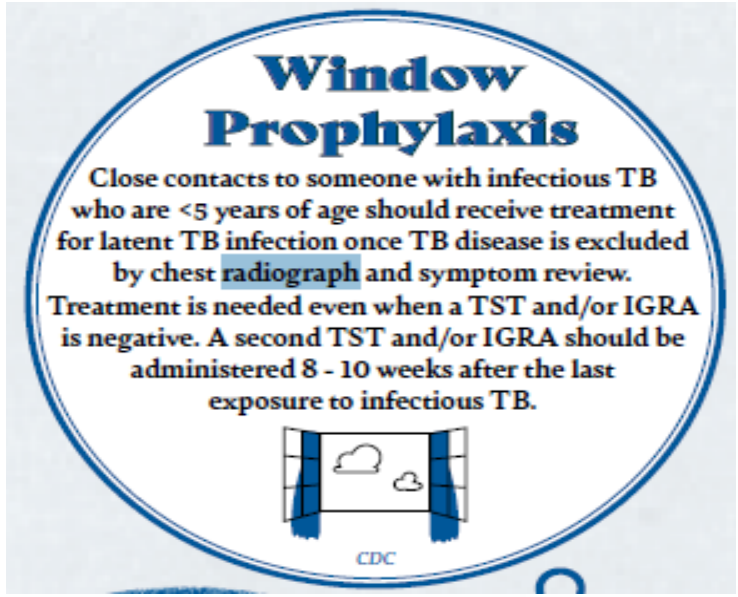
- Laboratory findings (pediatric TBM-review and meta-analysis)
  - Leukocytosis: **99.9%**
  - CSF lymphocytosis: **97.9%**
  - CSF AFB smear positivity: **8.9%**
  - CSF AFB culture positivity: **35.1%**



- CT or MRI with contrast:
  - basal meningeal enhancement
  - Hydrocephalus (87% in children, 12% in adults)
  - infarction (28% of patients, 83% MCA distribution)
  - Tuberculomas (contrast will highlight ring-enhancement)

TB Prevention After Exposure

- Household contact with contagious person
  - Teen or adult with pulmonary TB disease
  - Usually ≥ 4 hours of contact
- Initial TST/IGRA negative
  - Window period for TST conversion (8-10 weeks)
- CXR and physical exam normal



❖Window prophylaxis recommended:

- For children <5 yrs of age
- Immunosuppressed patients
- Patients on tumor necrosis factor-alpha blockers
- May prevent progression to disease during window period

- Repeat TST 8-10 wks after exposure
- May stop window treatment if 2nd TST/IGRA negative in immunocompetent patients

Slide shamelessly stolen from Dr. Kim Smith

5-month-old sister

- The patient's 5-month-old sister was being evaluated as part of a source case investigation
- Initially, her CXR was negative and she had no symptoms
- One week later she had cough and an abnormal CXR, she was referred to the ED for evaluation
- Her CSF showed
  - elevated WBC (54) – normal is 0-5!
  - elevated protein (68)
  - low normal glucose (51, serum glucose 79).
- The treating physician wanted to treat for LTBI……..

All the Feels……

From Dr. Yamba's email:

- I'm really grateful that Bella, Cameron County nurse, was proactive and consulted you on this case…….The hospital was about to start the baby on prophylactic treatment despite the CSF result, h/o of sibling with TB meningitis, current s/s and recent abnl CXR.

Some Take Home Points

- TBM is unique in children in that the brain is in the process of developing
- Early diagnosis is critical to prevent morbidity but, unfortunately, most diagnoses are made late (this needs to change)
- More studies are needed in children to maximize outcomes, from diagnosis to treatment

Thank you for your attention

Questions?

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