


The 4-month regimen for treatment of non-severe TB in children and adolescents

Sabine Verkuijl, WHO GTB
Virtual Medical Consilium
27 September 2024

World Health Organization

END TB

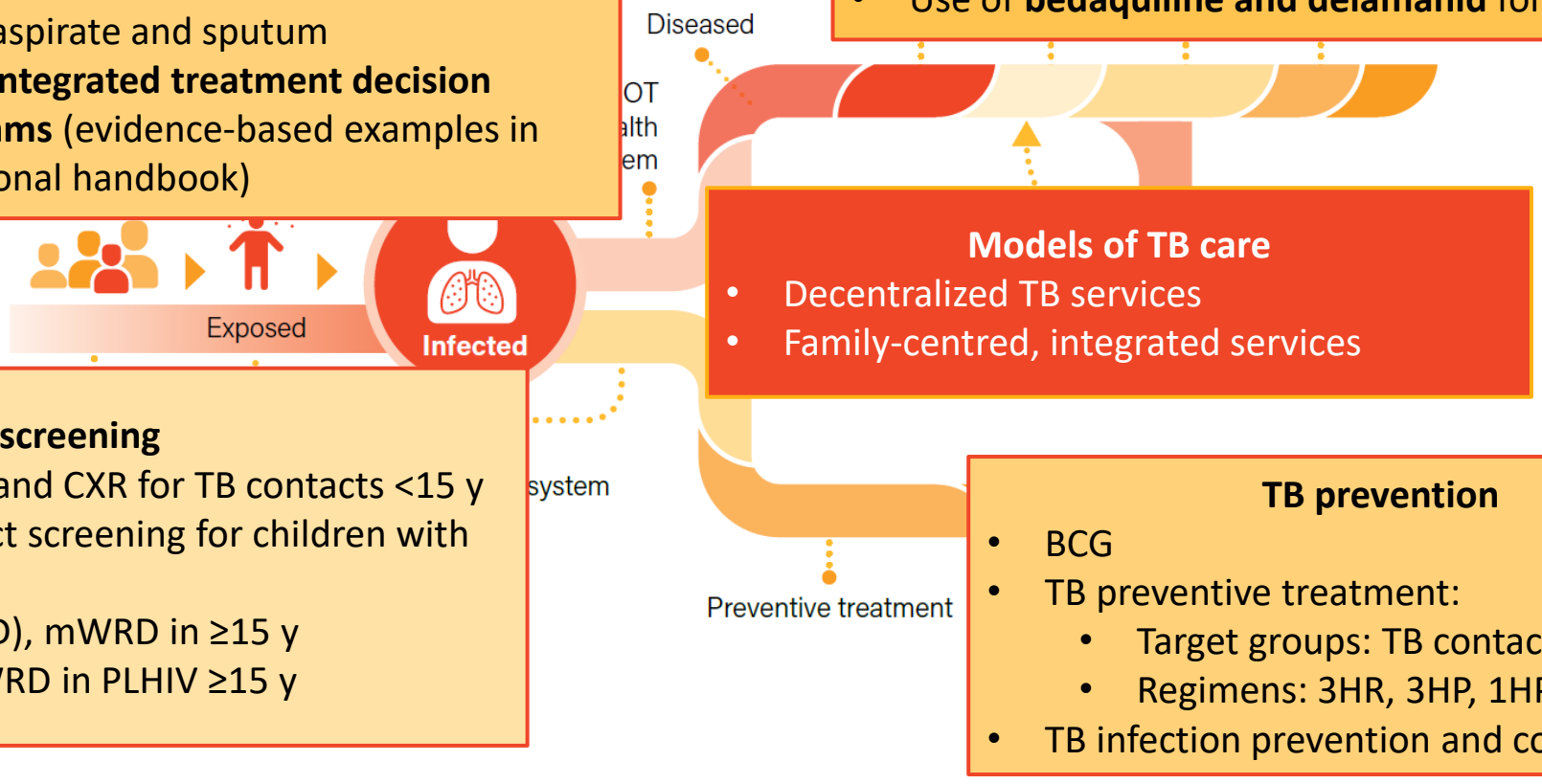
WHO policy guidance

TB treatment

- 4-month regimen (2HRZ(E)/2HR) for **non-severe TB** (3 months – 16 years) – eligibility criteria detailed in operational handbook
- Alternative regimens for **TB meningitis**: 6HRZEto and 2HRZ(E)/10HR
- Use of **bedaquiline and delamanid** for all ages (MDR/RR-TB)

TB diagnostic approaches

- Use of rapid diagnostic tests
- Xpert Ultra and MTB/RIF on **stool**, NPA, gastric aspirate and sputum
- Use of **integrated treatment decision algorithms** (evidence-based examples in operational handbook)



Models of TB care

- Decentralized TB services
- Family-centred, integrated services

TB screening

- Symptom screening and CXR for TB contacts <15 y
- Symptom and contact screening for children with HIV < 10 y
- Use of CXR (with CAD), mWRD in ≥15 y
- Use of CXR, CRP, mWRD in PLHIV ≥15 y

TB prevention

- BCG
- TB preventive treatment:
  - Target groups: TB contacts, CALHIV
  - Regimens: 3HR, 3HP, 1HP, 6-9H
- TB infection prevention and control

Guidelines: https://www.who.int/publications/i/item/9789240046764
Handbook: https://www.who.int/publications/i/item/9789240046832
WHO TB Knowledge Sharing Platform: https://extranet.who.int/tbknowledge

World Health Organization

END TB

Recommended regimens for drug-susceptible TB

	Intensive phase	Continuation phase
4-month regimens		
Non-severe PTB or peripheral LN TB in children and adolescents 3 months - 16 years	**2HRZ or 2HRZE**	**2HR**
PTB of any severity in adolescent ≥12 years	**2HPMZ**	**2HPM**
6-month regimen		
Any age, excludes severe EPTB	**2HRZ or 2HRZE**	**4HR**
Regimens for severe EPTB including TB meningitis		
Any age (0-19 years), bacteriologically confirmed or clinically diagnosed DS-TBM	**6HRZEto**	
Any child and adolescent with severe EPTB (TB meningitis & osteoarticular TB)	**2HRZE**	**10HR**

World Health Organization

END TB

E-courses on TB in children and adolescents

https://openwho.org/courses/TB-child-adolescent-EN

https://openwho.org/courses/TB-child-adolescent-programmatic

Register first on **openwho.org** before enrolling in the courses

World Health Organization

END TB

Shorter treatment duration in children with non-severe TB

In children and adolescents between 3 months and 16 years of age with non-severe TB (without suspicion or evidence of MDR/RR-TB), a 4-month treatment regimen (2HRZ(E)/2HR) should be used.

*(**Strong** recommendation, moderate certainty of evidence)*

SHINE: Shorter Treatment for Minimal Tuberculosis in Children

Remarks:

- ***Non-severe TB*** *is defined as: Peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease, confined to one lobe of the lungs, and without a miliary pattern*
- *Children and adolescents who* ***do not meet the criteria for non-severe TB*** *should receive the standard 6-month treatment regimen (2HRZE/4HR), or recommended treatment regimens for severe forms of EPTB*
- *The use of* ***ethambutol*** *in the first 2 months of treatment is recommended in settings with a high prevalence of HIV, or of isoniazid resistance*

Standard first-line medicines; continuation phase reduced to 2 months

World Health Organization

END TB

SHINE trial design

SHINE was an open-label phase III non-inferiority RCT comparing standard 6 months of treatment to 4 months in children with smear-negative non-severe (minimal) TB

Children aged <16 years with minimal TB (n=1200)

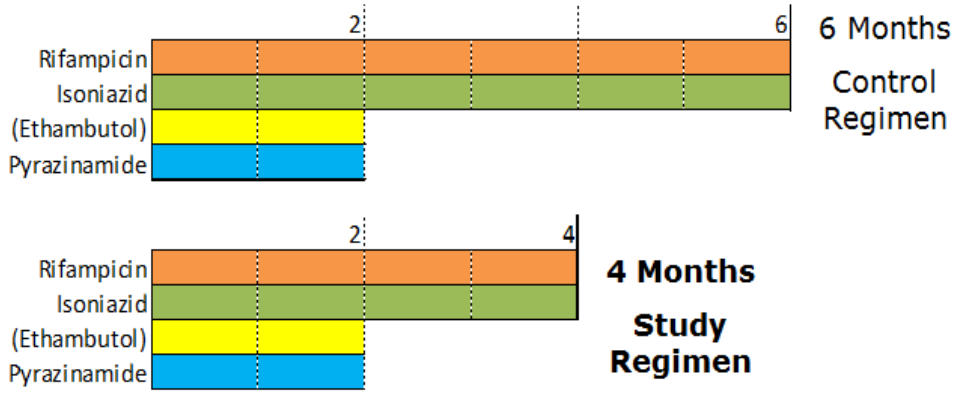
Randomisation (1:1)

6 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 16 weeks

4 month (n=600)
Intensive phase: 8 weeks
Continuation phase: 8 weeks

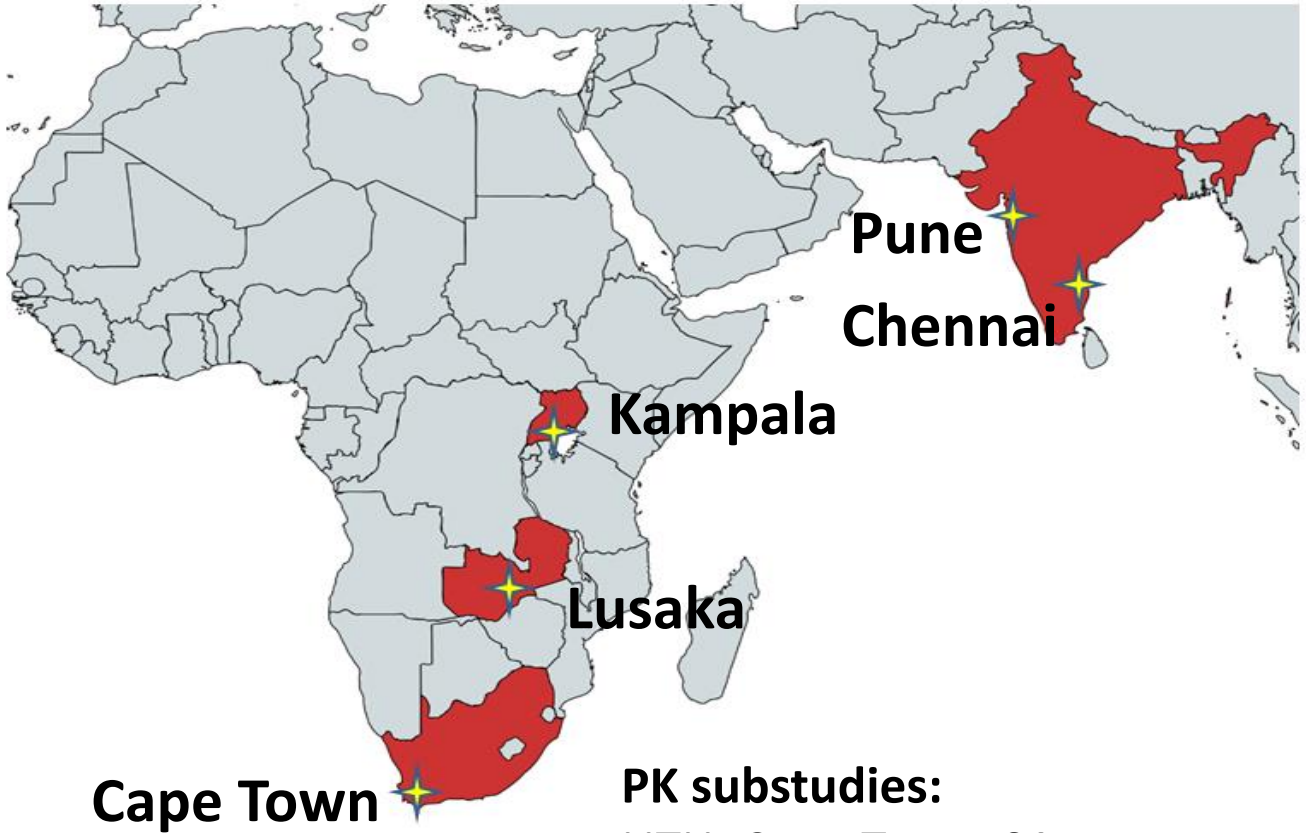
72 weeks follow-up for primary outcome assessment

Nested PK substudies undertaken in selected centres



Trial used WHO weight-bands and new dispersible fixed-dose formulations

SHINE trial sites and population



PK substudies:
UTH, Cape Town, SA
Nijmegen, Netherlands
Chennai, India

Coordination:
MRC CTU at UCL, London, UK

Main inclusion criteria:

- Age 0-16 years, weight ≥3kg
- No known drug resistance
- Clinical decision to treat TB
- Symptomatic but **non-severe TB***
- Smear-negative on respiratory samples
  - GeneXpert positive allowed
- Not treated for TB in previous 2y
- Known HIV status (pos or neg)

***Non-severe TB**: respiratory TB confined to one lobe (opacification of <1 lobe) with no cavities, no signs of miliary TB, no complex pleural effusion, and no clinically significant airway obstruction; or peripheral lymph node TB

Main efficacy outcomes

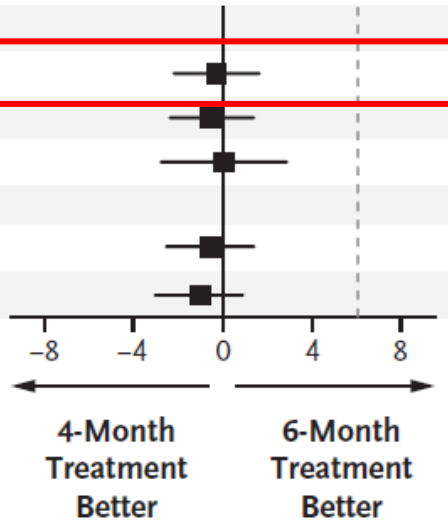
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 10, 2022 VOL. 386 NO. 10

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children

A. Turkova, G.H. Wills, E. Wobudeya, C. Chabala, M. Palmer, A. Kinikar, S. Hissar, L. Choo, P. Musoke, V. Mulenga, V. Mave, B. Joseph, K. LeBeau, M.J. Thomason, R.B. Mboizi, M. Kapasa, M.M. van der Zalm, P. Raichur, P.K. Bhavani, H. McIlleron, A.-M. Demers, R. Aarnoutse, J. Love-Koh, J.A. Seddon, S.B. Welch, S.M. Graham, A.C. Hesseling, D.M. Gibb, and A.M. Crook, for the SHINE Trial Team*

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)



34 unfavourable outcomes (mITT):

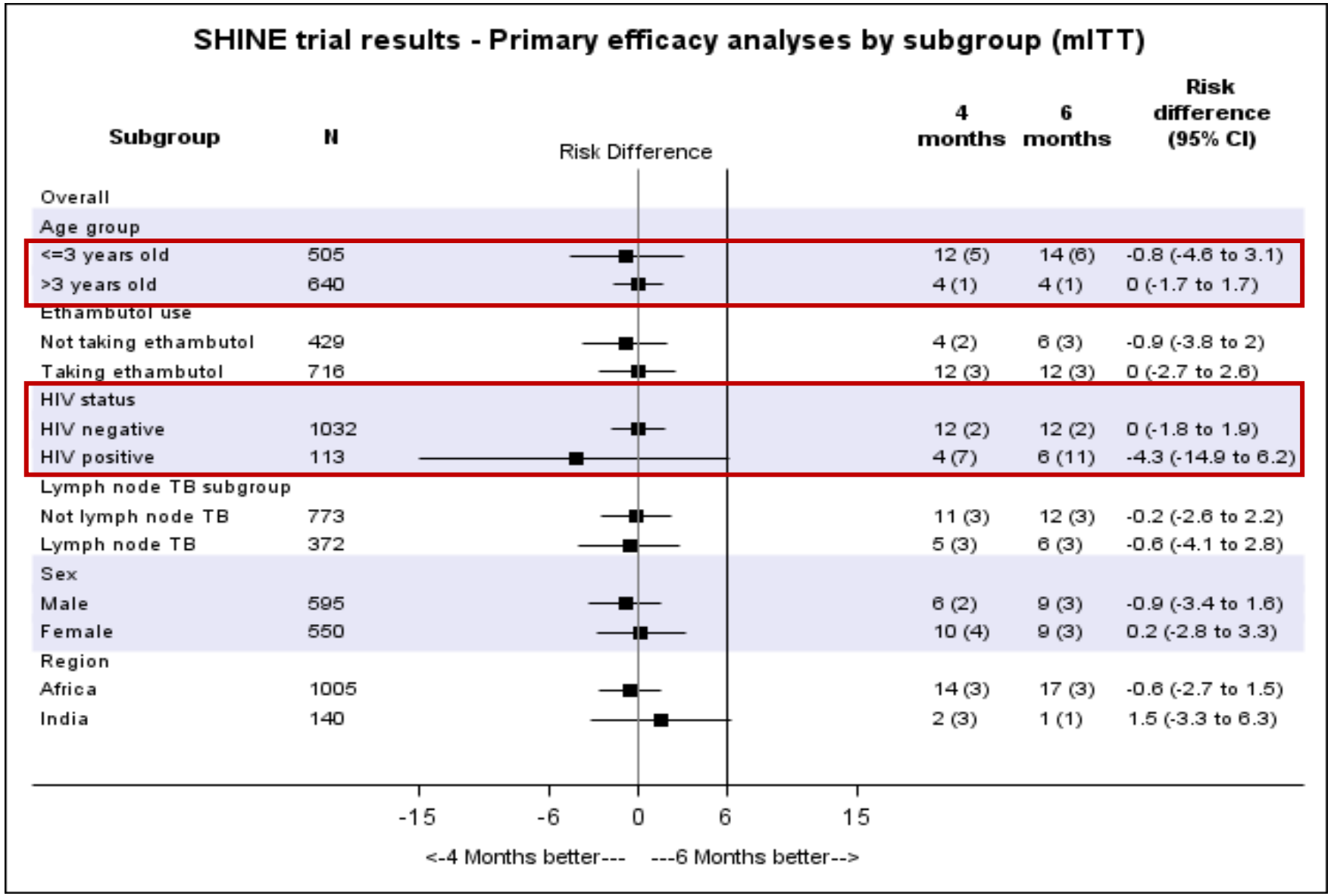
	4 Month N=16	6 Month N=18
Death from any cause (after week 16)	7	12
LTFU during treatment (after week 16)	0	1
TB recurrence	6	4
Treatment extension (treatment failure)	2	0
Restart/change of treatment (treatment failure)	1	1

World Health Organization

N Engl J Med 2022;386:911-22

END TB

Efficacy outcomes by subgroup (mITT)



World Health Organization

END TB

Safety outcomes

	4 Months N=602	6 Months N=602
Total number of grade ≥3 AEs on Rx	49	66
Children with at least 1 AE	47 (8%)	48 (8%)
After week 16: grade ≥3 AEs on treatment	14	14
Children with at least 1 AE	14 (2%)	12 (2%)
Adverse reactions (AR) *	**6 (1%)**	**11 (2%)**
Total number of SAEs	**88**	**104**
Participants with at least one SAE	75 (12)	75 (12)
Before week 16: number of SAEs	35	50
Participants with at least one SAE	33	40
After week 16: number of SAEs	53	54
Participants with at least one SAE	47	44
Number of Deaths	**12 (2%)**	**19 (3%)**
Before week 16: deaths	5	6
Deaths considered related to TB	3	2
After week 16: deaths	7	13
Deaths considered related to TB	2	6

*11 / 17 adverse reactions were raised liver enzymes

Deaths in SHINE

Deaths in SHINE, overall	31/1204 (2%)
Children with HIV	**13/127 (10%)**
Deaths considered related to TB	13
Pneumonia	6
Epilepsy/ convulsions	2
Septicaemia	1
Acute respiratory failure	1
Chronic diarrhoea	1
Congestive heart failure	1
Suspected pulmonary TB	1

Context: mortality in children <5 years in general population

India	35 per 1000 (4%)
South Africa	31 per 1000 (3%)
Uganda	41 per 1000 (4%)
Zambia	57 per 1000 (6%)

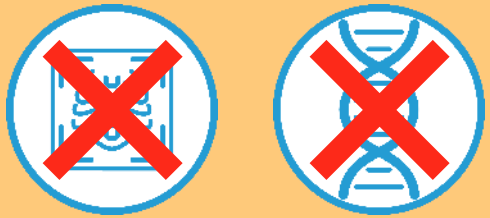
World Health Organization

UNICEF. Under five mortality 2020 https://data.unicef.org/topic/child-survival/under-five-mortality/

Assessing eligibility for the 4-month regimen

Main considerations:

Access to CXR and bacteriological testing, clinical assessment

 **3m-16y**	• Based on CXR features • Xpert MTB/RIF or Ultra neg, trace or (very) low • Mild symptoms not requiring hospitalization
 **3m-16y**	• Xpert MTB/RIF or Ultra neg, trace or (very) low (PTB) or isolated peripheral lymph node TB • Mild symptoms not requiring hospitalization
 **<10y**	• Isolated peripheral lymph node TB • Mild symptoms not requiring hospitalization

World Health Organization

END TB

Eligibility for the 4-month regimen for non-severe TB

Main considerations: Access to CXR and bacteriological testing, clinical assessment.

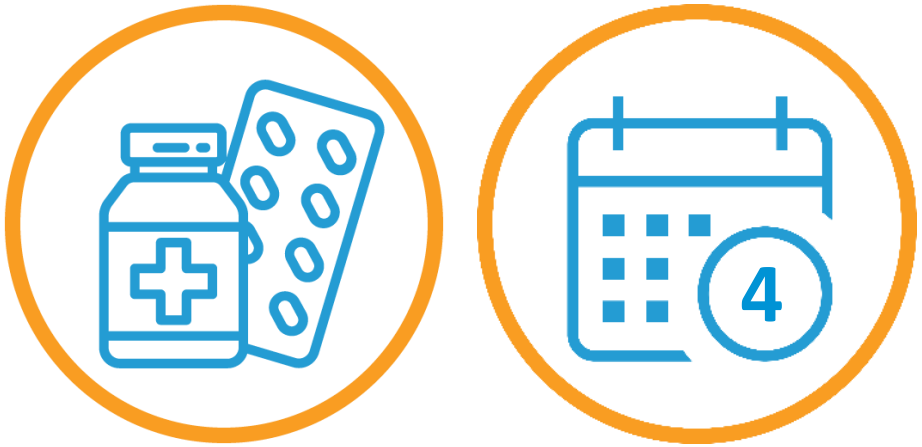
Mild symptoms:

- no danger signs, no asymmetrical and persistent wheezing, no signs of EPTB (other than lymph node TB)
- no severe acute malnutrition, respiratory distress, high fever, severe pallor, restlessness, irritability or lethargy

World Health Organization

END TB

Follow up after starting the 4-month regimen without CXR



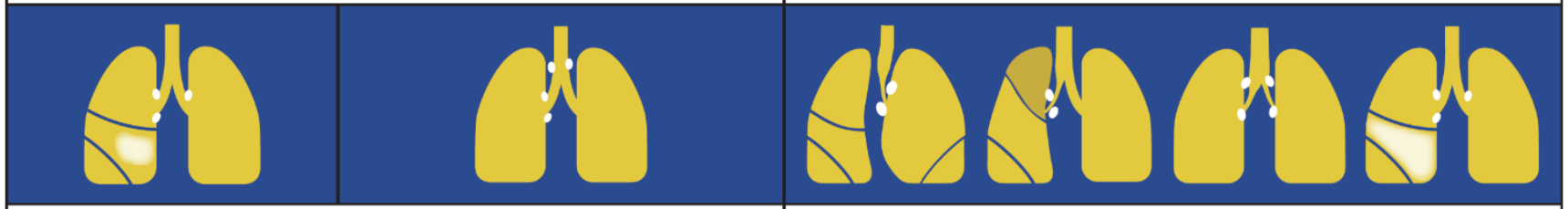
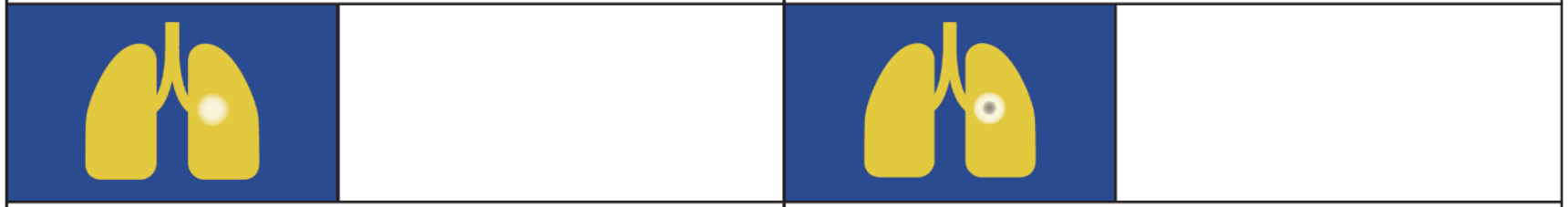
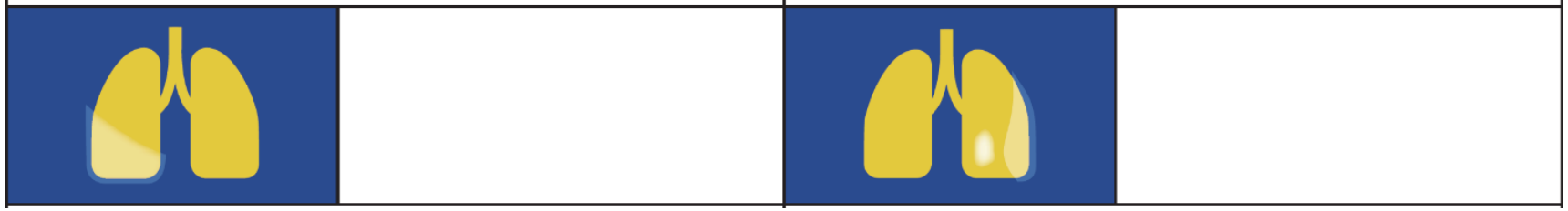
Children and adolescents started on 4-month regimen without CXR:

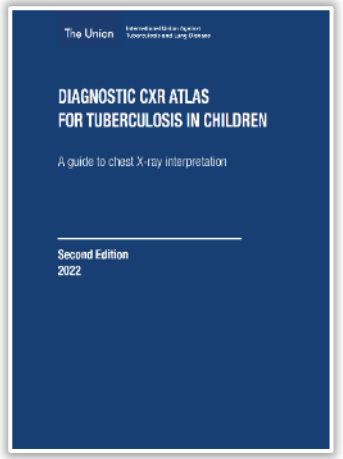
- follow up monthly
- symptoms expected to have resolved within 1 month
- expected to be well at 4 months (including nutritional status)
- continue treatment for 6 months if no response clinically after 4 months; evaluate for DR-TB, non-TB-related disease and poor treatment adherence

World Health Organization

END TB

Assessing severity: CXR

Non-Severe	Severe
Uncomplicated lymph node disease	Complicated lymph node disease
	
Primary (Ghon) focus	Primary (Ghon) focus with cavitation
	
Simple pleural effusion	Complicated pleural effusion
	

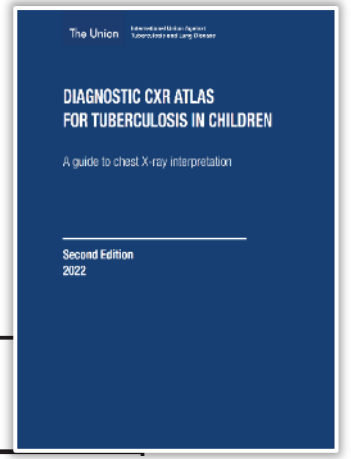


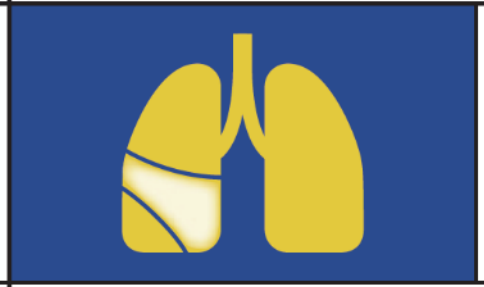
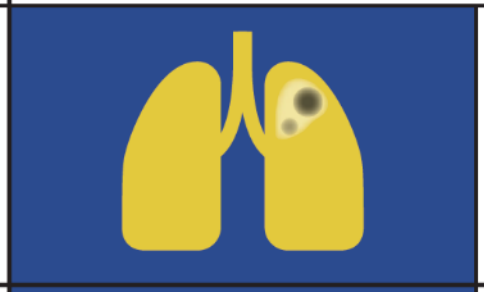
Diagnostic CXR atlas for paediatric pulmonary tuberculosis: a guide to chest X-ray interpretation to diagnose paediatric tuberculosis, second edition.
https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children
With image library

World Health Organization

END TB

Assessing severity: CXR

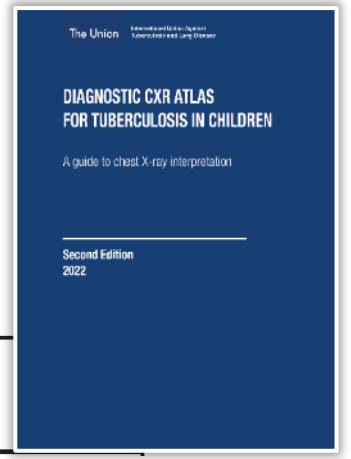


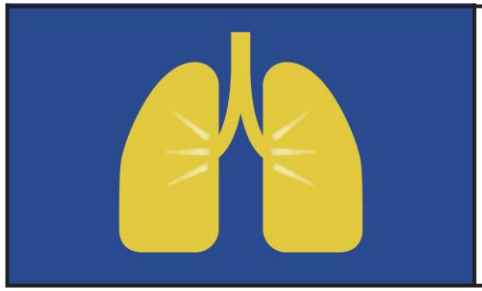
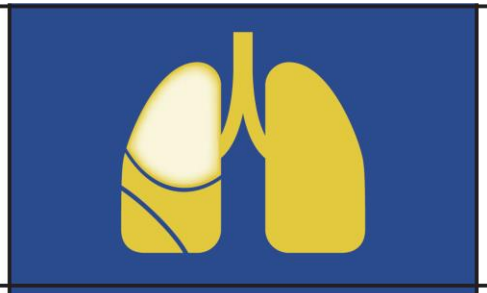
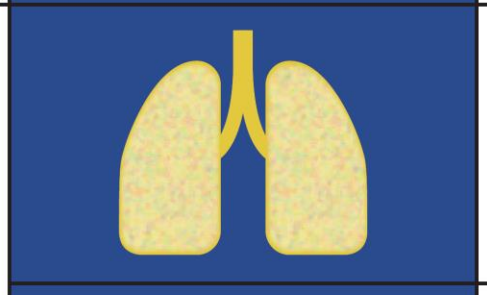
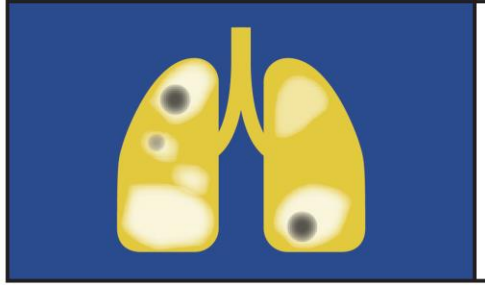
Non-Severe	Severe
Alveolar opacification: < 1 lobe	Alveolar opacification: involving a whole lobe or multiple lobes
	
Other:	Other:
 - Interstitial pneumonia	 - All cavitary disease

World Health Organization

END TB

Assessing severity: CXR

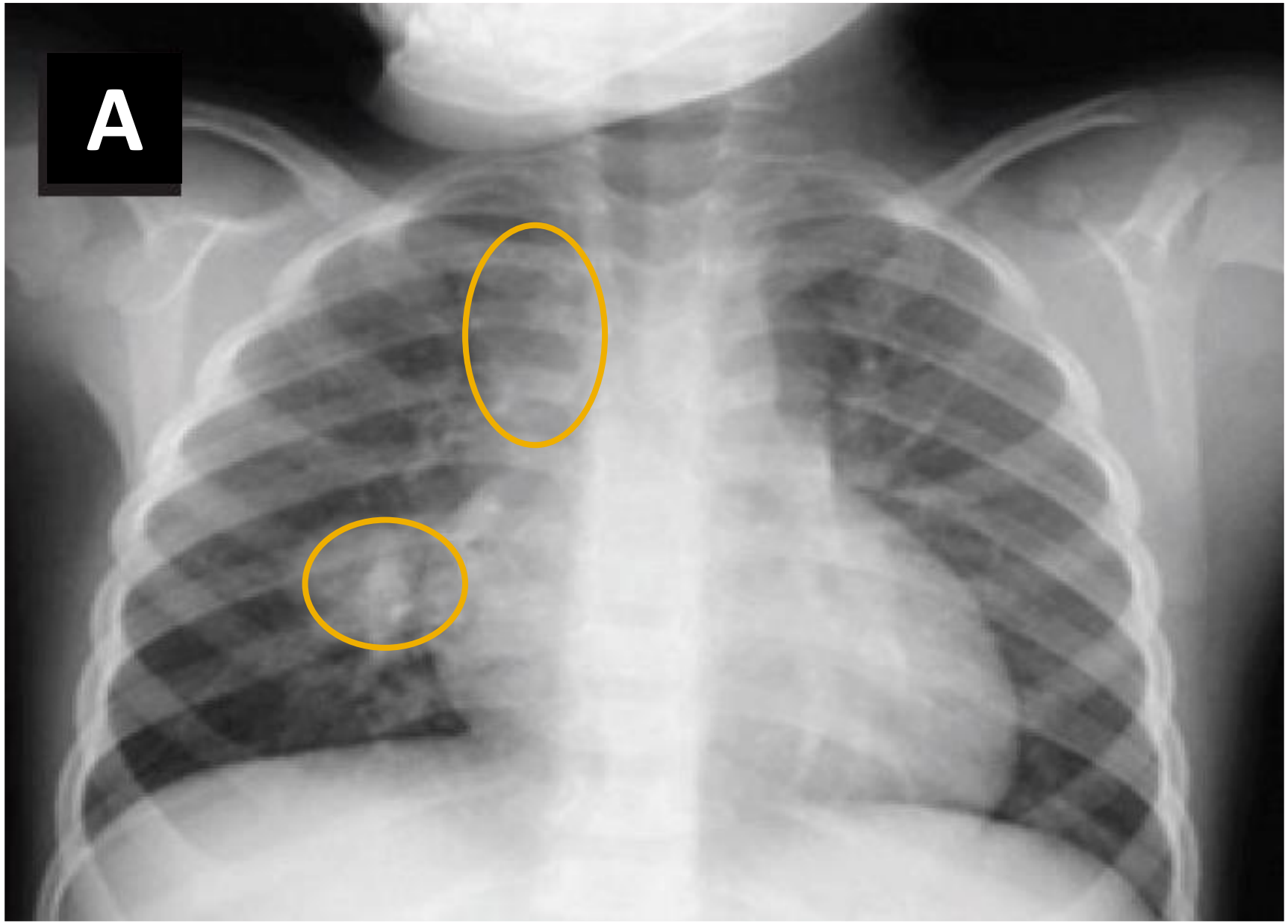


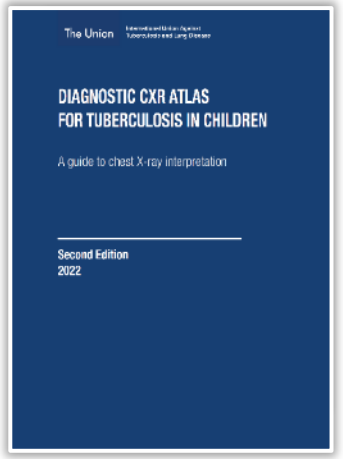
Non-Severe		Severe	
	- Perihilar infiltrates		- Expansile pneumonia
			- Miliary TB
			- TB bronchopneumonia

World Health Organization

END TB

Severe or non-severe TB?

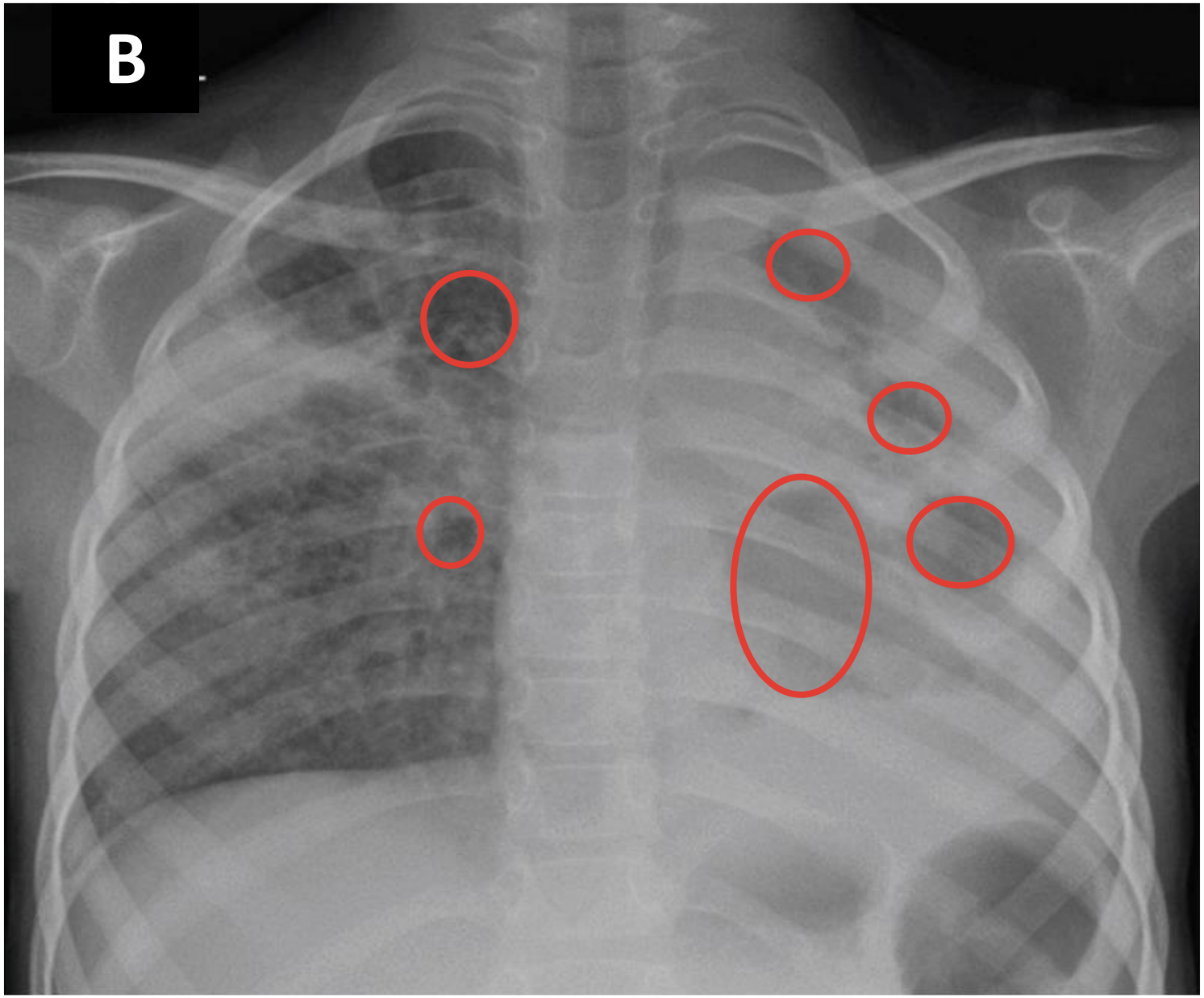


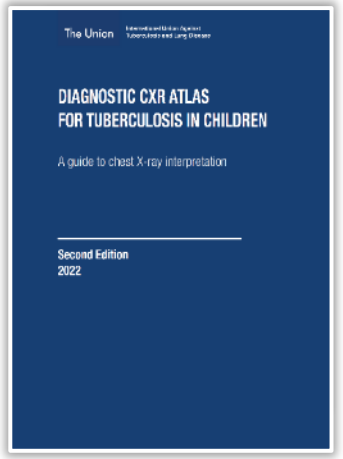


World Health Organization

END TB

Severe or non-severe TB?

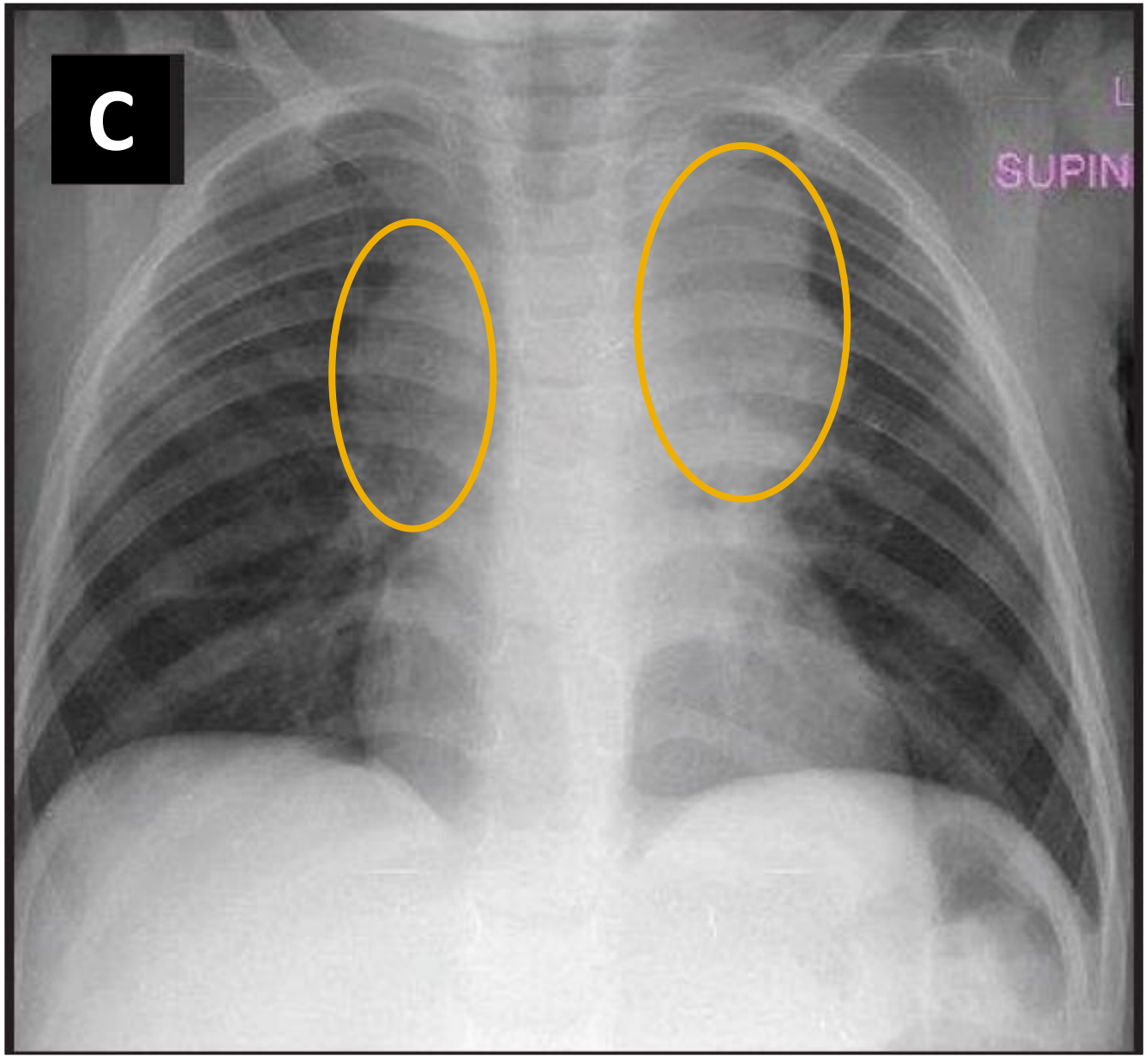


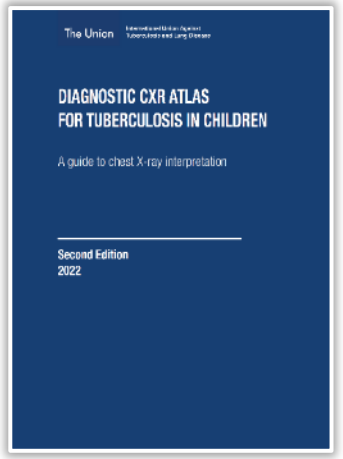


World Health Organization

END TB

Severe or non-severe TB?

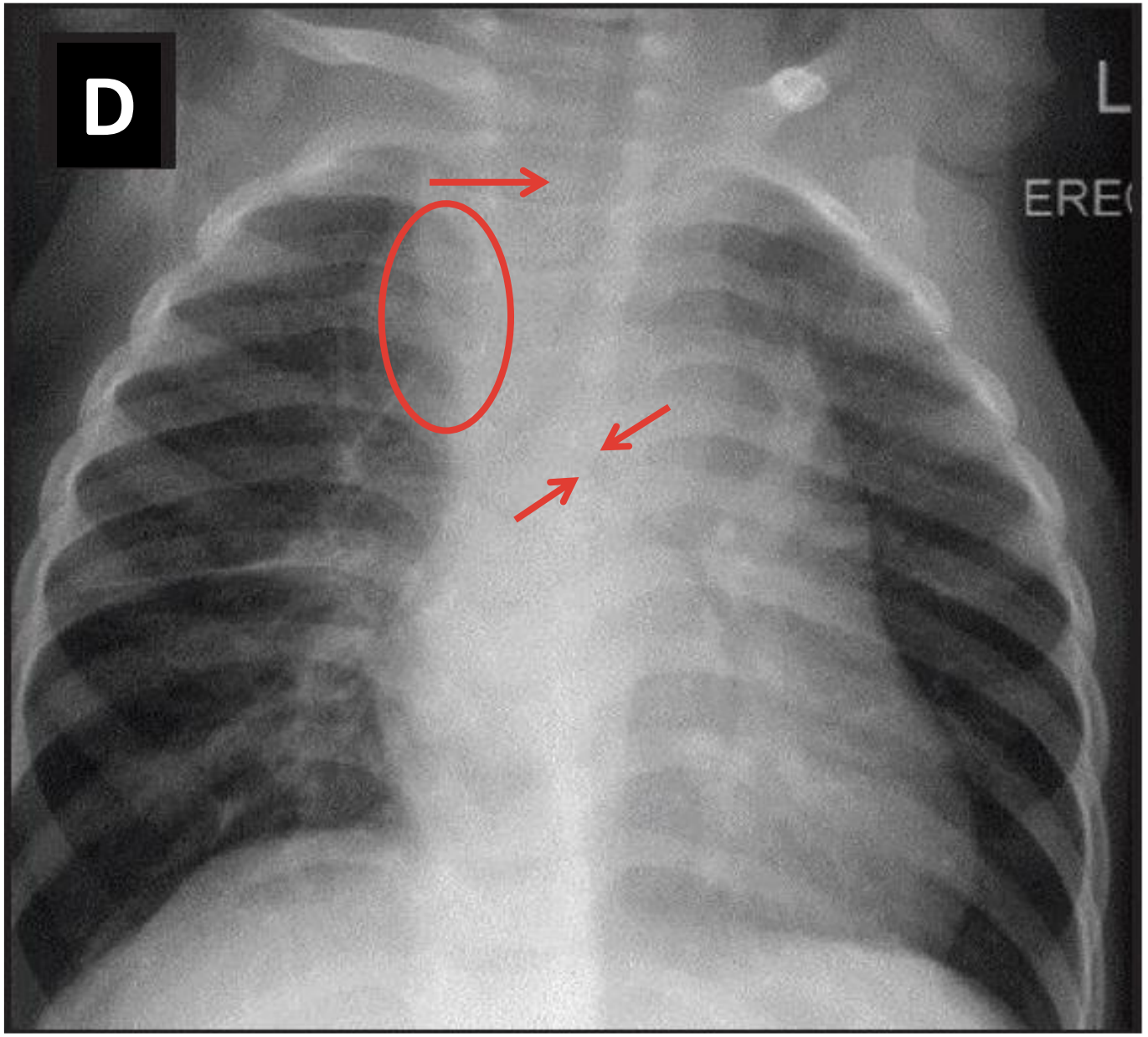


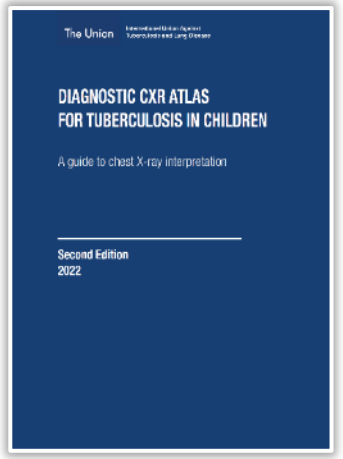


World Health Organization

END TB

Severe or non-severe TB?

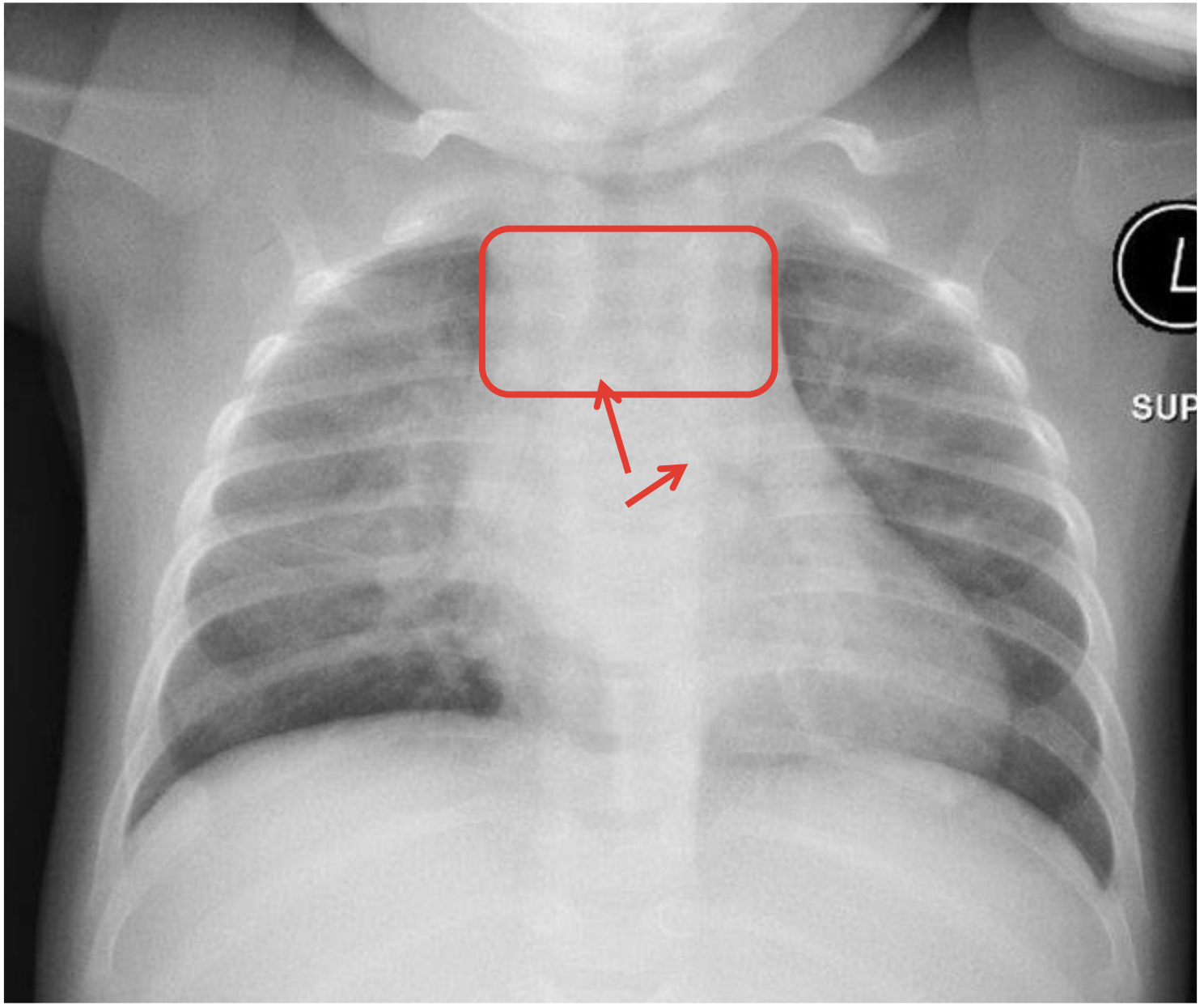


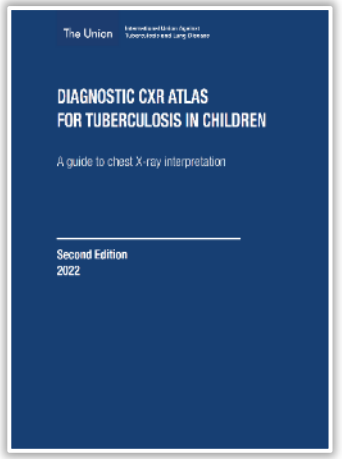


World Health Organization

END TB

Severe or non-severe TB?



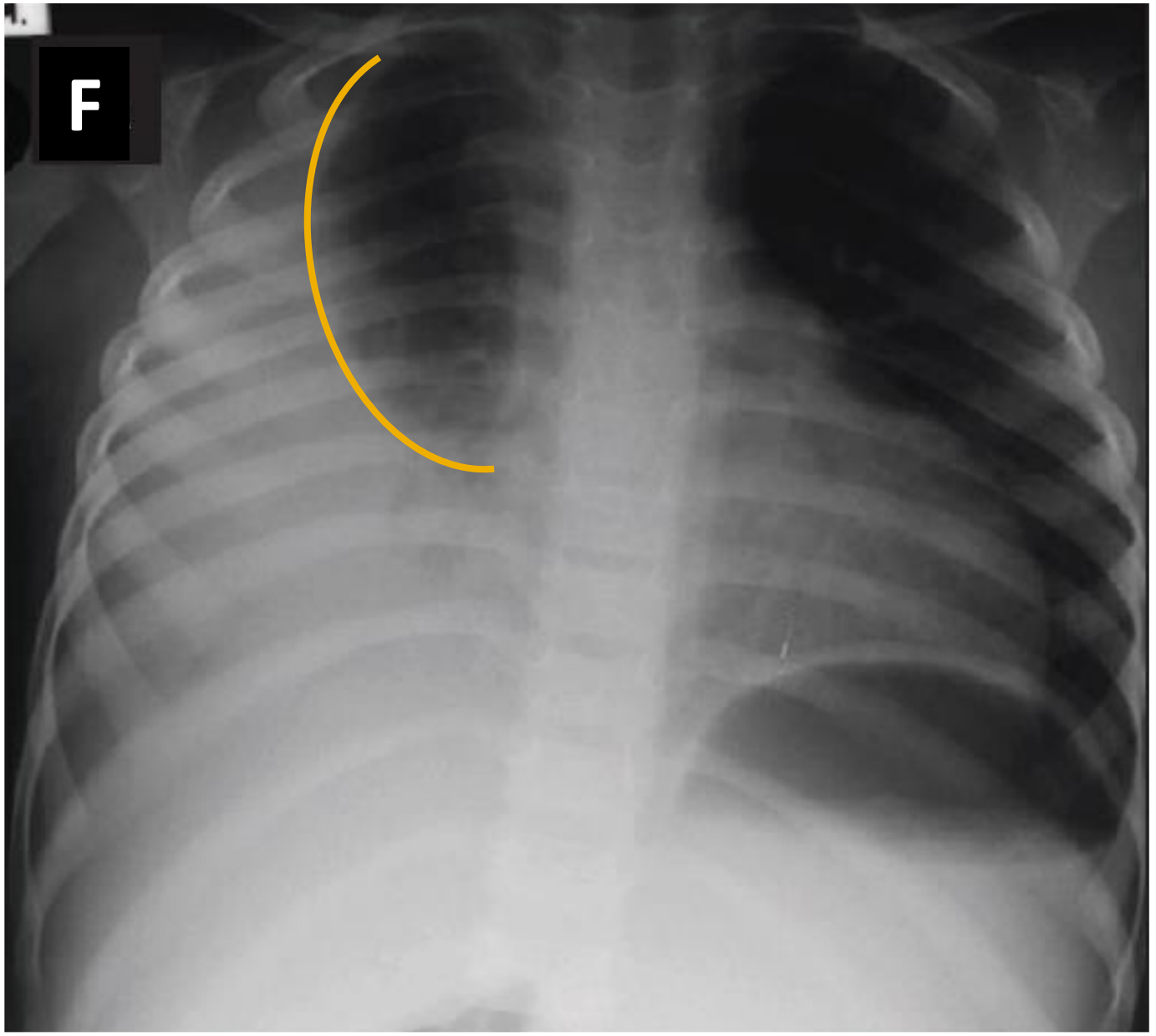


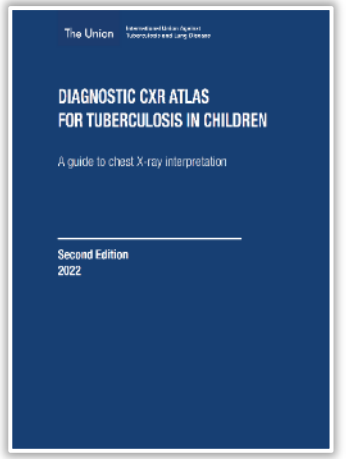
E

World Health Organization

END TB

Severe or non-severe TB?

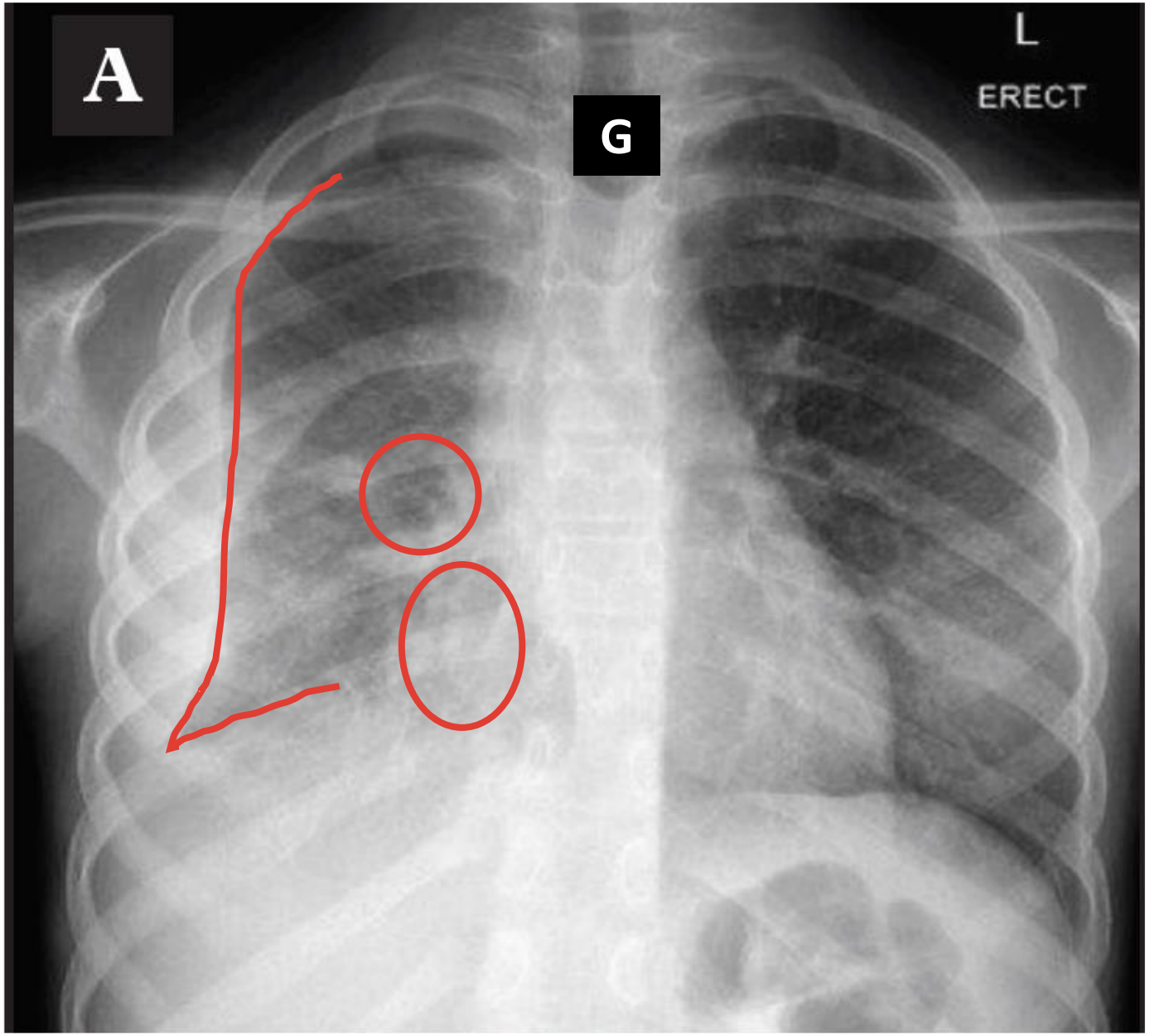


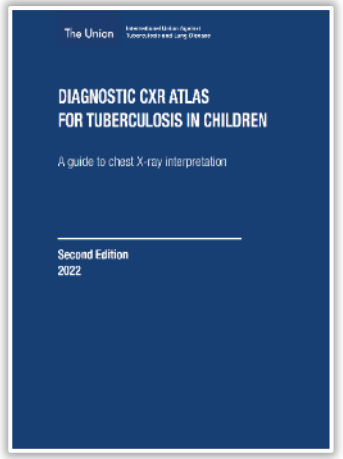


World Health Organization

END TB

Severe or non-severe TB?

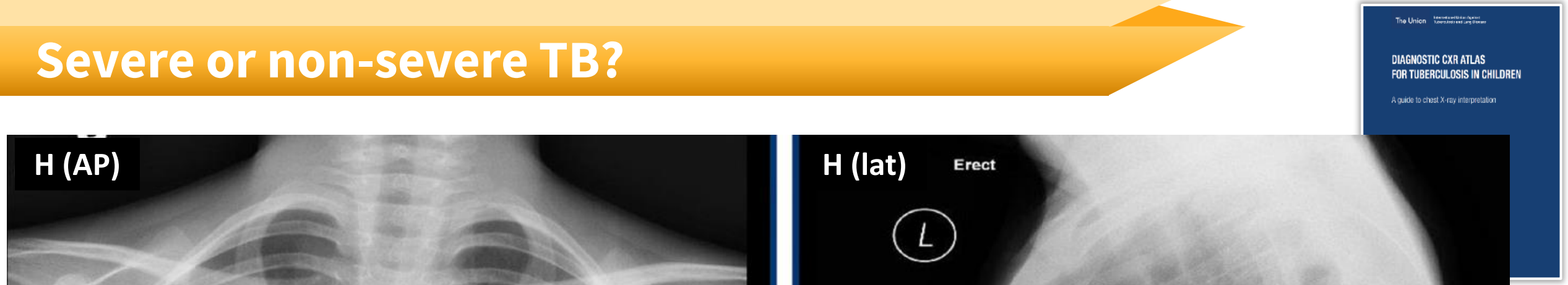


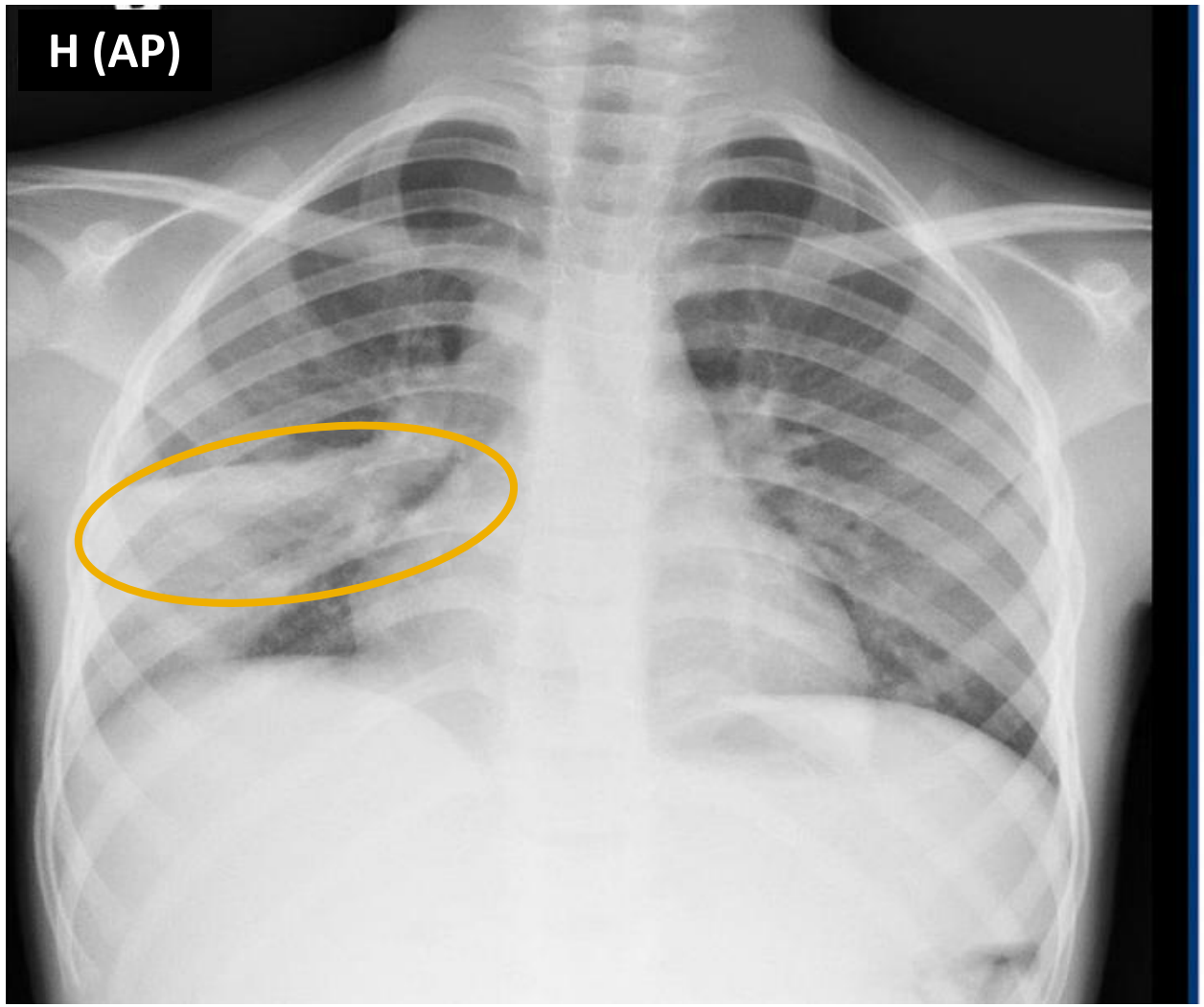


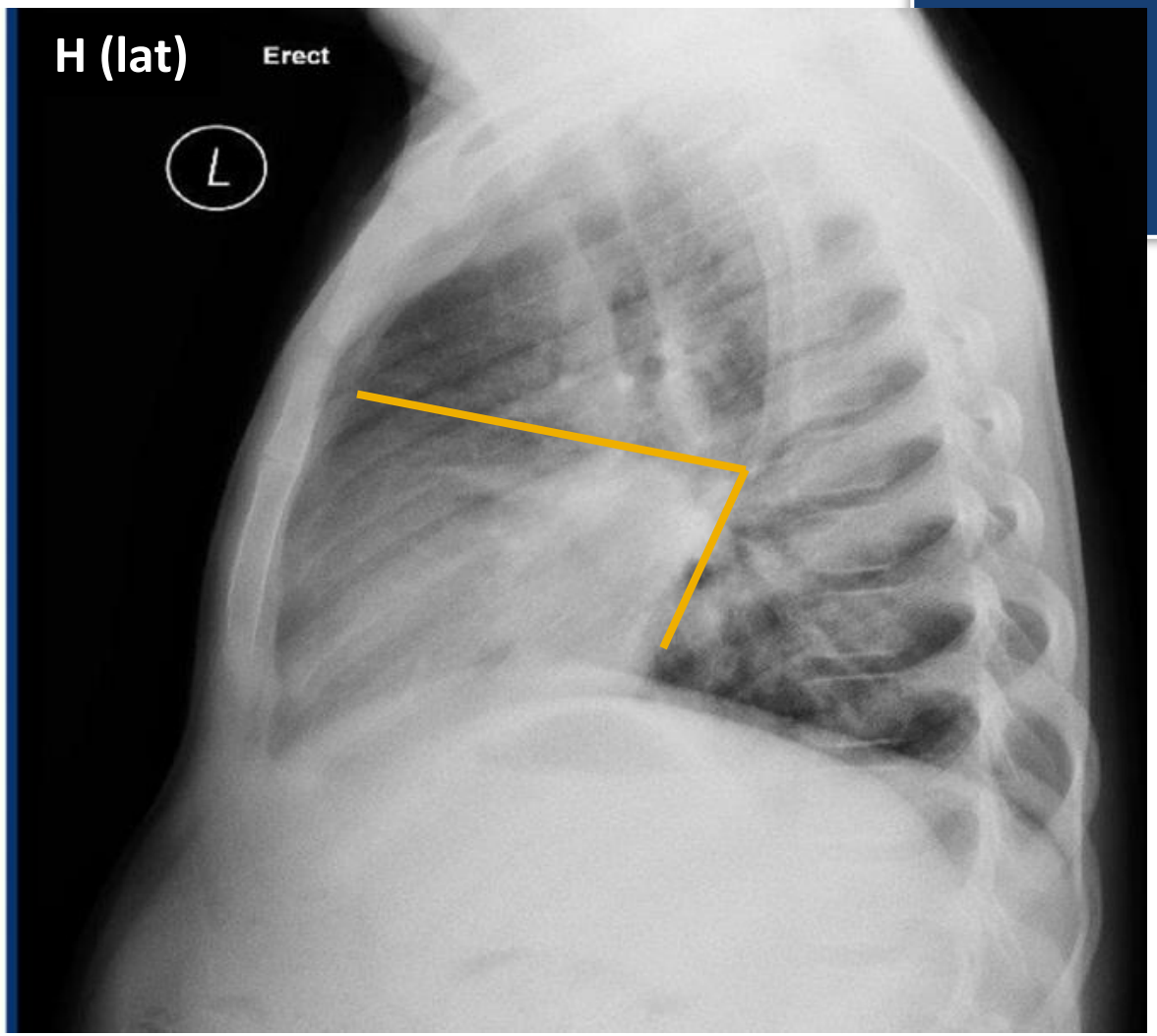
World Health Organization

END TB

Severe or non-severe TB?



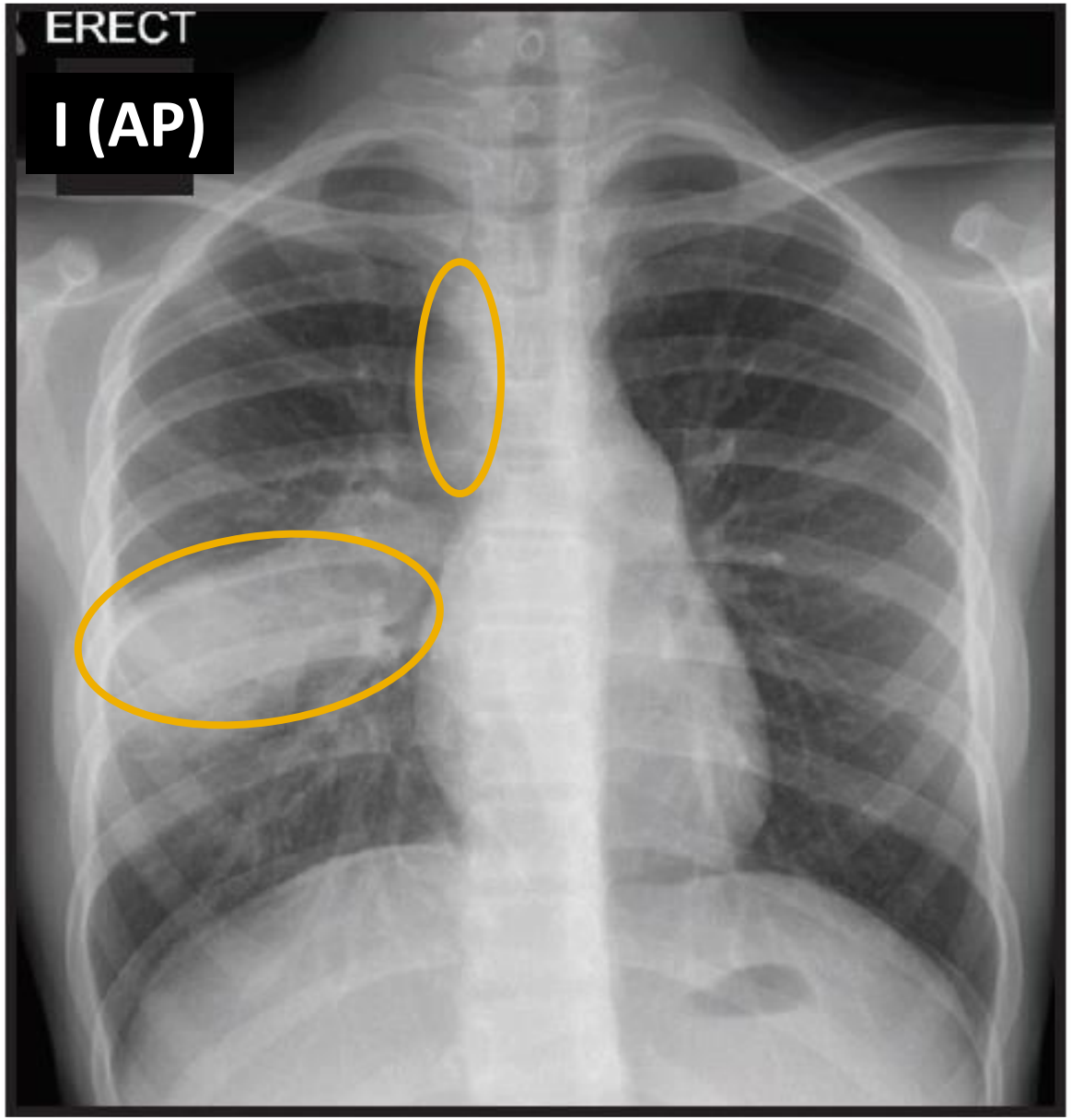


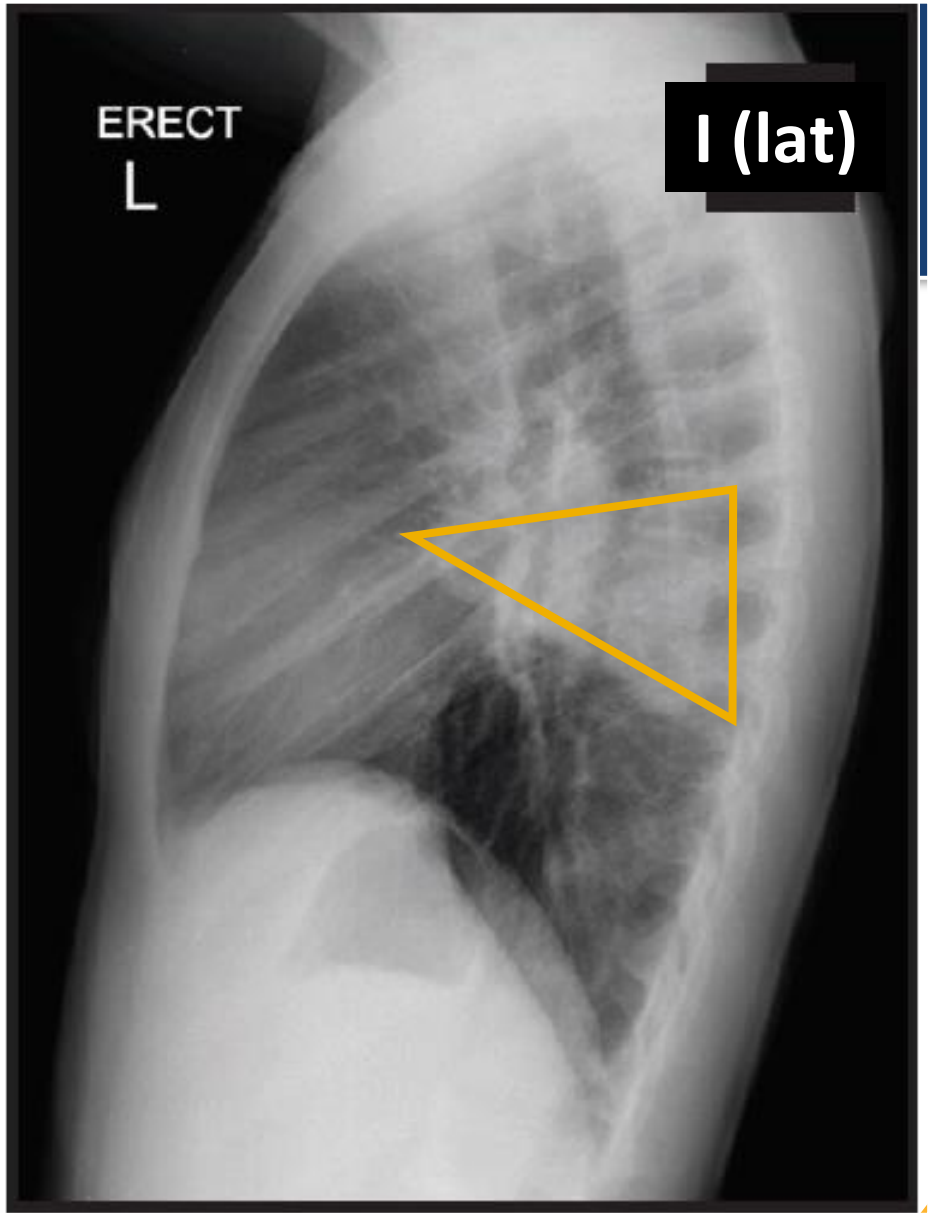


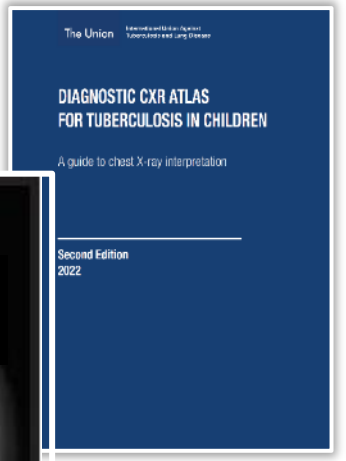
World Health Organization

END TB

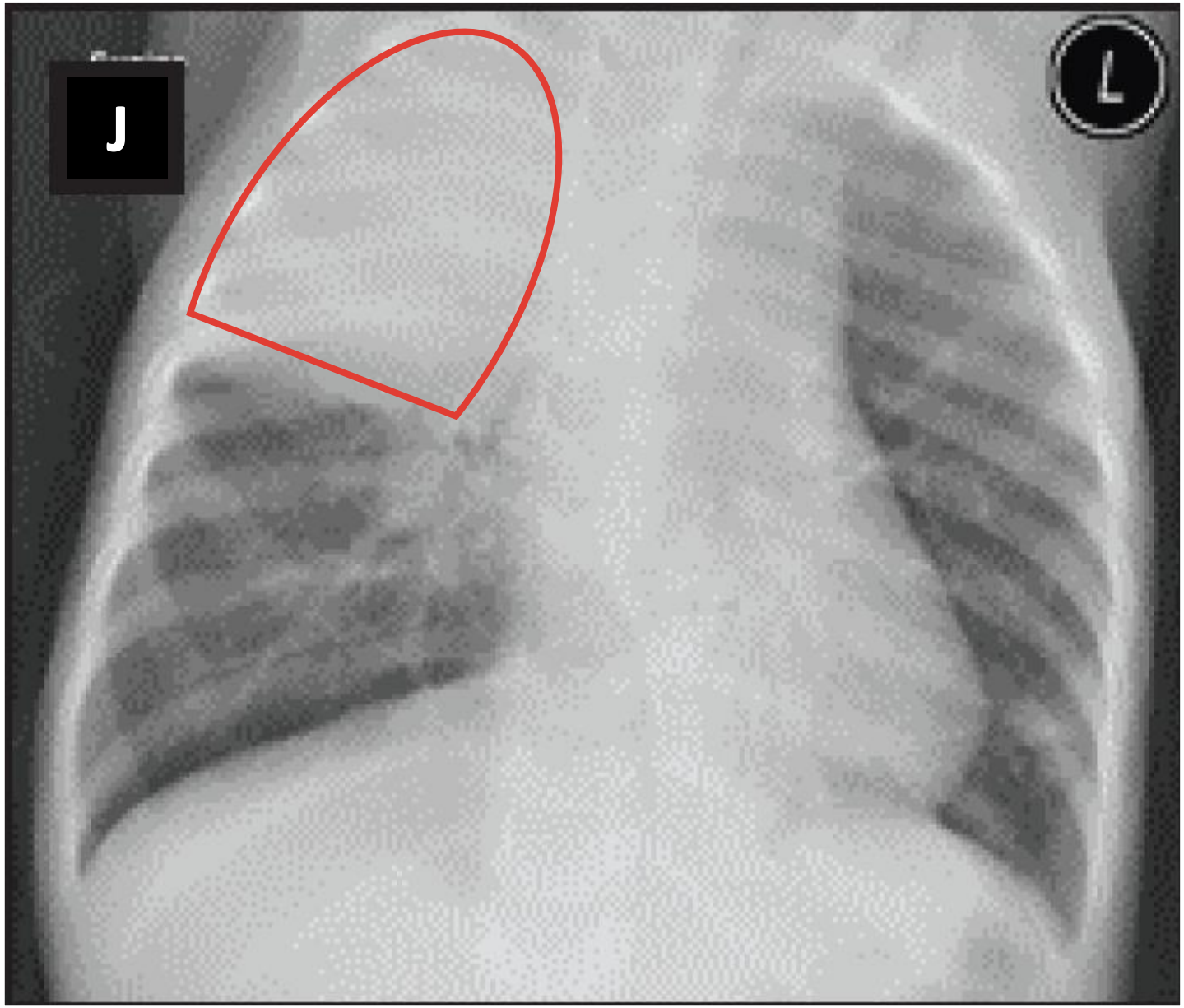
Severe or non-severe TB?

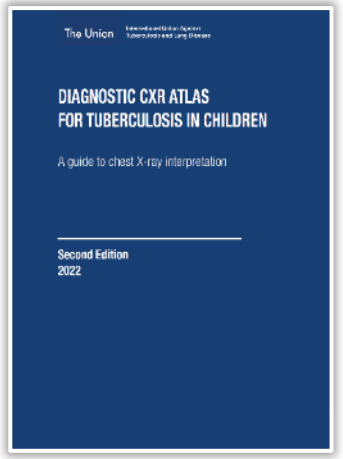






Severe or non-severe TB?

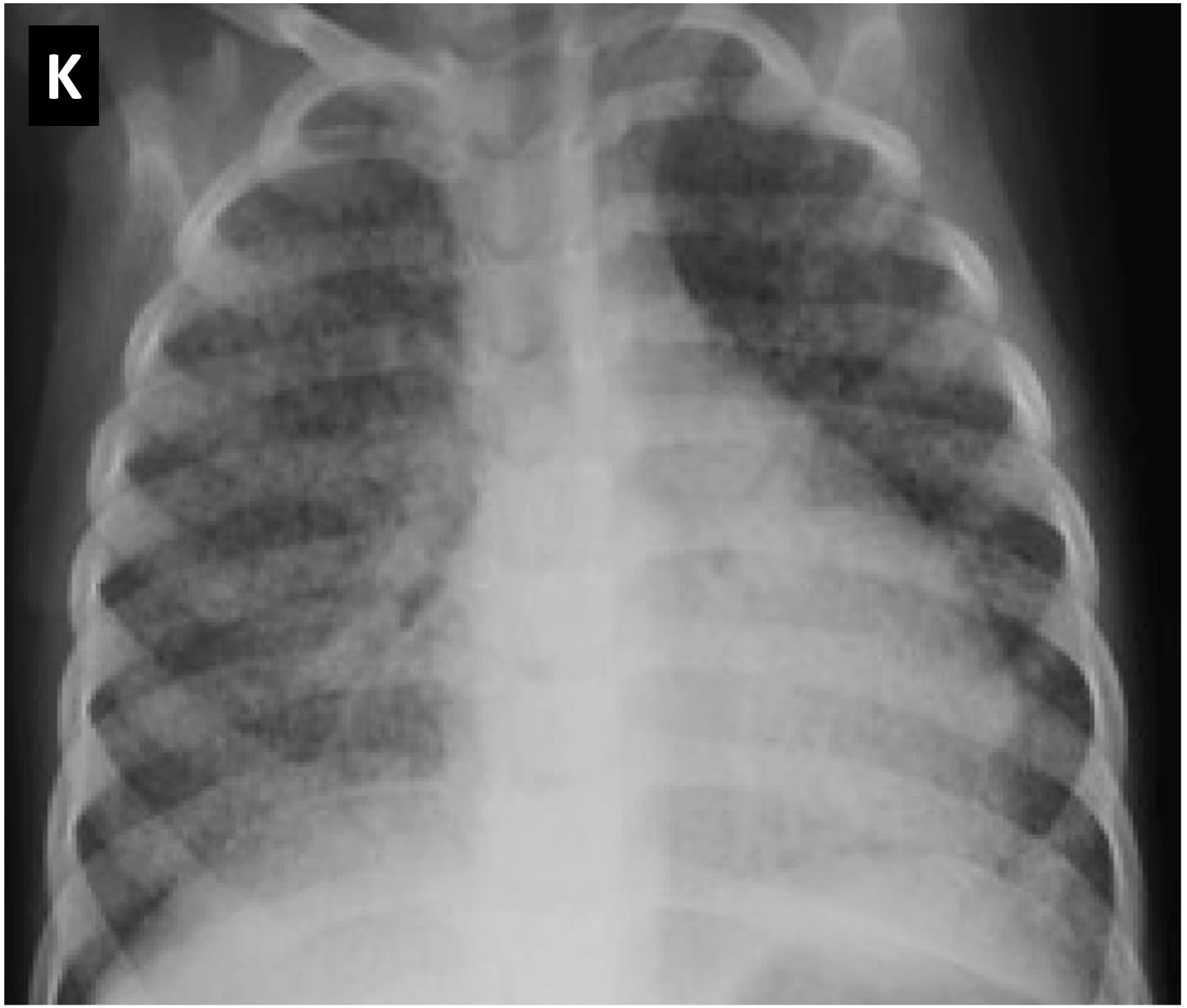


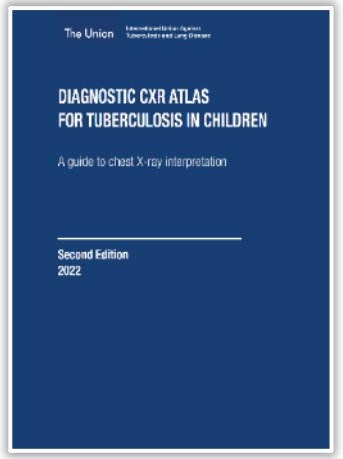


World Health Organization

END TB

Severe or non-severe TB?

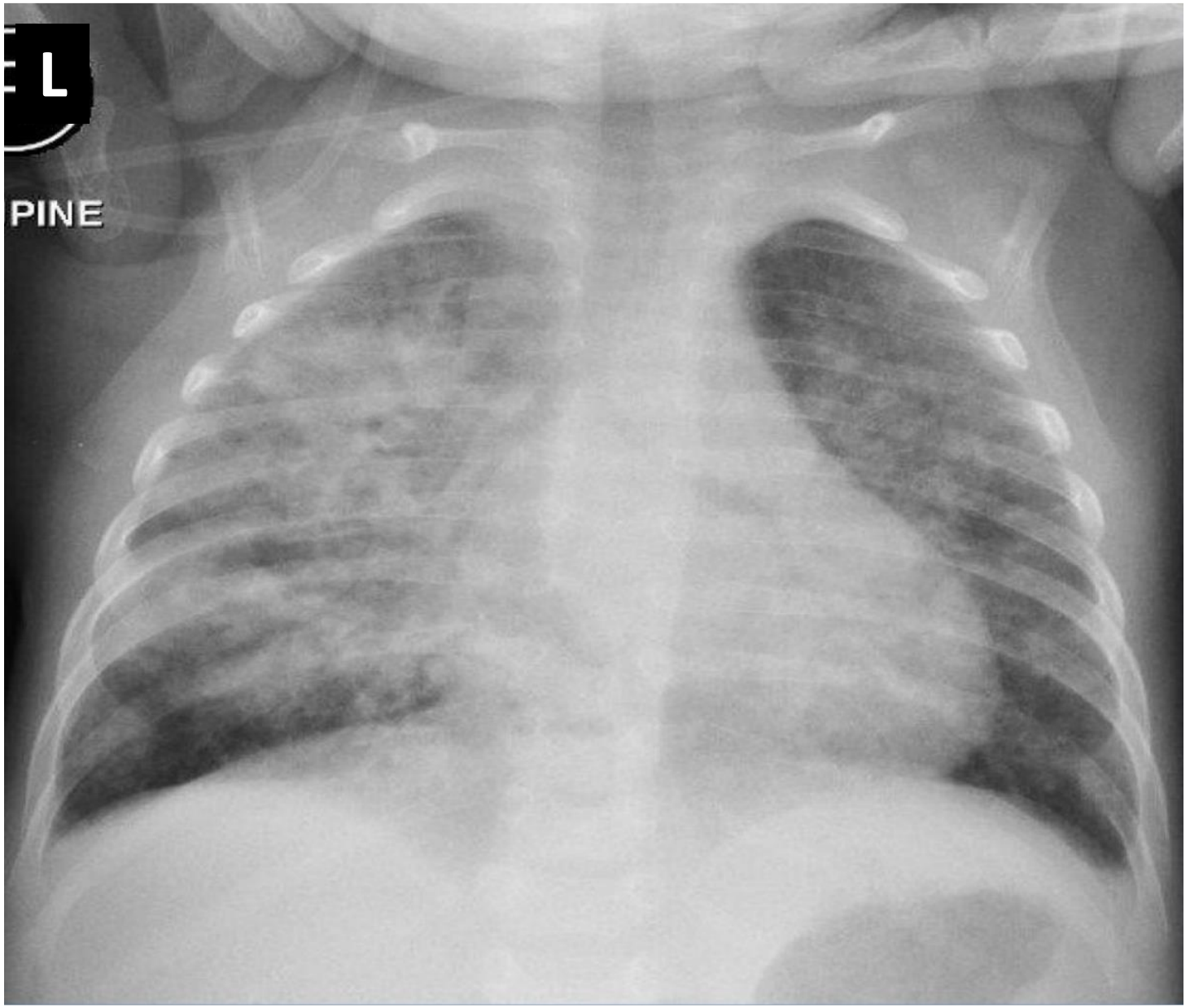


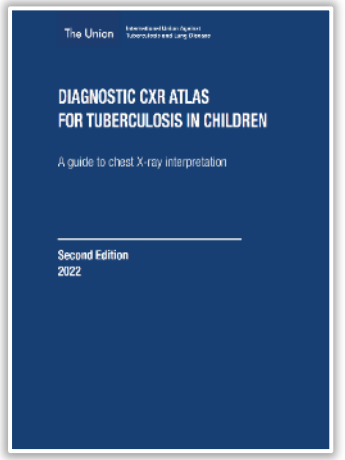


World Health Organization

END TB

Severe or non-severe TB?

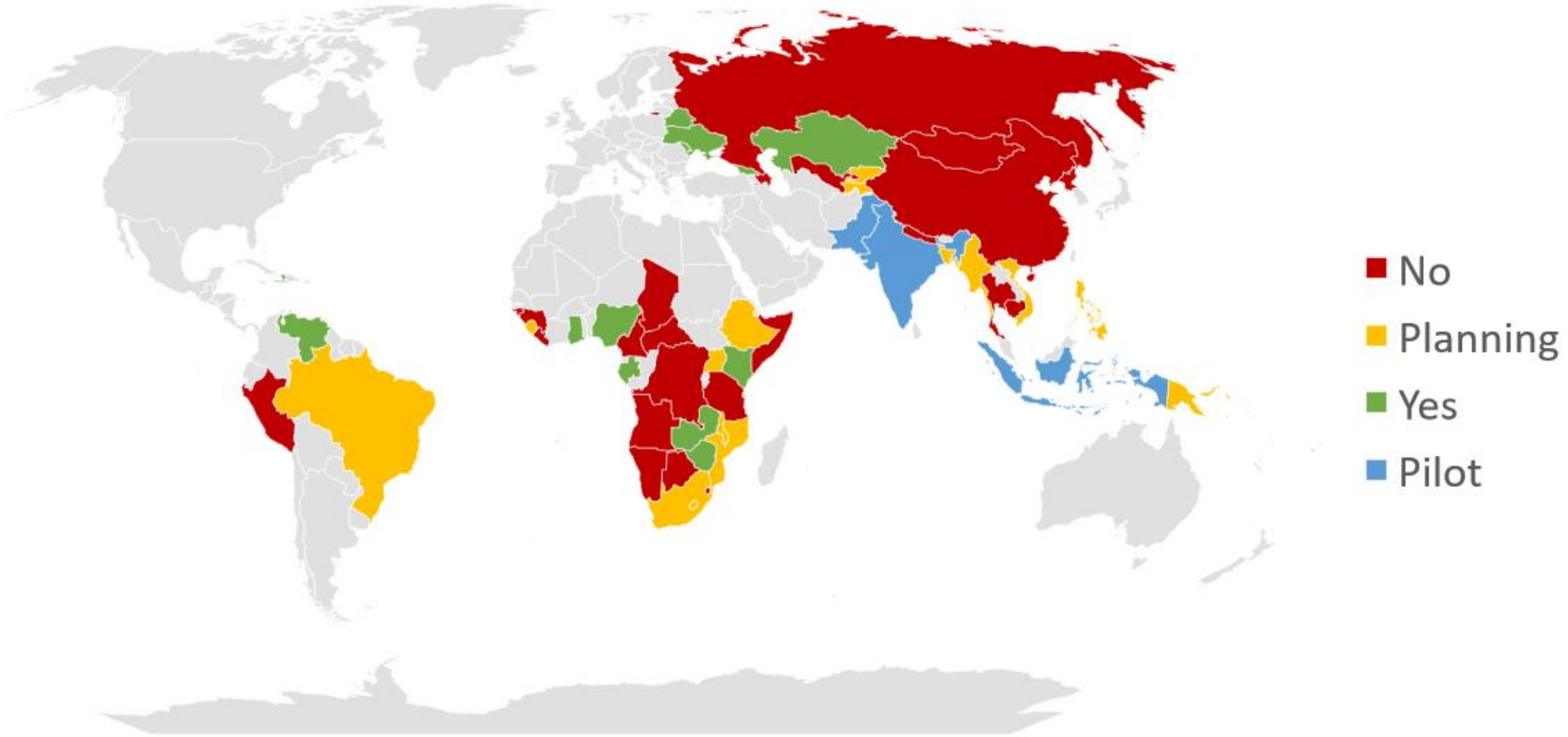




World Health Organization

END TB

Uptake



Implementation still limited

- Only 2 HBCs reporting children started on the regimen in 2023
- 9 non-HBCs reporting children started
- Challenges with deciding on national guidance around eligibility assessment

WHO GTB and TDR planning to develop implementation research package

World Health Organization

END TB

Acknowledgements

SHINE trial team

Kerri Viney, Tiziana Masini, Farai Mavhunga, PCD unit, WHO GTB

Tereza Kasaeva, Director WHO GTB

Thank you for your attention!

World Health Organization

END TB