MAYO CLINIC

Center for Tuberculosis

Special Considerations for Pediatric Tuberculosis

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Mayo Clinic Center for Tuberculosis

Pediatric TB and recent Local transmission

Reactivation TB from
remote exposure/infection.

Risk Factors: DM

New infection from
proximate exposure

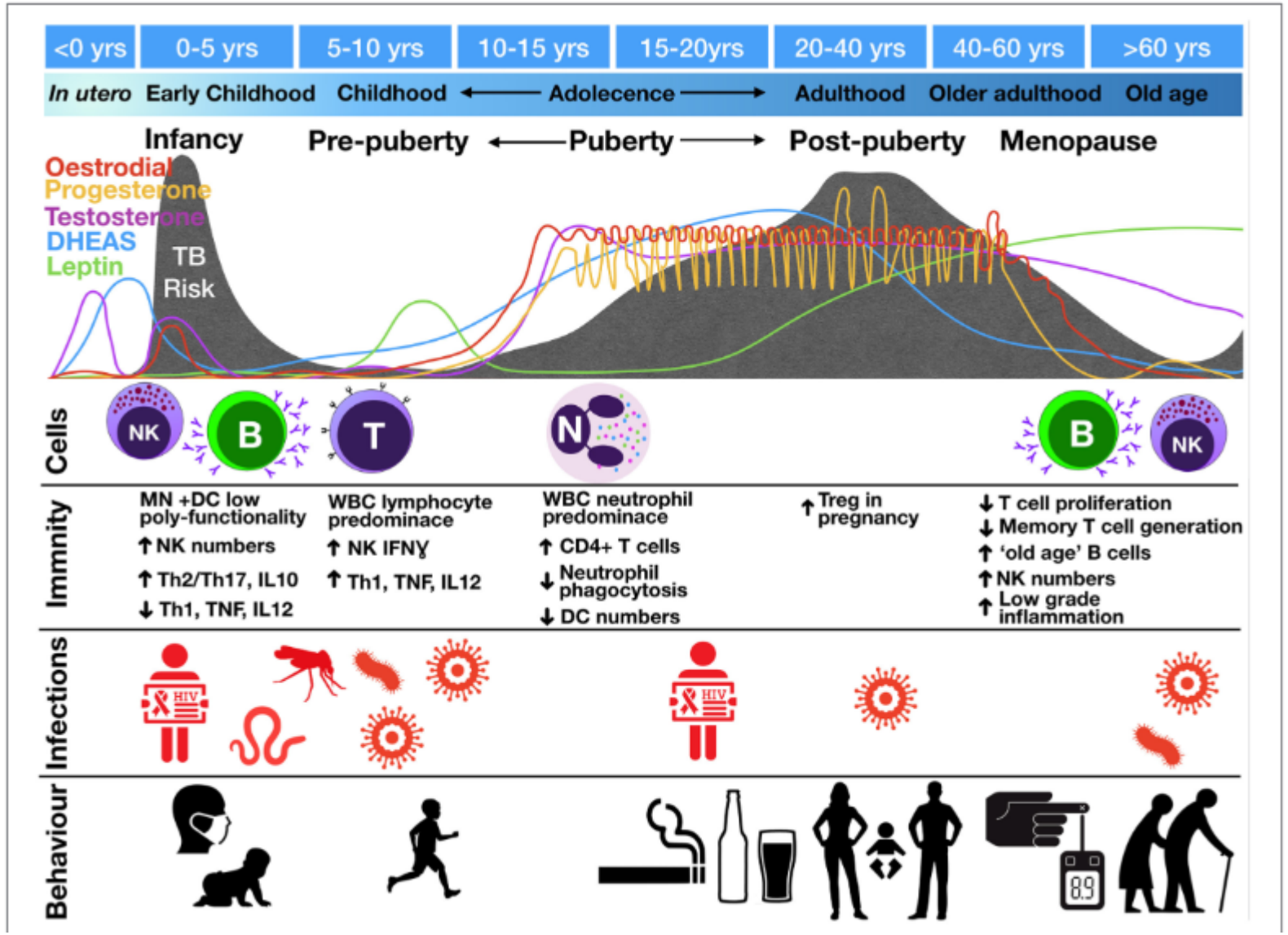
Risk factor: age

Source: Samoa News, 2020

Age-related progression from infection to active disease

Age	Pulmonary TB	Disseminated TB/ TB meningitis	No Disease
< 1 year	30-40%	10-20%	50%
1-2 years	10-20%	2-5 %	75-80%
2-5 years	5%	0-5%	95%
5-10 years	2%	< 0-5%	98%
> 10 years	10-20%	< 0-5%	80-90%

Adapted from Cruz et al, Clinical manifestations of tuberculosis in children. *Paediatr Resp Rev. 2007* Jun;8(2):107-17



Seddon JA, Chiang SS, Esmail H and Coussens AK (2018) The Wonder Years: What Can Primary School Children Teach Us About Immunity to Mycobacterium tuberculosis? Front. Immunol. 9:2946

Age-related Extrapulmonary disease presentation in pediatric TB

TABLE 1 Childhood tuberculosis cases with any extrapulmonary involvement by age group and selected sites of disease, United States, 1993 to 2015[a]

Site of disease	% occurrence among children in indicated age group			
	<1 yr (*n* = 2,160)	1–4 yrs (*n* = 10,328)	5–9 yrs (*n* = 4,753)	10–14 yrs (*n* = 3,982)
Lymphatic	7.8	19.2	22.3	19.5
Meningeal	8.4	4.0	1.7	2.1
Miliary	4.5	1.1	0.5	1.1
Bone/joint	0.4	1.3	1.8	2.4
Other	3.3	2.6	4.5	9.0
Total	24.4	28.2	30.8	34.2

a | Provided by the CDC. Data from reference 13.

Lamb et al. Tuberculosis in Infants and Children
Microbiology Spectrum 7 April 2017 Volume 5 Issue 2 10.1128/microbiolspec.tnmi7-0037-2016

Age-related rapidity of progression

- Children <5 years
- Time from enrollment to diagnosis
- No preventative treatment (controls)

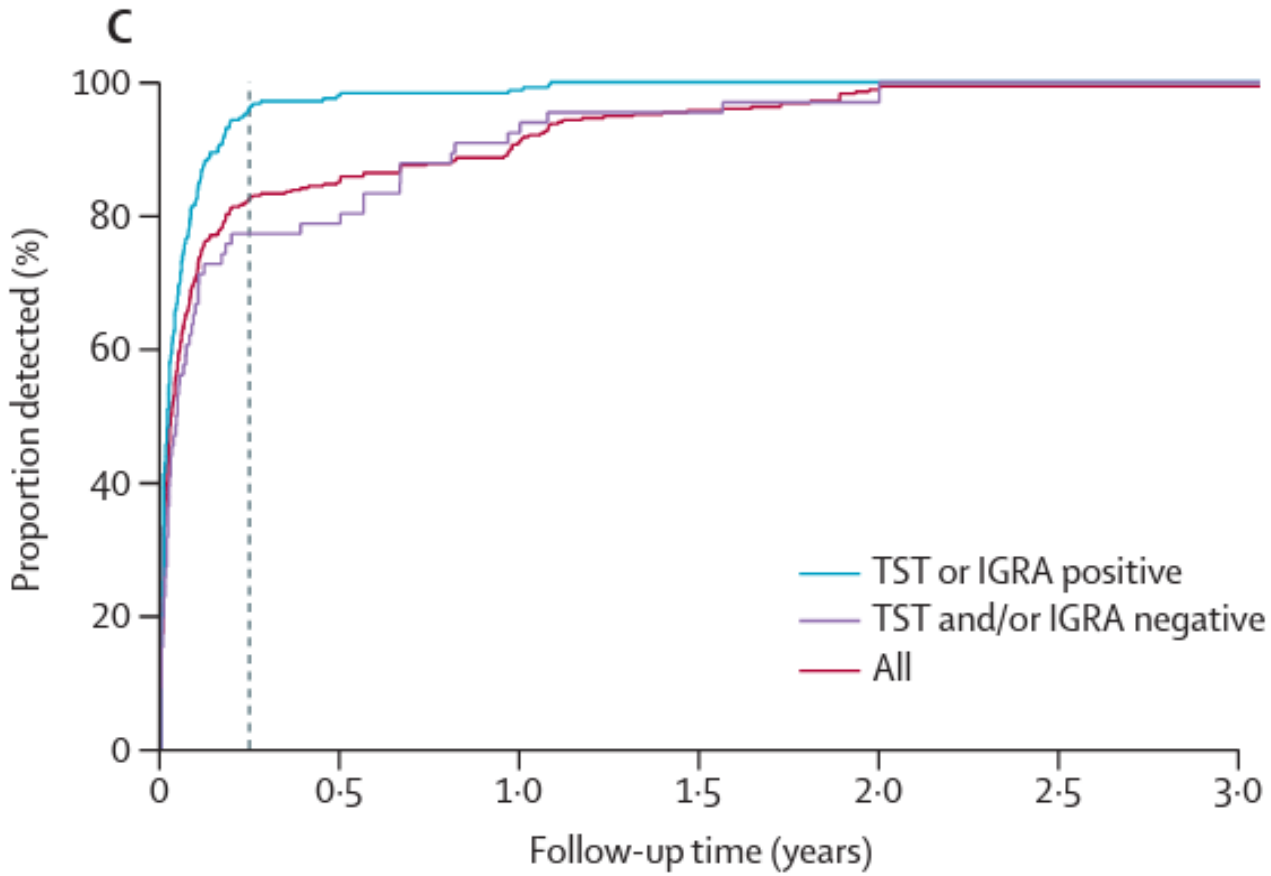


Figure 3: **Tuberculosis cases diagnosed over follow-up time**

Martinez et al. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet 2020; 395: 973–84

Clinical Presentation of pediatric TB

young children (<2 years)

Symptomatic: 64%

- Failure to thrive (51%)
- Persistent non-remitting cough (17%)
- Wheezing (12.6%)
- Weight loss (3%)
- Fever (2%)
- Lethargy (1%)

Randomized Controlled Trial > Pediatr Infect Dis J. 2015 Nov;34(11):1157-62.
doi: 10.1097/INF.0000000000000847.

The Role of Clinical Symptoms in the Diagnosis of Intrathoracic Tuberculosis in Young Children

Humphrey Mulenga [1], Michele D Tameris, Kany Kany A Luabeya, Hennie Geldenhuys, Thomas J Scriba, Gregory D Hussey, Hassan Mahomed, Bernard S Landry, Willem A Hanekom, Helen McShane, Mark Hatherill

Frequently, early pulmonary intrathoracic lymph node TB will be asymptomatic!

Clinical Presentation of pediatric TB

age 2-10

- Lower rates of progression to active disease
- Bronchial and intrathoracic disease most common
- Often asymptomatic

The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era.
Marais BJ, Gie RP, Schaaf HS, Hesseling AC, Obihara CC, Starke JJ, Enarson DA, Donald PR, Beyers N
Int J Tuberc Lung Dis. 2004 Apr;8(4):392-402.

Clinical Presentation of pediatric TB

Teenagers

- 80% with symptomatic disease
- Fever (63%)
- Cough (60%)
- Weight loss (30%)
- Extrathoracic TB in approximately 20%
  - Lymph node
  - Meningitis

Adolescents with tuberculosis: a review of 145 cases.
Cruz AT, Hwang KM, Birnbaum GD, Starke JR
Pediatr Infect Dis J. 2013 Sep;32(9):937-41.

WHEN IS A CHILD WITH TB INFECTIOUS?

- Teenagers
- Cavitary disease, smear positive disease, laryngeal disease—all of which are extremely rare in children

WHEN IS A CHILD NOT INFECTIOUS?

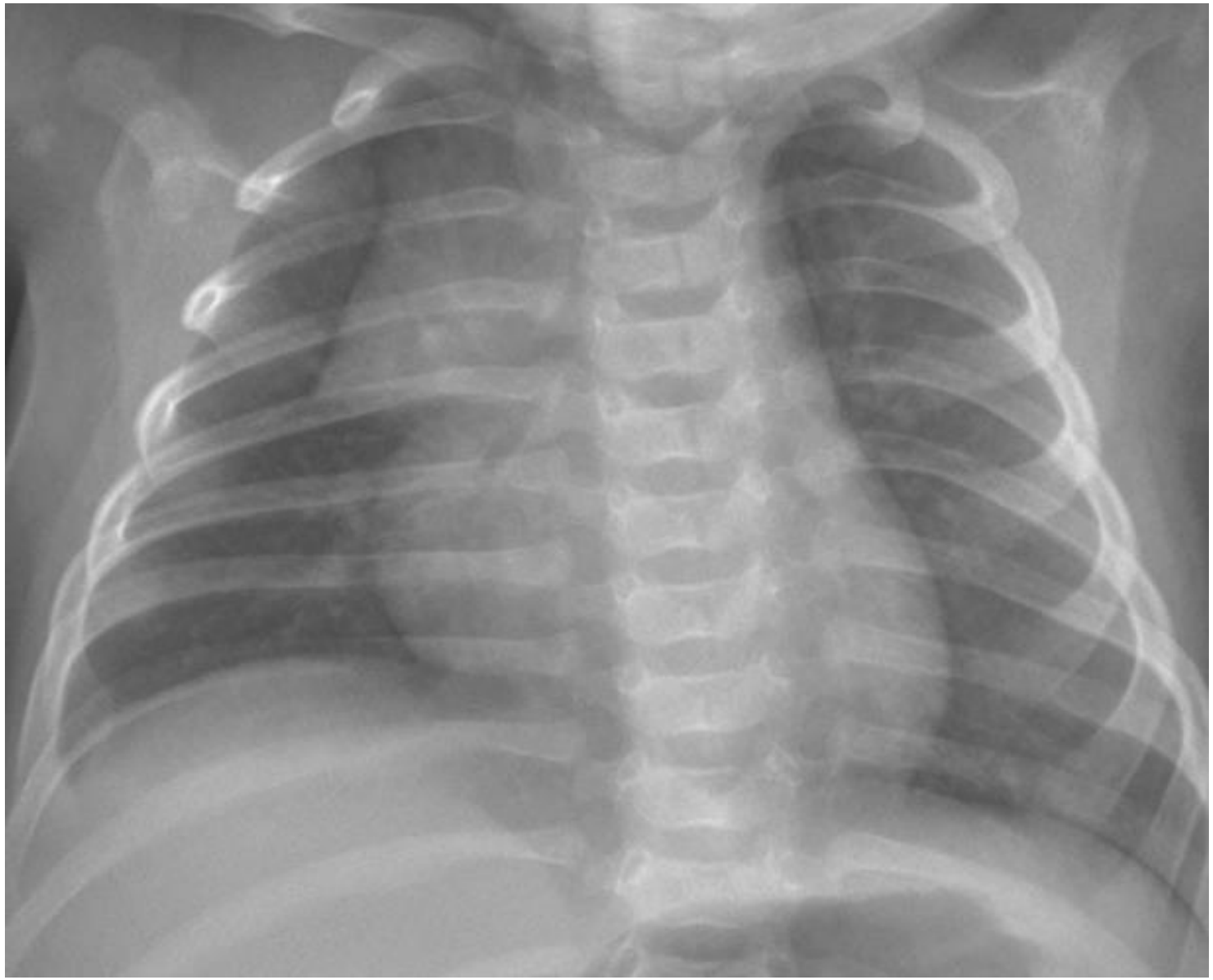
- Pre-teens, with exceptions above
- Infants and toddlers
- Intrathoracic lymph nodes, extra-pulmonary sites
- LTBI!

Pediatric TB Radiology

https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children

Radiologic Characteristics of Normal Pediatric X-Ray

Radiologic Characteristics of Normal Pediatric X-Ray



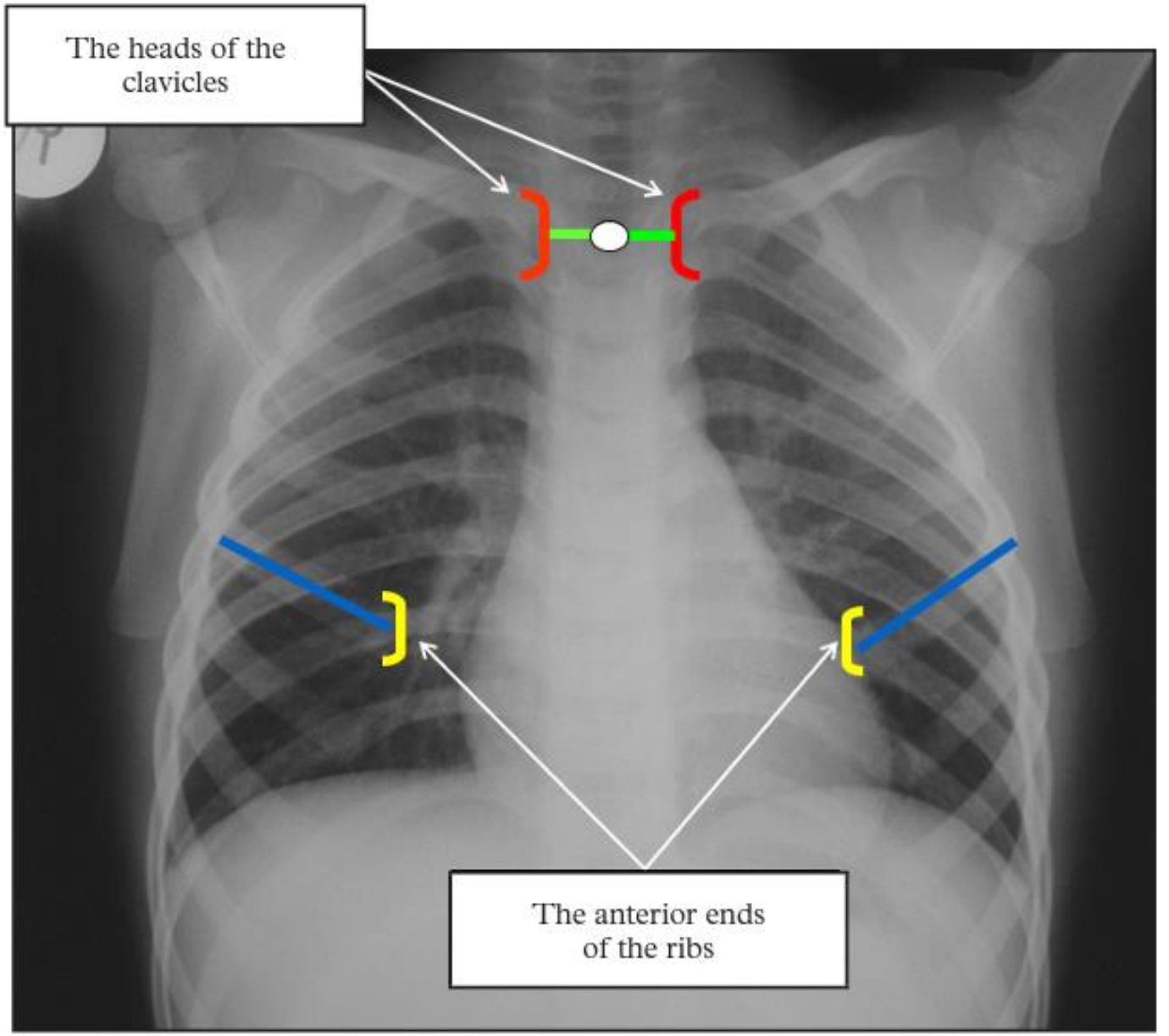
Normal CXR

Radiologic Characteristics of Normal Pediatric X-Ray

Normal Lateral CXR

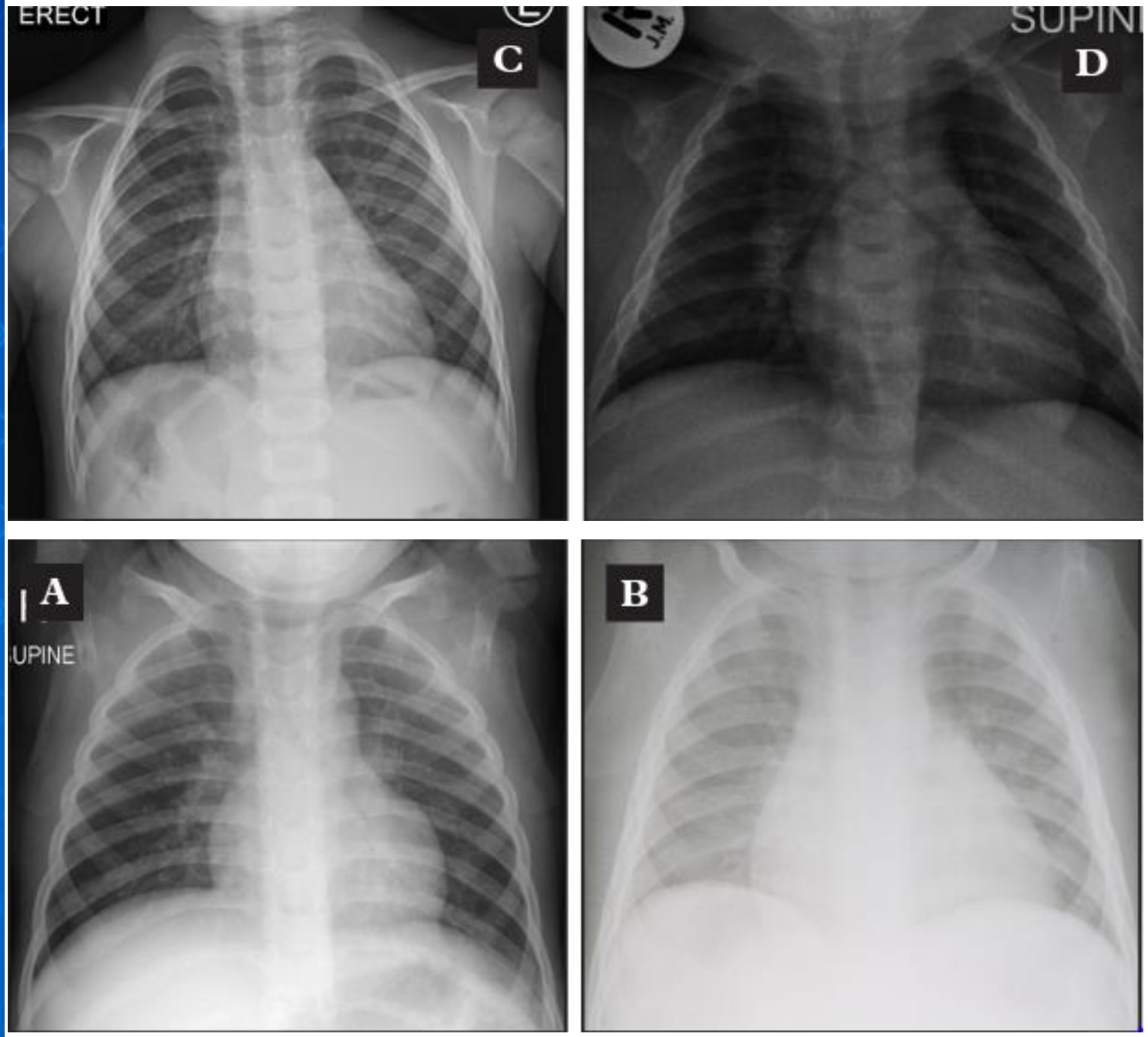
Assuring the quality of the pediatric CXR

Rotation



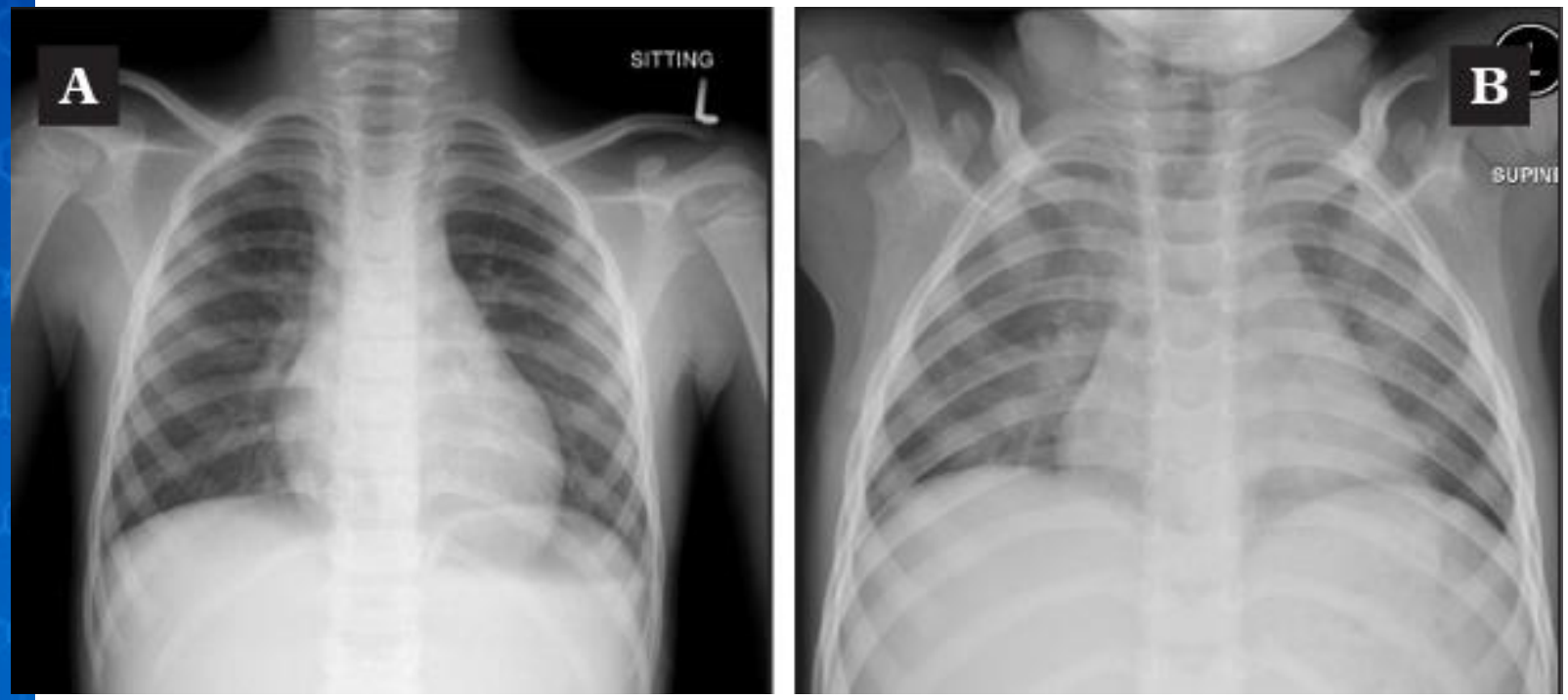
Assuring the quality of the pediatric CXR

Penetration

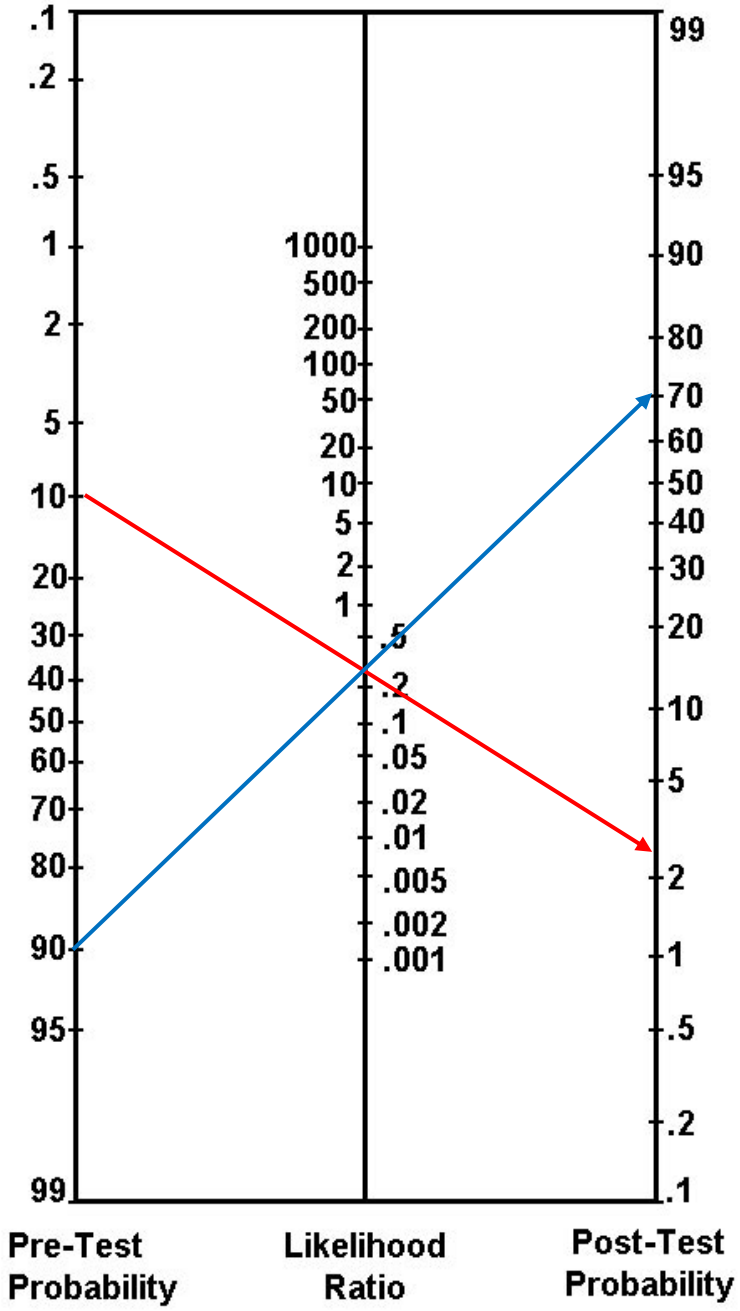


Assuring the quality of the pediatric CXR

Inspiration

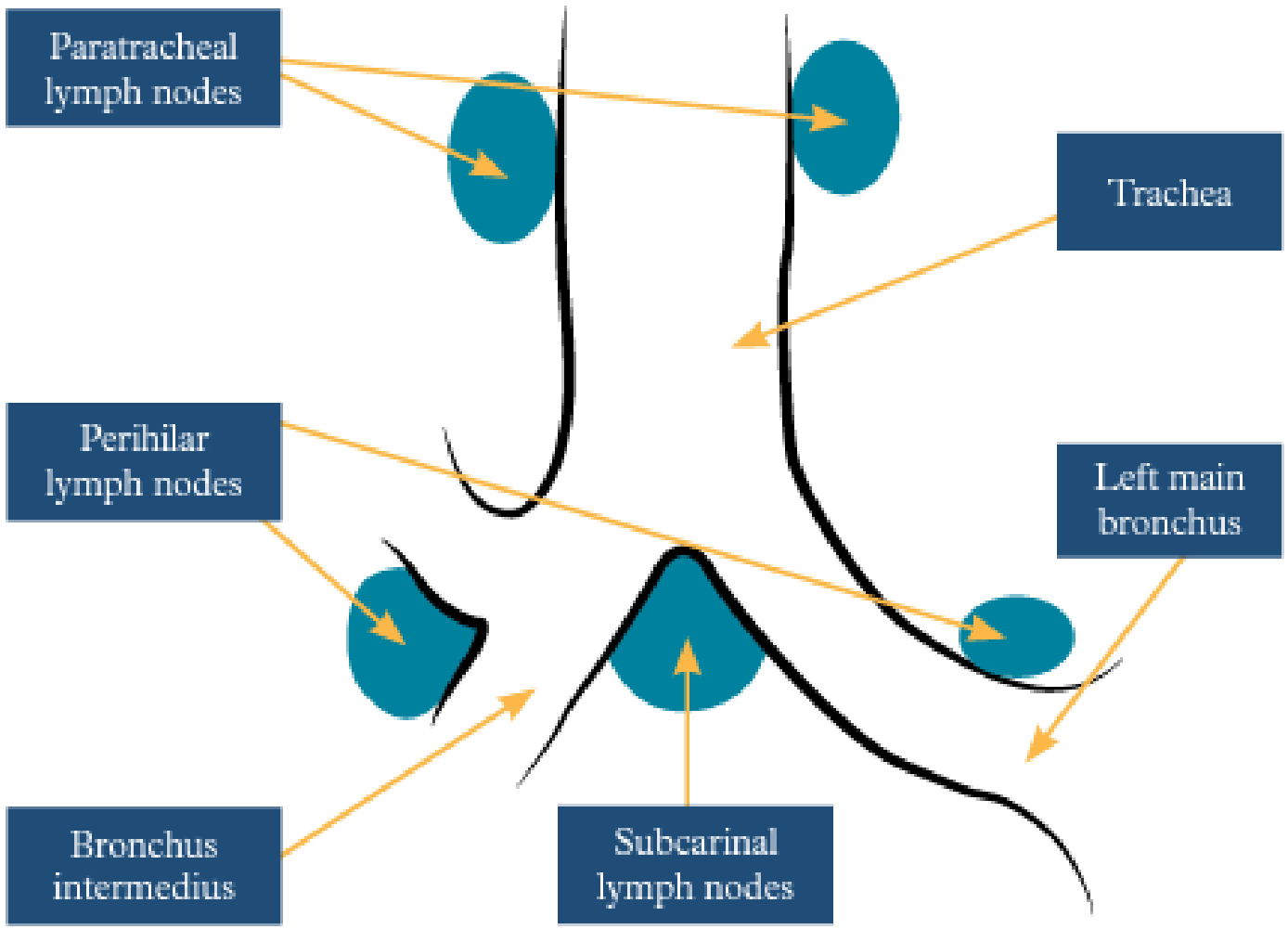


Pediatric TB interpretation: Impact of pre-test probability



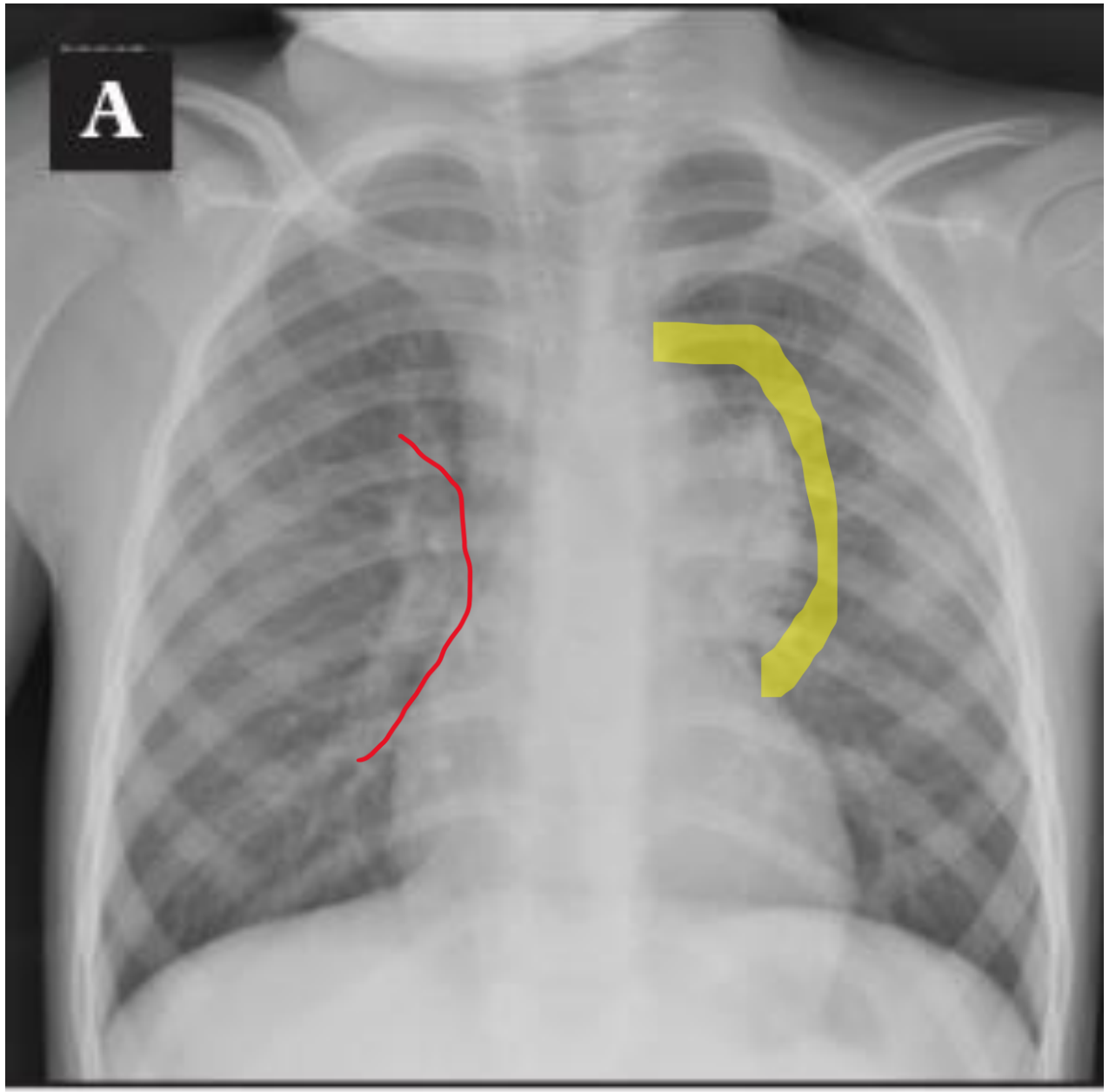
Radiographic TB disease patterns in children

Intrathoracic adenopathy



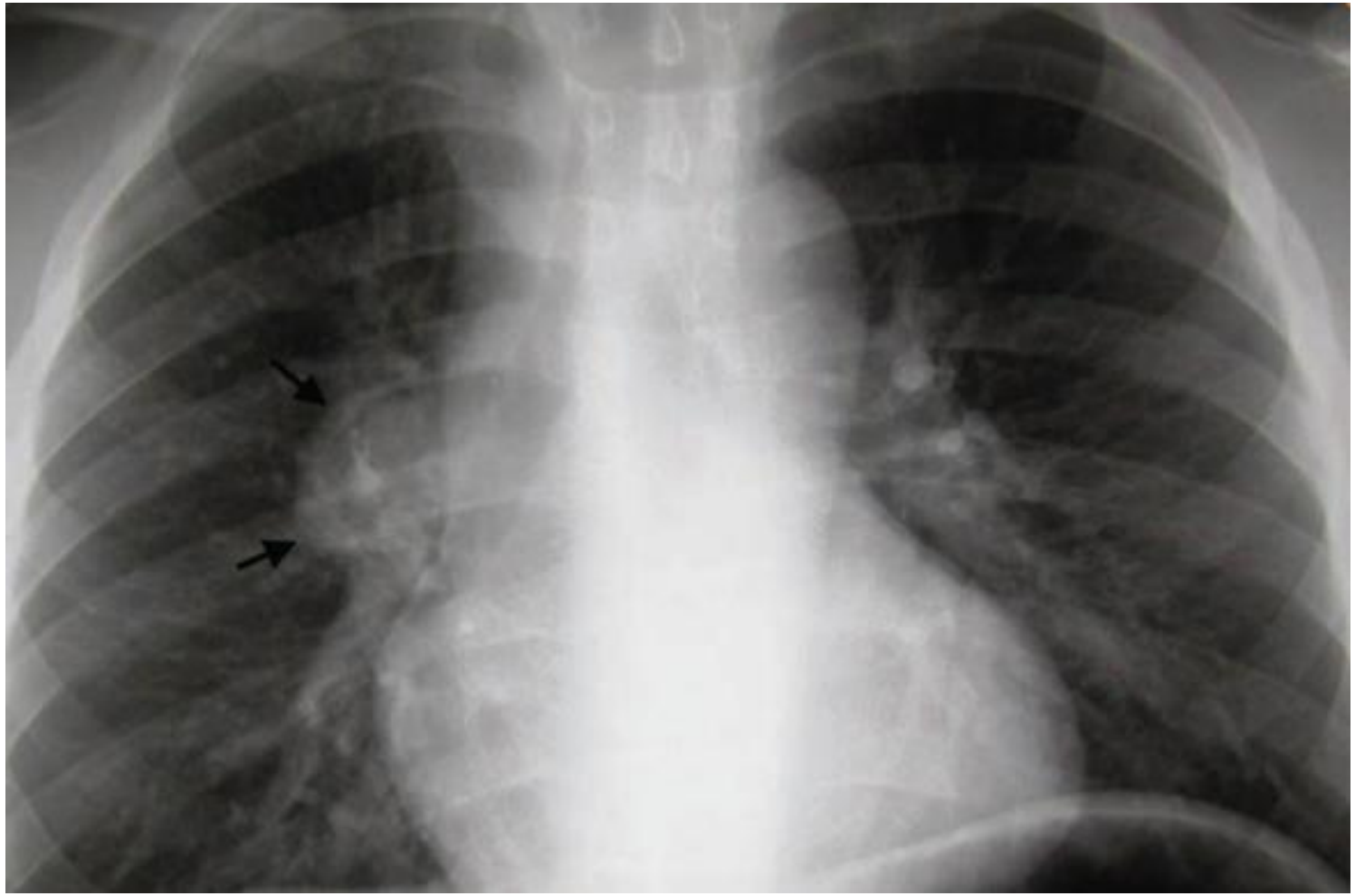
Radiographic TB disease patterns in children

Hilar adenopathy



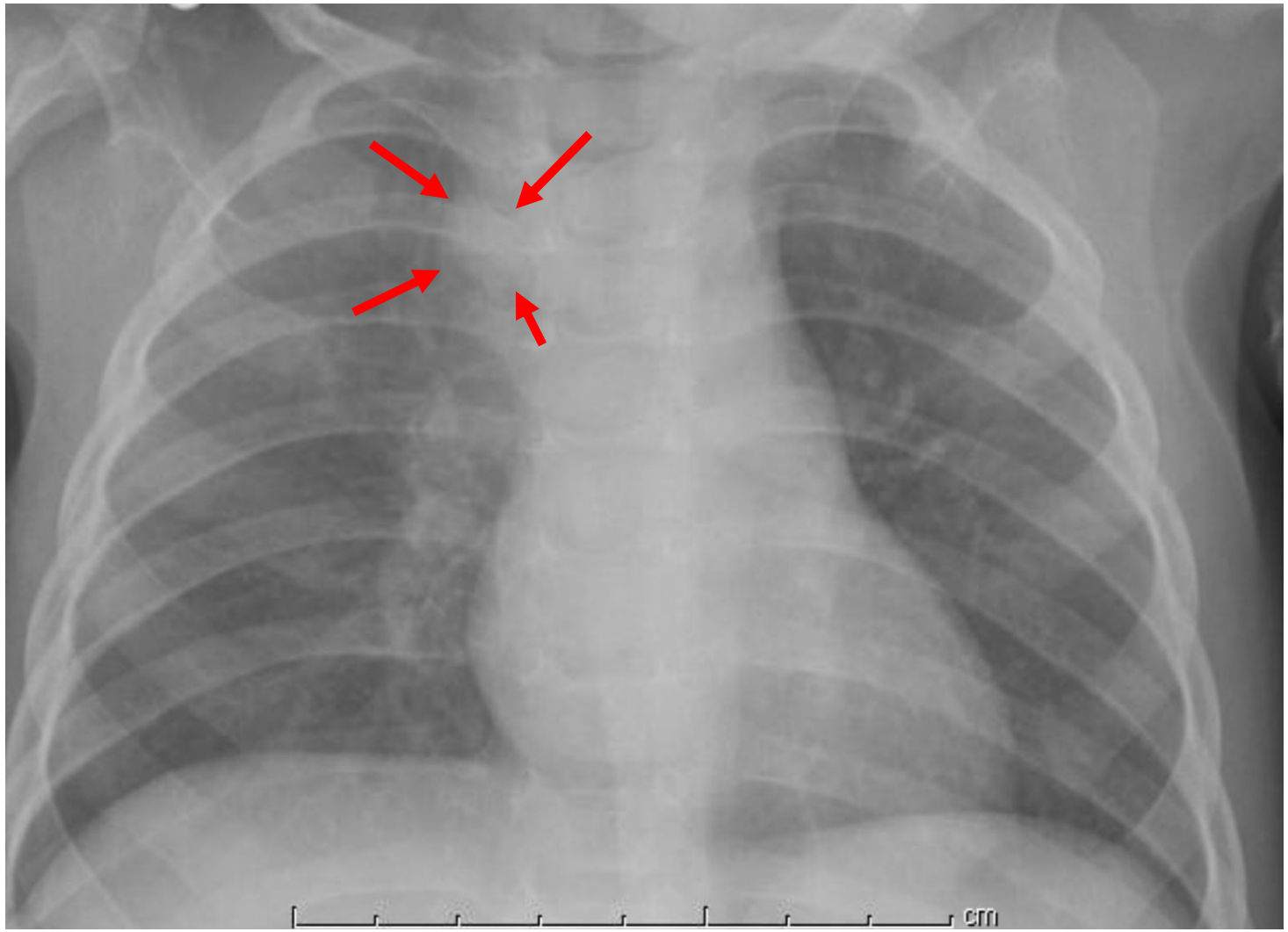
Radiographic TB disease patterns in children

Hilar adenopathy



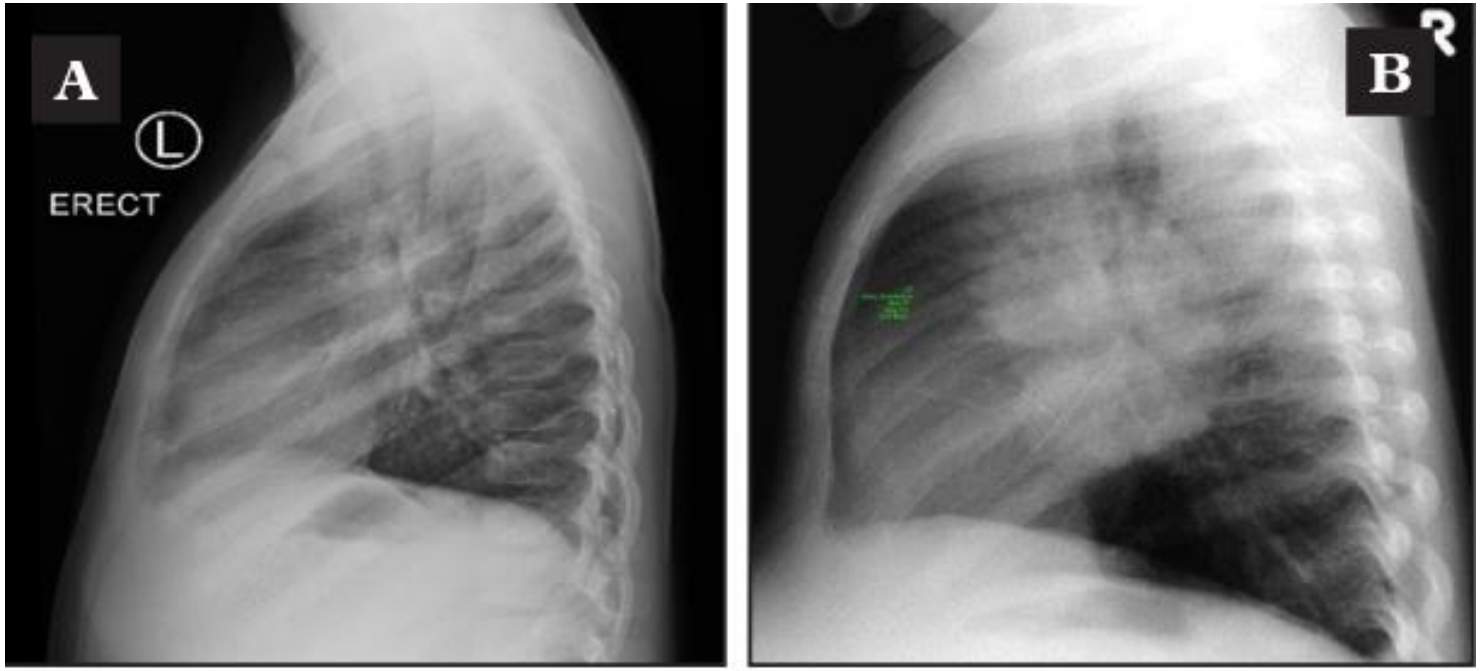
Radiographic TB disease patterns in children

Paratracheal Adenopathy



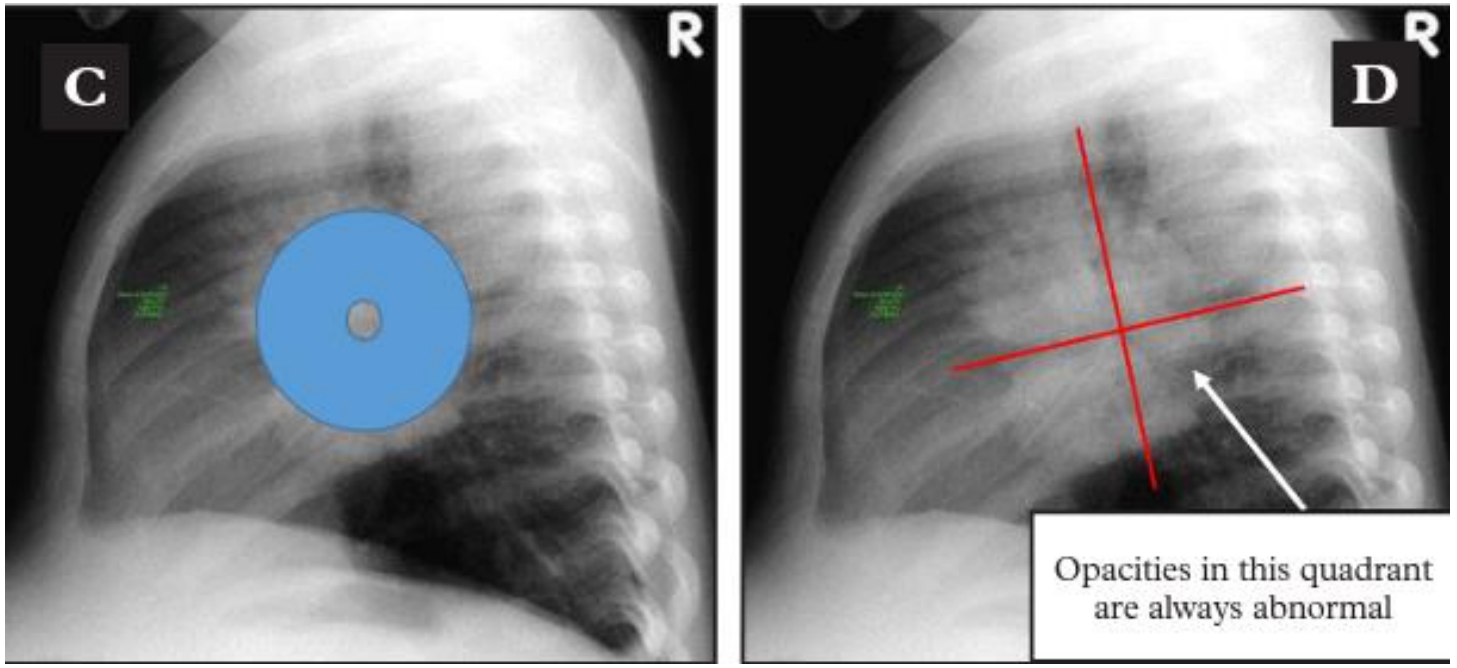
Radiographic TB disease patterns in children

Hilar adenopathy: importance of lateral film



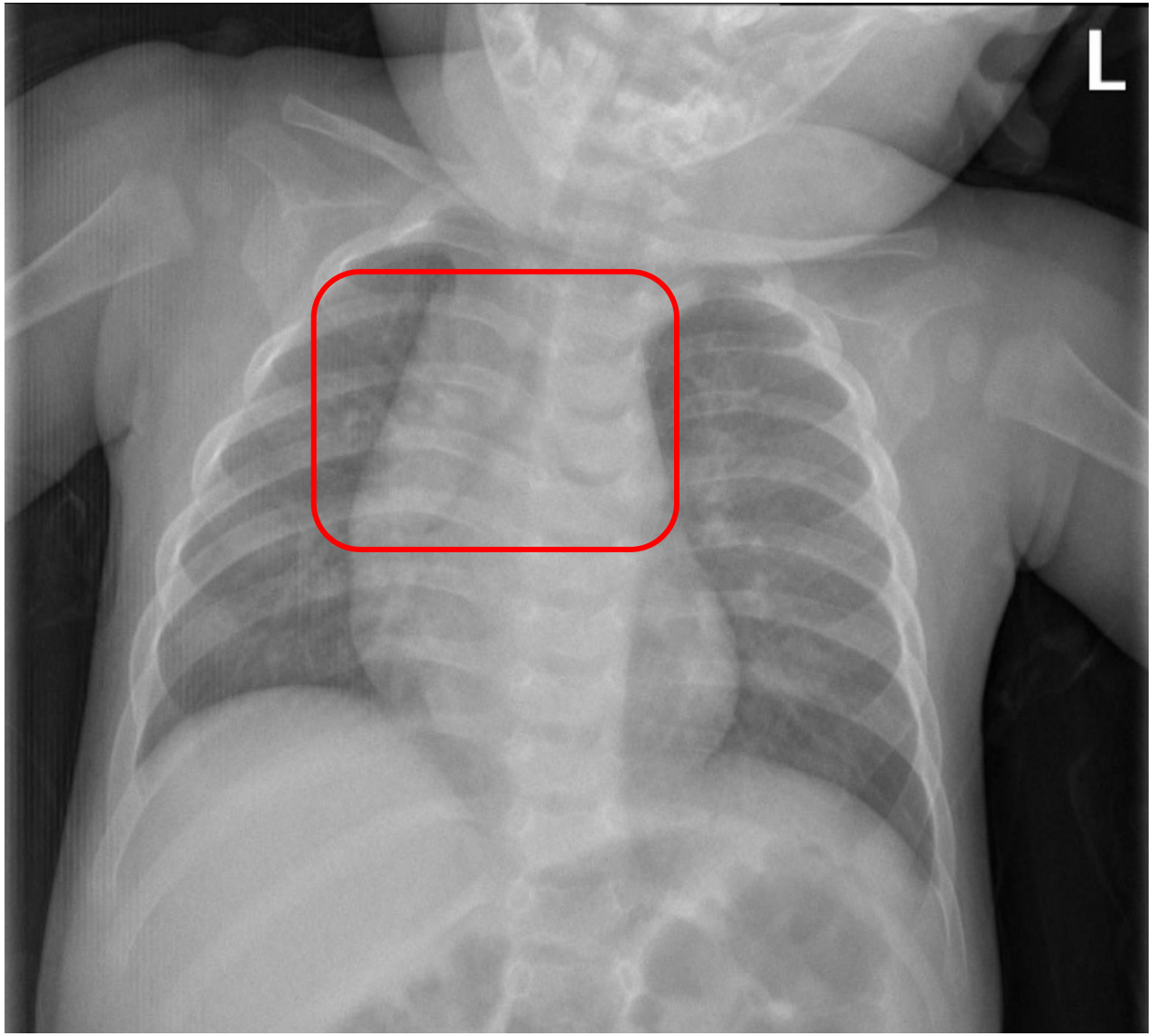
Radiographic TB disease patterns in children

Hilar adenopathy: importance of lateral film



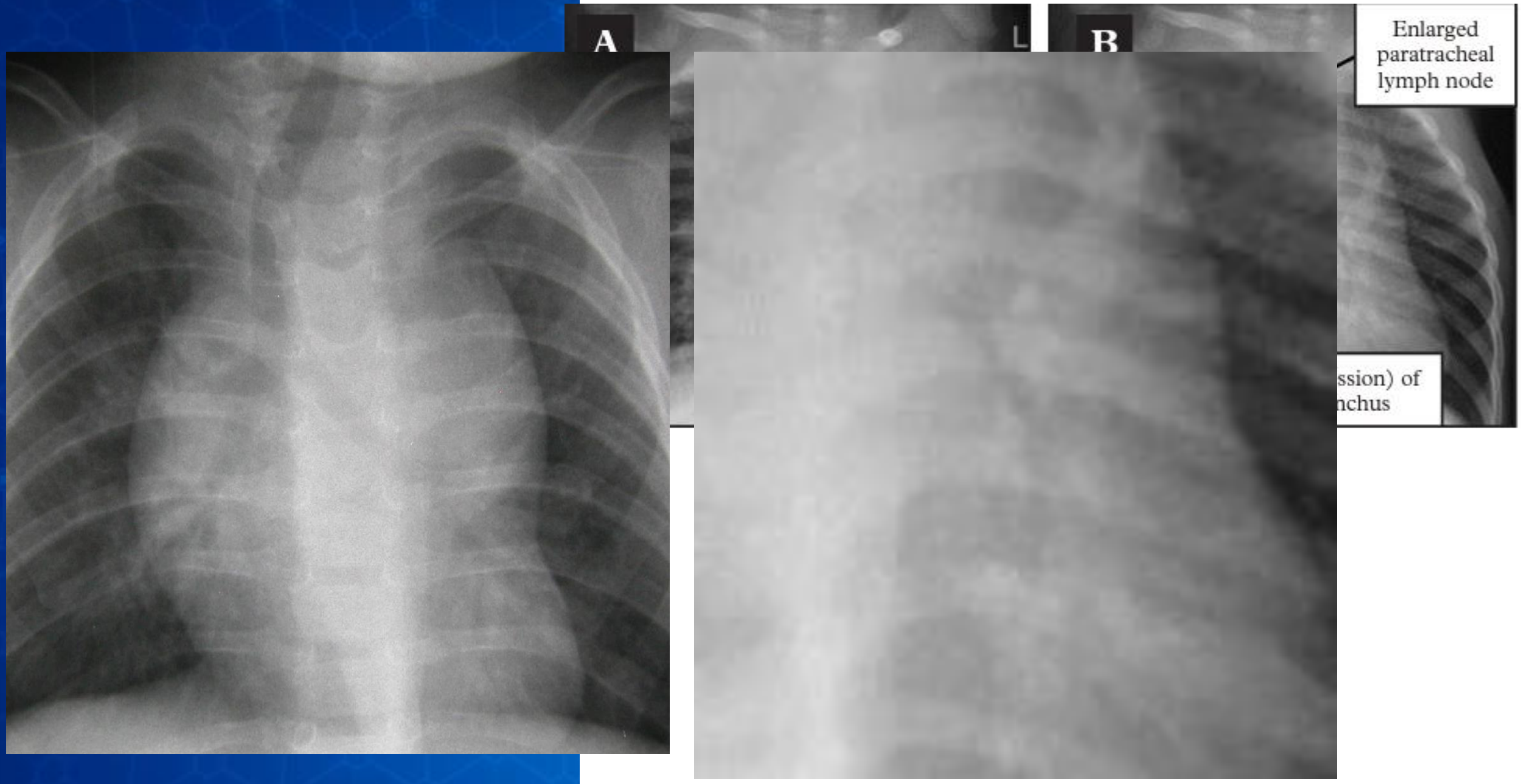
Radiographic TB disease patterns in children

Subtle signs of airway compression



Radiographic TB disease patterns in children

Subtle radiographic concerns, imperfect film, high stakes: Potential role for CT scan


A
L
B
Enlarged
paratracheal
lymph node
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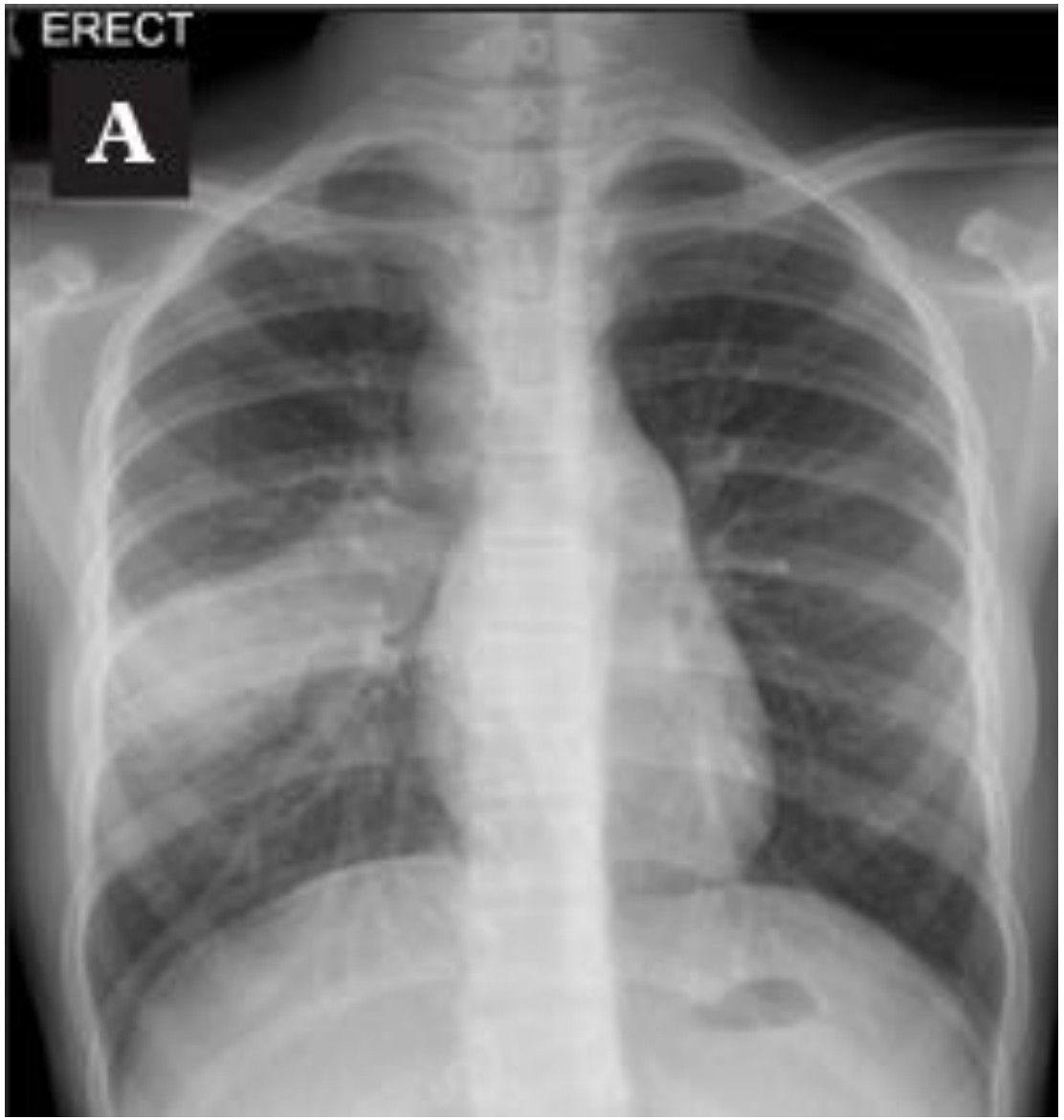
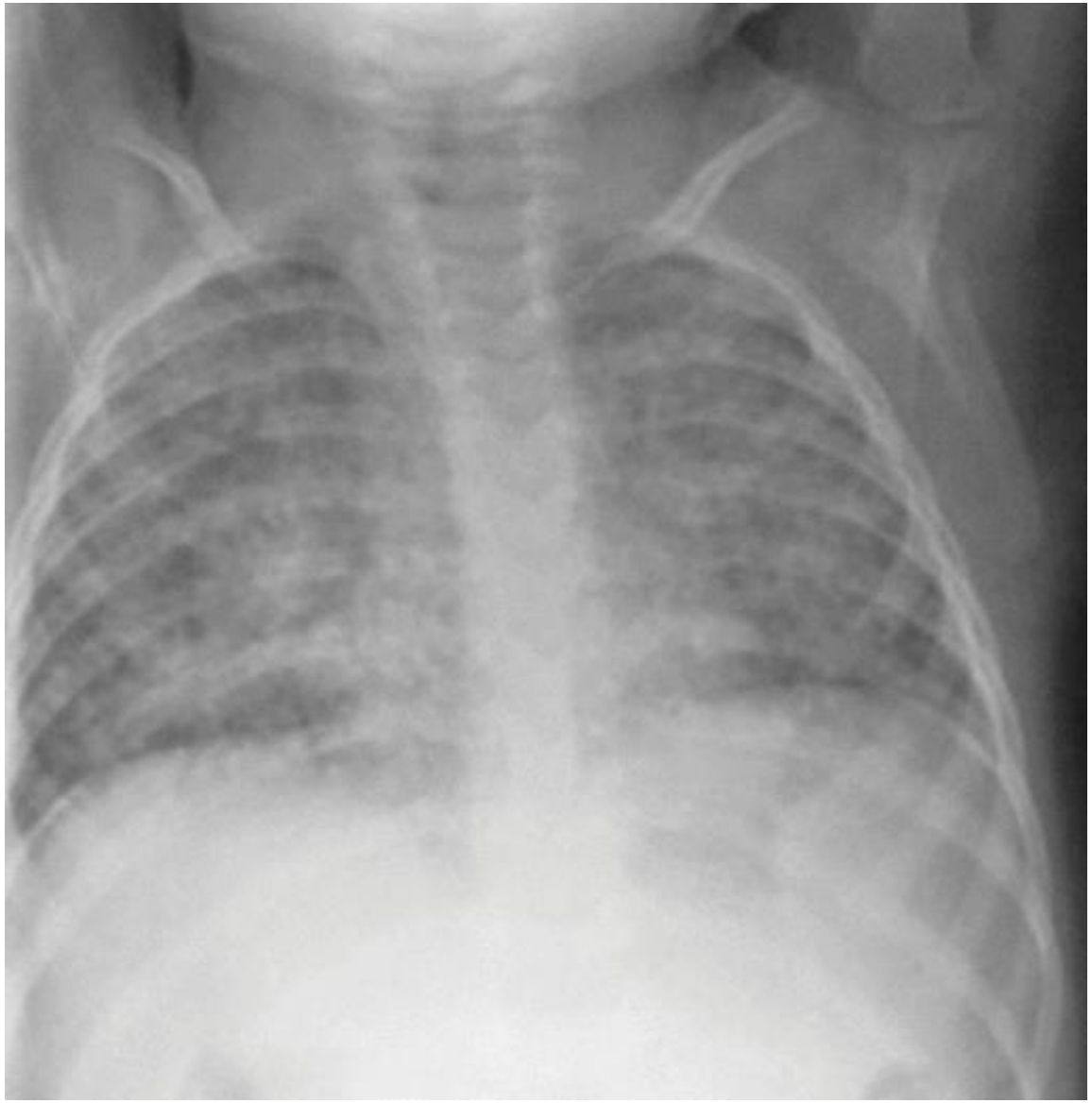
Radiographic TB disease patterns in children

Adenopathy with consolidation



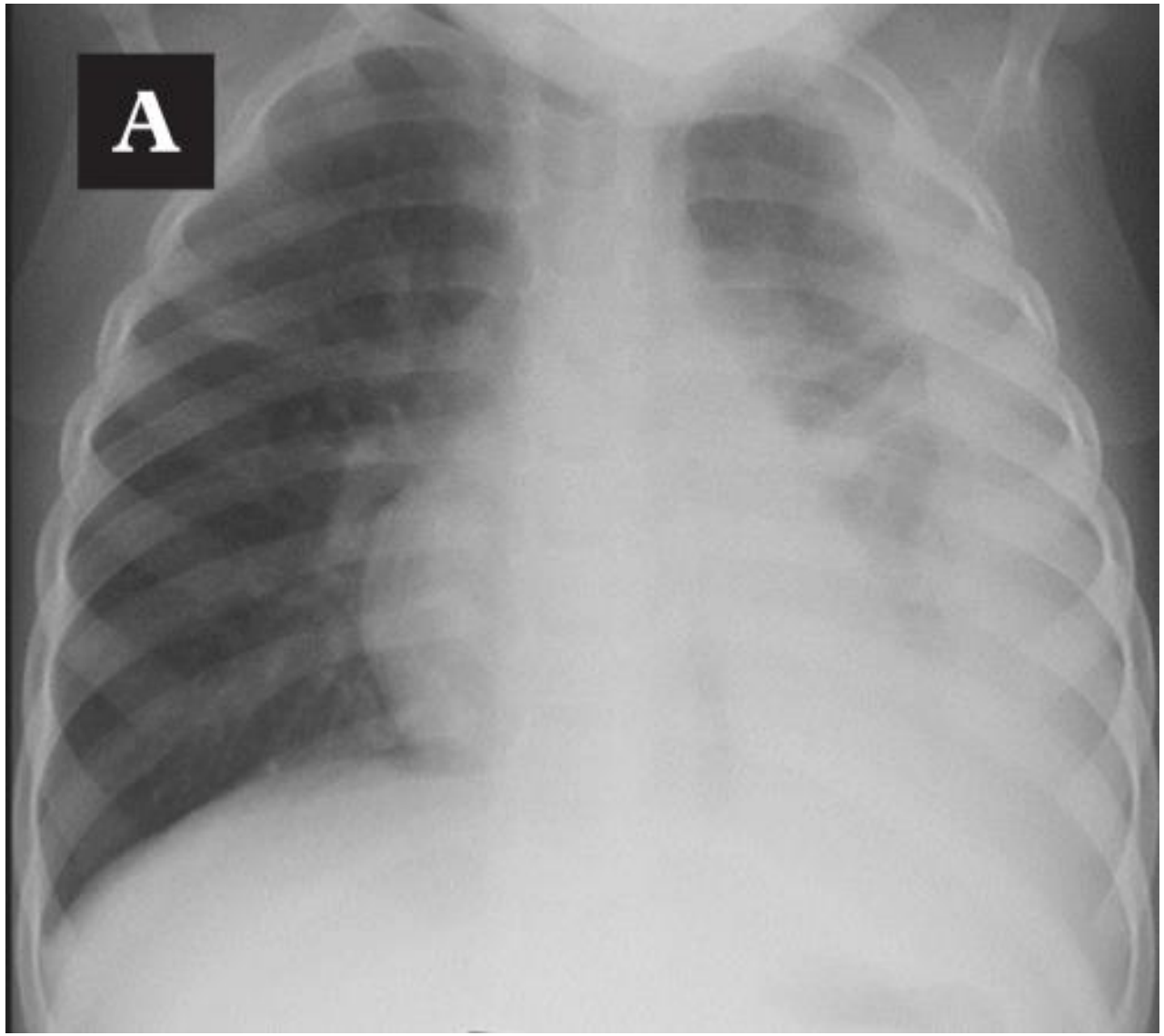
Radiologic characteristics of pediatric TB

Miliary pattern



Radiologic characteristics of pediatric TB

Pleural Effusion

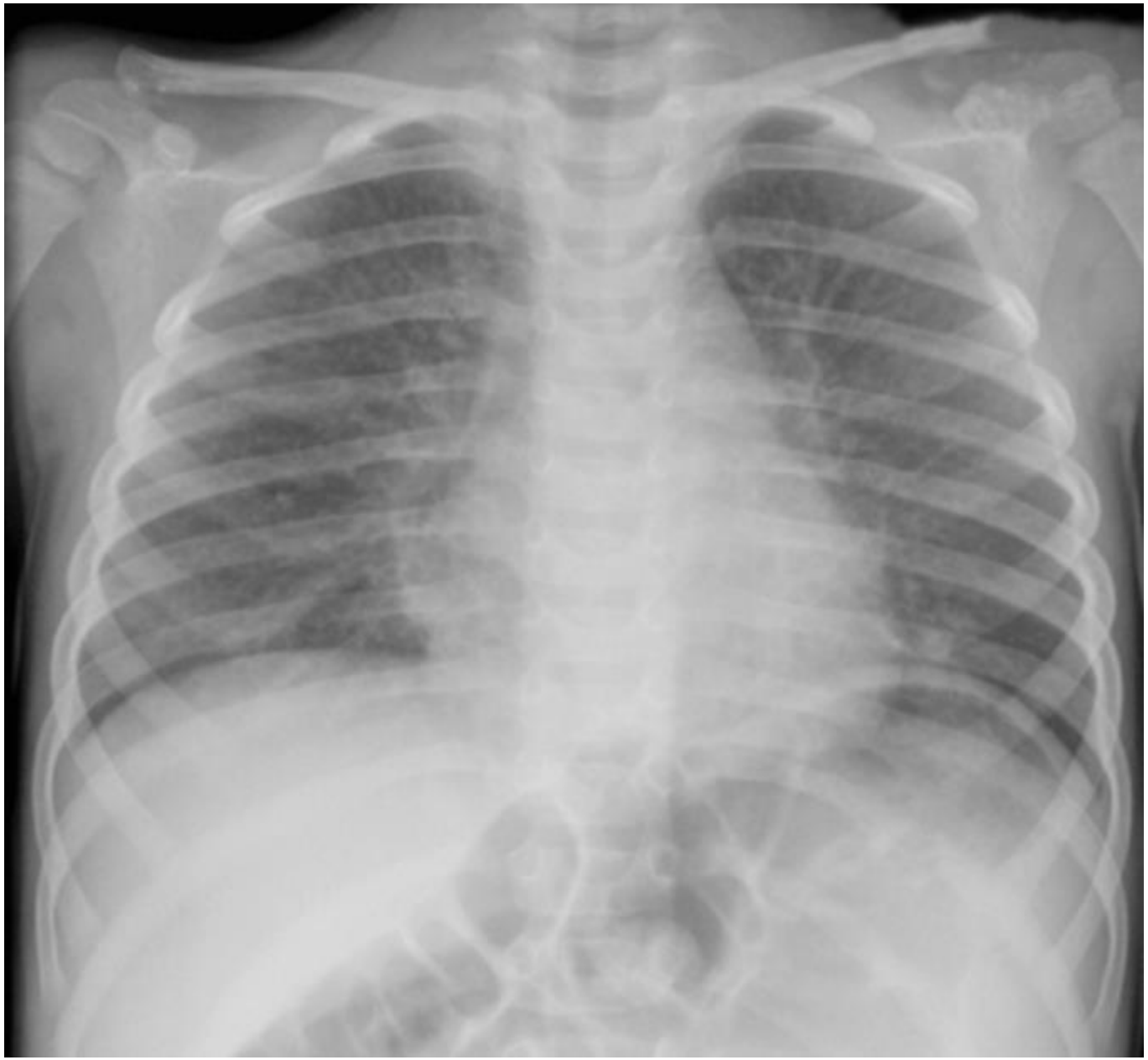


Radiologic characteristics of pediatric TB

Cavitary, upper lobe disease

Key non-TB Disease patterns

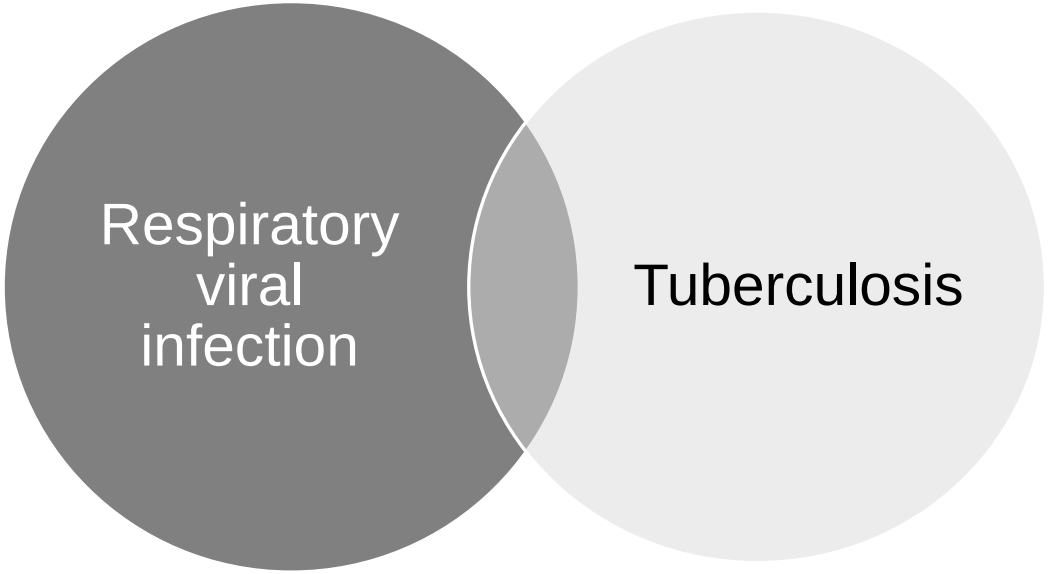
Viral pneumonitis, bronchiolitis,reactive airways disease



https://radiologykey.com/viral-pneumonia

Navigating diagnostic Uncertainty

School age child with household exposure, positive IGRA, cough



“Streaky RML density, potentially not inconsistent with an infectious etiology, which may not be exclusory of tuberculosis in the right clinical circumstances”

Navigating Uncertainty

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Center for Tuberculosis

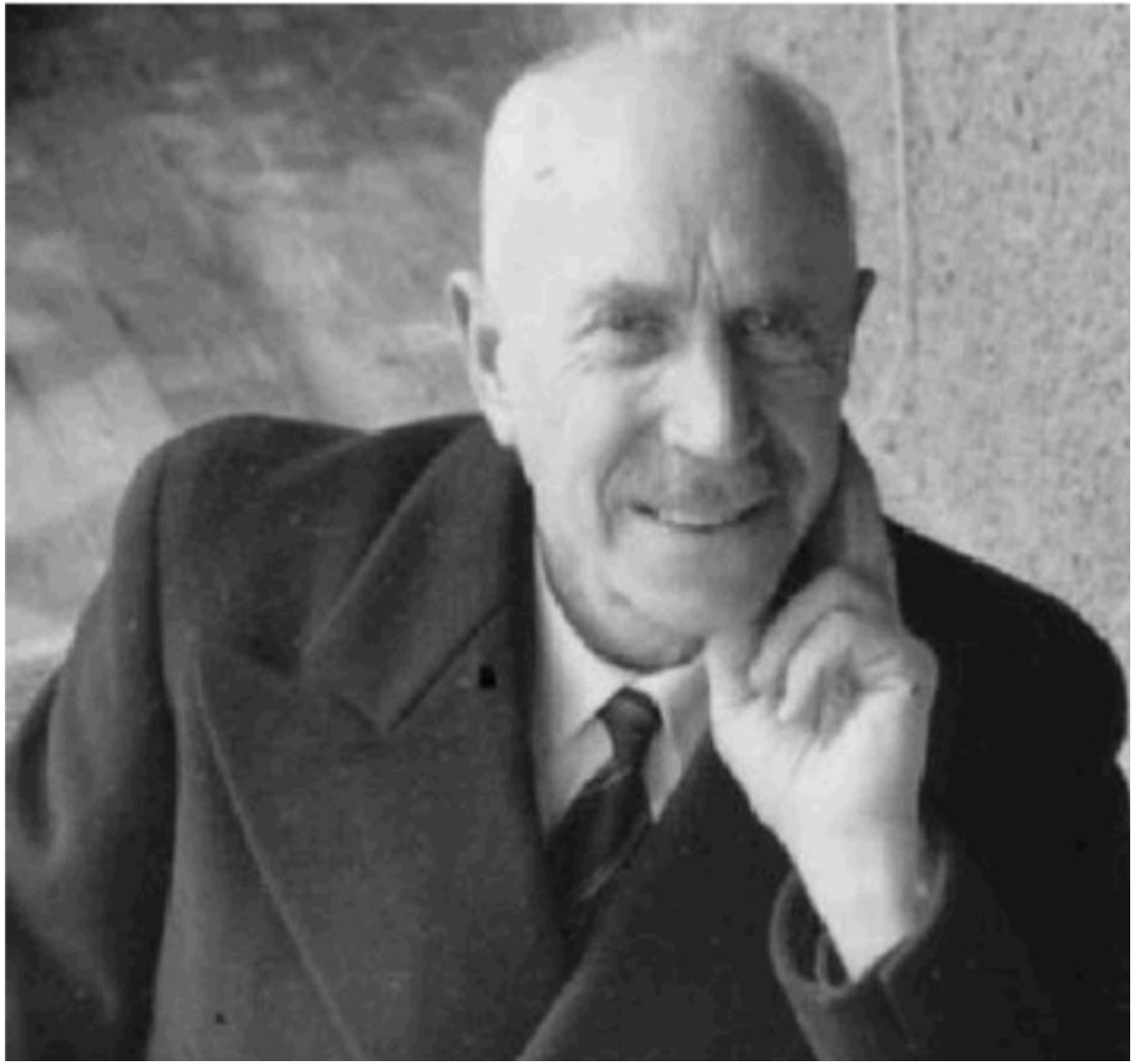
Diagnostics

Pediatric Considerations

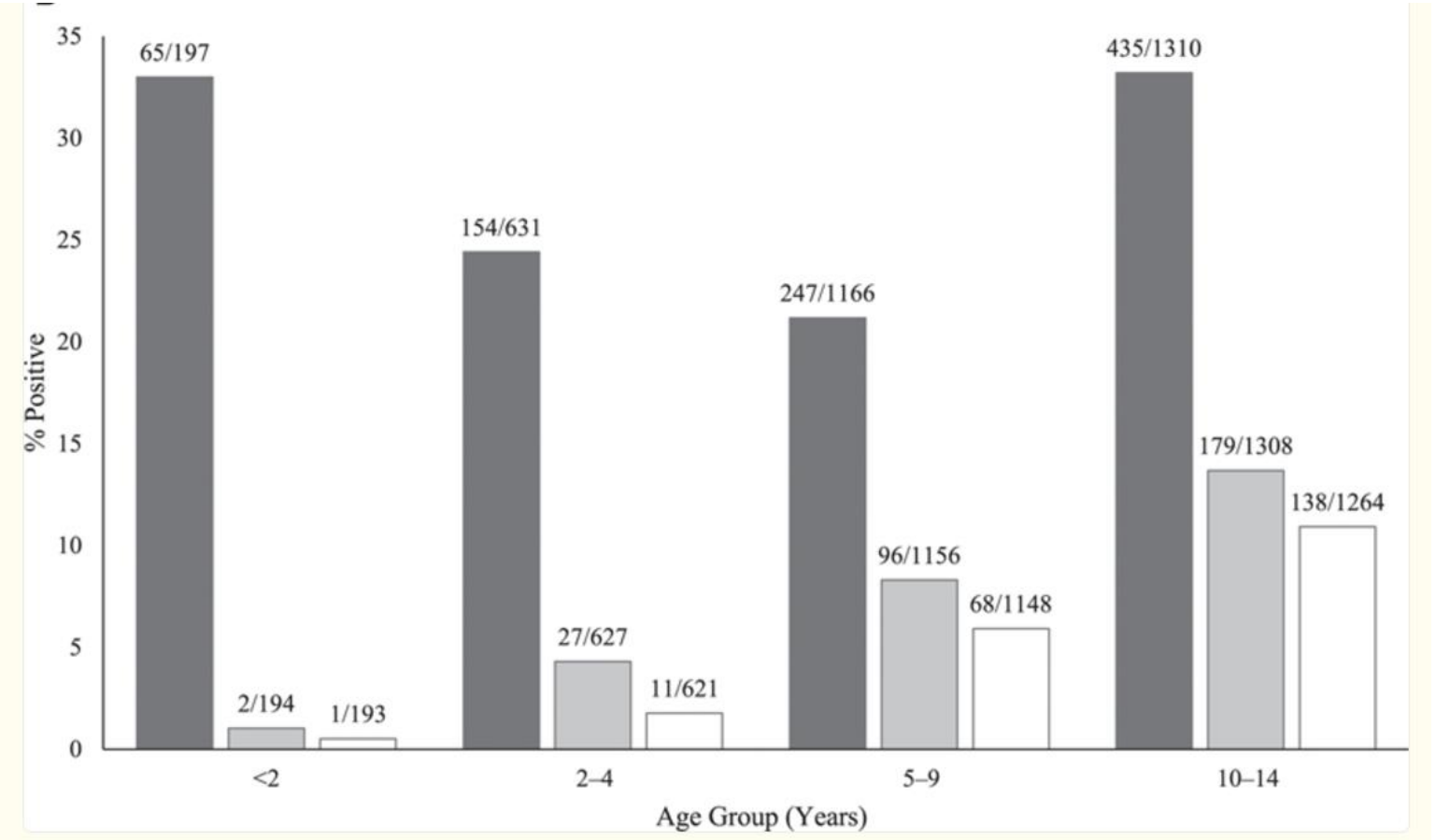
TST

CHARLES MANTOUX

Perfected the TST in 1908



TST vs IGRA in BCG-Vaccinated Children



Interferon-γ Release Assays in Children <15 Years of Age

Amina Ahmed [a], Pei-Jean I Feng [b], James T Gaensbauer [c], Randall R Reves [c], Renuka Khurana [d], Katya Salcedo [e], Rose Punnoose [f], Dolly J Katz [b]; TUBERCULOSIS EPIDEMIOLOGIC STUDIES CONSORTIUM

Novel TST products

International Journal of Infectious Diseases
Volume 141, Supplement, April 2024, 106992

Review

Is the new tuberculous antigen-based skin test ready for use as an alternative to tuberculin skin test/interferon-gamma release assay for tuberculous diagnosis? A narrative review

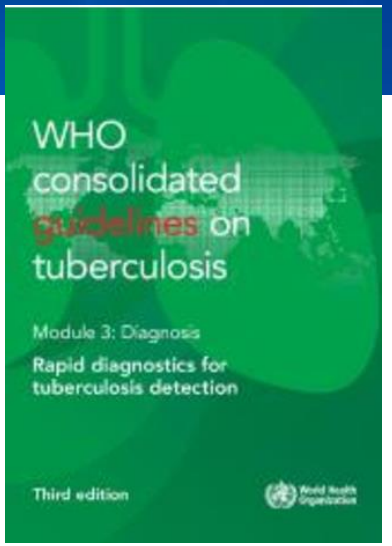
Kin Wang To [1 2], Rui Zhang [2], Shui Shan Lee [2]

Pediatric diagnostic considerations

Microbiologic diagnosis of active TB in children

- **Globally: only 10-30% of cases of pediatric TB are microbiologically confirmed**
- Use all available information on source case when available
- Collect multiple samples, use Xpert MTB/RIF
- Sample collection methods
  - Induced sputum (including infants)
  - Gastric aspirates, less preferred
  - Tissue, CSF, other specimens if indicated
  - Stool: Better with Xpert Ultra

Stool testing:
Xpert MTB/RIF Ultra



Recommendations on Xpert MTB/RIF and Xpert Ultra as initial tests in adults and children with signs and symptoms of pulmonary TB

2. In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool rather than smear microscopy/ culture and phenotypic DST.
(Strong recommendation, moderate certainty for accuracy in sputum; low certainty of evidence for test accuracy in gastric aspirate, nasopharyngeal aspirate and stool)

Stool PCR (Xpert Ultra)

Xpert MTB-RIF: Meta-analysis including 1592 individuals (172 culture-positive)

- Sensitivity (microbiologic standard) **61.5%** (95% CI 44.1-76.4)
- Sensitivity (composite reference standard) 16.3%; (95% CI 8.4-29.2).

Ultra: Meta-analysis of 200 culture positive patients

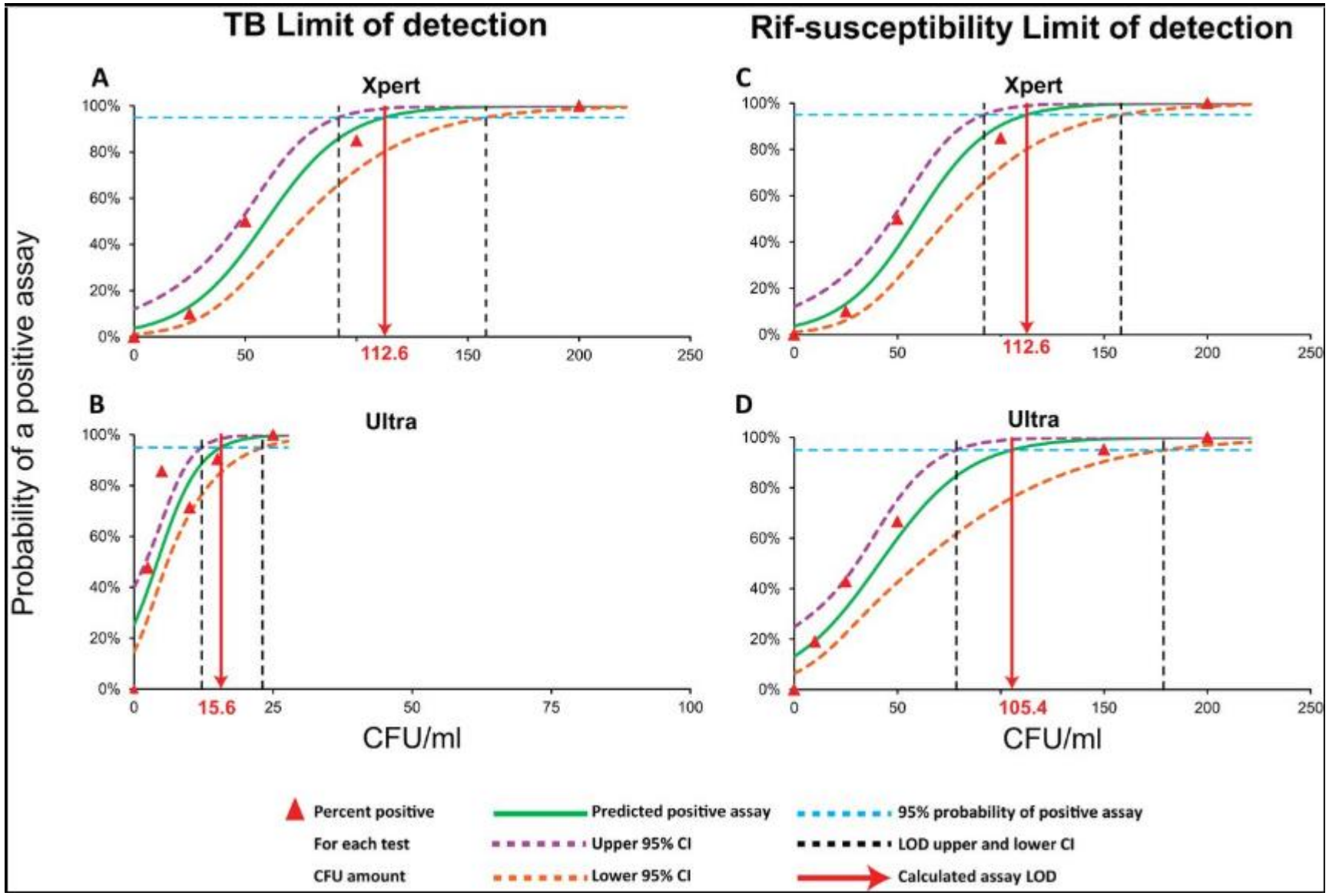
- Sensitivity (microbiologic standard) **56.1%** (95% CI 39.1 – 71.7)

Ultra: Meta-analysis of 13 African studies:

- Sensitivity (microbiologic standard) **68%** (95% CI 61-75%)

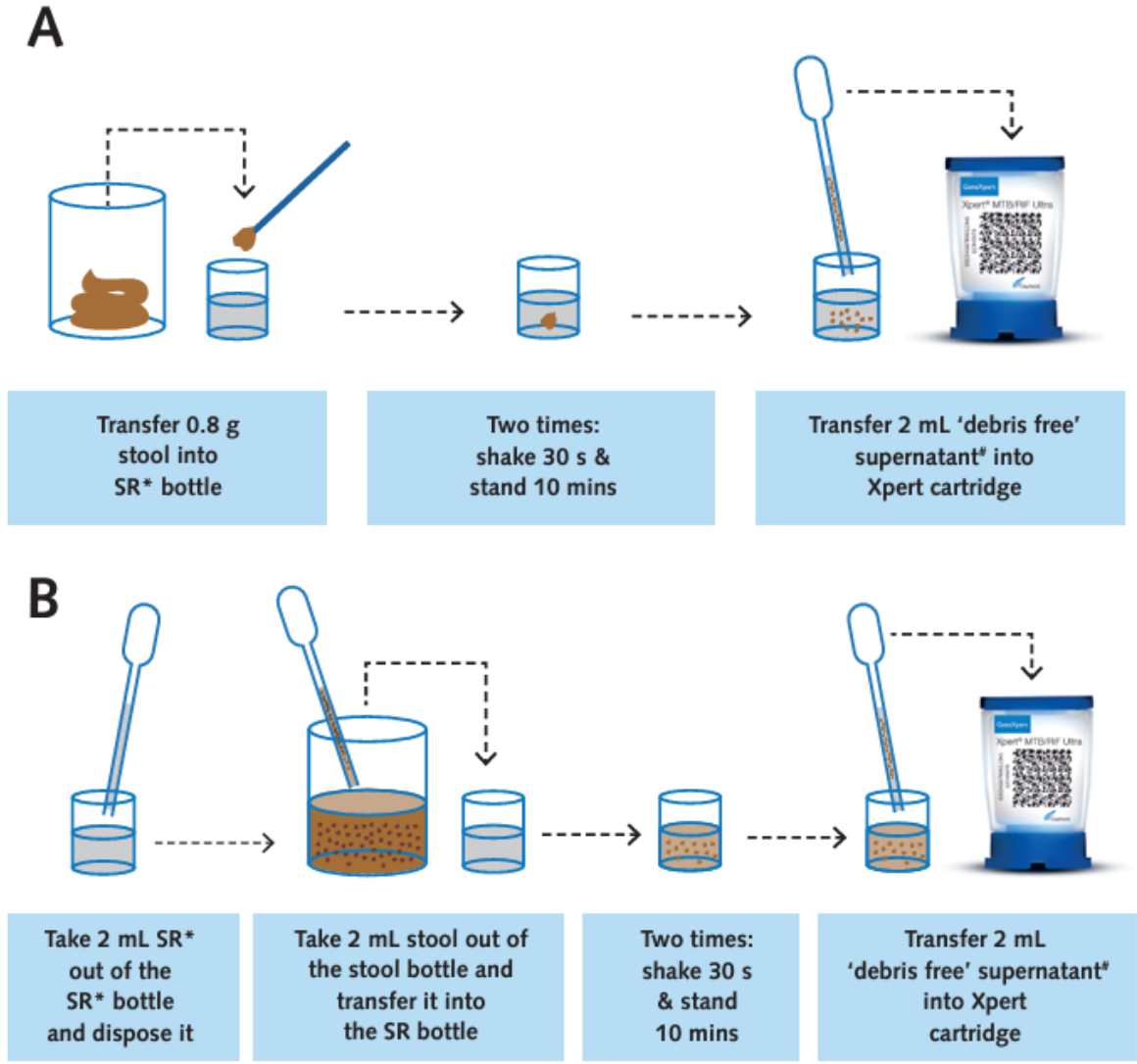
Incremental yield also consistently reported

Xpert MTB/RIF vs. Xpert MTB/RIF Ultra



Chakravorty et al. https://journals.asm.org/doi/full/10.1128/mbio.00812-17

Stool PCR (Xpert Ultra)



https://www.kncvtbc.org/uploaded/2021/03/Stoolbox-SOP1.pdf

Summary of Abstracts at 2024 Union Meeting

- Increasing utilization in national programs
- Stool Xpert Ultra positive in approx. 5-20% of TB suspects (from high-TB burden populations)
- Other assays emerging with similar performance
- Trace call associated with risk of progression to TB if treated as LTBI or false-positive

J Antimicrob Chemother. 2021 Dec; 76(12): 3237–3246.
Published online 2021 Sep 16. doi: 10.1093/jac/dkab336
PMCID: PMC8598292
PMID: 34529779

Pharmacokinetics and safety of high-dose rifampicin in children with TB: the Opti-Rif trial

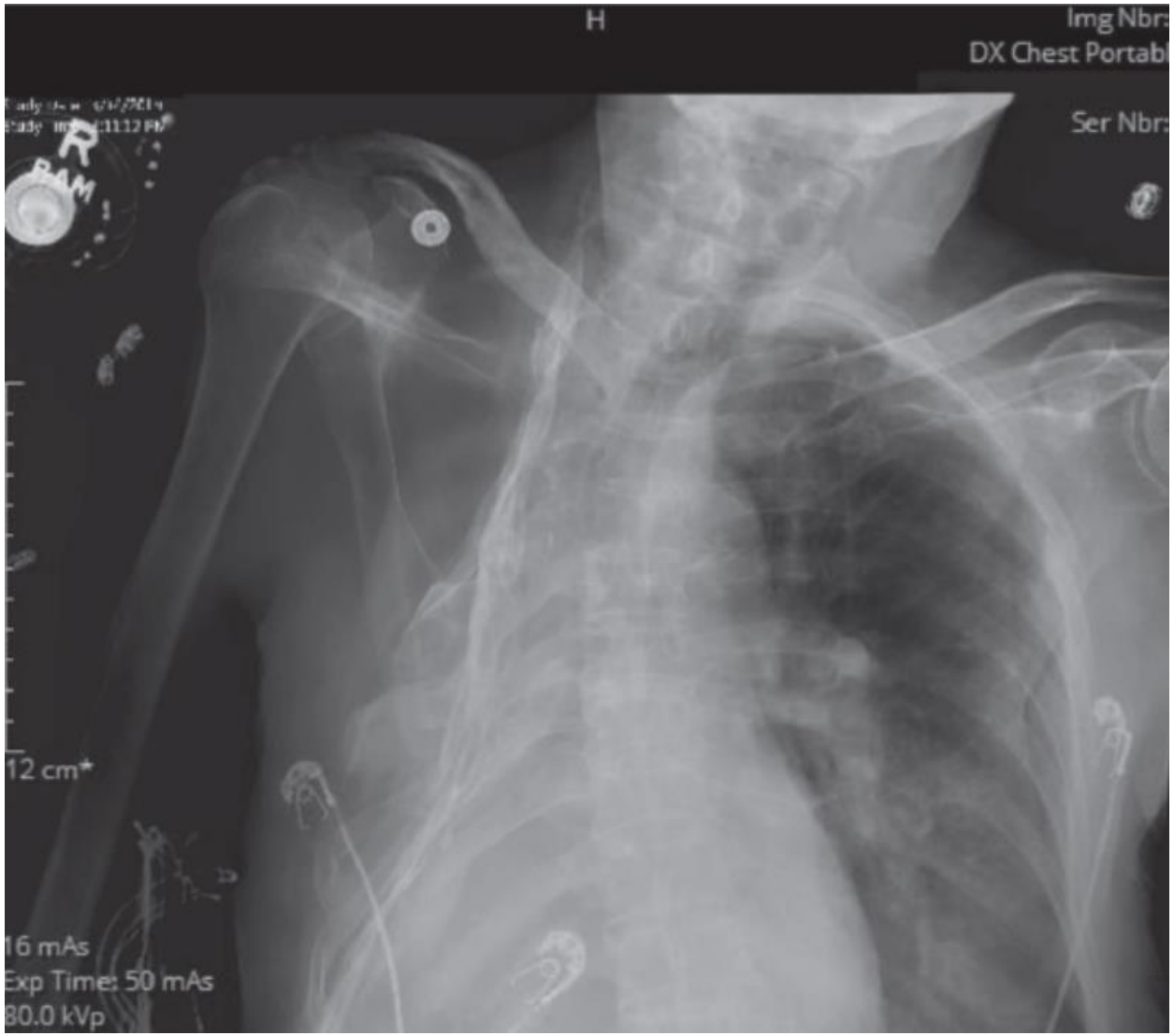
Rifampicin doses evaluated with simulations using the final model and virtual paediatric population (n = 5000; >6 months and <25 kg)

Weight band	Weight range (kg)	Current paediatric dose recommendation (mg)	Dose for target exposure of 235 mg/L·h (mg)
1	4–7.99	75	<7 kg: 450; 7–7.99 kg: 600
2	8–11.99	150	750
3	12–15.99	225	900
4	16–24.99	300	1200

15 mg/kg

60 mg/kg

Consider briefly how duration of treatment was determined



Factors influencing the duration of Tb treatment in children

- Bacillary load
- Dissemination/Extrapulmonary Disease
- Co-morbidities/general health
- Pharmacokinetics/ pharmacodynamics of TB drugs

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535

CLINICAL TRIAL

Design: An open-label, parallel-group, randomized, controlled trial examined whether 4 months of treatment would be noninferior to 6 months of treatment in children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative TB in sub-Saharan Africa and India.

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535

Intervention: 1204 children younger than 16 years of age were randomly assigned to 4 or 6 months of standard first-line anti-TB treatment with World Health Organization–recommended pediatric doses. The primary efficacy outcome was unfavorable status — defined as treatment failure or change, loss to follow-up during treatment, TB recurrence, or death — by 72 weeks.

Inclusion/exclusion Criteria: summary

<16 years old

Symptomatic, non-severe TB

- Smear negative
- Respiratory TB confined to one lobe
- No cavities
- No signs of miliary disease
- No pleural effusion
- No clinically significant airway obstruction

No documented or suspected drug-resistance

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535

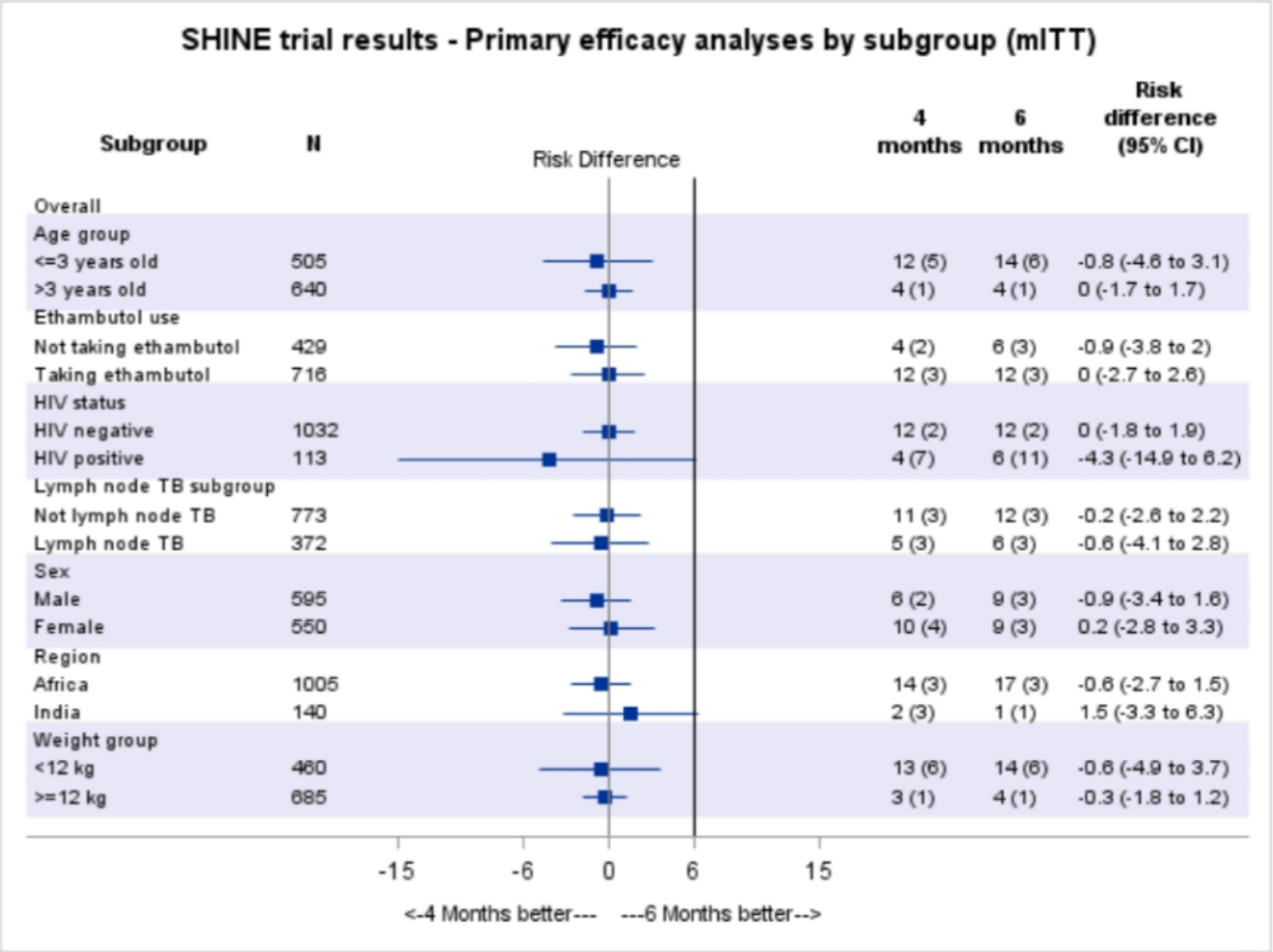
Table 2. Primary Efficacy Analysis (Modified Intention-to-Treat Population).*

Outcome	4-Month Treatment (N=572)	6-Month Treatment (N=573)	Difference (95% CI)	
			Adjusted Analysis†	Unadjusted Analysis
			percentage points	
Unfavorable status — no. (%)	16 (3)	18 (3)	−0.4 (−2.2 to 1.5)	−0.3 (−2.3 to 1.6)
Death from any cause after 4 mo	7 (1)	12 (2)		
Loss to follow-up after 4 mo but during treatment period	0‡	1 (<1)		
Treatment failure				
Tuberculosis recurrence	6 (1)	4 (1)		
Extension of treatment	2 (<1)	0		
Restart of treatment§	1 (<1)	1 (<1)		
Favorable status — no. (%)	556 (97)	555 (97)		

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535



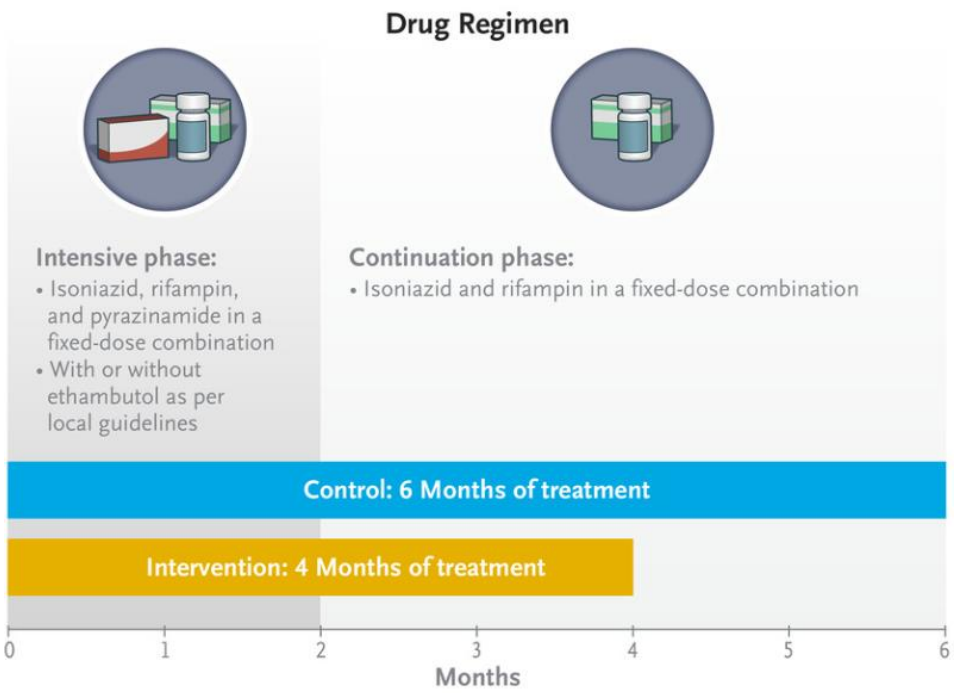
Additional outcomes

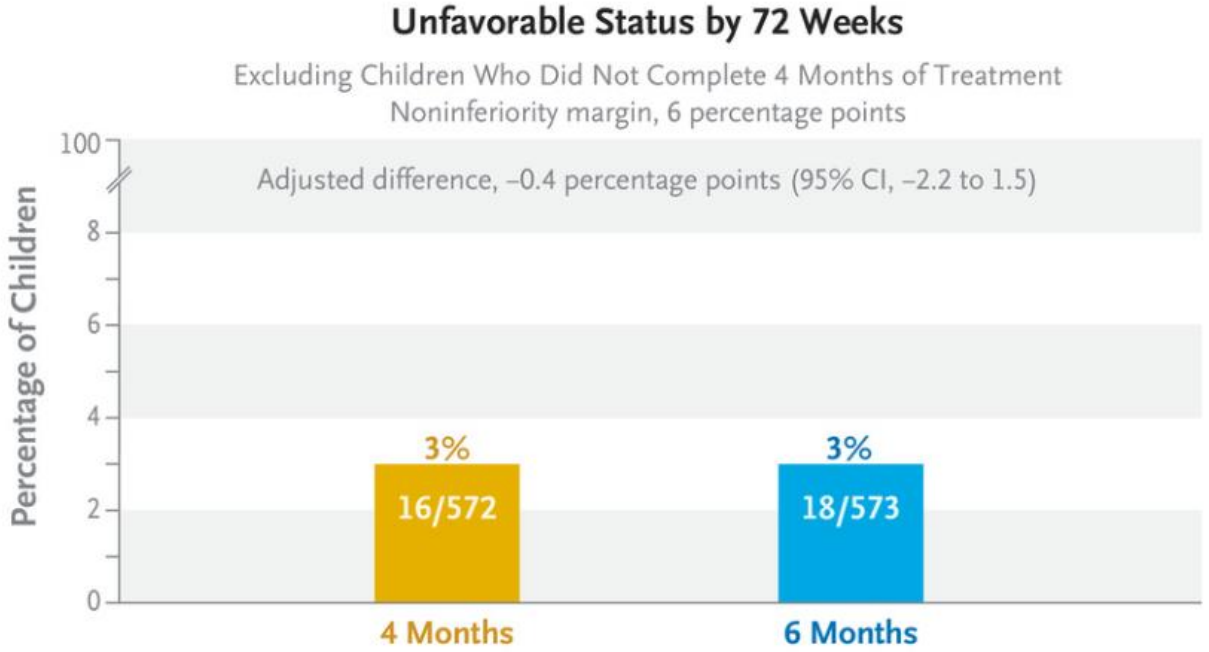
- No differences among microbiologically-confirmed TB
- No safety differences
- Improved cost in 4-month group

RESEARCH SUMMARY

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

Turkova A et al. DOI: 10.1056/NEJMoa2104535





CONCLUSIONS

Among children with nonsevere, drug-susceptible, smear-negative TB, a 4-month treatment regimen was noninferior to a 6-month regimen at 72 weeks of follow-up.

4-Month treatment regimen for pediatric non-severe TB

Minimal barriers to implementation

Does not apply to severe or extrapulmonary TB

Ideal for contact investigation setting in which most pediatric patients will have paucibacillary disease

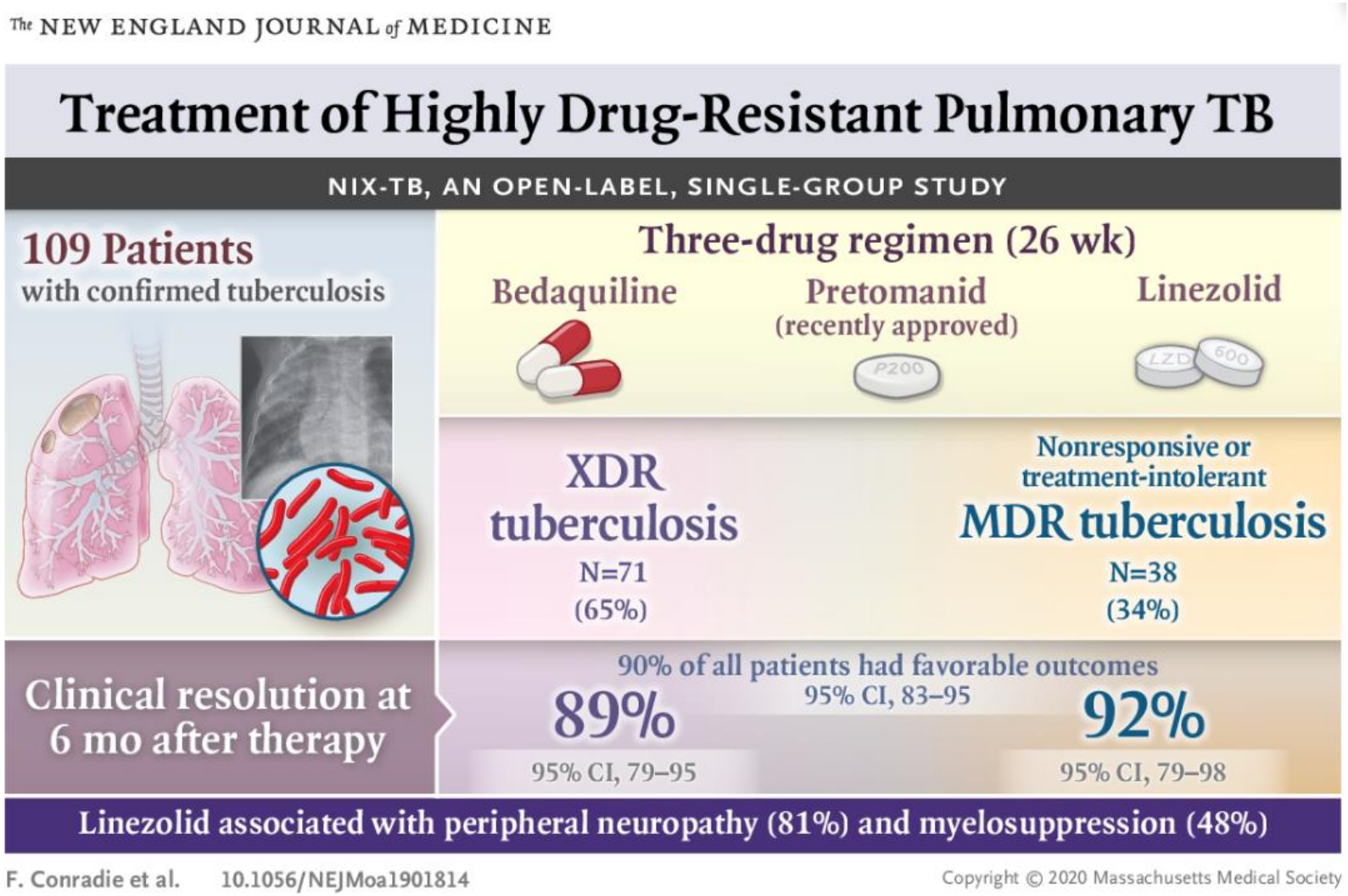
Key Clinical Trials

NixTB and ZeNix (Bedaquiline, Pretomanid, Linezolid (BPaL)

Treatment of Highly Drug-Resistant Pulmonary Tuberculosis

Francesca Conradie, M.B., B.Ch., Andreas H. Diacon, M.D., Nosipho Ngubane, M.B., B.Ch., Pauline Howell, M.B., B.Ch., Daniel Everitt, M.D., Angela M. Crook, Ph.D., Carl M. Mendel, M.D., Erica Egizi, M.P.H., Joanna Moreira, B.Sc., Juliano Timm, Ph.D., Timothy D. McHugh, Ph.D., Genevieve H. Wills, M.Sc., et al., for the Nix-TB Trial Team*

March 5, 2020
N Engl J Med 2020; 382:893-902
DOI: 10.1056/NEJMoa1901814

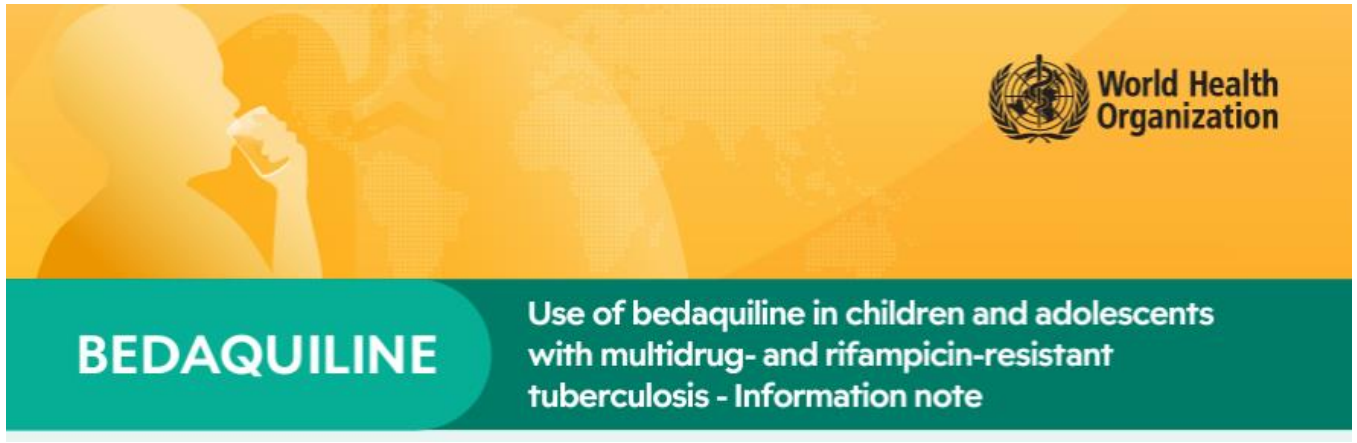


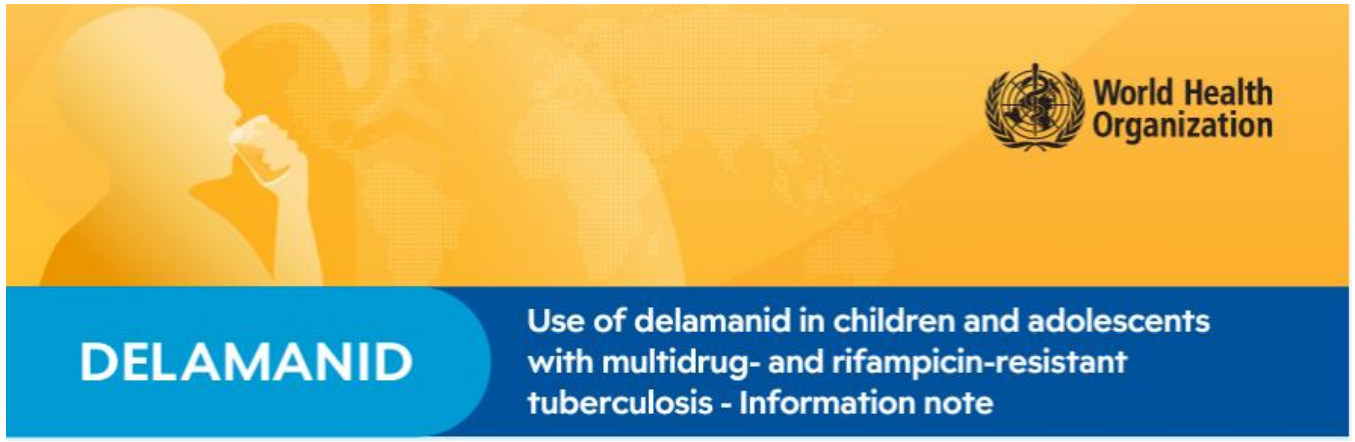
ZeNix Trial: Linezolid dose adjustment
Treatment success:

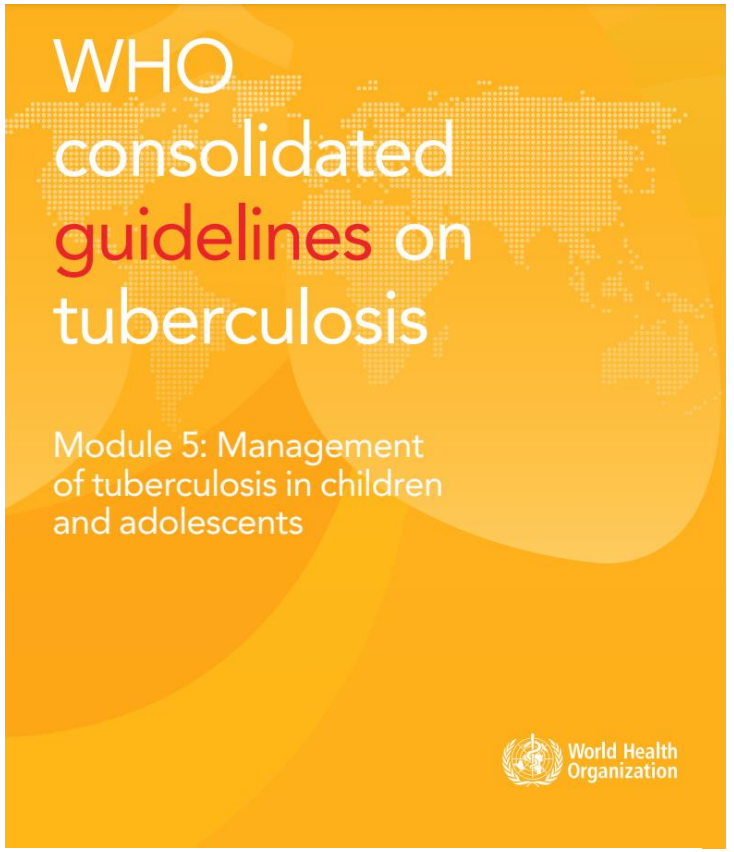
- 1200 mg x 6 months: 93%
- 1200 mg x 2 months: 89%
- 600 mg x 6 months: 91%
- 600 mg x 2 months: 84%

Decreased peripheral neuropathy and myelosuppression in lower dose arms

World health organization current guidance







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Thank you