Diagnosis and Management of Tuberculosis in Children

Albert M. Li
Department of Paediatrics
Prince of Wales Hospital
The Chinese University of Hong Kong

香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong

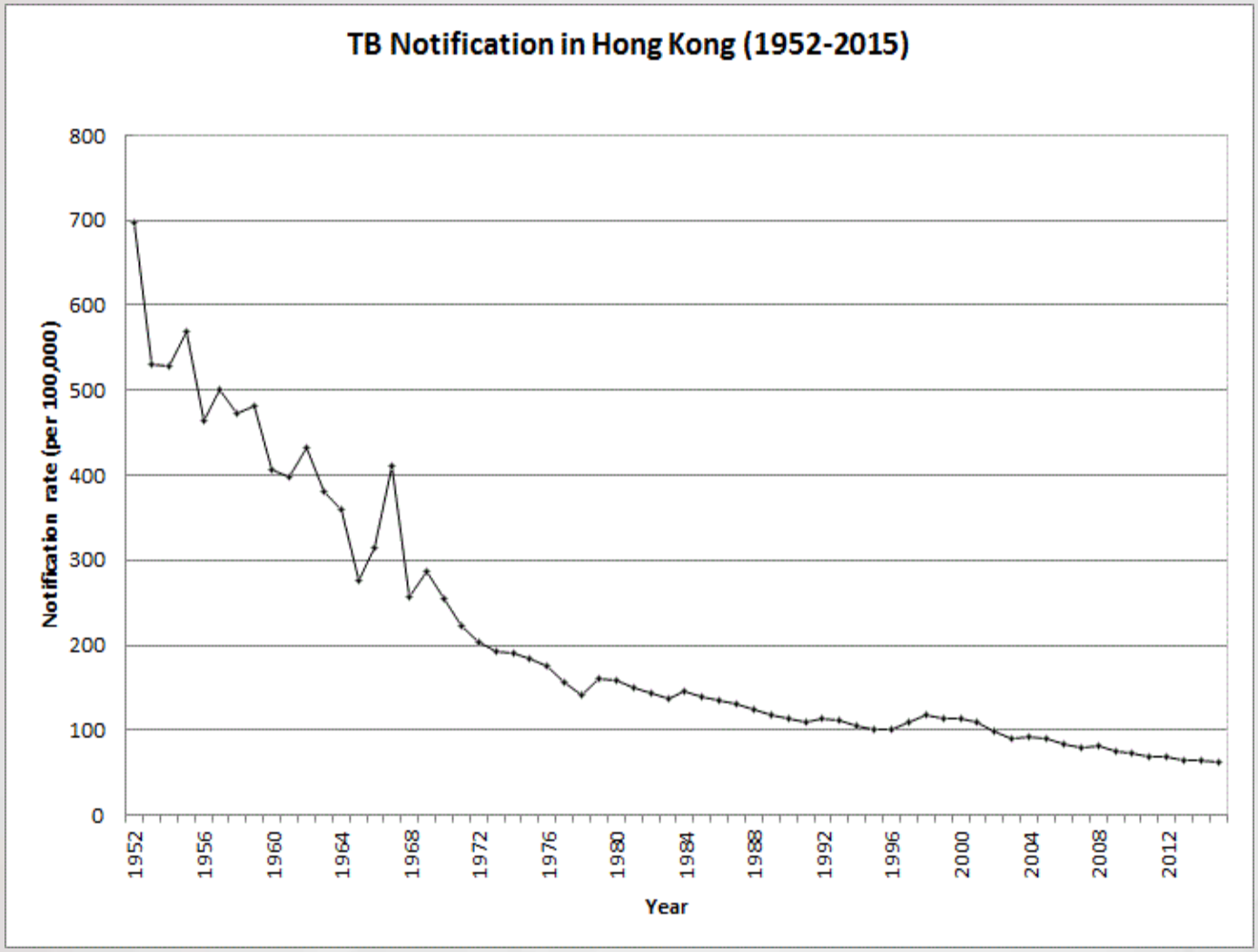
Conflict of interest

- None to declare

Aims and Content of Talk

- To review recent research in the management of childhood TB

- Diagnosis
- Sputum collection
- Treatment



0-4 yr. → 1.4

5-9 yr. → 1.8

10-14 yr. → 6.8

15-19 yr. → 28.5

Death rate per 100,000 in 2015 → 2.3

Childhood TB and Public Health

- Child TB historically afforded a low priority by NTPs:
  - Diagnostic difficulties
  - Usually not infectious
  - Limited resources
  - Lack of recording and reporting

But .....

- **this disregards the impact of TB on childhood morbidity and mortality**

- **child TB reflects recent TB control**

- **infected children become adults with disease**

Diagnostic difficulties

- TB can mimic many other common childhood diseases, non-specific clinical presentation
- Inability of pre-adolescent patients to expectorate sputum
- Lower bacillary load which is often smear negative
- Confirmation by culture which is gold standard diagnosis for adult TB, rarely > 30%

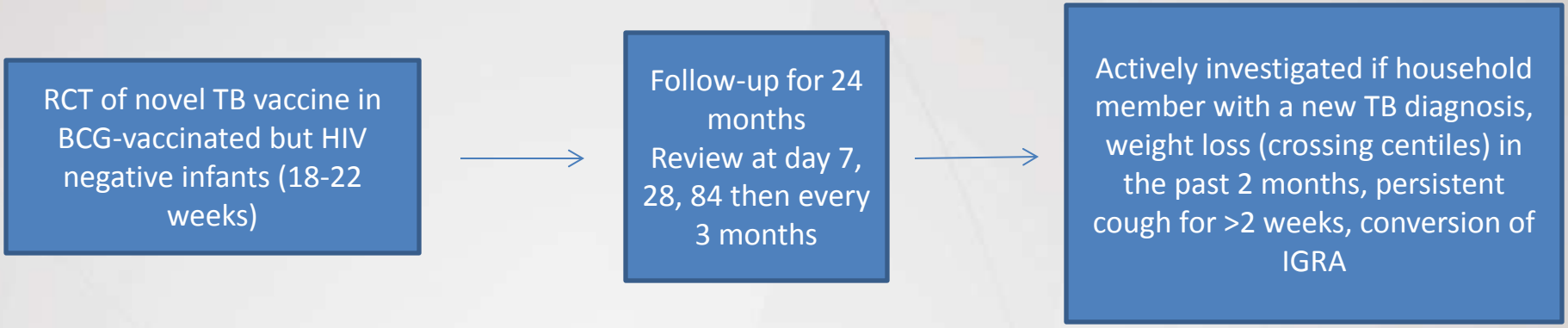
- SYMPTOM-BASED DIAGNOSIS

The Role of Clinical Symptoms in the Diagnosis of Intrathoracic Tuberculosis in Young Children

Humphrey Mulenga, MPH, Michele D. Tameris, MBChB,* Kany Kany A. Luabeya, MSc,* Hennie Geldenhuys, MFam Med,* Thomas J. Scriba, PhD,* Gregory D. Hussey, FCCH,† Hassan Mahomed, PhD,‡ Bernard S. Landry, MPH,¶ Willem A. Hanekom, FCP Paed,* Helen McShane, FRCP,§ and Mark Hatherill, MD**

The Pediatric Infectious Disease Journal • Volume 34, Number 11, November 2015

- Usefulness of symptoms for the diagnosis of TB disease
- Healthy, HIV-uninfected South African infants in a novel TB vaccine trial, followed for 2 years for suspected TB
- Incidence of TB (under 2 years) – 3000 per 100,000
- July 2009 – October 2012



- TB contact + symptom history
- Liquid MTB culture
- Xpert from 2 paired induced sputum and gastric lavage samples
- IGRA
- CXR, reviewed by 3 blinded independent radiologists, features suggestive of TB – airway compression, Ghon focus, mediastinal lymphadenopathy, pleural effusion, airspace opacification, miliary pattern, cavitation

Results

- 2,797 enrolled for the vaccine trial, 1,017 were investigated for incident TB
- Mean age at investigation – 19.2 months

- Of 1,017 children, 476 males, 38 (3.7%) had a positive culture for MTB or positive Xpert. 131 children had a CXR suggestive of intrathoracic TB

TABLE 1. Univariate and Multivariate Models of Demographic, Symptom, and Other Diagnostic Variables Associated with *Mycobacterium Tuberculosis* (MTB) Culture-positive Intrathoracic TB

	Culture +ve	Culture –ve	Univariate Analysis		Multivariate Analysis	
Variable	(n = 38)	(n = 979)	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender (males) (n, %)	21 (55)	455 (46)	1.42 (0.74–2.73)	0.29	1.37 (0.66–2.82)	0.40
Age* (mean, SD)	21 (8.5)	19 (7.4)	1.03 (0.99–1.07)	0.17		
WAZ (mean, SD)	–1 (1.2)	–1 (1.2)	0.89 (0.68–1.16)	0.38	0.79 (0.58–1.08)	0.14
Persistent cough (n, %)	17 (45)	155 (16)	4.3 (2.22–8.34)	0.001	3.27 (1.53–6.98)	0.002
Failure to thrive (n, %)	23 (60)	485 (50)	1.56 (0.81–3.03)	0.19		
Fever (n, %)	1 (3)	20 (2)	1.3 (0.17–9.92)	0.8		
Lethargy (n, %)	0 (0)	12 (1)	-	-		
Loss of appetite (n, %)	7 (18)	174 (18)	1.04 (0.45–2.41)	0.92		
Loss of weight (n, %)	5 (13)	27 (3)	5.34 (1.93–14.75)	0.001		
Wheeze (n, %)	4 (11)	124 (13)	0.81 (0.28–2.32)	0.70		
CXR positive (n, %)	21 (55)	110 (11)	9.66 (4.95–18.86)	0.001	4.03 (1.91–8.48)	0.001
QFT positive (n, %)	29 (76)	199 (20)	12.63 (5.8827.11)	0.001	10.8 (4.76–24.45)	0.001
HH TB contact (n, %)	9 (324)	320 (33)	0.64 (0.30–1.37)	0.25		

*Age at admission.

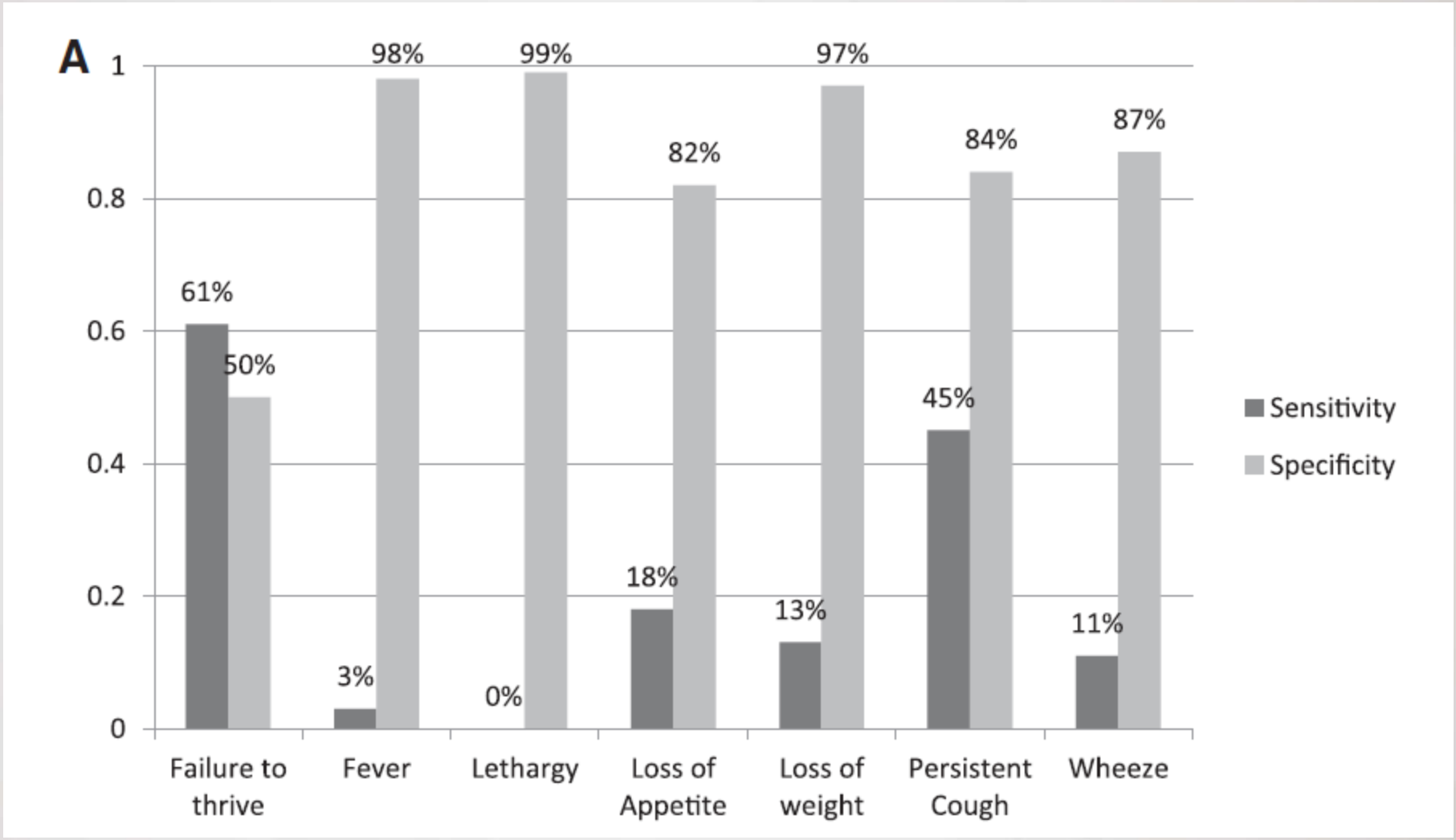
WAZ indicates weight-for-age Z score; SD, standard deviation; HH TB contact, household TB contact.

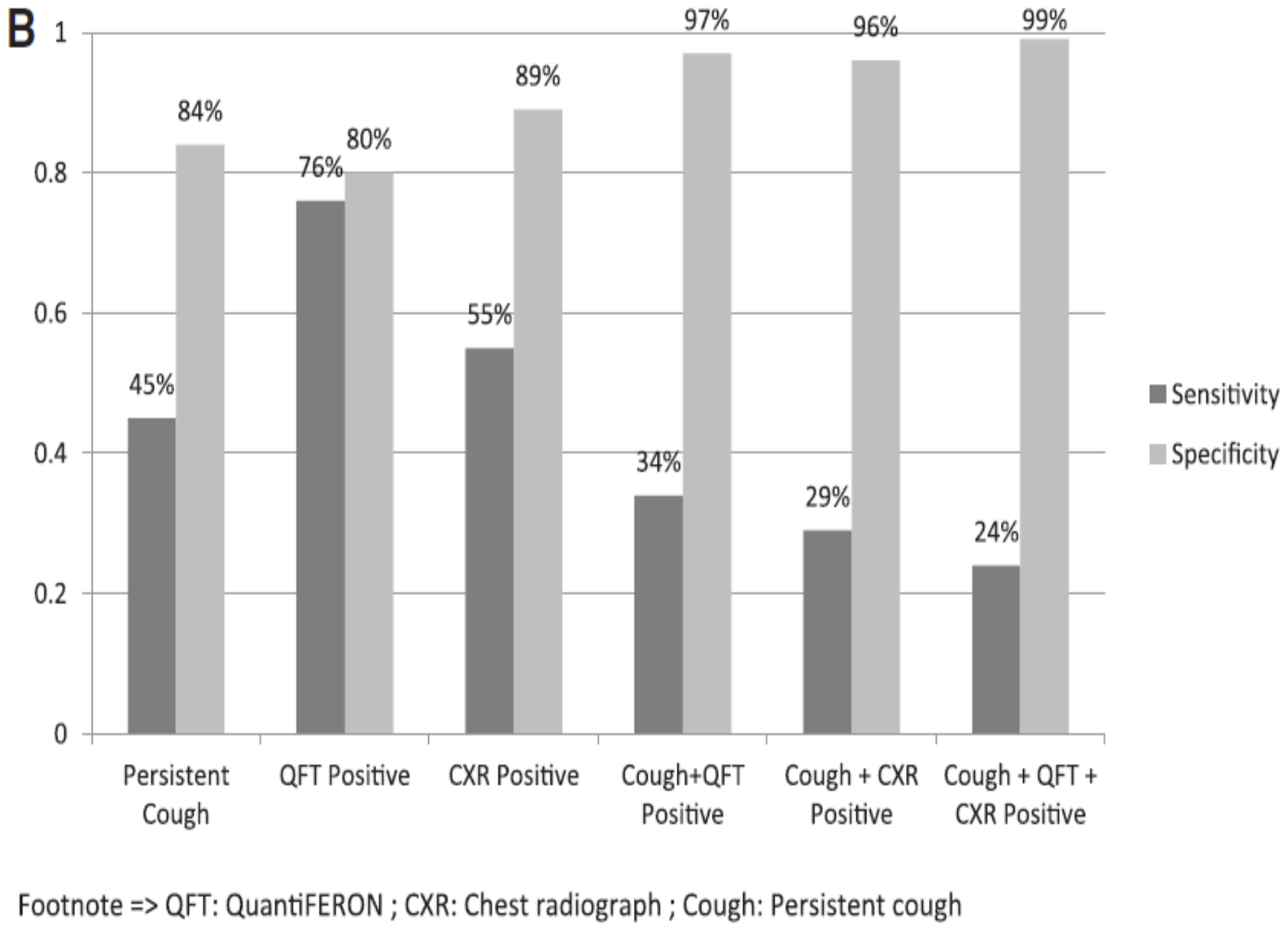
TABLE 2. Univariate and Multivariate Models of Demographic, Symptom, and Other Diagnostic Variables Associated with a CXR Compatible with Intrathoracic TB

	CXR +ve	CXR –ve	Univariate Analysis		Multivariate Analysis	
Variable	(n = 131)	(n = 886)	OR (95% CI)	*P*	OR (95% CI)	*P*
Gender (males) (n, %)	67 (51)	409 (46)	1.22 (0.85–1.76)	0.29	1.21 (0.81–1.80)	0.36
Age* (mean, SD)	20.5 (8)	18.9 (7.3)	1.03 (1.00–1.05)	0.03	1.01 (0.98–1.04)	0.31
WAZ (mean, SD)	–1 (1.2)	–1 (1.2)	1.02 (0.88–1.18)	0.83	1.07 (0.89–1.29)	0.44
Persistent cough (n, %)	50 (38)	122 (14)	3.87 (2.59–5.77)	0.001	3.48 (2.22–5.45)	0.001
Failure to thrive (n, %)	79 (60)	429 (48)	1.62 (1.11–2.35)	0.01	1.70 (1.07–2.70)	0.03
Fever (n, %)	3 (2)	18 (2)	1.13 (0.33–3.89)	0.85		
Lethargy (n, %)	2 (2)	10 (1)	1.36 (0.29–6.27)	0.70		
Loss of appetite (n, %)	23 (18)	158 (18)	0.98 (0.61–1.59)	0.94		
Loss of weight (n, %)	12 (9)	20 (2)	4.37 (2.08–9.16)	0.001		
Wheeze (n, %)	24 (18)	104 (12)	1.69 (1.04–2.75)	0.04		
Culture positive (n, %)	21 (16)	17 (2)	9.76 (5–19.06)	0.001	3.91 (1.82–8.37)	0.001
QFT positive (n, %)	63 (48)	165 (19)	4.05 (2.76–5.93)	0.001	3.61 (2.32–5.63)	0.001
HH TB contact (n, %)	33 (25)	296 (33)	0.67 (0.44–1.02)	0.062		

*Age at admission.

WAZ indicates weight-for-age Z score; SD, standard deviation; HH TB contact, household TB contact.


A
1
0.8
0.6
0.4
0.2
0
61%
50%
3%
98%
0%
99%
18%
82%
13%
97%
45%
84%
11%
87%
Failure to thrive
Fever
Lethargy
Loss of Appetite
Loss of weight
Persistent Cough
Wheeze
Sensitivity
Specificity



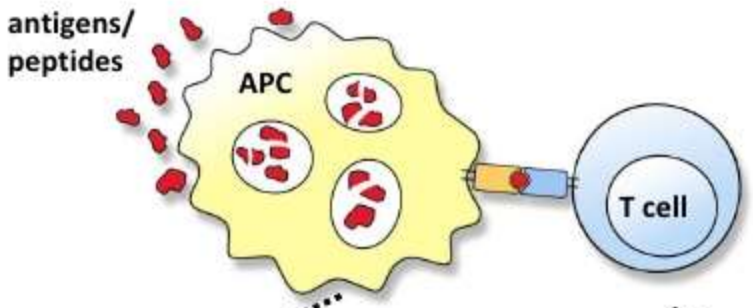
- 99% specificity by combining cough, CXR and IGRA, thus almost all children without culture positive TB could be excluded by this composite endpoint
- But low sensitivity

Cautions

- Young HIV uninfected children
- High incidence of TB!
- Under active surveillance for suspected TB

- IMMUNE-BASED DIAGNOSIS

2.) T-cell based tests



IGRA

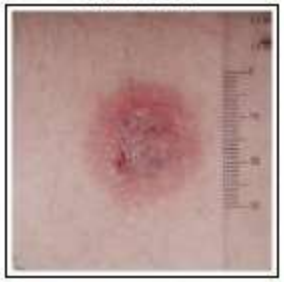
IFN-γ release assay

cytokine induction

cytokine induction

cytokine induction

Skin test



PPD (= tuberculin)

ELISA

QuantiFERON TB gold

ESAT-6, CFP-10, Tb7.7

ELISPOT assay

T.SPOT.*TB*

ESAT-6, CFP-10

RESEARCH ARTICLE Open Access

Performance of interferon-γ release assays in the diagnosis of confirmed active tuberculosis in immunocompetent children: a new systematic review and meta-analysis

Patrizia Laurenti, Matteo Raponi*, Chiara de Waure, Marta Marino, Walter Ricciardi and Gianfranco Damiani

Laurenti *et al. BMC Infectious Diseases* (2016) 16:131

Results: Fifteen studies were included in our meta-analysis. Results showed that there were no significant differences in sensitivity between TST (88.2 %, 95 % confidence interval [CI] 79.4–94.2 %), QFT-IT (89.6 %, 95 % CI 79.7–95.7 %) and T SPOT (88.5 %, 95 % CI 80.4–94.1 %). However, both QFT-IT (95.4 %, 95 % CI 93.8–96.6 %) and T-SPOT (96.8 %, 95 % CI 94.2–98.5 %) have significantly higher specificity than TST (86.3 %, 95 % CI 83.9–88.6 %).

Conclusions: QFT-IT and T-SPOT have higher specificity than TST for detecting active TB cases in immunocompetent children.

Diagnosis of active TB

- Predictive value of a combination of clinical, radiological and IGRA for diagnosing active TB
- 150 symptomatic HIV-negative children aged 3 months to 14 years
- 35 diagnosed with active TB
- Age and presence of lymphadenopathy discriminated active TB from other diseases with AUC of 0.7
- A positive IGRA result did not improve the discriminatory ability!

Togun TO et al., Eur Respir J 2016 Jan;47(1):223.232

- OBTAINING A SPUTUM SAMPLE

Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa

H J Zar, E Tannenbaum, P Apolles, P Roux, D Hanslo, G Hussey

Arch Dis Child 2000;**82**:305–308

- Whether sputum induction (SI) can be successfully performed in infants and young children, utility of SI vs. gastric lavage in diagnosing TB
- 149 subjects, median age 9 months
- Procedure was successful in 142, youngest subject was 1 month of age
- Epistaxis in 6, increase in coughing in 8 and wheezing responsive to ventolin in 3

- Performed on the day of enrolment after 2-3 hours fast
- Pre-treatment with salbutamol
- Jet nebuliser attached to 5 l/min oxygen, delivered 5ml of 5% saline, then physiotherapy applied
- Sputum obtained by either expectoration or suctioning through naso-/ oropharynx

Table 2 Diagnosis of children with tuberculosis by sputum induction or gastric lavage

	Gastric lavage	
Induced sputa	*Culture positive (n)*	*Culture negative (n)*
Culture positive (n)	8	7
Culture negative (n)	1	126

Sputum Induction in Children With Asthma: A Tertiary-Center Experience

Albert M. Li, MB,* Tony W.T. Tsang, MPhil, Dorothy F.Y. Chan, MB, Hugh S. Lam, MB, Hung K. So, PhD, Rita Y.T. Sung, MD, and Tai F. Fok, MD

Summary. Our aims were 1) to report on our experience with sputum induction (SI), and 2) to determine predictive factors associated with successful SI in asthmatic children. Children with asthma attending the chest clinic of a university teaching hospital between October 2003–December 2004 were recruited. They completed a visual analogue scale for symptom severity, and underwent physical examination, skin-prick test, exhaled nitric oxide (eNO) measurement, spirometry, and SI. Adequate sputum contained <50% squamous epithelial cells. Predictors for successful induction were evaluated using multivariate logistic regression analysis. One hundred and thirty subjects were recruited. The median age was 11.25 years (range 7.0–17.5), and the majority were boys (75%). All except two had normal percent predicted forced expired volume in 1 sec (>80%). The median eNO was 48.95 ppb. Sputum induction was successful in 93 subjects (74.5%). Sore throat and chest discomfort occurred in 20 (15%) and 8 (6%) subjects, respectively, and the procedure was prematurely terminated in three cases. Levels of eNO were found to be a predictor for successful induction (area under the ROC (receiver operator characteristics curves) curve, 0.634). Sputum induction was well-tolerated by all subjects, and was successful in 74.5% of cases. Exhaled nitric oxide may be a useful marker for successful induction. **Pediatr Pulmonol.**

Pediatric Pulmonology 41:720–725 (2006)

INT J TUBERC LUNG DIS 18(1):8–12

http://dx.doi.org/10.5588/ijtld.13.0132

Safety and efficacy of induced sputum in young children hospitalised with suspected pulmonary tuberculosis

N. S. Planting,* G. L. Visser,* M. P. Nicol,† L. Workman,‡ W. Isaacs,‡ H. J. Zar‡

*Erasmus Medical Centre, Rotterdam, The Netherlands; †Division of Medical Microbiology, Institute for Infectious Diseases and Molecular Medicine, University of Cape Town, National Health Laboratory Service, Groote Schuur Hospital, Cape Town, ‡Department of Paediatrics and Child Health, Red Cross War Memorial Children's Hospital, University of Cape Town, Cape Town, South Africa

- To investigate the safety of and yield from IS in children hospitalised with suspected pulmonary TB
- Prospective study, from Feb 2009 – Feb 2012
- Two IS samples obtained on consecutive days or at least 4 hours apart
- Safety by recording symptoms / signs before and for 30 mins after induction

Table 1 Demographics

	Total ($N = 690$) median [IQR] or n (%)
Age, months	27.3 [13.4 to 64.2]
Age group, months	
<12	146 (21.2)
12-60	356 (51.6)
>60	188 (27.2)
Sex, male	368 (53.3)
HIV infection	
Infected	164 (23.8)
Non-infected	525 (76.1)
Unknown	1 (0.1)
Total IS procedures	1270
IS1	690
IS2	580
Height-for-age	−1.3 [−2.3 to −0.3]
Malnourished	175 (25.4)
Weight-for-age	−1.4 [−2.7 to −0.4]
Weight/height-for-age	−0.5 [−1.9 to 0.5]
Patients presenting with	
Oxygen saturation, %	98 [96 to 99]
Receiving supplemental oxygen	33 (4.8)
Respiratory rate, bpm	36 [28 to 45]
Subcostal recession	115 (16.7)
Wheeze	95 (13.8)

IQR = interquartile range; IS = induced sputum; bpm = breaths per minute.

Table 2 Occurrence of side effects in 1270 sputum induction procedures obtained by coughing or suctioning

Side effects	Coughed	Suctioned	Unknown	All procedures ($N = 1270$) n (%)
None	259	744	7	1010 (78.7)
Nose bleed	4	239	6	249 (19.4)
Wheeze	3	11	0	14 (1.1)
Cough exacerbation	1	3	0	4 (0.3)
Vomiting	0	2	0	2 (0.2)
Other	0	5	0	5 (0.4)
Total	267	1004	13	1284

Table 3 Yield of *M. tuberculosis* from repeated induced sputum procedures

	Patients *n*	Culture-positive *n* (%)	Smear-positive *n* (%)	GeneXpert® MTB/RIF-positive *n* (%)
Total	690	129 (18.7)	53 (7.7)	104 (15.1)
First specimen	690	115 (16.7)	45 (6.5)	87 (12.6)
Second specimen	580	82 (14.1)	29 (5.0)	67 (11.6)

- Two samples on the same day in 220, of these 30 +ve, 28 from first sample
- Two consecutive days in 360, 75 +ve, 63 from first sample
- Yield was higher if samples taken on two consecutive days

- TREATMENT OF CHILDHOOD TB

Original Investigation

Treatment for Preventing Tuberculosis in Children and Adolescents

A Randomized Clinical Trial of a 3-Month, 12-Dose Regimen of a Combination of Rifapentine and Isoniazid

M. Elsa Villarino, MD, MPH; Nigel A. Scott, MS; Stephen E. Weis, DO; Marc Weiner, MD; Marcus B. Conde, MD; Brenda Jones, MD; Sharon Nachman, MD; Ricardo Oliveira, MD; Ruth N. Moro, MD, MPH; Nong Shang, PhD; Stefan V. Goldberg, MD; Timothy R. Sterling, MD; for the International Maternal Pediatric and Adolescents AIDS Clinical Trials Group (IMPAACT) and the Tuberculosis Trials Consortium (TBTC)

JAMA Pediatrics March 2015 Volume 169, Number 3

RESULTS Of 1058 children enrolled, 905 were eligible for evaluation of effectiveness. Of 471 in the combination-therapy group, 415 (88.1%) completed treatment vs 351 of 434 (80.9%) in the isoniazid-only group (P = .003). The 95% CI for the difference in rates of discontinuation attributed to an AE was −2.6 to 0.1, which was within the equivalence range. In the safety population, 3 of 539 participants (0.6%) who took the combination drugs had a grade 3 AE vs 1 of 493 (0.2%) who received isoniazid only. Neither arm had any hepatotoxicity, grade 4 AEs, or treatment-attributed death. None of the 471 in the combination-therapy group developed tuberculosis vs 3 of 434 (cumulative rate, 0.74%) in the isoniazid-only group, for a difference of −0.74% and an upper bound of the 95% CI of the difference of +0.32%, which met the noninferiority criterion.

CONCLUSIONS AND RELEVANCE Treatment with the combination of rifapentine and isoniazid was as effective as isoniazid-only treatment for the prevention of tuberculosis in children aged 2 to 17 years. The combination-therapy group had a higher treatment completion rate than did the isoniazid-only group and was safe.

Abstract

Traditional treatment of tuberculosis infection (TBI) is efficacious, but adherence is low. Eighty children with TBI received a 12-dose once-weekly isoniazid/rifapentine (3HP) regimen; 79 (99%) completed therapy, 94% reported no adverse events, 1 child had mildly elevated transaminases but 1 adolescent later developed pulmonary TB. 3HP is safe, well tolerated, and has much higher completion rates than traditional LTBI regimens.

Cruz AT and Starke JR. Pediatr Infect Dis J 2016 April 15 [ahead of print]

Summary

- Persistent cough is an important presenting symptom for intrathoracic TB
- Sputum induction allows higher yield in obtaining sputum sample
- More research is required to better delineate use of IGRA in the diagnosis of childhood TB
- Shorter duration combination therapy proven for TB infection

Thank you for your attention