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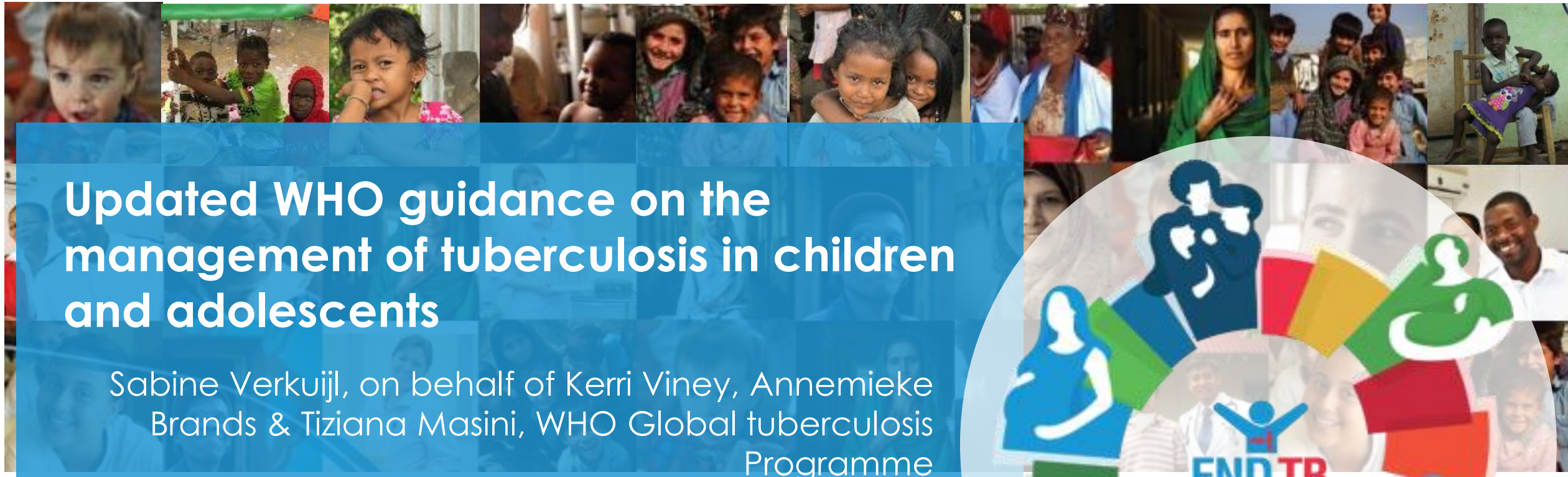

Updated WHO guidance on the management of tuberculosis in children and adolescents

Sabine Verkuijl, on behalf of Kerri Viney, Annemieke Brands & Tiziana Masini, WHO Global tuberculosis Programme

European Medical Consilium,
Session 2: Treatment of DS-TB, DR-TB and drug-susceptible TB meningitis (24 June)

END TB

Outline of sessions 1 and 2

Session 1 on 1 June 2022:

- Burden of TB in children and adolescents
- 2022 WHO Consolidated Guidelines and Operational Handbook on the Management of Tuberculosis in Children and Adolescents
- TB Screening and Contact investigation
- TB prevention in children and adolescents
- New diagnostic approaches

Session 2 on 24 June 2022:

- New WHO guidance on treatment of TB in children and adolescents
  - drug-susceptible PTB and EPTB
  - drug-resistant PTB and EPTB
  - adherence and management of interruption

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.**

*(**NEW:** 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*

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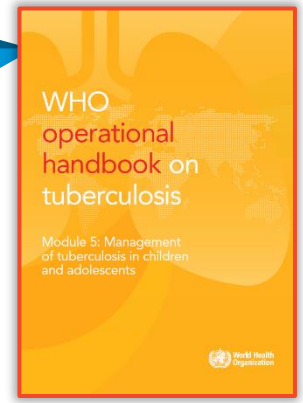
END TB

Practical guidance in the handbook: assessing severity



Non-severe TB: peripheral LN TB, intrathoracic LN TB without airway obstruction, uncomplicated TB pleural effusion; paucibacillary, non-cavitary disease confined to 1 lobe and without a miliary pattern

Settings with access to both **CXR** and **bacteriological testing**

Based on CXR features
Xpert MTB/RIF or Ultra neg, trace or (very) low
Mild symptoms not requiring hospitalization

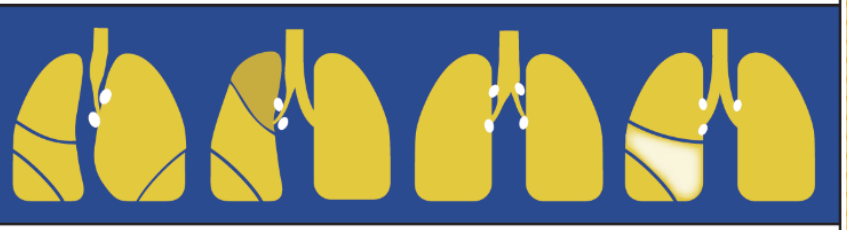
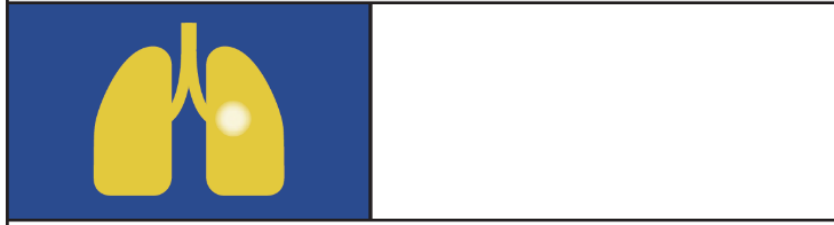
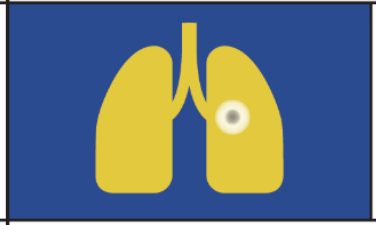
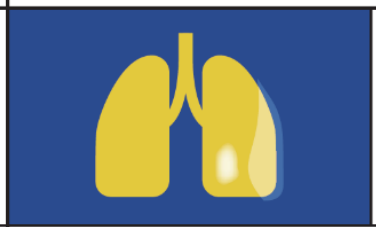
Settings **without access to CXR**

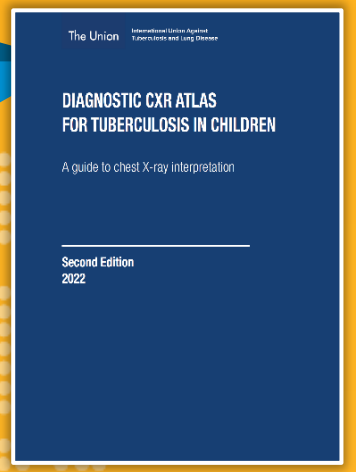
Xpert MTB/RIF or Ultra neg, trace or (very) low
Mild symptoms not requiring hospitalization

Settings **without access to CXR and bacteriological testing**

Isolated peripheral LN TB, (no involvement of other extrapulmonary sites)
Mild symptoms not requiring hospitalization

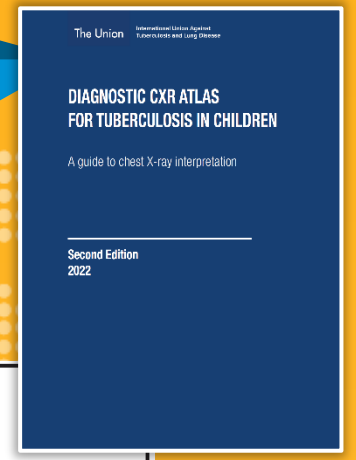
Assessing severity: CXR

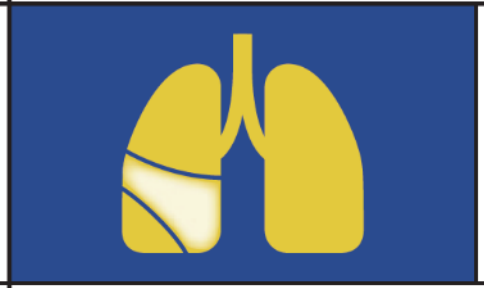
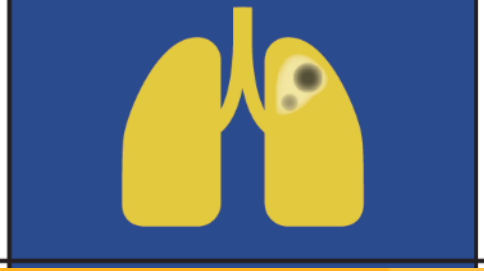
Non-Severe	Severe
Uncomplicated lymph node disease	Complicated lymph node disease
	
Primary (Ghon) focus	Primary (Ghon) focus with cavitation
	
Simple pleural effusion	Complicated pleural effusion
	



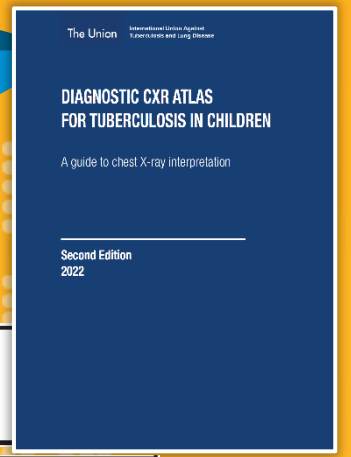
Diagnostic CXR atlas for paediatric pulmonary tuberculosis: a guide to chest X-ray interpretation to diagnose paediatric tuberculosis, second edition.
https://theunion.org/technical-publications/diagnostic-cxr-atlas-for-tuberculosis-in-children

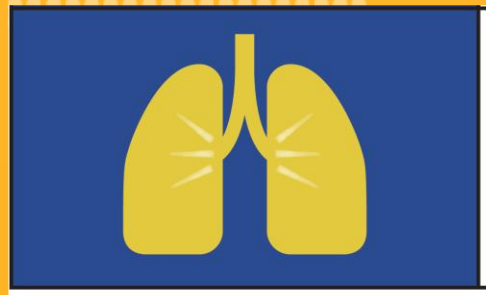
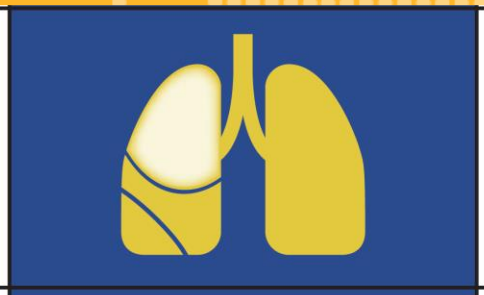
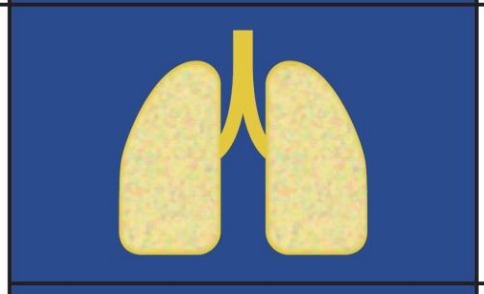
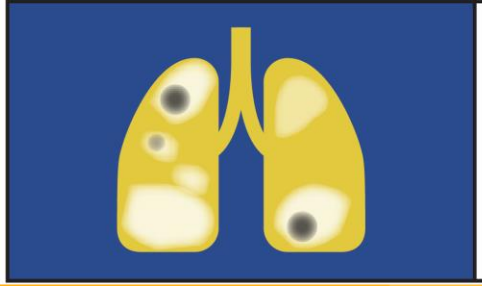
Assessing severity: CXR (2)

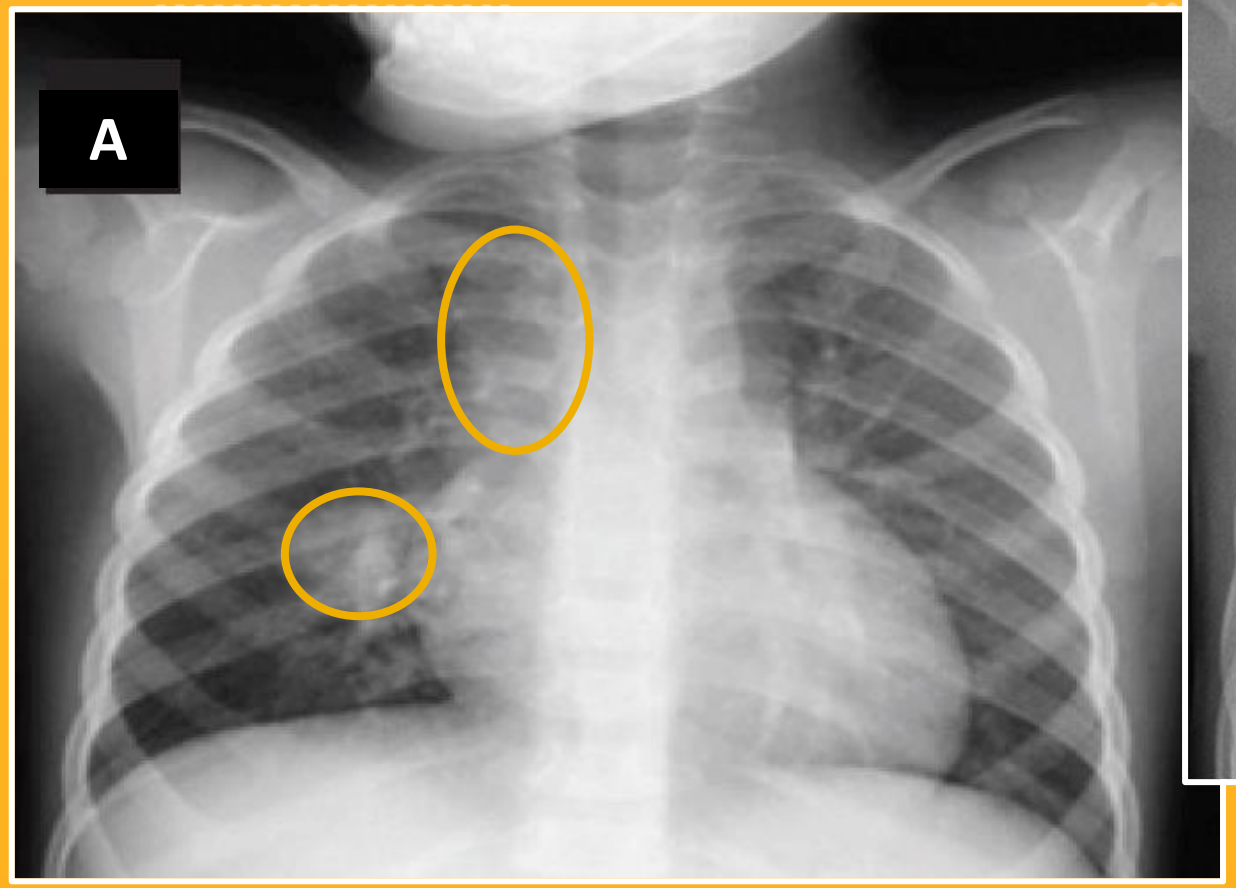


Non-Severe		Severe	
Alveolar opacification: < 1 lobe		Alveolar opacification: involving a whole lobe or multiple lobes	
			
Other:		Other:	
	- Interstitial pneumonia		- All cavitary disease

Assessing severity: CXR (3)



Non-Severe		Severe	
	- Perihilar infiltrates		- Expansile pneumonia
			- Miliary TB
			- TB bronchopneumonia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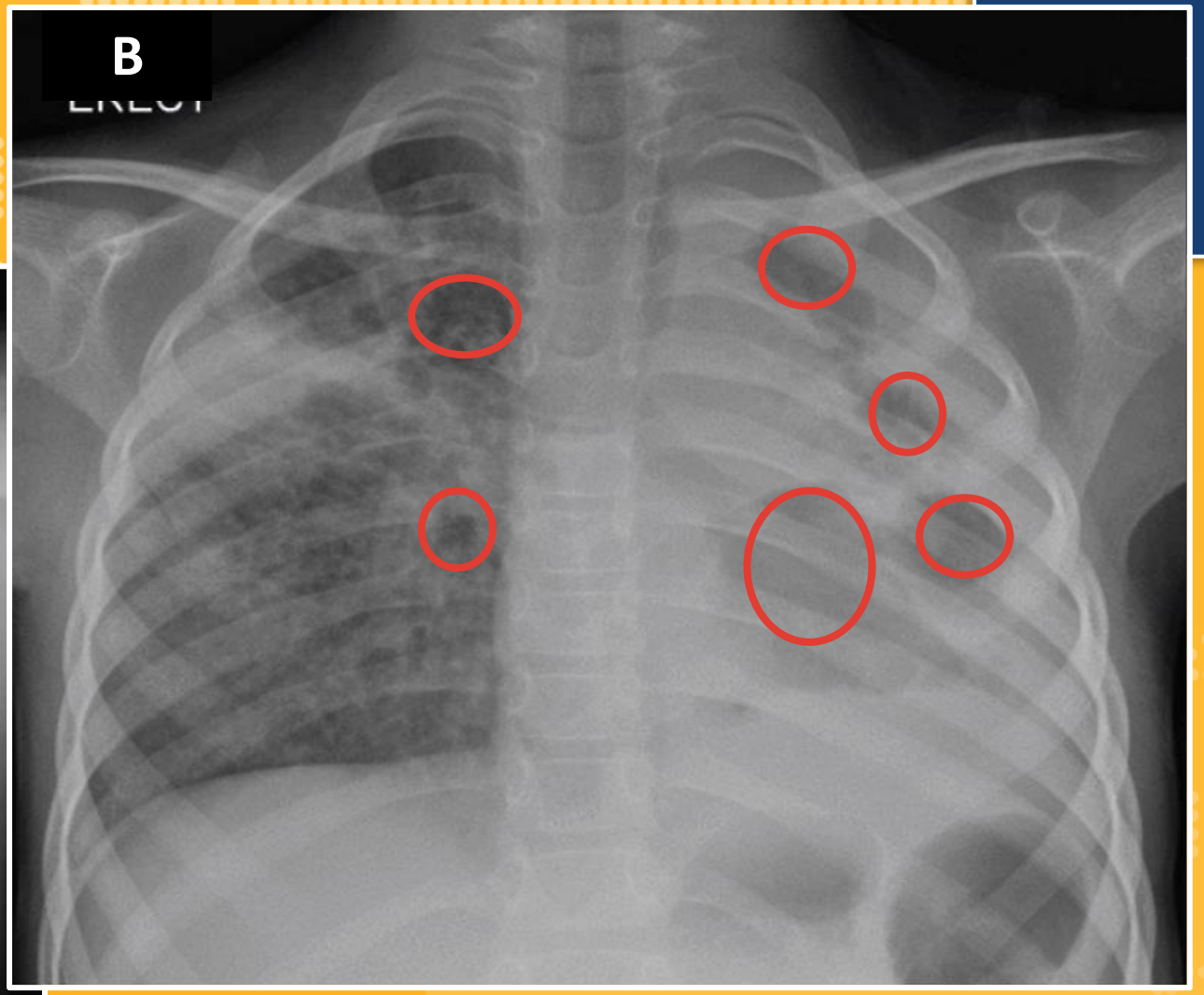
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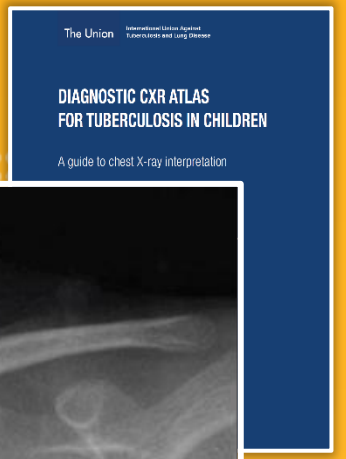
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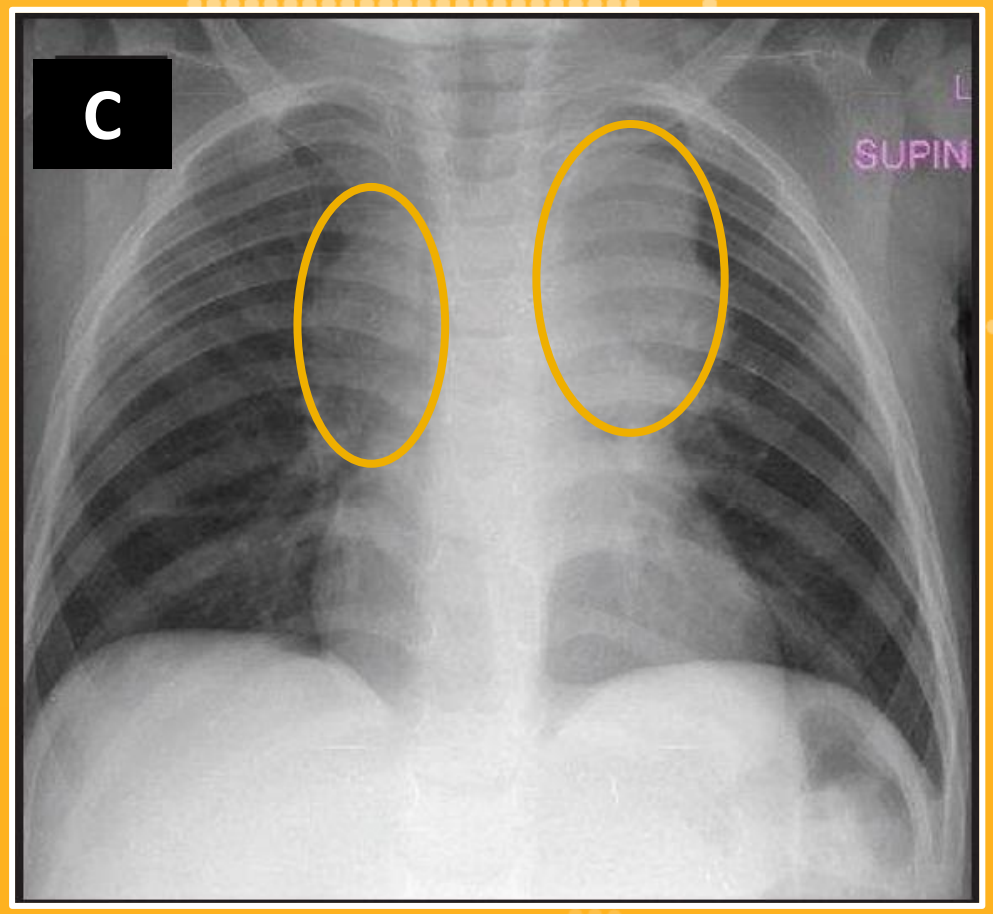
DIAGNOSTIC CXR ATLAS
FOR TUBERCULOSIS IN CHILDREN
A guide to chest X-ray interpretation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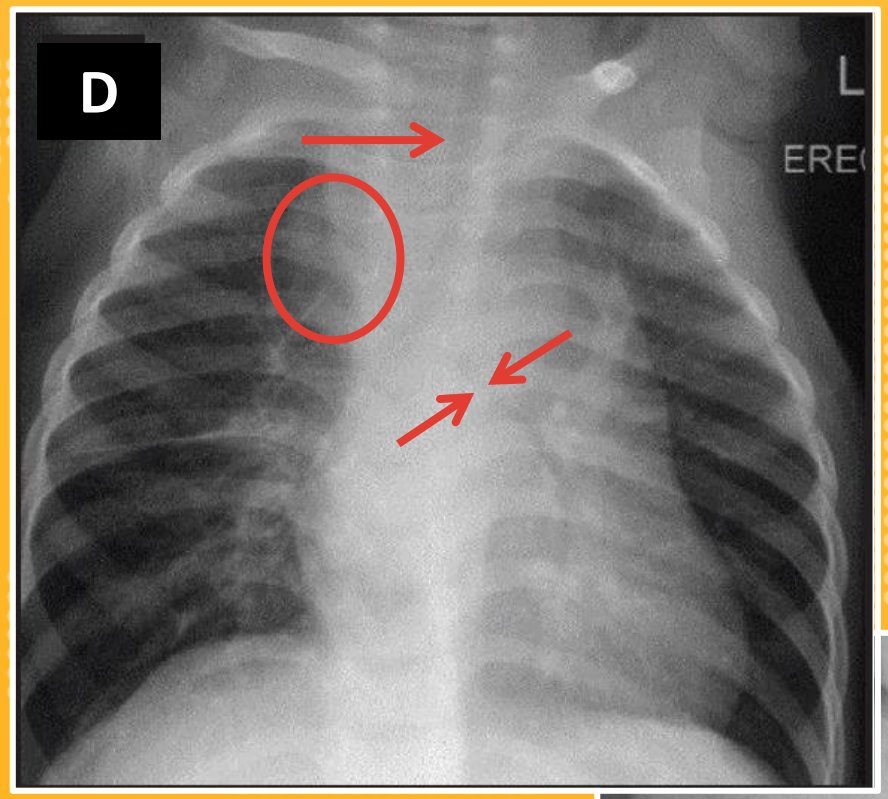
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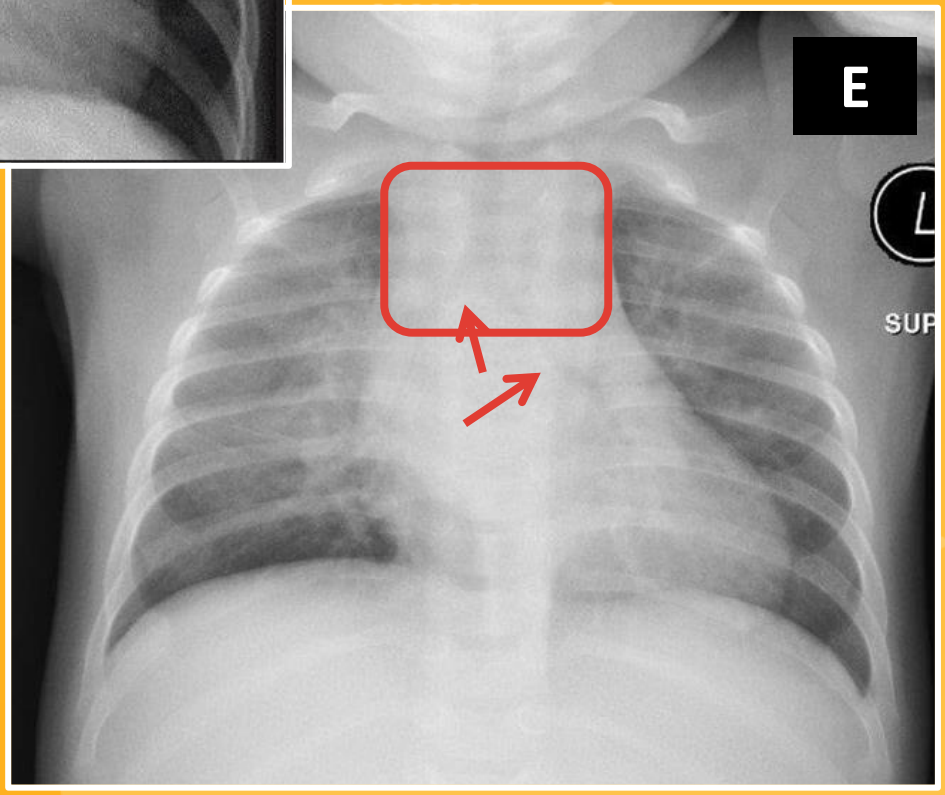
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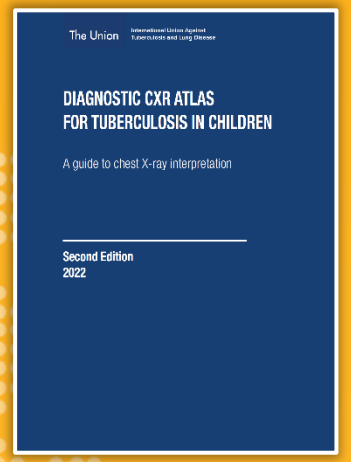
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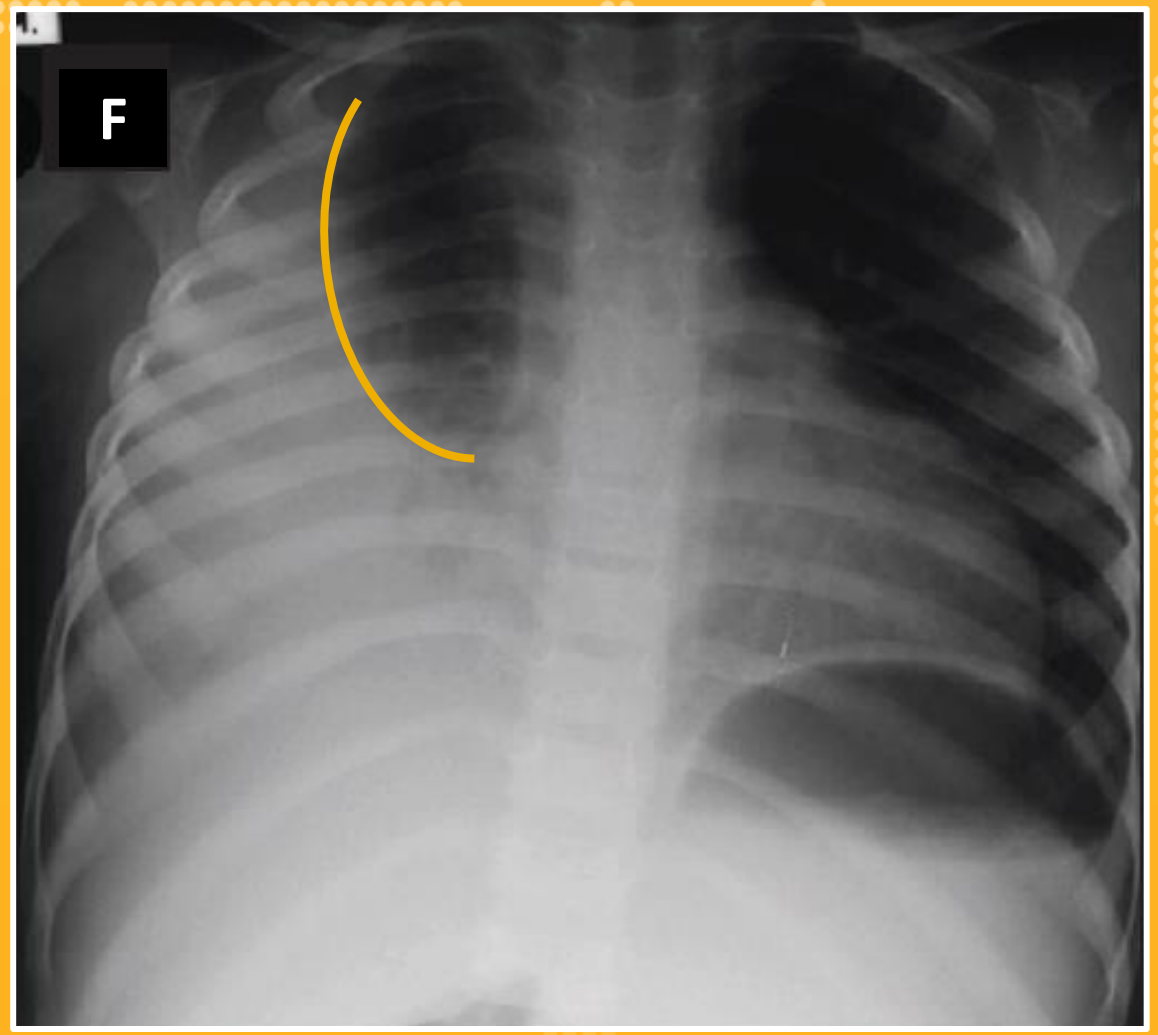
Second Edition
2022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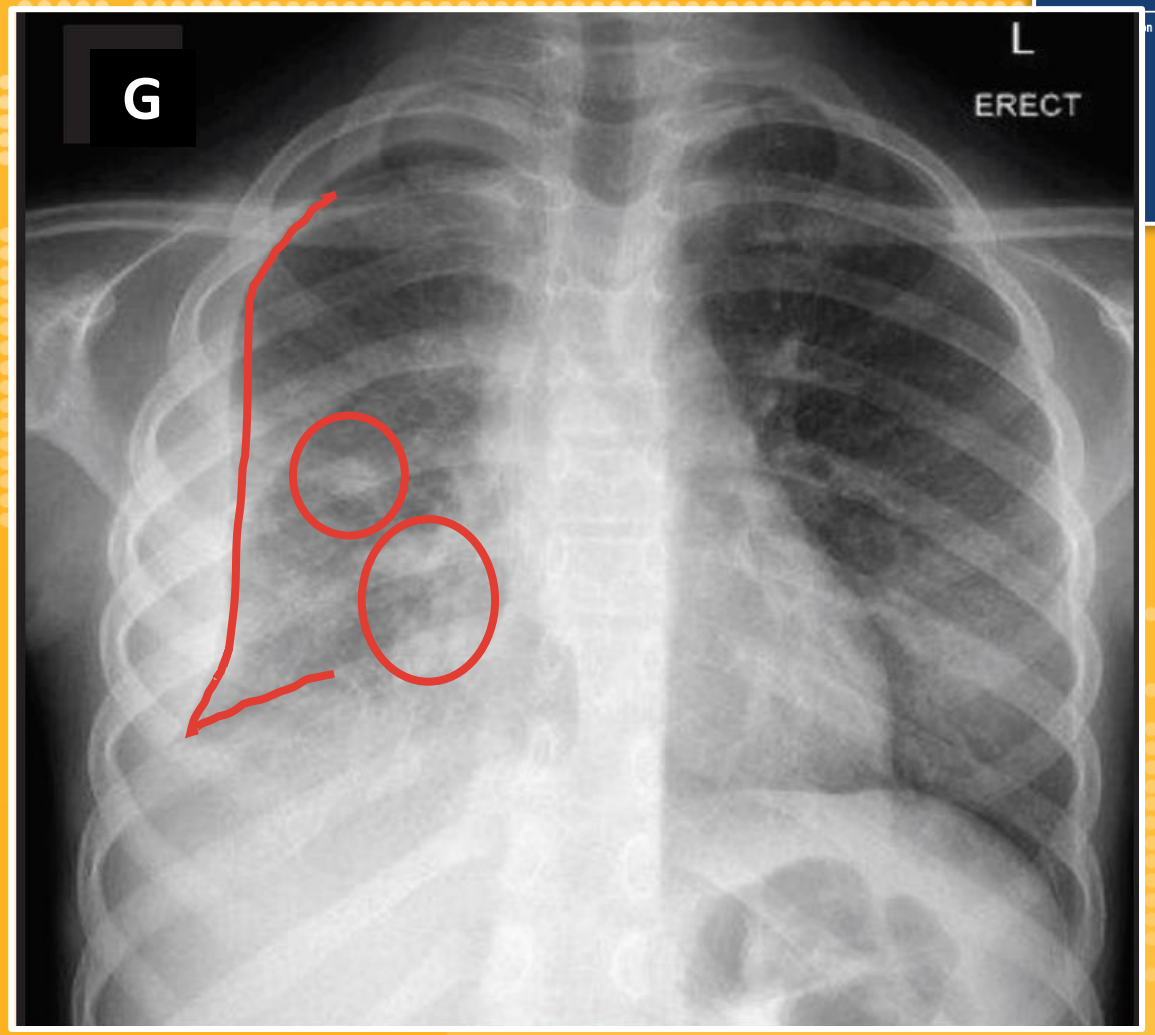
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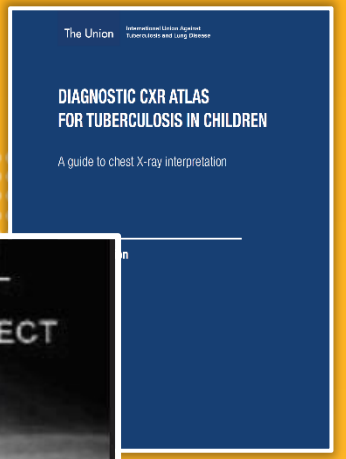
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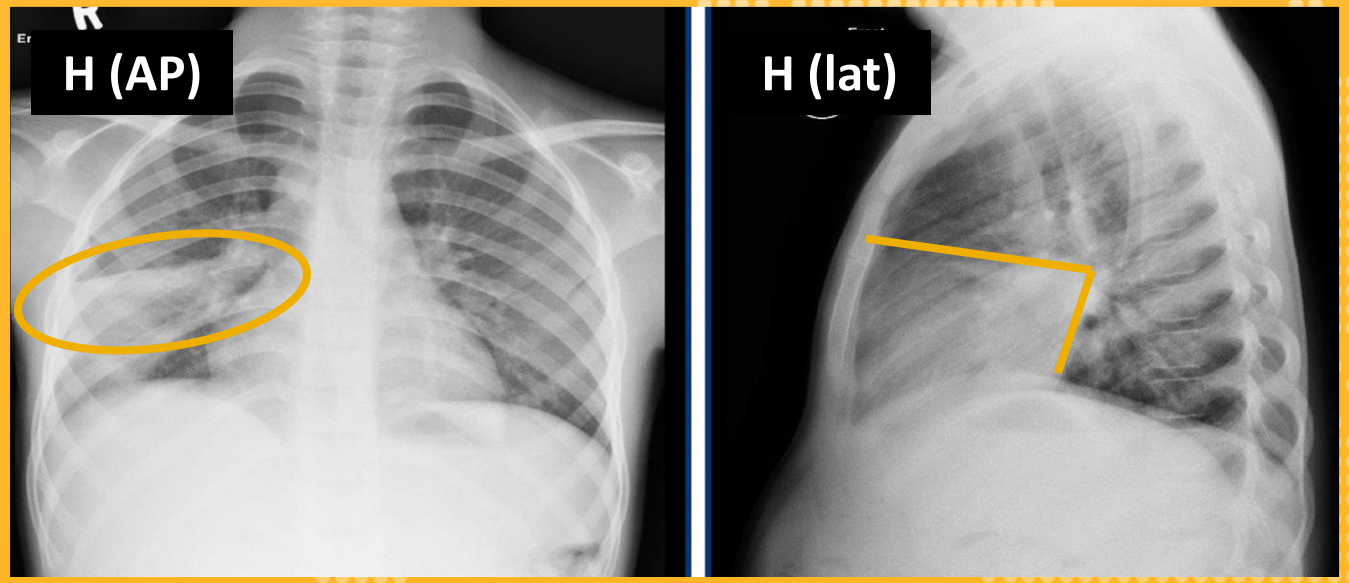
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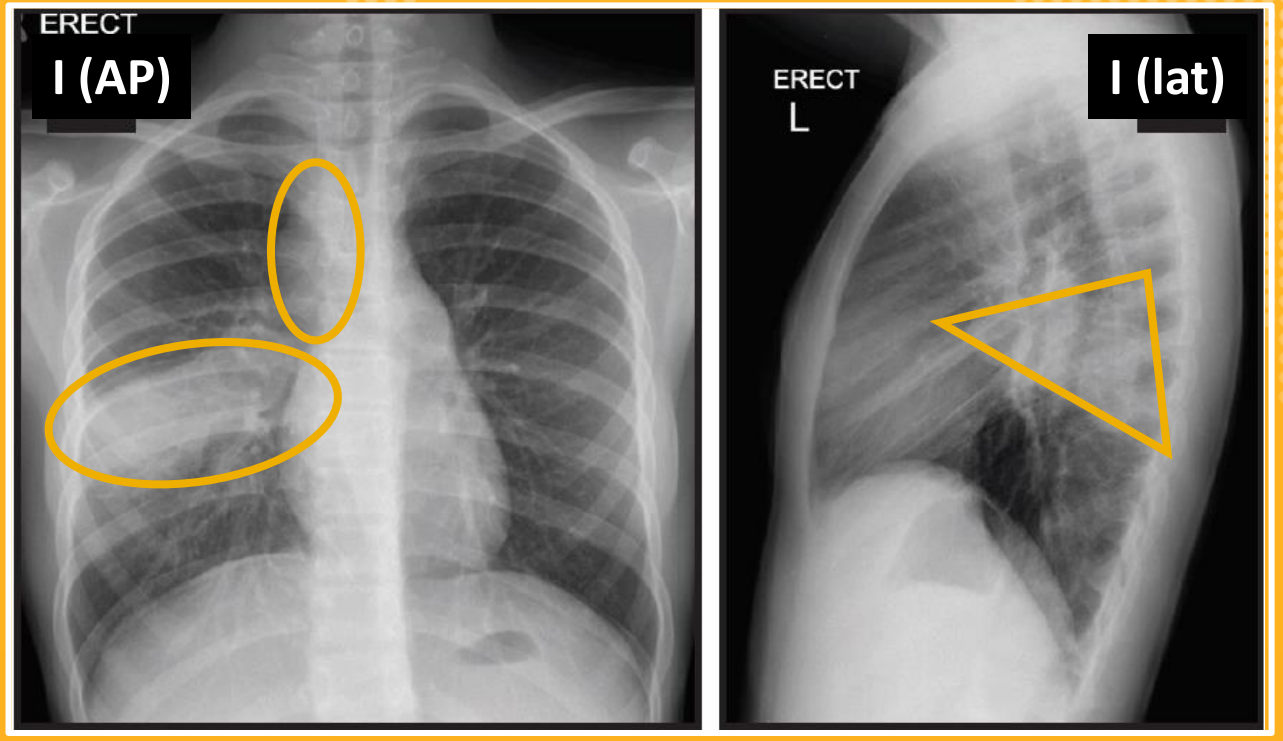
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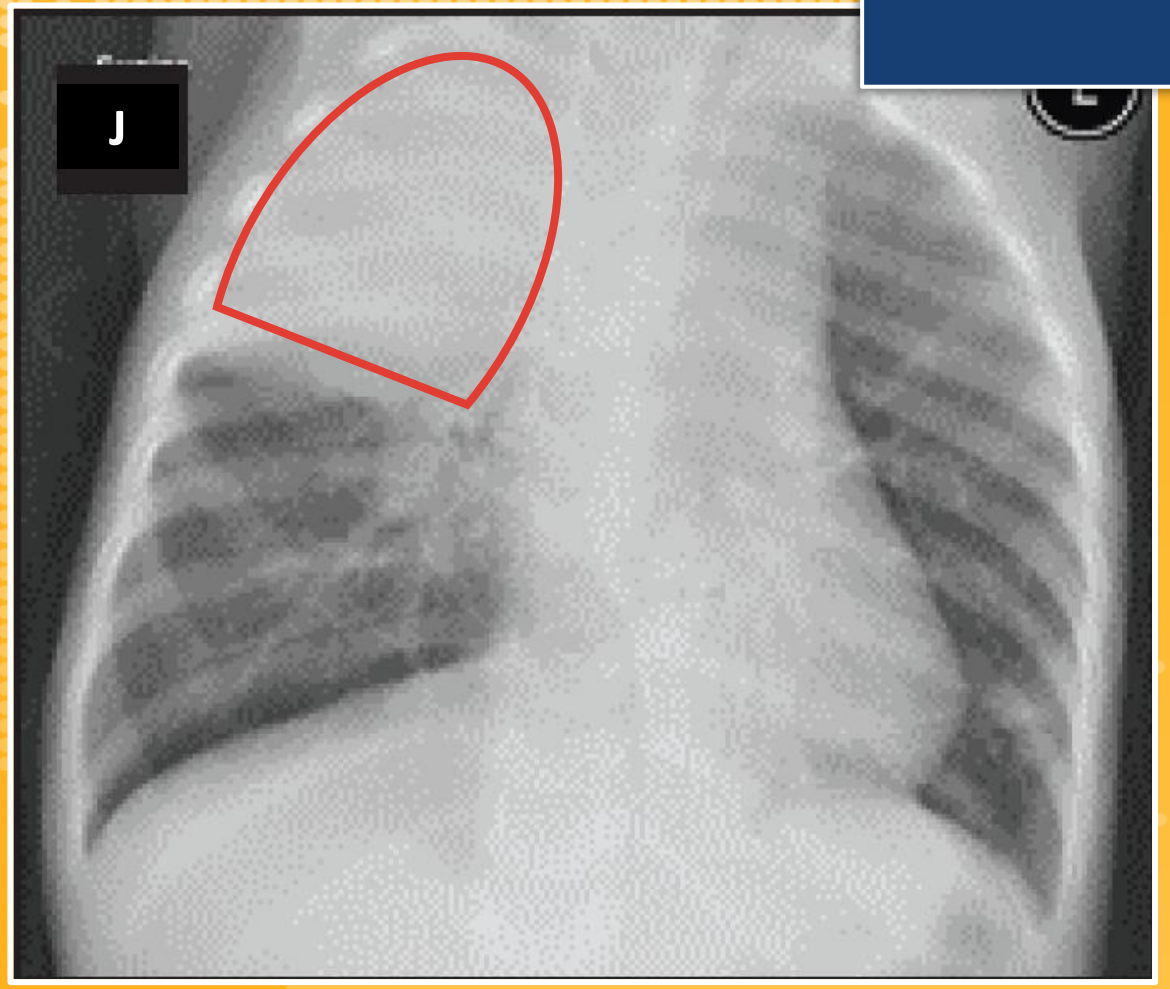
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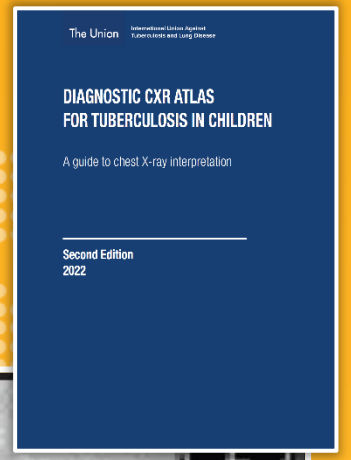
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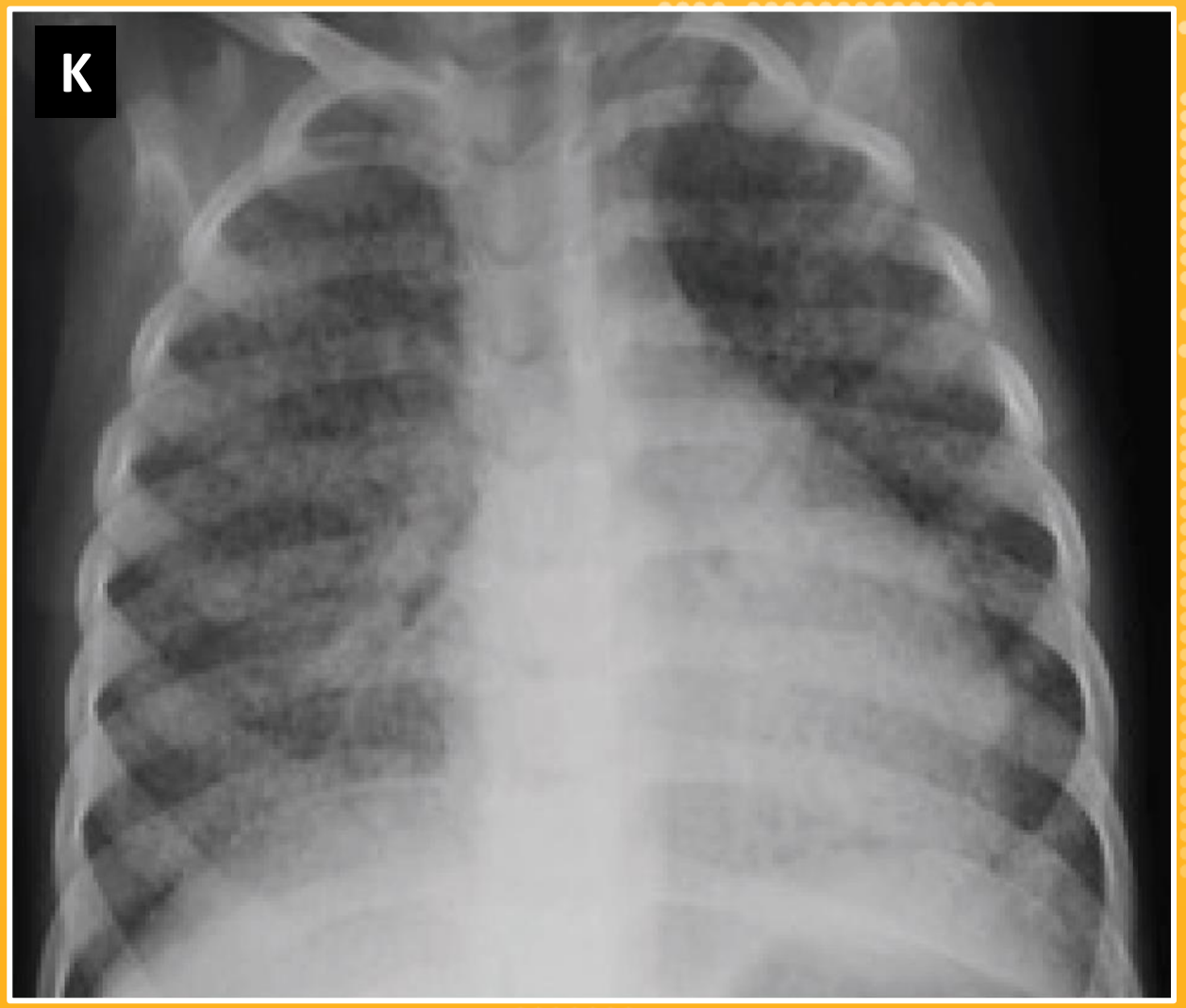
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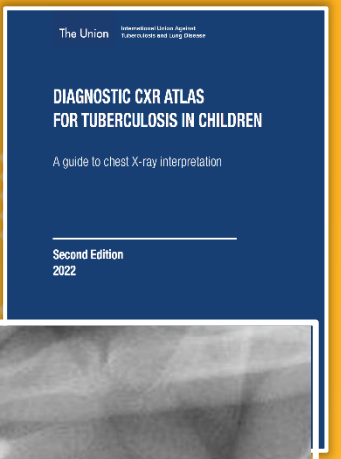
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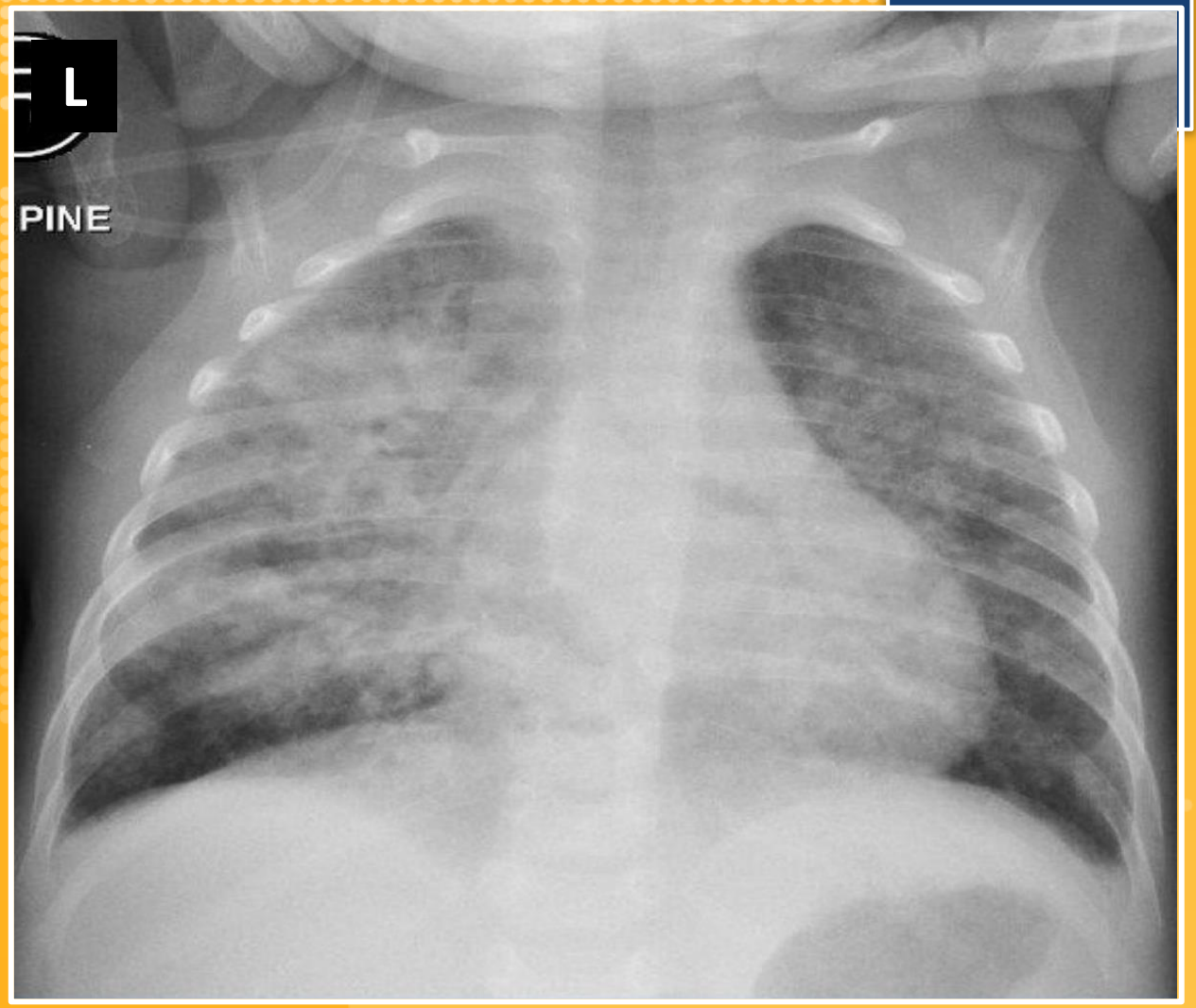
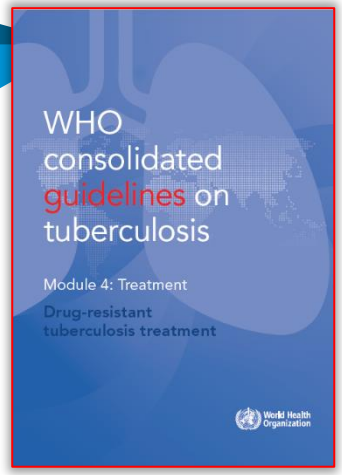

L
PINE

Shorter treatment duration in adolescents from 12 years



- **Patients aged 12 years or older with pulmonary DS-TB may receive a 4-month regimen of isoniazid, rifapentine, moxifloxacin and pyrazinamide (2HPMZ/2HPM)**

  *(**NEW:** Conditional recommendation, moderate certainty of evidence)*

Details:

- *Based on Study 31: international, multicentre, randomized, open-label, controlled, three-arm non-inferiority trial among adolescents and adults (aged 12 years and above) with smear-positive and culture-positive pulmonary DS-TB (13 countries)*
- *Rifapentine-moxifloxacin arm demonstrated non-inferiority compared to 2HRZE/4HR*
- *Primary end-points: disease-free survival at 12 months and ≥ grade 3 ADRs during treatment*
- *Applicable to subgroups for which evidence was available (but additional research desirable)*

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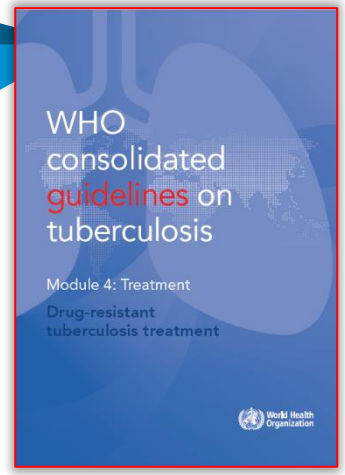
END TB

HPMZ regimen considerations



Subgroups excluded

- Weight < 40 kg
- severe forms of EPTB
- PLHIV with CD4 <100 cells/mm^3
- children <12 y (youngest trial participant 13 y)
- pregnant, breastfeeding and postpartum women (uncertainties about the safety of P, M, and Z)

Implementation considerations

- **DST**: baseline DST for fluoroquinolones not essential for patients with confirmed rif susceptibility by mWRD; DST for FQ highly recommended in settings with high FQ resistance
- **Treatment support**: important in the early stages given current pill burden in absence of an FDC
- **Pill burden**: may affect acceptability – will hopefully change in the future
- **Cost**: higher than 6-month regimen, driven by price of RPT
- **Administration with food**:
  - Exposure of RPT dose of 900 mg with high fat meal similar to that of 1200 mg without food
  - Proposed strategy: 1200 mg with modest food
- **Choice of regimen**: guided by eligibility criteria, age and patient preference

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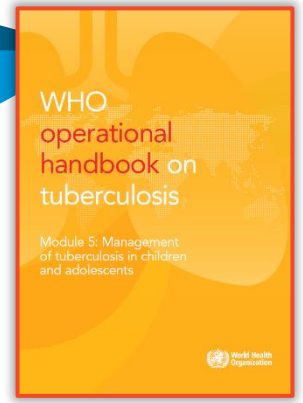
END TB

Treatment recommendations for children and adolescents: DS pulmonary TB



Age and severity of TB	Duration and composition of treatment regimen[a]	
	Intensive phase	Continuation phase
Infants aged <3 months or weighing <3 kg		
PTB of any severity	2HRZ or 2HRZE [b]	4HR
Children and adolescents aged 3 months to <12 years		
Non-severe PTB	2HRZ or 2HRZE [b]	2HR [c]
Severe PTB	2HRZE [c]	4HR
Adolescents aged 12–<16 years		
Non-severe PTB	2HRZ or 2HRZE [b]	2HR
Severe PTB	2HRZE [d]	4HR
PTB of any severity	2HPZM	2HPM
Adolescents aged 16–<20 years		
PTB of any severity	2HRZE [e]	4HR
PTB of any severity	2HPZM [f]	2HPM

Use of ethambutol in intensive phase (first 2 months):

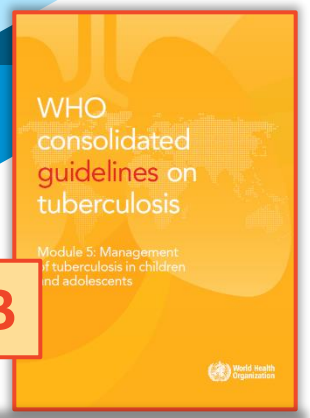
- **CLHIV or high HIV prevalence settings**

Dosing of 4-month regimens:

- **2HRZ(E)/ 2HR:** Standard WHO recommended dosing (by weight)
- **2HPZM/2HPM:** Standard WHO recommended dosing (adjusted for weight) for H and Z. M: 400mg daily and P: 1200mg daily

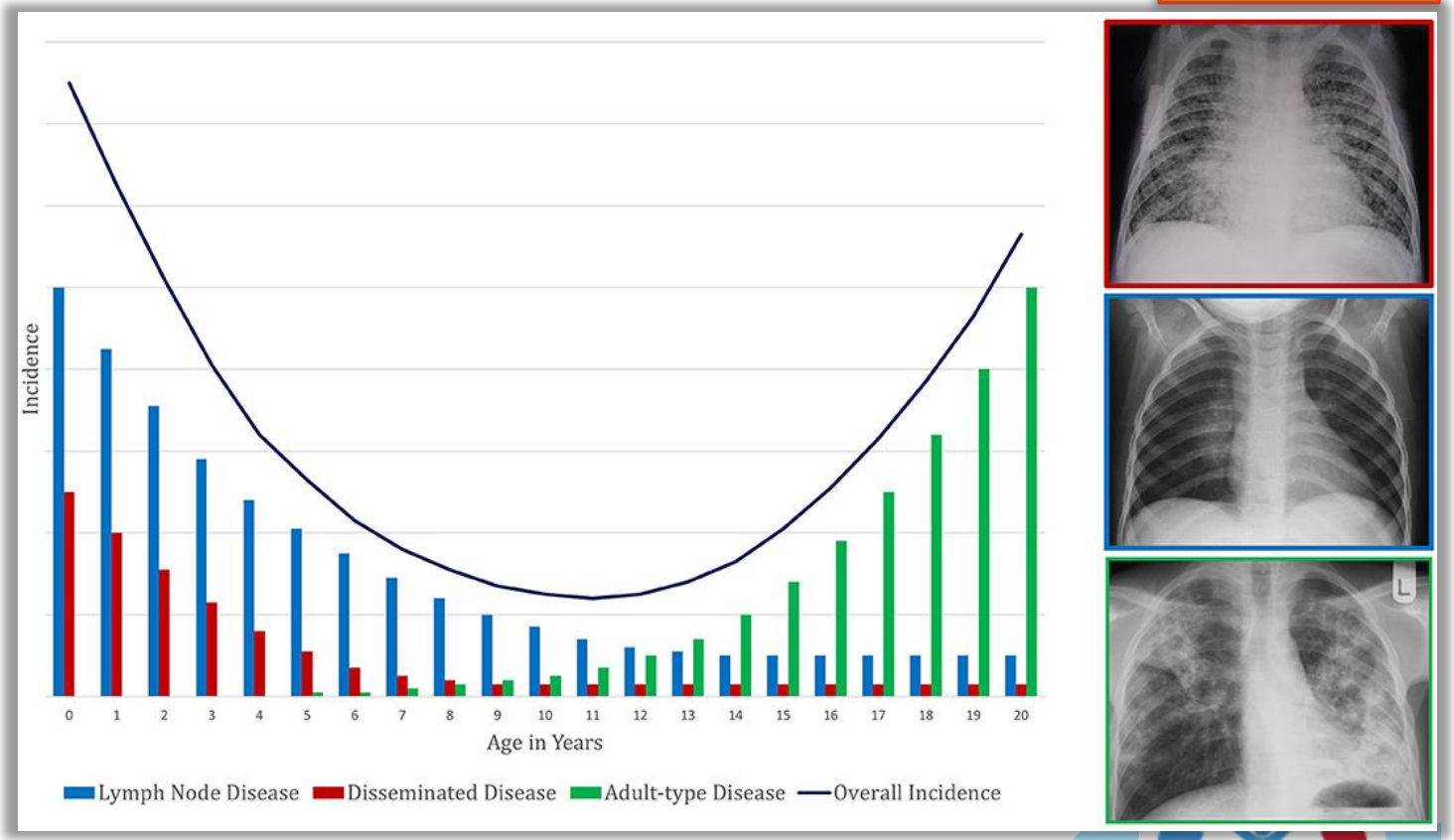
END TB

Classification of intrathoracic lymphadenopathy



Updated classification: **intrathoracic lymph node TB** now classified as **pulmonary TB**

- Better aligned with pathophysiology, radiological features and potential for bacteriological confirmation in respiratory samples
- Opportunity around the new guidance to convene an expert consultation
- Experts advised WHO to
  - classify intrathoracic LN TB as PTB in children <10y
  - Consider implementing for all ages (process initiated)



Seddon et al; Front. Immunol., 2018; https://doi.org/10.3389/fimmu.2018.02946

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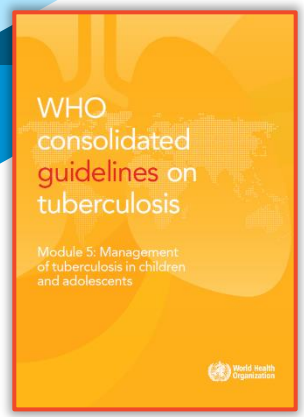
END TB

Treatment of TB meningitis in children and adolescents



- **In children and adolescents with bacteriologically confirmed or clinically diagnosed TB meningitis (without suspicion or evidence of MDR/RR-TB), a 6-month intensive regimen (6HRZEto) may be used as an alternative option to the 12-month regimen (2HRZE/10HR)**

  *(**NEW:** conditional recommendation, very low certainty of the evidence).*

Remarks

- *The shorter intensive regimen is suitable if there is no evidence of drug resistance or a low likelihood of drug resistant TB*
- *The 12-month regimen (2 HRZE/10HR) remains an option for the treatment of children and adolescents with suspected or confirmed TBM*
- *Due to a lack of data, the short intensive treatment regimen recommendation should not be used in children and adolescents living with HIV who are diagnosed with TB meningitis*

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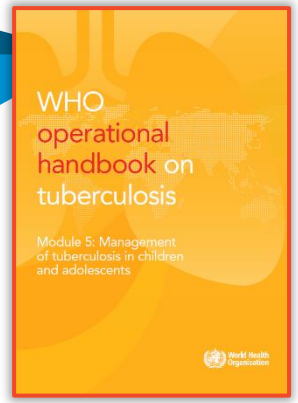
END TB

Treatment recommendations for children and adolescents: DS extra-pulmonary TB

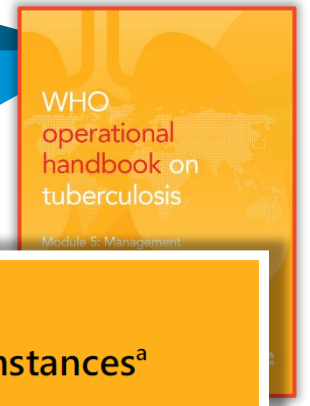


Age and type of EPTB	Treatment regimen [a]	
	Intensive phase	Continuation phase
Infants aged <3 months or weighing <3 kg		
Peripheral lymph node TB	2HRZ or 2HRZE [b]	4HR
Children and adolescents aged 3 months–<16 years		
Peripheral lymph node TB	2HRZ or 2HRZE [b]	2HR
Adolescents aged >16 years		
Peripheral lymph node TB	2HRZ or 2HRZE [b]	4HR
Children and adolescents aged 0–19 years		
EPTB [c]	2HRZE	4HR
TBM [d] (strong recommendation)	2HRZE	10HR
TBM [d] (conditional recommendation)	6HRZEto	
Osteoarticular TB	2HRZE	10HR

Dosing of TBM regimens:

- **2HRZE/ 10HR:** Standard WHO recommended dosing (by weight)
- **6HRZEto:** See dosing table in Operational Handbook, based on evidence assessed by the GDG, expert consultation and PK modelling. Evidence assessed was based on H: 20 mg/kg, R: 20mg/ kg, Z: 40 mg/kg and Eto: 20 mg/kg

ART in children and adolescents with TB



Timing of ART:

- As soon as possible within 2 weeks of initiating TB treatment
- Delay by 4-8 weeks after starting TBM treatment
- Consider steroids as adjuvant therapy for TBM

Choice of ART regimen:

- Follow 2021 consolidated HIV guidelines
- Preferred and alternative first-line ART regimens for children and adolescents on TB treatment (table on the right)
- Adjustments to ART regimens with TB treatment: dose adjustment or change or regimen

Age	Preferred first-line regimen, including initiation while on TB treatment	Alternative first-line regimen	Special circumstances[a]
Neonates	AZT + 3TC + RAL [b]	AZT + 3TC + NVP	AZT + 3TC + LPV/r [c]
Children	ABC + 3TC + DTG [d]	ABC + 3TC + LPV/r TAF + 3TC (or FTC) + DTG [e]	ABC + 3TC + EFV (or NVP) ABC + 3TC + RAL [f] AZT + 3TC + EFV [g] (or NVP) AZT + 3TC + LPV/r (or RAL)
Adolescents	TDF + 3TC (or FTC) + DTG [h]	TDF + 3TC + EFV 400 mg [i]	TDF + 3TC (or FTC) + EFV 600 mg [i] AZT + 3TC + EFV 600 mg [i] TDF + 3TC (or FTC) + PI/r [i] TDF + 3TC (or FTC) + RAL TAF [j] + 3TC (or FTC) + DTG ABC + 3TC + DTG [h]

- No dose adjustment needed with TB treatment.
- Dose adjustment needed with TB treatment.
- Change of regimen needed with TB treatment.

* If not possible to give preferred or alternative regimens, including toxicity, intolerance, inability to take the medicine in the available formulation, and unavailability / stockouts

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END TB

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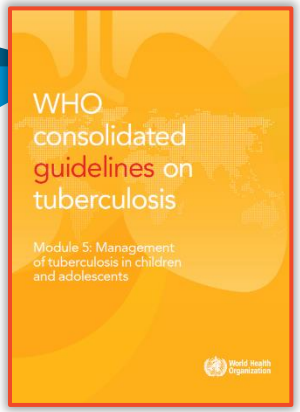
Questions & Answers for the first part

END TB

Treatment of DR-TB in children – use of bdq & dlm in children



- **In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used**
- **In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens**

*(**NEW:** both conditional recommendations, very low certainty of the evidence)*

Remarks:

- *Applies to and complements current WHO recommendations on shorter and longer regimens that contain bedaquiline*
- *Complements the current WHO recommendation on longer regimens that contain delamanid*

These recommendations make it possible to build all oral regimens for children of all ages

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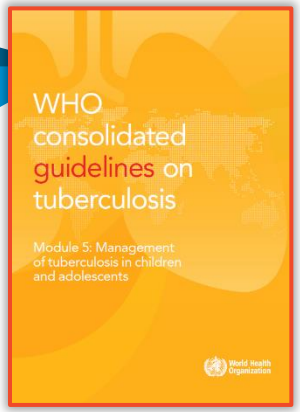
END TB

Treatment of DR-TB in children – use of bedaquiline



In children with MDR/RR-TB aged below 6 years, an all-oral treatment regimen containing bedaquiline may be used *(new: conditional recommendation, very low certainty of evidence)*

Applies to and complements current WHO recommendations:

- A shorter all-oral bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed MDR/RR-TB who have not been exposed to treatment with second-line TB medicines used in this regimen for >1 month, and in whom resistance to fluoroquinolones has been excluded *(conditional recommendation, very low certainty in the evidence)*

- Bedaquiline should be included in longer MDR-TB regimens for patients aged ≥18y *(strong recommendation, moderate certainty in the estimates of effect)*

- Bedaquiline may also be included in longer MDR-TB regimens for patients aged 6–17y *(conditional recommendation, very low certainty in the estimates of effect)*.

Group	Drug	Abbreviation
A	Levofloxacin or moxifloxacin	Lfx or Mfx (or M)
	Bedaquiline	Bdq (or B)
	Linezolid	Lzd (or L)
B	Clofazimine	Cfz
	Cycloserine or terizidone	Cs or Trd
C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin in combination with clavulanic acid (amoxiclav)	Ipm-Cln
	Meropenem in combination with clavulanic acid (amoxiclav)	Mpm
	Amikacin or streptomycin [a]	Am or S
	Ethionamide or prothionamide	Eto or Pto
	P-aminosalicylic acid	PAS

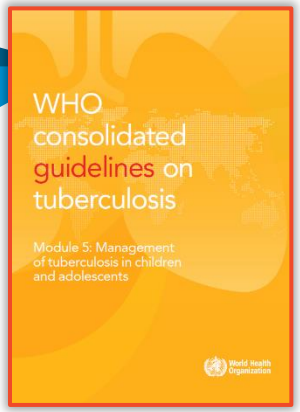
[a] Amikacin and streptomycin are to be considered only in adolescents aged over 18 years and only if DST results confirm susceptibility and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

Bedaquiline can therefore be used in children of all ages to treat MDR/RR-TB. Bedaquiline is currently a component of the standardized all oral shorter regimen and a Group A drug for individualized longer regimens.

Organization

END TB

Treatment of DR-TB in children – use of delamanid



In children with MDR/RR-TB aged below 3 years, delamanid may be used as part of longer regimens (conditional recommendation, very low certainty of the evidence)

This recommendation complements the current WHO recommendation on longer regimens that contain delamanid:

Delamanid may be included in the treatment of MDR/RR-TB patients aged ≥3 years on longer regimens
(conditional recommendation, moderate certainty in the estimates of effect)

Delamanid can therefore be used in children of all ages to treat MDR/RR-TB. Delamanid is currently a Group C drug for individualized longer regimens.

Group	Drug	Abbreviation
A	Levofloxacin or moxifloxacin	Lfx or Mfx (or M)
	Bedaquiline	Bdq (or B)
	Linezolid	Lzd (or L)
B	Clofazimine	Cfz
	Cycloserine or terizidone	Cs or Trd
C	Ethambutol	E
	Delamanid	Dlm
	Pyrazinamide	Z
	Imipenem-cilastatin in combination with clavulanic acid (amoxiclav)	Ipm-Cln
	Meropenem in combination with clavulanic acid (amoxiclav)	Mpm
	Amikacin or streptomycin [a]	Am or S
	Ethionamide or prothionamide	Eto or Pto
	P-aminosalicylic acid	PAS

[a] Amikacin and streptomycin are to be considered only in adolescents aged over 18 years and only if DST results confirm susceptibility, and if high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (i.e. is unavailable or there is documented resistance) and if DST results confirm susceptibility (i.e. resistance to streptomycin is not detectable with second-line molecular LPAs and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.

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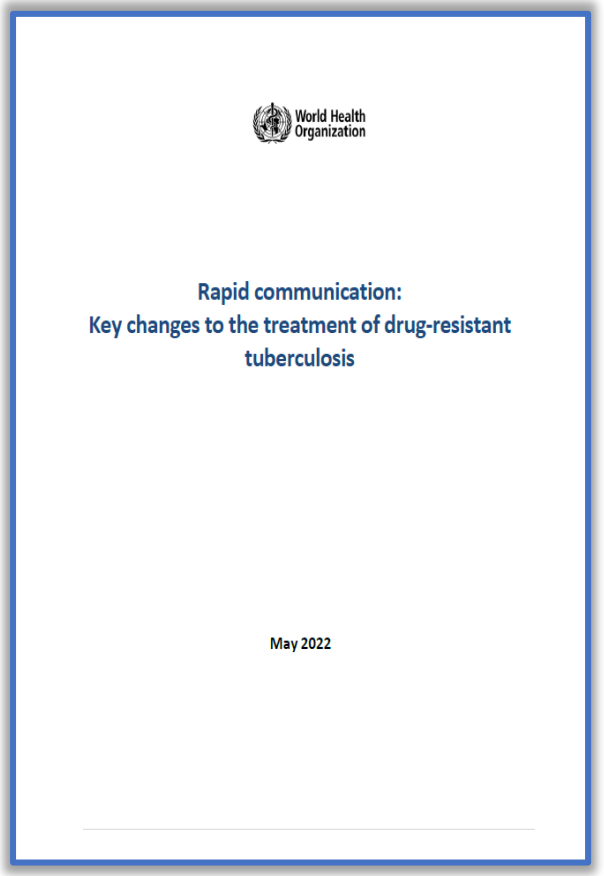
Rapid communication DR-TB May 2022

- **6-month BPaLM** (bedaquiline, pretomanid, linezolid (600mg), moxifloxacin) may be used programmatically (in adolescents ≥15y)
  - BPaL if fluoroquinolone resistant

- **9-month, all-oral, bedaquiline-containing regimens** are preferred over longer (>18 months) regimens in adults and children with MDR/RR-TB
  - 2 months of linezolid as alternative to 4 months of ethionamide
  - 4-6 Bdq [6]-Lfx [Mfx]-Lzd [2]-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E *or*
  - 4-6 Bdq [6]-Lfx [Mfx]-Eto-E-Z-H^h-Cfz / 5 Lfx [Mfx]-Cfz-Z-E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Rapid communication:
Key changes to the treatment of drug-resistant tuberculosis

May 2022

World Health Organization

https://apps.who.int/iris/rest/bitstreams/1420701/retrieve

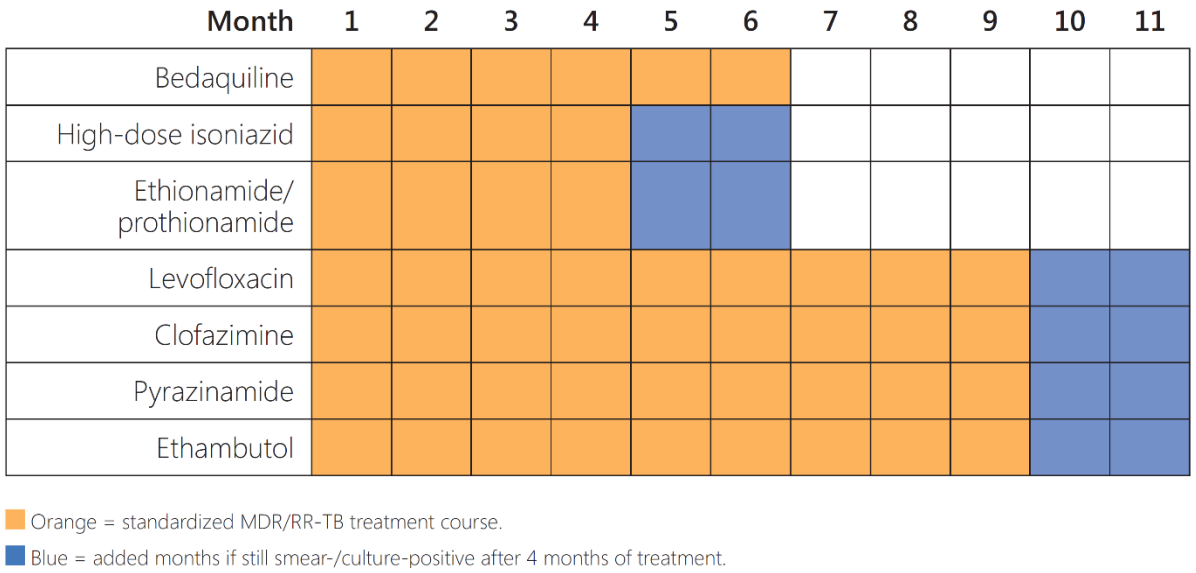
END TB

Shorter all oral bedaquiline containing regimen(s)

9 months all oral bedaquiline containing regimen

- Current eligibility criteria:
  - no resistance to fluoroquinolones
  - no previous exposure >1 month to SLD in this regimen (unless susceptibility confirmed)
  - no severe forms of EPTB (other than peripheral lymphadenopathy)
  - no extensive TB disease (presence of cavities or bilateral disease on CXR)
  - no inhA and katG mutations in child/ adolescent/most likely source case
- Children with rifampicin resistance without further DST can be treated with available bedaquiline-containing regimens at the discretion of the treating clinician

4–6 Bdq (6) – Lfx – Cfz – Z – E – H^h – Eto/5 Lfx – Cfz – Z – E



Note: relatively **high pill burden**, especially in the 1st 4–6 months may be challenging for young children, even if using dispersible formulations → **treatment support** important

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END TB

Individualized (longer) regimens - considerations

- At least 4 drugs likely susceptible; some drugs shorter period; 5th drug if extensive disease
- Prioritize group A and B drugs, add delamanid and other group C drugs
- Include bedaquiline for all ages; standard duration 6 months; extension beyond 6 months if no other options (consult paediatric DR-TB expert)
- Linezolid (Group A): frequent haematological toxicity – use often limited to 1st few months
- Delamanid: option to add if (suspected) FQ resistance or severe disease (5th drug) – standard duration 6 months
- Injectables should not be used in <18 years

Designing individualized MDR/RR-TB regimens

Fluoroquinolone susceptibility	Regimen [a]	Additional medicines
Fluoroquinolone-susceptible	Bdq–Lfx–Lzd–Cfz–(Cs)	Cs, Dlm, PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant	Bdq–Lzd–Cfz–Cs–(Dlm) [e]	Dlm [e], PAS, Eto [b,c] (E, Z) [d]
Fluoroquinolone-resistant and bedaquiline (±clofazimine)-resistant	Lzd–Cs–Dlm [e]–E–Z [d]	Mpm/Clav, Eto [b,c], PAS [c]

Bdq: bedaquiline; Cfz: clofazimine; Cs: cycloserine; Dlm: delamanid; E:ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem–clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

[a] Medicines in parentheses in this column are suggestions for a fifth medicine when there is severe disease.

[b] Use ethionamide only if the child or source case does not have a known or suspected *inhA* mutation.

[c] P-aminosalicylic acid and ethionamide showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are proposed only when other options to compose a regimen are not possible.

[d] Ethambutol and pyrazinamide should be considered if there is evidence of susceptibility and a regimen with sufficient medicines cannot be composed.

[e] When administering delamanid and cycloserine concurrently, monitoring for neuropsychiatric side-effects is important.

Organization

END TB

Duration of treatment

- Duration of treatment using individualized regimens depends on
  - **Site and severity** of disease
  - **Extent of resistance** (in addition to rif and INH)
- **Non-severe disease**: can treat for less than 18 months
  - In practice many clinicians treat for 9-12 months
- **Extensive disease**: longer durations (depends on clinical progress, site of disease, resistance pattern and number of effective medicines)

- **Child-friendly formulations** should be used whenever possible (see next presentation by GDF)

Extent of disease

In <15y, severe disease defined by:

- presence of cavities *or*
- bilateral lung parenchymal disease *or*
- bilateral mediastinal nodes with airway compression on CXR *or*
- EPTB other than peripheral LN

Other considerations:

- SAM *or*
- advanced immunosuppression *or*
- positive TB bacteriology

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DR-TB TBM

- Not eligible for short regimens
- Treatment guided by ability of medicines to cross the **blood-brain barrier** and resulting **CSF concentrations** (if known) – see table

Medicine	CSF penetration
Levofloxacin, moxifloxacin, linezolid, cycloserine, ethionamide, meropenem, pyrazinamide	Good penetration
Isoniazid in presence of isoniazid resistance, P-aminosalicylic acid, amikacin	Poor penetration, except in presence of meningeal inflammation
Ethambutol	Poor penetration
Bedaquiline, delamanid, clofazimine	Limited data available

- Prioritize fluoroquinolones, linezolid, cycloserine/terizidone and ethionamide (if susceptibility likely)
- At least 3 drugs with **good CSF penetration**
- Additional drugs depending on **severity and extent** (e.g. add bedaquiline if PTB as well)
- Longer duration of **linezolid** advisable if tolerated (good CSF penetration and lack of other options

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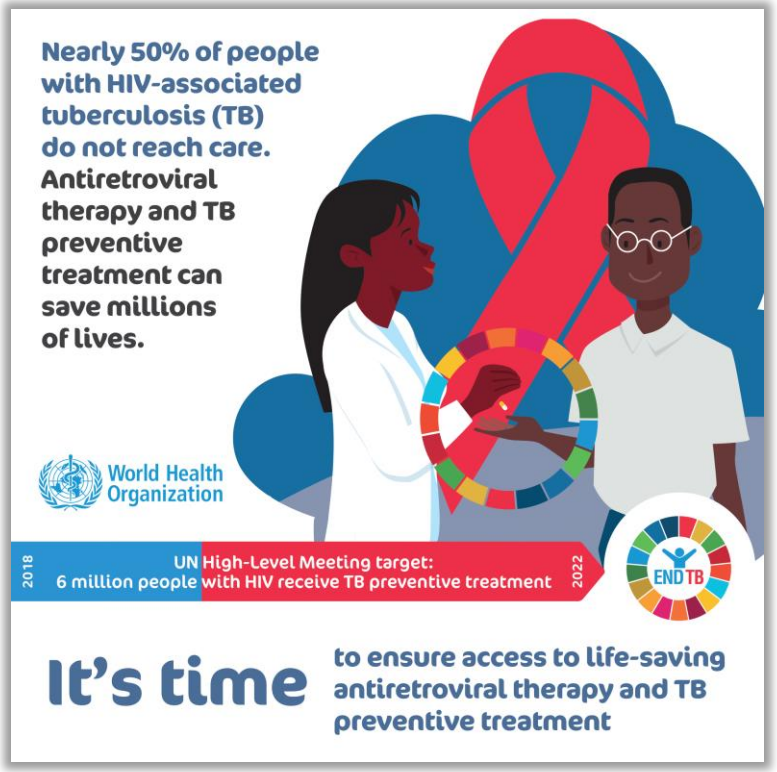
DR-TB and HIV

- Approach to regimen design similar regardless of HIV status
- Careful selection of SLD in the regimen with ART
- Considerations for **bedaquiline**:
  - Best option: **integrase inhibitors** (e.g. DTG) - no DDI expected
  - **Avoid EFV** (lowers BDQ concentrations)
- Other considerations:
  - **LPV/r** may result in ↑ bedaquiline exposure (but usually not leading to ↑ adverse effects) – can be considered with careful monitoring
  - **NVP**: not ideal choice considering reduced efficacy
  - **Triple NRTI**: not routinely recommended if other options exist



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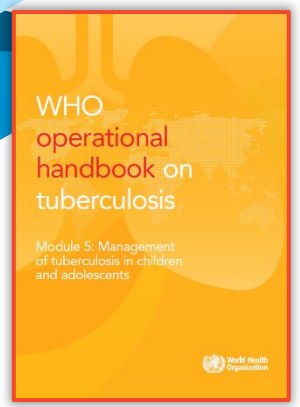
Dosing of regimens for the treatment DS pulmonary TB



Dosing tables:
pages 100-102

Table 5.5. Dosing table for first-line medicines (excluding the short intensive TBM regimen)

Weight (kg)	Number of tablets [a]		
	Intensive phase: HRZ 50/75/150 mg	E 100 mg [b]	Continuation phase: HR 50/75 mg
4–<8	1	1	1
8–<12	2	2	2
12–<16	3	3	3
16–<25	4	4	4
≥25	Adult dosages recommended		

Table 5.7. Recommended dosage by weight for children and adolescents weighing over 25 kg using adult fixed-dose combinations (excluding the short intensive TB meningitis regimen)

Weight band (kg)	Intensive phase	
	HRZE 75/150/400/275 mg	HR 75/150 mg
25–<30 [a]	2	2
30–<35	3	3
35–<50	4	4
50–<65	4	4
≥65	5	5

[a] Dosages based on expert opinion.

Table 5.8. Recommended dosage by weight for adolescents being treated with the 4-month HPZM regimen

Weight band (kg)	4-month 2HPMZ/2HPM regimen			
	Intensive and continuation phase			Intensive phase only
	Isoniazid (H)	Rifapentine (P)	Moxifloxacin (M)	Pyrazinamide (Z)
40–<50	300 mg	1200 mg	400 mg	1500–1600 mg [a]
50–<65				1500–1600 mg [a]
≥65				2000 mg

[a] Dose depends on use of Z 400 mg or 500 mg tablets.

Dosing of the new TB meningitis regimen using available formulations

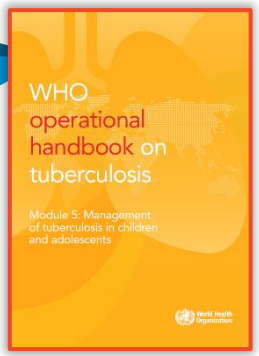


Table 5.6. Dosing table: Short intensive TB meningitis regimen (6HRZEto)

Weight band (kg)	Weight 3–<35 kg using child-friendly formulations [a]					Weight 25–<35 kg using adult formulations (with Z 400 mg tablet) [a]			Weight 25–<35 kg using adult formulations (with Z 500 mg tablet) [a]		
	HR 50/75 mg dispersible tablet [b]		Z 150 mg dispersible tablet [b]		Eto 125 mg dispersible tablet [b]	HR 75/150 mg tablet	Z 400 mg tablet	Eto 250 mg tablet	HR 75/150 mg tablet	Z 500 mg tablet	Eto 250 mg tablet
3–<4 [c]	<3 months 1.5 [b]	≥3 months 1.5 [b]	<3 months 0.5 [b]	≥3 months 1	0.5 [b]						
4–<5 [c]	<3 months 1.5 [b]	≥3 months 2	<3 months 0.5 [b]	≥3 months 1	0.5 [b]						
5–<6	2.5		1.5 [b]		1						
6–<8	3		2		1						
8–<10	3.5 [b]		2.5 [b]		1.5 [b]						
10–<13	4		3		2						
13–<16	5		3.5 [b]		2						
16–<20	6		4		2.5 [b]						
20–<25	7		5		3						
25–<30	9		6		4	4	2	2	4	2	2
30–<32	10		6		4	5	2	2	5	2	2
32–<35	10		6		4	5	3	2	5	2	2

- Using available **child-friendly dispersible fixed dose combination** tablets combined with single tablets
- For ≥ 25 kg, **adult formulations** can also be used (if they are the only ones available or to reduce pill burden)

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Treatment of DR-TB in children – updated dosing table in annex 6 of the handbook

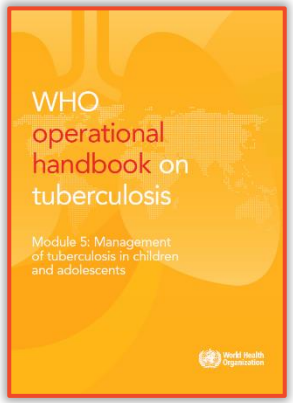
Group	Medicine	Weight-based daily dose[b]	Formulations (mg/mL, as applicable)	3 to <5 kg	5 to <7 kg	7 to <10 kg
A	Levofloxacin	15–20 mg/kg	100 mg dt	5 mL (0.5 dt)	1	1.5
			250 mg tab (250 mg in 10 mL = 25 mg/mL)	2 mL[c]	5 mL (0.5 tab)[c]	5 mL (0.5 tab)[c]
	Moxifloxacin	10–15 mg/kg (standard dose)[d]	100 mg dt (100 mg in 10 mL = 10 mg/mL)	4 mL	8 mL	1.5
			400 mg tab (400 mg in 10 mL = 40 mg/mL)	1 mL[c]	2 mL[c]	3 mL[c]
		High dose[d]	400 mg tab	-	-	-
	Bedaquiline	-	20 mg dt[e]	0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks ≥ 3 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks		0 to <3 months: 1.5 od for 2 weeks; then 0.5 od M/W/F for 22 weeks 3 to <6 months: 3 od for 2 weeks; then 1 od M/W/F for 22 weeks ≥ 6 months: 4 od for 2 weeks; then 2 od M/W/F for 22 weeks

Updates to the dosing table from the 2020 DR-TB handbook:

- Weight band added: 3 to <5kg
- Weight range: 3 to <46 kg
- Updates to presenting weight bands, e.g. 5-<7 kg instead of 5-6 kg
- Bedaquiline 20 mg formulation and delamanid 25 mg formulation
  - Note: age and weight-based approach for young children
- Linezolid 150 mg dispersible tablet
- Removal of dose ranges for certain drugs/weight bands
- Amikacin/streptomycin: not recommended <18y, dosing for salvage therapy in footnotes
- More details on administration of formulations diluted in water

Treatment monitoring

- Assess for resolution/persistence of **TB-related and other symptoms, adverse events**
- Measure **weight** – adjust dosages with weight gain
- Assess **adherence**
- Follow-up **sputum samples** (smear at 2 months and at treatment completion **if child was Xpert, smear or culture + at diagnosis**)
  - Most valuable makers: **symptomatic improvement and weight gain**
  - If follow-up smear +, complete additional investigations to assess for **drug resistance** and other causes of poor response
  - If child cannot expectorate, repeat specimen at end of treatment not necessary if specimen collected at 2 months is negative
- **Not indicated**: Repeat sample collection at 2 months in children **with unconfirmed** unless inadequate clinical response
- Follow-up **CXR not needed** if child responding well to TB treatment



Monitoring: pages 109-114

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END TB

Indications for referral and hospitalization

- **Referral to specialist** (if management capacity insufficient):
  - Severe forms of TB (TBM, peritonitis, pericarditis, renal, spinal, disseminated, osteoarticular TB)
  - Presumed MDR/RR-TB
- **Hospitalization**: reserved for specific clinical indications
  - severe malnutrition (for nutritional rehabilitation)
  - signs of severe pneumonia
  - other comorbidities (e.g. severe anaemia)
  - CALHIV (referral as needed for ART and CPT; hospitalization for severe HIV-associated diseases)
  - social or logistic reasons that could impact adherence
  - neonates weighing <4 kg
  - severe adverse reactions (e.g. hepatotoxicity)

http://www.childhoodtb.org/

Children on TB preventive treatment should not be hospitalized!

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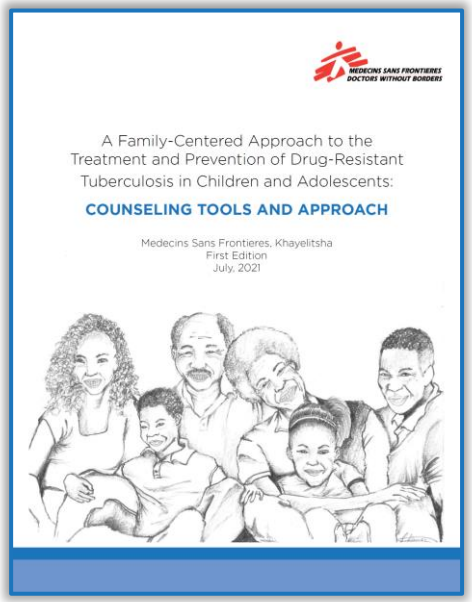
Treatment adherence

- Messages for **treatment supporters** of children and adolescents with TB
  - Have an **education session** with the adult who will support the child or adolescent: TB disease, medicines, dosages and preparations used, and adverse events
  - Get feedback to check they **understood** everything
  - Give information about **side-effects** and what to do if they occur
  - Show how to mark the **treatment card** (if given), check the card at each visit with the adult and child, and discuss **adherence**
  - Review the need for **transport or nutritional support** to enable successful follow-up, and provide resources if available
  - **Engage adolescents** in their care



http://sentinel-project.org/wpcontent/uploads/2021/12/Peds_Counseling_Outline_V3.pdf

https://www.msf.org/lifesaving-tb-medicines-still-out-reach-children-high-burden-countries

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Management of treatment interruption (DS-TB)

Treatment phase of interruption	Details of interruption	Management
Intensive phase		
Intensive phase: applies to 4- and 6-month regimens	Interruption <14 days	Continue treatment and complete all intensive phase doses
	Interruption ≥ 14 days	Restart intensive phase
Continuation phase (4-month 2HRZ(E)/2HR regimen)		
Continuation phase (4-month regimen)	Completed ≥80% of doses within 8 weeks	Further treatment not necessary
Continuation phase (4-month regimen)	Completed <80% of doses and cumulative interruption <1 month	Complete remaining doses of treatment
Continuation phase (4-month regimen)	Completed <80% of doses and cumulative interruption >1 month	Restart treatment from beginning of intensive phase

In all circumstances, if TB symptoms recur during the interruption, reassess with a rapid molecular test and culture/DST to assess for drug resistance

END TB

Management of treatment interruption (DS-TB) (2)

Treatment phase of interruption	Details of interruption	Management
Continuation phase (6-month 2HRZE/4HR regimen)		
Continuation phase (6-month regimen) and bacteriologically negative at initiation	Completed ≥80% of doses within 16 weeks	Further treatment not necessary
Continuation phase (6-month regimen) and bacteriologically positive at initiation	Completed ≥80% of doses within 16 weeks	Complete remaining doses of treatment If consecutive lapse is >2 months, use clinical judgement
Continuation phase (6-month regimen)	Completed <80% of doses and cumulative interruption <2 months	Complete remaining doses of treatment
Continuation phase (6-month regimen)	Completed <80% of doses and cumulative interruption ≥2 months	Restart treatment from beginning of intensive phase, particularly if interruption was consecutive

In all circumstances, if TB symptoms recur during the interruption, reassess with a rapid molecular test and culture/DST to assess for drug resistance

School attendance

- Most young children **do not have infectious forms** of TB - can return to (pre)school as soon as they are feeling better on treatment
- Older children and adolescents, and younger children with positive bacteriological tests, should not attend school **while they are infectious**
- **After 2 weeks of starting TB treatment** (with good adherence and clinical improvement) most children and adolescents are no longer infectious and can return to school
  - **no need to wear masks** for the purposes of preventing TB transmission!

https://slate.com/human-interest/2013/12/photos-open-air-schools-for-sick-kids-in-the-early-twentieth-century.html

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END TB

Acknowledgements and thanks

- Tereza Kasaeva, Farai Mavhunga, Kerri Viney, Annemieke Brands, Tiziana Masini and other colleagues from the WHO Global TB Programme

- Experts who contributed to the development of the guidelines and handbook, including the GDG, ERGs, technical partners, funding partners, members of the Child and Adolescent TB Working Group

Thank you for your attention!

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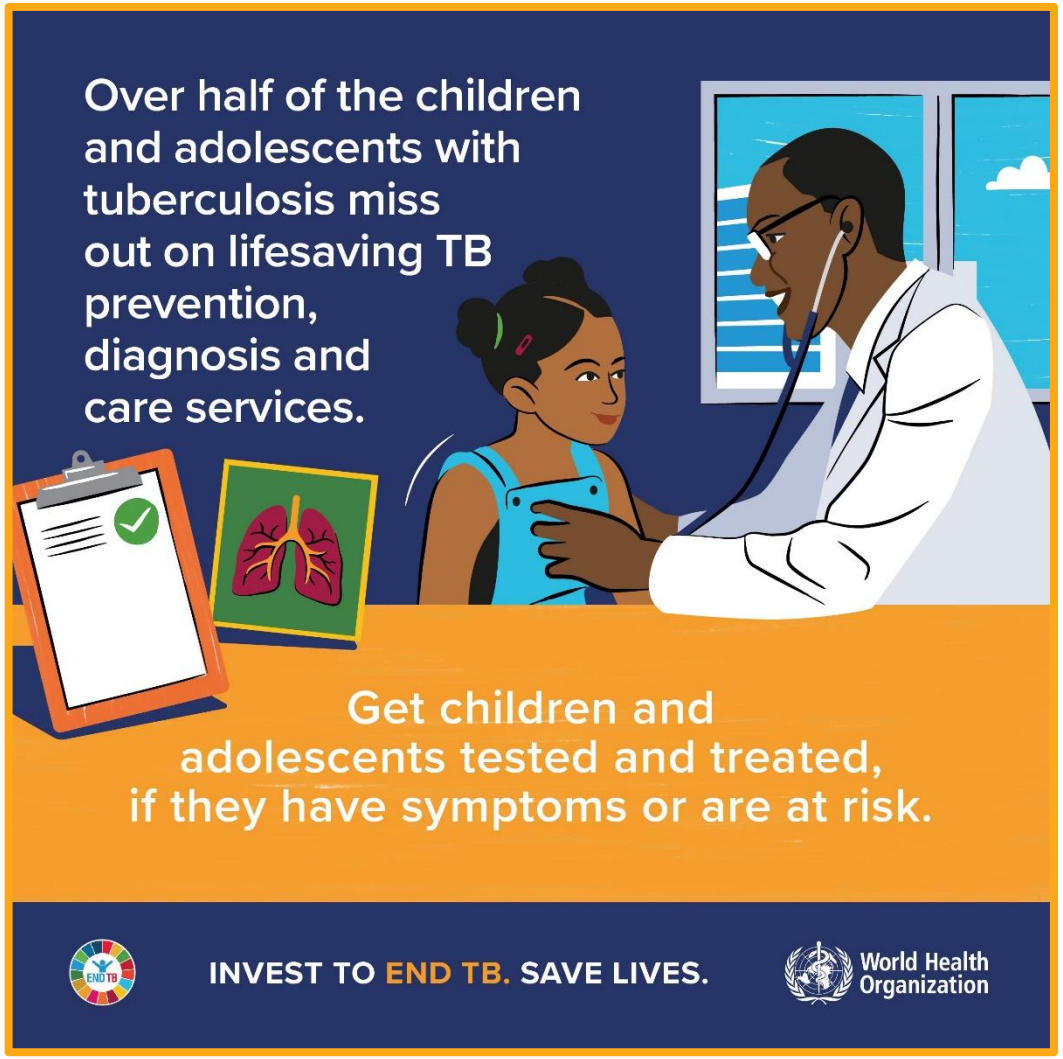

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Questions & Answers for the second part

END TB