2018 Tuberculosis course

Institut Pasteur/Nanshan CCDC
October 14-26
Shenzhen, China

Tuberculosis in children

Pr Christophe Delacourt
Pediatric Pulmonology
Necker Hospital, Paris, France

TB burden in children

Each year,

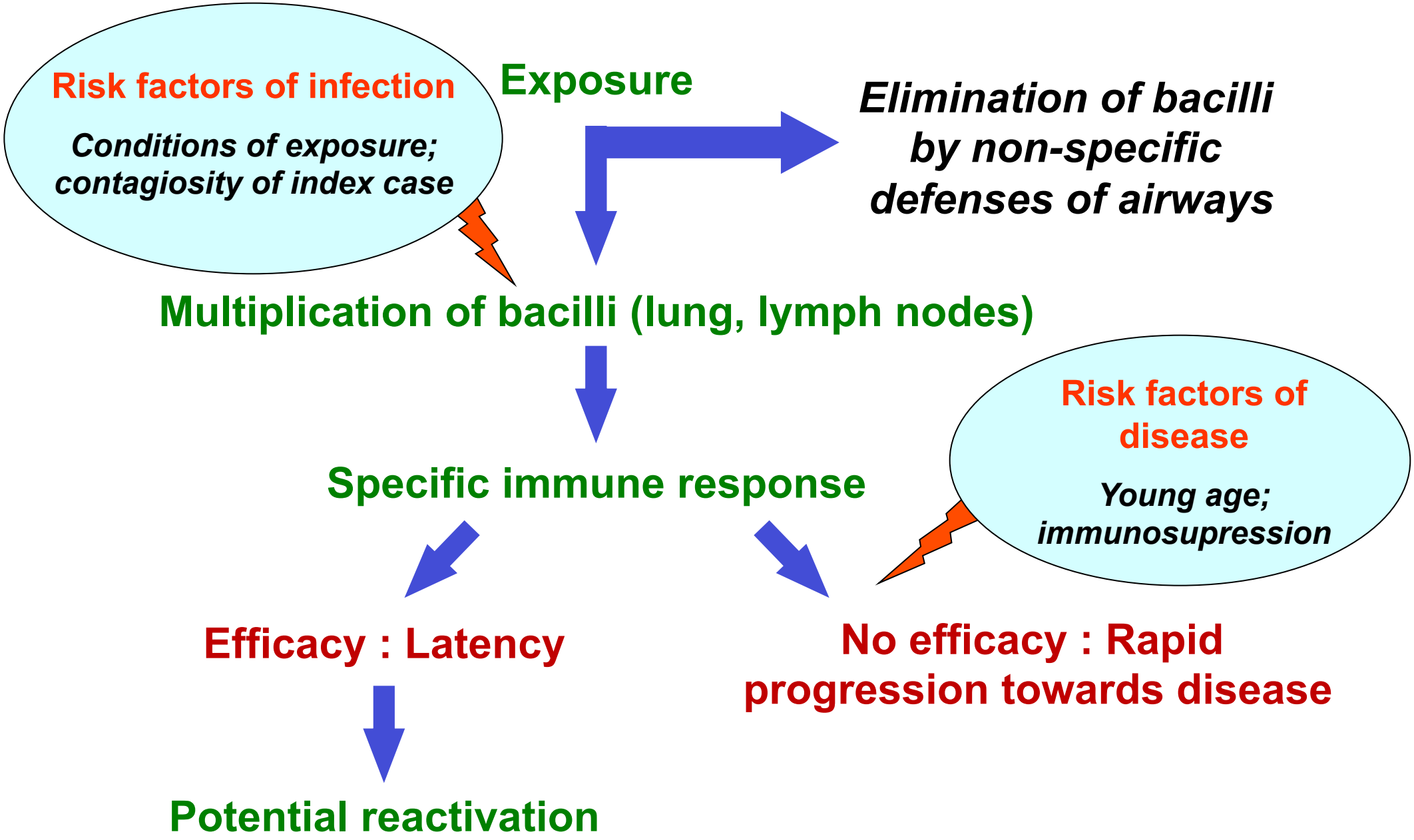
- **At least one million children (< 15 yrs) become ill with TB**
- **Around 234 000 children die of TB (40 000 HIV+)**

Tuberculosis often goes undiagnosed in children

→ **difficulty in establishing a definitive diagnosis**

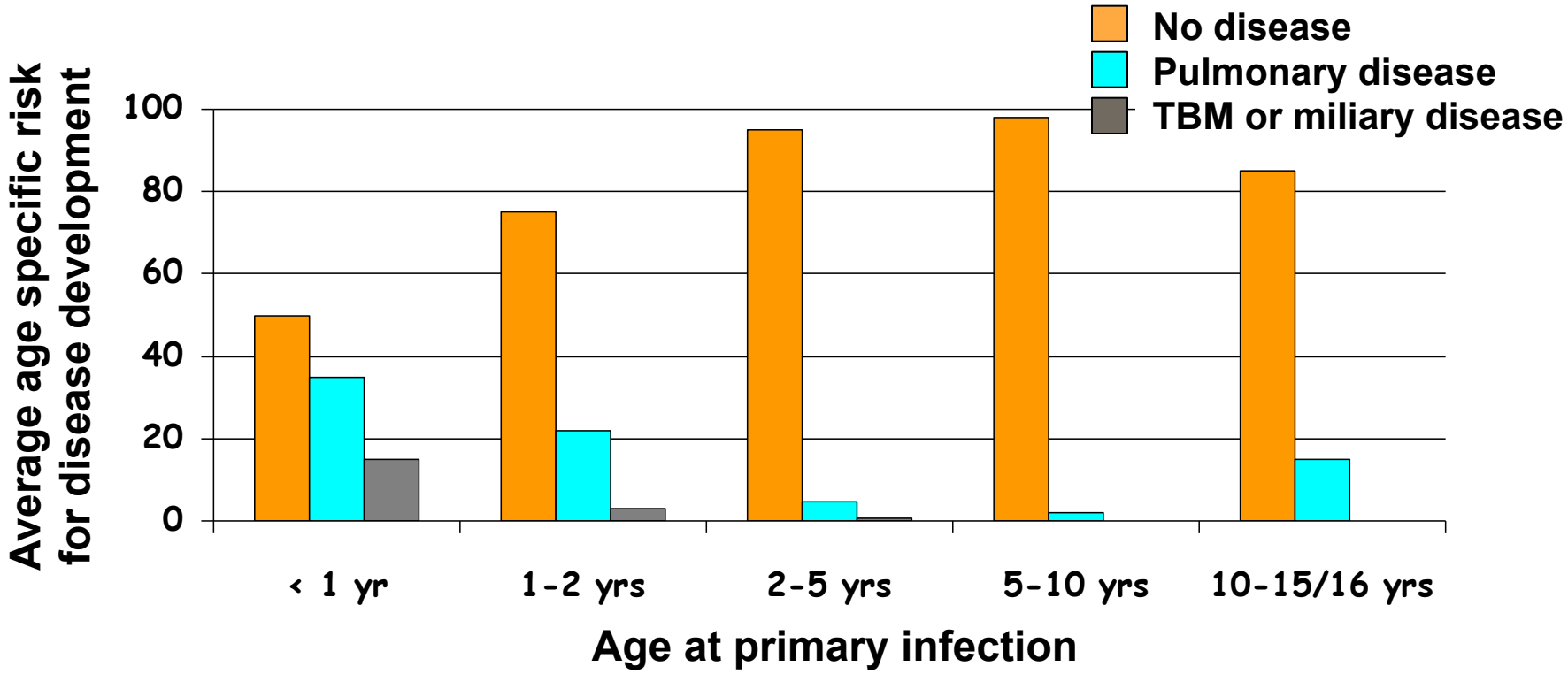
→ **lower public health priority (low rate of smear positive cases)**

Global TB report – WHO - 2018


Risk factors of infection
Conditions of exposure; contagiosity of index case
Exposure
Elimination of bacilli by non-specific defenses of airways
Multiplication of bacilli (lung, lymph nodes)
Specific immune response
Risk factors of disease
Young age; immunosupression
Efficacy : Latency
No efficacy : Rapid progression towards disease
Potential reactivation

Natural history of TB in children

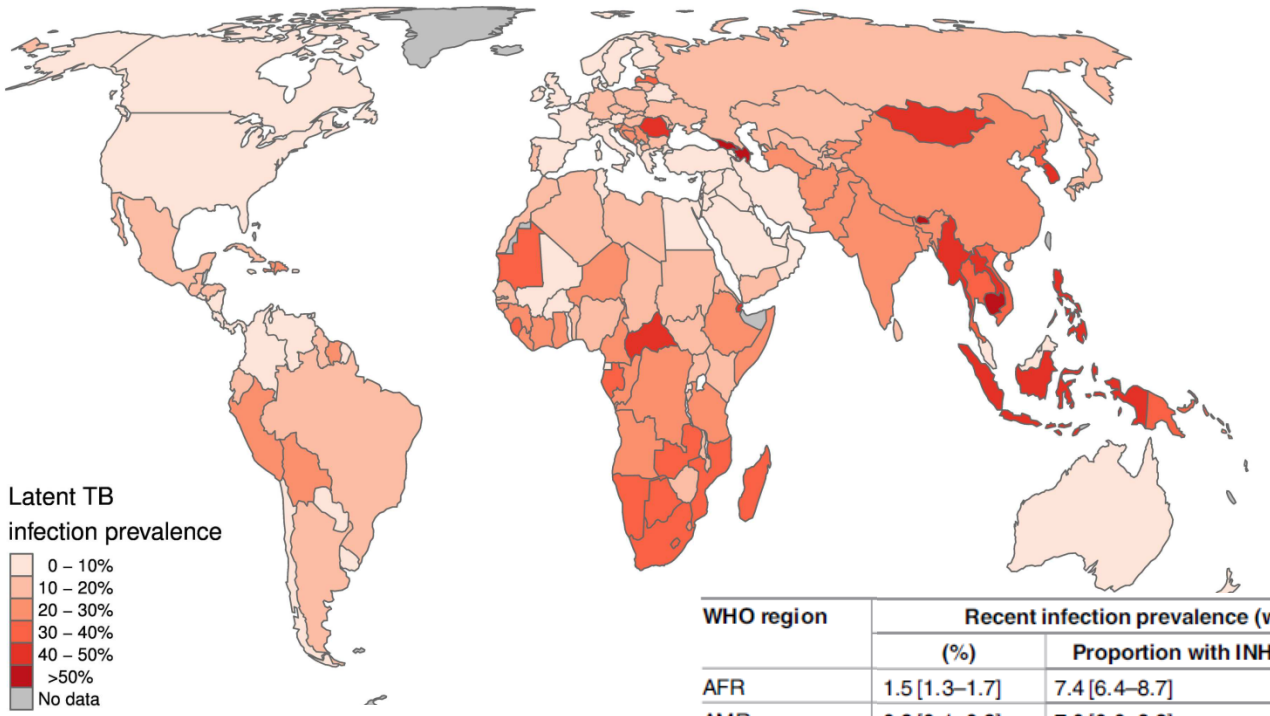
Original studies on childhood pulmonary TB, conducted between 1920 and 1950 (pre-chemotherapy), and with a study duration of at least 10 years



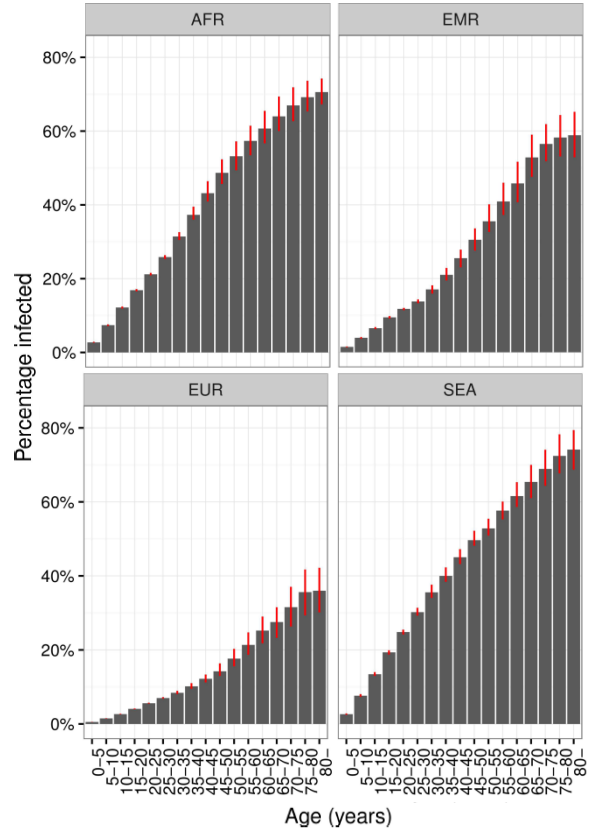
Marais et al. Int J Tuberc Lung Dis 2004

Global Burden of Latent Tuberculosis Infection

Construction of trends in annual risk in infection (ARI) for countries between 1934 and 2014 using a combination of direct estimates of ARI from LTBI surveys (131 surveys from 1950 to 2011) and indirect estimates of ARI calculated from WHO estimates of smear positive TB prevalence from 1990 to 2014. Calculation of the number and proportions of individuals infected by applying estimated ARI time-series to the demography in each country



WHO region	Recent infection prevalence (within 2 y)	
	(%)	Proportion with INH-R infection (%)
AFR	1.5 [1.3–1.7]	7.4 [6.4–8.7]
AMR	0.2 [0.1–0.2]	7.0 [6.0–8.8]
SEA	1.2 [0.9–1.6]	9.5 [8.8–10.3]
EMR	0.7 [0.5–1.0]	13.1 [10.0–15.5]
WPR	0.5 [0.4–0.7]	14.7 [13.9–15.6]
EUR	0.3 [0.2–0.3]	29.5 [23.8–45.1]
GLOBAL	0.8 [0.7–0.9]	10.9 [10.2–11.8]



Rein et al. PLOS Med 2016

LTBI treatment and prevention of disease

Missed Opportunities for Preventing Tuberculosis Among Children Younger Than Five Years of Age

Mark N. Lobato, MD*‡; Janet C. Mohle-Boetani, MD‡; and Sarah E. Royce, MD, MPH‡

Pediatrics 2000 Dec;106(6):E75

Improvements in contact investigations may have prevented TB in 40% of children found in a contact investigation,

Research paper

Potentially preventable tuberculosis cases in children exposed to a contaminant case

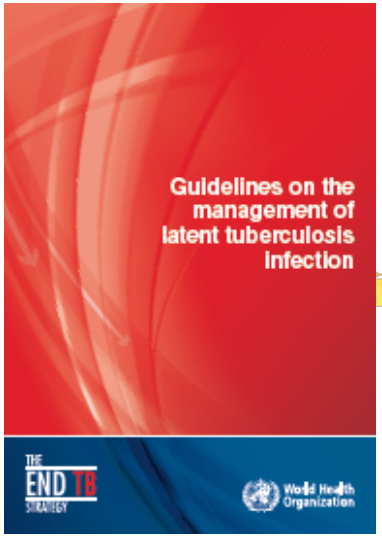
V. Ollier [a,*], F. Antoun [b], G. Thouvenin [c], A. Faye [d], I. Kone-Paut [e], G. Benoist [f], D. Antoine [g], C. Charlois [b], C. Delacourt [a]

Arch Pediatr 2018 Sep 13. [Epub ahead of print]

50% of pediatric TB cases (<10 yrs) had a missed opportunity for potential prevention, due to the absence of screening despite a known contaminant or to screening not in compliance with current recommendations

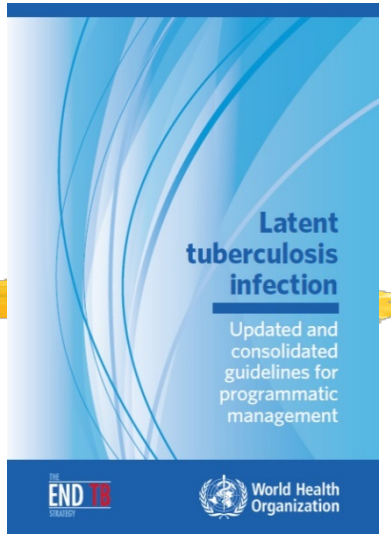
- ✓ **Too long interval between exposure and screening**
- ✓ **Absence of adequate reading of tuberculin test**
- ✓ **Absence of prophylaxis/treatment**

Identification and treatment of latent TB infection in children with known exposure to an index case are appropriate tools for prevention of TB disease in children



Extended guidelines in HIV negative children

2014 → 2018



- HIV-negative children aged < 5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment. *(Strong recommendation, high-quality evidence. Updated recommendation)*
- In countries with a low TB incidence, adults, adolescents and children who are household contacts of people with bacteriologically confirmed pulmonary TB should be systematically tested and treated for LTBI. *(Strong recommendation, high–moderate-quality evidence. Existing recommendation)*
- In countries with a high TB incidence, children aged ≥ 5 years, adolescents and adults who are household contacts of people with bacteriologically confirmed pulmonary TB who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. *(Conditional recommendation, low-quality evidence. New recommendation)*

Low-TB-incidence country: Country with a WHO-estimated TB incidence rate of < 100 per 100 000 population

Potential effect of household contact management on childhood tuberculosis: a mathematical modelling study

Peter J Dodd, Courtney M Yuen, Mercedes C Becerra, Paul Revill, Helen E Jenkins, James A Seddon

Mathematical modelling study with global and national estimates of the impact of moving from zero to full coverage of household contact management (with and without preventive therapy for TST-positive children > 5 yrs)

Scenario A: no household contact management
Scenario B: preventive therapy to children younger than 5 years and children who are HIV positive
Scenario C: preventive therapy to children younger than 5 years and children who are HIV positive or TST positive

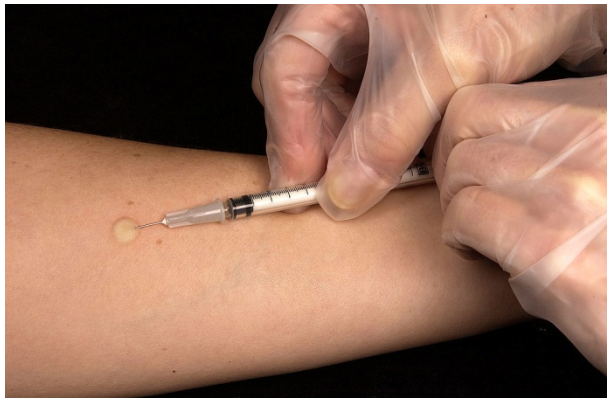
All children younger than 15 years	Difference between B and A	Difference between C and A
Tuberculosis cases	−66 700 (−72 370 to −59 790)	−159 500 (−170 900 to −147 000)
Tuberculosis deaths	−103 600 (−111 900 to −94 480)	−108 400 (−116 700 to −98 800)
Total life expectancy (years)	7 006 000 (6 373 000 to 7 567 000)	7 305 000 (6 663 000 to 7 874 000)

Lancet Global Health, 2018, 25 september

Diagnosis of LTBI in children : immune tests

Immune test = Evidence of specific response of lymphocytes to bacillar multiplication

TST



Limited specificity in BCG-vaccinated populations

Interferon γ Release Assays (IGRAs)

QuantiFERON-TB Gold Plus®

T-SPOT®

High specificity for infection with M. tuberculosis complex

Specificity of IGRAs in children

Meta-analysis of 31 studies (6183 children) with QFT-G-IT, 14 studies (2518 children) avec T-SPOT.TB, and 34 studies (6439 children) with TST

	TST	QFT-G-IT	T-SPOT.TB
Low income countries	0.90 (95%CI 0.87-0.92)	0.85 (95%CI 0.82-0.88)	0.93 (95%CI 0.87-0.96)
High income countries	0.92 (95%CI 0.89-0.93)	0.97 (95%CI 0.96-0.98)	0.98 (95%CI 0.96-0.99)
studies using the three assays simoultaneously	0.84 (95%CI 0.79-0.89)	0.97 (95%CI 0.93-0.99)	0.97 (95%CI 0.93-0.99)
Immunocompromised / HIV infected children	0.97 (95%CI 0.92-0.99)	0.90 (95%CI 0.81-0.95)	Not evaluable

Sollai *et al. BMC Infectious Diseases* 2014, **14**(Suppl 1):S6
http://www.biomedcentral.com/1471-2334/14/S1/S6

Sensitivity of IGRAs in children

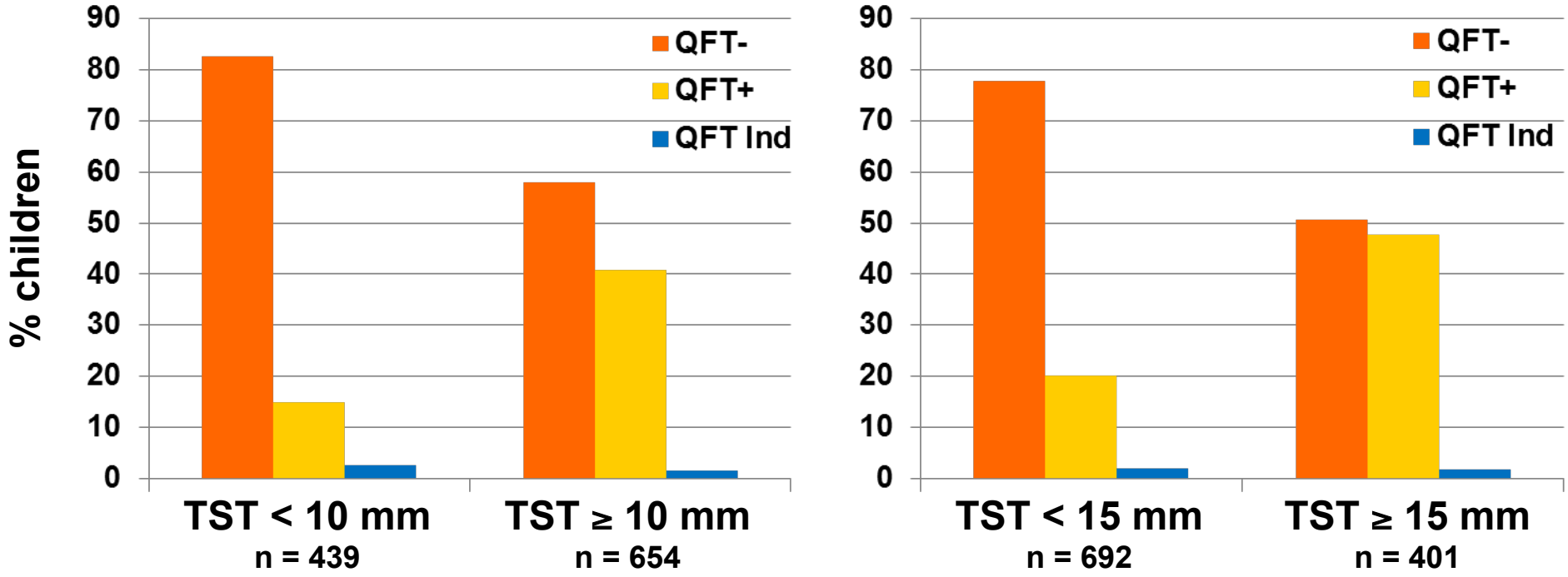
Meta-analysis of 31 studies (6183 children) with QFT-G-IT, 14 studies (2518 children) avec T-SPOT.TB, and 34 studies (6439 children) with TST

	TST	QFN-G-IT	T-SPOT.TB
Low income countries	0.67 (95%CI 0.64-0.70)	0.57 (95%CI 0.52-0.61)	0.61 (95%CI 0.57-0.65)
High income countries	0.78 (95%CI 0.74-0.82)	0.79 (95%CI 0.75-0.82)	0.67 (95%CI 0.62-0.73)
studies using the three assays simoultaneously	0.85 (95%CI 0.78-0.91)	0.78 (95%CI 0.70-0.84)	0.76 (95%CI 0.68-0.83)
microbiologically confirmed cases, in high income countries	0.86 (95%CI 0.79-0.91)	0.86 (95%CI 0.81-0.90)	0.79 (95%CI 0.69-0.87)
Immunocompromised / HIV infected children	0.54 (95%CI 0.49-0.59)	0.47 (95%CI 0.38-0.55)	Not evaluable

Sollai *et al. BMC Infectious Diseases* 2014, **14**(Suppl 1):S6
http://www.biomedcentral.com/1471-2334/14/S1/S6

DISCREPANCIES BETWEEN IGRAs AND TST IN CHILDREN

1128 children ≤ 16 years tested in 5 european countries. 61.7% BCG+. TST ≥ 10 mm : 60.5 % (682/1128), QFT + : 30.3 % (331/1093), T-SPOT + : 37.9 % (145/382)

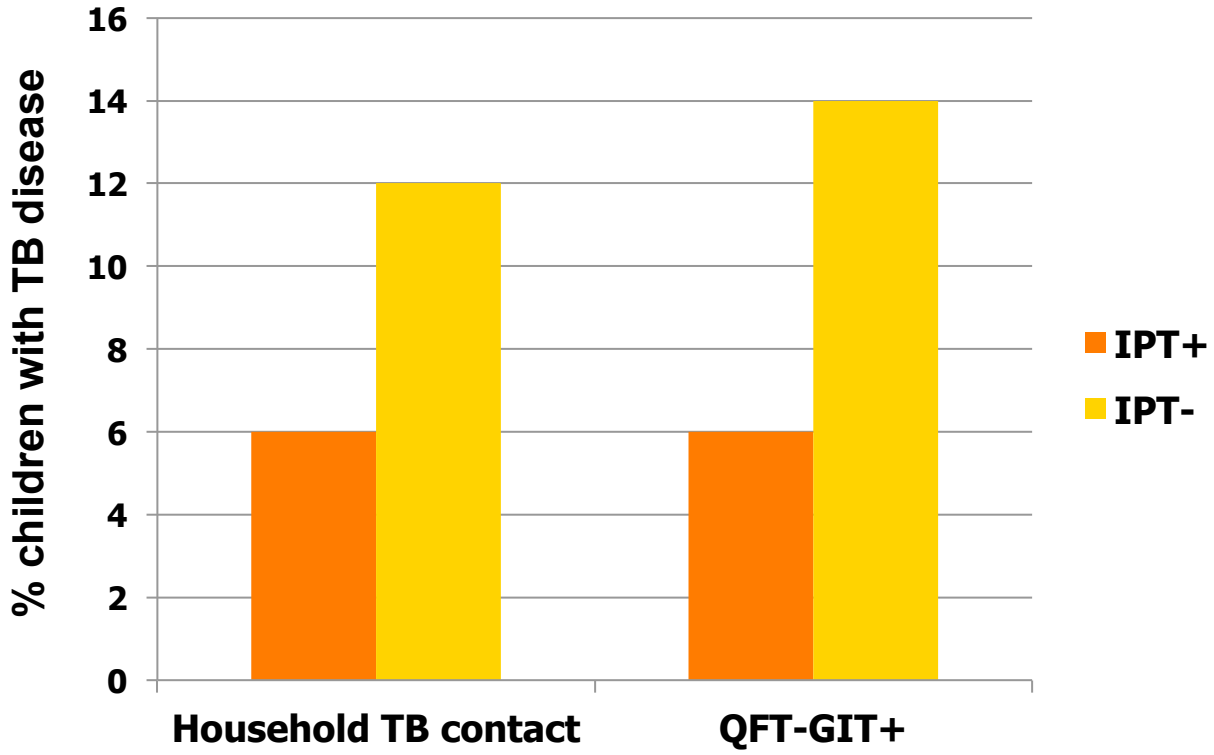


Basu Roy et al. AJRCCM 2012

PROGNOSTIC VALUE OF IGRAs IN CHILDREN

Studies in high prevalence countries

HIV-uninfected South African infants aged 4–6 months screened for enrolment in a TB vaccine trial (MVA85A), and excluded because of a baseline household TB contact (131/4749 [3%], no QFT performed), or no known contact but positive QFT-GIT result (279/4749, 6%). Outcome data are reported for 36 months after IPT referral.



Luabeya et al. Pediatr Infect Dis J 2015;34:1218

PROGNOSTIC VALUE OF IGRAs IN CHILDREN

Studies in high prevalence countries

QFT negative, HIV uninfected young children aged 18–24 weeks enrolled in a tuberculosis vaccine MVA85A efficacy trial (South Africa). Stratification of participants by quantitative QFT result at the intermediate study visit (day 336) and determination of risk of progression to active tuberculosis disease over the subsequent 6–24 months. Both placebo and vaccine groups included (no QFT differences between groups)

6% of the included population converted his/her QFT at J336

	N	Cases	Incidence (95% CI)	IRR (95% CI)	p value
Revised case definition 1			per 100 person-years		
<0·35 IU/mL	2232	16	0·7 (0·4–1·1)	Ref	Ref
0·35–4·00 IU/mL	79	2	2·5 (0·4–9·4)	3·7 (0·4–15·8)	0·23
>4·00 IU/mL	63	10	28·0 (14·9–45·7)	42·5* (17·2–99·7)	<0·0001
Culture or Xpert positive					
<0·35 IU/mL	2232	11	0·5 (0·2–0·8)	Ref	Ref
0·35–4·00 IU/mL	79	2	2·5 (0·4–9·4)	5·4 (0·6–24·8)	0·13
>4·00 IU/mL	63	7	19·6 (8·9–36·8)	43·3† (14·2–122·3)	<0·0001

Andrew et al. Lancet 2017

PROGNOSTIC VALUE OF IGRAs IN CHILDREN

Studies in low prevalence countries

European study (26 centers, 10 countries). 5,020 contacts of 1,023 index cases (QFT or TSPOT). 25 prevalent secondary cases at screening, and 24 incident cases among 4,513 contacts during 12,326 years of cumulative follow-up (3 years).

Development of TB during Follow-up Depending on IGRA Test Result and Preventive Chemotherapy

	Test Result	n	Prophylaxis	TB Cases	Progression Rate (%)	Person Time (*yr*)	Incidence/100 Patient-Years	Number Needed to Treat
QFT	Negative	2,419	No	3	0.12	6,349.8	0.047	807
	Negative	104	Yes	0	0	326.4	0	
	Positive	421	No	14	3.33	1,169.1	1.198	38
	Positive	481	Yes	3	0.62	1,296.5	0.231	
TSPOT	Negative	722	No	2	0.28	1,790.1	0.112	361
	Negative	58	Yes	0	0	316.1	0	
	Positive	73	No	2	2.73	247.8	0.807	37
	Positive	208	Yes	0	0	829.7	0	

Zellweger et al. AJRCCM 2015

PROGNOSTIC VALUE OF IGRAs IN CHILDREN

Studies in low prevalence countries

937 contacts with a smear positive case of TB (1/3 < 15 yrs ; 2/3 BCG+), followed up for 4 years (Barcelona, Spain). 15 cases developed active TB, all with initially positive QFT and TST ≥ 5 mm (14/81 untreated LTBI and 1/412 treated LTBI, p<0.001).

accumulated incidence and incidence rate of subjects who developed TB during follow-up of patients who did not undergo treatment

Test Results	No. of Contacts	No. of Cases	AI	IR	PPV (95% CI)	NPV (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Total	453	14	3.09	7.72	—	—	—	—	—	—
Pos QFN	81	14	17.28	43.21	17 (9–26)	100 (100–100)	100 (100–100)	85 (81–88)	7.53 (5.91–9.58)	0 (0–0)
Neg QFN	372	0	0	0						
TST ⩾ 5 mm	340	14	4.12	10.29	4 (2–6)	100 (100–100)	100 (100–100)	26 (22–30)	1.35 (1.27–1.42)	0 (0–0)
TST < 5 mm	113	0	0	0						
TST ⩾ 10 mm	233	13	5.58	13.95	6 (3–9)	100 (99–100)	93 (79–100)	50 (45–55)	1.86 (1.56–2.21)	0.14 (0.02–0.95)
TST < 10 mm	220	1	0.45	1.14						
TST ⩾ 15 mm	107	11	10.3	25.70	10 (5–16)	99 (98–100)	79 (57–100)	78 (74–82)	3.59 (2.59–4.98)	0.27 (0.1–0.75)
TST < 15 mm	346	3	0.86	2.17						

Definition of abbreviations: AI = accumulated incidence (%); IR = tuberculosis incidence rate during follow-up (cases per 1,000 person-years)

Altet et al. AJRCCM 2015

PROGNOSTIC VALUE OF IGRAs IN CHILDREN

Studies in low prevalence countries

937 contacts with a smear positive case of TB (1/3 < 15 yrs ; 2/3 BCG+), followed up for 4 years (Barcelona, Spain). 15 cases developed active TB, all with initially positive QFT ans TST ≥ 5 mm (14/81 untreated LTBI and 1/412 treated LTBI, p<0.001).

TB incidence among 937 contacts of smear-positive index cases monitored for 4 years, stratified by baseline TST induration and IFN-γ concentration

Test and Range of Results	n	No. of TB Cases	AI	IR	Sensitivity	Specificity	PPV (95% CI)	Positive LR (95% CI)	Pretest Probability (%)	Positive Posttest Probability (%)
IFN-γ concentration, IU/ml										
0–0.34	531	0	0	0	—	100	Reference	Reference	—	—
0.35–5	135	4	3.0	7.41	100	80	3 (0–6)	4.95 (4.33–5.89)	0.6	3
5.0–10	166	5	3.01	7.53	100	77	3 (0–6)	4.3 (3.75–4.92)	0.7	3
⩾10	105	6	5.7	14.3	100	84	6 (1–10)	6.36 (5.3–7.63)	0.9	6
TST induration, mm										
0–4	212	0	0	0	—	100	Reference	Reference	—	—
5–9	155	1	0.64	1.61	100	58	1 (0–2)	2.38 (2.11–2.68)	0.27	1
10–14	303	3	0.99	2.5	100	41	1 (0–2)	1.71 (1.59–1.84)	0.6	1
⩾15	267	11	4.3	10.74	100	45	4 (2–7)	1.83 (1.68–1.99)	2.3	7

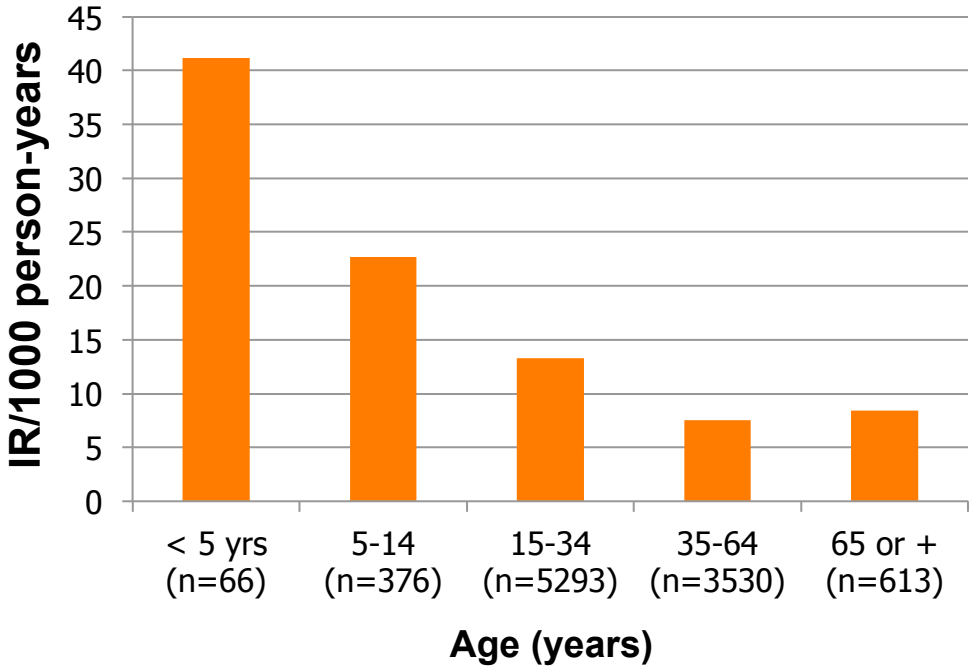
Definition of abbreviations: AI = accumulated incidence (%); IR = tuberculosis incidence rate during follow-up (cases per 1,000 person-years)

Altet et al. AJRCCM 2015

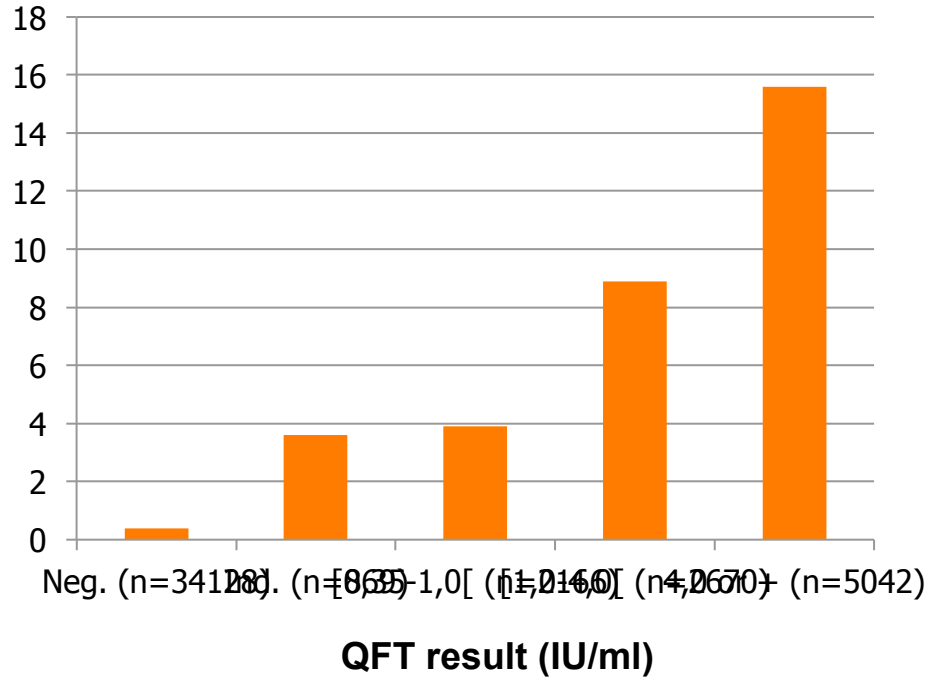
PROGNOSTIC VALUE OF IGRAs

Population-based prospective cohort (Norway): QFT results (1 January 2009–30 June 2014) linked with national registry data to assess the prognostic value of QFT for incident TB. Follow-up until 30 June 2016. 50 389 QFT results (22% positive) from 44 875 individuals, of whom 257 (0.6%) developed TB.

Incidence rates within 2 years after positive QFT according to the age



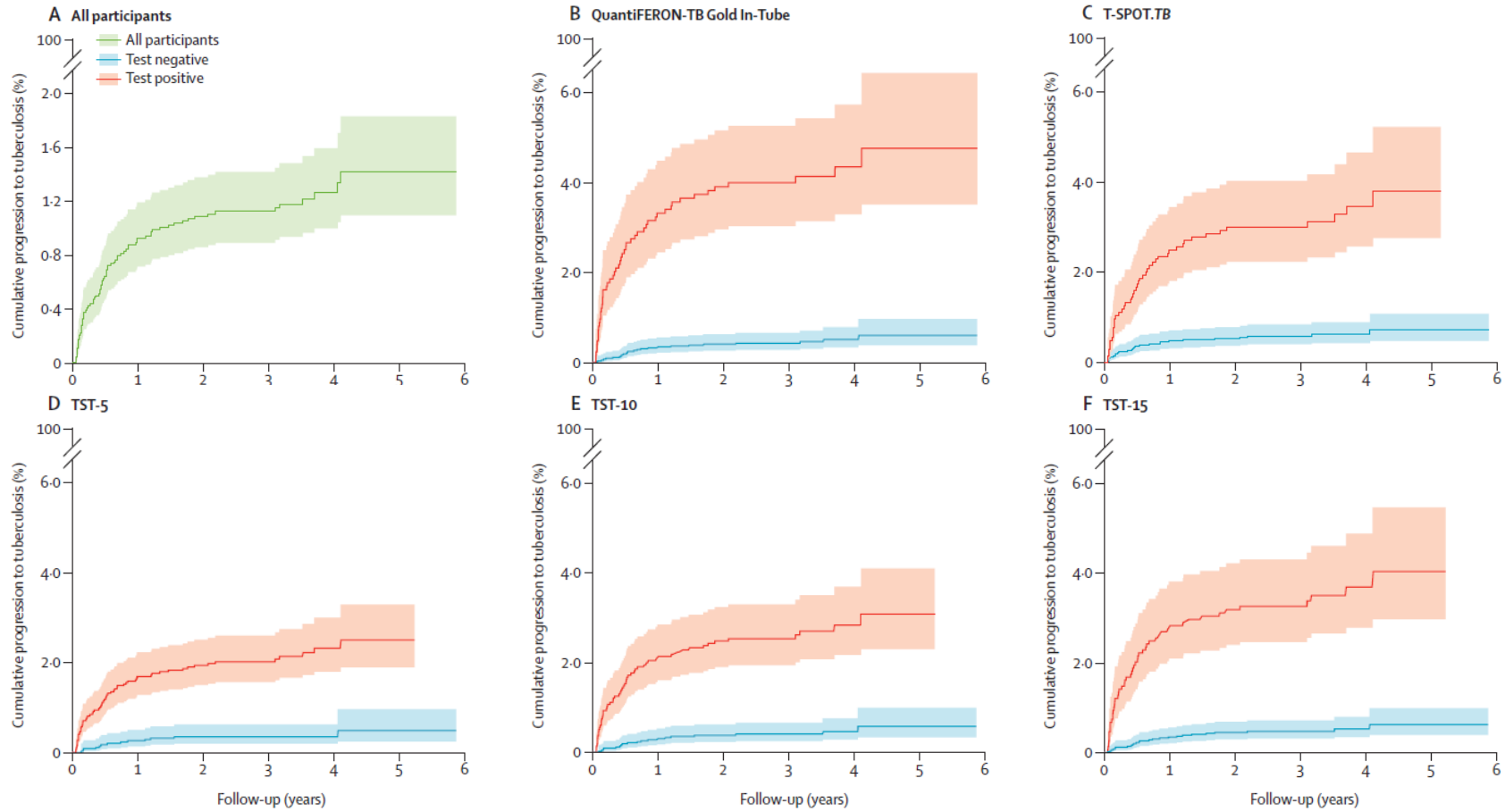
Incidence rates within 2 years after QFT, according to QFT result



Winje et al. Thorax 2018

PROGNOSTIC VALUE OF IGRAs IN ADULTS

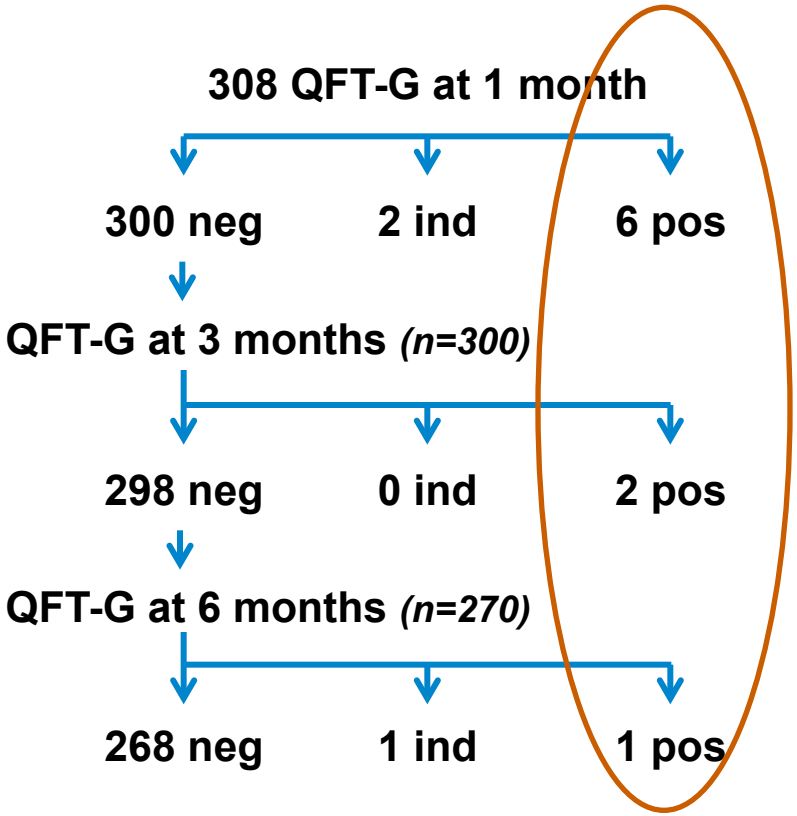
Prospective cohort study (54 centres, UK). Recent contact with active TB (n=4861) or migrant who had arrived in the UK in the past 5 years from a country with a high TB incidence (n=4749), and aged 16 years or older



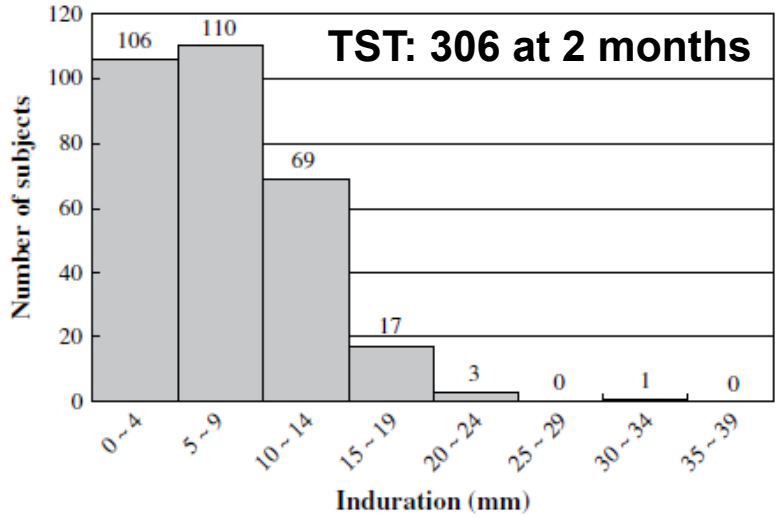
Abubakar et al. Lancet Infect Dis 2018

Prognostic value of discordant results TST+/ IGRA- in exposed children

313 children (8-9 years, 99% BCG+) exposed to a smear+ teacher : 41 close contact (≥ 90 h) ; 272 occasional contacts (≤ 18h). Treatment only if IGRA+



4/41 close contacts (10%)
5/269 occasional contacts (2%)



- 10 children with treatment : 9 IGRA+ and 1 IGRA-/ TST 15 mm (BCG-): no case of active TB
- 303 children with no treatment, all IGRA-, including 89 with TST ≥ 10 mm (13 close contacts) : no case of active TB at 3 years

Higuchi et al. J Infect 2009

Prognostic value of discordant results TST+/ IGRA- in exposed children

Retrospective evaluation of 215 children < 15 years, with positive TST (10 mm if no known contact, 5 mm if known contact, independently of BCG vaccination). Follow-up of untreated children with negative QFT (San Francisco)

158 discordant results TST+/QFT-

146 untreated children, and followed-up for a median duration of 5.7 years (including 8 contacts)

No case of TB

Grinsdale et al. J Pediatr Infect Dis Soc 2016

IGRAs IN YOUNG CHILDREN

Indeterminate tests

1128 children ≤ 16 yrs in 5 countries (Greece [n=491], Spain [n=459], UK [n=110], Italy [n=42], Bulgaria [n=26]). 99 (8.8%) < 2 yrs and 268 (23.8%) < 5 yrs. 61.7% BCG+

Assay	All Ages	Age, <2 yr	Age, 2–5 yr	Age, >5 yr
TST, n = 1,128				
Median induration, mm (IQR)	12 (8–16)	9 (0–13)	10 (0–15)	13 (10–17)
Positive, no. (%)	682 (60.5)	32/99 (32.3)	96/215 (44.7)	554/814 (68.1)
Negative, no. (%)	446 (39.5)	67/99 (67.7)	119/215 (55.3)	260/814 (31.9)
QFT-GIT, n = 1,093				
Positive, no. (%)	331 (30.3)	22/96 (22.9)	50/206 (24.3)	259/791 (32.7)
Negative, no. (%)	742 (67.9)	71/96 (74.0)	148/206 (71.8)	523/791 (66.1)
Indeterminate, no. (%)	20 (1.8)	3/96 (3.1)	8/206 (3.9)	9/791 (1.1)
T-SPOT.*TB*, n = 382				
Positive, no. (%)	145 (37.9)	9/36 (25.0)	19/73 (26.0)	117/273 (42.9)
Negative, no. (%)	231 (60.5)	26/36 (72.2)	51/73 (69.9)	154/273 (56.4)
Indeterminate, no. (%)	6 (1.6)	1/36 (2.8)	3/73 (4.1)	2/273 (0.7)

Basu Roy et al. AJRCCM 2012

IGRAs IN YOUNG CHILDREN

Indeterminate tests

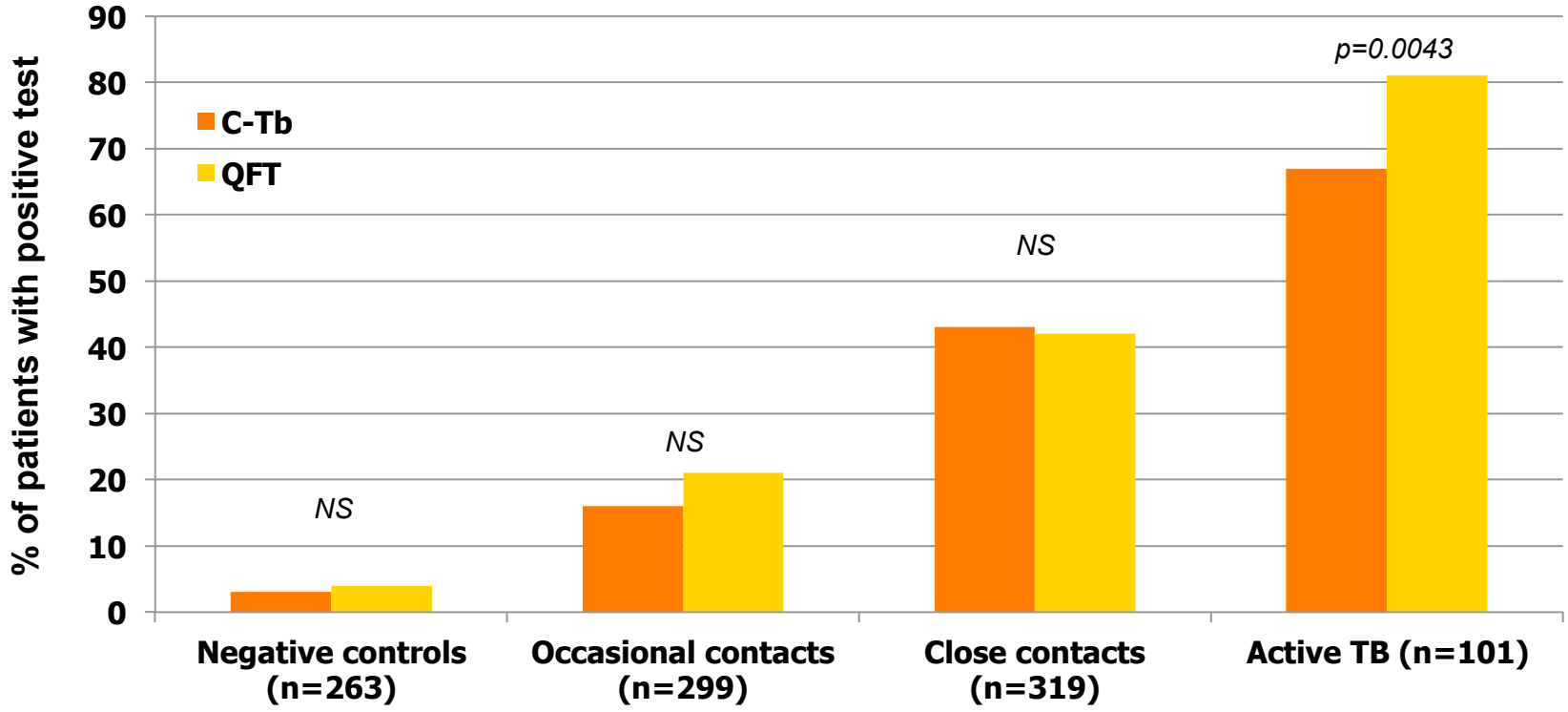
European multicentric study, with IGRA (QFT or T-SPOT) following exposure

	Total [*n (%)*]	IGRA Indeterminate
	n (col %)	n (col %) (row %)
Age group,		
0–4 yr	96 (1.9)	0 (0.0) (0.0)
5–14 yr	399 (7.9)	1 (3.7) (0.3)
15–34 yr	2,057 (41.0)	15 (55.6) (0.7)
35–64 yr	2,207 (44.0)	9 (33.3) (0.4)
⩾65 yr	237 (4.7)	2 (7.4) (0.8)
Unknown	24 (0.5)	0 (0.0) (0.0)

Zellweger et al. AJRCCM 2015

C-Tb : a new promising skin test ?

C-Tb (Statens Serum Institute, Denmark, 0.1 µg per 0.1 mL dose) = skin test based on recombinant ESAT-6 and CFP10, and designed to combine operational advantages of TST with specificity of IGRAs. Phase 3 trial. 970 patients evaluated (121 0-17 yrs). C-Tb positivity if induration 5 mm or larger 48–72 h after intradermal injection.



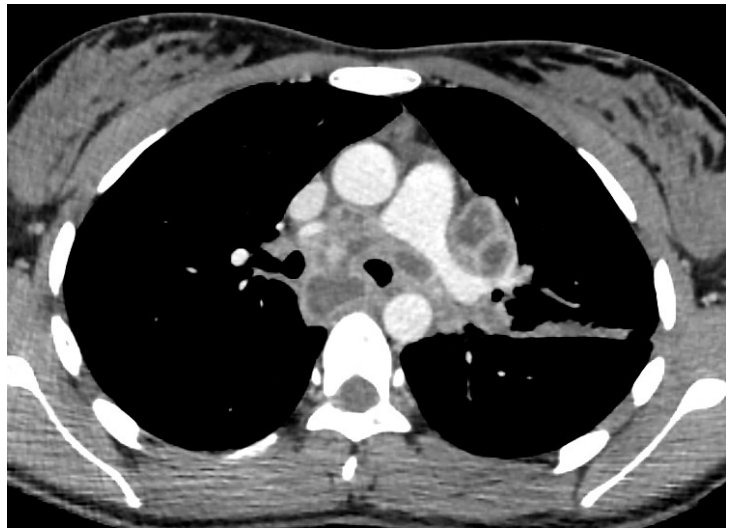
Ruhwald et al. Lancet Respir Med 2017

Specific features of TB disease in children

- **Disease is often paucibacillary**

  → diagnosis is usually not confirmed microbiologically, but relies on a body of epidemiological, clinical, radiological and immune arguments

- **Hilar and paratracheal lymphadenopathy are the characteristic lesion of childhood tuberculosis**



  → complications with airway obstruction are frequent

Case Definition	Refined Criteria[a]
Confirmed tuberculosis	Bacteriological confirmation obtained Requires *Mycobacterium tuberculosis* to be confirmed (culture or Xpert MTB/RIF assay) from at least 1 respiratory specimen

Unconfirmed tuberculosis	Bacteriological confirmation NOT obtained AND at least 2 of the following:
	• Symptoms/signs suggestive of tuberculosis (as defined)
	• Chest radiograph consistent with tuberculosis
	• Close tuberculosis exposure or immunologic evidence of *M. tuberculosis* infection
	• Positive response to tuberculosis treatment (requires documented positive clinical response on tuberculosis treatment—no time duration specified)
	- With *M. tuberculosis* infection
	  • Immunological evidence of *M. tuberculosis* infection (TST and/or IGRA positive)
	- Without *M. tuberculosis* infection
	  • No immunological evidence of *M. tuberculosis* infection

Unlikely tuberculosis	Bacteriological confirmation NOT obtained AND Criteria for "unconfirmed tuberculosis" NOT met
	- With *M. tuberculosis* infection
	  • Immunological evidence of *M. tuberculosis* infection (TST and/or IGRA positive)
	- Without *M. tuberculosis* infection
	  • No immunological evidence of *M. tuberculosis* infection

Classification of intrathoracic TB in children: Update 2015

1.

Pediatric TB diagnosis can not be based only on microbiology

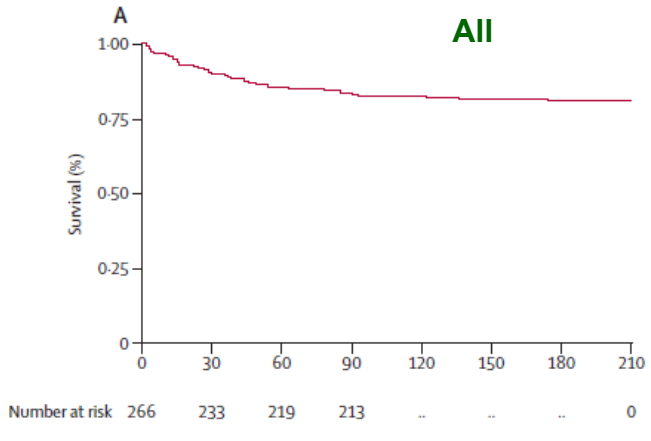
2.

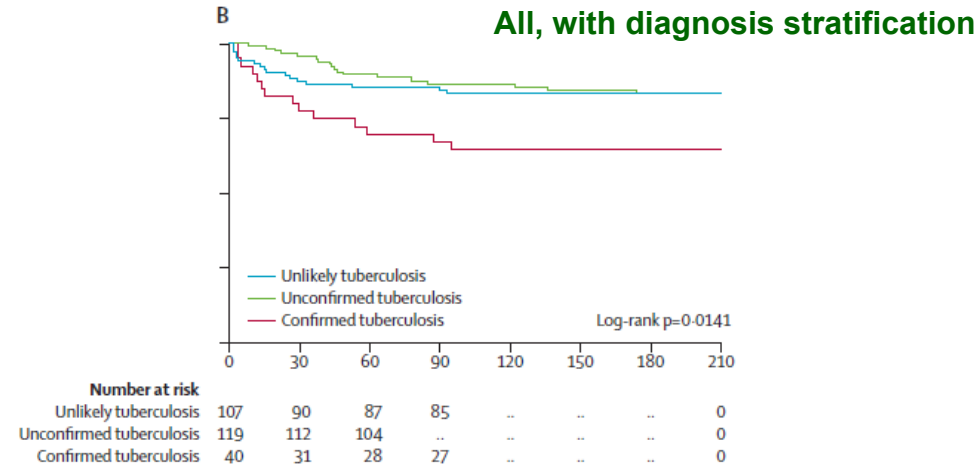
Evaluation of a child with TB suspicion should include :

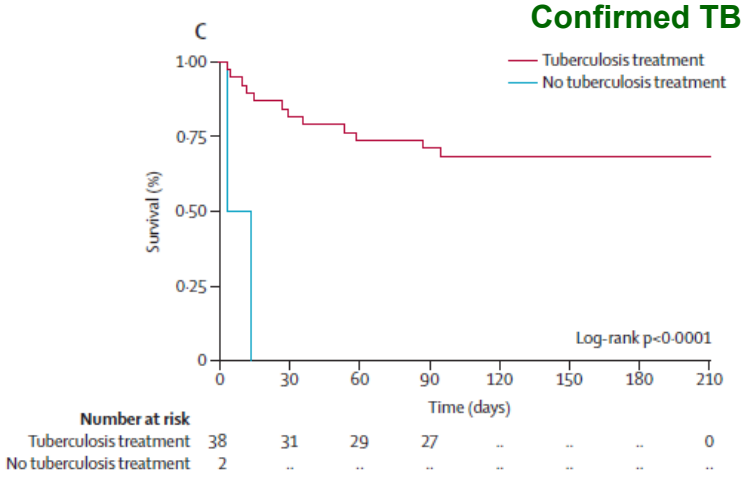
- **Clinical evaluation**
- **Notion of close exposure**
- **Chest X-ray**
- **Immune test**

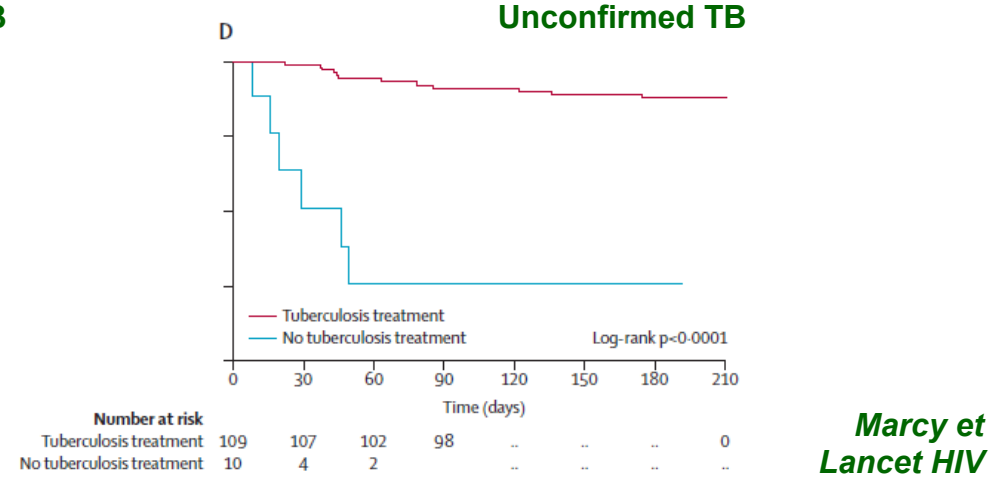
Pediatric TB: the challenges of an appropriate diagnosis

PAANTHER study: Prospective evaluation of 438 HIV+ children < 14 years, with pre-defined clinical suspicion of TB, including 226 with no ART at inclusion. Post-procedure diagnosis: 40 confirmed TB, 119 unconfirmed TB, 107 unlikely TB









Marcy et al. Lancet HIV 2017

Clinical symptoms

- **Clinical signs vary with diagnostic delays**

  → **When screening, approximately 50% of children with TB disease (abnormal Rx) are asymptomatic**

- **Clinical signs are non specific**

  → **They are not sufficient to affirm the diagnosis**

Diagnostic value of symptoms

428 children < 13 years with chronic cough (Cape Town, South Africa). Diagnostic of « TB » (n=197) if : (i) bacteriological confirmation (n=96) ; *or* (ii) consistent X-ray with concordance between two independent readers (n=75) ; *or* (iii) positive response to tuberculosis treatment (n=26)

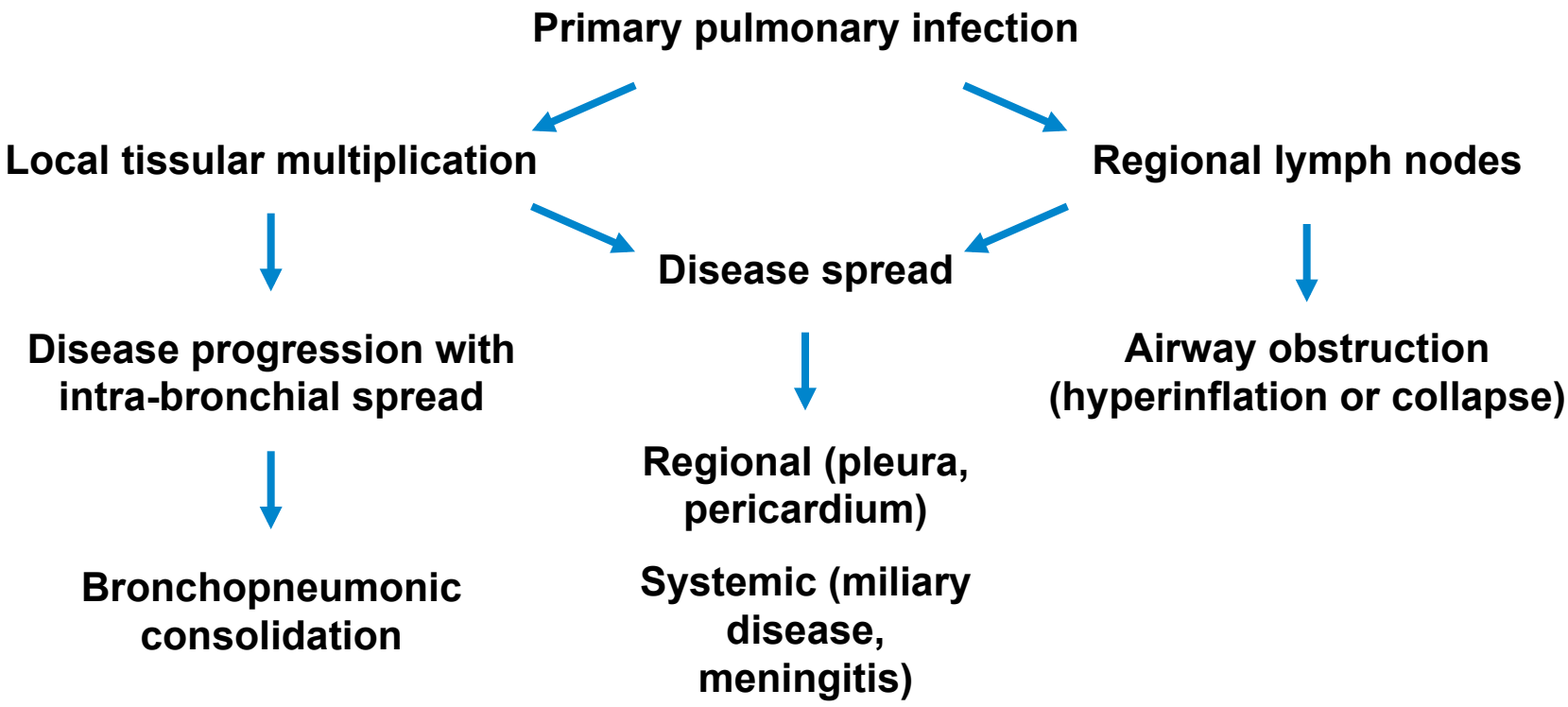
High sensitivity, low specificity **Low sensitivity, high specificity** **Acceptable ratio specificity/sensitivity**

Individual Variables at Presentation[a]	Low Risk HIV Uninfected ≥3 y			High Risk					
				HIV Uninfected <3 y			HIV Infected		
	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV	Sensitivity	Specificity	PPV
Cough >3 wk	90.7	65.7	33.8	80.9	58.1	33.5	100	45.0	60.7
Cough >4 wk	73.3	90.1	58.9	59.6	89.9	60.2	88.2	65.0	68.2
Chest pain	9.3	96.9	36.4	3.2	99.7	75.0	0	95.0	0
Hemoptysis	5.8	98.1	38.4	1.1	100	100	0	95.0	0
Respiratory distress	4.7	99.1	50.0	8.5	94.9	30.8	35.3	60.6	42.8
Fever	37.2	92.4	48.5	43.6	89.9	52.6	52.9	30.0	39.1
Night sweats	57.0	93.9	64.5	40.4	95.2	70.3	41.2	60.0	46.7
Fatigue	94.2	87.0	58.3	68.1	95.5	78.0	94.1	30.0	53.3
Weight loss subjective	70.9	84.8	47.3	60.6	91.9	65.5	88.2	30.0	51.7
Weight loss objective	82.4	84.4	75.0	75.3	79.1	82.1	82.3	35.0	51.9
TST positive	89.3	62.9	59.1	81.9	70.1	77.7	17.6	85.0	50.0
Household contact	48.8	72.3	52.5	69.1	53.6	67.0	52.9	60.0	52.9

Marais et al. Pediatrics 2006

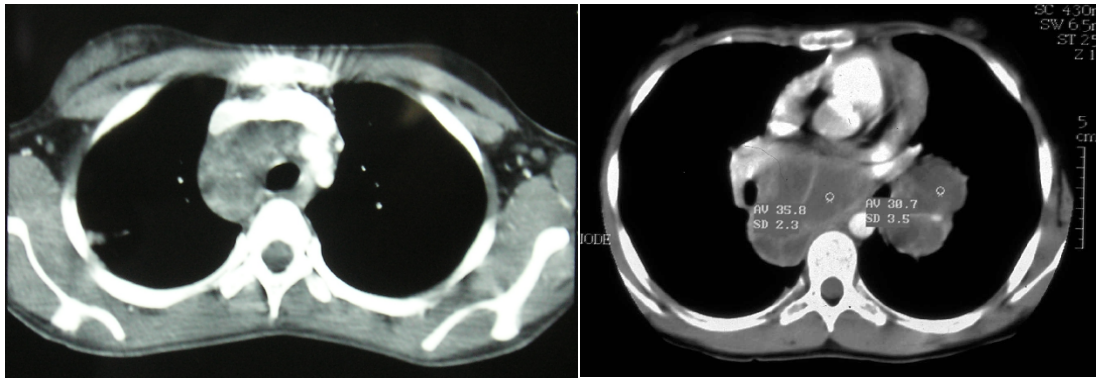
Imaging in childhood intra-thoracic TB

Radiological changes reflect the natural evolution of the disease

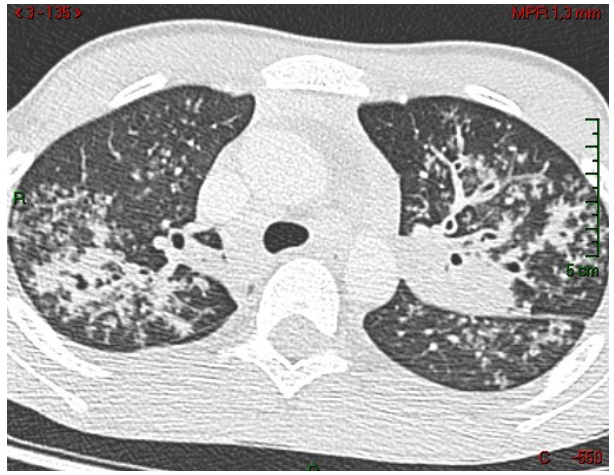


Imaging in childhood intra-thoracic TB

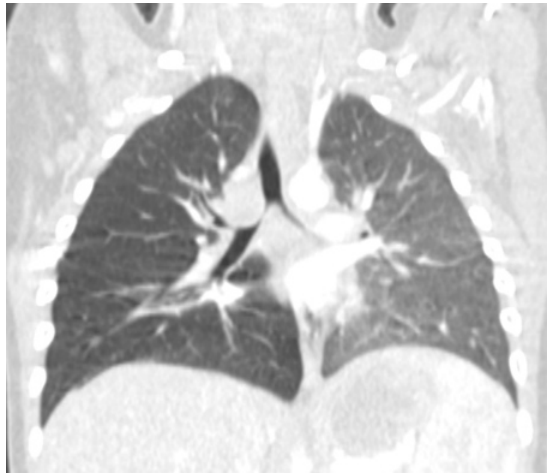
Regional lymph nodes



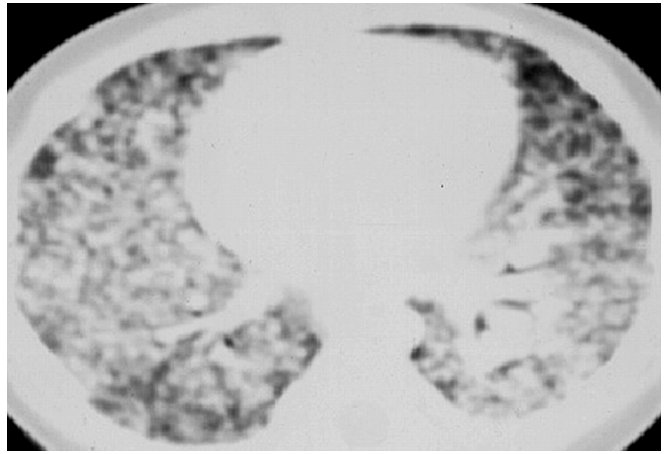
Bronchial spread (budding tree)



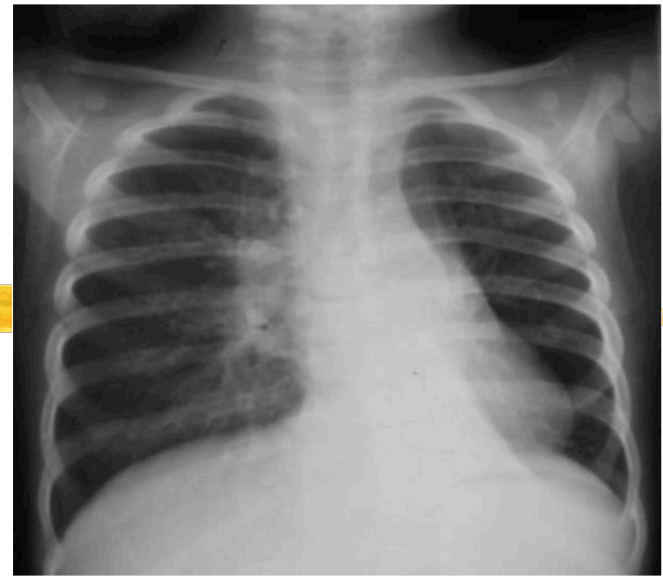
Partial airway compression and hyperinflation



Miliary disease

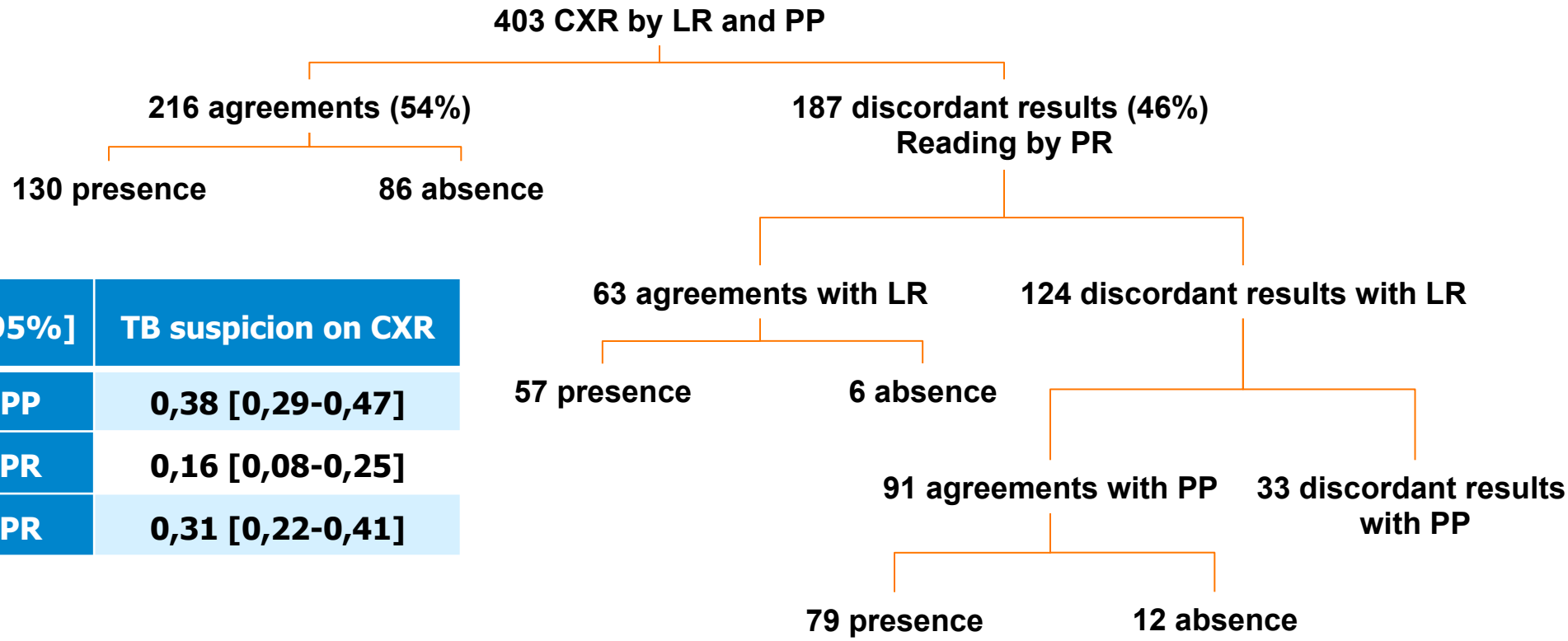


Limitations of Chest X-ray



PAANTHER study: 403 HIV+ children < 14 years, suspects of TB

Independent reading of all CXR images by local radiologists, a paediatric pulmonologist and a thoracic paediatric radiologist. CXR was considered consistent with TB if LR and PP agreed on the presence and site (right/left) of at least one of the pre-defined elementary lesions. Discordant findings were submitted to the PR, who was blinded to the previous findings.



K [CI95%]	TB suspicion on CXR
LR/PP	0,38 [0,29-0,47]
LR/PR	0,16 [0,08-0,25]
PP/PR	0,31 [0,22-0,41]

Berteloot et al. Int J Tuberc Lung Dis 2018

Limitations of Chest X-ray

Interpretation is difficult, even by « experts »

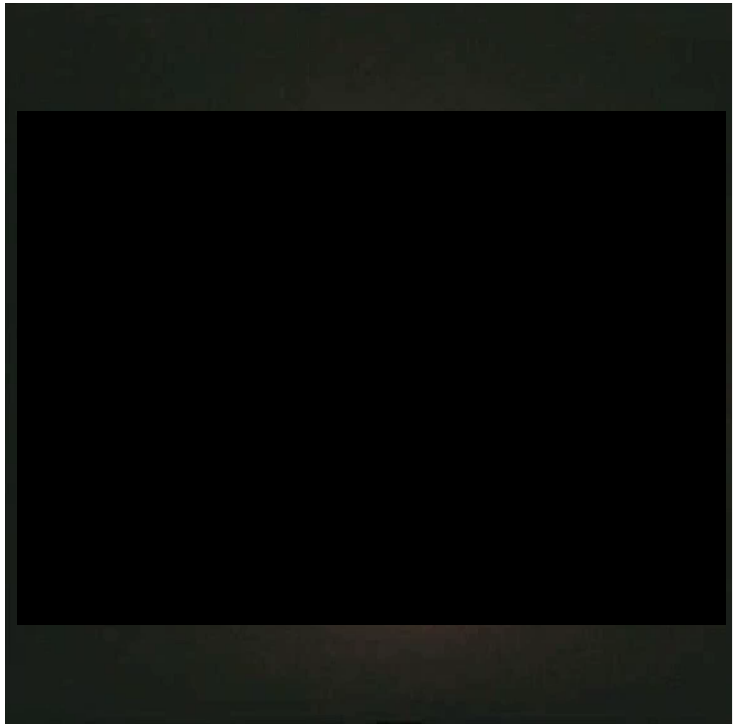
PAANTHER study : Prospective evaluation of 403 HIV+ children < 14 years, with suspicion of TB
Post-procedure diagnosis: 51 confirmed TB, 183 unconfirmed TB, 169 unlikely TB.
Independent reading of all CXR images by local radiologists, a paediatric pulmonologist and a thoracic paediatric radiologist.
Assessment of diagnostic accuracy of CXR in a case-control subanalysis (cases = children with confirmed TB; controls = children from the unlikely-TB group who were alive at 6 months without antituberculosis treatment). Overall Diagnostic Accuracy (ODA) = proportion of correctly classified children

	Sensitivity*			Specificity*			ODA	p value
	n/N	%	(95%CI)	n/N	%	95%CI		
Local Radiologist	31/51	60.8	(47.4 - 74.2)	85/149	57.0	(49.1 - 65.0)	58.0	0.0277
Pediatric Pulmonologist	38/51	74.5	(62.5 - 86.5)	72/150	48.0	(40.0 - 56.0)	54.7	0.0049
Pediatric Thoracic Radiologist	47/50	94.0	(87.4 - 100.0)	28/143	19.6	(13.1 - 26.1)	38.9	0.0244

Berteloot et al. Int J Tuberc Lung Dis 2018

Flexible bronchoscopy in childhood TB

Allows direct visualization of the endobronchial disease

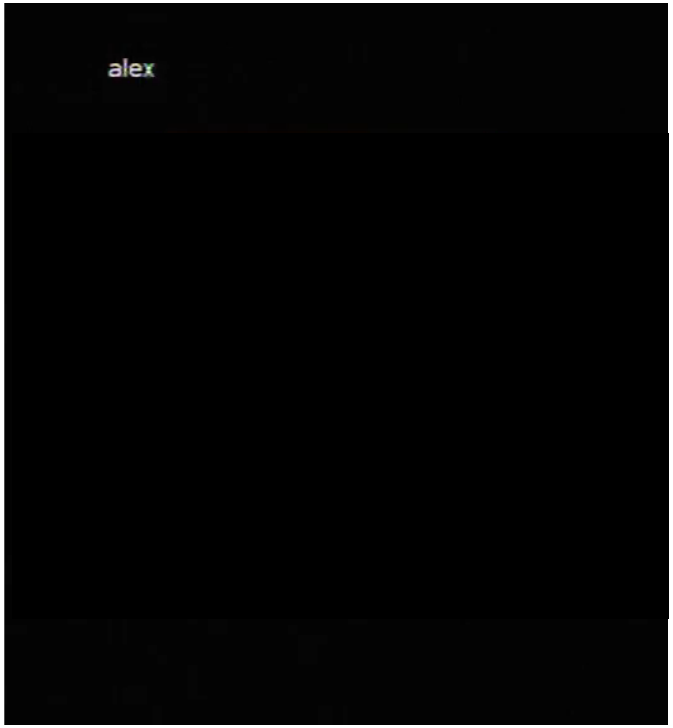


Very suggestive aspects (alone or in combination):

External compression

Granuloma

Obstructive caseum



Endoscopic significant compression ***(reduction of 50% or more of airway diameter)*** **is predicted by suggestion of bronchial compression on CT Scan ; No indication when CT scan shows no signs of airway compression** ***(Arlaud et al. Arch Dis Child 2010)***

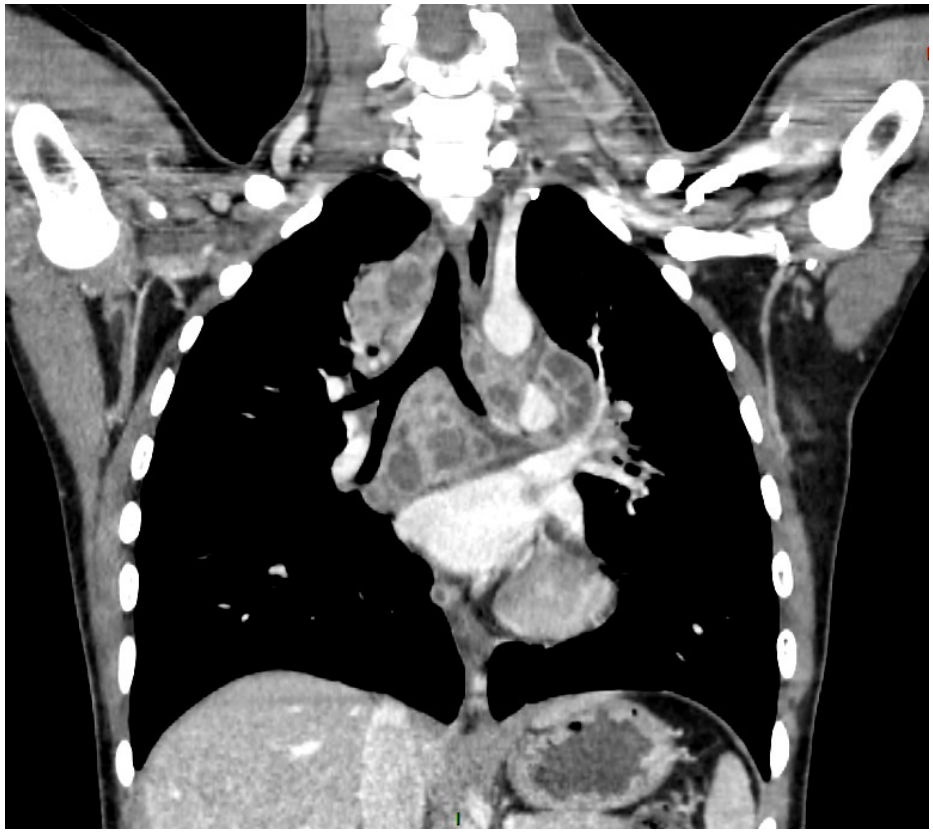
Imaging in childhood intra-thoracic TB

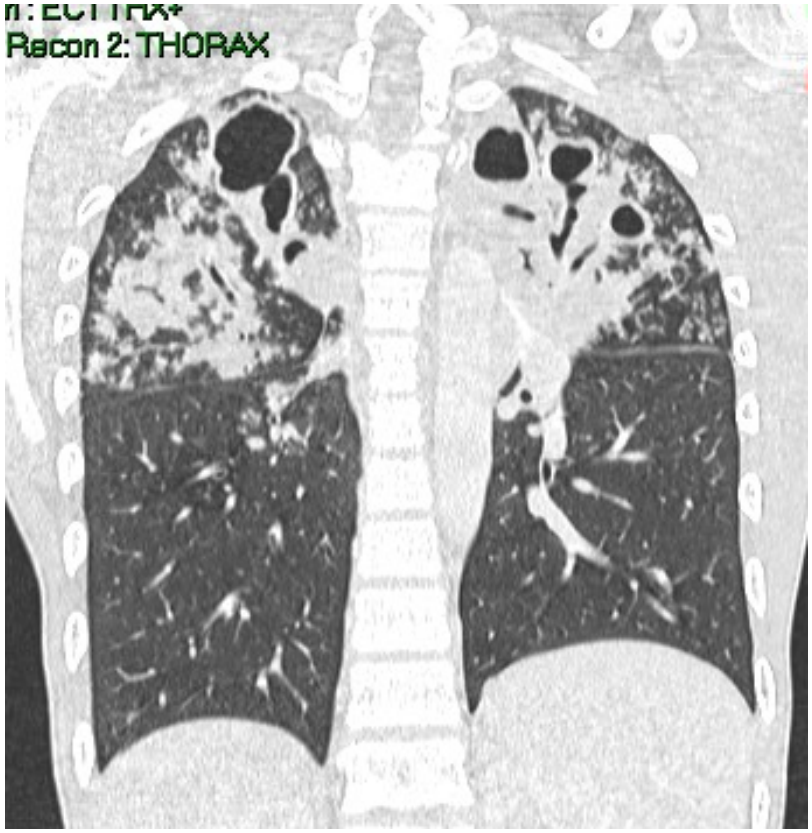
Particularities of adolescence

Pediatric-type TB (primary infection)

or

Adult-type TB (reactivation of primary infection)



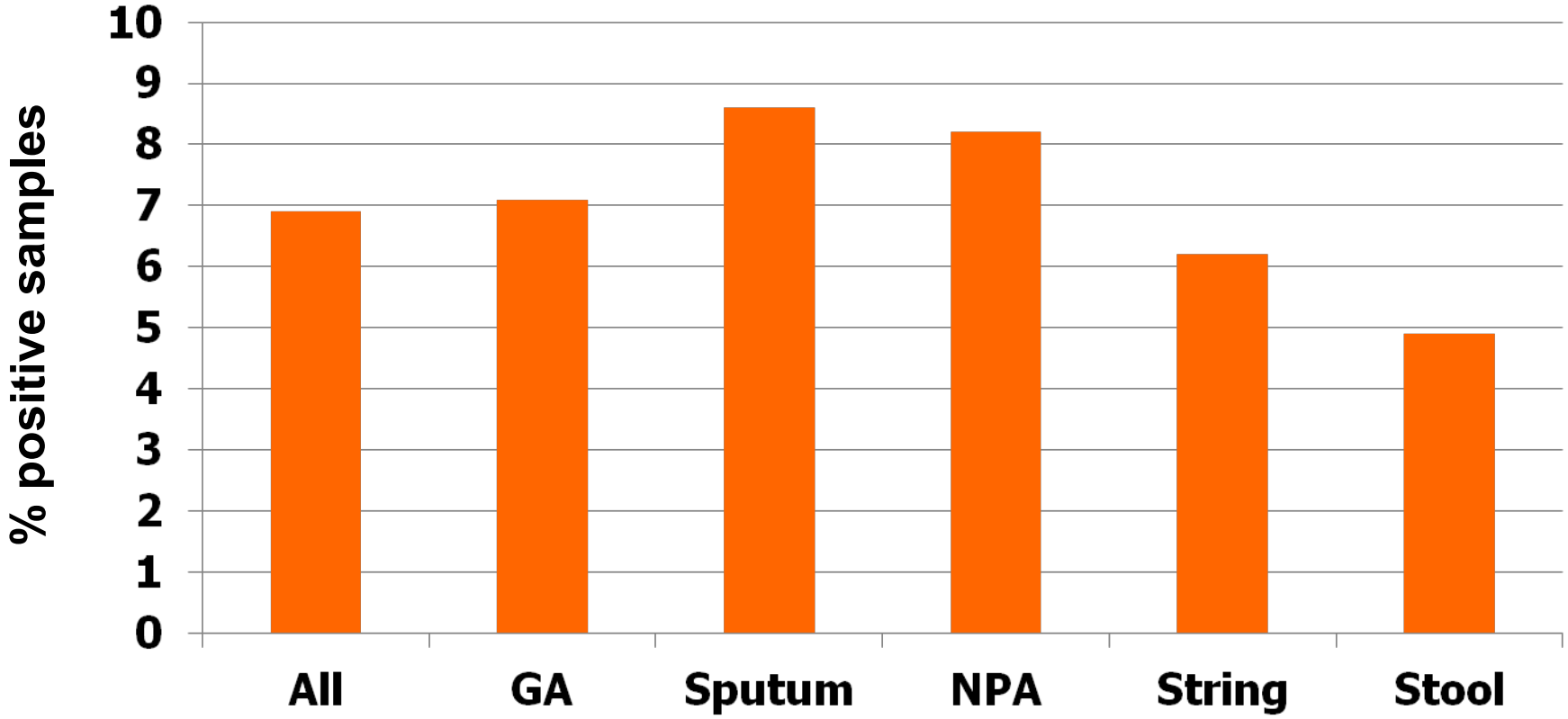


Microbiologic investigations : Could we improve the diagnostic yield of sampling methods ?

« Classicals »	« Alternatives »
Spontaneous expectoration	Induced expectoration
Gastric aspirate	Naso-pharyngeal aspiration
	String test
	Stools

Microbiologic investigations : Could we improve the diagnostic yield of sampling methods ?

PAANTHER Study (Cambodia, Vietnam, Cameroon, Burkina)
272 children, HIV+, with TB suspicion. Comparison of different sampling methods



Marcy et al. Clin Infect Dis 2016

Microbiologic investigations : Could we improve the diagnostic yield of sampling methods ?

« Valid specimens » include respiratory specimens from sputum sampled by expectoration, sputum induction, gastric aspirates, or naso-pharyngeal aspirates and can include a stool sample.

Xpert MTB/RIF : WHO 2014 guidelines

Guidance for national tuberculosis programmes on the management of tuberculosis in children –2nd ed

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

- **Recommendation 1** *(new)*

  Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

  (Strong recommendation, very low quality of evidence)

- **Recommendation 2** *(new)*

  Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

  (Conditional recommendation acknowledging resource implications, very low quality of evidence)

Xpert MTB/RIF: diagnosis value in children

930 children withTB suspicion (Zambia): sputum (n=142) ou GA (n=788); 58 (6%) culture +, including 15 (1.6%) smear+ ***(+ 30 smear+/culture-).*** **49 children with Xpert +**

Xpert MTB/RIF assay *vs culture* (Gastric lavage aspirate and sputum combined)

	sensitivity	specificity
<2 years (1·5% sputum)	12/19 (63·2%; 38·6–82·8)	442/443 (99·8%; 98·5–100·0)
2–4 years (4·0% sputum)	12/18 (66·7%; 41·1–85·6)	182/183 (99·4%; 96·5–100·0)
5–9 years (45·2% sputum)	3/6 (50·0%; 13·9–86·1)	115/118 (97·5%; 92·2–99·3)
10–15 years (50·0% sputum)	15/15 (100%; 74·7–100)	121/123 (98·4%; 93·7–99·7)

Bates et al. Lancet 2013

Xpert MTB/RIF: diagnosis value in children

930 children withTB suspicion (Zambia): sputum (n=142) ou GA (n=788); 58 (6%) culture +, including 15 (1.6%) smear+ ***(+ 30 smear+/culture-).*** **49 children with Xpert +**

Xpert MTB/RIF *vs culture* (GA + sputum combined)

	Sensitivity (smear positive)	Sensitivity (smear negative)
<2 years (1·5% sputum)	2/2 (100%; 19·8–100·0)	10/17 (58·8%; 33·5–80·6)
2–4 years (4·0% sputum)	5/6 (83·3%; 36·5–99·1)	7/12 (58·3%; 28·6–83·5%)
5–9 years (45·2% sputum)	1/1 (100%; 5·5–100·0)	2/5 (40%; 7·3–83·0)
10–15 years (50·0% sputum)	6/6 (100%; 51·7–100)	9/9 (100%; 62·9–100)

Bates et al. Lancet 2013

Xpert MTB/RIF: diagnosis value with different sampling methods in HIV children

Etude PAANTHER-ANRS. 272 HIV+ children with TB suspicion. 29 (10.7%) with at least 1 sample with positive culture.

Overall sensitivity: 79.3 (60.3–92.0)

Samples	Specificity % (95% CI)	Sensitivity in Smear–Positive Culture-Confirmed Tuberculosis n/N, % (95% CI)	Sensitivity in Smear–Negative Culture-Confirmed Tuberculosis n/N, % (95% CI)
All	97.5 (94.7–99.1)	14/14, 100 (76.8–100)	9/15, 60.0 (32.3–83.7)
Standard samples	98.4 (95.8–99.5)	14/14, 100 (76.8–100)	7/15, 46.7 (21.3–73.4)
Alternative samples	98.8 (96.4–99.7)	14/14, 100 (76.8–100)	8/15, 53.3 (26.6–78.7)

Marcy et al. CID 2016

Xpert MTB/RIF Ultra in children

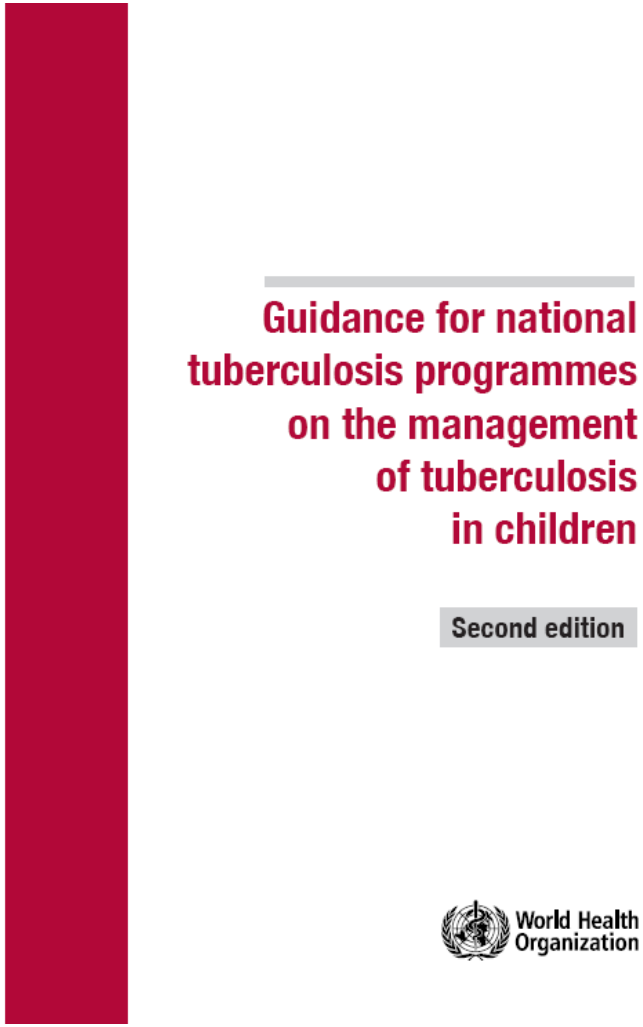
Retrospective evaluation of Xpert Ultra in a biological bank of induced sputum collected from 306 children. Comparison of valid Xpert and Xpert Ultra on same samples. « TB » if positive culture for at least one sample collected in each child (South Africa)

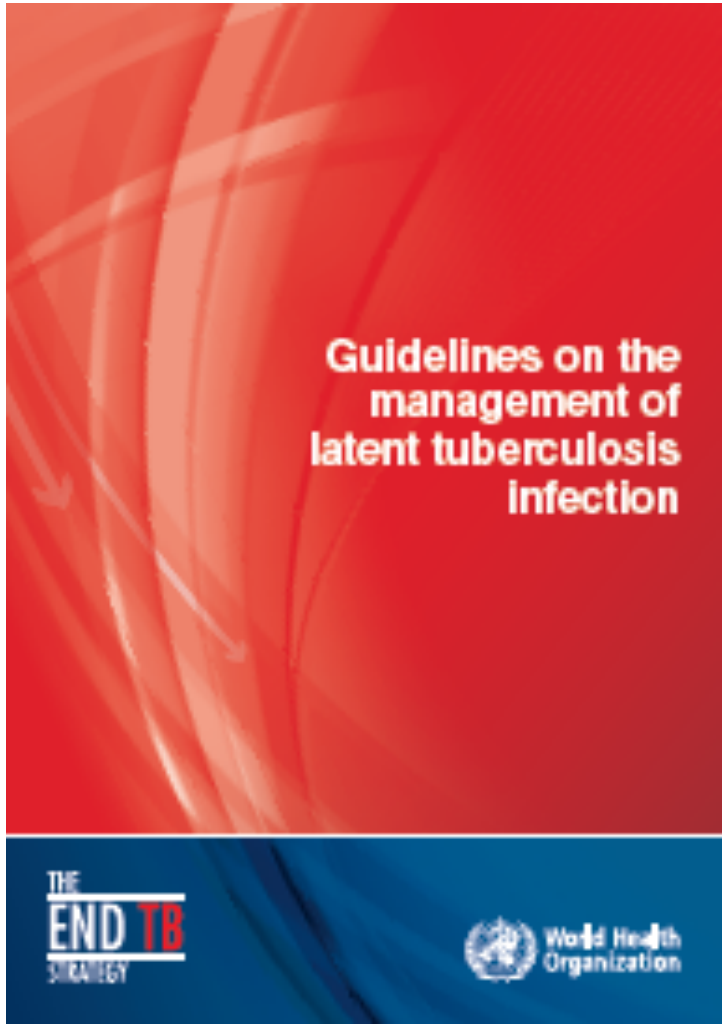
	Xpert	Xpert Ultra
Sensitivity	47/73 (64.4%, 95% CI 52.3-75.3)	48/73 (65.8%, 95% CI 53.7-76.5)
Specificity	232/233 (99.6%, 95% CI 97.6-100)	225/233 (96.6%, 95% CI 93.3-98.5)

Apparent loss of specificity
Interprétation ?

Nicol et al. Pediatr J Infect Dis 2018

TB treatment in children





Indications of HRZ 2 months / HR 4 months regimen

- **Children with suspected or confirmed pulmonary tuberculosis or tuberculous peripheral lymphadenitis,**

  AND:
  - **live in settings with low HIV prevalence**
    HIV prevalence <1% among adult pregnant women or <5% among TB patients
  - **or low resistance to isoniazid**
  - **are HIV-negative**

WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014

Indications of HRZE 2 months / HR 4 months regimen

- **Children with suspected or confirmed pulmonary tuberculosis or peripheral lymphadenitis**

  AND : **- living in settings where the prevalence of HIV is high**
  HIV prevalence ≥1% among adult pregnant women or ≥5% among TB patients

  - **resistance to isoniazid is high**

  - or both

- **children with extensive pulmonary disease**

WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014

Indications of HRZE 2 months / HR 10 months

- Children with TB meningitis (suspected or confirmed)
- Children with osteoarticular TB (suspected or confirmed)

WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014

Indications of corticosteroids

TB meningitis

TB pericaritis

Severe airway compression ?

Miliary with oxygen requirement ?

Which dosage ?

WHO: Recommended daily doses of first-line anti-TB drugs for children

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose (mg)
Isoniazid	10 (7-15)[a]	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	–
Ethambutol	20 (15–25)	–

[a] The higher end of the range for isoniazid dose applies to younger children; as the children grow older the lower end of the dosing range becomes more appropriate.

As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations

WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. 2014

Which dosage ?

Most of results from pharmacocinetic studies are given in mg/m2

isoniazid :	**200 mg/m^2** ***(Max = 300 mg)***
corresponding to :	**8-10 mg/kg if 0-5 years**
	6-8 mg/kg if 6-14 years
	5-6 mg/kg if 15-18 years
rifampicin :	**350 mg/m^2** ***(Max = 600 mg)***
corresponding to :	**14-15 mg/kg if 0-5 years**
	12-14 mg/kg if 6-12 years
	10-12 mg/kg if 15-18 years
Pyrazinamide :	**30 mg/kg** ***(Max = 2000 mg)***
Ethambutol :	**20-25 mg/kg** ***(Max = 1200 mg)***

Treatment of LTBI

Regimens that showed significant efficacy when compared to placebo and profile of heptotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Placebo	Isoniazid 6 months	0.61 (0.48–0.77)	Low	0.99 (0.42–2.32)	Low
Placebo	Isoniazid 12–72 months	0.53 (0.41–0.69)	Low	0.59 (0.23–1.55)	Very low
Placebo	Rifampicin 3–4 months	0.48 (0.26–0.87)	Moderate	-	-
Placebo	Rifampicin and isoniazid 3–4 months	0.52 (0.33–0.84)	Low	-	-

WHO. Guidelines on the management of latent tuberculosis infection. 2014

Treatment of LTBI

Comparison of efficacy of 6-month isoniazid with other regimens for the development of incident TB and hepatotoxicity

Comparator	Intervention	Development of incident TB		Hepatotoxicity	
		OR (95% CI)	Quality of evidence	OR (95% CI)	Quality of evidence
Isoniazid 6-month	Rifampicin 3–4 months	0.78 (0.41–1.46)	Moderate	0.03 (0.00–0.48)	Low
Isoniazid 6-month	Rifampicin and isoniazid 3–4 months	0.89 (0.65–1.23)	Low	0.89 (0.52–1.55)	Very low
Isoniazid 6-month	3-month weekly rifapentine plus isoniazid*	1.09 (0.60–1.99)	Low	1.00 (0.50–1.99)	Low
Isoniazid 9-month	3-month weekly rifapentine plus isoniazid	0.44 (0.18–1.07)	Low	0.16 (0.10–0.27)	Moderate