

Obrigada por ver esta apresentação
Gostaríamos de recordar-lhe que esta apresentação é
propriedade do autor.

É-lhe fornecida pela Sociedade Portuguesa de Pediatria
no contexto do 19º Congresso Nacional de Pediatria,
para seu uso pessoal, tal como submetido pelo autor

© 2018 pelo autor

Tuberculose em pediatria: diagnóstico, tratamento e controle

Luís Varandas

Hospital Dona Estefânia

Instituto de Higiene e Medicina Tropical

Faculdade de Ciências Médicas | NOVA Medical School

TB BURDEN IN CHILDREN AND ADOLESCENTS IS HUGE AND UNRECOGNIZED

7.5 million

children (0–14) infected
with TB each year

(Dodd et al., 2014 (12))



TB among
all ages

10 million



TB patients in 2017

1 million



children (0–14 years)
developed TB in 2017

52% <5 year olds

727 000 adolescents

(10–19 year-olds) developed TB in 2012

(Snow et al., 2018 (13))

1.6 million

TB deaths in 2017

233 000

children (0–14)
TB deaths in 2017

80% in
children
<5 years

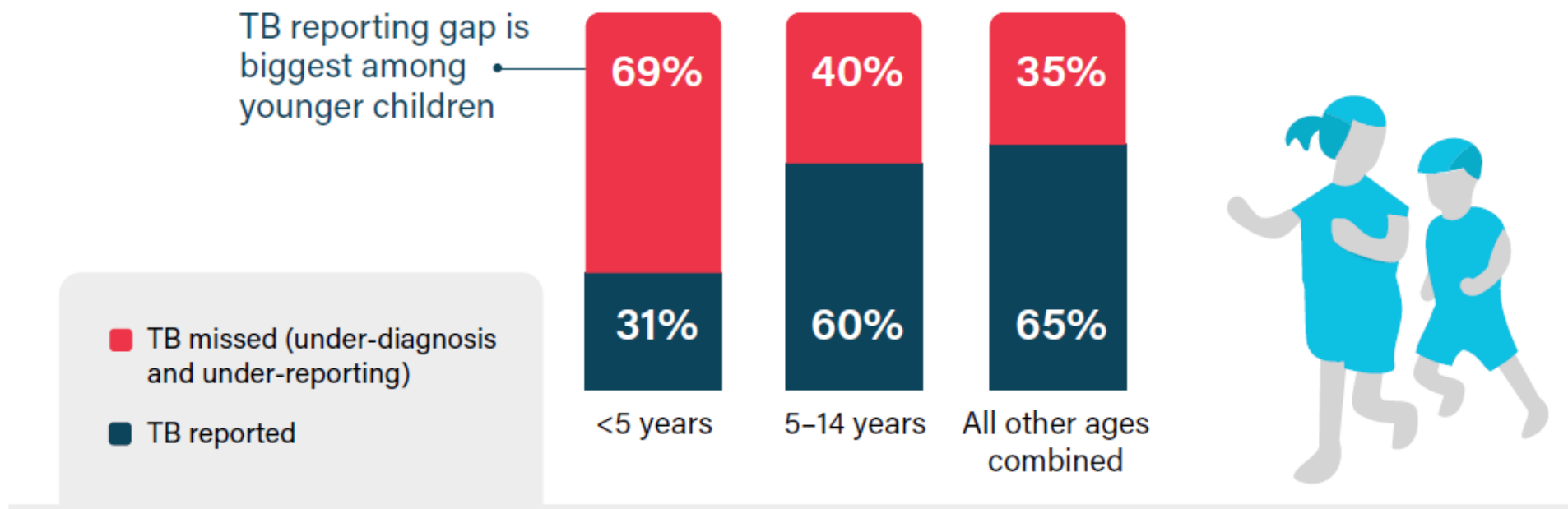
96% of
deaths in
children who
did not access
TB treatment

39 000
(17%) deaths
among
children living
with HIV

(Dodd et al., 2017 (16))

CASE DETECTION GAP

% of TB patients that are missed in different age groups

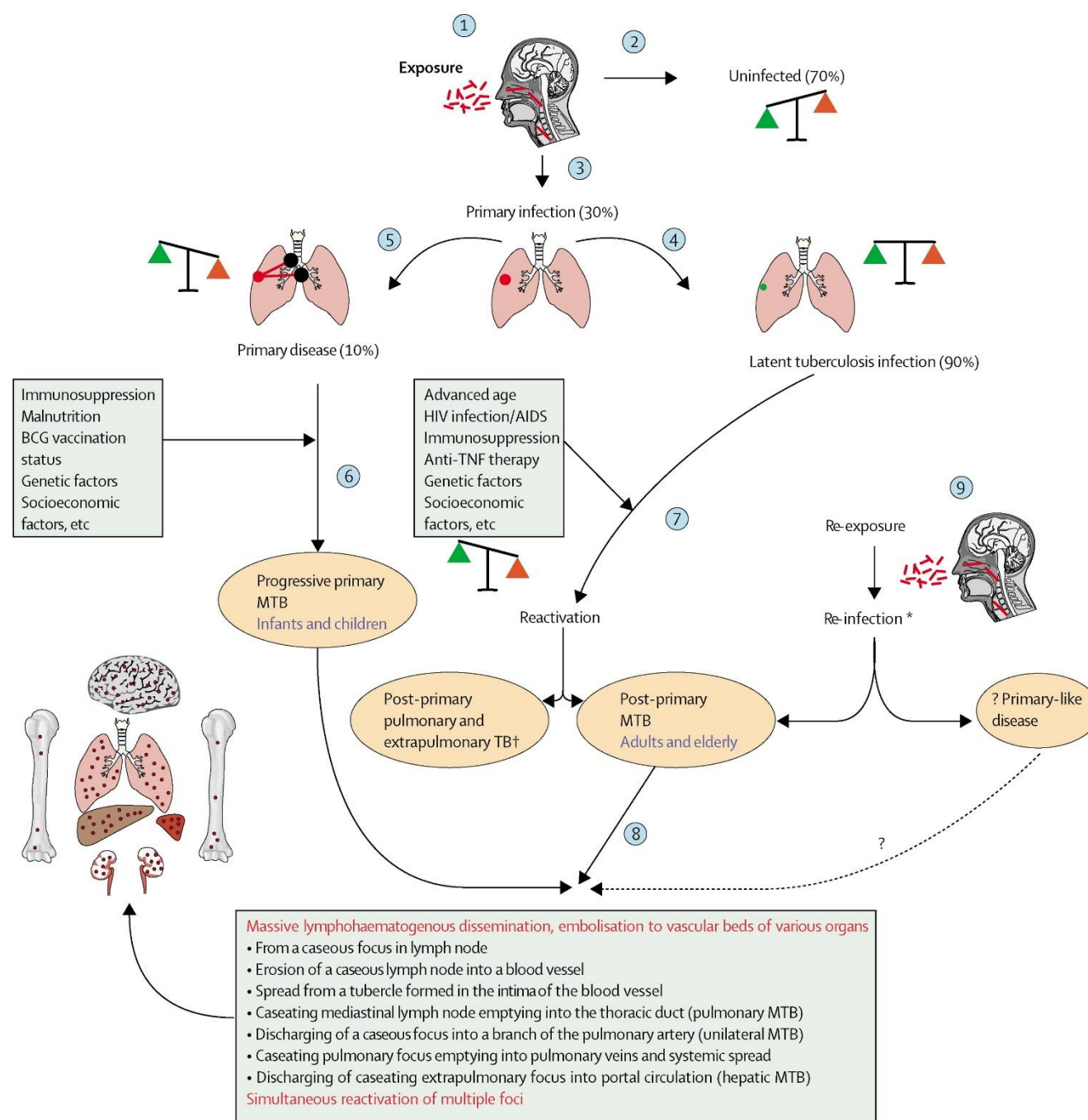


Overall 55% of estimated children with TB (0-14 years) are **not reported** to national TB programmes



TB can be a cause or co-morbidity of common child illnesses, especially **pneumonia and malnutrition**. More specific tests are needed to improve diagnosis.

(Oliwa et al., 2015 (14); Patel and Detjen, 2017 (15))



Age at primary infection						
	Infancy	1–2 y	2–5 y	5–10 y	10–15 y	Adulthood
Risk of pulmonary disease (%)	30–40	10–20	5	2	10–20	5–10 ^a
Risk of disseminated disease (%)	10–20	2–5	0.5	<0.5	<0.5	<0.5

Fig. 2. Age-related risks of TB disease after primary infection in the prechemotherapy era.^a Lifetime risk. (*Adapted from* Marais BJ, Gie RP, Schaaf HS, et al. The clinical epidemiology of childhood pulmonary tuberculosis: a critical review of literature from the pre-chemotherapy era. *Int J Tuberc Lung Dis* 2004;8(3):278–85.)

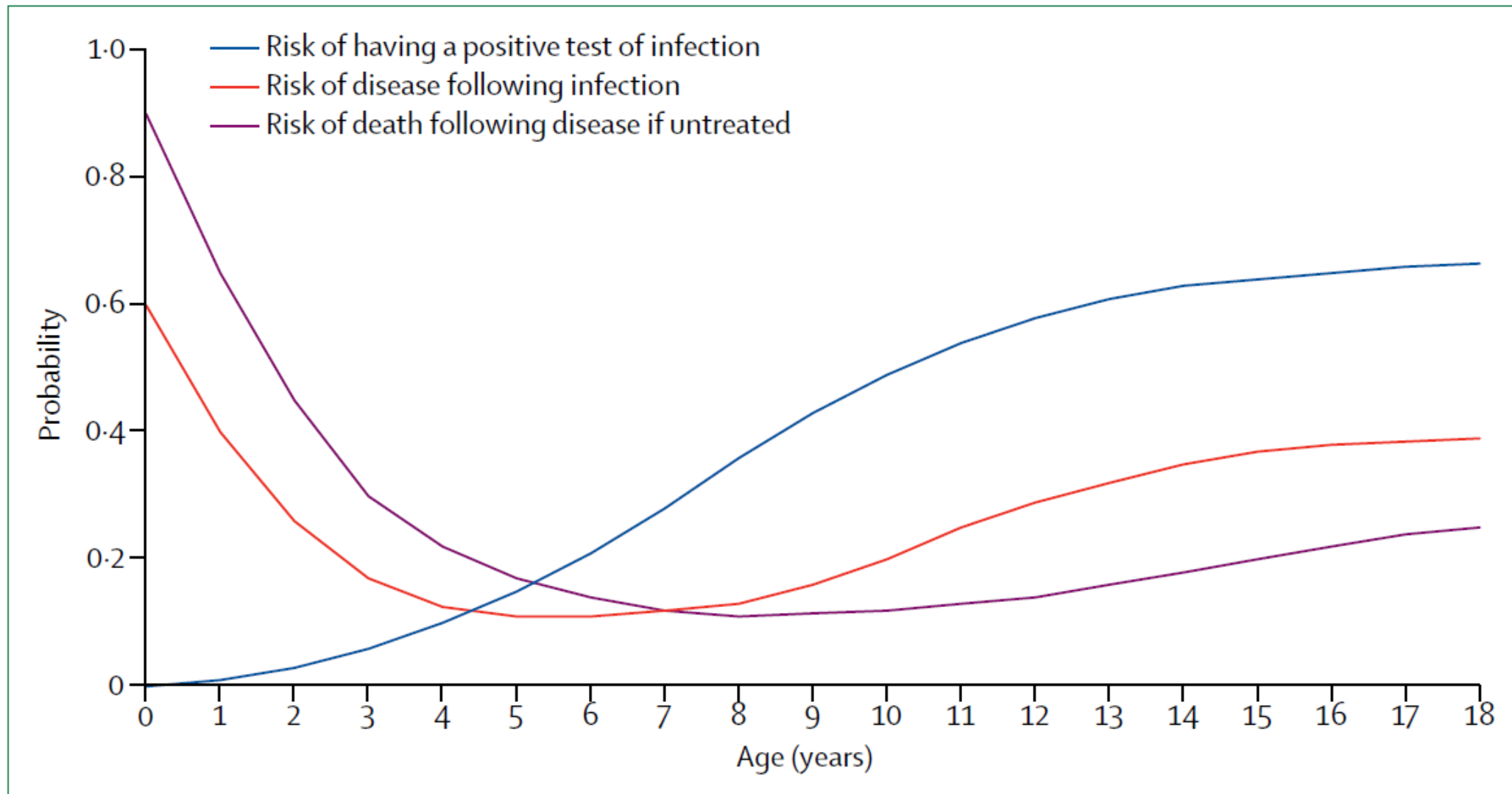


Figure 1: Schematic diagram of the effect of age on risks associated with *Mycobacterium tuberculosis* in high burden settings

Graph shows the probability of infection, disease, or death.^{8,9,10,11}

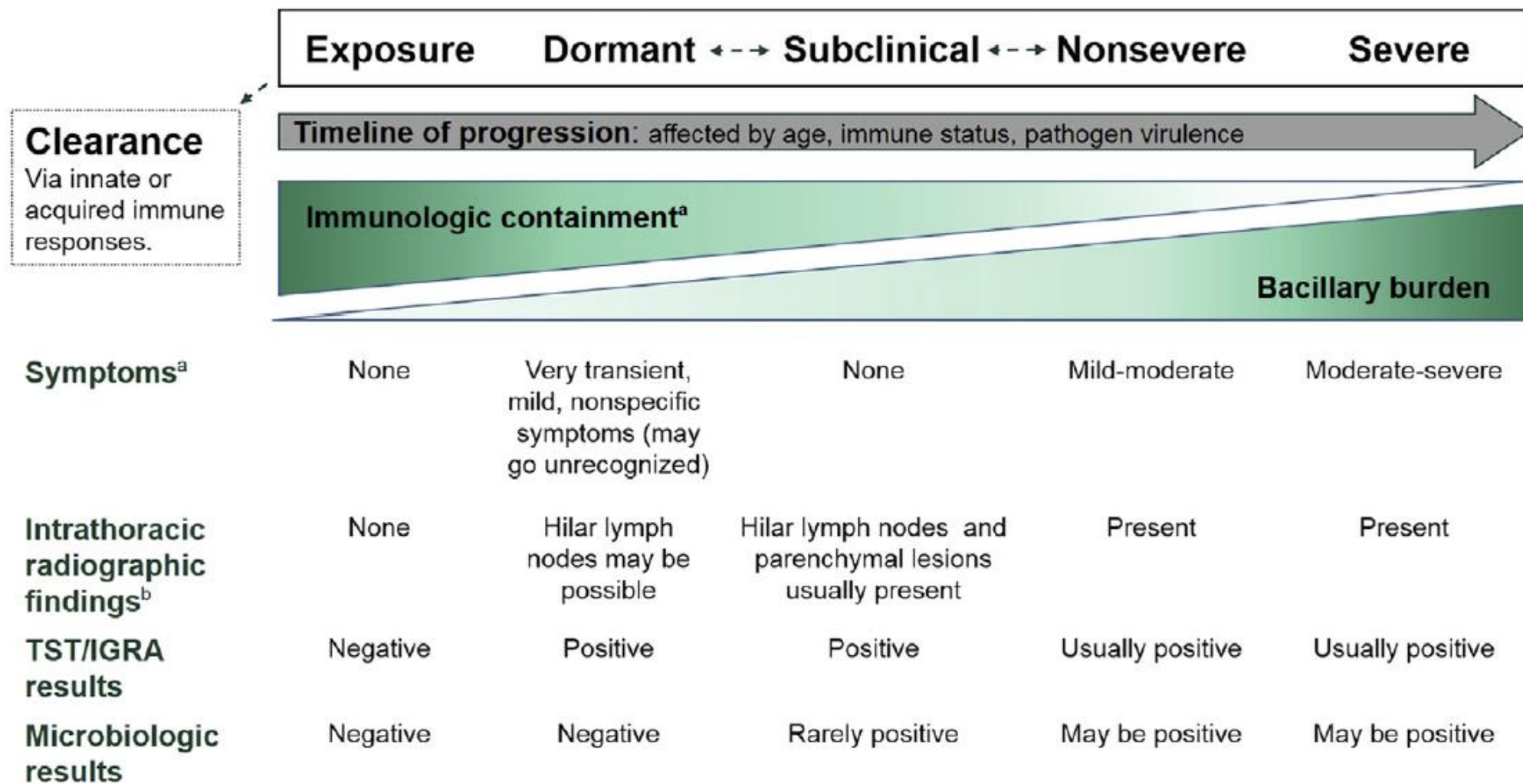


Fig. 3. Spectrum of TB in children. ^a Symptomatology may reflect the intense immunologic reaction to the bacilli, rather than the bacillary burden itself. ^b Findings may not be present if a child has extra-thoracic TB.

Desinfetar com álcool pele terço médio da face anterior do antebraço esquerdo



Usar seringa descartável de 1mL (graduada em centésimos de mL), com agulha de calibre 26 e 10 mm comprimento



Administração intradérmica de 0,1 mL de tuberculina purificada (**PPD RT 23**) no terço médio do antebraço esquerdo



Pápula de cerca de 5 mm de bordos bem delimitados que desaparece em 10-15 minutos

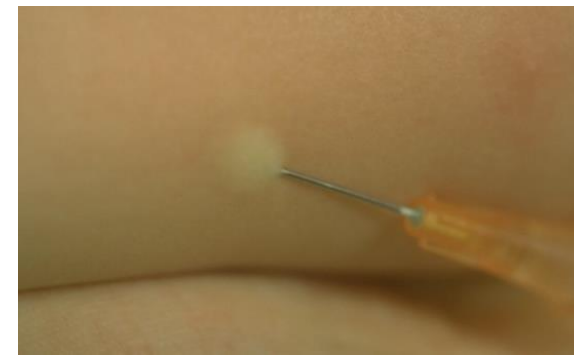
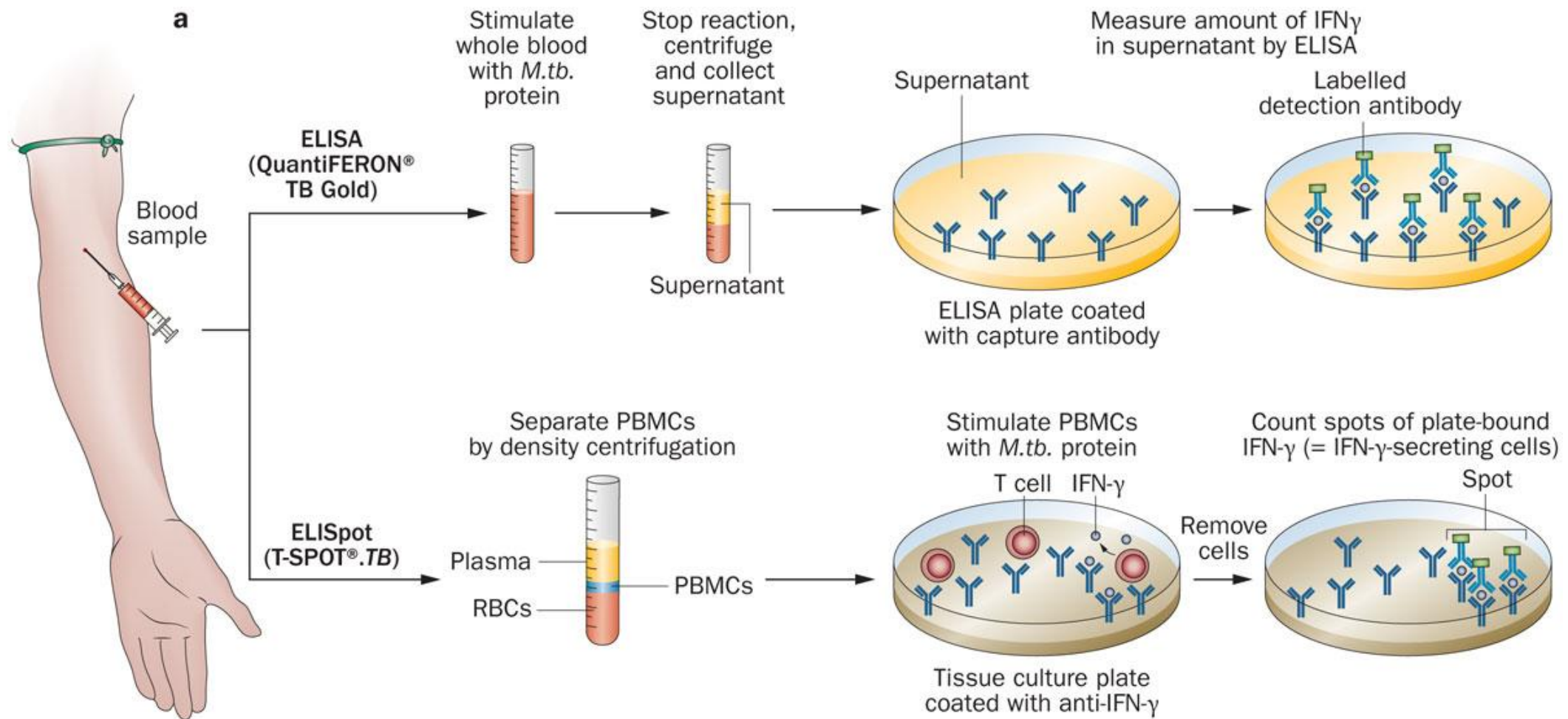
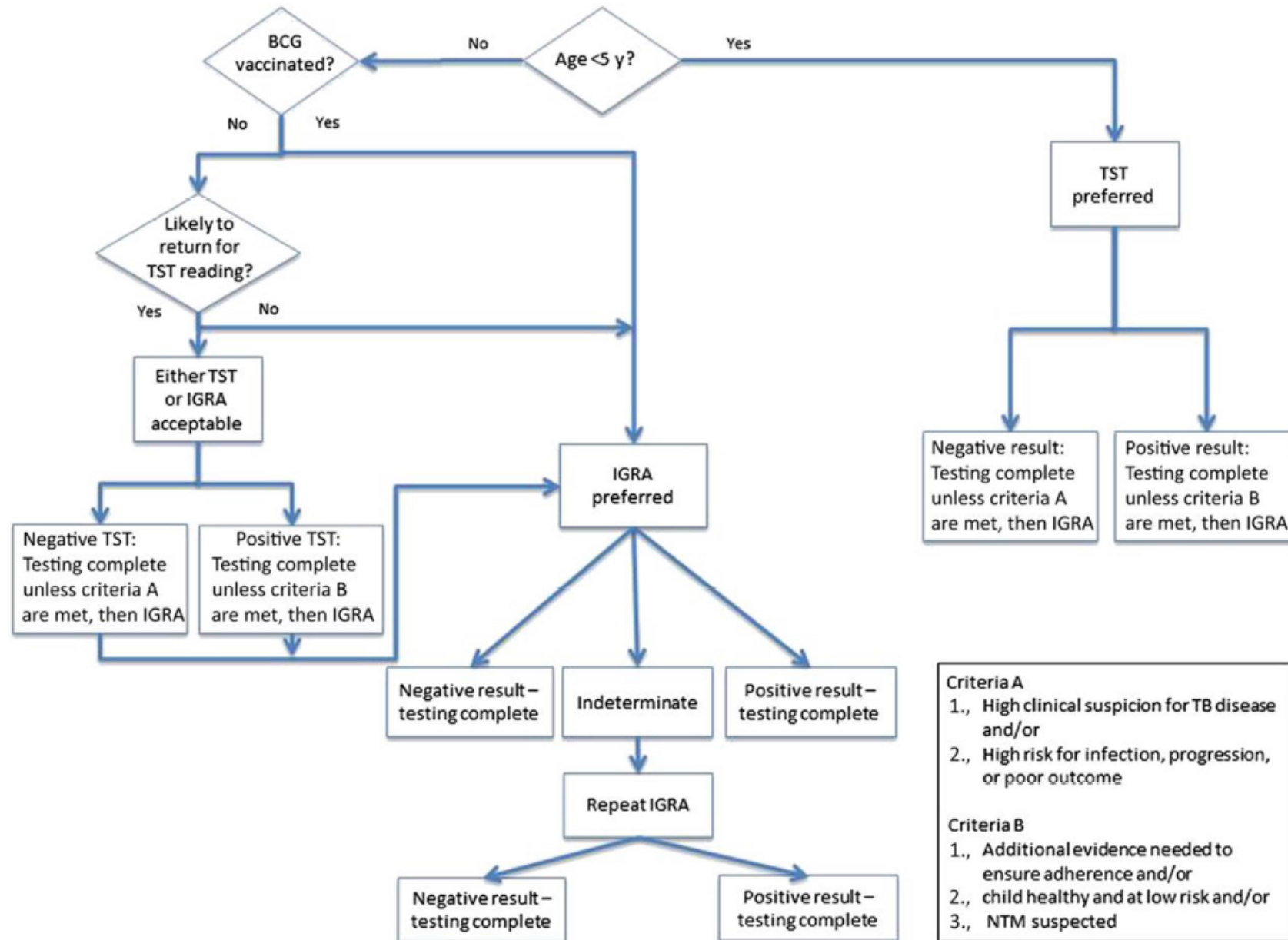


Figura 2. Técnica de realização do teste tuberculínico.



a | *Mycobacterium tuberculosis* IFN- γ -release assay. In the ELISA method (marketed as **QuantiFERON®-TB Gold In-Tube Test**; Quest Diagnostics, USA), whole blood is stimulated with *M. tuberculosis* proteins, and the amount of IFN- γ secreted into the supernatant is quantified by ELISA.⁶⁹ In the ELISPOT method (marketed as **T-SPOT.TB**; Oxford Immunotec, UK),⁶⁸ PBMCs are prepared by density gradient centrifugation. A defined number of cells is then stimulated with *M. tuberculosis* protein for 24 h on plates coated with anti-IFN- γ antibodies. Antigen-responsive cells secrete IFN- γ , which binds to these antibodies and is, after removal of the cells, subsequently detected by a second labelled anti-IFN- γ antibody. The number of spots on the plate corresponds to the number of IFN- γ ⁺ cells in the sample.

FIGURE 11 An algorithm for the use of the TST and IGRAs in children. Entry into the algorithm assumes that the child has at least 1 risk factor for TB infection. Note: many experts use age <2 years as the starting point. Reprinted from reference 107, with permission from the American Academy of Pediatrics Committee on Infectious Diseases.



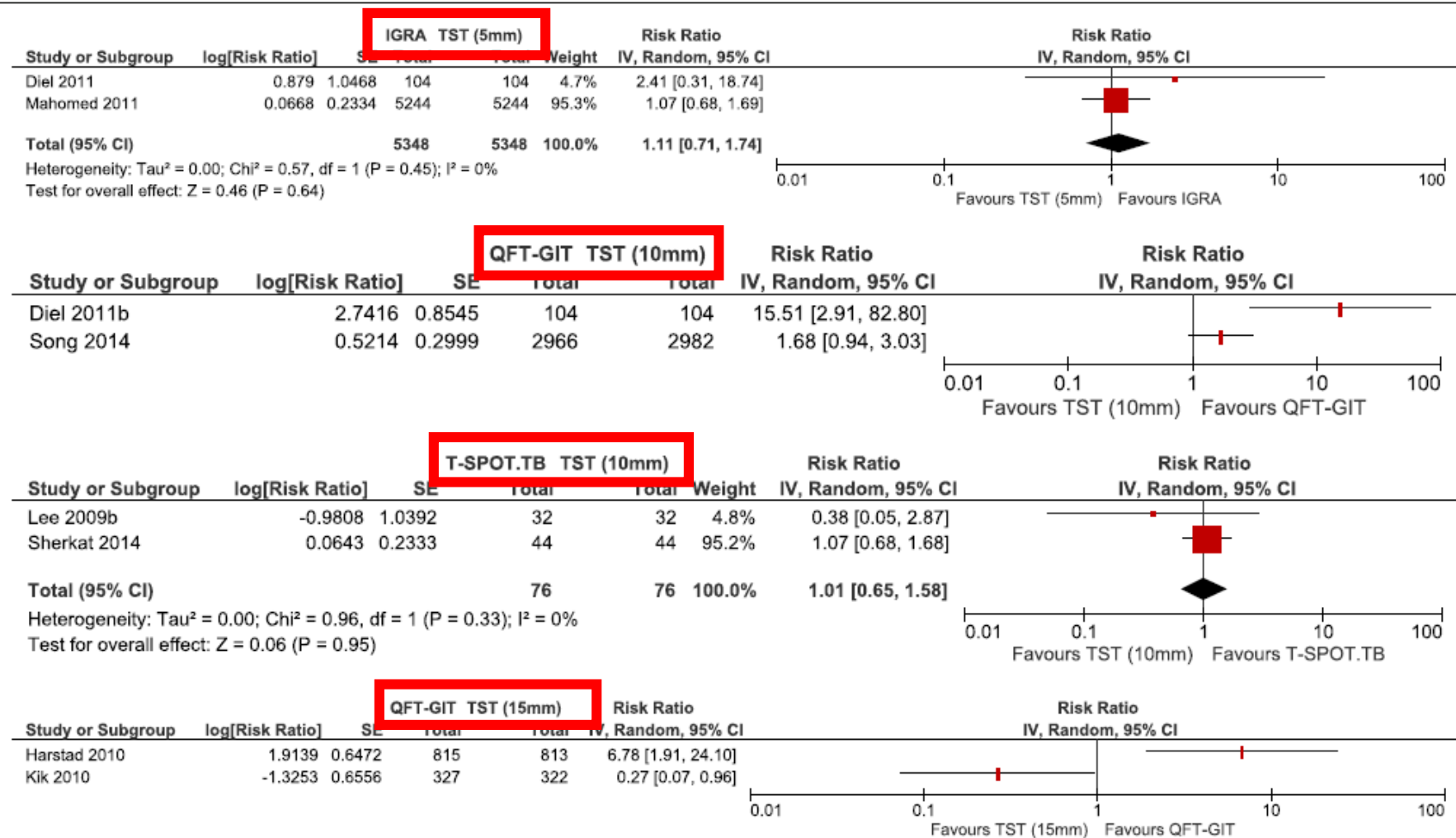


Fig. 2 Pooled cumulative incidence ratios for IGRAs versus TST in children, immunocompromised and recently arrivals. **a** Pooled cumulative incidence ratio of QFT-GIT versus TST (5 mm) for a child population. **b** Forest plot of cumulative incidence ratio of QFT-GIT versus TST (10 mm) for a child population. **c** Pooled cumulative incidence ratio of T-SPOT.TB versus TST (10 mm) for an immunocompromised population. **d** Forest plot of cumulative incidence ratio of QFT-GIT versus TST (15 mm) for a recent arrival population

Table 5 Diagnostic data and concordance values of the 8 studies that used both the TST and IGRA in immigrants

References	IGRA platform	Number of included participants	TST		IGRA		Concordance (κ)
			Testing positive (%)	Testing negative (%)	Testing positive (%)	Testing negative (%)	
Orlando et al. [66]	QFT-GIT	899 TST, 1,115 IGRA	407 (45 %)	492 (55 %)	337 (30 %)	778 (70 %)	Data not provided
Saracino et al. [67]	QFT-GIT	279	72 (26 %)	207 (74 %)	107 (38 %)	172 (62 %)	Fair (0.346)
Baker et al. [68]	QFT-GIT	195	108 (55 %)	87 (45 %)	105 (54 %)	90 (46 %)	Moderate (0.555)
Weinfurter et al. [69]	QFT-GIT	594	271 (46 %)	323 (54 %)	171 (29 %)	423 (71 %)	Moderate (0.461)
Pottumarthu et al. [70]	QFT	237	86 (36 %)	151 (64 %)	71 (30 %)	166 (70 %)	Moderate (0.554)
Carvalho et al. [71]	QFT-G	100	44 (44 %)	56 (56 %)	15 (15 %)	85 (85 %)	Fair (0.367)
Winje et al. [72]	QFT-GIT	912	311 (34 %)	601 (66 %)	264 (29 %)	648 (71 %)	Moderate (0.506)
Painter et al. [73]	QFT-GIT	479	236 (49 %)	243 (51 %)	161 (34 %)	318 (66 %)	Fair (0.316)

TST Tuberculin Skin Test, *QFT* QuantiFERON, *QFT-G* QuantiFERON-Gold, *QFT-GIT* QuantiFERON-Gold-In-Tube

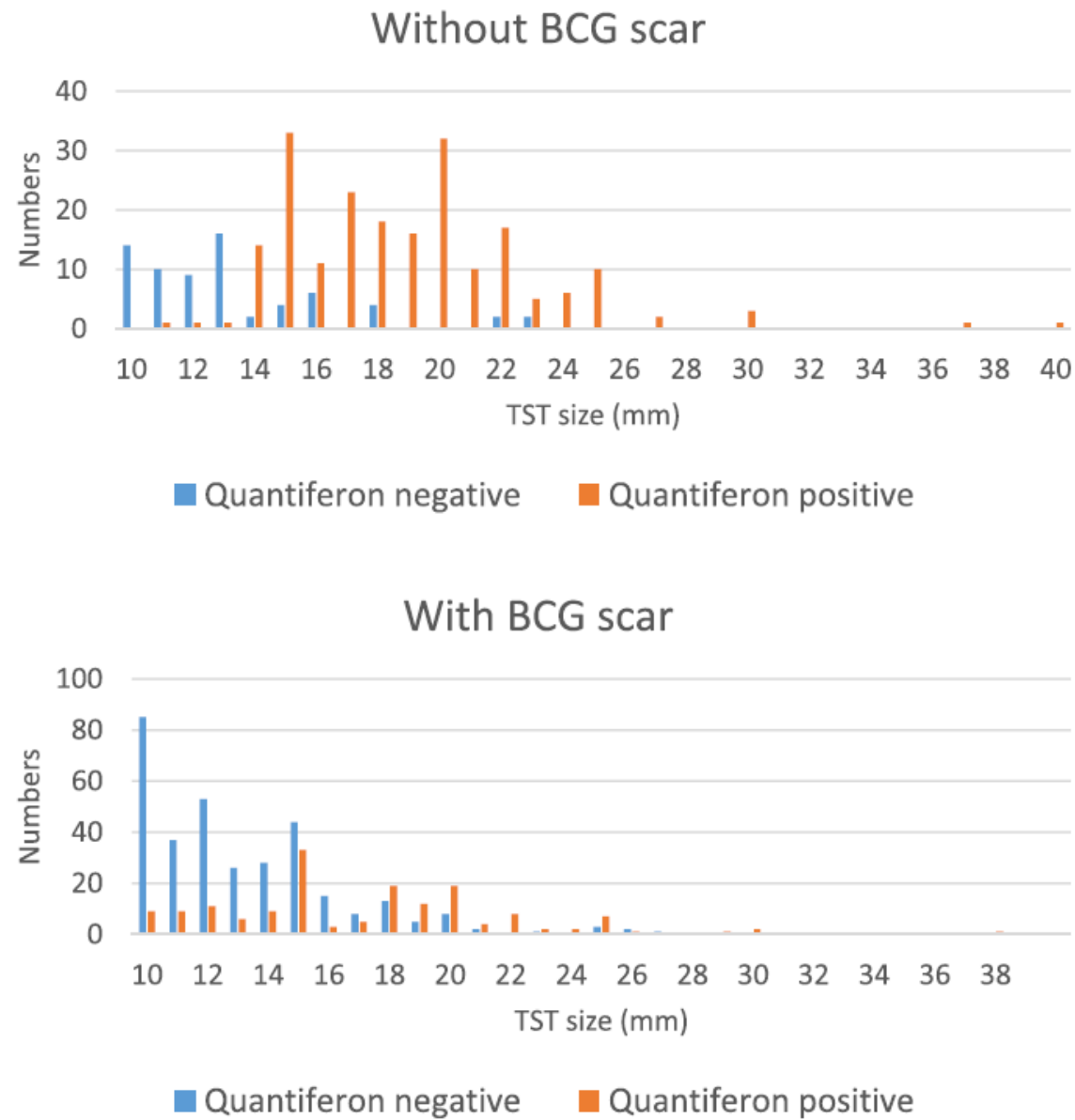


Fig. 1 TST diameters in Quantiferon negative and positive children

Table 2. Results of QuantiFERON-TB gold in-Tube and T-SPOT.TB assays in each diagnostic category.

		QuantiFERON-TB gold In-Tube			T-SPOT.TB		
		Positive	Negative	Indeterminate	Positive	Negative	Indeterminate
All patients (n = 100)	Latent TB (n = 38)	18 (47%)	20 (53%)	(0)	15 (39%)	19 (50%)	4 (10%)*
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 49)	2 (4%)	44 (90%)	3 (6%) [†]	1 (2%)	38 (78%)	10 (20%) [‡]
	No TST result (n = 4)	1 (25%)	3 (75%)	0	0	4 (100%)	0
Patients with TB contact (n = 44)	Latent TB (n = 22)	13 (59%)	9 (41%)	0	10 (46%)	10 (46%)	2 (9%) [§]
	TB disease (n = 9)	8 (89%)	1 (11%)	0	9 (100%)	0	0
	Uninfected (n = 11)	1 (9%)	8 (73%)	2 (18%)	1 (9%)	5 (45%)	5 (45%)**
	No TST result (n = 2)	1 (50%)	1 (50%)	0	0	2 (100%)	0

*3 inadequate PBMC; 1 cross contamination.

[†]1 high nil control; 2 inadequate mitogen control.

[‡]3 high nil control; 4 inadequate PBMC; 2 technical; 1 cross contamination.

[§]1 inadequate PBMC; 1 cross contamination.

^{||}1 inadequate mitogen control; 1 high nil control.

**3 inadequate PBMC; 1 technical; 1 high nil control.

doi:10.1371/journal.pone.0002624.t002

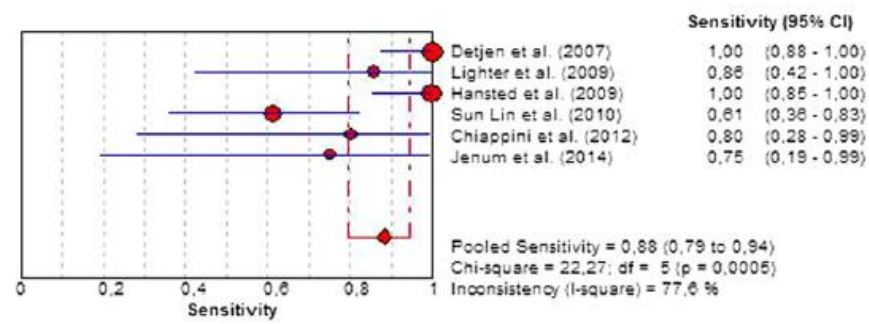
Table 3. Comparison of the results of QuantiFERON-TB gold in-Tube and T-SPOT.TB assays.

			QuantiFERON-TB gold In-Tube		
			Positive	Negative	Indeterminate
T-SPOT.TB	All patients (n = 100)*	Positive	22 (22%)	2 (2%)	1 (1%)
		Negative	4 (4%)*	56 (55%)*	1 (1%)
		Indeterminate	3 (3%)	10 (10%)	1 (1%)
Patients with latent TB infection (n = 38)		Positive	14 (37%)	1 (3%)	0
		Negative	2 (5%)	17 (45%)	0
		Indeterminate	2 (5%)	2 (5%)	0

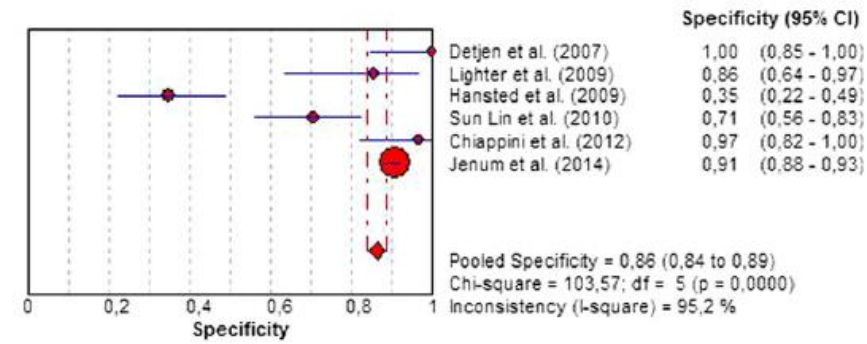
*Includes children where TST result was unavailable.

κ (95% CI) for agreement between T-SPOT.TB and QuantiFERON-TB gold In-Tube in all patients was 0.83 (0.65–0.91) and in patients with latent TB infection was 0.82 (0.54–0.92).

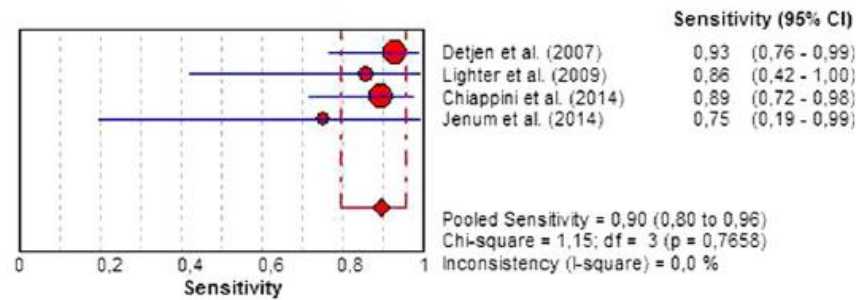
doi:10.1371/journal.pone.0002624.t003



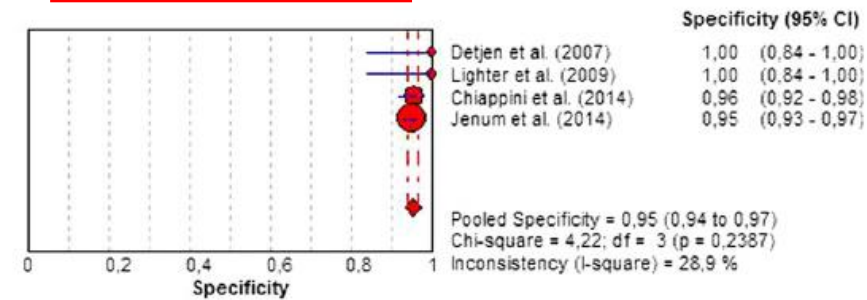
a Sensitivity of TST



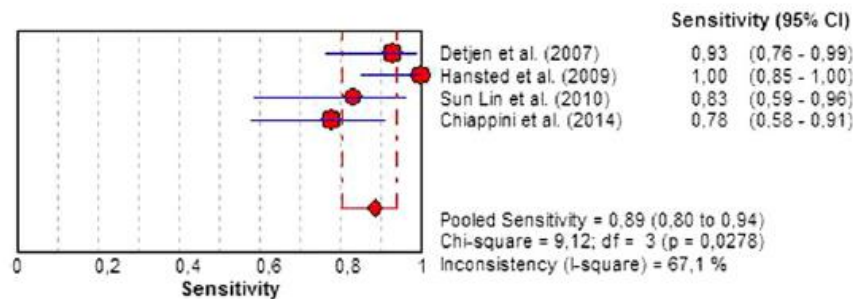
b Specificity of TST



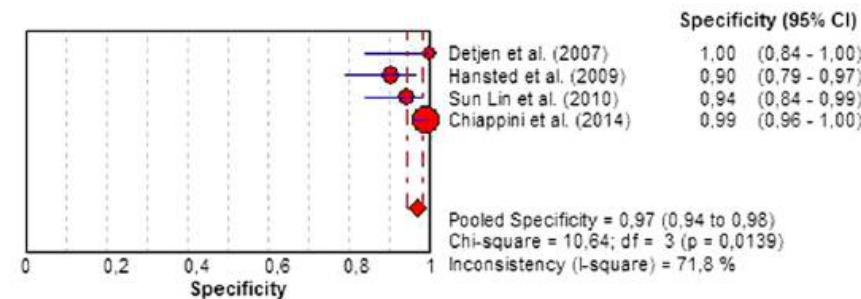
c Sensitivity of QFT



d Specificity of QFT



e Sensitivity of T-SPOT



f Specificity of T-SPOT

Fig. 3 Plot of individual studies and pooled estimates of sensitivity and specificity. **a** sensitivity of TST, **b** specificity of TST, **c** sensitivity of QFT, **d** specificity of QFT, **e** sensitivity of T-SPOT, **f** specificity of T-SPOT

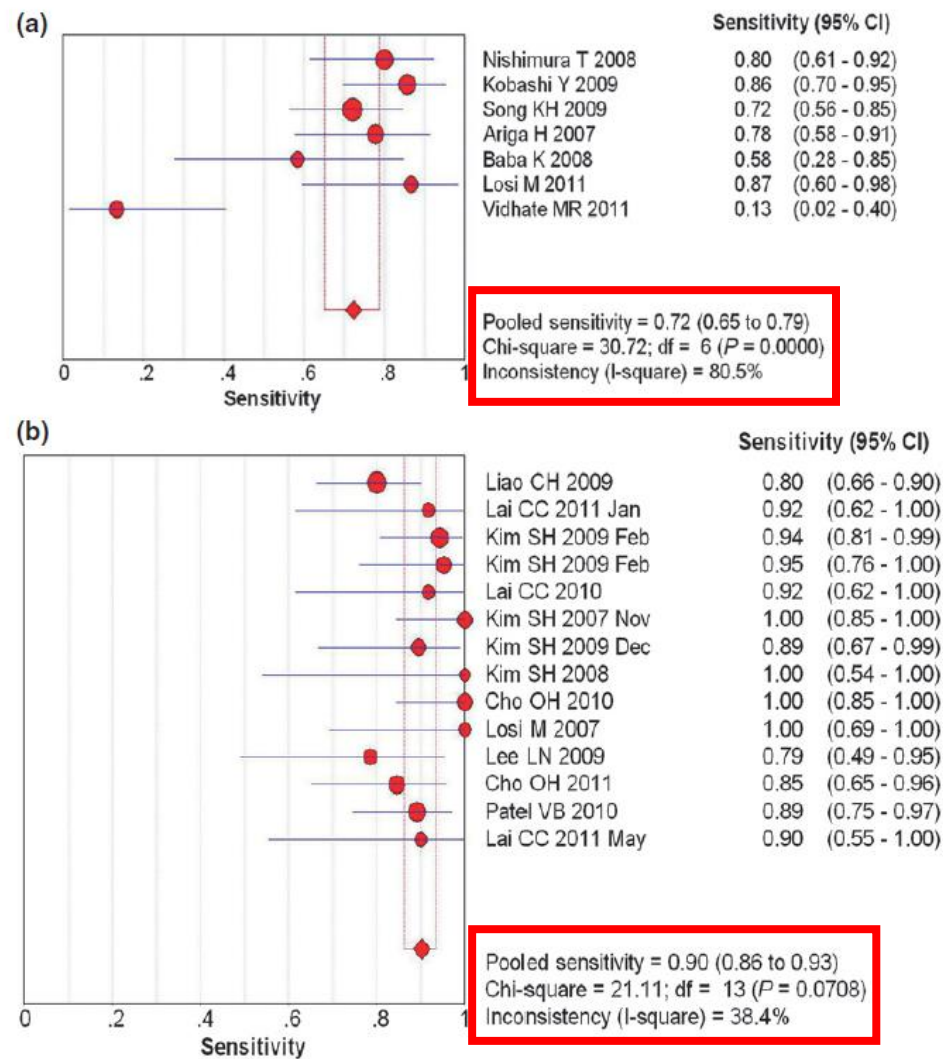


Fig. 2. Forest plot of estimate of sensitivity using QFT-G or GIT (a) and T-SPOT.TB (b) for the diagnosis of EPTB.

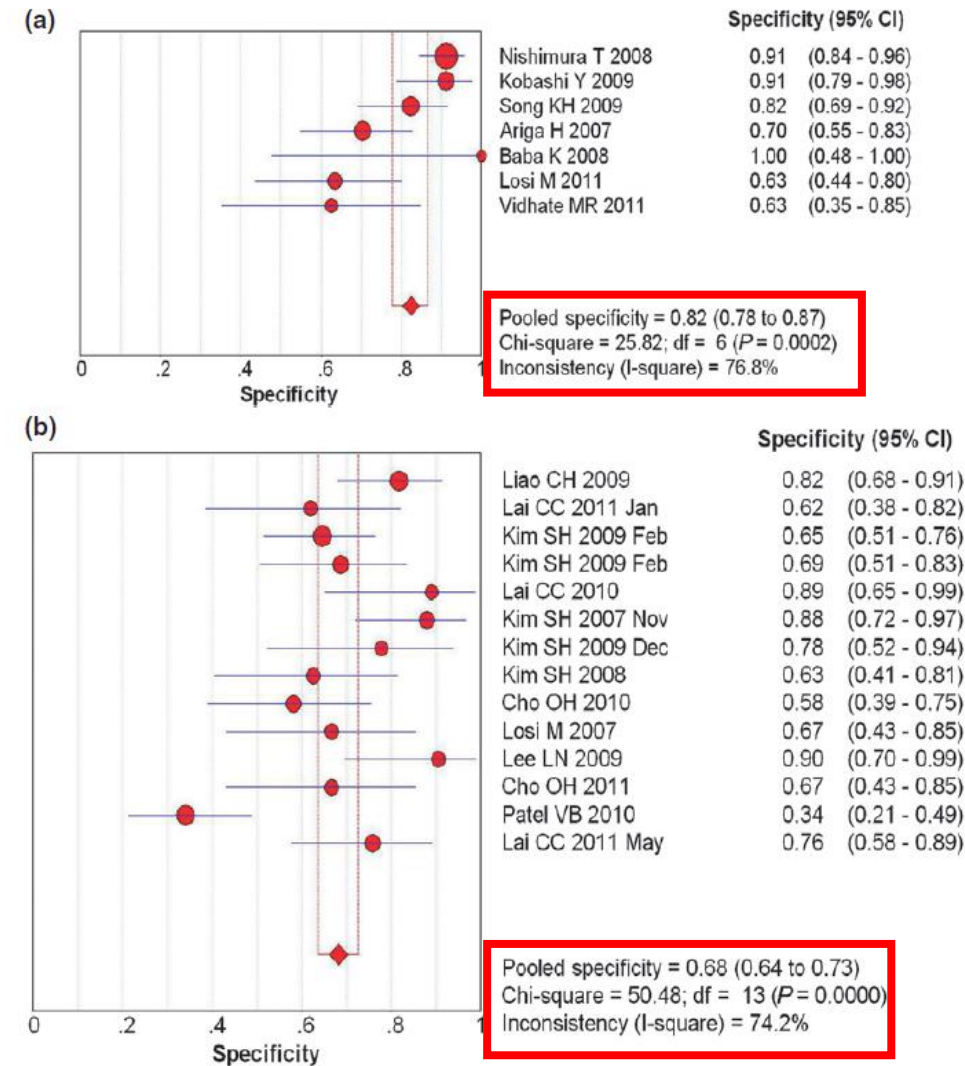
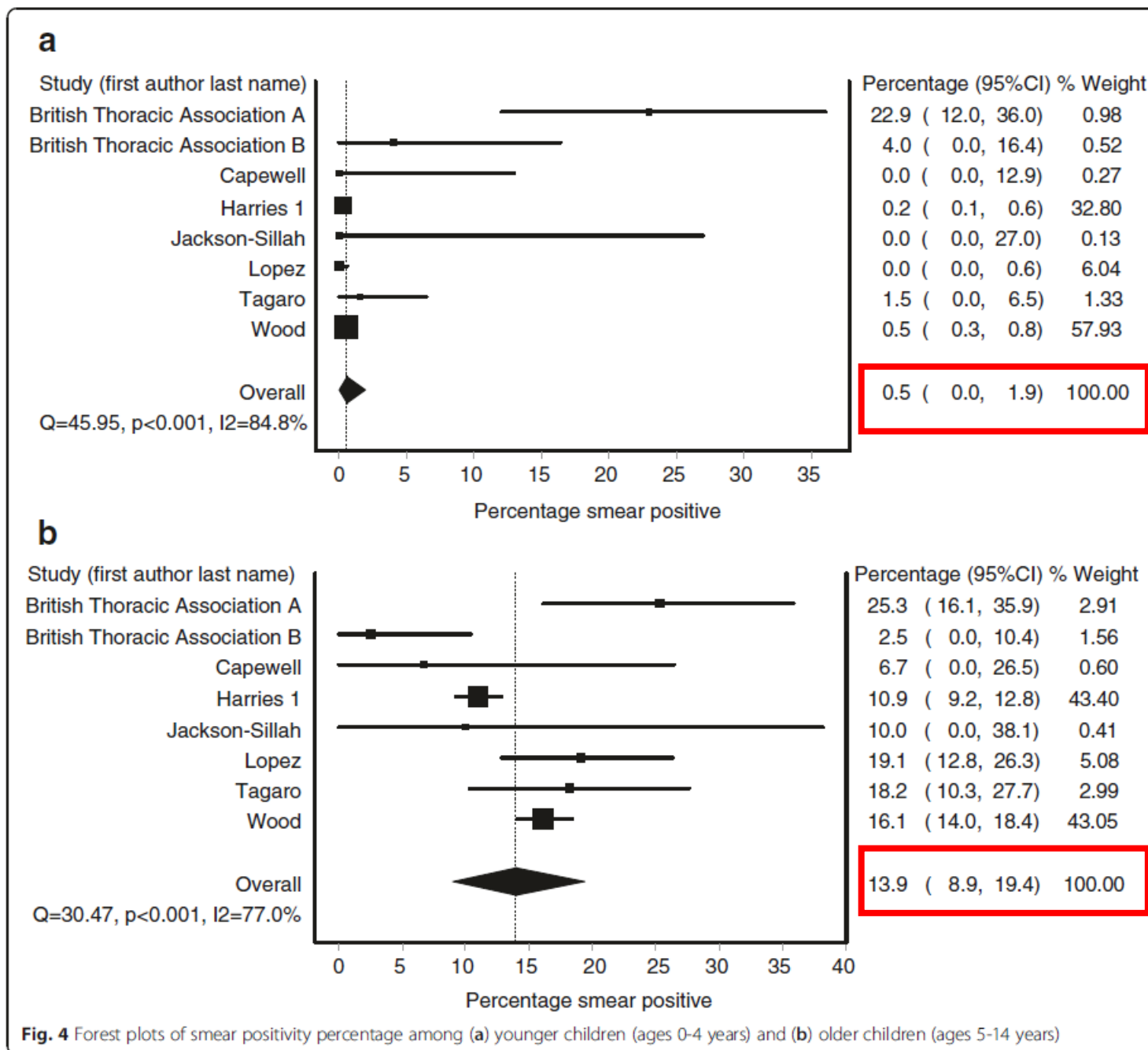


Fig. 3. Forest plot of estimate of specificity of QFT-G or GIT (a) and T-SPOT.TB (b).

Table 4 Specifications for collecting biological samples for diagnosing tuberculosis (TB)

Material	Requirements	Instructions	Unsuitable samples
Gastric aspirate	At least 5 mL collected in the morning after at least an 8-h fast on 3 consecutive days	Neutralisation with 100 mg of sodium bicarbonate	Saliva, pooled samples
Sputum	At least 5 mL of deep sputum collected in the morning on 3 consecutive days	Rinse the oral cavity with water before collecting the sample	
Induced sputum	At least 5 mL collected in the morning on 3 consecutive days	Delivery of hypertonic saline by nebulizer	
Broncholavage	At least 3 mL	Disinfection and sterilization of the bronchoscope	
Cavitary fluids	10–15 mL in a test tube with trisodium citrate		
Cerebrospinal fluid	At least 2 mL		
Bioptic samples	At least 1 g of tissue		Samples in formalin (although a molecular search is possible)
Pus	The maximum possible amount collected by means of a syringe and transferred into a sterile test tube		Swabs with transport medium
Urine	At least 40 mL of the first morning urine		24-h urine
Feces	At least 1 g	Not useful for a diagnosis of intestinal TB	



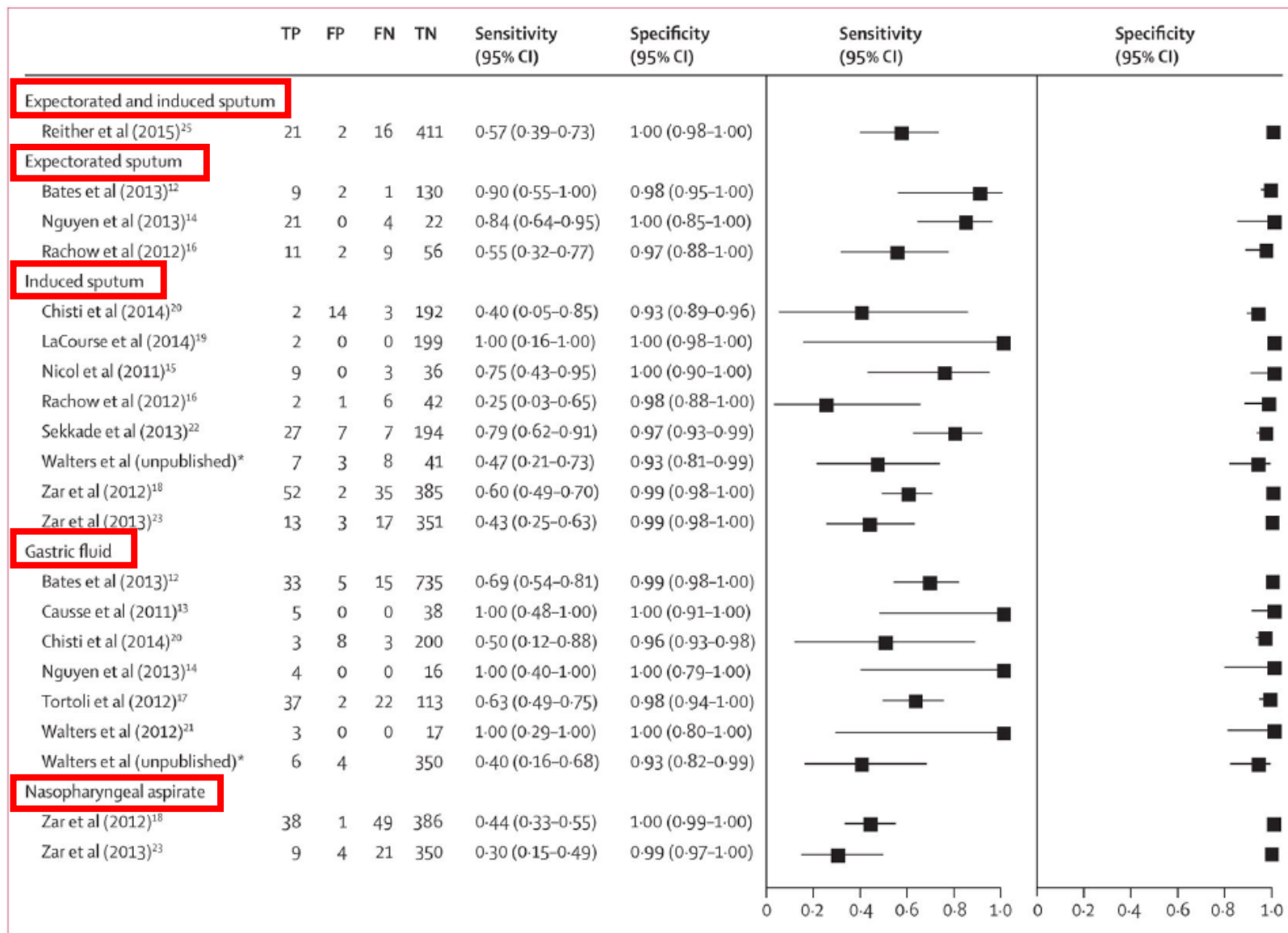


Figure 2. Sensitivity and specificity of Xpert against culture reference standard by study and specimen type

TP=true positive. FP=false positive. FN=false negative. TN=true negative. *Walters E,

Detjen, AK, et al. Xpert MTB/RIF assay for the
**diagnosis of pulmonary tuberculosis in
 children:** a systematic review and meta-analysis.
Lancet Respir Med. 2015 June ; 3(6): 451–461.

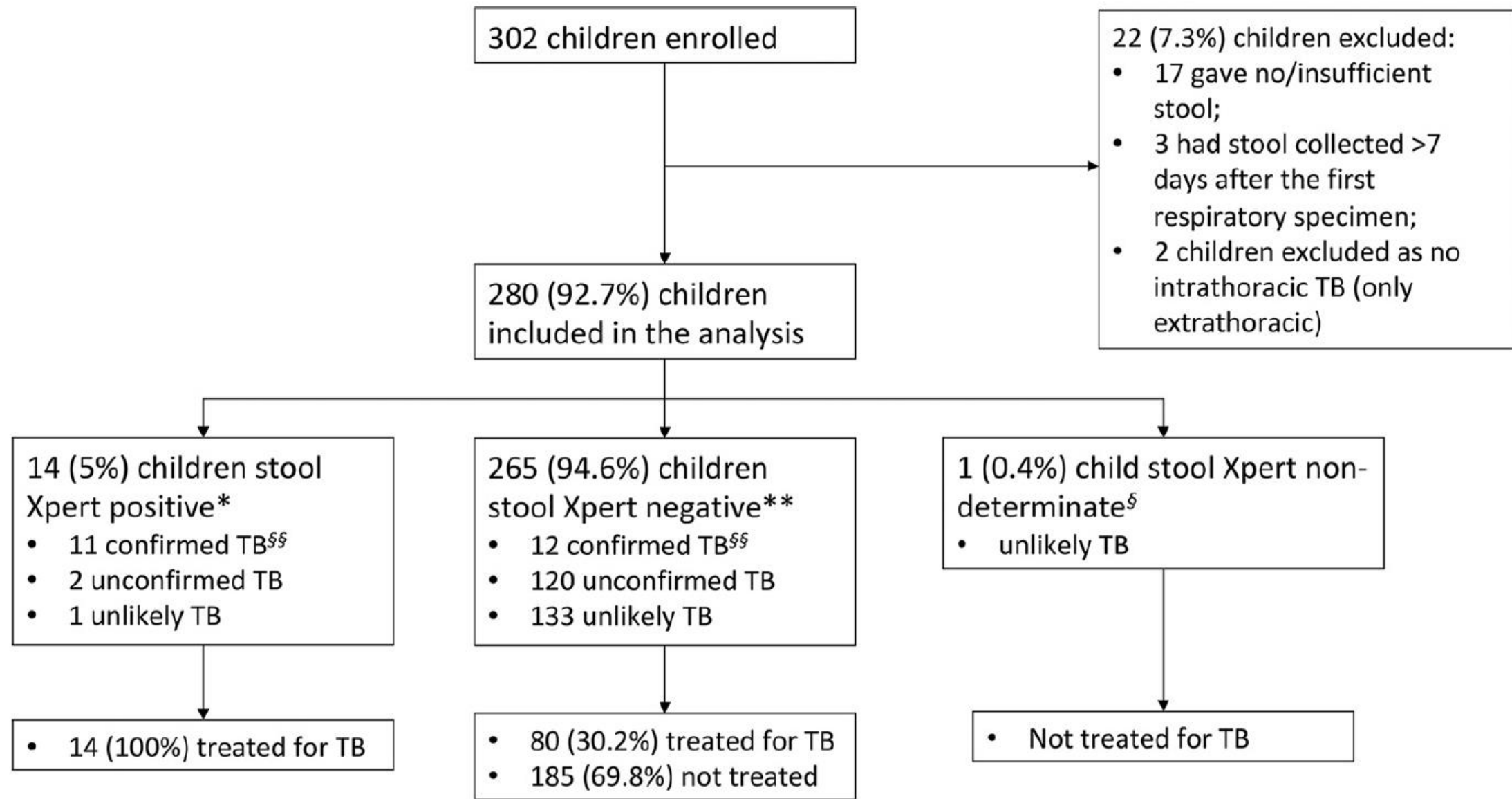


FIG 2 STARD cohort flow diagram, illustrating stool culture results by consensus case definition (13).

Table 3:
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

*exclusively among people living with HIV.

Recommended drug dosage

Drug regimen	Dose per body weight	Maximum dose
Daily Isoniazid alone for 6 or 9 months	Adults = 5 mg/kg Children = 10 mg/kg	300 mg
Daily Rifampicin alone for 3-4 months	Adults= 10 mg/kg Children = 10 mg/kg	600 mg
Daily isoniazid plus rifampicin for 3–4 months	Isoniazid Adults = 5 mg/kg Children = 10 mg/kg Rifampicin Adults and children = 10 mg/kg	Isoniazid = 300 mg Rifampicin= 600 mg
Weekly rifapentine plus isoniazid for 3 months (12 doses)	Adults and Children Isoniazid: 15 mg/kg Rifapentine (by body weight): 10.0–14.0 kg = 300 mg 14.1–25.0 kg = 450 mg 25.1–32.0 kg = 600 mg 32.1–49.9 kg = 750 mg ≥50.0 kg = 900 mg	Isoniazid = 900 mg Rifapentine = 900 mg

Table 3. 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.

Table 4. Recommended treatment regimens for new cases of TB in children

TB diagnostic category	Anti-TB drug regimens ^a	
	Intensive phase	Continuation phase
<i>Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings^b</i>		
Smear-negative pulmonary TB		
Intrathoracic lymph node TB	2HRZ	4HR
Tuberculous peripheral lymphadenitis		
Extensive pulmonary disease		
Smear-positive pulmonary TB	2HRZE	4HR
Severe forms of extrapulmonary TB (other than tuberculous meningitis/osteoarticular TB)		
<i>High HIV prevalence or high isoniazid resistance or both^b</i>		
Smear-positive PTB		
Smear-negative PTB with or without extensive parenchymal disease	2HRZE	4HR
All forms of EPTB except tuberculous meningitis and osteoarticular TB		
<i>All regions</i>		
Tuberculous meningitis and osteoarticular TB	2HRZE ^c	10HR
MDR-TB	Individualized regimens Chapter 7	

1.6. The use of adjuvant steroids in the treatment of extrapulmonary TB disease

Recommendation

- 1.6.1. In patients with tuberculous meningitis, an initial adjuvant corticosteroid therapy with dexamethasone or prednisolone tapered over 6-8 weeks should be used (Strong recommendation, moderate certainty in the evidence).*
- 1.6.2. In patients with tuberculous pericarditis, an initial adjuvant corticosteroid therapy may be used (Conditional recommendation, very low certainty in the evidence).*

Table 6. Medicines recommended for the treatment of RR-TB and MDR-TB^a

Group A. Fluoroquinolones^b	Levofloxacin	Lfx
	Moxifloxacin	Mfx
	Gatifloxacin	Gfx
Group B. Second-line injectable agents	Amikacin	Am
	Capreomycin	Cm
	Kanamycin	Km
	(Streptomycin) ^c	(S)
Group C. Other core second-line agents^b	Ethionamide / prothionamide	Eto / Pto
	Cycloserine / terizidone	Cs / Trd
	Linezolid	Lzd
	Clofazimine	Cfz
Group D. Add-on agents (not part of the core MDR-TB regimen)	D1 Pyrazinamide	Z
	Ethambutol	E
	High-dose isoniazid	H ^h
	D2 Bedaquiline	Bdq
	Delamanid	Dlm
	D3 <i>p</i> -aminosalicylic acid	PAS
	Imipenem–cilastatin ^d	Ipm
	Meropenem ^d	Mpm
	Amoxicillin–clavulanate ^d	Amx-Clv
	(Thioacetazone) ^e	(T)

Table 9. Summary of drug groups used to treat drug-resistant TB (4, 10)

Drug group	Drug name	Daily <i>adult</i> dose in mg/kg	Maximum <i>adult</i> daily dose (mg)	Daily <i>paediatric</i> dose in mg/kg (max. dose in mg) ^a
Group 1: first-line oral drugs ^b	Ethambutol	20-25	2 000	15
	Pyrazinamide	30-40	2 000	
Group 2: injectable agents ^c				
Aminoglycosides	Amikacin	15-20	1 000	15-22.5 (1000)
	Kanamycin	15-20	1 000	15-30 (1000)
Cyclic polypeptide	Capreomycin	15-20	1 000	15-30 (1000)
Group 3: fluoroquinolones	Ofloxacin	15-20	800	15-20 (800) 2x daily
	Levofloxacin	7.5-10	750	7.5-10 (750)
	Moxifloxacin	7.5-10	400	7.5-10 (400)
Group 4: second-line oral drugs ^d	Ethionamide (or prothionamide)	15-20	1 000	15-20 (1000) 2x daily
	Cycloserine (or terizidone)	10-20	1 000	10-20 (1000) 1x/2x daily
	p-aminosalicylic acid ^e (PAS; 4-g sachets)	150	12 000	150 (12 000) 2x/3x daily
Group 5: third-line drugs of unclear efficacy (not recommended by WHO for routine use in MDR-TB patients) ^f	High-dose Isoniazid ^g	15-20	400	
	Linezolid ^h	10-12, 2x daily	300, 1x/2x daily	
	Amoxicillin/clavulanate	15 amoxicillin 3x daily		
	Clarithromycin	7.5-15, 2x daily	500, 2x daily	
	Thioacetazone ⁱ	3-4	150	
	Imipenem/cilastatin	(only IV)		
	Clofazimine	3-5	300	

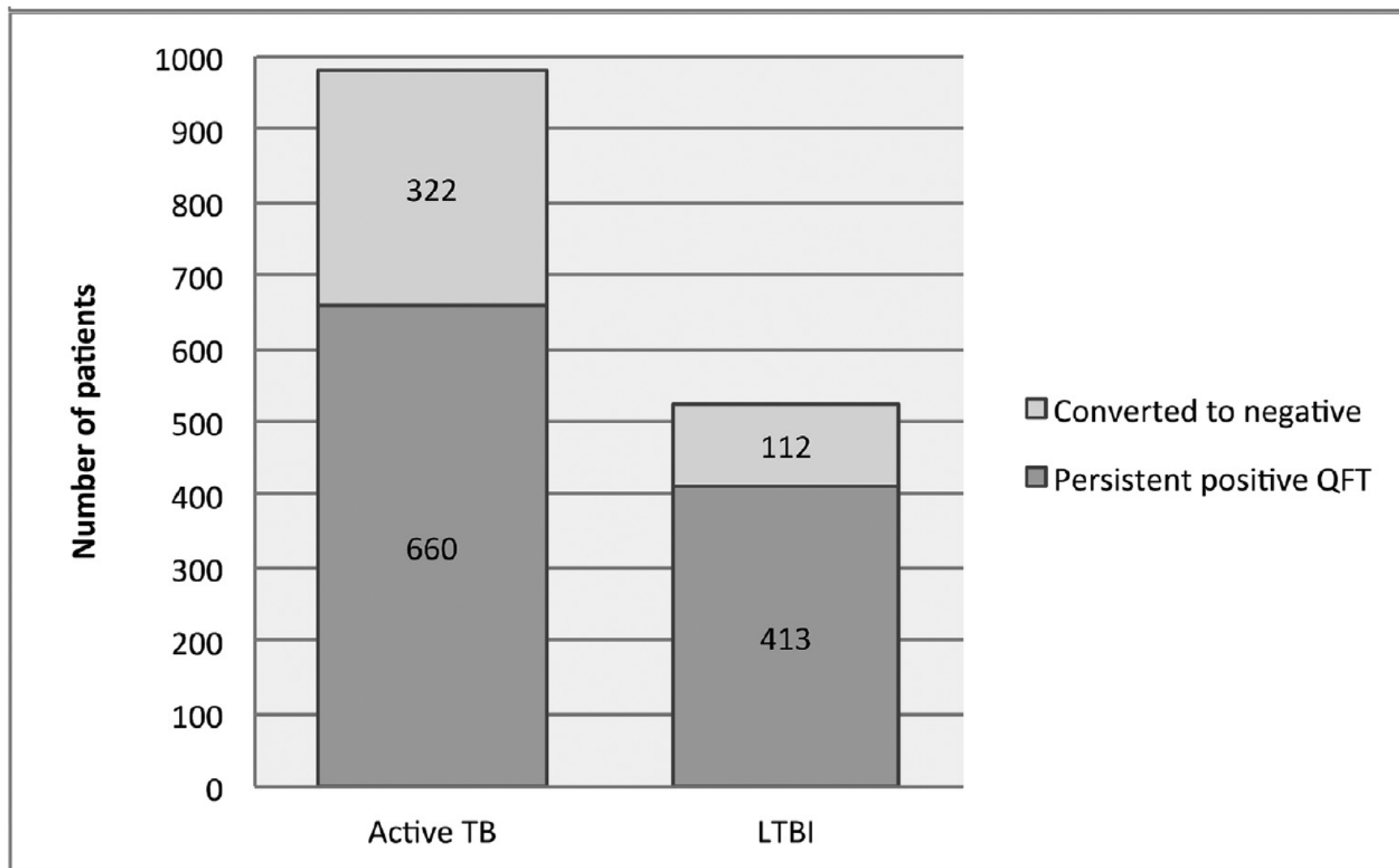
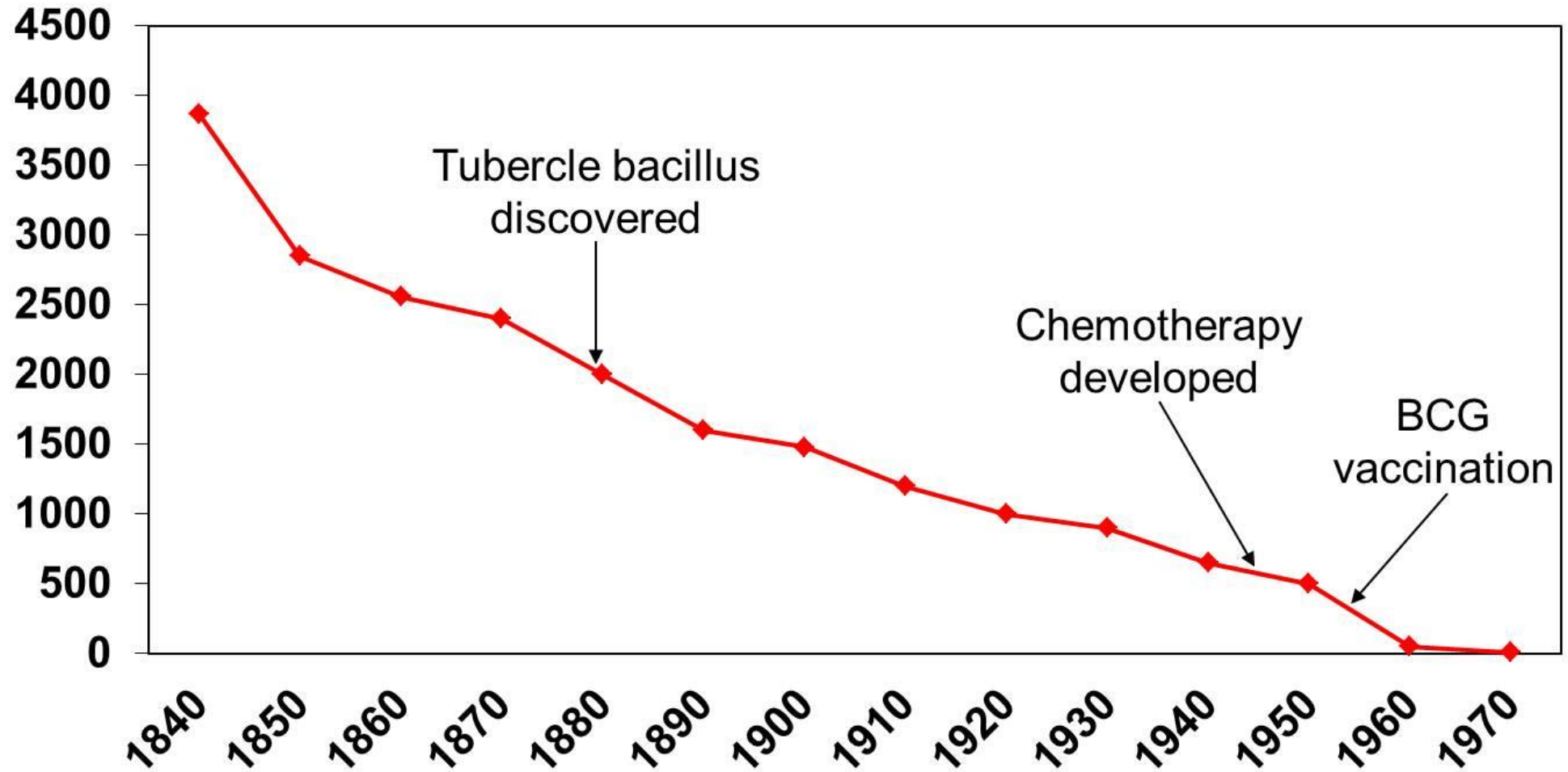


Figure 2. Change in QFT from the start to the end of treatment of active TB (top panel) and LTBI (middle panel) and overall results for active and LTBI (lower panel). These graphs only include patients with an initially positive QFT. Dark grey indicates persistently positive QFT. Light grey indicates conversion to a negative QFT.

Annual TB deaths per million population



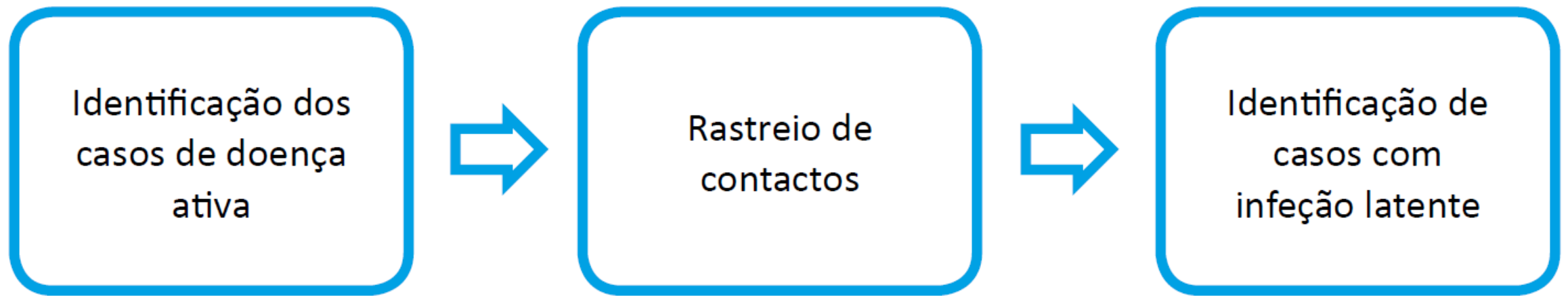


Figura 1. Controlo da tuberculose e transmissão da doença.

Tabela 1. Determinação do início e duração do período provável de infecciosidade em casos de tuberculose pulmonar, de acordo com as características do caso

Presença de sintomas	Laboratório	Radiologia	Período de infecciosidade
Sim	Exame direto positivo	Qualquer	Três meses antes do início de sintomas ou antes do primeiro achado consistente com a doença (por exemplo: alteração radiológica)
Sim	Exame direto negativo	Sem cavitação	Três meses antes da suspeita de tuberculose
Não	Exame direto negativo Exame cultural positivo	Sem cavitação	Quatro semanas antes da suspeita de tuberculose

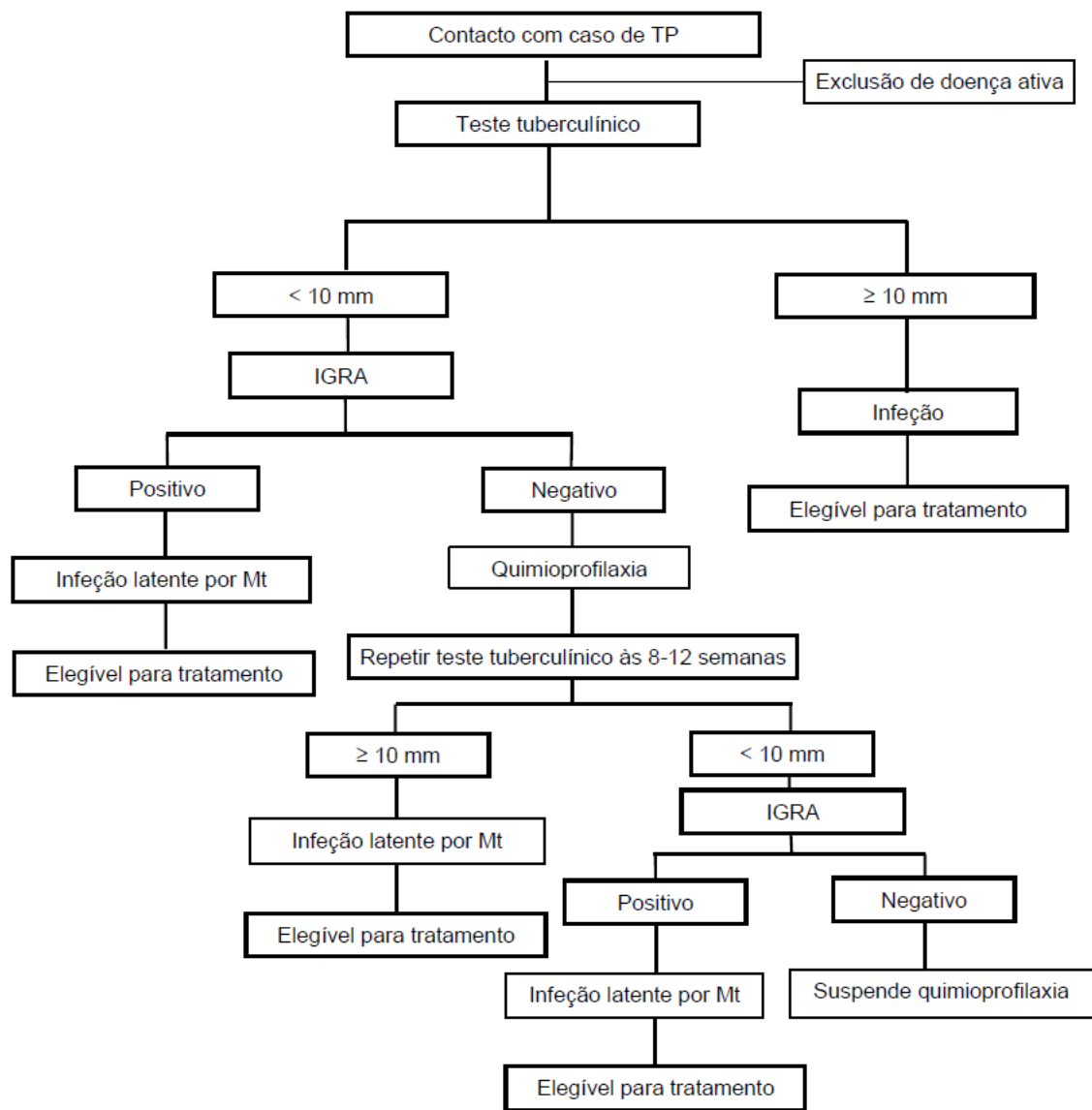


Figura 3. Abordagem da criança com idade igual ou inferior a 5 anos e contacto com tuberculose. Em caso de indisponibilidade de IGRA, a decisão clínica deve basear-se no valor do teste tuberculínico.

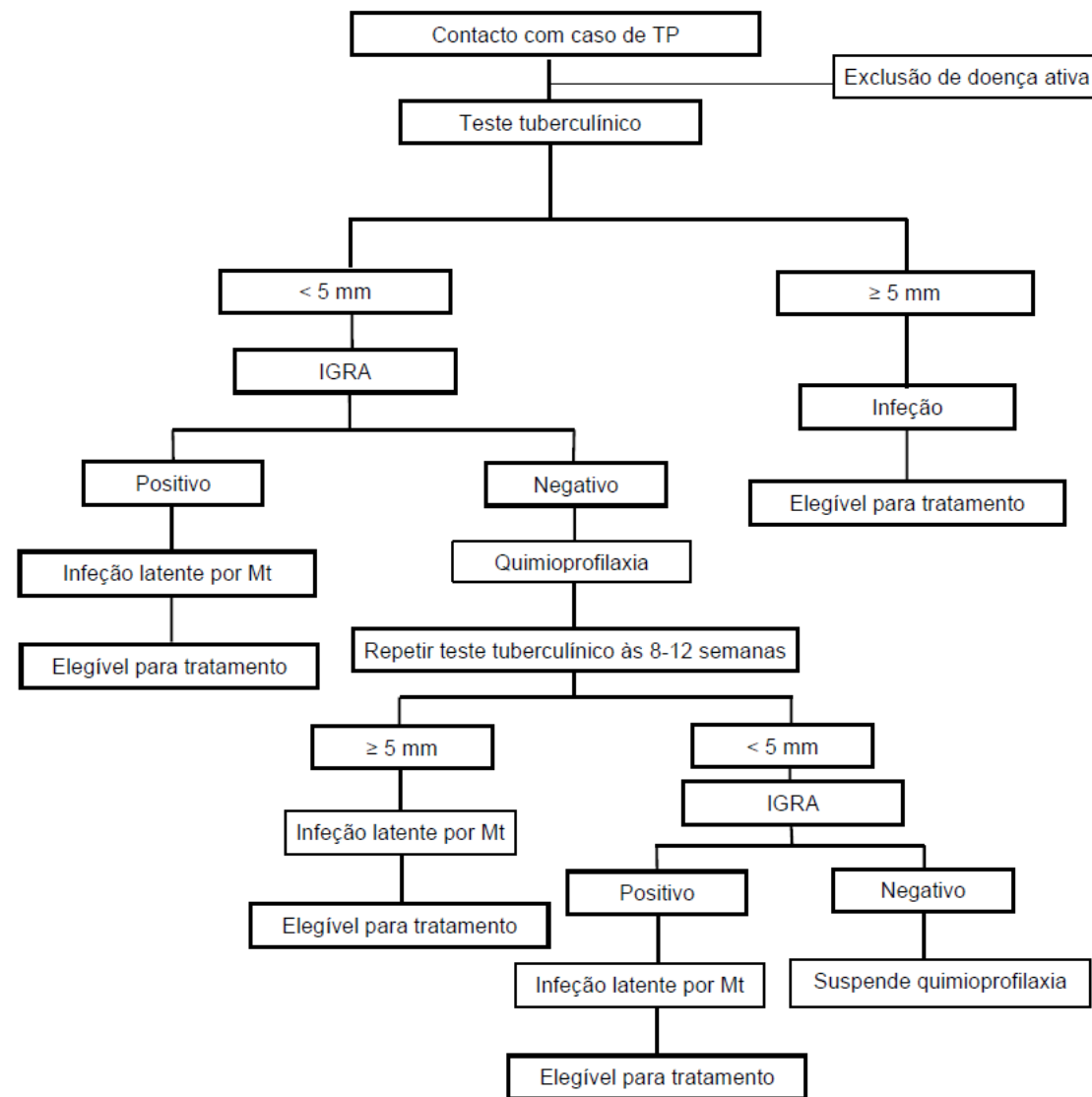


Figura 5. Abordagem da criança imunodeprimida ou com idade igual ou inferior a 5 anos e sem BCG, e com contacto com tuberculose. Em caso de indisponibilidade de IGRA, a decisão clínica deve basear-se no valor do teste tuberculínico.

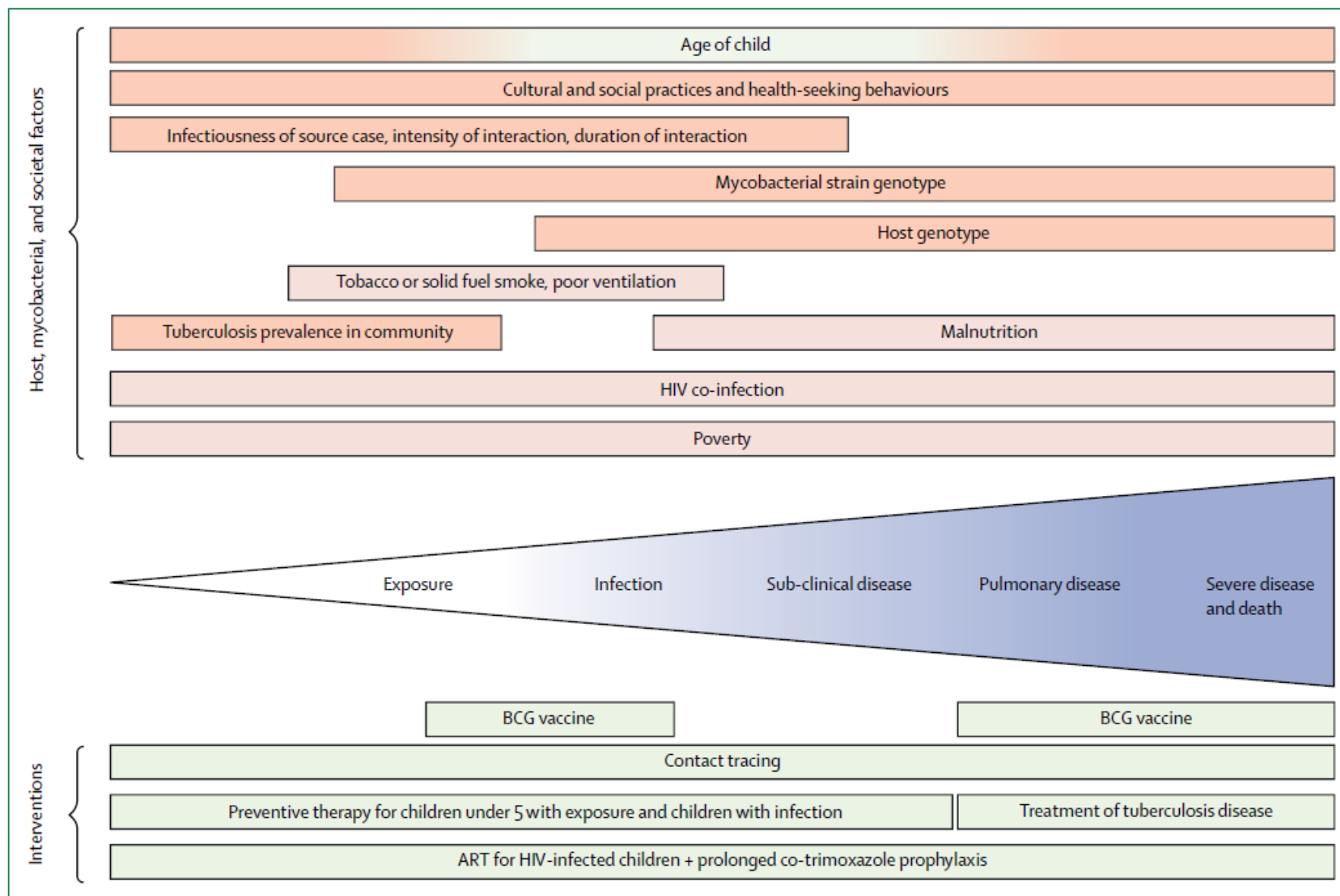


Figure 3: Schematic representation of risk factors and protective interventions in paediatric interactions with *Mycobacterium tuberculosis*. Red background denotes risk factors, green background denotes protective factors, and orange denotes factors that can be either protective or increase risk. ART=antiretroviral therapy.

Mensagens

- O diagnóstico de TB na criança pode ser apenas presuntivo
 - Não há dados suficientes para afirmar qual o melhor teste de rastreio da infeção latente
- O tratamento da TB sensível aos antituberculosos está padronizado
- O tratamento da MDR-TB é individualizado
- O controlo da TB em países de baixa incidência implica:
 - diagnóstico e tratamento atempado e adequado de casos de doença e infeção latente
 - rastreio ativo de contactos de doentes bacilíferos e quimioprofilaxia

Abubakar I, et al. Prognostic value of interferon- γ release assays and tuberculin skin test in predicting the development of active tuberculosis (UK PREDICT TB): a prospective cohort study. *Lancet Infect Dis* 2018; 8:1077–87

Findings: Between May 4, 2010, and June 1, 2015, 10 045 people were recruited, of whom **9610** were eligible for inclusion. Of this cohort, 4861 (50.6%) were contacts and 4749 (49.4%) were migrants. Participants were followed up for a median of 2.9 years (range 21 days to 5.9 years). **97 (1.0%) of 9610 participants developed active tuberculosis** (77 [1.2%] of 6380 with results for all three tests). In all tests, annual incidence of tuberculosis was very low in those who tested negatively (ranging from 1.2 per 1000 person-years, 95% CI 0.6–2.0 for TST-5 to 1.9 per 1000 person-years, 95% CI 1.3–2.7, for QuantiFERON-TB Gold In-Tube). **Annual incidence in participants who tested positively were highest for T-SPOT.TB** (13.2 per 1000 person-years, 95% CI 9.9–17.4), TST-15 (11.1 per 1000 person-years, 8.3–14.6), and QuantiFERON-TB Gold In-Tube (10.1 per 1000 person-years, 7.4–13.4). **Positive results for these tests were significantly better predictors of progression than TST-10 and TST-5** (eg, ratio of test positivity rates in those progressing to tuberculosis compared with those not progressing T-SPOT.TB vs TST-5: 1.99, 95% CI 1.68–2.34; $p < 0.0001$). **However, TST-5 identified a higher proportion of participants who progressed to active tuberculosis (64 [83%] of 77 tested) than all other tests and TST thresholds ($\leq 75\%$).**

Table 3

Strategies to prevent multidrug/extensively drug-resistant tuberculosis (M/XDR-TB) within the End TB Strategy framework

Pillar	M/XDR-TB prevention strategies
1. Integrated patient-centred care and prevention	• Early diagnosis with universal drug susceptibility testing • Screening of close contacts • Preventive therapy for infected high-risk contacts • Early and effective therapy for drug-resistant disease
2. Bold policies and supportive systems	• Effective infection control policies; scale-up of implementation • Optimized MDR/XDR-TB treatment models, including decentralized support systems and social protection • Active case finding in high-risk populations
3. Intensified research and innovation	• Overcome local barriers to improve infection control • Identify optimal preventive therapy strategies • Expedite the diagnosis of drug-resistant TB • Improve treatment outcome, short duration treatment with minimal adverse effects

Fox GJ, et al. Preventing the spread of multidrug-resistant tuberculosis and protecting contacts of infected individuals. *Microbiol Infect* 2017;23:147