

Overview of Post-TB sequelae in children and adolescents— emerging evidence in African children

Elisabeth Maleche-Obimbo & Marieke van der Zalm

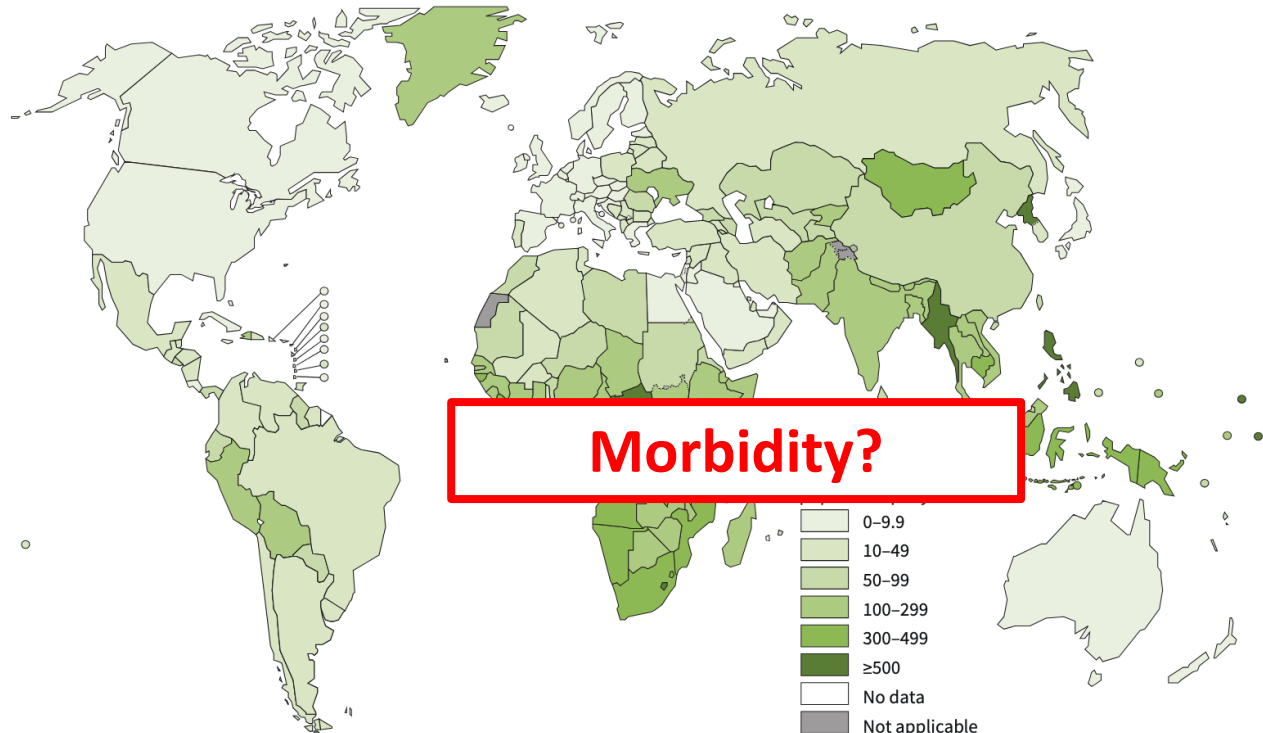
Child & Adolescent working group, 11-November-2024, Bali, Indonesia



Child
& Adolescent
TB Working Group

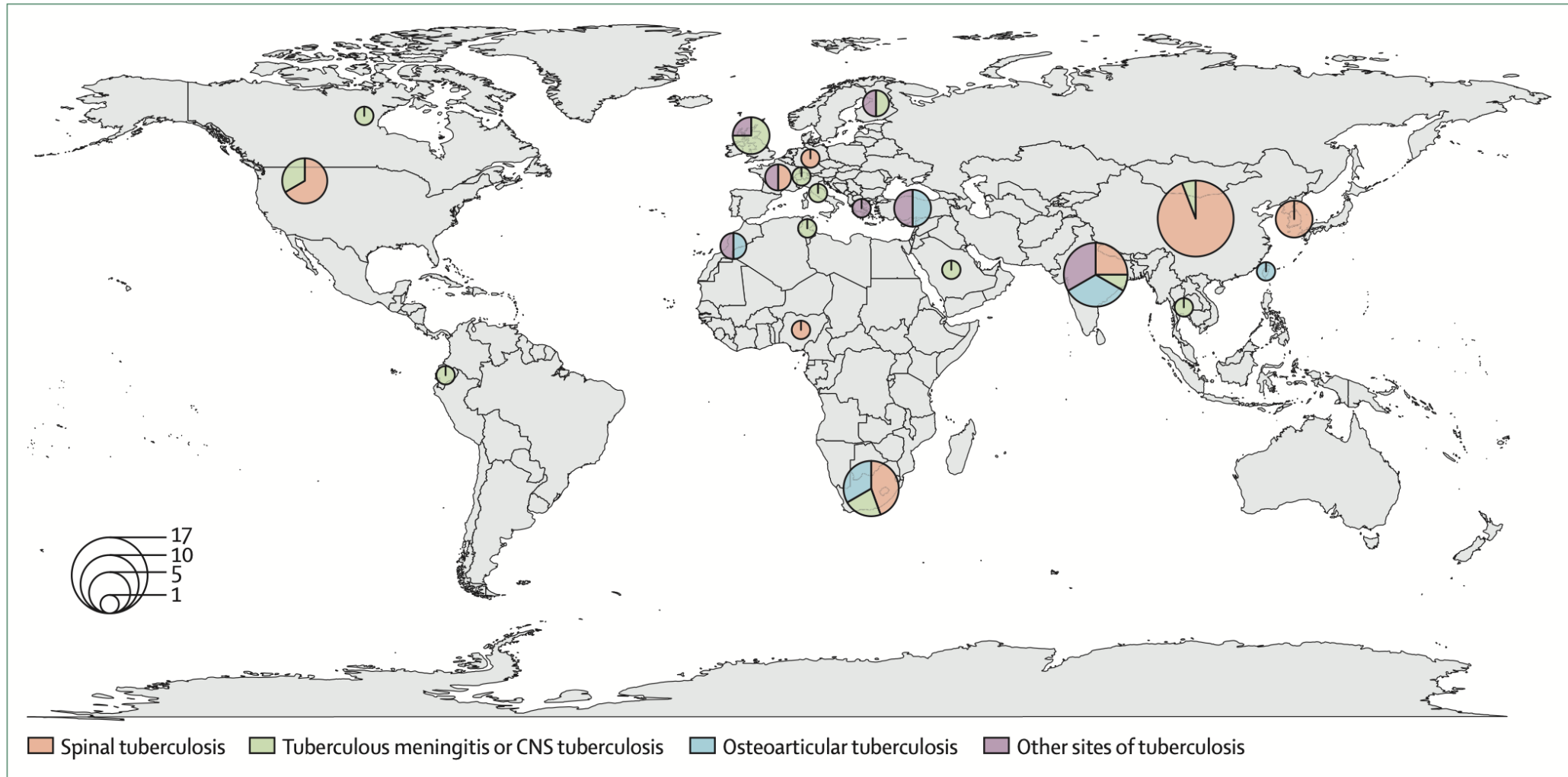
Post TB morbidity

Estimated TB incidence rates, 2023



- **In 2023:**
 - 1.3 million children and young adolescents (0-14y) got TB
- 155 million TB survivors (1980- 2019) were alive in 2020 and at risk for post TB
 - 18% were treated in last 5 years
 - 80% were treated in last 2 years
 - Up to 18 million were <15 years

Post-tuberculosis sequelae in children and adolescents: a systematic review



Sequelae following tuberculous meningitis or CNS tuberculosis

872 children, 17 studies; sequelae in 12.5–100%

- Intellectual disability
- Motor disorders
- Abnormal electroencephalogram patterns, epileptic seizures
- Behavioural problems and emotional disorders
- Language difficulties
- Headaches
- Visual impairment
- Hearing deficiency
- Endocrine disturbances: growth disorders, obesity, diabetes insipidus, precocious puberty, and delayed puberty
- Hydrocephalus
- Attention-deficit hyperactivity disorder

Sequelae following spinal tuberculosis

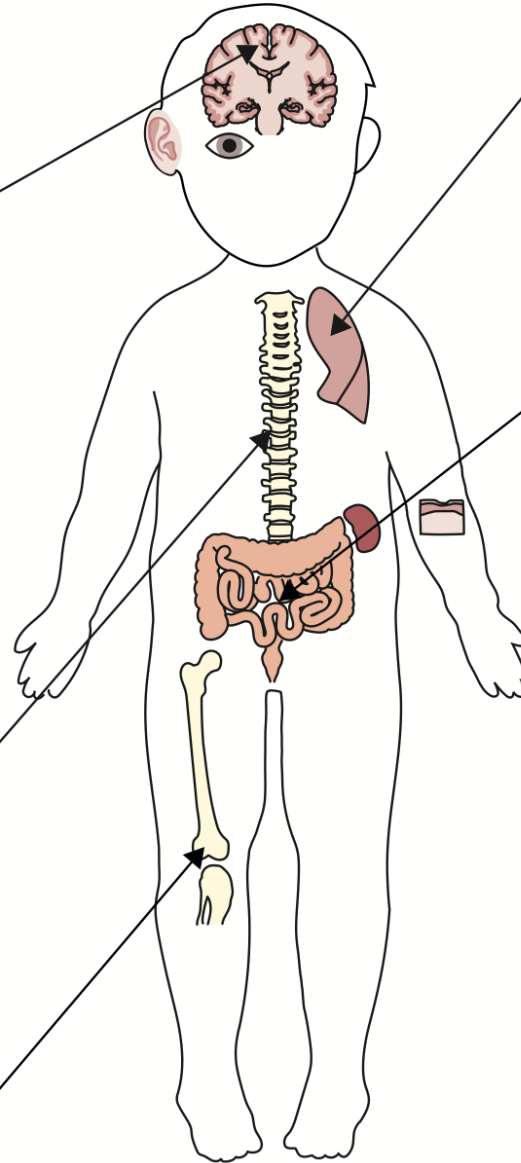
1249 children, 32 studies; sequelae in 0–43%

- Spinal deformity, kyphosis, loss of lordosis
- Body disproportions
- Osteoporosis
- Reduced physical activity
- Residual pain
- Loss of lung capacity
- Neurological disabilities and paraplegia

Sequelae following osteoarticular tuberculosis

231 children, 11 studies; sequelae in 0–75%

- Limb length discrepancy
- Limited mobility
- Bone deformity
- Residual pain



Sequelae following pulmonary tuberculosis

985 children, six studies; sequelae in 1–49%

- Radiological sequelae: fibrosis, calcifications, atelectasis, emphysema, bronchiectasis and lymphadenopathy
- Persistent coughing and wheezing

Sequelae following abdominal, urogenital, and cutaneous tuberculosis

202 children, five studies; sequelae in 0–100%

- Intestinal obstruction
- Urogenital obstruction
- Abnormal serum creatinine levels and chronic renal failure
- Skin scarring

Long-term psychosocial and economic effect of tuberculosis sequelae

- Reduced quality of life
- Stigmatisation
- Need for schools providing functional and educational assistance
- Social maladjustment
- Social dependency
- Institutional placement
- Limited productive life
- Financial burden for relatives
- Financial burden for health systems

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Sequelae following abdominal, urogenital, and cutaneous tuberculosis

202 children, five studies; sequelae in 0–100%

- Intestinal obstruction
- Genital obstruction
- Abnormal serum creatinine levels and chronic renal failure
- Irritation

Psychosocial and economic effect of tuberculosis sequelae

- Reduced quality of life
- Stigmatisation
- Need for schools providing functional and educational assistance
- Social maladjustment
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- Financial burden for health systems

Sequelae following spinal tuberculosis

1249 children, 32 studies; sequelae in 0–41%

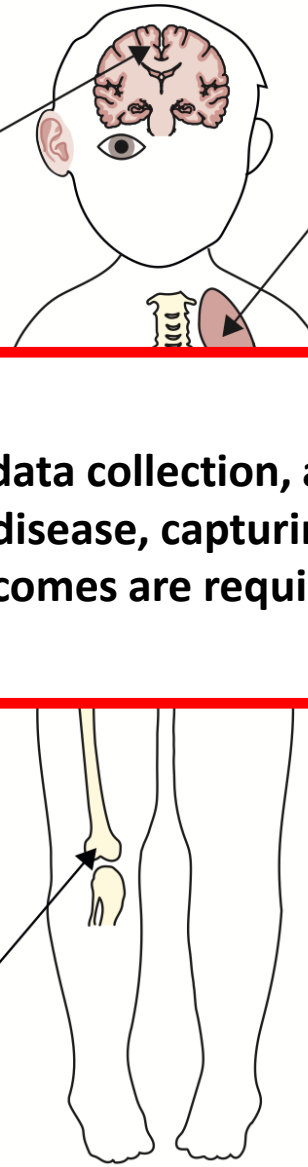
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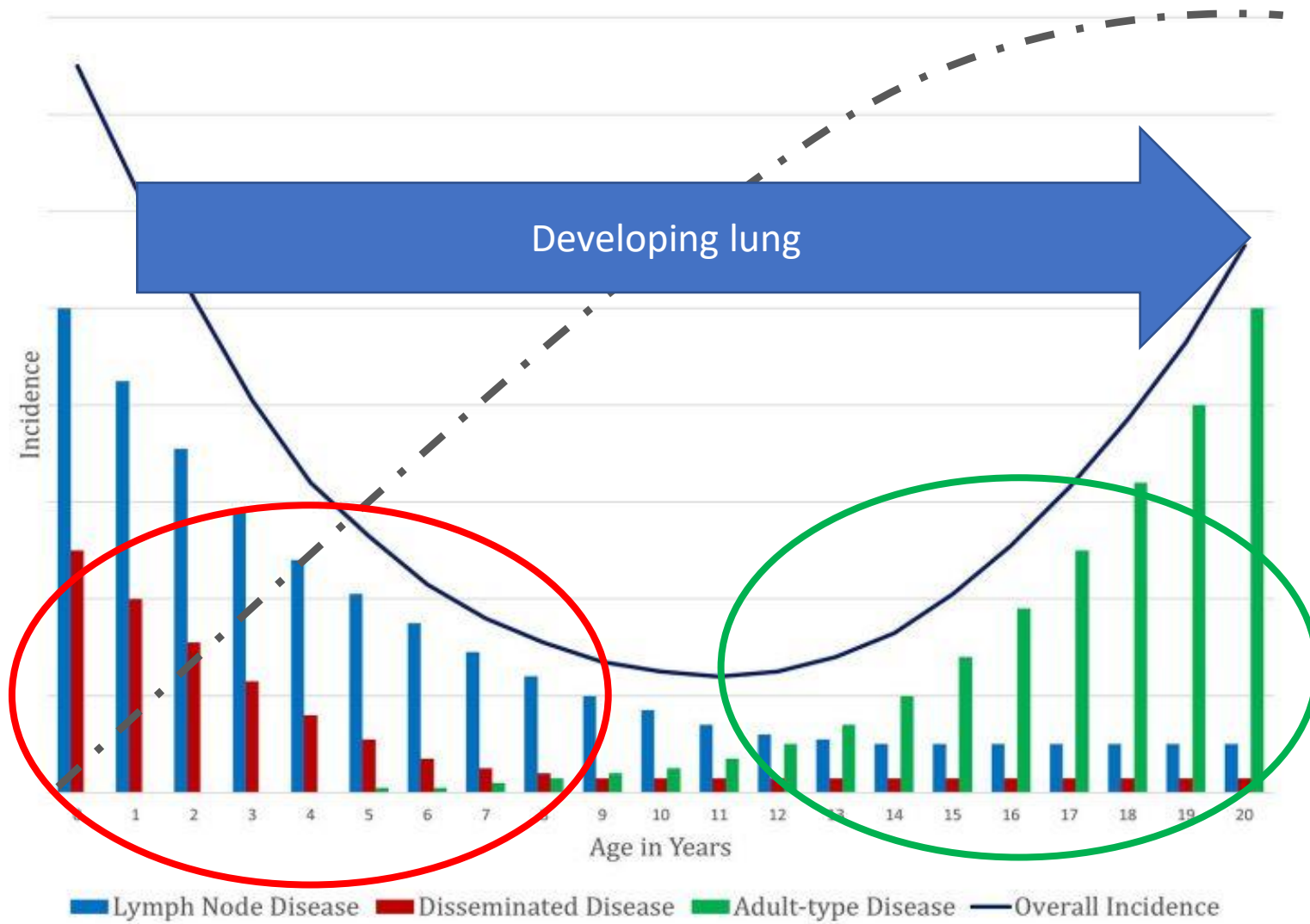
Standardized data collection, across the full spectrum of disease, capturing long-term outcomes are required



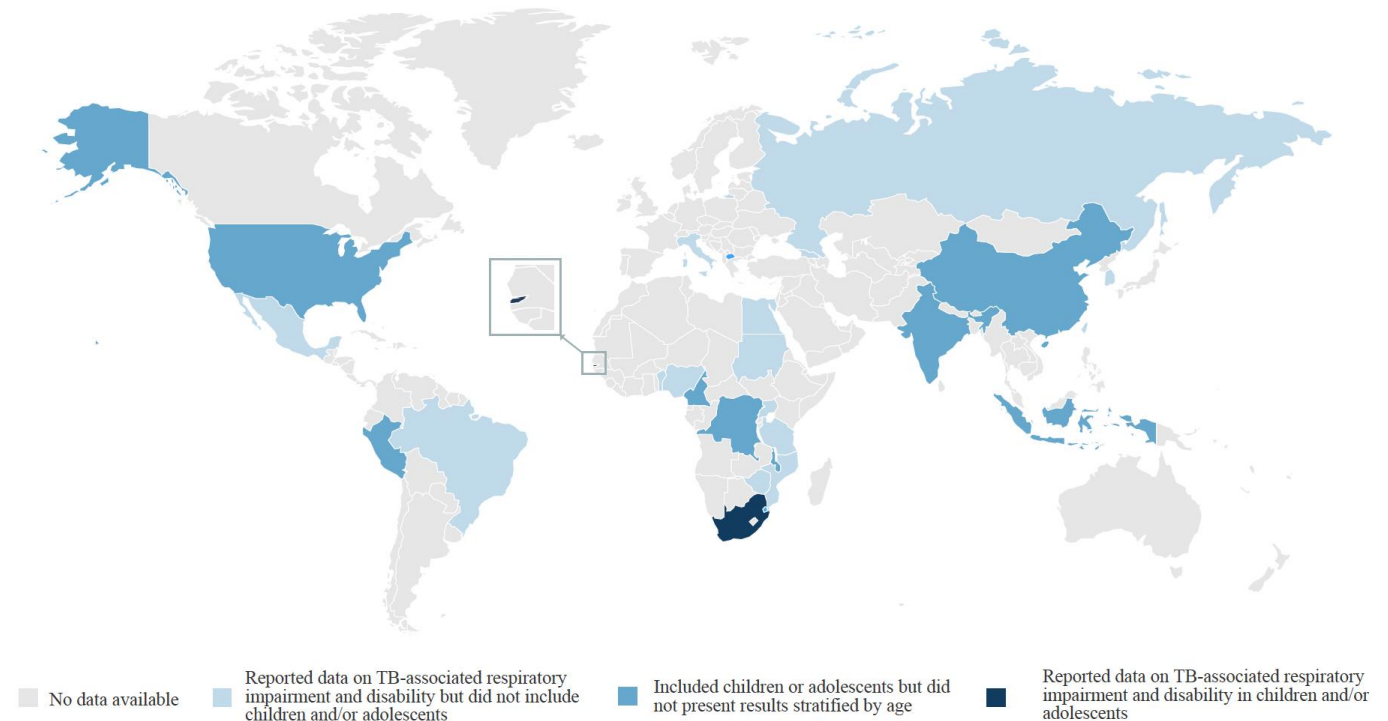
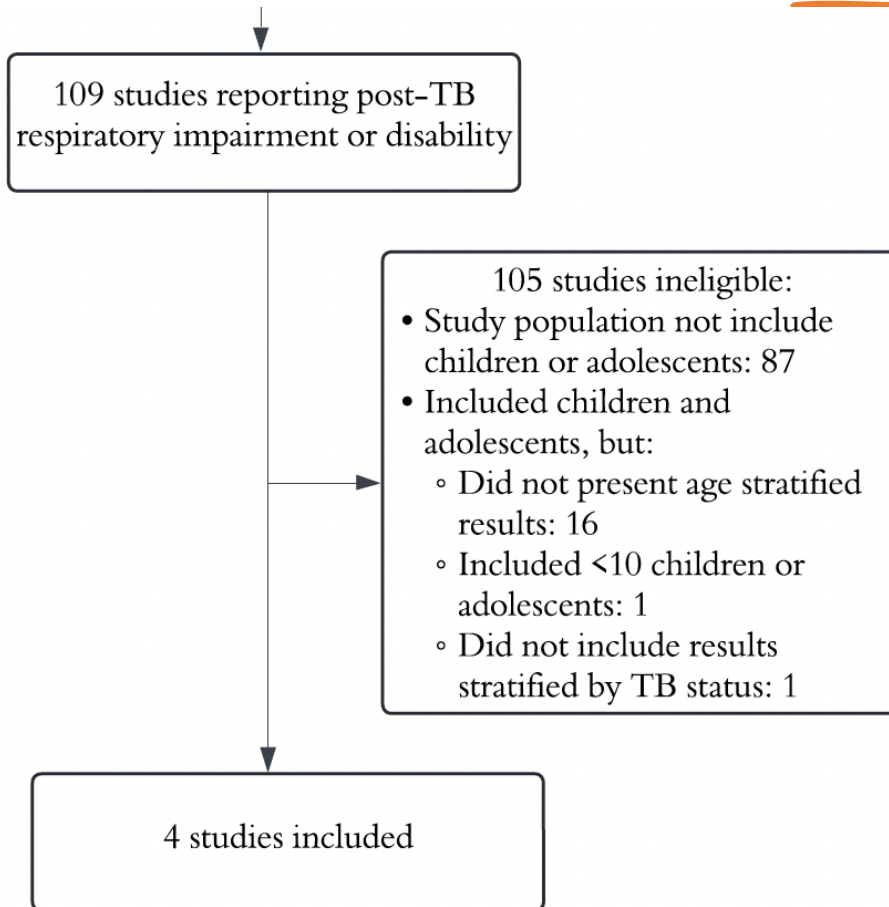
Post-TB lung disease

- Despite microbiological cure in >75% → up to 60% of adults experience respiratory sequelae and pulmonary impairment after TB
 - ±18% obstructive
 - ±21% restrictive
 - ±13% mixed
- **But what about children and adolescents?**
- Case definition for paediatric PTLD

“Evidence of chronic respiratory impairment in a child previously adequately treated for pulmonary tuberculosis in whom active TB is excluded, and in whom no other cause of chronic lung disease is the predominant cause.”



Systematic review on TB-associated respiratory conditions in children and adolescents



A photograph of three children in a sandy outdoor setting. On the left, a child is partially visible, wearing a dark, wrap-around garment. In the center, a child is seen from the back, wearing light green shorts. On the right, a young child is facing forward, wearing white shorts and has their hands clasped near their face. The background is a bright, sandy area with some blurred structures.

Summary of findings to date;
according to age groups

Children <5 years of age

Median age at TB dx	Measure	Author (year)	Timing of measurement#	Tool(s) used	Outcome(s)
<5	Wheeze	Martinez (2023)	At 6 weeks and 1 yoa and then annually until 5 yoa	Questionnaire^^ Diagnosed on auscultation by trained study staff	Children diagnosed with PTB or those with a chest X-ray suggestive of PTB were at higher risk of any wheeze (aIRR 1.9 [95% CI 1.1, 3.3]) or recurrent wheezing (aIRR 2.1 [95% CI 1.2, 3.7]).
	Growth limitations	Martinez (2023)^	At 6 weeks and 1 yoa and then annually until 5 yoa	Anthropometric measures	Children diagnosed with TB between 0 and 1 yoa age had lower weight-for-age z-scores (-0.5, 95% CI -0.8, -0.2) and body mass index z-scores (-0.5, 95% CI -0.83, -0.25) at 5 years, compared with children who did not develop TB Children diagnosed with TB between 1 and 4 years of age had lower length-for-age z-scores (-0.4, 95% CI -0.7, -0.1) and weight-for-age z-scores (-0.3, 95% CI -0.6, 0.0) at 5 years, compared with children who did not develop TB

Median age at TB dx	Measure	Author (year)	Timing of measurement#	Tool(s)	Outcome(s)
<5	Lung function	Martinez (2023)^	At 6 weeks and 1 yoa and then annually until 5 yoa	Tidal breathing Respiratory impedance by oscillatory Fractional exhaled nitric oxide Multiple breath washout Lung clearance index	Children diagnosed with TB between 0 and 1 yoa had reduced time to peak tidal expiratory flow over total expiratory time (-2.4%, 95% CI -4.9, -0.2) and higher fractional exhaled nitric oxide (2.9 ppb, 95% CI 0.6, 5.2) at 5 yoa, compared with children who did not develop TB. Children diagnosed with TB between 1 and 4 yoa impaired tidal volume (-9.3 ml, 95% CI -14.9, -3.8) and time to peak tidal expiratory flow over total expiratory time (-2.7%, 95% CI -5.5, 0.0) at 5 yoa, compared with children who did not develop TB.

Children 5-10 years of age

				<i>TB population</i>	<i>Comparator population</i>
Respiratory symptoms	Nkereuwen (2023)	Months since treatment completion: 19.2 (10.2, 44.4)	Study questionnaire	51.5	37.4
				<i>Chronic respiratory symptoms, %</i>	
					<i>Stunting %**</i>
Growth limitations	Nkereuwen (2023)	Months since treatment completion: 19.2 (10.2, 44.4)	Anthropometric measures	19.1	6.6
					<i>Underweight %</i>
				25.0	20.9
					<i>Parent-reported quality of life total score, median (IQR)</i>
Health related quality of life	Nkereuwen (2023)	Months since treatment completion: 19.2 (10.2, 44.4)	PedsQL V.4.0	82.6 (71.7, 93.5)	91.3 (82.6, 97.8)
					<i>Child-reported quality of life total score, median (IQR)</i>
				73.9 (65.2, 89.1)	78.3 (64.7, 89.1)

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				<i>TB population</i>				<i>Comparator population</i>			
				<i>Abnormal</i> %	<i>Restrictive</i> %	<i>Obstructive</i> %	<i>Mixed</i> %	<i>Abnormal</i> %	<i>Restrictive</i> %	<i>Obstructive</i> %	<i>Mixed</i> %
Lung function	Nkereuwen (2023)	Months since treatment completion: 19.2 (10.2, 44.4)	Spirometry	38.5*	36.4+	1.9	0.0	17.4*	15.1+	2.3	0.0

- 39 vs 17% abnormal spirometry
- Restrictive disease most common

Children >10 years of age

TB population

Comparator population

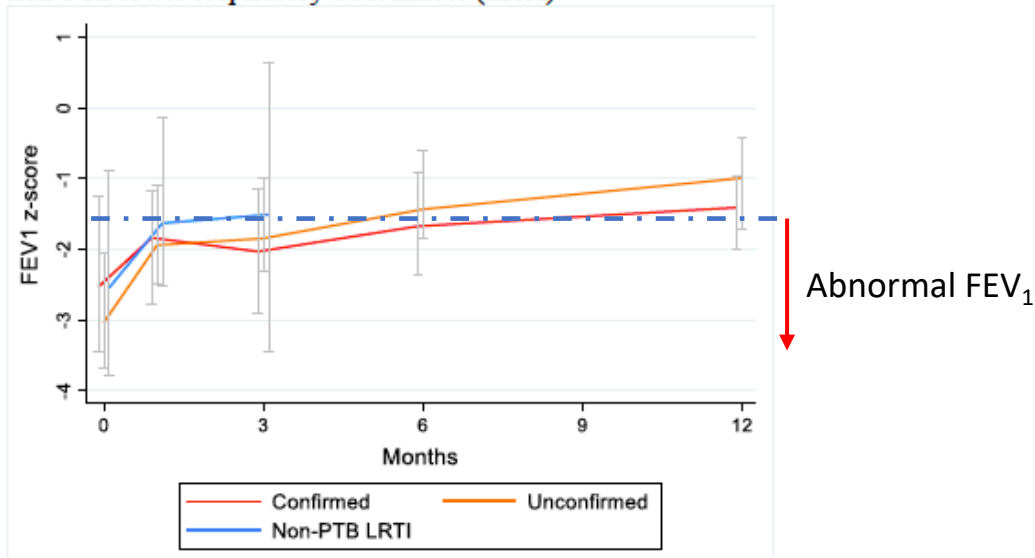
Respiratory symptoms	Nkereuwen (2024)	Weeks since treatment completion: 1.2 (0.8, 2.4)	St. George Respiratory Questionnaire	35.4	-
				<p><i>Chronic respiratory symptoms, %</i></p>	
Growth limitations	Nkereuwen (2024)	Weeks since treatment completion: 1.2 (0.8, 2.4)	Anthropometric measures	-0.7 (-1.4, -0.1)	-
				<p><i>Height-for-age z-score, median (IQR)</i></p>	
				<p><i>Body mass index-for-age z-score, median (IQR)</i></p>	
				-1.3 (-2.1, -0.5)	-
Functional limitations	van der Zalm (2024)	Months since treatment initiation: 13.3 (11.7, 14.3)	6-minute walk test	390 (340, 420)	428 (390, 480)
				<p><i>Distance walked, m (IQR)</i></p>	

Children >10 years of age

				<i>TB population</i>				<i>Comparator population</i>			
				<i>Abnormal %</i>	<i>Restrictive %</i>	<i>Obstructive %</i>	<i>Mixed %</i>	<i>Abnormal %</i>	<i>Restrictive %</i>	<i>Obstructive %</i>	<i>Mixed %</i>
Lung function	Nkereuwen (2024)	Weeks since treatment completion: 1.2 (0.8, 2.4)	Spirometry	57.0*	51.9+	0.0	5.1	-	-	-	-
	van der Zalm (2024)	Months since treatment initiation: 13.3 (11.7, 14.3)	Spirometry	60.0	27.0+	14.0	19.0	36.0	29.0	7.0	0.0
			Combination of plethysmography, diffusion capacity, and spirometry	65.0**	19.0**	14.0	19.0	58.0**	18.0**	7.0	0.0
Structural impairments	Nkereuwen (2024)	Weeks since treatment completion: 1.2 (0.8, 2.4)	Chest X-ray	<i>Abnormal CXR %</i>				47.4	-	-	-

- 60 vs 36% abnormal spirometry
- Restrictive disease most common

Figure 1a Median FEV₁ z-scores over time, by confirmed pulmonary TB (PTB), unconfirmed PTB, and non-PTB lower respiratory tract illness (LRTI)



N=169 children,
- 69 (41%) confirmed (DSTB),
- 70 (41%) unconfirmed and
- 30 (18%) non-TB LRTI

Median age 9.8 y
11% living with HIV
8% Previous history of TB

Figure 1b Median FVC z-scores over time, by confirmed pulmonary TB (PTB), unconfirmed PTB, and non-PTB lower respiratory tract illness (LRTI)

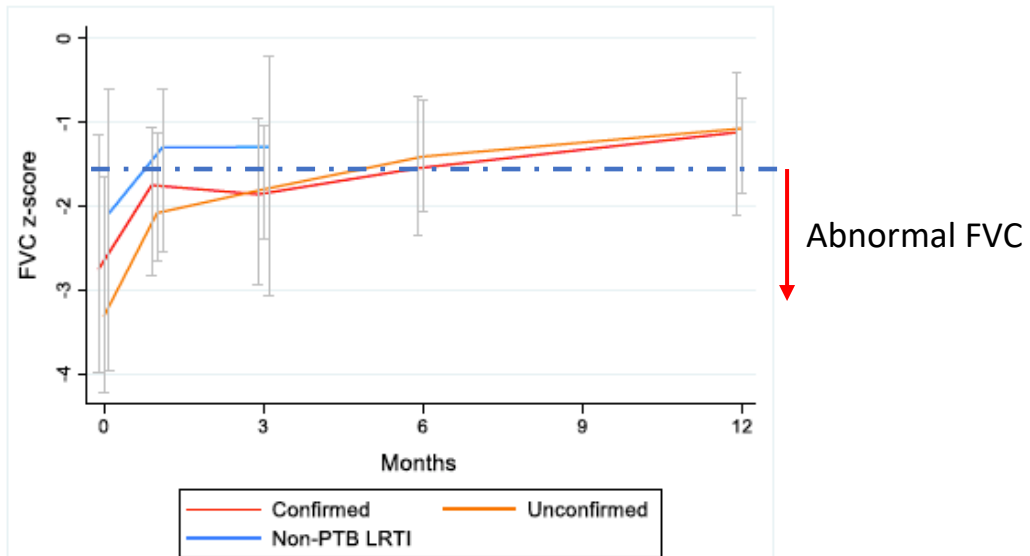
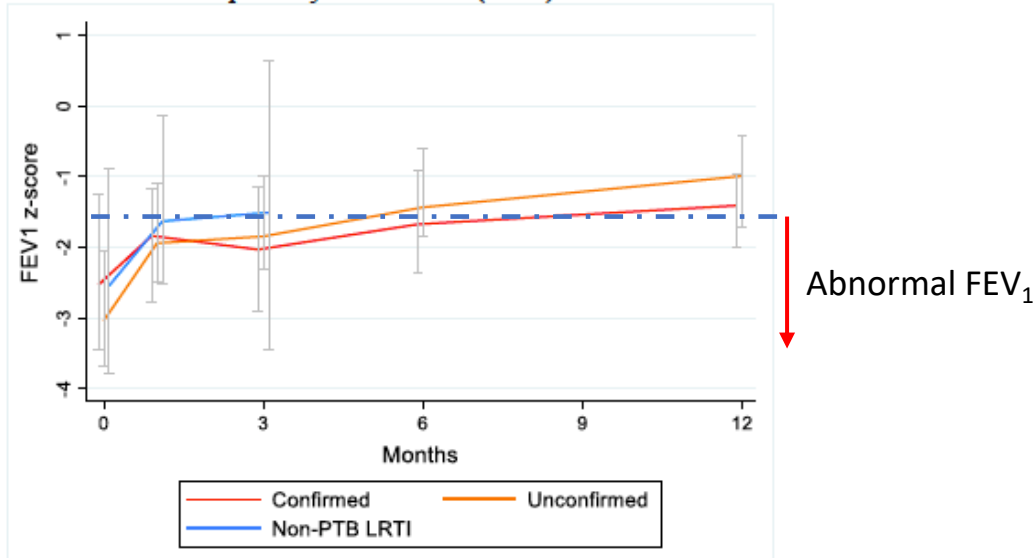


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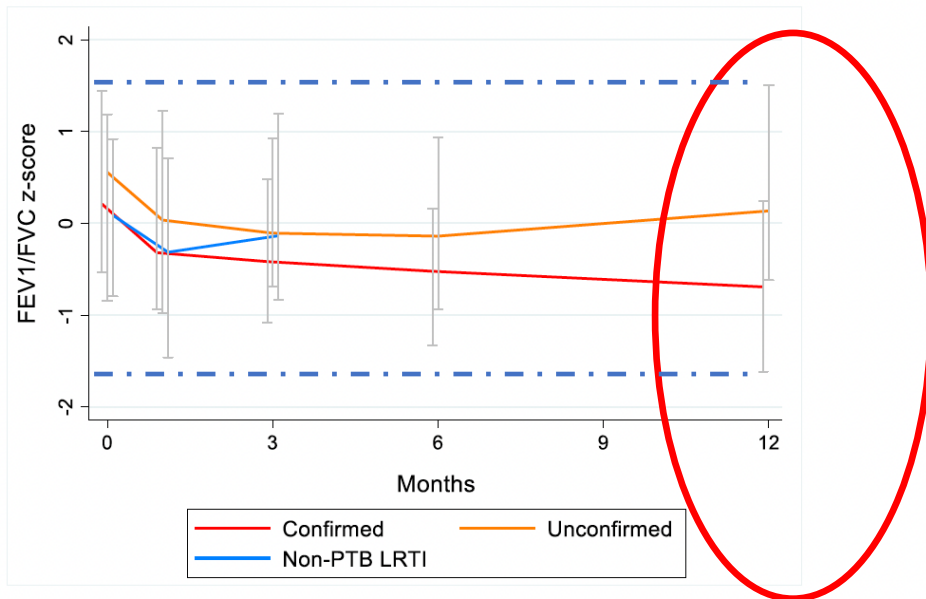
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11% living with HIV

8% Previous history of TB

- Confirmed TB ↓ z-FEV₁/FVC
- ↑ age, being female, CXR suggestive of PTB, poor baseline nutrition and cough at enrolment were significant predictors of lower z-FEV₁ or z-FVC

Figure 1c Median FEV₁/FVC z-scores over time, by confirmed pulmonary TB (PTB), unconfirmed PTB, and non-PTB lower respiratory tract illness (LRTI)



Conclusions

- The data shows that **especially adolescents** need to be screened for post TB lung disease PTLD
 - More data needed on younger children (especially <5)
 - Need for longitudinal data
- More data are needed for both children and adolescents in different high TB-burden settings
- Lung health needs to urgently be addressed



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Call for data for an IPD on TB-associated respiratory morbidity



Research priorities

Inclusive research design; children and adolescents

Spectrum, certainty & severity of TB diagnosis

Comparator groups; local control, symptomatic?

Geographic representation; other settings

Lung impairment screening; new lung function modalities

Impact on quality of life; other pt centered outcomes

Data harmonization; definitions, timing assessment

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P



EUROPEAN RESPIRATORY JOURNAL
CORRESPONDENCE
A. BYRNE ET AL.

“Post tuberculosis”: the urgent need for inclusion of lung health outcomes in tuberculosis treatment trials

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Data harmonization; definitions, timing assessment

Post-TB resp symptoms & signs in Kenyan children. *(Kamene M 2024)*

Study Design & Site:

- Cross-sectional study in Nairobi, Kenya
- 1 county hospital, 6 health centres

Inclusion criteria:

- Children & adolescents (0 – 19 yr)
- Completing treatment for pulmonary TB

Study procedures:

- Clinical assessment symptoms, signs
- Medical record review (TB clinic record)
- Exercise test 6MWT (N=56)

Results: 107 enrolled.

- Median age 6 yr (43% were <5yr)
- Low SES
- 79% unclean cooking fuel

Clinical symptom or sign	Freq (N=107)	%
Cough	23	21.5%
Chest congestion	10	9.3%
Chest tightness	5	4.7%
Wheeze	5	4.7%
Chest pain	4	3.7%
Breathlessness	3	2.8%
Total symptomatic	31	29%
RR $\geq 99^{\text{th}}$ centile	28	26.7%
O2 saturation $\leq 92\%$ at rest	8	7.5%
Desaturation with exercise*	11	19.6%
Crackles	15	14%
Exercise intolerance (6MWD $< 70\%$)	22	39%
Total with respiratory signs	60	56%

* Among 56 who did the 6MWT

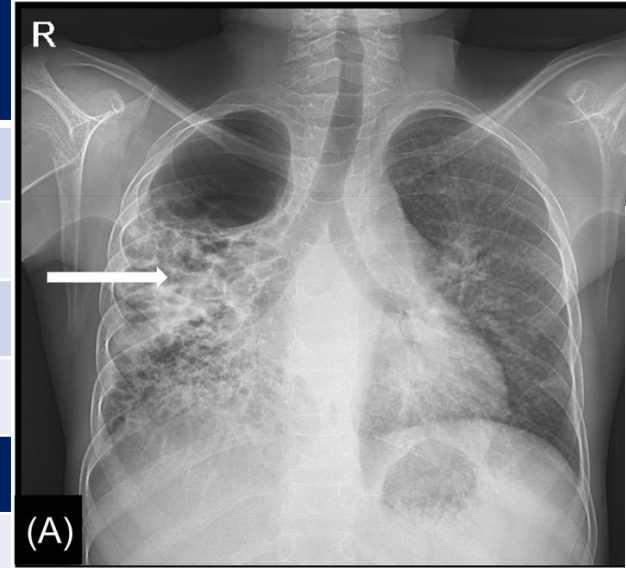
Clinical presentation of PTLD: African studies reporting post-TB symptoms/signs in Children

Author (Year)	Country	Age range	N	Cough		Breathlessness*		Sputum		Overall no with any symptom	
		Min, max		Freq	(%)	Freq	(%)	Freq	(%)	Freq	(%)
Attia E (2018)	Kenya	10 - 19	96	34	35%	17	18%	28	29%	52	54%
Maleche-Obimbo (2023)	Kenya	3 - 19	55	15	27%	26	48%	10	18%	30	55%
Nkereuwem E (2022)	Gambia	?	68	21	31%	6	9%	8	12%	35	52%
Kamene M (2024)	Kenya	0 – 19	107	23	22%	8	7%	10	9%	31	29%
Nkereuwem E (2024)	Gambia	5 - 19	79	21	27%	9	11%	14	17%	28	35%
Githua J (2024)	Kenya	< 15yr	189	44	23%	NR		NR		NR	NR

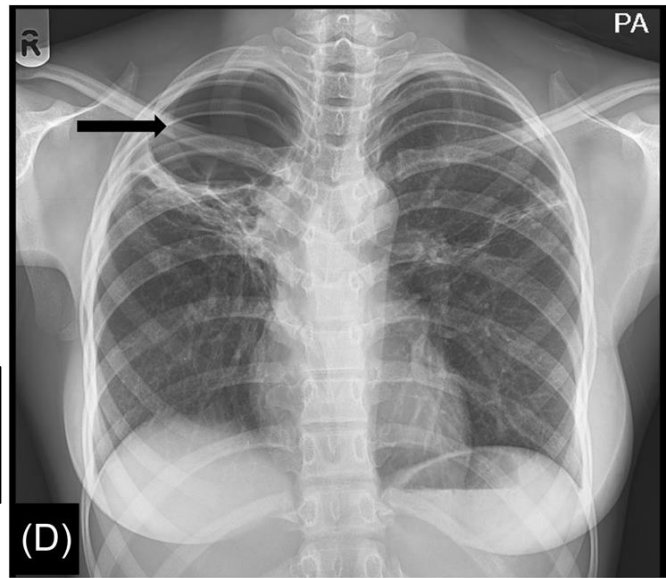
After completing TB treatment, >50% of children and adolescents have persisting symptoms
 Commonest symptoms/signs: cough, chest congestion/sputum, breathlessness
 Exam signs: tachypnoea, crepitations, desaturation with exercise, exercise intolerance.

CXR abnormalities post-TB: Gambian children <19 yr. (Nkereuwem)

Characteristic	Freq or median	Percent or IQR
Age in years	15.6	11.8, 17.9
Biomass smoke	75	95%
Weeks after end of TB Rx	1.2	0.8, 2.4
HIV infection	8	10%
CXR abnormalities	37	47.4%
Fibrosis	22	28.2%
Consolidation/infiltrates	6	7.7%
Cavities	3	3.9%
Bronchiectasis	6	7.7%
Pleural effusion	2	2.6%
Volume loss/collapse	10	8.3%



(A) Bronchiectasis with volume loss, right lung

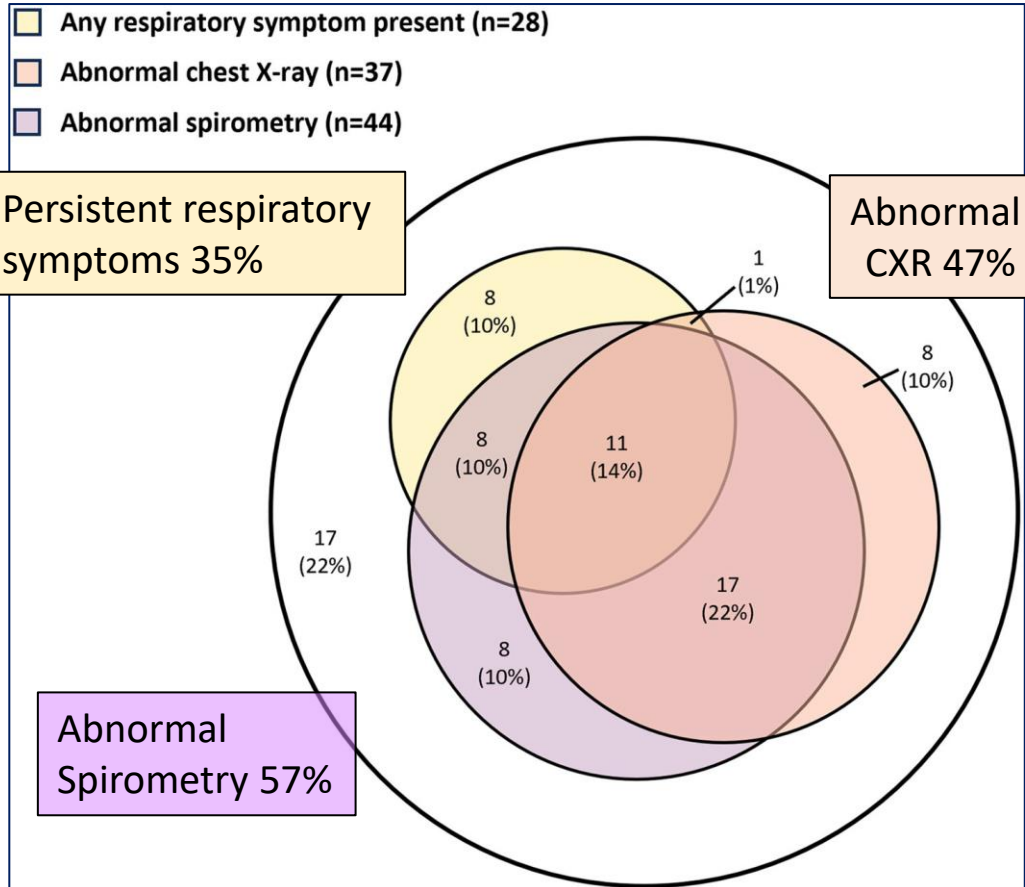


(D) Fibrosis Right upper lobe

Chest X-ray imaging from participants with severe radiological abnormalities. (Nkereuwem 2024)

Emerging insights from African children: TB sequelae has a varied presentation; Risk factors for developing PTLD

Gambian children: Varied presentation



Post-TB lung disease among 78 Gambian children 5– 19 yr. (Nkereuwem et al. Ped Pulm 2024)

Children were more likely to develop post-TB sequelae if they were....

Kenyan children: higher risk post-TB symptoms:

- Hospitalised at diagnosis, severe dx (*aOR* 6.9)
- Older – median age 6yr PTLD, vs 4 yr no PTLD
- HIV+ (*OR* 1.13)

Gambia: higher risk abnormal lung function

- Older >10yr (*aOR* 4.3)
- Underweight at end of TB Rx (*aOR* 8.3)
- Fibrosis on CXR vs other abnormalities (*aOR* 3.6)

Children: Recommended assessment at end of TB treatment

Table 7 End-of-treatment assessment for post-TB lung disease in children and adolescents*

	Non-severe PTB [†]	Severe PTB
Clinical assessment and symptom/signs screening	X [‡]	X
Imaging (CXR)		X
Lung function test (spirometry)		X
6MWT		X
HRQoL		X

* Source: Migliori G, et al.⁴⁶



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Clinical assessment and symptom/signs screening	X [‡]	X
Imaging (CXR)		X
Lung function test (spirometry)		X
6MWT		X
HRQoL		X

* Source: Migliori G, et al.⁴⁶

Clinical history:

- cough, sputum, shortness of breath
- wheeze, chest pain, haemoptysis,
- weight loss and fatigue

Clinical Exam:

- respiratory rate, heart rate
- anthropometry (WHZ, BMI)
- chest exam



Measures of oxygenation and ventilation:

- Resting pulse oximetry, walking oximetry,
- arterial blood gas (severe cases)



Assess at end of TB Rx: Symptoms, exam, lung function, imaging

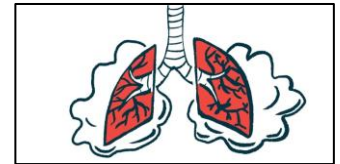
Exercise Test - Six minute walk test.

- Walk expected distance? Dyspnoea level?
- O2 desaturation? Severe fatigue?



Assessment of lung function:

- Spirometry (pre- and post-bronchodilator)
- Additional lung function tests where available (oscillometry, DCLO)



Lung imaging:

- CXR at the end of treatment, repeat where indicated during longterm monitoring
- Moderate to severe cases - Chest CT (with high resolution reconstruction, if available)

Prevent further lung infections, Treat Infective Exacerbations



Prevention

- Vaccination:
 - Pneumococcal, Influenza, Covid
- Airway disease / bronchiectasis:
 - preventive antibiotics - TB px, bacterial px
 - Airway clearance – chest physio
- Immune modulators
 - Macrolides, corticosteroids where indicated

Supportive care

- Optimise nutrition
- Psychosocial support
- Smoke and vaping cessation

Treat subsequent lung infections promptly

- Broad spectrum antibiotics 14 – 21 days
- Chest physio / sputum clearance
- Muco-active agents PRN (hypertonic saline nebulisation)

Pulmonary Rehabilitation



Management – Pulmonary Rehabilitation



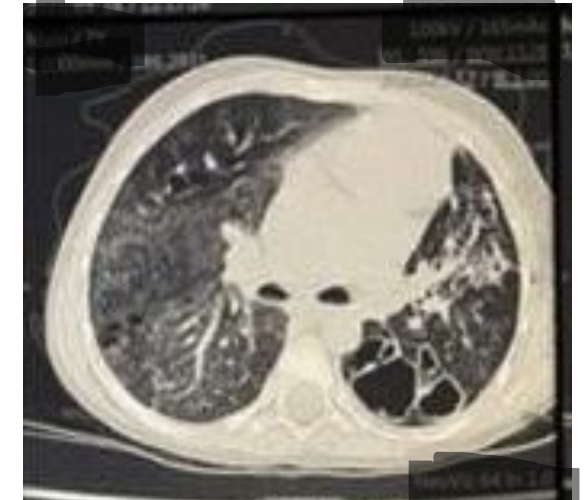
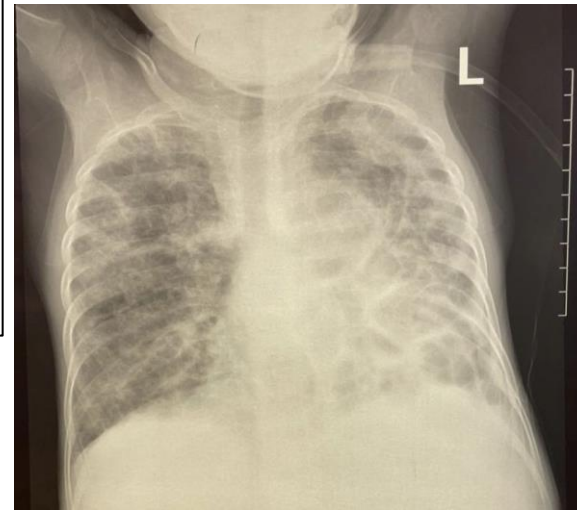
- Aerobic exercise: free walking
 - 30 min 2–5 times/week for 4–8 weeks
- Strength training: upper and lower extremities: free weights
 - 2–3 set of 6–12 repetitions, intensity set according to perceived muscles fatigue
- Inspiratory muscle training:
 - Interval training: 10 exercises followed by 10 seconds break between each.
- Airway clearance techniques (sputum+, bronchiectasis):
 - 15–30 min one or more times/day
- Nutritional Support – optimise BMI
 - Diet guidance, supplemental micronutrients
- Psychological Support
 - counselling, support groups.



Kenyan Child, TB & HIV diagnosis age 5 yrs. Severe Post-TB symptoms, Extensive lung pathology on CXR & Chest CT.

- Hx: Cough, fever, night sweats x 4wk
- Grandma had TB
- Hospitalised, Severe miliary & PTB
- HIV diagnosed child, CD4 336
- 6-mth TB Rx, ART, partial improvement

CXR Chest CT at 6yr, 12 mth post-TB: Bronchiectasis, fibrosis



CXR age 5yr: Miliary, hilar TB

- 6mth after TB....
- New pneumonia
- Recurrent lung infections in hospital
- COVID-19, Pseudomonas
- Progressive respiratory failure
- O2 dependant. Destroyed lung
- Died 2 years after TB



Thank you!
Asanteni!
Merci!
Grazias!





3rd INTERNATIONAL

POST-TUBERCULOSIS

SYMPOSIUM 2025

CHARTING THE COURSE

APRIL 14 - 16 | STIAS INSTITUTE, STELLENBOSCH, CAPE TOWN

**We are delighted to share that registration is now open for the
3rd International Post-Tuberculosis Symposium!**

In addition to registration, there are two new opportunities that we would like to