

Testing children for TB infection in the US

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Disclosures

- None

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What is “latent” tuberculosis?

A changing terminology:

“**Latent** tuberculosis infection” → “Tuberculosis infection”

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Outline

- A historical perspective and an evolving definition
- Why is it important to diagnose and treat TB infection in children?
- Who should we test?
- The evolving landscape of TB infection tests
- Practical considerations

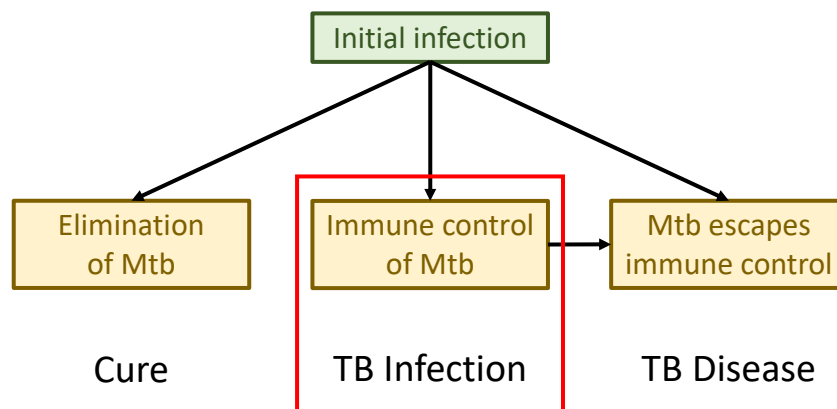
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TB pathogenesis



Mtb = *Mycobacterium tuberculosis*

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What is tuberculosis infection?

A practical definition:

Infection with *Mycobacterium tuberculosis*, with no clinical evidence of disease.

Diagnosed by detecting an **immune response to TB**, using Tuberculin Skin Test (**TST**) and/or Interferon Gamma Release Assay (**IGRA**).

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“Latent TB Infection” diagnosis – a history

Middle Pleistocene
(~400-500K years ago)

Evidence of TB in
Homo erectus

Pre-history

Now

Behr et al., *Am J Resp Crit Care Med*, 2021; Campbell & Dubois, et al., *JPIDS*, 2022

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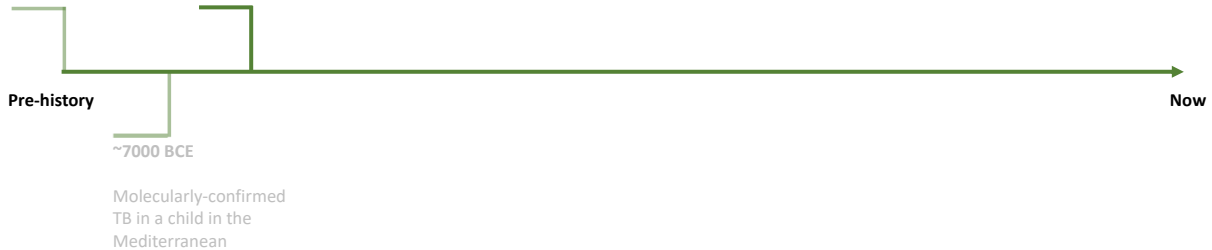
“Latent TB Infection” diagnosis – a history

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TB in antiquity

- “Yakṣma” (Atharvaveda, 1200 BCE)
- “Phthisis” (Hippocrates, 400 BCE)
- “Schachepheth” (Old Testament, 1200 BCE)



Behr et al., *Am J Resp Crit Care Med*, 2021; Campbell & Dubois, et al., *JPIDS*, 2022

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“Latent TB Infection” diagnosis – a history



Carving on false door in the tomb of Ankh Oudges, Egypt, Old Kingdom; Glyptothek Ny Carlsberg (Copenhagen)

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“Latent TB Infection” diagnosis – a history



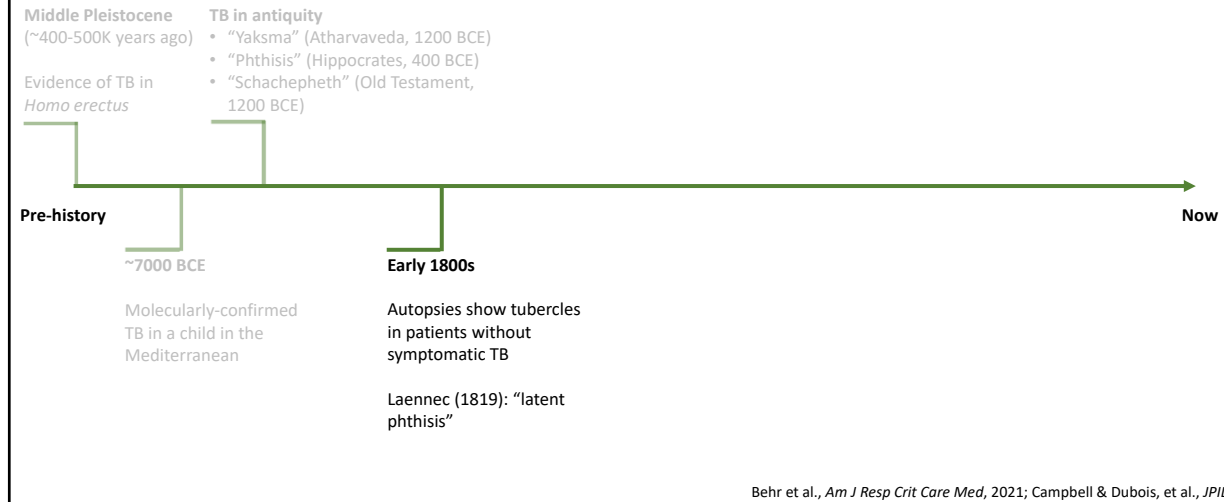
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Royal Touch, from *Les Grandes chroniques de France*, by Mahiet and the Master of the Cambrai Missal, illuminated manuscript, ca. 1340 (British Library, London)

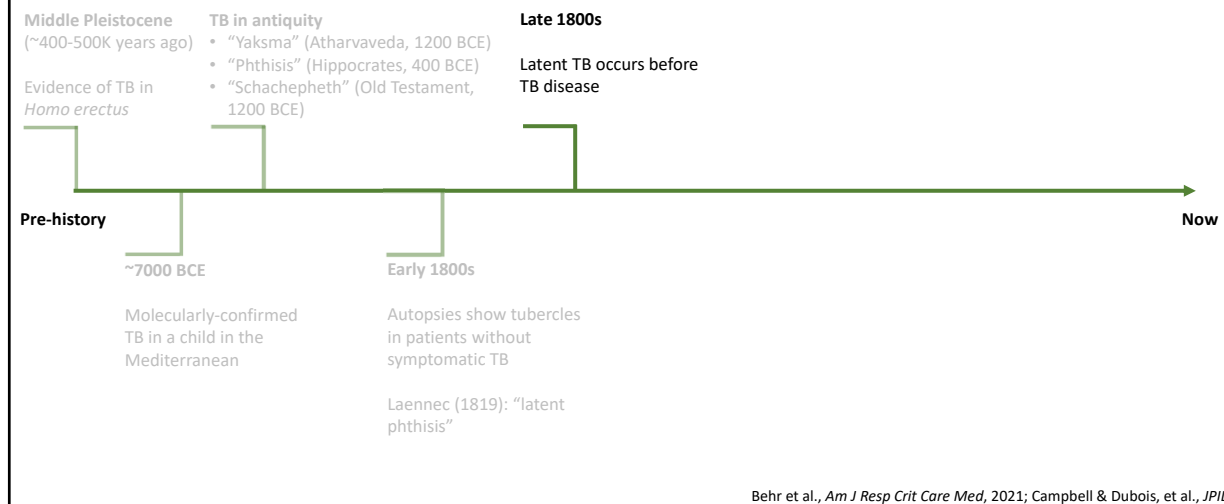
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“Latent TB Infection” diagnosis – a history



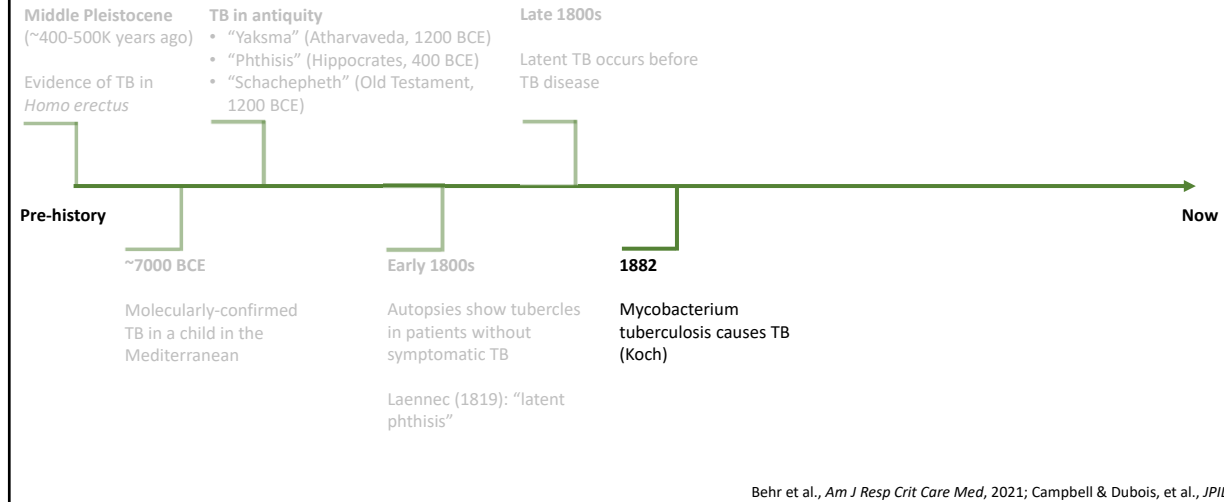
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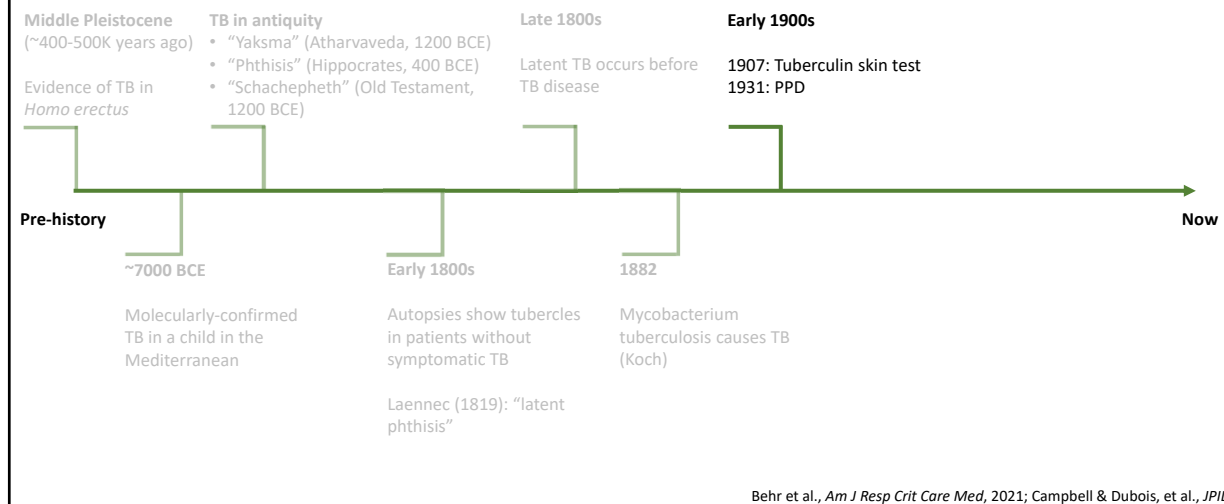
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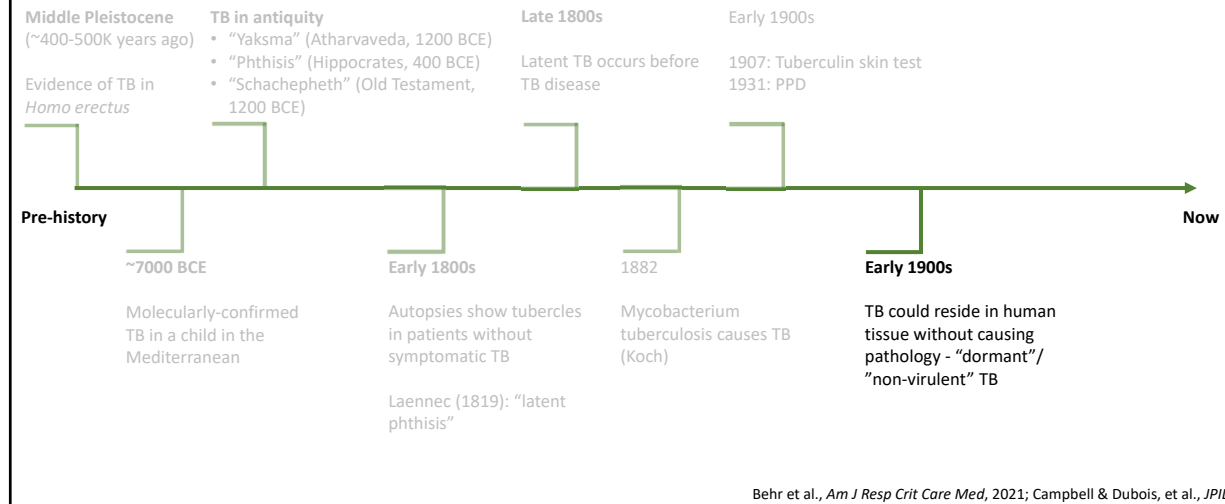
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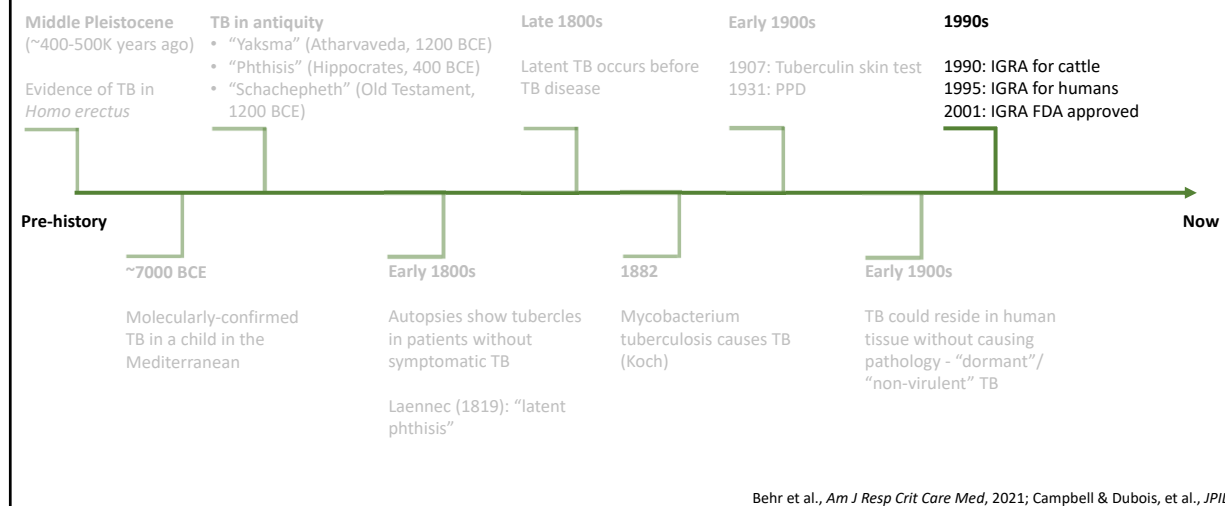
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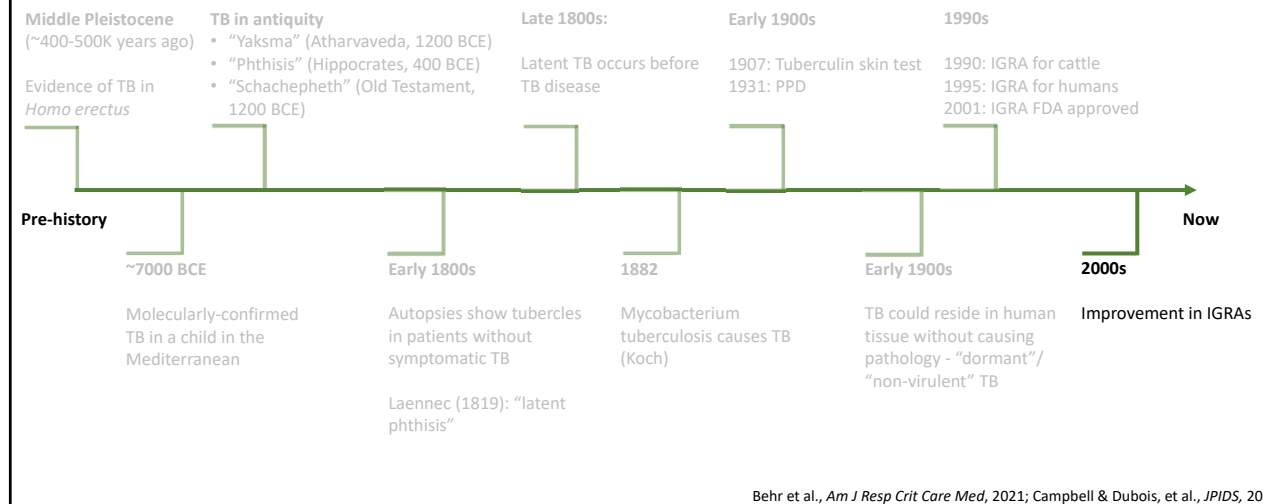
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“Latent TB Infection” diagnosis – a history



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“Latent TB Infection” diagnosis – a history



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What is “latent” tuberculosis?

- Before 1900: TB (tubercles) grossly visible in tissue; **no symptoms**
- 1900s: Dormant TB bacilli reside in the host; **no symptoms**
- 2000s: **Immune response to TB; no symptoms**
 - “Immunologic evidence” – positive TST and/or IGRA

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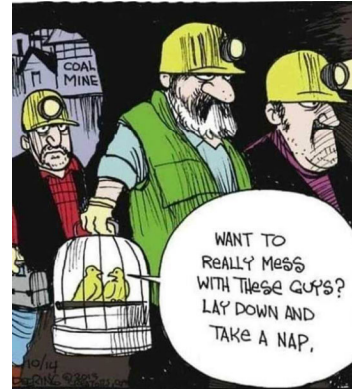
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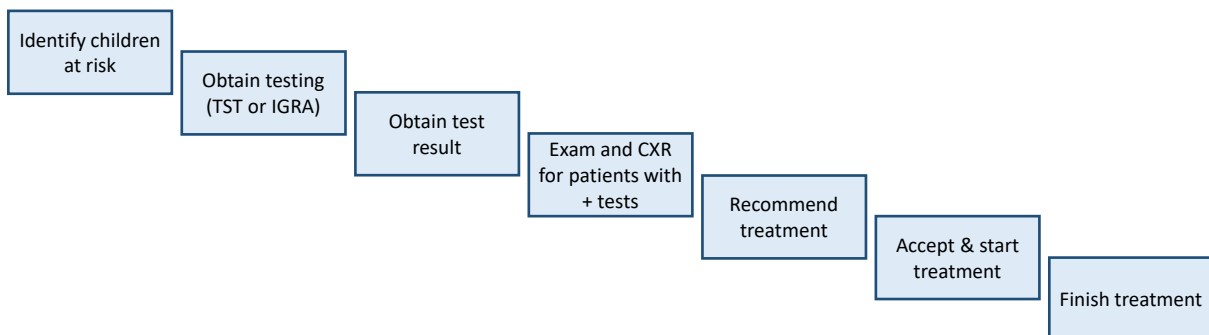
Why diagnose and treat TB infection in kids?

1. Prevent risk of progression to TB disease
 - a. TB preventive therapy decreases risk of TB disease by ~90%
2. Public health benefits
 - a. TB elimination in the US
 - b. Children as “canaries in the coal mine”



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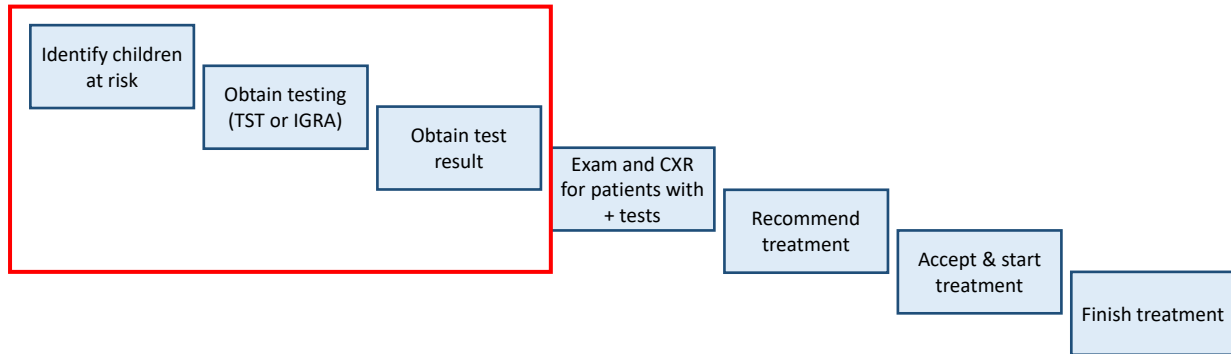
Preventing progression – the care cascade



Alsdurf et al., Lancet ID, 2016

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Preventing progression – the care cascade



Alsdurf et al., *Lancet ID*, 2016

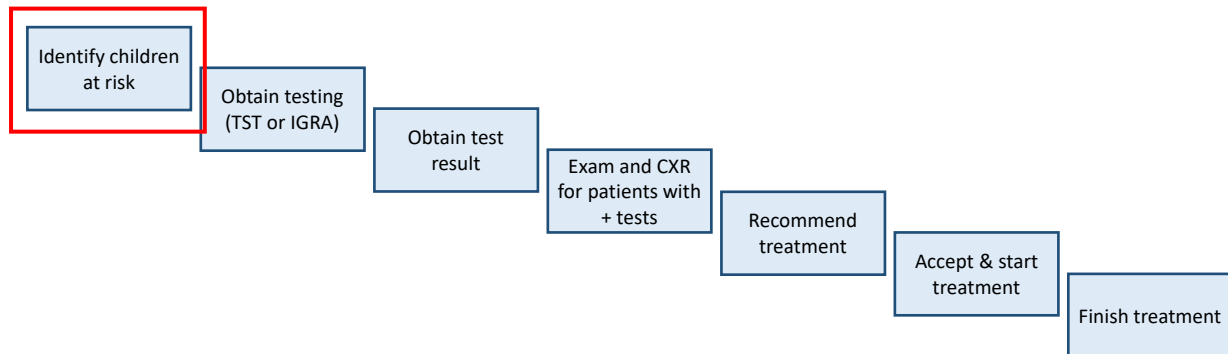
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Preventing progression – the care cascade



Alsdurf et al., Lancet ID, 2016

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Targeted testing

1. Most children with TB infection merit treatment
2. Testing implies a decision to treat
3. Need to identify patients most likely to benefit from treatment
 - Minimize false positive tests
 - Identify patients at high risk for progression

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How do we target testing?

Targeted Testing of Children for Tuberculosis: Validation of a Risk Assessment Questionnaire

Hervey Froehlich, MD*; Lynn M. Ackerson, PhD‡; Pius A. Morozumi, MD§; and the Pediatric Tuberculosis Study Group of Kaiser Permanente, Northern California

Evaluation of a Risk Assessment Questionnaire Used to Target Tuberculin Skin Testing in Children

Philip O. Ozuah, MD, MEd
Theresa P. Ozuah, MD
Ruth E. K. Stein, MD
William Burton, PhD
Michael Mulvihill, DrPH

Context Universal tuberculin skin testing of children has been shown to be costly and inefficient. In response, several authorities have recommended targeted screening based on epidemiological risk. In 1996, the New York City Department of Health (NYCDOH) developed questions to identify children who require a tuberculin skin test.
Objective To determine the sensitivity, specificity, and predictive validity of the NYCDOH tuberculosis risk assessment questionnaire.

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Recommendations in children

- Annual risk factor screening (during well-child checks)

Risks for TB infection in children

- Contacts of TB disease cases
- Immigrants from countries with endemic infections (including adoptees)
- “Significant” (>1 month) travel to countries with endemic TB, who have “substantial contact” with local populations

Risks for progression

- Immunosuppressive therapy
- Some chronic medical conditions (diabetes, renal failure)
- HIV (screen annually)

Red Book, 2024

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Limitations of these recommendations

- Validation studies performed before IGRAs were available
 - Captured false-positives from BCG?
- US-born children are more likely to be diagnosed with TB than foreign-born children
 - Associated with parents who were born abroad
 - Screening tools do not capture parents' information
- Written questionnaires are infrequently used

Cruz et al, Curr Op Ped, 2016; Lazar et al., J Comm Health, 2010

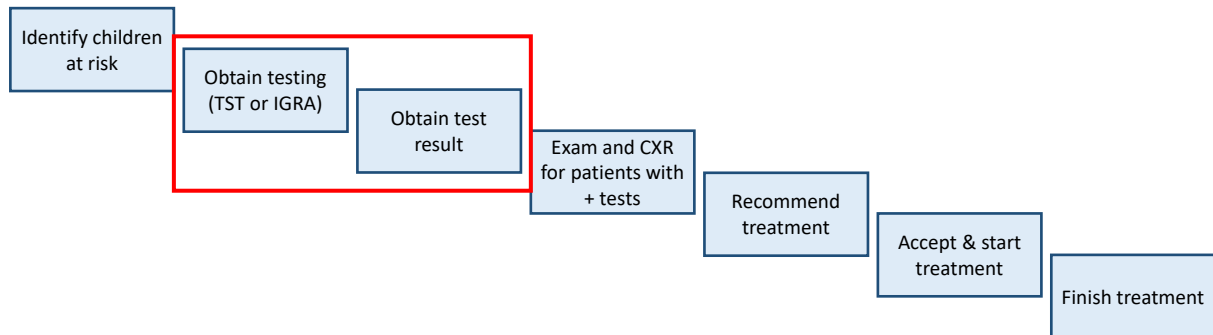
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Preventing progression – the care cascade



Alsdurf et al., *Lancet ID*, 2016

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Testing for TB infection in children



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Testing for TB infection in children

Tuberculin skin test

- Purified protein from human *Mycobacterium tuberculosis*
- Induces a delayed-type hypersensitivity reaction in individuals (previously) infected with *M. tb*
 - Reaction occurs over 48-72 hours

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Appealing features

- Widely used
- Extensive experience using TSTs in children of all ages (including <2yo)
- Relatively easy to place

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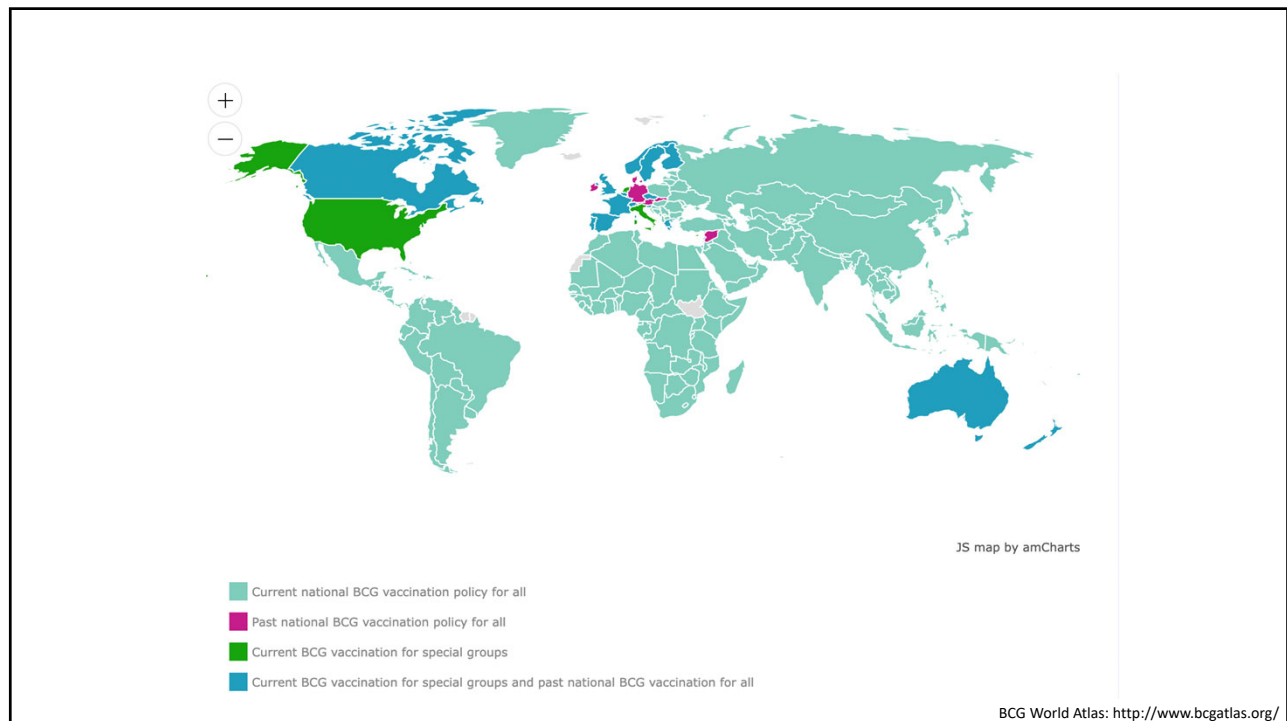
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Downsides

- Cross-reactivity with BCG and some environmental mycobacteria (though usually negative by 5yo)
- Requires 2 visits
- Interpretation may be challenging

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Testing for TB infection in children

Interferon gamma release assays (IGRA)

- Blood test using synthetic peptides representing ESAT-6, CFP-10-, and TB7.7 (QFT-GIT only) (TB proteins)
- Measure interferon gamma stimulation

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- Requires only 1 visit
- Results can be available quickly

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Testing for TB infection in children

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Appealing features

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Downsides

- Not recommended for use in children <2 years old
- Requires phlebotomy and quick blood processing

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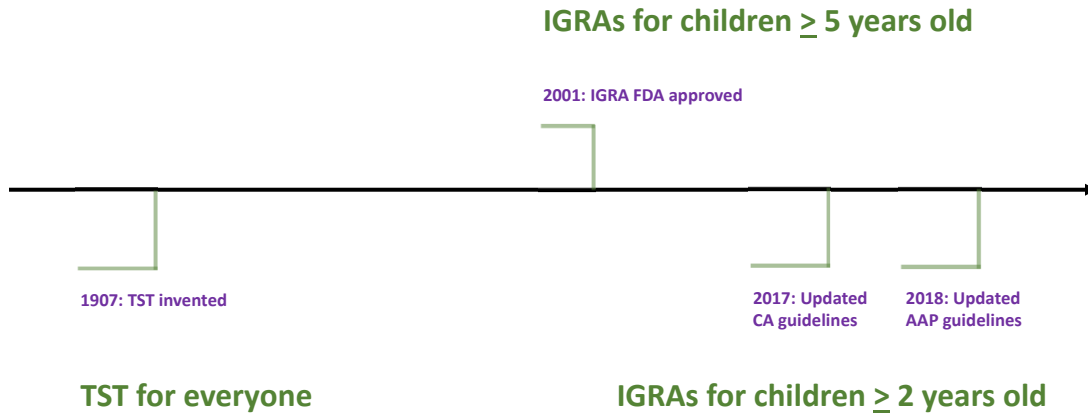
A changing landscape



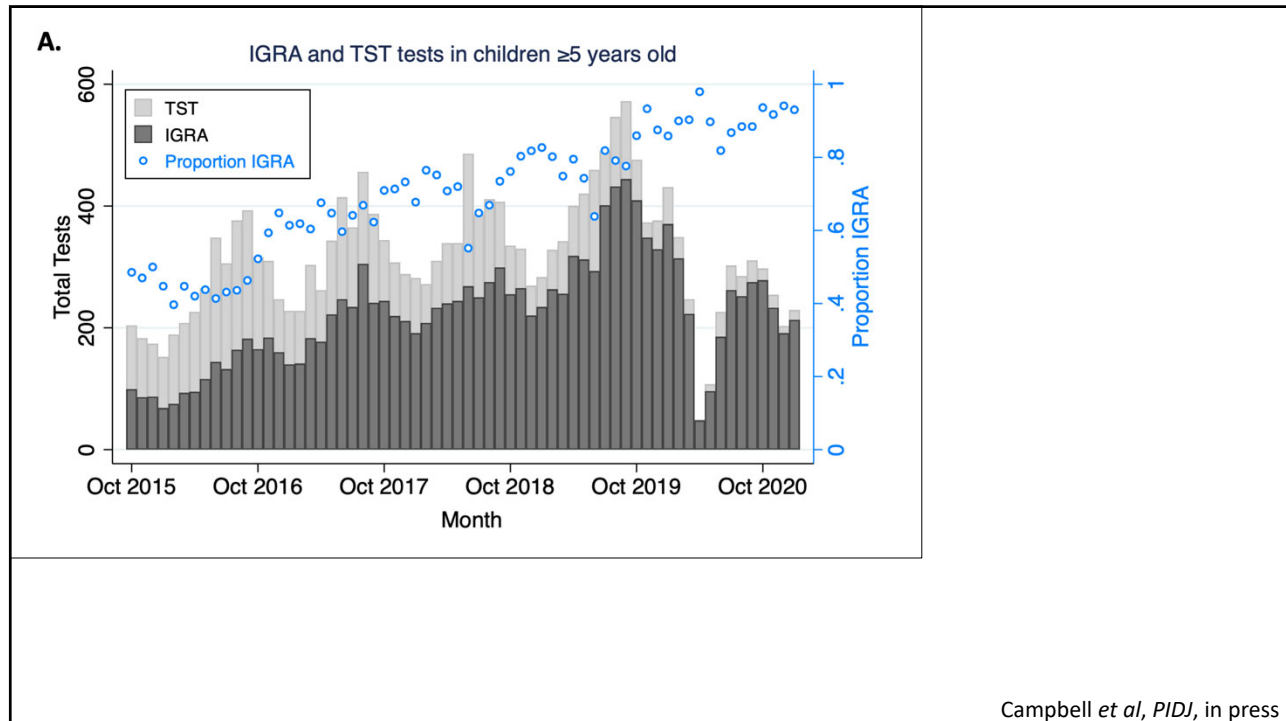
Pieter Bruegel the Elder, *The Harvesters*, Metropolitan Museum of Art

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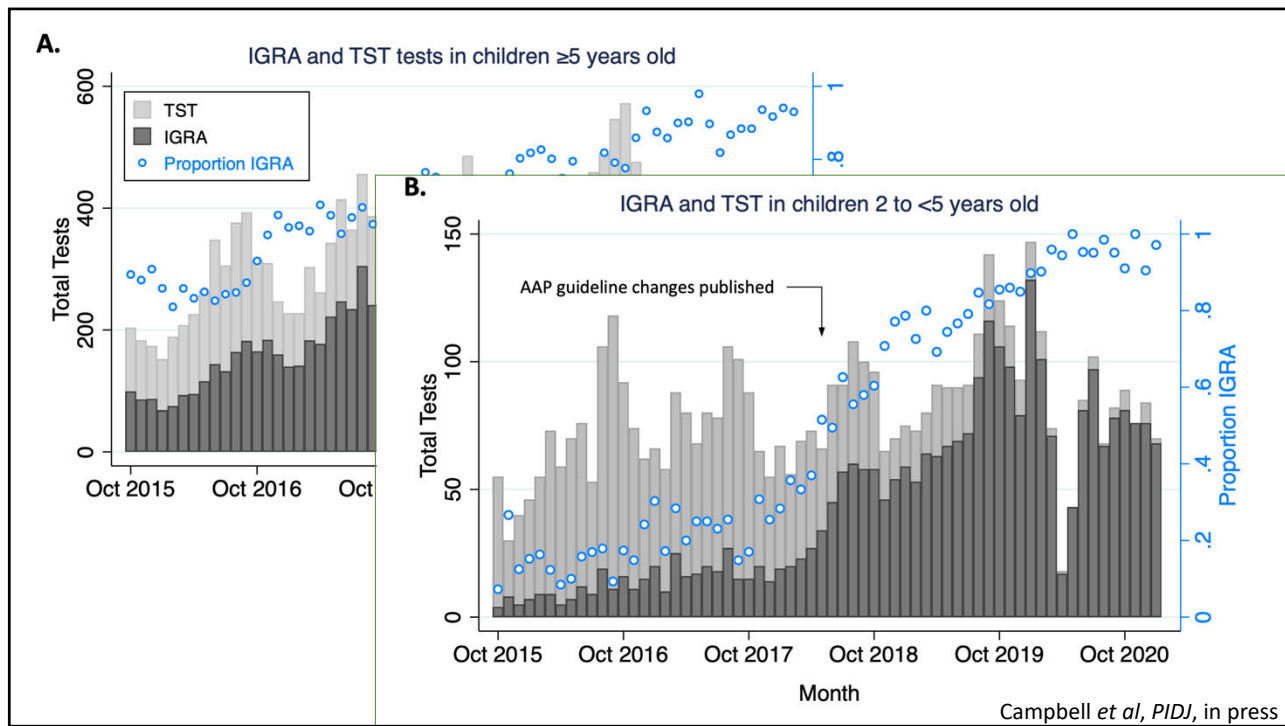
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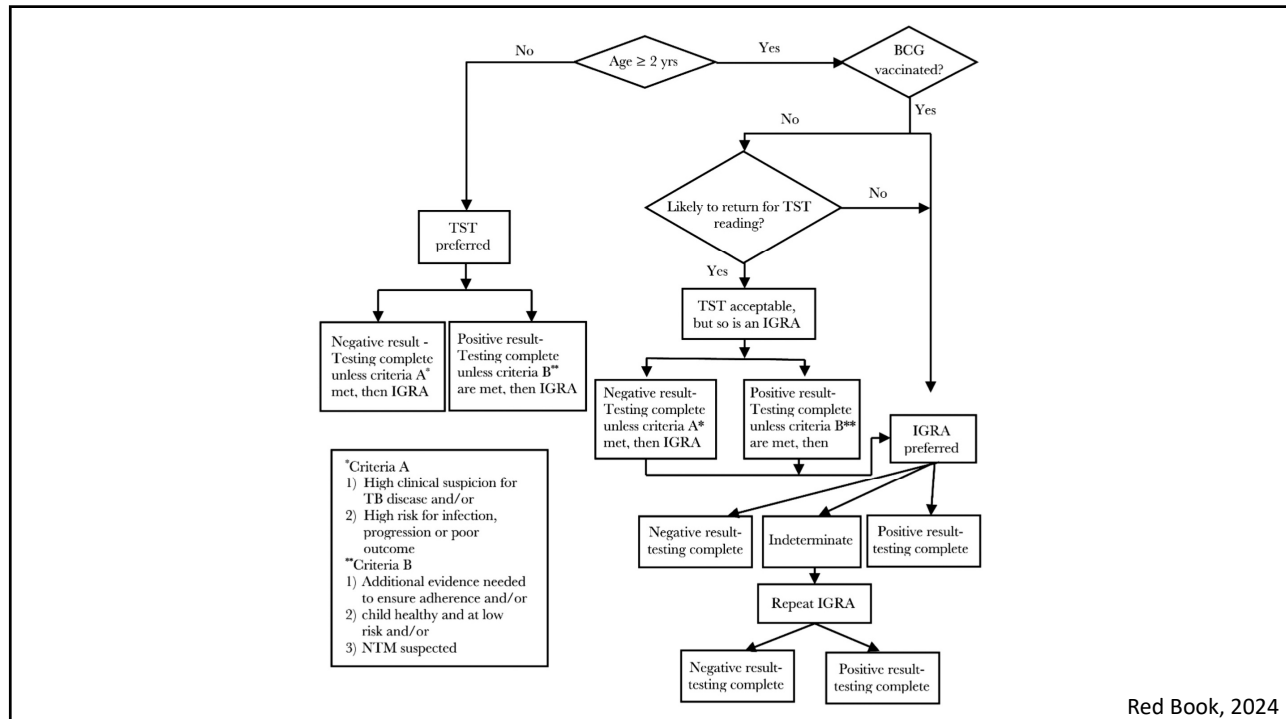
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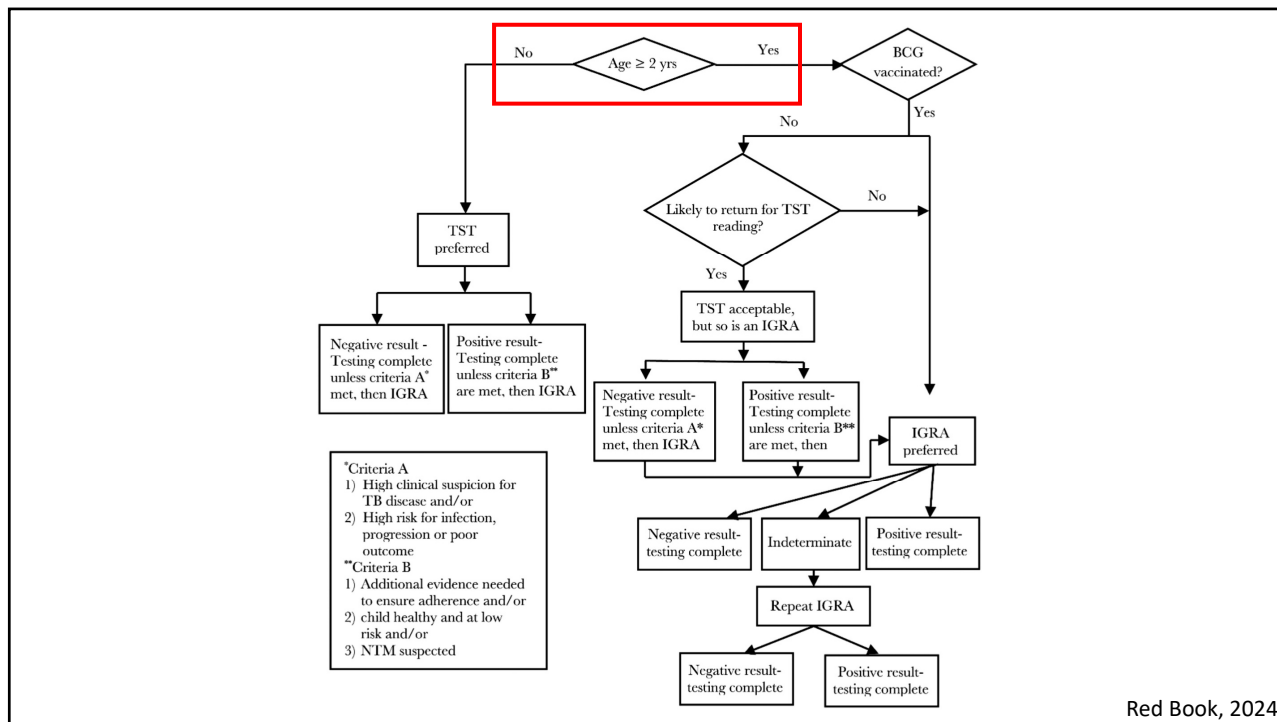
Practical considerations

- Testing children who have received BCG
 - IGRA preferred in children ≥ 2 yo
 - However...
 - BCG-TST cross-reactivity usually disappears by 5 years old (for children vaccinated as infants)
 - In children from high-burden countries, a positive TST is **often** from TB infection

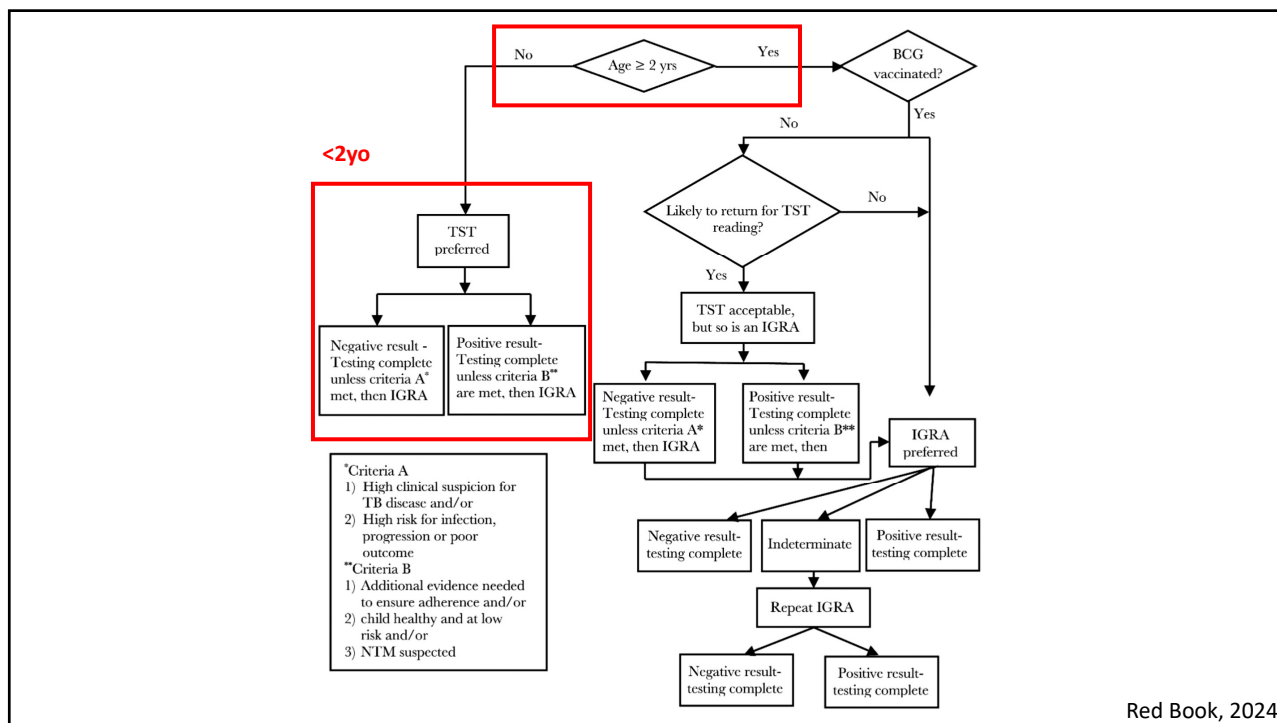
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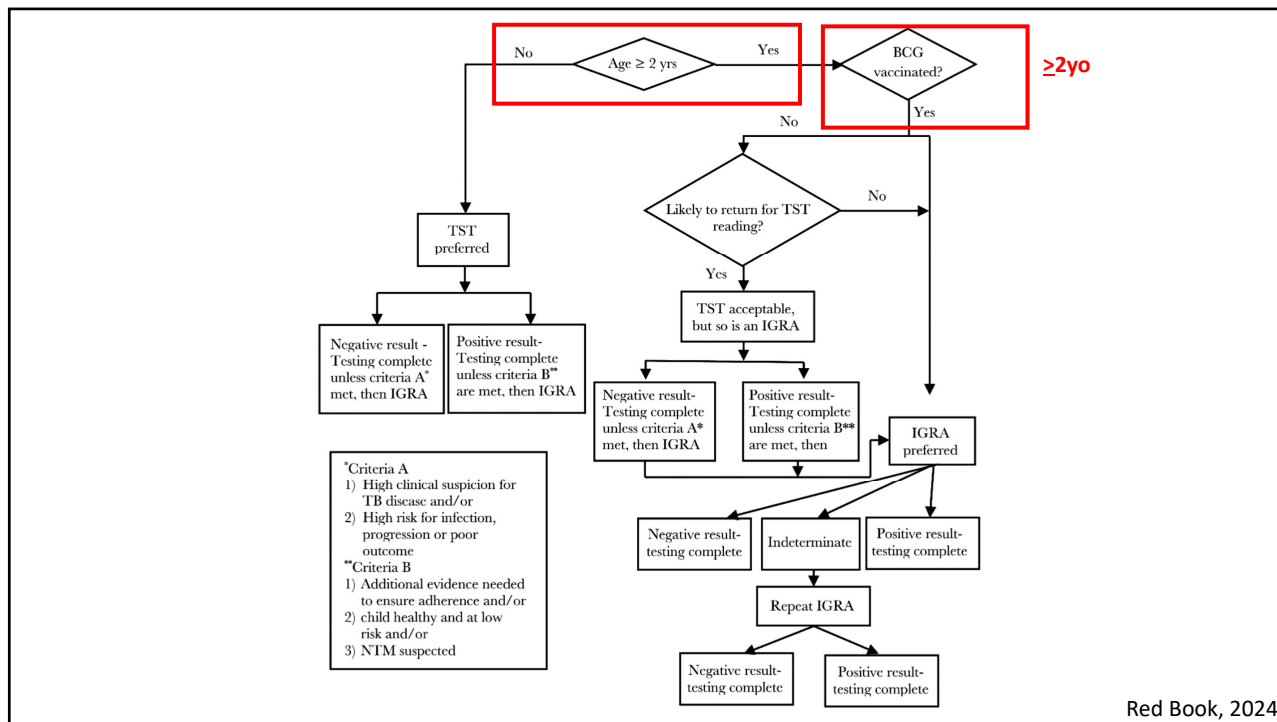
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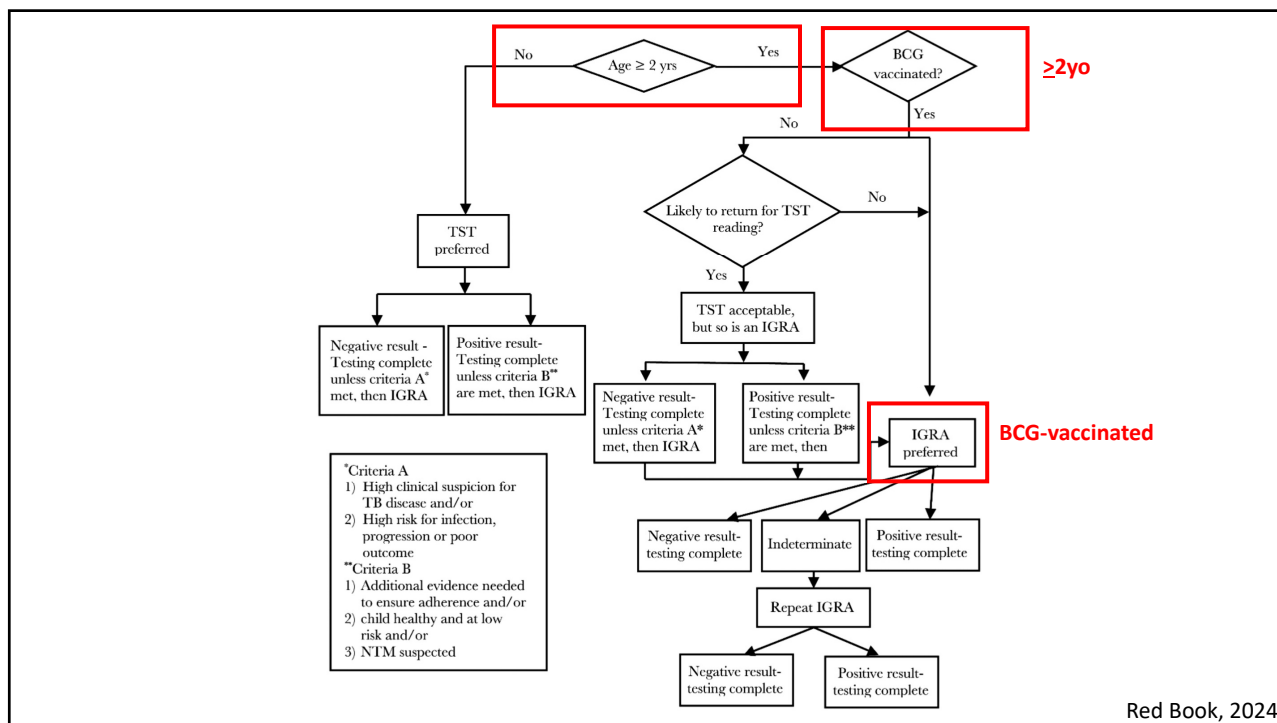
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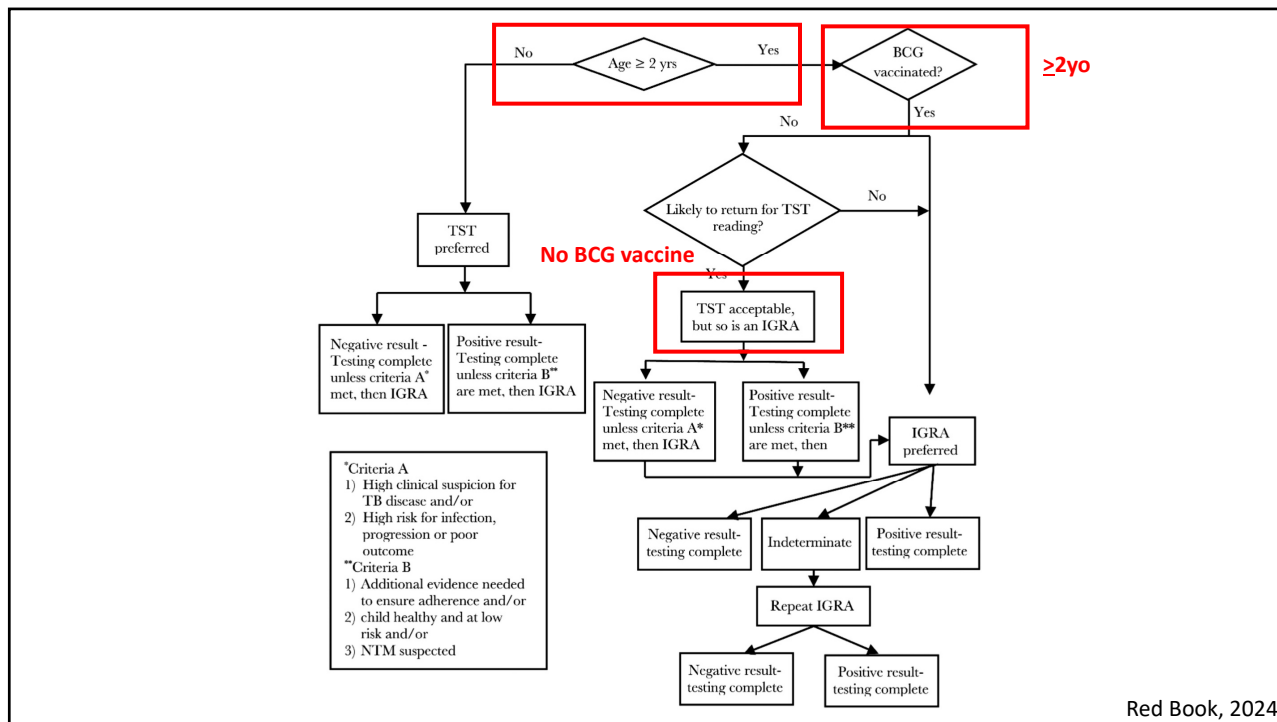
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Practical considerations

- Testing children who have received BCG
- Testing children after live virus vaccination

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Practical considerations

- Testing children who have received BCG
- Testing children after live virus vaccination
 - Measles vaccine (and probably mumps, rubella, varicella) → transient, mild immunosuppression that may interfere with TST and IGRA

CDC Pink Book

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Practical considerations

- Testing children who have received BCG
- Testing children after live virus vaccination
 - Measles vaccine (and probably mumps, rubella, varicella) → transient, mild immunosuppression that may interfere with TST and IGRA
 - In a patient needing MMR +/- V, as well as TB infection testing:
 - Obtain TST/IGRA **on the same day** as vaccination, or...
 - Wait at least **4 weeks after** vaccination before TST/IGRA

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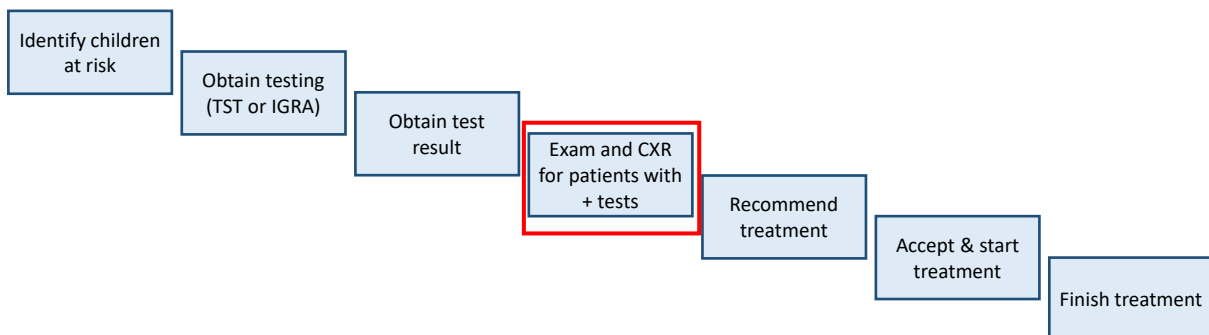
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- Testing children who have received BCG
- Testing children after live virus vaccination
- What happens when a child has a positive test?

CDC Pink Book

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Evaluation of children with positive tests



Alsdurf et al., Lancet ID, 2016

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Practical considerations

- Testing children who have received BCG
- Testing children after live virus vaccination
- What happens when a child has a positive test?
 - “Exclude TB disease”
 - Chest X ray → pulmonary TB
 - Physical exam → extra-pulmonary TB

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Practical considerations

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 - Can children go to school while awaiting a chest X ray?
 - If they are asymptomatic → Yes

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 - If they are asymptomatic → Yes
 - Can children go to school if they have TB infection? Yes

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Recap

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Recap

- A historical perspective and an evolving definition
 - Latent TB infection → TB infection
 - TB without symptoms/signs, detected immunologically
- Why is it important to diagnose and treat TB infection in children?
 - Reducing risk of TB disease
 - Public health control of TB
- Who should we test?
 - Targeted testing
- The evolving landscape of TB infection tests
 - Decreasing ages for IGRAs
- Practical considerations
 - Testing after BCG and MMR/V; next steps after a positive test

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Thank you!

Jeffrey Campbell, MD MPH

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Summary

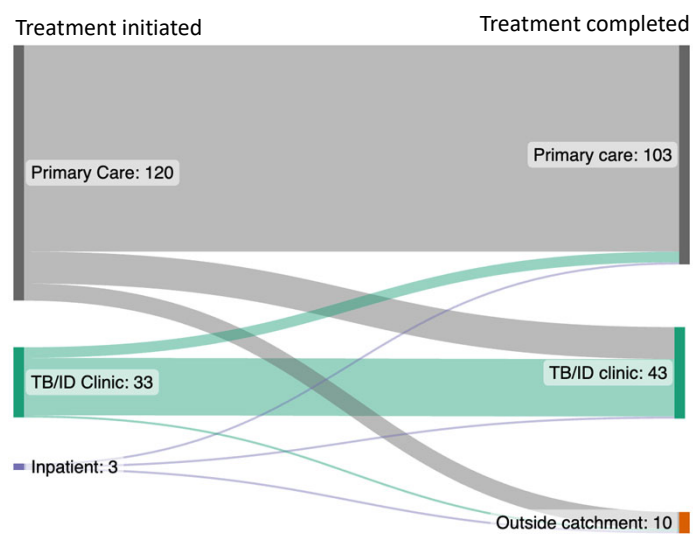
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Additional slides

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TB infection in complex care systems



Campbell *et al.*, Poster at IDWeek, 2022

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Innovation in pediatric TB infection care

Diagnosis

- Novel electronic health record tools to screen for TB risk factors
- Changes in TB infection testing selection
- New tests?

After diagnosis

- Strengthening primary care capacity to treat TB infection
- Re-envisioning the interface of primary and subspecialty care
 - Telehealth
- Shorter treatment regimens